SYNTHESIS OF 4-AMINOQUINUCLIDINE AND ITS DERIVATIVES

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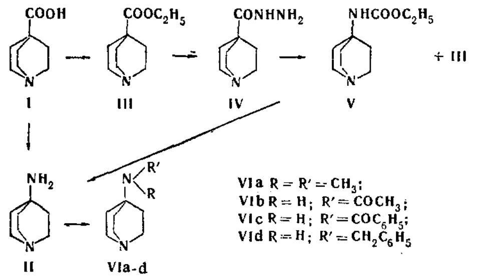
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 2, pp. 278–280, 1969

UDC 547.834.4.07

Two methods for preparing 4-aminoquinuclidine from quinuclidine-4-carboxylic acid have been developed. Acyl and alkyl derivatives of 4-aminoquinuclidine have been synthesized.

We have previously developed a method for obtaining 2-alkoxycarbonylamino quinuclidines (urethanes of the quinuclidine series) [1] and various methods for synthesizing 3-aminoquinuclidine and its derivatives [2] and have studied the properties of these compounds. In this paper we describe two methods for obtaining the previously unknown 4-aminoquinuclidine from quinuclidine-4-carboxylic acid [3]: the Schmidt and the Curtius reactions.



To carry out the Schmidt reaction, acid I was subjected to the action of sodium azide in the presence of concentrated sulfuric acid. The yield of 4-aminoquinuclidine was 18.5%. The bulk of the acid I was recovered unchanged. Varying the reaction conditions did not lead to an increase in the yield of the amine II.

Considerably better results were obtained by using the Curtius reaction. The starting material was the hydrazide of quinuclidine-4-carboxylic acid (IV), which was obtained by heating ethyl quinuclidine-4-carboxylate (III) with a large excess of hydrazine hydrate at 95–100° C. The use of a small excess of hydrazine hydrate (2.5–3 moles) and also the performance of the process at 110–120° C led to the formation of 1,2-bis(quinuclidin-4'-carbonyl) hydrazine. The hydrazide IV was then converted into the dihydrochloride, the reaction of which with isoamyl nitrite in ethanolic solution took place ambiguously; in addition to 4-ethoxycarbonylaminoquinuclidine (V) (70%), ethyl quinuclidine-4-carboxylate (III) (26.4%) was formed, these compounds being isolated in the form of the hydrochlorides. When the urethane V was boiled with hydrochloric acid, the dihydrochloride of 4-aminoquinuclidine (II) was obtained. The over-all yield of the amine II by this method was 60–62% calculated on the acid I.

The hydrazide of quinuclidine-2-carboxylic acid reacts with isoamyl nitrite similarly: in addition to 2-alkoxycarbonylaminoquinuclidine esters of quinuclidine-2-carboxylic acid are formed [1]. However, the hydrolysis of 2-ethoxycarbonylaminoquinuclidine, unlike that of 4-ethoxycarbonylaminoquinuclidine, is accompanied by the splitting out of ammonia with the formation of a polymeric compound, which is probably due to the instability of the 2-aminoquinuclidine arising.

4-Aminoquinuclidine (II) is a rather volatile crystalline substance that readily absorbs moisture and carbon dioxide from the air. It exhibits the general properties of a primary aliphatic amine; it is readily alkylated and acylated, and the reduction of the 4-acylaminoquinuclidines forms the corresponding 4-alkylaminoquinuclidines.

