Part I.

A Contribution to the Chemistry of Narcotine and Hydrastine

Part II.

A polarimetric Method for studying Intramolecular change in Inactive Substances.

Thesis presented by

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A Contribution to the Chemistry of Narcotine and Hydrastine

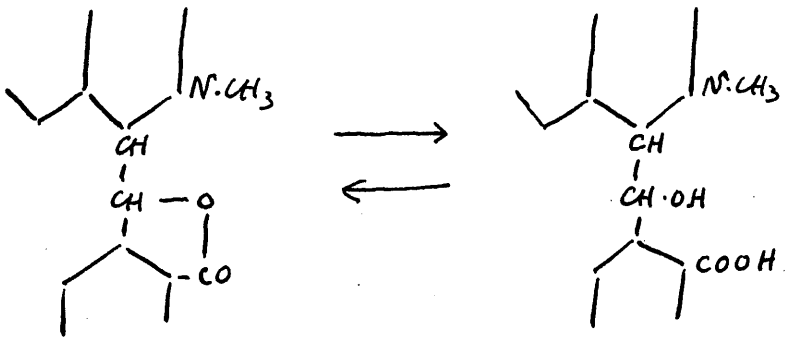
Introduction

The alkaloids Narcotine and Hydrastine, although derived from entirely different plants, are very closely allied to one another in chemical constitution. To Narcotine has been given the structure, built up principally from the researches of W. Roser, shown in Formula I, while our knowledge of Hydrastine, represented in constitution by Formula II, we owe to the work of M. Freund and E. Schmidt. From an examination of these formulae, it is at once seen that the whole difference lies in the fact that Narcotine contains one Methoxy-group more than Hydrastine and could be defined as methoxy-Hydrastine.

I

II

when viewed in the light of their chemical transformations, both alkaloids may be considered as basic lactones, and from the work of the foregoing investigators, exhibit the reversible changes shown in the following scheme:-



that is, they may be considered as inner esters of 1,2 Hydramines.

The investigation of such Hydramines, especially in the alkaloids of the Cinchona bark, has been taken up by Rabe[1]; the present paper deals with the corresponding investigation in the Narcotine and Hydrastine group of alkaloids.

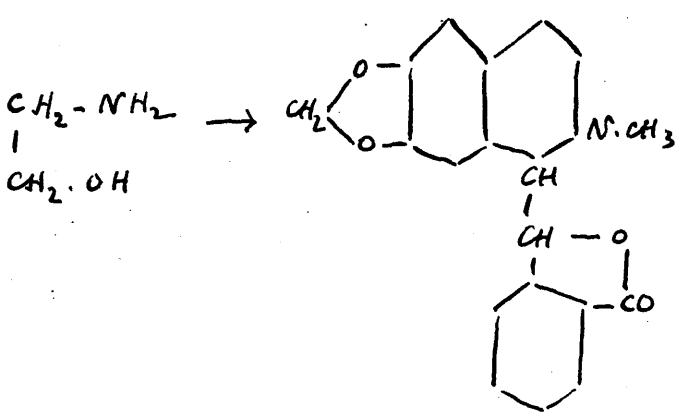
The most important step in the determination of the constitution of Narcotine was accomplished when Wöhler (Ann. 50 24 1844) discovered that, on oxidation Narcotine was converted into Opianic acid and Cotarnine, by the addition of one molecule water and one atom oxygen.

The second important step was the conversion by Freund of Hydrastin into methylhydrastine and further into methylhydrastinine by the action of alkali on the methyliodide compound;

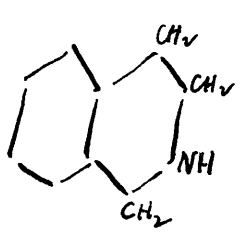
(1) Ber. 40 3280 [1907]; Ann. 365, 377 [1909]

a change, which corresponds in all points, with the formation of Narceine by the action of alkali on narcotine codmethylate.

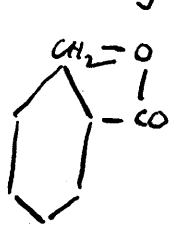
Narcotine and Hydrastine may be taken as derived from the simplest form of 1,2 Hydroamine, the <u>Ethanolamine</u>



The basic part consists of an isoquinoline ring



The alcohol part is a γ- lactone, a phthalid



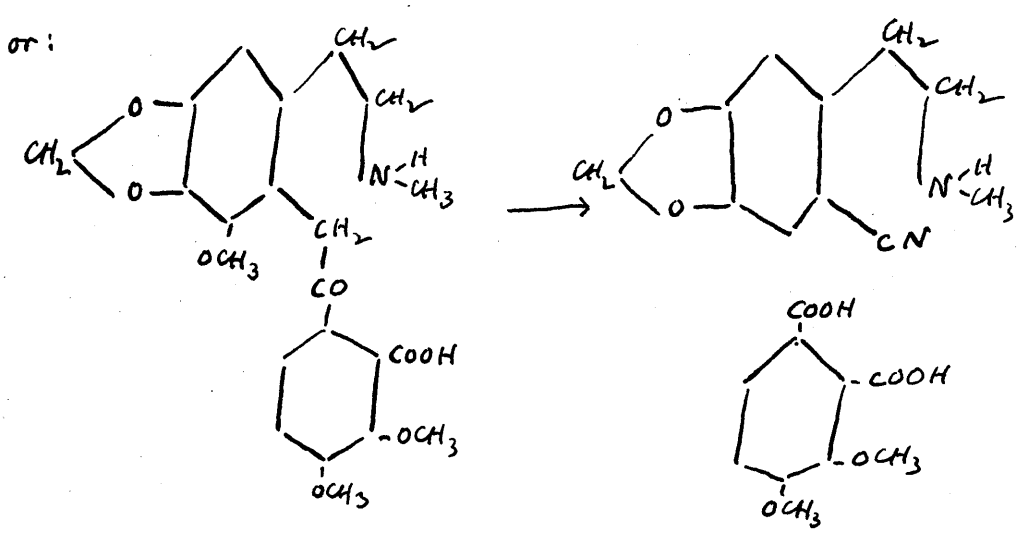
I. The constitution of Nornarceine and Methylhydrasteine

As has been already shown by Rabe (Ber. 40, 3280, 1907) Narcotine passes over into a keto-form when boiled for 3 days with dilute acetic acid. This keto body seemed to contain one CH_2 group less than Narceine and resembled this latter compound generally in properties, hence the name Nornarceine was given to it.

This Nornarceine is able to be broken up in the same manner as Cinchotoxine was some years previously (Ann 350, 180, 1906) by the aid of the Beckmann reaction, into Hemipinic acid, on the one hand, and a Nitrile on the other, thus:

$$-CH_2-CO \longrightarrow -C(=NOH)-CO \longrightarrow -CN-COOH$$

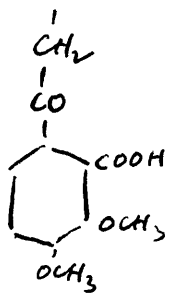
or:



we see that the CO group lies in the neighbouring position to the benzene ring; it is a γ-Keto carboxylic acid and, since Nornarceine and Narceine were known to be closely

connected in constitution, the position of the CO group and the COOH may be taken to be in similar positions.

In the same way, from Methylhydrastëine have been isolated Hemipinic acid and a Nitrile so that the presence of the Complex $\overset{CH_2}{CO}$: thus



has been clearly determined a further proof of the similarity in constitution of Narceine and Methylhydrastëine.

If, then, these results are considered together with the analogous cases in the Cinchona alkaloids, it cannot be doubted that the formulae, those of γ-lactones, for the parent alkaloids as established by Roser [Ann 245, 311 (1888)] are the correct ones.

II Identity of Normarceïne and Oxynarcotine

During the preparation of Narceïne from the Opium, Beckett and Wright [Journ. Chem. Soc. 29, 461 (1876)], isolated another substance to which they gave the name 'Oxynarcotine'. From the figures they give as analyses, it is impossible to decide whether this new compound differs from Narcotine by one atom of oxygen, or, whether it is in reality Narcotine + one molecule of water. On oxidation they found that this body yielded Cotarnine and Hemipinic acid, a dicarboxylic acid, while narcotine on oxidation gives Cotarnine and an aldehyde-acid, Opianic acid. From these data, they concluded that Narcotine and this new compound stood in the relation of aldehyde and acid to one another, and hence gave the name oxynarcotine. This latter substance, from a consideration of its properties cannot be other than Normarceïne. Unfortunately, no melting point is given but the description of the various properties ~~is~~ is sufficient for its identification. Further, the analyses figures can be taken as agreeing quite as well with Normarceïne [$C_{22}H_{25}NO_8$] as with Oxynarcotine ($C_{22}H_{23}NO_8$]. They further add that the compound is difficultly soluble in water and alcohol, insoluble in chloroform and benzene, forms little sandy crystals; further, that it is soluble

in alkali but not in alkaline carbonates, properties which agree entirely with those of Normarceine They give, however, that the hydrochloride crystallises with 2 mols. water while I have only been able to find one. It may be questioned whether Normarceine occurs together with its homologue Narceine in the opium or whether it is produced by hydrolysis during the purification processes.

