UNIVERSITY OF EDINBURGH

Thesis

for the Degree of Doctor of Science

presented by

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Part I.

THE ALKALOIDS OF CORYDALIS CAVA.

Part II.

ON THE RELATION BETWEEN THE ABSORPTION SPECTRA & THE CHEMICAL STRUCTURE OF CORYDALINE, BERBERINE, AND OTHER ALKALOIDS.

December, 1904.

C O N T E N T S.

Part I.

Part II.

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THE ALKALOIDS OF CORYDALIS CAVA.

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Introductory.

The alkaloids of Corydalis Cava were first investigated by Wackenroder in 1826 (Berzelius, Jahresber., 7. 220, 1826), who discovered and prepared in an impure condition, the alkaloid corydaline. Since then, especially within the last ten years, this group of alkaloids has been the subject of numerous investigations. The following is a complete list of the alkaloids which have, so far, been separated:-

1. Corydaline .... $C_{22}H_{27}NO_4$.
2. Corybulbine .... $C_{21}H_{25}NO_4$.
3. Iso-Corybulbine .... $C_{21}H_{25}NO_4$.
4. Corytuberine .... $C_{19}H_{25}NO_4$.
5. Bulbocapnine .... $C_{19}H_{19}NO_4$.
6. Corycavine .... $C_{23}H_{23}NO_5$.
7. Corycavamine .... $C_{21}H_{21}NO_5$.
8. Corydine ...... probably $C_{21}H_{23}NO_4$.

Of these, Corydaline is the only one which has been fully studied. In this Thesis, an account is given of the investigation of Corydaline which has led to the adoption of the constitutional formula now assigned to it, together with an account of corybulbine and corytuberine, as far as their investigation has been carried at present.

I gladly take advantage of this opportunity to express my great indebtedness to Dr James J. Dobbie, F.R.S., with whom the work on which this thesis is founded was carried out.

CORYDALINE.

Historical.

The rare alkaloid corydaline was discovered by Wackenroder in the year 1826 in the tubers of corydalis cava, (Syn. Bulbocapnus cavus; corydalis tuberosa; corydalis bulbosa) (Berzelius, Jahresber., 1826, 7, 220). The substance obtained by Wackenroder, however, was not the pure base, but a mixture of various alkaloids. For this reason also, the later workers, von Peschier, Winkler, Doeberiner, Ruickholdt, Műller and Leube[*] added little to our knowledge of the alkaloid.

The first real advance was made by Wicke, who, in 1866 (Ann. 137, 274) published a more complete and careful account of the alkaloid than had hitherto appeared, accompanied by numerous analyses of the base and its compounds. From these analyses, he deduced the formula $C_{18}H_{19}NO_4$ which has since been accepted as correctly representing the composition of the alkaloid. In 1888 Reichwald (Inaug.-Diss. Dorpat. 1888) gave $C_{20}H_{19}NO_2$ as the formula and 197° as the melting point of corydaline, and in 1890 Adermann (Inaug.-Diss. Dorpat.1890);

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[*] Gmelin-Kraut, Organischen Chemie 4, 1993, (1866); Hilger-Husemann, "Die Pflanzen Stoffe" (1882), p. 790.

Chem. Centralbl., 1891, I., 978) believed that he had proved the identity of corydaline and tetrahydroberberine, $C_{20}H_{21}NO_4$. It will be seen, therefore, that considerable doubt still existed as to the correct composition of the alkaloid at the time when the present investigation was undertaken.

PREPARATION OF PURE CORYDALINE AND DETERMINATION OF ITS FORMULA.

From what has already been stated in the Historical Introduction, it will be seen that before beginning an investigation of the decomposition products of corydaline, it was first necessary to prepare and analyse various specimens of the alkaloid of undoubted purity, with the object of definitely ascertaining its composition.

The crude material for the investigation was obtained from Schuchardt of Görlitz in different lots, prepared from the dried roots of corydalis cava, gathered partly in the Tyrol and partly in Thuringia. The corydaline from the various samples was purified and analysed separately, with the view of establishing definitely the identity of the alkaloid obtained from different sources. The substance supplied by Schuchardt as corydaline, was found to consist of a mixture of various alkaloids, and, after much investigation, the following method, of which full details are given in the Experimental Part (p.54) was finally adopted for the separation of pure corydaline.

The crude corydaline is first repeatedly extracted with boiling water; a green solution is thus obtained with a magnificent blue fluorescence, which, on cooling, deposits tufts of small slender needles. On investigation, this proved to be an alkaloid not hitherto isolated. Analysis showed it to have the formula $C_{19}H_{25}NO_4$, and it was named corytuberine from Corydalis tuberosa, a synonym for corydalis cava (Dec.). (Chem. Soc. Trans., 1893, 63, 485.) The further examination of this alkaloid is described below (p. 42).

The residue left after extraction with water, was next repeatedly extracted with hot alcohol, which easily removed the corydaline and left behind a difficultly soluble residue, which was afterwards found to consist largely of the alkaloid corybulbine $C_{21}H_{25}NO_4$ (p.44). From the alcoholic solution so obtained the corydaline crystallized on cooling. It was purified by repeated crystallization from alcohol and finally obtained in the form of colourless, flat, prismatic crystals. These crystals, and their solution in alcohol, are quickly coloured yellow by the action of light or heat, and care must be taken to preserve them from the action of light as much as possible. Pure corydaline, when heated, changes colour about 125°, softens about 133°, and melts finally at 134.5°. No difference could be detected between the melting points of the various specimens, when examined under similar conditions. The melting point given by Wicke was 130°. Corydaline dissolves readily in ether, chloroform, carbon disulphide, benzene, and, on warming, in alcohol. It is practically insoluble in cold, and only very slightly soluble in boiling water. It dissolves readily in dilute hydrochloric or sulphuric acids, but is insoluble in solutions of sodium and potassium hydrates. On warming corydaline with dilute nitric acid, a sparingly soluble nitrate is first formed, which is oxidised on further heating with the evolution of nitrous fumes (p.17). The solution of the alkaloid in alcohol or chloroform is strongly dextrorotatory.

Four separate specimens of the alkaloid were prepared and purified by the method above described. The entire agreement of the analyses (p.59) left no doubt as to the identity of the specimens and led to the formula $C_{22}H_{27}NO_4$ for corydaline. The following salts were also prepared and analysed, the results in every case agreeing with those required by the above formula (p.61):-

Corydaline Hydriodide ... $C_{22}H_{27}NO_4 HI$;
Corydaline Hydrobromide, $C_{22}H_{27}NO_4 HBr$;
Corydaline ethyl sulphate, $C_{22}H_{27}NO_4 . C_2H_5H SO_4 . H_2O$;

Corydaline platino-chloride $(C_{22}H_{27}NO_4)_2H_2\overset{Pt}{\cancel{Pt}}Cl_6$;
Corydaline Methiodide, $C_{22}H_{27}NO_4CH_3I$.

The more recent analysis made by Freund and Josephi and other chemists also confirm the correctness of this formula.*

THE CONSTITUTION OF CORYDALINE.

Determination of the number of methoxyl groups.
The number of methoxyl groups present in the alkaloid was determined, according to Zeisel's method, by heating with a concentrated solution of hydrogen iodide. The methyl iodide evolved was decomposed by passing through an alcoholic solution of silver nitrate, the precipitated silver iodide being collected and weighed in the usual manner. Corydaline was found to contain four methoxyl groups, the decomposition proceeding in accordance with the following equation:- $C_{18}H_{15}(OCH_3)_4N + 5\ HI = C_{18}H_{15}(OH)_4HI + 4\ CH_3I$. (p. 64).

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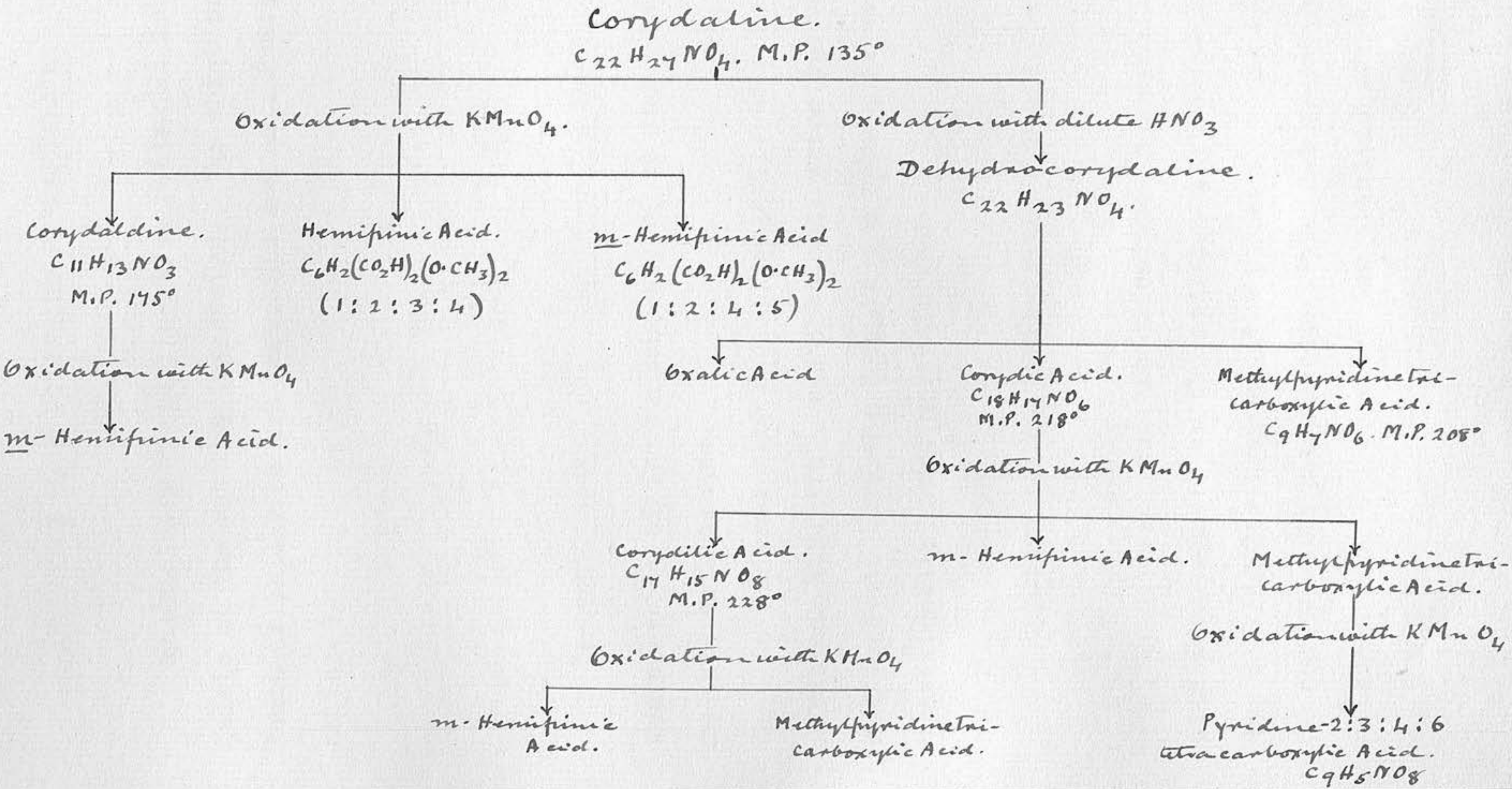
* (Freund and Josephi, Annalen 1893, 277, 1; Ziegenbein, Arch. Chem. Pharm., 1896, 234, 492; Martindale, ibid., 1898, 236, 214.)

OXIDATION OF CORYDALINE.

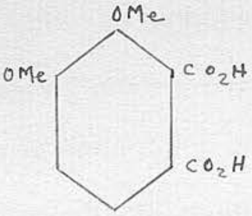
With the object of obtaining further information as to the constitution of corydaline, the alkaloid was oxidised with various oxidising agents under different conditions, and the decomposition products separated and examined. The oxidising agents which were found to give the most satisfactory results were potassium permanganate and dilute nitric acid. On account of the high cost of the material, it was only possible to work with quantities which were relatively small compared with the quantities oxidised in the investigation of some of the less costly alkaloids, such as berberine. The separation and purification of some of the decomposition products, which were only formed in small quantity, was thus a matter of considerable difficulty. The methods employed in the oxidation, and in the separation of the various decomposition products are given in detail in the Experimental Part (p.70). The following table shows the main decomposition products formed:-

OXIDATION PRODUCTS OF CORYDALINE.

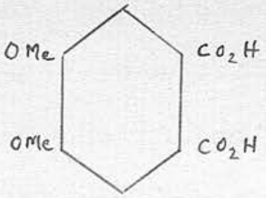


OXIDATION WITH POTASSIUM PERMANGANATE.

By oxidising corydaline with potassium permanganate at the boiling temperature, the chief products of oxidation are hemipinic and meta-hemipenic acids:-



Hemipinic Acid.



m-Hemipinic Acid.

The presence of two benzene nuclei in the alkaloid is thus established.

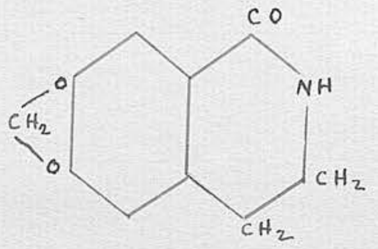
At the same time a small quantity of a neutral substance, M.P. 175°, was obtained, which proved, on analysis, to have the formula $C_{11}H_{13}O_3N$. It was provisionally named corydaldine.

CONSTITUTION OF CORYDALDINE, $C_{11}H_{13}O_3N$.

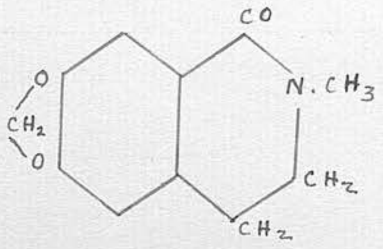
By carrying out the oxidation of corydaline with permanganate at the ordinary instead of at the boiling temperature, the yield of corydaldine is considerably increased. From 4-5 grams were obtained from 100 grams of the alkaloid. Corydaldine is easily soluble in water, chloroform, alcohol, and the ordinary solvents. In aqueous solution it has a neutral reaction. On heating it melts sharply at 175°. A determination of methoxyl groups by Zeisel's method showed that two were still present in this derivative. (p. 83). The further investigation of corydaldine yielded highly important results, and, in addition to throwing much light on the constitution of corydaline, showed also that a great similarity in structure exists between this alkaloid and the alkaloid berberine.

Corydaldine does not react with phenylhydrazine which proves the absence of an aldehydic or ketonic group. On the other hand, it shows the reactions of a secondary base and reacts readily with nitrous acid forming a characteristic nitroso-derivative. It thus bears a striking resemblance to nor-oxyhydrastinine obtained by Perkin by the oxidation of berberine (<u>Chem. Soc. Trans.</u>, 1890, 57, 1027.)

Perkin considered nor-oxyhydrastinine to differ only from oxyhydrastinine, the constitution of which had been determined by Freund and Will (<u>Ber</u>. 20, II., (1887), 2404), in having an atom of hydrogen, instead of a methyl group, attached to the nitrogen atom.



nor-Oxyhydrastinine.



Oxyhydrastinine.

That this was the true relation between these substances he proved by the conversion of nor-oxyhydrastinine into oxyhydrastinine by the following series of reactions:-

I. As a secondary base, nor-oxyhydrastinine reacts with nitrous acid forming a nitrosamine:-

$$CH_2<^{O}_{O}>C_6H_2<^{CO-NH}_{CH_2-CH_2} \rightarrow CH_2<^{O}_{O}>C_6H_2<^{CO-N.NO}_{CH_2-CH_2}$$

II. This nitrosamine, on heating with sodium hydrate, is decomposed with the formation of ω-oxyethylpiperonylic acid, nitrogen being split off, as follows:- $CH_2<^{O}_{O}>C_6H_2<^{CO-N.NO}_{CH_2-CH_2} + NaHO$

$$= CH_2<^{O}_{O}>C_6H_2<^{COO.Na}_{CH_2-CH_2.OH} + N_2$$

III. If this latter derivative is now successively treated with phosphorus pentachloride and methyl alcohol, it yields the methyl ester of ω-chlorethylpiperonylic acid:

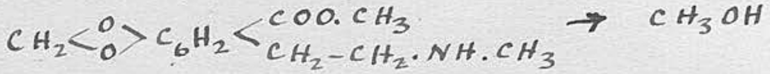
$$CH_2<^{O}_{O}>C_6H_2<^{COO.CH_3}_{CH_2.CH_2Cl}$$

IV. When this ester is heated with a solution of methylamine to 130°

$$CH_2<^{O}_{O}>C_6H_2<^{COO.CH_3}_{CH_2.CH_2Cl} + 2\,NH_2.CH_3$$

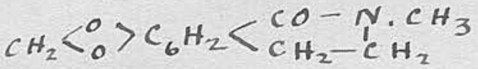
$$= CH_2<^{O}_{O}>C_6H_2<^{COO.CH_3}_{CH_2-CH_2-NH.CH_3} + NH_2.CH_3.HCl$$

and the product thus obtained is treated with alcoholic potash, methyl alcohol is split off and oxyhydrastinine is formed.



$$CH_2 <_{O}^{O}> C_6H_2 <_{CH_2-CH_2.NH.CH_3}^{COO.CH_3} \rightarrow CH_3OH$$

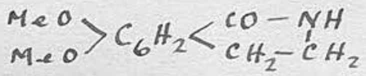
Methyl ester of ω-methylamido-ethyl piperonylic acid.



$$CH_2 <_{O}^{O}> C_6H_2 <_{CH_2-CH_2}^{CO-N.CH_3}$$

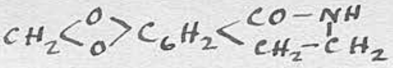
Oxyhydrastinine.

A comparison of the molecular formula of nor-oxyhydrastinine, $C_{10}H_9O_3N$, with that of corydaldine, $C_{11}H_{13}O_3N$, shows that they only differ by CH_4. It has further been pointed out that both are secondary bases, and that corydaldine still contains two methoxyl groups. It seemed not unlikely, therefore, considering the general similarity in their reactions, that corydaldine only differed from nor-oxyhydrastinine in containing two methoxyl groups in place of the dioxymethylene group present in the latter substance.



$$\begin{matrix} MeO \\ MeO \end{matrix} > C_6H_2 <_{CH_2-CH_2}^{CO-NH}$$

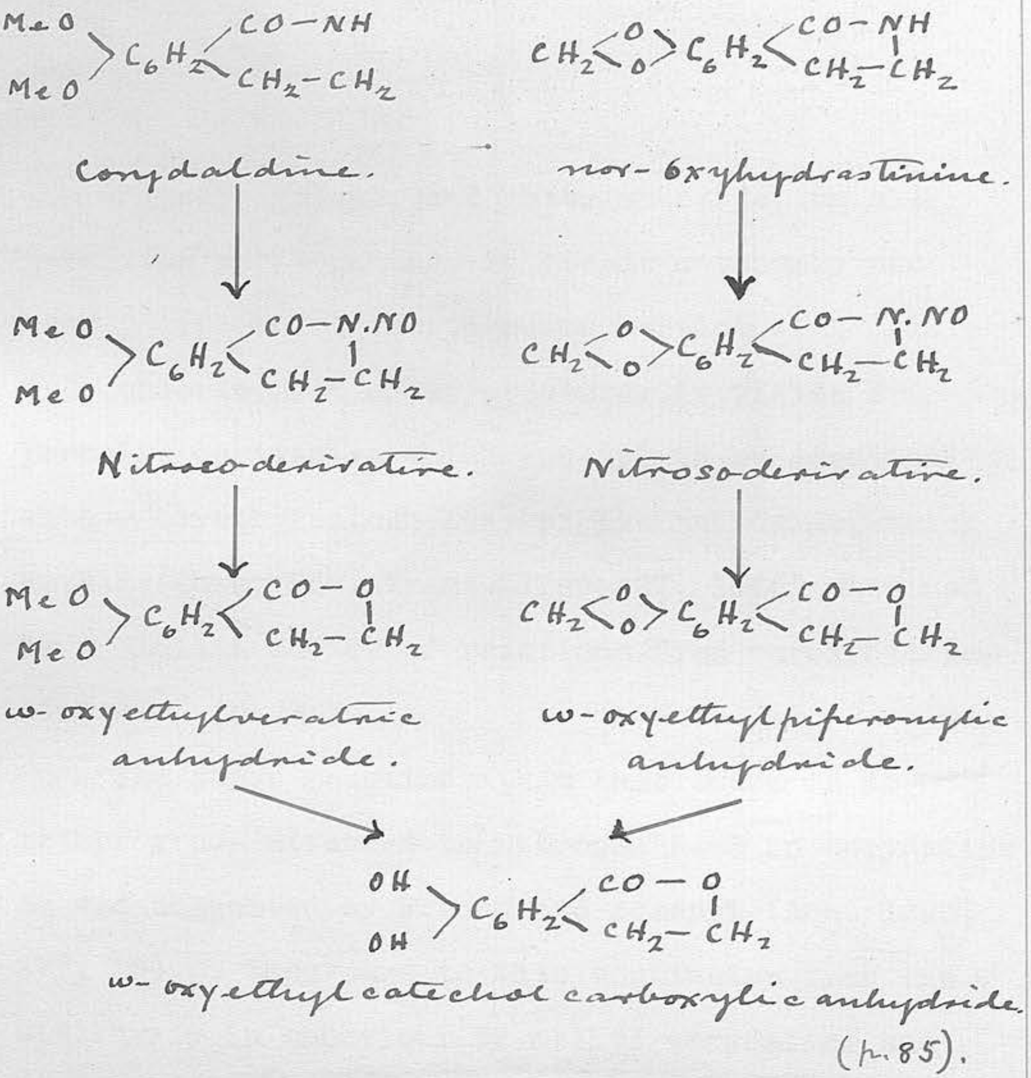
Corydaldine



$$CH_2 <_{O}^{O}> C_6H_2 <_{CH_2-CH_2}^{CO-NH}$$

Nor-Oxyhydrastinine.

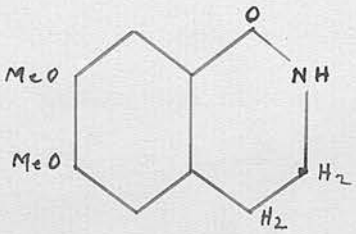
That this is actually the relation between the two bodies is shown by the following series of reactions:-



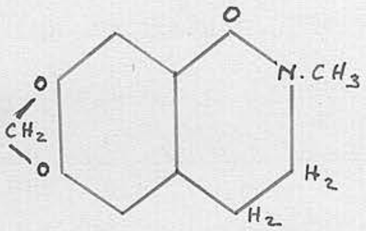
The formation of the nitroso-derivative of Corydaldine has already been described. When this is gently warmed with a dilute solution of sodium hydrate it goes into solution, nitrogen being evolved and the sodium salt of ω-oxyethylveratric acid formed. On treating this salt with hydrochloric acid, the ω-oxyethylveratric acid liberated, immediately loses a molecule of water and the anhydride and not the free acid is obtained. That this anhydride has the constitution assigned to it above, follows from the fact that it still contains two methoxyl groups, and that, on oxidation with potassium permanganate, it yields metahemipinic acid. (p. 91) Further, on heating with dilute hydrochloric acid under pressure, it yields a phenolic derivative which appears to be identical with ω-oxyethylcatecholcarboxylic anhydride, which Perkin (Chem. Soc. Trans. 1890, 57, 1026) obtained by a similar series of reactions from noroxyhydrastinine. (p. 89).

The above reactions show that there is no methyl group attached to the nitrogen atom in corydaline as was suggested by Freund and Josephi (Ann. 1893, 277, 10). They came to this conclusion from the similarity in behaviour of methyl corydaline and hydrohydrastinine, and especially from the stability of their alkyl haloid addition compounds towards alkali. That there is no methyl group attached to the nitrogen atom has been further confirmed by Herzig and Meyer (Monatsh., 1897, 18, 385), who found that corydaline only contains four methyl groups in all, which can be split off by the action of hydrogen iodide. Since it has already been shown that the alkaloid contains four methoxyl groups, it follows that all the methyl groups must be in combination with oxygen.

The constitutional formula assigned to corydaldine shows that corydaline is not only closely related to berberine, but also to hydrastine, narcotine, and papaverine, in common with which it contains an isoquinoline nucleus.



Corydaldine.



Oxyhydrastinine.

From oxyhydrastinine corydaldine only differs in containing two methoxyl groups in place of the dioxymethylene group, and in having an atom of hydrogen in place of a methyl group united to the nitrogen atom. That the arrangement of the groups attached to the benzene nucleus is the same in both substances, is confirmed by the oxidation on the one hand of ω-oxyethylveratric anhydride to *m*-hemipinic acid (p.91), and on the other hand, by the conversion of hydrastic acid to 4 : 5 dihydroxyphthalic acid, (nor-meta-hemipinic acid), by the action of phosphorus penta-chloride and water.

OXIDATION WITH DILUTE NITRIC ACID.

