

DIMERIC APORPHINE-BENZYLISOQUINOLINE AND APORPHINE-PAVINE ALKALOIDS

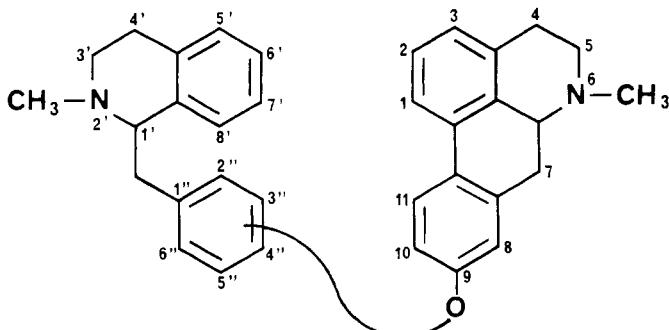
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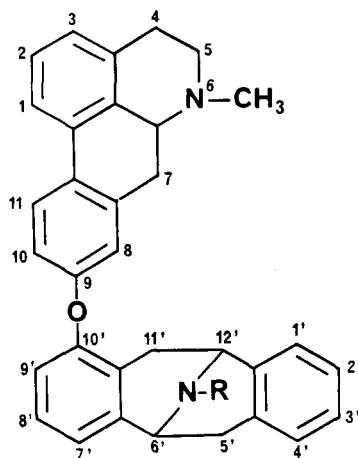
Aporphine-benzylisoquinoline dimers represent a small group of alkaloids; they have been found only in three genera, *Thalictrum* (Ranunculaceae), *Hernandia* (Hernandiaceae) and *Berberis* (Berberidaceae). At the present time, only two dimeric aporphine-pavine alkaloids have been found in *Thalictrum*. The first aporphine-benzylisoquinoline alkaloid to be fully characterized was thalcarpine by Kupchan (13) in 1963. The dimeric alkaloids found in the genus *Thalictrum* have been discussed in reviews on *Thalictrum* alkaloids by Schiff and Doskotch (34) in 1970, Mollov *et al.* (17) in 1971 and Tomimatsu (35) in 1965, 1967 and 1976. At the present time, more than 20 dimeric alkaloids are known.

The present review is concerned with a presentation of a complete listing of the dimeric aporphine-benzylisoquinoline and aporphine-pavine alkaloids together with their physical and spectral data as well as their sources. Hernandaline and related alkaloids, intermediate to the aporphine-benzylisoquinoline dimers, are not included in this review since they have been included in the aporphine alkaloids review.¹

The dimeric aporphine-benzylisoquinoline alkaloids are divided into three groups: the *thalcarpine-type* in which the ether linkage is between C-9 of the aporphine and C-2" of the disubstituted 4",5"-benzylisoquinoline unit; the *fetidine-type* in which the ether linkage is between C-9 of the aporphine and C-2" of the disubstituted 3",4"-benzylisoquinoline moiety; and the *pakistanine-type* in which the ether linkage lies between C-9 of the aporphine and C-4" of an arme-pavine residue. Within each section, the material has been arranged according to an ascending order of substitution pattern. For each alkaloid the description includes the structure, the molecular formula and molecular weight, the melting point and specific rotation, and when available the uv, ir, nmr, and mass spectral data, as well as the circular dichroism curve. The numbering of the skeleton is according to the accepted ruling.



¹H. GUINAUDEAU, M. LEBOEUF and A. CAVÉ. Aporphine Alkaloids. *Lloydia*, **33**: 275 (1975); H. GUINAUDEAU, M. LEBOEUF and A. CAVÉ. Aporphine Alkaloids, II. To be published.



Unless stated otherwise, the uv (nm, log ϵ) spectra were obtained in ethanol; the ir (cm^{-1}) spectra in nujol; and the nmr spectra in deuteriochloroform (60 MHz). Chemical shifts are in δ units, and the coupling constants are in Hz.

1 THALICTROGAMINE



668,309743

$[\alpha]^{25^\circ} D: \pm 135^\circ$ ($c \equiv 0.2$, CH_3OH) (24)

UV: 230 sh (4.39), 277 (4.11), 298 sh (3.98), 307 sh (3.82) (24)

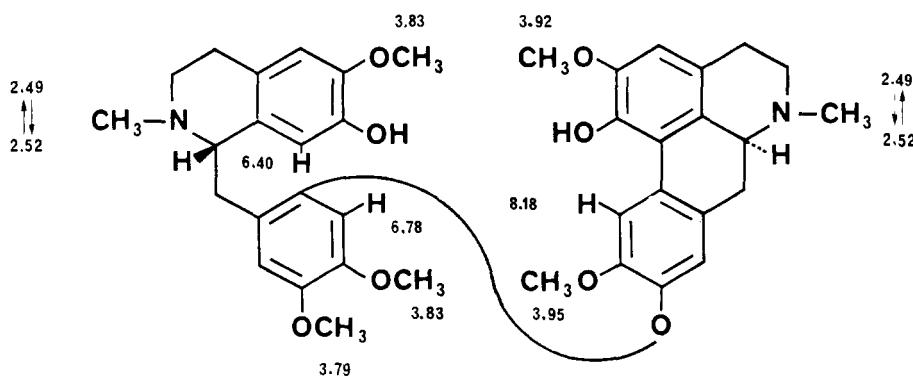
UV: 260 nm (

NMR: (24) (25) (32)

MASS: 668 (M^{\pm}) 476 326 309 192 (base) (24)

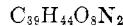
CD: $(\text{CH}_3\text{OH})[\theta]_{D^2} = +186000$, $[\theta]_{D^4} = -19300$, $[\theta]_{D^6} = -28200$ (42)

SOURCES: *Thalictrum polycarpum* (24). *Thalictrum dioicum* (31). *Thalictrum revolutum* (42).



4 aromatic H at 6.51, 6.57 (3 H) .

2 PENNSYLVANAMINE



668.309743

MP: 128-129° (acetone-ether), 107-108° (ether) (25)

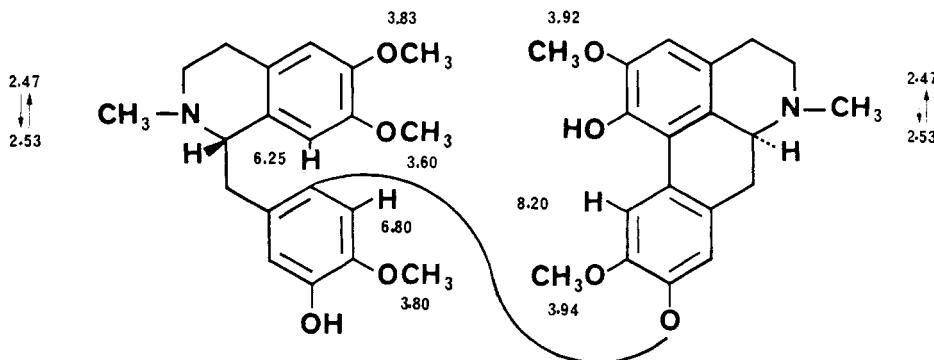
$[\alpha]^{25}D: +119^\circ$ ($c=0.94$, CH_3OH) (25)

UV: (CH₃OH) 276 sh (4.07), 284 (4.17), 297 sh (4.11), 312 sh (4.06) (25)

NMR: (25)

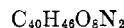
MASS: 668 (M^+), 462, 326, 325, 309, 206 (base) (25)

SOURCES: *Thalictrum polygamum* (25) (26)



4 aromatic H at 6.55 (2 H), 6.58 (2 H).

