XXXIII.—*Strychnine, Berberine, and Allied Alkaloids*

By WILLIAM HENRY PERKIN, jun., and ROBERT ROBINSON.

I.—*Strychnine and Brucine.*

SEVERAL years ago (Trans., 1889, **55**, 63; 1890, **57**, 992) one of us carried out a systematic study of the alkaloid berberine, and succeeded in obtaining a series of degradation products, the investigation of which made it possible to suggest a constitutional formula for berberine, and this formula, except for slight modifications in minor details, is still accepted as correct. The intention at that time was to use the experience obtained in order to attack the problem of the constitutions of several other alkaloids, and afterwards to attempt their synthesis, and a series of experiments on cryptopine* (Proc., 1891, **7**, 166) and on other opium alkaloids were commenced.

Owing, however, to the necessity for completing other investigations, these researches had, for the time, to be reluctantly put aside.

In recent years the difficult problem of the constitution of brazilin and hæmatoxylin made it imperative that we should very carefully study the constitution and nature of the groupings contained in natural products generally, and particularly in the alkaloids, and, in reviewing the work which had been published on strychnine, brucine, berberine, corydaline, and allied alkaloids, we were led to certain conclusions as to their constitutions which we think may be worth recording, and the validity of which we propose to test by experiment. Although the alkaloids, strychnine and brucine, have been the subject of detailed investigations, especially at the hands of Tafel and Leuchs, very few deductions have been made as to their constitutions. It is well known that strychnine, $C_{21}H_{22}O_2N_2$, while containing two atoms of nitrogen, is only a mon-acid base, yielding salts, such as the hydrochloride, $C_{21}H_{22}O_2N_2 \cdot HCl + 1\frac{1}{2}H_2O$, with only one equivalent of the acid. It is also known that the alkaloid is a tertiary base, and that it does not contain methoxy-groups. When strychnine is treated with alkalis (Loebisch and Schoop, *Monatsh.*, 1886, **7**, 75; Tafel, *Annalen*, 1891, **264**, 49), it suffers hydrolysis with the addition of a molecule of water and formation of strychnic acid (and isostrychnic acid, p. 317):

Strychnic acid is an imino-carboxylic acid, and at the same time

* Owing to the generosity of Messrs. T. and H. Smith, of Edinburgh, who have supplied me with considerable quantities of this very rare alkaloid, this investigation is being continued.—W.H.P., jun.

a tertiary base, since it yields metallic salts and, when treated with methyl iodide, is converted into methylstrychnic acid methiodide, $C_{20}H_{22}ON(MeI)(\cdot NMe) \cdot CO_2H$ (Tafel, *Annalen*, 1891, **264**, 59), and the presence of the imino-group is further demonstrated by the formation of a nitrosamine, $C_{20}H_{22}ON(\cdot N \cdot NO) \cdot CO_2H$, when the acid is treated with nitrous acid. These results, together with the fact that strychnic acid is readily converted into strychnine by heat, led Tafel to suggest that the relationship of strychnine to strychnic acid is probably that represented by the scheme:

and is similar to that existing between ψ -isatin and isatinic acid:

It can scarcely be doubted that this representation is correct, and the non-basic properties of the grouping $\cdot CO \cdot N \cdot$ affords an explanation of the fact that strychnine, although it contains two nitrogen atoms, is only capable of combining with one equivalent of an acid. Further confirmation of the presence of the grouping $\cdot CO \cdot N \cdot$ in strychnine is obtained from the study of the products which are formed when the alkaloid is treated with various reducing agents. When strychnine is reduced with phosphorus and hydriodic acid, it is converted into a substance, $C_{21}H_{26}ON_2$, called desoxystrychnine (Tafel, *Annalen*, 1892, **268**, 245), and this substance, the importance of which is emphasised in the following pages, evidently has the formula (A):

since, like strychnine itself, it is a mon-acid base, which, on hydrolysis, yields desoxystrychnic acid (B).