The action of dilute nitric acid on corydaline was first studied by Dobbie and Marsden. (Chem. Soc. Trans., 1897, 71, 651.) They found that the

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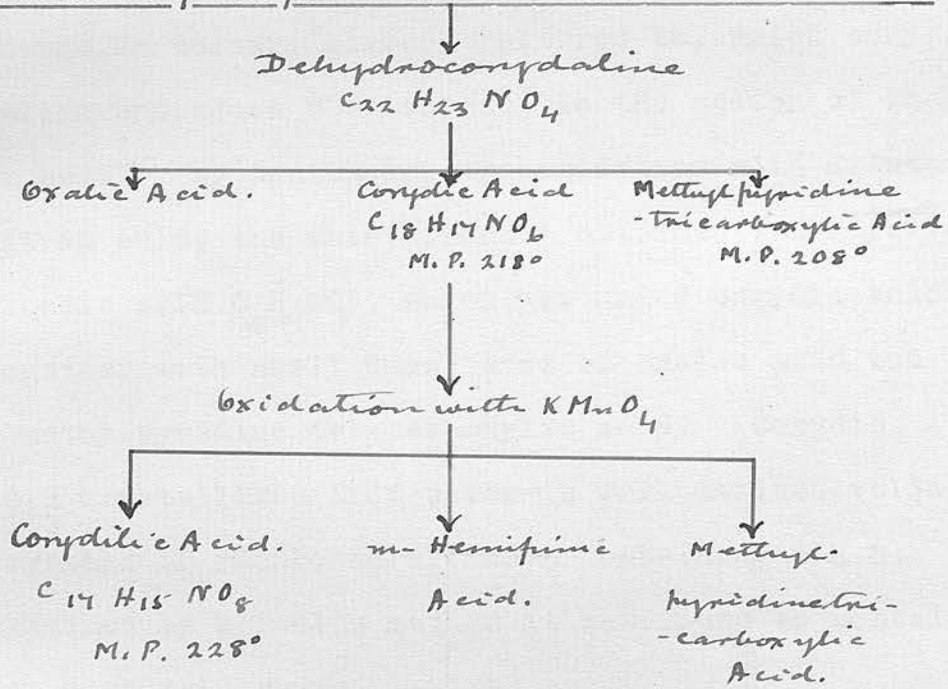
first action of the nitric acid was to remove 4 atoms of hydrogen from corydaline, with the production of a strongly yellow coloured base, dehydrocorydaline. On continuing the oxidation, the products shown in the following table were obtained:-

Oxidation of Corydaline with dilute Nitric Acid



Dehydrocorydaline, $C_{22}H_{23}NO_4$.

Dehydrocorydaline is easily reduced to corydaline by the action of zinc and hydrochloric acid. The base obtained in this way is identical in all respects, with the natural alkaloid except that it is optically inactive. The solutions of dehydrocorydaline and its soluble compounds are bright yellow in colour. Corydaline undergoes partial oxidation to dehydrocorydaline with great ease, the change being effected by an alcoholic solution of iodine, by boiling with moist silver oxide, or simply by long continued heating of the alkaloid in the steam oven. This is the explanation of the change in colour, already referred to, which corydaline undergoes when exposed to the action of light or heat. By continuing the oxidation with dilute nitric acid, the chief product obtained was a yellow dibasic acid $C_{18}H_{17}NO_6$, which was named corydic acid, together with small quantities of oxalic acid and a methylpyridine tri-carboxylic acid. Corydic acid crystallizes from water in well defined yellow crystals of rhombohedral habit containing $\frac{1}{2}$ H_2O. Examined by Zeisel's method it was found to contain two methoxyl groups.

OXIDATION OF CORYDIC ACID WITH POTASSIUM PERMANGANATE.

When corydic acid is boiled with a solution of potassium permanganate, oxidation takes place with the formation of a number of acids as shown in the table already given (p. 92). The oxidation proceeds rapidly at first, but much more slowly towards the end. The mixture is boiled until, on

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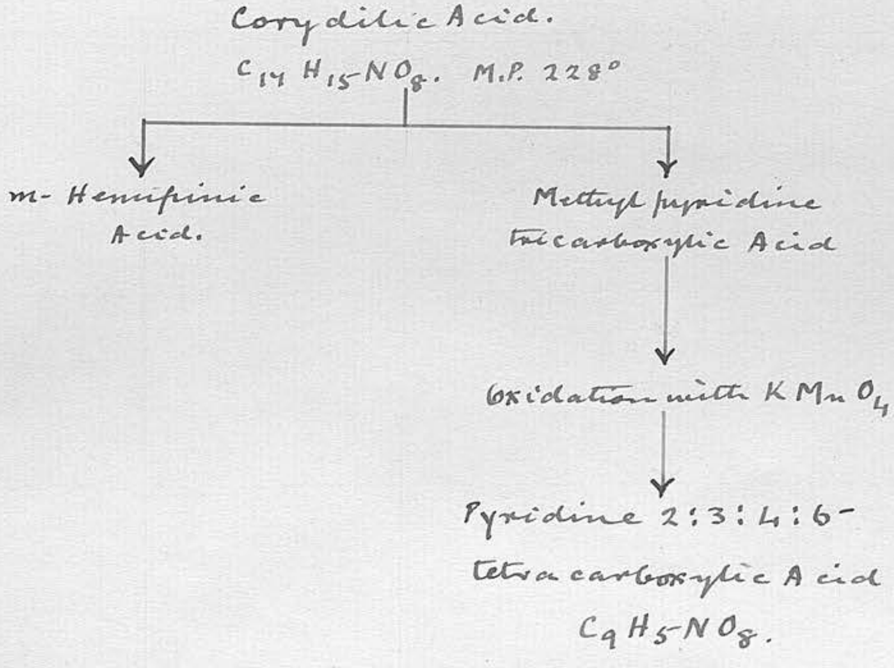
destroying the excess of permanganate and acidifying, the yellow colour due to the presence of corydic acid has entirely disappeared. When the oxidation is complete, the excess of permanganate is reduced by adding a little alcohol, the solution filtered from the manganese dioxide, concentrated and precipitated with lead acetate; the lead precipitate is then decomposed with hydrogen sulphide, filtered from the lead sulphide, and concentrated. While the solution is still very dilute, small, white, acicular crystals of an acid begin to separate; this is the principal product of the oxidation, and amounts to about 25 per cent. of the corydic acid used. It is easily separated from all the other products, all of which are much more soluble in water. Its analysis led to the formula $C_{17}H_{15}NO_8$ and it was afterwards named corydilic acid. It was found to contain two methoxyl groups, to be a tribasic acid, and to melt at 228°. From the mother liquors from which corydilic acid had been separated, two other acids were obtained by fractional crystallization, one, a non-nitrogenous acid which melted at 172°, the other a nitrogenous acid melting at 208°.

The non-nitrogenous acid proved to be meta-hemipinic acid. The nitrogenous acid was much less soluble than the *m*-hemipinic acid and the separation of the two acids was thus easily effected. Its analysis led to the formula $C_9H_7NO_6 + H_2O$, and it was found to be tribasic. It appears to be one of the methyl pyridine tri-carboxylic acids, but is not identical with any of the acids of this composition hitherto described.

To obtain the necessary material for a more complete examination of the decomposition products of corydic acid, the oxidation of corydaline with nitric acid was repeated on a larger scale. The method employed was that described above, originally worked out by Dobbie and Marsden and the results already published by them were confirmed.* The results obtained by the further oxidation of corydilic acid, and of methyl-pyridine tricarboxylic acid, with potassium permanganate, are shown in the following table:-



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*(Chem. Soc. Trans. 1902, 81, 145.)

EXAMINATION OF THE METHYLPYRIDINETRICARBOXYLIC ACID

This acid can be obtained, not only by the oxidation of corydic acid with permanganate, but also by the oxidation of corydaline with strong nitric acid in the manner followed by Weidel in the preparation of berberonic acid from berberine (Ber., 1879, 12, 410). The yield by this method is, however, unsatisfactory. The analysis and general properties of this acid have already been described by Dobbie and Marsden.* The copper salt, obtained by adding copper acetate to a neutral solution of the acid is blue in colour, and not yellow, as previously stated. This acid is undoubtedly a methylpyridinetricarboxylic acid, as is shown by its analysis and the analysis of its salts, but it is not identical with any of the known acids of this constitution. It has already been shown (p.16) that there is no methyl group attached to the nitrogen atom in corydaline. The correctness of this conclusion was confirmed by the fact that there was no evolution of methylamine on heating the methylpyridinetricarboxylic acid with sodium amalgam.

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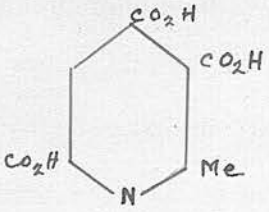
* (Chem. Soc. Trans., 1896, 71, 657.)

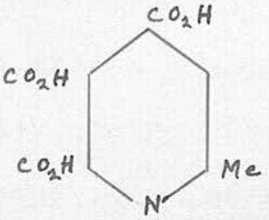
The methylpyridinetricarboxylic acid is an exceedingly stable substance and can be boiled for some time with a dilute solution of potassium permanganate without undergoing any appreciable amount of oxidation. When, however, it is dissolved in excess of potassium hydroxide and a solution of potassium permangate added, it slowly undergoes oxidation, the operation requiring from eight to nine days at the temperature of the water-bath for completion. Two experiments were made, one with 3 grams and the other with 2 grams of the acid. The excess of permanganate was reduced, the alkaline solution filtered, neutralised with nitric acid and treated with calcium nitrate to remove a small quantity of oxalic acid which had been formed. After filtering from the precipitated calcium oxalate, the solution was treated with lead acetate and the precipitate filtered off and washed. On decomposing this precipitate with hydrogen sulphide, a strongly acid solution was obtained, which on evaporation yielded a residue very soluble in water and insoluble in alcohol. This residue contained inorganic matter. Its solution was found to give an insoluble salt with copper acetate, which remained undissolved even when heated with acetic acid. It was therefore precipitated with copper acetate with the object of removing the inorganic matter, the blue copper precipitate filtered, well washed first with strong acetic acid and then with water, and decomposed with hydrogen sulphide. The acid obtained from the filtrate was still found, however, to be contaminated with a small quantity of inorganic matter, from which, by reprecipitation, it was impossible completely to purify it. It was thus not possible to get an accurate determination of the melting point or a specimen of the acid in a sufficiently pure state for analysis.

So far as the qualitative examination was concerned, the acid showed all the properties and gave all the reactions of 2:3:4:6-pyridinetetracarboxylic acid obtained by Michael (Annalen, 1884, 225, 121) from 2:4:6-trimethylquinolinecarboxylic acid, and by Fischer and Tauber (Ber., 1884, 17, 2925) from flavinol. It agreed with this acid in being very easily soluble in water and very sparingly so in alcohol; in giving with ferrous sulphate a dark cherry-red colour, and with ferric chloride a yellow precipitate. With calcium chloride, the free acid gave no precipitate, but with barium chloride a copious white precipitate. The copper salt, as already mentioned, was insoluble even in boiling acetic acid. The silver salt on ignition decomposed suddenly, swelling up and filling the crucible with reduced silver which resembled a mass of tea leaves, exactly as described both by Michael and by Fischer and Tauber.

Further information as to the identity of the oxidation product of the methylpyridinetricarboxylic acid was obtained by boiling it with strong acetic acid. When 2:3:4:5-pyridinetetracarboxylic acid is heated at 160°, 3:4:5-pyridinetricarboxylic acid is obtained, and 2:3:5:6-pyridinetetracarboxylic acid decomposes at 150° into 3:5-pyridinedicarboxylic acid. In both cases, the carboxyl groups which are eliminated are adjacent to the nitrogen atom. It was therefore to be anticipated that, under similar treatment, the tetracarboxylic acid obtained by the oxidation of the methylpyridinetricarboxylic acid would yield cinchomeronic acid by the elimination of the carboxyl groups 2 and 6. As a matter of fact, it was found that cinchomeronic acid was produced by boiling with acetic acid, and identified without difficulty. The tetracarboxylic acid was boiled for some time with strong acetic acid and the solution evaporated to dryness. The residue was insoluble in cold and only dissolved with difficulty in hot water. The aqueous solution deposited the acid on cooling in colourless, prismatic crystals, which after purification by recrystallisation melted at 260°. The acid was insoluble in chloroform, almost insoluble in ether, and only very slightly soluble in alcohol. It gave no reaction with ferrous sulphate or with ferric chloride. Silver nitrate and lead acetate gave white precipitates when added to its aqueous solution. Calcium and barium chlorides gave no precipitate even on the addition of ammonia. The copper salt was more soluble in cold than in hot water and was precipitated by warming a cold aqueous solution; the precipitate redissolved again on cooling. The last reaction, which is characteristic of cinchomeronic (pyridine-3:4-dicarboxylic) acid, taken in conjunction with the melting point, solubility, and the reactions above described, left no doubt as to the identity of the acid. Cinchomeronic acid might be formed either from pyridine-2:3:4:5-tetracarboxylic acid or -2:3:4:6-tetracarboxylic acid, by the elimination of the carboxyl groups 2 and 5, or 2 and 6 respectively. It could not be derived from the 2:3:5:6-acid. The tetracarboxylic acid which was obtained not only agreed in every respect with the 2:3:4:6-acid, but differed from the 2:3:4:5-isomeride in giving no precipitate with zinc sulphate in neutral solution. The difficulty of removing inorganic matter from the tetracarboxylic acid, referred to above, is characteristic of the 2:3:4:6-acid.

The methylpyridinetricarboxylic acid from corydaline must therefore have one or other of the following formulae:-





The position of one of the carboxyl groups must be adjacent to the nitrogen atom, since it follows that, when the isoquinoline nucleus is destroyed in the formation of methylpyridinetricarboxylic acid, the carbon atom next to the nitrogen atom, must have a carboxyl group attached to it representing the carbon atom which is common to the benzene and pyridine rings of the isoquinoline nucleus.

seeing that

The two remaining carboxyl groups must represent one of the rings of the corydaline molecule which has been destroyed by oxidation and must therefore occupy positions adjacent to one another.

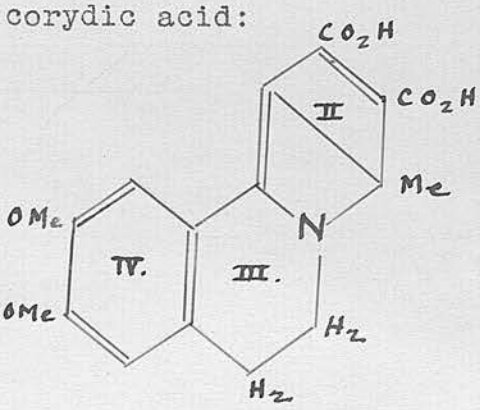
The position of the methyl group is fixed by the following considerations. It cannot occupy the position 4, because, in that case, the only arrangement possible would be ($CH_3:(CO_2H)_3=4:2:5:6$). This acid is known, and is not identical with the acid under investigation. The position 3 is likewise excluded, since, in that case, the tetracarboxylic acid obtained on oxidation would be ($(CO_2H)_4=2:3:4:5$ or $2:3:5:6$), having regard to the fact that two of the carboxyl radicles represent a ring destroyed by oxidation, and must therefore be adjacent to one another. By similar reasoning, position 5 is excluded; the methyl group must therefore occupy the position which is assigned to it in the formula. It will be shown later that the methyltricarboxylic acid is probably $CH_3:(CO_2H)_3=$ $2:3:4:6$), but there is no direct experimental evidence which would enable one to say definitely that this and not ($CH_3:(CO_2H)_3=2:4:5:6$) is the formula of the acid.

CONSTITUTION OF CORYDIC ACID:

The results just described afford a basis for the discussion of the constitution of corydic acid.

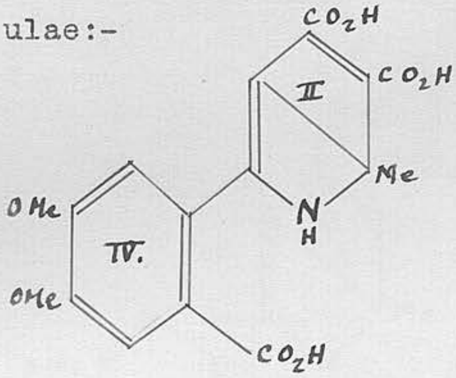
Corydic acid is derived from dehydrocorydaline by the destruction of one of the benzene nuclei, and, since it yields <u>m</u>-hemipinic acid on further oxidation, it follows that the nucleus which is destroyed in the formation of corydic acid is the one which yields hemipinic acid when corydaline is oxidised. The 2-methylpyridinetricarboxylic acid, which is also one of the oxidation products of corydic acid, contains 6 atoms of carbon exclusive of the carbon atoms of the carboxyl groups. It cannot, therefore, be derived from the pyridine ring of the isoquinoline nucleus, since the investigation of corydaldine has shown that this pyridine ring has no side chain attached to it. We thus arrive at the following formula for corydic acid:

the same nucleu

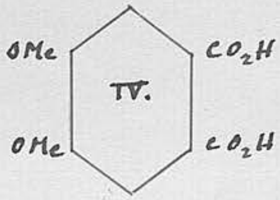


<u>Corydic Acid.</u>

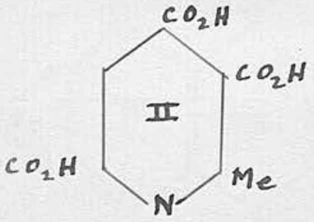
This formula accounts for the relation of the molecular formula of corydic acid to that of dehydrocorydaline; for the presence of the two carboxyl groups, and for the formation, on oxidation, of corydilic acid, the 2-methylpyridinetricarboxylic acid and m-hemipinic acid, as shown by the following formulae:-



Corydilic Acid.



m- Hemipinic Acid

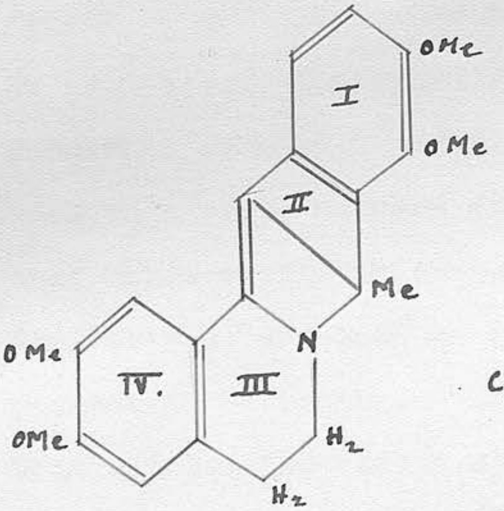


2-Methyl-pyridine-tricarboxylic Acid.

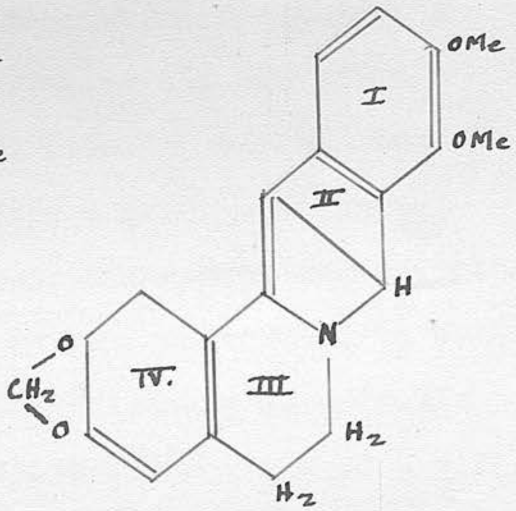
The formation of m-hemipinic acid establishes the position of the methoxyl groups. There is no direct experimental evidence to prove that the positions of the carboxyl groups are those assigned to them rather than the positions 4:5. It will be shown later, however, that there is considerable evidence in favour of the introduction of a direct link between the carbon atoms 2 and 5, which limits the carboxyl groups to the positions shown in the formula.

CONSTITUTION OF CORYDALINE:

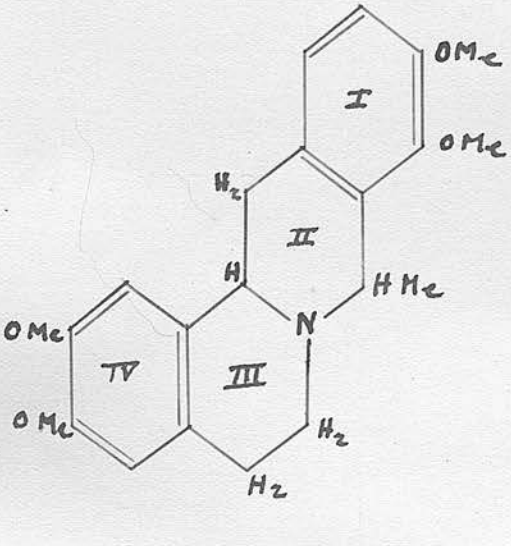
The formula of dehydrocarydaline (~~Fig~~ Page 31) follows from that assigned to corydic acid. Perkin's formula for berberine is placed side by side for comparison (Perkin, Chem. Soc. Trans., 1889, 55, 63):-



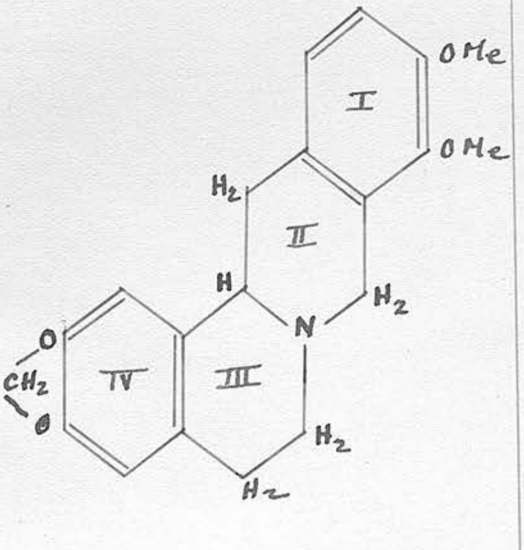
Dehydrocorydaline



Berberine.



Corydaline

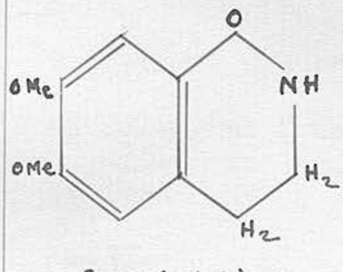


Tetrahydroberberine.

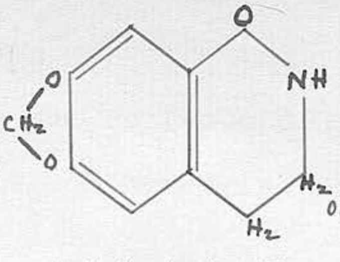
Corydaline differs from dehydrocorydaline in containing four more atoms of hydrogen. Having regard to the great ease with which corydaline can be oxidised to dehydrocorydaline and the latter substance reduced to corydaline, it may be assumed that we have to do here with a group similar to that which exists in certain anthracene and acridine derivatives, and such as Perkin has assumed to be present in berberine. The existence of a double bond between the carbon atoms 5 and 6 and of a direct bond between the carbon atoms 2 and 5 in ring

II. of the formula for dehydrocorydaline (~~Fig~~ Page 31) would explain the ease with which the one substance passes into the other.

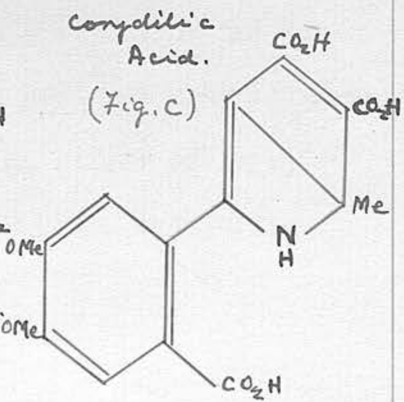
The formula proposed for corydaline, (~~Fig~~ Page. 31) explains the reactions and accounts for the formation of all the derivatives of the alkaloid which have been examined. By oxidation, the rings, which for convenience of reference have been numbered I. and IV. on the diagram, would yield hemipinic and *m*-hemipinic acids respectively, and ring II. methylpyridinetricarboxylic acid. Corydaldine, $C_{11}H_{13}O_3N$ (Fig. A), containing rings III. and IV., would result from the oxidation of corydaline in the same way as nor-oxyhydrastinine (Fig. B.) results from the oxidation of berberine:



Corydaldine.
(Fig. A.)



nor-oxyhydrastinine.
(Fig. B)

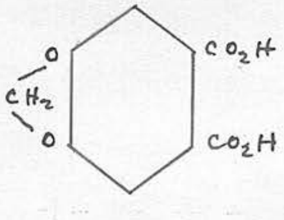


Corydilic Acid.
(Fig. C)

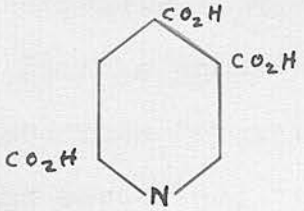
Corydic acid (~~Fig~~ Page 29) would be formed by the destruction of ring I., and corydilic acid (Fig. C) from corydic acid by the oxidation of ring III.

If these formulae are correct, they incidentally prove that Perkin's formula, quoted above, is to be preferred to the alternative formula suggested by him for berberine, in which the carbon atoms 2 and 5 are connected by a double bond, because, on account of the presence of the methyl group in dehydrocorydaline, no double bond is possible between the carbon atoms 2 and 5, and if a double bond existed in berberine in this position the very close resemblance between the two substances would not be satisfactorily explained.

When the decomposition products of berberine are compared with those of corydaline, a close parallelism is observed between them. Both alkaloids yield hemipinic acid as a derivative of ring I. From rings III. and IV. nor-oxyhydrastinine is obtained in the case of berberine, just as corydaldine is obtained from the corresponding rings of corydaline. Ring IV. of berberine yields hydrastic acid:-



the corresponding decomposition product of corydaline being *m*-hemipinic acid. The oxidation product obtained from ring II. is of special interest in the case of both alkaloids. Weidel (Ber., 1879, 12, 410), by oxidising berberine with strong nitric acid, obtained as chief oxidation product berberonic acid:



The same acid has also been obtained from a new derivative of berberine, which is described below. In discussing the constitution of berberine, Perkin does not take into account the occurrence of berberonic acid amongst its decomposition products. It is clear, however, that its occurrence affords important confirmation of the correctness of his formula, since it would result from ring II. by the oxidation of the attached rings I. and III., but could not result from ring III., which would yield cinchomeronic acid. There is thus direct evidence in the case of berberine, as well as in the case of corydaline, of the existence of a fourth closed chain in the molecule of the alkaloid. It is remarkable that both in the case of berberine and of corydaline, Ring II. is the more stable of the rings to which the nitrogen atom is common. From netiher alkaloid has any acid corresponding to ring III. been obtained. A further instance of the comparative ease with which ring III. in corydaline is broken up is afforded by the formation of corydilic acid from corydic acid.