3 THALICTROPINE



682.325392

MP: 167° (24)

$[\alpha]^{25}\text{D}$: +120° ($c=0.3$, CH₃OH) (24)

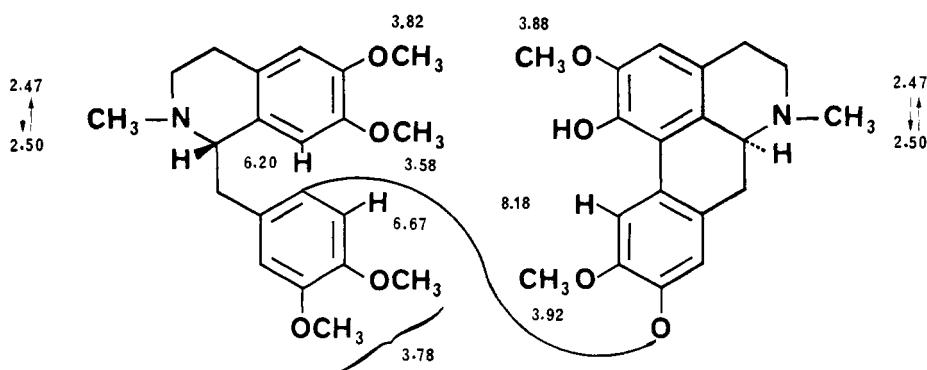
UV: 225 (4.46), 278 (4.12), 298 sh (3.88), 310 sh (3.70) (24)

IR: (CHCl₃) 3500 (24)

NMR: (24) (25) (32)

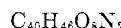
MASS: 682 (M⁺), 476, 326, 310, 206 (base) (24)

SOURCES: *Thalictrum polygamum* (24), *Thalictrum dioicum* (31)



4 aromatic H at 6.55 (3 H), 6.59 .

4 THALILUTIDINE



682.325392

$[\alpha]^{25}\text{D}$: +74 ($c=0.11$, CH₃OH) (44)

UV: (CH₃OH) 280 (4.38), 304 sh (4.21) (44)

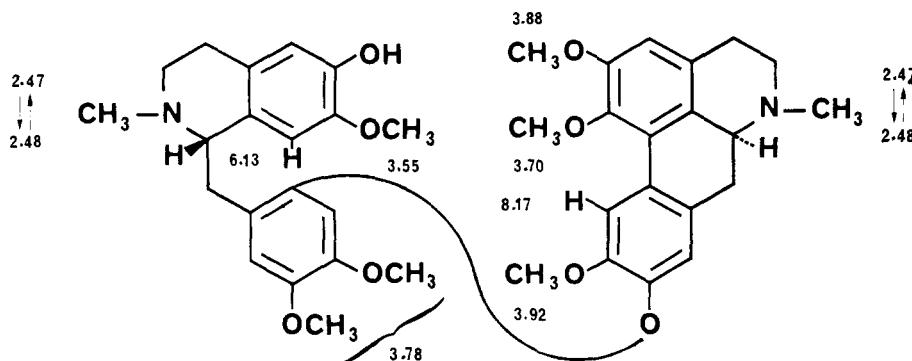
IR: (CHCl₃) 3540 (44)

NMR: (44)

MASS: 682 (M⁺), 490, 340, 324, 192 (base) (44)

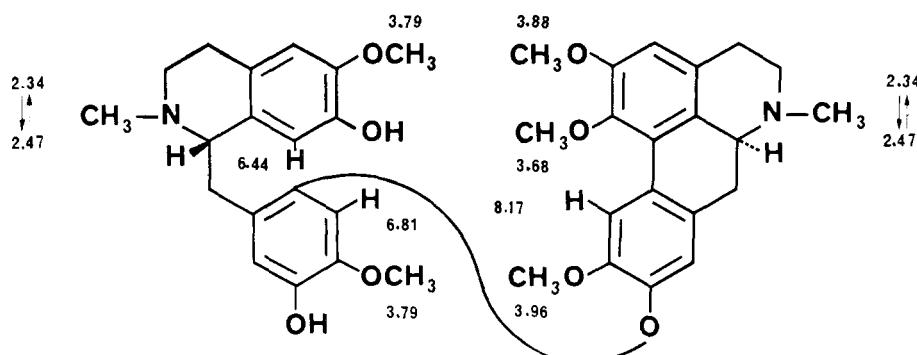
CD: $[\theta]_{238}+180000$, $[\theta]_{274}-16100$, $[\theta]_{306}-13900$ (44)

SOURCES: *Thalictrum revolutum* (44)

**5 THALIPINE**

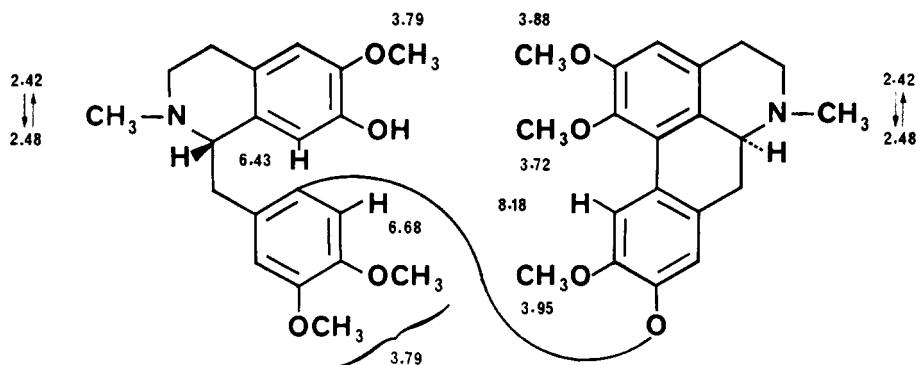
$[\alpha]^{25}\text{D}$: +141° ($c=0.19$, CH₃OH) (42)
 UV: 282 (4.49), 303 sh (4.34), 316 sh (4.19) (42)
 NMR: (90 MHz) (42)
 MASS: 668 (M⁺), 476, 340, 324, 192 (base) (42)
 CD: (CH₃OH) $[\theta]_{238}+214000$, $[\theta]_{271}-19000$, $[\theta]_{302}-14800$ (42)
 SOURCES: *Thalictrum polygamum* (28), *Thalictrum revolutum* (40) (42)

C₈H₄₄O₅N₂ 668.309743

**6 THALMELATINE**

MP: 131–135° (15)
 $[\alpha]^{21}\text{D}$: +110° ($c=1$, C₂H₅OH) (15)
 NMR: (25) (32)
 MASS: 682 (M⁺), 490, 324, 293, 192 (base), 190 (17)
 SOURCES: *Thalictrum minus* var. *elatum* (15) (16) (18), *Thalictrum dioicum* (31), *Thalictrum revolutum* (41)

C₄₀H₄₆O₅N₂ 682.325392



4 aromatic H at 6.52, 6.55, 6.60 (2 H).

