LITERATURE CITED

1. M. D. Mashkovsky and L. N. Jakhontov, Prog. Drug Res., 13, 293-339 (1969).
2. M. E. Kamina, Farmakol. Toksikol., No. 2, 229-231 (1975).
3. M. L. Belen'kii, Elements of the Quantitative Assessment of the Pharmacological Effect [in Russian], Riga (1959), p. 43.
4. M. D. Mashkovskii and K. A. Zaitseva, Farmakol. Toksikol., No. 6, 679-685 (1962).

SYNTHESIS AND ANTIARRHYTHMIC ACTIVITY OF 1,4-DIAZABICYCLO[4. m. 0]ALKANYL AMIDES OF p-NITRO- AND p-AMINOBENZOIC ACIDS

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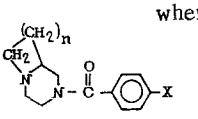
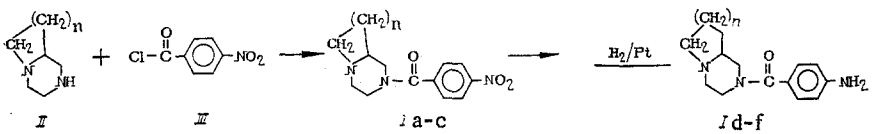
Compounds with psychotropic [1] and antianginal [2] actvity based on 1,4-diazabicyclo[4. m. 0]alkanes have been obtained previously. Data are presented in the present work on the synthesis and antiarrhythmic activity of previously unknown 1,4-diazabicyclo[4. m. 0]alkanyl amides of p-nitro- and p-aminobenzoic acids of general formula (Ia-f).



where a) X=NO$_2$, n=2
b) X=NO$_2$, n=3
c) X=NO$_2$, n=4
d) X=NH$_2$, n=2
e) X=NH$_2$, n=3
f) X=NH$_2$, n=4

Compounds (Id-f) may be considered as analogs of the antiarrhythmic preparation procainamide in which the diethylaminoethylamine residue is replaced by 1,4-diazabicyclo[4. m. 0]-alkanyl radicals. The synthesis of amides (I) was effected according to the scheme:



II III Ia-c Id-f

1,4-Diazabicyclo[4. m. 0]alkanes (II), obtained by methods described previously [3, 4], were converted into the corresponding amides (Ia-c) by acylation with p-nitrobenzoyl chloride (III). The reaction was carried out by boiling amines (II) with a small excess of acid chloride (III) in dichloroethane solution. Crystalline hydrochlorides of amides (Ia-c) were precipitated from the reaction mixture depending on the extent of heating. The bases of these amides, obtained by making alkaline aqueous solutions of the hydrochlorides with aqueous ammonia, were white crystalline substances soluble in organic solvents.

Amides (Ia-c) were reduced (the theoretical quantity of hydrogen was absorbed after 20-30 min) over a platinum catalyst in alcohol solution to the bases of the corresponding aminoamides (Id-f). These were obtained after removal of the catalyst and distilling off solvent as viscous oils crystallizing on rubbing with ether. The hydrochlorides of amides (Id-f) were very hygroscopic substances. The properties and yields of amides (Ia-f) are given in Table 1.

The obtained amides (Ia-f) were subjected to pharmacological study with the aim of clarifying their antiarrhythmic activity (procainamide was taken as standard). These compounds were tested as hydrochlorides and substances (Id-f) were prepared in dilute hydrochloric acid solution in order that the solution pH was within the limits 3.5-4.0.

