

LXXI.—CONTRIBUTIONS FROM THE LABORATORIES OF
THE HERIOT WATT COLLEGE, EDINBURGH.*On Berberine. Part II.**

By W. H. PERKIN, Jun., Ph.D., F.R.S.

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* Part I, *Trans.*, 1889, 63.

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Introduction.

IN a paper communicated to the Society some time since, I showed that berberine, $C_{20}H_{17}NO_4$, when very carefully oxidised with potassium permanganate in alkaline solution, yields, besides hemipinic acid and other simply constituted substances, a number of interesting derivatives, containing the same number of carbon atoms as the alkaloid itself.

The further study of the oxidation of berberine has led to the isolation of some new compounds still containing 20 carbon atoms, and

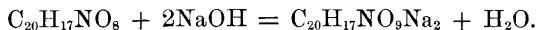
the exhaustive examination of these has given many results which afford a very clear insight into the constitution of the alkaloïd.

The most important of these derivatives are the following:—

Oxyberberine	$C_{20}H_{17}NO_5$,
Dioxyberberine.....	$C_{20}H_{17}NO_6$,
Berberal	$C_{20}H_{17}NO_7$,
Anhydroberberilic acid.....	$C_{20}H_{17}NO_8$,
Berberilic acid	$C_{20}H_{19}NO_9$.

and these, with the exception of the last-named, are derived from berberine by the addition of 1, 2, 3, and 4 oxygen atoms.

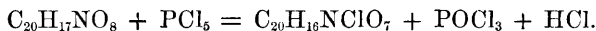
Before explaining in detail the methods employed in preparing and separating these compounds, I propose to give a short sketch of the results of the experiments which have thrown the most light on the constitution of berberine. In doing this it will be well to commence with anhydroberberilic acid, as the study of the properties of this substance served as a foundation on which the examination of the other derivatives was based. Anhydroberberilic acid is almost insoluble in aqueous alkalis and alkaline carbonates at ordinary temperatures, but when warmed with dilute sodium hydrate solution it is readily dissolved, yielding a salt of *berberilic acid*:—



As the free acid, at temperatures above 170° , is reconverted into anhydroberberilic acid, it was at first supposed that berberilic acid was a bibasic acid, containing two carboxyl groups in the ortho-position, and that anhydroberberilic acid was simply its anhydride; subsequent examination showed, however, that although the latter compound is undoubtedly an anhydride of berberilic acid, it is at the same time itself an acid and not a neutral compound.

In support of this statement the following facts may be mentioned:—

1. Under certain conditions (explained in detail in the experimental part of this paper) anhydroberberilic acid forms salts of the formula $C_{20}H_{16}NO_8M'$.
2. When treated with phosphorus pentachloride, anhydroberberilic is converted into the corresponding acid chloride $C_{20}H_{16}NClO_7$, thus:—



From this chloride, the amide $C_{20}H_{16}N(NH_2)O_7$ and the anilide $C_{20}H_{16}N(NH \cdot C_6H_5)O_7$ have been prepared.

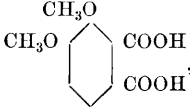
An insight into the constitution of anhydroberberilic acid was

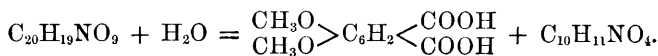
first obtained by the study of berberilic acid, $C_{20}H_{19}NO_9$. This acid is readily obtained by dissolving the anhydro-acid in warm dilute alkalis, and precipitating the alkaline solution with dilute hydrochloric acid; it is a bibasic acid forming salts of the formula $C_{20}H_{17}NO_9M'_2$.

The most interesting salt of this acid is the ammonium salt, $C_{20}H_{17}NO_9(NH_4)_2$, as this when gently warmed or allowed to stand over sulphuric acid in a vacuum, gradually loses half its ammonia, yielding the ammonium salt of anhydroberberilic acid:—

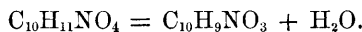


Although only slowly acted on by alkalis, berberilic acid dissolves readily in boiling dilute sulphuric acid, being at the same time

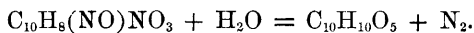
decomposed quantitatively into hemipinic acid, , and a new base, $C_{10}H_{11}NO_4$, thus:—



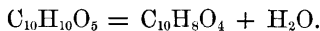
When heated at 180° or digested with strong aqueous potassium hydrate, or even when simply boiled with water for some time, this base loses the elements of a molecule of water, and is converted into its inner anhydride, $C_{10}H_9NO_3$, thus:—



This important substance is feebly basic, its salts being only stable in the presence of large quantities of acid. By the action of nitrous acid, it is converted into a yellow nitroso-compound, $C_{10}H_8(NO)NO_3$, which, when boiled with dilute caustic soda, rapidly dissolves with evolution of nitrogen, thus:—



This substance, $C_{10}H_{10}O_5$, is a monobasic acid, the salts of which are fairly characteristic. When heated to 150° or boiled with water, it readily loses 1 mol. of water and is converted into its inner anhydride, $C_{10}H_8O_4$, thus:—



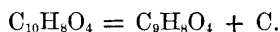
This anhydride is reconverted by dissolution in alkalis into the acid $C_{10}H_{10}O_5$.

Numerous experiments were tried with the object of oxidising this substance to some well known acid, but without success, the compound being either unacted on or else completely destroyed by the

oxidising agents employed. When gently fused with potash, the substance yields a mixture of catechol and protocatechuic acid. This reaction affords some clue to the constitution of this series of compounds, as it proves them to be derivatives of orthodihydroxybenzene; as, however, on the other hand, these substances give no reaction with ferric chloride, the absence of hydroxyl groups must be assumed.

When the anhydride $C_{10}H_8O_4$ was heated with hydriodic acid in Zeisel's apparatus (*Monatsh.*, **6**, 995), not a trace of methyl iodide was evolved, proving the absence of methoxy-groups; decomposition had, however, evidently taken place, as ether extracted from the residue in the retort a dark coloured substance which gave an intense green coloration with ferric chloride, but could not be obtained in a crystalline condition.

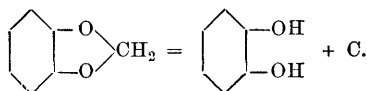
Hydrochloric acid at $170-175^\circ$ decomposes the compound $C_{10}H_8O_4$, apparently quantitatively, with deposition of carbon and formation of a new compound, $C_9H_8O_4$, thus:—



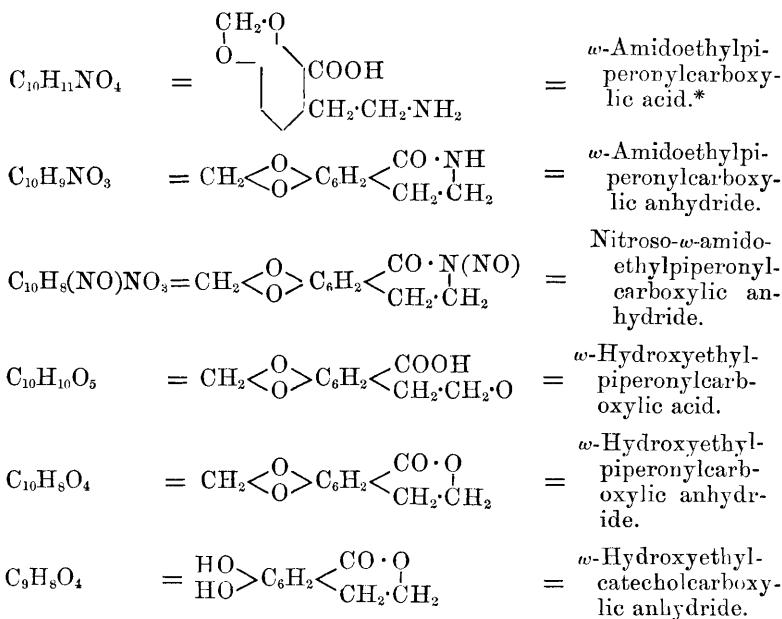
This, with ferric chloride, gives the most intense catechol reaction; it also gives a white precipitate with acetate of lead, and reduces both Fehling's solution and ammoniacal nitrate of silver. This decomposition into carbon and a catechol derivative on heating with water or dilute hydrochloric acid is characteristic of piperonyl derivatives* (Fittig, Remsen, *Annalen*, **159**, 139), and the above experiment, therefore, proves that the derivatives obtained from the base $C_{10}H_{11}NO_4$ (including the base itself) must contain the piperonyl group, $CH_2<\overset{O}{\underset{O}{\text{C}}}>C_6H_4$.

As also, the fact that the two compounds $C_{10}H_{11}NO_4$ and $C_{10}H_{10}O_5$ are readily converted into inner anhydrides proves that they, and therefore their derivatives, must contain two side chains in the ortho-position, the following formulæ may be taken as representing the constitution of these derivatives.

* The nature of this reaction may perhaps be rendered more clear by the partial equation—



For the sake of brevity, I propose that the group $C_6H_4<\overset{O}{\underset{O}{\text{C}}}>CH_2$, which occurs in such a large class of compounds, shall be simply called "*piperonyl*."



Freund and Will (*Berichte*, **20**, 2400), in their researches on hydrastine, describe a substance, oxyhydrastinine, obtained by the action of caustic potash on hydrastinine, which they subsequently

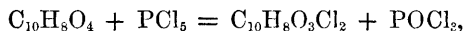
prove to have the constitution

$$\begin{array}{c} \text{CH}_2\cdot\text{O} \\ | \quad | \\ \text{O}-\text{C}_6\text{H}_4-\text{CO}\cdot\text{N}\cdot\text{CH}_3 \\ | \\ \text{CH}_2\cdot\text{CH}_2 \end{array}$$

If the formulæ assigned to the compounds above be correct, oxyhydrastinine must be a methyl derivative of the compound $\text{C}_{10}\text{H}_9\text{NO}_3$, and in order to confirm these formulæ every effort was made to convert the substance $\text{C}_{10}\text{H}_9\text{NO}_3$ into oxyhydrastinine.

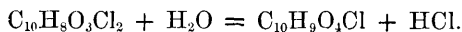
This proved to be extremely difficult, and numerous experiments, extending over several months, failed to bring about the desired result. The transformation was, however, ultimately accomplished in the following way:—

The compound $\text{C}_{10}\text{H}_8\text{O}_4$, when heated with phosphorus pentachloride, is converted into the chloride of *w*-chloroethylpiperonylcarboxylic acid, thus:—

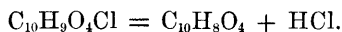


* The relative portion of the two pairs of ortho-side chains is very probably that given here, but further experiments are needed before this view can be definitely accepted.

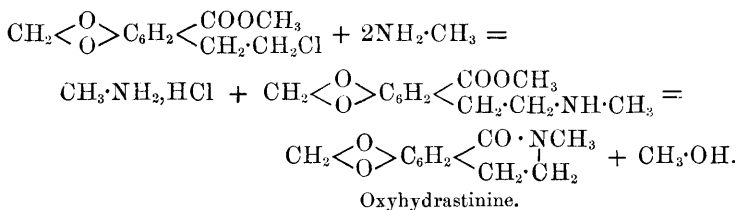
which, when decomposed by water, is converted into the acid $C_{10}H_9O_4Cl$, thus:—



This new acid is remarkable for the ease with which it loses hydrogen chloride, and is converted into the compound $C_{10}H_8O_4$, thus:—



This change takes place on heating at 150° , or on warming with alkalis or reducing with zinc-dust and acetic acid, and also on heating with methylamine in alcoholic solution in a sealed tube. In order to prevent this, the carboxyl group was protected by converting the chloro-acid into its methyl salt, $C_{10}H_8(CH_3)O_4Cl$. This methyl salt, when heated with methylamine in alcohol solution at 130° for six hours, and the product boiled with alcoholic potash, is almost quantitatively converted into oxyhydrastinine, thus:—



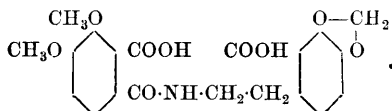
The substance thus obtained melts at 98° , and is identical with oxyhydrastinine, and the synthesis of this compound from *w*-amidoethylpiperonylcarboxylic acid affords conclusive proof that the constitutional formulæ given above to this substance and its derivatives are correct.

An examination of these formulæ shows also that berberine is an isoquinoline and not a quinoline derivative, and the decomposition of berberilic acid into hempinic acid and *w*-amidoethylpiperonylcarboxylic acid affords evidence that this alkaloïd must be closely related to papaverine, hydrastine, and narcotine (p. 1004).

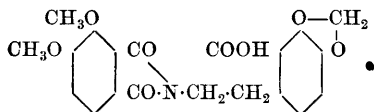
As berberine is an isoquinoline derivative, the statement of Bernheimer (*Gazzetta*, **13**, 342) that berberine, when fused with potash, yields quinoline cannot be correct; it is probable that the substance which he obtained was isoquinoline.

Constitution of Berberilic Acid and Anhydroberberilic Acid.

As berberilic acid is a bibasic acid, and as, on hydrolysis, it yields hempinic acid and *w*-amidoethylpiperonylcarboxylic acid, its constitution must be represented by the formula

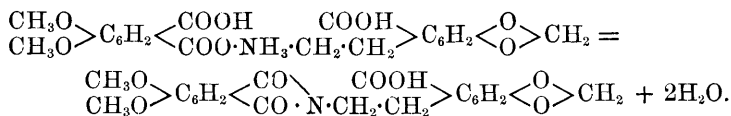


Anhydroberberilic acid is a monobasic acid, and is derived from berberilic acid by the elimination of one molecule of water; its formula is therefore



Additional proof of the correctness of these formulæ is afforded by the synthesis of anhydroberberilic acid.

This interesting synthesis is readily accomplished by heating the hemipinate of *ω*-amidoethylpiperonylcarboxylic acid, which is formed by evaporating mixed aqueous solutions of hempinic and *ω*-amidoethylpiperonylcarboxylic acids. This reaction is readily understood with the aid of the following equations:—



In Part I of this research (*loc. cit.*, pp. 78 and 84) two substances are described which have the same formula as berberilic acid.

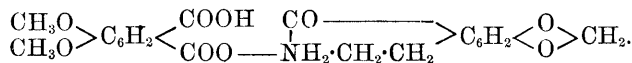
One of these compounds melts at 140—141°, and is very closely related to berberilic acid, because, when heated to 180°, it, like berberilic acid, is quantitatively converted into anhydroberberilic acid; as, however, berberilic acid melts at about 180°, it would seem that the two acids are isomeric and not identical.

The melting point of berberilic acid is, however, lowered to an unusually marked degree by the least trace of impurity, and it is therefore necessary that further experimental data should be forthcoming, before the isomerism of the two acids can be considered as proved. It is, nevertheless, interesting to note that, theoretically, two substances of the formula $\text{C}_{20}\text{H}_{19}\text{NO}_9$ are possible, both of which on heating would be converted into the same anhydroberberilic acid; and there seems to be no reason why, by slightly altering the conditions of formation or hydrolysis, the acid isomeric with berberilic acid might not be formed.

The constitution of one of these isomeric acids would be represented by the formula given above for berberilic acid; the second acid would have the constitution represented by the formula



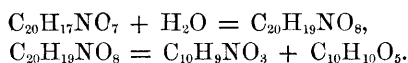
The other substance of the formula $\text{C}_{20}\text{H}_{19}\text{NO}_9$ (*loc. cit.*, p. 84) melts at $178\text{--}179^\circ$, and is decomposed by warm dilute sodium carbonate into *hemipinic acid* and *w-amidoethylpiperonylcarboxylic anhydride*. This substance must, therefore, be considered as the acid hemipinate of *w-amidoethylpiperonylcarboxylic anhydride*, and its constitution is therefore :—



Examination of Berberal, $\text{C}_{20}\text{H}_{17}\text{NO}_7$.

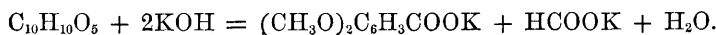
The experiments on the constitution of berberal were rendered extremely difficult from the fact that this substance is only produced in very small quantity in the oxidation of berberine; about 10 grams of pure substance was obtained from 1 kilo. of berberine hydrochloride.

The preparation and some of the properties of berberal have already been given in Part I of this research (pp. 81, 82), and it was there stated that this substance, although insoluble in alkalis in the cold, was apparently converted into the potassium salt of an acid by dissolution in potassium hydrate. In following up this reaction, it was found that, when treated with alcoholic potash, berberal yields three substances, namely: *w-amidoethylpiperonylcarboxylic anhydride* ($\text{C}_{10}\text{H}_9\text{NO}_5$); an acid $\text{C}_{10}\text{H}_{10}\text{O}_5$ (m. p. 121°), and a neutral substance $\text{C}_{20}\text{H}_{19}\text{NO}_8$ (m. p. 149°); these are formed according to the following equations :—

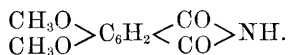


As the constitution of *w-amidoethylpiperonylcarboxylic anhydride* has already been proved (p. 997), there is no further need of discussing this compound here.

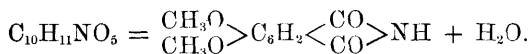
The acid $\text{C}_{10}\text{H}_{10}\text{O}_5$ is a monobasic acid forming salts of the formula $\text{C}_{10}\text{H}_9\text{O}_5\text{M}'$; it shows the following behaviour with reagents: (a) When treated with hydrogen iodide in Zeisel's apparatus, results were obtained which proved that the acid contained two methoxyl groups. (b) Fusion with potash converts the acid into protocatechuic acid; but if caustic potash solution (sp. gr. 1.4) is employed, and the acid simply digested with this in a reflux apparatus, veratric acid (m. p. $177\text{--}178^\circ$) and apparently also formic acid are produced, thus :—



(c) When subjected to the action of hydroxylamine, an oxime, $C_{10}H_{11}NO_5$, is produced. This melts at about 124° , but at once becomes solid again, and then does not again melt until the temperature is raised to 213° . Further experiments showed that this behaviour was due to the formation of hemipinide:—

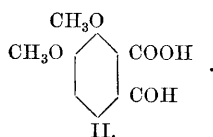
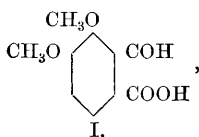


This decomposition is represented by the equation



(d) It is readily reduced by sodium amalgam, being converted into an acid, which when precipitated from its alkaline solution by the addition of mineral acids and recrystallised from water, loses 1 mol. of water, with formation of pseudomeconine, $\begin{array}{c} \text{CH}_3\text{O} \\ \text{CH}_3\text{O} \end{array} > \text{C}_6\text{H}_2 < \begin{array}{c} \text{CH}_2 \\ \text{CO} \end{array} > \text{O}.$

These experiments prove conclusively that the acid $C_{10}H_{10}O_5$ has the constitution represented by the formula I, and it thus bears a very close relationship to *opianic acid*, II—



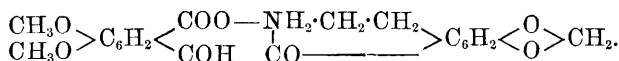
This relationship is brought out in a most interesting way by a parallel study of the reactions of the two substances; for instance, both are monobasic acids; both contain two methoxyl groups in the ortho-position; both, on reduction, yield meconines, and with hydroxylamine both yield oximes, which, when gently warmed, are converted into hemipinide. The acid $C_{10}H_{10}O_5$ may, therefore, be called *pseudopianic acid*.

The hydrolysis of berberal by means of dilute sulphuric acid was next studied, with the result that exactly similar decomposition products were formed in this case as in the hydrolysis by means of alcoholic potash, namely, the anhydride $C_{10}H_9NO_3$, pseudopianic acid, and the neutral substance $C_{20}H_{19}NO_6$.

Owing to the difficulty of obtaining any quantity of berberal, and the inadvisability of using up, for purely qualitative experiments, the small stock of this substance available, further information bearing on the constitution of this compound had to be in the first place obtained indirectly.

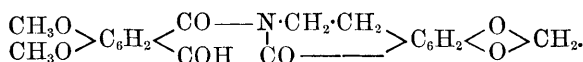
For this purpose a number of experiments on the action of opianic

acid (from narcotine) on the anhydride $C_{10}H_9NO_3$ were instituted and it was found that if these two compounds, in molecular proportions, are well mixed and dissolved in boiling water, a new substance, $C_{20}H_{19}NO_8$, crystallises out on cooling; this in its reactions shows very great similarity to the isomeric substance obtained from berberal, with which, however, it is not identical. The new compound is obviously the opianic salt of the anhydride $C_{10}H_9NO_3$, and its constitution is therefore represented by the formula

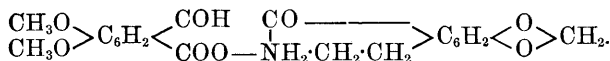


The most interesting property of this salt is that, when heated at 200° , it loses the elements of a molecule of water, and is converted into a compound $C_{20}H_{17}NO_7$ (m. p. 185°), which is isomeric with, and bears the strongest resemblance to berberal, for which reason I propose to name it *isoberberal*.

The constitution of this compound is represented by the formula

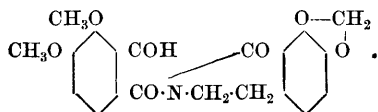


These experiments were next repeated with pseudopianic acid instead of opianic acid, with the result that exactly similar compounds were obtained. Pseudopianic acid and the anhydride $C_{10}H_9NO_3$ combine readily in aqueous solution with formation of the pseudopianic salt of the anhydride $C_{10}H_9NO_3$. This substance is identical with the compound $C_{20}H_{19}NO_8$, which is obtained by the action of alkalis on berberal. It is isomeric with the substance obtained by the action of opianic acid on the anhydride $C_{10}H_9NO_3$, and has the constitution represented by the formula

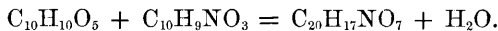


The relationship between these two substances is at once apparent from a comparison of their constitutional formulæ.

Just as the opianic salt of the anhydride $C_{10}H_9NO_3$, on heating at 180 – 200° , yields *isoberberal*, so this corresponding pseudopianate, under the same conditions, is converted almost quantitatively into berberal. *Berberal* has therefore the following constitutional formula:—



The synthesis of berberal may be still more conveniently accomplished by heating an intimate mixture of pseudopianic acid and the anhydride $C_{10}H_9NO_3$, in molecular proportion, at 200° for a few minutes. The reaction which takes place under these circumstances is the following:—

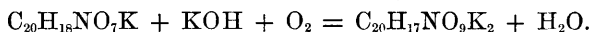


There is a possibility of synthesising berberine from berberal, and if this were to succeed, a most interesting isomeric alkaloid could be obtained from isoberberal. Experiments on this point are in progress.

Oxyberberine, $C_{20}H_{17}NO_5$.—This substance, which is formed only in very small quantities by the oxidation of berberine under the conditions described in this paper, is insoluble in alkalis, but combines with strong acids, forming salts; its basic properties are, however, very much less marked than those of berberine itself.

Oxyberberine is a tertiary base, incapable of forming an acetyl compound. It does not appear to combine with phenylhydrazine; it is not decomposed on boiling with alcoholic potash or on heating with alcoholic ammonia at 150° .

Dioxyberberine, $C_{20}H_{17}NO_6$.—This extremely interesting substance has scarcely any basic properties, but it dissolves in warm alcoholic potash, forming a deep-red solution; this, on cooling, deposits a beautiful, crystalline potassium salt, $C_{20}H_{18}NO_7K$, which is decomposed by acids with regeneration of dioxyberberine. In contact with oxygen or air, the solution of the potassium salt gradually loses its red colour, and in the course of a few days becomes almost colourless; on the addition of acids it then deposits a white precipitate of berberilic acid. This remarkable reaction may be represented by the equation

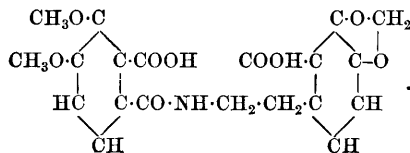


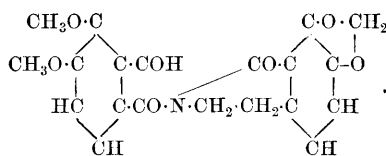
Further experiments will, it is hoped, throw some light on this very peculiar reaction.

Constitution of Berberine.—Although not conclusively proved by the above experiments, the constitution of berberine may be deduced with a considerable amount of certainty from the results obtained in the study of the constitution of berberilic acid and of berberal.

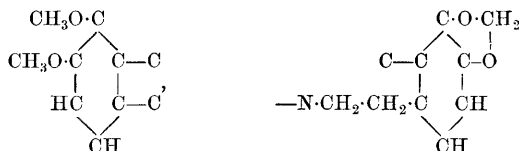
These two substances have the following constitutional formulæ:—

Berberilic acid,



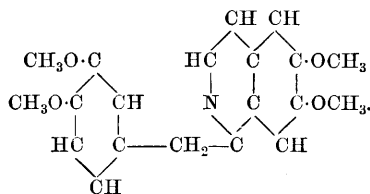
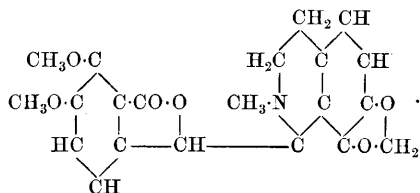
Berberal,

From an examination of these formulæ, it is readily seen that berberine, $\text{C}_{20}\text{H}_{17}\text{NO}_4$, must contain the following groups of atoms:—

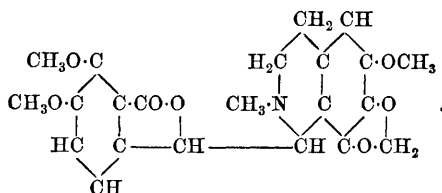


and as these already contain C_{20} , H_{16} , N , O_4 , it follows that, in assigning a constitutional formula to berberine, these two parts must be united with the addition of one atom of hydrogen only.

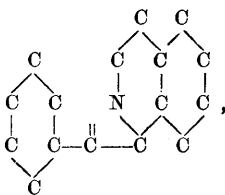
As the decomposition products of berberine are in many respects very similar to those obtained from papaverine, hydrastine, and narcotine, it is reasonable to suppose that these four alkaloids are all very closely related in constitution. The following formulæ are generally accepted as representing the constitution of papaverine, hydrastine, and narcotine:—

Papaverine (Goldschmiedt, *Monatsh.*, **6**, 667),*Hydrastine* (Freund and Rosenberg, *Ber.*, **23**, 414),

Narcotine (Roser, *Annalen*, **254**, 357),

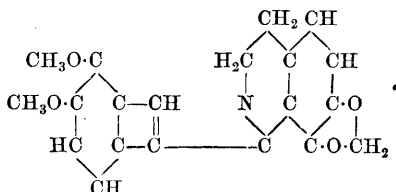


These alkaloids are all built upon the common foundation

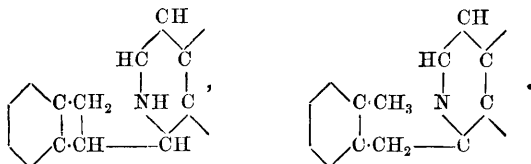


and a careful study of the properties of berberine and its derivatives leaves scarcely any doubt that this group of atoms or one very similar occurs also in berberine.

With this point in view, the simplest formula for berberine would be



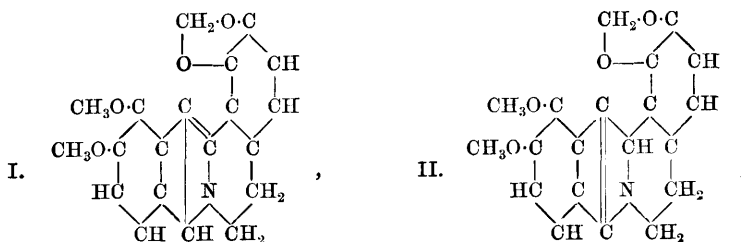
Berberine, when reduced, yields *tetrahydroberberine*, C₂₀H₂₁NO₄. This substance is a tertiary base. On treatment with oxidising agents (bromine, iodine, nitric acid, &c.), it is very readily reconverted into berberine; its constitution cannot therefore be derived from the above formula, as this, on reduction, would yield a compound which would contain one of the following two groups:—



A substance containing the former would be a secondary base, and a

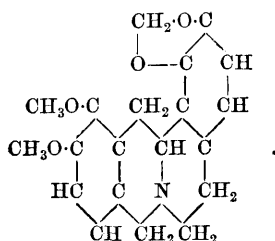
compound containing the latter would obviously not be reconverted into the alkaloïd on treatment with such oxidising agents as iodine.

There are, however, two formulæ, closely allied to the one given above, and built upon a very similar foundation, which account, in a satisfactory manner, for all the known reactions of berberine, namely :—



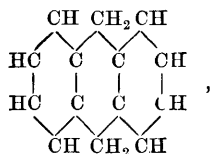
and, of these, formula I would seem to be the more plausible.

Both of these formulæ yield, on reduction, the same tetrahydroberberine :—



This formula accounts at once for the ready way in which tetrahydroberberine is reconverted into berberine on oxidation, as is apparent from the following considerations :—

In the first place, this formula contains a group of atoms very similar to that contained in hydranthracene,



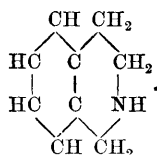
and this substance, on oxidation, is converted with the greatest ease into anthracene, $C_6H_4 \begin{smallmatrix} CH \\ | \\ CH \end{smallmatrix} C_6H_4$.

This point is still more clearly brought out from the comparison of the above formula for tetrahydroberberine with that of dihydro-

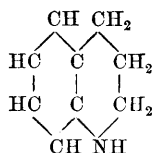
acridine,* $C_6H_4 < \begin{smallmatrix} CH_2 \\ NH \end{smallmatrix} > C_6H_4$, a substance which, when treated even with such feeble oxidising agents as alcoholic nitrate of silver, loses two atoms of hydrogen with formation of acridine, $C_6H_4 < \begin{smallmatrix} CH \\ N- \end{smallmatrix} > C_6H_4$.

From these considerations, it would appear at first sight as though tetrahydroberberine, $C_{20}H_{21}NO_4$, should, on oxidation, lose only two atoms of hydrogen with formation of a substance of the formula $C_{20}H_{19}NO_4$.

Tetrahydroberberine is, however, a derivative of tetrahydroisoquinoline,



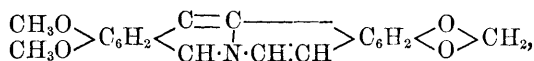
This substance has lately been prepared by Hoogewerff and Van Dorp (*Recueil des travaux chimiques des Pays-Bas*, **5**, 310), and has been found to be readily oxidised even by nitrate of silver, but the products of the oxidation have not yet been studied. On the other hand, tetrahydroquinoline,



which is very closely related to tetrahydroisoquinoline, is readily oxidised by bromine or dilute chromic acid solution to quinoline and its derivatives.

It is interesting to note that berberine itself contains a dihydroisoquinoline group, and the presence of this group accounts for the fact that the alkaloid reduces nitrate of silver, and is so readily attacked by oxidising agents.

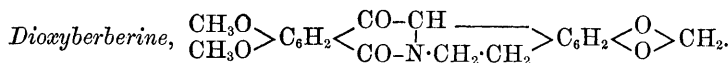
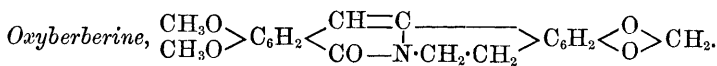
It is hoped that further experiments, which are in progress, will succeed in removing the two hydrogen atoms; and that in this way the mother substance of berberine, that is,



may be obtained.

