stantially , i.e., it is approximately three times as great as in the control animals. At the same time, the hemolytic activity of the serum and spleenocytes, characterizing the content of antibodies in the blood and the intensity of the production, remains in almost all cases at the level that is created by injection of the cytostatic. A comparison of the number of AFC in the spleen with the hemolytic activity of the cells of this organ suggests that the compounds studied decrease the synthesis of antibodies against sheep erythrocytes by a factor of 15-3; consequently, they may be of interest in cases when the need arises for stimulation of the cell-mediated immune reactions without any change in the humoral reactions.

Thus, the data obtained show the promise of the search for immunotropic agents among synthetic macrocyclic compounds and the study of the mechanisms of their action.

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SYNTHESIS AND β-ADRENOBLOCKING ACTIVITY OF 1-DIBENZOFURANYLOXY-3-AMINOPROPAN-2-OLS

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A whole series of β-adrenoblockers has been developed among the heterocyclic derivatives of 1-aryloxy-3-aminopropan-2-ols (AAP). Thus, in the series of benzofuran derivatives of AAP β-adrenoblocking agents were discovered having bicyclic (befunalol) and tricyclic structures (butocrolol, a furochromone derivative) [7, 8].

With the aim of searching for new β-adrenoblockers among AAP derivatives [2] 1-(1,2,3,4,4a-9b-hexahydrodibenzofuran-8-yloxy)-3-aminopropan-2-ols (Ia-b), 1-(1,2,3,4-tetrahydrodibenzofuran-6-yloxy)-3-ylaminopropan-2-ols (IIa-d), and 1-(dibenzofuran-1-yloxy)-3-aminopropan-2-ols (IIIa-c) have been synthesized. In addition to this derivative of 1-(1,2,3,4-tetrahydrodibenzofuran-8-yloxy)-3-cyclohexylaminopropan-2-ol (IVa-c) and analogs of propranolol (Va-c) containing O-acetyl, O-pivaloyl, O-1-adamantanoyl, or O-benzoyl groups, have been synthesized with the aim of searching for β-adrenoblockers with extended action. Thus, attention has been paid to information on increasing the action time of certain β-adrenoblockers by converting the hydroxyl group in the side chain of AAP into an ester grouping [4]. (See p. 688.)

The synthesis of (Ia, b), (IIa-d), and (IIIa-c) was effected on the basis of 1,2,3,4,4a-9b-hexahydrodibenzofuran-8-ol (VI), 1,2,3,4-tetrahydrodibenzofuran-6-ol (VII), and dibenzofuran-1-ol (VIII) by two methods. A) Compounds (Ia, b) and (IIIa-c) were obtained by reaction of (VI) and (VIII) with one equivalent of epichlorhydrin in the presence of aqueous alkali and subsequent amination of the resulting epoxides. B) Compounds (IIa-d) were obtained by reaction of (VII) with a multifold excess of epichlorhydrin in the presence of a catalytic amount of piperidine and subsequent interaction with amines.

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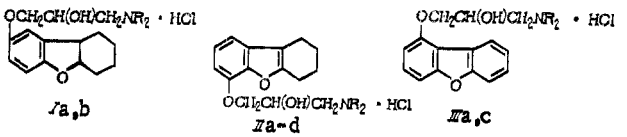
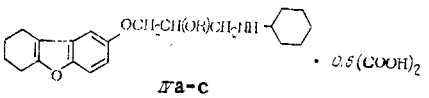


I, IIa, b

IIa-d

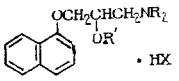
IIa, c

I — III: a) NR_2 = 2,6-dimethylpiperidyl
b) NR_2 = cyclohexylamino
IIc, IIIc: NR_2 = isopropylamino
IId: NR_2 = tert-butylamino



IIa-c

IVa: R = pivaloyl
IVb: R = benzoyl
IVc: R = adamantanoyl



Va-b

Va: NR_2 = 2,6-dimethylpiperidyl R′ = acetyl, HX = HCl;
Vb: NR_2 = isopropylamino, R′ = 1-adamantanoyl, HX = 0,5 $(COOH)_2$;
Vc: NR_2 = isopropylamino, R′ = pivaloyl, HX = HCl;
Vd: NR_2 = 2,6-dimethylpiperidyl, R′ = H, HX = HCl;
Ve: NR_2 = 2,6-dimethylpiperidyl, R′ = H, HX = CH_3SO_3H.

