SEARCH FOR LONG-ACTING β-ADRENOBLOCKERS AMONG 4-HYDROXYINDOLE DERIVATIVES

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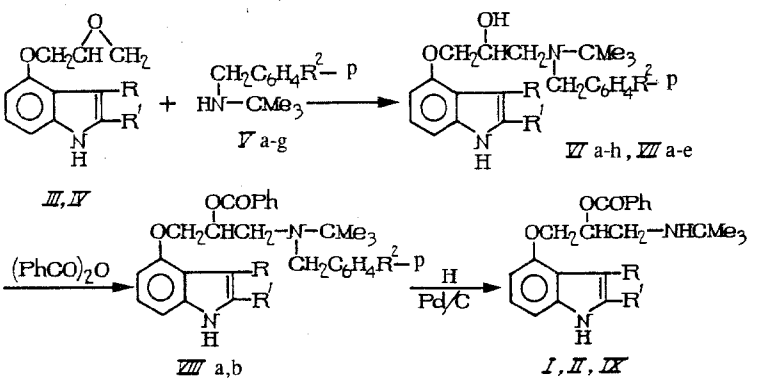
In searches for long-acting β-adrenoblockers, we have synthesized and studied some derivatives of 4-hydroxyindole-3-acetic acid. It is known from the literature that the compound bopindolol (I; 4-(2-benzyloxy-3-tert-butylaminopropoxy)-2-methylindole hydromalonate) has prolonged, β-adrenoblocking activity [7]. Pindolol (4-(2-hydroxy-3-isopropylaminopropoxy)indole) is also among indole derivatives that are widely used in medicine; it, however, is short-acting.

Due to the wide usage of β-adrenoblockers in treating cardiovascucular diseases and the need for their long-term use, it is of great importance to create new compounds of this group that have long-acting β-adrenoblocker activity.

We first prepared a bopindolol analogue having, in contrast to the latter, a methyl group at position 3 of the indole nucleus (II). This compound was synthesized from the corresponding epoxide (III) by reaction with amine Va, which contains a protecting benzyl group on the nitrogen atom. The resulting hydroxyamine (VIa) was benzoylated via the hydroxy group, and the benzyl group removed from resulting derivative VIIIa by hydrogenolysis. Compounds VIIIb and IX were obtained analogously.



R = Me (II, III, VIa-g, VIIIa), CH_2COOMe (IV, VIIa-e, VIIIb, IX); R^1 = Me (I); R^2 = H (a), Me (b), OMe (c), NO_2 (d), F (e), Cl (f), COOEt (g), COONa (h); unspecified R, R^1, R^2 = H.

Since the β-adrenoblocker activity of hydroxyamino compounds, in which the hydrogen of a secondary amino group is substituted, has been little studied [8-10], we have synthesized and studied intermediate hydroxyamine VIa, which contains a benzyl group, and its analogs with different substituents at position 4 of the benzyl group (VIb-h), as well as analogous derivatives that contain at position 3 of the indole ring a carbomethoxymethyl instead of a methyl group (VIIa-e).

To elucidate the role of the benzyl group, a homolog of hydroxyamine VIa was synthesized (X), which contains a phenethyl instead of a benzyl group on the nitrogen atom.

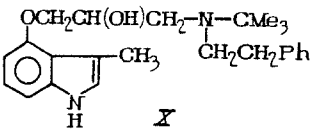


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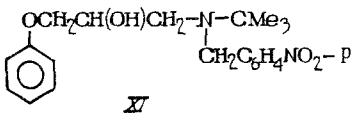
TABLE 1. Chemical Properties of Compounds Synthesized

