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CONTRIBUTIONS TO THE KNOWLEDGE OF
NARCOTINE and NARCEINE

by
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History and Literature.

Narcotine was first discovered in opium by Derosne' in 1803. He attributed to it the properties of an active principle, similar to those alkaloids then known to exist in opium. Serturner, however, only considered it as a morphine salt.

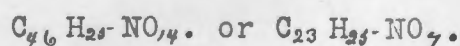
Robiquet² first pointed out its true chemical nature. Previously Dumas and Pelletier found 7.21% N, while Liebig only found 2.51% N. Such variance in results would point to a great difference in the purity of the compounds analyzed. Robiquet, however, obtained the substance in exceptionally pure condition by a method of his own. He chose the best opium and macerated it with water without the addition of acid. He believed the narcotine to exist for the greater part in the pith of the opium, and was rewarded by a considerable yield from his treatment. Hitherto the weak basic properties of narcotine had been overlooked, and its compounds with the acids were unknown or considered doubtful. Robiquet

1. Ann. d. Chemie. 14-257.
2. Ann. d. Pharmacie, 3-267.

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found, however, that the compounds resulting from its combinations with the acids were stable and crystallized as true salts. He determined the quantity of acid saturated by the narcotine in the formation of the sulphate, and found the amount to correspond closely to that required in the formation of morphine sulphate. He also formed salts with hydrochloric and acetic acids, obtaining like results. Others had by this time become interested and many properties were determined and compounds made. Dumas and Pelletier¹; Pelletier²; Liebig³; Regnault⁴; Couerbe⁵; R. Brandes⁶; and Wöhler⁷; all made important investigations with regard to the separation and preparation of the pure substance, and also made many derivatives.

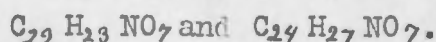
The composition of narcotine was first expressed by Blythe⁸ who gave it the formula:



He supported his composition by preparation and analysis of the chlorplatinate; and by the oxidation into opianic acid, $C_{10}H_{10}O_3$, and cotarnine, which was then $C_{13}H_{15}O_3$.

1. Annalen Chem. u. Phys. 24-188.
2. Annalen Chem. u. Phys. 1-269.
3. Annalen Chem. u. Pharmacie, 6-35.
4. Annalen Chem. u. Phys. 68-137.
5. Annalen Chem. u. Phys. 59-159.
6. Annalen Chem. u. Pharmacie, 2-274.
7. Annalen Chem. u. Pharmacie, 50-1.
8. Annalen Chem. u. Pharmacie, 50-29.

Wertheim', however, by distilling with potash, obtained from certain samples of opium - narcotine; methyl amine, ethyl amine, and trityl amine. From these decomposition products, he maintained the existence of two additional varieties of narcotine homologous to those of Blythe, giving the formulas:



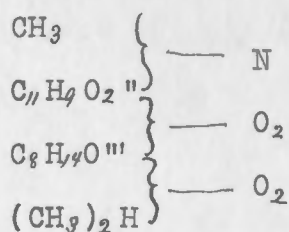
Hinterberger² prepared a double salt with mercuric chloride and from his analyses deduced the formula, $C_{21}H_{21}NO_7$.

Matthiesen and Foster,³ as well as Dr. Anderson⁴, rendered the existence of more than one substance doubtful. The former analyzed six samples of narcotine from different localities and obtained results concordant with the formula, $C_{22}H_{23}NO_7$.

They concluded that the same narcotine gave the different results obtained by Wertheim, since they obtained, by distillation under certain conditions, methyl, ethyl and trimethyl (not its isomer, trityl) amines.

1. Annalen Chem. u. Pharmacie, 70-71; 73-208.
2. Annalen d. Chem. u. Pharmacie, 82-312.
3. Phil. Trans. 1863 -345.
4. Annalen d. Chem. u. Pharmacie, 86-179.

The same authors' gave the following structural formula:



Matthiesen and Wright² showed the decomposition of narcotine into meconin and cotarine, by boiling with water or heating in sealed tubes at 100°. The following reaction took place:



When heated to 208° by itself narcotine undergoes a similar decomposition, but the cotarnine immediately decomposes under the influence of the high heat. On heating narcotine hydrochloride with ferric chloride the latter was reduced while the narcotine was converted into opianic acid and cotarnine.



Another interesting reaction was shown, when narcotine was heated with an excess of hydrochloric acid for a short time; methyl chloride was formed and narcotine, having one of its methyl groups replaced by hydrogen, was obtained. By further treatment for some days

1. Chem. Soc. Jol. (2) 6-257.
2. Paper for Royal Society Feb. 18, 1869.

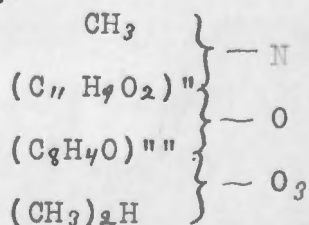
another methyl group was likewise replaced. When heated with hydriodic acid, methyl iodide was formed leaving a compound in which three methyl groups had been replaced by hydrogen. This compound, having the formula $C_{11}H_{17}NO_7$, was called normal narcotine, which became shortened to nornarcotine. The other compounds, having two and one methyl groups substituted, were called mono- and di-methyl nornarcotine, respectively.

The authors also gave the formula for cotarnine, $C_{12}H_{13}NO_3$, and by its reaction when heated with dilute sulphuric acid, obtained cotarnic acid and methyl amine:



Opianic acid was reduced by nascent hydrogen to meconin, and this oxidized by chromic acid to hemipinic acid.

All these reactions of narcotine and its decomposition products, led to the assumption of the rational formula:



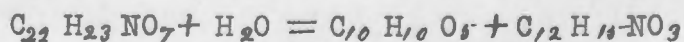
Beckett and Wright' prepared cotarnine from narcotine by the action of dilute H_2SO_4 and MnO_2 , and after the separation of opianic acid, precipitating it with strong soda solution. Purified by recrystallization they gave it the formula, $C_{12} H_{13} NO_3 \cdot H_2O$.

This cotarnine was converted readily into hydrocotarnine, by solution in dilute HCl and treating with granulated zinc. The free base obtained was in prismatic crystals of the composition, $2(C_{12}H_{13}NO_3 \cdot H_2O)$.

Thus hydrocotarnine is always produced in the preparation of cotarnine from narcotine in the manner above described.

Narcotine heated with $Ba(OH)_2$ yielded meconin but no opianic acid; heated with water to 150° it was decomposed, meconin and hydrocotarnine being formed.

