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COMMUNICATION I

Chemotaxonomy of the Lauraceae: *N*-Methyl-2,3,6-trimethoxymorphinandien-7-one, the Major Alkaloid from *Alseodaphne perakensis*

ABSTRAK

Daun pokok Alseodaphne perakensis *mengandungi satu alkaloid utama dan campuran kompleks alkaloid sampingan. Komponen utama telah dikenal pasti sebagai* N*-metil-2,3,6-trimetoksimorfinandien-7-on melalui analisis spektroskopi sebatian induk, garam metiodida dan hasil penurunan natrium borohidrida.*

ABSTRACT

The leaves of Alseodaphne perakensis *contain one major and a complex mixture of minor alkaloids. The major component was identified as* N*-methyl-2,3,6-trimethoxymorphinandien-7-one by spectroscopic analyses of the parent compound, its methiodide salt and sodium borohydride reduction products.*

INTRODUCTION

During a phytochemical survey in the Lancang area of West Malaysia, a specimen identified as *Alseodaphne perakensis* was selected for chemical investigation because of its high alkaloid content as indicated by the Culvenor-Fitzgerald field test method (Lajis *et al.* 1985). *A. perakensis* is a moderate sized tree growing in the lower mountain forest in the western part of Peninsular Malaysia and has been reported to provide a durable timber useful for house building. In addition, the aborigines of the Sakai tribe claimed that the fruit from this plant is poisonous (Burkill, 1936). It is also of interest to note that this species was formerly classified as *Dehaasia microcarpa*. A literature survey indicated that chemical investigation of a related species, A. *semicarpifolia* resulted in the isolation of a hydroxyaporphine alkaloid (Smolnycki *et al.* 1978) but that no work had been reported on *A. perakensis*. We now report the results from our work on the isolation and structural assignment of the major alkaloid from this latter species.

MATERIALS AND METHODS

General

The leaves and bark of this plant were collected from the vicinity of the Wild Life Training Center, Lancang, Pahang and the voucher specimen was deposited at the herbarium of the University Pertanian Malaysia.

Melting points were determined on a Kofler hot stage and are uncorrected. Infrared and ultraviolet spectra were recorded on Hitachi EPI-62 and Perkin Elmer 124 spectrophotometers respectively. Rotations were measured on Bendix NPL Automatic Polarimeter 143C at room temperature (23-25°C). ^{1}H nmr spectra were measured at 300 MHz on a Bruker CPX 300 instrument, and ^{13}C nmr spectra were taken on a Bruker WP80. Mass spectra were recorded on a MS 12 instrument at 70eV. Spectral data for known compounds are quoted only when the literature is incomplete. Column and thin layer chromatography utilized Merck 7734 and 7730 silica gel, respectively. Solvents were distilled before use.

Extraction of Plant Material

The leaves (1.8Kg) were air dried, ground in a hammer mill to give a powder which was steeped in methanol for 48 hrs. The methanol was removed by filtration and fresh methanol added to the plant material. This process was repeated until the residue gave a negative test for alkaloids (Meyers reagent). The methanol extracts were combined and evaporated under reduced pressure to give a green gum. The gum was taken up in chloroform and extracted repeatedly with 1M H_2SO_4 until the organic

layer gave a negative test for alkaloids. The acid extracts were then combined, basified with Na_2CO_3 and exhaustively extracted with chloroform. The chloroform extracts were combined, dried and the solvent removed to give the crude alkaloids as a dark brown amorphous solid (18 g, 1%).

Isolation of N-*methyl-2,3,6-trimethoxymorphinandien-7-one*

A portion of the crude alkaloids (3.8 g) was fractionated using centrifugal tlc. The major component was eluted at a solvent composition of $CHCl_3$:MeOH (9:1) and obtained, after evaporation of the solvent, as a brown gum. This material was further purified by tlc after which crystallization from benzene yielded yellowish cubes (2.1 g). The UV, IR, ^1H and ^{13}CNMR and MS were consistent with literature (Roblot *et al.* 1984); m.p.: 127.5-128°c, (lit. m.p. 124-125°C, Lu *et al.* 1985); $[\alpha]_D$ = 11.7°, MeOH (lit. $[\alpha]_D$ = 16.9°, MeOH; Bhakuni *et al.* 1980).

Quarternization of N-methyl-2,3,6-trimethoxymorphinandien-7-one

N-Methyl-2,3,6-trimethoxymorphinandien-7-one (149 mg) was dissolved in dry acetone containing excess methyl iodide. The reaction mixture was allowed to stand overnight at room temperture after which a crystalline solid formed. The material was recovered by filtration and subsequently recrystallized from methanol to give *N*-methyl-2,3,6-trimethoxymorphinandien-7-one methiodide (200 mg, 94%) as yellow cubes m.p.: 257-8°C. (lit. m.p.: 252-4°C, EtOH; Sivakumaran and Gopinath 1976).

