PURIFICATION OF 3-ETHOXYCARBONYLQUINUCLIDINE AND ITS CONVERSION TO 3-QUINUCLIDINECARBOXYLIC ACID AND 3-QUINUCLIDINYLMETHANOL

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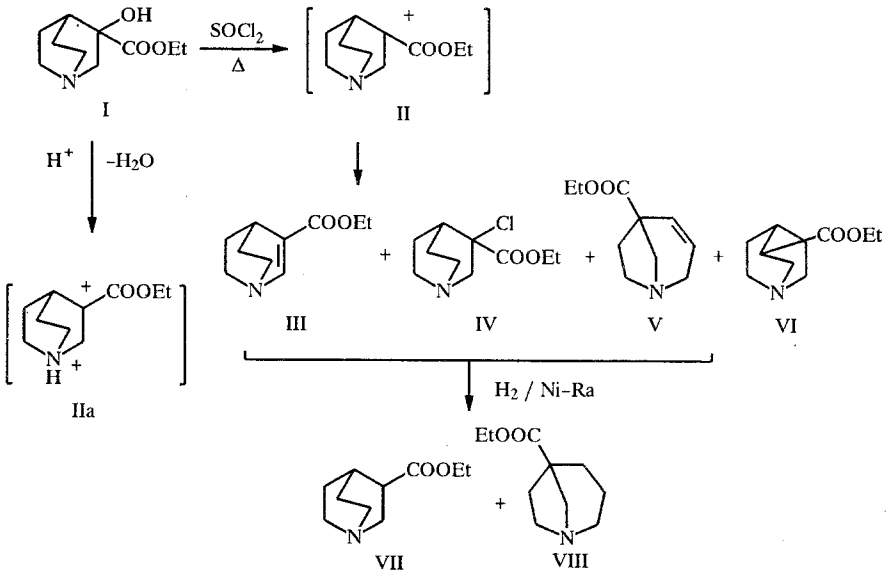
3-Ethoxycarbonylquinuclidine obtained by the Grob method is a mixture of 3-ethoxycarbonyl-1-azabicyclo-[2.2.2]- and, according to ^{13}C NMR data, 5-ethoxycarbonyl-5-azatricyclo[3.2.1.$0^{2,7}$]octanes (~16:2:1). 3-Ethoxy-carbonylquinuclidine was purified by recrystallization of the hydrochloride, hydrolyzed by water to 3-quinuclidinecarboxylic acid, and reduced by $LiAlH_4$ to 3-quinuclidinylmethanol.

Quinuclidine-3-carboxylates are the most widely used precursors for various derivatives at the $C^{(1)}$ atom (CH_2OH, CHO, COOH, CN, etc.) of 3-substituted quinuclidines [1-3] and starting compounds for synthesis of antiallergy drugs with reduced sedative effect: phencarol — diphenyl-3-quinuclidylmethanol; bicarphen — the corresponding di(o-tolyl) derivative [4]; Mequitazine — 10-(3-quinuclidylmethyl)phenothiazine [5-8], and the antiarrhythmic EO-122 — 2,6-xylidide of quinuclidine-3-carboxylic acid [9]. Practically the only method for synthesis of the above indicated esters is the Grob method, based on conversion of easily available 3-quinuclidone to cyanohydrin, alcoholysis of the CN group, dehydration of the hydroxyester, and subsequent hydration of the double bond [2, 10, 11].



Since the hydroxyester I is completely N-protonated in acid medium and its dehydration would occur through the energetically unfavorable dication IIa, the reaction of compound I with acid leads only to hydrolysis of the ester group [2] (for the same reason, 3-hydroxyquinuclidine is quantitatively oxidized by 98% sulfuric acid at room temperature to 3-quinuclidone

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[12], and is not dehydrated). The use of thionyl chloride makes it possible to avoid formation of the dication and to accomplish dehydration through the cation II.

