pared in Et_2O. It was recrystallized (Et_2O–EtOH) as white needles, mp 143–144°. *Anal.* ($C_{16}H_{17}ClN_2$) C, H, N.

N-(2-Propynyl)isoindole (2) Hydrochloride.—A solution of 11.9 g (0.1 mole) of 3-bromopropyne in 25 ml of Et_2O was added dropwise at 0° to a solution of 23.8 g (0.2 mole) of isoindoline[6] in 200 ml of anhydrous Et_2O. The mixture was allowed to stir in an ice bath for 3 hr and at room temperature overnight. Isoindoline hydrobromide was filtered off, and the Et_2O solution was dried (Na_2CO_3) and evaporated. The resulting orange oil was distilled at 65° (0.3 mm), resulting in 8.6 g (55%) of **2** as a slightly yellowish oil, $n^{25}D$ 1.5520. *Anal.* ($C_{11}H_{11}N$) C, H, N.

The **hydrochloride** of **2** was formed in Et_2O. It melted at 189–190° (from EtOH, dissolved at room temperature and cooled to −20°). *Anal.* ($C_{11}H_{12}ClN$) C, H, N.

Acknowledgment.—The authors wish to acknowledge the assistance of Drs. F. Rosenberg, M. D. Aceto, L. S. Harris, and R. A. Ferrari of the Sterling-Winthrop Research Institute for performing the pharmacological tests reported herein. The work was performed under contract DA18-108-AMC-103(A) with the U. S. Army Chemical Research and Development Laboratories, Edgewood Arsenal, Maryland.

β-Adrenergic Blocking Agents. IV. Variation of the 2-Naphthyl Group of Pronethalol [2-Isopropylamino-1-(2-naphthyl)ethanol]

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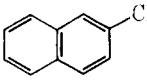
In attempts to improve the potency of the adrenergic β-receptor antagonist pronethalol [2-isopropylamino-1-(2-naphthyl)ethanol] the 2-naphthyl group has been replaced by, for example, 1-naphthyl, tetrahydro-2-naphthyl, 5-indanyl, and various tricarbocyclic groups. Analogs have also been made with substituents other than *i*-Pr on N. Structure–activity relationships are discussed. Several of the compounds described have the same level of potency as pronethalol.

In the course of our synthetic program[1] aimed at improving the potency of the adrenergic β-receptor antagonist 2-isopropylamino-1-(2-naphthyl)ethanol (pronethalol)[2] we have prepared the analogs described in



pronethalol

Table I. The 2-naphthyl group of pronethalol has been replaced by for example 1-naphthyl,[3] tetrahydro-2-naphthyl,[4] 5-indanyl,[4] and various tricarbocyclic groups[5] to provide a series of 16 compounds having an isopropylaminoethanol side chain. Analogs have also been made with substituents other than isopropyl on N. The compounds were prepared mainly by three of the methods described in part I.[1a]

In method A, an intermediate aminomethyl ketone (Table II) was reduced by $NaBH_4$ in good yield.

$$RCOCH_2X + R^1R^2NH \xrightarrow{B} RCOCH_2NR^1R^2 \xrightarrow[NaBH_4]{A} RCH(OH)CH_2NR^1R^2$$

X = Br or Cl

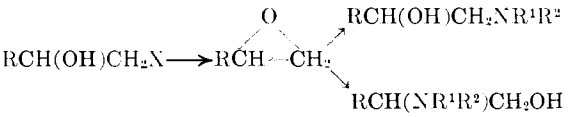
Several specific methods are described for the isolation of the salts of the aminomethyl ketones, in addition to the general method B. Yields were usually in the region 20–30% except for **48** (53%). Most of the intermediate halomethyl ketones were known. The orientation of 4-methyl-1-acetonaphthone,[6] obtained by acylation of 1-methylnaphthalene and used to prepare bromomethyl 4-methyl-1-naphthyl ketone, was checked by oxidation *via* 4-methyl-1-naphthoic acid to naphthalene-1,4-dicarboxylic acid.[7] Chloromethyl 1,2,3,4-tetrahydro-2-naphthyl ketone (**65**) was prepared by the following route.

$$RCOCl \longrightarrow RCOCHN_2 \longrightarrow RCOCH_2Cl$$

65

R = 1,2,3,4-tetrahydro-2-naphthyl

In method C an intermediate halohydrin was treated with an amine to give (*via* an epoxide) a mixture of



position isomers, which largely consisted of the desired secondary alcohol isomer. Purification by fractional crystallization gave the required isomer. Samples of **4**, **13**, and **15** obtained by method C were identical with those produced unambigously by method A. The structures of those compounds prepared only by method C were confirmed by nmr and, in particular, by the chemical shift of the proton –CH(O)– which in pronethalol (CCl_4) is τ 5.15 (X part of ABX). For those compounds in which there was no fused-ring junction at a ring carbon atom adjacent to the one bearing the side chain, *i.e.*, for **34**, **35**, and **42**, the chemical shift was τ 5.1–5.25. For those with an adjacent fused ring, *i.e.*, the α-naphthyl analogs **1**, **3**, **6**, **8**, **11**, and the phenanthrene **37**, the chemical shift was τ 4.35–4.5. For the ring-substituted compounds **17** and **18** the chemical shifts were τ 5.3 and 4.7 (nmr spectra in $CDCl_3$, except for **6**, **11**, and **18** which were measured in DMSO-d_6).

(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).

(2) Alderlin®.

(3) J. S. Stephenson and B. J. McLoughlin, British Patent 998,524 (1965).

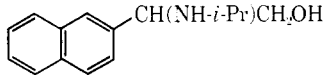
(4) R. Howe, L. H. Smith, and J. S. Stephenson, British Patent 1,005,026 (1965).

