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SEVEN NEW APORPHINE-BENZYLISOQUINOLINE ALKALOIDS FROM *THALICTRUM CULTRATUM*

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ABSTRACT.—*Thalictrum cultratrum* (Ranunculaceae), of Pakistani origin, has yielded the new aporphine-benzylisoquinolines (+)-thalibulamine (**1**), (+)-thalifaronine (**3**), (+)-thalifaramine (**4**), (+)-thalifaretine (**5**), (+)-thalifaricine (**6**), (+)-thalifarazine (**7**), and (+)-thalifaroline (**9**). Some trends concerning the structural features and stereochemistry of *Thalictrum* aporphine-benzylisoquinoline dimers have been noted.

The aporphine-benzylisoquinolines of *Thalictrum* species (Ranunculaceae) fall within five distinct subgroups denoted by the prototype alkaloids (+)-thalicarpine, (+)-fetidine, (+)-istanbulamine, (+)-thalifaberine, and (+)-uskudaramine (1). The classification is based upon the nature of the tetrahydrobenzylisoquinoline moiety involved, which may belong either to the *S*-reticuline or the *S*-coclaurine series, as well as upon the type and position of the bonding connecting the two halves of the dimer. An added idiosyncrasy of *Thalictrum* isoquinoline alkaloids is their marked tendency to incorporate extra oxygenation at the two top aromatic rings, specifically at C-3 of the aporphine and at C-5′ of the tetrahydrobenzylisoquinoline (2).

As a result of the study of the alkaloidal content of *Thalictrum cultratum* Wall. (3,4), we now report the isolation of twelve aporphine-benzylisoquinoline dimers, of which seven are new. One of the new dimers belongs to the (+)-istanbulamine series, while the six others are related to (+)-thalifaberine.

To set the stage for the detailed discussion of the structures of the new alkaloids, it is relevant to point out some of the particularly significant spectral features of *Thalictrum* aporphine-benzylisoquinolines.

Regardless of the subgroup to which they belong, aporphine-benzylisoquinolines show characteristic patterns in their mass spectra. The molecular ion is always small, usually less than 1%, and is in the range of 650 to 750 mass units (m.u.). The base peak is inevitably represented by rings A′ and B′ resulting from facile cleavage of the tetrahydrobenzylisoquinoline. A usually reliable method for ascertaining the molecular ion is through simple addition of the value of the base peak to the most intense ion around 500 m.u.

A constant feature of the ^{1}H-nmr spectra of *Thalictrum* aporphine-benzylisoquinoline dimers is the aromatic singlet near δ 8.0 due to H-11. The exact chemical shift of this absorption is, in fact, diagnostic of the nature and position of the diaryl bridge on ring D of the aporphine. In the case of a C-9 oxygenated bridge, the H-11 singlet will appear near δ 8.18. This same absorption will be around δ 8.03 when the bridge is at C-8. It must be noted, however, that in both instances, oxygenation of the aporphine at C-3 results in an upfield shift of the H-11 signal of 0.12-0.15 ppm.

The absorption pattern for the ring C′ aromatic protons is also characteristic of the subgroup involved. The presence of one-proton singlets is typical of thalicarpine

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TABLE 1. ^{1}H-nmr Spectra of Thalifaberine Type Dimers

Alkaloid	6-NMe	2′ NMe	H-1[a]	H-5′	H-8′	H-11′,13′[b]	H-10′,14′[b]	H-11	H-3	MeO-3	MeO-2	MeO-1	MeO-9	MeO-10	MeO-7′	MeO-6′
Thalifaronine (**3**)	δ2.35	2.61	3.82	6.56	5.92	6.78	6.98	8.03	6.62	—	3.90	3.71	3.80	3.90	3.53	3.83
Thalifaramine (**4**)	2.36	2.57	3.80	6.53	5.93	6.80	7.00	8.05	6.63	—	3.89[c]	3.71	3.80	3.91[c]	OH	3.84
Thalifaberine (**8**)	2.33	2.53	3.68	6.54	6.00	6.77	6.98	7.89	—	3.89	3.96	3.79	3.79[c]	3.92	3.56	3.82[c]
Thalifaretine (**5**)	2.34	2.53	3.69	6.51	6.00	6.78	6.98	7.90	—	3.90	3.96	3.80	3.83	3.93	OH	3.80
Thalifarazine (**7**)	2.33	2.54	3.70	6.60	5.93	6.77	6.97	7.89	—	3.90	3.97	3.80	3.80	3.93	3.57	OH
Thalifaroline (**9**)	2.33	2.58	3.74	6.56	5.96	6.78	6.98	7.82	—	OH	3.99	3.79	3.83[c]	3.93	3.55	3.79[c]
Thalifaricine (**6**)	2.32	2.54	3.70	6.52	5.99	6.80	6.98	7.90	—	3.89	3.96	3.77	OH	3.96	OH	3.80

