(5) D. I. Macht, *Ibid.*, Vol. XVII, No. 1 (January 1928).
(6) D. Matsumoto and D. I. Macht, *Jour. Urology*, III, No. 2 (April 1919), 63–85.

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CHEMICAL EXAMINATION OF α-PHENYL-β-AMINO-ETHANOL SULPHATE.*

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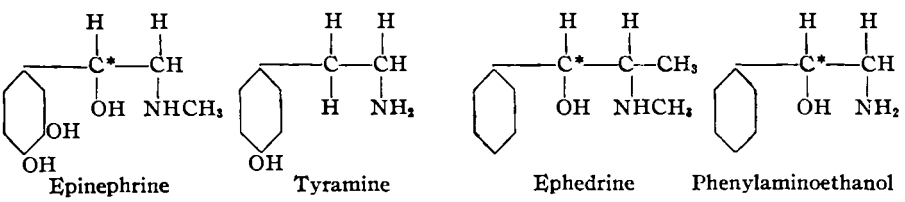
The varied therapeutic uses of epinephrine have created for it a demand that has led manufacturers and others to find in place of it compounds, either natural or synthetic, with variations within the molecule. Some of the variations have already found wide use; namely, ephedrine, isolated from Ma-Huang and tyramine, originally isolated from Ergot, but now prepared synthetically. Recently, a substance closely related to the three preparations described above has been described in the medical literature. More recently, a report detailing the clinical application of phenylethanolamine sulphate was submitted to the *Journal of the American Medical Association.*[1] As is the custom with papers dealing with new therapeutic agents the Council on Pharmacy and Chemistry was requested to make a preliminary report on the drug. In this connection, the Chemical Laboratory of the American Medical Association was asked to investigate the chemical constitution and character, and to elaborate standards for the drug.

Alles[2] has recently reported on the physiologic action of phenylethanolamine, or more specifically α-phenyl-β-aminoethanol. The compound has been previously described by others, notably by Mannich and Thiele,[3] who also prepared a number of derivatives and homologues of the compound.

A comparison of the structural formulas of epinephrine, ephedrine, tyramine and phenylaminoethanol[4] will serve to bring out the similarities and conversely the differences in their chemical nature.



Epinephrine Tyramine Ephedrine Phenylaminoethanol

It will be noted that the side chain of ephedrine contains three carbons, while the other three contain two; the former being a derivative of propyl benzene; the other three being derivatives of ethyl benzene. Epinephrine and tyramine both contain hydroxyl groups in the nucleus, hence may be expected to be more prone to oxidation, a serious objection pharmaceutically and therapeutically. Ephe-

* Contribution from the American Medical Association Chemical Laboratory.

[1] *J. A. M. A.*, 91 (1928), 1033.

[2] *J. Pharmacol.*, 32 (Dec. 1927), 121.

[3] *Archiv der Pharmazie*, 253 (1915), 181.

[4] The Council on Pharmacy and Chemistry of the American Medical Association has suggested that α-phenyl-β-aminoethanol sulphate be referred to as phenylaminoethanol sulphate. *J. A. M. A.*, 91 (1928), 1037.

drine and phenylaminoethanol being devoid of nuclear hydroxyl groups may be expected to be more resistant to oxidation, a fact which has been borne out in practice.[1,5] Phenylaminoethanol differs, however, from ephedrine in one important respect. Ephedrine base can be quantitatively extracted from its alkaline solution with ether. Phenylaminoethanol, on the other hand, decomposes into benzaldehyde, even in the presence of dilute ammonia water. This behavior was rather surprising, in view of the observation of Mannich and Thiele,[3] who found that the compound was stable in the presence of boiling 20 per cent hydrochloric acid and 15 per cent potassium hydroxide, which fact was confirmed by the writer. The concentration of the base used is probably a determining factor. A weighed quantity of phenylaminoethanol sulphate dissolved in water was treated with 15 per cent potassium hydroxide solution and boiled. No ammonia or benzaldehyde was revealed by appropriate tests. On the other hand, attempts to extract the free base from alkaline solution with ether and spontaneous evaporation of the ether gave far from quantitative results. In every attempt a pronounced odor of benzaldehyde was noticeable. The formation of benzaldehyde was confirmed by the isolation of benzaldehydephenylhydrazone melting at 154° C. Unfortunately, the decomposition does not proceed quantitatively, since it was hoped to take advantage of this behavior in the elaboration of a suitable assay method. Lack of time did not permit the study of this behavior in as great detail as the reaction apparently deserves.

