

THE PREPARATION AND PROPERTIES OF EPHEDRINE AND ITS SALTS.

By T. Q. CHOU.

(From the Department of Pharmacology, Peking Union Medical College, Peking, China.)

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PLATE 1.

With the development in scientific medicine of the clinical use of the alkaloid ephedrine, there has been an increasing interest in the preparation of this alkaloid, and an immediate need for accurate data in the standardization of its salts.

In these laboratories large amounts of ephedrine have been prepared and it has been found that the basic substance isolated from the Chinese drug Ma Huang, variously identified as *Ephedra vulgaris* Rich. var. *helvetica* Hk. et Thoms (1) and *Ephedra equisetina*, Bge., (2) consists chiefly of ephedrine together with about 20 per cent of its isomer pseudoephedrine. These two alkaloids were first prepared by Nagai (3) and Merck (4) respectively. They were found to be mutually convertible by boiling with hydrochloric acid and in other ways (5), and have the empirical formula $C_{10}H_{15}ON$.

The chemical structure of ephedrine, and its isomer $OH \cdot CH \cdot C_6H_5 \cdot CH \cdot CH_3NH \cdot CH_3$, has been studied by many workers (6-8) and synthetically proven for both alkaloids (9-12). It shows a close relationship in chemical structure to epinephrine, to which it has been found to have similar, and in some respects superior physiological effects (13-16).

The separation of the two alkaloids by some clear cut method has been the object of this investigation. While the salts of ephedrine are better crystallized and less soluble in water and alcohol than those of pseudoephedrine it has been found that the best means of separation depends upon the striking difference in the solubility of their oxalates in cold water.

Pure preparations of the alkaloids and their salts were made and studied. While some of the physical constants of the salts obtained do not agree with those published by Chen (17), they do confirm such as are published by several other workers (18). The pure base heretofore considered to be levorotatory was found to be dextrorotatory in water, and levorotatory in alcohol.

EXPERIMENTAL.

Extraction.—1 kilo of powdered Ma Huang was extracted with cold benzene in the presence of dilute Na_2CO_3 solution, and the benzene extract was shaken up with a sufficient quantity of dilute HCl to remove the basic substances. The acid solution was made alkaline with solid K_2CO_3 and the liberated base was then extracted with chloroform. The chloroform solution, when dried over anhydrous Na_2SO_4 and distilled, gave 2.6 gm. of crude base.

Preparation of Ephedrine HCl by Fractional Crystallization.—The crude base obtained as above was taken up with about twice its weight of alcohol and neutralized with concentrated HCl diluted with twice its volume of alcohol. Nearly pure ephedrine hydrochloride crystallized out on standing. After filtering it was washed with a mixture of alcohol and ether, and then with pure ether, and dried. A further quantity of ephedrine hydrochloride may be got by concentrating the mother liquors and washings. The final mother liquor was kept for the isolation of pseudoephedrine (see below).

Ephedrine hydrochloride crystallized out from alcohol in prismatic needles, m.p. $216^\circ\text{C}.$, $[\alpha]_D^{22} -32.5^\circ$ (see Fig. 1).

The salts prepared by fractional crystallization show no change in the melting point when recrystallized seven times. In many of our experiments the salts were recrystallized twelve times.

Separation of the Oxalates by Difference of Solubility.—The crude base as obtained when treated with oxalic acid gave a clear cut separation of the two alkaloidal salts. Ephedrine oxalate being only very slightly soluble in cold water and pseudoephedrine oxalate being exceedingly soluble, the soluble and insoluble products represented a separation of the two alkaloids.

Preparation of Pure Ephedrine Base.—5 gm. of pure ephedrine hydrochloride, dissolved in a sufficient quantity of water, were made alkaline with solid K_2CO_3 until two layers were formed and

extracted twice with chloroform. The chloroform solution was well dried over anhydrous Na_2SO_4 and distilled. On cooling the residue crystallized out in rhombic crystals. It was recrystallized by dissolving in a small quantity of alcohol and then adding a sufficient quantity of petroleum ether, m.p. 43°C . (see Fig. 2).