(5) R. Howe, British Patent 984,291 (1965).

(6) (a) R. D. Haworth and C. R. Marvin, *J. Chem. Soc.*, 2720 (1932); (b) J. Sauer, R. Huisgen, and A. Hauser, *Ber.*, 91, 1461 (1958).

(7) F. Mayer and A. Sieglitz, *ibid.*, 55, 1835 (1922).

In the position isomer **66** of pronethalol the chemical shift of the proton –CH(N)– was τ 6.0 (CCl_4). The new



66

halohydrins characterized in Table III were prepared by reduction of the related halomethyl ketone with $NaBH_4$.

The third main method (D) was reductive amination of a glyoxal using $NaBH_4$ as reducing agent.[1a] The new glyoxals listed in Table IV were prepared by SeO_2 oxidation of the corresponding methyl ketone or by the

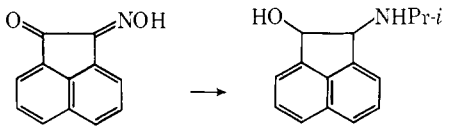
$$RCOCHO + H_2NR^1 \longrightarrow$$
$$(RCOCH{=}NR^1 \longrightarrow RCOCH_2NHR^1) \longrightarrow RCH(OH)CH_2NHR^1$$

action of DMSO on the corresponding bromomethyl ketone.[1a]

Three compounds were made by catalytic reductive alkylation of 2-amino-1-(1-naphthyl)ethanol (**67**) formed *in situ* from 1-hydroxyiminoacetylnaphthalene (**68**) (method E). The latter compound, mp 137–138°, was prepared by treatment of 1-acetonaphthone with AmONO in the presence of ethereal HCl. Wister and Robinson[8] prepared **68** under alkaline conditions and reported mp 183°. The two compounds may be *syn* and *anti* isomers, or 183° may be a clerical error for 138°. **67** was characterized by reduction of aminomethyl 1-naphthyl ketone hydrochloride (**69**) with $NaBH_4$. Catalytic reduction of either **67** or **69** in the presence of Me_2CO gave **2**.

The 5,6,7,8-tetrahydronaphthyl analog **20** was prepared by two special routes, reduction of pronethalol under pressure in the presence of Raney Ni, and reduction of the N-benzyl derivative[1a] of pronethalol in the presence of Pt and HCl. It was shown in part I that when Pd–C was used in the last reaction without added HCl, pronethalol was formed, *i.e.*, the benzyl group was hydrogenolyzed without the 2-naphthyl group being affected.

One further compound, **71**, in which the aminoethanol side chain is substituted across the *peri* positions of the naphthalene nucleus, was prepared by catalytic reductive alkylation of acenaphthenequinone monoxime **70**.



70 **71**

Structure–Activity Relationships.—The results of the biological screening tests[9] are given in Table I. The test procedure was identical with that reported previously.[1a]

Consider first those compounds with an isopropylaminoethanol side chain. The 1-naphthyl analog **2** of pronethalol had about the same β-adrenergic blocking potency as pronethalol, but resembled DCI [1-(3,4-dichlorophenyl)-2-isopropylaminoethanol][1a] in that it caused a marked increase in heart rate. Several other 1-naphthyl analogs caused a marked increase in heart rate. The similarity in potency of **2** and pronethalol contrasts with the propranolol series where the 1-naphthyl compound [propranolol[10] = 1-isopropylamino-3-(1-naphthoxy)-2-propanol] was about 25 times more potent than the 2-naphthyl analog.[1b] Potency was not improved in the five 1-naphthyl analogs examined.

The two tetrahydro-2-naphthyl analogs **20** and **24** had the same potency as pronethalol and did not raise the heart rate. Changing the six-membered saturated ring of **20** to the five-membered saturated ring of the 5-indanyl analog **27** did not change the potency. The three phenanthrenes **34**, **35**, and **37**, and the anthracene **41**, which exemplify the four ways of fusing a benzene ring onto the 2-naphthyl moiety of pronethalol, were some four to eight times less potent than pronethalol. The same relationship held for **42** and **43** and their bicyclic analogs **27** and **2**. It is possible that the tricarbocyclic nucleus of **34** to **43** is rather too large to occupy effectively the receptor site normally occupied by a catechol nucleus. Compound **71** was completely devoid of β-adrenergic blocking activity.

In the tetralin and indane series **20** and **27**, which have a Me group on the α carbon atom of the main alkyl chain of the substituent R^2, were more potent than **19** and **26** which have no such Me group.[1a] In the 1-naphthyl series the difference was less marked. Tertiary amines were not examined in much detail because they were uninteresting in the pronethalol series;[1a] however, **11** proved to be more potent than was expected. The complete lack of activity of **39** was surprising, but may be due to the presence of a large R^2 substituent and a bulky phenanthrene nucleus in the same molecule.

For several compounds in Table I two racemic diastereoismers are possible. Because more interesting series of compounds were available no special attempt was made to obtain both diastereoisomers, and none of the compounds was resolved into its optical isomers.

Experimental Section[11]

The general experimental methods A–E are representative for the compounds reported in Tables I and II. Melting points and recrystallizing solvents given in the tables are usually not repeated in the text. Hydrogenations were carried out at room temperature and atmospheric pressure unless stated otherwise.

A. 2-Isopropylamino-1-(5,6,7,8-tetrahydro-2-naphthyl)ethanol (20).—$NaBH_4$ (1 g, 0.026 mole) was added during 10 min to a stirred solution of **45**·HBr (3 g, 0.0096 mole) in MeOH (60 ml) at 0°. After 3 hr the MeOH was evaporated under reduced pressure, 0.5 *N* HCl (80 ml) was added, and the mixture was washed with Et_2O (20 ml). NaOH (2 *N*, 30 ml) was added to the aqueous acid layer and the product (**20**) was isolated with Et_2O.

