CCLXX.—l-*Methylephedrine, an Alkaloid from* Ephedra *Species.*

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THE Chinese drug Ma Huang derived from an *Ephedra* species has become of importance in Western medicine as the source of *l*-ephedrine, an alkaloid which has recently been found to possess a physiological action resembling that of adrenaline. In addition to *l*-ephedrine the drug contains *d*-ψ-ephedrine, and another alkaloid, the subject of the present communication, has now been isolated.

The constitutions of *l*-ephedrine and *d*-ψ-ephedrine

(OH·CHPh·CHMe·NHMe)

have been established beyond doubt by syntheses of the racemic bases and their resolution into the corresponding enantiomorphic forms, two of which are identical with the naturally occurring alkaloids *l*-ephedrine and *d*-ψ-ephedrine. The empirical formula and properties of the new alkaloid suggested that it was probably the *N*-methyl derivative of either *l*-ephedrine or *d*-ψ-ephedrine. The *N*-methyl derivatives were therefore prepared by methylation of the natural bases and it was found that the m. p. and specific rotation of *l*-methylephedrine were identical with those of the new alkaloid. Comparison of the m. p. and specific rotation of the

corresponding hydrochlorides and the methiodides afforded ample confirmation that the new alkaloid is identical with *l*-methylephedrine, OH·CHPh·CHMe·NMe_2.

EXPERIMENTAL.

The syrupy alkaloidal residue obtained in the manufacture of ephedrine, freed as completely as possible from *l*-ephedrine and *d*-ψ-ephedrine, was purified by distillation under reduced pressure and neutralised with aqueous oxalic acid and the solution was evaporated to dryness. The residue on extraction with alcohol gave an alcohol-soluble fraction, which was dissolved in water and treated with a saturated aqueous solution of picric acid. The oil which first separated became solid on standing, and subsequent crops separated in a crystalline condition. The picrate was treated with hydrochloric acid and ether, and the resulting solution of the hydrochloride evaporated to dryness. The residue, after several crystallisations from alcohol, gave l-*methylephedrine hydrochloride* in stout, colourless tablets, m. p. 188—189° (corr.) (Found: C, 61·3; H, 8·3; Cl, 16·2. $C_{11}H_{17}ON$,HCl requires C, 61·2; H, 8·4; Cl, 16·4%). It is readily soluble in water, less soluble in alcohol, and sparingly soluble in acetone. In water solution, it had $[\alpha]_D$ −29·8° (c = 4·6).

l-Methylephedrine, prepared by addition of concentrated potassium hydroxide solution to a solution of *l*-methylephedrine hydrochloride in water, separated as an oil which rapidly solidified. It crystallised readily from methyl alcohol in stout needles, m. p. 87—88° (corr.). Previously recorded values are 59—62° (Miller, *Arch. Pharm.*, 1902, **240**, 481), 78° (Eberhard, *ibid.*, 1915, **253**, 65), 84° (Nagai, Abstract by Chen and Kao, *J. Amer. Pharm. Assoc.*, 1926, **15**, 632) (Found: C, 73·5; H, 9·4. Calc. for $C_{11}H_{17}ON$: C, 73·7; H, 9·6%). The base can be titrated with standard acid with methyl-red as indicator: 0·7956 g. required 44·4 c.c. of 0·1*N*-sulphuric acid. $C_{11}H_{17}ON$ requires 44·4 c.c. In methyl alcohol it had $[\alpha]_D$ −29·2° (c = 3·0). When treated with methyl iodide in methyl-alcoholic solution, it gave a *methiodide* which crystallised from alcohol in stout tablets, m. p. 212—213° (corr.) and had $[\alpha]_D$ −21·8° (c = 2·9) (Found: I, 39·6. $C_{12}H_{20}ONI$ requires I, 39·5%).

Methylation of l-*Ephedrine.*—*l*-Ephedrine (28·4 g.), dissolved in methyl alcohol (28·4 c.c.), was boiled on a water-bath, and methyl iodide (27 g.) in methyl alcohol (27 c.c.) was added slowly. The solution was boiled for 2 hours, concentrated under diminished pressure, and treated with potassium hydroxide solution and ether; 23·6 g. of the methiodide then separated. The alkaline liquor was

extracted with ether and added to the first ethereal extract. After drying over potassium carbonate, the ethereal solution was distilled, the residual base neutralised with aqueous oxalic acid, and successive crops of *l*-ephedrine oxalate, m. p. 249° (corr.), were removed. The final syrupy mother-liquor was treated with excess of potassium hydroxide solution; an oil then separated which rapidly solidified. It melted at 86—87° (corr.) after crystallisation from light petroleum and at 87—88° (corr.) after a further crystallisation from methyl alcohol. When mixed with the alkaloid obtained from Ma Huang, it showed no depression in m. p. (Found: C, 73·7; H, 9·4. Calc. for $C_{11}H_{17}ON$: C, 73·7; H, 9·6%). It had $[\alpha]_D$ −29·5° in methyl alcohol ($c = 4·5$).