Whilst the formula proposed for corydaline satisfactorily accounts for the similarity between this alkaloid and berberine, it also explains the absence from amongst the decomposition products of corydaline of derivatives corresponding to berberal, $C_{20}H_{17}O_7N$, berberilic acid, $C_{20}H_{19}O_9N$, oxyberberine, $C_{20}H_{17}O_5N$, etc., all of which have an atom of oxygen attached to the carbon atom 2 of ring II. On account of the presence of the methyl group in combination with the corresponding carbon atom in corydaline, it would be impossible for an oxygen atom to occupy this position in similar derivatives of corydaline. On the other hand, the formation of corydic acid from corydaline suggested that it might be possible to obtain a similar acid from berberine, and, as a matter of fact, such an acid is readily produced by the oxidation of berberine with dilute nitric acid.

The new acid is readily obtained by a method similar to that already described for the preparation of corydic acid. Berberine nitrate was dissolved in water and oxidised at the temperature of the water bath with dilute nitric acid (1 in 20). The solution was neutralized with ammonia, the acid precipitated with silver nitrate, and the silver salt subsequently decomposed with sulphuretted hydrogen. The acid was purified by fractional crystallization. In order to completely free it from the tarry matter which always separated during crystallization, it was dissolved in sodium hydrate and precipitated with hydrochloric acid. The details of the preparation and the analyses are given on p. 95. For convenience of reference, this acid has been provisionally named berberidic acid. (Chem. Soc. Trans., 81, (1902), 157).

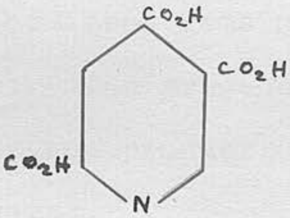
Berberidic acid crystallizes from water in radiating tufts of yellowish-brown prismatic crystals, which contain no water of crystallization. Analysis of the acid led to the formula $C_{16}H_{11}NO_6$. When heated in a capillary tube, it darkens at about 235° and remains without further change, as far as can be seen, until 285°, when it melts with decomposition. It is insoluble in cold, and only very sparingly soluble in boiling water.

Berberidic acid is dibasic. All its salts, with the exception of the two silver salts, appear to be soluble in water. When berberidic acid is heated with concentrated hydrogen iodide solution, no methyl iodide is evolved, a fact which proves that in the formation of this acid the ring of the berberine molecule containing the methoxyl groups is destroyed.

Oxidation of Berberidic Acid with Potassium Permanganate.

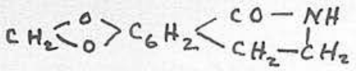
By the oxidation of berberidic acid with permanganate at the boiling temperature, two products were obtained: (see p.99).

1. An acid which agrees in every particular with the Berberonic acid



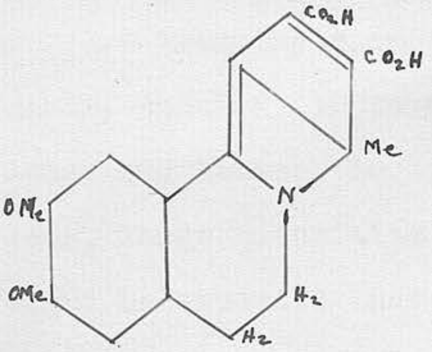
obtained by Weidel (Ber., 1879, 12, 410) by the direct oxidation of berberine with concentrated nitric acid.

2. Nor-oxyhydrastinine

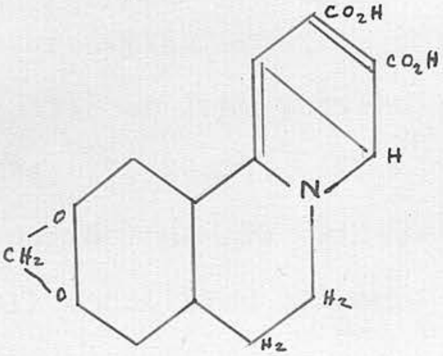


$$CH_2\left\langle{O \atop O}\right\rangle C_6H_2\left\langle{CO-NH \atop CH_2-CH_2}\right.$$

Berberidic acid clearly bears the same relation to berberine that corydic acid bears to dehydrocorydaline as is seen from the following formulae:-



Corydic Acid.



Berberidic Acid.

Since berberidic acid contains no methoxyl groups, it follows that the ring of the berberine molecule which yields hemipinic acid is destroyed in its formation. The occurrence of nor-oxyhydrastinine and berberonic acid amongst its oxidation products proves that it contains the three remaining rings of the berberine molecule. The presence of hydrastic acid amongst the oxidation products of berberidic acid has not been proved.

One further point remains to be dealt with, — the stability of the methyl group in ring II in corydaline. With the exception of the pyridinetetracarboxylic acid (see below), all the oxidation products in which ring II. is present, so far examined, contain this group. This is not remarkable when it is recalled that prolonged treatment with potassium permanganate in alkaline solution is required for the preparation of 2:3:4:6-pyridinetetracarboxylic acid, either from 2:4:6-trimethylquinolinecarboxylic acid (Michael, Annalen, 1884, 225, 121) or from flavinol (Fischer and Tauber, Ber., 1884, 17, 2925). When, however, large quantities of corydaline are oxidised it might be expected that small quantities of a monocarboxylic acid should be obtained. In some of the earlier experiments, in which several hundred grams of corydaline were oxidised with potassium permanganate at the boiling point, a small quantity (about 1.5 grams), of a colourless nitrogenous acid which crystallised in tufts of delicate, silky, needles, and melted sharply at 156° (Trans. 1895, 67, 17) was obtained. A nitrogen determination gave a result agreeing with that required by the formula $C_{21}H_{24}O_4N \cdot CO_2H$ (nitrogen, found 3.55; calculated, 3.50 per cent.). A determination of the methoxyl groups by Zeisel's method showed that the four methoxyl groups present in corydaline were also present in this acid, and the analysis of a silver salt showed that the acid possessed a high molecular weight.

By the oxidation of corydic acid with potassium permanganate at the ordinary temperature (p. 94.), a bright yellow dibasic acid, having the formula $C_{16}H_{17}NO_6$ was obtained. It is more soluble in cold water than corydic acid, and melts at 212-215°. Its exact relation to corydic acid has not yet been determined.

CORYTUBERINE.

The occurrence of this alkaloid amongst the alkaloids of corydalis cava and the method by which it is separated have already been described. (p.6.)

The crude corytuberine is readily purified by recrystallization from alcohol. The alcoholic solution is colourless when freshly prepared, but quickly assumes a pale pink colour, accompanied by a slight fluorescence, which becomes more intense on standing or heating. The green colour and fluorescence of the aqueous extract of corydaline are due apparently to the presence of a decomposition product. The alkaloid is colourless when pure, but on standing, even at the ordinary temperature, gradually becomes somewhat discoloured. On long continued heating at 100°, this change is more pronounced, the alkaloid assuming a slate-grey colour. When the altered substance is dissolved in alcohol, it gives a pink-coloured fluorescent solution, confirming the view that the fluorescence is due to a decomposition product of the alkaloid, and not to the pure substance. The alkaloid has no definite melting point. When heated to 200°, it blackens and slowly decomposes. The alcoholic solution of the pure substance is slightly dextrorotatory.

Analysis of the carefully purified alkaloid led to the formula $C_{19}H_{25}NO_4$. (Chem. Soc. Trans., 1893, 63, 485.) The following salts were also prepared and analysed (p. 104), the results in every case agreeing with those required by the above formula:

Corytuberine hydrochloride, $C_{19}H_{25}NO_4 \cdot HCl$;
Corytuberine sulphate, $(C_{19}H_{25}NO_4)_2 \cdot H_2SO_4$;
Corytuberine platinochloride, $(C_{19}H_{25}NO_4)_2 \cdot H_2PtCl_6$;
Corytuberine methiodide, $C_{19}H_{25}NO_4 \cdot CH_3I$.

ACTION OF HYDROGEN IODIDE ON CORYTUBERINE:

A determination of the methoxyl groups by Zeisel's method (p. 106) showed that two were present. Corytuberine, therefore, contains only two of its oxygen atoms in methoxyl groups, whereas corydaline has all its oxygen atoms present in this state of combination.

Freund and Josephi (Ann., 277, 1) have suggested that corytuberine may be identical with the "corydaline-nobiline" obtained by Birsmann from corydalis nobilis. (Inaug. Diss., Dorpat, 1892). A careful comparison of the results just described, with those of Birsmann, does not bear out this suggestion, the analysis, as well as the properties, of the substance described by him differing considerably from those of corytuberine. As, however, the quantity of material which Birsmann had at his disposal was insufficient for a thorough examination of his alkaloid, it is impossible to institute a perfectly satisfactory comparison between the two substances. If Birsmann was really working with corytuberine, he could hardly have overlooked the powerful fluorescence of its aqueous solution of which he makes no mention.

CORYBULBINE.

The occurrence of this alkaloid amongst the alkaloids of corydalis cava was first mentioned by Freund and Josephi (Ber., 25, 2411; Ann. 277, 1), who described the discovery of an alkaloid melting between 205° - 207° in a sample of crude corydaline obtained from Schuchardt of Görlitz. As the quantity of material at their disposal was, however, very small, they did not do more than make a slight examination of the new alkaloid.

Corybulbine is obtained from Schuchardt's crude corydaline by the following method. After the corydaline has been thoroughly exhausted with boiling water to remove the corytuberine, the residue, which consists of corydaline mixed with a small quantity of corybulbine, is repeatedly exhausted with hot alcohol, which easily removes the corydaline. The crude corybulbine is then dissolved in a large quantity of boiling alcohol, from which it separates, on cooling, in the form of a fine crystalline deposit, leaving the remainder of the corydaline in solution. The corybulbine obtained in this way is collected, dried, and dissolved in hot dilute hydrochloric acid. The acid solution, on cooling, deposits the hydrochloride, which, after recrystallisation, is dissolved in boiling water with the aid of a little hydrochloric acid, and the corybulbine, precipitated from this solution by the addition of ammonia, is finally crystallised from alcohol. This method of preparation affords an excellent means of separating corybulbine from the last traces of corydaline, the hydrochloride of which is much more easily soluble in water than that of the new alkaloid.

Corybulbine may also be prepared from the crude material, after freeing it from corytuberine, by dissolving it in hydrochloric acid, and precipitating the corydaline with excess of a solution of sodium hydroxide; the filtrate from the corydaline, when saturated with carbon dioxide, deposits the corybulbine.

Corybulbine is soluble in boiling alcohol, from which it separates, on cooling, as a fine crystalline powder. It is practically insoluble in water, and nearly so in ether; it is sparingly soluble in boiling methylic alcohol, readily in carbon bisulphide, chloroform, and hot benzene. It is distinguished from corydaline and corytuberine, as well as from the bases described by Freund and Josephi (Annalen, 277, 1) by its greater insolubility in alcohol. An alcoholic solution of the alkaloid rapidly reduces a solution of silver nitrate when heated with it. Corybulbine begins to soften at 210°, but does not melt till heated to 238 - 240°. Freund and Josephi state that the alkaloid softens at about 200°, and decomposes at 207 - 208°, but they sometimes found the melting point some degrees higher. A solution of the alkaloid in chloroform is dextrorotatory.

All the crystals of corybulbine, so far as examined, have been pale yellow in colour. Although repeated crystallization failed to remove the colour, it may possibly be due, as in the case of corydaline, to a slight trace of some decomposition product.

Analysis of the pure alkaloid led to the formula $C_{21}H_{25}NO_4$. (Chem. Soc. Trans., 1895, 67, 25). The following salts were prepared and analysed, the results, in every case, agreeing with the numbers required by the above formula (p.107);

Corybulbine Hydrochloride, $C_{21}H_{25}NO_4$, HCl.
Corybulbine sulphate, $(C_{21}H_{25}NO_4)_2 \cdot H_2SO_4$.
Corybulbine Platinochloride $(C_{21}H_{25}NO_4)_2\ H_2PtCl_6$.
Corybulbine methiodide $C_{21}H_{25}NO_4 \cdot CH_3I$.

A determination of the methoxyl groups by Zeisel's method (p.110), showed that three were present.

A comparison of the formula of corydaline $C_{22}H_{27}NO_4$, with that of corybulbine $C_{21}H_{25}NO_4$, shows that they only differ by CH_2. It will be remembered also, that corydaline contains four methoxyl groups, while corybulbine only contains three. With the object of ascertaining if the fourth oxygenatom in corybulbine is present in an OH group, the action of acetic anhydride on the alkaloid was next tried (Chem. Soc. Trans., 1901, 79, 87.)

Action of Acetic Anhydride on Corybulbine:

Corybulbine was dissolved in a considerable excess of acetic anhydride, and the solution boiled for 4-5 hours under a reflux condenser. The greater part of the acetic anhydride was then distilled off under reduced pressure, and the concentrated solution set to crystallize in a desiccator. The product, which separated as a thick crystalline crust, was crystallized from carefully dried alcohol, from which it separated in tufts of slender, colourless needles melting at 160°. It was dried over sulphuric acid, and, on analysis, proved to be acetyl corybulbine, $C_{18}H_{15}N(OCH_3)_3 \cdot O \cdot C_2H_3O$. For the analysis see p. 111 .

Having regard to the relations already established between the formulae of the two alkaloids, and to the fact that corybulbine contains an hydroxyl group, it appeared probable that the two alkaloids were related to one another in the same manner as morphine, $C_{17}H_{17}ON\,(OH)_2$ and codeine, $C_{17}H_{17}ON\,(OH).OCH_3$, corydaline being the higher homologue of corybulbine.

When corydaline and corybulbine are treated with hydrogen iodide, the methoxyl groups which they contain are replaced by hydroxyl radicles. If corybulbine and corydaline are related to one another in the manner above suggested, the phenolic derivatives yielded by the two alkaloids should be identical. The was found to be the case.

Action of Hydrogen Iodide on Corybulbine:

The corybulbine was boiled with a strong solution of hydrogen iodide under a reflux condenser until all the methyl iodide was expelled, 2 grams of corybulbine and 20 c.c. of hydrogen iodide being used for each operation. The crystalline solid which separated on cooling, was collected by the aid of the pump, well pressed between filter paper, and then recrystallised several times from water. The fine yellow crystals thus obtained were exactly similar in appearance to those of the corresponding substance prepared from corydaline. Both substances behaved in precisely the same way when heated side by side in capillary tubes, melting at about 270° to a clear brown liquid; both dissolve easily in water or alcohol, but only sparingly in ether, and not at all in chloroform. For analysis see p. 111

The relation of the two alkaloids to one another having been this established, the conversion of corybulbine into corydaline by the methods formerly employed in similar cases was next successfully attempted. In 1881, Grimaux converted morphine, $C_{17}H_{17}ON(OH)_2$, into codeine, $C_{17}H_{17}ON(OH)\cdot OCH_3$, by treating it with methyl iodide in presence of potassium hydroxide (Compt. rend., 1881, 92, 1140, 1228; 93, 67, 217) and ten years later, Grimaux and Arnaud converted cupreine, $C_{19}H_{22}N_2(OH)_2$, into quinine, $C_{19}H_{22}N_2(OH)\cdot OCH_3$, by the same method (Compt. rend., 1891, 112, 766, 1364; 1892, 114, 548, 672). By similar treatment, corybulbine is converted without difficulty into corydaline. The yield, however, is much larger than that obtained by Grimaux in the case of quinine. The corydaline formed can be isolated without difficulty, since the solubility of corybulbine in sodium hydroxide affords a means of separating any unchanged corybulbine, and the methiodides of both alkaloids being unstable in hot solution, no complication in effecting the separation is caused by their presence. The corydaline thus prepared, and the salts which have been examined (p. 111), agree in all respects with the natural alkaloid and its corresponding salts.

The corybulbine used for this purpose was purified from traces of corydaline by dissolving in potassium hydroxide, in which corydaline is insoluble, and subsequently precipitating with carbon dioxide. It was afterwards repeatedly recrystallised from alcohol. The purified corybulbine, in quantities of 2.5 grams at each operation, was boiled under a reflux condenser for 15-20 hours with the equivalent quantity of methyl iodide and potassium hydroxide dissolved in methyl alcohol. After cooling, the contents of the flask were filtered. The residue was found to consist almost entirely of unaltered corybulbine, which is very sparingly soluble in cold alcohol. The filtrate, which contained corydaline mixed with a small quantity of corybulbine, was evaporated to dryness and dissolved in dilute hydrochloric acid. The corydaline was then precipitated from the acid solution with excess of potassium hydroxide and afterwards boiled repeatedly with the alkali, to get rid of the last traces of corybulbine. The crude corydaline was washed with water until free from alkali, and recrystallised repeatedly from alcohol. Under these conditions it was found that from 25 to 30 per cent. of the corybulbine was converted into corydaline. For analyses see p. 111.

The corydaline thus obtained was carefully compared with the natural alkaloid. Specimens of the two were heated side by side in capillary tubes, and were found to behave in exactly the same way, both of them melting at 135°. The solubilities of the two substances in alcohol, ether, chloroform, benzene, or carbon disulphide were compared, but no difference could be detected between them.

The specific rotatory power was determined with the following result:

d 20°/4°, 0.7961; c, 0.7251; 1, 2 dcm.;

$a^{20^\circ}_{D}$ 4.60°; $[\alpha]^{20^\circ}_{D}$ + 317°.1

Two determinations of the specific rotatory power of the natural alkaloid gave $[\alpha]^{20^\circ}_{D} = +311^\circ$ and + 309.5°. ~~and 309.5°~~ (Trans., 1895, 67, 17).

The position of the hydroxyl group in corybulbine has not yet been definitely ascertained, but the evidence, so far as it goes, points to its presence in the isoquinoline nucleus. It will be remembered that when corydaline is oxidised with nitric acid, it readily yields corydic acid, $C_{14}H_9N(OCH_3)_2(CO_2H)_2$, $\frac{1}{2}H_2O$, which contains an isoquinoline nucleus. This acid, on further oxidation, yields, amongst other products, metahemipinic acid, $(CO_2H)_2:(OCH_3)_2 = 1:2:4:5)$, but no hemipinic acid $(CO_2H)_2:(OCH_3)_2 = 1:2:3:4$). Since corydaline on oxidation yields both hemipinic and metahemipinic acids, the benzene ring from which the former acid is derived must be the ring which is destroyed by the oxidation with nitric acid. If the hydroxyl group of corybulbine occurred in this ring, we should expect to obtain corydic acid on oxidising the alkaloid with nitric acid. All attempts, however to obtain this acid from corybulbine have hitherto failed.

EXPERIMENTAL.

Preparation of pure Corydaline:

As already mentioned in the Introduction, the corydaline used in this investigation was obtained form Schuchardt of Görlitz. It was prepared by him from the dried roots of Corydalis cava, gathered partly in the Tyrol and partly in Thuringia. The various samples were purified and analysed separately with the view of establishing definitely the identity of the alkaloid obtained from different sources.

The details of the method by which Schuchardt obtains the alkaloid from the roots are, of course, not known. Ehrenberg, however, (Ann. Chem. Pharm., 277, (1893), 19.) describes the following method of extraction. The finely divided roots are first extracted with alcohol. The extract is reduced to small bulk by distilling off the alcohol, weakly acidified, and filtered from resin. The filtrate, after being made alkaline with ammonia, is repeatedly extracted with ether. When the greater part of the ether has been distilled off, a fraction crystallizes out, which melts about 160°; this consists of about 60% bulbocapnine, 30% corydaline, and 10% corycavine. The ethereal mother liquor was again concentrated and the residue taken up with alcohol. From this solution a fraction melting between 126° and 130° is obtained, which consists of about equal parts of corydaline and bulbocapnine. From the last mother liquor an amorphous mass melting between 50° and 60° separates out, which is supposed to be identical with the alkaloid isolated by Merck and named corydine (Freund and Josephi, Ann. Chem. Pharm., 277 (1893), 19.)

To separate the corydaline from the first two fractions described above, Freund and Josephi employed the following method. The mixed alkaloids are dissolved in dilute hydrochloric acid and the solution shaken up with a 5% solution of sodium hydrate. In this way the corydaline and corycavine are precipitated, while the bulbocapnine (and any corybulbine present), remain in solution. From the alkaline solution the bulbocapnine can be precipitated by saturating with carbon dioxide, or by the addition of ammonium chloride. The mixture of corydaline and corycavine is separated by fractional crystallization from absolute alcohol in which the corydaline is less soluble than the corycavine. By converting the corycavine into the hydrochloride, it can be separated from the last traces of corydaline, the hydrochloride of which is extremely soluble in water. From 10 kilos. of the corydalis roots Ziegenbein (Inaug. Diss., Marburg, 1896.) obtained 57 grams corydaline, 41 grams bulbocapnine, 6 grams corycavine, and 4 grams corybulbine. From the same weight of roots, Martindale (Inaug. Diss., Marburg, 1898) obtained 90 grams corydaline.

After much investigation, the following procedure was found to give the most satisfactory results. The crude material obtained from Schuchardt was first thoroughly extracted by boiling up with large quantities of water and filtering, until a practically colourless filtrate was obtained. The filtrate, which was green in colour and possessed a magnificent blue fluorescence, deposited tufts of small slender needles on cooling. When collected on a filter, the crystals form a compact film with a metallic lustre, recalling that of freshly cut potassium. On investigation, this substance proved to be a hitherto undiscovered alkaloid to which the name corytuberine was given from Corydalis tuberosa, a synonym for corydalis cava (Dec.) (See p. 102) The residue, from which the corytuberine has been removed, is next repeatedly extracted with hot alcohol which dissolves the corydaline and leaves behind a residue consisting largely of corybulbine. The alcoholic solution, on cooling, deposited the alkaloid in large flat prismatic crystals which are colourless when quite pure. The corydaline was purified by repeated recrystallization from alcohol until the melting point was constant. As the alkaloid, both in the solid state and in solution, is very readily acted on by light with the formation of a yellow oxidation product, care was taken to keep it in the dark as much as possible.

After the final crystallization the crystals were collected with the aid of a filter pump and repeatedly washed with small quantities of alcohol. This treatment removed the last traces of the yellow colouring matter which is much more soluble in alcohol than corydaline.

Pure corydaline crystallizes in large flat prismatic crystals which sometimes measure an eighth of an inch in length. On heating corydaline, it changes colour about 125°, softens about 133° and finally melts at 134°.5. No difference was detected in the melting point of the various specimens examined when the determinations were made under similar conditions.

corydaline dissolves easily in alcohol, ether, chloroform, carbon bisulphide and benzene. It also dissolves in oil of turpentine, yielding a yellow solution. From a pure alcoholic solution, water precipitates it in the crystalline form. It is soluble in dilute hydrochloric and sulphuric acids. On warming with dilute nitric acid, a sparingly soluble nitrate is first formed. On further heating, oxidation takes place with the evolution of nitrous fumes and the formation of a dark orange red solution. (See p. 17).

The analysis of the pure alkaloid, prepared as above described, and dried in the dark over sulphuric acid, gave the following results:-

I.	0.2389	grams	gave	0.1700	H_2O	and	0.6245	CO_2	H = 7.90%	C = 71.29%	(A)
II.	0.2332	"	"	0.1656	"	"	0.6119	"	H = 7.88"	C = 71.54"	(A)
III.	0.2504	"	"	0.1740	"	"	0.6569	"	H = 7.72"	C = 71.54"	(B)
IV.	0.2413	"	"	0.1660	"	"	------		H = 7.65"	C = ------	(B)
V.	0.2080	"	"	------	"	"	0.5433	"	H = -----	C = 71.21"	(C)
VI.	0.2374	"	"	0.1639	"	"	0.6207	"	H = 7.67"	C = 71.31"	(D)
VII.	0.4396	"	"	0.1156	gram	Pt.			N = 3.84"		(A)
VIII.	0.4549	"	"	0.1214	"	"			N = 3.85"		(B)
IX.	0.4558	"	"	0.1230	"	"			N = 3.89"		(B)
X.	0.4188	"	"	0.1206	"	"			N = 3.68"		(B)
XI.	0.3802	"	"	0.1012	"	"			N = 3.83"		(C)
XII.	0.4559	"	"	0.1212	"	"			N = 3.83"		(D)

(<u>NOTE</u>:- The letters A, B,&c refer to the samples analysed.)

The mean of these numbers is:-

Carbon	71.37%
Hydrogen	7.76%
Nitrogen	3.82%

from which the formula $C_{22}H_{27}NO_4$ is deduced.

	Found.	Theory for $C_{22}H_{27}NO_4$.
Carbon	71.37%	71.48%
Hydrogen	7.76%	7.38
Nitrogen	3.82%	3.80
Oxygen	17.05%	17.34
	100.00	100.00

Wicke's formula, $C_{18}H_{19}NO_4$, the one hitherto adopted, requires the following numbers:-

Carbon	69.00%
Hydrogen	6.07%
Nitrogen	4.47%
Oxygen	20.46%
	100.00

Corydaline forms a large number of salts and derivatives, most of which can be prepared without difficulty. The hydrochloride and sulphate are difficult to crystallize on account of the tendency of their solutions to become gummy.

