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SYNTHESIS OF OCTAHYDROINDOLE DERIVATIVES

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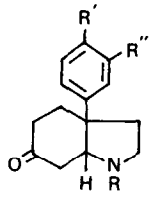
Our interests in mesembrine type compounds with respect to yet unspecified physiological activities and possible transformation to tetracyclic compounds, basic structure of which is common to some Amaryllidaceae alkaloids, prompted us to explore a general approach to I[1].



I

Mesembrine	$R' = R'' = OCH_3$, $R = CH_3$
Ia	$R' = R'' = H$, $R = H$
Ib	$R' = R'' = H$, $R = CH_3$
Ic	$R' = R'' = H$, $R = CH_2Ph$

Benzyl cyanide was alkylated with 1-bromo-3-ethylenedioxybutane to give II, $bp_{3.0}$ 162-164° (Y:67.9%), which gave III, mp 54.5-55°, by the second C-alkylation with ethyl bromoacetate (Y:64.1%). Reductive cyclization of III (Ra-Co) to the five membered lactam IV, mp 132-133° (Y:90.0%), IR(CCl_4) 1695 cm^{-1}, and reduction of IV with lithium aluminum hydride afforded the pyrrolidine derivative V, $bp_{0.1}$ 132-134° (Y:91.0%); V-hydrochloride, mp 166-167°. V was dehydrogenated with manganese dioxide in chloroform to give a mixture of pyrroline derivatives, $bp_{0.4}$ 145-152° (Y:85.6%), from which VI-hydrochloride, mp 84-86°, was isolated in 23.8% yield*, IR(nujol) 1640 cm^{-1}, 2500-2750 cm^{-1}; free base, IR(liq) 1620 cm^{-1}, NMR 7.64ppm 1H t(J=ca.2cps), 7.26ppm 5H s , 4.10-3.70ppm 2H , 3.87ppm 4H s, 2.07ppm 2H t(J=7cps), 2.10-1.30ppm 4H A_2B_2 system, 1.26ppm 3H s.

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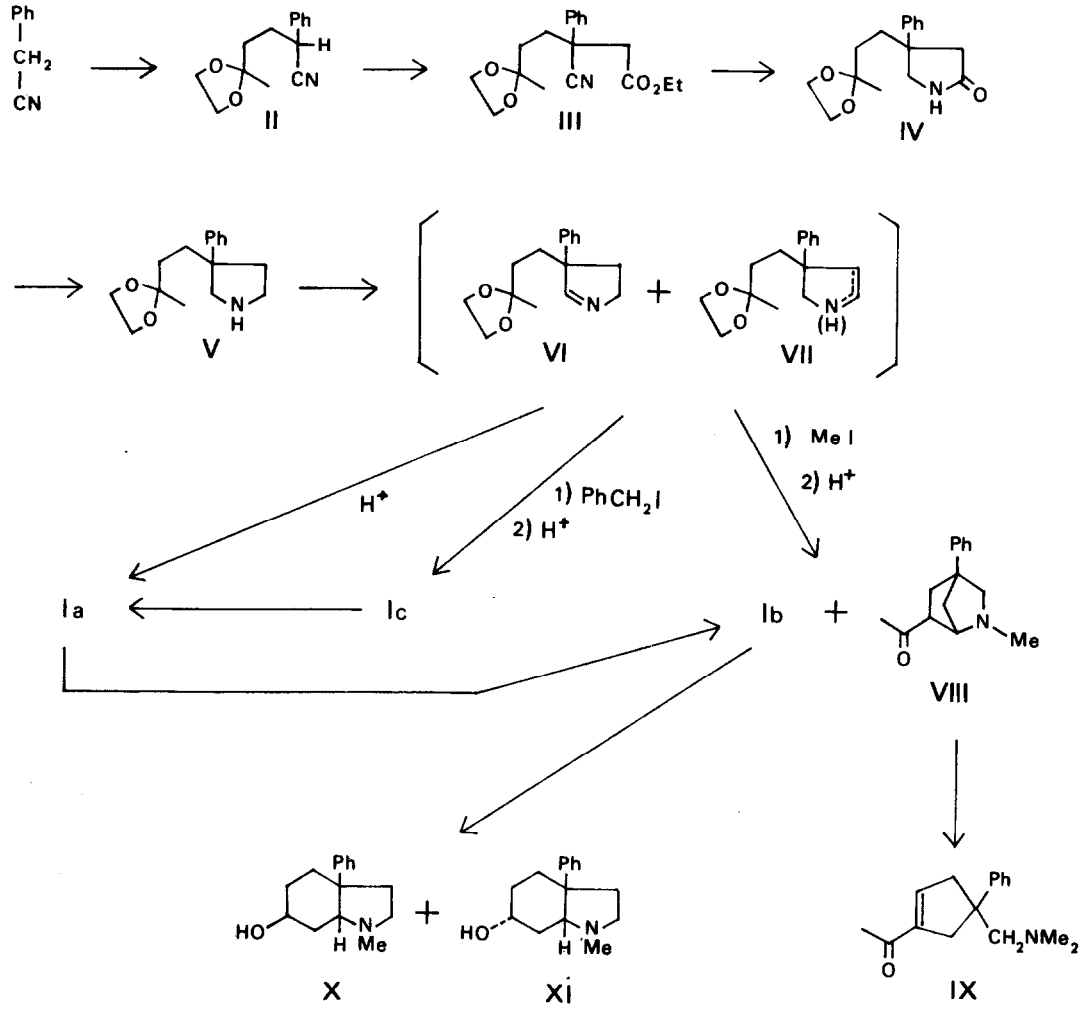
* This does not represent the actual yield of VI-free base in the mixture.