Phenylaminoethanol is isomeric with tyramine (para-hydroxyphenylethylamine), the difference being in the position of the hydroxyl group. In the latter, the hydroxyl group is in the benzene nucleus, while in phenylaminoethanol the hydroxyl group is found in the side chain. This difference of position of the hydroxyl group at once suggests important differences, which may be used for their distinction.

The nuclear hydroxyl of tyramine gives it phenolic characteristics, while the position of the hydroxyl group in the side chain of phenylaminoethanol is responsible for its secondary alcoholic nature and introduces an asymmetric carbon atom in the molecule. The present specimen is the synthetic racemic form, but it may be distinguished from its isomer by Millon's reagent. Tyramine gives a deep red color, while phenylaminoethanol yields a yellow precipitate, in no wise suggesting phenolic characteristics.

The product available for examination was prepared by the reduction of α-phenyl-β-nitroethanol.[1] The substance was fine, white, odorless, crystalline powder, possessing a bitter taste. It was readily soluble in hot water. It melted at 250–254° C. (corrected, U. S. P. X Method). It was optically inactive. In order to determine the homogeneity of the product, the coöperation of Prof. A. J. Walcott, professor of mineralogy and crystallography at Northwestern University, was secured. His report, which follows, indicates that the product is pure.

"Optical crystal properties of Racemic α-phenyl-β-amino ethanol sulphate. Biaxial; optically positive; 2 E medium; pronounced dispersion of optic axes showing violet greater than red; crystals are thin, flat and somewhat oblong. The majority show the habit of Fig. 1.

[1] Personal communication of Dr. Gordon A. Alles.

"The flat surface of the crystal is very nearly perpendicular to the acute bisectrix.

"The following indices of refraction have been determined:

$$\alpha = 1.561 \pm 0.001$$
$$\beta = 1.581 \pm 0.001$$

"No evidence has been observed to indicate the presence of an impurity."

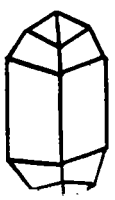


Fig. 1.

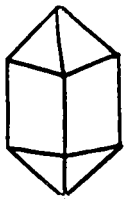


Fig. 2.

SOME CHEMICAL REACTIONS.

An aqueous solution of α-phenyl-β-aminoethanol sulphate yields a purple color immediately when treated with copper sulphate and sodium hydroxide. The color is discharged by acids and is insoluble in ether.

Benzaldehyde and phenylaminoethanol hydrochloride are formed when the base is extracted from alkaline solution with chloroform. This behavior has been noted in the case of ephedrine.[1]

The compound decomposes into benzaldehyde when treated with dilute alkali solutions. The following reaction is suggested to account for the formation of benzaldehyde:

$$C_6H_5CHOHCH_2NH_2 \longrightarrow C_6H_5CHO + CH_3NH_2$$

The substance readily yields an odor of carbylamine on treatment with potassium hydroxide and chloroform. This behavior distinguishes the compound from its homologue, ephedrine.

With Millon's reagent it yields a yellow precipitate unchanged by heating.

In aqueous solution it yields precipitates with phosphotungstic acid and palladium chloride, but with none of the other alkaloidal reagents tried.

The compound readily forms a picrolonate which melts sharply at 200–201° C. (corrected). It readily yields a monobenzoyl derivative, melting sharply at 149.5–150° C. (corrected).[2]

Moisture determinations were carried on over a period of hours. The product was apparently anhydrous and stable. The results of the determinations are given in Table I.

TABLE I.

MOISTURE DETERMINATIONS.

	6 hrs.	12 hrs.	24 hrs.	48 hrs.	72 hrs.	120 hrs.
Loss in weight by drying at 100° C.	0.25[1]	0.25	0.25	0.33	Constant	weight.
Loss in weight by drying at 120° C.	0.22	0.22	0.32	Constant weight.		
Loss in weight over Sulphuric Acid	0.02		Constant weight.			
Loss in weight over Potassium Hydroxide	0.00		Constant weight.			
Loss in weight over Phosphorus Pentoxide	0.01		Constant weight.			

