SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF SOME 1-PHENOXY-3-AMINO-PROPAN-2-OLS

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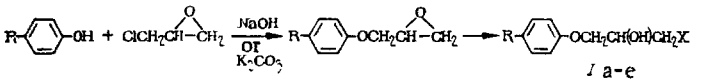
Interest has recently arisen in β-adrenoblocking agents as stress-protectant drugs. The spectrum of antistress activity of β-adrenoblockers includes a number of components, among which an important part is played by the blocking of the peripheral effects of endogenous adrenalin, which is released in substantial amounts at times of high psychoemotional tension [1]. One of the most important effects of adrenalin is an increase in glycogenolysis and appearance in the blood of large amounts of glucose and lactate [2]. From this point of view, the inhibitory effects of potential β-adrenoblockers on the hyperglycemia arising following administration of adrenalin may be used to measure stress-protectant activity.

In a search for compounds with β-adrenoblocking activity which also have inhibitory effects on adrenalin hyperglycemia, we have synthesized some 1-phenoxy-3-amino-propan-2-ol (Ia-e, IIa-d, III, IVa-b, and Va-d), with substituents in the 4-position of the benzene ring such as methoxycarbonyl, acetyl, hydroxyiminoalkylidene (oximes and their O-phenyl ethers of 4-acetyl derivatives), acylamino, and azomethine groups. At the same time, the structure of the amino moiety was varied, with, in addition to the usual isopropylamine and tert-butylamino residues, the 2,6-dimethylpiperidine radical being introduced for the first time.

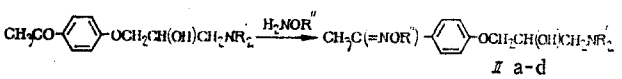
Compounds (Ia-e) were synthesized by the reaction between the sodium salts of the phenols and epichlorohydrin, followed by reaction of the resulting epoxides with amines:



I a-e

a: R = $COOCH_3$, X = 2,6-dimethylpiperidino; b: R = $COCH_3$, X = isopropylamino; c: R = $COCH_3$, X = tert-butylamino; d: R = H, X = 2,6-dimethlypiperidino e: R = NO_2, X = 2,6-dimethylpiperidino.

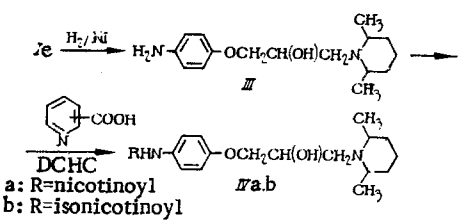
Reaction of the 4-acetyl compounds (Ib-c) with hydroxylamine and O-phenylhydroxylamine afforded (IIa-d):



II a-d

a: R = tert-butyl, R″ = H; b: R = isopropyl, R″ = H; c: R = tert-butyl, R″ = phenyl; d: R = isopropyl, R″ = phenyl

Hydrogenation of (Ie) over Raney nickel gave 1-(4'-aminophenoxy)-3-(2",6"-dimethylpiperidino)-propan-2-ol (III), which on acylation with nicotinic and isonicotinic acids in the presence of a carbodiimide afforded the 4-acylaminocompounds, i.e., analogs of practolol (IVa-b):



a: R=nicotinoyl
b: R=isonicotinoyl

IVa,b

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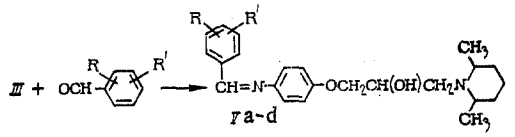
The azomethines (Va-d) were obtained by reacting (III) with aromatic aldehydes:



a: R = R′ = H; b: R 2-hydroxy, R′ = H; c: R 2-hydroxy, R′ = 3-methoxy, d: R = 3-methoxy, R′ = 4-methoxy

The structures and purities of the compounds obtained were confirmed by TLC and IR and PMR spectroscopy.

The compounds obtained were examined for β-1- and β-2-adrenoblocking activity, and for their inhibitory effects on adrenalin hyperglycemia.

EXPERIMENTAL CHEMISTRY

IR spectra were obtained on a Perkin-Elmer-45 spectrophotometer (Sweden). PMR spectra were recorded on a Varian T-60 spectrometer (USA). TLC was carried out on alumina (Brockman grades II and IV activity), development with iodine vapor.

