

## CORYDINEMETHINE: A NEW PHENANTHRENE ALKALOID FROM *BERBERIS CRETICA*

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*Berberis cretica* L. (Berberidaceae) is a small shrub growing in Anatolia. A previous investigation of its alkaloidal content had revealed the presence of the protoberberinium salts berberine, palmatine, and jatrorrhizine, as well as the aporphine magnoflorine (1).

Presently, a reinvestigation of this plant produced a wide array of isoquinoline alkaloids. We here describe the new amorphous phenanthrene base corydinemethine (1), C<sub>21</sub>H<sub>25</sub>NO<sub>4</sub>, obtained as a result of our study (2).

The 360 MHz <sup>1</sup>H-nmr spectrum of corydinemethine in CDCl<sub>3</sub> solution has been summarized around expression 1. Five aromatic protons were in evidence, a singlet at δ 7.25 representing H-2, two doublets at δ 7.36 and 7.40 due to H-7 and H-8, and another set of two doublets at δ 7.48 and 7.59 representing H-9 and H-10. Three methoxyl singlets were located at δ 3.75, 4.04, and 4.05, of which the upfield singlet at δ 3.75 may represent a methoxyl at either C-4 or C-5. A D<sub>2</sub>O exchangeable singlet at δ 10.49 indicated the presence of an acidic proton. Finally, a dimethylamino moiety was denoted by a six-proton singlet at δ 2.42.

The mass spectrum of corydinemethine (1) exhibited a small molecular ion *m/z* 355 and base peak *m/z* 58 due to the dimethyliminium cation.

The structural problem for corydine-

methine centered upon the determination of the phenolic site which had to be at either C-4 or C-5 based upon the nmr data.

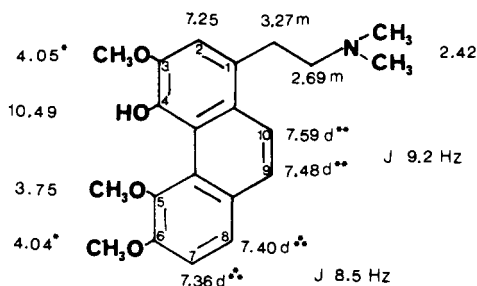
Fortunately, we had in our possession small amounts of the known aporphine alkaloids (+)-corydine [≡ (+)-2,10,11-trimethoxy-1-hydroxyaporphine] and (+)-menisperine chloride [≡ (+)-1,2,10-trimethoxy-11-hydroxyaporphine methochloride] (2). (+)-Corydine was first quaternized with methyl iodide and subjected to Hofmann β-elimination with methanolic NaOH. Two products were obtained from this reaction. The first was corydinemethine, which proved to be identical in all respects with the natural product. In particular, the nmr, uv, and mass spectra of this Hofmann product were essentially identical with those of the natural base. Additionally, the two materials exhibited identical tlc behavior in different solvent combinations.

The second product from the Hofmann β-elimination of corydine *N*-metho salt was the optically active and amorphous (-)-corydineisomethine (2), C<sub>21</sub>H<sub>25</sub>NO<sub>4</sub>, whose nmr spectrum has been summarized around its structure. Noteworthy is the presence of a vinylic ABX system, as well as an aliphatic AMX system due to the C-9 and C-10 protons.

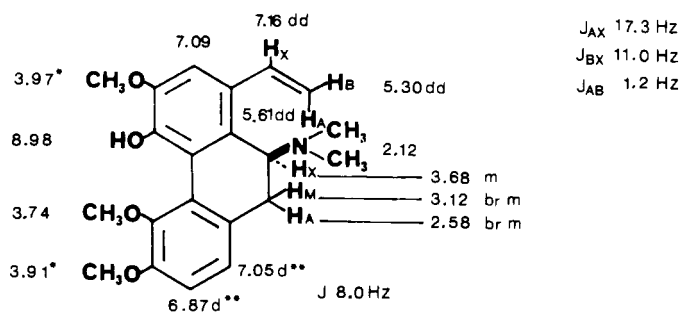
Whereas two products had been obtained from (+)-corydine *N*-metho salt, only one compound was generated from similar base treatment of the isomeric (+)-menisperine chloride. This was amorphous (-)-isocorydineisomethine (3), C<sub>21</sub>H<sub>25</sub>NO<sub>4</sub>.

