2-(3-AMINO-2-HYDROXYPROPOXY)PHENOXYMETHYLOXAZOLES AS POTENTIAL β- AND α-ADRENOBLOCKING AGENTS

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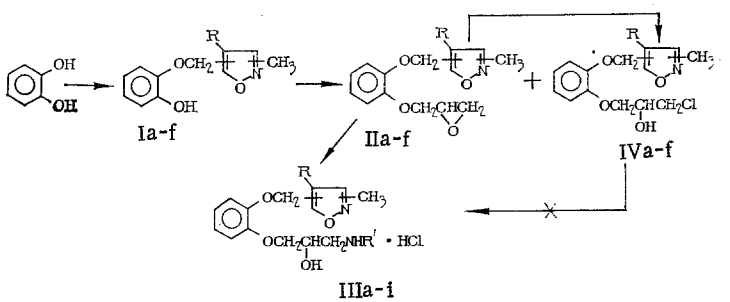
β-Adrenal blocking agents are used extensively in the treatment of cardiovascular diseases. Most adrenoblockers are not without their deficiencies, however, since they may induce bronchospasm or bradycardia, provoke cardiac insufficiency, and impair conductivity and peripheral blood circulation [1]. An important potential source of new, more sophisticated β-blockers would be compounds in which β-blocking activity is accompanied by α-blocking and vasodilating properties [2, 3]. At the present time, the principal drug which combines β- and α-blocking activity is labetalol [4]. Weak α-blocking activity is also found in the β-blocker oxyprenolol [5]. We here describe a search for novel β- and α-adrenal blocking agents among the isoxazole analogs of oxyprenolol.

The title compounds were synthesized by the most widely used method for introducing the 3-amino-2-hydroxypropyl group, involving alkylation of the appropriate 2-hydroxyphenoxymethylisoxazole (Ia-f) with epichlorohydrin, followed by nucleophilic fission of the resulting 2,3-epoxy derivatives of the phenoxymethylisoxazoles (IIa-f) with aliphatic amines to give the 3-amino-2-hydroxypropoxyphenoxymethylisoxazoles (IIIa-i).



(I)-(IIIa-c, g, h) (CH_3 group occurs in the 3-position of the isoxazole ring), a: R=H; b: R=Cl; c: R=Br; (IIIa-c): R'=$CH(CH_3)_2$; (IIIg, h): R=Cl; g: R'=$C(CH_3)_3$; h: R'=$CH(CH_3)C_2H_5$. (I-IIId-f, i) (CH_3 group in the 5-position of the isoxazole ring), d: R=H; e: R=Cl; f: R=Br; (IIId-f): R'=$CH(CH_3)_2$; (IIIi): R=H, R'=$C(CH_3)_3$.

The 2-hydroxy derivatives (Ia-f) were obtained by alkylating pyrocatechol with chloro-(or bromo-)methyloxazoles in the presence of sodium ethoxide by the method used for the preparation of (Ia) [6]. However, the yields under these conditions in no case exceeded 45%, partly as a result of resinification of the reaction mixture and the formation of substantial amounts of dialkylation products. Using the preparation of (Ib) as an example, we have shown that the alkylation of pyrocatechol with 3-methyl-4-chloro-5-bromomethylisoxazole in acetone in the presence of K_2CO_3 proceeds more selectively, to give (Ib) in a yield of 62%.

The compositions and structures of (Ib-f) were confirmed by their elemental analyses and their UV, IR, and PMR spectra. The presence of the isoxazole and phenol fragments was shown by the two absorption maxima in the UV spectra at 220-225 and 277-279 nm, respectively. The IR spectra showed absorption for stretching vibrations of the hydroxyl group at 3250-3300 cm^{-1}. The PMR spectrum of (If) contained signals for the protons of the methyl group at 2.23

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TABLE 1. 2-Hydroxyphenoxymethylisoxazoles (Ib-f)

