SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 2-BENZYLQUINUCLIDINE ANALOGS OF DOPAMINE

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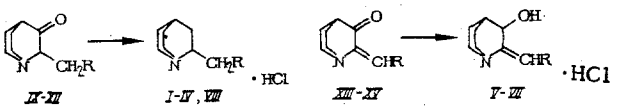
Derivatives of 2-benzylquinuclidine that contain hydroxyl groups in the aryl fragment of the molecule can be considered bicyclic analogs of the biogenic amine dopamine that have an aminomethyl residue included in the quinuclidine ring.

Dopamine [2-(3,4-dihydroxyphenyl)ethylamine], which is formed in the body in the process of epinephrine and norepinephrine biosynthesis, is a ligand for dopamine receptors [5, 6]. The mechanism of dopamine's pharmacological action is rather complex. In small doses it exhibits a specific stimulating effect on dopamine receptors, and in large doses it also stimulates α- and β-adrenergic receptors [7-9]. In medical practice dopamine HCl is used as a pressor agent in shock conditions in heart surgery and for the treatment of emergency conditions [2, 4, 10, 12, 13].

In connection with dopamine's high degree of pharmacological activity, we felt it would be of interest to synthesize and study its analogs and derivatives, particularly those compounds that contain, in addition to dopamine's alkyl aromatic fragment, a quinuclidine nucleus which is characterized by the high basicity of the tertiary nitrogen atom.

We have demonstrated earlier that quinuclidine compounds have a greater effect on cholinergic, histamine- and serotonin-producing systems than analogous derivatives of aliphatic or monocyclic amines [3, 11]. The practical result of those studies was the introduction of the new medicinal preparations aceclidine, oxylidine, temequine, phenkarol, and others.

The following compounds (I-VIII) were synthesized and studied for the purpose of comparing them to dopamine:



II-III I-IV, VIII XIII-XV V-VII

I: R = 3,4-$(HO)_2C_6H_3$; II, IX: R = 2-HOC_6H_4; III, X: R = 2-HO-5-$CH_3C_6H_3$; IV, XI: R= = 2-HO-5-$CH_3OC_6H_3$; V, XIII: R = 4-$CH_3OC_6H_4$; VI, XIV: R = 3,4-$(CH_3O)_2C_6H_3$; VII, XV: R = 2-ClC_6H_4; VIII, XII: R = 1-HO-(naphthyl-2)

With the exception of compound VII, all of the synthesized quinuclidine derivatives retained two carbon atoms between the phenyl nucleus and the amino group that is characteristic of dopamine, and an aromatic fragment of the molecule that contains a free or O-alkylated hydroxy group. The closest dopamine analog is compound I which has two hydroxyl group in positions 3 and 4, just as dopamine does. In contrast to the others, the aryl fragment in compound VIII is a naphthyl group which allowed us to determine the kind of effect that the aryl group would have on the biological properties of the substances under examination.

Compound I was obtained by the method described in [1]. Compounds II-IV and VIII were synthesized by the hydrazine hydrate reduction of corresponding substituted 2-benzyl-3-oxoquinuclidines (IX-XII) [1] in diethylene glycol in the presence of KOH. The 3-oxy-derivatives V-VII were synthesized by the sodium borohydride reduction of substituted 2-benzylidene-3-oxoquinuclidines (XIII-XV) [1].

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2-(2-oxybenzyl)quinuclidine (II). A mixture of 3 g (13 mmole) of 2-(2-oxybenzyl)-3-oxoquinuclidine (IX), 6 g of KOH, 6 ml of hydrazine hydrate, and 30 ml of diethylene glycol was heated for 5 h at 145-140°C, and then for 10 h at 170-175°C (oil bath). The reaction mixture was concentrated in a vacuum, and 30 ml of water were added to the residue. After the mixture was cooled (10°C), concentrated HCl was added to bring the pH to 1.0. The acidic solution was made alkaline by a 50% solution of patash and extracted with $CHCl_3$. After the $CHCl_3$ was distilled off, the residue was recrystallized from heptane. Yield of compound II 2 g (71%), mp 104-106°C. Found, %: C 77.36; H 8.87; N 6.45. $C_{14}H_{19}NO$. Calculated, %: C 77.38; H 8.81; N 6.44.

Hydrochloride — mp 241-243°C (from ethanol). Found, %: C 66.15; H 7.83; Cl 13.80; N 5.30. $C_{14}H_{19}O \cdot HCl$. Calculated, %: C 66.26; H 7.95; Cl 13.99; N 5.33. Compounds III and IV were obtained in a similar fashion.

2-(2-Oxy-5-methoxybenzyl)-3-oxyquinuclidine (III). A yield of 1.5 g (54%) of compound III was obtained from 3 g (12 mmole) of 2-(2-oxy-5-methylbenzyl)-3-oxoquinuclidine (X), mp 144-146°C (from ethyl acetate). Found, %: C 77.96; H 9.12; N 5.85. $C_{15}H_{21}NO$. Calculated, %: C 77.88; H 9.15; N 6.05.

