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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 1-AMINO-3-(TETRAHYDRO- AND HEXAHYDRODIBENZOFURAN-8-ILOXY-2)PROPANOLS

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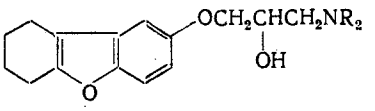
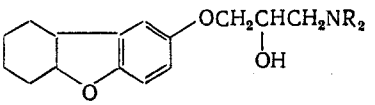
As a continuation of our research of new effective β-adrenoblocking agents [1] and for the purpose of studying the effect that dibenzofuran ring saturation and the nature of the amine residue in the aminopropanol group has on β-adrenoblocking activity, we synthesized derivatives of 1-amino-3-(1,2,3,4-tetrahydro- and 1,2,3,4,4a,9b-hexahydrodibenzofuran-8-iloxy)-2-propanols (Ia-c, e-k, and IIa-d). We also thought it would be of interest to study simultaneously the effect of the indicated structural factors in compounds I and II on hypotensive, spasmolytic, broncholytic, and neurotropic activity.

Compounds Ia-c, e-k, and IIa-d were synthesized by reacting 1,2,3,4-tetrahydrodibenzofuran-8-ol and 1,2,3,4,4a,9b-hexahydrodibenzofuran-8-ol with epichlorohydrin (ECH) in DMPA in the presence of NaH (method A) or in water in the presence of NaOH (method B) followed by treating the resultant epoxides with amines.



Ia-c, e-k



IIa-d

I and II: NR_2 = HNBu-t (a), HNBu (b), HNPr-i (c), imidazole-1-yl (IId), 2,6,-dimethylpiperidino (e), cyclohexylamino (f), NEt_2 (g), piperidino (h), N-methylpiperazino (i), morpholino (j), $N(Pr\text{-}i)_2$ (k).

The structure of the synthesized compounds was confirmed by PMR-spectroscopy of the hydrochlorides of compounds Ia, Ic, and IIa (Table 1). A characteristic feature of the PMR spectra for the examined compounds as recorded in $CDCl_3$ is that the weak magnetic field region has two broad signals whose integral intensity corresponds to a single proton. These broad signals which can be attributed only to protons of the NH_2^+ group, indicate that there is a slow exchange of protons at the nitrogen atom. When the temperature rises as a result of an accelerated rate of proton exchange at N^+, the signals broaden, shift to stronger fields, and converge in chemical shift values. A lowering of temperature results in a narrowing of the signals and their shift to a weak field. In addition, a nonequivalence of protons in the OCH_2 and NCH_2 groups is observed in the PMR spectra for the hydrochlorides of Ia, Ic, and IIa. The literature [2, 3] has data on the conformation of the 1-alkylamino-3-aryloxypropanol-2 salts. Thus, a study of the PMR-spectra for the latter, recorded in non-polar solvents, has led to the suggestion that there is a stable "rigid" conformation

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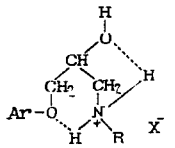
TABLE 1. PMR Spectra for Compounds I-III

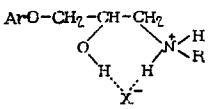
Compound	δ, ppm (J, Hz)										
	CH_3—C	$(CH_2)_4$	CH_2N	CH_2O	CH	OH	H_7	H_9	H_6	H_2	$\Delta\delta_{NH}$
Ia·HCl	1,45s	1,82 m, 2,59m	3,19m	4,05m	4,59 m	5,29s	6,69q	6,79 d ($J_{7,9}$ 2,5)	7,19 d ($J_{6,7}$ 8,5)	8,30 s, 9,55 s	1,30
Ic·HCl	1,43 d	1,81 m, 2,57 m	3,26m	4,01m	3,58m, 4,62m	5,39 s	6,65q	6,75 d ($J_{7,9}$ 2,5)	7,18 d ($J_{6,7}$ 8,5)	8,56 s, 9,46 s	0,90
IIa·HCl	1,46 s	1,81 m, 3,13 m	3,98m	4,56m	4,50 m	5,40s		6,70 m(3H)		8,20 s, 9,10 s	1,40
IIIa·HCl	1,51d	1,58 m, 2,16 m	3,16m	4,17m	4,64 m	5,45s		7,17 m(3H)		8,31 s, 9,43 s	1,12
IIIb·HCl	1,41 d	1,72 s, 2,54 m	3,32m	4,20m	3,35 m, 4,67m	5,45 s		6,36—6,77 m(3H)		8,60 s, 9,10 s	0,50