7 DEHYDROTHALMELATINE

MP: 126–128° (5)

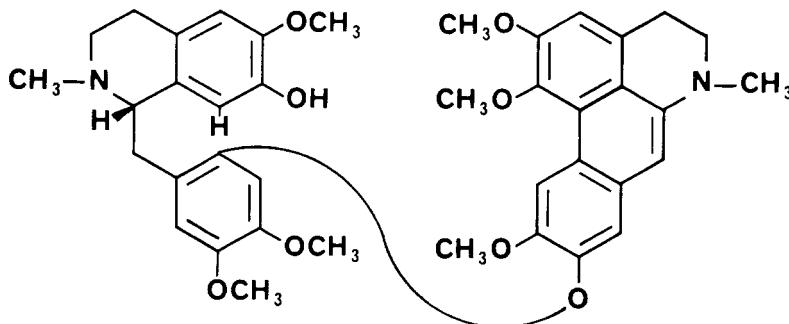
$[\alpha]^{25}\text{D}$: +31.9 ($c=0.15$, CHCl_3) (5)

UV: 268 (4.57), 330 (4.15) (5)

SOURCES: Synthesis (5)



680.309743



8 THALIDOXINE

$[\alpha]^{25}\text{D}$: +113° ($c=0.2$, CH_3OH) (32)

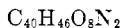
UV: (CH_3OH) 275 (4.23), 296 sh (4.08), 310 sh (4.02) (32)

IR: (CHCl_3) 3540 (32)

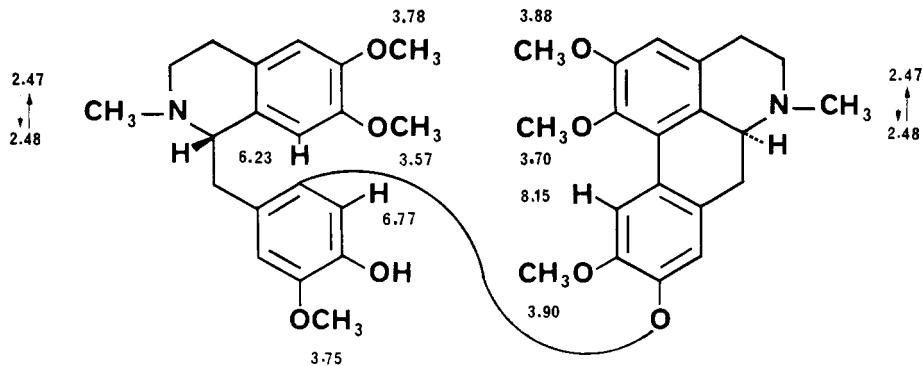
NMR: (25) (32)

MASS: 682 (M^+), 476, 340, 324, 206 (base) (32)

SOURCES: *Thalictrum dioicum* (32). In a subsequent reinvestigation of *Thalictrum dioicum*, no thalidoxine was obtained (31).



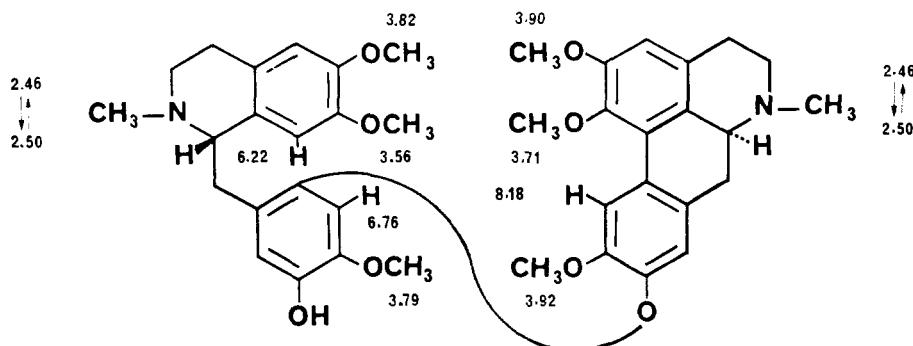
682.325392



4 aromatic H at 6.50 (3 H), 6.57.

9 PENNSYLVANINE

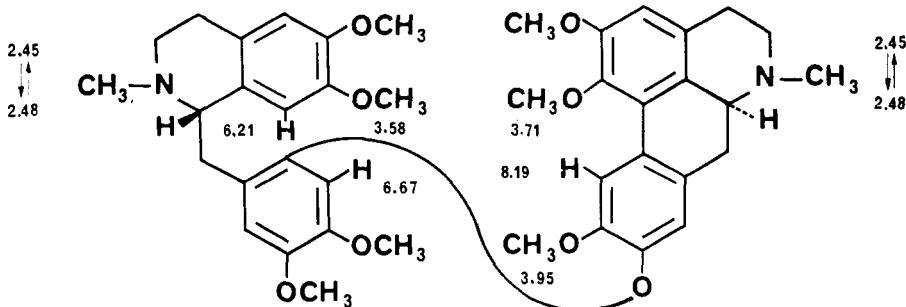
MP: 112–113° (25)
 $[\alpha]^{24}\text{D}$: +131° (c=0.7, CH₃OH) (25)
 UV: 284 (4.26), 304 (4.18), 320 sh (4.05) (25)
 NMR: (25)
 MASS: 682 (M⁺), 476, 340, 324, 206 (base) (25)
 CD: (CH₃OH) $[\theta]_{257}+235000$, $[\theta]_{271}-8900$, $[\theta]_{305}-6500$ (42)
 SOURCES: *Thalictrum polygamum* (25) (26), *Thalictrum dioicum* (31), *Thalictrum revolutum* (42) (45)



4 aromatic H at 6.52, 6.56, 6.59, 6.62.

10 THALICARPINE

MP: 153–155° (38)
 $[\alpha]^{27}\text{D}$: +78° (c=1, CHCl₃) (38)
 UV: 282 (4.33), 301 (4.22) (37)
 IR: 2935, 1600, 1505, 1460, 1060, 950 (39)
 NMR: (32)
 MASS: 696 (M⁺), 490, 324, 293, 206 (base), 204 (17)
 SOURCES: *Thalictrum dasycarpum* (11) (13) (36) (21), *Thalictrum dioicum* (31), *Thalictrum fendleri* (33), *Thalictrum flavum* (39), *Thalictrum foetidum* (1), *Thalictrum minus* (19), *Thalictrum minus* ssp. *elatum* (18), *Thalictrum minus* race B (7), *Thalictrum polygamum* (8), *Thalictrum revolutum* (36) (41), *Hernandia ovigera* (6) (38) (47).



4 methoxy at 3.80 (6H), 3.83, 3.91.

4 aromatic H at 6.53, 6.56, 6.60, 6.62.

