Tetrahedron. Vol 24, pp. 1455 to 1465. Pergamon Press 1968. Printed in Great Britain

THE CHEMISTRY OF CRYPTOPINE—I

THE EPICRYPTOPINES.[1]

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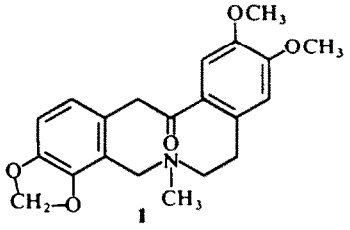
(*Received in UK* 20 *June* 1967; *accepted for publication* 20 *July* 1967)

Abstract—The chemistry of the epicryptopines, A, B and C, of the epimethylcryptopines A and B and of epicryptopirubin chloride has been re-examined, and some new structural proposals made.

CRYPTOPINE (**1**), $C_{21}H_{23}NO_5$ occurs in opium[2] to the extent of about 0·003%, and is also a minor component of several other plants.[3] Its structure was elucidated by W. H. Perkin, Jnr., and described by him in a monumental paper,[4] which is now cited as a classic example of work carefully planned, and results accurately reported. During the course of this investigation Perkin described more than fifty transformation products of cryptopine, and he assigned structures to most of them. Although the structure of cryptopine itself is in no doubt, modern knowledge and physical methods should clarify the chemistry of some of its derivatives.

Cryptopine (**1**) can be readily transformed into the 3-aryl-1,2-dihydroisoquinoline, anhydrocryptopine (**3**), which, when heated with conc HCl yielded two isomeric bases $C_{21}H_{23}NO_5$ named by Perkin epicryptopines A and B; structures **4** and **5**



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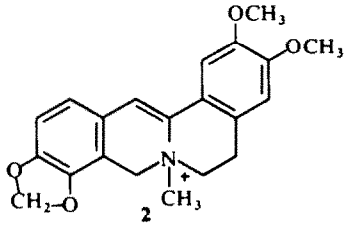

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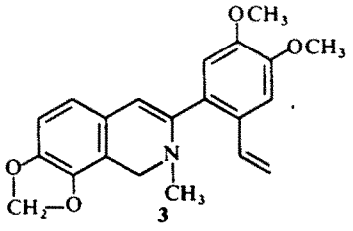

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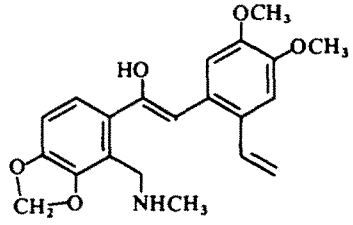
respectively were allotted to them. A third isomer, epicryptopine C (**6**) was formed when epicryptopine A was treated with dilute acetic acid, and this change was reversed by dilute HCl. All three isomers yielded the same N-acetyl derivative. When the A, but *not* the C, isomer was reacted with $POCl_3$ a red salt, epicryptopirubin

chloride was isolated and structure **7** was proposed for it. The interconversions are summarized in Chart 1.



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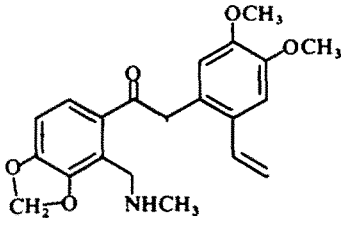

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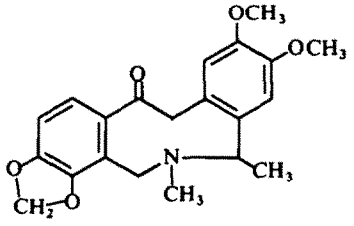

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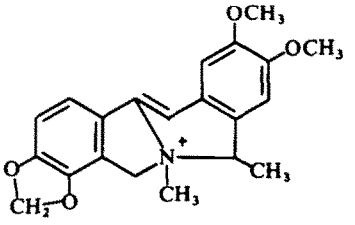

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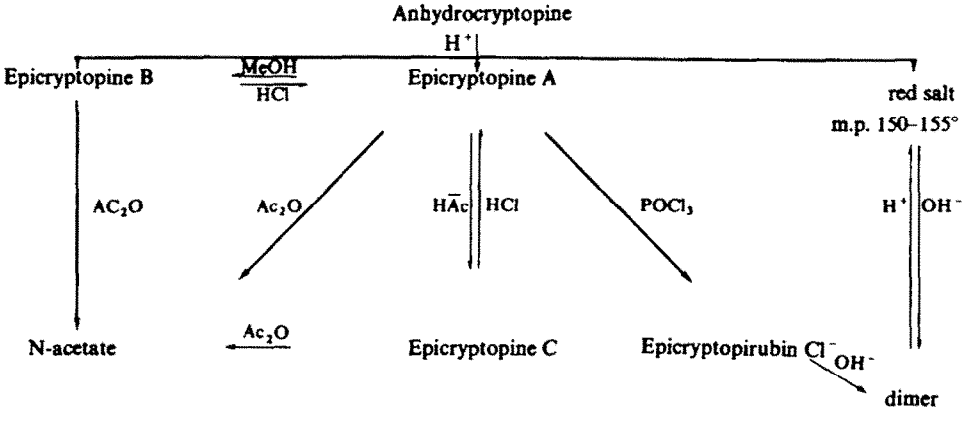
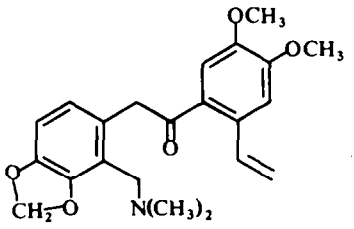
Chart 1



Now, Hofmann degradation of cryptopine methosulphate produces the polymorphic α and β methylcryptopines (**9**) together with γ-methylcryptopine (**8**). The latter, when digested with conc HCl gave small amounts of the isomeric epimethylcryptopines A and B, $C_{22}H_{25}NO_5$. Perkin suggested that epimethylcryptopine B is **10** and that the A-isomer is the enol form of this. No attempt was apparently made by Perkin to relate the epicryptopines with the epimethylcryptopines, although he did report that an epimethylcryptopine was *not* formed when the methochloride of anhydrocryptopine (**3**) was heated with conc HCl. The product was instead pseudocryptopine chloride, the chemistry of which is still being studied by us.

