the product, as described for IV, yielded 2 g of viscous oil. Column chromatography of this oil (column: 20 × 2 cm, Florisil, Fisher, 60–100 mesh, Et_2O 2000 ml) yielded 1.4 g of a waxy solid, mp 103–104° (fractions 300–1500 ml). *Anal.* ($C_{26}H_{39}NO_3$) C, H, N.

***cis*-5,9,10-H-5-(3,4,5-Trimethoxybenzamido)-2-methyldecahydroisoquinoline (VI).**—A solution of *cis*-5,9,10-H-5-acetamido-2-methyldecahydroisoquinoline (VIII) (8.0 g) and concentrated H_2SO_4 (8.0 ml) in H_2O (100.0 ml) was refluxed 24 hr. The solution was concentrated, made basic with NaOH, and extracted with Et_2O. The Et_2O solution was dried (Na_2SO_4) and concentrated to yield 6.16 g of *cis*-5,9,10-H-5-amino-2-methyldecahydroisoquinoline. A solution of this amine (3.0 g) in anhydrous C_6H_6 and 3,4,5-trimethoxybenzoyl chloride (5.0 g) in anhydrous C_6H_6 was refluxed 24 hr with the addition of anhydrous $KHCO_3$ (1.0 g). The crystalline product was collected by filtration and then recrystallized from EtOH to yield 5.90 g, mp 218.0–218.5°. Examination of the ir spectra of this amide showed it to be consistent with the proposed structure. An analytical sample melted at 218.0–218.5°. *Anal.* ($C_{20}H_{30}N_2O_4$) C, H, N.

***trans*-9,10-t-5-H-5-(3,4,5-Trimethoxybenzamido)-2-methyldecahydroisoquinoline (VII).**—A solution of *trans*-9,10-t-5-H-5-acetamido-2-methyldecahydroisoquinoline (IX) (3.0 g) and concentrated H_2SO_4 (7.6 ml) in H_2O (70.0 ml) was refluxed 144 hr. The solution was concentrated, made basic with NaOH, and extracted with Et_2O. The Et_2O solution was dried over Na_2SO_4 and concentrated to yield 2.0 g of *trans*-9,10-t-5-H-5-amino-2-methyldecahydroisoquinoline. A solution of this amine (2.0 g) in anhydrous C_6H_6 was treated with 3,4,5-trimethoxybenzoyl chloride (3.5 g) in a manner like that described above for the preparation of VI. The precipitated amide was isolated similarly and recrystallized from EtOH–Et_2O to yield 2.5 g of VII, mp 217.0–219.0°. The ir spectra of this amide was consistent with the proposed structure. An analytical sample melted at 217.0–219.0°, mmp 194–204° (VII and VI). *Anal.* ($C_{20}H_{30}N_2O_4$) C, H, N.

Acknowledgment.—The authors are indebted to Marion Laboratories Inc., Kansas City, Mo., for their continued generous financial support of this research work. Thanks are also due Dr. Norbert Wojciechowski for useful discussions during the course of this work and to Miss Mailand Stevens and Mrs. Amy Klyman for screening the compounds.

β-Adrenergic Blocking Agents. 1. Pronethalol and Related N-Alkyl and N-Aralkyl Derivatives of 2-Amino-1-(2-naphthyl)ethanol

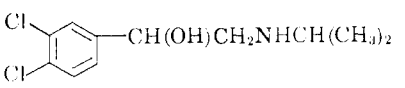
R. HOWE, A. F. CROWTHER, J. S. STEPHENSON, B. S. RAO, and L. H. SMITH

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

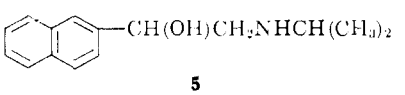
Received January 9, 1968

A series of 76 N-substituted derivatives of 2-amino-1-(2-naphthyl)ethanol (1) has been prepared by a variety of methods. One member of the series, pronethalol (**5**), was of some interest clinically as a β-adrenergic blocking agent but was found to cause thymic tumors after prolonged administration to mice. Structure–activity relationships in this series of β-adrenergic blocking agents resemble those previously reported for the isoproterenol series of β-mimetic agents.

For the past few years we have devoted considerable effort to the search for compounds possessing potent β-adrenergic blocking activity which would not also give rise to β-sympathomimetic effects. 1-(3,4-Dichlorophenyl)-2-isopropylaminoethanol (DCI)[1] (**72**) is unsatisfactory in the latter respect since for example it is capable of causing a marked increase in heart rate in the anesthetized cat.[2] At an early stage in our program 2-isopropylamino-1-(2-naphthyl)ethanol (pronethalol,[3] **5**) was synthesized[4] and found to meet to a large extent the criteria laid down at that time.[5] It proved clinically effective in the treatment of angina of



72



5

effort[5] and various types of cardiac arrhythmias,[6] and in the management of pheochromocytoma,[7] but was subsequently found to cause thymic tumors after prolonged administration to mice.[8]

We report here the synthesis of pronethalol (**5**) and a series of 75 related N-alkyl and N-aralkyl derivatives of 2-amino-1-(2-naphthyl)ethanol (**1**) (see Table I).[9] Many methods of synthesis were used for pronethalol and the more useful ones (methods A–H), given in the Experimental Section, were applied to the synthesis of analogs.

A few compounds were made by the route: $RCOCH_2Br + R^1R^2NH \rightarrow RCOCH_2NR^1R^2 \rightarrow RCH(OH)CH_2NR^1R^2$, where R = 2-naphthyl (throughout this paper), R^1 = H, alkyl, or aralkyl, and R^2 = alkyl or aralkyl.

This method has previously been used by Immediata and Day[10] for the preparation of compounds **2**, **3**, **6**, **37**, **39**, **41**, and **45**. No generally applicable conditions were found for the preparation and isolation of the intermediate amino ketones; each compound required specific conditions. Catalytic reduction of the amino ketone (method A) gave an almost quantitative yield of the corresponding amino alcohol, and reduction by $NaBH_4$ (method B) was effective and convenient. Reduction of isopropylaminomethyl 2-naphthyl ketone (**73**) with $LiAlH_4$ gave **5** but reduction with aluminum

(1) C. E. Powell and I. H. Slater, *J. Pharmacol. Exptl. Therap.*, **122**, 480 (1958).

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

(3) Alderlin®.

(4) J. S. Stephenson, British Patent 909,357 (1962).

(5) G. A. O. Alleyne, C. J. Dickinson, A. C. Dornhorst, R. M. Fulton, K. G. Green, I. D. Hill, P. Horst, D. R. Laurence, T. Pilkington, B. N. C. Prichard, B. Robinson, and M. L. Rosenheim, *Brit. Med. J.*, 1226 (1963).

(6) J. P. P. Stock and N. Dale, *ibid.*, 1230 (1963).

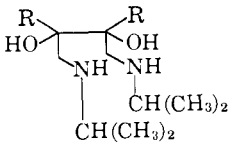
(7) A. C. Dornhorst and D. R. Laurence, *ibid.*, 1250 (1963).

(8) (a) S. J. Mecock and P. A. Bond, *Proc. European Soc. Drug Tox., 11th, Cambridge, England, July 1964*, 30 (1964); (b) R. Howe, *Nature*, **207**, 594 (1965).

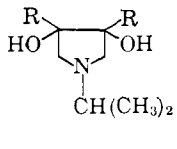
(9) A. F. Crowther, R. Howe, and L. H. Smith, British Patent 1,005,025 (1965).

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

isopropoxide in *i*-PrOH presumably proceeded bimolecularly to give an intermediate α,δ-diamine **74**, which, by elimination of isopropylamine, gave the pyrrolidine **75**.

