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The assignment of absolute configurations to the individual enantiomorphs of phenylpropylmethylamine and pipradrol hydrochloride

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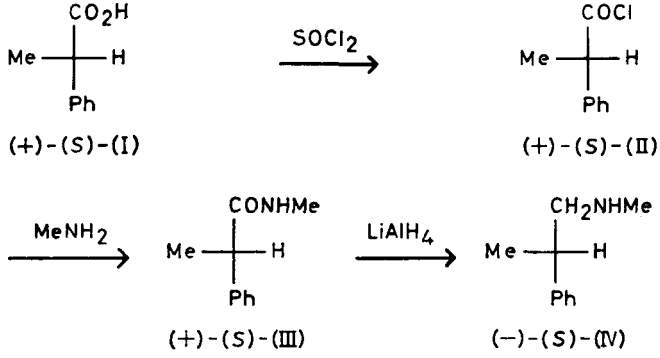
The configuration of the C-2 asymmetric centre of (−)-phenylpropylmethylamine (*N*-methyl-2-phenylpropylamine) has been related by a stereospecific route to that of the analogous centre of (+)-(*S*)-hydratropic acid. The configuration at the C-2 asymmetric centre of (−)-pipradrol (diphenylpiperid-2-ylmethanol) hydrochloride has been related by a stereospecific route to that of the analogous centre of (+)-(*R*)-pipecolic acid.

COMPOUNDS with the phenethylamine-(2-phenylethylamine) type structure, in general, exhibit an effect on the sympathetic nervous system. The classic paper of Barger & Dale (1910) showed that for those compounds with an asymmetric centre, the activity of one isomer is usually greater than that of its enantiomer. This was demonstrated more clearly by Gruber & Matthews (1953) who showed that (−)-adrenaline bitartrate and (−)-noradrenaline bitartrate were ten times more active than the (+)-isomers on dog intestine. Previously Pratesi, La Manna & others (1958, 1959) elucidated the absolute configuration of several of the important compounds exhibiting this effect. The aim of the present work is to relate the absolute configuration of (−)-phenylpropylmethylamine [(−)-*N*-methyl-2-phenylpropylamine] (IV) and (−)-pipradrol (diphenylpiperid-2-ylmethanol) hydrochloride (VII) to the analogous centres present in (+)-hydratropic acid (I) and (+)-pipecolic acid (V) respectively. It appears however that the pharmacology of the individual enantiomorphs of these two compounds has not as yet been investigated.

The stereospecific reaction sequences employed are shown below. (+)-Hydratropic acid (I) (obtained by resolution of racemic material by means of its strychnine salt) was converted to its (+)-*N*-methylamide



(+)-(S)-(I) (+)-(S)-(II) (+)-(S)-(III) (−)-(S)-(IV)

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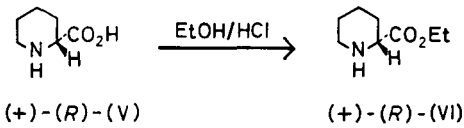
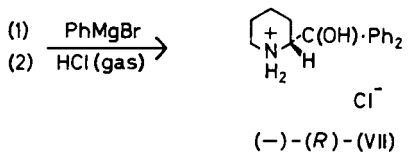
(III) via the (+)-acid chloride (II). Reduction of (+)-*N*-methylhydratropamide with lithium aluminium hydride afforded (−)-(*S*)-*N*-methyl-2-phenylpropylamine (IV) which was characterized as its hydrochloride. The sequence shown does not involve the asymmetric centre and hence the configuration of the (−)-*N*-methyl-2-phenylpropylamine will be the same as that of the starting (+)-hydratropic acid. The configuration of (+)-(*S*)-hydratropic acid has been established previously by Bernstein & Whitmore (1939) who related the (+)-acid to (+)-(*S*)-alanine and by Mislow & Heffler (1952) who, using the method of quasi-racemates, related (+)-hydratropamide derived from (+)-hydratropic acid, to (+)-(*S*)-α-chloro-α-phenylacetamide.

(+)-Pipecolic acid (V) [obtained by catalytic hydrogenation of picolinic acid and resolution of the resulting racemic acid with (+)-tartaric acid] was converted to its (+)-ethyl ester (VI) by a Fischer-Spier esterification. Reaction between this ester and phenyl magnesium bromide afforded diphenylpiperid-2-ylmethanol, which was converted to its (−)-(*R*)-hydrochloride (VII).



