(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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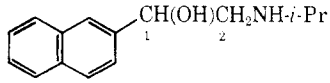
Analogs of pronethalol (**20**) and propranolol (**21**) with substituents in the aminoalkanol side chain have been synthesized. Adrenergic β-receptor blocking potency was generally reduced by substituting in the side chain. The *erythro* isomer of 2-isopropylamino-1-(2-naphthyl)-1-propanol was three 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 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.



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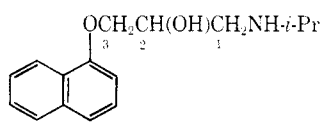

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When a methyl group is substituted on C-2 of the pronethalol side chain, *erythro* and *threo* forms of the compound are possible, corresponding in stereochemistry with ephedrine and ψ-ephedrine, respectively. The *erythro* form **3** was prepared 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).

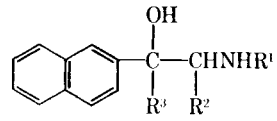
(2) Alderlin®.

(3) Inderal®.

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

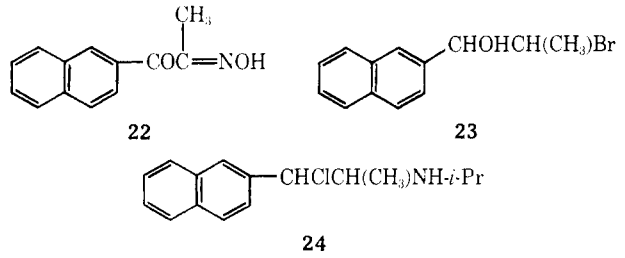
(5) W. H. Hartung and J. C. Munch, *ibid.*, **51**, 2264 (1929).

