β-Adrenergic Blocking Agents. III. The Optical Isomers of Pronethalol, Propranolol, and Several Related Compounds

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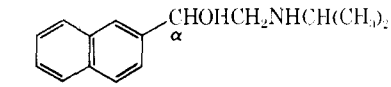
Pronethalol, propranolol, 2-(1,1-dimethyl-2-hydroxyethylamino)-1-(2-naphthyl)ethanol, 1-isopropylamino-3-(3-tolyloxy)-2-propanol, and 1-(3,4-dichlorophenyl)-2-isopropylaminoethanol (DCI) have been resolved. The (−) isomer was in each case the more potent adrenergic β-receptor antagonist, being twice as potent as the racemate and at least 40 times more potent than the (+) isomer. The absolute configuration (*R*) has been assigned to the (−) isomers of pronethalol and DCI by comparison of ORD curves. The four isomers of 2-(1-methyl-2-phenylethylamino)-1-(2-naphthyl)ethanol have been prepared and assigned absolute configurations.

In parts I[1] and II[2] the syntheses and biological properties of the adrenergic β-receptor antagonists 2-isopropylamino-1-(2-naphthyl)ethanol (**1**) (pronethalol[3]) and 1-isopropylamino-3-(1-naphthoxy)-2-propanol (**2**) (propranolol[4]) and many analogs were reported. Clinically propranolol has been shown to be of value in the treatment of angina pectoris, various cardiac arrhythmias, phaeochromocytoma, and hypertension.[5] It was necessary to provide the optical isomers of several adrenergic β-receptor antagonists for pharmacological and clinical studies. We report here the resolution of pronethalol, propranolol, 2-(1,1-dimethyl-2-hydroxyethylamino)-1-(2-naphthyl)ethanol (**3**),[1] and 1-isopropylamino-3-(3-tolyloxy)-2-propanol (**4**).[6] It was of particular interest to resolve 1-(3,4-dichlorophenyl)-2-isopropylaminoethanol (**5**, DCI)[7] to see whether adrenergic β-receptor blocking activity resided in one isomer and the undesirable sympathomimetic activity[8] in the other. The four possible isomers of 2-(1-methyl-2-phenylethylamino)-1-(2-naphthyl)ethanol (**6**)[1] have been prepared by asymmetric synthesis. Isopropyl-2-(2-naphthyl)ethylamine (**7**) and 1-(3-isopropylaminopropoxy)naphthalene (**8**), analogs of **1** and **2** which have H in place of OH, were prepared to compare their pharmacological properties with those of the optical isomers of **1** and **2**.

2-Isopropylamino-1-(2-naphthyl)ethanol (**1**) and 2-(1,1-dimethyl-2-hydroxyethylamino)-1-(2-naphthyl)-ethanol (**3**) were resolved[9] using the (+) and (−) forms of O,O-di-*p*-toluoyltartaric acid[10] as resolving agents. Subsequent attempts to use the (+) and (−) forms of tartaric acid as resolving agents for **1** were unsuccessful, even when (−)-base (+)-tartrate and (−)-base (−)-tartrate were used to seed (±)-base (+)-tartrate and (±)-base (−)-tartrate, respectively. 1-(3,4-Dichlorophenyl)-2-isopropylaminoethanol (**5**) was resolved readily using the (+) and (−) forms of tartaric acid. 1-Isopropylamino-3-(1-naphthoxy)-2-propanol (**2**) and 1-isopropylamino-3-(3-tolyloxy)-2-propanol (**4**) were resolved[11] using (−)-O,O-di-*p*-toluoyltartaric acid. For these two compounds the pure salts (+)-base (−)-acid and (−)-base (−)-acid were obtained by fractional crystallization of (±)-base (−)-acid.