* See also dihydrophenylacridine (Bernthsen, *Annalen*, **224**, 25), and methylhydrophenylacridine (Bernthsen, Bender, *Ber.*, **16**, 1815).

Assuming formula I (p. 1006) to represent the constitution of berberine, the constitution of oxyberberine and dioxyberberine is readily understood from the following formulæ:—



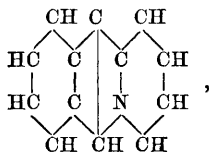
These formulæ explain the general character and reactions of these substances, and give a clear insight into the processes which take place in the production of these compounds from berberine, and in the subsequent splitting up of the central oxidised ring with formation of berberal and anhydroberberilic acid.

The dioxyberberine formula also explains the fact that this substance, on treatment with alcoholic potash, yields a potassium salt of the formula $\text{C}_{20}\text{H}_{18}\text{NO}_7\text{K}$; this would have the constitution



It is, however, difficult to account for the conversion of this salt into a salt of berberilic acid by the absorption of oxygen in alkaline solution.

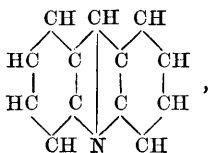
With the introduction of each oxygen atom into the molecule of berberine, the basic nature of the substance, and at the same time the intensity of its colour, decreases, until, as soon as the central ring is split, as in the case of berberal and anhydroberberilic acid, the derivatives become colourless, and show no appreciable basic properties. On the other hand, the methoxy-groups and the methylenedioxy-group appear to have little influence on the tinctorial property of berberine, because other alkaloids, such as narcotine and hydrastine, which are somewhat similarly constituted, and contain the same number, or even more, of such groups, are colourless. The group of atoms which appears to impart to berberine its intense yellow colour and tinctorial properties is the strongly basic group



which is absent in the colourless alkaloids papaverine, hydrastine, and narcotine. This group does not appear to have yet been investigated; but there are, on the other hand, a number of substances which contain groups of atoms very closely allied to this, and it is

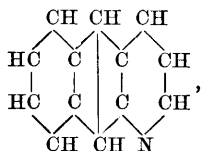
interesting to note that the salts of such substances, like those of berberine, are intensely yellow. The following instances, taken from a large number, will illustrate this point.

The whole series of *acridine* derivatives which contain the group



although sometimes colourless themselves, invariably yield intensely yellow salts.

α-Phenyl-α-naphthaquinoline, $\text{C}_{10}\text{H}_6 < \begin{array}{c} \text{C} \cdot \text{H} \cdot \text{CH} \\ \text{N} = \text{C} - \text{C}_6\text{H}_5 \end{array}$, which contains the very similarly constituted group,

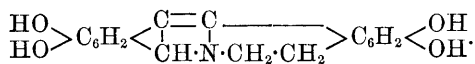


is yellow, and its salts are also intensely yellow. These instances might be multiplied to a considerable extent. It appears therefore that the formula proposed for berberine is in harmony with the fact that the alkaloïd is so intensely yellow. In Part I of this research (*loc. cit.*, p. 88), a substance is described, which results from the action of hydriodic acid on berberine, and which was termed *berberoline*. This compound (of which the sulphate was analysed) was then thought to have the composition $\text{C}_{18}\text{H}_{11}\text{NO}_2(\text{OH})_2$. It is, however, evident that this formula cannot be correct, as it is obviously produced from berberine by the elimination of the methylene and the methyl groups, thus:—



The analysis already given agrees well with the new formula.

The constitution of *berberoline* is represented by the formula



In the experimental part of this paper, a number of substances are described, some of which afford additional evidence as to the constitution of berberine, others, at first sight, appear to have little connection with this problem; but it must be borne in mind that

these new compounds were prepared and examined at a time when very little was known as to the constitution of the alkaloïd, and when their examination appeared likely to give important clues to the nature of the various complicated substances which were obtained from time to time.

I cannot conclude this part of the paper without expressing my thanks to Mr. Bertram Prentice for the very valuable assistance which he rendered, especially in the preparation of the large amount of material necessary for these experiments.

Oxidation of Berberine with Potassium Permanganate.

In continuing the investigation of the action of potassium permanganate on berberine, special care was taken that the berberine hydrochloride employed was pure, so that no doubt should exist that all the substances subsequently obtained were actually derived from berberine itself, and not from a small quantity of some other alkaloïd admixed therewith.

Commercial berberine hydrochloride, obtained from Merck, in Darmstadt, was first recrystallised from water, then dissolved in water, and the solution boiled with a small quantity of pure precipitated calcium carbonate for a few minutes; the liquid, originally of a yellow colour, is rendered distinctly brownish by this treatment, but the filtered solution, on cooling, deposits long, light brown needles of almost pure berberine hydrochloride, and these, after well washing and drying on a porous plate for some days at the ordinary temperature, gave the following numbers on analysis:—

I. 0.1484 gram substance gave 0.0806 gram H_2O and 0.2950 gram CO_2 .

0.5249 gram substance heated with nitrate of silver and nitric acid in a sealed tube gave 0.1592 gram $AgCl$.

0.3354 gram substance gave 9.5 c.c. N .; $t = 16^\circ$; bar. = 740 mm.

II. 0.1956 gram substance gave 0.1058 gram H_2O and 0.3884 gram CO_2 .

	Theory. $C_{20}H_{17}NO_4HCl + 4H_2O$.	Found.	
		I.	II.
C.....	54.13 per cent.	54.21	54.15 per cent.
H.....	5.86 ,,	6.03	6.03 ,,
Cl.....	7.98 ,,	7.62	— ,,
N.....	3.16 ,,	3.21	— ,,

Although the crystals obtained by this treatment are slightly brownish, this method of purification was almost always employed.

Recrystallisation first from dilute alcohol, and then from very dilute hydrochloric acid, entirely removes the brownish tinge, and the crystals have then a fine yellow colour and satiny lustre. In investigating the products formed by the oxidation of berberine by potassium permanganate, the following were the quantities usually employed :—

Berberine hydrochloride	7 grams.
Potassium permanganate	9 „
Dry potassium carbonate	1 „

In those cases, however, where an increased yield of some one of the oxidation products was desired, these quantities were varied, proportions more favourable to the formation of that particular product being employed, as will be mentioned in the description of the individual substances. The berberine hydrochloride was dissolved in about half a litre of water, at a temperature of about 70°, the potassium carbonate added, and then the strong hot solution of the permanganate, in half a litre of water, run in moderately rapidly, either drop by drop, or in a very fine stream from a tap funnel. The product from a large number of such operations was well cooled, treated with sulphurous anhydride (as explained in Part I, p. 77), and thus separated into a yellow, flocculent *precipitate* and a yellowish-coloured *solution*. The treatment of the *precipitate* was as follows :—The yellow, amorphous mass was thoroughly washed by grinding up with water, filtering through cloth, and squeezing; this operation being repeated at least three times, and the washings always added to the original *solution*. The *precipitate*, which, after drying on a porous plate, amounts to about 40 per cent. of the berberine hydrochloride used, was treated with dilute sodium carbonate solution, substantially in the same way as previously described (Part I, pp. 77–78), and thus separated into two portions :—

- I. *Soluble in Sodium Carbonate*.—This contains the acid $C_{20}H_{19}NO_9$ (α -berberilic acid), and a certain amount of the substance $C_{20}H_{17}NO_8$ (anhydroberberilic acid). Both of these compounds have been already described (Part I, pp. 78–80).
- II. *Insoluble in Sodium Carbonate*.—This portion is further resolved by boiling with acetic acid into *anhydroberberilic* acid, $C_{20}H_{17}NO_8$ (see p. 1037); *berberal*, $C_{20}H_{17}NO_7$ (see p. 1062); and berberine hydrogen sulphite, $C_{20}H_{17}NO_4 \cdot H_2SO_3$ (see p. 1097).

The *solution*, which in bulk frequently amounted to 150–200 litres, was rapidly evaporated in large, flat, enamelled iron pans, until its volume had been reduced by about one half. During the

evaporation a quantity of a yellow, flocculent substance separated, consisting for the most part of inorganic salts, but containing also, as examination showed, a considerable quantity of organic matter. This precipitate was collected on cloth bags, washed with water, transferred to a large evaporating basin, and gently warmed with a considerable bulk of 5 per cent. hydrochloric acid; quantities of sulphurous anhydride were evolved, and the greater part of the substance went into solution. The insoluble matter was collected, washed with water, and treated with very dilute hydrochloric acid, until the resulting yellow mass contained only traces of inorganic matter. This crude substance contains, besides varying quantities of anhydroberberilic acid, two new compounds, $C_{20}H_{17}NO_5$ (oxyberberine, p. 1085) and $C_{10}H_{17}NO_6$ (dioxyberberine, p. 1087); the methods of separation of these are given on pp. 1083-4.

The liquors from which this insoluble matter had been separated were again concentrated to half their bulk, allowed to cool, the inorganic salts which separated discarded, and the evaporation carefully continued until slight decomposition took place, as shown by rapid discoloration accompanied by empyreumatic odours. The liquor was transferred to large bottles, and extracted at least 20 times with ether, the separation of the two liquids being effected by syphoning off the aqueous layer. The colourless ethereal solution, which has a strong blue fluorescence, was evaporated in a large flask, and the semi-solid residue (about 35 grams from each kilo. of berberine hydrochloride used), which contains the substance $C_{20}H_{19}NO_9$ (see Part I, p. 84), hemipinic acid, and other products was treated as follows:—About $\frac{3}{4}$ litre of hot water was added, the whole heated on a sand-bath for five minutes, with sufficient sodium carbonate to make the solution decidedly alkaline, and the liquid rapidly filtered through a jacketed funnel. A small quantity of a dirty grey, insoluble substance (see p. 1094) which contained hemipinic anhydride was left on the paper.

The alkaline solution on cooling deposited a considerable quantity (about 13-14 grams) of beautiful, leafy crystals of a new substance, $C_{10}H_9NO_3$ (ω -amidoethylpiperonylcarboxylic anhydride), an exhaustive examination of which is given on p. 1013. The filtrate from these crystals was concentrated, allowed to stand 48 hours, so as to completely deposit any further quantities of the anhydride, $C_{10}H_9NO_3$, filtered, acidified with dilute hydrochloric acid, and gently warmed. A small quantity of a greyish substance which contained a new acid, $C_{20}H_{15}NO_8$ (berilic acid), remained undissolved, and was removed by filtration (see p. 1091).

The filtrate from this was repeatedly extracted with ether, and the ethereal solution evaporated, when a quantity of a yellowish semi-

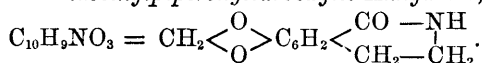
solid mass remained. This contains hemipinic acid, $C_{10}H_{10}O_6$, and hydrastic acid, $C_9H_8O_6$; the method of separation and purification of these acids is given on p. 1095.

The original concentrated solution which had been extracted with ether contains, besides the bulk of the inorganic salts, large quantities of organic matter, which appears to consist for the most part of hemipinic acid, together with varying quantities of the anhydride, $C_{10}H_8NO_3$, mentioned above.

The examination of these liquors is given on p. 1105. A long series of operations such as those involved in the separation of the numerous oxidation products of berberine is difficult to follow from mere description, and I have thought that it might facilitate reference if the methods employed were summarised in tabular form (p. 1014).

The following pages contain a detailed examination of the substances obtained from berberine by oxidation, as explained in the preceding pages.

ω -Amidoethylpiperonylcarboxylic Anhydride,



The crude product, the preparation of which is given on p. 1012, is readily purified by recrystallisation from boiling water, and is thus obtained in beautiful, colourless plates, which, after drying at 100° , gave the following results on analysis:—

- I. 0.1196 gram substance gave 0.0554 gram H_2O and 0.2753 gram CO_2 .
 0.1476 gram substance gave 9.1 c.c. N; $t = 17$; bar. = 740 mm.
 II. 0.1370 gram substance gave 0.0600 gram H_2O and 0.3143 gram CO_2 .

	Theory. $C_{10}H_8NO_3$.	Found.	
		I.	II.
C	62.82 per cent.	62.77	62.56 per cent.
H	4.71 „	5.15	4.79 „
N	7.33 „	7.23	— „

This beautiful substance melts at 181 — 182° ; when rapidly heated in small quantities in a test tube, it distils with only slight decomposition, and the oily distillate, on cooling, solidifies to a mass of colourless plates. It is very sparingly soluble in cold, but readily in hot water, the hot solution, on cooling, depositing beautiful, very characteristically shaped crystals, often grouped together in masses

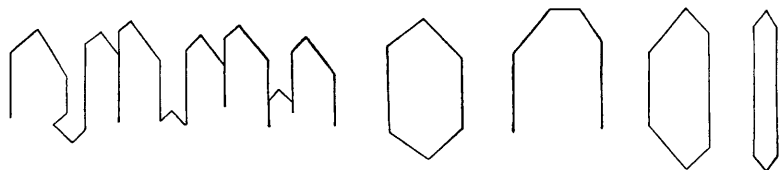
Berberine Hydrochloride is Oxidised with Potassium Permanganate, the Product treated with Sulphurous Anhydride, (see p. 1011) and Filtered.

Yellow precipitate treated with warm dilute sodium carbonate solution and filtered.

Yellow filtrate evaporated to half its bulk and filtered.

<p><i>Residue</i> contains Berberine hydrogen sulphite, $C_{20}H_{17}NO_4H_2SO_3$ (p. 1097).</p>	<p><i>Solution</i> on cooling deposits crystals which are separated by filtration.</p>	<p><i>Solution</i> contains Berberilic acid, $C_{20}H_{13}NO_6$, and some Anhydroberberilic acid, $C_{20}H_{17}NO_8$ (p. 1037).</p>	<p><i>Precipitate</i> contains Oxyberberine, $C_{20}H_{17}NO_6$ (p. 1085). Dioxyberberine, $C_{20}H_{17}NO_6$ (p. 1087). Anhydroberberilic acid, $C_{20}H_{17}NO_8$ (p. 1037).</p>	<p><i>Solution</i> evaporated to half its bulk and extracted 20 times with ether.</p>
	<p><i>Residue</i> contains Berberine anhydride, $C_{10}H_9O_5$ (p. 1094).</p>	<p><i>Solution</i> allowed to cool and filter.</p>	<p><i>Ethereal solution</i> evaporated, residue boiled with dilute sodium carbonate solution and filtered hot.</p>	<p><i>Aqueous solution</i> contains Hemipinic acid, $C_{10}H_{10}O_6$, <i>ω</i>-Amidoethylpiperonylcarboxylic anhydride, $C_{10}H_9NO_3$, and inorganic salts (p. 1105).</p>
	<p><i>Residue</i> contains Hemipinic anhydride, $C_{10}H_9NO_3$ (p. 1013).</p>	<p><i>Solution</i> acidified with hydrochloric acid and filtered.</p>	<p><i>Crystals</i> of <i>ω</i>-Amidoethylpiperonylcarboxylic anhydride, $C_{10}H_9NO_3$ (p. 1013).</p>	<p><i>Residue</i> contains Berberilic acid, $C_{20}H_{13}NO_8$ (p. 1091).</p>
	<p><i>Solution</i> contains Berberilic acid, $C_9H_6O_6$, and Hemipinic acid, $C_{10}H_{10}O_6$ (p. 1095).</p>			

very much resembling the teeth of a saw. These, when examined under the microscope, present the following appearance:—



It is very readily soluble in warm methyl alcohol; the warm solution, on slowly cooling, or, better still, on spontaneous evaporation, deposits well-formed, tabular crystals, which have a beautiful lustre. When examined under the microscope, these are seen to have forms almost exactly similar to those drawn above, the only difference being that the crystals from methyl alcohol were single examples and very well shaped, twins being almost entirely absent.

The anhydride $C_{10}H_9NO_3$ is also readily soluble in ethyl alcohol and in boiling benzene, xylene, or toluene, extremely soluble in chloroform and acetic acid, sparingly in ether, and almost insoluble in light petroleum. It crystallises from hot benzene in long, flat, ill-shaped plates. Its hot dilute aqueous solution gives no precipitate with mercuric chloride, but, on cooling, beautiful, colourless needles of a double compound separate. These are readily soluble in boiling water.

With a solution of phosphomolybdic acid, an aqueous solution of the anhydride $C_{10}H_9NO_3$, acidified with hydrochloric acid, even when very dilute, gives a yellowish-white precipitate, which dissolves appreciably in boiling water.

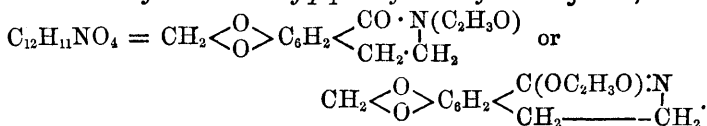
The anhydride $C_{10}H_9NO_3$ is insoluble in caustic potash solution, even on boiling; it dissolves readily in strong acids, forming salts, which, however, are very unstable, and could not be obtained in a state fit for analysis. From hot dilute acids, the substance crystallises unchanged.

Fusion of the Anhydride $C_{10}H_9NO_3$ with Potash.—Although it is not dissolved on boiling with strong solutions of potassium hydrate, the compound is readily decomposed by fusion with potash. It first of all melts to an oil, ammoniacal vapours are given off, and in a short time a clear, slightly brownish melt is formed. This is soluble in water, producing a purplish solution, which changes colour in the way so characteristic of a protocathechuic acid melt, and on acidifying and extracting with ether, a semi-solid mass is obtained, which shows the ferric chloride and other reactions of catechol or protocathechuic acid, and probably consists of a mixture of both these substances.

Attempts to obtain a Methyl Derivative of the Anhydride $C_{10}H_9NO_3$.—As already mentioned in the Introduction, the substance $C_{10}H_9NO_3$ is closely related to oxyhydrastinine, $CH_2<\overset{O}{\underset{O}{\text{C}}}>C_6H_2<\overset{CO \cdot N \cdot CH_3}{\underset{CH_2 \cdot CH_2}{\text{C}}}>$, and numerous experiments were made with the object of converting the former into the latter by treatment with methyl iodide under very varied conditions. The following is a short account of these experiments:—

1. The finely powdered substance $C_{10}H_9NO_3$ was heated for four hours with a large excess of methyl iodide in a flask connected with a reflux apparatus. The methyl iodide was then distilled off, and the residue recrystallised from water. The crystals obtained melted at $182-183^\circ$, and consisted of unchanged substance.
2. The substance $C_{10}H_9NO_3$ was dissolved in alcohol and heated at 100° with excess of methyl iodide in a sealed tube for five hours. No action took place.
3. 2 grams of the substance $C_{10}H_9NO_3$ was dissolved in a solution of 0.6 gram of caustic potash in pure methyl alcohol, 2 grams of methyl iodide added, and the mixture heated in a sealed tube at 100° for five hours. On cooling, a quantity of the unchanged substance separated, and from the solution the remainder was readily obtained by distilling off the alcohol and adding water.
4. 1.2 grams of the substance $C_{10}H_9NO_3$ was dissolved in a solution of sodium methoxide (containing 2 grams of sodium) and heated with 8 grams of methyl iodide at 140° for five hours. The clear solution was evaporated, the residue dissolved in a little cold water, acidified, and extracted with ether. A yellowish oil, readily soluble in water, was obtained; the solution gave with ferric chloride a dark-green coloration, showing that decomposition of the methylene-dioxy-group, $CH_2<\overset{O}{\underset{O}{\text{C}}}>$, had taken place (see footnote, p. 996).

Acetyl- ω -amidoethylpiperonylcarboxylic Anhydride,



In order to prepare this substance, the pure anhydride $C_{10}H_9NO_3$ was dissolved in acetic anhydride and the solution boiled for four hours in a flask connected with a reflux apparatus. The excess of

acetic anhydride and acetic acid was distilled off until only a small quantity of liquid remained, and this on cooling almost completely solidified to a cake of crystals. These were collected, well drained on a porous plate, dried at 110°, and analysed, with the following result:—

0.1578 gram substance gave 0.0692 gram H₂O and 0.3590 gram CO₂.

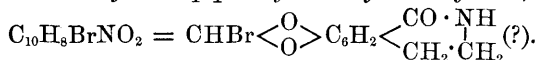
	Theory. C ₁₂ H ₁₁ NO ₄ .	Found.
C	61.80 per cent.	62.04 per cent.
H	4.72 ,,	4.87 ,,

This acetyl derivative crystallises from acetic anhydride in colourless needles which melt at 128—130°. It is readily hydrolysed on boiling with acids or alkalis, and, in order to further prove its constitution, a weighed quantity was hydrolysed and the amount of acetic acid produced estimated.

1.1086 gram substance was boiled with 30 per cent. sulphuric acid until completely dissolved, and the liquid distilled, with the addition of water when necessary, until the distillate no longer showed acid reaction.

The distillate required for complete neutralisation 49.7 c.c. of standard potassium hydrate solution (1 c.c. of which = 0.00597 c.c. acetic acid). 0.2967 gram of acetic acid was therefore produced, = 26.76 per cent. C₁₂H₁₁NO₄ on hydrolysis should yield 25.75 per cent. of acetic acid.

Amidoethylbromopiperonylcarboxylic Anhydride,



When treated with bromine, the anhydride C₁₀H₉NO₃ is readily attacked, one atom of bromine replacing one atom of hydrogen in the molecule, forming a compound of the formula C₁₀H₈BrNO₃. As the bromine atom in this compound is very readily removed by nitric acid and silver nitrate, it can scarcely be situated in the benzene ring, and it is probable that the substitution takes place in the methylene dioxy-group, and that the compound has the constitutional formula given to it above.

The compound C₁₀H₈BrNO₃ is readily prepared by exposing finely-powdered *ω*-amidoethylpiperonylcarboxylic anhydride, C₁₀H₉NO₃, (p. 1013) to the action of a large excess of bromine vapour, under a bell jar, in direct sunlight. After standing for two days, the original white powder has become converted into a dark-brown syrup; this, on exposure to a current of air, loses its excess of bromine, yielding

an ochre-coloured mass. This crude substance is best purified by repeated recrystallisation from boiling amyl alcohol, from which it is deposited on cooling in light-yellow, feathery crystals; these, after washing first with amyl alcohol and then with methyl alcohol and drying at 105°, gave the following results on analysis:—

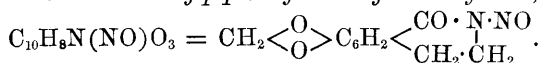
0.2003 gram substance gave 0.0564 gram H₂O and 0.3294 gram CO₂.

0.2240 gram substance, heated with nitric acid and silver nitrate in a sealed tube at 130—140°, gave 0.1543 gram AgBr.

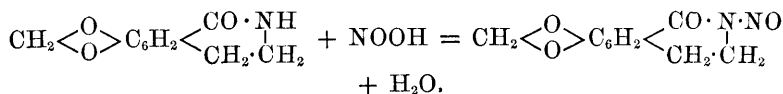
	Theory. C ₁₀ H ₈ BrNO ₃ .	Found.
C	44.44 per cent.	44.85 per cent.
H	2.97 "	3.12 "
Br	29.63 "	29.38 "

The bromo-derivative melts at 238—240°. It is readily soluble in chloroform, in boiling acetic acid, and in amyl alcohol; moderately soluble in hot xylene and alcohol, sparingly in carbon bisulphide, benzene, and light petroleum. It crystallises from amyl alcohol or xylene in slender, pale-yellow needles. It is readily decomposed by nitric acid and silver nitrate at ordinary temperatures, with separation of silver bromide.

Nitrosoamidoethylpiperonylcarboxylic Anhydride,



When treated with nitrous acid, the anhydride C₁₀H₉NO₃ (p. 1013) behaves as a secondary base, yielding a well-defined and very characteristic nitroso-derivative according to the equation



In preparing this substance the following quantities were found to give good results:—

C ₁₀ H ₉ NO ₃ (finely powdered)	3 grams.
Hydrochloric acid (sp. gr. 1.1)	100 c.c.
Water	75 "
Solution of sodium nitrite containing 10 grams NaNO ₂ in 100 c.c. water.....	15 "

The substance C₁₀H₉NO₃ is first dissolved in the hydrochloric acid (this being readily accomplished by warming gently on a water-

bath), the water is then added, the solution rapidly cooled to 20°, and lastly, the nitrite solution is run in, the flask being well cooled during the operation. The first few drops of the nitrite cause the solution to acquire a deep reddish-brown colour; this, however, soon disappears, and is succeeded by the separation of a yellow, amorphous precipitate, which ultimately causes the liquid to become quite thick. The whole operation must be quickly performed, otherwise the substance $C_{10}H_9NO_3$ is apt to crystallise out of the hydrochloric acid, and thus escape the action of the nitrous acid.

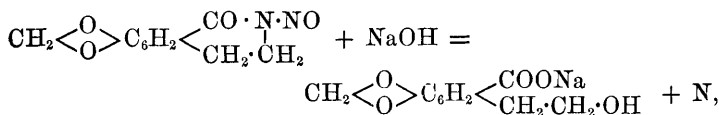
After standing for some time, the precipitate is collected, washed several times with water, dried on a porous plate, and recrystallised once or twice from alcohol. The pure substance is thus obtained in long, deep-yellow needles, which on analysis gave the following numbers:—

0.1575 gram substance gave 0.0580 gram H_2O and 0.3150 gram CO_2 .

0.1003 gram substance gave 10.7 c.c. N ; $t = 17^\circ$; bar. = 760 mm.

	Theory. $C_{10}H_9N(NO)O_3$.	Found.
C	54.54 per cent.	54.55 per cent.
H	3.63 "	4.04 "
N	12.73 "	12.70 "

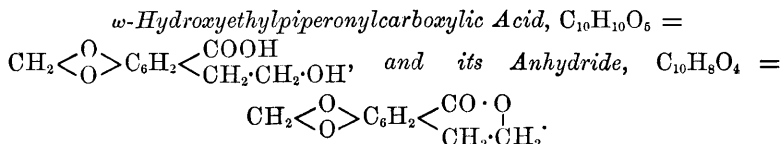
This interesting substance crystallises from alcohol in beautiful, long, glistening, yellow needles or four-sided prisms which melt at 194—195° with decomposition. It is readily soluble in boiling alcohol, chloroform, and benzene, almost insoluble in water or light petroleum, and very sparingly soluble in bisulphide of carbon. The solubility of this compound in solvents is very much influenced by its condition, the amorphous substance being far more readily dissolved than the crystalline variety. It is insoluble in acids and alkalis in the cold, but it dissolves readily in warm dilute sodium hydrate solution with evolution of nitrogen and formation of a salt of ω -hydroxyethyl-piperonylcarboxylic acid, thus:—



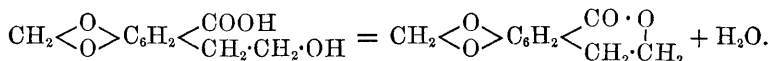
a decomposition which is described in detail on p. 1020.

The least trace of the nitroso-derivative, when treated with phenol and two drops of sulphuric acid, gives a red solution, which, on the addition of excess of dilute alkali, changes to a beautiful blue (Liebermann's nitroso-reaction).

The nitroso-compound seems to be readily reduced in alcoholic solution by tin and hydrochloric acid, the original yellow solution becoming almost colourless. No attempts were made to isolate the reduction product.



As mentioned in the last paragraph, the nitroso-derivative, $C_{10}H_8N(NO)O_3$, is readily decomposed by boiling with alkalis with evolution of nitrogen, and formation of a salt of a new acid, $C_{10}H_9O_5$. The latter, on the addition of an acid, is precipitated in the form of slender, white needles, which are somewhat difficult to purify on account of the ease with which they are converted into the inner anhydride $C_{10}H_8O_4$, thus:—



The best results were obtained by employing the crude amorphous nitroso-compound, as obtained directly by the action of sodium nitrite on the hydrochloric acid solution of the substance $C_{10}H_9NO_3$ (see p. 1019), as this is much more readily acted on by alkalis than is the crystalline product.

The yellow precipitate is well washed, mixed with a considerable quantity of water (3 grams of nitroso-compound to 100 c.c. of water), transferred to a porcelain basin, sufficient sodium hydrate added to make the liquid very distinctly alkaline, and the whole gently heated on a water bath. In a short time decomposition sets in, and the nitroso-compound rapidly disappears, considerable quantities of nitrogen being evolved. The product, if not quite clear, is filtered, well cooled, acidified with hydrochloric acid, and allowed to stand for about half an hour. The white, crystalline precipitate, which consists of the nearly pure acid $C_{10}H_9O_5$, is collected and well washed with small quantities of water, care being taken to preserve all the aqueous solutions, as these, when extracted with ether, yield further quantities of the acid. The purification of the acid $C_{10}H_9O_5$ is best accomplished by first converting it into its anhydride, $C_{10}H_8O_4$, recrystallising this several times, and then reconvertng the pure anhydride into the acid by dissolving it in alkali, and reprecipitating with hydrochloric acid.

For this purpose, the crude acid is dissolved in the least possible

quantity of boiling water, the solution gently boiled for about five minutes, and rapidly filtered through a jacketed funnel. The hot liquid, on cooling, deposits beautiful, glistening, colourless crystals of the anhydride $C_{10}H_8O_4$, which by recrystallisation from water are readily obtained pure. For analysis, the substance was dried at 105° .

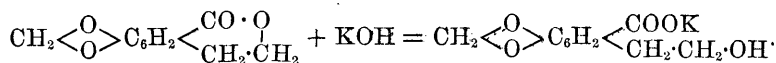
I. 0.1582 gram substance gave 0.0614 gram H_2O and 0.3620 gram CO_2 .

II. 0.1418 gram substance gave 0.0540 gram H_2O and 0.3252 gram CO_2 .

	Theory. $C_{10}H_8O_4$.	Found.	
		I.	II.
C	62.50 per cent.	62.40	62.54 per cent.
H	4.17 ,,	4.31	4.23 ,,
O	33.33 ,,	33.29	33.23 ,,

This anhydride, $C_{10}H_8O_4$, melts at $126-127^\circ$, and distils without decomposition when heated in small quantities. It is readily soluble in boiling water, and the hot solution on cooling deposits the substance in the form of beautiful, glistening crystals, which, however, as a rule, are ill-defined. It is sparingly soluble in cold water, and is readily extracted from its solution by ether. It is, further, readily soluble in alcohol, ether, and acetic acid, excessively soluble in chloroform. It dissolves sparingly in cold benzene and light petroleum.

The anhydride $C_{10}H_8O_4$ is insoluble in alkaline carbonates in the cold, and is only very slowly dissolved on boiling, but it dissolves in ammonia, and much more readily in potassium hydrate solution with formation of the potassium salt of the acid $C_{10}H_{10}O_5$,



In studying this reaction, the pure anhydride $C_{10}H_8O_4$ was ground up with a little water into a thin paste, a few drops of a clear solution of potassium hydrate added, and the whole gently warmed until complete solution had taken place. The solution was nearly neutralised with dilute hydrochloric acid, well cooled, an excess of acid added, the white, crystalline substance which separated collected, well washed with water, and dried on a porous plate, first at the ordinary temperature and then for a few minutes at 80° .

Analysis:—

0.1199 gram substance gave 0.0528 gram H_2O and 0.2510 gram CO_2 .

