β-Adrenergic Blocking Agents. 9. Absolute Configuration of Propranolol and of a Number of Related Aryloxypropanolamines and Arylethanolamines

M. DUKES AND L. H. SMITH*

Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England

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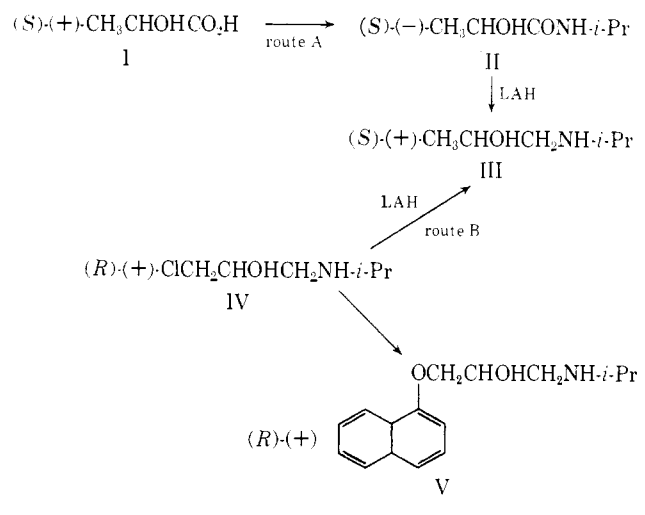
(+)-Propranolol has been shown to possess the *R* absolute configuration by correlation with (*S*)-(+)-lactic acid. The configurations of a number of aryloxypropanolamines have been related to the configuration of propranolol using Horeau's method of partial asymmetric synthesis.

In part III[1] the resolutions of a number of adrenergic β-receptor antagonists including 2-isopropylamino-1-(2-naphthyl)ethanol (pronethalol[2]) and 1-isopropylamino-3-(1-naphthoxy)-2-propanol (propranolol[3]) and the biological properties of their stereoisomers were reported. It was established that the ability to antagonize the effects of isoproterenol by compounds in both the arylethanolamine and aryloxypropanolamine series resides in the *l* isomers to a much greater extent than in the *d* isomers. Other workers have reported similar findings for 1-isopropylamino-3-(2-allylphenoxy)-2-propanol[4] and nifenalol.[5]

In the cases of pronethalol[1] and nifenalol[5] it has been reported that the *l* isomers possess the same (*R*) absolute configuration as that of the naturally occurring sympathomimetic catecholamines. We were interested to know the absolute configurations of other adrenergic β-receptor antagonists, particularly of the aryloxypropanolamine series.

To provide unequivocally the absolute configuration of a typical member of the aryloxypropanolamine series we have chemically related (+)-propranolol (V) to (+)-lactic acid (I) through the propanolamine derivative (III) (Scheme I). None of the reactions affects the

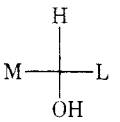
SCHEME I



asymmetric center. *l*-Propranolol therefore possesses the *S* absolute configuration which is stereochemically equivalent to the *R* configuration of the levorotatory arylethanolamines.

The correlation of the greater biological activity with the *l* isomers suggests that these may possess a common absolute configuration. To test this possibility we sought a simple means of determining the absolute configuration of any aryloxypropanolamine or arylethanolamine or at least a means of relating its configuration to that of an analog of known configuration. We here report the application of Horeau's method of partial asymmetric synthesis[6] to these compounds.

Horeau's method involves the partially asymmetric acylation of an optically active secondary alcohol with an excess of the acyl chloride or anhydride of 2-phenylbutyric acid. The configuration of the alcohol is linked to the sign of rotation of the recovered 2-phenylbutyric acid. If the acid is levorotatory the alcohol has the absolute configuration implicit in the Fischer projection



in which L represents a more sterically hindering group than M.

Horeau suggests that the anhydride of 2-phenylbutyric acid is superior to the acid chloride since, in pyridine, the latter more rapidly racemizes and thereby nullifies the asymmetry of the acylation. With (−)-1-isopropylamino-3-(1-naphthoxy)-2-propanol·HCl (**2**), however, the reaction with the anhydride was slow and the recovered acid was only feebly optically active [$[\alpha]^{20}D$ + 3.14° (*c* 17.6, MeOH)]. The acid chloride with **2** gave much more satisfactory results (Table I) and the optical activity was only reduced by half during 16 hr from the value after 2 hr [$[\alpha]^{20}D$ + 13.2° (*c* 5.0, MeOH)].