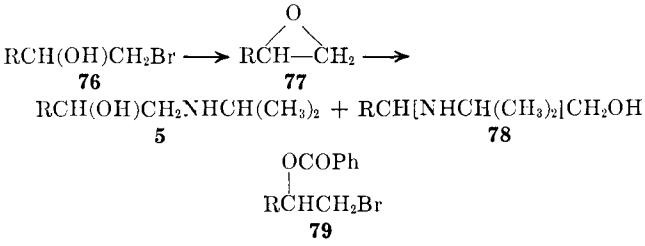


74



75

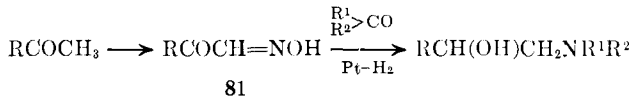
Reduction of bromomethyl 2-naphthyl ketone with $NaBH_4$ gave the bromohydrin **76**, which with ethanolic KOH gave the epoxide **77**. Treatment of the epoxide or the bromohydrin (which with base forms the epoxide) with, for example, isopropylamine (method C) gave a mixture of **5** and its position isomer **78**, in the ratio 4:1. These particular compounds were separated by fractional crystallization. In the case of **2**, **10**, **18**, **32**, **37**, and **42**, also made solely by this route, no special search was made for the primary alcohol isomers. Compounds **10** and **18** were later shown by nmr to be free from the position isomers.



The action of isopropylamine on the benzoate of the bromohydrin **79** was studied in an attempt to replace the bromine atom by the isopropylamino group directly, without the intermediate formation of the epoxide, thus eliminating the possibility of formation of **78**. The bromine atom in the benzoate **79** was relatively inert to attack by isopropylamine. Under forcing conditions **5** could be obtained, but none of its O-benzoyl derivative was detected. The reaction probably proceeded *via* the epoxide after initial aminolysis of the benzoyl group.

A useful intermediate in the synthesis of **5** and related N-substituted derivatives was 2-amino-1-(2-naphthyl)ethanol (**1**), which was conveniently prepared by reduction of aminomethyl 2-naphthyl ketone **80**[10] with $NaBH_4$. Reductive alkylation of **1** with an aldehyde or ketone was carried out using either Pt–H_2 (method D) or $NaBH_4$ (method E) as reducing agent. Use of methyl vinyl ketone as alkylating agent in method E gave the tertiary amine **44** and not the secondary amine **26**; the reaction had proceeded by addition of **1** to 2 moles of the unsaturated ketone and subsequent reduction of the carbonyl groups. The dimethylamino analog **39** was obtained by reductive alkylation of **1** with formaldehyde and formic acid.[11] Aminomethyl 2-naphthyl ketone (**80**) was also reductively alkylated with acetone by methods D and E to give pronethalol (**5**).

The amino alcohol **1** and the amino ketone **80** are probable intermediates in several preparative methods which follow. The route shown below suffers from the disadvantage that the intermediate 2-hydroxyiminoacetylnaphthalene **81** can not be obtained in good yield. The preparation of **81**, mp 93–94°, in 50% yield by the



81

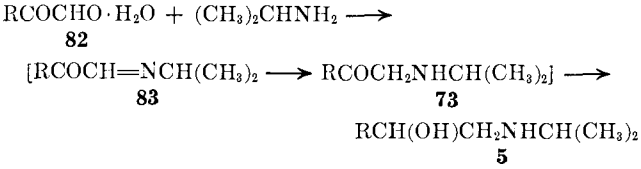
action of amyl nitrite on 2-acetonaphthone under basic conditions has previously been described.[12] Repeated experiments, under similar and slightly modified conditions, have given yields of about 20% of pure product, mp 105°. 2-Naphthoic acid, a further product of the reaction, is formed even under carefully controlled conditions, and is not readily separated from the desired product by fractional crystallization. Separation is best achieved by adjusting the pH of an aqueous alkaline solution of the mixture (pH 11) to pH 7.5 when 2-hydroxyiminoacetylnaphthalene, the weaker acid, is precipitated. At pH 4.5, 2-naphthoic acid separates.

The reaction between amyl nitrite and 2-acetonaphthone in the presence of HCl has been investigated. In one experiment, in which a large amount of HCl was used, 2-naphthoic acid was the only product. With catalytic amounts of HCl a mixture of the hydroxyiminomethyl ketone **81** and 2-naphthoic acid was obtained from which **81** was separated in 21% yield. Slater[13] has pointed out that ketones of the type $PhCOCH_3$ are sensitive to excess HCl during isonitrosation, whereas those of type $PhCOCH_2CH_3$ are reasonably stable.

The reduction of hydroxyiminomethyl ketones to β-amino alcohols is well known.[14] When the catalytic reduction of **81** was carried out with a Pt catalyst in the presence of an excess of a ketone (method F) the intermediate amino alcohol (or amino ketone) was reductively alkylated *in situ* to give the N-alkyl derivative.[15] When an aldehyde was used to provide the alkyl group it was necessary to use only 1 molar equiv if a mono-N-alkyl derivative (*e.g.*, **7**) was required; with excess aldehyde an N,N-dialkyl derivative (*e.g.*, **43**) was obtained.

Four methods used for the preparation of pronethalol involve reductive alkylation of the amino alcohol **1** (or the amino ketone **80**) formed *in situ* from (a) 2-naphthaldehyde cyanhydrin, (b) 2-naphthoyl cyanide, (c) azidomethyl 2-naphthyl ketone, and (d) diazomethyl 2-naphthyl ketone.[16] In each case reduction in glacial acetic acid solution in the presence of excess acetone using a 20% Pd–C catalyst gave **5** in about 20% yield.

The method of Fodor and Kovacs[17] has been applied and extended to the synthesis of pronethalol analogs.[18] 2-Naphthylglyoxal hydrate (**82**), previously prepared by SeO_2 oxidation of 2-acetonaphthone,[19] was conveniently



(11) H. T. Clarke, H. A. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

(12) B. B. Day and S. Rajagopalan, *Arch. Pharm.*, **277**, 385 (1939).

(13) W. K. Slater, *J. Chem. Soc.*, 587 (1920).

(14) Methoden der Organischen Chemie, Stickstoffe Verbindungen II, Houben-Weyl, p. 508.

(15) R. Howe, British Patent 953,010 (1964).

(16) R. Howe, British Patent 991,203 (1965).

(17) G. Fodor and O. Kovacs, *J. Am. Chem. Soc.*, **71**, 1045 (1949).

(18) R. Howe, British Patent 1,005,024 (1965).

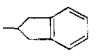
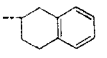
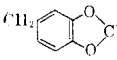
(19) L. N. Goldyrev and I. Ya. Postovskii, *J. Gen. Chem. USSR*, **10**, 39 (1940); *Chem. Abstr.*, **34**, 4732 (1940).