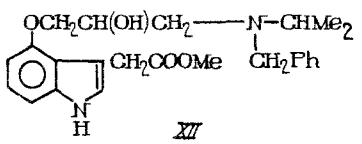
Compound	Yield, %	mp, °C	Empirical formula
II	87	233—4	$C_{23}H_{28}N_2O_3 \cdot HCl$
VIa	54	168—70	$C_{23}H_{30}N_2O_2 \cdot HCl$
VIb	47	122	$C_{24}H_{32}N_2O_2 \cdot C_3H_6O_3$[a]
VIc	61.5	126	$C_{24}H_{32}N_2O_3 \cdot C_3H_6O_3$[a]
VId	63	204—5	$C_{23}H_{29}N_3O_4 \cdot HCl$
VIe	59	177—8	$C_{23}H_{29}FN_2O_2 \cdot HCl$
VIf	75	116	$C_{23}H_{29}ClN_2O_2 \cdot C_6H_8O_7$[b]
VIg	72	180—1	$C_{26}H_{34}N_2O_4 \cdot HCl$
VIh		175	$C_{23}H_{29}N_2NaO_4$
VIIa	92.5	144—5	$C_{25}H_{32}N_2O_4 \cdot HCl$
VIIb	58	125—6	$C_{26}H_{34}N_2O_4 \cdot HCl$
VIIc	67	210[d]	$C_{25}H_{34}N_2O_5 \cdot HCl$
VIId	68	180—1[e]	$C_{25}H_{31}N_3O_6 \cdot HCl$
VIIe	92.5	131—3	$C_{25}H_{31}FN_2O_4 \cdot HCl$
IX	86	197—8	$C_{25}H_{30}N_2O_5 \cdot HCl$
X	81	150	$C_{24}H_{32}N_2O_2 \cdot C_6H_8O_7$[b]
XI		195—6	$C_{20}H_{26}N_2O_4 \cdot HCl$
XII		144—5	$C_{24}H_{30}N_2O_4 \cdot C_7H_6O_3$[c]

Notes. [a]Lactate; [b]citrate; [c]salicylate; [d]mp of base 93-94°C (from toluene); [e]mp of base (from alcohol).

In addition, we synthesized and studied an analog of compound VII (XI) which contains a phenyl group instead of an indole ring, and an analog of VIIa with an isopropyl group in place of the tertbutyl (XII).



XI



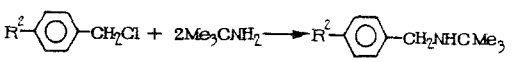
XII

Synthesis of 4-(3-amino-2-hydroxypropoxy)indole derivatives (VIa-g, VIIa-e, IX-XII) was accomplished by heating epoxy compounds III and IV with equimolar amounts of amines Va-g at 100-120° (in some cases a small excess of epoxy compound was used). The resulting base was converted to a salt with a pharmacologically acceptable acid. Chemical properties of compounds obtained are presented in Table 1.

Synthesis of epoxy compounds III and IV has been described by us previously [1]; secondary amines Va-g and phenylethyl-tert-butylamine (XIII) were obtained by alkylation of tert-butylamine with chlorides XIVa, c, and d, or with bromides XIVe, f, g, and phenylethylbromide (XV) in DMFA or dioxane, analogously to methods described in [4, 5].

Benzylisopropylamine (XVI), necessary for synthesis of XII, was prepared according to [12].

Characteristics of amines Va-g and XIII are given in Table 2.



XIVa-g Va-g

Starting chlorides XIVa and d were used as the reagent grade; chloride XIVc was prepared from anisyl alcohol and thionyl chloride according to [2]; bromides XIVb, e, f, and g were synthesized according to [6, 13, 15] by bromination of the methyl group with bromosuccinimide; and bromide XV was obtained from phenethyl alcohol as in [14].

EXPERIMENTAL (CHEMICAL)

Monitoring the course of chemical reactions was done by means of thin layer chromatography on Silufol UV-254 plates. As eluents, we used mixtures of benzene and acetone (4:1), isopropanol, aqueous ammonia, and water (8:1:1), or butanol,

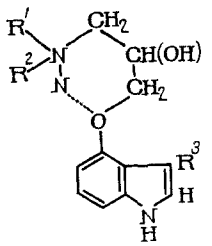
TABLE 2. Chemical Properties of Secondary Amines