A new route to the synthesis of dibenzofuran-1-ol (VIII), which is an intermediate compound for obtaining derivatives of AAP of the (IIIa-c) type, has been developed by us. Dihydroresorcinol was cyclized with O-phenylhydroxylamine to 1-hydroxy-1,2,3,4-tetrahydrodibenzofuran [3] with subsequent dehydrogenation with sulfur. Compound (VII) was obtained by us for the first time by demethylation of 6-methoxy-1,2,3,4-tetrahydrodibenzofuran (IX) [5] by means of piperidine hydrochloride.

Acyl derivatives of (IVa-c) and (Va-c) were synthesized by the interaction of the corresponding AAP with acid chlorides or anhydrides.

The structures and homogeneity of the synthesized compounds were confirmed by data of TLC, IR, and PMR spectroscopy.

There were stretching vibrations for NH_2^+ groups at 2640-2710 cm^{-1} and an ester carbonyl at 1730-1745 cm^{-1} in the IR spectra of compounds (IVc) and (Va-c) taken in Nujol.

The synthesized compounds were studied for β_1 and β_2 adrenoblocking activity.

EXPERIMENTAL CHEMISTRY

The IR spectra were taken on a Perkin-Elmer 457 spectrometer (England), PMR spectra were drawn on a Varian T-60 spectrometer (USA), TLC was carried out on Silufol 254 and on Al_2O_3 (Alkaline form, Brockman activity II and IV) plates with visualization by iodine vapor.

1,2,3,4-Tetrahydrodibenzofuran-6-ol (VII). A mixture of 6-methoxy-1,2,3,4-tetrahydrodibenzofuran (IX) (8.05 g: 0.038 mole) and pyridine hydrochloride (21.8 g: 0.19 mole) was heated for 1 h at 200°C with stirring in a stream of N_2. After 16 h water (25 ml) was added to the reaction mixture and (VII) (7.42 g: 99%) of mp 115-116°C (heptane) was obtained. Found, %: C 76.41; H 6.36. $C_{12}H_{12}O_2$. Calculated, %: C 76.56; H 6.42. PMR spectrum (d_6 = DMSO), δ, ppm: 2.05 (4 H, 2 CH_2 at C_1 and C_4), 2.9 (4H, 2 CH_2 at C_2 and C_3), 6.9-7.2 (3 H, arom.).

Dibenzofuran-1-ol (VIII). A mixture of 1-hydroxy-1,2,3,4-tetrahydrodibenzofuran [3] (4.5 g: 0.024 mole) and sulfur (1.35 g: 0.042 mole) was heated for 1.5 h at 240°C, cooled to room temperature, treated with 2 N KOH, filtered, the alkaline solution was acidified with 2 N HCl, and (VIII) (2.5 g: 56%) of mp 127-128°C was obtained. After distillation at 120-130°C (1 mm Hg) the substance had mp 139-139.5°C (according to data of [9], mp 140°C).

Hydrochlorides of 1-(1,2,3,4,4a,9b-Hexahydrodibenzofuran-8-yloxy)-3-aminopropan-2-ols (Ia, b). 1,2,3,4,4a,9b-Hexahydrodibenzofuran-8-ol (VI) [1] (2.35 g: 0.0125 mole) was added with stirring to a solution of NaOH (0.5 g: 0.0125 mole) in water (3 ml). After 30 min epichlorhydrin (1.15 g: 0.0125 mole) was added dropwise and the mixture was heated for 3 h at

TABLE 1. Derivatives of 1-(Dibenzofuranyloxy)- and 1-(1-Naphthyloxy)-3-aminopropan-2-ols

