

## SCIENTIFIC SECTION

### EPHEDRINE AND PSEUDOEPHEDRINE, THEIR ISOLATION, CONSTITUTION, ISOMERISM, PROPERTIES, DERIVATIVES AND SYNTHESIS. (WITH A BIBLIOGRAPHY).\*

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The recent pharmacological and clinical study of ephedrine reveals the fact that it acts qualitatively the same as epinephrine and that therapeutically it can replace or be used in conjunction with epinephrine in many instances. The advantages of ephedrine over epinephrine are its prolonged action and its effectiveness by mouth. There is also a similarity in their chemical structure. It is interesting to note that while ephedrine was prepared in its pure state sixteen years before epinephrine, its physiological investigation was delayed until recently. The chemical study of this compound and its isomer pseudoephedrine has occupied the last four decades, but a résumé of the work to date is yet wanting. The writers hope that the following review may be found of value for the identification of these compounds and of assistance in further researches.

#### I. ISOLATION.

Ephedrine and pseudoephedrine are two natural, optically active, isomeric, plant bases. The former is laevo-rotatory while the latter is dextro-rotatory. The stem of the plant yielding ephedrine has been known as Ma Huang in Chinese medicine for more than 5000 years, and fully discussed by Li Shih-cheng in his "Pentsao Kang Mu" written in 1596 A.D. It was, however, not until 1885 that G. Yamanashi first isolated an alkaloid in its impure state from the Chinese material at the Osaka Experimental Station, Japan. After the death of the discoverer, Nagai (1887), with the assistance of Y. Hori, continued the study, and named it ephedrine. The botanical name of the plant as given by Nagai was *Ephedra vulgaris*, Rich. var. *helvetica*, Hook. et Thompson. Merck of Germany claimed to have isolated the same principle from the same variety in 1888, but made no mention as to where the plant was obtained. In 1923 Chen re-isolated the same principle at Peking, China, from the material purchased in Peking and in its vicinity. The recent pharmacological and clinical reports in this country and Canada were made with this product.

In 1889 Ladenburg and Oelschlägel published their results on a second base, named pseudoephedrine, prepared by Merck and obtained from a plant belonging to the same genus *Ephedra*. In 1902 Miller was able to isolate only pseudoephedrine and no ephedrine in the European variety. His plant was identified by Arthur Meyer as *Ephedra vulgaris* var. *helvetica*. Caesar and Loretz at Halle as quoted by Miller had the same experience. It appears, therefore, probable that the plant *Ephedra vulgaris* var. *helvetica* yields ephedrine when grown in China, but pseudoephedrine when grown in Europe. Such analogy can be found in oil of turpentine, for the French and Spanish oils contain *l*- $\alpha$ -pinene whereas the American and Greek oils the dextrogyrate modification.

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The basic principle separated from *Ephedra monostachia*, although also called ephedrine is chemically and physiologically different from the two isomers described above (Spehr, Bagoslowky, Vesternik), and therefore is not discussed here.

The method of isolating ephedrine or pseudoephedrine is most simple and follows the general principle of preparing any common alkaloid. Nagai in his early method employed acidified water for extraction, while others used alcohol. On concentrating the extract, Nagai and Merck extracted ephedrine with ether after alkalization, whereas Ladenburg and Oelschlägel, and Chen extracted the base with chloroform after making the solution alkaline with ammonium hydroxide. The common salt (hydrochloride or sulphate) as made by those workers was by direct neutralization of the base by the corresponding acid without previous conversion to any other compound. The yield of ephedrine hydrochloride was given by Nagai as between 0.31 to 0.40 per cent of the crude material. Chen, employing pharmacopœial method of assay, reported the content of the free base, ephedrine, to vary from 0.018 to 0.091 per cent of the crude drug in the specimens he studied.

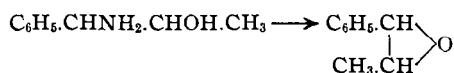
## II. CONSTITUTION.

The Asiatic and European investigators (Ladenburg and Oelschlägel, Nagai, Merck) all agree that both ephedrine and pseudoephedrine have the empirical formula  $C_{10}H_{15}NO$  as determined by elementary analysis, and by the depression of freezing point. The mydriatic action of ephedrine led Nagai to suspect its chemical similarity with atropine. But, on treating ephedrine with magnesium hydroxide, he could find no evidence of tropine or tropic acid. Upon decomposition with oxidizing agents or in hydrochloric acid solution, both ephedrine and pseudoephedrine yield methylamine and benzaldehyde or benzoic acid. Thus, Ladenburg and Oelschlägel (1889) recovered methylamine and benzoic acid from pseudoephedrine after the treatment with potassium permanganate. Nagai (1892) obtained the same substances by heating ephedrine in 25 per cent hydrochloric acid to 160–170° and subsequent treatment with potassium dichromate and sulphuric acid. Merck (1893) obtained methylamine and benzaldehyde which latter is soon oxidized to benzoic acid, by heating ephedrine aurichloride in hydrochloric acid with a reflux condenser on a water-bath. Schmidt (1914) resolved both ephedrine and pseudoephedrine into benzaldehyde and methylamine, by means of alkaline potassium ferricyanide, or one per cent potassium permanganate, or alkaline solution of chlorine or bromine. The presence of a benzene ring is thus established. Investigators of the East and the West further agree that both ephedrine and pseudoephedrine give a nitroso-compound, and, upon deamination, yield a N-free compound having the empirical formula  $C_9H_{10}O$  (Nagai, Miller, Schmidt, Rabe), proving that both are secondary bases, and that both contain methylamino group. Experiments further show that ephedrine does not react with hydroxylamine and phenylhydrazine (Nagai, Miller), and does not give any color reaction with phenolic reagents such as ferric chloride and Millon's reagent (Chen). The O-atom in the molecule therefore does not exist in the form of an aldehyde, a ketone, or a phenol, but in the form of an alcohol. The success in the preparation of the dibenzoyl derivative of ephedrine and pseudoephedrine establishes definitely the replaceability of the H-atoms of the —OH and =NH groups at the same time (Ladenburg and Oelschlägel, Nagai, Miller). From the above data, the partial structural

formula for both ephedrine and pseudoephedrine is  $C_6H_5.C_3H_5 \begin{matrix} \text{OH} \\ \diagdown \\ \text{NHCH}_3 \end{matrix}$  and its complete structure must conform to one of the following nine configurations:

- |                                 |     |                                  |     |
|---------------------------------|-----|----------------------------------|-----|
| $C_6H_5.CHOH.CH(NHCH_3).CH_3$   | (1) | $C_6H_5.CH_2.CH(NHCH_3).CH_2OH$  | (6) |
| $C_6H_5.CHOH.CH_2.CH_2(NHCH_3)$ | (2) | $C_6H_5.CH(CH_2OH).CH_2(NHCH_3)$ | (7) |
| $C_6H_5.CH_2.CHOH.CH_2(NHCH_3)$ | (3) | $C_6H_5.CO(CH_3).CH_2(NHCH_3)$   | (8) |
| $C_6H_5.CH(NHCH_3).CHOH.CH_3$   | (4) | $C_6H_5.C(NHCH_3)(CH_3).CH_2OH$  | (9) |
| $C_6H_5.CH(NHCH_3).CH_2.CH_2OH$ | (5) |                                  |     |

Among these formulas, according to Nagai, (2) and (5) should give rise to oxalic acid upon oxidation, (3) and (6) to phenyl-acetic acid, and (7), (8) and (9) to carbon dioxide. Since none of these substances is found in the decomposition of ephedrine and pseudoephedrine, and since the two compounds do not possess equivalent specific rotation, there must be more than one asymmetrical C-atom and the —OH and —NHCH<sub>3</sub> groups must be linked to the two C-atoms nearest the benzene ring respectively. Our discussion can now be limited to (1) and (4). The decomposition of ephedrine or pseudoephedrine to benzaldehyde and then to benzoic acid is suggestive of the presence of the —OH group in the C-atom adjacent to the benzene ring. Substantial evidence for the formula (1) is found in the fact that ephedrine or pseudoephedrine on deamination does not give rise to an ethylene-oxide corresponding to the one obtained from phenyl-methyl-oxyethylamine,

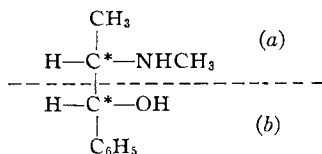


(Rabe) and that ephedrine or pseudoephedrine on dehydroxylation yields a compound identical with the synthetic *d*-β-phenyl-isopropyl-methylamine,  $C_6H_5.CH_2.CH(NHCH_3).CH_3$  (Ogata). The correctness of the formula (1) is finally confirmed by the synthesis and resolution to the optically active isomers (Späth and Göhring). Ephedrine or pseudoephedrine should therefore be termed chemically β-phenyl-β-hydroxy-α-methyl-ethyl-methylamine, or 1-phenyl-2-methylamino-propanol-1.

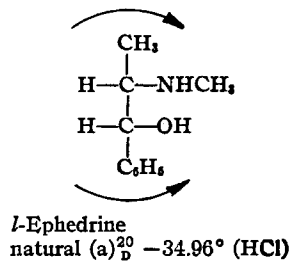
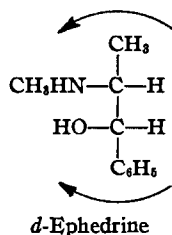
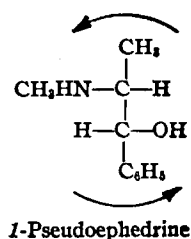
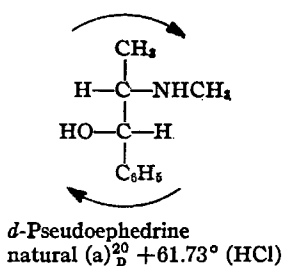
### III. ISOMERISM.

It has been mentioned that ephedrine and pseudoephedrine do not possess equivalent optical rotation in the opposite direction. In configuration they are therefore not optical antimers. Under suitable conditions they can be interconverted. Nagai (1892) first observed that by heating ephedrine with 25 per cent hydrochloric acid in a sealed tube at 130–140° for 3 hours, a dextro-rotatory base of the same formula is recovered which he called *isoephedrine*. The same substance is formed when chloephedrine hydrochloride ( $C_{10}H_{14}NCl.HCl$ ) is heated in aqueous solution at 160° under pressure for 3 hours, or reacted upon with silver nitrate in nitric acid. Nagai made special mention that isoephedrine is not present in Ma Haung. Flaecher (1904) and Schmidt (1906) found that this isoephedrine of Nagai is identical with the natural pseudoephedrine. Transformation of ephedrine to pseudoephedrine, partially or completely, also takes place in water at 200–205° (Schmidt), with concentrated sulphuric acid (Schmidt), with sodium