TABLE I



Compd	R¹	R²	R³	Stereochem (nmr)[a]	Method	Form	Crystn solvent[b]	Mp, °C, of amine or salt	Formula	Analyses	Infusion rate, μg/kg/min	% change in heart rate	% inhib of tachycardia
1	H	CH_3	H	*erythro* (5.40, 4.0)	As for **3**	HCl	MeOH	235[c]			200	−12	71
						Base	EtOAc	105–106	$C_{13}H_{15}NO$	C, H, N			
2	CH_3	CH_3	H	*erythro* (5.18, 4.0)	*d*	HCl	MeOH + EtOAc	243[d]			100	+1	33
						Base	P(40)	81–82	$C_{14}H_{17}NO$	C, H, N			
3	$CH(CH_3)_2$	CH_3	H	*erythro* (5.22, 4.0)	Exptl Sect	Base	EtOAc	123–124	$C_{16}H_{21}NO$	C, H, N	100	−3	30
						HCl	MeOH	240–241	$C_{16}H_{22}ClNO$	C, H, Cl, N			
4	$CH(CH_3)_2$	CH_3	H	*erythro*	As for **6**	N-Bz deriv	EtOAc	163–164	$C_{23}H_{25}NO_2$	C, H, N			
5	$CH(CH_3)_2$	CH_3	H	*threo* (5.88, 8.0)	Exptl Sect	Base	EtOAc	117–118	$C_{16}H_{21}NO$	C, H, N	100	−2	10
						HCl	MeOH + EtOAc	224–225	$C_{16}H_{22}ClNO$	C, H, Cl, N			
6	$CH(CH_3)_2$	CH_3	H	*threo*	Exptl Sect	N-Bz deriv	EtOAc	174–175	$C_{23}H_{25}NO_2$	C, H, N			
7	$C(CH_3)_3$	CH_3	H	*threo* (6.02, 8.2)	As for **5**	Base	P(40)	84–85	$C_{17}H_{23}NO$	C, H, N	100	+2	8
8	$CH(CH_3)(CH_2)_2CH_3$	CH_3	H	*erythro* (5.24, 4.0)	As for **3**	Base	EtOAc	108–109	$C_{18}H_{25}NO$	C, H, N	100	−4	Nil
											400	−30	58
9	$CH(CH_3)(CH_2)_6CH_3$	CH_3	H	*erythro* (5.24, 4.0)	Exptl Sect	HCl	MeOH + EtOAc	154–155	$C_{22}H_{34}ClNO$	C, H, N	200	−7	Nil
						Base		56–57	$C_{22}H_{33}NO$	C, H, N			
10	$C(CH_3)_2CH_2OH$	CH_3	H	*threo* (5.90, 8.2)	As for **5**	Base	EtOAc + P(40)	115–116	$C_{17}H_{23}NO_2$	C, H, N	100	−6	8
11	H	$CO_2C_2H_5$	H		Exptl Sect	HCl	MeOH + EtOAc	172–173	$C_{15}H_{18}ClNO_3$	C, H, N			
12	$CH(CH_3)_2$	$CO_2C_2H_5$	H		Exptl Sect	HCl	MeOH + EtOAc	174–175	$C_{18}H_{24}ClNO_3$	C, H, N	400	−2	23
13	$CH(CH_3)_2$	H	CH_3		Exptl Sect	HCl	MeOH + EtOAc	211–212	$C_{16}H_{22}ClNO$	C, H, Cl, N	800	+3	54
14	$CH(CH_3)_2$	H	CH_2CH_3		As for **13**	HCl	MeOH + EtOAc	226–227	$C_{17}H_{24}ClNO$	C, H, Cl, N	400	+5	17
15	$R^4OCH(CH_3)\underset{\displaystyle OH}{\underset{\vert}{C}}HCH_2NHCH(CH_3)_2$[e]				Exptl Sect	HCl	MeOH + EtOAc	158–159	$C_{17}H_{24}ClNO_2$	C, H, Cl, N	100	−24	44
16	$R^4OC(CH_3)_2\underset{\displaystyle OH}{\underset{\vert}{C}}HCH_2NHCH(CH_3)_2$[e]				Exptl Sect	HCl	MeOH + EtOAc	138–139	$C_{18}H_{26}ClNO_2$	C, H, Cl, N	25	−4	21
17	$R^4OC(CH_3)_2\underset{\displaystyle OH}{\underset{\vert}{C}}HCH_2NHC(CH_3)_3$[e]				As for **16**	HCl	MeOH + EtOAc	219	$C_{19}H_{28}ClNO_2$	C, H, Cl, N	20	0	25
18[f]	$R^4OCH_2\underset{\displaystyle OH}{\underset{\vert}{C}}(CH_3)CH_2NHCH(CH_3)_2$[e]				Exptl Sect	$(COOH)_2$	EtOH + EtOAc	179–180	$C_{19}H_{25}NO_6$	C, H, N	40	+11	46
19[g]	$R^4OCH_2\underset{\displaystyle OH}{\underset{\vert}{C}}HCH(CH_3)NHCH(CH_3)_2$[e]				As for **15**	HCl	EtOH + EtOAc	210–212	$C_{17}H_{24}ClNO$	C, H, N	50	−34	69

[a] The first figure is the τ value and the second figure is the coupling constant (cps) for the benzylic proton. [b] P(40), petroleum ether (bp 40–60°). [c] Lit.[4] mp 230–231°. [d] Lit.[10] mp 241–242°. [e] R^4 = 1-naphthyl. [f] This compound was made by Dr. B. J. McLoughlin whom I thank. [g] This compound was made by Mr. L. H. Smith whom I thank. The route was $ROCH_2CO_2H \rightarrow ROCH_2COCl \rightarrow ROCH_2COC(CH_3)N_2 \rightarrow ROCH_2COCH(CH_3)Br \rightarrow ROCH_2CHOHCH(CH_3)Br \rightarrow ROCH_2CHOHCH(CH_3)NHCH(CH_3)_2$, and the conditions were essentially those used for the preparation of **15**. Intermediates were not characterized.

