

Rearrangement of *o*-Nitrobenzaldehyde in the Hantzsch Reaction[†]

E. Angeles¹, H. Santillán¹, I. Menconi¹, I. Martínez¹, A. Ramírez¹, A. Velázquez¹, R. López-Castañares² and R. Martínez^{3,*}.

¹ Laboratorio de Química Medicinal, Facultad de Estudios Superiores Cuautitlán, Universidad Nacional Autónoma de México; E-mail: angeles@servidor.unam.mx.

² Facultad de Química, Universidad Autónoma del Estado de México.

³ Instituto de Química, Universidad Nacional Autónoma de México, Apartado Postal 70-213, Coyoacán, México, D.F. CP 04510, México.

† Contribution No. 1736 from the Instituto de Química, UNAM

* Author to whom correspondence should be addressed; E-mail: robmar@servidor.unam.mx .

Received: 13 December 2000; in revised form 6 June 2001 / Accepted: 16 July 2001 / Published: 21 July 2001

Abstract: The reaction of 5-hydroxy-2-nitrobenzaldehyde with ethyl acetoacetate in ammonia gave the two expected isomeric 1,4- and 1,2-dihydropyridines resulting from the normal Hantzsch reaction. However, the combination of 2-nitrobenzaldehyde with ethyl acetoacetate under the same conditions yielded four products: the two normal isomeric dihydropyridines and two tricyclic compounds. When we attempted to independently synthesize the two tricyclic compounds by reductive cyclization of 4-(2-nitrophenyl)-2,6-dimethyl-3,5-dicarboxy-1,4-dihydropyridine and 2-(2-nitrophenyl)-4,6-dimethyl-3,5-dicarboxy-1,2-dihydropyridine with tin (II) chloride in hydrochloric acid media, we obtained instead an indole and a quinoline derivative, respectively.

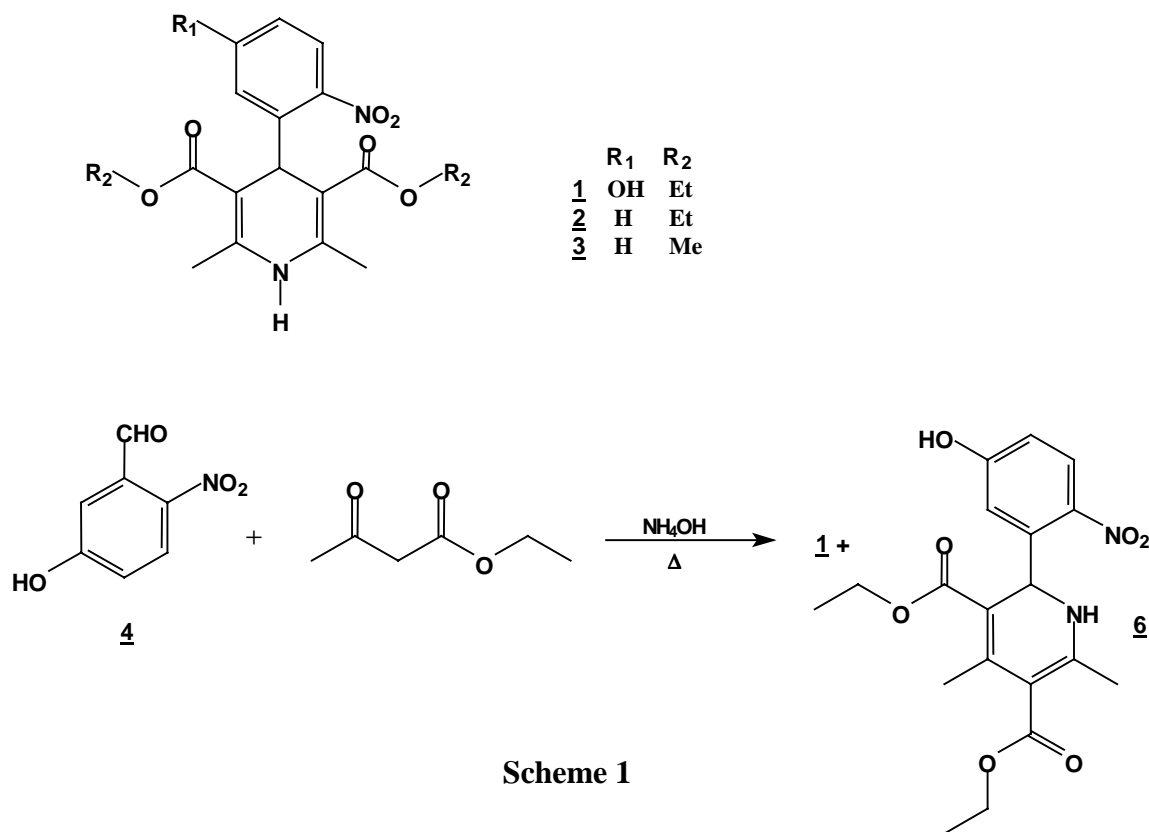
Keywords: Hantzsch reaction, cyclization, indole derivatives, quinoline derivatives