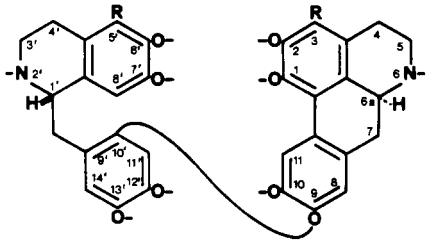
[a]multiplet;
[b]doublet, J_o 8.5 Hz.
[c]chemical shifts are interchangeable.

analogs while two *ortho*-doublets of one-proton each denote the fetidine variety. If, however, a C-11′ hydroxyl group is present in a fetidine dimer, then the two doublets collapse into a two-proton singlet or near singlet. In the event of an ABX system being present, one can assume an istanbulamine or uskudaramine analog. The thalifaberine series, on the other, is characterized by two *ortho*-doublets of two protons each.

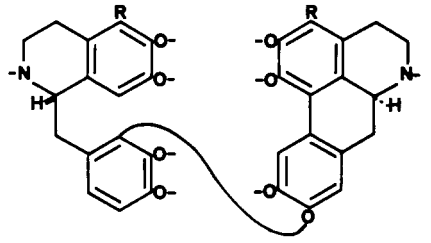
Using the above generalizations, it was readily apparent that four of our dimers belonged to the (+)-thalicarpine series and were identified as the known (+)-thalilutine, (+)-adiantifoline, (+)-thalmineline, and (+)-thalmelatidine (1).

Another of our dimers is the new (+)-thalibulamine (**1**) which was clearly identifiable as an analog of istanbulamine (**2**) (1). Its molecular ion and base peaks are each 14 m.u. greater than for istanbulamine (**2**), which suggests substitution of the C-7′ hydroxyl of istanbulamine by a methoxyl. This was confirmed by the presence of an extra ^{1}H-nmr methoxyl singlet upfield at δ 3.60, characteristic of such a function.

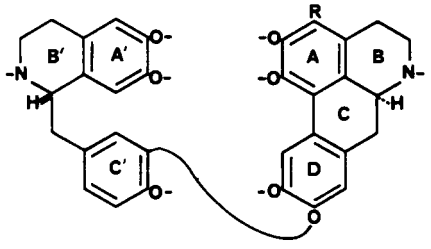
The seven remaining dimers presented in their nmr spectra a pattern of two *ortho*-aromatic doublets of two protons each, typical of the thalifaberine series. One of these seven was, in fact, identified as (+)-thalifaberine (**8**) itself (5,6). The other six alkaloids proved to be new and were labeled (+)-thalifaronine (**3**), (+)-thalifaramine (**4**), (+)-thalifaretine (**5**), (+)-thalifarazine (**7**), (+)-thalifaroline (**9**), and (+)-thalifaricine (**6**).



Thalicarpine type



Fetidine type



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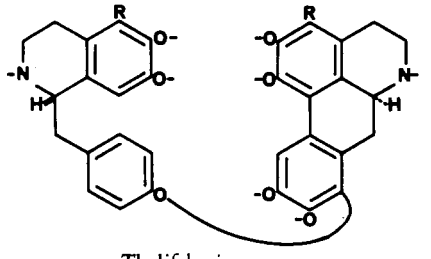
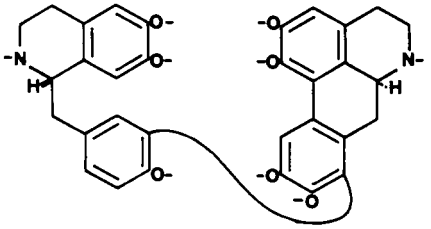
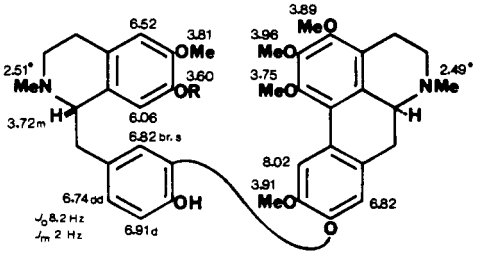