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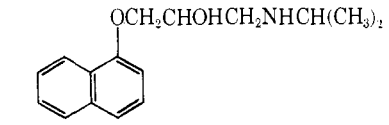

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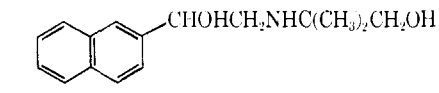

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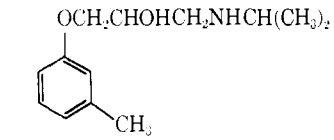

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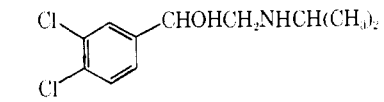

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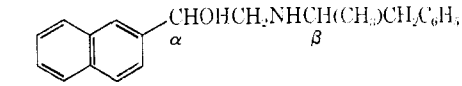

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Two optical isomers **6a** and **6b** were formed by reductive alkylation of (−)-amphetamine with 2-naphthylglyoxal using $NaBH_4$ as reducing agent.[1] The mixture of diastereoisomers thus obtained was separated by fractional crystallization. The other two isomers, **6c** and **6d**, were obtained similarly from (+)-amphetamine. Crystallization of a mixture of equal weights of the free bases of **6a** and **6c** gave the racemate (mp 93–94°) which was identical with that (**51B**) reported previously.[1]

Biological Results.—The compounds were initially

(1) R. Howe, A. F. Crowther, J. S. Stephenson, B. S. Rao, and L. H. Smith, *J. Med. Chem.*, **11**, 1000 (1968).
(2) A. F. Crowther and L. H. Smith, *ibid.*, **11**, 1009 (1968).
(3) Alderlin®.
(4) Inderal®.
(5) (a) R. Rabkin, D. P. Stables, N. W. Levin, and M. M. Suzman, *Amer. J. Cardiol.*, **18**, 370 (1966); (b) E. M. M. Bestermann and D. H. Friedlander, *Postgrad. Med. J.*, **41**, 526 (1965); (c) E. J. Ross, B. N. C. Prichard, L. Kaufman, A. I. G. Robertson, and B. J. Harries, *Brit. Med. J.*, **1**, 191 (1967); (d) B. N. C. Prichard and P. M. S. Gillam, *ibid.*, **2**, 725 (1964).
(6) A. F. Crowther, L. H. Smith, and T. M. Wood, British Patent 1,069,345 (1967).
(7) C. E. Powell and I. H. Slater, *J. Pharmacol. Exptl. Therap.*, **122**, 480 (1958).
(8) J. W. Black and J. S. Stephenson, *Lancet*, **11**, 311 (1962).
(9) R. Howe, British Patent 1,024,643 (1966).
(10) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 922 (1943).
(11) R. Howe, British Patent 1,069,343 (1967).

tested for their ability to block the tachycardia induced by isoproterenol in a chloralosed cat.[12,13] The results, except those for propranolol which have already been reported,[13] are shown in Table I.

TABLE I

Compd	Infusion rate, μg/kg/min	% change in heart rate	% inhib of tachycardia
(±)-1	50	−15	45
(−)-1	50	−11	83
(+)-1	100	−9	5
	1000	−18	53
(±)-3	100	−4	63
(−)-3	50	−12	57
(+)-3	100	+9	Nil
(±)-4	5	−15	48
(−)-4	2	−24	57
(+)-4	40	+3	7
(±)-5	50	+14	85
(−)-5	25	+36	94
(+)-5	200	+15	48
	800	−5	90
(+)-6a	400	−17	38
(−)-6b	25	+6	39
(−)-6c	25	0	31
(+)-6d	200	−9	Nil
Racemate 6a + c	50	+9	29
Racemate 6b + d	50	−4	34
7	1000	−8	45
8	100	−5	10

For compounds **1–5** the (−) isomer was the more potent adrenergic β-receptor antagonist, being twice as potent as the racemate and at least 40 times more potent than the (+) isomer. Compounds **7** and **8** had about the same potency as the (+) isomers of **1** and **2**, respectively. This observation is in line with the results obtained with (+)-epinephrine and (+)-norepinephrine and the related deoxy derivatives.[14] β-Receptor blocking activity and sympathomimetic activity both resided in the (−) isomer of DCI (**5**). The two (−) isomers **6a** and **6c** were about twice as potent as the corresponding racemates. One of the (+) isomers was inactive but the other did appear to have some β-receptor blocking activity. This is commented upon later.