B. *t*-Butylaminomethyl 5,6,7,8-Tetrahydro-2-naphthyl Ketone (46).—A solution of bromomethyl 5,6,7,8-tetrahydro-2-naphthyl ketone[12] (10 g, 0.04 mole) and *t*-$BuNH_2$ (8.7 g, 0.12 mole) in MeOH (60 ml) was kept at 0° for 16 hr and then the MeOH was evaporated. The residue was shaken with 0.5 *N* HCl and Et_2O. The aqueous extract was made alkaline with 4 *N* NaOH and then extracted with Et_2O. The dried extract was treated with ethereal HCl and **48**·HCl separated out.

Isobutylaminomethyl 1-Naphthyl Ketone (44).—A solution of bromomethyl 1-naphthyl ketone[13] (2.48 g, 0.01 mole) in Et_2O (50 ml) was added slowly to a stirred solution of *i*-$BuNH_2$

(8) J. Wister and R. Robinson, *J. Chem. Soc.*, **101**, 1307 (1912).

(9) 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).

(10) Inderal®.

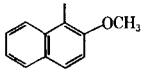
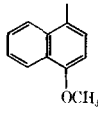
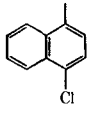
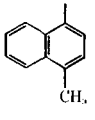
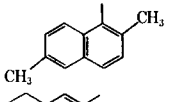
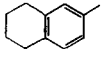
(11) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

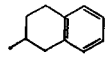
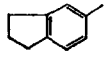
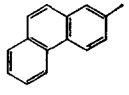
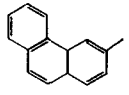
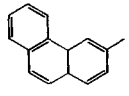
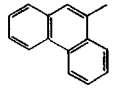
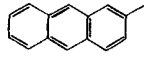
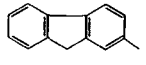
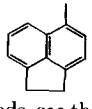
(12) C. T. Bahner, E. Kite, F. Pierce, L. M. Rives, M. D. Pickens, and C. Myers, *J. Am. Chem. Soc.*, **73**, 4011 (1951).

(13) O. Pampel and G. Schmidt, *Ber.*, **19**, 2896 (1886).

TABLE I

$RCH(OH)CH_2NR^1R^2$

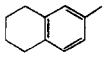
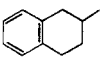
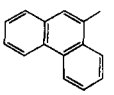
Compd	R	R^1	R^2	Methods[a]	Form	Crysin solvent[b]	Mp, °C, of amine or salt	Formula	Analyses	Infusion rate, μg/kg/min	% change in heart rate	% inhib of tachycardia
1		H	$(CH_2)_2CH_3$	C	Base	P(60)	100–101	$C_{15}H_{21}NO$	C, H, N	50	+12	40
2[c]		H	$CH(CH_3)_2$	E	Base	EtOAc + P(60)	113–114	$C_{15}H_{19}NO$	C, H, N	50	+12	76
					Oxalate	EtOH + EtOAc	216–218	$C_{32}H_{40}N_2O_8$	C, H, N			
3		H	$(CH_2)_3CH_3$	C	Base	P(60)	103–104	$C_{16}H_{21}NO$	C, H, N	100	+2	42
4		H	$CH_2CH(CH_3)_2$	A, C	HCl	MeOH + Me_2CO	198–200	$C_{16}H_{22}ClNO$	C, H, Cl, N	400	−6	48
					Base	EtOAc + P(60)	116–118	$C_{16}H_{21}NO$	C, H, N			
5		H	$CH(CH_3)CH_2CH_3$	D[d]	Oxalate	MeOH + EtOH	196–197	$C_{34}H_{44}N_2O_6$	C, H, N	50	−4	43
6		H	$C(CH_3)_3$	C	Oxalate	MeOH	217–218	$C_{34}H_{44}N_2O_6$	H, N; C[e]	50	+24	58
7		H	$CH(CH_3)(CH_2)_2CH_3$	E	Oxalate	EtOH + MeOH	194–195	$C_{36}H_{48}N_2O_6$	C, H, N	100	+30	61
8		H	$CH_2CH(OH)CH_3$	C	Base	C_6H_6 + P(60)	86–88	$C_{15}H_{19}NO_2$	C, H, N	200	+8	45
9		H	$CH(CH_3)(CH_2)_2C_6H_5$	E	HCl	MeOH + EtOH	205–206	$C_{22}H_{26}ClNO$	C, H, N	100	+10	82
10		CH_3	CH_3	C	Base	P(60)	69–70[f]	$C_{14}H_{17}NO$	H, N; C[g]	200	+2	11
11		CH_3	$CH(CH_3)_2$	C	Oxalate	Me_2CO	133–134	$C_{34}H_{44}N_2O_6$	H, N; C[h]	100	+16	62
12[c]		H	$CH(CH_3)_2$	D	Base	P(60)	108–109	$C_{16}H_{21}NO_2$	C, H, N	1000	−13	10
13		H	$CH(CH_3)_2$	A,[i] C	Base	EtOAc + P(60)	132–133	$C_{16}H_{21}NO_2$	C, N; H[k]	400	+10	62
14		H	$CH(CH_3)_2$	D[c]	Oxalate	EtOH + H_2O	239–240	$C_{32}H_{38}Cl_2N_2O_6$	C, H, Cl, N	100	+4	71
15		H	$CH(CH_3)_2$	A,[m] C	Hydrogen oxalate	EtOH	212	$C_{18}H_{23}NO_5$	C, H, N	50	+6	79
16		H	$C(CH_3)_3$	A[n]	Base	Et_2O	162–164	$C_{17}H_{23}NO \cdot 0.25H_2O$	C, N; H[o]	100	+16	62
17		H	$C(CH_3)_2CH_2OH$	C	Picrate[p]	EtOH	200	$C_{23}H_{26}N_4O_9$	C, H, N	200	+8	45
18		H	$CH(CH_3)_2$	C[q]	Base	EtOH + H_2O	120	$C_{17}H_{23}NO \cdot 0.5H_2O$	C, H, N	100	−4	64
19		H	CH_2CH_3	D	Base	EtOAc	85–86	$C_{14}H_{21}NO$	C, H, N	200	−14	57
20[r]		H	$CH(CH_3)_2$	A	Base	EtOAc + P(40)	84–85	$C_{15}H_{23}NO$	C, H, N	50	+2	72
					HCl	EtOAc	156–157[s]	$C_{15}H_{24}ClNO$	C, H, Cl; N[t]			
21		H	$C(CH_3)_3$	A	HCl	MeOH + Et_2O	203–204[f]	$C_{16}H_{26}ClNO$	C, H, Cl, N	50	−5	42
22		H	$C(CH_3)_2CH_2OH$	D	Base	EtOAc	118–119	$C_{16}H_{25}NO_2$	C, H, N	50	−7	52
23		H	$CH(CH_3)CH_2C_6H_5$	A	Hydrogen oxalate	MeOH + EtOAc	158–159	$C_{23}H_{29}NO_5$	C, H, N	200	−7	46

