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MINOR ALKALOIDS OF *GLAUCIUM FLAVUM*

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Key Word Index—*Glaucium flavum*; Papaveraceae; alkaloids; dihydropontevedrine; structure elucidation.

Abstract—The new aporphine base, dihydropontevedrine, has been found in an ethanol extract of *Glaucium flavum* along with a number of known alkaloids, some of which were isolated for the first time from this plant material.

INTRODUCTION

The alkaloids of *Glaucium flavum* Crantz. have been the subject of several investigations [1–8]. From these studies the following alkaloids have been identified: protopine [1–4, 7], glaucine [1, 3, 5, 7], sanguinarine [2–4], chelerythrine [2–4], chelirubine [2–4], (+)-isocorydine [1, 3, 4, 9], (−)-chelidonine [3, 9], α-allocryptopine [2, 3], (+)-corydine [3], (−)-norchelidonine [3, 4], 1,2,9,10-tetramethoxyoxoaporphine [9], 6′,7-dehydroglaucine, 6,6′-dehydronorglaucine [9–11], thalicmidine [10], isoboldine [4], norsaguinarine [8], oxysanguinarine [8], luguine [8], (+)-*N*-methyllindcarpine [8], corunnnine [5], pontevedrine [5], (+)-cataline [6], didehydroglaucine [8], arosine [8] and arosinine [8].

Since *G. flavum* is rich in isoquinoline alkaloids, especially in aporphine and benzophenanthridine bases, we decided to carry out a more detailed investigation of its alkaloidal content with a view to isolate other alkaloids. As a result of this study, we have observed the presence of several previously reported alkaloids from the plant, namely, didehydroglaucine, 6′,7-dehydroglaucine, (+)-glaucine, protopine, (+)-isocorydine, (+)-corydine, (−)-norchelidonine, (+)-cataline, 1,2,9,10-tetramethoxyoxoaporphine, α-allocryptopine, corunnine, isoboldine and norsanguinarine. We have also isolated a new aporphine base which has been identified as dihydropontevedrine (**1**) and three other minor alkaloids, dihydrosanguinarine (**2**), dihydrochelerythrine (**3**) and dihydrochelirubine (**4**), found for the first time in this plant material.

RESULTS AND DISCUSSION

The dihydropontevedrine (**1**) crystallized from ethanol as red needles, mp 251–253°. The mass spectrum of **1** had $[M]^+$ at *m/z* 383 (3.5) corresponding in composition to $C_{21}H_{21}NO_6$. There were fragment ions at *m/z* 381 ($[M-2]^+$, 100), 367 (35), 353 (16.5), 338 (26.2), 336 (35.5), 295 (8.7), 229 (10.5), 177 (12) and 94 (19).

The structure assigned to the alkaloid was supported by its 60 MHz ^{1}H NMR spectrum in $CDCl_3$. There were singlets at δ3.80 (3H, N-Me) 4.02 (3H, OMe), 4.04 (3H, OMe) and 4.10 (6H, 2 × OMe). The aromatic region of the spectrum contained peaks for five protons at δ7.30, 7.37, 8.20 and 9.14. Some of these peaks were not well resolved which probably arises from a pseudo base–iminium equilibrium in which state the alkaloid exists (see below). The UV spectrum of **1** which showed λ_{max}^{EtOH} (log ε) 244 (4.58), 3.12 (4.26), 325 (4.37) and 470 (4.0) nm was not affected by acid or base. In the IR spectrum (KBr) of the alkaloid absorption bands at 3600–3200 cm^{-1} (assoc. OH), 1665 cm^{-1} (C=O) and 1595 cm^{-1} (C=C and C $=N^+$) were observed. The alkaloid also gave a positive ferric chloride test. The colour reaction, UV and IR spectra of **1** are very similar to those of pontevedrine [5] but it differs in NMR and mass spectra as well as TLC behaviour.

The above spectral data completely support the structure assigned to dihydropontevedrine. They are close to those described for a synthetic product found in the mixture obtained after UV irradiation of glaucine and named dihydropontevedrine [12]. By direct comparison (IR, UV, mmp and TLC) the identity of **1** and this synthetic product was shown.

EXPERIMENTAL

General. IR spectra were recorded in $CHCl_3$ or KBr. ^{1}H NMR were measured at 60 or 100 MHz in $CDCl_3$ soln with TMS as int. std. Chemical shifts are expressed in δ (ppm from TMS). UV spectra were recorded in EtOH. Mps: uncorr. Al_2O_3 (Brockmann II neutral, Reanal) was used for CC. TLC was performed on silica gel F-254 plates (Merck) in C_6H_6 (S_1); toluene–EtOH–NH_3 (40:9:2) (S_2) and $CHCl_3$–C_6H_6–MeOH (1:1:1) (S_3). Plant material (whole plant with blossoms and unripe fruits) was collected in July 1983 in the vicinity of Ahtopol, Bulgaria. The identification of didehydroglaucine, dihydrochelirubine, norsanguinarine, (−)-norchelidonine and (+)-cataline was made by comparison of their spectroscopic properties with those given in the lit. All other alkaloids were identified by spectroscopic, mp, mmp and TLC comparison with authentic samples.