[1] Figures are reported in terms of percentage.

Quantitative determinations showed the compound to be of a good grade of purity. The results are tabulated in Table II.

[1] J. B. Peterson, *Ind. Eng. Chem.*, 20 (1928), 388; cp. W. A. Puckner, *Am. J. Pharm.*, 80 (1908), 72.

[2] Cp. F. Wolfheim, *Ber.*, 47 (1914), 1440.

From the analytical data, together with certain of the foregoing tests, it is concluded that the specimen of α-phenyl-β-aminoethanol sulphate examined is a pure product. The free base, however, is unstable in a dilute alkaline medium, decomposing into benzaldehyde and an amine, possibly of a volatile nature. The instability of the free base in dilute alkaline medium indicates that in common with many other products, therapeutic effects arising from the decomposition products are possible.

TABLE II.

RESULTS OF THE QUANTITATIVE DETERMINATIONS.

	Found.		Theory.
	Original specimen.	Calculated to the dried specimen.	Calculated for $[C_6H_5CHOHCH_2NH_2]_2.H_2SO_4$.
Moisture (loss by drying at 120° C.)	0.32[1]	...	...
Nitrogen (N)	7.25	7.27	7.52
Sulphuric acid (H_2SO_4)	26.72[2]	26.79	26.34
Free base ($C_6H_5CHOHCH_2NH_2$)	...	...	73.65
Ash	0.11	...	...

[1] Figures are reported in terms of percentage.

[2] Average of 4 determinations.

Based in part on the information in the literature and in part on the examination of the specimen of α-phenyl-β-aminoethanol sulphate described above, the following standards are suggested:

PHENYLAMINOETHANOL SULPHATE.—*Phenylaminoethanolae Sulphas.*—Phenylethanolamine sulphate.—Racemic alpha-phenyl-beta-aminoethanol sulphate.—Racemic-1-phenyl-2-amino ethan-1-ol sulphate. $[C_6H_5CHOHCH_2NH_2]_2.H_2SO_4$. The sulphate of an alkaloid obtained synthetically.

Phenylaminoethanol sulphate occurs as fine, odorless, white crystals. It is readily soluble in water and hot alcohol, but more difficultly soluble in cold alcohol. The water solution is neutral to litmus. It is optically inactive. It melts between 250–254° C. (corrected). The rate of heating must be *strictly* according to the method of U. S. P. X.

Dissolve 0.01 Gm. of phenylaminoethanol sulphate in 1 cc. of water and add 0.1 cc. of copper sulphate solution (10 per cent), followed by 1 cc. of sodium hydroxide (20 per cent). A purple color appears at once. The color is not extractable by ether.

Dissolve 0.1 Gm. of phenylaminoethanol sulphate in 10 cc. of water, add 1 cc. of ammonia water and shake out with two 15-cc. portions of chloroform, filter the chloroform and allow to evaporate spontaneously. Take up the residue in 5 cc. of water, filter. To 1 cc. of the filtered solution add 3 drops of diluted nitric acid and 1 drop of silver nitrate solution. A white precipitate forms. To 1 cc. of the filtered residue add 1 cc. of Fuchsin-sulphurous acid solution. A red coloration forms at once.

To 0.005 Gm. phenylaminoethanol sulphate contained in a test-tube add a solution containing 0.2 Gm. of potassium hydroxide in 1 cc. of 50 per cent alcohol and 3 drops of chloroform. Boil gently. A strong carbylamine odor is evolved. (*Distinction from ephedrine.*)

To 0.005 Gm. of phenylaminoethanol sulphate dissolved in 1 cc. of water add one drop mercurous nitrate solution and boil. A yellow precipitate unchanged by heating forms. (*Distinction from tyramine.*)

To 0.005 Gm. of phenylaminoethanol sulphate dissolved in 1 cc. of water add one drop of 1 per cent ferric chloride solution. No coloration is produced. (*Distinction from epinephrine.*)

To 0.2 Gm. of phenylaminoethanol sulphate dissolved in 10 cc. of water add 7 cc. of a saturated alcoholic solution of picrolinic acid and allow to stand 12 hours. Filter the crystals and dissolve it in 15 cc. of hot water, filter and allow the filtrate to cool. Fine, yellow, silky crystals which, after filtering and drying, melt sharply between 200–201° C. (corrected) are obtained.

