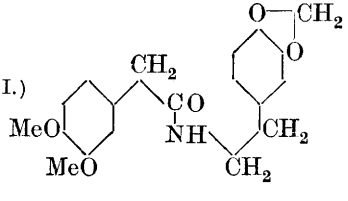
CCXIX.—*ψ-Berberine.*

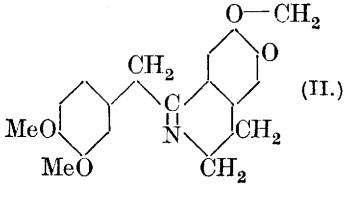
By Robert Downs Haworth, William Henry Perkin, junr., and John Rankin.

During the course of their experiments on the synthesis of tetrahydroberberine, Pictet and Gams (*Ber.*, 1911, **44**, 2480) condensed the chloride of homoveratric acid, $(MeO)_2C_6H_3\cdot CH_2\cdot COCl$, with homopiperonylamine, $CH_2{:}O_2{:}C_6H_3\cdot CH_2\cdot CH_2\cdot NH_2$, and obtained homoveratroyl-homopiperonylamine (I). This substance was converted, by the action of phosphorus pentoxide in boiling xylene, into 1-veratryl-6 : 7-methylenedioxydihydro*iso*quinoline (II) and this base was then reduced by means of tin and hydrochloric acid to veratrylnorhydrohydrastinine (1-veratryl-6 : 7-methylenedioxytetrahydro*iso*quinoline (III).*

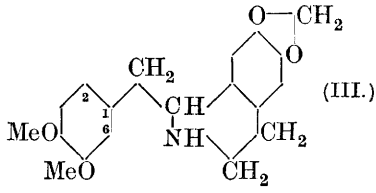
(I.)



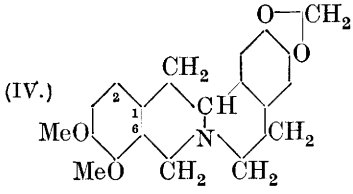
(II.)



* These formulæ have been rearranged so as to bring them into harmony with similar formulæ in the preceding paper on the synthesis of ψ-*epi*berberine.



The final step was to condense the latter substance with methylal in the presence of hydrochloric acid, when a sparingly soluble hydrochloride was obtained which, on decomposition with potassium carbonate, yielded a base (A) melting at 168° and having the formula $C_{20}H_{21}O_4N$. This condensation with methylal might conceivably take place in two directions, since either the hydrogen atom in the position 2 or that in the position 6 in the formula (III) may take part in the change. In other words, there are two possible formulæ for the base (A), namely (IV) or (V).



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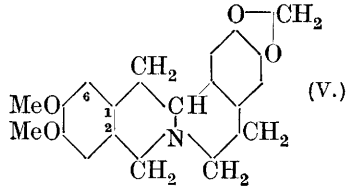


Pictet and Gams claim that the base (A) which they obtained as the result of this ring formation is tetrahydroberberine (IV), but, at the same time, they express surprise that this substance should have been formed and state that their expectation was that the condensation product would prove to be tetrahydro*iso*berberine (V). So far as we are aware, no other case is known of a condensation of this kind taking place in the direction claimed by Pictet and Gams, and the abnormality of the process has been commented on by Jones and Robinson (J., 1917, **109**, 905).

The evidence which Pictet and Gams bring forward in support of their contention that the synthetical base, $C_{20}H_{21}O_4N$, is tetrahydroberberine is as follows :

(i) The base, $C_{20}H_{21}O_4N$, melts at the same temperature as tetrahydroberberine (168°) and there was no depression in melting point when it was mixed with a specimen of tetrahydroberberine.

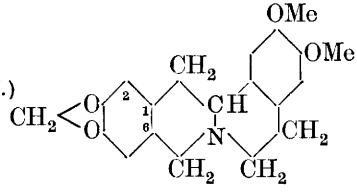
(ii) The base, $C_{20}H_{21}O_4N$, behaved on treatment with bromine or dilute nitric acid exactly like tetrahydroberberine and yielded salts which direct comparison proved to be identical with those of berberine. The picrate melted at 239—240° and, when mixed with the picrate of berberine, there was no depression in melting point.

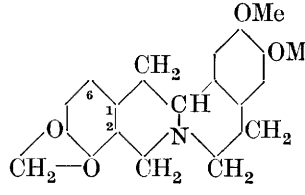
(iii) The hydrobromide, obtained by the action of bromine on the synthetical base, $C_{20}H_{21}O_4N$, behaved exactly like the hydrobromide of berberine and showed the characteristic conversion into oxyberberine (m. p. 199°) on treatment with sodium hydroxide.

In the communication on ψ-*epi*berberine which immediately precedes the present one, it is clearly proved that the condensation of 1-homopiperonyl-6 : 7-dimethoxytetrahydro*iso*quinoline with methylal (or formaldehyde) does not take place abnormally in the direction claimed by Pictet and Gams in their experiments on the synthesis of tetrahydroberberine, but gives rise to a base, $C_{20}H_{21}O_4N$, which is isomeric with tetrahydro*epi*berberine and which we have named tetrahydro-ψ-*epi*berberine.

