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TWO SPIROBENZYLISOQUINOLINE ALKALOIDS FROM *CORYDALIS STEWARTII*

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ABSTRACT.—Two new spirobenzylisoquinoline alkaloids obtained from Pakistani *Corydalis stewartii* are (+)-ochotensidine [**1**] and (+)-corystewartine [**4**]. The stereochemistry of the known (+)-raddeanamine [**5**] is identical to that of **4**.

Some 320 *Corydalis* plant species, belonging to the family Fumariaceae, have been recognized. They occur mostly in the northern hemisphere, particularly in the temperate and tropical zones of Asia. Among these species, 71 have been studied to some extent, and all have been found to produce isoquinoline alkaloids (1).

Corydalis stewartii Fedde grows in the mountainous regions of Pakistan. Initial studies indicated the presence of the aporphines (+)-isoboldine and (+)-domesticine, the protoberberines (+)-tetrahydrocoptisine and coptisine, and also the ketonic base protopine which is always present in *Corydalis* species (2–4).

Presently, a reinvestigation of *C. stewartii*, collected in Pakistan, afforded, besides the known phthalideisoquinoline (+)-adlumidine and the aporphine (+)-domesticine, four spirobenzylisoquinolines, namely (+)-ochotensidine [**1**], (+)-ochotensine [**2**], (+)-ochotensimine [**3**], and (+)-corystewartine [**4**]. Of these four, compounds **1** and **4** are new.

Because previous nmr spectral data for compounds **2** and **3** were limited or unavailable (5), our initial endeavor was to carry out a detailed analysis of the nmr spectrum of (+)-ochotensimine [**3**].

The spectral results are given around expression **3**. Significantly, the vinylic proton absorbing at δ 5.64 showed an nOe with H-12 (δ 7.11), while the vinylic proton at δ 4.90 displayed an nOe with H-6_{ax} (δ 2.96) and with H-1 (δ 6.29). It was also possible to differentiate between the two C-8 protons. H-8β (δ 2.96) exhibited reciprocating nOe's with H-1 (δ 6.29), whereas the *N*-methyl singlet (δ 2.15) showed an nOe with H-8α (δ 3.45). The chemical shifts in the nmr spectrum of (+)-ochotensine [**2**] were then assigned by analogy with those of alkaloid **3**.

The nmr spectrum of the new alkaloid (+)-ochotensidine [**1**] was clearly related to those for analogues **2** and **3**. The main difference was the presence of a methylenedioxy substituent on ring A in lieu of the two methoxyls of (+)-ochotensimine [**3**]. It should be noted that in the spectrum of **1**, the methylenedioxy protons on ring A absorb at higher field than those on ring D.

The mass spectrum of (+)-ochotensidine [**1**] presented molecular ion *m/z* 349 which was also the base peak. Loss of a methyl group then supplied the significant $[M-15]^+$ ion, *m/z* 334.

Our second new spirobenzylisoquinoline, (+)-corystewartine [**4**], $C_{21}H_{21}NO_5$, was different from the preceding three alkaloids in that its nmr spectrum was devoid of vinylic absorptions. Instead, a *C*-methyl singlet was in evidence at δ 1.26. The complete nmr spectral information is presented around expression **4**. Two methylenedioxy groups are clearly observable, with the one attached to ring D absorbing further downfield.