24		H	$CH(CH_3)_2$	A	Base	P(40)	56–57	$C_{15}H_{23}NO$	C, H, N	50	−6	45
25		H	CH_3	A	Base	P(60)	131–132[u]			100	+8	50
26		H	CH_2CH_3	D	Base	EtOAc	110–111	$C_{13}H_{19}NO$	C, H, N	100	+2	57
27		H	$CH(CH_3)_2$	A	Base	P(60)	98–99	$C_{14}H_{21}NO$	C, H, N	50	+2	73
28		H	$(CH_2)_3CH_3$	A	Base	P(40)	94–95	$C_{15}H_{23}NO$	C, H, N	100	−14	40
29		H	$CH(CH_3)CH_2CH_3$	A	Base	P(40)	75–76	$C_{15}H_{23}NO$	C, H, N	100	+6	59
30		H	$C(CH_3)_3$	A	Base	EtOAc	121–122	$C_{15}H_{23}NO$	C, H, N	50	+10	75
31		H	$C(CH_3)_2CH_2OH$	D	Base	EtOAc	115–116	$C_{15}H_{23}NO_2$	C, H, N	50	0	28
32		H	$CH_2CH_2C_6H_3$-3,4-$(OMe)_2$	A	Base	EtOAc	111–112	$C_{21}H_{27}NO_3$	C, H, N	100	−4	43
33		CH_2CH_3	CH_2CH_3	A	HCl	MeOH + EtOAc	125–126[v]			80	+3	7
34		H	$CH(CH_3)_2$	C	Base	EtOAc	146–148	$C_{19}H_{21}NO$	C, H, N	200	−14	20
35		H	$CH(CH_3)_2$	C	Base	EtOAc	124–125	$C_{19}H_{21}NO$	C, H, N	200	−28	48
36		H	$C(CH_3)_2CH_2OH$	D	Base	EtOAc + P(40)	120	$C_{20}H_{23}NO_2$	C, H, N	100	−8	38
37		H	$CH(CH_3)_2$	C	Base	P(60)	102–103	$C_{19}H_{21}NO$	C, H, N	200	−7	45
38		H	$C(CH_3)_2CH_2OH$	D	Base	EtOAc + P(40)	131–132	$C_{20}H_{23}NO_2$	C, H, N	100	−2	48
39		H	$CH(CH_3)CH_2C_6H_5$	D	Base	EtOAc	137–138	$C_{25}H_{25}NO$	C, H, N	40	+3	Nil
40		CH_3	$CH(CH_3)_2$	A	HCl	MeOH + EtOAc	162–163	$C_{20}H_{24}ClNO$	H, Cl, N; C[w]	200	−18	9
41		H	$CH(CH_3)_2$	C	Base	P(60)	124–126	$C_{19}H_{21}NO$	C, H, N	400	0	48
42		H	$CH(CH_3)_2$	C	Base	EtOAc	143	$C_{18}H_{21}NO$	C, H, N	400	0	32
43		H	$CH(CH_3)_2$	D[x]	Base	EtOAc + P(60)	143–144	$C_{17}H_{21}NO$	H, N; C[y]	200	−14	60

