SYNTHESIS AND PROPERTIES OF N-OXIDES OF QUINUCLIDINE AND ITS DERIVATIVES

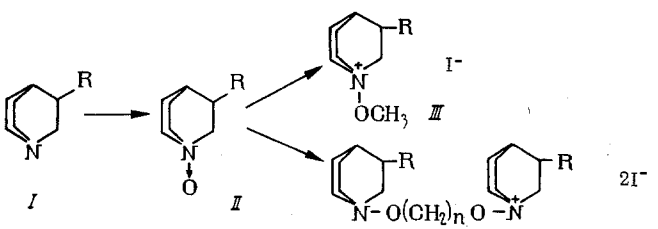
E. E. Mikhlina, V. Ya. Vorob'eva,
S. S. Bobyleva, and L. N. Yakhontov

UDC 547.834.4

Quinuclidine is a stable chemical compound [1-5]. N-Acylonium salts of quinuclidine N-oxide and their reaction to neutral, acidic, and basic hydrolysis are described [6]. We assigned ourselves the problem of synthesizing N-oxides of quinuclidine and its derivatives, to study the thermal stability, and also, considering that N-oxides of quinoxaline derivatives [7] have a significant antimicrobic activity, to investigate their bacteriostatic properties.

N-oxides of quinuclidine and its 3-substituted derivatives (II) were obtained by oxidation of bases (I) with a 25-30% solution of hydrogen peroxide at room temperature or with heating. Oxidation of quinuclidine (Ia) under these conditions does not go to completion. Subsequent extraction of the reaction products, which can be accomplished with chloroform only from concentrated solutions, led to conversion of unreacted (Ia) to its hydrochloride. To remove the latter, quinuclidine N-oxide (IIa) was converted to the picrate from which (IIa) was isolated by the usual method. Compound (IIa) was obtained in pure form only after sublimation in vacuum.

The tertiary amines (Ib-Id) reacted more completely with hydrogen peroxide and the isolation of their N-oxides did not present any difficulty. However, it was not possible to obtain 3-hydroxyquinuclidine N-oxide (IIe) upon oxidation of (Ie), evidently because of the difficulty of extracting it from water-base solutions. The N-oxide (IIe) was synthesized in high yield by oxidation of 3-acetoxyquinuclidine and subsequent hydrolysis of (IId) with hydrochloric acid:



Ia, IIa, IIIa: R=H

Ib, IIb, IIIb: $R=CH_2C_6H_5$; Ic, IIc, IIIc: $R=C_6H_5$

Id, IId: $R=OCOCH_3$, Ie, IIe: R=OH; *IVa:* R=H, n=6

IVb: $R=CH_2C_6H_5$, n=6; IVc: $R=CH_2C_6H_5$, n=9

Reaction of the N-oxides (IIa-IIc) with methyl iodide yielded the 1-methoxyquinuclidinium iodides (IIIa-IIIc), and reaction of (IIa) and (IIb) with α,ω-dihaloalkanes yielded the diquaternary salts (IVa-IVc).

The thermal stability of quinuclidine N-oxide was studied by heating this compound in dimethylformamide solution at 150°C and also without solvent up to 205-210°. Unchanged N-oxide (Ia) was recovered in the first case, and deoxygenation of the N-oxide occurred in the second case with sublimation of the quinuclidine formed. Cleavage of the quinuclidine molecule under these conditions was not observed.

In addition, it is known that pyrolysis of N-oxides of monocyclic amines is accompanied by a series of transformations: rearrangement with ring expansion, Cope rearrangement with formation of hydroxyl-

S. Ordzhonikidze All-Union Scientific Research Pharmaceutical Chemistry Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 3, pp. 15-19, March, 1969. Original article submitted October 23, 1968.

amine derivatives, deoxygenation. The character of the transformation is associated with the presence or absence of substituents in the α-position to nitrogen, their structure, and also with the ring size. The stability of N-oxides to pyrolysis has been observed in certain cases [8-10].

