The Structures of Partial Racemic Sceletium Alkaloid A_4 and Tortuosamine, Pyridine Alkaloids from *Sceletium tortuosum* N. E. Br.

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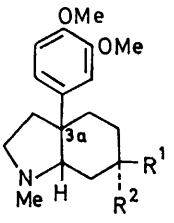
Summary The structures of partial racemic Sceletium alkaloid A_4 and tortuosamine are shown by spectral and chemical evidence to represent a new structural type of *Sceletium* alkaloid.

PREVIOUSLY[1] both partially racemic mesembranone (1; $R^1R^2 = 0$) and mesembranol (1; $R^1 = OH$, $R^2 = H$) were isolated from *Sceletium tortuosum* N.E. Br. In addition, extensive column and preparative layer chromatography of the total non-phenolic base fraction from the same plant yielded a nicely crystalline, chromatographically homogeneous, basic compound, m.p. 132—134° (EtOAc), $[\alpha]_D^{20} -$ 40·5° (*c* 1; MeOH). Both the m.p. and the specific rotation of the compound, contrary to partially racemic mesembranol, remained unchanged after successive recrystallisations.

The mass spectrum of the base, both at 70 and 15 eV, showed a molecular ion at *m/e* 324, which also is the base peak in the mass spectrum. Both analysis and an accurate mass measurement of the molecular ion in the mass spectrum provided the molecular formula as $C_{20}H_{24}N_2O_2$. This corresponds to Sceletium alkaloid A_4 previously isolated by

Popelak and Lettenbauer.[2] Furthermore, in the mass spectrum abundant ions were observed at *m/e* 323, 309, 296 ($C_{18}H_{20}N_2O_2$), 281 ($C_{18}H_{19}NO_2$), and 266 ($C_{17}H_{16}NO_2$). Most informatively however, moderately abundant ions were observed at *m/e* 219 ($C_{13}H_{17}NO_2$) and 57. All the mesembrane alkaloids which possess a 3a-dimethoxyphenyl substituent *e.g.* (1), show an abundant peak at *m/e* 219 which was attributed[3] to an ion of a structure (2). The ions at *m/e* 281 ($M - C_2H_5N$), 266 ($M - C_3H_8N$), and 57 (3) lend support to the presence of an *N*-methylpyrrolidine ring in Sceletium alkaloid A_4.



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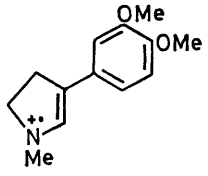

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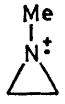

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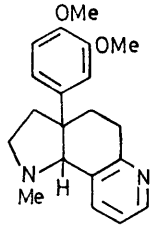

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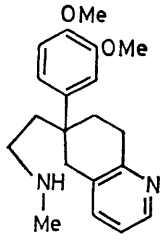

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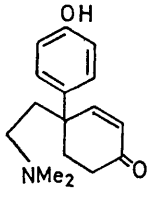


(6)

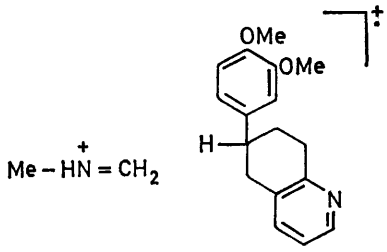
The presence of isolated 2,3-disubstituted pyridine and veratryl chromophores in Sceletium alkaloid A_4 was ascertained from its u.v. spectrum [λ_{max}(EtOH)(log ϵ_{max}) 232 (3·84), 268 (3·59), 274 (3·61), and 286 nm (3·47)]. It closely matches the summation u.v. spectrum of 2,3-lutidine and 3,4-dimethoxytoluene. The i.r. spectrum, ν_{max}(KBr) 1605, 1582, 1571, and 1520 cm^{-1}, simply confirmed the presence of aromatic rings.

The ^1H n.m.r. spectrum at 100 MHz ($CDCl_3$; Me_4Si as internal standard) showed three three-proton singlets at δ 2·34 (NMe), 3·70 (OMe), 3·77 (OMe), and a multiplet at δ 6·48—6·72 corresponding to three aromatic protons. Furthermore, a low-field AMX isolated spin system at 8·48 (dd, *J* 5 and 2 Hz, H_A), 7·56 (dd, *J* 7 and 2 Hz, H_M), and 7·15 (dd, *J* 7 and 5 Hz, H_X) was observed for a 2,3-disubstituted pyridine ring.

Accounting for the molecular formula of $C_{20}H_{24}N_2O_2$ with the two remaining methylene groups in an additional six-membered ring and the observed spectral information, led us to favour structure (4) for partially racemic Sceletium alkaloid A_4.

