X—*Corydaline*. Part III. *Oxidation with Potassium Permanganate*.

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IN a previous paper (Trans., 1892, **61**, 605), we showed that corydaline contains four methoxy-groups; by oxidising it with potassium permanganate, we have obtained further light on the constitution of the alkaloid. This oxidation was carried out with small quantities of the material, about 8 grams being used for each operation; for this purpose, the alkaloid was suspended in about 2 litres of boiling water, and a solution of potassium permanganate added until it was no longer reduced, the liquid in which the alkaloid was suspended being kept at the boiling point all the time: the amount of permanganate required was about 27 grams, dissolved in 2—3 litres of water. In the event of excess of potassium permanganate having been added, it was reduced by passing sulphur dioxide through the solution. The oxidation usually occupied three hours. The reduction of the permanganate was very rapid at first, ammonia being continuously evolved, but, after about three-fourths of the solution had been added, the oxidation proceeded very slowly. The corydaline employed was carefully purified by repeated recrystallisation until the melting point was constant.

When the oxidation was complete, the manganese precipitate was allowed to settle, the solution filtered off, and the precipitate thoroughly washed with boiling water until the washings were no longer alkaline to litmus paper. The filtrate was then evaporated to dryness, the organic matter extracted with absolute alcohol, the alcohol distilled off, the concentrated solution cautiously evaporated to dryness, and the residue dissolved in water. The potassium in the residue having been estimated, the amount of sulphuric acid required to convert it into potassium sulphate was added. At this stage a considerable quantity of black, tarry matter separated, and was removed by filtration; the solution was concentrated, filtered from a further precipitate of tarry matter, and the potassium sulphate in the filtrate precipitated by adding a large quantity of absolute alcohol; the alcoholic solution was then filtered from the precipitated potassium sulphate, the latter being washed with absolute alcohol until free from organic matter. The greater part of the alcohol was now distilled off, and the remaining solution placed in a desiccator over concentrated sulphuric acid, when the solution gradually deposited a crop of dark brown crystals of a nitrogenous organic acid. On concentrating the mother liquor, a further crop of crystals was ob-

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tained, but the separation of the last portions of the acid was rendered difficult by the presence of some of the black, tarry matter mentioned above, which is easily soluble in alcohol, and also, to a slight extent, in hot water in presence of the acid.

When the whole of the acid had been extracted, the mother liquor yielded, on evaporation, a clear, yellow, resinous mass. This residue is easily soluble in water and in alcohol, and contains an organic acid or acids, which are precipitable by silver and lead, but we have not, as yet, completed our examination of this product of the oxidation.

The yield of crystalline acid obtained by the method described was 20 per cent. of the corydaline used. A portion of the latter always escaped oxidation, and was recovered from the precipitated manganese oxides.

With the view of shortening the process described above, we adopted the following modification in some of our experiments. The potassium in the filtrate from the manganese precipitate was directly neutralised with sulphuric acid, and the potassium sulphate precipitated with absolute alcohol, the rest of the operation being carried on as already described. We found, however, when this modified process was employed, that the yield of acid was greatly diminished. Various other methods of working up the oxidation products were tried, such as precipitation with silver and lead, and subsequent decomposition with hydrogen sulphide, but none of them yielded satisfactory results.

The crude crystalline acid obtained by the process described above was found, on examination, to be homogeneous; it was purified by repeated crystallisation from water, in which it dissolved readily when hot, separating out again on cooling. The colouring matter was removed by treatment with animal charcoal, but even then the acid still retained a slight yellow tinge; when pure, it forms flat, six-sided prisms, which have the habit of monoclinic crystals. They contain $3\text{H}_2\text{O}$.

The acid, dried at 100° , gave the following results on analysis.

I.	0.3011	gave	0.5562 CO_2	and	0.1274 H_2O	; C = 50.38 ; H = 4.70.
II.	0.2778	„	0.5141	„	0.1158	„ C = 50.47 ; H = 4.63.
III.	0.2766	„	0.5094	„	0.1203	„ C = 50.23 ; H = 4.83
IV.	0.3224	„	0.0691 Pt.	N = 3.09.		
V.	0.2669	„	0.0529	„	N = 2.86.	
VI.	0.2735	„	0.0567	„	N = 2.99.	