CORYDALINE HYDRIODIDE:

This salt is very easily prepared by adding a solution of potassium iodide to a solution of the hydrochloride in water. The hydriodide separates out in pale yellow flocks which redissolve readily in hot water and crystallize out on cooling, in clusters of lemon yellow, short, prismatic crystals. The specimen analysed was purified by repeated recrystallization from water and dried at 100°. The following results were obtained:-

I. 0.3017 gave 0.1590 H_2O and 0.5896 CO_2
H = 5.85% C = 53.29%.

II. 0.3098 gave 0.1625 H_2O and 0.6052 CO_2
H = 5.82% C = 53.28%.

III. 0.4832 gave 0.0924 Pt. N = 2.75%.

IV. 0.3907 gave 0.0750 Pt. N = 2.76%.

V. 0.4799 gave 0.2279 Ag I I = 25.65%.

VI. 0.4718 gave 0.2232 Ag I I = 25.34%.

	Found. (Mean of above analyses)	Theory for $C_{22}H_{27}NO_4$ HI.
C =	53.28%	53.10%
H =	5.83%	5.68%
N =	2.75%	2.81%
I =	25.49%	25.50%
O =	12.65%	12.91%
	100.00	100.00

CORYDALINE HYDROBROMIDE:

This salt is easily obtained by adding potassium bromide to a solution of the hydrochloride in water. Like the corresponding hydriodide, it is pale yellow in colour. It is almost soluble in cold, but dissolves readily in hot water, from which it separates on cooling, in crystals resembling those of the hydriodide. Analysis of this salt, dried at 100°, gave the following results:-

I. 0.3988 gave 0.1658 Ag Br. Br = 17.68%
II. 0.3912 " 0.1642 " " Br = 17.74%

Found. (Mean of above numbers.)	Theory for $C_{22}H_{27}NO_4HBr$.
Br = 17.71%	17.76%

CORYDALINE ETHYL SULPHATE:

This compound is easily prepared in a state of purity, and, unlike the other salts of corydaline which are soluble in water, crystallizes from its aqueous solution without difficulty. It can be obtained as a white crystalline precipitate by mixing solutions of sodium ethyl sulphate and corydaline sulphate. It is, however, most easily prepared by adding sulphuric acid to an alcoholic solution of corydaline, evaporating to a syrupy consistency, and adding water, when the solution immediately sets to a crystalline mass. When this is dissolved in hot water and the solution allowed to cool slowly, beautiful, large colourless prismatic crystals containing 1 mol. H_2O separate out. Corydaline ethyl sulphate dissolves easily in hot water, alcohol, and chloroform, but is only very sparingly soluble in cold water and is insoluble in ether. The crystals melt at 152.5° to a clear yellow liquid. The addition of ammonia or potassium hydrate to their aqueous solution precipitates the corydaline. This salt is very stable and it is only after long continued boiling of its aqueous solution, that any precipitate of barium sulphate is obtained on the addition of barium chloride. When dried over sulphuric acid in a vacuum, it gave the following results on analysis:-

I. 0.2912 gave 0.1859 H_2O and 0.6014 CO_2.
H = 7.09% C = 56.32%.

II. 0.3025 gave 0.1866 H_2O and 0.6200 CO_2.
H = 6.85% C = 55.89%.

III. 0.4656 gave 0.0895 Pt. N = 2.77%.

IV. 0.4579 gave 0.0881 " N = 2.77%.

V. 0.4036 gave 0.1968 $BaSO_4$ S = 6.69%.

VI. 0.4294 gave 0.2100 " S = 6.72%.

	Found. (Mean of above Analyses.)	Theory for $C_{22}H_{27}NO_4 \cdot C_2H_5HSO_4 \cdot + H_2O$.
C	= 56.10%	56.10%
H	= 6.97 "	6.88 "
N	= 2.77 "	2.72 "
S	= 6.70 "	6.23 "
O	= 27.46 "	28.07 "
	100.00	100.00

The salt loses its water of crystallization when dried at 100°.

I. 0.5906 lost 0.0213 H_2O. $H_2O = 3.60\%$

II. 0.2705 " 0.0091 " $H_2O = 3.36\%$.

Found. (Mean of above numbers.)	Theory for $C_{22}H_{27}NO_4 \cdot C_2H_5HSO_4, H_2O$.
$H_2O = 3.48\%$.	3.50%

The corydaline in the salt was determined by precipitation with ammonia:-

I. 0.2752 gram of the salt, dried at 100°, gave 0.2050 gram corydaline.

II. 0.4030 gram of the salt, dried over sulphuric acid in a vacuum, gave 0.2859 gram corydaline.

		Found.	Theory.
I.	Corydaline	= 74.49%	74.55%
II.	"	= 70.94%	71.95%

CORYDALINE PLATINOCHLORIDE:

This salt is prepared in the pure state, suitable for exact analysis, by adding a solution of chloroplatinic acid, prepared by the action of chlorine and strong hydrochloric acid on pure spongy platinum, to a solution of pure corydaline in dilute hydrochloric acid. It has a pale buff yellow colour, which deepens to orange-red on continued heating in the water bath at 100°. It is soluble in hot water from which it separates on cooling in brown crystals. The sample used for analysis, after precipitation, was washed with cold water until the washings were free from acid. The following are the results of the analysis of the salt dried at 100°.

I. 0.2855 gave 0.1344 H_2O and 0.4853 CO_2.
H = 5.23% C = 46.35%.

II. 0.4332 gave 0.0795 Pt. N = 2.64%.
III. 0.4112 " 0.0739 " N = 2.58 "
IV. 0.2843 " 0.2084 Ag Cl CL = 18.12%
V. 0.2368 " 0.1769 " " = 18.45 "
VI. 0.2433 " 0.0414 Pt. Pt = 17.01 "
VII. 0.2919 " 0.0498 " " = 17.06 "
VIII. 0.2755 " 0.0465 " " = 16.84 "
IX. 0.3035 " 0.0511 " " = 16.83 "

Found. (Mean of above analyses.)		Theory for $(C_{22}H_{24}NO_4)_2\ H_2PtCl_6$.
C	= 46.35 %	46.00 %
H	= 5.23 "	4.93 "
N	= 2.61 "	2.45 "
Pt.	= 16.93 "	16.97 "
Cl.	= 18.28 "	18.54 "

CORYDALINE METHIODIDE:

This compound is obtained by dissolving corydaline in methyl iodide. The excess of methyl iodide employed must be removed by evaporation at the ordinary temperature, since distillation under the ordinary atmospheric pressure invariably decomposes the compound. Corydaline methiodide dissolves in absolute alcohol, from which it crystallizes in radiating tufts of pure white, needle shaped crystals. Analysis of this derivative dried at 100°, yielded the following results:-

I. 0.2777 gave 0.1486 H_2O and 0.5441 CO_2.
H = 5.95%; C = 53.43%.

II. 0.4427 gave 0.0827 Pt. N = 2.91 %

III. 0.4368 " 0.0881 " " = 2.89 "

IV. 0.4121 " 0.1892 Ag I I = 24.79 %

V. 0.4960 " 0.2261 " " = 24.63 "

Found. (Mean of above analyses.)	Theory for $C_{22}H_{27}NO_4 \cdot CH_3I$.
C = 53.43 %	53.99 %
H = 5.95 "	5.92 "
N = 2.90 "	2.75 "
I = 24.71 "	24.82 "

The compound with allyl iodide was prepared in the same way as the methyl derivative. Like the methyl compound, it dissolves easily in absolute alcohol, from which it crystallizes in beautiful prismatic crystals of a brown colour.

ACTION OF HYDROGEN IODIDE ON CORYDALINE.

Five grams of corydaline were boiled in a flask with 160 cc. of fuming hydrogen iodide, for several hours, using a reflux condenser which was kept at a temperature of 40-50°. The escaping vapours, after passing successively through the reflux condenser, and through potash bulbs filled with red phosphorus suspended in water and heated to 59-60°, were condensed and received in a flask surrounded with cold water. During the experiment a steady current of carbon dioxide was passed through the apparatus. The distillate was recognised as methyl iodide by its characteristic odour and by its boiling point (43°). The solution remaining in the distilling flask at the end of the operation, on cooling, deposited a yellow crystalline substance. After decanting off the excess of hydrogen iodide, the precipitate was slightly washed with cold, and dissolved in hot water, from which, on evaporation, it crystallized in clusters of yellow prisms. The purification of this salt caused much trouble on account of the difficulty of separating the last traces of iodine set free by the decomposition of the hydrogen iodide. The addition of sulphurous acid invariably caused decomposition. Eventually, the salt was obtained in a state of purity by repeatedly recrystallizing it from water and pressing the crystals between filter paper. It dissolves easily in water and in alcohol, less easily in ether, and melts with decomposition between 270° and 280°. Its aqueous solution gives a reddish precipitate with ammonia and potassium hydrate, which dissolves in excess of either reagent. Analyses of the salt, dried at 100° gave the following results:-

I. 0.2314 gave 0.0983 H_2O and 0.4158 CO_2.
H = 4.72 %; C = 49.00%.

II. 0.2401 gave 0.1011 H_2O and 0.4307 CO_2.
H = 4.68 %; C = 48.92%.

III. 0.3180 gave 0.0705 Pt. N = 3.20 %.
IV. 0.3376 " 0.0747 " N = 3.19 "
V. 0.3681 " 0.1962 AgI I = 28.79 %
VI. 0.3608 " 0.1913 " I = 28.65 "

	Found. (Mean of above analyses.)	Theory for $C_{18}H_{15}(OH)_4N.\ HI$
C	= 48.96 %	48.99 %
H	= 4.70 "	4.54 "
N	= 3.20 "	3.24 "
I	= 28.72 "	28.78 "
P	= 14.42 "	14.45 "
	100.00	100.00

(5)

This salt is, therefore, the iodhydride of a base derived from corydaline by the substitution of four atoms of hydrogen for four methyl groups, and bears the same relation to corydaline that papaveroline and berberoline bear to papaverine and berberine respectively. If the same system of nomenclature ~~is~~ was observed, this base would be termed corydaloline. The free base has not yet been obtained in a form suitable for analysis. It can be separated from the iodhydride by the cautious addition of dilute ammonia or of potassium hydrate. It dissolves in alcohol, forming a blood red solution, but it is insoluble in water and all the ordinary solvents. Its solution rapidly reduces silver salts in the cold, and, on evaporation, leaves a gummy residue which shows no tendency to crystallize.

The above formula for the base was confirmed by the direct determination of the number of methoxyl groups present in corydaline by Zeisel's method. (Ber., 19, 143.)

I. 0.2539 gave 0.6338 AgI CH_3O = 32.96 %.
II. 0.2920 " 0.7230 " " = 32.70 "
III. 0.2519 " 0.6320 " " = 33.13 "

Found. (Mean of above numbers.)	Theory for $4(CH_3O)$ in $C_{22}H_{27}NO_4$.
CH_3O = 32.93%	33.58%.

OXIDATION OF CORYDALINE WITH POTASSIUM PERMANGANATE:

The oxidation with permanganate is best carried out with small quantities of corydaline at a time, about 8 grams of the alkaloid being used in each operation. The alkaloid is suspended in about two litres of boiling water and a solution of permanganate added until it is no longer reduced, the liquid in which the alkaloid is suspended being kept at the boiling temperature all the time. The amount of permanganate required is about 27 grams dissolved in 2-3 litres of water. Any excess of permanganate, at the end of the oxidation, is reduced by the addition of a few drops of alcohol. The oxidation usually occupies three hours. The reduction of the permanganate is very rapid at first, ammonia in small quantity being continuously evolved, but, after about three-fourths of the permanganate solution has been added, the oxidation proceeds very slowly. The corydaline employed was carefully purified by repeated crystallization until the melting point was constant.

When the oxidation is complete, the manganese precipitate is allowed to settle, the solution filtered off, and the precipitate thoroughly washed

/ boiling water, until the washings are no longer alkaline to litmus paper. The filtrate is next evaporated to dryness, and the organic matter extracted with absolute alcohol; the bulk of the alcohol is then distilled off, the concentrated solution cautiously evaporated to dryness, and the residue dissolved in water. / with

The separation of the various products of oxidation, proved, for a time, a matter of considerable difficulty, until some clue was got as to the nature of the substances present. Hemipinic acid was the first of the oxidation products to be recognised and separated. At the same time, a sparingly soluble acid ammonium salt of *m*-hemipinic acid was discovered, but not identified until some time later. Corydaldine was obtained from the mother liquors from which these two acids had been removed.

The discovery of *m*-hemipinic acid amongst the oxidation products of corydic acid, suggested that it was probably also produced by the direct oxidation of corydaline with potassium permanganate. Once its presence amongst the oxidation products was suspected, its separation from hemipinic acid was accomplished without difficulty.

After trying various methods of separation, such as exact neutralization of the potash in the solution with sulphuric acid, and subsequent precipitation of the potassium sulphate with absolute alcohol, the following method was finally adopted as giving the most satisfactory results.

The solution obtained as described above was next neutralized and completely precipitated with lead acetate. The lead precipitate was filtered off, thoroughly washed with water and decomposed with sulphuretted hydrogen. The lead sulphide was filtered off, and the filtrate concentrated by evaporation. On standing, a crop of crystals was slowly deposited, which were filtered off and eventually separated into the following fractions by fractional crystallization:

1. A small quantity of slender yellow silky needles, which were sparingly soluble in water and melted at 221-222°.
2. A fraction melting about 199° (*m*-Hemipinic Acid.)
3. A fraction melting about 181° (Hemipinic Acid.)
4. A small quantity of a nitrogenous acid, very soluble in water, which crystallized in tufts of delicate silky needles and melted sharply at 175°.

SEPARATION AND IDENTIFICATION OF THE HEMIPINIC ACIDS:

The following table shows the properties of the two acids which were relied upon for their separation and identification:

	Hemipinic Acid.	Metahemipinic Acid.
M. p. in open capillary tube.	181°.	199°.
Solubility in water	Moderately soluble.	Much less soluble.*
Reaction of a 1 per cent. solution:		
1. with ferric chloride	Orange yellow ppt.	Cinnibar orange ppt.
2. with dilute solution of silver nitrate	No precipitate.	White crystalline ppt.
M. p. of ethylimide	92°.	228°.
Solubility of ethylimide in methylic alcohol	Very easily soluble.	Sparingly soluble.

* One part of metahemipinic acid requires for solution 130 parts water at 16.5°. The solubility of hemipinic acid is about twice that of metahemipinic acid at the same temperature.

Once the presence of both hemipinic and *m*-hemipinic acids had been ascertained, their separation by fractional crystallization was easily effected. The separation may also be effected by one or other of the following methods which were found useful for freeing one acid from traces of the other: (a) precipitation with silver nitrate in dilute solution, which throws down *m*-hemipinic acid but not hemipinic acid; (b) conversion into ethylimides and treatment with methyl alcohol in which the ethylimide of hemipinic acid is very easily soluble, whilst that of *m*-hemipinic acid is only sparingly so. When a weighed quantity of *m*-hemipinic acid is neutralized with ammonia, and a solution containing an equal weight of the acid is added, a sparingly soluble salt is obtained; the salt of hemipinic acid prepared in the same way is, at least, twenty times more soluble,and advantage can also be taken of this difference in solubility to effect the separation of the acids. The occurrence of this salt amongst the products of oxidation has already been referred to.

Of the four fractions described above, (1) and (4) were obtained in such small quantity that only a slight examination of their properties was possible.

FRACTION (2) (m-Hemipinic Acid.)

This fraction crystallized from concentrated solution in beautiful, colourless prisms which contained no water of crystallization, and in an open capillary tube melted at 189-190°. The acid was dried at 100° for analysis.

0.2530 gave 0.4900 CO_2 and 0.1017 H_2O

$C = 52.82\%$; $H = 4.46\%$.

$C_{10}H_{10}O_6$ requires $C = 53.90\%$; $H = 4.42\%$.

The methoxyl groups were determined by Zeisel's method:

0.2420 gave 0.4841 Agl. $OCH_3 = 26.42\%$.

$C_6H_2(OCH_3)_2\ (CO_2H)_2$ requires $OCH_3 = 27.43\%$.

SILVER SALTS:

The normal silver salt was prepared by neutralizing the acid with potassium hydrate, and precipitating with silver nitrate. It was dried at 100° for analysis.

I. 0.3910 gave 0.1920 Ag. Ag = 49.10 %

II. 0.3412 " 0.1678 " Ag = 49.12 "

$C_{10}H_8O_6Ag_2$ requires Ag = 49.09%.

The acid silver salt was obtained by adding silver nitrate to a concentrated aqueous solution of the acid, care being taken not to add an excess of silver. The precipitate obtained is gelatinous in appearance, but in reality consists of a thick mass of very delicate short needles. The salt was dried at 100° and analysed.

I. 0.2130 gave 0.0693 Ag. Ag = 32.53 %

II. 0.2457 " 0.0802 " Ag = 32.64 "

$C_{10}H_9O_6Ag$ requires ...... Ag = 32.44 "

BARIUM SALT:

The normal salt was prepared by adding a solution of the acid, neutralized with ammonia, to a solution of barium chloride, so as to have the latter always in excess. The solution at first remains perfectly clear, but, on gently heating, crystallization begins simultaneously at a great many different points, and the liquid appears to fill suddenly with a mass of fine crystals which slowly subside to the bottom of the beaker. This salt is appreciably soluble in cold water and contains no water of crystallization. It was dried at 100° for analysis.

I. 0.3320 gave 0.2152 $BaSO_4$. Ba = 38.12 %

II. 0.2396 " 0.1551 " Ba = 38.07 "

$C_{10}H_8O_6Ba$ requires ...... Ba = 38.13 "

POTASSIUM SALT:

The acid potassium salt was prepared by neutralizing an aqueous solution of the acid with potassium hydroxide, and evaporating to dryness. The residue was dissolved in water and recrystallized several times. It crystallizes in tufts of beautiful silky needles.

I. 0.1427 gave 0.0459 K SO_4. K = 14.44 %

II. 0.1043 " 0.0336 " K = 14.46 "

$C_{10}H_9O_6K$ requires ...... K = 14.77 "

LEAD SALT:

The normal lead salt was prepared by precipitating the acid, after neutralising with ammonia, with excess of lead acetate solution. A white gelatinous precipitate immediately formed, which became distinctly crystalline on standing, and, when collected, aggregated on the filter paper as a compact film possessing a magnificent silvery lustre. It contains no water of crystallization and is only slightly soluble in water. It was dried at 100° for analysis.

I. 0.2328 gave 0.1638 $PbSO_4$. Pb = 48.01 %

II. 0.3539 " 0.2486 " Pb = 47.97 "

$C_{10}H_8O_6Pb$ requires Pb = 48.03%.

As the melting points of the ethylimides of hemipinic and *m*-hemipinic acids differ by more than 130°, this derivative affords an excellent means of distinguishing between the two acids. The ethylimide was therefore prepared by the method given by Liebermann (Ber., 1886, 19, 2275). One gram of the pure acid was dissolved in an aqueous solution of ethylamine, evaporated to dryness, the residue heated over the naked flame, and then exhausted with boiling methyl alcohol. On concentration of the alcoholic solution, the ethylimide separated out. It was purified by repeated recrystallization from hot methyl alcohol, in which it is sparingly soluble. It melted sharply at 227°, and after drying at 100° gave the following numbers on analysis:

I. 0.2262 gave 0.5072 CO and 0.1157 H O
C = 61.14%; H = 5.67%.

II. 0.2805 gave 14.5 cc. nitrogen at 15° and 761 mm.
N = 6.16%.

$C_{10}H_8O_4 : NC_2H_5$ requires C = 61.28; H = 5.53;
N = 5.96%.

The acid, therefore, is *m*-hemipinic acid, and is identical with the hemipinic acid obtained by

Goldschmidt and Ostersetzer (Monatsh., 1888, 9, 762), from papaverine.

FRACTION (3) (Hemipinic Acid.)

This fraction melted between 170° and 180°. It was further purified by reprecipitation with lead acetate, and subsequent decomposition of the lead salt with sulphuretted hydrogen. The crystals, which were free from nitrogen, were dried at 100° and analysed.

I. 0.2862 gave 0.5552 CO_2 and 0.1235 H_2O.
C = 52.91; H = 4.79%.

II. 0.2285 gave 0.4402 CO_2 and 0.0932 H_2O.
C = 52.54; H = 4.53%.

$C_{10}H_{10}O_6$ requires C = 53.09; H = 4.42%.

SILVER SALT:

The normal silver salt was prepared by neutralizing the aqueous solution of the acid with ammonia, and precipitating with silver nitrate. It was dried at 100° for analysis.

I. 0.2551 gave 0.1251 Ag. Ag = 48.93%
II. 0.2765 " 0.1354 " Ag = 48.96 "
$C_{10}H_8O_6Ag_2$ requires ...... Ag = 49.09 "

The methoxyl groups were determined by Zeisel's method.

I. 0.2439 gave 0.4591 AgI. $OCH_3 = 26.80\%$.

Theory for two methoxyl groups in $C_{10}H_{10}O_6$ requires

27.43% OCH_3.

These results prove that this is one of the varieties of hemipinic acid.

The anhydride was prepared by heating 1 gram of the acid for about an hour at 200° and dissolving the residue in glacial acetic acid, from which the anhydride crystallizes in delicate colourless needles, melting sharply at 166-167°. The solution of the anhydride in acetic acid, especially when dilute, shows a beautiful blue fluorescence. It was dried at 100° for analysis.

I. 0.1149 gave 0.2439 CO_2 and 0.0412 H_2O.
$C = 57.88\%$; $H = 3.98\%$.

$C_{10}H_8O_5$ requires $C = 57.69$; $H = 3.83\%$.

The ethylimides was prepared by the method already described (p.79). It crystallized in beautiful long needle shaped crystals melting at 92°. The melting point given by Liebermann (loc. cit.) for the ethylimide of hemipinic acid is 96°. It was dired over sulphuric acid for analysis.

I. 0.2255 gave 0.5062 CO_2 and 0.1152 H_2O.
$C = 61.22\%$; $H = 5.69\%$.
$C_{10}H_8O_4 : NC_2H_5$ requires $C = 61.28\%$; $H = 5.53\%$.

CORYDALDINE:

The excess of lead was removed from the solution from which the hemipinic and *m*-hemipinic acids had been precipitated with lead acetate, by passing in sulphuretted hydrogen until the solution was saturated. The lead sulphide was filtered off, and the filtrate evaporated to small bulk and placed in an exhausted desiccator over sulphuric acid. After the lapse of several days, a crop of minute, colourless crystals was deposited. They were separated from the thick gummy mother liquor by means of the filter pump, and recrystallized several times from water or alcohol in both of which they are freely soluble. The crystals, which sometimes attain a considerable size (1/8 of an inch), have the appearance, when properly developed, of oblique prisms. They contain no water of crystallization and melt sharply at 175°. Their aqueous solution is neutral to test paper. For analysis it was dried at 100°.

I. 0.2394 gave 0.5549 CO_2 and 0.1393 H_2O.
C = 63.21; H = 6.46%.
II. 0.2480 gave 0.5753 CO_2 and 0.1509 H_2O.
C = 63.27; H = 6.76%.
III. 0.2844 gave 0.1361 Pt. N = 6.90%.
IV. 0.2936 " 0.1373 Pt. N = 6.74%.

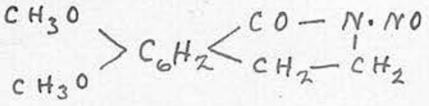
The mean of above numbers is
C = 63.24; H = 6.61; N = 6.82%,

from which the formula $C_{11}H_{13}NO_3$ is deduced. This requires C = 63.76; H = 6.28; N = 6.76%. The methoxyl groups were determined by Zeisel's method.

I. 0.2326 gave 0.5210 AgI. OCH_3 = 29.57%.
II. 0.2103 " 0.4714 AgI. OCH_3 = 29.59%.
Theory for two OCH_3 groups in $C_{11}H_{13}NO_3$ = 29.95% OCH_3.

As the yield of corydaldine by oxidation of corydaline with potassium permanganate at the boiling temperature was very small, various modifications of the method were tried with the view of increasing the yield.

After numerous experiments had been made, the following method was found to give the most satisfactory results: 10 grams of finely powdered corydaline were suspended in about 1 litre of water, and 18 grams of potassium permanganate, dissolved in about half a litre of water, were gradually added in small quantities at a time. The operation was conducted at the ordinary temperature, and required about 48 hours for completion. The precipitated manganese oxide, which was mixed with a considerable quantity of a colourless, crystalline substance, was removed by filtration, and the solution concentrated by evaporation. During concentration, a quantity of yellow, crystalline matter separated out. After filtration, the liquid was repeatedly extracted with chloroform until this was no longer coloured; the chloroform was then evaporated in a current of air at the ordinary temperature, and the residue, which was gummy in character, was thoroughly extracted with cold water. The aqueous extract, on concentration, yielded a crop of large, well-developed, prismatic crystals of corydaldine.. By this method, the yield of corydaldine was 4-5 grams from 100 grams of corydaline. The substance obtained in this way melts at 175°; it is very easily soluble in chloroform, easily soluble in water, alcohol, ether, benzene, and acetic acid, but is insoluble in light petroleum.



$$\begin{array}{l}CH_3O \\ \\ CH_3O\end{array}\!\!>C_6H_2<\!\!\begin{array}{l}CO-N\cdot NO \\ \qquad\quad\;\, | \\ CH_2-CH_2\end{array}$$

Nitroso-derivative.

The nitroso-derivative was easily obtained by the following method: 3 grams of the finely powdered corydaldine were dissolved in 100 cc. of hydrochloric acid of sp. gr. 1.1 by gently warming on the water-bath. The solution, after being diluted by the addition of 75 cc. of water, was cooled to 0° in a freezing mixture of ice and salt, and 15 cc. of a 10 per cent. solution of sodium nitrite were added drop by drop, the temperature being kept at 0° during the reaction. After a short time, the nitroso-derivative separated in yellow flocks. It was collected by the aid of a pump, well washed with water, and purified by crystallisation from alchol.

The nitroso-derivative is a yellow, crystalline substance which melts at 185°. It is easily soluble in hot alcohol, from which it crystallises in beautiful, yellow needles; it is also easily soluble in cold chloroform, and soluble in benzene or carbon bisulphide, but only sparingly so in boiling water or in ether, and insoluble in light petroelum. The nitroso-derivative is insoluble in cold alkali, bus is decomposed on gently heating, with evolution of nitrogen. When treated with phenol and sulphuric acid, it gives Liebermann's nitroso-reaction, the red colour which is at first produced changing to a beautiful blue on the addition of excess of dilute alkali.

On analysis, the pure substance, dried at 100°, gave the following results:-

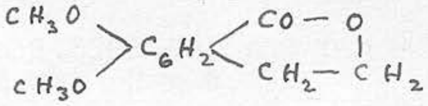
I. 0.2417 gave 0.500~~3~~2 CO_2 and 0.1122 H_2O. l2
C = 56.44; H = 5.15.