Reduction of N-*methyl-2,3,6-trimethoxymorphinandien-7-one*

The title compound (154 mg) was dissolved in ethanol (10 ml) and the flask cooled in an ice bath. Sodium borohydride (1.2 g) was added and the reaction mixture stirred for one hour after which water (2 ml) was added. The solution was concentrated and the remaining aqueous mixture extracted with chloroform. The crude product (177 mg) was fractionated by preparative tlc on silica gel using benzene:ethyl acetate:diethylamine (7:2:1 v/v/v) as eluant to give dienol I (46 mg) (Rf. 0.33) and dienol II (50 mg) (Rf. 0.19).

Dienol I

$[\alpha]_D$ = + 22.7° (MeOH)
UV λ_{max} nm (log ε) MeOH:
225 (sh) (4.08), 287(3.65)

IR υ_{max} cm^{-1} ($CHCl_3$ film):
3200-3600 (OH hydrogen bonded), 1656 (C = C), 1610 (w, aromatic), 1510 (s,aromatic).

^1H NMR (500 MHz, $CDCl_3$):
6.73 (s, 1H), 6.53 (s, 1H), 5.73 (d, J = 4 Hz, 1H, H-8), 5.27 (s, 1H, H-5), 4.64 (d, J = 4Hz, H-7), 3.83 (s, 3H, Ar-OCH_3), 3.81 (s, 1H, Ar-OCH_3), 3.69 (s, 3H, C_6 – OCH_3), 3.45 (d, J=6Hz, 1H, H-9), 3.19 (d, J = 17.8 Hz, 1H, H-10), 2.87 (dd, J = 6, 17.7 Hz, 1H, H-10), 2.80 (s, br, OH), 2.40-2.48 (m, 2H, H-16), 1.82 (ddd, J = 5.0, 12.7, 12.7 Hz, 1H, H-15), 1.54(ddd, J = 2.6, 2.6, 12.7 Hz, H-15).

^{13}C NMR (125.7 MHz, $CDCl_3$; DEPT-experiment)
154.49 (C-2 or C-3), 148.02 (C-2 or C-3), 142.10 (C-6), 134.0 (C-11 or C-12),129.16 (C-11 or C-12), 118.25 (CH,C-8),110.82(CH, C-1 or C-4) 108.87 (CH, C-1 or C-4), 101.76 (CH, C-5), 64.76 (CH, C-7), 61.31 (CH, C-9), 56.58 (OCH_3), 56.32 (OCH_3), 54.88 (OCH_3), 46.94 (CH_2, C-16), 42.34 (C-15 and N-CH_3), 39.96 (C-13), 31,34 (CH_2, C-10).

Ms m/e (%):
344 (M + 1, 11.2), 343 (M^+, 44.8), 342 (17.6), 328 (33.6), 326 (46.4), 325 (100), 310 (40), 269(36.8), 267 (46.4), 256 (20).

Dienol II

$[\alpha]_D$ = + 17.3° (MeOH)
UV λ_{max} nm (log ε) MeOH
255 (sh) (4.00), 288 (3.55)

IR υ_{max} cm^{-1} ($CHCl_3$ film)
3200-3600 (OH bonded), 1660 (C = C), 1615 (w, aromatic), 1520 (s, aromatic).

^1H NMR (500 MHz, $CDCl_3$):
6.74 (s,1H), 6.57 (s, 1H), 5.74 (d, J = 3.3 Hz, 1H, H-8), 5.26 (s, 1H, H-5), 4.52 (d, J = 3.3 Hz, H-7), 3.85 (s, 3H, Ar-OCH_3), 3.82 (s, 3H, Ar-OCH_3), 3.71 (s, 3H, C6 – OCH_3), 3.54 (d, J = 5.9 Hz, 1H, H-9), 3.24 (d, J =17.7 Hz, 1H, H-10), 3.18 (s, br, OH), 2.92 (dd, J = 6.1, 17.9 Hz,

1H, H-10), 2.45-2.57 (m, 2H, H-16), 2.45 (s, 3H, N-CH_3),1.97 Hz (ddd, J = 4.8, 12.5, 12.5 Hz, 1H, H-15), 1.59 (ddd, J = 2.75, 2.75, 12.6 Hz, 1H, H-15).

^{13}C NMR (125.7 MHz, $CDCl_3$; DEPT-experiment)
154.47 (C-2 or C-3), 148.11 (C-2 or C-3), 140.24 (C-6), 133.99 (C-11 or C-12), 128.92 (C-11 or C-12), 119.11 (CH, C-8), 110.90 (CH, C-1 or C-4), 108.43 (CH C-1 or C-4), 101.09 (CH, C-5), 64.31 (CH, C-7), 61.20 (CH, C-9), 56.35 (2 × OCH_3), 54.99 (OCH_3), 46.97 (CH_2, C-16), 42.118 (N-CH_3), 41.55 (CH_3, C-15), 39.95 (C-13), 31.98 (CH_2, C-10).

