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INDOLE ALKALOIDS

PRESENCE OF A N_α-CH_3 GROUP IN VOACHALOTINE

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THE presence of a N-CH_3 group in voachalotine (the major alkaloid of Voacanga Chalotiana), O-acetylvoachalotine, voachalotinol and O,O-diacetyl-voachalotinol was reported earlier.[1]

We have now been able to show conclusively that the methylated nitrogen atom is the indolic nitrogen (N_α). This finding is of particular interest because voachalotine thus appears to be the first true indole alkaloid* bearing a methyl group on N_α. The nearest approach to this structural feature is to be found in the mavacurine[3] and eburnamine[4] series, in which N_α is involved in an extra ring, formally built up by internal cyclization on N_α.

The presence of a N_α-CH_3 group in voachalotine is supported by the following evidence.

* By "true indole alkaloid" we mean an alkaloid in which the aromatic chromophore is limited to the indole chromophore, with or without substituents. According to this definition, alstonidine,[2] which has an indole N-methyl-harmane structure (N_α substituted-β-carboline chromophore), is not a "true indole alkaloid".

1 J. Pecher, N. Defay, M. Gauthier, J. Peeters, R.H. Martin and A. Vandermeers, Chem. & Ind. 1481 (1960).

2 H. Boaz, R.C. Elderfield and E. Schenker, J.Amer.Pharm.Assoc. 46, 510 (1957).

3 H. Bickel, H. Schmid and P. Karrer, Helv.Chim.Acta 38, 649 (1955).

4 M.F. Bartlett and W.I. Taylor, J.Amer.Chem.Soc. 82, 5941 (1960).

Nuclear magnetic resonance spectroscopy (cf. Table 1)

The 56.4 mc/sec NMR spectra of voachalotine, O-acetylvoachalotine, O,O-diacetylvoachalotinol and anhydrovoachalotine,* all show a sharp 3 proton singlet at $\tau = 6.42$, which certainly arises from a N_a-CH_3 group. This assignment is confirmed :

(a) by the presence of a similar peak in the specta of known N-methylindoles : N-methyl-1,2,3,4-tetrahydrocarbazole and N-methyl-3-[2-(methylamino)ethyl]indole;[5]

(b) by the absence of this band in indole derivatives characterized by an unsubstituted N_a-H group : 1,2,3,4-tetrahydrocarbazole, ibogaine and voacangine.

As was expected, the 3 proton singlet ($\tau = 6.42$) of voachalotine is shifted to $\tau = 7.64$ in perhydrovoachalotine.** This new peak is indeed characteristic of an aliphatic N-CH_3 group. This follows from comparison with suitable models, such as gelsemine,[6] 3-[2-(dimethylamino) ethyl]indole[5] and N-methyl-3-[2-(methylamino)ethyl]indole.[5]

These facts alone, show quite clearly the presence of a N_a-CH_3 group in voachalotine.

Infra-red spectroscopy (cf. Table 1)

The question of the presence or the absence of a N-H group in voachalotine could not be settled by a simple inspection of its infra-red spectrum. On the other hand, it is quite clear that there is no such structural feature in O-acetylvoachalotine, O-O-diacetylvoachalotinol and anhydrovoachalotine (absence of a characteristic band in the 2.9-3μ region - LiF prism-CS_2). In this connexion, it should be noted that the I.R. spectra

* Anhydrovoachalotine (m.p. 226-229°) was obtained in an attempted Oppenauer oxidation of voachalotine.

** Perhydrovoachalotine was prepared by catalytic hydrogenation of voachalotine, using Adam's platinum in MeOH/HCl.

5 L.A. Cohen, J.W. Daly, H. Kny and B. Witkop, J.Amer.Chem.Soc. 82, 2184(1960).

6 H. Conroy and J.K. Chakrabarti, Tetrahedron Letters No.4, 6 (1959).

TABLE 1

	NMR (τ)			I.R. (μ)	U.V. (mμ) methanol		
	N_α-H	N_α-CH_3	N_β-CH_3		λ_{max}	λ_{min}	λ_{max}
Voachalotine		6.42		2.78w	229	252	285
O-Acetylvoachalotine		6.42			229	251	285
Voachalotinol				2.88-2.98	229	251	285
O,O-Diacetylvoachalotinol		6.42			229	251	285
Anhydrovoachalotine		6.42			229	251	284
Perhydrovoachalotine		7.64					
N-Methyl-1,2,3,4-tetrahydrocarbazole		6.42			231	253	286
1,2,3,4-Tetrahydrocarbazole	2.54			2.96	228	251	282.5
Ibogaine	2.46			2.97			
Voacangine	2.25			2.92			
Gelsemine[6]			7.84				
3-[2-Dimethylamino)ethyl]indole[5]			7.65				
N-Methyl-3-[2-(methylamino)ethyl]indole[5]		6.35	7.62				
N-Methyl-indole[5]		6.63					

of voacangine and of ibogaine both have a strong band in this region (2.92μ and 2.97μ, respectively).

Ultra-violet spectroscopy (cf. Table 1)

The long wavelength maximum of voachalotine, O-acetylvoachalotine, voachalotinol, O,O-diacetylvoachalotinol and anhydrovoachalotine is situated within experimental errors of the long wavelength maximum of N-methyl-1,2,3,4-tetrahydrocarbazole, and shows a slight bathochromic shift as compared to that of 1,2,3,4-tetrahydrocarbazole. These findings, if not conclusive by themselves, confirm the NMR and I.R. evidence.

The presence of a N_a-CH_3 group in voachalotine and its absence in voacangine easily explains the following facts, if it is assumed that in both molecules the methoxycarbonyl group is in the same relative position to N_a.

(1) The wavelength of the C=O vibration (methoxycarbonyl group) in voachalotine is quite normal (5.75μ). On the other hand, the corresponding band in voacangine is shifted to longer wavelength (5.84μ). This shift is probably due to the formation of a hydrogen bond between N_a-H and the methoxycarbonyl group in voacangine. Such a bond is of course excluded in voachalotine.

(2) The alcohol prepared by reduction of the methoxycarbonyl group of voacristine (voacangarine) reacts with acetone to give a cyclic ketal.[7] We have recentlyfound that, under the same experimental conditions, voachalotinol remains unchanged. Here again, the presence of a N_a-CH_3 group in voachalotine would prevent the formation of the cyclic derivative.

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[7] D. Stauffacher and E. Seebeck, Helv.Chim.Acta 41, 169 (1958).