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SYNTHESIS AND SOME REACTIONS OF 3-FORMYLQUINUCLIDINE

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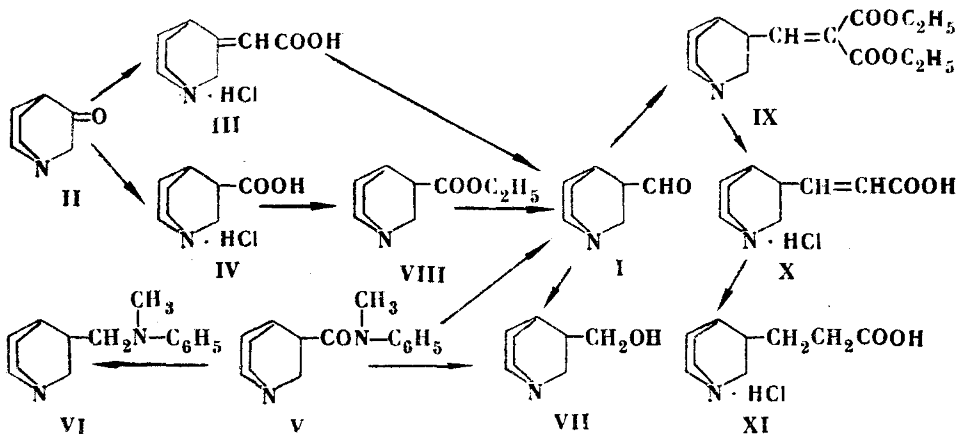
3-Formylquinuclidine is synthesized and converted to 3-hydroxymethylquinuclidine, β-(quinuclidyl-3) acrylic, and β-(quinuclidyl-3) propionic acids.

The great reactivity of formylquinuclidines make them of considerable interest as starting materials for various synthetic studies. Up to the present the synthesis of formylquinuclidines has been described in only two publications. 2-Formylquinuclidine has been prepared by reducing quinuclidine-2-carboxyl-N-methylanilide with the calculated quantity of lithium aluminum hydride [1], 4-formylquinuclidine by oxidizing 4-quinuclidylcarbinol with potassium dichromate [2]. 3-Formylquinuclidine is of particular interest for the preparation of 3-vinylquinuclidine, hitherto not described in the literature.

Several synthetic routes to 3-formylquinuclidine were investigated [3], starting from the accessible quinuclidine-3 (II)

