SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 2-SUBSTITUTED-3-ARYL-3-HYDROXYQUINUCLIDINES

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Quinuclidines which carry 3-hydroxy and 3-aryl groups may be regarded as bicyclic analogs or arylethanolimines in which the aminoethyl residue has been incorporated into the quinuclidine nucleus. Compounds of this type are therefore of interest for pharmacological study as compounds capable of interacting with the adrenergic systems of the body. 2-methyl-substituted 3-aryl-3-hydroxyquinuclidines are bicyclic analogs of ephedrine and ephedrine-like compounds.

The synthesis of 3-aryl-3-hydroxyquinuclidines was carried out in the 1950's by K. Grob et al. [1], and by E. E. Mikhlina and M. V. Rubtsov [2], the ability of these compounds to stimulate the central nervous system being noted [3].

2-Substituted 3-aryl-3-hydroxyquinuclidines have not been described in the literature. We used 2-methylene-3-oxoquinuclidine (I) as the starting material for their preparation. It is well known that α,β-unsaturated ketones on reaction with organometallic compounds are capable of giving 1,2- and 1-4-addition products, aryllithium compounds tending to give the first, and Grignard reagents the second type of product [4].

Reaction of the unsaturated ketone (I) with either aryllithium compounds or phenylmagnesium bromide results in the formation of mixtures of 2-methylene-3-aryl-3-hydroxyquinuclidines (II) and 2-benzyl-3-hydroxyquinuclidines (III), with 1,2-addition products (the hydroxy derivatives (II)) predominating in the first case, and 1,4-addition products (the ketones (III)) in the second case. In only one reaction (that between the unsaturated ketone (I) and phenyllithium) was the formation of the ketone (IIIa) not observed, as shown by GC-MS. The chromatogram of the products of this reaction displayed three main peaks: M ± 137, assigned to the original ketone (I), a peak with m/e 154, corresponding to biphenyl, and a strong peak for a compound with molecular ion 215. Fragmentation of the latter gave rise to peaks with m/e 77 ($C_6H_5^+$), 105 ($C_6H_5CO^+$), and 110 $(M-C_6H_5CO)^+$, and at higher mass numbers the fragments $[M-H]^+$, $[M-CH_3]^+$, $[M-OH]^+$, $[M-C_2H_4]^+$, $[M-C_2H_5]^+$. This breakdown of the molecular ion is in good agreement with the structure of (IIa).

Reaction of the ketone (I) with phenylmagnesium bromide gave a mixture of (IIa) and (IIIa) in a ratio of 1:9. The reaction did not proceed to completion, and the original ketone (I) was recovered in the form of its hydration product, 2-hydroxymethyl-3,3-dihydroxyquinuclidine hydrochloride (V), which is obtained when the reaction mixture is treated with hydrochloric acid. The chromatogram of the total reaction products after removal of (V) showed the presence of two more compounds. The mass spectrum of the main product was identical with that of the ketone (IIIa), synthesized by the reduction of 2-benzylidene-3-oxoquinuclidine [5]. This spectrum displayed a low-intensity peak for the molecular ion, m/e 215, and a strong peak for a fragment with m/e 187 $[M-CO]^+$. The mass spectrum of the second product coincided with that of (IIa).

Reduction of 2-methylene-3-hydroxy-3-arylquinuclidines (IIc, e) afforded the corresponding 2-methyl-3-hydroxy-3-arylquinuclidines (IVa and b).

EXPERIMENTAL PHARMACOLOGICAL PART

The hydrochlorides and the methiodides of the 2-methylene-3-aryl-3-hydroxyquinuclidines (IIa-e) were examined for their effect on the adreno- and cholinoreactive systems. Also studied were their antiarrhythmic, local anesthetic, antitussive, and analgesic activity, their general effects, and their toxicity. For the sake of comparison, 2-unsubstituted qui-

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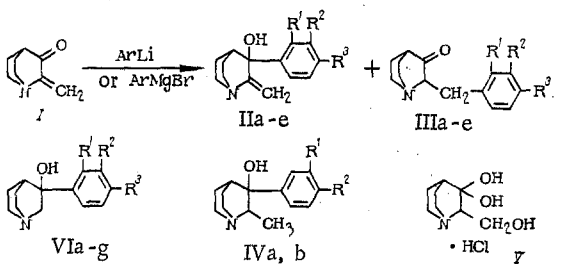
nuclidines of general formula (VI) were examined, together with the quinuclidine analog of ephedrine (2-methyl-3-hydroxy-3-(3'-tolyl)quinuclidine (VIa)).

