SYNTHESIS AND PHARMACOLOGICAL STUDY OF 3-(β-ARYL-β-HYDROXYETHYLAMINO)- AND 3-(γ-ARYLOXY-β-HYDROXYPROPYLAMINO)QUINUCLIDINES

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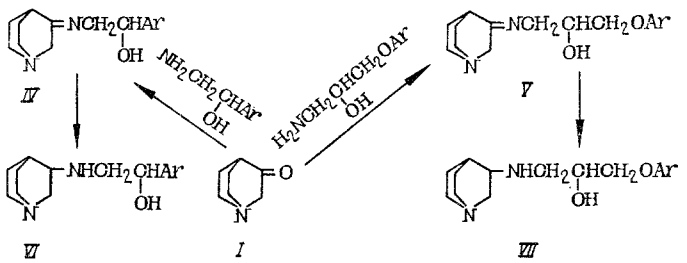
We have shown [1, 2] that quinuclidine derivatives have much higher activity toward the cholinergic, histaminergic, and serotoninergic systems than do the equivalent aliphatic and monocyclic compounds. Moreover by comparison with piperidine or pyrrolidine derivatives the quinuclidine compounds (analogs of the psychostimulant pyridrol, the antiemetic sulpiride, and the antitussive agent bithiodine) are devoid of pharmacological activity toward certain functions of the central nervous system [3].

There is considerable theoretical and practical interest in the question of the extent to which the distinctive features of the interaction of the deshielded lone pair of the quinuclidine nitrogen with receptors are common to different biochemical systems and in particular to adrenergic systems. In this context the β-aryl-β-hydroxyethylamino- and γ-aryloxy-β-hydroxypropylamino derivatives of quinuclidine demand attention, in that they contain groups found in the molecules of preparations (anapriline, etc.) that have become used as β-adrenergic blocking agents in medicine.

We have therefore synthesized 3-(β-aryl-β-hydroxyethylamino)- and 3-(γ-aryloxy-β-hydroxypropylamino)quinuclidines.

The starting compound for the synthesis was 3-quinuclidinone (I), which we reacted with β-aryl-β-hydroxyethylamines (II) and γ-aryloxy-β-hydroxypropylamines (III). We reduced the resulting azomethines (IV, V) with lithium aluminum hydride, sodium borohydride, or catalytically in the presence of platinum to 3-(β-aryl-β-hydroxyethylamino)- (VI) and 3-(γ-aryloxy-β-hydroxypropylamino)quinuclidines (VII).



II, IV, VI a: Ar = 1-$C_{10}H_7$
II, IV b: Ar = 4-$NO_2C_6H_4$
VI b: Ar = 4-$NO_2C_6H_4$

III, V, VII a: Ar = 1-$C_{10}H_7$
b: Ar = C_6H_5
c: Ar = 2-$CH_3C_6H_4$
d: Ar = 3-$CH_3C_6H_4$

We obtained hydroxy amine VIa as a single diastereomer and VIb as two diastereomers; compounds VII were mixtures of diastereomers.

We also examined the possibility of synthesizing hydroxyamine VIIa by reaction of 3-aminoquinuclidine with 1,2-epoxy-3-(1-naphthyloxy)propane. In this case the epoxide ring did not open at room temperature and we obtained by heating the components a mixture of compounds, from which we were unable to isolate pure VIIa.

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EXPERIMENTAL PHARMACOLOGICAL PART

We screened compounds VIa, VIb, and VIIa-d in terms of various pharmacological indices. Because of the similarity of their chemical structure to those of compounds that affect the andrenergic structures (isadrine, anaproline) or have vasodilator antiadrenergic properties (difril, bamethan sulfate), we gave most attention to their effects on the peripheral adrenergic systems. The presence of the quinuclidine nucleus motivated a study of their effect on the central and peripheral cholinergic systems. We also examined their antiarrhythmic and local anesthetic properties, general effect, and acute toxicity.