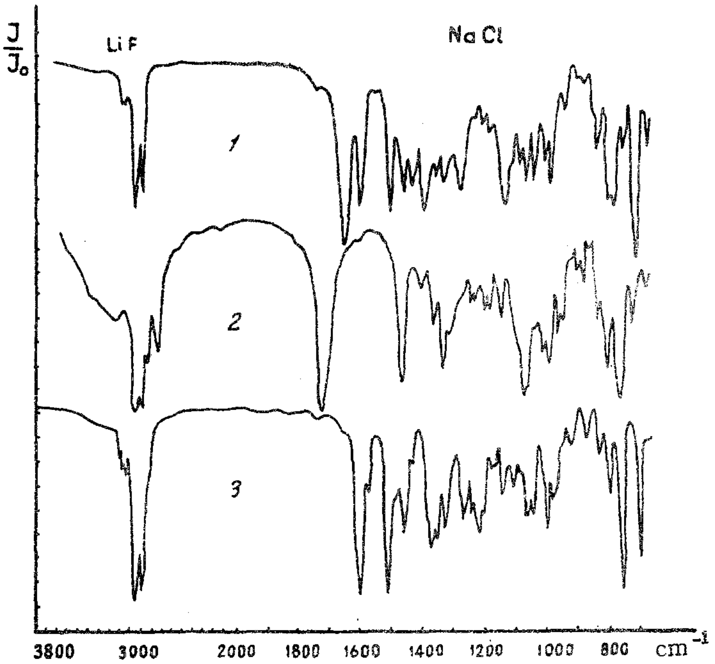


In the first variant I was converted by Horner's reagent into 3-(carboethoxymethylene) quinuclidine [4], which was saponified to 3-carboxymethylenequinuclidine hydrochloride (III) [5]. For the further conversion to 3-formylquinuclidine, the α, β-unsaturated acid III was rearranged under Schmidt reaction conditions, or by the Hofmann method via the corresponding amide [5]. The Hofmann reaction was run with sodium hypochlorite in boiling methanol, checking the course of the reaction by paper chromatography. However, the Hofmann reaction did not give I, but instead a mixture of compounds whose IR spectra lacked the characteristic aldehyde group absorption bands, though there were absorption bands of the nitrile (2240 cm^{-1}), ester (1755 cm^{-1}) and isonitrile (2180 cm^{-1}) groups. The best results were obtained by the Schmidt reaction, where III was treated with sodium azide and a mixture of benzene and concentrated sulfuric acid, when 3-formylquinuclidine was obtained in 13% yield.

A higher yield of I was obtained by operating a third variant of the synthesis via quinuclidine-3-carboxylic acid hydrochloride (IV), prepared from quinuclidone-3 by the method of [6]. Proceeding by analogy with the previously described synthesis of 2-formylquinuclidine [1], IV was converted, via its chloroanhydride, into the N-methylanilide V, and the latter reduced with the calculated amount of lithium aluminum hydride (0.5 mole of the latter per 1 mole of V). Varying the conditions for reducing V showed that, even when using the same molar amounts of reactants, different products could be obtained, depending on solvent and temperature. When the reaction was run in boiling ether, the main product of reducing V was 3-(N-phenyl-N-methylaminomethyl) quinuclidine (VI), which was isolated in 42.5% yield. When the reaction temperature was lowered to 0°, the aldehyde I was obtained in about 3% yield. Along with I was isolated the product of further reduction of I, quinuclidine-3-carbinol (VII), and about 35% V was recovered unchanged. Further lowering of the temperature to −5° raised the amount of unreacted N-methylanilide to 66%, while the yield of I was 3.4%. Use of tetrahydrofuran instead of ether as the solvent effected a clear-cut shift of the reaction in the direction of formation of I, for at −5° only 5% V was recovered unchanged, the yield of I rising to 29.5%.

But the highest yield of 3-formyquinuclidine was secured by extending the method of reducing esters with lithium aluminum hydride [7, 8] to 3-substituted quinuclidines. Ethyl quinuclidine-3-carboxylate (VIII) was reduced with the theoretical amount of lithium aluminum hydride in dry tetrahydrofuran at −50°, when the yield was 56%.

The synthesized 3-formylquinuclidine I is a light mobile liquid, boiling point 93-96° (8 mm), with a well-defined ammoniacal odor. Its IR spectrum contains characteristic aldehyde absorption bands at 1722, 2725, and 2827 cm^{-1} (see Fig.). It readily hydrates in air, being converted to colorless crystals melting point 49-52°; the aldehyde partly polymerizes on prolonged storage or on distillation. Like 4-formylpyridine [9], I forms a stable bisulfite compound, from which free aldehyde can be recovered by refluxing with 50% potassium carbonate followed by extraction with hot chloroform. The compound I gives characteristic aldehyde derivatives: an oxime, and a thiosemicarbazone; sodium borohydride in methanol at room temperature reduces it to VII. When I is condensed with malonic ester in pyridine solvent, in the presence of piperidine, it is smoothly converted into 3-(β, β-dicarboethoxyvinyl) quinuclidine (IX). Saponification and partial decarboxylation of IX gives the hydrochloride of β-(quinuclidyl-3) acrylic acid (X), and hydrogenation of the latter using platinum catalyst gives a homolog of the previously described [4, 10] quinuclidine-3-acetic acid, viz. β-(quinuclidine-3) propionic acid hydrochloride (XI).