Properties of Pure Ephedrine.—Ephedrine was found to be very soluble in water, alcohol, and chloroform and nearly insoluble in petroleum ether upon cooling. Being a strong base, ephedrine displaces ammonia from its salts. Solutions of the salts in water varying from 1 to 10 per cent were found to be exceedingly stable. No change in strength occurred after 6 months storage at room temperature. The solutions are quite stable at boiling temperature. Its specific rotation varied with the different solvents used.

1. $[\alpha]_D^{22} +13.75^\circ$ in water.
2. $[\alpha]_D^{22} - 5.5^\circ$ in absolute alcohol.

A part of the pure ephedrine so obtained was transformed into its corresponding salts. They gave the following physical constants.

Ephedrine Hydrochloride. $\text{C}_{10}\text{H}_{15}\text{ON} \cdot \text{HCl}$.—Prismatic needles; m.p. 216°C ., $[\alpha]_D^{22} -32.5^\circ$. Easily soluble in alcohol and water. Its aqueous solution is stable at boiling temperature.

Ephedrine Sulfate. $\text{C}_{10}\text{H}_{15}\text{ON} \frac{1}{2} \text{H}_2\text{SO}_4$.—Hexagonal plates; m.p. 257°C ., $[\alpha]_D^{22} -30^\circ$. Difficultly soluble in alcohol, easily soluble in water, neutral to litmus.

Analysis. 0.2 gm. substance gave 0.109 gm. BaSO_4 .
S = 7.48 per cent (theoretical 7.47 per cent).

Ephedrine Oxalate. $2\text{C}_{10}\text{H}_{15}\text{ON} \cdot \text{C}_2\text{H}_2\text{O}_4$.—Prismatic needles from water; m.p. 245°C . with decomposition; neutral to litmus; only very slightly soluble in cold water (see Fig. 3).

Ephedrine Phosphate. $\text{C}_{10}\text{H}_{15}\text{ON} \cdot \text{H}_3\text{PO}_4$.—Crystallized from alcohol in long silky needles; m.p. 178°C .; acid to litmus.

Analysis. 0.1 gm. substance gave 0.0412 gm. $\text{Mg}_2\text{P}_2\text{O}_7$.
P = 11.5 per cent (theoretical = 11.7 per cent).

Pseudoephedrine.

The alcoholic mother liquor obtained after the removal of ephedrine hydrochloride as indicated above was first concentrated

and then evaporated to dryness on a water bath. The residue was taken up with a little water, made alkaline with K_2CO_3 , extracted with chloroform, and distilled. The basic residue was transformed into its corresponding sulfate by neutralizing with concentrated sulfuric acid diluted previously with alcohol. The crude sulfate so obtained consisted chiefly of pseudoephedrine sulfate. Its free base was obtained by dissolving in water, making alkaline with K_2CO_3 , and extracting with chloroform. Pure pseudoephedrine crystallized out from alcohol in rhombic prisms, m.p. $118^\circ C.$, $[\alpha]_D^{22} +50^\circ$ (see Fig. 4). Unlike ephedrine it was only slightly soluble in water. Its salts were prepared and gave the following physical constants.

Pseudoephedrine Hydrochloride. $C_{10}H_{15}ON \cdot HCl$.—Crystallized from alcohol in stout needles; m.p. $179-181^\circ C.$, $[\alpha]_D^{22} +58.75^\circ$; very soluble in water and in alcohol (see Fig. 5).

Pseudoephedrine Sulfate. $C_{10}H_{15}ON \frac{1}{2} H_2SO_4$.—Prismatic needles; no sharp m.p.; $[\alpha]_D^{22} +52.5^\circ$; easily soluble in water and in alcohol.

Pseudoephedrine Oxalate. $2C_{10}H_{15}ON \cdot C_2H_2O_4$.—Needles; m.p. 218° with decomposition; difficultly soluble in alcohol; very soluble in cold H_2O ; neutral to litmus (see Fig. 6).

Action of HCl upon Ephedrine. Preparation of Pseudoephedrine.

50 gm. ephedrine HCl.
350 cc. concentrated HCl.
175 cc. H_2O .