	Theory. $C_{10}H_{10}O_5$.	Found.
C	57.14 per cent.	57.09 per cent.
H	4.77 ,,	4.87 ,,
O	38.09 ,,	38.04 ,,

ω -Hydroxyethylpiperonylcarboxylic acid melts at 146° , and is at the same time decomposed into its anhydride, $C_{10}H_8O_4$, and water. It is readily soluble in hot water, but sparingly so in cold. It may be recrystallised from warm water if the operation be quickly carried out, but boiling with water completely decomposes it, and the solution on cooling deposits the pure anhydride $C_{10}H_8O_4$. The acid is readily soluble in hot and cold alcohol, ether, and chloroform, but only sparingly in cold benzene and light petroleum. The dry substance may be heated at 100° for some time without undergoing much decomposition, but at a temperature of 120 — 130° it rapidly liquefies, and is soon completely converted into its anhydride. The acid dissolves very readily in concentrated solutions of hydrogen iodide or bromide, and on gently warming it is very rapidly converted into the anhydride, which, on the addition of water, separates in plates. The acid does not combine with hydroxylamine.

The dissociation constant for the electric conductivity of the acid $C_{10}H_{10}O_5$ at different concentrations was kindly determined by Dr. Walker and found to be $K = 0.0081$. The acid is therefore stronger than benzoic acid, and about as strong as metahydroxybenzoic acid or orthomethoxybenzoic acid.

The solution of the pure substance in dilute sodium carbonate does not decolorise potassium permanganate except after long standing, a proof that the acid is not unsaturated (compare Baeyer, *Annalen*, **245**, 146). An aqueous solution of the acid is not precipitated by lead acetate, neither does it reduce ammoniacal nitrate of silver or Fehling's solution.

Fusion of the Acid $C_{10}H_{10}O_5$ with Potash.—1 gram of the pure substance was dissolved in concentrated aqueous potassium hydrate, the solution evaporated in a silver basin, and heated at 180° for about 10 minutes. Water was added, the clear solution acidified, and extracted four times with ether. The ethereal solution, on evaporation, deposited a small quantity of a light brown oil, which was very soluble in water; the solution gave with ferric chloride a deep green coloration and other reactions characteristic of a catechol derivative.

Oxidation of the Acid $C_{10}H_{10}O_5$.—A large number of experiments were made on the action of oxidising agents on this acid, as it appeared probable that in this way some clue to its constitution might be obtained. 2 grams of the pure substance was dissolved in dilute

sodium hydrate, and a very dilute solution of potassium permanganate (5 grams) run in in the cold. Oxidation took place at once with formation of a brown solution, but no hydrated oxide of manganese was precipitated until the liquid was boiled. The product was filtered, the clear solution evaporated to a small bulk, and acidified with dilute hydrochloric acid. A white, crystalline precipitate separated at once, which weighed 1.2 grams, and consisted of the pure acid $C_{10}H_{10}O_5$.

Analysis:—

0.1678 gram substance gave 0.0740 gram H_2O and 0.3514 gram CO_2 .

	Theory. $C_{10}H_{10}O_5$.	Found.
C	57.14 per cent.	57.11 per cent.
H	4.77 ,,	4.89 ,,

The filtrate from these crystals was repeatedly extracted with ether, and on evaporating the ethereal solution a colourless oil remained which solidified on standing; on recrystallisation from water, it melted at 126° , and consisted of the anhydride $C_{10}H_8O_4$. No other product could be isolated. It is probable, therefore, that the oxidation completely destroys part of the substance, leaving the remainder untouched. This experiment was repeated several times under the most varied conditions, but always with the same result.

Negative results were also obtained on using dilute nitric acid, iodine and sodium carbonate, and chromic acid as oxidisers.

Salts of Hydroxyethylpiperonylcarboxylic Acid.

In order, in the first place, to determine the basicity of this acid, the pure anhydride was dissolved in excess of standard potassium hydrate solution, a trace of phenolphthalein added, and the solution neutralised with standard sulphuric acid:—

0.63 gram of substance required for neutralisation 33.8 c.c. of standard potassium hydrate solution, containing in 1 c.c. 0.005461 gram KOH; the amount required for neutralisation was therefore 0.185 gram KOH. This proves that the acid is monobasic, as on this assumption 0.184 gram KOH would be required for neutralisation.

Silver Salt, $C_{10}H_9O_5Ag$.—The preparation of a sample of this salt pure enough for analysis was attended with considerable difficulty. The preparation which gave the best results was obtained by dissolving the acid in a slight excess of ammonia, removing the excess by allowing the solution to stand over sulphuric acid until nearly

neutral, and then precipitating the slightly alkaline solution by nitrate of silver. The white, crystalline precipitate was well washed, and dried on a porous plate over sulphuric acid under reduced pressure.

Analysis :—

0.2651 gram substance gave 0.0720 gram H_2O , 0.3730 gram CO_2 , and 0.0894 gram Ag.

	Theory. $C_{10}H_9O_5Ag$.	Found.
C	37.85 per cent.	38.34 per cent.
H	2.84 „	3.02 „
Ag	34.07 „	33.72 „

Other analyses gave similar results, the carbon and hydrogen determinations being always too high, the silver determination too low; in one or two cases, the silver was found as low as 30—31 per cent. The explanation of this is that the silver salt always contained small quantities of the anhydride $C_{10}H_8O_4$, and it is extremely probable that perfectly accurate numbers might be obtained by dissolving the acid in dilute potassium hydrate solution, neutralising with dilute nitric acid, and then precipitating with silver nitrate (compare Salts of Berberilic Acid, p. 1049). The silver salt is crystalline, and moderately soluble in hot water.

A moderately dilute solution of the ammonium salt showed the following behaviour with reagents :—

Copper Sulphate.—A dark green precipitate readily soluble in hot water.

Lead Acetate.—A white precipitate readily soluble in hot water.

Zinc Sulphate.—

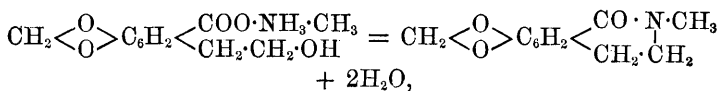
Cadmium Chloride.—

Barium Chloride.—

} No precipitate.

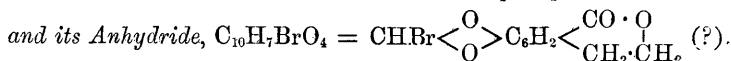
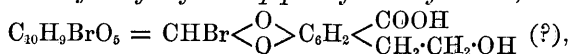
The *potassium salt* may be obtained in long needles by dissolving the anhydride $C_{10}H_8O_4$ in a warm and strong solution of pure potassium hydrate, and allowing the clear solution to cool slowly.

The *methylamine salt* was prepared by dissolving the pure acid in a slight excess of an aqueous solution of methylamine, and allowing the solution to evaporate over sulphuric acid under reduced pressure. A thick, oily residue was obtained which slowly crystallised. This salt was prepared, because it was thought very probable that on dry distillation it would yield oxyhydrastinine and water, thus :—



a decomposition which would be of considerable theoretical interest. The salt was rapidly distilled from a small retort, quantities of steam and methylamine were evolved, and an oily distillate was obtained, which, on cooling, solidified to a hard cake of crystals. These, after recrystallisation from water, melted at 126° , and showed all the properties of the anhydride $C_{10}H_8O_4$, and no trace of oxyhydrastinine could be isolated.

w-Hydroxyethylbromopiperonylcarboxylic acid,



The bromination of the anhydride $C_{10}H_8O_4$ is readily accomplished by exposing the finely-divided substance to bromine vapour under a bell jar, in the presence of direct sunlight. After standing for three days, a dark-brown semi-solid mass is obtained, which is freed from excess of bromine by exposure to a current of air, and then ground up with a little alcohol in a mortar. This treatment removes a quantity of dark-coloured impurity, leaving behind an almost colourless powder, which, after repeated recrystallisation from alcohol, is readily obtained pure in the form of colourless needles. For analysis, the substance was dried at 110° :—

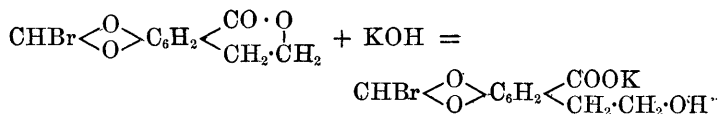
0.2015 gram substance gave 0.0480 gram H_2O and 0.3248 gram CO_2 .

0.2340 gram substance, heated in a sealed tube with nitric acid and nitrate of silver at 120 — 130° for four hours, gave 0.1638 gram $AgBr$.

	Theory. $C_{10}H_7BrO_4$.	Found.
C	44.28 per cent.	43.96 per cent.
H	2.47 „	2.64 „
Br.	29.52 „	29.76 „

This new substance melts at 146 — 147° . It is readily soluble in hot benzene and hot alcohol, excessively soluble in chloroform, moderately so in carbon bisulphide, but only sparingly in light petroleum or water. It crystallises from alcohol in wooly needles, from carbon bisulphide in hard balls of needles. It is insoluble in alkalis and alkaline carbonates in the cold, and is only very slowly decomposed even on long boiling with sodium hydrate solution. Alcoholic potash, on the other hand, readily dissolves it with forma-

tion of the potassium salt of *w*-hydroxyethylbromopiperonylcarboxylic acid, thus :—



2 grams of the pure compound $\text{C}_{10}\text{H}_7\text{BrO}_4$ was mixed with a little methyl alcohol, a considerable excess of methyl alcoholic potash added, and the whole heated to boiling. In a short time the crystals had entirely dissolved, but almost immediately afterwards a quantity of a white, crystalline substance separated, which was the potassium salt of the new acid $\text{C}_{10}\text{H}_9\text{BrO}_5$. Sufficient hot water was added to bring this again into solution, the liquid boiled to expel the methyl alcohol, and the well-cooled solution acidified with dilute hydrochloric acid. The very voluminous amorphous precipitate thus produced was collected, washed with water, dried on a porous plate, and dissolved in a little boiling 80 per cent. methyl alcohol. This solution on cooling deposited the new compound in the form of beautiful, colourless needles, which, after washing with methyl alcohol and drying first on a porous plate and then for a short time at 80° , gave the following numbers on analysis :—

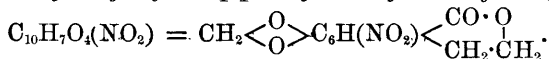
0.1654 gram substance gave 0.0480 gram H_2O and 0.2505 gram CO_2 .

	Theory. $\text{C}_{10}\text{H}_9\text{BrO}_5$.	Found.
C	41.52 per cent.	41.31 per cent.
H	3.11 „	3.27 „

This acid melts at 146 — 147° , and is at the same time decomposed into water and the anhydride $\text{C}_{10}\text{H}_7\text{BrO}_4$. It is readily soluble in hot alcohol, but is almost completely deposited on cooling ; it is sparingly soluble in benzene, light petroleum, chloroform, and hot water, almost insoluble in cold water. It dissolves very readily in fuming hydriodic acid, but not in fuming hydrochloric acid. It dissolves with great ease in alkalis and alkaline carbonates, but no salts have been analysed. The potassium salt crystallises from water, in which it is not very soluble, in long, slender needles. The acid $\text{C}_{10}\text{H}_9\text{BrO}_5$ dissolves readily in warm concentrated nitric acid, forming a deep-red solution, which, on warming, gets darker and darker until ultimately oxidation sets in. Water precipitates from this solution a salmon-coloured mass, which crystallises from alcohol, in which it is sparingly soluble, in slender needles ; these turn dark at 250° without melting. This substance contains both nitrogen and bromine ; it is insoluble in cold potassium hydrate, but on warming it dissolves forming an intense

reddish-violet solution. This compound is most probably *ω*-hydroxyethylbromonitropiperonylcarboxylic anhydride, $C_{10}H_8Br(NO_2)O_4$.

ω-Hydroxyethylnitropiperonylcarboxylic Anhydride,



The anhydride $C_{10}H_8O_4$ dissolves readily in concentrated nitric acid, forming a deep reddish-brown solution; on the addition of water, a yellow, crystalline precipitate is obtained, which consists of the almost pure nitro-compound. The precipitate was collected, washed with water, dissolved in boiling water, and filtered from a small quantity of insoluble matter. The clear solution, after a time, deposited long, thin, yellowish needles, which, after well washing and drying at 100° , gave the following numbers on analysis:—

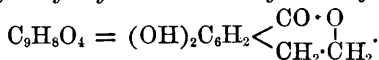
0.1524 gram substance gave 0.0430 gram H_2O and 0.2840 gram CO_2 .

0.1830 gram substance gave 9.6 c.c. N; $t = 18^\circ$; bar. = 759 mm.

	Theory. $C_{10}H_7O_4NO_2$.	Found.
C	50.63 per cent.	50.82 per cent.
H	2.95 „	3.13 „
N	5.90 „	6.17 „

This nitro-derivative melts at 197° . It is readily soluble in hot water and alcohol, but only sparingly in these liquids in the cold. It is also sparingly soluble in benzene and light petroleum. It is insoluble in sodium hydrate solution in the cold, but on warming it dissolves, forming a deep yellow solution, which rapidly darkens, becoming dark brown and ultimately of a beautiful violet colour. Acids destroy this colour, but it reappears on the addition of an alkali.

ω-Hydroxyethylcatecholcarboxylic Anhydride,



When heated in sealed tubes with dilute hydrochloric, hydrobromic, or hydriodic acid at 180° , or with distilled water at 210° , *ω*-hydroxyethylpiperonylcarboxylic anhydride, $C_{10}H_8O_4$, is decomposed, a deposit of carbon being formed on the sides of the tube. In all these cases ether extracts from the filtered solution a sticky substance; this dissolves readily in water and gives with ferric chloride an intense green coloration, which becomes violet and, finally, red on the addition of sodium hydrogen carbonate. This behaviour shows conclusively that the anhydride $C_{10}H_8O_4$ must be a derivative of catechol, in which

the hydroxyl hydrogens are substituted, probably by two methyl groups or by the methylene group.

In order to determine whether methoxy-groups were present in the molecule, 0.2345 gram of the substance was introduced into a Zeisel's apparatus (*Monatsh.*, **6**, 995) and heated with hydriodic acid, but, even after two hours, no trace of methyl iodide had been evolved, as shown by the fact that the alcoholic silver nitrate employed remained perfectly clear throughout. This proves that the substance $C_{10}H_8O_4$ contains no methoxy-group.

As all attempts to isolate the product of the reaction from the residual hydriodic acid solution gave unsatisfactory results, a large number of experiments on the action of hydrobromic and hydrochloric acids on the anhydride $C_{10}H_8O_4$ were made, the strength of the acids and the temperature of the decomposition being varied in each case. It was soon found that the product of the reaction could only be satisfactorily isolated when the strength of the acid (hydrochloric acid gave the best results) and the range of the temperature were kept within narrow limits. By carefully observing the following conditions excellent results were obtained:—

1 gram of the anhydride $C_{10}H_8O_4$ was ground up, mixed with 40 c.c. of water, 10 c.c. of ordinary concentrated hydrochloric acid (sp. gr. 1.168) added, and the mixture heated in a sealed tube for five hours at 170—175°.

The tube, which on cooling opened without pressure, was found to be filled with light flocks of charcoal, most of which adhered firmly to the under side of the tube. These were filtered off and the resulting almost colourless solution extracted six times with pure ether. The ethereal solution, after drying over calcium chloride and evaporating, deposited an almost colourless, crystalline residue. This was dissolved in a small quantity of hot water, the solution filtered into a glass dish, and allowed to evaporate to a small bulk over sulphuric acid under reduced pressure at the ordinary temperature. After standing for some time, the new substance separated in peculiar, hard, nodular masses, which were collected, washed with a little water, and dried at 100°.

The analyses gave the following results:—

I. 0.1618 gram substance gave 0.0686 gram H_2O and 0.3542 gram CO_2 .

II. 0.1316 gram substance gave 0.0554 gram H_2O and 0.2892 gram CO_2 .

	Theory. $C_{10}H_8O_4$.	Found.	
		I.	II.
C	60.00 per cent.	59.71	59.93 per cent.
H....	4.44 „	4.71	4.67 „
O	35.55 „	35.58	35.40 „

$$\text{CH}_2 \begin{smallmatrix} \text{O} \\ \text{O} \end{smallmatrix} \text{C}_6\text{H}_2 \begin{smallmatrix} \text{CO} \cdot \text{O} \\ \text{CH}_2 \cdot \text{CH}_2 \end{smallmatrix} = \text{C} + \begin{smallmatrix} \text{HO} \\ \text{HO} \end{smallmatrix} \text{C}_6\text{H}_2 \begin{smallmatrix} \text{CO} \cdot \text{O} \\ \text{CH}_2 \cdot \text{CH}_2 \end{smallmatrix}.$$
$$\text{CH}_2 \begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{O} \end{array} \text{C}_6\text{H}_3 \cdot \text{COOH} = \text{C} + \begin{array}{c} \text{HO} \\ \diagup \quad \diagdown \\ \text{HO} \end{array} \text{C}_6\text{H}_3 \cdot \text{COOH}.$$

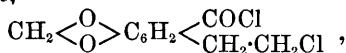
Piperonylic acid. Protocatechuic acid.

Action of Phosphorus Pentachloride on the Anhydride $C_{10}H_8O_4$.

ω-Chlorethylpiperonylcarboxylic Acid, C₁₀H₉ClO₄ =
 $\text{CH}_2 \begin{smallmatrix} \text{O} \\ \diagup \diagdown \\ \text{O} \end{smallmatrix} \text{C}_6\text{H}_2 \begin{smallmatrix} \text{COOH} \\ \diagup \diagdown \\ \text{CH}_2 \cdot \text{CH}_2\text{Cl} \end{smallmatrix}$

2 grams of the pure dry substance was dissolved in 25 grams of chloroform, and then 3 grams of powdered pentachloride of phosphorus added. Scarcely any action took place in the cold, but on heating on a water-bath, considerable quantities of hydrogen chloride were evolved. The mixture, after gently boiling on a reflux apparatus

for about half an hour, was cooled, 2 grams of phosphorus pentachloride added, and the heating continued for another half hour. The product on cooling deposited a quantity of yellowish crystals, which readily dissolved again on warming. These crystals seemed to consist of the acid chloride,



mixed with small quantities of phosphorus pentachloride, but although several attempts were made to isolate the pure substance, no very satisfactory numbers could be obtained on analysis. That this acid chloride is contained in this product is proved by the decomposition which it undergoes on being mixed with methyl alcohol (see p. 1033).

In examining the product formed in the above reaction, the excess of chloroform was distilled off, the resulting brownish oil cautiously added to a quantity of powdered ice, and the whole allowed to stand until the phosphorus oxychloride and excess of pentachloride had been completely decomposed. The liquid was extracted three times with ether, the ethereal solution washed with water, dried over calcium chloride, and evaporated, when a thick, unpleasantly-smelling syrup was obtained which on standing solidified almost completely. The crystalline cake was well pressed to remove adhering oily matter, washed with a little 80 per cent. methyl alcohol, and dissolved in a small quantity of boiling chloroform. From this solution, the substance separated on cooling in long, thin, colourless needles, which after recrystallisation were readily obtained pure.

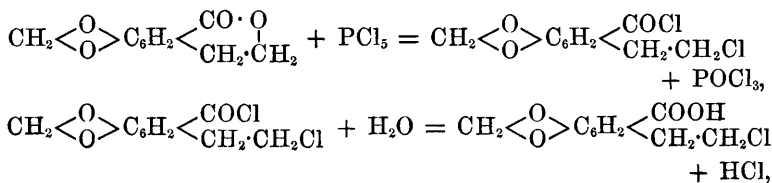
Analysis:—

0.1714 gram substance gave 0.0624 gram H_2O and 0.3310 gram CO_2 .

0.2149 gram substance, heated in a sealed tube with nitric acid and nitrate of silver at 180° for four hours, gave 0.1315 gram AgCl .

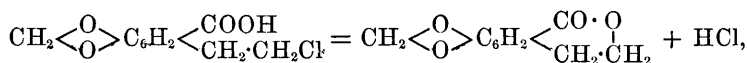
	Theory. $\text{C}_{10}\text{H}_9\text{O}_4\text{Cl}$.	Found.
C	52.54 per cent.	52.66 per cent.
H	3.94 „	4.04 „
Cl	15.49 „	15.10 „

This substance $\text{C}_{10}\text{H}_9\text{ClO}_4$ is evidently formed from the anhydride $\text{C}_{10}\text{H}_8\text{O}_4$, as shown in the following equations:—

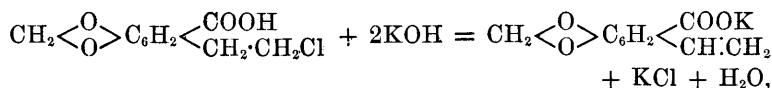


the acid chloride first formed being further decomposed on pouring the product into water. The substance $C_{10}H_9ClO_4$ crystallises from chloroform in long, thin, prismatic needles, which grow to a considerable length if the solution is allowed to cool slowly. It melts at $158-159^\circ$ with decomposition, is readily soluble in ether, methyl and ethyl alcohols, and acetic acid, sparingly in water and cold chloroform. This latter property renders the separation of the chloride from any unchanged or regenerated anhydride $C_{10}H_8O_4$, with which the crude product is nearly always contaminated, a matter of no difficulty, as the latter is excessively soluble in chloroform.

The substance $C_{10}H_9ClO_4$ dissolves readily in alkalis and alkaline carbonates. When heated in the dry state, it decomposes at about 160° , with evolution of hydrogen chloride and formation of the anhydride $C_{10}H_8O_4$, thus :—



a reaction very similar to that occurring in the formation of lactones from γ -halogen derivatives, *e.g.*, by the action of heat on γ -chlorobutyric acid (L. Henry, *Compt. rend.*, **101**, 1158—1161). When digested with alcoholic potash, the substance $C_{10}H_9ClO_4$ is readily decomposed with separation of potassium chloride. This reaction was studied in detail, because it was thought possible that an unsaturated derivative might result containing the side group $CH:CH_2$, thus :—



a decomposition which would be of considerable interest as determining the exact nature of the side chains in the compound $C_{10}H_8O_4$.

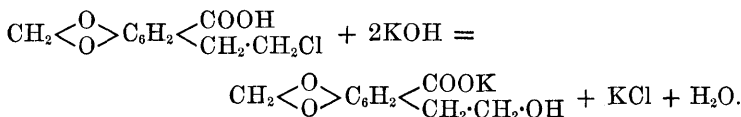
1 gram of the pure chloride was added to an excess of very strong alcoholic potash, and the whole boiled until the deposition of potassium chloride had ceased. The product was mixed with water, heated on a water-bath until free from alcohol, well cooled, and acidified with hydrochloric acid. The crystalline precipitate was collected, washed with water, and recrystallised from this solvent; when colourless needles were obtained which melted at 126° and showed all the properties of the anhydride $C_{10}H_8O_4$.

Analysis :—

0.1759 gram of substance gave 0.0663 gram H_2O and 0.4020 gram CO_2 .

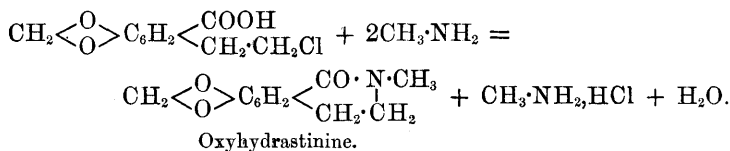
	Theory. C ₁₀ H ₈ O ₄ .	Found.
C	62·50 per cent.	62·39 per cent.
H	4·17 „	4·19 „

The regeneration of the anhydride C₁₀H₈O₄ in this reaction is easily accounted for by the following equation:—



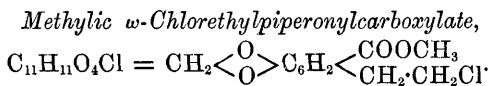
On acidifying with hydrochloric acid, the acid C₁₀H₁₀O₆ is precipitated, and this, on recrystallisation from water, is readily converted into its anhydride, C₁₀H₈O₄ (p. 1021).

As the experiments did not afford any clue to the nature of the side chains in the anhydride C₁₀H₈O₄, the action of methylamine on the compound C₁₀H₉ClO₄ was carefully studied. It seemed extremely probable that this reaction should lead to a synthesis of oxyhydrastinine, thus:—



a synthesis which would at once prove the constitution of the anhydride C₁₀H₈O₄. This experiment was repeated several times under the most varied conditions, and great care was taken to exclude every trace of water, but in all cases an almost quantitative yield of the anhydride C₁₀H₈O₄ was obtained, the methylamine acting obviously much in the same way as alcoholic potash.

Similar results were obtained in experiments on the reduction of the chloride C₁₀H₉ClO₄ with zinc and acetic acid, and other reducing agents; the anhydride C₁₀H₈O₄ being the only product which could be isolated.



This important substance has been prepared in considerable quantities for use in a number of synthetical experiments. It can be obtained in almost quantitative yield in the following way:—5 grams of the anhydride C₁₀H₈O₄ are dissolved in 30 grams of chloroform,

10 grams of powdered pentachloride of phosphorus added, and the mixture heated to boiling for half an hour in a reflux apparatus. The condenser is then removed, the chloroform boiled away, and the residual thick, oily mass, while still warm, poured in a thin stream into a considerable quantity of pure absolute methyl alcohol, the whole being well cooled during the operation. As soon as the very energetic reaction, which at once sets in, has subsided, the bulk of the methyl alcohol is distilled off, and the residue poured into cold water. The white, flocculent precipitate which separates is collected, well washed with water, dried on a porous plate, extracted with small quantities of boiling methyl alcohol, and the solution filtered from a small quantity of a white, insoluble substance. After distilling off the excess of methyl alcohol, the hot solution deposits, on cooling, long, beautiful, colourless needles of the nearly pure methyl salt. These were collected, recrystallised from methyl alcohol, and analysed with the following results:—

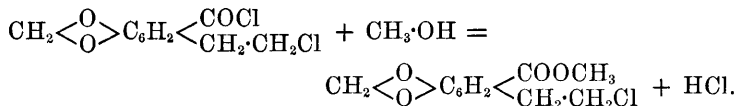
I. 0.1580 gram substance gave 0.0687 gram H_2O and 0.3144 gram CO_2 .

0.1530 gram substance gave 0.2570 gram AgCl .

II. 0.1517 gram substance gave 0.0662 gram H_2O and 0.3030 gram CO_2 .

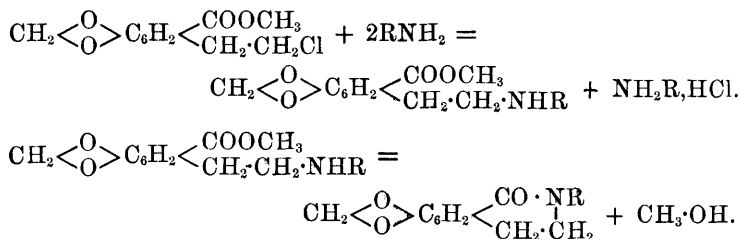
	Theory. $\text{C}_{11}\text{H}_{11}\text{O}_4\text{Cl}$.	Found.	
		I.	II.
C	54.45 per cent.	54.27	54.47 per cent.
H	4.54 „	4.82	4.84 „
Cl	14.61 „	14.79	— „

This methyl salt is obviously produced by the action of methyl alcohol on the acid chloride produced by the interaction of the phosphorus pentachloride and the anhydride $\text{C}_{10}\text{H}_8\text{O}_4$, thus:—

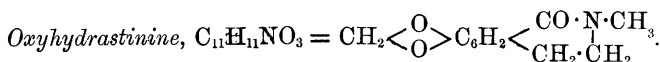


The pure substance melts at 82—83°. It is readily soluble in benzene, light petroleum, methyl alcohol, and chloroform, sparingly in water, but excessively soluble in ether. It crystallises best from 80 per cent. methyl alcohol. It is readily hydrolysed by boiling with alcoholic potash, with regeneration of the acid $\text{C}_{10}\text{H}_8\text{O}_4$.

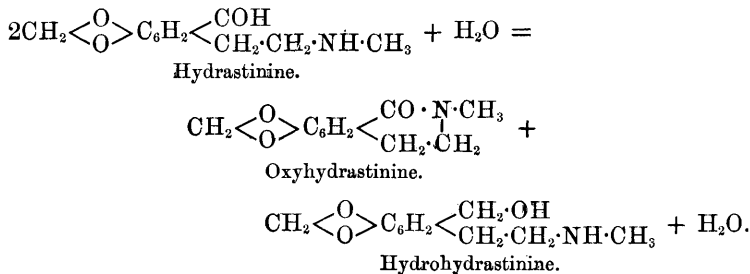
This methyl salt is of considerable value from a theoretical point of view, as when heated with primary amines it yields amido-derivatives, which, on hydrolysis with alcoholic potash, are converted into derivatives of isoquinoline, thus:—



Thus, when heated with methylamine, oxyhydrastine is formed; a synthesis which at once proves the constitution of the anhydride $\text{C}_{10}\text{H}_8\text{O}_4$, and indirectly that of the substance $\text{C}_{10}\text{H}_9\text{NO}_3$ (see Introduction, p. 998). Similarly constituted isoquinoline derivatives have also been obtained by heating the methyl salt with aniline and with ethylamine, as will be described in the subsequent chapters.



This substance, which has been proved to have the constitution assigned to it above, was first obtained by Freund and Will (*Ber.*, **20**, 2401; compare Freund and Lachmann, *Ber.*, **22**, 2323) by the action of potassium hydrate on hydrastinine, thus:—



It may be obtained synthetically from methylic *w*-chloroethylpiperonylcarboxylate by the action of methylamine in the following way:—

2 grams of the methylic salt were heated in a sealed tube with a strong alcoholic solution of methylamine (prepared by passing *dry* methylamine into absolute alcohol) for three hours at 100—120°, and then for three hours at 120—130°. The clear, almost colourless product was freed from excess of methylamine and from alcohol by evaporation, and the residue boiled for one hour with a strong alcoholic solution of potassium hydrate. Water was added, the alcohol driven off on a water-bath, and the product, which contained

oily drops, allowed to stand for 48 hours in a cool place; at the end of this time it was found that the oily drops had completely solidified. The hard, crystalline masses were collected, washed with water, freed from a trace of oily impurity by spreading on a porous plate, and purified by recrystallisation from dilute alcohol. In this way beautiful, colourless, glistening plates were obtained which, after drying first over sulphuric acid under reduced pressure and then at 80°, gave the following numbers on analysis:—

0.1562 gram substance gave 0.0798 gram H₂O and 0.3690 gram CO₂.

0.1366 gram substance gave 8.3 c.c. N; $t = 20^\circ$; bar. = 740 mm.

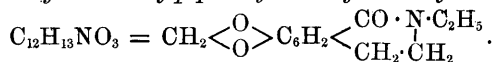
	Theory. C ₁₁ H ₁₁ NO ₃ .	Found.
C	64.39 per cent.	64.43 per cent.
H	5.36 „	5.67 „
N	6.83 „	6.80 „

It melts at 97—98°, and is identical in all its properties with oxyhydrastinine.

The yield of this substance, obtained in the above reaction, is almost theoretical; but a very small quantity of an acid is also produced at the same time, which remains dissolved in the strong alkali, and may be extracted by ether after acidifying with hydrochloric acid. It was not further examined.

The synthesis of oxyhydrastinine from methylic ω -chloroethylpiperonylcarboxylate is readily understood by substituting CH₃ for R in the general equation, p. 1034.

