Molecules **2006**, *11*, 726-730

molecules

ISSN 1420-3049
http://www.mdpi.org

Communication

Synthesis of New *N*-Quaternary-3-benzamidoquinuclidinium Salts

Renata Odzak [1,*] and Srdjanka Tomic [2]

[1] Department of Chemistry, Faculty of Natural Sciences, Mathematics and Education, University of Split, N. Tesle 12, 21 000 Split, Croatia
[2] Department of Chemistry, Faculty of Science, University of Zagreb, Horvatovac 102a, 10 000 Zagreb, Croatia; E-mail: stomic@chem.pmf.hr

* Author to whom correspondence should be addressed; E-Mail: rodzak@chem.pmf.hr

Received: 28 July 2006; in revised form: 30 August 2006 / Accepted: 21 September 2006 / Published: 28 September 2006

Abstract: The synthesis of racemic and enantiomerically pure *N*-*p*-methylbenzyl-3- and *N*-*p*-chlorobenzylbenzamidoquinuclidinium bromides (**6-8** and **9-11**, respectively) is described. These compounds were prepared from racemic or enantiomerically pure 3-benzamidoquinuclidines **3-5** using the appropriate quaternization reagents: *p*-methyl-benzyl bromide (**1**) and *p*-chlorobenzyl bromide (**2**).

Keywords: Quinuclidine, *N*-quaternary salts, quaternization

Introduction

Many natural and synthetic quinuclidine derivatives display a wide variety of biological activities and some of them, such as aceclidine, for example, are even commercially available as therapeutic agents [1]. 3-Substitued quinuclidine derivatives have also been shown to be potential antidotes against poisoning by organophosphorus compounds such as pesticides and chemical warfare agents [2-6]. Furthermore, 3-substituted derivatives of quinuclidine such as zacopride and RG 12915 are classical 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonists [7]. Since 3-substitued quinuclidines contain an asymmetric carbon atom, numerous investigations have concentrated on the resolution of the racemic compounds using chemical [8,9] and biocatalytical [10,11] methods, in order to provide an

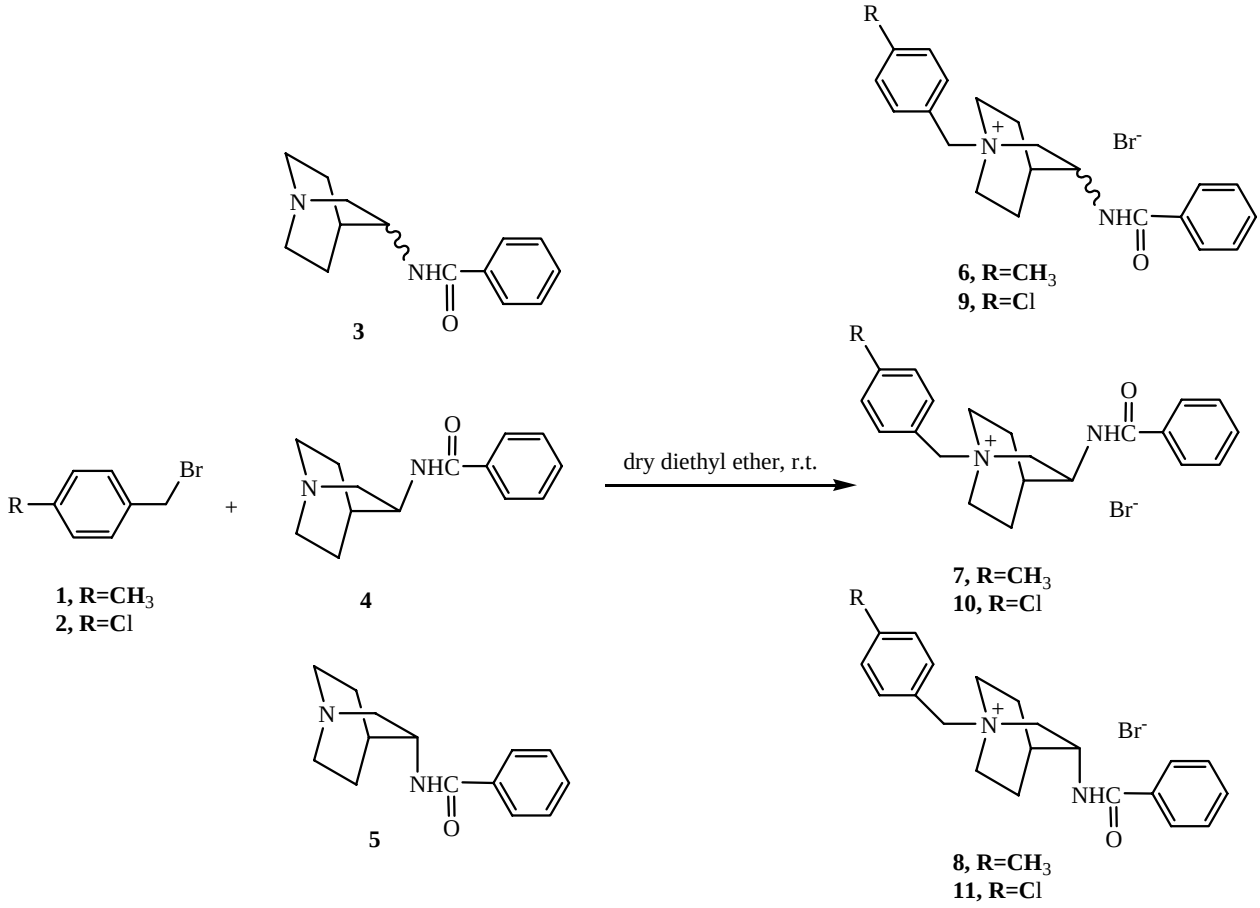
efficient, simple and inexpensive procedure. In our previous investigations we tested butyrylcholinesterase (BChE) as a possible biocatalyst in the resolution of racemic *N*-benzyl-3-benzamido- and *N*-benzyl-3-butanamidoquinuclidinium compounds. The expected resolution by hydrolysis of these amides did not occur, however, we discovered that these enantiomerically pure quaternary derivatives are good inhibitors of the tested enzyme. The best inhibitior of the enzyme was the (*S*)-enantiomer of *N*-benzyl-3-benzamidoquinuclidinum bromide, with a K_i = 3.70 ± 0.00 μM, while the corresponding (*R*)-enantiomer (with a K_i = 25.92 ± 0.01 μM) was a 7-fold weaker inhibitor than the (*S*)-enantiomer. Both enantiomers of quaternary 3-benzamidoquinuclidines were more potent inhibitors of BChE than enantiomers of quaternary 3-buatanamidoquinuclidines. The (*R*)-enantiomer of *N*-benzyl-3-butanamidoquinuclidinium bromide had a K_i value of 159.88 ± 0.47 and its (*S*)-enantiomer´s K_i was 241.96 ± 0.08 μM, showing that this compound was the weakest inhibitor, 65-fold weaker than the most potent one [12].

