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THE ABSOLUTE CONFIGURATION OF (−)-CORBASIL

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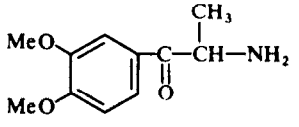
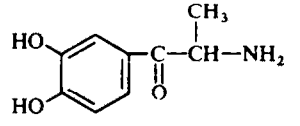
Abstract—The absolute configuration of (−)-corbasil (III) [3-(3',4'-dihydroxyphenyl)-3-hydroxy-2-aminopropane] is established by relating it stereochemically at the α-carbon atom to (+)-2-(3,4-dimethoxyphenyl)-isopropylamine (V) of known configuration,[5] by a series of reactions not involving this asymmetric centre.

IT IS well known that enantiomers of sympathomimetic amines differ in biological activity.[1] Differences in pressor activity, when related to a knowledge of the configuration of the isomers have largely contributed to current concepts of adrenergic mechanisms. (±)-Corbasil (III) has been shown to have an *erythro* configuration.[2] Its pressor activity resides mainly in the (−)-isomer.[3,4] We now report the determination of the absolute configuration of (−)-corbasil (III) by converting it to (+)-2-(3,4-dimethoxyphenyl)-isopropylamine (V) of known configuration,[5] by a series of transformations not affecting the α-asymmetric carbon atom.



I



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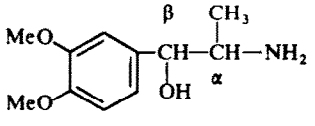
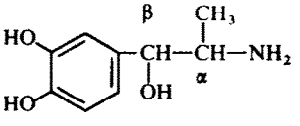
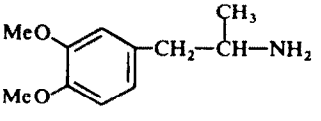


IV



III



V

(±)-2-Amino-3',4'-dimethoxypropiophenone hydrochloride (I) prepared as described by Beckett *et al.*[5] was O-demethylated by refluxing with 48% hydrobromic acid in an inert atmosphere to give (±)-2-amino-3',4'-dihydroxypropiophenone. This amino-ketone was soluble in acid but insoluble in the usual solvents. For this

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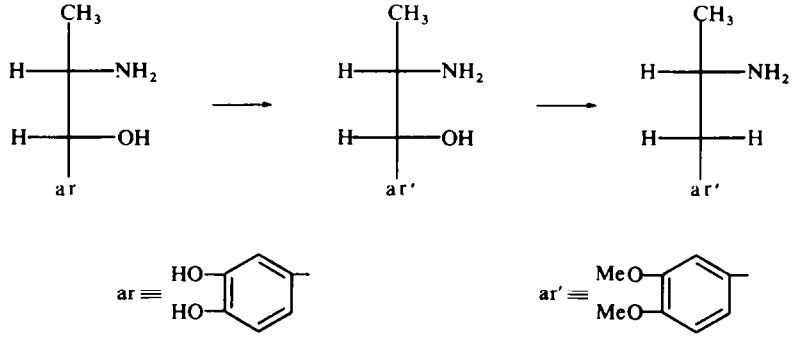
reason the crude form was used for subsequent reactions. Catalytic hydrogenation of the hydrochloride of II readily gave racemic amino-alcohol (III) but all attempts to resolve this compound were unsuccessful. Treatment of the amine (II) with (+)-α-methoxy-α-phenylacetic acid[6] in boiling water led to the isolation of the (−)-base-(+)-acid diastereoisomer, and hydrogenation of an aqueous solution of this salt in the presence of palladium on charcoal followed by treatment with concentrated ammonium hydroxide solution gave the (−)-*erythro*-aminoalcohol (III). This amino-alcohol was converted to its dimethoxy analogue (IV) by treating a methanolic solution of the hydrochloride salt with an ethereal solution of diazomethane. Hydrogenation of the (−)-*erythro*-amino-alcohol (IV) under conditions similar to those described by Rosenmund and Karg[7] gave the (+)-desoxy-amine (V).

In the above work the following configurational sequence applies:



(−)-Corbasil → (−)-(IV) → (+)-(V)

Now since (+)-(V) has the S-configuration[5] then (−)-corbasil must have an S-configuration at the α-carbon atom, and since corbasil is an *erythro* compound[2] it must have an R-configuration at the β-carbon atom. (−)-Corbasil is therefore 3R-[3-(3′,4′-dihydroxyphenyl)-3-hydroxy]-2S-aminopropane.

