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*Dedicated to the memory of Dr. Eduardo Guerreiro, a noted scientist and teacher who sadly passed away in 1999.

The 12th National Symposium of Organic Chemistry (XII SINAQO), Los Cocos, Cordoba, Argentina, 14-17 November 1999

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Publisher`s Notice

The current issue of Molecules contains short Original Communications based on the presentations at the 12th "Simposio Nacional de Quimica Organica" , XII SINAQO, which took place from the 14th to the 17th of November 1999 in the Hotel UTGRA, Los Cocos, Cordoba, Argentina. This conference was dedicated to the memory of Dr. Eduardo Guerreiro, a noted scientist and teacher who sadly passed away in 1999.

Over 140 papers were presented at this conference in Argentina, and with 250 participants, it signified a major contribution to scientific exchange in Latin America. Although mainly from Argentina, the symposium attracted participants from several neighbouring countries. We are glad to be able to contribute to the diffusion of the endeavours by our Latin American colleagues, and thank the participants for submitting their contributions for publication in this special issue of Molecules. Particularly, I would like to thank our Regional Editors in Argentina, Dr. Claudio J. Solomon and Dr. Guillermo Labadie for their efforts in bringing this volume of original work together. They ensured the timely review and fast delivery of the accepted papers.

The abstracts were selected and reviewed by the conference's Scientific Committee, as well as by the Regional Editors and Molecules' editorial staff, but have not been subjected to the more rigorous peer review all other publications in Molecules undergo. With this volume, we explore a new avenue for Molecules, namely providing early access for quality publications of original work in preliminary form. Molecules encourages the publication of complete experimental details, and the submission of samples to MDPI. to document structural diversity. The authors of these communications are encouraged to disclose their results with full experimental details at a later stage.

Esteban Pombo-Villar

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Conformational Study of New AZT Derivatives
Molecules **2000**, *5*, 409-410

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Computational Study of the Stereoselectivity of Diels-Alder Reactions of D-Glucose-Derived Dienophiles With Cyclopentadiene
Molecules **2000**, *5*, 411-412

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Comparative Study Of Hydrocarbon, Fluorocarbon and Aromatic Bonded RP-HPLC Stationary Phases by Linear Solvation Energy Relationships
Molecules **2000**, *5*, 413

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Cyclodimerization of Stilbenes and Styrenes Catalyzed by Heteropolyacid Supported on Silica
Molecules **2000**, *5*, 414-415

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Synthesis of Indanes *via* a [3+2] Cycloaddition
Molecules **2000**, *5*, 416-417

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Synthesis of Hetererocylic Compounds of Biological Interest from Carbohydrate Derivatives
Molecules **2000**, *5*, 418-419

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Nuclear Magnetic Resonance for the Structural Study of Bioactive Semicarbazones
Molecules **2000**, *5*, 420-421

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Antifeedant Activity Evaluation of Withanolides from *Jaborosa integrifolia*
Molecules **2000**, *5*, 422-423

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UV Spectral Properties of Benzophenone. Influence of Solvents and Substituents
Molecules **2000**, *5*, 424-425

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Determination of the pKa of Benzophenones in Ethanol-Water
Molecules **2000**, *5*, 426-427

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Synthesis and *In Vitro* Antifungal Properties of 4-Aryl-4-N-arylamine-1-butenes and Related Compounds
Molecules **2000**, *5*, 428-430

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$S_{RN}1$ and Stille Reactions: A New Synthetic Strategy
Molecules **2000**, *5*, 431-432

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Cytotoxic Activity of Extracts and Sesquiterpene Lactones from *Stachycephalum argentinum*
Molecules **2000**, *5*, 433-434

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Phytotoxic Activity of a Benzofuran Isolated from *Trichocline reptans*
Molecules **2000**, *5*, 435-436

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Fluorimetric Determination of Carbamate Pesticides in Host-Guest Complexes
Molecules **2000**, *5*, 437-438

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Synthesis of Ethylenic and Acetylenic Triorganotins with Bulky Organic Ligands
Molecules **2000**, *5*, 439-440

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New Spiranoid Withanolides From *Jaborosa Odonelliana*
Molecules **2000**, *5*, 441-442

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Synthesis of Aziridinosteroids
Molecules **2000**, *5*, 443-444

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3,3-Dimethylacylthioureas: "S", "-S", "U" or "W" Conformation?
Molecules **2000**, *5*, 445-446

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Synthesis of D-Homo Analogs of Neurosteroids
Molecules **2000**, *5*, 447-448

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A New Rearranged Non-Aromatic Salpichrolide from *Salpichroa Origanifolia*
Molecules **2000**, *5*, 449-450

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Reactivity Comparison of D–Glucose Derived Dienophiles. Analysis of the Conformational and Electronic Properties
Molecules **2000**, *5*, 451-452

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Theoretical Studies of the Stability of 8a-Alkyl-1,2,3,4,6,8a-hexahydronaphtalen-1-ones Using Semiempirical Methods
Molecules **2000**, *5*, 453-454

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Photochemical Study of the Reactions of the 2-Naphthoxide Ion with Haloadamantanes
Molecules **2000**, *5*, 455-456

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A Different Behaviour of the Phthalimide Ion in $S_{rn}1$ Reactions
Molecules **2000**, *5*, 457-458

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Variation in the Composition of the Essential Oil of *Senecio Filaginoides* Dc
Molecules **2000**, *5*, 459-461

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Gastric cytoprotective activity of ilicic aldehyde in rats and mice
Molecules **2000**, *5*, 462-464

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Chemical Components and Biological Activity of *Bidens Subalternans, B. Aurea* (Astereaceae) and *Zuccagnia Puntacta* (Fabaceae)
Molecules **2000**, *5*, 465-467

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Regioselective Opening of Epoxides Catalyzed by Sn (IV). A New Method for the Synthesis of Halo-hydrins?
Molecules **2000**, *5*, 468-469

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Phytochemical Study of Condalia microphylla Cav.
Molecules **2000**, *5*, 470-471

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Isomerisation of Methyl (E) 2-Bromo-3-(4-XC_6H_4)-propenoates
Molecules **2000**, *5*, 472-474

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Lipoxygenase-1 Activity of Soybean Genotypes Grown in Argentina
Molecules **2000**, *5*, 475-478

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^{1}H and ^{13}C-NMR Spectroscopic Study of Some 1H-4,5-Dihydroimidazolium Salts
Molecules **2000**, *5*, 479-480

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Improved Synthesis of N-Substituted Quinolinimides using Microwave Irradiation
Molecules **2000**, *5*, 481-482

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Conformational Analysis of Seven Membered Nitrogen Heterocycles Employing Molecular Modeling. Part II: 1-(O-Nitrophenyl)-2-Phenyl-1h-4,5,6,7-Tetrahydro-1,3-Diazepine
Molecules **2000**, *5*, 483-484

M.G. Johnston, V.M. Navarro, V. Nepote, N.R. Grosso, N.I. Brutti and C.A. Guzmán

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New Peanut Product: “Mayonnaise”. Some Chemical Aspects
Molecules **2000**, *5*, 485-486

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Antioxidant Activity of Methanolic Extracts from Peanut Skin
Molecules **2000**, *5*, 487-488

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Relationship Between the Conformation of the Cyclopeptides Isolated from the Fungus Amanita Phalloides (Vaill. Ex Fr.) Secr. and its Toxicity

Molecules **2000**, *5*, 489-490

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Synthetic Studies on Natural Stephaoxocanes. Elaboration of a Tetrahydrooxazaphenalene Potential Intermediate

Molecules **2000**, *5*, 491-492

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Elaboration of the Isochromane System of Stephaoxocanes Employing an Oxa-Pictet Spengler Type Cyclization

Molecules **2000**, *5*, 493-494

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Practical and Efficient Procedure for the *in situ* Preparation of B-Alkoxyoxazaborolidines. Enantioselective Reduction of Prochiral Ketones

Molecules **2000**, *5*, 495-496

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Synthetic Modifications of Lead Compounds as Antitrypanosomal Drugs

Molecules **2000**, *5*, 497-498

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Synthesis of 1,2,6-Thiadiazin 1,1-Dioxide Derivatives as Trypanocidal Agents
Molecules **2000**, *5*, 499-500

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Reactivity Studies of 5,6-Dimethyl- and 3,5,6-Trimethyl -1,2,4-Triazine –N $_4$-Oxide against Different Electrophiles
Molecules **2000**, *5*, 501-502

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Addition of Aromatic Nucleophiles to a C=N Double Bond of 1,2,5-Thiadiazole 1,1-Dioxide
Molecules **2000**, *5*, 503-504

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Studies on a New Synthetic Route towards Cassiol
Molecules **2000**, *5*, 505-507

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Synthesis and Characterization of New Naphthoquinonic Derivatives Containing the Pyrazole Ring: Pyrazolylnaphthoquinones
Molecules **2000**, *5*, 508-509

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Determination of the Formation Constant of the Inclusion Complex from a Naphthoquinone
Molecules **2000**, *5*, 510-511

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Binding Constant of Amines to Water/AOT/n-Hexene Reverse Micelles. Influence of the Chemical Structure
Molecules **2000**, *5*, 512-513

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New Withanolides from Two Varieties of *Jaborosa Caulescens*
Molecules **2000**, *5*, 514-515

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Formation of Complexes of Flavonoids and Metals. Determination of the Stoichiometry and Stability Constants
Molecules **2000**, *5*, 516-517

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Analysis by Mass Spectrometry of the Polar Lipids from the Cellular Membrane of Thermophilic Lactic Acid Bacteria
Molecules **2000**, *5*, 518-519

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Chemical Modifications of 1,2,5-Oxadiazole *N*-Oxide System Searching for Cytotoxic Selective Hypoxic Drugs
Molecules **2000**, *5*, 520-521

V. Schapiro, G. Seoane and G. García

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Approach to the A-B Ring System of Forskolin through Biotransformation of Toluene
Molecules **2000**, 5, 522-523

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Shelf-Life of an Extruded Blend of Peanut, Soybean and Corn
Molecules **2000**, *5*, 524-525

Jose A. Sintas, Norberto J. Macareno and Arturo A. Vitale

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A Facile High-Yield Synthesis of [^{10}B] -8-Dihydroxyboryl Harmine, a Potential Agent for Boron Neutron Capture Therapy
Molecules **2000**, *5*, 526-528

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Synthesis of Diads and Triads Derived from Carotenoids and Fullerene C60
Molecules **2000**, *5*, 529-530

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Synthesis of Asymmetrical Porphyrins Substituted in the meso-Position from Dipyrrolomethanes
Molecules **2000**, *5*, 531-532

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A Simple Enzymatic Preparation of 2',3'-Di-*O*-Acetylnucleosides Through a Lipase Catalyzed Alcoholysis
Molecules **2000**, *5*, 533-534

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Escherichia Coli Bl21: A Useful Biocatalyst for the Synthesis of Purine Nucleosides
Molecules **2000**, *5*, 535-536

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Solid-Phase Organic Chemistry: Synthesis of 2β-(Heterocyclylthiomethyl)Penam Derivatives on Solid Support
Molecules **2000**, *5*, 537-538

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Stereoelectronic Contributions to ^{1}H-^{1}H Coupling Constants
Molecules **2000**, *5*, 539-540

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Alkali Treatment of the Polysaccharides from the Cystocarpic Stage of *Iridaea Undulosa*
Molecules **2000**, 5, 541-542

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The 75% Isopropanol-Soluble Polysaccharides from the Endosperm of the Legume Seed of *Gleditsia Triacanthos*
Molecules **2000**, *5*, 543-544

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Studies of Lipids and Proteins in a Wild Species of the *Arachis (Fabaceae)* Gender
Molecules **2000**, *5*, 545-546

M. E. Godoy, A. Rotelli, L. Pelzer and C.E. Tonn

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Antiinflammatory Activity of Cinnamic Acid Esters
Molecules **2000**, *5*, 547-548

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Use of Cyclic Di- and Triperoxides as Initiators of Styrene Polymerization at High Temperature with a View to Their Use in Industrial Applications
Molecules **2000**, *5*, 549-550

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Polisaccharides from Cystocarpic Plants of the Red Seaweed *Callophyllis Variegata*
Molecules **2000**, *5*, 551-552

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Comparison Between Aqueous and Nonaqueous AOT-Heptane Reverse Micelles using Acridine Orange as Molecular Probe
Molecules **2000**, *5*, 553-554

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Synthesis of a Thienothiophene Conjugated Polymer
Molecules **2000**, *5*, 555-556

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Integral Chemical Analysis of the Amaranth (*Amaranthus greggii S. Wats*)
Molecules 2000, *5*, 557-559

Griselda Eimer, Pedro Girola, Lorena Tomas, Liliana B. Pierella and Oscar A. Anunziata

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Catalytic Activity of MEL Zeolites Modified with Metalic Couples for the Conversion of Ethane
Molecules **2000**, *5*, 560-561

G. P. Romanelli, J. L. Jios, O. Guaymas, R. Piovoso and J. C. Autino

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A Simple Method for *N*-Phenoxyethylation of Anilines
Molecules **2000**, *5*, 562-563

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First Synthesis of (20S) 3β,16β-dihydroxy-5-pregnen-20,16-carbolactone (Diosgeninlactone)
Molecules **2000**, *5*, 564-565

Gladis Ester Scoles, Silvia Haydeé Pattacini and Guillermo Federico Covas

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Separation of the Pigment of an Amaranth
Molecules **2000**, *5*, 566-567

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Chemical Study of the Essential Oil of *Mutisia Friesiana*
Molecules **2000**, *5*, 568-570

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Bioactive Constituents of *Conyza Albida*
Molecules **2000**, *5*, 571-573

Carola Ferreyra, Cristina Ortiz and M. M. de Bertorello

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Development and Validation of a Chromatographic Method for the Analysis of Multicompound Pharmaceutical Preparations
Molecules **2000**, *5*, 574-575

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Study of Cytotoxic and Antifungal Activities of Neolignans 8.O.4´ and Structurally Related Compounds
Molecules **2000**, *5*, 576-577

P.M. Mancini, G. Fortunato and A. J. Terenzani

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Kinetics of the Aromatic Nucleophilic Substitution Reaction Between 1-Fluoro-2,4- Dinitrobenzene and Perhydroazepine in Ethyl Acetate + Chloroform Solvent Mixtures
Molecules **2000**, *5*, 578-579

F. Giannini[1], C. Devia[1], A. Rodríguez[1], R. Enriz[1], F. Suvire[1], H. Baldoni[1], R. Furlan[2] and S. Zacchino[2]

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The Importance of Keto-Enol Forms of Arylpropanoids Acting as Antifungal Compounds
Molecules **2000**, *5*, 580-582

F. Suvire, R. Floridia, F. Giannini, A. Rodriguez, R. Enriz and E. Jauregui

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Molecular Interactions Between the Active Sites of RGD (Arg-Gly-Asp) with its Receptor (Integrine)
Molecules **2000**, *5*, 583-584

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A Conformational Study of Flexible Cyclic Compounds (Hydrocarbon Rings Of 9-12 Members)
Molecules **2000**, *5*, 585-586

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Solvatochromic and Kinetic Response Models in (Ethyl Acetate + Chloroform or Methanol) Solvent Mixtures
Molecules **2000**, *5*, 587-588

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Catalytic Hydrogenation Reaction of Naringin-Chalcone. Study of the Electrochemical Reaction
Molecules **2000**, *5*, 589-590

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Fluorescence Resonance Energy Transfer Using Spiropyran and Diarylethene Photochromic Acceptors
Molecules **2000**, *5*, 591-593

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Stereoselective Synthesis of 8-Trialkylstannylmenthols
Molecules **2000**, *5*, 594-595

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Polymerization Mechanism of α,α'-*bis*(Tetrahydrothiophenio)-*p*-xylene Dichloride
Molecules **2000**, *5*, 596-597

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Enantioselective Addition of Grignard Reagents to Aldehydes
Molecules **2000**, *5*, 598-599

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O-Sulfated Derivatives of Glucuronic Acid
Molecules **2000**, *5*, 600-601

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Synthesis and Computational Simulation of New Phosphorilated Sulfoximines with Insecticidal Activity
Molecules **2000**, *5*, 602-604

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Phytochemical Study *Conyza Sophiaefolia*. Antiinflammatory Activity
Molecules **2000**, *5*, 605-607

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Structure-Properties Relationship of Dimeric Surfactants from Butyl Glucosides
Molecules **2000**, *5*, 608-609

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Synthesis of 2,3-Butanedione over TS-1, Ti-NCl, TiMCM-41, Ti-Beta, Fe-Si, Fe-Beta and VS-1 Zeolites
Molecules **2000**, *5*, 610-611

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Reaction Mechanism for the Cyclization of 3-[γ,γ-Dimethylallyl]Coumaric Acid Methyl Ester in Dimethyl Sulfoxide (DMSO)
Molecules **2000**, *5*, 612-613

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Grindelic Acid Production in *Grindelia Pulchella* Cell Suspension Cultures Elicited with $CuSO_4$
Molecules **2000**, *5*, 614-615

Editorial

Foreword to the Proceedings of the 12th National Symposium of Organic Chemistry "Dr. Eduardo Guerreiro", Los Cocos (Córdoba), Argentina, 14-17 November 1999

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It is our pleasure to introduce this special issue of *Molecules* which consists of the Proceedings of the XII National Symposium of Organic Chemistry (XII SINAQO) "Dr. Eduardo Guerreiro", held on November 14-17 in Los Cocos (Córdoba), Argentina. The conference attracted more than 300 participants from Argentina, Chile, Uruguay, Venezuela.

The scientific program started with a plenary lecture given by Dr. A. Douglas Kinghorn (U.S.A.) entitled ***"Plant Secondary Metabolites as Potential Anticancer Agents and Cancer Chemopreventives".*** In addition, there were five plenary lectures given by Dr. Michael Chanon (France): ***"Experimental and Theoretical Studies on the Mechanism of Grignard Reagents Formation";*** Dr. Vicente Gotor (Spain): ***"Enzimas en Disolventes Orgánicos: Uso de Lipasas y (R)-Oxinitrilasa para la Preparación de Productos de Interés Biológico";*** Dr. Juan Garbarino (Chile): ***"Química del Género Calceolaria, Aspectos Estructurales y Biológicos";*** Dr. Waldemar Priebe (U.S.A.): ***"Targeting DNA with Anthracyclines: The Importance of Sugar Moiety";*** and Dr. Robert Dodd (France): ***"Aziridine Carboxylates, Carboxamides and Lactones: New Methods for their Preparation and their Transformation into a and b Amino Acid Derivatives".*** In addition there were six Invited Lecturers and 252 posters were presented in four sessions.

The purpose of this Conference is to bring together renowned scientists, researchers and students in order to reflect upon recent advances in Organic Chemistry. The meeting offered a strong representation of all the disciplines: Organic Spectroscopy (10 posters); Physical Organic Chemistry (62 posters); Natural Products and Bioorganic Chemistry (69 posters); Organometallic Chemistry (10

posters) and Synthetic Organic Chemistry (100 posters).

It has been a real challenge for us to organize and edit this issue as it is the first time that the material presented at The National Symposium of Organic Chemistry (SINAQO) is published as a Proceedings volume. We are strongly convinced that this Special Issue will increase and improve the diffusion of the research in Organic Chemistry carried out in South America, and particularly in Argentina. Thus, we are very grateful to the Organizing Committee for promoting the publication in Molecules, and last but not least, to all the participants who contributed with their research work to the success of this task.

Sincerely,

Dr. Guillermo R. Labadie Dr. Claudio J. Salomon

Guest editors

February, 2000

Plant Secondary Metabolites as Potential Anticancer Agents and Cancer Chemopreventives

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There is considerable interest in the screening of plant and other natural product extracts in modern drug discovery programs, since structurally novel chemotypes with potent and selective biological activity may be obtained [1-4]. A consideration of biological activity in addition to the isolation and structure elucidation stages in a phytochemical investigation may add a great deal to the overall scientific significance of the work. Phytochemists may gain considerable information by using panels of simple bioassays and/or more specialized *in vitro* bioassays to follow each step of a purification procedure [3]. In the following paragraphs, recent examples of bioactive compounds obtained in the author's laboratory in projects directed towards the search for novel anticancer agents and cancer chemopreventives from higher plants will be presented.

In the United States in 1999, it is estimated that over 1.2 million persons will be diagnosed with invasive forms of cancer, and over 1,500 people will die as a result of cancer each day [5]. Among many recent advances in cancer chemotherapy, plant natural products have played an important role in contributing to the arsenal of the approximately 60 cancer chemotherapeutic drugs on the market. For instance, in the United States, there are now four structural classes of plant anticancer agents available, constituted by the *Catharanthus* (Vinca) alkaloids (vinblastine, vincristine, vinorelbine), the epipodophyllotoxins (etoposide, etoposide phosphate, teniposide), the taxanes (paclitaxel and docetaxel), and the camptothecin derivatives (irinotecan and topotecan) [6]. Several other plant-derived compounds are currently in preclinical and clinical trials [6,7].

As part of a National Cooperative Natural Products Drug Discovery Group (NCNPDDG) research project funded by the United States National Cancer Institute (1995-2000), our collaborative team at the College of Pharmacy, University of Illinois at Chicago (Chicago, Illinois), and Research Triangle Institute (Research Triangle Park, North Carolina), and Bristol-Myers Squibb (Princeton, New Jersey) is evaluating about 400 plant samples per year, with the aim of discovering and evaluating novel plant-derived anticancer agents. During the funding period 1990-1995, the industrial partner was Glaxo Wellcome Medicines Research Centre (Sevenage, U.K.), and past progress made in the project has been reviewed [8]. Since 1995, the primary plant samples have been collected in the Dominican Republic, Peru, and Indonesia. Plant recollections have taken place mainly in Thailand and Zimbabwe in

recent years. Our funding agency requires that we obtain permission through formal written agreements to acquire plants for research. For each plant acquisition, a non-polar extract is prepared and screened against batteries of cultured human cancer cells and panels of mechanism-based assays. An LC-MS dereplication procedure has been developed to attempt to avoid the re-isolation of common classes of known cytotoxic compounds [9]. As a result of bioactivity-guided fractionation on selected plant leads, well over 100 active compounds have been isolated and structurally characterized in the project to date. Many of these of novel structure and several have been further evaluated in secondary *in vitro* bioassays and *in vivo* assays. Examples of active compounds obtained in this project include 1*H*-cyclopenta[*b*]benzofuran derivatives from *Aglaia elliptica* (Meliaceae) [10], phenanthrene derivatives from *Domohinea perrieri* (Euphorbiaceae) [11], resveratrol tetramers from *Vatica diospyroides* (Dipterocarpaceae) [12], and sesquiterpene lactones from *Ratidiba columnifera* (Asteraceae) [13].

Plant secondary metabolites also show promise for the cancer chemoprevention, which has been defined as "the use of non-cytotoxic nutrients or pharmacological agents to enhance physiological mechanisms that protect the organism against mutant clones of malignant cells" [14]. There has been considerable prior work on the cancer chemopreventive effects of extracts and purified constituents of certain culinary herbs, fruits, spices, teas, and vegetables, which have shown the ability to inhibit the development of cancer in laboratory animal models [15,16]. Clinical trials as cancer chemopreventive agents under the auspices of the United States National Cancer Institute are planned for plant products such as curcumin, ellagic acid, and phenethyl isothiocyanate [17].

In our project on cancer chemopreventive agents from plants, novel compounds are again isolated from plant extracts by activity-guided fractionation techniques, although a different panel of bioassays is employed in comparison to the anticancer agent project described above. The project is funded by the National Cancer Institute, through the Program Project mechanism, and all of the work is performed at the University of Illinois at Chicago [18,19]. The plant material is constituted both by food plants and by species collected in the field, and an organic-soluble extract is obtained from each milled plant part. Preliminary biological evaluation is carried out using a panel of about ten short-term *in vitro* bioassays, with some being relevant to each of the initiation, promotion, or progression stages of carcinogenesis [20]. Biological follow up occurs using a mouse mammary organ culture model [21], and, in a very few selected cases, evaluation in a two-stage mouse skin or rat mammary carcinogenesis model [22]. Once again, in the project to date over 100 active compounds have been obtained, of which some have been subjected to *in vivo* biological characterization. Examples of active compounds obtained in this project include a number of antimutagenic alkaloids, coumarins, and flavonoids from the seeds of *Casimiroa edulis* (Rutaceae) [23], withanolides from *Physalis philadelphica* (Solanaceae) ("tomatillos") with the ability to induce levels of the enzyme quinone reductase [24], antioxidant flavonoids from *Chorizanthe diffusa* (Polygonaceae) [25], and some steroidal alkaloids from *Pachysandra procumbens* (Buxaceae), which showed significant activity in an antiestrogen-binding assay [26].

Acknowledgements: Funding by NIH grants U19-CA52956 (P.I., A.D. Kinghorn) and P01-CA48112 (P.I., J.M. Pezzuto) by the National Cancer Institute is gratefully acknowledged. I am very grateful to many colleagues (both on the faculty of the University of Illinois and at other institutions), as well as to many postdoctorals and graduate students, whose names are indicated in the bibliography below, for their multiple contributions to this collaborative research.

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Experimental and Theoretical studies on the Mechanism of Grignard Reagent Formation

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May 2000 will mark the anniversary of Grignard's publication reporting the discovery of his reagent. (Grignard, V.C.R., Hebd Sceances Acad. Sci. (900, 130, 1322). Despite its pervasive practical importance in the everyday life of synthetic chemists, several aspects of the sequence of elementary steps leading to the corrosive dissolution of magnesium metal in the solution of RX to yield RMgX remain unclear.

The combined use of very active particules of Mg (metal vapors solubilized in THF), surface redox indicators, batteries of specifically designed free radical clocks, inhibition studies and de Moon theoretical calculations of Mg clusters has provided new insights on this mechanism for alkyl and aryl halides.

Several questions remain, however, which demand further experimental investigations. Both new aspects and these questions will be dealt with in this lecture.

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Enzymes in Organic Solvents: the Use of Lipases and (*R*)-Oxynitrilase for the Preparation of Products of Biological Interest*

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Abstract: The use of enzymes in organic solvents has acquired a special relevance in organic synthesis, and lipases are the enzymes most commonly used in transesterication reactions. In the past few years, we have shown the utility of enzymatic aminolysis and ammonolysis reactions for the preparation of amides and for the resolution of esters and amines. The enzymatic alkoxycarbonylation reaction is of great utility in chemoselective reactions of natural products. Lipases, enzymes much less exploited in organic synthesis, have an increasing interest, especially the use of (*R*)-oxynitrilases for the synthesis of optically active cyanohydrins.

Over the past few years our group has been working on the use of aminolysis and ammonolysis reactions for the synthesis of high value added products. We have studied the preparation of amides from α,β-unsaturated esters, β-hydroxyesters or β-ketoesters with excellent results, thus achieving a very simple way of chemoselectively preparing different types of amides. If racemic amines are used, the corresponding amides are prepared in very high enantiomeric excesses. The enzymatic ammonolysis of diethyl 3-hydroxyglutarate allows the preparation of the corresponding amidoester in enantiopure form, a product we have used as starting material for the preparation of (*R*)-4-amino-3-hydroxybutanoic acid, the precursor of carnitine. On the other hand, this methodology has allowed us to carry out resolutions of some heteroarylamines or different esters, offering an alternative to hydrolysis or enzymatic transesterification.

Recently we have accomplished a double resolution of esters and amines that allows the preparation of these substrates in enantiopure form in one step, since when the lipase of *Candida antarctica* (CAL) is used, the reaction takes place with high diastereoselectivity and enatioselectivity. Equally, when a prochiral ester and racemic amines are used the corresponding amidoester is prepared and the amines are resolved with enantiomeric exccesses grater than 95%.

The best conditions for the resolution of *trans*-1,2-cyclohexanediamine involve using diesters and CAL as the biocatalyst. For example, when diethylmalonate is used both substrate and product are prepared in practically enantiopure form. From both of these we have developed a very efficient method for preparing different types of azamacrocycles. This process has great synthetic value, as it allows us

to prepare different chiral macrocyles, compounds of great importance, as some of them have interesting properties concerning the recognition of chiral dianions.

As for the usefulness of enzymes in organic solvents in chemoselective transformations of natural products, our most outstanding results have been in the area of the nucleosides, especially with desoxyribonucleosides, and we are now investigating the possible applications of this methodology towards the synthesis of vitamin D. For this reason we have studied enzymatic acylation and alkoxycarbonylation reactions, particularly the latter, since they allow the regioselective preparation of carbonates which are suitable starting materials for the synthesis of other derivatives

In our studies of the enzymatic reactions of desoxyribonucleosides using esters or oxime carbonates we have achieved regioselective ayclation and alkoxycarbonylation at the 3' y 5' positions of the sugar. Thus, when the lipase of *Pseudomonas cepacia* (PSL) is used, acylation or alkoxycarbonylation at the 3' position is achieved, while, on the other hand, if CAL is used, the corresponding 5' isomers are prepared. The products obtained when the vinyloxycarbonyl group is introduced are starting materials for the preparation of nucleoside derivatives as yet not reported in the literature.

Presently we are studying different chemoenzymatic transformations in precursors of the A ring of 1α,25-dihydroxyvitamin D_3, which is the hormonally active form of vitamin D_3, as well as in the stereoisomers of the natural product, due to the importance of the stereochemistry of the chiral centers of this ring towards its biological responses. This allows us to prepare new derivatives of this important synthon through enzymatic alkoxycarbonylation reactions.

Another line of investigation in our group involves the use of oxynitrilases for the preparation of chiral cyanohydrins. (*R*)-oxynitrilase is a flavoprotein that catalyzes the addition of hydrogen cyanide onto the *si* face of benzaldehyde. The enzyme can be produced from almond flour and it can be used in different organic solvents, thus allowing it to react with a wide variety of aliphatic and aromatic aldehydes, and even ketones.

Recently we have investigated the cyanation-transcyanation reactions of some ω-bromoaldehydes using ketone cyanohydrins as the cyanide source. This reaction allows us to achieve a double objective: prepare chiral cyanohydrins from ketones of (*S*) configuration and the synthesis of ω-bromocyanohydrins. These cyanohydrins are precursors of different oxygenated and nitrogenated heterocycles. It is worth noting that using this methodology (*S*)-pipecolic acid and other alkaloid derivatives have been prepared. In addition, starting from the corresponding cyanohydrins of different ω-bromoaldehydes we have tackled the synthesis of heterocycles of more than six members, and have been able to isolate optically active azepane and azopane derivatives.

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**Note*: Translation by the Editorial Staff.

Aziridine Carboxylates, Carboxamides and Lactones: New Methods for Their Preparation and Their Transformation into α- and β-Amino Acid Derivatives

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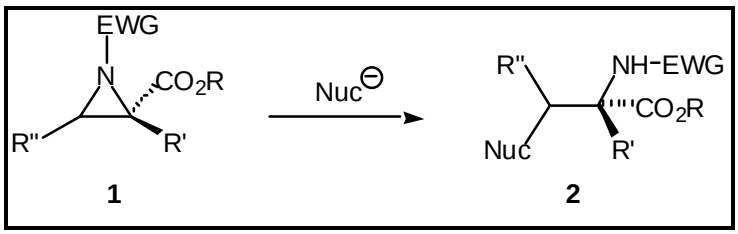
Abstract: The preparation of a variety of novel aziridine-γ-lactones (**3**) from carbohydrates is described. In contrast to aziridine-2-carboxylates, the lactones react regiospecifically at C-2 with soft nucleophiles to provide optically pure substituted β-amino acid precursors. Hard nucleophiles react exclusively at the C-3 position to provide α-amino acid precursors. The utility of this methodology was demonstrated by the preparation of (3S,4S)-dihydroxy-L-glutamic acid (DHGA) from the appropriate aziridine-γ-lactone. DHGA was subsequently shown to be a selective partial agonist of mGluR1 receptors. A more concise preparation of aziridine-γ-lactones was achieved by 1,4-Michael addition of benzylamine to 2-O-triflylbutenolides. Use of a 2-O-mesylbutenolide led, under the same conditions, to the corresponding aziridine-2-carboxamides or 2-carboxylates. Finally, a new Evans-type aziridinating agent, Ses-iminoiodinane, was developed and shown to react efficiently with unsaturated substrates to give the corresponding aziridines, whose N-Ses protecting groups can be removed under mild conditions.

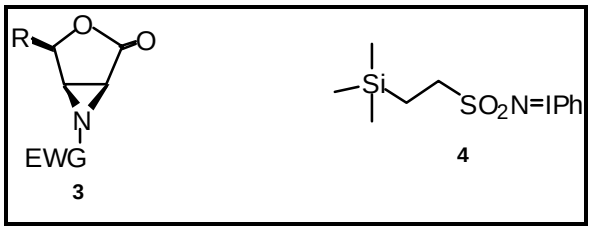
Introduction

α- and β-Amino acids, both natural and unnatural, are important synthetic targets in organic chemistry. While synthetic methodologies for the common amino acids encountered in nature have been well developed, those for less commonly occurring amino acids or for completely non-natural amino acids are areas of continuing effort. Many non-natural amino acids have been shown to display biological activity by virtue of their capacity to bind to receptors or to inhibit enzymes. Such molecules can also be used to impart biological and conformational stability to the peptides they are incorporated in. The use of chiral, substituted aziridine-2-carboxylates for the preparation of a variety of non-natural α-amino acids (e.g. **1**) has been amply demonstrated. Thus, attack of **1** by a nucleophile generally leads to opening of the aziridine ring at the C-3 position by an SN_2 process to give β-substituted (R=H) or α,β-substituted ($R^1 \neq H$) α-amino acids.



1 **2**

However, the preparation of chiral **1** can pose problems, complete stereoselectivity of the ring opening reaction is not always achieved and β-amino acid derivatives are generally not accessible by this process, at best mixtures of α- and β-amino acids being obtained. To bypass some of these problems, we describe the use of aziridine-γ-lactones **3** for the enantiospecific synthesis of α- or β-amino acid derivatives.

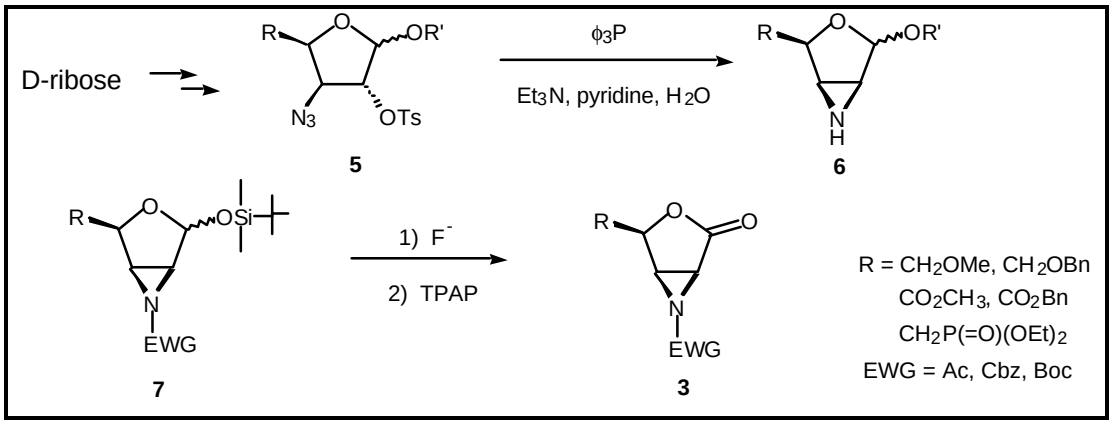


3 **4**

The development of a new Evans-type aziridinating agent, the Ses-iminophenyliodinane **4**, is also described.

Synthesis and Reactivity of Aziridino-γ-lactones

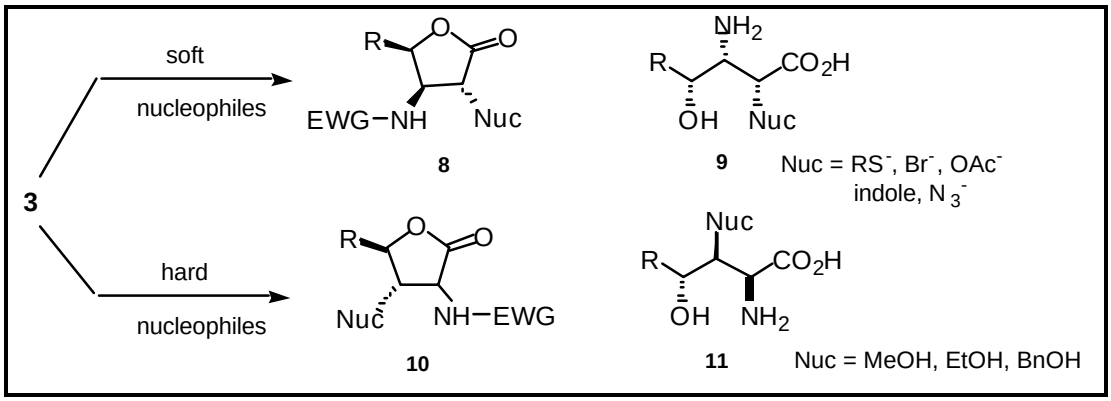
Optically pure 4-substituted 2,3-aziridino-γ-lactones can be prepared in 10 to 12 steps (depending on the substituent at the C-4 position) from carbohydrate precursors, notably D-ribose or D-lyxose. Key steps include the transformation of a 2-O-tosyl-3-azido furanoside (e.g., **5**) into an aziridine (e.g., **6**) via a modified Staudinger reaction and conversion of the trialkylsilylfuranoside **7** into the desired aziridine-γ-lactone by sequential treatment with fluoride anion and TPAP [1-4].



5 **6** **7** **3**

The reaction of aziridine-γ-lactones with a variety of nucleophiles led to different regioselectivities of aziridine ring opening depending on the nature of the nucleophiles [5,6]. Thus, soft nucleophiles

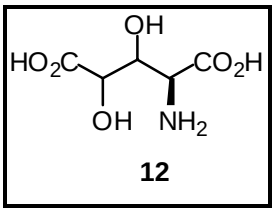
gave exclusively the product of C-2 attack, in contrast to reaction of these nucleophiles with aziridine-2-carboxylates (**1**), which attack only at the C-3 position (to give α-amino acids **2**). This unexpected regioselectivity in the case of aziridine-γ-lactones thus gives access to substituted β-amino acids (e.g., **9**) in an enantiospecific fashion.



On the other hand, reaction of aziridino-γ-lactones with hard nucleophiles (i.e. alcohols) leads uniquely to the product of C-3 attack (e.g. **10**), a precursor of optically active α-amino acids (e.g. **11**). The use of the equivalent aziridine γ-lactone prepared from D-lyxose produces amino acids having the D-configuration.

Use of Aziridine-γ-lactone Methodology for the Preparation of Biologically Active Amino Acids

3,4-Dihydroxy-L-glutamic acid (**12**) is a natural product of unknown configuration isolated from a variety of plants and mushrooms. As part of a program aimed at the discovery of novel, selective ligands of the glutamic acid receptors of the central nervous system, we undertook the synthesis of one of the stereoisomers of 3,4-dihydroxyglutamic acid (DHGA) in order to study its activity. This was done by first preparing the appropriate aziridine-γ- lactone **13** and reacting it with benzyl alcohol to give the protected glutamic acid derivative **14**. Hydrogenolysis of the latter led to isolation of the (3S,4S)-isomer of dihydroxy-L-glutamic acid [7]. Pharmacological study of this compound showed that it is a partial but selective agonist of metabotropic glutamic acid receptors of type 1 (mGluR1) [8].



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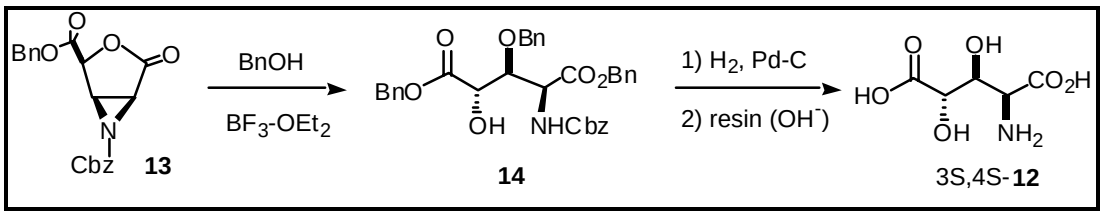
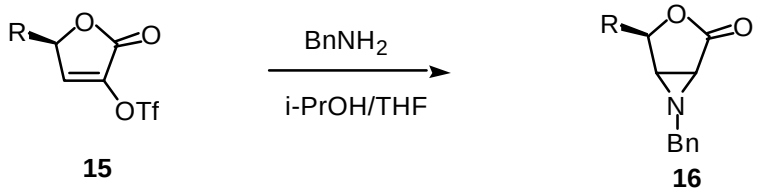
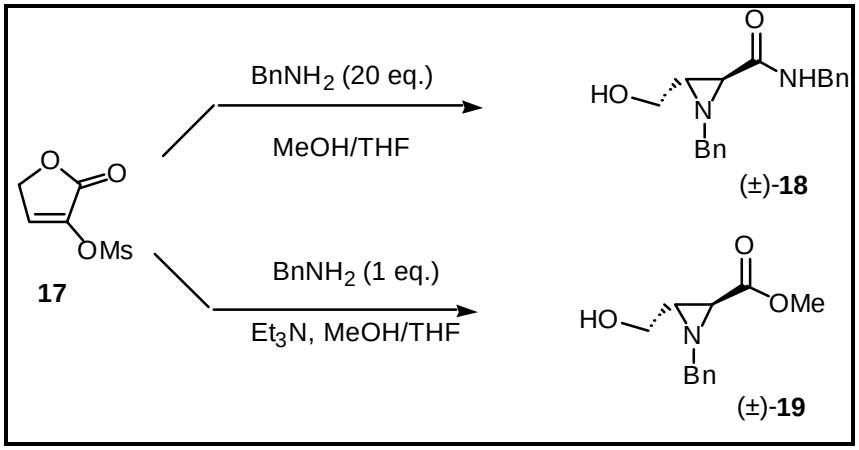


Development of a More Concise Procedure for the Preparation of Aziridine-γ-lactones

Having demonstrated the utility of aziridine-γ-lactones for the enantiospecific synthesis of multi-substituted α- and β-amino acids, we next turned our attention to the development of a more efficient route to these synthons. A very simple procedure was found to consist of 1,4-Michael addition of benzylamine to the 2-O-triflylbutenolides of type **15** to give in one step, the N-benzyl aziridino-γ-lactones **16**. In the case of R=H, a mixture of enantiomers was obtained. When R was a bulky substituent such as a benzyloxymethyl group, only a single isomer of **16** was obtained (aziridine ring *trans* to the R group), though in modest yield.

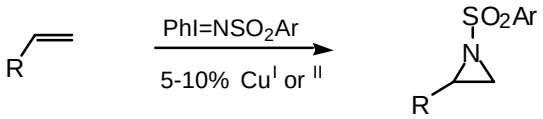


Interestingly, use of the mesylate analogue of **15** (i.e. **17**) gave entirely different results. The reaction of **17** with excess benzylamine in methanol-THF gave as major product the *trans* aziridine-2-carboxamide (±)-**18** while use of only one equivalent of benzylamine in methanol-THF led to formation of the analogous aziridine-2-carboxylate (±)-**19**. This represents a novel procedure for the formation of aziridine carboxylates and carboxamides.

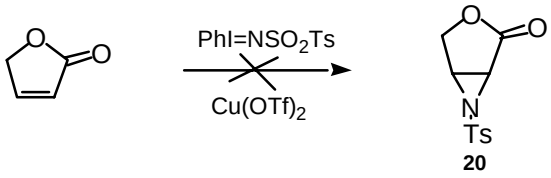


Development of a New Aziridination Reagent, Ses-iminophenyliodinane

The copper-catalyzed aziridination of olefins developed by Evans involves the formation of a nitrene generated from an (arenesulfonyl)iminophenyliodinane.

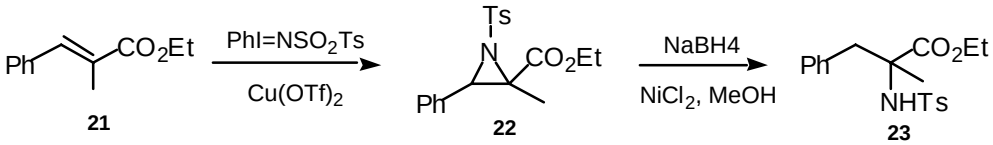


Enantioselectivity can be controlled by the addition of chiral ligands to the reaction mixture. While an attempt to prepare aziridine-γ-lactones (e.g. **20**) by Evans



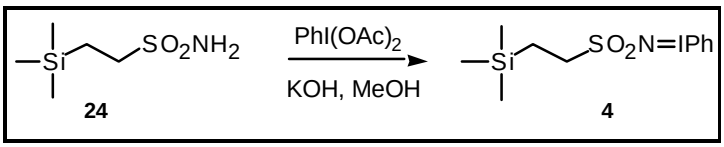
20

aziridination of a butenolide was unsuccessful, we have been able to prepare α–methyl α-amino acids by reaction of substituted acrylates and cinnamates with an iminoiodinane [9]. For example, treatment of cinnamate **21** with N-tosyliminoiodinane gave aziridine **22** which could be reductively opened to afford the α-methyl phenylalanine derivative **23**.

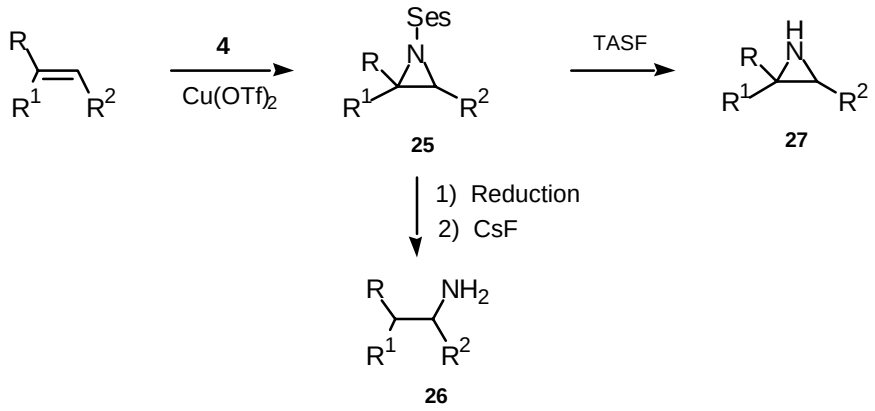


21 **22** **23**

Because N-arenesulfonyl blocking groups are sometimes difficult to remove, we decided to prepare an iminophenyliodinane-type reagent incorporating an easily removable (trimethylsilyl)ethanesulfonyl (Ses) functionality (e.g. **4**). This was achieved by reacting (trimethylsilyl)ethanesulfonamide **24** with iodosobenzene diacetate [10]. Reagent **4** reacts well with unsaturated substrates to give the corresponding N-Ses aziridines (**25**). The aziridine can be opened and the Ses group removed using fluoride anion (e.g. **26**). Alternatively, reaction of **25** with TASF yields the N-deprotected aziridine **27**.



24 **4**



Conclusion

Aziridine-γ-lactones can now be considered important synthons for the enantiospecific synthesis of a wide variety of substituted α- and β-amino acids. Moreover, their new method of preparation from butenolides makes these molecules easily accessible. While the new aziridinating agent developed, Ses-iminoiodinane, cannot be used to form aziridine-γ-lactones from butenolides, this reagent has been shown to be extremely efficient in forming N-Ses aziridines in general from unsaturated substrates, with the added advantage that the N-Ses blocking group can be easily removed either before or after nucleophilic opening of the aziridine ring.

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Targeting DNA with Anthracyclines: The Importance of the Sugar Moiety

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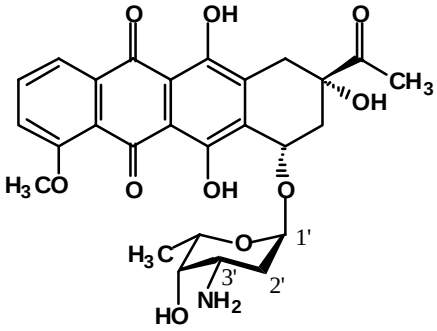
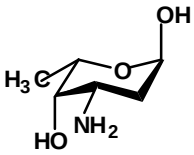
Our studies focusing on the role of the sugar portion in anthracycline-DNA interaction laid the foundation for the design of novel DNA interactive agents. We have designed and synthesized two new classes of such agents which: (1) bind with high affinity to specific sequences of DNA and (2) form cross-links with DNA.

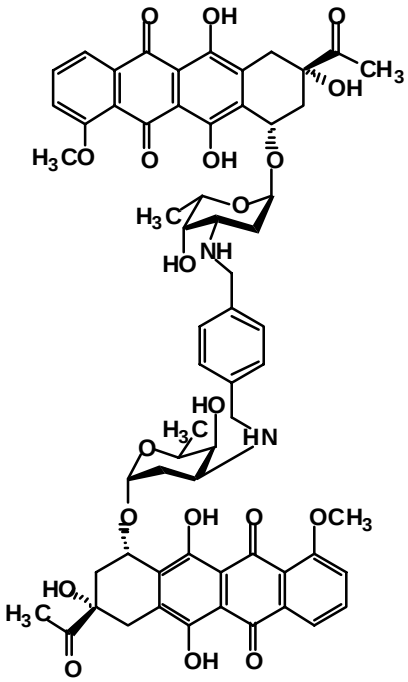
The design of agents binding with high affinity to specific sequences of DNA was based on studies of (1) the effects of a sugar portion's charge and its orientation on drug-DNA binding (daunosamine), (2) the assessment of energetic contribution to DNA binding (for daunosamine and other selected structural fragments), and (3) analysis of the crystallographic structure of the daunorubicin-DNA complex. Analysis of the structure of daunorubicin-DNA complex revealed that two daunorubicins face each other with sugar moieties and position their 3'-NH_2 groups within a distance of 6-7Å.



Daunorubicin



Daunosamine



WP631

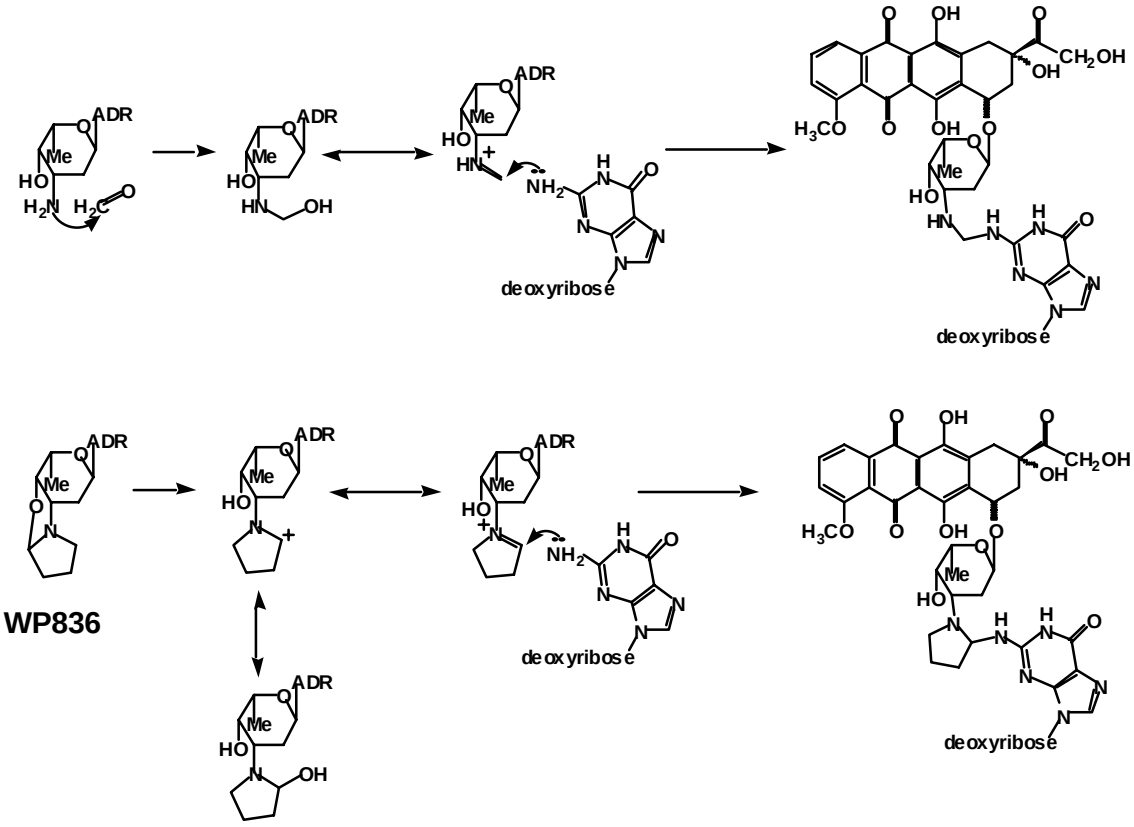
The aglycon part serves as an intercalator, while a sugar moiety serves as a minor groove binder and is responsible for the base-pair selectivity (CGA/T). We have designed linkers to create bisintercalating, groove-binding molecules and have demonstrated that compound WP631 is, in fact, a 6-bp-recognizing agent with a DNA binding constant of $2.7x10^{11}$ M^{-1}, exceeding that of daunorubicin by a factor of 23,000. The nature of the DNA binding by selected bisanthracyclines (WP631, WP652) was confirmed by several methods including solving the x-ray structure of a complex of WP631 bound to [d(CGATCG)]2 and NMR studies of WP631 and WP652 complexes with DNA oligomers.

The bisanthracyclines exhibited unique and diverse profiles of cytotoxicity. In vitro evaluation against sensitive, MDR, and MRP-mediated multidrug resistant cells indicated that selected analogs (e.g., WP631) had unusually high activity against MRP resistant cells but remained inactive against MDR cells, while other analogs were active against both MDR and MRP cell lines. Even more surprising, the NCI's in vitro disease-oriented primary antitumor screen allowed us to identify a bisanthracycline with selective cytotoxicity against melanomas but no noticeable activity against leukemias. The cytotoxicity of WP760 against melanomas was approximately 10- to 1000-fold higher than its average cytotoxicity against other tumor cell lines.

Our other studies explored novel strategies for designing and developing selective alkylators of DNA. We have demonstrated that formaldehyde can cross-link daunorubicin with DNA in a regioselective and base-specific manner and that such a process is sequence dependent and requires the presence of an amino group at the C-3' position of the sugar moiety and occurs only with N2 of guanine. Our working hypothesis is that the process of formaldehyde-mediated cross-linking can be mimicked by introducing a sugar-based substructure into daunorubicin or doxorubicin molecules so as to allow the formation of formaldehyde-mediated alkylating intermediates without an outside source of formaldehyde. If successful, this approach could lead to a unique class of selective DNA alkylators and allow for the design of other, even more selective, anticancer drugs.

Along these lines, we have designed and synthesized two novel 3' aminoanthracycline-based compounds, WP809 and WP836, which should alkylate DNA via a base-specific process. Both compounds displayed significantly higher cytotoxicity than that of either parental daunorubicin or doxorubicin against wild-type and multidrug-resistant tumor cell lines. In brief, the compound WP836 derived from doxorubicin was 500- to more than 100,000-fold more potent than doxorubicin in in vitro tests performed in sensitive and multidrug resistant cell lines. Increased activity was also noticed for analog WP809, obtained from daunorubicin.

COMPARISON OF HCHOAND WP836 MEDIATED DNA CROSSLINKING



Chemistry of the Calceolaria Genus. Structural and Biological Aspects

Juan A. Garbarino, María C. Chamy and Marisa Piovano

Departamento de Química, Universidad T.F.Santa María, Valparaíso, Chile

Abstract: Autochthonous species of the Calceolaria (Scrophulariaceae) genus are studied. From their apolar extracts 55 new diterpenes of six skeleton types, naphtoquinones and flavonoids have been isolated. Among the different diterpenes malonic substitutions and bis-diterpenes in which both units are joined by a malonic acid unit stand out. Pimaranes present C-9 epimerisation and, consequently, H-9 has the same orientation as Me-20. From C.sessilis naphthoquinones with anti-chagasic activity have been isolated; and the biotransformation of 2α,19-dihydroxy-9-epi-ent-pimara-7,15-diene with Giberella fujikuroi produced 7 new diterpenes.

The Calceolaria genus is one of the most abundant of the Scrophulariaceae.family. According to Engler [1] there are more than 5000 species distributed throughout New Zealand and especially, Central and South America. Some 86 species grow in Chile [2] and several of them are badly defined. They are known by the common names “capachito”, “zapatito” and “topa-topa”, and they are used in popular medicine as stomach tonics, bactericidal agents and sweeteners.

In a systematic study of the secondary metabolites of the genus 19 autochthonous species have been studied, with particular attention being paid to the geographical-botanical surroundings of Valparaíso (Region V).

From the apolar extracts we have isolated a series of 55 new diterpenes belonging to six skeletal types, naphthoquinones y flavonoids [3-14].

Among the different diterpenes isolated, the presence of malonic esters and bis-diterpenes- 5 with a pimarane skeleton - in which both units are joined by a malonic acid molecule is worth mention.

The biogenetic mechanism of cyclization of the pimaranes takes place via adoption of “chair-boat” conformation, instead of a "chair-chair" one, usually found in Nature [3]. This mechanism leads to an epimerization of C-9 and, consequently, H-9 is found in the same orientation as the Me-20 group. Form C. sessilis we obtained naphthoquinones that displayed promising trypanocidal properties [10]. Finally, the biotransformation of 2α,19-dihydroxy-9-epi-ent-pimara-7,15-diene with Gibberella fujikuroi produced 7 new diterpenes [15] among which oxidation of the diene at C-7 is prevalent.

Acknowledgements: We thank the Dirección General de Investigación y Posgrado of the UTFSM and FONDECYT (Proyects 408/90, 579/92, 1941048 y 1970124) for their financial support of this research.

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Synthesis of Polymers with Electro-optical Properties

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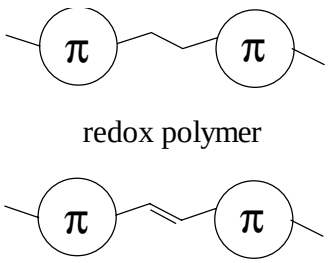
The electro-optical properties of organic and polymeric materials are regarded as holding potential for developments in charge storage, analytical sensors, electroluminescent devices, optical data processing and integrated optics. For example, nowadays it is clear that sensor sensitivities and specificity can be increased by using redox polymers [1] or that the parameters characterizing the relative strength of nonlinear optical, NLO, effects are typically 50 or 100 times greater in organic molecular systems than in inorganic dielectric insulators and semiconductors [2].

In addition, because of the availability of a enormous variety of organic molecules and of liquid crystalline oriented films or other ordered environments, the properties of polymeric materials may be tailored to optimize other parameters such as anisotropy, mechanical strength, processability, thermal stability, laser damage threshold, etc., while preserving intact the electronic structure responsible for the electro-optical effects. While the potential for applications is great indeed, the development of appropriate electro-optical polymeric materials is a combination of interdisciplinary tasks: (1) synthesis of macromolecules with π-electron systems, (2) control of the molecular morphology and the detailed nature of the electronic environment of the medium, and (3) characterization of the polymer material properties.

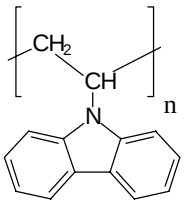
Electro-optical Polymers

The key structural feature of almost all the electro-optically active polymers is that they have π-electron systems as building blocks imbedded in its structure. These unsaturated systems can be considered either as chromophores or as electrophores depending on the kind of particles, light or electrons, they interact with. While charge uptake can lead to electric conductivity, charge storage or electroluminiscence (after ion recombination) [3]; the interaction with electromagnetic waves gives origin to photoconductivity, photovoltaic effects, em shielding, NLO effects and so on.



redox polymer

conjugated polymer

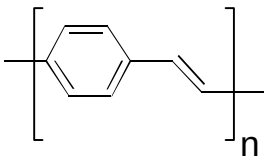


Poly(N-vinylcarbazole)

Another fundamental structural feature which defines the polymer electro-optical properties is the type of unit linking the π-electron systems [4]. In **redox polymers**, the active units are

linked by saturated spacers that isolate the π-electrons. Therefore, the polymer electro-optical properties [oxidation potentials, fluorescence, band gaps, etc.] are rather similar to their low molecular building blocks whereas the polymeric state is of importance by its contribution to the mechanical properties of the material. Poly(vinylcarbazole) that has been used as the photoconducting layer in photocopiers is an early example of this type of polymers. On the other hand, **conjugated polymers** have unsaturated linking units. As a result, the π-conjugation is extended over long segments of the polymer main chain until a defect, i.e. a saturated unit, interrupts the electron delocalization. The conjugated polymer electro-optical properties are intrinsic and they often differ substantially from the redox polymers[5]. Conjugated polymers have also received the name of conducting polymers which focuses on its ability to transport electrical charges upon oxidation or reduction, i.e. "doping".

The Precursor Route to Poly(Arylene Vinylene)s



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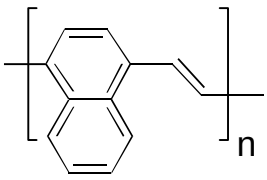

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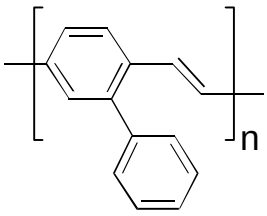

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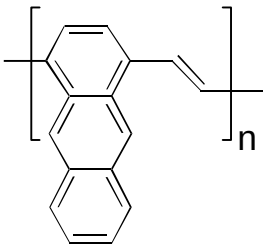

Ref. 10

In this report the focus will be placed on the synthesis of poly(arylenevinylene)s, PAV's, of general formula $[\text{-Ar-CH=CH-}]_n$. Some of the conjugated polymers such as polyaniline or polypyrrol are electrosynthesized on an electrode surface from which a film can be peeled off. This procedure permits to circumvent the biggest problem in the conjugated polymers synthesis, that is, its lack of processability. Due to the rigid main chain structure all this polymers are insoluble in all kind of solvents and decompose before melting. However, for some conjugated polymers, including the PAVs [6], an alternative synthetic route has been designed. The common feature of these procedures is that a processable precursor polymer is first obtained and later converted into the conjugated polymer. A great variety of PAVs as well as its copolymers have been obtained using this synthetic route, some of the homopolymers are listed in the scheme.

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Mechanisms of Water Catalysed Reactions

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Water Catalyzed Reactions

Water is unique among liquids for its ability for tetrahedral coordination with four neighbouring molecules. Water catalyzed reactions (or spontaneous reactions) are pH independent hydrolytic processes that involve the transfer of one or several protons to or from water molecules in the transition state (TS) of the rate determining step. Indeed, in these reactions one water molecule acts as a nucleophile while one or several act as general bases, and typically show a) high negative values of entropy of activation ($\Delta S^{\neq}$), and b) high kinetic solvent isotope effect (KSIE). In these reactions water is solvent, nucleophile and catalyst. The hydrolyses of alkyl halides, alkyl and aryl sulphonates, and derivatives of carboxylic acids (esters, amides) have been extensively studied. The reaction with derivatives of saturated carbons is quite different than the hydrolyses of esters and amides. At least two water molecules must be strongly bound at the TS to produce a high KSIE, restricting the number of possible positions of these molecules. The number of molecules involved in the proton transfer (two molecules per proton) can be determined by proton inventory. Polymolecular mechanisms have been found for these reactions with 3-5 molecules involved in the TS. Hydrophobicity and hydrophilicity of the substrate is determinant of the mechanism.

Supramolecular Catalysis Induced by Polysaccharides

The non-bonding interactions of carbohydrates with water depend on their stereochemistry. Kinetic medium effects induced by carbohydrates are important to the understanding of their role in the sugar-protein recognition involved in carbohydrate transport, the relationship antigen-antibody of the immunological system and hydrolytic enzymatic reactions. Monosaccharides, depending on their stereochemistry, inhibit specifically water catalyzed reactions of small molecules [1] while modified polysaccharides induce water molecules into a highly ordered supermolecular structure that can then catalyze a reaction on the polysaccharide matrix.

In 1991 it was observed that the water catalyzed reaction of a cellulose xanthate ester was about 2000 times faster than the small analogue molecule and it was proposed that the acceleration was a consequence of the highly ordered cybotactic region and that consequently $\Delta S^{\neq}$ should be nearly zero [2]. This assumption was confirmed in a detailed study of the water catalyzed hydrolysis of p-

nitrobenzyl cellulose xanthate (CelXNB). The rate determining step was the nucleophilic attack of a water molecule [3], catalyzed by a second water molecule that acts as a general base [4]. The water catalysis is not due to a neighboring OH effect [5] and $\Delta S^{\neq}$ is nearly zero (+3.6 cal.mol^{-1}.K^{-1}). The spontaneous hydrolysis of 2,4-dinitrophenyl cellulose xanthate in acetone-water mixtures confirmed that the hydrolysis does not occur through water polymers and that above 30 M there are no acetone molecules (or very few) in the highly-ordered cybotactic region of cellulose (selective solvation) [5].

Intramolecular Proton Transfer and Torsional Effect

The cleavage of aryl and some alkyl dithiocarbamates occurs through a water catalyzed intramolecular S to N proton transfer concerted with the C-N bond cleavage [6]. Theoretical *ab initio* calculations supported this hypothesis. The driving force to reach the TS is the torsional effect of the C-N bond that inhibits the resonance with the thiocarbonyl group increasing the basicity of the nitrogen and making the proton transfer thermodynamically favorable.

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N-Alkyl-N-methylacetamidinium Ions. Isomerization and Water Catalyzed Exchange Rates in D_2O

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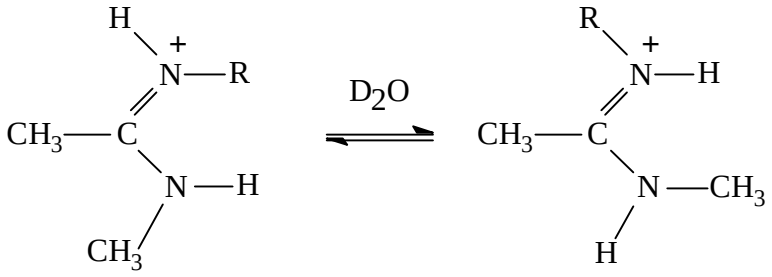
Previously we had reported results on the rate of stereoisomerization (see figure) in D_2O of N-benzyl-N´-methyllacetamidinium ion in an ample pD range (D_2O is used as a solvent).



ZE **EZ**

R = $CH_2C_6H_5$; CH_2-CH=CH_2 ; CH_2OCH_3 ; CH_2CF_3

We found that the sigmoided-type profile of kobs. vs. pD plot, fits the rate expression : kobs = $(k_1[D^+] + k_2Ka)/ (Ka + [D^+])$, where k_1 and k_2 are the rates of isomerization of the acetamidinium ion and the acetamidine respectively and Ka is the acidity equilibrium constant of the acetamidinium ion. These constants were evaluated by measuring the rates at each pD using dynamic NMR(H) (line shape analysis and saturation transfer). Based on the low barrier of 19.7 Kcal/mol at 25°C (k_1 = 0.02 s^{-1}) it was suggested that the isomerization (EZ-ZE) of the acetamidinium form procceds throw rotation of the C-N partial double bond. We argued that this relatively low barrier is due the steric repulsion of the N-benzyl group that destabilizes the ground state (planar amidinium) relative to its twisted transition state. On the other hand, our result supports that the E-syn-Z-anti isomerization of the acetamidine form proceeds via rotation about a C-N single bond as it had been proposed previously. We stated that the proposed mechanism was in agreement with the measured low barrier of 14.7 Kcal/mol at 25°C (k_1= 126 s^{-1}). In order to test the proposed mechanisms and in view of the biological importance of the acetamidines we have undertaken a systematic study on the isomerization of N´-alkyl-N-methylacetamidines as a complementary support to our previous results on the N-benzyl.N´-methylacetamidine. Therefore we have prepared the following acetamidines: N-allyl-N´-

methylacetamidine ($R=CH_2-CH=CH_2$), N-trifluoroethyl-N´-methylacetamidine ($R=CH_2CF_3$) and N-methoxiethyl-N´-methylacetamidine ($R=CH_2OCH_3$). The purpose of this study is to measure the isomerization rates under pD conditions in which both forms, acetamidinium ion and acetamidine, participate. Therefore, the rates k_1 and k_2 and the equilibrium, Ka of each of these compounds was determined. We then explore the existence of a structure-reactivitity relationship for each parameter. Finally we search on the rate of proton exchange, at low pD, were the D_2O acts as a base and we found the relative acidity between the –NH sites at the acetamidinium ions.

Natural Inhibitors of the Aromatase Enzyme*

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Abstract: The results of three years of search for natural aromatase inhibitors will be presented.

Estrogen biosynthesis is catalyzed by the aromatase enzyme complex. This complex if made up of a member of the cytochrome P450 superfamily of enzymes known as cytochrome P450 aromatase (P450arom, produced by the CYP19 gene). Associated with this enzyme one finds the flavoprotein NADPH cytochrome P450 reductase. These two enzymes catalyze the aromatization of the A ring of androgens to form the characteristic phenolic ring of the estrogens. This reaction involves three sequential oxidations of the C-19 methyl group of the substrate (testosterone and androstenedione), its elimination as formic acid and the aromatization of the A ring to afford 17β-estradiol y estrone, respectively. This is the only reaction found in vertebrates in which an aromatic ring is introduced in a molecule. The regulation of this enzyme plays an important role in several physiological processes and in certain diseases, the most important of which is hormone dependent breast cancer. The use of aromatase inhibitors to treat this disease is now very commonplace. There are two kinds of inhibitors, competitive ones and suicide inhibitors; both types include both steroidal and non-steroidal compounds. Due to their great therapeutic importance, presently the list of inhibitors is quite long, but only five have been shown to be relatively safe and to possess reasonable clinical efficacy. These are: aminoglutetimide, 4-hydroxyandrostenedione, anastrozol, letrozol y vorozol; the last three being third generation non-steroidal inhibitors. On the other hand, a few plant secondary metabolites have shown significant inhibitory activity towards the aromatase enzyme. For this reason we consider the search for and characterization of novel natural products with this type of activity to be interesting.