TABLE I
N-SUBSTITUTED 2-AMINO-1-(2-NAPHTHYL)ETHANOLS

Compd	R^1	R^2	Methods[a]	Form
1	H	H	B	Base
2	H	CH_3	C	Base
3	H	CH_2CH_3	H	Base
4	H	$(CH_2)_3CH_3$	C, H	Base HCl
5	H	$CH(CH_3)_2$	B, C, D, E, F, G, H	Base HCl HBr
6	H	$(CH_2)_3CH_3$	H	Base
7	H	$CH_2CH(CH_3)_2$	C, E, F,[a] H	Base HCl
8	H	$CH(CH_3)CH_2CH_3$	C, D, E, F, G	Base HCl
9	H	$C(CH_3)_3$	C, H	Base
10	H	$(CH_2)_4CH_3$	C	Base
11	H	$CH(CH_3)(CH_2)_2CH_3$	F	HCl
12	H	$CH(CH_2CH_3)_2$	F	Base
13	H	$CH(CH_3)CH(CH_3)_2$	F	HCl
14	H	$CH(CH_3)C(CH_3)_3$	H	Base
15	H	$CH(CH_2CH_3)(CH_2)_3CH_3$	F	HCl
16	H	$CH(CH_3)(CH_2)_6CH_3$	D	HCl
17	H	$(CH_2)_9CH_3$	H	HCl
18	H	CH_2CH_2OH	C	Base
19	H	$CH(CH_3)CH_2OH$	H	Base
20	H	$CH(CH_2CH_3)CH_2OH$	H	Base
21	H	$CH(CH_3)CH(OH)CH_3$	D[b]	Base
22	H	$C(CH_3)_2CH_2OH$	H	Base
23	H	$C(CH_2OH)_2CH_3$	H	Base
24	H	$CH_2CH{=}CH_2$	H	Base
25	H	$CH_2CH{=}CHCH_3$	E	Base
26	H	$CH(CH_3)CH{=}CH_2$	H	Base
27	H	$CH_2CH{=}C(CH_3)(CH_2)_2CH{=}C(CH_3)_2$	E[c]	HCl
28	H	$CH(CH_3)CH_2CO_2CH_2CH_3$	D	Base
29	H	$CH(CH_3)CH_2CO_2H$	See Exptl Section	Amino acid
30	H	$(CH_2)_3SCH_3$	H	Base
31	H	$(CH_2)_2N(CH_2CH_3)_2$	H	Base
32	H	$(CH_2)_3N(CH_3)_2$	C	Bis hydrogen oxalate
33	H	$CH(CH_3)(CH_2)_2N(CH_3)_2$	D	2HCl
34	H		H	Base
35	H		H	Base
36	H		D	Base
37	H		C	HBr
38	H		F	Base
39	CH_3	CH_3	See Exptl Section	Base
40	CH_3	$CH(CH_3)_2$	A, G	HCl
41	CH_2CH_3	CH_2CH_3	B	HCl
42	$CH(CH_3)_2$	$CH(CH_3)_2$	C	HCl
43	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	F[d]	Base
44	$(CH_2)_2CH(OH)CH_3$	$(CH_2)_2CH(OH)CH_3$	See Exptl Section	HCl
45	$-CH_2CH_2CH_2CH_2CH_2-$		A	HCl
46	H	C_6H_5	H	Base
47	H	$CH_2C_6H_5$	H	Base
48	H	$(CH_2)_2C_6H_5$	H	Base
49	H	$(CH_2)_3C_6H_5$	E	Base HCl[e]

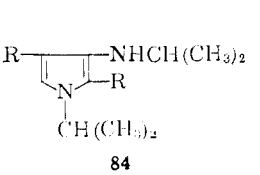
Crystn solvent[b]	Mp, °C, of amine or salt	Formula	Analyses	Infusion rate, μg/kg/min	% change in heart rate	% inhib of tachycardia
EtOAc	118[c]			400	+7	55
Et_2O	99[d]	$C_{13}H_{15}NO$	C, H, N	400	−10	57
EtOAc	110–111[e]	$C_{14}H_{17}NO$	C, H, N	100	−9	4
EtOAc	98–99	$C_{15}H_{19}NO$	C, H, N	400	−24	45
EtOH + Et_2O	192–193	$C_{15}H_{20}ClNO$	C, H, Cl, N			
EtOAc	107	$C_{15}H_{19}NO$	C, H, N	50	−15	45
MeOH + EtOAc	184	$C_{15}H_{20}ClNO$	C, H, Cl, N			
Me_2CO + H_2O	177–179	$C_{15}H_{20}BrNO$	C, H, Br, N			
EtOAc	94[f]	$C_{16}H_{21}NO$		100	−16	29
P (60)	95–96	$C_{16}H_{21}NO$	C, H, N	200	0	40
MeOH + Me_2CO	200–201	$C_{16}H_{22}ClNO$	Cl, N			
P (60)	82–83	$C_{16}H_{21}NO$	C, H, N	50	−12	61
MeOH + EtOAc	155–156	$C_{16}H_{22}ClNO$	H, Cl, N; C[h]			
EtOAc	129–130	$C_{16}H_{21}NO$	C, H, N	50	0	84
H	90	$C_{17}H_{23}NO$	C, N; H[i]	200	−7	46
MeOH + EtOAc	146–147	$C_{17}H_{24}ClNO$	C, H, N	100	−5	78
P (40)	74–75	$C_{17}H_{23}NO$	C, H, N	200	−14	25
MeOH + EtOAc	204–205	$C_{17}H_{24}ClNO$	C, H, Cl, N	200	+4	43
P (60)	89–90	$C_{18}H_{25}NO$	C, H, N	50	+4	25
MeOH + EtOAc	131–132	$C_{19}H_{28}ClNO$	C, H, Cl, N	400	−23	25
MeOH + EtOAc	142–143	$C_{21}H_{32}ClNO$	C, H, N	20 mg id[j]	0	20
MeOH + EtOAc	230–231	$C_{22}H_{34}ClNO$	C, H, Cl, N	20 mg id[j]	−4	22
$CHCl_3$	123–124	$C_{14}H_{17}NO_2$	C, H, N	200	−16	60
EtOAc	125–127	$C_{15}H_{19}NO_2$	C, H, N	100	−10	58
EtOAc	121–122	$C_{16}H_{21}NO_2$	C, H, N	1000	−24	78
EtOAc	100–101	$C_{16}H_{21}NO_2$	C, H, N	200	0	65
EtOAc	119–120	$C_{16}H_{21}NO_2$	C, H, N	100	−4	63
EtOAc	112–113	$C_{16}H_{21}NO_3$	C, N; H[l]	200	−1	43
P (60)	98–99	$C_{15}H_{17}NO$	C, H, N	200	−5	73
EtOAc	121–122	$C_{16}H_{19}NO$	C, H, N	200	−7	22
EtOAc + P (40)	96–97	$C_{16}H_{19}NO$	C, H, N	100	+2	78
MeOH + EtOAc	162–163	$C_{22}H_{30}ClNO$	C, H, Cl, N	20 mg id[j] (toxic)	−10	55
EtOAc + P (40)	73–74	$C_{18}H_{23}NO_3$	C, H, N	2 mg iv[n]	−4	87
H_2O	230–231	$C_{16}H_{19}NO_3$	C, H, N	100	−4	38
EtOAc	79–80	$C_{16}H_{21}NOS$	C, H, N, S	100	−24	57
EtOAc + P (40)	68–69	$C_{18}H_{26}N_2O$	C, H, N	400	−12	47
EtOH	170–172	$C_{21}H_{28}N_2O_9 \cdot H_2O$	H, N; C[o]	2.5 mg iv[n]	−9	Nil
MeOH + EtOAc	176–177	$C_{18}H_{28}Cl_2N_2O$	H, Cl, N; C[p]	1000	−24	68
EtOAc	94–95	$C_{19}H_{26}N_2O_2$	C, H, N	200	0	78
EtOAc	108–109	$C_{15}H_{17}NO$	C, H, N	100	−11	54
P (60)	103–104	$C_{17}H_{21}NO$	C, H, N	100	−10	44
H_2O	218–219[q]	$C_{18}H_{24}BrNO$	C, H, N	400	−12	60
P (40)	72–73	$C_{19}H_{25}NO$	C, H, N	400	−13	52
P (40)	57–58[r]	$C_{14}H_{17}NO$	C, H, N	200	−11	Nil
MeOH + EtOAc	177–178	$C_{16}H_{22}ClNO$	C, H, Cl, N	1000	−16	69
MeOH + EtOAc	142[s]			100	−10	7
MeOH + EtOAc	160–161	$C_{18}H_{26}ClNO$	C, H, Cl, N	400	−21	45
P (40)	62–63	$C_{20}H_{29}NO$	C, H, N	400	−3	Nil
MeOH + EtOAc	137–138	$C_{20}H_{30}ClNO_3$	C, H, Cl, N	400	−25	Nil
MeOH + Et_2O	212–213[u]			2.5 mg iv[n]	−29	18
EtOAc + P (40)	76–77	$C_{18}H_{17}NO$	C, H, N	200	−10	Nil
EtOAc	134–135[v]			800	−7	7
EtOAc	111–112[w]	$C_{20}H_{21}NO$	C, H, N	800	−21	52
EtOAc	136–137	$C_{21}H_{23}NO$	C, H, N	100	+9	51
MeOH + EtOAc	239–240	$C_{21}H_{24}ClNO$	C, H, Cl, N			

