β-Adrenergic Blocking Agents. II. Propranolol and Related 3-Amino-1-naphthoxy-2-propanols

A. F. CROWTHER AND L. H. SMITH

Imperial Chemical Industries Ltd., Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England

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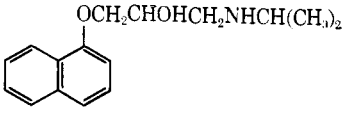
Several 1-amino-3-naphthoxy-2-propanols have been synthesized for the most part by well-established methods and tested against isoproterenol-induced tachycardia in anesthetized cats. Their β-adrenergic blocking activity proved in general to be superior to that of the 2-amino-1-(2-naphthyl)ethanols described in part I.[1] In this series, in contrast to that described in part I, those compounds in which the side chain is attached at the 1 position of the naphthalene residue were more active than those in which the 2 position was involved. Of the compounds tested 1-isopropylamino-3-(1-naphthyloxy)-2-propanol (propranolol)[2] was selected for clinical trial.

In part I work is described carried out in these laboratories on 2-isopropylamino-1-(2-naphthyl)ethanol (pronethalol)[3] and compounds related to it. This drug proved to be clinically effective as a β-adrenergic blocking agent but possessed some disadvantages. In the course of an extension of the work many compounds have been found that are effective at much lower doses than those required with pronethalol. Among these, a series of 1-amino-3-naphthoxy-2-propanols has shown promise.

We were led to consider the synthesis of this type of compound from the realization that antagonism of the effects of isoproterenol was confined to compounds with an ethanolamine residue, at least among relatives of pronethalol. One approach comprised the exploration of the effects of insertion into the pronethalol molecule of various groups between the ethanolamine and aryl residues. Results with the unbranched propanolamines (I, R = 1- or 2-naphthyl), which possessed modest activity, indicated that the carbinol residue need not be of a benzylic nature. Extension to the naphthoxypropanolamines gave a marked increase in activity.

$RCH_2CHOHCH_2NHCH(CH_3)_2$

I



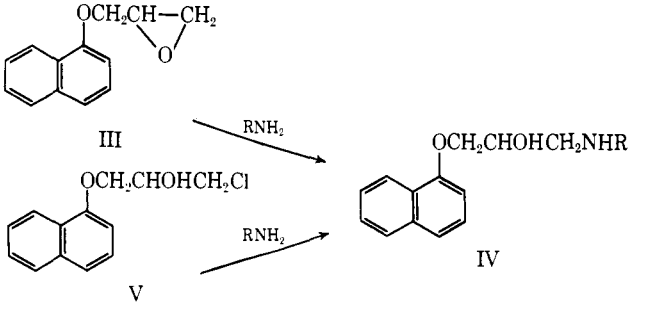
II

Thus, propranolol (II)[4] proved to be 10 to 20 times as potent as pronethalol. Surprisingly, the 2-naphthoxy isomer was considerably less active than propranolol.

Propranolol (II) has been tested clinically[5] and has been found to be effective in particular in angina pectoris, various cardiac arrhythmias, phaeochromocytoma, and hypertension. It did not produce tumors on prolonged administration to mice.

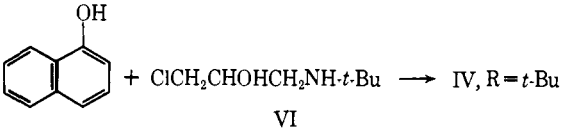
Chemistry.—The compounds were usually prepared by reaction of 1,2-epoxy-3-(1-naphthoxy)propane or 1-chloro-3-(1-naphthoxy)-2-propanol with the appropriate amine[6] (Scheme I). It is surmised that the chloro

SCHEME I



alcohol undergoes loss of HCl, by virtue of the base present, before reaction. Confirmation that the epoxide opened in the manner indicated was obtained by alternative syntheses, in the case of R = *t*-Bu, from 1-naphthol and 1-chloro-3-*t*-butylaminopropan-2-ol (VI) (Scheme II). Ir absorption and nmr spectra were