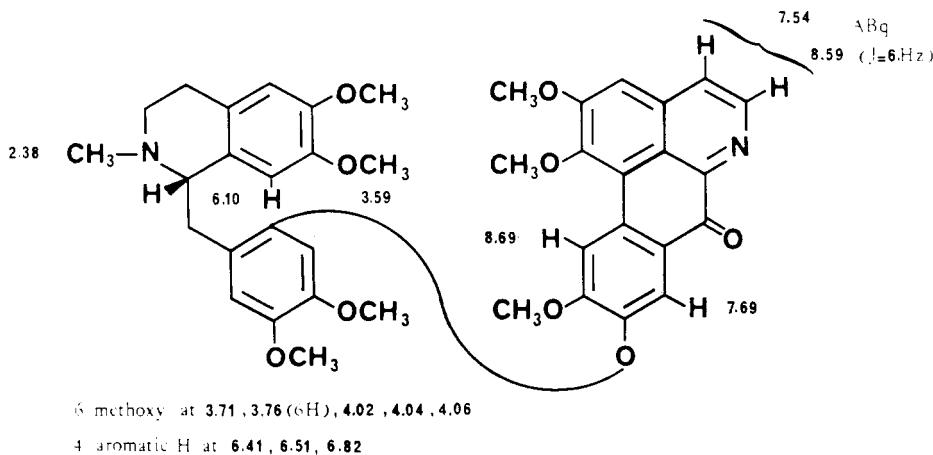
11 OXOTHALICARPINE

MP: 219–220° (dec.) (46)
 $[\alpha]^{26}\text{D}$: +115° (c=0.1, CHCl₃) (46)
 UV: 237 (4.52), 271 (4.44), 285 sh (4.34), 343 (3.93) (46)

C₄₀H₄₀O₈N₂ 692.2733

IR: 1020, 1200, 1600, 1660, 2815 (46)

NMR: (46)

SOURCES: *Hernandia ovigera* (46)**12 DEHYDROTHALICARPINE (Thalictucarpine)** $\text{C}_{41}\text{H}_{46}\text{O}_5\text{N}_2$

694.325392

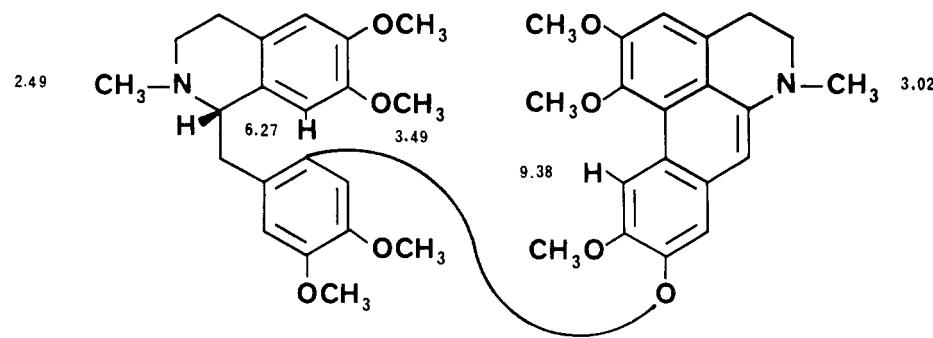
MP: 186–187° (12)

[α]²²D: +54° (c=1, CHCl_3) (4)

UV: 268 (4.82), 331 (4.34) (4)

IR: 2817, 2762, 1613, 1464, 1250, 1124 (12)

NMR: (4)

MASS: 694 (M^+), 488, 338, 206 (base), 204, 150 (17)SOURCES: *Thalictrum minus* ssp. *elatum* (4), *Thalictrum dasycarpum* (12), *Hernandia ovigera* (47)**13 THALILUTINE** $\text{C}_{41}\text{H}_{45}\text{O}_5\text{N}_2$

712.335955

[α]²⁰D: +92° (c=0.175, CH_3OH) (44)

UV: 282 (4.40), 303 sh (4.28), 312 sh (4.23) (44)

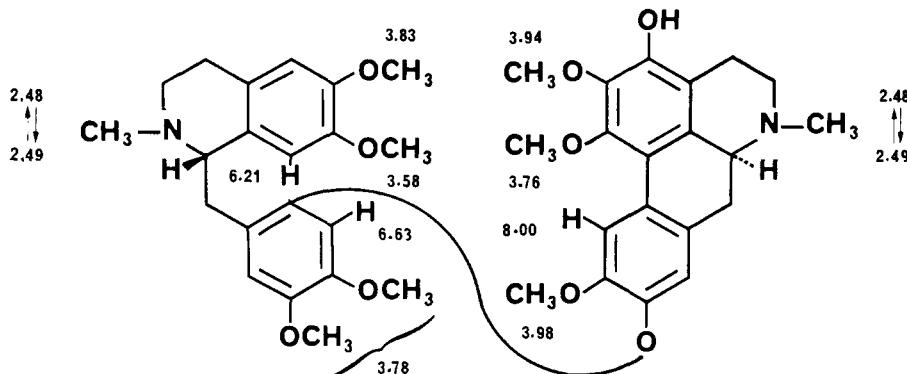
IR: (CHCl_3) 3530 (44)

NMR: (44)

MASS: 712 (M^+), 506, 372, 356, 340, 206 (base) (44)

CD: $[\theta]_{239} +198000$, $[\theta]_{276} -19300$, $[\theta]_{307} -15900$ (44)

SOURCES: *Thalictrum revolutum* (44)



3 aromatic H at 6.53, 6.56, 6.58 .

14 O-DESMETHYL-ADIANTIFOLINE*



712.335955

MP: 125–126° (19)

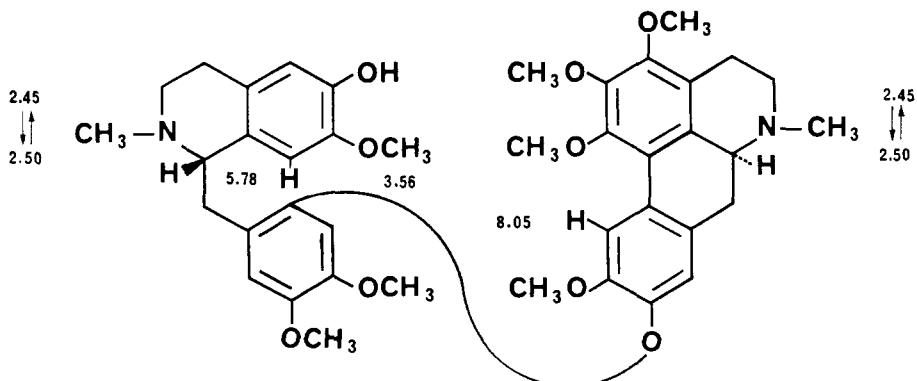
[α]²²D: +18° (c=0.4, CHCl₃) (19)

IR: 3505 (19)

NMR: (19)

SOURCES: *Thalictrum minus* (19), *Thalictrum minus* race B (14)

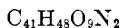
*Revised structure (14).