II. 0.2687 gave 0.5547 CO_2 and 0.1271 H_2O.
C = 56.30; H = 5.25.

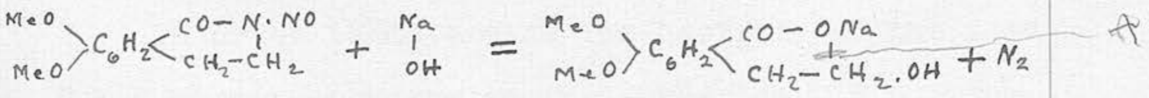
III. 0.2372 gave 23.2 cc. nitrogen at 12° and 761.5 mm. N = 11.78.

$C_{11}H_{12}N_2O_4$ requires C = 55.93; H = 5.08; N = 11.86%.

Preparation & Properties of the Anhydride,



When the nitroso-derivative is heated on the water-bath with a dilute solution of caustic soda, it goes into solution, nitrogen being evolved. The reaction that occurs may be represented as follows:



$$\begin{matrix}MeO\\MeO\end{matrix}\!\!>C_6H_2<\!\!\begin{matrix}CO-N\cdot NO\\|\\CH_2-CH_2\end{matrix} + \begin{matrix}Na\\|\\OH\end{matrix} = \begin{matrix}MeO\\MeO\end{matrix}\!\!>C_6H_2<\!\!\begin{matrix}CO-ONa\\CH_2-CH_2.OH\end{matrix} + N_2$$

On acidifying the filtered solution with hydrochloric acid, and leaving it for some time, beautiful clusters of long, thin, flat, prismatic crystals separate out which are readily purified by recrystallisation from water. The Anhydride melts at 138-139°, dissolves sparingly in cold, but readily in boiling water, and is also soluble in alcohol, ether, benzene, or acetic acid, very soluble in chloroform, but insoluble in cold light petroleum. It does not contain nitrogen. The pure substance, after draying at 100°, gave the following results on analysis:

I. 0.2208 gave 0.5103 CO_2 and 0.1163.H_2O
$C = 63.03$; $H = 5.85$.

II. 0.2330 gave 0.5422 CO_2 and 0.1230 H_2O.
$C = 63.46$; $H = 5.86$.

$C_{11}H_{12}O_4$ requires $C = 63.46$; $H = 5.77\%$.

Determination of methoxy-groups:

0.2173 gave 0.4834 AgI. $OCH_3 = 29.38$.
$C_9H_6O_2(OCH_3)_2$ requires $OCH_3 = 29.80\%$.

TITRATION OF THE ANHYDRIDE WITH POTASSIUM HYDROXIDE:

In order to determine the basicity of the acid $C_{11}H_{14}O_5$, corresponding to the anhydride $C_{11}H_{12}O_4$, the latter was dissolved in excess of a standard solution of potassium hydroxide, and the excess of alkali determined by titration with a standard solution of sulphuric acid, phenolphthalein being used as indicator.

0.3978 gram required 30.75 cc. KOH solution containing 0.00359 gram KOH in 1 cc. = 0.1103 gram KOH. This proves that the acid is monobasic, for on this assumption it would require 0.1074 gram KOH.

When the neutral solution is acidified with hydrochloric acid, the anhydride always separates instead of the acid.

ACTION OF THE HYDROCHOLRIC ACID ON THE ANHYDRIDE:

As it was found impossible to separate the phenolic substance corresponding to the anhydride $C_{11}H_{12}O_4$ from the residue obtained by heating the anhydride with hydriodic acid, an attempt was made to obtain it by heating with hydrochloric acid under pressure. In each experiment, 0.5 gram of the finely powdered anhydride, 5 cc. of hydrochloric acid of sp. gr. 1.168, and 20 cc. of water were used, and the mixture was first heated in a sealed tube for 5 hours at 170-175°, the temperature which Perkin found most advantageous for the preparation of ω-oxyethylcatecholcarboxylic anhydride from ω- oxyethylpiperonylcarboxylic anhydride. Under these conditions, the anhydride was almost completely decomposed, a considerable quantity of carbon separating out, and scarcely any crystalline matter could be extracted with ether from the liquid. At 140°, very little, if any, change took place. The best result was obtained at 147-153°. If a higher temperature than this was employed, a separation of carbon invariably occurred, whilst at lower temperatures a large proportion of the anhydride was not altered. The limits of temperature, therefore, within which the reaction takes place are very narrow, as Perkin found in the case of the corresponding derivative from berberine, and a large quantity of material was used up in determining them. The contents of two tubes which had been heated to 147-153° were thoroughly extracted with ether, the ethereal solution dried over calcium chloride, and evaporated to dryness at the ordinary temperature under diminished pressure. The almost colourless, crystalline deposit which remained had not a sharp melting point; the crystals, therefore were very gently warmed with successive small quantities of water, the aqueous solution evaporated to dryness at the ordinary temperature, and the residue dissolved in alcohol. When the alcoholic solution was evaporated at the ordinary temperature, small, thin crystals of the phenolic compound melting at 232° were obtained. The portion less soluble in water melted a little below the correct melting point of the anhydride $C_{11}H_{12}O_4$. It was found that the separation of the phenolic compound from the anhydride could also be effected by means of chloroform, in which the anhydride is much the more soluble.

The crystals of the phenolic compound obtained from the alcoholic solution dissolve in a solution of potassium hydrate, forming a yellow coloured liquid. In aqueous solution, they give a deep green colour with ferric chloride, and immediately reduce both an ammoniacal solution of silver nitrate and Fehling's solution in the cold; they also give a white, amorphous precipitate with lead acetate, which dissolves in hot water. The phenolic derivative, is more soluble in water than the anhydride, and is soluble in ethylic alcohol, but only sparingly so in chloroform. This substance gives, therefore, all the reactions of ω-oxyethylcatecholcarboxylic anhydride as described by Perkin; the melting point, however, is a few degrees higher. The stock of the anhydride $C_{11}H_{12}O_4$ having been exhausted in determining the conditions under which its phenolic derivative is formed, no analysis of the latter have yet been made.

OXIDATION OF THE ANHYDRIDE $C_{11}H_{12}O_4$ WITH POTASSIUM PERMANGANATE:

One gram of the anhydride was dissolved in hot water, and a dilute solution of potassium permanganate added until it was no longer decolorised, the oxidation being effected at the boiling point. After filtration from the manganese oxide and concentration, the solution was precipitated with lead acetate, and the precipitate, which was almost white in colour, washed with water and decomposed with sulphuretted hydrogen. The filtrate from the lead sulphide yielded, on evaporation, colourless, prismatic crystals, which, after recrystallisation, were found to melt at the same temperature as metahemipinic acid when the two substances were tested side by side. The acid, and the ethylimide prepared from it, gave all the tests for metahemipinic acid described above.

EXAMINATION OF CORYDILIC ACID, $C_{12}H_6N(O.CH_3)_2(CO_2H)_3$.

Corydilic acid is obtained along with *m*-hemipinic and 2-methylpyridinetricarboxylic acids when corydic acid is oxidised with potassium permanganate at the boiling point. From the former it is easily separated, but it is more difficult to free it entirely from the latter. Repeated recrystallisations are necessary to effect complete purification. This explains why the specimens formerly analysed gave results slightly lower than the theoretical numbers.* In addition to the reactions already described for this acid, the following additional observations have been made. Its aqueous solution gives no reaction with ferrous sulphate or ferric chloride, and no precipitate

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*. Dobbie & Marsden, Chem. Soc., Trans., 1897, 71, 651.

with barium chloride, calcium chloride, cadmium chloride, or copper acetate, even in presence of ammonia. From alkaline solution, corydilic acid is precipitated by the addition of excess of strong hydrochloric acid. If, however, the alkaline solution is exactly neutralised with dilute hydrochloric acid, no precipitation takes place, and a slight excess of hydrochloric acid may be added without causing the acid to separate. The solution so obtained has a faint green colour, and on standing, sometimes deposits pale, greenish-yellow crystals, which apparently consist of a hydrochloride of the acid. The crystals are very unstable, and decompose on the addition of water, leaving a residue of corydilic acid. Owing to its instability, it was not found possible to get this substance in a fit condition for analysis.

OXIDATION OF CORYDILIC ACID WITH POTASSIUM PERMANGANATE:

Corydilic acid is very stable, but on heating for several hours with potassium permanganate in alkaline solution, it gradually undergoes oxidation. The acid employed was carefully purified from every trace of the methylpyridinetricarboxylic acid. About 6 grams of the pure aced were oxidised in quantities of 2 grams at a time. After removal of the manganese oxides, the alkaline solution was concentrated and precipitated with lead acetate. This precipitate, on decomposition with sulphuretted hydrogen, yielded a mixture of acids, which, on separation by fractional crystallisation, was found to consist of undecomposed corydilic acid, *m*-hemipinic acid, and the 2-methylpyridinetricarboxylic acid. The two latter acids were compared with specimens prepared directly from corydaline and found to agree in every respect.

OXIDATION OF CORYDIC ACID WITH POTASSIUM PERMANGANATE AT THE ORDINARY TEMPERATURE:

Corydic acid was suspended in cold water and about twice its weight of potassium permanganate added in aqueous solution in small quantities at a time. The alkaline solution was precipitated with silver nitrate and the precipitate decomposed with sulphuretted hydrogen in the usual way. The filtrate, on evaporation, deposited a bright yellow acid which, after purification by repeated recrystallisation from water, melted at 212-215°. This acid is anhydrous, and differs from corydic acid in being more soluble in cold water and in giving a precipitate with silver nitrate in neutral solution. It was dried at 100° and analysed, with the following results:

0.2503 gave 0.5506 CO_2 and 0.1207 H_2O.
C = 59.99; H = 5.36.

0.2086 gave 0.4621 CO_2 and 0.0990 H_2O.
C = 60.42; H = 5.27.

0.2748 gave 10.6 cc. nitrogen at 16° and 758 mm.
N = 4.55.

$C_{16}H_{17}O_6N$ requires C = 60.18; H = 5.33;
N = 4.39%.

This acid is dibasic and forms both a normal and an acid silver salt. Its precise relation to corydic acid has not yet been determined.

PREPARATION OF BERBERIDIC ACID:

Ten grams of berberine nitrate were suspended in two litres of dilute nitric acid (1 in 20) and heated at the temperature of the water-bath until completely dissolved. When the solution cooled, a small quantity of the new acid was deposited as a yellow, crystalline precipitate. This was filtered off, the solution neutralised with ammonia, concentrated, and precipitated with silver nitrate. The silver precipitate was decomposed with sulphuretted hydrogen and the acid separated by fractional crystallisation from a more soluble substance not yet examined, which was formed along with it. In crystallising the acid, a considerable amount of tarry matter separated out. The acid was finally freed from this and obtained in a pure state, by dissolving in sodium hydroxide and precipitating with hydrochloric acid. In later preparations, the purification was greatly facilitated by fractional precipitation with silver nitrate, the first fraction carrying down most of the tar. The subsequent fractions were light in colour and practically pure. The yield of purified acid amounted to about 20 percent. of the berberine nitrate used. Berberidic acid crystallises from water in radiating tufts of yellowish-brown, prismatic crystals, which have a pure yellow colour when powdered. It contains no water of crystallisation. When heated in a capillary tube, it darkens at about 235° and remains without further change, so far as can be seen, until 285°, ~~and remains without further change, so far as can be seen, until 285°~~, when it melts with decomposition. It was dried at 100° and analysed, with the following results:

0.2637 gave 0.5925 CO_2 and 0.0866 H_2O.
C = 61.28; H = 3.61.

0.2831 gave 0.6344 CO_2 and 0.0917 H_2O.
C = 61.12; H = 3.59.

0.3243 gave 13.0 cc. nitrogen at 16° and 761.5 mm.
N = 4.75.

0.2808 gave 11.0 cc. nitrogen at 13° and 751 mm.
N = 4.63.

$C_{16}H_{11}O_6N$ requires C = 61.34; H = 3.51;
N = 4.47%.

Berberidic acid is insoluble in cold and only sparingly soluble in boiling water. It is very sparingly soluble in boiling alcohol and insoluble in ether or chloroform. It dissolves easily in sodium hydroxide to a dark blood-red solution, from which it is precipitated by hydrochloric acid.

Berberidic acid is dibasic. All its salts, with the exception of the two silver salts, appear to be soluble. The normal silver salt is obtained by precipitating a solution of the acid, which has been neutralised with ammonia, with silver nitrate. A curdy, yellow precipitate is obtained, which darkens on exposure to light. This salt was repeatedly prepared and analysed without exact results being obtained, owing, apparently, to admixture with the acid salt.

The acid silver salt is prepared by precipitating an aqueous solution of the acid with silver nitrate. The curdy precipitate so obtained is filtered, washed, and purified by repeated recrystallisation from water. It is finally obtained in stellate clusters of beautiful, yellowish-brown needles. On heating, it decomposes suddenly with evolution of thick, brown vapours. After being dried at 100°, it was analysed with the following results:-

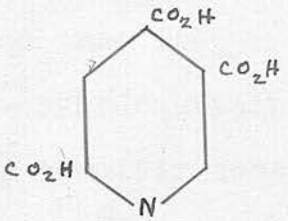
0.2470 gave 0.0828 AgCl. Ag = 25.23.
0.2616 " 0.0655 AgCl. Ag = 25.04.

$C_{16}H_{10}O_6NAg$ requires Ag = 25.71 per cent.

When berberidic acid is heated with concentrated hydrogen iodide solution, no methyl iodide is evolved, a fact which proves that in the formation of this acid the ring of the berberine molecule containing the methoxyl groups is destroyed.

OXIDATION OF BERBERIDIC ACID WITH POTASSIUM PERMANGANATE:

Five grams of berberidic acid were boiled with a dilute solution of permanganate until the permanganate was no longer reduced. The solution was filtered from the manganese oxide, concentrated, and precipitated with silver nitrate. The silver precipitate was decomposed with sulphuretted hydrogen and the filtrate from the silver sulphide evaporated to dryness. The residue was repeatedly exhausted with hot absolute alcohol, in which a considerable part of it dissolved. The portion of the residue insoluble in hot alcohol dissolved readily in boiling water, from which it separated on cooling in prismatic crystals. The acid so obtained was decolorised by boiling with charcoal and purified by repeated recrystallisation from water. It melted at 235° or 242°, according to the rate of heating. It dissolved with difficulty in cold, but was readily soluble in boiling water; it was insoluble in ether or chloroform. Its aqueous solution gave an orange red coloration with ferrous sulphate. The acid agrees in every particular with berberonic acid which was obtained by Weidel (Ber., 1879, 12, 410) by the direct oxidation of berberine with concentrated nitric acid. The melting point of berberonic acid is variously given at 238-242°.



The normal silver salt, which is almost insoluble in water, was prepared by precipitating a solution of the acid, previously neutralised with ammonia, with silver nitrate. After being dried at 100°, it was analysed with the following result:

0.2978 gave 0.1798 Ag. Ag = 60.38.

$C_8H_2O_6NAg_3$ requires Ag = 60.88 per cent.

The presence of hydrastic acid amongst the decomposition products of berberidic acid has not yet been proved. By dissolving berberidic acid in potassium carbonate and oxidising it with potassium permanganate at the ordinary temperature, a small quantity of a substance was obtained as a scum on the surface of the strongly alkaline solution. From its insolubility in potash, it was suspected that this substance might by nor-oxyhydrastinine, which is insoluble in alkaline solutions. On examination, it was found that it agreed in every particular with nor-oxyhydrastinine in its neutral reaction, solubility, peculiar mode of crystallisation, and behaviour with mercuric chloride. As the amount of substance obtained was too small to admit of complete purification, the melting point observed was slightly lower than that given by Perkin.

By oxidising berberidic acid with potassium permanganate at the ordinary temperature, a yellow derivative is obtained like that obtained from corydic acid by similar treatment.

CORYTUBERINE.

When Schuchardt's crude corydaline is treated with hot water, it yields a green solution with a magnificent blue fluorescence, from which tufts of small slender needles separate on cooling. When collected on a filter, the crystals form a compact film with a metallic lustre, recalling that of freshly cut potassium. The substance is readily purified by recrystallisation from alcohol, but if crystallised from water there is slight decomposition, indicated by the darkening of the solution. The alkaloid is nearly insoluble in cold, but dissolves readily in hot water. The green colour and fluorescence of the aqueous extract of corydaline are due apparently to the presence of a decomposition product. The alkaloid crystallises from alcohol in fine, silky needles, which dissolve easily in solutions of the caustic alkalis and ammonia, slightly in benzene, but not appreciably in ether or chloroform. The alkaloid is colourless when pure, but on standing, even at the ordinary temperature, gradually becomes somewhat discoloured. On long continued heating at 100°, this change is more pronounced, the alkaloid assuming a slate-grey colour. When the altered substance is dissolved in alcohol, it gives a pink-coloured fluorescent solution confirming the view that the fluorescence is due to a decomposition product of the alkaloid, and not to the pure substance. The alkaloid has no definite melting point. When heated to 200°, it blackens, and slowly decomposes.

The following are the results of the analysis of the alkaloid, purified by repeated recrystallisation from alcohol, and dried at 100°.

0.1931 gave 0.4893 CO_2 and 0.1260 H_2O.
C = 69.11; H = 7.25.

0.2866 gave 0.7271 CO_2 and 0.1852 H_2O.
C = 69.12; H = 7.18.

0.2761 gave 0.6988 CO_2 and 0.1909 H_2O.
C = 69.03; H = 7.68.

0.2712 gave 0.0810 Pt. N = 4.30.

0.2846 " 0.0824 Pt. N = 4.18.

The means of these numbers gave C = 69.09; H = 7.37; N = 4.24% $C_{19}H_{25}NO_4$, requires C = 68.88; H = 7.55; N = 4.23 per cent.

Corytuberine dissolves readily in acids, forming salts, some of which crystallise with ease.

CORYTUBERINE HYDROCHLORIDE:

This salt is prepared by dissolving corytuberine in hydrochloric acid, and evaporating until crystals begin to separate. The hydrochloride crystallises without water of crystallisation in small, well-developed, colourless rhombohedra. It is stable when dry, but its solution becomes brown when heated. The specimen analysed was crystallised from water and dried over strong sulphuric acid. The chlorine was determined by direct precipitation with silver nitrate.

I. 0.3042 gave 0.1205 AgCl = 9.79 Cl.
II. 0.3171 " 0.1256 " = 9.78 Cl.

$C_{19}H_{25}NO_4$, HCl requires Cl = 9.66 per cent.

CORYTUBERINE SULPHATE:

This compound is obtained by treating corytuberine hydrochloride with the calculated amount of silver sulphate. It is easily soluble in water, from which it crystallises with difficulty. It shows the same tendency to decompose as the hydrochloride, and we have not succeeded in obtaining it in well developed crystals. Analysis of this salt dried at 100° gave the following result:-

0.2951 gave 0.0948 $BaSO_4$ = 13.50 H_2SO_4.

$(C_{19}H_{25}NO_4)_2$, H_2SO_4 requires H_2SO_4 = 12.89%.

CORYTUBERINE PLATINOCHLORIDE:

The platinochloride is prepared by adding a solution of hydrogen platinochloride to a solution of corytuberine hydrochloride in water. It is a pale yellow, crystalline substance only slightly soluble in water, and therefore, easily purified from excess of hydrogen platinochloride by washing. Analysis of this salt dried at 100° gave the following results:-

I. 0.2778 gave 0.0496 Pt = 17.85 Pt.
II. 0.1998 " 0.0361 Pt = 18.07 Pt.

$(C_{19}H_{25}NO_4)_2$, H_2PtCl_6 requires Pt = 18.19%.

CORYTUBERINE METHIODIDE:

Corytuberine is only soluble to a slight extent in methyl iodide. The methiodide is prepared by digesting a solution of the alkaloid in alcohol with methyl iodide for several hours in a flask attached to a reflux condenser. On evaporating the solution, the methiodide crystallises out in small hemispherical tufts of needle-shaped crystals. This compound is colourless when pure, but it shows the same tendency to decompose as the other salts, and it was difficult for this reason and on account of the small amount of substance at our disposal, to obtain it in a pure condition. The salt was dried over strong sulphuric aicd.

I. 0.4325 gave 0.2065 AgI = 25.79 I.
II. 0.4908 " 0.2349 AgI = 25.85 I.
$C_{19}H_{25}NO_4$, CH_3I requires I = 26.84%.

ACTION OF HYDROGEN IODIDE ON CORYTUBERINE:

Corytuberine was treated with a fuming solution of hydrogen iodide by Zeisel's method. Methyl iodide was evolved, a yellow, crystalline compound, remaining in the distilling flask. The determination of the methoxy-groups in pure corytuberine, dried over sulphuric acid, gave the following results.

I. 0.2292 gave 0.3206 AgI = 18.47 CH_3O.
II. 0.2500 " 0.3509 AgI = 18.53 CH_3O.
Calculated for two CH_3O groups, $C_{19}H_{25}NO_4$ requires 18.73% CH_3O.

CORYBULBINE:

The occurrence, method of extraction, and properties of this alkaloid have already been described.

The following are the results of the analysis of the alkaloid, purified by repeated recrystallisation from alcohol, and dried at 100°.

I. 0.2167 gave 0.1382 H_2O. H = 7.08.

II. 0.2683 " 0.7023 CO_2 and 0.1732 H_2O.
C = 71.38; H = 7.17.

III. 0.2214 gave 0.5788 CO_2 and 0.1516 H_2O.
C = 71.29; H = 7.60.

IV. 0.3211 gave 0.0891 Pt. N = 4.00%.

V. 0.2993 " 0.0849 Pt. N = 4.09%.

Mean of the above analyses:- C = 71.33; H = 7.28; N = 4.04 per cent. These numbers lead to the formula $C_{21}H_{25}NO_4$, which requires C = 70.99, H = 7.04, N = 3.94 per cent.

Corybulbine forms easily crystallisable salts with hydrochloric acid and sulphuric acid.

CORYBULBINE HYDROCHLORIDE:

This salt is prepared by dissolving the alkaloid in hot hydrochloric acid, from which it separates, on cooling, in clusters of thick, prismatic crystals. It requires a large quantity of boiling water for solution, but this is greatly facilitated by the addition of a little hydrochloric acid. The salt contains no water of crystallisation. It was dried at 100°, and a complete analysis of it made, to serve as a check on the analysis of the alkaloid.

I. 0.2432 gave 0.5756 CO_2 and 0.1536 H_2O.
C = 64.55; H = 7.01.

II. 0.2880 gave 0.0736 Pt. N = 3.68 per cent.

III. 0.2891 " 0.1071 AgCl. Cl = 9.15 "

IV. 0.2679 " 0.1011 AgCl. Cl = 9.33 "

V. 0.2052 " 0.0769 AgCl. Cl = 9.26 "

$C_{21}H_{25}NO_4$,HCl requires C = 64.36; H = 6.64;
N = 3.57; Cl = 9.07%.

The addition of a solution of potassium iodide to a solution of the hydrochloride in water, produces a pale yellow precipitate of the hydriodide, which is insoluble in cold, but readily soluble in hot water.

CORYBULBINE SULPHATE:

The acid sulphate is obtained by dissolving the alkaloid in hot dilute sulphuric acid. When the solution is allowed to cool slowly, long, prismatic, colourless crystals separate; it contains no water of crystallisation. It is somewhat more easily soluble in hot water than the hydrochloride. It was dried at 100°, and gave the following results on analysis.

I. 0.3517 gave 0.1763 $BaSO_4$. S = 6.88.

II. 0.3494 " 0.1775 $BaSO_4$. S = 6.98.

$C_{21}H_{25}NO_4$, H_2SO_4 requires S = 7.06 per cent.

CORYBULBINE PLATINOCHLORIDE:

The platinochloride is obtained by adding a solution of hydrogen platinochloride to a solution of corybulbine hydrochloride in water. It is a pale yellow substance slightly soluble in water. It was dried at 100°, and gave the following results on analysis.

I. 0.2~~6~~78 gave 0.0441 Pt. Pt = 17.10. 15

II. 0.3257 " 0.0560 Pt. Pt = 17.19.

III. 0.4445 " 0.0771 Pt. Pt = 17.34

These analyses were made on different preparations of the salt; mean Pt = 17.21 per cent. $(C_{21}H_{25}NO_4)_2$,H_2PtCl_6 requires Pt = 17.41 per cent.

CORYBULBINE METHIODIDE:

This compound is prepared by digesting the alkaloid with a mixture of absolute alcohol and methylic iodide, for several hours, in a flask having a reflux condenser attached to it. On evaporating the solution, the methiodide crystallises out in clusters of large, yellow, prismatic crystals, which were purified by recrystallisation from alcohol. After being dried at 100°, the iodine was determined with the following results.

I. 0.2862 gave 0.1327 AgI. I = 25.05.

II. 0.2590 " 0.1214 AgI. I = 25.33.

$C_{21}H_{25}NO_4.CH_3I$ requires 25.55 per cent. I.

ACTION OF HYDROGEN IODIDE ON CORYBULBINE:

When Corybulbine is treated with a concentrated solution of hydrogen iodide (sp.gr. 1.7), methylic iodide distils over, and a yellow, crystalline compound separates from the liquid remaining in the flask. The methoxy-groups were determined by Zeisel's method with the following result.

I. 0.2091 gave 0.4032 AgI; 25.46 per cent. OCH_3.

Three methoxy-groups in $C_{21}H_{25}NO_4$ require OCH_3 = 26.19%.

ACTION OF ACETIC ANHYDRIDE ON CORYBULBINE:

The acetylcorybulbine, prepared as already described, was dried over strong sulphuric acid for analysis:

0.2676 gave 0.6820 CO_2 and 0.1736 H_2O.
C = 69.50%; H = 7.20%.

$C_{18}H_{15}N(OCH_3)_3 . O.C_2H_3O$ requires C = 69.47; H = 6.87%.

ACTION OF HYDROGEN IODIDE ON CORYBULBINE:

The hydriodide obtained by the action of hydrogen iodide was dried at 100° for analysis:

0.2813 gave 0.1496 AgI. I = 28.73%.

$C_{18}H_{15}N (OH)_4$ .HI requires I = 28.79%.

CONVERSION OF CORYBULBINE INTO CORYDALINE:

The corydaline prepared as already described gave the following results on analysis:

0.2515 gave 0.6586 CO_2 and 0.1740 H_2O.
C = 71.41%; H = 7.68%.

