SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 1-PHENOXY-3-AMINOPROPANOL-2-DERIVATIVES

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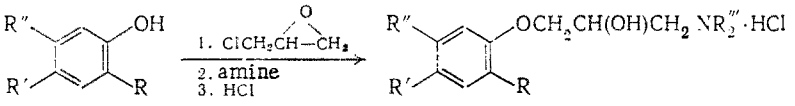
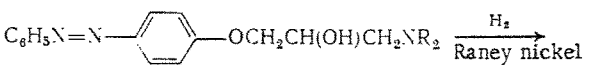
As a continuation of studies [3, 4] concerned with the search for new effective β-adrenergic blockers and structure-action relationships, we synthesized homologs of alprenolol which differs from many β-adrenergic blockers in its less pronounced internal sympathomimetic activity which leads to myocardial suppression [9, 11]. In order to study the effect of the methyl group in the meta- and para- positions relative to the side aminopropanol group in the series of 1-(2-allylphenoxy)-3-aminopropanols-2 (AAP) as well as the effect that the nature of the amine segment of AAP reactions between 4-methyl- and 5-methyl-2-allylphenols and epichlorohydrin in an alkaline medium and the subsequent action of amines have on the intermediate epoxides, we synthesized the following AAP (Ia-h):



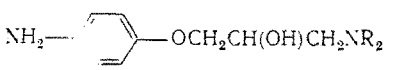
Ia-h

Ia-g $R = -CH_2CH=CH_2$; Ih $R = CH_3$; Ia, h: $R' = R'' = H$; Ib, d, e $R' = H$, $R'' = CH_3$; Ic, f, g $R' = CH_3$, $R'' = H$; Ia-c, h NR'''_2 = 2,6-dimethylpiperidino, Id, f $R''' = CH(CH_3)_2$; Ie, g $R''' = C(CH_3)_3$.

At the same time we devised a convenient method to obtain 1-(4-aminophenoxy)-3-aminopropanols-2 (IIa-d) which are the key compounds in the synthesis of 1-(4-acylaminophenoxy)-3-aminopropanols-2, many of which exhibit pronounced cardio-selective β-adrenergic blocking activity (Practolol, acetobutolol, Talinolol, and others) [5, 10]. The development of convenient methods for synthesizing anilines of II has been brought about by the need to enlarge the base of synthesized compounds and the disadvantages of existing methods that are due to the absence of a sufficiently multi-purpose method of selectively introducing amino- and acylamino groups inasmuch as these types of groups do not provide the required pharmacological effect (primarily cardioselectivity) when they are in other positions of the benzene ring. There are so far two principal methods of obtaining anilines of II: 1) hydrolytic cleavage of the acyl residue in the 1-(4-acylaminophenoxy)-3-aminopropanols-2 which essentially constitute the target products: 2) reduction of 1-(4-nitrophenoxy)-3-aminopropanols-2 [4, 7] which are obtained from 4 nitrophenols [6]. It is generally recognized that the nitration of phenols results in a mixture of ortho- and para- isomers whereas the azo group goes exclusively into the position para- to the oxygroup during the nitrogen coupling of the substituted phenols with the resultant formation of 4-oxyazobenzenes [1]. We obtained the 1-(4-aminophenoxy)-3-aminopropanols-2 (IIa-d) by the catalytic hydration of 1-(4-phenylazophenoxy)-3-aminopropanols-2 (IIIa-d). The latter can be synthesized by starting with 4-oxyazobenzene [8].