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
Ia	26	165—6	66,59	8,63	8,93	3,70	$C_{22}H_{33}NO_3 \cdot HCl$	66,73	8,65	8,95	3,53
Ib	31	165—6,5	65,80	8,73	9,18	3,68	$C_{21}H_{31}NO_3 \cdot HCl$	66,04	8,44	9,28	3,66
IIa	34	208—9	66,84	8,15	8,89	3,79	$C_{22}H_{31}NO_3 \cdot HCl$	67,07	8,18	9,00	3,55
IIb	26	107—8	73,66	8,54	—	4,36	$C_{21}H_{29}NO_3$	73,43	8,51	—	4,07
IIc	49	152,5—4	63,40	7,93	10,14	4,13	$C_{18}H_{25}NO_3 \cdot HCl$	63,61	7,71	10,43	4,12
IId	41	187—8	64,50	7,99	10,01	4,35	$C_{19}H_{27}NO_3 \cdot HCl$	64,48	7,97	10,01	3,95
IIIa	34	235—6	67,55	7,50	9,05	3,87	$C_{22}H_{27}NO_3 \cdot HCl$	67,76	7,23	9,09	3,59
IIIb	28	209—11	66,66	6,98	9,20	3,82	$C_{21}H_{25}NO_3 \cdot HCl$	67,09	6,97	9,43	3,72
IIIc	30	191—2	64,06	6,81	10,31	4,24	$C_{18}H_{21}NO_3 \cdot HCl$	64,37	6,60	10,55	4,17
IVa	90	174—6	68,74	8,23	—	3,30	$C_{26}H_{37}NO_4 \cdot 0,5\ C_2H_2O_4$	68,61	8,10	—	2,96
IVb	36	141—2	75,97	6,84	—	2,70	$C_{28}H_{33}NO_4 \cdot 0,5\ C_2H_2O_4$	76,07	6,95	—	2,84
IVc	53	199,5	71,82	8,07	—	2,63	$C_{32}H_{43}NO_4 \cdot 0,5\ C_2H_2O_4$	71,96	8,05	—	2,54
Va	69	194—6	67,57	7,66	9,12	...	$C_{22}H_{29}NO_3 \cdot HCl$	67,41	7,72	9,05	3,58
Vb	74	186—7	71,98	7,87	—	3,16	$C_{27}H_{35}NO_3 \cdot 0,5\ C_2H_2O_4$	72,07	7,77	—	3,00
Vc	60	131—1,5	66,31	3,02	9,62	3,84	$C_{21}H_{29}NO_3 \cdot HCl$	66,38	7,96	9,33	3,69
Vd	57	186—7	68,65	8,08	9,98	4,25	$C_{20}H_{27}NO_2 \cdot HCl$	68,66	8,07	10,14	4,00
Ve	39	121—2	...	...	7,84*	...	$C_{20}H_{27}NO_2 \cdot CH_3SO_3H$	61,6	7,58	7,82*	3,43

*Content S, %.

Note. Substances (Ia), (IIa), (IIIc), (IVa-c), and (Vb, d) were crystallized from absolute alcohol, (Ib) and (IIc, d) from isopropyl alcohol, (IIIa, b) from a mixture of absolute alcohol and ether, (Va, e) from a mixture of isopropyl alcohol and ether, (Vc) from ethyl acetate. For (Va) found, %: S 7.84; calculated, %: S 7.82.

35-40°C. After 18 h the reaction mixture was extracted with chloroform, the extract evaporated, the residue dissolved in alcohol (5 ml), cyclohexylamine (3 g: 0.03 mole) was added, the mixture boiled for 6 h, evaporated in vacuum, the residue dissolved in absolute ether, treated with an ether solution of HCl, and (Ib) hydrochloride (1.5 g) was obtained. The hydrochloride of (Ia) was obtained in a similar manner.

