

# THE IDENTIFICATION AND PROPERTIES OF $\alpha$ - AND $\beta$ -EUCAINE.<sup>1</sup>

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TWO new alkaloids under the names  $\alpha$ -eucaine and  $\beta$ -eucaine have recently been offered to the medical and dental professions for use as a local anesthetic. There is scarcely a reference to either in any strictly chemical journal but their use and physiological properties have been very fully discussed in medical and pharmaceutical publications. Although they are proprietary drugs the fact that  $\beta$ -eucaine is so often substituted for cocaine, in dental preparations, has fewer remedies, and other proprietary medicine, makes it highly desirable that their distinctive properties be carefully studied and that methods be found for their identification and separation from cocaine and other alkaloids. It was owing to the fact that I was called upon to analyze a special dental preparation containing eucaine that my attention was first called to the existence of the alkaloid, and I was greatly handicapped by the silence of chemical literature upon the subject.

$\alpha$ -Eucaine was first obtained by George Merling<sup>2</sup> by synthesis from triacetoneamine through triacetoneamincyanhydrin to triacetonealkamincarbonic acid, which, by the action of benzoyl chloride and subsequent action of methyl iodide in caustic potash solution, becomes *n*-methylbenzoyltetramethyl- $\gamma$ -oxypiperidincarbonic acid methylester or " $\alpha$ -eucaine". This, when treated with hydrochloric acid, acts like other alkaloids forming a hydrochloride, in which form it is prepared and sold.

$\beta$ -Eucaine was discovered by Albrecht Schmidt and George Merling<sup>3</sup> and was obtained by purifying the vinylacetonealkamine of Fischer<sup>4</sup> and substituting a benzoyl group for the hydrogen atom of the hydroxyl. Thus " $\beta$ -eucaine" or benzoylvinyldiacetonealkamine, is also an alkaloid which, when treated with hydrochloric acid, forms the hydrochloride.

It will be seen from the structural formulas of  $\alpha$ - and  $\beta$ -eucaine

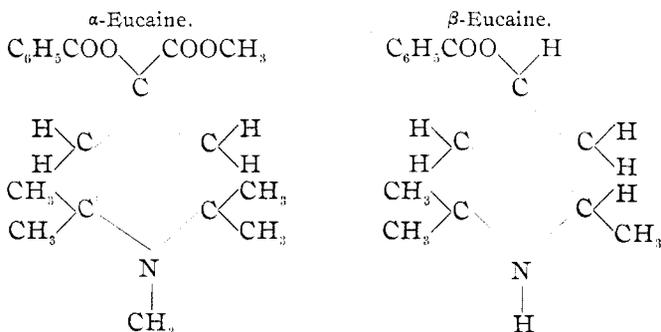
<sup>1</sup> Read at the Denver meeting of the American Chemical Society, August 29, 1901.

<sup>2</sup> *Apoth. Ztg.*, (1896), p. 293, 418, 448.

<sup>3</sup> *Virchow's Archives fur path. Anat. und Phys.*, (1896), vol. 145.

<sup>4</sup> *Ber. d. chem. Ges.*, 17, 1894.

that they have a close relation to cocaine and to tropacocaine.



It was this close chemical connection which led to the belief that they would show similar anesthetic properties.

It is not the purpose of this paper to enter into a discussion of the physiological and therapeutic effects of the eucaïnes but it is not out of place to state that the chief claims of their superiority over cocaine are that they are far safer to use, that they cause no excitation of the heart's action, that  $\beta$ -eucaïne, especially, is some four or five times less toxic, that they have equal analgesic power with cocaine, that they do not decompose by boiling and their hydrochlorides can hence be easily sterilized, and that their solutions will keep for an indefinite time without decomposition. The quite extended use of  $\beta$ -eucaïne would seem to show that many of these claims have been substantiated. It would be well to add that  $\alpha$ -eucaïne has at times an irritating action or smarting effect of its own before anesthesia sets in, which has rendered its acceptance and use somewhat doubtful. It is claimed that this is absent with  $\beta$ -eucaïne or at least is no more often the case than with cocaine.  $\beta$ -eucaïne is the one that is almost exclusively used and the firm which manufactures both furnishes only  $\beta$ -eucaïne when "eucaïne" alone is called for. Accordingly almost all preparations on the market consisting in part of eucaïne contain  $\beta$ -eucaïne hydrochloride and the question of analysis would generally be a distinction between this salt and cocaine.