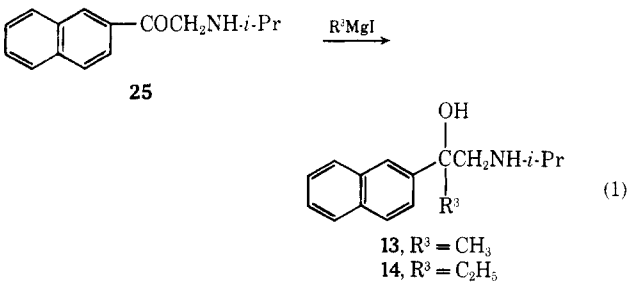


22 23 24

isopropylamine. Corrodi, *et al.*,[6] report the isolation of an *erythro* isomer when this route was used. The stereochemical assignments were confirmed by nmr, and in particular by the chemical shift and coupling constant of the benzylic proton –OC*H*–. The *erythro* isomer showed a doublet at τ 5.22 (J = 4 cps) and the *threo* isomer a doublet at τ 5.88 (J = 8.2 cps), values which correspond with those reported for ephedrine and ψ-ephedrine.[7] $SOCl_2$ converted both **3** and **5** to the hydrochloride of the chloro analog **24**. This is assigned the *threo* configuration on the basis of the coupling constant (9.0 cps) of the benzylic proton. Hydrolysis of **24** gave mainly the *threo* isomer **5**; the ratio *threo*/*erythro* was 10/1.[8] Also in agreement with the assignments, the N-benzoyl derivative **6** (of **5**) was smoothly converted in theoretical yield by ethanolic HCl to the hydrochloride of the O-benzoyl derivative of **5**. The same conditions converted the N-benzoyl derivative **4** (of **3**) in 12% yield to a 7:3 mixture of the hydrochloride of the O-benzoyl derivative of **3** and the corresponding derivative of **5**. Much **4** was recovered.[9]

Compounds **7** and **10**, prepared from the bromohydrin **23** were pure *threo* isomers by nmr. The chemical shift and coupling constant of the benzylic proton is given in Table I. Compounds **1** and **8**, prepared from **22**, were pure *erythro* isomers. Catalytic reductive alkylation of **1** with nonan-2-one proceeded without inversion of the azomethine intermediate and gave **9**. Compound **2**, an *erythro* isomer, was prepared by reduction of 1-methylaminomethyl 2-naphthyl ketone hydrochloride[10] with $NaBH_4$.

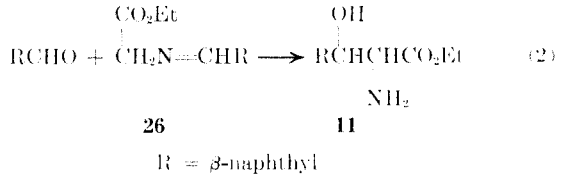
The tertiary alcohols **13** and **14** were prepared by the action of a Grignard reagent on isopropylaminomethyl 2-naphthyl ketone **25**[1a] (eq 1). The intermediate **11**



25 (1)

13, $R^3 = CH_3$
14, $R^3 = C_2H_5$

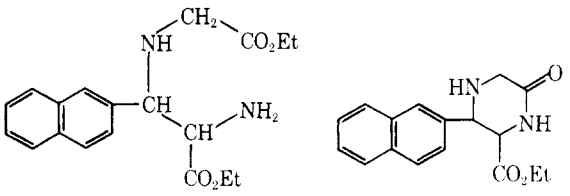
was obtained in low and uncertain yield by the route used by Erlenmeyer and by Bergmann[11] (eq 2). A



26 11 (2)

R = β-naphthyl

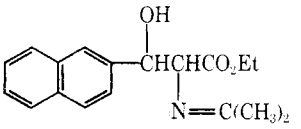
competing reaction gave the δ-amino ester **27** and the related piperazin-5-one **28**. Such products do not



27 28

appear to have been obtained by other workers. **27** could arise by the addition of hydrogen from **26** to the azomethine bond of a second molecule of **26** rather than to the carbonyl group of 2-naphthaldehyde.

Catalytic reductive alkylation of **11** gave **12** in low yield, together with 2-naphthylmethanol. Clearly part of the azomethine intermediate **29** for the alkylation underwent a reverse aldol condensation to give 2-naphthaldehyde which was then reduced.