Introduction

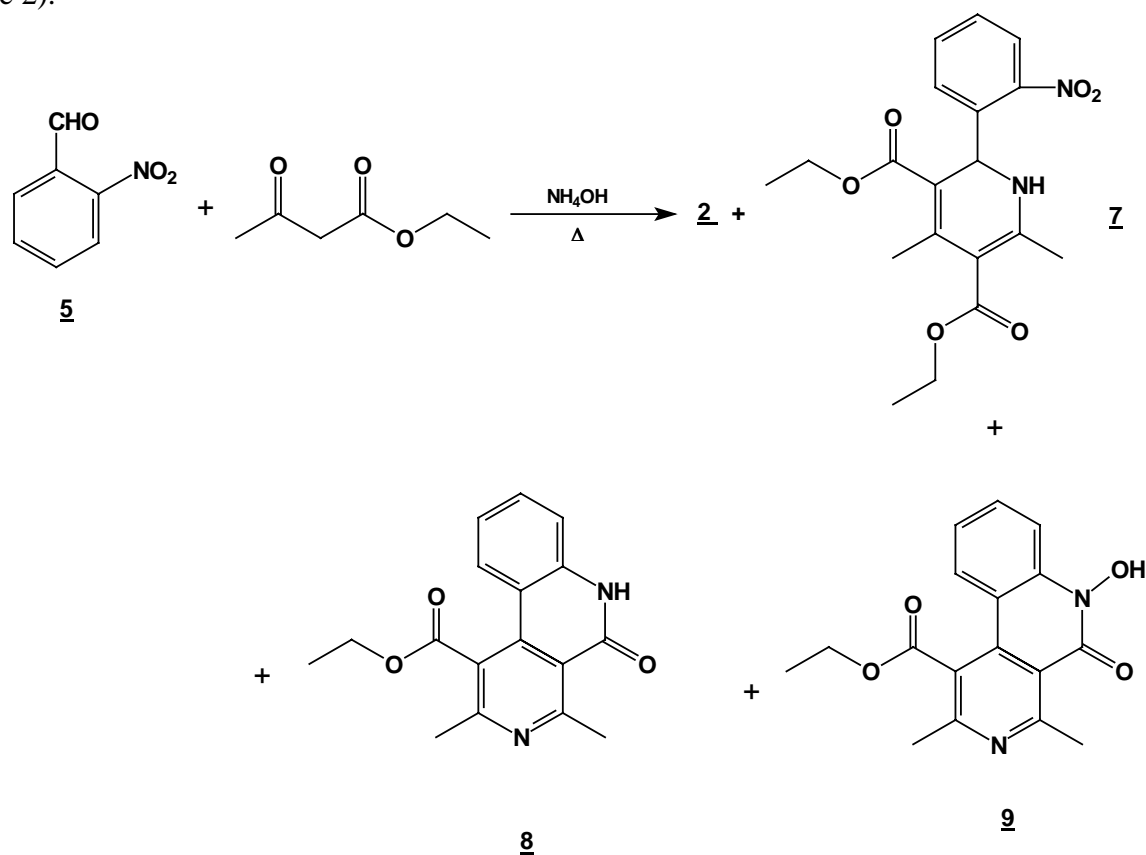
Dihydropyridine derivatives display a broad spectrum of medicinal activities, mainly as antihypertensive and antiarrhythmic drugs. They are also used as starting materials for cycloaddition and electrophilic reactions [1-4]. Recently we reported the preparation of 4-substituted-2-cyclohexenones by reductive cyclization of Hantzsch esters using sodium and ethanol as the solvent [5]. As a part of our drug design program [6], we were interested in the preparation of 1,4-dihydropyridines **1** and **2** [8] and the evaluation of their antihypertensive properties, since they are structurally similar to Nifedipine (**3**). In this paper we describe the attempted synthesis of **1** and **2** using the Hantzsch reaction of 5-hydroxy-2-nitrobenzaldehyde (**4**) and 2-nitrobenzaldehyde (**5**), respectively. We also describe here the results of the reductive cyclization of the 1,4-dihydropyridines **1** and **2** and the 1,2-dihydropyridines **6** and **7** with tin (II) chloride in hydrochloric acid.

Results and Discussion

Our approach to the synthesis of compounds **1** and **2** was based on the Hantzsch method. To this end a study was undertaken of the reaction of 5-hydroxy-2-nitrobenzaldehyde **4** with ethyl acetoacetate in ammonia. The reaction gave the isomeric 1,4- and 1,2-dihydropyridine products **1** (48%) and **6** (20%) resulting from the normal Hantzsch reaction (Scheme 1).