In continuation of these studies we present the synthesis of some new derivatives of *N*-quaternary-3-benzamidoquinuclidine with groups of different chemical and inductive characteristics (CH_3 and Cl) introduced at the 4-position of the benzyl ring.

Results and Discussion

Racemic and enantiomerically pure (*R*)- and (*S*)-3-benzamidoquinuclidines **3-5** have been synthesized by the reaction of the appropriate 3-aminoquinuclidine and benzoic acid anhydride [12]. Their quaternary salts **6-11** were prepared with *p*-methylbenzyl bromide and *p*-chlorobenzyl bromide as the respective quaternization agents (Scheme 1).

Scheme 1.



According to NMR spectroscopy the products were of satisfactory purity and therefore no further purification by recrystallization was necessary. The quaternary bromides were obtained in very good yields. ^{1}H- and ^{13}C-NMR signals of the quinuclidine moiety were completely in an accord with previous data [12]. The assignment of the aromatic benzyl ring ^{1}H- and ^{13}C-NMR signals was based on their chemical shifts and multiplicity (for the ^{1}H signals) and was unambiguously established with the aid of HETCOR data. The attributions of the aromatic ^{1}H-NMR chemical shifts are in full agreement with those previously reported for the *N*-benzyl-3-benzamidoquinuclidines [12] except that the signal of H-4 is missing due to *p*-substitution. On the other hand, the aromatic ^{13}C–signals are not in accord with the spectral data of *N*-benzyl-3-benzamidoquinuclidines [12]. The ^{13}C-chemical shifts of C-3, C-4 and C-5 atoms of the benzyl ring are displayed at higher values because the influence of *p*-substitution.

Experimental Section

General

Quaternization reagents were obtained from Sigma-Aldrich. Reactions were monitored by thin-layer chromatography using DC-Alufolien Aluminiumoxide 60 F_{254} (Merck) with 9:1 chloroform-methanol as the eluent. The detection of spots was achieved by UV light and by the reversible absorption of iodine. Melting points were determined in open capillaries using a Büchi B-540 apparatus and are uncorrected. Optical rotations (in degrees) were measured in chloroform on an Schmidt + Haensch Polartronic NH8 automatic polarimeter at ambient temperature. Elemental analyses were performed with a Perkin-Elmer PE 2400 Series II CHNS/O Analyser. FTIR spectra were recorded on a Bruker VECTOR 22 FT-IR spectrometer. All samples were prepared by mixing FTIR-grade KBr (Sigma-Aldrich) with 1% (w/w) salt and grinding to a fine powder. Spectra were recorded over the 400-4000 cm^{-1} range without baseline corrections. Charasteristic absorptions are given in cm^{-1}. ^{1}H and ^{13}C 1D and 2D (HETCOR) NMR spectra were recorded in $CDCl_3$ solutions on a Bruker AV500 spectrometer (300 MHz) at room temperature. Chemical shifts are reported as δ values in ppm using TMS as an internal standard. Coupling constants (*J*) are given in Hz.