This imino-acid has properties very similar to those of strychnic acid, and its whole behaviour indicates that the characteristic groups $N \cdot$ and $\cdot CO \cdot N \cdot$ of strychnine have undergone no change during the reduction to desoxystrychnine. When desoxystrychnine is treated with sodium and alcohol, it yields strychnoline (I), the $\cdot CO \cdot N \cdot$ group becoming $\cdot CH_2 \cdot N \cdot$, but electrolytic reduction proceeds further and causes the addition of another two atoms of hydrogen, and dihydrostrychnoline (II) results (Tafel, *Annalen*, 1898, **301**, 324 and 326):

Lastly, when strychnine itself is reduced electrolytically, it yields

tetrahydrostrychnine (III), the group $\cdot\text{CO}\cdot\text{N}\cdot$ being reduced to $\text{CH}_2(\text{OH})\text{NH}\cdot$, and this readily loses water with formation of strychnidine (IV) (Tafel, *Annalen*, 1898, **301**, 303):

One of the most characteristic properties of strychnine is the ease with which it is nitrated, since warming with very dilute nitric acid (5 per cent.) converts it into dinitrostrychnine hydrate, $\text{C}_{21}\text{H}_{22}\text{O}_3\text{N}_2(\text{NO}_2)_2\cdot\text{H}_2\text{O}$ (Tafel, *Annalen*, 1898, **301**, 299).

This behaviour, and also the fact that strychnine is very readily sulphonated (Leuchs and Schneider, *Ber.*, 1909, **42**, 2681), may be taken as proof of the presence of at least one benzene ring, and it will be shown later that all the evidence points to there being only one such ring in the molecule. There can, furthermore, be little doubt that this benzene ring forms part of a quinoline nucleus, and, although no known quinoline derivative has so far been obtained from strychnine, there is ample indirect evidence of the presence of such a nucleus.

Tafel (*Annalen*, 1898, **301**, 336) investigated the action first of dilute and then of strong nitric acid on strychnine, and showed that, under the conditions he employed, the alkaloid is nitrated and suffers degradation with the formation of dinitrostrychol-carboxylic acid, $(\text{NO}_2)_2\text{C}_9\text{H}_2\text{N}(\text{OH})_2\cdot\text{CO}_2\text{H}$, and this important acid, when heated at 200° , loses carbon dioxide, with the formation of dinitrostrychol, $(\text{NO}_2)_2\text{C}_9\text{H}_3\text{N}(\text{OH})_2$. There can be little doubt, as, indeed, Tafel has suggested, that this latter substance is a dinitro dihydroxyquinoline, and we are at present engaged in its investigation, not only with the object of proving this point, but also, at the same time, of determining the relative positions of the substituent groups in the quinoline nucleus. Still more conclusive evidence of the presence of the quinoline nucleus in strychnine has been obtained in the following way. Strychnine combines with methyl iodide to yield strychnine methiodide, $\text{C}_{21}\text{H}_{22}\text{O}_2\text{N}_2\cdot\text{MeI}$, and this, on treatment with silver hydroxide, or barium hydroxide, yields methylstrychnine, and, since this substance shows all the properties of a betaine, there can be little doubt that its formation is to be represented by the scheme:

Methylstrychnine has all the properties of a secondary base; it
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yields, for example, a nitrosamine, and reacts with methyl iodide to form dimethylstrychnine:

Tafel (*Annalen*, 1891, **264**, 43) has already pointed out how remarkably the properties of dimethylstrychnine resemble those of *N*-methyltetrahydroquinoline:

and dimethylaniline. Like these substances, dimethylstrychnine yields a green nitroso-derivative, and condenses with benzaldehyde in the presence of zinc chloride with the formation of the leuco-base of a green colouring matter, which closely resembles malachite-green and the green colouring matter obtained from *N*-tetrahydroquinoline under the same conditions; furthermore, it combines with diazobenzenesulphonic acid to yield a yellow azo-dye. Because of this behaviour, Tafel draws the conclusion, not only that strychnine contains a quinoline nucleus, but also that the :NMe group in dimethylstrychnine and the :NH group in methylstrychnine, and therefore the :N·CO· group in strychnine, is combined by one linking direct to the benzene ring, and that strychnine must therefore contain the grouping:

The consideration of the properties of strychnidine leads to exactly the same conclusions. This substance is produced, as explained on p. 307, by the reduction of the CO· group in strychnine to ·CH₂:

and this process converts a substance with the properties of acetanilide into one which again exhibits exactly the behaviour of dimethylaniline or *N*-methyltetrahydroquinoline towards reagents.