TABLE I (*Continued*)

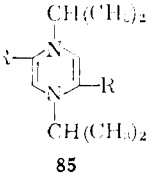
Compd	R¹	R²	Methods[a]	Form
50	H	$CH(CH_3)C_6H_5$	H	Base
51A[g]	H	$CH(CH_3)CH_2C_6H_5$	B, C, D, F, H	Base
				HCl
51B[g]				Base
				HCl
52A	H	$CH(CH_3)(CH_2)_2C_6H_5$	D[c,d]	Base
				HCl
52B				Base
				HCl
53	H	$CH(CH_3)(CH_2)_3C_6H_5$	D	HCl[e]
54A	H	$CH(CH_3)(CH_2)_4C_6H_5$	D	Base
				HCl
54B				Base
				HCl
55	H	$C(CH_3)_2CH_2C_6H_5$	G	Base
56	H	$C(CH_3)_2(CH_2)_2C_6H_5$	G	Base
57	H	$CH_2CH{=}CHC_6H_5$	E	HCl[e]
58	H	$CH(CH_3)CH_2OC_6H_5$	F	Base
59	H		D	Base
				HCl[f]
60	H		D	HCl[e]
61	H		E	Base
62	H		E	HCl[e]
63	H	$(CH_2)_2C_6H_3(OMe)_2$-*m*,*p*	H	Base
64	H	$CH(CH_3)CH_2C_6H_4Cl$-*p*	D	HCl[e,g]
65	H	$CH(CH_3)CH_2C_6H_4OMe$-*p*	H	Base
66	H	$CH(CH_3)CH_2C_6H_4OH$-*p*	H	HCl
67A	H	$CH(CH_3)(CH_2)_2C_6H_4OMe$-*p*	D	Base
				HCl[e]
67B				Base
				HCl
68A	H	$CH(CH_3)(CH_2)_2C_6H_4OH$-*p*	D	Base
				HCl
68B				Base
				HCl
69	H	$CH(CH_3)CH(OH)C_6H_5$	H[c]	HCl
70	H	$CH(CH_3)CH(OH)C_6H_4OH$-*p*	H[g,j]	Hydrogen oxalate
71	$CH(CH_3)_2$	$CH_2C_6H_5$	A,[k,l] B	HCl

[a] Methods refer to Experimental Section. [b] H, hexane; P 140), petroleum ether (bp 40–60°); P (60), petroleum ether (bp 60–80°). [c] Lit.[10] mp 113.5°. [d] Lit.[10] mp 109°. [e] Lit.[10] mp 110.5°. [f] Lit.[10] mp 95.6°. [g] 1 molar equiv of isobutyraldehyde was used. [h] C: calcd, 68.7; found, 68.2. [i] H: calcd, 9.0; found, 8.5 [j] Single dose 20 mg/kg intraduodenally. [k] Acetoin was used as ketone component. [l] H: calcd, 7.7; found 7.2. [m] Citral was used as aldehyde component. [n] Single injection given intravenously. [o] C: calcd, 53.6; found, 54.1. [p] C: calcd, 60.2; found, 59.7. [q] Lit.[10] mp 224° [r] Lit.[10] mp 53°. [s] Lit.[10] mp 142.5°. [t] 14 molar equiv of isobutyraldehyde was used. [u] Lit.[10] mp 213° [v] Lit.[10] mp 136–137°. [w] A. L. Allewelt and A. R. Day [*J. Org. Chem.*, **6**, 384 (1941)].

obtained in 90% yield by the action of dimethyl sulfoxide on bromomethyl 2-naphthyl ketone by the general method of Kornblum, *et al.*[20] Compound **5** was obtained in 55% yield by catalytic reductive amination of the glyoxal with isopropylamine (method G), or in 66% yield using $NaBH_4$ (method H). The catalytic reduction presumably proceeds *via* the intermediates **83** and **73**. In one slow catalytic reduction the aminopyrrole **84**, formed by condensation of two molecules of **73**, separated out. The structure of **84** follows from the nmr spectrum which eliminates the dihydropyrazine alternative **85**.



84



85

The hydrochloride of the N-benzyl derivative **71** of **5** was smoothly debenzylated to **5** by catalytic hydrogenolysis.[21]

When the substituent R^2 contains one or more asymmetric centers the chemical structure can stand for two or more racemic diastereoisomers. For some of the more interesting compounds, *e.g.*, **51**, **52**, **54**, **67**, and **68**,

[20] (a) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957); (b) I. M. Hunsberger and J. M. Tien, *Chem. Ind.* (London), 88 (1959).

[21] R. Howe and B. S. Rao, British Patent 1,005,027 (1965).