Note. m – multiplet, q – quartet.

with the formation of a [6,5]bicyclic chelate structure (A) which includes two intramolecular hydrogen bonds (IMHB) of the N^+—H...O type [2].



A



B

Our study of the PMR- and IR-spectra for toliprolol and its analogs has indicated the possible formation of a 7-member ring (B) in which the halide ion (X^-) is bound to the IMHB both through a proton of the hydroxyl group and with one of the protons of the NH_2^+ group [3]. In the case of the hydrochlorides of Ia, Ic, and IIa, the PMR-spectra data (temperature dependence of the chemical shifts for the NH_2 group) and the IR-spectra data (absence of a free hydroxyl group band) would seem to indicate the presence of a 7-membered conformation for B. The stability of the IMHB in the 7-membered ring in the structure of B is proportional to the difference in the values for the proton chemical shifts at $NH_2^+\Delta\delta NH$). The value for $\Delta\delta$NH is greater for compounds Ia and IIa which contain a tert-butyl substituent in the NH side chain group, and less for the isopropyl analog Ic. Thus, the stability of the resultant 7-membered ring depends on the nature of the substituent in the end amino group (in the case of the tert-butyl residue the IMHB formation is stronger). One should note that a comparison of the results we obtained to the PMR spectra of the previously synthesized isosters [1] of position I, i.e., the hydrochlorides of 1-R-amino-3-(1,2,3,4-tetrahydrodibenzofuran-6-iloxy)2-propanols (IIIa-b, where a: R = Bu-t, b: R = Pr-i) has shown that the latter (see Table 1) also form a 7-membered ring in non-polar solvents with a less stable IMHB (particularly in the case of the isopropyl derivative IIIb whose $\Delta\delta$NH is equal to 0.50).

EXPERIMENTAL (CHEMISTRY)

PMR-spectra were recorded on a Varian NA-100 spectrometer ($CDCl_3$), TMS internal standard. The found values for element analyses corresponded to the calculated values.

1-tert-Butylamino-3-(1,2,3,4-tetrahydrodibenzofuran-8-iloxy)-2-propanol (Ia). A. A solution of 1.7 g (0.009 mole) of 1,2,3,4-tetrahydrodibenzofuran-8-ol in DMPA was added dropwise at room temperature to a suspension of 0.35 g (0.016 mole) of NaH in a minimum amount of DMPA. The mixture was stirred for 30 min after which 6.7 g (0.072 mole) of ECH was added. This mixture was stirred for 1 h at 20°C and for 6 h at 55-60°C, decanted into water, extracted with ether, and the ether extract was dried over $MgSO_4$ and evaporated. The resultant epoxide was dissolved in 15 ml of methanol after which 2.6 g (0.036 mole) of H_2NBu-t was added. The mixture was then boiled for 3 h and evaporated. The residue was dissolved in ether. The addition of an alcohol solution of HCl yielded 2.8 g of compound Ia.

1-(2,6-Dimethylamieridino)-3-(1,2,3,4-tetrahydrobenzofuran-8-iloxy)-2-propanol Hydrochloride (Id·HCl). B. A 2.4 g (0.012 mole) portion of 1,2,3,4-tetrahydrodibenzofuran-8-ol was added upon stirring to a solution of 0.52 g (0.013 mole) of NaOH in 2 ml of water after which 1.25 g (0.013 mole) of ECH was added dropwise. The reaction mixture was then heated for 4 h at 30°C and left overnight, then extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and evaporated. The residue (4.2 g) was dissolved in 5 ml of 50%

