

STRUCTURAL VARIATIONS AMONG THE APORPHINE-BENZYLISOQUINOLINE DIMERS

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**Abstract:** Thalictrum minus L. var. microphyllum Boiss. (Ranunculaceae) has yielded (+)-istanbulamine (5) which is the first aporphine-benzylisoquinoline formed from one (+)-reticuline-type unit linked to a (+)-N-methylcocclaurine moiety. Other new dimers also present are (+)-bursanine (6) and (+)-iznikine (7).

The more than thirty naturally occurring aporphine-benzylisoquinoline dimers so far reported in the literature<sup>2</sup> may be considered to be formed, in a formal sense, through the condensation of two (+)-reticuline-type units<sup>3</sup> or two N-methylcocclaurines. It is known that dimers formed from two (+)-reticulines may be of the (+)-thalicarpine (1) or the (+)-fetidine (2) types; while dimers incorporating two N-methylcocclaurines belong to either the (+)-pakistanine (3) or the (-)-kalashine (4) series.<sup>2,4</sup> We now wish to describe the new alkaloid (+)-istanbulamine (5) which represents a new type of aporphine-benzylisoquinoline dimer and consists of a (+)-reticuline-type unit bonded to (+)-N-methylcocclaurine.

Work-up of 4 kg of the dried powdered roots and rhizomes of Thalictrum minus L. var. microphyllum Boiss. (Ranunculaceae), collected in the village of Mahmudiye, near the town of Eskişehir, in western Anatolia, yielded 17 mg of the diphenolic (+)-istanbulamine (5), C<sub>39</sub>H<sub>44</sub>O<sub>8</sub>N<sub>2</sub>, whose mass spectrum (Table I) shows a small molecular ion m/z 668 (0.2), and base peak m/z 192 due to facile formation of the dihydroisoquinolinium cation a through cleavage of the C-1' to C-α' bond. The UV spectrum of the alkaloid (Table I) is congruent with the presence of a 1,2,9,10- or 1,2,3,9,10-substituted aporphine system.<sup>2</sup>

The NMR spectrum of istanbulamine has been outlined around expression 5. Two salient features of this spectrum are the aromatic ABX pattern representing H-10', 13', and 14', and never encountered in the spectra of alkaloids of types 1-4, and a downfield proton singlet at δ8.03 indicating that C-11 is unsubstituted.<sup>5</sup>

In order to confirm the chemical shift assignments, an NMR nuclear Overhauser enhancement (NOE) study was carried out on istanbulamine, the results of which have been summarized in expression 5A.<sup>6</sup> There is a significant (8%) dipole-dipole relaxation enhancement of the C-2 methoxyl signal upon irradiation of the C-1 methoxyl, which serves to identify the chemical shift of the former substituent. Similarly, the 3% NOE shown by the C-10 methoxyl upon irradiation of H-11

serves to single out that methoxyl from similar substituents in the molecule, and proves that the diaryl ether terminal cannot be at C-10. The absolute configuration of (+)-istanbulamine (5) is indicated by its circular dichroism (CD) pattern (Table I), which generally resembles that of alkaloids belonging to the (+)-thalicarpine series.<sup>2</sup>

The same plant also produces the new alkaloids (+)-bursanine (6) and (+)-iznikine (7). The former belongs to the (+)-thalicarpine and the latter to the (+)-fetidine series.