Prompted by our interest in the chemistry of 1,2-dihydroisoquinolines, and by some recent alternative structural proposals,[5] we decided to re-investigate the com-



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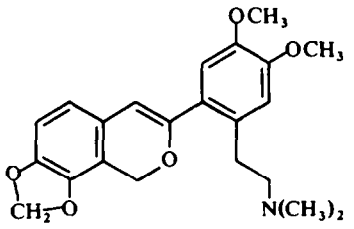

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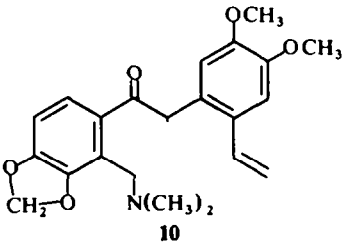

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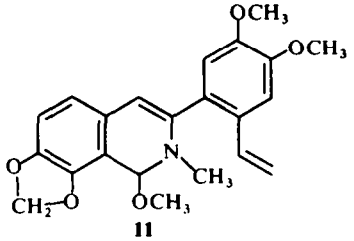
pounds and reactions described above. Any departures from Perkin's original experimental procedures are indicated in the experimental section.

The NMR spectrum of anhydrocryptopine (3)* shows the expected signals for NCH_3, 2 × OCH_3, CH_2O_2 and Ar—CH_2N<; the ABX pattern attributed to the vinyl group is partially obscured by the aromatic absorption. The UV and IR spectra together with chemical transformations described by Perkin are also all entirely in accord with structure 3. When anhydrocryptopine (3) is boiled with methanol *in the presence of air*, methoxyanhydrocryptopine (11) is produced—a typical reaction of 1,2-dihydroisoquinolines. The NMR spectrum (Fig. 1)* is entirely compatible with the proposed structure. It is interesting to note that this compound provides another example[6] where the O—CH_2—O signal is split into a fine quartet. The mode of preparation of γ-methylcryptopine from cryptopine, the formation of an oxime and



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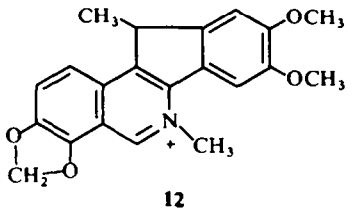

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an O-acetate, considered with the NMR, UV and IR spectra, are all compatible with 8, the structure proposed by Perkin.

* Taken in $CDCl_3$ with internal TMS as standard.

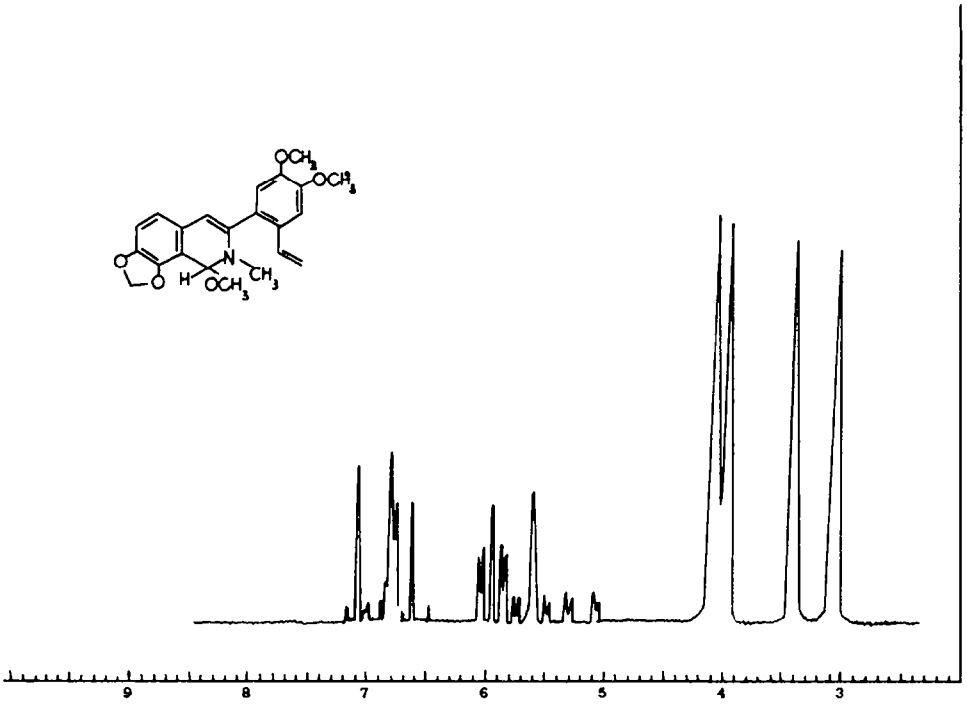
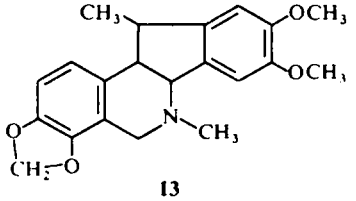


FIG. 1.