In other words, the condensation in this case takes place with the assistance of the hydrogen atom (6) of the veratryl nucleus and not with the aid of the hydrogen atom (2), and the result is tetrahydro-ψ-*epi*berberine (VI) and not tetrahydro*epi*berberine (VII).

(VI.)





(VII.)

In order to find some explanation for this puzzling difference in the direction of two such analogous condensations, we decided to undertake a re-investigation of the synthesis which Pictet and Gams claim leads to tetrahydroberberine. As a result of a long series of careful experiments conducted with very carefully purified material and many times repeated, we have been forced to the conclusion that the process described by Pictet and Gams, carried out under the conditions described in detail in the experimental section of this communication, does not lead to tetrahydroberberine (IV), but to the isomeric base (V), which we have named *tetrahydro-ψ-berberine*. That is to say that the condensation of veratrylnorhydrohydrastinine (III) with methylal has, in our experiments, proceeded in the direction indicated by experience. It is, of course, possible that we have inadvertently used conditions which have differed in some material aspect from those employed by Pictet and Gams, and the decision on this point must be left in the hands of independent investigators.

The following brief account of our experimental results should be

supplemented by reference to the experimental section of this investigation.

Homoveratroyl-homopiperonylamine (I) was, in our first experiments, prepared exactly as described by Pictet and Gams (*loc. cit.*, p. 2482), but we subsequently greatly increased the yield by modifying the process in the manner described on p. 1694. This substance melts at 135—136° and behaves towards solvents in the manner described by Pictet and Gams.

We next converted this base into veratrylmethylenedioxydihydro*iso*quinoline (II) by boiling in xylene solution with phosphorus pentoxide exactly as described by Pictet and Gams, but we afterwards found that the same base is obtained in much better yield by digesting the toluene solution with phosphorus oxychloride. Pictet and Gams describe this base as an amorphous substance melting at 68—70° and yielding indefinite salts.

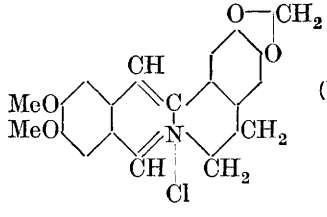
We find, on the contrary, that the base—whether prepared with the aid of pentoxide or oxychloride of phosphorus—is a crystalline substance melting at 88° and yielding well-characterised salts, of which the hydrochloride, hydriodide, and picrate have been prepared and the last two analysed. When this dihydro*iso*quinoline was reduced with tin and hydrochloric acid, it yielded veratrylnorhydrohydrastinine (III), and this crystallises from alcohol in long prisms melting at 84° and yields beautifully crystalline salts, of which the hydrochloride, sulphate, and picrate have been prepared. Pictet and Gams (*loc. cit.*, p. 2483), on the other hand, describe this base as melting at 208—210° and state that the salts in general are difficult to crystallise. In view of this curious discrepancy in the description of the properties of this base, it may be mentioned that it is improbable that a tetrahydro*iso*quinoline of the type under discussion would melt at a temperature approaching 208—210°, since all the substances of this nature which have so far been obtained melt below 100°. The only apparent exception was the so-called tetrahydropapaverine of Goldschmiedt (*Monatsh.*, 1886, **7**, 745; 1898, **19**, 324), which melts at 201—202°, but Pyman (J., 1909, **95**, 1610; 1910, **97**, 1320; 1915, **107**, 176) was able to show that this substance is in reality an abnormally constituted dihydropapaverine and named it "pavine." When veratrylnorhydrohydrastinine (m. p. 88°) was heated on the steam-bath with methylal and concentrated hydrochloric acid, exactly under the conditions described by Pictet and Gams (*loc. cit.*, p. 2484), a sparingly soluble, crystalline hydrochloride separated which, on decomposition with alkali, yielded a base, $C_{20}H_{21}O_4N$, crystallising well from alcohol and melting at 177°, whereas tetrahydroberberine

melts at 169°. Moreover, a mixture of this base with a sample of pure tetrahydroberberine melted at 142—144°, so that there can be no question of identity. This isomeride of tetrahydroberberine we have named *tetrahydro-ψ-berberine*.*

In the experiment just described, the yield of tetrahydro-ψ-berberine was small and considerable quantities of an amorphous substance were produced which was carefully examined, but we were unable to detect even a trace of tetrahydroberberine in this material. It was then found that a very much better yield of tetrahydro-ψ-berberine may be obtained by employing a modification of Decker's method (*Annalen*, 1913, **395**, 282) for the synthesis of *iso*quinoline derivatives. A methyl-alcoholic solution of veratryl-norhydrohydrastinine is warmed for a few minutes with formalin and the product poured into water. The intermediate semi-solid formyl derivative is readily converted into tetrahydro-ψ-berberine hydrochloride by warming with concentrated hydrochloric acid, the yield being at least 60 per cent. of that theoretically possible. In this case also, the base melted at 177°.