More detailed pharmacology and clinical results on some of the compounds described here have been published elsewhere.[15] A previous report requires correction. We reported[13] that propranolol and its (+) isomer were both effective in abolishing ouabain-induced arrhythmias in cats while the (−) isomer had little effect. Recent work has shown that the (−) isomer is active at lower doses than were used previously.[16] The apparent lack of activity was a result of administering the active compound at too high a dose and producing an overt toxicity.

Stereochemistry.—Pratesi and coworkers have shown by chemical methods that (−)-norepinephrine,[17] (−)-epinephrine,[18] and (−)-isoproterenol,[19] the active isomers of these sympathomimetic agents, have the absolute configuration (*R*). Comparison of the ORD curves[20] of the (−) isomers of pronethalol and DCI, which show a negative Cotton effect at about 300 mμ, with those of (*R*)-(−)-norepinephrine, (*R*)-(−)-epinephrine, and (*R*)-(−)-isoproterenol[21,22] shows that they too can be assigned the (*R*) configuration. Thus the (*R*) configuration at the α asymmetric center is associated with a negative rotational contribution. The configurations of **6a** ($[\alpha]_D$ + 22.2°) and **6b** ($[\alpha]_D$ −57.5°) which were prepared from (*R*)-(−)-amphetamine[21] (which forms the β asymmetric center in **6**) can therefore be assigned the configurations (α*S*,β*R*) and (α*R*,β*R*), respectively. Similarly **6c** ($[\alpha]_D$ −21.2°) and **6d** ($[\alpha]_D$ +57.6°) produced from (*S*)-(+)-amphetamine are assigned the configurations (α*R*,β*S*) and (α*S*,β*S*). As expected β-blocking activity was highest in the two isomers in which the α center had the (*R*) configuration. Activity was best when the β center also had the (*R*) configuration. The β-blocking activity of the (+) isomer **6a** was rather higher than might have been expected from the other results, being about one-fifteenth that of the corresponding (−) isomer **6c**. It could be that the "wrong" stereochemistry at the α center was to some extent being compensated for by the "correct" stereochemistry at the β center. Adrenergic β-blocking activity decreased in the order (α*R*,β*R*) > (α*R*,β*S*) ≫ (α*S*,β*R*) > (α*S*,β*S*). This is the same order as that reported[23] for the four isomers of 2-*sec*-butylamino-1-(5,6,7,8-tetrahydro-2-naphthyl)ethanol.[24]

Experimental Section[25,26]

The following resolution of **1** and the conversion of the optically active salts to the corresponding free bases is typical of those listed in Table II. When two enantiomers of the resolving acid were used the second salt listed was prepared from crude partially resolved base recovered from the mother liquors from the crystallization of the first salt. It is to be understood that when only one enantiomer of the resolving acid was used, *e.g.*, with **2** and **4**, then the salt which crystallized first is listed first. The other salt was obtained from the mother liquors.

(+)-2-Isopropylamino-1-(2-naphthyl)ethanol [(+)-1].—A solution of 20.0 g (0.0875 mole) of (±)-**1** and 16.85 g (0.0436 mole) of (−)-O,O-di-*p*-toluoyltartaric acid in 170 ml of MeOH and 90 ml of H_2O at 50° was cooled slowly to room temperature. The solid which separated was isolated by filtration and the filtrate was retained for further examination. The solid (21 g), mp 98–100°, $[\alpha]^{21}_D$ −60° (*c* 1, EtOH), was crystallized from aqueous 66% MeOH (by volume) until the rotation became

(12) 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).

(13) R. Howe and R. G. Shanks, *Nature*, **210**, 1336 (1966).