From these results it seemed probable that in the preparation of cotarnine from narcotine, the latter first split up into opianic acid and hydrocotarnine thus:



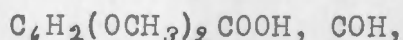
and that the hydrocotarnine was then oxidized to cotarnine.

1. Chem. News Vol. 31-181.

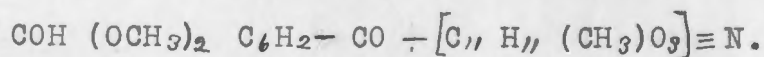
The authors' also ascertained that the action of water on narcotine hydrochloride is similar to that on the narcotine salt, splitting up into basic salts and HCl.

By prolonged action of ethyl iodide they obtained a noncrystalline easily decomposed addition product. From this they succeeded in obtaining a platinum salt.

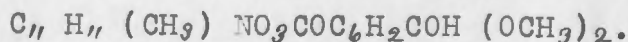
From the opianic acid formula,



they concluded narcotine to be



In another paper² the authors describe a new opium alkaloid, oxynarcotine,



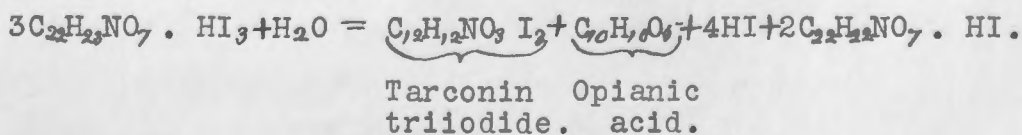
Their evidence for the formula of narcotine was not quite conclusive, since when heated with water, it forms meconin and hydrocotarnine. Dr. Wright assumed that opianic acid was first formed and was then reduced to meconin, but he did not prove such a reduction possible.

Fruitless attempts were made³ to elucidate the structure of cotarnine by breaking it down into simpler compounds.

1. Chem. News, Vol. 32-257.
2. Beckett and Wright, Chem. News, Vol. 32-298.
3. Beckett and Wright Chem. News, Vol. 35-249.

Jörgensen in his studies of the periodides of the alkaloids, found that by precipitating narcotine hydrochloride with potassium superiodide, a light yellowish brown voluminous precipitate was formed. This became crystalline on standing. It was prepared much quicker by addition of cold hydrochloric acid to alcoholic solution of narcotine, and then adding a water solution of iodine in potassium iodide with dilution to permanent cloudiness with water. The compound then separates in small rhombic plates. The compound produced in the above treatment dissolves on heating in water and melts when dry at 109°-120°C., to a black, tarry mass. Analyses showed it to be narcotine triiodide, expressed by Jörgensen as : $C_{22}H_{22}NO_7 \cdot HI_3$.

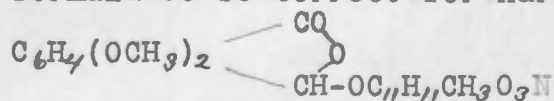
The triiodide dissolved quite easily in water, and by boiling he noticed a peculiar decomposition. On cooling the hot solution he obtained reddish brown crystals of a new decomposition product. In formation and properties it stood near to cotarnine, hence, it was named tarconin. The reaction is expressed as follows:



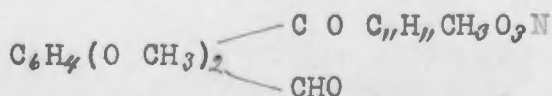
1. Journal Practische Chem. (2) 2-442.

The filtrate from the red crystals of tarconin triiodide was further shown to contain the opianic acid and narcotine hydroiodide. The crystals when dry melted at 151° -152°, and gave numbers in analyses for the following formula: $C_{12}H_{12}NO_3I_3$.

It is dissolved easily by a mixture of alcohol and ether. Jörgensen also showed several similar salts of tarconin and finally the free base tarconin oxyhydrate, which he obtained from the triiodide by silver oxide treatment. Roser¹ endeavored to clear up the structure of hydrocotarnin, obtained by the hydrolysis of narcotine, by studying the tarconin triiodide and some of the similar compounds. He improved on Jörgensen's method of preparation by treating narcotine hydrochloride directly in weak alcohol with iodine, obtaining, besides Jörgensen's triiodide, a monoiodine substitution product of this compound, or $C_{12}H_{11}INO_3I \cdot I_2$. From the study of these compounds and similar bromine derivatives, he considered the following formula to be correct for narcotine:



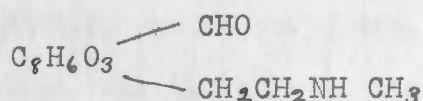
rather than that given by Beckett and Wright:²



1. Annalen 245-311.
2. Jol. Chem. Sec. 1877. II. 525.

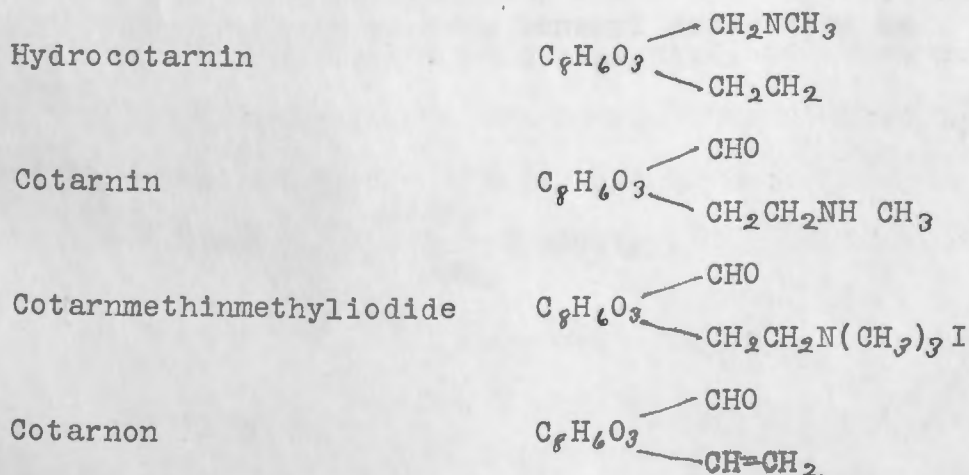
In a succeeding issue¹ Roser made a study of narcotine methyl chloride and its conversion into the new base pseudo-narceine. This will be given in detail in succeeding pages.

