VII.—*Nor*-d-*ψ-ephedrine, an Alkaloid from* Ephedra *Species.*

By SYDNEY SMITH.

FURTHER examination of the alkaloids from Ma Huang, a drug obtained from an *Ephedra* species collected in Northern China, has led to the isolation of a new subsidiary alkaloid in addition to *l*-methylephedrine recently described (Smith, J., 1927, 2056). The alkaloid is crystalline, forms well-defined crystalline salts and has the properties of a primary base. It has the empirical formula

$C_9H_{13}ON$ and since it forms *d*-ψ-methylephedrine methiodide on treatment with methyl iodide it must be *nor*-d-*ψ-ephedrine*, $OH\cdot CHPh\cdot CHMe\cdot NH_2$.

Nor-*d*-ψ-ephedrine forms a *monobenzoyl* and a *dibenzoyl* derivative. The monobenzoyl derivative is non-basic, but when it is warmed with dilute hydrochloric acid and alcohol, or kept for some time in acetone solution with hydrogen chloride, a transference of the benzoyl group from nitrogen to oxygen occurs with the formation of O-*benzoylnor*-d-*ψ-ephedrine hydrochloride.* This salt is stable and may be crystallised from water without decomposition. When it is treated with alkali, the original *N*-benzoyl derivative is recovered.

A similar migration of the acyl group in this type of compound has been recorded in the case of the *p*-nitrobenzoylephedrines (Seizo Kanao, *J. Pharm. Soc. Japan*, 1927, 20).

EXPERIMENTAL.

The syrupy alkaloidal residue obtained in the manufacture of ephedrine, freed as completely as possible from *l*-ephedrine, was diluted with water and fractionally precipitated with aqueous potassium hydroxide. After removal of successive crops of crystalline material consisting mainly of *d*-ψ-ephedrine, the fractions became oily. The final mother-liquor was extracted with ether, and the ethereal solution dried over potassium carbonate. The residue after removal of the ether was distilled under diminished pressure. The product was neutralised with 20% sulphuric acid and concentrated under diminished pressure; the sulphate of the new base then separated. *Nor*-d-*ψ-ephedrine sulphate* after repeated crystallisation from water separates in elongated, hexagonal plates. The m. p. varies with the rate of heating, but when placed in a bath at 290° and slowly heated the salt melts at 295° (corr.; decomp.) [Found : S, 8·1. $(C_9H_{13}ON)_2,H_2SO_4$ requires S, 8·0%]. It has $[\alpha]_{5461}^{20°} + 42{\cdot}9°$ in water ($c = 1{\cdot}0$).

Nor-d-*ψ-ephedrine*, prepared by addition of potassium hydroxide to a solution of the sulphate and extraction with ether, crystallises readily from benzene in plates, m. p. 77—78° (corr.). It has $[\alpha]_{5461}^{20°} + 32{\cdot}2°$ in methyl alcohol ($c = 2{\cdot}89$). The base is fairly easily soluble in water and in most organic solvents. It can be titrated with standard sulphuric acid and methyl-red (0·5606 g. required 37·0 c.c. of 0·1*N*-sulphuric acid. Calc., 37·1 c.c. Found : C, 71·6; H, 8·7. $C_9H_{13}ON$ requires C, 71·5; H, 8·7%).

When heated with excess of methyl iodide and potassium carbonate in dilute methyl alcohol, it gave a mixture of bases and a crystalline methiodide, m. p. 216—217° (corr.). There was no depression of the m. p. when the methiodide was mixed with *d*-ψ-methylephedrine methiodide. The specific rotation in water was that of *d*-ψ-methylephedrine methiodide, $[\alpha]_{5461}^{20^\circ}$ $+ 36{\cdot}8^\circ$ ($c = 2{\cdot}4$) (Found : I, 39·7. Calc. for $C_{12}H_{20}ONI$: I, 39·5%).

Nor-d-*ψ-ephedrine hydrochloride* was prepared by passing hydrogen chloride into a solution of the base in methyl alcohol. On addition of ether the salt separated in plates, m. p. 178—179° (corr.) (Found : Cl, 18·7. $C_9H_{13}ON,HCl$ requires Cl, 18·9%).

Nor-d-*ψ-ephedrine hydrogen tartrate*, prepared in aqueous solution, crystallises in needles. After drying in a vacuum at 95°, it melts at 149—151° (corr.) and has $[\alpha]_{5461}^{20^\circ}$ $+ 43{\cdot}0^\circ$ (in water; $c = 1{\cdot}7$). The air-dried salt loses on complete drying 5·7% (Calc. for

$$C_9H_{13}ON,C_4H_6O_6,H_2O :$$

H_2O, 5·6%. Found for the dry salt: C, 51·9; H, 6·4. $C_9H_{13}ON,C_4H_4O_6$ requires C, 51·8; H, 6·4%).

Dibenzoylnor-d-*ψ-ephedrine*, prepared from benzoyl chloride, the base, and excess of potassium hydroxide solution, crystallised from dilute acetone or benzene in plates, m. p. 156—157° (corr.). $[\alpha]_{5461}^{20^\circ}$ $+ 28{\cdot}0^\circ$ ($c = 2{\cdot}2$ in methyl alcohol) (Found: C, 76·5; H, 5·9. $C_{23}H_{21}O_3N$ requires C, 76·8; H, 5·9%).

N-*Benzoylnor*-d-*ψ-ephedrine* may be prepared by the partial hydrolysis of the dibenzoyl derivative. The latter (3 g.) was boiled for 1 hour with *N*-methyl-alcoholic potassium hydroxide (100 c.c.). The solution after concentration was diluted with water and extracted with ether, and the ethereal extract washed first with water and then with 5% hydrochloric acid. The ethereal solution after drying over potassium carbonate gave on evaporation a crystalline residue, m. p. 131—132° (yield, 1·8 g. Theoretical, 2·1 g.). It separated from solution in ethyl acetate with a little light petroleum in silky hairs, m. p. 132° (corr.). $[\alpha]_{5461}^{20^\circ}$ $+ 58{\cdot}3^\circ$ ($c = 2{\cdot}9$ in methyl alcohol) (Found : C, 75·3; H, 6·7. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7%). When it is kept for some hours in contact with hydrogen chloride in acetone, crystals of a *hydrochloride* separate. The same salt may be obtained by warming the monobenzoyl derivative with dilute hydrochloric acid and alcohol until solution is effected; on cooling, the hydrochloride separates in needles, m. p. 244—245° (corr.; decomp.). $[\alpha]_{5461}^{20^\circ}$ $- 32{\cdot}5^\circ$ ($c = 0{\cdot}9$ in water) (Found : Cl, 12·4. $C_{16}H_{17}O_2N,HCl$ requires Cl, 12·2%). If a solution of the hydrochloride in water is precipitated with sodium hydroxide, the *N*-benzoyl derivative, identified by the m. p. and specific rotation, separates.

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