SCHEME II



in conformity with the structures expected. We have not observed the formation of any of the 2-amino-3-naphthoxy-1-propanols that would be obtained by the alternative type of epoxide ring fission. This is in contrast with our observations in the naphthylethanol amino series where the bromohydrin (VII) with isopropylamine gave a mixture of both isomers (VIII, IX) (Scheme III). These differences in behavior are in line with those between styrene oxide and 1,2-epoxy-3-phenoxypropane.[6c]

It was found convenient in some cases to prepare (*sec*-alkyl)amino compounds from the parent primary amine by reductive alkylation using a ketone, hydrogen, and platinum catalyst. Reaction of the amino

(1) Part I: R. Howe, A. F. Crowther, J. S. Stephenson, B. S. Rao, and L. H. Smith, *J. Med. Chem.*, **11**, 1000 (1968).

(2) Inderal®.

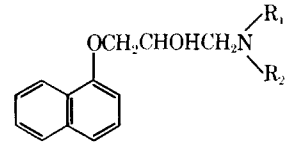
(3) (a) J. W. Black and J. S. Stephenson, *Lancet*, ii, 311 (1962); (b) J. S. Stephenson, British Patent 909,357 (1962).

(4) (a) A. F. Crowther and L. H. Smith, British Patent 994,918 (1965); (b) J. W. Black, A. F. Crowther, R. G. Shanks, L. H. Smith, and A. C. Dornhorst, *Lancet*, **1**, 1080 (1964).

(5) (a) R. Rabkin, D. P. Stables, N. W. Levin, and M. M. Suzman, *Amer. J. Cardiol.*, **18**, 370 (1966); (b) E. M. M. Besterman and D. H. Friedlander, *Postgrad. Med.*, **41**, 526 (1965); (c) E. J. Ross, B. N. C. Prichard, L. Kaufman, A. I. G. Robertson, and B. J. Harries, *Brit. Med. J.*, 191 (1967); (d) B. N. C. Prichard and P. M. S. Gillam, *ibid.*, 725 (1964).

(6) (a) V. Petrow and O. Stephenson, *J. Pharm. Pharmacol.*, **5**, 359 (1953); (b) W. Bradley, J. Forrest, and O. Stephenson, *J. Chem. Soc.*, 1589 (1951); (c) H. R. Ing and W. E. Ormerod, *J. Pharm. Pharmacol.*, **4**, 21 (1952); (d) E. R. Marle, *J. Chem. Soc.*, **101**, 305 (1912).