The most valuable evidence as to the internal structure of the other portion of the strychnine molecule is obtained from the consideration of the properties of an important monobasic acid, C₁₅H₁₇O₂N₂·CO₂H, which is produced when strychnine is oxidised by chromic acid (Hanssen, *Ber.*, 1884, **17**, 2849; 1885, **18**, 777 and 1917; 1887, **20**, 451). This acid is also obtained under the same conditions from brucine, an alkaloid which contains two

methoxy-groups and has properties so exactly similar to those of strychnine that there can be no doubt that it is dimethoxy-strychnine. Since the two methoxy-groups disappear during the formation of the acid $C_{15}H_{17}O_2N_2 \cdot CO_2H$ from brucine, it follows that the benzene ring of the quinoline nucleus in the two alkaloids, brucine and strychnine, is broken down during the formation of this acid, evidently in the following manner :

Now the acid $C_{15}H_{17}O_2N_2 \cdot CO_2H$ is a derivative of carbazole, because it yields this substance on distillation with zinc dust, and we therefore arrive at the conclusion that the molecule of strychnine must contain the two residues :

It has already been shown that the quinoline nucleus contains a benzene ring, and therefore, in order to account for the large number of hydrogen atoms in the strychnine molecule, it is necessary, as it appears to us, to conclude that not only the pyridine ring of the quinoline nucleus, but also the carbazole section of the molecule must be almost completely reduced. Adopting a line of argument which we have employed on previous occasions (Trans., 1890, **57**, 1004; 1902, **81**, 238; 1908, **93**, 491), we find that these facts afford a basis on which it is possible to build up constitutional formulæ for strychnine and its derivatives which, we are convinced, must at least be very near the truth.

The two residues just figured contain C_{22} , and as the formula of strychnine is $C_{21}H_{22}O_2N_2$, it follows that these two residues must be fused together in such a way that one carbon atom at least is common to both. It is clear that the basic nature of strychnine is not due to the nitrogen atom of the tetrahydroquinoline nucleus, because of its union with the CO group; it must therefore be due to the nitrogen atom of the carbazole residue. If we now attempt to construct a formula for strychnine on the assumption that the two residues are united in such a way that one carbon atom is common to both, we have to remember that strychnine is a tertiary base, and the nitrogen of the reduced carbazole residue must therefore be rendered tertiary by union with a carbon atom of the quinoline nucleus, whilst the CO group unites with the carbazole

nucleus. This would lead to formulæ which clearly cannot represent the skeleton of strychnine.

It seems to us that the only possible alternative is to assume that, in the fusion of the two nuclei, two carbon atoms become common to both,* and that the skeleton, which now contains C_{20} , is completed by the introduction of an additional carbon atom between the CO group and the basic nitrogen atom,† yielding, in the first place:

Further fusion may now take place in two ways, and two only, and leads us to the following alternative expressions for the skeleton of strychnine:

(I.)

(II.)

* If the two nuclei are fused together in such a way that three carbon atoms are common to both, then two additional carbon atoms must be introduced, and we obtain expressions such as the following for the skeleton of strychnine:

In such cases the carboxylic group in strychnic acid methiodide would be so far removed from the iodine atom that the formation of a betaine would appear to be out of the question (p. 307).

† For, if not, then the only other possible way of uniting the $N·CO·$ group with the rest of the molecule, in order to make the basic nitrogen atom tertiary, is the construction of a four-carbon ring, which is highly improbable.