[a] For methods, see the Experimental Section. [b] P(40), petroleum ether (bp 40–60°); P(60), petroleum ether (bp 60–80°). [c] Compound first prepared by Dr. J. S. Stephenson. [d] Intermediate 1-naphthylglyoxal hydrate: L. N. Goldyrev and I. Ya. Postovskii, *J. Gen. Chem. USSR*, **10**, 37 (1940); *Chem. Abstr.*, **34**, 4372 (1940). [e] C: calcd, 70.8; found, 70.1. [f] Picrate mp 178°: H. King and T. S. Work, *J. Chem. Soc.*, 1307 (1940), give mp 178–180°. [g] C: calcd, 78.1; found, 77.5. [h] C: calcd, 70.8; found, 71.3. [i] Compound kindly prepared by Dr. R. P. Slatcher. [j] Isopropylaminomethyl 4-methoxy-1-naphthyl ketone was prepared from iodomethyl 4-methoxy-1-naphthyl ketone[18] by the method given for **44**. It was not characterized before reduction. [k] H: calcd, 8.15; found, 7.5. [l] 4-Chloro-1-naphthylglyoxal was prepared by SeO_2 oxidation of 4-chloro-1-acetonaphthone: T. L. Jacobs, S. Winstein, J. W. Ralls, and J. H. Robson, *J. Org. Chem.*, 11, 27 (1946). It was used without characterization. [m] Isopropylaminomethyl 4-methyl-1-naphthyl ketone was prepared by the method given for **44**. It was not characterized before reduction. [n] *t*-Butylaminomethyl 4-methyl-1-naphthyl ketone was prepared by the method given for **44**. It was not characterized before reduction. [o] H: calcd, 9.0; found, 8.4. [p] Converted to free base, mp 184–186°, for biological tests and nmr study. [q] Intermediate bromohydrin not characterized. [r] G. Ferrari, C. Casagrande, and M. Canova, *Boll. Chim. Farm.*, **103**, 32 (1964), report mp 160–162°. [s] N: calcd, 5.2; found, 5.7. [t] Lit.[r] mp 196–198°. [u] R. Pfleger and K. Rauer, *Ber.*, **90**, 1500 (1957), report mp 124–125°. [v] Lit.[u] mp 124–126°. [w] C: calcd, 72.9; found, 72.1. [x] 5-Acenaphthenylglyoxal prepared by the SeO_2 method from 5-acetylacenaphthene: L. F. Fieser and E. B. Hershberg, *J. Amer. Chem. Soc.*, **61**, 1272 (1939). It was characterized as the quinoxaline derivative, mp 144–145°. *Anal.* ($C_{20}H_{14}NO_2$) H, N; C: calcd, 85.1; found, 84.5. [y] C: calcd, 79.95; found, 79.2. [z] Where there is a blank space in this column, the R group is the preceding structure.

TABLE II

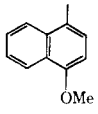
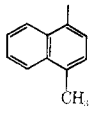
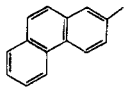
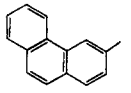
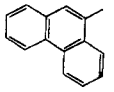
$RCOCH_2NR^1R^2$

Compd	R[k]	R^1	R^2	Method	Salt	Crystn solvent	Mp, °C	Formula	Analyses
44		H	$CH_2CH(CH_3)_2$	*j*	HCl	EtOH + EtOAc	213–214	$C_{16}H_{20}ClNO$	H, N, Cl; C[a]
45		H	$CH(CH_3)_2$	*j*	HBr	MeOH + EtOAc	221–223	$C_{15}H_{22}BrNO$	C, H, N; Br[b]
46		H	$C(CH_3)_3$	B	HCl	EtOH + Et_2O	240–241	$C_{16}H_{24}ClNO$	C, H, Cl, N
47		H	$CH(CH_3)CH_2C_6H_5$	*j*	HBr	MeOH + EtOAc	227–228	$C_{21}H_{26}BrNO$	C, H, Br, N
48		H	$CH(CH_3)_2$	*j*	HCl	MeOH + EtOAc	183–184	$C_{15}H_{22}ClNO$	H, N, Cl; C[c]
49		H	$CH(CH_3)_2$	B[d]	HCl	MeOH + Et_2O	220–221	$C_{14}H_{20}ClNO$	C, H, Cl, N
50		H	$(CH_2)_3CH_3$	B[e]	HCl	MeOH + Et_2O	209–210	$C_{15}H_{22}ClNO$	C, H, N; Cl[f]
51		H	$CH(CH_3)CH_2CH_3$	B[g]	HCl	EtOH	175–177	$C_{15}H_{22}ClNO$	C, H, N; Cl[h]
52		H	$C(CH_3)_3$	B[i]	HCl	MeOH + Et_2O	237–238	$C_{15}H_{22}ClNO$	C, H, Cl, N
53		H	$CH_2CH_2C_6H_3$-3-4-$(OMe)_2$		HBr	EtOH	215–216	$C_{21}H_{26}BrNO_3$	C, H, N
54		CH_3	$CH(CH_3)_2$	*j*	HCl	MeOH + EtOAc	208–209	$C_{20}H_{22}ClNO$	C, H, N

[a] C: calcd, 69.2; found, 68.5. [b] Br: calcd, 25.6; found, 24.9. [c] C: calcd, 67.3; found, 66.7. [d] Ketone (0.042 mole), amine (0.083 mole). [e] Ketone (0.042 mole), amine (0.125 mole). [f] Cl: calcd, 13.3; found, 13.8. [g] Ketone (0.042 mole), amine (0.08 mole). [h] Cl: calcd, 13.3; found, 13.8. [i] Ketone (0.042 mole), amine (0.125 mole). [j] See Experimental Section. [k] Where there is a blank space in this column, the R group is the preceding structure.

TABLE III

$RCH(OH)CH_2X$

Compd	R	X	Crystn solvent	Mp, °C	Formula	Analyses
55[a]		Cl	EtOAc + P(60)	73–74	$C_{13}H_{13}ClO_2$	C, H, Cl
56[b]		Br	C_6H_{12}	80–81	$C_{13}H_{13}BrO$	C, H, Br
57[c]		Br	MeOH	113	$C_{16}H_{13}BrO$	C, H
58[c]		Br	EtOAc + P(60)	85–86	$C_{16}H_{13}BrO$	C, H
59[c]		Br	MeOH	146–147	$C_{16}H_{13}BrO$	C, H, Br

[a] Intermediate chloro ketone described in ref 18. [b] Intermediate bromo ketone not characterized. [c] Intermediate bromo ketone described in ref 15.

