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THE STRUCTURE OF AKUAMMIDINE

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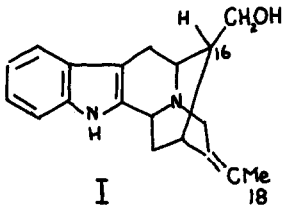
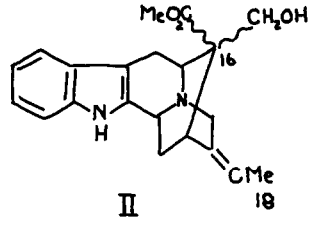
AKUAMMIDINE ($C_{21}H_{24}N_2O_3$, m.p. 234-6°, $[\alpha]_D^{20}$ + 24° [MeOH], $[\alpha]_D^{16}$ + 0.5° [acetone])[1,2] is one of a group of akuamma alkaloids which originally was isolated from seeds of Picralima klaineana.[1] Its structure has been related by degradative methods to that of normacusine-B (I) (i.e. desoxysarpagine, of known absolute configuration),[3] and it has been established to be (II), with the stereochemistry at C_{16} and C_{18} uncertain.[2]



I



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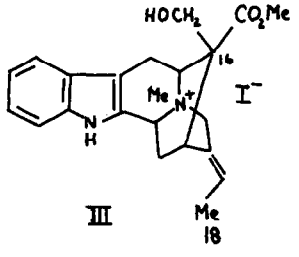
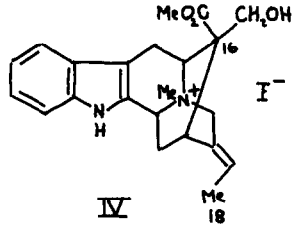


III



IV

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[1] T.A. Henry, J. Chem. Soc. 2759 (1932).

[2] J. Levy, J. Le Men and M.M. Janot, C.R. Acad. Sci., Paris 131 (1961).

[3] M.F. Bartlett, R. Sklar, W.I. Taylor, E. Schlittler, R.L.S. Amai, Peter Beak, N.V. Bringi and Ernest Wenkert, J. Amer. Chem. Soc. 84, 622 (1962).

The structure of macusine-A methiodide (III) ($C_{22}H_{27}N_2O_3^+I^-$, m.p. 274°)[4] has been solved by the X-ray method.[5] Since macusine-A methiodide and akuammidine methiodide ($C_{22}H_{27}N_2O_3^+I^-$, m.p. 233°, $[\alpha]_D^{18}$ + 16° [MeOH])[1] are not the same, the stereochemistry of akuammidine at C_{16} and/or C_{18} must differ from that of macusine-A.

This communication establishes (IV) to be the structure of the methiodide of an alkaloid recently isolated from the shrub Rhazya stricta Decaisne and named rhazine ($C_{21}H_{24}N_2O_3$, m.p. 234-6°, $[\alpha]_D^{25}$ ± 0° [$CHCl_3$]).[6,7] The physical constants of akuammidine and its methiodide are practically the same as those of rhazine and its methiodide, suggesting that rhazine and akuammidine may be the same.[8] That this is in fact so has now been established through the comparison of the single crystal X-ray diffraction patterns of the two methiodides and, also, their infrared spectra.[9] Thus the skeletal structure (II) for akuammidine has been confirmed and the stereochemistry at C_{16} and C_{18} has been determined.

The following was known of "rhazine", hereinafter called akuammidine, when the X-ray structure determination was undertaken: it was reported to be a tertiary base analysing for $C_{21}H_{26}N_2O_3$; containing an -OMe, two active hydrogens, a -CMe (50 per cent of theoretical), an N-H, an -OH, a methoxycarbonyl, and probably two -NMe functions; and showing a U.V. spectrum typical of indole.[6] In addition, it was said to have an ethylidene group (private communication, A. Chatterjee).

[4] A.R. Battersby, R. Binks, H.F. Hodson and D.A. Yeowell, J. Chem. Soc. 1848 (1960).

[5] A.T. McPhail et al., Proc. Chem. Soc. 223 (1961).

[6] A. Chatterjee, C.R. Ghosal, N. Adityachandhury and S. Ghosal, Chem. & Ind. 1014 (1961).

[7] A. Chatterjee, C.R. Ghosal and N. Adityachandhury, Chem. & Ind. 266 (1962).

[8] We should like to thank Dr. W.I. Taylor for pointing these facts out to us.

[9] We should like to thank Dr. J. Le Men for kindly supplying us with an authentic sample of akuammidine methiodide via Dr. W.I. Taylor.

