β-Adrenergic Blocking Agents. VIII. Reactions of β-Haloalkylamines Related to Pronethalol and Propranolol

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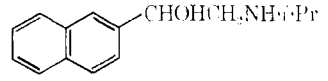
Some β-haloalkylamines related to pronethalol (**33**) and propranolol (**35**) have been prepared. Those of the pronethalol series are hydrolyzed *in vitro* and *in vivo* to the corresponding β-hydroxyalkylamines, and are β-adrenergic blocking agents. The β-chloroalkylamine **29** related to propranolol (**35**) is not a β-adrenergic blocking agent. It is hydrolyzed with difficulty *in vitro* to give mainly the position isomer **25** of propranolol which is not a β-adrenergic blocking agent. Pronethalol analogs having SH, NH_2, NHMe, and OMe in place of the OH group are much less potent as β-adrenergic blocking agents. Replacement of the ethereal O atom of propranolol by CH_2 markedly reduces blocking potency. A compound reported to be the β-chloroalkylamine related to epinephrine has been shown to be the cyclic sulfite ester of the reported compound.

The β-chloroethylamine **1**[1] (Table I) related to 2-isopropylamino-1-(2-naphthyl)ethanol (pronethalol)[2] (**33**) was originally prepared as a possible means for providing a slow release of pronethalol *in vivo*. It was known[3] that such β-aryl-β-chloroethylamines could be hydrolyzed *in vitro* to the parent ethanolamine and it



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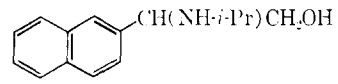

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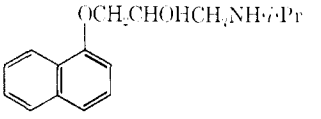
was surmised that the same might happen *in vivo*. The β-chloroethylamine **1** proved to be as potent as pronethalol as a β-adrenergic blocking agent. The onset of β-receptor blockade was rapid and the compound did not show significantly prolonged activity. The observed biological activity of **1** was presumed to be due to hydrolysis *in vivo* to pronethalol *via* the aziridinium cation of **18** and hydrolysis must be rapid because of the speed of onset of β-receptor blockade. This explanation was supported by the fact that, whereas the position isomer **34**[2b] of pronethalol was virtually inactive as a β-receptor blocking agent, the β-chloroethylamine **19** related to it was as active as pronethalol. Hydrolysis *in vivo* to pronethalol *via* the common aziridinium cation of **18** could explain the observed biological activity of **19**. Somewhat surprisingly, at the time of testing, the β-chloropropylamine **29** related to 1-isopropylamino-3-(1-naphthoxy)-2-propanol (propranolol[4]) (**35**) was devoid of β-receptor blocking activity, which suggested that it was not hydrolyzed to propranolol *in vivo*. It may however have been hydrolyzed *in vivo* to the position isomer **25** of propranolol, which is not a β-receptor blocking agent. These interpretations were substantiated by a study of the hydrolysis of **1**, **19**, and **29**.



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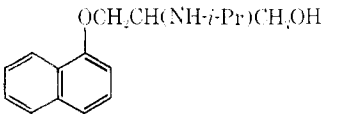

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The biological implications of the above results, particularly with reference to the carcinogenicity of pronethalol but not of propranolol in mice, have already been discussed.[1a,5] This paper reports the preparation of β-aryl-β-haloalkylamines related to pronethalol and propranolol, discusses some of their reactions, and describes their use as intermediates for the preparation of potential β-adrenergic receptor blocking agents. Experimental details are given for those hydrolytic experiments described previously[1a] which led to new compounds.

Most of the β-haloalkylamines listed in Table I were prepared by the action of $SOCl_2$ in $CHCl_3$ on the appropriate β-hydroxyalkylamine (method A). This method failed when applied to the primary alcohol **34** for which neat $SOCl_2$ was necessary to produce **19** (method B). The best method (C) for converting propranolol (**35**) into the related chloro compound **29** was the use of PCl_5 in $CHCl_3$. The 1,3,2-oxazaphospholidine **23**, recognized as a by-product in the last reaction, was more easily obtained by the action of $POCl_3$ and Et_3N[6] on propranolol, as exemplified for **17**.

Compound **1** was obtained unexpectedly from a reaction planned to give the HCl salt of the *O*-benzoyl derivative **36** of pronethalol. The conditions, BzCl at 115° for 4 hr, were slightly more vigorous than those applied to 2-amino-1-(2-naphthyl)ethanol by Immediata and Day.[7] **36**·HCl could be converted into the base by careful treatment with alkali. Immediata and Day were unable to obtain bases from salts of related primary and secondary amines. A sample of **36** base, examined after several years, consisted of the corresponding *N*-benzoyl analog **37** formed by O → N

(1) (a) R. Howe, *Nature*, **207**, 594 (1965); (b) R. Howe, British Patent Specification 1,005,021 (1965).

(2) (a) ALDERLIN Trademark; (b) Part I: R. Howe, A. F. Crowther, J. S. Stephenson, B. S. Rao, and L. H. Smith, *J. Med. Chem.*, **11**, 1000 (1968).

(3) F. Wolfheim, *Ber.*, **47**, 1451 (1914).

(4) (a) INDERAL,(R); (b) Part II: A. F. Crowther and L. H. Smith, *J. Med. Chem.*, **11**, 1009 (1968).