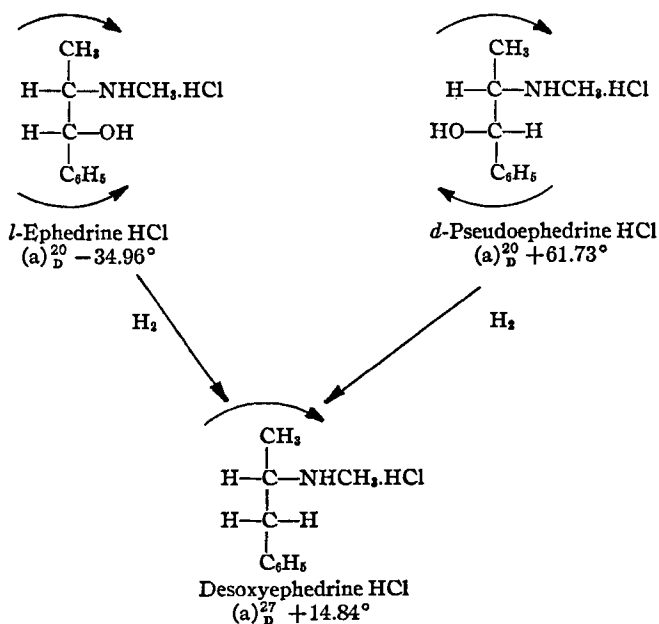
carbonate (Emde), in regeneration of the base from bromephedrine, and in the formation of acetyl-ephedrine or nitroso-ephedrine (Schmidt). In 1908 Schmidt succeeded in converting pseudoephedrine to ephedrine by heating with 25 per cent hydrochloric acid on a hot water-bath, and later (1912) Schmidt and Callies effected the conversion with barium hydroxide. It appears obvious that either ephedrine or pseudoephedrine can undergo intramolecular rearrangement and be transformed into the other, and that there are more conditions under which ephedrine is converted to pseudoephedrine than *vice versa*. The asymmetry of these two isomers has been ably elucidated by Ogata. The structural formula of ephedrine or pseudoephedrine shows two asymmetrical C-atoms, and differs from that of tartaric acid in having unlike halves (a) and (b).



(b) is more optically active because of a larger molecule. There are then six possible isomers, of which the four optically active ones may be represented as follows:



In natural ephedrine, the optical rotation of (a) and (b) is in the opposite direction, whereas, in natural pseudoephedrine, that of (a) and (b) is in the same direction. Pseudoephedrine is therefore more dextro-rotatory than ephedrine is laevo-rotatory. The correctness of this view has been proved by the fact that ephedrine and pseudoephedrine, upon dehydroxylation, give rise to the same dextro-rotatory compound termed by Ogata *desoxyephedrine*, as indicated below, which is identical with the synthetic *d*- $\beta$ -phenyl-isopropyl-methylamine,  $\text{C}_6\text{H}_5.\text{CH}_2.\text{CH}(\text{CH}_3).\text{NHCH}_3$ .



## IV. PROPERTIES.

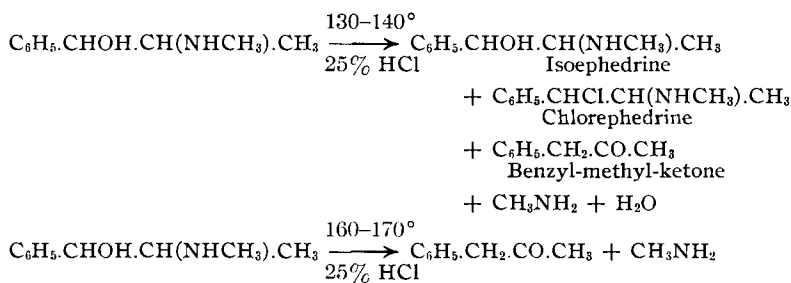
*Ephedrine*,  $\text{C}_6\text{H}_5 \cdot \text{CHOH} \cdot \text{CH}(\text{NHCH}_3) \cdot \text{CH}_3$  is an oily substance when shaken out with ether, but crystallizes in colorless, odorless needles or rosettes on standing. It melts at  $39-40^\circ$  (Nagai) and boils above  $200^\circ$  (Nagai, Merck). Chen in his first paper reported an abnormally high melting point ( $210^\circ$ ), but on reinvestigation found it to be due to contamination with the hydrochloride. Its specific rotation in absolute alcohol is  $(a)_D^{20} - 6.3^\circ$  (Gadamer). It is soluble in ether, chloroform, alcohol, petroleum ether, acetone and water, the aqueous solution having a strongly alkaline reaction. When dissolved in a small amount of water and heated, there is an aromatic odor evolved. Ephedrine reacts with some of the alkaloidal reagents. In the form of common soluble salts (hydrochloride or sulphate), it renders Mayer's solution turbid if dilute, but gives a white precipitate if concentrated. It produces an orange precipitate with Wagner's reagent; a greenish yellow precipitate becoming blue on standing, with phosphomolybdic acid; a heavy white precipitate with phosphotungstic acid; a yellow ring below and a pink ring above with Erdmann's reagent or concentrated sulphuric acid; and a bluish green color becoming brown on standing, with potassium dichromate and concentrated sulphuric acid (Chen). It forms crystals with auric chloride and platinic chloride, respectively, which are soluble in water but insoluble in alcohol ether mixture. It shows no visible changes with ferric chloride, Millon's reagent, tannic acid, picric acid, or concentrated nitric acid. A sensitive color test is found in its reaction with copper sulphate and sodium hydroxide, a purple color being obtained. The test was originally described by Nagai (1892), and its principle is most likely similar to the biuret reaction of proteins. The following procedure has been found by us to be satisfactory: To 1 cc. of the unknown solution, is added 0.1 cc. of 10 per cent copper sulphate and 1 cc. of 20 per cent sodium hydroxide in a 5-cc. tube. If ephedrine is present, a purplish color

is developed, which can be extracted by 1 cc. of ether. This test is sensitive to 2.5 mg. of ephedrine sulphate in 1 cc. of water and definitely positive with 5 mg. in 1 cc. of water. If the amount of ephedrine sulphate exceeds 25 mg. in 1 cc. of water, there will be formed a pinkish purple precipitate which is soluble in ether. Pseudoephedrine and synthetic ephedrine of Nagai give the same color reaction, but can be distinguished from ephedrine by their respective melting points and optical rotation. Whether the same method can be used for the quantitative colorimetric determination of ephedrine or not awaits investigation. Ephedrine is said to reduce Fehling's and Tollen's reagents gradually, and the free base to decompose the salts of several heavy metals to metallic oxides (Nagai).