*The ψ-Berberinium Salts, Oxy-ψ-berberine and Dihydro-ψ-berberine.**

Tetrahydro-ψ-berberine is readily oxidised by iodine with the formation of *ψ-berberinium iodide*, which is sparingly soluble, crystallises well, melts at 274° with decomposition, and is converted on digesting with water and silver chloride into *ψ-berberinium chloride*,

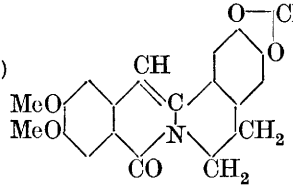
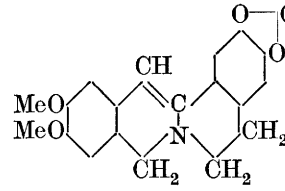


(VIII.)

Crystallised from water, this salt has the composition $C_{20}H_{18}O_4NCl,4\frac{1}{2}$ aq. and, on drying at 120°, $\frac{1}{2}$ aq. still remains. When, however, the substance is recrystallised from absolute alcohol, the anhydrous chloride is obtained and this separates in very pale yellow needles which darken at 270° and melt at 300°. The *picrate* crystallises in yellow needles and melts and decomposes at 305°, whereas berberinium picrate melts at 239°.

* Strictly speaking, these substances should be named tetrahydroanhydro-ψ-berberine and dihydroanhydro-ψ-berberine, but we have employed the usual names in this communication.

Oxy-ψ-berberine and *dihydro-ψ-berberine*,

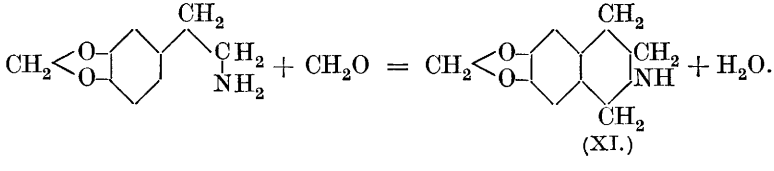
(IX)  and  (X.)

are readily obtained when ψ-berberinium chloride is warmed with aqueous potassium hydroxide. Oxy-ψ-berberine crystallises well from dilute acetic acid in nearly colourless needles and melts at 268° (oxyberberine melts at 200°). Dihydro-ψ-berberine also crystallises well in yellow prisms melting at 167° (dihydroberberine melts at 169°) and yields a characteristic hydrochloride melting with decomposition at 255°.

During the course of these experiments we have also re-investigated the process by which Pictet and Gams (*Ber.*, 1911, **44**, 2036) claim to have synthesised oxyberberine with a view to the extension of this method to the synthesis of alkaloids allied to berberine. It was shown by one of us (Perkin, J., 1918, **113**, 764) that oxyberberine may be reduced electrolytically to tetrahydroberberine, which may then, by the action of oxidising agents, be converted into salts of berberine; consequently a synthesis of oxyberberine is also a synthesis of berberine.

If, then, the isomerides of oxyberberine could be synthesised by a similar process, these should be capable of conversion into the known and unknown isomerides of berberine in which we are interested.

The starting point in the Pictet and Gams experiments on the synthesis of oxyberberine was methylene-6 : 7-dioxytetrahydro*iso*-quinoline (norhydrohydrastinine), which those authors obtained by condensing the hydrochloride of homopiperonylamine with methylal in the presence of hydrochloric acid :



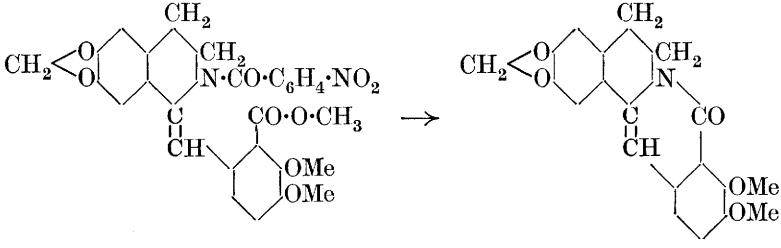
(XI.)

They describe the base as an oil distilling at 197—199°/50 mm. and yielding a hydrochloride melting at 255—257°. On repeating the process of Pictet and Gams, we obtained an oily mixture of bases from which we succeeded in isolating a small quantity of a

hydrochloride melting at 275°, and this, on treatment with alkali, yielded a solid base which crystallised well and melted at 80—81°. Apparently there is a tendency for methylal condensations of this type to lead to the formation of a mixture of bases since, quite recently, Kondo and Ochiai (*J. Pharm. Soc. Japan*, 1923, **313**, 219; Abstr., 1923, i, 837) have shown that the condensation of phenylethylamine hydrochloride with methylal gives rise to a mixture of several substances from which considerable quantities of di-β-phenylethylaminomethane, $CH_2(NH{\cdot}CH_2{\cdot}CH_2Ph)_2$, were isolated. In 1913 (*Annalen*, **395**, 354), Decker and Becker discussed the Pictet and Gams synthesis of norhydrohydrastinine and showed that, if the methylal is replaced by formaldehyde (*loc. cit.*, p. 351), a good yield of methylenehomopiperonylamine,

