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ALKALOIDS FROM SCELETIUM JOUBERTII L. BOL. THE STRUCTURE OF JOUBERTIAMINE, DIHYDROJOUBERTIAMINE, AND DEHYDROJOUBERTIAMINE

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Interest in the constituents of certain Sceletium species (fam. Aizoaceae), which are indigenous to Southern Africa, has its origin in their use for the preparation of the drug "Channa"[1] or "Kougoed".[2] The "Kougoed" used by the Bushmen of Namaqualand is a preparation of the dried aerial parts of Sceletium expansum L. Bol. and Sceletium tortuosum N.E. Br.[3] When chewed it is said to exert a strongly narcotic action, in many respects resembling that of cocaine.[4]

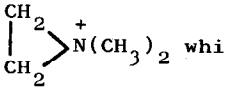
Alkaloidal substances were first detected in the "Channa" drug in 1896.[5] In view of more recent studies,[6] it was shown to consist of a mixture of alkaloids closely related to the major alkaloid mesembrine. The name mesembrine was derived from the then called genus Mesembryanthemum Dil which recently has been reclassified to the genus Sceletium N.E. Brown.

The basic skeleton of the mesembrine alkaloids is represented by mesembrane (I), an N-methyl-3a-(3',4'-dimethoxyphenyl)-cis-octahydroindole.

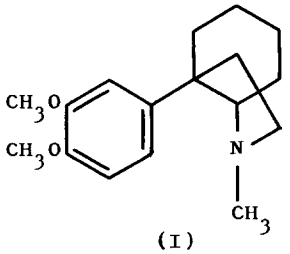
In the course of continuing search for new constituents from Sceletium species, three new alkaloids joubertiamine (II), dihydrojoubertiamine (III), dehydrojoubertiamine (IV) and a known alkaloid hordenine (V), were isolated from the species Sceletium joubertii L. Bol. Although the basic skeleton of these new alkaloids are biogenetically closely related to mesembrane (I), this is the first Sceletium species known, which lacks the presence of the mesembrine-like alkaloids.

Extraction (2% ethanolic tartaric acid) of the aerial parts of Sceletium joubertii L. Bol. (3.30 Kg), yielded a crude alkaloid mixture (1.10 g).

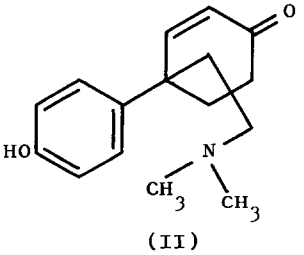
Separation of these alkaloids was achieved by repeated chromatography on alumina, and silica gel impregnated with Na_2CO_3.

High resolution mass spectrometry indicated the molecular formula of joubertiamine to be $C_{16}H_{21}NO_2$ (M^+, 259)*. The base peak at m/e 58 suggested the formation of the fragment $CH_2=^+N(CH_3)_2$ resulting from an α-cleavage with respect to the nitrogen atom. A weaker peak at m/e 72 analysed for the fragment  which indicates that the alkaloid contains an N-dimethylaminoethyl chain. The ultraviolet spectrum+ λ_{max} 226, 278 nm (ε 13,610, 1960 respectively) and λ_{max} (NaOH/EtOH) 228, 243 and 294 nm (ε 12,050, 13,810 and 2449 respectively) is in accordance with the presence of a monohydric phenol moiety and an α, β-unsaturated carbonyl chromophore. The infrared spectrum confirmed the latter, showing a strong band at 1688 cm^{-1} typical of a α, β-unsaturated six-membered ring ketone.

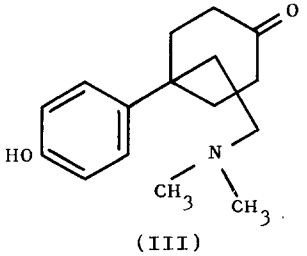
The n.m.r. spectrum was most informative, especially with regard to the substitution pattern of the benzene and cyclohexenone rings. The four aromatic protons appeared as two doublets at τ2.95(2H) and τ3.43(2H), J = 8Hz, indicating that the phenol is <u>para</u> substituted. The two olefinic proton signals appeared as two doublets at τ3.92(1H) and τ2.96(1H), J = 10Hz. The fact that the olefinic proton on the β-carbon was not further split indicated that the γ-carbon of the cyclohexenone ring was tetra-substituted. A six-proton singlet appeared at τ7.75 representing the $-N(CH_3)_2$ group. The structure II suggested for joubertiamine is in agreement with all the above data given.