*Pseudoephedrine*, sometimes termed  $\psi$ -ephedrine,  $\text{C}_6\text{H}_5\text{.CHOH.CH(NHCH}_3\text{).CH}_3$ , m. p. 117–118° (114–115° Ladenburg and Oelschlängel),  $(a)_D^{20} + 51.2^\circ$ , forms colorless crystals, and has a faint, pleasant odor. It is rhombic, 1 : b : c = 0.84492 : 1 : 1.8598 (Schwantke), readily soluble in ether and alcohol, but sparingly soluble in cold water.

Ephedrine and pseudoephedrine are interconvertible under different conditions as discussed above. Both isomers form addition compounds by the conversion of trivalent N to pentavalent N with acids or alkyl radicals. The H-atom of the imido group of each base can be replaced by a nitroso, alkyl, acetyl, benzoyl, or phenylthiourea radical. The H-atom of the hydroxyl group can be substituted by a benzoyl or acetyl radical. The whole hydroxyl group may be replaced by chlorine or bromine (Nagai, Schmidt).

The action of hydrochloric acid on ephedrine appears to have been most thoroughly studied by Nagai. While the European scholars noticed the conversion into pseudoephedrine, Nagai, in addition, detected other by-products by varying the degree and duration of heating in a sealed tube as plainly expressed in the following steps:



The N-free fragment having the formula  $\text{C}_9\text{H}_{10}\text{O}$  from the decomposition of ephedrine or pseudoephedrine is a compound of interest. It may be obtained by exhaustive methylation and subsequent distillation, by heating with 25 per cent hydrochloric acid in a sealed tube (Nagai), by heating with ethylbenzoate, or by distilling in a current of steam or carbon dioxide (Schmidt). The one from ephedrine is not identical but isomeric with the other from pseudoephedrine, for the former boils at 204°, the latter at 197–199° (Rabe). Nagai identified that obtained from ephedrine as benzyl-methyl-ketone  $\text{C}_6\text{H}_5\text{.CH}_2\text{.CO.CH}_3$ . Miller, Schmidt and Emde suggested that the substance might be an aromatic alcohol with an unsaturated side chain. Rabe considered them as isomeric forms of phenyl-methyl-

ethylene-oxide. Schmidt a little later (1915) reported that the product from ephedrine was a mixture of phenyl-ethyl-ketone  $C_6H_5.CO.CH_2.CH_3$ , and phenyl-propylene-oxide  $C_6H_5.CH \begin{matrix} | \\ CH_3 \end{matrix} \begin{matrix} \diagup \\ CH \end{matrix} O$ . The latter, on taking up water, becomes phenyl-propylene-glycol  $C_6H_5.CHOH.CHOH.CH_3$ .

#### V. DERIVATIVES.

*Ephedrine Hydrochloride*,  $C_6H_5.CHOH.CH(CH_3).NHCH_2.HCl$ , prepared by direct neutralization of ephedrine with hydrochloric acid, or by passing dry hydrochloric acid gas into the ether solution, crystallizes in colorless, fine needles, melts at  $214-216^\circ$  and rotates the plane of polarized light to the left.

$(a)_D^{15} - 36.66^\circ$  (Miller)

$(a)_D^{20} - 35.56^\circ$  (Schmidt and Bümning)

$(a)_D^{20} - 34.96^\circ$  (Emde)

$(a)_D^{20} - 35.00^\circ$  (Chen)

$(a)_D^{20} - 35.30^\circ$  (Gadamer)

It is soluble in water and alcohol and insoluble in ether. It is stable on standing or at  $100^\circ$ , and yields a precipitate with silver nitrate. The *platinichloride*,  $(C_{10}H_{15}NO.HCl)_2.PtCl_4$ , orange, long needles, m. p.  $184-186^\circ$  with decomposition, is soluble in water and alcohol but practically insoluble in ether. The *aurichloride*,  $(C_{10}H_{15}NO.HCl).AuCl_3$ , golden crystals, m. p.  $128-131^\circ$ , undergoes decomposition on standing, with the deposition of metallic gold.

*Ephedrine hydriodide*,  $C_{10}H_{15}NO.HI$ , m. p.  $155-156^\circ$ , forms rhombic, hemihedral crystals, a: b: c = 0.73703: 1: 0.28643 (Schwantke).

*Ephedrine sulphate*,  $(C_{10}H_{15}NO)_2.H_2SO_4$ , colorless, plate-like, rhombic crystals, m. p.,  $235-236^\circ$ , is soluble in water and warm alcohol, but difficultly soluble in cold alcohol or ether alcohol mixture. The melting point is constant only after numerous recrystallizations as shown below:

Fraction of crystallization	m. p.	Fraction of crystallization	m. p.
First	$211-212^\circ$	Twelfth	$235-236^\circ$
Second	$212-213^\circ$	Mixture of several high fractions	
Third to Seventh	$227-228^\circ$	from one preparation	$234-235^\circ$
Eighth	$235-236^\circ$	Mixture of several high fractions	
		from another preparation	$235-236^\circ$

This salt is of practical value because it is more easy to crystallize from alcohol than the hydrochloride.

*Ephedrine bisulphate*,  $C_{10}H_{15}NO.H_2SO_4$ , is difficultly soluble in water (Nagai).