Hydrogenation of VI-hydrochloride in ethanol (Pd-C) gave V in quantitative yield. The mixture was hydrogenated likewise to give V also in good yield, indicating that the mixture consisted of VI and a double bond isomer represented by VII.

VI and VII as the mixture were quarternarized with methyl iodide, followed by treatment with 10% hydrochloric acid at room temperature overnight to give Ib (Y:34.9% from V), NMR[2] 7.34ppm 5H s, 2.97ppm 1H t(J=3cps), 3.30-2.8 ppm 1H, 2.57ppm 2H d(J=3cps), 2.28ppm 3H s, 2.80-1.80ppm 7H; Ib-hydrochloride, mp 204-205°(dec), IR (nujol) 1710 cm^{-1}, 2420 cm^{-1} (broad) ;

Ib-picrate[2], mp 169-170°(dec), and 2-methyl-4-phenyl-6-acetyl-2-azabicyclo[2,2,1]heptane VIII (Y:8.5% from V), NMR 7.22ppm 5H s, 3.40-1.50ppm 8H, 2.42ppm 3H s, 2.17ppm 3H s; VIII-hydrochloride, mp 191-193°(dec), IR (nujol) 1710 cm^{-1}, 2460 cm^{-1}(broad). Hofmann degradation of the methiodide, mp 113-115°, of VIII gave IX, mp 75-76°(Y:91.7%), IR (CCl_4) 1620 cm^{-1}, 1660 cm^{-1}, NMR 7.25ppm 5H s, 6.73ppm 1H s(broad), 3.10-2.70ppm 4H, 2.40ppm (3.55ppm**) 2H s, 2.34ppm (2.45ppm**) 3H s, 1.91ppm (2.68ppm**) 6H s.

The N-benzyl derivative Ic, NMR 7.33ppm 5H s, 7.20ppm 5H s, 4.06ppm 1H d(J=12cps), 3.28ppm 1H t(J=3cps), 3.06ppm 1H d(J=12cps), 2.67ppm 2H d(J=3cps), 3.10-1.80ppm 8H, was synthesized in a similar way in 21.7% yield from V ; Ic-hydrochloride, mp 189-190°(dec), IR (nujol) 1710 cm^{-1}, 2450 cm^{-1} (broad).

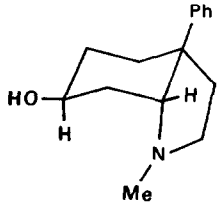
Hydrogenolysis of Ic-hydrochloride on Pd-C gave Ia in 68.0% yield; Ia-hydrochloride, mp 173-176°(dec), IR (nujol) 1705 cm^{-1}, 2750-2200 cm^{-1}; Ia-picrate, mp 169-170°(dec), IR (nujol) 1700 cm^{-1}, 2750-2350 cm^{-1}. Attempted cyclization of the pyrroline mixture (VI and VII) in 10% hydrochloric acid gave Ia only in 3% yield from V. Methylation of Ia with methyl iodide and potassium carbonate gave Ib in 74.1% yield.