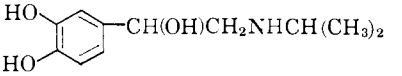
Crystn solvent[b]	Mp, °C, of amine or salt	Formula	Analyses	Infusion rate, μg/kg/min	% change in heart rate	% inhib of tachycardia
EtOAc	106–107	$C_{20}H_{21}NO$	C, H, N	200	+6	53
EtOAc + P (40)	81–82	$C_{21}H_{23}NO$	C, H, N	50	−4	−34
MeOH + EtOAc	131–132	$C_{21}H_{24}ClNO$	C, H, Cl, N			
EtOAc + P (40)	94–95	$C_{21}H_{23}NO$	C, H, N	50	+9	−29
MeOH + EtOAc	149–150	$C_{21}H_{24}ClNO$	H, N; C[z]			
EtOAc	108–109	$C_{22}H_{25}NO$	C, H, N	25	−6	65
MeOH + Me_2CO	202–203	$C_{22}H_{26}ClNO$	C, H, Cl, N			
EtOAc	112–113	$C_{22}H_{25}NO$	C, H, N	25	+5	24
MeOH + Me_2CO	178–179	$C_{22}H_{26}ClNO$	C, H, Cl, N			
MeOH + EtOAc	142–143	$C_{23}H_{28}ClNO$	C, H, Cl, N	50	0	50
EtOAc + P (40)	73–74	$C_{24}H_{29}NO$	C, H, N	0.5 mg iv[w]	−9	33
MeOH + EtOAc	154–155	$C_{24}H_{30}ClNO$	C, H, N			
EtOAc	112–113	$C_{24}H_{29}NO$	C, H, N	20	0	44
MeOH + EtOAc	167–168	$C_{24}H_{30}ClNO$	C, H, N			
EtOAc	141–142	$C_{22}H_{23}NO$	C, H, N	100	0	59
EtOAc	147	$C_{23}H_{27}NO$	C, H, N	50	−7	77
MeOH	238–239	$C_{21}H_{22}ClNO$	C, H, Cl, N	20 mg id[j] (toxic)		36
P (60)	94–95	$C_{21}H_{23}NO_2$	C, H, N	100	+8	53
EtOAc	122–125	$C_{21}H_{21}NO$	C, H, N	100	+6	19
MeOH + EtOAc	198–199	$C_{21}H_{22}ClNO$	C, H, N			
MeOH	229–230[bb]	$C_{22}H_{24}ClNO$	C, H, Cl, N	100	−13	17
EtOAc	100–101	$C_{17}H_{17}NO_2$	C, H, N	500	−2	62
MeOH + EtOAc	232–233	$C_{20}H_{20}ClNO_3$	C, H, Cl, N	20 mg id[j]	0	18
EtOAc	115–116	$C_{22}H_{23}NO_3$	C, H, N	100	+4	56
MeOH + EtOAc	137–138	$C_{21}H_{23}Cl_2NO$	C, H, Cl, N	100	−3	28
P (60)	128–129	$C_{22}H_{23}NO_2$	H, N; C[dd]	200	0	43
MeOH + EtOAc	167–168	$C_{21}H_{24}ClNO_2$	C, H, Cl, N	100	0	56
EtOAc	111	$C_{23}H_{27}NO_2$	C, H, N	50	−5	62
MeOH + EtOAc	210–211	$C_{23}H_{28}ClNO_2$	C, H, Cl, N			
EtOAc	130–131	$C_{23}H_{27}NO_2$	N	50	−2	31
MeOH + EtOAc	203–204	$C_{23}H_{28}ClNO_2$	C, H, N			
EtOAc	131–132	$C_{22}H_{25}NO_2$	C, H, N	50	−13	65
MeOH + EtOAc	174–175	$C_{22}H_{26}ClNO_2$	C, H, Cl, N			
EtOAc	151–152	$C_{22}H_{25}NO_2$	N	100	−3	54
MeOH + EtOAc	184–185	$C_{22}H_{26}ClNO$	C, H, Cl, N			
MeOH + EtOAc	195–196	$C_{21}H_{24}ClNO_2$	C, H, Cl, N	50[ff]	−12	60
MeOH + EtOAc	129–130	$C_{23}H_{23}NO_7 \cdot H_2O$	C, H, N, H_2O	100	−7	44
MeOH + EtOAc	154	$C_{22}H_{26}ClNO$	C, H, Cl, N	800	−7	35

reported mp 59–60°. [z] Isolated by the method used for **16**. [w] The letters A and B distinguish the two possible racemates. [z] C: calcd, 73.8; found, 73.2. [aa] Either 1-phenylbutan-3-one or 1-phenylbut-1-en-3-one may be used as the ketone component. [bb] Lit.[w] mp 211–212°. [cc] Isolated by $CHCl_3$ extraction. [dd] C: calcd, 78.8; found, 78.3. [ee] Norephedrine was used as amine component. [ff] Biological results were extremely variable. [gg] *p*-Hydroxynorephedrine was used as amine component. [hh] Free base was reduced using Pt catalyst.

the two possible racemates were separated by fractional crystallization.[22] The separation was readily monitored by observing the hydroxyl frequency at about 1070 cm^{-1} in the ir spectrum.

Biological Results and Discussion

The results of the screening test[23] given in Table I were obtained as follows. Cats were anesthetized with chloralose (80 mg/kg iv) and their heart rate and blood pressure were recorded. Drugs were administered through catheters in the femoral veins. Standard amounts of isoproterenol [1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol] (I) were administered intravenously at intervals of approximately 10 min. The amounts of I administered depended upon the sensitivity of the cat used and was generally between 0.25 and 0.5 μg/kg. The injection of isoproterenol caused an increase in heart rate and the mean of five responses was termed the control tachycardia. The test compound was administered by continuous intravenous



I

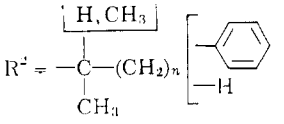
(22) The four optical isomers of **51** will be discussed in a later publication.

(23) 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).

infusion for 20 min at a steady rate. Any change in heart rate caused by the compound under test was recorded. Appropriate amounts of I were then administered at intervals of approximately 10 min. The compounds that possess β-adrenergic blocking activity inhibited the tachycardia that would otherwise have been caused by I. The activity of these compounds is expressed as the percentage inhibition of the control tachycardia. Under these test conditions DCI infused at 50 μg/kg/min increased the resting heart rate by 14%.

Structure–Activity Relationships.—Two features stood out most clearly, the first being that N,N-disubstituted derivatives of 2-amino-1-(2-naphthyl)-ethanol (**39–45** and **71**) were uniformly uninteresting as β-blocking agents. The second was that compounds having a methyl group on the α-carbon atom of the main alkyl chain of the substituent R^2 were invariably more active than the analog without the methyl group (compare **3** and **5**, **4** and **8**, **6** and **11**, **18** and **19**, **25** and **26**, **47** and **50**, **48** and **51**, and **49** and **52**). The higher activity was retained when a second methyl group was placed on the α-carbon atom (compare **5** and **9**, **19** and **22**, **51** and **55**, and **52** and **56**). An ethyl group on the α-carbon atom appeared to be less beneficial than a methyl group (compare **8** and **12**, and **19** and **20**), and comparison of **7** and **8** suggested that substitution of a methyl group on the β-carbon atom was not as good as on the α-carbon atom. Activity was usually retained and often increased when a phenyl group was placed at the end of the main alkyl chain. Activity remained high when hydroxy or methoxy substituents were substituted in the phenyl group. In the 2-monoalkylamino-1-(2-naphthyl)ethanols activity was maximal with alkyl groups of three to four carbon atoms branched at the α-carbon atom, *i.e.*, with isopropyl (**5**), *sec*-butyl (**8**), and *t*-butyl (**9**), and declined in the higher members of the series. In the 2-aralkylamino-1-(2-naphthyl)-ethanols high activity was found even when the alkyl moiety had six carbon atoms, *i.e.*, **54**.

In summary, β-adrenergic blocking activity about equal to that of pronethalol (**5**) is present in analogs having the side chain



where n = 1, 2, or 3. This is very similar to the pattern required for β-mimetic activity of the isoproterenol level in a series of analogs tested by Moed, *et al.*,[24] for bronchodilator effect against acetylcholine-induced bronchospasm in the guinea pig. Moed, *et al.*, propose that n = 1 or 2, but the results of Biel and coworkers,[25] who studied the effect of isoproterenol analogs against histamine-induced bronchoconstriction in the excised perfused guinea pig lung suggest that n can be up to 4. In the β-blocking series activity is high when n is 4 and the phenyl group is present; the corresponding isoproterenol analog has not been reported.

In 26 of the structures examined the presence of a substituent on the α-carbon atom of the main alkyl chain of R^1 makes that α-carbon atom asymmetric and thus two racemic diastereoisomers are possible. (Certain compounds, **21**, **38**, **69**, and **70**, have a third center of asymmetry). In five cases, **51**, **52**, **54**, **67**, and **68**, the two possible racemates were separated. The two racemates in each case did not differ greatly in potency; at best one isomer (**52A**) was two to three times more potent than the other (**52B**). Because of insolubility, **54A** had to be given by injection and so strict comparison was not possible. In each of the other cases the diastereoisomer with the higher frequency hydroxyl absorption in the ir was the better β-blocking agent. Because of the possibility that analogs of the same diastereoisomeric series are not being compared, no generalization of the effect of replacing a methyl group by an isosteric hydroxyl group, *e.g.*, **8** and **19**, **13** and **21**, or of introducing an ethylenic bond, *e.g.*, **8** and **26**, can be made.