*Ephedrine nitrate*,  $C_{10}H_{15}NO.HNO_3$ , colorless, transparent, flat needles, has about the same solubility as the sulphate.

*Ephedrine acetate*,  $(C_{10}H_{15}NO).HOOC.CH_3$ , colorless, crystalline needles, hygroscopic, is easily soluble in alcohol and ether.

*Ephedrine hydrobromide, phosphate, oxalate, tartrate, citrate, benzoate and salicylate* are said to have been prepared by Hori (Nagai).

*Pseudoephedrine hydrochloride*, colorless slender needles, m. p.  $176^\circ$ ,  $(a)_D^{20} + 61.73^\circ$  to  $+62.05^\circ$  (Emde, Flaecher), is very soluble in water and alcohol. The *aurichloride* crystallizes from water in long, branching needles. The *platinichloride, picrate, periodate, cadmium iodide and bismuth iodide* appear to be oily substances.

*Pseudoephedrine hydriodide*, m. p.  $172^\circ$  ( $165^\circ$  Ladenburg and Oelschlägel), is rhombic, holohedral (bipyramidal), a: b: c = 0.60282: 1: 1.3722 (Schwantke).

*Pseudoephedrine hydrobromide*, best crystallized from water, melts at  $174-175^\circ$ .

*Nitrosoephedrine*,  $C_6H_5.CHOH.CH(CH_3).NCH_3.NO$ , easily prepared with nitrous acid, is a yellow oily mass which solidifies on standing into flat needles, m. p.  $92^\circ$  (Nagai), soluble in alcohol and ether but difficultly soluble in cold water, and decomposes in hot water.

*Nitrosopseudoephedrine* melts at  $80-82^\circ$  (Ladenburg and Oelschlägel), Schmidt and Calliess (1912) claimed that ephedrine and pseudoephedrine yield the same nitroso-compound, m. p.  $80^\circ$ , due to the conversion of ephedrine to pseudoephedrine with nitrous acid.

*Ephedrine-phenyl-thiourea*,  $C_6H_5.CHOH.CH(CH_3).N(CH_3)(CS.NH.C_6H_5)$ , prepared from phenyl mustard oil (Gadamer), m. p.  $115^\circ$  with decomposition,  $(a)_D^{20} - 105.1^\circ$ , rosette prisms, is rhombic, hemihedral, sphenoidal, a: b: c = 0.81703: 1: 0.42834 (Blass).

*Pseudoephedrine-phenyl-thiourea*, m. p.  $122^\circ$  without decomposition,  $(a)_D^{20} + 22.8^\circ$ , is rhombic, a: b: c = 0.37134: 1: 0.62669.

*Benzoyl-ephedrine*,  $C_6H_5.CHOH.CH(CH_3).N(CH_3)(C_6H_5.CO)$ , colorless transparent crystals, m. p.  $113^\circ$ , is soluble in hot alcohol, but difficultly soluble in water (Nagai).

*Benzoyl ester of benzoyl-ephedrine*,  $C_6H_5.CH(O.C_6H_5.CO).CH(CH_3).N(CH_3)(C_6H_5.CO)$ , colorless, transparent, flat needles, m. p.  $134^\circ$  reported by Nagai ( $115-116^\circ$  Miller), is soluble in ether, chloroform and alcohol, but insoluble in water. The *dibenzoyl derivative of pseudoephedrine* melts at  $119-120^\circ$  (Ladenburg and Oelschlagel).

*Acetyl-ephedrine*,  $C_6H_5.CHOH.CH(CH_3).N(CH_3)(CH_3.CO)$ , m. p.  $87^\circ$ , was first prepared by Nagai (1892). Miller (1902) made two different monoacetyl ephedrines: One with acetic anhydride and sodium acetate, the *platinichloride* of which melts at  $210^\circ$ ; the other in the absence of sodium acetate, the *platinichloride* of which melts at  $185^\circ$ . He suggested that in one the acetyl group is attached to the N-atom, and in the other to the O-atom. Schmidt and Callies (1912) obtained an identical monoacetyl derivative from ephedrine and pseudoephedrine, and believed that during acetylation ephedrine is converted to pseudoephedrine. Their compound melts at  $101^\circ$ , its *hydrochloride* at  $176^\circ$ ,  $(a)_D^{20} + 96.8^\circ$ , its *platinichloride* at  $184^\circ$ , and its *aurichloride* at  $165^\circ$ . Upon heating, acetyl-ephedrine hydrochloride yields acetic acid, chloroephedrine isoeephedrine and ephedrine (Nagai).

*Methyl-ephedrine*,  $C_6H_5.CHOH.CH(CH_3).N(CH_3)_2$ , prepared with methyl iodide in methyl alcohol, colorless, transparent prisms, m. p.  $84^\circ$  (Nagai) ( $59-62^\circ$  Miller;  $78^\circ$  Eberhard),  $(a)_D^{15} - 18.96$  (Eberhard), is soluble in ether, chloroform, carbon bisulphide, alcohol, and slightly soluble in cold water giving basic reaction, and decomposes the salts of several heavy metals to metallic oxides. The *hydrochloride*, m. p.  $182-186^\circ$  (Eberhard), is soluble in water and alcohol. The *oxalate* is also soluble in water and alcohol. The *aurichloride*, m. p.  $120-123^\circ$  (Miller), ( $129^\circ$  Eberhard), forms yellow thin plates. The *platinichloride*, m. p.  $155-160^\circ$  ( $181^\circ$  Eberhard), is easily soluble in water, alcohol and ether. The *mercurichloride* is soluble in hot water, but difficultly soluble in cold water. The *benzoyl derivative* has been prepared (Nagai).