Formula I contains a seven-membered ring, and it is very unlikely that such a ring would be readily produced by the elimination of water from strychnic acid; on the other hand, such elimination leading to the formation of a six-membered ring is quite usual, and for this and other reasons we prefer formula II. If this formula be accepted as the skeleton of strychnine, there can be little doubt that desoxystrychnine, $C_{21}H_{26}ON_2$, the product of the reduction of strychnine with phosphorus and hydriodic acid (p. 306), must be written:

and this formula is in complete agreement with the properties of this substance. It exhibits desoxystrychnine as a derivative of tetrahydroquinoline, accounts for its conversion into desoxystrychnic acid, and for the behaviour of this acid, as well as of desoxystrychnine itself, towards methyl iodide, nitrous acid, etc.

Similarly, the highest product of the hydrogenation of strychnine, namely, dihydrostrychnoline, $C_{21}H_{28}N_2$ (p. 306), will be represented by the formula:

and the fact that further hydrogenation, without reduction of the benzene ring, is impossible is well indicated by this structure.

On the basis of skeleton formula II, it is possible not only to explain the recent important results of Leuchs (*Ber.*, 1908, **41**, 1711), Leuchs and Schneider (*ibid.*, 4393; 1909, **42**, 2494), and Leuchs and Weber (*Ber.*, 1909, **42**, 3703), but also to deduce a constitutional formula for strychnine which cannot be very far from the truth.

Leuchs and his collaborators find that strychnine, on oxidation in acetone solution with permanganate, is converted into a keto-dibasic acid, strychninonic acid, which has the composition,

On reduction with sodium amalgam, this acid yields the corresponding secondary alcohol dibasic acid, strychninolic acid, $\text{N:C}_{17}\text{H}_{18}(\text{:N}\cdot\text{CO})(\text{CH}\cdot\text{OH})(\text{CO}_2\text{H})_2$, and this substance, on treatment with dilute potassium hydroxide, is decomposed, yielding glycollic acid and strychninolone, $\text{C}_{19}\text{H}_{18}\text{O}_3\text{N}_2$, a substance which possesses neither acid nor basic properties. An exactly similar series of products was also obtained from brucine under the same conditions.

There can be no doubt that the formulæ for strychninonic and strychninolic acids suggested by Leuchs, which represent these acids as containing a tertiary nitrogen atom, are correct, and the absence of basic properties is amply explained by the presence of the two carboxyl groups. When strychninolic acid loses glycollic acid under the influence of alkali, the substance produced, strychninolone, is devoid of both acid and basic properties, and it is therefore obvious that, during its formation, mutual neutralisation has taken place between the two carboxyl groups and basic nitrogen atoms. Since two such atoms are required for this process, it follows that the section $\text{:N}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{N}'$ of the original strychnine skeleton must have lost the grouping $\cdot\text{CO}\cdot\text{CH}_2\cdot$, and this is therefore the source of the glycollic acid:

The cause of the non-basic nature of one of the nitrogen atoms in strychnine is thus removed, and the two :NH groups are now both basic and free to combine with two carboxyl groups to yield a neutral substance, such as strychninolone.

The problem which still remains is to discover the process by which the structure:

can be broken up in order to supply two carboxyl groups in such positions that they can combine with the two :NH groups to yield two neutral $\text{:N}\cdot\text{CO}\cdot$ groupings. The following appear to be the only two ways in which this can be satisfactorily accomplished:

If now the hydrogen atoms and the carboxyl and other groups in strychninonic acid, $N:C_{17}H_{18}(:N\cdot CO)(CO)(CO_2H)_2$, are filled into the first formula of scheme I, it will be found that the complete expression must contain one double linking, whereas, if the same process is carried out in the case of scheme II, two double linkings will be found to be necessary. This difference is due to the fact that, in developing scheme I from the skeleton formula of strychnine, one closed ring suffers fission, whereas in the case of scheme II two closed rings suffer disruption.

