STUDIES IN THIOLCAMPHOR AND IN NARCOTINE

by

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Thesis for Degree of Doctor of Philosophy.

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APRIL, 1927.

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Part I. Thiolcamphor.

Part II. Narcotine.

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The Metallic Derivatives of Thiolcamphor and of some Thiol-esters.

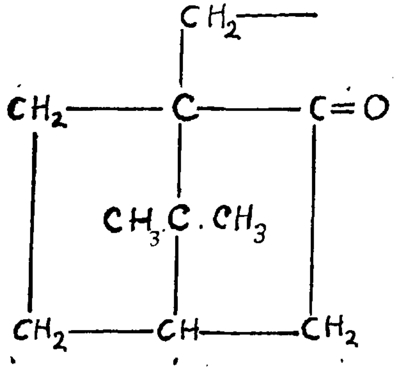
(DRUMMOND AND GIBSON, J.C.S., 1926, 129, 3073.)

During the course of some synthetic work on disulphoxides the facts with which this paper deals were brought to light, and the compounds which we discovered seem to be representatives of a class of which many interesting cases have been described since our work was completed.

The original aim was to prepare dicamphoryldisulphoxide, III, by the interaction of silver thiolcamphor, I, and camphorsulphonyl chloride, II.

$$\overline{\underline{C}}\cdot\underset{\text{I.}}{\text{SAg}} + \underset{\text{II.}}{\text{Cl}\,SO_2}\,\overline{\underline{C}} \rightarrow \overline{\underline{C}}\cdot\underset{\text{III.}}{S{\cdot}SO_2}\,\overline{\underline{C}}$$

where $\overline{\underline{C}}$ represents the group:



We thought we had obtained the requisite silver thiolcamphor by the interaction of equimolecular parts of silver nitrate and thiolcamphor in alcohol but our repeated failures to obtain any of substance III, and the fact that the mercaptide, I, was sometimes yellow and oily led us to examine/

examine it more closely. Attempting to remove the oil by washing the mercaptide with benzene, we were surprised to find that the whole product readily dissolved therein. This result was so unexpected that we prepared a fresh sample of the substance and were confused to find that, though the conditions of the previous preparation had been closely followed, the product was quite insoluble in benzene. The products of succeeding preparations were soluble, insoluble and partly soluble, until we discovered that two silver compounds existed, one white and insoluble in benzene and the other, yellow and very soluble in that solvent; and that the proportions in which the thiolcamphor and silver nitrate were taken determined which product would be obtained.

Slightly over twice the theoretical quantity of silver nitrate, when mixed with thiolcamphor in alcohol, produced a white, crystalline compound, which was remarkably insoluble in all solvents except chloroform. This substance yielded the brown ring, which characterises the nitrate radicle, and analysis revealed the composition, $C_{10}H_{15}O.SAg, AgNO_3, H_2O$. One half of the silver was found to be ionisable. Though insoluble in benzene, the substance was readily soluble in benzene containing thiolcamphor and from the resulting orange-red solution by precipitation with petroleum ether was obtained the yellow/

yellow silver compound. This substance also contained the nitrate radicle and analysis shewed the composition, $(C_{10}H_{15}O.SAg)_2, AgNO_3, H_2O$, and one third of the silver was found to be ionisable. The abnormal composition of both these mercaptides provides an explanation of the failure of the synthetic experiments.

It was found that slightly over one third of the quantity of thiolcamphor, which was combined in the first substance, was required to convert it into the compound soluble in benzene, that is, that *three* molecules of the white silver substance united with *one* molecule of thiolcamphor to produce the soluble, yellow compound.

The reaction was formulated as follows:-

$$3\,C_{10}H_{15}O.SAg, AgNO_3, H_2O + C_{10}H_{15}O.SH = 2\,(C_{10}H_{15}O.SAg)_2, AgNO_3, H_2O + HNO_3 + H_2O.$$

and the separation of water was actually observed in the benzene.

As the yellow compound depressed the freezing point of benzene very slightly, the possibility of the solution being colloidal was suggested to us; but neither the Tyndall cone nor Brownian movement was observed and solutions of the substance in both benzene and ethylene dibromide diffused rapidly through parchment.

During a trial preparation of thiolcamphor in which nickel was used instead of tin for the reduction of/

of camphorsulphinic acid, a nickel compound of a deep brown colour was observed in the steam distillate and it seemed probable that the thiolcamphor had united with nickel or nickel chloride to form a derivative of abnormal properties. The action of thiolcamphor on nickel chloride was therefore examined.

Thiolcamphor in alcoholic solution did not react readily with nickel chloride but the addition of an equivalent quantity of sodium carbonate or preferably sodium acetate (to provide nickel acetate in solution) produced an immediate reaction, which was indicated by the deep brown colour of the solution. From this was isolated a mahogany-coloured solid, very soluble in benzene and other organic solvents but quite insoluble in water. This substance rapidly softened on heating to a dark-coloured liquid. By analysis the apparent composition, $(C_{10}H_{15}O.S)_3Ni$, was obtained, and from its properties the compound appeared to be a co-ordinated complex rather than a salt.

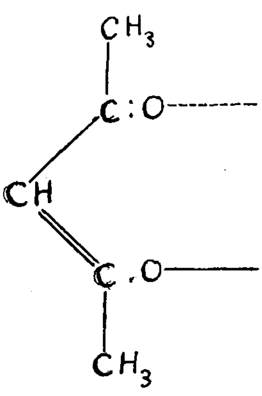
At this point it was thought advisable to undertake a survey of the literature with a view to discovering other examples possessing similar, abnormal properties, if such existed.

Attention was directed to the researches of Morgan and his collaborators on the metallic derivatives of/

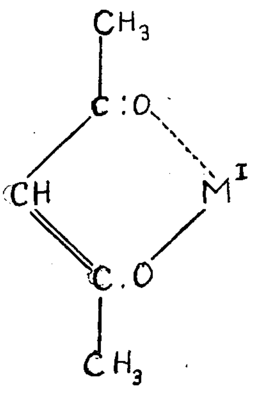
of acetylacetone and of related substances.

Morgan and Moss (J.C.S., 1914, 105, 189) preface an account of their work as follows:-

> "The remarkable properties exhibited by many acetylacetones, their non-ionisable character, their solubility in anhydrous organic solvents and, in certain instances, their anomalous colours, have led to the view that in these compounds the metallic atoms are combined with the unsaturated organic complex, not only through their principal valencies, but also by means of their residual affinity or auxiliary valency.
>
> Moreover, as the univalent organic complex (formula IV) consists of an open chain of five atoms, its intimate association with the metal is assumed to arise from the general tendency to form six membered rings (formula V), the metallic atom serving as the connecting link between the ends of the organic group.



IV

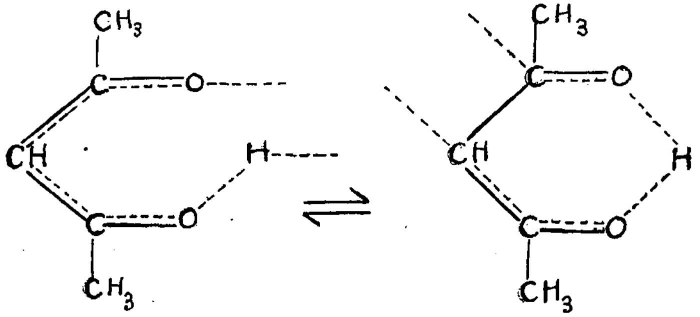


V

The behaviour of these metallic derivatives on heating justifies the contention that a symmetrical arrangement of associating units conduces to stability."

It is of interest to note that previous to this, in a study of the selective absorption of Ketones, Henderson and Heilbron (Proc. Roy. Soc., A. 89, 1913-1914, 416) suggest that in these substances alternate formation and breaking down of unstable ring systems takes place and, secondly, that the momentary formation of these ring systems is effected through the agency of free partial valencies, which, under certain conditions, make their appearance on the atoms of the compound.

Their formulation of acetylacetone, VI, closely resembles that afterwards suggested by Morgan and Moss.



VI

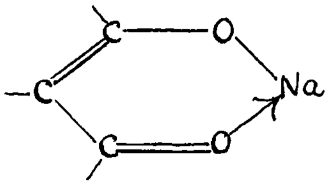
Morgan and his fellow-workers have also prepared and studied analogous metallic compounds from benzoylacetone, acetyl methylacetone, ethyl acetoacetate, acetyl mesityl oxide, and numerous other β-diketones and β-keto-esters.

The heterocyclic rings, which Morgan supposes to be present in these compounds, have been termed "chelate" rings because of the tenacity of the grip on the implicated metallic atom. (The term "chelate" is apparently derived from the "chela" or great claw of the lobster and of other crustaceans).

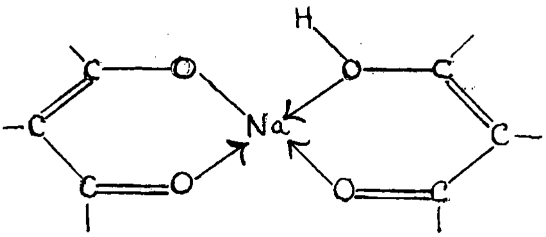
This conception of the implication of metallic atoms has been usefully applied to the lake dyes by the same author. (J.C.S., 1922, 121, 2857).

Sidgwick describes compounds of the alkali metals with β-diketones and β-keto-esters. (J.C.S., 1925, 127, 2379; see also J.C.S., 1924, 125, 527 for general discussion)

To these metallic derivatives he gives the type formulae, A and B.



A.



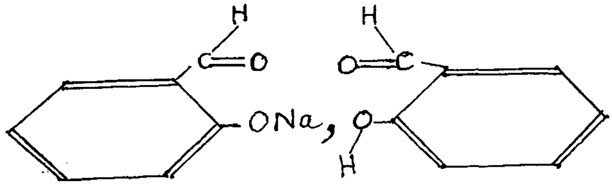
B.

While his method of formulation is slightly different from Morgan's, the underlying idea is the same. Sidgwick's reasons for such formulation are the abnormal properties of these substances. They are evidently not salts as they do not char on heating but have definite melting points and are readily soluble in hydrocarbons such as benzene and toluene.

Other substances are described by Sidgwick which are taken to be of the type shown in B. In these compounds one molecule of the organic body is chelated around the sodium atom as in compounds of type A, while another molecule of the organic substance is attached only by residual affinity. The enolic hydrogen is not replaced by the metallic atom. In many cases the addition compound is not stable and readily decomposes to a substance of type A.

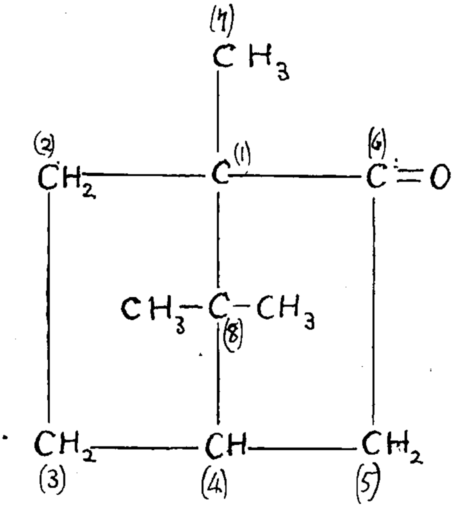
Compounds of the second type, B, possess definite melting points, usually forming clear liquids; they are soluble in organic solvents and are highly coloured.

Hantzsch (Ber., 1906, 39, 3089) reports a yellow compound of the addition type B from salicyl-aldehyde.