Later Roser² from the action of cotarnine as secondary base, offered as formula a somewhat different structure for cotarnine:

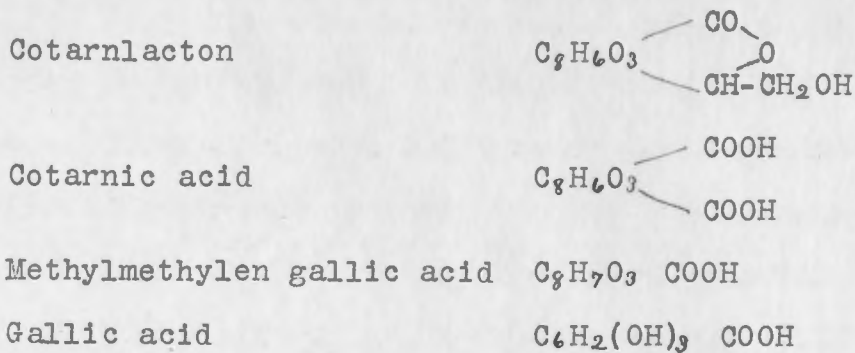


To support this formula and to clear up the constitution of the radicle, $\text{C}_8\text{H}_6\text{O}_3$, contained in cotarnine and cotarnic acid, he made exhaustive studies³ of many derivatives of the latter.

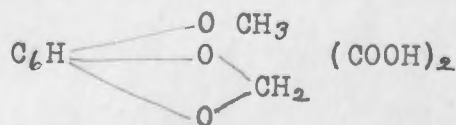
From cotarnin he showed the following changes leading to gallic acid, through several interesting steps:



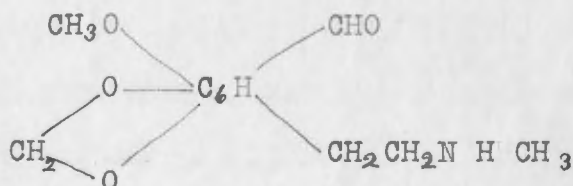
1. Annalen 247-167.
2. Annalen 249-168.
3. Annalen 254-334.



The presence of carbonyl in the constitutional formula of cotarnine, as above given, and the secondary nature of the base, was proven by its conversion into cotarnin-oxim, benzoylcotarnin, and benzoylcotarnin-oxim. Existence of an aldehyde was shown by the formation of a nitrile, by action of hydroxylamine on derivatives. Hydrocotarnine was shown to stand in the relation of an alcohol to an aldehyde. By the ease of splitting off the methyl group, and also the methylen, as formaldehyde, cotarnic acid was shown to be a benzoyl derivative as follows:

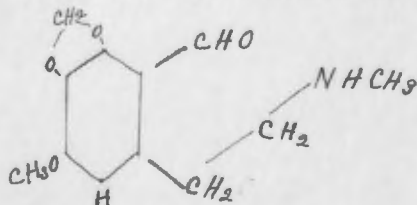


By heating cotarnic acid with hydriodic acid, gallic acid was obtained, showing the above structure correct. It is methylmethylenetrioxypthalic acid. For cotarnin he then derived the following formula:

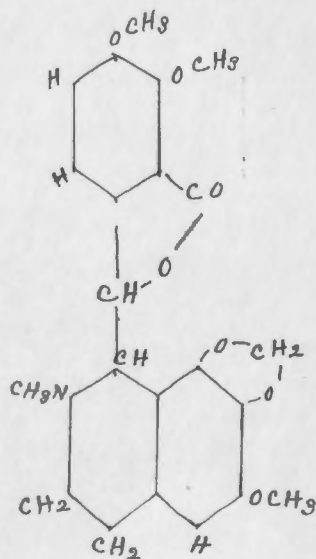


calling it a methylmethylenpyrogallocaldehyde -o-B - ethylmethyamine, in which the position of methoxyl and methylen groups remained unknown.

By the action of H_2S on the hydrobromide of tribromhydrocotarnin and heating, bromtarconin originates, while methyl bromide and 2H Br split off; the methyl comes from the methoxyl and the H Br from the pyridin ring. It was shown from this reaction that the positions of methoxyl and methylen groups were as expressed in the following formula, giving the constitution of cotarnine a firm and sure basis in all details:



Knowing this formula for cotarnine, that of narcotine was readily cleared up. In the latter are contained the radicles of opianic acid and hydrocotarnin, held, not by one of the oxygen atoms, but by a carbon atom which forms the aldehyde group in the decomposition into opianic acid and cotarnine. Thereby was given the following constitution for narcotine:



It was thus shown to be closely related to papaverine and to be a benzyl derivative of isoquinoline.

NARCEINE.

Pelletier first¹ discovered narceine in the dried juice of the poppy in 1832. His product was not pure and constituted only 0.2%. Difficulty was experienced in obtaining the pure substance. Wright and Beckett² freed it from chlorine by changing it to a sulphate and decomposing the latter by means of soda.

Claus³ obtained the pure base by oxidation of the impurities, by cautious addition of KMnO_4 to a certain degree of color.

Hesse⁴ gave the solubility of narceine as one part in 1285 parts of water, and 945 parts of 80% alcohol at 13°. Long, fine, white, prismatic needles separated out from the water solution. It is readily soluble in hot water and alcohol, but insoluble in chloroform and ether. The crystals of narceine became blue on the addition of water solution of iodine, probably forming an iodide.

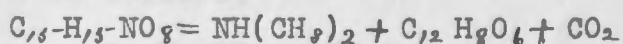
Pelletier⁵ from his later researches believed the formula of narceine to be $\text{C}_{16}\text{H}_{27}\text{NO}_8$. Couerbe⁶, however, gave $\text{C}_{14}\text{H}_{20}\text{NO}_6$.

1. Annalen 2 - 274.
2. Jol. Lond. Soc. 28-5699.
3. Berichte - 18-1571.
4. Annalen 129 -250.
5. Annalen 5-163.
6. Annalen 17- 171.

The formula now usually accepted is that given by Anderson', $C_{23}H_{29}NO_9$.

Beckett and Wright² found that narceine unites quite readily with halogen alkyls. They described an ethyl iodide which changes to an ammonium base by decomposition with silver oxide. Claus⁵, however, proved this to be incorrect, since he found that all alkyl halogen addition products revert to alkyl narceine by treatment with alkalies.

Beckett and Wright⁴ by oxidation with $K_2Cr_2O_7$ and H_2SO_4 , obtained hemipinic acid and methyl amine. With $KMnO_4$, in presence of H_2SO_4 , they obtained narceinic acid, $C_{16}H_{15}NO_8$, which decomposed by heating:

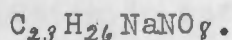


The substance having the formula $C_{12}H_9O_6$, is called dioxy naphthalin dicarbonic acid, since it may be reduced by fuming HI to naphthalene dicarbonic acid, which by further treatment may be changed to naphthalene.

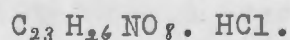
Anderson¹ and Hesse⁶ from analyses of the base crystallized from water, gave it as containing two molecules of water of crystallization, making the formula $C_{23}H_{29}NO_9 \cdot 2H_2O$.