$$CH_2{:}O_2{:}C_6H_3{\cdot}CH_2{\cdot}CH_2{\cdot}N{:}CH_2,$$

is obtained, and they describe the almost quantitative conversion of this substance into norhydrohydrastinine by warming with hydrochloric acid. These investigators state that the base melts at 81—83° and yields a hydrochloride melting at 274—276°, constants which are in close agreement with those observed by us. The next step in the Pictet and Gams synthesis of oxyberberine was the conversion of the crude norhydrohydrastinine into the *o*-nitrobenzoyl derivative, which they describe as melting at 104°. A mixture of this derivative and the methyl ester of opianic acid was left for 14 days in contact with concentrated sulphuric acid and, on heating the condensation product with alcoholic potassium hydroxide (15—20 per cent.) at 140—150° oxyberberine was obtained.



We have repeated this process using pure norhydrohydrastinine melting at 80—81°, and we find that the *o*-nitrobenzoyl derivative melts at 154° and not at 104° as stated by Pictet and Gams. This substance was left in contact with methyl opianate and sulphuric acid in the manner described by Pictet and Gams and yielded a brown solid from which nothing crystalline could be obtained. When this was heated at 140—150° with alcoholic potassium hydroxide (15—20 per cent.), we failed, in spite of careful search, to detect the presence even of traces of oxyberberine. In view of the work

of Spath and Lang (*Ber.*, 1921, **54**, 3071), during the course of which it was shown that tetrahydroberberine is decomposed on heating in a sealed tube with 20 per cent. methyl-alcoholic potassium hydroxide at 180° with elimination of the methylene group, it seemed improbable that oxyberberine could be produced under the conditions just mentioned. In order to test this view, pure oxyberberine was heated with alcoholic potassium hydroxide (15 per cent.) at 140° for 2 hours, as the result of which it was completely decomposed with the formation of a phenolic substance which was soluble in aqueous alkali and was readily oxidised in contact with air. We are, at the present time, engaged in the careful examination of the product of this decomposition.

EXPERIMENTAL.

3 : 4-*Dimethoxyphenylpyruvic Acid*, $(MeO)_2C_6H_3\cdot CH_2\cdot CO\cdot CO_2H$.—This acid was prepared from 3 : 4-dimethoxybenzaldehyde (veratraldehyde) by Kropp and Decker's method (*Ber.*, 1909, **42**, 1186) but the separation of the pyruvic acid from benzoic acid was greatly facilitated in the following way. The alkaline solution from the hydrolysis of the azlactone, containing the mixed acids, was cooled and saturated with sulphur dioxide when the benzoic acid was precipitated and removed by filtration.

The filtrate, containing the bisulphite derivative of the pyruvic acid, was made strongly acid with hydrochloric acid and heated on the steam-bath for several hours, when, on standing, nearly pure 3 : 4-dimethoxyphenylpyruvic acid separated. After one crystallisation from glacial acetic acid, it melted at 187° and the yield, calculated from the dimethoxybenzaldehyde employed, was about 50 per cent. of the theoretical.

3 : 4-*Dimethoxyphenylacetic Acid* $(MeO)_2C_6H_3\cdot CH_2\cdot CO_2H$.—This acid was obtained in a yield of 70 per cent. by oxidising 3 : 4-dimethoxyphenylpyruvic acid in alkaline solution with hydrogen peroxide, essentially as recommended by Cain, Simonsen, and Smith (J., 1913, **103**, 1036) for the preparation of *p*-methoxyphenylacetic acid. After drying in a desiccator, it melted at 98°.

3 : 4-*Methylenedioxycinnamic Acid*, $CH_2{:}O_2{:}C_6H_3\cdot CH{:}CH\cdot CO_2H$, *and its Conversion into* 3 : 4-*Methylenedioxyphenylethylamine*, $CH_2{:}O_2{:}C_6H_3\cdot CH_2\cdot CH_2\cdot NH_2$.—When piperonal (5 parts), fused sodium acetate (3 parts), and acetic anhydride (6 parts) were heated at 180° for 6 hours in a reflux apparatus, a 30 per cent. yield of the cinnamic acid was obtained, but for the preparation of large quantities of material the following method was found to be much more advantageous. Piperonal (100 gms.) and malonic acid (150 gms.) dissolved in pyridine (300 c.c.) and piperidine (5 c.c.), were heated