To establish means of identification of eucaïne, all the well-known reactions of the alkaloids have been tried and I have endeavored to find new ones applicable to this particular case.

In general the properties of the eucaïne alkaloids follow those of the strychnine group and especially do they very closely

resemble cocaine. The bases themselves are readily soluble in benzene, chloroform, ether, chloroform-ether, petroleum ether or gasoline, and amyl alcohol. They can be easily extracted from their salts by rendering their solutions in water slightly alkaline with ammonia and shaking out with any of the above solvents. This extraction is, however, most rapidly accomplished with light petroleum distillates or with ether.  $\alpha$ -Eucaine melts at  $103^{\circ}$ ,  $\beta$ -eucaine at  $91^{\circ}$ , and cocaine at  $98^{\circ}$ . In following out any scheme of analysis of the alkaloids they will probably always be found where cocaine would be expected and their identification becomes essentially a separation from each other and cocaine.  $\alpha$ - and  $\beta$ -eucaine are sold in the form of their hydrochlorides and it is upon this salt that most of the tests for their identification should be made. As usually prepared,  $\alpha$ - and  $\beta$ -eucaine hydrochlorides are white powders, identical in appearance. They are, however, easily crystallizable.

$\alpha$ -Eucaine hydrochloride melts at about  $200^{\circ}$  C. and decomposes at the same time. It is soluble at ordinary temperatures in about ten times its weight of water, solubility varying with temperature. It is more soluble in hot water, from which it crystallizes out to an approximately 10 per cent. solution on cooling. It is soluble in about its own weight of alcohol, 10 grams requiring from 8 to 9 grams of alcohol for solution. It is but slightly soluble in ether or olive oil, but glycerol dissolves it much the same as water.

$\beta$ -Eucaine hydrochloride melts at  $268^{\circ}$  C. with decomposition. At ordinary temperatures it is soluble in water to the extent of about 3 per cent., but is more than twice as soluble in hot water from which most of the excess crystallizes slowly after cooling. Its solubility in alcohol is greater than in water or about 11 per cent., varying somewhat with the temperature. This comparative insolubility is one of its chief characteristics especially differing from cocaine hydrochloride which dissolves in less than its own weight of either water or alcohol. It is almost insoluble in ether or olive oil.

REACTIONS IN WHICH THE HYDROCHLORIDES OF  $\alpha$ -EUCAINE,  
 $\beta$ -EUCAINE AND COCAINE ACT ALIKE.

Mayer's reagent gives with either  $\alpha$ - or  $\beta$ -eucaine a light yellowish amorphous precipitate.

Wagner's reagent gives a voluminous reddish brown precipitate even in dilute solutions.

Tannic acid (1 : 10) gives no precipitate or only a very slight transparent floccuency.

Picric acid (1 : 100) yields a fine lemon-yellow precipitate, in solutions stronger than 1 per cent., which is soluble in acids, but in dilute solutions yields no precipitate. Even in moderately strong solutions the precipitate formed by the first drop or two of reagent redissolves. The precipitate with  $\alpha$ -eucaine is more insoluble than either of the others, and comes down accordingly, in somewhat more dilute solutions.

Iodine in alcohol yields a brown precipitate soluble in excess.

Fröhde's reagent (sulphomolybdic acid) gives no precipitate.

Mercuric chloride (1 : 20) gives no precipitate in dilute solution but in moderately strong solutions gives a fine white precipitate, easily soluble in excess.

