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THALICTRUM ALKALOIDS—VII
TETRAHYDROTHALIFENDINE, N-METHYLTHALIDALDINE AND N-METHYLCORYDALDINE[1]

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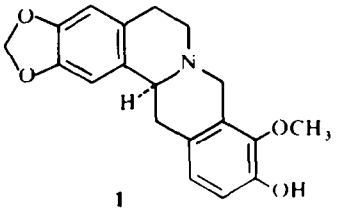
Abstract—Three new alkaloids have been obtained from *T. fendleri*, tetrahydrothalifendine (1), N-methylthalidaldine (2) and N-methylcorydaldine (3). Another alkaloid also present is veronamine (4).[1]

THE species *Thalictrum fendleri* Engelm. *ex* Gray (Ranunculaceae) native of Utah and other Western states has been found to be a rich source of isoquinoline alkaloids. Previous studies have demonstrated the presence of the new alkaloids thalifendlerine[3] (5), thalifendine,[3] thalidastine,[4] thaliporphine, thalidezine, and preocoteine.[5] Furthermore, known alkaloids also found in *T. fendleri* are berberine, jatrorrhizine, glaucine, magnoflorine, ocoteine, hernandezine[6] and thalicarpine.[7]

We now wish to report on the isolation and structural elucidation of three additional new alkaloids, namely tetrahydrothalifendine (1), N-methylthalidaldine



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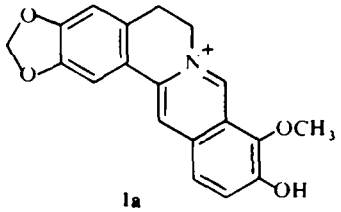

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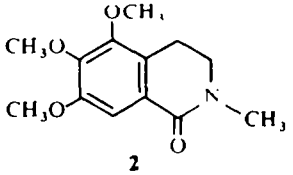

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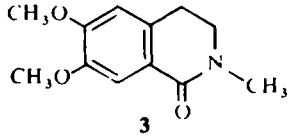

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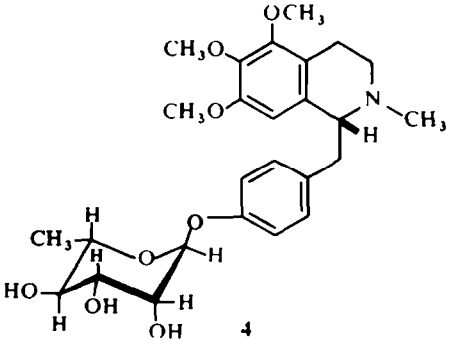

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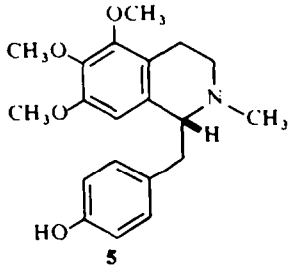

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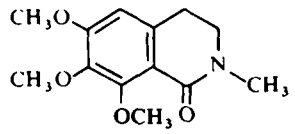

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(2), and N-methylcorydaldine (3). Furthermore, the procedures that led to the isolation and characterization of the alkaloid veronamine (4), whose structural elucidation has already been published,[1] are discussed in the Experimental.

General isolation procedures

The crude tertiary alkaloid hydrochlorides were chromatographed on a cellulose partition column. N-Methylcorydaldine (3), N-methylthalidaldine (2) and tetrahydrothalifendine (1) were obtained from the early fractions while veronamine (4) was found in one of the middle fractions. Alkaloids 2 and 3 were further purified by chromatography on a neutral alumina column. TLC was used in all cases as the ultimate step to obtain the pure compounds.

Tetrahydrothalifendine (1)

Tetrahydrothalifendine (1) was obtained as colorless crystals, m.p. 209–211°. The UV spectrum exhibited λ_{max}^{EtOH} 209 and 282 mμ (log ε 4·8 and 3·77), typical of a tetrahydroprotoberberine system.[8] Addition of base caused a bathochromic shift, and a positive ferric chloride test gave additional evidence for the presence of a phenolic group.

