HETEROCYCLIC α-AMINONITRILES AND THEIR PROPERTIES

The Synthesis and Reactions of 3-Cyano-3-tert-aminoquinuclidines

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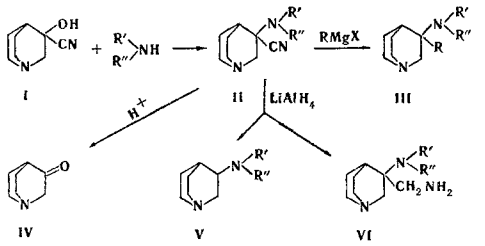
The conditions for the formation of 3-cyano-3-tert-aminoquinuclidines (II) from quinuclidine-3-one cyanohydrin and secondary amines are investigated. It is shown that the reaction of (II) with organomagnesium compounds gives 3-alkyl-3-tert-aminoquinuclidines (III), and reduction of II with lithium aluminohydride provides 3-tert-aminoquinuclidines (V), 3-aminomethyl-3-tert-aminoquinuclidines (VI), or a mixture of the two. Acid hydrolysis of II yields quinuclidine-3-one.

The synthesis and systematic investigation of the properties of heterocyclic α-aminonitriles have not been widely investigated [1–4]. No investigations have yet been carried out in the 1-azabicycloalkanes of this type. Among these, α-aminonitriles are of interest for conversion into alkyl(aryl)-tert-amino derivatives, which are difficult of access by other methods.

In this paper, the reaction of quinuclidine-3-one cyanohydrin (I) with secondary amines is examined with a view to the synthesis of 3-cyano-3-tert-aminoquinuclidines (II), and from these, 3-alkyl-3-tert-aminoquinuclidines.



II R′+R″= a $(CH_2)_5$; b $(CH_2)_4$; c $(CH_2)_4O$; d R′=R″=CH_3; e R′=R″=C_2H_5
III R′+R″= a $(CH_2)_5$; b $(CH_2)_4$; c $(CH_2)_4O$; d R′=R″=CH_3 where R=CH_3;
e $(CH_2)_5$; f $(CH_2)_4$; g $(CH_2)_4O$ where R=$CH_2C_6H_5$;
V, VI R′+R″= a $(CH_2)_4O$; b $(CH_2)_5$

The reaction of the cyanohydrin I with secondary amines proceeds in methanol at room temperature, or in benzene with azeotropic removal of water. In all cases save that of pyrrolidine, reaction of I with an insufficient excess of secondary amine led to the simultaneous formation of quinuclidine-3-one. The latter apparently results from dehydrocyanation under the reaction conditions.

We also observed the unusual ease of formation of quinuclidiene-3-one during the attempted hydrolysis and alcoholysis of the α-aminonitriles II in order to obtain the 3-tert-aminoquinuclidine-3-carboxylic acid or its ester. 3-Cyano-3-(N-pyrrolidino)quinuclidine (IIb) is converted into quinuclidine-3-one by hydrochloric acid even at room temperature, and the rate is considerably increased on warming. A similar process occurs during alcoholysis of the α-aminonitriles II, and on brief heating with 90% H_2SO_4 at 100° C.

According to the literature [5], alcoholysis, as well as acid and alkaline hydrolysis of α-aminonitriles, usually gives poor yields, or fails to give the desired products. Only when α-aminonitriles of N-alkylpiperidine were heated in 90% H_2SO_4 were good yields of the α-amino acid amides obtained [1]. However, no case of the formation of a ketone by hydrolysis of an α-aminonitrile was noted during a survey of the literature. The conversion of 3-cyano-3-tert-aminoquinuclidines (II) into quinuclidine-3-one appears to result from the ease of dehydrocyanation of II in acid solution The resulting 3-tert-amino-Δ^2-dehydroquinuclidines are further hydrolyzed to quinclidine-3-one.

In addition to the investigation of the behavior of the α-aminonitriles II on acid hydrolysis, the reaction of these compounds with Grignard reagents and with lithium aluminum hydride has also been examined. It is known that

α-aminonitriles can react with these reagents in two ways, leading either to the replacement of the cyano group by alkyl or aralkyl residues or by hydrogen, or to conversion of the cyano group to carbonyl or aminomethyl respectively [2, 4, 6, 7].

