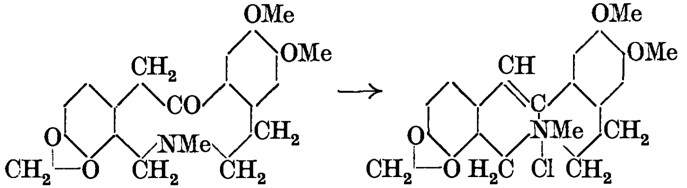
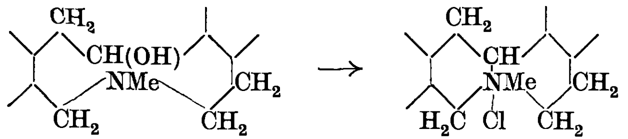
LVII.—*The Conversion of Berberine into β-Homochelidonine (α-alloCryptopine).*

By Robert Downs Haworth and William Henry Perkin, jun.

During the course of the investigation of cryptopine and protopine (Perkin, J., 1916, **109**, 815; 1918, **113**, 493, 722; 1919, **115**, 713) it was shown that these alkaloids contain a ten-membered ring, and that cryptopine and dihydrocryptopine are converted into quaternary chlorides, containing the berberine skeleton, when they are treated with phosphorus oxychloride :

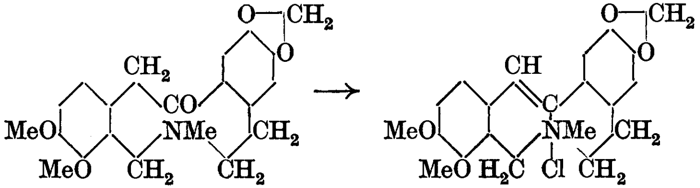


Cryptopine. *Dihydroepiberberine methochloride.*



Dihydrocryptopine. *Tetrahydroepiberberine methochloride.*

Subsequently Gadamer (*Arch. Pharm.*, 1919, **257**, 298; 1920, **258**, 148) found that β-homochelidonine, one of the alkaloids occurring in *Sanguinaria canadensis* and *Chelidonium majus*, is converted into dihydroberberine methochloride, and dihydro-β-homochelidonine into tetrahydroberberine methochloride under similar conditions. Gadamer therefore concluded that β-homochelidonine must, like cryptopine, contain a ten-membered ring and that the change into dihydroberberine methochloride is to be represented thus :

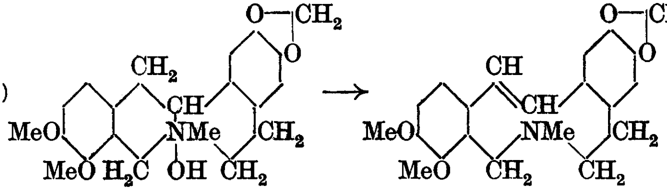

β-Homochelidonine. *Dihydroberberine methochloride.*

It is in view of this close relationship that Gadamer (*loc. cit.*) suggested the name α-*allo*cryptopine for β-homochelidonine.

The synthesis of berberine recently achieved by Perkin, Ray, and Robinson (J., 1925, **127**, 740; compare Späth, *Ber.*, 1925, **58**, 2268) will, it is hoped, serve as a basis for the synthesis of other alkaloids of similar constitution and it now became important to devise a method which would enable synthetical alkaloids of the berberine type to be converted into alkaloids like cryptopine, protopine, and β-homochelidonine with which they are clearly closely allied. The present investigation is concerned with such a method, namely, with the conversion of berberine into β-homochelidonine. The development of the process to the synthesis of cryptopine and the allied alkaloids will, it is hoped, form the subject of future communications.

It has long been known (Voss and Gadamer, *Arch. Pharm.*, 1910, **248**, 43; Freund, *Annalen*, 1913, **397**, 1; Pyman, J., 1913, **103**, 817; McDavid, Perkin, and Robinson, J., 1912, **101**, 1220; Perkin, J., 1916, **109**, 952) that tetrahydroberberine methohydroxide (I) loses water when its aqueous solution is evaporated in a vacuum and yields as chief product anhydrotetrahydromethylberberine (anhydromethylcanadine) (II), a remarkable change which results in the formation of a substance containing a ten-membered ring and in which the various groups occupy the same relative positions as in β-homochelidonine.

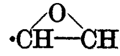
(I.)



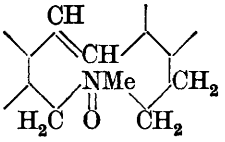
(II.)

