

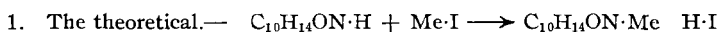
SCIENTIFIC SECTION

THE QUATERNARY AMMONIUM HALIDES OF EPHEDRINE.*

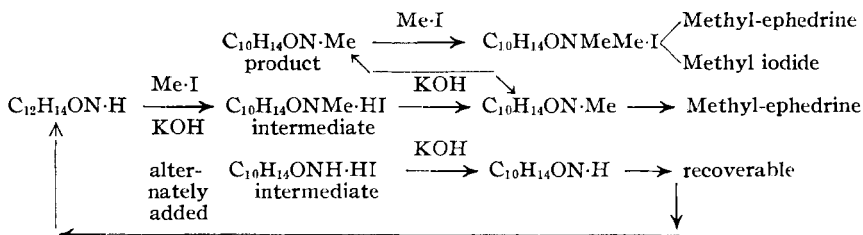
BY C. T. FENG.¹

INTRODUCTION.

During the preparation and study of "some derivatives of ephedrine" (4), the quaternary ammonium halides were left for further investigation. Our experiments showed that methylation of ephedrine with an equivalent of methyl iodide, yielded about 23 per cent of methyl-ephedrine, 30 per cent of methyl-ephedrine-methyl-iodide as a by-product, 35 per cent of the alkaloid was recovered unchanged, and 12 per cent was lost in residues. These reactions can be expressed as follows:



2. The experimental.—



Our modified methylation method previously reported (4) has been improved to increase the production of methyl-ephedrine, but we have now utilized this method for a study of:

1. Methods for isolating and purifying methyl-ephedrine-methyl-iodide, $C_{10}H_{14}ONMe \cdot Me \cdot I$.
2. Methods of converting the quaternary iodide into methyl-ephedrine-methylchloride, $C_{10}H_{14}ONMeMe \cdot Cl$, and methyl-ephedrine-methyl-bromide, $C_{10}H_{14}ONMeMe \cdot Br$.
3. A comparative study of these three quaternary ammonium halides.

Methyl-ephedrine-methyl-iodide has been synthesized by Schwantke (6), (1), and recently by Sydney Smith (7). Methyl-ephedrine-methyl-chloride has been synthesized by Eberhard (3), (2), (1). By our modified methods, the former can be obtained in pure condition from the methylation mixture in preparing methyl-ephedrine, and can be readily transformed into the latter. Methyl-ephedrine-methyl-bromide is a new compound not previously cited in the literature upon ephedrine. The main contribution of the present paper is the report of the particular properties, reactions, tests, etc., of these three halides.

PRODUCTION OF METHYL-EPHEDRINE-METHYL-IODIDE ($C_{10}H_{14}ONMEME \cdot I$).

Methylation.—The following solutions were prepared.

* Received for publication December 15, 1931.

¹ Department of Pharmacology, Peiping Union Medical College.

1. 100 Gm. ephedrine HCl treated with 100 cc. (one equivalent) of 5-N · KOH in methyl alcohol.
2. 75 Gm. (one equivalent) of methyl iodide dissolved in methyl alcohol to form 320-cc. solution.
3. 100 cc. (one equivalent) of 5-N · KOH in methyl alcohol diluted with methyl alcohol to 160 cc.

Solutions 2 and 3 were slowly and alternately added to 1 in the manner described in our last paper (5). This procedure was completed in 32 hours. Then an excess of about 10 cc. 5-N · KOH in methyl alcohol was added. After filtration and air-evaporation, an alcoholic residue was obtained containing methyl-ephedrine, methyl-ephedrine-methyl-iodide, unchanged ephedrine and a residue of potassium halides and the excess of potassium hydroxide.

Separation.—By treating the alcoholic residue with 20–40 cc. of 5-N · KOH in water and extracting it with portions of ether, methyl-ephedrine and the unchanged ephedrine were completely removed, leaving the methyl-ephedrine-methyl-iodide in the alkaline residue. After washing with small portions of cold water it was rendered almost free from the potassium compounds. It was then dissolved in 95 per cent alcohol, filtered, gently evaporated to dryness and finally washed with portions of ether.