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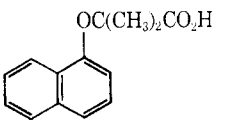
The halohydrin intermediates required for the preparation of the propranolol analogs **15**–**17** and **19** were prepared from the appropriate acid by the general route shown in eq 3. An attempt to prepare the acid



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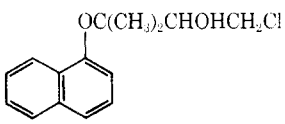
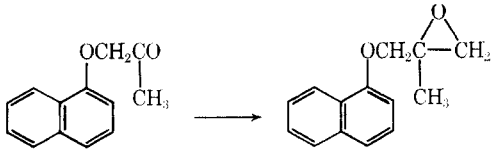
$$\text{RCOCl} \longrightarrow \text{RCOCHN}_2 \longrightarrow \text{RCOCH}_2\text{Cl} \longrightarrow$$



(3)

chloride of **30** with excess $SOCl_2$ in the absence of a solvent gave the 4-chlorosulfinyl derivative **31** (of **30**).

The tertiary alcohol **18** was prepared from the epoxide **33** obtained by the action of dimethylsulfoxonium methylide on 1-naphthoxyacetone (**32**).[12]



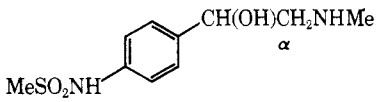
32 33

Structure–Activity Relationships.—The results of the

(6) H. Corrodi, H. Persson, A. Carlson, and J. Roberts, *J. Med. Chem.*, **6**, 751 (1963).
(7) G. G. Lyle and L. K. Keefer, *J. Org. Chem.*, **31**, 3921 (1966).
(8) H. Pfanz and H. Wieduwilt, *Arch. Pharm.*, **288**, 560 (1955).
(9) G. Fodor, V. Bruckner, J. Kiss, and G. Ohegyi, *J. Org. Chem.*, **14**, 337 (1949).
(10) A. A. Kropacheva and S. I. Sergievskaya, *Zh. Obshch. Khim.*, **21**, 2179 (1951); *Chem. Abstr.*, **46**, 8073 (1952).
(11) E. D. Bergmann, *et al.*, *J. Chem. Soc.*, 2673 (1951); 2564 (1953); 1064 (1954); 1662 (1956), and references cited therein.
(12) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

biological screening tests[13] are given in Table I. The test procedure was identical with that reported previously.[1a]

Introduction of substituents into the side chain of pronethalol and propranolol analogs generally gave compounds which were less potent than the unsubstituted analog. The reduction in potency which accompanied alkylation of the carbon atom α to the amino function, *i.e.*, C-2 in **20** and C-1 in **21**, appears to be fairly general for β-adrenergic blocking agents[6,14] and for β-adrenergic stimulants.[15,16] The *erythro* isomer **3** was about three times more potent than the *threo* isomer **5**, but only about one-third as potent as the unsubstituted analog (pronethalol[1a]). In the 2-amino-1-aryl-1-propanol series *erythro* isomers appear to be generally more potent than *threo* isomers in their action on β receptors.[14,17] The potencies of **1** and **2** were low, but were greater than might have been expected from knowledge of the potencies of the unsubstituted analogs.[1a] Uloth, *et al.*,[14] have previously noted that introduction of a methyl group in the *erythro* configuration on the α carbon atom of the N-methylamino compound **34** raised β-blocking potency.



34

Experimental Section[18]

Nmr spectra were measured in $CDCl_3$ (TMS) unless stated otherwise. Hydrogenations were carried out at room temperature and atmospheric pressure.

