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THE REARRANGEMENT OF 6-HYDROXYCRINAMINE TO CRIWELLINE

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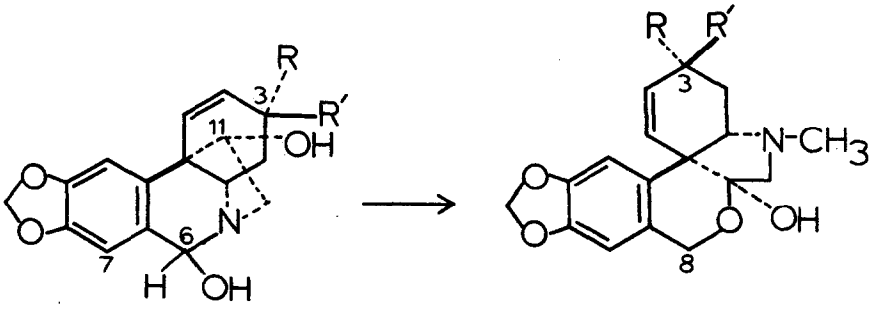
The epimeric alkaloids haemanthidine (Ia) and 6-hydroxycrinamine (Ib) are known to undergo rearrangement to give the corresponding C_3-epimers tazettine (IIa) and criwelline (IIb) respectively, upon treatment with methyl iodide followed by dilute base (1-3). The C_3-position seems not to be involved in the rearrangement, and it is most probable that both conversions follow the same mechanistic pathway. An intramolecular hydride shift has been suggested for the rearrangement, but no evidence for its validity has been presented to date (4). The present communication provides evidence for the correctness of our original mechanism.

