sure. The crystalline residue was washed with 30 ml of MeOH to yield 1.45 g (46.6%) of colorless prisms, mp 286–288° dec. The melting point was not raised by recrystallization from EtOH. *Anal.* ($C_{13}H_{14}N_2O_3$) C, H, N; mol wt: calcd, 230; found, 211 (osmometric measurement on a 0.091 m*M* solution in dioxane).

8-Methoxy-3,4,6,7-tetrahydro-1H,5H-azocin[4,5,6-*cd*]indole (V).—To a suspension of 638 mg of IV in 30 ml of THF was added gradually 10 ml of a 1.0 *M* solution of B_2H_6 in THF (ice cooling, stirring). After standing for 1 day at room temperature, excess B_2H_6 was decomposed by the addition of 10 g of ice. Evaporation under reduced pressure gave a B-containing crystalline residue, mp 268–270° dec. This complex was refluxed on a steam bath for 10 hr in 10 ml of EtOH containing 2 g of alkali. After removal of the EtOH, the mixture was extracted three times with 50-ml portions of hot C_6H_6. The combined extracts were evaporated under reduced pressure and dissolved in 0.1 *N* HCl. This solution was treated with a small amount of charcoal and filtered. To the clear filtrate was added a 1% aqueous solution of picric acid. The insoluble microcrystalline yellow picrate resulting was collected, washed (H_2O), and dried. The crude picrate was extracted with 30 ml of hot MeOH, filtered, and dried to yield 1.08 g. This material was suspended in a mixture of 20 ml of 2.0 *N* HCl and 100 ml of EtOAc and shaken with C_6H_6 to remove a small amount of picric acid. After addition of excess alkali, the H_2O layer was extracted three times with 50 ml of hot benzene. The combined benzene extracts were dried with KOH pellets and evaporated under reduced pressure to yield 483 mg (80%) of colorless crystals, mp 152–153°. Recrystallization from MeOH–H_2O gave colorless prisms, mp 153–154°. *Anal.* ($C_{13}H_{16}N_2O$) C, H, N.

The uv spectrum revealed typical indole absorption, $\lambda\lambda_{max}$ 279 nm (ϵ 6070), 289 (5010); the ir spectrum showed no carbonyl absorption.

5-Methoxy-1-acetyl-2,3-dihydropyrrolo[2,3-*d*]indole (VI).—To 132 mg of melatonin (0.57 mmole, Regis Lot P5-581) and 0.32 ml of Et_3N (2.28 mmoles, dried over KOH) in 25 ml of CH_2Cl_2 at −10° (ice–acetone bath) was added dropwise with stirring over 20 min, 10 ml of a 0.084 *M* solution of *t*-BuOCl (Nutritional Biochem. Corp., Cleveland, Ohio) in CH_2Cl_2. The reaction mixture was allowed to warm to 0° over 20 min. A solution of 0.96 ml of 1.0 *N* NaOH, diluted to 8 ml with absolute EtOH, was added dropwise with stirring at 0°. The turbid solution was stirred for several minutes, then filtered to afford a crop of microcrystalline material (81 mg after washing and drying, 61.8% yield), mp 250° dec. Tlc (silica gel G, 4% CH_3OH in $CHCl_3$) revealed very little dehydromelatonin (R_f 0.67, pink spot with *p*-dimethylaminocinnamaldehyde spray) in the filtrate. The compound was recrystallized from dichloroethane–hexane to give material of mp 250–255° dec. After sublimation (145–160°, high vacuum) material of mp 255–260° was obtained. Biological assays were run using this material: uv, $\lambda\lambda_{max}$ 318 nm (ϵ 20,800), 223 (16,400). *Anal.* ($C_{15}H_{14}N_2O_2$) H, N; mol wt: calcd, 230; found, parent peak (M^+) at *m/e* 230 in the mass spectrometer, with principal peaks at 188 ($M^+ - CH_2CO$), 187 ($M^+ - CH_3CO$), 173 ($M^+ - CH_2CO - CH_3$), and 145 ($M^+ - CH_2CO - CH_3 - CO$).

Lightening Effects on Frog Skin.[9]—Frog skin is removed and lightened by washing with several changes of Ringers solution. It is then darkened with a predetermined amount of MSH (in these experiments, 10 units of standard MSH). At 60 min the lightening agent is added, and the degree of lightening (increase in reflectance) is measured. The data indicate that 0.01 or 0.02 mg of dehydromelatonin (VI) has approximately the same lightening activity as 0.2×10^{-6} mg of melatonin; 0.2×10^{-7} mg of dehydromelatonin has very little lightening activity.

