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THE CHEMISTRY OF CRYPTOPINE—II

PSEUDOCRYPTOPINE CHLORIDE[1]

S. F. DYKE and D. W. BROWN

School of Chemistry and Chemical Engineering, Bath University of Technology, Claverton Down, Bath, Somerset, England

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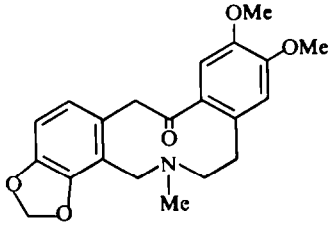
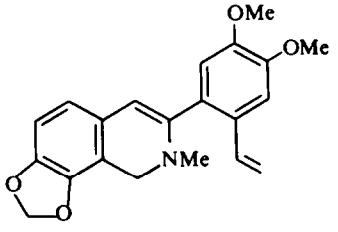
Abstract—The structure **4**, originally suggested by W. H. Perkin, for pseudocryptopine chloride, has been corrected to **13**.

IN A VERY thorough investigation, Perkin[2] elucidated the structure of the opium alkaloid cryptopine (**1**). During the course of this work it was found that anhydrocryptopine (**2**), which is readily obtainable from **1** by the successive treatment with $POCl_3$ and KOH, when treated with conc HCl is transformed into a mixture of epicryptopines A and B and epicryptopirubin chloride (**3**). The correct structures of these products were recently established.[3]



1



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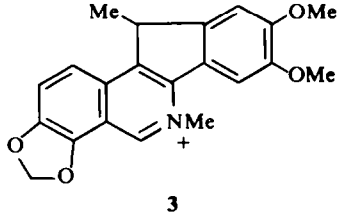

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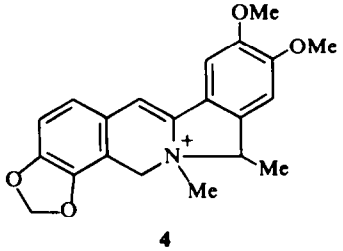
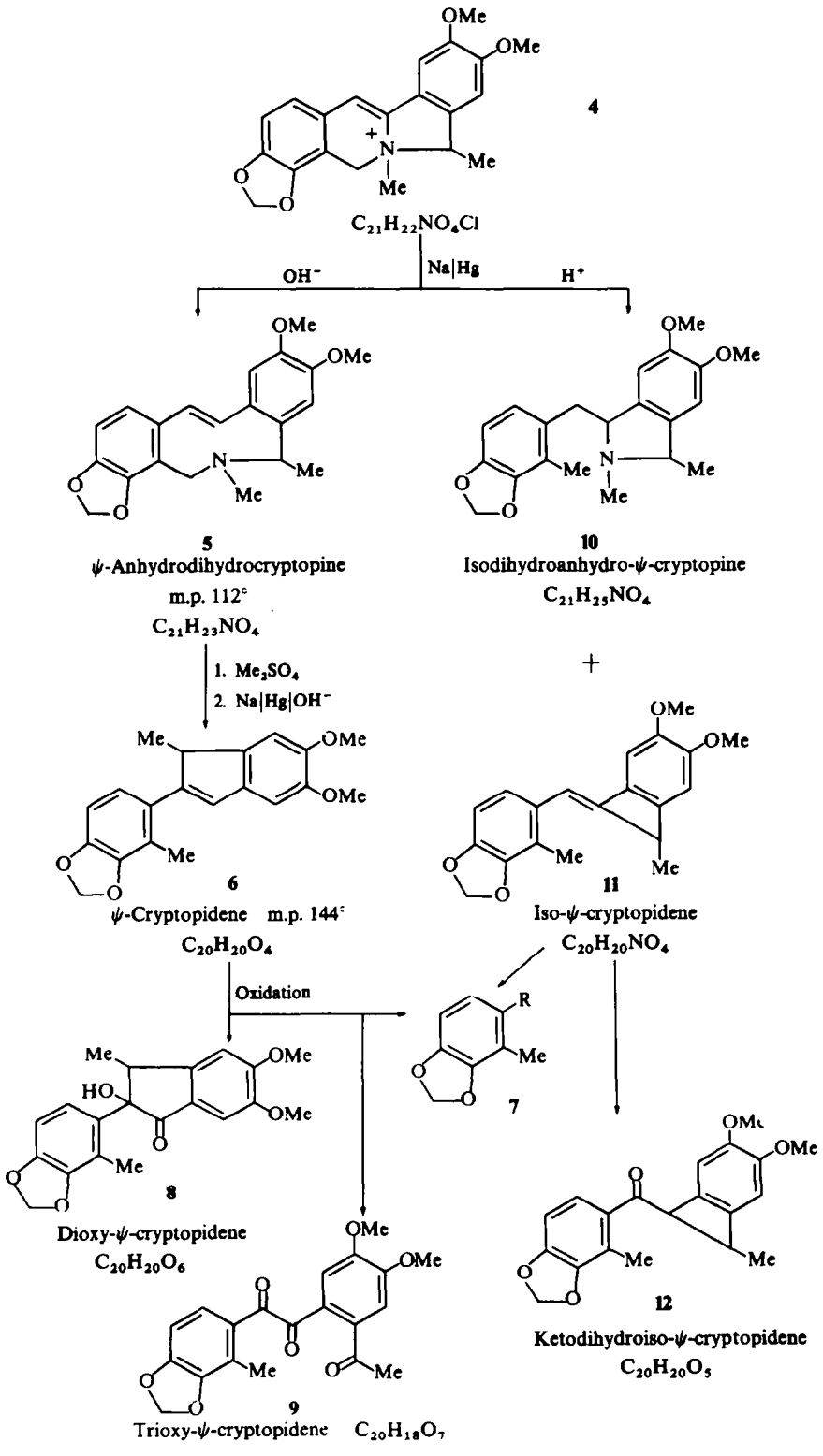