(+)-Bursanine (6), 37 mg,  $C_{40}H_{46}O_9N_2$ , has a mass spectrum with molecular ion  $m/z$  698 (0.1), and base peak  $m/z$  192. The UV spectrum (Table I) is close to that for istanbulamine (5). The NMR spectrum has been outlined around expression 6, and again the assignments of chemical shifts were ascertained by NOE studies, as summarized in 6A. Of particular relevance is the 5% NOE of H-11' upon irradiation of H-8, and the 3% NOE of the C-12' methoxyl due to irradiation of H-11'. It follows that the substitution pattern on ring C of the tetrahydrobenzylisoquinoline segment must be methoxyl at C-12' and hydroxyl at C-13'. The absolute configuration of (+)-bursanine (6) follows from the shape of its CD curve (Table I) which resembles those for the closely related alkaloids of the (+)-thalicarpine series.<sup>2</sup>

Only 9 mg of the minor alkaloid (+)-iznikine (7),  $C_{40}H_{46}O_9N_2$ , could be isolated. The mass spectrum has peaks  $m/z$  697 ( $M - 1$ )<sup>+</sup> (0.3), and 192 (100) (Table I). The base peak is in fact identical with that for (+)-istanbulamine (5) and (+)-bursanine (6). Similarly, the UV spectrum of 7 is close to the spectra of 5 and 6 (Table I).

As in the cases of (+)-istanbulamine and (+)-bursanine, the NMR spectrum of iznikine (7), coupled with NOE studies, was decisive in the structural assignments. A key trait of the NMR spectrum is a two-proton aromatic singlet at  $\delta$ 6.75 representing H-13' and 14'. Irradiation of this singlet produced a 3% NOE of the  $\delta$ 3.92 methoxyl signal. This substituent can, therefore, be positioned at C-12', and a phenolic function must be present at C-11'. The absolute configuration of (+)-iznikine is derived from the shape of its CD curve which resembles those for 5 and 6.

A general feature of dimers incorporating an aporphine moiety related to (+)-reticuline is that a methoxyl group is present at C-10. This is true in the (+)-thalicarpine (1), (+)-fetidine (2) and (+)-istanbulamine series, reflecting the fact that the tetrahydrobenzylisoquinoline (+)-reticuline also bears a methoxyl at that site. Such dimers, found among the Ranunculaceae and Hernandiaceae, are therefore probably formed by direct phenolic oxidative coupling of a 9-hydroxy-10-methoxyaporphine with a phenolic tetrahydrobenzylisoquinoline of the (+)-reticuline or (+)-N-methylcoclaurine type. On the other hand, dimers of the (+)-pakistanine (3) or (-)-kalashine (4) series, present among the Berberidaceae, still bear the scars of their biogenesis and possess a phenolic function at C-10 - a direct result of the dienone-phenol rearrangement of a proaporphine-benzylisoquinoline precursor.