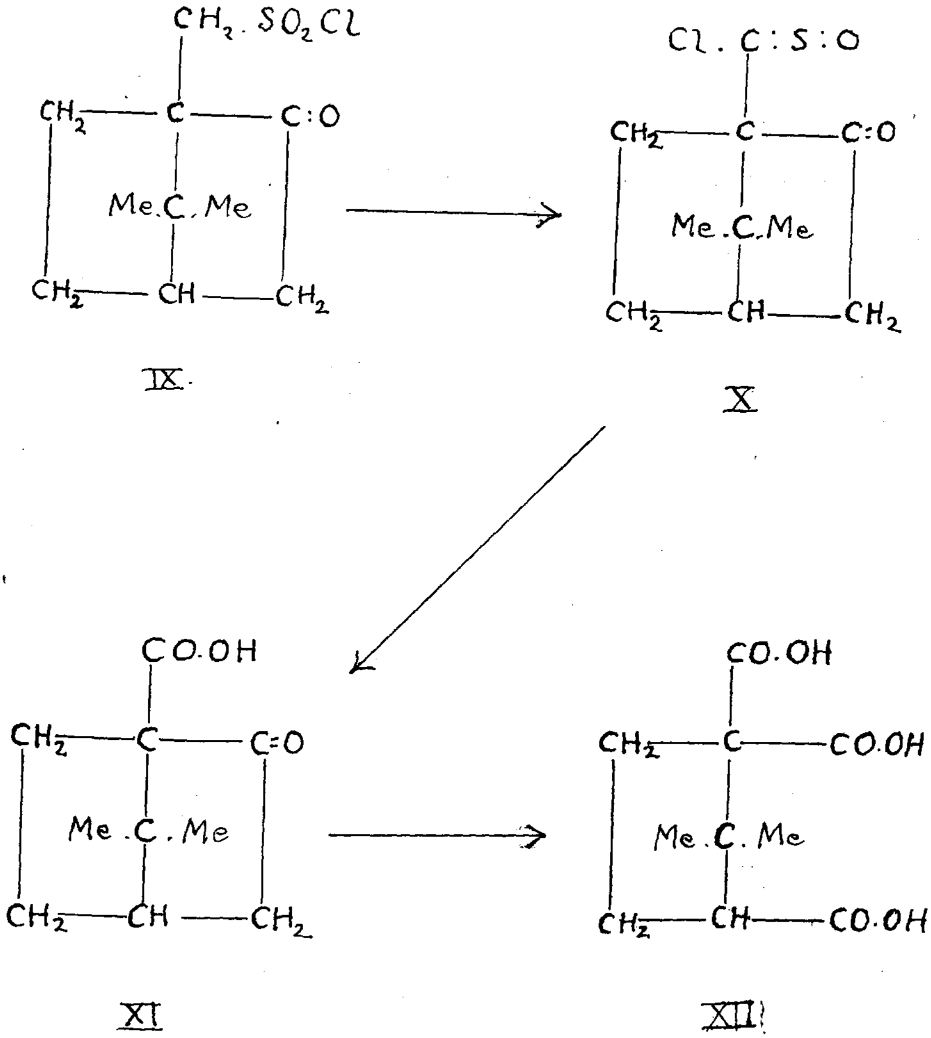
It is of importance to realise that this representation is merely an expository device and useful for purposes of classification, but does not pretend to explain the actual nature of the type of linkage in operation. Certain substances are observed to possess abnormal properties in common. It is also noticed that such bodies contain along with replaceable hydrogen one or more groups of unsaturated character, (carbonyl-, nitro-, amino-, etc.), and when the unsaturated group is absent, derivatives of normal properties are obtained. It is therefore, at least, permissible to assume that some causal connection exists between the presence of the unsaturated group and the abnormal properties.

With these considerations in view, Morgan and Sidgwick's conception has been applied to the metallic derivatives of thiolcamphor. Before, however, this can be done, it is necessary to consider the orientation of the thiolcamphor molecule. In this substance there is replaceable hydrogen in the thiol group and also an unsaturated group in the carbonyl of the camphor molecule, but a knowledge of the relative positions of these is required. As the constitution of the camphor molecule, VIII, and therefore the position of the ketonic group, is well established, it remains to consider the position of the substituent thiol grouping.



VIII

The latter point has been decided by the recent work of Wedekind, Schenk and Stusser (Ber., 1923, 56, 633). Starting with Reychler's camphorsulphonyl chloride, IX, they obtained a chlorosulphoxidocamphor, X, which by oxidation in several ways was converted into an acid, which was identified as the ketopinic acid, XI, described by Gilles and Renwick (J.C.S., 1897, 69, 1397, 1402). The constitution of this acid was confirmed by oxidation to carboxyapocamphoric acid, XII.



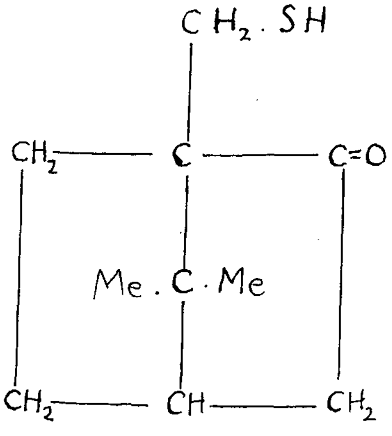
IX. X XI XII

It is thus evident that ketopinic acid is derived from camphor solely by alteration of the groups attached to carbon atom - 7 (formular VIII) and it follows that the substituents in Reychler's camphorsulphonyl chloride must also be present in this position.

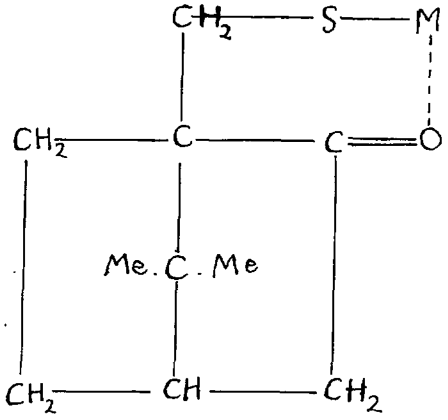
Burgess/

Burgess and Lowry from other evidence reach the same conclusion (J.C.S., 1925, 127, 279).

As thiolcamphor can be obtained by direct reduction of this sulphonyl chloride, it is formulated as in XIV.



XIV



XV

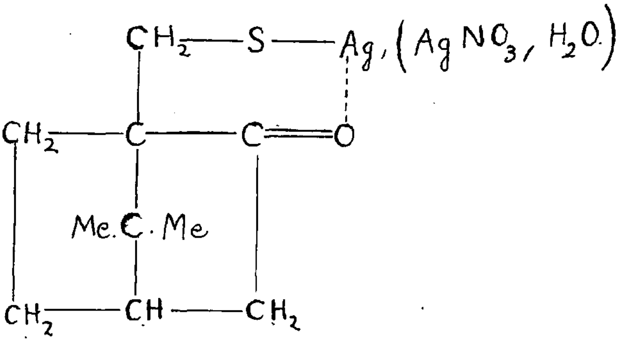
Such a configuration lends itself to the formation of six-membered rings and therefore, by analogy with Morgan and Sidgwick's compounds, the thiolcamphor derivatives will be of the type represented in XV, which, however, unlike Sidgwick's, possess six-membered rings containing only one double bond.

The white silver thiolcamphor derivative,

$$C_{10}H_{15}O \cdot SAg, AgNO_3, H_2O$$

is represented by XVI, in which one silver atom is united to the sulphur of the thiol group, replacing the/

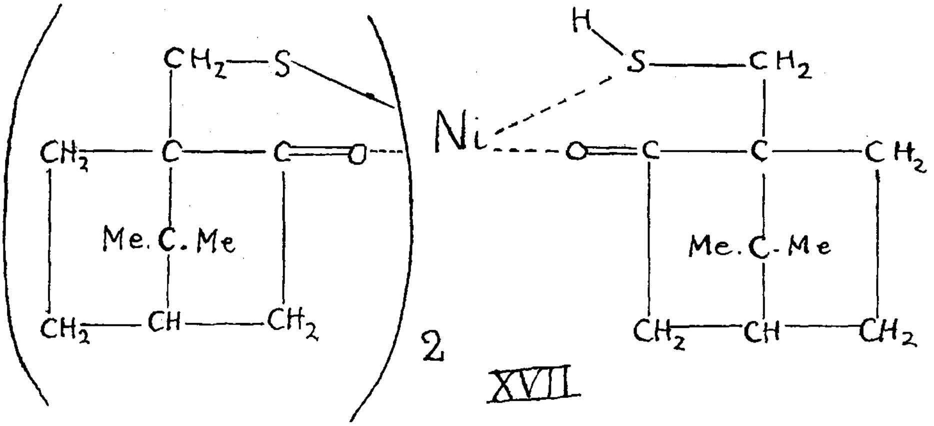
the hydrogen, and by auxiliary valency it is linked to the oxygen of the carbonyl. We are ignorant, however, of the nature of the union of the molecule of silver nitrate and of water with the rest of the molecule, but as half of the silver is ionisable it can be concluded that one silver atom is not co-ordinated.



XVI

The constitution of the yellow silver derivative, $(C_{10}H_{15}O.SAg)_2$, $AgNO_3$, H_2O, is beyond us, but the fact that in slightly aqueous alcohol one third of the silver is ionised indicates that two silver atoms are co-ordinated and the third not. But there is the possibility, supported by its solubility in benzene, that the substance is an unstable complex, which implicates the three silver atoms but which partially breaks down in aqueous alcohol.

The nickel derivative already described was formulated as $(C_{10}H_{15}O.S)_3Ni$ but in view of Sidgwick's addition compounds (page 8) it is now regarded as shown in XVII.



XVII

The third molecule of thiolcamphor is attached to the nickel atom entirely by auxiliary valency.

The modified formula is supported by the following facts:-

(1) The nickel derivative is formed by the immediate interaction of nickel acetate and thiolcamphor in the absence of any oxidising agent,

$$3\,\underline{\bar{C}}.SH \quad + Ni\bar{A} \quad = \quad (\underline{\bar{C}}.S)Ni,\underline{\bar{C}}.SH \quad + 2H\bar{A}.$$

$(\underline{\bar{C}}$ = camphoryl ; $\bar{A}$ = acetate.)

Under such circumstances it is unlikely that the product would contain <u>trivalent nickel</u>.

(2) The closely related nickel derivatives of methyl thiolpropionate and ethyl thiolacetate, which are described in a later part of this paper, are prepared under exactly similar conditions and contain quite definitely divalent nickel, as in these cases the addition of a molecule of the thiolester does not take place.

In the following table are listed the metallic derivatives of thiolcamphor.

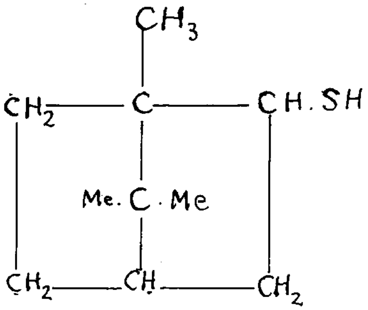
Silver thiolcamphor argentinitrate.	White crystals, soluble in chloroform, optically active.
Di-silver thiolcamphor argentinitrate.	Yellow solid, very soluble in benzene, optically active.
Zinc bromide	No derivative isolated, though stable derivative suspected by Lowry and Donnington, (J.C.S., 1903, 83, 480).
Thiolcamphor cadmi~~e~~bromide.	White crystals, insoluble.
Thiolcamphor mercurichloride.	White solid, sparingly soluble. (Lowry and Donnington).
Lead thiolcamphor.	Insoluble solid. (Lowry and Donnington).
Cupric chloride.	Oxidised thiolcamphor to camphor disulphide.
Ferric chloride.	Oxidised also. Great susceptibility to oxidation is characteristic of thiolcamphor.