The base was dissolved in ether and neutralised with hydrogen chloride. On crystallisation from alcohol the hydrochloride formed colourless tablets, m. p. 188—189° (Found: C, 61·4; H, 8·3; Cl, 16·4. Calc. for $C_{11}H_{17}ON,HCl$: C, 61·2; H, 8·4; Cl, 16·4%). It had $[\alpha]_D$ −29·8° in water ($c = 5·7$). There was no depression of the melting point after admixture with the hydrochloride obtained from Ma Huang.

l-Methylephedrine methiodide crystallises from alcohol in stout tablets, m. p. 212—213° (corr.) (Eberhard, *loc. cit.*, gave m. p. 204°). In aqueous solution it had $[\alpha]_D$ −21·3° ($c = 5·5$) (Found: I, 39·3. Calc. for $C_{12}H_{20}ONI$: I, 39·5%).

l-*Methylephedrine picrate* was prepared by adding a solution of the hydrochloride to a saturated aqueous solution of picric acid. It crystallised readily from alcohol and melted at 144° (corr.) (Found: C, 50·3; H, 4·5. $C_{17}H_{20}O_8N_4$ requires C, 50·0; H, 4·9%).

Methylation of d-*ψ*-*Ephedrine.*—*d*-*ψ*-Ephedrine (56·8 g.), dissolved in methyl alcohol (56·8 c.c.), was boiled on a water-bath, and methyl iodide (56·8 g.) added slowly. The mixture was boiled for 4 hours and treated with potassium hydroxide solution and ether; it then deposited crystals of the methiodide (24·1 g.). The alkaline liquor was extracted with ether and the united ethereal extracts were dried over potassium carbonate. After removal of the ether a crystalline residue (47·6 g.) was obtained which was fractionally crystallised from light petroleum; it then gave as a first crop 6·7 g. of crude *d*-*ψ*-ephedrine, m. p. 113°. Subsequent crops of low-melting base were obtained which were found by titration to consist of nearly pure methylephedrine.

The base was converted into the hydrogen tartrate and purified by recrystallisation from water.

d-*ψ*-*Methylephedrine hydrogen tartrate* crystallises in needles which melt at 84° (corr.) and, after drying in a vacuum over sulphuric acid, at 152° (corr.) (Found in air-dried salt: loss in a vacuum over

H_2SO_4, 10·0. $C_{11}H_{17}ON,C_4H_6O_6,2H_2O$ requires loss, 9·9%. Found in dried salt : C, 54·6; H, 6·9. $C_{11}H_{17}ON,C_4H_6O_6$ requires C, 54·7; H, 7·0%).

d-*ψ*-*Methylephedrine* was prepared by the addition of sodium hydroxide solution to a solution of the hydrogen tartrate in water. The base was extracted with ether and dried over potassium carbonate, and the ether removed by distillation. The residue crystallised readily on cooling and melted at 29—30° (corr.). Emde (*Arch. Pharm.*, 1906, **244**, 246) obtained the base as a thick oily liquid. It was recrystallised from light petroleum at −10°; thereafter it melted at 30° (corr.). d-*ψ*-*Methylephedrine* is readily soluble in the common organic solvents, and somewhat sparingly soluble in water (Found : C, 73·7; H, 9·4. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·6%). In methyl alcohol it had $[\alpha]_D$ +48·1° ($c = 4·7$). It can be titrated with standard acid and methyl-red : 0·6689 g. required for neutralisation 37·2 c.c. of 0·1*N*-sulphuric acid. $C_{11}H_{17}ON$ requires 37·3 c.c.

d-*ψ*-Methylephedrine methiodide crystallises readily from alcohol; m. p. 216—217° (corr.) (Emde, *loc. cit.*, gave m. p. 205°) (Found : I, 39·4. Calc. for $C_{12}H_{20}ONI$: I, 39·5%). In aqueous solution it had $[\alpha]_D$ +34·7° ($c = 2·9$).

d-*ψ*-*Methylephedrine picrate* was prepared by addition of a solution of the hydrochloride to a saturated solution of picric acid in water. It crystallised readily from alcohol and melted at 152—153° (corr.) (Found : C, 50·4; H, 4·9. $C_{17}H_{20}O_8N_4$ requires C, 50·0; H, 4·9%).

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