Hydrochloride — mp 191-193°C (from ethanol). Found, %: C 67.50; H 7.93; Cl 13.27; N 5.27. $C_{15}H_{21}NO \cdot HCl$. Calculated, %: C 67.28; H 8.28; Cl 13.24; N 5.23.

2-(2-Oxy-5-methoxybenzyl)quinuclidine (IV). A yield of 1.75 g (42%) of compound IV was obtained from 4.7 g (18 mmole) of 2-(2-oxy-5-methoxybenzyl)-3-oxoquinuclidine (XI), mp 123-125°C (from ethyl acetate). Found, %: C 72.57; H 8.69; N 5.91. $C_{15}H_{21}NO_2$. Calculated, %: C 72.84; H 8.56; N 5.60.

Benzoate — mp 146-147°C. Found, %: N 3.12. $C_{15}H_{21}NO_2$. Calculated, %: N 3.09.

2-(1-Oxynaphthyl-2-methyl)quinuclidine HCl (VIII). A mixture of 2 g (7 mmole) of 2-(1-oxynaphthyl-2-methyl)-3-oxoquinuclidine, 4 ml of hydrazine hydrate, 4 g of KOH, and 20 ml of diethylene glycol was heated for 4 h at 150-160°C, and then for 6 h at 180°C (oil bath). The reaction mixture was concentrated in a vacuum, treated with HCl (pH 1.0), and extracted with ether. The acidic solution was made alkaline by potash and the reaction products were extracted with ether. The ether was vacuum distilled, the residue was ground with heptane, and once again dissolved in ether and treated by an HCl alcohol solution. Yield 1.2 g (57%) of compound VIII, mp 230-233°C. Found, %: C 71.07; H 7.04; Cl 11.68; N 4.76. $C_{18}H_2NO \cdot HCl$. Calculated, %: C 71.16; H 7.29; Cl 11.65; N 4.61.

2-(4-Methoxybenzylidene)-3-oxyquinuclidine (V). A 5-g portion of $NaBH_4$ was added, with stirring, to a solution of 5 g (20 mmole) of 2-(4-methoxybenzylidene)-3-oxyquinuclidine (XIII) in 130 ml of ethanol. The reaction mixture was kept at 20°C for 24 h after which the ethanol was distilled off and the residue was dissolved in 25 ml of water and extracted with CH_2Cl_2. The extract was concentrated and the residue ground with ether. Yield 4 g (80%), mp 69-72°C. Found, %: C 73.56; H 7.95; N 5.82. $C_{15}H_{19}NO_2$. Calculated, %: C 73.44; H 7.84 N 5.71.

Hydrochloride — mp 182-184°C (from isopropanol). Found, %: Cl 12.74, N 5.07. $C_{15}H_{19}NO_2 \cdot HCl$. Calculated, %: Cl 12.58, N 4.97.

Compounds VI and VII were obtained in a similar fashion.

2-(3,4-Dimethoxybenzylidene)-3-oxyquinuclidine (VI). A yield of 4.8 g (95%) of compound VI was obtained from 5 g (18.2 mmole) of 2-(3,4-dimethyoxybenzylidene)-3-oxoquinuclidine (XIV), bp 185-186°C (0.4 mm), mp 101-103°C. Found, %: C 69.93; H 7.72; N 4.99. $C_{16}H_{21}NO_3$. Calculated, %: C 61.62; H 7.13; Cl 11.38; N 4.50.

2-(2-Chlorobenzylidene)-3-oxyquinuclidine (VII). A yield of 3.75 g (75%) of compound VII was obtained from 5 g (20 mmole) of 2-(2-chlorobenzylidene)-3-oxoquinuclidine (XV), mp 90-92°C (from a 1:1 mixture of heptane and petroleum ether). Found, %: C 66.94; H 6.48; Cl 14.18; N 5.72. $C_{14}H_{16}ClNO$. Calculated, %: C 67.33; H 6.46; Cl 14.20; N 5.61.

Hydrochloride — mp 209-211°C (with decomposition). Found, %: Cl 23.46. $C_{14}H_{16}ClNO \cdot HCl \cdot H_2O$. Calculated, %: Cl 23.31.

EXPERIMENTAL (PHARMACOLOGICAL SECTION)

Compounds I-VIII were tested for various pharmacological properties that are characteristic of dopamine and other catecholamines. Also examined was their influence on effects associated with the stimulation of central and peripheral cholinergic and histamine-producing systems. In addition, studies were made of their local anesthetic and overall activity, and "acute" toxicity.

As is known, small doses (10-20 μg/kg) of dopamine in narcotized cats usually reduces arterial pressure (AP) by 10-30 mm Hg. When the dose is increased to 100-250 μg/kg, the observed rise in AP is accompanied by shallower respiration and weakened third eyelid contraction.