III. The Constitution of Gnoscopine

Gnoscopine was first discovered by T. H. Smith [Pharm. Journ. Trans. 9, 82, (1878)] in the liquors left from the purification of Narcotine. It was found on the results of analysis to be isomeric with Narcotine and both gave the same products when treated with oxidising agents. Later investigation showed that the iodmethylate of Gnoscopine produced a compound Narceine identical with that isolated by Roser from the analogous compound of Narcotine: The very close relationship of the two alkaloids was thus evident. Gnoscopine is, however, quite indifferent to polarised light and this raised the question

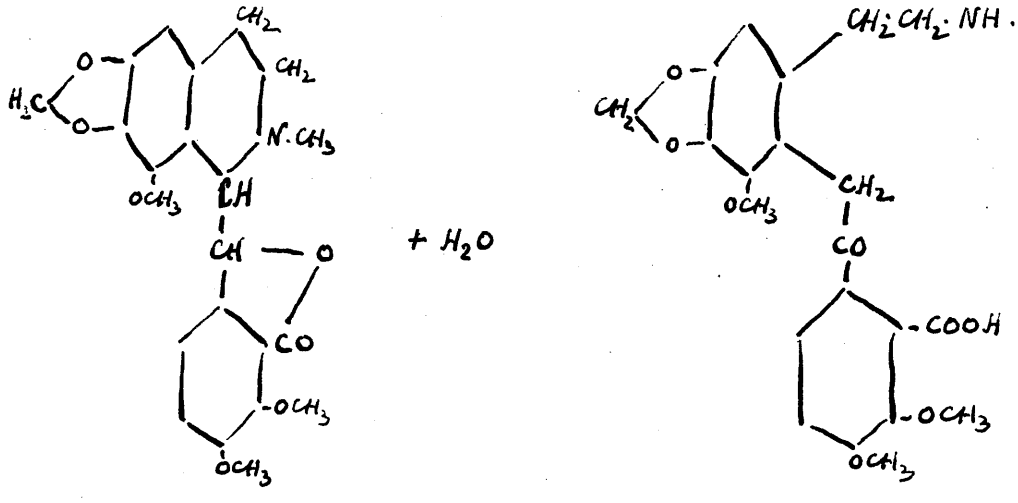
whether this Gnoscopine might not simply be the racemic form of Narcotine, the Narcotine undergoing racemisation during the process of purification.

I have investigated both the problem of the racemic and the isomeric nature of Gnoscopine and have decided beyond doubt that Gnoscopine is really racemic Narcotine. It may here be stated that the complete separation of the d- and l- forms of Narcotine from Gnoscopine has been accomplished by Perkin and Robinson [Proc. Chem Soc. 26 131 1910] who seemed to be investigating the problem simultaneously with us.

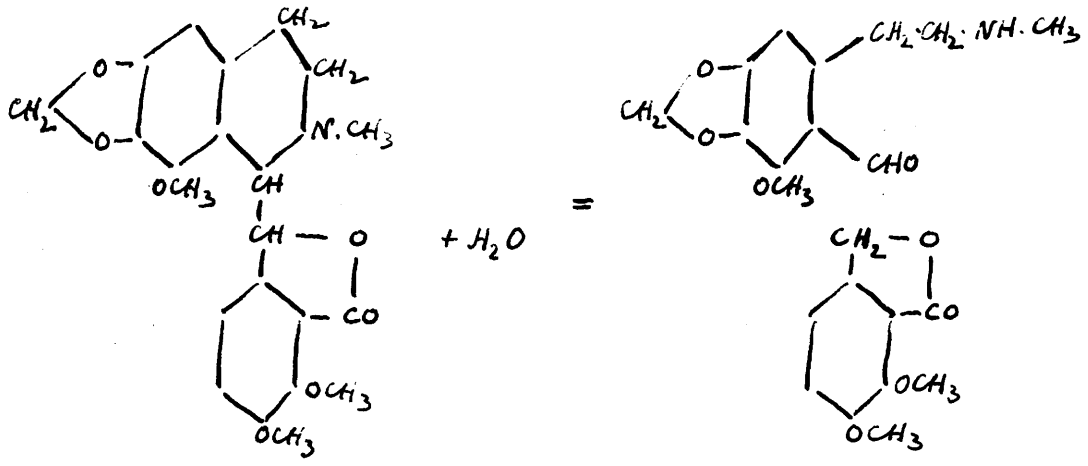
IV Concerning certain transformations (Umwandlungen) of Narcotine and Hydrastine.

In order that the conclusion which was drawn regarding the structure of Narcotine and Hydrastine, namely that, they were inner esters of 1, 2 Hydramines, might be placed on an absolutely firm basis, we have repeated a number of the reactions given in the literature and, while there are some corrections to be made and a few observations to be added, we have found the reactions to agree with the formulae given by Roser. In the case of Narcotine, two typical reactions present themselves:

1. The "hydrolytische Umbau" or transformation with the addition of one molecule of water into the Keto-carboxylic acid - Hydrocotarnine. This change may be represented in the following scheme and is analogous to the change of Cinchonine into Cincholoxine



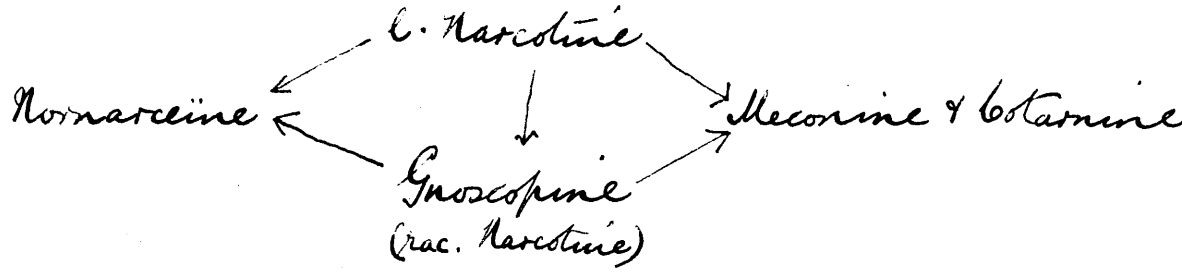
2. The "hydrolytische Spaltung" or breaking up of the Narcotine molecule into the basic aldehyde Cotarnine and the Lactone Meconine, with the addition of one molecule of water, as represented in the following scheme:



The above changes have been best studied in the case of Narcotine by boiling with dilute acetic acid. 15 grams l-Narcotine were boiled with acetic acid (dilute) under the same conditions for different intervals of time and the quantities of the different products determined as shown in the following table:

Period of heating (hours)	8	24	48
Unchanged Narcotine	4·8 grams	3·7 grams	2·4 grams
Gnoscopine (rac. Narcotine)	5·0 "	3·5 "	1·2 "
Hornarceine	0·6 "	1·7 "	2·9 "
Meconine	0·15	1·0 "	2·3 "
Cotarnine.	not	determined.	

It has already been shown (Ber. d. Chem. Ges. 40, 3286, 1907) that Gnoscopine when boiled with dilute acetic acid produces Nornarceïne, Meconine and Cotarnine, but, that Nornarceïne when treated in the same way gives only, but slowly, decomposition products.
The results of the above three analogous experiments, showing the racemisation and the two hydrolytic changes, may be ~~be~~ briefly represented in the following scheme.



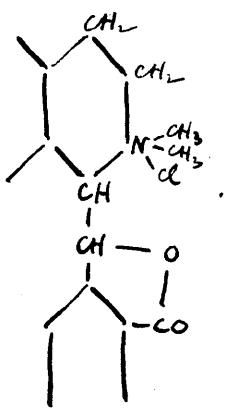
The relations of the numbers in the above table tends to show that probably l-Narcotine passes more easily into Nornarceïne than into Meconine and Cotarnine, the reverse taking place in the case of Gnoscopine. The explanation of this difference lies probably in the stereoisomeric nature of the two compounds as the molecule is disjointed with the formation of Meconine and Cotarnine at the point where the asymmetric carbon atoms lie.
Narcotine gives the same three transformations i.e. racemisation and the two hydrolytic changes when heated with baryta water and with dilute alcohol as with dilute acetic acid.

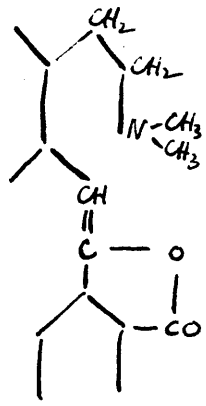
On the other hand, we have found that, when dilute sulphuric acid is used as the hydrolysing agent, Meconine and Cotarnine are formed very slowly and only in very small quantities. The other two changes i.e. racemisation and the "Umbau" to Romarceine either fail entirely out or take place extraordinarily slowly.

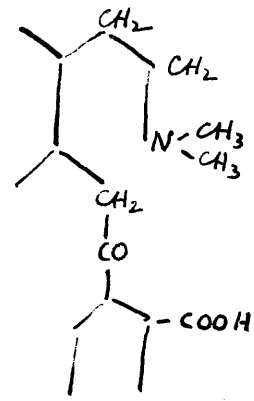
In the cases of the quarternary compounds of Narcotine and Hydrastine, we find that the "Umbau" into the basic Keto carboxy-acid takes place but we have not been able to observe the breaking up of the molecule into Meconine and Cotarnine, and, while the methylchloride compound gives rise to an unsaturated Lactone when the halogen atom is removed by Alkali, the free ammonium base passes into an isomeric neutral form which we may designate as "Oxybetaine".

The following table brings together the work, already done into line with our own investigations:

(1.)





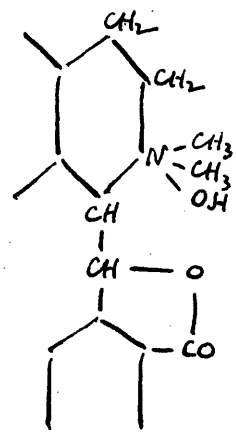


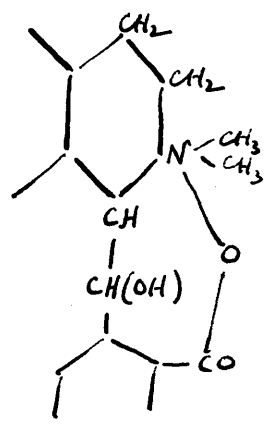
Narcotine methyl chloride
Hydrastine methyl chloride

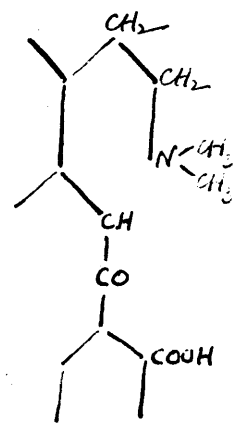
Methylnarcotine
Methylhydrastine

Narceine
Methylhydrasteine

(2.)