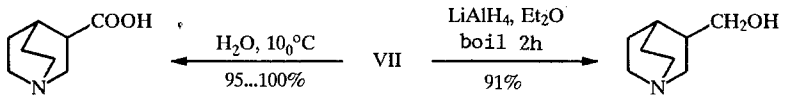
Earlier it was suggested that reaction of hydroxyester I with thionyl chloride leads to a mixture of Δ^2-dehydro-3-ethoxycarbonylquinuclidine (III) and the product of substitution of the hydroxy group by chlorine IV (1-5%), but recently 5-azatricyclo[3.2.1.$0^{2,7}$]octane-7-carboxylic acid was isolated from a commercial sample of VII [13]. Further investigations showed that in the ^{13}C NMR spectra of all the samples of VII obtained by the Grob method, in addition to the primary signal there are two additional partially overlapping sets of signals. The signal from the CH_2 groups with chemical shifts 14.9 (~5%) and 19.4 ppm (~15%) may be assigned to the $C^{(3)}$ atoms of compounds VI and VIII, the formation of which from cation II should be expected based on generally accepted ideas about the reactivity of carbocations (the 3-quinuclidinium cation obtained by action of Na on the tosylhydrazone of 3-quinuclidone gives a mixture of 5-azatricyclo[3.2.1.$0^{2,7}$]octane, quinuclidine, and Δ^2-dehydroquinuclidine, 12:2:1 [14]). Confirmation of the assignment made above comes from the retention in the ^{13}C spectrum of the "dehydrated" I signal at 14.9 ppm (~5%) and the appearance of two signals from olefin carbons at 123.4 and 132.5 ppm (~15%),* which does not contradict the values expected for the $C^{(3)}$ and $C^{(4)}$ atoms of V [15], which is the precursor of compound VIII.

Formation of compounds VI and VIII under relatively mild conditions is not only of theoretical interest (the reaction of 3-hydroxyquinuclidine with thionyl chloride, according to ^{13}C NMR data, leads only to 3-chloroquinuclidine) and evidence that the reaction occurs through cation II, but also is important from a practical standpoint. The physical properties of compounds VI, VII, and VIII are very similar; therefore they cannot be effectively separated by distillation, GLC, or HPLC or analyzed by these methods. The same is true for the series of derivatives obtained from the ester VII.

In the connection with the increasing interest in the pharmacology of derivatives of 3-substituted quinuclidine [16, 17, 20-24] and the significant dependence of the biological activity on the nature of the bicyclic amine [16, 17], we have developed a convenient method for purification of 3-ethoxycarbonylquinuclidine, its conversion to 3-quinuclidinecarboxylic acid and 3-quinuclidylmethanol, which up to the present time has been unknown in pure form. Since "3-quinuclidinecarboxylic acid" and its hydrochloride formed upon hydrolysis of the ester obtained by the Grob method are poorly purified even upon repeated recrystallization from water , aqueous or anhydrous methanol, ethanol and acetone, the mixture of the hydrochlorides of esters VI-VIII were recrystallized from acetone or ethanol with acetone.

The first crystallization reduces the content of compounds VI + VIII from ~20% to ~5%; the second recrystallization reduced this down to less than 1% (^{13}C NMR). The hydrochloride of VIII is slightly hygroscopic, but its aqueous solution is stable to hydrolysis (^1H NMR). At the same time, owing to the high basicity of the quinuclidine nucleus (pK_a 9.64 [18]), the ester VII is easily hydrolyzed by water to the acid IX. Thus, at 80°C in an initially 10% solution of compound VIII, after 30 min 40% of the starting ester remains; and after 90 min, 3% remains (^1H NMR). At 100°C for a 10% solution, the reaction goes to completion in 45 min (method A); for a 50% solution, in 3 h (method B). In all cases, the yield of acid is close to quantitative. Ester VII is completely miscible with water at room temperature, but its solubility decreases upon heating: A two-phase system is formed. In connection with the simplicity of the technique and the ease of scale-up, the proposed method is a good alternative to the chromatographic method descried in [13].