Dissolve 0.1 Gm. of phenylaminoethanol sulphate in 10 cc. of water, add an equal volume of potassium hydroxide solution (15 per cent) and boil. The vapors do not cause a strip of moist red litmus paper held above the tube to turn blue.

To 1 cc. of a solution containing 0.01 Gm. of phenylaminoethanol sulphate, add 4 drops of diluted hydrochloric acid, followed by 1 drop of barium chloride solution; a white precipitate forms.

Dissolve 0.05 Gm. of phenylaminoethanol sulphate in 30 to 40 cc. of distilled water, add 1 cc. of diluted nitric acid and 1 cc. of silver nitrate solution. No turbidity should result (*absence of chloride*).

A solution of 0.2 Gm. phenylaminoethanol sulphate dissolved in 10 cc. of water should yield a negative test for heavy metals when tested according to the U. S. P. X method (see U. S. P. X, page 439).

Dissolve about 0.3 Gm. of phenylaminoethanol sulphate, accurately weighed, in 200 cc. of water, add 1 cc. of diluted hydrochloric acid, followed by sufficient barium chloride solution to precipitate all the sulphate, allow to stand in a warm place for 6 hours, transfer the precipitate to a previously prepared Gooch crucible, wash well with hot water and then with cold water, dry at 120° C., cool in a desiccator and weigh: the sulphate (SO_4^{--}) calculated from the barium sulphate weighed is not less than 25.7 per cent, nor more than 26.3 per cent.

Transfer about 0.3 Gm., accurately weighed, to a 500-cc. Kjeldahl flask and determine the nitrogen content according to the method described in Medical War Manual No. 6, Laboratory Methods of the United States Army, page 221. The percentage of nitrogen corresponds to not less than 7.20 per cent, nor more than 7.80 per cent, when calculated to the dry substance.

The ash from 0.1 Gm. does not weigh more than 0.0001 Gm.

EPINEPHRINE, PHYSIOLOGICAL ACTION.

Influence of adrenaline on new sugar formation. E. Geiger and Schmidt—*Arch. exptl. Path. Pharmakol.*, 134 (1928), 173; through *Squibb's Abstract Bulletin.* Adrenaline treatment of phloridzin-diabetic dogs produces an increase of the quotient D/N (corresponding to the formation of sugar from fat) only once; this primary increase (not repeated with a subsequent administration) is due to the emptying of the muscle glycogen depot. Adrenaline does not change the fat content of the liver of these animals, which likewise speaks against the assumption that adrenaline promotes carbohydrate formation from fat. Adrenaline mobilizes muscle glycogen, which leads to a reduction of the albumin metabolism (which is pathologically increased by phloridzin) and likewise to an inhibition of the excretion of acetone bodies, which two phenomena are due simply to the liberated muscle sugar.—E. G.

EPHEDRINE, SYNTHESIS.

Synthesis of ephedrine and structurally similar compounds. R. H. F. Manske and T. B. Johnson—Meeting Am. Chem. Soc., Div. Org. Chem., 4 (Sept. 1928); through *Squibb's Abstract Bulletin.* In view of the interest aroused in the pharmacology of the alkaloid, ephedrine, by the work of K. K. Chen, the authors thought it desirable to study synthetic methods which might lead not only to ephedrine, but also to structurally similar bases. Späth's brilliant synthesis leaves no room for doubt regarding the constitution of this substance but his synthetical procedure is too involved to be of any value as a preparative method. The authors, after considerable work on the more obvious methods, finally developed the following surprisingly simple scheme which has been applied with success to a large number of amino alcohols including ephedrine.

$$C_6H_5CO.C.CH_3 + CH_3NH_2 \rightarrow C_6H_5.CO.C.CH_3 + H_2O$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \| \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad NCH_3$$
$$C_6H_5CO.C.CH_3 + 2H_2 \rightarrow C_6H_5CH.CH.CH_3$$
$$\qquad\quad \| \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad | \quad |$$
$$\qquad\quad NCH_3 \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OH\ NHCH$$

The alkaryl-diketone and a primary amine are dissolved in alcohol and the solution-mixture is reduced at once by means of hydrogen under pressure and in the presence of a catalyst.

May you have the joys of the Christmas season and, in 1929, the happiness of health and success.