Compound	Yield, %	bp (from literature), °C/mm Hg	Empirical formula	bp, °C/mm Hg	Reference
Va	46,6[a]	111—3/25	$C_{11}H_{17}N$	109—10/25	[6]
b	79[b]	90—3/3	$C_{12}H_{19}N$		
c	54[a]	108—10/2,5	$C_{12}H_{19}NO$	134—5/11	[13]
		mp 226 °C		mp 226 °C	[14]
d	89,7[a]	129—31/1,5	$C_{11}H_{16}N_2O_2$	mp . 29—30 °C	[13]
		mp 30 °C			
e	40[b]	68/1,5	$C_{11}H_{16}FN$		
f	91[b]	95—102/1,5	$C_{11}H_{16}ClN$	133—4/10	[13]
g	80[b]	120/2/1	$C_{14}H_{21}NO_2$		
XIII	39[b]	72—4/2	$C_{12}H_{19}N$		
XVI	87	75—9/7	$C_{10}H_{15}N$	66—8/1	[12]
		n_D^{20} 1,5010		45—6/1	[16]
				n_D^{20} 1,5010	

Notes. [a]Reaction carried out in DMFA; [b]in dioxane.

acetic acid, and water (4:1:5, upper layer of the mixture). Compounds were detected with UV light, as well as by spraying with solutions of 4-dimethylaminobenzaldehyde or ninhydrin.

The structures of compounds synthesized was verified by elemental analysis data (C, H, N, F; values obtained differed from those calculated by not more than 0.4%), mass spectrometry (MAT-112 spectrometer, with direct injection of sample into the ion source), and by ^{1}H-NMR spectra. One feature of NMR spectra of hydrochlorides of these compounds in DMSO-D_6 (Table 3, compounds VId and VIIa) is the presence of 2 sets of signals, corresponding to 2 diastereomeric forms (one of the asymmetric centers is the N^+ atom of the substituent at position 4 of the indole nucleus). In solvents with a mobile proton (CH_3OH, H_2O), only a single set of signals is observed, apparently due to rapid exchange between the two diastereomeric forms. The greatest differences in chemical shifts of analogous protons in diastereomers (in DMSO-D_6) are seen for 5-H ($\Delta\delta \cong 0.2$ ppm), which is 7 bonds removed from the asymmetric nitrogen atom. It may be proposed that the significant differences in chemical shifts for 5-H in the diastereomers is due to proximity of the asymmetric nitrogen to an indole atom, possibly as a result of the aminohydroxypropyl chain closing into a labile, six-membered ring, with a hydrogen bond between the protonated tertiary nitrogen and the oxygen at position 4 of the indole nucleus.



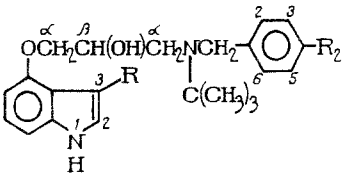
Similar diastereomeric forms of compounds VI and VII may exist at physiologic pH, where these highly basic tertiary amines must exist in the protonated form.

Benzyltert-butylamine (Va). A solution of 63.2 g (0.5 mole) benzyl chloride and 73 g (1.0 mole) of tert-butylamine in 150 ml DMFA was heated for 6 h on a boiling water bath with stirring. The residue was filtered, washed with DMFA, and the filtrate and wash liquid evaporated to a small volume under vacuum, and a second portion of residue filtered. A total of 70.76 g (71%) of Va hydrochloride was obtained. We mixed 70 g of hydrochloride, 126 ml water, and 21 g NaOH. The organic layer was separated, the aqueous extracted with toluene, and the toluene distilled. The residue was combined with the organic layer which was redistilled, yielding 38.0 g of colorless liquid, bp 111-113°C/25 mm Hg. Compounds Vc and d were obtained analogously from XIV c and d.

4-Fluorobenzyltert-butylamine (Ve) was prepared as described above, but using dioxane as the solvent. The tert-butylamine bromohydrate was separated, the filtrate evaporated, and the remaining base acidified with HCl in alcohol to give Ve hydrochloride. Amines Vb, f, and h and XIII were analogously prepared from XIVb, f, and h and XV.