***erythro*-2-Isopropylamino-1-(2-naphthyl)-1-propanol (3).**—A solution of **22**[4] (6 g) in Me_2CO (20 ml) was hydrogenated in the presence of Pt (0.5 g). The mixture was filtered and the filtrate was evaporated to dryness. The residue was shaken with 1 *N* HCl (800 ml) and Et_2O (200 ml). The acidic aqueous solution was made alkaline with 8 *N* NaOH and then extracted with Et_2O. The extract gave **3** (4 g), mp 123–124°, after fractional crystallization; τ 2.15–2.75 (multiplet, Ar-H, 7), 5.22 (doublet, J = 4.0 cps, >C*H*O, 1), 6.94 [quartet of doublets, J = 6.5 and 4.0 cps, –C*H*(CH₃)–], 7.07 [septet, C*H*(CH₃)₂], 8.95 [two doublets, CH(C*H*₃)₂, 6], 9.23 [doublet, J = 6.5 cps, –CH(C*H*₃)–, 3]. **3**·HCl was prepared by adding ethereal HCl to the base in MeOH + Et_2O.

2-Bromo-1-(2-naphthyl)-1-propanol (23).—$NaBH_4$ (3.0 g) was added during 45 min with stirring to a suspension of 1-bromoethyl 2-naphthyl ketone[10] (10 g) in MeOH (200 ml) at 0–5°. After 30 min the mixture was poured into 6 *N* HBr containing ice and extracted with Et_2O. The extract gave crude **23** as a gum, which was used without further purification.

***threo*-2-Isopropylamino-1-(2-naphthyl)-1-propanol (5).**—A solution of **23** (24.3 g) and *i*-$PrNH_2$ (100 ml) in EtOH (150 ml) was heated under reflux for 48 hr and then the EtOH and the excess *i*-$PrNH_2$ were evaporated. The residue was dissolved in 1 *N* HCl and the solution was washed with Et_2O. The acidic aqueous solution was made alkaline with 8 *N* NaOH and then extracted with C_6H_6. The extract gave an oil which was dissolved in the minimum amount of hot EtOAc. Compound **5** (11.1 g) separated on cooling, mp 117–118° depressed to 102–105° by **3**; τ 2.15–2.75 (multiplet, Ar-H, 7), 5.88 (doublet, J = 8.2 cps, –OC*H*–, 1), 7.14 [septet, C*H*(CH₃)₂, 1], 7.28 [quartet of doublets, J = 6.0 and 8.2 cps, –C*H*(CH₃)–], 8.9–9.2 [three sets of doublets, CH(C*H*₃)₂ and –CH(C*H*₃)–, 9].

N-[2-Chloro-1-methyl-2-(2-naphthyl)ethyl]isopropylamine Hydrochloride (24). (**a**) A solution of **3** (0.5 g) in $SOCl_2$ (5 ml) was heated under reflux for 12 hr and then the excess $SOCl_2$ was evaporated. The residual solid was crystallized from MeOH–EtOAc and gave **24**: mp 173°; τ 2.10–2.80 (multiplet, Ar-H, 7), 4.26 (doublet, J = 9.0 cps, –ClC*H*–, 1), 6.10–6.50 [multiplet, C*H*(CH₃) and C*H*(CH₃)₂, 2], 8.33, 8.42, and 8.57 [three sets of doublets, CH(C*H*₃)₂ and –CH(C*H*₃)–, 9]. *Anal.* ($C_{16}H_{21}Cl_2N$) C, H, Cl, N.

(**b**) In the same way **5** was converted to **24**, mp and mmp 173°. *Anal.* ($C_{16}H_{21}Cl_2N$) C, H, Cl, N.

Hydrolysis of 24.—NaOH (1 *N*, 1 ml, 1 equiv) was added to a solution of **24** (0.298 g) in H_2O (20 ml). The solution was heated at 100° for 1 hr and then more 1 *N* NaOH (1 ml, 1 equiv) was added. Heating was continued for 0.5 hr and then the solution was cooled, made strongly alkaline, and extracted with Et_2O. The Et_2O extract gave a mixture of **5** and **3** (ratio 10:1 by nmr), mp 115–117°.