Boiled gently with reflux condenser for 12 hours. The acid solution was evaporated low over a water bath and allowed to crystallize; the crystallized HCl salt consisted of nearly pure unchanged ephedrine hydrochloride. If the acid solution had been sufficiently concentrated practically all the unchanged ephedrine hydrochloride would have crystallized out. Filtered, washed with a little dilute HCl, and used the filtrate for the preparation of pseudoephedrine. The acid filtrate was then evaporated to dryness over a water bath. The residue was taken up with a little water, made alkaline with K_2CO_3 , and extracted with chloroform. The chloroform solution, when well dried over anhydrous Na_2SO_4 and concentrated, deposited pseudoephedrine in rhombic crystals. The base obtained melted at $118^\circ C.$ and was identical in all respects with pseudoephedrine obtained from the crude drug.

BIBLIOGRAPHY.

1. Botanical nomenclature, Shanghai, 1917, 1004.
2. Chou, T. Q., and Read, B. E., *Proc. Soc. Exp. Biol. and Med.*, 1926, xxiii, 618.
3. Nagai, N., *Pharm. Z.*, 1887, xxxii, 700.
4. *Merck's Ber.*, 1893, 13.
5. Schmidt, E., *Arch. Pharm.*, 1908, cxlvi, 210; 1912, cl, 154; 1913, cli, 320; *Apoth.-Ztg.*, 1913, xxviii, 667.
6. Ladenburg, A., and Oelschlägel, C., *Ber. chem. Ges.*, 1889, xxii, 1823.
7. Rabe, P., *Ber. chem. Ges.*, 1911, xlv, 824.
8. Schmidt, E., *Arch. Pharm.*, 1915, ccliii, 52.
9. Eberhardt, A., *Arch. Pharm.*, 1920, celviii, 97.
10. Fourneau, E., *An. soc. espan. fis. y quim.*, 1922, xx, 394.
11. Späth, E., and Göhring, R., *Monatsh. f. Chem.*, 1920, xli, 319.
12. Späth, E., and Koller, G., *Ber. chem. Ges.*, 1925, lviii, 1268.
13. Chen, K. K., and Schmidt, C. F., *J. Pharmacol. and Exp. Therap.*, 1924, xxiv, 339.
14. Amatsu, H., and Kubota, S., *Kyoto Igaku Zasshi*, 1917, xiv, 77.
15. Fetterolf, G., and Sponsler, M. B., *Arch. Otolaryng.*, 1925, ii, 132.
16. Miller, T. G., *Am. J. Med. Sc.*, 1925, clxx, 157.
17. Chen, K. K., *Am. Pharm. Assn.*, 1925, xiv, 189.
18. Henry, T. A., *Plant alkaloids*, London, 2nd edition, 1924.

EXPLANATION OF PLATE 1.

- FIG. 1. Ephedrine hydrochloride. M.p. 216°C ., $[\alpha]_{\text{D}}^{22} - 32.5^{\circ}$.
FIG. 2. Ephedrine. M.p. 43°C ., $[\alpha]_{\text{D}}^{22} + 13.75^{\circ}$ in water. $[\alpha]_{\text{D}}^{22} - 5.5^{\circ}$ in absolute alcohol.
FIG. 3. Ephedrine oxalate. M.p. 245°C .
FIG. 4. Pseudoephedrine. M.p. 118°C ., $[\alpha]_{\text{D}}^{22} + 50^{\circ}$ in alcohol.
FIG. 5. Pseudoephedrine hydrochloride. M.p. 179°C ., $[\alpha]_{\text{D}}^{22} + 58.75^{\circ}$.
FIG. 6. Pseudoephedrine oxalate. M.p. 218°C .



FIG. 1.



FIG. 2.

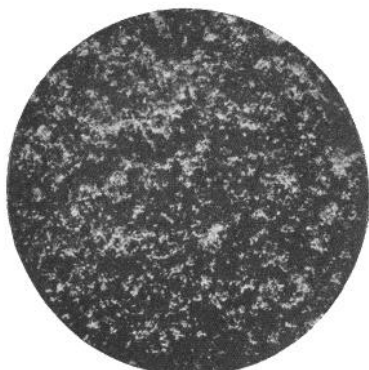


FIG. 3.



FIG. 4.



FIG. 5.



FIG. 6.

(Chou: Ephedrine.)