We examined the sympathomimetic properties in comparison with adrenaline in terms of their effect on the arterial pressure and the nictitating membrane in urethane-narcotized cats. In the same tests (in comparison with isadrine) we examined their effect on the cardiac frequency. The EKG was recorded with an EKIT-OZM electrocardiogram at the second standard contact point. We also assayed the peripheral sympathomimetic properties in terms of their effect on isolated rabbit ear tracheae.

We evaluated the α-sympatholytic activity from the ability to reduce the pressor action of adrenaline in narcotized cats and the adrenaline-induced contraction of the nictitating membrane. We assessed the β-adrenergic blocking activity from the reduction in the depressor response and in the cardiac acceleration induced by isadrine (0.5-2 μg/kg) in narcotized cats.

We assayed the antiarrhythmic activity in male rats of weight 100-160 g under urethane narcosis (10% solution, 1 ml per 100 g weight intraperitoneally). We examined the effect of the preparations on aconitine-induced arrhythmias (30 μg/kg intravenously) [4-6]. The EKG's were recorded at the second contact point.

We assessed the effect on the central m- and n-cholinergic systems from the modification of the convulsant effects of arecoline (15 mg/kg subcutaneously) and nicotine (10 mg/kg subcutaneously) in mice. We examined the peripheral cholinolytic activity in terms of their effect on spasm of rabbit intestine sections induced by acetylcholine ($2 \cdot 10^{-6}$ g/ml). We examined the local anesthetic effect on rabbit cornea by Reniot's method. The toxicity was determined intravenously in white mice; LD_{50} was calculated by Kerber's method.

Results and Discussion

Our work revealed that none of the compounds have sympathomimetic properties. In narcotized cats in doses of 1-5 mg/kg preparations VI and VII caused brief reduction in the arterial pressure, did not contract the nictitating membrane, and in a concentration of $1 \cdot 10^{-5}$ g/ml had a weak vasoconstrictor effect (5-10%). In contrast to the β-stimulator isadrine, which is active in a dose of 0.5 μg/kg, compounds VI and VII did not accelerate the cardiac contractions in narcotized cats.

In doses of 1-5 mg/kg the preparations did not reduce the pressor effect of adrenaline: the adrenaline-induced contraction of the nictitating membrane, and had no effect on the depressor response and cardiac acceleration induced by isadrine in narcotized cats, i.e., they had neither α- nor β-adrenergic blocking properties.

Compound VIa prevented the onset of aconitine arrhythmia in rats. The intravenous administration of aconitine to control rats in a dose of 30 μg/mg in all cases disrupted the cardiac rhythm. The effect developed 2-5 min after administration, the individual extrasystoles were replaced by ventricular bigeminia. The sinus rhythm was not restored in general in the first hour and ventricular fibrillation ensued with fatal outcome. Preparations VIa, VIb, and VIIa-d were administered intravenously in doses of 3.5 and 10 mg/kg (1/2 LD_{50}) 10 min before intravenous injection and 1 min after it. The preliminary administration (10 min in advance) of preparation VIa in doses of 3 and 5 mg/kg prevented the development of aconitine arrhythmia and death of the animals. The protective effect was not apparent on a background of established arrhythmia. The antiarrhythmic effect of the preparation was not connected with the β-blocking activity, since it did not modify the effect of isadrine. Preparations VIa and VIIa-d had no antiarrhythmic activity.

The tests on mice and on isolated rabbit intestine section revealed that the preparations have no effect on the peripheral and central cholinergic systems. In 0.5% and 1% solution preparation VIa had a slight local anesthetic effect but this was inferior to that of dicaine. The other preparations had no local anesthetic activity.

In white mice all the test compounds in the toxic doses caused dyspnea and slight tremor and convulsions, which intensified with increase in the dose.

The LD_{50} in white mice on intravenous administration of compounds VIa, VIb, and VIIa-d was 142.5, 119.5, 73, 71, 22.5, and 5.7 mg/kg respectively.