At this conference we will present the results of three years of joint research with colleagues from the Department of Clinical Biochemistry of our faculty, which may be summarized as follows:

a) A group of sesquiterpene lactones isolated from different species of *Asteraceae* inhibited the activity of the aromatase enzyme in human placenta microsomes. The three most active compounds were the guaianolides 10-epi-8-desoxycumambrine B, dehydroleucodine and ludartine.
b) Complete kinetic studies of these compounds as well as differential UV-Vis studies, were done to measure their binding affinity towards the iron of the heme group found in the active site of the enzyme.

c) To measure the specificity of each inhibitor, their activity towards two other enzymes of the steroidigenic cascade was evaluated.

d) Reduction of the characteristic exocyclic double bond of the most active compound, 10-epi-8-desoxycumambrine B, allowed us to prepare a dihydro derivative that retained the capability to inhibit the aromatase enzyme while at the same time displaying none of the precursor's cytotoxicty. This allowed us to successfully evaluate the inhibition of the enzyme found in JEG-3 choriocarcinome cells. It is important to mention that the literature to date contains reports of nearly 4,000 sesquiterpene lactones. Many of them display several types of biological activity, but always associated with the presence of the characteristic exocyclic double bond. In our case this is not so, which represents an important pharmacological novelty.

e) The results, combined with molecular modeling studies, allow us to propose an inhibition mechanism that shows that the exocylic double bond does not participate.

f) Semisynthetic derivatives were prepared from ludartine with the purpose of speculating about structure-activity relationships.

**Note*: Translation by the Editorial Staff.

Synthesis of New Anthihelmintic Analogs of Marine Natural Products*

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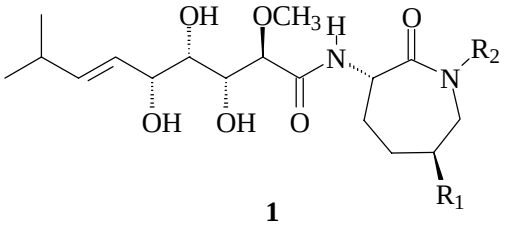
Abstract: The synthesis of new anthelmintic compounds derived from 2-amine-4-hydroxy-δ-valerolactams and 2,4-dialkylthiazoles is described. The synthetic procedures and biological activity data for these compounds will be presented.

Secondary metabolites of marine origin are a source of new molecular architectures with interesting and promising biological activities.

For some time our group has been carrying out a general program of discovery and development of new compounds with antihelmintic activity. For this purpose we have chosen a group of natural products isolated from sponges, which have displayed a very high antihelmintic activity. Such is the case of the Bengamides (**1**) and Micotiazol (**2**).



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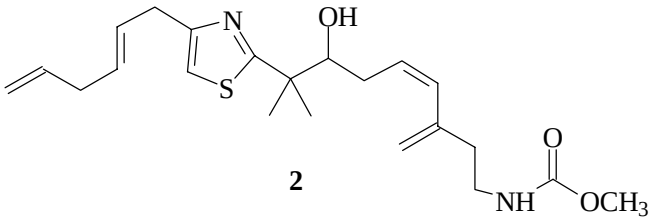
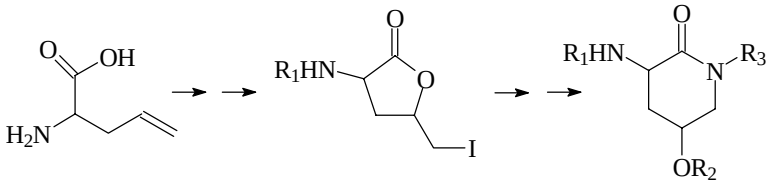


2

$R_1 = O_2C\text{-}(CH_2)\text{-}CH_3$ $R_2 = H ; CH_3$

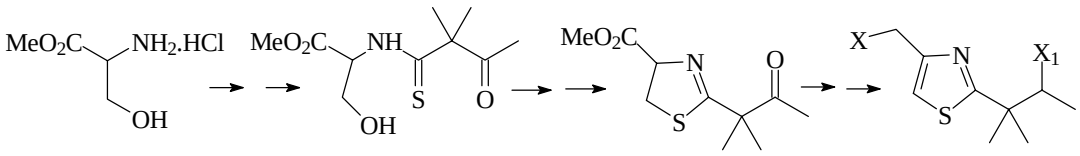
From a structural point of view these compounds share a common molecular pattern, in which a central heterocyclic ring, biogenetically derived from aninoacids, simultaneously bears sidechains with both lipo- and hydrophilic character. Molecular simplification of structures with proven biological activity is a classical tool used in Pharmaceutical Chemistry to obtain new lead compounds. This methodology was applied in our group starting from the basic structural patterns found in compounds of **1** and **2**.

In this lecture we will first present our results when a group of derivatives 2-amino-4-hydroxy-δ-valerolactam were prepared via a synthetic sequence involving lactonization followed by a lactone-lactam exchange, as shown in Scheme 1.



Scheme 1.

Second, we will describe the synthesis of 1,3-thiaza-2,4-disubstituted systems from acyclic precursors. We will discuss the results of different condensation and cyclodehydration methodologies, as well as the methods used to carry out controlled oxidations of the central heterocyclic system (Scheme 2).



Scheme 2.

In all cases the antihelmintic activity of the synthesized compounds and the biological models used to evaluate these activities will be presented.

**Note*: Translation by the Editorial Staff.

Synthesis of Derivatives of Biogenic Amines Labelled with Radioactive Tracers for Brain Imaging

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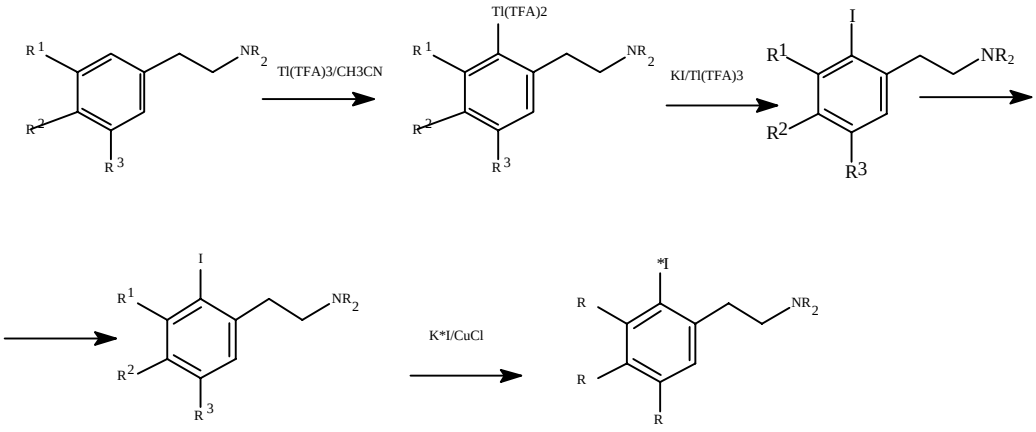
Abstract: Endogenous derivatives of biogenic amines, such as phenethylamines, indolalkylamines and harmines, have been extensively studied as usual constituents of body fluids. Methylated derivatives of indolalkylamines have been also related to mental disorders, *e.g.* schizophrenia and hallucination.

In vivo imaging constitutes a powerful tool for the evaluation of the state of the central nervous system (CNS), in particular the brain in normal and altered states due to mental disorders or occurrence of tumors.

SPECT (Single Photon Emission Tomography), and PET (Positron Emission Tomography) are the usual techniques. For SPECT a molecule labelled with a gamma-emissor is required. The label may be incorporated to the molecule either covalently, *e. g.* I-131 or I-125, or by means of the formation of complexes with some gamma-emissor metal, usually Tc-99m owing to its low-energy gamma-emission and short half life.

The new methodology developed in our laboratories for the synthesis of labelled molecules to be used with SPECT is to be discussed in this lecture.

Synthetic strategies of molecules belonging to the families of phenethylamines, indolalkylamines and harmanes labelled with I-131 will be described. These preparations involved thalium derivatives as shown in the scheme.



Preparation of alkylamines labelled with Tc-99m will be also discussed as well as the static biodistribution in laboratory animals.

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Role of Weak Molecular Interactions in the Mechanism of Action of a Series of Antihelmintics

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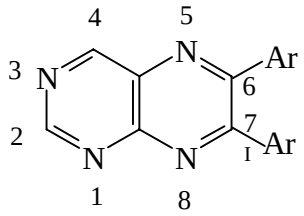
Abstract: Different physicochemical properties such as solute-solute and solute-solvent interactions, tautomerism, lipophilicity and solubility in water were determined for a serie of 6,7-diaryl-pteridines in order to relate those properties with their nematocide action.

Introduction

The pharmacological response of a drug can be the result of a complex formation between the drug and the receptor. This complex is generally the result of several types of interactions such as hydrophobic and electrostatic forces, hydrogen bonding and electron donor-acceptor complexes [1].

Previous works [2,3] have shown the nematocide activity for a serie of substituted 6,7-diaryl-pteridines (I) against different experimental models. Different structure-activity relationships (SARs) have been established for these compounds through neural networks [3].



Experimental

Synthesis and nematocide accion for the studied compounds were previously described [2,3].

Results and Discussion

For 18 substituted 6,7-diaryl-pteridines the following physicochemical properties were determined: polar and hydrogen bonding interactions with the solvent, solute-solute interactions, tautomerism,

solubility in water and lipophilicity.

It was observed that only lipophilic interactions are related with the measured nematocide action (%R) for these drugs.

The logarithm of the chromatographic retention factor extrapolated to pure water, log k'_w, was used as a lipophilicity index. A typical ODS column and methanol-water as mobile phase were used. A linear regression between log k' and the Reichardt solvent parameter, $E_T(30)$, for binary methanol-water mixtures was used to obtain log k'_w by extrapolation. This procedure is generally more appropriate than extrapolate from a log k' vs. % organic modifier plot since curvature is often observed [4].

The correlation matrix between % R (percentage of decrease in nematode concentration when 100 μg/ml of the drug in DMSO are used in *in vitro* assays) and log k'_w is shown below.

	%R	log k'_w
% R	1.0000	0.6769
log k'_w	0.6769	1.0000

This results indicate that 67.69% of the variance in the biological activity produced by changes in drug concentration can be explained by lipophilic interactions.

Acknowledgements: The authors aknowledge to CYTED, CONICET, CONICOR, FONCYT and SECyT-UNRC for the financial support.

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The $AlCl_3$–L Reagent and its Application to the Regioselective Carbon–Carbon Bond Formation

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Abstract: Use of the $AlCl_3$–L reagent in the regioselective acylation of benzodioxinic derivatives. Spectroscopic studies show the presence of coordination compounds as reaction intermediates, being the responsible of the observed regioselectivity.

Introduction

Carbon–carbon bond forming reactions are one of the most important processes in organic synthesis. Many of these transformations are promoted by ordinary Lewis acids, which activates a wide variety of functional groups. The reactions usually proceed efficiently but with low chemo– and regioselectivities. For this reason, it is of great interest the development of new methodologies to perform these organic transformations in a selective form.

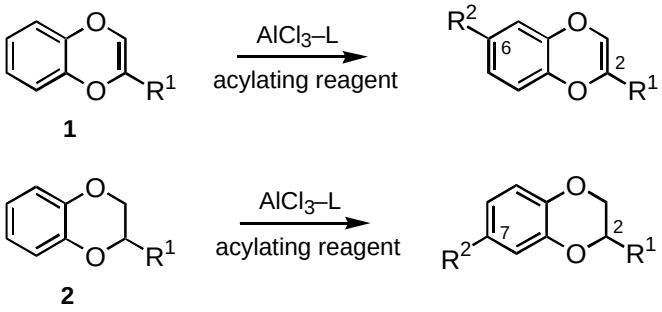
We have demonstrated that the combination of $AlCl_3$ with an organic donor ligand is an excellent reagent for the acylation reaction of benzodioxin derivatives, which is carried out in the absence of added solvent [1,2]. Derivatives of this nucleus bearing an acyl group in position 6 or 7 are key intermediates in the preparation of therapeutically valuable benzodioxin compounds [3].

Results and Discusion

The use of $AlCl_3$ in conjunction with DMF, DMSO or DMA and acyl halides or anhydrides produce the regioselective functionalization of benzodioxin derivatives in excellent yields.

Both the 6– and 7– position of the aromatic ring are activated towards the electrophilic attack. However, acylation of 2–substituted–1,4–benzodioxin derivative **1** provides the 6–acyl compound as the major or unique product, and the same reaction with the saturated analogs **2** affords the 7–acyl compound as the main product, whatever the nature of the R^1 group.

The experimental results demonstrate that the nature of the reacting electrophile and the donor ligand employed have almost no influence on the isomeric distribution which is function exclusively on the substrate structure.



R^1 = CO_2Me, CH_2OMe, CH_2OAc

R^1 = COMe, COPh

L = DMF, DMSO, DMA

Spectroscopic studies reveal the presence of coordination compounds as reaction intermediates. The NMR ^1H and ^{13}C spectra of reaction mixtures show a complexed entity between the $AlCl_3$–L reagent and the polar functionality of the aromatic substrate. The formation of this complex seems to be responsible for the inversion of the regioselectivity between the saturated and unsaturated benzodioxinic compounds.

Acknowledgements: Financial support from Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Universidad Nacional de Rosario and Agencia Nacional de Promoción Científica y Tecnológica is gratefully acknowledged.

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A Short Synthesis of the Main Lactone Ketal Backbone Present in Saudin

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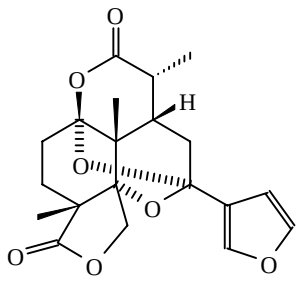
Abstract: We are describing a brief stereospecific synthesis of a model compound related to Saudin, with a lactone ketal backbone present in the natural product starting from a tricyclic epoxiketal.

Introduction

Saudin is a diterpene belonging to the labdane prefuranoid family; that was isolated from the toxic plant *Cluytia richardiana* (L), Euforbiaceae family, growing in Arabia Saudi, in 1985 [1]. The importance of this compound resides in its interesting potential biological properties as hypoglucemic agent.

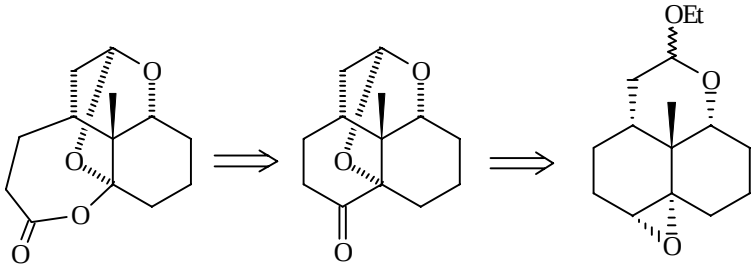


1

Continuing our efforts to the synthesis of intermediates related to Saudin, in this opportunity, we will present the synthesis of **2** which have the lactone-ketal structure found into the natural product with a 7 members ring instead of a 6 members as in Saudin.

Synthesis Design

According to the following retrosynthetic analysis:



2 **3** **4**

Compound **2** would be prepared from the intermediate **3** using a Baeyer-Villiger type reaction. In turn, compound **3** would be synthesize from the tetracyclic epoxiketal **4**, by means of an epoxide cleavage followed by oxidation and cyclic ketal formation.

Experimental

The epoxyketal intermediate **4** was synthesized from the α- tetralone by a five steps sequence previously developed in our research group [2] that includes: a Birch-alkylation reaction, the stereospecific reduction of the carbonyl group, a regio and stereospecific epoxidation followed by a bromo ketal formation, and finally a radical cyclization [3]. After different alternatives we found that by treatment of **4** with Jones´s reagent, in acetone, compound **3** was obtained in good yield.

After oxidation of this compound under Baeyer Villiger conditions with solid hydrogen carbonate, the product **2** was obtained regioselectively. The lactone-ketal **2** was characterized using the spectroscopic methods and the comparison of the ^{13}C NMR spectrum signals are in agreement with those reported for the natural product.

Acknowledgements: We thank to Universidad Nacional de Rosario, CONICET and Agencia Nacional de Promoción Científica y Tecnología.

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Using Empirical Rules from ^{13}C NMR Analysis to Determine the Stereochemistry of the Epoxide Located at the 5,6-position of Decalinic Systems

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Abstract: An empiric rule derived from the analysis of the ^{13}C NMR spectral data, allowed us to determine 5,6-epoxide stereochemistry on decalinic systems and a discussion of the scope and limitations of this rule and its extension to other carbon squeletons, is presented.

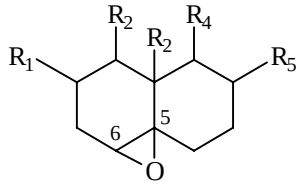
Introduction

^{13}C NMR and ^{1}H NMR techniques are the most convenient methods for the elucidations of the oxirane ring stereochemistry in condensed policyclic systems, and have been widely used in the research of epoxides from natural sources [1-3].

Very often, however, the methods used consider mainly the effects of the oxirane ring on the γ carbons [4-6].

Results and Discussion

From the analysis of the ^{13}C NMR data of a set of synthetic epoxides angularly substituted and placed on the C_5-C_6 position of decalin systems of known relative configurations; we could stablish an empirical correlation between the chemical shift difference of the oxirane carbons and the relative configuration of the epoxide. Therefore, using these chemical shift differences it is possible to predict the α or β orientation of the epoxide, that is, *trans* or *cis* stereochemistry of the epoxide relative to the C_{10} substituent (R_3).



Computing for each epoxide: $\Delta\delta_{(epoxide)} = \delta_{C-5} - \delta_{C-6}$, the subtraction between the ^{13}C NMR chemical shifts of both oxirane carbon signals, predicts:

$$\Delta\delta\ \alpha\text{-epoxide} > 5 \text{ ppm}$$
$$\Delta\delta\ \beta\text{-epoxide} < 3.8 \text{ ppm}$$

Besides, we will present a discussion of the scope and limitations of this rule, its possible extension to other carbon skeletons and the comparative analysis with those results obtained from the existent semiempirical calculation systems [5,6].

Experimental

The epoxides were synthesized from substituted α- tetralones through a sequence involving a Birch reductive alkylation followed by the reduction and epoxidation with *m*-CPBA in heterogeneous phase.

The determinations of the ^{13}C NMR spectra were realized in $CDCl_3$ solutions using standard conditions.

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Biotransformation of Ilicic Alcohol with *Aspergillus Niger*

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Abstract: 3β-hidroxyilicic alcohol was obtained from of ilicic alcohol using cultures of *Aspergillus niger.*

Introduction

Sesquiterpenes are wide spread *Asteracea Compositae* family. Their derivatives present several biological activities. Among them we have studied their gastrointestinal citoprotective action and the antinflamatory effects. The production of active metabolites by transformation of low funcionalized natural products is an attractive idea. In previous reports we have described the hydroxylation of the eudesmane, ilicic acid, in positions 1β y 2β [1] and the production of trihydroxyderivatives in positions 2β y 3α from kudtdiol [2] by *Cunningamella echinulata.*

Materials and methods

Culture Conditions: Modified Czapek broth [3] was used to carry out the biotransformation reactions. Agar Czapek was employed to maintain the strains. Taking into account a previous screening, we have chosen an *Aspergillus niger* strain, isolated from aerial parts of *Artemisia donglassiana*. Biotransformations were performed according to a two steps fermentation process.

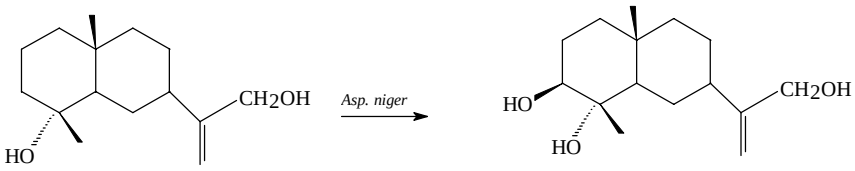
Biotransformation products were recover from the culture media by liquid-liquid extraction with Et_2O and purified by CC with a gradient of n-hexane/AcEt. 80mg of the biotransformation product were obtained. The hydroxylation position was defined by NMR and MS analysis.

Results and Discusion

The comparison of the ^{1}H NMR spectrums in CCl_3D of the new product versus the ones of the substrate suggested us that the hydroxylation position was 3β. The sing at δ 3.43 ppm was attributable to a geminal hydrogen in α-equatorial conformation. This proposal was confirmed through the coupling pattern (J=11.5 y 4.5 Hz). ^{1}H-NMR shifts are in accordance with the ones recently reported for 3β-hydroxylicic acid isolated from other sources [4]. The impossibility to obtain the acetonic derivative

confirm that the hydroxylic group was introduced in position in C-3, *trans* respect to the hydroxylixc group in C-4.

It was recently reported that *Cunninghamella echinulata* NRRL 3655 hydroxylated both, ilicic acid and kudtdiol in positions C-1β, C-2β y C-3α. These results, together with the ones reported here, shown us the ability of these microorganisms to hydroxylate in positions *cis* respect to the methyl grops in C-4 y C-10



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Applications of Olefination Reactions to Cassiol Synthesis

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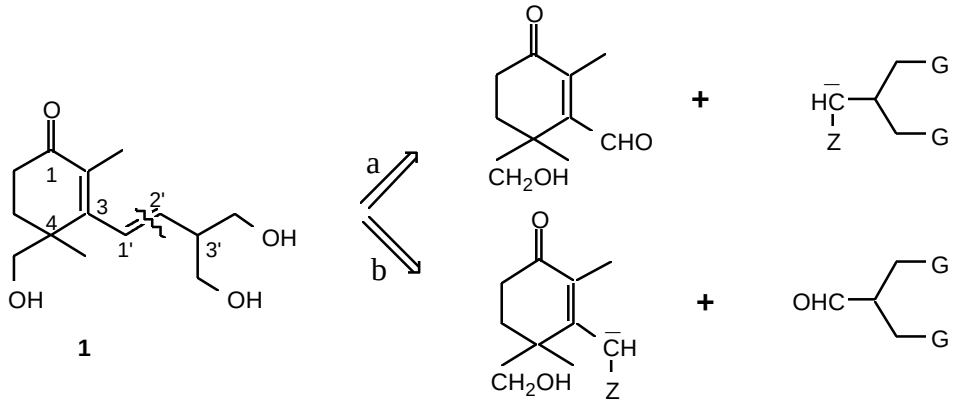
Abstract: Olefination reactions directed to the synthesis of cassiol from compounds **2-5** will be discussed.

Introduction

Cassiol (**1**), which exhibits a potent antiulcer activity, contains a functionalized cyclohexenone moeity with a quaternary stereogenic center at C-4 and a 2-vinyl-1,3-diol chain, which is connected at the C-3 position. Because of its structural features and pharmacological activity, a number of synthesis have been recorded [1]. Our approach toward the synthesis of **1** involves the C-1'- C-2' double bond disconnection through a carbonyl olefination procedure [2]. This sequence allow us to explore the olefination reaction in two differents ways, switching the polarity of the coupling partners as shown in the following scheme.



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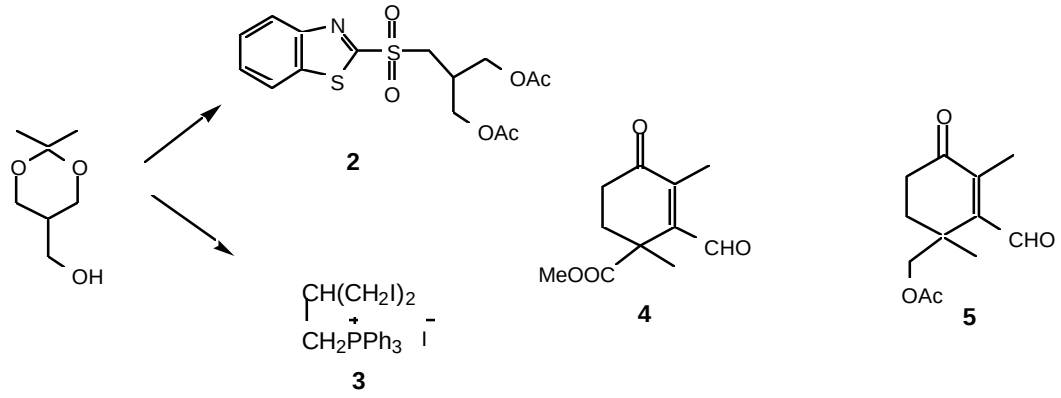
G= Protecting group, Z= Ph_3P; $MBTSO_2$- (2-mercaptobenzothiazolylsulfone)

By following approach **a**, a precursor of cassiol (**1**) was obtained in our laboratory, but unfortunately in an unsatisfactory low yield [3]. In order to improve the yield of the coupling reaction, compounds **2**-**5** were then selected for study.

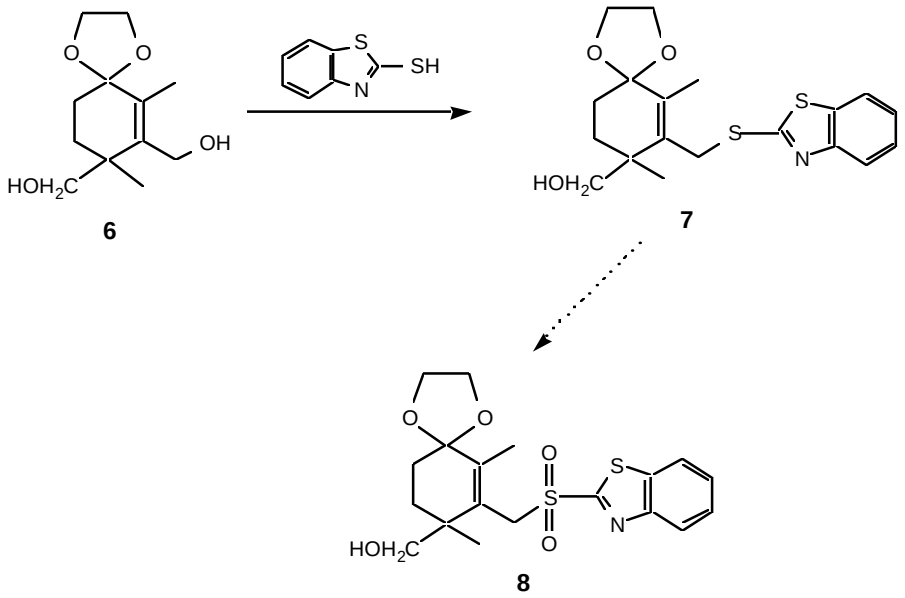
Experimental

Compounds **2-5** were prepared according to standard methods.



Discussion

Due to lack of success in the coupling of **4**-**5** with **2** and **3** by using differents conditions of solvents and bases we turned our attention to approach **b**.Starting with compound **4**, the diol **6** has been obtained. Treatment of **6** with mercaptobenzothiazole provided the corresponding sulfide **7**. Starting with **7** and through the corresponding sulfone **8** we hope to improve the yield of the coupling product, on the basis of the recent report of Hart and Kozikowski et al [4].



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New Anti-Neoplastics Obtained by a Molecular Connectivity Method

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Abstract: Molecular Connectivity is a method, which allows to discriminate different pharmacological activities on the basics of numeric parameters of the molecules in study, related with specific and exclusive indexes. In the present study, we propose two potentially anti-neoplasic compounds: *tricromil* and *zomepirac***,** by analyzing more than a hundred different chemicals.

Introduction

At the present, the most common methods for pharmacological compound design include the use of physical-chemical descriptors from QSAR methology, along with the possible complementary addition of quantum mechanics calculations or graphic methods based on molecular mechanics.

An alternative method, based on molecular topology and called «Molecular Connectivity», consists on numerically characterizing the molecule in study by a series of indexes that are specific and exclusive for each one.

The aim of the method is to obtain multi-lineal correlation between physical, chemical and biological properties of molecules, after their topology quantification. For this, correlation functions are obtained between these properties (connectivity functions) and a series of descriptors called topological indexes.

This technique has been applied to a group of diverse anti-neoplasic compounds finding connectivity functions that are capable of discriminating if a particular compound has cytotoxic activity or not.

Methods and Calculations

In this work, 62 indexes were used for determination of connectivity functions. Hence, regression

functions that describe each property were obtained by correlation of experimental values of properties with use of statistic packages for multi-lineal correlation.

In order to classify the chemicals by their anti-neoplasic activity, an equation was defined by use of discriminating lineal analysis and working on a database of about 12 thousand compounds. A large group of chemicals were selected and distributed into two subgroups: one with contrasted anti-neoplasic activity and another for which this activity has not been yet described.

Using connectivity indexes, correlation functions were chosen for different properties and used as filters for selection of possible anti-neoplasics. From application of the discriminating equation of choice, two pharmacological compounds, for which no anti-neoplasic activity had been described, were chosen.

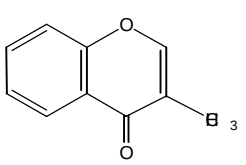
Results and Discussion

The chosen discriminating function was:

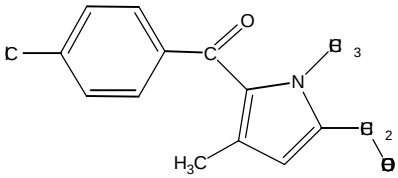
$D= - 9.06457 - 1.5237\ {}^{2}X^{V} + 2.06966\ {}^{4}X_{p} – 18.54615\ J_{2} + 34.43409\ J_{2}^{V}$

Once applied to the selected group of compounds, it correctly classified 90% of the active and 93.1% of the inactive compounds. The use of this method allows finding new active compounds within series defined by particular structural conditions.

In the present work, two potential cytostatic compounds were selected:



zomepirac



tricromil

The first of these compounds has an activity defined as anti-spasmodic and coronary vasodilator, while tricromil is known as an analgesic and anti-inflammatory.

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Octyl Phenol Synthesis Using Natural Clays

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Abstract: A series of clay minerals, HB, NB and Al-PILC have been studied in the alkylation reactions of 2-octanol with phenol at 180°C, under conditions of alcohol/phenol = 1 (mole ratio) and $W/F_A^{o}{}_{\circ}$= 64,27 ghmol^{-1}. The selectivity of Al-PILC was 77,12% for octyl phenol and 16,5% for dioctyl phenol.

Introduction

The aromatic alkylation is an interesting industrial reaction catalyzed by acids. Octylphenoles, can be obtained by alkylation of phenol with the corresponding olefin or alcohol. These chemicals are used as surfactants.

Generally these products are synthesized using catalysts such as: sulphuric acid, boron trifluoride, hydrofluoric acid and phosphoric acid, with all the involved environmental pollution problems.

In this paper are shown the results obtained when the traditional catalysts are replaced by a heterogeneous acid catalysts, obtained from natural clays, in order to decrease the environmental pollution.

Experimental

The catalysts were prepared starting from a natural bentonite, NB, and HB means a bentonite treated with hydrochloric acid according to [1], AL-PILC 10 to a bentonite pillared with an oligomer of Al (10 mmoles Al/g of bentonite) according to [2]. The catalysts were characterized by surface areas: NB=44 m^2/g; HB=64 m^2/g and AL-PILC=211 m^2/g.

The reactions were carried out at room pressure in a fixed bed reactor, using 0,5 g of catalysts under isothermic conditions, a mixture of phenol (Merck, 99.3%) and 2-octanol (molecular rate 1/1) was injected, preheated and diluted with a flow of dry nitrogen; the products and unreacted reagents were collected at 273°K and analyzed by GLC using a column of OV-101 (10%). The reaction products were identified by GC- mass, FT-IR and ^{1}H NMR. The conversion and selectivities are in moles per cent.

Results and Discussion

Phenol conversion and products selectivity at time on strem 2 hours, are shown in the next table.

CATALYSTS	PHENOL CONVERSION	SELECTIVITY			
		Alkylphenol	Dialkylphe-nol	Trialkylphe-nol	Ether
NB	4.48	56.93	2.38	0	40.68
HB	29.92	63.42	28.83	6.33	0
Al-PILC 10	35.50	77.12	16.65	5.97	0.25

We can observe that the increase in conversion correlates with the acidity of the solids; NB show a low acidity owing to terminal silanole groups. The acid treatment and the pillaring increase the acidity, the phenol conversion and the selectivity to the alkylation products.

Acknowledgements: The authors are grateful to Guillermo Ghione for the experimental collaboration and to the CONICOR for the economic aid AIF Nº 4425/97 and 4701/99.

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Total Synthesis of Marchantinquinone

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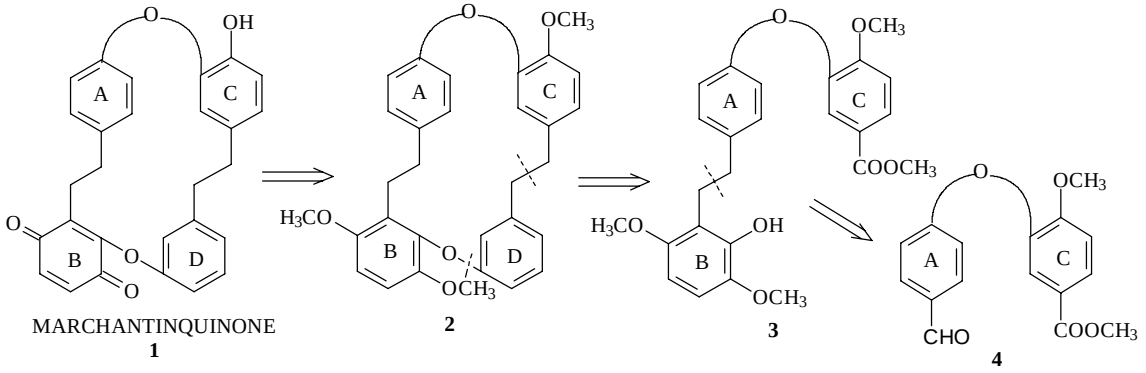
Abstract. During the last years, many bisbibenzylic macrocyclic ethers were isolated and identified in *Hepaticae*. One of them is MARCHANTINQUINONE, a quinonic macrocycle with interesting biological activity. In the following report, we present the last steps of the total synthesis.

Introduction

Bisbibenzylic systems such as Marchantins, Perrottetins, Riccardins are found only in *Hepatica* and have been shown to display a wide range of biological activities [1,2]. Marchantinquinone (**1**), from extracts of *Reboulia hemisphaerica*, formerly described as *Mannia subpilosa*, [3,4] was the first bisbibenzylic diether possessing a quinone structure isolated from Bryophytes. Herein its first synthesis is reported.

Experimental

Relevant steps of the synthesis are shown in the following retrosynthetic scheme:

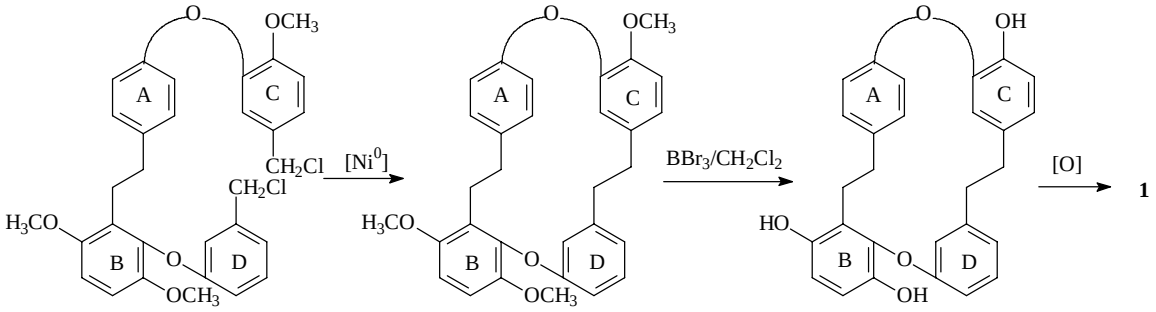


The global strategy of this synthesis is based on standard organic synthesis reactions: nucleophilic aromatic substitution, Wittig reaction, catalytic hydrogenation. It also includes redox reactions and

macrocyclization using Ni^{o} complex.

Results and Discussion

Previously, we described the synthesis of macrocycle (**2**) [5] an advance precursor of Marchantinquinone (**1**). Different conditions of macrocyclization, deprotection and oxidation to obtain the quinonic structure will be disclosed.



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Catalytic Epoxidation of Limonene

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Abstract: The epoxidation of limonene with hidrogen peroxide was studied over zeolite Ti-beta (a large pore material) and heteropoly acids on carbono and alumina supported. PW_{11}/C was catalyst the best tested.

Introduction

In the last years, the increase in environmental restrictions lead to the search for new oxydant systems to replace the traditionals in order to avoid the generation of polluting effluents.

The terpenes containing oxygen are very important to be used in the fragrances production; in our country we have great quantities of limonene and thus we studied its oxydation to 1,2-epoxilimonene using a heterogeneous catalysts system.

In a previous paper the pillared clays from mixed oligomers of Si-Ti [1] were studied, in this paper the results using supported heteropolyacids (HPA) an zeolites Ti-beta are shown.

Experimental

The HPA were prepared from phosphomolybdic acid (PMA) and tunstophosphoric acid (TPA) and then impregnated on alumina (A) or carbon (C) to fill the pores with solution in ethanol-water [2]. PW_{11} refers to a lacunar phase supported on C. Ti-beta zeolite (Ti-β) was prepared according to [3].

The reactions were run in a batch type glass reactor with vigorous stirring and at 343°K, the rate limonene/H_2O_2(35%) = 4 and 100 mg of catalysts and acetonitrile as solvent; the reaction was followed by taking samples at different times and analyzing them by GLC, the remanent H_2O_2 was determined by iodometric titration. The reaction products were identified by comparation with chromatographic authentic samples and mass spectroscopy.

Results and Discussion

Limonene and H_2O_2 conversion and products selectivity at time on strem 7 hours, are shown in the next table.

CATALYSTS	**CONVERSION**		**SELECTIVITY**			
(mmoles HPA/g)	% max.	H_2O_2	H_2O_2	Epoxide	Cetones	Others
TPA/A (1.120)	33,85	54,93	61,63	31,20	42,88	25,92
TPA/C (0,855)	13,03	33,92	38,41	22,95	41,49	35,56
MPA/A (1.280)	34,62	65,36	52,96	36,89	33,86	29,25
MPA/C (0,649)	22,35	33,46	66,80	24,28	32,78	42,94
PW_{11}/C (0,820)	38,22	71,58	53,40	58,74	30,23	11,04
Ti-β (2,6%TiO_2)	46,21	71,51	63,62	22,94	54,60	23,86

We can observe that supported HPA on A show a higher conversion and selectivity to the epoxide than the supported on C, which are more selective to other products (glycols and acid catalysis products), owing to a lower interaction between HPA and support. The catalyst with higher activity is Ti-β but the more selective is the lacunar phase PW_{11}/C, with high yield of epoxide derivative, because this phase has a vacancy compared with Keggin structure, whic is active for oxydation reactions.

Acknowledgements: The authors are grateful to Hernan Gabeta for experimental collaboration and financial support from CONICOR (project N^{o} 4230/97).

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Base-Catalyzed Formation of Imidazole Derivatives

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Introduction

Many 2-(2´-imidazolin-2´-yl)-3-carboxypyridines possess bioactive properties that caused their use in agriculture as herbicides and defoliants [1]. Their activity is based on inhibition of acetohydroxy acid synthesis, reducing level of valine, leucine and isoleucine to disruption of protein and DNA synthesis. Known methods of their synthesis are based on multistep processes and result in low yield of aiming products. The first of them developed by Los with co-workers starts from substitutes diethyl pyridinedicarboxylates which were hydrolized to correspondent diacids, then dehydrated to anhydrides, treated by and 2-amino-2,3-dimethylbutiramide, and finally cyclized to desired products [2]. Another method includes oxidative condensation of 2-methylnicotinic acid with and 2-amino-2,3-dimethylbutiramide in the presence of elementary sulfur [3]. Due to their disadvantages, a development of simple and effective method of these compounds preparation is actual. In the present work a reaction of one-step formation of imidazoline ring is studied.

Results and Discussion

The reaction proceeds readily at heating and the final product precipitates as sodium salt. It takes place in accordance with suggested mechanism (Scheme). Firstly, N-substituted imide of dicarboxylic acid is forming. This intermediate undergoes an intramolecular condensation of one of carbonyl groups at the pyridine ring with amide group of N-substituent. Finally, the hydrolysis of amide bond occurs. Surprisengly this reaction occurs selectively to 2-position of pyridinic ring while 3-(2´-imidazolin-2´-yl)-pyridine was not detected. This method was applied to ethyl pyridine-2,3-dicarboxylates with (or without) alkyl substituents in pyridinic ring.

Experimental

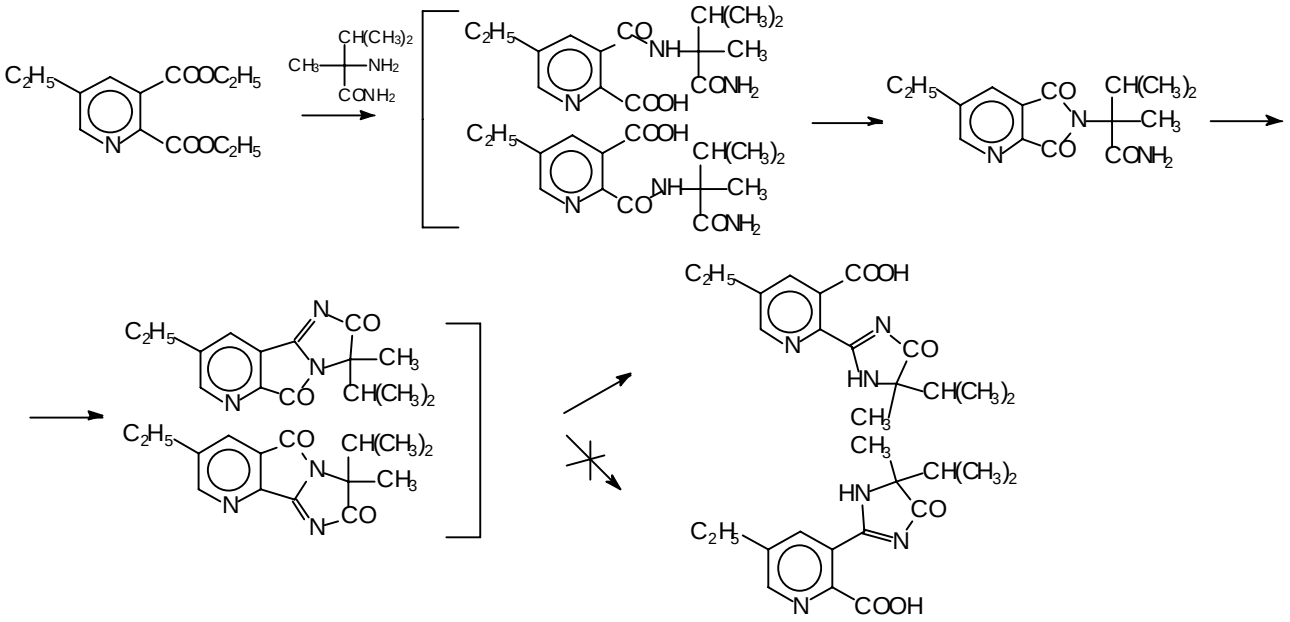
Synthesis of 5-ethyl-2-(2´-imidazolin-2´-yl)-pyridine-3-carboxylic acid

To solution of diethyl ester of 5-ethylpyridine-2,3-dicarboxylic acid (2,51 g, 0,01 mol) and 2-

amino-2,3-dimethylbutiramide (1,30 g, 0,01 mol) in 50 mL of dry toluene sodium metoxide (1,08 g, 0,02 mol) was added during 1 h at intensive stirring. The reactional mixture was refluxed for 1 h, cooled and white precipitate was filtered, washed by toluene, and dried on air. The yield of sodium salt of 5-ethyl-2-(2´-imidazolin-2´-yl)-pyridine-3-carboxylic acid was 2,39 g. The product was quantitatively converted into acidic form by dissolving in water and acidification to pH=3. Aiming compound was filtered, washed by water and dried at ambient temperature overnight. Yield 2.21 g (76.5%), m.p. 172-173ºC.

Spectral data

IR (Jasco FT/IR-5300, pellets with KBr) cm^{-1}: 1047, 1398, 1464, 1649, 1689, 1746; UV (Jasco UV/VIS-7800, acetonitrile) nm: 253.



Acknowledgements: The authors wish to thank Geol. J. Fernández for his assistance in spectral analysis and Prof. E. R. Herrero for helpful discussion.

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Organic Cosolvent Effect on the Estimation of the Solubility of Oil Residues in Soil

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Abstract: The solubility in water and the partition coefficients, K, in soils samples of residues of petroleum of different ages were determined using an organic cosolvent (methanol), and the solvophobic theory was applied for the interpretation of results. The behavior of the residuals turned out to be dependent of the cosolvent fraction. The values of K's vary among 900 (Lkg^{-1}) and 2,900 (Lkg^{-1}) showing a general and marked increase for residues of increasing age. The determined parameters are useful for the modeling of environmental impact in polluted soils.

Introduction

In the field of Environmental Chemistry is of interest to know the behavior of the pollutants in water since the transport and most of the degradation processes take place in water phase. The studied system is complex; therefore the solubility of each component should necessarily be affected by the presence of the other ones. The composition of each crude oil is unique and the oil in the environment is under very variable conditions, therefore a strong historical component exists in its current composition. This makes the testing in field samples to be of fundamental interest [1-3] since it is impossible to reproduce similar conditions in the laboratory. The oil residuals are hydrophobic but their solubility can be increased by means of the use of an organic cosolvent, as the alcohols.

This study intent to investigate on one hand, if the variations observed in the solubility and K (distribution coefficient) of the oil residuals, in the presence of different cosolvent fractions can be interpreted by the solvophobic theory and if, based on it, the solubility in water and the K's in complex mixtures can be estimated.

Experimental

Samples of polluted soils, were product of oil spills in different times at six locations in the surroundings of Comodoro Rivadavia city. For the measurement of the solubility in water experiences were carried out by means of the use of water and mixtures of water and organic cosolvent (methanol).

The following relationships were used for the interpretation of the measured data [1,4]: $\log S^m = \log S^w + \sigma f_c$ (**1**), where S^m is the solute solubility in the water- cosolvent mixture, S^w is the solubility in water, σ is 'the potential as cosolvent' and f_c is the volume fraction of the cosolvent. According to the solvophobic theory: $\ln (K^m/K^w) = - a \alpha \sigma f_c$ (**2**), where K^m is the partition coefficient in water (Lkg^{-1}); K^w is the partition coefficient in the mixture of solvents (Lkg^{-1}); a is the empirical constant accounting for water-cosolvent interactions, α is the empirical constant accounting for solvent-sorbent interactions; and σ is the cosolvency power of a given solvent and solute accounting for solvent-solute interactions.

Results and Discussion

For the oldest polluted samples the solubility in water calculated according to (**1**) are higher in all the cases to that experimentally measured. The differences increase with decreasing σ, indicating that probably the progressive loss of the potentiality of the cosolvent to solubilize has effect on the observed differences. The values of K's vary among 900 (Lkg^{-1}) and 2,900 (Lkg^{-1}) showing a general and marked increase when increasing age.

This information was related with the possibility of transport and it would contribute to the estimate of the mobility of oil residuals and the possibility of oil degradation.

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Preparation and Characterization of Solid Complexes of Naphtoquinone and Hydroxypropyl-β-Cyclodextrin

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Abstract*:* The formation of an inclusion compound between a naphthoquinone derivative (**I**) and HP-ß-CD was studied in solid state by X-ray diffractometry, DSC, and IR.

Introduction

The formation of inclusion complexes with cyclodextrins constitutes a widely used strategy to increase the aqueous solubility and to decrease the countereffects of many drugs. Isoxazolylnaphthoquinones belong to a family of compounds with bacterial and tripanocidal activity [1,2], as well as with very low solubility in water. In previous studies in our laboratory, we demonstrated that their hydrophilic capacity increases markedly through complexation with hydroxypropyl-ß-cyclodextrin (HP-ß-CD) in aqueous solution [3].

In this study we investigate the formation of complexes between 2-hydroxy-N-(3,4-dimethyl-5-isoxazolyl)-1,4-naphthoquinone-4-imine (**I**) and HP-ß-CD in solid state. Thermoanalytic techniques, X-ray diffraction and IR spectroscopy were performed [4].

Experimental

1. Materials

The synthesis and identification procedures for **I** have been described previously. HP-β-CD (MW = 1326 - 1400; degree of molar substitution, 7.0) was a gift from CERESTAR USA Inc. (Hammond, IN). All other materials and solvents were of analytical reagent grade.

2. Methods

2.1 Preparation of inclusion complexes

Formation of solid complexes: aqueous solutions were prepared between **I** and HP-ß-CD in concentrations of 1:0,5; 1:1 and 1:2, respectively. The solutions were then placed in a thermostat bath at 25ºC for 72 hours and subsequently filtered by using nylon membranes 0.45 μm pores. The solid complexes were obtained after water removal. The freeze drying technique (LABCONCO, Freeze Dry System) was used to prepare inclusion complexes of **I** and cyclodextrin in solid state. Physical mixtures were prepared in parallel by mixing the powders employing the same molar ratios of **I** and HP-ß-CD.

2.2 Characterization of inclusion complexes

2.2.1 Fourier Transformed Infra Red (FTIR) Spectral Studies

The spectra of **I,** physical mixtures and inclusion complexes were recorded in a KBr pellet using a NICOLET FT / IR 5-SXC Spectrophotometer.

2.2.2 Differential Scanning Calorimetry (DSC) Studies

The samples were subjected to DSC studies using a Shimadzu DSC-50 model. In , Sn, Pb and Zn were used as reference materials. The samples were scanned at the rate of 6^{o}C / min.

2.2.3 *Powder X-ray diffraction (XRD) Studies*

The XRD patterns were recorded using a Philips X-ray generator (PW 1010), using Cu-K_{α} radiation.

Results and Discussion

Differential Scanning Calorimetry (DSC) Studies

The appearance of two endothermal peaks corresponding to the melting of compound **I** and to the dehydration of HP-β-CD is clearly observed in the thermogram corresponding to the physical mixture. It can also be observed the disappearance of the melting point at 223,6^{o}C corresponding to compound **I** in the thermogram of the inclusion complex 1:1.

Powder X-ray diffraction (XRD) Studies

The XR model corresponding to the physical mixture resulted from the simple overlapping of the diffractograms of compound **I** in its crystalline form and of the amorphous diffractogram of HP-β-CD. The diffractograms corresponding to the inclusion complexes were free of interference due to the amorphous state of the product obtained after the liophilic process.

Fourier Transformed Infra Red (FTIR) Spectral Studies

No significant variations were observed in the absorption spectra corresponding to the physical mixtures which resulted from the overlapping of the simple spectra (compound **I** and HP-β-CD). On the other hand, a shift and attenuation in the absorption band corresponding to the carbonyl of compound **I** were observed when the complex is formed by liophilization.

Conclusions

The FTIR, DSC and XRD studies for the complexes showed significant evidence of complexation 1:1 when the complexes are prepared by the freeze drying technique. The results demonstrate the capacity of HP-β-CD to interact with compound **I**.

When the complex was prepared by mixing the powders, it was evident in all cases that there was no true inclusion taking into account a simple physical mixture of both compound **I** and HP-β-CD.

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Macrocyclic Trichothecene Production by the Fungus Epibiont of *Baccharis Coridifolia*

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Abstract: Cultures of the fungus epibiont from the herbaceous shrub *B. coridifolia* yielded four macrocyclic trichothecenes. As these toxins are the same as those found in *B. coridifolia*, the relationship between the plant and the epibiont must be considered as mutualistic.

Introduction

Baccharis coridifolia (Asteraceae) is a herbaceous shrub called “mio mio” o “romerillo”. It is one of the most poisonous plants to herbivorous mammals. Cattle deaths due to feeding on leaves of *B. coridifolia* are recorded in Brazil, Uruguay and Argentina. The toxins present in foliage, stems and seeds of the plant are macrocyclic trichothecenes. These metabolites are mycotoxins typically produced by cultures of *Myrothecium roridum* and *M. Verrucaria*.

Recently, we have reported the presence of a fungus epibiont on meristems in *Baccharis coridifolia* [3].

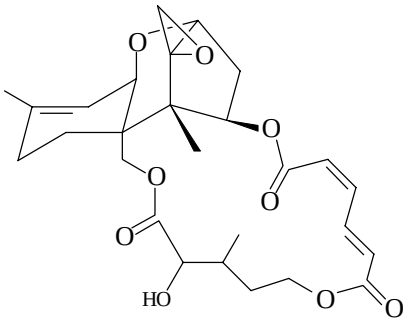
Experimental

The meristems were cultured in Petri dishes with 2% water-agar and incubated in the laboratory conditions for 30 days. The inoculum (blocks of mycelia) of *B. coridifolia* epibiont was first grown out into Erlenmeyer flasks containing a medium of glucose (15,6 g) and corn steep liquor (10 ml) in one liter of distilled water. After 30 days, 5 ml of medium were transferred to Erlenmeyer flasks containing a potato broth medium. The cultures were incubated for 30-60 days at room temperature. The mycelia were separated from the culture broth by filtration and the aqueous filtrates extracted with EtOAc. The EtOAc extract was purified by silica gel column chromatography and by preparative TLC.

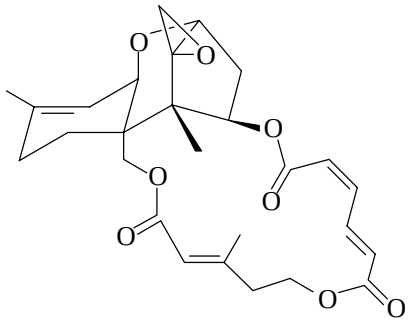
The pure compounds were identified by ^{1}H- and ^{13}C-NMR spectroscopy.

Results and Discussion

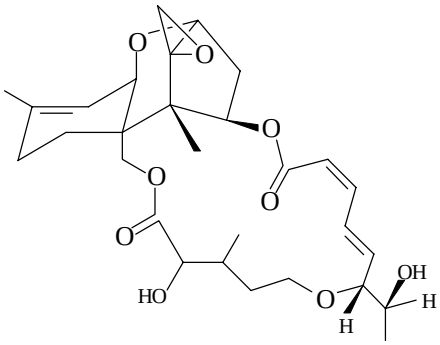
TLC analysis of the fractions obtained by purification of the AcOEt extract of the fungus epibiont of *B. coridifolia*, showed the presence of macrocyclic trichothecenes in two of these fractions. After chromatographic purifications, we isolated four macrocyclic trichothecenes whose structures were assigned by ^{1}H- and ^{13}C-NMR spectroscopy as verrucarin A, verrucarin J, roridin A and roridin E:



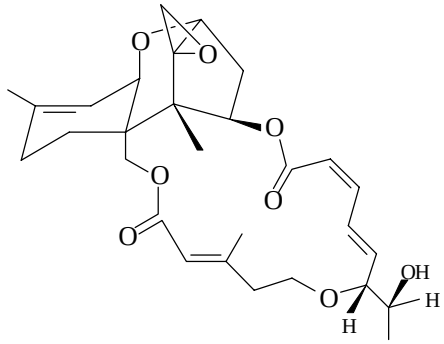
Verrucarina A



Verrucarina J



Roridina A



Roridina E

The fungus epibiont of *B. coridifolia* synthesizes the same macrocyclic trichothecenes as those found in the plant. The position of the epibiont on the meristems places it in an ideal location for colonizing all surfaces of the mature plant as foliage, stems and seeds, that are the parts of the plant where macrocyclic trichothecenes were detected. Taking into account these results, we suggest that the relationship between *B coridifolia* and the epibiont must be considered to be mutualistic, being the epibiont responsible for the presence of trichothecenes in the plant and for its toxicity to herbivorous mammals.

Acknowledgements: The authors are grateful to the University of Buenos Aires (Projects TX-85 and TX-59) and the International Foundation for Science (Project F/1583-3) for partial financial support.

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Sulfated Polyhydroxysteroids from the Antartic Ophiuroid *Gorgonocephalus Chilensis*

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Abstract: Five disulfated steroids and a mixture of monosulfated steroids were isolated from the ethanolic extract of the antarctic ophiuroid *Gorgonocephalus chilensis*. The structures were determined by ^{1}H-NMR, ^{13}C-NMR and FABMS.

Introduction

Sulfated polyhydroxysteroids have been described from a wide variety of marine organisms, in particular sponges and echinoderms. These compounds have exhibited interesting biological activities, in particular, cytotoxic action, inhibition of protein tyrosine kinases and anti-HIV properties [1]. Recently, we have demonstrated the antiviral activity of sulfated steroids isolated from the patagonic ophiuroid *Ophioplocus januarii* against four different pathogenic viruses in humans [2]. We have also isolated three novel sulfated polyhydroxylated steroids from the antarctic ophiuroid *Astrotoma agassizii* [3]. These compounds showed antiviral activity against herpes simples virus, polio virus and Junin virus, which causes a severe disease in humans known as Argentine hemorrhagic fever [4].

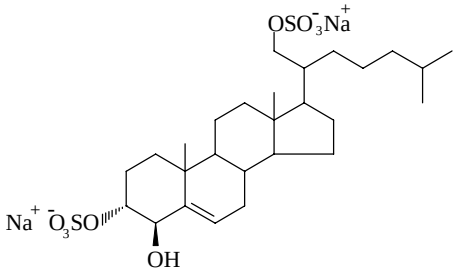
Experimental

The animals were homogenized in ethanol and the aqueous extract obtained after evaporation of the solvent was partitioned between water and cyclohexane. The aqueous phase was extracted with *n*-buthanol and the buthanolic extract was purified by Sephadex LH20 (MeOH). Fractions containing the polar steroids were purified by vacuum-dry column chromatography on sílica gel C-18 (MeOH/H_2O, MeOH) and HPLC. Structural determination of the purified compounds was performed by H-NMR, ^{13}C-NMR, FABMS and by solvolysis reactions.

Results and Discussion

We were able to isolate and characterize five disulfated polyhydroxysteroids (**1**-**5**). The compounds possess a sulfate group at C-21 and with exception of **2**, all have a sulfate group at C-3(α). Compounds

2 and **3** are isomers that differ only in the location of the sulfate group in ring A. Compound **2** presents a sulfate group at C-2(β). Recently, we have isolated steroid **2** from another antarctic ophiuroid *Astrotoma agassizii* (3) and demonstrated its antiviral activity against herpes simplex 2 virus (4).



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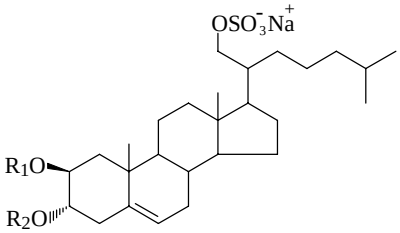
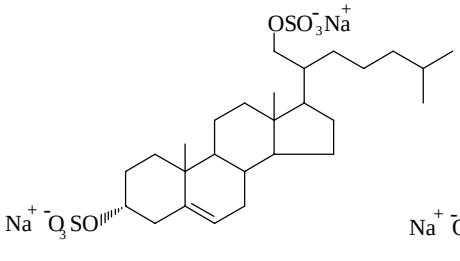


2 $R_1 = SO_3^- Na^+$, $R_2 = H$

3 $R_1 = H$, $R_2 = SO_3^- Na^+$



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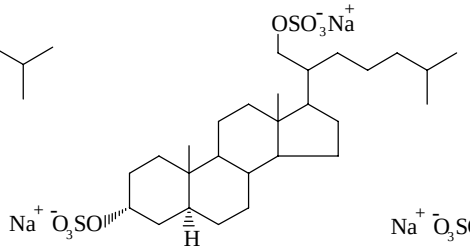

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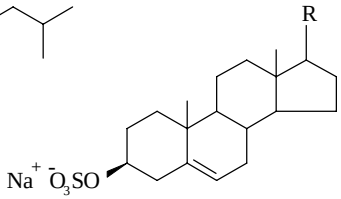

6

Compounds **4** and **5** differ in the insaturation in ring B and were separated by reversed phase HPLC. We have also isolated a mixture of monosulfated steroids at C-3(β). The composition of the mixture was determined by solvolysis of the sulfate group and analysis of the steroid mixture by glc.

Acknowledgements: We are grateful to the University of Buenos Aires (Project TX-85) and the International Foundation for Science (Project F/1583-3) for partial financial support.

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Labidiasteroside A, a Novel Saponin from the Antartic Starfish *Labidiaster Annulatus*

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Abstract: Purification of the ethanolic extract of the starfish L. annulatus led to the isolation of two sulfated glycosides and a pentahydroxylated steroid. One of the saponins contains a novel pentasaccharide chain attached to C-6 of the steroidal aglycone.

Introduction

Starfish are characterized by the content of saponins, toxic compounds acting as defense agents against predators [1]. These compounds present a sulfate group at C-3 and a oligosaccharide moiety at C-6 of the steroidal aglycone. In continuation of our studies on antarctic echinoderms [2] and with the aim of evaluating the antiviral activity of the secondary metabolites isolated from these organisms, we have investigated the ethanolic extract of the starfish *L. annulatus*.

Experimental

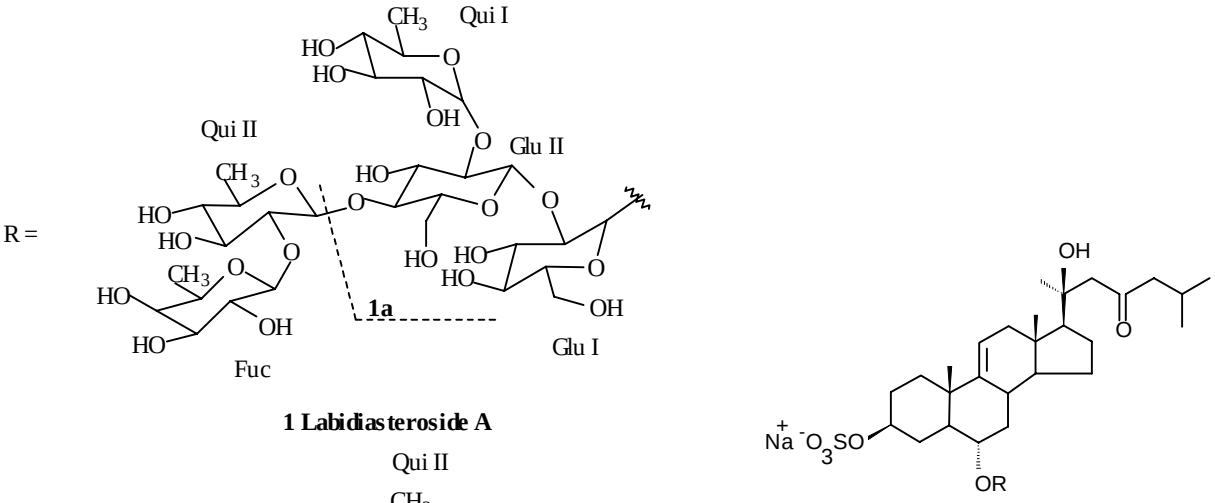
The organisms were extracted with ethanol and the aqueous extract was partitioned between water and cyclohexane. The aqueous phase was eluted through a column of Amberlite XAD-2, washed with water and eluted with methanol. The methanolic extract was purified by chromatography on Sephadex LH 60 and vacuum-dry column chromatography on silica gel C-18, using mixtures of methanol:water and methanol. Fractions containing the polar compounds were purified by HPLC.

Results and Discussion

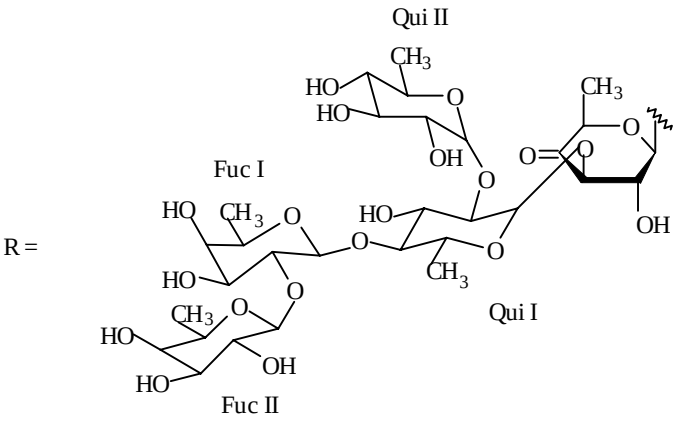
Purification of the ethanolic extract from *L. annulatus* led to the isolation of two sulfated pentaglycosides (**1**, **2**). Both compounds show the same steroidal aglycone and differ in the oligosaccharide chain. Saponin **1** contains a novel oligosaccharide chain not previously reported for this type of compounds. In order to determine its structure, we performed spectroscopic studies (^{1}H-NMR, ^{13}C-NMR,

FABMS) as well as acid hydrolysis to obtain the monosaccharides, which were analyzed by glc as the peracetilated alditols. Enzymatic hydrolysis of saponin **1** with a glycosidase mixture of *Charonia lampas* rendered triglycoside **1a**.

On the other hand, purification of the less polar fractions led to the isolation of (25S)-5α-cholestane-3β,6β,15α,16β,26-pentaol. The configuration of C-25 was determined as *S* by correlating ^{1}H-NMR data of their (+)-(*R*)- and (-)-(*S*)-α-methoxy-(α-trifluoromethyl)-phenylacetic acid esters with those of related steroids.



1 Labidiasteroside A



2 Ovarian asterosaponin 1

Acknowledgements: We are grateful to the University of Buenos Aires (Project TX-85) and the International Foundation for Science (Project F/1583-3) for partial financial support.

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Bioactive Steroidal Glycosides from the Starfish *Anasterias Minuta*

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Abstract: Cytotoxic fractions obtained by purification of the ethanolic extract of *Anasterias minuta* contain sulfated hexasaccharide glycosides. These compounds show antifungal activity against *Cladosporium cucumerinum*.

Introduction

Extracts and saponins isolated from starfish show a broad spectrum of biological effects: cytotoxic, hemolytic, antifungal and antiviral activities [1]. Although a high number of sulfated steroidal glycosides from starfish have been characterized in the last ten years [2], only a few studies concerning the biological activities of pure compounds have been reported. With the aim of correlating the antifungal activity of these compounds with their structures, we isolated and purified the glycoside fraction from the starfish *Anasterias minuta* and evaluated the antifungal activity of the pure saponins against *Cladosporium cucumerinum*.

Experimental

The organisms were extracted with ethanol and the aqueous extract was partitioned between water and cyclohexane. The aqueous phase was eluted through an Amberlite XAD-2 column, washed with water and the steroidal glycosides eluted with methanol. The methanol extract was purified by vacuum-dry column chromatography on silica gel C-18, using mixtures of methanol: water and methanol, and by Sephadex LH 60. Fractions containing the bioactive compounds were purified by reversed phase HPLC. The steroidal glycosides were characterized by ^{1}H-NMR, ^{13}C-NMR, ^{1}H-^{1}H COSY, HETCOR, FABMS and by enzymatic and acid hydrolysis.

Results and Discussion

Fractions obtained by purification of the ethanolic extract of the starfish *Anasterias minuta* by reversed phase C-18 chromatography were monitored with respect to their cytotoxic action against

Artemia salina [3]. The bioactive fractions contained sulfated steroidal glycosides and were further purified by Sephadex LH60 and HPLC. We were able to characterize three glycosides containing the same hexasaccharide chain but different steroidal aglycone structure. Acid hydrolysis of these glycosides and derivatization and analysis by glc of the monosaccharides showed the presence of quinovose, xylose, fucose and galactose in the ratio 2:1:1:2. Enzymatic hydrolysis with *Charonia lampas* glycosidase mixture rendered the corresponding triglycosides containing quinovose (1→2)-xylose (1→3)-quinovose attached at C-6 of the steroidal aglycone. The antifungal activity of the isolated glycosides was evaluated against *Cladosporium cucumerinum* [4] and correlated with the steroidal aglycone structure present in each glycoside.

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Bioactive Metabolites Produced by Fungi Cultures

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Abstract: A screening of metabolites guided by antimicrobial and citotoxic bioassays was conducted with several fungi. The bioactive compounds were isolated and identified from the active extracts.

Introduction

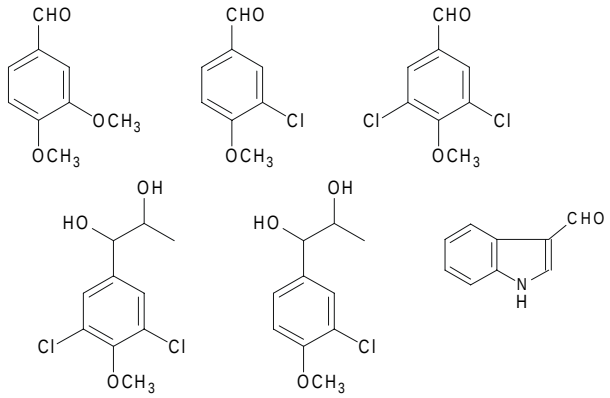
As fungi are increasingly being investigated for their production of biologically active secondary metabolites since they are known to produce compounds with a variety of biological activities, we undertook a screening program for antifungal and antibacterial fungal metabolites.