The total volume of the buffer, which contains the skin, is 20 ml. By dividing these numbers by 20 one gets the concentration of melatonin or dehydromelatonin that produces effective reversal of MSH darkening. The experiments indicate that 0.1 and 0.2 mg of dehydromelatonin is as effective a lightening agent as 0.2×10^{-6} mg of melatonin; 0.2×10^{-5}, 0.2×10^{-4}, and 0.2×10^{-3} mg of dehydromelatonin have no lightening effect on frog skin.

(9) We are greatly indebted to Dr. J. McGuire, School of Medicine, Yale University, New Haven, Conn., for carrying out these evaluations.

β-Adrenergic Blocking Agents. V. 1-Amino-3-(substituted phenoxy)-2-propanols

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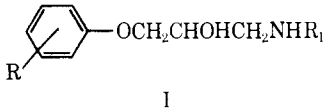
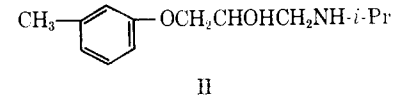
Several 1-amino-3-(substituted phenoxy)-2-propanols have been synthesized and tested against isoproterenol-induced tachycardia in anesthetized cats. Their β-adrenergic blocking activity proved in general to be similar to that of the propranolol analogs described in part II.[1a] Structure–activity relationships are discussed. Of the compounds tested, 1-isopropylamino-3-(3-methylphenoxy)-2-propanol was examined in detail in laboratory animals.

In our previous paper[1a] we described a series of 1-amino-3-naphthoxy-2-propanols which possessed potent β-adrenergic blocking properties. We now report the synthesis of a series of 1-amino-3-(substituted phenoxy)-2-propanols.[1b-e]



I

The biological evaluation of these compounds has shown that the ability to antagonize the effects of isoproterenol was widely spread over the series. From a large number of compounds synthesized the *m*-tolyl analog (II) was selected for further evaluation. It proved to be similar in potency to propranolol[2] in antagonizing the effects of isoproterenol in laboratory animals.[3] Evaluation of this compound in man has been reported by Hahnel.[4]



II

Chemistry.—The compounds were prepared in a manner analogous to that for the 1-amino-3-naphthoxy-2-propanols[1a] using the 1,2-epoxy-3-(substituted phen-

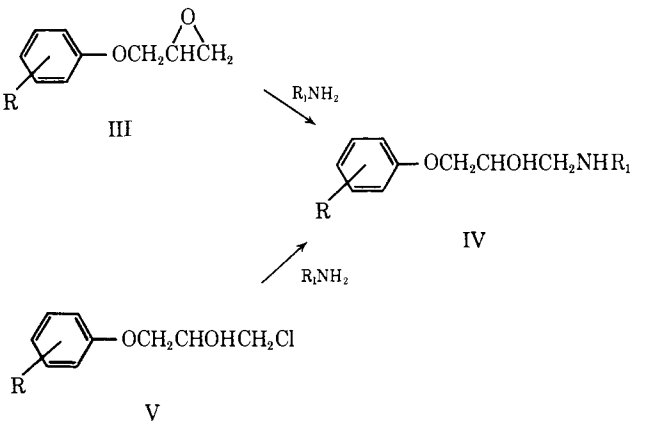
(1) (a) A. F. Crowther and L. H. Smith, *J. Med. Chem.*, **11**, 1009 (1968); (b) A. F. Crowther, L. H. Smith, and T. M. Wood, U. K. Patent 1,069,341 (1967); (c) A. F. Crowther, L. H. Smith, and T. M. Wood, U. K. Patent 1,069,345 (1967); (d) D. J. Gilman and B. J. McLoughlin, U. K. Patent 1,128,052 (1968); (e) B. J. McLoughlin, U. K. Patent 1,123,258 (1968).

(2) Inderal®.

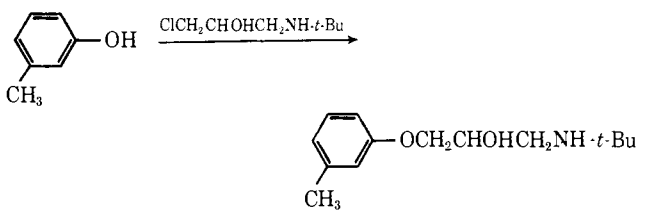
(3) R. G. Shanks and T. M. Wood, *Nature*, **212**, 88 (1966).

(4) J. Hahnel, *Z. Kreislaufforsch.*, **55**, 1023 (1966).