We regarded the deeply coloured epicryptopirubin chloride to be the key compound in the epicryptopine series, and we examined it first. Our analytical figures agree better with $C_{21}H_{20}NO_4Cl$, than the $C_{21}H_{22}NO_4Cl$ computed by Perkin. The UV spectrum of the salt is similar to the spectra of 3-arylisoquinolinium salts examined by us, and the NMR spectrum* is diagnostic for structure **13** (Fig. 2). The CH_3—CH< group absorbs as an AX_3 system with a three proton doublet centered at 1·8 ppm, (J = 7·5 c/s) and a one proton quartet centred at 4·4 ppm. The two hydrogens on ring A absorb as a two proton singlet at 7·9 ppm and the aromatic hydrogens on ring D absorb as two, one proton singlets at 7·4 and 7·7 ppm. The one proton singlet at 9·2 ppm is typical of the C_1 hydrogen of isoquinolinium salts. Reduction of epicryptopirubin chloride with $NaBH_4$ yields the 1,2,3,4-tetrahydroisoquinoline (**13**) whereas use of LAH produces the unstable 1,2-dihydroisoquinoline (**14**); treatment of the latter with HCl caused disproportionation to **12** and **13**, a characteristic reaction of 1,2-dihydroisoquinolines. The structure **14** was originally allocated



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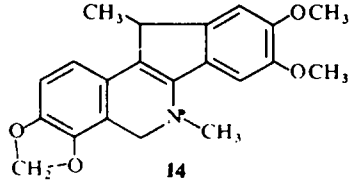

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* Taken in CF_3CO_2H.

by Perkin to isoanhydrocryptopine, another transformation product of anhydrocryptopine, the chemistry of which will be described in a subsequent paper in this series. The product of interaction of epicryptopirubin chloride and alkali is the straightforward pseudobase, and not a dimer as originally suggested, although the colour changes described by Perkin are unusual. Perkin's original analysis fits the pseudobase structure. We have not been able to isolate a red salt, m.p. 150–155° described by Perkin as dehydroepicryptopirubin chloride; in our hands treatment of the pseudobase with HCl regenerated epicryptopirubin chloride.

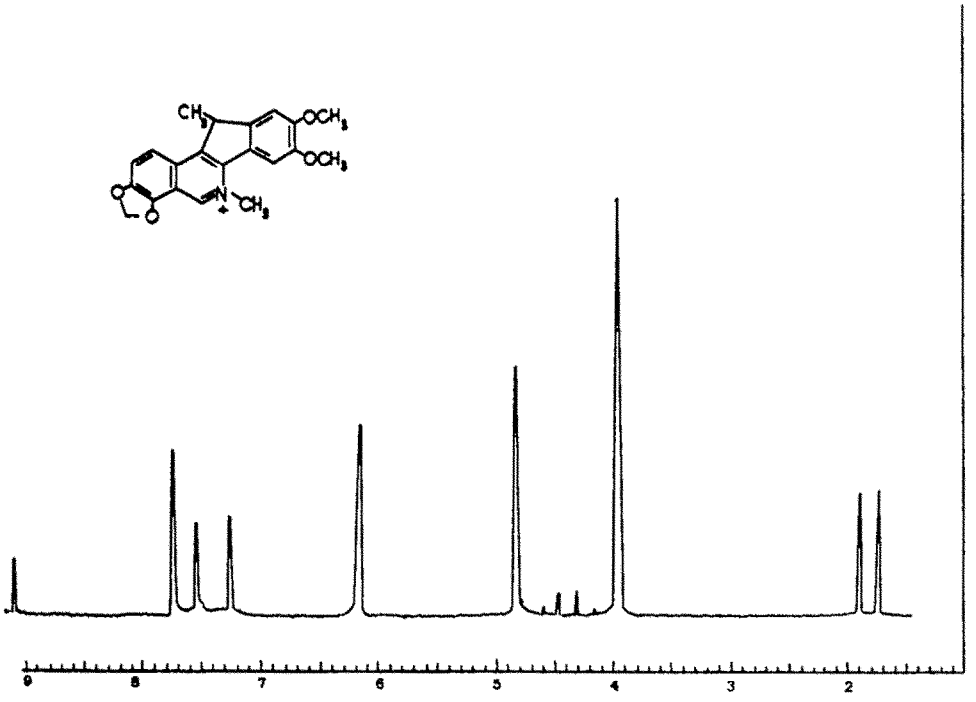


FIG. 2.

Whilst the vinyl grouping in anhydrocryptopine (3) and in γ-methylcryptopine (8) are readily detectable in their NMR spectra, it is obviously absent from the spectra of the epicryptopines A, B and C. The UV spectrum of epicryptopine A suggests a conjugated system whereas the spectra of the isomers B and C are benzenoid. The IR spectrum of epicryptopine A exhibits a band at 3333 cm^{-1} (>NH) and a medium intensity band at 1665 cm^{-1}, which is attributed to a ketone carbonyl group, although all attempts to reduce it failed. (The CO group of cryptopine itself absorbs in the IR to produce a medium intensity band at 1665 cm^{-1}). The IR spectra of the epicryptopines B and C, which are superimposable, are devoid of bands in the —OH, >NH and >C=O regions. The study of epicryptopine A was complicated by the observation that its IR spectrum, in $CHCl_3$ solution changed with time.