Ethylamidoethylpiperonylcarboxylic Anhydride,



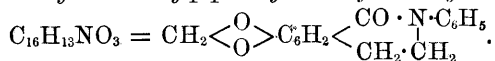
This may be prepared by the action of an alcoholic solution of ethylamine on methylic ω -chloroethylpiperonylcarboxylate, the method being similar to that employed in the synthesis of oxyhydrastinine. The product of the reaction, after boiling with alcoholic potash as described above, was a thick oil which, even on long standing, did not solidify. It was extracted from the alkaline liquors with pure ether, the ethereal solution washed, dried over calcium chloride, carefully filtered, and the ether evaporated. The residual, almost colourless oil was completely freed from moisture and ether by standing over sulphuric acid under reduced pressure, and then analysed with the following result:—

0.2264 gram substance gave 13.7 c.c. N; $t = 18^\circ$; bar. = 746 mm.

	Theory. $C_{12}H_{13}NO_3$.	Found.
N	6.39 per cent.	6.80 per cent.

Ethylamidopiperonylcarboxylic anhydride is a colourless oil which, when heated in small quantities, distils almost undecomposed. The yield obtained in the above synthesis is almost quantitative, and the crude product evidently nearly pure.

Phenylamidoethylpiperonylcarboxylic Anhydride,



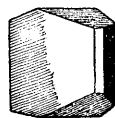
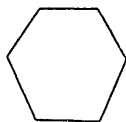
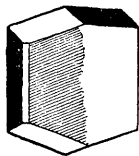
In preparing this substance, pure methylic *w*-chloroethylpiperonylcarboxylate was dissolved in alcohol, excess of aniline added, and the mixture boiled in a reflux apparatus for half an hour. The alcohol was distilled off, the oily residue heated at 170–180° for half an hour, and the resulting dark-coloured mass hydrolysed by boiling with alcoholic potash. The product was mixed with water, the alcohol and excess of aniline driven off by distillation in a current of steam, and the residual liquid, which contained a dark-coloured, resinous substance, digested for five minutes with very dilute hydrochloric acid. The solid substance which separated was collected, washed with water, and ground up in a mortar with a little 80 per cent. alcohol. In this way a quantity of a dark, resinous substance was removed, leaving a brownish, crystalline mass; this, when dissolved in boiling alcohol, was deposited in beautiful glistening, colourless prisms as the solution cooled; the separation is very much hastened by the addition of a crystal of the crude substance.

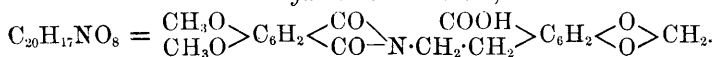
The analysis gave the following numbers:—

0.1927 gram substance gave 9.1 c.c. N; $t = 23^\circ$; bar. = 746 mm.

	Theory. $C_{16}H_{13}NO_3$.	Found.
N	5.24 per cent.	5.22 per cent.

This substance melts at 157°. It is very soluble in hot alcohol, benzene, and xylene, sparingly in water, cold alcohol, light petroleum, and carbon bisulphide, and exceedingly soluble in chloroform. Beautiful crystals are obtained by allowing the solution in benzene to evaporate spontaneously; these have the following forms:—



Anhydroberberilic Acid,

This important compound is the principal constituent of the yellow precipitate obtained by the oxidation of berberine with potassium permanganate and subsequent treatment with sulphurous anhydride, as described on p. 1011. The methods employed in the isolation and purification of this substance are given in Part I of this research (*loc. cit.*, pp. 79 and 80).

Even after repeated recrystallisation from acetic acid, anhydroberberilic acid is almost always slightly discoloured by the presence of a very small quantity of a yellowish impurity which can only be completely removed with difficulty. On several occasions a beautifully pure product has been obtained by recrystallising the crude compound, first from large quantities of alcohol and then from glacial acetic acid.

An analysis confirmed the formula previously arrived at as representing the composition of this substance :—

0.1860 gram substance gave 0.0742 gram H_2O and 0.4095 gram CO_2 .

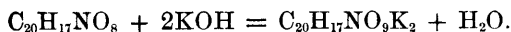
0.2248 gram substance gave 7.1 c.c. N ; $t = 16^\circ$; bar. = 740 mm.

	Theory. $\text{C}_{20}\text{H}_{17}\text{NO}_8$	Found.	Mean of previous analyses.
C	60.15 per cent.	60.04 per cent.	59.84 per cent.
H	4.26 „	4.43 „	4.47 „
N	3.51 „	3.53 „	3.54 „

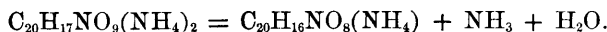
Anhydroberberilic acid, when quite pure, is colourless, and has a most beautiful, satiny lustre. It is very sparingly soluble in alkalis and alkaline carbonates in the cold, but when in a very finely-divided state (as obtained by grinding with water) it dissolves readily, even in alkaline carbonates at a temperature of $30\text{--}40^\circ$, and is reprecipitated unchanged on the addition of an acid. It therefore has acid properties, and is not a neutral substance, as was at first thought to be the case. In addition to the properties already given in Part I of this research, may be added that anhydroberberilic acid is not acted on by phenylhydrazine or by prolonged boiling with methyl iodide.

Salts of Anhydroberberilic Acid.

Very considerable difficulty was experienced in preparing salts directly derived from this acid, for the reason that when dissolved in ammonia or solutions of caustic alkalis, salts of berberilic acid (see p. 1048) are formed, thus :—



It was, however, subsequently observed that the ammonium salt of berberilic acid, $\text{C}_{20}\text{H}_{17}\text{NO}_9(\text{NH}_4)_2$, on long standing over sulphuric acid in a vacuum, or much more rapidly on warming its aqueous solution, gradually gives off one-half of its ammonia, and yields the ammonium salt of anhydroberberilic acid, thus:—



This salt, on the addition of an acid, now gives a precipitate of anhydroberberilic acid, instead of one of berberilic acid, as was the case at first.

This behaviour accounts for the fact that previously (Part I, p. 81) good numbers could not be obtained in the analysis of the silver salt prepared by precipitating a solution of the ammonium salt with silver nitrate. The analysis gave numbers lying between those required for the bibasic salt $\text{C}_{20}\text{H}_{17}\text{NO}_9\text{Ag}_2$ and those required for the monobasic salt $\text{C}_{20}\text{H}_{16}\text{NO}_8\text{Ag}$, showing that the bibasic ammonium salt used had already undergone some decomposition.

Silver Salt.—In re-examining the salts of anhydroberberilic acid, the pure substance was ground up with water to the consistency of a thin paste, rendered decidedly alkaline with ammonia, and gently warmed on a water-bath at 30–40° until the whole had dissolved. The solution was then placed in a dish over sulphuric acid in a vacuum, and allowed to evaporate almost to dryness. The gelatinous residue was dissolved in water with the aid of a drop of ammonia, heated at 60° on a water-bath for two or three hours, filtered, and the solution precipitated by silver nitrate in three fractions, at a temperature of about 40°, a preliminary precipitate of a small quantity being discarded. By this method the silver salt is obtained as a white, granular powder which is readily washed, whereas, if the precipitation takes place in the cold, the salt is gelatinous. The middle fraction was well washed with cold water, dried on a porous plate, first over sulphuric acid in a vacuum and then at 60°, and analysed with the following results:—

I. 0.1514 gram substance gave 0.0483 gram H_2O , 0.2620 gram CO_2 , and 0.0328 gram Ag.

II. 0.2684 gram substance gave 0.0560 gram Ag.

	Theory. $\text{C}_{20}\text{H}_{16}\text{NO}_8\text{Ag}$.	Found.		per cent.
		I.	II.	
C.....	47.43 per cent.	47.20	—	
H.....	3.16 ,,	3.55	—	,,
Ag.....	21.34 ,,	21.66	20.86	,,

This silver salt is sparingly soluble in water, and very stable; even prolonged heating at 100° scarcely decomposes it; for ordinary purposes it may therefore be dried at 100°.

Copper Salt, $(C_{20}H_{16}NO_8)_2Cu + 2H_2O$.—This salt was obtained as a brilliant, light-blue precipitate by the addition of a solution of copper sulphate to the solution of the ammonium salt. It was well washed with water and dried over sulphuric acid in a vacuum.

Analysis:—

0.2632 gram substance, heated at 100° till the weight became constant, lost 0.0104 gram = 3.99 per cent.

$(C_{20}H_{16}NO_8)_2Cu + 2H_2O$ contains 4.02 per cent. Aq.

The dry substance (0.2528 gram), on ignition in a current of air, left 0.0247 gram CuO .

	Theory. $(C_{20}H_{16}NO_8)_2Cu$.	Found.
Cu.	7.36 per cent.	7.79 per cent.

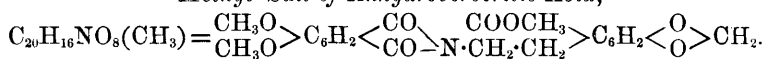
A dilute neutral solution of the ammonium salt shows the following behaviour with reagents:—

Cadmium Chloride.—A white, gelatinous precipitate.

Lead Acetate.—A white, gelatinous precipitate, somewhat soluble in hot water.

Barium and Calcium Chlorides.—No precipitates.

Methyl Salt of Anhydroberberilic Acid,



In order to be certain as to the basicity of anhydroberberilic acid, it was thought necessary to prepare some crystalline salt which could be readily purified, and from which trustworthy numbers could be obtained. As the metallic salts did not crystallise, and for this reason gave only imperfect numbers on analysis, attention was next directed to the preparation of a *methyl salt*. This salt is readily prepared by the action of methyl iodide on the silver salt, $C_{20}H_{16}NO_8Ag$. 2 grams of the pure dry silver salt was mixed with 20 c.c. of pure ether, a large excess of methyl iodide (5–10 grams) added, and the whole heated to boiling in a flask connected with a reflux apparatus. As soon as the decomposition was complete, the ether and excess of methyl iodide were distilled off, and the residue extracted three or four times with boiling absolute alcohol. The filtered extract, on evaporation, deposited an almost solid cake of the crude methyl salt; this was purified by spreading on a porous plate and subsequent

recrystallisation, twice from alcohol and once from acetic acid. The beautifully white glistening crystalline powder thus obtained was dried at 100°, and analysed with the following results:—

- I. 0.1352 gram substance gave 0.0601 gram H₂O and 0.3016 gram CO₂.
 0.1783 gram substance gave 5.2 c.c. N; $t = 14^\circ$; bar. = 740 mm.
 II. 0.1670 gram substance gave 0.0710 gram H₂O and 0.3720 gram CO₂.
 III. 0.1724 gram substance gave 0.0734 gram H₂O and 0.3844 gram CO₂.

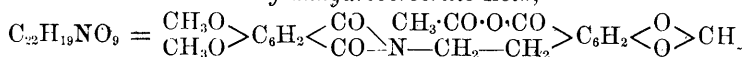
	Theory. C ₂₀ H ₁₆ (CH ₃)NO ₈ .	Found.			
		I.	II.	III.	
C	61.01 per cent.	60.84	60.75	60.81	per cent.
H	4.60 „	4.93	4.72	4.73	„
N	3.39 „	3.33	—	—	„

This methyl salt melts at 178—179°. In a finely-divided condition it is moderately soluble in carbon bisulphide, boiling benzene, and alcohol, but the crystals are only very sparingly soluble in these solvents. It crystallises best from acetic acid, being deposited as a fine, crystalline powder, which, when examined under the microscope, is seen to consist of four-sided plates with bevelled edges. This methyl salt is readily hydrolysed by boiling with hydrochloric acid or alcoholic potash. In order to make sure that it was in reality a methyl salt, and that the CH₃ group was not attached to the nitrogen atom in the molecule C₂₀H₁₇NO₈, the number of methoxy-groups which it contained was determined by Zeisel's method (*Monatsh.*, **6**, 995).

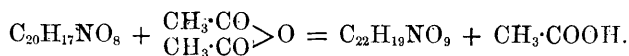
0.3016 gram substance, when heated with fuming hydriodic acid (sp. gr. 1.96), and the resulting methyl iodide passed into an alcoholic solution of silver nitrate, gave 0.4982 gram AgI.

(CH ₃ O)	Theory for 3(OCH ₃) groups in C ₂₀ H ₁₆ (CH ₃)NO ₈ .	Found.
	22.52 per cent.	21.91 per cent.

Three OCH₃ groups are therefore contained in this methyl salt, two from the original berberine molecule, and one in the form of COOCH₃; this substance is therefore the true methyl salt of anhydroberberilic acid.

Acetylanhydroberberilic Acid,

Acetic anhydride reacts readily with anhydroberberilic acid with formation of an acetyl derivative, thus:—



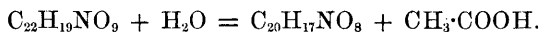
In preparing this acetyl derivative, 2 grams of pure anhydroberberilic acid was mixed with 30 grams of acetic anhydride, and the mixture heated to boiling in a flask connected with a reflux apparatus for about three hours. The resulting brown solution, which was strongly fluorescent, was evaporated to a small bulk and allowed to stand for 12 hours. The crystals which separated were collected, washed with a little acetic anhydride, and recrystallised from this solvent. The acetyl derivative was thus obtained pure in hard, glistening, slightly yellowish prisms, which, after drying at 105° for two hours, gave the following results on analysis:—

0.1665 gram substance gave 0.0690 gram H₂O and 0.3644 gram CO₂.

0.3108 gram substance gave 9.4 c.c. N; $t = 8^\circ$; bar. = 745 mm.

	Theory. C ₂₂ H ₁₉ NO ₉ .	Found.
C	59.82 per cent.	59.69 per cent.
H	4.28 „	4.60 „
N	3.17 „	3.51 „

Acetylanhydroberberilic acid melts at 139–140°, and at a higher temperature it decomposes with formation of an oil which smells strongly of acetic anhydride. It is very readily soluble in acetic acid, moderately in boiling alcohol, sparingly in boiling benzene and xylene, and almost insoluble in bisulphide of carbon and light petroleum. It crystallises from boiling xylene in peculiarly striated, needle-shaped crystals. The acid is very readily hydrolysed, boiling with water for a short time being sufficient to ensure complete decomposition into anhydroberberilic acid and acetic acid:—



The composition of the acetyl derivative may be accurately controlled by determining the amounts of these products produced on hydrolysis.

4.0610 grams of the pure substance was finely powdered and

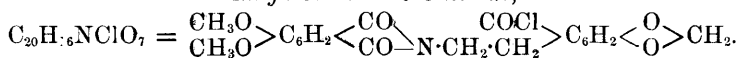
boiled in a flask connected with a reflux apparatus with 200 c.c. of 5 per cent. sulphuric acid. In a short time, complete hydrolysis had taken place with separation of colourless, flocculent masses of anhydroberberilic acid. These were collected on a filter, washed with water, and the yellow filtrate distilled in a current of steam until the distillate no longer showed any acid reaction. The acid liquid required for neutralisation 93 c.c. of standard solution of potassium hydrate (1 c.c. = 0.00598 gram of acetic acid).

This corresponds with 0.5561 gram of acetic acid = 13.7 per cent. According to the above equation, $C_{22}H_{19}NO_9$ gives 13.6 per cent.

The anhydroberberilic acid produced in this hydrolysis was very thoroughly washed with water until quite free from sulphuric acid, dried first on a plate and then at 100° until constant. It then weighed 3.688 grams = 90.8 per cent., whereas, according to the above equation, 90.5 per cent. should be produced.

These facts leave scarcely any doubt that the acetyl derivative is in reality a mixed anhydride of acetic and anhydroberberilic acids, and as such it has been represented at the head of this section. This accounts for the readiness with which it is decomposed into acetic and anhydroberberilic acids in contact with water.

Anhydroberberilic Chloride,



The action of phosphorus pentachloride on anhydroberberilic acid seems to be complicated, and the results obtained vary considerably with the quantity of the reagent employed and the subsequent treatment of the product.

Experiment I.—3 grams of pure anhydroberberilic acid was mixed with 50 grams of chloroform, and 6 grams of powdered phosphorus pentachloride added. As no action seemed to take place in the cold, the mixture was heated to boiling for half an hour; 2 grams more pentachloride added, and the heating continued for another half-hour. The residual light-brown liquid, which, on cooling, deposited a quantity of crystals, was, while still hot, transferred to a dish and freed from phosphorus oxychloride and excess of chloroform by heating on a water-bath. The yellow, crystalline residue was powdered, dissolved in boiling benzene, and the filtered solution allowed to stand 24 hours. In this way a considerable crop of garnet-coloured crystals was obtained, which, after repeated recrystallisation from benzene, gave the following numbers on analysis:—

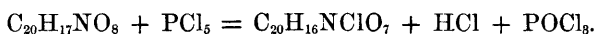
0.1674 gram substance gave 0.0584 gram H_2O and 0.3540 gram CO_2 .

0.3962 gram substance, heated with nitric acid and silver nitrate in a sealed tube at 180° for four hours, gave 0.1410 gram AgCl.

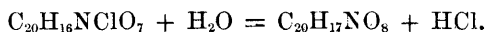
0.2984 gram substance gave 8.8 c.c. nitrogen; $t = 17^{\circ}$; bar = 736 mm.

	Theory. $C_{20}H_{16}NClO_7$.	Found.
C	57.49 per cent.	57.70 per cent.
H	3.83 "	3.87 "
N	3.35 "	3.32 "
Cl	8.50 "	8.74 "

This substance is the chloride of anhydroberberilic acid; its formation in the above reaction is represented by the equation.



This chloride melts at 167° , and is sparingly soluble in cold benzene, alcohol, and acetic acid. It crystallises from benzene in hard, thick, almost colourless prisms. It is practically insoluble in water, and for this reason is only very slowly acted on by this solvent. If, however, the powdered chloride is boiled with 80 per cent. acetic acid, it gradually dissolves, and, on cooling, anhydroberberilic acid crystallises out, thus:—



The yield of crystalline chloride obtained in the above method of preparation is about 70 per cent. of the theoretical. A small quantity remains behind in the benzene mother liquors; by concentrating the solution, this may be recovered as a dark-coloured, crystalline mass, which is, however, difficult to purify.

Experiment II.—2 grams of anhydroberberilic acid, 12 grams of phosphorus oxychloride, and 6 grams of phosphorus pentachloride were mixed together and heated on a water-bath. In a short time the whole of the anhydro-acid dissolved, hydrogen chloride being liberated in abundance. After heating for an hour, 3 grams of phosphorus pentachloride was added, and the heating continued for another hour. The product, which, on cooling, solidified to a mass of crystals, was melted and poured, in a thin stream, into much water, the whole being kept as cool as possible during the operation. As soon as the energetic reaction, which at once sets in, had subsided, the brick-red precipitate which separated was collected, washed well, dried on a porous plate, and extracted with boiling alcohol. The greater part dissolved, leaving, however, a slight residue of regenerated anhydroberberilic acid. The alcoholic solution was evaporated to a small bulk and allowed to stand, when a brown, crystalline

powder was obtained, which, after boiling in alcoholic solution with freshly ignited animal charcoal, and adding a little water, deposited an almost colourless, semi-crystalline precipitate. This was dissolved in alcohol, mixed with an equal bulk of water, and the solution allowed to stand exposed to the air. In a short time, crystalline crusts formed on the bottom of the dish, which, after well washing with dilute alcohol and drying over sulphuric acid in a vacuum, melted at 180—182°, and showed all the properties of berberilic acid (p. 1048).

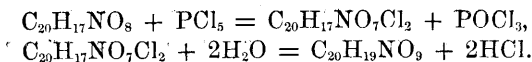
The analysis gave confirmatory results :—

0·1439 gram substance gave 0·0619 gram H_2O and 0·3039 gram CO_2 .

0·2059 gram substance gave 5·8 c.c. nitrogen; $t = 17^\circ$; bar. = 745 mm.

	Theory. $C_{20}H_{19}NO_9$.	Found.
C	57·55 per cent.	57·59 per cent.
H	4·55 „	4·70 „
N	3·36 „	3·20 „

As anhydroberberilic acid is not attacked by dilute hydrochloric acid in the cold, it seems that under the above conditions phosphorus pentachloride converts anhydroberberilic acid into the chloride of berberilic acid, which, when mixed with water is decomposed with formation of berberilic acid, thus :—



Experiment III.—3 grams of anhydroberberilic acid were mixed with 40 grams of chloroform, 6 grams of phosphorus pentachloride added, and the mixture heated to boiling in a reflux apparatus for half an hour. The chloroform was then distilled off, and the residual hard cake of crystals broken up and shaken with a large quantity of water, the whole being well cooled during the operation. As soon as all action had subsided, the yellowish-brown precipitate was collected, dried on a porous plate, and dissolved in a large quantity of boiling ethyl alcohol.

The alcoholic solution was concentrated, allowed to stand for 24 hours, and the yellow crystals, which completely filled the liquid, collected, washed with a little alcohol, and dried on a porous plate. The fine, yellow, crystalline mass thus obtained contains two substances which are very readily separated by extraction with boiling benzene, in which the one present in the smallest quantity is very sparingly soluble. The insoluble substance was collected, dried at

100°, and recrystallised from acetic acid; the resulting crystalline mass melted at 236° and showed all the properties of anhydroberberilic acid. The filtrate from the crude anhydroberberilic acid was heated on a water-bath till free from benzene, and the residue recrystallised three times from alcohol.

The beautiful, pale yellow needles thus obtained were free from chlorine; they gave the following results on analysis:—

- I. 0.1794 gram substance gave 0.0807 gram H_2O and 0.4064 gram CO_2
 0.2813 gram substance gave 8.3 c.c. nitrogen; $t = 19^\circ$; bar. = 740 mm.
- II. 0.1696 gram substance gave 0.0775 gram H_2O and 0.3851 gram CO_2 .
- III. 0.1537 gram substance gave 0.0701 gram H_2O and 0.3483 gram CO_2 .
- IV. 0.1471 gram substance gave 0.0674 gram H_2O and 0.3335 gram CO_2 .

	Theory. $C_{20}H_{19}NO_7$.	Found.			
		I.	II.	III.	IV.
C.....	62.33 per cent.	61.78	61.91	61.80	62.24 per cent.
H.....	4.93 „	4.99	5.07	5.06	5.13 „
N.....	3.63 „	3.35	—	—	— „

Each of these analyses was made with a different preparation.

This substance melts at 139—140°, it is readily soluble in hot alcohol, sparingly in the cold; the hot solution, on cooling, deposits the substance in beautiful, slender, pale-yellow needles. It is extremely soluble in benzene and chloroform, very sparingly in light petroleum, and the solutions show a beautiful fluorescence like that exhibited by solutions of quinine. It is insoluble in boiling dilute solutions of alkalis and alkaline carbonates and also in acids, but dissolves readily in warm alcoholic potash. As it seemed probable that this decomposition might throw some light on the constitution of this remarkable substance, about 1 gram was dissolved in dilute alcoholic potash, the solution heated to boiling for a few minutes, diluted with water, and the clear solution nearly neutralised and heated in an open basin on a water-bath until free from alcohol. The liquid was then well cooled, acidified with dilute hydrochloric acid, and the white, semi-solid precipitate which separated, collected, washed with water, and dried on a plate.

The hard mass thus obtained had all the properties of berberilic acid; it was identified by boiling with 50 per cent. sulphuric acid and collecting the crystalline precipitate of anhydroberberilic acid which

formed. This, after recrystallisation from acetic acid, melted at 236° , and gave the following results on analysis:—

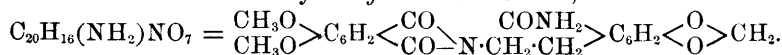
0.1510 gram substance gave 0.0630 gram H_2O and 0.3330 gram CO_2 .

	Theory. $\text{C}_{20}\text{H}_{17}\text{NO}_8$.	Found.
C.....	60.15 per cent.	60.14 per cent.
H.....	4.26 „	4.63 „

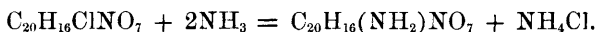
The formation of berberilic acid from a substance of the formula $\text{C}_{20}\text{H}_{19}\text{NO}_7$ by boiling with alcoholic potash is extremely difficult to understand, and although many experiments have been instituted, no clue to the constitution of this remarkable substance has, as yet, been found.

The amount of the substance $\text{C}_{20}\text{H}_{19}\text{NO}_7$ formed in the above decomposition varies very considerably; in some cases as much as 60 per cent. has been obtained, whereas in other experiments, conducted seemingly under exactly similar conditions, anhydroberberilic acid was the principal product.

Amide of Anhydroberberilic Acid,



The substance is readily prepared by the action of ammonia on the chloride of anhydroberberilic acid, thus:—



The finely-divided chloride was mixed in a sealed tube with a large excess of a strong solution of ammonia in absolute alcohol. On standing in the cold, it was noticed that considerable decomposition took place, and after heating at 100° for five hours, the whole of the chloride had disappeared, and the tube was filled with feathery crystals of the amide. These were collected, washed with alcohol, and dissolved in a considerable quantity of 85 per cent. alcohol; this solution, on cooling, deposited beautiful, colourless, feathery crystals which, after drying at 100° , gave the following numbers on analysis:—

0.1446 gram substance gave 0.0638 gram H_2O and 0.3197 gram CO_2 .

0.1888 gram substance gave 11.8 c.c. nitrogen; $t = 20^{\circ}$; bar. = 746 mm.

	Theory. $\text{C}_{20}\text{H}_{16}(\text{NH}_2)\text{NO}_7$.	Found.
C.....	60.30 per cent.	60.36 per cent.
H.....	4.53 „	4.90 „
N.....	7.03 „	7.01 „

This amide melts at 203° . It is readily soluble in boiling alcohol, but only sparingly in the cold; the hot solution, on cooling, deposits the substance as a very voluminous feathery mass, which, when dry, has a fine, satiny lustre.

The amide is insoluble in, and only very slowly hydrolysed by dilute acids; even boiling alcoholic hydrogen chloride seems to have little action on the substance. Alkalis on the other hand, act readily on the amide; on boiling with dilute alcoholic potash, the substance is readily dissolved with evolution of ammonia. The product was mixed with water, nearly neutralised with dilute hydrochloric acid, evaporated until free from alcohol, cooled, and acidified with dilute hydrochloric acid. The white, amorphous precipitate which separated, after being recrystallised from dilute alcohol, showed all the properties of berberilic acid:—

0.1820 gram substance gave 5.2 c.c. nitrogen; $t = 12^{\circ}$; bar. = 740 mm.

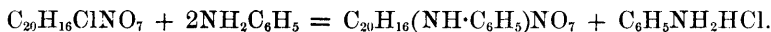
	Theory. $C_{20}H_{19}NO_9$.	Found.
N	3.36 per cent.	3.38 per cent.

The decomposition of this amide into berberilic acid and ammonia by boiling with alcoholic potash takes place according to the equation



Anilide of Anhydroberberilic Acid, $C_{20}H_{16}(NHC_6H_5)NO_7$.

The chloride of anhydroberberilic acid reacts readily with aniline in the cold, with evolution of heat and formation of the corresponding anilide:—



The finely-powdered chloride was mixed with an excess of pure aniline, allowed to stand for a few minutes, and then gradually heated to 180° . The resulting, almost colourless melt was poured in a thin stream into very dilute hydrochloric acid, the thick, oily precipitate well shaken and stirred until quite solid, collected, washed, and dissolved in boiling 90 per cent. alcohol. On cooling, this solution deposited the anilide in feathery tufts of fine needles. Analysis:—

0.2086 gram substance gave 11.3 c.c. nitrogen; $t = 22^{\circ}$; bar. = 746 mm.

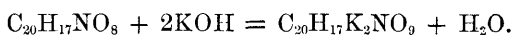
	Theory. $C_{20}H_{16}(NH \cdot C_6H_5)NO_7$.	Found.
N	5.91 per cent.	6.01 per cent.

The anilide melts at 199°. It is readily soluble in hot alcohol and benzene, sparingly in cold alcohol and carbon bisulphide, insoluble in water and light petroleum. It crystallises from alcohol in feathery tufts which, when dry, have a fine, satiny lustre and a distinct, blue fluorescence.

Berberilic Acid,



Although almost insoluble in alkalis in the cold, anhydroberberilic acid dissolves readily in dilute aqueous potassium hydrate at a temperature of 30—40° with formation of the potassium salt of berberilic acid:—

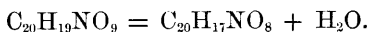


In studying this decomposition, very carefully purified anhydroberberilic acid was ground up with water into a fine paste, warmed to about 35°, and potassium hydrate solution then run in, drop by drop, until the whole had dissolved. The clear solution was well cooled, nearly neutralised with hydrochloric acid, cooled again, filtered if necessary, and then an excess of dilute hydrochloric acid added, drop by drop, the liquid being well agitated after each addition. The white, semi-solid precipitate, thus thrown down, was collected, washed with water, and dried on a plate; this preparation consists of practically pure berberilic acid, and as such was employed in all future operations. Considerable difficulty was experienced in obtaining this acid in a crystalline condition; the best results were obtained by dissolving the acid in methyl alcohol, adding about an equal bulk of water, and allowing the solution to stand in an open dish exposed to the air. As the methyl alcohol evaporated, the acid was deposited in the form of a hard, crystalline cake on the bottom of the dish. This was washed with dilute methyl alcohol, dried on a porous plate, and analysed with the following result:—

- I. 0.1649 gram substance gave 0.0752 gram H_2O and 0.3449 gram CO_2 .
 0.3090 gram substance gave 9.0 c.c. nitrogen; $t = 17^\circ$; bar. = 740 mm.
- II. 0.1320 gram substance gave 0.0590 gram H_2O and 0.2760 gram CO_2 .

	Theory. $\text{C}_{20}\text{H}_{19}\text{NO}_9$.	Found.	
		I.	II.
C	57.55 per cent.	57.01	57.21 per cent.
H	4.55 „	5.06	4.96 „
N	3.36 „	3.30	— „

Berberilic acid melts at about 177—182°, being at the same time decomposed into water and anhydroberberilic acid :—



This melting point is only approximate, as the presence of even traces of impurity causes the substance to soften at a much lower temperature.

It is very readily soluble in methyl and ethyl alcohol. It dissolves appreciably in hot water; and if warm dilute solutions of the salts of the acid are precipitated and filtered, the clear filtrate gradually deposits colourless, granular masses of pure berberilic acid. When heated above its melting point, berberilic acid is completely converted into its anhydride, and the oily product on cooling solidifies to a transparent, fluorescent resin, which will remain in this condition for weeks; in contact with glacial acetic acid, however, this at once becomes crystalline, and after recrystallisation from this solvent, melts at 237°, and consists of pure anhydroberberilic acid.

Basicity of Berberilic Acid.—Two experiments were made with the object of determining the basicity of this acid.

Experiment I.—0·8629 gram of pure anhydroberberilic acid was ground up with water, mixed with 50 c.c. of standard potassium hydrate solution (1 c.c. = 0·005461 gram KOH), warmed to 35°, and kept at this temperature until complete solution had taken place. After the addition of a trace of phenolphthaleïn, 5 c.c. of standard sulphuric acid were required to completely neutralise the product. 0·8629 gram of substance required, therefore, for neutralisation 45 c.c. of potassium hydrate solution = 0·2457 gram KOH; whereas a bibasic acid, $\text{C}_{20}\text{H}_{19}\text{NO}_8$, requires for neutralisation 0·2422 gram KOH.

Experiment II.—0·5355 gram of berberilic acid required 26 c.c. of standard potassium hydrate solution for neutralisation = 0·1419 gram KOH. Theory for a bibasic acid, $\text{C}_{20}\text{H}_{19}\text{NO}_8 = 0·1433$ gram KOH.

Berberilic acid is therefore a *bibasic acid*.

Salts of Berberilic Acid.