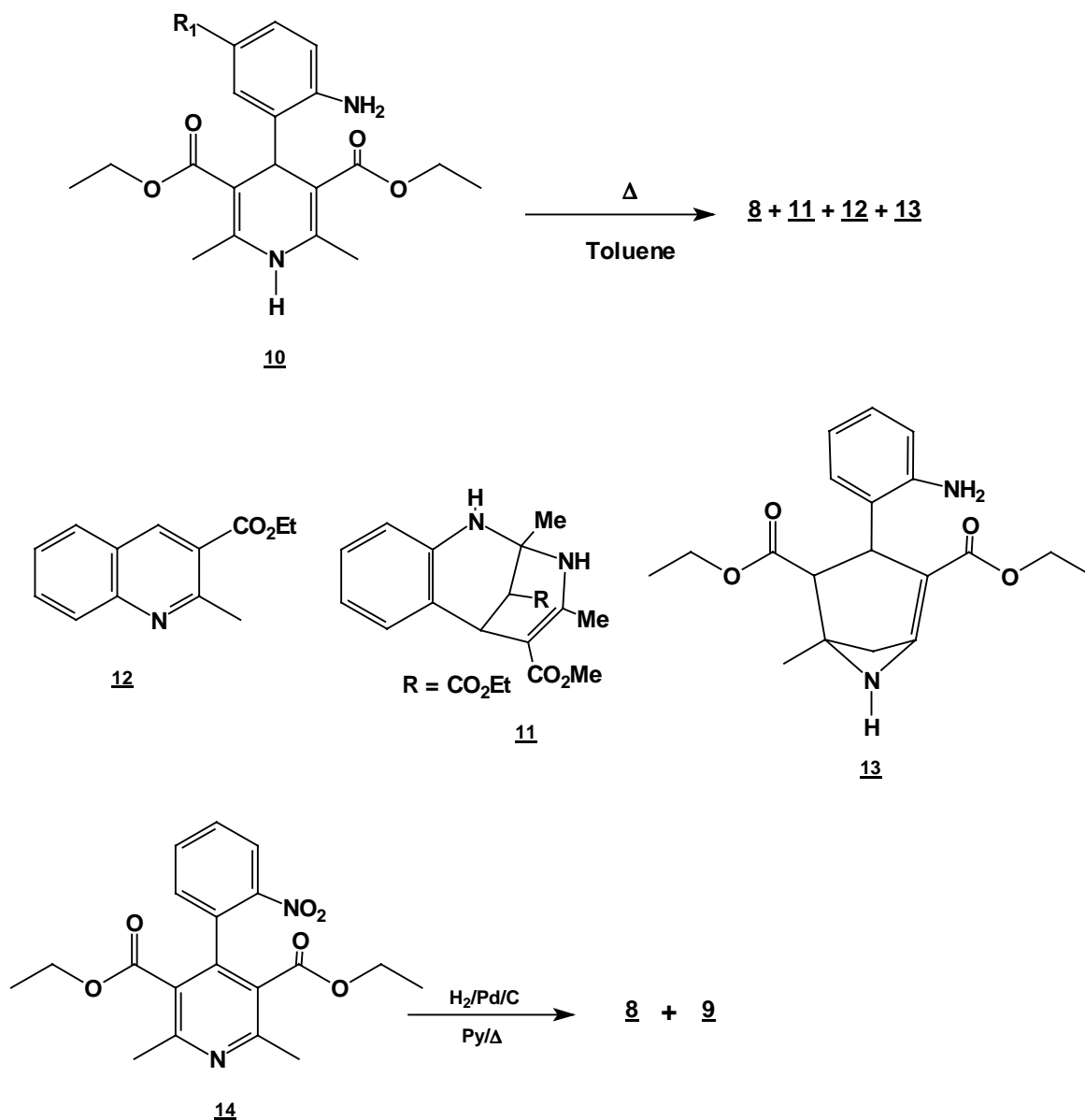


The proposed structures of all products were confirmed by analytical and spectral data and by comparison with melting points reported in previous work [7,8]. The analytical and spectral data of **6** were consistent with the 1,2-dihydro isomeric system in which the resonance of the hydrogen attached to esters groups produces different shifts in the $^1\text{H-NMR}$ spectrum. The combination of 2-nitrobenzaldehyde **5** with ethyl acetoacetate yielded interesting results. Separation of the products using column chromatography yielded the normal isomeric dihydropyridines **2**[8] and **7** as crystalline solids in 35% and 20% yields, and the compounds **8** and **9** in yields of 15% and 20%, respectively (Scheme 2).

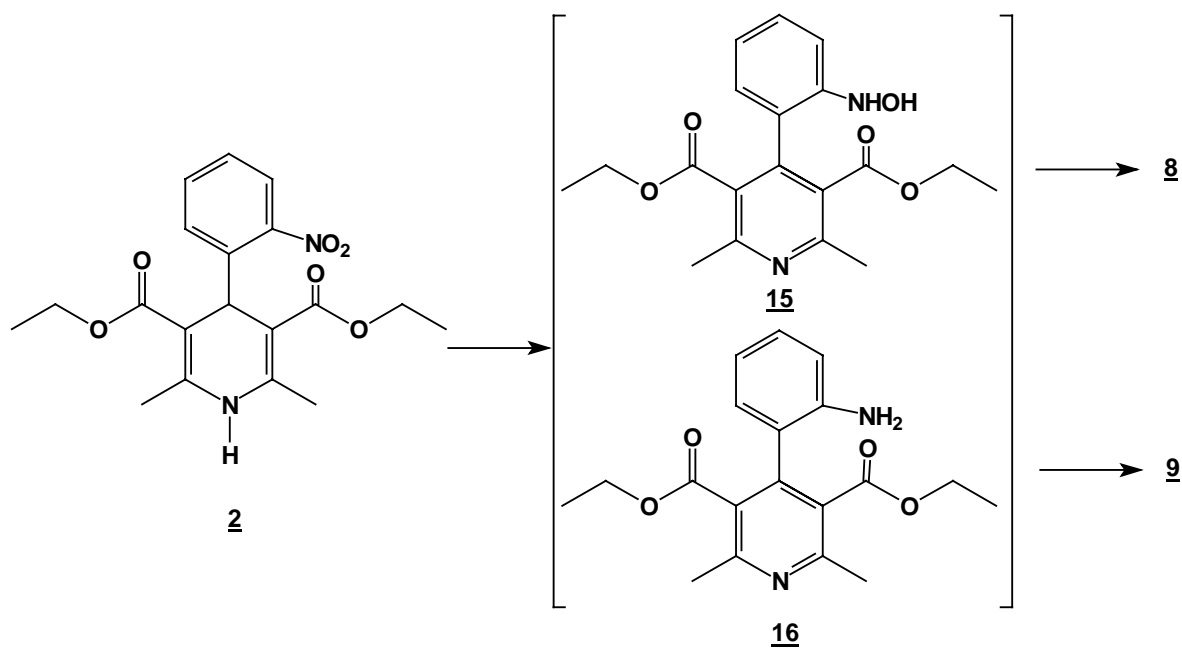


Scheme 2

Careful examination of the spectral and analytical data of compounds **8** and **9** indicated that they are the ethyl esters of 5,6-dihydro-2,4-dimethyl-5-oxobenzo[c][2,7]naphthyridine-1-carboxylic acid and 5,6-dihydro-6-hydroxy-2,4-dimethyl-5-oxobenzo[c][2,7]naphthyridine-1-carboxylic acid. Kim [9] has reported that refluxing of 4-(2-aminophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylic acid diethyl ester **10** in toluene gave four compounds: **8**, **11**, **12** and **13** (Scheme 3). He also reported that catalytic hydrogenation in the presence of palladium-charcoal of 2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic acid diethyl ester **14**, followed by treatment of the crude product with boiling pyridine, afforded a mixture of **8** and **9** in a ratio of approximately 1:1. To the best of our knowledge isolation of compounds **8** and **9** from a Hantzsch reaction has not been described in the literature.

