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SOME ACID CATALYSED REARRANGEMENTS OF ANHYDROCRYPTOPINE

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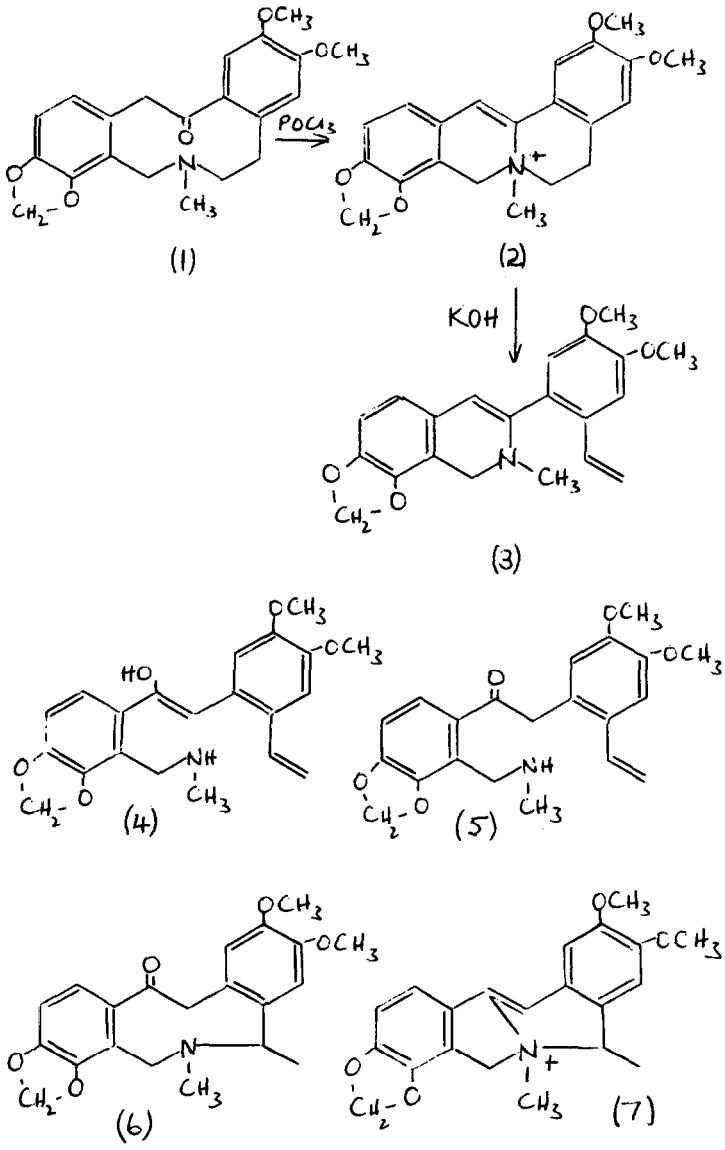
When the opium alkaloid cryptopine (1) is treated[1] with phosphorus oxychloride, ring-closure occurs to yield (2), which is transformed by potassium hydroxide into anhydrocryptopine (3), $C_{21}H_{21}NO_4$. In the course of Perkin's classical studies[1] on cryptopine he described the reactions of anhydrocryptopine with both concentrated and dilute hydrochloric acids. Prompted by our interest in the chemistry of 1,2-dihydroisoquinolines[2] we decided to re-investigate these reactions.

After boiling anhydrocryptopine (3) with conc. HCl for 45 seconds Perkin isolated three bases, which he named epicryptopines A, B and C, $C_{21}H_{23}NO_5$, and for which he proposed the structures (4), (5), and (6), respectively. No structure was suggested for a fourth, red compound "dehydroepicryptopirubin chloride", $C_{21}H_{20}NO_4Cl$ m.p. 150-155°. Perkin reported that epicryptopine A easily gave an N acetate, and that epicryptopine C formed, with difficulty, the same N acetate; treatment of epicryptopine A with phosphorus oxychloride yielded a red solid named epicryptopirubin chloride, $C_{21}H_{20}NO_4Cl$, m.p. 220-223°, and allocated structure (7). In our hands epicryptopirubin chloride has m.p. 219-221°, and is identical with the fourth, red, solid described by Perkin as dehydroepicryptopirubin chloride; we have been unable to isolate a red salt m.p. 150-155° as a product of the action of conc. HCl on anhydrocryptopine. The ultraviolet spectrum of epicryptopirubin chloride. [λ_{max} (ϵ_{max}): 210 (shoulder) (18,700), 225 (23,400), 242 (31,600), 275 (shoulder) (14,500), 368 (broad) (21,000) is very similar to the spectra of 3-aryl isoquinolinium salts and the N.M.R.[3]