TABLE 2. 1-Amino-3-(tetra- and hexahydrodibenzofuran-8-iloxy)-2-propanols

Compound	Hydrochloride yield, %	Method	mp, °C (solvent)	Empirical formula	mp of hydrochloride, °C (abs. alcohol)
Ia*	87	A	86—8 (hexane)	$C_{19}H_{27}NO_3$	158—61
Ib	38	A	66—7 (hexane)	$C_{19}H_{27}NO_3$	178—80
Ic	80	A	84—5 (petroleum jelly)	$C_{18}H_{25}NO_3$	159—61
Ie·HCl	30	B	213,5—15 (abs. alcohol)	$C_{22}H_{31}NO_3 \cdot HCl$	—
If·HCl	40	B	201—2,5 (abs. alcohol)	$C_{21}H_{29}NO_3 \cdot HCl$	—
Ig · HCl	48	A	111—1,5 (abs. ether)	$C_{19}H_{27}NO_3 \cdot HCl$	—
Ih	64	A	67—8 (petroleum jelly)	$C_{20}H_{27}NO_3$	178—80
Ii	51**	A	102—3 (hexane)	$C_{20}H_{28}N_2O_3$	238,5—40
Ij · HCl	37	A	190—2 (abs. alcohol)	$C_{19}H_{25}NO_4 \cdot HCl$	—
Ik · HCl	45	A	162—3 (abs. alcohol)	$C_{21}H_{31}NO_3 \cdot HCl$	—
IIa·HCl***	34	A	143—4 (abs. alcohol)	$C_{19}H_{19}NO_3 \cdot HCl$	—
IIb	30	A	85,5—6,0 (petroleum jelly)	$C_{19}H_{29}NO_3$	130—2
IIc	62**	A	66—8 (petroleum jelly)	$C_{18}H_{27}NO_3$	110—11
IId · HCl	48	A	124—5[4]*	$C_{18}H_{22}N_2O_3 \cdot HCl$	—

*IR-spectrum ($CHCl_3$, c 0.002 M), cm^{-1}:3340 (νOH comb.), 2860 and 2770 (νNH_2).
**Yield of base.
***IR-spectrum ($CHCl_3$, c 0.002 M), cm^{-1}:3340 (νOH comb.) 2865 and 2780 (νOH_2).
[4]*After purification of base on Al_2O_3.

TABLE 3. Adrenergic-Blocking, Hypotensive Activity, and Acute Toxicity of 1-Amino-3-(tetrahydro- and Hexahydrobenzofuran-8-iloxy)-2-propanols

Compound	β_1-Adrenergic blocking activity, ED_{50}, mg/kg	β_2-Adrenergic blocking activity, ED_{50}, mg/kg	Selectivity, β_1/β_2	Arterial pressure		Heart beat frequency		Toxicity, LD_{60}, mg/kg
				mm Hg	% in comparison to control	per minute	% in comparison to control	
Ia	0,97	2,37	2,44	—	—	—	—	130
Ib	2,15	8,72	4,18	117±23,8	76	280±24,9	82	203
Ic	0,83	2,59	3,27	—	—	—	—	145
Ie	1,38	2,04	1,48	—	—	—	—	202
If	4,17	6,68	1,60	113±13,5	74	264±8,9	77	154
Ig	0,43	2,34	5,44	—	—	—	—	115
Ih	2,58	5,54	2,18	—	—	—	—	144
Ii	3,21	10,12	3,15	—	—	—	—	130
Ij	4,27	12,30	2,88	—	—	—	—	182
Ik	4,21	10,03	2,38	—	—	—	—	214
IIa	0,54	1,12	2,07	—	—	—	—	123
IIb	1,51	2,27	1,50	—	—	—	—	126
IIc	0,29	0,76	2,62	—	—	—	—	184
IId	3,28	7,51	2,29	—	—	—	—	151
Propranolol	0,0114	0,0126	1,1	151±17,3	98	335±14,8	99	110
Control	—	—	—	154±7,5	100	340±40,0	100	—

alcohol after which 6.8 g (0.06 mole) of 2,6-dimethylpiperidine in 7 ml of 50% alcohol was added to the mixture which was then heated for 1 h at 100°C. The mixture was then cooled, decanted into water, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated. The residue was treated with an alcohol solution of HCl to yield 1.5 g of the hydrochloride Id.