Thiolcamphor stannochloride.	Feathery crystals. M.P. 187°, very soluble in organic solvents.
Nickel thiolcamphor.	Mahogany-coloured solid, very soluble in benzene, etc., softens with heat.
Cobalt chloride.	No derivative isolated but blue solution in benzene of unstable compound.
Potassium hydroxide.	No derivative formed. (Lowry and Donnington).

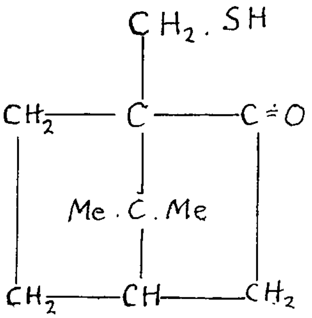
In preparing these compounds in a state of purity suitable for analysis, it was necessary to use the reactants in their equivalent quantities, as some of the derivatives could not be purified readily by either crystallisation or precipitation, and in the earlier stages of the study of the substances, repeated trials were required to discover what the equivalent quantities were before a pure compound could be obtained.

With a view to confirming the view that the carbonyl group in thiolcamphor functions in the production of the abnormal metallic derivatives, it was decided to examine the metallic derivatives of a mercaptan as closely related/

related to thiolcamphor as possible but from which the carbonyl group was absent. For this purpose thioborneol was chosen, XVIII.



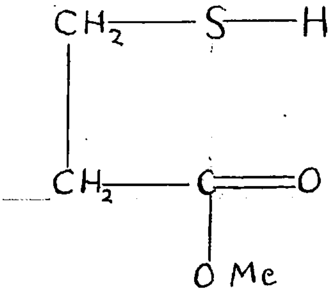
XVIII



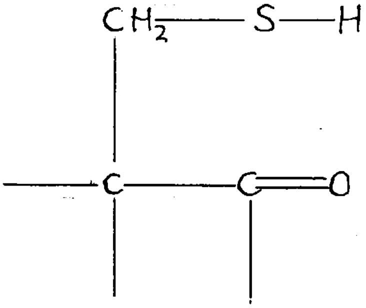
THIOLCAMPHOR.

We did not, however, find the derivatives of thioborneol to be abnormal in any way, which would imply that the presence of the carbonyl group is a necessary condition for the abnormalities which we have described.

The comparison was extended to the simplest substance which contains the grouping present in thiolcamphor, a condition fully filled by methyl thiolpropionate, XIX.



XIX

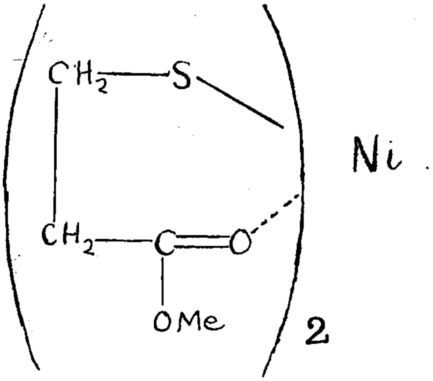


THIOLCAMPHOR.

The ester was chosen rather than the acid to avoid the complication of the carboxylic hydrogen. Bragg and Morgan (Proc. Roy. Soc., 1923, (A), <u>104</u>, 437) conclude that in esters the carbonyl retains its integrity and unsaturated character, while in the free acids the nature of the group is somewhat different.

The metallic derivatives of the ester show abnormalities similar to those of the thiolcamphor compounds. The silver derivative, $C_4H_7O_2SAg, AgNO_3, H_2O$, is of analogous composition, but is only sparingly soluble in a solution of the parent ester in benzene, thus a second silver compound, corresponding to the yellow silver derivative of thiolcamphor, was not obtained.

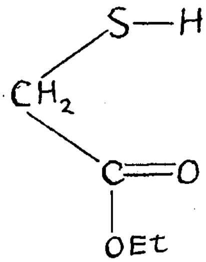
The nickel derivative, XX, was mahogany-coloured, crystalline, very soluble in benzene and softened readily on heating, but, unlike the nickel compound from thiolcamphor, it did not contain an additional molecule of the thiolester.



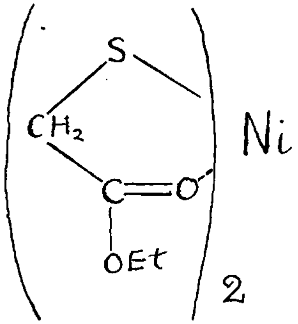
XX

The simpler body, ethyl thiolacetate, XXI, which lends itself to the formation of five-membered rings, yielded a silver compound of analogous composition, $C_4H_7O_2SAg, AgNO_3, H_2O$. Rouiller (J.Amer.Chem.Soc., 1919, 41, 777) describes a silver derivative of this ester, $AgS.CH_2.CO.OEt$, but his work is largely invalidated by his confession of unsatisfactory analysis, which he does not seem to have traced to the abnormality of the compound. In fact all the work on the metallic derivatives of "ethyl thioglycollate" (ethyl thiolacetate), which his paper contains, requires careful repetition.

The nickel derivative of the ester, XXII, is the most interesting of all the derivatives we have described. It was obtained in lustrous, violet needles, very soluble in benzene and melted sharply without decomposition at 101° to a deep coloured liquid. This five-membered ring derivative is more stable and better defined than the corresponding six-membered compounds.



XXI

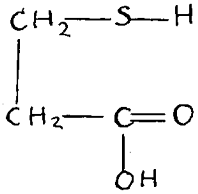


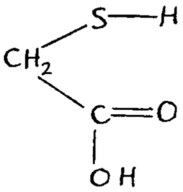
XXII

From the cases studied it appears that the carbonyl and thiol groups function together in the formation of these unusual compounds; and, in general, substances of this type can be detected by adding the organic body to a solution of nickel chloride and sodium acetate, followed by shaking the mixture with benzene. The abnormality is indicated by the resulting mahogany-brown colouration in the benzene layer.

The nickel derivatives of β-thiolpropionic acid, XXIII, and of thiolacetic acid, XXIV, were prepared.

XXIII

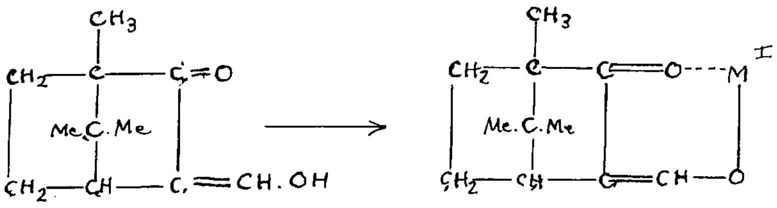




XXIV

The first was similar to the previous nickel compounds in colour only, which may indicate that it is a complex of a different kind; and the latter was dirty green and evidently contained ionisable nickel.

Lipschitz (Rec. trav. chim., 1922, 41, 627) describes metallic derivatives from hydroxymethylene-camphor, XXV, which are probably of the type shown, though he does not ascribe any constitution to them.



XXV

The preceding experiments were rendered possible by the discovery that Lowry and Donnington's original method (J.C.S., 1903, 83, 480) for preparing thiolcamphor from camphor sulphonyl chloride is materially improved by first reducing the chloride to the sulphinic acid and then reducing this to the mercaptan. This method arose from the consideration that probably the poor yield obtained by these authors was due to the hydrolysis of a large part of the sulphonyl chloride to sulphonic acid before the reducing agent was able to take effect. To test this supposition we examined roughly the rate of hydrolysis of the sulphonyl chloride in boiling water and found it to be very rapid.

Hilditch (J.C.S., 1910, 97, 1096) has shown that the reduction of sulphonyl chloride to sulphinic acid can be economically effected. When this acid is carefully reduced as described in the experimental part of this paper, the yield of thiolcamphor is three times the best claimed by Lowry and Donnington.

$\underline{\bar{C}} . SO_2.OH$ sulphonic acid.

↓

$\underline{\bar{C}} . SO_2Cl$ sulphonyl chloride.

↓

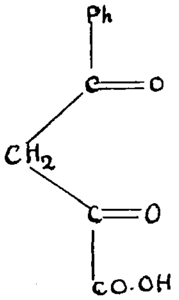
$\underline{\bar{C}} . SO.\dot{O}H$ sulphinic acid.

↓

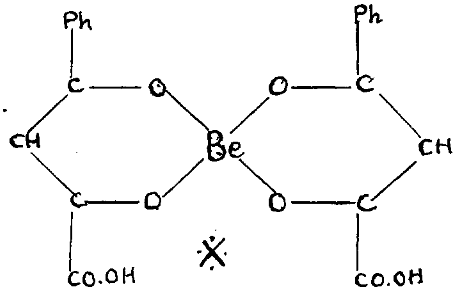
$\underline{\bar{C}} . SH$ thiolcamphor.

Since the above work was remitted for publication there has appeared an excellent verification of the chelate conception in the work of Mills and Gott. (J.C.S., 1926, <u>129</u>, 3121).

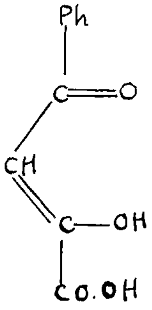
These authors have obtained from benzoylpyruvic acid, XXVI, beryllium, copper and zinc derivatives of type XXVII, which they have shown to be capable of existing in <u>dextro</u> and <u>laevo</u> modifications.



XXVI



XXVII



XXVIII

These observations shew that the derivative is not a simple beryllium salt of the enolic form of the β-diketone XXVIII, since a beryllium derivative of benzoylpyruvic acid thus constituted could not exist in enantiomorphous forms.✕ Mills indicates the linkings in the six-membered rings in formula XXVII by single lines with the intention of leaving open the question of the nature of these bonds, though the metallic atom is regarded as being linked to the four oxygen atoms, ~~that~~/

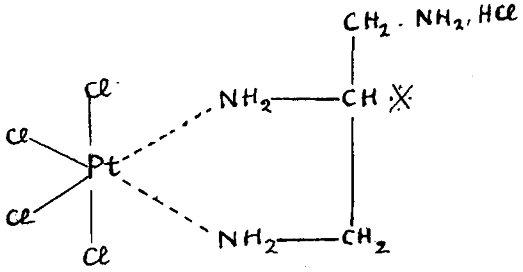
that is to say, as regards enantiomorphism the auxiliary valency is as real as the ordinary valency. The optical activity is accounted for on the supposition that the four oxygen atoms to which the beryllium is linked are disposed tetrahedrally.

It is probable that such a disposition is present in the nickel derivatives of methyl thiolpropionate and ethyl thiolacetate.

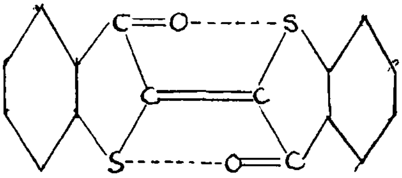
In this connection may be cited a communication to Nature (1927, March 5, 351) by Pope and Mann, who describe a compound of formula XXIX.

This substance has been resolved into optically active modifications with molecular rotations of -502° and +501°. The asymmetric carbon atom ·X· obviously must owe its activity to the reality of auxiliary valency.