(I)



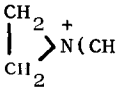
(II)



(III)

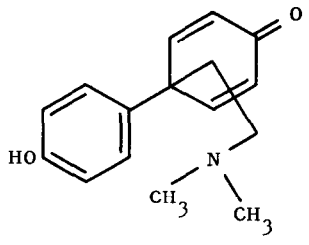
* Satisfactorily accurate mass analyses were obtained for all the peaks mentioned in the text.

\+ Unless otherwise stated, all i.r. spectra were done in $CHCl_3$, u.v. spectra in 96% EtOH and n.m.r. spectra in $CDCl_3$ on a HA-100 Varian instrument.

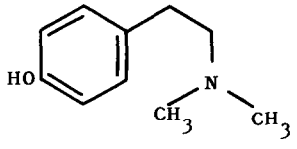
That the second alkaloid dihydrojoubertiamine (III), $C_{16}H_{23}NO_2$ (M^+, 261), was closely related to joubertiamine was evident from the similarity of the spectrometric data: λ_{max} 226, 278 nm (ε 7905, 1857 respectively) and λ_{max} (NaOH/EtOH) 245, 296 nm (ε 11,290, 2610 respectively); υ_{max} 1710 cm^{-1} (sat. six-membered ring ketone). In addition to the molecular ion peak the mass spectrum gave a base peak at m/e 58 [$CH_2=^+N(CH_3)_2$] and a weak peak at m/e 72 for the fragment  . The n.m.r. spectrum gave a singlet at τ7.70 [$-N(CH_3)_2$] and showed the same pattern for the four aromatic protons as in II, at τ2.88 (doublet, 2H) and τ3.47 (doublet, 2H), J = 8Hz. However no olefinic proton signals were observed.

Final correlation between joubertiamine and dihydrojoubertiamine was obtained by catalytic hydrogenation of the two alkaloids (PtO_2/H_2) to yield an identical product, viz. dihydrojoubertiaminol (VI), $C_{16}H_{25}NO_2$ (M^+, 263), m.p. 226 - 228°; λ_{max} 226, 278 nm (ε 6625, 1218 respectively), λ_{max} (NaOH/EtOH) 245, 286 nm (ε 8604, 1980 respectively); υ_{max} 3200 (OH); 1618, 1598, and 1520 cm^{-1} (aromatic).

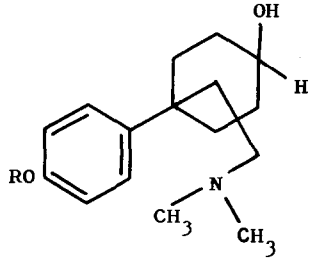
Dihydrojoubertiaminol on treatment with diazomethane gave the methyl ether VII, $C_{17}H_{27}NO_2$ (M^+, 277). The n.m.r. spectrum showed a singlet at τ6.10(3H) due to the $-OCH_3$ protons.



(IV)



(V)



(VI):R=H; (VII):R=CH_3

The third new alkaloid dehydrojoubertiamine (IV), $C_{16}H_{19}NO_2$ (M^+, 257) was isolated in very minute quantities. Even in the purest form it was still contaminated with small amounts of II and III. The n.m.r. spectrum of IV showed two superimposed AB systems in the olefinic region, τ3.71(2H) and τ3.13(2H), J = 10 Hz, indicative of a cross-conjugated dienone system. Hydrogenation of dehydrojoubertiamine (PtO_2/EtOH) also yielded the hydrogenation product VI.

In addition to the three new alkaloids, a known alkaloid hordenine (V), $C_{10}H_{15}NO$ (M^+, 165), m.p. 110°, was isolated and identified by comparison with an authentic sample (mixed m.p., chromatography). The presence of hordenine in this Aizoaceae species is of special interest since it has been shown that for both hordenine and mesembrine, tyrosine is the biosynthetic precursor.[7,8] Experiments are in progress to investigate the biosynthetic route of these alkaloids isolated from Sceletium joubertii L. Bol.

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