Silver salt, $\text{C}_{20}\text{H}_{17}\text{Ag}_2\text{NO}_8$. This was prepared as follows :—Pure anhydroberberilic acid was dissolved in a dilute solution of pure potassium hydrate, titrated with dilute nitric acid until only very faintly alkaline, warmed to 30°, and a large excess of silver nitrate added, the whole being violently agitated during the addition. The resulting white precipitate was collected, well washed with water, and dried first on a porous plate over sulphuric acid in a vacuum, and then at 80°.

The analysis gave the following numbers :—

- I. 0.2199 gram substance gave 0.0626 gram H_2O , 0.3103 gram CO_2 , and 0.0761 gram Ag.
 II. 0.2143 gram substance gave 0.0602 gram H_2O , 0.3036 gram CO_2 , and 0.0726 gram Ag.

	Theory. $C_{20}H_{17}Ag_2NO_9$.	Found.	
		I.	II.
C	38.08 per cent.	38.52	38.64 per cent.
H	2.70 „	3.16	3.12 „
Ag	34.32 „	34.60	33.88 „

This silver salt is very sparingly soluble in water. It is very stable, and only very slowly acted on by light; it may be heated at 100° for a considerable time without undergoing decomposition.

The neutral solution of the potassium salt shows the following behaviour with reagents :—

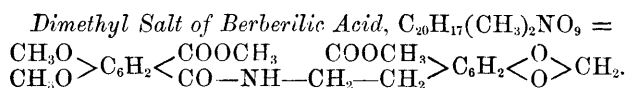
Zinc Sulphate.—A white, gelatinous precipitate, moderately soluble in hot water, from which it separates on cooling as a white, amorphous mass.

Copper Sulphate.—A light green precipitate, very sparingly soluble in water.

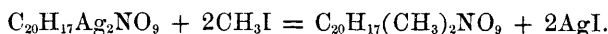
Cadmium Chloride.—A white, amorphous precipitate, soluble in hot water, separating out on cooling very much in the same way as the zinc salt.

Barium Chloride and Calcium Chloride.—No precipitate even on boiling.

The *ammonium salt* is mentioned on p. 1038, and its decomposition into ammonia and the ammonium salt of anhydroberberilic acid described.



This interesting salt is readily prepared by treating silver berberilate with excess of methyl iodide, thus :—



The pure dry silver salt was ground up, and heated with a large excess of methyl iodide and some pure ether for about two hours in a flask connected with a reflux apparatus. The ether and excess of methyl iodide were then distilled off, and the residue extracted three times with boiling absolute alcohol. The alcoholic solution was

concentrated, and the crop of crystals which separated on standing, collected, washed with a little alcohol, and recrystallised from this solvent. The pure dimethyl salt was thus obtained in the form of long, thin, colourless needles, which, after drying at 100°, gave the following results on analysis:—

0.1590 gram substance gave 0.0756 gram H_2O and 0.3460 gram CO_2 .

0.1966 gram substance gave 5.6 c.c. nitrogen; $t = 24^\circ$; bar. = 744 mm.

	Theory. $C_{20}H_{17}(CH_3)_2NO_9$.	Found.
C	59.32 per cent.	59.24 per cent.
H	5.17 ,,	5.28 ,,
N	3.15 ,,	3.15 ,,

Dimethyl berberilate melts at 173—174°. It is readily soluble in hot methyl and ethyl alcohols, but only sparingly in the cold. The hot alcoholic solution, on cooling, deposits the substance in the form of a voluminous mass of snow-white needles, which when dry resemble cotton wool. The dimethyl salt is also readily soluble in hot benzene and xylene, very soluble even in cold chloroform, sparingly in light petroleum and carbon bisulphide. It is readily hydrolysed by boiling with alcoholic potash, with regeneration of berberilic acid.

Action of Heat on Berberilic Acid.

When heated to temperatures not greatly exceeding 180—190°, this acid is converted into anhydroberberilic acid, as already mentioned; but at higher temperatures a much more complicated decomposition sets in, which it is more difficult to follow.

In studying this change, 8 grams of the pure acid was melted in a flask heated in a paraffin-bath, and the temperature gradually raised to 250°, and kept at this for 10 minutes. Abundance of steam and some carbon dioxide were liberated, the substance became darker and darker, and on cooling solidified to a dark brown, almost black resin. This was dissolved in boiling glacial acetic acid, the solution separated from a small quantity of black, insoluble matter by filtration, and the acetic acid evaporated off on a water-bath. The residue was boiled with dilute potassium hydrate solution, which removes nearly all the black resin, leaving a light greenish powder. This was well washed, dried on a porous plate, and extracted with boiling light petroleum (b. p. 90—110°), filtered from insoluble matter, and allowed to stand for 24 hours. The almost colourless

crystals which separated were recrystallised from water, dried at 100°, and analysed with the following result:—

I. 0.1612 gram substance gave 0.0740 gram H₂O and 0.3710 gram CO₂.

0.1715 gram substance gave 10.8 c.c. nitrogen; $t = 14^\circ$; bar. = 746 mm.

II. 0.1495 gram substance gave 0.0379 gram H₂O and 0.3452 gram CO₂.

	Theory. C ₁₀ H ₉ NO ₃ .	Found.	
		I.	II.
C	62.82 per cent.	62.76	62.97 per cent.
H	4.71 „	5.10	5.04 „
N	7.33 „	7.40	— „

This substance melts at 181—182°, and is identical with α -amido-ethylpiperonylcarboxylic anhydride (p. 1013); it was, in fact, the first sample of this substance obtained.

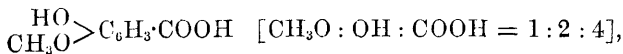
The dark brown alkaline solution which was separated from the crude substance C₁₀H₉NO₃, as described above, gave with hydrochloric acid a dark brown, amorphous precipitate. Boiling water dissolved the greater part of this precipitate, leaving a dark, resinous substance, which was separated by filtration. After treatment with animal charcoal, the hot aqueous solution deposited, on cooling, a light yellowish, crystalline powder, which, after repeated recrystallisation, became almost colourless, and gave the following numbers on analysis:—

0.1158 gram substance gave 0.0510 gram H₂O and 0.2430 gram CO₂.

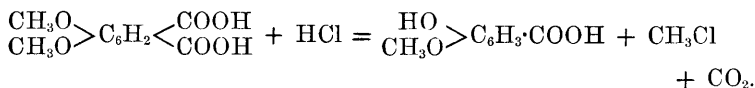
	Theory. C ₈ H ₈ O ₄ .	Found.	
C	57.14 per cent.	57.23 per cent.	
H	4.76 „	4.89 „	
O	38.09 „	37.88 „	

This acid melts at 245—247°, and when strongly heated in a stream of air, it gives a white, needle-shaped sublimate. It is readily soluble in hot water and alcohol, but sparingly so in the cold. The aqueous solution gives with ferric chloride a slight brownish coloration, and reduces ammoniacal nitrate of silver solution very readily. The acid dissolves in sulphuric acid, and on heating the solution to 100°, an intense green coloration is produced, which on standing becomes reddish-brown.

There can be no doubt that this substance is identical with isovanillic acid (methylprotocatechuic acid),

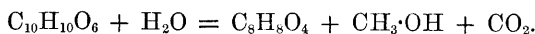


which Foster and Matthiessen (*Annalen*, Suppl. **2**, 378) obtained by the action of hydrogen chloride on hemipinic acid.



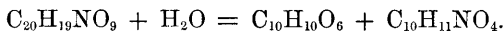
Isovanillic acid melts at 250°, and has properties very similar to those described above.

At the high temperature employed, berberilic acid is evidently first split up into hemipinic acid and the anhydride $\text{C}_{10}\text{H}_9\text{NO}_3$ (see p. 1013); the hemipinic acid is then further decomposed by the steam evolved into isovanillic acid, carbon dioxide, and methyl alcohol, thus:—



Hydrolysis of Berberilic Acid. Preparation of w-Amidoethylpiperonyl-carboxylic Acid, $\text{C}_{10}\text{H}_{11}\text{NO}_4 = \text{CH}_2 < \begin{array}{c} \text{O} \\ \text{O} \end{array} > \text{C}_6\text{H}_2 < \begin{array}{c} \text{COOH} \\ \text{CH}_2\text{CH}_2\text{NH}_2 \end{array}$.

Although anhydroberberilic acid is scarcely attacked by boiling dilute acids, berberilic acid is very readily decomposed by this treatment, with formation of hemipinic and amidoethylpiperonylcarboxylic acids, thus:—



This decomposition is best carried out as follows:—Anhydroberberilic acid, which should be as pure as possible, is dissolved in dilute potassium hydrate solution at 40°, the solution filtered, acidified, and the precipitated berberilic acid collected, washed, and ground up into a thin paste with water. 10 grams of this acid, in the form of paste, is mixed with 200 c.c. of 5 per cent. sulphuric acid, and the mixture vigorously boiled in a flask connected with a reflux apparatus. Decomposition sets in immediately, and in a short time the greater portion of the acid has passed into solution, giving place to a small quantity of a voluminous precipitate which floats in the liquid. The product is filtered, the precipitate washed well, dried on a porous plate, and recrystallised from acetic acid. The colourless, glistening needles thus obtained melt at 236°, and consist of pure anhydroberberilic acid. Analysis:—

0.1975 gram substance gave 0.0812 gram H_2O and 0.4332 gram CO_2 .

	Theory. $\text{C}_{20}\text{H}_{17}\text{NO}_8$.	Found.
C	60.15 per cent.	59.82 per cent.
H	4.26 ,,	4.56 ,,

The amount of anhydroberberilic acid formed in this hydrolysis varies with the strength of the sulphuric acid employed. Under the above conditions, 10—15 per cent. of the berberilic acid is converted into anhydroberberilic acid, $C_{20}H_{17}NO_8$, whereas, if 50 per cent. sulphuric acid is used, as much as 50 per cent. of this acid is produced.

The acid solution containing the principal products of the reaction is evaporated to 100 c.c. and extracted at least 20, but better 30, times with small quantities of ether; the ethereal solution, which has a beautiful blue fluorescence, is washed with a little water, dried over calcium chloride, and evaporated, and the solid residue spread on a plate to remove traces of oily mother liquor. The crude hemipinic acid thus obtained may be purified by recrystallisation from water, but it is better to first convert the crude acid into its calcium salt and then to decompose this with hydrochloric acid. For this purpose, the crude acid is dissolved in warm water, neutralised with sodium hydrate, the solution filtered, cooled well, and mixed with a large excess of a strong solution of calcium chloride. The clear solution is then heated to boiling, the heavy, sandy precipitate of the calcium salt which forms, collected, washed with hot water, and dissolved in a small quantity of hot very dilute hydrochloric acid. This solution, on standing, deposits pure hemipinic acid in beautiful, lustrous prisms, which, after drying at 100° , gave the following results on analysis:—

I. 0.1430 gram substance gave 0.0595 gram H_2O and 0.2770 gram CO_2 .

II. 0.1375 gram substance gave 0.0561 gram H_2O and 0.2678 gram CO_2 .

		Found.	
		I.	II.
Theory. $C_{10}H_{10}O_6$.			
C	53.10 per cent.	52.82	53.12 per cent.
H	4.42 „	4.61	4.52 „
O	42.48 „	42.57	42.36 „

Allowing for regenerated anhydroberberilic acid, the amount of hemipinic acid obtained is very nearly theoretical.

During the extraction with ether, a quantity of a white precipitate generally separates, which consists of the sulphate of the new base $C_{10}H_{11}NO_4$; this is best removed by filtration from time to time, otherwise it is difficult to separate the ethereal and aqueous layers effectually. The acid liquors, which should be as free from hemipinic acid as possible, are carefully evaporated to about 50 c.c., care being taken to stop the evaporation as soon as any signs of charring are noticed. This solution, after standing for two days, deposits a large crop of beautifully-formed tabular crystals of the sulphate of the base

$C_{10}H_{11}NO_4$. These are collected, washed with a little water, dissolved in a small quantity of warm water, and barium hydrate solution carefully added until the sulphuric acid is *exactly* precipitated, care being taken that there is no excess of barium hydrate present in the liquid. The filtrate from the barium sulphate is evaporated at a gentle heat ($70-80^\circ$) on a water-bath until sufficiently concentrated, and allowed to stand 24 hours, when a fine crop of slightly brownish, tabular crystals will have separated. These are collected, washed with a little water, and recrystallised from warm water. The air-dried crystals contain approximately one molecule of water of crystallisation, which is given off gradually over sulphuric acid in a vacuum, but much more readily at 100° , the crystals becoming quite opaque.

0.3141 gram substance, heated at 100° till constant, lost 0.0234 gram.

0.4384 gram substance, heated at 100° till constant, lost 0.0328 gram.

	Theory. $C_{10}H_{11}NO_4 + H_2O$.	Found.	
		I.	II.
H_2O	7.93 per cent.	7.45	7.49 per cent.

The crystals, dried at 100° , gave the following results on analysis:—

I. 0.1598 gram substance gave 0.0802 gram H_2O and 0.3372 gram CO_2 .

0.1087 gram substance gave 6.2 c.c. N; $t = 15^\circ$; bar. = 738 mm.

II. 0.1060 gram substance gave 0.0542 gram H_2O and 0.2228 gram CO_2 .

	Theory. $C_{10}H_{11}NO_4$.	Found.	
		I.	II.
C	57.42 per cent.	57.54	57.32 per cent.
H	5.26 „	5.57	5.68 „
N	6.70 „	6.70	— „

This beautiful substance melts at $180-182^\circ$ with evolution of gas. It is sparingly soluble in alcohol, benzene, acetone, and carbon bisulphide, readily soluble in hot water, moderately soluble in cold water.

On slowly cooling a moderately concentrated aqueous solution of the base, beautiful, tabular crystals gradually form. Professor Haushofer was kind enough to examine these for me, and has sent the following description:—

“The crystals of the base $C_{10}H_{11}NO_4$ belong to the *monoclinic* system, and represent the simple combination, $0P : \infty P$. Owing to the predominance of the basal surface, the crystals have a tabular form. The following angles were measured:—

“ $\infty P : \infty P$ (clinodiagonal prism face) $78^\circ 53'$
 $0P : \infty P$ (angle of the base and prism face). $101^\circ 22'.$ ”
 4 A 2

Salts of the Base C₁₀H₁₁NO₄.

This substance has very feeble acid properties, but, on the other hand, its basic properties are well marked, and it combines with acids, forming well-characterised salts.

The *sulphate*, (C₁₀H₁₁NO₄)₂.H₂SO₄ + 2H₂O, crystallises from water in beautiful, colourless prisms, readily soluble in hot, moderately so in cold, water. It melts at about 202—203° with decomposition. The water of crystallisation was determined in a sample of the salt which had stood for some days exposed to the air.

I. 0.9246 gram substance, heated at 100° till constant, lost 0.0592 gram.

II. 0.8680 gram substance, heated at 100° till constant, lost 0.0537 gram.

	Theory. (C ₁₀ H ₁₁ NO ₄) ₂ .H ₂ SO ₄ + 2H ₂ O.	Found.	
		I.	II.
H ₂ O	6.40 per cent.	6.29	6.19 per cent.

For analysis, the substance was dried at 100° until the weight was constant.

0.2050 gram substance dissolved in water and acidified with hydrochloric acid gave, on precipitation with barium chloride, 0.0942 gram BaSO₄.

0.1470 gram substance gave 0.0612 gram H₂O and 0.2514 gram CO₂.

	Theory. (C ₁₀ H ₁₁ NO ₄) ₂ .H ₂ SO ₄ .	Found.	
C	46.51 per cent.	46.64	per cent.
H	4.65 „	4.60	„
SO ₄	18.60 „	18.93	„

The *hydrochloride*, C₁₀H₁₁NO₄.HCl, crystallises from water in colourless, microscopic needles, readily soluble in water, very sparingly in solutions containing much free hydrochloric acid.

The salt, dried over sulphuric acid, does not lose weight at 100°, and, therefore, contains no water of crystallisation. The following results were obtained on analysis:—

0.1376 gram substance gave 0.0621 gram H₂O, and 0.2450 gram CO₂.

0.5292 gram substance, dissolved in water, acidified with nitric acid, and precipitated with nitrate of silver, gave 0.3076 gram AgCl.

	Theory. C ₁₀ H ₁₁ NO ₄ .HCl.	Found.	
C	48.90 per cent.	48.56	per cent.
H	4.89 „	5.02	„
Cl	14.42 „	14.39	„

The Acid Oxalate, $C_{10}H_{11}NO_4 \cdot C_2H_2O_4$.—This beautiful salt is readily obtained by mixing a warm concentrated solution of the base with a considerable excess of oxalic acid and allowing the mixture to cool slowly. After standing for some time, long, pale-yellow needles make their appearance, and continue to grow until they almost fill the liquid. The crystals were collected, allowed to remain on a porous plate at the ordinary temperature for some days, and then analysed:—

0·1616 gram substance gave 0·2860 gram CO_2 and 0·0650 gram H_2O .

	Theory. $C_{10}H_{11}NO_4 \cdot C_2H_2O_4$.	Found.
C	48·16 per cent.	48·26 per cent.
H	4·35 „	4·47 „

It is readily soluble in hot water, moderately in cold water. It melts at about $202-203^\circ$ with decomposition and rapid evolution of gas.

The Platinochloride, $(C_{10}H_{11}NO_4)_2 \cdot H_2PtCl_6$.—This was prepared by adding platinum chloride to the hot strong solution of the hydrochloride of the base, and allowing the solution to stand over night. The beautiful mass of light-reddish needles was collected, washed with water, recrystallised from this solvent, dried at 100° , and analysed.

I. 0·1940 gram substance gave 0·0557 gram H_2O , 0·2046 gram CO_2 , and 0·0459 gram Pt.

II. 0·4568 gram substance gave 0·1074 gram platinum.

III. 0·3578 „ „ 0·0832 „

IV. 0·2291 „ „ 0·0542 „

	Theory. $(C_{10}H_{11}NO_4)_2 \cdot H_2PtCl_6$.	Found.			
		I.	II.	III.	IV.
C	29·00 p. c.	28·77	—	—	— p. c.
H. ...	2·90 „	3·19	—	—	— „
Pt	23·50 „	23·66	23·51	23·25	23·66 „

This salt crystallises from water in long, slender, straw-coloured needles, which, when rapidly heated in a capillary tube, became dark-coloured at about 200° , and melt with rapid decomposition at 222° with evolution of gas; when slowly heated, it becomes dark at $195-200^\circ$, and decomposes completely at about 212° .

The Aurochloride, $C_{10}H_{11}NO_4 \cdot HAuCl_4$.—This double salt is precipitated on the addition of gold chloride to a strong solution of the hydrochloride of the base as a light, chocolate-coloured, crystalline

mass. It was dissolved in a little boiling water, filtered from a small quantity of a red, insoluble substance, and the solution allowed to stand for some hours. The crystalline precipitate which separated was collected, washed, dried at 100° , and analysed with the following result:—

0.3354 gram substance gave 0.1204 gram of gold.

	Theory. $C_{10}H_{11}NO_4.HAuCl_4$.	Found.
Au.....	35.87 per cent.	35.89 per cent.

This salt thus obtained forms a chocolate-coloured, crystalline powder, which can be recrystallised from water, but not without slight decomposition.

Action of Heat on the Base $C_{10}H_{11}NO_4$.

In recrystallising this substance from boiling water, it was repeatedly noticed that if the boiling is continued for some time, decomposition takes place, and, instead of the thick, tabular plates of the original substance, thin, glittering plates were deposited as the solution cooled. These were collected, recrystallised from water, and analysed with the following results:—

0.1794 gram substance gave 0.0821 gram H_2O and 0.4125 gram CO_2 .

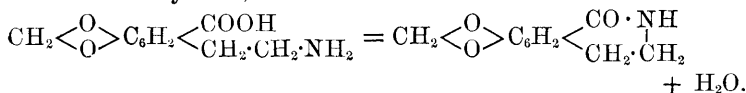
0.1623 gram substance gave 10.1 c.c. N; $t = 16^{\circ}$; bar. = 740 mm.

	Theory. $C_{10}H_9NO_3$.	Found.
C.....	62.82 per cent.	62.71 per cent.
H.....	4.71 „	5.08 „
N.....	7.33 „	7.30 „

This substance is identical with the anhydride $C_{10}H_9NO_3$ previously described (p. 1013).

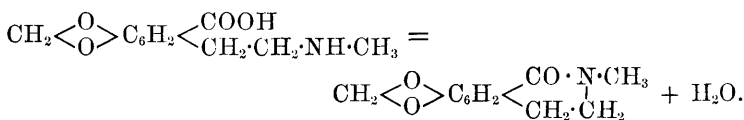
The base $C_{10}H_{11}NO_4$ is also decomposed when heated for some little time at its melting point, and the residue, after recrystallisation from water, consists of the pure anhydride $C_{10}H_9NO_3$; it is therefore probable that the temperature $181-182^{\circ}$, given as the melting point of the base $C_{10}H_{11}NO_4$, is, more correctly, the temperature at which this substance is converted into the anhydride $C_{10}H_9NO_3$.

The explanation of this decomposition is that the compound $C_{10}H_{11}NO_4$, being both an acid and a base, on heating is converted into its inner anhydride, thus:—



Action of Methyl Iodide on the Substance C₁₀H₁₁NO₄.

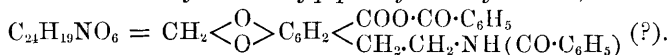
In assigning the correct constitution to this base, it was very important to obtain a methyl derivative which on heating would yield oxyhydrastinine, thus:—



With this object, the following experiments were instituted:—

1. The finely-divided base was dried at 100° and heated with a large excess of methyl iodide on a water-bath for two hours.
2. The pure, dry base was dissolved in methyl alcohol and heated in a sealed tube at 100° with excess of methyl iodide for one hour.
3. The base (1 mol.) was dissolved in methyl alcohol, a solution of potassium hydrate (1 mol.) in methyl alcohol added, and the whole heated with excess of methyl iodide at 100° for two hours.
4. Sodium ethylate was substituted for potassium hydrate in Experiment 3.

In no case could any methylated base be isolated, but in nearly every experiment an almost quantitative yield of the anhydride C₁₀H₉NO₃ was obtained. It is possible that the methylation of the base might take place at lower temperatures, but as the synthesis of oxyhydrastinine was accomplished in another way (p. 1034), these experiments were not continued.

Dibenzoylamidoethylpiperonylcarboxylic Acid,

As all attempts to prove the presence of an amido-group in the substance C₁₀H₁₁NO₄ by means of methyl iodide had failed, experiments were next tried on the action of benzoyl chloride on the base, and good results were obtained by using this reagent, together with sodium hydrate solution (Baumann's method). 2 grams of the pure base was dissolved in warm water, and 50 c.c. of 10 per cent. sodium hydrate solution and 7 grams of benzoyl chloride added alternately in small quantities at a time, the whole being well cooled during the operation. The reddish, resinous substance which separated was collected, washed with water, dissolved in boiling methyl

alcohol, and the solution, after being concentrated considerably, allowed to stand 24 hours. At the end of this time, a quantity of almost colourless crystals had separated; these were collected, washed well with methyl alcohol, recrystallised from this solvent, and analysed with the following result:—

0.1492 gram substance gave 0.064 gram H_2O and 0.3781 gram CO_2 .

0.1446 gram substance gave 4.3 c.c. nitrogen; $t = 14^\circ$; bar. = 747 mm.

	Theory. $\text{C}_{24}\text{H}_{19}\text{NO}_6$.	Found.
C.....	69.09 per cent.	69.10 per cent.
H.....	4.56 ,,	4.79 ,,
N.....	3.35 ,,	3.42 ,,

This beautiful substance melts at $148-150^\circ$, with slight previous softening. It is moderately soluble in hot alcohol, chloroform, and benzene, but only sparingly in these liquids in the cold, and almost insoluble in water and light petroleum. It is insoluble in aqueous hydrochloric acid and in ammonia in the cold, and seems to be only very slowly attacked by these reagents on boiling. This behaviour would seem to indicate that hydrogen atoms, both in the amido- and carboxyl-groups in the substance $\text{C}_{10}\text{H}_{11}\text{NO}_4$, had been replaced by benzoyl as shown in the formula assigned to this substance at the head of this section.

Action of Nitrous Acid on Amidoethylpiperonylcarboxylic Acid. Formation of Hydroxyethylpiperonylcarboxylic Acid (p. 1020).

In order to further confirm the formula assigned to the base $\text{C}_{10}\text{H}_{11}\text{NO}_4$, its behaviour towards nitrous acid was carefully studied.

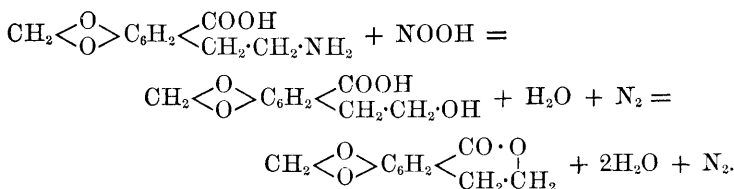
2 grams of the pure base was dissolved in 100 c.c. of warm water, 1 gram of pure sodium nitrite added, and then dilute hydrochloric acid (2 c.c. concentrated HCl and 10 c.c. water) gradually poured in, pieces of powdered ice being thrown in from time to time to prevent the temperature from rising. As the clear solution, even on standing, gave no precipitate, it was heated to boiling on a sand-bath for five minutes, and evaporated to about 50 c.c. Abundance of nitrogen and some nitrous acid were evolved during the decomposition, and on standing a crystalline precipitate separated, which was collected, washed with water, recrystallised from this solvent, and analysed with the following results:—

I. 0.1448 gram substance gave 0.0577 gram H_2O and 0.3310 gram CO_2 .

II. 0.1619 gram substance gave 0.0638 gram H_2O and 0.3698 gram CC_2 .

	Theory. $\text{C}_{10}\text{H}_8\text{O}_4$.	Found.	
		I.	II.
C.....	62.50 per cent.	62.34	62.79 per cent.
H.....	4.16 „	4.43	4.37 „
O.....	33.33 „	32.23	32.84 „

This substance melts at 126° , and is identical with *hydroxyethyl-piperonylcarboxylic anhydride*, obtained by the action of potassium hydrate on the nitroso-compound, $\text{C}_{10}\text{H}_8\text{N}(\text{NO})\text{O}_3$ (p. 1020). Its formation in the present instance is readily understood from the following equations:—



The yield of the substance $\text{C}_{10}\text{H}_8\text{O}_4$ obtained in this reaction was good, but not quantitative.

Synthesis of Anhydroberberilic Acid.

As this substance is produced from berberilic acid by the action of heat, and as berberilic acid on hydrolysis yields hemipinic acid and the base $\text{C}_{10}\text{H}_{11}\text{NO}_4$, it was thought probable that by combining these two substances under suitable conditions a partial synthesis of anhydroberberilic acid might be accomplished.

With this object, the hemipinic salt of the base $\text{C}_{10}\text{H}_{11}\text{NO}_4$ was first prepared as follows:—1.2 grams of hemipinic acid, dissolved in 10 grams of water, was mixed with 1 gram of the base $\text{C}_{10}\text{H}_{11}\text{NO}_4$ (dissolved in 20 grams of water), the solution evaporated to a small bulk, and allowed to stand in a cold place. After 48 hours, a quantity of peculiar light yellow balls, grouped together in reniform masses, had separated. These were collected, washed with water, dried at 100° , and analysed with the following result:—

0.2798 gram substance gave 7.6 c.c. nitrogen; $t = 19^\circ$; bar. = 750 mm.

	Theory. $\text{C}_{20}\text{H}_{21}\text{NO}_{10}$ ($\text{C}_{10}\text{H}_{11}\text{NO}_4 \cdot \text{C}_{10}\text{H}_{10}\text{O}_6$).	Found.
N.....	3.10 per cent.	3.22 per cent.

This salt melts at about 155–160° with decomposition, becoming solid again almost at once. It is readily soluble in hot, moderately in cold water.

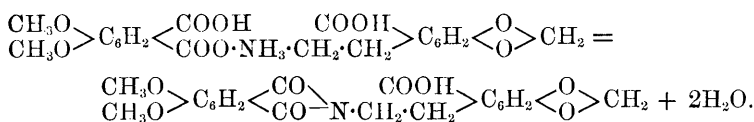
The pure, dry salt was now gradually heated to 180° in a wide test-tube in an oil-bath. Decomposition set in at about 160° with frothing and evolution of a quantity of water-vapour; this gradually subsided, and at the end of about 10 minutes the temperature was raised to 200° for a few minutes to complete the reaction. The resulting light brown oil, on cooling, solidified to a hard, transparent resin, which, however, when rubbed with a glass rod moistened with glacial acetic acid, soon became crystalline. The solid mass was ground up and dissolved in boiling 90 per cent. acetic acid, from which it separated on cooling in beautiful, glistening plates. These were collected, recrystallised from acetic acid, and analysed with the following result:—

0·1718 gram substance gave 0·0680 gram H₂O and 0·3786 gram CO₂.

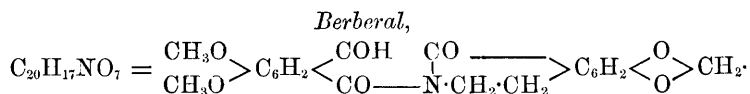
0·2148 gram substance gave 6·3 c.c. nitrogen; *t* = 18°; bar. = 750 mm.

	Theory. C ₂₀ H ₁₇ NO ₈ .	Found.
C.....	60·15 per cent.	60·10 per cent.
H.....	4·26 ,,	4·39 ,,
N.....	3·51 ,,	3·41 ,,

This beautiful substance melts at 236–237°, and is identical in every respect with the anhydroberberilic acid obtained by the oxidation of berberine, as described above (p. 1011). The formation by the above reaction is readily understood from the following equation:—



The yield of anhydroberberilic acid seemed to be nearly quantitative.



The isolation of this substance from the mother liquors of anhydroberberilic acid, C₂₀H₁₇NO₈, by dilution with water, as explained in Part I of this research (p. 81), requires very carefully carrying

out, as otherwise the crystals formed are so mixed up with tarry products that their subsequent purification is a matter of the utmost difficulty. In dealing with large quantities of these mother liquors, the bulk of the acetic acid was distilled off, the hot solution mixed with a very small quantity of boiling water, and allowed to stand for at least a week; the sides of the vessel containing it being scratched in several places with a glass rod. If no crystals had then formed, a small quantity more water was added, and the solution again allowed to stand, this treatment being repeated until the crystals deposited are so contaminated with tar that subsequent purification was almost impossible. In any case, a considerable quantity of the substance remains in the mother liquor. The yield varies with different preparations, but is rarely more than 10 grams from 1 kilo. of berberine hydrochloride.

A very pure sample of berberal was subjected to analysis with the following results:—

0.1433 gram substance gave 0.0590 gram H_2O and 0.3289 gram CO_2 .

0.1995 gram substance gave 6.5 c.c. N; $t = 18.8^\circ$; bar. = 760 mm.

	Theory. $C_{20}H_{17}NO_7$.	Found.	Mean of previous analyses.
C.....	62.66 per cent.	62.53 per cent.	62.66 per cent.
H.....	4.43 „	4.57 „	4.62 „
N.....	3.66 „	3.76 „	3.77 „

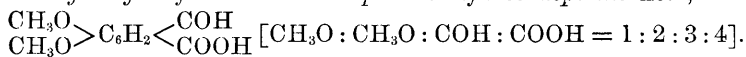
The properties of berberal are given in detail in Part I of this research (p. 82).