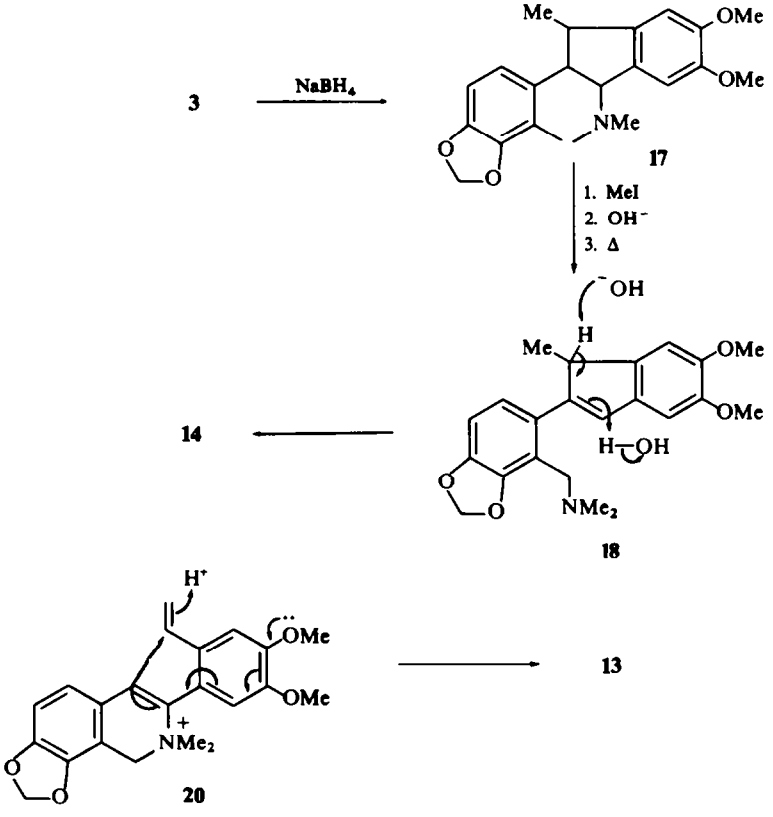
4

Perkin found that when the methosulphate of anhydrocryptopine (**2**) is reacted with conc HCl a new quaternary salt, pseudocryptopine chloride, is formed. To this he allotted structure **4** on the basis of some degradations involving reductions with sodium amalgam in both acid and alkaline solution. These results, and Perkin's interpretations, are summarized in Chart I. When pseudocryptopine chloride was degraded with sodium amalgam in alkaline solution, a base, pseudoanhydrodihydrocryptopine (**5**) was produced which, on further, similar degradation, yielded the