Adrenomimetic activity was compared with that of adrenaline with respect to their effects on arterial pressure and the tonus of the third eyelid in urethane-narcotized cats. In the same experiments, the effects of the drugs on the frequency of cardiac contractions were compared with that of izedrine (isoproterenol). The peripheral adrenomimetic activity was also assessed from the effects of the drugs on the isolated rabbit ear vessels. α-Adrenolytic activity was determined by the ability to reduce the pressor effects of adrenalin in narcotized cats and the resulting contraction of the third eyelid. β-Adrenolytic activity was assessed by the reduction in the depressor reaction and the increased frequency of cardiac rhythm caused by izedrine (0.5-2 μg/kg) in narcotized cats.

Antiarrhythmic activity was examined in male rats weighing 100-160 g under urethane narcosis (1 ml of a 10% solution per 100 g body weight, intraperitoneally). The effects of the drugs on arrhythmia induced by aconitine (30 μg/kg intravenously) [6-8] were studied. ECG's were recorded with an EKlT-03M electrocardiograph in II standard leads.

Effects of the central m- and n-cholinereactive systems were assessed from the changes in the convulsive activity of arecoline (15 mg/kg subcutaneously) and nicotine (10 mg/kg subcutaneously) in mice. Peripheral cholinolytic activity was studied by the effects on spasms in sections of rabbit intestine induced by acetylcholine ($2 \cdot 10^{-6}$ g/ml).

Antitussive activity was studied in cats under Barbamyl (amobarbital sodium) narcosis by the method of Domenjoz [9] involving electrical stimulation of the superior laryngeal nerve. Analgesic activity was determined in white mice by the method of Woolfe and MacDonald [10]. Toxicity was determined in white mice following administration into the abdominal cavity. The LD_{50} was calculated by Kerber's method.



II, III: a) $R^1 = R^2 = R^3 = H$; b) $R^1 = CH_3$; c) $R^2 = CH_3$; d) $R^3 = CH_3$; e) $R^2 = R^3 = CH_3$; IV: a) $R^1 = CH_3$; b) $R^1 = R^2 = CH_3$; VI: a) $R^1 = R^2 = R^3 = H$; b) $R^2 = CH_3$; c) $R^3 = CH_3$; d) $R^1 = R^3 = CH_3$; e) $R^3 = OCH_3$; f) $R^1 = OCH_3$; g) $R^3 = Cl$ (when not shown R=H).

Results. Examination showed all the compounds to display adrenomimetic activity. In narcotized cats at a dose of 1-5 mg/kg, compounds (IIa-e) (hydrochlorides and methiodides) gave rise to a brief reduction in arterial pressure, did not shorten the third eyelid, and in concentrations of $1 \cdot 10^{-5}$ g/ml had slight vasoconstrictor effect (10-15%). Unlike the β-stimulator isoproterenol, which is active at a dose of 0.5 mg/kg, these compounds did not accelerate cardiac contractions in narcotized mice.

In doses of 1-5 mg/kg the compounds didnot diminish the pressor effects of adrenaline and the resulting shortening of the third eyelid, and they did not affect the depressor and acceleration of cardiac contractions caused by isoproterenol in narcotized cats, i.e., they had neither α- nor β-adrenoblocking activity.

Experiments on rats showed that none of the compounds possess antiarrhythmic activity.

In experiments on mice and on isolated segments of rabbit intestine, it was found that the compounds were without effects on the peripheral and cholinoreactive systems. They were devoid of analgesic activity and had no effect on the analgesic activity of promedol. Intravenous administration of the drugs in a dose of 5 mg/kg to narcotized cats did not affect the cough reflex. The compounds did not possess local anesthetic activity in concentrations of 0.5 and 1%.

In white mice, compounds (IIa-e) in toxic doses gave rise to dyspnea, slight tremor, and convulsions, which increased in severity with increasing doses. The LD_{50} of the hydrochlorides of (IIa-e) in white mice following administration via the abdominal cavity were 35, 21, 69,

185.5, and 175 mg/kg respectively, and of (IIa-e) methiodides, 118, 92.5, 127.5, 77, and 127.5 mg/kg. In the same tests, (VIa-g) did not display pharmacological activity. Compound (VIa), which may be regarded as a bicyclic analog of ephedrine, had no stimulant activity on the central nervous system in the experimental animals (mice, rats, and cats), and did not display the pressor and vasoconstrictive effects typical of ephedrine and other arylalkylamines.