A cyclic alkyl group had lower activity than the corresponding open-chain α-methyl analog (compare **5** and **35**, **11** and **36**, **51** and **59**, and **52** and **60**). The considerably lower activity of the cyclohexyl analog (**37**) compared with the cyclopentyl analog (**36**) was noted by Biel, *et al.*, in the isoproterenol series.

The position isomer (**7**) of pronethalol (**5**) was virtually inactive as a β-blocking agent. At an infusion rate of 200 μg/kg/min it did not affect the resting heart rate and blocked the isoproterenol-induced tachycardia to the extent of only 7%.

Most of the compounds caused a fall in the resting heart rate. A few produced an increase, but never to the extent of that caused by DCI. Increase in heart rate appeared to be more commonly associated with N-aralkyl compounds than with N-alkyl analogs.

Experimental Section[26]

The general experimental methods A–H are representative for the compounds reported in Table I. Melting points and recrystallizing solvents given in Table I are usually not repeated in the text. All hydrogenations were carried out at room temperature and atmospheric pressure.

Isopropylmethylaminomethyl 2-Naphthyl Ketone.—Isopropylmethylamine (14 g, 0.19 mole) was added to a solution of bromomethyl 2-naphthyl ketone (25 g, 0.1 mole) in Et_2O (300 ml) at 20°. The mixture was kept at 20° for 2.5 hr and then at 2° for 15 hr. The Et_2O solution was decanted and then extracted with 1 *N* HCl. The aqueous extract was made alkaline with 2 *N* NaOH and then extracted with Et_2O. The dried extract was treated with ethereal oxalic acid and the solid which separated was crystallized from MeOH. Isopropylmethylaminomethyl 2-naphthyl ketone hydrogen oxalate had mp 185–187°. *Anal.* ($C_{18}H_{21}NO_5$) C, H, N.

Method A. 2-Isopropylmethylamino-1-(2-naphthyl)ethanol (40).—A solution of isopropylmethylaminomethyl 2-naphthyl ketone hydrogen oxalate (3 g) in EtOH (50 ml) and H_2O (15 ml) was hydrogenated for 6 hr in the presence of Pd–C (5%, 0.3 g). The mixture was filtered and the solvents were evaporated. The residue was made alkaline with 1 *N* NaOH and then extracted with Et_2O. Addition of ethereal HCl to the dried extract gave the hydrochloride of **40** in almost quantitative yield.

Isopropylaminomethyl 2-Naphthyl Ketone (73).—A mixture of bromomethyl 2-naphthyl ketone (50 g, 0.2 mole), *i*-$PrNH_2$ (12 g, 0.2 mole), and EtOH (100 ml) was stirred at room temperature for 18 hr and then the mixture was filtered. The solid

(24) H. D. Moed, J. van Dijk, and H. Niewind, *Rec. Trav. Chim.*, **74**, 919 (1955).

(25) J. H. Biel, E. G. Schwarz, E. P. Sprengeler, H. A. Leiser, and H. L. Friedman, *J. Am. Chem. Soc.*, **76**, 3149 (1954).

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

residue was washed with EtOAc and then crystallized from MeOH–EtOAc. Isopropylaminomethyl 2-naphthyl ketone hydrobromide formed plates, mp 268°, yield 27 g (44%). *Anal.* ($C_{15}H_{18}BrNO$) C, H, Br, N.

The hydrogen oxalate melted at 234–235° (from EtOH). *Anal.* ($C_{17}H_{19}NO_5$) C, H; N: calcd, 4.4; found, 4.9.

1-Methyl-2-phenylethylaminomethyl 2-Naphthyl Ketone.—A mixture of bromomethyl 2-naphthyl ketone (10 g, 0.04 mole), 1-methyl-2-phenylethylamine (5.4 g, 0.04 mole), and MeOH (50 ml) was kept at room temperature for 18 hr and then the MeOH was evaporated. The residue was stirred with a little EtOAc and the solid which did not dissolve was isolated and then crystallized from a mixture of MeOH and EtOAc. 1-Methyl-2-phenylethylaminomethyl 2-naphthyl ketone hydrobromide had mp 220–222°, yield 1.95 g (12.7%). *Anal.* ($C_{21}H_{22}BrNO$) C, H, N; Br: calcd, 20.8; found, 20.2.

2-Isopropylamino-1-(2-naphthyl)ethanol (5).—Isopropylaminomethyl 2-naphthyl ketone hydrobromide (5 g) was shaken with Et_2O (100 ml) and $NaHCO_3$ solution (10%, 25 ml), and then the Et_2O extract was dried. LAH (2 g) was added during 15 min to the dry Et_2O solution at room temperature, and after 30 min the mixture was heated under reflux for 12 hr. The excess of LAH was decomposed by adding ice and the organic material was isolated with Et_2O. The extract gave **5**, mp 106°.

3,4-Dihydroxy-1-isopropyl-3,4-di(2-naphthyl)pyrrolidine (75).—A solution of isopropylaminomethyl 2-naphthyl ketone hydrogen oxalate (0.4 g) and aluminum isopropoxide (1.3 g) in dry *i*-PrOH (25 ml) was slowly distilled during 7 hr to remove Me_2CO and then the solution was evaporated to dryness. The residue was made alkaline with 1 *N* NaOH and then extracted with Et_2O. The extract gave **75** as prisms: mp 146°, from EtOAc–petroleum ether (bp 60–80°); nmr ($CDCl_3$), τ 2.2–3.0 (multiplet, Ar-H, 14), 5.7 (OH, 2), 6.53 (AB quartet, CH_2 of pyrrolidine, 4), 7.04 (septet, isopropyl CH, 1), 8.75 (doublet, isopropyl CH_3, 6). *Anal.* ($C_{27}H_{27}NO_2$) C, H, N.

Method B. 2-Amino-1-(2-naphthyl)ethanol (1).—$NaBH_4$ (10 g) was added during 25 min to a stirred suspension of aminomethyl 2-naphthyl ketone hydrobromide[10] (25 g) in MeOH (250 ml) at 5°. After 1 hr the MeOH was evaporated and the residue was made alkaline with 1 *N* NaOH and then extracted with $CHCl_3$. The extract gave 1, mp 118°, yield 15.5 g (89%).

Method C. 2-Isopropylamino-1-(2-naphthyl)ethanol (5) and 2-Isopropylamino-2-(2-naphthyl)ethanol (78).—A solution of 2-bromo-1-(2-naphthyl)ethanol (220 g, 0.875 mole) and *i*-$PrNH_2$ (200 ml, 2.35 moles) in EtOH (400 ml) was heated under reflux for 3 hr and then the EtOH and the excess of *i*-$PrNH_2$ were evaporated. EtOAc (200 ml) was added to the hot residual oil and the crude 2-isopropylamino-1-(2-naphthyl)ethanol hydrobromide, mp 172–174°, which separated on cooling, was collected. The filtrate was retained. The crude hydrobromide was converted to the crude free base which was then converted to the hydrochloride. This was recrystallized from MeOH–EtOAc and gave pure 2-isopropylamino-1-(2-naphthyl)ethanol hydrochloride, mp 184°. The corresponding free base (**5**) is characterized by ir absorption bands at 1086, 1070, and 1018 cm^{-1} and by the absence of such bands at 1058 and 1032 cm^{-1} (in $CHCl_3$ solution); nmr (CCl_4 + trifluoroacetic acid (TFA)), τ 2.1–2.8 (multiplet, Ar-H, 7), 5.15 (X part of ABX, OCH<, 1), 6.4 (NH and OH, 2), 7.0–7.7 (multiplet, AB part of ABX, –(O–)$CHCH_2N$<, and septet, isopropyl CH, 3), 9.0 (2 doublets, isopropyl CH_3, 6). *Anal.* ($C_{15}H_{19}NO$) C, H, N.