Isolation of alkaloids. Air-dried plant material (2 kg) was extd exhaustively with EtOH in a Soxhlet apparatus, the extract concd nearly to dryness and then treated with 2% aq. HCl. The resulting acid soln was extracted with Et_2O until the extract was nearly colourless and then it was made basic with aq. NH_3. The alkaline soln was extracted firstly with Et_2O and secondly with

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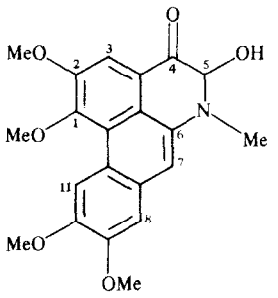

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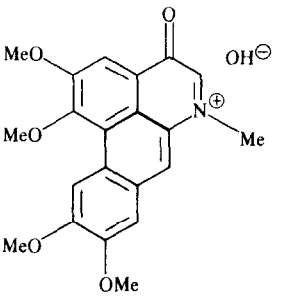

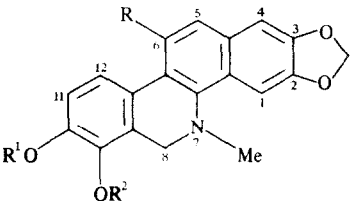

2 $R^1 + R^2 = CH_2$, R = H
3 $R^1 = R^2 = Me$, R = H
4 $R^1 + R^2 = CH_2$, R = OMe

$CHCl_3$. After removal of solvents the two fractions showed (TLC) an almost identical alkaloidal content. The combine yield was 26 g (1.3%) of crude alkaloids.

Separation of alkaloid mixture. Crude alkaloids (26 g) were chromatographed on Al_2O_3 (1 kg). The column was eluted first with C_6H_6 and then with C_6H_6 containing increasing amounts (from 0.5 to 10%) MeOH. The different fractions (each 25 ml) were collected into five groups (major fractions), A to F, based on their TLC characteristics. The components of each of these fractions was further fractionated by rechromatography, fractional recrystallization or prep. TLC.

Fraction A. Fraction A (2.3 g) eluted with C_6H_6 was fractionated by rechromatography on a small column. Didehydroglaucine, dihydrochelirubine (20 mg), dihydrosanguinarine (32 mg, colourless prisms mp 190–191° (EtOH) [13]), norsanguinarine (35 mg), dihydrochelerythrine [(22 mg, colourless prisms, mp 164–165° (EtOH) [13]) and 6',7-dehydroglaucine (0.850 g, yellowish prisms, mp 134–136° (EtOH) [11]), were obtained. S_1 was used for TLC.

Didehydroglaucine, unstable, yellow, amorphous. IR: ($CHCl_3$) ν_{max} 1650 and 1610 cm^{-1} (C=C and aromatic ring). 60 MHz ^1H NMR: ($CDCl_3$) δ3.35 (3H, *s*, N-Me), 4.31 (3H, *s*, OMe), 4.20 (3H, *s*, OMe) and 4.28 (6H, *s*, 2 × OMe); unsplit protons at δ7.17 (1H, *s*), 6.78 (1H, *s*) and 6.30 (1H, *s*); one doublet at δ5.91 and 6.60 (J = 7.5 Hz). These spectral data are almost identical with those reported for didehydroglaucine [6].

Dihydrochelirubine, colourless prisms, mp 205–207° (EtOH). UV: (EtOH) λ_{max}(log ε) 230 (4.58), 281 (4.52) and 339 (4.32) nm. 60 MHz ^1H NMR: ($CDCl_3$) δ2.61 (3H, *s*, N-Me), 6.08 (2H, *s*, CH_2O_2), 6.11 (2H, *s*, CH_2O_2), 3.85 (3H, *s*, OMe), 4.05 (2H, *s*, CH_2), 7.05 (1H, *s*), 7.35 (1H, *s*) and a pair of *ortho* protons appeared as an ABq at δ7.50 and 8.33 ($J_{11,12}$ = 8.5 Hz). On the basis of these spectral data, which are close to those reported for dihydrobocconine [15] (= dihydrochelirubine [16, 17]), the alkaloid was identified as dihydrochelirubine.