Results and Discussion

Different strains of fungi were cultured in small scale. Extracts of the mycelium and medium were made. The extracts were bioassayed. Antibiotic activity against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus and Candida albicans*, and cytotoxicity against different tumor cell lines were assayed. The fungi with active extracts were cultured in a greater scale. From a first collection of ten fungi, two were selected because of their antibiotic activity against Gram positive bacteria. These strains were *Bjerkandera adusta* and *Coriolellus malicola.*

The extracts of these cultures were fractionated by vacuum chromatography and then the active compounds were separated and purified by preparative thin layer chromatography or HPLC. The pure compounds were identified by spectroscopic methods, 1D and 2D NMR and Mass Spectrometry.

The following compounds were isolated and identified from the extract of the culture of *Bjerkandera adusta*. The halogenated compounds are responsible for the antibiotic activity.



The bioactive compounds isolated and identified from *Coriolellus* malicola were known triterpene acids.

Experimental

Most of the fungi were culture in malt extract medium at 25ºC. For the culture of *B. adusta* a special medium was employed [1].

Acknowledments: We thank LANAIS-EMAR (CONICET-FCEN, UBA) for the mass spectra, UM-YMFOR (CONICET-FCEN, UBA) for the NMR spectra, Dras Bals de Kier Hoffe and Puricelli (Instituto Roffo) for the cytotoxicity assays and CONICET, Fundación Antorchas and Universidad de Buenos Aires for their partial financial support.

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Microbial Hydroxylation of Tedonodiol with Cultures of *Aspergillus Niger*

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Abstract: Microbial hydroxylation of tedonodiol, an eremophilane alcohol, was carried out with *Aspergillus niger* cultures, yielding the 2α - hydroxyderivative.

Introduction

Since 1986, we have performed a project enclose in a extraction of carbonyl α,β-insaturated compounds from natural sources and chemical transformations of them, in order to provide metabolites to be tested as gastrointestinal citoprotective agents[1]. In this context we have carried out biotransformation reactions of tedonodiol, an eremophilane alcohol, isolated from *Tessaria dodoneaefolia* [2]. Several *Aspergillus niger* strains were used with this purpose.

Experimental

Culture media

Modified Czapek broth [3] was used for performed bioconversions assays, and agar Czapek was used to maintainning the strains.

Strains

Aspergillus niger ATCC 11394, Aspergillus niger Buenos Aires and a regional *Aspergillus niger* strain isolated from leaves of *Artemisia douglassiana* Besser.

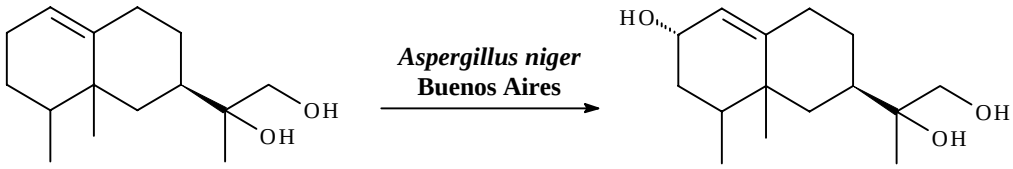
Culture conditions

Biotransformations were carried out by two steps fermentation procedure [4]. Fermentations were performed in conical flasks (3 x 125 ml) with 25 ml of culture medium, on shaken at 180 r.p.pm. and incubated at 28^{o}C. Substrate was dissolved in DMSO and added to 72 h old cultures (final concentra-

tion 1mg.ml^{-1}). The process was continued for 7 days. Biotransformation product was recovered from the broth by liquid - liquid extraction with Et_2O. Extracts were concentrated, and the solid was purified by C.C. with *n*-hexane - EtOAc mixtures of increasing polarity.

Results and Discussion

Only the fermentation process carried out with *Aspergillus niger* Buenos Aires yield a more polar product than tedonodiol in the fraction *n*- hexane - EtOAc (20 : 80). By the comparison of the sustrate and product ^{1}H - NMR spectra it was possible determinated that an α - hydroxyl group incorporated on C-2 A new signal at δ 4.12 *ddd* (J_1=J_2= 2.9 Hz y J_3= 3,8 Hz) corresponding to the new allylic oxygenated methine group, confirm this fact.



Usually, microbial hydroxylation shows high *regio*selectivity on molecules with activated positions [5], like tedonodiol C-2 allylic position.

Acknowledgements: This work was performed with support of CONICET and U.N.S.L. (Project 7301).

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Synthesis and Physicochemical Study of a Quinoxaline Derivative with Potencial Antineoplasic or Anti-HIV Activity

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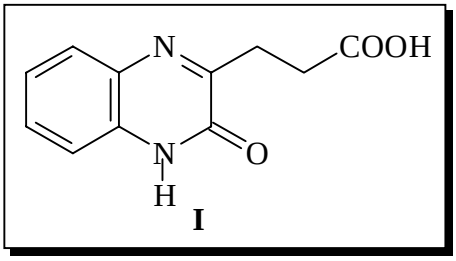
Abstract: Kinetics of the synthesis of 3-[3-quinoxaline(1H)-one]propionic acid (**I**) were performed. This compound was achieved from reaction between o-phenylenediamine and α-ketoglutaric acid under different experimental conditions, and it was sent to the National Cancer Institute (USA) for its pharmacological evaluation.

Introduction

Trying to gain more insight into the nature of heterobicyclic chromophores, leading to potential antitumoral compounds [1], we analyzed the influence of an alkylcarboxilic chain in the C-3 of the heterocycle **I** upon the pharmacological activity [2].



I

Experimental

Anelation was achieved by reaction of o-phenylenediamine with α-ketoglutaric acid in organic solvents and also in aqueous buffer solutions over a pH range –0.24 -11.5, at room temperature. Kinetics were performed by UV spectrophotometry at 350 nm.

Compound **I** was insoluble in water so it was transformed into its ammonium salt in order to able the evaluation of its biological activity.

Results and Discussion

Compound **I** was obtained with good yields (85%) in lab-scale using anhydrous methanol as reaction solvent at room temperature. It was identified by qualitative and quantitative analysis and also by its spectroscopic properties (UV, IR, ^{1}H NMR).

Kinetic studies determined that two competitive reactions take place in acidic buffers (pH –0.24-5.8) with a pseudo first-order rate constant for **I** formation, $k_{obs} = 2.18 \pm 0.05 \times 10^{-2}$ min^{-1}. The reaction is not catalyzed by acids and occurs via formation of several open intermediates.

It is concluded that the presence of the alkylcarboxilic chain in C-3 of the heterocycle is responsible for the lack of reactivity, not only in basic buffer solutions but also in organic non-polar solvents, if compound **I** is compared with other non-acidic quinoxalinone derivatives descripted previously [3,4].

Acknowledgements: We thank to Karina Piton and Laura Belinque for their technical assistance.

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Effect of Substituents on the O-O Bond Rupture of Different Organic Peroxides in Toluene Solution

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Abstract: The thermal decomposition reaction of cyclic organic peroxides was studied in toluene solution in a wide temperature range. The kinetic data show an important substituent effect on the unimolecular homolysis of the O-O bond of these molecules.

Introduction

Previous studies [1] demonstrated that a solvent effect is operative on the kinetic parameters of the thermal decomposition reaction of cyclic organic peroxides in solution.

In this work, effects of substituents on the O-O bond homolytic rupture of s cyclic organic peroxides with structures like 1,2,4,5-tetroxanes, 1,2,4-trioxanes, 1,2,4,5-trioxazines and 1,2,4,5,7,8-hexaoxacyclononanes were evaluated.

Experimental

Organic peroxides were prepared in this laboratory with methods described elsewhere [2]. The cyclic peroxides remaining in the solution were quantitatively determined by GC.

Results and Discussion

The thermal decomposition reaction of cyclic organic peroxides reported in this work follow a first order kinetic law up to *c.a.* 50% peroxide conversion. The rate constant values at different temperatures were determined. A linear relationship between the activation enthalpies and entropies of the unimolecular thermolysis reaction of the cyclic peroxides can be found (Fig. 1). The ranges of activation enthalpies and entropies ($\Delta\Delta H^{\#}$: 22.2 kcal/mol and $\Delta\Delta S^{\#}$: 54.2 e.u.) are large compared to the probable errors of those parameters. The highest activation parameter values were found for nine membered ring (1,2,4,5,7,8-hexaoxacyclononanes derived from acetone, diethylketone and cyclohexanone).

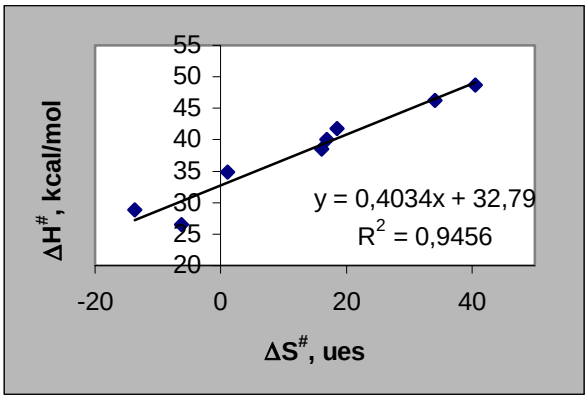

Figure 1. Compensation Law according to Leffler criteria [3] applied to cyclic organic peroxides in toluene.

The lowest values obtained corresponded to a six membered ring, the 1,2,4,5-tetraoxacyclohexanes derived from acetone. In both series considered (six or nine members rings) the cyclic peroxides with methyl groups as substituents showed the lowest activation parameters, probably because of the reduce steric hindrance and highly interaction with the solvent.

The slope of the representation in Fig. 1 corresponds to the "isokinetic temperature" (β) which in this case is 130.4°C.

Acknowledgements: This research project was financially supported by the Facultad de Ingeniería, the SECyT de la Uiversidad Nacional del Centro de la Provincia de Buenos Aires and CIC de la Provincia de Buenos Aires.

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Thermal Decomposition Reaction of cis-6-Phenyl-5,6-(2-phenyl-propilydene)-3,3-tetramethylene-1,2,4-trioxacyclohexane in Different Solvents

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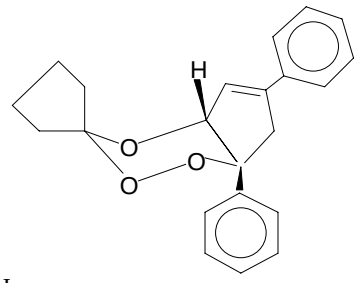
Abstract: The kinetics of the thermal decomposition reaction of cis-6-phenyl-5,6-(2-phenyl-propilydene)-3,3-tetramethylene-1,2,4-trioxacyclohexane (**I**) was investigated in the temperature range of 100-130°C in selected solvents of different physicochemical properties to evaluate a solvent effect on the reaction.

Introduction

It is interesting to mention that the antimalarial activity of the plant extract Qinghaosu is associated with the presence of the 1,2,4-trioxane ring in molecules of compounds (Artemisinin) found in its composition [1].



I

Here, available kinetic data on the thermal decomposition reaction of **I** in solvents with different physicochemical properties are presented to learn about the solvent effect on its thermolysis.

Experimental

Materials

The trioxane **I** was prepared by methods described elsewhere [2]. The organic solvents were com-

mercial analytical reagents purified by standard techniques.

Kinetic methods

Glass ampoules half filled with the appropriate **I** solution were thoroughly degassed under vaccum and immersed in a thermostatic bath at selected temperatures. The remaining concentration of **I** in the reaction solution was quantitatively determined by RP-HPLC (UV detection). In benzene solvent, kinetic data were obtained by GC analysis (FID detection). The reaction products were identified by GC-MS and RP-HPLC.

The first order rate constant values were obtained by least mean squares treatment of the data plotting the values of the [**I**] vs. time. The activation parameters were calculated according to the Eyring equation [3].

Results and Discussion

Rate measurements on the thermal decomposition of **I**, up to at least *c.a.* 60% of **I** conversion in each solvent, show an evident effect of the solvent in the temperature and initial concentration ranges of 100-130°C and 0.36-1,70 x 10^{-3} M, respectively, (Table 1). The rate constant values increase as the solvent polarity increases.

Table 1. First-order rate constant values at 120°C in solution.

SOLVENT	10^3 x [I], mol/L	10^6 x k_{exp}, s^{-1}
n-hexane	0.60	4.00
benzene	0.50	93.3
acetonitrile	0.65	173
metanol	0.36	390

The temperature effect was evaluated by the Arrhenius equation and the corresponding activation parameters for the O-O bond unimolecular homolysis of **I** were calculated. The first step of the reaction mechanism is the formation of a biradical which later decomposes.

A stepwise mechanism was confirmed by analysis of the reaction products.

Acknowledgements: This research project was financially supported by CONICET, PROGRAMA LADECOM, Facultad de Ingeniería-SECyT de la UNCPBA y CIC de la Provincia de Buenos Aires.

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Thermal Decomposition Reaction of Acetophenone Cyclic Diperoxide in Solvents of Different Physicochemical Properties

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Abstract: The thermal decomposition reaction of acetophenone cyclic diperoxide (trans-3,6-dimethyl-3,6-diphenyl-1,2,4,5-tetroxane; APDP) at the initial concentration of *c.a.* 0.01 mol kg^{-1} and temperature ranges of 135.5 to 185.0° C has been investigated in dioxane and acetonitrile solutions, and in an 2-propanol/benzene mixture.

Introduction

The aim of this work is to study the thermal decomposition of acetophenone cyclic diperoxide (APDP) in solvents of different physicochemical properties, in order to correlate the kinetic parameters of the reaction and to compare the results with the previous studies in benzene solution [1].

Experimental

The diperoxide was prepared and conveniently purified as described elsewhere [2], and the solvents employed were purified by standar methods [3]. The 2-propanol was destilled from ethylenediaminetetraacetic acid (EDTA) to remove traces of metallic ions.

The diperoxide remaining in the solutions and the reaction products were determined by RP-HPLC.

Results and Discussion

The APDP thermolysis was made in the temperature range of 135,0 - 185,0°C at diperoxide initial concentration *c.a.* 0.01 $molkg^{-1}$. The observed rate constant values for APDP thermolysis at 150,0°C in various solvent are shown in Table 1. The reaction follows a first - order kinetic law up to at least c.a. 50% APDP conversion. In this case, the reactivity of the APDP is higher in polar solvent than in no polar-solvent.

Table 1. First order rate constant values for APDP thermolysis in different solvents at 150,0°C.

Solvent	10^5 k; s^{-1}
Acetonitrile	1,46[a]
Dioxane	1,85
2-propanol/benzene	6,9
Benzene[b]	0,51

[a] 153°C

[b] Ref. (1)

The experimental data were statistically treated in order to verify the existence of a true isokinetic relationship and to obtained the value of the isokinetic temperature (β=154,5°C). This value is compared with an other obtained by a different criteria described for kinetic data treatment.

The yields of the reaction products (acetophenone, methane, ethane) supports a stepwise mechanism and make possible to discuss the nature of solvent effects on the reaction.

Acknowledgements: The authors thank the Facultad de Ingeniería and the SECyT of the Universidad Nacional del Centro de la Provincia de Buenos Aires and the Comisión de Investigaciones Científicas de la Provincia de Buenos Aires (C.I.C.) by their sponsorship.

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Synthesis and Bioactivity of Teasterone and Typhasterol Analogs

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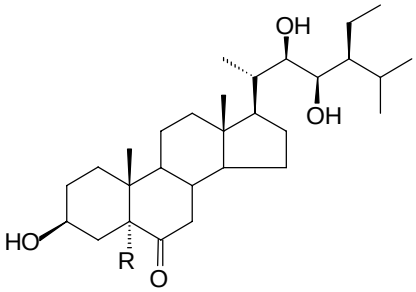
Abstract: Four brassinosteroids analogs of homoteasterone and homotyphasterol bearing 5α-OH and 5α-F groups have been synthesized and their bioactivities evaluated.

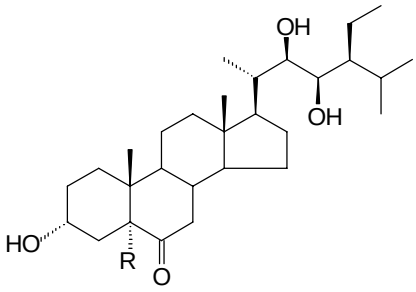
Introduction

Brassinosteroides are a new class of phytohormones with properties of enhancing plant growth and plant cell division. Since the discovery of brassinolide, in 1979 –first compound of this series— a wide variety of research programs arose concerning biosynthesis, mechanisms of action [1] and possible applications in agriculture [2].

It has been already stablished that the presence of a substituent at C-5 with the ability to form an hydrogen bonding with the substituent of C-3 may change the bioactivity response of these compounds [3]. In our laboratory we have already synthesized two natural brassinosteroids homoteasterone (**I**) and homotyphasterol [4] (**II**) and in this work we introduce the synthesis of four new analogs in which the 5α-H group of compounds **I** and **II** has been replaced by a 5α-OH group (compounds **III** and **IV**) or a 5α-F group (compounds **V** and **VI**), respectively.



R = H 28-homoteasterone **I**
R = OH **III**
R = F **V**

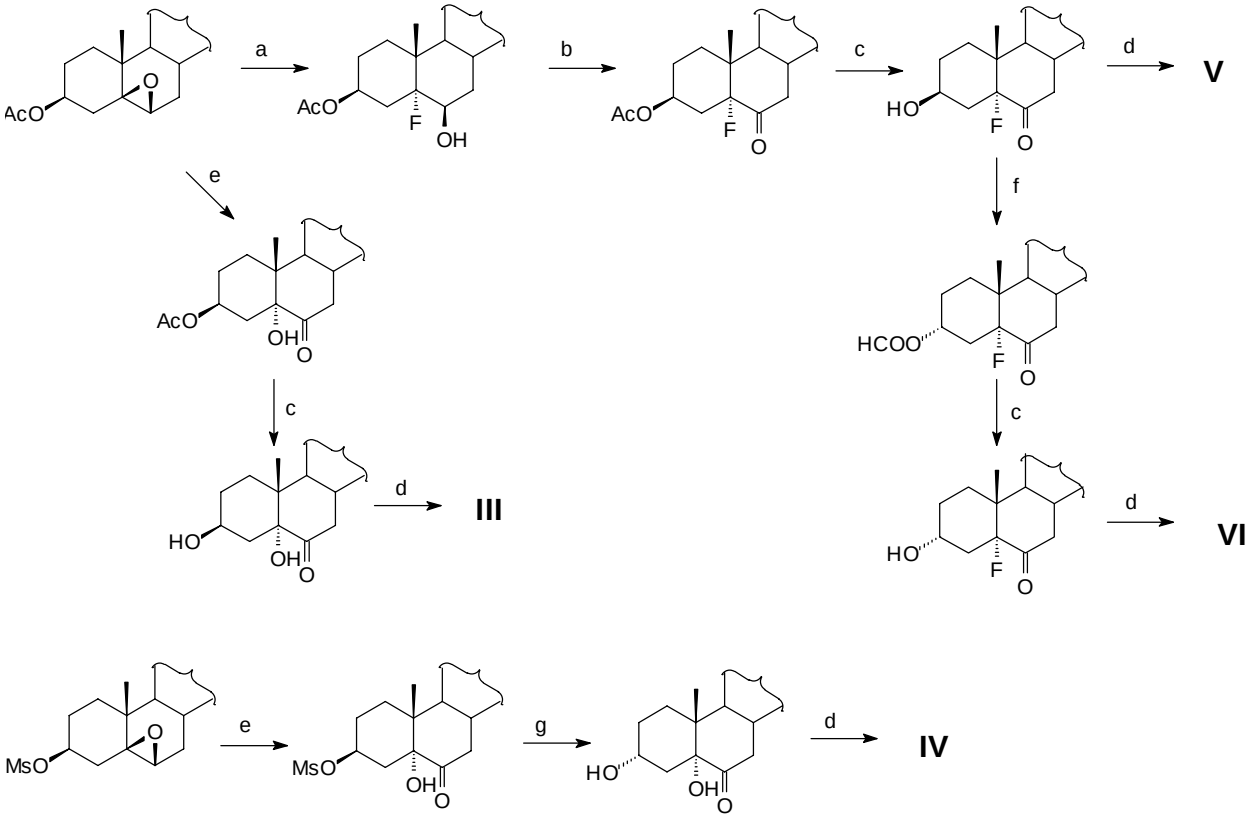


R = H 28-homotyphasterol **II**
R = OH **IV**
R = F **VI**

Bioactivities of new compounds have been evaluated with the rice lamina inclination bioassay [5] using the mentioned natural brassinosteroids as standards.

Results and Discussion

New compounds have been synthesized as shown in the following scheme.



a) $BF_3{\cdot}Et_2O$ / Et_2O / t.a. b) PCC / CH_2Cl_2 / t.a. c) K_2CO_3 / MeOH / THF / t.a. d) K_2OsO_4**.** $2H_2O$ / $(DHQD)_2Phal$ / methansulfonamide / $K_3Fe(CN)_6$ / K_2CO_3 / t-BuOH / H_2O / t.a. / e) Jones / t.a. f) DEAD / PPh_3 / HCOOH / benzene / t.a. g) Li_2CO_3 / DMF / water / reflux.

All the compounds have been characterized by ^1H, ^{13}C and ^{19}F NMR spectroscopy. First data concerning bioactivities of the analogs show the same decreasing effect when an OH or a F group were introduced at C-5. This result may induce some interesting information concerning biochemical action of these compounds at a molecular level.

Acknowledgements: This work has been done with grants from UBACyT and CONICET. We wish to thank UMYMFOR for spectroscopic determinations.

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Chemo- and Stereoselective Reduction of Polyfunctional Carbonyl Compounds by *Mucor rouxii*

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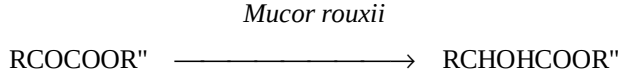
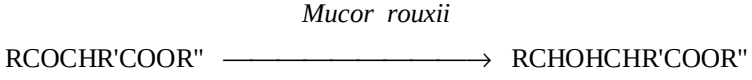
Abstract: Several polyfunctional carbonyl compounds, such as α- and β-ketoesters, were chemo- and stereoselectively reduced by *Mucor rouxii* cultures in water and in organic solvents. Results show that reductions can be carried out in a variety of organic solvents.

Introduction

In recent years, microorganism whole cells as sources of biocatalysts have widely been used in the laboratory and industry [1]. It is well known the application of baker's yeast oxidoreductases in reduction of carbonyl compounds such as aldehydes, ketones, ketoesters and ketoacids [2-4]. Recently, it has been reported their use in presence of organic solvents [5]. In order to extent this methology to other microorganisms, we have studied the behavior of fungus *Mucor rouxii* in the reduction of polyfunctional carbonyl compounds, such as α and β ketoesters:





R: $-CH_3$; $(CH_3)_2CH-$; $C_6H_5CH_2CH_2-$; $BrCH_2-$
R': H; $-CH_3$
R": CH_3CH_2-, $(CH_3)_2CH-$, $CH_3OCH_2CH_2-$,

Mucor rouxii is a saprophytic and dimorphic fungus with spores that can germinate as a cenocytic mycelium or as yeast-like cells.

Experimental

Oxidoreductase activity was assayed on the biomass of fresh cultures, grown in rich medium YPG (yeast extract, peptone, glucose) harvested immediately before the assays. The incubations with the different substrates were perfomed in a nutrient-free medium, in order to avoid the putative metabolization of the substrates by the fungal cells. Biomasses obtained from cultures at different growth stages were incubated with different organic solvents such as ethyl acetate, toluene, hexane, dioxane, etc, alone or in biphasic systems mixed with sterile water; pure water and water plus glucose were also used. The substrates to be analyzed were added to these systems and incubations were performed at 28°C with agitation at 120 rpm for different times. The reaction was stopped by centrifugation at 10000 rpm; the supernatants were removed and when applied, water phases were extracted with ethyl acetate. Extracts were analyzed by GC and isolated products identified by spectroscopic methods: ^{1}H NMR and MS. Optical purity of products was determined by specific rotation.

Results and Discussion

It was observed the complete and chemoselective carbonyl group reduction of β-ketoesters to give the correponding β-hydroxyesters, keeping ester carbonyl group unchanged by working with both mycelium and yeast-like cells. This behavior was observed in aqueous medium and in mixtures of water and organic solvents such as toluene and hexane by using yeast like-cells. Microorganism suspension in pure hexane showed a 100% conversion to alcohol in 21 hs. On the other hand, pure toluene and dioxane afforded lower yields. Stereoselectivity was variable and dependent on the polarity of the solvent. High stereoselectivity (93% e.e. of *S*-alcohol) was observed when the biocatalytic reduction was performed with yeast-like cells in hexane. In water, % e.e. decreased in both morphologies.

Acknowledgements: We thank CONICET for CPM fellowship and partial financial support.

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Lipase-Catalyzed Polymerization of Glycerol and Dicarboxylic Acids in an Organic Medium

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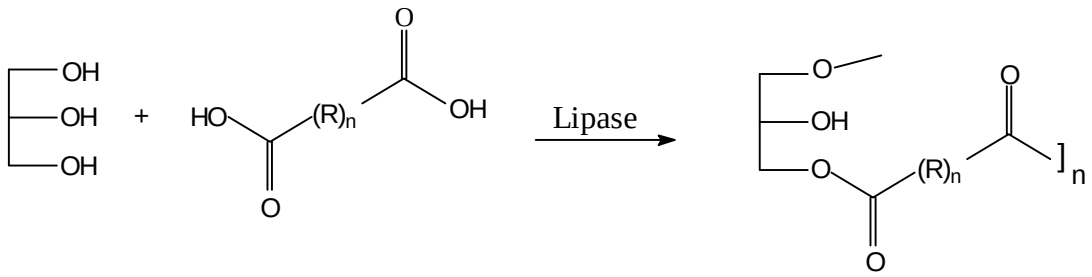
Abstract: Lipases from different sources catalyze the polyesterification of glycerol and several dicarboxylic acids in presence or organic solvents

Introduction

Enzymatic polymerizations are receiving much attention as a new method for polymer production since biocatalysis is expected to generate environmentally acceptable properties such as biodegradability and biocompatibility [1]. The opportunities available in the use of enzymes in polymer science include enhanced control of regioselectivity, enantioselectivity, molecular weight and dispersity and the ability to synthesize entirely new polymers [2].

Lipases in organic solvents are efficient catalysts in polyesterification [3] and oligomerization reactions. In these polymerizations, the use of traditional chemical catalysis is limited because catalysts tend to have an undesirable effect on the subsequent polymerization reactions.

Lipase-catalyzed condensations reported in literature describe use of hydroxyacids and diols as hydroxylated monomers, but at this moment poliols, such as glycerol, have not been investigated [3]. Here we report the lipase-catalyzed regioselective polyesterification of glycerol and several carboxylic acids.



R: $-(CH_2)_2-$; $-(CH_2)_8-$; $-C_6H_4-$ (o and p)

Experimental

The procedure involved addition of enzyme to a solution of glycerol and the carboxylic acid in the appropriate solvent with molecular sieves 0.4 nm when indicated. The suspension was held at 200 rpm and 30°C for 72 h. Disappearence of monomers was monitored by TLC. The enzyme was filtered off and washed with solvent. The filtrate was evaporated *in vacuo* and the resultant polymer was dried. The product was analyzed by UV-MALDI-TOF-MS, NMR and FTIR.

Results and Discussion

Enzymatic polymerization was performed under different experimental conditions. Lipase-catalyzed polymerization was studied with several enzymes such as porcine pancreatic lipase, *Candida rugosa* lipase, *Mucor miehei* lipase and *Candida antarctica* lipase (CAL). Best results were obtained with CAL Different solvents were used: dioxane, tetrahydrofuran, etc.

Average number (M_n) (1695-1979) and weight average (M_w) (1704-2110) molecular masses of products obtained by polymerization in presence of molecular sieves were calculated from UV-MALDI-TOF-MS spectra.. Spectra of lipase-catalyzed polymers showed a remarkable monodispersity (Dp: 1.01-1.07) which is difficult to achieve by conventional polymerization procedures.200 MHz ^{1}H-NMR spectra of polymers showed broad signals between 4.10 and 4.30 ppm. Lower field signals were not observed indicating that secondary hydroxyl is not esterified and that lipase catalyzes polycondensation in a regioselective way. Different experimental conditions changed molecular weight of polymers but not its regioselectivity. Highest molecular weights were obtained by withdrawing water from the system with molecular sieves and anhydrous dioxane as solvent. Without molecular sieves only oligomers were obtained.

In summary, the lipase-catalyzed polyesterification here presented provides a simple, regioselective and economical method for preparing polyhydroxylated low molecular weight polyesters from glycerol and dicarboxylic acids. This enzymatic approach has the advantage of obtaining a complex structure polymer which is difficult to be performed in a satisfying way by traditional polymerization methods.

Acknowledgements: We thank Dr. Rosa Erra-Balsells and Dr. Hiroshi Nonami, Ehime University for realization of UV-MALDI-TOF-MS and CONICET for partial financial support.

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Electrosynthesis of 3-Nitrophenotiazine. Nitration in Non-Aqueous Solutions

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Abstract: The nitration of Phenothiazine (PHEN) in acetonitrile (ACN) in the presence of excess $NaNO_2$ has been studied in detail. First, the electrochemical behavior of the reactants was investigated by cyclic voltammetry to determine the electrolysis conditions. Controlled-potential electrolysis was used for the electrosynthesis.

Introduction

Although the nitration of organic compounds is an area in expansion since the beginning of the century principles, its interest has not diminished. In this way, new nitration methods that outline new challenges for the interpretation of the mechanisms have appeared. The principal interest resides in that the nitrated products are fundamental source of diverse synthetic products [1-3]. The traditional nitration methods, which use aggressive mixtures of nitric and sulfuric acid, are being left, due to the high cost of the effluents treatment [4]. The electrochemical methods are an excellent way to produce the nitration intermediates [5]. Besides, it constitutes an interesting alternative procedure from the mechanistic point of view.

Experimental

An EG & PAR model 273 potensiostat-galvanostat was used for cyclic voltammetry (CV) and controlled-potential electrolysis (CPE) measurements, using a conventional three-compartment Pyrex cell, stirring with a Teflon paddle for the EPC. The working electrodes were Pt wires of area 0.235 cm^2 for CV, and Pt electrodes of larger area (ca.16 cm^2) for CPE. The counter-electrode was a stainless steel foil of large area. All the potentials were referred to a saturated calomel electrode (SCE) and were corrected for *IR* drop by positive feedback techniques.

The disappearance of the reagent and the consequent apparition of the nitrated product were followed by HPLC analyses. 3-Nitrophenotiazine (3-NO_2PHEN) was thermally synthesized as described in the literature [6].

Results and Discussion

CV studies shows that the oxidation of PHEN to proceed in two reversible one-electron steps, giving the radical cation $PHEN^{+\bullet}$ and the dication $PHEN^{++}$, respectively, peak I (E_{pI} = 0.58 V) and peak II (E_{pII} = 1.00 V). Since for the electrosynthesis we are only interested in the generation of the $PHEN^{+\bullet}$, the CV were registered until 0.8 V. The peak current I_{pI} shows a linear dependence on $v^{1/2}$ in the range of sweep rates used (i.e. 0.01 to 0.3 V s^{-1}) and E_{pI} as well as ΔE_{pI} give a constant value on v. This is the expected behavior for a fast diffusion controlled process. At the same potential, the ion NO_2^- is oxidized to NO_2. Nevertheless, CV studies showed that the nitrated product is formed by the reaction between the FEN^{++} (formed by desproportionation of $PHEN^{+\bullet}$ and the NO_2^- ion

CPE was performed at E = 0.5 V. Several samples were taken to different times of electrolysis, following by HPLC the increase of the peak of the product (τ = 23 min). A yield greater than 90% of 3-NO_2PHEN was obtained under optimized conditions. A reaction mechanism is proposed.

Acknowledgements: Financial support from CONICET, CONICOR, FONCYT and the Secretaría de Ciencia y Técnica de la Universidad Nacional de Rio Cuarto is gratefully acknowledged. Patricia Perlo thanks CONICOR for a research fellowship.

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Chemical Characteristics of *Passiflora Caerulea* Sedd Oil and Residual Seed Meal

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Abstract: Seeds from *Passiflora caerulea* were defatted with n-hexane yielding 29,9% of crude oil (dry basis). The crude oil was examined in their physicochemical characteristics. Fatty acid composition value showed only three acids in significative proportion: **16:0, 18:1** and **18:2**. The residual seed meal analysis included: moisture value, ash, metals content, sugars, crude fiber, protein and available lysine.

Introduction

Passiflora caerulea, commonly known as "passion blue flower", is one of the 400 species that belong to the *Passiflora* genre (Passifloraceae family). It is cultivated for ornamentation and, as it is considered to have sedative and anticonvulsive properties, it is being used in homeophatic treatments. Also its fruit is eatable. This research work has investigated the chemical characteristics of *Pasiflora caerulea* seed oil and residual seed meal.

Materials and Methods

The seeds harvested in Olavarría (Province of Buenos Aires, Argentina), were manually separated from the ripe fruit. After having determined their physical characteristics, the seeds were ground. The seed oil was extracted from crushed seeds with n-hexane in a Soxhlet apparatus followed by evaporation of the solvent in a rotary evaporator. The oil content in the seeds was determined gravimetrically. Remaining solvent was removed from the residual meal (45^{o}C-50 ^{o}C, vacuum).

The physical and chemical characteristics of the lipid fractions were determined according to the methods: AOAC, AOCS, IUPAC. The fatty acid composition was analysed by means of gas chromatography/mass spectrometry (GC-MS). The methyl esters of the total fatty acids was investigated spectrophotometrically (FTIR, UV).

The residual meal characteristics were determined according to the methods of the AOAC, AOCS

and specifics.

Results and Discussion

The seed moisture value was 6.5%. The crude oil extracted with n-hexane (soxhlet) turned to be gray, limpid at room temperature with a pleasant smell and a 29,9% (dry basis) yield. It presented the following characteristics: refractive index: (25°C); 1,4709; iodine index: 132; acid value: 2,4; saponification value (mg KOH/g) : 171; unsaponifiable matter (%): 2,6; iodine value of the unsaponifiable matter: 150,5; total phosphorous (μg/g) 127; total sterols (% as sitosterol): 0,27; peroxide index: 2,8.

The acid composition demonstrates that the major components of the *Passiflora caerulea L.* oil are the acids **18:2** (63,1%), **18:1** (17,6%) and **16:0** (10,1%). There is a low concentration of the acid 18:3. 4% of the acid composition belongs to the fatty acids with more than eighteen-carbon atoms.

All the methyl esters ultraviolet spectrophotometric analysis disclosed a low concentration of conjugated diene, triene and tetraene (% C_2 = 0,56; % C_3 = 0,04).

The FTIR analysis of *Passiflora caerulea L.* oil, detected the presence of conjugate diene and the hydroxyl group.

The residual meal proteic content (23,8%) and the available lysine value fulfil the requirements suggested by the Food and Agriculturue Organization of the United Nation (F.A.O.)

From this first explorative research work it is possible to foresee, previous verification of the seed innocuousness and digestibility, a potencial utilization of these seeds, mainly from the nutritional point of view.

Table 1. Chemical composition of residual meal.

Dry material (%)	92,8	Urease activity	0,25
Ash (%)	4,3	Copper (μg/g)	62
Crude Protein (Nx 6,25) (%)	23,8	Calcium (μg/g))	77
Crude fiber (%)	32,5	Phosphorus (μg/g)	3270
Available lysine (g/16g N)	4,49	Zinc (μg/g)	75
Reducing sugars % (as glucose)	7,4	Magnesiun (μg/g)	1640
Non reducing Sugars % (as sucrose)	1,6	Sodium (μg/g)	2500
Hydrolizable Carbohydrates % (as starch)	4,7		

All the results are in dry basis.

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Photodynamic Effect Of 5,10,15,20-Tetrakis(4-Methoxyphenyl) Porphine (TMP) on Hep-2 Cell Lines

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Abstract: The photodynamic effect of 5,10,15,20-tetrakis(4-methoxyphenyl)porphine (TMP) on Hep-2 cell line is reported. The incorporation of TMP was analyzed at different times and photosensitizer concentrations. The irradiation of cell cultures produces cell mortality, while no toxicity was observed in dark condition.

Introduction

Photodynamic therapy (PDT) is based on the administration of a photosensitizer that becomes concentrated in tumor cells and upon subsequent irradiation with visible light in the presence of oxygen, specifically destroy the tumors. Porphyrins and their analogs have attracted much attention as photo-therapeutic agents, for the treatment of tumors in combination with visible light.[1] The photodynamic process of the sensitizers on neoplastic tissues is still not well understood, although it is generally accepted that singlet oxygen ($^1O_2$), produced after the exposure of the sensitizer to light, is the main species responsible for cell inactivation. Therefore, the photodynamic effects of porphyrin derivatives on cells are very interesting for the development of new photosensitizers to PDT.[2]

Experimental

Cell cultures. Hep-2 larynges carcinoma human cell line.

Photosensitizer uptake. The incorporation of TMP by Hep-2 cells was determined by fluorescence spectroscopy as described in reference [3].

Irradiation. Visible light. Slide projector with lamp of 150 W (26 mW/cm^2).

Citotoxicity. The viability of the cells was estimated by microscopy using trypan blue (TB).

Results and Discussion

Uptake of TMP. TMP was incorporated for different times of incubation with Hep-2 cells. Several concentrations of TMP (1-10 μM) were used in the medium. The uptake increases initially very rapid at low incubation times (<5h) and tends to a saturation value after long incubations (≥24h). The kinetic of incorporation increases with TMP concentration reaching a similar value after 24 h of incubation.

Citotoxicity under dark. Cell toxicity induced by TMP was analyzed in dark condition at different concentrations of photosensitizer (1-10 μM) and several incubation periods. No toxicity, in terms of cell survival, was detected at any evaluated time for 24 h..

Citotoxicity under irradiation conditions. The cells were irradiated with visible light, after incubation with TMP for different periods. The results show an increase in the cell inactivation with an increase in the irradiation time. A higher effect was observed when the cells were longer treated with TMP. Thus, when TMP was incorporated for 45 min, a mortality of ~50% was reached in 30 min of irradiation, while this value increases to ~90% of lethality when the TMP was incorporated for 24 h. On the other hand, no toxicity was observed in dark condition or by irradiation de cell cultures without TMP. Therefore, the cell mortality, obtained after irradiation with visible light of the cell cultures, correspond to the photosensitized effect of TMP produced by the visible irradiation.

Acknowledgements: Authors are grateful to Fundación Antorchas, SECYT of the Universidad Nacional de Río Cuarto and Consejo Nacional de Investigaciones Científicas y Técnicas of Argentina, for financial support.

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Synthesis and Characterization of Some N-Heterocyclic Carbohydrate Derivatives

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Abstract: The nucleophilic bimolecular substitution on 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose with NH_2-heterocyclic derivatives allows us to obtain some new compounds with potential biological activities. The characterization of them as well as a discussion of their reactivities toward sulfur analogues are present.

Introduction

The synthesis of heterocyclic compounds containing a carbohydrate moiety has been of great interest due to the possibility to obtain nucleosides and their analogues, which have, in some cases, therapeutic importance [1]. Due to this interest, in our laboratory we had carried out researches on S-alquilation of bioactive heterocyles [were the alkyl group is the 6-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopiranose)] [2]. Following with those experiences, we decided perform the synthesis of N-alkyl heterocycles. In this work we present the obtained results.

Experimental

The S-alkylation of sulfur heterocycles was carried out by reaction of thiol group on 6-*O*-tosyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopiranose. However, when this procedure was applied to amino heterocycles it did not provide the desired results. To achieve the substitution we must to modify the nature of living group on C-6. Using a better nucleofugue and treated this intermediate product *in situ* with some amino heterocycles we could obtain the N-alkylated products with moderated yields.

Results and Discussion

According with the obtained results, it is evident that the nucleofilicity of sulfur is higher than the nitrogen. This behavior could be attributed to a better superposition of ***n*** orbital of nitrogen with the aromatic ring, so, the non bonding electrons are disable to made the nucleophilic attack, and their re-

activity decreases. In order to accomplish an experimental comprobation, we performed the substitution using an aliphatic amine on tosyl derivative. As was expected, we can isolate the N-substitution product but with moderated yield. When we used 2-amino-1,3,4-thiadiazol-5-tiol, we could isolate only the S-alkykated product, and anomalous results wiht 2-amino-1,3,4-thiadiazol were obtained.

Acknowledgements: Authors thank to UBA and CONICET for financial support for this research and to UMYMFOR for mass spectra.

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Synthesis and Characterization of Bent-rod Liquid Crystals

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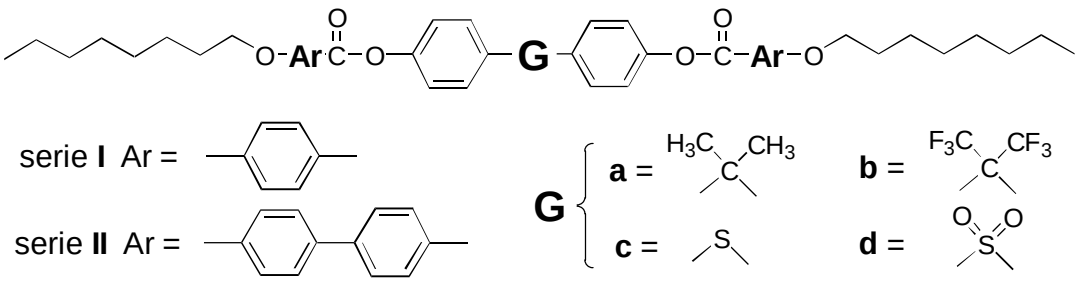
Abstract: Two series of diesters with bend-rod shapes were synthesized and their thermal properties characterized by POM and DSC. The central group conformational mobility and polarity as well as the length of the mesogenic groups were varied in order to correlate these parameters with mesophase stability. Results indicate that series **II** diesters are enantiotropic and that their mesophase sensitivity to central group structural changes is limited.

Keywords: liquid crystals, bend-rod, diesters.

Introduction

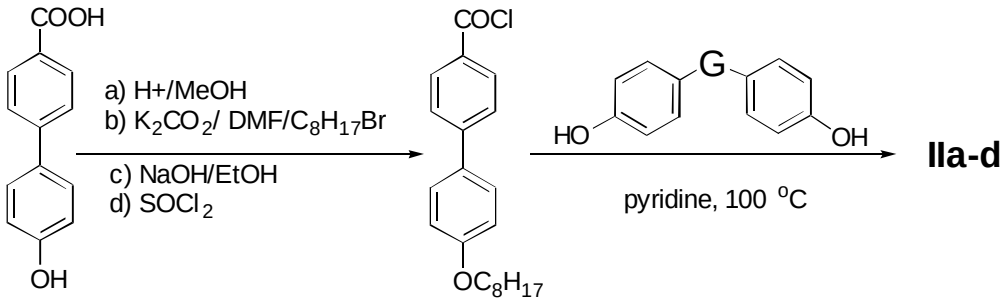
Most of the liquid crystals synthesized to present have the conventional anisodiametric rod-like structure. As yet, only this conventional type of liquid crystals have been used in technological applications. Liquid crystals with non-conventional structures that apart from the lineal geometry are important for the theoretical understanding of the liquid crystalline phenomena and they have potential new applications. It was found recently that two achiral bent-rod shape liquid crystalline systems spontaneously generate helical structures in smectic arrangements [1]. Likewise, nematics arrangements of this type of mesogens are also interesting while the origin of this ferroelectric behavior is still under investigation [2]. The goal of this study was the synthesis and characterization of the mesomorfic properties of a series of diesters were the length of the mesogenic groups as well as polarity and conformational mobility of the central group was varied as shown in Scheme 1.



Scheme 1.

Experimental

The diesters were synthesized by reaction of either 4-*n*-octiloxybenzoyl choride or 4'-*n*-octiloxybifenil-4-carbonyl chloride with the corresponding diphenols at near reflux temperature in pyridine as shown in Scheme 2. Structural characterization and purity checks of the diesters were perform by tlc and ^{1}H RMN. Thermal transitions were characterized by differential scanning calorimetry, DSC, (scanning rate 10ºC/min, temperature range: 50-260ºC) and polarizing optical microscope, POM (Temperature range: r. t.-260ºC).



Scheme 2.

Results and Discussion

The mesogen deviation from the preferential geometry to generate mesophases due to the introduction of a non lineal central group, **G**, does not preclude mesomorphic organisation in the heating cycles, HC, or cooling cycles, CC, as long as the mesogenic arms have a minimum length. Thus, none of series **I** compounds showed mesomorfic properties. On the contrary, all series **II** compounds are enantiotropic liquid crystals. The preliminary results indicate that the mesophase stability (Ti). is not very sensitive to variations either in the angle or in the polarity of **G**. Likewise, mesophase range (Ti-Tm) present only small variations.

Thermal Properties of diesters **II**					
		IIa	*IIb*	**IIc**	**IId**
HC	Tm	182	175	175	160
	Ti	249	260	245	240
CC	Td	248	259	244	220
	Tc	180	170	170	175

Acknowledgements: Financial support for this research was provided by ANPCyT and SGCyT-UNS. P. D. R. thanks SGCyT-UNS for a fellowship.

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Two New Labdane Diterpene Glycoside from Flowers of *Bacchris Medulosa* DC

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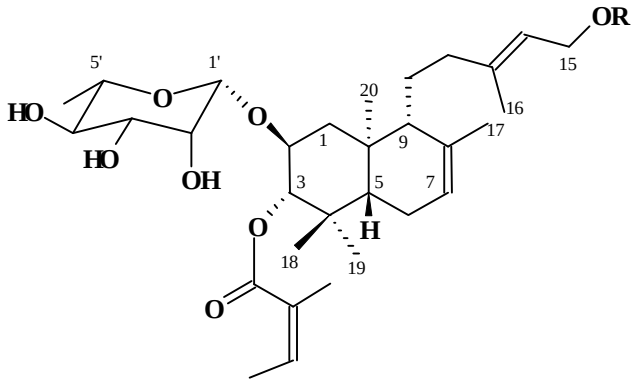
Abstract: Two new labdane-type diterpene glycoside, were isolated from the flowers of *Baccharis medulosa* DC (Asteraceae). Structures of these compounds were established by application of various spectroscopic techniques.

Introduction

In continuation of our studies on diterpenic compounds of *Baccharis* [1] genus (Compositae, tribe Astereae), we have investigated *B. medulosa* DC. In the present work, we described the isolation, characterization and structural determination of two new labdane-type diterpene glycoside [2] (**1** and **2**).



1 R=Ac **2** R=H

Experimental

Plant material. *B. medulosa* DC, was collected in Juana Koslay, San Luis, Province of Argentina in March 1998. Voucher Nº 986. UNSL.

Extraction and isolation. Fresh flowers (2 Kg) of *B. medulosa* were extracted with Me_2CO at room temp. The Me_2CO extract was dissolved in MeOH: H_2O (8:2) and the soln was successively partitioned against, *n*-hexane, CCl_4, $CHCl_3$ and EtOAc. The CCl_4 and $CHCl_3$ extracts were subjected to several

several C.C. purifications on Si gel eluted with *n*-hexane, *n*-hexane:EtOAc increasing polarity mixtures and EtOAc -MeOH (97:3). The more polar fractions were purified by Sephadex LH-20 and RP-18 C.C., eluted with MeOH-H_2O (90:10 and 85:15) to yield 1 (300 mg) and 2 (250 mg). The sugar residues as TMS derivative were identified by GC analysis using suitable sugar standard after acid hydrolysis [3] of the natural products.

Results and Discussion

The NMR spectroscopical data for these compounds suggested nearly structural relationship according with a labdane-type glycoside framework. The ^{13}C NMR spectrum of **1**, gave 33 carbon signals, which were coupled with DEPT experiments. Signals attributable to seven quaternary carbons, nine methyl carbons, five methylenes and twelve methine groups, were observed. The ^{1}H NMR spectral data showed the presence of three tertiary methyl groups at δ 0.85 s, 0.97 s and 0.82 s attributable each one to H-18, H-19, and H-20 on the decaline moiety. Two overlapping olefinic protons at δ 5.35 brt and δ 5.40 brs, both allylically coupled with methyl groups (δ 1.69 brs and 1.71 brs) were assigned to H-7 and H-14, respectively. From the COSY spectrum cross peaks observed between signals at δ 3.87 (ddd, J=12.0, 11.0, 3.8 Hz) and δ 4.72 (d , J=10.5Hz), were associated with H-2 and H-3, both on oxygenated carbons. Additional signals at δ 2.08 s and δ 4.59 (brd, J=7.3 Hz) indicated the presence of an acetate group on the allylic hydroxymethyl function at C-15. On the other hand, signals at δ_C 103, δ_H 4.19 (d, J=7.1 Hz) were agreeable with an anomeric proton; whose coupling constant indicated that the glycosidic linkage had β-configuration. One signal at δ_H 1.25 d (J=7.0 Hz) suggested that the sugar moiety was a methylpentose (L-rhamnose). Typical signals at δ_H 6.15 qq, 1.99 dq, 1.92 dq were in agreement with the presence of an angelate group. The site of attachment of the saccharide residue as well as the position of the angelate group were established on the basis of long range HMBC experiments.

Except for the acetoxymethylene group signals, NMR spectral data of compound **2** were closely related with the spectral data observed for compound **1**. In place of the signals at δ_H 4.59, one signal at δ_H 4.12 brd for an hydroxymethyl group, was observed.

Acknowledgements: Financial support of CONICET and UNSL. We thank Ing. L.A. del Vitto for plant identification, Professors E. Manta, P.C. Rossomando and E. Garcia for NMR measurements, Professor O. Varela for sugar standards.

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Reactivity of β-Stannylketones. Elimination vs. Substitution

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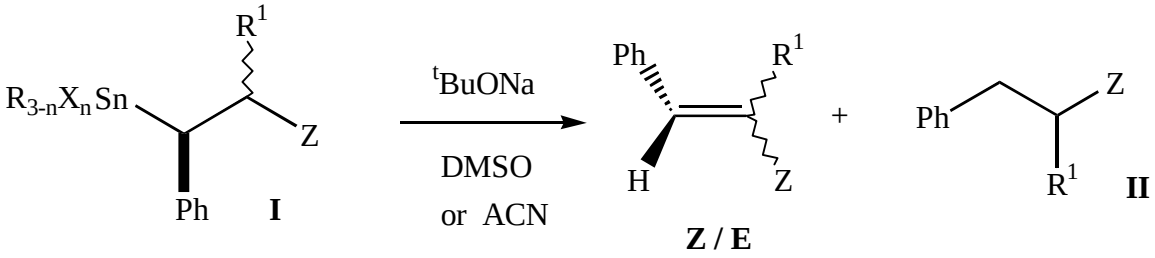
Abstract: In the present work we report the results obtained in the reaction of β-stannylketones (**I**) with *t*-BuONa in dimethylsulfoxide (DMSO) and acetonitrile (ACN) as solvents. The reaction mechanisms probably involved are proposed.

Introduction

In the reaction of β-functionalized organotin compounds (**I**) with *t*-BuONa in *t*-BuOH there is a competition between an elimination reaction [$(E1cB)_R$], leading to olefins with high diastereoselectivity, and a nucleofilic substitution reaction yielding the reduction product (**II**) [1]. Now we report on the reactions of β-stannylketones (**I**) with *t*-BuONa in DMSO and ACN in order to compare the reactivity in these solvents.



Z = COPh, CN ; R^1 = Me, Ph ; R = Me, Ph ; X = Cl, Br ; n = 1, 3

Experimental

Anhydrous solvents and sublimated *t*-BuONa were used. The β-stannylketones were synthesized in our laboratory [2-3]. The reaction mixtures were analysed by CGL. The reaction conditions are detailed in the Table.

Results and Discussion

The results summarised in the Table show that these reactions lead to higher yields in shorter reaction times, depending on the substrates. Thus, while β-stannylketones carrying electron-withdrawing groups attached to tin lead to the elimination product in high yield, β-trialkylstannylketones give mainly the reduction product.

Table. Reactions of $R_{3-n}X_nSn$-CH(Ph)-CH(R^1)-COPh with ^tBuONa[a].

N°	R^1	$R_{3-n}X_nSn$	*DMSO*	*ACN*
			% Elim (Z/E)	% Elim (Z/E)
1	Me	Ph_3Sn	58 (10/90)[b]	39 (1/99)[c]
2	Me	Ph_3Sn	86 (19/81)[b]	85 (0/100)[c]
3	Me	Ph_2BrSn	84 (10/90)	83 (0/100)
4	Me	Me_3Sn	-[d]	37 (30/70)[d]
5	Me	Cl_3Sn[e]	92 (0/100)	85 (0/100)
6	Me	Cl_3Sn[f]	81 (100/0)	80 (100/0)
7	Ph	Me_3Sn[e]	-[d]	76 (16/84)[c]
8	Ph	Me_3Sn[f]	-[d]	58 (17/83)[c]
9	Ph	Cl_3Sn[g]	98 (89/11)	69 (90/10)

[a]Substrate/base ratio 1/1.1 Similar results are obtained from both *erythro* and *threo* isomers; [b]Starting substrate is recovered like a diastereoisomeric mixture; [c]No isomerization of the starting substrate was observed; [d]High yield of the reduction product; [e]*Erythro* isomer; [f]*Threo* isomer; [g]*Erythro/threo* 13/87.

The stereochemical results show that, in most cases, these reactions are stereoconvergent. The same ratio Z/E is obtained independently of the configuration of the starting substrate. (Table, entries 1-4,7 and 8). Taking into account the stereochemistry observed we are able to say that, probably, the elimination reaction goes through an $(E1cB)_R$ mechanism in DMSO and through an $(E1cB)_I$ in ACN.

On the other hand, β-trichlorostannylketones (Table, entries 5, 6 and 9) give high yields of olefins through a stereospecific elimination reaction. Two possible mechanisms could be proposed to explain these results: a concerted E2, or an $(E1cB)_I$ in which, because of electronic interactions between the trichlorostannyl group and the oxygen atom, the intermediate carbanions are not interconvertibles.

Acknowledgements: This work was partially supported by CIC, CONICET and UNS (Argentina). The authors thank Dr. M. González Sierra (IQUIOS, Argentina) for the NMR spectra.

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Addition of Organotin Anions to α,β-Unsaturated Nitriles

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Abstract: The addition reaction of triorganotin anions to α,β-unsaturated nitriles leads to α-alkyl-β-stannylnitriles with high diastereoselectivity.

Introduction

The reaction of triphenyl- and trimethyltin anions with α,β-unsaturated ketones in acetonitrile as solvent is rather instantaneous and leads with high diastereoselectivity and in nearly quantitative yields, to β-stannylketones [1]. On the other hand, there are few reports in the literature concerned with the reaction of triorganostannyl anions with α,β-unsaturated nitriles which would lead to β-stannylnitriles through an 1,4-addition. Taking into account the application of these adducts as intermediates in organic synthesis [2,3] we started some studies on the reaction of triphenyl- and trimethyltinpotassium with compounds **I**, **II** and **III**, in acetonitrile (ACN) as solvent.

Experimental

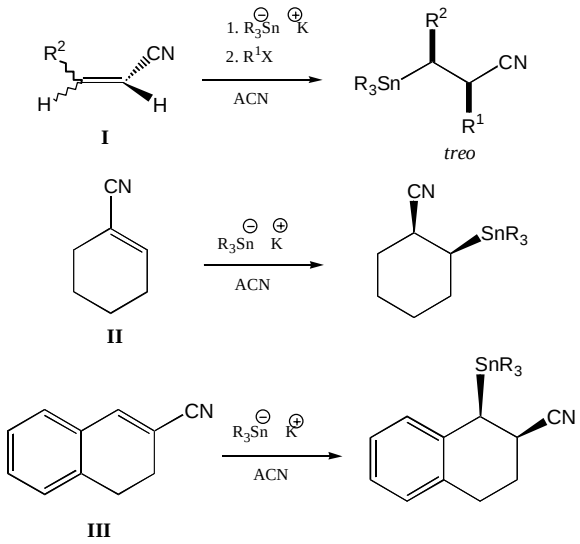
To a solution of the stannyl anion (from the reaction between an organotin hydride and potassium *tert*-butoxide [1]) was added a solution of the nitrile in ACN. The reaction was quenched by the addition of water or an alkyl halide and then worked as usual. The adducts were purified by column chromatography, distillation or recrystallization and characterized by ^{1}H and ^{13}C NMR.

Results and Discussion

The experimental results indicate that the addition reaction to α,β-unsaturated nitriles is partially inhibited by the presence of one substituent in the α- or β- positions. Thus, while acrilonitrile lead to the adduct in an 85% yield, metacrilonitrile and 2-butenonitrile gave lower yields (62% and 43% respectively). On the other hand, the addition is highly inhibited by the presence of α- and β-substituents in open chain olefinic systems (2,3-diphenylpropenonitrile gave a null reaction) but not in cyclic ones (1-cyanocyclohexene and 2-cyano-3,4-dihydronaphthalene gave 63% and 67% yield, respectively).

The stereochemical results show that these reactions are highly diastereoselective. Thus, we only

obtained pure *threo* isomers from open chain nitriles and *cis* adducts from the cyclic ones. Trapping the intermediate carbanions with different alkyl halides would allow the diastereoselective synthesis of a large number of α-alkyl-β-stannylnitriles.



The diastereocontrol observed in the addition of stannyl anions to activated nitriles arises from stereoelectronic and steric effects.

Acknowledgements: This work was partially supported by CIC, CONICET and UNS (Argentina). The authors thank Dr. M.González Sierra (IQUIOS, Argentina) for the NMR spectra.

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N,N-Diethyl-1-Tosyl-3-Indoleglyoxylamide as a Dienophile in Diels-Alder Reactions. Hyperbaric vs. Thermal Conditions

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Abstract: Under high pressure conditions, the Diels-Alder reaction involving *N,N*-diethyl-1-tosyl-3-indoleglyoxylamide and 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene produces a highly functionalized intermediate for the synthesis of Indole Alkaloids, in shorter times and higher yields than under thermal conditions.

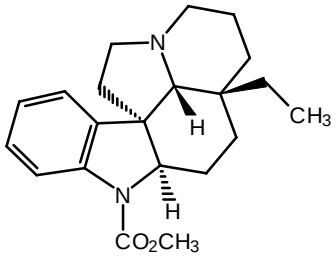
Introduction

From the limited number of heteroaromatic compounds which can act as dienophiles in normal Diels-Alder (D-A) reactions [1], 1-tosyl-3-nitroindole proves to be the most reactive, leading to high yields in dihydrocarbazoles with nitrous acid extrusion in the reactions involving isoprene (155ºC, 26 hours), 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene (90ºC, 96 hours) and 1-(*N*-benzoyl-*N*-benzylamino)-1,3-butadiene (130ºC, 96 hours) [1,2]. The reactions with Danishefsky diene (65ºC, 24 hours) produces adducts that keep the original functionality [3]. Under hyperbar conditions (12 kbar, room temperature), the named reactions offer products keeping the nitro-substitution, except with the dienamides, where the dihydrocarbazole is still the main product [3]. The *N,N*-diethyl-1-tosyl-3-indoleglyoxylamide **1** is, between the acyl-substituted indoles, the one that produces the highest yields reacting with isopren [1], constituting therefore a potentially suitable substrate for the comparative study of the D-A reactions with 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene **2** under hyperbar and thermal conditions. Complementary, it would allow to synthesise properly substituted intermediates for the advanced synthesis of Indole Alkaloids, such as (-)-*Aspidospermine* (Scheme 1).

Experimental

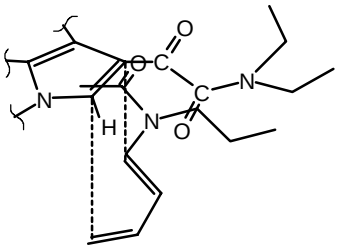
The thermal reaction between the indoleglyoxamide **1** and the dienamide **2** should be carried out at high temperatures in order to induce the dienophilic character of **1**. The maximum limit of temperature is set in 130ºC, due to the thermal instability of the dienamide **2**. Under thermal conditions (120ºC, 96 hours) the reaction leads to two diastereomeric adducts (total regioselectivity) in very low yields (ca.

9%). Under hyperbar conditions (11.5 kbar, 40ºC, 48 hours), the reaction leads to 50% of a single isomer **3** (Scheme 3), which arises from the *exo* addition (Scheme 2). This experimental condition allows to recover ca. 48% of the unreacted dienophile.



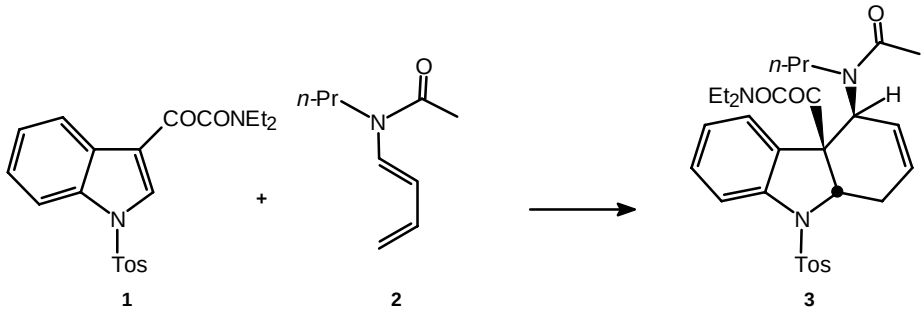
(-)-*Aspidospermine*

Scheme 1.



Exo addition

Scheme 2.



Scheme 3.

Results and Discussions

The D-A reaction between *N*,*N*-diethyl-1-tosyl-3-indoleglyoxamide and 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene, carried out under hyperbar conditions, is clean, fast and leads to higher yields compared to thermal conditions, since it allows to produce a single adduct which holds the basic skeleton and appropriate functionality of (-)-*Aspidospermine* and related *Plumerane* alkaloids.

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Synthesis of Poly(*m*-pyridylene-1,2-diphenylvinylene)

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Abstract: The synthesis by dehalogenating polycondensation and characterization of a new soluble conjugated polymer, poly(*m*-pyridylene-1,2-diphenylvinylene), DP-PPyV, is reported here. It shows good mechanical properties and a λ_{max} = 330 nm. The maximum intensity peak of MALDI-TOF corresponds to 1.800 Da.

Keywords: conjugated polymers, pyridine units, synthesis.

Introduction

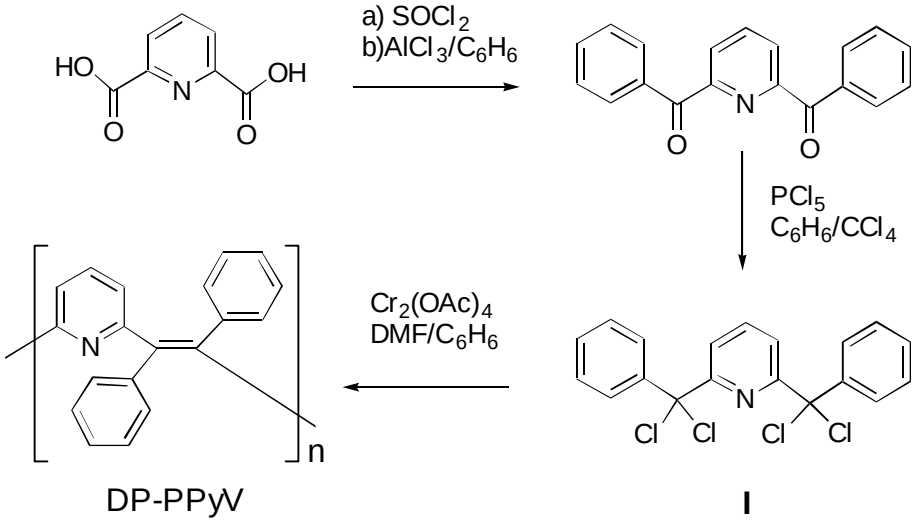
Pyridine-containing conjugated polymers are considered promising candidates for light-emitting devices [1]. Polymers such as poly(*para*-pyridylenevinylene), PPyV, or their copolymers, ie., poly(*meta*-pyridylvinylene) co-(*para*-phenylenevinylene) are highly luminescent [2]. Since these nitrogenated polymers have a higher electron affinity than the non-nitrogenated ones, they are more resistant to oxidation and show better electron transport properties. Moreover, their higher electroaffinity allows the use of more stable metals, ie. Al or Au, or doped-polyaniline as the electron injecting electrode in polymer light-emitting diodes. The lineal polymer P*p*-PyV emits at *ca.* 600 nm (orange red) so polymer structural changes are necessary in order to get a broader emissive spectral range. As it is well known the reduction of the cromophore effective length results in a bathocromic shift. Therefore, poly(*m*-pyridylene-1,2-diphenylvinylene), DP-PPyV, is a potential candidate to be used in the lower wavelength of the visible spectral region. The synthesis by dehalogenating polycondensation and characterization of this new soluble conjugated polymer, DP-PPyV, is reported here.

Experimental

The synthetic route is shown in Scheme 1. Monomer and low molecular weight compounds were characterized by ^{1}H NMR, ^{13}C NMR, FTIR and elemental analysis. In adition to these techniques, the polymer was characterized by UV, GPC and MALDI-TOF.

Results and Discussion

The polymer is soluble in common organic solvents. Then, it was possible to perform GPC characterization on it. This technique, however, gave inconsistent results. In THF, a Mn *ca.* 6,500 Da. and a non-typical value for the polydispersion (*ca.* 5.0) were obtained. On the other hand, much higher values were observed in DMF, i.e., Mn = 21.000 and Mw/Mn = 52. So, the former values could indicate that there are some polymer aggregation phenomena as well as some adsorption on the GPC column gel. The absolute determination of the molecular mass by the MALDI-TOF technique indicated that the maximum intensity signal corresponded to a 1,800 Da and that the molecular weight distribution was near to the one expected for a polycondensation reaction. Moreover, it was possible to determine that the polymer terminal groups were -CH_2Ph, -CHOHPh and -CHOAcPh. Therefore, it is clear that the AcO^- anions play a important role in the polymerization termination steps. DP-PPyV forms stable films on several substrates and possess a λ_{max} = 330 nm.



Scheme 1.

Acknowledgements: Financial support was provided by ANPCyT and SGCyT-UNS. We are indebted to Prof. Dr. K. Mullen (MPI-P, Germany) for help in getting the MALDI-TOF data.

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Structure-Fluorescence Relationships in Antimicrobial Fluoroquinolones (AMFQs)

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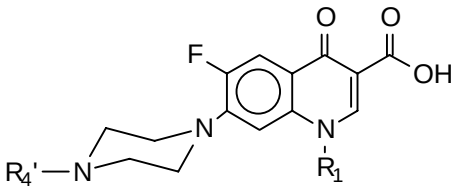
Abstract: The analysis of fluorescence spectra of a set of structurally related AMFQ let to identify the effects of structural changes and the presence of electric charge generated by acid-base reaction on the emission spectra.

Introduction

The fluorescence produced by quinolone ring has been extensively used in analytical determination of AMFQs in biological fluids and bacterial uptake studies.

It is well known the effect of polarity and pH on both intensity and wavelength of the emission of some AMFQs like norfloxacin (**I**) and ciprofloxacin (**II**). Variation of the emission of **I** and **II** as a consequence of pH changes is related to the variation in the proportions of the species (+0), (00), (+-), and (0-).

Compound	R_1	R'_4
I	$-C_2H_5$	H
II	$c\text{-}C_3H_5$	H
III	$-C_2H_5$	$-I^-(CH_3)_2$
IV	$-C_2H_5$	$-CO\text{-}CH_3$
V	$-C_2H_5$	$SO_2\text{-}C_6H_4\text{-}NH_2$
VI	$-C_2H_5$	$SO_2\text{-}C_6H_4\text{-}NH\text{-}CH_3$
VII	$-C_2H_5$	$SO_2\text{-}C_6H_4\text{-}N\text{-}(CH_3)_2$
VIII	$c\text{-}C_3H_5$	$SO_2\text{-}C_6H_4\text{-}NH_2$
IX	$c\text{-}C_3H_5$	$SO_2\text{-}C_6H_4\text{-}NH\text{-}CH_3$
X	$-C_2H_5$	$SO_2\text{-}C_6H_4\text{-}CH_3$
XI	$c\text{-}C_3H_5$	$SO_2\text{-}C_6H_4\text{-}CH_3$



In order to identify the main factors that affect light emission in aqueous solution, a set of 11 structurally related compounds was used (table I). Compounds **V**-**XI** are new active AMFQs synthesized in our laboratory.

Emission spectra were recorded at two pHs (4.8 and 8) which were selected taken into account the pKa of the ionizables groups.

Results and Discussions

The analysis of such results let to relate the emission parameters with both presence and type of electric charge in the molecules.

Compound	**Excitation**	**Emission**				**U.V. Absortion Coeficients**
	λ_{max} (pH= 4,8 - 8)	**Intensity (pH = 4,8)**	**λ_{Max} (pH = 4,8)**	**Intensity (pH = 8,0)**	**λ_{max} (pH = 8,0)**	**ξ (L.mol^{-1}.cm^{-1})**
I	272 nm	5040	444 nm	2402	415 nm	32400
II	270 nm	5885	447 nm	3074	417 nm	28800
III	278 nm	6968	440 nm	2634	409 nm	33846
IV	272 nm	600.0	443 nm	3085	435 nm	35733
V	272 nm	540.3	445 nm	2178	427 nm	54900
VI	274 nm	664.0	440 nm	833.5	424 nm	53430
VII	272 nm	589.7	443 nm	625.2	420 nm	49252
VIII	272 nm	659.8	442 nm	1788	431 nm	41000
IX	270 nm	874.9	444 nm	763.8	426 nm	48700
X	274 nm	--------	---------	3388	428 nm	33900
XI	276 nm	--------	---------	3950	431 nm	42200

Emission at pH 4.8. In this condition $^{+}$HBH is the prevalent species of **I** and **II**, their spectra exhibit a higher intensity and a emission λ_{max} shifted to the red with respect to that recorded at pH 8. A similar behavior is observed with **III**, in which the prevalent species is $^{+}$BH and exhibits the highest intensity registered. On the other hand, compounds **IV**-**IX** exhibit emission λ_{max} which are not significatively different from those of their zwitterionic analogs I-**III**, however, their quantum yields are 8 to 10 times lower.

