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The preparation and pharmacological properties of ψ-corbasil

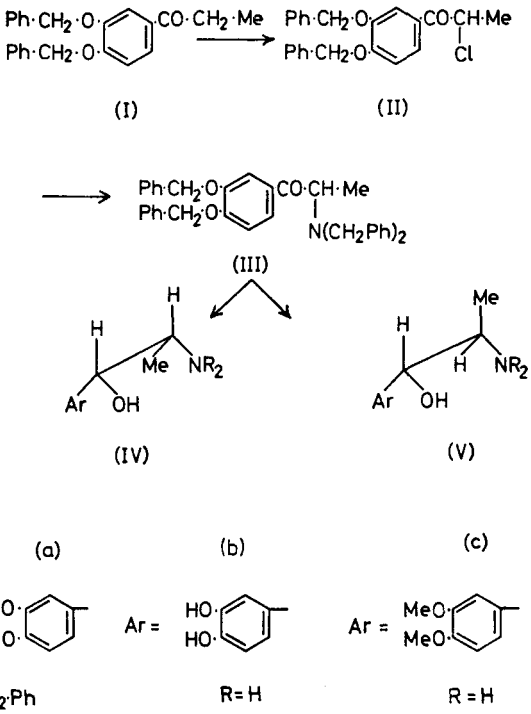
M. T. FARRUGIA, W. H. HUNTER AND G. KIRK

Pharmacy Department, Chelsea College (University of London), Manresa Road, London, S.W.3, England

The synthesis is described of *threo*-α-methyl noradrenaline (ψ-corbasil). The assignments of the *erythro* and *threo* configurations to corbasil and ψ-corbasil respectively are supported by the evidence of the nmr spectra. Some preliminary results are reported for the relative pharmacological activity of the two isomers at α- and β-adrenergic receptors.

The sympathomimetic amine, 2(3′,4′-dihydroxyphenyl)-2-hydroxyisopropylamine (α-methylnoradrenaline; corbasil) has been described (Bruckner & Fodor, 1943) and its pharmacological properties examined (Luduena, Hoppe & others, 1958). Since corbasil has two asymmetric centres it can exist as two pairs of racemic mixtures. The (±)-*erythro* pair, corbasil, has been resolved and each epimer examined pharmacologially (Luduena, Euler & others, 1957; Luduena & others, 1958).

The corresponding *threo* pair, ψ-corbasil, has not been prepared although Waldeck (1968) reported that treatment of the *erythro* compound, corbasil, with hot acid gave the *threo* isomer, characterized by its non-identity with corbasil and by its fluorescence spectrum which differed from that of corbasil.



In our hands this method gave a dark-coloured material of variable composition consisting mainly of oxidation products of corbasil.

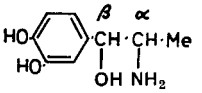
We now report the synthesis of authentic ψ-corbasil and its configurational assignment to the *threo* series.

The dibenzyl ether (I) was converted to the chloroketone (II) with sulphuryl chloride, a procedure that avoided the disproportionation which occurs on direct treatment of I with halogens. Treatment of II with dibenzylamine in acetone gave the tertiary amine (III) which served as starting material for preparation of the *threo* and *erythro* alcohols (IV) and (V).

Catalytic reduction of III gave the *erythro* compound (IVb) by simultaneous reduction of the carbonyl group and hydrogenolysis of all four benzyl groups to yield (±)-corbasil.

Reduction of the carbonyl group of the aminoketone (III) without affecting the benzyl groups, was achieved with lithum aluminium hydride in ether when (±)-*threo*-2-(3′,4′-dibenzyloxyphenyl)-2-hydroxy-*NN*-dibenzyl isopropylamine (Va) was obtained in high yield. Catalytic debenzylation gave Vb as the free base forming a stable hemihydrate whose composition was verified by analysis and by the broad background absorptions at 3500–2400 and 1800–1000 cm^{-1}, in the infrared spectrum. These bands are characteristic of compounds containing traces of water.