(+)-(*R*)-(V) (+)-(*R*)-(VI)



(−)-(*R*)-(VII)

The above sequence does not involve the asymmetric centre and hence the configuration of the (−)-diphenylpiperid-2-ylmethanol hydrochloride will be the same as that of the starting material, (+)-pipecolic acid. The configuration of (+)-(*R*)-pipecolic acid has been established previously by King, King & Warwick (1950), who prepared the (−)-acid by hydrogenation of (−)-baikiane, which they related to a derivative of (+)-(*S*)-aspartic acid.

Experimental

Hydratropic acid. Redistilled hydratropaldehyde (b.p. 95–98°/10 mm) (50 g) and silver nitrate (138 g) were dissolved in 50% aqueous ethanol (400 ml). Sodium hydroxide (52 g) in water (1,000 ml) was slowly added during 1·5 hr to the well-stirred mixture. The suspension was finally heated on a water bath for 1 hr, and the precipitate formed filtered off and washed with water and ether. The combined filtrate and washings were extracted with ether (1·5 litres), and the aqueous layer was acidified

with hydrochloric acid and re-extracted with ether (2·0 litres). This second ethereal extract was dried over anhydrous sodium sulphate, the ether removed by distillation, and the residual oil distilled, the fraction boiling between 110–112° at 1·2 mm being hydratropic acid (40 g) [Eliel & Freeman (1952) report b.p. 144–147°/11 mm].

Resolution of hydratropic acid. Hydratropic acid (35 g) and strychnine (78 g) were dissolved in 25% aqueous ethanol (350 ml). After storage at 0° for 18 hr, the solution deposited the strychnine salt (61 g), which was crystallized a further four times to yield strychnine (+)-hydratropate (4·5 g), $[\alpha]_D^{22}$ −30·2° (*c*, 1·46 in $CHCl_3$).

The rotation of the salt was unchanged on further recrystallization. The (+)-acid, liberated from the salt with dilute aqueous hydrochloric acid and extracted with chloroform, crystallized on removal of the solvent under vacuum and standing at 0° (1·2 g), m.p. 22°, $[\alpha]_D^{22}$ + 74·8° (*c*, 3·94 in $CHCl_3$). [Arcus & Kenyon (1939) report m.p. 29°, $[\alpha]_D$ + 74·8° (*c*, 3·06 in $CHCl_3$), Bakshi & Turner (1961) report m.p. 31·5–32°, $[\alpha]_D^{25}$ + 76·3° (*c*, 1·6, in $CHCl_3$).]

(+)-*Hydratropyl chloride.* (+)-Hydratropic acid (1·1 g) and thionyl chloride (1·1 g) were allowed to react at 50–60° for 1 hr. The product was distilled, (+)-hydratropyl chloride (b.p. 100–105°/0·5 mm) being collected as a colourless liquid (1·1 g), $[\alpha]_D^{22}$ + 106·1 (*c*, 7·5 in benzene). [Bakshi & Turner (1961) report b.p. 81–83°/10 mm, $[\alpha]_D^{22}$ + 101·5° (*c*, 2·44 in benzene).]

(+)-N-*Methylhydratropamide.* (+)-Hydratropyl chloride (1·1 g), dissolved in dry benzene (15 ml), was treated with dry methylamine gas for 10 min. The solvent was removed under vacuum and the residue, crystallized from water, gave (+)-*N*-methylhydratropamide as colourless plates, m.p. 80–81°, $[\alpha]_D^{22}$ + 53·2° (*c*, 2·63 in $CHCl_3$) [Carrington, Vassey & Waring (1953) report m.p. 82° for racemic material].

(−)-N-*Methyl*-2-*phenylpropylamine.* (+)-*N*-Methylhydratropamide (980 mg), in dry ether (40 ml), was refluxed for 5 hr with lithium aluminium hydride (500 mg). The reaction mixture was treated with dilute hydrochloric acid and the aqueous layer extracted with ether. The extracted aqueous liquid was made alkaline with dilute sodium hydroxide solution, saturated with sodium potassium tartrate and finally extracted with ether. The ether was removed from the extract on a water-bath and the residual oil distilled, the fraction boiling between 60–70° at 0·2 mm being (−)-*N*-methyl-2-phenylpropylamine (520 mg), $[\alpha]_D^{23}$ − 18·2° (*c*, 4·42 in EtOH).

