N-METHYLSECOGLAUCINE, A NEW PHENANTHRENE ALKALOID FROM FUMARIACEAE

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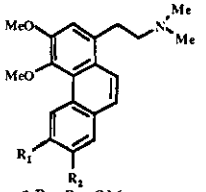
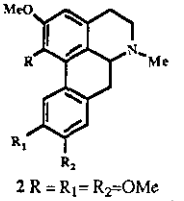
Abstract -The isolation and its total synthesis of the new phenanthrene alkaloid N-methylsecoglaucine (**1**) from *Platycapnos spicata* are reported.

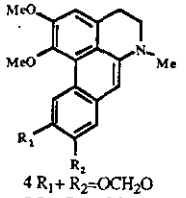
The phenanthrene alkaloids are a group of optically inactive bases probably derived biogenetically by Hofmann elimination in aporphine salts. They can therefore be included among the isoquinoline alkaloids. [1] More than 30 phenanthrene alkaloids have been isolated from natural sources, most as secondary or tertiary amines but some as quaternary salts and N-oxides.[2] They occur in several plant families, [3] though as far as we know there is only one previous report of their occurrence in Fumariaceae. [4] As part of our continuing research on the alkaloid content of Iberian Fumariaceae we have determined and report here the alkaloid content of *Platycapnos spicata* . This work included the isolation and total synthesis of the new phenanthrene alkaloid N-methylsecoglaucine (**1**).[5] *Platycapnos spicata* collected in the surroundings of Madrid was extracted with methanol and the methanolic extract was subjected to standard acid-base fractionation to afford 1.63 % of crude dichloromethane soluble alkaloid extract which nmr showed to be formed mainly of the aporphine alkaloids glaucine (**2**) and nantenine (**3**). Chromatography of this extract separated the known alkaloids glaucine (**2**), nantenine (**3**), dehydronantenine (**4**), dehydroglaucine (**5**), O-methylatheroline (**6**), oxonantenine (**7**), domesticine (**8**), N-methyllaurotetanine (**9**), corunnine (**10**), thalictuberine (**11**) and the new phenanthrene alkaloid N-methylsecoglaucine (**1**). Apart from the major aporphines glaucine (**2**) and nantenine (**3**), the alkaloid content of *Platycapnos spicata* is thus mainly formed of biogenetically related alkaloids such as the corresponding oxoaporphines and dehydroaporphines, and the phenanthrenes N-methylsecoglaucine (**1**) and thalictuberine (**11**).



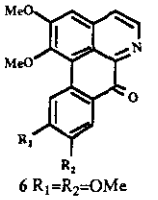
1 R_1=R_2=OMe
11 R_1+R_2=OCH_2O



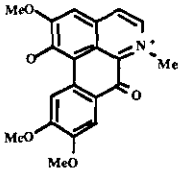
2 R = R_1= R_2=OMe
3 R = OMe, R_1+ R_2=OCH_2O
8 R = OH, R_1+ R_2=OCH_2O
9 R = R_1=OMe, R_2=OH



4 R_1+ R_2=OCH_2O
5 R_1=R_2=OMe



6 R_1=R_2=OMe
7 R_1+ R_2=OCH_2O



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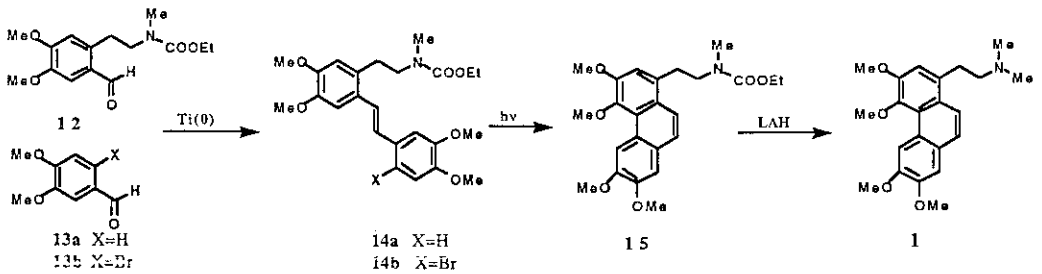
All the known alkaloids were identified by their spectroscopic data and by comparison with authentic samples. The ^{1}H-nmr spectrum of the new base N-methylsecoglaucine (**1**) exhibits five aromatic protons, three as singlets at δ 9.27, 7.21 and 7.19 and two as an AB system centred at 7.76 and 7.55 with a coupling constant of 9.1 Hz (H-9 and H-10 of the phenanthrene structure); four methoxy groups at δ 4.07, 4.05, 4.03 and 3.92, and also two 2H multiplets (centred at 3.28 and 2.72) and a 6H singlet (at δ 2.43) corresponding to the $CH_2CH_2NMe_2$ side chain. The ^{13}C-nmr signals of N-methylsecoglaucine are very similar to those of thalictuberine (**11**) (see Experimental part).

