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THREE NEW DIMERIC APORPHINOIDS FROM *BERBERIS* SPECIES

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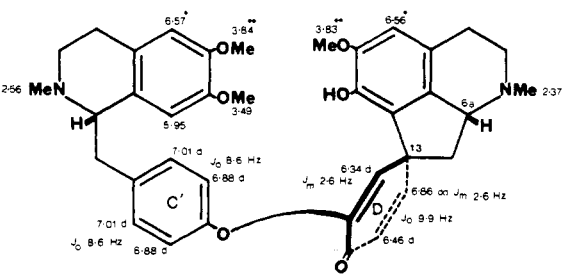
Berberis species (Berberidaceae) have so far yielded two types of proaporphine-benzylisoquinoline dimers which differ in stereochemistry at the C-13 spiro center. Those belonging to the *normal* series incorporate H-6a and the ring D aryloxy substituent in an *anti*-relationship, whereas in the *epi*-series, these functions are in a *syn*-arrangement. Although six proaporphine-benzylisoquinolines of the normal series are known—(+)-pakistanamine (1), (+)-valdivianine (1), (+)-valdiberine (1), (+)-berbivaldine (1), (+)-rupancamine (2), and (+)-patagonine (1)—only two of the somewhat less common *epi*-variety have been recognized so far, these being (+)-epivaldiberine (1) and (+)-epiberbivaldine (2). We now describe a third *epi*-dimer, namely (+)-epivaldivianine (**1**), $C_{37}H_{40}N_2O_6$, obtained from *Berberis valdiviana* Phil., ν max ($CHCl_3$) 1635, 1665, and 3670 cm^{-1}.

The 200 MHz ($CDCl_3$) ^{1}H-nmr spectrum of (+)-epivaldivianine is summarized in **1**. The notable feature of this spectrum is the characteristic ring D vinylic doublet downfield at δ 6.34. This shift is diagnostic of the *epi*-series, since for normal compounds the vinylic doublet is found near δ 6.1 (1,2). Another significant trait of the spectrum pointing to the *epi*-stereochemistry is the well-defined A_2B_2 system at δ 6.88 and 7.01 representing the protons in the *para*-substituted ring C′ (2).

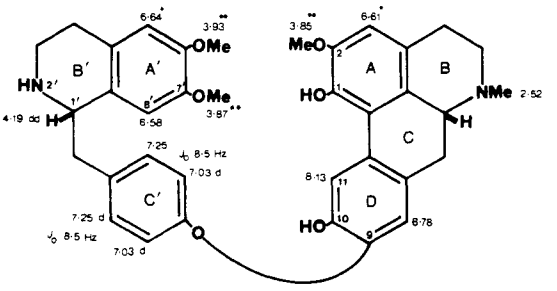
The mass spectrum of (+)-epivaldivianine (**1**) includes molecular ion *m/z* 608 and base peak *m/z* 206 due to rings A′ and B′ of the tetrahydrobenzylisoquinoline moiety.

Final proof of structure was derived from acid catalyzed rearrangement of the alkaloid that furnished the known aporphine-benzylisoquinoline (−)-kalashine in which the aporphine is 1,2,10,11-substituted. If (+)-epivaldivianine had belonged to the normal series, a C-1,2,9,10-oxygenated aporphine would have been obtained (1).

The second new dimer we report is the aporphine-benzylisoquinoline (+)-2′-norpakistanine (**2**), $C_{36}H_{38}N_2O_6$, also found in *B. valdiviana*. The 360 MHz ($CDCl_3$) nmr spectrum is outlined in **2**. Only one *N*-methyl singlet at δ 2.52 is present, which was assigned to the aporphine portion. Interestingly, the H-8′



1



2

singlet absorption at δ 6.58 is not as upfield as in other related aporphine-benzylisoquinolines (3). This is because of the NH function in ring B′ which encourages a conformational change such that ring C′ is closer to ring B′ than to A′. Similarly, the C-7′ methoxyl falls within the δ 3.87 to 3.93 span rather than in the more common δ 3.40-3.60 range (3). In line with the presence of an NH function in ring B′, the H-1′ signal is relatively downfield at δ 4.19.

