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# BERBIDINE: A SIMPLE ISOQUINOLINE-ISOQUINOLONE DIMER

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ABSTRACT.—Berbidine [**1**], the first simple isoquinoline-isoquinolone dimer, has been obtained from *Berberis brandisiana* of Pakistani origin.

The botanical family Berberidaceae is known for the production of isoquinoline alkaloids, including in particular bisbenzylisoquinolines (1). Presently, as a result of an investigation of the alkaloids of *Berberis brandisiana* Ahrendt, a plant native to the mountains of northern Pakistan, we report the isolation and structure elucidation of berbidine [**1**], $C_{23}H_{28}N_2O_5$, $\nu$ max ($CHCl_3$) 1605, 1640 $cm^{-1}$, which is the first known simple isoquinoline-isoquinolone dimer. We believe that this alkaloid throws new light upon the catabolism of bisbenzylisoquinolines.

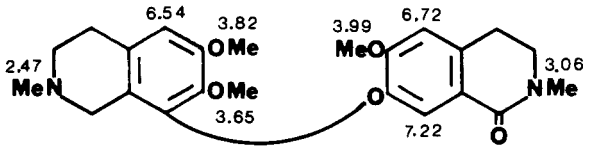
The $^1$H-nmr spectrum (200 MHz, $CDCl_3$) of berbidine is outlined around expression **1**. Two *N*-methyl singlets are in evidence, the first at $\delta$ 2.47 associated with an amine function and the second further downfield at $\delta$ 3.06 and related to a lactam. Three aromatic methoxyl singlets are also present, one of which, relatively upfield at $\delta$ 3.65, can be assigned to a C-7 methoxyl by comparison with the nmr spectra of related bisbenzylisoquinolines (2). The aromatic region of the spectrum displays a simple picture consisting of only three one-proton singlets, one of which, situated downfield at $\delta$ 7.22, represents the proton peri to the lactam oxygen.

The mass spectrum of berbidine [**1**] shows molecular ion *m/z* 412 (51%) and base peak $[M-1]^+$ 411. Other significant fragments are *m/z* 221, 206, and 190, obtained by cleavage of the dimer on either side of the diaryl ether bridge.

A clue to the biogenesis of berbidine [**1**] was offered by the accompanying base (+)-chenabinol methyl ether [**4**], $C_{38}H_{44}N_2O_7$, obtained from the chromatographic extracts. This compound is closely related to the known secobisbenzylisoquinoline alkaloid (+)-chenabine [**2**] found in *Berberis lycium* (3). In our hands, $NaBH_4$ in MeOH reduction of (+)-chenabine [**2**] gave (+)-chenabinol [**3**], $C_{37}H_{42}N_2O_7$, which upon treatment with cold methanolic HCl afforded (+)-chenabinol methyl ether [**4**]. Additionally, $KMnO_4$ in $Me_2CO$ oxidation of (+)-chenabinol methyl ether [**4**] yielded berbidine [**1**].

Berbidine [**1**], (+)-chenabine [**2**], and (+)-chenabinol methyl ether [**4**] should be juxtaposed by the known secobisbenzylisoquinoline (+)-sindamine [**5**] obtained from *B. lycium* (4) and the bisbenzylisoquinoline (+)-berbamine [**6**] which occurs as a main alkaloid in both *B. brandisiana* and *B. lycium* (5).

Dimers **1**, **2**, and **5** can then be understood as in vivo metabolic products of (+)-berbamine [**6**]. On the one hand, oxidation of (+)-berbamine [**6**] at the less hindered




**1**

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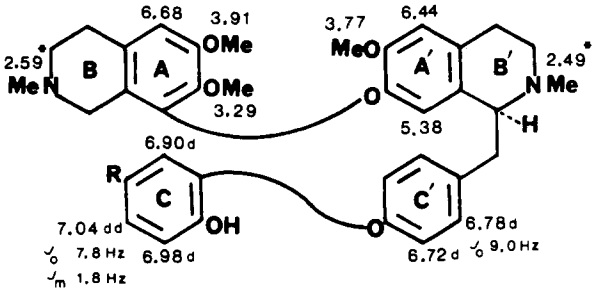
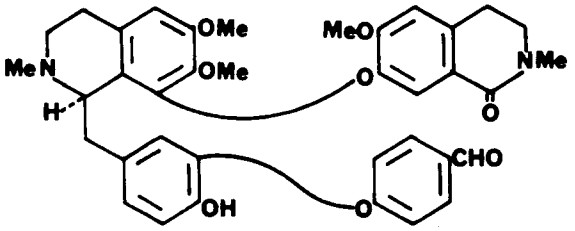
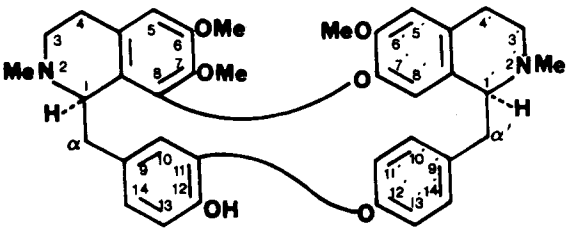



**2** R=CHO
**3** R=$CH_2OH$
**4** R=$CH_2OMe$ ($^1H$ nmr)
($CH_2OMe$: $CH_2$, s, δ 4.30;
OMe, s, δ 3.32)




**5**




**6**

C-1′ center, close to the unsubstituted C-8′, affords the aldehydo lactam (+)-sindamine [**5**]. On the other hand, oxidation at the more hindered C-1 center, close to the substituted C-8 site, leads to the amino aldehyde (+)-chenabine [**2**]. It is likely that the latter oxidation provides initially an iminium salt as part of ring B, which is readily reduced to the tertiary amine actually isolated. Berbidine itself could then be derived in vivo by further transformations of either (+)-chenabine [**2**] or (+)-sindamine [**5**].

