Registry No. 1, 20163-71-7; **2a**, 100-52-7; **2b**, 104-88-1; **2c**, 123-11-5; **2d**, 120-14-9; **2e**, 98-03-3; (*E*)-**3a**, 58058-77-8; (*E*)-**3b**, 58058-79-0; (*E*)-**3c**, 83831-67-8; (*E*)-**3d**, 83831-68-9; (*E*)-**3e**, 83831-69-0; (*E*)-**4a**, 83831-70-3; (*E*)-**4b**, 83831-71-4; (*E*)-**4c**, 83831-72-5; (*E*)-**4d**, 83831-73-6; (*E*)-**4e**, 83831-74-7; **5a** (R = Me), 3558-61-0; **5a** (R = Et), 79309-63-0; **5a** (R = *i*-Pr), 83831-75-8; **5b** (R = Me), 10399-10-7; **5c** (R = Me), 59845-69-1; **5d** (R = Me), 83831-76-9; **5e** (R = Me), 19204-08-1; **11**, 83831-77-0; **12**, 5394-87-6.

Communications

(+)-Uskudaramine: A Novel Type Aporphine–Benzylisoquinoline Alkaloid

Summary: (+)-Uskudaramine (**1**) is the first aporphine–benzylisoquinoline dimer whose two constituent entities are bonded together through carbon to carbon coupling.

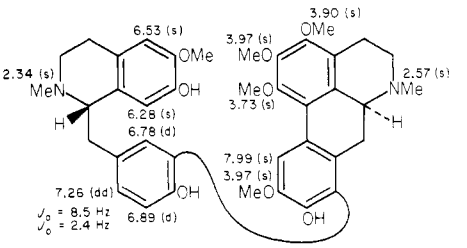
Sir: In a continuing investigation of the alkaloids of *Thalictrum minus* L. var. *microphyllum* (Ranunculaceae), collected in western Anatolia,[2] we have isolated the new amorphous triphenolic aporphine–benzylisoquinoline dimer (+)-uskudaramine (**1**), $C_{39}H_{44}O_8N_2$. This base is structurally isomeric with the known diphenolic alkaloid (+)-istanbulamine (**2**) found in the same plant.[2,3]

The 360-MHz (FT) NMR spectrum in deuteriochloroform of uskudaramine has been summarized around expression **1**, and for comparison purposes that of istanbulamine is cited around expression **2**. Each spectrum shows the presence of five methoxyl and two *N*-methyl singlets, as well as an aromatic singlet near δ 8.00 specifically associated with H-11 of an aporphine. But whereas the istanbulamine spectrum exhibits absorptions for a total of seven aromatic protons, the uskudaramine spectrum has only six such protons. More specifically, the aromatic peak present in the spectrum of istanbulamine (**2**) and conspicuously missing in that of uskudaramine (**1**) is the singlet at δ 6.84 assigned to H-8.

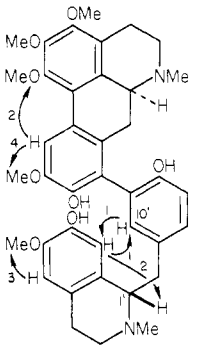
The logical conclusion is thus to move the terminal of the connecting bridge between the two moieties making up the aporphine–benzylisoquinoline dimer from the oxygen atom at C-9 of istanbulamine (**2**) to the adjacent C-8 position in uskudaramine (**1**). Such a structural change would satisfy the NMR spectral requirement by eliminating an aromatic proton in **1**, while at the same time creating an extra phenolic function at C-9 that would be congruent with the fact that uskudaramine (**1**) is triphenolic while its companion, istanbulamine (**2**), is only diphenolic.

In analogy with the mass spectrum of istanbulamine (**2**),[2] the mass spectrum of uskudaramine (**1**) displays a small molecular ion m/z 668 and base peak m/z 192 due to the dihydroisoquinolinium cation a formed through facile fission of the C-1′ to C-α′ bond. In both instances, there is a small but significant m/z 476 peak due to cation b that corresponds to $(M - a)^+$ (Table I).

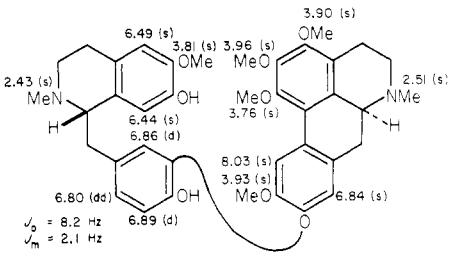
The UV spectrum of uskudaramine (**1**; Table I) exhibits an absorption at 312 nm diagnostic of an aporphine system.