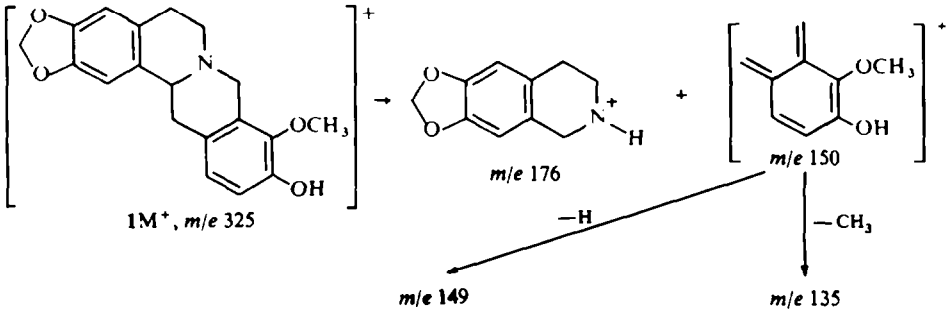
The NMR spectrum of tetrahydrothalifendine showed a OMe singlet absorption at δ 3·82 (3H) and a methylenedioxy peak at δ 5·92 (2H). A complex multiplet of aromatic hydrogens between δ 6·50 and 7·08 denoted the aromatic protons.

Two absorption bands in the IR spectrum, one at 9·6 μ and the second between 10·6 and 10·8 μ were also suggestive of a methylenedioxy group.

The mass spectrum of tetrahydrothalifendine disclosed a molecular ion at *m/e* 325 ($C_{19}H_{19}O_4N$) and a base peak at *m/e* 176. Other important peaks were at *m/e* 150, 149 and 135. These peaks are explained in Scheme I.

SCHEME I

Electron impact cleavage of tetrahydrothalifendine (I)



Bearing in mind that the quaternary protoberberine alkaloid thalifendine (**1a**) had already been found in *T. fendleri*, it was logical to assume that the new alkaloid could correspond to the optically active tetrahydro derivative of **1a**.[3] Indeed, when thalifendine was reduced with Adams catalyst, the product was racemic tetrahydrothalifendine identical with the natural product in terms of UV, NMR, and mass spectra, as well as TLC R_f values. This chemical correlation completely settled the positions of the substituents in tetrahydrothalifendine (**1**).

Naturally occurring (−)-tetrahydrothalifendine exhibits $[\alpha]_D$ − 175° (MeOH), and shows a negative Cotton effect with a trough at 306 mμ. The C-14 hydrogen must, therefore, be *alpha*, as indicated in expression **1**, by analogy with (−)-tetrahydropalmatine and other tetrahydroprotoberberines of established configuration.[9, 10]

The oxidation of a tetrahydroprotoberberine to a quaternary protoberberine salt, e.g. tetrahydrothalifendine (**1**) to thalifendine (**1a**), must be a facile conversion in a plant. It is, therefore, safe to conclude that whenever a quaternary protoberberine salt is found in a plant, there is a high probability that the corresponding tetrahydroprotoberberine base is also present.

N-*Methylthalidaldine* (**2**)

N-Methylthalidaldine (**2**), the second new alkaloid to be reported here, was present in *T. fendleri* only in very small amounts, and was obtained as a colorless, optically inactive oil.

The IR spectrum showed a strong band at 6·12 μ characteristic of a lactam, while the absence of any significant absorption near 3·0 μ pointed to the absence of OH or NH groups.

The NMR spectrum of N-methylthalidaldine was relatively simple and is described in Table 1. The important features to note are the presence of 3 OMe groups, one lactam N-Me, and only one aromatic hydrogen.

TABLE 1. NMR SPECTRUM OF N-METHYLTHALIDALDINE (**2**)

Functional group	Chemical shift, δ	Protons
—CH_2—C	2·90	2 (triplet)*
>N—CH_3	3·11	3 (singlet)
—C—CH_2—	3·50	2 (triplet)*
—O—CH_3	3·83	3 (singlet)
—O—CH_3	3·86	3 (singlet)
—O—CH_3	3·88	3 (singlet)
C-8 H	7·43	1 (singlet)