The results of our investigation indicate the thermal stability of quinuclidine N-oxide to ring opening, which is evidently associated with the high symmetry of the quinuclidine molecule.

S. N. Milovanova and A. L. Mikerin, having carried out a biological investigation of the N-oxides (II) and their derivatives (III) and (IV) under the direction of G. N. Pershin, associate member of the Academy of Medicinal Sciences of the USSR, showed that of all the compounds only (IVb) and (IVc) possess a weak germistatic activity in relation to the majority of the microorganisms examined.

EXPERIMENTAL

Quinuclidine N-Oxide (IIa). To 2 g (18 mmoles) of quinuclidine was added with ice-water cooling 5 ml of 30.8% hydrogen peroxide (45 mmoles) and the mixture was heated for 10 h at 60°. Next, 10 ml of water was added and the mixture was evaporated in vacuum. The operation was repeated two times. The residue was made basic with solid potassium carbonate and extracted repeatedly with chloroform; the chloroform solution was dried with potassium carbonate and evaporated in vacuum. The residue (2.2 g) was a mixture of quinuclidine N-oxide and quinucludine hydrochloride. For their separation, a solution of the mixture in 20 ml of ethanol was treated with an alcoholic solution of picric acid. Here 4.3 g of the picrate of quinuclidine N-oxide was separated. Mp 268-269°. Found, %: C 44.27; H 4.81; N 15.71. $C_7H_{13}NO \cdot C_6H_3N_3O_7$. Calculated, %: C 43.82, H 4.52; N 15.72.

We mixed 4.3 g of the picrate with 40 ml of concentrated hydrochloric acid; the picric acid was extracted with hot benzene, the hydrochloric acid solution was evaporated in vacuum, and the residue was made basic with solid potassium carbonate and extracted with chloroform. After distillation of the chloroform the residue was sublimated in vacuum (7 mm) at 180-182°. We obtained 0.95 g (41.5%) of (IIa) as colorless hygroscopic crystals, very soluble in water and organic solvents. Mp 229-231° (dec.). Found,%: C 65.60; H 10.17; N 10.64. $C_7H_{13}NO$. Calculated, %: C 66.10; H 10.32; N 11.01.

3-Benzylquinuclidine N-Oxide (IIb). To a solution of 9.65 g (48 mmoles) of 3-benzylquinucludine in 10 ml of methanol was added 14 ml of a 23.5% solution of hydrogen peroxide (97 mmoles) and the mixture was left for 48 h. The excess hydrogen peroxide was decomposed with sodium sulfite, the solution was evaporated in vacuum, and the residue was made basic with a 50% solution of sodium hydroxide and extracted with chloroform. Yield 6.55 g (52.8%). Colorless crystals, very soluble in water, alcohols, acetone, and insoluble in ether. Mp 86-88° (from a mixture of acetone and ether). Found, %: C 66.53; H 8.92; N 5.49; H_2O 14.82. $C_{14}H_{19}NO \cdot 2H_2O$. Calculated, %: C 66.37; H 9.15; N 5.54; H_2O 14.30.

Picrate has mp 166-167°. Found, %: C 54.46; H 4.94; N 12.22. $C_{14}H_{19}NO \cdot C_6H_3N_3O_7$. Calculated, %: C 53.81; H 4.96; N 12.55.

1-Methoxy-3-phenylquinuclidinium Iodide (IIIc). We maintained 2.45 g (13 mmoles) of 3-phenylquinuclidine (Ic), 2.9 g of a 30.8% solution of hydrogen peroxide (26 mmoles), and 3 ml of ethanol for 72 h. The reaction mixture was treated as in the preparation of (Ia). N-Oxide (IIc), obtained as a viscous noncrystallizing liquid, was subjected to methylation. For this, a mixture of (IIc), 2.84 g (20 mmoles) of methyl iodide, and 50 ml of acetone was heated for 6 h at 50-55°. The solution was evaporated, the residue was triturated with ether, and 1.9 g (42.2%) of (IIc) was obtained. Colorless crystals which are very soluble in ethanol, methanol, water, and insoluble in ethyl acetate, acetone, and ether. Mp 133-135° (from a mixture of ethanol and ethyl acetate). Found, %: I 37.07; N 4.12. $C_{14}H_{20}INO$. Calculated, %: I 36.77; N 4.06.

