SYNTHESIS AND PROPERTIES OF 3-HYDROXYPYRAZOLO[4,3-b]QUINUCLIDINE

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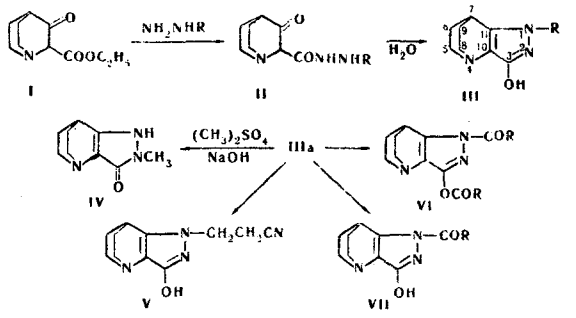
The reaction of 2-ethoxycarbonyl-3-oxoquinuclidine with hydrazine hydrate and with methylhydrazine has been examined. It has been shown with the aid of the IR and NMR spectra that the products are 3-hydroxypyrazolo[4,3-b]quinuclidine and its N-methyl derivative, together with alkylation, cyanoethylation, and acylation products.

Among numerous papers on the synthesis of quinuclidines, most of which have appeared in the last decade, only one publication deals with the preparation of condensed systems based on quinuclidine [1-3]. In such systems, an examination of the effect of the rigid bicyclic quinuclidine structure on the properties of the third ring is of considerable interest.

The present investigation was devoted to the synthesis of a representative of this class of compounds, i.e., a condensed quinuclidine–pyrazole system, which was prepared by reaction of 2-ethoxycarbonyl-3-oxoquinuclidine (I) with hydrazine hydrate. The first stage in this reaction is the formation of 3-oxoquinuclidine-2-carboxylic hydrazide (IIa), whose structure was established by analysis and the IR spectrum (recorded in Vaseline oil on a UR-10 spectrometer), which showed the presence of a CO group (1670 cm^{-1}) and a CONH group (1635 cm^{-1}). On recrystallization from water, or on heating in xylene or in vacuo at 210° C, the hydrazide IIa was readily converted into 3-hydroxypyrazolo[4,3-b]quinuclidine (IIIa). (Since this work was completed, a paper has appeared describing the preparation of IIIa [3]. The latter can be obtained without isolating IIa, by reacting the ketoester I with hydrazine hydrate in boiling alcohol or benzene.

Compound I reacts similarly with methylhydrazine. In this case also, the reaction proceeds via the formation of the corresponding hydrazide of 3-oxoquinuclidine-2-carboxylic acid (IIb), which is further converted, by the loss of a molecule of water into 1-methyl-3-hydroxypyrazolo[4,3-b]quinuclidine (IIIb).



R=H IIa, IIIa; R=CH_3 IIb, IIIb; R=CH_3 VIa, VIIa; R=C_6H_5 VIb, VIIb

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TABLE 1. NMR Spectra of Quinuclidine Derivatives

Compound	Name	Chemical shift of protons on carbon atoms, δ ppm				$\Delta\delta_{5,8}$	Solvent
		C=4	C=2	C=6,7	C=5,8		
VIII	3-Quinuclidone	2.43	3.27	2.73—3.05	1.83—2.05	0.22	$CHCl_3$
I	Ethyl 3-oxoquinuclidine-2-carboxylate	2.41	3.98	2.60—3.50	1.75—2.0	0.25	CCl_4
IX	3-Quinuclidone phenylhydrazone	2.65	3.55	2.80—3.05	1.75—1.95	0.25	$CDCl_3$
V	1-(β-Cyanoethyl)-3-hydroxypyrazolo[4,3-b]	3.45	—	2.80; 3.20	1.55—2.0	0.45	$CHCl_3$
VIa	1-Acetyl-3-acetoxypyrazolo[4,3-b]quinuclidine	4.20	—	2.68; 3.16	1.55—1.95	0.40	$CHCl_3$
VIIa	1-Acetyl-3-hydroxypyrazolo[4,3-b]quinuclidine	4.23	—	2.66; 3.21	1.55—2.0	0.45	$CHCl_3$
VIIb	1-Benzoyl-3-hydroxypyrazolo[4,3-b]quinuclidine	4.25	—	2.80; 3.30	1.65—2.0	0.35	$CHCl_3$
X	Methyl Δ^2-dehydroquinuclidine-3-carboxylate	3.19	7.40	2.55; 2.94	1.32—1.82	0.50	$CDCl_3$

Compound IIIa is sparingly soluble in water, but is soluble in alkalies; it forms a silver salt and mono- and dihydrochlorides; and it is stable on heating with acids and alkalis, and to the action of lithium aluminum hydride.