Ferric chloride and potassium ferricyanide mixed give no precipitate except a white one in strong solutions. Allen<sup>1</sup> states that cocaine gives a precipitate of Prussian blue, but I have not been able to obtain it. Ferric chloride is stated by some authors to turn red on boiling one or two drops of a dilute solution with cocaine, owing to the formation of benzoate of iron. But as it also turns red with either of the eucaines or simply with distilled water the reaction is of no value. It gives no precipitate even in strong solution.

Cadmium iodide gives a white precipitate.

Potassium ferrocyanide gives in solution of about 10 per cent. a slight colorless gelatinous precipitate. A saturated solution of  $\beta$ -eucaine does not yield this precipitate probably because the solution is too weak.

Potassium ferricyanide gives a white precipitate in moderately strong solutions, which is more easily thrown down if solution is acid with hydrochloric acid.

Potassium bromide, chloride, or bromate give no reaction.

If a few drops of a solution of either of the hydrochlorides of  $\alpha$ - or  $\beta$ -eucaine or cocaine be acidified with strong nitric acid, evaporated to dryness in a watch-glass, and treated with 1 or 2 drops of a solution of alcoholic potash, a very characteristic odor of benzoic ethyl ester is obtained. This reaction would probably also be given with other alkaloids containing the benzoyl group.

<sup>1</sup> "Commercial Organic Analysis," Vol. III, part II, p. 275.

REACTIONS CHARACTERISTIC OF  $\alpha$ -EUCAINE SALTS.

Potassium iodide (1 : 10) gives, in even moderately dilute solutions of  $\alpha$ -eucaine hydrochloride, a white silky and glistening precipitate. This precipitate has much the same appearance as the one obtained when stannous chloride is added to a cold dilute solution of mercuric chloride.  $\beta$ -Eucaine and cocaine give no reaction.

Ammonia, even in dilute solution, precipitates the bases  $\alpha$ - or  $\beta$ -eucaine or cocaine, but  $\alpha$ -eucaine is almost insoluble in excess. In 1 per cent. solution the white precipitate is at once thrown down, and in the case of  $\beta$ -eucaine or cocaine dissolves immediately on addition of about their own volume of strong ammonia.  $\alpha$ -Eucaine, so precipitated, can be diluted at least ten times with strong ammonia without solution. In stronger solutions the difference still exists but is not so easily recognized. A 3 per cent. solution of  $\beta$ -eucaine or cocaine requires about five times its own volume of ammonia to be dissolved and stronger solutions much in proportion to the per cent. present. In other words a strong solution of ammonia will dissolve about one-half of one per cent. of the bases  $\beta$ -eucaine or cocaine, while it will dissolve but a very small fraction of a per cent. of  $\alpha$ -eucaine. In dilute solutions this is a very characteristic reaction for  $\alpha$ -eucaine and strong solutions are, of course, very easily rendered dilute for the test.

Potassium dichromate, in strong solution, added drop by drop to a 0.5 to 1 per cent. solution of  $\alpha$ -eucaine, begins to throw down a fine lemon-yellow precipitate after addition of 1 or 2 drops. The precipitate is then much increased by 1 or 2 drops of strong hydrochloric acid, and is then quite insoluble, dissolving only after several times diluting the volume of the solution. With stronger solutions the precipitation takes place at once, the first drop giving a more and more permanent precipitate as the solution grows stronger. The precipitate is notably insoluble in either water or hydrochloric acid. More dilute solutions either show no precipitate or only after addition of hydrochloric acid. Cocaine, 1 per cent. solution, is not precipitated by potassium dichromate, but the addition of 1 or 2 drops of concentrated hydrochloric acid throws down a yellow precipitate easily soluble in very slight excess of hydrochloric acid or on dilution of the solution with water. Weaker solutions do not precipitate while stronger solu-