The presence of an >NH group in epicryptopine A is supported by the presence of

a one proton singlet at 1·6 ppm in its NMR spectrum (Fig. 3) which disappears when the sample is shaken with D_2O. In the acetate the >NH absorption is no longer apparent in either the IR or NMR spectra; apart from the expected differences due to the presence of an acetate group, these spectra are very similar to the corresponding spectra of epicryptopine A itself, suggesting a close similarity in C—N skeleton between epicryptopine A and the acetate. The UV spectra are indeed identical. A band at 1640 cm^{-1} in the IR of the acetate confirms the presence of an amide grouping as proposed by Perkin, and the identity of the acetates derived from all three epicryptopines was also confirmed by their superimposable IR spectra and their mixed m.ps.

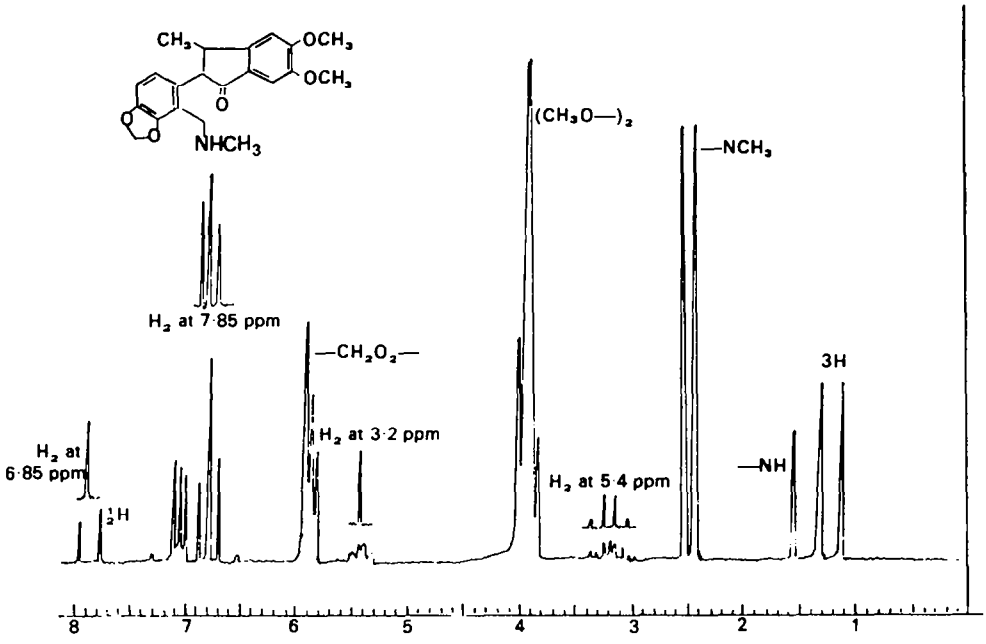
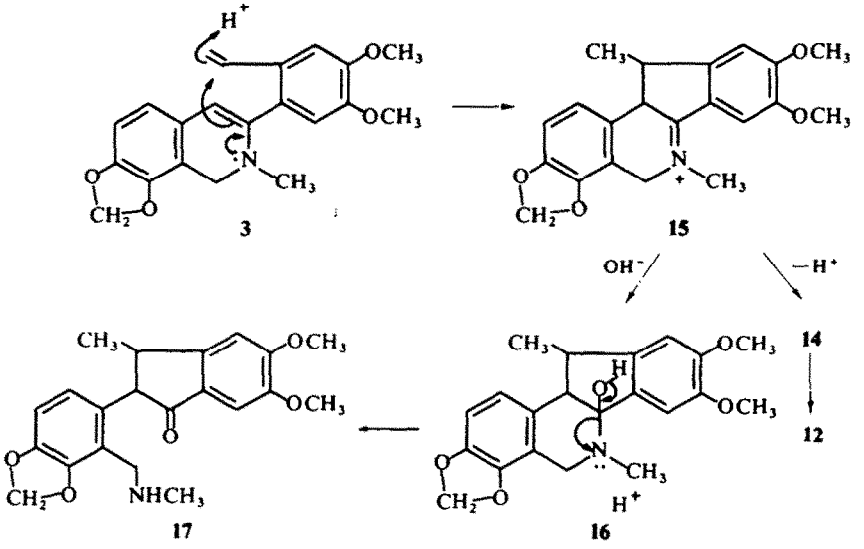


FIG. 3. Solvent $CDCl_3$.

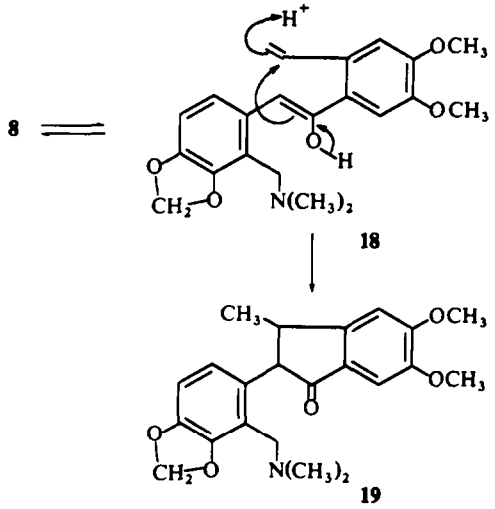
With the structure of epicryptopirubin chloride (**12**) secure, and the presence of an >NH group in epicryptopine A established, the most probable structure for the base is **17**. Its formation from anhydrocryptopine (**3**) is then unexceptional and involves intramolecular electrophilic attack by the vinyl group at C_4 of the enamine **3** to yield the imminium salt **15**; nucleophilic addition of hydroxide ion to this produces the pseudobase **16**, which is hydrolysed under the prevailing acid conditions to the amino-ketone **17**. The salt **15** may alternatively lose a proton from C_4 to form the 1,2-dihydroisoquinoline (**14**), and disproportionation or aerial oxidation of this would account for the formation of epicryptopirubin chloride. Epicryptopines B and C are now regarded as being the isomeric pseudobases (**16**), and the interconversions of all three isomers described by Perkin are simply tautomeric changes. In our experience, the OH group of pseudobases seldom absorbs in the IR region of the spectrum.