Table 1. *Nmr spectra of corbasil and ψ-corbasil, 10% w/v in trifluoroacetic acid*



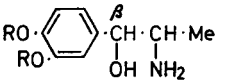
Isomer	Group	τ (ppm)	Integral	Multiplicity	J (Hz)
Corbasil	Aromatic H	3·05	3	Multiplet	–
	α-H	6·08	1	Multiplet	–
	α-Me	8·44	3	Doublet	6
	β-H	4·92	1	Doublet	5
	OH, NH_3	3·15	6	Singlet	–
ψ-Corbasil	Aromatic H	3·02	3	Multiplet	–
	α-H	6·02	1	Multiplet	–
	α-Me	8·58	3	Doublet	7
	β-H	5·45	1	Doublet	7·5
	OH, NH_3	2·54	6	Singlet	–

The configurational assignments for corbasil and ψ-corbasil are supported by the nmr spectral data shown in Table 1. Due to the insolubility of the compounds in the usual solvents the spectra were determined in trifluoroacetic acid. The dimethyl ethers of corbasil (IVc) and of ψ-corbasil (Vc) were therefore prepared. Details of the spectra of these in deuterochloroform and deuterium oxide are given in Table 2.

Comparison of the spectra of the *erythro* and *threo* pairs of the corbasils (IVb and Vb) and of their methyl ethers (IVc and Vc) shows that their only point of difference lies in the chemical shifts of the β–CH doublets, that for the *erythro* isomer lying downfield from the corresponding signal for the *threo* isomers. The coupling constant of the *erythro* isomer is also smaller than that of the *threo* isomer (Table 2). Similar findings have been reported for the ephedrine isomers (Hyne, 1961; Lyle & Keefer, 1966), as well as for the isomers of 2-(2-dimethylaminomethylphenyl)-1,2-diphenylethanol (Randall, Vaulx & others 1965). Hyne (1961) reported

the β-proton doublet of ephedrine (*erythro*) as 55 Hz downfield of the corresponding signal in ψ-ephedrine (*threo*) but apart from this the spectra were almost identical. For the pair corbasil/ψ-corbasil, this change in chemical shift is 32 Hz in the same direction (solvent-trifluoroacetic acid) (Table 2). For the free bases and hydrochlorides of the methyl ethers, the shifts, again in the same direction, are 16 Hz and 17 Hz in deuterochloroform and deuterium oxide respectively (Table 2).

Table 2. *Comparison of chemical shifts and coupling constants of β-proton for* threo *and* erythro *isomers*



R	Solvent	τ(*threo*)	τ(*erythro*)	$\tau_T - \tau_E$	J_T	J_E
H	T.F.A.	5·45	4·92	0·53	7·5	5
Me	$CDCl_3$	5·90	5·64	0·26	7	6
Me	D_2O	5·30	5·02	0·28	10	4·5

The coupling constant for the α–β protons is also different in the *erythro* and *threo* isomers, the value for the *erythro* compound being smaller than that of the *threo* isomer in every case (Table 2). Similar relations have been reported by several authors for *threo/erythro* pairs of a variety of compounds (Hyne, 1961; Randall, 1965, Kingsbury & Best, 1967). For the *erythro* isomers of corbasil (IVb), the dimethylether (IVc) and its hydrochloride, $J_{\alpha\beta}$ = 7–10 Hz whereas for the corresponding *threo* isomers Vb, Vc and Vc hydrochloride $J_{\alpha\beta}$ = 4·6—6 Hz (Table 2).

These values serve to distinguish the *erythro* and *threo* compounds from each other.

PHARMACOLOGICAL ACTIVITY

Muscholl & Lindmar (1967) reported that corbasil and ψ-corbasil cannot be distinguished from each other on the basis of their uptake, storage or release at adrenergic sites, whilst Waldeck (1967) observed the *threo* isomer to have slightly lower affinity for storage sites than the *erythro* isomer. Thus the relative potency of the two isomers at adrenergic receptors should be a measure of their direct effect at the receptor and should not arise from differences in their ability to release endogenous catecholamines.

(±)-Corbasil and (±)-ψ-corbasil were compared with noradrenaline for α-stimulant potency on the vasopressor response in the spinal rat and as β-stimulants in guinea-pig isolated atria. Results are shown in Fig. 1, a–d.

Fig. 1a shows the dose-response curves for (±)-corbasil and (—)-noradrenaline as α-stimulants. The maximum response to corbasil (at about 40 μg) is less than that due to noradrenaline. The corresponding results for ψ-corbasil are shown in Fig. 1b. The maximum response to ψ-corbasil (at about 200 μg) is lower than that due to corbasil and much lower than that due to noradrenaline. The results indicate that both corbasil and ψ-corbasil have a lower affinity for α-receptors than has noradrenaline.