EXPERIMENTAL

(±)-2-*Amino*-3′,4′-*dihydroxypropiophenone* (II)

A soln of (±)-2-amino-3′,4′-dimethoxypropiophenone hydrochloride[5] (10·0 g) in 48% HBr (150 ml) was heated at 120° for 17 hr under a stream of N_2. The soln was evaporated to dryness, dissolved in EtOH, charcoaled, partly evaporated and basified using conc NH_4OH, to give II (5·2 g), a yellow powder, m.p. 202–203° (dec). Grüttefein gives m.p. 212°.[8] (Found: C, 58·9; H, 6·0; N, 8·0. $C_9H_{11}NO_3$ requires: C, 59·7; H, 6·1; N, 7·7%).

3R-[3-(3′,4′-*dihydroxyphenyl*)-3-*hydroxy*]-2S-*amino propane* (III)

A mixture of II (23·2 g) and (+)-α-methoxy-α-phenylacetic acid[6] (23·5 g) was dissolved in boiling water (235 ml). The brown solid which separated on cooling was filtered off and recrystallized from water to give (−)-2-amino-3′,4′-dihydroxypropiophenone-(+)-α-methoxy-α-phenylacetate, (7·9 g) m.p. 105·5° (dec), $[\alpha]_D^{19.5}$ +35·9° (*c*, 0·501 in EtOH). An aqueous soln of this salt (1·3 g) was hydrogenated in the presence of 10% Pd–C (0·25 g) until no more H_2 was taken up. The catalyst was filtered off under reduced press using a filter stick, the filtrate was evaporated to small bulk under reduced press, cooled under N_2 and basified with conc NH_4OH to give III (0·26 g), a buff powder, m.p. 206·5–208·5° (dec), $[\alpha]_D^{24}$ −20·7° (*c*, 0·493 in 0·1N HCl). Ludueña *et al.*[9] give m.p. 211·8–212·2°, Merck Index[10] gives $[\alpha]_D^{25}$ −31·0 (*c*, 0·5 in 0·1N HCl).

3R-[3-(3',4'-*dimethoxyphenyl*)-3-*hydroxy*]-2S-*aminopropane* (IV)

The hydrochloride of III was prepared by bubbling HCl through a dry methanolic suspension of III (1·0 g, 1·0 mol). An ethereal soln of diazomethane (2·1 g, 11 mols) was added and the reaction mixture was kept in the refrigerator and shaken at intervals until the solid which had formed dissolved and the soln gave a − ve reaction with $FeCl_3$. It was evaporated to dryness, and the residue extracted with hot benzene. The benzene solution was evaporated to small bulk; addition of pet. ether (40/60) gave 3R-[3-(3',4'-*dimethoxyphenyl*)-3-*hydroxy*]-2S-*aminopropane* (IV, 0·75 g), yellow crystals, m.p. 129–130°, $[\alpha]_D^{22}$ −28·6° (*c*, 0·500 in 0·1N HCl). (Found: C, 62·3; H, 8·0; N, 6·3. $C_{11}H_{17}NO_3$ requires: C, 62·5; H, 8·0; N, 6·6%).

S-(+)-2-(3',4'-*dimethoxyphenyl*)-*isopropylamine hydrochloride* (V)

A soln of IV (0·5 g) in glacial AcOH (10 ml) was hydrogenated in the presence of 72% $HClO_4$ (0·6 ml) and 10% Pd–$BaSO_4$ (0·2 g) for 20 hr at 70°. The catalyst was filtered through kieselguhr, the filtrate basified with conc NH_4OH and the product extracted into $CHCl_3$. Removal of the $CHCl_3$ gave a brown residue which was dissolved in ether and treated with HCl. The brown oily hydrochloride was evaporated to dryness, dried in a vacuum desiccator and crystallized from EtOH–ether to give S-(+)-2-(3',4'-*dimethoxyphenyl*)-*isopropylamine hydrochloride* (V, 0·13 g), brown prisms, m.p. 137–138°, $[\alpha]_D^{22}$ +21·6° (*c*, 0·676 in H_2O). Beckett *et al.*[5] give m.p. 137·5–138°, $[\alpha]_D^{21}$ +23° (*c*, 1·00 in H_2O).

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