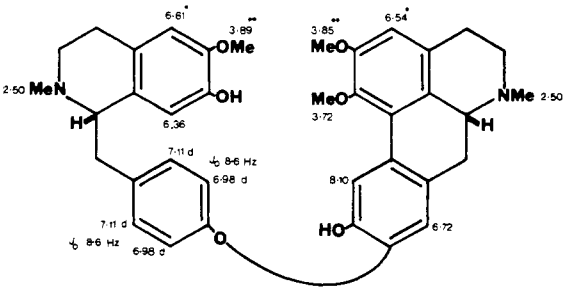
Significantly, the mass spectrum of (+)-2′-norpakistanine (**2**) showed molecular ion *m/z* 594 and base peak *m/z* 192 representing rings A′ and B′ of the tetrahydrobenzylisoquinoline unit. Finally, and as expected, Eschweiler-Clarke *N*-methylation of **2** supplied the known (+)-pakistanine.

An interesting point concerning (+)-2′-norpakistanine (**2**) is that it is the first *nor* compound known among dimers of the pakistanine-kalashine series, all of which are derived biogenetically from the condensation of two coclaurinoid moieties (3).

Our third new natural product is (+)-1-*O*-methylchitraline (**3**), $C_{37}H_{40}N_2O_6$, isolated from *Berberis darwinii* Hook. This aporphine-benzylisoquinoline dimer had previously been obtained in vitro through acid rearrangement of the normal proaporphine-benzylisoquinoline (+)-patagonine (1).

The ^{1}H-nmr chemical shifts in the 200 MHz ($CDCl_3$) spectrum for (+)-1-*O*-methylchitraline are presented around expression **3** and correspond closely to those previously reported for the semisynthetic material (1). The mass spectrum of the natural product showed molecular ion *m/z* 608 and base peak *m/z* 192 due to rings A′ and B′ of the tetrahydrobenzylisoquinoline portion.

A significant feature of all aporphine-benzylisoquinoline dimers so far obtained from *Berberis* species, such as (+)-pakistanine, (+)-porveniramine, (+)-chitraline, (−)-khyberine, and (−)-kalashine (3) is that they inevitably include a hydroxyl group at C-10 of the aporphine moiety. This is, of course, a reflection of their biogenetic origin since they are derived from the dienone-phenol rearrangement of the corresponding proaporphine-benzylisoquinoline dimers. It will be interesting to observe



in the future just to what extent this trend continues to apply.

EXPERIMENTAL

PLANT COLLECTION AND EXTRACTION.—*B. valdiviana* (20 kg, dry stems) was collected near Valdivia, Chile (4,5). *B. darwinii* (18 kg, dry stems) was gathered near Osorno, Chile (4-6). The plants were air-dried, powdered, and extracted with cold EtOH. The basic alkaloidal extracts were fractionated by silica gel column and thin layer chromatography.

(+)-EPIVALDIVIANINE (**1**).—Amorphous, 4.5 mg from *B. valdiviana*; λ max (MeOH) 234 sh, 285 nm (log ε 4.50, 3.93); ms *m/z* 608 (M^+) (0.02), 604 (0.28), 588 (0.14), 575 (0.12), 401 (0.6), 295 (8), 207 (14), 206 (100); $[\alpha]^{25}D$ +69.4° (c 0.1, MeOH).

REARRANGEMENT OF **1** TO (−)-KALASHINE.—(+)-Epivaldivianine (1 mg) was refluxed in 2N HCl for 2 h. Work-up provided kalashine, $[\alpha]^{25}D$ −27.4° (c 0.06, MeOH), identified by spectral comparisons.

(+)-2′-NORPAKISTANINE (**2**).—Mp 148° (MeOH), 10 mg from *B. Valdiviana*; λ max (MeOH) 224, 268, 277, 292, 308 nm (log ε 4.66, 4.16, 4.26, 4.05, 4.12); ms *m/z* 594 (M^+) (0.4), 593 (2), 592 (6), 591 (8), 590 (15), 588 (11), 575 (6), 207 (6), 206 (62), 192 (100); $[\alpha]^{25}D$ +9.1° (c 0.05, MeOH).

N-METHYLATION OF **2**.—Dimer **2** (2 mg) was dissolved in HCOOH (0.5 ml) and aqueous formaldehyde (0.5 ml), and the solution was refluxed for 4 h. Work-up provided (+)-pakistanine identified by its spectral data and by comparison with an authentic sample.

(+)-1-*O*-METHYLCHITRALINE (**3**).—Amorphous, 5 mg from *B. darwinii*; λ max (MeOH) 226, 269, 279, 304 nm (log ε 4.55, 4.06, 4.17, 3.98); identified by spectral comparisons.

ACKNOWLEDGMENTS

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