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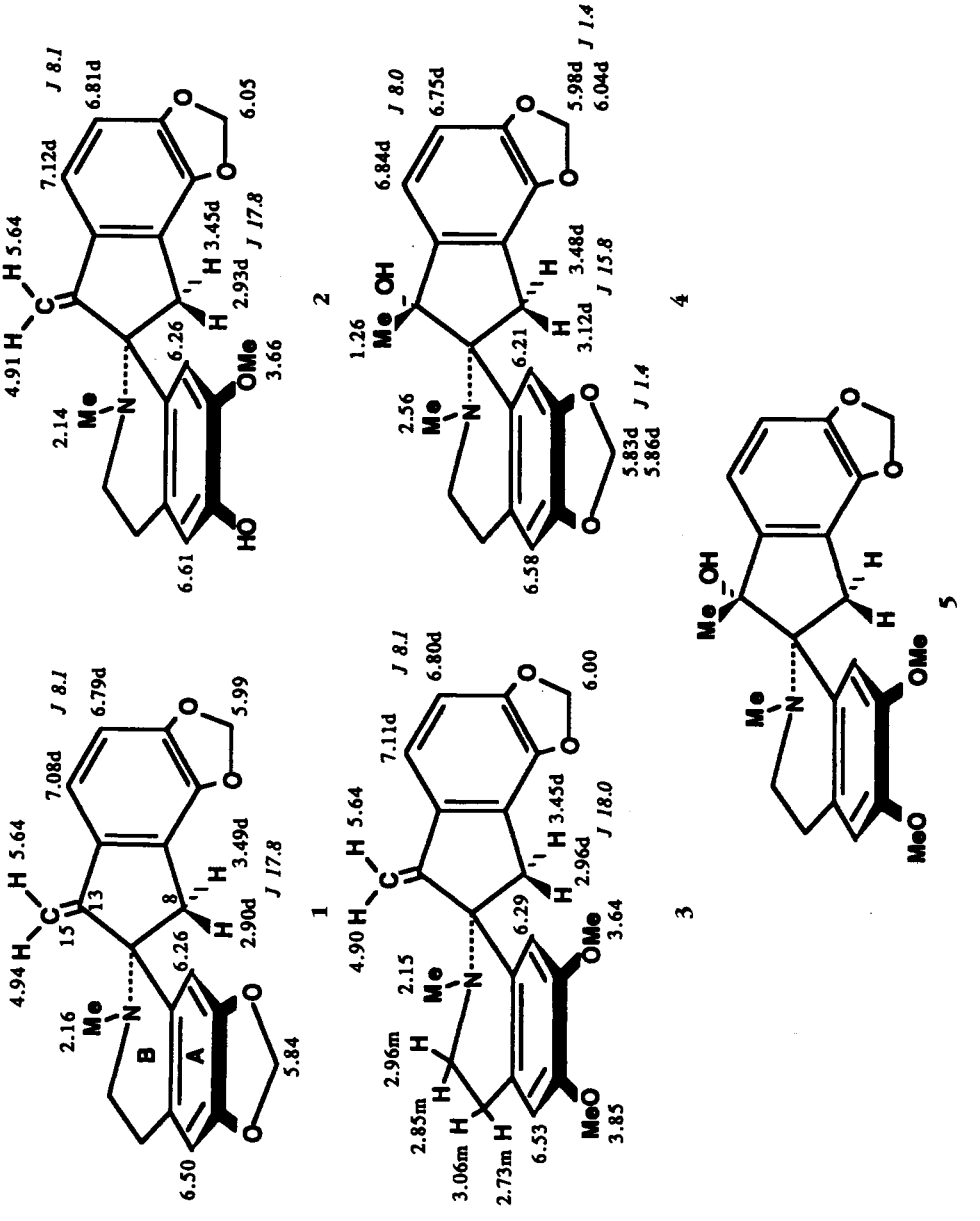
1
2
3
4
5

The mass spectrum of (+)-corystewartine [**4**] included small molecular ion *m/z* 367 (3%). An important peak was *m/z* 352 (64%) formed mostly by loss of the 13-Me group. Alternatively, loss of H_2O from the molecular ion produced ion *m/z* 349 (9%). Base peak *m/z* 190 is due to rings A and B.

Attempted acetylation of (+)-corystewartine [**4**] using Ac_2O in pyridine furnished instead (+)-ochotensidine [**1**], thus directly interrelating the two new alkaloids.

An nmr nOe study was carried out on (+)-corystewartine [**4**] specifically for the purpose of establishing the relative stereochemistry at C-13. Reciprocating nOe's were observed between H-1 (δ 6.21) and the 13-Me singlet (δ 1.26), indicating that the methyl group lies *syn* to ring A.

It should be noted that the known spirobenzylisoquinoline alkaloid (+)-raddeanamine [**5**], which also bears methyl and hydroxyl substituents at C-13, shows an nmr spectrum with a 13-Me singlet at δ 1.23 (6,7). This value compares very well with the corresponding value for (+)-corystewartine [**4**], δ 1.26, so that raddeanamine must have the identical stereochemistry at C-13.