Crystallization.—The well-washed product was purified by crystallization from hot water. By fractional crystallization from dilute aqueous solution, pure methyl-ephedrine-methyl-iodide was obtained in rhombic plates (Fig. 1) with constant properties.

Properties.—Melting point 208.0–209° C. (uncorr.); $(\alpha)_D^{22} -32.3^\circ$ in methyl alcohol ($c = 5.0$); $(\alpha)_D^{22} -22.3^\circ$ in water ($c = 5.0$); Iodine 39.45% (theoretical 39.53%); “Biuret test” no color reaction.

It has a fairly bitter taste, insoluble in ether, readily soluble in alcohol and hot water but sparingly soluble in cold water. It readily crystallizes out in different forms from aqueous solutions according to the concentration in rhombic, plate like, prismatic, and other types (Fig. 2). It is one of the ephedrine derivatives which has been found absolutely negative to the “Biuret test” while the others are somewhat positive (4), (5). Its particular tests and reactions will be described under the heading of the “comparative study of the quaternary ammonium halides of ephedrine.”

FORMATION OF METHYL-EPHEDRINE-METHYL-CHLORIDE, $C_{10}H_{14}ONMEME \cdot CL$.

I. PREPARATION BY DISPLACEMENT METHOD.—It was found in testing methyl-ephedrine-methyl-iodide that free chlorine can displace iodine in this compound as well as iodine in the alkali-iodides, thus,

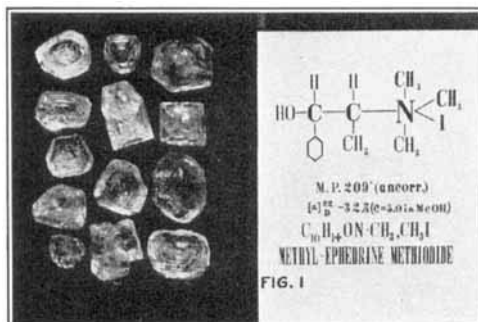
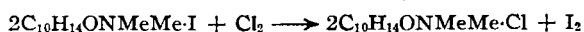


Fig. 1.—Methyl-ephedrine-methyl-iodide (ordinary type), illustrated with structural formula.