The mean result of Analyses I and III for carbon and hydrogen, and of IV and VI for nitrogen, gives C = 50.30 ; H = 4.76 ; N = 3.04. From these numbers we deduce the formula $\text{C}_{19}\text{H}_{21}\text{NO}_{12}$, which requires C = 50.11 ; H = 4.62 ; N = 3.07. The water of crystallisa-

tion was determined in specimens of the acid which were dried in a vacuum over strong sulphuric acid.

0.6549 lost 0.0700 at 100°. $\text{H}_2\text{O} = 10.68$.

1.1365 „ 0.1182 „ $\text{H}_2\text{O} = 10.40$.

The mean of the two determinations is $\text{H}_2\text{O} = 10.54$ per cent.

$\text{C}_{19}\text{H}_{21}\text{NO}_{12} \cdot 3\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 10.61$ per cent.

In determining the water of crystallisation, the substance must not be heated above 100°, as at higher temperatures and even on long continued heating at this temperature, there is an appreciable loss of weight, owing to the volatility of the acid. In the second of the two estimations quoted above, the acid was heated at 100° for six hours and weighed; it was then heated for one hour more and again weighed, and as it was found to have lost only 0.0006 gram, the weight was taken as constant.

We propose the name corydalnic acid for this substance. It is freely soluble in hot, but only to a slight extent in cold, water; it is also soluble in methylic and ethylic alcohols, but is insoluble in ether, chloroform, benzene, and carbon bisulphide. When heated, corydalnic acid melts between 175° and 180°, undergoing decomposition. Long before its melting or decomposing point is reached, however, the acid begins to sublime; when heated on a large watch glass covered with a funnel, a sublimate of beautiful, silky, colourless needles is obtained. Their identity with corydalnic acid was proved by analysis of their silver salt and a determination of their decomposing or melting point, which was found to correspond with that of the unsublimed acid.

We attempted to determine the vapour density of the acid at a temperature sufficiently high to ensure its complete volatilisation, but we were only partially successful, owing to the fact that slight decomposition invariably accompanies volatilisation at a high temperature, a small residue, insoluble in water, being left. In one determination, made with Victor Meyer's apparatus, using the vapour of boiling diphenylamine to volatilise the acid, the density found was 252.6, the theoretical value for $\text{C}_{19}\text{H}_{21}\text{NO}_{12}$ being 227.5.

The acid forms well-defined salts, most of which are suitable for analysis.

Potassium Salt.—An aqueous solution of the acid was neutralised with potassium hydrate, evaporated to dryness, and the residue dissolved in water and recrystallised several times. The salt crystallised in tufts of beautiful, silky needles, and gave the following results on analysis.

0.1427 gave 0.0459 K_2SO_4 . $\text{K} = 14.44$.

0.1043 „ 0.0336 „ $\text{K} = 14.46$.

$\text{C}_{19}\text{H}_{19}\text{NO}_{12}\text{K}_2$ requires $\text{K} = 14.68$ per cent.

Silver Salts.—We have prepared a normal and an acid silver salt of corydalinic acid. The normal salt, $C_{19}H_{17}NO_{12} \cdot Ag_4$, was obtained by exactly neutralising the acid with ammonia and precipitating with silver nitrate. The salt separates from a concentrated solution in the form of a thick, curdy precipitate, but from more dilute solutions in the form of a crystalline precipitate. This salt is appreciably soluble even in cold water. It was dried at 100° , and gave the following results on analysis.

- I. 0.4826 gave 0.2333 Ag. Ag = 48.34.
 II. 0.3350 „ 0.1640 „ Ag = 49.10.
 III. 0.2684 „ 0.1313 „ Ag = 48.91.
 IV. 0.1518 „ 0.0742 „ Ag = 48.88.

Mean result of Analyses II and III. Ag = 49.00 per cent.

$C_{19}H_{17}NO_{12}Ag_4$ requires Ag = 48.92 per cent.