It is also known that dextrorotatory spirobenzylisoquinolines such as ochotensine [**2**] exhibit in their cd spectra a positive Cotton effect centered around 280 nm (8). (+)-Ochotensidine [**1**] also presents a similar cd pattern (see Experimental section), which indicates that compounds **2** and **4** incorporate the identical chirality. The absolute configuration of (+)-corystewartine [**4**] is settled by its ready conversion into (+)-ochotensidine [**1**].

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Cc was on Si gel 60 (70–230 mesh). Tlc was on Merck F-254 Si gel glass plates. Nmr spectra are in $CDCl_3$ at 360 MHz.

PLANT COLLECTION AND EXTRACTION.—*C. stewartii* (6.5 kg, dry, whole plant) was collected in the Kaghan Valley of northern Pakistan. The plant was identified by Dr. E. Nasir of the Pakistan National Herbarium in Islamabad, where a voucher specimen was deposited. The powdered plant was extracted with cold EtOH. The solvent was evaporated without excessive heat and the residue extracted with 5% HCl. The acidic layer was separated and basified with NH_4OH and then extracted with $CHCl_3$. Evaporation of the organic layer left a dark residue (20 g) which was placed on a Si gel column. Elution was with $CHCl_3$ gradually enriched with MeOH. Final purification was by tlc using such systems at $CHCl_3$-MeOH (90:10) and C_6H_6-$CHCl_3$-MeOH-iPrOH-NH_4OH (50:50:10:1:1). Alkaloids obtained were (+)-ochotensidine [**1**] (28 mg); (+)-ochotensine [**2**] (30 mg); (+)-ochotensimine [**3**] (205 mg); and (+)-corystewartine [**4**] (8 mg). The phthalideisoquinoline (+)-adlumidine (4 mg) and the aporphine (+)-domesticine (19 mg) were also obtained. The main alkaloid was protopine.

(+)-OCHOTENSIDINE [**1**].—Ms *m/z* $[M]^+$ 349 (100), 348 (61), 334 (16), 320 (13), 190 (11), 189 (27); uv λ max (MeOH) 232, 291 nm (log ε 4.41, 4.18); $[\alpha]_D$ +44° (0.13, MeOH); cd Δε (nm) (MeOH) 0 (319), +6.0 (295), 0 (279), −4.6 (248), positive tail below 245 nm.

(+)-OCHOTENSINE [**2**].—Ms *m/z* $[M]^+$ 351 (100), 350 (83), 336 (37), 322 (29), 308 (17), 206 (7), 205 (9), 205 (6).

(+)-OCHOTENSIMINE [**3**].—Ms *m/z* $[M]^+$ 365 (100), 364 (61), 350 (29), 336 (40), 205 (14), 204 (12); uv λ max (MeOH) 230, 286 nm (log ε 4.99, 4.17); $[\alpha]_D$ +49° (0.15, MeOH); cd Δε (nm) (MeOH) 0 (315), +6.0 (292), 0 (275), −5.3 (249). Principal nmr nOe's are H-1 to H-15a (3%), H-15a to H-1 (2%), H-1 to H-8β (5%), H-8β to H-1 (10%), H-15b to H-12 (21%), H-12 to H-15b (8%), H-4 to 3-OMe (16%), 3-OMe to H-4 (25%), H-4 to H-5_{eq} (3%), H-5_{eq} to H-4 (3%), H-15a to H-6_{ax} (1%), H-6_{ax} to H-15a (3%), N-Me to H-8α (2%).

(+)-CORYSTEWARTINE [**4**].—Ms *m/z* $[M]^+$ 367 (3), 366 (6), 353 (14), 352 (64), 349 (9), 310 (12), 204 (5), 191 (14), 190 (100); hrms calcd for $C_{21}H_{21}NO_5$, 367.1420, found 367.1424; uv max (MeOH) 242 sh, 288 nm (log 4.01, 3.83); $[\alpha]_D$ +82° (0.12, $CHCl_3$). Treatment of **4** with Ac_2O in pyridine at room temperature supplied **1**.

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