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ALKALOIDS FROM *CORYDALIS REMOTA*

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ABSTRACT.—Thirteen alkaloids were isolated from the nonphenolic basic fraction of the tubers of *Corydalis remota* cultivated in Dalian, Liaoning province. The most interesting of these is corymotine, a new tetrahydroprotoberberine alkaloid that bears an unusual 13,13-dimethylated substitution pattern.

The tubers of *Corydalis remota* Fisch. (Fumariaceae) have been used as an analgesic in northeastern China in place of "yanhusuo," a well-known traditional Chinese herbal medicine from the tubers of *Corydalis yanhusuo* W.T. Wang. No systematic chemical studies on this plant have been previously reported in the literature, although past experimental work on *Corydalis* is noted (1–3). Chemical investigations of the tubers of *C. remota* cultivated in Dalian, Liaoning province, were carried out in our laboratory with a view towards finding correlations, if any, between the two plant species.

From the nonphenolic basic fraction of the methanolic extracts of the tubers of *C. remota*, 13 alkaloids were separated by routine flash chromatography and preparative tlc. Among these alkaloids, 12 were found to be known compounds that widely occur in the genus *Corydalis*. A minor nonphenolic base, corymotine [**1**], was unusual and deserved special attention.

The new protoberberine alkaloid, corymotine, is the first tetrahydroprotoberberine dimethylated at C-13. Its uv spectrum was indicated with a maximum at 281 nm. The mass spectrum displayed major peaks at *m/z* $[M]^+$ 383, 368, 352, 192, and 177, indicating a fragmentation pattern of a tetrahydroprotoberberine (4). A retro-Diels-Alder decomposition is in Figure 1. The base peak *m/z* 192 corresponding to ions **a** and **b** indicated that both rings A and B plus rings C and D might each possess two methoxyl groups. In the ^{1}H-nmr spectrum of corymotine, two singlet signals at δ 0.99 and δ 1.50 revealed the possibility of a *gem*-methyl group. H-14 appeared as a singlet and certified the *gem*-methyl group at C-13 rather than at C-8. Some previous studies (5,6) supported the conclusion that the chemical shifts at δ 1.0 and δ 1.5 were indicative of

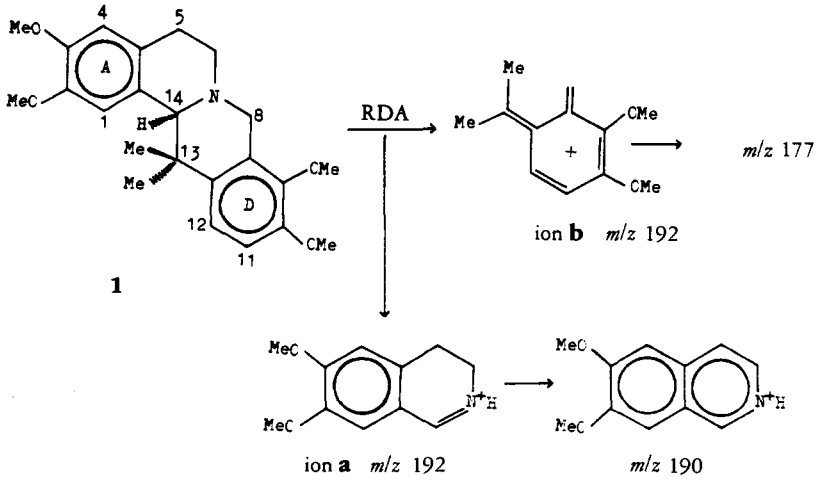

FIGURE 1. Mass spectral fragmentation schemes for corymotine [**1**].

the 13-Me_{ax} and 13-Me_{eq}, while signals are at δ 1.4 and δ 1.5 for 8-Me_{ax} and 8-Me_{eq}, respectively.

The signal at δ 6.62 was assigned to H-4 in ring A based upon the fact that upon irradiation at δ 2.28 of the aliphatic proton H-5, only the signal at δ 6.62 was sharpened and increased by 21% of the peak area. Upon irradiation at δ 3.86 (-OMe), the nOe enhancement of 20% and 21% of peak areas at δ 6.62 and δ 6.79, respectively, was observed. Thus, δ 6.79 was assigned for H-1. The chemical shifts of the two low-field protons of H-8 at δ 3.76 and δ 4.17 were deshielded by the aromatic ring D, the lone pair on the adjacent nitrogen, and the oxygen at C-9 (5). The chemical shift of the other two aromatic protons at δ 7.07 and δ 6.82 appeared as double duplet peaks could only be ortho-coupled ($J=9$ Hz). It indicated that the two methoxyl groups in ring D may be assigned to 9,10 substitution. In alkaloids with 10,11 substitution, the H-8 would appear as a broad singlet centered at δ 4.05 (6). The H-11, H-12 substituted dimethoxyl compound had not yet been found to occur naturally. Therefore, the rational structure of corymotine [**1**] must be a 2,3,9,10-tetramethoxyl substitution pattern.