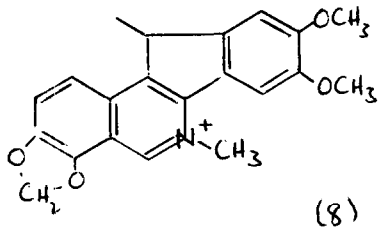

OCH3
OCH3
O
N
CH3
CH2
POCl3
N+
KOH
HO
NH
(1)
(2)
(3)
(4)
(5)
(6)
(7)

spectrum [Fig.I] (taken in trifluoracetic acid with tetramethylsilane as an internal reference) is diagnostic for structure (8). Reduction of this salt with lithium aluminium hydride yields the 1,2-dihydroisoquinoline (17), whose N.M.R. spectrum confirms this structure.

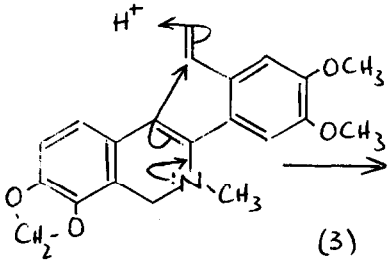
Whilst the vinyl grouping in anhydrocryptopine (3) is easily detectable in its N.M.R. spectrum, it is obviously absent from the spectra of the epicryptopines A, B and C. Further the I.R. spectra of epicryptopine B (a resin) and epicryptopine C (m.p. 164°) are superimposable. The I.R. spectrum of epicryptopine A indicates the presence of an NH group (3333 cm^{-1}) and a carbonyl group (1665 cm^{-1}); the N.M.R. spectrum, coupled with a consideration of the most likely mechanism for the reaction of anhydrocryptopine with acids, leads us to suggest that the structure of epicryptopine A is more correctly represented by (9). Epicryptopine C, we suggest, is the carbinolamine (10). The interpretation of the chemistry of these bases in the light of (9) and (10) will be discussed in our full paper.

When cryptopine methosulphate is reacted with alkali, γ-methylcryptopine is produced, for which Perkin proposed structure (11); we have no reason to doubt this structure. When γ-methylcryptopine was digested with HCl, Perkin isolated epimethylcryptopines A and B in small yield, and structures (12) and (13), respectively, were suggested for them. A much more likely structure, supported by our spectral data, for epimethylcryptopine A (the only isomer that we were able to isolate), is (15), formed from (11) as shown in (11) → (14) → (15). We have also been able to show that the methiodies of epicryptopine A (9) and epimethylcryptopine A (15) are identical (I.R. spectra).

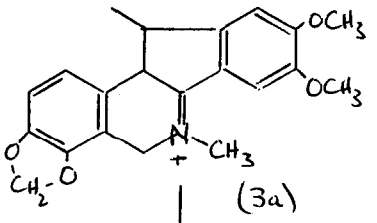
By treating anhydrocryptopine (3) with dilute HCl Perkin isolated two more rearrangement products, hydroxyisoanhydrodihydrocryptopines A and B, $C_{21}H_{23}N\,O_5$, and structure (16) was assigned to them. When either of these compounds is treated with conc. HCl, or when the isomer A is reacted with $POCl_3$, isoanhydrocryptopine, $C_{21}H_{21}NO_4$ is formed, and Perkin suggested structure (17) for this product. We have found that this latter product is not identical with the production of reduction of epicryptopirubin chloride (8) with lithium aluminium hydride. The N.M.R. spectrum of isoanhydrocryptopine [Fig.II] (taken in $CDCl_3$ with TMS as an