Narcotine methylhydroxide
Hydrastine methylhydroxide

"oxybetaine"
from Narcotine
from Hydrastine (1)

Narceine
Methylhydrasteine

If we view all the facts in the above table and arrange them from a general standpoint, we are drawn to the conclusion that there is a connection between the valency of the Nitrogen atoms and the art of the change (Umwandlung). we see that the "hydrolytische Spaltung" i.e. formation of Cotarnine and Meconine takes place

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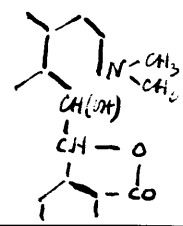
(1) Freund has previously assigned to this body the formula of a carbinol. The discussion regarding the truth of this formula will be found in the Experimental part.



where the molecule contains trivalent Nitrogen, while the presence of pentavalent Nitrogen seems to favour the formation of the keto-carboxy-acid. The difference in the effect of acetic acid and sulphuric acid on Narcotine is doubtless due to the fact that the Narcotine acetate undergoes more hydrolysis into acetic acid and tertiary amine than the corresponding Narcotine sulphate.

In conclusion, the above investigation may be taken as setting aside the last doubts regarding the accepted constitutions of Narcotine and Hydrastine. Further, it shows that Oxynarcotine and Gnoscopine are products of Narcotine and not separate alkaloids as described in the literature and are probably formed by the purification of the alkaloid. Finally, the "hydrolytische Umwandlungen" of Narcotine and Hydrastine have been submitted to a comparative investigation. The investigation has in view the object of clearing up some of the manifold reactions of 1, 2 Hydroamines to which belong, in addition to the alkaloids under consideration, other important natural products.

The <u>experimental part</u> may be divided as follows :-

A.

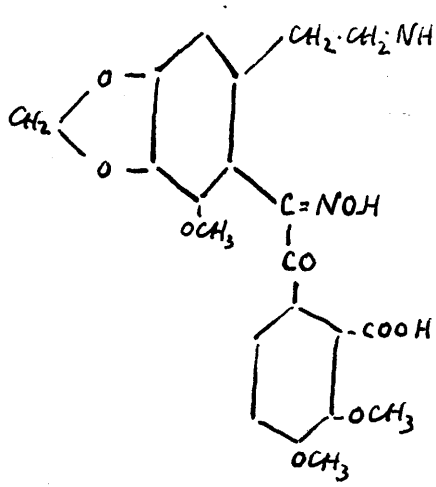
1. Constitution of Nornarceïne
2. Constitution of Methylhydrasteïne
3. Constitution of Gnoscopine
   (a.) Isomerism
   (b.) Racemic
4. Hydrolytic transformations of Narcotine with various reagents : [to throw light on the manifold changes of 1.2 Hydramines].
5. Hydrolytic transformations [Umwandlungen] of the quaternary compounds of Narcotine and Hydrastine
6. Isolation of Methylnarcotine.

B. Some analogous reactions in Cinchonine

I. The constitution of Normarceïne

The constitution of Normarceïne has been determined, as shown in the introduction, by the Beckmann reaction, namely by converting it first into the isonitroso-compound and then by breaking this latter compound into a nitrile and Hemipinic acid.

Isonitrosonormarceïne



In the first attempts to prepare this compound, Amylnitrite was used, but owing to the sparing solubility of the Sodium salt of Normarceïne, it was difficult to prepare the substance in large quantity. Afterwards, it was found much more convenient to use Ethylnitrite and this in large excess, as, owing to its very low boiling point, the excess can be very easily removed. A mixture of 25 grams Normarceïne (Ber. 40, 3284, 1907) 120 ccm. sodium ethylate containing 6 grams Na and 66 grams Ethyl nitrite was shaken together for about 60 hours and the solution became gradually brown colored. The Ethylnitrite and alcohol

were afterwards removed by passing a stream of air through the solution, at the same time warming it to about 40° C. The oily mass, which remained behind, was dissolved in water and the solution made acid with acetic acid. The isonitroso-compound gradually separated out in solid form and was recrystallised from water. The yield was about 9,4 grams but contained some Nitrosamine formed by the action of the ethylnitrite on the imido group. The melting point was 167 - 169° C.

Analysis:

0,2942 grams. (dried at 80°C) gave 18·6 ccm at 20° C and 747 mm pressure

$C_{22}H_{24}O_9N_2$ requires 6.09 N.

$C_{22}H_{23}O_{10}N_3$ " 8·59 N.

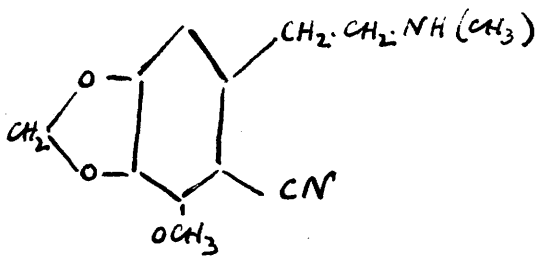
Found 7·39 N.

"Breaking up" of the Isonitrosonornarceïne

16 grams of the crude isonitroso compound were suspended in 200 ccm. chloroform and 23 grams phosphorus pentachloride added, the solution being meanwhile cooled with ice water. The reaction went rapidly and, during the night a salt, which proved to be the hydrochloride of the nitrile separated out. The chloroform solution contained the hemipinic acid, together with any of the hydrochloride

which might possibly be in solution.
The chloroform solution was shaken with ice water in order to remove any undecomposed PCl_5 and the water separated, treated with K_2CO_3 to liberate the nitrile and shaken with ether. The solid hydrochloride of the nitrile was treated with Na_2CO_3 (solid), after being dissolved in a small quantity of water, and the oil removed by shaking the aqueous solution with ether. The ethereal solution was dried over K_2CO_3 and the ether afterwards evaporated. An oil remained behind, which on standing in the ice chest became solid. The yield of crude nitrile base was 3 grams.

1. Methylaminoethyl-2-cyan-3 methoxy 4,5-methylenedioxybenzene.



The crude nitrile base was recrystallised by dissolving in ether and cooling in a freezing mixture. It consisted of a colourless, micro-crystalline powder and melted at 61°C. It is diffucultly soluble in water, turns litmus blue and forms well defined salts:

Analysis:

·1658 grams. gave 0·3728 gr. CO_2 and 0·0898 gr. H_2O

·1594 " " 17·1 ccm. N, temp. 23°C. Bar. 741 mm

		C	H	N
$C_{12}H_{14}O_3N_2$	requires	61·53	5·98	11·96
	Found	61·32	6·01	12·16

The Hydrochloride was prepared by adding the required quantity of nitrile to an alcoholic solution of hydrochloric acid. The salt dissolves readily in water, more difficultly in alcohol. It decomposes at 206–207° C.

·2520 gram gave 0·1299 gr. AgCl

Cl

$C_{12}H_{14}O_3N_2HCl$ requires 13·12

Found 12·75

The Iodomethylate is formed by treating 1 Mol. nitrile with 2 Mol. methyl iodide and 1 Mol. Sodium and is identical with the compound described by Freund and Oppenheim as produced from Narceine. It crystallises in colourless needles and can be recrystallised from water. It decomposes at 226° C.

Analysis:

0·0992 gram gave 0·0594 AgI

I

$C_{13}H_{19}O_3N_2I$ requires 32·56

Found 32·32

The Picrate and Picrolonate are obtained by bringing together the respective substances in equivalent proportions in alcoholic solution. The former is yellow coloured and melts at 168° C, the latter forms a brown powdery substance and decomposes at 232° C.

Analyses:

Picrate: 0.1382 gram. gave 18.1 ccm. N. ($t° = 19.5°$ Bar. 745 mm)

		N
$C_{18}H_{17}O_{10}N_5$	requires	15.12
	Found	15.10

Picrolonate: 0.1358 gram. gave 19.9 ccm. N ($t° = 21.5°$ Bar. 745 mm)

		N
$C_{22}H_{22}O_8N_6$	requires	16.87
	Found	16.80

Hemipinic Acid.

The chloroform solution was first dried and the chloroform afterwards distilled off. The crude hemipinic acid is purified by means of the lead salt. It crystallises with 2 Mol. of water, and forms fine colourless needles, sparingly soluble in water. The dried salt melts at 185 - 186° C.

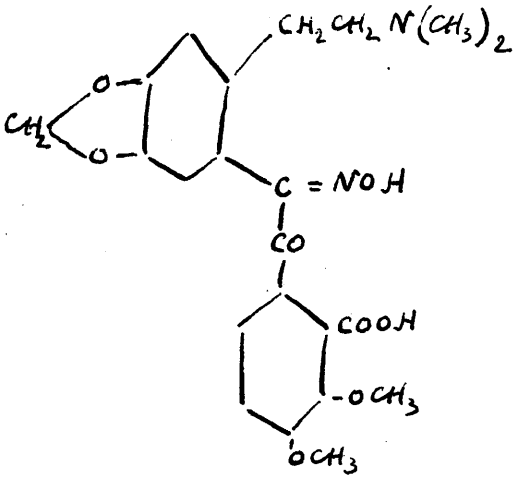
Analyses: 0.6671 gr. lost 0.0931 gr. at 105°C.
0.2125 " gave 0.4130 " CO_2 and 0.0849 H_2O

			H_2O	
$C_{10}H_{10}O_6 \cdot 2H_2O$	requires		13.74	
	Found		13.95	
$C_{10}H_{10}O_6$	requires	C	53.10	H. 4.42
	Found	"	52.98	" 4.44

II. The Constitution of Methylhydrasteïne

Methylhydrasteïne has already been described by Schmidt (Arch. der. Pharm. 228 247 1890) and also by Freund and Rosenberg (Ber. 23. 404 1890). The constitution has been determined in the same way as in the case of Normarceïne namely by the "breaking up" of the isonitroso compound into a nitrile and Hemipinic acid.