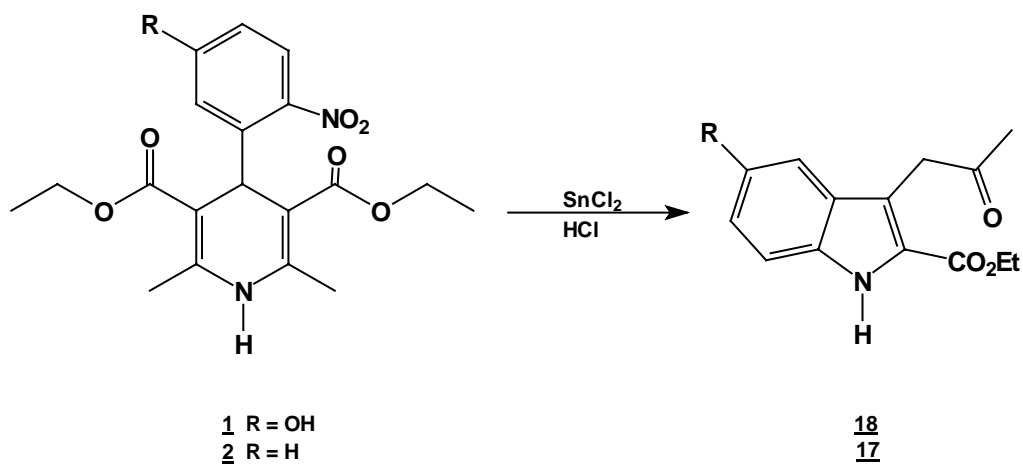


The formation of compounds **8** and **9** can be explained by an *in situ* intramolecular oxidation-reduction reaction of compound **2** (Scheme 4), since it is well known that the dihydropyridine moiety behaves as a reductive system [10-12] and the nitrophenyl framework could act as an oxidizing agent [13]. We presume that one of the first steps could be the formation of the N-OH intermediates **15** and subsequent cyclization gives compound **8**. The total reduction of the nitro group to amine **16**, and its subsequent cyclization with one of the ethyl ester groups, gives compound **9**. With the aim of testing the above statement compound **2** was treated with tin (II) chloride in hydrochloric acid [14-16].



Scheme 4

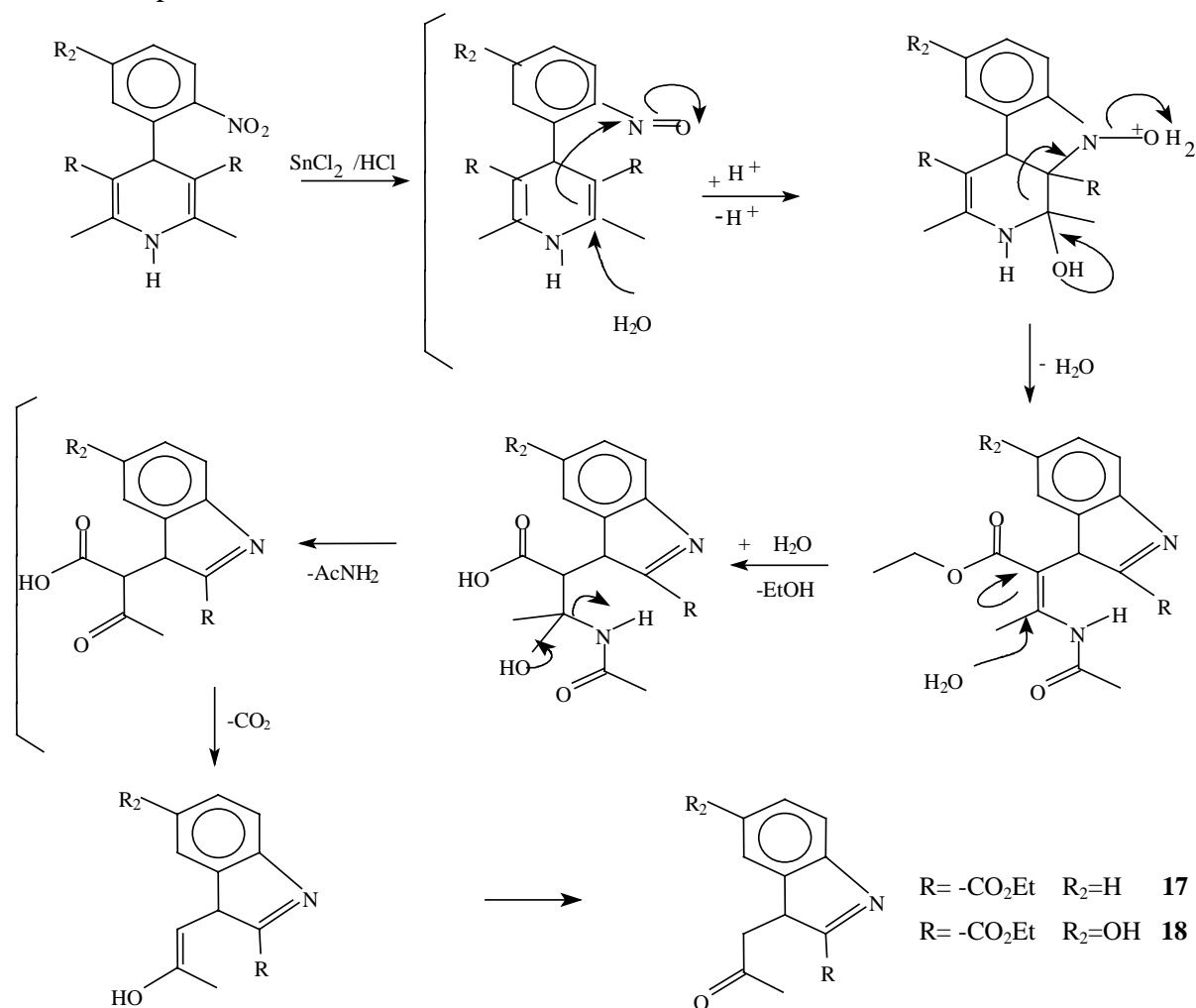
Unexpectedly the compound that was obtained in 40 % yield was proven to be **17** (Scheme 5). The structure of **17** was confirmed by comparing its melting point and spectral data with literature data [17,18].