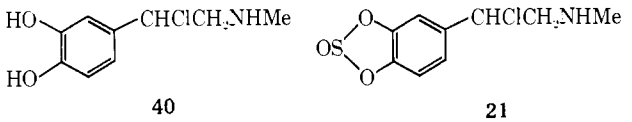
(5) P. A. Bond and R. Howe, *Biochem. Pharmacol.*, **16**, 1261 (1967).

(6) A. Larizza and G. Brancaccio, U. S. Patent 3,193,572 (1965).

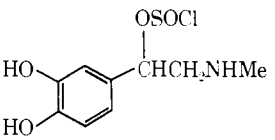
(7) T. Immediata and A. R. Day, *J. Org. Chem.*, **5**, 512 (1940).

benzoyl migration. Authentic **37** was prepared (a) by forming the *O,N*-dibenzoyl derivative **38** of pronethalol and then selectively hydrolyzing the ester and (b) by benzoylating isopropylaminomethyl 2-naphthyl ketone and then reducing the product **39** with $NaBH_4$. Authentic **36**·HCl was prepared from **37** by HCl catalyzed N→O benzoyl migration.

The β-chloroethylamine **40** related to epinephrine was reported to be an unstable solid by Hukki and Seppalainen,[8] and by Heacock, *et al.*[9] We have repeated



40 21



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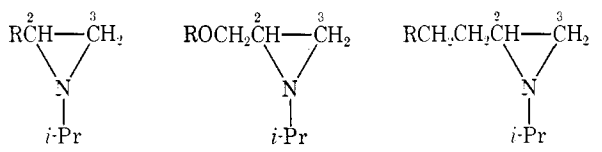
their work and shown that the solid obtained is the cyclic sulfite **21** of **40**; the chlorosulfite **41** is excluded by mass spec, *m/e* 247. The cyclic sulfite **21** is hygroscopic and unstable, even in a desiccator, but gives the correct elemental analysis for a few hours after preparation. When **21** was heated with EtOH the ethyl ether **22** of epinephrine was obtained.

The aziridine **18** related to pronethalol was obtained by treating **1**·HCl with 5% $NaHCO_3$ to give **1** free base, which on standing dismutated to a readily separable equimolecular mixture of **1**·HCl and the aziridine **18**. The more stable aziridine **24** was obtained by the action of NaOH on **29**. Whereas the aziridine **18** related to pronethalol readily gave pure pronethalol, and no trace of the position isomer **34**, when hydrolyzed at 100° with **1**.1 equiv of 0.1 *N* H_2SO_4 for 15 min, the aziridine **24** related to propranolol was relatively resistant to these conditions.[1a] With 20% H_2SO_4 at 100° for 1 hr, the position isomer **25** of propranolol was obtained in 11% yield. Its structure was confirmed by nmr; the nmr spectrum of propranolol is included for comparison.

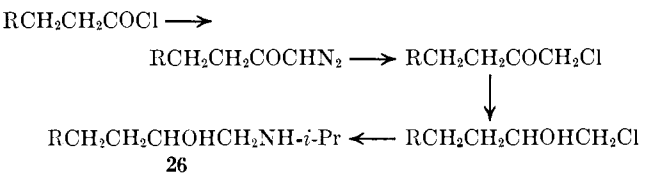
The difference in the ease of hydrolysis and in the type of product formed from the aziridines **18** and **24** is no doubt largely due to the fact that C-2 in **18** is benzylic and is better able to support the partial positive charge which must be developed in the course of the reaction than is C-2 in **24**. The effect of the O atom



18 24 28

R = 1-naphthyl

in **24** will be to make C-2 less able than C-3 to support a partial positive charge and thus favor the formation of **25**. To determine more precisely the effect of the O atom in **24** the analog **28** which has CH_2 in place of O was prepared. The intermediate propranolol analog **26** was made by the route:



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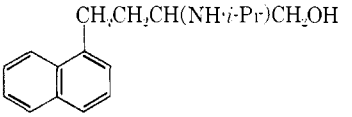
R = 1-naphthyl

The properties of aziridine **28** closely resembled those of **24**. Compound **28** was relatively resistant to **1**.1 equiv of 0.1 *N* H_2SO_4 at 100° for 15 min. Duplicate hydrolyses of **24** and **28** with 20% H_2SO_4 were carried out. As much as 68% of **24** was recovered, and ~6.5% of **25** and ~2% of propranolol (**35**) were obtained after repeated preparative tlc. Compound **28** (75%) was recovered, and **26** (~7%) and the position isomer **42** of **26** (~7%) were obtained. These amounts support the idea that the benzylic nature of C-2 in **18** is mainly responsible for the differing reactivities of **18** and **24**, and agree with what would be expected on replacement of the ethereal O of **24** by CH_2.



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The β-chloroalkylamines **27** and **29** behaved similarly with Ac_2O and $NaHCO_3$, and gave the *O*-acetates **43** and **44** of the corresponding secondary alcohols **26** and **35**. By contrast **1** gave the secondary alcohol **33** and its *N*-Ac derivative **45**. An authentic sample of the *N*-Ac derivative **45** was prepared by acetylation of pronethalol with AcCl in C_5H_5N.

The thiol analog **13** of pronethalol was prepared conventionally from the chloro analog **1** *via* the thiouronium compound **12**. More vigorous conditions were required to produce **31** and thence **32**, which by nmr was found to consist of about a 1:1 mixture of the compound shown and its position isomer of type **25**. The amino (**14**), methylamino (**15**), and methoxy (**16**) analogs of pronethalol were obtained by heating **1** with NH_3, $MeNH_2$, and MeOH, respectively.