Fig. 1c, shows the comparison of (±)-corbasil with (—)-noradrenaline at β-receptors. The β-stimulation of corbasil is positive but is much less than that due to noradrenaline whilst the maximum response to corbasil (at 25 μg/ml) is attained at a lower dose than that to noradrenaline; this suggests that corbasil may have a

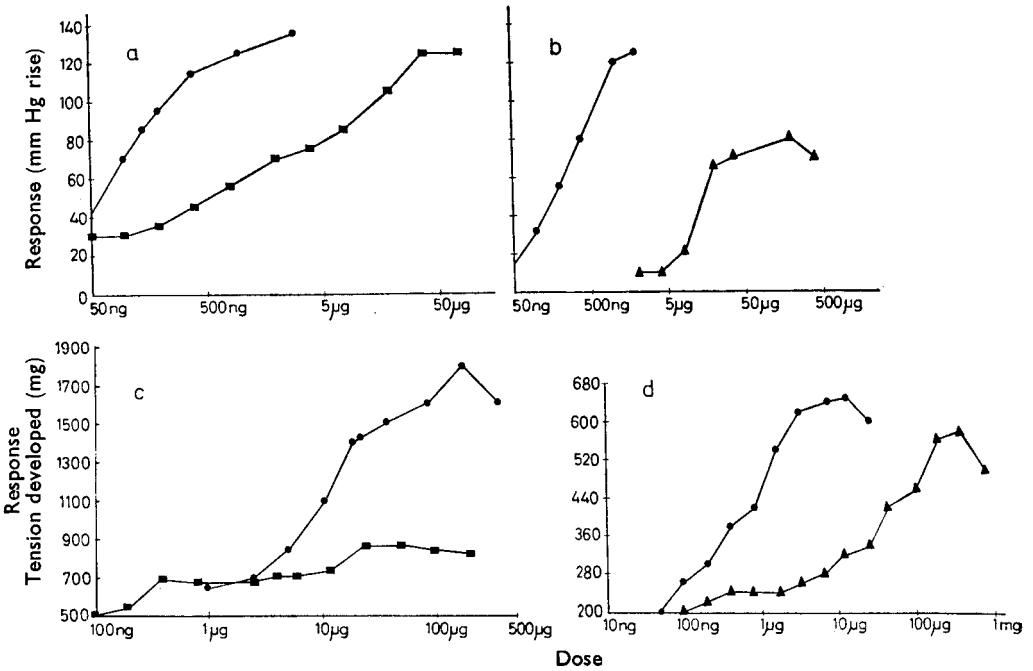


FIG. 1. Dose response curves for corbasil (■), noradrenaline (●) and ψ-corbasil (▲) on the spinal rat (α-stimulation; a, b) and guinea-pig isolated atria (β-stimulation; c, d).

greater affinity for β-receptors than has noradrenaline even though it has a lower activity. Since the dose - response curves are not parallel it is not possible to calculate a meaningful ratio for the potency.

The results for β-stimulation by ψ-corbasil are shown in Fig. 1d, the maximum response occurs at about 400 μg/ml. ψ-Corbasil therefore appears to have less affinity than noradrenaline for β-receptors although its activity at the receptor is comparable with that of noradrenaline.

Since corbasil and ψ-corbasil displace endogenous catecholamines to the same extent, the difference in the α- and β-stimulant activity of these two drugs must therefore be due to the differences in their activity at the receptor sites. The relatively high β-stimulation of ψ-corbasil compared with corbasil might possibly contribute to the smaller vasopressor effect of ψ-corbasil (Fig. 1a and b) for the result of β-stimulation is vasodilatation which would oppose the vasoconstriction due to α-stimulation.

Further work is in progress to prepare the two optical isomers of ψ-corbasil and to study their pharmacological action in the presence of α- and β-blocking agents.

EXPERIMENTAL

Infra-red spectra were recorded as Nujol mulls on a Unicam SP200 spectrophotometer.

Nmr spectra were determined on a Perkin–Elmer R 10 instrument, operating at 60 mHz.

Melting points are uncorrected.