4-[2-Hydroxy-3-tert-butyl(4-nitrobenzyl)aminopropoxy]skatole Hydrochloride (VId). A mixture of 8.72 g (0.043 mole) 4-(2,3-epoxypropoxy)skatole (III) and 8.5 g (0.041 mole) of 4-nitrobenzyltert-butylamine (Vd) were heated 20 h at 110-120°C, the melt cooled and mixed with 20 ml alcohol, the residue filtered, and crystals washed with 10 ml ethyl acetate to

TABLE 3. NMR Spectra of



Compound	Solvent	Protons of indole nucleus					Protons of substituent at position 3		Protons of substituent at position 4 of indole nucleus				Protons of phenyl nucleus		
		1 (NH)	2	5	6	7	CH_2	CH_3	CH_2	β CH	γ $CH_3C(CH_3)_3$	NCH_2	2,6	3,5	4 (or protons or substituent)
VIa[a]	$CDCl_3$	7,86	6,72	6,30	6,97	6,85	–	2,45	3,80 q 3,93 q	~3,58	2,85	1,17	3,86 d 3,58	7,20—7,33	
VIb	CD_3OD	–	6,82	6,21	6,88—6,91		–	2,43	3,80 d	3,23—4,46 m		1,48	4,41 d 4,04 d	7,41	7,12 2,80
VIc	CD_3OD	–	6,82	6,22	6,88—6,91		–	2,43	3,80	3,25—3,48 m		1,49	4,06 d 4,44 d	6,86	7,45 3,74
VId	DMSO	9,49 [9,71]	6,75	6,06[c] [6,26]	6,70—6,87		–	2,72	3,73	3,08	~3,5	1,55	4,63 m 4,30 m	8,05	8,10 8,21
VId[a]	$CDCl_3$	7,84	6,80	6,32	7,01	6,91	–	2,42	3,95	3,63	2,89	1,16	4,0 d 3,68 d	7,50	8,10
VIe	DMSO	9,45 [9,68]	6,88	6,19 [6,33]	6,85		–	2,35	3,69	3,07	3,47	1,53	4,20 m 4,65 m	7,17	7,87
VIf	CD_3OD	–	6,82	6,22	6,89—6,91		–	2,43	3,82	3,25—3,50 m		1,50	4,12 d 4,47 d	7,31	7,56
VIIa	DMSO	9,56	7,06	6,16 [6,38]	6,96	6,92	3,75	3,34	3,4—3,7	3,09	3,4—3,7	1,55 1,51	4,10 m 4,56 m	7,79	7,37
VIIa[a]	$CDCl_3$	8,11 –	6,85 7,45	6,30	6,85—7,45		3,87	3,61	2,89	3,64—3,90		1,19 1,29	3,54— 3,90	6,95	7,45
VIIb	D_2O		7,11	6,14	6,94—7,20		3,83	3,63	3,70	3,00	3,24	1,54 1,43	3,33 d 4,62 d	7,07	7,30 2,13
VIIc	CD_3OD		7,03	6,23	6,94—6,98		3,88	3,63	3,78	3,14	~3,48	1,59	4,17 d 4,66 d	6,85	7,52 3,72
VIId[a]	$CDCl_3$	8,01	6,98	6,28	7,02	6,92	3,80	3,57	3,82— 4,01	3,74	2,86	1,15	3,82— 4,01	7,51	8,02 –
X	CD_3OD		6,84	6,46	6,94—6,97		–	4,50	4,10 q 4,28 q	4,54 m	3,58	1,48	3,18 3,40	7,20	7,36
XII	DMSO	10,91	7,07	6,36	6,94		3,85	3,57	3,93	2,90	2,98	d	4,05	7,48	7,32

Notes. a) Chemical shifts of protons of base; b) doublets of protons for NCH_2Ph group have $J \approx 1.2$ Hz; c) in brackets are given chemical shifts for protons of minor forms, distinguished from the values for predominant forms (see above); d) signals for protons of isopropyl group 1.38 ppm (br s, CH_3), 3.50 ppm (m, CH).

yield 10.1 g of base VId. The base was dissolved with heating in 125 ml acetone, cooled, and acidified with a solution of HCl in alcohol to pH 4.5-5.0. This was left at 5°C for 12 h, and the residue was filtered and washed with 10 ml of acetone to give 8.92 g of orange crystals with mp 204-205°C. An additional 2.65 g of product was isolated from the mother liquor. Total yield was 63%. VIa-c and e-g, X (from III and XIII), and XI (from phenylglycidyl ether and Ve) were obtained analogously (see Table 2).