Biological Results.—The results of the biological screening tests[10] are given in Table I. β-Adrenergic blocking potency was determined in the usual way.[2b]

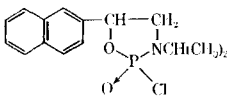
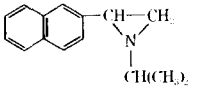
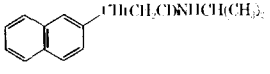
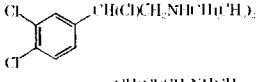
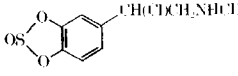
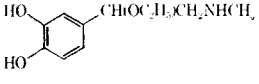
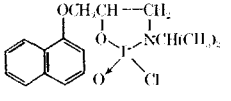
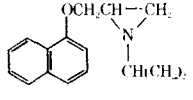
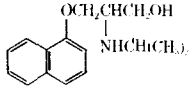
The potencies of the β-haloethylamines **1** to **9** and the phosphate esters **10** and **11** were similar to those of the corresponding β-hydroxyethylamines related to pronethalol, as would be expected if hydrolysis of **1** to **11** occurred *in vivo*.[1a] Compound **5**, which has two asymmetric centers, may belong to a different stereoisomeric series from the hydroxyethylamine analog **8** in Table I of part I.[2b] A single chloro analog **8** (this paper) was obtained from both diastereoisomers 51A and 51B (in part I)[2b] of the corresponding hydroxy compound. The oxazaphospholidine **17** was more potent than expected from a comparison with pronethalol (45% inhibition at 50 μg/kg per min) and with **23** and

(8) J. Hukki and N. Seppalainen, *Acta Chem. Scand.*, **12**, 1231 (1958).

(9) R. A. Heacock, O. Hutzinger, and B. D. Scott, *Can. J. Chem.*, **43**, 2437 (1965).

(10) Biological testing was carried out by Dr. J. W. Black and Mr. D. Dunlop. For further information see J. W. Black, W. A. M. Duncan, and R. G. Shanks, *Brit. J. Pharmacol.*, **25**, 577 (1965).

TABLE I

Compound	R	X	Method[a]	Form	Cryst solvent[b]	Mp °C	Formula	Analyses	Infusion rate μg/kg per min	% change in heart rate	% inhibition of tachycardia
					β-Naphthyl-CH(X)CH_2HNR						
1	$CH(CH_3)_2$	Cl	A, C[c]	HCl	MeOH–EtOAc	185	$C_{15}H_{19}Cl_2N$	C, H, Cl, N	50	+12	66
2	$CH(CH_3)_2$	Br	C[d]	HBr	MeOH–EtOAc	165–166	$C_{15}H_{19}Br_2N$	C, H, N	200	0	89
3	$(CH_2)_3CH_3$	Cl	A	HCl	MeOH–EtOAc	189–190	$C_{16}H_{21}Cl_2N$	C, H, Cl, N	100	−2	31
4	$CH_2CH(CH_3)_2$	Cl	A	HCl	MeOH–EtOAc	179–180	$C_{16}H_{21}Cl_2N$	C, H, Cl, N	100	+5	27
5	$CH_2(CH_2)CH_2CH_3$	Cl	A[e]	HCl	MeOH–EtOAc	175–176	$C_{16}H_{21}Cl_2N$	C, H, Cl, N	50	0	29
6	$CH(CH_2CH_3)_2$	Cl	A	HCl	MeOH–EtOAc	136–137	$C_{17}H_{23}Cl_2N$	C, H, N	200	−5	31
7		Cl	A	HCl	MeOH–EtOAc	189–190	$C_{17}H_{23}Cl_2N$	C, H, Cl, N	250	−6	75
8	$CH(CH_3)CH_2C_6H_5$	Cl	A[e]	HCl	MeOH–EtOAc	163–164	$C_{22}H_{25}Cl_2N$	C, H, Cl, N	50	+8	40
9	$C(CH_3)_2CH_2Cl$	Cl	B	HCl	MeOH–EtOAc	170–171	$C_{16}H_{18}Cl_3N$	C, H, N, Cl[f]	100	−1	56
10[g]	$CH(CH_3)_2$	$OP(O)(OH)OCH_3$	*h*	HCl	MeOH–EtOAc	155–157	$C_{16}H_{20}ClNO_4P$	C, H, P, Cl[f]	50	+1	39
11[g]	$CH(CH_3)_2$	$OP(O)(OH)_2$	*h*	Hydrate	H_2O	160–162	$C_{15}H_{20}NO_4P \cdot H_2O$	C, H, N	50	−8	18
12	$CH(CH_3)_2$	$SC(=NH)NH_2$	*h*	2HCl	MeOH–EtOAc	219–220	$C_{16}H_{20}Cl_2N_2S$	C, H, Cl, N[f]	400	+7	17
13	$CH(CH_3)_2$	SH	*h*	HCl	MeOH–EtOAc	223–225	$C_{15}H_{19}ClNS$	C, H, Cl, N, S	200	0	12
14	$CH(CH_3)_2$	NH_2	*h*	2HCl	MeOH–EtOAc	264–265	$C_{15}H_{20}Cl_2N_2$	C, H, Cl, N	100	0	12
15	$CH(CH_3)_2$	$NHCH_3$	As 14	2HCl	MeOH–EtOAc	238–239	$C_{16}H_{22}Cl_2N_2$	C, H, Cl, N	100	−8	20
16	$CH(CH_3)_2$	OCH_3	*h*	HCl	MeOH–EtOAc	189–190	$C_{16}H_{22}ClNO$	C, H, Cl, N	400	+7	33
17			*h*		P(60)	135–136	$C_{15}H_{17}ClNO_2P$	C, H, Cl, N, P[f]	20	+15	60
18			*h*	Picrate Base	Not crystallized	135 Oil	$C_{29}H_{32}N_4O_7$ $C_{15}H_{17}N$	C, H, N C, H, N	10 mg/kg i.d.[i]	+16	38
19			B	HCl	MeOH–EtOAc	194–195	$C_{24}H_{34}Cl_2N$	C, H, Cl, N	50	+4	16
20			A[e]	HCl	MeOH–EtOAc	189–190	$C_{16}H_{16}Cl_4N$	C, H, Cl, N	100	−1	29
21			*h*	HCl	Not crystallized		$C_{14}H_{14}Cl_2NO_2S$	C, H, Cl, N, S			
22			*h*	HCl	MeOH–EtOAc	162	$C_{14}H_{17}ClNO_3$	C, H, Cl, N			
23			As 17		P(60)	118–120	$C_{24}H_{29}ClNO_3P$	C, H, Cl, N, P	20	−2	68
24				Picrate Base	DMF–EtOH	195–196 Oil	$C_{29}H_{32}N_4O_7$ $C_{16}H_{19}NO$	C, H, N C, H, N	10 mg/kg i.d.[i]	Nil	Nil
25				HCl Base	MeOH–EtOAc Petol	181 62–63	$C_{16}H_{22}ClNO_2$ $C_{16}H_{21}NO_2$	C, H, Cl, N C, H	5 100	−1 −5	Nil 5