From the previous studies (7) of the stereochemistry of tetrahydroprotoberberine, it could be inferred that corymotine existed in solution as a mixture of *cis* and *trans* conformers at the B/C ring junction. This observation is supported by the fact that the ^{13}C-nmr signal for C-6 at 49.4 and the ^{1}H-nmr chemical shift difference of 0.41 ppm for the protons at H-8 as well as the weak Bohlmann bands at 2745, 2780, and 2830 cm^{-1} were all in good agreement with those reported (8,9) for tetrahydroprotoberberines with a mixture of *cis* and *trans* conformers. The specific rotation of corymotine was $[\alpha]^{25}D$ −188° in $CHCl_3$, so that, the absolute conformation should be assigned as 14*S* (10) for corymotine.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points are uncorrected. Ir spectra were obtained with a Hitachi 270-30 ir spectrometer and uv spectra in EtOH with a Perkin-Elmer Lambda-5 uv spectrometer. Optical rotations were measured on Perkin-Elmer 241 MC. Ms were recorded on a JMS-DS 300 and nmr on JNM-G 400 (400 MHz) or Varian EM-300 (90 MHz) with TMS as internal reference. Both flash chromatography and preparative tlc were carried out on Si gel G. The mobile phase used in flash chromatography was cyclohexane-EtOAc-diethylamine (gradiently eluting from 15:1:0.5, 12:1:0.5, 10:1:0.5, 8:1:0.5, to 6:1:0.4), and the developing systems in tlc were toluene-EtOH-NH_4OH (40:4:1.5) (S_1) and petroleum ether-EtOAc (5:1.5) saturated with NH_3 (S_2).

PLANT COLLECTION.—The plant materials were collected from Dalian, Liaoning province, in 1986, and authenticated by Baozhen Zhu, deputy chief pharmacist of Dalian Institute for the Drug Control, and Damu Yao, associate professor of our institute. A voucher specimen has been deposited in our laboratory.

EXTRACTION AND ISOLATION.—The dried powdered tubers (7500 g) of the plant were macerated with MeOH at room temperature. The MeOH solution was evaporated at reduced pressure. The extracts were then processed following the routine acid-base work-up procedures, and the nonphenolic base fractions were obtained.

Part of the nonphenolic fraction (25 g) was chromatographed (flash chromatography) to yield fraction 1 (tetrahydrocorysamine), fraction 2, fraction 3 (α-allocryptopine), and fraction 4 (corybulbine). Acetylcorynoline cavidine, tetrahydrocoptisine, corydaline, band 5, tetrahydropalmatine, corycavine, and protopine were separated from fraction 2 by preparative tlc using S_1 as developing system. Band 5 was subjected to preparative tlc and developed by S_2 to obtain corymotine, sinactine, and corynoline.

CORYMOTINE [**1**].—Corymotine [**1**] was recrystallized from MeOH yielding colorless prisms (15 mg), mp 148–149°; $[\alpha]^{25}D$ −188° ($c=0.087$, $CHCl_3$); uv λ max (EtOH) nm (log ε) 281.3 (3.57); ir (KBr) ν max (cm^{-1}) 2930, 2830, 2780, 2745 (Bohlmann bands), 1615, 1520, 1497, 1460, 1420, 1380, 1360, 1325, 1279, 1270, 1230, 1195, 1175, 1110, 1080, 1030, 875, 855, 800, 780; ms (70 eV) *m/z* (%) $[M]^+$ 383 (49.5), $[M-Me]^+$ 368 (6.5), $[M-OMe]^+$ 352 (7.8), [ions **a** and **b**] 192 (100), 190, 177 (40), 149 (30); ^1H nmr (400 MHz, $CDCl_3$) 0.99 (3H, s, C_{13}-Me), 1.50 (3H, s, C_{13}-Me), 3.68 (1H, s, 14-H), 3.76 (1H, d, $J=16$ Hz, 8-H), 4.17 (1H, d, $J=16$ Hz, 8-H), 3.86 and 3.88 (12H, s, OMe), 6.62 (1H, s, 4-H), 6.79 (1H, s, 1-H), 6.82 and 7.07 (2H, dd, $J=8.8$ Hz, 11-H and 12-H). The decoupling and nOe

experiments were performed on a 90 MHz spectrometer. ^{13}C nmr ($CDCl_3$) 26.4 (13-Me), 29.7 (13-Me), 29.9 (C-5), 49.4 (C-6), 53.8 (C-8), 55.8 (2×OMe), 56.0 (2×OMe), 40.7 (C-13), 60.2 (C-14), 111.2, 111.4, and 112.1 (C-1, C-4, C-11, and C-12), 122.4 (C-4′, C-14′, C-8′, C-12′), 144.4, 146.3, 147.7, 149.7 (C-2, C-3, C-9, and C-10).

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