The salt used for the first analysis was prepared without previously neutralising the acid with ammonia, and that used in number IV was prepared from corydalinic acid, which had been sublimed.

The acid silver salt was prepared 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.

- 0.2130 gave 0.0693 Ag. Ag = 32.53.
 0.2457 „ 0.0802 „ Ag = 32.64.
 0.1120 „ 0.0361 „ Ag = 32.23.

Mean result of above analyses, Ag = 32.46 per cent.

$C_{19}H_{19}NO_{12}Ag_2$ requires Ag = 32.29 per cent.

When the acid silver salt is carefully heated, a beautiful sublimate of short, needle-shaped crystals was obtained; this sublimate was proved to be corydalinic acid by taking its melting point, and testing it with the reagents which precipitate this acid.

Barium Salts.—The normal salt was prepared by adding a solution of corydalinic acid neutralised 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, crystallisation 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 crystallisation. It was dried at 100° for analysis.

- 0.3320 gave 0.2152 $BaSO_4$. Ba = 38.12.
 0.2396 „ 0.1551 „ Ba = 38.07.

Mean result of the above analyses, Ba = 38.09.

$C_{19}H_{17}NO_{12}Ba_2$ requires Ba = 37.82.

An acid salt was prepared by adding barium chloride to an aqueous solution of corydalnic acid neutralised with ammonia. The precipitation takes place in the same manner as that of the normal salt, but the precipitate in this case forms a very bulky jelly. The salt is slightly soluble in water, and may be obtained in the crystalline form from dilute solutions. It was dried at 100° and analysed.

0.2616 gave 0.0985 BaSO₄. Ba = 22.15.

C₁₉H₁₉NO₁₂Ba requires Ba = 23.24 per cent.

This was one of the first salts of corydalnic acid which we prepared, and as we were ignorant of the properties of the acid at the time, no special precautions were taken to obtain an acid salt.

Lead Salt.—The normal lead salt was prepared by precipitating the acid, after neutralisation 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. This is by far the most beautiful salt of corydalnic acid which we have obtained. It contains no water of crystallisation, and is only very slightly soluble in water. It was dried at 100° for analysis.

0.2328 gave 0.1637 PbSO₄. Pb = 48.01.

0.3539 „ 0.2486 „ Pb = 47.97.

Mean result of above analyses, Pb = 47.99 per cent.

C₁₉H₁₇NO₁₂Pb₂ requires Pb = 47.85 per cent.

The salts of corydalnic acid show a marked tendency to assume the gelatinous condition. When great care is not taken to observe exactly the conditions under which the normal and acid salts respectively are formed, a compound intermediate in composition is almost invariably obtained. It is obvious from inspection of the formulæ of the salts described that corydalnic acid is tetrabasic.

With the view of determining whether any of the four methoxy-groups present in corydaline had been removed by the oxidation with potassium permanganate, we treated the acid with fuming hydrogen iodide solution by Zeisel's method, as described in our second paper on corydaline (*Trans.*, 1892, **61**, 605). The results, although invariably somewhat low, showed conclusively that all four methoxy-groups are still present in the acid. The following were the results obtained.

0.2373 gave 0.4599 AgI. OCH₃ = 25.58.

0.2633 „ 0.5099 „ OCH₃ = 25.57.

0.1916 „ 0.3778 „ OCH₃ = 26.04.

0.3068 „ 0.5996 „ OCH₃ = 25.81.

Theory for four OCH₃ groups in C₁₉H₂₁NO₁₂ = 27.25 p. c. OCH₃.

„ three „ „ „ = 20.44 „

Corydalinic acid may therefore be represented by the formula $C_{11}H_5N(OCH_3)_4(COOH)_4$.

As we have found in previous researches that Zeisel's method for determining methoxy-groups is capable of yielding very accurate results, and as we used every precaution in applying it in this case, we are unable to account for the discrepancy between the theoretical numbers and those actually obtained, unless it is connected with the fact that the action of hydrogen iodide breaks up the acid into several simpler compounds.

Corydalic acid.