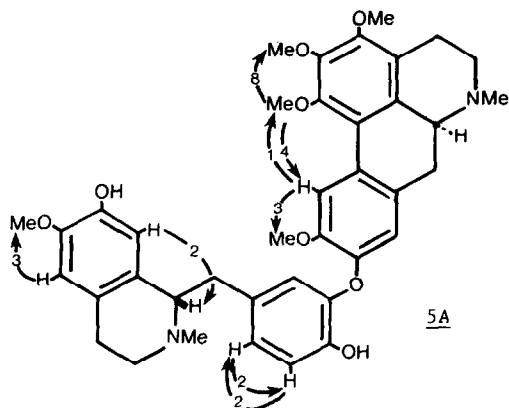
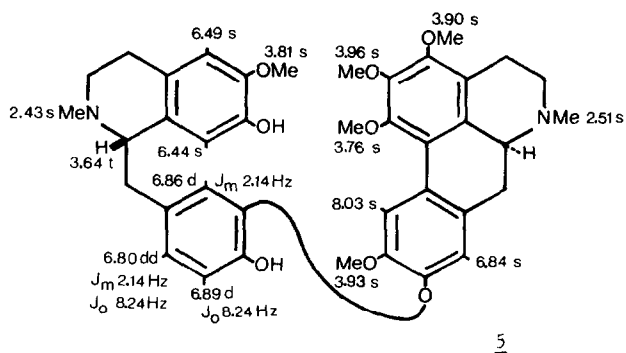
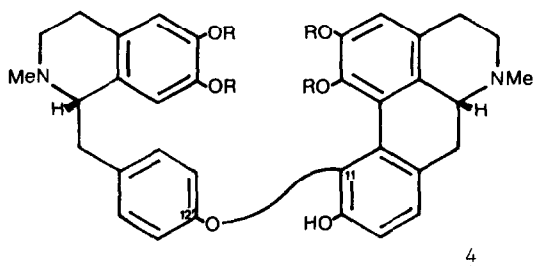
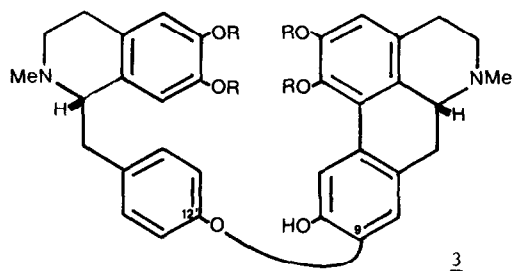
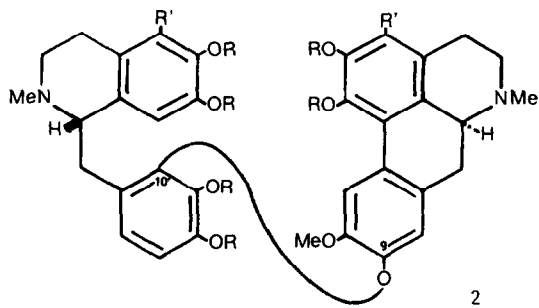
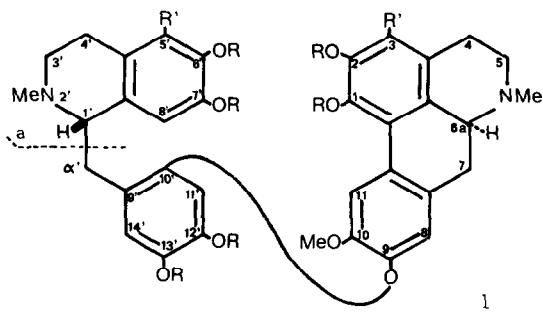
Table I. Spectral and Physical Properties of Alkaloids

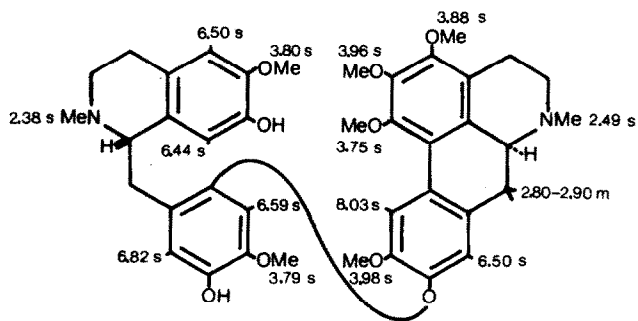
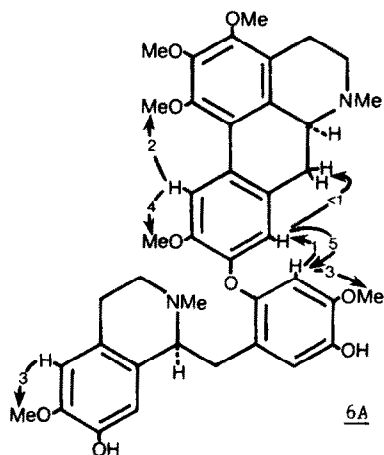
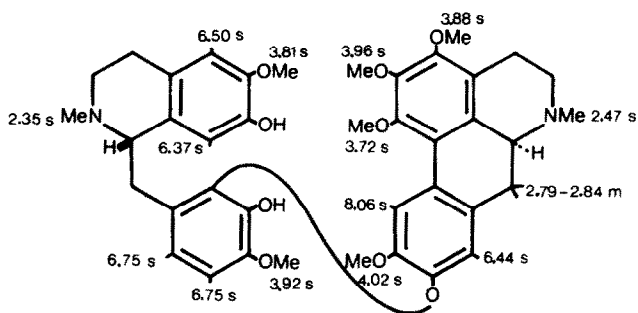
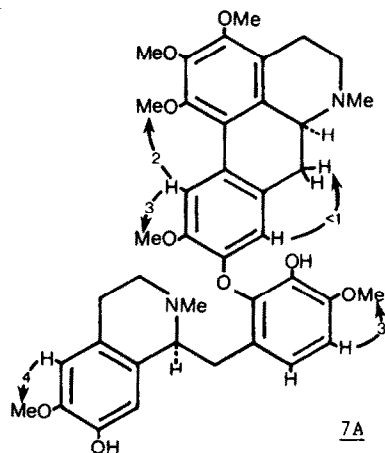
NMR spectra are at 200 MHz (FT) in  $CDCl_3$  solution. UV spectra and CD curves are in MeOH solution. Istanbulamine (5):  $\lambda$  max 205, 225 sh, 270 sh, 282, 304 sh, 313 nm ( $\log \epsilon$  4.87, 4.75, 4.20, 4.34, 4.15, 4.12); MS  $m/z$  668 ( $M^+$ , 0.2), 666 (1), 638 (0.6), 608 (0.3), 476 ( $M - a$ , 4), 475 (6), 369 (0.4), 354 (1), 192 ( $a$ , 100);  $CD_{\Delta\epsilon}$  (nm) -15.3 (306), -8.7 (284), -10.9 (275), +61.2 (243), -16.0 (210);  $[\alpha]_D^{25} +60^\circ$  (c 0.09 MeOH).