Reaction of the α-aminonitriles II with methylmagnesium iodide and benzylmagnesium chloride results only in the replacement of the nitrile group by methyl or benzyl, giving 3-alkyl-3-tert-aminoquinuclidines (III). Reaction of IIb with methyl lithium does not go to completion (either with direct or reverse order of addition of the reactants), about 50% of the starting nitrile IIb being recovered, together with 3-methyl-3-(N-pyrrolidyl)quinuclidine (IIIb). No products of the reaction of methyl lithium with the nitrile group of IIb were obtained, although reactions of organolithium compounds with α-aminonitriles usually occur at the nitrile group with the formation of ketones [2, 8].

Reduction of the α-aminonitriles II with lithium aluminum hydride leads, according to the nature of the tert-amino group in II, either to the fission of the $>$C—CN bond with the formation of 3-tert-aminoquinuclidines (V), or to reduction of the nitrile group to aminomethyl (VI). In one case (IIa), the reaction follows both paths, giving a mixture of amines (Vb and VIb), the boiling points of which were too close to permit their separation by distillation. The mixture was separated by converting VIb into its benzoyl derivative, from which the amine was regenerated by hydrolysis.

Pharmacological examination of the 3-alkyl-3-tert-amino-quinuclidines did not reveal any compounds with a high level of activity. (The pharmacological evaluation was carried out in the pharmacology section of the All-Union Scientific-Research Chemicopharmaceutical Institute, by scientific assistant K. A. Zaitseva, under the direction of corr. member of the Academy of Medical Sciences of the USSR, Prof. M. D. Mashkovskii).

EXPERIMENTAL

3-Cyano-3-(N-pyrrolidyl)quinuclidine (IIb). A solution of 6.7 g (53 mM) of quinuclidine-3-one cyanohydrin (I) and 4 g (56.5 mM) pyrrolidine in 100 ml of methanol was kept at room temperature for 5 days. The reaction mixture was evaporated in vacuo, and the residue distilled to give 8.4 g (93%) of IIb as a mobile, colorless liquid, readily soluble in organic solvents and sparingly soluble in water. Bp 127–128° C (1 mm). Found, %: C 70.25; H 9.40; N 20.42 . Calculated form $C_{12}H_{19}N_3$, %: C 70.20; H 9.33; N 20.42.

3-Cyano-3-dimethylaminoquinuclidine (IId). Ten grams (66 mM) of quinuclidine-3-one cyanohydrin (I) was dissolved in 150 ml of methanol containing 70 g (1.55 mole) of dimethylamine, and the mixture treated as described above. After removal of the solvent, 0.4 g of quinuclidine-3-one distilled first, followed by 10.8 g (91.7%) of IId, bp 138–140° C (20 mm), mp 61° C (from ethyl acetate). Found, %: C 67.05; H 9.33; N 23.09. Calculated for $C_{10}H_{17}N_3$, %: 67.00; H 9.54; N 23.00.

3-Cyano-3-diethylaminoquinuclidine (IIe). A) From 15.2 g (0.1 mole) of I, 9 g (0.123 mole) of diethylamine and 300 ml of methanol, after keeping at 20° C for 5 days, there was obtained 6.7 g of I, 2.9 g of quinuclidine-3-one, and 4.75 g (23.3%) of IIe, bp 140–141° C (10 mm). Found, %: C 69.03; H 9.78; N 19.98. Calculated for $C_{12}H_{21}N_3$, %: C 69.52; H 10.21; N 20.27.

B) From 3 g (0.02 mole) of I, and 20 ml (0.195 mole) of diethylamine in 45 ml of methanol, there was obtained, after keeping for 10 days, 3.8 g (93%) of IIe.

3-Cyano-3-(N-morpholyl)quinuclidine (IIc). A) 30 g (0.197 mole) of I, 60 ml (0.6 mole) of morpholine, and 120 ml of benzene were heated in a Dean and Stark apparatus until no more water separated. The reaction mixture was evaporated in vacuo, and the residue distilled at 20 mm to give 5.7 g of quinuclidine-3-one. The resulting solid mixture was triturated with acetone, and 29.3 g (67%) of IIc filtered off. Colorless crystals, readily soluble in acetone and alcohol, but sparingly so in ethyl acetate, and insoluble in water, mp 107–109° C (from ethyl acetate). Found, %: C 65.34; H 8.81; N 19.05. Calculated for $C_{12}H_{19}N_3O$, %: 65.13; H 8.67; N 18.98.

B) From 3 g (19.7 mM) of I, 20 ml (0.18 mole) of morpholine, and 45 ml of methanol, after standing at room temperature for 15 days, there was obtained 3.9 g (91.5%) of IIc.