*Methyl-pseudoephedrine* is an oily base, the *aurichloride* of which melts at  $119-123^\circ$  (Emde).

*Methyl-ephedrine-methyl-iodide*,  $C_6H_5.CHOH.CH(CH_3).N(CH_3)_2I$ , is a by-product of the preparation of methyl-ephedrine, in colorless, prismatic crystals, rhombic, hemihedral, a: b: c = 0.97926: 1: 0.76088 (Schwantke), m. p.  $203^\circ$  ( $199^\circ$  Emde), easily soluble in alcohol and warm water but difficultly soluble in cold water. Upon treatment with silver chloride, *methyl-ephedrine-methyl chloride*,  $C_6H_5.CHOH.CH(CH_3).N(CH_3)_2Cl$ , right angled plates, m. p.  $230^\circ$ ,  $(a)_D^{15} - 30.54^\circ$  (Eberhard), is obtained of which the *aurichloride* melts at  $188-190^\circ$ , the *platinichloride* at  $247^\circ$  ( $250^\circ$  Emde), and the *mercurichloride*,  $C_{10}H_{14}NO(CH_3).CH_3Cl.3\frac{1}{2}HgCl_2$ , forms colorless cubes, difficultly soluble in water (Merck). The *acetyl derivative*,  $C_{10}H_{13}NO(CH_3).CH_3Cl.(CH_3.CO)$ , forms a *platinichloride*, m. p.  $186-188^\circ$  (Miller).

*Methyl-pseudoephedrine-methyl-iodide*, rhombic, holohedral (bipyramidal), a: b: c = 0.64227: 1: 1.2088 (Schwantke), melts at  $205^\circ$ . *Methyl-pseudoephedrine-methyl-chloride* forms a *platinichloride*, m. p.  $204-205^\circ$ , and an *aurichloride*, m. p.  $194^\circ$  (Emde).

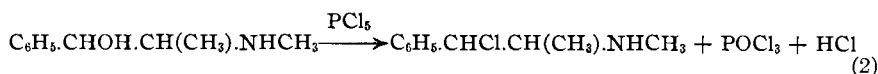
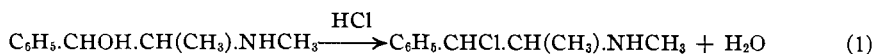
*Methyl-ephedrine (and pseudoephedrine)-methyl-hydroxide*,  $C_6H_5.CHOH.CH(CH_3).N(CH_3)_2-OH$ , can be prepared by treating silver oxide with methyl-ephedrine (or pseudoephedrine)-methyl-iodide. Upon distillation it yields trimethylamine and a N-free fragment having the empirical formula  $C_9H_{10}O$  the nature of which has been discussed above. This substance may condense with ephedrine in the reaction of methyl-ephedrine-methyl-iodide with sodium amalgam (Eberhard), and has been known under the name of *ephedrine-phenyl-propylene-oxide*.  $C_{10}H_{15}NO.C_9H_{10}O$ , plates, m. p.  $125^\circ$ ,  $(a)_D^{15} - 3.59^\circ$  to  $-3.63^\circ$ . The *hydrochloride*, right-angled plates, m. p.  $155-156^\circ$ ,  $(a)_D^{15} + 14.74^\circ$  to  $+ 14.93^\circ$ , forms an *aurichloride*, m. p.  $144-145^\circ$ , and a *platinichloride*, m. p.  $176.5-177^\circ$ . Methylation of this compound under various conditions yields two isomeric derivatives: the methyl-iodide and methyl-chloride of the one melt at  $183^\circ$  and  $203^\circ$ ; whereas the corresponding iodide and chloride of the other melt at  $164^\circ$  and  $165-167^\circ$ , respectively.

*Ethyl-ephedrine*,  $C_6H_5.CHOH.CH(CH_3).N(CH_3)C_2H_5$ , prepared in the same manner as methyl-ephedrine (Nagai), forms a *hydrochloride*, m. p.  $156^\circ$ , and a *platinichloride*, m. p.  $97^\circ$ .



*Benzal-ephedrine*,  $C_6H_5.CHOH.CH(NHCH_3).CH.CH.C_6H_5$ , formed in the decomposition of ephedrine by potassium ferricyanide or potassium permanganate (Schmidt), m. p. 72–73°, slowly decomposed in the cold, rapidly when heated, forms a *platinichloride* and an *aurichloride* which are reddish yellow powders. *Benzal-pseudoephedrine*, similarly prepared, m. p. 65°, forms a *platinichloride* which is also a reddish yellow powder.

*Chlorephedrine*,  $C_6H_5.CHCl.CH(CH_3).NHCH_3$ , can be prepared by heating ephedrine in hydrochloric acid, or by treating ephedrine with phosphorus pentachloride (Nagai), as shown below:

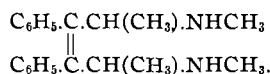


It is colorless, viscous, transparent liquid, with "anesthetic odor," alkaline in solution, soluble in alcohol and ether, difficultly soluble in water, decomposes salts of heavy metals to metallic oxides, and gives the nitroso reaction. When treated with silver nitrate and nitric acid, pseudoephedrine (isoeephedrine) is produced. The *hydrochloride*, small colorless needles, m. p. 168–170°, forms an *aurichloride*, m. p. 118°, and a *platinichloride*, a yellow powder.

*Bromephedrine*,  $C_6H_5.CHBr.CH(CH_3).NHCH_3$ , prepared from phosphorus pentabromide and ephedrine (Schmidt and Bümbling), forms a hydrobromide, plates or leaflets, m. p. 174.5°,  $(a)_D^{19} - 92.54^\circ$ . On standing, or reacting with silver nitrate, pseudoephedrine is regenerated. The *platinichloride* melts at 188–189°, the *aurichloride* at 138–139°, and the *acetyl derivative*, prisms,  $(a)_D^{15} + 80^\circ$ , at 175°. *Brompseudoephedrine* is identical with bromephedrine.