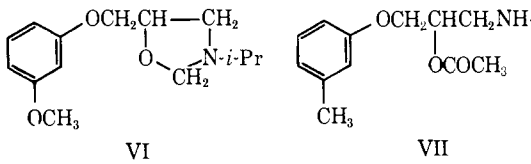
oxy)propane or 1-chloro-3-(substituted phenoxy)-2-propanol with the appropriate amine.[5]



The epoxide III and chlorohydrin V intermediates were used without purification in most cases. The route *via* the epoxide (method A) was preferred when the starting phenol contained a reactive group that might have interfered at the final stage. As in our previous work[1a] we surmised that the chloropropanols (used in method B) in the presence of base lost HCl to give the 1,2-epoxypropane. Confirmation that the epoxide ring of III opened up in the manner indicated was obtained when *m*-cresol condensed with 1-chloro-3-*t*-butylamino-2-propanol[6] in the presence of base to give the same compound (**56**, Table II) as that already obtained by method A. An alternative method of



preparation, sometimes useful when the substituent attached to nitrogen was secondary, was the reductive alkylation of the parent primary amine with a ketone, H_2, and Pt catalyst (method C). The over-all yields, however, were generally lower than those obtained by methods A and B. The oxazolidine VI was formed when the amino alcohol (**7**, Table I) as the free base was treated with formaldehyde in hot EtOH. Reaction of the amino alcohol II in AcOH with Ac_2O gave the acetate ester VII.



Structure–Activity Relationships.—The results of the biological tests are given in Tables I and II. The test procedure was identical with that used in the propranolol series.[7] The effects of varying the propanolamine side chain or the nuclear substituents are summarized below.

In the 1-amino-3-(2-ethylphenoxy)-2-propanol series the activity was maximal when the amine residue was secondary, bearing an alkyl group of three to four C atoms branched at the α-carbon atom, *e.g.*, *i*-Pr, *t*-Bu, and 2-hydroxy-1,1-dimethylethyl (**3**, **61**, **63**). Of the unbranched alkyl members the *n*-Pr (**60**) compound was moderately active. Activity fell sharply with the unsaturated allyl group (**62**). The α-methylaralkyl and aryloxyalkyl members (**64**–**67**) were moderately active; this declined with **67**. Tertiary amines were not examined in great detail as they had proved less potent than secondary amines in the propranolol series.[1a] Of the three compounds examined, the N-methyl-N-isopropyl compound (**69**) was quite active but the others (**79**, **82**) had low activity.

In the 1-isopropylamino-3-(substituted phenoxy)-2-propanol series, high activity was obtained when the benzene nucleus had a substituent in the 2 or 3 position. Halogens, in general, in the 2 or 3 position conferred very high activity (**13**, **14**, **16**–**18**), nitro compounds were also highly active (**23**, **24**), as were alkoxy (**6**–**8**), hydroxy (**21**), aryl (**31**), and aryloxy (**28**, **29**) derivatives. Compounds with substituents in the 4 position, in general, were not as active.

When there were two substituents in the nucleus, occupation of the 3 and 5 positions appeared to give maximal activity (**39**, **48**). Trisubstituted compounds were quite active (**51**, **52**), but with five substituents activity fell considerably (**53**, **54**).

Few changes in the propanolamine side chain were examined. The oxazolidine VI and the ester VII paralleled in activity the corresponding derivatives in the propranolol[1a] series, being less active than the parent compounds. Both compounds were readily hydrolyzed by dilute alkali to give the parent amino alcohol.

Experimental Section[8,9]

1-Isopropylamino-3-(3-methylphenoxy)-2-propanol (1) (Method A).—1-Chloro-3-(3-methylphenoxy)-2-propanol[10] (2.0 g) and 15 ml of *i*-$PrNH_2$ were heated together in a sealed vessel for 10 hr at 100°. The mixture was diluted with 50 ml of H_2O, acidified with concentrated HCl, and shaken with 50 ml of Et_2O. The acid phase was separated and basified with 11 *N* NaOH. The solid was collected, dried, and recrystallized from petroleum ether (bp 40–60°); yield 1.4 g (63%), mp 79°.

1-(3-Ethoxyphenoxy)-3-isopropylamino-2-propanol Oxalate (8) (Method B).—1,2-Epoxy-3-(3-ethoxyphenoxy)propane[11] (3.0 g) and 25 ml of *i*-$PrNH_2$ were heated together under reflux for 2 hr. The mixture was evaporated to dryness and the residue was stirred with 50 ml of 1 *N* HCl and 50 ml of Et_2O. The acid phase was basified with 11 *N* NaOH and extracted with 50 ml of Et_2O. The ether extract was dried ($MgSO_4$) and added to excess ethereal oxalic acid. The solid oxalate was collected and crystallized (DMF); yield 1.3 g (28%), mp 155–156°.

