(4*R*)-(—)-*O*-Methyljoubertiamine and *O*-Methyldihydrojoubertiamine, Two Minor Alkaloids from *Sceletium subvelutium* L. Bolus

By **Jacobus J. Nieuwenhuis**, (the late) **Franz Strelow**, **Heinrich F. Strauss**, and **Adriaan Wiechers**,* Department of Chemistry, University of Pretoria, Pretoria, 0002, Republic of South Africa

(4*R*)-(—)-*O*-Methyljoubertiamine and *O*-methyldihydrojoubertiamine, two new *seco*-mesembrane alkaloids, have been isolated from *S. subvelutium* L. Bol.

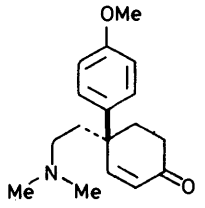
THE total synthesis of racemic *O*-methyljoubertiamine (±)-(1) has been the subject of many synthetic programmes,[1] although its isolation from natural sources has hitherto not been reported. The closely related alkaloids joubertiamine (2) and dihydrojoubertiamine (3a) were previously isolated by Arndt and Kruger from *S. joubertii*.[2] Also, (—)-3'-methoxy-*O*-methyljoubertiamine (4) was recently isolated by Jeffs and co-workers from *S. namaquense*.[3] We now report the isolation and characterization of the two new alkaloids (4*R*)-(—)-*O*-methyljoubertiamine (1) and *O*-methyldihydrojoubertiamine (3b).

RESULTS AND DISCUSSION

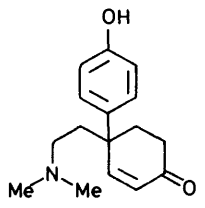
The total non-phenolic base fraction from *S. subvelutium* L.Bol. consisted of two major components, which were separated by preparative layer chromatography on alumina. The major component was thus isolated as a syrupy base, b.p. 110—120 °C (bath temperature/0.01 mmHg), $[\alpha]_D^{25}$ —51° (*c* 1.45, MeOH). The mass spectrum at 14 eV showed a molecular ion at *m/e* 273 (also the base peak), accurate measurement of which provided the molecular formula as $C_{17}H_{23}NO_2$. Furthermore, an abundant ion at *m/e* 58 ($Me_2\overset{+}{N}{=}CH_2$) and a moderately abundant ion at *m/e* 72 (dimethylaminoethyl side-chain) were observed. The u.v. spectrum [$\lambda_{max.}$ (MeOH) (log $\varepsilon_{max.}$) 227 (4.19), 276 (3.25), and 282.5 (3.21) nm] is in accord with the presence of enone and anisyl chromophores. The i.r. spectrum [$\nu_{max.}$ (neat, NaCl) 1 676, 1 608, 1 579, 1 515, 1 460, 1 250, and 836 cm^{-1}] simply confirmed the presence of an enone and a 1,4-disubstituted oxygenated aromatic ring.

The ^1H n.m.r. spectrum showed a six-proton singlet at δ 2.12 (NMe_2) and a three-proton singlet at δ 3.77 (ArO*Me*). An AB double doublet (*J* 10 Hz) at δ 6.14 and 7.08 was indicative of an isolated enone spin system. An AA'BB' pattern (*J* 8 Hz) was observed at δ 6.85 and 7.18 for the anisyl ring.

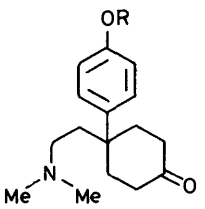
The structure (1) for *O*-methyljoubertiamine is in full agreement with all the observed spectral information above. It also fits exactly the spectra of synthetic racemic *O*-methyljoubertiamine [1b] and has identical chromatographic (t.l.c.) properties with the synthetic product. In addition, when (—)-*O*-methyljoubertiamine was subjected to selective catalytic hydrogenation (Pd–C) in ethanol at room temperature and atmospheric pressure, 1 mol equiv. of hydrogen was consumed to yield *O*-methyldihydrojoubertiamine. The chromatographic (t.l.c.) and m.s. ($M^{+\cdot}$, *m/e* 275) spectral properties fully corroborate with that of natural *O*-methyldihydrojoubertiamine (3b) (see below).