It is clearly only necessary to convert the group ·CH:CH· in the latter formula into ·CO·CH$_2$· in order to achieve the synthesis of β-homochelidonine.

The realisation of this comparatively simple change proved to be a very difficult problem, mainly because the usual methods are not applicable to anhydrotetrahydromethylberberine. This substance exhibits a remarkable tendency, when treated with many of the usual reagents, and indeed merely on boiling with alcohol or chloroform, to revert to tetrahydroberberine methohydroxide or its salts with consequent loss of the ten-membered ring (compare Pyman, *loc. cit.*, p. 834). We observed the same change when an ice-cold solution of the base in chloroform was treated with bromine, since the crystalline perbromide which separated yielded tetrahydroberberine methobromide on decomposition with sulphurous acid. A series of experiments on the action of oxidising agents on anhydrotetrahydromethylberberine did not lead to the desired result, although interesting oxidation products were obtained, when this base was treated with silver hydroxide or hydrogen peroxide, which will be discussed in a future communication.

Some years since (*Ber.*, 1909, **42**, 4811; 1910, **43**, 959), Prileshajew carried out an important piece of work in the course of which he showed that ethylene derivatives, $\cdot CH{=}CH\cdot$, yield ethylene oxides,  $\cdot \overset{\frown O \frown}{CH{-}CH}\cdot$, on treatment with perbenzoic acid, and it seemed probable that, if this change could be brought about in the case of anhydrotetrahydromethylberberine, the resulting ethylene oxide grouping might be made to isomerise to $\cdot CO\cdot CH_2\cdot$ and thus lead to the formation of β-homochelidonine (compare Weitz and Scheffer, *Ber.*, 1921, **54**, 2344).

When an ice-cold solution of the base (II) in chloroform is added to an ice-cold solution of perbenzoic acid, the ethylene oxide derivative does not appear to be produced. Oxidation takes place rapidly, however, and a base, $C_{21}H_{23}O_5N$, isomeric but not identical with β-homochelidonine, is obtained in good yield. This curious substance crystallises from water, decomposes at 135°, and yields a hydrochloride, $C_{21}H_{23}O_5N,HCl$, which is sparingly soluble in water. These and other properties seem to indicate that it is an amine oxide containing the group



(III.)

In connexion with the formation and properties of this substance, it is interesting to note that Meisenheimer (*Ber.*, 1919, **52**, 1667) has observed that perbenzoic acid converts methylallylaniline into the amine oxide, $CH_2{:}CH\cdot CH_2\cdot NMePh{:}O$, without affecting the ethylenic linking of the allyl group. He shows that this amine oxide undergoes a curious isomeric change to phenylmethylallylhydroxylamine, $CH_2{:}CH{\cdot}CH_2{\cdot}O{\cdot}NMePh$, when heated with alkalis, and Bamberger and Leyden (*Ber.*, 1901, **34**, 12) state that dimethylaniline oxide is converted into a mixture of *o*- and *p*-dimethylaminophenol by contact with sulphuric acid.

These curious isomeric changes encouraged us to examine in detail the action of various reagents on anhydrotetrahydromethylberberine oxide (III) and it was ultimately observed that in the presence of glacial acetic acid and hydrochloric acid, this amine oxide isomerises to a basic substance which crystallises from ethyl acetate in colourless prisms, m. p. 160—161°, and is identical with β-homochelidonine. The synthetic alkaloid gave no depression in m. p. when mixed with a specimen of β-homochelidonine, for which we are indebted to Professor Gadamer; the hydrochloride was readily soluble in water and crystallised from alcohol–ether in colourless needles which were identical in appearance and behaviour with the hydrochloride of the naturally occurring alkaloid. The garnet-red aurichloride, m. p. 190—192° (decomp.), had all the properties of the double salt prepared from the natural product, whilst the colour reactions of the synthetic and the natural alkaloid with concentrated sulphuric acid, Fröhde's, and Erdmann's reagents were indistinguishable. We propose to investigate the mechanism of the above synthesis, more particularly in regard to the action of other reagents on the amine oxide, and details of this work as well as of the extension of the method to the synthesis of cryptopine, protopine, and allied alkaloids are reserved for a later communication.

EXPERIMENTAL.