(1.46 g, 0.02 mole) in Et_2O (50 ml) at <10°. The mixture was stirred for 1 hr and then filtered. Ethereal HCl was added to the filtrate and the **44**·HCl which separated was first warmed with Me_2CO to remove gummy material and then crystallized from EtOH–EtOAc.

Isopropylaminomethyl 5,6,7,8-Tetrahydro-2-naphthyl Ketone (45).—A solution of bromomethyl 5,6,7,8-tetrahydro-2-naphthyl ketone[12] (3 g, 0.012 mole) and *i*-$PrNH_2$ (0.75 g, 0.013 mole) in EtOH (25 ml) was kept at 20° for 16 hr and then EtOAc (*ca.* 100 ml) was added to precipitate **47**·HBr.

1-Methyl-2-phenylethylaminomethyl 5,6,7,8-Tetrahydro-2-naphthyl Ketone (47).—A solution of bromomethyl 5,6,7,8-tetrahydro-2-naphthyl ketone[12] (5 g, 0.02 mole) and amphetamine (2.67 g, 0.02 mole) in MeOH (25 ml) was kept at 20° for 60 hr and then the MeOH was evaporated. The residue was stirred with EtOAc to remove gummy material and the solid **49**·HBr was then crystallized from MeOH–EtOAc.

Isopropylaminomethyl 1,2,3,4-Tetrahydro-2-naphthyl Ketone (48).—A solution of chloromethyl 1,2,3,4-tetrahydro-2-naphthyl ketone (5.0 g, 0.024 mole) and *i*-$PrNH_2$ (3.5 g, 0.06 mole) in EtOH (50 ml) was heated under reflux for 16 hr and then the EtOH was evaporated. **50**·HCl (3.4 g, 53%) was isolated in the same way as **49**·HBr.

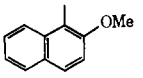
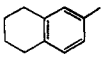
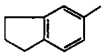
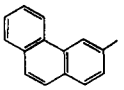
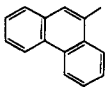
2-(3,4-Dimethoxyphenyl)ethylaminomethyl 5-Indanyl Ketone (53).—A solution of bromomethyl 5-indanyl ketone[14] (1.1 g, 0.0046 mole) and 2-(3,4-dimethoxyphenyl)ethylamine (0.5 g, 0.00275 mole) in MeOH (20 ml) was kept at 20° for 16 hr during which time **53**·HBr separated out.

Isopropylmethylaminomethyl 9-Phenanthryl Ketone (54).—A solution of bromomethyl 9-phenanthryl ketone[15] (3 g, 0.01 mole) and isopropylmethylamine (2 g, 0.0275 mole) in C_6H_6 (15 ml) was heated under reflux for 3 hr. The solution was cooled and then extracted with 0.5 *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 HCl and **56**·HCl separated out.

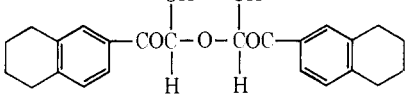
Chloromethyl 1,2,3,4-Tetrahydro-2-naphthyl Ketone (65).—A solution of 1,2,3,4-tetrahydro-2-naphthoic acid[16] (28.5 g,

(14) W. Borsche and M. Pommer, *Ber.*, **54**, 102 (1921).
(15) E. Mosettig and J. van de Kamp, *J. Am. Chem. Soc.* **55**, 3449 (1933).
(16) E. L. Eliel and T. E. Hoover, *J. Org. Chem.*, **24**, 938 (1959).

TABLE IV
RCOCHO

Compd	R	Method	Crystn solvent	Mp, °C	Formula	Analyses
60		SeO_2	EtOAc + P(60)	119–120	$C_{13}H_{10}O_3 \cdot 0.5H_2O$	C, H
61[a]		DMSO[b]	EtOAc + P(60)	98–99[c]	$C_{24}H_{26}O_5 \cdot 0.67C_4H_8O_2$	C, H
62		DMSO[d]	H_2O	123–124	$C_{11}H_{10}O_2 \cdot H_2O$	C, H
63		DMSO[e]	MeOH	101–102	$C_{16}H_{10}O_2 \cdot H_2O$	C, H
64		DMSO[e]	Et_2O	119–121	$C_{16}H_{10}O_2$	C, H

[a] Forms a quinoxaline derivative, mp 85–86°. *Anal.* ($C_{18}H_{16}N_2$) C, H, N. [b] Intermediate bromo ketone, described in ref 12. [c] An EtOAc complex of the hemiacetal **72**, τ ($CDCl_3$) 2.1–2.3 (multiplet, 1, 3, 1′, and 3′, Ar-H, 4), 2.87 (doublet, J = 7 cps, 4 and 4′, Ar-H,



72

2), 3.71 (doublet, J = 10 cps, collapsed to singlet by D_2O, C*H*(OH), 2), 4.96 (doublet, J = 10 cps, exchanged with D_2O, CH(O*H*), 2), 7.05–7.4 (multiplet, CH_2's next to aromatic ring, 8), 8.1–8.35 (multiplet, CH_2, 8), and appropriate signals for 0.67EtOAc [see H. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1895 (1963)]. [d] Intermediate bromo ketone, described in ref 14. [e] Intermediate bromo ketone, described in ref 15.