N-Benzoyl Derivative of 5.—KOH (5%, 50 ml) was added during 0.5 hr with shaking to a solution of **5** (0.5 g) and C_6H_5COCl (0.51 g) in Et_2O (30 ml). The Et_2O layer was washed successively with H_2O, 1 *N* HCl, and H_2O. The dried Et_2O solution gave **6**: τ 2.1–3.0 (multiplet, Ar-H, 12), 3.36 (doublet, J = 8.0 cps, O*H*, 1), 4.96 (doublet of doublets, J = 8.0 and 5.0 cps, –OC*H*–, 1), 6.2–6.6 [multiplet, C*H*(CH₃)₂ and –C*H*(CH₃)–, 2], 8.4, 9.04, and 9.83 [doublets, CH(C*H*₃)₂ and –CH(C*H*₃)–, 9].

A similar procedure gave **4**: τ 2.0–2.9 (multiplet, Ar-H, 12), 3.6 (broad singlet, O*H*, 1), 4.78 (broad singlet, –(OH)C*H*–, 1), 6.1 [septet, –C*H*(CH₃)₂, 1], 6.52 [quartet of doublets, J = 7.0 and 1.7 cps, –C*H*(CH₃)–, 1], 8.59, 8.85, and 8.95 [doublets, CH(C*H*₃)₂ and –CH(C*H*₃)–, 9].

O-Benzoyl Derivative of 5.—A solution of HCl in EtOH (5 *N*, 1 ml) was added to a solution of **6** (0.35 g) in EtOH (10 ml) at room temperature. After 3 hr the solution was evaporated and a solid residue was obtained. An nmr spectrum was determined on this solid residue. The HCl of the O-benzoyl derivative of **5** had mp 247° from MeOH–EtOAc; τ (DMSO-d_6 + D_2O) 4.02 (doublet, J = 9.0 cps, –OC*H*–, 1). *Anal.* ($C_{23}H_{26}ClNO_2$) C, H, N.

When **4** was treated in the same way, a mixture of the HCl salts of the O-benzoyl derivatives of **3** and **5** (ratio 7:3) was obtained (12% yield): mp 209–210° from MeOH–EtOAc; τ (DMSO-d_6 + D_2O) 3.55 (doublet, J = 3.0 cps, –OC*H*–, *erythro* isomer), 4.02 (doublet, J = 9.0 cps, –OC*H*–, *threo* isomer). *Anal.* ($C_{23}H_{26}ClNO_2$) C, H, N. **4** was recovered from the mother liquors of the crystallization.

2-(1-Methyloctylamino)-1-(2-naphthyl)-1-propanol (9).—A solution of **1** (base, 0.5 g) in EtOH (5 ml) and nonan-2-one (2.5 ml) was hydrogenated in the presence of Pt (0.25 g). The mixture was filtered and the filtrate was evaporated to dryness. The residue was shaken with 2 *N* HCl and Et_2O. **9**·HCl separated as a white solid at the interface.

2-Methylamino-1-(2-naphthyl)-1-propanol (2).—$NaBH_4$ (0.5 g) was added during 30 min to a stirred solution of 1-methylaminoethyl 2-naphthyl ketone hydrochloride[10] (0.92 g) in MeOH (20 ml) at 0°. After 12 hr the solution was evaporated to dryness *in vacuo*. **2**·HCl was isolated in the same way as **9**·HCl.

Ethyl 2-Amino-3-hydroxy-3-(2-naphthyl)propionate (11).—A solution of glycine ethyl ester (0.72 g), 2-naphthaldehyde (4.16 g, 3.8 equiv), and piperidine (0.1 ml) in EtOH (10 ml) was heated at 70° for 2 hr and then kept at room temperature overnight. The EtOH was evaporated *in vacuo* and then a slight excess of HCl in MeOH was added, followed by excess Et_2O. The solid which separated was fractionally crystallized from MeOH–EtOAc to give **11**·HCl (0.3 g, 15%).