TABLE I: 1-AMINO-3-(1-NAPHTHOXY)-2-PROPANOLS



No.	R_1	R_2	Mp, °C	Crystn solvent	Formula[a]	Method of prepn	Dose, μg/kg/min	% inhib of isoproterenol-induced tachycardia
1	H	H				Ref 6c	100	53
2	H	CH_3	94–96	Cyclohexane	$C_{14}H_{17}NO_2$	A	20	17
3	H	C_2H_5	109–110	Cyclohexane	$C_{15}H_{19}NO_2$	A	20	83
4	H	*n*-C_3H_7	104	Cyclohexane	$C_{16}H_{21}NO_2$	A	20	57
5	H	*i*-C_3H_7	162–163	EtOH	$C_{16}H_{21}NO_2 \cdot HCl$	A	2.5	57
			96	Cyclohexane	$C_{16}H_{21}NO_2$	B, C, D		
6	H	*n*-C_4H_9	160–162	H_2O	$C_{17}H_{23}NO_2 \cdot HCl$	A	50	56
7	H	*t*-C_4H_9	230 dec	H_2O–EtOH	$(C_{17}H_{23}NO_2)_2 \cdot C_2H_2O_4$	A, B, D	2.5	65
8	H	*sec*-C_4H_9	60–61	*n*-Hexane	$C_{17}H_{23}NO_2$	A	5	54
9	H	*i*-C_4H_9	166–168	H_2O	$C_{17}H_{23}NO_2 \cdot HCl$	A	40	36
10	H	*n*-C_5H_{11}	148–149	EtOH–EtOAc	$C_{18}H_{25}NO_2 \cdot HCl$	B	20	4
11	H	$CH(CH_3)C_5H_{11}$-*n*	137–138	EtOH–EtOAc	$C_{20}H_{29}NO_2 \cdot HCl \cdot 0.5H_2O$	C	5	50
12	H	$CH(CH_3)C_7H_{15}$-*n*	116–118	EtOAc	$C_{22}H_{33}NO_2 \cdot HCl \cdot 0.5H_2O$	C	10	49
13	H	$C(CH_3)_2CH_2C(CH_3)_3$	210	EtOH–EtOAc	$C_{21}H_{31}NO_2 \cdot HCl$	A	5	0
14	H	$CH(CH_3)C_{15}H_{31}$-*n*	105–106	EtOAc	$C_{30}H_{49}NO_2 \cdot HCl \cdot 0.5H_2O$	C	100	19
15	H	$(CH_2)_2OH$	84	Hexane	$C_{15}H_{19}NO_3$	A	5	20
16	H	$C(CH_3)_2CH_2OH$	148	EtOH	$C_{17}H_{23}NO_3$	A	10	48
17	H	$CH(CH_3)CH_2OH$	115	C_6H_6	$C_{16}H_{21}NO_3$	B	10	54
18	H	$(CH_2)_3OCH_3$	148–149	*n*-PrOH	$C_{19}H_{23}NO_3 \cdot C_2H_2O_4$	B	20	37
19	H	$(CH_2)_2O(CH_2)_2OC_4H_9$-*n*	138 dec	H_2O	$C_{21}H_{31}NO_4 \cdot C_2H_2O_4$	B	100	62
20	H	$(CH_2)_2OC_3H_7$-*n*	105–107	EtOAc	$C_{18}H_{25}NO_3 \cdot HCl$	A	20	57
21	H	$CH_2CH{=}CH_2$	148	EtOH–EtOAc	$C_{16}H_{19}NO_2 \cdot HCl$	A	10	48
22	H	$CH_2C_6H_5$	169	EtOH–EtOAc	$C_{20}H_{21}NO_2 \cdot HCl$	A	20	23
23	H	$(CH_2)_2C_6H_5$	120–122	EtOH–EtOAc	$C_{21}H_{23}NO_2 \cdot HCl \cdot 0.5H_2O$	A	5	0
24	H	$CH(CH_3)CH_2C_6H_5$	186	EtOH–EtOAc	$C_{22}H_{25}NO_2 \cdot HCl \cdot 0.5H_2O$[e]	C	10	50
25	H	$CH(CH_3)(CH_2)_2C_6H_5$	162–164	MeOH–EtOAc	$C_{23}H_{27}NO_2 \cdot HCl$	A	20	53
26	H	$C(CH_3)_2(CH_2)_2C_6H_5$	210–211	$HOC_2H_4OC_2H_5$	$(C_{24}H_{29}NO_2)_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$	B	10	57
27	H	$CH_2C_6H_4OCH_3$-*p*	195–196	EtOH	$C_{21}H_{23}NO_3 \cdot HCl \cdot 0.5H_2O$	C	20	35
28	H	$CH(CH_3)(CH_2)_2C_6H_3OMe$-*p*	176–178	EtOH	$C_{24}H_{29}NO_3 \cdot HCl$	C	10	55
29	H	$(CH_2)_2C_6H_3$-3,4-$(OCH_3)_2$	209	*n*-PrOH–H_2O	$C_{23}H_{27}NO_4 \cdot C_2H_2O_4$	A	100	53
30	H	$(CH_2)_2OC_6H_3$-2,4-Cl_2	115	Petr ether (bp 100–120°)	$C_{21}H_{21}Cl_2NO_3$	B	25	40
31	H		208–209	EtOH	$C_{18}H_{23}NO_2 \cdot HCl$	C	10	47
32	H		198–200	MeOH–EtOAc	$C_{19}H_{25}NO_2 \cdot HCl$	A	50	30
33	H	$(CH_2)_3N(CH_3)_2$	234–235	MeOH	$C_{18}H_{28}N_2O_2 \cdot 2HCl$	B	200	39
34	H	$(CH_2)_3N$ 	89–91	Cyclohexane	$C_{20}H_{28}N_2O_3$	A	20	50