The EtOAc mother liquors retained above, from which as much crude hydrobromide, mp 172–174°, as possible had been removed, were evaporated to dryness. The residual gum was shaken with C_6H_6 and sufficient 1 *N* NaOH to make the aqueous solution alkaline. The C_6H_6 extract gave 2-isopropylamino-2-(2-naphthyl)ethanol, mp 108°, from petroleum ether (bp 80–100°), depressed to 94° by 2-isopropylamino-1-(2-naphthyl)ethanol, mp 107°. *Anal.* ($C_{15}H_{19}NO$) C, H, N. This free base is characterized by ir absorption bands at 1086, 1058, and 1032 cm^{-1} and by the absence of such bands at 1070 and 1018 cm^{-1}; nmr (CCl_4 + TFA), τ 2.1–2.7 (multiplet, Ar-H, 7), 6.0 (X part of ABX, NCH<, 1), 6.2–6.5 (AB part of ABX, –(N–)$CHCH_2O$–, 2), 7.0–7.5 [multiplet (septet, isopropyl CH) + OH + NH, 3], 8.95 (two doublets, isopropyl CH_3, 6).

The hydrochloride melted at 210–211° (from MeOH–EtOAc). *Anal.* ($C_{15}H_{20}ClNO$) C, H, Cl, N.

2-Naphthylethylene Oxide (77).—A solution of 2-bromo-1-(2-naphthyl)ethanol (2.5 g, 0.01 mole) in EtOH (5 ml) was added to a solution of KOH (0.84 g, 0.015 mole) in EtOH (7.5 ml). After 15 min, H_2O (50 ml) was added and the mixture was extracted with Et_2O. The dried extract gave 2-naphthylethylene oxide, mp 58–59°, from petroleum ether (bp 40–60°). *Anal.* ($C_{12}H_{10}O$) H; C: calcd, 84.7; found, 84.1.

2-Bromo-1-(2-naphthyl)ethyl Benzoate (79).—Benzoyl chloride (3.25 g) was added to a solution of 2-bromo-1-(2-naphthyl)-ethanol (5 g) in dry pyridine (15 ml) at 0°. After 16 hr, the pyridine was evaporated at 40° under reduced pressure. H_2O was added, and the organic material was isolated by Et_2O extraction. The extract furnished **79**, mp 83° (from MeOH), yield 6.2 g (87%). *Anal.* ($C_{19}H_{15}BrO_2$) C, H; Br: calcd, 22.5; found, 23.1.

Method D. 2-(1-Methylpropylamino)-1-(2-naphthyl)ethanol (8).—A suspension of 1 (20 g) in EtCOMe (50 ml) and EtOH (50 ml) was hydrogenated in the presence of PtO_2 (0.5 g). The mixture was filtered and the filtrate was evaporated to dryness. The residue was shaken with 1 *N* HCl and Et_2O. The acidic aqueous solution was made alkaline with 2 *N* NaOH and then extracted with Et_2O. The extract gave **8**, mp 82–83°.

2-(1-Methyloctyl)amino-1-(2-naphthyl)ethanol (16).—A solution of 1 (3 g) in 2-nonanone (10 ml) and EtOH (30 ml) was hydrogenated in the presence of PtO_2 (0.3 g). The mixture was filtered and the filtrate was evaporated to dryness. The residue was shaken with 1 *N* HCl and Et_2O. The hydrochloride of **16** separated as a white solid at the interface. It was crystallized from MeOH–EtOAc, mp 142–143°. A further crop of hydrochloride was isolated from the Et_2O extract.

Method E. 2-Isopropylamino-1-(2-naphthyl)ethanol (5).—$NaBH_4$ (2 g) was added during 90 min to a stirred solution of 1 (2 g) in MeOH (40 ml) and Me_2CO (10 ml) at 5°. After 30 min the MeOH and the excess of Me_2CO were evaporated. Compound **5** was isolated in the same way as **8** (method D), mp 106°, yield 2.2 g (92%).

2-Di(3-hydroxybutyl)amino-1-(2-naphthyl)ethanol (44).—$NaBH_4$ (1.5 g) was added during 90 min to a mixture of 1 (1 g), methyl vinyl ketone (5 g), and MeOH (60 ml). After 15 min the solvent was evaporated. The residue was shaken with 1 *N* HCl and Et_2O. The acidic aqueous solution was made alkaline with 2 *N* NaOH and then extracted with Et_2O. The dried extract was evaporated and the residual oil was chromatographed on alumina. Compound **44** was eluted with $CHCl_3$ and was converted to the hydrochloride, mp 137–138°.

2-Dimethylamino-1-(2-naphthyl)ethanol (39).—Compound 1 (5 g), formic acid (98%, 7 ml), and formalin (40%, 7 ml) were heated under reflux for 16 hr. The cooled solution was shaken with H_2O and Et_2O and then the aqueous solution was made alkaline with 2 *N* NaOH and extracted with Et_2O. The extract gave **39**.

2-Isopropylamino-1-(2-naphthyl)ethanol (5) from Aminomethyl 2-Naphthyl Ketone. (**a**) A solution of aminomethyl 2-naphthyl ketone hydrobromide (0.4 g) in EtOH (20 ml) and Me_2CO (30 ml) was hydrogenated in the presence of PtO_2 (0.1 g). The mixture was filtered and the filtrate was evaporated to dryness. The residual solid was shaken with 1 *N* NaOH and Et_2O. The Et_2O extract gave **5**, mp 105–106°.

(**b**) $NaBH_4$ (1 g) was added during 90 min to a stirred solution of aminomethyl 2-naphthyl ketone hydrobromide (1 g) in a mixture of MeOH (20 ml) and Me_2CO (5 ml) at 5°. After 30 min the MeOH and excess of Me_2CO were evaporated. Compound **5** was isolated in the same way as **8** (method D), mp 105–106°, yield 0.82 g (95%).

2-Hydroxyiminoacetylnaphthalene (81). (**a**) A solution of 2-acetonaphthone (102 g) in absolute EtOH (100 ml) was added to a stirred solution of Na (13.8 g) in absolute EtOH (200 ml) at −5 to 0° and then AmONO (27.7 g) was added during 2 hr. The mixture was stirred at room temperature for 4 days and then filtered. The residue was washed with a little cold EtOH and then with Et_2O. The solid was stirred with cold H_2O (2 l.) and filtered to remove insoluble material, then the filtrate (pH ~11) was adjusted to pH 7.5 with concentrated HCl. The solid 2-hydroxyiminoacetylnaphthalene which separated formed prisms, mp 105° (from EtOAc), yield 20 g (17%). *Anal.* ($C_{12}H_9NO_2$) C, H, N.

The pH of the aqueous filtrate, remaining after the isolation of 2-hydroxyiminoacetylnaphthalene, was adjusted to 4.5. 2-Naphthoic acid separated out, mp and mmp 182° (from EtOAc).