Data on compounds Ia-k and IIa-d are given in Table 2.

EXPERIMENTAL (PHARMACOLOGY)

The hydrochlorides of compounds I and II were tested for β_1- and β_2-adrenergic blocking, antihypertensive, spasmolytic, broncholytic, and neurotropic-anxiolytic activity as well as for their acute toxicity.

β_1- and β_2-adrenergic blocking activity of the I and II hydrochlorides were compared to that of propranolol in accordance with the methods described earlier [1].

Hypotensive activity was tested in experiments on spontaneous-hypertensive rats (Yamamoto – Aeki breed) by administering the test substances in over a period of five days (twice daily) at a dose of 10-15 mg/kg, and compared to the effects of propanolol. Dosage of the administered compounds was calculated by the formula $LD_{50} \times 3{:}50$. Arterial pressure was measured with an electromanometer.

Spasmolytic activity of the I and II hydrochlorides was tested on guinea pig intestine sections and evaluated by the substances' ability to suppress $BaCl_2$-induced spasms at compound concentrations of $1 \cdot 10^{-5}$-$1 \cdot 10^{-7}$ g/ml in comparison to papaverine.

The effect of the substances on bronchial tension and histamine-induced bronchospasms was tested on urethane-anesthetized guinea pigs which were also given the myorelaxant diplacin. Neurotropic activity was assayed in experiments on white mice (weighing 18-20 g) and non-pedigree white rats (weighing 180-200 g). Effects were recorded 30 min after the ip administration of the compounds. The following tests were employed: Effect on the duration of thiopental anesthesia (administered iv at 30 mg/kg), on spontaneous motor activity, the ability to prevent corazol-induced tremor (administered subcutaneously at 10 mg/kg), phenamine stereotypy (phenamine administered ip at 13 mg/kg), and the ability to induce myorelaxation.

Acute toxicity was evaluated in white mice weighing 18-20 g by the number of surviving animals 24 h after administration of the test substances.

Data on adrenergic blocking activity are given in Table 3.

As can be seen from Table 3, the hydrochlorides of compounds Ia-c, e-k, and IIa-d are significantly inferior to propranolol in β_1- and β_2-adrenergic blocking activity. The greatest activity was exhibited by compounds IIa, IIc, and Ig. One should note that there are compounds among the tetrahydrodibenzofuran derivatives (Ig, Ib, Ic, and Ii) that have a cardioselectivity index (β_1/β_2 ratio) that is 3-5 times greater than that of propranolol. The degree of cardioselectivity was seen to decrease in the series of IIa-d hexahydrodibenzofuran derivatives. Compounds Ib and If were tested on spontaneous-hypertensive rats (Yamamoto-Aeki breed). The satistically reliable results (see Table 3) indicate that the hydrochlorides Ib and If exhibit hypotensive activity and affect contraction frequency in hypertonic animals.

Our study of spasmolytic activity showed that the hydrochlorides Ia-b, f-e, and IIc suppress intestinal section contraction at a concentration of $1 \cdot 10^{-7}$-$5 \cdot 10^{-7}$ g/ml that is proportional to concentration. The least spasmolytic activity of the compounds was exhibited by the hydrochlorides Ic, Ig-k, and IIa, d which, like papaverine, suppress intestinal section contractions only at a concentration of $1 \cdot 10^{-5}$-$5 \cdot 10^{-5}$ g/ml. The tests for broncholytic activity showed that the hydrochlorides Ib, e, f, and IIb at doses of 1-3 mg/kg reduced bronchial tension by 30-50% (propanolol increased bronchial tension by 100% at a dose of 3 mg/kg). The hydrochlorides Ie-f at doses of 3-10 mg/kg reduced histamine-induced bronchospasms by 50-80%. The tested compounds compared favorably to propanolol with respect to guinea pig mortality caused by the inspiration of histamine aerosol and primarily caused by bronchial spasm.