Scholl (Annual Reports Chem. Soc., 1926, 155) considers that the auxiliary valency is powerful enough to prevent transformation taking place between *cis* and *trans* forms in thioindigo, XXX.

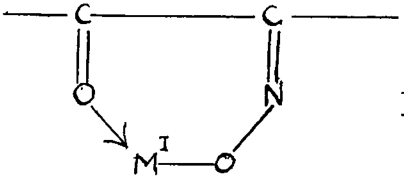


XXIX



XXX

Metallic derivatives of certain monoximes, possessing the abnormalities, which we have described, have been prepared by Taylor and Ewbank (J.C.S., 1926, November, 2818). These are of type shown in XXXI.



XXXI

Some of the cobalt compounds resulting from the interaction of the oxime and cobaltous acetate are considered to be of the type R_3Co, but our experience with the nickel derivative of thiolcamphor makes it probable that these substances are of the type R_2Co, RH (cf. formula XVII)

While in our case the detector of abnormality was the solubility and colour of the nickel derivatives in benzene, in the case of monoximes the blue solution of the ferrous compounds in that solvent is employed for this purpose.

EXPERIMENTAL.

The Preparation of Thiolcamphor.

As each stage in the preparation requires carefully regulated conditions for efficient yields, we have described it at length.

Camphorsulphonyl chloride.

Reychler's camphorsulphonic acid (180 gm.) was refluxed on a waterbath with freshly distilled thionyl chloride (95 cc.) until evolution of fumes ceased. The resulting syrup was poured on ice with stirring, and after thorough washing with cold water, the precipitated sulphonylchloride was filtered and dried over sulphuric acid in a vacuum desiccator. Yield, 190 gm. This was crystallised from a mixture of petroleum ether and acetone. The solvent originally recommended was dry ethyl acetate, but this we found partially decomposed the sulphonylchloride.

Camphorsulphinic acid.

(cf. Hilditch, J.C.S., 1920, 97, 1096).

The sulphonyl chloride (15 gm.) was added in small lumps at a time to a boiling, saturated solution of sodium sulphite (crystallised, 45 gm.). The completion of the reaction which followed each addition was indicated by frothing. After the last addition, the solution was refluxed for one hour, and was then acidified cautiously by addition of concentrated sulphuric acid (30 cc.) to the well-cooled liquid. The oil which separated was extracted with ether and from this was obtained the sulphinic acid as/

as a yellow, viscous oil. When larger quantities were required, several preparations, using the quantities given above, were conducted in series. This process gave better yields than one preparation involving large amounts.

Thiolcamphor.

The reduction of this sulphinic acid to thiolcamphor was thoroughly investigated. At first the reductions were conducted at room temperature, but a few trials at 60-100° soon effected improvement in the yield.

The reducing action of hydrochloric acid and the metals, tin, aluminium, magnesium, zinc and nickel, was studied. Aluminium and magnesium were used in small block form to reduce the vigour of the reaction, but without success as no trace of thiolcamphor was obtained. In the case of the latter, a small quantity of a white solid, m.p. 125-130°, steam-distilled but was not identified. Nickel produced a curious result, for little of the mercaptan was obtained but a brown nickel compound collected in the receiver. The presence of nickel in the distillate was verified by first strongly acidifying to decompose at least part of the complex and then by addition of ammonium hydroxide and ammonium sulphide. Zinc in cold concentrated hydrochloric acid was found by Lowry and Donnington (J.C.S., 1903, 83, 480) to be very inefficient and at boiling point we found little improvement. These authors suspected that the thiolcamphor formed a zinc derivative, which was not readily decomposed by acids and therefore likely to seriously affect the/

the yield of mercaptan. But our attempts to prepare a zinc derivative from thiolcamphor were singularly fruitless, which can hardly be said to support Lowry and Donnington's view. In the cold the yields with tin were variable but never above 25% of theoretical. With heating a pronounced improvement was produced and where the conditions described below were closely followed yields up to 45% were obtained.

It was observed that in those reductions with tin, which miscarried, addition of titanous chloride, followed by steam distillation, in part remedied the fault. It would seem that the powerful reducing agent was effecting reduction either of camphor disulphide or disulphoxide. Previous to this, we had tried, with little success, the addition of sodium sulphide, after making the liquid alkaline.

A strong reducing mixture of concentrated hydrochloric acid (500 cc.) and powdered tin (20 gm.) was heated almost to boiling in a large distilling flask. When a vigorous evolution of hydrogen was taking place, the oily camphor-sulphinic acid (20 gm.), mixed with a little water to reduce its viscosity, was slowly added from a dropping funnel. Fumes of hydrochloric acid, accompanied by a little thiolcamphor, appeared in the receiver. We later discovered that a considerable quantity of a volatile tin compound came over also and therefore in future we discarded the first portion of the distillate. When the addition of the sulphinic/

sulphinic acid was completed, more tin and hydrochloric acid were added and a current of steam was blown into the flask. In a few minutes the fumes ceased and a more rapid collection of thiolcamphor began in the condenser. The brittle lumps of the mercaptan were filtered off and crushed before drying over sulphuric acid in vacuo. Yield, 40-45% theoretical.

This product was contaminated with a slight amount of the tin compound already referred to. This was removed by several crystallisations from aqueous alcohol, and the crystals, which were deposited when the solution cooled, were needle-shaped and melted at 66°. On evaporation the mother liquor deposited cubic crystals of the same melting point, which could be converted into the former by crystallisation from the hot solvent.

Silver thiolcamphor argentinitrate.

$$C_{10}H_{15}O.SAg, AgNO_3, H_2O.$$

In the earlier preparations of this substance silver nitrate was added to thiolcamphor in the proportions of molecular equivalents, which resulted in the production of a mixture of silver substances, contaminated with the excess of thiolcamphor as insufficient silver nitrate was being used for complete reaction. The product of each preparation varied in colour, solubility and analysis. When the thiolcamphor was added to the silver nitrate, a more homogeneous substance was obtained, and this seemed to indicate that an excess of the nitrate was a necessary condition. Thus the following method evolved.

5 gm. of thiolcamphor, dissolved in 50 cc. alcohol, was slowly added to a solution of 11 gm. of silver nitrate in 100 cc. of 90% alcohol, during constant stirring. The reactants were mixed in this order to ensure the presence of an excess of the latter. At each addition a flocculent yellow precipitate momentarily formed and dissolved again, and when the solution, which had heated during the admixture, was left to cool in subdued light, minute white crystals of silver thiolcamphor argentinitrate were deposited. The yield was 14 gm., almost theoretical. It seems probable that the yellow precipitate, which is evidently the first product of the reaction, is the yellow silver derivative described below.

The white compound is soluble in chloroform, ethylene dibromide and boiling alcohol, but insoluble in benzene and other solvents. The solution in the first two solvents is not permanent, as decomposition and precipitation occurs in a few days. The substance chars at 200-210°, and gives the brown ring test for nitrate. It is soluble in benzene, containing thiolcamphor, forming an orange-red solution. With a large excess of thiolcamphor the solution is bright red.

Analysis.

(1) .1855 gm. substance gave .1112 gm. AgCl.
(2) .2236 " " " .1331 " "

.1424 gm. substance required 23.3 cc. .0128 N.NH_4CNS.

.1616 gm. substance gave .0836 gm. $BaSO_4$.

.1672 gm. substance gave 4.7 cc. N_2 at 15° and 759 mm.

.1442 gm. substance gave .1333 gm. CO_2; .0460 gm. H_2O.

$C_{10}H_{15}O{\cdot}SAg, AgNO_3, H_2O$.	Found.	Calc.
Ag	45.1, 44.8	45.1
Ag (ionised)	22.6	22.6
S	7.1	6.7
N	3.2	2.9
C	25.2	25.1
H	3.7	3.6

Optical Rotation.

.2075 gm. substance in 20 cc. chloroform.

$\alpha = +.22°$ in 1 dm. layer.

$$[\alpha]^{19°}_{5461} = +21°.$$

Di-silver thiolcamphor argentinitrate.

$$(C_{10}H_{15}O{\cdot}SAg)_2, AgNO_3, H_2O.$$

Our experience in the last preparation led us to the conclusion that this silver derivative could not be obtained free from contamination with the white derivative by the method employed in previous case, however much the relative proportions of the reactants were altered. The solubility of the white silver substance/

substance in benzene containing thiolcamphor suggested to us the following method.

2 gm. of silver thiolcamphor argentinitrate were warmed with a solution of 2 gm. of thiolcamphor in 12 cc. dry benzene. Only a few minutes heating was required and the resulting bright red solution was separated from the globule of water which was formed during the reaction. The liquid was reduced to small bulk in a vacuum and was dropped, with rapid stirring, into 50 cc. of petroleum ether (B.P. 80-100°). A yellow solid, the *di-silver thiolcamphor argentinitrate,* was precipitated in 80% yield.

To determine the limiting quantity of thiolcamphor, the preparation was repeated with 0.8 gm. of the mercaptan instead of 2 gm. An identical compound was obtained, as verified by analysis. It is thus evident that slightly over *one* molecular proportion of thiolcamphor is all that is necessary to produce complete solution in benzene of *three* molecular proportions of the white derivative to form the yellow compound.

The latter substance decomposes above 230° and is extremely readily soluble in benzene, less soluble in alcohol and chloroform and quite insoluble in water. It rapidly reacts with sulphonylchlorides in benzene as medium to precipitate silver chloride. This immediate activity in a non-polar solvent is an interesting feature of the compound. The substance also dissolved in carbon disulphide to form a bright red solution, which/

which, however, decomposed after a few days, producing a colourless solution and a black precipitate.

0.2 gm. of the yellow derivative, dissolved in 10 cc. benzene, was placed in a parchment dialysing thimble. This was surrounded by 10 cc. of pure benzene. The external liquid rapidly assumed a yellow colour, which in less than an hour was equal in intensity to that within the thimble.

An even more rapid dialysis was observed in an experiment in which ethylene dibromide was used.

Analysis.

(1) .1484 gm. substance gave .1715 gm. CO_2; .0492 gm. H_2O.
(2) .2207 " " " .2574 " " .0819 " "

.1420 gm. substance gave .0848 gm. Ba SO_4.
.1920 gm. substance gave 2.3 cc. N_2 at 16° and 756 mm.

(1) .2203 gm. substance gave .1221 gm. AgCl.
(2) .1560 " " " .0875 " "

.1960 gm. substance required 19.1 cc. .0128 N. NH_4CNS.

$(C_{10}H_{15}O\cdot SAg)_2, AgNO_3, H_2O$	Found. %	Calculated. %
C	31.8, 31.5	31.2
H	4.1, 3.9	4.2
S	8.2	8.3
N	1.6	1.8
Ag	41.8, 42.2	42.1
Ag (ionised)	13.5	14.0

Optical Rotation.

.1123 gm. substance in 25 cc. chloroform, $\alpha = +.15^\circ$ layer, .52 dm. $[\alpha]^{15^\circ}_{5461} = +64^\circ$.

Thiolcamphor cadmibromide. $C_{10}H_{15}O\cdot SCdBr$.

The interaction of thiolcamphor and cadmium bromide was examined to compare the product with Lowry and Donnington's mercurichloride.

The first preparation was conducted by mixing alcoholic solutions of cadmium bromide (0.4 gm.) and thiolcamphor (0.4 gm.) and then by adding a solution of sodium carbonate in water (0.33 gm.). A white crystalline product rapidly formed. The addition of sodium carbonate proved unnecessary and in later preparations this was omitted. The cadmibromide separated in fine, white crystals, insoluble in all the usual solvents. Boiling with benzene containing thiolcamphor had no effect on the substance, which appears to be very stable, non-reactive and analogous to the thiolcamphor mercurichloride.