The oily nature of the product from the acylations of aryloxpropanolamine and arylethanolamine derivatives rendered their characterization difficult. However, on examining the reaction mixture of propranolol·HCl at intervals throughout the course of the reaction, it was possible to assign ir absorption maxima to the various components of the mixture. The ν_{max} 1810 cm^{-1} due to the acid chloride was extinguished over 3 hr and a strong ν_{max} 1740 cm^{-1} due to O-acylation appeared within minutes while even after 20 hr only a weak ν_{max} 1645 cm^{-1} due to N-acylation was present (ν_{max} 1710 cm^{-1} also appeared during the reaction, presumably due

(1) R. Howe and B. S. Rao, *J. Med. Chem.*, **11**, 1118 (1968).
(2) Alderlin.
(3) Inderal.
(4) B. Ablad, G. Johnson, A. Norby, and L. Sölvell, *Acta Pharmacol. Toxicol.*, **25**, 85 (1967).
(5) L. Almirante and W. Murmann, *J. Med. Chem.*, **9**, 650 (1966).
(6) (a) A. Horeau, *Tetrahedron Lett.*, 506 (1961). (b) A. Horeau, *ibid.*, 965 (1962). (c) A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964). (d) A. Horeau, A. Nouaille, and K. Mislow, *J. Amer. Chem. Soc.*, **87**, 4957 (1965). (e) A. Horeau and A. Nouaille, *Tetrahedron Lett.*, 3953 (1966).

Table I
Propanolamines

	Compound	Rotation of 2-phenylbutyric acid in MeOH, degrees	Absolute configuration	ED_{50},[a] μg/kg per min
1	(+)-1-Isopropylamino-3-(1-naphthoxy)-2-propanol·HCl	−7.8 (*c* 3.8)	*R*	90.6
2	(−)-1-Isopropylamino-3-(1-naphthoxy)-2-propanol·HCl	+6.2 (*c* 5.5)	*S*	1
3	(−)-1-Isopropylamino-3-(1-naphthoxy)-2-propanol	+4.05 (*c* 4.6)	*S*	
4	(−)-1-Isopropylamino-3-(4-methoxy-1-naphthoxy)-2-propanol·HCl	+7.0 (*c* 5.2)	*S*	8.4 (15)[b]
5	(+)-1-Isopropylamino-3-(4-acetylaminophenoxy)-2-propanol·HCl	−6.15 (*c* 5.9)	*R*	110
6	(−)-1-Isopropylamino-3-(4-acetylaminophenoxy)-2-propanol·HCl	+4.6 (*c* 8.1)	*S*	5
7	(−)-1-Isopropylamino-3-(2-allylphenoxy)-2-propanol·HCl	+7.5 (*c* 6.2)	*S*	0.56 (4)[b]
8	(+)-1-Isopropylamino-3-(2-ethoxyphenoxy)-2-propanol·HCl	−18.6 (*c* 11.5)	*R*	(2)[b]
9	(−)-1-(*N*-Benzyl-*N*-isopropylamino)-3-(1-naphthoxy)-2-propanol	+3.35 (*c* 5.8)	*R*	
10	(−)-1-(*N*-Benzyl-*N*-isopropylamino)-3-(1-naphthoxy)-2-propanol·HCl	+5.5 (*c* 5.2)	*R*	

Table II
Ethanolamines

	Compound	Rotation of 2-phenylbutyric acid in MeOH, degrees	Absolute configuration	ED_{50},[a] μg/kg per min
11	(−)-Epinephrine	−5.95 (*c* 7.0)	*R*	
12	(+)-2-Isopropylamino-1-(2-naphthyl)ethanol·HCl	+14.7 (*c* 7.1)	*S*	600 (50)[b]
13	(−)-2-Isopropylamino-1-(*p*-nitrophenyl)ethanol·HCl	−13.9 (*c* 5.0)	*R*	31
14	(+)-2-Isopropylamino-1-(*p*-nitrophenyl)ethanol·HCl	+11.75 (*c* 5.5)	*S*	400