for an hour on the steam-bath, when a rapid elimination of carbon dioxide took place and the reaction was completed by boiling the solution for 5 minutes.* The product was cooled, poured into water, and the almost quantitative yield of pure 3 : 4-methylenedioxycinnamic acid (m. p. 233°) collected. 3 : 4-Methylenedioxyphenylpropionic acid was prepared in a yield of 85 per cent. from this cinnamic acid by reduction with sodium amalgam as described by Perkin and Robinson (J., 1907, **91**, 1079). 3 : 4-*Methylenedioxyphenylpropionamide*, $CH_2{:}O_2{:}C_6H_3{\cdot}CH_2{\cdot}CH_2{\cdot}CONH_2$. This derivative proved to be difficult to prepare, but ultimately the following method was found to give excellent results. The acid (100 gms.), dissolved in chloroform (340 c.c.), is allowed to react for 12 hours with thionyl chloride (74 c.c.) at the room temperature and the product is then poured into a solution containing sodium hydroxide (50 gms.) and concentrated ammonia (1200 c.c.). The chloroform is removed by distillation and, after filtering from traces of tar, the filtrate is cooled, when the amide (100 gms.) separates in a state sufficiently pure for the next operation. The conversion into 3 : 4-*methylenedioxyphenylethylamine* was brought about by treatment with sodium hypochlorite essentially as recommended by Decker (*Annalen*, 1915, **395**, 291) in the case of the preparation of homopiperonylamine and the yield was about 50 per cent. of the theoretical.

Homoveratroyl-homopiperonylamine (I).—(i) 3 : 4-Dimethoxyphenylacetyl chloride was prepared by dissolving the acid (10 gms.) in chloroform (30 c.c.) and boiling with thionyl chloride (10 gms.) until the evolution of hydrogen chloride had ceased. The chloroform and excess of thionyl chloride were removed by distillation and the residual syrup was gradually added to a suspension of 3 : 4-methylenedioxyphenylethylamine (8 gms.) in 10 per cent. potassium hydroxide solution. The mixture was shaken vigorously and cooled, when the homoveratroylhomopiperonylamine gradually solidified and, after shaking for 3 hours, the solid was collected, recrystallised from alcohol, and obtained in a yield of 6 grams.

(ii) 3 : 4-Methylenedioxyphenylethylamine (24 gms.) and 3 : 4-dimethoxyphenylacetic acid (28·5 gms.) were heated under reflux for 6 hours at 180°. The mixture was dissolved in a little boiling alcohol and, on cooling, 35 gms. of homoveratroyl-homopiperonylamine separated. Prepared by either of these methods, this substance melted at 135—136° and had all the properties ascribed to it by Pictet and Gams (*loc. cit.*, p. 2482).

1-*Veratryl*-6 : 7-*methylenedioxydihydroisoquinoline* (II).—In our earlier experiments, this substance was prepared from homo-

* This method was suggested to us by Professor R. Robinson.

veratroyl-homopiperonylamine by dehydration with phosphorus pentoxide in boiling xylene as described by Pictet and Gams (*loc. cit.*, p. 2482). The ethereal extract gradually deposited the dihydro*iso*quinoline in colourless prisms, m. p. 86—87°. The yield was, however, very small and the ether mother-liquors, on concentration, deposited a basic substance which, after crystallisation from alcohol, melted at 150—151° (see below); about 20 per cent. of the amine was recovered unchanged from the xylene solution.

A much better method for the preparation of this base is as follows: Homoveratroyl-homopiperonylamine (6 gms.), dissolved in toluene (30 c.c.), is boiled for 1½ hours with phosphorus oxychloride (12 c.c.). The solution is cooled, diluted with light petroleum (b. p. 80—100°), the solvent decanted, the residual syrup dissolved in a little hot alcohol, made alkaline by the addition of alcoholic potassium hydroxide, and poured into a large bulk of water. On standing, the dihydro*iso*quinoline separates in small, colourless needles in a yield of 75 per cent. of the theoretical.

1-Veratryl-6 : 7-methylenedioxydihydro*iso*quinoline melts at 87—88° and is soluble in benzene, acetone, or chloroform, sparingly soluble in ether or petroleum, and insoluble in water. The *hydrochloride* separates from the concentrated aqueous solution of the base in dilute hydrochloric acid in pale yellow prisms containing water of crystallisation and melting at 62°. After drying over phosphorus pentoxide in a vacuum, the crystals are opaque and paler in colour and melt at 125°. The dry substance rapidly absorbs moisture on exposure to air, again becoming yellow and melting at 62°. The *hydriodide* is precipitated, on the addition of potassium iodide to the aqueous solution of the hydrochloride, as a crystalline mass which separates from alcohol or water in pale yellow prisms, m. p. 239—240° (Found : C = 50·5; H = 4·3. $C_{19}H_{20}O_4NI$ requires C = 50·3; H = 4·3 per cent.). The *picrate* was obtained by mixing alcoholic solutions of the base and picric acid and crystallises from glacial acetic acid in small, yellow needles, m. p. 206° (Found : C = 54·0; H = 3·9. $C_{25}H_{22}O_{11}N_4$ requires C = 54·1; H = 4·0 per cent.). The base is characterised by a remarkable tendency to undergo oxidation with the formation of a new crystalline base, $C_{19}H_{17}O_5N$, melting at 151°. This oxidation takes place when alcoholic, ether or benzene solutions of the base are exposed to the air for a few hours, but does not appear to occur in acid solution. This new base is being subjected to detailed examination, the results of which will be submitted in a future communication.

