Joubertinamine: A Novel *seco*-Mesembrane Alkaloid

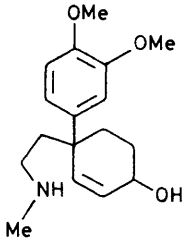
By **Klaus Psotta,*† (the late) Franz Strelow,** and **Adrian Wiechers,** Department of Chemistry, University of Pretoria, Pretoria, South Africa

Joubertinamine, a novel alkaloid isolated from *Sceletium joubertii* L. Bolus, has been shown to be 4-(*N*-methylaminoethyl)-4-(3,4-dimethoxyphenyl)cyclohex-2-en-1-ol (1).

DURING a recently conducted chemical screening of several *Sceletium* species (family *Aizoaceae*),[1] the novel *seco*-mesembrane alkaloid joubertinamine (1) ‡ was isolated from *Sceletium joubertii* L. Bolus. Subsequent spectrometric and chemical studies ascertained its constitution.

RESULTS AND DISCUSSION

Extensive extraction of the wet plant material with 2% methanolic tartaric acid solution and chromatography of the obtained crude base fraction over neutral alumina, followed by preparative t.l.c. on buffered (Na_2CO_3) silica gel plates, afforded chromatographically-homogeneous joubertinamine.



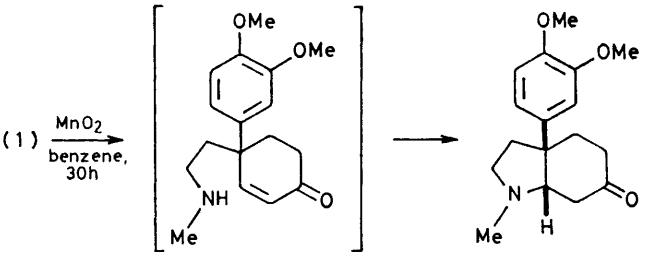
(1)

(2)

The mass spectrum of jourbertinamine showed a molecular ion at *m/e* 291, which is also the base peak. Accurate mass measurement established the molecular formula as $C_{17}H_{25}NO_3$ (Calc., *M* 291.183 4. Found, M^+ 291.183 4). A peak at *m/e* 44 (76%) suggested formation of the fragment $Me-NH^+=CH_2$, resulting from an α-cleavage with respect to the nitrogen atom. A peak at *m/e* 58 (9%) suggested the fragment (2) which is indicative of an *N*-methylaminoethyl side chain. The *N*-methyl group was confirmed by n.m.r. spectroscopy, where it appeared as a three-proton singlet at δ 2.34.

The presence of a veratryl group in the molecule was evident from its u.v., n.m.r., and i.r. spectra. The u.v. spectrum [$\lambda_{max.}$ (96% EtOH) 231, 280, and 284 (shoulder) nm (log ε 3.9, 3.5, and 3.45, respectively)] is characteristic of compounds containing the veratryl moiety, as exemplified in the work of Pfäffli and Hauth.[3] The n.m.r. spectrum showed two three-proton singlets at δ 3.84 and 3.85 for aromatic methoxyls and a multiplet between δ 6.7 and 7.0, corresponding to three aromatic protons. In the i.r. spectrum the strong bands at 1 250and 1 020 cm^{-1} are characteristic of the asymmetric and symmetric C–O–C stretching vibrations of alkyl aryl ethers. A weak i.r. band at 3 600 cm^{-1}, together with a broad, weak band between 2 500 and 3 500 cm^{-1}, indicated the presence of a hydroxyl-group. A D_2O-exchangeable two-proton singlet at δ 2.50 confirmed the presence of both the *NH* of the *N*-methylaminoethyl side chain and a hydroxylic proton. A one-proton multiplet between δ 4.0 and 4.3 was assigned to the methine proton adjacent to the deshielding hydroxy-group, thereby confirming the secondary nature of the hydroxy-group. A broadened two-proton singlet at δ 5.90 was assigned to olefinic protons. This assignment was confirmed by a moderately strong i.r. band at 1 665 cm^{-1}, characteristic of an unconjugated, *cis*-disubstituted double bond. Correlation with previously encountered mesembrane alkaloids suggested this double bond to be part of a substituted cyclohexane ring.

Mild oxidation of joubertinamine with activated manganese dioxide[4] afforded stereospecifically (—)-mesembranone (4) in good yield. This rather unexpected result can only be explained if the six-membered rings of both joubertinamine and mesembranone are oxygenated in the same position. This confines the olefinic bond of joubertinamine to one position only. Michael-type addition of the amine to the oxidatively formed enone intermediate (3) then affords mesembranone (4).



(3) (4)

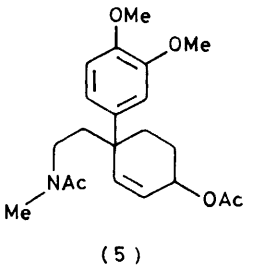
These spectral and chemical results constitute firm evidence for the formulation of joubertinamine as (1). In addition, the results of two derivatization reactions were in full agreement with this formulation.