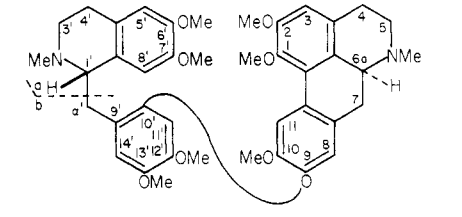
1



1a



2



3

The spectrum also shows the expected bathochromic shift in base due to the phenolic functions. More importantly, there is also a hyperchromic effect that accompanies the bathochromic shift. This hyperchromic effect is associated with the presence of a phenolic function at either C-3 or C-9 of the aporphine moiety, with C-9 being in the present case the more logical site for the phenol.[4]

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(2) Guinaudeau, H.; Freyer, A. J.; Minard, R. D.; Shamma, M. *Tetrahedron Lett.* **1982**, *23*, 2523.

(3) There is a particular tendency for benzylisoquinolines of *Thalictrum* species to acquire an extra oxygen at C-5. Such a species would then provide an aporphine oxygenated at C-3 as in alkaloids **1** and **2**.

(4) Abu Zarga, M. H.; Shamma, M. *J. Nat. Prod.*, **1982**, *45*, 471. Shamma, M.; Yao, S. Y.; Pai, B. R.; Charubala, R. *J. Org. Chem.* **1971**, *36*, 3253.

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Table I. Physical and Spectral Data for Uskudaramine and Derivative

Uskudaramine (1)

UV (MeOH) λ_{max} 209 nm, 221 (sh), 286, 300 (sh), 312 (sh) (log ϵ 4.78, 4.73, 4.35, 4.18, 4.06); UV (MeOH-OH^-) λ_{max} 210 nm, 262 (sh), 303, 321 (sh) (log ϵ 4.90, 4.26, 4.37, 4.20); MS, *m/z* 668 (M^+, 0.1), 667 (0.1), 608 (0.3), 476 (3.3), 461 (1.2), 460 (2.6), 446 (1.8), 416 (0.7), 192 (100), 177 (13); CD (MeOH) $\Delta\epsilon$ (nm) −4.8 (297), −3.9 (280), +48 (244), −32 (212); $[\alpha]^{25}_D$ +84° (*c* 0.15, MeOH)

Triacetyluskudaramine

NMR (200 MHz, FT, $CDCl_3$) δ 1.96, 2.04, 2.26 (3 × 3 H, s, 3 acetyls), 2.46 (6 H, s, 2 NCH_3), 3.79, 3.80, 3.90, 3.91, 3.96 (5 × 3 H, s, 5 OCH_3), 6.40 (1 H, s, H-8′), 6.64 (1 H, s, H-5′), 7.00-7.20 (3 H, m, H-10′, H-13′, H-14′), 8.11 (1 H, s, H-11); MS, *m/z* 794 (M^+, $C_{45}H_{50}O_{11}N_2$, 0.1), 752 (0.2), 709 (0.1), 560 (0.4), 518 (1.4), 477 (2.4), 446 (1.3), 434 (1.4), 234 (100), 192 (81), 177 (5)

In order to provide additional support for the presence of the phenolic function at C-9, we treated the new alkaloid with acetic anhydride in pyridine to yield the corresponding triacetate ester, $C_{45}H_{50}O_{11}N_2$, whose NMR spectrum displays a downfield shift of H-11 from δ 7.99 to 8.11 (Table I). It follows that in species 1 a phenolic group must be present in the same aromatic ring as H-11, more specifically at C-9.

To further ascertain the structure of the new alkaloid, we carried out an NMR NOE study on a deoxygenated deuteriochloroform solution of the alkaloid, the results of which have been summarized in expression **1a**.[5] The relative position of each of the six aromatic protons was determined in relation to each of the methoxyl substituents. Separate irradiations of the aromatic hydrogens substantiated the fact that all of these protons belong to the benzylisoquinoline moiety except for H-11 (δ 7.99) whose irradiation produces a 2% NOE of the C-1 methoxyl (δ 3.73) and a 4% NOE of the C-10 methoxyl (δ 3.97). It should be pointed out as an aside that, in the NMR spectrum of uskudaramine (1), the chemical shift of H-11 at δ 7.99 is in keeping with the presence of a substituent at C-3 of the aporphine, since if C-3 were unsubstituted H-11 would have appeared downfield from δ 8.10.[2]

Other significant NMR NOE findings are that irradiation of H-8′ (δ 6.28) caused a 1% dipole-dipole relaxation enhancement of H-10′ (δ 6.78) and a 2% enhancement of the H-1′ signal (δ 3.67), while irradiation of H-10′ led to a 1% enhancement of H-8′. These NOE results not only confirm the structure of the alkaloid but also lead to some understanding of the conformation of the molecule.