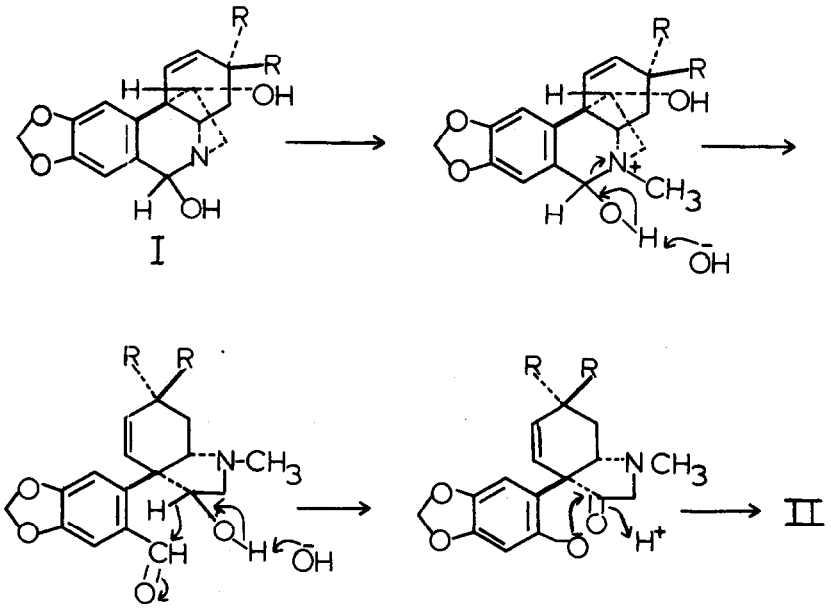


Ia) Haemanthidine; R=H, R'=OCH_3

Ib) 6-Hydroxycrinamine; R=OCH_3, R'=H

IIa) Tazettine; R=H, R'=OCH_3

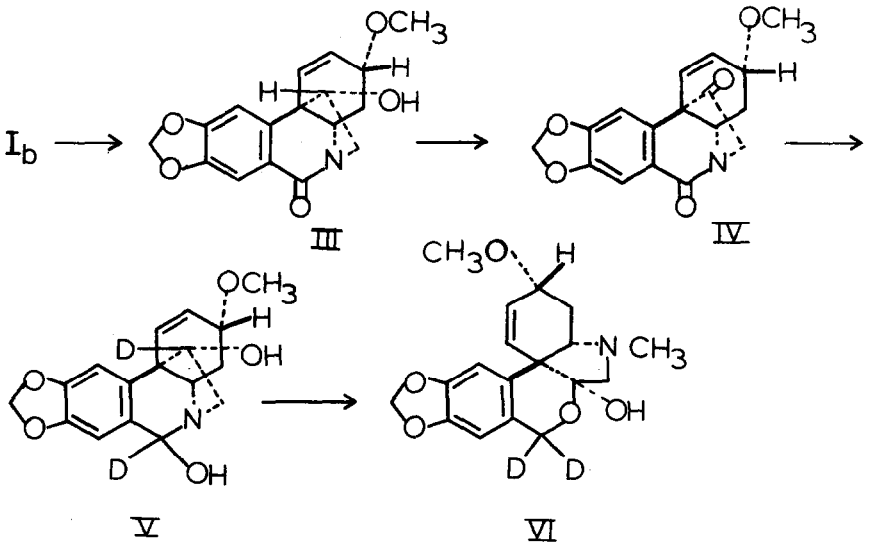
IIb) Criwelline; R=OCH_3, R'=H



Oxidation of 6-hydroxycrinamine (Ib) with manganese dioxide gave the bridgehead lactam (III),* m.p. 208-209°; λ_{max}^{EtOH} 232, 274 and 323 mμ (log ε = 4.45, 3.88 and 3.76 respectively). Reported (5): m.p. 195-196°; λ_{max}^{EtOH} 234, 275 and 326 mμ (log ε = 4.36, 3.79 and 3.71 respectively). Oxidation of III with chromium trioxide in dimethylformamide (6) containing a trace of sulfuric acid afforded IV, m.p. 199-200°; λ_{max}^{EtOH} 224, 234, 277 and 326 mμ (log ε = 4.20, 4.21, 3.78 and 3.56 respectively); λ_{max}^{KBr} 5.72, 5.92 and 6.18 μ. The ketolactam (IV) was

* Satisfactory analyses have been obtained for all compounds cited in this communication.

reduced with lithium aluminum deuteride in tetrahydrofuran to 6-hydroxycrinamine-6,11-d_2 (V), m.p. 208-209°. Found: D, 1.59 atoms (7). Methylation of V with methyl iodide in acetone afforded a methiodide which was rearranged by dilute base to criwelline-8-d_2 (VI), m.p. 206-207°. Found: D, 1.74 atoms.



The nuclear magnetic resonance spectra of 6-hydroxycrinamine, criwelline and their deuterated analogs are given in figures 1 and 2. Proton assignments were made on the basis of expected chemical shifts and by comparison with other derivatives. Deuteration experiments showed that the C_6 and C_{11} hydroxyl protons of Ib are centered at 8.0 and 2.4 p.p.m. respectively. The hydroxyl proton of criwelline appears at 2.9

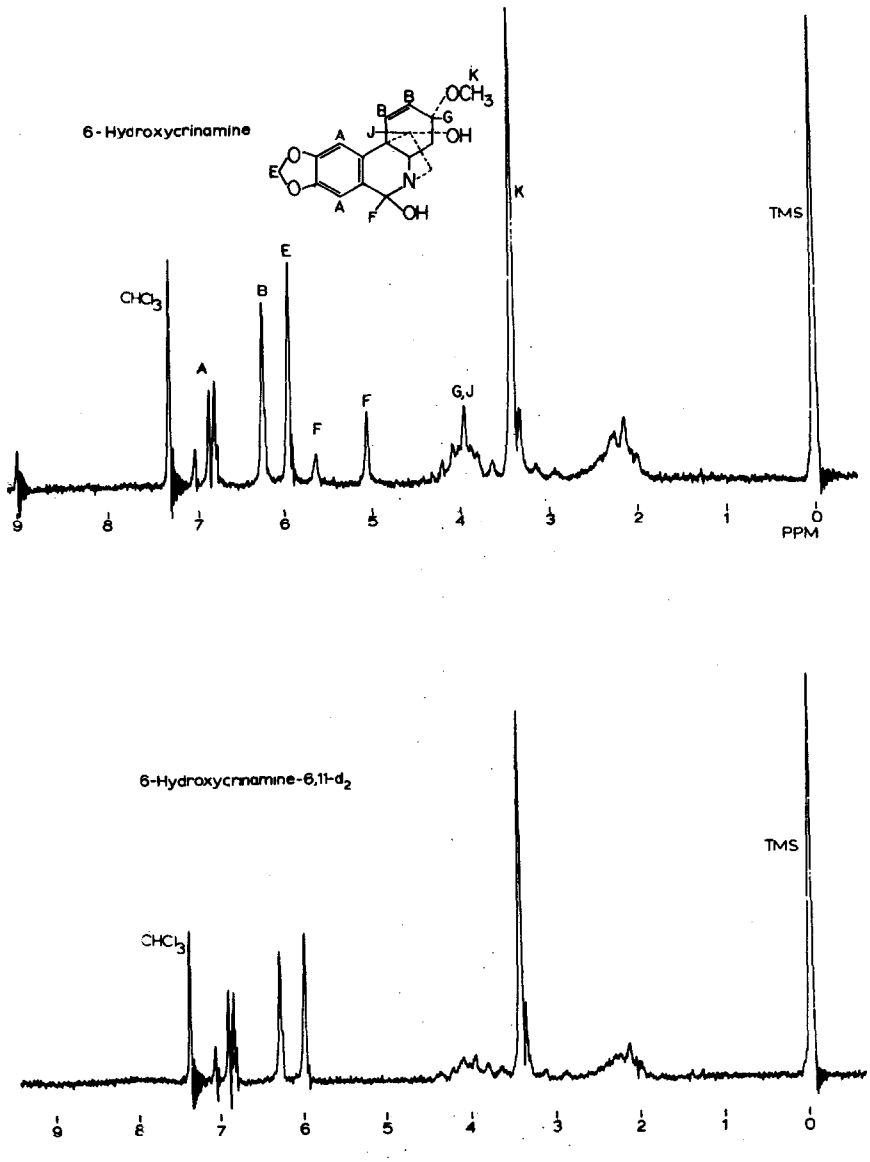

6-Hydroxycrinamine
K
OCH3
B
B
G
OH
J
A
O
E
O
N
A
F
OH
K
TMS
E
B
CHCl3
A
F
F
G,J
9
8
7
6
5
4
3
2
1
0
PPM
6-Hydroxycrinamine-6,11-d2
TMS
CHCl3
9
8
7
6
5
4
3
2
1
0