[a] These data were kindly supplied by Professor A. M. Barrett. [b] The figure in parentheses refers to the ED_{50} of the racemic compound.

to hydrolysis of acid chloride by H_2O absorbed by the pyridine). This evidence suggests that the asymmetric O-acylation precedes N-acylation; an initial, rapid N-acylation followed by rapid migration of the acyl function from N to O is precluded by kinetic and thermodynamic considerations. The asymmetry of the acylation is itself therefore governed by the relative steric bulks of the aryloxymethyl and isopropylaminomethyl moieties as present in pyridine solution.

The results obtained with a number of aryloxypropanolamines are shown in Table I. With one exception, that of the tertiary base (−)-1-(*N*-benzyl-*N*-isopropylamino)-3-(1-naphthoxy)-2-propanol (**9**), the results are self-consistent; all the *l* isomers of the secondary amines left (+)-2-phenylbutyric acid in excess and the *d* isomers left the (−)-acid in excess. This we believe provides useful evidence that the more biologically active *l* isomers possess the same absolute configuration.

While it relates the configurations of these aryloxypropanolamines, the Horeau method does not itself provide the absolute configuration since it is not obvious whether to assign the aryloxymethyl or the isopropylaminomethyl as the more hindering group. However, incorporating the absolute configurations of (+)- and (−)-propranolol provided by the correlation with lactic acid, establishes that the isopropylaminomethyl group does in fact provide the greater hindrance to the acylation of the OH group.

This information emphasizes the exceptional behavior of the tertiary base **9**. The absolute configuration of **9** is necessarily *R* since it is derived from (+)-propranolol (**1**).[7] Relating this configuration to the results of the asymmetric acylation reveals that, in this case, the amino function carrying the additional benzyl group actually serves as the lesser hindering group. This apparent anomaly is of interest and will be examined further.

(7) L. H. Smith, British Patent 1,136,918 (1968).

The results obtained with three arylethanolamines are shown in Table II. These are again self-consistent and, taking the aryl group to be the more hindering,[8] accord with the absolute configurations previously reported for these compounds.[1,5]

Experimental Section[9-12]

The esterifications of the alkanolamines listed in Tables I and II and the recovery of the optically active 2-phenylbutyric acid were carried out by the following procedure.

A mixt of (−)-1-isopropylamino-3-(1-naphthoxy)-2-propanol·HCl (1.5 g, 0.005 mole), 2-phenylbutyryl chloride (1.8 g, 0.01 mole), and AR pyridine (50 ml) was stirred at room temp for 18 hr. The mixt was poured onto a mixt of ice (100 g) and 11 *N* HCl (60 ml) and extd twice with Et_2O (50 ml). The combined Et_2O exts were extd twice with 50 ml of satd aq $NaHCO_3$. The combined $NaHCO_3$ solns were cooled and acidified with 11 *N* HCl and extd twice with Et_2O (50 ml). The dried Et_2O ext was evapd and the oily residue was seeded with 2-phenylbutyric acid. The crystalline acid obtained was dried at room temp *in vacuo* over P_2O_5: $[\alpha]^{20}D$ + 6.2 (*c* 2.7, MeOH); the ir spectrum was in accord with Sadtler standard spectra No. 5873.

(+)-1-Isopropylamino-2-propanol (III). Route A.—(*S*)-(+)-Lactic acid (I) (2.5 g) was converted into its Me ester with ethereal CH_2N_2 and isolated by evapn of the Et_2O. The ester was boiled under reflux in *i*-$PrNH_2$ (20 ml) for 18 hr and the excess amine then evapd *in vacuo*. The product (II) (3.45 g) possessed ν_{max} 1650 cm^{-1} and $[\alpha]^{20}D$ −22.8° (*c* 0.9, MeOH) and was used without further purification.