These experimental findings show that the incorporation of the alkylamine chain of the phenylalkylamine in the quinuclidine system results in a substantial decrease in sympathomimetic activity. The compounds did not display either α- or β-adrenomimetic activity, nor did they possess α- or β-adrenoblocking activity. In contrast to ethers of 3-hydroxyquinuclidine (aceklidine and its "charged" analogs), the compounds examined also did not display cholinolytic activity. They were also of low activity in other tests (for antiarrhythmic activity, analgesic effects, and local anesthetic activity).

EXPERIMENTAL CHEMICAL PART

IR spectra were obtained in Vaseline oil on a Perkin-Elmer instrument (Sweden) and on a UR-10 (East Germany). The mass spectrum was obtained on a Varian MAT-111 chromatograph-mass spectrometer at 70 eV, carrier gas helium, 20 ml/min.

2-Methylene-3-phenyl-3-hydroxyquinuclidine (IIa). To an ether solution of phenyllithium, prepared from 3.3 g (0.47 g-atom) of lithium and 38.3 g (244 mmole) of bromobenzene in 120 ml of ether, was added at 6-8°C a solution of 15.8 g (115 mmole) of (I) in 50 ml of ether. The mixture was kept at 20°C for 20 h, then treated at 1-4°C with 135 ml of water. The ether was distilled off, and the alkaline aqueous solution extracted with chloroform. After removal of the chloroform, the residue was distilled *in vacuo*. The fraction collected over the range 200-220°C (28 mm) was triturated with light petroleum to give 8.6 g (34.2%) of (IIa), mp 125-126°C (from heptane). IR spectrum: ν 1657 (C=C), 3060 (OH) cm^{-1}. Found, %: C 78.22; H 7.83; N 6.31. $C_{14}H_{17}NO$. Calculated, %: C 78.15; H 7.92; N 6.52.

Hydrochloride. mp 218-220°C (decomp., from ethanol). Found, %: Cl 14.33. $C_{14}H_{17}NO \cdot HCl$. Calculated, %: Cl 14.21.

Methiodide. mp 170-172°C. Found, %: C 50.14; H 5.33; I 35.21. $C_{15}H_{20}INO$. Calculated, %: C 50.32; H 5.58; I 35.51.

2-Methylene-3-(2'-tolyl)-3-hydroxyquinuclidine (IIb) was obtained similarly to (IIa), by reacting 15.8 g (115 mmole) of the ketone (I) with 2-tolyllithium, obtained from 1.7 g (0.243 g-atom) of lithium and 20.5 g (120 mmole) of 2-bromotoluene in 100 ml of ether. Following removal of the ether, the reaction mixture was acidified with 10% hydrochloric acid, and nonbasic material was extracted into benzene from the acid solution. It was then basified with 40% sodium hydroxide solution, and extracted with chloroform. The residue after removal of the solvent was distilled *in vacuo*, the fraction with bp 148-154°C (0.8 mm) being collected. This was a mixture of (IIb) and (IIIb) (from the IR spectrum), the former being predominant. The mixture was triturated with light petroleum to give 6.1 g (23%) of (IIb), mp 120-121°C (from heptane). IR spectrum: ν 1654 (C=C), 3200 (OH) cm^{-1}. Found, %: C 78.72; H 8.04; N 6.33. $C_{15}H_{19}NO$. Calculated, %: C 78.64; H 8.29; N 6.12.

Hydrochloride. mp 206-207°C (decomp.). Found, %: Cl 13.42. $C_{15}H_{19}NO \cdot HCl$. Calculated, %: Cl 13.36.

Methiodide. mp 172-174°C. Found, %: I 34.64. $C_{16}H_{22}INO$. Calculated, %: I 34.26.

2-Methylene-3-(3'-tolyl)-3-hydroxyquinuclidine (IIc). This was obtained similarly to (IIa) from 23.7 g (173 mmole) of the ketone (I) and 3-tolyllithium prepared from 2.5 g (0.357 g-atom) of lithium and 30.6 g (179 mmole) of 3-bromotoluene in 100 ml of ether. The alkaline aqueous solution after removal of ether was extracted with chloroform. The solvent was distilled off, and the residue triturated with light petroleum to give 15.4 g (41.5%) of (IIc), mp 124-126°C (from heptane). IR spectrum, ν: 1658 (C=C), 3160 (OH) cm^{-1}. Found, %: C 78.75; H 8.34; N 6.34. $C_{15}H_{19}NO$. Calculated, %: C 78.64; H 8.29; N 6.12.