0.16 mole) in $SOCl_2$ (29 g, 0.24 mole) was heated under reflux for 2 hr and then the $SOCl_2$ was evaporated. The residual oil was dissolved in petroleum ether (bp 60–80°) and then the solvent and traces of $SOCl_2$ were removed by evaporation. The residual oil had an absorption band at 1785 cm^{-1} characteristic of an acid chloride. A solution of the acid chloride (32 g, 0.165 mole) in dry Et_2O (100 ml) was added to a slight excess of CH_2N_2 in Et_2O, the mixture was kept at 0° for 16 hr, and then the Et_2O was evaporated. The residual oil had an absorption band at 2095 cm^{-1} characteristic of a diazo compound. The crude diazo ketone was dissolved in Et_2O (350 ml) and then HCl was passed in to saturate the solution. The solution was washed successively three times with H_2O (100 ml), three times with 10% Na_2CO_3 (100 ml), and three times with H_2O (100 ml). The extract gave **65**, mp 44–45° from petroleum ether, ν_{max} 1710 cm^{-1}. *Anal.* ($C_{12}H_{13}ClO$) C, H, Cl.

Bromomethyl 2,6-Dimethyl-1-naphthyl Ketone.—Br_2 (16 g, 0.2 mole) was added dropwise to a stirred solution of 2,6-dimethyl-1-acetonaphthone[17] (19.8 g, 0.1 mole) in Et_2O (100 ml) at 10°, and then the solution was stirred for 0.5 hr. It was poured into ice–water, and then the product was isolated by Et_2O extraction, mp 66° from C_6H_{12}. *Anal.* ($C_{14}H_{13}BrO$) C, H; Br: calcd, 28.9; found, 28.2.

C. **2-Isopropylamino-1-(4-methoxy-1-naphthyl)ethanol (13).**—Compound **55** (4 g, 0.017 mole), *i*-$PrNH_2$ (8 g, 0.135 mole), and EtOH (100 ml) were heated under reflux for 12 hr and then evaporated to dryness. The residue was dissolved in a slight excess of 2 *N* HCl and washed with Et_2O, and then the aqueous acidic solution was made alkaline with 2 *N* NaOH. The product **13** was isolated by extraction with Et_2O and then fractionally crystallized from EtOAc–petroleum ether.

2-Chloro-1-(4-methoxy-1-naphthyl)ethanol (55).—$NaBH_4$ (1.5 g, 0.039 mole) was added during 15 min to a stirred solution of chloromethyl 4-methoxy-1-naphthyl ketone[18] (2 g, 0.0085 mole) in EtOH (60 ml) at 0–5°. The mixture was stirred for 1 hr and then poured onto ice. The mixture was extracted with Et_2O (three 100-ml portions), and the combined extracts were washed (H_2O, 5% $NaHCO_3$, H_2O). The dried Et_2O extract gave **55**.

D. **2-Ethylamino-1-(5-indanyl)ethanol (26).**—$NaBH_4$ (1 g, 0.026 mole) was added during 30 min to a stirred solution of **62**·H_2O (2 g, 0.01 mole) and $EtNH_2$ (1.2 g, 0.027 mole) in MeOH (50 ml) at 0°. The mixture was stirred at 0° for 2 hr and then the solvent was evaporated *in vacuo*. HCl (0.5 *N*, 100 ml) was added and then the mixture was washed with Et_2O. NaOH (2 *N*, 35 ml) was added to the aqueous acidic solution and then the product **26** was isolated by Et_2O extraction.

5-Indanylglyoxal (62).—A solution of bromomethyl 5-indanyl ketone[14] (15 g, 0.063 mole) in DMSO (100 ml) was kept at room temperature for 48 hr and then poured onto ice. **62** was isolated by Et_2O extraction and then crystallized from H_2O.

2-Methoxy-1-naphthylglyoxal (60).—A solution of 2-methoxy-1-acetonaphthone[19] (10 g, 0.05 mole) and SeO_2 (5.6 g, 0.05 mole) in aqueous dioxane (1:3, 8 ml) was stirred and heated at 100° for 4 hr. The cooled mixture was filtered and the filtrate was evaporated to dryness. The residual oil was distilled to give **60**, bp 180–195° (3 mm), which slowly solidified on standing in moist air.

E. **2-Isopropyl-1-(1-naphthyl)ethanol (2).**—A solution of **68** (1.7 g, 0.0085 mole) in EtOH (10 ml) and Me_2CO (20 ml, 0.27 mole) was hydrogenated in the presence of Pt catalyst (0.43 g). The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residual solid (**2**) was crystallized from EtOAc.

1-Hydroxyiminoacetylnaphthalene (68).—AmONO (58.5 g, 0.5 mole) was added during 1 hr to a stirred solution of 1-acetonaphthone (85.0 g, 0.5 mole) in saturated ethereal HCl (500 ml). A further amount of saturated ethereal HCl (100 ml) was then added and after 1.5 hr the mixture was poured into 2 *N* NaOH (2000 ml) containing ice. The Et_2O layer was separated and thoroughly extracted with 1 *N* NaOH. The pH of the combined aqueous extracts was adjusted to 7 with concentrated HCl and **68** separated out, mp 137–138° (from $CHCl_3$), 26 g (28%). *Anal.* ($C_{12}H_9NO_2$) C, H, N.

2-Amino-1-(1-naphthyl)ethanol (67).—$NaBH_4$ (4 g, 0.105 mole) was added during 0.25 hr to a stirred suspension of aminomethyl 1-naphthyl ketone hydrochloride[20] (10 g, 0.045 mole) in EtOH (120 ml) at 5°. After 1 hr the mixture was poured into excess 2 *N* HCl containing ice and extracted with Et_2O (two 100-ml portions). The combined Et_2O extracts were washed twice with 2 *N* HCl, the combined acid solutions were made alkaline with 8 *N* NaOH, and the product was isolated by Et_2O extraction. The extract gave **67**, mp 125–126° (from EtOAc). *Anal.* ($C_{12}H_{13}NO$) C, H, N.