IIIa-d



IIa-d

IIa, IIIa NR_2 = isopropylamino, IIb, IIIb NR_2 = tert-butylamino, IIc, IIIc NR_2 = 2,6-dimethylpiperidino; IId, IIId NR_2 = N-phenylpiperazino

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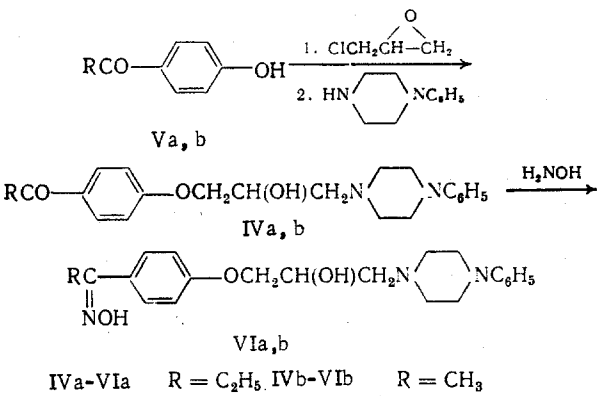
The structure of the synthesized IIa-d anilines was confirmed by IR spectra data. There are stretching vibration bands of the HO and NH_2 groups in the 3450-3315 cm^{-1} region in the IR spectra of these compounds. The IR spectra of compounds IIa-b containing a secondary amino group also have stretching vibration ($\sim$3220 cm^{-1}) and deformation vibration (1660-1670 cm^{-1}) bands of the NH groups.

In connection with the fact that β-adrenergic blockers are used for the treatment of a number of psychic illnesses (schizophrenia, anxiety states, alcoholism) and that substances with pronounced antidepressant action (Centropazine IVa) [9] were found among the aryloxypropanolamines containing a N-phenylpiperazine residue in the amine segment of the molecule, we synthesized 1-(4-acylphenoxy)-3-aminopropanols-2 (IVa, b) and their oximes (VIa, b) starting with acylphenols (Va, b) according to the following pattern:



The indicated compounds IV and VI along with compound IId were tested for antidepressant activity.

EXPERIMENTAL CHEMICAL PART

IR spectra were recorded on a Perkin-Elmer 45 spectrophotometer (Sweden).

1-(2-Allylphenoxy)-3-(2,6-dimethylpiperidino)-2-propanol HCl (Ia). A 2.7-g portion (0.02 mole) of 2-allylphenol was added to a solution of 0.88 g (0.22 mole) of NaOH in 4 ml of water. While this mixture was being water-cooled, 2.36 g (0.024 mole) of epichlorohydrin was added to the reaction mixture which was then kept for 3 h at 40-45°C. Following ether extraction, the extract was washed with water, dried over anhydrous Na_2SO_4, and vacuum evaporated after which 4.5 g (0.04 mole) of 2,6-dimethylpiperidine were added to the residue. The reaction mass was then boiled for 3 h, the amine excess was vacuum distilled, and treated with a 1:10 mixture of ether and petroleum ether which resulted in the product 1-(2-allylphenoxy)-3-(2,6-dimethylpiperidino)propanol-2. Yield 3.8 g (63%), mp 89-89.5°C (from a mixture of benzene and petroleum ether). Found, %: C 75.33; H 9.63. $C_{19}H_{29}NO_2$. Calculated, %: C 75.21; H 9.63. The base was converted to the hydrochloride Ia by the usual method.

The hydrochlorides Ib-g were obtained in the same manner.

1-(2-Methylphenoxy)-3-(2,6-dimethylpiperidino)-2-propanol HCl (Ih). A mixture of 3 g (1.8 mmole) of 2-(2,3-epoxypropoxy)toluene and 8 ml of 2,6-dimethylpiperidine was boiled for 5 h and the excess amine was vacuum distilled. After the addition of absolute benzene the mixture was vacuum evaporated which resulted in a yield of 5.2 g (85%) of the base of Ih with a mp 111-112°C (from a mixture of benzene and petroleum ether). The base was converted to the hydrochloride of Ih, mp 186°C (with decomposition). Found, %: Cl 11.25. $C_{17}H_{28}ClNO_2$. Calculated, %: Cl 11.29.