0.4088 gave 0.1089 Pt. N = 3.84%.

$C_{22}H_{27}NO_4$ requires C = 71.54; H = 7.32; N = 3.79%.

PLATINOCHLORIDE OF SYNTHETICAL CORYDALINE:

The platinochloride of synthetical corydaline was prepared by dissolving the alkaloid in dilute hydrochloric acid and precipitating with platinic chloride. The pale yellow precipitate was collected and washed with water until free from acid. It was dried at 100° for analysis:

0.3058 gave 0.0517 Pt. Pt. = 16.90%.

$(C_{21}H_{27}NO_4)_2\ H_2PtCl_6$ requires Pt = 16.97%.

The salt was exactly similar to corydaline platinochloride in appearance, and the behaviour of the two substances, when heated side by side in capillary tubes, was identical. Both softened at 194°, began to decompose at 203°, and were completely decomposed at 210°. The two salts were compared as regards their solubility in water, alcohol, and ether, and were found to agree in all respects.

Part II.

ON THE RELATION BETWEEN THE ABSORPTION SPECTRA AND THE CHEMICAL STRUCTURE OF CORYDALINE, BERBERINE, AND OTHER ALKALOIDS.

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ON THE RELATION BETWEEN THE ABSORPTION SPECTRA AND THE CHEMICAL STRUCTURE OF CORYDALINE, BERBERINE, AND OTHER ALKALOIDS.

Introduction.

The first attempt to establish a connection between the constitution of an alkaloid and its absorption spectra, was made by Professor W. N. Hartley nearly twenty years ago. In a paper which he then communicated to the Royal Society (Phil. Trans., 1885, Part II., 471), he showed that the principal alkaloids give highly characteristic absorption spectra, which can be used for their identification and for ascertaining their purity.

It is further shown that alkaloids closely related to one another, like quinine and quinidine, cinchonine and cinchonidine, morphine and codeine, give very similar spectra. At the time at which this paper was published, however, little prgress had been made with the investigation of the alkaloids, and it was not possible, therefore, to trace any close connection between their structure and their spectra.

The constitution of the principal members of the group of alkaloids to which corydaline and berberine belong, namely, papaverine, hydrastine, narcotine, and narceine, has now been definitely determined, and the examination of this group furnishes a good basis for the study of the relationship between the absorption spectra and the constitution of the alkaloids.

METHOD EMPLOYED IN PHOTOGRAPHING THE SPECTRA:

Before giving an account of the results obtained in this investigation, it may be convenient to give first a short description of the method employed in photographing the spectra.

The apparatus employed is shown in elevation in Fig. 1 and in plan in Fig. 2, and is substantially the same as that employed by Hartley in his earlier investigations. The spectroscope, which is provided with quartz prisms, is rigidly mounted on a heavy stand, and has, in place of the usual eyepiece, a camera (AB) attached as shown in the illustrations. The dark shutter carrying the plate can be raised by means of the screw C (Fig. 1) and a series of ten or twelve separate photographs taken on the same plate. The source of light used was an electric spark passing between electrodes consisting of an alloy of cadmium and tin, and cadmium and lead respectively (D. Fig. 1.) The solution under examination was contained in a small cell with quartz ends; these were simply made by fixinf two circular plates of quartz by means of paraffin wax to a piece of glass cut to the appropriate shape and thickness. The cells could thus

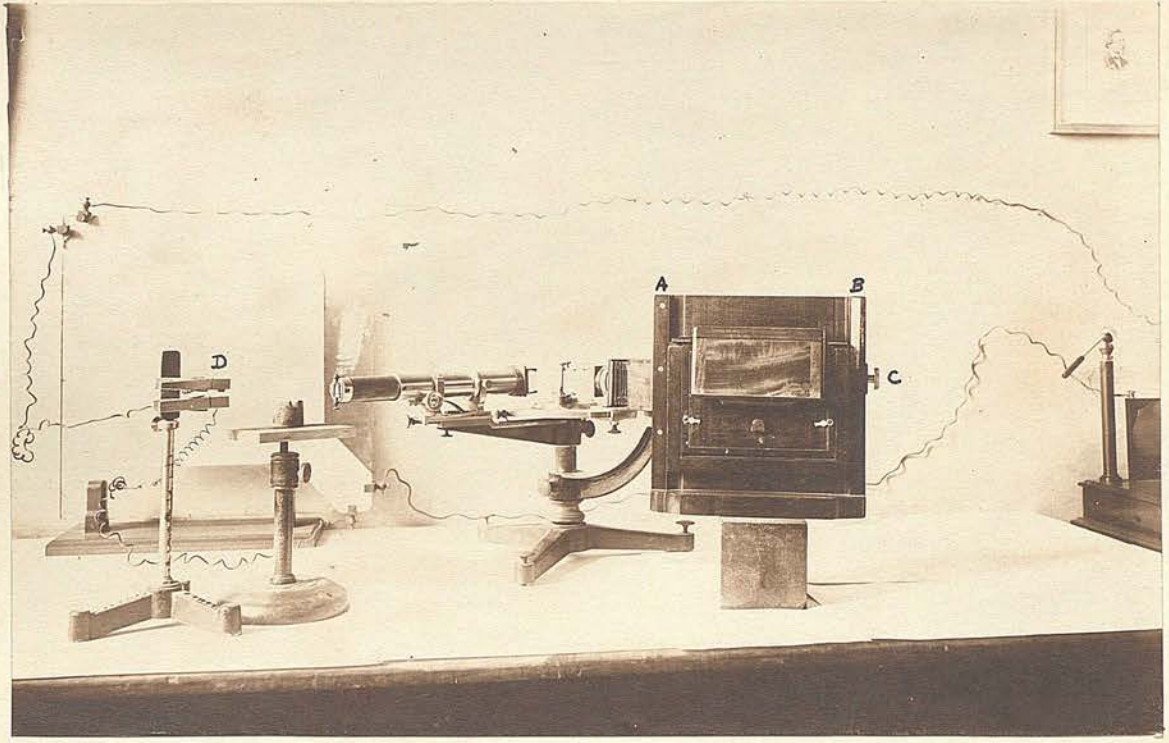


Fig. I.

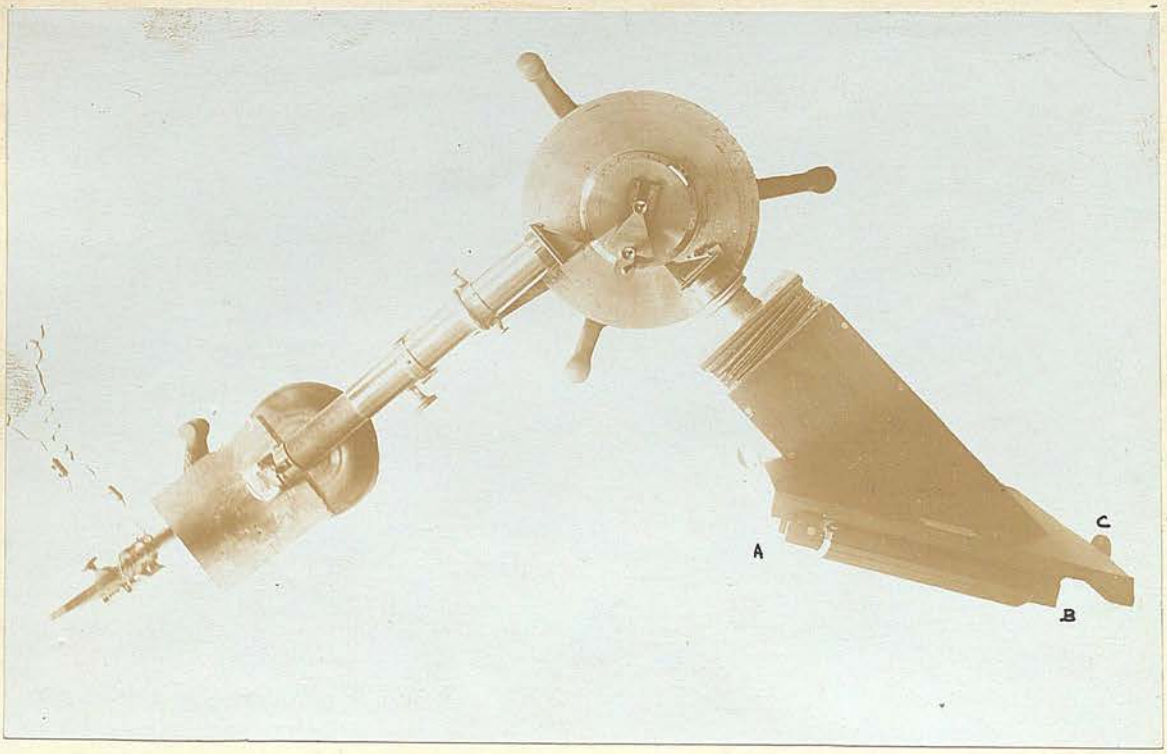


Fig. II.

be easily taken to pieces and thoroughly cleaned. The exposure was 15 seconds, the time being measured by a small sand-glass. Care was taken always to work under as constant conditions as possible, as regards the intensity of the spark, development of the plates, etc. A comparison of the results obtained by different workers using the same instrument, showed that with reasonable care, no appreciable error was introduced by any of these causes.

In every case equimolecular solutions were employed. Starting with 1 mill. mol. in 100 cc., layers of 5-1 mm. were successively photographed; the solution was then diluted to five times its volume (so that 1 mill. mol. was then contained in 500 cc.) and the solution photographed as before. The dilution was continued until the whole spectrum was transmitted.

The photograph at the top of each series of photographs (Figs. 3, 4, 5 ----) shows the spectrum of the Cadmium-Lead - Cadmium-Tin alloys used as electrodes, and it will be noticed that whereas the cadmium lines stretch right across the spectrum, the lead and tin lines only stretch about twothirds of the way across on opposite sides. Two separate alloys were used as electrodes, rather than pure metals, for two reasons. In the first place, a larger and more evenly distributed series of lines was obtained than if cadmium alone had been employed; further, the fact that the lead and tin lines were shorter than those of cadmium facilitated the identification of the different lines.

By a careful comparison of the spectrum given by the alloys, with the maps of the spectra of Cadmium, lead, and tin respectively, the principal lines in the spectrum of the various elements were identified and their wave lengths recorded. A very fine ivory scale was next fixed to the photographic plate, a certain line being fixed upon as the zero point, and the zero of the scale carefully adjusted to it. The positions of the various lines which had been identified were next read off on the scale with the aid of a lens, and the values so obtained plotted as abscissae,the reciprocals of the corresponding wave lengths being plotted as ordinates. In this way a curve was obtained, which gave the wave length corresponding to any point on the arbitrary scale. In order to reduce errors of measurement as much as possible, the curves were drawn on a large scale, their total length being about 10 ft.

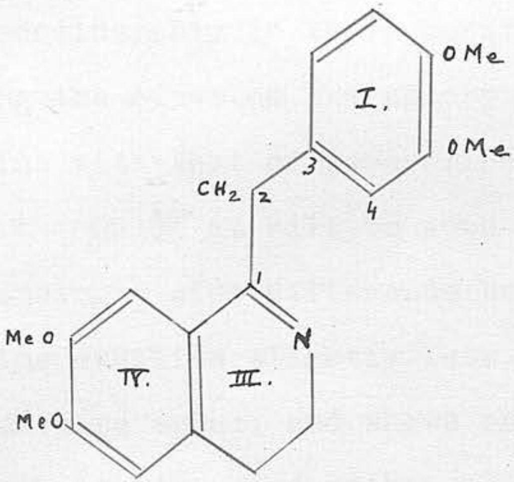
In determining the amount of absorption caused by any particular substance, the arbitrary scale was applied to the photographic plate and the zero mark carefully adjusted. By reading off on the scale the width of the absorption band, or the extent to which the spectrum was transmitted, and then referring to the curve, the amount of absorption, expressed in terms of the wave length, could readily be ascertained.

It was, of course, necessary to take great care that the adjustment of the instrument was not altered in any way after the curves had been drawn. The spectrum of the alloys was carefully measured from time to time while the work was in progress and, in the only case were any alteration was found, the instrument was readjusted and fresh curves drawn.

THE ISOQUINOLINE GROUP OF ALKALOIDS:

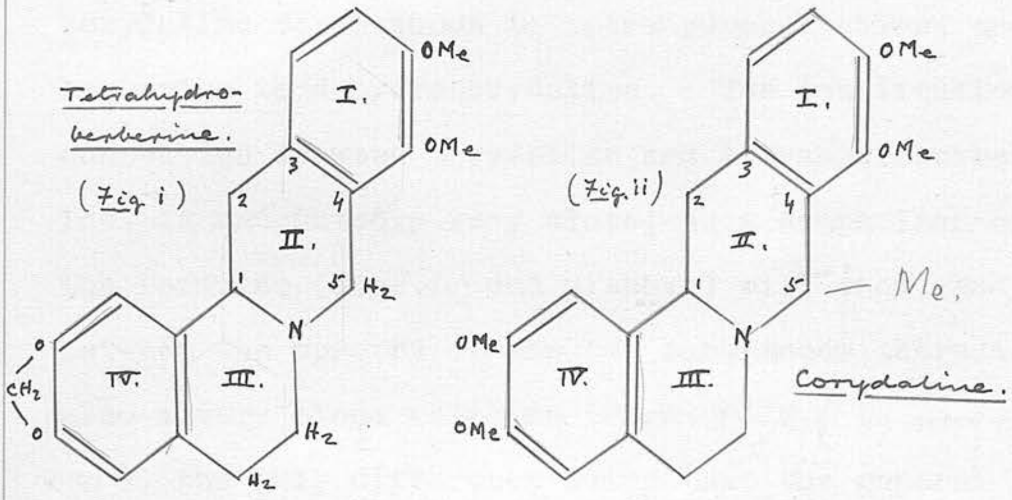
Papaverine, Narcotine, Hydrastine, Narceine, Berberine and Corydaline.

Since papaverine is, in some respects, more simply constituted than the other members of the group, it will be convenient to consider each of the others with reference to it. According to Goldschmiedt, the structure of papaverine is represented by the following formula:



A ~~graphic~~ representation of the absorption spectra of papaverine is given in Fig. 3, p. 136. The spectra show two absorption bands, the first lying between $1/\lambda$ 2998 (λ = 3335) and $1/\lambda$ 3295 (λ = 3035), and the second between $1/\lambda$ 3956 (λ =2528) and $1/\lambda$ 4555 (λ = 2195).

Hydrastine differs structurally from papaverine in the following particulars: (i) the isoquinoline nucleus is partially reduced. (ii) The two methoxyl radicles of the isoquinoline nucleus are replaced by a di-oxymethylene group. (iii) A methyl group is attached to the nitrogen atom. (iv) A carbonyl group is attached to the carbon atom (4), and through the medium of an oxygen atom is also linked to carbon atom (2), which has only one atom of hydrogen attached to it. From this comparison, it is obvious that the two substances differ considerably in their constitution. On comparing ~~the curve of~~ the absorption spectra of hydrastine with that of papaverine (Figs. 5 & 3 pages 138 & 136), it will be seen that there is a correspondingly wide difference between them; hydrastine exhibits slightly less general absorption than papaverine, and shows only one absorption band which is wider and much more persistent than either of the absorption bands of papaverine. Narcotine only differs from hydrastine in containing an additional methoxyl group attached to ring IV., and the two alkaloids give practically identical absorption spectra (Figs. 5 & 6; pages 138 & 139). Assuming corydaline to have the constitution assigned to it in Part I. of this thesis, it is represented by the second of the following formulae:


Tetrahydro-berberine. (Fig. i)

(Fig. ii) Corydaline.

On comparing this formula with that of papaverine, the differences will be seen to consist in the partial reduction of the isoquinoline nucleus and in the presence of carbon atom (5), which, with its associated methyl group, is linked on the one hand to carbon atom (4), and on the other to the nitrogen atom, thus forming a fourth closed chain in the molecule. Here, again, the difference between the absorption spectra abd those of papaverine is very marked. The amount of general absorption is less, and there is only one absorption band, which is, however, better defined and more persistent than the papaverine bands (Figs. 7 & 3 pages 140 and 136.).

In discussing the relations between corydaline and berberine, it is to be remembered that corydaline corresponds to tetrahydroberberine, and berberine to dehydrocorydaline. The constitutional connection between corydaline and tetrahydroberberine, is undoubtedly very close, as a comparison of the formulae (Figs.(i) and (ii) above) will show, and between the spectra of the two substances there is also a very close relation (Figs. 7 & 8; pages 140 & 141), the only difference being that the general absorption of tetrahydroberberine is slightly greater than that of corydaline.

When papaverine is reduced to tetrahydropapaverine, it is brought structurally very near to corydaline. A comparison of the formulae of the two substances shows that the former substance differs from the latter in the absence of carbon atom (5) of ring II. with its associated hydrogen atom and methyl group. The spectra of the two compounds are almost identical (Figs. 4 and 7; pages 137 & 140).

Re Viewing corydaline as derived from tetrahydropapaverine by the addition of CH_2 forming a fourth closed chain in the molecule, it might have been anticipated that the difference between the absorption spectra of the two substances would be greater than is found to be the case. It should be noted, however, that ring II. in corydaline is a reduced ring, and would not therefore exert the same influence on the absorption spectra as the formation of a pyridine ring. It might be expected to produce an effect comparable with that produced by the substitution of a dioxymethylene for two methoxyl groups, which it will be shown later, is slight in compounds of high molecular weight (Hartley, Trans., 1885, 47, 692; Hartley and Dobbie, Trans. 1900, 77, 846.)

Narceine is the extreme member of this group. It has two benzene nuclei, but no pyridine ring, and in other particulars differs considerably in constitution from papaverine. The absence of any absorption band differentiates the spectra widely from those of the other members of the group (Fig. 9, page 142).

It has already been shown in Part I., that corydaline and berberine give rise to a parallel series of derivatives. The absorption spectra of the corresponding derivatives are related to one another in the same way as the spectra of the parent substances. When corydaline is acted on with mild oxidising agents, four atoms of hydrogen are removed, and a yellow substance is obtained, which stands in the same relation to corydaline as berberine to tetrahydroberberine.

Oxidation with dilute nitric acid converts corydaline and berberine respectively into the dibasic corydic and berberidic acids:

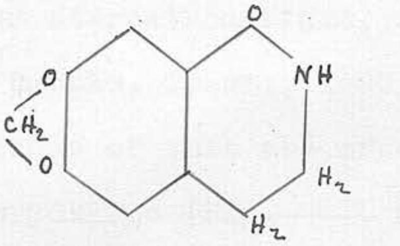
$$C_{13}H_6(CH_3)(OCH_3)_2\cdot N(CO_2H)_2$$

Corydic Acid.

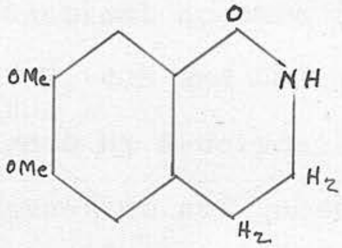
$$C_{13}H_7(CH_2O_2)\cdot N(CO_2H)_2.$$

Berberidic Acid.

whilst oxidation with permanganate gives rise, amongst other products, to corydaldine in the former case, and to nor-oxyhydrastinine in the latter. The corresponding derivatives differ structurally from one another in the same way as corydaline and tetrahydroberberine, excepting that, in the case of corydaldine and nor-oxyhydrastinine, ring II. having disappeared, the difference between the two compounds is confined to the replacement of the two methoxyl groups of the former by dioxymethylene in the latter.



nor-Oxyhydrastinine.



Corydaldine.

The spectra of the corresponding derivatives (Figs. 10 & 11; pages 143 & 144; 12 & 13; pages 145 & 146; 14 & 15; p. 147 & 148) exhibit the same close relationship as those of the alkaloids themselves. The general absorption of the berberine derivatives is, however, always slightly greater than that of the corresponding corydaline derivatives. This is probably due to the influence of the dioxymethylene group, and the correctness of this inference is supported by the fact that piperonylic acid, $C_6H_3(CH_2O_2)\cdot CO_2H$, shows slightly greater general absorption than veratric acid, $C_6H_3(OCH_3)_2\cdot CO_2H$ (Figs. 16 & 17; pages 149 & 150).

THE INFLUENCE OF SPECIFIC DIFFERENCES OF CONSTITUTION ON THE SPECTRA:

It is now known that many alkaloids which possess the same formula are stereoisomerides.

Alkaloids which are related in this way give, like other stereoisomerides, identical spectra (Hartley and Dobbie, Trans., 1900, 77, 408 and 509). Illustrations of this are afforded by d-corydaline and i-corydaline ~~(Fig.),~~ narcotine and gnoscopine ~~(Fig.),~~ tetrahydroberberine and canadine~~, (Fig.)~~. Quinidine (conquinine) and cinchonidine also give absorption spectra identical with those of quinine and cinchonine respectively, of which substances they are probably stereoisomeric forms (Figs. 18 & 19; p. 151). This relationship might sometimes be used to assist the investigation of cases of suspected stereoisomerism. Where, for example, two compounds of the same formula are known, one active and the other inactive, it may be inferred that they are not optical isomerides if they have different absorption spectra.

A case in point is afforded by canadine and papaverine, which possess the same molecular formulae but give widely different absorption spectra. Even if it were not known otherwise that these two substances are structurally different, this might be inferred from the differences in their absorption spectra (Figs. 8 & 3; pages 141 and 136).

Canadine has long been regarded as a stereoisomeride of tetrahydroberberine. This question might have been decided by a comparison of the spectra of the two substances, and with this end in view, their comparison had already been undertaken, when Gadamer (Arch. Pharm., 1901, 239, 648) published an account of the resolution of tetrahydroberberine into its active components, and showed that one of them was identical with canadine. The result of the spectroscopic examination points to the same conclusion.~~(Fig. 13,).~~

According to Gadamer (Arch. Pharm., 1902, 240, 19)- inactive corydaline exists in two modifications, one melting at 134-135°, and the other at 158-159°. The latter of these only can be resolved into d- and i-corydalines. The inactive modification of lower melting point which cannot be resolved, might either be a structural or a stereoisomeric modification of corydaline. The fact that its spectra are identical with those of natural corydaline ~~(Fig.)~~ affords strong presumption in favour of the view that the two are structurally identical.

Homologous alkaloids guve practically identical spectra. It has been shown from the examination of many homologous substances that the replacement of an atom of hydrogen by a methyl group produces very little effect on the spectra even when the compounds are of low molecular weight (Hartley, Phil. Trans., 1879, Part I., 257). The effect is still less noticeable when the replacement occurs in substances of high molecular weight, such as the alkaloids.

Codeine and morphine (Fig. 20 p. 152) were examined by Hartley (Phil. Trans., 1885, Pt. II., 471), and his curves show clearly the relation between these two compounds. Numerous other cases of homologous alkaloids have been examined, and it is found that they all give practically identical spectra. The curves of corybulbine, $C_{21}H_{25}O_4N$ (Fig. 21 ~~27~~, p. 153 ~~0.625~~), and corydaline, $C_{22}H_{27}O_4N$ (Fig. 7 p), p-p. 140 and those of quinine, $C_{20}H_{24}O_2N_2$, and cupreine $C_{19}H_{22}O_2N_2$ ~~(Fig. 24)~~, may be referred to as examples. When, therefore, the formulae of two alkaloids differ by CH_2, it may be inferred with certainty, if they give dissimilar spectra, that they are not homologous. On the other hand, it cannot be inferred with certainty that two substances which differ by CH_2, and have very similar spectra, are really homologous, because the difference in the formulae may be due to other slight structural differences.

The formula of bulbocapnine, $C_{19}H_{19}O_4N$, differs from that of papaverine, $C_{20}H_{21}O_4N$, and of tetrahydroberberine, $C_{20}H_{21}O_4N$, by CH_2, but the wide difference between the spectra of all three substances (Figs. 22, 3, 28; p. 154, 136, 141) renders it highly improbable that bulbocapnine is homologously related to either of the others. What is known of the chemistry of bulbocapnine entirely bears out this conclusion (Gadamer and Ziegenbein, Arch. Pharm., 1902, 240, 81).

Many minor modifications of structure in alkaloids are unaccompanied by any marked difference in the spectra even where the same modifications would produce an appreciable effect on the spectra of compounds of low molecular weight. Corydaline, tetrahydroberberine, and their derivatives afford instances in which the replacement of $2OCH_3$ by CH_2O_2 does not markedly alter the spectra and narcotine and hydrastine furnish an example in which the introduction of an additional methoxyl group is unaccompanied by any considerable effect.

The case of cinchotenine and cinchonine may be quoted as another instance. In cinchotenine the side chain $\cdot CH:CH_2$ of cinchonine is oxidised to a carboxyl group without the spectra being appreciably affected. The resemblance between the two series of spectra is so close that it would at once suggest a near structural relation of the substances, even if nothing were known of their chemistry.

The reduction of closed chain compounds is accompanied by a complete change in the character of the spectra (Hartley, Trans., 1885, 47, 691; and Hartley and Dobbie, Trans., 1900, 77, 846). Good illustrations of this are afforded by the widely different spectra of berberine and tetrahydroberberine (Figs. 8 & 11; p.141 & 144), dehydrocorydaline and corydaline (Figs. 10 & 7; p.143 & 140), papaverine and tetrahydropapaverine (Figs. 3 & 4; p.136 & 137.). There are, however, cases in which partial reduction produces very little change. Hydroquinine, $C_{20}H_{26}O_2N_2$, is unquestionably very closely related to quinine, $C_{20}H_{24}O_2N_2$, from which its formula only differs in containing two more atoms of hydrogen. The difference between the spectra of the two substances is hardly perceptible, and it is highly probable, therefore, that the addition of the two atoms of hydrogen is unaccompanied by any important change of structure. The change probably consists in the reduction of the side chain.

From the examination of a large number of alkaloids,* it may be laid down as a general rule that those which agree closely in structure give similar absorption spectra, whilst those which differ in essential points of structure give dissimilar spectra.