*Desoxyephedrine* (Ogata), or  $\beta$ -phenyl-isopropyl-methylamine,  $C_6H_5.CH_2.CH(CH_3).NHCH_3$ , is dehydroxylated ephedrine or pseudoephedrine, prepared by treating the base with hydriodic acid and yellow phosphorus. Both yield the same compound. It is a liquid, having an amine odor, and boils at 208–210°. The *hydrochloride*,  $(a)_D^{27} + 14.8^\circ$ , melts at 170–171°, the *bitartrate* at 118–119°, the *mercurichloride* at 152–153°, the *aurichloride* at 127°, the *platinichloride* at 214–215°, and the *picrate* at 144.5°. The same compound was prepared by Nagai and Schmidt.

*Ephedridin* (Nagai),  $C_6H_5.CH.C(CH_3).NHCH_3$ , is anhydrous ephedrine, obtained by heating chlorephedrine. It boils at 185°, and forms a *hydrochloride*, m. p. 174°, and an *aurichloride*, m. p. 135°. Schmidt (1914) also prepared an anhydrous ephedrine, named *apoephedrine*, from either ephedrine or pseudoephedrine with concentrated sulphuric acid, to which Schmidt ascribes the formula



The *dibromide*, *platinichloride* and *aurichloride* are all amorphous.

*Mydriatine* (Nagai),  $C_6H_5.CHOH.CH(CH_3).NH_2$ , is demethylated ephedrine. Its mydriatic action is believed to be more powerful than that of ephedrine (Amatsu and Kubota).

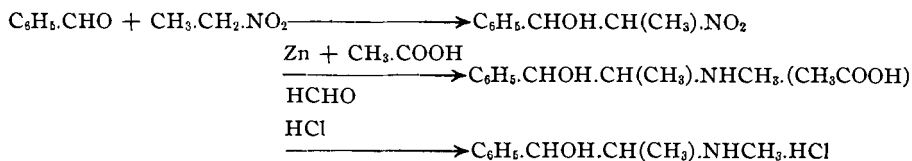
*Mydrine* (Merck), is not a chemical entity, but a mixture of ephedrine and a trace of homatropine for ophthalmological uses.

## VI. SYNTHESIS.

The success in the synthesis of ephedrine and pseudoephedrine marks one of the triumphs attained in the field of synthetic organic chemistry. Schmidt and his associates made various attempts to convert cinnamylamine,  $C_6H_5.CH:CH.CH_2.NH_2$ , and phenyl-ethyl-ketone,  $C_6H_5.CO.CH_2.CH_3$ , to ephedrine but they did not succeed in obtaining the desired compound.

Nagai (1909), by treating phenyl-ethyl-ketone with nitrous acid and subsequent reduction and methylation, also could find no trace of ephedrine. Later, he succeeded in making a racemic ephedrine, and patented it (1916) in the United States, Canada and England, under the name of *methyl-mydriatine*. His process

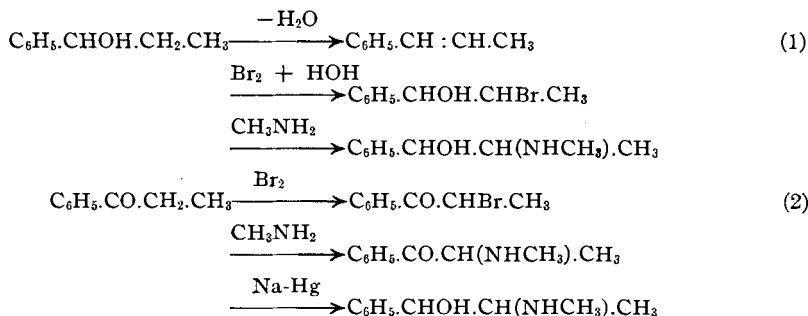
consists of condensation of benzaldehyde with nitroethane in weak alkali, and subsequent reduction in the presence of formaldehyde, as shown below:



The *hydrochloride*, m. p. 182°, reacts with cupric hydroxide as ephedrine hydrochloride. It is said that Nagai resolved his product into *l*- and *d*-varieties, and reported the results to the Tokyo Chemical Society in 1918 (Ogata).

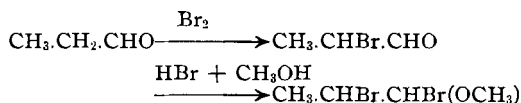
It was not until the method of methylation was improved that Schmidt's original suggestion of synthesizing ephedrine from phenyl-ethyl-ketone was realized. Thus Eberhard succeeded in obtaining an inactive ephedrine by reduction of  $\alpha$ -methylamino-ethyl-phenyl-ketone,  $\text{C}_6\text{H}_5.\text{CO}.\text{CH}(\text{CH}_3).\text{NHCH}_3$  (1915), and later (1920) by treatment of  $\alpha$ -bromomethyl-phenyl-ketone,  $\text{C}_6\text{H}_5.\text{CO}.\text{CHBr}.\text{CH}_3$ , with methylamine. The *base*, as reported by him (1915), melts at 114–115°, the hydrochloride at 180–181°, the *aurichloride* at 126°, and the *platinichloride* at 190–191°.