(14) E. J. Ariëns, *Proc. Intern. Pharmacol. Meeting, 1st, Stockholm, Aug 1961*, **7**, 247 (1963).

(15) (a) B. R. Lucchesi, *J. Pharmacol. Exptl. Therap.*, **148**, 94 (1965); (b) L. S. Whitsitt and B. R. Lucchesi, *Life Sci.*, **6**, 939 (1967); (c) R. G. Shanks and D. Dunlop, *Cardiovascular Res.*, **1**, 34 (1967); (d) G. Howitt, E. G. Wade, M. Husaini, W. F. W. E. Logan, and R. G. Shanks, *Brit. Heart J.*, **29**, 442 (1967); (e) L. S. Whitsitt and B. R. Lucchesi, *Circulation Res.*, **21**, 305 (1967); (f) W. W. Parmley and E. Braunwald, *J. Pharmacol. Exptl. Therap.*, **158**, 11 (1967); (g) J. Levy and V. Richards, *Proc. Soc. Exptl. Biol. Med.*, **122**, 373 (1966).

(16) M. Barrett and V. A. Cullum, *Brit. J. Pharmacol.*, in press.

(17) P. Pratesi, A. La Manna, A. Campiglio, and V. Ghislandi, *J. Chem. Soc.*, 4062 (1959).

(18) P. Pratesi, A. La Manna, A. Campiglio, and V. Ghislandi, *ibid.*, 2069 (1958).

(19) P. Pratesi, A. La Manna, A. Campiglio, and G. Pagani, *Farmaco (Pavia), Ed. Sci.*, **15**, 3 (1960).

(20) Kindly determined by Professor W. Klyne. A manually operated Rudolf polarimeter was used

(21) G. G. Lyle, *J. Org. Chem.*, **25**, 1779 (1960).

(22) A. Campiglio, *Farmaco* (Pavia), *Ed. Sci.*, **19**, 377 (1964).

(23) C. Casagrande and G. Ferrari, *ibid.*, **21**, 225 (1965).

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

(25) 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.

(26) Further experimental details are given in ref 9 and 11.