Thus of these quinuclidine derivatives compound VIa — 3-[β-hydroxy-β-(1-naphthyl)ethylamino]quinuclidine dichloride — has antiarrhythmic and local anesthetic activity. It is less active than known antiarrhythmic and local anesthetic agents.

These compounds have no sympathomimetic, sympatholytic, cholinomimetic, or cholinolytic activity.

EXPERIMENTAL CHEMICAL PART

3-[β-Hydroxy-β-(1-naphthyl)ethylamino]quinuclidine (VIa). A. A mixture of β-hydroxy-β-(1-naphthyl)ethylamine (IIa) (4 g, 21.4 mmole) and 3-quinuclidinone (2.67 g, 21.4 mmole) in benzene (50 ml) was heated under a Dean—Stark trap for 6 h. The benzene was then stripped off. The residue of azomethine IVa was dissolved in absolute ethanol (70 ml) and hydrogenated in the presence of platinum oxide (0.5 g) until the uptake of hydrogen ceased. The catalyst was filtered off, the alcohol was stripped under vacuum, and the residue was dissolved in ether. On cooling compound VIa (2.33 g, 38.5%) precipitated as a single diastereomer, mp 103-105°C (from ether). Found, %: C 65.21, H 8.51, N 7.82, H_2O 15.32. $C_{19}H_{24}N_2O \cdot 3H_2O$. Calculated, %: C 65.15, H 8.34, N 7.96, H_2O 15.42.

Dichloride, mp 241-242°C (decomposition; from ethanol—methanol). Found, %: C 58.80, H 7.46, Cl 18.53. $C_{19}H_{24}N_2O \cdot 2HCl \cdot H_2O$. Calculated, %: C 59.0, H 7.64, Cl 18.32.

The base (1.45 g) was isolated from the ethereal mother liquor with mp 80-87°C, it was a mixture of two diastereomers of VIa.

B. A solution of amine IIa (4.7 g, 25 mmole) and ketone I (3.14 g, 25 mmole) in toluene (50 ml) was heated in the presence of several small crystals of p-toluenesulfonic acid until the liberation of water ceased. The reaction mixture was decolorized with carbon and evaporated under vacuum. The residue was dissolved in a mixture of ether (50 ml) and benzene (50 ml). Lithium aluminum hydride (2 g, 53 mmole) was added to the resulting solution over a period of 30 min and the mixture was stirred under reflux for 3 h. It was then cooled and treated with water (4 ml). The hydroxide was filtered off and washed with hot chloroform. The combined solutions were evaporated. The residue was dissolved in ether (10 ml) and heptane was added until it became cloudy. After 20 h a precipitate formed and was filtered off. The yield of base VIa was 4.6 g (62%), mp 99-101°C.

Alcoholic hydrogen chloride precipitated the dihydrochloride from acetone solution of base VIa, it was recrystallized from ethanol in a yield of 1.3 g with mp 241-242°C. The compound was identical to the sample prepared by method A.

3-[β-Hydroxy-β-(4-aminophenyl)ethylamino]quinuclidines (VIb). A mixture of β-hydroxy-β-(4-nitrophenyl)ethylamine (7.35 g, 40 mmole), ketone I (5.25 g, 42 mmole), and several small crystals of p-toluenesulfonic acid in toluene (100 ml) was heated with azeotropic removal of water. When the liberation of water ceased the reaction mixture was decolorized with carbon and evaporated under vacuum. The oily residue of compound IVb was dissolved in ethanol (100 ml) and the alcoholic solution was hydrogenated in the presence of platinum oxide (0.5 g). After the end of hydrogenation the platinum was filtered off, the alcohol was stripped off, and the residue was triturated with acetone (10 ml). Ether (60 ml) was added and after 20 h compound VIb (6.4 g, 58.5%) was filtered off as a mixture of two diastereomers, mp 118-122°C. The mixture (3 g) was recrystallized from ethyl acetate (150 ml) to give isomer A (1.15 g), mp 165-167°C. Found, %: C 68.81, H 8.58, N 16.08. $C_{15}H_{23}N_3O$. Calculated, %: C 68.88, H 8.86, N 16.13. The mother liquor after the removal of isomer A was treated with carbon and kept at 4°C for 20 h to give isomer B (0.7 g), mp 129-130°C. Found, %: C 68.56, H 8.92, $C_{15}H_{23}N_3O$. Calculated, %: C 68.88, H 8.56.