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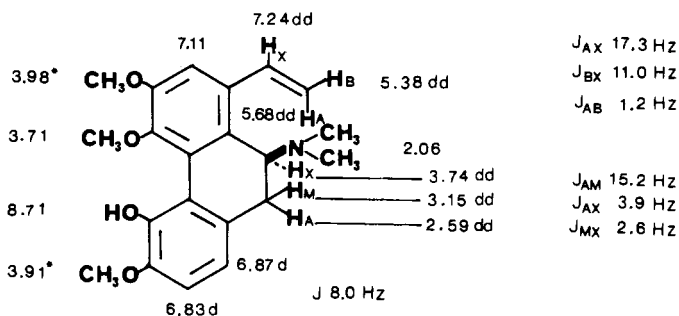
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1



2



3

The nmr spectra of (-)-**2** and (-)-**3** exhibit only minor differences. It may be significant to note that the chemical shift difference between H-7 and H-8 (δ 7.05 and 6.87) is larger for corydineisomethine (**2**), where the ring C substituents are two methoxyl groups, than for isocorydineisomethine (**3**) (δ 6.87 and 6.83), which bears a hydroxyl and a methoxyl substituent. The nmr spectrum of **3** also displayed a very small (< 1 Hz) long distance coupling between H-8 and the H-9 aliphatic absorption at δ 2.59. This allowed us to differentiate

between the H-7 (δ 6.83) and H-8 (δ 6.87) absorptions.

The importance of corydineisomethine resides in the fact that it is the first phenanthrene alkaloid known to possess a substituent at the hindered C-5 position. Corydineisomethine is a C-3, C-4, C-5, C-6 tetraoxygenated phenanthrene alkaloid, and it is such tetraoxygenated species that account for the further biogenetic formation of the lactonic alkaloids taspine (**2**), chiloenamine (**3**), andesine (**4**), santiagonamine (**5**), and aconcaguine (**6**), all of which signifi-

cantly enough have also been found among members of the Berberidaceae.

Nineteen known alkaloids were also detected in our plant, eight of which proved to be bisbenzylisoquinolines, (+)-isotetrandrine, (+)-berbamine, (+)-oxyacanthine, (+)-obaberine, (+)-obamegine, (+)-thalrugosine, (+)-aromoline, and (+)-berbamunine. Four were aporphines, (+)-isoboldine, (+)-thaliporphine, (+)-glaucine, and (+)-magnoflorine. The remaining seven were protoberberines: berberine, palmatine, jatrorrhizine, columbamine, canadine, berberrubine, and oxyberberine. There is a possibility that the berberrubine and oxyberberine obtained could have been formed from berberine on the chromatographic column by *O*-demethylation in one case and oxidation in the other (7).

## EXPERIMENTAL

### GENERAL EXPERIMENTAL PROCEDURES.—

All uv spectra and specific rotations are in MeOH unless indicated otherwise, and ir spectra are in CHCl<sub>3</sub>. Nmr spectra are in CDCl<sub>3</sub> at either 200 MHz or 360 MHz. Mass spectral measurements are at 70 eV. Column chromatography was on Merck Silica Gel 60, and tlc was on Merck Silica Gel F-254 glass plates with 0.25 mm or 0.5 mm thickness.

### PLANT COLLECTION AND EXTRACTION.—

*B. cretica* (12.35 kg dry, whole plant) was collected on Sipil Dag, Manisa, Turkey, in July 1984. A voucher specimen, No. 902, was deposited in the herbarium of the Department of Pharmacognosy, Faculty of Pharmacy, Ege University, Izmir, Turkey.

The powdered plant was extracted with cold EtOH (210 liter). The solvent was evaporated without excessive heat. The residue (1.3 kg) was shaken with 5% HCl and the acidic layer separated. This layer was basified with NH<sub>4</sub>OH and repeatedly extracted with CHCl<sub>3</sub>. Evaporation of the organic solvent left a residue (45 g) that was placed on a silica gel column (1.5 kg). Elution was with CHCl<sub>3</sub> containing increasing amounts of MeOH. Final purification was by tlc using the solvent systems: (I) CHCl<sub>3</sub>-MeOH (95:5); (II) CHCl<sub>3</sub>-MeOH-NH<sub>4</sub>OH (90:10:trace); (III) CHCl<sub>3</sub>-C<sub>6</sub>H<sub>6</sub>-MeOH (4:2:1); (IV) C<sub>6</sub>-H<sub>6</sub>-MeCOOEt (60:40); (V) CHCl<sub>3</sub>-MeOH-H<sub>2</sub>O (80:20:1); (VI) C<sub>6</sub>H<sub>6</sub>-CHCl<sub>3</sub>-MeOH-NH<sub>4</sub>OH (45:45:10:trace); (VII) CHCl<sub>3</sub>-MeOH-H<sub>2</sub>O (63:38:2). The alkaloids isolated were: (+)-