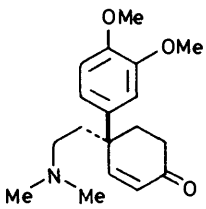
(1)



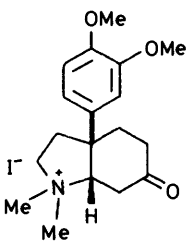
(2)



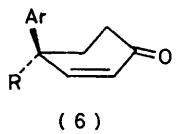
(3a) R = H
(3b) R = Me



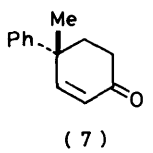
(4)



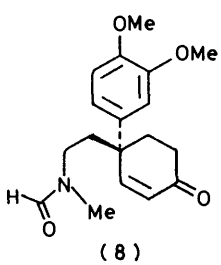
(5)



(6)



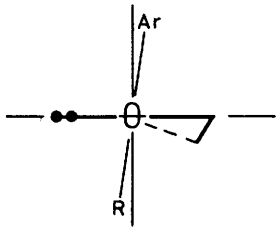
(7)



(8)

The c.d. spectrum of (4*R*)-(—)-mesembranone methine [3] (4), rapidly formed by β-elimination of mesembranone methiodide (5) with 0.5N potassium hydroxide

solution at room temperature, shows two negative maxima in the $n\rightarrow\pi^*$ (*ca.* 330 nm) region. The c.d. spectrum if (−)-*O*-methyljoubertiamine is of similar sign and shape, and of somewhat lower rotational strength. Hence the absolute configuration of (−)-*O*-methyljoubertiamine is (4*R*), as in (1). Empirically it has been found [4] that cyclohexenones with a coplanar transoid chromophore give a negative Cotton effect if the ring has the conformation in the Figure. Therefore, at



FIGURE

room temperature the cyclohexenone ring of (−)-*O*-methyljoubertiamine prefers the half-chair conformation with a pseudo-axial disposition of the 4-methoxyphenyl ring, *e.g.* (6). Finally, the syntheses of (4*R*)-(+)-4-methyl-4-phenylcyclohex-2-en-1-one [5] (7) and compound (8) [6] have been reported. Both showed positive Cotton effects in the 350-nm region.

The mass spectrum, at 12 eV, of the minor component of the total non-phenolic base fraction, showed a molecular ion at *m/e* 275, accurately measured as $C_{17}H_{25}NO_2$. The base peak in the mass spectrum appeared at *m/e* 58 ($Me_2\overset{+}{N}=CH_2$). The presence of anisyl and cyclohexanone rings in *O*-methyldihydrojoubertiamine was ascertained from the u.v. [$\lambda_{max.}$ (MeOH)(log $\varepsilon_{max.}$) 226 (3.24), 276 (2.51), and 283 (2.45) nm] and i.r. [$\nu_{max.}$ (neat, NaCl) 1 607, 1 580, 1 515, 1 465, 1 245, and 825 cm^{-1}] spectra. The ^1H n.m.r. spectrum provided confirmatory evidence. Besides a six-proton singlet at δ 2.10 (NMe_2) and a three-proton singlet at δ 3.76 (ArO*Me*), an isolated AA'BB' spin system, characteristic of a 1,4-disubstituted oxygenated aromatic ring, was observed at δ 6.88 and 7.24 (*J* 9 Hz). The structure (2b) for *O*-methyldihydrojoubertiamine is in full agreement with all the data given above.

EXPERIMENTAL

I.r. spectra were obtained on a Unicam SP200 spectrophotometer, and ^1H 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 operating at the ionising potential stated. The percentage abundances of peaks relative to the base peak (100%) in each spectrum are given in parentheses. U.v. spectra were recorded with a Unicam SP800 spectrophotometer. Optical rotations were determined on a Perkin-Elmer model 141 polarimeter. Circular dichroism spectra were determined on a Jasco ORD/UV-5 instrument with attachment for c.d. measurements.