Hydrochlorides of 1-(1,2,3,4-Tetrahydrodibenzofuran-6-yloxy)-3-aminopropan-2-ols (IIa-d). Anhydrous piperidine (3 drops) was added to a solution of (VII) (0.94 g: 0.005 mole) in epichlorhydrin (4.25 g: 0.05 mole), the mixture heated for 5.5 h at ~100°C, the excess of epichlorhydrin was distilled off in vacuum, anhydrous toluene (10 ml) was added and evaporated in vacuum twice, the residue was dissolved in ether, filtered, the filtrate evaporated, the residue dissolved in absolute alcohol (in the case of IIa and IId the reaction was carried out in the absence of solvent), and the solution heated for several hours at 40-45°C with an excess of the corresponding amine. The reaction mixture was evaporated in vacuum, treated with 2 N HCl, with benzene, the aqueous solution made alkaline, extracted with benzene, the extract evaporated, and bases (IIa-d) obtained. Bases were converted into the hydrochlorides by the usual route.

Hydrochlorides of 1-(Dibenzofuran-1-yloxy)-3-aminopropan-2-ols (IIIa-c). Compound (VIII) (2.2 g: 0.012 mole) was added with stirring to a solution of NaOH (0.46 g: 0.012 mole) in water (5 ml) and epichlorhydrin (1 g: 0.012 mole) was added dropwise after 30 min. The reaction mixture was heated for 10 h at 50-60°C, after ~18 h the mixture was extracted with ether, the ether extract washed with water and with 2 N NaOH, evaporated, the residue dissolved in benzene, and the solution filtered through a layer of Al_2O_3 (Brockman grade IV). The residue after evaporation of the filtrate was dissolved in absolute alcohol (20 ml), 2.6-dimethylpiperidine (0.98 g: 0.0086 mole) in alcohol (10 ml) was added, the mixture boiled for 6 h, poured into water, the precipitated solid was dissolved in absolute alcohol, the solution was treated with an ether solution of HCl, and (IIIa) hydrochloride (1.6 g) was obtained. The hydrochlorides of (IIIb-c) were obtained in a similar manner.

Hydrochloride of O-Acetyl-1-(1-naphthyloxy)-3-(2,6-dimethylpiperidyl)propan-2-ol (Va). A mixture of 1-(1-naphthyloxy)-3-(2,6-dimethylpiperidino)propan-2-ol (Va base) (0.8 g: 0.0026 mole) and Ac_2O (5 ml: 0.5 mole) was boiled for 3 h, the mixture was poured into water (15 ml) and 2 N HCl (2 ml), made alkaline with potassium carbonate, and extracted with ether. An ether solution of HCl was added to the extract and (Va) hydrochloride (0.6 g) was obtained.

Oxalates of O-Acyl Derivatives of 1-(1,2,3,4-Tetrahydrodibenzofuran-8-yloxy)- and 1-(1-Naphthyloxy)-3-aminopropan-2-ols (IVa-c) and (Vb). A mixture of 1-(1-naphthyloxy)-3-isopropylaminopropan-2-ol hydrochloride (X) (2.37 g: 0.008 mole) and adamantane 1-carboxylic acid chloride (3.33 g: 0.0168 mole) in anhydrous chloroform (20 ml) was boiled for 9 h, the reaction mixture was evaporated, the residue was treated with 10% NaOH, and with ether, the ether solution was washed with water, and evaporated. The residue was dissolved in absolute ether, a solution of anhydrous oxalic acid (0.6 g) in absolute alcohol (6 ml) was added, and (Vb) oxalate (2.76 g) was obtained. The oxalates of (IVa-c) were obtained in a similar manner.

Hydrochloride of O-Pivaloyl-1-(1-naphthyloxy)-3-isopropylaminopropan-2-ol (Vc). A mixture of (X) (1.2 g: 0.004 mole) and pivaloyl chloride (1.03 g: 0.0082 mole) in anhydrous chloroform (55 ml) was boiled for 15 h, the solvent was evaporated off, the residue treated with ether, and (Vc) hydrochloride (0.91 g) obtained.