Emission at pH 8. The ionization of 3-COOH yields zwitterionic and/or anionic species. Thus, at pH 8 the proportion of prevalent species of I or II are in the order $^{+}HB^{-} > B^{-} \geq BH^{oo}$; the resulting λ_{em} are shifted 30 nm to the blue and quantic yields lowered with respect to pH 4.8. A similar change oc-

curs with **III** also, which is essentially as $^{+}B^{-}$ in this condition and it λ_{em} is 409 nm.

Compounds **IV**-**XI** are essentially as B^{-}, their λ_{em} lie in the range 420-435 nm, that is, at higher wavelengths than **I**-**III**. Therefore, it seems that the emission of fluorescence of zwitterionic species $^{+}HB^{-}$ and $^{+}B^{-}$ occurs at lower wavelengths than that of anionic species B^{-}.

In summary: a) cationic species ^{+}HBH exhibit the higher fluorescence intensity; b) the emission of zwitterionic species $^{+}HB^{-}$ and $^{+}B^{-}$ is about a half of that of the formers; c) the emission of anionic species B^{-} is highly variable, ranging from ones even higher than that of zwitterions to others sensible lower; d) neutral species BH exhibit the lower emission.

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Reaction of 2,4-Dinitrochlorobenzene with Aromatic Amines in Toluene: Effect of Nucleophile Structure

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Abstract: The kinetics of the reaction of 2,4-dinitrochlorobenzene (DNClB) with aniline and substituted anilines such as p-anisidine, p-toluidine and N-methylaniline have been studied in toluene. Except for N-methylaniline the reactions have shown a third order in amine rate dependence which is consistent with aggregates of the amine acting as the nucleophile. On the other hand, the reaction of DNClB with N-methylaniline under the same conditions shows a linear dependence of the second order rate coefficient, k_A, *vs* [amine], which is consistent with the previous mechanism.

Introduction

Previous research carried out in our laboratory on aromatic nucleophile substitutions (S_NAr) of 2,4-dinitrochlorobenzene in aprotic solvent [1,2] have shown formation of aniline dimers acting as nucleophile, formation of molecular complexes substrate-nucleophile and substrate-product reaction, formation of mixed aggregates aniline-HBA additive and specific effects solvent on S_NAr mechanism.

In order to investigate the relevance of nucleophile structure in defining the mechanism of S_NAr with amines in aprotic solvent, kinetic studies of the reaction of DNClB with aniline, p-anisidine, p-toluidine, 2,4-dimethylaniline and N-methylaniline in toluene at 40°C have been carried out.

Experimental

Aniline, p-toluidine, 2,4-dimethylaniline and N-methylaniline were distilled over zinc powder and then over sodium under nitrogen at reduced pressure; p-anisidine was purified to constant melting point by recrystallization with toluene; DNClB was crystallized twice from absolute ethanol. Toluene was kept over sodium wire for several days and distilled twice over sodium. The reaction products

were prepared and purified following the procedure previously reported [3].

Results and discussion

The second order rate coefficients, k_A, were found to increase rapidly with amine concentration, [B], the plots of k_A *vs* [B] show a quadratic dependence for the reaction of the primary anilines. The present results can be interpreted in terms of "dimer nucleophile" mechanism in which a dimeric aggregate of the amine (B:B) is considered to attack the substrate in the first step [1].

In order to evaluate the magnitude of the curvature obtained, the experimental values were fitted to a second-degree polynomial function. The quadratic coefficients, except for N-methylaniline, are significantly different from zero.

When 2,4-dimethylaniline is used, the second order rate coefficients are considerably smaller than for aniline at any concentration and the quadratic coefficient is also much less relevant than for the other anilines. These results are consistent with the "dimer nucleophile" mechanism and can be easily explained by decreasing dimerization due to the steric hindrance produced by the methyl group at the ortho position.

For the reaction of DNClB with N-methylaniline in toluene, the plot of k_A *vs* [B] shows a clear linear dependence with a zero intercept; where the spontaneous decomposition of the zwitterionic intermediate is negligible. This kinetic behaviour is consistent with what could be expected for the N-alkylanilines, considering that they undergo less-association than aniline. For this reason the attack by the "dimer nucleophile" is not relevant.

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1-Nitronaphtalene as a Dienophile in Diels-Alder Reactions

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Abstract*:* the utilization of substitued dienes with electron-donor groups and under high pressure conditions, induces the dienophilic character of 1-nitronaphtalene in Diels-Alder reactions, giving the products with and without the nitro-group, the yield depending on the nature of the dienes substituent groups.

Introduction

The Diels-Alder reaction has been subject of extensive studies for both theoretical and mechanistic purposes, and because of the synthetic advantages it offers. However, the exploration of this reaction using aromatic compounds as dienophiles is scarce [1], particularly for compounds showing a special stability like in the case of 1-nitronaphthalene [2]. Though the nitro-substituent promotes the dienophilicity of such a compounds, the lack reactivity in reactions with isoprene and other simple dienes has been evident, either under thermal or hyperbar conditions [3]. Therefore, it was interesting the study of reactivity of this dienophile with more complex and reactive dienes like 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene and 1-methoxy-3-trimethylsilyloxi-1,3-butadiene (Danishefsky diene). They proved to successfully revert the precedent tendency, specially under high pressure conditions, leading to highly functionalyzed adducts.

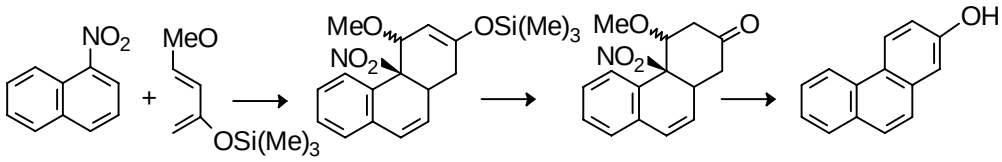
Experimental

The Diels-Alder reactions between 1-nitronaphthalene and 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene or 1-methoxy-3-trimethylsilyloxi-1,3-butadiene, were carried out at 40ºC and 11.5 kbar of pressure, during 53 hours.

Results and Discussion

The dienophilic character that 1-nitronaphthalene exhibit in the reaction with the Danishefsky diene leads to a mixture of adducts keeping the nitro-substitution, which under the purification conditions suffer aromatization with extrusion of nitrous acid and methanol. (Scheme 1), the dienophile recover

being 30% and yield 90% (based on consumed starting nitronaphtalene). Instead, traces of products are obtained when 1-(*N*-acetyl-*N*-propylamino)-1,3-butadiene is used as diene, concluding that this diene doesn´t hold a electrondonor substituent strong enough to induce the 1-nitronaphthalene to react in the expected way. It is worth mentioning in first place, the importance of the study of 1-nitronaphtalene´s behavior as dienophile, not exaustively explored, and in second instance, the possibility of synthesis of adducts with the base skeleton of diterpenes through one-step reactions as it is the Diels-Alder



reaction.

Acknowledgements: We are indebted to the Science and Technology Secretariat - Universidad Nacional del Litoral, República Argentina, for the financial support, CAI+D Program (96-00-024-161). The authors want to thank Prof. Serge Piettre from IRCOF - Université de Rouen, France, for his valuable advice, and Dr. Gonzalez Sierra from the IQUIOS – UNR (Argentina) for the NMR experiments.

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Cyclodextrin Effect on Intramolecular Catalysis

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Abstract: HPCD inhibits the hydrolysis reaction of monoamides and monoesters of phthalic and maleic acid at pH 2. The magnitude of inhibition depends on the leaving group. For some of the substrates, the reaction in the cavity is more than 100 times slower than that in solution.

Introduction

Cyclodextrins (CD) are doughnut-shaped, macrocyclic oligosacharides constructed of glucose units linked by α- (1→4) bonds. The compound with seven glucose units is known as β-cyclodextrin (β-CD)[1]. Hidroxypropyl-β-cyclodextrin is a derivative was several of the HO^- groups are substituted by hydroxypropyl groups and is more soluble in water than β-CD. Organic compounds included in CD form complexes with different properties from those of the free substrate [2]. Meassuring the changes occurring in some of these properties, it is possible to determine the association constant, K_{as}.

The mechanism of hydrolysis of monoamides and monoesters of phthalic acid [3] maleic acid [4] is known to involve intramolecular catalysis by the neighboring carboxyl group. The formation of an inclusion complex with cyclodextrins may affect the efficiency of the catalysis by favoring or hindering the interaction of the hydroxyl group with the reactive center. This effect should result in modification of the hydrolysis rate. We report here results regarding the effect of HPCD on the hydrolysis of compounds **1-3**

Experimental

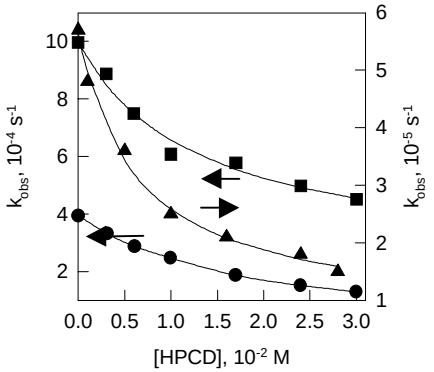
The substrates **1-3** were prepared by reaction of phthalic or maleic anhydride (sublimated) with aniline, 4-nitro-aniline, adamanthylamine and phenol. All products were purified and characterized by MS and ^{1}H and ^{13} C NMR.

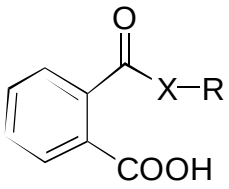
The rate constants were determined by measuring the absorption changes with time at 380 nm for **1a**, 276 nm for **1b** and **2b**, 225 nm for **1c**, and 300 nm for **3b**. The reaction conditions were: pH 2, 40°C for **1a,b,c 2b** and 25°C for **3b**, ionic strength 0.5 M using NaCl as compensating electrolyte and

water as solvent with 4% of dioxane (for 1) or acetonitrile (for **1b,c 2b** and **3b**).

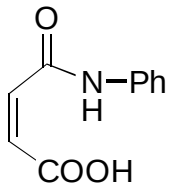
Results and Discussion

The addition of HPCD decreased the hydrolysis rate of all the substrates. The Figure representative plot of the observed rateconstant as a function of the HPCD concentration (**1a** (triangules), **1b** (squares) and **2b** (cicles))



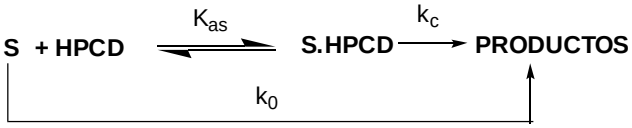


X=NH, R= p-NO_2-Ph, **1a** ;
Ph, **1b** ; adamantyl, **1c**
X= O, R= Ph **,3b**



2b

These results are interpreted in terms of the formation of 1:1 complexes as shown in the following scheme:



Acknowledgements: This research was supported in part by CONICET, FONCYT, SECYT-UNC, CONICOR and Antorchas Foundation.

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Kinetic Study of the Hydrolisys of Phenyl Perfluorooctanoate in Water: Deaggregation Effect of β-Cyclodextrin

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Abstract: The kinetics of the hydrolysis of phenyl perfluorooctanoate was studied at pH 6.00 and 9.90 in water. The substrate is aggregated under all working reaction conditions, which is indicated from the decrease in the reaction rate when the substrate concentration is raised. The addition of β-cyclodextrin produces the deaggregation of the ester catalyzing the reaction.

Introduction

The hydrolysis of amides derived from long chain perfluoroalkyl acids undergoes aggregation in water at very low concentrations. The addition of β-cyclodextrin breaks such interactions and catalyzes the hydrolysis. [1] To evaluate the effect of the change of the polar head group on the aggregation properties, we studied the hydrolysis of phenyl perfluoroalkyl esters bearing different chain lengths. We present here the results obtained from the kinetics of the hydrolysis reaction of phenyl perfluorooctanate in water, in presence and in absence of β-cyclodextrin.

Experimental

The reactions at pH 6 were followed in a conventional spectrophotometer whereas those at pH>9 were carried out in a stopped flow equipment.

The reaction conditions were: temperature 25.1 ± 0.1°C.; ionic strength 0.2 M; cosolvent acetonitrile 3,8%; buffer concentration 0.1 M.

Results and Discussion

We found that the rate constants decrease as the substrate concentration increases which indicates that it is aggregated under all working concentrations. This aggregation phenomenon was also observed in the UV spectrum.

The kinetics of the hydrolysis at pH 6.00 and at concentrations between 8.4 x 10^{-6} and 1.8 x 10^{-5} M corresponded to only one process that fits to a single exponential. On the other hand, at concentrations higher than 2.4 x 10^{-5} M, the change in absorbance with time no longer fits to a single exponential equation. Two processes could be observed at some wavelengths, that is, an initial rise at very short times followed by a decay. The first process became more important compared to the second one as the substrate concentration increased. The former process is attributed to the aggregation of the substrate and the latter arises from its hydrolysis. Similar results were obtained for the reactions measured at pH 9.90.

We also found that small amount of β-cyclodextrin results in a remarkable increase in the rate constant. Such increment reaches a maximum value that remains almost unchangeable with later addition of the host. The absorbance vs. time plot can be fit by a single exponential equation. Besides, in the presence of cyclodextrin, the observed rate constant is independent of substrate concentration and its value is in the order of that expected for the free substrate in solution. These results indicate that the host deaggregates the substrate at very low concentration and suggest the formation of an inclusion complex. The rates of hydrolysis of the free and included substrate are about the same probably because the reacting ester group protrudes outside the cavity

Acknowledgements: This research was supported in part by SECyT(UNC), CONICOR, FONCYT and CONICET.

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Conformational Study of New AZT Derivatives

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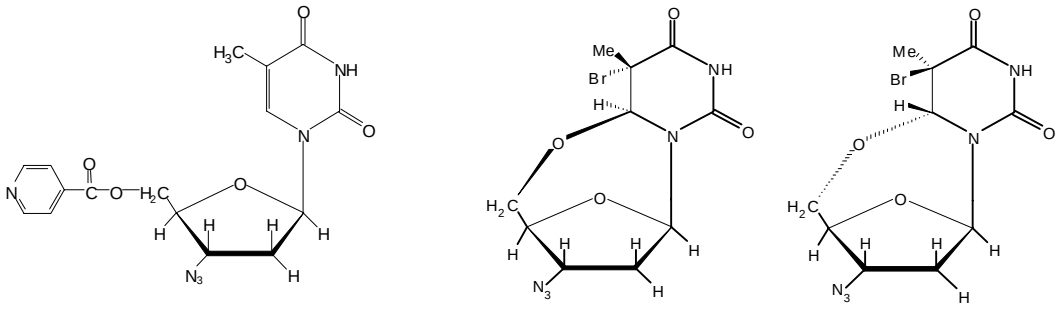
Abstract: A conformational study of three new AZT derivatives was made by semiempirical methods in order to find a structural correlation between these derivatives and AZT.

Introduction

Background information of the conformational properties of 3'-azide-3'-deoxythymidine (AZT) and its derivatives in aqueous solution may contribute to the understanding of the relationship between chemical structure and biological activity of 2',3'-deoxynucleosides and consequently to help in the design of more active drugs. Besides, it has been suggested that the inhibitory action of these compounds may be related to the preferred conformation of modified furanose sugar. Our aim was to find out the conformational structure of three new AZT derivatives **1, 2** and **3** [1] as well as their differences with AZT.



1

Experimental

Study of the different potential surfaces of the three AZT derivatives using AM1 [2] was performed. The stationary points were characterized by force constant calculation. Results were correlated with spectroscopic data.

Results and Discussion

The study of **1, 2** and **3** with semiempirical methods have enable to find different conformers. Based on these results, the following correlation may be established:

- AZT and **1** exhibit similar conformers confirming the analogous behavior with other pyrimidinic nucleosides which display a dynamic equilibrium in solution where the two conformers (North and South) experience constant transformation [3].
- Studies of (-)-*trans*-(5S,6S)-**2** and (+)-*trans*-(5R,6R)-**3** compounds show an abnormally distinct conformation from AZT.[1] The estimate of the pseudorotation phase angle reveals the rigid structures of these drugs, which do not evidence conformational equilibrium in solution, the azide being the only free rotation group.
- Diastereomers **2** and **3** exhibit an extra conformational parameter compared with other pyrimidinic nucleosides: the *chair* or *boat* conformation in the third ring formed between the sugar and the base.

In all cases, a reasonable correlation was noticed between theoretical and spectroscopic data.

Acknowledgements: CONICET, CONICOR, SECyT-UNC.

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Computational Study of the Stereoselectivity of Diels-Alder Reactions of D-Glucose-Derived Dienophiles with Cyclopentadiene

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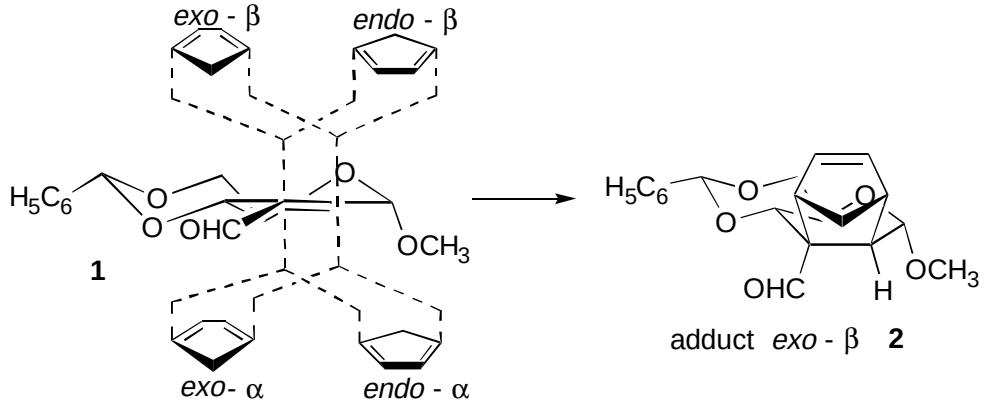
Abstract: A computational study was performed in order to rationalize the high *exo* stereoselectivity in the cycloaddition reactions of sugar-derived dienophiles with cyclopentadiene.

Introduction

The sequence of Diels-Alder reactions for the synthesis of pentalenolactones showed a marked preference toward the formation of cycloadducts *exo*-β. The aldehyde α,β-insaturated **1,** in particular, rendered the cycloadduct *exo*-β **2**, [1,2] showing complete stereoselectivity control.



The formation of this reaction product is not predicted on the basis of the Alder rules that postulate the cycloadduct *endo* as the most favoured one.

Experimental

The heats of formation were calculated for the different reaction products using the semiempirical AM1 [3] method as implemented in the AMPAC 2.1 package. The stationary points obtained were characterized by force constants calculations. The reaction paths were calculated by the reaction coordinate method. The calculations provided the localizations of the transition states for such cycloaddition reactions.

Results and Discussion

Theoretical calculations were carried out to examine the thermodynamic of the formation of adduct *exo*-β **2**. Therefore, the heats of formation of four possible stereoisomers were calculated, indicating higher stability for β adducts than for α adducts (4-5 Kcal/mol). Nevertheless, the energy difference between the *endo* and *exo* adducts (0.02 Kcal/mol) was too small to account for the *exo* selectivity of the cycloaddition process.

When the reaction pathways were studied, we found transition states that would support the observed *endo*/*exo* stereoselectivity.

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Comparative Study of Hydrocarbon, Fluorocarbon and Aromatic Bonded RP-HPLC Stationary Phases by Linear Solvation Energy Relationships

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The retention properties of eight alkyl, aromatic and fluorinated reversed-HPLC bonded phases were characterized through the use of Linear Solvation Energy Relationships (LSERs). The stationary phases were investigated in a series of methanol-water mobile phases. LSER results show that *solute molecular size* under all conditions and *hydrogen bond acceptor basicity* are the two dominant retention controlling factors and that these two factors are linearly correlated when either different stationary phases at a fixed mobile phase composition or different mobile phase compositions at a fixed stationary phase are considered.

The large variation in the dependence of retention on solute molecular volume as only the stationary phase is changed indicate that the dispersive interactions between nonpolar solutes and the stationary phase are quite significant relative to the energy of the mobile phase cavity formation process.

Principal Component Analysis (PCA) results indicate that one PCA factor is required to explain the data when stationary phases of the same chemical nature (alkyl, aromatic and fluoroalkyl phases) are individually considered. However, three PCA factors are not quite sufficient to explain the whole data set for the three classes of stationary phases. In spite of this, the average standard deviation obtained by the use of these principal components factors are significantly smaller than the average standard deviation obtained by the LSER approach. In addition, selectivities predicted through the LSER equation are not in complete agreement with experimental results.

These results show that *the LSER model does not properly account for all molecular interactions involved in RP-HPLC*. The failure could reside in the V_2 solute parameter used to account for both dispersive and cohesive interactions since “shape selectivity” predictions for a pair of structural isomers are very bad.

Cyclodimerization of Stilbenes and Styrenes Catalyzed by Heteropolyacid Supported on Silica

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Abstract: Several stilbenes and styrenes have been treated with heteropolyacid] (HPA) supported over silice. The compounds obtained were characterized by ^{1}H and ^{13} C- NMR and the yields were compared with those obtained using H_2SO_4 (c) and ethyl poliphosphate] (PPE).

Introduction

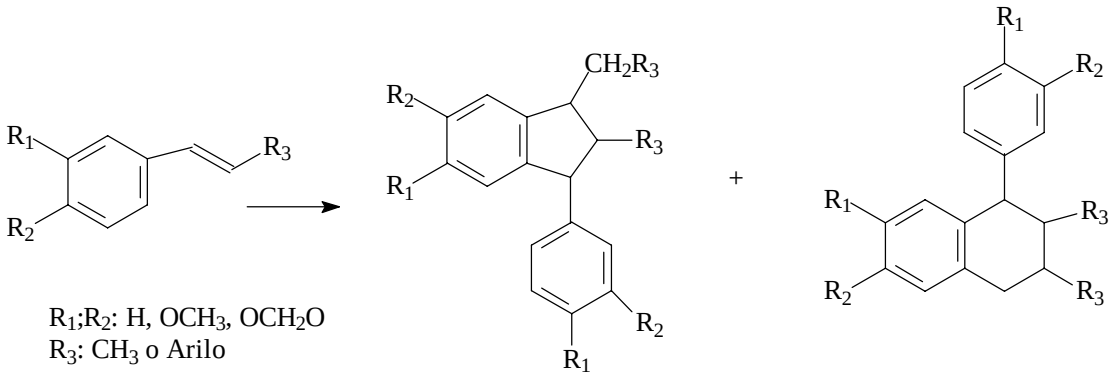
The cyclodimerization of stilbenes and styrenes with acid reagents have been thoroughly descripte in the literature. We have observed that the formation of indanes and/ or tetralines from estilbenes for treatment with as acid differents as the H_2SO_4 (c) and PPE relies on the substitution of the aromatic rings [1]. In this work it are introduced the study of the behavior of several stilbenes and styrenes in presence of Molybdophosphoric acid (AMP) and tungstophosphoric (ATP) supported on sílice [2].

Experimental

The catalyst was prepared on base the AMP and APT acids supported on sílice employing the technique of impregnation in equilibrium during 72 hs. The support employing was SiO2 Grace. The catalysts was dried to 25°C, calcined to 200°C and washed with chloroform, where it was carried out the cyclodimerization reaction. The contents of AMP and ATP, of the washed catalysts, was from 0.39 and 0.37 g/ g of respectively catalyst. To the chloroform solution of stilbenes and styrenes was added the catalyst (0.l meq./ meq. of reagent). The mixture was heated at refluxe. The reaction was followed for t.l.c. The catalyst was filtered and the solvent evaporated under reduced pressure. The products of reaction were purified and identified by physics and spectroscopy dates. The catalysts were washed with chloroform and reused with the same effectiveness until four time.

Results and Discussion

The results obtained in the reactions of cyclodimerization of stilbenes and styrenes have resulted extremely satisfactory. The two catalysts showed a similar behavior in these reactions. The conditions of reaction were soft and the yield very good (80-100%). The formation of lateral products is not observed, which facilitates the purification.



R_1;R_2: H, OCH_3, OCH_2O
R_3: CH_3 o Arilo

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Synthesis of Indanes *Via* a [3+2] Cycloaddition

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Abstract: The acid -promoted [3+2] cycloaddition of alkenes with benzhydrylic alcohols afford products in good yield and with remarkable stereoselectivity.

Introduction

The formal [3+2] cycloaddtion, promoted by a Lewis acid, of alkenes with benzylic cations afford dihydroindenes in good yield and remarkable stereoselectivity [3]. These dihydroindene skeleton forms part of many natural products and of synthetic compounds that possess a significant biological activity [2]. These benzylic cations affords good yield of cycloadducts when the styrene appropriate provided, as long as there was a phenol para to the alcohol and at least one meta alkoxy or alkyl group. Using the diarylcarbinols 1 and 2 like the precursors of the cation and several alkenes of a varied electronics wealth, we observed that was not necessary the presence of a hydroxil group para to the alcohol and that this could be replaced by metoxi group. As for the proven alkenes, those conjugated to a carbonil group doesn't give the cycloaddition but if those gives it that they are also conjugated to a group electron-rich [3]. Following with this study we proved the cycloaddition using like alkenes: a) double bond conjugated to an aromatic ring and to a withdraw electron group and b) aromatic heterocyclics compounds condensed at benzenic ring.

Experimental

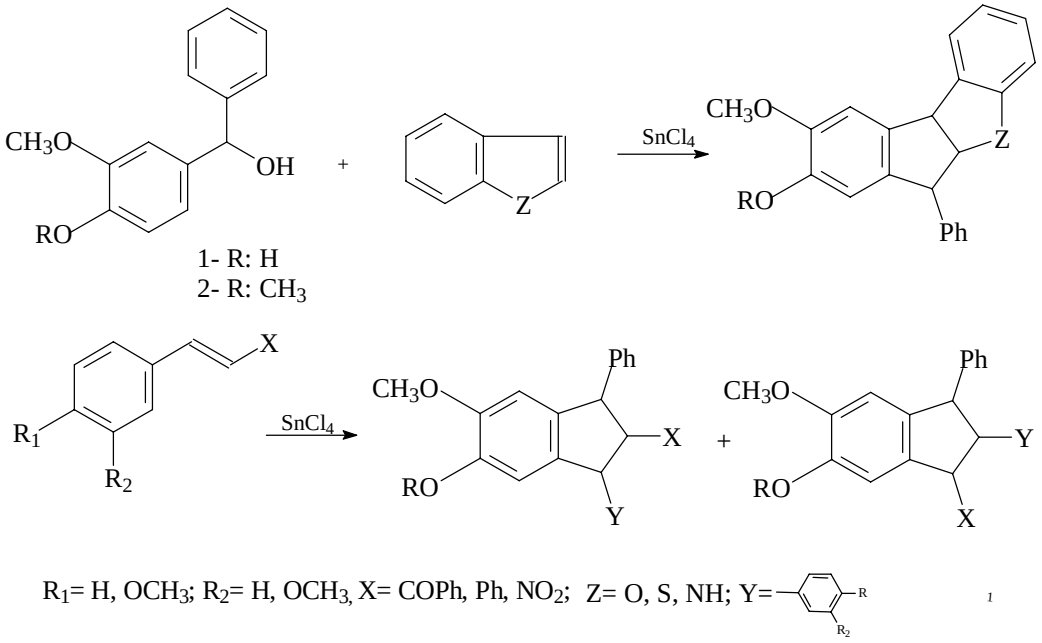
The alkene and the $SnCl_4$ are sequentially added to a solution of alcohol in Cl_2CH_2. The resulting solution is stirred for a time at 0º and then poured into a solution of $NaHC0_3$ 5% Aqueous workup ($NaHCO_3$, CH_2Cl_2) . Dry the organic extract over Na_2SO_4 and remove the solvent under reduced pressure. The purification of product is carried out in thin layer chromatography.

Results and Discussion

The stereochemical assignment for the adducts was followed directly from ^{1}H-RMN coupling constants. The results obtained with the group a) show an *trans-trans* orientation in the products, con-

firmed by the coupling constants J[H(1)- H(2)] and J[H(2)-H(3)] (8.46 to 9.9 Hz). These values demonstrate that the *trans* orientation of the alkene is retained in the product.

With regard to b) group the benzotiophene and the indol doesn't give the cycloaddition but rather the products of the electrophilic substitution in position 2 and 3. Three products are obtained with the benzofurane: one of them is resulted of electrophilic substitution by the cation in position 2 and the other two are cycloadducts. These are obtained in greater proportion.



R_1= H, OCH_3; R_2= H, OCH_3, X= COPh, Ph, NO_2; Z= O, S, NH; Y=

1

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Synthesis of Heterocylic Compounds of Biological Interest from Carbohydrate Derivatives

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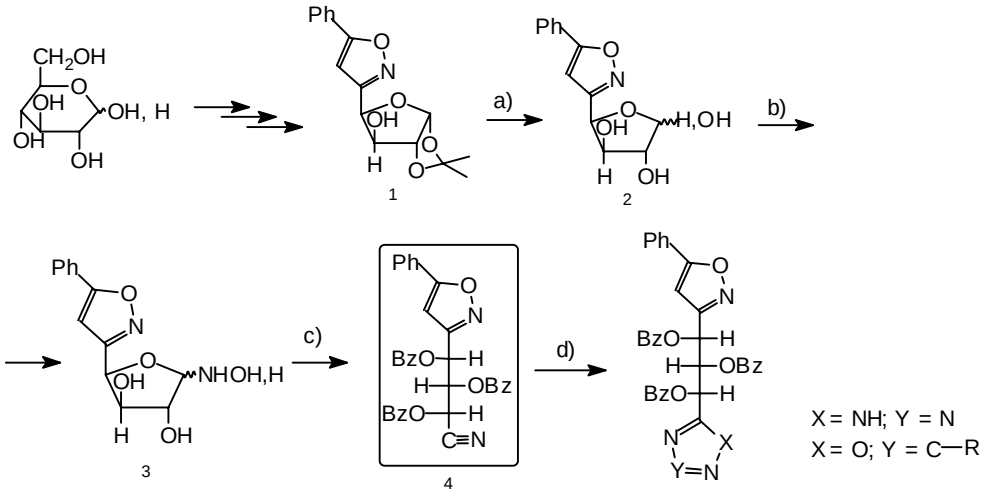
Abstract: The synthesis of some isoxazolic compounds from carbohydrate derivatives is described. These products are obtained by 1,3-dipolar cycloaddition reaction and their functionalization leads to derivatives with potential biological activities.

Introduction

The isoxazoles derivatives are a family of interesting compounds due to their biological activities. Some of these are used as muscle relaxants [1] and for the treatment of hypercholesteremia, arteriosclerosis, and hyperlipidemia [2].

In previous papers we performed the synthesis of 3-glycosyl-5-substituted-2-isoxazoles by 1,3-dipolar cycloaddition, where the N-oxide came from protected carbohydrate derivatives [3]. In this work we describe the deprotection and functionalization of the polihydrated moiety as synthetic precursors of new di-heterocyclic compound.

Experimental part



The following synthetic route is applied.

Results and discussion

The 3-(1',2'-*O*-isopropylidene-α-**D**-xilofuranos-4'-il)-5-phenyl-2-isoxazol (**1**) was obtained by 1,3-dipolar cycloaddition, where the N-oxide was a glucose derivative and the dipolarophile was phenylacetylene. The treatment of compound **1** with acetic acid (10%) yielded compound **2.** The reaction of **2** with hydroxylamine gave the oxime (**3**). The benzoylation of the oxime allowed us to obtain the nitrile **4**, which is the suitable synthetic intermediate to prepare different heterocyclic compound with biological interest.

All the compounds were characterized for ^{1}H-MNR, ^{13}C y mass spectrometry.

Acknowlegments: The authors thank to UBA and CONICET for financial support research and to UMYMFOR for mass spectra.

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Nuclear Magnetic Resonance for the Structural Study of Bioactive Semicarbazones

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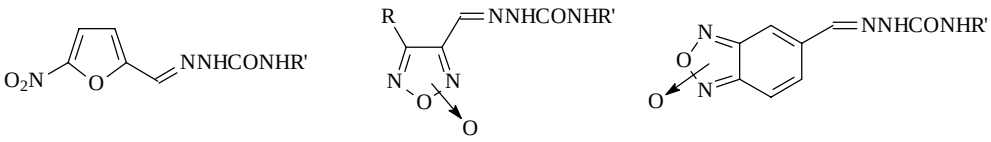
Abstract: NMR studies of bioactive semicarbazones are described.

Introduction

Within our work on the development of bioactive compounds, we have employed the semicarbazone moiety as a joining function between different pharmacophores.



Knowing the geometric isomer at the iminic union of the semicarbazone group, as well as the *N*-oxide positional isomer that was obtained in the synthetic procedure, were very important for determining the structure of the biologically active compound. The lack of crystals to determine unequivocally the exact structure of the product obtained led us to use NMR spectroscopy for this purpose.

Experimental

All the experiments were carried out on a DPX-Bruker 400 (400 y 100 MHz) instrument. We carried out NOE difference (1D y 2D) experiments at different mixing times in order to determine the geometric isomer of the iminic junction.

We also carried out ^{1}H-NMR and ^{13}C-NMR experiments at variable temperatures and EXSY experiments in order to determine the *N*-oxide position.

Results and Discussion

All the semicarbazones studied were in the *E* isomeric form. The *N*-oxide moiety in the derivatives

of the heterocycle 1,2,5-oxadiazoles was found fixed at the 2 position. The derivatives of the heterocycle benzo[1,2-*c*]1,2,5-oxadiazoles were presented as a mixture of the different positional isomers of the *N*-oxide function, at room temperature.

Acknowledgements: C.H.L.C.C., PEDECIBA.

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Antifeedant Activity Evaluation of Withanolides from *Jaborosa integrifolia*

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Abstract: Antifeedant activity of the 4-deoxi-27-hydroxi-withanolides (**1**, **2** y **3**) isolated from *Jaborosa integrifolia* (*Solanaceae*) was investigated in caterpillar *Spodoptera littoralis* on Leaf Disk Choice Bioassay. Results indicate that the best feed inhibition effect is due to *Jaborosalactone A*.

Introduction

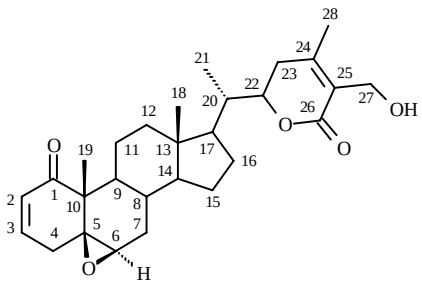
Jaborosa integrifolia (Solanaceae) is native from Argentina. Our phytochemical studies on this species confirm the occurrence of withanolides in roots. The compounds named Jaborosalactones A (**1**), B (**2**) and D (**3**) were isolated in previous studies of this species and from *Vassobia breviflora* (SENDTN.) HUNZ. (Sub. nom.: *Acnistus brevilorus* GRISEB.) [1-4].

In an interdisciplinary project for bioactive compounds research from natural sources we determined biological properties of the tree withanolides (**1**, **2** and **3)** isolated from *J. integrifolia*. These compounds were evaluated as antifeedant on leaf choice disk test with fresh leaf of *Zea mais* and *Cucurbita peppo.*

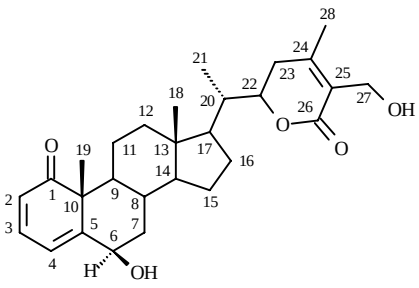
From the consumed area dates is calculated the antifeedant index as **(1 - T/C) x 100**, where **T** and **C** are, the consumed area of treated and control disks respectively [5].

Experimental

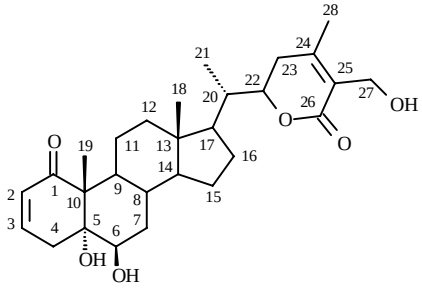
The dried and powered roots of *J. integrifolia* were extracted with ethanol at room temperature and concentrated at reduced pressure. The residue was taken with hexane-methanol-water and so deffated. The methanolic layer was concentrates *in vacuo*, the methanol was eliminated and the water was extracted with chloroform. The chloroformic layer was concentrated *in vacuo* and the extract was processed by chromatography yielding three withanolides Jaborosalactone A (**1**), Jaborosalactone B (**2**) and Jaborosalactone D (**3**). Bioassays with *S. littoralis* were made according standard procedure.



(1) Jaborosalactone A



(2) Jaborosalactone B



(3) Jaborosalactone D

Results and discussion

Results indicate that the compound **1** show a potent feeding inhibitory effect for the caterpillars. We observe a 74% of feeding inhibition (p = 0,05) in the disk treated with 20 μg-cm^2. The dates for compounds **2** and **3** indicate that these compounds has not significant effect (+ 19% and – 19%, p = 0.05, respectively) on the alimentation of the caterpillars. We conclude that exist correlation between the marked difference on the antifeedant effect and the differential structural arrangement in A and B rings of the withanolides tested.

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UV Spectral Properties of Benzophenone. Influence of Solvents and Substituents

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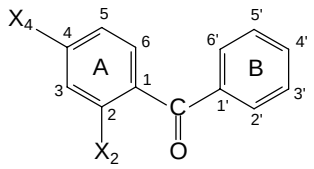
Abstract: The effect of the solvent and the substituents on the UV spectroscopic properties of substituted benzophenones was studied.

Introduction

Benzophenones (BP) are of great biochemical [1], medicinal [2], industrial [3,4] and physicochemical [5-7] interest. The effect of solvent on the UV spectra of substituted benzophenones was studied in order to detect the existence of molecular interactions and determine their UV spectroscopic behavior.

Experimental



The following compounds were analyzed: **1**: BP (X_2=X_4=H); **2**: 4-MeO-BP (X_2=H, X_4=MeO); **3**: 4-OH-BP (X_2=H, X_4=OH); **4**: 2-OH-BP (X_2=OH, X_4=H); **5:** 2OH,4MeO-BP (X_2=OH, X_4=MeO). The UV spectra and corresponding molar absorptivities were recorded at 25ºC, in *n*-Heptane (*n*-Hp), Cyclohexane (Cy), Ethanol (EtOH) and 38% Ethanol:Water (EtOH:H_2O) with a Shimadzu UV 160A.

Results and Discussion

In the Benzophenones, both phenyls can interact with the C=O group through σ (inductive effect) and π (mesomeric effect) bonds. The overlapping between the π bonds of the rings and of the C=O form a MO that comprises all the molecule. Due to this π-electronic delocalization, the C=O group loses part of its individual character and partially integrates with the phenyls, leading to system stabili-

zation and transference of the electronic deficiency from the atom of $C_{carbonylic}$ toward the atoms of the positions 2, 4, 6, 2', 4' and 6'. **A)** ***Effect of solvent.*** The UV spectrum of BP in *n*-Hp exhibits 3 bands: I: 203.6, II: 248.2 and III: 346.6nm. The UV spectrum of Cy is very similar, while in EtOH differences were noted: I: 205.6, II: 252.2 and III: 334.0nm. The shifts of bands I, II and III were: $\Delta\lambda$=+1.6, $\Delta\lambda$=+4.0 y $\Delta\lambda$=-12.6nm. These $\Delta\lambda$ [8,9] indicate that bands I and II are due to $\pi \rightarrow \pi*$ transitions (benzene), while band III is originated by a $n \rightarrow \pi*$ transition (O of the carbonyl). **B)** ***Effect of substituent.*** The UV spectra of **2** and **3** in *n*-Hp are characterized by I: 201.6, II: 247.6, III: 339.2nm y I: 205.8, II: 250.4, III: 332.0nm, respectively. The relation $\lambda = 31.91\ \sigma_p + 346$ (R=0.971) was found, where σ_p is the Hammett constant. With electron-donating groups, the resonant structure with separate charges are the most probable in the resonance hybrid, requiring more energy for the $n \rightarrow \pi*$ transition. **C) H*ydrogen bonds.*** The blue shift of band III of **1**, when passing from *n*-Hp to EtOH, is due to H bonds between the solute and the solvent [10]. The intensity of these intermolecular bonds might account for the absence of band III of **2** and **3**, in EtOH and EtOH-H_2O. In **4**, band III can be clearly seen in *n*-Hp (338.2nm), EtOH (336.8nm) and EtOH-H_2O (335.8nm). The $\Delta\lambda$=-1.4nm y $\Delta\lambda$=-2.4nm observed are lower than those of **1**. This is due to the fact that solute-solvent intermolecular H bonds are of less importance than the strong H intramolecular bond exhibited by compound **4.** The UV behavior of BP **5** is similar to that of **4.**

Acknowledgements: This work was supported by Secretaría de Ciencia y Técnica de la Universidad Nacional de San Luis and by CONICET.

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Determination of the pKa of Benzophenones in Ethanol-Water

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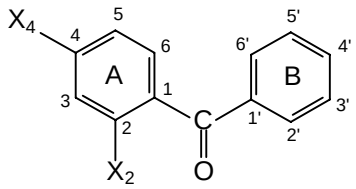
Abstract: The pKa of monohydroxylated benzophenones was determined by UV spectroscopy. The values obtained are coherent with the resonant forms and hydrogen bond intramolecular of the analyzed compounds.

Introduction

The pKa of a drug is one of the most important parameters to explain its physicochemical behavior and acid-base properties [1], to program assays of pharmaceutical preformulation [2], etc. In this work, the pKa values of monohydroxylated benzophenones (BP) were determined by UV-visible spectroscopy. These substances exhibit interesting adsorptive properties, they act as ligands in the complexation of metallic ions and, also, they have biochemical applications as antimicrobial agents and in industry as commercial sun blocks [3].

Experimental



The figure shows the basic structure of the analyzed aromatic ketones: **1:** 4(OH)-BP (X_2=H, X_4=OH); **2:** 2(OH)-BP (X_2=OH, X_4=H); **3:** 2(OH),4(CH_3O)-BP (X_2=OH, X_4=CH_3O). For pKa determination, a UV-vis spectroscopic procedure based on the Henderson-Hasselbalch [4] was used. The buffer solutions used were: a) HCl-KCl, pH 1.5; b) NaOH-KCl, pH 12.5; c) KH_2PO_4-Na_2HPO_4 0.01M for a 7.2-8.0 pH interval; d) Na_2CO_3-$NaHCO_3$ 0.01M, pH 9.2-10.0. All buffer solutions were prepared with a 20% w/w ethanol-water mixture, keeping the ionic strength constant (0.05) with KCl.

Results and Discussion

The maximum absorption wavelengths record for the acid (λa) and ionized (λb) forms of the BP were: λa (**1**) 294.5nm, λb (**1**) 348nm; λa (**2**) 334nm, λb (**2**) 382nm; λa (**3**) 320nm, λb (**3**) 372nm. The pKa determined were the following: pKa (**1**)=7.83; pKa (**2**)=9.54 and pKa (**3**)=9.60. The carbonyl group of the benzophenones interacts with the adjacent aromatic rings through the σ and π bonds, favoring the π-electronic delocalization of the molecules. The participation of the C=O group in the conjugate molecular system is reflected in its bonding characteristics and in the influence it exerts on the acid-base properties of the hydroxyl groups. The increase of the pKa values in the order pKa (**1**) < pKa (**2**) < pKa (**3**) is coherent with the resonant forms and intramolecular hydrogen bonds exhibited by BPs **2** and **3**. The pKa of **1** is markedly lower than that of 4(OH)-chalcone, pKa=8.17 [5]. This indicates that the C=O α,β-unsaturated group of the chalcone, increase the π-electronic delocalization of the molecule, decreasing the acidity of the H atom the OH group at position 4.

Acknowledgements: This work was supported by Secretaría de Ciencia y Técnica de la Universidad Nacional de San Luis and by CONICET.

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Synthesis and *In Vitro* Antigungal Properties of 4-Aryl-4-N-arylamine-1-butenes and Related Compounds

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Abstract: A new series of 4-aryl and 4-alkyl-4-N-arylamine-1-butenes (homoallylamines) were synthesized and some of them transformed to 4-aryl or alkylquinolines. All of them showed strong antifungal activities against human pathogenic fungi *in vitro*, being *Epidermophyton floccosum* the most susceptible species.

Introduction

As part of our project devoted to the search for antifungal agents [1-3], we synthesized a series of new 4-aryl- or 4-alkyl-N-arylamine-1-butenes and transformed some of them into biologically important 2-substituted 4-methyl-tetrahydroquinolines and quinolines [4]. We evaluated them for antifungal properties with agar dilution assays and studied their structure-activities relationships (SAR).

Experimental

Chemistry. Homoallylamines **12-22** were prepared *via* the addition of Grignard reagent to aldimines **1-11.** Electrophilic cyclization of two of them, compounds **12** and **13** under acidic conditions, led to tetrahydroquinolines **23** and **24**, which were oxidised to quinolines **25** and **26** with DDQ (Scheme 1)

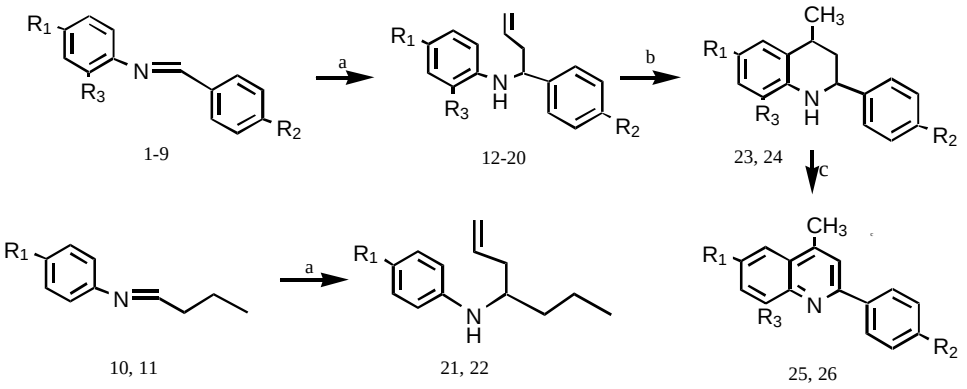
Microorganisms. We used standardized human pathogenic fungi from CEREMIC or ATCC. at concentrations up to 50 μg/mL [1,2].

*Antifungal evaluation.*The dilution agar method was used according with reported procedures [1,2].

Results and Discussion

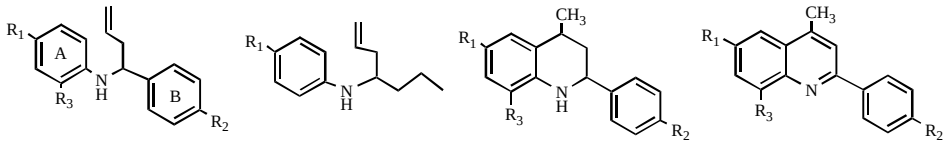
All compounds tested showed antifungal properties against dermatophytes (3.12<MIC<50 μg/mL), in particular against *Epidermophyton floccosum,* similar to those obtained with Amphotericin or Ketoconazole (Table 1). Substituents on benzene rings A or B increased four times the activity respective the non-substituted analogs. The change of an OMe from position 4 to 2 in rings A or B increased the activity twice.

Scheme 1



a)Allyl bromide+Mg/Et_2O, 1O°C; b)H_2SO_4 75% W/V; c)DDQ/Bz,

Table I. MIC values (μg/mL) of homoallylamines, tetrahydroquinolines and quinolines acting against dermatophytes.



Compd	Type	R_1	R_2	R_3	*M. c.*[a]	*M.g.*[b]	*T. m.*[c]	*T. r.*[d]	*E. f*[e]
12	C	H	H	H	30	30	30	30	12.5
13	C	CH_3	H	H	30	>50	>50	>50	3.12
14	C	OCH_3	H	H	30	>50	30	30	3.12
15	C	F	H	H	>50	>50	>50	>50	30
16	C	Cl	H	H	>50	>50	>50	>50	30
17	C	Br	H	H	>50	>50	>50	>50	30
18	C	H	OCH_3	H	30	>50	>50	>50	3.12
19	C	Cl	$N(CH_3)_2$	H	>50	>50	>50	>50	>50
20	C	H	H	CH_3	30	>50	>50	>50	3.12
21	D	H	-	-	>50	>50	>50	>50	>50
22	D	CH_3	-	-	>50	>50	>50	>50	>50
23	E	H	H	H	50	25	25	25	12.5
24	E	CH_3	H	H	50	25	25	25	12.5
25	F	H	H	H	25	12.5	12.5	25	12.5
26	F	CH_3	H	H	0.75	12.5	25	12.5	12.5
Amp.[f]					>50	6.25	6.25	25	0.3
Ket.[g]					15	6.25	12.5	15	25

[a]Microsporum canis C 112. [b]Microsporum gypseum C 115.[c]Trichophyton mentagrophytes ATCC 9972. [d]Trichophyton rubrum C 113. [e]Epidermophyton floccosum C 114. [f]Amp.= amphotericin B. [g]Ket.=ketoconazole.

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$S_{RN}1$ and Stille Reactions: A New Synthetic Strategy

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Abstract: The photostimulated reaction of Me_3Sn^- ion with mono, di and trichloro arenes in liquid ammonia gave very good yields of stannanes by the $S_{RN}1$ mechanism. These products reacted by a palladium-catalized cross coupling reaction with halobenzenes to give phenylated products also in very goods yields. Similar yields can be obtained in one-pot reactions.

Introduction

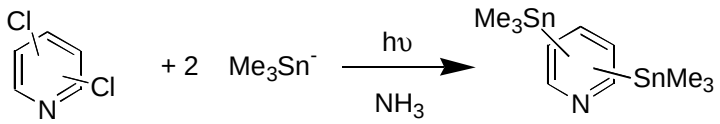
The radical nucleophilic substitution, or $S_{RN}1$ reaction, is a process through which a nucleophilic substitution is obtained [1]. The scope of the process has considerably increased and nowadays it is an important synthetic possibility to achieve substitution of different substrates. Several nucleophiles can be used, such as carbanions and anions from compounds bearing heteroatoms, which react to form new C-C or C-heteroatom bonds in good yields. We thought that the photostimulated reaction of mono-, di- and trichloro- arenes with Me_3Sn^- ions in liquid ammonia to synthesize the trimethylarylstannanes followed by the Pd(0) cross coupling reaction with haloarenes (Stille Reaction) [2,3] would be an important approach for the synthesis of arylated or polyarylated compounds [4]. Thus, we undertook the study of the palladium catalyzed reaction of trimethylarylstannanes, synthesized by the $S_{RN}1$ mechanism, with mono-, di- and trichloro- arenes as a model reaction for this methodology. Also we performed both reactions in one-pot procedures.

Experimental

Organotin compounds were obtained by photostimulated reactions in liquid ammonia. Irradiation was conducted in a reactor equipped with two 250-W UV lamps emitting maximally at 350 nm. Cross coupling reactions were carried out with $Pd(PPh_3)_2Cl_2$ as catalist (3-6%) and DMF as solvent.

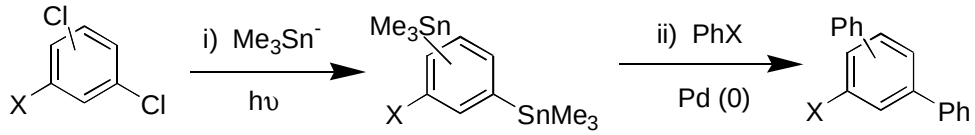
Results and Discussion

The photostimulated reactions of Me_3Sn^- with dichloropyridines, di- and trichlorobenzenes afford di and tritin compounds in very goods yields:



2,5: 88%
2,6: 86%
3,5: 80%

The palladium catalized cross coupling reactions of stannanes and aryl halides (PhBr or PhI) gave the respective arylated compounds:

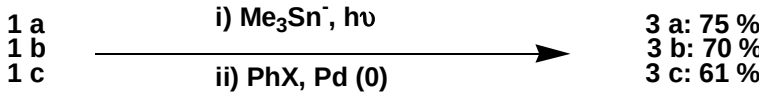


1 a: X=H, *m*
1 b: X=H, *p*
1 c: X=Cl, *m*

2 a: X=H, *m* (90%)
2 b: X=H, *p* (88%)
2 c: X=Me_3Sn, *m* (71%)

3 a: X=H, *m* (97%)
3 b: X=H, *p* (90%)
3 c: X=Ph, *m* (89%)

We also studied the possibility of performing the synthesis of the stannane and the Stille reaction in a one-pot procedure:



All these results indicated that the $S_{RN}1$ mechanism is an excellent method to obtain stannanes by the photostimulated reactions of mono-, di- and trichloro arenes with Me_3Sn^- in liquid ammonia. The stannanes thus obtained can be arylated by further reaction with bromo or iodoarenes through the palladium catalyzed reactions (or to perform other palladium-catalyzed reactions). Further work is in progress to examine reactions in a stepwise or one-pot conditions.

Acknowledgements: This work was supported in part by CONICOR, FONCYT AND CONICET. E.C. gratefully acknowledges receipt a fellowship from Conicet.

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Citotoxic Activity of Extracts and Sesquiterpene Lactones from *Stachycephalum argentinum*

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Abstract: The extracts and sesquiterpene lactones of *S.argentinum* were assayed to determine their biological activity on *Artemia salina*. The most active compound was costunolide (**1**) with LD_{50}= 62 ppm.

Introduction

Our previous phytochemical study of ***Stachychephalum argentinum*** (*Asteraceae*), revelead the presence of several skeletal types sesquiterpene lactones [1].

In order to explore new natural bioactive products, we started an study of different extracts from *S. argentinum* and some of the sesquiterpene lactones isolated, to determine the citotoxic effect against the microorganism *Artemia salina* (Leach).

The Brine Shrimp Bioassay determine that compounds with values of LD_{50}< 1000 ppm could be considered as citotoxic products [2].

Experimental

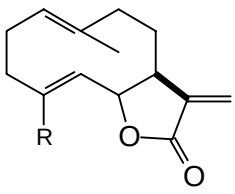
Citotoxic Bioassay against *Artemia salina* was has been described previously [3].

Results and Discussion

Extracts **B** and **C** resulted in a marked loss of toxic activity against *A. salina*. Extract **B** showed 60% lethality and Extract **C** showed 33% lethality at 1000 ppm.

Active compounds against this organism appeared to be costunolide (**1**) (100%), 15-acetoxycostunolide (**2**) (60%) and 8-desoxysalonitenolide (**3**) (100%). Compounds such as the eudesmanolides: **4**, **5** and **6** were inactive against *A. salina*.

The most citotoxic compound was costunolide (**1**) with LD_{50}= 62 ppm.

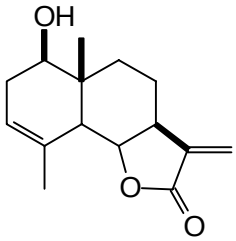


R

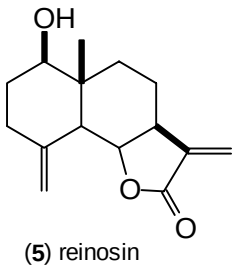
CH_3 (**1**) costunolide

CH_2OAc (**2**) 15-acetoxycostunolide

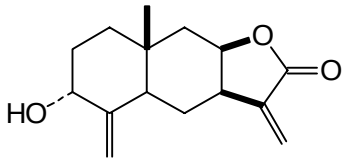
CH_2OH (**3**) 8-desoxysalonitenolide



(**4**) santamarin



(**5**) reinosin



(**6**) isotelekin

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Phytotoxic Activity of a Benzofuran Isolated from *Trichocline reptans*

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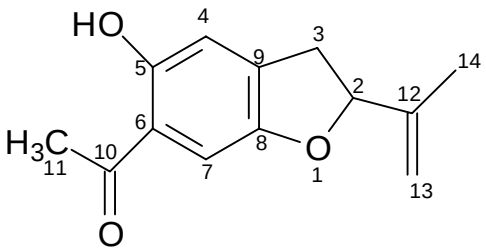
Abstract: Phytotoxic Activity of the 6-acetyl-5-hydroxy-2isopropenyl-2,3-dihydrobenzofurane (**1**) isolated from *Trichocline reptans* (*Asteraceae*) was investigated in two weed species. Results indicate that the best growth inhibition effect ocurres on *Chenopodium album* weed. Phythotoxic effect of the *T. reptans* chloroformic extract and of the benzofurane are discussed and compared in the two weed species.

Introduction

In previous phytochemical study in *Trichocline reptans* (*Asteraceae*) collected in Salta, Argentina, we identified benzofurane **1**, linear furanocoumarins and coumarins [1].



(1)

Regarding the importance of benefical or toxic biochemical interactions that ocurrs between higher plants, where Allelopatie is the reference [2], we evaluated the phytotoxic effect of both the extract of *T. reptans* and the benzofurane on two weed species that affect our country cultivars, *Chenopodium album* and *Sorghum halepense*. We tested the inhibitory effect on radicle and leaf growth [3].

Experimental

Dihydrobenzofurane **1** was isolated from the Cl_3CH extract by “dry column chromatography” method. The structure of this compound was elucidated by spectroscopic methods: UV, IR, ^{1}H- RMN ,

^{13}C- RMN and EM.

The Phytotoxic Assay [3], was carried out on *Chenopodium album* and *Sorghum halepense* with aqueous solutions (80 ppm) of the $HCCl_3$ extract and the dihydrobenzofurane. The data were taken after 7 days of incubation. Examination and summaries of data are based on analyses of variance (block design ANOVA).

Results and Discussion

The results of phytotoxic assay, led us to suggest that **1** produces significant effect on the growth of Dicotiledoneous weed *Ch. album*, where there is a marked radicle inhibition (>50%) than on the Monocotiledoneous weed *S. halepense.* We compared the treatments with the extract and the pure compound and the selectivity of their phytotoxic action.

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Fluorimetric Determination of Carbamate Pesticides in Host-Guest Complexes

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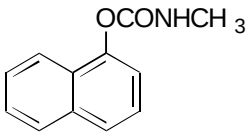
Abstract: From the effect of β-cyclodextrin and hydroxypropyl-β-cyclodextrin on the UV-visible and fluorescence spectra of carbaryl and carbofuran, the values of association constants were determined. The ratio of the fluorescence quantum yields for the bound and free substrates indicated an enhanced fluorimetric method of detection.

Introduction

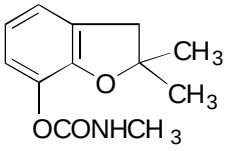
The study of organized systems has proved to be very useful for analytical purposes.[1] These microheterogeneous systems can be classified into: molecular aggregates (micelles, vesicles, monolayers, etc.) and polymolecular species (polysilicates such as zeolites; polysugars such as cyclodextrins (CD); polyethers such as crown ethers). The cavities or pores with defined sizes in these permanent molecular systems favour inclusion or complexing small molecules leading to high selectivity of these molecules. In these complexes, known as supramolecular species, are produced specific interactions that play an important role in the modification of physical and chemical properties of the substrates included.[2] Several photochemical and photophysical studies have been done with these receptors to investigate inclusion with substrates that have, for example, luminiscent properties. A remarkable increase of these properties was found.

The molecular luminiscent spectrometry and in particular molecular fluorescence has become a routine technique with many analytical applications [3] that offers a lower detection limit and with higher selectivity than the absorption spectroscopy.

Some pesticides from the carbamate group (-$OCONH_2$) derived from fluorescent nuclei such as naphthalene, for example carbaryl (1-naphthyl-N-methylcarbamate, **CY**), or such as benzofuran, for example carbofuran (2,2-dimethyl,2-3-dihidro-7-benzofuranyl-N-methylcarbamate, **CF**) are widely used for plant protection against insects. However, the high toxicity of these pesticides requires sensitive and reliable methods to detect their presence in fruits and seeds. Therefore, an improved determination of these pesticides in presence of certain receptors is here proposed.



CY



CF

Experimental [4]

UV-Visible absorption spectra of **CY** and **CF** (analytical grade commercial reactives) were performed in neutral aqueous, acid or basic medium in absence and in presence of 10 mM β-CD (cyclic oligomer with 7 glucose units) or HP-β-CD (CD derivatized). The two carbamates **CY** and **CF** showed decomposition at alkaline pH so pH=7 was selected for the determinations. The presence of β-CD and HP-β-CD produced changes in the UV-Visible spectra. The excitation wavelengths (λ_{ex}) chosen for the fluorescent measurements were the λ where the substrate and the complexed substrate presented the same molar absorptivity (ε); it being 280 nm for **CY** and 273 nm for **CF**. Fluorescence emission spectra of the aqueous solutions were taken from each substrate at absorbance concentrations lower than 0.050 at the λ_{ex} chosen in each case with 10 nm excitation and emission widthbands, at low gain for emision spectra. The spectrofluorimeter cell was thermostatized at 25.0±0.1 °C. The areas below the curves (F) and the fluorescent intensities at different λ (F_λ) were recorded. All measurements were performed using a substrate solution at pH=7 as reference, to check the response of the apparatus.

Results and Discussion

The association constants (K_{ass}, M^{-1}) could be determined by UV-visible and fluorimetry obtaining values of 190 and 123 for **CF** and 350 and 644 for **CY** with CD and HP-β-CD respectively. The values of the quantum yield ratios ($\Phi_{complexed}/\Phi_{free}$) were 1.30 for **CY** but 7.02 and 9.48 for **CF**. The detection limits expressed as a limit concentration (C_L= ng/mL) were determined employing the corresponding analytical and statistical methods. Notable enhancement of these limits was achieved for the compounds studied.

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Synthesis of Ethylenic and Acetylenic Triorganotins with Bulky Organic Ligands

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Abstract: The syntheses of trineophyl- (1a) and tri-(-)-menthylstannyl phenylacetylene (**1b**) as well as that of (E)-1-trineophylestannyl-2-phenylethene (**2**) and (E)-1-trineophylstannyl-1,2-diphenylethene (**3**) are described. The hydrostannation of **1a** with an excess of trimethyltin hydride led to 1,1,1-tris(trimethyltin)-2-phenylethane (**4**) and/or 1,1-bis(trimethyltin)-2-phenylethene (**5**) depending on the reaction conditions.

Keywords: tin hydride, vinylstannanes, addition, stereoselectivity, substitution.

Introduction

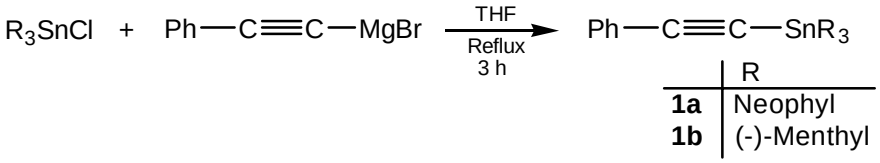
In previous studies carried out with trineophyltin hydride we have found that the size of the organic ligands attached to the tin atom affects not only the reactivity but also the stereoselectivity of the reactions of this hydride [1]. In order to study the effect of the size of the organic ligands on the stereochemistry of the hydrostannation, trineophyltin hydride was added to acetylenic systems under radical conditions. It was also started a study on the synthesis of organotin compounds with more than one triorganotin moiety, *via* the addition of trimethyltin hydride to trineophylstannyl phenylacetylene (**1a**).

Experimental

Compounds of type **1** were obtained with an average yield of 60% by modification of known techniques [2]. The hydrostannation reactions were carried out under free radical conditions as shown in the Scheme.

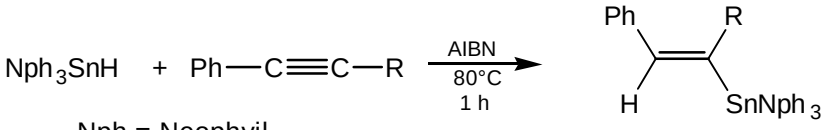
Results and Discussion

The obtained results are summarized in the following Scheme. The radical addition (Eq. 2) of trineophyltin hydride to both phenyl- and diphenylacetylene leads stereoselectively to the E isomers.



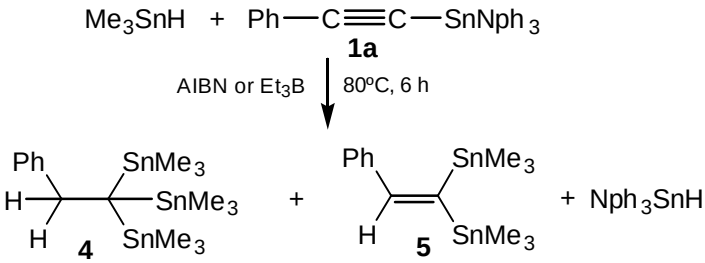
(1)

	R
1a	Neophyl
1b	(-)-Menthyl



(2)

	R
2	H (99%)
3	Ph (80%)



(3)

Whereas the addition of trimethyltin hydride to **1a** in a ratio hydride/**1a** = 5/1 gave a mixture of compound **4** (65%) and trineophyltin hydride, using a ratio hydride/**1a** = 4/1 a mixture of trineophyltin hydride and compounds **4** (73%) and **5** (27%) was obtained. This strongly suggests that the first step in these reactions might be the substitution of the trineophyltin moiety by the trimethyltin group followed by the addition of the trimethyltin hydride.

Acknowledgements: This work was supported by CONICET (Buenos Aires), CIC (Provincia de Buenos Aires) and Universidad Nacional del Sur (Bahía Blanca, Argentina).

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New Spiranoid Withanolides From *Jaborosa Odonelliana*

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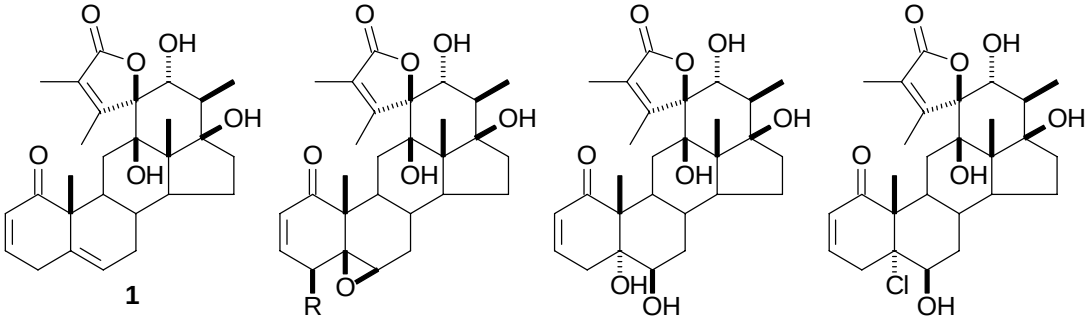
Abstract: From whole *Jaborosa odonelliana* plants four new withanolides containing a spiranic lactone in the side chain, were isolated and their structures elucidated by spectroscopic methods.

Introduction

As part of our studies of the withanolides of argentine species of the genus *Jaborosa* we have reinvestigated *Jaborosa odonelliana* from which we had isolated several years ago the unusual withanolide jaborosalactone P (**1**) [1]. *J. odonelliana* grows in the northwest of Argentina, mainly in arid and sandy soils. From plants collected in the province of Salta we have now isolated, besides jaborosalactone P, four new spiranoid withanolides (**2**-**5**), which differ from **1** in the substitution pattern of rings A and B.



Experimental

Plant material and isolation procedure: Whole plants of *J. odonelliana* A. T. Hunziker were collected in El Jardín, Depto la Candelaria, Salta. Dried and pulverized plants, were extracted succesively with ether and ethanol at room temperature and both extracts evaporated. The combined residues were

fractionated by flash chromatography, RP-HPLC and prep. TLC rendering **1** and four more polar withanolides.

Results and Discussion

The ^{1}H and ^{13}C NMR spectra of compounds **2-5** showed resonances for rings C, D and the side chain, almost identical to those of jaborosalactone P (**1**); thus, the main difference among the five withanolides was established to be in the functionalization of rings A and B. Compound **3**, differed from the other four in the multiplicity pattern of the olefinic protons H-2 and H-3 which corresponded to a 4-substituted withanolide. The presence of additional resonances asigned to an oxygenated CH in the ^{1}H and ^{13}C NMR spectra (δ 3.76 and 69.3 respectively) confirmed the 4β-hydroxy substitution. The epoxide, diol and clorohydrin substituents of **2**, **4** and **5** were identified by comparison of the NMR spectra with similarly substituted withanolides and by MS. To this date, spiranoid withanolides containing a C-C bond between (C-12) and the side chain (C-23) have only been found in *J. odonelliana*, *J. araucana* and *J. runcinata* [1,2]. The spiranoid withanolide, jaborosalactone **1** [2], isolated from the latter species, showed antitumor activity in *in vitro* tests for induction of quinone reductase on mouse hepatoma cells (hepalclc7) [3].

Acknowledgements: We thank CONICET (Argentina) and Universidad de Buenos Aires for financial support.