This principle has already been recognised and applied in previous investigations, but it is probably capable of a more extended application in the case of the alkaloids than in that of any other group of substances. This is due to the fact that most of these compounds have a high molecular weight, and changes may be effected in their molecules without alteration of the spectra which, in substances of lower molecular weight, would be attended by wide diffferences. Thus, the essential identity of constitution subsisting between two alkaloids can often be detected by the spectroscope in spite of differences of structure

* In connection with this investigation, an independent examination of more than thirty alkaloids has been made, including quinine, cinchonine, cinchonidine, cinchonamine, homocinchonidine, quinidine,

which, in substances of lower molecular weight, would give rise to spectra so dissimilar that no close chemical relationship between them could be suspected. An example of this is afforded by the absorption spectra of piperonylic and veratric acids, from which no safe conclusion could be drawn as to the relationshop of the two substances, whereas a comparison of the absorption spectra of corydaline and tetrahydroberberine, between which the same difference exists, leaves no doubt as to the essential similarity of their structure. Again, cinchonine and cinchotenine give practically identical spectra, whereas styrolene and benzoic acid, which differ in the same way, give very different spectra. If, therefore, an alkaloid of unknown constitution is found to give spectra closely resembling those of an alkaloid of known constitution, it may with great probability be inferred that the two only differ in the details of their structure. The results can also be represented graphically as shown in Figs. 23 and 24/. In drawing the

p. 155 & 156.

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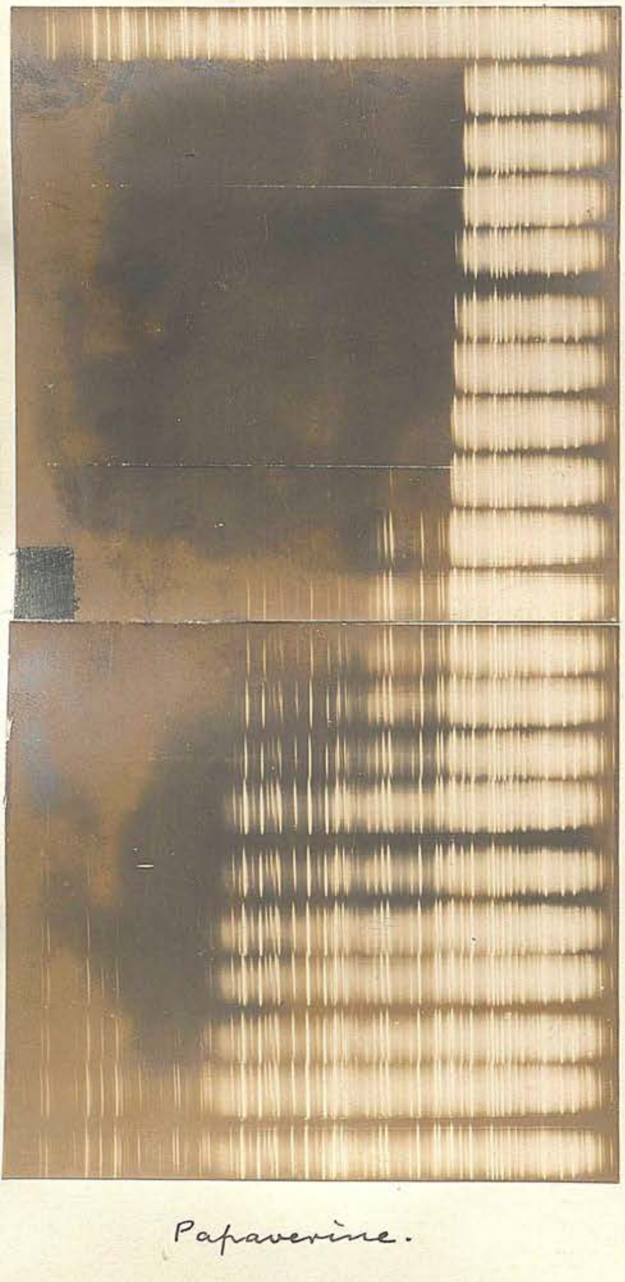
cupreine, hydroquinine, strychnine, brucine, papaverine, narcotine, gnoscopine, narceine, morphine, codeine, thebaine, laudanine, laudanosine, cryptopine, protopine, hydrastine, canadine, berberine, corydaline, bulbocapnine, corybulbine, corytuberine, and chelidonine.

curve, the ordinate representing thickness of layer is reduced at each dilution to 1/5 of its former size. Each vertical scale division represents, therefore, an equal number of molecules in solution. The abscissae are reciprocals of wavelengths. It is difficult by means of curves to give a proper representation of the plates, it being found impracticable to represent adequately differences of intensity as well as extent of absorption upon which the similarity or difference between two plates often to a large extent depends. By far the most satisfactory comparison is that which is made by the actual inspection of the photographs.

(136)

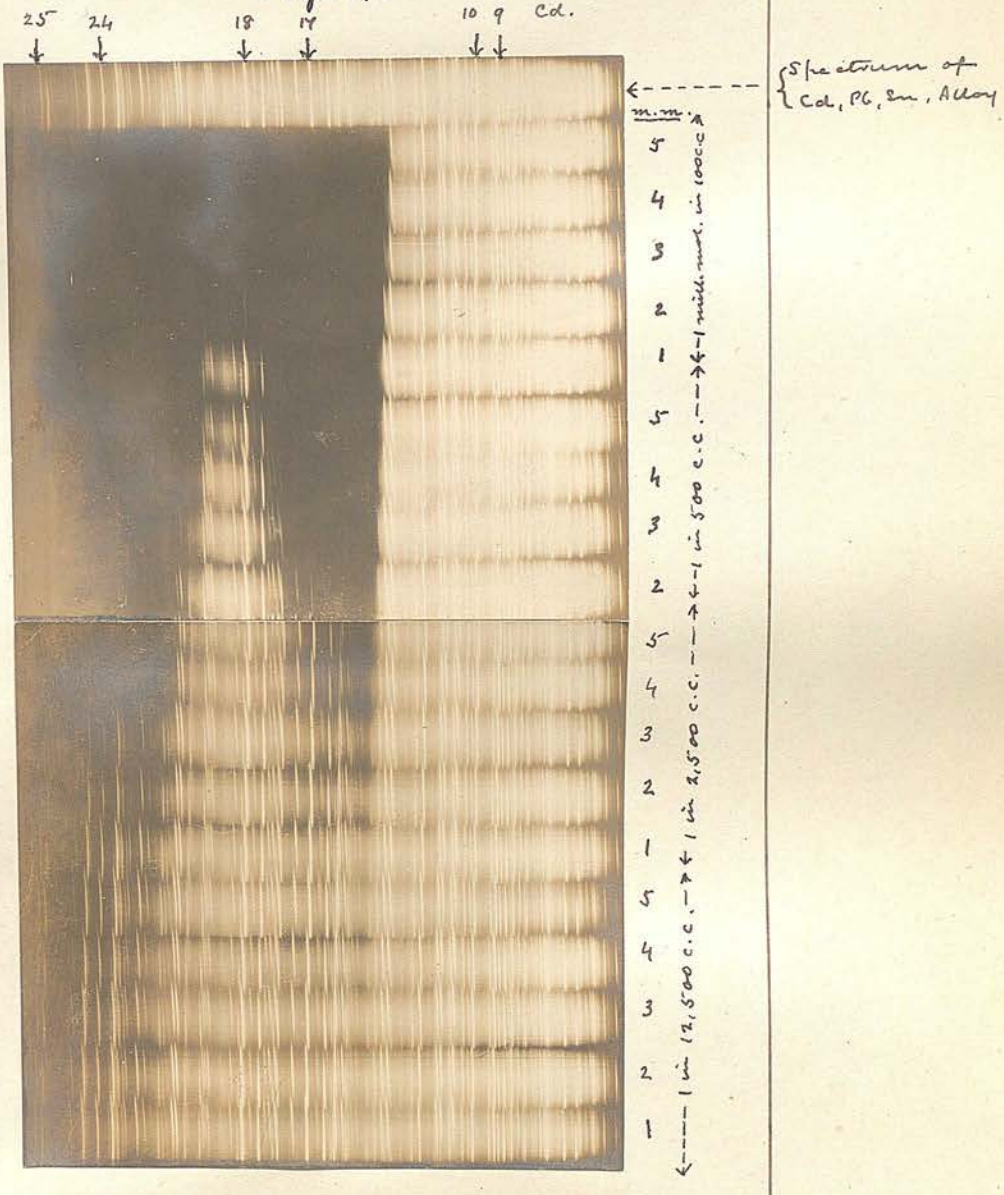
Fig. 3.



Papaverine.

1

Fig. 4.

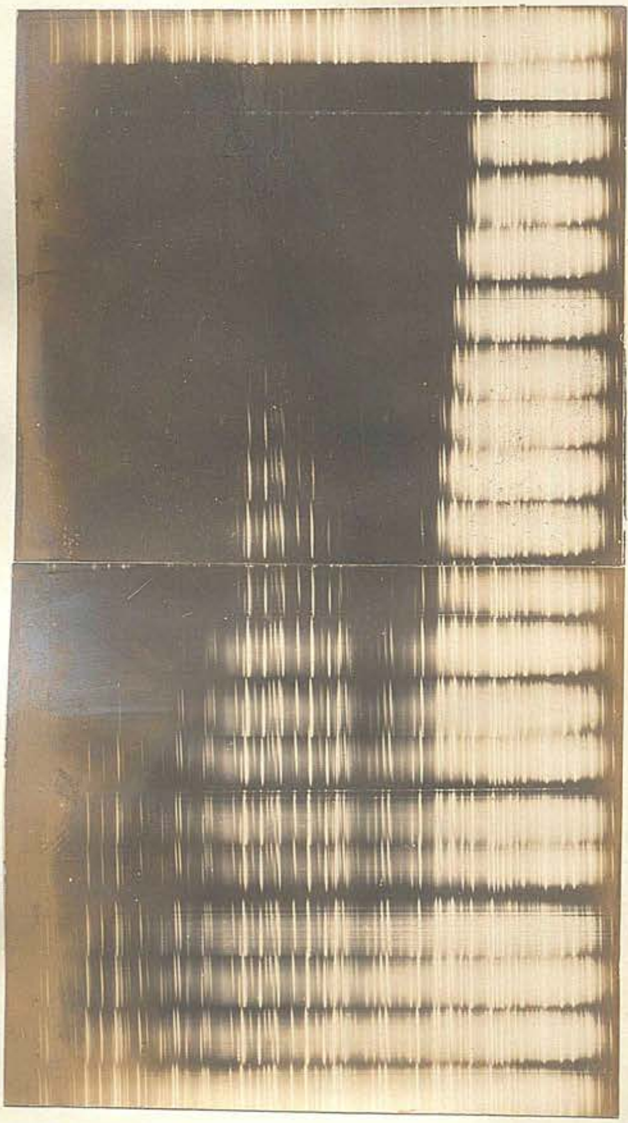


Tetrahydropapaverine.

Cd 9 ~~#~~ λ = 3611·8
Cd 10 λ = 3466·8
Cd 17 λ = 2747·7
Cd 18. λ = 2572·2
Cd 24 λ = 2288·4
Cd 25 λ = 2196·4

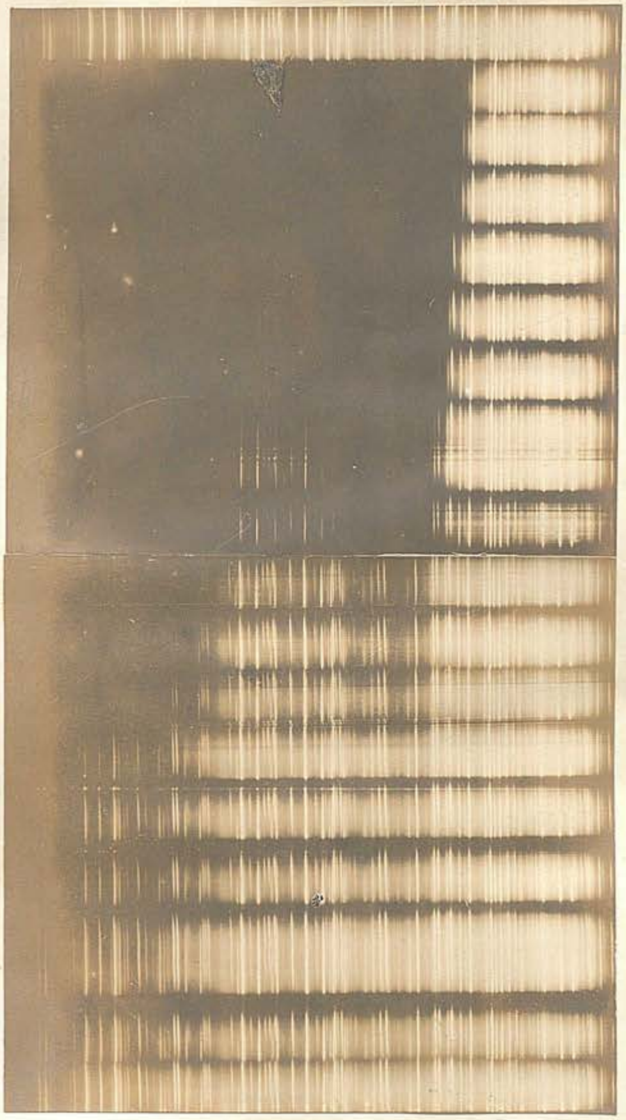
Limits of visible spectrum λ = 7606 to λ 3900

Fig. 5



Hydrastine.

Fig. 6.



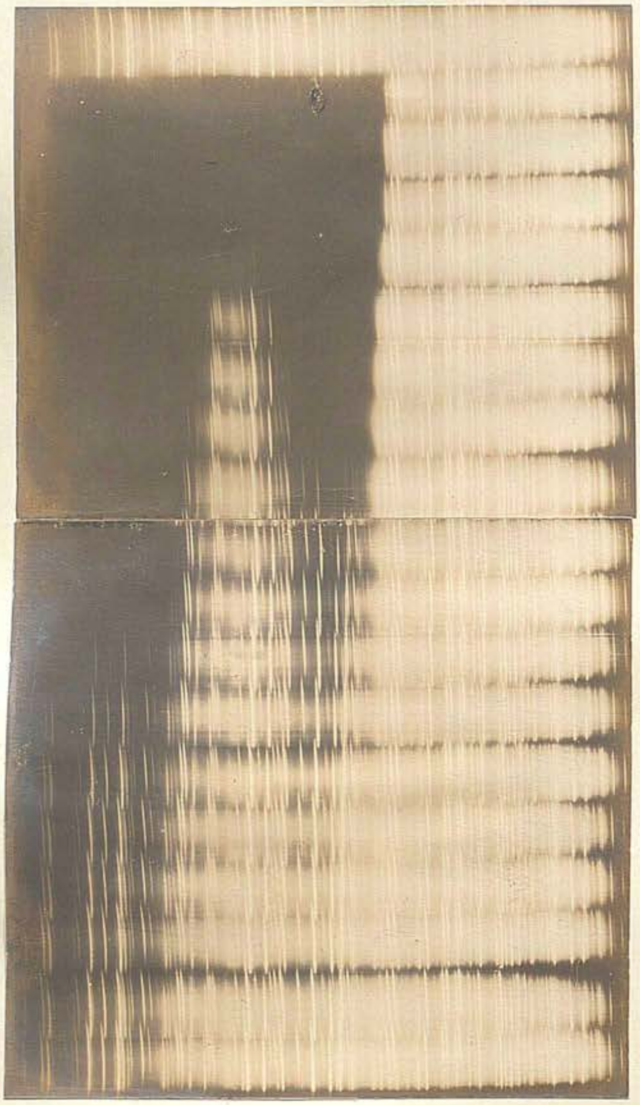
Narcotine.

The spectra of Gnoscopine are identical with the above.

2

(140)

Fig. 7.

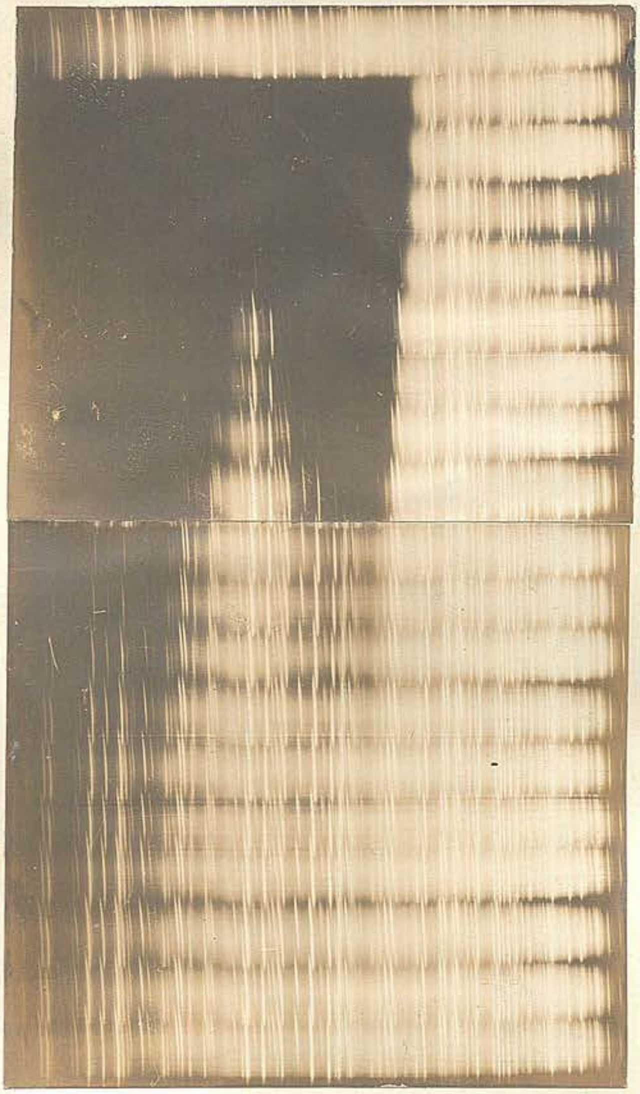


Corydaline.

[d-Corydaline is identical with this.]

3

Fig. 8.

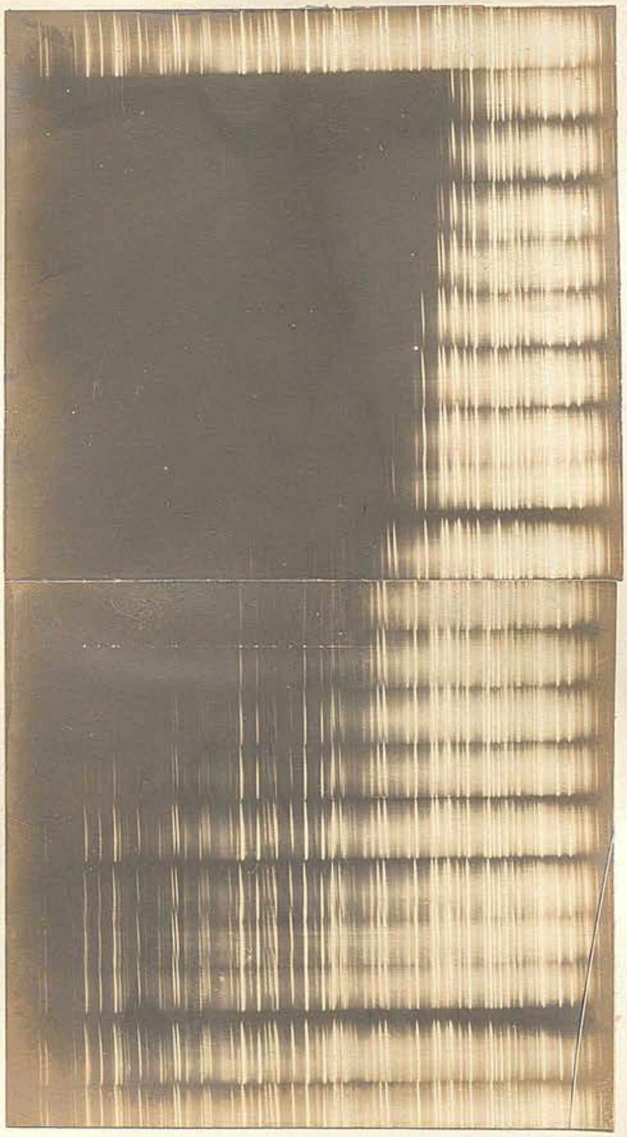


Tetrahydroberberine.

[Canadine is identical with this.]

3

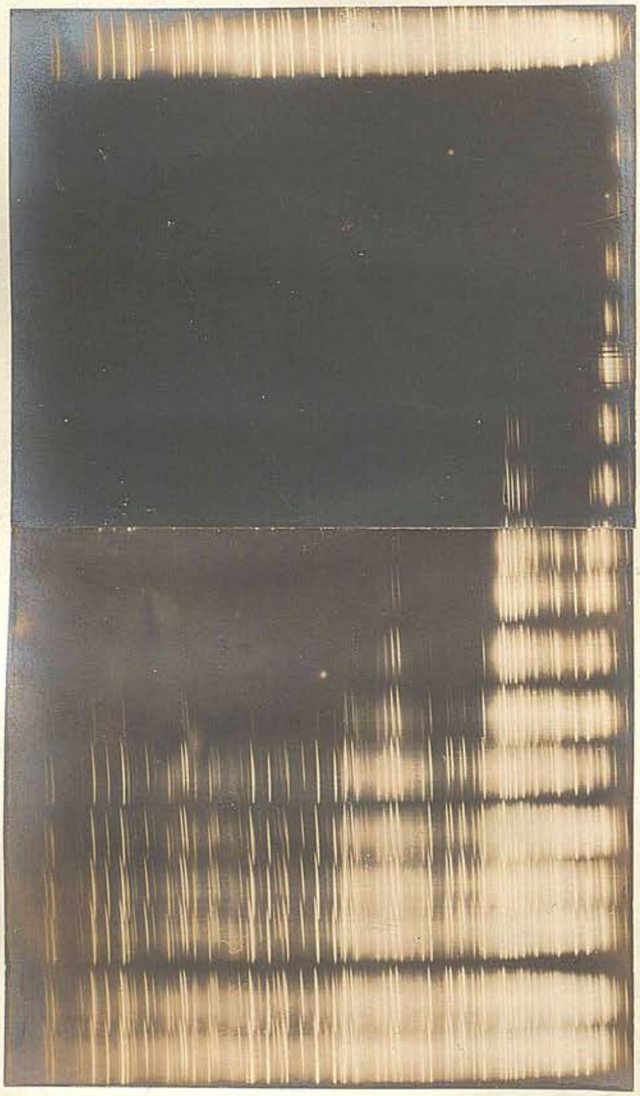
Fig. 9.



Narceine.

(143)

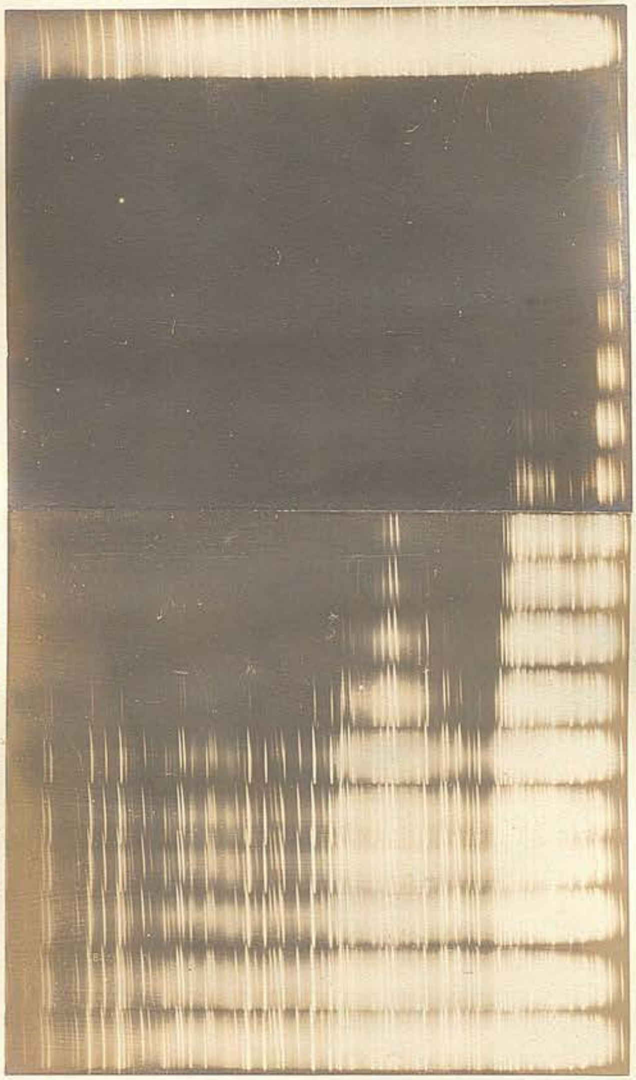
Fig. 10.



Dehydro-corydaline.

5

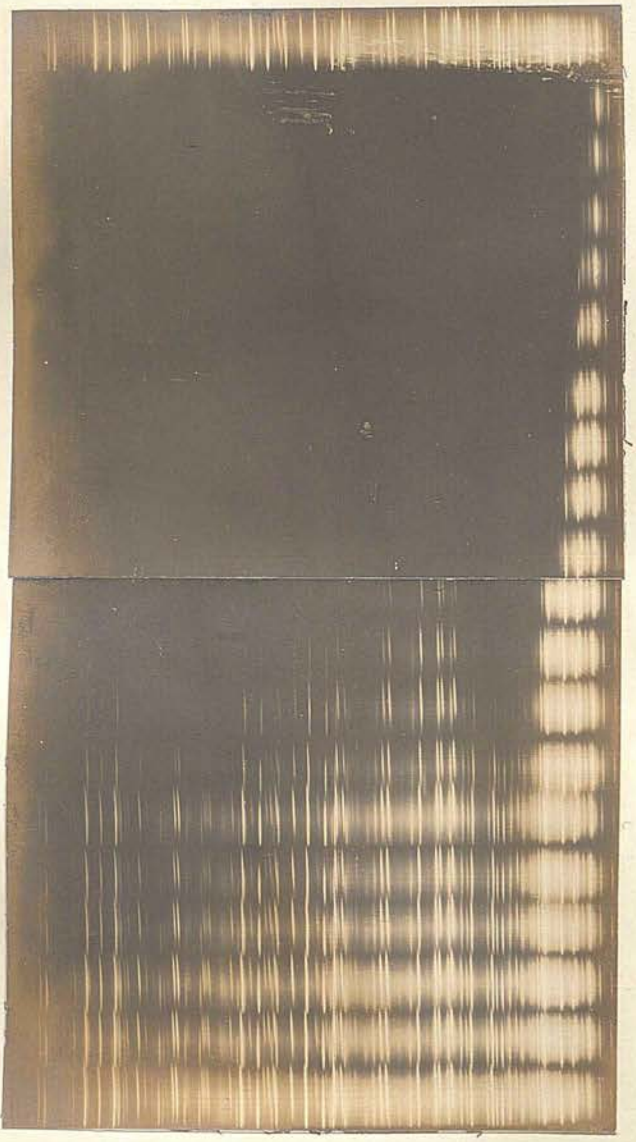
Fig. 11.