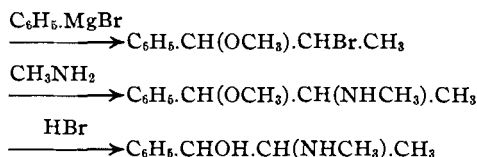
Fourneau (1904), by treating phenyl-propylene-iodohydrin,  $\text{C}_6\text{H}_5.\text{CHOH}.\text{CHI}.\text{CH}_3$ , with methylamine, obtained a compound having the formula of ephedrine (the *base*, b. p. 155–156°/31, m. p. 60°; the *hydrochloride*, m. p. 178°; the *dibenzoyl derivative*, m. p. 92°). The same substance was apparently obtained later by Fourneau and Puyal (1922) and Fourneau and Kanao (1924). In one instance, phenyl-ethyl-carbinol is dehydrated, and the resulting phenyl-propylene brominated and treated with methylamine; while in the other, phenyl-ethyl-ketone is brominated, treated with methylamine and reduced as shown below:



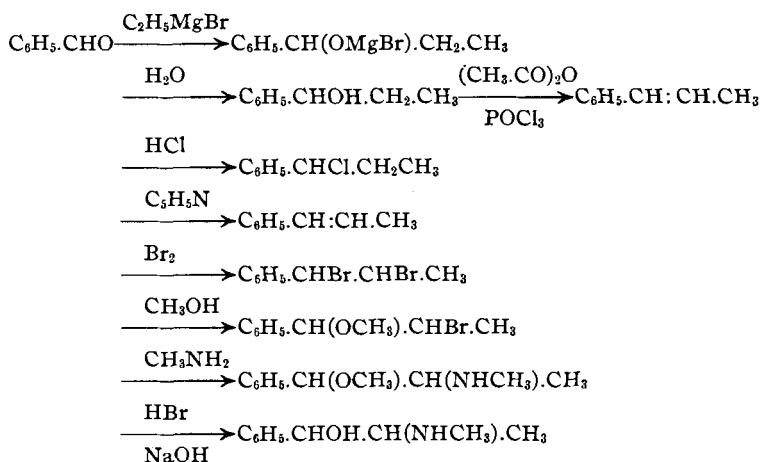
By acetylation those authors state that they were able to isolate pseudoephedrine identical with the natural (the *base*, m. p. 117°; the *hydrochloride*, m. p. 175°).

Späth and Göhring (1920) finally succeeded in isolating all the optically active ephedrines and pseudoephedrines. Their method of preparing the inactive compound, requiring propionaldehyde and phenyl-magnesium-bromide, differs considerably from any of their predecessors, and is illustrated below:





The final product is *dl*-pseudoephedrine (the base, m. p. 117–117.2°; the hydrochloride, m. p. 164°; the aurichloride, m. p. 186–187°). The *l*-pseudoephedrine is first separated as *d*-tartrate (the base, m. p. 118–118.7° ( $a_D^{22.5} - 52.5^\circ$ ); the hydrochloride, m. p. 181.5–182.5°, ( $a_D^{20} - 62.1$ ); the aurichloride, m. p. 126.5–127.5°; the phenyl-thiourea, m. p. 120–121°, ( $a_D^{20} - 23.1^\circ$ ), and the *d*-tartrate, m. p. 178°). The *d*-pseudoephedrine is identical with the natural pseudoephedrine (the *l*-tartrate, m. p. 178.5°). By heating with hydrochloric acid, *d*-pseudoephedrine is converted to *l*-ephedrine which is identical with the natural ephedrine. Similarly, *l*-pseudoephedrine can be converted to *d*-ephedrine (the base, m. p. 39–40°; the hydrochloride, m. p. 217.3–217.7°, ( $a_D^{20} + 35.8^\circ$ )). A mixture of equal quantity of each base constitutes *dl*-ephedrine (the base, m. p. 73–74°; the hydrochloride, m. p. 188.5–189°). Recently, Späth and Koller (1925) achieved another method of synthesizing racemic pseudoephedrine from benzaldehyde through phenyl-propylene, as shown in the following steps:



The molecular isomer of ephedrine, 1-phenyl-1-methylamino-propanol-2- $\text{C}_6\text{H}_5\cdot\text{CH}(\text{NHCH}_3)\cdot\text{CHOH}\cdot\text{CH}_3$ , has been synthesized and called ephedrine by some (Émde, Fourneau).

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## DOES CASCARA SAGRADA CONTAIN A TANNIN?\*

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As the official drug, Cascara Sagrada, the last four revisions of the United States Pharmacopœia have recognized the dried bark of the trunk and branches of *Rhamnus Purshiana*, DeCandolle.

Except for use as a cathartic by the Indians of the Pacific slope of North America, this bark was not employed until about fifty years ago, at which time its purgative effects were brought to the attention of the medical profession.

While the history of the introduction of cascara sagrada, the botany of the drug and all branches of its pharmacology have been dealt with by many contributors to this knowledge, reference will be limited to such parts of the literature of this and other drugs as shall seem to be needed for a relevant report on the question under consideration.

As mentioned by Warren (*JOUR. A. PH. A.*, p. 254, (1924)) although this drug has been the subject of research by many skilful analysts its chemistry is still obscure and "the subject is so full of interrogation points that no one can to-day assert with assurance a statement of the exact chemical constituents of this drug."

That is true not only as regards the important constituents of cascara but equally the case with respect to the medicinally unimportant principles, as for example "tannin," which is listed as a constituent of ranking importance by some text and reference books, while other books do not mention tannin as present in this drug.

In the hope of removing one of the aforesaid interrogation points by determining the presence or absence of tannin, this review of the literature and examination of the bark were undertaken.

It is also true that, while much has been written on cascara sagrada, the matter of tannin as a constituent has had but casual consideration, as will be made evident by bringing the comparatively few and very meagre references together.

That such has been the case is not at all strange, as cascara bark would scarcely be suspected of containing a tannin if decision had to depend on the recognition of an astringent taste, for bitterness is the continuous impression from the first

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