Reduction of the purified ester VII by lithium aluminum hydride gives the crystalline hygroscopic carbinol X (for hydride/ester ratio less than 1:1, the yield is substantially decreased). The oil described earlier in [2] undoubtedly contained the corresponding 1-azabicyclo[3.2.1]- and 5-azatricyclo[3.2.1.$0^{2,7}$]octylmethanols.



IX X

Thus, using thionyl chloride for dehydration of the hydroxyester I makes it possible to avoid formation of the energetically unfavorable dication IIa but not rearrangements of the monocation II, leading to a mixture of the related compounds III, V, and VI. Therefore, we must be careful when referring to published data on the physical [2, 3, 18, 19] and biological

*The ^{13}C NMR spectrum of III ($CDCl_3$, ppm relative to TMS) is: 14.2 (CH_3CH_2); 26.0 (4-C); 28.0 (5.8-C); 48.4 (6.7-C); 60.4 (CH_3CH_2); 140.3 (3-C); 152.7 (2-C), 164.6 (CO).

[15-24] properties of derivatives of quinuclidine and Δ^2-dehydroquinuclidine (especially those purified by distillation) obtained by the Grob method. At the present time, only we can reliably monitor their purity only by using ^{13}C NMR.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were taken on the Varian XL-200; the IR spectra were taken on the Perkin–Elmer 457; the mass spectra were taken on the Varian MAT-112 (EI, 70 eV, ions with greater than 10% intensity and m/z greater than 60 are given). The T_{mp} were not corrected. TLC in the system $CHCl_3$:MeOH:25% NH_4OH — 10:10:1 on Silufol plates, visualization by Dragendorff's reagent.

The elemental analysis data for C, H, and N correspond to the calculated values.

Purification of 3-Ethoxycarbonylquinuclidine (VII). A 1170 ml portion (6.36 moles) of a 5.4 N HCl solution in absolute ether was added to a solution of 1059 g (5.78 moles) commercial 3-ethoxycarbonylquinuclidine [10] in 3 liters anhydrous acetone at 10-15°C. The residue was filtered, washed with ether, and dried at 80°C (25 GPa). Yield, 830 g (65%); T_{mp} 145-146°C. Single TLC: R_f 0.9 (VI + VIII content, ~5%). The residue obtained (630 g) was crystallized from a mixture of 5 liters acetone and 150 ml 99.8% ethanol. Obtained: 415 g (66%) hydrochloride of VII, T_{mp} 162-163°C, purity 98.5% (^{13}C NMR). IR spectrum (Vaseline): 1715 (C=O), 2100-2700 (N–H), 3250-3500 cm^{-1} (N–H). ^1H NMR (CD_3OD): 1.29 (3H, t, CH_3); 1.80-2.10 (4H, m, 5-H, 8-H); 2.50 (1H, m, 4-H); 3.16 (1H, m, 3-H); 3.10-3.30 (4H, m, 6-H, 7-H), 3.45-3.65 (2H, m, 2-H), 4.24 ppm (2H, q, CH_2).

The base VII was obtained by addition of 130.5 g (0.94 moles) K_2CO_3 to a solution of 415 g (1.89 moles) of the hydrochloride in 500 ml water, cooled down to 5-10°C. This was extracted with 5 × 200 ml $CHCl_3$, dried with K_2CO_3. The solvent was driven off under vacuum. Vacuum distillation yields 329 g (95%) of a colorless liquid with T_{mp} 123-124°C (15 GPa); n_D^{20} 1.4780; d^{20} 1.0611. IR spectrum (film): 1725 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): 1.27 (3H, t, CH_3); 1.30-1.50 (4H, m, 5-H, 8-H); 2.1 (1H, m, 4-H); 2.52 (1H, m, 3-H); 2.57 (1H, m, 2a-H); 2.65-2.90 (4H, m, 6-H, 7-H); 2.99 (1H, m, 2b-H); 4.17 ppm (2H, q, CH_2). ^{13}C NMR ($CDCl_3$): 14.3 ($\underline{C}H_3CH_2$); 24.4 (4-C); 22.4, 26.9 (5-C, 8-C); 41.6 (3-C); 47.1, 47.2 (6-C, 7-C); 49.7 (2-C); 60.3 ($CH_3C\underline{H}_2$); 174.8 ppm (CO). Mass spectrum: m/z 183 (M^+).