TABLE II

Compd	Final crystn solvent	Mp, °C	$[\alpha]^{21}D$, deg	Concn in EtOH, %	Formula	Analyses
(+)-1 (−)-O,O-di-*p*-toluoyltartrate trihydrate[a]	MeOH + H_2O	106–108	−41.5	1.08	$C_{50}H_{56}N_2O_{10}\cdot 3H_2O$	C, H, N; H_2O[b]
(+)-1 (−)-O,O-di-*p*-toluoyltartrate[c]		113–114	−45.0	1.3	$C_{50}H_{56}N_2O_{10}$	C, H, N
(+)-1	EtOAc	108–109	+28.4	0.99	$C_{15}H_{19}NO$	C, H, N
(+)-1 hydrochloride	MeOH + EtOAc	209–210	+52.3	1.02	$C_{15}H_{20}ClNO$	C, H, Cl, N
(−)-1 (+)-O,O-di-*p*-toluoyltartrate trihydrate[d]	MeOH + H_2O	106–108	+41.4	0.97	$C_{50}H_{56}N_2O_{10}\cdot 3H_2O$	H_2O[e]
(−)-1 (+)-O,O-di-*p*-toluoyltartrate[c]		113–114	+45.0	1.0	$C_{50}H_{56}N_2O_{10}$	H, N; C[f]
(−)-1	EtOAc	108–109	−29.0[g]	1.3	$C_{15}H_{19}NO$	C, H, N
(−)-1 hydrochloride	MeOH + EtOAc	209–210	−52.6	1.02	$C_{15}H_{20}ClNO$	C, H, Cl, N
(−)-1 (+)-tartrate	MeOH + EtOAc	182	−26.3[g]	1.01	$C_{34}H_{44}N_2O_8$	C, H, N
(−)-1 (−)-tartrate	MeOH + EtOAc	182	−51.0	0.98 in H_2O	$C_{34}H_{44}N_2O_8$	C, H, N
(+)-2 hydrogen (−)-O,O-di-*p*-toluoyltartrate hydrate[a]	MeOH	170	−62.0	1.01	$C_{36}H_{39}NO_{10}\cdot H_2O$[h]	H_2O
(+)-2	P(40–60°)[i]	73	+10.6	1.02	$C_{16}H_{21}NO_2$	C, H, N
(+)-2 hydrochloride	MeOH + EtOAc	192	+22.2	0.99	$C_{16}H_{22}ClNO_2$	C, H, N
(−)-2 hydrogen (−)-O,O-di-*p*-toluoyltartrate hydrate[a]	MeOH	166–167	−89.0	1.0	$C_{36}H_{39}NO_{10}\cdot H_2O$[j]	H_2O[k]
(−)-2	P(40–60°)[i]	73	−10.2	1.02	$C_{16}H_{21}NO_2$	C, H, N
(−)-2 hydrochloride	MeOH + EtOAc	192	−22.7	1.0	$C_{16}H_{22}ClNO_2$	C, H, N
(−)-3 hydrogen (−)-O,O-di-*p*-toluoyltartrate[a]	MeOH[l]	162–163	−96.2	1.01	$C_{36}H_{39}NO_{10}$	H, N; C[m]
(−)-3	EtOAc	116–117	−26.6	1.0	$C_{16}H_{21}NO_2$	H, N; C[n]
(+)-3 hydrogen (+)-O,O-di-*p*-toluoyltartrate[a]	MeOH	162–163	+97.5	1.01	$C_{36}H_{39}NO_{10}$	C, H, N
(+)-3	EtOAc	116–117	+27.6	1.03	$C_{16}H_{21}NO_2$	C, H, N
(+)-4 hydrogen (−)-O,O-di-*p*-toluoyltartrate hydrate[a]	MeOH + H_2O[o]	148–149	−63.1	1.0	$C_{33}H_{39}NO_{10}\cdot H_2O$	C, H, N
(+)-4	P(40–60°)[i]	54–55	+10.0	1.08	$C_{13}H_{21}NO_2$	C, H, N
(+)-4 hydrochloride	MeOH + EtOAc	119	+28.0	1.0	$C_{13}H_{22}ClNO_2$	C, H, Cl, N
(−)-4 hydrogen (−)-O,O-di-*p*-toluoyltartrate[a]	MeOH + H_2O	164	−95.2[p]	1.0	$C_{33}H_{39}NO_{10}$	C, H, N
(−)-4	P(40–60°)[i]	54–55	−9.9[p]	0.99	$C_{13}H_{21}NO_2$	C, H, N
(−)-4 hydrochloride	MeOH + EtOAc	119	−27.4[p]	1.01	$C_{13}H_{22}ClNO_2$	C, H, Cl, N
(−)-5 hydrogen (+)-tartrate[a]	MeOH[q]	162	−20.2	1.08 in H_2O	$C_{21}H_{21}Cl_2NO_5$	C, H, Cl, N
(−)-5	P(40–60°)[i]	101	−24.1[r]	0.97	$C_{11}H_{15}Cl_2NO$	C, H, Cl, N
(−)-5 hydrochloride	MeOH + EtOAc	177–178	−46.0	0.98	$C_{11}H_{16}Cl_3NO$	C, H, Cl, N
(+)-5 hydrogen (−)-tartrate[a]	MeOH	162	+20.5	1.18 in H_2O	$C_{21}H_{21}Cl_2NO_5$	C, H, Cl N
(+)-5	P(40–60°)[i]	101	+24.7	1.03	$C_{11}H_{15}Cl_2NO$	C, H, Cl, N
(+)-5 hydrochloride	MeOH + EtOAc	177–178	+46.6	1.03	$C_{11}H_{16}Cl_3NO$	C, Cl, N; H[s]
(+)-5 hydrogen (+)-tartrate	MeOH + EtOAc	89–90	+37.4	0.99 in H_2O	$C_{21}H_{21}Cl_2NO_5$	C, H, N; Cl[t]
(+)-6a hydrochloride	MeOH	172–173	+26.1	1.01	$C_{21}H_{24}ClNO$	C, H, N
(+)-6a	EtOAc	105–106	+22.2	1.01	$C_{21}H_{23}NO$	C, H, N
(−)-6b hydrochloride	MeOH	168–169	−60.6	0.99	$C_{21}H_{24}ClNO$	C, H, N
(−)-6b	EtOAc + P(40–60°)[i]	65–66	−57.7	1.05	$C_{21}H_{23}NO$	C, H, N
(−)-6c hydrochloride	MeOH	172–173	−25.6	1.04	$C_{21}H_{24}ClNO$	C, H, N
(−)-6c	EtOAc	105–106	−21.2	1.01	$C_{21}H_{23}NO$	C, H, N
(−)-6d hydrochloride	MeOH	168–169	+60.2	0.97	$C_{21}H_{24}ClNO$	C, H, N
(−)-6d	EtOAc + P(40–60°)[i]	65–66	+57.6	1.0	$C_{21}H_{23}NO$	C, H, N