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TABLE 1. 1,4-Diazabicyclo[4. m. 0]alkanyl Amides of p-Nitro- and p-Aminobenzoic Acids (Ia-f)

Compound	Yield, %	Mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	N	Cl′		C	H	N	Cl′
Ia	57.8	106—8	61.41	6.24	15.31	—	$C_{14}H_{17}N_3O_3$	61.08	6.22	15.26	—
Ia hydrochloride		185—6	—	—	13.27	11.53	$C_{14}H_{17}N_3O_3 \cdot HCl$	—	—	13.47	11.37
Ib	62	126—7	62.41	6.66	14.81	—	$C_{15}H_{19}N_3O_3$	62.27	6.62	14.52	—
Ib hydrochloride	—	244—5	—	—	—	10.67	$C_{15}H_{19}N_3O_3 \cdot HCl$	—	—	—	10.88
Ic	61.1	119—21	63.59	6.95	13.75	—	$C_{16}H_{21}N_3O_3$	63.35	6.98	13.85	—
Ic hydrochloride	—	251—2	—	—	12.21	10.84	$C_{16}H_{21}N_3O_3 \cdot HCl$	—	—	12.36	10.43
Id	94.2	169—70	68.61	7.89	16.99	—	$C_{14}H_{19}N_3O$	68.54	7.81	17.13	—
Ie	83	140—41	69.50	7.99	16.41	—	$C_{15}H_{21}N_3O$	69.47	8.16	16.20	—
If	85.3	129—30	70.02	8.46	15.11	—	$C_{16}H_{23}N_3O$	70.30	8.48	15.37	—

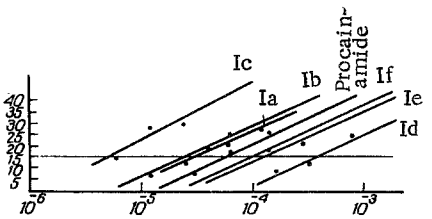

Fig. 1. Comparative antiarrhythmic activity of amides.

The investigation was carried out in two experimental models in experiments *in vitro* and *in vivo* (see Experimental section).

On studying amides (Ia-f) in experiments *in vitro* it was established that they all, like procainamide, possessed the ability to some extent to increase the refractory period of the isolated auricle reducing the maximum reproducible frequency of contractions (Fig. 1). The carried out experiments made it possible to clarify the dependence between the chemical structure of the studied substances and the degree of their antiarrhythmic activity. According to the test data, amides (Ia-c) were the most effective. Within this group the structure of the 1,4-diazabicyclo[4, m, 0]alkane portion of the molecule proved to have a strong influence on the extent of antiarrhythmic activity. An increase in ring size (n = 2, 3, 4) led to a strengthening of antiarrhythmic action. Thus compound (Ic) (n = 4) exceeded procainamide in activity 11.6 times while amides (Ib) (n = 3) and (Ia) (n = 2) were only 2.2 and 2 times more active respectively than procainamide.

Amides of p-aminobenzoic acid (Id-f) were significantly less active than both compounds (Ia-c) and procainamide. The expression of action grew with an increase in ring size as in the case of the nitro derivatives (Ia-c). Thus the activity of compounds (Id) (n = 2), (Ie) (n = 3), and (If) (n = 4) was lower than that of procainamide by 6.4-, 2-, and 1.6-fold, respectively.

Further investigations of the antiarrhythmic properties of compounds (Ia-f) in experiments *in vivo* showed that they did not prevent the development of aconitine arrhythmia in difference to procainamide at comparable doses. The absence of an effect is seemingly explained by the fact that on intravenous injection aconitine causes disturbance of cardiac rhythm not only as a result of direct action on the conducting system of the heart, but also as a result of extracardial neurogenic influences. It may be suggested that the studied compounds (Ia-f) only show the direct influence on the myocardium in difference to procainamide and consequently do not give an antiarrhythmic effect in the experimental arrhythmia model under consideration.