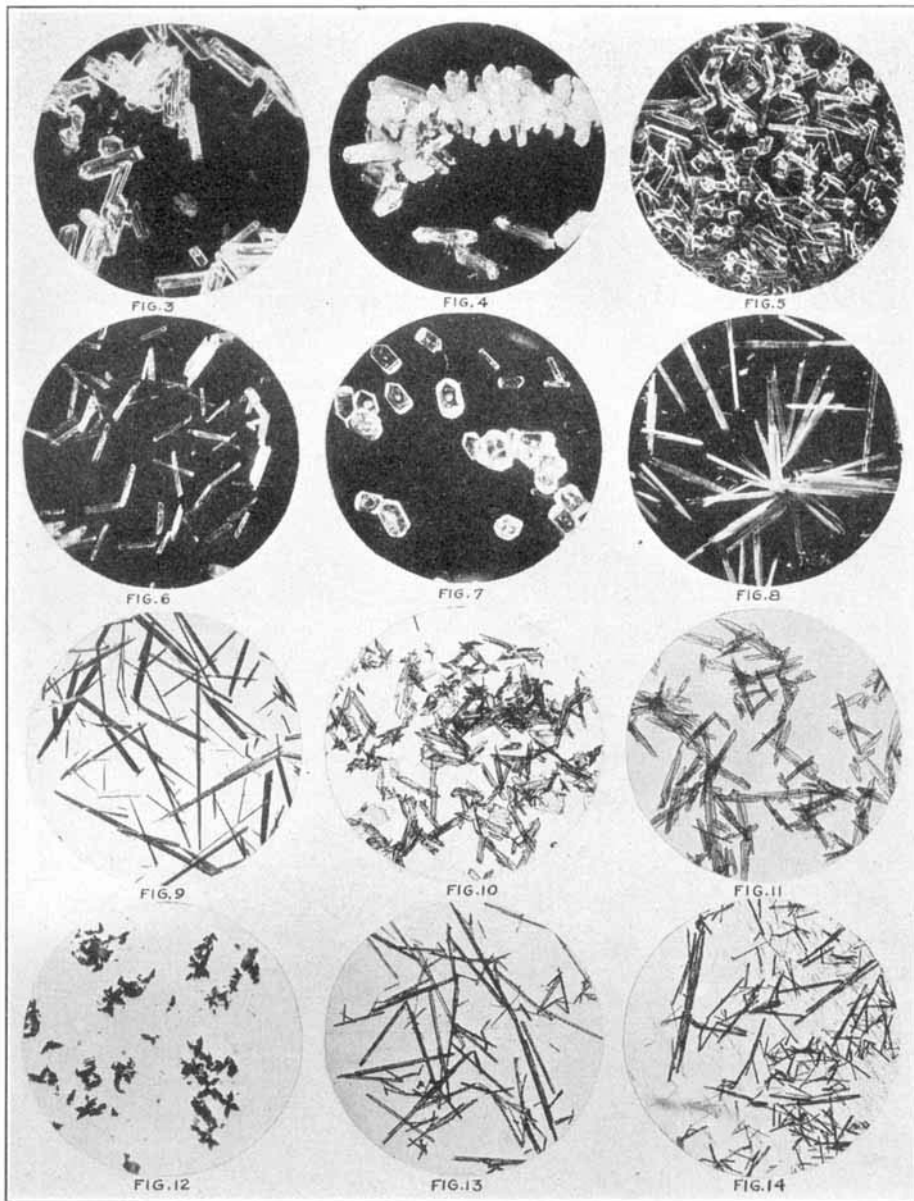


Fig. 3.—Methyl-ephedrine-methyl-chloride (ordinary type). Fig. 4.—Methyl-ephedrine-methyl-bromide (ordinary type). Fig. 5.—Methyl-ephedrine-methyl-chloride from ethereal-alcoholic solution. Fig. 6.—Methyl-ephedrine-methyl-chloride from concentrated ethereal-alcoholic solution. Fig. 7.—Methyl-ephedrine-methyl-bromide from ethereal alcoholic solution. Fig. 8.—Methyl-ephedrine-methyl-bromide from concentrated ethereal-alcoholic solution. Fig. 9.—Methyl-ephedrine-methyl-dichromate (the only type). Fig. 10.—Methyl-ephedrine-methyl-auric-chloride. Fig. 11.—Methyl-ephedrine-methyl-auric-bromide. Fig. 12.—Methyl-ephedrine-methyl-auric-iodide. Fig. 13.—Methyl-ephedrine-methyl-platinic-chloride. Fig. 14.—Methyl-ephedrine-methyl-platinic-bromide.

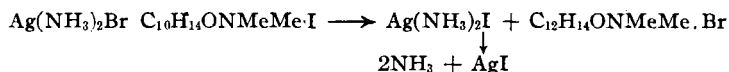
was crystallized out from different concentrations of ethereal-alcohol mixtures in different forms (Fig. 3, 5 and 6) similar to those of methyl-ephedrine-methyl-iodide (Fig. 1 and 2). Pure methyl-ephedrine-methyl-chloride in its various crystalline forms have the following constant properties:

Melting point, 245.0° C. (uncorr.) with decomposition;
 $(\alpha)_{\text{D}}^{22} - 45.2^\circ$ in methyl alcohol ($c = 5.0$);
 $(\alpha)_{\text{D}}^{22} - 31.2^\circ$ in water ($c = 5.0$);
 Chlorine 15.40% (theoretical 15.44%);
 "Biuret test" no color reaction.

Other properties and tests will be described in comparison with those of the iodide and the bromide.

FORMATION OF METHYL-EPHEDRINE-METHYL-BROMIDE ($\text{C}_{10}\text{H}_{14}\text{ONMEME}\cdot\text{BR}$).

By using an equivalent of AgBr in the place of AgCl required by the transformation method, methyl-ephedrine-methyl-bromide was readily formed in the ammoniacal solution by boiling till the white precipitate changes to yellow, as shown by the following equations:



The same procedure and observations as those forming for the chloride were carried out. The pure product was finally crystallized out from ethereal-alcoholic solution mostly in rhombic, prismatic plates (Fig. 4) possessing the following properties:

Melting point, 238.0° C. (uncorr.);
 $(\alpha)_{\text{D}}^{22} - 37.9^\circ$ in methyl alcohol ($c = 5.0$);
 $(\alpha)_{\text{D}}^{22} - 25.8^\circ$ in water ($c = 5.0$);
 Bromine 29.10% (theoretical 29.16%);
 "Biuret test" no color reaction.