Compound	mp, °C	Yield, %	Found, %			Empirical formula	Calculated, %			IR spectrum, ν OH, cm^{-1}	UV spectrum, λ_{max}, nm (lg ε)
			C	H	N (Cl)		C	H	N (Cl)		
Ib	80—80,5	37	55,13	4,20	(14,82)	$C_{11}H_{10}ClNO_3$	55,12	4,21	(14,80)	3300	224 (3,41) 277 (4,08)
Ic	92,5—3,5	45	46,58	3,70	4,79	$C_{11}H_{10}BrNO_3$	46,50	3,55	4,93	3300	225 (3,99) 278 (3,41)
Id	82—83	40	—	—	6,85	$C_{11}H_{11}NO_3$	—	—	6,85	3250	220 (4,04) 279 (3,41)
Ie	117—8	32	55,11	4,31	(14,52)	$C_{10}H_{10}ClNO_3$	55,12	4,21	(14,80)	3300	225 (3,98) 277 (3,45)
If	117—8	34	46,47	3,49	...	$C_{10}H_{10}BrNO_3$	46,50	3,55	—	3280	225 (4,03) 278 (3,33)

Note. The yield of (Ib) by method B was 62%.

TABLE 2. 2-(2,3-Epoxypropoxy)phenoxymethylisoxazoles (IIa-f)

Compound	mp, °C	Yield, %	Found, %			Empirical formula	Calculated, %		
			C	H	N (Cl)		C	H	N (Cl)
IIa	73—74	40	64,21	5,90	5,36	$C_{14}H_{15}NO_4$	64,36	5,78	5,36
IIb	63—64	67	56,56	4,65	4,74	$C_{14}H_{14}ClNO_4$	56,87	4,74	4,74
IIc	60—61	51	49,40	4,30	4,05	$C_{14}H_{14}BrNO_4$	49,43	4,15	4,12
IId	42—43	57	64,21	5,58	5,17	$C_{14}H_{15}NO_4$	64,36	5,78	5,36
IIe	82—83	71	—	—	(12,26)	$C_{14}H_{14}ClNO_4$	—	—	(12,00)
IIf	76—77	50	49,34	4,06	4,04	$C_{14}H_{14}BrNO_4$	49,43	4,15	4,12

TABLE 3. 2-(3-Amino-2-hydroxypropoxy)phenoxymethylisoxazole Hydrochlorides (IIIa-i)

Compound	mp, °C	Yield, %	Found, %			Empirical formula	Calculated, %			IR spectrum, ν_{OH}, cm^{-1}	UV spectrum, λ_{max}, nm (lg ε)
			C	H	N		C	H	N		
IIIa	116—117	82	—	—	7,91	$C_{17}H_{25}ClN_2O_4$	—	—	7,85	3300	276 (3,35)
IIIb	103—104	64	52,39	6,32	7,17	$C_{17}H_{24}Cl_2N_2O_4$	52,18	6,18	7,16	3300	225 (4,06) 275 (3,31)
IIIc	111—112	52	46,93	5,39	6,26	$C_{17}H_{24}BrClN_2O_4$	46,85	5,55	6,43	3340	225 (4,06) 275 (3,36)
IIId	117—118	80	57,16	7,05	7,88	$C_{17}H_{25}ClN_2O_4$	57,22	7,06	7,85	3330	222 (4,11) 276 (3,34)
IIIe	111—112	85	52,29	6,20	6,92	$C_{17}H_{24}Cl_2N_2O_4$	52,18	6,18	7,16	3320	226 (4,06) 275 (3,33)
IIIf	112—113	50	46,86	5,57	6,85	$C_{17}H_{24}BrClN_2O_4$	46,85	5,55	6,43	3330	226 (4,03) 275 (3,37)
IIIg	115—117	52	53,52	6,50	6,88	$C_{18}H_{26}Cl_2N_2O_4$	53,34	6,46	6,91	3280	226 (4,04) 275 (3,37)
IIIh	92—93	50	53,26	6,23	6,72	$C_{18}H_{26}Cl_2N_2O_4$	53,34	6,46	6,91	3310	225 (4,11) 275 (3,37)
IIIi	57—58	75	58,10	7,23	—	$C_{18}H_{27}ClN_2O_4$	58,29	7,34	—	3300	222 (4,15) 276 (3,40)

ppm (3H, s, 5-CH_3 of isoxazole), the hydroxymethylene group at 5.20 ppm (2H, s, CH_2O), and a multiplet for the protons of the benzene ring at 6.8-7.2 ppm.

The physicochemical properties of (Ia-f) are given in Table 1.