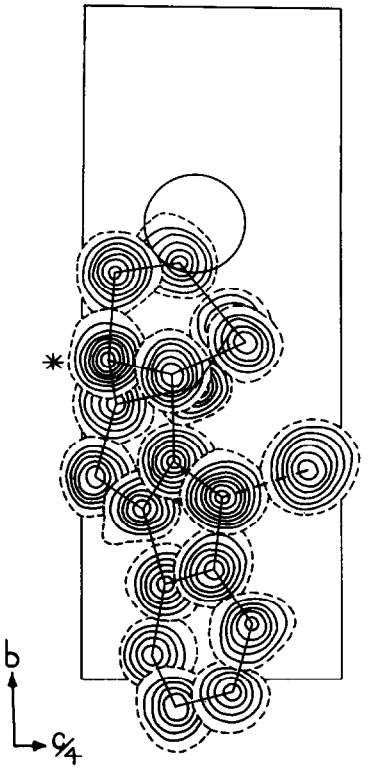

FIG. 1

Composite electron density of the basic ring structure of akuammidine methiodide viewed along a. Contours at approximately 1 e A^{-3}, beginning at 1 e A^{-3}. Water hydrogen bonding to indole indicated by broken line, quaternary nitrogen by asterisk, iodine by open circle.

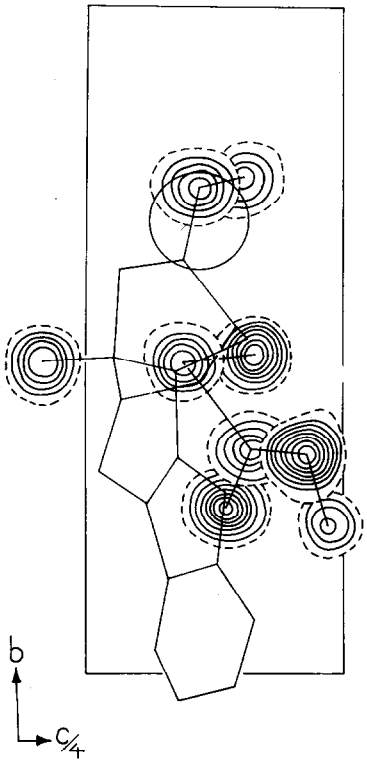

FIG. 2.

Composite electron density of the side chains of akuammidine methiodide viewed along a. Contours as in Fig. 1. The ethylidene is below iodine.

The structure of akuammidine methiodide has been solved employing single crystal X-ray crystallographic techniques.[10] Suitable crystals were grown by slow evaporation from an aqueous solution. The crystals belong to the orthorhombic space group $P2_12_12_1$; their lattice dimensions are a = 9.86 Å,

$\underline{b} = 12.34$ Å, $\underline{c} = 18.75$ Å; and there are 4 molecules/unit cell.

The structure was solved by the heavy atom method. Since the iodide ion was expected to dominate the diffraction pattern, only the three principal Patterson projections were considered in determining iodide positions. The Patterson function was sharpened by $(\underline{z}_I/\underline{f}_I)^2$, where $\underline{z}_I$ and $\underline{f}_I$ are, respectively, iodine's atomic number and scattering form factor. Phases based on iodine were assigned to the observed data, and a three dimensional electron density was computed. Of the 35 peaks in this density greater than 2.2 e $Å^{-3}$, 27 belonged to the molecule, 3 were improbable by virtue of their position, and 4 were spurious. The basic ring structure of sarpagine was recognized as were some side chains. The only uncertainties about the complete structure were (1) the location of the methyl ester's methyl group (2) a $-CH_2OH$ or crystallographic equivalent group with a large C-C distance and (3) a peak of 3.1 e $Å^{-3}$, possibly a water molecule, within hydrogen bonding distance of the indole nitrogen.

Two structure factor computations were then carried out. One was based on iodine plus 24 atoms (omitting the above uncertainties) and the other on iodine plus 11 atoms (the reasonably certain indole and the two atoms connected to it). The $\underline{R}$ factors for these computations were, respectively, 0.180 and 0.272. A comparison of the electron densities determined by the above two sets of phases verified the 24 atoms included in the larger structure factor computation and, furthermore, revealed the remainder of the structure. One more structure factor computation based on iodine plus 28 atoms, including a hydrogen bonded water molecule, was carried out, and R dropped to 0.149. The electron density determined by these phases is shown in Figs. 1 and 2. In the structure, the methyls of the ethylidene and ester functions are directed away from the quaternary nitrogen.

[10] We wish to thank Dr. A. Chatterjee for supplying us with 10 mg of the methiodide derivative.

Refinement is in progress in order to obtain better bond angles and distances. A more detailed account of the structure determination will appear elsewhere.

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