Isonitrosomethylhydrasteïne



9 grams Methylhydrasteïne when treated with 50 gram. Natrium Ethylate containing 2 gr. Na and 70 gr. Ethylnitrite produced 7.8 grams of the isonitrosobody. It was purified by crystallisation from water and is a colourless microcrystalline powder of melting point 189-190°C. It is difficultly soluble in water and alcohol, more readily soluble in hot water and insoluble in ether.

Analysis: 0.2227 gr. gave 12.3 ccm. N. [t°=18° Ber. 751 mm]

	N
$C_{22}H_{24}N_2O_8$ requires	6.31
Found	6.39

Conversion of the isonitroso compound into the nitrile and hemipinic acid.

7 grams isonitrosomethylhydrasteine were added to 100 ccm. chloroform and 7 grams phosphorous pentachloride. The nitrile and the acid were isolated in exactly the same way as in the case of Narceine.

The yield of crude base was 2·3 grams. This was recovered in the form of a dark oil which did not go solid although kept for some time in a freezing mixture. It was, therefore, not possible to obtain the substance pure enough for analysis and the iodmethylate and picrate were prepared. The nitrile base itself has the formula $C_{12}H_{14}O_2N_2$ and may be characterised as

1-Dimethylaminoethyl-2-cyan-4-5 methylene-dioxybenzene.

The Iodmethylate is easily prepared by treating the base with excess of methyl iodide in methyl alcohol solution. It separates in colourless needles from water and decomposes at 260°C.

Analysis:

0·2538 gram. gave 0·1648 gr. AgI

I

$C_{12}H_{14}O_2N_2 \cdot CH_3I$ requires 35·28

Found 35·09

The Picrate is a yellow crystalline substance of melting point 188 - 189°C. It is difficultly soluble in alcohol.

Analysis : 0.2377 gram. gave 32.4 ccm. N [$t° = 22°$ Bar. 755]

		N
$C_{18} H_{17} O_9 N_5$	requires	15.66
	Found	15.77

The Hemipinic Acid was purified as before by means of the lead salt :

Analyses: 0.4843 gram. lost 0.0676 gram at 105° C.

0.1928 " gave 0.3762 CO_2 ; 0.0736 H_2O

		H_2O
$C_{10} H_{10} O_6 \; 2H_2O$	requires	13.75
	Found	13.96

		C	H
$C_{10} H_{10} O_6$	requires	53.10	4.42
	Found.	53.21	4.33

III The constitution of Gnoscopine

Isomerism of Narcotine and Gnoscopine

Gnoscopine was first isolated in 1878 from the mother liquors left in the purification processes of Narcotine. From the fact that it produces the same products on oxidation and that the iodmethylate compound produced on treatment with alkali a substance agreeing in all respects with Narceine, it has long been held that the structure of both alkaloids must be very much alike. Narcotine and Gnoscopine, however, differ in this respect that while the former rotates the plane of polarised light, the latter is quite indifferent and shows no rotation. It was, therefore, suggested some few years ago by Rabe (Ber. 40, 3284, 1907) that Gnoscopine might simply be the inactive or racemic form of Narcotine. We have made a fairly complete investigation of this alkaloid both as regards its isomeric and racemic nature. Gnoscopine is perhaps most conveniently prepared by heating Narcotine with alcohol to 170° C in sealed. The crude product is best crystallised by dissolving in chloroform and precipitating with alcohol in which it is very sparingly soluble. The purified substance melts at 232-233° and is difficultly soluble in benzene.

A solution in chloroform (C = 1·055) showed no rotation in a 200 mm. tube. The substance is, therefore, inactive.

Analysis :-

0·1016 gram gave 0·2378 CO_2 ; 0·0487 H_2O

0·3477 " gave 11·2 ccm N [t° = 24° Bar. 749 mm)

0·2718 " dissolved in 12·21 gms benzene showed a raising of the boiling point equal to 0·156°

0·3540 gram. Narcotine dissolved in 11·92 gms benzene raised the boiling point of the latter by 0·185°

	C	H	N	Mol. weight
$C_{22}H_{23}O_7N$ requires	63·93	5·57	3·39	413
Found	63·83	5·33	3·65	381, 428

From these numbers we see that the analyses figures are in entire agreement with those calculated from the formula of Narcotine.

Isomerism of Narcotine and Gnoscopine

Oxidation of Narcotine and Gnoscopine by HNO_3.

3,9 grams Narcotine were mixed with 10 grams Nitric acid (Sp. gr. 1.4) and heated in the water bath for three hours at a temperature of 50°C. The Narcotine melted to a yellow mass and afterwards dissolved without giving off gases. After filtering the solution and making the filtrate strongly alkaline with NaOH, 2 grams Cotarnine were isolated

1.3 grams Gnoscopine were treated in the same way and produced 0.5 grms Cotarnine.
The oxidation of the alkaloids by sulphuric acid and Manganese dioxide has already been carried out [Pharm. Journ. Trans. 52, 794, 1893].

Action of water on both alkaloids at a high temperature.

5 grams Narcotine were heated with 8 grams water at 140°C for 7 hours and yielded after the mixture was treated with acid and alkali 0.2 gram Meconine and 0.2 gram Hydrocotarnine respectively.
5 grams Gnoskopine were treated in the same way and produced 0.2 gram Meconine but only a trace of Hydrocotarnine. In this reaction we should expect that Hydrocotarnine and Opianic acid would be formed according to the Equation:

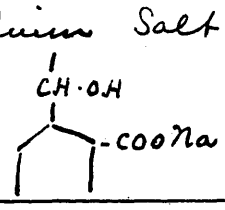
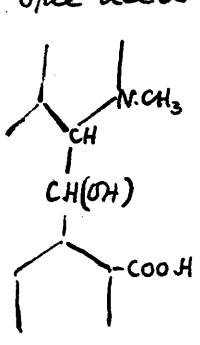
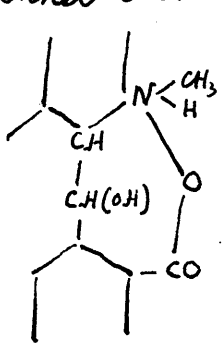
$$C_{22}H_{23}O_7N + H_2O = C_{12}H_{15}O_3N + C_{10}H_{10}O_5$$

This doubtless takes place in the first instance

but the opianic acid is afterwards reduced to Meconine.

Behaviour of Narcotine and Gnoscopine towards acids and bases.

Narcotine is, on the one hand, a tertiary base and, on the other, a lactone and is, therefore, a substance capable of undergoing many reactions. We have compared the two stereoisomeric substances in their behaviour towards acids and bases. The following table gives a brief review of the properties and reactions of the compounds formed.

	Narcotine	Gnoscopine
Melting point	176°	232°
in alcohol	moderately soluble	very difficultly soluble
in chloroform	easily soluble	easily soluble
Hydrochloride	In alcohol moderately soluble; in water easily soluble accompanied by slow separation of Narcotine	In alcohol difficultly soluble, in water not easily soluble accompanied by rapid separation of Gnoscopine.
Sodium Salt 	difficultly soluble in water	very easily soluble in water.
Free acid  Inner Salt 	only known in solution; very easily soluble in water; gradually with formation of the lactone structure passes into Narcotine.	known in solid condition: melting point same as that of Gnoscopine; passes over into Gnoscopine slowly at ordinary temperature, rapidly on heating; difficultly soluble in water.

A glance at the above table shows that the two stereoisomeric forms differ considerably in their reactions.

Narcotine Hydrochloride

4·13 grams Narcotine were heated with 10 ccm. of an alcoholic solution of hydrochloric acid. The salt separates in white needles which decompose at 215°.

Gnoscopine hydrochloride crystallises also in needles and decomposes at 238°.

Analyses:

(1) 0·1450 gram gave 0·3114 gr. CO_2 ; 0·0676 gr. H_2O

0·4962 " " 0·1556 " AgCl

(2) 0·1394 " " 0·2990 gr. CO_2 ; 0·0673 gr. H_2O

0·3594 " " 0·1136 " AgCl.

	C	H	Cl
$C_{22}H_{23}NO_7 HCl$ requires	58·70	5·34	7·89
Narcotine hydrochloride : found	58·57	5·17	7·76
Gnoscopine - -	58·50	5·36	7·82

Sodium salt of Narcotine :

As has been already shown by Wöhler (Ann 50 25 1844) and Hesse (Ann 176, 192, 1875) Narcotine passes over into a Sodium salt by the gradual addition of one molecule NaOH. This salt we prepared by heating 4,2 grams Narcotine with 40 ccm. n - Sodium hydrate solution, alcohol being added to facilitate the solution of the Narcotine. After

evaporating the alcohol and cooling the solution, 2 grams of the salt were recovered in the form of thin tablets melting at 85-87°. The salt contained 5 molecules of water of crystallisation.