**Bursanine (6):**  $\lambda$  max 209, 221 sh, 283, 304 sh, 314 nm (log  $\epsilon$  4.81, 4.75, 4.34, 4.24, 4.19); MS  $m/z$  698 ( $M^+$ , 0.1), 696 (0.7), 506 (7), 476 (4), 369 (1), 192 (a, 100); CD  $\Delta\epsilon$  (nm) -5.2 (306), -2.6 (290), -4.9 (275), +49.0 (241), -11.0 (214);  $[\alpha]_D^{25}$  +117° (c 0.17 MeOH).

**Iznikine (7):**  $\lambda$  max 208, 222 sh, 281, 301 sh, 312 nm (log  $\epsilon$  4.68, 4.54, 4.17, 4.03, 3.98); MS 697 ( $M - 1$ )<sup>+</sup> (0.3), 608 (0.8), 506 ( $M - a$ ) (1.7), 367 (0.8), 192 (a, 100); CD  $\Delta\epsilon$  (nm) -6.6 (305), -1.3 (285), -5.3 (273), +27.5 (241), -3.4 (220);  $[\alpha]_D^{25}$  +76° (c 0.068 MeOH).

In expressions 1 and 2 below,  $R'$  = H, OH, or OMe; while OR denotes the usual OH, OMe or OCH<sub>2</sub>O substituents.



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#### References and Footnotes

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2. For a listing of aporphine-benzylisoquinoline dimers, see H. Guinaudeau, M. Leboeuf and A. Cavé, *J. Nat. Prod.*, **42**, 325 (1979).
3. *Thalictrum* alkaloids have a particular tendency towards additional oxygenation at C-3 of an aporphine or at C-5 of a tetrahydrobenzylisoquinoline.
4. S.F. Hussain and M. Shamma, *Tetrahedron Lett.*, **21**, 3315 (1980).
5. For aporphines, H-11 appears generally upfield from  $\delta$ 8.10 if an oxygenated substituent is present at C-3, and further downfield if C-3 is unsubstituted.
6. NOE measurements were carried out at 360 MHz (FT). All samples were degassed. NOE values were obtained by the NOE difference technique where differences as small as 0.5% are significant.

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