Analysis.

(1) .1614 gm. substance gave .0886 gm. $CdSO_4$.
(2) .2015 " " " .1095 " "

.1050 gm. substance gave .0538 gm. AgBr.

$C_{10}H_{15}O\cdot SCdBr$	Found.	Calc.
Cd	29.3, 29.6.	30.0%
Br	21.8	21.4%.

Action of Zinc Bromide on Thiolcamphor.

In view of Lowry and Donnington's suspicion that thiolcamphor formed a zinc derivative, which was not readily decomposed by acids, we fully expected to obtain the derivative without any difficulty.

Our attempts, however, were quite unsuccessful. These were conducted in alcohol and ether and even the addition of sodium acetate or sodium carbonate to the former solvent was ineffective. In each case unchanged thiolcamphor was recovered. Thus in its reaction towards thiolcamphor zinc differs radically from cadmium and mercury.

Thiolcamphor stannochloride.

During the preparation of thiolcamphor a volatile tin compound was observed in the steam distillate. This led us to examine the action of stannous chloride on thiolcamphor.

A freshly prepared, filtered solution of 0.4 gm. of stannous chloride in ether was added to 0.3 gm. thiolcamphor in the same solvent. After an hour a few clusters of white, lustrous flakes began to appear. Crystallisation was promoted by shaking and after some time the crystals were filtered, washed with ether and dried.

The substance was readily soluble in benzene and other organic solvents and melted to a clear liquid at 187°. It was found to be optically inactive. When successive quantities of the/

the substance were heated in a crucible, followed by addition of a few drops of nitric acid, very variable amounts of stannic oxide were left. This pointed to the volatility of the compound, but an attempt to distil it in a vacuum was unsuccessful as charring took place shortly after the melting point was reached. Addition of silver nitrate to an alcoholic solution of the tin compound indicated partial ionisation of the chlorine in that solvent.

Analysis.

(1) .1357 gm. substance gave .0600 gm. H_2O
(2) .0893 " " " .0418 " "

.2226 gm. substance gave .0729 gm. SnO_2

.1272 gm. substance gave .0954 gm. $BaSO_4$.

.0798 gm. substance .0513 gm. AgCl.

$(C_{10}H_{15}O\cdot S)_3Sn_2Cl_4$	Found. %	Calc. %
C	-	-
H	5.2, 4.9	4.9
Sn	25.8	25.7
S	10.3	10.4
Cl	15.8	15.4

Considerable difficulty was experienced in the analysis of this compound. The chlorine was estimated by Robertson's modification (J.C.S., 1915, <u>107</u>, 902) of the Baubigny and Chavanne method/

method, as metastannic acid interfered with the usual Carius' method. In estimation of sulphur by the Carius' method the metastannic acid was removed before precipitating with barium chloride. Our experience in combustion for carbon and hydrogen was similar to Pope's (J.C.S., 1926, 129, 487, footnote) and we were able to report hydrogen percentage only.

Action of Cupric Chloride on Thiolcamphor.

.2 gm. of thiolcamphor in alcohol was added to .2 gm. of cupric chloride in aqueous spirit. The blue precipitate which appeared dissolved immediately on shaking, leaving a green solution. As no crystals or deposit appeared, a small quantity of sodium acetate was added to facilitate reaction. Finally, the solution was reduced in bulk by evaporation and a few white crystals made their appearance. After crystallisation from ether, this substance melted at 223° and a mixed melting point determination with dicamphoryl disulphide gave no depression.

Also when a small quantity of benzene containing thiolcamphor was refluxed with a few crystals of cupric chloride, the greenish colour of the crystals rapidly disappeared and a white solid resembling cuprous chloride remained. On evaporation of the benzene solution and extraction of the residue with petroleum ether (B.P. 40-60), a crystalline product, m.p. 222°, was obtained which was confirmed to be the disulphide as before. Cupric chloride is analogous to ferric chloride in its behaviour towards thiolcamphor/

thiolcamphor (Lowry and Donnington) and clearly shows the great susceptibility of this mercaptan to oxidation.

Action of Cobalt Chloride on Thiolcamphor.

0.4 gm. of crystalline cobalt chloride in alcoholic solution was mixed with 0.4 gm. of thiolcamphor in the same solvent and 0.1 gm. of sodium acetate was added. The deep brown liquid, which was obtained, was evaporated to dryness in a vacuum desiccator. The bluish-green residue was extracted with benzene, which assumed a bright blue colour that rapidly faded. The formation of an unstable thiolcamphor derivative seemed to be indicated.

Modifications of the process of preparation were equally unsuccessful in isolating a stable cobalt derivative.

Nickel Thiolcamphor.

When 0.4 gm. of thiolcamphor was mixed with 0.8 gm. of crystalline nickel chloride in slightly aqueous alcohol, a dirty greenish-brown solution resulted, but addition of 0.4 gm. of sodium acetate produced immediate action and the solution assumed a red-brown colour. This was evaporated in a heated vacuum desiccator and the residue was extracted with benzene with a view to separating the soluble nickel compound from the inorganic salts. Evaporation of the mahogany-coloured extract was effected as before and a similarly coloured solid was obtained. In some cases the residue was oily but solution in the least possible alcohol and subsequent pouring/

pouring into water yielded the solid. This substance was very soluble in all the usual organic solvents and in default of crystallisation the compound was purified by precipitation. It melted between 100-150°, which may have been due to gradual separation of the additional molecule of thiolcamphor (cf. formula).

Analysis.

(1) .1112 gm. substance gave .0514 gm. Ni dimethylglyoxime.
(2) .0908 " " " .0431 " "

.0908 " " " .1025 gm. $BaSO_4$.

Found: Ni, 9.4, 9.6; S, 15.5%

$(C_{10}H_{15}O\cdot S)_2Ni,(C_{10}H_{15}O\cdot SH)$ requires Ni, 9.7; S, 15.8%

Silver and Nickel Thioborneol.

Failing to obtain thiolborneol by the action of potassium xanthate on pinene hydrobromide, followed by treatment with ammonia, we had to resort to the troublesome method described by Houben (Ber., 1906, 39, 3503). Silver nitrate yielded a normal mercaptide, negative to the brown ring test, and nickel acetate precipitated a dirty coloured solid quite insoluble in benzene.

Methyl thiolpropionate.

β-thiolpropionic acid was prepared from β-bromopropionic acid by xanthate method. (See Organic Syntheses, Vol.III, 25, 57; Biilmann, Annalen, 348, 125).

β-thiolpropionic acid (8 cc.), anhydrous methyl alcohol (40 cc.) and conc. sulphuric acid (8 cc.) were refluxed for 4 hours. Excess alcohol was distilled off, and the remainder was poured into water and extracted with ether. From this was obtained an oil which was distilled in vacuo. A colourless, mobile liquid collected. B.P. 54-55° at 14 mm. $\mu_{19^\circ} = 1.4628$. The oil possessed a pungent, offensive smell, mixed with an ethereal odour.

.1405 gm. substance gave .2690 gm. $BaSO_4$.

Found: S, 26.3% $C_4H_8O_2S$ requires 26.6%.

Methyl silver β-thiolpropionate.

The ester (0.6 gm.) was added to silver nitrate (1.8 gm.) in aqueous alcohol in the way described under silver thiolcamphor argentinitrate. The substance was white, crystalline and contained the nitrate radicle, and was closely similar to the thiolcamphor derivative. Boiling with benzene containing the parent ester produced a red colouration but only very slight solution of the silver compound.

Analysis.

.1242 gm. substance gave .0724 gm. $BaSO_4$.
.1363 " " " .0947 " AgCl.
.1404 " " " .0966 " "

$C_4H_7O_2SAg, AgNO_3, H_2O$.	Found.	Calc.
S	8.0	7.7%
Ag	52.3, 51.8	52.0%

Methyl nickel β-thiolpropionate.

This substance was prepared from the ester and nickel chloride and sodium acetate as described under nickel thiolcamphor The mahogany-coloured compound obtained resembled the latter in solubility and in its behaviour towards heat. With difficulty, it was obtained in brown rhombic plates by crystallisation from ether.

Analysis.

.1008 gm. substance gave .0977 gm. Ni dimethylglyoxime.
.1050 " " " .1628 " $BaSO_4$.

$(C_4H_7O_2S)_2Ni$.	Found.	Calc.
Ni	19.7	19.9%
S	21.3	21.5%

Ethyl thiolacetate

The ester was prepared by the action of potassium xanthate on potassium chloracetate followed by treatment with ammonia. (Biilmann, Annalen, 1905, 339, 351).

Ethyl nickel thiolacetate.

A mahogany-coloured solution of the derivative in benzene was obtained in the way described in previous cases, but in place of complete evaporation, concentration to small bulk was substituted. To this was added petroleum ether (B.P. 80-100°) and the liquid was laid aside. Violet, lustrous needles were deposited in good yield overnight. The estimation of the sulphur content gave anomalous results, and as the crystals/

crystals smelt faintly of the parent ester, we heated the substance for 10 minutes at 70°C. at 0.1 mm. pressure. The smell was removed and the compound now melted sharply at 101° without decomposition to a ~~clear~~ brown liquid. The substance was somewhat less soluble than the corresponding thiolcamphor derivative and seemed more stable.

Analysis.

.1213 gm. substance gave .1194 gm. Ni dimethylglyoxime.
.1224 " " " .1872 " $BaSO_4$.

$(C_4H_7O_2S)_2Ni$.	Found.	Calc.
Ni	20.0	19.9%
S	21.0	21.5%

Ethyl silver thiolacetate argentinitrate. $C_4H_7O_2SAg, AgNO_3, H_2O$.

This substance was prepared as described under corresponding silver derivatives. It was a white crystalline compound and possessed properties closely similar to methyl silver thiolpropionate argentinitrate. The presence of the nitrate group was confirmed (cf. Rouiller, J.Amer. C.S., 1919, 41, 777.. This has evidently escaped his notice and his analyses are very unsatisfactory).

.1971 gm. substance gave .1402 gm. AgCl.

Found: Ag, 52.3%. Calc. 52.0%.

Nickel thiolpropionate - $(C_3H_5O_2S)_2Ni$.

This substance was prepared from thiolpropionic acid and nickel acetate in aqueous alcohol. The mahogany-coloured precipitate was insoluble in benzene and most other organic solvents, but was soluble in alkalies without precipitation of nickel hydroxide and was reprecipitated from solution by addition of acid. The substance therefore appears to be a nickel complex of acidic properties.

.0980 gm. substance gave .1076 gm. Ni dimethylglyoxime.

Found: Ni, 22.3. Calc: 21.9%.

Under the same conditions nickel acetate and thiolacetic acid gave a dirty green solid of unknown constitution.

Analysis.

.1521 gm. substance gave .2128 gm. Ni dimethylglyoxime.
.1038 " " " .1486 " " "

.1221 " " " .0998 " $BaSO_4$.

Found: Ni, 28.4, 29.1; S, 11.2%.