1-(4-Aminophenoxy)-3-isopropylamino-2-propanol (IIa). A 1.57 g (0.005 mole) portion of 1-(4-phenylazophenoxy)-3-isopropylaminopropanol-2 (IIIa) was hydrated in methanol over 0.5 g of Raney nickel until 0.01 mole of H_2 was absorbed. The catalyst was filtered off and washed with methanol. The methanol solution was vacuum evaporated, and the residue was crystallized from a mixture of benzene and petroleum ether (1:5) with charcoal. Yield 0.8 g (72%) of IIa, mp 122.5-123.5°C. According to literature data [6], the mp is 123.5-125°C.

1-(4-Aminophenoxy)-3-tert-butylamino-2-propanol (IIb) was obtained in a similar manner by the hydration of 0.98 g (0.003 mole) of 1-(4-phenylazophenoxy)-3-tert-butylaminopropanol-2.

TABLE 1. Derivatives of 1-Phenoxy-3-amino-2-propanols

Compound	Yield, %	mp, °C (solvent)	Found, %				Empirical formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
Ia	63	149—50	—	—	10,37	—	$C_{13}H_{21}NO_2 \cdot HCl$	—	—	10,43	—
Ib	48	170—1 (abs. alcohol)	67,80	9,20	10,37	—	$C_{20}H_{31}NO_3 \cdot HCl$	67,87	9,11	10,01	—
Ic	56,5	168—9 (abs. alcohol)	67,83	9,16	—	—	$C_{20}H_{31}NO_3 \cdot HCl$	67,87	9,11	—	—
Id	38,0	101—2 (abs. alcohol + ether)	—	—	11,87	—	$C_{14}H_{21}NO_2 \cdot HCl$	—	—	11,83	—
Ie	42,0	89—90 (abs. alcohol + ether)	—	—	11,73	—	$C_{13}H_{21}NO_2 \cdot HCl$	—	—	11,30	—
If	46,0	107—8 (isopropanol + ether)	—	—	11,54	—	$C_{14}H_{21}NO_2 \cdot HCl$	—	—	11,83	—
Ig	58,0	127—8 (isopropanol + ether)	—	—	11,36	—	$C_{13}H_{21}NO_2 \cdot HCl$	—	—	11,30	—
Ih	85,0	186	—	—	11,25	—	$C_{13}H_{21}NO_2 \cdot HCl$	—	—	11,30	—
IId	67,0	134—5 (benzene + petroleum ether)	69,85	7,74	—	12,82	$C_{19}H_{23}N_3O_2 \cdot HCl$	69,70	7,70	—	12,88
IVb	42,5	165—70 (alcohol)	71,24	7,35	—	8,07	$C_{21}H_{26}N_2O_3$	71,16	7,39	—	7,90
VIa	73,0	173—3,5	69,18	7,95	—	11,14	$C_{22}H_{28}N_2O_3$	68,90	7,62	—	10,95
VIb	90,0	193—4 (alcohol)	68,30	7,37	—	11,28	$C_{21}H_{26}N_2O_3$	68,27	7,37	—	11,37

Yield of IIb 0.6 g (83%), mp 128-129°C (from benzene). According to literature data [6] is 128-129°C.

1-(4-Aminophenoxy)-3-(2,6-dimethylpiperidino)-2-propanol (IIc). In a similar manner 3.67 g (0.01 mole of 1-(4-phenylazophenoxy)-3-(2,6-dimethylpiperidino)propanol-2 was hydrated to yield 2.4 g (87%) of IIc, mp 93.5-94°C (from 40% alcohol). According to literature data [4], mp is 93.5-94°C.

1-(4-Aminophenoxy)-3-(N-phenylpiperazino)-2-propanol (IVb). In a similar manner, 4.16 g (0.01 mole) of 1-(4-phenylazophenoxy)-3-(N-phenylpiperazino)propanol-2 was hydrated to yield 2.2 g (67%) of IId.

1-(4-Acetylphenoxy)-3-(N-phenylpiperazino)-2-propanol (IVb). A mixture of 1.5 g (8 mmoles) of 4-(2,3-epoxypropoxy)acetophenone and 1.3 g (8 mmoles) of N-phenylpiperazine in 2 ml of alcohol was boiled for 2 h, cooled, and filtered to yield 1.2 g of IVb.