Reduction of joubertinamine with both sodium borohydride and lithium aluminium hydride resulted in the quantitative recovery of starting material. Acetylation of joubertinamine with acetic anhydride and pyridine afforded the *NO*-diacetate (5); $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1} (C=O); δ($CDCl_3$) 1.91 (s, 3 H, OAc), 1.97 and

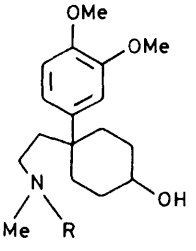
† *Present address:* National Timber Research Institute of the CSIR, PO Box 395, Pretoria, South Africa.

‡ This name is not to be confused with that of another *seco*-mesembrane, joubertiamine.[2]

1.99 (2 s, 3 H, 2 forms of NAc), and 2.82 and 2.85 (2 s, 3 H, 2 forms of N*Me*Ac); *m/e* 375 ($M^{+\cdot}$).



(5)



(6) R = Et
(7) R = Me

Catalytic hydrogenation of joubertinamine in absolute ethanol afforded (6), *m/e* 321 ($M^{+\cdot}$), as indicated by the disappearance of the i.r. band at 1 655 cm^{-1} and the two-proton singlet at δ 5.90. The methine proton shifted to δ 3.54, and there appeared a three-proton triplet (*J* 7 Hz, N–CH_2–*Me*) at δ 0.98 and a two-proton quartet (*J* 7 Hz, N–CH_2–Me) at δ 2.46. Similarly hydrogenation in methanol afforded (7), with *m/e* 307 ($M^{+\cdot}$) and ^{1}H n.m.r. at δ 2.15 (s, 6 H, NMe_2).[5]

EXPERIMENTAL

I.r. spectra were obtained on a Unicam SP 200 spectrophotometer as solutions in chloroform. N.m.r. spectra were recorded with a Varian HA100 spectrometer in $CDCl_3$ with tetramethylsilane as internal reference. Mass spectra were determined with an A.E.I. model MS-9 spectrometer with direct-probe insertion and operated at an ionising potential of 70 eV. The probe inlet temperature and the percentage abundances of peaks relative to the base peak (100%) in each spectrum are given in parentheses. The microanalysis was performed by CSIR, Pretoria. The u.v. spectrum was recorded with a Unicam SP 800 spectrophotometer. Optical rotations were determined with a Perkin-Elmer model 141 polarimeter. T.l.c. and preparative t.l.c. were performed on plates prepared from Merck Silica Gel GF_{254}.

Isolation of Joubertinamine (1).—Fresh *Sceletium joubertii* L. Bolus plants (1.7 kg) were extracted in 2% methanolic tartaric acid (5 l) for three days. The resulting pulp was filtered (filter aid) and the filter cake was extracted with refluxing 2% methanolic tartaric acid solution (3 l) for 24 h. Filtration (filter aid) and solvent evaporation of the combined extracts afforded an aqueous residue (*ca.* 180 ml) which was acidified to pH 2 (2N HCl) and filtered again. The filter cake was extensively washed with water. Extraction of the combined filtrate and washings with ether (6 × 60 ml) removed the non-basic material. Basification (solid Na_2CO_3) and extraction ($CHCl_3$; 12 × 60 ml) followed. The combined chloroform extract was reduced to *ca.* 200 ml and washed successively with 3% aqueous sodium hydroxide (5 × 20 ml) and water (30 ml). Drying (Na_2CO_3) and solvent evaporation afforded the total base fraction (10 g), which was chromatographed over basic alumina II—III (950 g). Gradient elution with benzene (2 l), dichloromethane (3 l), chloroform (3 l), and methanol (3.5 l) afforded four main fractions. The methanol fraction (0.4 g) was chromatographed preparatively using chloroform–methanol (7 : 3 v/v) on buffered (0.2M Na_2CO_3) silica gel plates to yield an oil. Filtration through neutral alumina V (4 g) afforded homogeneous (t.l.c.) *joubertinamine* (150 mg); $[\alpha]_D^{20}$ −18° ($CHCl_3$); $\lambda_{max.}$ (96% EtOH) (log $\varepsilon_{max.}$) 231 (3.9), 280 (3.5), and 284 (sh) nm (3.45); $\nu_{max.}$ 3 600w, 3 500—2 500w,br, 2 900, 2 810s, 1 655m, 1 603w, 1 585m, 1 500, 1 460s, 1 250s, 1 145s, 1 020s, and 850m cm^{-1}; δ 1.2—2.2 (m, 6 H), 2.50 (s, 2 H, D_2O exchangeable), 2.2—2.7 (m, 2 H), 2.33 (s, 3 H), 3.84 and 3.85 (2s, 6 H), 4.1—4.3 (m, 1 H), 5.89 (s, 2 H), and 6.7—7.0 (m, 3 H); *m/e* (160 °C) 292 (23), 291 (100%, $M^{+\cdot}$), 234 (53), 233 (22), 215 (9), 203 (14), 180 (23), 151 (16), 58 (9), and 44 (76) (Found: C, 70.15; H, 8.70; N, 4.96%; $M^{+\cdot}$, 291.183 4. $C_{17}H_{25}NO_3$ requires C, 70.07; H, 8.65; N, 4.81%; *M*, 291.183 4).