1-*Veratryl*-6 : 7-*methylenedioxytetrahydro*iso*quinoline* (III).—This substance is prepared by dissolving the dihydro*iso*quinoline (II) in

concentrated hydrochloric acid and boiling in a reflux apparatus with a large excess of granulated tin. After a few minutes, the sparingly soluble tin double salt of the dihydro*iso*quinoline separates and, to complete the reduction, it is necessary to redissolve this by the addition of alcohol. After 12 hours, the colourless solution is decanted from the tin, the alcohol evaporated, and the solution cooled, when the colourless tin double salt of the tetrahydro*iso*quinoline separates and is collected and washed. It is then dissolved in boiling water, filtered from traces of yellow impurity, the tin removed as sulphide, and the filtrate concentrated until the hydrochloride of the tetrahydro*iso*quinoline commences to separate. This is collected, dissolved in hot water, and decomposed with sodium hydroxide, when an oily base separates which rapidly solidifies and crystallises from alcohol in elongated prisms (Found : C = 69·5; H = 6·4. $C_{19}H_{21}O_4N$ requires C = 69·7; H = 6·4 per cent.).

1-Veratryl-6 : 7-methylenedioxytetrahydro*iso*quinoline is soluble in the usual solvents with the exception of petroleum, crystallises readily, and melts at 84°. The *hydrochloride* separates from water in beautiful, colourless, rectangular prisms which melt to a clear liquid at 236°. It is sparingly soluble in cold water and alcohol and particularly so in dilute hydrochloric acid (Found : C = 62·7; H = 5·9. $C_{19}H_{21}O_4N$,HCl requires C = 62·7; H = 6·0 per cent.). The *sulphate* crystallises from water in colourless plates, m. p. 136—137°, and is soluble in boiling alcohol. The *picrate*, prepared in alcoholic solution, crystallises from alcohol in long, bright yellow needles melting, with slight decomposition, at 185—187°.

Tetrahydro-ψ-berberine (VI).

Two methods were employed in the synthesis of this substance. (i) 1-Veratryl-6 : 7-methylenedioxytetrahydro*iso*quinoline (5 gms.), dissolved in concentrated hydrochloric acid (25 c.c.), was heated on the steam-bath for 1½ hours during the gradual addition of methylal (8 gms.). The sparingly soluble hydrochloride soon commenced to separate in the hot solution and, after cooling, was collected, dissolved in hot water, and converted into the base by decomposition with sodium hydroxide. This separated as an oil which rapidly solidified and the crude product was dissolved in alcohol, mixed with ether, and the alcohol removed by washing several times with water. The ethereal solution was dried over potassium carbonate, concentrated, and then allowed to evaporate slowly, when small needles of *tetrahydro-ψ-berberine* gradually separated. After recrystallisation from alcohol, the substance melted at 177.°

The hydrochloric acid mother-liquors were made slightly alkaline

with sodium hydroxide, when large quantities of a dark-coloured, amorphous base separated. This was sparingly soluble in alcohol or ether, but no tetrahydroberberine could be isolated by extracting with ether in a Soxhlet apparatus. The extract consisted of a white, amorphous, high-melting substance of unknown composition and our experience is that similar substances are frequently met with in methylal condensations of this type.

(ii) A much better method for the preparation of tetrahydro-ψ-berberine was found to be the following: 1-Veratrylmethylenedioxytetrahydro*iso*quinoline (5 gms.), dissolved in methyl alcohol (10 c.c.), is warmed at about 60° for a few minutes with 40 per cent. formaldehyde solution (10 c.c.). The product is mixed with water, the solution decanted from the syrup, and this freed from formaldehyde by washing several times with water. The syrup is then dissolved in concentrated hydrochloric acid and heated on the steam-bath for a few minutes; the sparingly soluble hydrochloride separates, and increases in amount on cooling. This is collected, dissolved in boiling water, decomposed with sodium hydroxide, and the base recrystallised from alcohol. It then melts at 177° and the yield is 60 per cent. of the theoretical. Careful search in the mother-liquors did not reveal the presence of any trace of tetrahydroberberine.

Tetrahydro-ψ-berberine crystallises in small needles melting sharply at 177°. It is sparingly soluble in ether, but readily soluble in benzene, chloroform, acetone, or hot alcohol. It dissolves in concentrated sulphuric acid to a pale yellow solution which becomes greenish-brown and then red on the addition of a crystal of potassium nitrate. When mixed with a specimen of tetrahydroberberine which had been prepared by the reduction of berberinium chloride and melted at 169—170°, a depression in melting point of 26° was observed (Found: C = 70·5; H = 6·4. $C_{20}H_{21}O_4N$ requires C = 70·8; H = 6·2 per cent.).

The *hydrochloride* is sparingly soluble in cold water and particularly so in dilute hydrochloric acid, but can be crystallised from much hot water, from which it separates in small, colourless, elongated prisms which soften and darken at 222° and melt at 228—230°. The *hydriodide* is immediately precipitated by the addition of potassium iodide to a hot aqueous solution of the hydrochloride. It is very sparingly soluble in hot water, from which it crystallises in small prisms which soften at 170° and decompose at 222°. The *sulphate* is sparingly soluble in cold water and crystallises from hot water in long, slender needles melting at 168°. The *picrate* separates in bright yellow needles melting at 176° when an alcoholic solution of picric acid is added to the hot alcoholic

solution of tetrahydro-ψ-berberine. The *methiodide* is obtained by boiling the base with methyl iodide for ½ hour; the excess of methyl iodide is removed by distillation and the residual methiodide crystallised from much hot water, from which it separates in rosettes of prismatic needles melting at 256° and decomposing at 260°.