26[n]		*h*	HCl	MeOH–EtOAc	181–183	$C_{21}H_{24}ClNO$	C, H, N	100		−15	14
27		*C*	HCl	MeOH–EtOAc	182–183	$C_{17}H_{23}Cl_2N$	C, H, N	100		−6	Nil
28		As 24	Picrate	EtOH	145–146	$C_{23}H_{26}N_4O_7$	C, H, N				
				α-Naphthyl-$OCH_2CH(X)CH_2NHCH(CH_3)_2$							
29	Cl	*C*	HCl	MeOH–EtOAc	175–176	$C_{17}H_{24}Cl_2NO$	H, Cl, N, C[o]	50–200		−10	Nil
30[p]	$OP(O)(OH)_2$	*h*	Hydrate	H_2O	185–186	$C_{16}H_{22}NO_5P \cdot H_2O$	C, H, N, P[p]	5		−4	36
31[q]	$SC(=NH)NH_2$	As 12[r]	2HCl	MeOH–EtOAc	230–231	$C_{17}H_{25}Cl_2N_3OS$	C, H, Cl, N, S	25		+5	36
32[q]	SH	As 13	HCl	MeOH–EtOAc	175–176	$C_{16}H_{22}ClNOS$	C, H, N, S, Cl[s]	100		−2	24

[a] Methods refer to Experimental Section. [b] P(40) and P(60) refer to petroleum ether bp 40–60° and bp 60–80°. [c] See also Experimental Section. [d] PBr_3 used in place of PCl_3. [e] Compound **8** was obtained from both racemic diastereoisomers of the parent alcohol (**51A** and **51B** in ref 2b). Only one racemic diastereoisomer of the alcohol from which **5** was prepared is known (**8** in ref 2b); **5** may belong to a different stereoisomeric series from the parent alcohol. [f] Cl: calcd, 32.0; found, 31.5. [g] Kindly prepared by Mr. P. J. Taylor. [h] See Experimental Section. [i] Cl: calcd, 9.9; found, 9.4. [j] N: calcd, 11.7; found, 11.2. [k] P: calcd, 10.0; found, 10.5. [l] Free base dosed intraduodenally. [m] Starting material reported by C. E. Powell and I. H. Slater, *J. Pharmacol. Exp. Ther.*, **122**, 480 (1958). [n] Preparative details kindly supplied by Mr. L. H. Smith. [o] C: calcd, 61.1; found, 60.5. [p] P: calcd, 8.7; found, 8.1. [q] **32** was shown by nmr to be a mixture (~1:1) of the compound of structure shown and its position isomer of type **25**. By implication **31** is also a mixture. [r] Solvent *i*-PrOH. Reflux time 3 days. [s] Cl: calcd, 11.4; found, 10.8.

propranolol (57% inhibition at 2.5 μg/kg per min); perhaps it is transported or distributed more effectively than pronethalol before hydrolysis. Compounds **29** and **24** are probably not active because they are not hydrolyzed to propranolol *in vivo*, an explanation for which chemical support is given here. The activity of the P compounds **23** and **30** suggests that there is some hydrolysis to propranolol *in vivo* by a mechanism which does not involve an intermediate aziridinium cation.

Replacement of the OH group of pronethalol by $SC(=NH)NH_2$ (**12**), SH (**13**), NH_2 (**14**), NHMe (**15**), and OMe (**16**) and that of propranolol by $SC(=NH)NH_2$ (**31**) and SH (**32**) groups reduced potency markedly, underlining further[11] the contribution of the OH group toward the affinity of the compounds for β-receptors. Replacement of the side chain OH group of epinephrine by NH_2 reduced the pressor activity to 0.1[12] and the hypoglycemic activity to 0.05[13] that of epinephrine.

Replacement of the ethereal O of propranolol by CH_2 (**26**) reduced potency most markedly to <0.01 that of propranolol. This profound effect suggests that the ethereal O is directly involved in binding to the receptor by means of its unshared electrons; a contribution to binding may also arise from the inductive effect of the O atom.