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Synthesis of Aziridinosteroids

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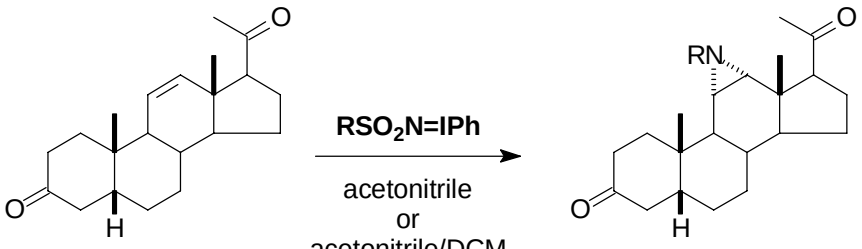
Abstract: 11α,12α-aziridinosteroids **(2a**, **b**, **c**) were prepared from 5β-H-11-pregnene-3, 20-dione (**1**) using different iminophenyliodinanes and cloramine aziridination reagents.

Introduction

The presence of an heteroatom, either replacing a methylene group of the steroid nucleus or as a substituent gives rise to major changes in the biological activity of steroid derivatives [1]. Thus, many steroidal nitrogen derivatives are pharmacologically important. Furthermore, 12α-amino steroids have recently found application as chiral templates for combinatorial synthesis [2]. As an alternative way to introduce nitrogen functionalities into the steroid nucleus, we have explored the aziridination of steroidal double bonds. Aziridine ring opening with a nucleophile would yield aminosteroids with defined stereochemistry [3,4]. We describe the synthesis of 11α,12α-aziridinosteroids **(2a**, **b**, **c**) by reaction of 11-pregnen-3,20-dione (**1**) with different aziridination reagents.



1

2a R = Ts
2b R = Ns
2c R = SES

Experimental

Typical aziridination procedure: Copper (I) triflate (0.065 mmol) and 11-pregnen-3,20-dione (**1**, 0.65 mmol) were added under argon to a suspension of molecular sieves 4 Å (185 mg) in dry acetonitrile (1.65 ml). SES-iminophenyliodinane (1.7 eq) was then added in 15 portions every 30 min with

vigorous stirring and stirring continued for 24 h at 25°C. The reaction mixture was filtered, evaporated to dryness and purified by column chromatography to yield **2c** (53% yield).

Results and Discussion

The aziridination reaction was carried out on several olefins (ciclohexene, styrene, norbornene, methyl acrylate, etc.) with a series of N-sulfonyl iminophenyliodinanes and N-SES chloramine sodium salt and different catalysts (Cu (I) and Cu (II) triflate, PTAB, Py.HBr_3). With ciclohexene and (p-chlorobenzenesulfonyl)-iminophenyl iodinane the aziridine was obtained in 52% yield; cleavage with thiophenol followed by removal of the PhS group gave cycloheylamine in 95% yield.

Steroid **1** was treated with (tosylsulfonyl) and (nosylsulfonyl)-iminophenyliodinane in acetonitrile-dichloromethane 1:1, rendering stereospecifically the 11α,12α-aziridinosteroid (**2a**, **b**) with moderate yields (25-30%). Stereochemistry was established from the NOESY spectra (correlations H-19/H-11β and H-18/H-12β).

Attempts to aziridinate the 5,6 double bond in pregnenolone and pregnenolone acetate gave complex mixtures. On the other hand, the 4,5 conjugated double bond in progesterone was inert under the reaction conditions used.

To facilitate the deprotection step to give the free aziridine, (N-(2-trimethylsilyl)-ethanesulfonyl)-iminophenyliodinane (PhI=NSES) was used as aziridination reagent. In this case, using acetonitrile as solvent, **1** rendered derivative **2c** in 53% yield. Aziridination of **1** with the sodium salt of (N-(2-trimethylsilyl)-ethanesulfonyl)-chloramine in acetonitrile gave **2c** in only 27% yield.

Acknowledgements: We thank Universidad de Buenos Aires, ANPCYT (Argentina) and ECOS (France) for financial support.

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3,3-Dimethylacylthioureas: "S", "-S", "U" or "W" Conformation?

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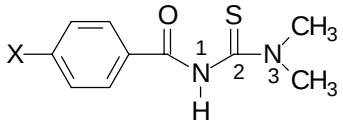
Abstract: We report a study of 3,3-dimethyl substituted acylthioureas. X ray data and quantum mechanical calculations demonstrated that the "S" conformation is the most stable both for the acylthioureas and the corresponding anions. The high regioselectivity towards S-alkylation is explained on the basis of the localization of the HOMO mainly over the sulfur atom.

Introduction

The acylthioureid group present in acylthioureas [1], contains three heteroatoms of different hardness. Thus it is expected that depending on the reaction conditions different series of N, O, or S alkylated derivatives may result [2]. The goal of this work was to study the reasons that favor the experimentally observed isothiourea formation (S-alkylation product) [3].

Experimental

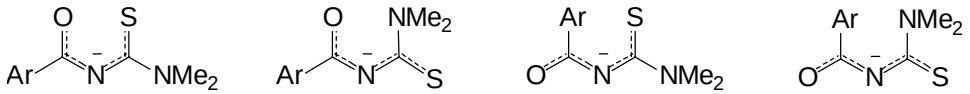
Acylthioureas studied: 1-(4'-X-benzoyl)-3,3-dimethylthiourea, with X = H, Me, Br, Cl were obtained by a 3 step synthetic sequence as described previously [2]. X-ray difraction studies were carried out on single crystals of the latter 3 compounds.



Geometry optimization: Were carried out with the programs Hyperchem 5.02, MOPAC 6.0 and Gaussian 94.

Results and Discussion

The main 4 conformers (S, -S, U and W) of the compounds mentioned in Experimental and their corresponding anions were optimized using semiempirical (AM1 and PM3) and *ab initio* methods. The calculated structures were compared with single crystal X-ray difraction data when available. Experimental and calculated geometries, predict the S conformation as the most stable for the four thioureas. HF calculations also predict the S conformation as the most stable for the corresponding anions, independently of the electronegativity of the substituent X.



U **S** **-S** **W**

Frontier orbital calculations, show that the HOMO in the anions is localized mainly over the sulfur atom. Larger substituents on N-3 (*e.g.* 3,3-diethyl substituted analogs), do not show differences regarding the preferred conformation.

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Synthesis of D-Homo Analogs of Neurosteroids

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Abstract: 17(13→18)-Abeo and D-homo analogs of the natural neurosteroid 3α-hydroxy-5αH-pregnan-20-one were prepared by anionic or radical (mercury (II) hydride mediated) rearrangements of steroidal cyclopropylketones respectively.

Introduction

Certain steroids show an inhibitory effect on the central nervous system by a fast non-genomic action on the γ-aminobutiric acid receptor (GABA-A), similar to that produced by benzodiazepines [1]. Structure-activity relationship studies for this interaction, indicate that the requirements for activity are a reduced pregnane or androstane skeleton (A/B *cis* or *trans*), a 3α-hydroxyl and a carbonyl at C-20 (or C-17 in androstanes). Several of these compounds have shown anticonvulsant properties (potential antiepileptics) [2]. Conformational studies are very limited and cannot be used to assess the influence of steroid conformation on activity. Our group has developed several efficient procedures for the preparation of steroid hormone analogs, based on radical or anionic expansión of fused cyclopropylketones [3,4]. We have now adapted these procedures for the preparation of 17(13→18)-*abeo* and D-homo analogs of natural neuroesteroids, with enhanced flexibility in the C/D ring junction.

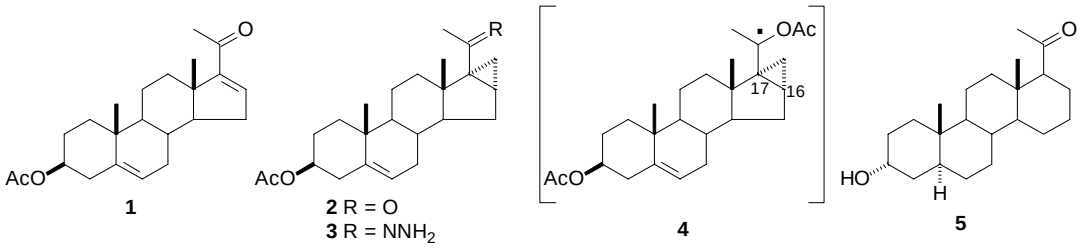
Experimental

16-Dehydropregnenolone acetate (**1**) and 11α-hydroxyprogesterone were used as starting materials. Products were purified by flash chromatography on silicagel and fully characterized by ^{1}H and ^{13}C NMR (1D and 2D) and MS.

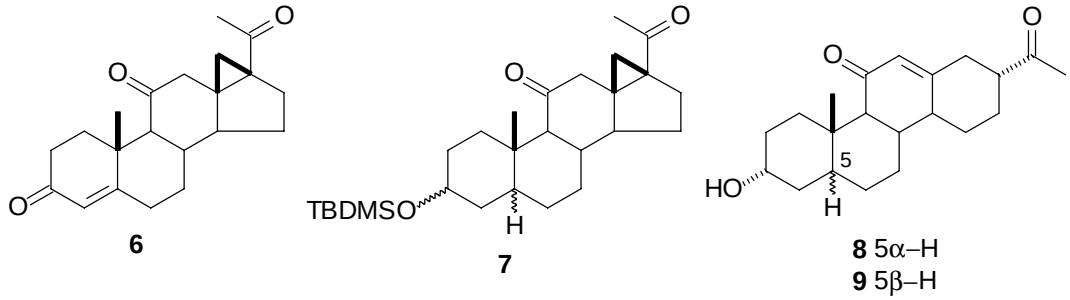
Results And Discussion

Radical rearrangement: Cyclopropylketone **2** obtained by reaction of 16-dehydropregnenolone (**1**) with dimethylsulfoxide methylide, was converted into hidrazone **3** (N_2H_4/BaO); reaction of **3** with HgO/$Hg(AcO)_2$ followed by treatment with $NaBH_4$ produced ethe alkoxycarbinyl radical **4** which rearranges with cleavage of the 16,17 bond to give the 6 membered D ring. Hydrolysis of the acetate at C-

3, reduction of the 5,6 double bond (H_2/Pd-C) and Mitsunobu inversion at C-3 rendered D-homo analog **5**. This compound presents a closer similarity with the natural steroids than the 17(13→18)-*abeo*analogs (see below), as the side chain is not displaced and the angular methyl at C-13 is preserved.



Anionic rearrangement: The 5α-H (**8**)and 5β-H (**9**) analogs of 3α-hydroxy-17(13→18)-abeopregn-12-ene-11,20-dione were prepared by anionic rearrangement of the enolate from the mixture of cyclopropyldiketones (**7**) (NaOH/MeOH) [3]. Other key steps were the chemoselective reduction of the conjugated system in ring A of **6** (Ni/Al, MeOH/HONa) to give the isomer mixture at C-5 and C-3 and the selective deprotection of the TBDMS group from the equatorial hydroxyls at C-3 in the presence of the axial isomers for both series of analogs.



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A New Rearranged Non-Aromatic Salpichrolide from *Salpichroa Origanifolia*

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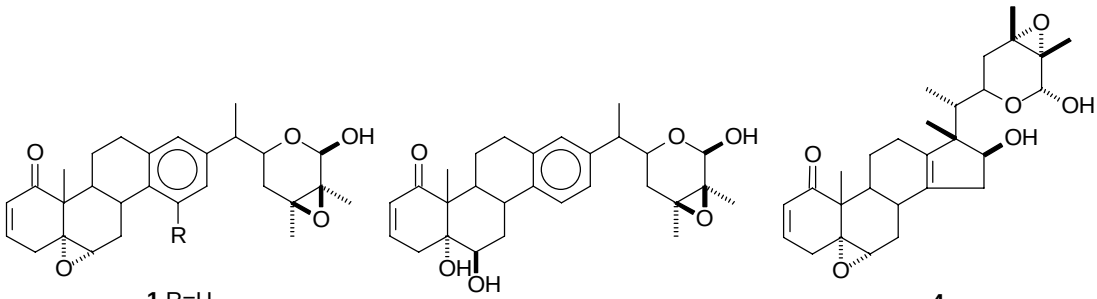
Abstract: From the aerial parts of *Salpichroa origanifolia* a new withanolide in which the C-13 angular methyl has migrated to C-17, was isolated and characterized by spectroscopic methods.

Introduction

In previous studies of *Salpichroa origanifolia* (Lam.) Thell collected in the provinces of Cordoba [1,2], Buenos Aires [3,4] and Salta [5], we have isolated thirteen withanolides (salpichrolides), eleven of which contain an aromatic D ring. The main withanolides salpichrolide A (**1**), salpichrolide G (**2**) and salpichrolide C (**3**), are feedant deterrants for *Tribolium castaneum* and *Musca domestica* [6].



Continuing the isolation and characterization studies of the less abundant withanolides in *S. origanifolia* collected in Salta, we have isolated a new withanolide, salpichrolide N (**4**) which would derive *via* C-13/C-18 cleavage, from the postulated fused cyclopropane intermediate (17,18-cycloergostane) in the biosynthetic pathway leading to expansion and aromatization of the D ring.

Experimental

Plant material and isolation procedure: Whole plants of *S. origanifolia* were collected in Salta, and extracted immediately with ether and ethanol at room temperature. Both extracts were evaporated and the pooled residues fractionated by flash chromatography and prep. TLC to yield compounds **1** and **3** and five minor withanolides, four of which have been described previously by us [5]; the seventh withanolide, salpichrolide N (**4**), was characterized by spectroscopic methods.

Results and Discussion

The ^{1}H and ^{13}C NMR resonances of rings A, B and the side chain of salpichrolide N were closely related to those of salpichrolide A (**1**) [1], However there were no aromatic H signals. The ^{13}C NMR spectra showed two nonprotonated carbon resonances at δ 134.6 y 138.1 which were indicative of a tetrasubstituted double bond in rings C/D and five methyl groups. Analysis of the HMQC, HMBC and COSY-45 spectra (400 MHz), indicated that the double bond was placed at the C/D ring junction (13,14) and that the angular CH_3-18 had been shifted to position 17. Diagnostic correlations in the HMBC spectrum were observed for the methyl H-18 with C-13, C-16, C-17 and C-20. The stereochemistry of the proposed structure (**4**) was confirmed by the strong H-18/H-15β correlation in the NOESY spectrum, H-16 couplings and molecular modelling calculations.

Acknowledgements: We thank Universidad de Buenos Aires and CONICET (Argentina) for financial support and Dr E. Manta and G. Hernandez (Universidad de la República, Uruguay) for the NMR spectra at 400 MHz.

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Reactivity Comparison of D–Glucose–Derived Dienophiles. Analysis of the Conformational and Electronic Properties

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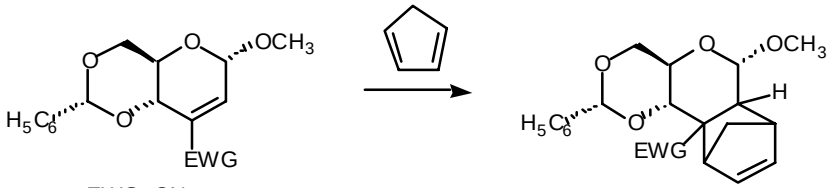
Abstract: Semiempirical calculations were performed to carry out a conformational analysis for carbohydrate-derived dienophiles **1-4**. For α,β-unsaturated carbonylic compounds **2-4**, a good correlation between Diels-Alder reactivity with calculated values for LUMO energies was observed.

Introduction

As part of our studies on the Diels–Alder reactions of D–glucose–derived dienophiles with cyclopentadiene,[1,2] we undertook a theoretical investigation on the conformational and electronic properties of the dienophilic structures **1-4**.



1, EWG=CN
2, EWG=CHO
3, EWG=C(O)CH_3
4, EWG=C(O)CH_2CH_3

The application of the frontier molecular orbital theory could be of interest since the reactivity of the dienophiles in normal Diels–Alder reaction could be correlated with their LUMO energies. This kind of theoretical treatment has been used to make important qualitative studies on the reactivity and outcome of cycloaddition reactions in different dienophilic systems, including some sugar–derived dienophiles.[3]

Experimental

The search for the minimum on the potential energy surface for the dienophiles **1-4** and cyclopentadiene were carried out using the semiempirical program AMPAC version 2.1. The calculations were performed at the Restricted Hartree–Fock (RHF) AM1 level of theory. The stationary points were obtained through adequate algorithms and characterized through a hessian matrix calculation. Finally, the relative stability and the LUMO values of the different conformers corresponding to each dienophile were analyzed.

Results and Discussion

The comparison of the energy differences between $HOMO_{diene}$-$LUMO_{dienophile}$ *versus* HOMO-dienophile- $LUMO_{diene}$ demonstrated that the frontier molecular orbitals for the processes under study were the HOMO of the diene and the LUMO of the dienophile . These results confirmed that the Diels–Alder reactions were normal ones. A comparative analysis of the LUMO energies for the series of α,β-unsaturated carbonylic dienophiles showed that longer side chain favored the existence of no coplanar structures, and this effect is in concordance with the spectroscopic data recorded from these compounds. Furthermore it was observed an increased of the LUMO energies, thus, diminishing the reaction rate. This fact is sustained by the experimental results which indicated that longer side chains correspond to lower dienophile reactivity.

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Teorethical Studies of the Stability of 8a-Alkyll-1,2,3,4,6,8a-hexahydronaphtalen-1-ones Using Semiempirical Methods

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Abstract: The Birch alkylation products are very unstable. We are showing, in this communication, the results of a theoretical study that compares different decomposition reaction mechanisms. The conclusions are in agreement with our experimental results.

Introduction

Our research group have been working in Birch reductive alkylation reactions of bencylic ketones for several years[1]. An example of the outcome of this type of reactions is showed in the Figure 1. The 8a-Alkykl-1,2,3,4,6,8a-hexahydro-naphtalen-1-ones, produced in this reaction have a high functionality but, at the same time, a high instability.

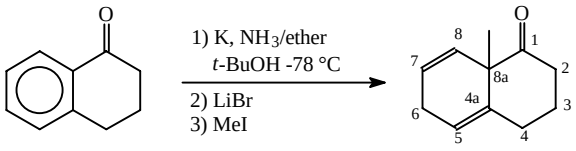
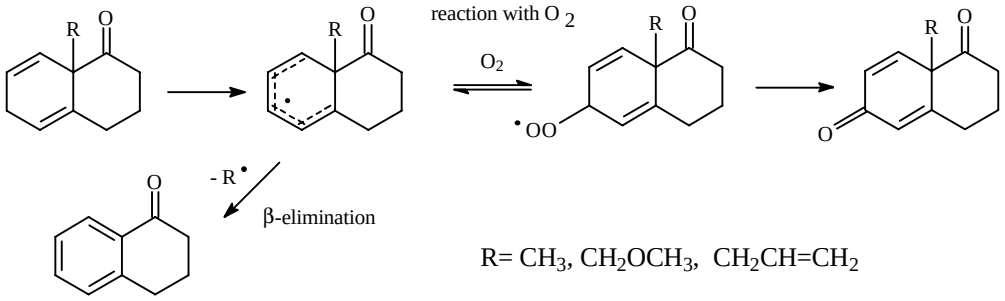


Figure 1.

In the course of our work, we soon found that this instability leads in a short time to α-tetralone as the main decomposition product. According to a work reported by Beckwith[2] on the decomposition behavior of substituted 2,5-ciclohexadienes, the main decomposition product is that formed through an allylic oxidation. He proposes a mechanism that begins with the formation of a radical in the allylic position, which then may follow two different pathways: a) reaction with oxygen to produce a dienone, or b) promoting a β-elimination to achieve aromaticity. Therefore, Beckwith's results for the monocyclic compounds indicated a preference for the oxidation pathway.

By extending the mechanism proposed by Beckwith to the bicyclic systems we conclude, in function of our experimental results, that for them, the β elimination reaction pathway is favored over their reaction with oxygen to form the peroxi radical that leads to the dienone.



Scheme 1.

Results and Discussion

To explain the pathway preference shown by the bicyclic system, we used semiempirical methods (AM1-UHF) to study the energy associated to both process in a series of substitued bicyclic dienes (R= methyl, allyl and metoxymethyl) Scheme 1. In the first place we search for the minimum energy conformations for the reactives and products. Then, using quadratic synchronous transit methodology we search for the transition states. For the reaction with oxygen we consider its approximation from both sides of the diene to produce both α and β peroxi-radicals.

For comparison, we also performed a similar analysis for 1-Carboximetil-1-methyl-cyclohexa-2,5-diene; the Birch alkylation product of methyl benzoate. The analysis of activation energys for the different reactions (oxidation vs. β-elimination) are in agreement with the experimental results found. We have also analyzed the influence of the different radical leaving groups (methyl, allyl and metoxymethyl) in the β-elimination reactions.

Acknowledgements: Universidad Nacional de Rosario – CONICET.

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Photochemical Study of the Reactions of the 2-Naphtoxide Ion with Haloadamantanes

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Abstract: The fluorescent excited state of 2-naphtoxide ion is quenched by haloadamantanes (**X-Ada**) as electron acceptors according to an electron-transfer mechanism. This mechanism is proposed on the basis of:1) decreasing quenching rate constant as the reduction potential of **X-Ada** is made more negative and 2) the analysis of reaction products.

Introduction

It is known that the 2-naphtoxide ion reacts with a variety of aryl halides under photostimulation in liquid ammonia yielding 1-aryl-2-naphtoxides as substitution products.[1] It was proposed that these reactions occur by the $S_{RN}1$ mechanism, and involve the participation of radicals and radical anions as intermediates. However, no quantitative photochemical studies of these reactions have been performed. Considering that the photophysics of 2-naphtoxide ion was determined by Soumillion and coworkers, [2] we undertook a systematic study of the photoinduced reaction of this ion with haloadamantanes.

Results and Discussion

The deactivation of the singlet excited state of 2-naphtoxide ion by haloadamantanes, **X-Ada**, was studied in dimethylsulfoxide (DMSO) by fluorescence stationary techniques. The results obtained from the inhibition of the fluorescence of 2-naphtoxide ion by 1-iodo, 1-bromo and 1-chloroadamantane showed Stern-Volmer linear plots. The quenching rate constants from these plots show a good correlation with the reduction potentials of the adamantyl halides. (Table 1).

Table 1. Fluorescence quenching of the 2-naphtoxide ion by X-Ada.

X-Ada (Q)	k_{SV}	kq (10^9 $M^{-1}s^{-1}$)	*log kq*	E_{red} [3]
1-Iodoadamantane	103	5.7	9.8	-2,20
1-Bromoadamantane	2.2	0.12	8.1	-2,54
1-Chloroadamantane	0.81	0.045	7.65	-2,64

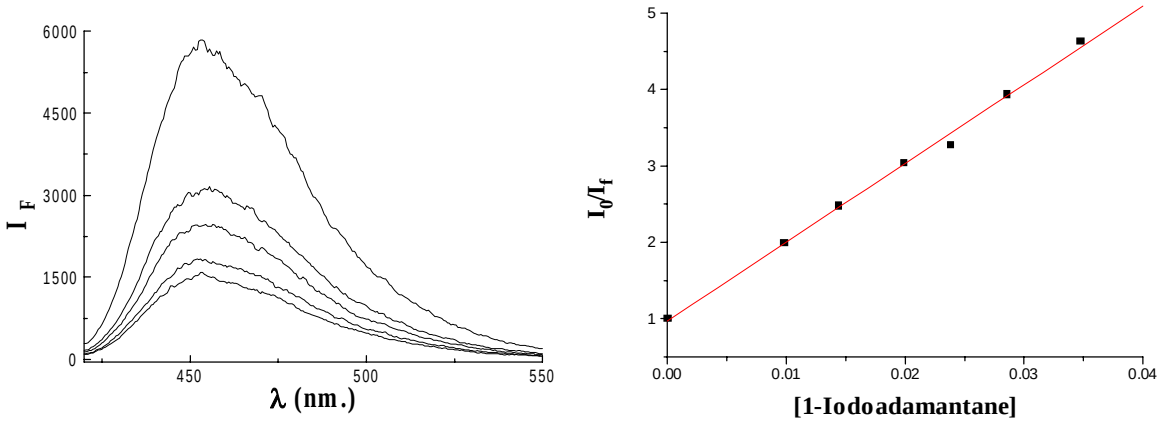

Figure 1. Quenching of 2-naphtoxide ion by 1-Iodoadamantane.

1-Iodoadamantane quenches the fluorescence of 2-naphtoxide ion with a rate constant near the diffusion limit (k_{diff} for DMSO = $3{,}3 \times 10^9$ $M^{-1}s^{-1}$) [4] . A plot of the logarithm of the rate constants *vs.* the change in free energy follows a typical behavior for an electron transfer reaction. From the photochemical study we performed a detailed analysis of the reaction products. Thus, the photoinduced reaction of 2-naphtoxide ion with 1-iodoadamantane in DMSO rendered a mixture of adamantane (coming from the reduction of the adamantyl radical intermediate), substitution products (which arise from the addition of the adamantyl radical to the 3, 6 and 8 positions of the ion) as well as 1-adamantanol and minor amounts of 1-adamantyl-2-naphthylether.

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A Different Behaviour of the Phthalimide Ion in $S_{rn}1$ Reactions

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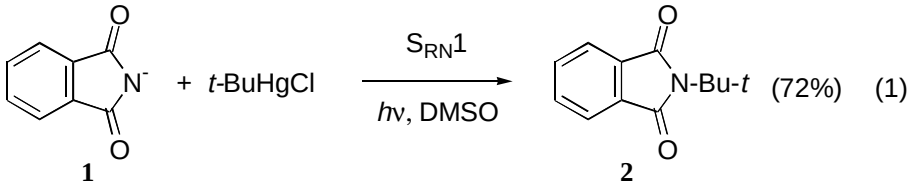
Abstract: The phthalimide anion reacts by the $S_{RN}1$ mechanism under photostimulation with different substrates. Whilst with 1-iodonaphthalene only reduction of the naphthyl radical is observed, with 1-iodoadamantane coupling at the carbon instead of at the nitrogen takes place.

Introduction

The mechanism of Radical Nucleophilic Substitution ($S_{RN}1$) is a chain process with radicals and radical anions as intermediates [1]. Different substrates and nucleophiles participate in these reactions. It is known that within the nitrogen-centered nucleophiles, aromatic amines react with aryl halides to yield the substitution product on the carbon atom and none on the nitrogen atom. For example, the photoinduced reaction of 2-naphthylamine with aryl halides renders mainly 1-aryl-2-naphthylamines [2]. However, the phthalimide ion (**1**) reacts with *ter*-butyl radicals yielding N-*ter*-butylphthalimide (**2**) (eq.1) [3].

Taking into account these results we began to study the photoinduced reactions of phthalimide ion with different substrates.



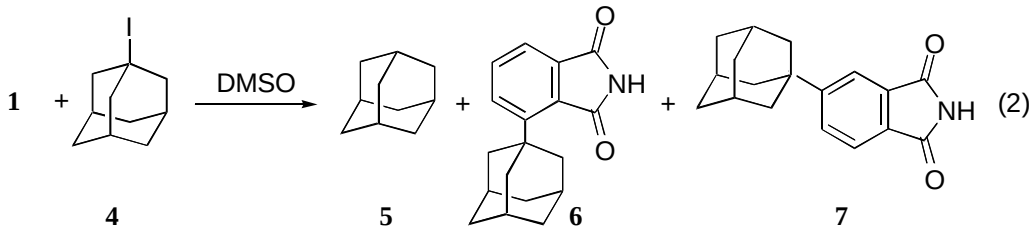
1 **2**

Results and Discussion

The photoinduced reaction of anion **1** with 1-iodonaphthalene (**3**) in dimethylsulfoxide (DMSO) and in the presence of 18-crown-ether renders 72% of iodide ions after three hours and naphthalene is the only product observed. This reaction does not occur in the dark.

The reaction of anion **1** with 1-iodoadamantane (**4**) under the same conditions, yields a 78% of io-

dide ions, adamantane (**5**) and the substitution products **6** and **7** which arise from the coupling reaction of the adamantyl radical at the carbon 4 and 5 of anion **1** respectively. When this reaction was performed in the presence of a radical trap as di-*ter*-butylnitroxide (di-*t*-BuNO) or a better electron acceptor than **4** as *p*-dinitrobenzene (*p*-DNB), results in strong inhibition. (eq.2). In the dark, no reaction was observed between **1** and **4**.



4 **5** **6** **7**

hν	21%	12%	45% (isolated)
20% di-*t*-BuNO	7%	2.5%	18%
20% *p*-DNB	3%	<1%	20%
dark	-	-	-

These results showed that a photoinduced electron transfer from anion **1** to substrates **3** and **4** renders the naphthyl or the adamantyl radical intermediates respectively. While only hydrogen abstraction is observed for the naphthyl radical yielding naphthalene as reduction product, the adamantyl radical adds surprisingly to the carbon atoms instead of the nitrogen atom giving distonic radical anions. This behavior is different from the previously described reaction of this anion with *ter*-butyl radicals [3]. In the present communication we will discuss the reactivity of this anion with different substrates.

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Variation in the Composition of the Essential Oil of *Senecio Filaginoides* Dc

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Introduction

The gender *Senecio (Asteraceae)* it is one of the richest in species of the angiospermas. *Senecio filaginoides is* very frequent in arid areas, extending from the region of the Fluna until the county of Santa Cruz. It is a hemispheric bush of 0,50 m of height, densely rarnoso, with cylindrical shafts, albo-tomentosos, hojosos until the alternating ápice.Hojas, fineares, whole or with some isolated tooth, tomentosas in both expensive ones or almost glabras in old copies. The chapters are discoides, prepared in summits dense corimbiformes, in the ends of the branches. 1 involve cy1indrical fiared, caliculado, shorter than the flowers with 8 to 13 brácteas involve them. The flowers are yellow, isomorfas, hermaphrodite, with corofia tubulosa. Aquenios densely papiloso-pubescentes. Abundant white papus (Goatherd, 1971) [1].

It is a very variable species in density of the indumento, size of the leaves, height of the 1 involve and bracteas number involves them.

Descripto two varieties S. *filaginoides is* had var DC. *filaginoides* and S. *filaginoides* var. *lobulatus* (Hook. Et Arn.) Goatherd those that differ for the presence in the second variety of 1-3 couples of teeth or short lobes for leaf.

In spite of being a very abundant species in the south of our country, we don't have knowledge of antecedents referred to the study of the essential oil and their properties to evaluate their eventual industrial use.

The present work this guided to determine the chemical composition of the essential oils of *Senecio filaginoides* and to detect if there are differences among the varieties and in different state fenológico.

Experimental

The work was carried out on a population located in Comodoro Rivadavia's proximities.

Copies of both varieties were marked for studies morfoanatómicos, fenológicos and chemical. They were carried out collections of branches non fignificadas, young and mature leaves of copies in vegetative and reproductive state.

The collected material dried off during 24 hours and then she was carried out the extraction of the essential oil for the distillation method for haulage with vapor of water. They were carried out three extractions of those that a yield average of 0,9% was obtained. The yield this expressed as m1 of essential oil by each 100 g of vegetable.

For the determination of the composition of the oil a gassy chromatography Konik 3000 HRGC was used, provided of a column RTX 1 (30m, 0,53 mm, 1 um) and a detecting FID. The following program of temperatures was used: Initial temperature at 50ºC during 2 minutes, then up to 200ºC during 7 minutes, at 10ºC per minute. The analyses of CG-EM were carried out in the Department of Chemistry and Engineer Chemistry of the UNS, in a gas chromatograph Hewlett Packard HP 6890 with detecting EM.

The compound identification of the different ones was achieved through the use of standard chromatography databases belonging to the CG-EM and pertinent bibliography.

The spectra UV was carried out, using nail polish remover like pay, in a spectrophotometer of diode arrangement Hewlett Packard 8452 in a range of wave longitudes understood between 190nm and 820nm.

The refraction index was carried out in a refractometer of ABBE PZO it marks WARSZAWA model RL2.

Results and Discussion

Through the chromatography analysis you can detect that the composition of the essential oil is very complex, having some few majority compounds but with a great number of compound minority.

Until the present components have been identified that represent in their composition 63.91% for *Senecio filaginoides* var *filaginoides* and 53,73% for *Senecio filaginoides* var *lobulatus.* A Majority Compound Tr = 20,5 that it represents 25% for the first one and 32,5% for the second are without determining since it doesn't correspond to the patterns that we possess and their spectrum of mass is not in the database neither in the bibliography consulted [2,3,4]. You began their separation to be able to carry out their identification.

The percentual composition of the essential oil of the *Senecio filaginoides var filaginoides* according *to* the different states fenológicos *and Senecio filaginoides* var *lobulatus.*

	Senecio filaginoides var. filaginoides Vegetative state	*Senecio filaginoides var. filagínoídes Reproductive state*	*Senecio filaginoides var. lobulatus Reproductive state*
α - pinene	*9*	*13,15*	*0,46*
β -pinene	*5,6*	*6,2*	*4,8*
β - Terpinene	*3,5*	*6,74*	*4,13*
α - Terpinene + p- Cimene	*41,67*	*39,5*	*41,22*
R-Silvestrene	*1,34*	*4,45*	*0,32*
3 - Carene	*0,37*	*0,12*	*0,25*
Spathulenol	*0,47*	*0,26*	*1,05*
Guaiol	*0,38*	*0,23*	*1,50*

In the chart II the data of refraction index and wave wavelength are included where the absorption is maximun.

	Senecio filaginoides var. *Filaginoides* Vegetative state	*Senecio filaginoides* var. *filaginoides* Reproductive state	*Senecio filaginoides* var. *lobulatus* Reproductive state
1máx.(nm)	*342 y 360*	*340 y 360*	*334*
n_D^{20}	*1,4978*	*1,4942*	*1,4928*

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Gastric Cytoprotective Activity of Ilicic Aldehyde in Rats and Mice

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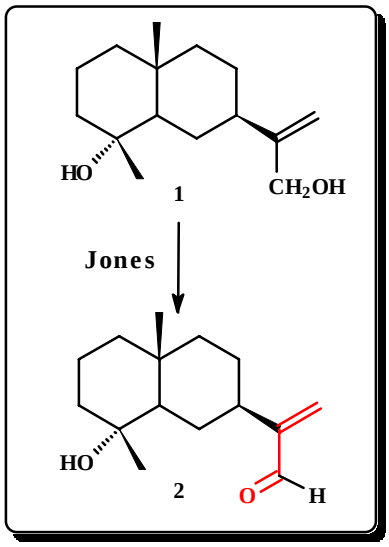
Abstract: Ilicic alcohol, a natural sesquiterpene, was converted into an aldehyde by using Jones' oxidation. The gastroprotective activity of ilicic aldehyde was evaluated in mice and rats.

Introduction



It is well known that gastric cytoprotective activity is closely related to the presence of α,β-unsaturated carbonyl groups [1]. Taking into account this fact, we have studied the activity of ilicic aldehyde. This compound was obtained by oxidation of the corresponding natural alcohol. This work reports the gastroprotective ability against different necrotizing agents (absolute ethanol, NaOH 0.2 N, HCl 0.6 N, NaCl 25%, in rats and absolute ethanol in mice).

Material and Methods

Oxidation

Ilicic alcohol [1], an eudesmane sesquiterpene, isolated from *Fluorensia oolepis* [2] was oxidised with Jones' reagent, by the usual method proposed for allylic alcohols [3]. Through this reaction it was possible to obtain ilicic aldehyde [2].

Pharmacological assays

Wistar rats, were grouped in six lots: 1, 2 y 3: received as necrotizing agent NaOH 0.2 N (*p.o.*) (n=6), HCl 0.6 N (*p.o.*) (n=5) and NaCl 25% (*p.o.*) (n=5), respectively. Lots 4, 5 y 6: were administered with ilicic aldehyde (**2**), 40 mg/kg, 1 ml (*p.o.*, n=5) 60 min before the administration of necrotizing agents, NaOH 0.2 N, HCl 0.6 N and NaCl 25%, respectively. The degree of erosion in the glandular part of the stomach was assessed from a scoring system designed by Marazzi, Uberti and Turba [4]. In another experiment, gastric mucosal damage in Wistar rats was induced by absolute ethanol (EA, 1 ml/rat, *p. o.*) according to Robert *et al.* (1979) [5]. Four experimental groups received **2** (1 ml, 25, 50, 75 and 100 mM). The effective dose, ED_{50}, were obtained with software ALLFIT (De Lean *et al.*, 1988) [6]. In another experiment with Rockland mice, EA was employed as the necrotizing agent (0,1 ml/10 g, *p.o.*), according to the method of Robert *et al.* (1979) [5]. The results were expressed as Ulcer Index (UI) and as the percentage cytoprotection, method by Yamasaki *et al.* (1989) [7]. The statistical significance of difference among means was assessed by analysis of variance (ANOVA) with the multiple comparison method by Tukey, and by Students´s *t*-test.

Results and discussion

The results were expressed as follows (Ulcer Index) :

- In the first experiment: L. 1: 4,80 ± 0,27; L. 2: 4,37 ± 0,25; L. 3: 4,33 ± 0,57; L. 4: 1,50 ± 0,50*; L. 5: 0,83 ± 0,28*; L. 6: 0,75 ± 0,28** (*p<0,00001; **p<0,0001 *vs.* controls. Each value represents the mean ± SEM).
- In the experiment performed to study whether **2** protects the gastric mucosa in rats at different doses: 25 mM: 1,5 ± 0,11; 50 mM: 1,08 ± 0,12; 75 mM: 0,6 ± 0,11; 100 mM: 0,20 ± 0,10. ED_{50} = 21,57 ± 4,22 mM.
- In the evaluation of gastroprotective activity in mice: L. control: 4,75 ± 0,15; L. 0,43 ± 0,11* (91% of cytoprotection) (*p<0,00001 *vs.* control).

These results indicate that **2** prevents the formation of gastric mucosal lesions induced by absolute ethanol and by other necrotizing agents in rats and mice.

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Chemical Components and Biological Activity of *Bidens Subalternans, B. Aurea* (Astereaceae) and *Zuccagnia Puntacta* (Fabaceae)

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Abstract: The aim of this work was to evaluate the activity in the gastrointestinal tract of the several extracts and pure components isolated from *Bidens* species and *Zuccagnia puntacta*

Introduction

The interest in the phytochemical study of the species belonging to the genus *Bidens* (Astereaceae) derives from the fact that several of them, particularly those widely used in popular medicine, have been reported to have significant pharmacological and therapeutics properties [1-4]. *Bidens subalternans* D.C., popularly known as “amor seco” is an annual herb widely distributed in the northern and central parts of Argentina. *Bidens aurea* (Aiton) Sherff is a European herb widely distributed in the Mediterranean areas and commonly used as digestive and sedative. *Zuccagnia puntacta* Cav. (Fabaceae) is a monotypical specie distributed in dry areas of Argentina and Chile, popularly known as “jarilla macho” and used in popular medicine as rubefacient and anti-inflammatory.

The objetive of the present work was to assess the biological activity in the gastrointestinal tract of different extracts of these species and to identify and characterize secondary metabolites present in them.

Experimental

The methodology employed was the usual one in chemical-pharmacological investigations of natural product studies.

1. Determination of gastric cytoprotective activity of several isolated extracts and products in rats and/or mice.

The ulcer experimental model of *g*astric lesions were produced in according to the method of Robert *et al.* [5]. Absolute ethanol administered orally was employed as the necrotizing agent. The degree

of erosion was assessed from a scoring system designed by Marazzi-Uberti and Turba [6]. The results were expressed in terms of an ulcer index (UI) or as cytoprotection percentage, according to Yamasaki *et al.* [7].

2. Determination of small intestinal transit in mice

The effect of samples on small intestinal transit was tested using Ueda *et al*. method [8]. The length traversed by the charcoal marker was calculated as a percentage of the intestine length.

The statistical significance of difference among means was assessed by Student's *t*-test or analysis of variance (ANOVA) with multiple comparison method by Tukey.

Chromatographic processing with different adsorbents of the chloroform soluble fractions obtained from the methanol extracts, allowed as to obtain the following compounds:

Bidens subalternans: maslinic acid, oleanolic acid, stigmasterol (I), stigmasterol-3-O-β -D-glucoside (II).

Bidens aurea: 2'-hydroxy-4,4'-dimetoxychalcone, (I) and (II).

Zuccagnia puntacta: 2',4'-dihydroxy-3'-metoxychalcone; 2',4'-dihydroxychalcone; 7-hydroxyflavanone and 7-hydroxy-8-metoxyflavanone.

Identification was performed by uni- and bidimensional spectroscopic techniques ^{1}H-NMR y ^{13}C-NMR, ME and GC-ME combined techniques.

Results and Discussion

The results obtained are reported in the tables below.

Treatment previous to EtOH	Ulcer Index (X ± SEM)	Damage inhibition
MeOH ext. of *B. aurea*	3,87 ± 0,12*	20%
Cl_3CH ext. of *B. aurea*	2,83 ± 0,33*	41%
MeOH ext. of *B. subalterna*	3,50 ± 0,20*	27%
MeOH ext. of *Z. punctata*	0,75± 0,25***[a]	84%
Z.punctata aqueous infusion	2,75 ± 0,43**[b]	43%
2',4'-diOH-3'-metoxychalcone	3,6 ± 0,54**[a]	25%
2',4'-diOH-chalcone	1,75± 0,25***[b]	63%
vehicle	4,83 ± 0,16	--

Treatment previous to C	Intestinal transit (%) (X ± SEM)
B. aurea extract	45,57 ± 3,49**
B. subalterna extract	52,90 ± 2,98
MeOH ext. of *Z. punctata*	35,61 ± 2,97 ***[a]
Z. punctata aqueous infusion	46,82 ± 2,04*[b]
2',4'-diOH-3'-metoxychalcone	47,17 ± 1,85**[c]
2',4'-diOH-chalcone	44,82 ± 2,51***[c]
vehicle	57,86 ± 3,09

*p<0,05; **p<0.02; ***p<0.001 vs. controls, respectively; a≠b (p<0.01) (Student's *t*-test or analysis of variance (ANOVA) with multiple comparison method by Tukey.

The higher activity of the chloroform extracts compared to the methanol extracts ones or aqueous infusions can be accounted for the higher concentration of active compounds in extracts.

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Regioselective Opening of Epoxides Catalyzed by Sn (IV). A New Method for the Synthesis of Halohydrins?

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Abstract*:* The regioselective opening of epoxides with organotin oxides **1** and **2**, in presence of halogenated alcohols was developed, yielding the halohydrin derivatives.

Introduction

Epoxides are among the most versatile intermediates in organic chemistry due to the particular polarity and strength of their three member ring. Those characteristics make them in a very suitable substrate to the attack or many nucleophilic and electrophilic reagents [1].

The regioselective opening of oxiranes has been the subject of interest for many years, since these heterocyclics are frequently used as starting material for the preparation of natural products and biological active compounds [2].

Many different organotin reagents have been employed to effect the regio- and stereoselective cleavage of oxiranes in the presence of nucleophiles affording 1,2-alcoxialcohols, 1,2-aminoalcohols, 1, 2-azidoalcohols, etc [3].

Results and Discussion

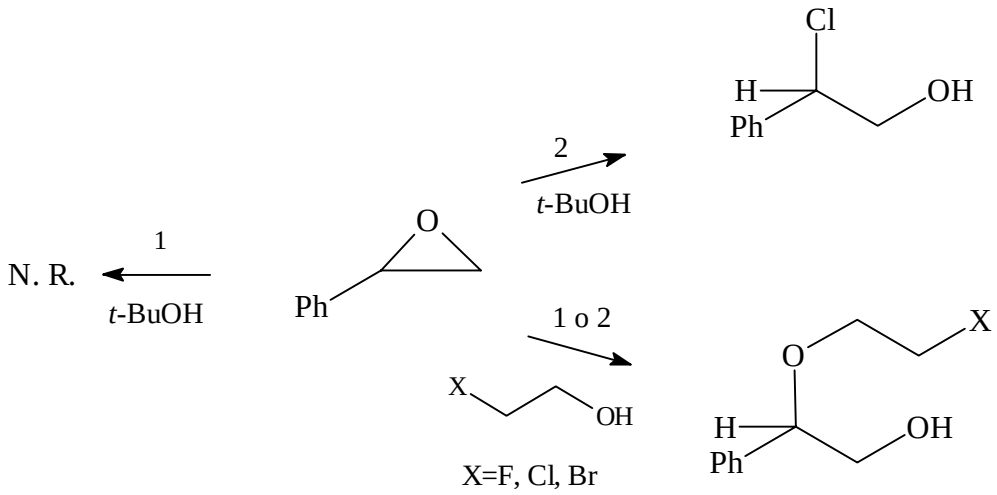
As a part of our ongoing research work concerning the development of organotin reagents for the opening of epoxides [4], the bis(tributyltin) oxide (**1**) and bis(chlorodibutyltin) oxide (**2**) were subjected to act as Lewis acids assisting the opening of epoxides in the presence of halogenated alcohols.

When styrene oxide was reacted with *t*-BuOH and **1**, the starting material was recovered unchanged after 5 days, probably due to steric hindrances. However, when the same reaction was carried out using the oxide **2**, after 3 days a compound was isolated and identified as the chlorohydrin. In this case, bis(chlorodibutyltin) oxide would act as a Lewis acid and, moreover, as a chloride donor.

In view of the result described above, we decided to extend the study using a series of halogenated alcohols as a nucleophiles in the presence of the organotin oxides **1** or **2**.

These results outlined in Scheme 1, shows the formation of the halohydrin derivatives in very good

yield by the highly regioselective opening of styrene oxide.



However, when the same methodology was applied to other monosubstituted epoxides, the results obtained were different. While the oxide **1**, showed a low reactivity towards aliphatic oxiranes, the oxide **2** was able to assist the cleavage of those heterocycles by the nucleophilic attack of the alcohol, or by the chloride anion originated from $(ClBu_2Sn)_2O$.

The unusual formation of the chlorohydrin compounds would be due to the reaction of the nucleophile with the reagent **2**, and the subsequent nucleophilic attack of the chloride over the epoxide.

In summary, $(ClBu_2Sn)_2O$ emerge as a new reagent for the regioselective opening of epoxides yielding the chlorohydrin derivatives, in mild and non-hydrolytic conditions.

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Phytochemical Study of Condalia microphylla Cav.

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Abstract: From the petroleum ether extract of the aereal part of Condalia microphylla Cav, hydrocarbons, sterols, alcohols, and fatty acids were isolated. From fruits of the same plant anthocyanins were also isolated and characterized by chromatographic and spectroscopic methods.

Introduction

Condalia microphylla Cav. Species belongs to the Ramnaceae family, and its common name is "Piquillín". It generally grows in the runningboard of the saw being a shrub with a mass of branches up to 2m height. The leaves are dote, dark green with yellow flowers and the fruit is a red berry [1]

This plant has not been chemically studied in our country, but the presence of hydrocarbons and fatty acids have been informed [2] in leaves and seeds. We report now a study on the petroleum ether extract from the aerial part of the plant including the less-polar components (hydrocarbons, alcohols, sterols and fatty acids) and characterization of antocyanins which have been isolated from the fruit extract with MeOH/HCl 1%.

Experimental

General

GLC analysis were performed with a Varian 3700 using a FID, and a KONIK 500 Liquid Chromatograph using a UV detector. UV Spectra were run with a GBC Spectral equipment.

Plant material

The plant was collected in Medanos, Province of Buenos Aires during the month of February.

Leaves and branches

Aerial parts of the plant were dried, grinded and extracted with petroleum ether; then each fraction

obtained by chromatography on Silica gel 60 was processed on TLC with Silica gel 60 G and GLC.

Saponification

A sample of the petroleum ether extract was saponificated with MeOH/KOH 10%, after the common treatment the acid fraction was methylated (H_2SO_4 1.5%/MeOH) and was compared by GLC with authentic samples.

Fruits

The berries were extracted with MeOH/HCl 1% during 24 h at room temperature.

The anthocyanins were isolated and purified by paper chromatography Whatmann 3MM. Identification was achieved by analytical paper chromatography using four different solvents systems; HPLC, acid hydrolysis, degradative oxidation and UV-Vis spectroscopy [3]

Results and Discussion

From the petroleum extract hydrocarbons, sterols and alcohols were identified as well as fatty acids in the saponificated fraction. As for the sterols, it could be observed that the main component in the aerial part was sitosterol. The major alcohol was C22. The fatty acids found in higher proportion were: behenic (22:0), lignoceric (24:0), palmitic (16:0) and linoleic (18:2). The major hydrocarbons found were C31, C33 and C35, this showing that the hydrocarbons with odd number carbon atoms prevail.

On the other hand, four anthocyanins were isolated from the fruit methanolic extract. Two of them identified as malvidin-3genciobioside and malvidin-3-glucoside. The other two are under study.

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Isomerisation of Methyl (E) 2-Bromo-3-(4-XC_6H_4)-propenoates

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Abstract: The geometric isomerisation of the title compound induced by bromine or chlorine appears to involve ionic pair species resulting from the nucleophilic attack of the halogen.

Keywords: isomerisation, propenoates.

Introduction

The title compounds show geometrical isomerisation when subjected to the action of halogen (chlorine or bromine) Since these systems are involved in addition reactions [1,2], the examination of the nature of the isomerisation is required to define the details of the whole process. We here report on a study on the reaction of

(E) 4-XC_6H_4CH= CBrCOOMe

induced by chlorine or bromine in various solvents.

Experimental

The isomeric pure acids were obtained by fractionated reprecipitation from the E and Z isomers mixture. Then, the E-esters were prepared from the corresponding acids. Finally, the α-β unsaturated esters were treated either with chlorine or with bromine in a series of solvents. The isomerization reaction was followed measuring the E/Z ratio by glc.

Results and Discussion

From inspection of the data summarised in the Table, some general conclusion can be drawn.

1. The halogen participates in the rate determining stage
2. The observed reactivity of the substrates increases with decreasing dielectric constant of the solvent which is related to a transition state involving the action of molecular halogen.

For the polar medium, the rate seems to be disfavoured by the protic nature of the solvent. This might be attributed to solvation of the halogen exerted by the latter which leads to a reduction of its actual concentration.

$$Hal^{\delta+} \text{ —— } Hal^{\delta-} \text{ - - - - - - - - } H \text{ —— } OMe$$

3. The influence of the aromatic substituent appears to depend on the nature of the solvent. Thus, a decrease in the reactivity occurs with increasing electron release when the reaction is carried out in benzene or in methanol. The former observations can be reconciled with an halogen attack which, though molecular in nature, proceeds through its nucleophilic end. This would lead to an intermediate with an olefinic bond weak enough to allow the molecule isomerise to the more stable form.

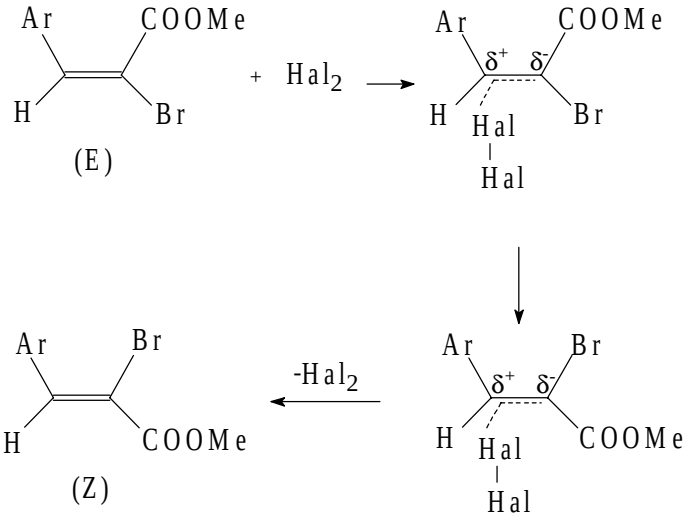

Table. Rate coefficients for the isomerisation (E→Z) of (E) 4-XC_6H_4CH= CBrCOOMe [$dm^3mol^{-1}min^{-1}$] promoted by halogen at 30^0C.

Hal	***X***	***MeOH***	***MeCN***	***Benzene***
	H	*0,307*[a]	*1,16*[a]	*39,98*[b]
Br_2	*Me*	*0,103*[a]	*1,74*[a]	*27,52*[b]
	Cl	*0,342*[c]	*0,25*[c]	*66,59*[b]
	H	*0,0127*[a]	*0,017*[a]	*18,1*[b]
Cl_2	*Me*	*0,0090*[a]	*0,102*[a]	*6,33*[b]
	Cl	*0,0212a*	*0,038*[d]	*20,80*[b]

[a] $[Hal_2]$ = 0,2 mol dm^{-3}; [b] $[Hal_2]$ = 0,006 mol dm^{-3};
[c] $[Hal_2]$ = 0,03 mol dm^{-3}; [d] $[Hal_2]$ = 0,4 mol dm^{-3}

When acetonitrile is used as solvent the reactivity sequence appears to be the opposite. On the basis of the available evidence, it is difficult to draw a full explanation of the observed results and additional evidence will be required to establish the mechanism of the whole reaction.

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Lipoxygenase-1 Activity of Soybean Genotypes Grown in Argentina

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Abstract: The lipoxygenase-1 (LOX-1) activity of 19 soybean genotypes was quantified in two consecutive years. The LOX-1 activity produced by any cultivar was essentially the same in both, 1995 and 1996 crop years. The lowest values of LOX-1 activity were found in NK 555 cultivar whereas Asgrow 5409 cultivar had the highest values.

Introduction

Lipoxygenase (LOX) was first reported in soybeans almost 67 years ago [1]. LOX catalyzes the hydroperoxidation of polyunsaturated fatty acids containing a cis, cis-1, 4-pentadiene system, but structures other than fatty acids are known to be oxidised [2, 3]. The cleavage of fatty hydroperoxides into short-chain aldehydes and alcohols has been studied, suggesting that lipoxygenase could be used as a versatile biocatalyst [4].

Normal soybean seeds contain three lipoxygenase isozymes, named LOX-1, LOX-2 and LOX-3 which differ in substrate specificity, optimum pH for catalytic activity, isoelectric point and thermal stability [5, 6]. LOX-1, an enzyme with a pH optimum of 9 to 10, represents a large class of other less-studied LOX of this type. For the biocatalytic production of a natural aroma compound, lipoxygenase is needed on a large scale and the alkaline isozyme (LOX-1) seems to be the most suitable for this purpose [7]. The objectives of this work were to screen and compare the soybean LOX-1 activity in some genotypes cultivated in Argentine in two consecutive years.

Results and Discussion

The biosynthesis of LOX isozymes in soybean is under genetic control [8, 9]. Furthermore, weather conditions have been found to play a considerable role in influencing the activities of the LOX isozymes [7]. In the present work, the differences in activity among the different cultivars from the same year were larger than those between the generations (crop years) of a cultivar. The LOX-1 activity produced by any cultivar was essentially the same in both, 1995 and 1996 crop years (Table 1). These results are not in agreement with the data obtained by Márczy *et al.* [7] suggesting that, in the samples

studied, genetic is stronger than environmental influences.

Table 1. Lipoxygenase-1 activity (ΔOD.mg prot^{-1}.min^{-1}) in 19 soybean cultivars during 1995 and 1996 crop years. Mean values ± standard deviations (n = 3).

Cultivar	Crop year	
	1995	1996
NK 555	7.44 ± 0.14^{a}	7.81 ± 0.16 ^{a}
Forrest	8.53 ± 0.13^{b}	8.98 ± 0.17^{b}
NK 641	8.75 ± 0.15^{bc}	8.96 ± 0.16^{b}
Tancacha	8.85 ± 0.10^{bcd}	8.66 ± 0.14^{c}
Copetona 53	9.02 ± 0.15^{cd}	9.22 ± 0.19^{b}
Prata	9.24 ± 0.14^{d}	9.51 ± 0.11^{d}
Asgrow 5308	9.83 ± 0.30^{e}	9.96 ± 0.24^{e}
Federada Casilda	10.0 ± 0.20^{ef}	10.8 ± 0.14^{f}
RA 587	10.3 ± 0.10^{f}	10.1 ± 0.13^{e}
Federada 1 INTA	10.9 ± 0.10^{g}	12.3 ± 0.12^{g}
Granera 73	11.4 ± 0.12^{h}	11.2 ± 0.16^{h}
Asgrow 6404	11.5 ± 0.15^{h}	11.6 ± 0.11^{i}
Tacuarí	12.2 ± 0.20^{i}	12.7 ± 0.18^{ij}
Montera 74	12.8 ± 0.10^{j}	13.2 ± 0.12^{k}
RA 702	13.1 ± 0.15^{j}	12.5 ± 0.15^{j}
Torcaza 63	13.1 ± 0.10^{j}	13.3 ± 0.13^{k}
Charata 76	13.9 ± 0.15^{k}	13.4 ± 0.12^{k}
Torcacita 58	14.5 ± 0.20^{m}	14.8 ± 0.16^{m}
Asgrow 5409	16.0 ± 0.20^{n}	16.5 ± 0.23^{n}

[a]Mean values within each column followed by the same letter do not differ statistically P=0.05.

Statistically significant variations were found among genotypes in both, 1995 and 1996 crop years. A total of 13 groups with different enzymatic activity were observed. In 1995, the LOX-1 activity ranged from 7.44 (NK 555) to 16.0 (Asgrow 5409) ΔOD.mg $prot^{-1}.min^{-1}$; whereas in 1996 it varied between 7.81 (NK 555) and 15.5 (Asgrow 5409) ΔOD.mg $prot^{-1}.min^{-1}$. In general, mean values from 1996 were higher than those from 1995, with exception of Tancacha, RA 587, Granera 73, RA 702 and Charata 76 cultivars.

In the last decade, many attempts to improve the flavours of soybean products have centered around the genetic elimination of LOX from the seeds [8-10]. More recently some works [4,6] focus on the potential of LOX for the efficient production of useful compounds. Hence, cultivars with high LOX activity, such as Torcacita 58 and Asgrow 5409, could be used as a source of the Lox-1 isozyme.

Experimental

Plant material

Nineteen soybean genotypes were chosen. The experiment was conducted at the Estación Experimental Agropecuaria (EEA-INTA) of Manfredi, Córdoba, Argentina. Seeds were harvested, in the crop years 1995 and 1996, by hand at maturity when seed moisture was reduced to 10% or less. One hundred seeds (taken randomly from each seed sample) were powdered by grinding and soybean flour of each cultivar was extracted according to Pignata *et al.* [11].

Lipoxygenase assay

The method of Axelrod *et al.* [5] was followed with a slight modification. The activity of LOX-1 isozyme was determined via the increase in absorbance at 234 nm after addition of linoleic acid in 0.1M phosphate buffer (pH 9.0). Lipoxygenase-1 activity was expressed as an optical density increase per mg $protein^{-1}$ per $minute^{-1}$ (ΔOD.mg $prot^{-1}.min^{-1}$).

Protein content

Protein determinations were performed by the method of Kalckar [12].

Statistical analysis

Lipoxygenase-1 determinations were conducted in triplicate. Statistical differences among genotypes from each crop year were estimated from ANOVA test at the 5% level (P=0.05). Whenever ANOVA indicated significant difference, a pairwise comparison of means by least significant difference (LSD) was carried out.

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^{1}H and ^{13}C-NMR Spectroscopic Study of Some 1*H*-4,5-Dihydroimidazolium Salts

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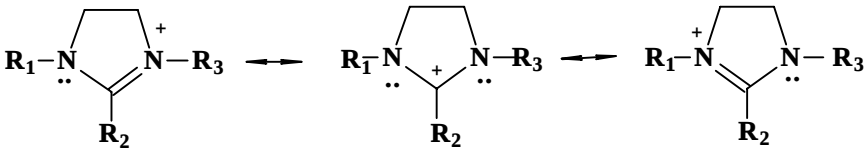
Abstract: The ^{1}H y ^{13}C-NMR spectra of some 1,3 and 1,2,3-trisubstituted 1*H*-4,5-dihydroimidazolium salts are analyzed.

Introduction

1*H*-4,5-Dihydroimidazolium salts are typical cyclic amidinium compounds where the cation is resonance stabilized and the positive charge can be delocalized either on the nitrogen atoms or on the C_2:



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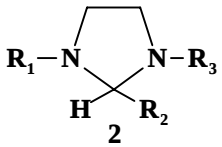

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NMR spectra analysis and its comparison with the corresponding saturated compounds (imidazolidines 2), allows to reach conclusions about the contribution of such structures.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker MSL-300 spectrometer using deuterochloroform as the solvent.

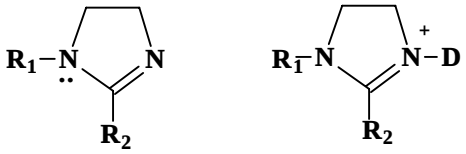
Results and Discussion

The ^{1}H and ^{13}C-NMR spectroscopic study of a series of 1,3-di and 1,2,3-trisubstituted 1*H*-4,5-dihydroimidazoliom salts **1** (Table) is presented.

Table 1.

R_1	R_2	R_3	X^-
C_6H_5	H	C_6H_5	Cl^-
p-$CH_3C_6H_4$	H	*p*-$CH_3C_6H_4$	Cl^-
p-Cl-C_6H_4	H	CH_2-C_6H_5	Cl^-
C_6H_5	C_6H_5	CH_3	I^-
p-$CH_3C_6H_4$	C_6H_5	CH_3	I^-
p-$CH_3OC_6H_4$	C_6H_5	CH_3	I^-
p-$NO_2C_6H_4$	C_6H_5	CH_3	I^-

In order to assign the heterocyclic hydrogens and carbons in the 1,2-diaryl-3-methyl substituted compounds, the spectroscopic study of the parent 1*H*-4,5-dihydroimidazoles **3** and their salts **4** had been carried out.



3 **4**

The unequivocal assignment of the hydrogen and carbon signals of the 1,2,3-trisubstituted salts has been done by the HMQC and HMBC spectra.

The important electronic deficit at the level of the heterocyclic ring in compounds **1** has been clearly demonstrated by comparison of the spectroscopic features of the salts **1** with the corresponding imidazolidines **2**. The iminium structure contribution (A,C) was analyzed according to the chemical shifts and the heteronuclear $^{1}J^{13}C$-H coupling constants of the heterocyclic ring carbons and N-CH_3.

Improved Synthesis of N-Substituted Quinolinimides Using Microwave Irradiation

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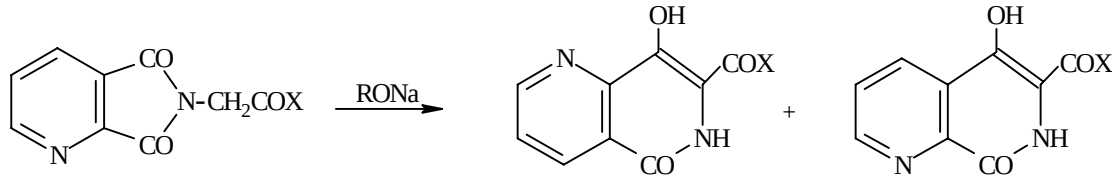
Abstract: The synthesis of several quinolinimidoacetic acid derivatives (**I**) by two different routes, starting from quinolinic anhydride or quinolinimide, is described. In all cases better yields and decreased reaction times were achieved employing microwave irradiation as an alternative source of energy.

Introduction

A number of 1,6- and 1,7-naphthyridines were synthesized [1] by expansion reactions induced by alkoxides of quinolinimidoacetic acid derivatives (**I**). These compounds were obtained with low yields after several hours using conventional heating methods.



I

Here we present the improved results obtained when reactions have been carried out under microwave irradiation.

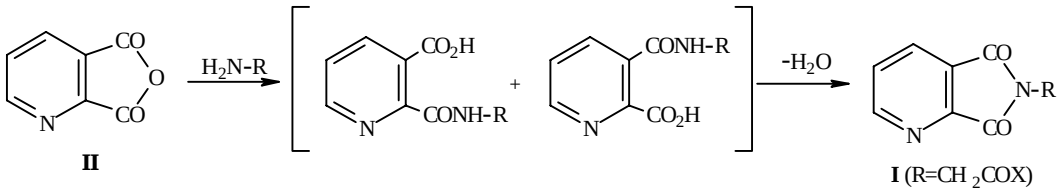
Experimental

Ordinary kitchen microwave oven was used to perform the reactions.

Results and discussion

Compounds **I** were obtained by two ways:

a) By heating quinolinic anhydride (**II**) and aminoacetic acid derivatives. The yields are low owing to decarboxylation reactions of the intermediate quinolinic acid monoamides.

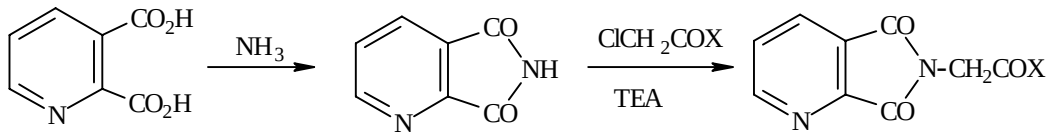


II **I** (R=CH_2COX)

When reactions have been carried out with microwave heating remarkable rate enhancements and dramatic savings in reaction times were observed.

This method was extended and optimized for synthesis of N-substituted alkyl, aryl or heterocyclic quinolinimides as well as for N,N-disubstituted 2-carbamoyl-nicotinic and 3-carbamoylpicolinic acids.

b) Compounds **I** were also obtained by N-alkylation of quinolinimide **III,** which was prepared with high yields from quinolinic acid and aqueous ammonia with microwave heating (7min., 500w).



III **I**

The best results in N-alkylation reactions were achieved in DMF using Et_3N as base.

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Conformational Analysis of Seven Membered Nitrogen Heterocycles Employing Molecular Modeling. Part II: 1-(*O*-Nitrophenyl)-2-Phenyl-*1h*-4,5,6,7-Tetrahydro-1,3-Diazepine

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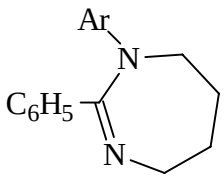
Abstract: Geometry optimization of 1-(o-nitrophenyl)-2-phenyl-1H-4,5,6,7-tetrahydro-1,3-diazepine is performed by means of molecular modeling. Results are correlated with theoretical and experimental UV spectra.

Introduction

As a part of our study about seven-membered cyclic amidines, we report here the conformational analysis of 1-(*o*-nitrophenyl)-2-phenyl-*1H*-4,5,6,7-tetrahydro-1,3-diazepine **1** (Ar= *o*-$NO_2C_6H_4$) employing computer molecular modeling, being this study a continuation of another one about the conformational analysis of 1-(*p*-nitrophenyl)-2-phenyl-1*H*-4,5,6,7-tetrahydro-1,3-diazepine (**1**, Ar= *p*-$NO_2C_6H_4$) [1].



1

Experimental

Conformational space was explored by means of molecular mechanics. Thus, potential energy maps were obtained varying all dihedral angles belonging both to the seven-membered ring and to the substituents, employing MMX as implemented in the software PCModel for Windows. Conformations corresponding to minimum energy of these surfaces, were taken as input structures for Molecular Dynamics procedure, employing MM^+ as implemented in HYPERCHEM 5.1. Conformations were reoptimized at the AM1 level as implemented in HYPERCHEM 5.1.

Conformations which presented $\Delta(\Delta H_f)>3$ kcal/mol with the others were discarded. Theoretical ultraviolet-visible spectra were calculated for all different geometries obtained, and compared with the experimental spectra performed in chloroform solution. Those geometries, whose theoretical UV-visible spectra better fitted experimental one, were selected for the final analysis.

Results and Discussion

Bond lengths and angles, dihedral angles, improper torsion angles and charge densities were measured for the remaining conformations.

Five chairs and eleven twisted boats were obtained in this way for compound **1** (Ar=*o*-$NO_2C_6H_4$). The higher number of conformations corresponding to minimum energy than those previously found for **1** (Ar= *p*-$NO_2C_6H_4$) [1] proved to be due to different orientation of the unsymmetrical *o*-nitrophenyl substituent.

Hybridization of N1 resulted between sp^2 and sp^3, independently of the predetermined hybridization considered in the input structure, as it was observed for compound **1** (Ar= *p*-$NO_2C_6H_4$) [1]. However, N1-C_{ipso} bond length showed absence of conjugation between N1 lone pair and *o*-nitrophenyl substituent, in contrast to those results previously obtained for the *p*-nitrophenyl derivative **1** (Ar= *p*-$NO_2C_6H_4$) [1].

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New Peanut Product: "Mayonnaise". Some Chemical Aspects

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Abstract: The percentage composition, fatty acids and oxidation stability was obtained from *"peanut mayonnaise"* in comparison with commercial mayonnaise and sunflower oil. *"Peanut mayonnaise"* showed better chemical quality than commercial mayonnaise.

Introduction

The consume of saturated fatty acids (SFA), trans-fatty acids, cholesterol and oxisterols increase degenerative arterial process. On the contrary, unsaturated fatty acids (UFA) are an equilibrium factor to the fatty metabolism [1,2].

The AMERICAN HEART ASSOCIATION [3] had published recommendations to fat and cholesterol consume: Fat 25-30% of the total calories; SFA less than 10% of the total calories; Polyunsaturated Fatty Acids (PFA) until 10% of the total calories; Monounsaturated Fatty Acids (MFA) between 10-15% of the total calories, cholesterol less than 300mg per day.

Experimental

Material: The "Peanut Mayonnaise" was developed with blanched peanut, sunflower oil, and additives to color and flavor.

Percentage Composition: Percentages were obtained as follow: proteins by Kjeldhal; ashes by muffle 550-600ºC for 6hr; fats by soxlhet apparatus for 12hr; moisture by drying into oven 60ºC for 72hr; and carbohydrates by difference between 100% and the other components percentage [4].

Fatty Acids Composition: The fatty acid were determined by gas chromatography as fatty acid methyl – esters, prepared whit oil extracted from "peanut mayonnaise", commercial mayonnaise and sunflower oil [4].