IR spectra: 1) quinuclidine-3-carbox-N-methylanilide (V); 2) 3-formylquinuclidine (I); 3) 3-(N-phenyl-N-methylaminomethyl) quinuclidine (VI).

Experimental

Quinuclidine-3-carboxyl-N-methylanilide (V). A mixture of 1 g (5 mmole) quinuclidine-3-carboxylic acid hydrochloride (IV) [6] and 10 ml purified thionyl chloride was heated for 40 min at 60° until the precipitate dissolved completely. The excess thionyl chloride was distilled off under reduced pressure. The residue was thrice extracted with dry benzene, and the latter was then distilled off under reduced pressure. 1.82 g (17 mmole) N-methylaniline and 5 ml dry ether were added to the quinuclidine-3-carboxylic chloroanhydride hydrochloride. The reaction mixture was carefully stirred, then treated with 10 ml 50% potassium carbonate solution, and repeatedly extracted with ether. The ether extracts were dried over potassium carbonate, and evaporated under reduced pressure. The residue was distilled, and a cut bp 143-145° (0.8 mm) taken, yield of V 0.95 g (74.8%). Colorless crystals mp 61-63°. The compound was readily soluble in alcohols, chloroform, acetone, benzene, less soluble in ether, sparingly soluble in heptane and water. IR spectrum: 1652 cm^{-1} $\left(-\mathrm{CON}\langle\right)$* (Fig.). Found: C 73.61, 73.44; H 8.16, 8.06; N 11.41, 11.38%. Calculated for $C_{15}H_{20}N_2O$: C 73.73; H 8.25; N 11.46%.

3-Formylquinuclidine (I).

A solution of 0.44 g (8 mmole) sodium aluminum hydride in 4.6 ml dry tetrahydrofuran was added, in a nitrogen atmosphere, to a solution of 5 g (27 mmole) ethyl quinuclidine-3-carboxylate* (VIII) in 45 ml dry tetrahydrofuran,

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* All IR spectra were measured with a UR-10 spectrophotometer.

stirred and cooled to −50°. The reaction mixture was stirred for a further 2 hr at −50° to −45°, then 1 ml water added, and stirring continued for 15 min more, at −50° to −35°. The reaction mixture was brought to room temperature, 12 ml 23% sodium bisulfite solution added, and the whole stirred for 1 hr 30 min. The crystalline bisulfite derivative was separated off from the tetrahydrofuran solution, and washed with ether. The tetrahydrofuran solution and ether washings were bulked, dried with magnesium sulfate, and evaporated under reduced pressure. The residue (1 g) was vacuum-distilled, and a cut bp 124-125° (15 mm) taken. 0.86 g (17.2%) of the starting compound VIII was recovered. The bisulfite compound was decomposed by boiling with 30 ml 50% potassium carbonate solution, and I extracted with hot chloroform (8 times, each time with 10 ml). The bulked chloroform extracts were dried over potassium carbonate and vacuum-distilled, and the residue distilled, taking a cut bp 93-96° (8 mm). Yield of I 2.15 g (56.6%). It was a volatile mobile liquid with an ammoniacal odor, readily soluble in water, alcohols, and chloroform. IR spectrum: 1722, 2725, 2827 cm^{-1} (—CHO) (Fig.). Found: C 69.03, 69.46; H 9.37, 9.49; N 9.85%. Calculated for $C_8H_{13}NO$: C 69.03; H 9.41; N 10.06%.

The thiosemicarbazone formed colorless crystals mp 184° (decomp, ex ethanol). Sparingly soluble in water and ordinary organic solvents. Found: N 26.63; S 15.11%. Calculated for $C_9H_{16}N_4S$: N 26.39; S 15.10%.