35	H	$N(CH_3)_2$	135	EtOH–EtOAc	$C_{15}H_{20}N_2O_2 \cdot C_2H_2O_4$[b]	A	400	46	
36	CH_3	CH_3	82–83	Petr ether (bp 60–80°)	$C_{15}H_{19}NO_2$	A	20	25	
37	C_2H_5	C_2H_5				Ref 6c	10	47	
38	CH_3	i-C_3H_7	120–122	EtOH	$C_{17}H_{23}NO_2 \cdot C_6H_3N_3O_7$	A	10	0	
39	i-C_3H_7	i-C_3H_7				Ref 6c	20	15	
40	n-C_4H_9	n-C_4H_9	163	EtOH	$C_{20}H_{31}NO_2 \cdot C_2H_2O_4 \cdot H_2O$[c]	A	10	0	
41	sec-C_4H_9	sec-C_4H_9	160–161	EtOH	$C_{21}H_{33}NO_2 \cdot C_2H_2O_4$	A	40	50	
42	C_2H_5	n-C_4H_9	100	EtOH–EtOAc	$C_{19}H_{27}NO_2 \cdot C_2H_2O_4 \cdot H_2O$	B	40	58	
43	C_2H_5	$(CH_2)_2OH$	157–158	EtOH	$C_{17}H_{23}NO_3 \cdot C_6H_3N_3O_7$	A	50	40	
44	$(CH_2)_2OH$	$(CH_2)_2OH$	161–163	EtOH	$C_{17}H_{23}NO_4 \cdot C_6H_3N_3O_7$[d]	A	10	24	
45	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	120	n-PrOH	$C_{19}H_{23}NO_2 \cdot C_2H_2O_4$	B	5	0	
46	C_2H_5	$(CH_2)_2OC_6H_5Cl$-p	149	H_2O	$C_{23}H_{26}ClNO_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$	B	40	29	
47	$CHC{=}CH$	$CH_2C_6H_5$	166–168	n-PrOH	$C_{24}H_{25}NO_2 \cdot C_6H_3N_3O_7$	B	40	41	
48	$CH_2C_6H_5$	$CH_2C_6H_5$	170–171	EtOH	$C_{27}H_{27}NO_2 \cdot HCl$	A	40	12	
49						Ref 6c	100	56	
50			95–96	EtOH–H_2O	$C_{19}H_{21}NO_2$	A	100	64	
51	H	C_6H_5	80–82	Petr ether (bp 60–80°)	$C_{19}H_{17}NO_2$	B	40	0	
52[e]	H	i-C_3H_7	138–140	EtOH	$C_{16}H_{21}NO_2$	A	50	50	

[a] C: calcd, 69.8; found, 69.2. [b] N: calcd, 8.0; found, 7.4. [c] N: calcd, 3.2; found, 3.7. [d] C: calcd, 51.7; found, 52.3. [e] (2-Naphthoxy) isomer of **5**. [f] All compounds were analyzed for C, H, N.

Scheme III

alcohol hydrochloride with acetyl chloride gave the acetate ester X. The oxazolidine (XI) was formed when the amino alcohol base was treated with formaldehyde in hot ethanol.

Structure–Activity Relationships.—Activity in the alkylamino(1-naphthoxy)propanols was maximal with alkyl groups of three to four carbon atoms branched at the α-carbon atom, *i.e.*, with isopropyl, *sec*-butyl, and *t*-butyl (**5**, **8**, **7**). There was still measurable activity in members (**11**, **12**) much higher in the series provided that the chain was branched at the α-carbon atom. Branching at the β-carbon atom, as in the isobutyl compound (**9**), was disadvantageous. With unbranched alkyl groups, activity increased from methyl to ethyl and *n*-propyl and then declined with higher members (**2**, **3**, **6**, **10**). The parent primary amine (**1**) showed some activity, unexpectedly, since it is structurally analogous to norepinephrine which has minimal cardiac β-sympathomimetic activity in anesthetized cats and it might have been expected that agonist and antagonist activity would run parallel with respect to variation of the amino moiety.

Of the (substituted-alkyl)amino compounds, hydroxy derivatives (**15**–**17**) retained a high proportion of the activity of the unsubstituted parent compounds, but alkoxy- (**18**–**20**) and dialkylaminoalkylamino (**33**, **34**) compounds appeared to be less effective. Unsaturation in, or cyclization of, the alkyl group allowed retention of activity at least among the lower members (**21**, **31**, **32**).