The ψ-Berberinium Salts.

ψ-Berberinium Iodide.—This quaternary salt is readily obtained in the following manner: Tetrahydro-ψ-berberine (3 gms.), dissolved in ethyl alcohol (100 c.c.) containing potassium acetate (4 gms.), is heated to boiling and a 2 per cent. alcoholic solution of iodine (250 c.c.) slowly added, when the periodide soon separates as a mass of long, felted, brown needles. After boiling for ½ hour, the whole is cooled, the crystals are collected, suspended in boiling water, and sulphur dioxide is passed, when the iodide separates in yellow needles which are recrystallised from water (Found: C = 51·5; H = 4·1. $C_{20}H_{18}O_4NI$ requires C = 51·8; H = 3·9 per cent.).

ψ-Berberinium iodide is sparingly soluble in boiling alcohol or water, but separates from a large volume of boiling water as a felted mass of long, canary-yellow needles melting with decomposition at about 274°.

ψ-Berberinium Chloride (VIII), was obtained by boiling an aqueous suspension of the iodide with excess of freshly-precipitated silver chloride for 6 hours. After filtering, the filtrate was mixed with hydrochloric acid, when the chloride soon began to separate as a mass of pale yellow needles. This fine salt was crystallised from a little dilute hydrochloric acid and allowed to remain on porous porcelain until air-dry. The substance then had the composition $C_{20}H_{18}O_4NCl,4\frac{1}{2}$ aq. and, after drying at 120°, the composition was $C_{20}H_{18}O_4NCl,\frac{1}{2}$ aq. The loss at 120° was 16·5, whereas that calculated for the loss of $4H_2O$ is 16·0 per cent. The chloride (dried at 120°) gave C = 63·4; H = 5·1, whereas $C_{20}H_{18}O_4NCl,\frac{1}{2}$ aq. requires C = 63·0; H = 5·0 per cent.

This chloride (dried at 120°) was boiled for 3 hours with absolute alcohol, in which it is rather sparingly soluble, and after filtering and allowing to cool slowly, the mass of pale yellow slender needles was left over sulphuric acid in a vacuum desiccator for 2 days. Analysis showed that the salt was then anhydrous (Found: C = 64·3; H = 4·9. $C_{20}H_{18}O_4NCl$ requires C = 64·5; H = 4·8 per cent.). This salt darkens at 270° and decomposes at 300°, and the same behaviour is exhibited by the hydrated salt after drying at 120°. It dissolves in concentrated sulphuric acid, yielding a greenish-yellow solution.

The *picrate*, $C_{20}H_{17}O_4N,C_6H_3O_7N_3,H_2O$, was prepared by adding

an alcoholic solution of picric acid to a hot alcoholic solution of the chloride and rapidly separated as a mass of yellow needles (Found : C = 53·9; H = 3·8. $C_{26}H_{22}O_{12}N_4$ requires C = 53·6; N = 3·8 per cent.). This picrate decomposes at 305° and is sparingly soluble in boiling alcohol or acetic acid. For the sake of comparison, a specimen of berberine picrate was prepared. It melted at 239°, as stated by Pictet and Gams (*loc. cit.*, p. 2485) and yielded on analysis : C = 53·8; H = 3·9 per cent.

Oxy-ψ-berberine (IX) *and Dihydro-α-berberine* (X).

These substances result from the action of alkalis on ψ-berberinium chloride. The chloride, suspended in a large excess of 25 per cent. potassium hydroxide, is heated for 4 hours in a rapidly boiling water-bath. The whole is cooled, diluted with water, filtered, and the residue extracted several times with small quantities of warm dilute hydrochloric acid. The dark brown mass is then dissolved in hot glacial acetic acid and a little hot water added, when, on cooling, oxy-ψ-berberine separates in long, pale buff needles, m. p. 265—266°. A second crystallisation from dilute acetic acid yielded almost colourless needles, m. p. 268° (Found : C = 68·1; H = 4·9. $C_{20}H_{17}O_5N$ requires C = 68·4; H = 4·8 per cent.). *Oxy-ψ-berberine* is sparingly soluble in the usual solvents with the exception of glacial acetic acid. It dissolves in concentrated sulphuric acid to a yellow solution, which becomes green and then purple on the addition of a crystal of sodium nitrate. When it was mixed with a specimen of oxyberberine (m. p. 200°), prepared from berberinium chloride, the mixture melted at about 184—186°.

Dihydro-ψ-berberine.—This substance was isolated in the form of its hydrochloride by adding a large excess of concentrated hydrochloric acid to the combined dilute hydrochloric acid extracts of the crude mixture with oxy-ψ-berberine obtained in the manner described above. After remaining over-night, the pale yellow prisms were collected and purified by dissolving in a little water and precipitating with concentrated hydrochloric acid. This *hydrochloride* of dihydro-ψ-berberine melts with decomposition at 253—255° and is readily soluble in hot water.