Alkylation of (Ia-f) with epichlorohydrin, either in aqueous dioxane in the presence of sodium hydroxide, or in acetone with potassium carbonate, in all cases gave, in addition to the main products (IIa-f) (Table 2), up to 20% of the 3-chloro-2-hydroxypropoxyphenoxymethylisoxazoles (IVa-f). Chromatographic separation of the products of the reaction of (Ib) with epichlorohydrin gave the byproduct (IVb) in the pure state. It was identical in its chromatographic mobility and IR spectrum with a sample specially prepared by a known method [7] involving selective fission of the epoxide ring of the 2,3-epoxy compound (IIb) with alcoholic hydrogen chloride.

It is known that in chlorohydrins of this type, nucleophilic replacement of the chlorine by an amino group requires relatively severe conditions (prolonged heating in a sealed ampul at temperatures in excess of 100°C) [8]. Under these conditions, chlorohydrin (IVb) resinified almost completely, apparently owing to the sensitivity of the isoxazole ring to alkalis at elevated temperatures. However, opening of the epoxide ring of (IIa-f) with amines occurred almost completely on boiling in methanol for 0.5-1 h. The resulting (IIIa-i) were readily separated as their hydrochlorides from unreacted chlorohydrins (IVa-f). For this reason, the epoxy compounds (IIa-f) could be used to synthesize (IIIa-i) without further purification. The properties of the compounds (IIIa-i) are given in Table 3.

EXPERIMENTAL CHEMISTRY

IR spectra were obtained on a Perkin-Elmer-402 spectrometer (Sweden) in vaseline oil, UR spectra on a Perkin-Elmer-402 instrument (Sweden) in ethanol, and PMR spectra on a Varian-X-100-A-12 instrument (USA; 100 MHz) in deuterochloroform, internal standard tetramethylsilane.

3-Methyl-4-chloro-5-bromomethylisoxazole. This was obtained by brominating 3,5-dimethyl-4-chloroisoxazole as described in [9]. 3-Methyl-5-chloromethyl- and 5-methyl-3-chloromethylisoxazoles were obtained by treatment of the appropriate alcohols with $SOCl_2$ [10]. Chlorine and bromine were introduced into the 4-position of isoxazole by means of hydrochloric or hydrobromic acid in the presence of hydrogen peroxide, as described in [11].

3-Methyl-4-chloro-5-(2-hydroxyphenoxymethyl)isoxazole (Ib). Method A. To a solution of 3.6 g (0.15 mole) of sodium in 60 ml of ethanol was added with stirring under nitrogen a solution of 16.5 g (0.15 mole) of pyrocatechol in 40 ml of ethanol. The mixture was stirred at 20°C for 1 h, then heated to 70-80°C, and a solution of 31.3 g (0.15 mole) of 3-methyl-4-chloro-5-bromomethylisoxazole in 80 ml of ethanol was added dropwise. The mixture was boiled for 2 h, and kept overnight with cooling (0-5°C). The solid which separated was filtered off and washed with cold alcohol. The filtrate was evaporated to dryness *in vacuo*, and the residue was treated with 100 ml of 2 N sodium hydroxide, the solid filtered off, washed with 2 N sodium hydroxide, and with water. The filtrate was acidified with conc. hydrochloric acid to pH 1-2, extracted with ether, dried over sodium sulfate, and the ether distilled off to give 13.3 g (37%) of (Ib). Similarly obtained were (Ic-f), the properties of which are given in Table 1.

Method B. A mixture of 11.0 g (0.1 mole) of pyrocatechol, 16.7 g (0.075 mole) of 3-methyl-4-chloro-5-bromomethylisoxazole and 13.8 g of anhydrous potassium carbonate was boiled with vigorous stirring for 10 h. The acetone was removed *in vacuo*, and the residue was treated with 100 ml of water and 50 ml of concentrated sodium hydroxide solution. The solid was filtered off, and washed with a concentrated solution of potassium hydroxide (3 × 20 ml) and water. The alkaline mother liquors were acidifed with cooling with conc. hydrochloric acid to pH 1-2, and the solid filtered off and washed with water until neutral, to give 11.3 g (62%) of (Ib).

3-Methyl-5-[2-(2,3-epoxypropoxy)phenoxymethyl]isoxazole (IIa). To a solution of 1.2 g (0.03 mole) of sodium hydroxide in 12 ml of water was added a solution of 6.15 g (0.03 mole) of (Ia) in 15 ml of dioxane, and the mixture was stirred for 1 h. To the reaction mixture was added 5.5 g (0.06 mole) of epichlorohydrin, and the mixture heated on the water bath for 3 h. After cooling, the mixture was extracted with ether, dried over magnesium sulfate, the ether evaporated, and the residue recrystallized from hexane to give 3.2 g (40%) of (III). Similarly obtained were (IIb-f), the data for which are given in Table 2.