Whereas an arylamino group (**51**) led to total loss of activity, aralkylamino compounds (**24**–**29**), particularly those with an alkyl α substituent, were markedly active. Ring substitution of the aralkylamino group had little effect on potency.

Tertiary amines (**36**–**50**) were in general less potent than the secondary amines and those derived from cyclic bases were even less active, even when an α-methyl group (as in the 2-methylpiperidino compound, **50**) was used to simulate an isopropyl residue.

The effect of substituents in the nucleus of the 1-naphthoxy compounds was in general rather disappointing although the 4-methyl derivative (**58**) of propranolol was approximately equiactive with the parent compound. The 4-methoxy derivative (**63**) and, particularly, the 4-hydroxy derivative (**64**) were of interest, the

TABLE II: AMINO-3-(SUBSTITUTED 1-NAPHTHOXY)-2-PROPANOLS

No.	R	R_2	Mp, °C	Crystn solvent	Formula[a]	Method of prepn	Dose, $\mu g/kg/min$	% inhib of isoproterenol-induced tachycardia
53	*i*-C_3H_7	4-Cl	186–188	EtOH	$C_{16}H_{20}ClNO_2 \cdot C_2H_2O_4$	A	100	58
54	*i*-C_3H_7	2-Cl	160–161	EtOH–EtOAc	$C_{16}H_{20}ClNO_2 \cdot HCl$	B	20	41
55	*i*-C_3H_7	5-Cl	150	EtOH–EtOAc	$C_{16}H_{20}ClNO_2 \cdot C_2H_2O_4 \cdot 1.5H_2O$[b]	B	20	41
56	*i*-C_3H_7	2,4-Cl_2	194–195	*i*-PrOH–EtOAc	$C_{16}H_{19}Cl_2NO_2 \cdot HCl$	B	100	60
57	*i*-C_3H_7	5,8-Cl_2	115	Cyclohexane	$C_{16}H_{19}Cl_2NO_2$	A	5	15
58	*i*-C_3H_7	4-CH_3	90–91	Cyclohexane	$C_{17}H_{23}NO_2$	A	10	70
59	*t*-C_4H_9	4-CH_3	146	EtOAc	$C_{18}H_{25}NO_2 \cdot HCl$	A	5	73
60	*i*-C_3H_7	4-$COCH_3$	95	Petr ether	$C_{18}H_{23}NO_3$	B	40	42
61	*i*-C_3H_7	5-$SO_2N(CH_3)_2$	190–193	*n*-C_4H_9OH	$C_{18}H_{26}N_2O_4S \cdot HCl$	A	40	0
62	*i*-C_3H_7	4-$SO_2N(C_2H_5)_2$	97–99	Cyclohexane	$C_{20}H_{30}N_2O_4S$	A	40	50
63	*i*-C_3H_7	4-OCH_3	168–170	EtOH–EtOAc	$C_{17}H_{23}NO_3 \cdot HCl$	B	20	68
64	*i*-C_3H_7	4-OH	176–178	*i*-PrOH	$C_{16}H_{21}NO_3 \cdot HCl$	*d*	1	43
65	*i*-C_3H_7	4-OC_2H_5	150–152	*i*-PrOH	$C_{18}H_{25}NO_3 \cdot HCl$	B	50	67
66	*i*-C_3H_7	4-*i*-OC_3H_7	164–165	EtOAc	$C_{19}H_{27}NO_3 \cdot HCl$	B	100	50
67	*i*-C_3H_7	2-CH_3-4-OCH_3	122–124	EtOAc	$C_{18}H_{25}NO_3$	B	50	0
68	*i*-C_3H_7	2-Br-5-OCH_3	148–158	*i*-PrOH	$C_{17}H_{22}BrNO_3 \cdot C_2H_2O_4$	B	50	8
69	*n*-C_3H_7	4-OCH_3	151–153	1 *N* HCl	$C_{17}H_{23}NO_3 \cdot HCl$	B	5	45

[a] All compounds were analyzed for C, H, N. [b] H: calcd, 6.14; found, 5.66. [c] Bp 100–120°. [d] See Experimental Section.

latter because it proved to be identical with the main urinary metabolite of propranolol.[7]

Changes in the propanol chain led to some loss of activity. Esters such as X and the derived oxazolidines, *e.g.*, XI, both of which were readily hydrolyzed to the amino alcohol *in vitro* and might therefore be expected to give the parent compound *in vivo*, were usually only slightly less active than the alcohol. Extension of the side chain by one carbon unit, to give XII, led to total loss of activity.