If we consider, in the first place, the development of a formula for strychninonic acid on the basis of the first skeleton formula of scheme II, we arrive at expressions of the types:

It can be shown in several ways that such formulæ cannot represent strychninonic acid, and the same is true of any other formulæ built up on the basis of the first skeleton formula of scheme II, but only one reason for this need be given here.

Strychninonic acid is obtained from strychnine by a simple permanganate oxidation, and it must therefore be possible to reconstruct the formula of strychnine in a comparatively simple manner from that of strychninonic acid. If we select formula I, and attempt to construct from it a formula for strychnine, we arrive at the expression :

which cannot be correct, because oxidation with permanganate would attack the double linking combined with the benzene ring, and it would therefore be impossible to obtain from this expression the formula for strychninonic acid from which it was derived, and the same line of argument applies equally to all other formulæ derived from the first skeleton formula of scheme II.

Whilst, then, scheme II is out of the question, careful consideration shows that scheme I leads to the following expressions for strychninonic acid and strychnine:

Strychninonic acid. *Strychnine.*

which seem to us to be in every way satisfactory, since they account in a comparatively simple manner for all the known reactions of these substances. From the several possibilities we were led to select the positions assigned to the double linkings in the strychnine formula for various reasons, and of these the following need only be discussed. If the formula assigned to strychninonic acid is correct, the formation of this acid by the oxidation of strychnine clearly points to one of the double linkings occupying the position marked *a*. The position *b* was selected for the second double linking, because this linking must be situated in a stable portion of the molecule, otherwise it would also suffer oxidation under the conditions employed in the preparation of strychninonic acid, and experience of heterocyclic systems has shown that the double linkings in nuclei, such as:

are not readily oxidised. Strychninonic acid is a keto-dibasic acid, and there can be little doubt that the keto-group is produced by the oxidation of a secondary alcohol group; in other words, the molecule of strychnine contains a :CH(OH) group (compare Leuchs, *Ber.*, 1908, **41**, 1711), and the difficult problem remaining to be solved is that of assigning the correct position to this group.

It cannot occupy the position *g*, because this would make strychninonic acid a derivative of benzoylacetic acid, and *f* and *e* seem also to be out of the question, for the reason that hydroxy-groups in these positions would be γ - and δ - to one of the carboxyl groups in strychninonic acid, and this acid does not appear to have any tendency to yield a lactone. So far no definite experimental evidence is available to enable us to select with any certainty either of the remaining positions *d* or *e*, but we have

chosen *c* as the result of a comparison of strychnine with quinine and other natural products in which a similar grouping occurs.

This argument, based on lactone formation, might appear to apply also to a hydroxyl group in the position *c*, but the examination of a model shows that a hydroxyl group in this position is too far removed from the carboxyl group to make lactone formation probable.

The formula which we have suggested for strychninonic acid leads to the following expressions for strychninolic acid and strychninolone:

and these also appear to agree in a satisfactory manner with the properties of these substances so far as they have been investigated. A possible objection to the formula assigned to strychninolone is the stability of this substance towards oxidising agents, which may not be considered compatible with the presence of the $\text{CH}\cdot\text{OH}$ group, but, in our opinion, this argument does not carry much weight.

It has already been pointed out (p. 309) that brucine is dimethoxystrychnine, and the positions of the methoxy-groups in the benzene nucleus seem to be fixed by the observation of Leuchs and Weber (*Ber.*, 1909, **42**, 3709) that brucinolone is readily oxidised by nitric acid, with elimination of the methoxy-groups and formation of a quinone which crystallises in red needles, and yields a quinol on reduction with sulphurous acid. Since an *o*-quinone would hardly be produced under these conditions, it is probable that the substance is a *p*-quinone of the constitution:

and its formation is a strong indication that the methoxy-groups occupy the position assigned to them in the following formula for brucine:

One other very interesting point in connexion with strychnine and brucine which we have already mentioned (p. 305) is the behaviour of these alkaloids on hydrolysis. When strychnine is digested with sodium methoxide or barium hydroxide, it yields strychnic and *isostrychnic* acids:

and these isomeric acids are converted by the action of heat into the isomeric alkaloids, strychnine and *isostrychnine*. Brucine exhibits an exactly similar behaviour. Strychnic and *isostrychnic* acids resemble each other so closely in all their reactions that it might at first sight appear that they were simply stereoisomeric modifications of the same substance. The conversion of these acids into the isomeric strychnines is, however, scarcely in accordance with this view, and it is far more probable that the isomerism is due to a difference in the position of one of the double linkings in the molecule, probably in the sense represented by the formulæ:

If the formulæ suggested for strychnine and brucine be examined with the view of discovering some reason for the extremely poisonous

nature of these alkaloids, it would seem that the only section to which this property can be ascribed is the grouping (C):

containing the two nitrogen atoms. Schotten (*Ber.*, 1888, **21**, 2244) has called attention to the fact that α -ketopiperidine (α -piperidone) (D) has poisonous properties of the same kind as those exhibited by strychnine and brucine, and it is not at all improbable that the introduction of the second nitrogen atom into this molecule may have the effect of much intensifying these poisonous properties.

We are at present engaged in synthesising substances containing the above di-nitrogen group, and propose to have these examined in order to find out whether they have poisonous properties similar to those of strychnine and brucine.

II.—Berberine, Corydaline, and Allied Alkaloids.

The constitution of berberine, $C_{20}H_{17}O_4N$, is generally accepted as being represented by the formula:

and this formula is based on the investigation of the long series of products which result from the degradation of the molecule by oxidation with permanganate (*Trans.*, 1889, **55**, 63; 1890, **57**, 992).

The position of the methylenedioxy-group* is determined by the fact that hydrastic acid (I) and ω -aminoethylpiperonylcarboxylic anhydride (II) are found among the products of this oxidation:

* It is unfortunate that this group should have been wrongly placed in the original papers.—W. H. P., jun.

On the other hand, the fact that hemipinic acid (III) is produced in considerable quantities during the oxidation of berberine does not definitely fix the positions of the methoxy-groups, since the formula for berberine:

would also account for the formation of hemipinic acid on oxidation.

On carefully considering this matter, it appeared to us that the only oxidation product of berberine which is able to afford definite information as to the position of these methoxy-groups is *berberal* (Trans., 1890, 57, 1000 and 1062). This substance, on hydrolysis, yields ψ -opianic acid and ω -aminoethylpiperonylcarboxylic anhydride, and conversely it may be synthesised by simply heating ψ -opianic acid and ω -aminoethylpiperonylcarboxylic anhydride at 180° . When this experiment was described (*loc. cit.*, p. 1079), this important synthesis was assumed to take place according to the equation:

and it was suggested (p. 1002) that the constitution of *berberal* must be represented thus:

The formula for berberine itself, given at the commencement of this section, was largely based on this constitutional formula for *berberal*. ψ -Opianic acid was first obtained as the result of these experiments on the oxidation of berberine, and, as it is difficult to prepare in any quantity by this process, and no other method of preparation has yet been discovered, the mechanism of its condensation with basic substances has not been investigated in detail.

If, however, the formulæ of ψ -opianic acid is compared with that of opianic acid, it will be seen that they are both *o*-aldehydo-

acids, and differ only in the positions of these groups relative to the methoxy-groups:

ψ-Opianic acid.

Opianic acid.

and as this is the only difference in constitution, it may be safely assumed that they will behave in an exactly similar manner when taking part in reactions characteristic of *o*-aldehydo-acids.

Important evidence in support of this view has already been obtained, since it was shown in the earlier papers (*Trans.*, 1890, 57, 1081) that opianic acid condenses with *ω*-aminoethylpiperonyl-carboxylic anhydride to yield a substance:

which has properties exactly similar to those of berberal, and was therefore named *isoberberal*. During recent years opianic acid has been the subject of detailed investigation, and the results which have been obtained necessitate a modification of our views as to the constitution of *isoberberal*, and consequently of berberal and of berberine itself. Liebermann (*Ber.*, 1886, 19, 2284; 1896, 29, 175) has shown that opianic acid reacts with aniline in the cold to yield anilino-opianic acid, and expressed the opinion that, during this process, the opianic acid reacts as a derivative of hydroxyphthalide in accordance with the equation:

and from the study of this and many other similar condensations, it is clear that, in condensations of opianic acid with basic substances, it is always the carbon atom of the aldehyde group which is attached to the nitrogen atom in the final product. There can be little doubt that a similar process takes place when opianic acid reacts with *ω*-aminoethylpiperonylcarboxylic anhydride to yield *isoberberal*, and the constitution of this substance is therefore not that originally assigned to it (p. 319), but must be modified to:

isoBerberal.

Furthermore, since ψ -opianic acid is so exactly similarly constituted to opianic acid, and exhibits in all its reactions so close an analogy with this acid, it cannot be doubted that, when it condenses with basic substances, it also reacts in a similar manner.

It follows, therefore, that in the formation of berberal by the condensation of ψ -opianic acid with ω -aminoethylpiperonylcarboxylic anhydride, the aldehydic carbon atom of the ψ -opianic acid becomes combined with the nitrogen atom, and the constitution of berberal must therefore be represented by the formula:

Berberal.

and not by that originally assigned to it (p. 319).*

This new expression is in complete agreement with the properties of berberal, and its acceptance involves the alteration of the position of the methoxy-groups in the old berberine formula (p. 318), so that the constitution of the alkaloid must now be written (compare p. 319):

Berberine.

* The actual mechanism of the condensation of opianic acid or ψ -opianic acid with basic substances is probably not so simple as that suggested by Liebermann (*loc. cit.*). When the syntheses of berberal and *isoberberal* were described (Trans., 1890, 57, 1080 and 1082), it was proved that in both cases the first step is the formation of the salt of the acid with the base. Thus, for example, ψ -opianic acid combines with ω -aminoethylpiperonylcarboxylic anhydride to form the salt,

which, when heated at 180°, yields berberal. Most probably aldol formation first takes place during this change, followed by rearrangement according to the scheme :

The synthesis of *isoberberal* takes place in an exactly similar manner, and it is very probable that all such condensations between opianic acid or ψ -opianic acid and basic substances proceed on similar lines.

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The formation of berberal by the oxidation of berberine is now easy to understand, and evidently takes place according to the scheme:

The salts of berberine are derived from the hydroxyl formula given above (compare J. Gadamer, *Arch. Pharm.*, 1905, **243**, 31), but there is reason to believe that the alkaloid itself exists in the corresponding aldehyde modification. Gadamer (*Chem. Zeit.*, 1902, **26**, 291) has shown that, when berberine sulphate is treated with barium hydroxide, it yields a brownish-red, strongly alkaline solution, which doubtless contains the hydroxy-modification of berberine. If, however, this solution is mixed with excess of sodium hydroxide, a yellow modification of berberine is obtained, which apparently has the properties of an aldehyde, and Gadamer has named this modification *berberinal*. The constitution of this modification, based on the new formula for berberine which we have proposed, will be the following:

Berberinal.

Berberinal yields an oxime, reacts with magnesium alkyl iodides with formation of homologues of berberine (Freund and Beck, *Ber.*,

1904, **37**, 3336 and 4673), and, when treated with a large excess of alkali, is reduced to dihydroberberine and simultaneously oxidised to hydroxyberberine, the aldehyde grouping being converted into $\cdot\text{CH}_2(\text{OH})$ and $\cdot\text{CO}_2\text{H}$ in the manner characteristic of aromatic aldehydes.

The proposed modification of the positions of the methoxy-groups in the berberine formula receives further confirmation from the consideration that berberine occurs along with hydrastine in *hydrastis canadensis*, and the close relationship between these alkaloids becomes very striking if the new formula for berberinal is placed by the side of that of hydrastine:

Berberinal.

Hydrastine.

These alkaloids are, indeed, so closely related as to suggest that hydrastine is either formed in the plant from berberine, or that they are both derived from some common parent.

THE UNIVERSITY,
MANCHESTER.