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THE STEREOCHEMISTRY OF MAYUMBINE AND STRUCTURALLY RELATED OXINDOLE ALKALOIDS[1]

Ernest Wenkert,[2] Börje Wickberg and Curtis Leicht

Department of Chemistry, Iowa State University

Ames, Iowa

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A RECENT chemical and proton magnetic resonance spectral study of ajmalicinoid indole alkaloids revealed that ajmalicine, its 3-iso derivative, tetrahydroalstonine and akuammigine represent the four possible stereochemical forms (III-VI, respectively) of the gross alkaloid structure I possessing 15α-H and 19α-methyl functions.[3] We now wish to report an extension of the PMR investigation to the indole base mayumbine (I)[4] and the structurally related oxindole alkaloids (II) formosanine,[5] mitraphylline and isomitraphylline,[5] which reflects their relative stereochemistry.

Previous data[4] and the lack of identity of the PMR spectrum of mayumbine with that of any of the compounds III-VI shows it to be the C (19)

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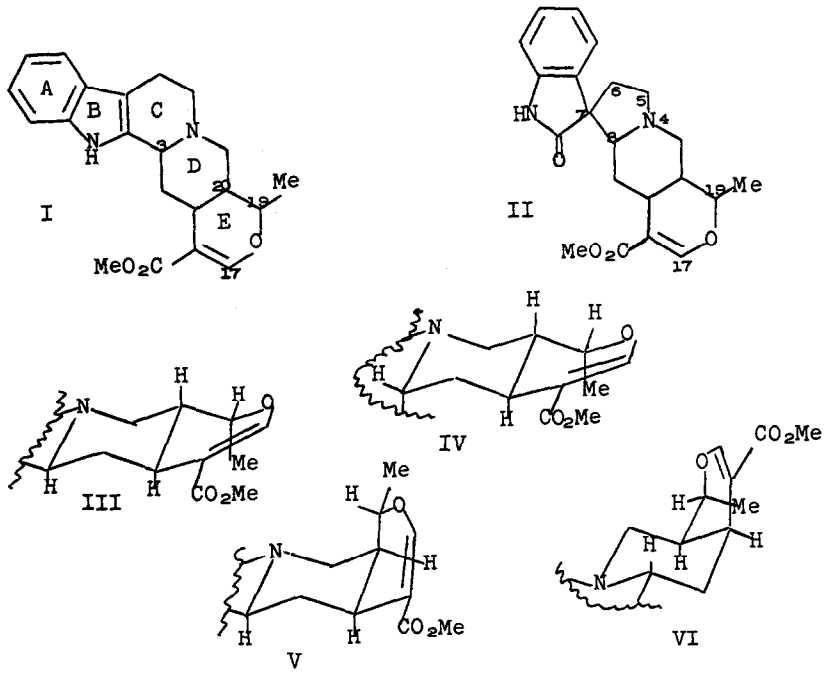
[2] Present address: Department of Chemistry, Indiana University, Bloomington, Indiana.

[3] E. Wenkert, B. Wickberg and C.L. Leicht, J.Amer.Chem.Soc. 83, in press (1961).

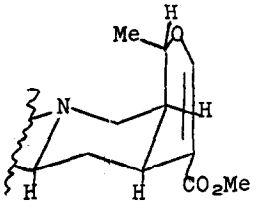
[4] M.M. Janot, R. Goutarel and J. Massonneau, C.R.Acad.Sci.,Paris 234, 850 (1952).

[5] J.C. Seaton, M.D. Nair, O.E. Edwards and L. Marion, Canad.J.Chem. 38, 1035 (1960) and references contained therein.

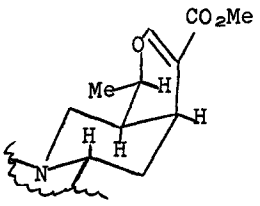


epimer of one of the four bases. The absence of a one-proton downfield signal, characteristic of the equatorial C (3)-H of pseudo compounds,[3] eliminates 19-iso-IV, while the low spin-spin coupling constant ($J_{H\ (19)H\ (20)}$ = 2.6 cps) speaks against a 19,20-trans diaxial hydrogen arrangement and hence, eliminates both D/E trans structures, 19-iso-III and 19-iso-IV. Thus, mayumbine must be 19-isotetrahydroalstonine (VII) or 19-isoakuammigine (VIII). In contrast to the consistent chemical shift ($\delta = 4.41 \pm 0.08$) of the C (19)-H signal in all ajmalicinoid alkaloids inspected,[3] mayumbine and formosanine (II) have their one-proton octet centered farther upfield ($\delta = 3.76$). This $\Delta\delta$ indicates that the C (19) hydrogen is oriented more favourably for intramolecular shielding by the ring E double bond in these alkaloids than in any of their stereoisomers, a condition satisfied by the C (19)-H quasi-axial conformation in VIII. This argument and an independent one for formosanine (vide infra) support a 19-isoakuammigine (VIII)

structure for mayumbine.