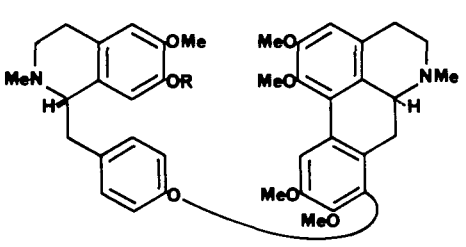
Thalifaberine type



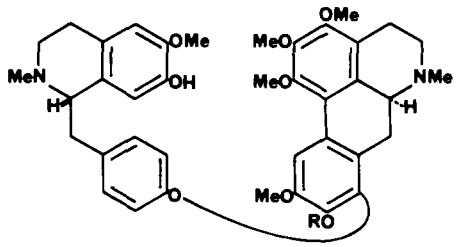
Uskudaramine type



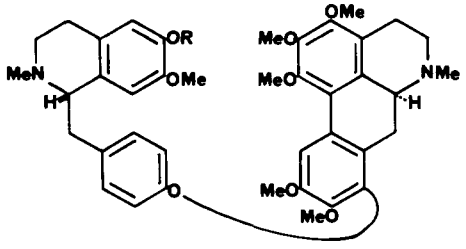
1 R=Me (^{1}H nmr)
2 R=H



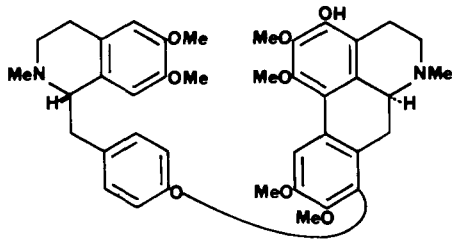
3 R=Me
4 R=H



5 R=Me
6 R=H



7 R=H
8' R=Me



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The nonphenolic (+)-thalifaronine (**3**) exhibits in its mass spectrum molecular ion *m/z* 666 which is 30 m.u. smaller than for the corresponding ion in thalifaberine (**8**). This indicates one less methoxyl substituent in the former alkaloid. Furthermore, since the base peaks, *m/z* 206, are identical, the difference between the two alkaloids must reside on the aporphine. The main difference between the ^{1}H-nmr spectra of the two dimers is that thalifaronine (**3**) shows one less downfield methoxyl absorption. This is accompanied by an H-11 signal at δ 8.03. Position C-3 in thalifaronine (**3**) is, therefore, unsubstituted. A complete ^{1}H-nmr nOeds study (see Experimental section) on this alkaloid then supplied the chemical shift assignments for the remaining methoxyl singlets, for the two *N*-methyl singlets, and for all of the aromatic protons.

The phenolic (+)-thalifaramine (**4**) shows a mass spectral molecular ion and base peaks 14 m.u. smaller than for (+)-thalifaronine (**3**). Additionally, the nmr methoxyl singlet at δ 3.53 is missing. The phenolic function must, therefore, be located at C-7′.

(+)-Thalifaretine (**5**) is also phenolic. Its molecular ion and base peaks are 14m.u. smaller than for (+)-thalifaberine (**8**). The nmr δ 3.56 methoxyl absorption of (+)-thalifaberine (**8**) is significantly missing in the spectrum of (+)-thalifaretine (**5**) so that this species must bear a phenolic function at C-7′.

(+)-Thalifarazine (**7**) has essentially the same mass spectrum as (+)-thalifaretine (**5**), with base peak *m/z* 192. Since one of the three methoxyl absorptions near δ 3.80 is missing, while a methoxyl singlet appears at δ 3.57, the phenolic function can be assigned to C-6′ rather than to C-7′ as in (+)-thalifaretine (**5**). This assignment was further confirmed by nOeds measurements (see Experimental section).

The phenolic (+)-thalifaroline (**9**) has a mass spectrum with a molecular ion 14 m.u. less than that of (+)-thalifaberine (**8**) while the base peak for both species is *m/z* 206. The substitution pattern on the tetrahydrobenzylisoquinoline moiety is thus similar, and the phenolic function must be on the aporphine. The uv spectrum of (+)-thalifaroline (**9**) exhibits both a bathochromic shift and a hyperchromic effect in base, so that the phenolic function must be either at C-3 or at C-9 (7). A signal at δ 3.90 corres-

ponds to a methoxyl group at C-3 while one near δ 3.82 is due to a methoxyl at C-9. In the spectrum of thalifaroline (**9**), the absence of a δ 3.90 peak indicates that the phenol is at C-3.

Our last alkaloid, (+)-thalifaricine (**6**), is diphenolic. Its mass spectrum includes base peak *m/z* 192, suggesting a phenol on ring A′. The absence of an upfield nmr methoxyl absorption near δ 3.55 signifies that this phenolic function is at C-7′.