Action of Hydrogen Iodide on Corydalinic acid.—By the action of hydrogen iodide on corydalinic acid we should expect to obtain an acid bearing the relation to corydalinic acid indicated by the following formulæ.

In reality, however, the decomposition goes much further than this. About 4·5 grams of corydalinic acid were boiled with 130 c.c. of a fuming solution of hydrogen iodide of sp. gr. 1·70 for three hours, using a reflux condenser, which was allowed to get warm at first so that the methyl iodide might escape. The solution was allowed to stand over night, when a mass of long, slender, silky needles separated; on concentrating the mother liquor, a further crop was obtained, but the total weight of the crystals was always less than half the weight of the corydalinic acid decomposed. The crystals were drained by aid of a filter pump until most of the hydrogen iodide solution had been removed, pressed between slightly damp filter paper, and finally heated in the water oven at 100° for several hours. After this treatment, the crystals were found to be quite free from hydrogen iodide; they were further purified by recrystallisation from water, in which they are easily soluble. This substance is a powerful non-nitrogenous acid, and contains no water of crystallisation. It was dried at 100° for analysis.

I. 0·2546 gave 0·4124 CO_2 and 0·0927 H_2O . C = 44·18; H = 4·04.

II. 0·2432 „ 0·3942 „ „ 0·0881 „ C = 44·21; H = 4·02.

III. 0·2687 „ 0·4396 „ „ 0·0937 „ C = 44·62; H = 3·87.

Mean result of Analyses I and II, C = 44·19; H = 4·04 per cent.

From which we deduce the formula $C_9H_{10}O_8$, which requires C = 43·90; H = 4·06 per cent. We shall refer to this acid for the present under the name of *corydalic acid*, until the further investigation of its properties, in which we are now engaged, has enabled us to determine exactly its relation to acids of known constitution.

Corydalic acid dissolves readily in water and in alcohol. It melts with decomposition at 200° . When silver nitrate is added to its concentrated aqueous solution, a copious white precipitate is obtained after some time; this dissolves readily on heating with partial reduction of the silver, whilst the addition of ammonia causes immediate reduction, even in the cold. Ammonia and potassium hydrate produce a pink coloration in solutions of the acid; an alcoholic solution of potassium hydrate added to an alcoholic solution of the acid throws down a precipitate which is white at first, but rapidly darkens, and finally becomes dirty yellowish-brown. A solution of copper acetate heated with the acid is reduced to the red oxide. With an aqueous solution of the acid, ferric chloride gives an intense, deep green coloration, which is changed to violet by the addition of ammonia or sodium carbonate, the reaction resembling in all respects that which is characteristic of the pyrocatechin derivatives. Dilute nitric acid (1 : 5), heated with a solution of corydalic acid, is reduced, nitrous fumes being evolved; the solution thus obtained, after neutralisation with ammonia, gives a yellow precipitate with lead acetate, totally different in appearance from that obtained with corydalic acid. When the acid is heated with lime, a phenol is produced.

Owing to its powerful reducing properties, and to its tendency to form mixtures of acid and neutral salts, the preparation of the salts of corydalic acid presents special difficulties; so far, we have only succeeded in obtaining one salt which gave satisfactory results on analysis.

Lead Salt.—When lead acetate is added to a cold aqueous solution of corydalic acid, a white, curdy precipitate is immediately thrown down. This precipitate was dried at 100° and analysed.

0.1568 gave 0.1447 PbSO_4 . Pb = 63.02.

0.1149 „ 0.1052 „ Pb = 62.53.

Mean result of above analyses, Pb = 62.78 per cent.

$\text{C}_9\text{H}_6\text{O}_8\text{Pb}_2$ requires Pb = 63.11 per cent.

When the acid is precipitated with lead acetate in presence of ammonia, the precipitate contains a higher percentage of lead than the above salt, but we have not been able in this way to obtain a compound of definite composition. We found in two cases 65.97 and 66.55 per cent of lead; $(\text{C}_9\text{H}_5\text{O}_8)_2\text{Pb}_3$ requires Pb = 68.23 per cent. Barium chloride produces no precipitate either in a hot or cold solution of corydalic acid, and the addition of ammonia only causes a precipitate after boiling. The only analysis which we made of the precipitate obtained in this way gave an unsatisfactory result.