1. Annalen 86-182.
2. Society Royal of London, 28-699.
3. Berichte 18-1571.
4. Society, 29-467.
5. Annalen 86-182.
6. Annalen 129-250.

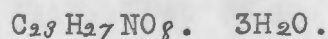
By the action of dilute alkali a soluble compound is formed in which hydrogen has been replaced by alkali metal. But instead of giving results from analyses corresponding to the above formula, they gave the following:



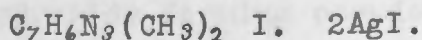
By decomposition of this salt with hydrochloric acid, a chlorhydrate was formed:



Like results were obtained by treatment with halogen alkyl. These results led to the assumption of the formula containing three molecules of water of crystallization as follows:



Roser² found that narcotine by warming with an excess of methyl iodide was completely converted to narcotine methyl iodide. By digestion of this compound in water with silver chloride, an analogue of Zinke and Lawson's dimethyltoluolazammoniumsilveriodide was obtained.



1. Dr. Frankforter. Inaug.Dissert. Berlin 1893.
2. Annalen 247-167.

In this compound three-fourths of the narcotine is found. As a by product narcotine methyl chloride was obtained. This was readily soluble in water and alcohol. Upon long standing of a concentrated solution, a mass of bunches of fine, white needles was obtained. A solution in water gave a platinum salt:



No precipitate was formed by treatment with Na_2CO_3 , but on standing a precipitate formed which, on heating, changed to an oil probably containing narcotine methyl hydroxide. By standing with water, or better, by boiling, the whole mass was converted into fine, white needles of a new base:



This new base Roser called pseudonarceine. It is slightly soluble in cold water, readily so in hot water and alcohol, and insoluble in ether. It forms fine white felt-like crystals melting at 175° . At 100° it loses three molecules of water of crystallization.

Roser also obtained in a similar manner narcotine ethyl hydroxide forming pseudo homonarceine.

Roser saw the great resemblance between his new base and narceine, and he hoped to prove their identity. He made out a table of comparison of the properties of his substance with Merck's pure narceine, as follows:

Pseudonarceine.

Narceine.

175° ←———— Melting point —————→ 165°

Optically inactive

Solubilities identical

Colored blue by treatment with Iodine.

Same results with Cl -NH₄OH and H₂SO₄

Soluble in Alkalies and Ammonia.

Hydrochloride only stable in presence of hydrochloric acid in the water solution.

Sulphate forms fine needles.

Platinum salt crystallizes in fine needles from dilute hydrochloric.

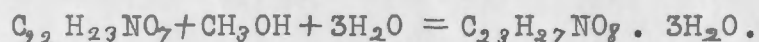
196° - 198° ←———— Melting point —————→ 195° - 196°

Mercury salt crystallizes in fine needles.

120° - 123° ←———— Melting point —————→ 118° - 122°

Gold double salt falls as flaky precipitate and melts on heating under water.

Roser expressed the change of the methyl hydroxide to pseudo narceine by the following reaction:



The change from ammonium to a tertiary base was thus a new analogue to those changes in piperidine bases whose clearing up is due to the researches of Hoffman and von Ladenburg.

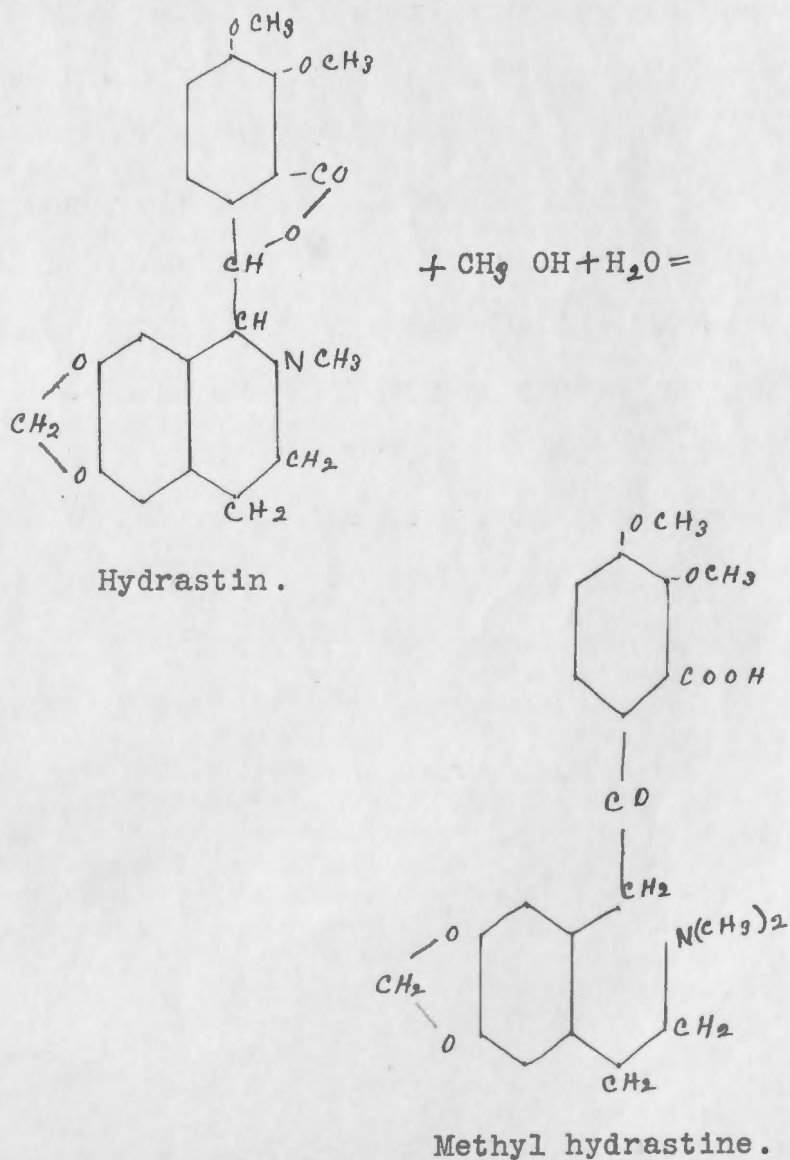
Roser did not completely prove the identity of the two substances. His substance was physiologically inactive, while narceine was supposed to be very active. Dr. Frankforter', however, carried out the researches in a new way, and proved without a doubt the identity of the two substances. This is especially apparent by the formation of metallic salts where the combination takes place, as though the substance were combined with three rather than two molecules of water. New physiological studies also proved the activity of narceine to be due to impurities, the pure substance being quite as inactive as is the pseudo compound.