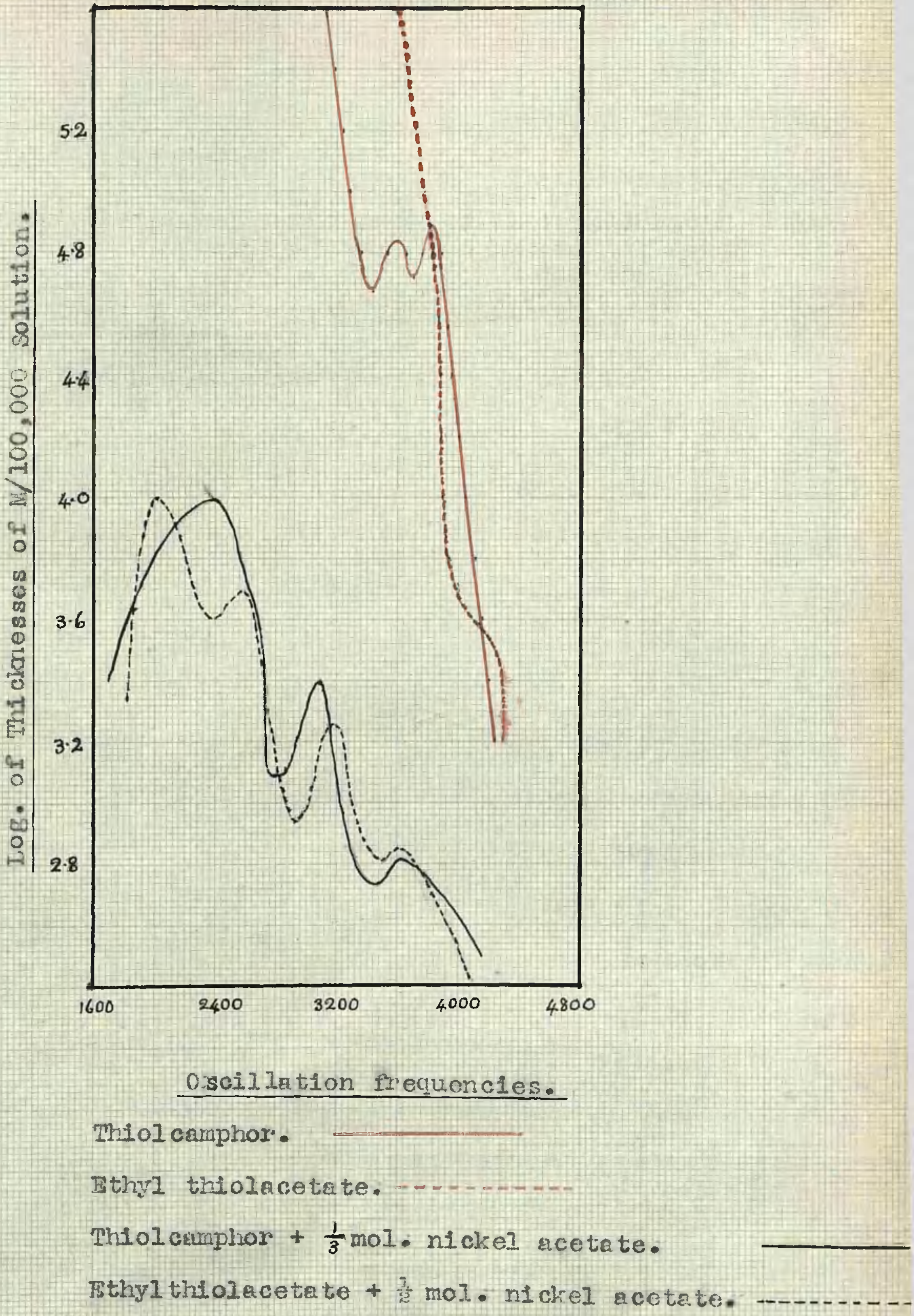
B. The Absorption Spectra of Thiolcamphor, Ethyl thiolacetate and their Nickel Derivatives.

Morgan and Moss (J.C.S., 1913, 103, 81; 1914, 105,189) have found that close similarity exists between the absorption spectra of the β-diketones and their metallic derivatives. We have examined the absorption spectra of thiolcamphor, ethylthiolacetate and their nickel derivatives, but do not observe such similarity.

Pure alcohol was used as solvent and the iron arc was the source of radiation. The thiolcamphor was repeatedly crystallised from aqueous alcohol and the thiol-ester was distilled twice in a vacuum. As it was difficult to obtain the nickel derivatives spectrographically pure, the following procedure was adopted: Pure nickel acetate was prepared from pure nickel chloride, certified free from iron and cobalt. To N/100 solutions of the thiol-compounds were added sufficient nickel acetate to produce the combinations, (1) thiolcamphor + $\frac{1}{3} NiA_2 \cdot 4H_2O$ (2) ethylthiolacetate + $\frac{1}{2} NiA_2 \cdot 4H_2O$ which were very similar in colour.

The thiolcamphor bands at frequencies 3400 and 3700 are feeble relics of the characteristic band in the spectrum of camphor at frequency 3500 (J.C.S., 1908, 93, 961). Other instances of reduction of persistence of bands by introduction of thiol group into the molecule are recorded. (Fox and Pope, J.C.S., 1913, 103, 1266).

The curves of the spectra of the nickel derivatives shew/


Log. of Thicknesses of M/100,000 Solution.
5·2
4·8
4·4
4·0
3·6
3·2
2·8
1600
2400
3200
4000
4800
Oscillation frequencies.
Thiolcamphor.
Ethyl thiolacetate.
Thiolcamphor + $\frac{1}{3}$ mol. nickel acetate.
Ethylthiolacetate + $\frac{1}{2}$ mol. nickel acetate.

shew that the similarity of colour, perceived in the visible, also extends to the ultraviolet. In both curves, corresponding shallow bands are shown at frequencies 2800 and 3400. The curves of the nickel derivatives differ widely from those of the parent substances.

C. Attempts at the Synthesis of d.l.-Dicamphoryl Disulphoxide.

Many investigations have been undertaken to determine which of the formulae, I and II, better represents the reactions of the disulphoxides.

I $R \cdot SO_2 \cdot SR$ $R \cdot SO \cdot SO \cdot R$ II

Hilditch (J.C.S., 1910, 97, 1071), who examined the optical rotations of camphordisulphoxide and of related substances, supported the constitution II, but the recent work of Smiles (J.C.S., 1924, 125, 176) is decidedly in favour of I, and during the course of this work final proof of the unsymmetrical structure was advanced by the same author. (J.C.S., 1925, 127, 224).

Our aim was to prepare d-camphoryl l-camphoryl disulphoxide, for according as this substance is I or II it should be optically active or internally compensated.

The following methods of synthesis were considered. ($\overline{\underline{C}}$ represents the camphoryl radicle).

I. $\overline{\underline{C}} \cdot SO_2\boxed{Ag \quad + \quad Cl} \cdot S\overline{\underline{C}}$

silver camphorsulphinate camphor sulphur~~ic~~ chloride.

II. $\overline{\underline{C}} \cdot SO_2 \vdots Ag + SCN \vdots S \cdot \overline{\underline{C}}$

camphor sulphur thiocyanate.

III (a) $\overline{\underline{C}} \cdot SO_2 \vdots Cl + Ag \vdots S \cdot \overline{\underline{C}}$

sulphonyl chloride silver mercaptide.

(b) $\overline{\underline{C}} \cdot SO_2 \vdots Br + Ag \vdots S \cdot \overline{\underline{C}}$

(c) $\overline{\underline{C}} \cdot SO_2 \vdots I + Ag \vdots S \cdot \overline{\underline{C}}$

IV $\overline{\underline{C}} \cdot SO_2 \vdots Cl + HgCl \vdots S \cdot \overline{\underline{C}}$

thiolcamphor mercurichloride.

V $\overline{\underline{C}} \cdot SO_2 \cdot S \vdots Na + Br \vdots \overline{\underline{C}}$

sodium camphorthiolsulphonate "β-bromo-camphor."

In I, Lecher's method of chlorination of mercaptans (Ber., 1924, 57, 755) was applied to thiolcamphor, but the yellow oily product, on treatment with silver camphorsulphinate, did not yield a crystalline disulphoxide. In II, thiolcamphor was treated with thiocyanogen in the manner described by Lecher (Ber., 1921, 632; 1922, 1474) with similar result. These methods were finally discarded on account of the unsatisfactory nature of the sulphur-chloride and sulphur-thiocyanate. The third method was more fully investigated, but III(c) was impracticable as camphorsulphonyliodide could not be obtained (Otto, Ber., 24, 478); and ultimately the failure of III(a) and III(b) to produce the disulphoxide was traced to the abnormal constitution of the silver derivative (cf. earlier part of this paper). IV was vitiated by the non-reactive character/

character of the mercurichloride, and V was rejected untried on account of the unusual properties of β-bromocamphor.

It seems that synthesis of *d*-camphoryl *l*- camphoryl disulphoxide is impracticable and now remains the consideration of obtaining another suitable compound to test the suggestion of page 44. Possible compounds may be typified

(1) *d*-bornyl $OOC\cdot CH_2\,SO_2\cdot S\,CH_2COO$ *l*-bornyl

(2) d-octyl $\cdot SO_2\cdot S\cdot$ *l*-octyl

Any attempt to prepare a substance of type (1) would likely fail for same reason as before. The presence of both a thiol group and a carbonyl indicates that a similarly abnormal silver derivative would be formed. As regards (2), Otto's experience with the simpler alkyl disulphoxide, which he obtained as impure oils, does not encourage the hope that octyl disulphoxide could be obtained chemically pure, much less optically so.

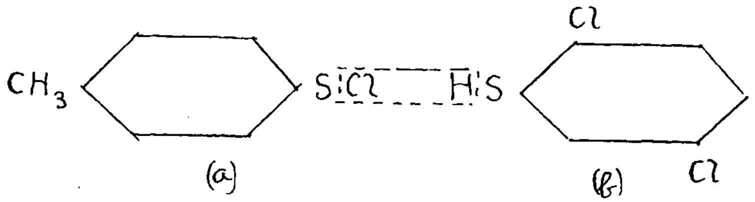
Meanwhile Phillip's discovery (J.C.S., 1925, *127*, 2552) that the sulphoxide group $-\underset{\underset{O}{\|}}{S}-$ may itself become a centre of optical activity convinced us that the projected test had lost its supposed conclusiveness and that further attempts to prepare a test disulphoxide would be time unprofitably spent.

D. Incidental Experiments conducted during the Projected Synthesis of Camphor Disulphoxide.

(a) p.Tolyl sulphurchloride.

(b) 1.4-Dichlorophenyl 2-sulphurthiocyanate.

(a) In the synthetical work reported above (synthesis I) a trial chlorination of p.tolyl mercaptan was conducted. From this a red oil of composition C_7H_7SCl (a) was obtained.



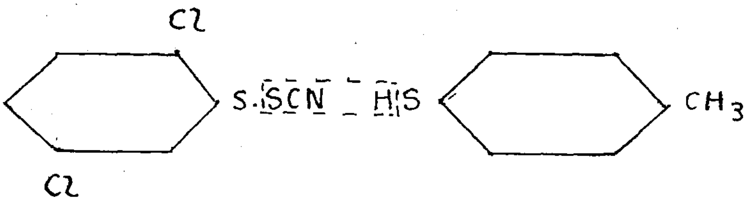
This substance reacted with .14-dichlorophenyl 2-mercaptan (b) to give the mixed disulphide, p.tolyl-1.4-dichlorophenyl-2-disulphide, which was confirmed by comparison with a sample prepared by Smiles and Gibson (J.C.S., 1924, 176). Some months after the completion of this work, Lecher (Ber., ~~1906~~ 1925, ~~39, 3503~~ 58, 409) described the preparation of this sulphurchloride, which in all essentials was similar to our method.