6 methoxy at 3.77, 3.80(6H), 3.83, 3.96(6H) .

4 aromatic H at 6.43, 6.50, 6.60 (2H) .

15 THALIADANINE



712.335955

[α]²⁶D: +81° (c=0.41, CH₃OH) (14)

UV: 281 (4.33), 302 (4.18), 312 (4.11) (no shift in base) (14)

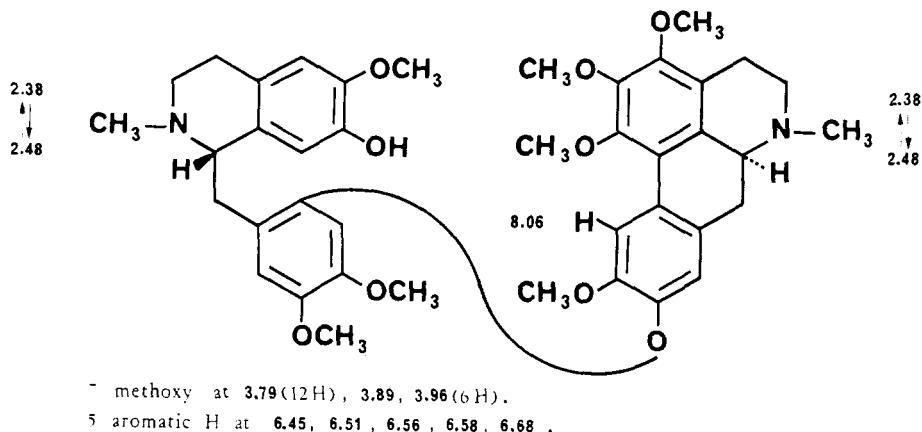
IR: (CHCl₃) 3540 (14)

NMR: (14)

MASS: 712 (M^+), 520, 370, 354, 192 (base) (14)

CD: $[\theta]_{241} +166000$, $[\theta]_{276} -17600$, $[\theta]_{308} -15900$ (14)

SOURCES: *Thalictrum minus* race B (14)

**16 ADIANTIFOLINE**

726.351604

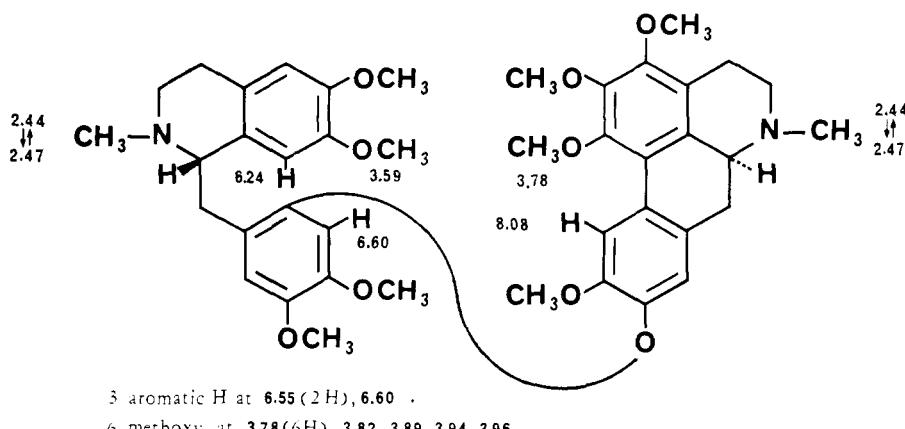
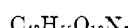
MP: 143–144° (2)

[α]₂₅D: +90° (c=0.11, CH₃OH) (2)

UV: 283 (4.51), 302 (4.39), 312 (4.34) (2)

NMR: (32)

MASS: 521, 520, 519, 206 (base) (2)

CD: [θ]₂₄₁+234000, [θ]₂₇₅-31200, [θ]₃₀₅-33800 (3)SOURCES: *Thalictrum minus* var. *adiantifolium* (2, 3), *Thalictrum minus* race B (7, 14), *Thalictrum minus* (19)**17 THALMINELINE**

742.346518

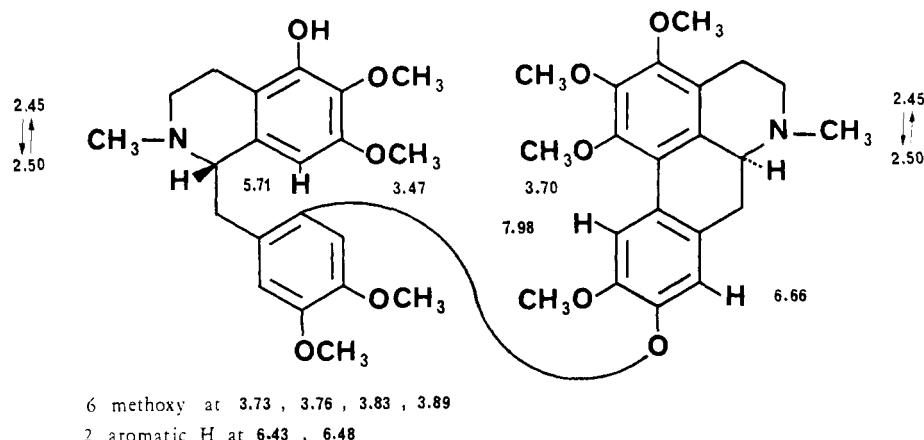
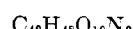
MP: 96–98° (ether-heptane), 108–110° (C₂H₅OH) (22)[α]₂₄D: +22° (c=0.9, CH₃OH) (22)

UV: 283 (5.46?) (22)

IR: 3480, 2970, 1620, 1590, 1525, 1480, 1425, 1405, 1350, 1275, 1230, 1215, 1200, 1125, 1060, 1025, 880, 780 (22)

NMR: (100 MHz) (22)

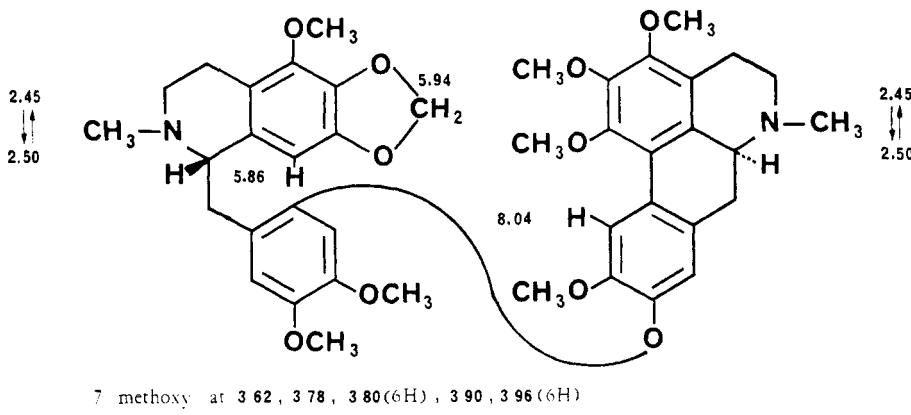
MASS: 742 (M⁺), 521, 520, 519, 222, 206 (22)SOURCES: *Thalictrum minus* var. *elatum* (22)