The uv spectrum of (+)-thalilfaricine (**6**) displays a bathochromic shift and a hyperchromic effect in base, pointing to the second phenolic group being either at C-3 or C-9. The absence of a methoxyl absorption in the δ 3.82 range, while a δ 3.89 peak is present, attests to the second phenolic group being at C-9.

All six new thalifaberine type alkaloids show positive specific rotations and possess very close cd spectra, pointing to the identical absolute configuration.

With the characterization of the above seven new compounds, the total number of known *Thalictrum* aporphine-benzylisoquinolines is over 40. It is now possible, therefore, to delineate some trends concerning their structural features. (a) All dimers possess the 1′*S*, 6a*S* configuration, except when an iminium or enamine system is present. (b) The aporphine moiety is originally derived from (+)-*S*-reticuline and always bears methoxyl substituents at C-2 and C-10. (c) When the left hand tetrahydrobenzylisoquinoline moiety is derived from (+)-*S*-reticuline, as in (+)-thalicarpine, (+)-fetidine, and their congeners, the C-12′ substituent is usually methoxyl. The sole exception to this trend appears to be (+)-thalirevoline which bears a hydroxyl at that site.[3]

The only other botanical family which has so far furnished similar aporphine-benzylisoquinolines is the Hernandiaceae. Interestingly enough, however, dimers from the Hernandiaceae are sometimes more highly oxidized than in *Thalictrum*. For example, oxoaporphine-benzylisoquinolines have been obtained from the Hernandiaceae, while none are known among the *Thalictrum* bases (1).

EXPERIMENTAL

GENERAL PROCEDURES AND ISOLATION.—For the isolation and purification procedure, see Hussain *et al* (3). Nmr spectra are at 200 or at 360 MHz in $CDCl_3$. Uv and cd spectra were recorded in MeOH. All compounds isolated are amorphous. From 11 kg of dried whole plant, the crude alkaloids fraction (176 g) furnished the following alkaloids as percentages of the crude alkaloids fraction: thalilutine, 0.005; adiantifoline, 0.006; thalmineline, 0.7; thalmelatidine, 0.02; thalifaramine (**4**), 0.004; thalifaretine (**5**), 0.005; thalifarazine (**7**), 0.005; thalifaroline (**9**), 0.02; thalifaricine (**6**), 0.11.

(+)-THALIBULAMINE (**1**).—*M/z* 682 $(M)^+$ ($C_{40}H_{46}N_2O_8$) (0.07), 681 (0.2), 680 (0.3), 476 (1), 475 (2), 206 (100), 190 (4); λ max 225, 270 sh, 281, 301, 314 nm (log ε 4.79, 4.42, 4.31, 4.24); Δε (nm) 0 (320), −5.6 (300), −8.0 (272), 0 (255), +80 (239), negative tail below 230 nm; $[\alpha]_D$ +63° (c 0.2, MeOH.

(+)-THALIFARONINE (**3**).—*M/z* 666 $(M)^+$ ($C_{40}H_{46}N_2O_7$) (0.3), 665 (0.6), 664 (0.5), 460 (1), 459 (1), 206 (100), 190 (4); λ max 227, 268 sh, 280, 304 sh nm (log ε 4.75, 4.30, 4.38, 4.08); Δε (nm) 0 (310), −4.0 (297), −1.7 (287), −8.1 (270), 0 (255), +74 (236), negative tail below 232 nm; $[\alpha]_D$ +68° (c 0.1, MeOH). Important nOe's are H-11 to OMe-1, 9%; OMe-1 to H-11, 7%; H-11 to OMe-10, 19%; OMe-10 to H-11, 20%; H-3 to OMe-2, 22% OMe-2 to H-3, 15%; H-5′ to OMe-6′, 14%; OMe-6′ to H-5′, 14%; H-8′ to OMe-7′, 9%; OMe-7′ to H-8′, 10%; H-11′,13′ to OMe-9, 6%; OMe-9 to H-11′,13′, 5%; H-1′ to 2′-NMe, 4%; H-1′ to H-8′, 4%; H-8′ to H-1′ (4%).

(+)-THALIFARAMINE (**4**).—*M/z* 652 $(M)^+$ ($C_{39}H_{44}N_2O_7$) (0.8), 651 (1), 637 (0.4), 460 (2), 459 (3), 192 (100), 177 (8); λ max 228, 270 sh, 280, 308 nm (log ε 4.75, 4.35, 4.42, 4.04); Δε 0 (310), −4 (300), −8 (270), 0 (250), +87 (237), negative tail below 234 nm; $[\alpha]_D$ +76° (c 0.06, MeOH).