Reduction of 2-Isopropylamino-1-(2-naphthyl)ethanol to 2-

(17) K. Dziewonski, K. Stec, and P. Zagala, *Roczniki Chem.*, 18, 480 (1938); *Chem. Abstr.*, **33**, 1713 (1939).

(18) B. B. Dey and S. Rajagopalan, *Arch. Pharm.*, 277, 377 (1939).

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(20) Parke Davis and Co. Ltd., U. S. Patent 2,545,092 (1951); *Chem. Abstr.*, **45**, 7150 (1951).

Isopropylamino-1-(5,6,7,8-tetrahydro-2-naphthyl)ethanol (20).—A mixture of 2-isopropylamino-1-(2-naphthyl)ethanol[18] (10 g, 0.0435 mole), EtOH (10 ml), and Raney Ni (1 g) was hydrogenated at 125° and 125 atm for 6 hr. The mixture was cooled, EtOH (50 ml) was added, the mixture was filtered, and the filtrate was evaporated to dryness *in vacuo*. HCl (2 *N*, 50 ml) was added to the residue and the solution was washed with Et_2O (50 ml). NaOH (11 *N*, 20 ml) was added to the aqueous acidic solution and the product which separated was isolated by Et_2O extraction. The extract furnished **20**, mp and mmp 84–85° from petroleum ether.

2-Isopropylamino-1-(5,6,7,8-tetrahydro-2-naphthyl)ethanol (20) from 2-Benzylisopropylamino-1-(2-naphthyl)ethanol.—A solution of 2-benzylisopropylamino-1-(2-naphthyl)ethanol[18] (1 g, 0.003 mole) in EtOH (10 ml) containing concentrated HCl (0.05 ml) was hydrogenated in the presence of Pt (0.3 g). The mixture was filtered and the filtrate was evaporated to dryness. The residual solid (**20**) had mp and mmp 156–157° from EtOAc.

2-Isopropylamino-1-acenaphthenol (71).—Acenaphthenequinone monoxime[21] (2 g, 0.01 mole) was hydrogenated in EtOH (15 ml) and Me_2CO (20 ml, 0.27 mole) in the presence of Pt (0.43 g). The deep red mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc, decolorized by treatment with C, and then converted to the hydrogen oxalate, mp 184–186° dec from MeOH–Et_2O. *Anal.* ($C_{17}H_{19}NO_5$) C, H, N.

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The Synthesis of 2,4,5-Trihydroxyphenylalanine (6-Hydroxydopa). A Centrally Active Norepinephrine-Depleting Agent

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The synthesis of 2,4,5-trihydroxyphenylalanine (6-hydroxydopa) (III) was accomplished through the reaction of 2,4,5-tribenzyloxybenzyl bromide (II) with dibenzyl carbobenzyloxyaminomalonate, followed by reductive removal of the blocking groups and thermal decarboxylation of the resulting amino(2,4,5-trihydroxybenzyl)-malonic acid (VI). Alternate synthetic approaches (Schemes I and II) were unsuccessful. 6-Hydroxydopa was found to undergo enzymatic decarboxylation *in vitro* and *in vivo* to form 6-hydroxydopamine, a known norepinephrine-depleting agent. 6-Hydroxydopa in this way causes depletion of norepinephrine both in the peripheral and central nervous system. A concomitant reserpine-like syndrome is observed in mice.

Almost 10 years after the discovery of 2,4,5-trihydroxyphenethylamine (6-hydroxydopamine) as an autoxidation product and metabolite of dopamine[2-4] the importance of this amine as a pharmacological tool for the selective destruction of adrenergic nerve terminals has been realized.[5-7] The first metabolic studies with 6-hydroxydopamine indicated only the formation of O-methylated products *in vivo* and *in vitro*[8] while pharmacological studies indicated that its actions resembled that of guanethidine and reserpine.[9] These pharmacological effects were subsequently found to result from a prolonged depletion of peripheral norepinephrine and it was posulated that 6-hydroxydopamine produced an irreversible destruction of norepinephrine binding sites.[10] It was reported that free 6-hydroxydopamine or basic metabolites could not be detected in the heart 3 hr after administration of the drug,[11] but that when 6-hydroxydopamine-2′-^{14}C was utilized, radioactivity was found to persist in the heart for 2–3 weeks and to correlate with the extent of norepinephrine depletion.[12] It is now apparent that this persistent radioactivity results from an irreversible combination of 6-hydroxydopamine with tissue constituents.[7] The amine is actively concentrated by the adrenergic nerve terminal, where at low concentrations it serves as a "false transmitter," while at high concentrations it first functionally impairs nerve transmission and then produces degeneration of the nerve terminal.[7] These results are in agreement with the observations that depletion of norepinephrine by 6-hydroxydopamine is prevented[13-15] by agents such as cocaine, metaraminol, and desmethylimipramine which are known to inhibit the active transport of amines at the axon membrane.[16] Reserpine, however, does not appear to prevent depletion of norepinephrine by 6-hydroxydopamine.[14,15] This suggests that uptake of 6-hydroxydopamine by the norepinephrine storage granule, which presumably should be blocked by reserpine,[16] is not necessary to the activity of this drug. Bretylium, on the other hand, blocks the release of norepinephrine by reserpine and that caused by 6-hydroxydopamine as well.[14,15]

Related amines such as 6-hydroxynorepinephrine and 6-hydroxyepinephrine were also found to cause release of cardiac norepinephrine-^{3}H,[17] but neither of these compounds was as stable or as effective in causing depletion of norepinephrine as 6-hydroxydopamine. Two other compounds, α-methyl-6-hydroxydopamine and 6-aminodopamine, have been reported[13] as similar in action to 6-hydroxydopamine. No depletion of brain norepinephrine has been observed[13,14] with these amines.

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