**18 THALMELATIDINE**

740.330869

MP: 120–122° (20)
 $[\alpha]^{25}\text{D}$: +47° (c=1, CHCl₃) (20)
 IR: 950 (20)
 NMR: (20)

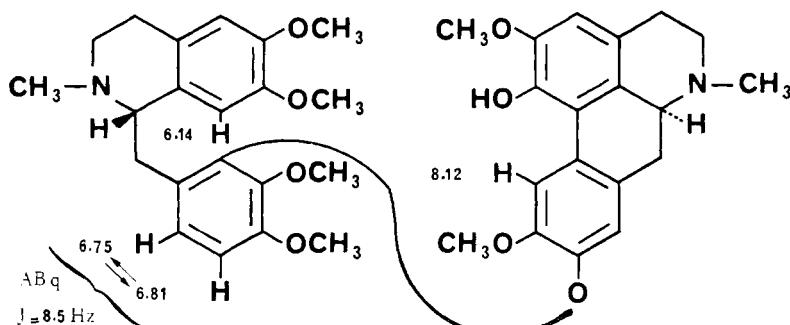
SOURCES: *Thalictrum minus* (19), *Thalictrum minus* ssp. *elatum* (20)

**19 FETIDINE (Foetidine)***

682.325392

MP: 132–135° (23)
 $[\alpha]^{25}\text{D}$: +121 (c=2.57, CH₃OH) (23)
 UV: 220 (4.80), 280 (4.36), 305 (4.24) (9)
 IR: 3400, 2830, 2800, 1605, 1580, 1515 (9)
 NMR: (220 MHz) (1)
 MASS: 476, 341 (M⁺⁺), 327, 284, 206 (base), 191, 177 (10)
 SOURCES: *Thalictrum foetidum* (9) (23)

*Revised structure (1).

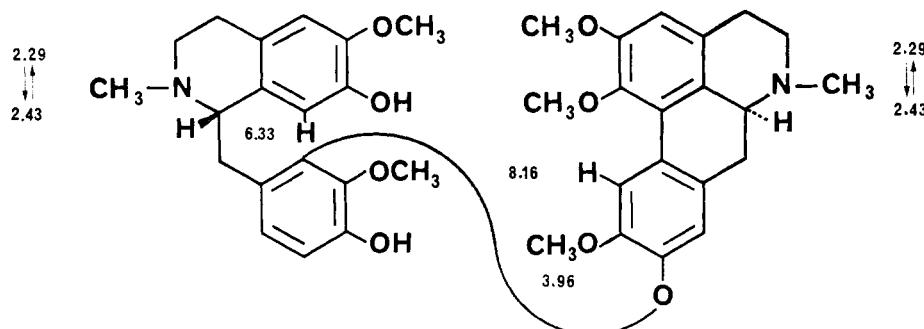
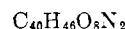
**20 REVOLUTOPINE**

668.309743

[α]²⁵D: +126° (c=0.1, CH₃OH) (42)UV: (CH₃OH) 281 (4.40), 302 (4.24), 314 sh (4.15) (42)

IR: (KBr) 3410 (42)

NMR: (40) (42)

MASS: 668 (M⁺), 667, 476, 340, 324, 192 (base) (42)CD: (CH₃OH) $[\theta]_{240}+43000$, $[\theta]_{275}-5300$, $[\theta]_{305}-4700$ (42)SOURCES: *Thalictrum revolutum* (40) (42)**21 THALIREVOLINE**

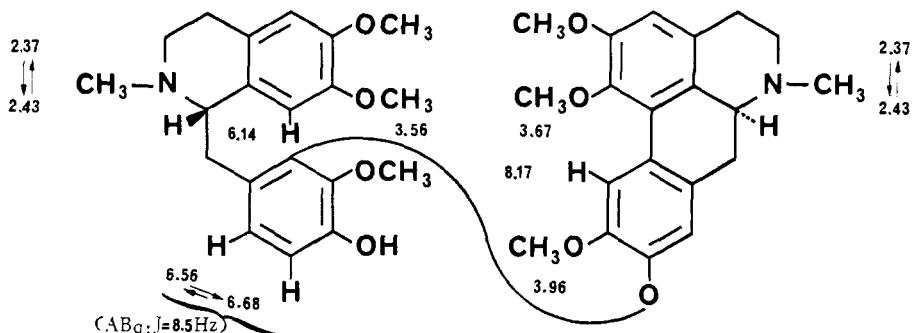
682.325392

MP: 123–125° (44)

[α]²⁰D: +95° (c=0.1, CH₃OH) (44)UV: (CH₃OH) 270 sh (4.31), 280 (4.40), 301 (4.24), 310 sh (4.18) (44)

NMR: (44)

MASS: 682 (M⁺), 476, 341, 340, 324, 206 (base) (44)CD: $[\theta]_{240}+122000$, $[\theta]_{277}-12800$, $[\theta]_{300}-11700$ (44)SOURCES: *Thalictrum revolutum* (42) (44)



³ methoxy at 3.80, 3.87 (6H).
³ aromatic H at 6.46, 6.52, 6.57.

22 THALIREVOLUTINE



696.341041

MP: 105–108° (44)

$[\alpha]^{20^\circ}\text{D}$: +134 ($c=0.1$, CH₃OH) (44)

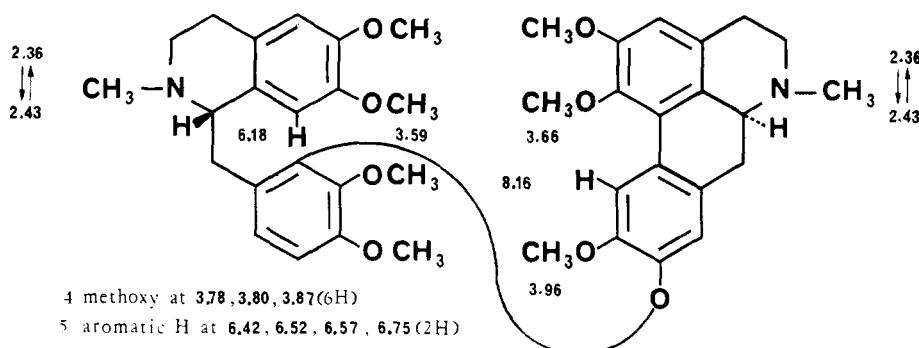
UV: 270 sh (4.31), 280 (4.38), 302 (4.21), 315 sh (4.10) (44)

NMR: (44)

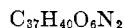
MASS: 696 (M^+), 490, 355, 340, 324, 206 (base) (44)

CD: $[\theta]_{240}+240000$, $[\theta]_{277}-26100$, $[\theta]_{300}-20200$ (44)

SOURCES: *Thalictrum revolutum* (44)



23 PAKISTANINE



608.288617

MP: 154–156° (30)

$[\alpha]^{25^\circ}\text{D}$: +106° ($c=0.57$, CH₃OH) (30)

UV: 206 (4.69), 218 (4.61), 270 sh (4.13), 277 (4.21), 307 (4.07) (30)