Catalytic hydrogenation of Ib in isopropanol over platinum[3] gave stereoisomeric alcohols, X, mp 110-111°(Y:56.7%) and XI, mp 62-63°(Y:24.6%). The major product X showed a widely spread signal of C-6 proton at 4.20-3.60ppm (axial proton), while the minor product XI showed the signal at 3.92ppm with half-band width of ca. 8cps (equatorial proton) in NMR spectra[4]. This most probably indicates the presence of an equatorial hydroxyl group for the former and axial one for the latter.

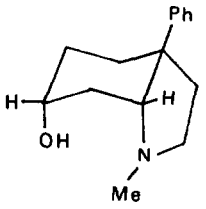
Infrared spectrum of XI showed a significant intramolecular hydrogen bond (OH----N, max. 3320 cm^{-1}, remained unchanged on dilution to 1.0 x 10^{-2}M in CCl_4). On the other hand, X revealed only a band due to free OH (max. 3590 cm^{-1}, 1.0 x 10^{-2}M in CCl_4).

This observation, coupled with the NMR data, confirmed the stereochemistry of X and XI as Xa and XIa respectively, precluding alternative conformation Xb and XIb.

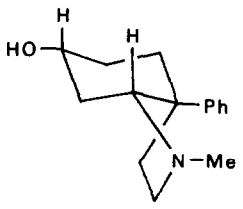
** These values were observed by adding CF_3COOD to the sample solution.



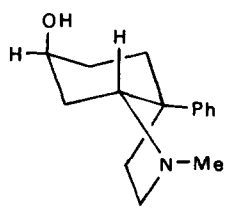
Xa



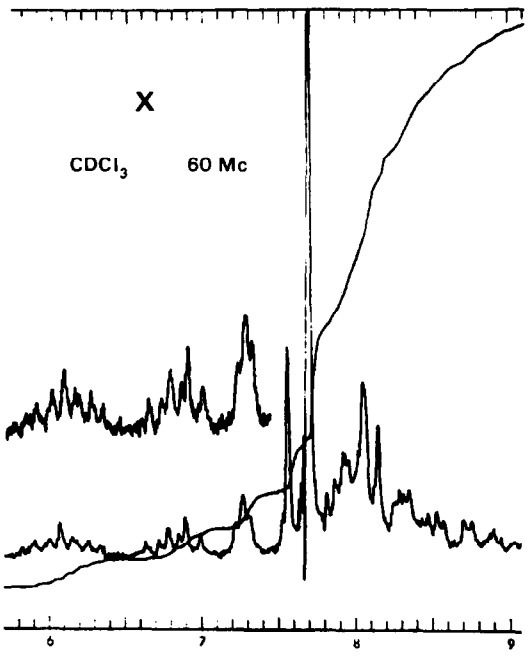
XIa

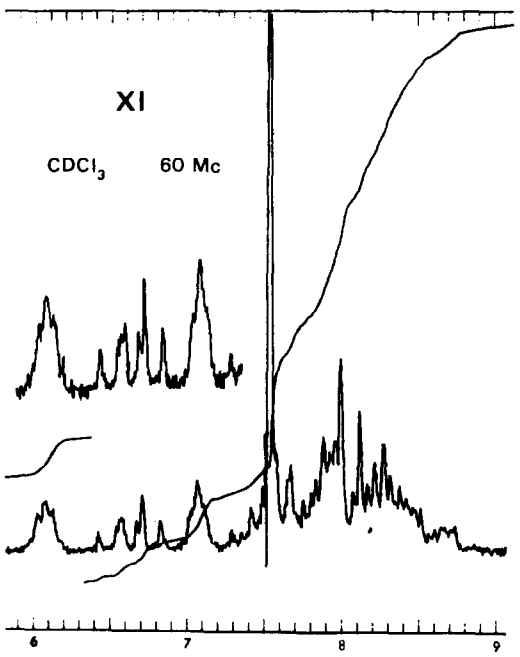


Xb



XIb





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References

1) Synthesis of dl-mesembrine and its trans isomer has been completed in our laboratory; T. Oh-ishi and H. Kugita, Tetrahedron Letters, in press.

2) Spectral pattern was identical with that presented recently; R. V. Stevens and M. P. Wentland, Tetrahedron Letters, 2613 (1968).

3) This reduction was carried out following the method employed in the reduction of mesembrine to mesembrinol; K. Bodendorf and W. Krieger, Arch. Pharm. 290, 441 (1957).

4) N. S. Bhacca and D. H. Williams, Application of NMR spectroscopy in Organic Chemistry, p.77 Holden-Day, Inc. (1964).