Ethyl 2-Amino-3-(ethoxycarbonylmethylamino)-3-(2-naphthyl)-propionate (27) and 3-Ethoxycarbonyl-2-(2-naphthyl)piperazin-5-one (28).—A solution of glycine ethyl ester (1.44 g) and 2-naphthaldehyde (8.3 g, 3.8 equiv) in EtOH (20 ml) was heated at 70° for 2 hr and then kept at room temperature overnight. The EtOH was evaporated *in vacuo* and then a slight excess of HCl in MeOH was added, followed by excess Et_2O. The solid which separated was fractionally crystallized from MeOH–EtOAc to give **11**·HCl, mp 172–173° (0.02 g); **27**·2HCl: mp 154–156°

(13) Biological testing was carried out by Drs. J. W. Black and R. G. Shanks 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).

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(0.38 g); τ (DMSO-d_6) 1.0–5.0 (broad, exchanged with D_2O, NH_3^+, and NH_2^+, 5), 1.9–2.6 (multiplet, Ar-H, 7), 5.0 and 5.2 (multiplets, each becoming a pair of doublets with D_2O, -(NH)-C*H*CH<, 2), 5.6–6.1 (multiplet, C*H*$_2$CH$_3$, 4), 6.4 (multiplet, becoming an AB pattern with D_2O, NC*H*$_2$CO, 2), 8.82 and 8.9 (triplets, CH$_2$C*H*$_3$, 6) [*Anal.* ($C_{19}H_{26}Cl_2N_2O_4$) C, H, Cl, N]; and **28**·HCl: mp 245° (0.34 g); τ (on free base) 2.1–2.7 (multiplet, Ar-H, 7), 3.22 (singlet, H at position 1, exchanged by D_2O, 1), 5.65 (AB pattern, H's at positions 2 and 3, 2), 6.05 (quartet, C*H*$_2$CH$_3$, 2), 6.42 (singlet, H's at position 6, 2), 7.55 (broad singlet, exchanged with D_2O, H at position 4, 1), 9.07 (triplet, CH$_2$C*H*$_3$, 3); *m/e* 298 [*Anal.* ($C_{17}H_{19}ClN_2O_3$) C, H, Cl, N].

Ethyl 3-Hydroxy-2-isopropylamino-3-(2-naphthyl)propionate (12).—A solution of **11**·HCl (0.55 g) in H_2O (30 ml), 1 *N* NaOH (1.85 ml), and Me_2CO (10 ml) was hydrogenated in the presence of Pt (0.25 g). The mixture was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in Et_2O, the solution was washed with H_2O, and then dried. A slight excess of ethereal HCl was added to precipitate **12**·HCl. The mixture was filtered, the filtrate being retained. **12**·HCl (0.145 g), mp 174–175°, was obtained. The retained Et_2O filtrate was washed with H_2O and then dried. The Et_2O was evaporated and the residual oil (in C_6H_6) was chromatographed on Al_2O_3. Elution with $CHCl_3$–C_6H_6 (3:7) gave 2-naphthylcarbinol as plates (0.025 g), mp 80° from petroleum ether (bp 40–60°), lit.[19] mp 80°. *Anal.* ($C_{11}H_{10}O$) H; C: calcd, 83.5; found, 83.0.

2-Isopropylamino-1-methyl-1-(2-naphthyl)ethanol (13).—A solution of MeMgI in Et_2O (130 ml) was prepared from Mg powder (2.88 g) and MeI (17 g). **25**·HBr (6 g) was added and after the vigorous reaction had subsided the mixture was heated under reflux for 1 hr, and then stirred at room temperature for 12 hr. HCl (1 *N*) was added to extract the basic product, and the extract was washed with Et_2O. The acidic aqueous solution was made alkaline with 8 *N* NaOH and then extracted with $CHCl_3$. The $CHCl_3$ was evaporated, the residual oil was dissolved in cold petroleum ether (bp 40–60°) (50 ml), and the solution was filtered to remove insoluble material. The filtrate was evaporated to dryness, the residual oil was dissolved in Et_2O, and ethereal HCl was added to precipitate **13**·HCl (3.3 g).