Subjecting the base to catalytic hydrogenolysis[4] (Pd/C) in water at 55° and atmospheric pressure, one mole of hydrogen was taken up to yield an oil. The spectral (i.r., u.v., m.s., and n.m.r.) and chromatographic properties of this oily base exactly fit those of tortuosamine (5) (*vide infra*).

Chromatographical elaboration of the total non-phenolic base fraction from the same plant afforded yet another alkaloid, named tortuosamine. Tortuosamine (5), a relatively polar, noncrystalline compound, $[\alpha]_D^{20}$ − 29° (*c* 1·04; MeOH), which, chromatographically (t.l.c. and g.l.c.) proved to be homogeneous, represents a variant of the recently isolated seco-mesembranes, *e.g.* joubertiamine[5] (6).



(7) (8) (9)

An accurate mass determination of the molecular ion in the mass spectrum at 70 eV provided the molecular formula of tortuosamine as $C_{20}H_{26}N_2O_2$. The presence of isolated 2,3-disubstituted pyridine and veratryl chromophores in tortuosamine was ascertained from its u.v. spectrum [λ_{max}(EtOH)(log ϵ_{max}) 230 (4·05), 252 (3·73), 258·5 (3·82), 265 (3·88), 272 (3·9), and 279 nm (3·9)]. The i.r. spectrum, ν_{max}($CHCl_3$) 1600, 1578, 1520, and 1455 cm^{-1}, confirmed the presence of a benzene and a pyridine ring in tortuosamine.

The ^1H n.m.r. spectrum of tortuosamine at 60 MHz in deuteriochloroform showed, in addition to an exchangeable (D_2O) proton at δ 1·9, three three-proton singlets at δ 2·32 (NMe), 3·77 (OMe), 3·81 (OMe), and a multiplet at δ 6·7—6·8 corresponding to three aromatic protons. Similarly an AMX isolated spin system at δ 8·3 (dd, *J* 5 and 2 Hz, H_A), 7·44 (dd, *J* 7·5 and 2 Hz, H_M), and 7·02 (dd, *J* 7·5 and 5 Hz, H_X) additionally was observed for a 2,3-disubstituted pyridine ring at characteristically low field.

Considering the molecular formula of $C_{20}H_{26}N_2O_2$ with three methylene groups in presumably an additional ring and the spectral information above, a C_3H_8N fragment is left unaccounted for. This fragment is best accounted for as a 2-methylaminoethyl chain. Confirmative evidence was obtained from the mass spectrum of tortuosamine at 70 eV which showed a base peak at *m/e* 44, attributable to the ion (7). On deuterium exchange both the molecular ion and the base peak showed $\Delta m = 1$. In addition, an abundant ion (8) at *m/e* 269, measured as $C_{17}H_{19}NO_2$, was observed both at 70 and 15 eV.

On acetylation with acetic anhydride tortuosamine rapidly afforded an *N*-acetate, ν_{max}($CHCl_3$) 1633 cm^{-1}, M^+ at *m/e* 368. Clarke–Eschweiler *N*-methylation of tortuosamine gave an oil with *m/e* 340 (M^+, 86%), 268 (100%), and 58 (83%). Both 3-(4-*N*-methylaminobutyl)pyridine[4,6] (9; R = H) and 3-(4-*NN*-dimethylaminobutyl)pyridine[4] (9; R = Me) were employed as reasonable model compounds for spectral and chemical correlative studies.

Biogenetic reasoning[7] led us to favour structure (5) for tortuosamine. However, different positioning of the 2,3-disubstituted pyridine ring suggests several other possible structures. Previously Sceletium alkaloid A_4 was hydro-

genolytically related to tortuosamine, which therefore must have structure (5).

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[1] F. O Snyckers, H. W. Pretorius, and A. Wiechers, unpublished results.
[2] A. Popelak and G. Lettenbauer, in "The Alkaloids", Vol. IX, ed. R. H. F. Manske, Academic Press, New York, 1967, p. 467.
[3] P. W. Jeffs, G. Ahmann, H. F. Campbell, D. S. Farrier, G. Ganguli, and R. L. Hawks, *J. Org. Chem.*, 1970, **35**, 3512.
[4] H. Erdtman, F. Haglid, and I. Wellings, *Acta Chem. Scand.*, 1963, **17**, 1717.
[5] R. R. Arndt and P. E. J. Kruger, *Tetrahedron Letters*, 1970, 3237.
[6] O. Hromatka, *Ber.*, 1942, **75**, 522.
[7] P. W. Jeffs, personal communication.