Hydrochloride of 1-(1-Naphthyloxy)-3-(2,6-dimethylpiperidyl)propan-2-ol (Vd). α-Naphthol (6 g: 0.042 mole) was added to a solution of NaOH (1.83 g: 0.046 mole) in water (6 ml), after 30 min epichlorhydrin (4 g: 0.043 mole) was added, and the mixture was kept for 5 h at 40°C. The reaction mixture was extracted with ether, the extract washed with water, dried over anhydrous K_2CO_3, and evaporated in vacuum. The residue was dissolved in alcohol (30 ml), boiled for 4 h with 2,6-dimethylpiperidine (14 ml: 0.1 mole), evaporated in vacuum, the residue treated with benzene and 2 N HCl, the aqueous layer was made alkaline with 2 N NaOH, extracted with ether, the extract evaporated, (Vd) base was obtained, and was converted into the hydrochloride by the usual method.

The methanesulfonate (Ve) was obtained by the interaction of equimolar quantities of methanesulfonic acid and (Vd) base in absolute ether.

Data on compounds (Ia, b), (IIa-d), (IIIa-c), (IVa-c), and (Va-e) are shown in Table 1.

TABLE 2. β_1- and β_2-Adrenoblocking Activity of 1-(Dibenzofuranyloxy)-3-aminopropan-2-ols and Analogs of Propranolol

Compound	β_1-Adrenoblocking activity (ED_{50}, mg/kg)	Comparative activity relative to propranolol	β_2-Adrenoblocking activity (ED_{50}, mg/kg)	Comparative activity relative to propranolol	β_2/β_1
Ia	2,51	0,0045	3,12	0,004	1,24
Ib	0,88	0,0120	0,97	0,012	1,07
IIa	0,39	0,029	0,52	0,024	1,33
IIb	0,97	0,01	4,17	0,003	4,29
IIc	0,013	0,83	0,015	0,84	1,15
IId	0,016	0,71	0,016	0,78	1,0
IIIa	5,24	0,0021	7,20	0,001	1,37
IIIb	1,29	0,0028	2,03	0,0062	1,57
IIIc	0,015	0,78	0,016	0,78	1,0
IVc	>10	...	>10	...	...
Va	5,34	0,0021	8,21	0,0014	1,53
Vb	>10	...	>10	...	...
Vc	0,012	0,95	0,014	0,90	1,16
Vd	>10	<0,001	>10	<0,001	...
Ve	>10	<0,001	>10	<0,001	...

EXPERIMENTAL PHARMACOLOGY

β_1-Adrenoblocking activity was studied in rats anesthetized with pentobarbital sodium (120 mg/kg intraperitoneally) and β_2-adrenoblocking activity was determined in another series of experiments on rats anesthetized with urethane (1.78 g/kg intraperitoneally) from the extent of inhibition of tachycardia and hypotension caused by the β-adrenostimulator isopropylarterenol (the dose of the latter for stimulation of β_1 receptors was 0.1 μg/kg and for stimulation of β_2 receptors 0.215 μg/kg intravenously) [6]. The arterial pressure (AP) in the common carotid artery was measured with an electromanometer, a measure of the momentary tachycardia was derived from the arterial pressure curve. The β-adrenoblocking activity of substances was compared with the corresponding activity of propranolol.

Study of the duration of the β-adrenoblocking action was carried out in unanesthetized dogs four days after catheters had been inserted into the common carotid artery and the external jugular vein and pin electrodes placed in the paws under general narcosis. Substances were administered at a dose of 0.5 mg/kg intravenously and through a fistula into the stomach. Testing of the state of β receptors was carried out with isopropylarterenol at a dose of 1 mg/kg intravenously before and after injection of the investigated compounds.

Data on the β-adrenoblocking activity are given in Table 2.

As is evident from Table 2, introduction of 2,6-dimethylpiperidino and cyclohexylamino residues as substituents of AAP led to a reduction in potency and in the duration of β-adrenoblocking activity both in the dibenzofuran series of derivatives (Ia, b), (IIa, b), and (IIIa, b) and among the closer analogs of propranolol (Vd, e).