Oxidation Test: The "peanut mayonnaise", commercial mayonnaise and sunflower oil were accelerate oxidized in oven at 60ºC for 7 days. The Peroxide Value (PV) of each sample was obtained by

the AOAC method [5].

Statistic Analysis: Data were analyzed by ANOVA and LSD test (n = 3: confidence level 95%).

Results and Discussion

Percentage Composition: The results showed that "peanut mayonnaise" had higher protein, carbohydrate (fiber included) and moisture percentage, and lower fat proportion than commercial mayonnaise.

Moreover, in recent works, vitamin and mineral percentages had been obtained from peanut an commercial mayonnaise, showing, "peanut mayonnaise" better quality than commercial mayonnaise.

Fatty Acid Composition: "Peanut mayonnaise" showed a better oleic/linoleic ratio (O/L) and higher proportion of UFA than commercial mayonnaise and sunflower oil.

Oxidation Test: The oxidation test was developed to study the "peanut mayonnaise" stability (aptitude time) in comparison with commercial mayonnaise and sunflower oil. The results showed that the autooxidation process followed similar curvature, without significant differences.

To conclude, the "peanut mayonnaise" is a food product with better chemical quality, in comparison with commercial mayonnaise, because of its lower fat content, lower SFA, higher MFA, fiber content and cholesterol absence.

Acknowledgements: CONICET, SECYT-FCEFyN-UNC, CONICOR for economical support.

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Antioxidant Activity of Methanolic Extracts from Peanut Skin

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Abstract: Antioxidant activity of skin from runner peanut was performed on sunflower refined oil. The skin was obtained from industrial blanching process. The oil was oxidized at 60ºC. The methanolic extracts show antioxidant activity in relation to the oil (without additives). However these extracts do not reach the activity level from BHT.

Introduction

The skin obtained from the peanut industrial blanching process is a solid waste, and it is not used to make sub-products.

This work was based on previous experiments made on peanut hull, that had showed antioxidant activity, where polyphenolic compounds were involved [1]. On the other hand, synthetic antioxidants, such as butylated hydroxianisole (BHA), butylated hydroxytoluene (BHT) and tert-butyl hydroquinone (TBHQ) are widely used on food, because of its efficacy and lower costs in comparison with natural antioxidants. However, the safety of synthetic antioxidants has been questioned, some works reported BHA to be carcinogenic in animal experimental [2].

The objective of this work was to examine the antioxidant efficacy of methanolic extract from peanut skin, to know its potentiality as antioxidant substance from natural sources.

Experimental

Material: Skin from runner-type peanut, obtained by industrial blanching from "Lorenzati, Ruesch y Cia.", Ticino, Argentina.

Extraction: Two methanolic extracts was obtained as follow:

Methanolic Extract (**ME**): 100g of skin was extracted, passively, with 1000ml of methanol for 24hr, at room temperature and darkness. Then the extract was filtered and evaporated to 50ml final volume [4].

The dry weight was obtained by evaporation to dryness of a ME aliquot into oven at 60ºC.

Defatted Methanolic Extract (**DME**): A 100ml aliquot of the first ME diluted was partitioned with 100ml of hexane, the methanolic phase was evaporated until 5ml final volume.

Total Phenols: The phenols concentration was determined by the Folin-Ciocalteu method [5].

Antioxidant Activity: 5 beakers with 150g of refined sunflower oil were accelerated oxidized into oven at 60ºC [6]. One beaker with control oil (without BHT or extracts), the others with 1,8ml ME; 1,8ml DME; 1,5ml methanol and 0,02% BHT. All of them homogenized with glass stick.

The Peroxide Value (PV) was determined by the AOAC method [7], at intervals for 20 days.

Statistic Analysis: The results were analyzed by ANOVA and LSD test (n = 3, confidence level 95%)

Results and Discussion

The dry weight of ME was 171mg/ml, and total phenols 68mg/ml, to DME total phenols were 125mg/ml.

The oxidation test showed that sunflower with ME and DME had less PV, in comparison with control. Those differences were significant from the 7^{th} day. However, the antioxidant activity of ME y DME was lower than BHT. It could be because of the blanching process, that include soft heating and airflow, that conduce to phenols oxidation and lost of activity.

To continue with the work, we propose to obtain the peanut skin by softer process, and the identification of the phenolic compounds with antioxidant activity.

*Acknowledgement*s: CONICET, SECYT-FCEFyN-UNC, CONICOR for the economical support.

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Relationship Between the Conformation of the Cyclopeptides Isolated from the Fungus *Amanita Phalloides* (Vaill. Ex Fr.) Secr. and Its Toxicity

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Abstract: The electronic structures and conformational studies of the cyclopeptides, *O*-methyl-α-amanitin, phalloidin and antamanide, were obtained from molecular parameters on the basis of semiempiric and *ab initio* methods.

Introduction

During this century *Amanita phalloides* - the most toxic fungus known up to now - has been studied from different points of view. This basidiomycete biosynthesizes mono- and bicyclic peptides composed of rare amino acids. In order to determine the structure/activity relationships chemical modifications were carried out and the properties of these compounds were evaluated. These results were confirmed by studying the conformations of three selected compounds representative of the major groups of the macroconstituents of this fungus.

Experimental

Hyperchem package (HyperCube, version 5.2) was used for semiempirical studies, the molecular geometry being optimized by STO-631G. Net charges were calculated with HyperCube PM3 and the Polack-Ribiere algoritm. GAUSSIAN 98 was used for *ab initio* studies.

Results and Discussion

We were interested in obtaining information on the conformations that the cyclic peptides may adopt and about the potential energy maps in order to locate the regions related to the binding to protein molecules, such as F-actin and RNA-polymerase. *O*-methyl-α-amanitin, phalloidin and antamanide were selected. Minimal energy, polarizability, interaction regions, intra- and intermolecular hydrogen bonding, potential energy maps and charge density on each atom were calculated for the molecules mentioned above.

Thus, the ***O*-methyl-α-amanitin** contains a tryptathionine moiety with a sulphur atom as sulfoxide with *R*-configuration, which we have now demonstrated that is positioned ahead of a marked hydrophobic area. Upon opening the C-S bond, one of the cycles is lost, giving rise to an unstable structure with a concomitant conformational change. These results explain the loss of activity. The other face is surrounded by a cycle with highly hydroxylated side chains around, which are being stabilized by intramolecular hydrogen bonding. The dipolar moments of the hydroxyls contribute to the solubility in solvents of high dielectric constants. The side amino acid moieties are distributed all over the borders and practically all separated enough to form a globular picture, which is further stabilized by hydrogen bonding that misshape them by reaching the terminal portions and shifting them to the upper side of the molecule.

Phalloidin shows a similar conformation to that of the methyl derivative of α-amanitin with the heterocycle clearly exposed. In one of the faces, stereochemical changes as well as modifications of the total energy and the dipolar moment are recorded. The sulphur of the thioether and the tryptathionine adopt a unique conformation due to the occurrence of the (*n*) unpaired electrons, which affects the whole molecule. These facts result in an alteration in one of the side rings, which is therefore sloped towards the face containing the tryptathionine moiety. Hence, this molecule shows a different reactivity in comparison to the former.

Antamanide is a monocyclic compound, which contains ten amino acids and aromatic residues well exposed. It is remarkable the occurrence of two of them in the internal region, which due to be able to induce dipoles give rise to a selected molecule inclusion. The whole conformation is rather non-polar and of planar type without any folding. Certain cations may affect this conformation depending on the inclusion degree into the internal cavity.

Both semiempirical and *ab initio* methods have been compared, showing coincidence in the trends.

Acknowledgements: The authors are indebted to the Universidad de Buenos Aires, CONICET (Argentine) and ANPCyT (Argentine) for financial support.

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Synthetic Studies on Natural Stephaoxocanes. Elaboration of a Tetrahydrooxazaphenalene Potential Intermediate

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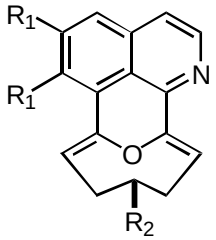
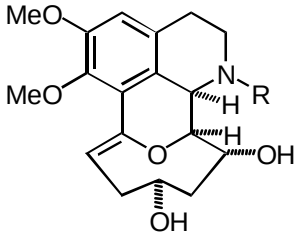
Abstract: The elaboration of a 2,3,7-9a-tetrahydro-1H-8-oxa-1-aza-phenalen-9-one derivative, as a potential key intermediate for the synthesis of stephaoxocanes, employing Jackson's tosylamidoacetal cyclization, is presented.

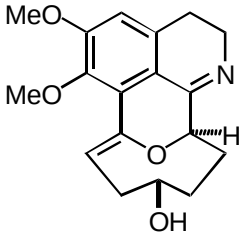
Stephania excentrica and *S. cepharantha* (Menispermaceae) have been used since ancient times in traditional Chinese medicine. *Stephania cepharantha*, which is widely cultivated in Japan, is native of Taiwan where its tuberous root is known as *ber-yao-zi*. Phytochemical studies on the methanolic extract of the tubers of *S. cepharanta* allowed the isolation of new bisbenzylisoquinolines, hasubananes, and morphinanes, as well as a host of known alkaloids. More detailed investigations carried out since 1992 exposed novel and interesting tetracyclic isoquinoline derivatives bearing an oxocane ring system (Figure), the first in their class, for which the term stephaoxocanes was coined [1].



R_1= MeO, R_2= OH
Stephaoxocanidine (**1**)
R_1= R_2 = H, Stephaoxocane



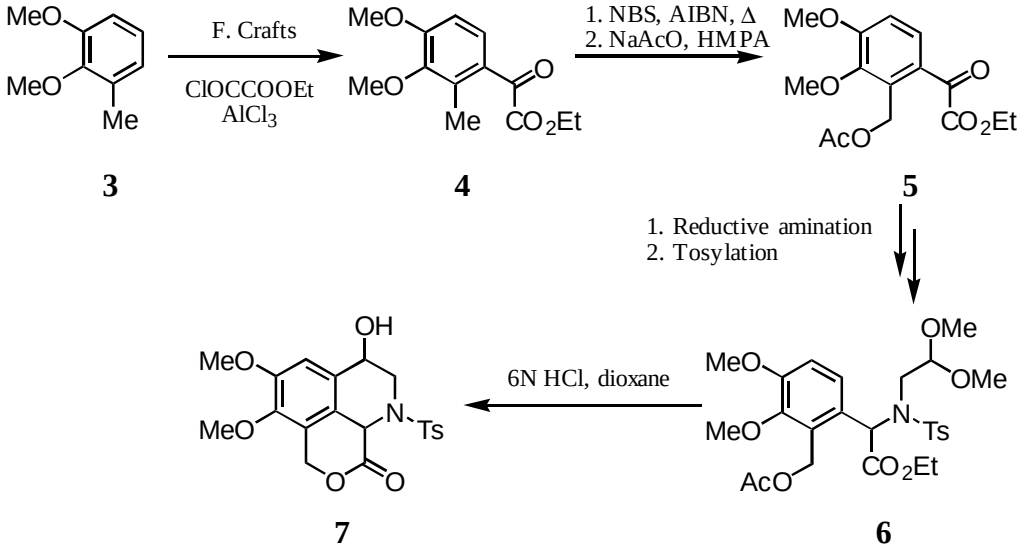
R= H Excentricine
R= Me 2-N-Methylexcentricine



Stephaoxocanine

This rare family of natural products has very few members and the tiny amounts of them found in the natural sources constitute a serious obstacle in better defining their biological activity and usefulness, if any, and making new developments. As part of our research projects on interesting isoquinoline type natural products synthesis by the use of Jackson's cyclization [1], we recently started to study the elaboration of model molecules for the total synthesis of natural stephaoxocanes, particularly stephaoxocanidine (**1**), displaying less structural complexity.

In this communication, the elaboration of tricyclic lactone **2**, a potential key intermediate for the synthesis of stephaoxocanes, bearing their characteristic tetrahydrooxazaphenalene skeleton, is reported. The lactone was obtained by Friedel Crafts acylation of toluene derivative **3**, followed by functionalization of the resulting intermediate **4** to ketoester **5** and application of Jackson's sequence on the latter, which allowed the simultaneous construction of rings B and C of **2**, by cyclization of sulfonamidoacetal **6** (Scheme). The chemical transformations involved in this synthetic sequence as well as their outcome will be discussed.



Acknowledgments: To Fundación Antorchas, CONICET, SECyT-UNR and ANPCyT for grants received.

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Elaboration of the Isochromane System of Stephaoxocanes Employing an Oxa-Pictet Spengler Type Cyclization

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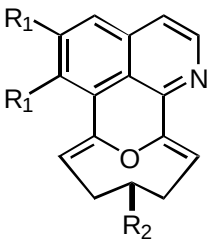
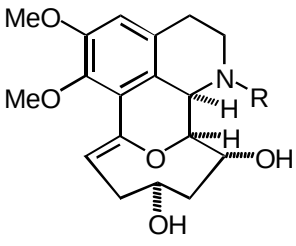
Abstract: An approach to the synthesis of the isochromane moiety embodying the AC-ring system of the stephaoxocanes, by the use of an Oxa-Pictet Spengler type cyclization strategy, is reported.

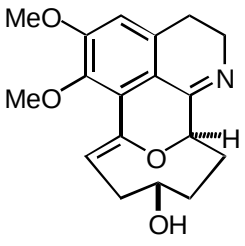
Stephania excentrica and *Stephania cepharantha* (Menispermaceae) are herbs employed since ancient times in traditional Chinese medicine. They are the source of many interesting natural products, among them the stephaoxocanes, a small family of tetracyclic isoquinoline alkaloids with only a few known members [1].



R_1= MeO, R_2= OH
Stephaoxocanidine (**1**)
R_1= R_2 = H, Stephaoxocane



R= H Excentricine
R= Me 2-N-Methylexcentricine



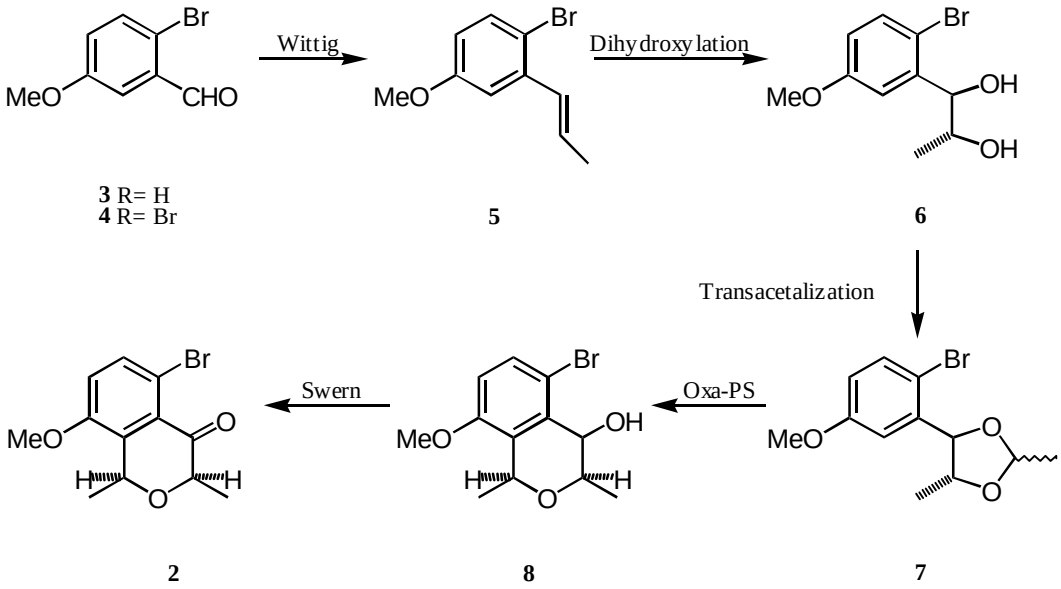
Stephaoxocanine

The interesting structural characteristics of these natural products in relationship with our research work [2] prompted us to study the elaboration of models for the total synthesis of natural stephaoxocanes, particularly stephaoxocanidine (**1**).

In this communication, we report the elaboration of isochromanone **2** starting from commercially available *m*-anisaldehyde (**3**), following an Oxa-Pictet-Spengler type strategy [3].

As shown in the Scheme, bromination of **3** with bromine in AcOH provided bromoaldehyde **4**, which olefination under Wittig conditions gave olefins **5**. Next, dihydroxylation of the double bond followed by transacetalization of the resulting diol with acetal furnished acetal **7**, which $TiCl_4$ pro-

moted cyclization [4] yielded isochromanol **8**. Finally, Swern oxidation of **8** allowed the obtention of ketone **2**.



3 R= H
4 R= Br

5 **6** **7** **8** **2**

Only one diastereoisomer is shown

The Wittig reaction resulted in a mixture of olefins the isomerization of which was not studied in this preliminary approach; therefore, products **6-8** as well as **2** were obtained as diastereomeric mixtures, keeping the product the proportion found in the starting material.

Details of the synthesis, the cyclization reaction course with different model molecules and synthetic potential of this strategy will be discussed.

Acknowledgements: To Fundación Antorchas, CONICET, SECyT-UNR, AUGM and ANPCyT for grants received.

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Practical and Efficient Procedure for the *In Situ* Preparation of *B*-Alkoxyoxazaborolidines. Enantioselective Reduction of Prochiral Ketones

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Abstract: A new method for the in situ elaboration of B-alkoxyoxazaborolidines is presented. Their use in the enantioselective reduction of prochiral aromatic ketones provides excellent chemical and optical yields of chiral alcohols.

Since the development of Corey [1], the *B*-alkyloxazaborolidines (**OAB**) have gained reputation as efficient catalysts in the enantioselective reduction of prochiral ketones. In addition to provide alcohols in high optical purity [2], they can be employed in small quantities and their reaction mechanism allows the prediction of the stereochemistry of the newly generated chiral center.

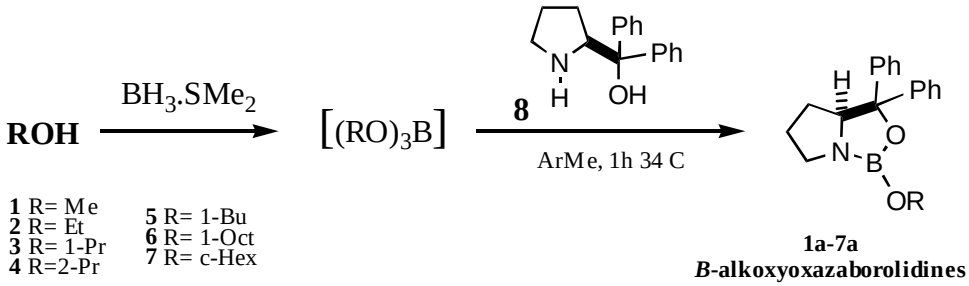
Numerous **OAB** synthesized from different aminoalcohols have been reported [3], however the most used **OAB** is that derived from α,α-diphenylpyrrolidinemethanol (**8**) developed by Corey.

In spite of the advantages of this new type of catalysts, the various methods described for their obtention, many times discourage their use, being time consuming [4] or requiring extensive separation steps prior to their use [5].

In order to avoid these inconvenients, we decided to study the synthesis of *B*-alkoxyoxazaborolidines, reacting alkyl borates with **8** by analogy with the strategies reported for the elaboration of alkyl-**OAB**, and then to evaluate the ability of the product to enantioselectively reduce prochiral aromatic ketones.

In this communication we introduce a new, practical and efficient method for the *in situ* elaboration of *B*-alkoxyoxazaborolidines employing inexpensive reagents and avoiding separation steps which could alter the optical quality of the reduction.

We also demonstrate the efficiency and capability of the *B*-alkoxyoxazaborolidines as catalysts through the reduction of several substituted acetophenones. The enantioselectivity obtained is generally comparable to that observed with the *B*-methyloxazaborolidine developed by Corey.



Product	*B*-alkoxy-**OAB**	ee(%)	Yield (%)
R-1-(3,4-dimethoxyphenyl)ethanol	**1a-7a**	>95	>93
R-1-(4-acetoxy-3-methoxyphenyl)ethanol	**5a**	97	≈100
R-1-(4-hydroxy-3-methoxyphenyl)ethanol	**6a**	>98	98
R-1-(2,4-dimethoxyphenyl)ethanol	**6a**	90	≈100
R-1(4-nitrophenyl)ethanol	**6a**	>95	≈100
R-1(4-aminophenyl)ethanol	**6a**	95	≈100
R-1(4-bromophenyl)ethanol	**6a**	97	98

Acknowledgements: To Fundación Antorchas, CONICET, SECyT-UNR, AUGM and ANPCyT for grants received. VLP thanks CONICET for a fellowship.

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Synthetic Modifications of Lead Compounds as Antitrypanosomal Drugs

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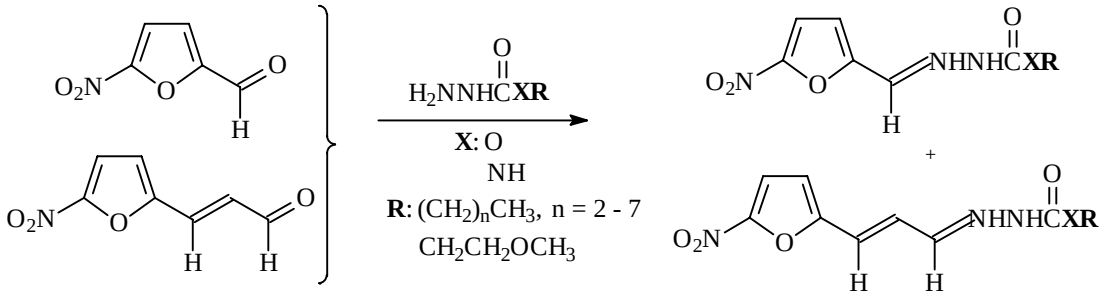
Abstract: Following our work in the synthesis of compounds with antichagasic activity, we describe new potential products in which the same "leader" compound was modulated.

Introduction

We have previously reported the synthesis and biological activity against *Trypanosoma cruzi* epimastigote forms *in vitro* and *in vivo*, of a series of semicarbazone derivatives of 5-nitrofurfural ("leader" compounds) [1,2].

Experimental

The synthesis of the new compounds is shown in the following scheme:



This compounds (I-IX), treated with Lawesson' reagent, produced the thiocarbonyl compounds.

Results and Discussion

The new compounds were identified by ^{1}H-NMR, ^{13}C-NMR, IR, MS and were tested *in vitro* against epimastigote forms of *Trypanosoma cruzi.*

Acknowledgements: The authors thank PEDECIBA Química and RELAQ (Red Latinoamericana de Ciencia Química).

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Synthesis of 1,2,6-Thiadiazin 1,1-Dioxide Derivatives as Trypanocidal Agents

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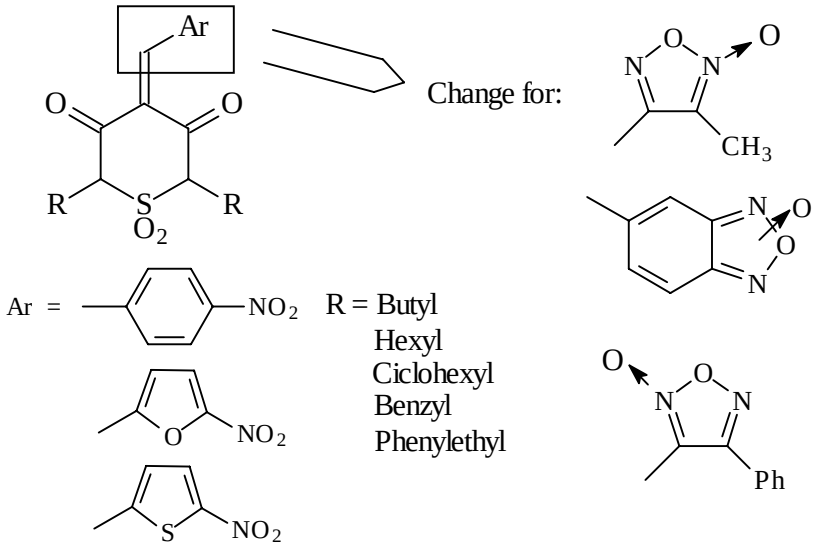
Abstract: It describes the synthesis of new 1,2,6-Thiadiazin 1,1-dioxide derivatives using condensation of the Knoevenagel type. The products are evaluated *in vitro* as trypanocidal agents.

Introduction

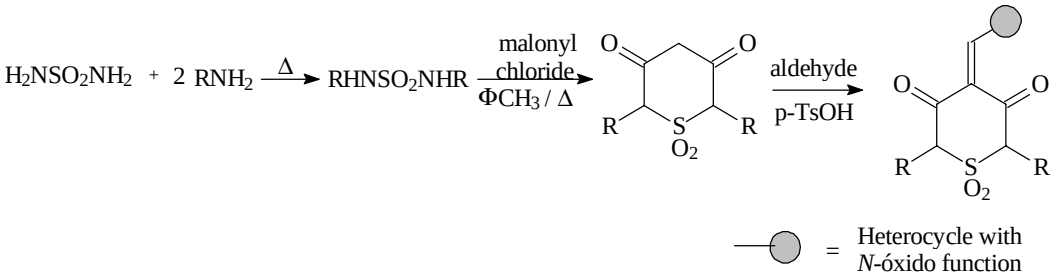
We have previously reported the synthesis of three series of new compounds and the biological evaluation against *Trypanosoma cruzi* of 1,2,6-Thiadiazin 1,1-dioxide derivatives, structurally related to Nifurtimox [1,2]. The *in vitro* assay showed that some of them exhibit significant activity against epimastigote forms of *T. cruzi*, but the cytotoxicity of this type of compounds against Vero cells was highest than the reference drug.

Experimental

In this work we design new structures, changing the free radical generator.



All the compounds were prepared according to the following synthetic pathway



Results and Discussion

All the compounds have been obtained with good yields, and have been characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS.

All the products were tested *in vitro* against *T. cruzi* epimastigote forms and that more promising were tested their cytotoxicity.

Acknowledgements: The authors thank CYTED (Ciencia y Tecnología para el desarrollo) and RELAQ (Red Latinoamericana de Ciencia Química).

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2. Synthesis and antichagasic properties of new 1,2,6-Thiadiazin-3,5-dione 1,1-dioxides and related compounds. *Arzneimittel Ferschung* (in press).

Reactivity Studies of 5,6-Dimethyl- and 3,5,6-Trimethyl -1,2,4-Triazine–N_4-Oxide Against Different Electrophiles

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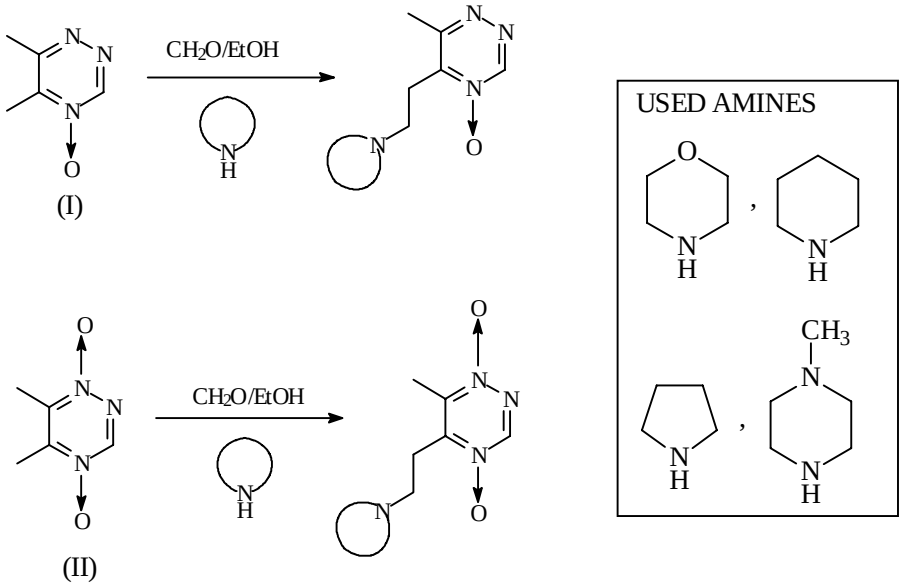
Abstract: It describes the regioselectivity studies of 5,6-Dimethyl-1,2,4-triazine-N_4-oxide using different electrophiles.

Introduction

Within our group we have developed a series of derivatives of *N*-oxide y *N, N'*-dioxide of 1,2,4-triazine, they were tested as biorreductives cytotoxic agents against V79 cells in oxia and hypoxia conditions [1]. In the search of bioactives compounds, the derivatives 5,6-Dimetil-N_4-óxido-1,2,4-triazina (I) y 5,6-Dimetil-N_1,N_4-dióxido-1,2,4-triazina (II) were subdued to Mannich conditions using different amines. In this reaction we observed an interesting regioselectivity [2]. We always obtained the mono-substituted product in 5 position.



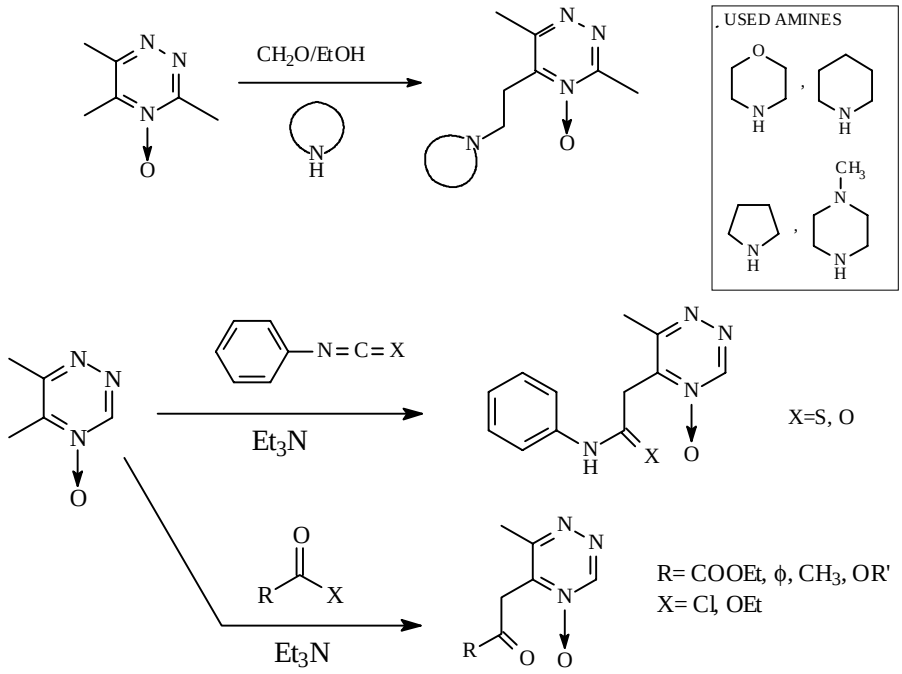
In order to generalize the observed regioselectivity we designed:

1. To study the behavior of the 3,5,6-Trimethyl-N_4-óxido-1,2,4-triazine (III) subdue to the Mannich reaction.

2. To study other electrophilic reagents.

Experimental

The reactions developed are shown.



Results and Discussion

The unequivocally characterization of all the products was done by 2D-RMN experiments. The products obtained may asseverate that the 5 position of the compounds on study (I and III) showed a selective nucleophilia for the kind of reactions studied.

Acknowlegment: C.H.L.C.C., CYTED, PEDECIBA.

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Addition of Aromatic Nucleophiles to a C=N Double Bond of 1,2,5-Thiadiazole 1,1-Dioxide

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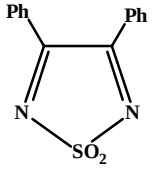
Abstract: A new synthesis of 3,4-diphenyl-4-aryl-1,2,5-thiadiazolines 1,1-dioxide through the addition of aromatic derivatives to 1,2,5-thiadiazole 1,1-dioxide is presented. Anhydrous $AlCl_3$ is used as catalyst.

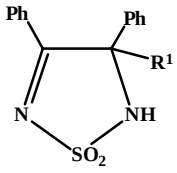
Introduction

Compounds of the 1,2,5-thiadiazolidines 1,1-dioxide type (**3**) are interesting owing to a number of therapeutic and synthetic applications [1]. Their are almost exclusively obtained through the condensation reaction of vicinal diamines or amino-alcohols with sulfamide. The availability of the precursors limits the synthetic possibilities.

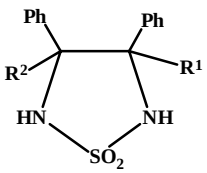
A recently reported new method [2] for the synthesis of **3** uses substituted thiadiazolines intermediates (**2**), obtained from thiadiazoles (**1**) by addition with Grignard reagents.



1



2



3

A new method for the addition of activated aryl nucleophiles to the C=N double bond of **1** is presented in this work. The addition is carried out in solution at room temperature and with adequate yields, using ACl_3 as a catalyst.

Experimental

The synthesis were carried out in Cl_2CH_2 solution, except in the cases of toluene and anisole addition, were these reagents were also used as solvents.

Anhydrous $AlCl_3$ was added at room temperature to a magnetically stirred solution of **1**, in a molar ratio R = [$AlCl_3$] / [**1**] ≅ 10. The course of the reaction was followed by TLC.

Results and Discussion

The nucleophiles used were anisole, toluene, phenol, N,N-dimethylaniline, resorcinol and benzene. The products and yields obtained were: 3,4-diphenyl-4-(4-methoxyphenyl)- (η= 64%), 3,4- diphenyl -4-(4-methylphenyl)- (η= 92%), 3,4- diphenyl -4-(4-hidroxyphenyl)- (η= 90%) and 3,4- diphenyl -4-(4-N,N-dimethylaminophenyl)-1,2,5-thiadiazoline 1,1-dioxide (η (unoptimized) = 38%).

The products were purified, their EA was obtained and crystals were grown for X-ray diffraction structure measurements. Spectroscopic (IR, ^{1}H-RMN, ^{13}C-RMN and EM) characterization was also performed.

In the case of benzene, a complex mixture of reaction products, containing mainly polymers derived from benzene, was obtained. Three as yet unidentified reaction products were obtained with resorcinol.

Acknowledgements: This work has been financially supported by the National University of La Plata (Argentine), the National University of São Carlos (Brazil), CNPQ, CONICET and CIC.Pcia of Bs. As. We are grateful with UMyMFOR for the performance of the NMR spectra.

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Studies on a New Synthetic Route towards Cassiol

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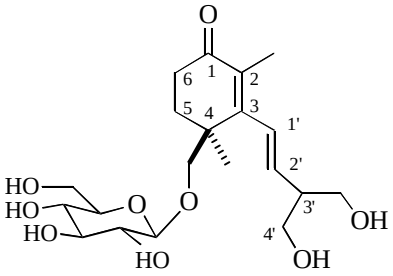
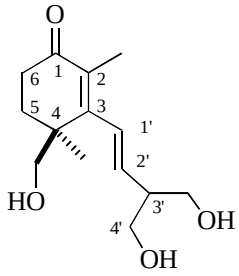
Abstract: The synthesis of the acyclic intermediate **7** towards the preparation of cassiol (**2**) is described. The cyclization of **7** led to **5**, a precursor of **2** and to the unexpected product **8**.

Introduction

Cassioside is a glucoside isolated from *Cinnamomum cassia* Blume which, together with its aglycone, cassiol, are two potent antiulcer agent. The structural features and pharmacological activity of both products have aroused the interest of synthetic organic chemists and several contributions to its synthesis have appeared in the literature in recent years [1,2].

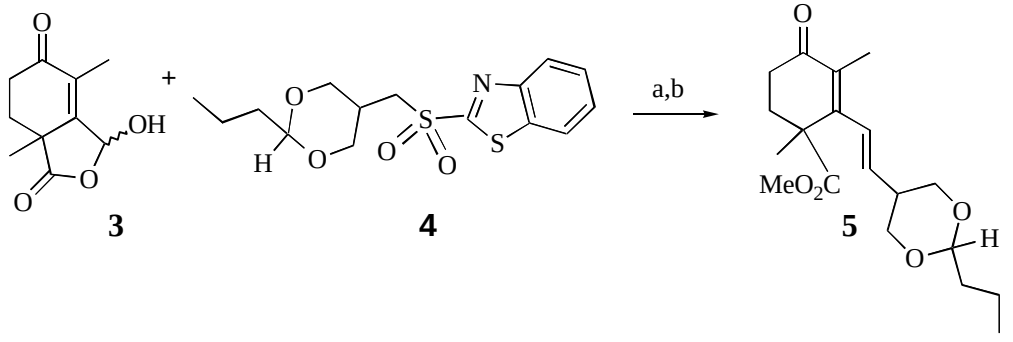


cassioside (1)



cassiol (2)

We have recently developed a rather simple synthetic sequence for the preparation of **5**, a precursor of cassiol, by using an olefination reaction of lactol **3** with the 2-benzothiazoleylsulfone 4, under the conditions reported by S. Julia [3] with a 18% yield.



3 **4** **5**

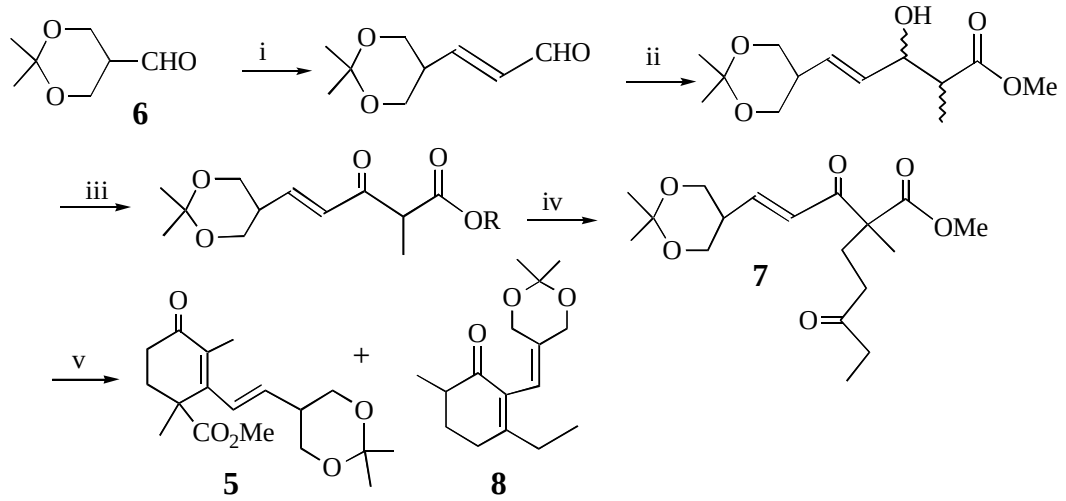
Unfortunately, all our attempts to improve the yield of **5** were unsuccessful. A careful analysis of the reaction mixture allowed us the identification of unchanged starting material and some products that suggested that lactol **3** would suffer a Canizzaro-type reaction under the olefination reaction conditions, indicating a low reactivity of the carbonyl group of **3** under these conditions, probably due to steric hindrance [4].

Discussion and Experimental Part

In view of the results described above and hoping to prepare **2** in better yield, we decided to develop an alternative synthetic sequence, involving a Michael addition followed by an aldol condensation of an open chain substrate like **7**.

The preparation of **7**, starting with aldehyde **6**, was carried out in good overall yield, following the conditions described in Scheme 1.

Scheme 1



Reagents and conditions: i) (triphenylphosphoranylidene)acetaldehyde, benzene, reflux; ii) methyl propionate, THF, LDA, -78°C ; iii) PDC, CH_2Cl_2, RT, 24h; iv) EVK, EtOH, NaOH; v) 4% KOH (aq), MeOH, reflux, 7 h.

However, an attempt of cyclization of **7**, with aqueous potassium hydroxide in methanol under reflux, afforded a mixture of **5** (10%) and the unexpected product **8** (60%). By analyzing the mechanism of formation of **8** a new sequence for the synthesis of cassiol (**2**) will be suggested.

Acknowledgments: We thank Universidad Nacional de Rosario (UNR), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) and Agencia Nacional de Promoción Científica y Tecnológica.

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Synthesis and Characterization of New Naphthoquinonic Derivatives Containing the Pyrazole Ring: Pyrazolylnaphthoquinones

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Abstract: The reaction of 3-aminopyrazole (**1**) with 1,2-naphthoquinone-4-sulfonic acid sodium salt (**2**) was studied in different aqueous media. The novel pyrazolylnaphthoquinones synthesized were physical and spectroscopically characterized, including 2D NMR spectroscopy (HETCOR). The possible reaction mechanism is proposed.

Introduction

Quinones and naphthoquinones are widely distributed in nature and play a vital role in certain celullar functions [1]. On the other hand, pyrazoles are important synthetic intermediates in the construction of many complex molecules with interesting biological activities [2,3].

For these reasons, and in our search of compounds with important bioactivities, we have prepared a new type of naphthoquinonic derivatives containing the pyrazole ring as nitrogenated heterocycle.

In this communication we describe the synthesis and characterization of a new type of compounds, the pyrazolylnaphthoquinones **3-5**, which were obtained by the reaction of 3-aminopyrazole (**1**) and 1,2-naphthoquinone-4-sulfonic acid sodium salt (**2**).

Experimental

IR (KBr), UV-visible (MeOH), NMR and mass spectra were recorded in a Nicolet 5-SXC FT IR, Shimadzu UV-160A, Bruker AC 200 E and a Finningan 3300 (at 30 y 70ev), respectively.

The ^{1}H and ^{13}C spectra were run in DMSO- d_6 (the center of the solvent peak was used as internal standard which was related to TMS) and they were calculated by the ACD program. Compounds **1** and **2** were purchased from Aldrich Co. and Sigma, respectively.

Derivatives **3-6** were isolated and purified by radial preparative chromatography, electrophoresis and recrystallization from organic solvents.

Results and Discussion

Preliminary experiments investigating the reaction between 3-aminopirazole (**1**) and 1,2-

naphthoquinone-4-sulfonic acid sodium salt (**2**) showed different structures. It was seen that the medium conditions (basic, neutral, acidic and heat) were responsible for the pathway of the reaction. Therefore, the reaction was studied exhaustively and was found that in the pH range 10.4-2.0 and at room temperature, 2-hydroxy-N-(3-pyrazolyl)-1,4-naphthoquinone-4-imine (**3**) was obtained as unique product (71%). In aqueous HCl 0.5 N and at room temperature, a mixture of **3** (20%), N-(3-pyrazolyl)-4-amino-1,2-napththoquinone (**4,** 5%) and 2- (3-pyrazolylamino)-N-(3-pyrazolyl)-1,4-naphthoquinone-4-imine (**5,** 43%) were isolated. On the other hand, in aqueous HCl 0.5 N at reflux, the reaction afforded a mixture of **4** (7%) and 2-hydroxy-1,4-naphthoquinone (***Lawsone,*** 17%).

The spectral data [including the 2D NMR spectroscopy (HETCOR)] were consistent with the proposed structures for **3**-**5**. The possible reaction mechanism is discussed and evidence is presented to discard the existence of isomers arising from the tautomeric equilibrium of the pyrazole ring.

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Determination of the Formation Constant of the Inclusion Complex from a Naphthoquinone

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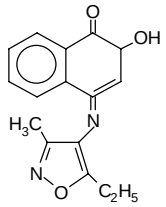
Abstract: Inclusion complexation of 1 with HP-β-CD or HP-β-CD:PVP K30 in aqueous solution was spectroscopically studied and the formation constant for a 1:1 complex was determined from these measurements.

Introduction



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Previously we have demonstrated by means of phase solubility diagrams that hydroxypropyl-β-cyclodextrin (HP-β-CD) increases the aqueous solubility of 2-hydroxy-N-(3-methyl-5-ethyl-4-isoxazolyl)-1,4-naphthoquinone-4-imine (**1**) [1], a compound that has antibacterial and tripanosidal activity [2]. Also, we have demonstrated that the improvement in solubility of **1** can be further increased by adding 0.5% (w/v) of polyvinylpyrrolidone K30 (PVP K30) to the HP-β-CD solution.

In this work our aim is to determine the formation constants of the inclusion complex (K_c) between the HP-β-CD and the naphthoquinone.

Experimental

The K_c values were determined by the UV spectrophotometric method (Shimadzu UV 160 UV/visible spectrophotometer).

Results and Discussion

The UV-visible spectrum of **1** is affected in the presence of HP-β-CD or HP-β-CD:PVP K30. The absorption band around 280 nm shifted towards longer wavelengths (306 nm) with increasing concentration of HP-β-CD together with an increase in the intensity of the absorption band located between 400 and 550 nm. These spectral changes allowed us to obtain the K_c value using the Scott's equation: $(a\ b)/d = 1/(K_c\ \varepsilon_c) + b/\varepsilon_c$, which assumes a complex stoichiometry of 1:1, where ***a*** is the total molar concentration of **1**, ***b*** is the total molar concentration of the complexing agent, $\boldsymbol{\varepsilon_c}$ is the difference of the molar absorptivities for free and complex **1** and ***d*** is the change in absorbance of **1** caused by addition of the complexing agent [3].

The K_c between **1** and HP-β-CD was also studied in buffer solutions (ionic strength of 0.5 M) and was observed that K_c increased with the increment of the pH (the pK_a value of **1** is 8.19). K_c between **1** and PVP K30 was significantly lower than K_c between **1** and HP-β-CD, but its value increased markedly in presence of 5% (w/v) HP-β-CD.

On the other hand, no bigger changes than those observed for the absorption spectra of zero order could be noticed in the derivative spectra.

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Binding Constant of Amines to Water/AOT/n-Hexene Reverse Micelles. Influence of the Chemical Structure

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Abstract: The distribution of different amines between n-hexane bulk and the micellar pseudophase of AOT reverse micelles were measured by a fluorometric method. An independent method was used to corroborate the incorporation of the amines to the interface. The effect of the amine structure on the binding constant was analysed.

Introduction

The increase of the solubility in the presence of supramolecular aggregates is an important phenomenon in a variety of scientific and technological areas. Even though, there are extensive data regarding to the solubilization of small molecules in biological membranes, liposomes and direct micelles. However, in reverse micelles systems data are scanty [1]. In our group we have studied the binding constant of nitroanilines and diphenylamines to water/AOT/n-hexane reverse micelles [2,3].

The aim of the present contribution was to determine the binding constant of different aliphatic and aromatic amines to water/AOT/ n-hexane reverse micelles by steady-state fluorescence measurements. The formation of the $Ru(bpy)_3^{+1}$ ion by laser flash photolysis of a mixture of $Ru(bpy)_3^{+2}$ and amines was used as a further confirmation of the distribution of the amines between the micellar pseudophase and the organic bulk.

Experimental

The following amines: n-butylamine, isobutylamine, tert-butylamine and piperidine from Fluka, N,N-dimethylaniline (BDH) and N-methylaniline (Riedel de Haën) were distilled from sodium under nitrogen atmosphere prior to be used. The binding constants were measured by two different approaches: a) a direct method where the amine act as a quencher of a fluorophore incorporated to the micelle [4]; b) Abuin and Lissi´s method [5] for compounds that do not fluoresce or act as quenchers, provided that they modified the bimolecular rate between a microphase incorporated fluorophore

($Ru(bpy)_3^{+2}$) and a quencher ($Fe(CN)_6^{-3}$).

For the radical ion determination, the samples were excited with a Nd:YAG laser operated at 355 nm. The signal was transfer from the oscilloscope to the PC through and IEEE interface.

Results and Discussion

The results show the importance of the hydrogen bond interaction of the amines with the AOT polar heads in the their distribution between the two pseudophases. Similar behaviour was found before with other substrates. In this way, primary amines has the larger binding constant, while the tertiary amines are not incorporated to the micellar pseudophase. The influence of the amine solubility in the organic phase, as an extra driving force for the distribution, should be taking into account.

The laser flash photolysis experiments allowed us to confirm that tertiary amines, aliphatic and aromatics, are not incorporated to the micellar pseudophase since the $Ru(bpy)_3^{+1}$ ion, previously observed in water, was not detected in the micellar media

Acknowledgements: We gratefully acknowledge the financial support from CONICET, CONICOR, FONCYT, SECyT-UNRC.

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New Withanolides from Two Varieties of *Jaborosa Caulescens*

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Abstract: The phytochemical study of two species of ***Jaborosa caulescens*** (***var. caulescens*** and ***var. bipinnatifida***) yielded the four new withanolides **1-4**. The structures of the new compounds were determined using a combination of spectroscopic techniques (including 1D and 2D NMR) and Molecular Modeling.

Introduction

The tribe ***Jaboroseae (Solanaceae***) is comprised by three genera: ***Jaborosa*** and ***Salpichroa,*** both Southamerican, and ***Nectouxia***, a monotipic genus endemic of Mexico.

Our research interest is focused on the phytochemical study of the ***Jaborosa*** genus. This genus is comprised by 23 species and 22 growth in Argentina [1-2].

Experimental

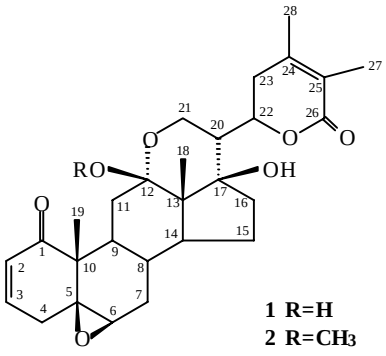
The aerial parts of ***Jaborosa caulescens var. caulescens*** and ***Jaborosa caulescens var. bipinnatifida*** were exhaustively extracted with ethanol. After evaporation of the solvent, the crude dried extract was partitioned with hexane-methanol-water (10:9:1). The methanol-water phase was then extracted with methylene chloride. The withanolides were isolated from this extract using different chromatografic techniques like CC, prep. TLC and prep. HPLC. The structures elucidation was performed by a combination of spectroscopic techniques (^{1}H-NMR, ^{13}C-NMR, DEPT, COSY, NOESY, HETCOR, IR, MS, CD) and Molecular Modeling.

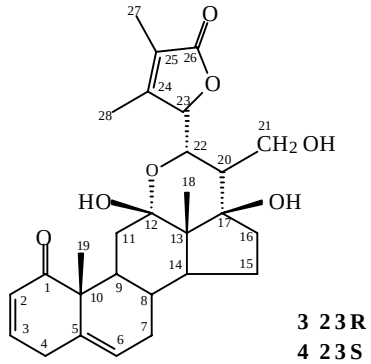
Results and Discussion

J. caulescens var. caulescens yielded the withanolides **1** and **2**. These two compounds resemble the structures of Jaborosalactona R, S and T (isolated from ***J. sativa*** [3]), with respect to the presence of the hemiketal function between C-21 and C-12, but differ in the substitution pattern of ring A and B.

Compound **2**, once isolated from the plant extract, rapidily demethylate to give compound **1**. These evidences rule out the possibility that the methylation be an extraction artifact.

On the other side, compounds **3** and **4** were isolated from ***J. caulescens var. bipinnatifida***. Both compounds possessed a trechonolide type-structure. Their spectroscopic profiles were very similar and also showed the same molecular weight in the MS spectrum. A detailed analysis of the spectroscopic data led us to propose that both structures only differ in the stereochemistry at C-23. This was confirmed by Circular Dichroism experiments, in which the respective spectra of compound **3** and **4** showed opposite Cotton effect al 217 nm. The sign of the Cotton effect of compound **3** (-) was the same as trechonolide A, indicating the R stereochemistry.





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Formation of Complexes of Flavonoids and Metals. Determination of the Stoichiometry and Stability Constants

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Abstract: The complexes between some flavonoids and metals (Co(II), Cu(II), Mn(II), Mg(II), Sn(II)) have been studied by spectrophotometric methods in order to determine the stoichiometry and stability constants.

Introduction

Flavonoids are poliphenolic compounds, which are characterized by showing a variety of pharmacological activities, e.g. antioxidant, antihelmintic, antiinflamatory, antiviral, antitumor, etc. Most of these activities are due to their ability to inhibit enzymes, such as trypsine, protein kinases, topoisomerases.

The complex formation of these compounds and metals of the active enzyme site or complexes between certain amino acids of the active site and the metals of the medium is probably the reason of this enzymatic inhibition.

This study deals with the determination of the stoichiometry of the complexes of some flavonoids and a variety of metals (Co(II), Cu(II), Mn(II), Mg(II), Sn(II)) as well as the determination of each stability constant.

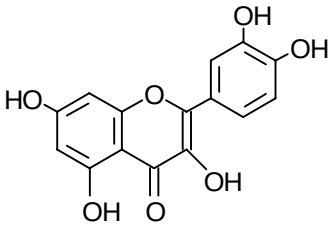
Experimental

Spectrophotometric methods were used. Solutions of each flavonoid and metal salts in a molar rate (metal mols/total mols) in the range of 0.09 and 0.9 were prepared using methanol.

UV-Visible spectra for each molar rate were performed, and plotting Absorbance vs Molar rate or Initial metal concentration the exact stoichiometry of each complex was determined.

Results and discussion

Formation of species with a 1:1 (metal:ligand) stoichiometry were obtained for the flavonoids tested. The stability constant of each complex was determined.



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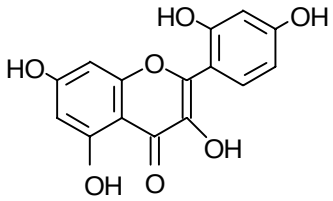

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Acknowledgment: The authors are indebted to CONICET (Argentine) and the Universidad de Buenos Aires for financial support.

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Analysis by Mass Spectrometry of the Polar Lipids from the Cellular Membrane of Thermophilic Lactic Acid Bacteria

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Abstract: Fast atom bombardment (FAB) technique was employed to determine the structure of polar lipids from the cellular membrane of *Lactobacillus delbruekii ssp. bulgaricus* and *Streptococcus salivarius ssp. thermophilus*. Analysis of spectra provided useful information about the molecular species and aminoacids constituents of the samples.

Introduction

Lactobacillus delbruekii ssp. bulgaricus and *Streptococcus salivarius ssp. thermophilus*, thermophilic lactic acid bacteria, are used as starter cultures for the manufacture of yogurt and different types of cheeses on a worldwide scale. However, the high sensitivity of these microorganisms to cryogenic treatments results in structural and physiological injury that makes their preservation difficult. Both the bacterial cell wall and membrane are damaged after freezing-thawing processes [1].

Membrane destabilization is the result of cell dehydration occurring in response to the osmotic stress and membrane phase transitions, changes that are related to the membrane lipid composition [2]. As lipids are important in maintaining cell membrane structure of Gram-positive microorganisms it would be of interest to know whether the different types of lipids and the fatty acids distribution on them are involved in the cell membrane integrity during freezing.

Fast Atom Bombardment (FAB) techniques were recognized early as being a useful analytical techniques for the analysis of polar lipids [3, 4]. In large part, this was due to the unique chemical behavior of these compounds, having a highly lipophilic region, which enable the molecule to orient on the surface of FAB-matrices as well as polar functionalities, which readily accept either positive or negative charge sites in the gas phase [3].

Results and Discussion

The polar lipids of thermophilic acid lactic bacteria were characterized by their characteristic mi-

grations on thin-layer chromatographic (TLC) plates. The preliminary characterization of the lipids was done by spraying plates with specific reagents. The extracts of *S. thermophilus* and *L. bulgaricus* gave positive reactions for glycolipids, phospholipids, and one species of aminophospholipid. These results were confirmed by Fast Atom Bombardment-mass spectrometry (FAB-MS). This technique showed information on the different molecular species present in the samples.

The presence of cardiolipin (CL) and diacylphosphophatidylglycerol (PG) was established by negative-FAB MS. Glycolipids and aminophospholipids fractions were analyzed by positive-FAB MS. The results indicated, on the basis of the molecular weights, the presence of diglycosyldiglycerides and hydroxylysyl-phospholipids.

The aminoacid OH-lysine is not a common constituent of phospholipids molecules in bacteria membranes. Serine and ethanolamine are most frequently aminoacid found in the aminophospholipids of bacteria. This study was completed by traditional techniques of hydrolysis and fatty acids and aminoacid analysis.

Acknowledgements: We thank LANAIS-EMAR (CONICET-FCEN,UBA) for mass spectra, UMYMFOR (CONICET-FCEN,UBA), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), and Universidad de Buenos Aires for partial financial support.

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Chemical Modifications of 1,2,5-Oxadiazole *N*-Oxide System Searching for Cytotoxic Selective Hypoxic Drugs

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Abstract: New analogues of 3-Formyl-4-phenyl-1,2,5-oxadiazole N-oxide **(1)** are prepared and evaluated as cytotoxic selective agents in hypoxia.

Introduction

As part of our research project on biorreducible drugs in hypoxia conditions, we have developed a series of compound derivatives of *N*-oxide of 1,2,5-oxadiazoles system. They were evaluated as cytotoxic agents against V79 cells in oxia and hypoxic conditions. None of them showed selectivity in hypoxic conditions, but the derivative **1** presented a good profile of Cytotoxicity (**Figure 1**). In order to gain insight the mechanism of action and to obtain a selective compound, we designed the following modifications.

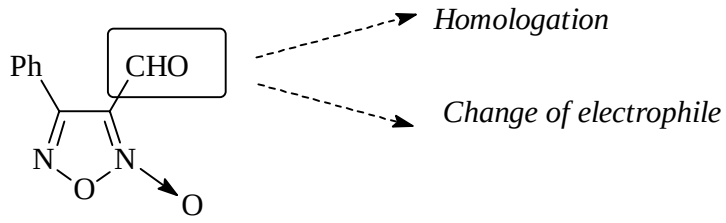

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Figure 1.

Experimental

Following, we showed the modifications outlined.

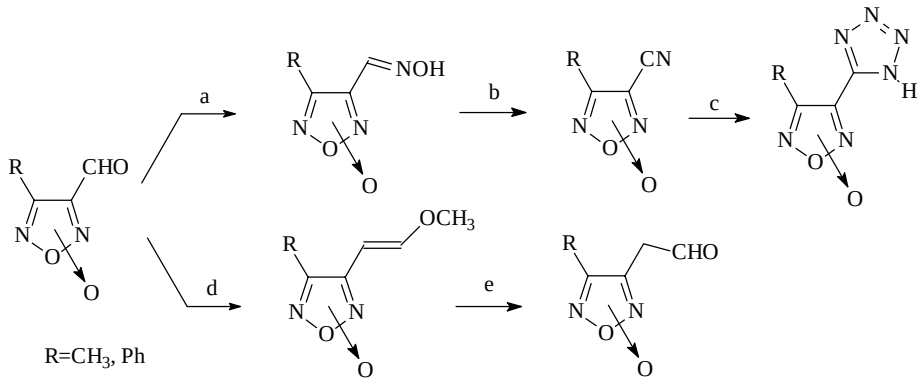

Figure 2. *Conditions:* (a) $NH_2OH.HCl$/*p*-TsOH/EtOH; (b) $SOCl_2$/DMF; (c) NaN_3/NH_4Cl/DMF; (d) $Ph_3P^+CH_2OCH_3\ Cl^-$; (e) H_3O^+.

All the products were characterized by ^1H RMN, ^{13}C RMN, (1D, 2D), EM, IR and in same cases elemental microanalysis. The cytotoxicity of the synthesized products was tested against V79 cells in oxia and hipoxia conditions at a concentration of 20 µM, following a protocol previously described [1].

Results and Discussion

All the synthetic procedures conducted to the products of interest with variable yields. As the drug-modulations previously described [2], the new ones may asseverate that the substituent at the 3 position of the 1,2,5-oxadiazol *N*-oxide plays an important role in the cytotoxic activity of this kind of compounds.

Acknowledgment: C.H.L.C.C., CYTED, PEDECIBA.

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Approach to the A-B Ring System of Forskolin through Biotransformation of Toluene

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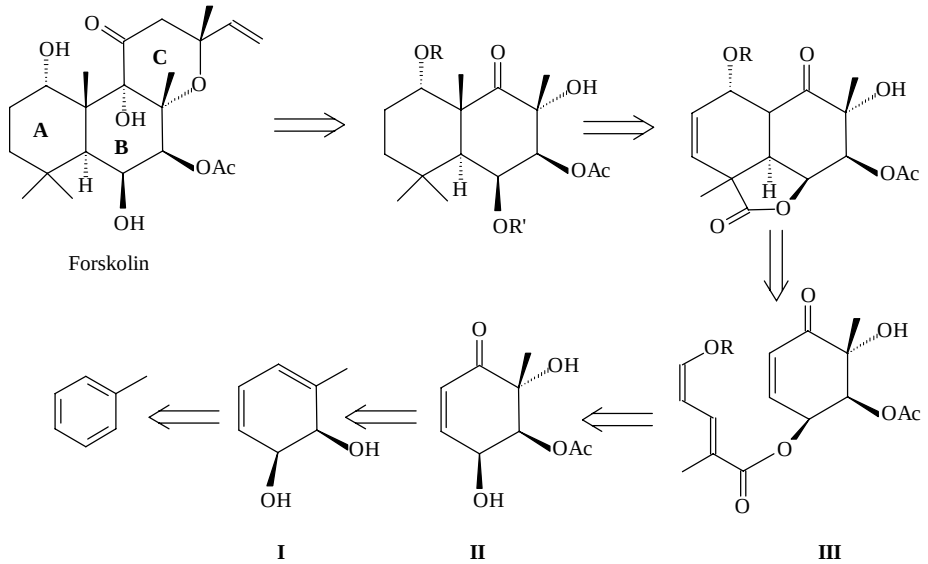
Abstract: In the present work, we will intend to show that diol **I**, microbially derived from toluene using Pseudomonas putida 39D, is a suitable synthon for the synthesis of the A-B ring system of forskolin. The functionalization of diol **I**, to be used as ring-B, and the attempts of ring-A closure, will be disclosed.

Introduction

Chiral cyclohexadiendiols of the type of **I**, produced by microbial oxidation of arenes, have been extensively used as starting materials for the enantioselective synthesis of natural products. In this work, we present an approach to the synthesis of forskolin, based in a transfer of chirality from the homochiral diol **I** to the B ring of the diterpene, as shown in the retrosynthetic analysis.

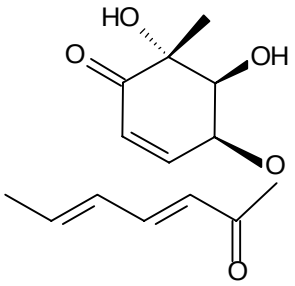


Experimental

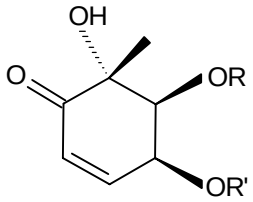
We will present the optimization of the synthetic route to obtain a structure of type **II**, via oxidation reactions and selective protection-deprotection sequences of the hydroxyl groups. We will also present the synthetic approaches to an structure of type **III** which allows the ring A closure through an intramolecular Diels-Alder reaction. We will also discuss the attempts to close ring A using an intermolecular Diels-Alder cycloaddition, studying the viability of the reaction with different dienes and experimental conditions.

Results and Discussion

We have synthesized enone **IV**, as a model to study the intramolecular Diels-Alder reaction. To date, results have shown serious difficulties in terms of reactivity and stability of the model molecule. That's why we are trying different intermolecular cyclizations with molecules of type **V**, utilizing more reactive dienes.



IV



V

R = H, Ac, MOM

R' = H, THS, Ac

Acknowledgments: CSIC, PEDECIBA, CONICYT.

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Shelf-Life of an Extruded Blend of Peanut, Soybean and Corn

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Abstract: The Shelf-Life (SL) of peanut, soybean and corn blend extruded without (A) and with butylhydroxytoluol (B) and extract of Rosmarinum sp (C) was determined. Only B significativaly increased SL. In function of temperature would be defined by: A- $SL = e^{-0.0465x + 5.1762}$, B- $SL = e^{-0.0421x + 5.3332}$, C- $SL = e^{-0.581x + 5.626}$

Introduction

In order to attain a nutritional, low cost and consumer accepted food, Bustamante et al (1998) developed an extruded blend of peanut, soybean and corn. The main chemical deterioration, that could limit the extrudate stability, is oxidation due to its low water activity and its proportion of unsaturated fatty acids: >80%. The objective of this study was to determine the shelf-life of the extrudate with and without antooxidants (natural and synthetical) in function of temperature.

Experimental

Treatments: *A*- Extrudate of peanut, soybean and corn, *B*- *A* + butylhydroxytoluol, *C*- *A* + extract of *Rosmarinum sp*. The extrudates were accomplished in a prototype extruder of the INIQUI (UNSa) and were subjected at different times and temperatures.

Chemical analysis: The oil matter was extracted with n-hexane in a Soxhlet apparatus for 4 h. On this fraction were performing the following assay: Peroxide index (PI) and acidity index (AI) according to *AOAC* (1980), and unsaturated fatty acids (uFA) according to Maestri and Guzmán (1995).

Sensory evaluation: Preselection, training and selection of panelists were performed through ranking test, and the assay of *A*, *B* and *C* through triangle test (*IRAM*, Jellinek 1985).

Shelf-Life and value Q_{10}: were determined working at 30 and 40°C (Fennema 1993).

Statistical analysis: ANOVA, Duncan and lineal regression ($n = 3$, $P \leq 0.05$) were used. The results of the triangle test were analysed according to Jellinek (1985).

Results and Discussion

Chemical analysis: **PI**- Only *B* offered significant protection against oxidation. **AI**- The free acids of *B* increased in less proportion than *A* and *C*. **uFA**- Its proportion decreased in time function, being less evident to *B* and more evident to *A*.

Sensory evaluation: From 40 participants, 11 panelists were selected. The treatment did not detected was: 40 days, 40°C of *A*, *B* and *C*. Few panelists detected it, they defined it like "the more *soft*". The shelf-life could be established for detriment of its organoleptic characteristics, rather than presence of minimal intensity of rancidity.

Shelf-Life (*SL*) and value Q_{10}: The *SL* of *A*, *B* and *C* was determined from lineal tendency of the PI in time function at 30 and 40 °C. The PI of *B*, 40 days, 40°C was used like threshold. Therefore, *SL* in function of the temperature resulted: *A*- $SL = e^{-0.0465x + 5.1762}$, *B*- $SL = e^{-0.0421x + 5.3332}$, *C*- $SL = e^{-0.581x + 5.626}$. Value Q_{10}: 1.59, 1.52 and 1.79 to *A*, *B* and *C*, respectively. Theoretical *SL* of each extrudate at 60°C was estimated and was compared with experimental *SL*: resulted resembling, specially *A* and *C*.

Acknowledgements: To CONICET, CONICOR, SECYT, INIQUI (UNSa), UNC and participants of sensory evaluation.

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A Facile High-Yield Synthesis of [^{10}B]-8-Dihydroxyboryl Harmine, a Potential Agent for Boron Neutron Capture Therapy

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The resurgence of interest in Boron Neutron Capture Therapy (BNCT) as a treatment for malignant lesions has resulted in the synthesis of numerous boron compounds as candidates for clinical use. BNCT is a selective radiotherapy using boron-10 which absorbs thermal neutrons and releases high Linear Energy Transfer (LET) alpha particles by ^{10}B (n, α) ^{7}Li reaction. The alpha radiation kills cells in the range of 5-9 μm from the site of the α generation. Therefore, it is theoretically possible to kill tumor cells without affecting adjacent healthy tissues, if ^{10}B-compounds could be selectively delivered. Boron analogues of amino acids constitute a topic of major importance, and also peptides, antibodies, nucleosides and nucleotides [1], etc. In spite of the promising results with p-boronophenylalanine (BPA) and $B_{12}H_{11}SH^{2-}(Na^{+})$ (BSH), which presently attract considerable clinical interest, they display far from optimal selectivity for cancer cells.

The anatomical distribution of [^{3}H]Harmalas binding sites was determined by quantitative autoradiography in rat brain slices [2]**.** They have a well know brain distribution, so these compounds, labeled with ^{10}B are potential agents for BNCT. A general synthetic method has been developed for the rapid and efficient production of boronated Harmine.

Results And Discussion

Iodination

The methods for iodination have been used previously for indolealkylamine [4] and phenethylamines [4] using thallium trifluoroacetate as specific oxidizing agent of molecular iodine for iodination of aromatic compounds [5].

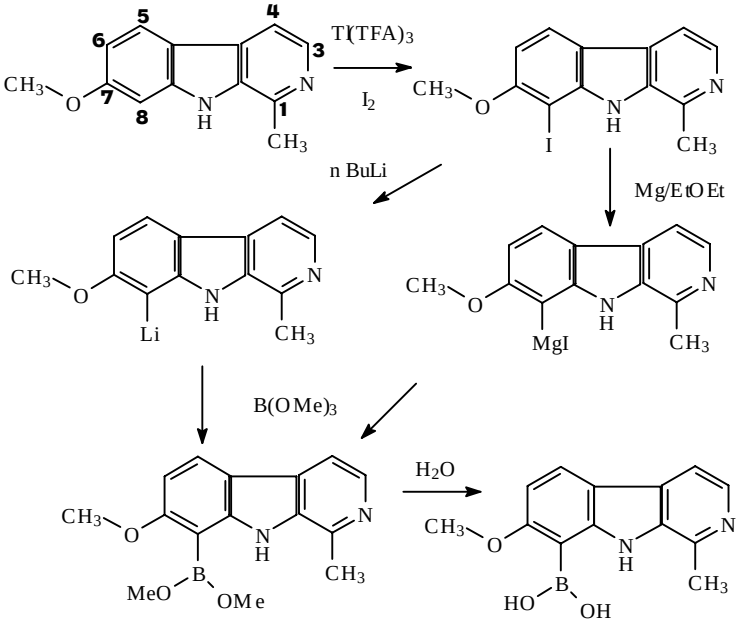
Boronation

We used the condensation of the Grignard reagent from 8-I-Harmine with trimethylborate. This method was previously used [6] for preparation of phenol from phenylbromide and trimethylborate with formation of phenylboronic acid as intermediate and for preparation of boronic analogue of cho-

line [7]. An alternative synthesis previously used for preparation of boronic analogues of nucleosides and nucleic bases [8-11] consist in treating the halogenated substrate with n-buthyllithium in THF followed by addition of trimethylborate at –86ºC. Trimethylborate was prepared by standard procedures [12] from 95% ^{10}B-enriched or natural isotope abundance boric acid and methanol and recovered from the formed azeotrope.