CHART I


OMe
OMe
Me
Me
4
$C_{21}H_{22}NO_4Cl$
OH^-
Na|Hg
H^+
5
ψ-Anhydrodihydrocryptopine
m.p. 112°
$C_{21}H_{23}NO_4$
10
Isodihydroanhydro-ψ-cryptopine
$C_{21}H_{23}NO_4$
1. Me_2SO_4
2. Na|Hg|OH^-
6
ψ-Cryptopidene m.p. 144°
$C_{20}H_{20}O_4$
11
Iso-ψ-cryptopidene
$C_{20}H_{20}NO_4$
Oxidation
HO
8
Dioxy-ψ-cryptopidene
$C_{20}H_{20}O_6$
R
7
9
Trioxy-ψ-cryptopidene $C_{20}H_{18}O_7$
12
Ketodihydroiso-ψ-cryptopidene
$C_{20}H_{20}O_5$

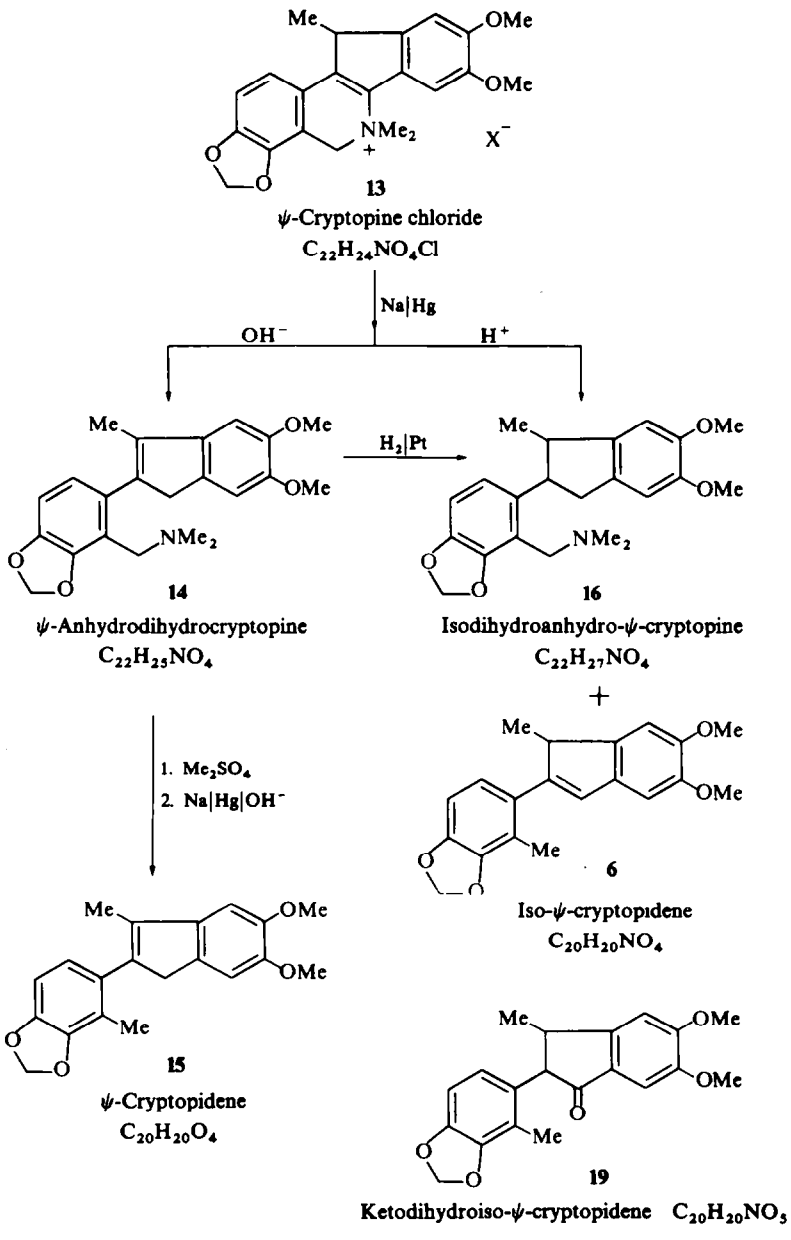
nitrogen free compound pseudocryptopidene (**6**). Oxidation of this substance gave 5,6-methylenedioxy-*o*-toluic acid (**7**, R = CO_2H), together with a dioxypseudocryptopidene and a trioxy derivative which were assigned structures **8** and **9**, respectively. Perkin was intrigued by a N-demethylation which had seemingly occurred in the formation of pseudocryptopine chloride from **2**, but said little about the molecular rearrangement necessary to account for the formation of **6** from **5**. When degradation of pseudocryptopine chloride was conducted in acid solution, Perkin isolated a base, isodihydroanhydropseudocryptopine (**10**), as the major product together with a small amount of isopseudocryptopidene, which was allocated structure **11**. The latter, upon oxidation gave **7** (R = CO_2H), **7** (R = CHO) and a ketodihydroisopseudocryptopidene, believed to be **12**.