1-Cyclopentylamino-3-(3-methylphenoxy)-2-propanol (Method C).—1-Amino-3-(3-methylphenoxy)-2-propanol hydrochloride[12]

(5) (a) V. Petrow and O. Stephenson, *J. Pharm. Pharmacol.*, **5**, 359 (1953); (b) W. Bradley, J. Forrest, and O. Stephenson, *J. Chem. Soc.*, 1959 (1951); (c) H. R. Ing and W. E. Ormerod, *J. Pharmacol. Exptl. Therap.*, **4**, 21 (1952); (d) E. R. Marle, *J. Chem. Soc.*, **101**, 305 (1912).

(6) H. G. Eggert, W. Dietrich, and H. Rath, German Patent 1,010,971 (1957).

(7) J. W. Black and J. S. Stephenson, *Lancet*, **2**, 311 (1962).

(8) All melting points were taken using open capillaries and are uncorrected.

(9) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

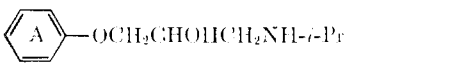
(10) H. Lefebvre, E. Levas, and E. Levas, *Compt. Rend.*, **222**, 1439 (1946).

(11) Prepared according to the method of ref 3a and used without purification.

(12) J. R. Merchant and A. S. U. Choughuley, *Current Sci.* (India), **30**, 99 (1961).