Summary and Conclusions

We have described a method for preparation of [^{10}B]-enriched-8-dihydroxyborylharmine (III) and characterized it by their spectral properties (MS, IR and NMR). This compound is a potential BNCT agent.



Scheme 1. Synthesis of boronated harmine.

Acknowledgments: Thanks are due to CONICET and Universidad de Buenos Aires (UBA; Argentina) for financial support. One of us, (J.A.S), also thank CONICET for research fellowship.

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Synthesis of Diads and Triads Derived from Carotenoids and Fullerene C60

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Abstract: A convenient procedure for the synthesis of supramolecules bearing carotenoids and fullerene C60 is reported. The amphipathic nature and the high yield of charge separation of these compounds make them candidates in the formation of transmembrane charge gradients.

Introduction

Photochemical and photophysical studies of fullerene C60 (buckminsterfullerene) have shown that C60 is a good electron-acceptor, has a low fluorescence and high triplet quantum yield (≅100%) [1]. In carotenoid-fullerene diads, the lowest excited singlet state of the fullerene is strongly quenched by electron transfer from the carotenoid moiety to generate the charge separated species [2,3]. The high yield of charge separation and the amphipathic nature of these supramolecules, make then a likely candidates for use in the formation of transmembrane charge gradients, producing proton transport across phospholipid membranes, upon absorption of light [4].

Experimental

All the products were characterized by ^{1}HNMR and MS spectroscopies. The precursor methanofullerenecarboxylic acid was prepared according to the method described in the literature [1]. The Wittig-Horner reactions were performed in THF/KOH medium.

Results and Discussion

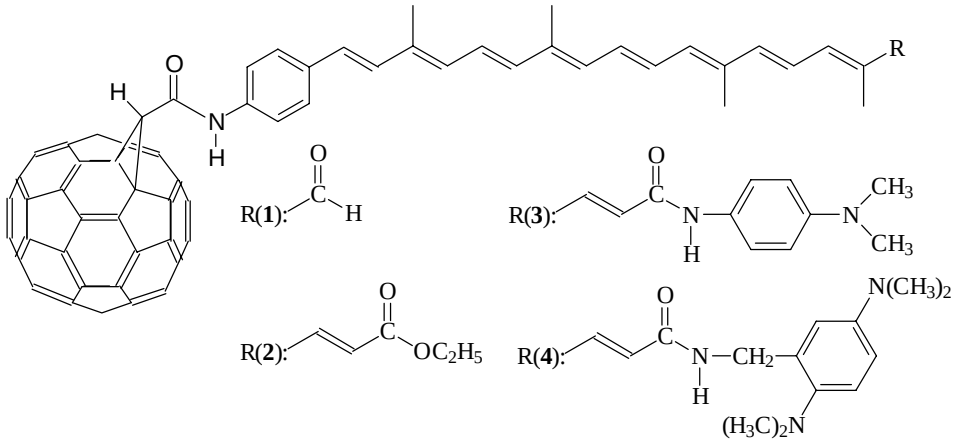
Synthesis of Bifunctional Carotenoids

Bifunctional carotenoids, substituted on both sides of the conjugate chain, were synthesized from crocetindial. An aminophenyl group was incorporated on one side of the chain by the Wittig reaction.

In the other side, remains an aldehyde group, which was used for attach different structures by formation of a new double bond using Wittig-Horner reactions.

C60 derivatives

The methanofullerenecarboxylic acid (C60-acid) was synthesized from C60 using the method described by Diederich [1]. This compound is a versatile starting material for the preparation of amphipathic fullerene derivatives. The coupling reaction of carotenoids to C60-acid was performed using dicyclohexylcarbodiimide catalyzed by 1-hydroxybenzotriazole, 4-dimethylaminopyridine and triethylamine (44-50% yields).



Acknowledgements: Authors are grateful to Fundación Antorchas, Consejo Nacional de Investigaciones Científicas y Técnicas of Argentina and National Science Foundation for financial support.

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Synthesis of Asymmetrical Porphyrins Substituted in the meso-Position from Dipyrrolomethanes

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Abstract: A convenient procedure for the synthesis of 5-(4-acetamidophenyl)-10,15,20-tris(4-substituted phenyl) porphyrins from dipyrrolomethane is reported. *meso*-(4-Substituted phenyl) dipyrrolomethanes were obtained in yields of 72-84%. The amide porphyrins were isolated with appreciable yields of 15-17%.

Introduction

The design of new material systems involves the synthesis of asymmetric porphyrins. Thus, porphyrin covalentely linked to carotenoids has been used in the design of artificial photosynthetic membranes, which mimic the natural process of solar energy conversion [1]. Also, electroactive porphyrins have been employed in the design of molecular electronic systems [2]. In these cases, the synthesis of porphyrins substituted in *meso*-position by phenyl groups, where one differs of the other three (AB_3-porphyrins), results particularly interesting [3].

Experimental

All the products were characterized by ^{1}HNMR spectroscopy, MS spectroscopy, and elemental analysis of C, H and N. The reactions were performed according to the methodology described in ref. 3.

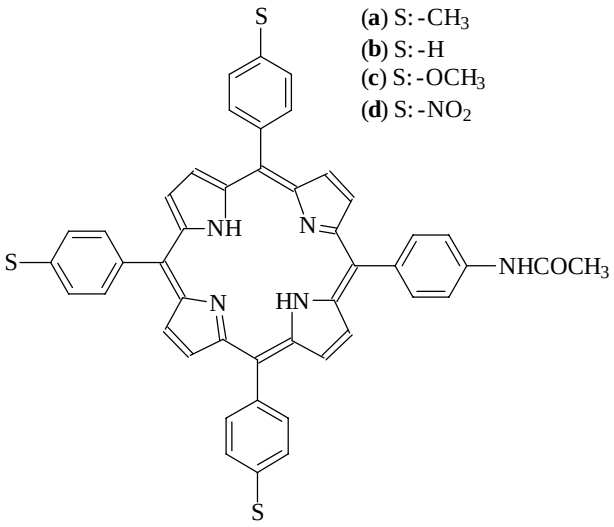
Results and Discussion

Synthesis of dipyrrolomethanes

The *meso*-substituted dipyrrolomethanes were synthesized by the condensation of the corresponding benzaldehydes and excess pyrrole. The reaction is catalyzed by acids. Under these conditions, pyrrole acts as reactant and solvent, causing direct formation of dipyrrolomethane. These compounds were isolated with high purity and used in the AB_3-porphyrin synthesis.

Synthesis of asymmetric tetraphenylporphyrins

The tetraphenylporphyrins (AB_3-porphyrins) were synthesized by the condensation of the appropriated benzaldehydes and dipyrrolomethanes (Scheme). The reaction requires catalytic amount of $BF_3{\cdot}O(Et)_2$ in chloroform. This condensation produces porphyrin in its reduced form, therefore the reaction mixture was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). This reaction yielded a mixture of three porphyrins, which were separated with high purity by flash chromatography (yields 15-17%).



Scheme.

Acknowledgements: Authors are grateful to Fundación Antorchas and Consejo Nacional de Investigaciones Científicas y Técnicas of Argentina, for financial support.

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A Simple Enzymatic Preparation of 2',3'-Di-*O*-Acetylnucleosides Through a Lipase Catalyzed Alcoholysis

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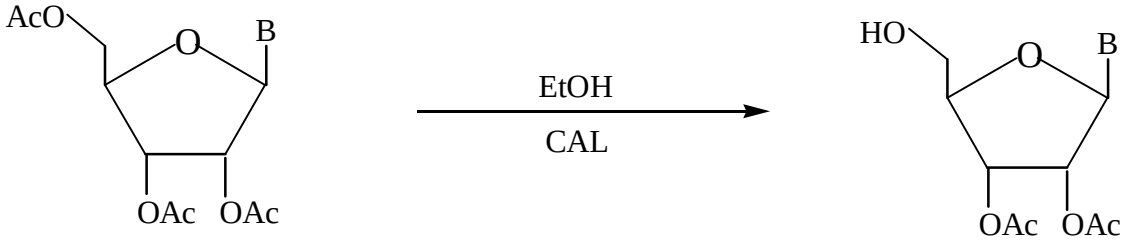
Abstract: Several 2',3'-di-O-acetylnucleosides (**2a-d**) were obtained regioselectively through a *Candida antarctica* B lipase catalyzed alcoholysis.

Introduction

Much effort has been devoted to the synthesis of nucleoside analogues as most of the antiviral agents used at present against extensive viral affections belong to this family of compounds [1]. Due to the polyfunctional nature of nucleosides, selective transformations are usually required to prepare these molecules in good yields. However, such reactions are frequently difficult to carry out satisfactorily by means of traditional synthetic procedures [2]. For instance, in the synthesis of oligonucleotides and nucleosides prodrugs, regioselective protection and deprotection of hydroxyl groups are carried out through multy-steps processes.

Enzymes have become nowadays well-recognized regio- and stereoselective catalysts in synthetic chemistry [3], and lipases are one of the most useful biocatalysts due to their efficiency, easy work up and stability in organic solvents. These facts prompted us to study lipase-catalyzed deacylation of nucleosides **1a-d** through a *Candida antarctica* B lipase (CAL) catalyzed alcoholysis:



1 a-d **2 a-d**

Scheme. a R= H, B= 1-uracyl; **b** R= CH_3, B= 1-uracyl; **c** R= H, B= 9-hypoxantyl; **d** R= H, B= 9-guanyl.

Experimental

The alcoholysis shown in the Scheme were performed at 200 rpm and 28º C. The reaction mixtures were analyzed by both TLC and HPLC, using a C-18 column. After a convenient time was reached, the enzyme was filtered off and products **2a-d** were isolated by column chromatography, affording satisfactory spectral data (^{1}H and ^{13}C NMR).

Results and Discussion

Although the reactions depicted in the Scheme were studied employing three lipases: Lipozyme^{R} (*Mucor miehei* lipase), *Candida rugosa* lipase and CAL, only the latter exhibited activity. With this biocatalyst, compounds **2a-d** could be obtained regioselectively in good yields. The ethanol/nucleoside ratio and the solvent showed a dramatic effect on the selectivity and the yield of the biotransformation.

In contrast to the non enzymatic synthesis of compounds **2a,c,d,** which requires three steps, the regioselective enzymatic alcoholysis presented herein avoids one step and is carried out under simple and mild conditions.

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Escherichia Coli Bl21: A Useful Biocatalyst for the Synthesis of Purine Nucleosides

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Abstract: E. coli BL21 cells were able to synthesize several purine nucleosides from pyrimidine ones. Kinetics and yields of this reaction showed a strong dependence on pH, temperature, reagent concentrations and weight of wet cell paste. Yields over 90% were reached in the synthesis of adenosine.

Introduction

Modified nucleosides are wide diffused as antiviral and antitumor drugs as well as starting materials for antisense oligonucleotides. In contrast to classical chemical synthesis of these, good results as far as yield, simplicity and regiostereospecificity are concerned can be achieved at low cost using pure enzymes or whole cells as biocatalysts.

The methodology employed in the synthesis of purine nucleosides involves the transfer of a sugar residue from a donor pyrimidine nucleoside to an acceptor purine base. This process requires the presence of enzymes belonging to the family of transferases, specially the purine and pyrimidine nucleoside phosphorylases (PNP and PyNP) which are present in most of the microorganisms [1].

In this work, several experimental variables have been studied in order to select the best conditions necessary for the E.Coli BL21 catalyzed synthesis of purine nucleosides.

Experimental

The E. coli strain was grown in Lb medium in shaked flasks at 27ºC until saturation, centrifuged and washed with the suitable buffer. The resultant wet cell paste was used as catalyst of the reaction [2] after suspending in phosphate buffer (5 ml) and addition of the nucleoside and purine base. The mixture was stirred and heated at constant temperature in glycerin bath and the reaction products were analyzed by tlc and hplc.

Results and Discussion

One of the biotransformations studied in this work is shown in Figure 1.

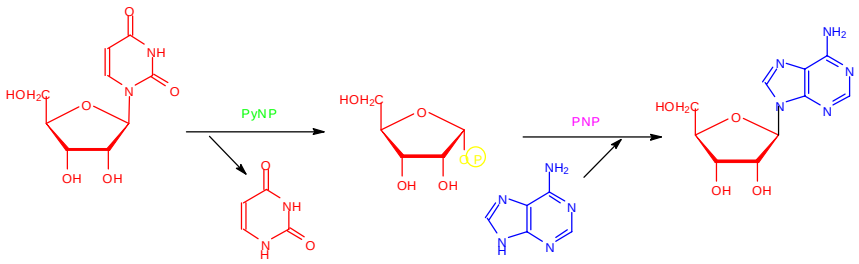

Figure 1. Enzymatic synthesis of adenosine.

The reagents tested were the nucleosides uridine and thymidine and the bases adenine, hypoxanthine and guanine. The following variables have been studied: temperature, reagent concentrations, pH and buffer concentration, biocatalyst amount and reaction time [3]. For example, adenosine was obtained with a yield higher than 90% working at 60ºC in 30 mM phosphate buffer at pH 7, with excess of uridine during 1 hour. Longer reaction times have been observed when tymidine was used as ribose donor.

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Solid-Phase Organic Chemistry: Synthesis of 2β-(Heterocyclylthiomethyl)Penam Derivatives on Solid Support

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Abstract: The synthesis of 2β-(heterocyclylthiomethyl)penam derivatives on solid support has been developed. Compounds are obtained in good to high yields (based on loading of the original resin). The key step is the solid-phase double rearrangement of the corresponding penicillin sulfoxide.

Introduction

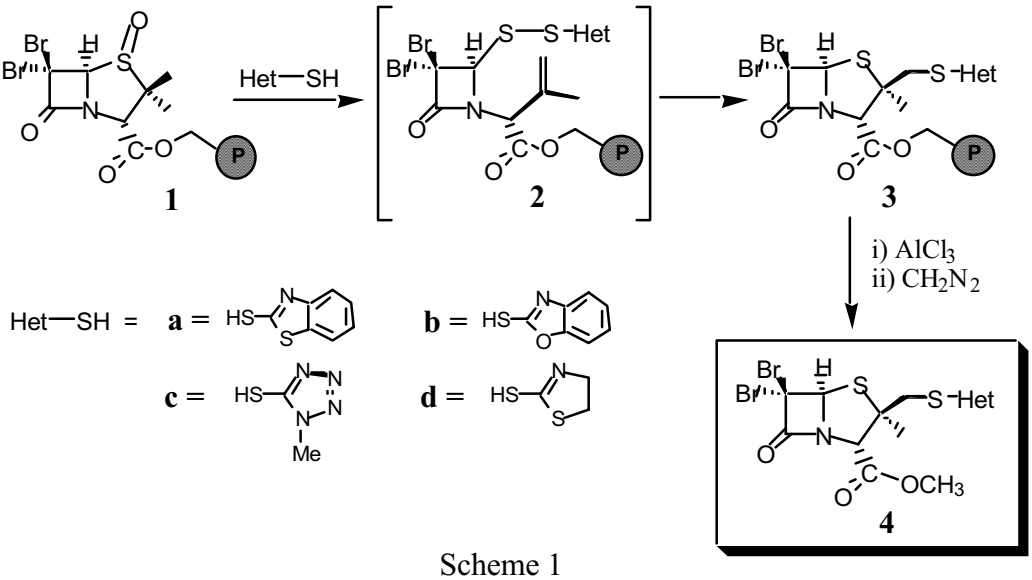
The impact of combinatorial chemistry of small molecules on the drug discovery process is now widely recognized by the scientific community [1]. Solid-phase organic synthesis (SPOS) is a valuable tool for the generation of structurally diverse compounds for combinatorial libraries.

In our work dealing with the solid-phase synthesis of biologically interested compounds, we have developed methodologies for tethering funtionalized polystyrene resins to penicillin derivatives. Our research has also established a new, mild and efficient procedure for the removal of sensitive molecules from Merrifield and Wang resins, using aluminum chloride ($AlCl_3$) [2].

Results and discussion

Heterocyclic thio substituents have been identified as pharmacophores in β–lactam chemistry, particularly with activity against methicillin-resistant *staphylococcus aureus* (MRSA) [3]. Thus, we considered the solid-phase synthesis of 2β-(heterocyclylthio)methyl substituted penicillins as a rapid and efficient method for the generation of combinatorial libraries.

The key step of this synthesis of the double rearrangement of sulfoxide **1** (Scheme 1). The thermal rearrangement of **1** generates the sulfenic acid which is trapped by the corresponding heterocyclic thiol (Het-SH) to give the disulfide intermediate **2**. Then, a new rearrangement rebuilds the thiazolidine ring to obtain the 2β-(heterocyclylthio)methyl penams (**3**).



Scheme 1

This work began with the immobilization of penam derivative onto Merrifield resin and oxidation with *m*-chloroperbenzoic acid (MCPBA, 1.4 equiv.) to obtain the resin-bound sulfoxide **1**. These reactions were monitored by FT-IR. In the case of the reaction of sulfoxide **1** with 2-mercaptobenzothiazole (2-MBT) (**a**) in the presence of catalytic amounts of *p*-toluenesulfonic acid, the resin-bound 2β–(benzothiazol-2-yl)thiomethyl derivative (**3a**) was obtained. After cleavage with $AlCl_3$ and esterification with diazomethane, compound **4a** was obtained with an overall yield of 45% (based on initial loading of the Merrifield resin).

The versatility of this methodology has been demonstrated by the synthesis of different 2β-(heterocyclylthio)methyl penams. For example, using 2-mercaptobenzoxazole (**b**), the Merrifield resin-bound 2β–(benzoxazol-2-yl)thiomethyl derivative (**3b**) was obtained. After cleavage and esterification, compound **3b** was transformed into the ester **4b** (overall yield: 50%). Similarly, a series of closely related derivatives have been prepared with overall yields ranging from 45 to 55% .

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Stereoelectronic Contributions to ^{1}H-^{1}H Coupling Constants

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Abstract: The effect of stereoelectronic interactions on coupling constants is shown. The analysis is done with a new approach in which a selected interaction is deleted and the effect over the couplings is analyzed. ^{1}H-^{1}H magnetic couplings three and four bonds apart in hydrocarbons are shown.

Introduction

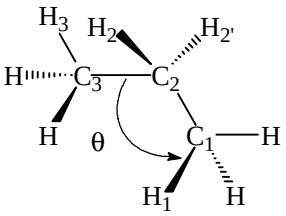
Coupling constants have been widely used to carry out conformational analysis in molecules. In these studies the relationship between structural parameters (dihedral angles) and experimental data (magnetic coupling constants) are provided. For this reason it is interesting to analyze the intramolecular interactions that produce Karplus-like curves.

Results and Discussion

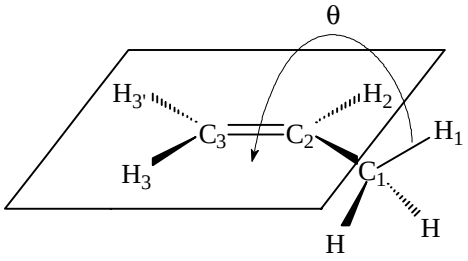
The methodology presented here implies, as a first step, a Natural Bond Order [1] (NBO) localization, followed by the deletion of selected Fock matrix elements (written in the NBO basis) representative of the interaction between selected orbitals. The next step is to recalculate the density matrix in the AO basis using the modified Fock matrix and then calculate the electronic polarization propagator [2]. With this propagator it is possible to determine several second order properties, like magnetic couplings, which are of interest in this work. The magnitude calculated in this way is then compared with the magnitude obtained without deletions and so it is possible to evaluate the effect of the interactions corresponding to the deletions considered. The computations were done with Gaussian 98 (geometry optimizations and NBO analysis) and SYSMO (magnetic properties).

Using the present formalism we analyzed coupling constants between protons three and four bonds apart. In the former, the main contributions to the angle dependence of the coupling constants came from the vicinal interactions between the C-H bonds and antibonds corresponding to the coupled protons. The geminal interactions between C-H and C-C bonds and antibonds along the way of the coupled protons are also important, but of less magnitude.

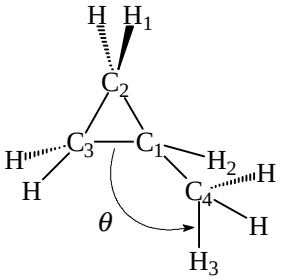
In the case of $^4J_{HH}$, three model compounds were considered, in order to analyze magnetic couplings transmitted through sigma, pi and cyclopropane bonds:



Propane (**1**)



Propene (**2**)



Ethylcyclopropane (**3**)

In the first case **1** the main interactions came from the vicinal interactions {The following abbreviation is consider for the stereoelectronic interactions: $\alpha(A_i\text{-}A_j)\leftrightarrow\beta(A_k\text{-}A_l)$ is the same as $\alpha(A_i\text{-}A_j)\rightarrow\beta^*(A_k\text{-}A_l) + \beta(A_k\text{-}A_l)\rightarrow\alpha^*(A_i\text{-}A_j)$, where α, β indicate σ or π orbitals, and A_i stands for atom i, etc.} $\sigma(C_1\text{-}C_2)\leftrightarrow\sigma^*(C_3\text{-}H_3)$, $\sigma(C_2\text{-}C_3)\leftrightarrow\sigma^*(C_1\text{-}H_1)$ and the direct interaction $\sigma(C_1\text{-}H_1)\leftrightarrow\sigma^*(C_3\text{-}H_3)$. A detailed analysis of the two kinds of interactions shows that the vicinal ones are more important in the θ interval between 0° and 120°, while the four bond apart interaction is more important between 120° and 180°, being the last one the so called "W" conformation, which usually gives rise to "visible" $^4J_{HH}$ couplings.

In the case of **2**, the most important interactions are those whose localized orbitals correspond to the mobile $C_1\text{-}H_1$ and the double bond $C_2\text{=}C_3$: $\sigma(C_1\text{-}H_1)\leftrightarrow\sigma^*(C_2\text{=}C_3) + \sigma(C_1\text{-}H_1)\leftrightarrow\pi^*(C_2\text{=}C_3)$. Among these, the most important is the $\pi(C_2\text{=}C_3)\rightarrow\sigma^*(C_1\text{-}H_1)$.

In the last case considered **3**, it is necessary to take account a larger quantity of stereoelectronic interactions than in the previous ones, in order to take into account the angular dependence of the couplings: $\sigma(C_1\text{-}C_2)\leftrightarrow\sigma(C_4\text{-}H_3) + \sigma(C_1\text{-}H_2)\leftrightarrow\sigma(C_4\text{-}H_3) + \sigma(C_1\text{-}C_3)\leftrightarrow\sigma(C_4\text{-}H_3) + \sigma(C_1\text{-}C_4)\leftrightarrow\sigma(C_4\text{-}H_3) + \sigma(C_1\text{-}C_2)\leftrightarrow\sigma(C_1\text{-}C_4) + \sigma(C_1\text{-}C_2)\leftrightarrow\sigma(C_2\text{-}H_1) + \sigma(C_2\text{-}H_1)\leftrightarrow\sigma(C_1\text{-}H_2) + \sigma(C_1\text{-}C_4)\leftrightarrow\sigma(C_2\text{-}H_1) + \sigma(C_1\text{-}C_3)\leftrightarrow\sigma(C_2\text{-}H_1) + \sigma(C_2\text{-}H_1)\leftrightarrow\sigma(C_4\text{-}H_3)$. The most important interaction is the vicinal $\sigma(C_1\text{-}C_2)\leftrightarrow\sigma(C_4\text{-}H_2)$.

In **1** and **2** a few interactions contribute to the couplings, while in **3** there are no main contributions. From a general point of view, the methodology proposed here is rigorous and is approximately additive. One of the drawbacks is the necessity of testing all possible interactions in order to know which are the most important.

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Alkali Treatment of the Polysaccharides from the Cystocarpic Stage from *Iridaea Undulosa*

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Abstract: The polysaccharides from cystocarpic *Iridaea undulosa*, soluble and insoluble in 2M potassium chloride, Cs and Ci, respectively, were treated with alkali and fractionated by precipitation with increasing concentrations of KCl. They were later separated by ion-exchange chromatography, to yield fractions enriched in an α-(1→6)-glucan, agaroids and carrageenans.

Introduction

The red seaweed *Iridaea undulosa* is an important source of carrageenans. The structure of the galactans from cystocarpic and tetrasporic thalli has been studied [1]. The presence of galactans containing *L*-Gal was proved in the 2M KCl-soluble fractions from cystocarpic *Gigartina skottsbergii* after alkali treatment and further KCl precipitation [2], and also in the soluble fraction of the polysaccharides from tetrasporic *Iridaea undulosa* [3].

Herein we report the results of the alkali treatment of the 2M KCl-soluble and -insoluble fractions of cystocarpic *Iridaea undulosa* polysaccharides, and of their further fractionation by ion-exchange chromatography.

Experimental

The polysaccharide from cystocarpic *Iridaea undulosa* was fractionated with 2M KCl. Both the insoluble (**Ci**) and soluble (**Cs**) weres obtained after centrifugation, dialysis and liophylization. **Cs** and **Ci** were treated with 1M NaOH (5 h, 80°C), and their solutions, after dialysis and freeze-drying (**CsT** and **CiT**), were refractionated with KCl from 0.1M to 2M. The fractions soluble in 2M KCl (**CsTs-2** and **CiTs-2**) were subfractionated by ion-exchange chromatography on DEAE Sephadex A-50 mixed up with Sephadex G-100 stabilized on 0.2M NaCl, by elution with increasing concentrations of NaCl (up to 4 M). The constituting monosaccharides were determined by GC, after hydrolysis with 2 M TFA and derivatization to the corresponding aldononitriles and aminoalditols acetates [1,4].

Results and Discussion

The first fractionation of the polysaccharide yielded 31% of **Cs** and 62% of **Ci**. After alkali treatment, 95% of **Cs** was recovered (**CsT**), yielding four new fractions after precipitation with increasing concentrations of KCl: **CsTi-0.1**, **CsTi-1**, **CsTi-2** and **CsTs-2**. The first one (81%) is a carrageenan (88% D-Gal), with traces of L-Gal, Glc and Rha. On the other hand **CiT** was similarly fractioned with KCl, yielding also four equivalent fractions. The major one, **CiTi-0.1**, (92%) contained 93% of D-Gal and trace amounts of 3-*O*- and 6-*O*-Me-*D*-Gal. Fractionation of **CsTs-2** by ion-exchange chromatography yielded 5 main fractions. The one eluted with 0.2M NaCl contained a α-1,6 glucan and significant amounts of agaroids (26% of *L*-Gal). Subfractions **F1/s** and **F1.5/s** contained D- and L-Gal (3:1 ratio for both). The late-eluting fraction **F2/s**, contained 80% of D-Gal and minor proportions of Glc, 3-*O*-methyl and 6-*O*-methyl-*D*-Gal.

Acknowledgements: This work constitutes part of the Research Projects from UBA, CONICET and UNPSJB.

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The 75% Isopropanol-Soluble Polysaccharides from the Endosperm of the Legume Seed of *Gleditsia Triacanthos*

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Abstract: The 75% isopropanol-soluble material from the endosperm of the legume-seed of *Gleditsia triacanthos* was isolated. The material extracted with boiling water was fractionated by ion-exchange chromatography and characterized. Besides minor amounts of galactomannans, major proportions of arabinans and/or arabinogalactans appear.

Introduction

The galactomannans from the endosperm of the seed of the legume *Gleditsia triacanthos* have been widely studied in our lab [1]. The system of carbohydrates of this seed also comprise low-molecular weight galactomannans, soluble in 85% ethanol, extractable at room temperature [2]. Herein is reported the extraction, purification and characterization of an arabinose-rich product extracted with boiling water, and soluble at high alcohol concentrations.

Experimental

The endosperm of seeds of *Gleditsia triacanthos* was milled and extracted exhaustively with water at room temperature, then at 50° and then at 95°. Extractions were aided with mechanical stirring. The residues were centrifuged off, and the extracts precipitated with 3 vol. of isopropanol. The supernatants were concentrated, and the final material was obtained by freeze-drying.

Analyses (total carbohydrates, proteins, etc.) were carried out following reported procedures [1,2]. The constituting monosaccharides were quantitated after hydrolysis with 2M TFA (90 min, 120°C) by HPLC-AEC. Anion-exchange chromatography was performed on DEAE Sephadex A-50. Exhaustive methylation was carried out with the technique of Ciucanu and Kerek [3]; the permethylated product was hydrolyzed and analyzed by GC of the alditol acetates.

Results and Discussion

The 75% isopropanol-soluble material (**S**) of the extract (95°C) from the endosperm from *Gleditsia triacanthos* was obtained with a yield of 2.3% (endosperm dry weight basis). Its analysis indicated the presence of carbohydrates (70%) and proteins (26%). The main constituent sugars were galactose, mannose and arabinose. Fractionation of **S** by anion-exchange chromatography resulted in two fractions: one eluted with water (**N**, 23% yield), and another eluted with 0.2M ammonium carbonate (**C**, 50% yield). Both reveal similar analyses: 80-85% carbohydrates, with arabinose as their major moosaccharide (63% in **C**, 45% in **N**); although **C** is richer in protein content.

The ^{13}C-NMR spectra of both fractions are similar: three anomeric signals corresponding to furanose sugars appear at 110.2, 109.9 and 109.1 ppm. However, in the hexopyranose anomeric region, while **C** shows a major signal at 105.8 ppm, possibly originated in a β-galactose moiety, **N** shows two signals, at 102.7 and 101.4 ppm, characteristic of the Gal/Man moieties of a galactomannan. Analysis of permethylated **C** and **N** indicate the presence of galactomannans (2,3,4,6-tetra-*O*-methylGal, 2,3-di-*O*-mehyl and 2,3,6-tri-*O*-methylMan), concurrently with arabinans or arabinogalactans, as, besides the above mentioned products, derivatives of arabinose methylated at 2,3,5-, 2,3- and 3- appear as major components, together with minor amounts of other derivatives of this sugar.

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Studies of Lipids and Proteins in a Wild Species of the *Arachis (Fabaceae)* Gender

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Abstract: Chemical components of eight wild species of *Arachis* were studied. The objectives were to know the chemical composition and establish chemotaxonomic relationships. The results indicate that *A. villosa* is suitable for breeding program of cultivated peanut. *A. monticola* and *A. batizocoi* showed major chemical affinity with *A. hipogaea*.

Introduction

The chemical composition of the *Arachis hipogeae* (peanut) has been extensively studied [1-5] for being the cultivated species of the *Arachis* gender, however, studies of the wild species are limited.

The knowledge of this plant could facilitate methods of crossing among them with cultivation of *A. hipogeae* in order to obtain seeds of optimum quality.

The objectives of this paper are: 1) To determine the lipidic-proteic chemical composition of seeds of wild species of *Arachis*, to contribute to the chemical knowledge of the species 2) To establish possible chemotaxonomic relationships 3) To contribute to the plans of genetic improvement of *A. hipogeae*.

Experimental

Wild seeds of *Arachis* (*A. correntina, A. duranennensis, A. monticola, A. batizocoi, A. cardenasii, A. helodes, A. chacoensis y A. villosa*) were used. The total contents of protein was determined (kjeldahl) and the extraction of oil for quantification was carried out.

The methyl esters of fatty acids were quantized and identified (GC), and also the iodine indexes were determined. The results were presented in a phenograph and in two- and three-dimensional graphics.

Results and Discussion

The results of the chemical studies of the peanut s wild species showed that: 1) *A. batizocoi* is the

species that contains the highest percentage of oil and *A. villosa* the highest protein content 2) The best oleic/linoleic relation and iodine index are found in *A. villosa* 3) The samples of the wild species (except *A. villosa*) present a lower oleic/ linoleic relation and higher iodine indexes than the cultivated peanut 4) In relation to the numerical analysis, it can be observed that some samples of species separate one from each other because they have little chemical affinity, meaning they have differences at the level of their genotypes 5) The species more chemically related by affinity to the cultivated peanut are *A. monticola* and *A. batizocoi*.

Acknoledgements: To CONICET, CONICOR , CEPROCOR e INTA de Manfredi (Córdoba).

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Antiinflammatory Activity of Cinnamic Acid Esters

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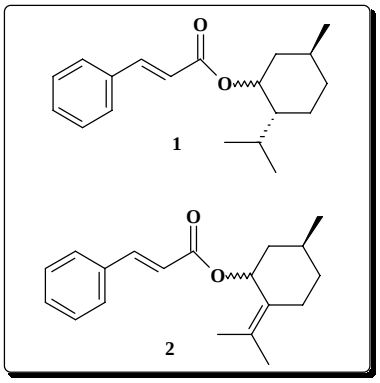
Abstract: The cinnamate esters of 3-p-menthanol (trivial name, menthol) (**1**) and 4(8)-p-menthen-3-ol (trivial name, pulegol) (**2**) were prepared and their anti-inflammatory activity was measured. Some of the monoterpenoid esters displayed interesting anti-inflammatory activity.

Introduction



Natural phenylpropanes, represented by the bornyl esters of coumaric, caffeic y ferulic acid have shown effectiveness as antiinflammatory drugs [1,2]. Bearing in mind these precedents, in this work we report the results of our tests, by the carregeenan induced-edema test method, of the antiinflammatory activity of some cinnamic acid esters prepared in the laboratory.

Experimental Part

Ester Preparation

Pulegyl and menthyl cinnamates were obtained following the previously describde nmethodology [3]. The corresponding acid chloride was prepared under an inert atmosphere using thionyl chloride in refluxing anhydrous benzene. The acid chloride was added to the monoterpene alcohol dissolved in dry benzene containing a few Mg shavings and then refluxed for 8 hrs [4]. The esters were identified by their physical constants, ^{1}H and ^{13}C NMR and MS. Pulegol was prepared from pulegone by $NaBH_4$ reduction in the presence of $CeCl_3$.

Carrageenan Test

Acute mouse paw edema was induced by administration of 3.5% carrageenan. Previously the animals had received an interperitoneal dose of 75 mg/kg of the compounds under study, while the reference animal received 80 mg/kg of phenylbutazone. The volumes of the mice paws were compared 1, 3,

5, and 7 hrs after administratoion of carregeenan to measure the anti-inflammatory effect [5,6].

Results and Discussion

All the compounds tested displayed interesting activity although the effects of pulegyl cinnamate were particularly noteworthy (Table 1).

Table 1. Carrageenan Test.

Products	Percentages of Inhibition of Acute Inflammation			
	1 hr	3 hrs	5 hrs	7 hrs
Phenylbutazone	69(i)	73(i)	73(i)	69(i)
Cinnamic acid	58(b)	45(c)	52(d)	27
Pulegol	54(g)	54(d)	45(e)	47(g)
Pulegyl cinnamate	49(a)	62(j)	56(h)	50(b)
Menthyl cinnamate	48(f)	49(j)	32	47(a)

(a) $p<0.002$; (b) $p<0.0002$; (c) $P<0.0007$; (d) $p<0.0001$; (e) $p<0.003$;
(f) $p< 0.008$; (g) $p<0.001$; (h) $p<0.0003$; (i) $p<0.000001$; (j) $p<0.00001$.

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Use of Cyclic Di- and Triperoxides as Initiators of Styrene Polymerization at High Temperature with a View to Their Use in Industrial Applications

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Abstract: In industry, the bulk free radical polymerization of styrene takes place with the aid of peroxide initiators such as benzoyl peroxide. In this work di- and trimeric cyclic peroxides were used as initiators of the styrene polymerization in order to increase the rate of polymerization and molecular weights simultaneously.

Introduction

In the production of polystyrene (PS) various synthetic methods [1-3] such as cationic, anionic or free radical mechanisms have been applied the latter being the most important from an industrial point of view. Industrial free radical processes for the synthesis of PS generally use three reactors connected in series and the temperature is increased from 90 to 180°C reaching 60-80% of conversion. In the final step, a devolatilizer is used at temperatures of 200-220°C to recover the residual monomer. In spite of homopolymerization of styrene takes place at this temperature it is not sufficient enough to reach 100% conversion hence this step represents a problem in the economy of the process. On the other hand, the intrinsic characteristics of radical processes make it impossible to obtain high rates of polymerization and high molecular weights simultaneously.

The use of polifunctional initiators containing two or more labile groups is a way to optimize the final properties of the polymers obtained and the polymerization processes. With the aid of these type of compounds the traditional mechanism can be completely modified and high rates of polymerization can be obtained without sensibly lowering the final molecular weights of the synthesized polymers.

Experimental section

The synthesis of different polystyrenes were carried out dissolving the appropriate amount of initiator in fresh distilled styrene (0.01M). The solutions were placed into glass tubes which were evacu-

ated, sealed and kept at temperatures in the range of 90-200°C during 3 hours in order to evaluate the optimal temperature at which each of the initiators present it better performances taking into account the values of conversion and molecular weights (Mw).

The polymer samples were dissolved in THF and precipitated by adding excess methanol. This procedure was repeated several times to ensure that unreacted monomer was completely eliminated. The samples were dried in *vacuo*, and the monomer conversion was measured gravimetrically. The molecular weight and molecular weight distribution of polystyrene were determined by gel permeation chromatography using THF as a solvent. The residual monomer was analyzed by G.C injected Head Space technique. Similarly, the evolution on conversion and Mw for each of the initiators at their optimal temperature were studied at different polymerization times.

Results and Discussion

Under appropriate experimental conditions the cyclic bi- and trifunctional initiators: cyclohexanone triperoxide (CHTP), diethylketone triperoxide (DEKTP), acetone triperoxide (ATP), cyclohexanone diperoxide (CHDP) and pinacolone diperoxide (PDP) can be effectively used in styrene bulk polymerization at high temperatures to produce polymers with high molecular weights and narrow polydispersity at a high reaction rate. Varying the temperature and the initiator concentration, the free radicals concentration can be controlled throughout the sequential decomposition of the labile groups contained in the cyclic initiator molecule leading to the synthesis of polystyrene with higher molecular weights than the polystyrene produced with conventional initiators.

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Polisaccharides from Cystocarpic Plants of the Red Seaweed *Callophyllis Variegata*

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Abstract: The crude polysaccharide from cystocarpic *Callophyllis variegata* was fractionated with potassium chloride yielding three minor fractions which precipitated between 0.05-0.10 M KCl, 1.20-1.25 M KCl and 1.80-2.00 M KCl, and a main product soluble in 2.00 M KCl. These fractions were analysed and structural analysis of the major one was carried out by methylation, FT-IR and ^{13}C NMR.

Introduction

Callophyllis variegata belongs to the family Kallymeniaceae and there are only two previous studies [1,2] on seaweeds from the same genus, *Callophyllis rhynchocarpa* and *Callophyllis hombroniana*. These studies report the isolation of carrageenan-type polysaccharides.

Experimental

The crude polysaccharide and the fractions were analyzed using the methods mentioned in ref. [3]. The fraction soluble in 2.00 M KCl was converted into the corresponding triethylammonium salt and was methylated by the Hakomori procedure as described in ref. [3]. The samples were subjected to reductive hydrolysis and further acetylation, and were analyzed by GC [3]. The D:L-galactose ratio was determined by the method of ref. [4].

Results and discussion

Cystocarpic plants of *Callophyllis variegata*, collected in Puerto Deseado (Provincia de Santa Cruz), were extracted with water at room temperature and the crude product was analyzed (carbohydrate content, sulphate, primary sulphate and protein; composition in monosaccharides, D:L-galactose ratio). These analyses showed a molar ratio Gal:3,6-AnGal:sulfate of 1.00:0.24:0.56 and the absence of L-galactose suggesting the presence of a carrageenan. The usual way to fractionate a system of carrageenans is based on the solubility of the component polysaccharides in solutions of different potas-

sium chloride concentration; the preparative fractionation yielded three fractions which precipitated between 0.05-0.10 M KCl, 1.20-1.25 M KCl and 1.80-2.00 M KCl, and a main product soluble in 2.00 M KCl. These fractions were analyzed as described for the crude polysaccharide. Chemical analysis of the soluble fraction gave a molar ratio Gal:3,6-AnGal:sulfate of 1.00:0.16:1.47 and a D-:L-galactose ratio of 5.5:1.0. The structural analysis (methylation, FT-IR and ^{13}C NMR) of this fraction will be reported.

Acknowledgements: This work was supported by grants from CONICET (PIA N° 6714) and the University of Buenos Aires (TW83).

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Comparison Between Aqueous and Nonaqueous AOT-Heptane Reverse Micelles Using Acridine Orange as Molecular Probe

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Abstract: Aqueous and nonaqueous AOT/n-heptane reverse micelles where characterized by UV-Visible and fluorescence spectroscopy of AO. The study shows the presence of the dimer in aqueous reverse micelles which is not present in the nonaqueous systems. It seems that there is a conversion of the dimer to monomer in the aqueous reverse micelles at high AOT concentration. In the nonaqueous systems, there is only partition of the monomer. The apparent constants of these processes were calculated.

Introduction

Reverse micelles are aggregates of surfactant molecules with their polar groups concentrated in the interior while the hydrophobic moieties extend into and are surrounded by, the bulk apolar solvent. Thus, water or other polar solvent with high dielectric constants and unmiscible in the hydrocarbon solvent such as ethyleneglycol (EG), N,N-Dimethylformamide (DMF), glycerol (GY), Propileneglycol (PE) can be solubilized in the polar core. The last ones are called nonaqueous microemulsions and present a series of advantages over the aqueous reverse micelles for example can be useful media for organic reaction such as Diels- Alder [1] and others.

The microemulsions can be characterized by using molecular probes such as: 1-methyl-8-oxyquinolinium betaine (QB) or the free base of the dye acridine orange AO [2]. The aim of the present contribution is to investigate the properties of the base AO in aqueous and nonaqueous AOT/n-heptane microemulsions. Thus, the spectroscopic behavior of AO in AOT/n-heptane using water, DMF and EG as polar solvents has been studied by the absorption and fluorescence spectra.

Experimental

Sodium 1,4-bis(2-ethylhexyl) sulfosuccinate (AOT) from SIGMA was dried under vacuum over P_2O_5. The molar ratio between polar solvent and AOT is defined as W_s = [polar solvent]/[AOT]. The free base of AO from SIGMA was used as received. The polar solvent ethyleneglycol (EG) and N,N-

Dimethylformamide (DMF) all from ALDRICH (more than 99% of purity) were used without further purification. Ultrapure water was obtained from Labonco equipment model 90901-01.

Results and discussion

The absorption spectra of AO in water [3] at pH <10 (cationic form, AOH^+), show two bands, at 468 and other at 490 nm which can be attributed to the dimer and monomer specie respectively. At pH >10 (basic form) only the monomer´s band is present. Thus, only AOH^+ is the species that can suffer the dimerization process.

In aqueous reverse micelles systems, there are four processes that AO can suffer, a) distribution between the organic phase and the micellar interface; b) protonation to give AOH^+; c) dimerization of AOH^+ and d) conversion of the dimer to monomer by the micelle. The spectra of AO with AOT concentration show the disappearance of the band originally present in n-heptane (λ= 417 nm) and the appearance of the dimer band at 462 nm. The monomer band appears at [AOT] >$3.4x10^{-4}$M. There are two isosbestic points, at 427 and 467 nm. The fluorescence spectra show the band of the dimer at 644 nm at low [AOT] and the band of the monomer at 544 nm. On the other hand, in the nonaqueous microemulsion, AOH^+ was not detected and only the distribution of the AO between the two pseudophases is observed. The absorption and the emission spectra are consistent with these facts.

The value of the distribution constant, K_{dist} for the process a) was calculated by the Ketelaar approach [4] and, the value of the dimer dissociation K_{des} for the process d) was calculated by the method showed in Ref [5].

The values of K_{dist} show the following order: $K_{dist}^{Water} > K_{dist}^{EG} > K_{dist}^{DMF}$. This can be explained considering the micropolarity of the interfaces and hydrogen bond interactions.

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Synthesis of a Thienothiophene Conjugated Polymer

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Abstract: A new conducting polymer was prepared by chemical and electrochemical polymerization of 3,6-dimethylthieno[3,2-b]thiophene. The galvanostatic deposition afforded uniform, adherent and dark blue films of PDMTT. Electrochemical characterization by cyclic voltammetry showed that it can be repeatedly driven between the doped and undoped species with a coulombic efficiency of nearly 100%.

Keywords: conjugated polymers, electropolymerization, thienothiophene.

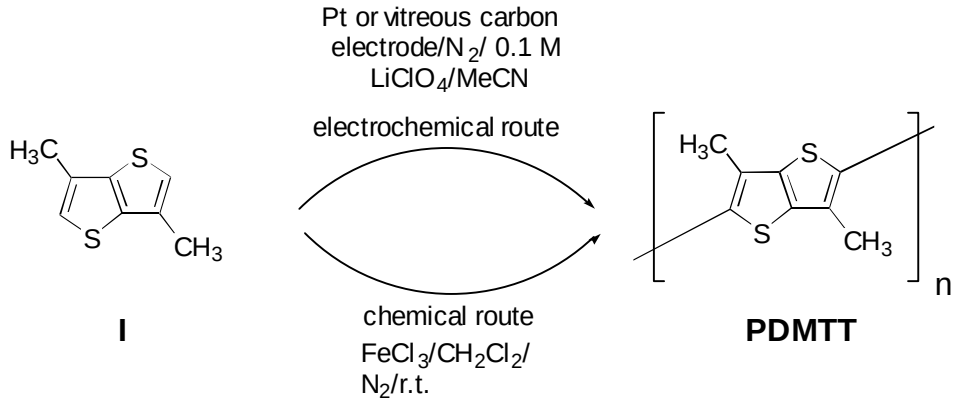
Introduction

Synthetic precursors (syntons) that contain thiophene units have originated series of polymers whose properties are being studied intensely [1]. For example, a significant increase of the non linear optical activity (NLO) in poly(arylenevinylene)s has been obtained by replacement of phenylene units by thiophene ones [2]. This result could be interpreted as an indication of the d-orbitals contribution to the NLO activity. It would be expected, therefore, that a further increase on the content of the highly polarizable sulfur atom in the backbone of the polymer will led to even higher values of the nonlinear electro-optical coefficients. Likewise, redox activity will be also changed by means of this structural change. We report here the chemical and electrochemical synthesis of poly(3,6-dimethylthieno[3,2-b]thiophene), PDMTT, that represents a synthetically viable system in which these concepts could be examined.

Experimental

Monomer **I** can be obtained in the gram-scale in one-step reaction. The monomer was characterized by GC, ^{1}H-NMR, ^{13}C-NMR y MS. This reaction offer the possibility to obtain a highly symmetric derivative of thieno[3,2-b]thiophene whose regiochemistry is easier to control than the non-substituted parent compound. PDMTT was prepared as shown in Scheme 1 either chemically using $FeCl_3/CHCl_3$ or electrochemically from a solution 10^{-3} M of **I** in acetonitrile with $LiClO_4$. The potential cyclic polymerization was performed either on a vitreous carbon or on a platinum electrode in the potential

range of 0.5 V and 1.5 V. In addition, **I** was also galvanostatically electropolymerizated at current densities between 0.05 and 0.5 mA/cm^2.



Scheme 1.

Results and Discussion

The chemical synthesis of PDMTT yielded a solid whose characterization is being carried on. On the other hand, this polymer was prepared by electropolymerization as a film supported by the electrode. However, in cyclic potential conditions it was not possible to obtain a self-standing film since the homogeneous growth at longer electropolymerization times only afforded a film of pulverulent nature with poor mechanic properties and low density. However, the galvanostatic deposition at density current of 0.1 mA/cm^2 afforded uniform and adherent films. The electrochemical characterization by cyclic voltammetry showed that the polymer can be repeatedly interchanged between the doped and undoped species with a coulombic efficiency of nearly 100% during four hours without degradation signs.

Acknowledgments: Financial support for this research was provided by ANPCyT and SGCyT-UNS.

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Integral Chemical Analysis of the Amaranth (*Amaranthus greggii S. Wats*)

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Abstract: The objective of this work was to obtain information on *Amaranthus greggii* S. Wats., related to its nutritional value, its agricultural application as leaf vegetable and for animal consumption. The following variables were analyzed: dampness, ashes, protein, mineral, ethereal extract (fat), brute fiber, oxalic acid, nitrates and carbohydrates.

Introduction

One of the species of the genus *Amaranthus* whose study is of a high interest due to its economical and nutritional value, has been identified botanically as *Amaranthus greggii* S. Wats. The excellent qualities of some annual amaranth as vegetables, owing to their nutritional value and pleasant taste, have also been determined (Castañeda *et al*., 1987).

Experimental Area

The green material of amaranth was dried in a stove with air forced to 60º C until stable, and was then ground and dehydrated. Different types of chemical assays were carried out: dampness, ashes by calcination in muffle at 550º C (Pearson, 1976), proteins by the Kjeldahl method (N x 6,25) (Skoog, West and Holler, 1995); Ca and Mg by complexmetric (Hamerly *et al*., 1984), P and Fe by colorimetry (Jackson, 1964), ethereal extract (extraction by Soxhlet), gross fiber and oxalate following (AOAC 1984), nitrate by colorimetry (Cataldo *et al*., 1975) and carbohydrates (according to difference).

Results and Discussion

The chemical composition determined on dried basis of leaves of *A. greggii*, is detailed on Table 1; the data were compared with the data obtained by Cattaneo *et al*. (1994) and Arellano *et al*. (1992) for *A. mantegazzianus* and spinach.

It was observed that *A. greggii* leaves have a protein content similar to spinach and *A. mantegazzianus* has values which surpass other types of amaranth (Rawate,1983).

The relatively high value of ashes denotes important contents of minerals, having an outstanding content of calcium and magnesium in *A. greggii*, which surpasses spinach and *A. mantegazzianus*, although inferior to the ones found by Rawate. Comparing the value of the content of iron with other amaranths, it was observed that its content is high, the values were similar to *A. mantegazzianus* and superior to spinach (Castañeda *et al.*,1987). The percentages of phosphorus found in the foliage during the analysis were near the ones mentioned by Troiani *et al.* (1992).

The results obtained for nitrate and oxalate in *A. greggii* compared with the results obtained by Gomez *et al.* (1986) and Arellano *et al.* (1992) for *A. mantegazzianus* and spinach are shown in Table 2; the values are below the ones considered as toxic (Avila *et al.*, 1987).

The analysis performed on *Amaranthus greggii* show similar values to the blanks which allows us to infer that this species is another alternative to the human diet.

Table 1. Proximal Chemical Composition of the tested *A. greggii*, confronted with *A.mantegazzianus* and spinach.

	A. greggii	A. mantegazzianus	Spinach
Dampness %b.s.	8.83 +-0.056	10.13	7.81
Ashes % b.s.	26.80 +-0.370	25.14	28.18
Gross Protein %b.s.	28.28 +-0.349	28.44	28.60
Gross Fiber %b.s.	13.25 +-0.343	12.14	7.75
Ethereal extract %b.s.	2.18 +-0.361	3.59	4.79
Calcium % b.s.	1.28 +-0.219	2.27	1.03
Magnesium % b.s.	0.62 +-0.190	0.67	1.10
Phosphorus %b.s.	0.62 +- 0.153	0.69	0.89
Iron mg % b.s.	45.15 +- 0.204	45.2	41
Carbohydrates[1] % b.s.	20.66 +-0.730	20.56	22.87

[1]They were determined by difference.

Table 2. Antinutrients of the tested *A. greggii*, confronted with *A. Mantegazzianus* and spinach.

Antinutrients	A. greggii	A. mantegazzianus	Spinach
Oxalate % b.s.	3.15 +-o.331	4.92	9.3
Nitrate % b.s.	0.18 +- 0.062	0.63	1.22

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Catalytic Activity of MEL Zeolites Modified with Metallic Couples for the Conversion of Ethane

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Abstract: The transformation of ethane into aromatic hydrocarbons over Zn-metal- containing zeolites at W/F=10 gh/mol and 550°C was studied in a flow reactor at atmospheric pressure. Zn-metal-zeolite modified the activation mode of the alkane, generating highly reactive intermediates and enhancing the aromatic selectivity.

Introduction

The transformation of light alkanes into more valuable compounds, such as aromatic hydrocarbons (AH), is of great importance from both the industrial and academic points of view. MEL and MFI zeolites loaded with metal cations, such as zinc and molybdenum have been successfully used for this purpose showing very pronounced selectivity for aromatic hydrocarbons [1-6]. At the moment, the utilization of zeolites modified with metalic couples for the paraffin conversion has not been reported. Here we discuss the catalytic behavior of MEL zeolites modified with Zn-metal couples in the activation of ethane and suggest a relation between structure - activity.

Experimental

Zeolites with a Si/Al molar ratio of 17 were synthesized by hydrothermal crystallization in Na_2O-Al_2O_3-SiO_2 systems, in the presence of tetrabutylammonium hydroxide as template agent. The cations were incorporated by ion exchange of NH_4-zeolite except the molybdenum, which was incorporated by incipient impregnation. Catalytic reactions were carried out in a continuous flow quartz reactor at atmospheric pressure. Products were withdrawn periodically from the outlet of the reactor and analyzed by an on-line gas chromatograph equipped with a FID detector. Conversion and products distribution were expressed on a carbon-atom basis.

Results and Discusion

Table 1 shows the results of catalytic activity of acidic and Zn-metal- containing zeolites for ethane

transformation. The ethane conversion is very low over the protonic form of ZSM-11. The metal species loading improved the conversion of ethane as well as the selectivity to aromatics.

Table 1. Ethane conversion and reaction products selectivity over various catalysts at 550°C, W/F= 10 gh/mol, total pressure of 1 atm and TOS= 20min.

Catalyst	Conversion mol % (C)	Selectivity, mol % (C)			
		C1	C2=	C3-C5	AH
H-ZSM-11	1.5	29.3	46.7	7.3	16.7
Zn-ZSM-11	11.26	2.44	54.74	9.10	33.72
ZnPb-ZSM-11	8.24	2.82	43.05	8.59	45.54
ZnMo-ZSM-11	12.34	5.47	40.08	8.38	46.05
ZnCu-ZSM-11	5.72	1.68	59.03	7.69	31.60

FT-IR data for chemisorbed pyridine after adsorption at room temperature and after further outgassing the samples at 250, 350 and 400°C indicate that the number and strength of Lewis sites increases by incorporation of metal cations into the zeolite. Zn-metal-ZSM-11 could act as a hydride abstractor in the ethane activation and. the function of metal species would be the dehydrogenation of ethane into ethylene and of the naphthenic intermediates into aromatics [3,5].

Conclusions

MEL zeolites modified with metallic couples are effective for the activation and aromatization of ethane. The first step would be the direct abstraction of a hydride from ethane, producing a ethylcarbenium surface ion through the electron-donor acceptor adduct (EDA) formation, and then by deprotonation ethylene. Ethylene would undergo secondary transformations toward the aromatization.

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A Simple Method for *N*-Phenoxyethylation of Anilines

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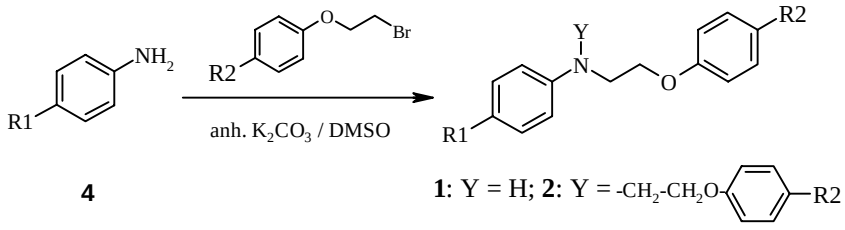
Abstract: We wanted to search for new reaction conditions to prepare the title compounds, to be checked later in novel syntheses of heterocyclic compounds. To the best of our knowledge, there was no report in the literature of any well-established method for the preparation of *N*-(2-phenoxyethyl)anilines **1**.

The scarce previously reported preparations involved large excesses of some starting materials, relatively high temperatures and long reaction times [1, 2]. We have recently reported a general procedure for that preparation [3] although at that stage only moderate yields were obtained. We describe here a better and simpler procedure for achieving not only compounds **1** in good yields, but also for extending the scope of the reaction to the synthesis of the related bis-*N*-(2-phenoxy-ethyl)anilines **2**. In order to avoid β-elimination reactions in molecules bearing a phenoxyethyl group, the reaction was carried out precluding strong acidic or basic media, see Scheme.



Scheme. N-phenoxyethylation reaction of anilines.

Dependimng on the product desired, 1-bromophenoxyethanes (**3**) or anilines (**4**) were used in molar excess. To prepare mono-*N*-(2-phenoxyethyl)anilines (**1**) the reagent **4** was used in excess, yielding 70-80% (see Table), whereas an excess of **3** lead to **2** with yields ranging in 50-70%.

Reaction conditions involve typically 90°C, DMSO as solvent and anhydrous K_2CO_3 as the base. Yields are substantially improved as compared with those already obtained using triethylamine [3]. New compounds **2b** and **2c** gave satisfactory analytical and spectroscopic data.

Table. Selected examples of N-(2-phenoxyethyl)anilines **1** and **2**.

Compound	R1	R2	% Yield
1a	H	H	75
1b	H	OMe	72
1c	H	NO_2	71
1d	OMe	H	79
1e	NO_2	H	58
2a	H	H	55
2b	H	Cl	59
2c	Cl	H	63

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First Synthesis of (20S) 3β,16β-Dihydroxy-5-pregnen-20,16-carbolactone (Diosgeninlactone)

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Abstract: Diosgeninlactone (**1**), a natural product from Solanum vespertilio, was stereoselectively synthesized in high yield from 3β-hydroxy-5-androstene.

Introduction

Our development of synthetic approaches to *cis*-20,16-γ-carbolactones originated during the course of studies on the catabolic pathway by which tomato plants degrade steroidal alkaloids into 3β-hydroxy-5α-pregn-16-en-20-ona.

The isolation of some related compounds, such as (23R)-23-acetoxytomatidine and (23S)-23-acetoxysoladulcidine from *Lycopersicum esculentum,* suggested a probable mechanism for the degradation of nitrogen containing rings [1].

In addition, products containing the 20,16-*cis*-γ-lactone moiety have been isolated from different vegetable sources, and postulated to be metabolic products of the corresponding sapogenins. At the moment none of them have been synthesized. In 1971 Diosgeninlactone (**1**) was isolated from the ethanolic extract of the fruits of *Solanum vespertilio* [2].

In view of the highly efficient protocol developed by us, in the synthesis of tigogeninlactone [3,4] we decided to explore this synthetic strategy to obtain **1**.

Experimental

Wittig reaction on 3β-(dimethyl-*t*-butylsilyloxy)-5-androsten-17-one yielded the Z-olefin stereoselectively with the introduction of a two-carbon lateral side chain at C-17.

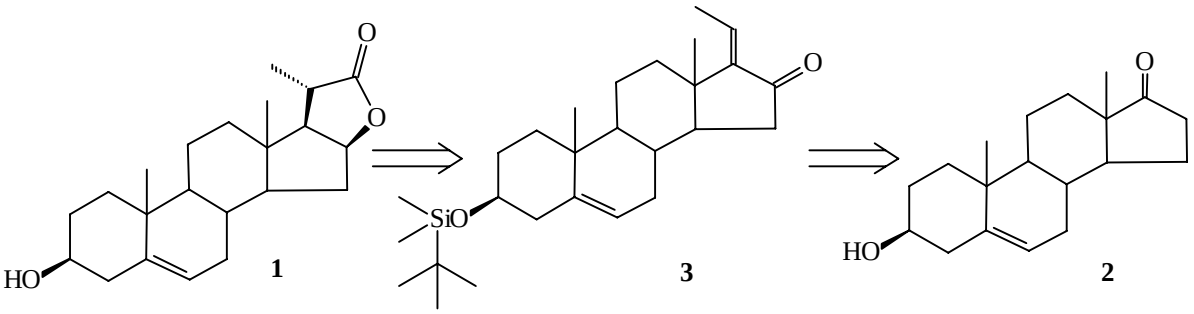
Allylic hydroxylation on C-16 with *t*-butylhydroperoxide in the presence of catalytic amounts of selenium dioxide introduced the hydroxy group from the α-face of the steroid nucleus.

Swern oxidation produced the conjugated ketone **3** in very good yield.

Michael addition of sodium cyanide in a THF/EtOH/H_2O mixture introduced the third carbon atom in the side chain. The addition from the α-face afforded only the 17β-(20S) nitrile isomer.

Stereoselective reduction of the ketonitrile with lithium tri-*t*-butoxy aluminohydride produced the 16β-hydroxy-derivative. As expected, the bulky hydride approaches the carbonyl group from the less-hindered α-face, producing in excellent yield and selectivity the needed β-orientation for the hydroxy group on C-16.

Alkaline hydrolysis of the hydroxy-nitrile followed by an acidic work-up produced lactone **1**, as lactonization and deprotection of the 3β-OTBDMS group took place during acidic work-up.



1 **3** **2**

Results and Conclusions

Many strategies have been explored for the construction of the β-fused γ-lactonic ring E. The attachment of a 2-carbon side chain on C-17 previously to the allylic oxidation of C-16 was the key step in the synthesis.

Early studies involving the connection of a 3-carbon side chain on C-17 of a 17-oxo-16β-acetoxyandrostane led to the epimeric α-oriented γ-lactone [3,4].

In conclusion, a highly efficient stereoselective protocol has been developed for the β-oriented 20,16-*cis*-γ-carbolactones. Thus, Diosgeninlactone (**1**) were stereoselectively synthesized in high yield from 3β-hydroxy-5-androsten-17-one (**2**).

Acknowledgments: We thank Universidad de Buenos Aires and CONICET (Argentina) for partial financial support.

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Separation of the Pigment of an Amaranth

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Abstract: It is known that current quality requirements require the utilization of natural colorants in the foods. The objective of the present work is to extract the pigment amaranthus from fresh leaves of *Amaranthus hypochondriacus* L. cv Don Pedro to characterize it through spectroscopic techniques, to be used as natural colorants.

Introduction

Historically, the tinted amaranth has been used to extract the coloring matter, which is soluble in water and was used for the dyeing of drinks, food and other products in Mexico, Bolivia and Ecuador (Sauer, 1950). In India and Mexico the women used the amaranth juice as facial rouge (Ruxton, 1861).

The obtainment of coloring matter based on natural products is of considerable importance since the United States have banned the use of synthetic coloring in foods. Thus, the tinted amaranth is of interest due to the fact that dyes for food which are not artificial are needed.

The typical pigment of the tinted amaranth is called “amaranthine”; it belongs to the group of the betacyanines (Mabry and Dreiding, 1968) and was identified as 5-0-[-2-0-(β-D – glycopyranosyluronic acid) β-D- glucopyranoside] of the betanidine (Piatelli et al. 1964) and (Piatelli and Minale, 1966), the betanine have been used as colorants in many types of food (Von Elbe,1977).

The factors which affect the stability of the pigment are pH, temperature, light, oxygen, activity in water (von Elbe et al. 1974. Sapers and Hornstein, 1979. Pasch and von Elbe, 1979. Sttoe and von Elbe, 1982).

The amaranth studied, *Amaranthus hypochondriacus* L. cv. Don Pedro has its pigment “amaranthine” distributed all over the plant, this pigment is extracted from fresh leaves and characterized by spectroscopic techniques, for its possible application in the colouring of drinks and food at an industrial level.

Experimental

The green vegetable material collected was kept in freezer at –15ºC, during 48 hours, then the

leaves were whitened, ground and extracted with water. Aliquots of the extract obtained were chromatographed over columns of Sephadex G-25 (Pharmacia K 100/100) and then over one column of Amberlite XAD-7. The colored fraction was separated in column of Sephadex LH20, using MeOH as solvent (elution). Although fractions enriched by the colorant were obtained, due to their scarce amount, they were not enough to perform spectroscopic determinations.

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Chemical Study of the Essential Oil of *Mutisia Friesiana*

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Abstract: The composition of essential oil of *Mutisia friesiana* (*Asteracae*) was studied. The oil is a complex system in which 127 compounds were identified. The major components are monoterpenes: β-phellandrene, (*Z*)-β-ocimene, α and β-pinene and sabinene.

Introduction

Coumarins, chromones, aromatic glycosides, sitosterol, lupeol, among others, have been found in *Mutisia* class species (Asteraceae family). The *Mutisia friesiana* Cabrera plant is an endemic species of the Argentinean northwest used in the popular medicine and have a pleasing and persistent perfume. It was of interest to do the chemical study of secundary metabolites and determine in a first stage the presence of substance volatile. Studies referred to essential oils (EO) are not found in bibliography for this class.

Experimental

Wild specimens of *M. friesiana,* identified as **Ma** (herbarium: Ahumada 7183) y **Mb** (herbarium: HG1115) were collected in two high places of the Jujuy province: Puna and Quebrada. The EO was extracted from the aerial part by hydrodistillation. It was analyzed by gas chromatography with flame ionization detector and capillary columns DB1, HP5, HP1 y HP-INNOWAX with H_2 carrier. The Ma GC/MS was made in a GC-MS Shimadzu QP-500 (LANAIS-EMAR-CONICET) and the Mb analysis in a GC HP 6890 MS HP 5972 A (Agua de los Andes) with He carrier and DB1 y HP5 columns.

Results and Discussion

The EO yield is similar to other aromatic species (0,33% to 0,80% v/w over dry material). One hundred and twenty seven components were identified by comparison of their mass spectra with those reported in literature. Percentage contributions of the different compound families are given in the attached Table. The EO composition of the two different zones of Jujuy is qualitatively similar. Linalool (E)-β-damascenone, hexanol and (Z)-3-hexenol contribute to the perfume of the essential oil.

PERCENTAGE DISTRIBUTION OF COMPOUNDS CHEMICAL FAMILIES IN THE COMPOSITION OF E. O. OF *Mutisia friesiana*

	Skeleton of	Ma	Mb
MONOTERPENES			
Hidrocarbonated Acycles		13.81	15.56
Monocycles	p-mentane	25.87	25.43
Bicycles	tuyane	8.92	5.11
	pinane	15.83	11.31
	isocanfane	0.55	0.20
Alcohols Acycles		0.74	0.19
Monocycles	p-mentane	9.75	5.11
Bicycles	carane	0.46	-
	pinane	0.90	0.16
Ésters Acycles		1.41	0.48
Monocycles	p-mentane	1.86	-
Aldehydes Monocycles	p-mentane	0.20	0.07
Oxides Monocycles	p-mentane	t	0.22
Peroxides Monocycles	p-mentane	1.54	-
Ketones Bicycles	Thujane	1.01	9.68
SESQUITERPENES *Hydrocarbonates*			
Skeleton of Ma Mb			
Bisabolane - 0,10	Eudesmane	0.08	0.24
Amorfane 3.36 4.24	Cyclogerrmacrane	-	0.88
Copaene 0.06 0.16	Maaliane	0.01	013
Humulane - 0.66	Aristolane	-	0.01
Cariofilane 0.20 1.83	Guaiane	-	0.12
Germacrane 0.01 0.88	Aromadendrane	0.34	0.28
Elemane 0.01 1.21	Isocomane	0.07	-
Alcohols			
Skeleton of Ma Mb			
Amorfane 3.70 7.09	Eudesmane	-	0.35
Humulane 0.84 -	Guaiane	0.01	0.34
Cariofilane 0.01 0.01	Aromadendrane	1.83	0.88
Elemane - 0.17	Bourbonane	-	0.13
Ketones	Oplopane	-	0.70
Oxides	Humulane	-	0.21
	Cariofilane	0.01	0.24
NORTERPENOIDES		0.09	0.46
OTHER COMPOUNDS			
(E)-propenylphenols		-	0.26
(E) Cinnamo Acid Derivates		0.72	0.10
Ketones		0.73	-
Esters		4.14	3.35

Acknowledgments: To Dr. E. Gros because of his support and the revision of the present work. To the Fac. Ing. (UNJu) for partial financial support.

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Bioactive Constituents of *Conyza Albida*

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Abstract: Alkynes and spathulenol were isolated from *Conyza albida* (Asteraceae); some of the compounds were lethal against *Artemia* sp. and cytotoxic against KB cells.

Introduction

Conyza albida Willd. ex Sprengel (Compositae) is a species growing in Argentina. Formerly, it was included as a synonym of *C. bonariensis* var. *microcephala* Cabr., but, there is enough evidence to consider it a valid entity at species level [1].

Conyza albida is reported to have expectorant, antitussive, and antiinflamatory activities [2,3]. Since *C. albida* usually grows together with *C. bonariensis* populations, it is believed that both species are useful in the treatment of urinary affections, liver diseases, stomach ulcers, and to wash sores [4] as well as an antihelmintic, digestive and diuretic [5,6,7].

There are no phytochemical studies, nor information on the active constituents of *C. albida*. We now present the results on the bioactivity-guided fractionation of an active extract of the leaves of *C. albida* and the evaluation of the activity of the pure compounds against *Artemia* sp., KB cells and as topoisomerase I inhibitors.

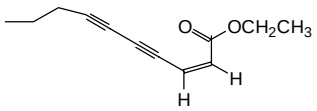
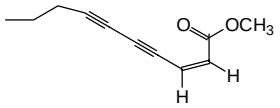
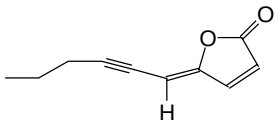
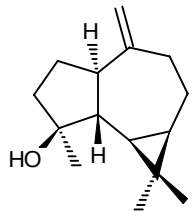
Experimental Procedures

Dry leaves of *Conyza albida* were extracted with CH_2Cl_2. The total extract MeOH-H_2O 20% was partitioned between hexane, Et_2O, EtOAc and H_2O. All the extracts, including the water extract, were concentrated to dryness and tested in the brine shrimp toxicity test (BSTT). The hexane and Et_2O extracts gave positive results with LC_{50} = 99 μg/ml and LC_{50} = 96 μg/ml, respectively. They were fractionated, guided by the BSTT, by vacuum liquid, centrifugal planar and preparative thin layer chromatographies. The isolates were identified by a combination of the following spectroscopic methods:

GC-MS, IR, UV, ^{1}H NMR and ^{13}C NMR.