Scheme 5

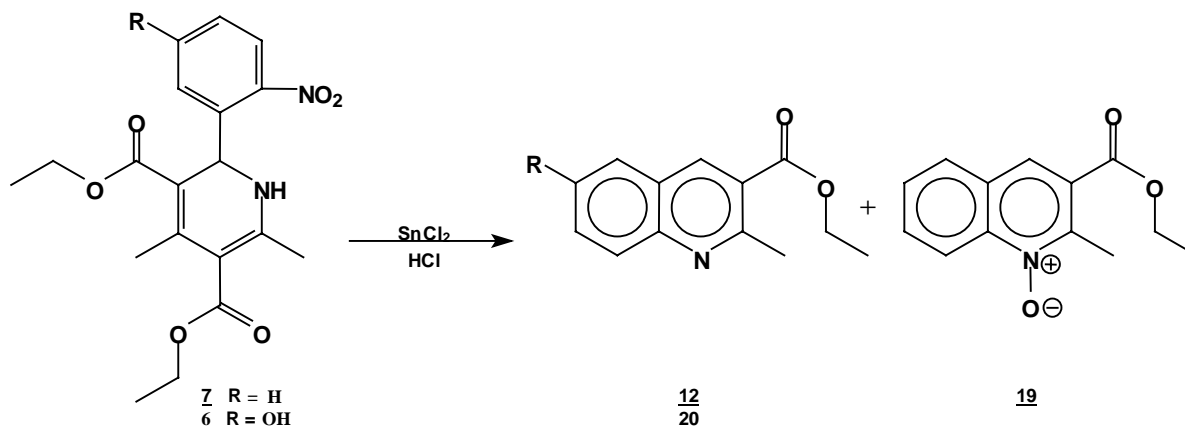
This prompted us to also investigate the behavior of 4-(5-hydroxy-2-nitrophenyl)-1,4-dihydropyridine **1** towards tin (II) chloride in acid media conditions, and this time the corresponding indole derivative **18** was obtained in 56% yield. Starting from **1** and **2** the following mechanistic pathway

leading to the indole compounds **17** and **18** can be formulated (Scheme 6). It starts with the reduction of the 2-nitro group to the nitroso functionality. This suffers a nucleophilic attack at C-3 on the dihydropyridine moiety mediated by a Michael type addition of water to C-2 of the same moiety. The pyridine unit undergoes a ring opening reaction facilitated by the loss of a water molecule from the nitrogen of the incipient indole group. Subsequent decarboxylation and isomerization processes lead to the indole compounds.



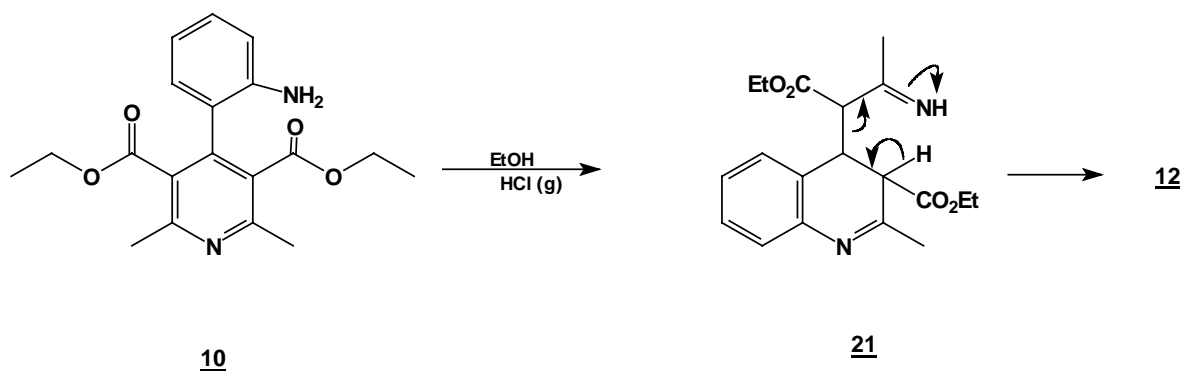
Scheme 6

In order to provide evidence for this proposed mechanism the reduction reaction was studied using the 1,2-dihydropyridines **6** and **7** (Scheme 7). Treatment of **7** with tin (II) chloride in acid media afforded a mixture of quinoline compounds **12** and **19** instead of the expected indole. The major product from this reaction exhibited spectral data consistent with structure **12** [9].



Scheme 7

The spectral and melting point data of the minor product (72-74 °C) indicated it to be **19**, a product not described in the literature. However, when the 1,2-dihydropyridine **6** reacted under similar conditions it gave the substituted 6-hydroxyquinoline **20** as the only product. Kim [9] has reported that treatment of 4-(2-aminophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid diethyl ester **10** with ethanol pretreated with hydrogen chloride gas gave the quinoline **12** and proposed a plausible mechanism for this conversion that involves the intermediate **21** (Scheme 8). Considering these observations we propose a similar mechanism to explain the conversion of 1,2-dihydropyridines **6** and **7** into quinoline derivatives (Scheme 8). In addition, Hazard has reported the electrochemical transformation of Nifedipine into a mixture of indole and quinoline compounds [17].



