The Structure of Sceletium Alkaloid A_4, a Pyridine Alkaloid from *Sceletium namaquense*: Direct Method *X*-Ray Determination

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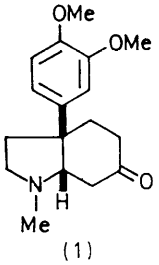
Summary The structure of the title alkaloid is shown by spectral evidence and direct method *X*-ray analysis to embody a 2,3-disubstituted pyridine ring in a novel variant of the known alkaloid ring system of the mesembrine series.

PREVIOUS studies have led to the isolation of two basic structure-types of alkaloids from *Sceletium* species of the Aizoaceae family. The mesembrine group,[1] based on the 3a-aryl-octahydroindole ring system and exemplified by mesembrine (**1**), represents the more common type. The second type, represented by joubertiamine (**2**), has been



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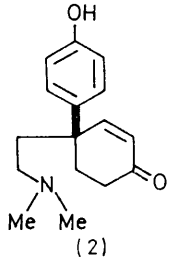

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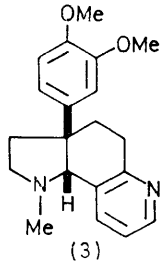

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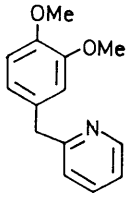

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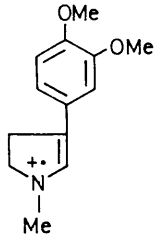

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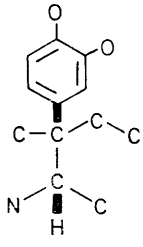

(7)

recently reported.[2] We now report on the structure of the alkaloid (**3**), which represents a new structural type of *Sceletium* alkaloid and contains a 2,3-disubstituted pyridine moiety.

Extensive chromatographic separation of the alkaloid fraction of *S. namaquense* provided a small amount of a base which crystallized from ethyl acetate as prisms, m.p. 153·5—154·5°, $[\alpha]_D$ + 131°. An accurate mass determination of the molecular ion in the mass spectrum established the molecular formula as $C_{20}H_{24}N_2O_2$. The similarity of these data to those reported by Popelak and Lettenbauer[1a] for "Sceletium A_4," an alkaloid of then unknown structure, suggested their identity; this was confirmed by direct comparison of samples.† The presence of a second nitrogen atom in the molecular formula required that this base must belong to a new structural class of Sceletium alkaloid.

The ^1H n.m.r. spectrum at 220 MHz showed essentially first order patterns in the aromatic region of the spectrum and provided clear evidence for the presence of a 3,4-disubstituted phenyl ring and a 2,3-disubstituted pyridine ring. The protons of the latter appear as an AMX pattern at typically low field: δ ($CDCl_3$) Me_4Si, 8·48 (dd, *J* 5·0 and 2·0 Hz, H_A), 7·56 (dd, *J* 7·8 and 2·0 Hz, H_M), 7·15 p.p.m. (dd, *J* 5·0 and 7·8 Hz, H_X).[3] A second AMX system at δ 6·70 (d, *J* 8·0 Hz, $H_{A'}$), 6·65 (d, *J* 2·0 Hz, $H_{M'}$) and 6·56 p.p.m. (dd, *J* = 2·0 and 8·0 Hz, $H_{X'}$) together with two three-proton singlets at δ 3·71 and 3·78 established the existence of a 3,4-dimethoxyphenyl group. In addition, a three proton singlet at δ 2·34 indicated an *N*-methyl group. The u.v. spectrum [λ_{max} 225 nm (3·59), 267 (3·39), 273 (3·42) and 285 (3·10)] is that expected for isolated 2,3-disubstituted pyridine and veratryl chromophores, and closely resembles that of the model system (**4**) [λ_{max} 231 nm (3·27), 262 (3·23), 268 (3·19), 282 (2·99)]. The slight bathochromic shift observed in the $\pi \rightarrow \pi^*$ bands at 267 and 273 nm in the alkaloid relative to the model compound is in acccord with the known additive auxochromic effect of alkyl substituents

† A sample of Sceletium Alkaloid A_4 was kindly provided by Dr. A. Popelak for this comparison.

on pyridine.[4] The i.r. spectrum of Sceletium Alkaloid A_4 displays absorption maxima at 1605 and 1580 cm^{-1}, consistent with the presence of a pyridine and a benzene ring.

The mass spectrum shows a moderately abundant fragment ion at *m/e* 219 corresponding to $C_{13}H_{17}NO_2$. This ion is reminiscent of the characteristic fragmentation of the mesembrine alkaloids which afford an ion of the same composition to which structure (**5**) has been assigned.[1b] Observation of a strong C_3H_7N fragment (**6**) together with ions of high abundance due to the loss of C_2H_5N and C_3H_8N from the molecular ion are consistent with the presence of an *N*-methyl pyrrolidine ring and support structure (**5**) proposed for the *m/e* 219 ion.

With the identification of the *m/e* 219 ion as (**5**) and knowledge of the presence of a 2,3-disubstituted pyridine ring, only two methylene groups and one ring are left unaccounted for. On this basis six possible structures may be written for the alkaloid Although biogenetic arguments led us to favour structure (**3**) over the alternatives, conclusive evidence was lacking. Since a paucity of material precluded a chemical approach to structural elucidation, the problem was approached by a direct method *X*-ray analysis.

Crystals of (**3**) are monoclinic, space group $P2_1$, with $a = 8{\cdot}33$, $b = 14{\cdot}74$, $c = 7{\cdot}18$ Å, $\beta = 95{\cdot}04°$, $Z = 2$, $D_c = 1{\cdot}227$ g. cm.$^{-3}$, $D_m = 1{\cdot}23$ g. cm.$^{-3}$. *X*-Ray intensity data were recorded photographically with Cu-$K\alpha$ radiation and estimated visually. A fifteen atom partial structure (**7**) was derived from two successive *E* maps based on 385 | *E* | values $> 1{\cdot}0$ for which phases were generated by application of the symbolic addition method[5] and tangent-formula refinement.[6] Following least-squares adjustment of the positional and thermal parameters of these atoms, a three-dimensional F_0 Fourier synthesis at *R* 0·37 clearly revealed the positions of the remaining non-hydrogen atoms. Atomic positional and anisotropic thermal parameters were then refined by full-matrix least-squares calculations. The pyridine nitrogen atom was identified at a late stage by its relatively low thermal parameter when treated as a carbon atom in the least-squares calculations and from the values of the diagonal elements of the least-squares normal equation matrix. Hydrogen atoms have been included at their calculated positions and the present *R* over 1523 independent reflections is 0·10.

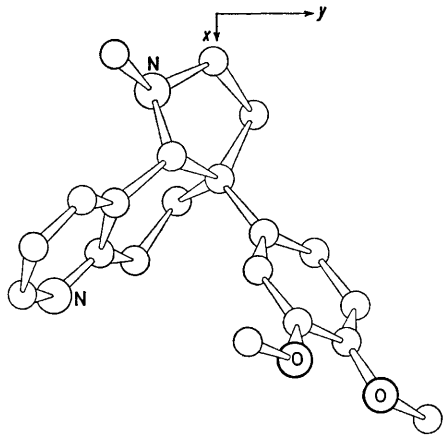

FIGURE. *Structure of Sceletium Alkaloid* A_4.

The results of independent studies by Weichers and co-workers on a related alkaloid tortuosamine and Sceletium alkaloid A_4 are reported in the following communications.

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