TABLE I

1-ISOPROPYLAMINO-3-(SUBSTITUTED PHENOXY)-2-PROPANOLS

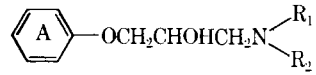


No.	Substituents in ring A	Mp, °C	Crystn solvent	Formula[a]	Method of prepn	Dose, μg/kg/min	% inhib of isoproterenol-induced tachycardia
1	3-Me	79	Petr ether (40–60°)	$C_{13}H_{21}NO_2$	A	10	80
1a		121–122	EtOH–EtOAc	$C_{13}H_{21}NO_2 \cdot HCl$			
2	4-Me	91–92	Cyclohexane	$C_{13}H_{21}NO_2$	A	10	66
3	2-Et	66–67	Petr ether (60–80°)	$C_{14}H_{23}NO_2$	A	2.5	74
4	4-*i*-Pr	179–180	EtOH–EtOAc	$C_{15}H_{23}NO_2 \cdot 0.5C_2H_2O_4$	A	20	43
5	$2CH_2Cl—CH_2$	107–109	EtOAc	$C_{15}H_{23}NO_2 \cdot HCl$	B	5	64
6	2-OMe	82–83	Cyclohexane	$C_{13}H_{21}NO_3$	A	5	86
7	3-OMe	72–73	Cyclohexane	$C_{13}H_{21}NO_3$	A	2.5	55
8	3-OEt	155–156	DMF	$C_{14}H_{23}NO_3 \cdot 0.5C_2H_2O_4$	B	2.5	60
9	2-OEt	87–88	Petr ether (60–80°)	$C_{14}H_{23}NO_3$	A	2	83
10	2-*i*-BuO	85–86	Petr ether (60–80°)	$C_{16}H_{27}NO_3$	A	5	73
11	2-*n*-$C_7H_{13}O$	77	Petr ether (80–100°)	$C_{19}H_{33}NO_3$	A	40	55
12	$2-OCH_2CH=CH_2$	75–76	Petr ether (60–80°)	$C_{15}H_{23}NO_3$[b]	A	1	61
13	2-Cl	88–89	Cyclohexane	$C_{12}H_{18}ClNO_2$	A	2.5	99
14	3-Cl	88–89	Petr ether (60–80°)	$C_{12}H_{18}ClNO_2$	A	5	82
15	4-Cl	99–100	Cyclohexane	$C_{12}H_{18}ClNO_2$	A	20	46
16	3-Br	94–95	Cyclohexane	$C_{12}H_{18}BrNO_2$	A	2.5	63
17	2-I	99	Cyclohexane	$C_{12}H_{18}INO_2$	A	5	89
18	3-F	88–89	Cyclohexane	$C_{12}H_{18}FNO_2$	B	5	55
19	$2-CF_3$	76–78	Cyclohexane	$C_{13}H_{18}F_3N_2$	B	5	64
20	$3-CF_3$	135–136	EtOAc–Et_2O	$C_{15}H_{18}F_3NO_2 \cdot 0.5C_2H_2O_4$	A	20	86
21	2-OH	207–208	H_2O	$C_{12}H_{19}NO_3 \cdot C_6H_3N_3O_7$	A	10	69
22	4-OH	167–168	EtOH–EtOAc	$C_{12}H_{19}NO_3 \cdot HCl$	E	2.5	67
23	$2-NO_2$	157–158	H_2O	$C_{12}H_{18}N_2O_4 \cdot C_6H_3N_3O_7$	A	2.5	79
24	$3-NO_2$	110–111	EtOAc	$C_{12}H_{18}N_2O_4$	A	5	47
25	4-COMe	88	Cyclohexane	$C_{14}H_{21}NO_3$	A	50	38
26	$2-OCF_2CHCl_2$	152–153	EtOAc	$C_{14}H_{18}Cl_2F_2NO_3HCl$	A	2	60
27	2-O- 	189–191	*n*-BuOAc	$C_{17}H_{27}NO_3 \cdot 0.5C_2H_2O_4 \cdot H_2O$	A	10	67
28	$2-OC_6H_5$	120–122	EtOAc	$C_{18}H_{23}NO_3 \cdot HCl \cdot 0.5H_2O$	B	2.5	80
29	$3-OC_6H_5$	119–121	EtOAc	$C_{18}H_{23}NO_3 \cdot HCl \cdot 0.5H_2O$	B	10	64
30	2-O-(C_6H_4-4-Me)	117–119	EtOAc–Et_2O	$C_{19}H_{25}NO_3 \cdot HCl$	B	2.5	78
31	$2-C_6H_5$	67–68	Cyclohexane	$C_{18}H_{23}NO_2$	A	5	54
32	$2-CH_2C_6H_5$	106–107	EtOAc	$C_{19}H_{25}NO_2 \cdot HCl \cdot 0.5H_2O$	B	5	68
33	$2-COC_6H_5$-5-OMe	195	*n*-PrOH	$C_{20}H_{25}NO_4 \cdot C_2H_2O_4$	B	10	73
34	$2-S-C_6H_5$	76–78	2 *N* HCl	$C_{15}H_{23}NO_2S \cdot HCl \cdot H_2O$	A	25	94
35	$2,3-Me_2$	112–113	Petr ether (60–80°)	$C_{14}H_{23}NO_2$	A	10	60
36	$2,4-Me_2$	76–77	Petr ether (60–80°)	$C_{14}H_{23}NO_2$	A	10	50
37	$2,5-Me_2$	68–69	Petr ether (60–80°)	$C_{14}H_{23}NO_2$	A	10	41
38	$3,4-Me_2$	148–149	EtOH–EtOAc	$C_{14}H_{25}NO_2 \cdot HCl$	A	5	50
39	$3,5-Me_2$	108–109	Cyclohexane	$C_{14}H_{23}NO_2$	A	5	63
40	3-Me-5-Et	86–87	Petr ether (60–80°)	$C_{15}H_{25}NO_2$	A	20	81
41	2-*t*-Bu-5-Me	175–176	EtOH–EtOAc	$C_{17}H_{29}NO_2 \cdot HCl$	A	10	47
42	$3,5-(OMe)_2$	149–150	EtOH–EtOAc	$C_{14}H_{23}NO_4 \cdot 0.5C_2H_2O_4 \cdot 0.5H_2O$	B	40	50
43	$2,5-(OMe)_2$	77–79	Petr ether (60–80°)	$C_{14}H_{23}NO_4$	B	10	65
44	3-*t*-Bu-4-OMe	95	Petr ether (100–120°)	$C_{17}H_{30}NO_3$	A	10	54
45	$2,3-Cl_2$	96–97	Cyclohexane	$C_{12}H_{17}Cl_2NO_2$	A	5	83
46	$2,5-Cl_2$	83	Cyclohexane	$C_{12}H_{17}Cl_2NO_2$	A	5	80
47	$3,4-Cl_2$	124–125	Cyclohexane	$C_{12}H_{17}Cl_2NO_2$	A	40	58
48	$3,5-Cl_2$	117–118	Cyclohexane	$C_{12}H_{17}Cl_2NO_2$	A	2.5	53
49	4-Cl-3-Me	119	Cyclohexane	$C_{13}H_{20}ClNO_2$	A	10	46
50	2-Cl-4-Me	165–166	EtOH–EtOAc	$C_{13}H_{20}ClNO_2 \cdot HCl$	A	5	48
51	$2,4,5-Cl_3$	114–115	Cyclohexane	$C_{12}H_{16}Cl_3NO_2$	A	10	59
52	4-Cl-3,5-Me_2	142	Cyclohexane	$C_{14}H_{22}ClNO_2$	A	5	51
53	$2,3,4,5,6-Cl_5$	127–128	Cyclohexane	$C_{12}H_{14}Cl_5NO_2$	A	10	39
54	$2,4,6-Br_3$-3,5-Me_2	145	Cyclohexane	$C_{14}H_{20}Br_3NO_2$	A	40	48

[a] All compounds were analyzed for C, H, N. [b] N: calcd, 5.3; found, 4.8. [c] H: calcd, 8.4; found, 7.9.