Scheme 8

Conclusions

The Hantzsch reaction of 5-hydroxy-2-nitrobenzaldehyde gave the expected 1,4- and 1,2-dihydropyridines. However, the same reaction with 2-nitrobenzaldehyde gave four compounds: the

two isomeric dihydropyridines and two tricyclic compounds that we propose arise from an *in situ* oxidation-reduction reaction. Likewise, the reaction of 1,4- and 1,2-dihydropyridines with tin (II) chloride in hydrochloric acid gave derivatives of indole and quinoline, respectively.

Acknowledgments

We are grateful to C. Contreras, B. Quiróz, H. Rios, L. Velasco and F.J. Pérez for their help in obtaining the IR, NMR and mass spectral data and to C. Pérez and D. Jiménez for their technical assistance. We thank also to DGAPA, UNAM and CONACyT for financial support.

Experimental

General

All melting points are uncorrected. The IR spectra were recorded on a Nicolet FT-55X spectrophotometer. The $^1\text{H-NMR}$ spectra were determined on a Varian FT-200 and Varian FT-300S instruments. All NMR spectra were obtained with the pulse sequence included with the spectrometer's software and, unless specified otherwise, were determined in deuteriochloroform solutions containing tetramethylsilane as the internal standard. Chemical shifts (δ) are expressed in ppm downfield from the reference peak. Mass spectra were recorded on a Jeol SX-102 mass spectrometer using the direct inlet system with an ionization energy of 70 eV, an emission current of 100 μA and an ion source temperature of 150 $^\circ\text{C}$.

Synthesis of 4-(5-hydroxy-2-nitrophenyl)-1,4-dihydropyridine (1) + 2-(5-hydroxy-2-nitro-phenyl)-4,6-dimethyl-1, 2-dihydropyridine-3,5-dicarboxylic acid diethyl ester (6).

A mixture of 5-hydroxy-2-nitrobenzaldehyde (5g, 0.30 mole), ethyl acetoacetate (7.8g, 0.60 mole) and 30% ammonium hydroxide (25 mL) in ethanol (250 mL) was stirred under reflux for 2 h. The solution was concentrated (rotary evaporator) to afford a solid residue. This mixture was then separated by column chromatography (silica gel, hexane/ ethyl acetate gradient) into compounds **1** (5.57 g, 48%) and **6** (2.32g, 20%); m.p. 206-208 $^\circ\text{C}$ (hexane/ethyl acetate); IR (CHCl_3 film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3346, 3240, 1701, 1656; $^1\text{H-NMR}$: 10.3 (s, 1H, OH), 7.96 (d, $J=6.0\text{Hz}$, 1H, H3*), 6.97 (d, $J=6.0\text{Hz}$, 1H, H6*), 6.80 (dd, $J=6.0$, $J=1.8$ Hz, 1H, H4*), 6.52 (d, $J=2.5$ Hz, 1H, NH), 6.18 (d, $J=2.5$ Hz, 1H, H2), 4.20 (q, $J=9.4$ Hz, 2H, H10), 4.0 (q, $J=9.4$ Hz, 2H, H13), 2.51 (s, 3H, H7), 2.14 (s, 3H, H8), 1.28 (t, $J=9.4$ Hz, 3H, H14), 1.06 (t, $J=9.4$ Hz, 3H, H11); $^{13}\text{C-NMR}$: 167.2 (C=O, C9), 165.0 (C=O, C12), 163 (C5*), 154.5 (C6), 148.3 (C4), 139.8 (C2*), 138.5 (C3), 127.0 (C3*), 116.4 (C6*), 114.7 (C4*), 107.0 (C1*), 102.2 (C5), 59.0 (C13), 58.8 (C10), 50.2 (C2), 20.8 (C7), 18.6 (C8), 13.8 (C14), 13.4 (C11); M.S. IE m/z (%) = 390 (15, M^+), 373 (18), 345 (30), 299 (100).

Synthesis of 2,6-Dimethyl 4-(2-nitrophenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (2) + 4,6-Dimethyl 2-(2-nitrophenyl)-1,2-dihydropyridine-3,5-dicarboxylic acid diethyl ester (7) + 5,6-Dihydro-2,4-dimethyl-5-oxobenzo[c][2,7]naphthyridine-1-carboxylic acid ethyl ester (8) and 5,6-Dihydro-6-hydroxy-2,4-dimethyl-5-oxobenzo[c][2,7]naphthyridine-1-carboxylic acid ethyl ester (9).

A mixture of 2-nitrobenzaldehyde (10g, 0.066 mole), ethyl acetoacetate (17.2g, 0.122 mole) and 30% ammonium hydroxide (30mL) in ethanol (60 mL) was stirred under reflux for 2 h. The solution was concentrated (rotary evaporator) to afford a solid mixture. This mixture was then separated by column chromatography (silica gel, hexane/ethyl acetate gradient) into **2** [8] (8.6 g, 35%), **8** [9] (2.94 g, 15%), **9** [9] (4.1 g, 20%) and **7** (4.90g, 20%), m.p. 158-160 °C; IR (CHCl₃ film) $\nu_{\max}/\text{cm}^{-1}$: 3450 (NH), 1710 (C=O), 1650 (C=O); ¹H-NMR: 8.29-7.35 (m, Ar-H, 4H), 4.35 (q, J=7.4 Hz, 2H, H10), 4.09 (q, J=7.4 Hz, 2H, H9), 2.51 (s, 3H, H13), 2.21 (s, 3H, H14), 1.65 (s, 1H, NH), 1.35 (t, J=7.4 Hz, 3H, H11), 0.95 (t, J=7.4 Hz, 3H, H12); ¹³C-NMR: 166.3 (C=O, C7), 164.0 (C=O, C8), 122-140 (C-Ar), 62.0, (C2), 61.0 (C9, C10), 31 (C13), 27.2 (C14), 14.2 (C11), 13.4 (C12).

