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SYNTHESIS AND ANTIARRHYTHMIC ACTIVITY OF SUBSTITUTED 3-p-CHLOROPHENOXY-ACETYLAMINOQUINUCLIDINES

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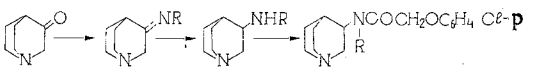
In continuation of the investigations previously carried out by us on the search for new antiarrhythmic agents among 3-amino and 2-aminomethylquinuclidines [1] we have synthesized and studied the antiarrhythmic action of new derivatives of 3-aminoquinuclidine containing a p-chlorophenoxyacetyl group as an acyl residue.

The synthesis of the substituted 3-p-chlorophenoxyacetylaminoquinuclidines (IVa-d) was effected according to the following scheme:



I IIa-d IIIa-d IVa-d

II — IV a: R = C_6H_5, b: R = p — ClC_6H_4, c: R = o-ClC_6H_4, d: R = $C_6H_5CH_2$.

According to the procedure described in the previous paper [1] quinuclid-3-one (I) was condensed with primary aromatic or aliphatic—aromatic amines and the resulting imino compounds (II) reduced to the secondary amine (III). Acylation of compounds (III) was effected with the acid chloride of p-chlorophenoxyacetic acid in a medium of boiling chloroform checking for the end of the reaction by the disappearance of the initial amine (III) by TLC. The process occurred fairly slowly (from 30 to 60 h) which is evidently linked with the steric hindrance of the substituted amino group in the quinuclidine nucleus.

On using sterically hindered aromatic amines (2,6-dichloroaniline, mesidine, etc.) difficulty was encountered even at the stage of obtaining the imino derivatives (II). Various procedures for condensation were studied, in boiling toluene or xylene in the presence of toluene-p-sulfonic acid with azeotropic distillation of water [1], melting in the presence of the same catalyst at 200°C, the use of molecular sieve type 3A as a water removing agent [2], phosphorus oxychloride [3], phosphorus pentoxide [4], etc., which did not lead to the appropriate imino compound (II).

The synthesized compounds (IVa-d) in the form of hydrochlorides displayed marked but short-term antiarrhythmic activity in experiments in animals. In addition these same compounds, as shown by the investigations of G. N. Pershin and L. M. Polukhina in the Laboratory of Chemotherapy of the All-Union Scientific-Research Institute of Pharmaceutical Chemistry (VNIKhFI), possessed marked activity in in vitro experiments in relation to gram positive bacteria (MTC 31.2-125 mg/ml) and acid-sensitive mycobacteria (MTC 15.6-62.5 μg/ml) but were weakly active in relation to gram negative bacteria and pathogenic fungi.

EXPERIMENTAL CHEMISTRY

3-[N-Phenyl-N-(p-chlorophenoxyacetyl)]aminoquinuclidine (IVa). p-Chlorophenoxyacetyl chloride (2.11 g:10 mmole) was added dropwise with stirring and water cooling to a solution of (IIIa) (1.8 g: 8.9 mmole) in dry chloroform (30 ml). The mixture was boiled for 57 h, checking the course of the reaction by TLC (system CH_3OH—$CHCl_3$—NH_4OH 20:20:1, R_f IVa 0.55, R_f IIIa 0.32). The reaction mixture was cooled, water (20 ml) added, then concentrated hy-

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drochloric acid (1 ml) to pH 1.0, and extracted with chloroform. The extract was washed with 25% potassium carbonate solution, dried over magnesium sulfate, and evaporated. An oily substance (3.4 g) was obtained which was triturated with ether and recrystallized from heptane (100 ml). Compound (IVa) (1.54 g: 46%) was obtained as colorless crystals mp 101-103°C. The substance was readily soluble in benzene, acetone, chloroform, and alcohols, poorly soluble in water, cold ether, heptane, and toluene. Found, %: C 68.15; H 6.36; Cl 9.63; N 7.56. $C_{21}H_{23}ClN_2O_2$. Calculated, %: C 67.90; H 6.28; Cl 9.60; N 7.56.