The greatest activity (close to the activity of propranolol) was possessed by compounds (IIc, d) and (IIIc) in which the side 2-hydroxy-3-aminopropoxy grouping was added onto a benzene ring of the dibenzofurans at the ortho position relative to the furan ring and the substituents in the amino portion of the molecule were isopropyl or tert-butyl groups.

The blocking activity of the studied compounds was not selective in relation to β-adrenoreceptors of different localities (the β_2/β_1 index was equal to 1). The exception was substance (IIc) in which the β_2/β_1 index equaled four.

The presence of such O-acyl residues as acetyl, benzoyl, adamantanoyl, and pivaloyl in the dibenzofuran and naphthalene series of AAP led to a sharp reduction in blocking activity. At the same time no appreciable prolongation of their action was recorded for compounds (IVa, b) and (Va-c), which indicated the limitation of the possibility of prolonging the action of compounds with β-blocking activity by acylation of the side chain hydroxyl.

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SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF A SERIES OF 1-SUBSTITUTED 2-PYRROLIDONES STRUCTURALLY CLOSE TO THE PREPARATION PYRACETAM

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It was established previously in [6] that 1-carbamidomethylpyrrolid-2-one (pyracetam) (I) reacted readily with the diethylacetal of dimethylformamide (II) with the formation of the N-dimethylaminomethylene derivative (III). Some properties of the acylamidine (III) and of a series of synthesized compounds based on it, which are structurally similar to pyracetam (I), have been investigated in the present work. The biological activity of the obtained compounds has been studied.

In the first stage of the work attempts were made to synthesize acylamidines of type (IV) by the transamination of (III) with primary amines. However, on interacting compound (III) with benzyl-, β-phenylethyl-, homoveratryl-, and β-diethylaminoethylamines, pyracetam was isolated in place of the expected amidines (IV), i.e., fission of the amidine fragment had taken place. In the example of the interaction of amidine (III) with homoveratrylamine it was shown (by chromato-mass spectrometry) that the second reaction product was N,N-dimethyl-N'-homoveratrylformamidine (V), i.e., on interacting acylamidine (III) with amines, stabilization of the intermediate acylaminal (VI) was effected by splitting off the appropriate formamidine and not dimethylamine as took place for amidines containing no N-acyl residue in [3].

It is known from [9] that acylamidines are hydrolyzed in AcOH to N-formyl derivatives and are able to react in this solvent with arylhydrazines with the formation of triazole derivatives. Treatment of amidine (III) with 70% AcOH like this led to N-formylpiracetam (VII) and on interaction of (III) with phenylhydrazine in AcOH at 20°C 1-(1-phenyl-1,2,4-triazolyl-5-methyl)pyrrolid-2-one (VIII) was formed.

In the reaction under consideration the formation of the other isomeric triazole (IX) is possible in principle. Attempts to isolate the intermediate compound (X) or (XI), the structure of which should give unambiguous proof of the structure of the final triazole, were not crowned with success. The triazole cyclization in the present case evidently proceeded more rapidly than transamination. In order to record the formation of the intermediate product, acylhydrazines of reduced basicity compared to phenylhydrazine, viz., p-nitrophenyl- and 2,4-dinitrophenylhydrazines, were put into a similar reaction. In these cases the intermediate acylamidrazones (IIa, b) were successfully isolated and their structures followed from data of elemental analysis and spectra (Table 1). By heating compound (XIIa) in AcOH the triazole derivative (XIII) was obtained. However, the basicity of the NH group in the dinitro derivative (XIIb) was reduced so much that intramolecular cyclization did not even take place, on heating (XIIb) in AcOH a fission of the side chain was observed and the N-acyl derivative (XIV) was successfully isolated. Compound (XIV) was also obtained by an alternative synthesis from 2,4-dinitrophenylhydrazine (XV) by the procedure of [7]. The 1,5 (and not the 1,3) di-

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