The carcinogenicity of **1** in mice has previously been reported.[1a] More recently my colleagues Tucker[14] and Leonard[15] have shown that it is a potent carcinogen in rats and mice, producing thymic lymphosarcomas in mice and multiple tumors, chiefly leukemias and mammary carcinomas, in rats. The fact that this compound produces several different types of leukemia which can be readily transplanted into newborn rats makes it a valuable experimental tool. The leukemogenic properties appear to be due to a direct chemical effect on the white cell precursors.

Experimental Section[16]

Experimental methods A, B, and C are representative for the compounds in Table I. Melting points and solvents given in Table I are not repeated here. Petroleum ether had bp 60–80° unless specified. Nmr spectra were obtained on base in $CDCl_3$.

A. ***N*-[2-Chloro-2-(2-naphthyl)ethyl]isopropylamine·HCl (1).**—Compound **33** (6 g, 0.026 mol), $SOCl_2$ (4.8 g, 0.04 mol), and $CHCl_3$ (120 ml) were heated under reflux for 1 hr and then the $CHCl_3$ and excess $SOCl_2$ were evaporated. The residue was crystallized to give **1** (5.8 g, 78%).

B. ***N*-[2-Chloro-1-(2-naphthyl)ethyl]isopropylamine·HCl (19).**—Compound **34** (0.5 g) and $SOCl_2$ (5 ml) were heated under reflux for 16 hr and then excess $SOCl_2$ was evaporated. The residue was crystallized to give **19** (0.31 g, 50%).

C. ***N*-[2-Chloro-3-(1-naphthoxy)propyl]isopropylamine·HCl (29).**—Compound **35** (89 g, 0.34 mol), PCl_5 (63.4 g, 0.3 mol), and $CHCl_3$ (350 ml) were heated under reflux for 20 hr and then evaporated to dryness. The residual gum was crystallized to give **29** (66.0 g, 61%).

2-Chloro-5-(2-naphthyl)-3-isopropyl(1,3,2-oxazaphospholidine) 2-Oxide (17).—$POCl_3$ (5 ml) in C_6H_6 (25 ml) was added slowly to a stirred solution of **33** (11.45 g) and Et_3N (15 ml) in C_6H_6 (150 ml) at below 50°. The mixture was stirred at room tem-

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perature for 4.5 hr and then filtered to remove $Et_3N \cdot HCl$. The filtrate was evaporated *in vacuo* to remove C_6H_6. The residual solid (12 g) was washed eight times with cold Et_2O (100 ml each time) and the Et_2O washings were discarded. The solid residue was extracted (ten times) with boiling petroleum ether (100 ml each time). The combined extracts gave **17** (4 g, 26%).

***N*-[2-Chloro-2-(2-naphthyl)ethyl]isopropylamine·HCl (1) and 2-Isopropylamino-1-(2-naphthyl)ethyl Benzoate·HCl (36).**—Compound **33** (2.25 g, 0.01 mol) and BzCl (6.3 g, 0.43 mol) were heated at 115° for 4 hr. The cold mixture was twice stirred with Et_2O (30 ml), and the supernatant was decanted each time. EtOAc (20 ml) was added to the residue and the solid **1** which separated (1.1 g) was isolated by filtration. The EtOAc filtrate gave **36**·HCl (0.7 g), mp 204° from MeOH–EtOAc. *Anal.* ($C_{22}H_{24}ClNO_2$) C, H, Cl, N.

NaOH (0.1 *N*) was added to a suspension of **36**·HCl (0.29 g) in H_2O (25 ml) and Et_2O (25 ml) until the solid had dissolved and the aqueous phase was just alkaline. The Et_2O extract gave 2-isopropylamino-1-(2-naphthyl)ethyl benzoate (**36**) as needles, mp 44° from petroleum ether (bp 40–60°), ν 1710 cm^{-1} (Nujol). *Anal.* ($C_{22}H_{23}NO_2$) C, H, N. Several years later the sample had mmp 108–109° (with **37**) and ir spectrum identical with that of **37**.

***N*-Benzoyl-2-isopropylamino-1-(2-naphthyl)ethyl Benzoate (38).**—BzCl (4.2 g, 0.03 mol) was added to a solution of **33** (3.2 g, 0.014 mol) in dry C_5H_5N (15 ml) at 0°, and after 16 hr the C_5H_5N was evaporated *in vacuo*. The residue was extracted into Et_2O and the solution was washed with HCl (1 *N*) to remove C_5H_5N. The extract gave **38**, mp 128° from EtOAc–petroleum ether, ν 1712, 1630 cm^{-1}. *Anal.* ($C_{29}H_{25}NO_3$) C, H, N.

***N*-Benzoyl-2-isopropylamino-1-(2-naphthyl)ethanol (37).**—Compound **38** (2.8 g, 0.0064 mol), NaOH (0.5 g, 0.0125 mol), MeOH (75 ml), and H_2O (5 ml) were kept at room temperature for 2.5 hr and then the MeOH was evaporated *in vacuo* at room temperature. The gum which separated was extracted into Et_2O and then separated by washing with HCl (1 *N*) into a neutral part and a basic part. The neutral part gave **37** (1 g), mp 113° from EtOAc–petroleum ether, ν 1600, 1612 cm^{-1}. *Anal.* ($C_{29}H_{25}NO_2$) C, H, N. The basic part yielded **33**, mmp 106° (0.05 g).

Conversion of 37 into 36·HCl.—Compound **37** (0.2 g) in MeOH (10 ml) previously saturated with HCl gas was kept at room temperature for 4 days and then the MeOH was evaporated. The residue of **36**·HCl had mmp 203° from MeOH–EtOAc.