Isolation of (R)-(−)-O-*Methyljoubertiamine* (1) *and* O-*Methyldihydrojoubertiamine* (2b) *from* Sceletium subvelutium *L.Bol.*—Wet plant material (5.7 kg, whole plants) was homogenized in 2% methanolic tartaric acid solution (5 l) and left soaking at room temperature for 12 days, with occasional stirring and agitation of the plant pulp. After filtering the plant homogenate through Celite, at the water pump, the resulting filter cake was re-extracted with boiling methanol (5 l) for 24 h and again filtered through Celite. The methanol from the combined methanolic extracts was evaporated under reduced pressure and the residual aqueous phase (*ca.* 1 l) acidified (pH *ca.* 2) with 6N-hydrochloric acid solution (350 ml). The aqueous acidic solution was filtered through Celite and the filter pad repeatedly washed with water. The combined filtrate was then washed with ether (4 × 100 ml). The aqueous phase was basified with solid potassium carbonate (pH *ca.* 9) and extracted with chloroform (7 × 100 ml). The volume of the combined chloroform extract was reduced to *ca.* 300 ml, washed with water (1 × 75 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford the total base fraction (1.07 g).

The total base fraction was re-dissolved in chloroform (50 ml) and washed successively with portions of 1N-sodium hydroxide solution (5 × 10 ml), and the combined sodium hydroxide extract was washed once with chloroform (10 ml). The combined chloroform extract was washed with water (1 × 10 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give the total non-phenolic base fraction (180 mg). The fraction was chromatographed on basic alumina (25 g; activity III; the column was packed in anhydrous benzene). The column was eluted with benzene (75 ml), benzene–chloroform (4 : 1, v/v, 50 ml), chloroform–benzene (4 : 1, v/v, 50 ml), chloroform (20 ml), chloroform–methanol (1 : 1, v/v, 50 ml) and methanol (75 ml). A mixture (108 mg) of mainly two components, R_F 0.8 and 0.72 [Al_2O_3, MeOH–CH_2Cl_2 (1 : 99 v/v), Dragendorf] was eluted with chloroform–benzene (1 : 1, v/v). The mixture (108 mg) was preparatively separated [Al_2O_3, MeOH–CH_2Cl_2 (1 : 99 v/v), 0.5-mm thickness) and the alumina scrapings from the bands, R_F 0.8 and 0.72, were extracted with chloroform.

The individual components were separately subjected to preparative layer chromatography (see above) on alumina (10 g; CH_2Cl_2). The higher R_F component afforded chromatographically homogeneous syrupy *O*-methyljoubertiamine (16 mg); R_F 0.80 [Al_2O_3, MeOH–CH_2Cl_2 (1 : 99, v/v), Dragendorf); b.p. 110—120 °C (bath temperature)/0.01 mmHg; $[\alpha]_D^{25}$ −51° (*c* 1.45, MeOH); c.d. (*c* 0.138 mg ml^{-1}, MeOH at 21 °C) $[\theta]_{356}$ 0, $[\theta]_{340}$ −654, $[\theta]_{325}$ 0, $[\theta]_{300}$ 0, $[\theta]_{294}$ −327, and $[\theta]_{288}$ 0; $\nu_{max.}$ (neat; NaCl) 1 676 (C=C–C=O), 1 608, 1 579, 1 515 (aromatic-ring), 1 460, 1 250, and 836 (1,4-disubstituted aromatic-ring) cm^{-1}; $\nu_{max.}$ ($CHCl_3$) 1 680, 1 610, 1 580, 1 520, and 825 cm^{-1}; $\lambda_{max.}$ (MeOH) (log $\varepsilon_{max.}$) 227 (4.19), 276 (3.25), and 282.5 (3.21) nm; δ 2.12 (s, 6 H, NMe_2), 2.20—2.35 (m, 8 H), 3.77 (s, 3 H, Ar–O*Me*), 6.14 (d, 1 H, *J* 10 Hz), 7.08 (d, 1 H, *J* 10 Hz), 6.85 (2 H, *J* 8 Hz, BB' part of AA'BB' pattern), and 7.18 (2 H, *J* 8 Hz, AA' part of AA'BB' pattern); *m/e* (at 14 eV) 273 (M^+, 100%), 271(36), 71(5), 72(5), and 58(28); *m/e* (at 70 eV) 273 ($M^{+\cdot}$, 11%), and 58 ($Me_2\overset{+}{N}=CH_2$, 100) (Found: M^+, 273.172 0. Calc. for $C_{17}H_{23}NO_2$: *M*, 273.172 9).