Final confirmation of structure **1** for N-methylsecoglaucine has been obtained by comparison with a synthetic sample prepared by total synthesis (Scheme 1) using our new methodology based on the photocyclization of stilbenes obtained by low valent titanium coupling of two suitable aldehydes.[6] Low valent titanium coupling of 2-(N-carbethoxy-N-methyl-2-aminoethyl)-4,5-dimethoxybenzaldehyde (**12**) and 3,4-dimethoxybenzaldehyde (**13a**) gave stilbene **14a** in 56% yield. Coupling of aldehyde **12** with 2-bromo-4,5-dimethoxybenzaldehyde (**13b**) gave stilbene **14b** in 52% yield. The phenanthrene **15** was obtained in 49% yield by photocyclization of **14a** under oxidant conditions, and in 45% yield by photocyclization of stilbene **14b** under dehydrohalogenation conditions. Lithium aluminium hydride reduction of **15** afforded N-methylsecoglaucine (**1**) [7] in 93% yield.



Scheme 1

EXPERIMENTAL

Melting points are uncorrected. Mass spectra were recorded with a Kratos Ms-50 instrument at 70 eV ionizing energy. Proton and carbon nmr spectra were measured on a Bruker WM-250 (250 MHz for ^{1}H and 62.83 MHz for ^{13}C) in $CDCl_3$ solutions; all signals are expressed as δ values ppm downfield from TMS as internal standard. Column chromatography was carried out on Merck silica gel (Type 60) and Woelm N (grade IV) neutral alumina. Tlc was performed on Merck GF-254 Type 60 silica gel and neutral alumina plates with the solvent systems CH_2Cl_2 and CH_2Cl_2-MeOH (19:1), (9:1), (17:3). Alkaloids were detected by uv and after sprayed with Dragendorff's reagent or iodine vapour. Elemental analyses were carried out in a Perkin Elmer 24000-13 instrument. Dried solvents were distilled under argon from sodium benzophenone ketyl radical prior to use.

Extraction of alkaloids

Dried, powdered aerial parts (1.5 kg) of *Platycapnos spicata* collected in Morata de Tajuña and San Martin de la Vega (Madrid) were extracted with methanol (3 l) in a Soxhlet until a Mayer's test was negative. After removal of the solvent under reduced pressure, the dark green residue (357 g) remaining was taken up in 10 % HCl (ca. 1 l) and filtered.The acidic aqueous extracts were washed with ethyl ether to remove neutral components. The aqueous solution was basified by addition of concentrate aqueous ammonia (pH 7-8) and extracted with dichloromethane (24.5 g, 16.33 g/kg dry plant) and *n* -butanol (50 g, 33.33g/kg dry plant). The dichloromethane extract (24.0 g) was loaded on a silica gel column and eluted with dichloromethane containing increasing percentages of methanol and finally with methanol-acetic acid (1-5 %). The first fractions collected were purified

by fractional crystallization and preparative tlc to afford the two major alkaloids glaucine (**2**) (14.9 g) and nantenine (**3**) (3.9 g) and the minor alkaloids dehydronantenine (**4**) (134 mg), dehydroglaucine (**5**) (26 mg), O-methylatheroline (**6**) (37 mg), oxonantenine (**7**) (6 mg), domesticine (**8**) (304 mg), N-methyllaurotetanine (**9**) (89 mg), corunnine (**10**) (7 mg), thalictuberine (**11**) (26 mg) and N–methylsecoglaucine (**1**) (15 mg). All the known alkaloids were identified by comparison of their tlc Rf values and ms and ^{1}H-nmr with those of authentic samples.

N-Methylsecoglaucine (**1**). Amorphous powder. ^{1}H-Nmr: 9.27 (s, 1H, H-5), 7.76 and 7.55 (AB, J=9.1Hz, H-9 and H-10), 7.21 (s, 1H, H-8), 7.19 (s, 1H, H-2), 4.07, 4.05, 4.03, 3.92 (4s, 12H, 4xOMe), 3.28 (m, 2H, $ArCH_2$), 2.72 (m, 2H, NCH_2), 2.43 (s, 6H, NMe_2). ^{13}C-Nmr: 150.24 (s), 148.69 (s), 148.34 (s), 144.74 (s), 133.34 (s), 128.10 (s), 125.50 (s), 124.56 (d), 124.26 (s), 120.60 (d), 113.89 (d), 108.86 (d), 107.68 (d), 60.75 (t), 59.76 (q), 56.34 (q), 55.51 (q), 55.46 (q), 45.23 (q), 32.31 (t). Ms m / z (%): 369 (M^+, 100), 311 (32), 265 (24), 152 (14). The structure was further confirmed by comparison of the spectroscopic and chromatographic data with those of the synthetic compound (**1**), which were identical.

Thalictuberine (**11**): ^{13}C-Nmr: 150.39 (s), 147.65 (s), 146.99 (s), 145.22 (s), 133.27 (s), 129.53 (s), 125.77 (s), 125.21 (d), 124.73 (s), 120.91 (d), 114.41 (d), 106.41 (d), 105.29 (d), 101.14 (t), 60.92 (t), 59.76 (q), 56.60 (q), 45.42 (q), 32.54 (t).