We have re-examined these reaction sequences and now wish to propose an entirely different structure for pseudocryptopine chloride, which has the considerable merit that demethylation reactions need no longer be postulated. Our results are summarized in Chart II, with revised molecular formulae deduced from spectroscopic and repeated elemental analytical data. The structure of anhydrocryptopine methosulphate was confirmed by an examination of its NMR spectrum (as an enamine, anhydrocryptopine may be alkylated at either carbon or nitrogen). Our analytical figures for pseudocryptopine perchlorate (**13**) are in close agreement with the formula

$C_{22}H_{24}NO_4 \cdot HClO_4$ rather than $C_{21}H_{20}NO_4 \cdot ClO_4$. The NMR spectrum of pseudocryptopine chloride was not very informative, but that of the degradation product pseudoanhydrodihydrocryptopine (Fig. 1) is diagnostic for structure **14**. In particular the spectral characteristics of the methylindene ring are in close agreement with those reported[4] for 3-methylindene itself. Further degradation to pseudocryptopidene (**15**) is now unexceptional, and the structure **13** for pseudocryptopine

CHART II



chloride follows. The compound **14**, when hydrogenated in the presence of PtO_2 yields a base identical in all respects with isodihydroanhydropseudocryptopine, which must therefore be **16**.

Structure **14** for pseudoanhydrodihydrocryptopine was confirmed by an independent synthesis from epicryptopirubin **3**, which was first reduced with $NaBH_4$ to the expected tetrahydro base **17**. Hofmann degradation of **17** gave **14**, presumably via **18**, which isomerizes under the basic conditions employed. We believe that isopseudocryptopidene has structure **6**, the structure originally proposed by Perkin for pseudocryptopidene. We now consider that **18** is the initial product formed from pseudocryptopine chloride when it is treated with sodium amalgam in acid or alkaline solution. Whereas in acid solution further reduction of **18** to form **16** predominates, with some further degradation to **6**, in alkaline solution isomerization of **18** to **14** occurs, and this is resistant to further reduction. We believe that degradation of pseudocryptopine chloride precedes reduction since we have been unable to degrade the methiodide of **17** with sodium amalgam.