We have been able to show that epicryptopine A is converted into epicryptopirubin chloride (**12**; 70% yield) by HCl, as well as by the original reagent $POCl_3$, and since epicryptopine C is converted into the A isomer by HCl, it is not surprising that no epicryptopine C can be isolated from the interaction of anhydrocryptopine and HCl. We have further shown that epicryptopine B, but not epicryptopine C, is converted into **12** by $POCl_3$, and this difference in reactivity is probably due to the steric hindrance to phosphate ester formation in the case of the OH group of epicryptopine C. The formation of the same N-acetate from all three isomers, its ready formation from epicryptopine A, and its structural similarity with the A-isomer are all readily explicable in terms of structures **16** and **17**.

The NMR spectrum of epicryptopine A (**17**) in $CDCl_3$ at 60 Mc/s exhibits two singlets at 1·0 and 1·30 ppm (downfield from internal TMS) in freshly prepared solutions, but a distorted quartet at 0·85, 1·1, 1·3 and 1·5 ppm in others. The apparent instability of the compound in chloroform solution has already been noted. When the NMR spectrum of a freshly prepared solution of epicryptopine A in $CDCl_3$ was measured at 100 Mc/s (Fig. 3), the presence of a $CH_3—\overset{|}{C}H—CH<$ grouping is suggested from the absorption at 1·3, 3·2 and 5·4 ppm.

The IR spectrum of epimethylcryptopine A exhibited a band at 1660 cm^{-1} ($>C=O$) but, as expected, there was no absorption attributable to —OH or $>NH$ groups. The IR spectra of epicryptopine A methiodide and epimethylcryptopine A methiodide were identical so that epimethylcryptopine A must be **19**; its formation from γ-methylcryptopine (**8**) proceeds presumably through the enol **18**. We have been unable to isolate a compound described by Perkin as epimethylcryptopine B, and indeed, on the formulation **19** such a compound should not exist. The non-existence of a third isomer, and of an epicryptopirubin type salt is readily understood. Structure **19** is also in accord with Perkin's inability to prepare a nitroso or N-acetyl derivative.



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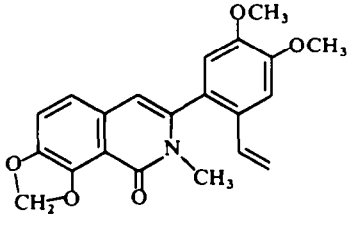
19

The main product from the action of conc HCl upon γ-methylcryptopine is a compound named by Perkin isoepimethylcryptopine and allocated structure **19** by him. However no CO absorption could be detected in its IR spectrum; the chemistry of this compound is still being examined by us.

Oxidation of anhydrocryptopine (**3**) with potassium permanganate yields the weakly basic ketoanhydrocryptopine, $C_{21}H_{19}NO_5$, considered by Perkin to be the isocarbostyril (**20**). Better yields are obtained by treating methoxyanhydrocryptopine (**11**) with alkali. The UV, IR and especially the NMR spectra are all compatible with structure **20**. Perkin found that when **20** was reacted with $POCl_3$ a scarlet salt, named ketoisoepicryptopirubin hydrochloride, was produced; this was allotted structure **21** and was easily hydrolysed by water to a weakly basic substance, $C_{21}H_{19}NO_5$, m.p. 235–240°, for which no structural proposal was made. Like ketoanhydrocryptopine (**20**) itself, this compound dissolved in conc HCl to form a deeply coloured solution, whose UV spectrum is almost identical with that of epicryptopirubin chloride.

The NMR spectrum of ketoisoepicryptopirubin hydrochloride is identical with that of epicryptopirubin chloride (**12**) except that the C_1 proton absorption at 9·2 ppm has been replaced by a broad 1 proton singlet at 2·0 ppm. Structure **21** should thus be replaced by **22**. The hydrolysis product is then expressed by structure **23**, a formulation that is strongly supported by the fact that reduction of it with LAH, followed by $NaBH_4$, gave **13**, (presumably via **14**), identical with the compound derived from epicryptopirubin chloride (**12**).



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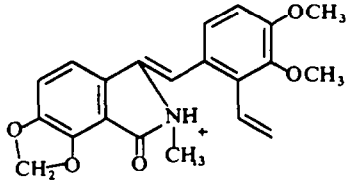

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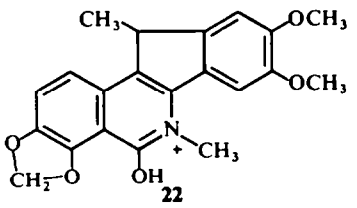

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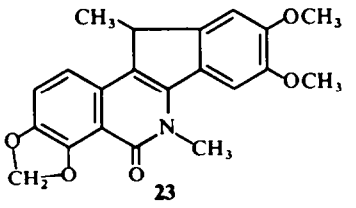

23

EXPERIMENTAL

M.p's are uncorrected.