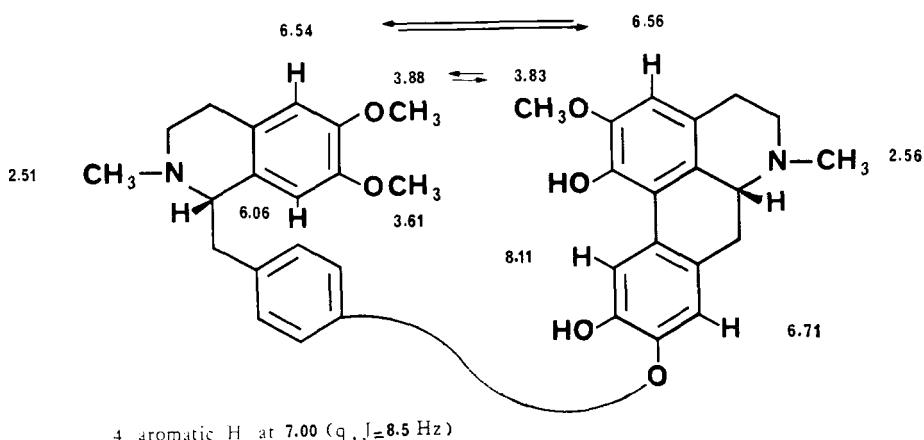
IR: 3450, 2860, 2800 (30)

NMR: (30)

MASS: 608 (M^+), 402, 312, 296, 206 (base), 107 (30)

ORD: (CH₃OH) $\alpha_{660}+226^\circ$, $\alpha_{315}+2736^\circ$, $\alpha_{252}-11208^\circ$, $\alpha_{240}-6698^\circ$ (30)

SOURCES: *Berberis baluchistanica* (29) (30)

**24 1-O-METHYL-PAKISTANINE** $C_{38}H_{42}O_6N_2$

622.304266

MP: 117° (30)

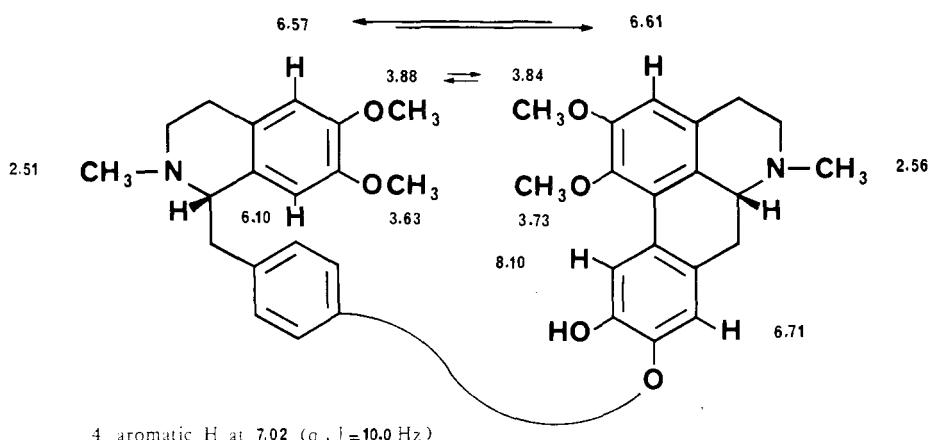
[α]₂₅D: +85° ($c=0.40$, CH₃OH) (30)

UV: 207 (4.88), 225 sh (4.75), 270 sh (4.28), 277 (4.37), 304 (4.16) (30)

NMR: (30)

MASS: 622 (M^+), 416, 326, 310, 267, 206 (base), 190 (30)ORD: (CH₃OH) $\alpha_{360}+130^\circ$, $\alpha_{310}+1507^\circ$, $\alpha_{245}-11087^\circ$, $\alpha_{210}-10884^\circ$ (30)

SOURCES: Synthesis (30)

**25 1,10-DI-O-METHYL-PAKISTANINE** $C_{38}H_{44}O_6N_2$

636.319915

MP: 139–141° (30)

[α]₂₅D: +66° ($c=0.40$, CH₃OH) (30)

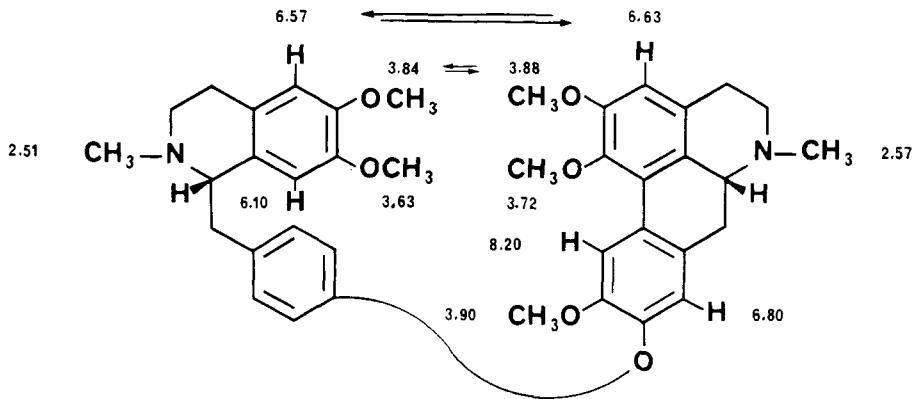
UV: 215 (4.60), 270 sh (4.27), 277 (4.29), 301 (4.09) (30)

IR: (CHCl₃) 2855, 2800 (30)

NMR: (30)

MASS: 636 (M^+), 430, 340, 324, 206 (base), 190, 107 (30)ORD: (CH₃OH) $\alpha_{245}-6066^\circ$, $\alpha_{230}-7049^\circ$, $\alpha_{360}-607^\circ$, $\alpha_{320}+246^\circ$ (30)

SOURCES: Synthesis (29) (30)



4 aromatic H at 7.00 (q, $J=9.5$ Hz)

26 PAKISTANAMINE*



622.3042

MP: 215° (HCl) (30)

$[\alpha]^{25}_D: +20^\circ$ ($c=0.34$, CH₃OH) (30)

UV: 206 (4.86), 225 sh (4.63), 280 (4.12), 310 sh (3.61) (30)

IR: 1640, 1670 (30)

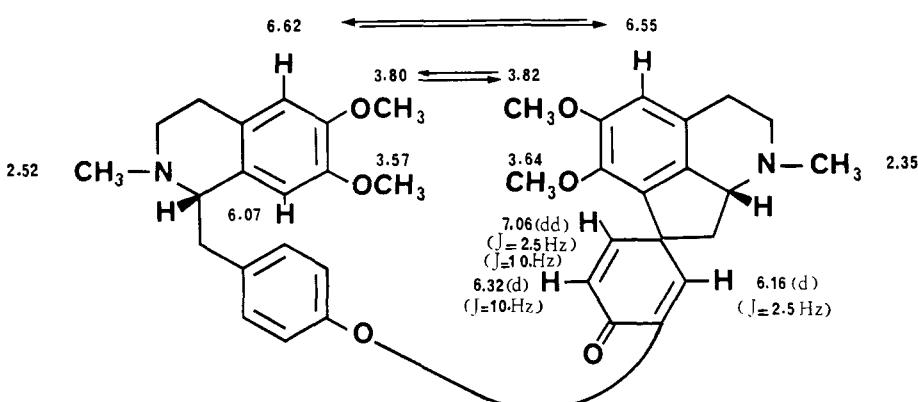
NMR: (30)

MASS: 622 (M⁺), 608, 416, 326, 310, 267, 206 (base), 190, 107, 91 (30)

ORD: (CH₃OH) $\alpha_{240}-2333^\circ$, $\alpha_{285}+2200^\circ$, $\alpha_{360}+82^\circ$ (30)

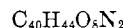
SOURCES: *Berberis baluchistanica* (29) (30)

*Pakistanamine is a proaporphine-benzylisoquinoline; since it is the precursor of pakistanine and closely related to it, pakistanamine has been included in this review.