Analysis : 0·5948 gram lost 0·0998 H_2O at 70°

0·4672 " gave 0·0634 Na_2SO_4

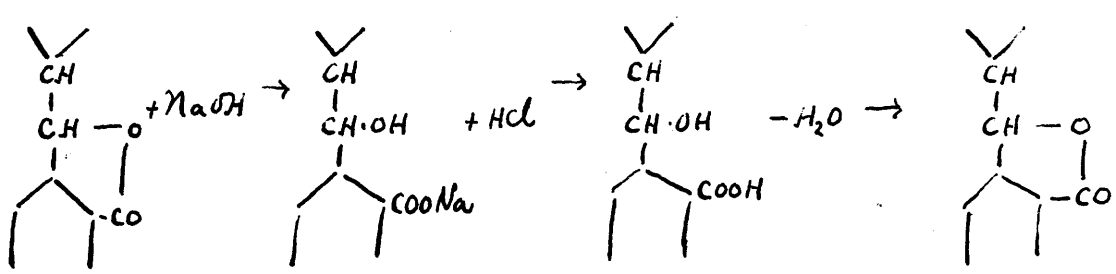
		Na	H_2O
$C_{22}H_{24}O_8NNa + 5H_2O$	requires	4·26	16·57
	found	4·37	16·77

0·4842 gram of the substance dried at 70° gave 0·0782 Na_2SO_4

		Na
$C_{22}H_{24}O_8NNa$	requires	5·08
	found	5·23

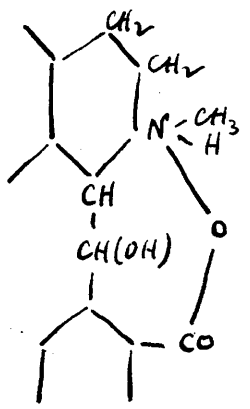
When the salt was allowed to stand in aqueous solution, Narcotine gradually separated out. This separation took place much more rapidly when the quantity of mineral acid required to liberate the free acid was added. The separation of Narcotine indicates that, in the solution, we have in the first instance an oxybase or inner salt present which, by the splitting off, of water, is converted into the lactone form.

Thus:



Sodium salt of Gnoscopine

If we attempt to prepare the corresponding sodium salt of Gnoscopine, we find that it cannot be isolated in solid form, for, if the aqueous solution is concentrated the difficultly soluble Gnoscopine falls out and not the sodium salt. If the solution of the sodium salt be treated with the requisite quantity of acid, Gnoscopine does not separate out, as might be expected, but the inner salt of the basic oxyacid of this form:



This substance $C_{22}H_{25}O_8N + 1\frac{1}{2} H_2O$ passes, slowly on standing, rapidly on heating at 100°, into Gnoscopine at the same time giving up $2\frac{1}{2}$ Mol. H_2O. Before heating the substance is insoluble in chloroform but readily soluble in alcohol; after heating, it is soluble in chloroform but precipitated by the addition of alcohol, properties which agree with the solubility of Gnoscopine in these solvents:

0.3234 gram lost 0.0314 H_2O at 108°

	H_2O
$C_{22}H_{23}O_7N + 2\frac{1}{2} H_2O$ requires	9.83
Found	9.70

Picrates and Picrolonates of Narcotine and Gnoscopine

To conclude the chapter on the isomerism of Narcotine and Gnoscopine, the picrates and picrolonates of both alkaloids were prepared and analysed. These salts are readily found when the respective components are brought together in equimolecular proportions in alcoholic solution. The picrates are well defined crystalline substances yellow in colour; the picrolonates are amorphous and of a darker colour.

Narcotine Picrate melted at 178-179°

0.1581 gr. gave 12.1 ccm. N [t° = 15°; Bar 737 mm]

Gnoscopine picrate melted at 185-186°

0.1955 gr. gave 14.9 ccm. N [t° = 15°; Bar. 729 mm.]

		N
$C_{28}H_{26}O_{14}N_4$	requires	8.72
Narcotine picrate	found	8.87
Gnoscopine "	"	8.73

Narcotine picrolonate decomposed at 232°

0.1802 gram gave 16.5 ccm. N [t = 16.5°; Bar 734 mm]

Gnoscopine picrolonate decomposed at 232°

0.2225 gram gave 20.2 ccm. N [t = 17°; Bar 728 mm]

		N
$C_{32}H_{31}O_{12}N_5$	requires	10.34
Narcotine picrolonate	found	10.51
Gnoscopine "	"	10.32

Concerning the racemic of Gnoscopine

Narcotine, being a weak base, forms salts which as a general rule do not crystallise very readily. This is also true of Gnoscopine and difficulty was at first experienced in finding a salt which would admit of fractional crystallisation. It was found, however, that by treating Gnoscopine iodmethylate with the required quantity of the silver salt of d-bromcamphorsulphonic acid that a well defined crystalline salt was formed, which was difficultly soluble in water. By a fractional crystallisation of this salt, it was found possible to separate two fractions which gave a different rotation in alcoholic solution. This was sufficient to determine the racemic nature of Gnoscopine. The corresponding Narcotine methyl-bromcamphorsulphonate was prepared and the salt separated as white needles difficultly soluble in water.

Analyses:

0·3074 gram gave 0·0988 $BaSO_4$;

0·3260 " gave 5·8 ccm. N [$t° = 24°$; Bar. 748 mm]

		N	S
$C_{33}H_{40}NBrSO_{11}$	requires	1·90	4·34
	Found	2·01	4·49

This substance dissolved in alcohol showed the following rotation: $\alpha_D^{23°}$ (200 mm) = 5·08° [C = 2·515]

i.e. $[\alpha]_D^{23°}$ = 101·0°

Groscopine methyl-bromcamphorsulphonate was prepared in the same way.

Analysis: 0·4146 gram gave 0·1382 $BaSO_4$

	S
$C_{33}H_{40}O_{11}NBrS$ requires	4·34
Found	4·56

This salt was then dissolved in boiling water and a fraction separated, which crystallised out at a temperature above 50°C, and, afterwards, a second fraction which separated at a temperature above 30°C.. Alcoholic solutions of approximately the same strength were made with these fractions and the rotations determined:

Fraction above 50° C $\alpha_D^{23°}$ (200 mm) = +3·27° [c = 2·509]

" " 30° C $\alpha_D^{23°}$ (200 mm) = +2·12 [c = 2·513]

We see, then, that the difference in rotation is over one degree for a concentration of only 2·5 per cent. When we cast a look over the data given, the similarity in molecular weight, and in the percentage of carbon, hydrogen and nitrogen, the similar chemical behaviour of the two substances when acted on by oxidising agents, alkalis and acids and finally, the difference of the rotations of these two fractions as given above, there can no longer be any doubt that Groscopine is in reality the racemic form of Narcotine and does not occur naturally in the opium juice but is produced from Narcotine during manufacturing processes.

IV. Concerning certain transformations (Umwandlungen) of Narcotine with the addition of 1 Mol H_2O

1. Heating Narcotine with dilute acetic acid.

Nornarceine was first isolated by boiling Narcotine with dilute acetic acid for 72 hours. This experiment has been carefully repeated and the influence of time on the course of this complicated reaction studied. It has always been noticed that in the above reaction, a certain quantity of unchanged narcotine is always recovered. This recovered product, we have purified by crystallisation and heated it once more with dilute acetic acid for the same period with the result that it breaks up again giving the same products and leaving also a little unchanged Narcotine.

3 grams, when heated, gave
- 0.2 Narcotine
- 0.1 Hydrocotarnine
- 0.6 Nornarceine
- 0.7 Cotarnine
- 0.8 Meconine

The Narcotine, then, as purchased may be taken as homogeneous and not as containing some other substance which might possibly give rise to the substances formed, leaving the Narcotine itself unattacked.

In the following three experiments, 15 grams Narcotine, 168 grams Water and 31 grams Acetic acid were heated in the oil bath (120°) with a

reflux condenser. The reaction solutions were 'worked up' exactly as before, care being taken to use the same quantities of solvents etc., etc.. The solutions were boiled [I] for 8 hours; [II] for 24 hours; [III] for 48 hours respectively and the following quantities of the reaction products isolated:

	I	II	III
Narcotine	4·8 grams	3·7 grams	2·4 grams
Gnoscopine	5·0 "	3·5 "	1·2 "
Hornarceine	0·6 "	1·7 "	2·9 "
Meconine	0·15 "	1·0 "	2·3 "

The Cotarnine produced may be taken as equal to the Meconine.

Heating Narcotine with dilute Sulphuric acid:

We have again studied the action of dilute sulphuric acid on Narcotine with a view to determining if Gnoscopine and Hornarceine are produced as in the case of heating with acetic acid. The results of two experiments are in agreement with observations already made on this reaction, namely that Meconine and Cotarnine are produced but no traces of Gnoscopine or Hornarceine could be found by us.

10 grams Narcotine, 100 ccm. Water and 10 grams concentrated H_2SO_4 were heated with reflux condenser for 24 hours. After the reaction mixture

had been neutralised with NaOH a dark coloured Mass separated out. From this 5 grams Narcotine and traces of Meconine were isolated but evidently a deep set decomposition had taken place.

A second experiment was carried out, in which 15 grams alkaloid, 100 grams Water and 12 grams conc. H_2SO_4 were boiled for 72 hours. Here again 10 grams Narcotine and traces of Meconine were isolated.

It is a somewhat remarkable fact that this point in the behaviour of the strong and weak acids comes before us in the analogous 'Umlagerungen' in the alkaloids of the cinchona group. The explanation must lie in the different degrees of dissociation of the salts so formed by the different acids or is dependent on the concentration of the hydrogen ion in the acids used.

Heating of Narcotine with baryta water

Narcotine was heated with excess of baryta water, the barium removed by adding a slight excess of H_2SO_4 and the acid solution 'worked up' in the same way as described under the experiment with acetic acid. In this case, the same products were isolated as with acetic acid: 10 grams Narcotine were boiled with 200 ccm Water and 10 grams barium hydrate for 24 hours. The following substances were isolated:

6 grams unchanged Narcotine
0·15 " Gnoscopine
0·1 " Nornarceine
0·1 " Meconine

A second experiment in which 15 grams Narcotine, 15 grams barium hydrate and 200 ccm Water were heated for 72 hours gave the following:

5.6 grams unchanged Narcotine
0·4 " Gnoscopine
1·1 " Nornarceine
0·2 " Meconine

Heating Narcotine with alcohol, absolute and dilute, and with water under pressure.

These experiments were carried out with the view of ascertaining whether Gnoscopine and Nornarceine were formed or not. In the case of the dilute alcohol all five products: Gnoscopine Meconine, Cotarnine, Nornarceine and unchanged Narcotine were found; with water at 130° Nornarceine could not be isolated.