Anhydrotetrahydromethylberberine was prepared as recommended by Pyman (*loc. cit.*, p. 833), but we found it advisable to use as little excess of silver hydroxide as possible in the preparation of tetrahydroberberine methohydroxide. Tetrahydroberberine methiodide, dissolved in boiling water, is agitated for ½ hour with the calculated amount of silver hydroxide, and the solution is filtered hot and tested for unchanged methiodide with silver nitrate. If iodide is still present, a further small quantity of silver hydroxide is added and the process repeated if necessary. The whole is then filtered and the solution evaporated exactly as described by Pyman. The perbenzoic acid used in these experiments was prepared by the method of Baeyer and Villiger (*Ber.*, 1900, **33**, 1575). It was extracted with ether and the content of the ethereal solution estimated, immediately before use, by titration with potassium iodide and $N/10$-sodium thiosulphate.

Anhydrotetrahydromethylberberine Oxide.—Anhydrotetrahydromethylberberine (2 g.), dissolved in dry chloroform, was gradually added to a solution of perbenzoic acid (estimated as 1·8 g.) in ether (100 c.c.), maintained below 5° by immersion in ice. An oil gradually separated which sometimes crystallised on standing. After remaining over-night, the mixture was shaken with 10% sodium hydroxide; the amine oxide then solidified as a white solid (1·5 g.) and was collected after several hours. A second crop may be obtained from the filtrate by the careful addition of strong sodium hydroxide.

Anhydrotetrahydromethylberberine oxide crystallises from water in colourless, slender prisms, m. p. 135° (decomp.) (Found: C, 68·1; H, 6·5. $C_{21}H_{23}O_5N$ requires C, 68·3; H, 6·2%). It is soluble in chloroform or acetic acid, moderately easily soluble in ethyl acetate, and almost insoluble in ether or petroleum. It dissolves in hot water, but is less soluble in sodium hydroxide solution. On cooling the solution of the base in hot dilute hydrochloric acid, the *hydrochloride* separates in colourless nodules, m. p. 203° (decomp.) with previous darkening. It is more soluble in water than in dilute hydrochloric acid (Found: C, 62·2; H, 6·0. $C_{21}H_{23}O_5N,HCl$ requires C, 62·1; H, 5·9%).

β-*Homochelidonine.*—The amine oxide (1·5 g.), dissolved in glacial acetic acid (10 c.c.) and concentrated hydrochloric acid (5 c.c.), was heated in rapidly boiling water for an hour, the pale yellow solution diluted with water, made alkaline with potassium hydroxide,* and the cream-coloured solid collected. This was dissolved in methyl alcohol (20 c.c.), mixed with ether (200 c.c.), the ethereal solution washed with water until free from methyl alcohol, rapidly dried over potassium carbonate, and concentrated to a small bulk. On standing, β-homochelidonine separated; it crystallised from ethyl acetate in brilliant, colourless, monoclinic prisms, m. p. 160—161° (Found: C, 68·3; H, 6·5. Calc. for $C_{21}H_{23}O_5N$: C, 68·3; H, 6·2%). The crystals were exactly like those of a specimen of β-homochelidonine which Professor Gadamer very kindly sent us and there was no change in melting point when the two specimens were mixed.

Synthetic β-homochelidonine dissolves in concentrated sulphuric

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* The base is not completely precipitated from its salts by the addition of ammonia, and this property of β-homochelidonine is made use of in the isolation of the alkaloid from the plant (Schmidt and Selle, *Arch. Pharm.*, 1890, **228**, 441).

acid to a yellow solution which rapidly becomes violet and slowly changes to bright red. With Fröhde's reagent, a yellow solution is obtained which soon becomes violet and then passes through brilliant blue to bluish-green. The base dissolves in Erdmann's reagent to a yellow solution which rapidly becomes violet and then dirty violet. These colour reactions are indistinguishable from those exhibited by the specimen of naturally occurring β-homochelidonine under similar conditions. The hydrochloride was obtained by dissolving the base in dilute hydrochloric acid and evaporating to dryness. The residue dissolved readily in alcohol and, on addition of ether, the hydrochloride slowly separated in slender, colourless, silky needles which turn yellow and shrink at about 170° and decompose at about 190°. The hydrochloride of the natural alkaloid possessed identical properties. The aurichloride separated on addition of gold chloride to the solution of the base in dilute hydrochloric acid, and crystallised from alcohol in warts of garnet-red crystals, m. p. 190—192° (decomp.). No alteration in m. p. was observed when this sample was mixed with the garnet-red aurichloride prepared in the same way from natural β-homochelidonine.

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THE DYSON PERRINS LABORATORY,
OXFORD.

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