Roser, however, gave no formula for his substance. Its structure was also worked out by Dr. Frankforter by its relation to narcotine, the structure of which was so admirably shown by Roser.

1. Inaug. Dissert. Berlin 1893.

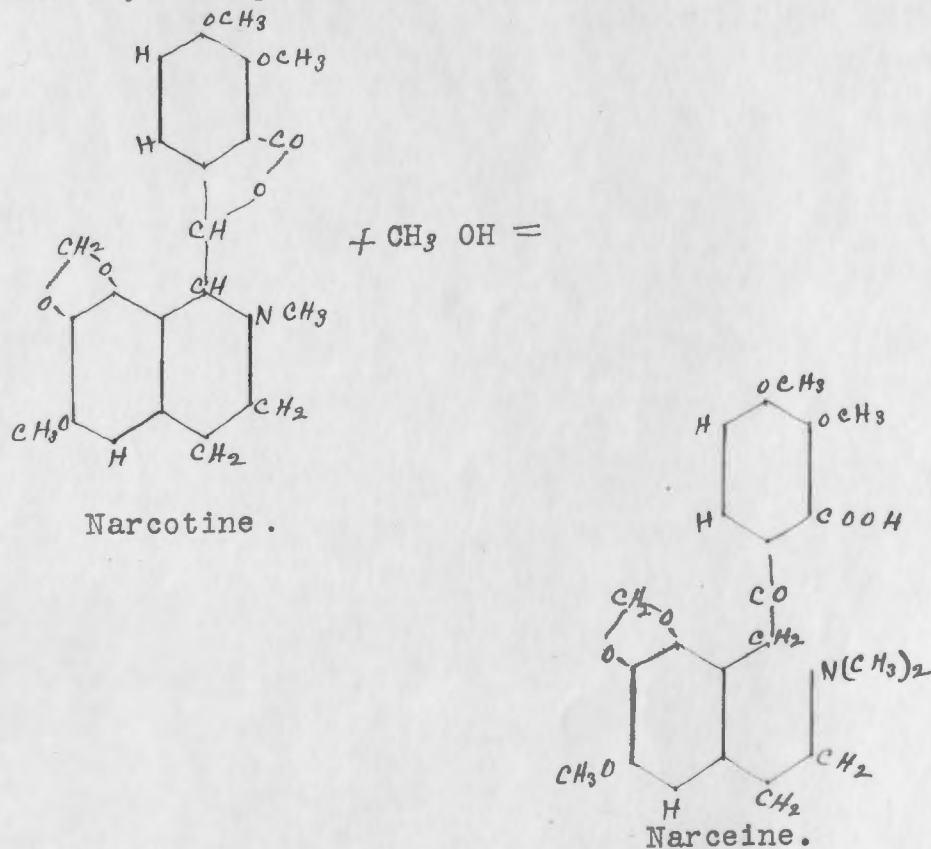
Narceine thus bears the same relation to narcotine as methyl hydrastine does to hydrastin.

Freund' represented the change from hydrastin to methyl hydrastine as follows:



1. Annalen 271-311.

Naturally then, the change from narcotine to narceine may be represented as follows:



The presence of the carboxyl group is abundantly proved by the formation of metallic salts and organic esters. As is seen in both cases, the pyridin ring is broken, the change being from an ammonium to a tertiary base.

-oOo-

EXPERIMENTAL PART.

Part I.

The identity of Roser's pseudonarceine and Merck's narceine having been proved² by the preparation and comparison of their respective salts and compounds, a new process was developed for the commercial preparation of narceine, which hitherto had been obtained wholly from opium. Roser's method, although much cheaper than the extraction from the natural source, is not perfectly satisfactory, inasmuch as a relative small proportion of the narcotine is converted into narceine. One-fourth only of the narcotine methyl iodide, upon digestion with silver chloride, is changed to the methyl chloride; the remaining three-fourths are converted into the by product dimethyltoluolazammonium silver iodide.

A method, by which a greater percentage of narcotine methyl iodide could be converted to the corresponding chloride, would mean a considerable cheapening of narceine and its salts, some of which possess valuable physiological properties.

1. Annalen 247 - 167.

2. Inaug. Dissert. Berlin. Dr.G.B.Frankforter.

The general action of chlorine replacing iodine in its compounds, naturally suggested a similar replacement of the iodine in narcotine methyl iodide by the use of chlorine water. The effort was successful and a very satisfactory conversion accomplished.

The treatment was the following: Narcotine methyl iodide was prepared by digesting the alkaloid, Merck's narcotine melting point 170°C , with an excess of redistilled methyl iodide, for several hours at a gentle heat on a water bath. Upon evaporation of the excess of methyl iodide the compound remained as an amorphous, light lemon colored, sticky mass, which changed to an oily consistency on treatment with water. A solution in alcohol was treated with a small amount of chlorine water, containing some hydrochloric acid. A light yellowish precipitate appeared, but was almost immediately dissolved by the alcohol present. Upon the addition of more chlorine water, the precipitate was again formed. At first it appeared to be a finely divided amorphous substance, but upon standing for a few minutes it collected into flocks and settled to the bottom. The clear supernatant liquid had a light yellow color due to some of the material having dis-

solved in it. Upon examination under the microscope the substance was found to be a mass of fine, needle-shaped, yellowish crystals. Upon warming, the solution became darker from the solution of more of the precipitate. After filtering, more crystals were obtained by again treating the filtrate with chlorine water. The second lot was identical with the first. Both lots were purified and analyzed with results as tabulated later on.

The ready solubility of narcotine methyl chloride in water led to an examination of the filtrate to ascertain if the attempt at conversion was successful. The filtrate was carefully evaporated on a water bath. A brownish gum-like substance was left. After standing, this gradually changed to a mass of crystals, which were subsequently identified as narcotine methyl chloride. A quantitative determination of the amount converted was then made with small quantities of narcotine methyl iodide:

Narcot. methyl iodide into Narcot. Meth. Chloride.

I.	2.86 grams	"	1.22 gms.	42.7%
II.	3.00 "	"	1.39 "	46.3%
III.	5.00 "	"	2.62 "	52.4%

With the use of larger quantities of iodide the loss becomes relatively smaller, and the yield greater. Thus over sixty per cent have been converted practically.