Reaction of 2,6-Dimethyl 4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (2) with Tin (II) Chloride in Hydrochloric Acid.

A solution of 1,4-dihydropyridine **2** (1.0 g, 0.0026 mol) in ethanol (25 mL) was added to a solution of tin (II) chloride (5.4 g, 0.018 mole) in 30% hydrochloric acid (7 mL) at 5 °C. The reaction was allowed to warm to room temperature and then heated to reflux for 5 h. The solution was neutralized with a 10% sodium bicarbonate solution and extracted with ethyl acetate (10 mL × 3). The organic layer was dried (anhydrous sodium sulfate), filtered, and concentrated to afford crude product, which was purified by recrystallization from ethyl acetate/hexane to give 3-(2-oxopropyl)-1H-indole-2-carboxylic acid ethyl ester (**17**) (0.21 g, 40%); m.p. 114-116 °C; IR (KBr pellet) $\nu_{\max}/\text{cm}^{-1}$: 3337 (N-H), 1724 (C=O), 1674 (C=O); ¹H-NMR: 8.92 (sbr, 1H, N-H), 7.6 (ddd, J= 1.0 Hz, J= 8.0 Hz, 1H, H7), 7.38-7.10 (m, 3H, H4,H5, H6), 4.40 (q, J= 14.2 Hz, 2H, H9), 4.21 (s, 2H, H11), 2.18 (s, 3H, CH₃), 1.41 (t, J= 14.2 Hz 3H, H10); ¹³C-NMR: 206.1 (C12), 161.8 (C8), 135.8 (Ca), 127.9 (Cb), 125.9 (C6), 124.2 (C2), 120.7 (C4), 120.5 (C5), 116.5 (C3), 111 (C7), 61.0 (C9), 40.3 (C11), 29.1 (C13), 14.2 (C10); MS *m/z* (%), 245 (50, M⁺), 202 (100) [M-C₂H₃O], 156 (90) [M-C₄H₉O₂]

Reaction of 2,6-Diethyl 4-(5-hydroxy-2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (1) with Tin (II) Chloride in Hydrochloric Acid.

A solution of 1,4-dihydropyridine **1** (1.0 g, 0.0025 mol) in ethanol (25 mL) was added to a solution of tin (II) chloride (5.4 g, 0.018 mole) in 30% hydrochloric acid (7mL) at 5 °C. The reaction was allowed to warm to room temperature, and then heated to reflux for 5 h.. The solution was neutralized with a 10% sodium bicarbonate solution and extracted with ethyl acetate (10 mL × 3). The organic

layer was dried (anhydrous sodium sulfate), filtered, and concentrated to afford crude product, which was purified by recrystallization from ethyl acetate/hexane to afford *3-(2-oxopropyl)-5-hydroxy-1H-indole-2-carboxylic acid ethyl ester* (**18**), m.p. 154-156 °C; yield 0.313 g (56 %). IR (KBr pellet) $\nu_{\max}/\text{cm}^{-1}$: 3550 (OH), 3337 (N-H), 1720 (C=O), 1680 (C=O); $^1\text{H-NMR}$: 8.92 (sbr, 1H, N-H), 7.6 (ddd, $J=1.0$ Hz, $J=8.0$ Hz, 1H, H7), 7.38-7.10 (m, 3H, H4, H5, H6), 4.40 (q, $J=14.2$ Hz, 2H, H9), 4.21 (s, 2H, H11), 2.18 (s, 3H, CH₃), 1.41 (t, $J=14.2$ Hz 3H, H10); $^{13}\text{C-NMR}$: 206.1 (C12), 161.8 (C8), 135.8 (Ca), 127.9 (Cb), 125.9 (C6), 124.2 (C2), 120.7 (C4), 120.5 (C5), 116.5 (C3), 111 (C7), 61.0 (C9), 40.3 (C11), 29.1 (C13), 14.2 (C10).

Reaction of 4,6-Dimethyl 2-(2-nitrophenyl)-1,2-dihydropyridine-3,5-dicarboxylic acid diethyl ester (7) with Tin (II) Chloride in Hydrochloric Acid.

A solution of 1,2-dihydropyridine **7** (1.0 g, 0.0026 mol) in ethanol (25 mL) was added to a solution of tin (II) chloride (5.4 g, 0.018 mole) in 30% hydrochloric acid (7 mL) at 5 °C. The reaction was allowed to warm to room temperature, and then heated to reflux for 5 h. The solution was neutralized with a 10% sodium bicarbonate solution and extracted with ethyl acetate (10 mL \times 3). The organic layer was dried (anhydrous sodium sulphate), filtered, and concentrated to afford crude product, which was purified by column chromatography and then recrystallized from ethyl acetate/hexane to give *2-methyl-quinoline-3-carboxylic acid ethyl ester* (**12**), m.p. 74-76 °C (lit [18, 19] 70-72 °C) and *6-hydroxy-2-methyl-oxyquinoline-3-carboxylic acid ethyl ester* (**19**), 0.3 g (54%); m.p. 98-100 °C; IR (KBr pellet) $\nu_{\max}/\text{cm}^{-1}$: 1716 (C=O); $^1\text{H-NMR}$: 8.8 (d, $J=1.2$ Hz, 1H, Hg), 8.26 (s, 1H, H4), 7.9-7.6 (m, 3H, H5, H6, H7), 4.45 (q, $J=14.1$ Hz, 2H, H11), 2.96 (s, 3H, H9), 1.46 (t, $J=14.1$ Hz, 3H, H12); $^{13}\text{C-NMR}$: 165.3 (C=O, C10), 146.3 (C2), 142.3 (Ca), 132.3 (C4), 129.0 (C6), 128.4 (C7), 127.6 (C5), 127.0 (C3), 126.0 (Cb), 119.9 (C8), 62 (C11), 15.8 (C9), 14.2 (C12); MS m/z (%), 231 (75, M⁺), 214 (15) [M-OH], 186 (100) [M-45].