EXPERIMENTAL

Reaction of quinuclidine-4-carboxylic acid with hydrazoic acid. A mixture of 2.6 g (14.3 mM) of quinuclidine-4-carboxylic acid hydrochloride [3], 6.5 ml of concentrated sulfuric acid, and 10 ml of anhydrous benzene was heated to 40° C. At this temperature, 1.06 g (16.3 mM) of sodium azide was added over 2 hr. The mixture was stirred at 40° C for 3 hr 30 min and at the boil for 2 hr. The cooled mass was poured onto ice and the resulting mixture was made alkaline with 50% caustic soda solution and extracted with chloroform. The chloroform solution was extracted with 17% hydrochloric acid; the hydrochloric acid extract was evaporated in vacuum, and the residue was triturated with acetone. This gave 0.53 g (18.5%) of 4-aminoquinuclidine dihydrochloride, mp above 360° C. Found, %: C 42.02; H 8.29; Cl 35.92; N 13.78. Calculated for ($C_7H_{14}N_2 \cdot 2HCl$), %: C 42.21; H 8.10; Cl 35.65; N 14.05.

Quinuclidine-4-carboxylic acid hydrazide (IV). A mixture of 8.73 g of III (47.7 mM) and 100 ml of hydrazine hydrate was heated at 95–100° C for 10 hr. The reaction mixture was evaporated in vacuum and the residue was triturated with ether. The yield of hydrazide was 7.8 g (96.5%), in the form of colorless crystals, mp 190–193° C. Found, %: (C 56.11; H 8.95; N 24.48). Calculated for ($C_8H_{15}N_3O$), %: C 56.64; H 8.93; N 24.80. **Dihydrochloride**—mp 263–264° C (decomp.). Found, %: C 39.80; H 7.10; Cl 29.47. Calculated for ($C_8H_{15}N_3O \cdot 2HCl$), %: C 39.68; H 7.07; Cl 29.28.

Reaction of quinuclidine-4-carboxylic acid hydrazide (IV) with isoamyl nitrite. Over 40 min, with stirring and ice cooling, 8.28 g (70.6 mM) of isoamyl nitrite was added to a suspension of 8.55 g (35.3 mM) of the dihydrochloride of IV in 100 ml of absolute ethanol. The reaction mixture was stirred at room temperature for 2 hr and at the boil for 6 hr. The precipitate formed was filtered off and washed with ethanol, giving 5.8 g (70%) of the hydrochloride of 4-ethoxycarbonylaminoquinuclidine (V), mp above 360° C (from a mixture of ethanol and methanol). Found, %: C 51.28; H 8.13; Cl 15.16; N 11.79. Calculated for ($C_{10}H_{18}N_2O_2 \cdot HCl$), %: C 51.17; H 8.15; Cl 15.10; N 11.92.

4-Ethoxycarbonylaminoquinuclidine—mp 92–95° C (from a mixture of benzene and petroleum ether). Found, %: C 60.70; H 9.15; N 14.21. Calculated for ($C_{10}H_{18}N_2O_2$); %: C 60.59; H 9.15; N 14.13. IR spectrum: 3260 cm^{-1} (NH); 1710 cm^{-1} ($NCOOC_2H_5$). The alcoholic mother liquor after the separation of the hydrochloride of **V** was evaporated in vacuum, and the residue was triturated with acetone. This gave 2.5 g of the hydrochloride of III, mp 255–256° C, 297–299° C. The free ester III formed a colorless mobile liquid with bp 133–134° C (18 mm). Found, %: C 65.85; H 9.38; N 8.01. Calculated for ($C_{10}H_{17}NO_2$), %: C 65.54; H 9.35; N 7.74.

4-Aminoquinuclidine (II). A mixture of 6.2 g (26.8 mM) of the hydrochloride of **V** and 150 ml of concentrated hydrochloric acid was boiled for 10 hr. The hydrochloric acid solution was evaporated and the residue was triturated with acetone to give 5 g (95%) of the dihydrochloride of **II**, mp above 360° C (from a mixture of ethanol and methanol). Found, %: C 42.10; H 8.18; Cl 35.81; N 14.01. Calculated for ($C_7H_{14}N_2 \cdot 2HCl$), %: C 42.21; H 8.10; Cl 35.65; N 14.05. To isolate the free 4-aminoquinuclidine, a solution of 1 g (5 mM) of the dihydrochloride in 10 ml of water was treated with 0.4 g (0.01 mole) of caustic soda and evaporated to dryness in vacuum. Compound **II** was isolated from the solid residue by vacuum sublimation at 60° C (0.4 mm). Colorless very volatile hygroscopic crystals, rapidly forming the hemihydrate in the air. Found, %: C 62.45; H 10.96; N 20.5. Calculated for ($C_7H_{14}N_2 \cdot 1/2H_2O$), %: C 62.17; H 11.18; N 20.71.