(**b**) AmONO (14.5 g) was added during 2 hr to a stirred solution of 2-acetonaphthone (20 g) in dry Et_2O (150 ml) at 0° and during that time a few milliliters of dry HCl gas were passed into the solution every 15 min. The mixture was stirred for 0.5

hr and then the Et_2O was evaporated. The residue was shaken with Et_2O and NaOH (5%, 100 ml). 2-Hydroxyiminoacetylnaphthalene was isolated from the aqueous alkaline solution as described in a; mp 105°, yield 5 g (21%).

Method F. 2-(1-Ethylpropylamino)-1-(2-naphthyl)ethanol (12).—A solution of 2-hydroxyiminoacetylnaphthalene (4 g, 0.02 mole) in Et_2CO (40 g, 0.465 mole) and EtOH (10 ml) was hydrogenated in the presence of PtO_2 (0.5 g). Compound **12** was isolated in the same way as **8** (method D).

2-Naphthaldehyde Cyanhydrin.—Solutions of KCN (1.3 g) in H_2O (10 ml), H_2SO_4 (0.98 g) in H_2O (20 ml), and 2-naphthaldehyde (1.5 g) in Et_2O (30 ml) were shaken together for several minutes at 0° and then the Et_2O layer was separated, washed with H_2O, and then dried. The Et_2O solution gave 2-naphthaldehyde cyanhydrin, mp 106–108° (from petroleum ether, bp 60–80°). *Anal.* ($C_{12}H_9NO$) C, H, N.

2-Naphthoyl Cyanide.—A mixture of 2-naphthoyl chloride (4.68 g) and $Cu_2(CN)_2$ (3.6 g; obtained by heating the hydrate at 110° for 3 hr) were heated at 220–230° for 1.5 hr. During this time the yellow liquid which condensed and solidified on the cooler parts of the vessel was periodically collected. Crystallization from Et_2O gave material, mp 114–115°.[27]

2-Isopropylamino-1-(2-naphthyl)ethanol (5) from 2-Naphthoyl Cyanide.—A solution of 2-naphthoyl cyanide (0.65 g) in glacial AcOH (20 ml) and Me_2CO (20 ml) was hydrogenated in the presence of Pd-C (20%, 0.4 g). The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was heated at 100° with 1 *N* NaOH (50 ml) for 30 min. The cooled solution was acidified with concentrated HCl and then extracted with Et_2O. Basification of the acidic aqueous solution and extraction with Et_2O gave **5**, mp 106°, yield 0.2 g (24%).

2-Naphthylglyoxal Hydrate (82).—A solution of bromomethyl 2-naphthyl ketone (40 g) in DMSO (240 ml) was kept at room temperature for 48 hr and then poured onto ice. The solid **82** was crystallized from H_2O and formed needles, mp 108°, yield 28.9 g (88%). *Anal.* ($C_{12}H_{10}O_3$) C, H.

When heated with *o*-phenylenediamine in EtOH solution, **82** gave 2-(2-naphthyl)quinoxaline, mp 140–141° (from EtOH). *Anal.* ($C_{18}H_{12}N_2$) C, H, N.

Method G. 2-Isopropylamino-1-(2-naphthyl)ethanol (5).—A solution of **82** (2 g, 0.01 mole) in EtOH (20 ml) and i-$PrNH_2$ (20 ml, 0.235 mole) was hydrogenated in the presence of PtO_2 (0.4 g). Compound **5** was isolated in the same way as **8** (method D); mp 106°, yield 1.4 g (55%).

1-Isopropyl-3-isopropylamino-2,4-di(2-naphthyl)pyrrole (84).—2-Naphthylglyoxal hydrate (11.35 g, 0.056 mole), i-$PrNH_2$ (15 ml, 0.176 mole), and EtOH (15 ml) were hydrogenated in the presence of PtO_2 (0.4 g). The reaction was unexpectedly sluggish and was incomplete after 3 days. The mixture was filtered and the solid (**84**) which had separated during hydrogenation was crystallized from Et_2O: mp 195°; nmr ($CDCl_3$), τ 1.75–2.85 (multiplet, Ar-H, 14), 2.98 (pyrrole hydrogen, 1), 5.7 (septet, isopropyl CH, 1), 7.0 (septet, isopropyl CH, 1), 7.28 (NH, 1), 8.65 (doublet, isopropyl CH_3, 6), 9.2 (doublet, isopropyl CH_3, 6). *Anal.* ($C_{30}H_{30}N_2$) C, H, N.

Method H. 2-Isopropylamino-1-(2-naphthyl)ethanol (5).—$NaBH_4$ (0.5 g) was added during 45 min to a stirred solution of **82** (2 g) in MeOH (20 ml) and i-$PrNH_2$ (5 ml) at 0°. After 3 hr the MeOH and the excess i-$PrNH_2$ were evaporated. Compound **5** was isolated in the same way as **8** (method D), mp 106°, yield 1.7 g (66%).

2-Carboxy-1-methylethylamino-1-(2-naphthyl)ethanol (29).—Compound **28** (0.3 g) was heated under reflux with NaOH (20%, 15 ml) for 20 hr. The solution was cooled and the pH was adjusted to 7.5. The solid product (**29**) which separated was crystallized from H_2O.

Benzylisopropylaminomethyl 2-Naphthyl Ketone.—A solution of bromomethyl 2-naphthyl ketone (10 g, 0.04 mole) and benzylisopropylamine (12 g, 0.08 mole) in MeOH (70 ml) was heated under reflux for 1 hr and then about 60 ml of MeOH was evaporated. EtOAc (100 ml) was added and the benzylisopropylamine hydrobromide which separated was removed by filtration. The filtrate was evaporated and the residue was shaken with Et_2O and dilute HCl. The aqueous acidic layer was made alkaline and then extracted with Et_2O. The dried extract was evaporated and gave benzylisopropylaminomethyl 2-naphthyl ketone, mp 65–67° dec (from EtOAc), yield 7.9 g (62%). *Anal.* ($C_{24}H_{25}NO$) C, H, N.

The hydrochloride melted at 185–187° (from MeOH–EtOAc). *Anal.* ($C_{22}H_{24}ClNO$) H, Cl, N; C: calcd, 74.7; found, 74.0.

2-Isopropylamino-1-(2-naphthyl)ethanol (5) from 2-Benzylisopropylamino-1-(2-naphthyl)ethanol (71).—A solution of **71**·HCl (1 g) in EtOH (30 ml) was hydrogenated in the presence of Pd-C (20%, 0.3 g). The mixture was filtered and the filtrate was evaporated to dryness. The residue was shaken with 1 *N* NaOH and Et_2O. The Et_2O extract gave **5**, mp 105° (from EtOAc).

2-(1-Methyl-3-phenylpropylamino)-1-(2-naphthyl)ethanol (52A and 52B).—A solution of **1** (3 g) in 1-phenylbut-1-en-3-one (2.6 g) and EtOH (20 ml) was hydrogenated in the presence of PtO_2 (0.3 g). EtOAc (40 ml) was then added, the mixture was filtered, and the filtrate was evaporated to dryness. The residue was shaken with 1 *N* HCl (30 ml) and Et_2O (30 ml) and the white solid which separated at the interface was isolated by filtration. This solid was fractionally crystallized from MeOH–EtOAc to give the least soluble isomer of **52**·HCl, mp 200–201°, and the more soluble isomer, mp 178°. The corresponding free bases, isolated in the conventional way had mp 108–109° and mp 112–113°, respectively. The former free base is characterized (in Nujol) by absorption at 1074 cm^{-1} and by the absence of a band at 1068 cm^{-1}. The latter free base is characterized (in Nujol) by absorption at 1068 cm^{-1} and by the absence of a band at 1074 cm^{-1}.

(27) N. P. Buu-Hoï, *Ann.*, **556**, 1 (1944).