Tartrate of Isomer A, mp 101-102°C. Found, %: C 49.8, H 7.0. $C_{15}H_{23}N_3O \cdot C_4H_6O_6 \cdot 1.5H_2O$. Calculated, %: C 49.9, H 7.0.

Tartrate of Isomer B, mp 93-94°C. Found, %: C 53.2, H 7.8 $C_{15}H_{23}N_3O \cdot C_4H_6O_6 \cdot H_2O$. Calculated, %: C 52.9, H 8.0.

β-Hydroxy-γ-(1-naphthyloxy)propylamine (IIIa). To 1,2-epoxy-3-(1-naphthyloxy)propane (7.25 g, 36.3 mmole) was added 23% methanolic ammonia (100 ml). The resulting solution was kept at room temperature for 48 h. The reaction mixture was evaporated under vacuum and the residue was triturated with dry ether. The yield was 6.2 g (79%), mp 97-99°C [7]. Found, %: C 71.95, H 6.76, N 6.33. $C_{13}H_{15}NO_2$. Calculated, %: C 71.84, H 6.93. N 6.45.

The same method was used to prepare: a) β-hydroxy-γ-(3-tolyloxy)propylamine (IIId), reaction time 90 h, yield 88%, mp 77-78°C [8]. Found, %: N 7.67. $C_{10}H_{15}NO_2$. Calculated, %: N 7.74; b) β-Hydroxy-γ-(2-tolyloxy)propylamine (IIIc), reaction time 92 h, yield 78%, mp 64-66°C [9]. Found, %: C 66.11, H 8.24. $C_{10}H_{15}NO_2$. Calculated, %: C 66.32, H 8.34.

3-[γ-Hydroxy-γ-(1-naphthyloxy)propylamino]quinuclidine (VIIa) was prepared from amine IIIa (6.5 g, 30 mmole) and 3-quinuclidinone (3.75 g, 30 mmole) by the method used to synthesize compounds VI. An alcoholic solution of hydroxy amine VIIa (60 ml) was mixed with a solution of d-tartaric acid (4.5 g, 30 mmole) in ethanol (60 ml); the tartrate precipitated. The alcohol was decanted. The residue was triturated with acetone (50 ml), dissolved in ethanol (30 ml), and poured into hot acetone (60 ml). The precipitate was filtered off and washed with acetone to give the tartrate of VIIa (4.35g, 28%) mp 92-93,C (decomposition). Found, %: C 55.41; H 6.97; N 4.91. $C_{20}H_{26}N_2O_2 \cdot C_4H_6O_6 \cdot 2.5H_2O$. Calculated, %: C 55.27, H 7.15, N 5.36.

3-[β-Hydroxy-γ-(2-tolyloxy)propylimino]quinuclidine (Vc). A mixture of β-hydroxy-γ-(2-tolyloxy)propylamine (5.1 g, 28.2 mmole), 3-quinuclidinone (3.25 g, 28.2 mmole), several small crystals of p-toluenesulfonic acid, and toluene (50 ml) was heated for 10 h with azeotropic removal of water. The reaction mixture was treated with carbon and then evaporated. The residue was distilled. The yield was 5.3 g (65.5%), bp 188-190°C (0.4 mm). Found, %: C 70.70, H 8.26, N 9.73. $C_{17}H_{24}N_2O_2$. Calculated, %:C 70.78, H 8.37, N 9.71.