The structure of IIIa and IIIb is determined by their IR spectra. In the spectrum of IIIa and its silver salt, and of IIIb, no bands characteristic of the —CO—N< , are found, as they are, for example, in pyramidone (1-phenyl-2,3-dimethyl-4-dimethylamino-5-pyrazolone) at 1680 cm^{-1}. Instead, absorption occurs at 1610-1628 cm^{-1} which is probably due to $-C=N$. The spectra of IIIa and IIIb also show a broad band at 1900-2400 cm^{-1}, characteristic of strong hydrogen bonding.

Reaction of IIIa with dimethyl sulfate in the presence of one equivalent of NaOH gives a single methylation product, 2-methyl-3-oxopyrazolo[4,3-b]quinuclidine (IV), which shows a typical carbonyl band in the IR spectrum at 1692 cm^{-1}.

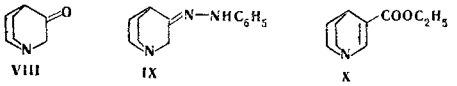
Cyanoethylation of IIIa in alkaline solution gives 1-(β-cyanoethyl)-3-hydroxypyrazolo[4,3-b]quinuclidine (V), as shown by the presence in the IR spectrum of a band due to the $-C=N-$ group at 1636 cm^{-1}, and bands due to the associated hydroxyl group at 2380-2700 cm^{-1}. The UV spectra of IIIa and V have the same absorption maxima, at 227 nm.

Acylation of IIIa with one equivalent of acetic anhydride or benzoyl chloride yielded 1-acetyl(benzoyl)-3-hydroxypyrazolo[4,3-b]quinuclidine (VIIa and VIIb). Use of an excess of acetic anhydride, or of two equivalents of benzoyl chloride, gives 1-acetyl(benzoyl)-3-acetoxy(benzoyloxy)-pyrazolo[4,3-b]quinuclidine (VIa and VIb), respectively. The IR spectra of the latter show absorption bands due to the carbonyl in the amide and ester groups (1735 and 1778, and 1700 and 1758 cm^{-1} for VIa and VIb, respectively). The monoacyl derivatives VIIa and VIIb show bands characteristic of the amide group only (1727 and 1702 cm^{-1}). The hydroxyl groups in VIIa and VIIb are strongly associated, and appear as wide bands at 2380-2750 cm^{-1}, as is also observed in the compounds III and V, which have a similar structure.

The structures of V, VIa, VIIa, and VIIb also agree well with their NMR spectra*. The signal due to the C-2 proton of the quinuclidine ring was absent from all of these spectra (for convenience, only the carbon and nitrogen atoms of the quinuclidine ring are numbered in the discussion of the NMR spectra),

*The NMR spectra were recorded on a JNM-4H-100 (100 MHz) instrument, using TMS as internal standard (the solvents are given in table 1). Owing to the poor solubility of IIIa, we were not able to obtain sufficiently concentrated solutions for the determination of the spectrum.

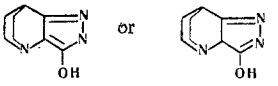
indicating the presence of a double bond at this carbon atom. The signals due to the α-protons (at C-6 and C-7) appear as two multiplets, with a distance between their centers of ~ 0.4-0.5 ppm (see table). In the β-proton region (at C-5 and C-8), a broad multiplet is seen, with a spacing between the outer peaks (to half height) of ~ 0.4 ppm. Comparison of these results with those obtained for a number of compounds with endocyclic (X) and exocyclic (VIII and IX) double bonds in the quinuclidine ring shows that the double bond in V, VIa, VIIa, and VIIb occurs in the C-2—C-3 position. In fact, in the compounds having exocyclic double bonds (VIII and IX), the differences in the chemical shifts of both protons at C-5 (C-8), and of both protons at C-6 (C-7) are small (the protons at C-6 and C-7, and at C-5 and C-8 are equivalent pairs in these compounds, as a result of the existence of a plane of symmetry in the molecules.)