(b) Lecher's work (Ber., 1921, 632; 1922, 1474) on the action of thiocyanogen on mercaptans showed that under carefully regulated conditions it is possible to obtain compounds of the structure R.S.SCN, which have properties similar to those of the sulphurhalides.

A preliminary test thiocyanogenaton was conducted

on/

on 1.4-Dichlorophenyl-2-mercaptan, yielding a product (c) whose constitution was confirmed by its reaction with p.tolyl mercaptan (d) to form the disulphide already described, p.tolyl-1.4-dichlorophenyl-2-disulphide.



(c) (d)

With insufficient excess of thiocyanogen the sole product was sym-dichlorophenyl disulphide [illegible].

p.Tolyl-sulphur-chloride.

A current of pure, dry chlorine was passed rapidly through dry carbon tetrachloride (150 cc.), ice-cooled, mechanically stirred and shaded from light. When the liquid was saturated, p.tolyl mercaptan (6 gm) in carbon tetrachloride (50 cc.) was very slowly dropped into the apparatus over a period of three hours, during which time a steady stream of chlorine was maintained.

The reddish liquid was immediately vacuum-distilled. After the chlorine and carbon tetrachloride were removed, a red oil distilled at 86-92° at 12 mm. This substance possessed a pungent smell and fumed in air.

Analysis. Chlorine.

0.0966 gm. substance gave 0.0835 gm. AgCl ∴ Cl %age was 21.4

C_7H_7SCl requires 22.3% Cl.

p.-Tolyl-1.4-dichlorophenyl disulphide.

p.Tolyl mercapto-chloride (2.6 gm.) in anhydrous ether (20 cc.) was mixed with 2.9 gm. 1.4-dichlorophenyl-2-mercaptan in 20 cc. ether. The red colour disappeared almost at once, and after being refluxed for half an hour, the ether was removed. The white crystalline residue was recrystallised several times from aqueous alcohol.

Yield of pure product, 3 gm. White feathery crystals, m.p. 71.5°, confirmed by mixed melting point determinations with sample of substance synthesised in another way by Smiles and Gibson.

1.4-Dichlorophenyl-2-mercapto-thiocyanate.

7.5 gm. Lead thiocyanate were added under ice-cooling to 40 cc. dry ether, containing 1 cc. bromine, and the mixture was shaken for half an hour. The now colourless solution of thiocyanogen was filtered from the insoluble lead bromide, which was washed with 60 cc. of dry ether. During two hours a solution of 2.5 gm. 1.4-dichlorophenyl mercaptan in 20 cc. dry ether was dropped into the first, which was contained in the apparatus used in last experiment. The resulting solution was extracted with ice-cold water four times, dried over calcium/

calcium chloride, and evaporated to small bulk. After two days the yellow, polymerised thiocyanogen was filtered off, giving an ethereal solution of the desired substance, which was confirmed by the following synthesis.

p.Tolyl-1.4-dichlorophenyl disulphide.

To the ethereal solution above was added an excess of p.tolyl mercaptan in ether. After refluxing for half an hour a substance was obtained, which crystallised from aqueous alcohol, melted at 71°, and by comparison was proved to be identical with the disulphide described above.

The Reactivity of the Mercurichlorides of Mercaptans.

The synthesis of disulphoxides (I) by interaction of sulphonyl chlorides (a) with silver mercaptides (b) is usually

$$\text{I} \qquad \underset{(a)}{R.SO_2Cl} + \underset{(b)}{AgS.R}$$

invalidated by the occurrence of a consecutive reaction, II.

$$\text{II} \qquad \begin{array}{r:l} R.SO_2 & SR \\ Ag & SR \end{array}$$

Each molecule of disulphoxide as it is formed is decomposed by the reactive silver salt. As a possible means of escape from this difficulty the reactivity of the thiol-mercurichlorides was examined.

2.5 gm. of thiocresol mercurichloride ~~(c)~~ (Marker, Annalen, 136, 79) was boiled with 1.5 gm. tolyl-disulphoxide ~~(d)~~ in alcohol for two hours and the entire disulphoxide was isolated unchanged. This suggested the possibility of securing the synthesis of the disulphoxide as follows:

$$\mathrm{CH_3{\cdot}(C_6H_4)\,SO_2\boxed{Cl + HgCl}\,S\,(C_6H_4)\,CH_3}$$

Equivalent quantities of tolyl sulphonyl chloride and the mercurichloride were boiled in benzene for two hours <u>without reaction</u> and a similar result was obtained from thiolcamphor mercurichloride and camphorsulphonyl chloride.

Evidently the mercurichlorides are characterised by remarkable non-reactivity.

PART II

The Oxidation of Narcotine by Hydrogen Peroxide.

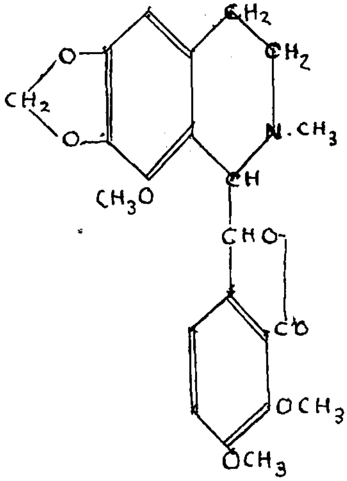
HISTORICAL.

(DRUMMOND AND McMILLAN, J.C.S. 1926, 129, 2702; ANNUAL REPORTS CHEM. SOC. 1926, p. 163.)

A. The Constitution of Narcotine.

From a study of the degradation products of narcotine, Roser (Annalen, 1888, 249, 141; 1889, 254, 334-359; 1893, 272, 221) proposed formula I for narcotine.

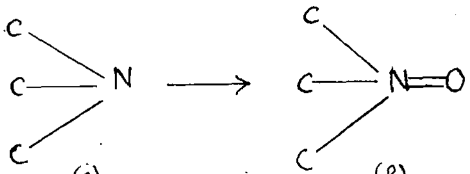
This structure has been confirmed by Perkin and Robinson's synthesis of gnoscopine, which Rabe and McMillan (Ber., 1910, 43, 800) had previously identified as racemic narcotine, and by subsequent resolution d and l narcotine were obtained. (J.C.S. 1911, 99, 775).



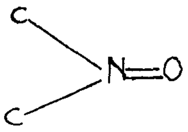
I

B. Oxidation of Alkaloids by Hydrogen Peroxide.

The formation of amine oxides (b) by the action of hydrogen peroxide on alkaloids containing a nitrogen atom linked to three different carbon atoms (a) is now well established.



(a) (b)



(c)

Pictet (Ber., 1905, 38, 2786) states that this nitrogen-linking is essential to the production of such substances, and thus hydrogen peroxide is regarded as a means of detecting such a linking in alkaloids. (Compare, however, Meisenheimer, (Ber., 1925, 58, 2334), who describes an aminoxide containing the group (c)). Aminoxides have been prepared from strychnine, brucine, quinine and morphine (Pictet and Mathieson, Ber., 1905, 38, 2782, Freund and Speyer, Ber., 1910, 43, 3310; Speyer and Becker, Ber., 1922, 55, 1321, 1829) and also from nicotine, tropine and sparteine (Pinner and Wolffenstein, Ber., 1891, 24, 63; Merling, Ber., 1892, 25, 3124). Among these differences in the reactivity of the amine-oxidic oxygen atoms are found, as shown by their action on aqueous potassium iodide and by the degree of readiness with which they are reduced to the parent substances.

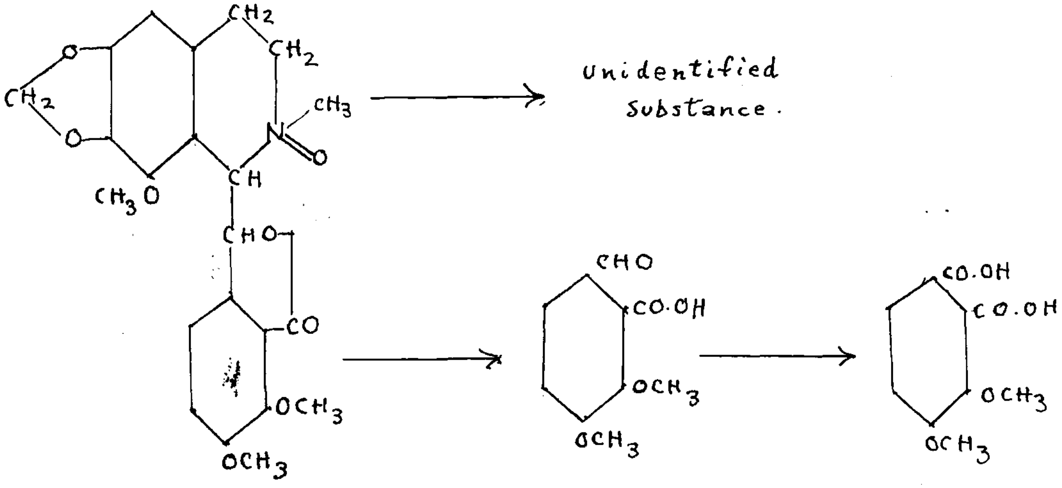
THEORETICAL.

It was expected that narcotine, by virtue of its tertiary nitrogen atom, would react in a similar manner with hydrogen peroxide to form an aminoxide.

The oxidation of l-narcotine by hydrogen peroxide under varying conditions of solvent and temperature was studied. The media, acetone, dilute sulphuric acid and glacial acetic acid were used, the effect of ferrous sulphate as a catalyst was examined and the temperature was varied from 15°C. to the decomposition temperature, 60°, of the hydrogen peroxide solution. Most/

Most attempts failed but ultimately moderate yields of a crystalline product were obtained under carefully regulated conditions in glacial acetic acid.

This substance, after crystallisation from acetone, melted at 229° and had a composition corresponding to narcotine + 1 atom of oxygen. It was feebly basic and the possibility of its being gnoscopine (racemic narcotine, M.P. 232°) was eliminated by the discovery that it was dextro-rotatory. From its insolubility in sodium hydroxide solution, it was inferred that the lactonic structure, originally present in the narcotine, had remained intact. Otherwise a carboxyl group would undoubtedly have been produced. The substance was formulated as an aminoxide, II.



II III IV

Whilst oxidation of narcotine by other means (Wohler, Annalen, 1844, 50, 18; Anderson, Annalen, 1853, 56, 187) has resulted in the fission of the molecule between the isoquinoline and/

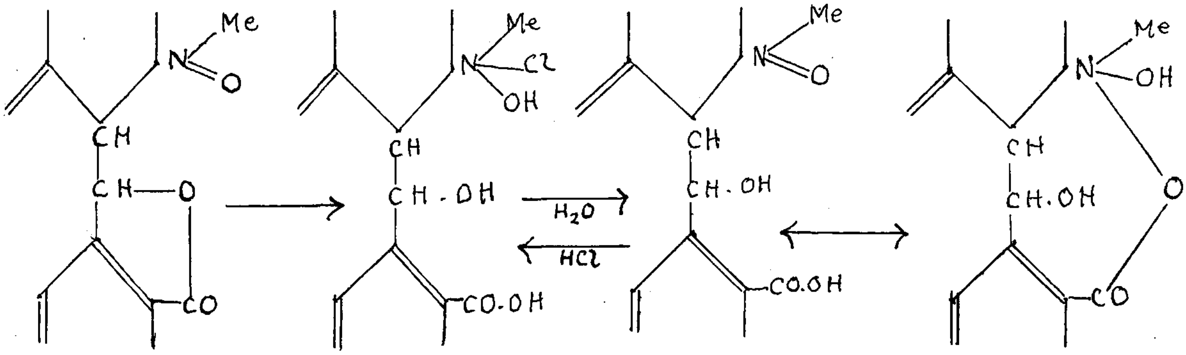
and the benzenoid nuclei, with hydrogen peroxide the complexity of the molecule is preserved. Confirmation of the presence of the narcotine skeleton in this new substance has been obtained by oxidation. Anderson (loc.cit.) oxidised narcotine by nitric acid to a base cotarnine, opianic acid, III, and the dibasic acid, hemipinic acid, IV, formed by further oxidation of the latter. Under similar conditions we obtained from the narcotine aminoxide an acid, readily identified as IV. We failed to isolate the basic part of the molecule.