A soln of II (3.45 g) in anhyd Et_2O (50 ml) was added over 15 min to a suspension of LAH (1.3 g) in Et_2O (100 ml) and the mixt was refluxed for 4 hr. Excess hydride was decompd with EtOAc (25 ml), then H_2O (150 ml) was added, and the org layer was removed. The aq phase was treated with 4 *N* NaOH (25 ml) and continuously Et_2O extd for 8 hr. The Et_2O soln was dried [mol sieve

(8) H. Falk and K. Schloegl, *Monatsh. Chem.*, **96**, 276 (1965).

(9) All melting points were taken using open capillaries and are uncorrected.

(10) All specific rotations were measured on a Bellingham and Stanley visual polarimeter using the Na D line.

(11) Glc data was obtained with a Pye 104 Model 64 dual FID instrument.

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

(type 4A)] and evapd *in vacuo* at room temp. The residual oil was purified by glc. The major product was 1-isopropylamino-2-propanol (III) which had retention time 8.7 min on a column, 1.52 m × 0.63 cm of 10% Carbowax, 2 *M*, and 5% KOH on Chromosorb W (60–80 mesh), at 110° with flow rate 40 ml/min (N_2). It possessed the following nmr features[13] in $CDCl_3$: 8.94, d, J = 6 cps, 6 H; 8.85, d, J = 6 cps, 3 H; 7.7 q (A component of ABX system), J_{AB} cps, J_{AX} = 4.5 cps, 1 H; 7.3, q (B of ABX) J_{BX} = 2 cps, 1 H; 7.22, septet, J = 6 cps, 1 H; 6.26, m (X of $ABXY_3$), 1 H; 7.53, b, 2 H exchangeable; and had $[\alpha]^{20}D$ + 48° (*c* 6.0, $CDCl_3$).

(+)-1-Isopropylamino-2-propanol (III). Route B.—LAH (2 g) was added during 15 min to a stirred soln of (+)-1-chloro-3-isopropylaminopropan-2-ol (−)-di-*O,O*-*p*-toluoyltartrate (5.4 g) in dry THF at 5–10°. The mixt was refluxed for 3 hr and cooled and H_2O (2 ml), 2 *N* NaOH (2 ml), and H_2O (6 ml) were then added. The mixt was filtered and the THF was removed by distn at 1 atm; the residue consisted of an aq and an oily phase. The solid residue from the filtration was combined with the aq phase and the mixt was Et_2O extd continuously for 18 hr. The Et_2O ext was dried ($MgSO_4$) and evapd at 1 atm. The residual oil was purified by glc.

The major product had identical glc and nmr characteristics to those of the product of route A, and possessed $[\alpha]^{20}D$ + 46.4° (*c* 5.5, $CDCl_3$).

(+)-1-Chloro-3-isopropylamino-2-propanol (−)-Di-*O,O*-*p*-toluoyltartrate (IV).—A mixt of 2 *N* NaOH (15m l), 1-chloro-3-isopropylamino-2-propanol·HCl (27.36 g), H_2O (450 ml), and NaCl (150 g) was extd 4 times with 300 ml of Et_2O. The Et_2O exts were dried ($MgSO_4$) and added to a soln of (−)-di-*O,O*-*p*-toluoyltartaric acid (69.6 g) in Et_2O (200 ml). The mixt was filtd and the solid residue was crystd 5 times from *i*-PrOH, yield 6 g, mp softens 100°, decomp 140–144°. A sample was converted into the hydrochloride, mp 106°, $[\alpha]^{20}D$ + 25.9° (*c* 2.0, EtOH).

1-Chloro-3-isopropylamino-2-propanol·HCl.—A soln of *i*-Pr-NH_2 (85 ml) in MeOH (400 ml) was added slowly with stirring to epichlorohydrin (15.6 ml) at 25°. The mixt was stirred for 2 hr at ambient temp and then evapd under reduced pressure. The residue was distd; bp 72–76° (2.8 mm). The distillate was dissolved in Et_2O (100 ml) and acidified with ethereal HCl. The mixt was filtered and the solid residue was crystd twice from CPrOH–Et_2O (1:2); yield 3.65 g (10%), mp 93–94°. *Anal.* *i*-($C_6H_{14}ClNO$·HCl) C, H, N.