The hydrochloride was precipitated from an ethereal solution of the free base by treating with dry hydrogen chloride. The hydrochloride crystallized from ethanol-ether, had m.p. 152° [Woodruff, Lambooy & Burt (1940) report m.p. 148–159° for racemic material].

Pipecolic acid. Picolinic acid (50 g) in water (150 ml) was shaken in the presence of hydrogen with platinum oxide (1·25 g), whereupon three moles of hydrogen were absorbed. The catalyst was removed by filtration and the solution treated with charcoal (2 g). After removal of the charcoal by filtration, the solvent was evaporated under reduced pressure

and the residue crystallized from methanol-ether to yield pipecolic acid as colourless needles, m.p. 262° (50 g). [Heilbron & Bunbury (1946) quote m.p. 264°.]

(+)-*Pipecolic acid.* Pipecolic acid (52 g) and (+)-tartaric acid (57 g) were dissolved in ethanol (1 litre), the solution boiled for 30 min and allowed to stand for 18 hr, whereupon the salt crystallized (57 g). The solid was crystallized three times from aqueous acetone to yield (+)-pipecolic acid hydrogen (+)-tartrate (19·5 g), $[\alpha]_D^{25}$ + 21·1° (*c*, 4·0 in H_2O). This salt, whose rotation was unchanged on further recrystallization, was dissolved in distilled water (250 ml), the solution passed through a column of Amberlite IR4b (OH^- form) resin (300 g), and the column washed with distilled water until the eluate was no longer alkaline. The total eluate was treated with charcoal (0·2 g) and filtered to remove the charcoal. The filtrate was evaporated under reduced pressure and the residue crystallized from aqueous acetone to yield (+)-pipecolic acid (7·0 g) as colourless needles, m.p. 280°, $[\alpha]_D^{23}$ + 24·6° (*c*, 3·35 in H_2O). [Heilbron & Bunbury (1946) quote m.p. 270°, $[\alpha]_D$ + 24·5°.]

(+)-*Ethyl pipecolate.* (+)-Pipecolic acid (6·5 g) was refluxed for 12 hr with ethanol (60 ml) containing hydrogen chloride (2·5 g). The reaction mixture was cooled on ice, treated with potassium carbonate to neutralize the acid, and the suspension filtered, the solid being washed with ethanol and ether. The solvent was removed under reduced pressure from the combined filtrate and washings and the residual oil distilled, (+)-ethyl pipecolate being collected as a colourless oil, b.p. 80–85°/1·0 mm (5·0 g), $[\alpha]_D^{23}$ + 10·0° (*c*, 4·08 in EtOH).

(−)-*Diphenylpiperid-2-ylmethanol hydrochloride.* A solution of (+)-ethyl pipecolate (4·8 g) in benzene (10 ml) was added to a Grignard reagent prepared from bromobenzene (12·0 g), magnesium (2·1 g) and ether (20 ml). The mixture was heated under reflux for 90 min and the product decomposed by pouring into a saturated aqueous solution of ammonium chloride (50 ml). The aqueous layer was made alkaline with aqueous sodium hydroxide (2N), the organic layer removed and the aqueous layer extracted with ether. The ethereal solution was extracted with hydrochloric acid (2N), and the aqueous layer made alkaline with sodium hydroxide solution (2N) and re-extracted with ether. The final ethereal extract was washed with water, dried over anhydrous sodium sulphate and the solvent evaporated off to yield a residual brown oil. The oil was distilled, the fraction boiling between 130–135° at 0·8 mm being crystallized from benzene-light petroleum (60–80°) to yield colourless needles of (−)-diphenylpiperid-2-ylmethanol (2·4 g), m.p. 71–72°.

The free base, dissolved in ethyl methyl ketone (30 ml), was treated with hydrogen chloride, and the precipitated solid was crystallized from ethyl methyl ketone to yield colourless needles (2·1 g), m.p. 306°, $[\alpha]_D^{25}$ − 64·3° (*c*, 1·74 in H_2O). [Tilford, Shelton & Campen (1948) report m.p. 308–309° for racemic material.]

Melting points were measured using an Electrothermal capillary melting point apparatus and were uncorrected.

Optical rotation measurements were taken using a Bellingham and Stanley Ltd. polarimeter. Probable limits of error involved in the measurement of $[\alpha]_D$ are about $\pm 5\%$.

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