1-(4'-Methoxycarbonylphenoxy)-3-(2",6"-dimethylpiperidino)-propan-2-ol Hydrochloride (Ia). To a mixture of 6.2 g (0.04 mole) of methyl p-hydroxybenzoate and 11.1 g (0.12 mole) of epichlorohydrin was added over 1.5 h with stirring 50 ml of 1 N NaOH, and stirring continued for 1 h. After around 16 h at 20°C, the mixture was extracted with chloroform, the extract dried over anhydrous Na_2SO_4, and evaporated under reduced pressure, finally with the addition of toluene. The residue was dissolved in methanol, 5.7 g (0.05 mole) of 2,6-dimethylpiperidine added, and the mixture boiled for 6 h, following which it was evaporated under reduced pressure. The solid residue was crystallized from light petroleum, dissolved in dry ether, and ethereal hydrogen chloride added to give 6.7 g of the hydrochloride (Ia).

4-[(2'-Hydroxy-3'-tert-butylamino)propoxy]acetophenone Hydrochloride (Ic). 4-Hydroxyacetophenone (2.72 g, 0.02 mole) in 4 ml of dry DMF and 3.0 g (0.022 mole) of anhydrous potassium carbonate were stirred at 20°C for 15 min, and to the resulting suspension was added 2.7 g (0.03 mole) of epichlorohydrin. The mixture was heated for 1 h at 100°C, cooled, diluted with water, extracted with eather, and the ether layer washed with water and dried over potassium carbonate. The ether was distilled off, the residue treated with 4.38 g (0.06 mole) of tert-butylamine, the mixture heated for 2 h at 70°C, poured into water, extracted with ether, and the ether solution extracted with 10% hydrochloric acid. The acid solution was basified with 10% NaOH, extracted with chloroform, and the extract dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was dissolved in dry ether, and treated with ethereal hydrogen chloride to give 3.3 g of (Ib) hydrochloride.

4-[(2'-Hydroxy-3'-isopropylamino)propoxy]acetophenone Hydrochloride (Ib). This was obtained similarly to hydrochloride (Ic), using isopropylamine (20 h at 20°C).

1-Phenoxy-3-(2',6'-dimethylpiperidino)-propan-2-ol Hydrochloride (Id). This was obtained in the same way as (Ia). In the PMR spectrum on changing the solvent from $CDCl_3$ to a mixture or $CDCl_3$ and CF_3COOH the greatest stift to low field (from 2-2.2 to 3-3.5 ppm) was experienced by the four protons adjacent to the nitrogen atom, confirming structure (Id), with the piperidine ring attached to the distal C atom of the propane moiety.

1-(4'-Nitrophenoxy)-3-(2",6"-dimethylpiperidino)-propan-2-ol (Ie). To a a solution of 8.8 g (0.22 mole) of NaOH in 20 ml of water was added 27.8 g (0.2 mole) of 4-nitrophenol, followed with stirring and water cooling by 63 g (0.68 mole) of epichlorohydrin in 40.5 ml of methanol. The mixture was boiled for 3 h, evaporated under reduced pressure, the residue treated with water, filtered, and washed with ether to give 37.4 g of crude 1-(4'-nitrophenoxy)-2,3-epoxypropane. This was heated on the oil bath with 41.8 g (0.382 mole) of 2,6-dimethylpiperidine at 100°C for 6 h, and the reaction mixture was then diluted with ether and filtered to give 31.6 g of (Ie).

4-(2'-Hydroxy-3'-tert-butylaminopropoxy)acetophenone Oxime Hydrochloride (IIa). A mixture of 2.0 g of free base (Ib) in 20 ml of alcohol, 1.45 g (0.021 mole) of $NH_2OH \cdot HCl$ in 20 ml of water, and 2.8 g (0.021 mole) of $CH_3COONa \cdot 3H_2O$ in 15 ml of water was heated at 100°C for 1 h, basified with 10% NaOH to pH 9.0, and the solid filtered off to give 2 g of the oxime (IIa), which was converted to the hydrochloride.

4-(2'-Hydroxy-3'-isopropylamino)acetophenone Oxime Hydrochloride (IIb). This was obtained in the same way as (IIa).

4-(2'-Hydroxy-3'-tert-butylaminopropoxy)acetophenone Oxime O-Phenyl Ether (IIc) Hydrochloride (IIc). A mixture of 2.65 g (0.01 mole) of the base (IIa) in 20 ml of absolute alcohol and 1.61 g (0.01 mole) of O-phenylhydroxylamine hydrochloride in 20 ml of absolute alcohol was kept at 20°C for 20 h, evaporated under reduced pressure, basified with 10% NaOH, extracted with chloroform, the extract dried over anhydrous potassium carbonate, and evaporated under reduced pressure to give 2.6 g of the base, which was converted into (IIc) hydrochloride.

4-(2'-Hydroxy-3'-isopropylaminopropoxy)acetophenone Oxime O-Phenyl Ether Hydrochloride (IId). This was obtained in the same way as (IIc).