XII

Results of biological tests are given in Tables I and II. The percentage inhibition of isoproterenol-induced tachycardia in anesthetized cats is shown at a dose, in as many cases as possible, that produced very roughly a 50% inhibition. Compounds were administered by steady intravenous infusion over 30 min.[3a]

Experimental Section[8,9]

1-Isopropylamino-3-(1-naphthoxy)-2-propanol (5) (Method A).—1-Chloro-3-(1-naphthoxy)-2-propanol[10] (4.4 g) and 20 ml of *i*-$PrNH_2$ were heated in a sealed vessel for 10 hr at 100°. The mixture was diluted with 50 ml of H_2O, acidified with concentrated HCl, and extracted with 50 ml of Et_2O. The acid phase was separated and basified with 11 *N* NaOH. The solid was collected, dried, and crystallized from cyclohexane; yield 2.9 g (77%), mp 96°.

1-*n*-Propylamino-3-(4-methoxy-1-naphthoxy)-2-propanol Hydrochloride (69) (Method B).—1,2-Epoxy-3-(4-methoxy-1-naphthoxy)propane (1.15 g) and 10 ml of *n*-$PrNH_2$ were heated under reflux for 2 hr. The mixture was evaporated to dryness and the residue was dissolved in 25 ml of hot 1 *N* HCl. The solution so formed was carbon treated, filtered, and cooled to give the hydrochloride, mp 151–153°.

Other compounds made by this method were usually isolated as their hydrochlorides formed in ethereal solution.

The 1,2-epoxy-3-(substituted 1-naphthoxy)propanes and 1-chloro-3-(substituted 1-naphthoxy)-2-propanols used as intermediates to prepare the amines in Table II were prepared according to ref 6a and 10 and, without purification, were satisfactory in quality for further reaction.

1-Cyclopentylamino-3-(1-naphthoxy)-2-propanol Hydrochloride (31) (Method C).—1-Amino-3-(1-naphthoxy)-2-propanol hydrochloride[6b] (1.25 g, 0.005 mole), 0.84 g (0.01 mole) of cyclopentanone, 40 ml of EtOH, and 0.1 g of PtO_2 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 triturated with Me_2CO and filtered and the solid residue was crystallized from EtOH, mp 208–209°.

1-*t*-Butylamino-3-(1-naphthoxy)-2-propanol Hydrochloride (7) (Method D).—A mixture of 1.4 g (0.01 mole) of α-naphthol, 2.0 g (0.01 mole) of 1-*t*-butylamino-3-chloro-2-propanol hydrochloride,[11] 1.2 g (0.03 mole) of NaOH, and 50 ml of EtOH was heated in a sealed vessel at 100° for 10 hr. The mixture was evaporated to dryness, stirred with 20 ml of 2 *N* HCl, and washed three times with 25 ml of Et_2O. The acid phase was basified with 11 *N* NaOH to precipitate a gum which was washed with H_2O and then dissolved in 25 ml of EtOAc. The dried solution ($MgSO_4$) was acidified with ethereal HCl to give the hydrochlo-

(7) P. A. Bond, *Nature*, **213**, 721 (1967).

(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) O. Stephenson, *J. Chem. Soc.*, 1571 (1954).

(11) H. G. Eggert, W. Dietrich, and H. Rato, German Patent 1,000,971 (1957).

ride; yield 0.35 g (10%), mp and mmp 176-178°. Ir trace was identical with that of 1-*t*-butylamino-3-(1-naphthoxy)-2-propanol hydrochloride, mp 178-180°. *Anal.* ($C_{17}H_{23}NO_2 \cdot HCl$) C, H, N.