The lower-R_F 0.72 component gave, after chromatography on alumina, chromatographically homogeneous syrupy *O*-methyldihydrojoubertiamine (10 mg); R_F 0.72 [Al_2O_3, MeOH–CH_2Cl_2 (1 : 99, v/v), Dragendorf]; $\nu_{max.}$ (neat; NaCl) 1 706 (C=O), 1 607, 1 580, 1 515 (aromatic-ring), 1 465

(CH_2), 1 245 (Ar–O–C), and 825 (1,4-disubstituted aromatic-ring) cm^{-1}; $\nu_{max.}$ ($CHCl_3$) 2 850, 1 710, 1 610, 1 580, 1 520, 1 460, and 820 cm^{-1}; $\lambda_{max.}$ (MeOH) (log $\varepsilon_{max.}$) 226 (3.24); 276 (2.51), and 283 (2.45) nm; δ 2.10 (s, 6 H, NMe_2), 1.70—2.60 (m, 12 H), 3.76 (s, 3 H, Ar–O*Me*), 6.88 (d, 2 H, *J* 9 Hz), and 7.24 (d, 2 H, *J* 9 Hz); *m/e* (at 12 eV and 120 °C) 275 ($M^{+\cdot}$, 59%), 167(7), 73(8), 72(5), and 58 ($Me_2\overset{+}{N}{=}CH_2$, 100); *m/e* (at 70 eV and 110 °C) 275 ($M^{+\cdot}$, 9%) and 58(100) (Found: M^+, 275.190 9. Calc. for $C_{17}H_{25}NO_2$: *M*, 275.197 9).

Catalytic Hydrogenation of O-Methyljoubertiamine.—A solution of *O*-methyljoubertiamine (11.8 mg, 0.043 mmol) in absolute ethanol (2 ml) was added to a suspension of pre-reduced 10% palladium–carbon catalyst (5 mg) in ethanol (1 ml). The hydrogenation mixture was stirred under hydrogen (1 atm) at room temperature for 1 h. The catalyst was then filtered off and washed with absolute ethanol. The ethanol from the filtrate and washings was evaporated under reduced pressure. The residual syrupy product (14.0 mg) was preparatively purified (SiO_2 GF_{254}, buffered with 0.1N Na_2CO_3, 0.5-mm thickness, eluant MeOH). The relevant band, R_F 0.2, was scraped off and the silica gel scrapings were eluted with hot methanol. Evaporation of the methanol afforded oily *O*-methyldihydrojoubertiamine (4.5 mg, 40%), R_F 0.2 (SiO_2 GF_{254}, buffered with 0.1N Na_2CO_3, MeOH); chromatographically (t.l.c.) and mass spectrometrically the product was identical with natural *O*-methyldihydrojoubertiamine.

Mesembranone Methiodide.[3]—A stirred solution of (−)-mesembranone (470 mg), $[\alpha]_D^{22}$ −59° (*c* 1.1, MeOH), in methyl iodide (20 ml) was refluxed under nitrogen for 30 h. On complete reaction (t.l.c. control), the excess of methyl iodide was evaporated to give solid mesembranone methiodide (500 mg).

Mesembranone Methine (5).[3]—A solution of mesembranone methiodide (384 mg) in 0.5N aqueous potassium hydroxide solution (20 ml) was shaken at room temperature for 1 h (t.l.c. control). The aqueous solution was extracted with chloroform (10 × 15 ml). The combined chloroform extract was washed with water (20 ml), dried ($MgSO_4$), and evaporated under reduced pressure to afford a yellowish, viscous oil (230 mg). The syrupy product was preparatively chromatographed (SiO_2 PF_{254}, buffered with 0.1N Na_2CO_3, 0.75-mm thickness, 20 × 40 cm) eluting with methanol. The band of R_F 0.2 was scraped off and the scrapings repeatedly extracted with boiling methanol (8 × 20 ml). The combined methanolic extract was evaporated under reduced pressure and the residue chromatographed on alumina [5 g, basic, activity III; column packed in anhydrous benzene; product eluted with benzene–chloroform (1 : 1 v/v)]. Combination of the relevant fractions (t.l.c.) and evaporation of the solvent under reduced pressure afforded chromatographically homogeneous, syrupy mesembranone methine (145 mg, 42%), b.p. 170 °C (bath temperature)/0.025 mmHg; $[\alpha]_D^{22}$ −56° (*c* 1.51, MeOH); c.d. (*c* 0.233 mg ml^{-1}, MeOH at 21 °C) $[\theta]_{380}$ 0, $[\theta]_{344}$ −1 353, $[\theta]_{320}$ −600, $[\theta]_{296}$ −1 320, and $[\theta]_{284}$ 0; $\nu_{max.}$ (neat, NaCl) 1 674 (C=C–C=O) cm^{-1}; $\lambda_{max.}$ (MeOH; log $\varepsilon_{max.}$) 239 (3.76), 277 (sh, 3.5), 290 (3.51), and 287.5 (sh, 3.43) nm; $\lambda_{max.}$ (CH_3CN; log $\varepsilon_{max.}$) 228.5 (4.21), 276 (sh, 3.51), 281 (3.54), and 288 (sh, 3.45) nm; δ 2.19 (s, 6 H, NMe_2), 1.9—2.5 (m, 8 H), 3.82, 3.85 (6 H, 2 × Ar–O*Me*), 6.14 (d, 1 H, *J* 11 Hz), 7.12 (d, 1 H, *J* 11 Hz), and 6.75—6.9 (m, 3 H, aromatic protons); *m/e* (at 70 eV and 175 °C) 303 ($M^{+\cdot}$, 100%), 289(13), 288(5), 237(5), 232(32), 218(6), 201(8), and 58(51) (Found: C, 71.1; H, 8.2; N, 4.6. Calc. for: $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62%).

We thank the C.S.I.R. and the A.E.B., Pretoria, for financial support, and Dr. P. R. Enslin for recording the c.d. spectra.

[0/121 *Received*, 23*rd January*, 1980]

REFERENCES

[1] (*a*) R. V. Stevens and J. T. Lai, *J. Org. Chem.*, 1972, **37**, 2138; (*b*) H. F. Strauss and A. Wiechers, *Tetrahedron*, 1978, **34**, 127; (*c*) S. F. Martin, T. A. Puckette, and J. A. Colapret, *J. Org. Chem.*, 1979, **44**, 3391; (*d*) C. P. Forbes, W. J. Schoeman, H. F. Strauss, E. M. M. Venter, G. L. Wenteler, and A. Wiechers, *J.C.S. Perkin I*, 1980, 906

[2] R. R. Arndt and P. E. J. Kruger, *Tetrahedron Letters*, 1970, 3237.

[3] T. M. Capps, K. D. Hargrave, P. W. Jeffs, and A. T. McPhail, *J.C.S. Perkin II*, 1977, 1098.

[4] G. Snatzke, 'Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,' Heyden and Son Ltd., London, 1976, p. 208 and refs. cited.

[5] G. Otani and S. Yamada, *Chem. Pharm. Bull.* (*Japan*), 1973, **21**, 2112.

[6] G. Otani and S. Yamada, *Chem. Pharm. Bull.* (*Japan*), 1973, **21**, 2130.