corydinemethine (**1**) (9 mg), (+)-isotetrandrine (72 mg), (+)-berbamine (67 mg), (+)-obaberine (23 mg), (+)-oxyacanthine (520 mg), (+)-obamegine (18 mg), (+)-thalrugosine (8 mg), (+)-aromoline (112 mg), (+)-berbamunine (35 mg), (+)-isoboldine (36 mg), (+)-thaliporphine (28 mg), (+)-glaucine (16 mg), (+)-magnoflorine (11 mg), berberrubine (33 mg), berberine chloride (15 g), palmatine chloride (200 mg), jatrorrhizine chloride (94 mg), columbamine chloride (5 mg), canadine (6 mg), and oxyberberine (42 mg). Known alkaloids were identified from spectral and optical data, or by comparison with authentic samples.

**CORYDINEMETHINE (1).**—Uv  $\lambda$  max 244, 259, 319, 328, 366, 383 nm (log  $\epsilon$  4.32, 3.94, 3.92, 3.35, 3.33),  $\lambda$  max (MeOH+OH<sup>-</sup>) 259, 317, 328, 364, 381 nm (log  $\epsilon$  4.42, 3.94, 3.94, 3.59, 3.55); ir  $\nu$  max 1260, 1405, 1455, 1590, 2930, 3530 cm<sup>-1</sup>; ms *m/z* 355 (M<sup>+</sup>) (2), 297 (M-58)<sup>+</sup> (1), 58 (100), 43 (8); tlc Rf 0.18, 0.26, 0.50 in systems I, VI, and II, respectively.

### CONVERSION OF CORYDINE INTO **1** AND **2**.

—Corydine (3 mg) was treated with MeI (5 ml) in acetonitrile with gentle refluxing for 2 h. The resulting methiodide salt was treated with 10% NaOH in MeOH (10 ml) containing two drops of H<sub>2</sub>O under N<sub>2</sub> for 3 h. Workup gave **1** (1.2 mg) and **2** (0.8 mg) which were separated by tlc using system II.

**CORYDINEISOMETHINE (2).**—Uv  $\lambda$  max 227, 259, 276 sh, 310 nm (log  $\epsilon$  4.45, 4.32, 4.18, 3.77);  $\lambda$  max (MeOH+OH<sup>-</sup>) 261, 312 nm (log  $\epsilon$  4.27, 3.95); ir  $\nu$  max 1455, 1595, 2995 cm<sup>-1</sup>; ms *m/z* 335 (M<sup>+</sup>) (59), 354 (6), 340 (35), 311 (100), 280 (35), 249 (21); [ $\alpha$ ]<sup>25</sup>D -110° (c 0.05), tlc Rf 0.76 and 0.25 in systems II and IV, respectively.

**CONVERSION OF MENISPERINE CHLORIDE INTO ISOCORYDINEISOMETHINE (3).**—The aporphine salt (3.5 mg) was dissolved in 10% NaOH in MeOH (10 ml) containing two drops of H<sub>2</sub>O, and the solution was refluxed under N<sub>2</sub> for 1.5 h. Workup provided **3** (2 mg).

**ISOCORYDINEISOMETHINE (3).**—Uv  $\lambda$  max 229, 235, 247, 310 nm (log  $\epsilon$  4.66, 4.65, 4.64, 3.86);  $\lambda$  max (MeOH+OH<sup>-</sup>) 255, 311 nm (log  $\epsilon$  4.68, 4.02); ir  $\nu$  max 1455, 1585, 2930, 2990 cm<sup>-1</sup>; ms *m/z* 355 (M<sup>+</sup>) (92), 354 (7), 340 (36), 311 (100), 280 (43); [ $\alpha$ ]<sup>25</sup>D -114.9° (c 0.174); tlc Rf 0.71 and 0.22 in systems II and IV, respectively.

## ACKNOWLEDGMENTS

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