Quinuclidine-3-carboxylic Acid* (IX). A. A 1.83 g portion (10 moles) of 3-ethoxycarbonylquinuclidine and 16.47 ml water were boiled in an open vessel for ~45 min. The second layer disappeared after a few minutes. TLC control: R_f VII — 0.9, VIII — 0.1, the mixture was evaporated into dryness under vacuum. The residue was washed with 2 × 10 ml benzene and dried at 100°C (25 GPa). Yield, 1.47 g (95%); T_{mp} 245-246°C (lit. value [12], 243-245°C). The acid obtained is sufficiently pure. IR spectrum (Vaseline): 1590 (C=O), 1800-2450 (COO^-), 3260, 3430, 3480 cm^{-1} (OH). ^1H NMR (D_2O, dioxane-d_8): 1.80-2.05 (4H, m, 5-H, 8-H); 2.43 (1H, m, 4-H); 2.83 (1H, m, 3-H); 3.20-3.35 (4H, m, 6-H, 7-H); 3.38 (1H, m, 2b-H); 3.68 ppm (1H, m, 2a-H). Mass spectrum, m/z (%): 155 M^+ (74), 254 (13), 140 (17), 125 (25), 110 (84), 96 (53), 95 (18), 83 (54), 82 (100), 69 (18), 68 (13).

B. A solution of 5.5 g (30 millimoles) of ester VII in 5.5 ml water was heated at 100°C until disappearance of the second layer (~3 h) and treated as described above. Yield, 4.65 g (quantitative), T_{mp} 242-244°C. Recrystallization from 9.5 ml 99.8% EtOH gives 4.01 g (95%) acid with T_{mp} 248-249°C.

3-Quinuclidylmethanol (X). A solution of 7.4 g (40 millimoles) compounds VII in 20 ml ether was added to a stirred solution of 3 g (79 millimoles) $LiAlH_4$ in 30 ml anhydrous ether. This was boiled for 2 h and decomposed by 1.57 ml water, 1.57 ml 15% NaOH and 4.71 ml water. The organic layer was decanted. The solid residue was extracted for 5 h with ether in a Soxhlet apparatus. The combined ether extracts were dried with K_2CO_3 and the ether was driven off. The residue was dried by azeotropic distillation with 3 × 20 ml benzene on a rotary evaporator. The oil obtained (5.55 g, 97%) was dissolved in an equal volume of ether and hexane. After a few minutes, exothermic crystallization was observed. The colorless residue was filtered off and dried at 30°C (2 GPa). Yield, 5 g (91%). T_{mp} 36-38°C. Since it was very hygroscopic, a satisfactory elemental analysis was not obtained. IR spectrum (Vaseline): 3000-350 (OH) cm^{-1}. ^1H NMR (D_2O, dioxane): 1.30-1.90 (5H, m, 3-H, 5-H, 8-H); 1.84 (1H, m, 4-H); 2.34 (1H, m, 2b-H); 2.70-2.90 (4H, m, 6-H, 7-H); 3.00 ppm (1H, m, 2a-H). ^{13}C NMR

*The ^{13}C NMR spectrum in D_2O of compound IX has been described earlier, but $CDCl_3$ was erroneously given as the solvent [12].

($CDCl_3$): 21.7 (4-C); 21.0, 27.6 (5-C, 8-C); 38.2 (3-C); 46.9, 47.4 (6-C, 7-C); 54.4 (2-C); 63.5 ppm (CH_2OH). Mass spectrum, m/z (%): 141 M^+ (78), 140 (11), 126 (14), 125 (11), 124 (M^+ — OH, 100), 113 (14), 112 (35), 111 (13), 110 ($C_7H_{12}N^+$, 53), 98 (13), 97 (23), 96 (30), 84 (11), 83 (21), 82 (74), 81 (12), 70 (25), 69 (18).