1-(4'-Aminophenoxy)-3-(2",6"-dimethylpiperidino)-propan-2-ol (III). A solution of 3.08 (0.01 mole) of (Ie) in 80 ml of methanol was hydrogenated over Raney nickel until 0.03 mole of hydrogen had been taken up. The catalyst was filtered off, the filtrate evaporated, and the residue treated with light petroleum to give 2.37 g of (III).

1-(4'-Nitrotinoylaminophenoxy)-3-(2",6"-dimethylpiperidino)-propan-2-ol (IVa). To a solution of 1.39 g (0.005 mole) of (III) in 20 ml of anhydrous pyridine was added 0.62 g (0.005 mole) of nicotinic acid and 1.03 g (0.005 mole) of dicyclohexylcarbodiimide (DCHC). The mixture was stirred for 4 h at 20°C, kept for 16 h, a further 1.03 g (0.0005 mole) of DCHC added, stirred for 8 h, the solid which separated filtered off, washed with ether and ethyl acetate, the combined filtrates evaporated under reduced pressure, the residue treated with 10% hydrochloric acid, filtered, and basified with 10% NaOH to give 1.2 g of (IVa). IR spectrum (in oil), ν, cm^{-1}: 3375 (NH), 1651 (NHCO), 1536.

1-(4'-Isonicotinoylaminophenoxy)-3-(2",6"-dimethylpiperidino)-propan-2-ol (IVb). This was obtained in the same way as (IVa).

1-(4'-Benzylideneamine)phenoxy-3-(2",6"-dimethylpiperidino)-propan-2-ols (Va-c). General Method. A mixture of 1.39 g (0.005 mole) of the amine (III) and 0.005 mole of aromatic aldehyde in 25 ml of absolute alcohol was boiled for 3-10 h to give azomethines (Va-c). IR spectrum of (Vb) (KBr), ν, cm^{-1}: 3520 (OH), 1650 (C=N), 1585.

1-[4'-(3",4"-Dimethoxybenzylideneamino)phenoxy]-3-(2",6"-dimethylpiperidino)-propan-2-ol (Vd). To a mixture of 1.30 g (0.005 mole) of (III) and 0.83 g (0.005 mole) of veratrole in 50 ml of dry toluene was added a catalytic amount of p-toluenesulfonic acid, and the mixture boiled for 1 h with simultaneous removal of water in a Dean and Stark apparatus. The toluene was distilled off, and residue triturated with ether to give 1.84 g of (Vd).

The properties of (Ia-e), (IIa-d), (III), (IVa-b), and (Va-d) are given in Table 1.

EXPERIMENTAL PHARMACOLOGY

The β-adrenoblocking activity of the compounds was examined in narcotized rats, using a method based on the ability of the test compounds to suppress isadrine tachycardia and hypertension [3]. Propranolol was used as the standard.

β-1-Adrenoblocking activity was determined in spinal rats, obtained by administration of pentobarbital sodium in an intraperitoneal dose of 120 mg/kg, followed by connection to an artificial respiration apparatus. β-2-Adrenoblocking activity was measured in rats narcotized with urethane (1.78 g/kg intraperitoneally). Arterial pressure was measured in the common carotid artery using an electromanometer, the instantaneous cardiac contraction frequency index was projected from the arterial pressure curve, and the hemodynamic factors were recorded on a Mingograf-81 polygraph. To study β-1- and β-2-adrenoblocking activity, isoproterenol wad administered intravenously in doses of 0.1 and 0.215 μg/kg respectively.

The experimental results show that (Ia), (Ie), (IIa-d), (III), (IVb), and (Vc) possess β-adrenoblocking activity, but are much less active than propranolol.

Experiments on the inhibitory effects of the compounds on adrenalin hyperglycemia were carried out in female mongrel white mice of weight 18-20 g. The experimental program for the experimental group included intraperitoneal administration of the test compound in a dose equimolar to a dose of propranolol of 10 mg/kg, followed after 1 h by the subcutaneous administration of adrenalin hydrochloride in a dose of 0.5 mm/kg. In the control experiment, the animals were first treated with a 0.9% solution of sodium chloride intraperitoneally, followed after 1 h by adrenalin. In another control group, the animals were treated twice