3,4-*Dibenzyloxy-α-chloropropiophenone* (*II*). A solution of sulphuryl chloride (10 ml) in methylene chloride (20 ml) was added dropwise to a stirred solution of 3,4-dibenzyloxypropiophenone (Bockmöhl, 1934) (40 g) in methylene chloride (100 ml). The mixture was stirred at room temperature until no hydrogen chloride or sulphuryl chloride could be detected by starch–KI paper. Evaporation under reduced pressure at room temperature gave a pale yellow oil which crystallized from cyclohexane - light petroleum (b.p. 40–60°) to give 3,4-*dibenzyloxy-α-chloropropiophenone* as colourless crystals (31 g, 75%) m.p. 65·5–67°. Found: C, 72·8; H, 5·2; Cl, 9·4%. $C_{23}H_{21}ClO_3$ requires: C, 72·5; H, 5·6; Cl, 9·3%. Nmr spectral details are in Table 3.

(±)-3,4-*Dibenzyloxydibenzylaminopropiophenone* (*III*). Dibenzylamine (25 ml) was added to 3,4-dibenzyloxy-α-chloropropiophenone (25 g) and potassium iodide (0·5 g) in acetone (150 ml). After 3½ days at 10°, ether was added to complete the precipitation of dibenzylamine hydrochloride, and this, together with the potassium iodide, was filtered off: solvent was evaporated under reduced pressure. The residual brown oil was examined by thin-layer chromatography on silica gel, using chloroform as solvent and shown to consist of dibenzylamine (Rf 0·2) and a second component of Rf 0·9. The residual oil in benzene (80 ml) was passed through a column of alumina (125 g type H) in benzene. Elution with benzene (600 ml) was monitored by thin-layer chromatography and gave one component only. This was recrystallized three times from methanol to give (±)-3,4-dibenzyloxydibenzylaminopropiophenone as colourless crystals (23 g, 65%), m.p. 78–80° (Bochmöhl (1934) gives m.p. 84–86°). Found: C, 81·4; H, 6·5; N, 3·2%. Calc. for $C_{37}H_{35}NO_3$: C, 82·0; H, 6·5; N, 2·6%. Nmr spectral details are in Table 3.

(±)-threo-2-(3′,4′-*Dibenzyloxyphenyl*)-2-*hydroxy*-N-*dibenzylisopropylamine* (*Va*). A solution of (±)-3,4-dibenzyloxydibenzylaminopropiophenone (1 g) in dry ether (40 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (100 mg) in dry ether (10 ml). The reaction mixture was then refluxed gently (1 h). After cooling, excess reagent was decomposed cautiously with water (2 ml). The mixture was allowed to stand for a short time and then filtered through kieselguhr. The ethereal layer of the filtrate was dried (Na_2SO_4) and the solvent evaporated. The yellow residual oil crystallized from methanol to give (±)-threo-2-(3′,4′-*dibenzyloxyphenyl*)-2-*hydroxy*-N-*dibenzylisopropylamine* off-white crystals (0·82 g, 81%), m.p. 96–97°. Found: C, 81·3; H, 7·1; N, 2·6%. Calc. for $C_{37}H_{37}NO_3$: C, 81·7; H, 6·9; N, 2·6%. Nmr spectral details are in Table 3.

(±)-threo-2-(3′,4′-*Dihydroxyphenyl*)-2-*hydroxyisopropylamine* (*Vb*) (*ψ-corbasil*). Concentrated hydrochloric acid (1·9 ml) was added to a suspension of (±)-*threo*-2-(3′,4′-dibenzyloxyphenyl)-2-hydroxy-*N*-dibenzylisopropylamine (10 g) in 96% ethanol (250 ml). The mixture was warmed gently to yield a slightly acid solution and when cool this was hydrogenated over 10% palladium-charcoal (2 g) at room temperature until uptake ceased. The catalyst was filtered off and the solvent evaporated under reduced pressure. The oily residue in water (5 ml) was basified with conc. ammonia. The mixture, which darkened rapidly, was scratched and the solid which slowly precipitated filtered off and washed with a little water. Recrystallization from water gave (±)-threo-2-(3′,4′-*dihydroxyphenol*)-2-*hydroxyisopropylamine* as a light buff powder (1·37 g, 40%), m.p. 112–114° (decomp.). Found: C, 55·2; H, 7·2; N, 7·1%. Calc. for $C_9H_{13}NO_3.\frac{1}{2}H_2O$: C, 56·2; H, 7·3; N, 7·3%. The nmr spectral details are shown in Table 1.