[3]The alkaloid (+)-revolutopine shows a ^{1}H-nmr spectrum with H-13′,14′ as a two-proton singlet at δ 6.67 (1). This indicates that the phenolic function is at C-11′ rather than at C-12′. In the alternate case of the 11′-methoxy and 12′-hydroxy combination, the absorption for H-13′,14′ would have appeared as two *ortho*-doublets (8).

(+)-THALIFARETINE (**5**).—*M/z* 682 $(M)^+$ ($C_{40}H_{46}N_2O_8$) (0.8), 490 (1.2), 192 (100), 177 (5), λ max 222, 272 sh, 283, 293 sh, 310 sh nm (log ε 4.76, 4.24, 4.39, 4.27, 4.04); Δε (nm) 0 (314), −8.4 (300), −10 (273), 0 (255), +81 (239), negative tail below 230 nm; $[\alpha]_D$ +61° (c 0.1, MeOH). Important nOe's are H-11 to MeO-10, 19%; MeO-10 to H-11, 19%, H-11 to MeO-1, 15%; MeO-1 to H-11, 13%; H-11′,13′ to MeO-9, 15%; MeO-9 to H-11′,13′, 4%; MeO-6′ to H-5′, 18%; H-5′ to MeO-6′, 24%; 2′-NMe to H-1′, 10%; H-1′ to H-8′, 8%; H-8′ to H-1′, 10%; H-10′,14′ to H-1′, 10%; H-1′ to H-10′,14′, 5%.

(+)-THALIFARAZINE (**7**).—*M/z* 682 $(M)^+$ ($C_{40}H_{46}N_2O_8$); *m/z* 682 $(M)^+$ (0.23), 681 (0.37), 680 (0.41), 490 (2.2), 192 (100), 177 (7); max 228, 270 sh, 283, 297 sh, 310 sh nm (log ε 4.70, 4.29, 4.38, 4.25, 4.02); Δε (nm) 0 (315), −4.7 (297, −9.4 (272), 0 (255), +80 (240), negative tail below 232 nm; $[\alpha]_D$ +72° (c 0.06, MeOH). Important nOe's are H-11 to MeO-10, 14%; MeO-10 to H-11, 22%; H-11 to MeO-1, 10%; MeO-1 to H-11, 14%; H-11′,13′ to MeO-9, 10%; MeO-9 to H-11′,13′, 4%; MeO-7′ to H-8′, 17%; H-8′ to MeO-7′, 8%; 2′NMe to H-1′, 3%; H-1′ to H-8′, 6%.

(+)-THALIFAROLINE (**9**).—*M/z* 682 $(M)^+$ ($C_{40}H_{46}N_2O_8$) (0.1), 681 (0.3), 478 (0.16), 477 (0.5), 476 (0.8), 206 (100), 190 (4); λ max 225, 275 sh, 285, 300 sh, 310 sh nm (log ε 4.69, 4.28, 4.37, 4.24, 4.16); λ max (MeOH + OH^-) 284 sh, 292 sh, 325 nm (log ε 4.15, 4.17, 4.34); Δε (nm) 0 (315), −4.2 (305), −5.6 (272), 0 (257), +68 (241), negative tail below 237 nm; $[\alpha]_D$ +73° (c 0.1, MeOH).

(+)-THALIFARICINE (**6**).—*M/z* 668 $(M)^+$ ($C_{39}H_{44}N_2O_8$) (0.1), 667 (0.2), 666 (0.2), 476 (2.2), 192 (100), 177 (8); λ max 224, 274 sh, 283, 295 sh, 310 sh nm (log ε 4.74, 4.31, 4.40, 4.31, 4.17); λ max (MeOH + OH^-) 282 sh, 315 nm (log ε 4.19, 4.29); Δε (nm) 0 (315), −5.2 (300), −2 (288), −6.6 (275), 0 (255), +73 (240), negative tail below 236 nm; $[\alpha]_D$ +66° (c 0.1, MeOH). Important nOe's are H-11 to MeO-10, 16%; MeO-10 to H-11, 20%; H-11 to MeO-1, 12%; MeO-1 to H-11, 9%; H-5′ to MeO-6′, 13%; MeO-6′ to H-5′, 16%; 2′-NMe to H-1′, 10%, H-1′ to 2′-NMe, 4%; H-1′ to H-8′, 9%; H-8′ to H-1′, 5%; H-1′ to H-13′,14′, 8%; H-4a to MeO-3, 12%.

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