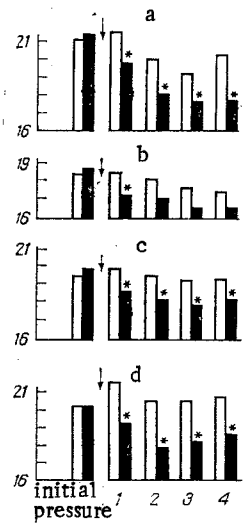

Fig. 1

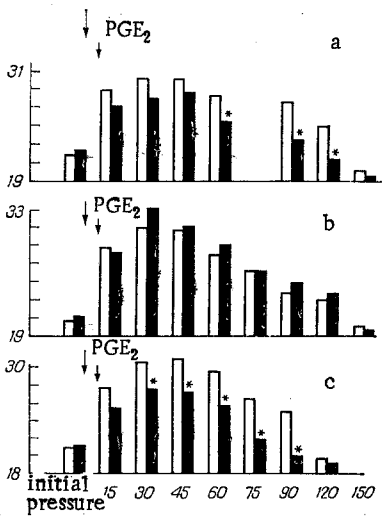

Fig. 2

Fig. 1. Effects of (IIIb) (a), (IIId) (b), thymolol (c), and propranolol (d) on intraocular pressure in normal rabbits. Asterisks denote $P < 0.05$. Horizontal axis) time after administration of compound; vertical axis) intraocular pressure (mm Hg).

Fig. 2. Effects of (IIIb) (a), thymolol (b), and propranolol (c) on intraocular pressure in rabbits with prostaglandin hypertension. PGE_2 is prostaglandin E_2. The β-blockers (IIIb, thymolol, and propranolol) were administered 60 min before administration of PGE_2. Asterisks denote $P < 0.05$. Horizontal axis) time after administration of compound; vertical axis) intraocular pressure (mm Hg).

3-Methyl-5-[2-(3-isopropylamino-2-hydroxypropoxy)phenoxymethyl]isoxazole Hydrochloride (IIIa). A mixture of 3.2 g (0.012 mole) of (IIa) and 5 ml (3.5 g, 0.06 mole) of isopropylamine in 15 ml of methanol was boiled for 0.5-1 h. The methanol and excess isopropylamine were evaporated *in vacuo*, and the residue was recrystallized from light petroleum (bp 70-100°C). The solid was filtered off and dissolved in absolute ethanol, and the solution was treated with ether saturated with hydrogen chloride until an acid reaction was obtained. The solid was filtered off and washed with dry ether to give 3.5 g (82%) of (IIIa).

Similarly obtained were (IIIb-i), the properties of which are given in Table 3.

EXPERIMENTAL PHARMACOLOGY

The pharmacology of (IIIa-i) was examined. Using narcotized male rats weighing 250-300 g, the β-adrenoblocking activity of (IIIa-i) by internal administration was determined as the ED_{50}, from the reduction in the positive chronotropic and depressor effects of isadrin (1 μg/kg), and the α-adrenoblocking activity from the reduction in the pressor effect of mesaton (0.1 mg/kg). The local anesthetic activity of the compounds was determined by Regnier's method in rabbits. The effects of some of the compounds (IIIb, d, g) on the normal intraocular pressure and on ocular hypertension induced by the instillation (or subconjunctival injection) of prostaglandin E_2 (Upjohn) in a dilution of 1:3 were determined in waking rabbits of weight 2.5-3 kg. Acute toxicities were determined in mice of weight 16-17 g, by intravenous administration. The activities and toxicities of the test compounds were compared with those of the β-blockers propranolol, oxypropranolol, and pindolol, the β- and α-blocker labetalol, and the α-blocker fentolamine. Local anesthetic activity was determined in comparison with dicaine and lidocaine, and the effects of intraocular pressure in comparison with the β-blockers propranolol and thymolol, which are the most widely used drugs for the treatment of glaucoma.