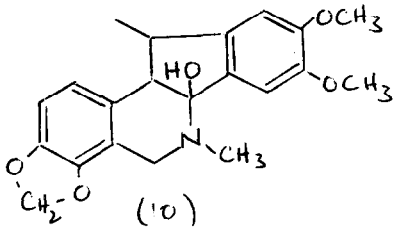
(8)



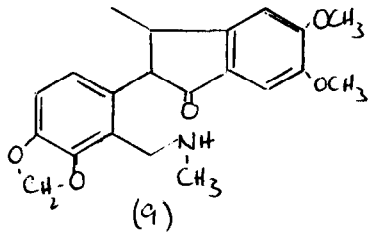
(3)



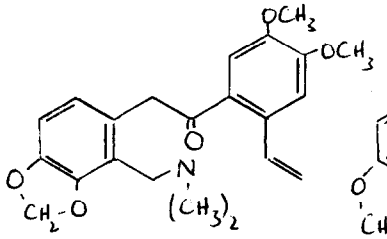
(3a)



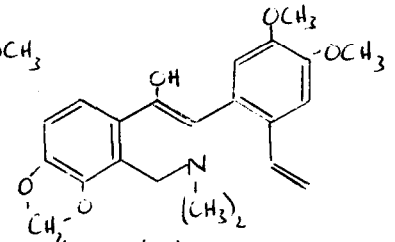
(10)



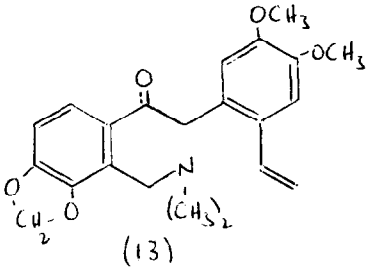
(9)



(11)

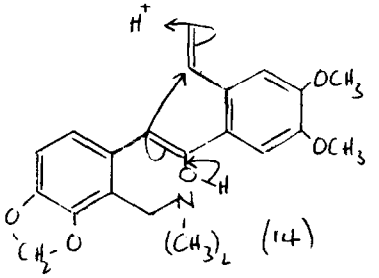


(12)

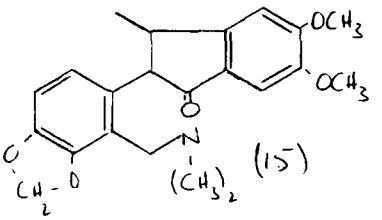


(13)

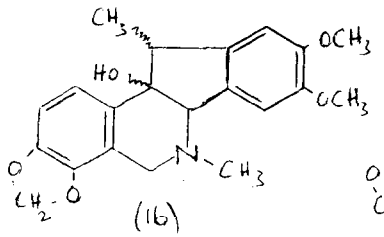
(11) ⇌



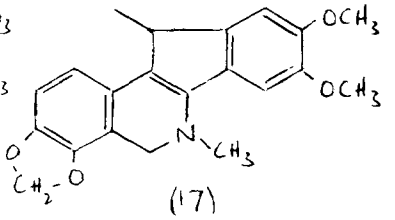
(14)



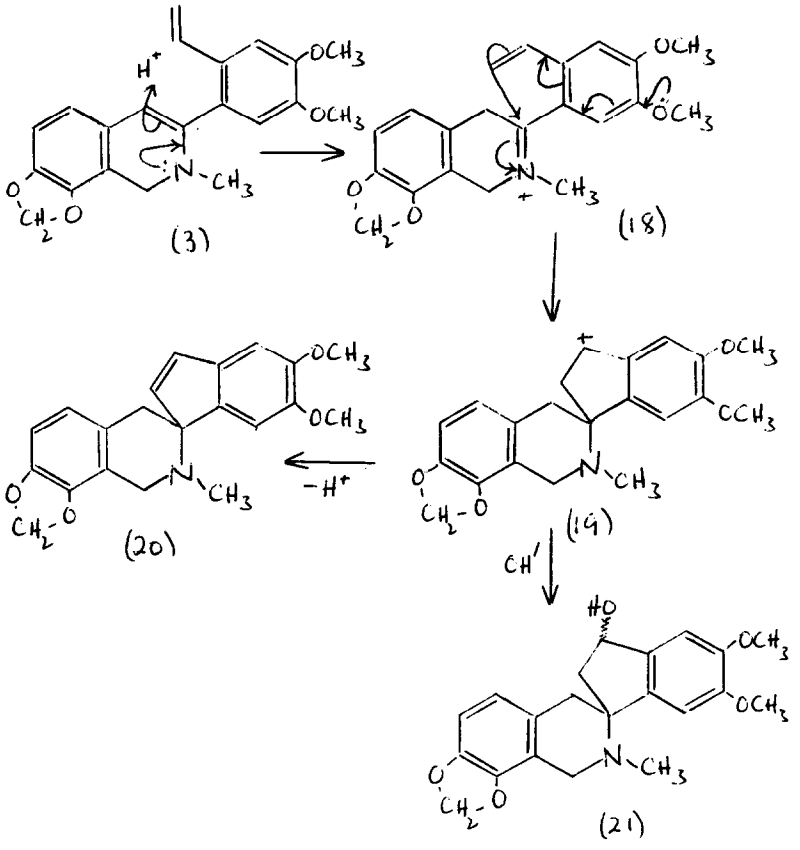
(15)