Anhydrocryptopine (3)

Cryptopine (14·0 g) was converted to isocryptopine chloride[4] (13·5 g) which on treatment with methanolic KOH[4] yielded 3 (12·0 g), m.p. 108–110°, (lit.[4] m.p. 110–111°), ν_{max} (nujol) 1620, 1605 and 1570 cm^{-1}; λ_{max} (EtOH) (ε) mμ 259 (21,200), 315–350 (12,100); NMR ($CDCl_3$) ppm 2·4 (3H, s), 3·85 (3H, s), 3·95 (3H, s), 4·45 (2H, s), 5·3 (1H, s), 5·9 (2H, s), 6·45 (2H, AB 8 c/s), 6·9 (1H, s), 7·4 (1H, s); vinyl group; 5·0, 5·2, 5·4, 5·7 (2H, dd), 6·8, 6·9, 7·1, 7·2 (1H, ss), J_{AM} = 1·5 c/s, J_{AX} = 18 c/s, J_{MX} = 11 c/s.*†

Epicryptopirubin chloride (12)

(i) Epicryptopine A (0·4 g) was converted (Ref. 4, p. 1014) to 12 (0·3 g), m.p. 221–223°, (lit.[4] m.p. 220–223°), ν_{max} (nujol) 1640, 1605, 1570, 1530 cm^{-1}; λ_{max} (EtOH), (ε) mμ 242 (32,000), 274 (sh) (14,600), 368 (21,000); λ_{min} 313 (3,800); NMR (CF_3COOH) ppm 1·8 (3H, d, 7·5 c/s), 3·95 (6H, s), 4·4 (1H, qu, 7·5 c/s), 4·85 (3H, s), 6·2 (2H, s), 7·4 (1H, s), 7·7 (1H, s), 7·9 (2H, s), 9·2 (1H, s). (Found: C, 65·2; H, 5·3; Cl, 8·9. $C_{21}H_{20}NO_4Cl$ requires: C, 65·3; H, 5·2; Cl, 9·2%).

(ii) Epicryptopine B (50 mg) was dissolved in $POCl_3$ (0·5 ml) and heated on a steam bath for 20 min. On cooling, ice was added to the reaction mixture and the resulting soln heated a further 1½ hr. The cooled soln deposited 12 (31 mg) m.p. 220–223°, over two days.

(iii) The scarlet aqueous filtrate* obtained in the preparation of epicryptopine A[4] on standing for 2 weeks deposited 12 (0·2 g) which on recrystallization from dil HCl acid gave (0·17 g), m.p. 221–223°.

(iv) Compound 3 (0·5 g) was heated in $POCl_3$ (2 ml) on a steam bath for 1½ hr. The pale yellow soln was cooled, treated with pet. ether (b.p. 60–80°; 20 ml) and the solvent layer decanted. The residue was dissolved in hot water and on cooling a dark material was deposited. The aqueous layer was decanted and the residue triturated with acetone. The insoluble red salt was collected and on crystallization from dil HCl acid yielded 12 (0·07 g), m.p. 220–223°.

(v) Epicryptopine A (0·25 g) was treated with 3% HCl (20 ml) and the resulting suspension of the hydrochloride heated at 100° for 28 hr while air was passed through it. At the end of this time the clear dichromate coloured soln was cooled and 12 (0·23 g) m.p. 219–222° crystallized.

The 12 obtained by methods (ii), (iii), (iv) and (v) did not depress the m.p. of the material obtained by method (i). The IR spectra of all these materials were superimposable upon each other.

Epicryptopines A (17), *B* (16), were prepared from 3 once according to the method of Perkin (Ref.,[4] p. 1008), in subsequent preparations the following procedure was employed. A soln of 3 (2·0 g) in conc HCl (10 ml) was boiled in a test tube for 45 sec, the resulting permanganate coloured soln was diluted with water (20 ml) and the soln allowed to stand overnight when the solid material (1·6 g) which had separated was collected and the scarlet aqueous filtrate† retained. The mixture of hydrochlorides of 17 and 16 was triturated with 4% HCl (50 ml) and the mixture heated on a steam bath for 60 min. The solid material was filtered off, dissolved in a large volume of water, basified with ammonia and the ppt filtered off and recrystallized from benzene.

Compound 17 (0·8 g) m.p. 206–208° was obtained as a chalky powder, concentration of the mother liquor yielded a further crop (0·3 g), m.p. 196–198°. Repeated recrystallizations from benzene gave 17, m.p. 210–212° (lit.[4] 210–212°), ν_{max} (nujol), 3333, 1665, 1615 cm^{-1}; λ_{max} (EtOH) (ε) mμ, 287 (9,300), 333

* See below.

S = singlet; d = doublet; qu = quartet; m = multiplet; sh = shoulder.

† See above.

(12,500), 350 (13,000), 366 (7,500); λ_{min} 265 (5,400), 307 (6,500). (Found: C, 68·5; H, 6·35; N, 3·75; OCH_3, 16·8. Calc. for $C_{21}H_{23}NO_5$: C, 68·3; H, 6·2; N, 3·8; OCH_3, 17·4%.)

Epicryptopine B. Compound **17** (1·0 g) was heated under reflux in MeOH for 3 hr, when the MeOH was evaporated. The residue was extrated with ether. The ethereal extracts were dried and evaporated leaving **16** (0·8 g).