Results and Discussion

The ethyl ether extract afforded two bioactive fractions with similar chemical composition. After further purification the following compounds were identified: alkenynes **1**, **2** [8,9], **3** [8,9], and spathulenol **4** [10]. The hexane fraction contained alkenynes **1**-**3** and 1-dodecen-7,11-dimethyl-3-methylene [11] which was inactive. This is the first report on compound **1**, although the *trans* isomer was obtained by synthesis [12].

Compound	BSTT (μg/ml)	KB (μg/ml)	DNA Topoisomerase I (%)
 **1**	**1.3**	**7.3**	**-**
 **2**	**1.2**	**9.2**	**-**
 **3**	**5.2**	**19.1**	**21**
 **4**	**4.2**	**9**	**39**

Positive controls: BSTT, berberine LC_{50} = 8.4 μg/ml; against KB cells, colchicine IC_{50} = 0.02 μg/ml.

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Development and Validation of a Chromatographic Method for the Analysis of Multicompound Pharmaceutical Preparations

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Abstract: A reverse phase high performance liquid chromatographic assay was carried out for the simultaneous determination of two out of three active principles present in a pharmaceutical preparation. This method was developed to assess the quality of the product.

Introduction

At present some highly complex pharmaceutical preparations in the pharmacy do not only fail to be analyzed by the traditional chemical methods but also require modern highly selective and sensitive instrumental techniques.

The authorised pharmaceutical product must have certain specific information such as: formulation method, therapeutic prescription, counter effects and quality control. This last procedure involves the performance of assays of the raw material, of the components in the production process, analysis of the final product and stability studies that aim to achieve an efficient medicinal product.

The analytical procedures employed nowadays for the analysis of the pharmaceutical active principles need a chemical substance for reference. Therefore, in the first stage of this study the standard references were prepared for their application to the quality control of a pharmaceutical preparation with commercial use in the Province of Córdoba (Argentina). The two active principles selected for this study were phenylpropanolamine hydrochloride (**I**) and caffeine (**II**).

Experimental

The High Pressure Liquid Chromatography (HPLC) system was equipped with a Konik 500 G pump, a Konik integrator model SP-4290, a variable wavelength UVIS-200 UV detector and a Rheodyne model 7125 injector with a 20 μL loop. A Supelcosil column LC-18 (250 x 4,6 mm) was operated at a 0.6 mL/min flow, sensitivity 0.02 AUFS, chart speed 0.25 cm/min and wavelength 254 nm. The mobile phase, methanol:water (50:50 v/v) was filtered (0,45 μm Nylon-66 membrane) and degassed before use.

Results and Discussion

The quality control of the standard references comprised the following steps: sampling, identification technique, IR (ν_{max} cm^{-1}, KBr) **I**: 3197 (NH_3^+); 3340 (O-H) **II**: 1658 (C=N); 1702 (C=O); Thin-Layer Chromatography (methanol : acetic acid : diethyl ether: benzene - 0.7 : 1.5 : 5 : 10) R_f **I**=0,07; R_f **II**=0,24; UV spectroscopy (λ_{max} nm-methanol) **I**: 254; **II**: 275; Loss on Drying **I**: 0.50%, **II**: 0.28%; Melting Range **I**: 191-194^oC ; **II**: 230–232^oC and Purity Degree **I**: 99.53%; **II**: 99.76%. After these studies, the next step involved selection of the appropriate analytical method, its validation and finally quantification of the active principles in a pharmaceutical preparation of wide commercial use in Córdoba (Argentina). The quality parameters determined were: precision (CV) **I** 2.5%; **II** 1.0%, limit of detection (LOD-µg/mL) **I** 0.28; **II** 0.11 and limit of quantification (LOQ-µg/mL) **I** 0.93, **II** 0.36.

The selected and validated HPLC method was applied to the pharmaceutical preparation to assure the quality of the final product. The results were expressed in mg ± CV (n=5) for **I** 12.8 ± 2.2 and **II** 39.8 ± 1.6.

These data indicate that HPLC is an efficient method for simultaneous quantification of the active principles without previous preparation of the sample. Likewise and due to the intensive use of this preparation in the Province of Córdoba and to the lack of quality control, it is planned to continue the analysis of the remaining active principle so as to determine the overall composition of the pharmaceutical preparation.

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Study of the Cytotoxic and Antifungal Activities of Neolignans 8.O.4´ and Structurally Related Compounds

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Abstract: In the present work we report the antifungal and cytotoxic activities of a neolignan 8.O.4´series. The most active antifungal compounds show a significant cytotoxic effect which might be related.

Introduction

Fungal infections have emerged during the past two decades as important pathogens causing morbidity and mortality in an increasingly diverse and progressively expanding populations of inmunocompromised patients. Unfortunately there are only very limited therapeutic options, especially for systemic mycotic infections.

In the search of new antifungal compounds we reported that neolignans 8.O.4´ have a moderated but significant antifungal activity against dermatophytes fungi [1,2].

Using the classic techniques of molecular simplification, we recently reported a systematic study on the antifungal properties of arylpropanoids which are constitutive parts of neolignans [3]. Our results indicate that some arylpropanoids possess strong antifungal effects which are comparable to those of amphotericine B and ketoconazole.

In the present work we report a comparative study on the antifungal and cytotoxic activities of these compounds and their length and limitations as antifungal agents.

Experimental

Cytotoxicity bioassay: Cytotoxicity was evaluated in a lymphocyte culture evaluating the incorporation of thymidine tritiated [4].

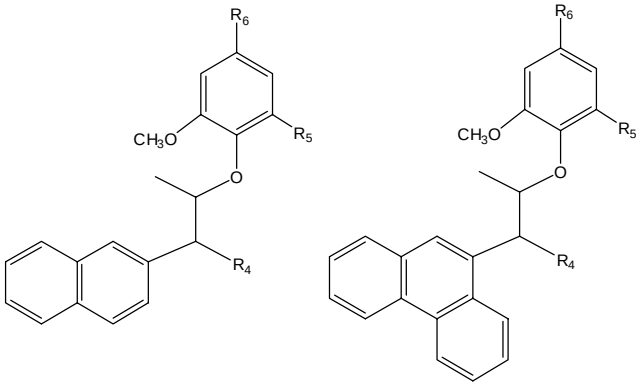
Antifungal assay: the dilution agar method was used [1]. Different human pathogenic fungi were used in the bioassays.

Results and Discussion

Our results indicate that all the arylpropanoids having strong antifungal activity also have a significant cytotoxic activity.

It should be noted that the cytotoxic activity obtained for arylpropanoids is comparable to those obtained for commercial drugs like amphotericine B, cilofungine, ketoconazole and miconazole.

Neolignans 8.O.4´ show a low cytotoxic effect, however they only have a moderate antifungal activity too. With the aim to separate the antifungal activity with the cytotoxic effect we synthesized the follow compounds.



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Kinetics of the Aromatic Nucleophilic Substitution Reaction Between 1-Fluoro-2,4-Dinitrobenzene and Perhydroazepine in Ethyl Acetate + Chloroform Solvent Mixtures

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Abstract: In the present work, the kinetic behavior of the title reaction in ethyl acetate + chloroform solvent mixtures is studied. The experimental results are compared with previous findings.

Introduction

In a recent publication [1a], the kinetic synergetic effect of the ethyl acetate + chloroform solvent mixtures on the reaction between 1-fluoro-2,4-dinitrobenzene and piperidine (Pip) or morpholine (Mo) was reported.

We observed a special enhancement effect on the reaction rate at some intermediate compositions of the mixed solvents, with respect to the corresponding one in the pure components, part of the mixtures. This phenomenon was explained as a combination of factors related to the variation of the influence of base catalysis and specific solvent effects, particularly hydrogen bond interactions.

Experimental

The kinetics of the reaction was studied by monitoring the absorbance of the product at *ca* 383 nm with a Perkin-Elmer Model 124 UV-Vis spectrophotometer equipped with a data-acquisition system based on a microprocessor.

The reactions were carried out under pseudo-first order conditions. The pseudo-first order (k_φ) and second-order (k_A) rate constants were obtained as described previously [1].

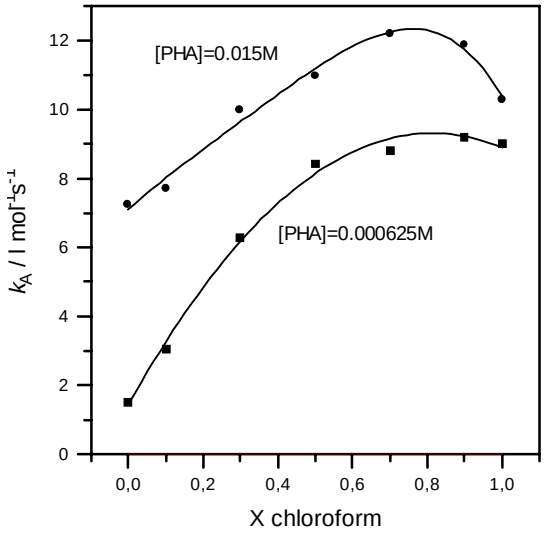
Results and discussion

The variations of the second-order rate coefficients k_A of the studied reaction, measured at 25°C in ethyl acetate + chloroform solvent mixtures, are shown in the figure as a function of the mole fraction

of the cosolvent, for the maximum and minimum explored concentrations of perhydroazepine.

In spite of fact that the kinetic synergetic effect is observed over the whole range of amine concentration, this special effect is more significant at high values of the nucleophile concentration and in the *cosolvent rich zone.*

These results are not in agreement with those obtained [1a,2,3] for the corresponding reactions with piperidine or morpholine as nucleophiles in which the kinetic synergetic effect was observed at low amine concentrations and in the *cosolvent poor zone.*



Acknowledgment: The authors are grateful to the C.A.I.+D. Program of the U.N.L. for the financial support. (Projects: 94-0858-007-054 and 96-00-024-162).

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The Importance of Keto-Enol Forms of Arylpropanoids Acting as Antifungal Compounds

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Abstract: We report here the importance of a keto-enol equilibrium of an arylpropanoid series acting as antifungal agents. An interesting relationship between ln MIC, ΔE enolization and net atomic charges was found. Two compounds were synthesized and their MIC evaluated in order to prove the above relationship.

Introduction

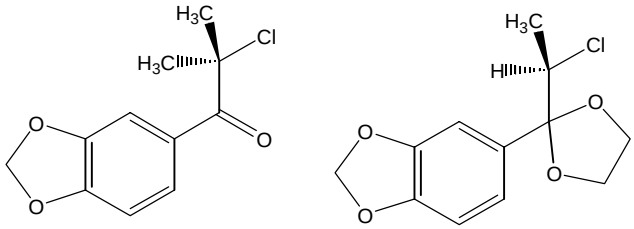
In the course of our screening program for antifungal activity, we reported that 8.O.4'-neolignans possess a moderate but significant antifungal activity against dermatophytes [1,2]. We performed a systematic study of antifungal properties of arylpropanoids portions and structurally related compounds [3], in order to gain insight into structural requirements for their activity. We found that some arylpropanoids possess strong antifungal effects displaying a biological behaviour similar or better than the currently used antifungal agents such as *amphotericin B* and *ketoconazole*.

Structure-activity relationship studies indicated that the C=O group was an indispensable moiety for the antifungal activity of arylpropanoids as well as the apparently necessary α-hydrogen. These results suggest that keto-enol tautomerization could possibly play a role in the bioactivity of antifungal arylpropanoids. The present work reported here has three phases:

1- An exhaustive conformational and electronic study of this series using different levels of theory.

2- A correlation study between antifungal activity and computed parameters (ΔE of enolization and net atomic charges).

3- Synthesis and evaluation of antifungal activity of compounds **[a]** and **[b]** to corroborate the results obtained on steps 1 and 2.



[a] **[b]**

Experimental

Chemistry

Compound **[a]** 2-methyl-2-chloro-1-methylenedioxypripiophenone was synthesized via a chlorination reaction with Cl_2Cu, ClLi in DMF, 16 hs., 120ºC. Compound **[b]** 1-ethylendioxy-1-methylendioxyphenyl-2-chloro-propane was prepared from [a] by reaction with ethylene glycol in dry benzene catalyzed by 10-camphorsulfonic acid in a Dean and Stark apparatus, 16 hs.

Calculation Methods

The calculations were performed at semiempirical level, using AM1 from MOPAC 7 program, and *ab initio* levels using the GAUSSIAN 94 program system.

Results and Discussion

From all the methods employed, the keto-forms were computed to be more stable than the enol forms. Also the cis-endo forms of the enol were systematically more stable than the other forms [4]. On the other hand, a correlative trend was observed when the ln [MIC] values were plotted against computed molecular properties, such as ΔE of enolization and net atomic charges. These results suggest that keto-enol tautomerization may be one of the mechanism of antifungal activity.

In order to corroborate this hypothesis two structurally related compounds, which could not undergo keto-enol tautomerization were synthesized. The experimental results are an additional support for our hypothesis

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Molecular Interactions Between the Active Sites of RGD (Arg-Gly-Asp) with its Receptor (Integrine)

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Abstract: A study of the molecular interactions between the active sites of RGD (Arg-Gly-Asp) with it receptor using simulations is reported. Our calculations indicate that the guanidine-carboxylate complex is energetically favoured with respect to the guanidine-methyl tetrazole complex.

Introduction

It is well documented that peptides and peptidomimetics containing the RGD (Arg-Gly-Asp) sequence are capable of effectively inhibiting the binding of fibrinogen to the GP IIb – IIIa receptor (1). Thus these compounds show promise for improving the immediate treatment of arterial occlusion.

On the other hand both guanidine and carboxylate groups play a determinant role in the recognition and dock process (2).

In the present work we report a simulation study for the molecular interactions between model systems which are mimetizing the guanidine-carboxylate and guanidine-tetrazole interactions.

Calculation Methods

Guanidine-carboxylate and guanidine- tetrazole interactions were optimized using MM2, AM1 and PM3 calculations. These structures were finally optimized using ab-initio RHF/3-21G* calculations. All calculations were carried out using the SPARTAN program. With the aim to obtain a more suitable electronic description we performed B3LYP / 6-31++G** single point calculations from the GAUSSIAN 94 program.

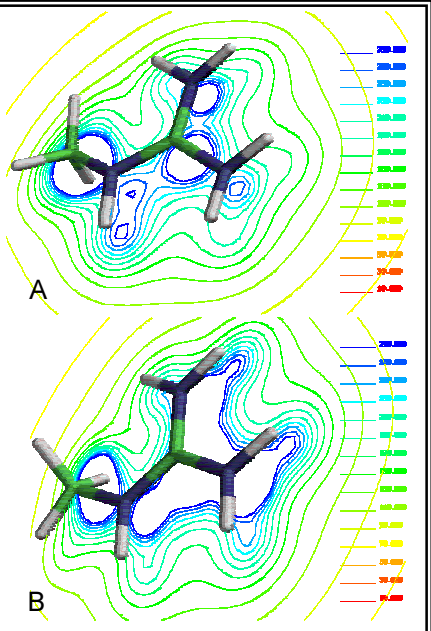

Figure 1: Molecular electrostatic potential from different theory levels by methyl guanidine cations. A) Semiempirical method PM_3 and B) Ab-initio HF/3-21G*

The used equation was: $\Delta H_F = \Sigma\Delta H_{\text{Products}} - \Sigma\Delta H_{\text{Reactives}}$

Results and Discussion

Our results show a significant difference for the electronic description of the molecules using different levels of theory (Figure 1). It should be noted a believable electronic description of these compounds is an essential requirement in order to explain the molecular interactions involved in this process.

The ab-initio results indicate a positive charge distribution focused on acidic – protons the preference for the planar forms of the complex. In contrast the semiempirical results predict a positive charge distribution on the imine group indicating that no-planar forms are also available.

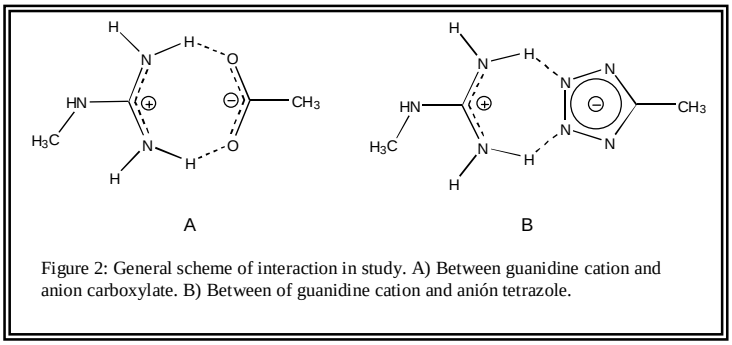

Figure 2: General scheme of interaction in study. A) Between guanidine cation and anion carboxylate. B) Between of guanidine cation and anión tetrazole.

These results show that it is necessary to perform calculations at high level of theory (at least at RHF /3-21G) to obtain an acceptable electronic description which is essential to evaluate the complex formation process.

From the medicinal chemistry point of view it is interesting to note that our results suggest that the guanidine-carboxylate interactions are energetically favoured with respect to the guanidine-tetrazole interactions (Figure 2). These results indicate that tetrazole group it is not good enough to replace the carboxylate group and therefore they are in a complete agreement with the experimental results reported for the above groups.

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A Conformational Study of Flexible Cyclic Compounds (Hydrocarbon Rings of 9-12 Members)

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Abstract: We report here a conformational study of cyclic flexible compounds (rings with 9-12 members). Two methods of systematic search for the minima were used. The results were compared with those obtained using other exploratory methods.

Introduction

It is clear that the choice of good starting geometries for conformationally flexible molecules is one of the greatest challenges, in applying quantitative molecular orbital calculations. There are several reasons for extending the search for new algorithms and to improve the available methods. The principal problem is that the various energy minimization processes do not go through potential energy barriers. They only move down-hill from the trial starting structure towards the nearest minimum, which may of course be only a local minimum. Even worse, after a search has been completed, there is no immediate indication of whether important conformers have been missed. A particular attention was devoted to the cyclic molecules [1-3] because the conformational search in these compounds is more complex.

Recently, we have reported a systematic search method (GASCOS) (4) which has a number of advantages over methods described previously. In the present study we report the conformational study of cyclic compounds (rings with 9-12 members) using two algorithms one of them developed by our group.

Calculation Methods

Two methods were used in the systematic conformational search.

a) Osawa's method from the SPARTAN program.

b) GASCOS method which was developed by our group. The mathematical bases of this method were reported in references 4 and 5.

The starting points obtained from the above methods were geometrically optimised using MM2 and ab-initio calculations.

Results and Discussion

Results obtained from programs using systematic search (OSAWA and GASCOS) were more complete in comparison with those previously reported using Monte Carlo (1) and Annealing simulation techniques (2) or estochastic methods (3).

The results obtained using OSAWA and GASCOS methods are summarised in Table 1.

Although in general all the methods are able to found the low-energy conformations in the MM2 hypersurface of the Potential Energy, only the systematic algorithms can obtain the overall spectrum for the conformational possibilities.

Acknowledgements: The research was supported by grants from the UNSL and Fundación Antorchas. Dr R. D. Enriz is a carrier researcher of CONICET (Consejo Nacional de Ciencia y Tecnología) Argentina.

Table 1. Structural characteristics of the eight previously reported MM2 stable structures of cyclononane.

CONF.	ϕ1	ϕ2	ϕ3	ϕ4	ϕ5	ϕ6	ϕ7	ϕ8	ϕ9	RELAT. ENERGY*
01	125.39	-56.20	-56.03	125.30	-56.11	-56.21	125.44	-56.08	-56.16	0.00
02	102.85	-85.91	102.97	-51.27	-70.26	66.74	66.33	-70.66	-50.78	0.76
03	-122.04	85.65	-73.24	117.71	-64.76	-64.86	117.71	-73.23	85.68	0.78
04	51.52	37.55	-103.71	128.90	-53.07	-57.25	68.82	51.30	-134.03	3.17
05	-103.01	117.74	-88.22	55.5	-90.38	148.07	-59.71	-47.10	96.53	2.23
06	-84.28	68.45	-84.52	130.36	-122.06	40.05	40.06	-122.05	130.19	5.67
07	105.42	-101.36	74.58	-33.60	-170.72	-171.00	-33.61	74.68	-101.77	21.55
08	-0.67	53.90	45.01	-60.43	-60.57	44.91	54.10	-0.77	-86.63	10.36

*in kcal/mol

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Solvatochromic and Kinetic Response Models in (Ethyl Acetate + Chloroform or Methanol) Solvent Mixtures

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Abstract: The present work analyzes the solvent effects upon the solvatochromic response models for a set of chemical probes and the kinetic response models for an aromatic nucleophilic substitution reaction, in binary mixtures in which both pure components are able to form intersolvent complexes by hydrogen bonding.

Introduction

Recently, we analyzed the preferential solvation of a set of solvatochromic solutes 2,6-diphenyl-4-(2,4,6-triphenyl-1-pyridinio)phenolate (I), *N*,*N*-diethyl-4-nitroaniline (II), 4-nitroanisole (III), 4-nitroaniline (IV), 4-nitrophenol (V), and β-carotene (VI) (corresponding to the parameters $E_T(30)$, π^*, α, β y π_2^*) by the application of preferential solvation models [1] (PSM), in mixtures of the following type: aprotic strong hydrogen-bond acceptor solvent and an aprotic cosolvent with hydrogen-bond donor capability [ethyl acetate (EAc) + chloroform] [2a,b].

On the other hand, we extended the preceding analysis to the kinetic data of an aromatic nucleophilic substitution (SNuAr) reaction between 1-fluoro-2,4-dinitrobenzene and morpholine carried out in the explored mixtures, relating the solvatochromic response model with the kinetic one.

Now, it is of interest to apply the preceding analysis to binary mixtures of EAc with a strong hydrogen-bond donor cosolvent (EAc + methanol), with the object to establish the influence of the acidity of the cosolvent.

Experimental

The experimental data were obtained by the methods reported previously [1]. The parameters of solvation were calculated by the application of the MATLAB 4.2 Program (The Mathworks, 0.1 inc.).

Results and Discussion

The preferential solvation models were applied to the solvatochromic data. The parameters of sol-

vation $f_{2/1}$ and $f_{12/1,}$ which measure the tendency of the solutes to be solvated by an individual component of the mixture or by the mixed solvent, indicate similar solvatochromic response model for (EAc + $CHCl_3$) [2a] and (EAc + MeOH) mixtures. The observed general trends are: (i) the solutes are preferentially solvated by the mixed solvent (donor acceptor complexes) and by the cosolvent, in preference to the EAc ($f_{2/1}$ and $f_{12/1} > 1$); (ii) the preferential solvation order is complex > CoS > EAc ($f_{12/1} > f_{2/1}$); (iii) the solute of reference β-carotene shows a tendency to ideality ($f_{12/1}$ and $f_{2/1} \approx 1$).

We extended the application of the PSM to the kinetic data. The analysis was performed at constant amine concentration and as a function of the solvent composition. The obtained results show a similar general tendency: preferential solvation by the cosolvent $CHCl_3$ or MeOH in preference to the complex and EAc.

Both mixtures, which are capable to form complexes by hydrogen bonding between the EAc and the cosolvent, and also with self –association in the case of MeOH, reveal similar solvatochromic and kinetic response models.

Acknowledgements: We are indebted to the Universidad Nacional del Litoral (UNL), República Argentina. This work received financial support from the Science and Technology Secretariat, UNL, CAI+D Program (Projects 94-0858-007-054).

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Catalytic Hydrogenation Reaction of Naringin-Chalcone. Study of the Electrochemical Reaction

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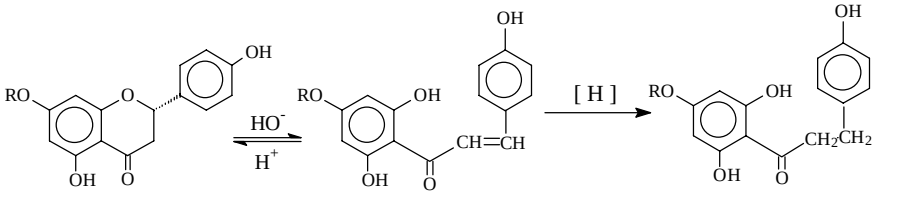
Abstract: The electrocatalytic hydrogenation reaction of naringin derivated chalcone is studied. The reaction is carried out with different catalysts in order to compare with the classic catalytic hydrogenation.

Introduction

The electrocatalytic hydrogenation reaction of an unsaturated organic molecule involves mechanisms implicating a hydrogen electroadsorption process and the adsorption of the substrate on the catalyst surface [1]. The difficulties of the hydrogenation reactions result from the competence between this reaction and the chemical or electrochemical desorption of the hydrogen. The electrocatalytic reaction can be carried out in more moderate conditions of pressure and temperature compared with the classic catalytic one [2]. Some electrochemical hydrogenation reactions of compounds such as aromatics molecules, alkenes and oils have been done using catalysts as Raney nickel, palladium, platinum and rhodium [3].

Naringin, a flavonoid extracted from the peel of some citric fruits and responsible for their bitterness, is the precursor of dihydrochalcone compound. This kind of substances derived from flavonoids presents a very intense sweet taste [4] therefore their synthesis become interesting because of their industrial potential as a sweetener.



Naringin Chalcone Dihydrochalcone

R=β-D-ramnosyl-(1,2)-D-Glucose

Experimental

In order to study the reaction where the dihydrochalcone is formed, the experiences were carried out in alkaline media (pH = 12) where the equilibrium between the flavanone and the chalcone is shifted to the chalcone form. The position of this equilibrium was evaluated by UV-Vis absorption spectroscopy. The electrochemical reductions were carried out in a glass with a two-compartment cell where working electrode was separated from the counter electrode by a glass sinter. Platinum sheet was used as counter electrode and saturated calomel as reference separated by a bridge containing potasium hydroxide solution. Different kinds of working electrodes were used: pure platinum sheet (geometric area 1 cm^2), a palladium-gold net and a carbon paste modified with PtO_2 (geometric area 49 m^2/g). The hydrogenation reaction products were analyzed by UV-Vis absorption spectroscopy, HPLC and TLC.

Results and Discussion

Considering that the catalysts nature and their active area are very important, different catalysts were studied. For initial studies of chalcone oxidation-reduction behavior a pure platinum electrode was used. Current-potential curves were performed to analyze the electrochemical reactivity of chalcone solutions. The results show that there is no evidence of chalcone reaction in the potential region of both hydrogen and oxygen evolutions. On the other hand, the adsorption of organic molecule on platinum was also studied. The chalcone was adsorbed in the hydrogen electroadsorption potential zone. These results show that reaction is possible.

The electrocatalytic hydrogenation reactions were performed at constant potential with PtO_2 and palladium-gold electrodes and the dihydrochalcone was obtained. The classic hydrogenation reaction was also done using PtO_2 as catalyst for comparing purposes of the yields. Although both results are quite similar, work is in progress to further improve the efficiency of the process.

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Fluorescence Resonance Energy Transfer Using Spiropyran and Diarylethene Photochromic Acceptors

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Abstract: We describe the preparation and photophysical characterization of two model compounds designed to test a new approach for the quantitative determination of Fluorescence Resonance Energy Transfer (FRET) in biological systems. The method enables modulation of FRET by exploiting the unique reversible spectral properties of photochromic diarylethenes and spiropyrans to create switchable energy acceptors.

Introduction

Fluorescence resonance energy transfer [1] (FRET) is a physical process by which energy is transferred in a non-radiative manner through a dipole-dipole interaction. Previously, we have proposed a method based on the modulation of fluorescence emission of a donor by a photochromic acceptor [2,3], in which only the absorption of one of its photochromic-isomeric forms overlaps with donor emission. A light-induced structural transition of the acceptor results in changes of its excitation properties, which in turn can "switch on" and "off" donor fluorescence in a reversible fashion. The method is especially suited for microscopy because it operates over a range (< 100 Å) that surpasses optical resolution of most light microscopes (~ 0.3 µm) and it generates the necessary reference sate required for quantitative FRET determinations without the need of photochemical destruction of donor of acceptor [4]. Additionally, continuous observations within living cells are feasible.

In this work we perform a comparative analysis of photochromic spiropyrans and diarylethenes as potential acceptors for FRET.

Experimental

*Synthesis. Lucifer yellow cadaverine-6-nitroBIPS (LYC-BIPS) (**1**) or Lucifer yellow cadaverinediarylethene (**2**)*

Lucifer yellow cadaverine was coupled with the succinimidyl ester of 1',3'-dihydro-3',3'-dimethyl-

1'-(2-carboxy)-6-nitrospiro [2H-1-benzopyran-2',2'-(2H) indole] (6-nitroBIPS) or carboxyethyldiarylethene in dry acetonitrile to yield compounds **1** or **2.** The products were HPLC purified and identified by ^{1}H-NMR and mass spectrometry.

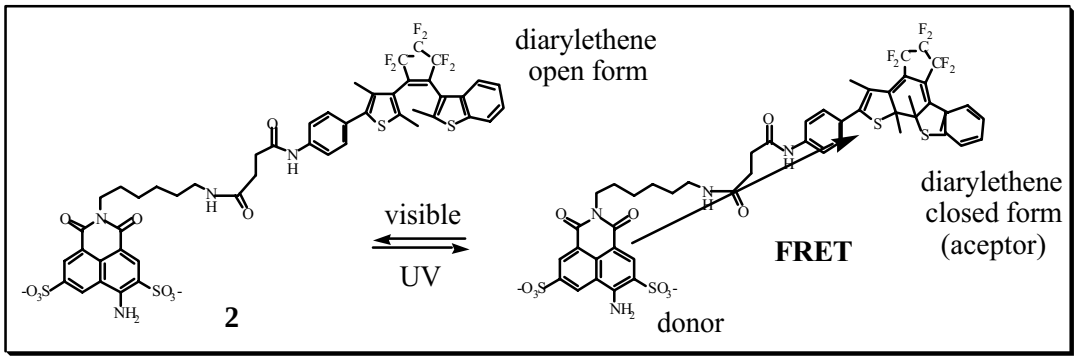
Photophysical studies

Absorption spectra of compounds **1** and **2** were performed at different stages of acceptor photoisomerization. The kinetics of thermal reversion was studied for the spiropyran derivative. FRET was determined by evaluating the donor emission steady state spectra (ex. 420 nm) in each of the acceptor forms and donor lifetime emission, measured by the phase and modulation method.

Results and Discussion

Light induced photo-conversion at 254 nm of the spiropyran form of 6-nitroBIPS to the merocyanine form (FRET acceptor) resulted in a 35% decrease in donor emission quantum yield. Irradiation at 546 nm yielded the initial spiropyran form with the original donor emission intensity. The irradiation could be repeated for at least 8 cycles without any apparent fatigue. In addition to this light driven process, the merocyanine reverts to the spiropyran form by a thermal mechanism (k_T = 0.039 min^{-1}). The light-independent transition from spiropyrans to merocyanine in polar solvents limits the use of this compound in aqueous solutions.

Thermally stable diarylethenes were used as acceptors for FRET in model compound 2. Photoisomerization from the open to the closed form induced by irradiation at 313 nm switched "on" and "off" the FRET process (E = 0.25). The modulation of the absorption and fluorescence could be cycled at least 20 times without any noticeable degradation. The degree of conversion between open and closed form was wavelength dependent. In contrast to the merocyanine acceptors, thermal stability of both open and closed diarylethene forms allowed repeated absorption and fluorescence determinations. The excellent performance of diarylethene acceptors encourages their use for future studies in FRET microscopy.



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Stereoselective Synthesis of 8-Trialkylstannylmenthols

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Abstract: Trialkyltin menthones of type **2** are obtained selectively by 1,4-addition of trialkylstannyl lithium to (-)-pulegone. Reduction of **2** with borane in THF using as catalyst the reagent prepared from borane and (S)-valinol gave a mixture of the corresponding trialkyltin alcohols **3** (Me: 84%; n-Bu: 90,6%) and **4** (Me: 16% and n-Bu: 9,4%).

Introduction

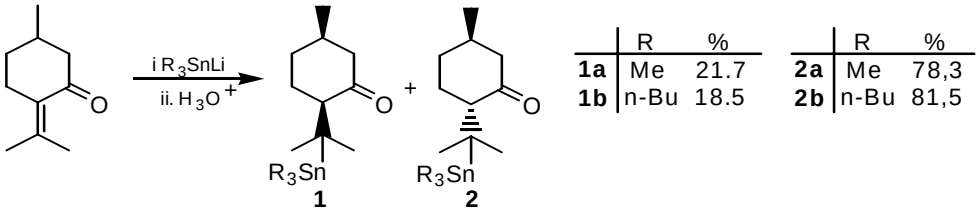
Taking into account the excellent results obtained with the (-)-8-phenylmenthyl group as a chiral auxiliary, we considered of interest the synthesis of some organotin analogues. The 8-triorganotinmenthyl moiety might affect the stereoselectivity due to its bulk and also to electronic effects. The stereoselective synthesis of these compounds was carried out according to Schemes 1 and 2.

Experimental

The 1,4-addition of trimethyl- and tri-n-butyl lithium to (-)-pulegone led to menthones of type **1** and **2** with an average yield of 72% following standard techniques [1]. Compounds **1** and **2** were separated by column chromatography (silica gel 60). The reduction of type **2** ketones with borane in THF using (S)-valinol as a catalyst was carried out according to known procedures [2].

Results and Discussion

The reduction of (-)-menthone carried out with the reagent prepared from borane and (S)-valinol in THF in order to determine the degree of asymmetric induction which can be achieved with this reagent, yielded quantitatively a mixture of (-)-menthol (80%) and (+)-neo-menthol (20%), i.e., 60% of diastereoisomeric excess (d.e.).

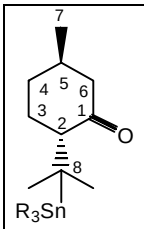


	R	%
1a	Me	21.7
1b	n-Bu	18.5

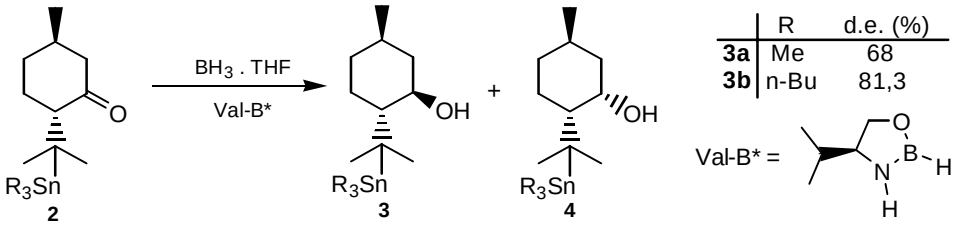
	R	%
2a	Me	78,3
2b	n-Bu	81,5

Scheme 1. 1,4-Addition of trialkylstannyl lithium to (-)-pulegone.

Table 1. ^{119}Sn- and some selected ^{13}C NMR values of the new organotin compounds **2a** and **2b**[a].

	N°	δ $C_1(^3J)$	δ $C_2(^2J)$	δ $C_3(^3J)$	δ $C_8(^1J)$	^{119}Sn	$[\alpha]_D^{20}$(conc.)[b]
	**2a**	213.42 (17.8)	61.25 (7.7)	28.41 (31.0)	32.59 (243,0)	12.7	-35.6º (0,874)
	2b	213.16 (16.1)	61,40 (6.8)	27.94 (NO)	26.47 (388.2)	-8.3	-22.2º (1,94)

a) in $CDCl_3$; ^{n}J(Sn,C) in Hertz; NO = Not Observed. b) In $CHCl_3$.



	R	d.e. (%)
3a	Me	68
3b	n-Bu	81,3

Scheme 2. Stereoselective reduction of trialkylstannylmenthones of type **2.**

Under the same reaction conditions, the reduction of **2a** (d.e. 68%) and **2b** (d.e. 81,3%) led to the corresponding 8-trialkylstannylmenthols with better diastereoisomeric excesses.

Acknowledgements: This work was supported by CONICET (Buenos Aires), CIC (Provincia de Buenos Aires) and Universidad Nacional del Sur (Bahía Blanca, Argentina).

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Polymerization Mechanism of α,α'-*bis*(Tetrahydrothiophenio)-*p*-xylene Dichloride

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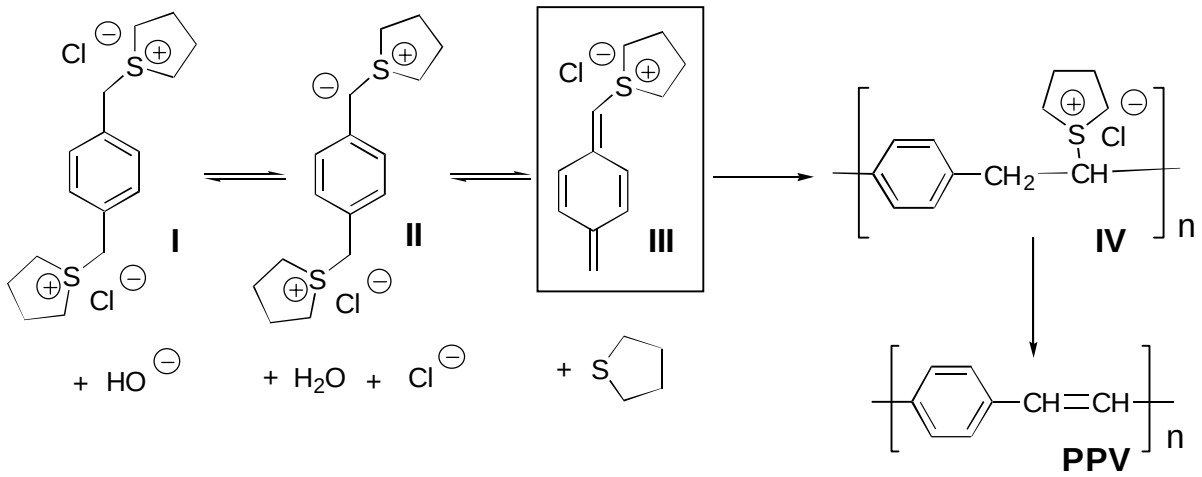
Abstract: A experimental study was performed regarding the influence of the base nature and solvent on the reactive intermediate concentration in the base-promoted *bis*sulfonium salts polymerization. Such polymerization reaction is part of a synthetic procedure used to prepare conjugated polymers. In addition, a theoretical study suggest that a one-electron transfer could be involved in the initiation step.

Keywords: conjugated polymers, poly(phenylene vinylene), precursor route.

Introduction

The interest on poly(p-phenylene vinylene)s, PPV, lies on its unique photoconducting, electroactive, and non-linear optical properties. Although there are numerous ways to synthesize PAV's, the route through a precursor polyelectrolyte, **IV**, as show in Scheme 1, yields the highest molecular weight attainable for these systems and allows to cast films of very good optical quality. It is well known that the reactive intermediate **III** is formed *in situ* when the *bis*sulfonium salts are treated with a base[1]. However, the polymerization reaction mechanism is still not known in detail, thus radical and anionic mechanisms were proposed; being the first mechanism the most accepted at present [2]. Moreover, the initiator nature and the termination mechanism step are not known.



Scheme 1.

Experimental

The appearance and decay of the intermediate **III** in the reaction mixture was observed through its band in the UV-Vis spectra; λ_{max} 312nm, using water or water:acetonitrile-(1:4) as solvents and a spectrophotometer equipped with temperature controlled sample chambers at 25ºC. The molecular modeling was performed with the semiempirical programs PM3 and AM1.

Results and Discussion

The UV-Vis spectroscopy study showed that a decrease in solvent polarity accelerated the formation of the intermediate **III** as well as its decay. We also observed that higher concentrations of the ylid did not affect **III** decay rate. However, **III** decay rate was dependent on base concentration. These results may suggest that the base OH^- could be involved in the polymerization initiation step either as a electron-transfer agent or as polar group that promotes secondary reactions which produce free-radicals [3]. Nevertheless, additional studies are necessary to confirm these assumptions. As a initial step towards this objective, a computational study was carried out in order to determine if the base OH^- can act as a electron-transfer agent. Therefore, the products and reactants heat of formations of the reaction **III** + OH^- was calculated by semiempirical methods. These calculations indicated that the electron-transfer reaction was thermodynamically feasible and that the LUMO(**III**) has a lower energy than the HOMO(OH^-). In addition, the calculations were repeated in the solvent box, water.

Table. Heat of formation (kcal mol^{-1}).

	III	**OH**	**OH**	**Radical Anion of III**	**ΔH_R**
AM1	187.05	-14.12	0.63	41.08	-131.22
PM3	208.13	-17.52	2.82	63.52	-124.27
AM1*	165.96	-6.89	-12.10	32.13	-139.04

* Heat of formation in water.

Acknowledgments: Financial support for this research was provided by ANPCyT and SGCyT-UNS. M. A. thanks SGCyT-UNS for a fellowship.

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Enantioselective Addition of Grignard Reagents to Aldehydes

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Abstract: The addition of Grignard reagents to aldehydes in the presence of chiral aminoalcohols shows a moderate enantioselectivity. The study carried out with a series of ligands allows the correlation between the structural characteristics and their reactivity.

Introduction

The use of chiral aminoalcohol to lead asymmetrically nucleophilic additions of organometallics to carbonyl compounds is a field of great potentiality in synthesis [1]. It is based on the coordination of amines and ethers to organolithium and Grignard reagents; the efficiency of the asymmetric induction depends, among other factors, on the characteristics of the metal [2], its aggregation state [3] and on the chiral ligand structure [4].

Experimental

General Procedure

To a mixture of 1 mmol of aldehyde and the corresponding amount of chiral ligand in the reaction solvent, 1.7 mL of a 0.6M of PrMgBr in the same solvent were added at -78ºC. The quenching was carried out using 1 mL of HCl 5%. The products in the reaction mixture were investigated by GC and polarimetry.

Results and Discussion

The addition of PrMgBr to 3-phenylpropanal, **1**, and benzaldehyde, **2**, was carried out in the presence of asymmetric ligands derived from 2-aminobutanol and ephedrine in different solvents and reagent:ligand:substrate ratio (see Table). Several new ligands were designed and synthesized.

Table. Reactions of PrMgBr with 3-phenylpropanal, **1**, and benzaldehyde, **2**, in the presence of chiral ligands.

Chiral Ligand[a]	Alde-hyde	Reagent:Ligand: Aldehyde ratio	Solvent	Yield (%)	Absolute Con-figuration	% ee
3	**1**	1.2:0.2:1.0	toluene	77	S-(+)	5
4	**1**	2.0:0.5:1.0	ether	98	R-(-)	2
5	**1**	1.2:0.2:1.0	toluene	98	S-(+)	5
	1	1.2:0.2:1.0	ether	100	S-(+)	7
6	**2**	4.0:2.0:1.0	THF	98	R-(+)	3
7	**1**	4.0:2.0:1.0	THF	90	S-(+)	8
	1	6.0:2.0:1.0	toluene	85	S-(+)	29
	2	6.0:2.0:1.0	toluene	51	S-(-)	40
8	**2**	4.0:2.0:1.0	THF	60	R-(+)	9
9	**1**	3.0:1.0:1.0	toluene	96	R-(-)	2

[a] **3** = (-)-2-dipropylaminobutanol, **4** = (-)-(1-benciloxymethylpropyl)-dipropylamine, **5** = (-)-4-ethyl-2,2-dimethyl-oxazolidine, **6** = (-)-ephedrine, **7** = (-)-pseudoephedrine, **8** = (-)-2,2,3,4-tetramethyl-5-phenyl-oxazolidine, **9** = (-)-N-propylephedrine.

Several conclusions can be extracted from this table:

- Donor solvents influence negatively the effectivity of the asymmetric catalysis, likely because these solvents compete in the coordination of the attacking reagent.
- The ligands with two asymmetric centers have higher effect in the asymmetric addition. The substitution by bigger groups in the nitrogen leads to lower selectivities.
- The use of oxazolidines does not lead to fine enantiomeric excess, probably due to the conformational rigidity.
- The asymmetric induction in the formation of aromatic secondary alcohols is more pronounced than in the aliphatic secondary alcohols.

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O-Sulfated Derivatives of Glucuronic Acid

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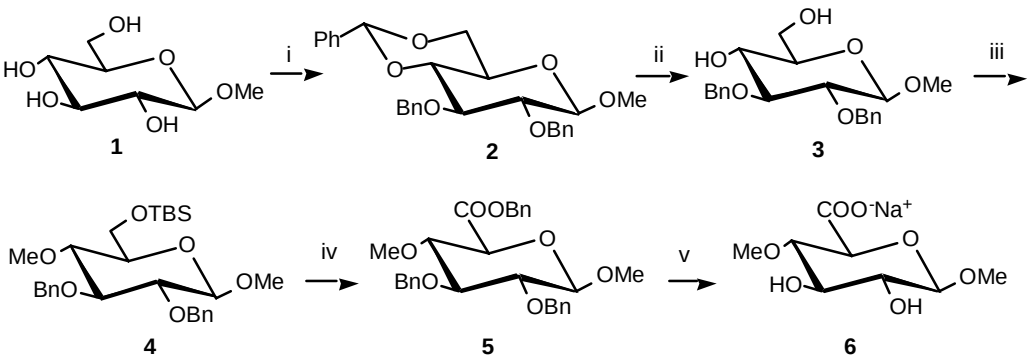
Abstract: 4-*O*-Substituted D-glucuronic acid derivatives were synthesized from D-glucose in order to study the regioselectivity of sulfation.

Introduction

Glycosaminoglycans, as heparin and heparan sulfate, interact with various proteins, and their binding properties are related to the glycosidic sequence and the number and position of sulfate groups. In our laboratory, we performed a variety of chemical modifications of the polysaccharide chain. On sulfation of heparan sulfate, the regioselective sulfation of glucuronic acid units in *O*-2 has been observed.[1] This result is interesting due to biological properties of heparan sulfate.

Experimental

The synthesis of derivatives of glucuronic acid was performed as shown in Fig. 1.



i. $Ph(OMe)_2$, PTSA; NaH, BnBr. ii. MeOH, H^+. iii. TBSCl, Et_3N, DMAP; MeOTf.
iv. H_2SO_4, CrO_3, acetone. v. H_2, Pd-C.

Figure 1.

Sulfation of **6** was accomplished with $SO_3.Et_3N$ in DMF in the reaction conditions employed for heparan sulfate. The products were purified by chromatography and characterized by NMR (^1H and ^{13}C).

Results and Discussion

Sulfation of methyl 4,6-*O*-benzylidene D-glucopyranoside, and methyl 4-*O*-benzoyl-D-glucopyranosiduronate showed no selectivity 2- and 3-*O*-sulfated derivatives. This result is in accordance with previous reports on similar reactivity of HO-2 and HO-3 in acylation reactions of compounds of D-*gluco* configuration.

The selectivity observed in heparan sulfate would therefore be related to the structure of the glycosidic chain. In this polysaccharide, the regular sequence is composed by a β-D-glucuronic acid unit linked to HO-4 of *N*-acetyl or *N*-sulfate-D-glucosamine residue. The linking of the glucosamine to the next glucuronate is α, giving an alternating sequence. This anomeric configuration would allow the formation of hydrogen bonds between both residues, involving the HO-3 of glucuronic acid units, preventing their sulfation. Oligosaccharide models needed to study this hypothesis can be prepared from compound **3**.

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Synthesis and Computational Simulation of New Phosphorilated Sulfoximines with Insecticidal Activity

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Abstract: New organophosphorus insecticides of dialkylsulphoximines derived with activity upon acetylcholinesterase were synthesized. The obtained compounds were characterized by NMR and IR, and anticholinesterase activity and toxicity was measured. A simulation through computer was done in order to establish the relationship between structure and activity.

Introduction

The objective of this work was to synthesise a new family of organophosphorus insecticides with anticholinesterasic activity. It is known that the inhibition of AchE is the principal mode of action for organophosphorus compounds and that this inhibition depends on the electrophilic character of the P atom, strongly influenced by the nature of the attached groups.

Thus, it was of interest to study the toxicity of the synthesized phosphorothionate compounds (LD_{50}) against houseflies (*Musca domestica)* and to measure the anticholinesterasic activity (I_{50}) for the corresponding phosphates in comparison with a known direct inhibitor such as paraoxon.

A simulation through a computer program was performed in order to establish some correlation between chemical structure and insecticidal activity.

Experimental Methodology

Diethyl phosphorothionate of dipropyl and dibutylsulfoximine and the corresponding phosphates were synthesized from the sulfoximines and diethylphosphorothiochloridate and diethylphosphorochloridate according to described methodology (Wieczorkowski et al, 1983 and Licastro S.A. et al, 1986). The crude products were purified by column chromatography and characterized by NMR and IR spectroscopy.

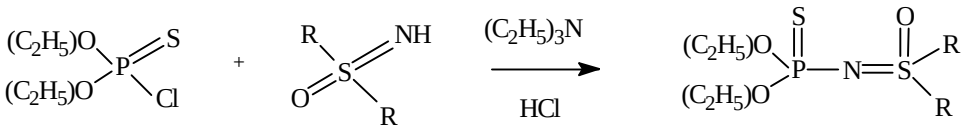
Anticholinesterasic activity was measured for the synthesized phosphates using acethylthiocholine as substrate by the Ellman's method (Ellman G.L.et al, 1961), bovine erythrocyte AchE and housefly AchE prepared as a crude homogenate of houseflies heads (Licastro S.A.et al, 1982).

Insecticidal activity was determined for the synthesized phosphorothionates using a susceptible strain of *Musca domestica* by topical application as previously described (Picollo et al, 1976). Mortalities were recorded after 24 h and the data analyzed using a probit analysis program based on Litchfield and Wilcoxon method (1949).

Computational simulation for the obtained sulfoximines was performed using GROMOS 96 software.

Results and Discussion

Phosphorylated dipropyl and dibutyl sulfoximines were obtained according to equation 1, purified and characterized.



R= propyl and butyl

LD_{50} values were determined on houseflies (*Musca domestica)* for both phosphorothionates (table 1) showing less toxicity for the dibutyl derivative. Compounds with longer alkyl chain were going to be synthesized to establish some correlation between structure and activity.

I_{50} values for housefly AchE and Bovine erythrocytes AchE (Table 2) shows the synthesized compounds were very good inhibitors compared with paraoxon with a significant difference between insect and mammalian enzyme.

With respect to computational simulation, the synthesized compounds were a similar charge in phosphorus than paraoxon.

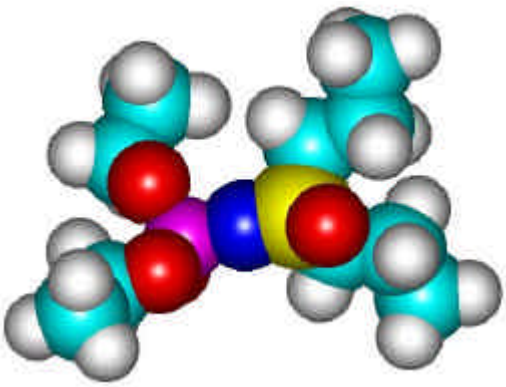


Table 1. Insecticidal activity *Musca domestica.*

Compounds	LD_{50} µg/insect
DPSNHPS (diethylphosphorothio propylsulfoximine)	0.2786
DBSNHPS (diethylphosphorothio butylsulfoximine)	0.5572

Table 2. Anticholinesterasic activity.

Compounds	I_{50} mol L^{-1}	
	Housefly	Bovine erythrocyte
DPSNHPO diethylphosphoropropylsulfoximine	$1.1\ 10^{-8}$	$1.1\ 10^{-6}$
DBSNHPO diethylphosphorobutylsulfoximine	$1.8\ 10^{-8}$	$1.8\ 10^{-6}$
Paraoxon	$2.9\ 10^{-8}$	$8.9\ 10^{-7}$

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Phytochemical Study *Conyza Sophiaefolia*. Antiinflammatory Activity

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Abstract: From the aerial parts of Conyza sophiaefolia a new alicyclic furan diterpene was isolated and characterized as an E-isomer in C_6 of centipedic acid. In addition, the new clerodane type diterpene 12-epi-bacchotricuneatin A as well as two known related diterpenoids were identified. The flavone apigenine was also isolated. Structures were determined on the basis of spectroscopic evidence.

Introduction

The genus *Conyza* comprises about 50 species, which are mainly distributed in tropical and subtropical areas. It is well known that this genus produces sesquiterpenes, diterpenes, acetogenic lactones, flavones and cumarines.

Experimental

Plant Material

Conyza sophiaefolia (Asteraceae, Asteroidae, Astereae), was harvested in «El Volcán», February 1998, and identified by Ing. L. A. Del Vitto, E. M. Petenatti & O. S. Giordano. A Voucher specimen is deposited at the Herbario of UNSL Nº 6758.

Isolation Procedure

The dried ground aerial parts were extracted with Me_2CO, the residue obtained was dissolved with MeOH-H_2O 9:1 and partitioned with *n*-hexane (Extract **A**) and chloroform (Extract **B**). These residues were subjected, several times, to a combination of chromatography procedures on Si gel 60 using mixtures of *n*-hexane-ethyl acetate as eluents and Sephadex LH 20 with methanol as eluent.

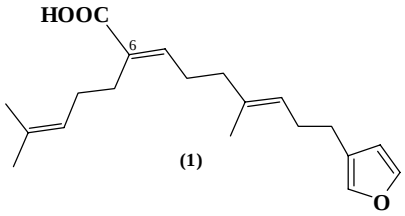
Result and Discussion

Hawtriwaic acid [1], 2β hidroxyhardwickiic acid [2], apigenin and the diterpenes **1**, 12-*epi*-

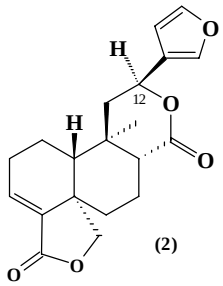
bacchotricuneatina A and **2** [3] were isolated from extract **B**. Structures were determinate by EM, ^{1}H y ^{13}C-RMN (**Table 1**) and confirmed by bidimentional experiments (COSY, NOESY, ROESY, HMBC, HMQC).

Table 1.

H/C	δ_H (Compound **1**)	δ_C
1	1.68 *br s*	25.7 *q*
2		132.1 *s*
3	5.19 *br t* (6.0)	124.1 *d*
4	2.10 *br t* (4.0)	28.0 *t*
5	2.25 *m*	28.7 *t*
6		131.7 *s*
7	6.72 *t* (7.3)	145.6 *d*
8	2.35 *m*	27.0 *t*
9	2.30 *m*	38.5 *t*
10		134.4 *s*
11	5.20 *br t* (6.8)	125.1 *d*
12	2.23 *m*	27.4 *t*
13	2.45 *br q* (7.5)	25.1 *t*
14		128.2 *s*
15	6.28 *br s*	111.2 *d*
16	7.31 *br s*	142.8 *d*
17	7.20 *br s*	139.2 *d*
18	1.60 *br s*	15.8 *q*
19		174.3 *s*
20	1.60 *br s*	17.6 *q*



(1)



(2)

*200 MHz, C_6D_6.

*Mass fragments: [M^+] *m/z*=316; -Me=301; -C_6H_5=247; pirilio$^+$=81; $C_5H_9^+$=69

The anti-inflammatory activity of all the extracts has been evaluated by paw edema test [4] **(Table 2).**

Table 2.

Product	Acute inflammation inhibit %				Dunnet's Test
	1H	3Hs.	5Hs.	7Hs.	
Acetonic extract	-	37	45(b)	49(a)	(a) p<0.02
Chloroformic extract **A**	14	22	45(b)	35	(b) p<0.04
n-hexane extract **B**	-	12	36	26	(c) p<0.002
Phenylbutazone	55	65(d)	65(c)	52(a)	(d) p<0.0003

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Structure-Properties Relationship of Dimeric Surfactants from Butyl Glucosides

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Abstract: Carbohydrate containing dimeric surfactants were synthesized starting from D-glucose. Three different spacers were used to link the sugar moieties. The critical micelle concentration (CMC) for these new compounds was determined.

Introduction

Alkyl glucosides are found in nature as glycolipids, and are biosynthesized by micro-organisms using rhamnose, sophorose and trehalose as carbohydrate sources. Industrially they are prepared from fatty alcohols and carbohydrates. These compounds have surfactant properties when the alkyl chain contains at least 4 carbon atoms. Alkyl glucosides are replacing usual non ionic surfactants due to their biodegradability and to the absence of toxic effects.

Recently, a new class (type) of surfactants, named dimeric [1] or gemini [2] have been prepared. They have 2 hydrophobic chains, 2 hydrophilic groups, and a spacer (flexible or rigid) keeping away the two polar groups.

In this communication, we report on the synthesis of dimmer surfactants from butyl α-D-glucopyranoside, and we analyze their interfacial properties.

Experimental

Gemini surfactants were prepared by condensation between suitable protected butyl α-D-glucopyranoside and acyl dichlorides [3,4] (Fig. 1). The products were characterized by spectroscopic /methods (NKr, IR., MS). Molecular formula were confirmed by elemental analysis. Critical micelle concentrations (CMK) of two compounds was determined by the maximum bubble pressure methods [5].

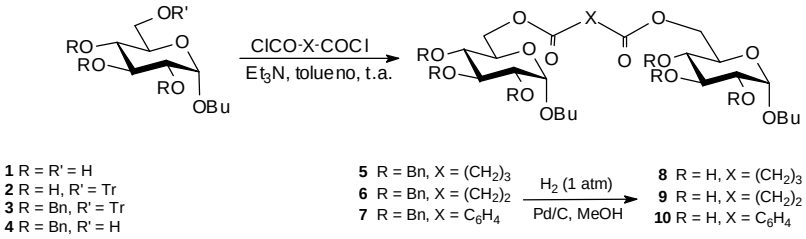

Figure 1.

Results and Discussion

CMC data showed an important (one order of magnitude) diminution of CMC of dimeric surfactants when compared to their monomeric counterpart.

On the order hand, differences in interfacial properties were observed varying the nature of the spacer and the position of linking, that can be explained from the conformation adopted by the surfactant molecule (Fig. 2).

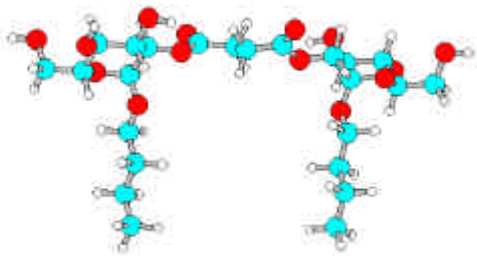

Figure 2. Optimized structure of 1,4-bis-[2-*O*-(*n*-butyl-α-D-glucopyranosid] succinate calculated by AM1 method.

Acknowledgements: This work have been performed with financial support of Universidad de Buenos Aires (UBA) and the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET).

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Synthesis of 2,3-Butanedione over TS-1, Ti-NCl, TiMCM-41, Ti-Beta, Fe-Si, Fe-Beta and VS-1 Zeolites

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Abstract: The purpose of this work is the synthesis of 2,3-butanedione (diacetyl) by selective oxidation of 2-butanone (methyl ethyl ketone) in the presence of O_2 and H_2O_2 30% as oxidants. All the tests were performed over several selective oxidation zeolite catalysts, synthesized and characterized in our laboratory.

Introduction

2,3-Butanedione or diacetyl, a flavor compound having a distinct buttery character accumulates during alcoholic and malolactic fermentation of wine and beer. The synthesis of 2,3-butanedione has been reported by heterogeneous catalysis, using Cs-K/V_2O_5 [1-4].

Experimental

Catalyst preparation, characterization and catalytic activity

All the samples were prepared by sol-gel method using raw amorphous SiO_2/HeteroatomO_2 gels. The following reactants were used: TEOS (tetraethylorthosilicate), as source of Silicon. TiPOT (tetraisopropylorthotitanate) and TNBOT (tetrabutylorthotitanate) as raw material for titanium. ferric nitrate as source of Iron. vanadyl sulfate as source of vanadium. TPAOH (tetrapropylammonium hydroxide) and TBAOH (tetrabutylammonium hydroxide) as template for TS-1; TEAOH (tetraethylammonium hydroxide) for TiBEA; DTMA (dodecyltrimethylammonium bromide) for MCM-41 and HMTBOH (N,N'-hexamethylenebis [tributylammonium hydroxide]) for NCL-1 zeolite. The final product was filtered, washed with distilled water, dried at 110°C and calcined at 500°C for 12 h. We obtained the following zeolites: TS-1, Fe-Si, Ti-Beta, Fe-Beta, Ti-NCL-1, Ti-MCM-41 and VS-1. The catalysts were characterized by AA, XRD- Synchrotron, BET, FT-IR and TPD of templates [5]. The standard reactions of oxidation of 2-butanone (methyl ethyl ketone, MEC, Sintorgan 99%) were performed in a flow reactor using oxygen as oxidant, the results are showed in table 1. According with the dates in table 1, the VS-1 sample is active and selective for the synthesis of 2,3-butanedione, Fe-Beta sample

is active but the selectivity is poor. In addition, this reaction was performed in presence of H_2O_2/MEK=6 and W/F=20ghmol^{-1} over VS-1 obtaining low conversion (7% at 200°C) but high selectivity to diacetyl. The reaction products were analyzed by Gas Chromatography with a capillary AT-Wax column of 30m and Mass Spectroscopy using a GC-MS 823.

Table 1. MEC conversion and selectivity to 2,3-butanedione using O_2, over zeolites at different reaction conditions.

Catalyst	O_2/MEC	T(°C)	W/F (g.h.mol^{-1})	Conversion (mol%)	Selectivity to 2,3-Butanedione (mol%)
Ti-MCM-41	1.3	250	12	3.0	25.0
Ti-NCL-1	1.3	250	12	2.5	32.0
Fe-Beta	3.4	250	24	40.5	4.0
VS-1	1.3	250	24	15.2	57.7

The influence of reaction temperature on the oxidation of 2-butanone is shown in Fig. 1. In this figure the conversion and selectivity versus temperature are plotted for VS-1 and O_2 as oxidant. We can observe that the conversion increases with temperature but the selectivity decreases notably.

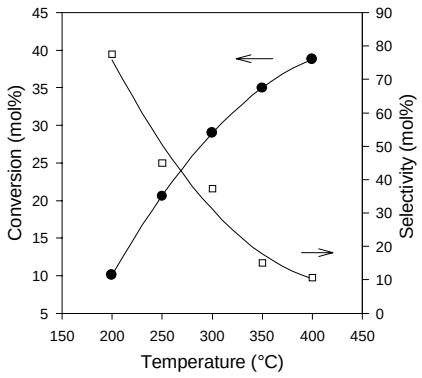

Figure 1. Activity of VS-1. O_2/MEK=3.4 and W/F=24g.h.mol^{-1}.

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Reaction Mechanism for the Cyclization of 3-[γ,γ-Dimethylallyl]Coumaric Acid Methyl Ester in Dimethyl Sulfoxide (DMSO)

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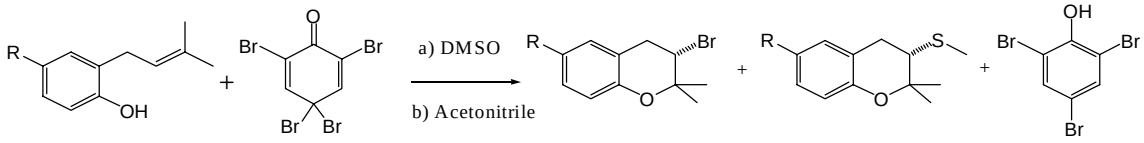
Introduction

The reagents used to oxidize alcohols to ketones in DMSO are believed to form sulfoxonium intermediate species by electrophilic attack at the DMSO oxygen [1,2]. In this work we studied the reaction of 3-[γ,γ - dimethylallyl] – coumaric acid methyl ester with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBC).

Experimental

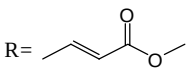
The reaction (Scheme 1) was followed using ^{1}H NMR and GC-EIMS. The products were isolated using TLC and HPLC. Conductimetric measurements of solutions of TBC in acetonitrile and DMSO as a function of time were carried out.



1 3-[4-hidroxy-3-(3-methyl-but-2-enyl)-phenyl] acrylic acid methyl ester

2 3-(3-Bromo-2,2-dimethyl-chroman-6-il)-acrylic acid methyl ester

3 3-(2,2-dimethyl-3-methylsulfanyl-chroman-6-yl)-acrylic acid methyl ester



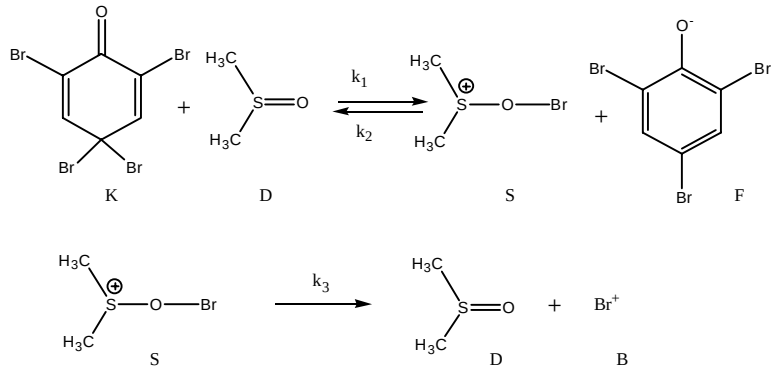
Scheme 1

Results and Discussion

GC-EIMS experiments indicate that tribromophenol (TBF) is formed almost completely during the first minute of the reaction as long as ester slowly diminishes its concentration. This suggests the existence of an intermediate species that captures the bromonium ion. If TBF participate in this specie, significant changes should not be expected when solvent is changed. However, the reaction speed and

the yield of the brominated cycle increase when the reaction is made in DMSO related to acetonitrile. Therefore, we propose the species $(CH3)_2S^+$-O-Br, which would act as a carrier of bromonium to produce the cyclization. The postulation of this species would also explain the product **3**, which was characterized by ^{1}HNMR and GC-EIMS. From this point of view the reaction can be considered as similar to a reaction of Pummerer [3].

In order to test this hypothesis, the conductance of solutions of 2, 4, 4, 6 - tetrabromo - 2, 5 - cyclohexadienone (TBC) in DMSO and acetonitrile respectively, as a function of time, was measured. Results indicate that the first step the reaction would involve the following balance:



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Grindelic Acid Production in *Grindelia Pulchella* Cell Suspension Cultures Elicited with $CuSO_4$

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Introduction

Abiotic elicitors affect both, biomass and secondary metabolite production in cell suspension cultures. In this work we have studied CuSO4 effect on the accumulation of grindelic acid in *Grindelia pulchella* cell suspension cultures.

Material and Methods

Cell suspension cultures

MS media supplemented with indolbutiric acid and bencilamine purine was employed. Samples of 20 ml were taken, after filtration biomass dry weight was evaluated.

Grindelic acid production evaluation

Liquid media was acidified to pH 5.00 with HCl 10% and submitted to liquid-liquid extraction procedure with Et_2O (x3). Cells were extracted by reflux in MeOH 4h (x3). The methanolic extract was dried, recovered with distilled acidified water (pH 5.00) and extracted with Et_2O (x3). Samples were methylated with CH_3N_2 and evaluated by GC. Each assay was repeated three times.

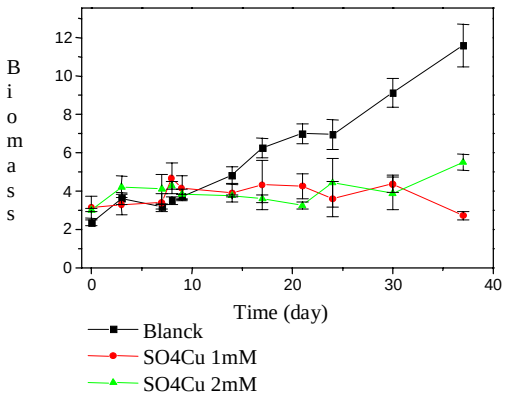
Elicitation with $CuSO_4$

$CuSO_4$ (final concentration 1 y 2 mM sterilized by filtration) was added at day 7.

Results and Discussion

Cu SO_4 addition in both concentrations inhibited the biomass production. This effect may be attributed to the fact that heavy metals (Cu or Cd) cause an increment in the catabolic activity or suppress the lipid biosynthesis.

Grindelic acid accumulation, in cultures elicited with $CuSO_4$ (1mM), was completely inhibited. On the other hand the addition of $CuSO_4$ (2mM) induced a grindelic acid accumulation dismissing at the early times of the cell cycle but increased the production in the stationary phase.



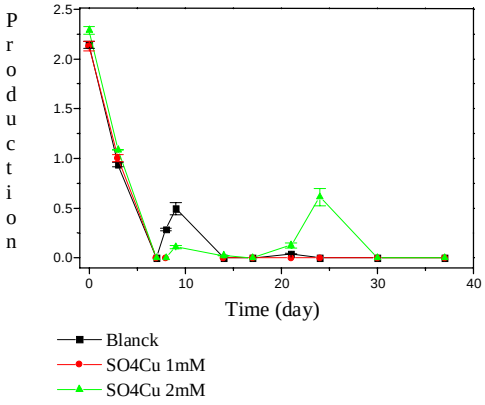


Figure 1. Cu SO_4 effect on biomass production [Biomass (g dry weigth/ml)].

Figure 2. $CuSO_4$ effect on grindelic acid accumulation [Production (mg/ g cell)].

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