Our pharmacological study indicates that compounds Ib, f, and g-i reduce spontaneous motor activity by 30-60% whereas propranolol reduces that activity by only 17%. The most active compounds Ib and If significantly prolonged the duration of sodium thiopental anesthesia by 169-254%.

The tested compounds did not affect corazol-induced convulsions, somewhat reduced phenamine stereotypy, and did not exhibit myorelaxant properties. Consequently, these compounds exhibit central-depressant activity.

The LD_{50} values for the tested compounds are given in Table 3.

Thus, the hydrochlorides I and II exhibit less pronounced β-adrenergic blocking activity than the previously [1] studied 1-amino-3-(1,2,3,4-tetrahydrobenzofuran-6-iloxy)-2-proanolamines (III) and 1-amino-3-(dibenzofuran-1-iloxy)-2-propanolamine.

A characteristic feature of the tested compounds I and II is that in contrast to known β-adrenergic blockers, they do not increase bronchial tension and bronchospasm, but in fact decrease them.

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SYNTHESIS OF BENZ[G]INDOLE AMINOMETHYL DERIVATIVES

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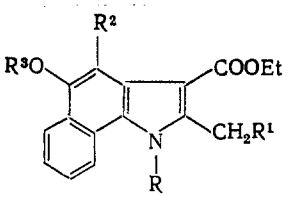
Aminomethyl derivatives of indole have been found to include compounds with a high degree of antiviral [6] and antitubercular activity [4] as well as compounds which exhibit antiarrhythmic, antifibrillatory, and anticonvulsive activity [5]. At the same time there has been little study of the aminomethyl derivatives in the benz[g]indole series. A description has been given for the synthesis of N-methyl and N-phenyl-2-methyl-3-ethoxycarbonyl-4-dimethylaminomethyl-5-oxybenz[g]indoles by treating corresponding derivatives of 5-oxybenz-[g]indoles with bisdimethylaminomethane [1]. However, information about their biological activity is lacking.

We synthesized the benz[g]indoles [III-XVIII] in order to test the antiviral activity of the aminomethyl derivatives of 2-methyl-3-ethoxycarbonylbenz[g]indole.



I—XVIII

R = Me (I, V, VI, XVIII), Ph (II—IV, VII—XVII); R^1 = H (I—VII, XVIII), Br (VIII), NMe_2 (IX, XII), $N(CH_2CH_2)_2O$ (X, XIII, XV), $N(CH_2)_5$ (XI, XIV, XVI), SPh (XVII); R^2 = H (I, II, VII—XIV, XVII, XVIII), CH_2NMe_2 (III), $CH_2N(CH_2CH_2)_2O$ (IV, VI, XV), $CH_2N(CH_2)_5$ (V, XVI); R^3 = H (I—VI, XII—XVII), Ac (VII—XI, XVIII).

The aminomethyl derivatives III-VI are formed upon the aminomethylation of 5-oxybenz[g] indoles I and II by method [1]. The substituent in position 2 was modified through the bromide of VIII which was obtained reacting bromosuccinimide with 2-methyl-5-acetoxybenz[g]indole VII. The treatment of compound VII with secondary amines results in the synthesis of 2-aminomethyl derivatives IX-XI whose hydrolysis and subsequent aminomethylation of the intermediate 5-oxybenz[g]indoles result in the formation of 2,4-diaminomethylbenz[g]indoles XV and XVI. The reaction between potassium thiophenolate and 2-bromomethylbenz[g]indole VIII is accompanied by the hydrolysis of the acetyl group which results in the formation of 2-thiophenylmethyl-3-ethoxycarbonyl-5-oxybenz[g]indole XVII which we were not able to aminomethylate on position 4. One should note that when we reacted bromosuccinimide with 1,2-dimethyl-5-acetoxybenz[g]indole XVIII [2], we did not observe the formation of the corresponding 2-bromomethyl derivative. It is generally known that the antiviral activity of this series of compounds is associated with the presence of an o-quinoline structure [3].

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