Methyl Ester of 4-[2-Hydroxy-3-tert-butylbenzylaminopropoxy)indolyl-3-acetic Acid Hydrochloride (VIIa). A mixture of 2.61 g (0.01 mole) of the methyl ester of 4-(2,3-epoxypropoxy)indolyl-3-acetic acid (IV) and 1.63 (0.01 mole) tert-butylbenzylamine was heated in an argon stream at 110-120°C for 5 h, and the resulting base dissolved in 10 ml alcohol and acidified with HCl in alcohol to pH 4.5-5.0. The residue was filtered and washed with 10 ml of alcohol and 20 ml ether to yield 4.26 g (92.5%) colorless crystals, mp 144-145°C. Compounds VIIb-e, X, and XII (from IV and XVI) were obtained analogously (see Table 2).

When necessary, the bases was crystallized from alcohol, toluene, tetrahydrofuran, methylene chloride, and/or their solutions in chloroform were passed over a layer of Al_2O_3. Conversion to the salt was carried out in alcohol, tetrahydrofuran, ethyl acetate, and acetone.

Ethyl ester VIg was saponified by boiling in an aqueous-alcoholic NaOH solution and gave an internal salt of VIh (R−COOH, mp 229-230°C), which with sodium methylate forms sodium salt VIh (R−COONa, pH 8.0, mp 175°C).

4-(2-Benzoyloxy-3-tert-butylaminopropoxy)skatole Hydrochloride (II). To a solution of 2.76 g (7.53 moles) VI in 20 ml of dioxane was added 2.4 g (10.6 mmoles) of benzoic anhydride. This was left for 48 h, poured into a mixture of ice and ether, and the ether layer washed with 2% NH_4OH and water, evaporated, and the residue crystallized from methanol to yield 2.6 g of colorless crystals of base 4-(2-benzyloxy-3-tert-butylamino)propoxyskatole VIII, mp 131-132°C. The base was dissolved in 25 ml tetrahydrofuran and hydrogenolysis carried out over Pd/C at atmospheric pressure, the catalyst was filtered,

TABLE 4. β-Adrenoblocking Activity, Duration of Action, and Acute Toxicity of 4-(2-Hydroxy-3-alkylaminopropoxy)indole

Compound	β-Adrenoblocking activity in rats			Duration of β-adrenoblocking action, h		(LD_{50}, mice, mg/kg)	
	intravenously		internally				
	dose decreasing techycardia caused by isadrine administration to 50%, ED_{50}, mg/kg	dose decreasing techycardia caused by isadrine administration to 50%, ED_{50}, mg/kg	dose decreasing hypotension caused by isadrine administration to 50%, ED_{50}, mg/kg	rats	cats	intravenously	internally
II	0,07	0,05	0,5	<24		96,0	270,0
VIa	1,25	0,8	1,1	24		37,0	440,0
VIb	>2,0	>2,0	10,0	<24		37,0	
VIc	>2,0	>2,0	2,0	<24		25,0	
VId	0,6	1,7	0,3	24—48	144—168	65,0	1000,0
VIe	0,24	1,9	0,8	24—48	144—168	40,0	1000,0
VIf	>2,0	>2,0	0,6	24		40,0	1000,0
VIg	>2,0	>2,0	7,5	24		48,0	
VIh	>2,0	>2,0	8,2	24		390,0	
VIIa	0,3	4,6	1,7	24—48	24—48	96,0	1000,0
VIIc	>2,0	>2,0	2,7	<24		64,0	
VIId			10,0	<24		170,0	
VIIa			3,5	<24		105,0	
IX	1,1	1,0	0,3	<24		27,0	300,0
X			4,0	<24		35,0	
XI			50,0	<24		35,0	
XII			35,0	<24		68,0	
Pindolol	0,025	0,02	0,05	8—15	24—48	20,0	200,0
Bopindolol	0,24	0,1	0,8	24	24—48	14,0	

and the solution acidified with HCl in alcohol to give 2.0 g (87%) of II. We obtained VIIIb analogously from VIIb, mp 137-138°, yield 73.5%, and IX.