TABLE II

1-AMINO-3-(SUBSTITUTED PHENOXY)-2-PROPANOLS



No.	Substituents in ring A	R_1	R_2	Mp, °C	Crystn solvent	Formula[a]	Method of prepn	Dose, μg/kg/min	% inhib of isoproterenol-induced tachycardia
55	3-Me	H	*n*-Pr	86–87	Petr ether (60–80°)	$C_{13}H_{21}NO_2$	A	40	53
56	3-Me	H	*t*-Bu	204–205	EtOH–EtOAc	$C_{14}H_{23}NO_2 \cdot 0.5C_2H_2O_4$	A, D	5	55
57	3-Me	H	$CH(Me)C_7H_{15}$-*n*	110–120	EtOAc	$C_{19}H_{33}NO_2 \cdot HCl$	C	20	44
58	3-Me	H	CMe_2CH_2OH	86–87	EtOH–H_2O	$C_{14}H_{23}NO_3 \cdot 0.5C_2H_2O_4$	A	5	48
59	3-Me	H	$CH(Me)(CH_2)_2C_6H_5$	148–154	EtOH–EtOAc	$C_{20}H_{27}NO_2 \cdot HCl$	B	25	81
60	2-Et	H	*n*-Pr	77–79	Petr ether (60–80°)	$C_{14}H_{23}NO_2$	B	10	63
61	2-Et	H	*t*-Bu	174–176	*i*-PrOH–H_2O	$C_{15}H_{25}NO_2 \cdot C_2H_2O_4$	B	2.5	82
62	2-Et	H	$CH_2CH{=}CH_2$	165–167	*i*-PrOH–H_2O	$C_{14}H_{21}NO_2 \cdot C_2H_2O_4$	B	40	60
63	2-Et	H	CMe_2CH_2OH	160–162 dec	*i*-PrOH	$C_{15}H_{25}NO_3 \cdot 0.5C_2H_2O_4$	B	2.5	48
64	2-Et	H	$CH(Me)(CH_2)_2C_6H_5$	105–106	*n*-BuOAc	$C_{21}H_{29}NO_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$	B	10	75
65	2-Et	H	$CH(Me)CH_2OC_6H_5$	100–101	Cyclohexane	$C_{20}H_{27}NO_3$	B	10	71
66	2-Et	H	$CH(Me)CH_2CH_2$-C_6H_4Cl-*p*	114–116	EtOAc–Et_2O	$C_{22}H_{30}ClNO_2 \cdot HCl \cdot H_2O$	B	10	48
67	2-Et	H	$CH(Me)CH_2C_6H_4$-OMe-*p*	154–156	*i*-PrOH	$C_{21}H_{19}NO_3 \cdot HCl$	B	20	47
68	3-OMe	H	*n*-Pr	146–148	EtOH–EtOAc	$C_{13}H_{21}NO_3 \cdot C_2H_2O_4$	A	10	50
69	3-OMe	CH_3	*i*-Pr	99–100	EtOH–H_2O	$C_{14}H_{23}NO_3 \cdot C_6H_3N_3O_7$	A	5	43
70	2-OEt	H	*t*-Bu	95–99	Xylene	$C_{15}H_{25}NO_3 \cdot C_2H_2O_4$	A	2.5	72
71	2-OEt	H	*n*-Pr	86–87	Petr ether (80–100°)	$C_{14}H_{23}NO_3$	A	10	60
72	2-OEt	H		87–88	Petr ether (60–80°)	$C_{16}H_{24}NO_3$	A	25	72
73	2-OEt	H	Me	91–93	Petr ether (80–100°)	$C_{12}H_{19}NO_3$	B	25	56
74	2-OEt	H	CMe_2CH_2OH	86–88	*n*-BuOAc	$C_{15}H_{25}NO_4 \cdot HCl$	B	2.5	50
75	2-$OCH_2CH{=}CH_2$	H	*t*-Bu	105–106	EtOAc	$C_{16}H_{25}NO_3 \cdot C_2H_2O_4$	B	5	67
76	2-O- 	H		186–187	EtOH	$C_{19}H_{29}NO_3 \cdot 0.5C_2H_2O_4$	A	10	47
77	3,5-Me_2	H	$CH_2CH{=}CH_2$	67–69	Petr ether (40–60°)	$C_{14}H_{21}NO_2$	B	50	38
78	3,5-Me_2	H	$CH(Me)(CH_2)_2C_6H_5$	139–142	EtOAc	$C_{21}H_{29}NO_2 \cdot HCl$	B	1	65
79	3,5-Me_2	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	113–114	EtOAc	$C_{17}H_{23}NO_2 \cdot C_2H_2O_4$	B	100	46
80	2,3-Cl_2	H	*sec*-Bu	159	EtOH–EtOAc	$C_{13}H_{19}Cl_2NO_2 \cdot HCl$	A	10	68
81	2,5-Cl_2	H	*n*-Pr	126–127	Cyclohexane	$C_{12}H_{17}Cl_2NO_2$	A	20	50
82	2,5-Cl_2			171–172	EtOH–EtOAc	$C_{14}H_{18}Cl_2NO_2 \cdot HCl$	A	20	52
83	4-Cl-3-Me	H	CMe_2CH_2OH	192	EtOH–H_2O	$C_{14}H_{22}ClNO_3 \cdot 0.5C_2H_2O_4$	A	20	40