REFERENCES

1. L. N. Yachontov, Advances in Heterocyclic Chemistry, Academic Press, New York (1970), p. 473.
2. C. A. Grob and E. Renk, Helv. Chim. Acta, **37**, 1689 (1954).
3. C. A. Grob, A. Kaiser, and E. Renk. Helv. Chim. Acta, **40**, 2170 (1974).
4. M. D. Mashkovsky and L. N. Yachontov, Progress in Drug Research, E. Jucker (ed.), Birkhauser Verlag, Basel/Stuttgart (1969), Vol. 13, p. 293.
5. C. Gueremy, Ger. Pat. 2,009,555; Chem. Abstr., **13**: 131017 (1970).
6. Soregas, Fr. Pat. 2,117,750; Chem. Abstr., **78**: 976854 (1973).
7. Drugs Today, **15**, 193 (1979).
8. Drugs Future, **15**, 537 (1990).
9. E. Oppenheimer, E. Kaplinsky, and S. Cohen, US Pat. 4,146,628; Chem. Abstr., **89**: P146786v (1978).
10. J. Goütz, W. Orth, W. Weiss, D. E. Neckarhausen, and H. W. Kleffner, Ger. Pat. 3,827,117; Chem. Abstr., **119**: 6167 (1990).
11. L. N. Yakhontov and R. G. Glushkov, Synthetic Drugs [in Russian], Meditsina, Moscow (1983), p. 192.
12. L. N. Koikov and N. A. Alekseeva, Khim.-farm. Zh., No. 1, 67 (1991).
13. G. P. Zhikhareva, L. N. Yakhontov, M. F. Marshalkin, K. F. Turchin, E. F. Kuleshova, and Yu. N. Sheinker, Khim.-farm. Zh., No. 1, 32 (1991).
14. V. Georgian and W. H. Koster, Heterocycles, **7**, 1017 (1977).
15. R. Bussmann and A. Heesig, Chem. Ber., **120**, 1767 (1987).
16. J. Saunders, M. Cassidy, S. B. Freeman, E. A. Harley, L. L. Iversen, C. Kneen, A MacLeod, K. Merchant, R. J. Snow, and R. Baker, J. Med. Chem., **33**, 1128 (1990).
17. T. Rosen, A. A. Nagel, J. P. Rizzi, J. L. Ives, J. B. Daffeh, A. H. Ganong, K. Guarino, J. Heym, S. McLean, J. T. Nowakowski, A. W. Schmidt, T. F. Seeger, C. J. Siok, and L. A. Vincent, J. Med. Chem., **33**, 2715 (1990).
18. C. A. Grob, Helv. Chim. Acta, **68**, 882 (1985).
19. A. M. MacLeod and R. Herbert, J. Chem. Soc., Chem. Commun., No. 2, 100 (1990).
20. R. Baker, R. J. Snow, J. Saunders, and G. A. Showell, Eur. Pat. Appl. 3,071,471; Chem. Abstr., **111**: 153786 (1988).
21. A. M. MacLeod, R. Baker, S. B. Freedman, S. Patel, K. J. Merchant, M. Roe, and J. Saunders, J. Med. Chem., **33**, 2052 (1990).
22. L. Street, J. Backer, T. Book, C. O. Kneen, A. M. MacLeod, K. Merchant, G. F. Stowell, J. Saunders, R. H. Herbert, S. B. Freedman, and E. A. Harley, J. Med. Chem., **33**, 2690 (1990).
23. P. Sauerberg, J. W. Kindtler, L. Nielsen, M. J. Sheardown, and T. Honore, J. Med. Chem., **34**, 687 (1991).
24. G. A. Showell, T. L. Gibbons, C. O. Kneen, A. M. MacLeod, K. Merchant, J. Saunders, S. B. Freedman, S. Patel, and R. Baker, J. Med. Chem., **34**, 1086 (1991).