(±)-erythro-2-(3′,4′-*Dimethoxyphenyl*)-2-*hydroxyisopropylamine* (*IVc*). Dry hydrogen chloride was passed through a solution of (±)-*erythro*-2-(3′,4′-dihydroxyphenyl)-2-hydroxyisopropylamine in dry methanol (10 ml) until solution was complete. Nitrogen was passed to remove excess hydrogen chloride, and the solution was kept under nitrogen, to prevent atmospheric oxidation. A chilled solution of diazomethane (1·03 g, 10·5 mol) in ether was added quickly portionwise to the chilled solution of amine hydrochloride and the reaction mixture, securely stoppered to prevent access of atmospheric moisture, was allowed to stand (16 h) at 0° then 24 h at 20°. Evaporation of solvent gave a brown crystalline residue which was refluxed in benzene and filtered. Evaporation gave a sticky yellow solid (0·48 g), m.p. 117–124°, whose methanolic solution gave no green colour with $FeCl_3$.

Table 3. *Nmr spectra of compounds II, III, IVc, Va and Vc*

	Group	τ	Integral	Multiplicity	J value (Hz)
Compound II (10% w/v in $CDCl_3$)	Aromatic hydrogen	2·70	13	Multiplet	—
	Benzyl CH_2	4·85	4	Doublet	—
	Side-chain CH	4·90	1	Quartet	6
	Side-chain CH_3	8·35	3	Doublet	6
Compound III (6% w/v in $CDCl_3$)	Phenyl aromatic hydrogen	2·68	23	Multiplet	—
	Benzyl aromatic hydrogen	2·84		Singlet	—
	Benzyloxy CH_2	4·90	4	Doublet	9
	Side-chain CH	5·74	1	Quartet	6
	N-Benzyl CH_2	6·40	4	Singlet	—
	Side-chain CH_3	8·70	3	Doublet	6
Compound IVc hydrochloride (12·5% w/v in D_2O)	Aromatic hydrogen	2·95	3	Multiplet	—
	Side-chain βCH	5·02	1	Doublet	4½
	Aromatic methoxy	6·12	6	Doublet	—
	Side-chain αCH	6·28	1	Octet	αH–βH 4·5 αH–CH_3 7·5
	Side-chain αCH_3	8·74	5	Singlet	—
	OH, NH_3^+	5·25	5	Singlet	—
Compound IVc free base (7% w/v in $CDCl_3$)	Aromatic hydrogen	3·20	3	Multiplet	—
	Side-chain βCH	5·64	1	Doublet	6
	Aromatic methoxy	6·16	6	Singlet	—
	Side-chain αCH	6·94	1	Octet	αH–βH 6 αH-CH_3 6
	Side-chain α-CH_3	9·04	3	Doublet	6
	OH, NH_2	7·96	3	Singlet	—
Compound Va (8% w/v in $CDCl_3$)	Benzyl aromatic hydrogen	2·72	20	Multiplet	—
	Phenyl aromatic hydrogen	3·35	3	Multiplet	—
	Benzyloxy CH_2	5·00	4	Doublet	7
	Side-chain βCH	5·87	1	Doublet	10
	N-benzyl CH_2	6·40	4	Quartet	14
	Side-chain α CH	7·32	1	Octet	αH-βH 10 αH-CH_3 7
	Side-chain α CH_3	9·24	3	Doublet	7
Compound Vc (7·5% w/v in $CDCl_3$)	Aromatic hydrogen	3·24	3	Multiplet	—
	Side-chain βCH	5·90	1	Doublet	7
	Aromatic methoxy	6·18	6	Singlet	—
	Side-chain αCH	7·05	1	Octet	αH-βH 7 αH-CH_3 6
	Side-chain αCH_3	9·05	3	Doublet	6
	OH, NH_2	7·78	3	Singlet	—

Re-crystallization from benzene-light petroleum (b.p. 40–60°) gave (±)-erythro-2-(3′,4′-*dimethoxyphenyl*)-2-*hydroxyisopropylamine*, as a yellow powder (0·28 g, 49%), m.p. 136–8°. Fodor, Bruckner & others (1949) give m.p. 139° for material prepared by hydrogenation of 3,4-dimethoxy-2′-aminopropiophenone. Nmr spectral details are shown in Table 3.

(±)-threo-2-(3′,4′-*Dimethoxyphenyl*)-2-*hydroxyisopropylamine* (Vc), prepared similarly, had m.p. 128–130°. Pfeiffer, Breitbach & Scholl (1940) give m.p. 128–129°. Nmr spectral details are shown in Table 3.

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