The CD spectrum of (+)-uskudaramine (1), with a Cotton effect maximum at 244 nm and a negative trough at 212 nm (Table I), is very close to that of (+)-istanbulamine (**2**),[2] and generally resembles that of alkaloids belonging to the (+)-thalicarpine (**3**) series. All of these dimers thus possess the identical absolute configuration.[6]

The importance of (+)-uskudaramine (1) resides partly in the fact that it is the first among some 35 aporphine-benzylisoquinoline alkaloids known[6] whose two constituent entities are bonded together directly through carbon to carbon coupling rather than the much more usual oxygen to carbon linkage.

(+)-Uskudaramine (1) and (+)-istanbulamine (**2**) are accompanied in the plant by the (+)-thalicarpine (**3**) analogues (+)-*N*-2′-noradiantifoline, (+)-adiantifoline, and (+)-thaliadanine. All of these bases incorporate a methoxyl group at C-10. They are formed by direct oxidative coupling of a fully evolved 1,2,9,10-tetraoxygenated or 1,2,3,9,10-pentaoxygenated aporphine derived from (+)-reticuline with a tetrahydrobenzylisoquinoline.[2] In the case of (+)-uskudaramine and (+)-istanbulamine, this tetrahydrobenzylisoquinoline is (+)-*N*-methylcoclaurine, while in (+)-thalicarpine and its analogues, coupling is instead with a (+)-reticuline unit. No proaporphine-benzylisoquinoline is involved in the biogenesis of these dimeric alkaloids. This stands in contrast to the dimeric aporphine benzylisoquinolines found in the Berberidaceae, such as pakistanine and khyberine. These alkaloids are derived from the condensation of two *N*-methylcoclaurine units, and their biogenesis does proceed through proaporphine-benzylisoquinoline dimers.[7]

Very recently, two in vivo studies using labeled precursors have appeared in the literature in which it was firmly established that the 1,2,9,10-tetraoxygenated aporphines (+)-boldine and (+)-isoboldine are efficient precursors of (+)-thalicarpine (**3**).[8,9] These results furnish direct support for oxidative coupling between a benzylisoquinoline and an aporphine to supply an aporphine-benzylisoquinoline dimer.[10]

Acknowledgment. This research was supported by Grant CA-11450 from the National Cancer Institute, National Institutes of Health, USDHHS.

(5) NMR NOE values were obtained by the NOE difference technique, using a 360-MHz FT spectrometer.

(6) For a listing of aporphine-benzylisoquinoline dimers, see Guinaudeau, H.; Leboeuf, M.; Cavé, A. *J. Nat. Prod.* **1979**, *42*, 325.

(7) Guinaudeau, H.; Elango, V.; Shamma, M.; Fajardo, V. *Chem. Commun.* **1982**, 1122.

(8) Bhakuni, D. S.; Jain, S. *Tetrahedron* **1982**, *38*, 729.

(9) Sidjimov, A. K.; Marekov, N. L. *Phytochemistry* **1982**, *21*, 871.

(10) In ref 8 above, it was concluded that thalicarpine (**3**) is formed via a dienone-phenol intermediate. This conclusion is unwarranted and is not supported by the experimental findings.

(11) Four kilograms of the dried roots and rhizomes was extracted with cold ethanol. The chloroform-soluble alkaloidal fraction was chromatographed on Merck silica gel H for TLC, elution being with $CHCl_3$-MeOH-NH_4OH (90:10:0.2). Further purification was by TLC on Merck silica gel F-254 using the system CH_3CN-C_6H_6-EtOAc-MeOH-NH_4OH (40:30:20:5:5). Seventeen milligrams of uskudaramine was thus obtained.

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General Stereospecific Synthesis of Trisubstituted Alkenes via Stepwise Hydroboration

Summary: Iodination of alkenylalkylbromoboranes, obtained via the hydroboration of internal alkynes with alkylbromoboranes, in the presence of sodium methoxide in methanol, results in the formation of trisubstituted alkenes of established stereochemistry, thus providing a general synthesis of trisubstituted alkenes with unambiguous stereochemistry.

Sir: Synthesis of trisubstituted alkenes of defined stereochemistry is one of the important objectives of organic

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