To identify the substance its properties were determined and found to be identical with those of the compound prepared by Roser. It was readily soluble in water, alcohol and chloroform. On addition of ether to concentrated solutions in the two latter solvents, it was precipitated as a sticky, white deliquescent powder. It gave fine characteristic salts with gold and platinum chlorids. A part was converted into the platinum double salt, and subjected to analysis. This salt when first precipitated is a yellowish amorphous powder, slightly soluble in water and readily so in alcohol, from which fine, yellow, needle-shaped crystals were obtained. When dried, it melted at 221° C. Analyses of the substance dried at 100°-103° C gave the following results:

I. 0.2090 gms. double salt gave 0.0319 g. Pt.
 II. 0.1946 " " " " 0.0298 " "

Calculated for

Found

$(C_{2x} H_{2y} NO_z . CH_3Cl)_x Pt Cl_y$ Pt = 15.39	I.	II.
	15.27	15.31

The pure narcotine methyl chloride, as indicated by these analyses, was then converted into narceine by the method of Roser.¹ The water solution was neutralized with dilute sodium hydroxide or carbonate, and a strong current of steam passed through it. On cooling, the substance appeared as a mass of fine felt-like needles, which were filtered off and identified as narceine by characteristic tests. The same results were obtained by allowing the neutralized solution to stand several days. In both cases the conversion is little less than quantitative. The dried narceine melted at 172°C.

In the preparation with chlorine water, care must be exercised not to add too large an amount of this reagent. Otherwise a small quantity of the substance is decomposed, coloring the liquid dark brown, and making it necessary to re-crystallize and purify the narceine several times. It is best to add just enough chlorine water and then filter as soon as the precipitate settles, leaving the narcotine methyl chloride in a light amber colored solution from which the narceine is obtained comparatively pure.

1. Annalen 247-167.

Narcotine methyl triiodide.



The formation of the precipitate above mentioned, on the addition of chlorine water, shows that part of the narcotine methyl iodide is converted into this bye product, leaving the greater part in solution as the corresponding chloride. In order to ascertain the nature of the reaction this substance was examined. When first precipitated, it melted at 146° C; but, when recrystallized from alcohol, it was raised to 149° C., where it remained constant. It was almost insoluble in cold water, slightly soluble in hot. It dissolved readily in methyl and ethyl alcohols; from these solutions it was again obtained in fine reddish brown needles. It was likewise very soluble in chloroform and acetone, from which it was obtained as a gum or varnish. It was almost insoluble in ether, and entirely so in carbon bi-sulphide. The crystals contained no water of crystallization.

Analyses gave the following results:

I.	0.2082	grms. substance	gave	0.2583	CO ₂	and	0.0633	H ₂ O
II.	0.1995	"	"	0.1754	AgI			
III.	0.2036	"	"	0.1803	"			
IV.	0.2473	"	"	0.3081	CO ₂	"	0.0723	H ₂ O

Calculated for:

Found.

C₂₂H₂₃I₂NO₇CH₃I

I

II.

III.

IV.

C = 34.25

33.83

33.98

H = 2.98

3.38

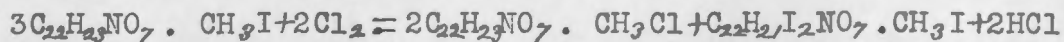
3.25

I = 47.12

47.50

47.84

From the large percentage found, it is evident that the iodine of the narcotine methyl iodide has been concentrated in this byproduct. Thus, one molecule of narcotine methyl iodide has been combined with two atoms of iodine liberated by chlorine in the formation of two molecules of narcotine methyl chloride. This may be shown by the equation:



According to this equation, from three molecules of narcotine methyl iodide, two molecules or about sixty-five per cent of narcotine methyl chloride and one molecule or about thirty-five percent of narcotine methyl triiodide are formed.

The following determinations sustain this reaction:

Narc. methyl iodide into - triiodide and - chloride.

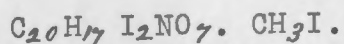
I.	3.00 grms.	"	0.979 grms.	"	1.390 grms.
II.	5.00 "	"	1.640 "	"	2.620 "

By the method of Roser, only twenty-five per cent is theoretically convertible, while by this method sixty-six per cent of narcotine may be changed to its methyl chloride. This fact combined with the simplicity of the process makes it in every way preferable.

The narcotine methyl triiodide is peculiarly like the narcotine triiodide described by Jørgensen'. He gives it the formula $C_{22}H_{23}NO_7 \cdot HI \cdot I_2$. In this he attaches HI to the nitrogen atom, just as CH_3I is in the above compound. He does not, however, replace hydrogen by the other two iodine atoms, simply adding them to the formula. This does not appear satisfactory; it is preferable to replace the hydrogen by iodine in the two carbon atoms lying next to the nitrogen in the pyridin ring.

1. Journal Practische Chemie. 2 - 311.

Methylnornarcotinemethyltriiodide.

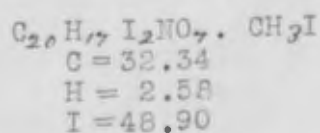


It was noticed while working with narcotine methyl triiodide that the melting point of the substance was considerably raised by heating on the water bath with an excess of chlorine water. In order to determine the nature of the change ten grams of narcotine methyl iodide were dissolved in alcohol and 200 c.c. of strong chlorine water added to it. Immediately a precipitate of the triiodide was formed. This was heated on a water bath for several hours, with addition of chlorine water from time to time. The substance did not appear to have changed any excepting to have grown a little darker in color. The whole precipitate was filtered off and washed with cold water. It melted at 178°C. After solution and recrystallization several times from hot alcohol, the crystals had a constant melting point of 186°C. They exhibited the same properties and solubilities as those of the narcotine methyl triiodide heretofore described.

As shown by Matthiesen and Wright, narcotine when heated with hydrochloric acid has two methoxyl groups successively replaced by hydroxyls forming di- and mono-methyl nornarcotine. The chlorine water used in the above experiments contained a considerable amount of free acid; so, naturally, one might expect a similar substitution to take place in this case. We would then have narcotine methyl triiodide in which the two methoxyls of the opianic acid radicle have been replaced by hydroxyls. And such was proven to be the case by the following analyses:

I.	0.2099	grms. substance	gave	0.1901	AgI
II.	0.2444	"	"	0.2887	CO ₂ and 0.0729 H ₂ O
III.	0.2222	"	"	0.2634	" " 0.0659 "

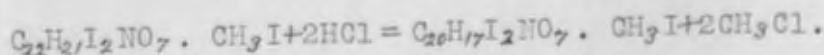
Calculated for:



Found.

I.	II.	III.
	32.22	32.32
	3.31	3.30
48.93		

The reaction may be expressed thus:



1. Proc. Roy. Soc. XVI - 340.

PART II.

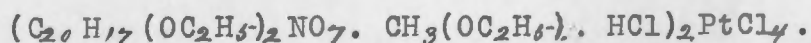
Ethyl ester of the base obtained from nornarcotine triiodide.