## EXPERIMENTAL

PLANT MATERIAL AND ISOLATION.—The aerial parts of *B. brandisiana* (7 kg) collected in the Ushu valley in Swat, northern Pakistan, were air dried, powdered, and extracted with EtOH at room temperature. The semisolid viscous mass obtained upon removal of the solvent below 45° was taken up in 5% HCl and filtered, and the filtrate was extracted several times with $CHCl_3$. The aqueous acidic solution was filtered again, basified with $NH_4OH$, and extracted with $CHCl_3$. Removal of the solvent furnished 30 g of alkaloidal fraction which was chromatographed over Si gel (Merck, 70–230 mesh). Elution was with $CHCl_3$ gradually enriched with MeOH. The fractions collected were monitored by tlc and were combined into groups.

BERBIDINE [**1**].—Amorphous, 4.4 mg; λ max (MeOH) 224 sh, 260, 269 sh, 296, 304 sh nm (log ε 4.60, 4.04, 3.98, 3.79, 3.75); ν max ($CHCl_3$) 1640, 1605 $cm^{-1}$; eims *m/z* $[M]^+$ 412 (51), 411 (100), 397 (67), 381 (10), 365 (18), 354 (21), 338 (15), 222 (18), 221 (25), 206 (60), 190 (14).

(+)-CHENABINOL METHYL ETHER [**4**].—Amorphous, 33.5 mg; $[\alpha]_D$ +21° (*c* = 0.11, MeOH); λ max (MeOH) 225 sh, 281 nm (log ε 4.70, 4.01); eims *m/z* $[M]^+$ 640 (0.1), 639 (0.3), 609 (0.5), 411 (2), 397 (100), 365 (10), 198 (6), 174 (10).

(+)-CHENABINOL [**3**].—(+)-Chenabine (3.5 mg) dissolved in MeOH (5 ml) was stirred with $NaBH_4$ (15 mg) for 1 h. Workup yielded **3** (2.8 mg); λ max (MeOH) 226 sh, 282 nm (log ε 4.37, 3.69); $^1H$ nmr (360 MHz, $CDCl_3$) δ 2.51 (s, 3H, 2′-NMe), 2.63 (s, 3H, 2-NMe), 3.37 (s, 3H, 7-OMe), 3.78 (s, 3H, 6′-OMe), 3.92 (s, 3H, 6-OMe), 4.55 (s, 2H, $ArCH_2O$), 5.44 (br s, 1H, H-8′), 6.46 (s, 1H, H-5′), 6.71 (s, 1H, H-5), 6.73 (d, $J_o$ = 8.5 Hz, 2H, H-11′,13′), 6.80 (d, $J_o$ = 8.5 Hz, 2H, H-10′,14′), 6.92 (d, $J_m$ = 1.8 Hz, 1H, H-10), 7.01 (d, $J_o$ = 8.2 Hz, 1H, H-13), 7.06 (dd, $J_o$ = 8.2 Hz, $J_m$ = 1.8 Hz, 1H, H-14); eims *m/z* $[M]^+$ 626 (<0.1), 411 (0.6), 397 (100), 365 (22), 198 (10), 174 (12).

METHYLATION OF (+)-CHENABINOL.—Base **3** (2.8 mg) was kept overnight at room temperature in dry methanolic HCl (5 ml). Workup including tlc in $C_6H_6$-$CHCl_3$-$Et_2NH$ (5:4:1) supplied **4** (1.8 mg).

OXIDATION OF (+)-CHENABINOL METHYL ETHER.—Ether **4** (20 mg) was dissolved in $Me_2CO$ (20 ml), and a solution of $KMnO_4$ (25 mg) in $Me_2CO$ (20 ml) was added with constant stirring during 30 min. Stirring was continued for another 3 h. The mixture was filtered and the solvent removed in vacuo. Preparative tlc in $C_6H_6$-MeOH (95:5) afforded **1** (5 mg).

ACETYLATION OF CHENABINOL METHYL ETHER.—A solution of **4** (3 mg), $Ac_2O$ (0.5 ml) and pyridine (5 drops) was kept overnight at room temperature. Workup afforded *O*-acetylchenabinol methyl ether (1.8 mg): ν max ($CHCl_3$) 1760, 1605 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ 2.18 (s, 3H, Ac), 2.39 (s, 3H, 2′-NMe), 2.43 (s, 2-NMe), 3.35 (s, 3H, $CH_2OCH_3$), 3.68 (s, 3H, 7-OMe), 3.82 (s, 3H, 6′-OMe), 3.92 (s, 3H, 6-OMe), 4.36 (s, 2H, $ArCH_2O$), 6.20 (s, 1H, H-8′), 6.55 (s, 1H, H-5′), 6.64 (s, 1H, H-5), 6.78 (d, *J* = 8.6 Hz, 2H, H-11′,13′), 6.88 (d, 1H, $J_m$ = 1.8 Hz, H-10), 6.97 (d, *J* = 8.5 Hz, 2H, H-10′,14′), 7.07 (m, 2H, H-13,14); eims *m/z* $[M-1]^+$ 681 ($C_{40}H_{46}N_2O_8$, 0.3), 651 (0.2), 397 (100), 365 (10), 198 (10), 174 (5).

ACKNOWLEDGMENTS

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