Berberine.

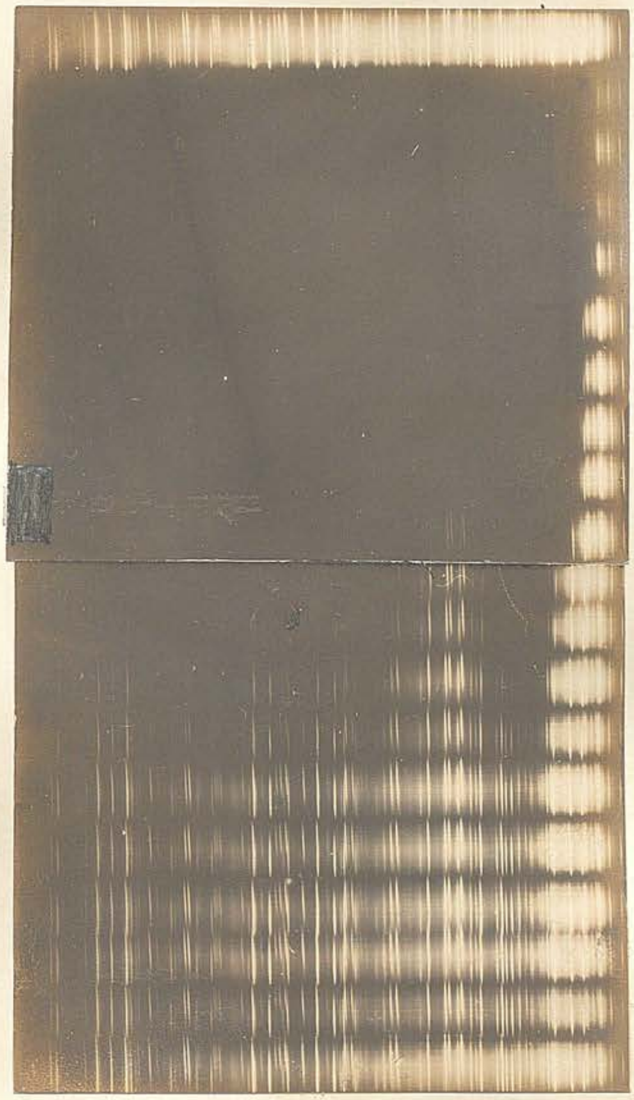
5

Fig. 12.



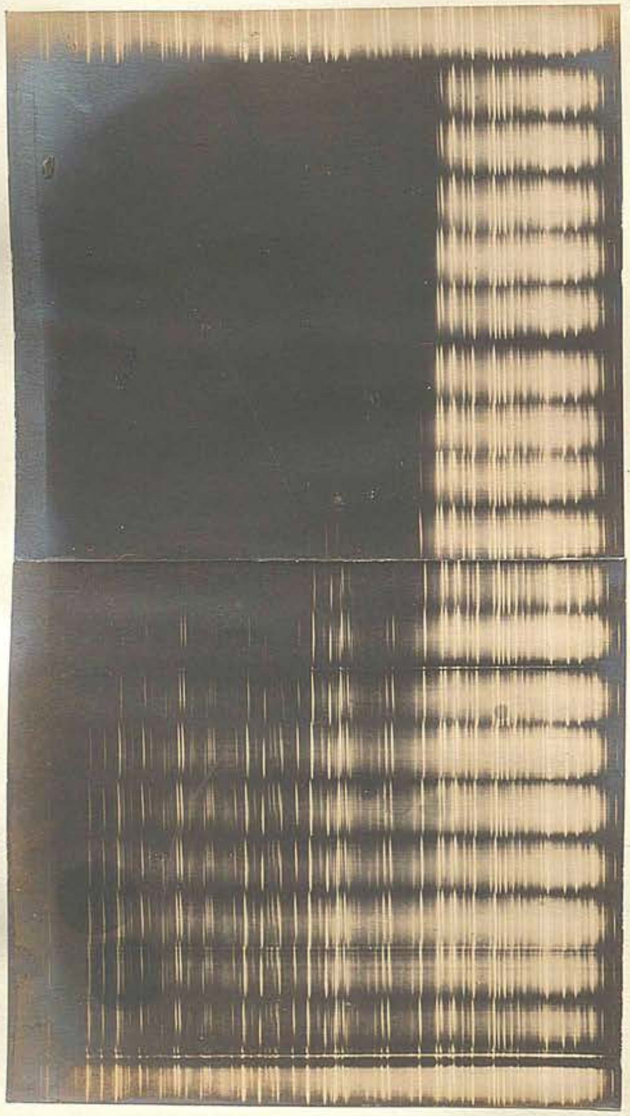
Corydic Acid.

Fig. 13.



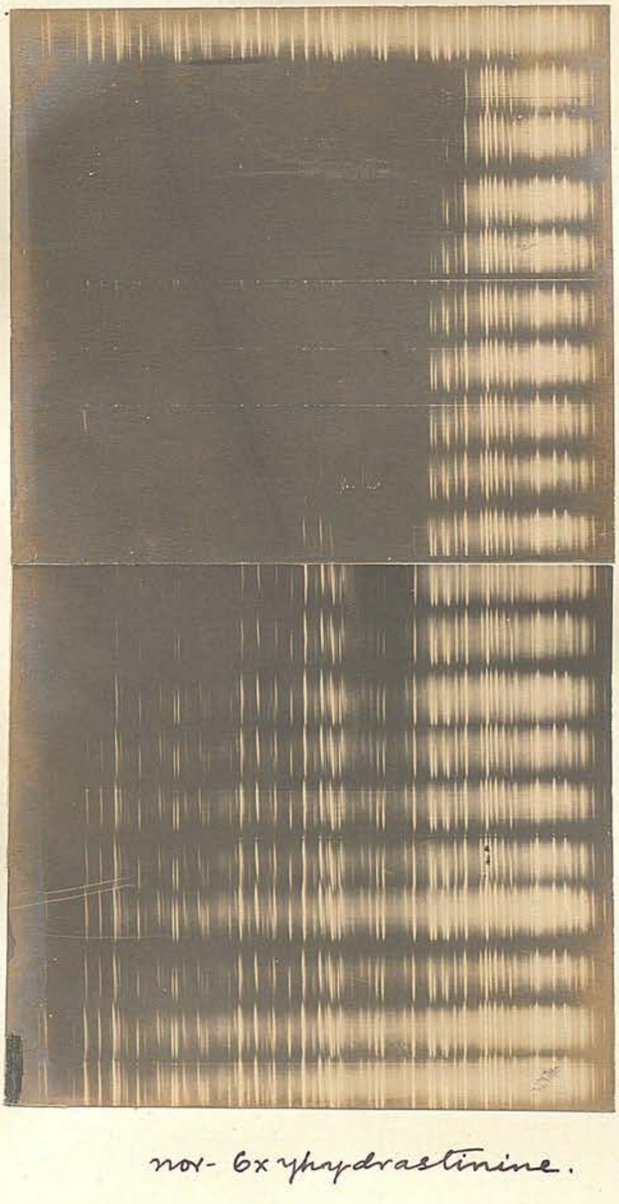
Berberidic Acid.

Fig. 14.



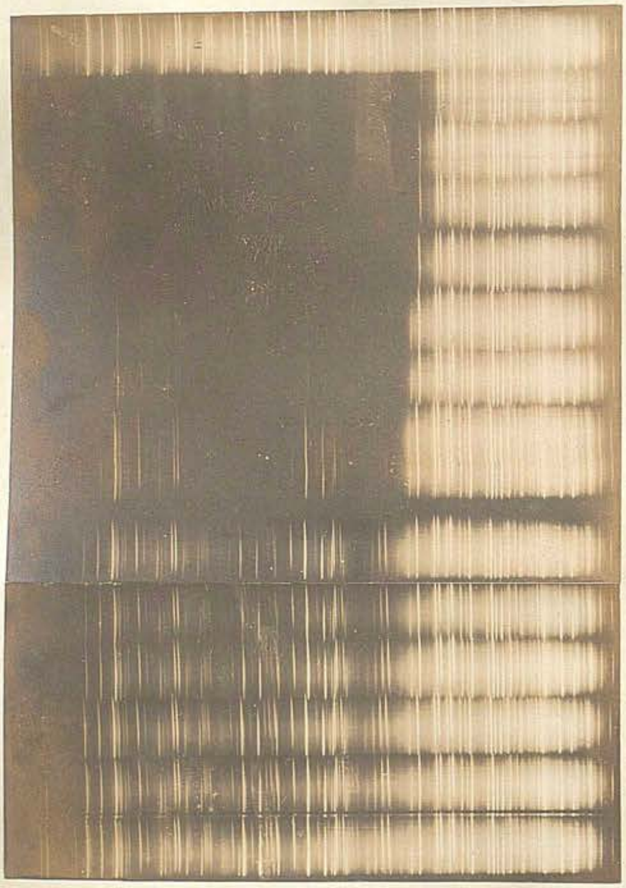
Corydaldine.

Fig. 15.



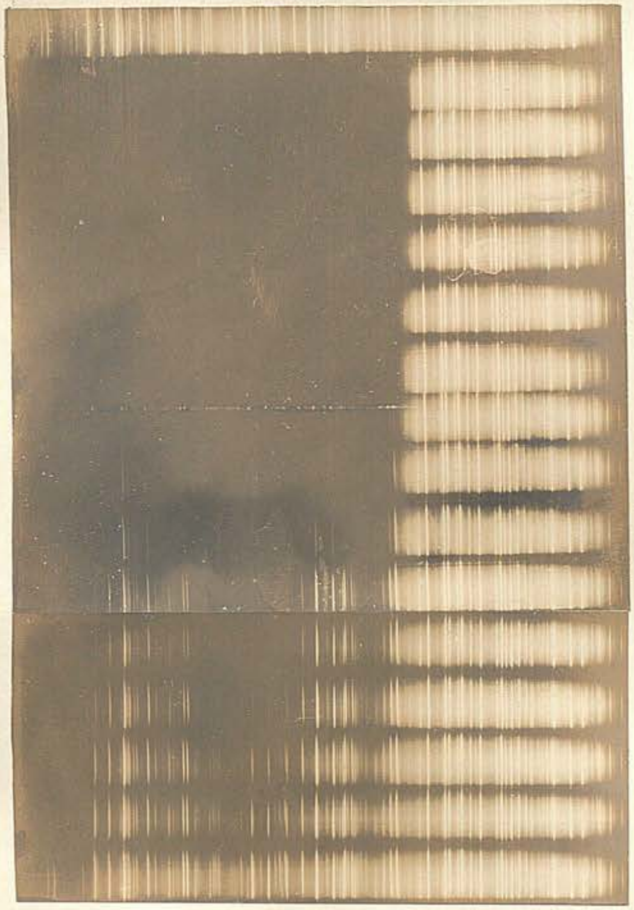
nor-Oxyhydrastinine.

Fig. 16.



Piperonylic Acid.

Fig. 17.

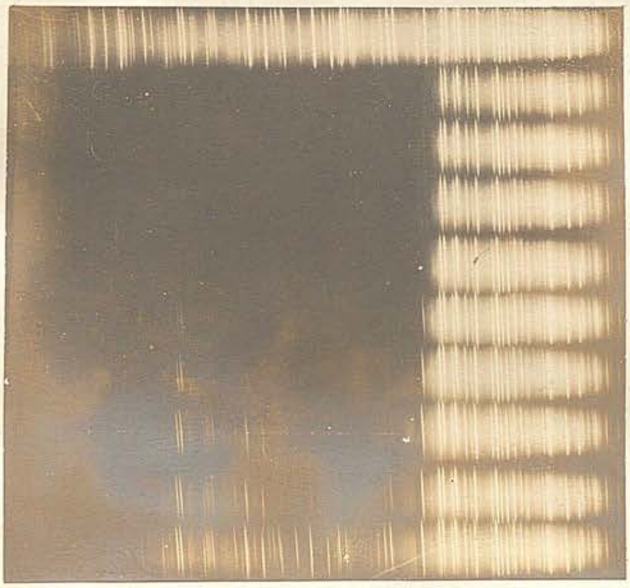


Veratric Acid.

Fig. 18.

Quinine.

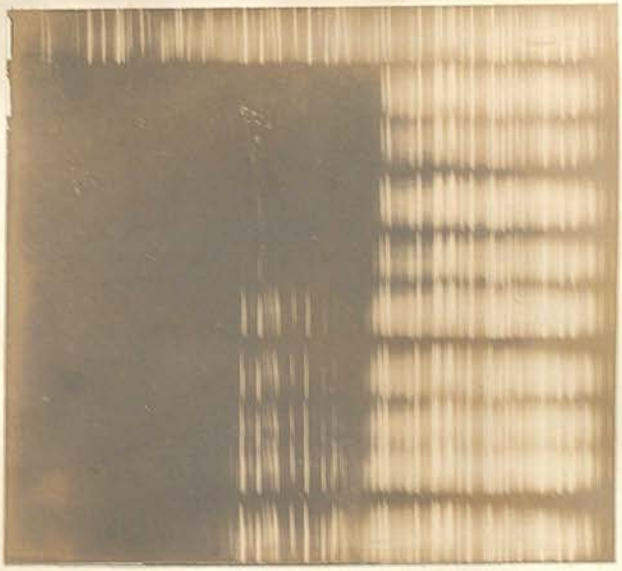
Fig. 19.



Cinchonine.

The absorption spectra of Quinidine & Cinchonidine are identical with those of Quinine & Cinchonine respectively.

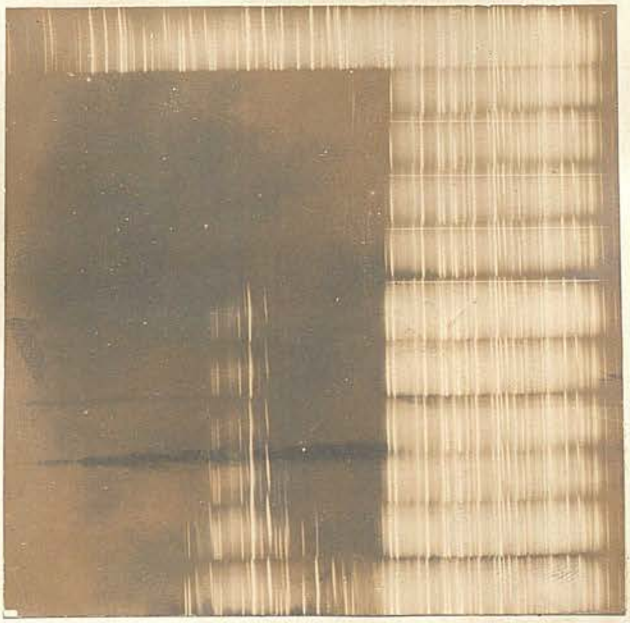
Fig. 20.



Morphine.

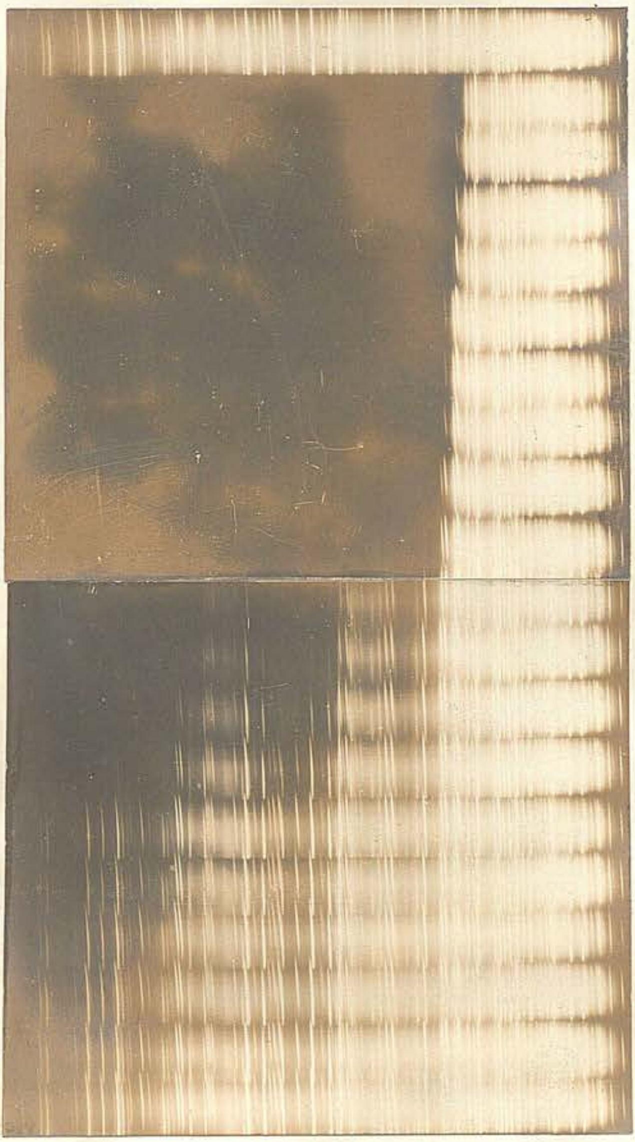
The absorption spectra of Codeine are identical with those of Morphine.

Fig. 21.

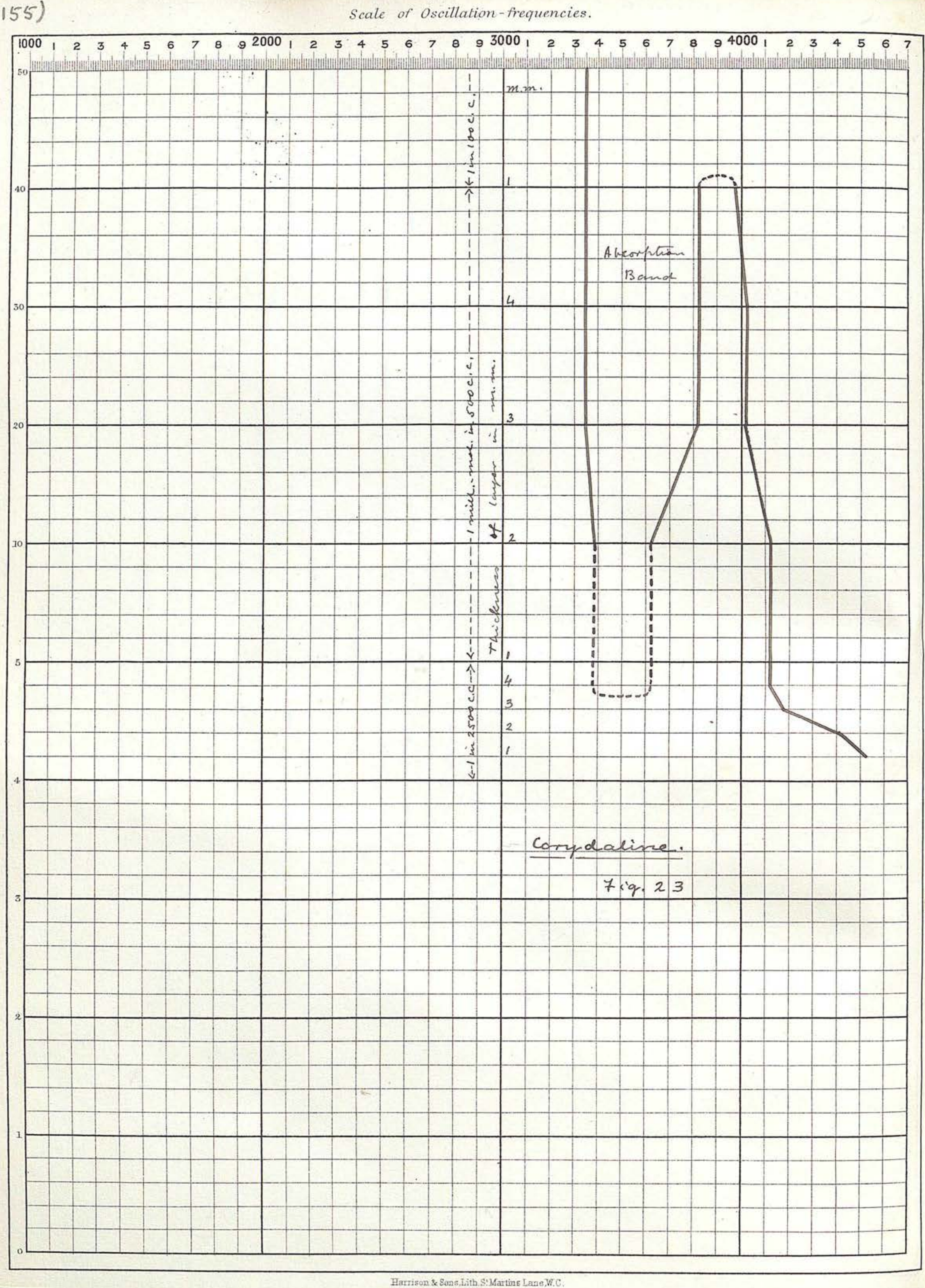


Corybulbine.

Fig. 22.



Bulbocapnine.

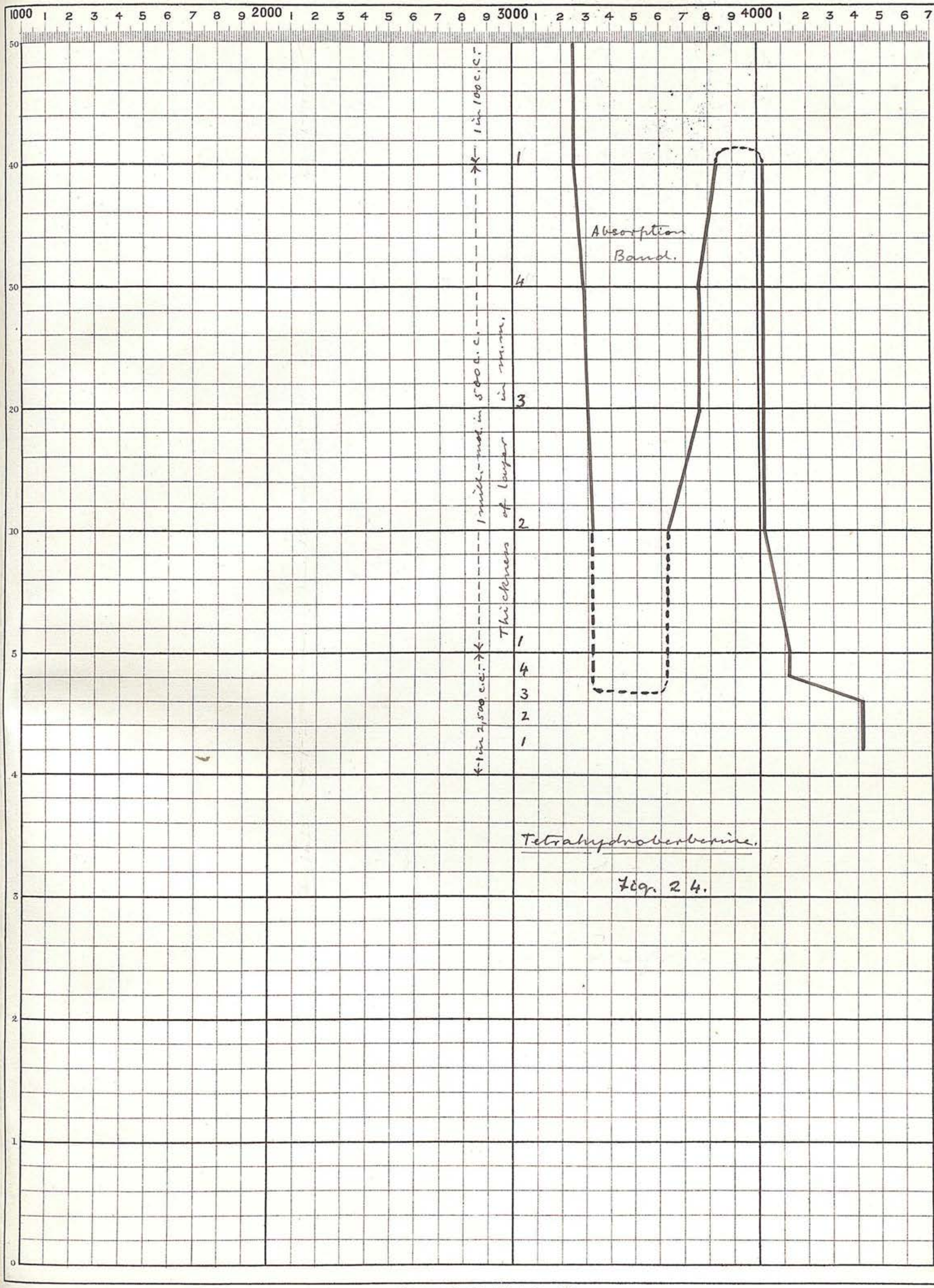


Corydaline.

Fig. 23

Harrison & Sons, Lith. St Martins Lane, W.C.

Scale of Oscillation-frequencies.



Tetrahydroberberine.

Fig. 24.

Harrison & Sons, Lith. St Martins Lane, W.C.