EXPERIMENTAL (PHARMACOLOGICAL)

Compounds II, VIa-h, VIIa, c, d, and e, and IX-XII were subjected to pharmacologic study. β-Adrenoblocking activity was determined on narcotized male cats weighing 200-250 g, by intravenous and oral administration to the ED_{50} with respect to inhibition of the positive chronotropic and depressor effects of isadrine (1 mg/kg IV). Duration of activity on oral administration was studied in cats and rats. Acute toxicity was determined in experiments on white mice weighing 16-17 g, with intravenous administration.

Compound VId, having the highest activity, was studied in greater detail. β-Adrenoblocking activity of this compound was tested in experiments in vivo and in vitro. In experiments on isolated plasma membranes of rabbit heart, prepared according to [11], we determined the effect of VId on binding of ^{3}H-dihydroalprenolol to β-adrenoreceptors according to [3]. β-Adrenoblocking activity of this compound was also studied by intravenous administration to narcotized cats weighing 3-4 kg, and duration of action — by oral administration to awake dogs.

The activity, duration of action, and acute toxicity of compounds studied was compared with bopindolol and pindolol.

It was found that most of the compounds tested possess β-adrenoblocking activity to different degrees with intravenous administration to narcotized rats (Table 4). The most pronounced β-adrenoblocking effect was observed with compounds II, VId, and VIe. These compounds were similar in activity to bopindolol, but were inferior in strength to pindolol (by 3-95 fold). Compared with bopindolol and pindolol, the other compounds (VIa-c and f-h, VIIa, c, d, e and XI-XII) were weakly active. Compounds VId and VIe were inferior in activity to the benzoyl ether of 4-hydroxyskatole (compound II) and pindolol, but surpassed the latter, as well as bopindolol, in duration of action (24-48 h in rats and 144-168 h in cats, compared to 24-48 h for compound II, pindolol, and bopindolol).

In experiments on isolated sarcolemmas from rabbit myocardium, compound VI, similarly to bopindolol, was able to displace ^{3}H-dihydroalprenolol only at concentrations above 10^{-6} M (K_i is equal to 6 and 2.5 μM, respectively), whereas pindolol displays inhibitory activity starting at concentrations of 10^{-9} M (K_i = 1.9 nM). With intravenous administration in cats, compound VI is considerably inferior to pindolol and bopindolol (ED_{50} for effect on chronotropic activity of isadrine is 0.5, 0.003, and 0.007 mg kg, respectively, and for effect on depressor activity of the latter —0.4, 0.002, and 0.008 mg/kg).

The duration of β-adrenoblocking effect of VId (10 mg/kg orally) in dogs is 6 days (complete blockade of effects of isadrine for 5 days), whereas pindolol (1 mg/kg) causes blockade of isadrine's effects for a total of 8 days.

Thus, among 4-(2-hydroxy-3-alkylaminopropoxy)indole derivatives, along with compounds not inferior to pindolol and bopindolol in β-adrenoblocking activity (methyl esters of 4-hydroxyindole-3-acetic acid) [1], substances have also been found that exceed the reference preparations in duration of action (p-fluoro- and p-nitrobenzyl derivatives of 4-hydroxyskatole – compounds VIe and VId.

Concerning the connection between structure and activity of the compounds studied, it may be noted that their duration of action depends on the presence not only of a benzyl substituent instead of free hydrogen on the nitrogen of the side chain, but also tert-butyl and not isopropyl moieties (compounds VIIa and XII). At the same time, β-adrenoblocking activity of the compounds depends mainly both on the presence of an unchanged aminopropanol side chain and on the nature of the heterocycle (disappearance of β-adrenoblocking effect with substitution of a phenyl for the indole ring in compound XI). The studies carried out indicate the advisability of further studying derivatives of 4-hydroxyindole-3-acetic acid to obtain new, long-acting β-adrenoblockers.

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