EXPERIMENTAL (CHEMICAL)

N-(p-Nitrobenzoyl-1,4-diazabicyclo[4, m, 0]alkanes (Ia-c). A solution of p-nitrobenzoyl chloride (0.022 mole) in dry dichloroethane (30 ml) was added dropwise over 15 min to a solution of (II) (0.02 mole) in dry dichloroethane (10 ml) with stirring and cooling with ice water. The reaction mixture was then boiled for 1.5 h. The crystalline solid, which precipitated after cooling the reaction mixture, was filtered off, washed with dry dichloroethane, and dried. The solid was dissolved in water (30 ml) and 10% aqueous ammonia solution was add-

ed to pH 9.0-10.0. The precipitated crystalline solid of the corresponding amide (Ia-c) was filtered off, washed many times with water, dried in vacuum at 60-70°C, and recrystallized from alcohol with carbon. Constants, yields, and analyses of the obtained amides (Ia-f) are given in Table 1.

Hydrochlorides of amides (Ia-f) were obtained by mixing dichloroethane solutions of amides (I) ($X = NO_2$) with an ether solution of hydrogen chloride. The precipitated solid was filtered off, washed many times with dry dichloroethane, and dried in vacuum. Constants, yields, and analyses of the obtained hydrochlorides are given in Table 1.

N-(p-Aminobenzoyl)-1,4-diazabicyclo[4. m. 0]alkanes (Id-f). Platinum oxide (0.05 g) prepared according to Adams was added to a solution of N-(p-nitrobenzoyl)-1,4-diazabicyclo[4. m. 0]alkane (0.005 mole) in methyl alcohol (40 ml). The reaction mixture was stirred at room temperature in an atmosphere of hydrogen until absorption of the theoretical amount of the latter for which 20-30 min was usually required. The catalyst was filtered off and the solvent distilled in vacuum. The residual oily substance crystallized on rubbing under ether, the crystalline solid was filtered off, washed with ether, and dried in vacuum. Constants, yields, and analyses of the obtained aminoamides (Id-f) are given in Table 1.

EXPERIMENTAL (PHARMACOLOGICAL)

Pharmacological investigations were carried out on two experimental models. In experiments *in vitro* the influence of substances was studied on the maximum reproducible frequency of contractions of isolated auricle at constant intensity of stimulation by the method of Dawes [5] as modified by Alles and Ellis [6]. The method is based on the determination of the threshold frequency which represents the size of the refractory period. The activity of compounds in relation to procainamide was determined by comparing the concentration of the studied substances (in mole per liter) reducing the maximum reproducible frequency of contractions by 15%. The use of higher concentrations (effect greater than 30%) is undesirable since it may lead to the appearance of unusual changes in the tissues of the auricle and make impossible further work on the auricle being used.

In experiments *in vivo* the ability of substances to prevent the development of aconitine arrhythmia was determined in rats without anesthesia. Aconitine was administered intravenously at doses of 40-50 μg/kg. Disturbance of heart rhythm was caused during 1-3 min and had a diverse character. ECG were recorded on the second normal removal each 3, 5, 10, 15, and 20 min. The duration of arrhythmia amounted to 1.5-2 h on average. The investigated substances were given intravenously 1-5 min before the injection of aconitine. The activity of the studied compounds was compared with the activity of procainamide.

LITERATURE CITED

1. L. S. Nazarova, A. M. Likhosherstov, K. S. Raevskii, et al., Khim.-Farm. Zh., No. 4, 49-55 (1976).
2. L. S. Nazarova, A. M. Likhosherstov, G. A. Markova, et al., Khim.-Farm. No. 6, 84-89 (1978).
3. A. M. Likhosherstov, L. S. Nazarova, and A. P. Skoldinov, Zh. Org. Khim., 6, 1729-1734 (1970).
4. L. S. Nazarova, A. M. Likhosherstov, K. S. Raevskii, et al., Khim.-Farm. Zh., No. 1, 88-92 (1976).
5. G. S. Dawes, Br. J. Pharmacol., 1, 90-112 (1946).
6. G. A. Alles and C. H. Ellis, J. Pharmacol. Exp. Therm., 94, 416-425 (1948).