***N*-Benzoylisopropylaminomethyl 2-Naphthyl Ketone (39).** BzCl (5.7 g, 0.04 mol) in C_5H_5N (25 ml) was added to a suspension of isopropylaminomethyl 2-naphthyl ketone·HBr (10 g, 0.0325 mol) in C_5H_5N (50 ml) at 0°. After 4 days the C_5H_5N was evaporated *in vacuo*. HCl (1 *N*, 50 ml) was added and the neutral organic material was isolated by Et_2O extraction to give **39**, mp 119–120° from EtOAc (3 g, 28%), ν 1695, 1624 cm^{-1}. *Anal.* ($C_{22}H_{21}NO_2$) H, N; C required 79.7, found 80.3.

Reduction of 39 to 37.—$NaBH_4$ (0.5 g, 0.013 mol) was added during 10 min to a stirred solution of **39** (1 g, 0.003 mol) in MeOH (50 ml) at 0°. After 18 hr the MeOH was evaporated *in vacuo*. The organic material was taken up in Et_2O and washed with HCl (1 *N*). The Et_2O solution gave **37**, mmp 112°.

***N*-[2-Chloro-2-(3,4-sulfinyldioxyphenyl)ethyl]methylamine·HCl (21).**—L-Epinephrine (0.5 g) was added to $SOCl_2$ (15 ml) under N_2 at 0°. After 15 min a clear solution resulted and after 16 hr a solid crust formed. The solid was isolated by filtration, quickly stirred with dry Me_2CO, and then reisolated. The Me_2CO treatment was repeated twice. The solid **21** was dried *in vacuo* at room temperature and analyzed 2 hr later, *m/e* 247. It was extremely hygroscopic and dissolved easily in H_2O at room temperature, and the solution smelled immediately of SO_2. When **21** was heated under reflux with EtOH, it gave the ethyl ether **22**.[8]

1-Isopropyl-2-(2-naphthyl)aziridine (18).—Compound **1** (5 g) was shaken with $NaHCO_3$ (5%, 120 ml) and Et_2O (100 ml). The dried Et_2O extract was evaporated to give **1** (free base) as an unstable oil. This oil, which rapidly deposited solid **1**·HCl (mmp 185–186°), was warmed with petroleum ether (bp 40–60°) to complete the dismutation. The material (1.76 g) soluble in petroleum ether was the oily aziridine: nmr τ 2.1–2.8 (multiplet, ArH, 7), 7.5–7.7 (4 lines, J = 7 and 3.5 cps, CH of aziridine, 1), 8.07 (doublet, J = 3.5 cps, >CHH of aziridine, 1), 8.35 (doublet, J = 7 cps, >CHH of aziridine, 1), 8.3–8.8 [multiplet, $CH(CH_3)_2$, 1], 8.8 [doublet, $CH(CH_3)_2$, 6]; *m/e* 211. The picrate, prepared in cold EtOAc, was not recrystallized.

1-Isopropyl-2-(1-naphthoxymethyl)aziridine (24).—Compound **29** (0.5 g) and NaOH (2 *N*, 25 ml) were heated at 100° for 4.5 hr. The oily aziridine was isolated by Et_2O extraction: nmr τ 1.6–3.4 (multiplet, ArH, 7), 5.75–6.18 (8 lines, $OCH_2CH<$, 2), 8.0–8.25 (multiplet, CH< of aziridine, 1), 8.25 (doublet, >CHH of aziridine, 1), 8.3–8.87 [multiplet, $CH(CH_3)_2$, 1], 8.6 (doublet, >CHH of aziridine, 1), 8.80 and 8.87 [doublets, $CH(CH_3)_2$, 6]; *m/e* 241.

2-Isopropylamino-3-(1-naphthoxy)-1-propanol (25).—Compound **24** (1.0 g) and H_2SO_4 (20%, 10 ml) were heated at 100° for 1 hr. The cooled solution was made alkaline and then extracted with Et_2O. The dried extract was treated with Et_2O–HCl to give **25**·HCl (135 mg, 11%): nmr τ 1.78–1.88 (multiplet, ArH at C-8, 1), 2.12–2.30 (multiplet, ArH at C-5, 1), 2.50–2.80 (multiplet, ArH at C-3, -4, -6, and -7; 4), 3.18–3.28 (multiplet, ArH at C-2; 1), 5.84–5.96 [multiplet, AB part of ABX, $OCH_2CH(OH)$, 2], 6.13–6.50 (multiplet, AB part of ABX, $HOCH_2CH<$, 2), 6.60–6.90 (multiplet, X part of 2ABX, >CHNH, 1), 6.98 [septet, $CH(CH_3)_2$, 1], 7.85 (broad singlet, NH and OH, 2), 8.86–8.92 [2 doublets, $CH(CH_3)_2$, 6]; propranolol nmr τ 1.72–1.85 (multiplet, ArH at C-8, 1), 2.20–2.40 (multiplet, ArH at C-5, 1), 2.55–2.85 (multiplet, ArH at C-3, -4, -6, and -7; 4), 3.28–3.38 (multiplet, ArH at C-2, 1), 5.77–6.10 (multiplet, OCH_2CHOH, 3), 6.70 (singlet, NH and OH, 2), 7.05–7.42 (multiplet, $CH_2NHCH<$, 3), 8.97 [doublet, $CH(CH_3)_2$, 6].