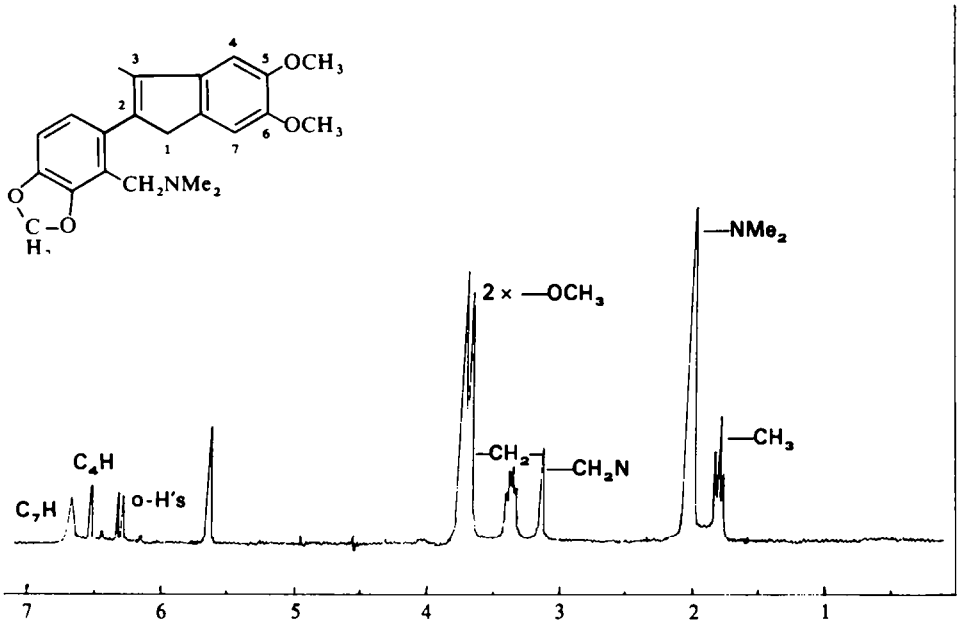


FIG. I

The oxidation fragments described by Perkin are easily accounted for on the revised structures presented in Chart II, with the exception of ketodihydroisopseudocryptopidene for which **19** is a better expression.

Whereas the formation of **3** from **2** can be formulated as a typical enamine reaction, the cyclization of the quaternary salt of **2** to pseudocryptopine chloride (**13**) is most easily rationalised as shown in **20**.

In a preliminary communication[5] we also corrected the structures of the hydroxyisoanhydrodihydrocryptopines and it is very pleasing to see this structure confirmed very recently[6] from a study of the analogous reactions of protopine.

EXPERIMENTAL

All m.ps are uncorrected. UV spectra were determined as EtOH solns and IR spectra as Nujol mulls. NMR spectra were determined at 60 MHz and chemical shift values quoted as ppm downfield from TMS as internal standard.

Anhydrocryptopine (**2**) *methosulphate*

Anhydrocryptopine[2,3] (10·0 g) was converted by the prescribed method[2a] to its methosulphate (10·5 g), m.p. 235–238° (Lit.[2a] m.p. 237–238°). ν_{max} cm^{-1}, 1600, 1570, 1510, λ_{max} (ε) nm, 275, 320; NMR (CD_3SOCD_3): 3·85 s [3H]; 3·90 s [3]; (2 × OMe); 5·1 s [1] (—CH=C<); 5·2, 5·4, 5·75, 6·0 broad singlets [2H] (=CH_2), 6·7–7·3 complex [1] (—CH = CN_2); 6·9 s [1], 7·3 s [1] (p-H's); 7·1 s [2H] (o-H's). (Found: C, 58·0; H, 5·9; NMe, 11·7; OMe, 21·2. Calc. for $C_{23}H_{27}NO_8S$: C, 57·8; H, 5·7; NMe, 12·1; OMe, 19·5%).

Pseudocryptopine perchlorate (13)

Pseudocryptopine chloride (2·5 g) was obtained from the above methosulphate (5·0 g) as a brown crystalline solid of variable m.p. The perchlorate crystallized from a large volume of EtOH as colourless plates m.p. 292°. (Found: C, 57·0; H, 5·2; N, 3·0; Cl, 7·45. $C_{22}H_{24}NClO_8$ requires: C, 56·85; H, 5·2; N, 3·0; Cl, 7·4%).

