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APPLICATIONS OF INTERNAL NUCLEAR OVERHAUSER EFFECTS (NOE) IN ORGANIC CHEMISTRY : DEHYDROVOACHALOTINE.

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Internal nuclear effects have been used - to assign the low field aromatic NMR multiplet to H(9) - to confirm the geometry of the ethylidene side chain - in dehydrovoachalotine.

The 60 MHz spectra ($CDCl_3$) of indole alkaloids, *unsubstituted in ring A*, usually show a complex multiplet (ABCD system) in the aromatic region, extending from 420 to 455 c/s (Table 1).

2-Acylindole alkaloids and dehydrovoachalotine (I) however give rise to much broader patterns with two distinct multiplets [ABCX system : 420-450 c/s (3H) and 455-470 c/s (1H)] (Table 1).

(I)

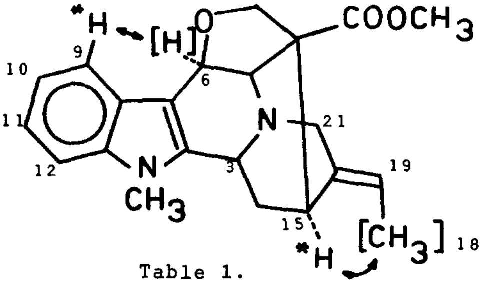

Table 1.

Frequency range (c/s: 60 MHz) and relative area of the aromatic signals.

Indole alkaloids : Voachalotine $^{5)}$: 420-456 (4H); Dihydrovallesiachotamine $^{6)}$: 420-453 (4H); O-acetylakuammidine $^{7)}$: 410-455 (4H); Dehydrovoachalotine $^{3)}$: 417-442 (3H), 450-470 (1H).

2-Acylindole alkaloids : Vobasine $^{8)}$: 415-447 (3H), 455-470 (1H); Ochropamine $^{8)}$: 422-450 (3H), 455-472 (1H); N_β-acetylperivine $^{9)}$: 415-446 (3H), 450-468 (1H); Vincadiffine $^{9)}$: 416-446 (3H), 453-468 (1H).

In the case of 2-acylindole alkaloids, the deshielding of one of the aromatic protons is essentially due to the influence of the carbonyl group on the charge distribution in the indole ring system.

The origin of the corresponding deshielding observed in dehydrovoachalotine had not been investigated so far.

This deshielding could be due to the anisotropy of the C_6-O bond and (or) to van der Waals interactions. In both cases, the deshielded aromatic proton would undoubtedly be H(9).

We have now fully confirmed this hypothesis by the study of *internal nuclear Overhauser effects*, as described below.

This very promising technique, first applied to stereochemical problems by Anet and Bourn 2), should prove invaluable in the study of natural products.

For a preliminary investigation of NOE's in the field of indole alkaloids, dehydrovoachalotine was particularly suitable for the following reasons :

- The molecule has a very rigid skeleton.
- In the NMR spectrum of this compound, the signals of every alicyclic proton can be assigned by first order analysis 3).

In a recent publication 4), we have shown that NOE's can be used to determine the geometry of the ethylidene side chain in the two isomeric 3-ethylidene-1-azabicyclo[2,2,2]octanes (3-ethylidene quinuclidines).

The same technique has now been applied with success to confirm that the CH_3 of the ethylidene side chain of dehydrovoachalotine is *cis* with respect to the bridg-head H atom (C_{19}-CH_3 *cis* to C_{15}-H).

<u>Experimental results</u>: For NOE experiments, a 10% $CDCl_3$ solution of pure dehydrovoachalotine was thoroughly degazed under high vacuum and sealed under helium. This solution was studied, at 100 MHz, by a frequency sweep method, using T.M.S. as an internal field frequency lock. The results are summarized in Table II.

TABLE II.

Irradiation	Area of the signals in arbitrary units				Increase in % (± 3)
	$H(9)^*$	$H(15)^*$	H(10) + H(11) + H(12)	H(3) + 2H(21)+ NCH_3 + OCH_3	
None	23,6	-	100	-	-
at H(6)	29,4	-	100	-	25 H(9)
None	-	15,2	-	200	-
at $CH_3(18)$	-	19,2	-	200	26 H(15)

* Average of three different runs.

- Saturation of H(6) results in a 25 ± 3% enhancement of the integrated area of the low field aromatic multiplet, the other part of the aromatic region remaining unaltered.

  This conclusively proves that H(9) is the deshielded aromatic proton.

  No Overhauser effect was observed when the reverse experiment was carried out [looking at H(6) while saturating H(9)].
- Irradiation at the $CH_3(18)$ frequency gives a 26 ± 3% increase of the integrated area of the signals of H(15), thus proving that $CH_3(18)$ is *cis* to H(15).

NOE studies on Quebrachamine type alkaloids, and on 7- and 10-membered C ring indole alkaloids are in progress.

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