An attempt was made to replace the iodine in methylnornarcotine triiodide by hydroxyl groups. Some of the purified substance was dissolved in hot alcohol and shaken several hours with freshly prepared and carefully washed silver oxide. The oxide gradually became greenish yellow from the formation of silver iodide. After about eight hours thorough shaking, the precipitate of silver oxide and iodide was filtered off. The alcoholic filtrate had a yellowish color, while the alcoholic solution of the iodide was a dark reddish brown. It was then carefully evaporated on a water bath, when a brownish gummy mass was left. It differed entirely from the original iodide, which crystallized on the evaporation of an alcoholic solution. All attempts to make the substance assume a crystalline form were fruitless. Stirring for several hours under water or ether had no apparent effect. The substance was evidently

very deliquescent. It was soluble in methyl and ethyl alcohols, but insoluble in ether. It was also readily soluble in chloroform, acetone, benzene and toluene. From all these solutions it was deposited as a gummy mass. It was reprecipitated from a chloroform solution by the addition of ether.

As soon as the ether was evaporated it changed to a gummy consistency. It appeared to have deliquesced in the small amount of water present in the ether. It was soluble in dilute hydrochloric acid, especially on warming. From this solution it could be precipitated by the addition of dilute potassium hydroxide. With strong hydrochloric or sulphuric acid, it gave a white cloudy precipitate which dissolved on warming with an excess of water.

Platinum double salt.



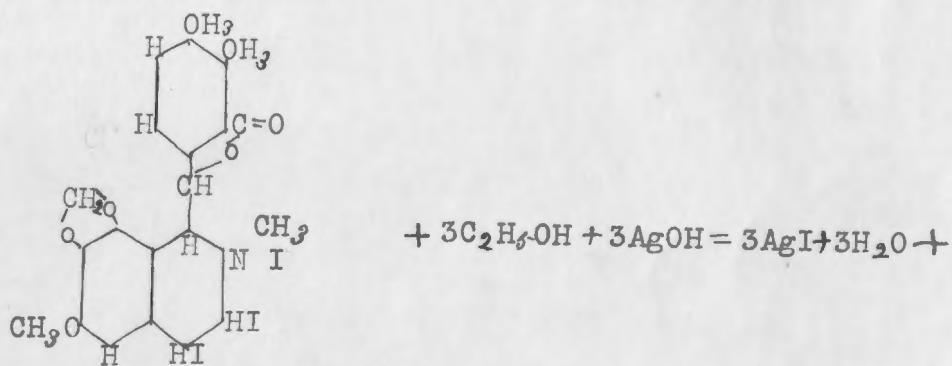
When the dilute hydrochloric acid solution of the above base was treated with platinic chloride, a heavy yellow flocculent precipitate was formed. This was somewhat soluble in water, more so in alcohol.

After thorough drying, it melted at 164°C. Analyses gave the following numbers:

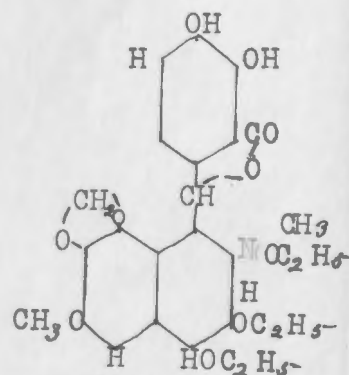
I. 0.1958 grms. substance gave 0.0254 grms. Pt.
 II. 0.2120 " " " 0.0274 " "

Calculated for	Found
$(C_{20}H_{17}(OC_2H_5)_2NO_7 \cdot CH_3OC_2H_5 \cdot HCl)_2PtCl_4$.	I. II.
Pt = 13.17	12.97 12.92

From these results it would appear that the iodine in methylnornarcotine had been replaced, not by hydroxyl but by ethoxyl groups. The changes may be expressed by this structural reaction:



Methylnornarcotinemethyltriiodide



Ethyl ester of diethoxymethylnornarcotinemethylhydroxide.

These determinations may not be entirely conclusive, but more compounds of this base are in preparation, and it is hoped that by their study the results already obtained will be confirmed. If this replacement be so, then Jørgensen's formula $C_{22}H_{23}NO_7 \cdot HI \cdot I_2$ is not applicable to the iodides under discussion, since one would hardly expect three hydroxyls or ethoxyls to be attached to the nitrogen, but rather to the carbon atoms as represented above.

PART III.

Bromides from Narcotine Methyl Iodide.

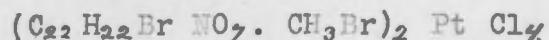
Chlorine water having answered its purpose so well, bromine water was likewise tried to see if similar substitutions could be brought about.

Narcotine methyl iodide, when dissolved in alcohol and treated with moderately strong bromine water, formed a light yellow cloudy precipitate, which, on standing, or gentle warming, changed to masses of fine yellow needle-shaped crystals, resembling those obtained by a similar addition of chlorine water. Upon the addition of an excess of bromine water, the solution changed slightly, remaining light yellow in color. The precipitate was filtered off and examined, the result of which will be given later. The filtrate was supposed to contain the narcotine methyl bromide. Upon careful evaporation of the filtrate a light yellow varnish-like substance remained. If, however, the solution was left to evaporate spontaneously for several days, magnificent long white needles were obtained.

The crystals were very readily soluble in water and in alcohol. From the solution in the latter the substance was again precipitated in white, flocculent form, by the addition of ether. The substance deliquesced, unless all the alcohol was removed by repeated washing with ether. The crystals were also readily soluble in chloroform and acetone, but sparingly so in toluene, benzene and methyl alcohol; insoluble in ether and petroleum ether.

The crystals were somewhat sticky and melted at 65° - 70°; dried in a desiccator and afterward at 100° - 102°; they melted at 214° - 216° C.

Platinum double salt.



When a water solution of the crystals was treated with platinum chloride, a heavy yellow flocculent precipitate was obtained. Upon standing it tended to become crystalline. It was not soluble to any extent in water or alcohol. When filtered off and washed with

hot water and alcohol, it melted, after thorough drying, at 223°C.

Assuming the above soluble compound to be narcotine methyl bromide, narceine, by its conversion, should be obtained, just as it may be obtained from narcotine methyl chloride.