3-Cyano-3-(N-piperidyl)quinuclidine (IIa). A) Thirty grams (0.197 mole) of I, 40 ml (0.4 mole) of piperidine and 300 ml of benzene were reacted as described for IIc, method (A), giving 5.75 g of quinuclidine-3-one and 28.3 g (65.4%) of IIa as a colorless liquid, readily soluble in water and organic solvents, bp 140–142° C (1 mm). Found, %: C 71.10; H 9.70; N 18.96. Calculated for $C_{13}H_{21}N_3$, %: C 71.19; H 9.66; N 19.15.

B) From 3 g (19.7 mM) of I, 20 ml (0.2 mole) of piperidine and 45 ml of methanol, after 15 days at 20°C, there was obtained 4 g (93.5%) of **IIa**.

3-Methyl-3-(N-piperidyl)quinuclidine (IIIa). To a solution of methylmagnesium iodide, prepared from 1.48 g (0.06 mole) of magnesium and 7.3 g (51.4 mM) of methyl iodide in 120 ml of dry ether, was added with stirring at 0–5° C a solution of 4.4 g (0.02 mole) of 3-cyano-3-(N-piperidyl)quinuclidine (**IIa**) in 100 ml of ether. The reaction mixture was kept at room temperature for 24 hr, then boiled for 6 hr, cooled, and treated successively with 20 ml of water and 15 ml of conc HCl. The hydrochloric acid solution was basified with 50% potassium hydroxide solution, and extracted with ether to give 3.8 g (89%) of **IIIa** as a colorless, mobile liquid, readily soluble in organic solvents and in water, bp 107–109° C (1 mm). Found, %: C 74.88; H 11.31; N 13.23. Calculated for $C_{13}H_{24}N_2$, %: C 74.94; H 11.61; N 13.44. Dihydrochloride, colorless crystals, mp 260–262° C. Found, %: Cl 25.31; N 9.89. Calculated for $C_{13}H_{24}N_2$, %: Cl 25.23; N 9.96.

The following 3-alkyl-3-tert-aminoquinuclidines (**III**) were obtained similarly:

A) **3-Methyl-3-(N-pyrrolidyl)quinuclidine (IIIb),** bp 82–84° C (1 mm), yield 73%. Found, %: C 74.29; H 11.07; N 14.30. Calculated for $C_{12}H_{22}N_2$, %: C 74.16; H 11.37; N 14.47. Dihydrochloride, mp 268–270° C. Found, %: Cl 26.20; N 10.21. Calculated for $C_{12}H_{22}N_2 \cdot 2HCl$, %: Cl 26.57; N 10.48.

B) **3-Methyl-3-(N-morpholyl)quinuclidine (IIIc),** bp 114–116° C (1 mm), yield 65.6%. Found, %: C 68.80; H 10.50; N 13.32. Calculated for $C_{12}H_{22}N_2O$, %: C 68.53; H 10.54; N 13.32. Dihydrochloride, mp 255–257° C. Found, %: Cl 24.73; N 9.86. Calculated for $C_{12}H_{22}N_2O \cdot 2HCl$, %: Cl 25.03; N 9.89.

C) **3-Methyl-3-dimethylaminoquinuclidine (IIId),** bp 115–117° C (20 mm), yield 44.5%. Found, %: C 70.92; H 11.78; N 16.93. Calculated for $C_{10}H_{20}N_2$, %: C 71.37; H 11.96; N 16.67.

D) **3-Benzyl-3-(N-piperidyl)quinuclidine (IIIe),** mp 95–96° C (from ether), yield 79%. Found, %: C 80.05; H 9.95; N 9.62. Calculated for $C_{19}H_{28}N_2$, %: C 80.23; H 9.93; N 9.85. Dihydrochloride, mp 258–260° C. Found, %: Cl 20.08; N 7.74. Calculated for $C_{19}H_{28}N_2 \cdot 2HCl$, %: Cl 19.88; N 7.88.

E) **3-Benzyl-3-(N-pyrrolidyl)quinuclidine (IIIf),** bp 178° C (1 mm), yield 86.3%. Found, %: C 78.79; H 9.50; N 9.77. Calculated for $C_{18}H_{26}N_2$, %: C 79.95; H 9.69; N 10.36.