[a] Salt obtained by resolution. [b] H_2O: calcd, 6.0; found, 6.6. [c] Obtained by heating the trihydrate salt at 60° *in vacuo* for 3 hr. [d] H_2O: calcd, 6.0; found, 6.5. [e] C: calcd, 71.4; found, 70.4. [f] RD (*c* 0.11, MeOH), room temperature; $[\phi]_{600}$ −10°, $[\phi]_{500}$ −40°, $[\phi]_{400}$ −125°, $[\phi]_{350}$ −160°, $[\phi]_{330}$ −175°, $[\phi]_{320}$ −55°. [g] $[\alpha]^{21}D$ −30.0° (*c* 0.99, H_2O). [h] The anhydrous salt was obtained by drying *in vacuo* at 100°. *Anal.* ($C_{36}H_{39}NO_{10}$) H, N; C: calcd, 66.9; found, 66.4. [i] Petroleum ether, bp 40–60°. [j] The anhydrous salt was obtained by drying *in vacuo* at 100°. *Anal.* ($C_{36}H_{39}NO_{10}$) C, H, N. [k] H_2O: calcd, 2.7; found, 2.2. [l] After the first crystallization from MeOH + H_2O (2:1 by volume). [m] C: calcd, 67.0; found, 66.4. [n] C: calcd, 74.1; found, 73.5. [o] 2:1 by volume. [p] $[\alpha]^{20}D$. [q] After the first crystallization from MeOH + EtOAc (1:2 by volume). [r] RD (*c* 0.11, MeOH), room temperature; $[\phi]_{600}$ −30°, $[\phi]_{500}$ −70°, $[\phi]_{400}$ −145°, $[\phi]_{350}$ −200°, $[\phi]_{330}$ −225°, $[\phi]_{315}$ −260°, $[\phi]_{310}$ −250°, $[\phi]_{300}$ −240°, $[\phi]_{250}$ −225°. [s] H: calcd, 5.6; found, 6.1. [t] Cl: calcd, 17.8; found, 17.3.

constant. (+)-**1** (−)-O,O-di-*p*-toluoyltartrate trihydrate was obtained.

The free base was obtained by shaking a mixture of 8.75 g of (+)-**1** (−)-O,O-di-*p*-toluoyltartrate trihydrate and 50 ml of 0.5 *N* NaOH with C_6H_6 (three 80-ml portions). The C_6H_6 extract furnished (+)-**1**.

(−)-2-Isopropylamino-1-(2-naphthyl)ethanol [(−)-1].—The filtrate retained in the above experiment was evaporated *in vacuo*

at 25° to remove MeOH. NaOH (100 ml, 0.5 *N*) was added to the residue and the mixture was extracted with C_6H_6. This extract furnished crude product, mp 102°, $[\alpha]^{21}D$ −17.3° (*c* 0.98, EtOH). A solution of 9 g (0.0393 mole) of this crude base and 7.58 g (0.0196 mole) of (+)-O,O-di-*p*-toluoyltartaric acid in 60 ml of MeOH and 45 ml of H_2O at 50° was cooled slowly to room temperature. The solid which separated was isolated and crystallized from aqueous 66% MeOH (by volume) until the rotation became constant. (−)-**1** (+)-O,O-di-*p*-toluoyltartrate trihydrate was obtained.