Pseudoanydrodihydrocryptopine (**14**)

(i) Pseudocryptopine chloride (**13**) (2·0 g) was reduced in alkaline soln with NaHg (100 g, 2%) as described.[2a] The reaction mixture was decanted from the metallic layer and extracted with ether. The ethereal layer was extracted with 2N HCl, the aqueous layer separated, basified with ammonia and the basic material again extracted with ether. The residue obtained on evaporation of the dried ethereal extracts was leeched with successive portions of pet. ether (60–80°) leaving a small brown residue. Evaporation of the pet. ether left a colourless oily residue (0·5 g) which showed only one spot on TLC. Methosulphate m.p. 175–177° (Lit.[2a] 175–180°), methiodide m.p. 198–201° (Lit.[2a] 197–200°). On standing under a 1:5:10 MeOH, ether, pet. ether soln for some days colourless blades of **14** m.p. 112° (Lit.[2c] 112°) were produced, ν_{max} cm^{-1} 1605, 1590 (equal intensities). λ_{max} (ε) nm 235(s), 305(m); NMR ($CHCl_3$) 1·85 tr, J = 2Hz [3H] (CH_3—C=); 2·0 s [6H] (N—Me_2); 3·1 s [2H] (—CH_2N—); 3·4 broadened q, J = 2Hz [2H] (—CH_2—C=); 3·7 and 3·75 two singlets [6H] (2 × OMe); 5·65 s [2H] (—OCH_2O—); 6·2, 6·3, 6·35, 6·45 q [2H] (o-H's); 6·5 s [1H] C_4H; 6·65 broadened s [1H] (C_7H). (Found: C, 71·5; H, 6·5 $C_{22}H_{25}NO_4$ requires: C, 71·9; H, 6·8%), methiodide, (Found: C, 53·9; H, 5·7; $C_{23}H_{28}NO_4I$ requires: C, 54·3; H, 5·55%).

(ii) Tetrahydroepicryptopirubin[3] **17** (0·2 g) was dissolved in ether (30 ml) and MeI (0·5 ml) added. The soln was kept at RT for two days during which time **17** methiodide separated as a buff powder. Recrystallization from EtOH gave pale yellow microcrystals (0·15 g) m.p. 231–233°. (Found: C, 53·1; H, 5·25; N, 3·0; $C_{22}H_{26}NO_4I$ requires: C, 53·35; H, 5·29; N, 2·83%).

17 Methiodide (0·2 g) was dissolved in 25% methanolic KOH and the soln heated under reflux for 2½ hr. The resulting soln was poured into water (150 ml) and the basic product extracted into ether. Evaporation of the dried ethereal layer gave a brown oil (0·08 g) which could not be induced to crystalize; Methiodide m.p. 196–198°, methosulphate m.p. 173–176°. The m.ps of both salts were undepressed on mixture with those obtained by method (i), and the IR spectra of the two methiodides and methosulphates are superimposable.

Isodihydroanhydropseudocryptopine (**16**)

(i) This was prepared from **2** methosulphate (2·0 g), by the method of Perkin,[2] as a colourless oil (0·8 g), picrate m.p. 195–197° (Lit.[2a] 196–197°), ν_{max} cm^{-1}, 1605, λ_{max} (ε) nm 208 (s), 242 (shoulder), (11,000), 295 (7,500); NMR (CCl_4) indicated that two epimers are present in almost exactly equal amounts; their spectra differ only in the CH_3—CH< absorption region. Thus one epimer exhibited: 0·75 d, J = 7·5 Hz [3H] (CH_3CH<); 2·2 s [6H] (NMe_2); 2·3 s [2H] (CH_2N); 3·75 s [6H] (2 × OMe); 5·9 s [2H] (CH_2O_2); 6·6–6·8 complex [4H] (aromatic H's); 2·9–4·2 complex [4H]. The second epimer has 1·2 d, J = 7·0 Hz [3H] (CH_3—CH<) and the remainder of the spectrum is exactly similar to the above.

(ii) **14** (0·2 g) was dissolved in glacial AcOH (10 ml) and shaken in the presence of PtO_2 (0·03 g) under H_2 for 2 hr at atm. press. The suspension was then filtered, diluted with water (50 ml) and the soln made alkaline with ammonia. The free base was extracted into ether and the dried ethereal extracts evaporated

to yield a white oil (0·2 g), the IR spectrum of which is identical with the base obtained by method (i). A small amount of the picrate m.p. 194–196° was obtained, the m.p. of which was undepressed when mixed with the picrate obtained by method (i).

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