1-(3-Hydroxy-4-isopropylaminobutyl)naphthalene (26).—3-(1-Naphthyl)propionyl chloride (25 g) in Et_2O (300 ml) was treated with excess CH_2N_2 in Et_2O at 0°. After 18 hr the Et_2O and excess CH_2N_2 were evaporated. The residual oily diazomethyl 2-(1-naphthyl)ethyl ketone (ν 2105 cm^{-1}) (25 g) in Et_2O (500 ml) was saturated with HCl gas at 0°. Ice (250 g) was added and the mixture was shaken. The Et_2O solution was washed successively with H_2O (100 ml, 3 times), aqueous Na_2CO_3 (10%, 100 ml, 3 times), and H_2O (100 ml, 3 times). The Et_2O extract was evaporated to give chloromethyl 2-(1-naphthyl)ethyl ketone as an oil (ν 1730 cm^{-1}). $NaBH_4$ (12 g, 0.315 mol) was added during 1 hr to a stirred solution of this ketone (28 g, 0.12 mol) in MeOH (500 ml) at 0°. After 16 hr the MeOH was evaporated, H_2O (300 ml) was added, and the mixture was extracted with Et_2O (100 ml, 3 times). The extract gave 1-(4-chloro-3-hydroxybutyl)naphthalene as an oil. This chlorohydrin (25 g, 0.106 mol), *i*-$PrNH_2$ (80 ml, 1 mol), and EtOH (250 ml) were heated in an autoclave at 100° for 10 hr, and then the EtOH and excess *i*-$PrNH_2$ were evaporated. HCl (1 *N*, 300 ml) was added and the solid which separated was extracted into $CHCl_3$ (200 ml, 3 times). The extract gave **26**, mp 181–183°. The aqueous acid solution from the extraction was basified and then extracted with Et_2O. This extract, treated with Et_2O–HCl, gave more **26**, mp 181–185°.

Duplicate Hydrolyses of 1-Isopropyl-2-(1-naphthoxymethyl)-aziridine (24) and 1-Isopropyl-2-[2-(1-naphthyl)ethyl]aziridine (28). a.—Compound **28** (0.5 g) and H_2SO_4 (20%, 5 ml) were heated at 100° for 1 hr. The cooled solution was extracted with Et_2O. The aq solution was basified with 8 *N* NaOH and then extracted with Et_2O. The extract gave an oil (440 mg) which was separated by preparative tlc (silica gel GF, 1%, NH_4OH in EtOH) into **28** (R_f 0.83, 378 mg, 75%), **26** (R_f 0.23, 30 mg, ~7%), and 1-(4-hydroxy-3-isopropylaminobutyl)naphthalene (**42**) (R_f 0.35, 33 mg, ~7%). **42**·HCl had mp 160°, from MeOH–EtOAc: nmr τ 1.95–2.80 (multiplet, ArH, 7), 6.20–6.75 (8 lines, AB part of ABX, $>CHCH_2OH$, 2), 6.83–7.40 (multiplet, $ArCH_2$ + $>CHNHCH<$, 4), 8.83 (singlet, OH and NH, 2), 8.05–8.30 (multiplet, $CH_2CH_2CH<$, 2), 8.96 and 9.02 [2 doublets, $CH(CH_3)_2$, 6]. *Anal.* ($C_{17}H_{23}ClNO$) H, N; C, calcd, 69.5; found 69.0. For comparison, **26** nmr τ 1.85–2.80 (multiplet, ArH, 7), 6.23–6.55 (10 lines, X part of 2ABX patterns, $CH_2CHOHCH_2$, 1), 6.40–7.05 (multiplet, $ArCH_2$, 2), 7.10–7.80 (multiplet, OH + NH + $CH_2NHCH<$, 5), 8.08–8.30 (multiplet, $CH_2CH_2CH<$, 2), 8.97 [doublet, $CH(CH_3)_2$, 6].

b.—Compound **24** (0.5 g) treated as in **a** gave an oil (440 mg) which was separated into **24** (R_f 0.63, 340 mg, 68%), **25** (R_f 0.52, 35 mg, ~6.5%), and propranolol **35** (R_f 0.32, 12 mg, ~2%).

1-Isopropylaminomethyl-2-(1-naphthoxy)ethyl Acetate (43).—Compound **29**·HCl (2 g) and H_2O (20 ml) were warmed briefly to effect solution, cooled to 0°, and then treated with Ac_2O (5 g) followed by $NaHCO_3$ (10 g). After 1.5 hr the mixture was extracted with EtOAc to give **43**·HCl[35] (1.9 g, 88%), mmp 171° from MeOH–EtOAc.

1-Isopropylaminomethyl-3-(1-naphthoxy)propyl Acetate (44). Compound **27**·HCl treated as above gave **44**·HCl, mp 158–159° from MeOH–EtOAc, ν 1745 cm^{-1}. More **44**·HCl was obtained by adding Et_2O–HCl to the mother liquors from the crystallization. *Anal.* ($C_{18}H_{26}ClNO_3$) C, H, Cl, N.

***N*-Acetyl-2-isopropylamino-1-(2-naphthyl)ethanol (45).** **a.**

1·HCl (2 g) treated as above gave **33**·AcOH (0.25 g), mmp 111°, and **33** (0.6 g), mmp 106°, by fractional crystallization. The mother liquors were separated chemically to give a nonbasic part which yielded **45** (0.6 g), mmp 85° from EtOAc–petroleum ether.

b.—AcCl (1.57 g, 1 equiv) in C_5H_5N (10 ml) was added to **33** (4.58 g) in C_5H_5N (25 ml) at 0°. After 18 hr Et_2O (100 ml) was added and the solution was washed with 2 *N* HCl. The Et_2O solution gave a gum containing ester impurity (ir). MeOH (90 ml) and NaOH (10%, 5.8 ml) were added. After 2.5 hr the MeOH was evaporated *in vacuo*, Et_2O was added, and the Et_2O solution was washed with 2 *N* HCl. The Et_2O solution gave **45**, mp 86–87° from EtOAc–petroleum ether (bp 40–60°). *Anal.* ($C_{17}H_{21}NO_2$) C, H, N.