4-Dimethylaminoquinuclidine (VIa). A solution of 1 g (5 mM) of the dihydrochloride of **II** in 3 ml of water was treated with 0.4 g (0.01 mole) of caustic soda, 1 g (12 mM) of 36% formalin, and 1.4 g (30.2 mM) of formic acid. The mixture was heated at 100° C for 22 hr, evaporated, made alkaline with 25% caustic soda solution, and extracted with ether. This gave 0.6 g (77.6%) of **VIa** in the form of colorless crystals, bp 130-132° C (50 mm); mp 18-20° C. Found, %: C 69.86; H 11.84; N 18.04. Calculated for ($C_9H_{18}N_2$), %: C 70.07; H 11.76; N 18.14. **Dihydrochloride**—mp 265-267° C (decomp.). Found, %: C 47.58; H 8.93; Cl 30.90; N 12.30. Calculated for ($C_9H_{18}N_2 \cdot 2HCl$), %: C 47.77; H 8.94; Cl 31.2; N 12.31.

4-Acetylaminoquinuclidine (VIb). A solution of 1 g (0.05 mole) of the dihydrochloride of **II** in 20 ml of methanol was treated with 0.4 g (0.01 mole) of caustic soda, the sodium chloride was filtered off with suction, and the methanolic solution was evaporated. The residue was treated with 5 ml of acetic anhydride, and the mixture was heated in the water bath for 2 hr, evaporated, made alkaline with potassium carbonate, and extracted with benzene. Yield 0.57 g (61%). Colorless crystals with mp 123-126° C (from a mixture of acetone and ether). Found, %: C 57.90; H 9.77; N 14.97. Calculated for ($C_9H_{16}N_2O \cdot H_2O$), %: C 57.98; H 9.73; N 15.04. **Hydrochloride**, mp 294-296° C (decomp.). Found, %: C 52.59; H 8.22; Cl 17.33; N 13.64. Calculated for ($C_9H_{16}N_2O \cdot HCl$), %: C 52.81; H 8.37; Cl 17.32; N 13.68.

4-Benzoylaminoquinuclidine (VIc). The free 4-aminoquinuclidine isolated from 2 g (0.01 mole) of the dihydrochloride was treated with 30 ml of benzene, and 1.4 g (0.01 mole) of benzoyl chloride was added over 30 min. The reaction mixture was boiled for 5 hr, cooled, made alkaline with 50% potassium carbonate solution, and extracted with chloroform. The chloroform was distilled off and the residue was triturated with ether to give 1.7 g (73.8%) of **VIc**. Colorless crystals, mp 184-186° C. Found, %: C 67.59; H 8.07. Calculated for ($C_{14}H_{18}N_2O \cdot H_2O$), %: C 67.71; H 8.12.

4-Benzylaminoquinuclidine (VId). 1.45 g (6.3 mM) of **VIc** was added to a suspension of 0.76 g (0.02 mole) of lithium aluminum hydride in 30 ml of ether and 30 ml of benzene. The mixture was heated at the boil for 24 hr. Yield 0.7 g (51.5%). Colorless crystals, bp 135-137° C (0.4 mm); mp 36-39° C. Found, %: C 77.45; H 9.23; N 13.18. Calculated for ($C_{14}H_{20}N_2$), %: C 77.73; H 9.32; N 12.95.

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24 November 1966

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