Epicryptopine C. Compound **17** (1·2 g) was treated with dil AcOH (Ref.[4], p. 1003) giving epicryptopine C (0·8 g) m.p. 165–167° (lit.[4], 164–166°). The spectral characteristics of B and C are identical. ν_{max} (nujol) 1605 cm^{-1}; λ_{max} (EtOH) (ε) mμ, 235 (s) (15,700), 288 (10,900); λ_{min} 257 (2,400).

Epicryptopine A acetate (**17a**). The acetates of **17** and **16** were prepared (Ref.[4], p. 1010, 1012, 1014) and found to have identical spectral characteristics. ν_{max} (nujol) 1665, 1640, 1610 cm^{-1}; λ_{max} (EtOH) (ε) mμ, 290, 338, 355, 365; λ_{min} 265, 307; NMR $CDCl_3$ ppm 1·1 and 1·3 (3H broad s), 2·1 (3H, s), 2·8 and 2·85 (3H, s), 3·95 (6H, m), 4·8 (2H, s), 5·3 (1H, m), 6·0 (2H, s), 6·5–7·3 (3½H, m), 7·85 (½H, d, 8 c/s). (Found: C, 66·9; H, 6·05; N, 3·4. Calc. for $C_{23}H_{25}NO_6$: C, 67·1; H, 6·1; N, 3·4%.)

Epimethylcryptopine A (**19**). Cryptopine methosulphate (10·7 g), m.p. 236–238°, was prepared from **1** (10·0 g) (Ref.[4], p. 880) (lit.[4], 236–238°).

γ-Methylcryptopine (**8**) (4·0 g) m.p. 109–110°, was prepared from cryptopine methosulphate (10·7 g) (Ref.[4], p. 960) (lit.[4], 110°). ν_{max} (nujol), 1680, 1600, 1560 cm^{-1}; λ_{max} (EtOH) (ε) mμ, 235 (22,400), 290 (11,200); λ_{min} 268 (7,000). NMR $CDCl_3$, ppm., 2·1 (6H, s), 3·3 (2H, s), 3·85 (3H, s), 3·95 (3H, s), 4·3 (2H, s), 5·9 (2H, s), 6·65 (2H, s), 7·0 (1H, s), 7·3 (1H, s). Vinyl group: 5·1, 5·3, 5·4, 5·7 (2H, d), 7·0, 7·2, 7·35, 7·55 (1H, s), J_{AM} = 1·5 c/s, J_{AX} = 18 c/s, J_{MX} = 12 c/s.

Epimethylcryptopine A (**19**) (0·2 g), m.p. 221–222°, was prepared from **8** (4·0 g) (Ref.[4], p. 1020) (lit.[4], 222–223°); ν_{max} (nujol), 1660, 1610 cm^{-1}; λ_{max} (EtOH), (ε) mμ, 290 (10,200), 333 (12,300), 350 (13,800), 368 (sh, 8,200); λ_{min} 265 (6,400), 308 (7,900).

Reductions of epicryptopirubin chloride

Tetrahydroepicryptopirubin (**13**). Compound **12** (0·2 g) was dissolved in 30% aqueous EtOH (15 ml) and treated with $NaBH_4$ (0·2 g) and the mixture heated on a steam bath for 45 min. The reaction mixture was poured into water (100 ml) and extracted with ether. Evaporation of the solvent left a colourless oil which dissolved in a small volume of EtOH and soon crystallized as colourless needles, (0·12 g), m.p. 158–159°; ν_{max} (nujol) 1615 cm^{-1}; λ_{max} (EtOH) (ε) mμ, 238 (11,400, 288 (6500); λ_{min} 260 (1,000); NMR ($CDCl_3$) ppm, 1·4 (3H, d, 7·5 c/s), 2·4 (3H, s), 3·9 (6H, s), 2·8–3·8 (3H, m), 3·3, 3·5, 3·8 and 4·0 (CH_2N, AB, 16 c/s), 5·8 (O—CH_2—O, AB, 1·5 c/s), 6·8 (2H s), 6·85 (1H, s), 7·0 (1H, s). (Found: C, 71·25; H, 6·5; N, 4·1. $C_{21}H_{23}NO_4$ requires: C, 71·35; H, 6·55; N, 3·95%.).

Dihydroepicryptopirubin (**14**). Very finely ground **12** (0·6 g) was added portionwise to a stirred mixture of LAH (0·5 g) and ether (100 ml). A green/blue fluorescence rapidly developed and stirring was continued until no more red solid remained. The excess hydride was decomposed with water and the dried ethereal layer on evaporation gave **14** (0·4 g) as a pale green solid which rapidly become red on exposure to air, λ_{max} (EtOH). 360 mμ; NMR $CDCl_3$ ppm, 1·4 (3H, d, 7·5 c/s), 3·0 (3H, s), 3·5 (1H, q, 7·5 c/s), 3·95 (6H, s), 4·2 (2H, broad s), 5·8 (2H, s), 6·5 and 6·9 (2H, AB, 8 c/s), 7·5 (1H, s), 7·6 (1H, s).

Disproportionation reaction of dihydroepicryptopirubin (**14**). The base **14** (0·4 g) was dissolved in conc HCl (2 ml) and the soln boiled for 45 sec. The dark red soln so produced was diluted with water (10 ml) when a buff coloured hydrochloride salt crystallized. This was collected and converted to the free base and recrystallized from EtOH when colourless needles of tetrahydroepicryptopirubin, m.p. 158°, were obtained, identical (mixed m.p. and IR) with the $NaBH_4$ reduction product of **12**. The aqueous layer from which the hydrochloride was filtered gradually deposited a red solid (0·2 g), m.p. 208–212°, which on recrystallization from dil HCl gave **12** (0·15 g), m.p. 219–222°.