Large doses (1-5 mg/kg) are found to result in a distinct adrenomimetic reaction, i.e., a pronounced rise in AP and third eyelid contraction.

In contrast to dopamine, its quinuclidine analog I, even at a dose as low as 20 μg/kg, after a brief AP reduction, causes a constant AP rise, accelerated and increased respiration, and third eyelid contraction. At doses of from 100-250 μg/kg compound I causes a significant hypertensive reaction that greatly exceeds the hypertension action of dopamine. Prolonged, stable third eyelid contraction is simultaneously observed (see Fig. 1).

At doses of from 20-100 μg/kg, compound I intensifies AP, respiratory, and third eyelid responses to epinephrine. At concentrations of 10^{-6} and 10^{-5} g/ml it simulates dopamine's vasoconstrictor effect on isolated rabbit ear, but to a lesser extent (the vasoconstrictor action of compound I was 13% and 65%, respectively , whereas that of dopamine was 76% and 98%).

An analysis of the mechanism underlying the action of compound I demonstrated that the hypertensive phase of the reaction, third eyelid contraction, and respiratory stimulation are not only due to dopamine's excitation of peripheral and α-adrenoreceptors, but also due to the stimulating effect upon autonomic nervous system ganglia. Actually, the AP rise and third eyelid contraction induced by compound I are diminished by α-adrenergic blocking agents such as phentolamine (0.2 mg/kg) and tropaphen (0.5 mg/kg), and the hypertensive reaction and respiratory stimulation are also significantly reduced by the ganglion blocker hexonium (2 mg/kg). At the same time, dopamine's hypertensive reaction is potentiated by hexonium.

In contrast to compound I, compounds II-IV and VIII at doses of from 0.1 to 5 mg/kg, induce an acute brief drop in AP which is accompanied by respiratory arrest. The hypertensive phase induced by the administration of compounds V-VII was observed to be unstable and was manifested only at high doses (10-20 mg/kg). No third eyelid contraction was observed upon the administration of quinuclidine derivatives II-VIII.

At a dose of 5 mg/kg, all of the compounds, except the 3-oxy derivatives of quinuclidine VI and VII, somewhat potentiated arterial pressure and third eyelid response to epinephrine. In contrast to dopamine, compounds II-VIII did not cause vasoconstriction in the isolated rabbit ear. At a dose of 5 mg/kg compounds II and III inhibited vagal cardiac stimulation for a period of 2 h whereas compound VIII inhibited that action for 30 min. However, compounds II and III did not affect the depressor response induced by the administration of acetylcholine. Compounds II and III exhibit a central n-cholinolytic action. When they were administered intravenously to white mice (at 4 and 7 mg/kg, respectively) at a level which was one-third of the LD_{50} dose, they reduced the frequency of nicotine-caused fatalities and convulsion.

Experiments on mice and isolated rabbit intestine section demonstrated that compounds I-VIII do not affect the peripheral and central m-choline-responsive systems. For example, at a concentration of 10^{-6} g/ml they did not affect the spastic action of arecoline in white mice, and reduced the spasmogenic action of acetylcholine only at a concentration of 10^{-5} g/ml.

Experiments on isolated guinea pig intestine demonstrated that compounds I-VIII do not have any local anesthetic action.

The LD_{50}s for white mice upon the intravenous administration of compounds I-VIII were 5.7, 12.5, 19.5, 43, 225.5, 247.5, 136.5, and 42 mg/kg, respectively. The LD_{50} for dopamine was 180 mg/kg.

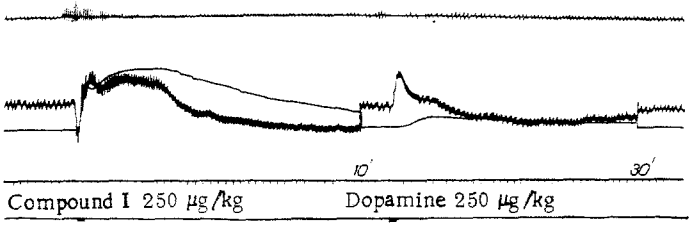

Fig. 1. Effect of compound I and dopamine at a dose of 250 μg/kg on arterial pressure, respiration, and third eyelid contraction of a urethane-narcotized cat. From top to bottom: Arterial pressure, third eyelid tonicity, time (5 sec) and kymograph stop marker, and preparation administration marker.

Thus, if the alkyl amine fragment of the dopamine molecule is replaced by a bicyclic quinuclidine nucleus, there is a significant change in pharmacological activity. 2-(3,4-dioxybenzyl)quinuclidine HCl has a significantly greater sympathomimetic action than dopamine and primarily affects autonomic ganglia. The quinuclidine analog is significantly more toxic than dopamine.

The introduction of an oxy group in position 2 of the phenyl ring (compounds II and III) results in weak central peripheral n-cholinolytic activity. The cholinergic and adrenergic systems are not affected by the remaining compounds (IV-VIII).

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