VIII IX X

Their spectra show only two multiplets, each having an intensity of 4 proton units, corresponding to the α-protons (multiplet width ~ 0.25 ppm), and the β-protons (width of multiplet ~ 0.2 ppm). At the same time, in X, which has an endocyclic double bond like the pyrazoloquinuclidines under discussion, the difference in the chemical shifts of the corresponding protons is significantly greater, particularly for the two C-6 protons, where it amounts to ~ 0.4-0.5 ppm. Examination of molecular models shows that a similar difference in the values of the chemical shifts for quinuclidines with exo- and endocyclic double bonds may be due to differences in the orientation of the protons relative to the magnetoanisotropic double bond. Comparison of these signals in V, VIa, VIIa, VIIb, and IX shows that, for the first four compounds, which have endocyclic double bonds in the quinuclidine ring, the signal due to the C-4 protons is shifted toward a lower field by 0.3-0.4 ppm in comparison with the similar signal for IX. In addition to the anisotropy of the magnetic field of the double bond (as we have previously found in the isomeric 3-ethylidenequinuclidines [4]), the value of the chemical shift of the C-4 proton must also be influenced by the approach of any other atoms to the C-4 proton, to a distance less than that of the sum of the van der Waals radii. In 1-substituted 3-oxopyrazole[4,3-b]quinuclidines, both these effects must operate in the same direction, resulting in the experimentally observed shift of the C-4 protons toward a lower field.

These investigations have shown that nearly all the quinuclidines which we prepared are 3-hydroxypyrazole derivatives, in agreement with literature information on the tautomerism of substituted 3-hydroxypyrazoles [5]. It appears that the endocyclic location of the double bond in the quinuclidine ring is energetically more favored than the exocyclic multiple bond which could occur in other tautomeric enol forms of the following type:



Cyanoethylation and acylation take place at the 1-position, which "solidifies" the 3-hydroxypyrazole structure which is characteristic of an unsubstituted tricycle. Only one of the reactions examined, that of IIIa with dimethyl sulfate in the presence of NaOH, gave a substituted 2-methyl-3-pyrazolone. The entry position of the methyl group established the structure of IV as a 3-pyrazolone rather than a 3-hydroxypyrazole. If the latter structure had been correct, the energetically less favored compound having double bonds exocyclic to the quinuclidine ring would have been formed.

EXPERIMENTAL

3-Oxoquinuclidine-2-carboxylic Acid Hydrazide (IIa). To 3 g (15.5 mmole) of 2-ethoxycarbonyl-3-oxoquinuclidine (I) in 12 ml of ethanol was added 2 g (62.5 mmole) of hydrazine hydrate. The mixture was kept for 3 hr at room temperature, and the precipitate which separated was filtered off and washed with alcohol to give 2.65 g (96%) of IIa as colorless crystals (it was not possible to determine the mp, since it is converted into 3-hydroxypyrazolo[4,3-b]quinuclidine (III) on heating). Found, %: C 52.12; H 7.07; N 22.68. Calculated for $C_8H_{13}N_3O_2$, %: C 52.45; H 7.15; N 22.94.

3-Hydroxypyrazolo[4,3-b]quinuclidine (IIIa). A) A 2-g (1.1 mmole) quantity of 3-oxoquinuclidine-2-carboxylic acid hydrazide (IIa) was dissolved in 25 ml of boiling water. From the cooled solution there

separated 1.3 g (72%) of IIIa as colorless crystals, mp 290.5° C, insoluble in organic solvents and sparingly soluble in water. Found, %: C 58.45; H 6.48; N 25.46. Calculated for: $C_8H_{11}N_3O$, %: C 58.17; H 6.71; N 25.44. On boiling IIa in xylene for 2 hr, a 98% yield of IIIa was obtained. Heating IIa in vacuo (10-15 mm) for 4 hr at 200-210° C gave a 99% yield of IIIa.

B) A 3-g (15.3 mmole) quantity of I, 20 ml of hydrazine hydrate, and 100 ml of benzene were boiled in an apparatus fitted with a Dean and Stark attachment until no more water was evolved. The benzene was removed in vacuo, the residue triturated with ether, and the crystals filtered off to give 2.5 g (99%) of IIIa, mp 290.5° C. After boiling 3 g (15.3 mmole) of I and 2 g (62.5 mmole) of hydrazine hydrate in 12 ml of ethanol for 4 hr, 2.45 g (97.5%) of crystalline IIIa separated mp 290.5° C.

3-Hydroxypyrazolo[4,3-b]quinuclidine Hydrochloride. The free base IIIa was dissolved with heating in 10% HCl. The acid solution, on cooling, deposited the hydrochloride of IIIa, mp 208-210° C (from alcohol). Found, %: C 44.05; H 6.25; Cl 16.17; N 18.76; H_2O 8.76. Calculated for $C_8H_{11}N_3O \cdot HCl \cdot H_2O$, %: C 43.74; H 6.42; Cl 16.14; N 19.13; H_2O 8.23.

3-Hydroxypyrazolo[4,3-b]quinuclidine Dihydrochloride. A 1-g (6.1 mmole) quantity of IIIa was boiled with 10 ml of 17% HCl. The acid solution was evaporated, the residue triturated with acetone, and the crystals were filtered off to give 1.4 g (97.5%), mp 199-200° C (decomp., from a mixture of methanol and ethanol). Found, %: C 39.82; H 5.42; Cl 29.65; N 17.70. Calculated for $C_8H_{11}N_3O \cdot 2HCl$, %: C 40.35; H 5.50; Cl 29.78; N 17.65.

Silver Salt of 3-Hydroxypyrazolo[4,3-b]quinuclidine. To a suspension of 0.5 g (3.02 mmole) of IIIa in 10 ml of water was added a solution of 0.17 g (3.02 mmole) of KOH in 10 ml of water. The resulting solution was treated with 0.515 g (3.02 mmole) of silver nitrate, and the silver salt was filtered off, washed with water, and dried, mp 238° C (decomp). Found, %: C 33.55; H 4.38; N 13.92; H_2O 5.44. Calculated for $C_8H_{10}AgN_3O \cdot H_2O$, %: C 33.05; H 4.15; N 14.3; H_2O 6.2.

2-Methyl-3-oxopyrazolo[4,3-b]quinuclidine (IV). A 6-g (36.5 mmole) quantity of IIIa was dissolved in 40 ml of 25% methanol containing 1.45 g (36.5 mmole) of NaOH, and 4.6 g (36.5 mmole) of dimethyl sulfate was added. The mixture was boiled for 16 hr, then cooled and acidified with alcoholic HCl. The precipitated hydrochloride of IV was filtered off and washed with methanol to give 7.83 g (90%), mp 248-250° C (from 50% methanol). Found, %: C 49.95; H 6.50; Cl 16.38; N 19.30. Calculated for $C_9H_{13}N_3O \cdot HCl$. %: C 50.12; H 6.49; Cl 16.42; N 19.48.

To obtain the free base, a solution of 3 g (13.9 mmole) of IV hydrochloride in 50 ml of alcohol was treated with a solution of 0.56 g (13.9 mmole) of NaOH in 10 ml of alcohol. The NaCl precipitate was filtered off, and the alcohol removed in vacuo to give 3 g (83.5%) of IV as colorless crystals, insoluble in acetone, benzene, and chloroform, but readily soluble in alcohol and water, mp 222-224° C (from a mixture of alcohol and acetone). Found, %: C 55.15; H 7.43; N 21.31; H_2O 9.3. Calculated for $C_9H_{13}N_3O \cdot H_2O$, %: C 54.81; H 7.66; N 21.25; H_2O 9.13.

1-Benzoyl-3-hydroxypyrazolo[4,3-b]quinuclidine (VIIb). To a solution of 2 g (12.2 mmole) of IIIa in 15 ml of water containing 0.485 g (12.2 mmole) of NaOH was added at 5-7° C 1.7 g (12.2 mmole) of benzoyl chloride. The mixture was stirred for 1 hr 30 min, and the resulting precipitate was filtered off and washed with water to give 2 g (61.3%) of VIIb as colorless crystals, insoluble in water, ether, and acetone, but soluble in aqueous solutions of caustic alkalis and sparingly soluble in tetrahydrofuran, mp 205-207° C (from tetrahydrofuran). Found, %: C 66.93; H 5.74; N 15.56. Calculated for $C_{15}H_{15}N_3O_2$, %: C 67.27; H 5.61; N 15.62.

1-Benzoyl-3-benzoyloxypyrazolo[4,3-b]quinuclidine (VIb). A 2-g (12.2 mmole) quantity of IIIa was dissolved in 30 ml of water containing 0.97 g (24.4 mmole) of NaOH, and 3.4 g (24.2 mmole) of benzoyl chloride was added at 10-15° C. The reaction mixture was stirred for 4 hr, and the precipitate which separated was filtered off and washed with water to give 3.8 g (84.5%) of VIb as colorless crystals, insoluble in water and in aqueous solutions of caustic alkalis mp 148-150° C (from acetone). Found, %: C 71.03; H 5.38. Calculated for $C_{22}H_{19}N_3O_3$, %: C 70.76; H 5.13.

1-(β-Cyanoethyl)-3-hydroxypyrazolo[4,3-b]quinuclidine (V). To a solution of 2 g (12.2 mmole) of IIIa in 15 ml of ethanol containing 0.49 g (12.2 mmole) of NaOH was added 0.65 g (12.2 mmole) of acrylonitrile, and the mixture was boiled for 5 hr. The alcohol was removed in vacuo, and the residue was dissolved in 12 ml of 1-N HCl and extracted with chloroform. On standing, V separated from the chloroform

solution as colorless crystals, soluble in alkalis, alcohol, and chloroform, but insoluble in water and ether. Yield 1 g (36.8%), mp 222-223.5° C (from alcohol). Found, %: C 60.53; H 6.46; N 25.26. Calculated for $C_{11}H_{14}N_4O$, %: C 60.53; H 6.47; N 25.67.

1-Acetyl-3-acetoxypyrazolo[4,3-b]quinuclidine (VIa). A 1-g (6.1 mmole) quantity of IIIa in 10 ml of acetic anhydride was boiled for 5 hr. The excess acetic anhydride was removed in vacuo, and the residue recrystallized from ethyl acetate to give 0.85 g (56%) of VIa as colorless crystals, readily soluble in chloroform, but insoluble in water, mp 127-128° C. Found, %: C 58.00; H 6.10; N 16.76. Calculated for $C_{12}H_{15}N_3O_3$, %: C 57.82; H 6.07; N 16.86. Hydrochloride. Colorless crystals, soluble in water and alcohol, but less soluble in acetone, and insoluble in ether and benzene, mp 214-217° C (from alcohol). Found, %: C 50.52; H 5.82; Cl 12.03; N 14.50. Calculated for $C_{12}H_{15}N_3O_3 \cdot HCl$, %: C 50.51; H 5.63; Cl 12.45; N 14.72.

1-Acetyl-3-hydroxypyrazolo[4,3-b]quinuclidine (VIIa). A) A 0.5-g (2 mmole) quantity of VIa was stirred at room temperature with 2 ml of 1-N NaOH. The pH of the solution, initially 8, fell to 7 after 15 min, and to 6 after 1 hr. The precipitate was filtered off and washed with water, alcohol, and ether to give 0.13 g (31%) of VIIa as colorless crystals, readily soluble in aqueous caustic alkalis, but insoluble in water, alcohol, and ether, and sparingly soluble in methanol, mp 212-214° C (from methanol). Found, %: C 57.67; H 6.31; N 20.46. Calculated for $C_{10}H_{13}N_3O2$, %: C 57.96; H 6.32; N 20.28.

B) To a suspension of 3 g (18.2 mmole) of IIIa in 10 ml of pyridine was added 1.85 g (18.2 mmole) of acetic anhydride at 100° C. The mixture was heated at this temperature for an additional 7 hr. Unreacted IIIa (1 g) was filtered off, and the filtrate evaporated to give 2.52 g (67%) of VIIa, mp 212-214° C (from methanol). The compound gave mp depression on mixing with material obtained by method A).

3-Oxoquinuclidine-2-carboxylic Acid Methylhydrazide (IIb). To a solution of 2.44 g (61 mmole) of NaOH in 20 ml of alcohol was added with stirring 4.38 g (30.2 mmole) of methylhydrazine sulfate, followed by 3 g (15.1 mmole) of I. After 24 hr, the sodium sulfate was filtered off, the filtrate was concentrated to half its volume, and the crystals which separated were filtered off to give 1.2 g (44%) of IIb as colorless crystals, mp 227-230° C, readily soluble in alcohol and water, but insoluble in ether and acetone. Found, %: C 54.94; H 7.90; N 21.53. Calculated for $C_9H_{15}N_3O_2$, %: C 54.81; H 7.67; N 21.30.

1-Methyl-3-hydroxypyrazolo[4,3-b]quinuclidine (IIIb). A) A 0.6 g (3 mmole) of IIb was heated in 10 ml of toluene in a Dean and Stark apparatus for 8 hr. The toluene was distilled off in vacuo, and the residue was recrystallized from a mixture of alcohol and acetone to give 0.55 g (98%) of IIIb as colorless crystals, soluble in alcohol, but insoluble in acetone, mp 224° C (from a mixture of alcohol and acetone). Found, %: C 59.97; H 7.40; N 23.2. Calculated for $C_9H_{13}N_3O$, %: C 60.32; H 7.31; N 23.45. Dihydrochloride, mp 194-197° C (decomp). Found, %: C 43.12; H 6.07; Cl 28.21; N 16.52. Calculated for $C_9H_{13}N_3O \cdot 2HCl$, %: C 42.87; H 5.99; Cl 28.12; N 16.66.

B) To a solution of 4.38 g (30.2 mmole) of methylhydrazine sulfate in 20 ml of ethanol was added with stirring 2.44 g (61 mmole) of NaOH in 10 ml of ethanol, followed by 3 g (15.1 mmole) of I. The mixture was boiled for 5 hr, the sodium sulfate was filtered off, the alcoholic solution was evaporated, and the residue triturated with ether to give 0.7 g (26%) of product, mp 244° C (from a mixture of alcohol and acetone).

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