(16)



(17)


H+
OCH3
OCH3
N-CH3
O
CH2-O
(3)
(18)
(20)
(19)
-H+
CH'
HO
(21)

internal reference) is compatible with (20), and a reasonable mechanism for its formation from anhydrocryptopine is shown in (3) (18) (20). The hydroxyisoanhydrodihydrocryptopines are then represented by structure (21). Isoanhydrocryptopine readily forms a dihydro derivative when reduced catalytically, whereas hydrogenation of (17) would be expected to be difficult.

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REFERENCES

1. W. H. Perkin, J. Chem. Soc., 1916, 71, 815.
2. M. Sainsbury and S. F. Dyke, Tetrahedron, 1966 in the press and previous papers in the series.
3. A Varian A.60 spectrometer was used for Fig.I and an HA.100 for Fig.II.
4. K. W. Bentley, private correspondence; see also "The Isoquinoline Alkaloids", Pergamon Press, 1965, p.175.

Figure I

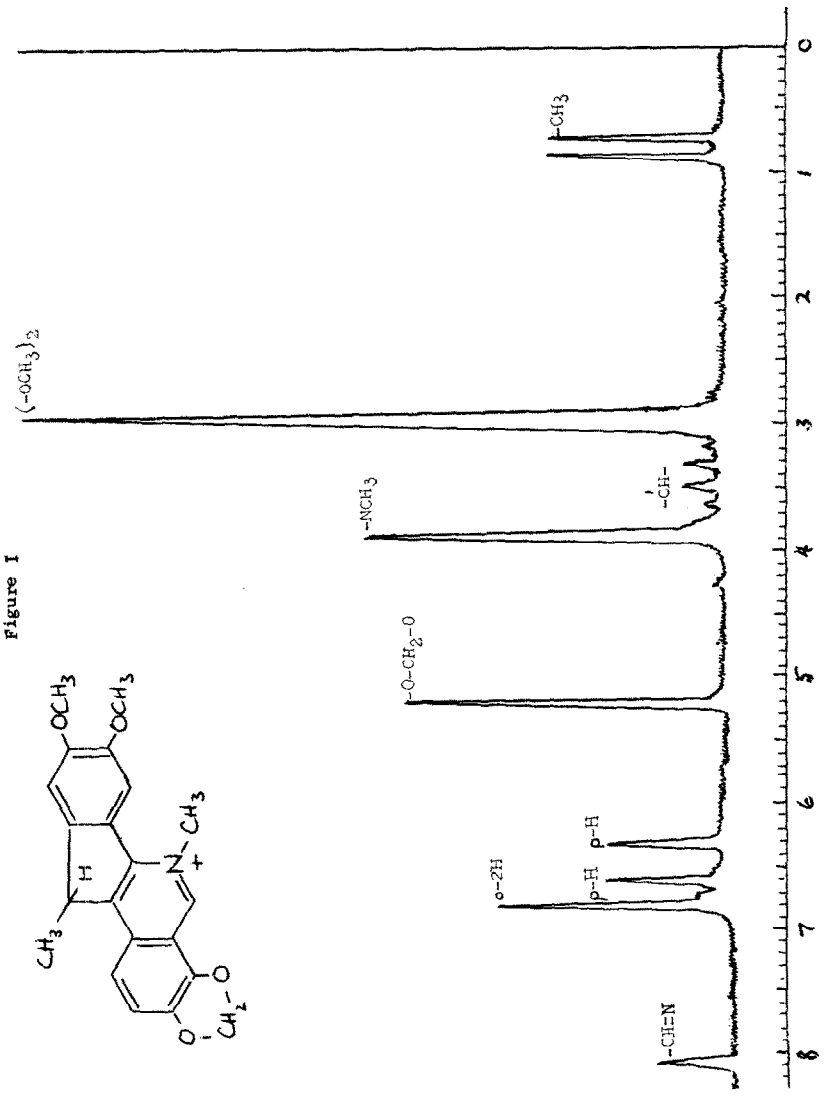
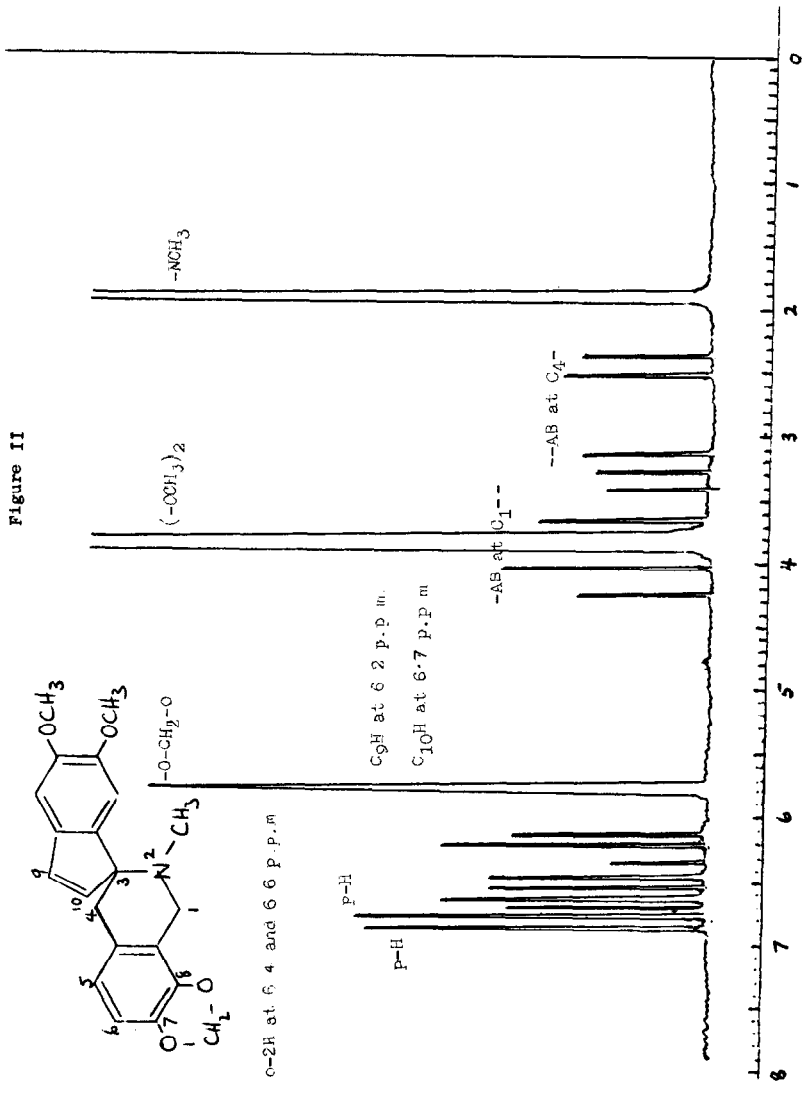


Figure II


-NCH3
(-OCH3)2
-O-CH2-O
C9H at 6·2 p.p.m.
C10H at 6·7 p.p.m
-AB at C1--
--AB at C4-
p-H
p-H
o-2H at 6·4 and 6·6 p.p.m
OCH3
OCH3
N
CH3
O
CH2
O
0
1
2
3
4
5
6
7
8