$\text{C}_9\text{H}_6\text{O}_8\text{Ba}_2$ requires Ba = 53.14 per cent. Found 51.26 per cent.

The ethylic salt of corydalic acid, which is a crystalline substance, was prepared by dissolving the acid in absolute alcohol, and saturating

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the hot solution with gaseous hydrogen chloride. The quantity prepared was too small for analysis.

We have not yet completed our examination of the mother liquor from which the corydalic acid was obtained, but we have ascertained that it contains a mixture of substances, amongst which is a nitrogenous compound.

The reactions of corydalic acid show that it contains both hydroxyl and carboxyl groups, and the fact that it yields a phenol when heated with lime shows further that it is a derivative of benzene; moreover, the analysis of the lead salts proves the presence of five atoms of displaceable hydrogen. Remembering that the acid contains nine carbon and eight oxygen atoms, the only formula which reconciles these facts with its formation from corydalinic acid is

As corydalic acid has all its oxygen present in methoxy- and carboxyl groups, and as the action of hydrogen iodide converts the former into hydroxyl groups, the simplest explanation of all the facts is that the acid formed by the action of hydrogen iodide on corydalinic acid is, as represented in the above formula, a dihydroxytricarboxylic derivative of a partially-reduced benzene ring.

Although it would be premature to speculate as to the precise constitution of corydaline, the results of the oxidation with potassium permanganate have in this, as in so many other cases, given an important clue. The formation of corydalinic acid from corydaline is, perhaps, most easily explained on the assumption that corydaline is a derivative of a naphthaquinoline, and that when oxidation takes place the alkaloid is broken up as in the conversion of the naphthaquinolines into phenylpyridinedicarboxylic acids, the benzene and the pyridine ring each having attached to it two of the methoxy-groups, the carboxyl group of the pyridine ring and one of the carboxyl groups of the benzene ring representing the third ring of the naphthaquinoline which has undergone oxidation, whilst the remaining two carboxyl groups of the benzene ring represent the oxidation of the side chains, or fourth ring, whose loss is indicated by the removal of three atoms of carbon on oxidation. According to this view, corydalinic acid is a tetramethoxy-tetracarboxyl derivative of a partially-reduced phenylpyridine, from which, by the action of hydrogen iodide, the pyridine ring is eliminated together with one of the carboxyl and two of the hydroxyl groups, leaving corydalic acid.

Corydaline contains a larger number of hydrogen atoms than any of the other alkaloids of *Corydalis cava*. and it is noteworthy in this connection that that part of corydaline which is represented by corydalic acid consists of a partially-reduced benzene ring.

The facts connected with the constitution of corydaline which have been established so far are the following.

- I. That it contains four methoxy-groups.
- II. That on oxidation with permanganate it yields an acid which is derived from a nitrogenous compound having the formula $C_{11}H_{13}N$.
- III. That this acid, on treatment with hydrogen iodide yields a non-nitrogenous acid which is a derivative of benzene.
- IV. That the methoxy-groups in corydaline are distributed equally between the nitrogenous and the non-nitrogenous rings.
- V. That some, and probably all, of the carbon atoms which are removed during oxidation are attached to the benzene ring.

We anticipate that the investigation of the other products of oxidation, on which we have been engaged for some time, will throw further light on the problem.

Although we have not yet brought to a conclusion the investigation of the action of other agents on corydaline, it may not be out of place to indicate briefly some of the results which we have obtained.

Oxidation with Potassium Hydrate.—We have made numerous attempts to act on corydaline with fused potassium hydrate, varying the proportions of alkali to alkaloid, the temperature, and the length of time during which the fusion was continued, but have always found that even after prolonged heating only a small portion of the alkaloid is affected until the temperature is raised to the point at which it chars and decomposes completely.

Distillation with Zinc Dust.—When distilled with zinc dust, corydaline yields trimethylamine, phenolic products, and a thick, tarry substance; the last-mentioned, on distillation with steam, yields a clear, oily liquid, the greater part of which passes over between 224° and 236° .

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