The same method was used to prepare: a) 3-(β-hydroxy-γ-phenoxypropylimino)quinuclidine (Vb), yield 55%, bp 183-186°C (1.5 mm). Found, %: C 69.73; H 7.95; N 10.36. $C_{16}H_{22}N_2O_2$. Calculated, %: C 70.10; H 8.03; N 10.36; b) 3-[β-Hydroxy-γ(3-tolyloxy)propylimino]quinuclidine (Vd), yield 81.5%, bp 191-193°C (0.3 mm). Found, %: C 70.78; H 7.37; N 9.71. Calculated, %: C 70.78; H 7.37; N 9.71.

3-[β-Hydroxy-γ-(2-tolyloxy)propylamino]quinuclidine (VIIc). To a solution of azomethine Vc (4 g, 22 mmole) in ethanol (70 ml) was added sodium borohydride (2 g) over 20 min. The reaction mixture was kept at room temperature for 20 h and then evaporated under vacuum. The residue was mixed with water (40 ml) and extracted with chloroform. After removal of the chloroform the residue was distilled. The yield was 2.95 g (73.5%), bp 211-213°C (1.5 mm). Found, %: C 70.32; H 9.03; N 9.67. $C_{17}H_{26}N_2O_2$. Calculated, %: C 70.31; H 9.04; N 9.66.

Tartrate, mp 96-99°C (decomposition). Found, %: C 55.63; H 7.15; N 5.8. $C_{17}H_{26}N_2O_2 \cdot C_4H_6O_6 \cdot H_2O$. Calculated, %: C 55.26, H 7.07, N 6.14.

The same method was used to prepare 3-[β-hydroxy-γ-(3-tolyloxy)propylamino]quinuclidine (VIId), yield 63%, bp 207-209°C (1 mm). Found, %: C 69.9, H 8.99, N 9.55, $C_{17}H_{26}N_2O_2$. Calculated, %: C 70.31, H 9.04, N 9.66.

Tartrate, mp 91-94°C. Found, %: C 55.51, H 7.27, N 6.31. $C_{17}H_{26}N_2O_2 \cdot C_4H_6O_6 \cdot H_2O$. Calculated, %: C 55.26, H 7.28, N 6.14.

3-(β-Hydroxy-γ-phenoxypropylamino)quinuclidine (VIIb), yield 69%, bp 179-181°C (0.6 mm). Found, %: C 69.61, H 8.81, N 10.32. $C_{16}H_{24}N_2O_2$. Calculated, %: C 69.60, H 8.72. N 10.14.

Tartrate, mp 82-84°C (decomposition). Found, %: C 51.88, H 6.92. $C_{16}H_{24}N_2O_2 \cdot C_4H_6O_6 \cdot 2H_2O$. Calculated, %: C 52.0, H 7.36.

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BIOLOGICAL ACTIVITY OF TRANSFORMED STEROIDS. XIV.* SYNTHESIS AND BIOLOGICAL ACTIVITY OF ISOXAZOLINO- AND ISOXAZOLIDINO[16α, 17α-d] STEROIDS

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It is known that heterocyclic steroids containing an oxazole ring condensed with the steroid molecule have high biological activity [2].

We carried out the reaction of 1,3-dipolar cycloaddition of nitronic esters to 16-dehydro-20-ketosteroids (1), which leads to the class of isoxazolidino- and isoxazolino-[16α, 17α-d] steroids [3, 4].

In the present article we describe the synthesis and the results of testing the biological activity of several representatives of this class of modified steroids. The synthesis was carried out as shown in the scheme. Depending on the conditions for carrying out the cycloaddition, either isoxazolidino steroids of type II or isoxazolino steroids of type III are obtained. The latter were obtained during a catalytic (Lewis acids) variant of cycloaddition, while the fully saturated N-methoxy compounds of type II were obtained by the cycloaddition of the nitronic esters to I at high pressure. Since the reaction of 16-dehydroprogesterone with nitronic esters in the presence of boron trifluoride ethereate was accompanied by a considerable resinification of the reaction mixture, we developed a prepara-

*Article XIII, see [1].

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