Similar to the iodide and chloride, different types of crystals are formed from different concentrations (Fig. 7 and 8). It has a bitter taste, insoluble in ether, readily soluble in alcohol and cold water. Most of its properties and reactions are found as the medium between the iodide and the chloride, as compared in next section.

COMPARATIVE STUDY OF THE QUATERNARY AMMONIUM HALIDES.

1. *Analogous Points.*—These three quaternary ammonium halides resemble one another in their crystalline forms, solubilities, stability against alkalis and inactivity to the "biuret reaction."

2. Their molecular rotations are found to be equal, as estimated from their specific rotations which were determined in the same solvent with the same conditions, as shown in Table I.

TABLE I.—ROTATORY ANALOGY BETWEEN THE THREE QUATERNARY HALIDES OF EPHEDRINE.

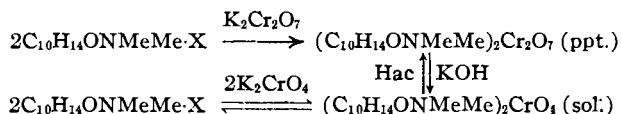
Methyl-Ephedrine-Methyl.	Chloride.	Bromide.	Iodide.
Molecular formula	$\text{C}_{20}\text{H}_{20}\text{ON}\cdot\text{Cl}$	$\text{C}_{20}\text{H}_{20}\text{ON}\cdot\text{Br}$	$\text{C}_{12}\text{H}_{20}\text{O}\cdot\text{N}$.
Molecular weight	229.63	274.08	321.1
Sp. R. $(\alpha)_{\text{D}}^{22}$ in MeOH ($c = 5$)	-45.2°	-37.9°	-32.3°
in H_2O ($c = 5$)	-31.2°	-25.8°	-22.3°
Mol. R. $(\alpha_{\text{M}})_{\text{D}}^{22}$ in MeOH ($c = 5$)	-103.8°	-103.9°	-103.7°
in H_2O ($c = 5$)	-71.64°	-71.71°	-71.61°

From the above table, it is seen that the "atomic rotations" of these three halogens in their respective analogous halides are the same.

3. *Upon Treatment with Potassium Dichromate.*—The neutral aqueous solutions of these three halides readily produce a precipitate of methyl-ephedrine-methyl-dichromate, $(C_{10}H_{14}ONMeMe)_2Cr_2O_7$. The precipitate crystallized in characteristic yellow needles, difficultly soluble in alcohol and dilute acetic acid, but readily soluble in dilute alkalis and hot water. After filtering, washing with alcohol and ether, and re-crystallizing from different concentrations of aqueous solution, the yellow needles are reformed without noticeable variation in form (Fig. 9).

Methyl-ephedrine-methyl-dichromate has no sharp melting point—165–185° with decomposition. On standing intramolecular oxidation takes place, darkening the color and giving an odor somewhat like burning ephedrine.

Potassium chromate does not produce any precipitate in neutral solution, but it does so when the solutions are acidified with acetic acid. It is assumed that these reactions are as follows:



4. Their dilute solutions, about one per cent, are equally sensitive to potassium-mercuric iodide, forming a precipitate of $(C_{10}H_{14}ONMeMe)_2HgI_4$. These are yellowish white and remain undissolved on the addition of dilute acetic or hydrochloric acid. This test could be more satisfactorily used for distinguishing these three halides from other ephedrine preparations than for distinguishing between methyl-ephedrine and ephedrine (8) as suggested by Smith.

5. They are equally responsive to the following reagents:

Gold chloride, platinum chloride, mercuric chloride, phospho-molybdic acid, bismuth nitrate, potassium bismuth iodide, picric acid, Wagner's reagent (iodine in potassium iodide solution), etc.

Some of these reactions will be discussed in a later paper as they can be applied qualitatively to ephedrine and all of the derivatives which we have prepared (4), (5). Some of them, used in distinguishing between these three halides, are described as follows.