1-Chloro-3-(1-naphthoxy)-2-butanone.—A solution of 2-(1-naphthoxy)propionic acid[20] (20 g) and $SOCl_2$ (16.5 g) in $CHCl_3$ (200 ml) was heated under reflux for 3 hr and then evaporated to dryness. The residual oil was dissolved in petroleum ether (bp 60–80°), treated with charcoal, and filtered, and the solvent was evaporated. The residual oil had an ir band at 1770 cm^{-1} characteristic of an acid chloride. A solution of the acid chloride in Et_2O was treated with a slight excess of CH_2N_2 in Et_2O. After 12 hr the solvent was evaporated. The residual solid had an ir band at 2100 cm^{-1} characteristic of a diazo compound. A solution of the diazo ketone in Et_2O was saturated with HCl at 0°. After 1 hr ice was added, and the Et_2O layer was separated and then washed successively with 10% Na_2CO_3 and H_2O. The Et_2O solution gave the chloro ketone (21.4 g), mp 70–71° from petroleum ether (bp 60–80°). *Anal.* ($C_{14}H_{13}ClO_2$) C, H, Cl.

1-Isopropylamino-3-(1-naphthoxy)-2-butanol (15).—$NaBH_4$ (7.5 g) was added during 45 min to a stirred solution of 1-chloro-3-(1-naphthoxy)-2-butanone (15 g) in MeOH (250 ml) at 0°. After 12 hr the MeOH was evaporated, the residual gum was dissolved in Et_2O, and the solution was washed with H_2O. The dried Et_2O solution was evaporated and the residual gum (12.8 g) was heated with *i*-PrNH$_2$ (45 g) in a Carius tube at 100° for 10 hr. The excess *i*-PrNH$_2$ was evaporated, the residue was dissolved in 1 *N* HCl, and the solution washed with Et_2O. The acidic aqueous solution was made alkaline with 8 *N* NaOH and then extracted with Et_2O. The Et_2O solution was dried and then a slight excess of ethereal HCl was added. **15**·HCl separated.

1-Isopropylamino-3-methyl-3-(1-naphthoxy)-2-butanol (16).—A solution of 2-methyl-2-(1-naphthoxy)propionic acid[21] (68.3 g) and $SOCl_2$ (53 g, 1.5 equiv) in $CHCl_3$ (300 ml) was heated under reflux for 3 hr and then evaporated to dryness. The residual oil was dissolved in petroleum ether (bp 60–80°), treated with charcoal, and filtered, and then the solvent was evaporated. The acid chloride so obtained was converted to **16**·HCl by the method described for **15**·HCl. Intermediates were characterized only by ir spectra.

2-Methyl-(4-chlorosulfinyl-1-naphthoxy)propionic Acid (31).—A suspension of 2-methyl-2-(1-naphthoxy)propionic acid (10 g) in $SOCl_2$ (20 ml) at room temperature gradually formed a solution and after 30 min a new solid (**31**) separated. It was crystallized from EtOAc: mp 142–143° dec. *Anal.* ($C_{14}H_{13}ClO_4S$) C, H, Cl; S: calcd, 10.25; found 9.7.

A solution of **31** in 5% $NaHCO_3$ was acidified with 6 *N* HCl. The 2-methyl-(4-hydroxysulfinyl-1-naphthoxy)propionic acid which separated was crystallized from Et_2O: mp 128°. *Anal.* ($C_{14}H_{14}O_5S$) C, H; S: calcd, 10.8; found, 11.3.

1-Isopropylamino-2-methyl-3-(1-naphthoxy)-2-propanol (18).—A 50% dispersion of NaH in oil (1.04 g) was added to a stirred suspension of trimethylsulfoxonium iodide (4.8 g) in DMSO (50 ml) under N_2. The mixture was heated at 60° for 30 min and then 1-naphthoxyacetone[22] (4 g) in DMSO (30 ml) was added. After 2 hr at 60°, the mixture was cooled and poured into H_2O. The intermediate 1-methyl-1-(1-naphthoxymethyl)oxirane, which was isolated by Et_2O extraction, was heated under reflux with *i*-PrNH$_2$ (30 ml) for 1 hr. **18** was isolated in the same way as **15** and then converted to the hydrogen oxalate.

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