(αS,βR)-(+)-2-(1-Methyl-2-phenylethylamino)-1-(2-naphthyl)ethanol and (αR,βR)-(−)-2-(1-Methyl-2-phenylethylamino)-1-(2-naphthyl)ethanol.—$NaBH_4$ (5 g) was added during 30 min to a stirred solution of 2-naphthylglyoxal hydrate (21.5 g, 0.106 mole) and (*R*)-(−)-1-methyl-2-phenylethylamine (13.6 g, 0.101 mole) in MeOH (180 ml) at 0°. The mixture was stirred for 16 hr and then the solvent was evaporated. HCl (500 ml, 1 *N*) was added to the residue and the mixture was extracted with $CHCl_3$ (300 ml). The extract was washed (H_2O) and dried, and then the $CHCl_3$ was evaporated. The residual oil was dissolved in EtOAc (30 ml) and ethereal HCl was added until a slight excess of HCl was present. Et_2O was added and the solid which separated was isolated by filtration, the filtrate being retained for further examination. The solid, mp 167–168°, $[\alpha]^{21}D$ +23.1° (*c* 0.97, EtOH), was crystallized from MeOH–EtOAc and then from MeOH until the rotation became constant. (αS,βR)-(+)-**6** hydrochloride was obtained.

The Et_2O–EtOAc filtrate retained above and the MeOH–EtOAc mother liquors remaining after as much of the (αS,βR)-(+) isomer as possible had been removed were combined and evaporated to small volume. The solid, mp 145–146°, $[\alpha]^{21}D$ −40.6° (*c* 0.98, EtOH), which separated on cooling the solution was recrystallized from MeOH–EtOAc and then from MeOH until the rotation became constant. (αR,βR)-(−)-**6** hydrochloride was obtained.

(αR,βS)-(−)-2-(1-Methyl-2-phenylethylamino)-1-(2-naphthyl)ethanol and (αS,βS)-(+)-2-(1-Methyl-2-phenylethylamino)-1-(2-naphthyl)ethanol.—The previous experiment was repeated using (*S*)-(+)-1-methyl-2-phenylethylamine in place of (*R*)-(−)-1-methyl-2-phenylethylamine.

Racemic 2-(1-Methyl-2-phenylethylamino)-1-(2-naphthyl)-ethanol.—Equal weights of (αS,βR)-(+)- and (αR,βS)-(−)-2-(1-methyl-2-phenylethylamino)-1-(2-naphthyl)ethanol were mixed and the mixture was crystallized from EtOAc–petroleum ether (bp 40–60°). The racemate formed prisms, mp 93–94°, identical in melting point, mixture melting point, and ir spectrum with the racemate **51B**.[1]

Isopropyl-2-(2-naphthyl)ethylamine.—A solution of 2-(2-naphthyl)ethylamine (0.88 g) in EtOH (20 ml) and Me_2CO (5 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of PtO_2 (0.3 g). The organic base was isolated, dissolved in EtOAc, and converted to the hydrochloride by adding ethereal HCl. Isopropyl-2-(2-naphthyl)ethylamine hydrochloride formed plates, mp 206–207°, from MeOH–EtOAc. *Anal.* ($C_{15}H_{22}ClNO$) C, H, N.