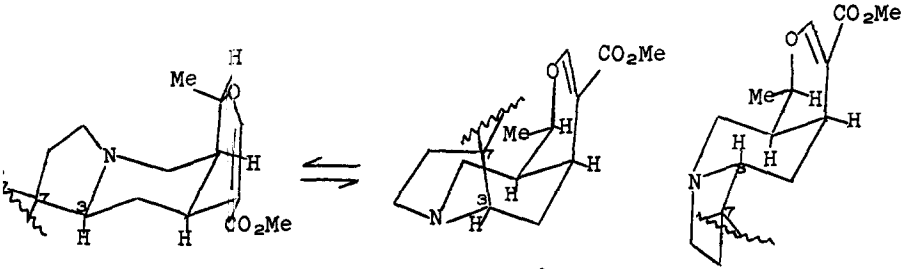


VII



VIII

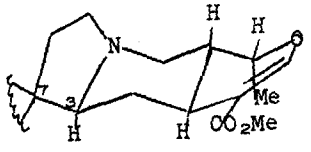
All PMR data relating to the C (19) evironment show formosanine (II) to be the oxindole analogue (IX or X) of amyumbine [Formosanine: C (19)-H octet at δ = 3.76 (J_{HH} = 2.9 cps) and C (19)-Me doublet at δ = 1.29 (J = 6.1 cps); mayumbine: C (19)-Me doublet at δ = 1.34 (J = 7.0 cps)]. Equilibration of formosanine and isoformosanine, a process affecting the asymmetric centers of only C (3) and/or C (7),[5,6] has revealed this pair of epimeric alkaloids to be of comparable stability [K(form./isoform.) = 4],[5] while a compound of the unstable configuration of IX, irrespective of its C (7) configuration, would be expected to be isomerized completely to X at equilibrium. As a consequence, formosanine possesses the 19-isoakuammigine stereochemistry depicted in X and isoformosanine its C (7) epimeric configuration.



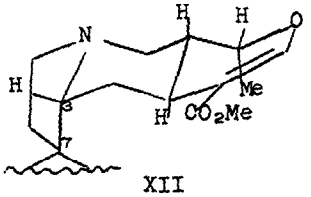
IX X

[6] E. Wenkert, J.H. Udelhofen and N.K. Bhattacharyya, J.Amer.Chem.Soc. 81, 3763 (1959).

The PMR spectra of mitraphylline (II) and isomitraphylline (II), another C (3) and/or C (7) isomeric pair of oxindole alkaloids,[5] show these substances to be related stereochemically to ajmalicine (III) or 3-iso-ajmalicine (IV) [C (19)-H octet: mitrophylline— $\delta = 4.34$ ($J_{HH} = 2.5$ cps), isomitraphylline— $\delta = 4.39$ ($J_{HH} = 2.4$ cps), III— $\delta = 4.44$ ($J_{HH} = 2.7$ cps),[3] IV— $\delta = 4.38$ ($J_{HH} = 1.8$ cps).[3] C (19)-Me doublet: mitraphylline— $\delta = 1.11$ ($J = 6.4$ cps), isomitraphylline— $\delta = 1.13$ ($J = 6.3$ cps), III— $\delta = 1.16$ ($J = 6.0$ cps),[3] IV— $\delta = 1.19$ ($J = 7.0$ cps)[3]]. A distinction between the resulting stereoformulas XI and XII can be made on the basis of available equilibrium data. As in the case of the formosanines (vide supra) the mitraphyllines are of not too dissimilar energy content [K(mit./isomit.) = 4],[5] whereas, a compound of the pseudo configuration XII with a resultant axial quaternary C (3) substituent would be expected to be fully converted to XI at equilibrium. Hence, the ajmalicine stereochemistry depicted in XI and its C (7) isomeric configuration represent mitraphylline and isomitraphylline, respectively.



XI

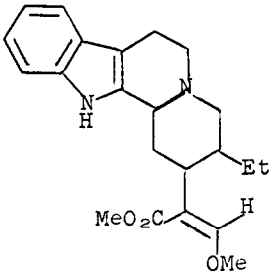


XII

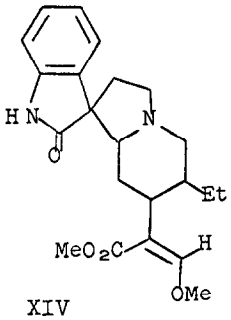
While the C (17) olefinic hydrogen appears in the PMR spectra of all ajmalicinoid indole alkaloids as a singlet at $\delta = 7.54 \pm 0.02$, it shows up at 7.32 p.p.m. in the spectra of the ring E seco alkaloids corynantheine and corynantheidine (XIII) and at 7.23 or 7.30 p.p.m. in the spectrum of rhyncophylline (XIV).[7] This upfield shift indicates that the methoxymethylene group in the seco alkaloids has the stereochemistry indicated in XIII and

[7] J.C. Seaton and L. Marion, Canad.J.Chem. 35, 1102 (1957) and references contained therein.

XIV.[8,9,10]



XIII



XIV

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8 L.M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry pp.119-125. Pergamon Press, London (1959).

9 The authors are most grateful to Dr. Raymond-Hamet for a gift of the oxindole alkaloids used in this investigation.

10 The PMR spectra were obtained with ca. 25% deuterochloroform solutions on a Varian Model HR60 spectrometer at 60 mc/sec with tetramethylsilane acting as internal standard. The position of major peaks was determined by the audiofrequency sideband technique, that of minor peaks by linear interpolation.