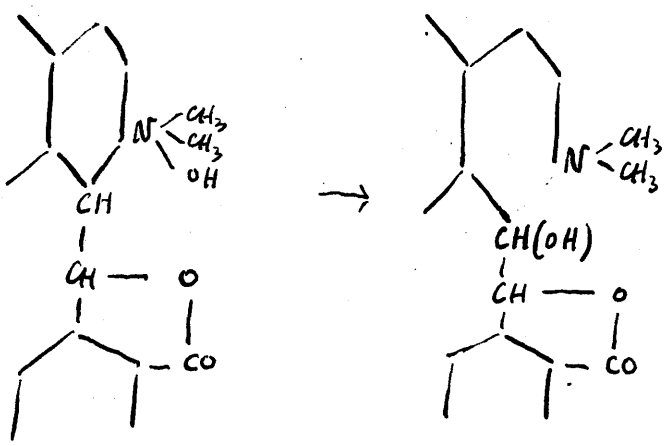
50 grams Narcotine, 800 ccm alcohol and 800 ccm Water were boiled for 8 days - The following were isolated:

8·5 grams Gnoscopine
3·0 " Nornarceine
1·8 " Meconine
2·0 " Cotarnine

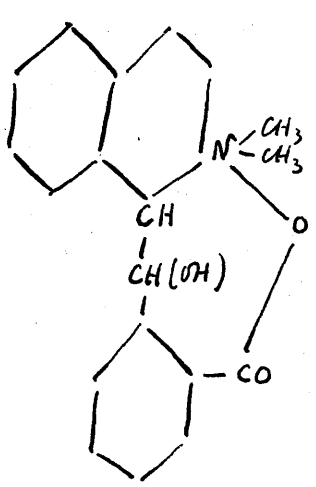
V Hydrolytic transformations of the quaternary compounds of Narcotine and Hydrastine.

In the investigations on Hydrastine, the changes and reactions of the quaternary compounds have been more particularly studied, and this owing mainly to the costly nature of the material. Hydrastine was boiled with dilute acetic acid for 72 hours but, as yet, no compound corresponding to Gnoscopine and no compound corresponding to ~~*~~ Normarceine has been isolated. Hydrastinine and Mecnine have however, been isolated, showing a breaking in the molecule corresponding to that observed in the case of Narcotine. The ammonium base $C_{21}H_{21}O_6N\langle^{CH_3}_{OH}$ has been prepared independently by Schmidt and Freund by treating the iodmethylate with moist silver oxide. From the concentrated solution Freund isolated a body which, in his first communication, he gave as melting at 238° but later corrected this value and gave the melting point as 242°. This latter value has been verified by us. It is quite clear that if the change of halogen for hydroxyl, a true ammonium base is formed which remains in solution, a circumstance which is amply proved by the strong alkaline reaction. This solution however, on standing becomes neutral and on concentration deposits this compound

melting at 242°. The properties given by Freund, namely, that it is neutral, does not react with methyl iodide, and forms the original iodomethylate by dissolving in hydrochloric acid and adding excess of Potassium iodide, are quite correct and further we may add that the compound is optically active. But a substance with such properties could not agree with the formula given by Freund thus:



Such a body, one would expect to react alkaline, and to unite with methyl iodide to form an addition product. The better explanation is that the ammonium base is passes into an inner salt of form



which we may designate as the "oxybetaine of hydrastine".

A body, so constituted, would agree with the above properties.

Analysis :-

0·4416 gram lost 0·0170 H_2O when dried at 105°

0·1890 " gave 0·4384 CO_2 ; 0·1080 H_2O

		H_2O
$C_{22}H_{25}O_7N.H_2O$	requires	4·15
	Found	3·85

		C	H
$C_{22}H_{25}O_7N$	requires	63·61	6·02
	Found	63·28	6·34

---

1 gram of the inner salt was dissolved in HCl and solid potassium iodide added. The hydrastine iodmethylate separated first, in an oily condition, but on standing went solid and showed a melting point of 208°

Analysis:

0·1568 gram gave 0·0696 gram AgI

		I
$C_{21}H_{21}O_6N\,CH_3I$	requires	24·19
	Found	24·08

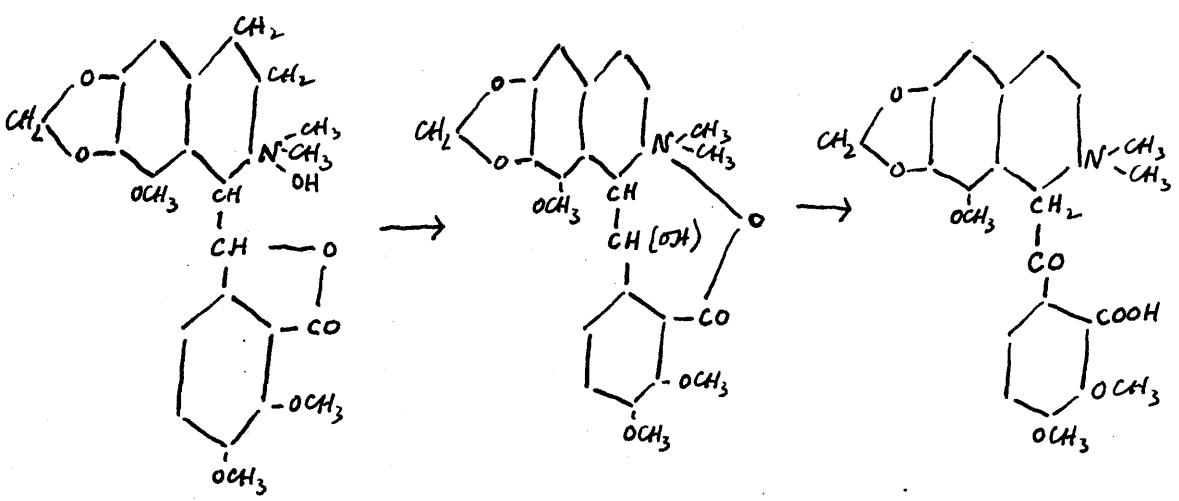
This inner salt was heated for several hours in alcoholic solution with methyl iodide, but only the original substance could be recovered.

0·209 gram in alcoholic solution gave a rotation

$$\alpha_D^{18°} = +2·97 \quad [C = 1·145].$$

Many experiments have been carried out in order to isolate this inner salt from Narkotine but without success. That it exists in solution, is without doubt, ~~but~~ since the aqueous solution is at first alkaline but gradually becomes neutral and, on standing for some time, intramolecular change takes place with the formation of Narceine

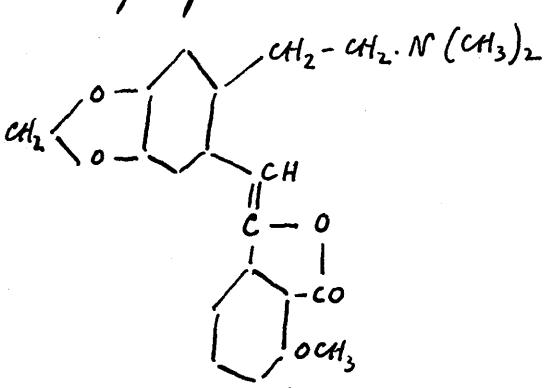
Thus:



Ammonium base Inner salt Narceine

(only known in solution)

If the Hydrastine iodomethylate be treated with aqueous alkali instead of silver oxide, the substance Methylhydrastine



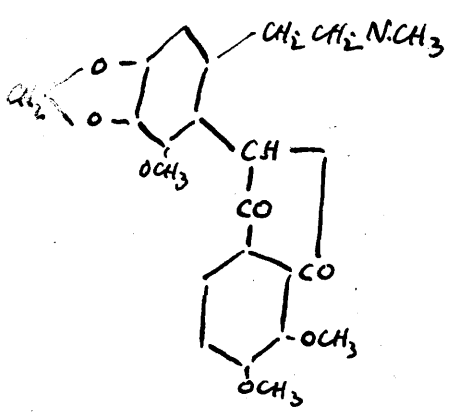
is formed, by the removal of the hydriodic acid

and the opening of the isoquinoline ring.
This substance is optically inactive, basic to litmus and unsaturated. It is distinguished from other Hydrastine derivatives by its yellow colour, and passes into Methylhydrasteïne when heated with strong alkali by the addition of one molecule H_2O.

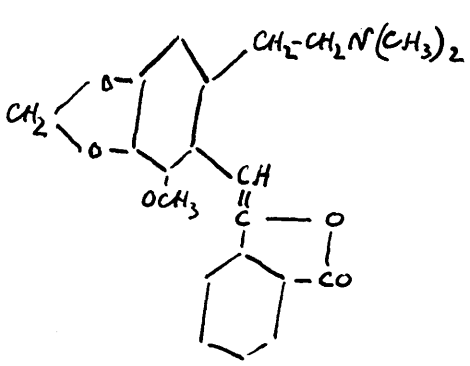
Some experiments were carried out with the quaternary compounds of Hydrastine in order to ascertain whether we find a 'breaking' of the molecule with the formation of Meconine and Methylhydrastinine. This however was found in no case to take place.
An aqueous solution of the Hydrastin methyl-hydroxide was allow to stand, a similar solution was treated with moist silver oxide and NaOH respectively but no Meconine and no Methylhydrastinin could be isolated. The oxybetaïne compound was found in all three cases and a little Methylhydrastine in the last two.
A solution of Hydrastinchlormethylate was heated with acetic acid and produced oxybetaïne compound and also Methylhydrasteïne. A solution of the corresponding Narcotine compound treated into the same way, gave a quantitative yield of Narceïne. In these last two experiments, Sodium

acetate must be present to remove the halogen acid.