3-Acetoxyquinuclidine N-Oxide (IId). We maintained 2 g (12.8 mmoles) of 3-acetoxyquinuclidine, 1.8 ml of a 30.8% solution of hydrogen peroxide (16.4 mmoles), and 20 ml of glacial acetic acid for 120 h. The reaction mixture was treated as described above. After distillation of the chloroform the residue was triturated with petroleum ether. We obtained 0.4 g (18.3%) of (IId). Mp 138-140° (from acetone). Found,%: C 53.19; H 8.31; N 6.80. $C_{19}H_{15}NO_3 \cdot H_2O$. Calculated, %: C 53.18; H 8.43; N 6.90.

The low yield of N-oxide (IId) is due to hydrolysis of a portion of the material to the N-oxide (IIe) in the process of the reaction. Isolation of (IId) from the mixture with (IIe) is accompanied by significant losses of the former.

3-Hydroxyquinuclidine N-Oxide (IIe). We boiled 5.47 g (27 mmoles) of technical 3-acetoxyquinuclidine N-oxide and 40 ml of a 17% solution of hydrochloric acid for 3 h. The hydrochloric acid solution was decolorized with carbon and evaporated in vacuum. The residue was dried by periodic addition and distillation with benzene and dissolved in anhydrous ethanol; the alcohol solution was filtered, evaporated, and the obtained material was crystallized from a mixture of acetone and ethanol. We obtained 3.54 g (73%) of (IIe) hydrochloride. Colorless hygroscopic crystals, very soluble in water, alcohols and insoluble in ether, acetone. Mp 268-270° (dec.). Found, %: C 46.52; H 8.03; Cl 19.50; N 7.57. $C_7H_{13}NO_2 \cdot HCl$. Calculated, %: C 46.80; H 7.85; Cl 19.73; N 7.80.

Reduction of 3-Benzylquinuclidine N-Oxide. We shook 1 g (4 mmoles) of (IIb), 2 g of Raney nickel catalyst, and 30 ml of methanol with hydrogen. One mole of hydrogen was absorbed. The catalyst was filtered, the methanol solution was evaporated in vacuum, and the residue was distilled. We obtained 0.5 g (62.5%) of 3-benzylquinuclidine. Bp 105-106° (0. 5 mm) [11]. Found, %: C 82.93; H 9.32; N 6.89. $C_{14}H_{19}N$. Calculated, %: C 83.48; H 9.45; N 6.95.

Catalytic reduction of N-oxide (IIa) in the presence of platinum oxide yielded quinuclidine. Mp 154° [1].

1-Methoxyquinuclidinium Iodide (IIIa). A solution of 1 g (7.9 mmoles) of (IIa) and 1.34 g (9.4 mmoles) of methyl iodide in 8 ml of acetone was maintained for 48 h. The precipitated solid was filtered, washed with acetone, and recrystallized from a mixture of 10 ml of acetone and 2 ml of ethanol. Yield 1 g (47.4%). Colorless crystals, very soluble in water and alcohol, and insoluble in acetone, and ethyl acetate. Mp 140-141°. Found, %: I 47.05; N 5.28. $C_8H_{16}INO$. Calculated, %: I 47.14; N 5.20.

1-Methoxy-3-benzylquinuclidinium Iodide (IIIb). A solution of 1 g (4 mmoles) of (IIb) and 0.85 g (6 mmoles) of methyl iodide in 30 ml of acetone was heated for 6 h at 50-55°. The acetone was distilled in vacuum and the residue was triturated with a mixture of ethanol and ether. Yield 1.05 g (67.4%). Mp 149-151° (dec., from a mixture of ethanol and methanol). Found, %: I 34.9; N 4.04. $C_{15}H_{22}INO$. Calculated, %: I 35.22; N 3.90.