4-(2-Oxy-3-N-phenylpiperazinopropoxy)acetophenone Oxime (VIb). A mixture of 1.77 g (5 mmoles) of the ketone of IVb, 1.04 g (15 mmoles) of hydroxylamine HCl, and 2.04 g (15 mmoles) of $CH_3COONa \cdot 3H_2O$ in 50% alcohol was boiled for 3 h and 1.8 g of the oxime VIb was filtered off.

4-(2-oxy-3-N-phenylpiperazinopropoxy)propriophenone (VIa) was obtained in the same manner as VIb.

The properties of the substances Ia-h, IId, IVb, and VIa, b are given in Table 1.

EXPERIMENTAL PHARMACOLOGICAL PART

β-Adrenergic block activity was tested on narcotized rats by the method described earlier [4]. Propanolol was used as the basis for comparison.

The test results (Table 2) indicate that the highest degree of β_1- and β_2-adrenergic block activity among the compounds under study that approached the activity of Propranolol and Alprenolol was exhibited by the Id-e analogs of Alprenolol which contain a methyl group in the meta-position with respect to the side aminopropanol group. The introduction of a methyl group in the para-position with respect to that group (compounds If-g) reduced the activity by a factor of 10. The other derivatives of 1-phenoxy-3-aminopropanol that contain a tertiary amino group in the side chain (Ia-c, h, IIc and VIb) exhibited β-adrenergic block activity that is significantly less than that of Propranolol. A series of 1-phenoxy-3-aminopropanols-2 (compound IId, Centropazine IVa, VIa) containing a N-phenylpiperazine residue was studied by tests used to evaluate antidepressant properties [2]. The pharmacological investigations showed that compounds IId, IVa and VIa are capable of potentiating the stereotypical behavior elicited by phenamine. Compound IId at a dose of 0.5 mg/kg was effective in 33% of the animals, and at doses of 1 and 2.5 mg/kg the compound was ef-

TABLE 2. β-Adrenergic Block Activity of 1-Phenoxy-3-amino-2-propanol Derivatives

Compound	β_1-Adrenergic block activity ED_{50}, mg/kg	Activity relative to propranolol	β_2-Adrenergic block activity ED_{50}, mg/kg	Activity relative to propranolol	Selectivity index
Ia	6,37	0,0018	9,12	0,0013	1,46
Ib	4,26	0,0026	5,71	0,0022	1,34
Ic	4,87	0,0023	6,44	0,0020	1,28
Id	0,018	0,61	0,019	0,63	1,05
Ie	0,017	0,64	0,018	0,66	1,05
If	0,28	0,039	0,26	0,046	0,92
Ig	0,20	0,055	0,18	0,066	0,9
Ih	5,62	0,002	9,71	0,0012	1,72
IIc	1,35	0,0084	1,47	0,0085	1,08
VIb	>10	—	>10	—	—

fective in 66% of the animals and exceeded the activity of Amitriptyline and Imipramine, but was less active than Fluorocizine. Centropazine (compound IVa) exhibited moderate phenamine-potentiating action (this effect was observed only in some animals and never reached the 50% level). The replacement of the NH_2- or propionyl group by the hydroxyliminoalkylidene residue (compound VIa) lowered phenamine potentiation which was only observed in a narrow range of doses (about 1 mg/kg). Centropazine IVa exhibited a clear ability to potentiate the effects of 5-oxytryptophan. The number of head twitches increased by 1.57 times at a dose of 0.25 mg/kg, and by 5.35 times at a dose of 5 mg/kg. In comparison to Centropazine, compound IId did not significantly affect the action of 5-oxytryptophan at doses of 0.25-1 mg/kg, but serotonin-negative action was observed at a dose of 5 mg/kg. A similar action was exhibited by another analog of Centropazine — compound VIa which reduced head twitching at high doses. Thus, the presence of a propionyl residue in position 4 of the phenoxy group is essential to the manifestation of serotonin-positive activity.

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