With Narcotine, the transformations capable of being undergone ~~and~~ are entirely analogous to those already described for Hydrastine. The end product is Narceine and the "between" products Methyl Narcotine and the oxybetaine compound which is known only in solution. This intermediary product Methyl Narcotine is already known by the name Aponarceine, having been prepared by Jäger and Tambach [Ann. 349 189 (1906)] by acting on Narceine with phosphorus oxychloride. Jäger and Tambach assigned to this Aponarceine the following formula



but this was afterwards shown by Freund to be wrong and the following



is more in agreement with its chemical reactions.

and also shows its close relation to Methylhydrastine. It, however, differs from this latter compound in its tendency to add on a molecule of water and pass into Narceine. The presence of water alone is able to facilitate this change and on heating the transformation is much more rapid.

A number of experiments were carried out with the quaternary ammonium compounds of Narcotine analogous to those already described for hydrastine to ascertain whether Meconine and Betaine were produced. The solution of the methylhydroxide was allowed to stand, treated with Heat and moist Silver oxide but while, in all cases, Narceine was produced, no trace of Meconine or Betaine could be found. The absence of the oxybetaine compound of Narcotine throughout is worthy of note.

VI

Methylnarcotine.

A solution containing 10 grams of Narcotine-chlormethylate was treated with 20 c.cm n/1 NaOH and the yellow substance which separated immediately dissolved in ether. It separates first in an oily condition and dissolves more rapidly in the ether, if not allowed to become crystalline. The ethereal solution was dried over K_2CO_3 and the ether afterwards evaporated. 5 grams of Methylnarcotine were obtained and gave a melting point of 113 - 115°.

To the description already given by Jäger and Tambach, we may add that the substance is optically inactive, not very soluble in ether, has an alkaline reaction and is unsaturated. It forms an addition product with methyl iodide and passes very rapidly into narceine, especially on boiling with dilute alkali.

Freund has shown that methylhydrastenine when treated with concentrated hydrochloric acid gives rise to methylhydrastinine, Narceine, however, when treated in the same way does not seem to pass into Methylnarcotine. The explanation of this difference doubtless lies in the stability of the two intermediary compounds, the hydrastenine derivative being much more stable than the narcotine.

Analysis:

0.2448 gram gave 0.5084 CO_2 and 0.1189 H_2O

		C	H
$C_{23}H_{25}NO_7$	requires	64.64	5.85
	Found	64.55	6.15

The <u>Iodmethylate</u> was prepared by bringing the methylnarcotine and methyl iodide together in benzene. The substance crystallised in the form of yellow crystals and decomposed at 260°

Analysis:

0.2748 gram gave (Carius method) 0.1115 AgI

		I
$C_{23}H_{25}O_7N.CH_3I$	requires	22.32
	Found	21.93

In attempting to prepare this latter derivative in the usual manner namely, by bringing the constituents together in methyl alcohol solution, ~~It~~ it was found that the iodmethylate did not separate until some time had elapsed and further, from the analysis, what separated out as colourless crystals was not the iodmethylate of methylNarcotine but the iodmethylate of the methyl ester of Narceine; the lactone ring had opened and one molecule methyl alcohol had added itself.

Analysis :

(I) 0.2039 gram gave 0.0788 Ag I

(II) 0.3034 " " 0.1173 "

		I
$C_{25} H_{32} O_8 N I$	requires	21.12
	Found	20.87 ; 20.88.

The Lactone ring can further be opened by leaving the substance in alcoholic solution which contains hydrochloric acid. The yellow hydrochloride of methylnarcotine does not separate but the colourless salt of the ethyl ester of Narceine, which melts at 206°.

The <u>picrate</u> separates as a yellow substance when the two constituents are brought together in alcoholic solution. Melting point 134°.

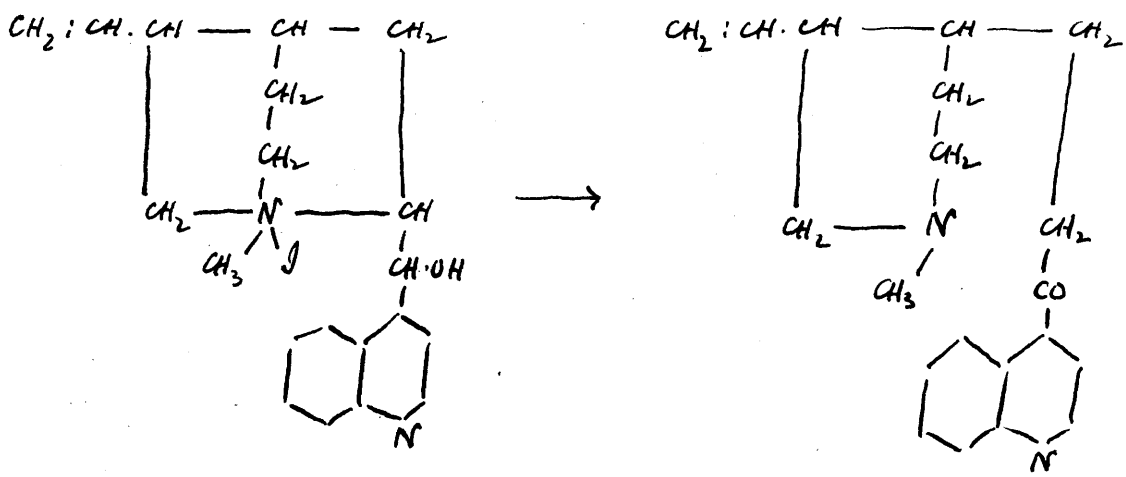
Analysis :

0.2196 gram gave 15.60 c.cm N [$t° = 18.5°$; Bar 748].

		N
$C_{29} H_{28} O_{14} N_4$	requires	8.54
	Found	8.27

Reactions of the quaternary compounds of Cinchonine

In connection with the transformations of the quaternary compounds of Narcotine and Hydrastine into Narceine and Methylhydrastine respectively, it seemed of interest to ascertain if the analogous compound of Cinchonine passed into the corresponding Keto derivative methyl Cinchotoxine. Thus



7 grams Cinchonincodinethylate were converted into the more soluble chlormethylate by excess of Ag Cl. A small quantity of this solution was acted on by Baryt to find if any body of the nature of Methylhydrastine or the corresponding Narcotine compound separated. The mixture was allowed to stand for some time but nothing separated.

The remainder of the chlormethylate solution was treated by moist Silver oxide and converted into the ammonium base.

The solution of the Ammonium base which was

strongly alkaline, was evaporated to dryness on the water bath. The residue was boiled with a strong solution of KOH and, after boiling for some hours with a reflux condenser, oily drops appeared on the solution. After cooling, the solution was extracted with ether. The ethereal solution was dried and after removing the ether, the oily residue solidified and was recrystallised from a mixture of ether and ligroin. The substance crystallised in little cubes and gave a melting point of 75°.

Analysis:

0·1578 gram gave ·4522 CO_2 ; ·1082 H_2O

		C	H
$C_{20}H_{24}N_2O$	requires	77·92	7·79
	Found	78·13	7·62

The transformation into the Keto-derivative, therefor, takes place in this case also.

Concerning a curious relation between the strength and the action of acids

In section IV of this investigation it was shown that, while Narcotine passed readily into Notnarcotine by the action of dilute acetic acid, such a transformation was not found to takes place when sulphuric acid was used in place of acetic. In his investigations on the transformation of Cinchonine into Cinchotoxine by the influence of acetic acid, Rabe had observed that the change did not take place when a mineral acid, such as hydrochloric was used as the hydrolysing agent. On his suggestion, I repeated the experiment with hydrochloric acid and carried the investigation further to include other organic acids, the dissociation-constant of which had been determined, in order to ascertain if any relation could be seen to exist between the rate of change and the strength or degree of dissociation of the acid used. The change of Cinchonine into Cinchotoxine was used in preference to the analogous case of Narcotine because the latter change is accompanied by the formation of Cotarnine and Meconine.

9 grams Cinchonine were mixed with 5 Equivalents of the different acids and 108 ccm. Water. The solutions were heated for different periods

in sealed tubes at a temperature of 98°.

The reaction mixture was, then, made strongly alkaline with NaOH and the liberated Cinchotoxine dissolved in ether – The ethereal solution was dried, as the ether distilled off and the residues allowed to stand in an evacuated ~~xxx~~ desiccator until two consecutive weighings showed no change.

The acids used were (1.) Hydrochloric (2) Oxalic (3) tartaric (4) Formic (5) Phosphoric (6) Succinic (7.) Acetic and the results show clearly, in spite of small irregularities, consequent upon the somewhat crude method (no other being available) of separating the Cinchotoxine, that the rate of the change does not rise but falls with the rise in the dissociation Constant. As Cinchonine and Cinchotoxine are both optically ~~x~~ active, a polarimetric determination of the rate of change would have been of the greatest use but this was impossible owing the deep colouration assumed by the solutions when heated.

Acid	Dissociation Constant	Cinchotoxine isolated after 8 hours	16½ hours	50 hours
Hydrochloric		–	–	–
Oxalic	–	–	0·368 gr.	1·540 gr.
Tartaric	0·097	3·472 "	3·908 "	7·070 "
Formic	0·0214	3·111 "	5·341 "	7·173 "
Phosphoric		2·472 "	6·475 "	7·185 "
Succinic	0·0066	5·675 "	6·037 "	7·279 "
Acetic	0·0018	7·258 "	7·818 "	8·222 "

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Like all other reactions in nature, chemical reaction requires a certain time to complete itself. This time can be a second or it can be a hundred years and depends on the nature of the substance undergoing change and also on the external circumstances controlling the reaction, such as temperature, pressure, presence of catalytic agents and the like.