Hexamethylene-1,6-dioxy-di(quinuclidinium-1',1'-iodide) (IVa). We boiled 1 g (7.9 mmoles) of (IIa), 1 g (3.9 mmoles) of diiodohexane, and 4 ml of acetonitrile for 5 h. The mixture was evaporated under vacuum and the residue was triturated with acetone. Yield 0.95 g (47.5%). Mp 173-174° (from a mixture of acetone and ethanol). Found, %: I 42.44; N 4.93. $C_{20}H_{38}I_2N_2O_2$. Calculated, %: I 42.85; N 4.74.

Hexamethylene-1,6-dioxy-di(3'-benzylquinuclidinium-1',1'-iodide) (IVb). We boiled 1 g (4 mmoles) of (IIb), 0.67 g (2 mmoles) of 1,6-diiodohexane, and 30 ml of acetone for 5 h. We obtained 0.75 g (49.2%) of (IVb). Mp 148-150°. Found, %: I 32.70; N 3.71. $C_{34}H_{50}I_2N_2O_2$. Calculated, %: I 32.85; N 3.63.

Nonomethylene-1,9-dioxy-di(3'-benzylquinuclidinium-1',1'-iodide). We boiled 1 g (4 mmoles) of (IIb), 0.75 g (2 mmoles) of diiodononane, and 30 ml of acetone for 25 h. Yield 0.8 g (49.8%). Mp 144-146° (from alcohol). Found, %: I 31.50; N 3.36. $C_{37}H_{56}I_2N_2O_2$. Calculated, %: I 31.15; N 3.44.

Thermal Decomposition of Quinuclidine N-Oxide. We heated 0.6 g of quinuclidine N-oxide for 40 min in a flask fitted with a reflux condenser at 200-210° (bath). During this, 0.2 g (38%) of quinuclidine sublimed and settled on the walls of the condenser. Mp 156-157° [1]. Found, %: N 12.65. $C_7H_{13}N$. Calculated, %: N 12.59.

The remaining portion of the material was dissolved in 10 ml of water, and the aqueous solution was purified with carbon and evaporated in vacuum; the residue was dissolved in 5 ml of alcohol and treatment with picric acid yielded 0.22 g of the picrate of quinuclidine N-oxide. Mp 268-269°. Found, %: C 43.81; H 4.69; N 15.83. $C_7H_{13}NO \cdot C_6H_3N_3O_7$. Calculated, %: C 43.82; H 4.52; N 15.72.

CONCLUSION

It was shown that quinuclidine N-oxide, similarly to tertiary amines and quaternary salts of the quinuclidine series, displays thermal stability to ring opening and undergoes only deoxygenation upon pyrolysis.

LITERATURE CITED

1. I. Maisenheimer, Justus Liebigs Ann. Chem., 420, 190 (1920).
2. R. Lukes, Collect. Czech. Chem. Commun., 14, 655 (1949).

3. R. Lukes and I. Ernest, Ibid., 665.
4. T. Perrine, J. Org. Chem., 22, 1484 (1957).
5. V. Prelog and K. Balenovic, Chem. Ber., 74, 1508 (1941).
6. R. Huisgen and W. Kolbeck, Tetrahedron Lett., No. 12, 783 (1965).
7. E. N. Padeiskaya, A. S. Elina, G. N. Pershin, et al., Farmakol. Toksikol., No. 5, 617 (1966).
8. L. D. Quin and G. L. Roof, J. Org. Chem., 27, 4451 (1962).
9. L. D. Quin and F. A. Schelburne, Ibid., 30, 3135 (1965).
10. W. Carruthers and R. Johnstone, J. Chem. Soc., 1653 (1965).
11. E. E. Mikhlina, V. Ya. Vorob'eva, and M. V. Rubtsov, Zh. Organ. Khim., 31, 2609 (1961).