tions precipitate at once. The precipitate is, however, easily soluble as before.  $\beta$ -Eucaine acts like cocaine. The precipitate in all cases is lemon-yellow. The  $\alpha$ -eucaine precipitate is quite crystalline. All three may throw down a small amount of a yellow colloidal precipitate which sticks to the side of the test-tube and dissolves but slowly, although this in no wise interferes with the test and does not take place if reagents are added slowly. While this test depends upon the very much greater insolubility of the  $\alpha$ -eucaine salt, the non-precipitation in dilute solutions of a certain strength until after the addition of hydrochloric acid is quite characteristic for all. The correct strength is about 0.5 per cent. solution of  $\alpha$ -eucaine and about 1 per cent. for  $\beta$ -eucaine and cocaine. In the case of cocaine and  $\beta$ -eucaine, the test may be conveniently applied by precipitating a stronger solution than 1 per cent. with potassium dichromate solution, diluting carefully with water until precipitate just dissolves. On addition of a drop of concentrated hydrochloric acid the precipitate will at once re-form. This can not be done with  $\alpha$ -eucaine for precipitate once formed it is difficult to get it to dissolve at all. Chromic acid (1 : 20) acts similarly to the dichromate.

REACTIONS OF COCAINE DISTINGUISHING IT FROM EITHER  
 $\alpha$ - OR  $\beta$ -EUCAINE OR FROM BOTH.

If a small amount of cocaine hydrochloride be rubbed up with dry mercurous chloride (calomel), and then moistened with alcohol, it rapidly turns to a grayish black.  $\alpha$ -Eucaine hydrochloride becomes slowly a dark gray.  $\beta$ -Eucaine hydrochloride is not affected.

Platinic chloride throws down slowly a yellow crystalline precipitate from a 1 per cent. solution of cocaine hydrochloride which is insoluble in hydrochloric acid.  $\alpha$ - and  $\beta$ -eucaine hydrochloride in 1 per cent. solution are not altered. In stronger solutions all three hydrochlorides are immediately precipitated by platinic chloride but the cocaine precipitate is not soluble in hydrochloric acid while the precipitates by either eucaine are at once dissolved.

F. Giesel<sup>1</sup> has pointed out that the permanganate of cocaine is much more stable than that formed by most other alkaloids. This fact gives rise to one of its most distinguishing reactions.

<sup>1</sup> *Pharm. Ztg.*, p. 132 (1886).

The test is best applied upon a microscopic slide or in a small watch-glass. A drop of a solution of the hydrochloride is placed upon the glass and a very small drop of a solution of potassium permanganate is added. If the solution is strong enough for a precipitate to appear at once the change can be observed on the precipitate but it is preferable to watch the change of color of the solution itself. With either of the eucaines the color almost immediately begins to change to brown while with pure cocaine the original color holds generally for fully half an hour but also eventually changes to brown. The cocaine precipitate examined under the microscope is a beautiful violet-red which also in time turns to brown. This is true of the eucaine precipitates at first but they rapidly change to brown. Excess of permanganate should be avoided.

Cocaine hydrochloride in solution in either water or alcohol polarizes light strongly to the left. Antrich<sup>1</sup> states that this is the best test for the purity of the salt. According to this authority for aqueous solution  $S_{\alpha} = -52.2$  and for solution in alcohol of 0.9355 sp. gr.,  $S_{\alpha} = -68.06$ . A solution of the hydrochlorides of either  $\alpha$ - or  $\beta$ -eucaine does not polarize light.

Cocaine when used in the eye almost always causes mydriasis.  $\beta$ -Eucaine does not dilate the pupil.

#### REACTIONS CHARACTERISTIC OF $\beta$ -EUCAINE·HYDROCHLORIDE.

The chief characteristic property of  $\beta$ -eucaine hydrochloride is its comparative insolubility in water and alcohol and it is readily distinguished from cocaine by this property. A small test sample of cocaine hydrochloride, if moistened with its own volume of alcohol or water, dissolves at once, while  $\beta$ -eucaine hydrochloride is little affected. In making the test, however, where weighed quantities are not used it should be remembered that even  $\beta$ -eucaine is soluble to the extent of 11 per cent. in alcohol and a too large amount of the solvent should not be used. Just enough to moisten is all that is necessary to dissolve cocaine or  $\alpha$ -eucaine hydrochloride.