II. SPECIFIC.—1. These three halides are responsive to the ordinary tests for alkali halides and can be distinguished one from another by such reagents as silver nitrate, chlorine water, lead nitrate, mercuric chloride, potassium permanganate, etc.

2. The chloride and bromide form leaflet crystals with auric chloride and platonic chloride, respectively (Fig. 10, 11, 13 and 14), which are generally soluble in water and alcohol, insoluble in ether, and somewhat slightly soluble in chloroform. The chloride gives light green-color-like crystals and the bromide gives orange red-color-like crystals and the iodide is dark violet. These colors are similar to the colors of the halogens themselves.

3. The iodide forms clustered leaflets with auric chloride (Fig. 12) and fine clusters with platonic chloride (Fig. 13). The former is soluble in chloroform and

spective precipitates of ephedrine (1) and other ephedrine derivatives (to be reported later) formed in the same manner require 5 to 20 days to show the same color change.

6. *Tests for the Iodide Only.*—Ferric chloride produces a reddish brown precipitate and copper sulphate a yellowish brown one. On the addition of sodium thiosulphate, the former dissolves entirely to form a clear solution but the latter only partially. Ephedrine and other ephedrine derivatives do not show these reactions.

SUMMARY.

1. Methyl-ephedrine-methyl-iodide was isolated in pure form from the methylation mixture used for preparing methyl-ephedrine-iodide.

2. Pure methyl-ephedrine-methyl-chloride and methyl-ephedrine-methyl-bromide were prepared from the iodide by a modified transformation method.

3. These three quaternary ammonium halides were found to produce no "biuret coloration." Their "molecular rotations" were equal, showing that the "atomic rotations" of these three halogens in their respective quaternary ammonium halides are the same.

4. Potassium di-chromate, auric chloride, platinum chloride, etc., are found to be good reagents for testing these three halides.

5. Methyl-ephedrine-methyl-iodide forms methyl-ephedrine-methyl-auric-iodide, $(C_{10}H_{14}ONMeMe)AuI_4$, which possesses most of the general physical properties of iodine except the coloration with starch.

6. Bismuth can be detected, by methyl-ephedrine-methyl-iodide, in an aqueous solution slightly acidified with nitric acid containing 0.001% bismuth nitrate.

7. These three halides crystallize into variable forms and with certain reagents produce characteristic crystals (Fig. 1 to 14).

LITERATURE.

- (1) K. K. Chen and C. H. Kao, *Jour. A. Ph. A.*, 15 (1926), 629, 632 (625-639).
- (2) A. Eberhard, *Arch. Pharm.*, 258 (1920), 97.
- (3) H. Emde, *Ibid.*, 244 (1906), 241.
- (4) C. T. Feng, *Chinese J. Physiol.*, 1 (1927), 397-406.
- (5) C. T. Feng, *Ibid.*, 4 (1930), 231-246.
- (6) Schwantke, *Zeit. Kryst. Mineralogy*, 46 (1909), 73; cited by Chen and Kao.
- (7) Sydney Smith, *J. Chem. Soc.*, 270 (1927), 2056-2058.
- (8) T. and H. Smith, *Pharmaceutical J.*, 125 (1929, No. 3452), 606.

ON THE ASSOCIATE ACTION OF QUININE AND OF ETIOLOGIC URETHANE IN REGARD TO THEIR USE IN THE THERAPY OF MALARIA.

BY PROF. ANGELO SPANIO.

Etiologic urethane is very little used in therapy, and would have been completely forgotten if it had not been for Gaglio who suggested its particular use in dissolving quinine chloride for intramuscular injections for the cure of malaria. Although this solution (Gaglio Solution) is very widely used, nevertheless a few cases of sudden death through its use, influenced Prof. Spanio to make a pharmacological study of urethane. He arrived at the following conclusions:

1. The minimum lethal dose of etiologic urethane, by intravenous injection, is two Gm. per each Kg. of body weight of the animal.

2. Death is caused principally through the paralysis of the respiratory center.

3. Death is due to the direct action of the drug on the nerve center.—*Archivio di Farmacologia Sperimentale e Scienze Affini, Roma*, November 1931.