1-(3-Isopropylaminopropoxy)naphthalene.—1-Naphthol (21.6 g) was added to a solution of Na (3.45 g) in absolute EtOH (120 ml). The resulting solution was added during 1 hr to a boiling solution of 1-bromo-3-chloropropane (30 ml) in absolute EtOH (60 ml). The mixture was refluxed overnight and then the EtOH was evaporated. The residue was shaken with a mixture of H_2O and Et_2O. The Et_2O extract was washed with 5% NaOH (400 ml) and then H_2O and dried. The Et_2O was evaporated and the 1-(3-chloropropoxy)naphthalene was distilled, bp 164–168° (2 mm). 1-(3-Chloropropoxy)naphthalene (3 g) and *i*-$PrNH_2$ (10 ml) were heated at 100° for 10 hr in a sealed tube. Excess *i*-$PrNH_2$ was evaporated, 2 *N* NaOH (25 ml) was added, and the mixture was extracted with Et_2O. The extract was dried and then a slight excess of ethereal HCl was added. 1-(3-Isopropylaminopropoxy)naphthalene hydrochloride was obtained; mp 185–186°, from MeOH–EtOAc. *Anal.* ($C_{16}H_{22}ClNO$) C, H, N.

Some Epinephrine Analogs

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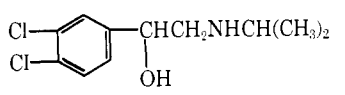
A number of epinephrine analogs and corresponding 1-aryl-2-alkylaminoethyl chloride hydrochlorides and bromide hydrobromides have been prepared. The central intermediates of the syntheses were the 5-aryl-3-alkyl-2-oxazolidones (IV), accessible by alkylation of the product obtained using the Reformatzky reaction of an aromatic aldehyde with ethyl bromoacetate. The results of a pharmacological study of the products obtained are summarized.

Based on the great variety of epinephrine analogs which have been studied, some theories have been advanced regarding the correlation between structure and activity, especially in the case of antiadrenergic activity.[1] The latter has been observed in halogen-substituted compounds carrying halogen either in the benzene ring of the 2-alkylamino-1-phenylethanol skeleton or instead of the hydroxyl group in this structure. An example of the former is dichloroisoproterenol (I), which blocks the β-adrenergic receptors;[2] examples for the second group, the α-adrenergic receptor blocking agents, have been described, *e.g.*, by Chapman and Triggle,[3] and investigated pharmacologically by Hunt,[4] Ferguson and Wescoe,[5] and Graham and Karrar.[6]

An additional stimulus for a further study of this series was the observation that epinephrine accelerates glycolysis in the liver and in the muscle.[7]



I

One of the aims of this investigation was to prepare and study the nuclear-fluorinated 2-amino- and 2-alkylamino-1-phenylethanols and the corresponding 1-

(1) *Cf.* (a) N. B. Chapman, K. Clarke, and R. D. Strickland, *Proc. Roy. Soc.* (London), **163B**, 116 (1965); (b) N. B. Chapman and G. D. P. Graham in "Drugs Affecting the Peripheral Nervous System," A. Burger, Ed., Marcel Dekker, Inc., New York, N. Y., 1967, p 473 ff; (c) B. Belleau, *Can. J. Biochem. Physiol.*, **36**, 731 (1958); (d) D. J. Triggle, *J. Theoret. Biol.*, **7**, 241 (1964); (e) B. Belleau, *Ann. N. Y. Acad. Sci.*, **139**, 580 (1967).

(2) B. Levy and R. P. Ahlquist, *J. Pharmacol. Exptl. Therap.*, **130**, 334 (1960); E. E. Vogin and W. W. Baker, *Am. J. Pharm.*, **133**, 314 (1961).

(3) N. B. Chapman and D. J. Triggle, *J. Chem. Soc.*, 1358 (1963).

(4) C. C. Hunt, *J. Pharmacol. Exptl. Therap.*, **95**, 177 (1949).

(5) F. C. Ferguson and W. C. Wescoe, *ibid.*, **100**, 100 (1950).

(6) G. D. P. Graham and M. A. Karrar, *J. Med. Chem.*, **6**, 103 (1963).

(7) *Cf.* A. Holzbauer and J. H. Gaddum, *Vitamins Hormones*, **15**, 151 (1957).