FIG. 1

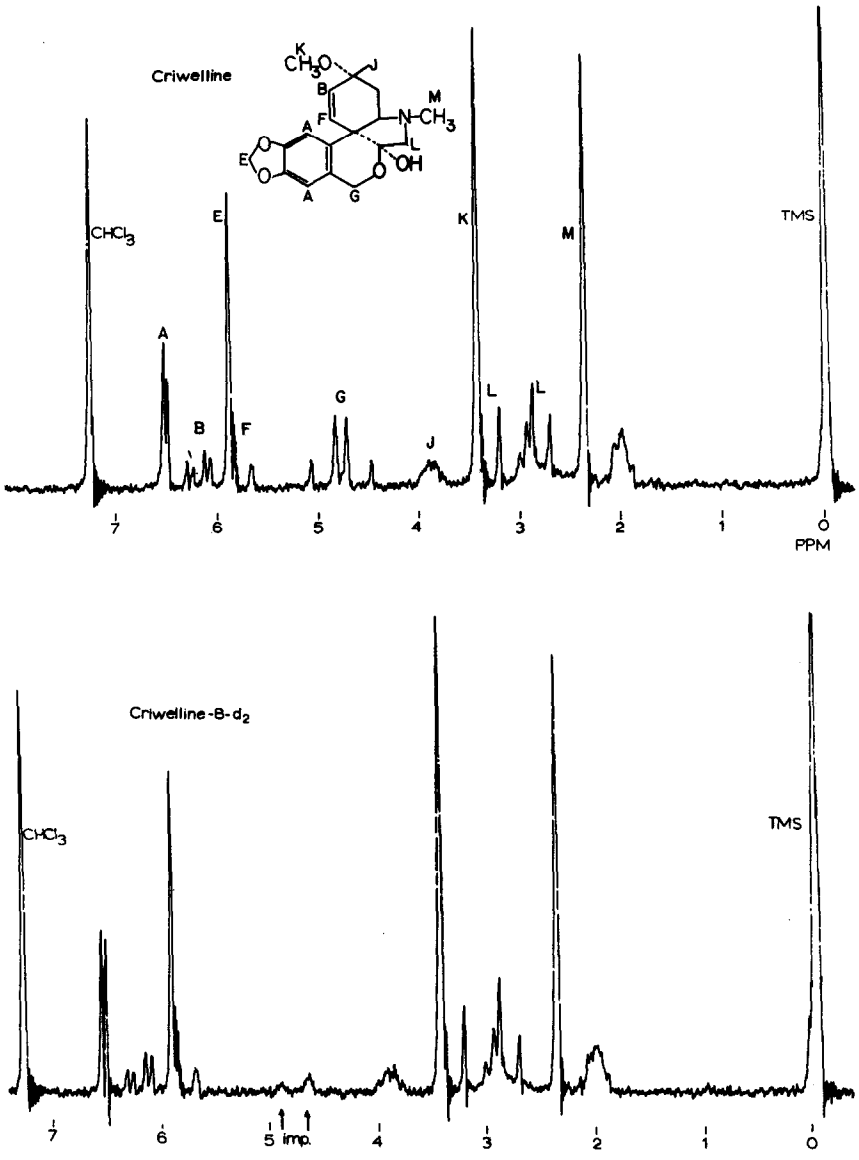


FIG. 2

p.p.m. The spectrum of 6-hydroxycrinamine is particularly significant because both the benzylic and C_7 protons appear at two different positions in the spectrum. The two peaks at 5.05 and 5.65 p.p.m. correspond to the benzylic proton (F), while peaks from 6.8 to 7.1 p.p.m. represent the aromatic protons. Concurrent spectroscopic studies of haemanthidine, haemanthamine and crinamine suggest that this phenomenon is due to a solution equilibrium of C_6 hydroxyl epimers and not to an impurity or a mixture of compounds.

The spectrum of criwelline shows an ABX splitting pattern (J_{BF} = 10.6 c.p.s., J_{BJ} = 3.2 and J_{FJ} = 1.0 c.p.s.) and two AB patterns (J_{GG} = 15.5 c.p.s., J_{LL} = 11.5 c.p.s.). The latter splittings arise because of the rigid ring system of criwelline. The spectrum of 6-hydroxycrinamine-6,11-d_2 is identical with that of the parent alkaloid except for the absence of the C_6 and C_{11} proton resonances. The C_7 proton resonance is still in two positions because the equilibrium as related to the C_7 proton still exists. The criwelline-8-d_2 spectrum shows no AB pattern corresponding to resonances in the benzylic position. The absence of any benzylic proton resonance shows that two deuterium atoms now are substituted in that position.

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