1-Isoindolino-3-(1-naphthoxy)-2-propanol Hydrogen Oxalate.—A solution of 3.47 g (0.01 mole) of 1-(1-naphthoxy)-3-phthalimido-2-propanol[6c] in 50 ml of dried THF was added, dropwise, at 20-30° to a stirred mixture of 3.47 g (0.087 mole) of $LiAlH_4$ in 70 ml of dried THF. The mixture was then refluxed for 2 hr, cooled, and filtered. The filtrate was treated with H_2O, filtered, and then evaporated. The residue was dissolved in 20 ml of EtOAc and acidified with a saturated solution of oxalic acid in ether to yield the oxalate which was recrystallized (MeOH); mp 193-194°. *Anal.* ($C_{21}H_{21}NO_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

1-(4-α-Hydroxyethyl-1-naphthoxy)-3-isopropylamino-2-propanol.—A solution of 0.5 g of 1-(4-acetyl-1-naphthoxy)-3-isopropylamino-2-propanol (**60**) in 20 ml of MeOH was stirred and cooled in a salt–ice freezing mixture. $NaBH_4$ (0.3 g) was added over 15 min. The solution was stirred for 2 hr, poured onto 20 g of ice, acidified with 2 *N* HCl, and then basified with 2 *N* NaOH. The liberated base was extracted into Et_2O, the dried extract was evaporated, and the residue was crystallized (EtOAc); mp 154-156°. *Anal.* ($C_{18}H_{25}NO_3$) C, H, N.

1-(4-Hydroxy-1-naphthoxy)-3-isopropylamino-2-propanol Hydrochloride (64).—A mixture of 6.0 g of 1-isopropylamino-3-(4-methoxy-1-naphthoxy)-2-propanol hydrochloride (**63**) and 12.0 g of pyridine hydrochloride was heated with stirring, under N_2, for 2 hr at 180°. The mixture was cooled and dissolved in 60 ml of H_2O. The solution so formed was stirred, under N_2, for 1 hr with 40 ml of EtOAc, 100 ml of Et_2O, and 12.5 g of $NaHCO_3$. The mixture was filtered and the solid residue was washed with Et_2O and dissolved in 30 ml of EtOAc and 100 ml of Et_2O. The dried solution ($MgSO_4$) was acidified with ethereal HCl and the mixture was cooled and filtered. The solid residue was washed with Et_2O and recrystallized (*i*-PrOH–H_2O); yield 3.9 g (65%), mp 176-178°.

3-Isopropyl-5-(1-naphthoxymethyl)oxazolidine Hydrochloride (XI).—A mixture of 2.9 g of 1-isopropylamino-3-(1-naphthoxy)-2-propanol (**5**), 1 ml of 40% formalin, and 20 ml of EtOH was heated under reflux for 3 hr. The mixture was evaporated under reduced pressure and the residue was dissolved in 25 ml of EtOAc and acidified with ethereal HCl. The mixture was filtered and the solid residue was recrystallized (*n*-PrOH–Et_2O); yield 1.4 g (47%), mp 156°. *Anal.* ($C_{17}H_{21}NO_2 \cdot HCl$) H, N; C: calcd, 66.2; found, 65.6.

Hydrolysis of XI.—The oxazolidine hydrochloride (50 mg) was stirred with 2 *N* NaOH at 20°. After 5 min the mixture was extracted with Et_2O. The dried extract was evaporated and the residue was crystallized from petroleum ether (bp 60-80°); mp 92°; ir trace identical with that of **5**, mp 96°.

1-Isopropylaminomethyl-2-(1-naphthoxy)ethyl Acetate Hydrochloride (X).—A mixture of 5.0 g of **5**·HCl and 5 ml of AcCl was heated under reflux for 2 hr. The mixture was then evaporated to dryness and the residue was evaporated twice with 50 ml of C_6H_6 to remove traces of AcCl. The solid residue was recrystallized (*i*-PrOH); yield 3.4 g (52%), mp 170-171°. *Anal.* ($C_{18}H_{23}NO_3 \cdot HCl$) C, H, N.