Hydrochloride of (IVa). This was a white crystalline powder mp 235-237°C. The substance was poorly soluble in water, acetone, benzene, ethyl and isopropyl alcohols, readily soluble in methanol and chloroform. Found, %: C 61.74; H 5.92; Cl 17.35; N 6.85. $C_{21}H_{23}ClN_2O_3 \cdot HCl$. Calculated, %: 61.80; H 5.94; Cl 17.40; N 6.86.

3-[N-(p-Chlorophenyl)-N-(p-chlorophenoxyacetyl)]aminoquinuclidine (IVb). p-Chlorophenoxyacetyl chloride (3.66 g: 18 mmole) was added dropwise with stirring and water cooling to a solution of (IIIb) (3.6 g: 15 mmole) in dry chloroform (50 ml). The mixture was boiled for 30 h, checking the course of the reaction by TLC (system CH_3OH—NH_4OH 20:2 R_f IVb 0.71, R_f IIIb 0.43). Water (60 ml) and concentrated hydrochloric acid (1.5 ml) were added to the cooled reaction mixture to pH 1.0. The solution was extracted with chloroform, the extract dried with magnesium sulfate, and evaporated. An insignificant amount of contaminating dark oily substance remained. The aqueous acid solution after separating off the chloroform was made alkaline with 25% potassium carbonate solution, and once again extracted with chloroform. The chloroform extract was dried with magnesium sulfate and evaporated. The residue was triturated under heptane and drecrystallized from heptane (130 ml). Yield was 2.4 g (38%) of colorless crystals mp 148-150°C. The substance was readily soluble in benzene, toluene, acetone, chloroform, and alcohols, poorly in water, cold ether, and heptane. Found, %: C 62.20; H 5.46; Cl 17.10; N 7.13; $C_{21}H_{22}Cl_2N_2O_2$. Calculated, %: C 62.20; H 5.43; Cl 17.50; N 6.92.

Hydrochloride of (IVb). This formed colorless crystals mp 232-234°C. The substance was poorly soluble in water, chloroform, acetone, cold ethyl and isopropyl alcohols. It was readily soluble in methanol. Found, %: C 56.02; H 5.14; Cl 23.47; N 6.07. $C_{21}H_{22}Cl_2N_2O_2 \cdot HCl$. Calculated, %: C 56.0; H 5.33; Cl 23.72; N 6.22.

3-[N-(o-Chlorophenyl)-N-(p-chlorophenoxyacetyl)]aminoquinuclidine (IVc). p-Chlorophenoxyacetyl chloride (5.29 g: 26 mmole) was added dropwise with stirring and water cooling to a solution of (IIIc) (5.2 g: 22 mmole) in dry chloroform (50 ml). The mixture was boiled for 50 h, the end of the reaction being determined by TLC (system CH_3OH—$CHCl_3$—NH_4OH, 20:20:1, R_f IVc 0.66, R_f IIIc 0.18). The reaction mixture was cooled, water (40 ml) added then concentrated hydrochloric acid (1.5 ml) to pH 1.0, the mixture was extracted with chloroform, the chloroform extract dried with magnesium sulfate, and evaporated. Since the isolation of a crystalline substance from the obtained oily mass by trituration failed, it was dissolved in water, the solution made alkaline with 25% potassium carbonate solution, and extracted with chloroform. The chloroform extract was dried with magnesium sulfate and evaporated. The residue was triturated with hexane and (IVc) (4.15 g: 47.5%) was obtained as colorless crystals of mp 108-110°C. The substance was readily soluble in chloroform, benzene, toluene, alcohols, and hot pentane, and was insoluble in ether. Found, %: C 62.38; H 5.48; Cl 17.42; N 6.94. $C_{21}H_{22}Cl_2N_2O_2$. Calculated, %: C 62.20; H 5.43; Cl 17.50; N 6.92.