The sparingly soluble aminoxide did not enter into the reactions which characterise many members of the class, but its feeble basicity, evidenced by its refusal to form salts, would account for its inactivity. It was, however, soluble in strong acids and from a trial reduction to the parent narcotine by means of tin and hydrochloric acid, a crystalline substance was obtained, M.P. 191°. At first this was thought to be a reduction product, but the discovery that the compound was an acid rendered this view highly improbable. Treatment of the aminoxide with concentrated hydrochloric acid alone showed that the substance could be obtained in the absence of tin, which seemed to indicate that hydrolysis had occurred.

This compound was found to be a hydrochloride (attached to the nitrogen atom) and contained a carboxyl group. As the aminoxide did not contain the latter, this compound could not be regarded simply as the hydrochloride of that substance. Analysis revealed the composition $C_{22}H_{25}O_9N, HCl$ and

hydrolytic/

hydrolytic rupture of the lactone ring was probably the source of the carboxyl group (formula VI). The optical activity of the aminoxide had disappeared, as the hydrochloride was inactive.



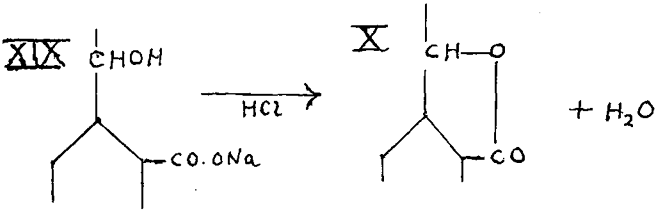
II VI VII VIII

The substance was unstable and readily hydrolysed to an unusually insoluble acid, $C_{22}H_{25}O_9N$, M.P. 212°, and reconversion to the hydrochloride was readily effected. The open lactone, presumed to be present in the hydrochloride, has evidently been left intact (formula VII). The stability of this substance as a hydroxy-acid appears remarkable, but a parallel is found in the case of the hydroxy-acid from gnoscopine.

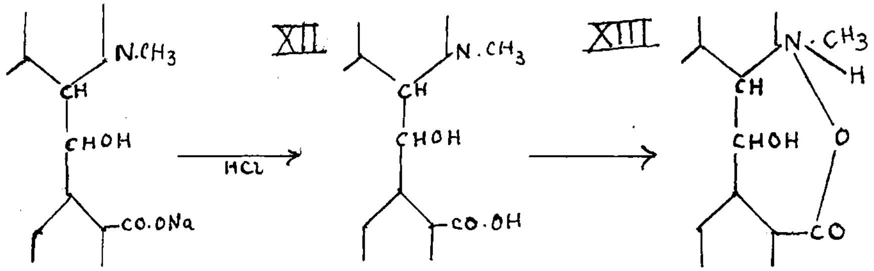
Rabe and McMillan (Annalen, 1910, <u>377</u>, 242) have shewn this substance to be much more stable than the corresponding compound from narcotine. When a solution of the sodium salt of narcotine, IX, is acidified, ordinary lactonic narcotine is gradually/

gradually precipitated, indicating that lactonisation has taken place in solution; but when a solution of the sodium salt of gnoscopine, XI (which is much more soluble than the corresponding salt of narcotine) is acidified, the expected gnoscopine is not precipitated but the insoluble gnoscopine hydroxy-acid, XII, is thrown out in solid form.

Narcotine.



Gnoscopine.



In the latter case the substance leaves the solution before lactonisation can occur. To us, then, it seems that the unusual stability of the racemic hydroxy-acid is due to its great insolubility. Rabe and McMillan suggest the possibility that this substance may assume the betaine structure XIII, which would conduce to stability.

The stability of the aminoxide hydroxy-acid, VII, which we have obtained, may also be due to its undoubted insolubility and by analogy we suggest the betaine formula VIII.

EXPERIMENTAL.

Oxidation of Narcotine by Hydrogen Peroxide.

The oxidations conducted in aqueous hydrogen peroxide (30% concentration) and in more dilute solutions in acetone and dilute sulphuric acid generally yielded tarry matter. In a few trials in sulphuric acid a small quantity of the crystalline aminoxide was obtained. With ferrous sulphate as catalyst in strong hydrogen peroxide solution a vigorous action, accompanied by much charring, took place.

In the earlier trials attempts were made to purify the tarry material. It was found to be very soluble in acetone and chloroform, sparingly soluble in benzene and ethyl alcohol and insoluble in ether and ligroin. Crystallisation from all the common organic solvents and from suitable mixtures of these was tried without success. Precipitation with excess of ether from a saturated solution in chloroform was found ineffective and attempts to extract a basic product as picrate were unavailing. This residue seems to consist of complex, highly polymerised oxidation products somewhat resinous in nature.

Oxidation of narcotine in acetic acid solution gave steady and satisfactory yields when the conditions described below were rigidly followed.

20 gm. lots of l-narcotine (1 mol.) were dissolved in 50 cc. pure glacial acetic acid, and the solutions were put in stoppered bottles on a shelf exposed to sunlight. Each day 1 cc. of aqueous hydrogen peroxide (concentration 30%) was added to each/

each bottle from a burette and a shake was administered. After 12 cc. (2 mols.) of hydrogen peroxide had been added, the now golden-yellow contents of each bottle were combined and the liquid was almost neutralised with sodium carbonate, sufficient acid being left to retain any unchanged narcotine in solution; and the sticky mass, which separated, was extracted with chloroform. This extract was shaken with dilute sodium carbonate solution followed by water to remove acidity and was dried over anhydrous sodium sulphate. On evaporation, the extract yielded a viscous material which, when stirred with 150 cc. of dry acetone, and cooled in ice, left a yellow amorphous solid. Yield 25% of theoretical. The substance, narcotine oxide, was found to be fairly soluble in boiling acetone, though almost insoluble in cold, and was thus readily crystallised from this solvent. The crystals were needle-shaped and grew in curious clusters, each being composed of crystals radiating from the centre. The substance melted at 223°, but further crystallisation raised the melting point to 229°.

Analysis.

.1562 gm. substance gave .3506 gm. CO_2; .0731 gm. H_2O.
.0961 " " " .2164 " .0467 "

.1884 " " " 5.2 cc. N_2 at 23° and 765 mm.

$C_{22}H_{23}O_8N$	Found.	Calc.
C	61.2, 61.4	61.1%
H	5.2, 5.4	5.4%
N	3.1	3.3%

Optical rotation.

.1491 gm. substance in 11 cc. chloroform. $l = .5$ dm.

$\alpha = +.94^{\circ}$ $\qquad [\alpha]^{16^{\circ}}_{5461} = + 139^{\circ}$

This compound does not liberate iodine from aqueous potassium iodide. It was unaffected by treatment with sulphur dioxide in chloroform solution and also by warming with alkaline sodium sulphite in aqueous solution, each of which usually produce reduction of aminoxides to the parent substances. The compound was moderately soluble in chloroform, sparingly in alcohol and practically insoluble in the ordinary organic solvents, readily soluble in concentrated acids and was unaffected by alkali. Picric acid in acetone and platinic chloride in hydrochloric acid had no effect on the substance.

We are indebted to Dr. Cuthbertson for an examination of its physiological properties, which, however, do not appear to be marked. This is in agreement with the recent results obtained by Polonovski (Compt. rend., 1925, 181, 887) in connection with other alkaloidal aminoxides.

Oxidation of Narcotine Oxide with Nitric Acid.

3 gm. of the oxide were treated with a solution of 8 cc. of concentrated nitric acid in 30 cc. of water at 50°. The oxidation was slow on account of the sparing solubility of the oxide and after 14 days the unchanged material was filtered off. The solution was extracted with ether, and the extract, after being shaken with powdered calcium carbonate to remove acidity/

acidity, yielded a white crystalline acid, which was recrystallised from dry ether, M.P. 176°.

Equivalent.

.0922 gm. acid required 39.05 cc. .0211 N.NaOH.

Found: equivalent 112 . $C_8H_8O_2(CO.OH)_2$ requires 113.

A mixed melting point determination with a sample of hemipinic acid gave no depression.

From the aqueous liquor, after complete neutralisation, evaporation and extraction with alcohol, a small quantity of a yellow oil was obtained which was not identified.

Action of Hydrochloric Acid on Narcotine Oxide.

The oxide, dissolved in chloroform, was unaffected by hydrogen chloride; but from a solution of 5 gm. of the substance in 100 cc. of concentrated hydrochloric acid a solid began to separate after 24 hours and the amount increased on addition of water. This substance, the hydrochloride of narcotine aminoxide hydroxy-acid, readily crystallised from absolute alcohol and was soluble in aqueous sodium carbonate, but insoluble in water and ether. It melted at 191°.

Analysis.

.1121 gm. substance gave .2261 gm. CO_2; .0555 gm. H_2O.
.1362 " " " .2727 " " .0699 "

.0981 " " " .0288 " AgCl.

$C_{22}H_{25}O_9N,HCl$.	Found.	Calc.
C	55.0, 54.6	54.7%
H	5.5, 5.7	5.4%
Cl	7.1	7.3%

It was stable in the presence of hydrochloric acid, but repeated crystallisation from aqueous alcohol or exposure to the air gradually converted it into the hydroxy-acid itself, M.P. 212°, which was insoluble in all ordinary organic solvents. This change was accelerated by warming with water.

Analysis.

.1200 gm. substance gave .2588 gm. CO_2; .0554 gm. H_2O
.1023 " " " .2198 " " .0534 " "

.1880 " " " 5.5 cc. N_2 at 21° and 759 mm.

$C_{22}H_{25}O_9N$.	Found.	Calc.
C	58.8, 58.6	59.1%
H	5.5, 5.8	5.6%
N	3.3	3.1%

Excess of concentrated hydrochloric acid was added to a solution of this acid in aqueous sodium hydroxide. A crystalline solid rapidly separated, and was identified as the hydrochloride, M.P. 191°.

The addition of lead acetate to a solution of the ammonium salt precipitated a yellow lead salt.

,0978 gm. substance gave .0269 gm. $PbSO_4$.

Found: Pb, 18.2 $(C_{22}H_{24}O_9N)_2$—Pb requires Pb, 18.8%.

Dilute sulphuric acid precipitated from a solution of the sodium salt a viscous oil, which dissolved on being gently warmed. From this solution there separated a sulphate in/

in small, white needles, M.P. 148°.

.1685 gm. substance gave .0372 gm. $BaSO_4$.

Found: SO_4, 9.1. $(C_{22}H_{25}O_9N)_2,H_2SO_4$ requires SO_4, 9.3%

The author desires to express his indebtedness to Professor G. G. Henderson, F.R.S., Dr A. McMillan and Dr D. T. Gibson for advice and facilities to carry out this work.

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