Hydrolysis of X.—A solution of 0.25 g of X, 0.5 ml of 2 *N* NaOH, and 5 ml of MeOH was kept at room temperature for 4 hr. The mixture was evaporated to dryness and shaken with a mixture of 6 ml of 1 *N* AcOH and 10 ml of Et_2O. The acid phase was separated and basified with 2 *N* NaOH to give 1-isopropylamino-3-(1-naphthoxy)-2-propanol, mp and mmp 96°. The ether phase was evaporated to dryness to give an uncrystallizable oil which probably consisted mainly of 1-(N-acetyl-N-isopropylamino)-3-(1-naphthoxy)-2-propanol; the ir trace showed a very strong tertiary amide carbonyl band at 1640 cm^{-1} as well as a medium strength ester carbonyl band at 1740 cm^{-1}.

1-Isopropylamino-3-(1-naphthyl)-2-propanol Hydrogen Oxalate (I, R = 1-naphthyl).—A mixture of 5.0 g of 1-chloro-3-(1-naphthyl)-2-propanol[12] and 15 ml of *i*-$PrNH_2$ was heated in a sealed tube for 10 hr at 70-80°. The mixture was evaporated to dryness under reduced pressure and extracted with a mixture of 2 *N* HCl and Et_2O. The acid phase was separated and basified with 11 *N* NaOH solution. The liberated base was extracted into ether and the ether phase was dried ($MgSO_4$) and poured into an excess of ethereal oxalic acid. The mixture was filtered and the hydrogen oxalate was recrystallized (EtOH); yield 2.6 g (35%), mp 182° dec. *Anal.* ($C_{16}H_{21}NO \cdot C_2H_2O_4$) H, N; C: calcd, 64.9; found, 64.3.

1-Isopropylamino-3-(2-naphthyl)-2-propanol (I, R = 2-naphthyl).—The above procedure was repeated using 2.2 g of 1-chloro-3-(2-naphthyl)-2-propanol.[13] The free base was crystallized from petroleum ether (bp 40–60°); yield 1.4 g (58%), mp 64–66°. *Anal.* ($C_{16}H_{21}NO$) C, H, N.

3-(1-Naphthoxy)propionyl Choride.—A mixture of 15.0 g of 3-(1-naphthoxy)propionic acid,[14] 7.5 ml of $SOCl_2$, and 150 ml of $CHCl_3$ was heated under reflux for 45 min. The mixture was evaporated under reduced pressure and the residue was extracted twice with 60 ml of petroleum ether (bp 60–80°). The combined extracts were evaporated to dryness to give an oil. A small portion of the oil was characterized by conversion to the anilide and was recrystallized (EtOH-H_2O); mp 125°. *Anal.* ($C_{19}H_{17}NO_2$) C, H, N.

1-Bromo-4-(1-naphthoxy)-2-butanone.—An ether solution of CH_2N_2 from 17.7 g of nitrosomethylurea was dried (KOH) and then carefully stirred in a flask which had been precooled to −10°. To the ether solution there was added, dropwise, 7.0 g of 3-(1-naphthoxy)propionyl chloride, the maximum temperature during the addition being −10°. The mixture was then kept at 20° for 18 hr. It was then kept at −10° while 20 ml of 40% HBr was added dropwise with stirring over 1 hr. The ether phase was then separated, washed (H_2O), dried, and evaporated to dryness. The bromo ketone was recrystallized (cyclohexane): yield 2 g (23%), mp 74–76°; it could not be obtained analytically pure, but it was suitable for subsequent reaction.

1-Isopropylamino-4-(1-naphthoxy)-2-butanol Hydrochloride (XII).—$NaBH_4$ (0.25 g) was added with stirring to a solution of 1.45 g of 1-bromo-4-(1-naphthoxy)-2-butanone in 20 ml of MeOH at −10°. The mixture was stirred for 2 hr, poured onto ice, and extracted with Et_2O. The dried extract was evaporated to dryness and the residue was heated in a sealed tube with 15 ml of *i*-$PrNH_2$ for 10 hr at 100°. The mixture was then evaporated to dryness and the residue was extracted with 25 ml of 2 *N* HCl. The extract was basified with NaOH and extracted with Et_2O. The dried extract was acidified with ethereal HCl to give the hydrochloride which was recrystallized (EtOAc–*n*-PrOH); yield 0.25 g (17%), mp 130°. *Anal.* ($C_{17}H_{23}NO_2 \cdot HCl$) C, H, N.

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