[a] All compounds were analyzed for C, H, N.

(1.09 g, 0.005 mole), 0.84 g (0.01 mole) of cyclopentanone, 0.1 g of PtO_2, and 50 ml of EtOH were shaken under H_2 at room temperature and atmospheric pressure until the uptake of H_2 ceased. The mixture was then filtered and evaporated. The residue was stirred with 50 ml of 2 *N* HCl and 50 ml of Et_2O. The acid phase was basified with 11 *N* NaOH and extracted twice with 25 ml of Et_2O. The combined extracts were dried ($MgSO_4$) and evaporated to dryness and the residue was crystallized from petroleum ether (bp 60–80°); yield 0.3 g (23%), mp 80–81°. *Anal.* ($C_{15}H_{23}NO_2$) C, H, N.

1-(*t*-Butylamino-3-(3-methylphenoxy)-2-propanol Oxalate (56) (Method D).—A mixture of 0.54 g (0.005 mole) of *m*-cresol, 1.0 g (0.005 mole) of 1-*t*-butylamino-3-chloro-2-propanol hydrochloride,[6] 0.6 g (0.015 mole) of NaOH, 20 ml of EtOH, and 1 ml of H_2O was heated in a sealed vessel at 100° for 10 hr. The mixture was evaporated to dryness and stirred with 20 ml of 2 *N* HCl and 25 ml of Et_2O. The acid phase was basified with 11 *N* NaOH and filtered, and the solid residue was washed (H_2O) and dried. The dried product was dissolved in Et_2O and ethereal oxalic acid was added to pH 1 to give the oxalate, yield 0.15 g (10%), mp and mmp 205–206°, and ir trace identical with that of **56** prepared by method A.

3-Isopropyl-5-(3-methoxyphenoxymethyl)oxazolidine Hydrogen Oxalate (VI).—A mixture of 0.25 g of 1-isopropylamino-3-(3-methoxyphenoxy)-2-propanol (**7**), 20 ml of EtOH, and 1 ml of 40% formalin was heated under reflux for 18 hr. The mixture was evaporated under reduced pressure and the residue was dissolved in 25 ml of EtOAc and added to an excess of ethereal oxalic acid. The mixture was filtered and the solid residue was recrystallized (EtOAc); yield 0.1 g (30%), mp 98–100°. *Anal.* ($C_{14}H_{21}NO_3 \cdot C_2H_2O_4$) C, H, N.

Hydrolysis of VI.—The oxazolidine hydrogen oxalate VI (25 mg) and 2.5 ml of 2 *N* NaOH were kept at room temperature for 4 hr, and the mixture was extracted with 20 ml of Et_2O. The dried ether extract was evaporated and the residue was crystallized (cyclohexane) to give **7**, mp and mmp 72–73°.

1-Isopropylaminomethyl-2-(3-methylphenoxy)ethyl Acetate Hydrochloride (VII).—A mixture of 2.2 g of 1-isopropylamino-3-(3-methylphenoxy)-2-propanol (**1**), 10 ml of AcOH, and 2 ml of Ac_2O was kept at room temperature for 18 hr. Ice was then added and the mixture was basified (NH_4OH, sp gr 0.88) and shaken with 50 ml of Et_2O. The ethereal phase was dried ($MgSO_4$) and acidified with ethereal HCl. The mixture was filtered and the solid residue was washed with Et_2O and crystallized (Et_2O–C_6H_6); yield 0.8 g (37%), mp 130–132°, ir ester carbonyl band at 1740 cm^{-1}. *Anal.* ($C_{16}H_{25}NO_3 \cdot HCl$) C, H, N.

Hydrolysis of VII.—A solution of 0.5 g of VII in 1 ml of 2 *N* NaOH and 10 ml of MeOH was kept at room temperature for 4 hr. The mixture was evaporated to dryness and shaken with 6 ml of 1 *N* AcOH and 10 ml of Et_2O. The acid phase was basified with 2 *N* NaOH and extracted with Et_2O. The extract was dried ($MgSO_4$) and acidified with ethereal HCl to give **1a**, mp and mmp 122–124°.