In the former paper (p. 83), it was mentioned that a solution of 0.7558 gram of berberal in 42.1296 grams of glacial acetic acid (m. p. 16.447°) was employed for the determination of the molecular weight of the substance by Raoult's method. This solution, on standing for 18 months, deposited long, colourless, transparent, prismatic needles; these were collected, washed with a little acetic acid, and drained on a porous plate. The crystals melted, not very sharply, at $115-120^\circ$. When heated at 105° for some hours, they became chalky, giving off acetic acid. The residual, very brittle mass melted at $148-150^\circ$, and gave, on analysis, the following numbers:—

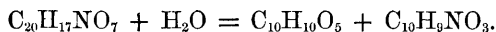
0.2057 gram substance gave 6.8 c.c. N; $t = 15.5^\circ$; bar. = 740 mm.

	Theory. $C_{20}H_{17}NO_7$.	Found.
N.....	3.66 per cent.	3.72 per cent.

The substance was berberal, which, therefore, under certain conditions, crystallises with acetic acid in long, thin, transparent prisms.

Hydrolysis of Berberal. Preparation of Pseudopianic Acid,

The most important property of berberal, and the property which affords the best clue to its constitution, is the decomposition which it undergoes when boiled with dilute sulphuric acid, when it is split up into pseudopianic acid and amidoethylpiperonylcarboxylic anhydride (p. 1013), thus:—



In carrying out this hydrolysis, the very finely-divided pure substance is transferred to a flask connected with a reflux apparatus and boiled briskly with an excess of dilute sulphuric acid (25 per cent.), the whole being vigorously shaken from time to time. In the course of about half an hour, the greater part of the substance dissolves, forming a deep reddish-brown solution, in which a small quantity of a tarry matter swims about. This tarry substance, which completely solidifies on cooling, is collected, washed with water, and recrystallised from alcohol. When analysed, it gave the following result:—

0.1440 gram substance gave 0.0607 gram H_2O and 0.3302 gram CO_2 .

	Theory. $\text{C}_{20}\text{H}_{17}\text{NO}_7$.	Found.
C	62.66 per cent.	62.53 per cent.
H	4.43 „	4.68 „

It melts at 149° , and consists of unchanged berberal.

The conditions in the experiments on the hydrolysis of berberal were very considerably varied, but in every instance similar tarry substances were formed which did not become appreciably less even after six hours' boiling. It is probable that the small quantity of tar always produced coats a certain portion of the berberal, and thus prevents it from coming in contact with the acid; and, indeed, unless the berberal employed be very pure and in a very fine state of division, it is scarcely attacked by boiling dilute sulphuric acid.

The products of the hydrolysis were isolated as follows:—

The acid liquor was evaporated to about three-fourths of its bulk, extracted 20 times with ether, the ethereal solution washed with a little water, and evaporated. The yellowish-white crystalline residue, which contains two substances, was boiled with a little very dilute sodium carbonate solution, until completely dissolved, and the alkaline liquid filtered and allowed to stand in a cold place for some

hours. The crystals which separated were collected, washed with a little water, and recrystallised from this solvent.

They then melted at 182° , and were found to consist of the pure amidoethylpiperonylcarboxylic anhydride $C_{10}H_9NO_3$ (p. 1013).

Analysis:—

0.1153 gram substance gave 0.0536 gram H_2O and 0.2650 gram CO_2 .

	Theory. $C_{10}H_9NO_3$.	Found.
C	62.82 per cent.	62.68 per cent.
H	4.71 „	5.16 „

As the anhydride $C_{10}H_9NO_3$ is only sparingly soluble in ether, the amount extracted in this way is small, and the bulk of the substance remains behind in the sulphuric acid liquors. To recover it, the liquors are boiled with excess of barium carbonate, filtered hot, and evaporated to a small bulk; the solution, on cooling, deposits a quantity of crystals of almost pure anhydride, $C_{10}H_9NO_3$.

The alkaline solution from which the small quantity of the anhydride, $C_{10}H_9NO_3$, had crystallised, as described above, was evaporated to half its bulk, cooled well, filtered from a small quantity of the anhydride which separated, and acidified with hydrochloric acid. The beautifully white, crystalline mass which separated was collected, washed with water, and purified by repeated recrystallisation from this solvent. An analysis of a portion of the substance, dried at 100° , gave the following numbers:—

0.1591 gram substance gave 0.0722 gram H_2O and 0.3332 gram CO_2 .

	Theory. $\begin{matrix} CH_3O \\ CH_3O \end{matrix} > C_6H_2 < \begin{matrix} COH \\ COOH \end{matrix}$.	Found.
C	57.14 per cent.	57.13 per cent.
H	4.76 „	5.04 „
O	38.09 „	37.83 „

Pseudopianic acid melts at 121 — 122° . It is readily soluble in hot water, alcohol, acetone, benzene, and chloroform, sparingly in cold water and light petroleum. It crystallises from hot water in long, slender needles, grouped together to a wool-like mass; from benzene it crystallises in slender needles, and from chloroform in long, flat needles. In its appearance and properties it bears considerable resemblance to opianic acid. When warmed with phenol and much sulphuric acid, a green solution is formed, which, on further heating, becomes violet-brown; the addition of an equal bulk of water to this produces a beautiful violet solution, which, on the careful addition of

alkali, turns first a brilliant blue and finally green. (Compare the Formation of Opiaurin from Opianic Acid. Liebermann and Seidler, *Ber.*, **20**, 873.)

Fusion of Pseudopianic Acid with Potassium Hydrate.—A small quantity of the acid was dissolved in a strong solution of potassium hydrate, the liquid evaporated in a silver dish, and the residue gently fused at about 180—200°. The residue was dissolved in water, acidified with dilute sulphuric acid, and repeatedly extracted with ether. The ethereal solution, on evaporation, deposited a thick, pale-brown syrup, from which, on standing, a small quantity of a crystalline substance separated. The solution of the latter in water gave, with ferric chloride, an intense green coloration, becoming violet, and ultimately red, on the addition of sodium bicarbonate; it also reduced Fehling's solution and ammoniacal nitrate of silver in the cold.

This experiment shows that pseudopianic acid is a catechol derivative.

Estimation of the Methoxyl Groups in Pseudopianic Acid by Zeisel's Method.—The previous experiment showed that pseudopianic acid contains two hydroxyl groups in the ortho-position; but as the acid itself gives no coloration with ferric chloride, it follows that these must be present, either as two methoxy-groups (CH_3O) or as a methylene dioxy-group ($\text{CH}_2<\overset{\text{O}}{\text{O}}$). In order to decide this point the action of fuming hydriodic acid on the acid was investigated; the apparatus described by Zeisel (*Monatsh.*, **6**, 995) being employed for the purpose.

0.3726 gram substance was heated with a large amount of fuming hydriodic acid (sp. gr. 1.96), and the escaping methyl iodide, led into an alcoholic solution of silver nitrate, gave 0.8164 gram AgI.

Theory for 2(OCH_3) groups in $\text{C}_{10}\text{H}_{10}\text{O}_5$.		Found.
(OCH_3)...	29.5 per cent.	28.9 per cent.

Pseudopianic acid, therefore, contains two methoxy-groups in the ortho-position.

Basicity of Pseudopianic Acid.—In order to determine the basicity of this acid, a weighed quantity was dissolved in water and titrated with a standard solution of potassium hydrate, with the result that the acid was shown to be *monobasic*.

0.8432 gram substance required for neutralisation 41.3 c.c. of potassium hydrate solution, 1 c.c. of which contained 0.005461 gram KOH.

This corresponds with 0.2256 gram KOH, and agrees closely with the amount required for a monobasic acid, that is, 0.2249 gram.

Salts of Pseudopianic Acid.—In order to prepare the salts of this acid, the pure substance was dissolved in hot water, a slight excess of ammonia added, and the solution allowed to stand over sulphuric acid until quite neutral. On adding silver nitrate to this neutral solution, a white, crystalline precipitate of the *silver salt*, $C_{10}H_9O_5Ag$, was formed. This was collected, well washed with water, dried on a porous plate over sulphuric acid in a vacuum, and analysed with the following result:—

0.1960 gram substance gave 0.0569 gram H_2O , 0.2709 gram CO_2 , and 0.0662 gram Ag .

	Theory. $C_{10}H_9O_5Ag$.	Found.
C	37.85 per cent.	37.70 per cent.
H	2.84 ,,	3.22 ,,
Ag	34.07 ,,	33.77 ,,

This salt, when examined under the microscope, is seen to consist of slender needles; these are moderately readily soluble in hot water, and when heated in a capillary tube decompose at about 195° with blackening.

A dilute neutral solution of the ammonium salt shows the following behaviour with reagents:—

Copper Sulphate.—A pale green, amorphous precipitate, especially on warming.

Lead Acetate.—A white, amorphous precipitate, soluble in hot water.

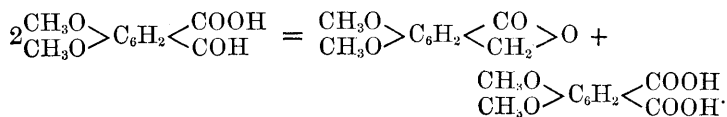
Zinc Sulphate.—A white, amorphous precipitate, more readily produced in warm solutions.

Calcium Chloride and Barium Chloride.—No precipitate.

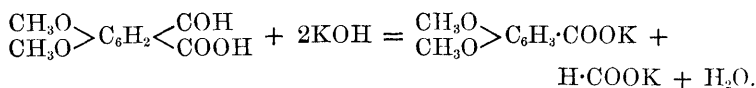
The *potassium salt* of pseudopianic acid separates from its concentrated solution in long, transparent needles, on the addition of strong potassium hydrate solution (sp. gr. 1.4). It is very readily soluble in water.

Action of Potassium Hydrate on Pseudopianic Acid. Formation of Veratric Acid, $(CH_3O)_2C_6H_3COOH$ [$CH_3O : CH_3O : COOH = 1 : 2 : 4$].

According to Matthiessen and Forster (*Annalen*, Suppl. 1, 332), opianic acid is decomposed by boiling concentrated potassium hydrate into meconine and hemipinic acid, thus:—



Pseudopianic acid, when similarly treated, is acted on quite differently, the products of its decomposition being veratric and formic (?) acids, thus :—



In studying this decomposition, the acid was dissolved in a little dilute potassium hydrate, an excess of a concentrated solution of potassium hydrate (sp. gr. 1·4) added, and the whole boiled for one hour. The potassium salt of pseudopianic acid, which first separates out, dissolves readily on warming, and the solution, although it remains quite clear, becomes slightly yellow as the reaction proceeds. The product was diluted with a considerable quantity of water, acidified with hydrochloric acid, and extracted ten times with pure ether. The ethereal solution, after washing with a little water and drying over calcium chloride, deposited, on evaporation, a yellowish, crystalline residue, which, after repeated recrystallisation from hot water, was obtained pure, in the form of colourless needles.

Analysis :—

0·1308 gram substance gave 0·0640 gram H_2O and 0·2855 gram CO_2 .

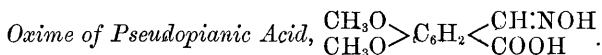
	Theory. $\text{C}_9\text{H}_{10}\text{O}_4$.		Found.
C	59·34 per cent.		59·53 per cent.
H	5·49 ,,		5·44 ,,
O	35·17 ,,		35·03 ,,

The acid melts at 176—178°. It is readily soluble in hot, but only sparingly in cold water; the hot solution, on cooling, deposits the substance in slender needles. It is also readily soluble in alcohol and ether, and its aqueous solution gives no coloration with ferric chloride. From the results of the analysis and the study of the properties of this substance, there can scarcely be a doubt that it is veratric acid, which melts at 179·5°.

In order, however, to be certain of the identity of the two substances, the acid from pseudopianic acid was converted into the voluminous, crystalline silver salt, and this, after careful drying, digested for half an hour with methyl iodide and a quantity of pure ether. The ethereal solution was filtered from the precipitated silver iodide, evaporated, and the residual, colourless, crystalline mass purified by repeated recrystallisation from a mixture of benzene and light petroleum. In this way, the methyl salt was obtained in the form of colourless needles melting at 58—59°; this corresponds

exactly with the melting point of methyl veratrate. Unfortunately the amount of methyl salt obtained was too small for analysis; but a direct comparison of the acid and its methyl salt with veratric acid and its methyl salt left no doubt as to the identity of the two preparations.

According to the equation at the head of this chapter, which is supposed to represent the action of potassium hydrate on pseudopianic acid, formic acid should be produced. In order to test this, the acid liquors from which the veratric acid had been extracted by ether, as explained above, were distilled in steam. The distillate had a distinctly acid reaction and slight reducing powers, but the quantity of formic acid, which in any case could have been present, was so small, that this test can scarcely be looked on as satisfactory.



In order to prepare this interesting substance, 1 gram of the pure acid was dissolved in dilute potassium hydrate solution (containing 3 grams of KOH), a solution of 1 gram of hydroxylamine hydrochloride in a little water added, and the whole allowed to stand for 24 hours. The product was rendered slightly acid with hydrochloric acid, the white, sandy precipitate which separated collected, washed well, and dried on a porous plate over sulphuric acid in a vacuum. It gave the following results on analysis:—

0.1842 gram substance gave 0.0880 gram H_2O and 0.3577 gram CO_2 .

0.1997 gram substance gave 11.2 c.c. N; $t = 20^\circ$; bar. = 740 mm.

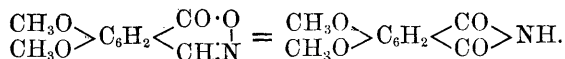
	Theory. $\text{C}_{10}\text{H}_{11}\text{NO}_3$.	Found.
C	53.33 per cent.	52.91 per cent.
H.....	4.88 ,,	5.30 ,,
N.....	6.22 ,,	6.20 ,,

Pseudopianic oxime melts approximately at 124° , but its melting point could not be accurately determined, owing to the fact that the substance decomposes entirely at about 120° with evolution of gas, and it then becomes quite solid, but melts again at about 215° . The study of this decomposition is given in the next section. Pseudopianic oxime crystallises from water in little balls of needles. It is readily soluble in alkalis and alkaline carbonates, also in hot water and alcohol, but only sparingly so in benzene, chloroform, and light petroleum.

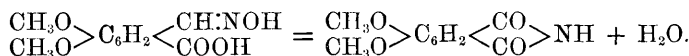
Action of Heat on the Oxime of Pseudopianic Acid.

Formation of Hemipinimide, $\begin{smallmatrix} \text{CH}_3\text{O} \\ \text{CH}_3\text{O} \end{smallmatrix} > \text{C}_6\text{H}_2 < \begin{smallmatrix} \text{CO} \\ \text{CO} \end{smallmatrix} > \text{NH}.$

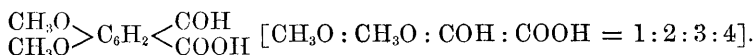
The anhydride of the oxime of opianic acid, when heated slightly above its melting point (115°), undergoes a very remarkable molecular change, and is converted into hemipinimide (Liebermann, *Ber.*, **19**, 2924).



As already stated, the oxime of pseudopianic acid is decomposed at its melting point, and on studying this reaction it was found that in this case also hemipinimide is formed, thus:—



This very important fact proves conclusively that pseudopianic acid has the constitution



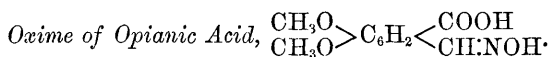
The conversion of the oxime of pseudopianic acid into hemipinimide may be accomplished in a variety of ways, as, for instance, by boiling with dilute hydrochloric acid; but the simplest method is to heat the substance for about 10 minutes in a test-tube at 160–180°. The crystals first melt, then water vapour is given off, and the whole finally solidifies to a hard, crystalline cake. This is ground up, dissolved in the least quantity of boiling alcohol (it is but very sparingly soluble in this solvent), filtered, and the solution allowed to stand. In a short time needle-shaped crystals separate, which consist of pure hemipinimide.

Analysis:—

0·1856 gram substance gave 11·2 c.c. of nitrogen; $t = 23$; bar. = 755.

	Theory. $\text{C}_{10}\text{H}_9\text{NO}_4$.	Found.
N.....	6·77 per cent.	6·78 per cent.

The substance melted at 224–226°, and showed all the properties of hemipinimide.



Liebermann (*Berichte*, **19**, 2923) found that when opianic acid or its ethyl salt is treated in alcoholic solution with hydroxylamine

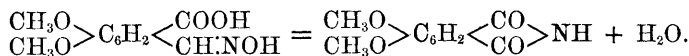
hydrochloride in the cold, a substance, $C_{10}H_9NO_4$ (opianoxime anhydride), is formed, which would seem to be the inner anhydride of the oxime of opianic acid, $C_{10}H_{11}NO_5$, and he thus seems to draw the conclusion from his experiments that the oxime itself is not capable of existence. This substance may, however, be readily prepared in the following way:—The pure acid (1 mol.) is dissolved in a dilute solution of potassium hydrate (4 mols.), mixed with hydroxylamine hydrochloride ($1\frac{1}{2}$ mols.), and left for 12 hours. If the clear solution is then acidified and allowed to stand, long, slender, needle-shaped crystals separate; these are collected, well washed with water, and dried for some days on a porous plate at the ordinary temperature and then for a few minutes at 50° . This substance is the oxime of opianic acid, as is apparent from the following analytical results:—

0.1630 gram substance gave 0.0738 gram H_2O and 0.3227 gram CO_2 .

0.1504 gram substance gave 8.0 c.c. nitrogen; $t = 14^\circ$; bar. = 740 mm.

	Theory. $C_{10}H_{11}NO_5$.	Found.
C.....	53.33 per cent.	53.37 per cent.
H.....	4.88 ,,	5.03 ,,
N.....	6.22 ,,	6.09 ,,

The oxime of opianic acid melts at about $82-83^\circ$, but the melting point varies considerably with the rapidity with which the heating is conducted; on further rapid heating, it remains liquid till about 130° , when it suddenly becomes solid, owing to formation of hemipinimide, thus:—



This remarkable isomeric change takes place sometimes at much lower temperatures; thus, if the oxime is heated at 80° , after some time the whole becomes converted into a solid cake of hemipinimide. This change is accompanied by the evolution of a very considerable amount of heat (compare Liebermann, *Ber.*, **19**, 2924), and in one case, when an ethereal solution of about 10 grams of the oxime was evaporated on a water-bath, the temperature rose so rapidly as to crack the flask in several places.

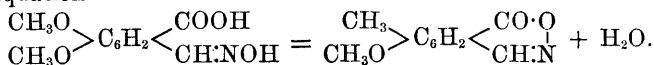
The oxime of opianic acid is extremely soluble in alcohol, readily in ether, hot chloroform, and benzene, but only sparingly in light petroleum and carbon bisulphide. It is very readily soluble in warm water, moderately in cold water; the hot solution, on cooling, deposits the substance in needles.

If, however, the aqueous solution is boiled for a short time, decomposition into water and opianoxime anhydride takes place, and on cooling, this anhydride separates in small, colourless, needle-shaped crystals. These, after recrystallisation, and drying, for some days at the ordinary temperature and then for a few minutes at 40—50°, gave the following results on analysis:—

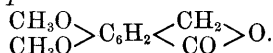
0.1739 gram substance gave 0.0720 gram H₂O and 0.3667 gram CO₂.

	Theory. C ₁₀ H ₉ O ₄ .	Found.
C.....	57.97 per cent.	57.51 per cent.
H.....	4.34 „	4.60 „

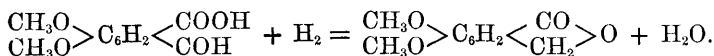
This substance showed all the properties ascribed to opianoxime-anhydride by Liebermann (*Ber.*, **19**, 2923). The crystals melted apparently at 112—115°, but the mass solidified again at once, owing to its being converted into hemipinimide. This decomposition of the oxime of opianic acid into its anhydride is probably represented by the equation



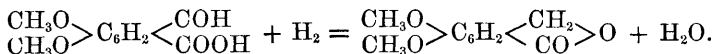
Reduction of Pseudopianic Acid. Formation of Pseudomeconine,



Opianic acid is readily reduced by sodium amalgam with formation of meconine (Matthiessen, Foster, *Chem. Soc. J.*, 1863, 446):—



Pseudopianic acid under the same treatment yields pseudomeconine, thus:—



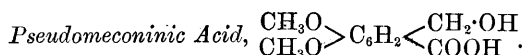
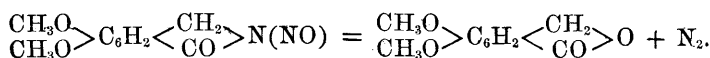
1 gram of the pure acid was dissolved in a dilute solution of sodium carbonate, and then 50 grams of 2½ per cent. sodium amalgam gradually added. After standing for 24 hours, the aqueous layer was poured off the mercury, nearly neutralised, filtered, and acidified with hydrochloric acid. The white, crystalline precipitate which separated was collected, washed with water, and recrystallised from this solvent. The crystals obtained melted between 117° and 122°, and were therefore not quite pure; they were dissolved in hot water, the solution cooled until the substance just commenced to crystallise out, two or

three drops of sodium carbonate solution added, and the whole allowed to stand until quite cold. The resulting colourless needles were collected, washed with water, dried at 100°, and analysed with the following result:—

0.1525 gram substance gave 0.0716 gram H₂O and 0.3450 gram CO₂.

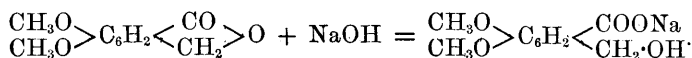
	Theory. C ₁₀ H ₁₀ O ₄ .	Found.
C.....	61.85 per cent.	61.69 per cent.
H.....	5.16 ,,	5.22 ,,
O.....	32.99 ,,	33.09 ,,

This substance melts at 123—124°, and is in all its properties identical with pseudomeconine, which Salomon (*Ber.*, **20**, 884) obtained by boiling nitrosohemipinimidine with sodium hydrate:—

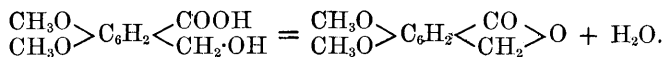


In experimenting with meconine and pseudomeconine, it was found that although they are very similar in their general reactions, yet they differ widely in the following respect:—

Meconine dissolves readily in dilute sodium hydrate solution with formation of the sodium salt of meconinic acid:—



On the addition of acids, the free meconinic acid is at once split up into its anhydride, meconine, and water thus:—

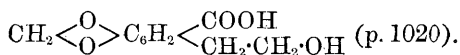


Pseudomeconine is also readily soluble in alkalis, with formation of a salt of pseudomeconinic acid, and on acidifying, the free acid, which is much more stable than meconinic acid, does not decompose, but gradually separates in a pure condition in the form of long, slender, colourless needles. A quantity of this beautiful acid was prepared, washed with water, dried at the ordinary temperature for some days, and then at 40—50° for some minutes, and analysed with the following results:—

0.1446 gram substance gave 0.0728 gram H₂O and 0.3007 gram CO₂.

	Theory.	Found.
	$\begin{array}{c} \text{CH}_3\text{O} \\ \text{CH}_3\text{O} \end{array} > \text{C}_6\text{H}_2 < \begin{array}{c} \text{CH}_2\text{OH} \\ \text{COOH} \end{array}$	
C.....	56·60 per cent.	56·71 per cent.
H.....	5·66 ,,	5·60 ,,
O.....	37·73 ,,	37·69 ,,

Pseudomeconinic acid is very readily converted into pseudomeconine on heating, and it therefore shows practically the same melting point as the latter, the melting of the substance in this case being, however, accompanied by evolution of bubbles of gas (steam). It is much more soluble in water and in most other solvents than pseudomeconine, and differs from its anhydride in the fact that it dissolves readily in a solution of sodium carbonate in the cold. When boiled with water, pseudomeconinic acid dissolves, and, on cooling, beautiful needle-shaped crystals of pseudomeconine separate. In this respect, and in its general behaviour, this acid shows a great similarity to ω -hydroxyethylpiperonylcarboxylic acid,



The wide difference in tendency to form inner anhydrides exhibited by two such closely allied substances as meconinic acid and pseudomeconinic acid is very interesting, and experiments are in progress with a view to obtaining further evidence which may throw light on this point.

Salts of Pseudomeconinic Acid.—Pseudomeconinic acid is a strong monobasic acid, as the following experiments show:—

0·3477 gram of the pure acid was dissolved in an excess of standard KOH solution, and the excess titrated back with standard sulphuric acid, using phenolphthaleïn as an indicator. It was found that this amount of substance required for neutralisation 0·0987 gram KOH, whereas on the assumption that a salt, $\text{C}_{10}\text{H}_{11}\text{O}_5\text{K}$, had been formed, 0·0915 gram of KOH is required.

Silver Pseudomeconinate, $\text{C}_{10}\text{H}_{11}\text{O}_5\text{Ag}$.—To prepare this salt, the pure acid was dissolved in a slight excess of a dilute solution of ammonia, the excess of ammonia allowed to evaporate over sulphuric acid in a vacuum, and the neutral solution precipitated with nitrate of silver. A white, curdy precipitate was obtained, which rapidly became crystalline. It is readily soluble in hot water, and crystallises on cooling in long, slender needles.

Analysis:—

I. 0·1724 gram substance gave 0·0539 gram H_2O , 0·2370 gram CO_2 , and 0·0583 gram Ag.

II. 0·4372 gram substance gave 0·1484 gram Ag.

	Theory. $C_{10}H_{11}O_5Ag$.	Found.	
		I.	II.
C.....	37·66 per cent.	37·49	— per cent.
H.....	3·45 „	3·48	— „
Ag.....	33·77 „	33·89	33·94 „

The neutral solution of the ammonium salt gives no precipitate with lead acetate, barium chloride, or zinc sulphate; a bright green precipitate is produced on the addition of copper sulphate.

Action of Alkalis on Berberal.

Formation of Pseudopianic Acid, $C_{10}H_{10}O_5$; Pseudopianate of ω -Amidoethylpiperonylcarboxylic Anhydride, $C_{20}H_{19}NO_8$; and of ω -Amidoethylpiperonylcarboxylic Anhydride, $C_{10}H_9NO_3$.

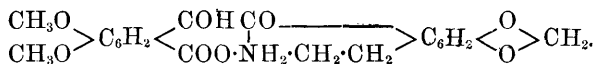
Berberal is insoluble in aqueous alkalis and in alkaline carbonates, but when treated with alcoholic potash, it is readily decomposed, and on the addition of an acid, the above three substances are obtained, the study of which has afforded a clear insight into the constitution of berberal.

In carrying out this hydrolysis, finely powdered berberal is mixed into a thin paste with a little methyl alcohol, heated just to boiling, and then methyl alcoholic potash added drop by drop until the substance has just dissolved, and a drop of the solution mixed with warm water gives only a very slight precipitate. Water is now added, the solution boiled until free from alcohol, acidified with dilute hydrochloric acid, and allowed to stand in a cool place for an hour. A new substance is thus obtained in colourless needles, which, after recrystallisation from water and drying at 100° , gave the following numbers on analysis:—

- I. 0·1114 gram substance gave 0·0542 gram H_2O and 0·2438 gram CO_2 .
- 0·1180 gram substance gave 3·7 c.c. nitrogen; $t = 18^\circ$; bar. = 725 mm.
- II. 0·1540 gram substance gave 0·0714 gram H_2O and 0·3380 gram CO_2 .
- III. 0·1069 gram substance gave 0·0488 gram H_2O and 0·2336 gram CO_2 .

	Theory. $C_{20}H_{19}NO_8$.	Found.		
		I.	II.	III.
C.....	59·85 per cent.	59·58	59·85	59·69 per cent.
H.....	4·74 „	5·20	5·04	5·07 „
N.....	3·49 „	3·58	—	— „

This new substance is the *pseudopianate* of *w-amidoethylpiperonyl-carboxylic anhydride* (p. 1080), and has the constitution

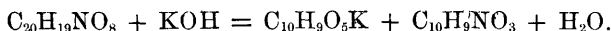


It melts at 149° , and as this temperature corresponds very closely with that noticed as the melting point of berberal ($149\text{--}150^\circ$), it is probable that at this temperature the substance $\text{C}_{20}\text{H}_{19}\text{NO}_8$ is converted into berberal with elimination of water, thus:—



a change which certainly takes place at higher temperatures (p. 1081). The substance $\text{C}_{20}\text{H}_{19}\text{NO}_8$ is readily soluble in boiling water, but only sparingly in cold; the hot solution, on cooling, deposits the substance in the form of slender, colourless needles. It is also readily soluble in methyl and ethyl alcohol and benzene, but only sparingly in light petroleum or carbon bisulphide.

The substance $\text{C}_{20}\text{H}_{19}\text{NO}_8$ is very readily decomposed by alkalis and alkaline carbonates, with formation of pseudopianic acid and *w-amidoethylpiperonylcarboxylic anhydride*, thus:—



In studying this decomposition, the finely divided substance was mixed with dilute ammonia solution, warmed gently, and shaken vigorously. A considerable portion dissolved, but in a short time a white, crystalline precipitate settled out. This was collected, washed with water, recrystallised from this solvent, and analysed with the following result:—

0.1204 gram substance gave 0.0540 gram H_2O and 0.2778 gram CO_2 .

	Theory. $\text{C}_{10}\text{H}_9\text{NO}_3$.	Found.
C.....	62.83 per cent.	62.92 per cent.
H.....	4.71 ,,	4.98 ,,

It melts at 181° , and is identical with *w-amidoethylpiperonyl-carboxylic anhydride* (p. 1013).

The filtrate from this substance was boiled on a reflux apparatus for about half an hour, and allowed to stand over night, when an almost colourless, crystalline substance separated, which after recrystallisation from alcohol melted at $149\text{--}150^\circ$, and showed all the properties of berberal.

The clear alkaline liquid was acidified with hydrochloric acid, and the crystalline precipitate which formed collected, washed with

water, and recrystallised from this solvent. In this way, thin, colourless needles were obtained, which were dried at 100° , and analysed with the following result:—

0.1060 gram substance gave 0.0484 gram H_2O and 0.2219 gram CO_2 .

	Theory. $C_{10}H_{10}O_5$.	Found.
C.....	57.14 per cent.	57.09 per cent.
H.....	4.76 "	5.07 "
O.....	38.09 "	37.84 "

This acid melts at $119-120^{\circ}$, and is identical with pseudopianic acid, $\begin{matrix} CH_3O \\ CH_3O \end{matrix} > C_6H_2 < \begin{matrix} COH \\ COOH \end{matrix}$, the properties of which are given in detail on p. 1065.

Dilute acids appear to decompose the substance $C_{20}H_{19}NO_8$ with almost as great ease as alkalis. A few crystals of it, boiled in a test-tube with a little 10 per cent. sulphuric acid, rapidly dissolved, and on cooling crystals separated which, after recrystallisation from water, were readily identified as the anhydride $C_{10}H_9NO_3$. Ether extracted from the acid liquor a white, crystalline acid, which showed all the properties of pseudopianic acid. The substance $C_{20}H_{19}NO_8$ is, however, perfectly stable in neutral solutions, and may be recrystallised several times from water without seeming to undergo the least decomposition.

Action of Phenylhydrazine on Berberal.

In order to obtain some further clue to the constitution of berberal, a number of experiments on the behaviour of this substance towards reagents, and especially towards phenylhydrazine, were instituted; but although the conditions of the experiment were varied as much as possible, no definite compound of the two substances could be isolated with certainty.