Most of the test compounds (IIa-i) had differing β- and α-blocking activity (Table 4). β-Blocking properties were shown by compounds with an isopropyl or sec-butyl group on the side chain nitrogen (IIIa-f, h), irrespective of the location of the halogen and methyl groups in the isoxazole ring. The greatest β-blocking activity was shown by (IIIb), which contains a chlorine atom in the 4-position of the isoxazole ring. This compound was 3 and 6 times more active in its β-blocking activity than oxyprenolol and propranolol, respectively, and

TABLE 4. Results of Pharmacological Studies of 3-Amino-2-hydroxypropoxyphenoxymethylisoxazole Hydrochlorides (IIIa-i)

Compounds	Test subjects: rats: β-blocking effects: ED_{50} (mg/kg, i-v) for the depressor effects of isadrin	rats: β-blocking effects: ED_{50} (mg/kg, i-v) for the blocking of the chronotropic effects of isadrin	rats: α-blocking effects: ED_{50} (mg/kg, i-v) for the blocking of the depressor effects of mesaton	rabbits: local anesthetic activity: Regnier's index (1% solution)	mice: acute toxicity: LD_{50} (mg/kg, i-v)
IIIa	0,020	0,160	10,0	235	59
IIIb	0,017	0,070	8,0	258	61
IIIc	0,055	0,150	11,0	428	61
IIId	0,051	0,380	14,5	215	78
IIIe	0,018	0,150	—	122	35
IIIf	0,100	0,300	16,0	222	45
IIIg	>2,0	>2,0	—	748	45
IIIh	0,100	0,300	8,5	299	32
IIIi	>2,0	>2,0	—	558	47
Oxyprenolol	0,055	0,260	37,5	—	20
Propranolol	0,092	0,420	—	—	28
Pindolol	0,020	0,025	...	...	49
Labetalol	3,300	0,700	12,0	...	97
Fentolamine	...	...	1,0	...	...
Lidocaine	...	...	...	252	...
Dicaine, 0.1%	...	...	...	673	...

10-200 times more active than labetalol, but it was inferior to indolol (but only in its β_1-blocking activity). Compounds containing the tert-butyl substituent on the side chain nitrogen (IIIg, i) had low β-blocking activity. In their α-blocking activity, most of the compounds [apart from (IIIe)] were similar to labetalol, were superior to oxyprenolol, but were less active (by an order of magnitude) than fentolamine. On instillation into the eye of the rabbit as an 0.1-1% solution, all the compounds gave rise to dose-dependent superficial anesthesia for 30-40 min. The greatest local anesthetic activity was found in (IIIg, i), which were devoid of β-blocking activity. These compounds were similar to lidocaine (as the 1% solution) in their local anesthetic activity, but were inferior to dicaine.* Of the three compounds tested (IIIb, d, g), only one (IIIb) in a concentration of 2%, caused (like propranolol) a significant reduction in intraocular pressure, both in rabbits with normal intraocular pressure, and in prostaglandin-induced ocular hypertension (Figs. 1 and 2). Compound (IIId) caused a slight, short-lived reduction in intraocular pressure only in rabbits with normal intraocular pressure, but (IIIg) was inactive in both cases.

Thus, compounds with an isopropyl group on the side-chain nitrogen and a chlorine atom in the isoxazole ring, linked to the benzene ring via an oxymethyl group, such as is typical of most β-blockers (IIIb, e), show high β-blocking activity. Replacement of isopropyl by sec-butyl (IIIh), or chlorine by bromine (IIIc, f) results in a considerable decrease in activity, and when isopropyl is replaced by tert-butyl (IIIg, i) the compounds are virtually inactive. As in the case of local anesthetic activity, the α-adrenolytic activity of the test compounds was independent of the nature of the substituent on the side-chain nitrogen or in the isoxazole ring.

The ability of (IIIb) to reduce intraocular pressure appears to be directly or indirectly related to its high β-blocking activity, since the slightly active (IIId) and inactive compounds (IIIg) in respect of β-blocking activity did not cause any significant reduction in intraocular pressure.

Foreign workers have recently reported [12] the occurrence of compounds with β,α-blocking activity in isoxazole analogs of oxyprenolol. These compounds differ from our compounds in possessing an ethylene group between the benzene and isoxazole rings. It is noteworthy that the β-blocking activity of these compounds is independent to a large extent of the presence of an isopropyl or tert-butyl group on the side-chain nitrogen, but is reduced by the introduction of a chlorine atom into the 4-position of the isoxazole ring.

*Local anesthetic activities were determined by Candidate of Medical Sciences T. K. Trubitsin.

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