Manganese Dioxide Oxidation of Joubertinamine.—Activated manganese dioxide [4] (30 mg, 0.35 mmol) was suspended in a solution of joubertinamine (12 mg, 0.041 mmol) in benzene (5 ml) and stirred at room temperature for 30 h (t.l.c. control). Dilution of the mixture and filtration (filter aid), followed by thorough washing of the filter cake ($CHCl_3$, 10 × 30 ml), afforded homogeneous (t.l.c.) (−)-mesembranone (10.5 mg; 88%), $[\alpha]_D^{20}$ −55° (MeOH),[1] identical with an authentic specimen.

Joubertinamine NO-*Diacetate.*—Joubertinamine (13 mg, 0.04 mmol) was treated with pyridine–acetic anhydride (1 : 2 v/v; 2 ml) under nitrogen at room temperature for 3 h (t.l.c. control). Subsequent work-up and chromatography over alumina III (5 g; dichloromethane eluant) afforded chromatographically homogeneous (5) (11 mg; 66%); $[\alpha]_D^{20}$ +21° ($CHCl_3$); $\nu_{max.}$ 1 720s cm^{-1}; δ 0.5—2.4 (m, 6 H), 1.91 (s, 3 H), 1.97 and 1.99 (2 s, each 3 H), 2.82 and 2.85 (2 s, each 3 H), 2.9—3.3 (m, 2 H), 3.82, 3.84, 3.85, and 3.87 (4 s, 6 H), 5.2—5.4 (m, 1 H), 5.8—6.1 (m, 2 H), and 6.7—7.0 (m, 3 H); *m/e* (130 °C) 375 (28, $M^{+\cdot}$), 215 (100), 100 (18), 57 (16), and 44 (26) (Found: $M^{+\cdot}$, 375.204 8. $C_{21}H_{29}NO_5$ requires *M*, 375.204 6).

Catalytic Hydrogenation of Joubertinamine.—The same procedure was employed for hydrogenation in both methanol and ethanol. A solution of joubertinamine (18 mg, 0.056 mmol) in the absolute alcohol (5 ml) was added rapidly to 10 mg of pre-reduced platinum catalyst in the same solvent (5 ml). The mixture was stirred under 1 atm of hydrogen for several hours (t.l.c. control). Filtration and chromatography on buffered (0.1N Na_2CO_3) silica gel plates afforded the chromatographically pure products: (6) (11 mg; 55%), $[\alpha]_D^{20}$ −6° ($CHCl_3$); $\nu_{max.}$ 3 600w cm^{-1}; δ 0.98 (t, 3 H, *J* 7 Hz), 1.1—2.6 (m, 13 H, 1 H being D_2O exchangeable), 2.20 (s, 3 H), 2.46 (q, 2 H, *J* 7 Hz), 3.54 (broad m, $W_{\frac{1}{2}}$ 6.5 Hz, 1 H), 3.89 (s, 6 H), and 6.84 (s, 3 H); *m/e* (125 °C) 321 (25, $M^{+\cdot}$), 236 (31), and 72 (100) (Found: $M^{+\cdot}$ 321.229 7. $C_{19}H_{31}NO_3$ requires *M*, 321.230 4): or (7) (14 mg; 74%); $\nu_{max.}$ 2 500—3 600w,br cm^{-1}; δ 1.3—2.5 (m, 13 H, 1 H being D_2O exchangeable), 2.15 (s, 6 H), 3.4—3.7 (br m, 1 H), 3.85 (s, 6 H), and 6.7—6.9 (m, 3 H); *m/e* (90 °C) 307 (13, $M^{+\cdot}$), 236 (40), 58 (100) (Found: $M^{+\cdot}$, 307.214 3. $C_{18}H_{29}NO_3$ requires *M*, 307.214 7).

We thank the Council for Scientific and Industrial Research and the Atomic Energy Board, Pretoria, for financial support.

[8/619 *Received*, 5*th April*, 1978]

REFERENCES

[1] A. Popelak and G. Lettenbauer in, ' The Alkaloids,' vol. IX, ed. R. H. F. Manske, Academic Press, 1967, p. 467.

[2] R. R. Arndt and P. E. J. Kruger, *Tetrahedron Letters*, 1970, 3237.
[3] P. Pfäffli and H. Hauth, *Helv. Chim. Acta*, 1973, **56**, 347.
[4] A. J. Fatiadi, *Synthesis*, 1976, 65.
[5] For related alkylations of amines by alcohols in the presence of hydrogenation–dehydrogenation catalysts, see E. F. Pratt and E. J. Frazza, *J. Amer. Chem. Soc.*, 1954, **76**, 6174, and references cited therein.