Norsanguinarine, colourless prisms, mp 290–292° (EtOH). UV: (EtOH) λ_{max}(log ε) 243 (4.62), 281 (4.51), 295 sh (4.39) and 329 (4.21) nm; 100 MHz ^1H NMR: ($CDCl_3$) δ6.13 (2H, *s*, CH_2O_2), 6.29 (2H, *s*, CH_2O_2), one ABq at δ7.88 and 8.17 ($J_{11,12}$ = 9.0 Hz), another ABq at 8.33 and 7.47 ($J_{5,6}$ = 9.0 Hz) and three singlets at δ7.26 (1H), 8.70 (1H) and 9.67 (1H); MS: 317 ([M]$^+$, 100), 287 (2), 259 (10.3), 201 (19.8), 174 (4) and 159 (3.5). These spectral data characterize the alkaloid as norsanguinarine [18, 19].

Fraction B. This fraction (17.5 g) eluted with C_6H_6 + 0.5% MeOH comprised (−)-norchelidonine (95 mg), (+)-glaucine [11.5 g, colourless prisms, mp 135° (Et_2O)], protopine [1.2 g, mp 206–207°] and (+)-isocorydine [11 mg, colourless prisms, mp 184–185° (EtOH)]. The alkaloids were sepd by fractional crystallization in EtOH and prep. TLC (S_2).

(−)-Norchelidonine, colourless prisms, mp 210–211 (lit. [20] 199°), $[\alpha]_D^{20}$ − 110° (EtOH). IR: (KBr) ν_{max} 3350–3200 cm^{-1} (assoc. OH) and 1650 cm^{-1} (aromatic bands); UV: (EtOH) λ_{max} (log ε) 240 (3.88) and 294 (3.95) nm; 100 MHz ^1H NMR: ($CDCl_3$) δ3.12 (1H, *s*, half band width 7 Hz, C-5H), two br singlets at 4.25 (1H, half band width 7 Hz, C-6H), 5.97 (4H, *s*, 2 × CH_2O_2), four aromatic protons appearing at δ6.78 (2H, *s*), 6.65 (1H, *s*) and 6.76 (1H, *s*); MS: 339 ([M]$^+$, 100), 321 ([M − 18]$^+$, 83.8), 304 (74.2), 294 (54.1), 293 (46.9), 246 (19.7), 235 (15.8), 174 (31.8), 162 (65), 148 (63.8, 135 (22) and 91 (8.9). All these data conform to structure of norchelidonine [3, 20].

Fraction C. This fraction eluted with C_6H_6 + 2% MeOH (0.3 g) contained (+)-corydine [15 mg, colourless prisms, mp 149–150° (Et_2O)] and dihydropontevedrine (35 mg). The latter was obtained in a pure state after recrystallization from EtOH of the substance eluted from the red coloured zone on the TLC plates (S_3).

Fraction D. This fraction (0.350 g) was collected from a orange-yellow zone of the column when it was eluted with C_6H_6 + 5% MeOH. Three alkaloid spots were detected (TLC) in this mixt., one of which was orange-yellow coloured. The mixt. was dissolved in hot EtOH and after cooling orange-yellow crystals of 1,2,9,10-tetramethoxyoxoaporphine [75 mg, mp 224° (EtOH)] were obtained [9, 21]. α-Allocryptopine [15 mg, colourless prisms, mp 160–161° (EtOH)] and (+)-cataline (40 mg) were sepd by prep. TLC (S_3) from the mother liquor.

(+)-Cataline, colourless prisms, mp 176–178° (MeOH + H_2O, $[\alpha]_D^{22}$ 163° (EtOH). IR: (KBr) ν_{max} 3530 (OH), 1605 and 1520 (C=C and aromatic bands); UV: (EtOH) λ_{max}(log ε) 302 (4.25 and 283 (4.14) nm; 60 MHz ^1H NMR: ($CDCl_3$) δ2.58 (3H, *s*, N-Me), 3.60 (3H, *s*, OMe), 3.84 (3H, *s*, OMe), 3.90 (6H, *s*, 2 × OMe), 4.54 (1H, *br s*, H-4), 8.05 (1H, *s*, H-11), 6.82 (1H, *s*, H-3), 6.66 (1H, *s*, H-8) and 3.02 (1H, *br s*, H-5). These data are similar to those described for cataline [6, 22].

Fraction F. This fraction (0.230 mg) was collected from a green-coloured zone of the column, eluting with C_6H_6 + 10% MeOH. It was fractionated by TLC (S_3) to furnish (+)-isoboldine [13 mg, colourless prisms, mp 121–123° (EtOH)] and corunnine [55 mg, green-violet prisms, mp 268–269° (EtOH)]. The two alkaloids were identified by direct comparison (IR, mmp, TLC) with authentic samples.

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