Synthesis of stilbene **14a**

Lithium pieces (330 mg, 47.3 mmol) were added to a stirred slurry of $TiCl_3$ (2.1 g, 13.5 mmol) in 30 ml of dry DME under an argon atmosphere, and the mixture was refluxed for 2 h. The black slurry was then cooled to room temperature and 500 mg (1.69 mmol) of **12** and 420 mg (2.5 mmol) of **13a** dissolved in 10 ml of dry DME were added. The mixture was stirred for 4 h at room temperature and then refluxed for 13 h. After cooling at room temperature, the reaction mixture was filtered, a saturated aqueous solution of K_2CO_3 was added, the organic layer was separated and the aqueous layer was extracted with chloroform (3 x 50 ml). The pooled organic phases were dried (Na_2SO_4) and the solvent was evaporated to afford the crude product. This was purified by flash column chromatography using 20% EtOAc-hexane as eluent; 410 mg of **14a** (56%) were obtained, mp 167°C (EtOAc/hexane). ^{1}H-Nmr : 7.35-6.83 (m, 6H, ArH and HC=CH), 6.65 (m, 1H, ArH), 4.02 (m, 2H, $OC\underline{H_2}CH_3$), 4.00, 3.93, 3.90 and 3.89 (4s, 12H, 4xOMe), 3.42 (t, J=7.2 Hz, 2H, $ArCH_2$), 2.94 (m, 2H, NCH_2), 2.84 (br s, 3H, NMe), 1.28 (m, 3H, $OCH_2C\underline{H_3}$). Ms m / z (%): 429 (M^+, 100), 348 (8), 327 (24), 231 (25). Anal. Calcd for $C_{24}H_{31}NO_6$: C 67.13, H 7.23, N 3.26. Found: C 66.70, H 6.82, N 3.35.

Synthesis of stilbene **14b**

The stilbene **14b** was obtained, in 52% yield, in the same way as above, mp 122°C (EtOAc/hexane). ^{1}H-Nmr : 7.45-7.04 (m, 5H, ArH and HC=CH), 6.68 (br s, 1H, ArH), 4.02 (m, 5H, $OC\underline{H_2}CH_3$ and OMe), 3.95, 3.90 and 3.89 (3s, 9H, 3xOMe), 3.41 (m, 2H, $ArCH_2$), 2.95 (m, 2H, NCH_2), 2.86 (s, 3H, NMe), 1.22 (t, J=7.0 Hz, 3H, $OCH_2C\underline{H_3}$). Ms m/z (%): 509 and 507 (M^+, 11), 312 (56), 116 (100). Anal. Calcd for $C_{24}H_{30}NO_6Br$: C 56.69, H 5.90, N 2.75. Found: C 56.23, H 5.72, N 2.25.

Synthesis of N-carbethoxysecoglaucine **15**

a) Photocyclization of stilbene **14a**

A solution of 100 mg (0.2 mmol) of the stilbene **14a** in 10 ml of ether and iodine (cat.) was irradiated with a Hannovia lamp (400 w) during 3 h at room temperature. After purification by flash column chromatography (10% EtOAc-hexane), 43 mg of **15** (49%) were obtained as a solid which crystallized from ethanol.

b) Photocyclization of stilbene **14b**

A solution of 50 mg of **14b** in 200 ml of benzene, 3 ml of *t* -butanol and 11 mg of potassium *t* -butoxide under argon atmosphere was irradiated with a Hannovia lamp (200 w) for 8 h at room temperature, 19 mg (45%) of **15** were obtained, mp 110-112°C (ethanol). ^{1}H-Nmr : 9.28 (s, 1H, H-5), 7.90 and 7.84 (2d, J=9.0 Hz, 1H, H-10), 7.56 (d, J=9.0 Hz, 1H, H-9), 7.21 (s, 1H, H-8), 7.19 and 7.11 (2s, 1H, H-2), 4.10 - 4.04 (m, 2H, OCH_2CH_3), 4.07, 4.04, 4.03 and 3.92 (4s, 12H, 4xOMe), 3.65-3.55 (m, 2H, $ArCH_2$), 3.38-3.24 (m, 2H, NCH_2), 2.95 and 2.85 (2s, 3H, NMe), 1.32-1.22 (m, 3H, OCH_2CH_3). Ms m/z (%): 427 (M^+, 35), 311 (100), 116 (28), 44 (93).

Reduction of **15** with lithium aluminium hydride

Lithium aluminium hydride (33 mg, 0.92 mmol) was added under argon to a stirred solution of the N-carbethoxy compound **15** (182 mg, 0.42 mmol) in 25 ml of dry THF. The solution was refluxed for 2 h. After cooling at room temperature, a saturated solution of NH_4Cl was added, the solvent was evaporated and the residue was extracted with dichloromethane. The organic layer was separated and the solvent was eliminated under vacuum to give 150 mg (93% yield) of the corresponding N-methyl compound **1**. Hydrochloride, mp 249-251°C (methanol/ethyl ether). Anal. Calcd for $C_{22}H_{27}NO_4$: C 65.10, H 6.90, N 3.45. Found: C 64.82, H 6.48, N 3.58. The ^{1}H-nmr and ^{13}C-nmr spectra of the free base were identical to those of the natural product.

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