MS m/e (%)
344 (M+1, 12.8), 343 (M^+57.6), 342 (22.4), 328 (40), 326 (48), 325 (100), 310 (36.8), 269 (27.2), 267 (25.6), 256 (19.2).

RESULTS AND DISCUSSION

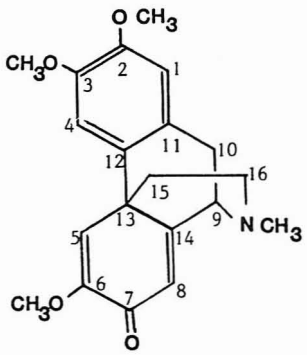
Alseodaphne perakensis is a rich source of alkaloids, with crude bases being isolated from the leaves in 1% yield. This mixture was complex, but with one major component, 1, isolated by various chromatographic methods and purified by multiple recrystallisation.

The mass spectrum of 1 showed a molecular ion of m/e 341 corresponding to a molecular formula of C_{20} H_{23} NO_4. The UV spectrum displayed strong absorption bands at λ_{max} 280 and 238 nm (log ε = 3.94 and 4.20 respectively) and the IR spectrum indicated the presence of an α–β unsaturated carbonyl functionality (υ_{max} 1662, 1641, 1620 cm^{-1}).

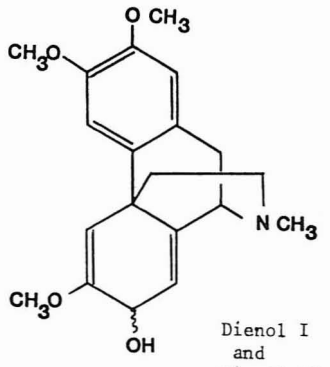
The ^{1}H and ^{13}C NMR data suggested a morphinandienone skeleton and scrutiny of the literature indicated the known *N*-methyl-2,3, 6-trimethoxymorphinandien-7-one as the probable structure (Roblot *et al.* 1984). Support for the structural assignment was forthcoming by the sodium borohydride reduction (Battersby *et al.* 1981). Thus, reduction of the parent alkaloid gave a pair of diastereomeric alcohols, designated as I and II in a 1:1 ratio, in quantitative yield. These were readily separated using preparative thin layer chro-matographic techniques. The ^{1}H nmr spectra of these compounds were consistent with the proposed structures, and the absence of vicinal coupling to H-7 supported the placement of one of the methoxy groups in the parent ketone at C-6. In addition, signals at δ 6.35 and δ 6.32 on the parent ketone can be assigned as the cyclohexadienyl protons since they shift upfield on reduction of the carbonyl group.

Further examination of the literature revealed that the parent alkaloid occurs under three names, either *O*-methylflavinantine (Gerard *et al.* 1986), *O*-methylpallidine (Kametani *et al.* 1969) or sebiferine (Bhakuni and Singh 1979) depending on its configuration. In the present work, the optical rotation of the compound indicated that the alkaloid from *A. perakensis* is identical with sebiferine (Bhakuni and Singh 1979).

Sebiferine and its (–) isomer have been isolated from several other plants including *Cocculus laurifolius* (Menispermaceae) (Bhakuni and Jain 1980), *Rhigiocarya racemifera* (Menis-



(1)



Dienol I
and
Dienol II

(2)

permaceae) (Tackie *et al.* 1974) and *Litsea sebifera* (Lauraceae) (Sivakumaran and Gopinath 1974).

Pharmacological studies have been reported on *O*-methylflavinantine and it has been shown to depress the response of the isolated guinea pig ileum to coaxial electrical stimulation (Naomesi 1980). In addition, biological screening has shown it to have uterine stimulating properties; it is also hypotensive, an analgesic agent and results in reduction of motor activity (Kanjanapothi 1987). This range of activity is of interest and warrants similar investigation for other compounds in this general class.

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NORDIN H. LAJIS
ZURINA MAHMUD

Chemistry Department,
University Pertanian Malaysia
43400 UPM Serdang, Selangor Darul Ehsan,
MALAYSIA.

LAILY BIN DIN

Chemistry Department
University Kebangsaan Malaysia
43600 Bangi, MALAYSIA.

ROBERT F.TOIA

Department of Organic Chemistry
University of New South Wales
Kensington, NSW 2033 AUSTRALIA.

Present Address: Pesticide Chemistry and Toxicology Laboratory,
University of California, Berkeley,
CA 94720, USA.

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