Dihydro-ψ-berberine, obtained by adding sodium hydroxide to the aqueous solution of the hydrochloride, was recrystallised from acetone (Found : C = 71·0; H = 5·6. $C_{20}H_{19}O_4N$ requires C = 71·2; H = 5·6 per cent.). It separates from acetone in small, pale yellow needles, m. p. 165—167°, and, when mixed with a specimen of dihydroberberine (m. p. 169°) which had been prepared from berberinium chloride, the mixture melted at about 141—143°.

Norhydrohydrastinine (XI).

In our first experiments on the preparation of this substance, we followed the method recommended by Pictet and Gams (*Ber.*, 1911, **44**, 2042) and by subjecting the mixture of hydrochlorides obtained after the reduction with tin and hydrochloric acid to careful fractionation first from alcohol and then from water, we were able to isolate a small quantity of norhydrohydrastinine hydrochloride, m. p. 275°. When the aqueous solution was decomposed by alkali, the base rapidly solidified; it crystallised from dilute alcohol in needles, m. p. 80—81°.

The mother-liquors of this hydrochloride contain large quantities of secondary bases, but we were unable to isolate any substance from this mixture in a pure condition. We then investigated the process recommended by Decker and Becker (*Annalen*, 1913, **395**, 350) for the preparation of norhydrohydrastinine and with very satisfactory results. Using the quantities recommended by them, we dissolved the homopiperonylamine in a little methyl alcohol, warmed for a few minutes with the 40 per cent. formaldehyde, diluted with water, decanted the liquid from the semi-solid mass which had separated, and washed this well with water. The mass was dissolved in a little 20 per cent. hydrochloric acid and warmed for ½ hour on the steam-bath, when, on cooling, the hydrochloride of norhydrohydrastinine separated in a yield of 70 per cent. of theory. After recrystallisation, the hydrochloride melted at 274—275° and on decomposition with alkali, yielded norhydrohydrastinine as a solid which, after recrystallisation from dilute alcohol, melted at 81—83° as stated by Decker and Becker.

N-*o*-*Nitrobenzoylnorhydrohydrastinine*.—This substance was prepared by warming a solution of the hydrochloride (6 gms.) in water (25 c.c.) with *o*-nitrobenzoyl chloride (6 gms.) during the gradual addition of a 30 per cent. solution of potassium hydroxide. The mixture was well shaken during this addition and, after about ½ hour, the *o*-nitrobenzoyl derivative separated as an oil which solidified on cooling. It crystallised from alcohol in colourless needles, m. p. 154° (Found : C = 62·7; H = 4·5. $C_{17}H_{14}O_5N_2$ requires C = 62·6; H = 4·3 per cent.).

Condensation with Methyl Opianate.—The methyl opianate was prepared in the way recommended by Bain, Perkin, and Robinson (J., 1914, **105**, 2398). The *o*-nitrobenzoyl derivative (3 gms.) and methyl opianate (2·5 gms.) were dissolved in concentrated sulphuric acid (10 c.c.) and allowed to remain at room temperature for 14 days. The solution developed a brown colour and was gradually converted into a jelly-like mass. This was poured into cold water,

when a brown, amorphous solid separated which could not be purified. It was sparingly soluble in the usual organic solvents, but rapidly dissolved to a brown liquid on warming with a solution of sodium hydroxide. It was precipitated from this solution by mineral acids, but not by carbon dioxide.

This brown solid (1 gm.) was heated with 15 per cent. alcoholic potassium hydroxide for 2 hours in a sealed tube at 140—150° (Pictet and Gams, *loc. cit.*, p. 2044). On diluting with water, the whole dissolved and hydrochloric acid precipitated a brown solid which was collected, dried, and extracted with alcohol in a Soxhlet apparatus. The brown, amorphous residue did not melt at 280° and was insoluble in the usual solvents and also in dilute mineral acids, but dissolved readily and completely in dilute sodium hydroxide to a brown solution and was not precipitated by carbon dioxide. There was clearly no oxyberberine present in this substance. The alcoholic extract was concentrated, when a small quantity of a brown, amorphous solid separated which was completely soluble in dilute sodium hydroxide and therefore did not contain any oxyberberine. On repeating the above experiment, exactly the same results were obtained.

Action of Alcoholic Potassium Hydroxide on Oxyberberine.—Carefully purified and finely powdered oxyberberine (1 gm.) and alcoholic potassium hydroxide (5 c.c. of 15 per cent.) were heated in a sealed tube for 2 hours at 140—150°, when, on cooling, a deposit of bright yellow needles of a potassium derivative was found to have separated. On adding water, the liquid discoloured rapidly in the air, and, as the potassium derivative was also found to be soluble in water, it was obvious that the whole of the oxyberberine had been changed by this treatment. We are at present engaged in an examination of these products of the decomposition of oxyberberine.

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