The Laws governing chemical change have only formed a subject of study in comparatively recent times. About the year 1777 Wenzel had observed that the time required for the solution of metals in acids depended on the concentration of the acid used, the process taking a much longer period in a dilute solution than in one more concentrated. The latter problem was made a subject of study by Berthollet at a later time and, while arriving at the same conclusions as were previously known, he made the further observation, that the rate of reaction became slower, the nearer the reaction reached completion. While the above investigators had to a certain extent come to the laws governing chemical change, neither of them had attempted to formulate them into a mathematical equation. This was, however,

accomplished by Wilhelmy in his famous researches on the inversion of sucrose.
When sucrose is dissolved in water and a little acid added, it breaks up into dextrose and laevulose, the rotation of the solution rapidly changing with time during the course of the reaction. Wilhelmy assumed that the quantity transformed in a small interval of time was proportional to the quantity of sugar present. If A represent the original quantity and at the time θ the quantity x be transformed, as, in a small interval of time, we have

$$\frac{dx}{d\theta} = k(A-x)$$ where $A-x$ represents the

quantity of sugar not transformed and k is a constant.

$\frac{dx}{d\theta}$ shall represent the velocity of the reaction.

By taking the change in rotation as being directly proportional to the quantity of substance transformed and substituting the values in the equation found by integrating the equation given up

thus $$k = \frac{1}{\theta} \log_e \frac{A}{A-x}$$

The initial rotation i.e. the rotation of the solution the instant it is made up, is found by extrapolation.
Wilhelmy found that the value obtained for "k" was a 'constant'. The truth of the above Equation has been amply shown by its application to other reactions of quite different characters.

It will be evident, then, that to obtain good results in experiments of this nature, the equilibrium of the reacting substances should be disturbed as little as possible. Hence, it must be admitted that the polarimeter lends its peculiarly to such work and presents a method, which is at the same time, easy and exact. A method, involving the use of the polarimeter, for the measurement of nitramolecular change has been frequently used, first by Wilhelmy and again by Lowry in his study of the mutual conversion of the nitro- and the ψ-nitro derivatives of Camphor (Trans. 1899, 75, 211) with the most satisfactory results, but, in all such cases, the substance which undergoes change is the active substance itself, a fact which somewhat limits the method being used in a comparatively small number of cases.

In the following research is given a description, with satisfactory experimental results, of a method in which the polarimeter is used, but, in which the inactive substance is undergoing change, the active constituent being only used as an indicator of the rate of transformation.

The class of compounds, capable of undergoing such change, to which the method has been as yet principally applied is that of the oximes.

It has long been known that benzsynaldoxime readily passes into its isomeric form

benzantialdoxime, which is the more stable variety. The velocity of change of certain salts of these substances, viz. the acetates, have been studied and already measured by two investigators, in the first instance, by Hantzsch (Zeitsch. phys. Chem. 1894, 13, 509) who has determined the rate of conversion of the acetates of the synoximes into nitriles and, again, by Ley (Zeitsch. phys. Chem. 1895, 18, 376) who has measured the rate of transformation of the acetates of the syn-oximes into the acetates of the anti-oximes by the action of hydrochloric acid, but no method has been hitherto described for directly measuring the change of a syn-oxime into the isomeric anti-form.

It was found that the solvent effect produced by the synoxime on the rotation of ethyl tartrate was very much greater than that produced by the corresponding anti oxime and that, by watching the gradual change in rotation which accompanied the intra-molecular rearrangement of the dissolved substances, it was possible to measure the velocity of transformation.

The synoxime is generally prepared from the anti-form by dissolving the latter in ether and precipitating the hydrochloride by dry hydrochloric acid gas. The hydrochloride is, afterwards dried, decomposed by a dilute solution of Na_2CO_3 and subsequently recrystallised from a suitable solvent.

The first part of this investigation (Trans. 1907 91 504).

deals with the solvent effect of benzantialdoxime and benzsynaldoxime on the rotation of ethyl tartrate, which substance has been used throughout as the active indicator. Benzantialdoxime as will be seen from the graph has quite a remarkable effect. The curves (page 507) connecting rotation and temperature for solutions containing 79.9 per cent. and 49.6 per cent. lie above the corresponding curve for the pure ester while the curves for $p = 22.9$ and $p = 10.4$ lie below it. [p = grams of ethyl tartrate per 100 gram solution]. The specific rotations for solutions of different concentrations at 20° and 100° are shown in the following table.

p	$[\alpha]_D^{20°}$	$[\alpha]_D^{100°}$	p	$[\alpha]_D^{20°}$	$[\alpha]_D^{100°}$
100.0	+7.76°	+13.5	22.82	+0.2	+12.8°
79.9	+12.9	+16.4	10.37	−7.7	+9.9
49.62	+10.8	+16.1	0.0	−16.0	+7.0

When these values are plotted on curves, we see that, by the addition of oxime up to $p = 70$, there is an increase in the rotation of the tartrate. If more oxime is added, the rotation diminishes until at infinite dilution the specific rotation falls to about −16°.

The solvent effect of the isomeric synoxime on ethyl tartrate was next tested and the magnitude of the difference produced on the rotation of the latter substance was quite beyond expectation, the synoxime, even for very dilute solutions, being found to raise the rotation in a very pronounced way. It was also found

that, if a solution of the syn-oxime in ethyl tartrate was allowed to stand, the rotation of the solution gradually diminished with the transformation of the substance, until it finally assumed a value which corresponded exactly with a solution containing anti oxime and of the same concentration. This fact, then, was made use of, in measuring the rate of intramolecular change, of the one oxime into the other.

The influence of temperature on the velocity of change was next investigated and, it was found, as was only to be expected that the rate of change increased rapidly with rise of temperature

The transformation of the oximes of anisaldehyde was investigated with entirely satisfactory results, the difference between the initial and final rotations being no less than 2·5° for a solution containing only 5 percent. of oxime.

It next seemed of interest to test whether the change could be observed and, to what extent, in the presence of a third solvent. For this purpose, solutions were made up containing syn-oxime, ethyl tartrate and benzene, iso-butyl alchol and chloroform respectively. It was possible to follow the transformation as before although, in the case of the chloroform solution, the change was very small, due doubtless to the depressing effect, chloroform has on the rotation of active substances. The values found for 1000 K were 3·0, 8·4 and 4·5 for the solutions containing iso Butyl alcohol, benzene and chloroform respectively.

The method was further applied to the transformation of the keto-enol forms of Ethylformylphenylacetate.

In the second part of this investigation (Ber 40 2564 1907) the method, described in the previous publication, was applied to other active esters and the rate of change of anis-syn-aldoxime into anis-anti-aldoxime when dissolved respectively in methyl tartrate, ethyl tartrate, propyl tartrate and the corresponding malates, was determined and compared.

It was found that in the case of the tartrates, the rate of change decreased with rise in molecular weight and so seems to be in no way dependent on viscosity. It might have been expected that the rate of change would have been more rapid in the comparatively liquid propyl tartrate than in the viscid methyl tartrate.

In the case of the malates, the reverse was found to be the case, the rate of change increasing with increase in molecular way.

It is also worthy of note that in the case of the tartrates the fall in rotation is considerably greater than that found for the malates.

The following table shows the comparative results.

	1000 K		1000 K
Methyl tartrate	3.0	Methyl Malate	5.0
Ethyl -	1.8	Ethyl -	6.7
Propyl -	1.0	Propyl -	8.4

Further the rate of change of the m-nitrobenz-syn-aldoxime into its isomeric form was determined in propyl tartrate, 1000 k being found equal to 0·5; the rate of change was consequently slower than for anis oxime in the same solvent. This fact was also found by Hantzsch in his work on the conversion of the m-nitro syn-acetate into the Anticle, the value found being ·000128 while for anis syn-acetate the value is ·000412.

The third part of this investigation (Trans. 1908 93 1041) deals principally with the influence of temperature on the velocity and a verification of the van't Hoffian equation dealing with velocity and temperature namely,

$$a = \frac{T_0 T_1}{T_1 - T_0} \log_e \frac{K_1 T_1}{K_0 T_0}$$

[a = a constant, T_0, T_1 the absolute temperatures, K_1, K_0 the corresponding values of the velocity constant]

as suggested by van't Hoff.

The temperatures chosen ranged for 20° to 30°, going in stages of two degrees at a time.

Two solutions containing 5 per cent. oxime were made up for each temperature experiment and the mean value taken as the velocity constant.

The experimental values for 1000 k found agreed quite satisfactorily with those calculated from the above equation, as is shown

in the following table

Temperature	1000k (calculated)	1000k (observed)	Δ
20	0·418	0·520	0·102
22	0·574	0·580	0·006
24	(0·782)	(0·782)	—
26	1·063	1·114	0·051
28	1·440	1·440	·000
30	(1·941)	(1·941)	—

The oxime used in these experiments was Isperonalsyproxime.

It is also shown that the purer the specimen of ethyl tartrate is, the slower is the velocity constant. It is well known that ethyl tartrate always contains traces of ethyl chloride, alcohol and other impurities formed during its preparation. These impurities are usually removed by repeated distillation under reduced pressure. A specimen of ethyl tartrate which was twice distilled was used to determine the rate of change of isperonal-syproxime and the value for 1000k found 0·689. A further distillation reduced this value to 0·352 and after four distillations the velocity constant found for a specimen of the same isperonalsyproxime was 1000k = ·150 Thus each distillation had a pronounced effect on the velocity constant.

In conclusion, may be mentioned some miscellaneous examples of such intramolecular changes which have been studied by us. In the first place, the velocity of transformation of o-iso Nitrotoluene into o-nitrotoluene was found to be 2·59 for 1000 K at a temperature 19·5°. This change has been measured by Hantzsch and Davidson by mixing the Sodium salt with hydrochloric acid and observing the gradual change in electrical conductivity but they only arrived at qualitative results.

Further, we have, measured the rate of change for p-iodobenzoynaldoxime in propyl tartrate and applied this new method to a determination of the point of equilibrium of Ammonium thiocyanate and thiocarbamide and also the transformation of Ammonium Cyanate into Carbamide. This latter does not give a 'Constant' when calculated according to the Equation for a monomolecular action but this is in accordance with the results of Walker, who has already determined the change as being of the second order.

The accompanying papers give a complete account of the experimental figures.