(+)-1-Isopropylamino-3-(1-naphthoxy)-2-propanol·HCl (V).—A mixt of 1-naphthol (0.7 g), EtOH (50 ml), (+)-1-chloro-3-isopropylamino-2-propanol (−)-di-*O,O*-*p*-toluoyltartrate (2.5 g), NaOH (0.6 g), and H_2O (5 ml) was heated under reflux for 3 hr. The mixt was filtered and the filtrate was evapd under reduced pressure. The residue was dissolved in Et_2O and acidified with ethereal HCl. The mixt was filtered and the solid residue crystd from Et_2O–EtOH: mp 190–192°; $[\alpha]^{20}D$ + 29.8° (*c* 0.44, EtOH).

(13) Nmr data are recorded in order of chemical shift (TMS), multiplicity (d = doublet; q = quartet; m = multiplet; b = broad), coupling constant in cps, and integration.

Acknowledgment.—We are indebted to Dr. T. Leigh for supplying us with compounds **4**, **5**, **6**, **7**, and **8**; to Mr. B. Crooks for the purification of (+)-1-isopropylamino-2-propanol by gas phase chromatography; and to Mr. P. J. Taylor for providing, and helpfully commenting upon, the ir spectra.

Antihypertensive Agents. Substituted 3-Pyrrolemethylamines

CHARLES H. TILFORD,†

Chemistry Department, Emory University, Atlanta, Georgia 30322

W. J. HUDAK,* AND RICHARD E. LEWIS

Cardiovascular Section, Department of Pharmacology, The Wm. S. Merrell Company, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215

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1-Aryl-, aralkyl-, cycloalkyl-, and heterocyclic 2,5-dimethylpyrroles, prepared by reaction of primary amines with acetonylacetone, were formylated using $POCl_3$ and DMF. The resulting 1-substituted-2,5-dimethyl-3-pyrrolecarboxaldehydes were then converted into the desired 3-pyrrolemethylamines using a series of di- and triamines in the KBH_4-reductive alkylation procedure. In hypotensive tests, the most potent compound (**7**, Table I) caused a 75% drop in mean arterial blood pressure in dogs at 0.1 mg/kg iv that lasted over 1 hr.

A search for new types of compounds for lowering blood pressure led to the use of commercially available 2,5-dimethyl-1-phenyl-3-pyrrolecarboxaldehyde as a starting material. When activity was found in the first few amines prepared by reduction of Schiff's bases of this aldehyde, a series of diverse 3-pyrrolemethylamines was prepared to seek a product worthy of clinical testing. The compounds listed in Table I were prepared by the reaction sequence outlined in Scheme I.

As shown in Table I, A is an alkyl group substituted with a terminal basic function.

Herz and Settine[1] report the preparation of *tert*-3-pyrrolemethylamines from pyrroles of type I *via* the Mannich reaction, which might be considered an alternate method for preparing type IV compounds. However, the Mannich method could give appreciable 3,4-bisamine formation which might complicate isolation procedures beyond practicality.

The method shown in Scheme I minimizes bisamine formation. The procedure of Rips and Buu-Hoï[2] was used for formylating 1-substituted-2,5-dimethylpyrroles (I) with DMF–$POCl_3$. As illustrated by the preparation of 2,5-dimethyl-1-phenyl-3-pyrrolecarboxaldehyde (73% yield),[2] their procedure gives good yields of 3-pyrrolecarboxaldehydes (II) which are readily separated from small amounts of the corresponding biscarboxaldehydes by fractional distillation. Thus, 3-pyrrolemethylamines IV obtained from aldehydes II prepared according to Rips and Buu-Hoï should not be contaminated with bisamines. As it was, decomposition problems were encountered when amines IV obtained by KBH_4 reduction of the Schiff's bases III were vacuum distilled. For example, in 3 successive experiments, attempts to distill crude base **8** (Table I)—actually the

† Present address: 2167 Greensward Drive, NE, Atlanta, Ga. 30345.

(1) W. Herz and R. L. Settine, *J. Org. Chem.*, **24**, 201 (1959).

(2) R. Rips and N. P. Buu-Hoï, *ibid.*, **24**, 372 (1959).