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O-METHYLPALLIDINE *N*-OXIDE, THE FIRST MORPHINANDIENONE *N*-OXIDE ALKALOID

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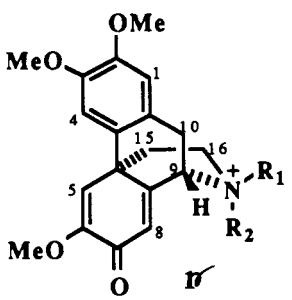
ABSTRACT.—*O*-methylpallidine *N*-oxide has been isolated from *Sarcocapnos enneaphylla* (L.) DC (Fumariaceae). Its structure has been established spectroscopically and confirmed by synthesis from *O*-methylpallidine.

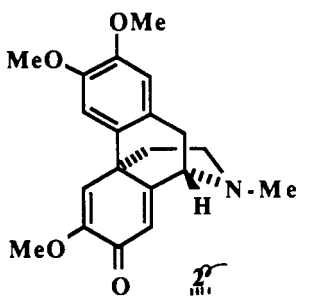
In our continuing study of the alkaloids of *Sarcocapnos enneaphylla* (L.) DC. (Fumariaceae) (1), we have isolated *O*-methylpallidine *N*-oxide [**1**], $C_{20}H_{23}NO_5$, the first example of a morphinandienone *N*-oxide. Its structure has been established through spectroscopic data and has been confirmed by synthesis from *O*-methylpallidine [**2**], an alkaloid also present in the same plant and its probable biogenetic precursor.

O-methylpallidine *N*-oxide [**1**], $[\alpha]D$ +20° ($CHCl_3$, $c=2.1$), was obtained as an amorphous, colorless substance. Its uv spectrum, λ max (EtOH) 240, 286 nm (log ε 4.47, 3.99) and ir spectrum ν max (film) 1670, 1640, 1620 cm^{-1}, were reminiscent of a morphinandienone (2). The aromatic region of the ^1H-nmr spectrum (250 MHz, $CDCl_3$) exhibited four one-proton singlets at 6.87, 6.62, 6.52, and 6.38, a pattern very close to that of *O*-methylpallidine [**2**], as well as three singlets at 3.91, 3.87, and 3.82 for three methoxyl groups. In addition, the H-9 doublet centered at 4.32 ($J=5.3$ Hz), and the downfield chemical shift of the *N*-methyl singlet (δ 3.40) suggested the presence of an *N*-oxide functionality. This assumption was confirmed by the ms spectrum, which showed the molecular ion at *m/z* 357.1587 (10) (calcd 357.1576) and other significant peaks at *m/z* $[M-16]^+$ 341 (13), 298 (40), and 284 (100). Further proof for structure **1** was obtained from the ^{13}C-nmr spectrum which was very close to that of *O*-methylpallidine (3), the only difference lying in the signals of groups bound to N (Me, C-9, and C-16) which appear on the *N*-oxide at about 15 ppm lower field. Similar differences were observed for the ^{13}C nmr of thebaine and its *N*-oxide (4).

To confirm the structure and to determine the configuration at the nitrogen asymmetric center, we prepared the two isomeric *N*-oxides **1** and **3** by treatment of *O*-methylpallidine [**2**] with *m*-chloroperbenzoic acid. Two products were obtained, but one of them readily decomposed; the other proved to be identical to the *N*-oxide isolated. Sig-



1 R_1=Me, R_2=O^-
3 R_1=O^-, R_2=Me



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nificantly, it is known that thebaine *N*-oxides exhibit similar behavior (5), the isomer with oxygen at the equatorial position being the unstable one due to its favorable orientation for a Cope elimination. On this basis we assigned for *O*-methylpallidine *N*-oxide the configuration shown in **1**.

This *N*-oxide could be an artifact formed during isolation. However, *O*-methylpallidine is a very minor alkaloid in this plant (10 mg/kg of plant) from which thirty other alkaloids have been isolated, none of which was obtained as its *N*-oxide. Assuming the conditions for oxidation are roughly the same for most of the alkaloids, it may be significant that only *N*-oxide **1** was isolated from this plant.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Analytical and preparative tlc were carried out on Si gel 60 GF-254 plates (E. Merck), developed with 5% MeOH/CH_2Cl_2. Both ^{1}H-nmr and ^{13}C-nmr spectra were recorded in $CDCl_3$ on a Bruker WM-250 spectrometer with TMS as internal standard. Routine ms spectra were obtained using a Kratos MS-25 instrument operating at 70 eV, and the high resolution ms spectrum was determined on a Kratos MS9/50 spectrometer.

PLANT MATERIAL.—*S. enneaphylla* was from a collection made in June 1982, at Cuenca, Spain. A voucher specimen was deposited in the Herbarium of the Department of Botany, Faculty of Pharmacy, University of Santiago de Compostela, Spain.

ISOLATION OF *O*-METHYLPALLIDINE.—The ground, air-dried whole plant (10 kg) was exhaustively extracted with MeOH. The MeOH extract was concentrated to a small volume and kept cold to leave a resinous precipitate. The extract was filtered and concentrated to a viscous residue that was dissolved in 5% HCl. The acid solution was washed with Et_2O, made slightly alkaline by addition of 20% NaOH, and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and evaporated to give 80 g of an oily residue which was chromatographed over 2 kg of Si gel using a CH_2Cl_2/MeOH step gradient to afford 38 fractions. Fraction 25 after preparative purification gave *O*-methylpallidine *N*-oxide (30 mg): ^{13}C nmr 179.9 (C=O), 155.3, 152.0, 149.2, and 149.1 (C-6, C-2, C-3, and C-14), 130.4 (C-12), 126.9 (C-11), 123.8 (C-8), 116.7 (C-5), 116.5 (C-4), 109.1 (C-1), 76.1 (C-9), 60.1 (C-16), 55.2 (N-Me), 57.7, 56.3, and 56.0 (3 × OMe), 40.4 and 36.7 (C-13 and C-15), 35.6 (C-10).

PREPARATION OF *N*-OXIDES **1** AND **3**.—*O*-Methylpallidine (25 mg, 0.073 mmol) was dissolved in $CHCl_3$ (2 ml), and *m*-chloroperbenzoic acid (25 mg) was added at 0°. The ice-cold mixture was stirred for 1.5 h, brought to room temperature, diluted with $CHCl_3$, and washed with 10% aqueous $KHCO_3$. The organic extract was washed with a little H_2O, dried (Na_2SO_4), and concentrated under vacuum to an amorphous oil. Tlc showed the presence of two *N*-oxides which were separated by preparative tlc. The faster running fraction readily decomposed to give a series of spots on tlc, and the other proved (R_f, [α]D, uv, ir, ^{1}H nmr, ms) to be identical to the *N*-oxide **1**.

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