The following experiment, however, gave interesting results:—2 grams of berberal, 5 grams of phenylhydrazine hydrochloride, 15 grams of crystallised sodium acetate, and about 100 c. c. of 70 per cent. alcohol were heated together in a sealed tube at 130° for four hours. The resulting slightly yellowish solution was transferred to a dish, mixed with water, and gently heated on a water-bath, until all the alcohol had evaporated. During this operation, a reddish-brown, flocculent substance separated, which was collected, washed well with water, and ground up in a mortar with a little methyl alcohol. This treatment removed a sticky, resinous substance, leaving an almost colourless powder, very insoluble in the usual

solvents. It was ultimately purified by repeated recrystallisation from isoamyl alcohol, the crystals well washed, first with isoamyl alcohol, then with methyl alcohol, and dried at 100°.

The analysis gave the following numbers:—

- I. 0.1488 gram substance gave 0.0812 gram H₂O and 0.3710 gram CO₂.
 0.2052 gram substance gave 25.2 c.c. N; *t* = 15°; bar. = 753 mm.
- II. 0.1483 gram substance gave 0.0786 gram H₂O and 0.3684 gram CO₂.
 0.2404 gram substance gave 29.5 c.c. N; *t* = 17°; bar. = 756 mm.
- III. 0.1654 gram substance gave 0.0950 gram H₂O and 0.4119 gram CO₂.

	Found.		
	I.	II.	III.
C	68.07	67.75	67.32 per cent.
H	6.06	5.88	6.37 „
N	14.23	14.40	— „

The above analyses, each of which was performed with a different preparation, agree fairly well with either of the two formulæ, C₃₈H₃₇N₇O₅ or C₂₂H₂₂N₄O₃, thus:—

	C ₃₈ H ₃₇ N ₇ O ₅ .	C ₂₂ H ₂₂ N ₄ O ₃ .
C	67.95 per cent.	67.69 per cent.
H	5.51 „	5.65 „
N	14.60 „	14.36 „

The first of these formulæ results from the combination of berberal with three molecules of phenylhydrazine with loss of two molecules of water, thus:—C₂₀H₁₇NO₇ + 3C₆H₅·NH·NH₂ = C₃₈H₃₇N₇O₅ + 2H₂O. The second formula represents the phenylhydrazide of the phenylhydrazine compound of pseudopianic acid, thus:—C₁₀H₁₀O₅ + 2C₆H₅·NH·NH₂ = C₂₂H₂₂N₄O₃ + 2H₂O.

This compound would be represented by the formula



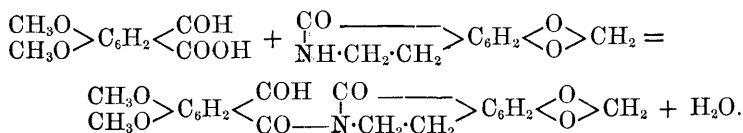
A more careful examination of the course of the reaction appears to favour the latter view. The mother liquors, aqueous as well as alcoholic, from the crude phenylhydrazine compound were mixed with a little dilute hydrochloric acid, evaporated to a small bulk, and filtered hot. The solution on standing deposited a small quantity of brownish plates, which after recrystallisation melted at

178—180°, and showed all the properties of the anhydride $C_{10}H_9NO_3$. It is, therefore, probable that in the above reaction berberal is first decomposed under the influence of water at 180° into the anhydride $C_{10}H_9NO_3$ and pseudopianic acid, and the latter then combines with two molecules of phenylhydrazine as described above. Experiments on the action of phenylhydrazine on pseudopianic acid would settle this point, but these, owing to lack of material, have not yet been instituted.

The phenylhydrazine compound $C_{22}H_{22}N_4O_3$ is very sparingly soluble in water, ethyl and methyl alcohols, benzene, chloroform, and cold amyl alcohol, but readily in hot amyl alcohol; from the latter it crystallises on cooling in small, glistening, yellow needles, which do not melt when heated to 250°. It dissolves readily in hot glacial acetic acid, but does not crystallise out again on cooling. When heated with alcoholic hydrogen chloride, the compound is readily decomposed, with formation of phenylhydrazine hydrochloride.

Synthesis of Berberal.

It has been shown in the preceding sections that berberal is readily decomposed by boiling dilute sulphuric acid into the anhydride $C_{10}H_9NO_3$ and pseudopianic acid; and it appeared extremely interesting to determine whether by bringing these two substances together under suitable conditions berberal might be reproduced, thus:—



After numerous fruitless experiments, this synthesis was ultimately accomplished by simply heating the two substances together:—0·4 gram of $C_{10}H_9NO_3$ and 0·5 gram of pseudopianic acid were very finely powdered, intimately mixed, and heated in a test-tube gradually to 180°, kept at that temperature for 15 minutes, and then heated at 210° for 15 minutes. During the operation a quantity of water was given off, and the strongly fluorescent, brownish, oily residue solidified to a transparent resin, which cracked all over. This was ground up, dissolved in boiling alcohol, and the solution concentrated and allowed to stand for 24 hours. The sandy, crystalline precipitate which separated was collected, washed with a little alcohol, and twice recrystallised from that solvent. In this way, beautiful glistening plates, were obtained, which melted at 148—150°, and gave the following results on analysis:—

0.1558 gram substance gave 0.0652 gram H_2O and 0.3566 gram CO_2 .

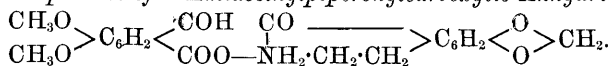
0.2310 gram substance gave 7.9 c.c. nitrogen; $t = 22^\circ$; bar. = 745 mm.

	Theory. $\text{C}_{20}\text{H}_{17}\text{NO}_7$.	Found.
C	62.66 per cent.	62.42 per cent.
H	4.43 ,,	4.65 ,,
N	3.66 ,,	3.73 ,,

A careful comparative examination showed that this substance was identical with berberal in every respect, and as the yield obtained was over 60 per cent. of the theoretical, if pseudopianic acid could be obtained in any quantity, the above would be by far the best method for preparing berberal, especially as the resulting product is so very readily purified.

Experiments on the synthesis of pseudopianic acid and of the substance $\text{C}_{10}\text{H}_9\text{NO}_3$ are in progress; as also on the synthesis of berberine from berberal.

Pseudopianate of ω -Amidoethylpiperonylcarboxylic Anhydride,



In order to prepare this interesting substance, 1.6 grams of ω -amidoethylpiperonylcarboxylic anhydride and 1.8 grams of pseudopianic acid were intimately mixed and dissolved in a little boiling water. The hot solution, on standing, deposited slender needles, which were collected, washed with a little water, recrystallised from this solvent, and analysed with the following result:—

0.1304 gram substance gave 0.0601 gram H_2O and 0.2858 gram CO_2 .

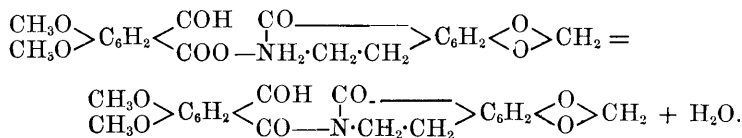
0.1770 gram substance gave 5.5 c.c. nitrogen; $t = 17^\circ$; bar. = 740 mm.

	Theory. $\text{C}_{20}\text{H}_{19}\text{NO}_8$.	Found.
C	59.85 per cent.	59.77 per cent.
H	4.74 ,,	5.12 ,,
N	3.49 ,,	3.55 ,,

This substance melts at 149° , and is identical with the compound $\text{C}_{20}\text{H}_{19}\text{NO}_8$, obtained by treating berberal with alkalis as explained on p. 1075, and the formation of this substance under these conditions is evidently due to the fact that berberal on hydrolysis first yields pseudopianic acid and ω -amidoethylpiperonylcarboxylic anhydride,

which on solution in water again combine, forming the compound $C_{20}H_{19}NO_8$.

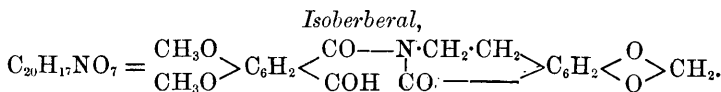
When heated at 180° , the compound $C_{20}H_{19}NO_8$ loses 1 mol. H_2O and is converted into berberal. This interesting decomposition is easily understood with the aid of the equation



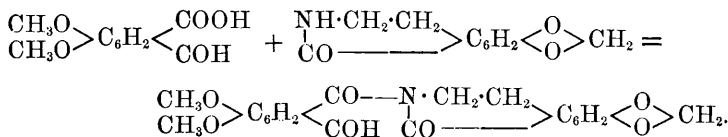
A sample of berberal obtained in this way gave the following results on analysis:—

0.0998 gram substance gave 3.2 c.c. nitrogen; $t = 17^\circ$; bar. = 740 mm.

	Theory. $C_{20}H_{17}NO_7$.	Found.
N	3.66 per cent.	3.81 per cent.



This very interesting substance is readily prepared by heating together *opianic acid* and the anhydride $C_{10}H_9NO_3$, thus:—



1.6 grams of the anhydride $C_{10}H_9NO_3$ and 1.8 grams of opianic acid (prepared from narcotine by oxidation with dilute nitric acid) were ground up together and the mixture heated in a small flask, at $210\text{--}215^\circ$ for thirty minutes. The reaction took place exactly as described in the synthesis of berberal (p. 1079), and the resulting brown, fluorescent oil solidified on cooling to an exactly similar, transparent resin. This was ground up and boiled with a considerable quantity of alcohol until completely dissolved, the solution concentrated, filtered, and allowed to stand for about two hours. The crystalline precipitate, which was slightly greyish and possessed a remarkable satiny lustre, was collected, washed with a little alcohol, dried on a porous plate, and recrystallised from boiling toluene. The solvent leaves undissolved a small quantity of a brownish substance, and on

cooling beautiful, faintly yellow, lustrous plates are obtained, which, after drying at 100°, gave the following results on analysis:—

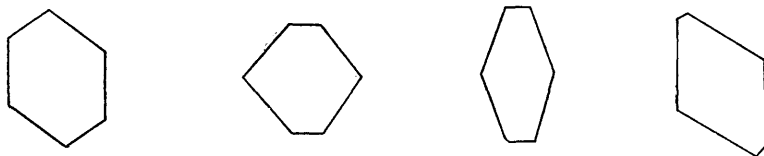
0·1490 gram substance gave 0·0629 gram H₂O and 0·3422 gram CO₂.

0·1986 gram substance gave 6·3 c.c. nitrogen; $t = 15^\circ$; bar. = 740 mm.

	Theory. C ₂₀ H ₁₇ NO ₇ .	Found.
C	62·66 per cent.	62·53 per cent.
H	4·43 ,,	4·57 ,,
N	3·66 ,,	3·76 ,,

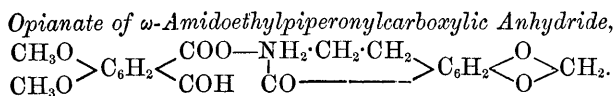
Isoberberal melts at 185° (*berberal* melts at 149—150°). It is very readily soluble in hot and cold glacial acetic acid, moderately in boiling xylene, toluene, or benzene, and alcohol, but only very sparingly soluble in these solvents in the cold, as also in light petroleum. The solutions fluoresce in exactly the same way as those of *berberal*.

Isoberberal crystallises from boiling xylene in stellate groups, from boiling toluene in flat plates. The best shaped crystals were obtained by allowing a moderately concentrated solution of the substance in hot dilute acetic acid to cool very slowly. Beautiful, colourless crystals were deposited which, when examined under the microscope, were seen to have the following forms:—



Isoberberal, like *berberal*, is apparently very readily hydrolysed by acids and alkalis, the products being obviously opianic acid and ω -amidoethylpiperonylcarboxylic anhydride.

The yield of *isoberberal* obtained by the above synthesis is good, and although only small quantities of material have so far been employed, as much as 80 per cent. of pure *isoberberal* has in one or two cases been obtained.



This was prepared by mixing equimolecular parts of opianic acid and ω -amidoethylpiperonylcarboxylic anhydride and dissolving the

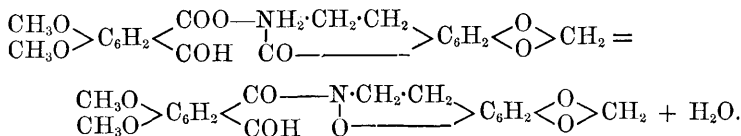
mixture in boiling water. The hot solution, on cooling, deposited the salt in the form of beautiful, feathery groups of needles, which were recrystallised from water and analysed with the following results:—

0.1544 gram substance gave 0.0688 gram H_2O and 0.3394 gram CO_2 .

0.2258 gram substance gave 7.1 c.c. nitrogen; $t = 17^\circ$; bar. = 742 mm.

	Theory. $\text{C}_{20}\text{H}_{19}\text{NO}_8$.	Found.
C	59.85 per cent.	59.95 per cent.
H	4.74 ,,	4.94 ,,
N	3.49 ,,	3.56 ,,

This substance melts at about $130\text{--}132^\circ$ with decomposition. It is readily soluble in hot water, moderately in cold water, extremely soluble in alcohol, but only sparingly in bisulphide of carbon, chloroform, benzene, and light petroleum. It is isomeric with the corresponding pseudopianic salt (p. 1080), and behaves in a manner exactly similar to this salt on heating at 180° , yielding isoberberal:—



The salt was heated at 180° for about ten minutes, and the resulting oil, which solidified to a transparent resin on cooling, recrystallised from boiling toluene. The beautiful, satiny crystals which separated melted at 185° and showed all the properties of isoberberal.

Analysis:—

0.1323 gram substance gave 4.2 c.c. nitrogen; $t = 14^\circ$; bar. = 738 mm.

	Theory. $\text{C}_{20}\text{H}_{17}\text{NO}_7$.	Found.
N	3.66 per cent.	3.74 per cent.

Separation of Oxyberberine, Dioxyberberine, and Anhydroberberilic Acid.

These three compounds occur, together with inorganic salts, in the precipitate which separates from the sulphurous acid liquors on evaporation (p. 1012).

Before proceeding to the separation of the organic compounds, the precipitate is gently warmed with 5 per cent. hydrochloric acid, until the evolution of sulphurous anhydride ceases, filtered, washed

with water, and dried on a porous plate. It is then tested by heating on a platinum spatula, and the treatment with dilute hydrochloric acid repeated if more than traces of inorganic matter are left. The separation of the organic compounds is a matter of some difficulty, but may be accomplished fairly completely by either of the following methods:—

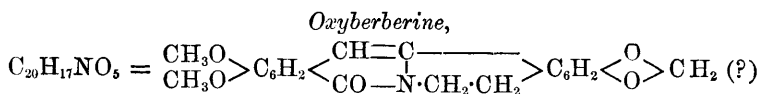
Method I.—The precipitate is boiled with glacial acetic acid, until about two-thirds of it has dissolved; the solution is filtered hot, and the yellow residue, which contains dioxyberberine, washed with a little acetic acid and purified as described on p. 1088. The dark-coloured filtrate is evaporated to half its bulk and allowed to stand in a cool place; in a short time the separation of beautiful, orange-coloured crystals of oxyberberine acetate commences, and at the end of seven days these are collected, washed with acetic acid, dried at 100°, and further purified as described on p. 1085. The dark-coloured mother liquors from these crystals, after evaporation to a small bulk, deposit a further quantity of orange-coloured crystals of oxyberberine acetate, mixed with a small quantity of silky needles of anhydroberberilic acid. These two substances may be separated with difficulty by repeated recrystallisation from glacial acetic acid, but the quantity of either ultimately obtained is but small.

Method II.—The precipitate is dissolved in boiling dilute alcoholic potash, the solution filtered hot and rapidly cooled under the tap. The beautiful, needle-shaped crystals of oxyberberine which separate are collected, washed with alcohol, and purified as described on p. 1085. The alcoholic mother liquor from these is evaporated to about half its bulk, cooled, filtered from a further quantity of oxyberberine which separates, acidified with dilute sulphuric acid, and boiled for a few minutes to decompose any berberilic acid present. The tarry mass which separates is collected, washed with water and repeatedly triturated with hot alcohol; this treatment removes a dark-brown, resinous substance, leaving a yellow, amorphous powder which consists for the most part of dioxyberberine (p. 1087).

Method I is best employed if dioxyberberine is the principal product required, whereas method II appears to give the best yield of oxyberberine.

The relative quantities of these substances present in the crude precipitate varies with almost every preparation, but in one or two cases approximately the following amounts have been obtained from 1 kilo. of berberine hydrochloride:—

Crude yellow precipitate	25 grams.
Oxyberberine	10 „
Dioxyberberine	4 „
Anhydroberberilic acid	2 „



This interesting substance differs from berberine in containing 1 oxygen atom more than the alkaloid; it may, therefore, be looked on as the primary product of the oxidation of berberine. It is best purified by recrystallisation either from xylene or from glacial acetic acid. The pure substance dried at 100° gave, on analysis, the following numbers:—

- I. 0.1628 gram substance gave 0.0752 gram H_2O and 0.4088 gram CO_2 .
 0.2457 gram substance gave 8.9 c.c. nitrogen; $t = 25^\circ$; bar. = 740 mm.
- II. 0.1635 gram substance gave 0.0743 gram H_2O and 0.4088 gram CO_2 .
- III. 0.1654 gram substance gave 0.0770 gram H_2O and 0.4162 gram CO_2 .

	Theory. $\text{C}_{20}\text{H}_{17}\text{NO}_5$.	Found.		
		I.	II.	III.
C	68.39 per cent.	68.48	68.19	68.63 per cent.
H	4.84 „	5.13	5.04	5.17 „
N	3.96 „	3.93	—	— „

This beautiful, yellow substance melts at 198—200° to a deep-yellow liquid, which may be heated to 250° without decomposition; even at 280° it is only slightly discoloured. It is moderately soluble in boiling toluene and xylene, very soluble in hot acetic acid (see below), and still more so in acetic anhydride; sparingly soluble in alcohol and benzene, almost insoluble in light petroleum and water; the alcoholic solution shows a slight blue fluorescence. It crystallises from xylene in beautiful, lustrous, yellow plates. Oxyberberine is slightly soluble in hydrochloric acid, readily so in an alcoholic solution of hydrogen chloride; the addition of alcoholic platinum chloride to this produces a yellow precipitate which appears to be amorphous, but crystallises from alcohol in slender, silky needles.

Oxyberberine is very sparingly soluble in dilute sulphuric acid (1 : 4) but dissolves readily in warm 50 per cent. sulphuric acid, and the yellow solution, on cooling, deposits beautiful, light-yellow needles. It gives the following very delicate reaction, by means of which the smallest trace of the substance may be detected. A minute particle of the substance is dissolved in a little warm 50 per cent. sulphuric acid, cooled, and one drop of ordinary concentrated nitric acid added.

A deep-brown coloration is at once produced, which rapidly changes to an intense violet; on the addition of water the colour is not destroyed, but turns a fine reddish-violet, which is very similar in appearance to the colour of a very dilute solution of permanganate.

Oxyberberine dissolves in a warm solution of hydrogen iodide, and if a trace of iodine is added, a brown precipitate is produced, which crystallises from alcoholic hydrogen iodide in green plates or groups of slender microscopic needles.

In order to determine whether oxyberberine is capable of forming an acetyl derivative, a small quantity of the substance was boiled with an excess of acetic anhydride in a reflux apparatus for four hours, evaporated to a small bulk, and allowed to stand over night. The beautiful, yellow, needle-shaped crystals which formed were collected, washed with acetic anhydride, and dried at 130°.

The analysis showed that the substance was unchanged :—

0.1548 gram substance gave 0.0712 gram H_2O and 0.3904 gram CO_2 .

	Theory. $C_{20}H_{17}NO_5$.	Found.
C.....	68.39 per cent.	68.78 per cent.
H.....	4.84 „	5.11 „

Oxyberberine Acetate, $C_{20}H_{17}NO_5, C_2H_4O_2$.

Although oxyberberine, as compared with berberine, is a very feeble base, it forms a very well characterised acetate; this is readily obtained in a pure state by dissolving the substance in boiling glacial acetic acid, and allowing the solution to stand for some days. The acetate gradually separates in beautiful, lustrous, yellow crystals; these are collected, drained on a porous plate, and dried by exposure to the air for three days. An analysis gave the following numbers :—

0.1370 gram substance gave 0.0642 gram H_2O and 0.3238 gram CO_2 .

	Theory. $C_{20}H_{17}NO_5, C_2H_4O_2$.	Found.
C.....	64.23 per cent.	64.39 per cent.
H.....	5.11 „	5.21 „

It is moderately stable at ordinary temperatures, if the crystals are large, but the finely-powdered substance gradually loses acetic acid on exposure to the air. A sample of the preparation analysed above was finely powdered and allowed to stand exposed to the air for four days; on analysis it gave $C = 65.30 : H = 5.28$, and on drying at 100° it lost only 10.9 per cent. of acetic acid.

Dried at 100°, the beautifully lustrous crystals become opaque, and

rapidly lose the whole of their acetic acid, leaving a residue of pure oxyberberine. A small quantity of the acetate dried at 100° for two hours gave, on analysis, the following results:—

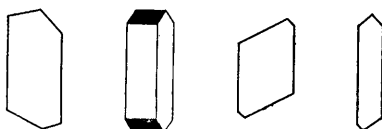
0·1474 gram substance gave 0·0660 gram H₂O and 0·3704 gram CO₂.

	Theory. C ₂₀ H ₁₇ NO ₅ .	Found.
C.....	68·39 per cent.	68·53 per cent.
H.....	4·84 „	4·97 „

1·8586 gram of the pure acetate, heated at 100° until the weight was constant, lost 0·2702 gram of acetic acid = 14·54 per cent.

C₂₀H₁₇NO₅(C₂H₄O₂) contains 14·59 per cent. of acetic acid.

The beautiful crystals of oxyberberine acetate, when examined under the microscope, seem to have the following forms:—

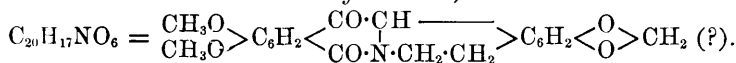


As this acetate is moderately easily soluble in glacial acetic acid, its molecular weight was carefully determined by Raoult's method, with the following result:—

Substance taken	1·5730 grams.
Acetic acid taken	100·4 „
Melting point of acetic acid	16·262°
„ „ mixture	16·112°
Depression of the melting point. .	0·150°
Molecular weight of the substance found from the above data	407
Theory for C ₂₀ H ₁₇ NO ₅ , C ₂ H ₄ O ₂	411

The yield of oxyberberine is about 10 grams from 1 kilo. of berberine hydrochloride, and as it can thus be obtained in considerable quantity, I hope to make it the subject of a future investigation.

Dioxyberberine,



This remarkable substance, which probably results from the further action of oxidising agents on oxyberberine, is unfortunately produced in such small quantity and is so difficult to purify, that it has

been found impossible to investigate it as thoroughly as could have been wished.

The crude yellow product obtained as explained on p. 1012, is almost insoluble in the usual solvents, but it may be obtained pure by recrystallisation either from boiling aniline, nitrobenzene, or ethyl benzoate, the former being preferable on account of its somewhat lower boiling point. In recrystallising it, the powder is added to boiling aniline as long as it is dissolved, the solution rapidly filtered, and allowed to cool; the whole operation being conducted as quickly as possible, as boiling with aniline decomposes the substance and great loss occurs. The hot solution, on cooling, deposits the new substance in glistening, yellow needles, which are collected, washed first with aniline and then with methyl alcohol, and dried on a porous plate.

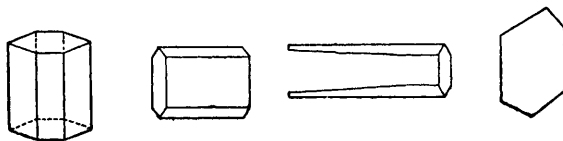
For the analysis the substance was dried at 100° for one hour:—

- I. 0.1740 gram substance gave 0.0802 gram H_2O and 0.4196 gram CO_2 .
 0.3469 gram substance gave 11.7 c.c. nitrogen; $t = 16^{\circ}$; bar. = 766 mm.
- II. 0.1867 gram substance gave 0.0882 gram H_2O and 0.4470 gram CO_2 .
- III. 0.2272 gram substance gave 0.1013 gram H_2O and 0.5470 gram CO_2 .

	Theory. $C_{20}H_{17}NO_6$.	Found.		
		I.	II.	III.
C....	65.39 per cent.	65.76	65.29	65.66 per cent.
H....	4.64 „	5.17	5.25	4.95 „
N....	3.82 „	3.92	—	— „

Each of these analyses was made with a separate preparation: I was recrystallised once from aniline; II, twice from the same solvent; and III was recrystallised from ethyl benzoate.

Dioxyberberine is almost insoluble in alcohol, benzene, and light petroleum, sparingly soluble in boiling glacial acetic acid, readily in boiling aniline, nitrobenzene, or ethyl benzoate, but only sparingly in these liquids in the cold. It crystallises from ethyl benzoate in small, well-defined crystals, which, when examined under the microscope, are seen to have the following forms:—



Some of the crystals were very curiously striated: twin crystals were frequent, as also single examples with very imperfectly formed edges.

Dioxyberberine shows the following characteristic reactions:—

It dissolves in concentrated sulphuric acid, producing a reddish-violet solution; on warming, the colour gradually changes and ultimately becomes intensely olive-green.

It dissolves in nitric acid with a fine violet colour. If a drop of nitric acid is added to its solution in cold concentrated sulphuric acid, a beautiful, deep bluish-violet coloration is produced, which is destroyed on the addition of water (compare the corresponding reaction with oxyberberine, p. 1085).

Finely-divided dioxyberberine is turned a dark green by the addition of a few drops of concentrated hydrochloric acid; on warming with an excess of hydrochloric acid, the greater part dissolves, forming a yellowish-green solution, which, on addition of a drop of platinum chloride, gradually becomes intensely violet-coloured.

Action of Alkalis on Dioxyberberine.

Although only sparingly soluble in aqueous solutions of alkalis, dioxyberberine dissolves with great readiness in warm alcoholic potash, forming a deep orange-red solution, which, if sufficiently concentrated, deposits on cooling, beautiful, deep orange-coloured needles of a potassium salt. In order, if possible, to obtain this in a state pure enough for analysis, pure dioxyberberine was dissolved in a strong solution of pure potassium hydrate in 80 per cent. methyl alcohol, the solution allowed to stand, and the crystals which separated quickly collected, washed with a little methyl alcohol, spread on a porous plate, and transferred to a vacuum desiccator.

Two separate preparations gave the following results on analysis:—

1. 0.2179 gram substance gave, after decomposition with sulphuric acid, 0.0404 gram K_2SO_4 = 8.31 per cent. of K.
2. 0.3371 gram substance gave 0.0698 gram K_2SO_4 = 8.09 per cent. K.

Theory for $C_{20}H_{18}NO_7K$ 9.22 per cent. K.

„ „ $C_{20}H_{18}NO_7K + 3H_2O$.. 8.17 „ K.

Unfortunately, owing to the small amount of material at my disposal, it was not possible to make any further analyses of this interesting salt, but it seems probable that when dioxyberberine dissolves in alcoholic potash it forms a potassium salt of the formula



which crystallises from 80 per cent. methyl alcohol with 3 mols. of water of crystallisation. This potassium salt is partially decomposed by much water, with separation of a small quantity of a yellowish-white substance. Acids decompose the salt with separation of a light ochre-coloured precipitate, which consists of pure dioxyberberine. In order to be certain of this, the precipitate was collected, washed with water and methyl alcohol, dried on a porous plate at 100° , and analysed with the following results:—

0.1595 gram substance gave 0.0685 gram H_2O and 0.3830 gram CO_2 .

	Theory. $C_{20}H_{17}NO_6$.	Found.
C.....	65.39 per cent.	65.48 per cent.
H.....	4.63 ,,	4.77 ,,

Hydroxylamine has no action on a dilute solution of the potassium salt. In order to prove this, 0.75 gram of pure dioxyberberine was dissolved in a considerable excess of dilute methyl alcoholic potash, 1 gram of hydroxylamine hydrochloride, dissolved in a little water, added, and the solution, after standing for 24 hours, heated to boiling for half-an-hour. The bulk of the methyl alcohol was distilled off, the residue acidified with hydrochloric acid, and the precipitate which separated washed well, and analysed with the following result:—

0.2163 gram substance gave 6.8 c.c. nitrogen; $t = 21^{\circ}$; bar. = 746 mm.

	Theory. $C_{20}H_{17}NO_6$.	Found.
N.....	3.82 per cent.	3.70 per cent.

The substance was therefore unchanged dioxyberberine.

The most remarkable property of the potassium salt of dioxyberberine is that, on standing in the air, it gradually loses its colour, and is converted into the potassium salt of berberilic acid. In studying this decomposition, 2 grams of pure dioxyberberine was converted into the potassium salt by dissolving it in methyl alcoholic potash, and the product, which consisted of red crystals suspended in a yellow solution, was agitated with air in a large flask for about a week, the whole being gently warmed from time to time. The solution gradually became colourless, and the red crystals ultimately entirely disappeared, giving place to a small quantity of a white, crystalline precipitate. The product was dissolved in water, neutralised with dilute hydrochloric acid, evaporated until free from alcohol, and acidified. The white, semi-solid precipitate of berberilic acid which separated was collected, washed with water, and converted into anhydroberberilic acid by boiling with 50 per cent. sulphuric acid

for a few minutes. The white, crystalline precipitate thus obtained was recrystallised from much alcohol, dried at 100°, and analysed with the following result:—

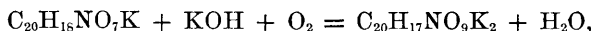
0·1392 gram substance gave 0·0564 gram H₂O and 0·3070 gram CO₂.

0·1560 gram substance gave 4·8 c.c. nitrogen; $t = 21^\circ$; bar. = 756 mm.

	Theory. C ₂₀ H ₁₇ NO ₈ .	Found.
C	60·15 per cent.	60·15 per cent.
H	4·26 ,,	4·48 ,,
N	3·51 ,,	3·49 ,,

This substance melts at 237° and is identical with anhydroberberilic acid.

The formation of berberilic acid from the potassium salt of dioxyberberine may be explained by the following equation:—

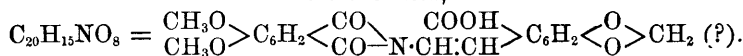


but it is extremely difficult to understand the *modus operandi* of the reaction. In order, however, to prove that oxygen was actually taken up in this reaction, 0·22 gram of dioxyberberine was dissolved in methyl alcoholic potash and placed in a eudiometer in an atmosphere of oxygen over mercury. After remaining for five days, with constant agitation and gentle application of heat from time to time, it was found that 11 c.c. of oxygen had been absorbed. A blank experiment was then carried out with methyl alcoholic potash solution alone, under exactly similar conditions, and, although slight absorption did take place, the diminution in the volume of oxygen after six days was only 3·2 c.c.

This experiment seems to prove that the transformation of dioxyberberine into berberilic acid in alkaline solution is due to the absorption of oxygen from the air.

Further experiments which are in progress will, it is hoped, throw light on this extremely interesting decomposition.