A solution of the substance was accordingly neutralized with sodium carbonate and boiled for at least half an hour. Upon cooling and standing for several hours, the vessel became filled with a fine white deposit, composed of very fine felt-like needles. The formation and appearance of the substance resembled narceine very much, giving the characteristic blue color with iodine. It was slightly soluble in cold, but readily soluble in hot water and alcohol. From the hot water solution it was again deposited, upon cooling, as a mass of fine needles, which made it appear as though the entire solution had solidified. This scheme was used to purify the substance. After repeated recrystallizations from hot water, the dried substance melted at 188°C., instead of 175°C., as expected for narceine. This surprising fact led to a comparison of the platinum

salt with the platinum salt of narceine. The substance was dissolved in a small quantity of dilute hydrochloric acid and precipitated by addition of platinic chloride. A heavy yellow double salt was formed which, after thorough washing with hot water and alcohol, and then drying at 100°-103°C., melted at 184°C. The corresponding compound of narceine melts at 196°-198°C. Analyses of this platinum salt gave the following results:

I.	0.2126	grms. substance	gave	0.0287	grms. Pt	=13.50%
II.	0.2470	"	"	0.0334	"	=13.52%
III.	0.2738	"	"	0.0366	"	=13.36%

These results are decidedly low when compared to the platinum content of narceine platinum chloride or 14.96%.

To clear up this dissimilarity of melting points and analyses, the original bromide from which this supposed narceine was obtained, was examined. Analyses were made of the platinum double salt with the following results:

I.	0.2064	grms. gave	0.0265	grms. Pt	= 13.32 %
II.	0.2783	"	0.0367	"	= 13.20 %
III.	0.2465	"	0.0320	"	= 13.192%

These results differed considerably from those given by the double chloride of narcotine methyl bromide

which contains 14.37 % Pt. A bromine determination of the soluble bromide was then made.

The results showed almost conclusively that the original substance was not a narcotine methyl bromide, and consequently its conversion would not result in the hydroxide and finally in narceine.

The numbers did, however, correspond closely to those required by a dibromide of methyl narcotine, or rather, monobromnarcotine methyl bromide. This substance probably would have the following formula:



The results obtained agree closely with such a structure.

Bromine determination.

0.2093 grms. substance gave 0.1340 gms. AgBr.

Calculated for	Found
$C_{22}H_{22}Br NO_7 \cdot CH_3 Br$	
Br = 27.26	27.24

Platinum double salt.

Calculated for	Found		
	I.	II.	III.
$(C_{22}H_{22}Br NO_7 \cdot CH_3Br)_2 Pt Cl_4$			
Pt = 12.87	13.32	13.20	13.192

If this structure be correct then when neutralized and boiled the conversion would be not to narceine but to oxynarceine. This substance would resemble narceine greatly, excepting for the presence of an hydroxyl group in place of one of the hydrogens.

The analyses of the platinum double salt gave:

I.	0.2126	grms. substance	gave	0.0287	gms. Pt
II.	0.2470	"	"	0.0334	" "
III.	0.2738	"	"	0.0366	" "

Calculated for		Found		
(C ₂₃ H ₂₆ OH NO ₇ . HCl) Pt Cl ₄		I.	II.	III.
Pt = 13.85		13.50	13.52	13.36

The substance, however, tenaciously retained small quantities of halogen, so there is a possibility of a mistake. But the analyses of the original bromide gave almost conclusive evidence of two bromine atoms present in the molecule; and one would naturally expect it to have been converted into a substance having two correspondingly placed hydroxyl groups. Work is now being done and this point will be cleared up.

As stated before, upon the addition of bromine water to narcotine methyl iodide, a light yellow precipitate was formed. This first precipitate, if filtered off before any considerable quantity of bromine water

was added, melted at 149°. This shows it to be the same narcotine methyl triiodide formed by chlorine water. When, however, the precipitate was allowed to remain in the solution, and considerable excess of bromine was added, the melting point raised considerably. It first was 170°, later 175°, then 184°, and then 189°. This last substance, when dissolved in alcohol and recrystallized, melted at 192°-195°C. These precipitates obtained at the various stages resembled each other very closely in everything excepting their melting points. They had the same general properties and solubility described for narcotine methyl triiodide. A great many analyses were made, but no satisfactory results were obtained. They ran in carbon content from 33.88% to 40.40%. It would thus appear that there was a gradual transition in the compounds from triiodide probably to tribromide. Evidently the substances obtained were mixtures of these different substitution products.

It was noticed, however, that when the precipitate first formed was filtered off, and its alcoholic solution heated with excess of strong bromine water, considerable free iodine was liberated and given off in violet vapors. The attempt was then made to completely

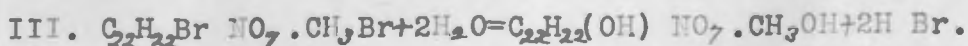
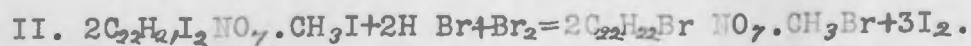
remove the iodine in this manner: Bromine water was added to the alcoholic solution; a light yellow precipitate was formed but dissolved on warming. Most of the alcohol was then evaporated off, carrying with it considerable iodine. Then more alcohol was added and followed by treatment with bromine water and evaporation. Each time upon cooling, a large quantity of fine yellow needles would crystallize out, but would dissolve when warmed. This treatment was kept up successively for over twelve hours until finally no test for iodine was given by the solution. The solution, which was originally dark reddish, was now light yellow, and, when evaporated to small bulk and cooled, no crystals were formed. However, after standing for a day or two, long white needles commenced to form into magnificent bunches and rosettes. They very much resembled those formed in concentrated solution of the dibromide, before described. When filtered off and carefully dried, they melted at 214°C ., the exact point of the dibromide. The crystals were readily soluble in water, and, in fact, had all the properties of the dibromide. A fine platinum salt was obtained, melting at 223°C ., and gave the following

numbers on analyses:

I.	0.2419	grms.	gave	0.0316	grms.	Pt = 13.06%
II.	0.2060	"	"	0.0274	"	" = 13.30"
III.	0.2086	"	"	0.0274	"	" = 13.13"
IV.	0.2724	"	"	0.0358	"	" = 13.14"

-Average- = 13.16% Pt.

This result is practically the same as that obtained from analyses of the platinum salt from the dibromide or 13.23% Pt. This proves beyond a doubt that there is a transition of the narcotine methyl triiodide to narcotine methyl dibromide by treatment with excess of bromine water. Now by the changing of this dibromide to oxynarceine we have made the conversion from narcotine almost complete. The reactions taking place might be represented somewhat as follows:



These interesting results are being worked out more completely and, if the formation of oxynarceine is correctly assumed, there is a large field for research in derivatives of this new base.

If this oxynarceine could be reduced to narceine there would be an almost complete conversion of narcotine into narceine. The following diagram shows the changes from narcotine to narceine, assumed on the formation of oxynarceine and the probability of its reduction:

