SYNTHESIS OF 2-ARYL-3-HYDROXYPYRAZOLO-[4, 3-b]QUINUCLIDINES

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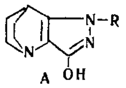
The reaction of 2-ethoxycarbonyl-3-ketoquinuclidine with arylhydrazines has been examined It is shown that the first stage in the reaction is the formation of 2-ethoxycarbonyl-3-(β-arylhydrazino)-Δ^2-dehydroquinuclidines, which are then converted into 2-aryl-3-hydroxypyrazolo[4, 3-b]quinuclidines (III). The O-methyl- and O-benzoyl- derivatives of III have been synthesized.

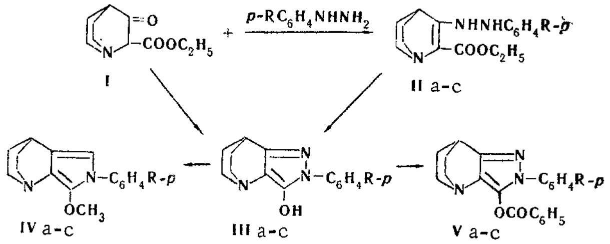
The synthesis of 3-hydroxypyrazolo[4, 3-b]quinuclidine and its 1-methyl derivative (A) by the reaction of 2-ethoxycarbonyl-3-ketoquinuclidine (I) with hydrazine hydrate and with methylhydrazine has been described in a previous communication [1].



A

R=H, CH_3

In continuation of this work, we have synthesized pyrazoloquinuclidines with aryl substituents in the pyrazole moiety, and we have investigated the structure and some reactions of these compounds.



II-V: a R=H; b R=CH_3; c R=OCH_3

It has been noted previously [1] that the first stage in the reaction of the ketoester II with hydrazine hydrate and alkylhydrazines is the formation of hydrazides of 3-ketoquinuclidine-2-carboxylic acid. In contrast, I reacts with arylhydrazines, at room temperature or at 80°, to give the hydrazones. According to their IR spectra (obtained in Vaseline oil on a UR-10 spectrometer), these compounds are 2-ethoxycarbonyl-3-(β-arylhydrazino)-Δ^2-dehydroquinuclidines (II). They exhibit characteristic absorption bands in the 3130-3300 cm^{-1} region due to the NH bonds of the hydrazine moiety, bands at 1658-1653 cm^{-1} due to the ester carbonyl, and bands at 1590 cm^{-1} attributed to C=C multiple bonds.

In compounds IIa-e, the occurrence of the enehydrazine rather than the hydrazone structure is apparently the result of a gain in energy on passing to the conjugated system.

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Further heating of the enehydrazines II in xylene with azeotropic distillation resulted in the elimination of a molecule of alcohol, with the formation of 2-aryl-3-hydroxypyrazolo[4, 3-b]quinuclidines (III). The latter were also formed directly from the ketoester I and arylhydrazines under analogous conditions. The structure of IIIa-c follows from their IR spectra, which are generally similar for all three compounds. Amide carbonyl bands are absent, while absorption occurs at 1590-1635 cm^{-1}, attributable to the system of double bonds, and a broad hydroxyl band with associated hydrogen bonds, at 2100-2500 cm^{-1}. The structure of III as derivatives of 5- rather than 3-hydroxypyrazoles is due apparently to the following factors. In 2-arylpyrazoloquinuclidines (III), formed from the enehydrazines II, the N-aryl group is adjacent to the C=O, and the single hydrogen atom in the pyrazole moiety of the molecule converts the oxo group to the enol, which is then stabilized by intermolecular association, resulting in the establishment of structure III, having exocyclic double bonds with respect to the quinuclidine ring. When no N-substituent is present on the nitrogen adjacent to the carbonyl group, the enol form occurs in the 3-hydroxypyrazole structure (A), with a different, thermodynamically more favorable, disposition of the double bonds with respect to the quinuclidine ring.

The 2-aryl-3-hydroxypyrazolo[4, 3-b]quinuclidines (III) were methylated and benzoylated to give the O-methyl- (IV) and O-benzoyl- (V) derivatives. In the IR spectrum of IV, absorption in the multiple bond region coincided with that for unmethylated III. The spectra of the benzoyl derivatives (V) exhibited vinyl ester carbonyl bands $-C=C-OCOC_6H_5$(1750, 1752, and 1765 cm^{-1}), which established unambiguously the structure of these compounds.

It is noteworthy that acylation and alkylation of III was facilitated in alkaline media, which provided the conditions for conversion of III into the anion. On the other hand, the reactivity of the OH group in the absence of alkali was reduced, and on boiling III with acetyl chloride, no acetylation occurred, starting material III being isolated from the reaction mixture.

EXPERIMENTAL

2-Ethoxycarbonyl-3-(β-phenylhydrazino)-Δ^2-dehydroquinuclidine (IIa). Five grams (25 mmole) of 2-ethoxycarbonyl-3-ketoquinuclidine (I), 3 g (27.8 mmole) of phenylhydrazine, and 30 ml of dry benzene were boiled for 5 h. The precipitate which was obtained on cooling was filtered off and washed with benzene to give 4.5 g of IIa. Evaporation of the mother liquors afforded a further 1.87 g, overall yield 6.37 g (87%), mp 138-140° (from aqueous dioxane). Found: C 66.59; H 7.20; N 14.39%. $C_{16}H_{21}N_3O_2$. Calculated: C 66.87; H 7.36; N 14.63%. Hydrochloride, colorless crystals (from ethanol), mp 173-174°. Found: C 59.53; H 6.77; Cl 11.16; N 12.69%. $C_{16}H_{21}N_3O_2 \cdot HCl$. Calculated: C 59.47; H 6.8; Cl 10.97; N 12.95%.

2-Ethoxycarbonyl-3-(β-p-tolylhydrazino)-Δ^2-dehydroquinuclidine (IIb). A portion of I [3.35 g (17 mmole)], 2.1 g (17 mmole) of p-tolylhydrazine, and 30 ml of dry ethanol were kept for 48 h at room temperature. The precipitate was filtered off and washed with acetone to give 2.48 g (48%) of IIb as colorless crystals, mp 149-151°. Found: C 67.42; H 7.50; N 14.23%. $C_{17}H_{23}N_3O_2$. Calculated: C 67.75; H 7.69; N 13.94%.

2-Ethoxycarbonyl-3-(β-p-methoxyphenylhydrazino)-Δ^2-dehydroquinuclidine (IIc) was obtained similarly to IIb, from 1.97 g (10 mmole) of I and 2.2 g (15 mmole) of p-methoxyphenylhydrazine in 30 ml of dry ethanol. Yield 1.8 g (56%), colorless crystals, mp 142-144°. Found: C 63.96; H 7.22; N 13.53%. $C_{17}H_{23}N_3O_3$. Calculated: C 64.33; H 7.30; N 13.25%.

2-Phenyl-3-hydroxypyrazolo[4, 3-b]quinuclidine (IIIa). A portion of I [5 g (25 mmole)], 5.4 g (50 mmole)] of phenylhydrazine, and 50 ml of xylene were boiled in a Dean and Stark apparatus for 20 h. The xylene was then removed in vacuo, and the residue was triturated with ether to afford 6.12 g (87%) of IIIa colorless crystals, mp 254-256° (from water). Found: C 69.49; H 6.10; N 17.27%. $C_{14}H_{15}N_3O$. Calculated: C 69.68; H 6.02; N 17.41%. Hydrochloride, colorless crystals mp 192-194° (from alcohol). Found: C 60.40; H 5.67; Cl 13.03; N 15.33%. $C_{14}H_{15}N_3O \cdot HCl$. Calculated: C 60.54; H 5.81; Cl 12.76; N 15.13%.

2-p-Tolyl-3-hydroxypyrazolo[4, 3-b]quinuclidine (IIIb). A portion of I [17.5 g (89 mmole)], 10.82 g (89 mmole) of p-tolylhydrazine, and 100 ml of xylene were boiled for 15 h, with azeotropic distillation, giving 9.3 g (41%) of IIIb, mp 246-248° (from dioxane). Found: C 70.32; H 6.83; N 16.57%. $C_{15}H_{17}N_3O$. Calculated: C 70.56; H 6.71; N 15.49%. Hydrochloride, colorless crystals, mp 235-236° (from aqueous ethanol). Found: Cl 12.00; N 14.49%. $C_{15}H_{17}N_3O \cdot HCl$. Calculated: Cl 12.15; N 14.40%.

2-(p-Methoxyphenyl)-3-hydroxypyrazolol[4, 3-b[quinuclidine (IIIc). Obtained similarly to IIIb, from 3 g (15 mmole) of I and 3 g (22 mmole) of p-methoxyphenylhydrazine in 50 ml of xylene. Yield 1.93 g (46.7%) mp 223-224° (from benzene). Found: C 66.69; H 6.57; N 15.49%. $C_{15}H_{17}N_3O_2$. Calculated 66.40; H 6 31; N 15.48%. Hydrochloride IIIb, mp 225-226° (from ethanol). Found: Cl 11.50; N 13.87%. $C_{15}H_{17}N_3O_2 \cdot HCl$. Calculated: Cl 11.51; N 13.65%.

2-Phenyl-3-methoxypyrazolo[4, 3-b]quinuclidine (IVa). A portion of IIIa hydrochloride [4.65 g (16.7 mmole)], 2.15 g (16.7 mmole) of dimethyl sulfate, 1.34 g (33.5 mmole) of sodium hydroxide, 15 ml of water, and 50 ml of ethanol were boiled for 18 h. The solution was evaporated, and the residual oil was treated with an alcoholic solution of hydrogen chloride. The precipitate was filtered off, dried, and boiled with anhydrous ethanol. From the alcoholic solution there was obtained 1 g (20.5%) of IVa hydrochloride as colorless crystals, mp 199-200° (from ethanol). Found: C 61.62; H 6.18; Cl 12.53; N 14.47%. $C_{15}H_{17}N_3O \cdot HCl$. Calculated: C 61.73; H 6.22; Cl 12.15; N 14.40%.

2-(p-Tolyl)-3-methoxypyrazolol[4, 3-b]quinuclidine (IVb). A portion of IIIb[2 g (7.5 mmole)], 0.99 g (7.8 mmole) of dimethylsulfate, 0.31 g (7.8 mmole) of sodium hydroxide, 5 ml of water, and 15 ml of ethanol were treated as described in the previous preparation, to give 0.75 g (31.4%) of IVb hydrochloride as colorless crystals, mp 212-213° (from ethanol). Found: C 62.66; H 6.43; Cl 11.24; N 13.58%. $C_{16}H_{19}N_3O$. Calculated: C 62.84; H 6.59%; Cl 11.59; N 13.74%.

2-(p-Methoxyphenyl)-3-methoxypyrazolo[4, 3-b]quinuclidine (IVc). From 2 g (7.1 mmole) of IIIc, 0.93 g (7.4 mmole) of dimethyl sulfate, 0.3 g (7.5 mmole) of sodium hydroxide, 5 ml of water, and 15 ml of ethanol, there was obtained 0.8 g (34%) of IVc hydrochloride, colorless crystals, mp 202-204° (from ethanol). Found: C 59.59; H 6.20; Cl 10.94; N 13.00%. $C_{16}H_{19}N_3O_2 \cdot HCl$. Calculated: C 59.73; H 6.27; Cl 11.01; N 13.06%.

2-Phenyl-3-benzoyloxypyrazolo[4, 3-b]quinuclidine (Va). To a solution of 1.8 g (7.5 mmole) of IIIa in 7 ml (7.5 mmole) of 1 N aqueous sodium hydroxide was added at 2-5° 1.05 g (7.5 mmole) of benzoyl chloride. The mixture was stirred for 1 h, and the precipitate was filtered off and recrystallized from ethyl acetate to give 0.5 g (19.5%) of Va, mp 184-186° Found: C 72.84; H 5.57; N 12.31%. $C_{21}H_{19}N_3O_2$. Calculated: C 73.02; H 5.54; N 12.16%.

Similarly were obtained: 2-(p-tolyl)-3-benzoyloxypyrazolo[4, 3-b]quinuclidine (Vb), mp 179-181° (from ethyl acetate). Found: C 73.38; H 6.06; N 11.41%. $C_{22}H_{21}N_3O_2$. Calculated: C 73.52; H 5.89; N 11.63%; 2-(p-methoxyphenyl)-3-benzoyloxypyrazolo[4, 3-b]quinuclidine (Vc), mp 192-193° (from benzene). Found: C 70.47; H 5.67; N 11.30%. $C_{22}H_{21}N_3O_3$. Calculated: C 70.38; H 5.59; N 11.19%.

LITERATURE CITED

1. E. E. Mikhlina, V. Ya. Vorob'eva, K. F. Turchin, N. P. Kostyuchenko, Yu. N. Sheinker, and L. N. Yakhontov, KhGS, 651 (1970).