4 aromatic H at 7.02

27 PENNSYLPAVINE



680.3097

MP: 122-123° (26)

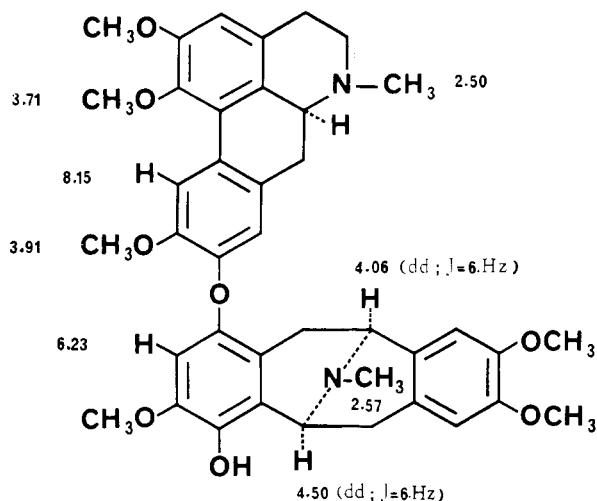
$[\alpha]^{25}_D: -174^\circ$ ($c=0.6$, CH₃OH) (26)

UV: 230 (4.62), 280 sh (4.38), 288 (4.40), 308 sh (4.23), 320 sh (4.15) (26)

NMR: (26)

MASS: 680, 649, 648, 637, 529, 475, 355, 340, 204 (base) (26)

SOURCES: *Thalictrum polygamum* (26)



4 methoxy at 3.76 (6 H), 3.78, 3.88

4 aromatic H at 6.48 (2 H), 6.52, 6.60

28 PENNSYLVAVOLINE



666.2941

MP: 145-146° (26)

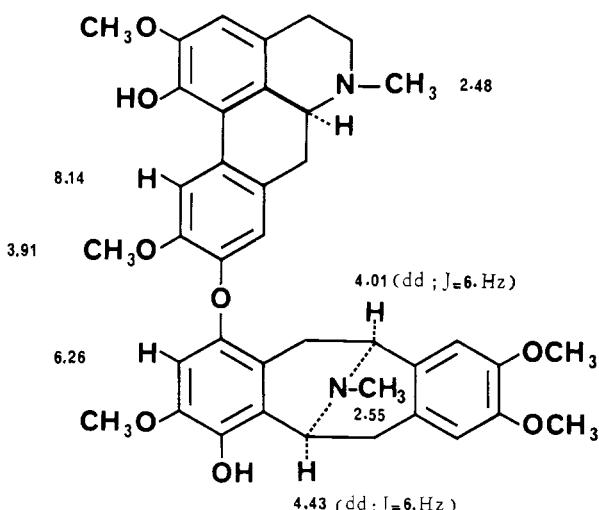
$[\alpha]^{25}D$: -245° (c=0.66, CH₃OH) (26)

UV: 230 (4.47), 280 sh (4.06), 288 (4.13), 306 sh (4.01), 320 sh (3.96) (26)

NMR: (26)

MASS: 666, 515, 461, 355, 326, 204 (base) (26)

SOURCES: *Thalictrum polygamum* (26)



4 methoxy at 3.75, 3.78 (6 H), 3.81,

4 aromatic H at 6.45, 6.49, 6.55 (2 H).

TABLE 1. Calculated molecular weights of aporphine-benzylisoquinoline dimers and aporphine-pavine dimers.

608.2886	C ₃₇ H ₄₆ O ₆ N ₂	Thalidoxine 8
Pakistanine 23		Pennsylvanine 9
622.3043	C ₃₅ H ₄₂ O ₆ N ₂	Fetidine 19
1-O-methylpakistanine 24		Thalirevoline 21
*Pakistanamine 26		692.2733
636.3199	C ₃₉ H ₄₄ O ₆ N ₂	Oxothalicarpine 11
1,10-Di-O-methylpakistanine 25		694.3254
666.2941	C ₃₉ H ₄₂ O ₈ N ₂	Dehydrothalicarpine 12
Pennsylpavoline 28		696.3410
668.3097	C ₃₉ H ₄₄ O ₈ N ₂	Thalicarpine 10
Thalictrogamine 1		Thalirevolutine 22
Pennsylvanamine 2		712.3359
Thalipine 5		Thalilutine 13
Revolutopine 20		O-Desmethyladiantifoline 14
680.3097	C ₄₀ H ₄₄ O ₈ N ₂	Thaliadanine 15
Dehydrothalmelatine 7		726.3516
Pennsylpavine 27		Adiantifoline 16
682.3254	C ₄₀ H ₄₆ O ₈ N ₂	740.3309
Thalictropine 3		Thalmelatidine 18
Thalilutidine 4		742.3465
Thalmelatine 6		Thalmineline 17
		C ₄₁ H ₄₈ O ₉ N ₂
		C ₄₁ H ₄₆ O ₈ N ₂
		C ₄₂ H ₅₀ O ₁₀ N ₂
		C ₄₂ H ₅₀ O ₁₀ N ₂

*Proaporphine-benzylisoquinoline.

TABLE 2. Names and synonyms of aporphine-benzylisoquinoline dimers and aporphine-pavine dimers.

Adiantifoline 16	Revolutopine 20
Dehydrothalicarpine 12	Thaliadanine 15
Dehydrothalmelatine 7	Thalicarpine 10
O-Desmethyladiantifoline 14	Thalictrogamine 1
1,10-Di-O-methylpakistanine 25	Thalictropine 3
Fetidine 19	Thalictrucarpine 12
Foetidine 19	Thalidoxine 8
1-O-methylpakistanine 24	Thalilutidine 4
Oxothalicarpine 11	Thalilutine 13
Pakistanine 23	Thalipine 5
*Pakistanamine 26	Thalirevoline 21
Pennsylpavine 27	Thalirevolutine 22
Pennsylpavoline 28	Thalmelatidine 18
Pennsylvanamine 2	Thalmelatine 6
Pennsylvanine 9	Thalmineline 17

*Proaporphine-benzylisoquinoline.

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