Hydrochloride of (IVc). This formed colorless crystals of mp 209-212°C. The substance was readily soluble in chloroform, alcohols, and hot benzene, poorly soluble in water, acetone, ether, and toluene. Calculated, %: C 57.08; H 5.20; Cl 24.12; N 6.34. $C_{21}H_{22}Cl_2N_2O_2 \cdot HCl$. Calculated, %: C 57.20; H 5.10; Cl 23.99; N 6.26.

3-[N-Benzyl-N-(p-chlorophenoxyacetyl)]aminoquinuclidine (IVd). p-Chlorophenoxyacetyl chloride (3.09 g: 15 mmole) was added dropwise with stirring and water cooling to a solution of (IIId) (2.7 g: 12 mmole) in dry chloroform (40 ml). The mixture was boiled for 47 h, the end of the reaction being determined by TLC (system CH_3OH—NH_4OH, 20:2, R_f IVd 0.69, R_f IIId 0.21). The reaction mixture was cooled, water (30 ml) was added, and then concentrated hydrochloric acid (1.5 ml) to pH 1.0. The mixture was extracted with chloroform, the chloroform extract washed with 25% potassium carbonate, dried with magnesium sulfate, and evaporated. An oily substance (1.8 g) was obtained, trituration of which was unsuccessful. The substance was dissolved in ether and the hydrochloride obtained which was recrystallized from isopropanol (60 ml) with a yield of 1.5 g (33%).

Hydrochloride of (IVd). This formed colorless crystals of mp 218-219°C. The substance was poorly soluble in water, benzene, acetone, ethyl and isopropyl alcohols, and was readily soluble in methanol and chloroform. Found, %: C 62.76; H 6.19; N 6.33. $C_{22}H_{25}ClN_2O_2 \cdot HCl$. Calculated, %: C 68.70; H 6.50; N 7.28.

Compound (IVd) Base. This formed colorless crystals of mp 100-101°C. The substance was readily soluble in benzene, toluene, acetone, chloroform, and alcohols, and poorly soluble in water, cold ether, heptane, and hexane. Found, %: C 68.86; H 6.44; Cl 9.13; N 7.34, $C_{22}H_{25}ClN_2O_2$. Calculated, %: C 68.70; H 6.50; N 7.28; Cl 9.22.

EXPERIMENTAL CHEMISTRY

The antiarrhythmic activity of the synthesized compounds was studied on two forms of arrhythmia in rats, on the aconitime arrhythmia model of [5] and on the arrhythmia model caused by calcium chloride of [6]. Experiments were conducted on male rats of weight 100-170 g under urethane anesthesia (1 ml 10% solution per 100 g body weight intraperitoneally). The ECG were recorded at output II. Arrhythmia was caused in the first case by the intravenous injection of aconitine (30 µg/kg) and in the second by the intravenous injection of calcium chloride (0.35 ml 10% solution per 100 g body weight). The inhibitory action of preparations on aconitine arrhythmia was investigated on administration at doses of 0.1, 0.2, and 0.5 LD_{50} 1 min after the development of arrhythmia and the prophylactic antiarrhythmic action of preparations was investigated on administration intravenously 15 min before calcium chloride. Toxicity was determined in white mice on intravenous administration, the LD_{50} was determined by the method of Kerber. This parameter (mg/kg) was 45 (33.5-56.7) for (IVa), 172.5 (152.9-192.1) for (IVb), and 24.5 (24.2-24.7) for (IVc).

All the investigated compounds at a dose of 0.2 LD_{50} proved to have 100% prophylactic antiarrhythmic action, compounds (IVb, c) at the same doses restored the correct rhythm for contractions of cardiac muscle disturbed by the administration of aconitine. However, this effect was temporary and its duration lasted 1-2 min.

The investigated substances therefore proved to be less active in antiarrhythmic activity in comparison with oxylidine the therapeutic quinuclidine preparation which was studied previously in [7].

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