The oxime hydrochloride formed colorless crystals mp 207° (decomp). It was readily soluble in water, sparingly soluble in ethanol, insoluble in ether, chloroform, ethyl acetate. Found: N 14.47; Cl 18.75%. Calculated for $C_8H_{16}N_2O \cdot HCl$: N 14.54; Cl 18.40%.

b) 15 ml concentrated sulfuric acid and 40 ml benzene were added to 5 g (25 mmole) 3-carboxymethylenequinuclidine hydrochloride (III) [5], the mixture stirred, and 2 g (31 mmole) sodium azide added in portions. The reaction mixture was then held at 40-50° for 5 hr while being stirred, at the end of which time gas evolution ceased. The gaseous reaction products were collected, and their CO_2 content determined. In all 830 ml gas was obtained, 110 ml of which was CO_2 (found by absorption with 10% NaOH solution). The reaction products were cooled, and 100 ml 50% potassium carbonate solution added gradually (until the solution was strongly alkaline to phenolphthalein.) The precipitate of inorganic salts formed was washed with chloroform. The water layer was extracted 10 times with hot chloroform, the bulked extracts dried over potassium carbonate, and evaporated under reduced pressure. The residue (1.68 g) was distilled, and a cut bp 93-96° (8 mm) collected, yield of I 0.44 g (12.9%).

c) 8.94 g (36 mmole) V was dissolved in 90 ml dry tetrahydrofuran. 0.93 g (18 mmole) 75% lithium aluminum anhydride was added in 10 min to that solution, stirred and cooled to −5°, after which stirring was continued for another 8 hr, then 1.8 ml water added. The mixed lithium and aluminum hydroxides were filtered off, and carefully washed with ether. 11 ml 23% solution of sodium bisulfite was added to the filtrate, and the bisulfite compound which separated worked up in the way previously described (see [a]), to give 1.49 g (29.2%) I bp 93-96° (8 mm). After removing the I bisulfite compound, the organic solvents layer gave on distillation 3.2 g (81.7%) N-methylaniline bp 78° (16 mm), and 0.13 g (1.5%) starting V bp 143-145° (0.8 mm). Specimens of I synthesized by different methods (a, b, c) had the same IR spectra and the same R_f 0.64 (lilac-rose color). **

3-(N-phenyl-N-methylaminomethyl) quinuclidine (VI). 0.37 g (7.5 mmole) 75% lithium aluminum hydride was added in 10 min to a stirred solution of 3.7 g (15 mmole) V in 40 ml dry ether at room temperature. The reaction mixture was then refluxed for 5 hr, cooled to 0°, and 0.8 ml water added. The mixed lithium and aluminum hydroxides were filtered off, and well washed with ether. 4.8 ml 23% sodium bisulfite solution was added to the filtrate, and the mixture shaken in a separating funnel. The ether solution was poured off, and the precipitate washed with ether. The bulked ether solutions were dried over potassium carbonate and vacuum-distilled, to give 0.48 g (13%) of the starting V bp 143-145° (0.8 mm). The precipitate formed after adding the sodium bisulfite was boiled with 50% potassium carbonate solution, and extracted with hot chloroform. The chloroform extract was dried over potassium carbonate, and vacuum-distilled. The residue distilled over at 145-152° (0.8 mm), mass 1.53 g, colorless viscous liquid, readily soluble in the usual organic solvents, insoluble in water n_D^{20} 1.5732. R_f 0.68 (rose colored). The IR spectrum of the compound lacks the absorption bands characteristic of the groups —CHO, $-\mathrm{CON}\langle$, and NH (Fig.), and the elementary analysis of the compound corresponds to that of VI. Yield 45%. Found: C 78.15; H 9.30; N 12.49. Calculated for $C_{15}H_{22}N_2$: C 78.20; H 9.63; N 12.16%.