No chemical reactions of a positive character have been found characteristic of  $\beta$ -eucaine, but the results with permanganate, mercurous chloride, platinic chloride, and polarized light, will identify cocaine, while the tests with potassium iodide, potassium

<sup>1</sup> *Ber. d. chem. Ges.*, 20, 310.

chromate and ammonia will distinguish it from  $\alpha$ -eucaine. These with the other reactions noted will serve to separate it from other alkaloids.

#### MICROSCOPIC CHARACTERISTICS.

A careful examination of many of the precipitates which the various reagents yield with either of the eucaines or with cocaine failed to disclose any special characteristic of value. Many of them are beautifully crystalline and give striking displays of color with polarized light, but they vary too much with different conditions to be used with certainty as a means of identification. An examination of the alkaloids themselves as precipitated by ammonia and crystallized from chloroform also give negative results. Fortunately, however, the hydrochlorides, when pure, are easily identified under the polarizing microscope and especially is cocaine hydrochloride recognizable at once.

The slides are best prepared by allowing a drop of an aqueous solution to spontaneously evaporate. Cocaine under these conditions does not always crystallize at once even when quite dry. But if set aside for a few hours the crystals will form and the peculiar feathery and fan-shaped radiations, resembling very closely those seen on a broken nodule of wavellite, are recognizable even with the naked eye. The examination is most satisfactorily performed with a magnifying power of about 250 diameters.

$\alpha$ -Eucaine hydrochloride in saturated solution tends to crystallize in little spots which, under polarized light, look like very highly colored rosettes made up of very small crystals, so that the field is always bright, never showing any constancy of extinction directions. On edges of drop, the rosettes sometimes show small feathery forms of crystals of which the extinction directions vary but are more often diagonal. A 5 per cent. solution gives much the same result. The rosettes frequently appear to be made up of concentric rings of very small crystals, the center of rosettes being thicker than edges and only the edges showing plate or feather forms large enough to be examined as individuals. Interference colors are very bright. When crystallized from dilute solution the rosette forms may become very small and numerous, covering the entire field while the interference colors are only gray or black. The forms of gray and black overlying feathers

are at times very prominent in  $\alpha$ -eucaine and resemble nothing so closely as the small feathers of Plymouth Rock poultry.

$\beta$ -Eucaine hydrochloride from saturated solution shows broad feathery or fern-like forms, sometimes blade-like or tabular. Usually the tabular forms show concentric rings of high color around the edges and the extinction directions are easily determined. They are usually slightly oblique to the main axis of the crystal, but different crystals show two separate angles of extinction, one being the complement of the other and due to the fact that the individuals are viewed from opposite sides. The forms already mentioned are more apt to be found around the outer edge of the evaporated drop while the center is made up of isolated individuals which show brilliant tabular and prismatic forms sometimes quite small and rod-like. Rarely they are diamond-shaped. These diamond-shaped forms sometimes show extinction directions symmetrical to the main axis, but more often slightly oblique. The individual crystals are large and much more easily studied than those of  $\alpha$ -eucaine. If more dilute solutions of less than 1.5 per cent. are used, the characteristics do not come out so plainly, the crystal forms being smaller and showing very low interference colors, mainly light grays. Also these sometimes show feathery forms and rosette forms something like  $\alpha$ -eucaine.

Cocaine hydrochloride in 10 per cent. to 1 per cent. solution crystallizes in fan-like shapes. A 2 per cent. solution gives a solid field of radiating forms, the individuals of which resemble very closely the forms sometimes seen on a frosted window. Extinction is parallel and perpendicular to the main axis of the crystals. Colors are brilliant and the whole field is characteristic, enabling one to distinguish cocaine immediately. With dilute solutions the fan-like shapes are still marked, but the field is sometimes broken and interference colors are a low order of light grays.

In conclusion it is perhaps well to suggest that in working on unknown substances all tests for eucaine and cocaine, as with other alkaloids, are much more valuable when compared with those of samples whose identity is known.