Berberilic Acid,



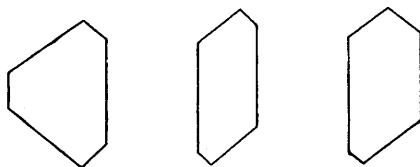
The crude residue, obtained as explained on p. 1012 was collected from several operations; it weighed about 6 grams, and formed a semi-solid, dark-greyish mass, from which it was extremely difficult to obtain anything crystalline. It was digested with glacial acetic acid, the dark-green solution filtered, evaporated to a small

bulk, and allowed to stand for about seven days in a cool place. At the end of that time a quantity of glistening plates had separated; these were collected, well washed with glacial acetic acid, and twice recrystallised from this solvent. In this way beautiful, colourless, glistening plates were obtained, which, after drying at 105° , gave the following results on analysis:—

- I. 0.1437 gram substance gave 0.0555 gram H_2O and 0.3312 gram CO_2 .
 0.1725 gram substance gave 5.6 c.c. nitrogen; $t = 15^{\circ}$; bar. = 730 mm.
 II. 0.1638 gram substance gave 0.0618 gram H_2O and 0.3762 gram CO_2 .
 III. 0.1580 gram substance gave 0.0608 gram H_2O and 0.3633 gram CO_2 .

	Theory. $C_{20}H_{15}NO_8$.	Found.		
		I.	II.	III.
C	62.99 per cent.	62.85	62.64	62.71 per cent.
H	3.94 „	4.29	4.19	4.27 „
N	3.67 „	3.71	—	— „

This new acid has therefore probably the composition $C_{20}H_{15}NO_8$. When heated in a capillary tube, it darkens in colour at about 195° , and melts at $198-200^{\circ}$ with blackening and evolution of gas; in this respect, the substance differs very markedly from any of the other compounds obtained in this research. It is only sparingly soluble in water, but readily in boiling glacial acetic acid, from which it is deposited on cooling in magnificent, lustrous plates; these, when examined under the microscope, are seen to have the following forms:—



This acid dissolves readily in sulphuric and hydrochloric acids; the solution in hydrochloric acid gives with platinum chloride a yellowish-white, amorphous precipitate, which dissolves moderately easily in hot water, and crystallises out again, on cooling, in yellow needles.

Salts of Berilic Acid.

This acid dissolves readily in alkalis, and gives very characteristic salts. The *ammonium salt* was prepared by dissolving the acid in

excess of ammonia, and allowing the solution to stand over sulphuric acid in a vacuum for some days.

The silver salt, $C_{20}H_{14}AgNO_8$, was obtained, by precipitating the ammonium salt with silver nitrate, as a white, curdy precipitate, somewhat soluble in water. The well-washed salt was dried at 100° , and analysed with the following result:—

0.1966 gram substance gave 0.0570 gram H_2O and 0.3446 gram CO_2 .

0.1906 gram substance gave 0.0407 gram Ag.

	Theory. $C_{20}H_{14}AgNO_8$.	Found.
C	47.61 per cent.	47.81 per cent.
H.....	2.78 ,,	3.22 ,,
Ag.....	21.43 ,,	21.35 ,,

A solution of the ammonium salt shows the following behaviour with reagents:—

Calcium Chloride.—In dilute solutions, at first there is no change, but, on standing, the calcium salt separates in glistening, leafy crystals readily soluble in hot water, sparingly in cold water.

Barium Chloride.—No precipitate in moderately dilute solutions.

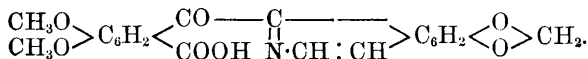
Zinc Sulphate.—Gives at once a white precipitate, consisting of tufts of needles, sparingly soluble in hot water, from which it crystallises on cooling in groups of needles and four-sided plates.

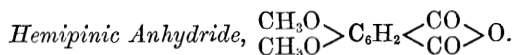
Copper Sulphate.—A light-green, amorphous precipitate, which, on warming, changes to a very light-blue, apparently crystalline precipitate, almost insoluble both in hot and cold water.

Cadmium Chloride.—A white precipitate consisting of minute tufts of needles; it dissolves in much hot water, but is more insoluble than the zinc salt.

Lead Acetate.—A white, curdy precipitate, soluble in hot water, from which it crystallises on cooling in plates, which have almost the same form as the crystals of the acid itself.

A further study of the properties of this interesting acid will, it is hoped, give more definite evidence as to its constitution, which, in the meantime, may either be represented by the formula at the head of this section or by



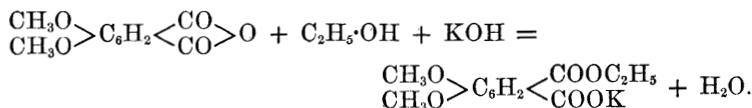


This substance, which is only produced in very small quantities in the oxidation of berberine under the conditions stated on p. 1012, was purified by repeated recrystallisation from glacial acetic acid, and thus obtained in the form of long, slightly brownish needles, which on analysis gave the following numbers:—

- I. 0.1554 gram substance gave 0.0548 gram H_2O and 0.3255 gram CO_2 .
 II. 0.1553 gram substance gave 0.0574 gram H_2O and 0.3266 gram CO_2 .

	Theory. $\text{C}_{10}\text{H}_8\text{O}_5$.	Found.	
		I.	II.
C	57.69 per cent.	57.12	57.32 per cent.
H	3.86 „	3.91	4.10 „
O	38.54 „	38.97	38.58 „

This substance melts at 167° , and has properties very similar to those of hemipinic anhydride (m. p. 167°). On studying, however, its behaviour towards alcoholic potash, an acid melting at 146° was obtained instead of hemipinic acid (m. p. 180°), and it was not until the action of alcoholic potash on a sample of hemipinic anhydride prepared from the pure acid itself had been studied that the cause of this reaction could be explained. It was then found that hemipinic anhydride, when boiled with dilute alcoholic potash, is converted into ethyl hydrogen hemipinate:—



0.5 gram of the anhydride from berberine was boiled with dilute alcoholic potash for 10 minutes, mixed with twice its bulk of water, heated on a water-bath until the alcohol was expelled, cooled, and acidified with dilute hydrochloric acid. The white, crystalline precipitate formed was collected, washed with water, and recrystallised from this solvent. In this way, beautifully glistening, colourless needles were obtained, which, on drying at 100° , lost their lustre, and therefore probably contained water of crystallisation. The analysis gave the following numbers:—

- I. 0.1456 gram substance gave 0.0748 gram H_2O and 0.3006 gram CO_2 .

II. 0.1504 gram substance gave 0.0777 gram H_2O and 0.3115 gram CO_2 .

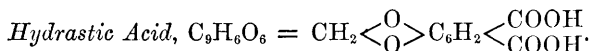
	Theory.	Found.	
	$\begin{matrix} \text{CH}_3\text{O} \\ \text{CH}_3\text{O} \end{matrix} > \text{C}_6\text{H}_2 < \begin{matrix} \text{COOC}_2\text{H}_5 \\ \text{COOH} \end{matrix}$	I.	II.
C	56.69 per cent.	56.31	56.48 per cent.
H	5.51 „	5.71	5.74 „
O	37.79 „	37.98	37.78 „

It melted sharply at 146° .

According to Anderson (*Annalen*, **86**, 194), ethyl hydrogen hemipinate melts at 132.2° ; Wegscheider (*Monats.*, **3**, 369), on the other hand, gives 141 — 142° as the melting point of this salt.

In order to prove the constitution of this compound, a small quantity was dissolved in dilute sodium hydrate solution, boiled for about 10 minutes, cooled, neutralised with dilute hydrochloric acid, an excess of a strong solution of calcium chloride added, and the whole heated to boiling for a few minutes. The crystalline calcium salt which separated was collected, washed with water, and dissolved in a little hot dilute hydrochloric acid; this solution, on cooling, deposited beautiful, colourless crystals of pure hemipinic acid (m. p. 180°).

The formation of ethyl hydrogen hemipinate by the action of boiling alcoholic potash on hemipinic anhydride is very remarkable, and, in looking over the properties of a series of similar anhydrides, I have not been able to find a parallel case.



The crude acid solution obtained as described on p. 1013 contains two acids, namely hydrastic acid and hemipinic acid; these were separated and identified as follows:—The aqueous solution was extracted 20 times with ether, the ethereal solution dried over calcium chloride and evaporated, when a pale-yellow syrup was obtained, which, even after standing over sulphuric acid in a vacuum, showed very little sign of crystallising. As all attempts to make this syrup crystallise failed, recourse was had to the following method of purification:—The crude substance was dissolved in water, neutralised with potassium hydrate, the cold solution mixed with a large excess of a strong solution of calcium chloride, filtered, and heated to boiling. This caused the precipitation of a very sparingly soluble calcium salt, which was collected, washed with hot water, and dissolved in a sufficient quantity of boiling 5 per cent. hydrochloric acid. This solution, on cooling, deposited a quantity of brownish, leafy plates which, after repeated recrystallisation and treatment with animal charcoal, were obtained as colourless, glistening plates.

After being dried at 100°, it gave the following numbers on analysis:—

0.1540 gram substance gave 0.0455 gram H₂O and 0.2903 gram CO₂.

0.1520 gram substance gave 0.0434 gram H₂O and 0.2832 gram CO₂.

	Theory. C ₉ H ₆ O ₆ .	Found.	
		I.	II.
C	51.43 per cent.	51.41	50.81 per cent.
H	2.86 „	3.27	3.17 „
O	45.71 „	45.32	46.02 „

This acid melts at 180°, is moderately soluble in water, and crystallises from this solvent in colourless, leafy plates.

The silver salt, C₉H₄Ag₂O₆, was prepared by dissolving the acid in excess of ammonia, allowing the solution to stand over sulphuric acid in a vacuum until neutral, and then adding an excess of nitrate of silver solution. The white, amorphous precipitate thus produced was collected, washed with water, dried over sulphuric acid in a vacuum, and analysed with the following result:—

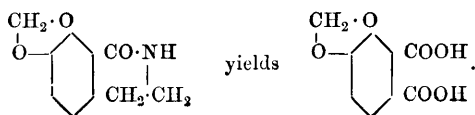
0.2009 gram substance gave 0.0230 gram H₂O and 0.1820 gram CO₂.

0.2966 gram substance gave 0.1506 gram Ag.

	Theory. C ₉ H ₄ O ₆ Ag ₂ .	Found.
C	25.48 per cent.	24.69 per cent.
H	0.94 „	1.27 „
Ag	50.94 „	50.78 „

This acid is therefore bibasic, and is probably identical with hydrastic acid, C₉H₆O₆, obtained by Freund and Lachmann (*Ber.*, **22**, 2325), which melts at 175°; as, however, no further description of the properties either of the acid itself or of its salts has as yet been published, it is impossible to speak with certainty of the identity of the two acids.

The presence of hydrastic acid among the products of the oxidation of berberine is readily understood, as this substance would result from the action of oxidising agents on *ω*-amidoethylpiperonylcarboxylic anhydride or one of its derivatives, thus:—



The first mother liquors from this acid were evaporated, and the syrupy residue heated in a large test-tube at $180-190^{\circ}$ for one hour. During this operation water vapour escaped, and a small quantity of a sublimate, consisting of fine, colourless needles, formed in the cooler portions of the tube. The residue was powdered and repeatedly extracted with boiling alcohol, the alcoholic solution concentrated and allowed to stand for some hours; and the crystals which separated, collected, washed with alcohol, and repeatedly recrystallised from this solvent. In this way almost colourless needles were obtained which melted at 167° , and showed all the properties of hemipinic anhydride. It was dissolved in a little boiling alcoholic potash, and the solution diluted with water, and boiled for half an hour. The product was evaporated to a small bulk, acidified with hydrochloric acid, repeatedly extracted with ether, the ethereal solution evaporated, and the residue recrystallised from water. The crystals obtained melted at $178-180^{\circ}$, and showed all the properties of hemipinic acid.

Berberine Hydrogen Sulphite, $C_{20}H_{17}NO_4 \cdot H_2SO_3$.

In oxidising berberine with potassium permanganate, a small amount of the alkaloid always escapes the action of the oxidising agent, and this, during the subsequent treatment with sulphurous acid, is converted into berberine hydrogen sulphite. This very insoluble substance is obtained in small quantity during the purification of anhydroberberilic acid (p. 1014) as a light yellow precipitate; and for a long time its constitution was a matter of doubt, as it seemed very improbable that a sulphite of berberine could be so sparingly soluble in water. It was purified by recrystallisation from very large quantities of water, dried at 100° , and analysed with the following results:—

I. 0.1734 gram substance gave 0.0749 gram H_2O and 0.3629 gram CO_2 .

0.2319 gram substance gave 7 c.c. nitrogen; $t = 19^{\circ}$; bar. = 748 mm.

1.4174 gram substance, boiled with dilute nitric acid until the evolution of nitrous fumes had ceased, largely diluted with water, and precipitated with barium chloride, gave 0.7750 gram $BaSO_4$.

II. 0.1188 gram substance gave 0.0504 gram H_2O and 0.2510 gram CO_2 .

	Theory. $C_{20}H_{17}NO_4 \cdot H_2SO_3$.	Found.	
		I.	II.
C	57.55 per cent.	57.08	57.62 per cent.
H	4.55 „	4.80	4.71 „
N	3.36 „	3.48	— „
SO ₄	23.02 „	22.71	— „

This salt is remarkably stable, and crystallises from dilute solutions of potassium carbonate unchanged. It dissolves readily in dilute nitric acid, and on cooling berberine nitrate crystallises out.

0.1712 gram substance gave 0.0740 gram H₂O and 0.3799 gram CO₂.

	Theory. $C_{20}H_{17}NO_4 \cdot HNO_3$.	Found.
C	60.30 per cent.	60.40 per cent.
H	4.52 „	4.80 „

Berberine hydrogen sulphite dissolves readily in dilute hydrochloric acid, and on the addition of platinum chloride a yellow precipitate of berberine platinumchloride is thrown down.

This was collected, washed with water, dried at 100°, and analysed with the following result:—

0.2284 gram substance gave 0.0718 gram H₂O and 0.3708 gram CO₂.

0.3739 gram substance gave 0.0670 gram Pt.

	Theory. $(C_{20}H_{17}NO_4)_2 \cdot H_2PtCl_6$.	Found.
C	44.47 per cent.	44.22 per cent.
H	3.33 „	3.49 „
Pt	18.02 „	17.96 „

As soon as the composition of this substance had been determined in this way, confirmatory experiments were made, with the object of preparing this salt directly from berberine; and it was found that when a solution of berberine hydrochloride is mixed with a solution of sodium hydrogen sulphite containing an excess of sulphurous acid, a precipitate is produced which has properties exactly similar to those of the salt described above. It was not thought necessary to analyse it.

Examination of the Mother Liquors of Berberilic Acid and of Berberal.

Using the methods of separation described in the preceding sections, the actual weight of crystalline substances obtained by oxidising 1 kilo. of berberine hydrochloride is only about 350—400

grams; at least half the product remains in the alcoholic mother liquors of berberilic acid and in the acetic acid mother liquors of berberal (pp. 1041, 1063, and Trans., 1889, pp. 78 and 81).

These, on evaporation, deposit thick, almost black, tarry masses, from which only small quantities of crystalline substances could be obtained by treatment with solvents. As, however, it seemed probable that very interesting compounds might be contained in these tars, the investigation of which might throw additional light on the question of the constitution of berberine, a large number of experiments were instituted with the object of decomposing these tars and thus obtaining crystalline decomposition products, the study of which would reveal the nature of the compounds actually contained in the tars. After numerous failures, the following method gave unexpectedly good results:—

The *mother liquors* of *berberilic acid* were first experimented with. These were gently heated in a dish on a water-bath until free from alcohol, and the black residue boiled briskly in a large, enamelled pan with a considerable quantity of 8–10 per cent. sulphuric acid; the whole being well stirred during the operation. After boiling for two hours, the greater portion had dissolved, forming an orange-coloured solution; this was allowed to cool, decanted from the undissolved tar, and the latter again boiled with fresh dilute sulphuric acid, the operation being continued until only a small quantity of a pitch-like substance remained, which was not further acted on by the sulphuric acid.

The resulting liquors were treated by one of the two following methods:—

Method I.—The liquors were extracted 20 times with ether; the resulting, almost colourless, flocculent ethereal solution, on standing in a cold place, deposited a quantity of crystals. These were collected, washed with ether, and recrystallised twice from water, and in this way beautiful, lustrous plates were obtained, which, after drying at 100°, gave the following numbers on analysis:—

0.1510 gram substance gave 0.0638 gram H_2O and 0.3175 gram CO_2 .

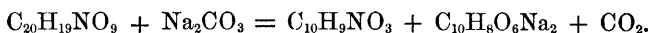
0.2010 gram substance gave 6.5 c.c. nitrogen; $t = 21^\circ$; bar. = 740 mm.

	Theory. $C_{20}H_{19}NO_9$.	Found.
C	57.55 per cent.	57.34 per cent.
H	4.55 „	4.69 „
N	3.35 „	3.47 „

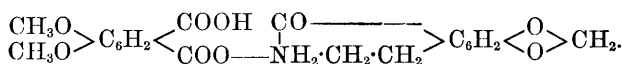
This substance melts at 180° , and is identical with the compound $C_{20}H_{19}NO_9$, described in Part I of this research (p. 84); it is

isomeric with berberilic acid, from which it differs in the following point:—The substance dissolves readily in hot dilute sodium carbonate solution, and, on standing, lustrous crystals of the substance $C_{10}H_9NO_3$ (p. 1013) separate, and the alkaline liquors, on examination, are found to contain hemipinic acid, which can be isolated as its calcium salt in the usual way (p. 1095). A quantitative determination of the relative amounts of these decomposition products formed gave the following results:—

1·18 grams of substance yielded 0·49 gram of the anhydride $C_{10}H_9NO_3$ and 0·66 gram of calcium hemipinate. The compound $C_{20}H_{19}NO_9$ is therefore decomposed according to the equation



according to which 1·18 grams should have yielded 0·54 gram of the substance $C_{10}H_9NO_3$ and 0·74 gram of calcium hemipinate. The substance is therefore the hydrogen hemipinic salt of $C_{10}H_9NO_3$, and has the following constitution:—



Berberilic acid, with which this substance is isomeric, has the following somewhat similar constitution:—



The ethereal mother liquors from this substance, on evaporation, deposited considerable quantities of a yellow, crystalline mass, which, on examination, was found to be almost pure hemipinic acid. It was purified by means of the calcium salt, recrystallised twice from water, and the beautifully colourless, lustrous prisms thus obtained were analysed with the following results:—

0·1258 gram substance gave 0·0528 gram H_2O and 0·2446 gram CO_2 .

	Theory. $C_{10}H_{10}O_6$.	Found.
C	53·09 per cent.	53·02 per cent.
H	4·42 „	4·66 „
O	42·48 „	42·32 „

0·5610 gram substance, dried at 100° , lost 0·0792 gram.

$C_{10}H_{10}O_6 + 2H_2O$ contains 13·74 per cent. of water of crystallisation.

Found..... 14·11 „ „ „ „

The sulphuric acid mother liquors, from which the substance, $C_{20}H_{19}NO_9$ and hemipinic acid had been separated by extraction with

ether, were mixed with just sufficient baryta-water to remove the sulphuric acid, filtered, and the yellow filtrate evaporated to a small bulk. The solution, on standing, deposited crystals, which were found to consist of a mixture of the substances $C_{10}H_{11}NO_4$ (p. 1055) and $C_{10}H_9NO_3$ (p. 1013), and in this way considerable quantities of these substances were prepared for use in subsequent work.

From these experiments, it appears that the tarry substances contained in the alcoholic mother liquors of berberilic acid still contain large quantities of this acid, which is hindered from crystallising by the presence of a small quantity of a black, tarry decomposition product.

Method II.—The acid liquors were evaporated to the crystallising point, without extracting with ether, and set aside to crystallise. After standing for seven days, the almost colourless, crystalline cake which had formed at the bottom of the dish was separated from the mother liquor, washed with a little water, and drained on a porous plate. The liquors were then carefully evaporated, allowed again to crystallise, the operation being continued as long as crystals separated. The various crops of crystals were mixed, boiled with sufficient water to completely dissolve them, the solution filtered, allowed to stand for two days, the crystals which separated collected, and recrystallised twice from water. In this way, magnificent, pale-yellow, lustrous crystals were obtained which on analysis gave the following numbers :—

- I. 0.1308 gram substance gave 0.0608 gram H_2O and 0.2746 gram CO_2 .
0.1910 gram substance gave 7.3 c.c. nitrogen ; $t = 15^\circ$; bar. = 750 mm.
- II. 0.1450 gram substance gave 0.0648 gram H_2O and 0.3096 gram H_2O and 0.3096 gram CO_2 .
0.2310 gram substance gave 9.6 c.c. nitrogen ; $t = 12^\circ$; bar. = 740 mm.
- III. 0.1512 gram substance gave 0.0765 gram H_2O and 0.3201 gram CO_2 .
0.2526 gram substance gave 10.0 c.c. nitrogen ; $t = 20^\circ$; bar. = 742 mm.
- IV. 0.1518 gram substance gave 0.0680 gram H_2O and 0.3250 gram CO_2 .
0.1338 gram substance gave 5.1 c.c. nitrogen ; $t = 18^\circ$; bar. = 750 mm.

	Theory.		Found.			
	$C_{30}H_{30}N_2O_{13}$.	$C_{30}H_{28}N_2O_{12}$.	I.	II.	III.	IV.
C	57·51 p. c.	59·21 p. c.	57·19	58·22	57·74	58·38 p. c.
H	4·79 „	4·57 „	5·17	4·96	5·62	4·97 „
N	4·47 „	4·57 „	4·40	4·80	4·40	4·32 „

Each of these analyses was made with a different preparation.

The formula $C_{30}H_{30}N_2O_{13}$ represents the *hemipinate* of the substance $C_{10}H_9NO_3$, crystallising with one molecule of water = $(C_{10}H_9NO_3)_2C_{10}H_{10}O_6 + H_2O$; the formula $C_{30}H_{28}N_2O_{12}$ represents the anhydrous salt; it is probable that the former is the correct formula. This beautiful substance melts at about 187—189° if very quickly heated, but if slowly heated it melts at about 177° with decomposition. It is sparingly soluble in alcohol, benzene, and cold water, moderately in hot water, readily soluble in acetic acid.

The pure substance dissolves readily in hot dilute sodium carbonate solution, and on cooling, beautiful plates of the substance $C_{10}H_9NO_3$ separate out, whilst the alkaline solution contains hemipinic acid. When heated at 180—200° for a short time, decomposition sets in, a quantity of water vapour is given off, and the residue dissolved in a little boiling acetic acid deposits, on cooling, crystals of hemipinic anhydride (m. p. 167°). The substance $C_{10}H_9NO_3$ may be obtained from the mother liquors of these crystals by evaporation and recrystallising the residue from water.

The aqueous mother liquors from these yellow crystals contain considerable quantities of a second substance, which is much more readily soluble and crystallises with difficulty. The concentrated liquors on long standing deposit feathery crystals, which are difficult to obtain quite pure, owing to the fact that when recrystallised from water, they are decomposed to some extent with formation of the yellow crystals described above. A very carefully recrystallised sample of this substance gave the following results on analysis:—

0·1602 gram substance gave 0·0772 gram H_2O and 0·2964 gram CO_2 .

0·2902 gram substance gave 10·7 c.c. nitrogen; $t = 20^\circ$; bar. = 745 mm.

0·2930 gram substance, dissolved in water, acidified with hydrochloric acid, and precipitated with barium chloride, gave 0·0881 gram $BaSO_4$.

	Theory. $C_{30}H_{34}O_{14}N_2(SO_4) =$ $C_{10}H_{10}O_6(C_{10}H_{11}NO_4)_2, H_2SO_4.$	Found.
C	48·52 per cent.	50·45 per cent.
H	4·59 ,,	5·35 ,,
N	3·77 ,,	4·10 ,,
SO ₄	12·94 ,,	12·35 ,,

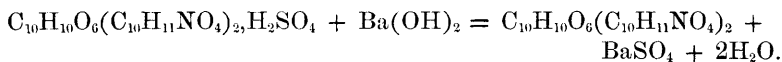
This substance is a mixed sulphate and hemipinate of the base $C_{10}H_{11}NO_4$. It crystallises from water, in which it is readily soluble, in colourless feathery leaflets, which melt at about 190° with decomposition. The constitution of this salt is readily shown from the following experiment:—

A quantity of the substance was dissolved in warm water, just sufficient barium hydrate solution added to remove all the sulphuric acid, the product filtered, and the clear filtrate evaporated to a small bulk on a water-bath. After standing for two days, peculiar, pale-yellow, nodular crystals had formed; these were collected, washed with water, dried at 100° , and analysed with the following result:—

- I. 0·1501 gram substance gave 0·0719 gram H_2O and 0·3053 gram CO_2 .
 0·2722 gram substance gave 9·5 c.c. nitrogen; $t = 12^\circ$; bar. = 755 mm.
 II. 0·2680 gram substance gave 9·9 c.c. nitrogen; $t = 14^\circ$; bar. = 758 mm.

	Theory. $C_{30}H_{33}N_2O_{14} =$ $C_{10}H_{10}O_6(C_{10}H_{11}NO_4)_2.$	Found.	
		I.	II.
C	55·90 per cent.	55·47	— per cent.
H	4·97 ,,	5·32	— ,,
N	4·35 ,,	4·07	4·33 ,,

The formation of this salt from the double salt just described is represented thus—



The di-hemipinate of the base $C_{10}H_{11}NO_4$ is readily soluble in hot and moderately in cold water; it crystallises after long standing in nodular masses somewhat resembling the hydrogen hemipinate of the same base (p. 1061). It melts at about 175° with decomposition; it is moderately soluble in hot alcohol, very readily in acetic acid, and almost insoluble in benzene. The strong solution in water, acidified with hydrochloric acid and mixed with platinum

chloride, gives a precipitate of the platinochloride of $C_{10}H_{11}NO_4$, and on extracting the solution with ether, and evaporating the ethereal extract, a residue of hemipinic acid is obtained.

Either of the above methods may be employed for preparing considerable quantities of the substance $C_{10}H_9NO_3$ from the tarry mother liquors of berberilic acid, and both give good results, but, as a rule, method I was adopted in dealing with large quantities of these mother liquors.

Examination of the Mother Liquors of Berberal.

Before experimenting with these mother liquors, the greater bulk of the water and acetic acid was distilled off; the black, tarry residue, which obviously still contained considerable quantities of berberal, was then treated with various solvents with the view of isolating this substance, but without success. The whole of the tar was then boiled with large quantities of 20 per cent. sulphuric acid for some hours, filtered from any undissolved matter, and the reddish-brown solution allowed to stand. In the course of a few days a large quantity of bright-reddish needles had separated, these were collected, washed with water, and recrystallised from very dilute sulphuric acid; a large quantity of bright-yellow needles were obtained which were identified as sulphate of berberine.

The platinochloride prepared from this salt gave on analysis the following numbers :—

0.3271 gram substance gave 0.0587 gram platinum.

	Theory. ($C_{20}H_{17}NO_4$) ₂ .H ₂ PtCl ₄ .	Found.
Pt.	18.02 per cent.	17.94 per cent.

In one case, in which 1 kilo. of berberine hydrochloride had been oxidised, in the usual way, nearly 100 grams of unchanged berberine sulphate was recovered from the mother liquors of berberal by the above method.

The mother liquors from which the berberine sulphate had crystallised were concentrated, and extracted 20 times with ether; the solution on evaporation deposited a quantity of almost colourless crystals, which could not be obtained pure, but which appeared for the most part to consist of the pseudopianic salt of the substance $C_{10}H_9NO_3$ (m. p. 149°, see p. 1080). The whole quantity was dissolved in boiling sodium carbonate solution; this solution, on cooling, deposited colourless crystals of the anhydride $C_{10}H_9NO_3$, and the

alkaline solution contained a considerable quantity of pseudopianic acid.

The sulphuric acid liquors which had been extracted with ether still contain a large amount of the substance $C_{10}H_9NO_3$, which may be extracted by precipitating the sulphuric acid with baryta-water and evaporating the solution. The product thus obtained is, however, very crude and difficult to purify.

These experiments seem to prove that the mother liquors of berberal and of berberilic acid do not contain any other products than those already described in this paper.

Examination of the Aqueous Mother Liquors from the Oxidation of Berberine (p. 1013).

These aqueous mother liquors, from which the bulk of the neutral organic substances had been extracted by ether, deposited, on evaporation, a quantity of a solid residue, which on examination was found to contain large quantities of organic matter.

As it was important to determine the nature of these organic substances, some qualitative experiments were first instituted. To a portion of the solution, phosphomolybdic acid was added, the precipitate which formed collected, washed, treated with alkalis, and the white, crystalline mass which separated recrystallised from water. In this way colourless plates were obtained, which after recrystallisation from water melted at $181-182^\circ$, and consisted of the anhydride $C_{10}H_9NO_3$ (p. 1013).

A second portion of the solution was acidified, extracted several times with ether, the ethereal solution evaporated, the residue neutralised, boiled with calcium chloride, and the precipitate which formed dissolved in a little hot dilute hydrochloric acid. After standing for some time, an acid separated which showed all the properties of hemipinic acid, but which seemed to be mixed with small quantities of another acid. In order to determine approximately the amount of hemipinic and other acids present in the solution, the liquors from 1 kilo. of berberine hydrochloride were neutralised, mixed with a large quantity of a saturated solution of calcium chloride, and heated to boiling for half an hour. The precipitate which formed was collected on cloth bags, well washed with hot water, and extracted with hot dilute hydrochloric acid, until no more organic matter passed into solution. The acid solution was filtered from the mass of calcium sulphate which is necessarily always present, evaporated to the crystallising point, and the dark-brown crystalline crust which separated on cooling dissolved in dilute sodium

carbonate solution and boiled with freshly ignited animal charcoal for one hour. The pale-yellow filtrate was neutralised with hydrochloric acid, boiled with calcium chloride, the calcium salt which separated decomposed with hydrochloric acid, and the acid thus obtained recrystallised from water. The white, crystalline powder which was deposited from the hot solution was dried at 100°, and analysed with the following result:—

- I. 0.1450 gram substance gave 0.0552 gram H₂O and 0.2808 gram CO₂.
 II. 0.1550 gram substance gave 0.0550 gram H₂O and 0.3016 gram CO₂.
 III. 0.1562 gram substance gave 0.0573 gram H₂O and 0.3016 gram CO₂.

	Theory. C ₁₀ H ₁₀ O ₆ .	Theory. C ₉ H ₈ O ₆ .	Found.		
			I.	II.	III.
C....	53.10 p. c.	51.43 p. c.	52.81	53.06	52.66 p. c.
H...	4.42 "	2.86 "	4.22	3.94	4.07 "
O....	42.48 "	45.71 "	42.97	43.00	43.27 "

These analyses were made with different preparations.

This substance melts at 165—168° with decomposition and evolution of gas. It shows all the properties of hemipinic acid, and undoubtedly consists for the most part of this substance contaminated with a second acid (hydrastic acid?) which contains much less hydrogen.

In order to prove the presence of hemipinic acid, about 2 grams of the substance was heated at 200° for one hour, and the residue recrystallised twice from glacial acetic acid. The beautiful, colourless needles thus obtained melted at 167°, and showed all the properties of hemipinic anhydride.

Analysis:—

0.1552 gram substance gave 0.0554 gram H₂O and 0.3272 gram CO₂.

	Theory.		
	$\begin{array}{c} \text{CH}_3\text{O} \\ \text{CH}_3\text{O} \end{array} > \text{C}_6\text{H}_2 < \begin{array}{c} \text{CO} \\ \text{CO} \end{array} > \text{O}.$		Found.
C	57.69	per cent.	57.49 per cent.
H	3.84	„	3.96 „
O	38.46	„	38.55 „