F) **3-Benzyl-3-(N-moroholyl)quinuclidine (IIIg),** mp 95–96° C (from ethyl acetate), yield 83%. Found, %: C 75.15; H 9.08; N 9.92. Calculated for $C_{18}H_{26}N_2O$, %: C 75.15; H 9.09; N 9.79. Dihydrochloride, mp 250–252° C. Found, %: Cl 19.95; N 7.83. Calculated for $C_{18}H_{26}N_2O \cdot 2HCl$, %: Cl 19.73; N 7.78.

3-(N-Pyrrolidyl)quinuclidine (Va). To a suspension of 5 g (0.13 mole) of lithium aluminum hydride in 100 ml of dry ether was added at −5° a solution of 5 g (24.4 mM) of 3-cyano-3-(N-pyrrolidyl)quinuclidine (**IIb**) in 50 ml of ether. The reaction mixture was stirred at room temperature for 20 hr, then 10 ml of water was added, and the reaction product extracted with benzene, giving 3.7 g (84.2%) of **Va** as a colorless, mobile liquid, soluble in organic solvents and water, with bp 96–96.5° C (1 mm). Found, %: C 73.05; H 11.21; N 15.65. Calculated for $C_{11}H_{20}N_2$, %: C 73.28; H 11.18; N 15.53. Salicylate, mp 109–111° C. Found, %: C 65.85; H 7.20; N 6.25. Calculated for $C_{11}H_{20}N_2 \cdot C_7H_6O_3$, %: C 65.59; H 6.94; N 6.43.

3-Aminomethyl-3-(N-morpholyl)quinuclidine (VIa). Five grams (22.6 mM) of 3-cyano-3-(N-morpholyl)quinuclidine (**IIc**) was reduced with 5 g (0.13 mole) of lithium aluminum hydride by the method described above, to afford 3.65 g (71.5%) of **VIa** as a colorless liquid, bp 149–150° C (0.6 mm). Found, %: C 63.57; H 10.54; N 18.47. Calculated for $C_{12}H_{23}N_3O$, %: C 63.96; H 10.29; N 18.64.

Reaction of 3-cyano-3-(N-piperidyl)quinuclidine with lithium aluminum hydride. Five grams (22.8 mM) of 3-cyano-3-(N-piperidyl)quinuclidine (**IIa**) was reduced with 5 g (0.13 mole) of lithium aluminum hydride as described above. There was obtained 4.15 g of colorless liquid, bp 115–140° C (15 mm), which was a mixture of 3-(N-piperidyl)quinuclidine (**Vb**) and 3-aminomethyl-3-(N-piperidyl)quinuclidine (**VIb**).

This mixture was separated as follows. To 3.5 g of the mixture was added a solution of 0.73 g of sodium hydroxide in 20 ml of water, the mixture cooled to 0° C, and 2.5 g of benzoyl chloride added at 0–5° C during 15 min. The mixture was stirred for 30 min and extracted with benzene. The benzene was distilled in vacuo, the residue triturated with ether, the solid filtered off and washed carefully with ether, giving 1.5 g of 3-benzoylaminomethyl-3-(N-piperidyl)-quinuclidine (**VII**) as colorless crystals, readily soluble in alcohol, acetone and benzene, sparingly soluble in ethyl

acetate, and insoluble in ether. Mp 140–141° C (from ethyl acetate). Found, %: C 73.64; H 9.14; N 12.51. Calculated for $C_{20}H_{29}N_3O$, %: 73.35; H 8.92; N 12.83.

The ether mother liquors, after removal of VII, were evaporated in vacuo, and the residue distilled giving 1 g of Vb as a colorless, mobile liquid, readily soluble in water and organic solvents, bp 89–90° C (0.2 mm). Found, %: 73.95; H 11.20. Calculated for $C_{12}H_{22}N_2$, %: C 74.17; H 11.41.

No band was observed in the IR spectrum in the region of the NH_2 group.

3-Aminomethyl-3-(N-piperidyl)quinuclidine (VIb). 3.1 g (9.5 mM) of 3-benzoylaminomethyl-3-(N-piperidyl)quinuclidine and 30 ml of 17% HCl were heated in a sealed tube at 180° C for 20 hr. The hydrochloric acid solution was evaporated in vacuo, and the residue basified with 50% potassium carbonate solution, and extracted with benzene to give 1.2 g (57%) of the amine VIb, bp 194–196° C (22 mm). Found, %: C 70.10; H 11.16; N 18.71. Calculated for $C_{13}H_{25}N_3$, %: C 69.86; H 11.28; N 18.81.

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