General procedure for the synthesis of N-*quaternary quinuclidinium salts* **6**-**11**

To the solution of the appropriate 3-benzamidoquinuclidine (**3**-**5**, 0.22 mmol) in dry diethyl ether equimolar amounts of *p*-methylbenzyl bromide (**1**) were added at room temperature. The reaction mixture was kept in the dark overnight to obtain a solid. The excess of the solvent was then removed under reduced pressure and the solid was washed several times with dry diethyl ether to give compounds **6**-**8** as white crystals.

(±)-N-p-Methylbenzyl-3-benzamidoquinuclidinium bromide (**6**). Yield: 99%; mp: 244.2-245.6°C; IR: 3225, 2960, 1648, 1523, 1306, 716; ^{1}H-NMR δ: 1.75-2.16 (m, 4H, H-5 and H-8), 2.35 (m, 3H, CH_3), 2.44-2.56 (m, 1H, H-2), 3.39-3.45 (m, 4H, H-6 and H-7), 3.67-3.74 (m, 2H, H-2 and H-4), 4.54 (s, 2H, CH_2*Bnl*), 4.94-4.98 (m, 1H, H-3), 7.18-7.47 (m, 7H, H-2*Bnl*, H-3*Bnl*, H-5*Bnl* and H-6*Bnl*, H-3*Bz*, H-4*Bz* and H-5*Bz*), 8.22 (d, *J*=7.06, 2H, H-2*Bz* and H-6*Bz*), 8.80 (d, *J*=5.89, 1H, CONH); ^{13}C-NMR δ:

18.90 (C-5), 21.25 (CH_3), 22.44 (C-8), 25.08 (C-4), 46.12 (C-3), 52.93 (C-6), 54.62 (C-7), 57.63 (C-2), 67.39 (CH_2*Bnl*), 123.05 (C-1*Bnl*), 128.11 (C-3*Bz* and C-5*Bz*), 128.26 (C-2*Bnl* and C-6*Bnl*), 130.00 (C-2*Bz* and C-6*Bz*), 131.75 (C-4*Bz*), 132.80 (C-1*Bz*) 132.86 (C-3*Bnl* and C-5*Bnl*), 141.21 (C-4*Bnl*), 167.80 (C=O) Anal. calcd. for $C_{22}H_{27}BrN_2O$: C 63.61, H 6.55, N 6.74. Found: C 63.76, H 6.67, N 6.81.

(R)-N-p-Methylbenzyl-3-benzamidoquinuclidinium bromide (**7**). Yield: 99%; mp: 226.8-227°C; $[\alpha]_D^{25}$ -74° (c=0.41, $CHCl_3$). IR, ^{1}H- and ^{13}C-NMR were identical to those of **6**.

(S)-N-p-Methylbenzyl-3-benzamidoquinuclidinium bromide (**8**). Yield: 98%; mp: 231.4-232.4°C; $[\alpha]_D^{25}$ +76° (c=0.38, $CHCl_3$). IR, ^{1}H- and ^{13}C-NMR were identical to those of **6**.

The same reaction procedure as described for **6-8** was followed using *p*-chlorobenzyl bromide (**2**) as the other quaternization agent and the appropriate 3-benzamidoquinuclidines **3-5** to give compounds **9-11** as white crystals.

(±)-N-p-Chlorobenzyl-3-benzamidoquinuclidinium bromide (**9**). Yield: 99%; mp: 250.8-252.3°C; IR: 3224, 2961, 1646, 1523, 1485, 1305, 720; ^{1}H-NMR δ: 1.27-1.29 (m, 1H, H-5), 1.65-1.67 (m, 2H, H-8), 2.02-2.09 (m, 2H, H-4 and H-5), 3.01-3.25 (m, 2H, H-2), 3.27-3.61 (m, 4H, H-6 and H-7), 4.47 (s, 2H, CH_2*Bnl*), 4.60-4.84 (m, 1H, H-3), 7.35-7.55 (m, 7H, H-2*Bnl*, H-3*Bnl*, H-5*Bnl* and H-6*Bnl*, H-3*Bz*, H-4*Bz* and H-5*Bz*), 8.27 (d, *J*=6.95, 2H, H-2*Bz* and H-6*Bz*), 8.79 (d, *J*=5.72, 1H, CONH); ^{13}C-NMR δ: 18.90 (C-5), 22.48 (C-8), 24.82 (C-4), 46.16 (C-3), 53.62 (C-6), 54.89 (C-7), 57.76 (C-2), 66.89 (CH_2*Bnl*), 124.36 (C-1*Bnl*), 128.12 (C-3*Bz* and C-5*Bz*), 128.43 (C-2*Bnl* and C-6*Bnl*), 129.87 (C-2*Bz* and C-6*Bz*), 131.95 (C-4*Bz*), 132.54 (C-1*Bz*) 134.28 (C-3*Bnl* and C-5*Bnl*), 137.73 (C-4*Bnl*), 167.91 (C=O) Anal. calcd. for $C_{21}H_{24}BrN_2O$: C 57.88, H 5.55, N 6.43. Found: C 58.39, H 5.83, N 6.61.