The mother liquor after removal of (IIc) was evaporated, acidified with hydrochloric acid, and nonbasic material extracted with benzene. The acidic aqueous solution was then basified and extracted with ether. The extract was evaporated, and the residue distilled *in vacuo* (0.8 mm). Two fractions were collected, bp 1) 135-200°C, and 2) 200-245°C. The first fraction was a mixture of approximately equal amounts of the hydroxy-compound (IIc) and the

ketone (IIIc). It was not possible to isolate the pure compounds from the mixture. The second fraction, in which the ketone (IIIc) predominated, was again distilled, and triturated with light petroleum to give 0.7 g of the ketone (IIIc), mp 80-82°C (from heptane). IR spectrum, ν: 1720 (C=O) cm^{-1}. Found, %: C 78.74; H 8.44; N 6.32. $C_{15}H_{19}NO$. Calculated, %: C 78.64; H 8.29; N 6.12.

Hydrochloride. mp 208-210°C (decomp.). Found, %: Cl 13.04. $C_{15}H_{19}NO \cdot HCl$. Calculated, %: Cl 13.36.

Methiodide. mp 174-176°C (from ethanol). Found, %: C 51.43; H 5.99; I 33.84. $C_{16}H_{22} \cdot INO$. Calculated, %: C 51.50; H 5.93; I 34.26.

2-Methylene-3-(4'-tolyl)-3-hydroxyquinuclidine (IId) was obtained by reacting 12 g (87.5 mmole) of the ketone (I) with 4-tolyllithium [from 1.3 g (0.186 g-atom) of lithium and 15.9 g (93 mmole) of 4-bromotoluene in 100 ml of ether]. The reaction mixture was treated with water, and the precipitate filtered off and washed with water to give 10 g (50%), mp 134-136°C (light petroleum:heptane, 1:6). IR spectrum, ν: 1652 (C=C), 3140 (OH) cm^{-1}. Found, %: C 78.81; H 8.38; N 6.11. Calculated, %: C 78.64; H 8.29; N 6.12.

Hydrochloride. mp 217-219°C (decomp., from ethanol). Found, %: Cl 13.13. $C_{15}H_{19}NO \cdot HCl$. Calculated, %: Cl 13.36.

Methiodide. mp 179-181°C. Found, %: C 51.54; H 5.89; I 34.12. $C_{16}H_{22}INO$. Calculated, %: C 51.50; H 5.93; I 34.26.

2-Methylene-3-(3',4'-dimethyl)-3-hydroxyquinuclidine (IIe). This was obtained similarly to (IId) by reaction of 16 g (116 mmole) of the ketone (I) with 3,4-dimethylphenyllithium [from 0.243 g-atom) of lithium and 22.4 g (120 mmole) of 3,4-dimethylbromobenzene in 100 ml of ether] The reaction products were extracted with chloroform, and the residue after removal of the solvent was distilled *in vacuo*. The fraction bp 165-180°C (1.5 mm) crystallized on standing to give 8.7 g (32%), mp 142-144°C (from heptane). IR spectrum, ν: 1643 (C=C), 3160 (OH) cm^{-1}. Found, %: C 79.08; H 8.66; N 5.70. $C_{16}H_{21}NO$. Calculated, %: C 79.0; H 8.64; N 5.77.

Hydrochloride. mp 205-207°C (decomp., from isopropanol). Found, %: Cl 12.72. $C_{16}H_{21} \cdot NO \cdot HCl$. Calculated, %: Cl 12.70.

Methiodide. mp 170-171°C. Found, %: C 52.70; H 6.15; I 32.66. $C_{17}H_{24}INO$. Calculated, %: C 53.14; H 6.23; I 32.94.

2-Benzyl-3-oxoquinuclidine (IIIa). To an ethereal solution of phenylmagnesium bromide obtained from 7.8 g (4.93 mmole) of bromobenzene and 1.15 g (4.78 mmole) of magnesium in 40 ml of ether, was added at 2-4°C 6.47 g (4.67 mmole) of (I) in 10 ml of ether. The mixture was kept for 20 h at 20°C, then treated with cooling with a 10% solution of hydrochloric acid. The solid which separated was filtered off and washed with water to give 3 g of the hydrochloride of 2-hydroxymethyl-3,3-dihydroxyquinuclidine (V), mp 265-267°C (from water) [11]. Found, %: C 42.31; H 7.84; Cl 15.22; N 6.04. $C_8H_{15}NO_3 \cdot HCl \cdot H_2O$. Calculated, %: C 42.22; H 7.93; Cl 15.61; N 6.14.