3-Hydroxymethylquinuclidine (VII). 0.6 g (16 mmole) sodium borohydride was added in 20 min to a stirred solution of 1.8 g (13 mmole) I in 25 ml methanol, stirring at room temperature continued for a further 30 min, and the

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*VIII was prepared in this laboratory by esterifying IV, and will be described in a subsequent publication.

**Here and in all other cases the chromatograms were on special chromatograph brand paper, they were descending ones, and n-butanol–water–acetic acid (5 : 4 : 1) was used. The visualizer was Dragendorf's reagent (complex color given in brackets).

methanol then distilled off. 10 ml water was added, the mixture extracted with chloroform, the chloroform solution dried over potassium carbonate, evaporated under reduced pressure, and the residue distilled, a 114-115° (3 mm) cut being taken. Yield VII 1.12 (68%). The substance crystallized at room temperature, giving colorless crystals, mp 47-50°, readily soluble in the usual organic solvents and water. IR spectrum: wide band at 3100-3400 cm^{-1} (poly-associated alcohol), R_f (lilac-colored). Found: C 68.07; H 10.56; N 10.00%. Calculated for $C_8H_{15}NO$: C 68.04; H 10.71; N 9.92%.

The picrate formed yellow crystals mp 189-189.5° (ex ethanol) [6].

3-(β, β-Dicarboethoxyvinyl) quinuclidine (IX). A mixture of 1.39 g (10 mmole) freshly-distilled I, 1.56 g (10 mmole) ethyl malonate, 6 ml pyridine, and 5 drops of piperidine was left at room temperature for 4 days. The darkened transparent solution was evaporated under reduced pressure below 50°, and 10 ml dry ether added to the residue (2.75 g). The white amorphous precipitate (I polymer) was filtered off from the solution, and vacuum-dried. The rest was distilled, and a cut bp 145-147° (1 mm) taken, yield of IX 2.05 g (73%). Colorless oily compound, soluble in the common organic solvents, insoluble in water, n_D^{20} 1.4919. IR spectrum: 1733 cm^{-1} $\left[>C=C-(COOC_2H_5)_2 \right]$. Found: C 63.85; H 8.26; N 5.35%. Calculated for $C_{15}H_{23}NO_4$: C 64.03; H 8.24; N 4.98%.

β-(Quinuclidyl-3) acrylic acid hydrochloride (X). A solution of 0.68 g (2.5 mmole) IX in 7 ml concentrated hydrochloric acid was refluxed for 6 hr, and then evaporated to dryness on a water bath. 2 ml absolute ethanol was added to the residue. The crystals of X which separated out were filtered off, and washed with dry ethanol. Yield of X 0.26 g (49%), colorless crystals mp 244-245° (ex ethanol). The compound was readily soluble in water, hot alcohols, and dimethylformamide, sparingly soluble in cold alcohols, insoluble in ether, ethyl acetate, acetone, and chloroform. IR spectrum: 1712 cm^{-1}, wide band at 2680-3050 cm^{-1} $\left(>C=CH-COOH \right)$. Found: N 6.38; Cl 16.24; 16.15%. Calculated for $C_{10}H_{15}NO_2 \cdot HCl$: N 6.43; Cl 16.29%.

β-(Quinuclidyl-2) propionic acid hydrochloride (XI). 0.28 g (1.3 mmole) X was dissolved in 10 ml 17% hydrochloric acid, and 0.2 g Adams catalyst added. The reduction was run at room temperature, the excess hydrogen pressure amounting to 20-30 cm water. The catalyst was then filtered off, and the filtrate evaporated under reduced pressure. 5 ml dry acetone was added to the residue, and the crystals of XI filtered off, yield 0.28 g (quantitative), colorless crystals mp 208-209°, readily soluble in water and hot alcohols, insoluble in ether, benzene, ethyl acetate, acetone, chloroform, and dioxane. Found: N 6.61; Cl 15.96%. Calculated for $C_{10}H_{17}NO_2 \cdot HCl$: N 6.38; Cl 16.14%.

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