***S*-[2-Isopropylamino-1-(2-naphthyl)ethyl]isothiourea·2HCl (12).**—Compound **1** (4 g) and thiourea (1.1 g) in EtOH (150 ml) were heated under reflux for 9 hr and then the EtOH was evaporated to give **12**.

2-Isopropylamino-1-(2-naphthyl)ethanethiol (13).—Compound **12** (3.8 g), 1 *N* NaOH (65 ml), and MeOH (200 ml) were heated under reflux for 4 hr and then the MeOH was evaporated. Et_2O extraction gave **13**, converted into its HCl by Et_2O–HCl: nmr τ 2.15–2.80 (multiplet, ArH, 7), 6.25 (X part of ABX, SC**H**<, 1), 7.85–7.97 (multiplet, AB part of ABX, CH_2N, 2), 7.20–7.60 (septet, *i*-Pr C**H**, 1), 8.72 (singlet, N**H** and SH, 2), 9.08 and 9.13 [2 doublets, $CH(CH_3)_2$, 6].

***N*-[2-Methoxy-2-(2-naphthyl)ethyl]isopropylamine·HCl (16).**—Compound **1** (1.5 g) in MeOH (40 ml) was heated under reflux for 5 days and then most of the MeOH was evaporated. EtOAc was added to precipitate **16**: nmr τ 2.15–2.65 (multiplet, Ar**H**, 7), 5.45–5.60 (X part of ABX, C**H**O, 1), 6.75 (singlet, OC**H**$_3$, 3), 6.97–7.30 (multiplet, C**H**$_2$NC**H**<, 3), 7.98 (singlet, N**H**, 1), 8.93 and 8.98 [2 doublets, $CH(CH_3)_2$, 6].

2-Isopropylamino-1-(2-naphthyl)ethylamine·2HCl (14).—Compound **1** (0.5 g) and saturated EtOH–NH_3 (20 ml) were heated in a Carius tube at 130° for 6 hr and then the EtOH and NH_3 were evaporated. NaOH (1 *N*) was added, **14** was isolated by Et_2O extraction, and converted into the HCl salt by Et_2O–HCl.

2-Isopropylamino-1-(2-naphthyl)ethyl Methyl Hydrogen Phosphate Hydrochloride (10).—Compound **17** (5.0 g), MeOH (200 ml), and 0.1 *N* HCl (100 ml) were kept at room temperature for 18 hr and then freeze dried. The solid **10** was stirred with Me_2CO to remove gummy material before crystallization (2.6 g, 47%).

2-Isopropylamino-1-(2-naphthyl)ethyl Dihydrogen Phosphate (11).—Compound **10** (0.5 g) in H_2O (2 ml) was kept for 15 min and then the solid **11** which had separated was isolated by filtration.

1-Isopropylamino-3-(1-naphthoxy)-2-propyl Dihydrogen Phosphate (30).—Compound **23** (50 mg) in H_2O (30 ml) was refluxed for 5 min, filtered, and then concentrated to 1 ml. Compound **30** separated on cooling.

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A New Class of Sympathetic β-Receptor Blocking Agents. 3,4-Dihydro-3-hydroxy-1,5-benzoxazocines

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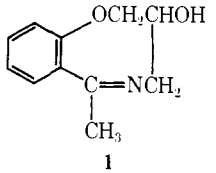
A series of 3,4-dihydro-3-hydroxy-1,5-benzoxazocines has been prepared one of which, 3,4-dihydro-3-hydroxy-6-methyl-1,5-benzoxazocine (**1**), has high sympathetic β-receptor blocking activity. The chemistry of the dihydro-1,5-benzoxazocine system is discussed.

During the last few years, many sympathetic β-receptor blocking compounds have been described containing the 2-isopropylamino-1-hydroxyethyl[1] (I) or 3-isopropylamino-2-hydroxypropyloxy[2] (II) side chain or minor

$-CHOHCH_2NHCHMe_2$ (I) $\quad -OCH_2CHOHCH_2NHCHMe_2$ (II)

variants[3] attached to an aromatic or heterocyclic nucleus. These compounds possess a number of pharmacological properties *e.g.*, β-blocking, quinidine-like, local anesthetic, and possibly hypotensive properties,[4] and we considered the possibility of synthesizing structures in which the mobility of the side chain was restricted in the hope of achieving some specificity of pharmacological action. One approach entailed linking the side chain with the aromatic nucleus to form benzoxazocines such as **1** and **23**.



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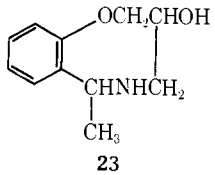

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In fact, 3,4-dihydro-3-hydroxy-6-methyl-**1**,5-benzoxazocine (**1**) was found to possess significant β-blocking properties and we report here the synthesis of this compound and 30 related analogs. Furthermore, since the 1,5-benzoxazocines represent a new heterocyclic system some of its chemical reactions are described.

Chemistry.—Most of the benzoxazocines were prepared by treatment of the appropriate *o*-acetylphenoxypropane epoxide III with NH_3 in MeOH at room temperature.

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