The acid mother liquors were extracted with ether, then basified with potassium carbonate and extracted with chloroform. The chloroform extracts were evaporated, and the residue triturated with light petroleum to give 5.6 g (78%), mp 85-87°C (from hexane) [5]. IR spectrum, ν: 1716 (C=O) cm^{-1}. Found, %: C 78.16; H 7.72; N 6.34. Calculated, %: C 78.15; H 7.92; N 6.52.

Diastereomeric 2-Methyl-3-(3'-tolyl)-3-hydroxquinuclidines (IVa). A solution of 5 g (17.8 mmole) of (IIc) in a mixture of 40 ml of methanol and 40 ml of 1 N hydrochloric acid was hydrogenated over 1.4 g of 5% palladium on charcoal until one equivalent of hydrogen had been taken up. The catalyst was filtered off, the solution evaporated, and the residue basified with 10% potassium hydroxide and extracted with chloroform. The solvent was distilled off, and the residue triturated with light petroleum to give 2.2 g (44.5%), mp 111-113°C (from heptane). IR spectrum, ν: 3140 (OH) cm^{-1}. Found, %: N 5.83. $C_{15}H_{21}NO$. Calculated, %: N 6.06.

Diastereoisomeric 2-Methyl-3-(3',4'-dimethylphenyl)-3-hydroxyquinuclidines (IVb). These were prepared similarly to (IVa). Yield 56%, mp 123-125°C (from heptane). IR spectrum, ν: 3100 (OH) cm^{-1}. Found, %: C 78.50; H 9.33; N 5.85. $C_{16}H_{23}NO$. Calculated, %: C 78.44; H 9.36; N 5.72.

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SYNTHESIS AND CYTOSTATIC ACTIVITY OF 1-α-L-ARABINOPYRANOSYL-6-NITROINDOLE AND 1-β-D-GALACTOPYRANOSYL-5-NITROINDOLE

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The observation of antitumor activity in 5- and 6-nitroindole 1-α-L-arabinopyranosides stimulated our search for new active compounds of this type [1, 2]. Of particular interest was the introduction of substituents which increase the hydrophilicity of the compounds.

The starting material which we employed was 1-(2',3',4'-tri-O-acetyl-α-L-arabinopyranosyl)-6-nitroindole (I) [3], which on reaction with DMF in the presence of $POCl_3$ (Vilsmeier reaction) was converted into 1-(2',3',4',tri-O-acetyl-α-L-arabinopyranoxyl)-3-formyl-6-nitroindole (II). Deacetylation of the aldehyde (II) by the Zemplen method gave 1-α-L-arabinopyranosyl-3-formyl-6-nitroindole (III). The aldehydes (II) and (III) were converted into their thiosemicarbazones (IX) and (X). The acetylated aldehyde (II) was converted into its oxime (IV), which was then dehydrated by heating in acetic anhydride to give 1-(2',3',4'-tri-O-acetyl-α-L-arabinopyranosyl)-3-cyano-6-nitroindole (V), deacetylation of which gave 1-α-L-arabinopyranosyl-3-cyano-6-nitroindole (VI). Hydrolysis of the nitrile (VI) with 10% aqueous caustic alkali gave the corresponding amide (VII), also characterized as its tri-O-acetyl derivative (VIII).

It was of interest to obtain also the close analog of 1-α-L-arabinopyranosylindole, 1-β-D-galactopyranosylindole. Starting from 5-nitroindoline (XI) [4], condensation with D-galactose in an alcohol–water–acetic acid mixture followed by acetylation with acetic anhydride in pyridine afforded 1-(2',3',4',6'-tetra-O-acetyl-β-D-galactopyranosyl)-5-nitroindoline (XII), which was dehydrogenated with MnO_2 in dry benzene with azotropic removal of water to form 1-(2',3',4',6'-tetra-O-acetyl-β-D-galactopyranosyl)-5-nitroindole (XIII). Deacetylation of the latter afforded 1-β-D-galactopyranosyl-5-nitroindole.

The properties of the compounds prepared are shown in Table 1, and their PMR spectral data in Table 2.

All the compounds had high $J_{1,2}$ values (8-10 Hz), indicating α-configuration of the arabinosides and β-configuration of the galactosides, and $^4C_1$-conformation of the sugar residue in the compounds obtained.

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