1-(4-Benzyloxyphenoxy)-3-isopropylamino-2-propanol.—A mixture of 20.0 g of *p*-benzyloxyphenol, 11.6 ml of epichlorohydrin, 4.8 g of NaOH, and 100 ml of H_2O was stirred at room temperature for 18 hr. The mixture was extracted twice with 50 ml of $CHCl_3$. The combined dried ($MgSO_4$) extracts were evaporated and the residue was refluxed for 2 hr with 50 ml of *i*-$PrNH_2$. The mixture was then evaporated to dryness, stirred with 100 ml of 2 *N* HCl, and washed twice with 50 ml of Et_2O. The acid phase was basified with 11 *N* NaOH and the mixture was filtered. The solid residue was washed with H_2O, dried, and recrystallized (cyclohexane); yield 9.0 g (29%), mp 100–101°. *Anal.* ($C_{19}H_{25}NO_3$) H, N; C: calcd, 72.4; found 71.9.

1-(4-Hydroxyphenoxy)-3-isopropylamino-2-propanol Hydrochloride (22) (Method E).—A mixture of 3.0 g of 1-(4-benzyloxyphenoxy)-3-isopropylamino-2-propanol, 0.1 g of 5% Pd–C, 40 ml of EtOH, and 1 ml of concentrated HCl was shaken under H_2 at room temperature and atmospheric pressure until the uptake of H_2 ceased. The mixture was then filtered and evaporated. The residue was crystallized (EtOH–EtOAc); mp 167–168°.

β-Adrenergic Blocking Agents. VI. Pronethalol and Propranolol Analogs with Alkyl Substituents in the Alkanol Side Chain

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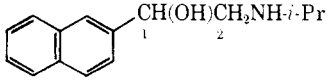
Analogs of pronethalol (**20**) and propranolol (**21**) with substituents in the aminoalkanol side chain have been synthesized. Adrenergic β-receptor blocking potency was generally reduced by substituting in the side chain. The *erythro* isomer of 2-isopropylamino-1-(2-naphthyl)-1-propanol was three times more potent than the *threo* isomer. Ethyl 2-amino-3-(ethoxycarbonylmethylamino)-3-(2-naphthyl)propionate (**27**) and 3-ethoxycarbonyl-2-(2-naphthyl)piperazin-5-one (**28**), obtained as by-products, were formed by self-condensation of the azomethine derived from 2-naphthaldehyde and glycine ethyl ester.

In the course of our synthetic program[1] on β-adrenergic blocking agents the analogs of pronethalol[2] (**20**) and



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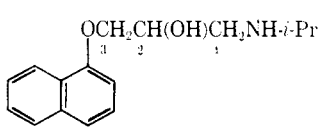

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propranolol[3] (**21**) described in Table I have been prepared. The pronethalol analogs have methyl, ethyl, or ethoxycarbonyl substituents in the aminoethanol side chain, and the propranolol analogs have methyl substituents in the aminohydroxypropoxy side chain.

When a methyl group is substituted on C-2 of the pronethalol side chain, *erythro* and *threo* forms of the compound are possible, corresponding in stereochemistry with ephedrine and ψ-ephedrine, respectively. The *erythro* form **3** was prepared by catalytic reductive alkylation[1a] of 2-(2-hydroxyiminopropionyl)naphthalene[4] (**22**), a method which in the norephedrine series gave predominantly the *erythro* form.[5] The *threo* isomer **5** was prepared from the bromohydrin **23** and

(1) (a) Part I: R. Howe, A. F. Crowther, J. S. Stephenson, B. S. Rao, and L. H. Smith, *J. Med. Chem.*, **11**, 1000 (1968); (b) part II: A. F. Crowther and L. H. Smith, *ibid.*, **11**, 1009 (1968); (c) part III: R. Howe and B. S. Rao, *ibid.*, **11**, 1118 (1968); (d) part IV: R. Howe, B. J. McLoughlin, B. S. Rao, L. H. Smith, and M. S. Chodnekar, *ibid.*, **12**, 452 (1969); (e) part V: A. F. Crowther, D. J. Gilman, B. J. McLoughlin, L. H. Smith, R. W. Turner, and T. M. Wood, *ibid.*, **12**, 638 (1969).

(2) Alderlin®.

(3) Inderal®.

(4) W. H. Hartung, J. C. Munch, and F. S. Crossley, *J. Am. Chem. Soc.*, **57**, 1091 (1935).

(5) W. H. Hartung and J. C. Munch, *ibid.*, **51**, 2264 (1929).