TABLE 1. 1-Phenoxy-3-amino-propan-2-ols

Compound	Yield, %	Mp, °C (solvent)	Found, %				Molecular formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
Ia·HCl	47	188 (decomp.; isopropanol)	...	...	9,94	...	$C_{18}H_{25}ClNO_4$	...	...	9,91	...
Ib·HCl	55	187—8 (decomp.)	...	...	11,78	...	$C_{15}H_{24}ClNO_3$	...	...	11,75	...
Ic·HCl	70	123—4 (decomp; abs. alcohol)	...	...	12,10	5,02	$C_{14}H_{22}ClNO_3$	...	...	12,32	4,87
Id·HCl	57	159 (decomp; abs. alcohol)	...	...	11,86	...	$C_{16}H_{26}ClNO_2$	...	...	11,83	...
Ie	51,5	142—3 (benzene–heptane)	62,32	7,85	—	9,28	$C_{16}H_{24}N_2O_4$	62,31	7,85	—	9,08
IIa·HCl	90	199—200	...	...	11,32	8,79	$C_{15}H_{25}ClN_2O_3$	...	...	11,19	8,84
IIb·HCl	50*	173—4	...	...	11,75	9,14	$C_{14}H_{23}ClN_2O_3$	...	...	11,71	9,25
IIc·HCl	73	147,5—8,5	64,02	7,35	8,71	7,19	$C_{21}H_{29}ClN_2O_3$	64,19	7,44	9,03	7,13
IId·HCl	50	120—1 (abs. alcohol—heptane)	63,07	7,26	9,36	7,47	$C_{20}H_{27}ClN_2O_2$	63,39	7,18	9,35	7,39
III	85	93,5—4,0	68,86	9,43	—	10,26	$H_{16}H_{26}N_2O_2$	69,02	9,41	—	10,06
IVa	63	165—6 (alcohol)	68,62	7,96	—	11,08	$C_{22}H_{29}N_3O_3$	69,90	7,62	—	10,96
IVb	95	172—3 (alcohol)	69,03	7,62	—	10,93	$C_{22}H_{29}N_3O_3$	69,90	7,62	—	10,96
Va	80	110—1 (heptane)	74,95	8,30	—	7,96	$C_{23}H_{30}N_2O_2$	75,37	8,25	—	7,64
Vb	76	143,5—4,5	71,95	7,91	—	7,54	$C_{23}H_{30}N_2O_3$	72,21	7,90	—	7,32
Vc	90	82—3 (heptane)	69,99	7,90	—	6,92	$C_{24}H_{32}N_2O_4$	69,87	7,81	—	6,79
Vd	87	118—9 (alcohol)	70,29	8,22	—	6,89	$C_{25}H_{34}N_2O_4$	70,39	8,03	—	6,56

*Base, yield 87%, mp 160-161°C. Found, %: C 63.21; H 8.20; N 10.55. $C_{14}H_{22}N_2O_3$. Calculated, %: C 63.13; H 8.33; N 10.52.

TABLE 2. Effect of 1-Phenoxy-3-amino-propan-2-ols on the Hyperglycemic Activity of Adrenalin

Compound	Inhibition of adrenalin hyperglycemia, %
Ia	72
IIb	50
IIc	43
IId	40
Propranolol	73
Practolol	61
Atenolol	8
Talinolol	Potentiation of adrenalin effect

with a 0.9% solution of sodium chloride at an interval of 1 h. Forty minutes after the administration of adrenalin or 0.9% sodium chloride solution, the animals were decapitated, and the blood collected separately from each mouse. The test compounds were administered in aqueous solution with the addition of Tween, or as a finely-divided suspension (in the case of sparingly soluble compounds). Each dose (of the test compound and adrenalin) was administered in a volume of 0.1 ml per 20 g of body weight. The blood glucose content was measured by the o-toluidine method. Each experimental group consisted of 6-20 mice. Measurements of the effects of each compound were made in not less than 3 experiments. The index of the inhibitory effect on adrenalin hyperglycemia was calculated as the ratio (in percent) of the absolute increase in the blood glucose concentration following administration of adrenalin in the presence of the test compound to the increase in concentration of glucose following administration of adrenalin alone (in comparison with the controls). This ratio was calculated when the differences in the concentrations were statistically significant, as determined by Student's criterion. For purposes of comparison, β-adrenoblockers with different types of activity were used (propranolol, practolol, atenolol, and talinolol); these compounds were administered in doses equimolar to a dose of propranolol of 10 mg/kg. It follows from the results presented in Table 2 that the most active of the known adrenoblockers in blocking the hyperglycemic effect of adrenalin is the nonselective adrenoblocker propranolol, the cardioselective β-1-adrenoblockers being less active, with talinolol even enhancing the hyperglycemic effect of adrenalin. Of the compounds synthesized, (Ia) is equally as effective as propranolol, with the remaining comounds being less active. These results therefore show that a search for potential stress-protectants in the 1-phenoxy-3-amino-propan-2-ol series is to be desired.

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