Reaction of 2-(5-Hydroxy-2-nitrophenyl)-4,6-dimethyl-1,2-dihydropyridine-3,5-dicarboxylic acid diethyl ester (6) with Tin (II) Chloride in Hydrochloric Acid

A solution of 1,2-dihydropyridine **6** (1.0 g, 0.0025 mol) in ethanol (25 mL) was added to a solution of tin (II) chloride (5.4g, 0.018 mole) in 30% hydrochloric acid (7 mL) at 5 °C. The reaction was allowed to warm to room temperature, and then heated to reflux for 5 h.. The solution was neutralized with a 10% sodium bicarbonate solution and extracted with ethyl acetate (10 mL \times 3). The organic layer was dried (anhydrous sodium sulphate), filtered, and concentrated to afford crude product, which was purified by column chromatography and then by recrystallization from hexane/ethyl acetate to give *6-hydroxy-2-methylquinoline-3-carboxylic acid ethyl ester* (**20**), yield 0.35 g (60 %); m.p.153-155 °C; IR (KBr pellet) $\nu_{\max}/\text{cm}^{-1}$ = 3431, (OH), 1725 (C=O); $^1\text{H-NMR}$ (CDCl₃+DMSO): 9.56 (s, 1H, OH), 9.56 (s, 1H, H4), 7.8 (d, $J=9$ Hz, 1H, H8), 7.4 (dd, $J=2.7$ Hz, $J=9$ Hz, 1H, H7), 7.15 (d, $J=2.7$ Hz, 1H,

H5), 4.42, (q, J=14.3Hz, 2H, ester CH₂), 2.9 (s, 3H, CH₃- 2), 1.45 (t, J=14.3Hz, 3H, ester CH₃); ¹³C-NMR (CDCl₃ +DMSO): 166.1 (C=O, C10), 155 (C6), 154 (C2), 143 (Ca), 137.5 (C4), 128.9 (C8), 126.4 (C3), 123.7 (C7), 123.4 (Cb), 108.5 (C5), 60.6 (C10), 24.6 (C12), 13.7 (C11); MS *m/z* (%), 231 (100, M⁺), 216 [M-15] (4), 202 [M-C₂H₅] (20), 186 [M-OEt] (45).

References

1. Phillips, A.P., *J. Am. Chem. Soc.*, **1949**, *71*, 4003-4007.
2. Norcross, B.E. Clement, G., Weistein, M., *J. Chem. Educ.*, **1969**, *46*, 694-695.
3. Stout, D.M., Meyers, A.I., *Chem. Rev.*, **1982**, *82*, 223-243.
4. Katritzky, A.R., Ostercamp, D.L., Yousaf, T.I., *Tetrahedron*, **1987**, *43*, 5171- 5186, and references therein.
5. Martinez, R., Mendoza, H. M., Angeles. E., *Synth. Commun.*, **1998**, *28*, 2813-2820.
6. Angeles, E., Martínez, P., Keller, J., Martínez, R., Rubio, M., Ramírez, G., Castillo, R., López-Castañares, R., Jiménez. E., *J. Mol. Struct. (Theochem)*, **2000**, *504*, 141-170.
7. Lepetit, D., *Ber. Dtsch. Chem. Ges.*, **1887**, *20*, 789-791.
8. Hinkel, L.E., Ayling, E.E., Morgan, W.H., *J. Chem. Soc.*, **1931**, *133*, 1835-1857.
9. Kim, D.H., *J. Heterocycl. Chem.*, **1986**, *23*, 1471-1474
10. Dolle, F., Hinnen, F., Valette, H., Fuseau, C., Duval, R., Peglion, J., Crouzel, C. *Bioorg. Med. Chem.*, **1997**, *5*, 749-764.
11. Hernández-Gallegos, Z., Lehmann, P.A.F., Hong, E, Posadas, F and Hernández-Gallegos, E., *Eur. J. Med. Chem. Chim. Ther.*, **1995**, *30*, 355-364.
12. Patrick, G.L., Kinsman, O. S., *Eur. J. Med. Chem. Chim. Ther.*, **1996**, *31*, 615-624.
13. Menconi, I., Angeles, E., Martínez, L., Posada, M.E., Toscano, R.A., Martínez, R., *J. Heterocycl. Chem.*, **1995**, *32*, 831-833.
14. Buck, J.S., Ide, W.S., *Org. Synth., Coll. Vol II.*, **1943**, 130-133.
15. Ferry, C.W., Buck, J.S., Baltzly, R., *Org. Synth., Coll. Vol III*, **1955**, 239-241.
16. Woodward, R.B., *Org. Synth., Coll. Vol III*, **1955**, 453-455.
17. Hazard, R., Hurvois, J.P., Moinet, C., Tallec, A., Burgot, J.L., Eon-Burgot, G., *Electrochim. Acta*, **1991**, *46*, 1135-1141.
18. Friedlander, P., Gohring, C.F., *Ber. Dtsch. Chem. Ges.*, **1883**, *16*, 1883-1839
19. Bassett, A., Luheshi, N., Salem, S.M, Smalley, R.K., *Tetrahedron Lett.*, **1990**, *31*, 6561-6564.

Sample availability: Available from the authors.