Dehydroepicryptopirubin hydroxide. This quaternary salt was obtained (Ref.[4], p. 1016) from **12** in high yield as black crystals m.p. 215–220° (indistinct). Treatment of the hydroxide with a few drops of conc HCl regenerated quantitatively **12**, m.p. 220–223°.

Ketoanhydrocryptopine (**20**). (i) Compound **3** (2·0 g) was oxidized using $KMnO_4$ (Ref.[4], p. 994) to **20** (0·15 g), m.p. 162–163°. Subsequent preparations were carried out by (ii).

Methoxyanhydrocryptopine (**11**). Compound **3** (2·5 g) was dissolved in MeOH and allowed to stand in an open beaker for 2 days. On scratching the wall of the beaker **11** (2·0 g) separated as pale yellow needles, m.p. 186–188° (lit.[4], 186–188°). λ_{max} (EtOH) mμ 260 (strong), 320 (medium); λ_{min} 300; NMR ($CDCl_3$) ppm, 2·95 (3H, s), 3·3 (3H, s), 3·9 (3H, s), 4·0 (3H, s), 5·6 (1H, s), 6·0 (1H, s), 5·9 and 6·05 (2H, AB, 1·5 c/s), 6·6

and 6·8 (2H, AB, 8 c/s), 6·75 (1H, s), 7·15 (1H, s). Vinyl group 5·05, 5·2, 5·45 and 5·75 (2H, d), 6·7–7·3 (1H, obscured by aromatics).

Ketoanhydrocryptopine (**20**). Compound **11** (2·0 g) was heated under reflux with 25% 50/50 ethanolic KOH aq (50 ml) for 2 hr. The resulting black soln was poured into 3N HCl (150 ml) and extracted with a large volume ether. Evaporation of the ethereal extracts gave a brown material (0·65 g) which on recrystallization from MeOH yielded the desired product (0·6 g) as stout yellow needles, m.p. 162–163°), identical (mixed m.p. and IR spectrum) with that obtained directly by oxidation of **3**, ν_{max} (nujol), 1660, 1640, 1610 cm^{-1}. λ_{max} (EtOH), mμ, 255 (sh medium), 296 (medium), 306 (medium), 358, 363, 380 (weak). NMR ($CDCl_3$) ppm, 3·1 (3H, s), 3·75 (3H, s), 3·85 (3H, s), 6·0 (2H, s), 6·1 (1H, s), 6·55 (1H, s), 6·90 (1H, s), 6·7 and 6·9 (2H, AB, 8 c/s). Vinyl group; 4·85, 5·05, 5·25, 5·55 (2H, d), 6·1, 6·25, 6·35, 6·5 (1H, s), J_{AM} = 1·3 c/s, J_{AX} = 17 c/s, J_{MX} = 10 c/s.

Ketoisoepicryptopirubin Hydrochloride (**22**). Compound **20** (0·4 g) was treated with $POCl_3$ (0·8 ml) (Ref.[4], p. 1017) to give **22** (0·4 g), m.p. 136–140°, ν_{max} (nujol) 3500–2100, 1620, 1605, 1570, 1550 cm^{-1}; λ_{max} (EtOH) (ε) (mμ) 250 (30,000), 290 (sh) (7,000), 305 (sh) (6,000), 368 (21,000); λ_{min} 323 (3,200); NMR (CF_3COOH) ppm, 1·7 (3H, d, 7 c/s), 2·0 (1H, broad s), 3·95 (6H, s), 4·35 (1H, q, 7 c/s), 4·8 (3H, s), 6·2 (2H, s), 7·3 (1H, s), 7·5 (1H, s), 7·65 (2H, s). (Found: C, 63·2; H, 4·9. $C_{21}H_{20}NO_5Cl$ requires: C, 62·8; H, 4·9%.)

Ketoisoepicryptopirubin Base (**23**). The amide **23** (0·15 g), was obtained (Ref.[1], p. 1018) from **22** (0·30 g) as pale brown prisms, m.p. 234–238° (lit.[4], 235–240°); ν_{max} (nujol) 1650, 1625, 1610, 1585, 1570 cm^{-1}; λ_{max} (EtOH) mμ 260 (sh), 350, 385. (Found: C, 69·1; H, 5·3; N, 4·0; $C_{21}H_{19}NO_5$ requires: C, 69·1; H, 5·2; N, 3·9%.)

Reduction of **23**. The amide **23** (50 mg) was added to a slurry of LAH (100 mg) in ether (150 ml) and heated under reflux with stirring for 4 hr. The ethereal soln had a green fluorescence and a soln of a few drops in EtOH had a UV spectrum (λ_{max} 360 mμ) identical with that of **14**. Excess hydride was decomposed with water and the ethereal layer separated and evaporated under reduced press. The residue was immediately treated with 20% aqueous EtOH (5 ml) containing $NaBH_4$ (50 mg) and the mixture heated on a steam bath for 30 min. The reaction mixture was diluted with water (20 ml) and extracted with ether (4 × 50 ml). The combined extracts were dried and evaporated leaving a small amount of a brown oil which on dissolving in a small volume of hot EtOH and cooling yielded **13** (15 mg) as colourless needles m.p. 153–156°, the m.p. was undepressed on mixture with **13** prepared by $NaBH_4$ reduction of **12**.

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