(R)-N-p-Chlorobenzyl-3-benzamidoquinuclidinium bromide (**10**). Yield: 92%; mp: 239.7-241.9°C; $[\alpha]_D^{25}$ -40° (c=0.2, $CHCl_3$); IR, ^{1}H- and ^{13}C-NMR were identical to those of **9**.

(S)-N-p-Chlorobenzyl-3-benzamidoquinuclidinium bromide (**11**). Yield: 99%; mp: 242.3-244.7°C; $[\alpha]_D^{25}$ +40° (c=02, $CHCl_3$); IR, ^{1}H- and ^{13}C-NMR were identical to those of **9**.

Acknowledgements

This work was supported by the Ministry of Science, Education and Sports of the Republic of Croatia, Project No. 0119610.

References

1. Mashkovsky, M.D.; Yakhontov, L.N.; Kaminka, M.E.; Mikhlina, E.E. Further developments in research on the chemistry and pharmacology of synthetic quinuclidine derivatives. *Prog. Drug. Res.* **1983**, *27*, 9-61.

2. Sterling, G.H.; Doukas, P.H.; Sheldon, R.J.; O'Neill, J.J. *In vivo* protection against toxicity by known inhibitors of acetylcholine synthesis *in vitro*. *Biochem. Pharmacol.* **1988**, *37*, 379-384.
3. Sterling, G.H.; Doukas, P.H.; Jackson, C.; Caccese, R.; O'Neill, K.J.; O'Neill, J.J. 3-Carbamyl-*N*-alylquinuclidinium bromide. Effects on cholinergic activity and protection against soman. *Biochem. Pharmacol.* **1993**, *45*, 465-472.
4. Amitai, G.; Balderman, D.; Bruckstein-Davidovici, R.; Spiegelstein, M. *US Patent 4,675,326*, **1987**.
5. Amitai, G.; Rabinovitz, I.; Zomber, G.; Chen, R.; Cohen, G.; Adani, R.; Raveh, L.; *Proceedings of the 5th International Symposium On Protection Against Chemical and Biological Warfare Agents*; Stockholm, Defence Research Establishment, Umea, Sweden, **1995**, pp. 247-254.
6. Simeon-Rudolf, V.; Reiner, E.; Škrinjarić-Špoljar, M.; Radić, B.; Lucić, A.; Primožič, I.; Tomić, S. Quinuclidinium-imidazolium compounds: synthesis, mode of interaction with acetylcholinesterase and effect upon Soman intoxicated mice. *Arch. Toxicol.* **1998**, *72*, 289-295.
7. Langlois, M.; Soulier, J.L.; Allainmat, M.; Shen, S.; Gallais, C. Derivatives of quinuclidine as 5-HT3 receptor antagonists: Influence of an additional carbonyl group on the recognition of chirality by the receptor. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1555-1558.
8. Ringdahl, B.; Jope, R.S.; Jeden, D.J. Inhibition of high affinity choline transport by stereoisomers of some 3-quinuclidinol derivatives. *Biochem. Pharmacol.* **1984**, *33*, 2819-2822.
9. Sternbach, L.H.; Kaiser, S.; Antispasmodics. II. Esters of Basic Bicyclic Alcohols *J. Am. Chem. Soc.* **1952**, *74*, 2219-2221.
10. Kalir, A.; Sali, E.; Shirin, E. Preparation of (+)-3-quinuclidinol. *Isr. J. Chem.* **1971**, *9*, 267-268.
11. Rehavi, M.; Maayani, S.; Sokolovsky, M. Enzymatic resolution and cholinergic properties of (±) 3-quinuclidinol derivatives. *Life Sci.* **1977**, *21*, 1293-1302.
12. Odžak, R. Tomić, S. 3-Amidoquinuclidine derivatives: Synthesis of compounds and inhibition of butyrylcholinesterase. *Bioorg. Chem.* **2006**, *34*, 90-98.

Sample Availability: Samples of the compounds are available from authors.