* J = 7Hz

The mass spectrum of N-methylthalidaldine (**2**) had a molecular ion at *m/e* 251 ($C_{13}H_{17}O_4N$). The base was at *m/e* 221; and other intense peaks corresponded to 208, 180 and 165. Three metastable peaks were also present in the spectrum and these are listed in Table 2. The fragmentation pattern in Scheme II can, therefore, be written for N-methylthalidaldine.[11]

SCHEME II

Electron impact cleavage of N-*methylthalidaldine* (2)

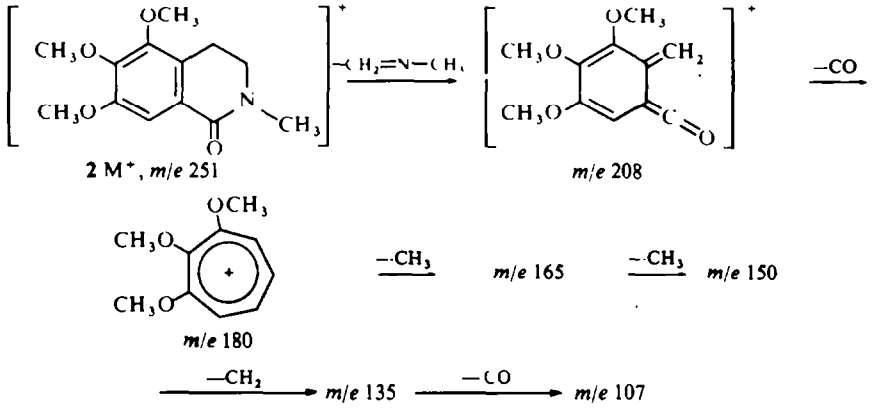


TABLE 2. METASTABLE MASS SPECTRAL PEAKS OF N-METHYLTHALIDALDINE (2)[11]

Fragment (a)	Fragment (b)	Metastable peak (m)
251	208	172
208	180	156
180	165	151

$m = b^2/a$

The final differentiation between the correct structure **2** for N-methylthalidaldine and the alternate structure **6** was achieved by chemical means. The occurrence of such alkaloids as thalifendlerine (**5**), thalidezine, hernandezine, preocoteine and veronamine (**4**) in *T. fendleri* made it more than probable that expression **2** represented the correct structure for N-methylthalidaldine. A sample of naturally occurring (−)-thalifendlerine (**5**) was, therefore, carefully oxidized with dilute potassium permanganate in acetone. The product proved to be N-methylthalidaldine (**2**), identical in all respects with the natural product.

N-*Methylcorydaldine* (**3**)

Another isoquinoline type alkaloid also obtained from *T. fendleri* together with N-methylthalidaldine is N-methylcorydaldine (**3**). As with N-methylthalidaldine (**2**), N-methylcorydaldine (**3**) exhibited a strong band at 6·12 μ for a lactam carbonyl, and no absorption near 3·0 μ denoting the absence of OH or NH groups. The NMR spectrum, given in Table 3, was very similar to that of N-methylthalidaldine, and confirmed the assignment of expression **3** to the alkaloid. The mass spectrum of N-methylcorydaldine (**3**), showed a molecular ion at *m/e* 221 ($C_{12}H_{15}O_3N$), a base peak at *m/e* 178 ($C_{10}H_{10}O_3$), and other intense peaks at *m/e* 150, 135 and 107, reflecting the difference of one OMe group between this compound and N-methylthalidaldine. The metastable peaks were at *m/e* 144 and 126, corresponding to $178^2/221$ and $150^2/178$ respectively.

Finally, naturally occurring N-methylcorydaldine was found to be identical with the same compound previously obtained in the laboratory from the oxidative degradation of the bisbenzylisoquinoline alkaloid cissampareine.[12]

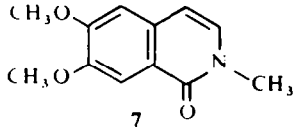
It was at first believed that N-methylcorydaldine was not a new alkaloid, since a compound of this structure was reported to have been isolated from *Hernandia ovigera* L., although no physical constants were given.[13] In a recent paper, however, it was pointed out that a double bond was missing from the structure originally written for the *Hernandia* alkaloid which is now assigned expression 7.[14] It follows that the N-methylcorydaldine (3) isolated in the present study is a new alkaloid.

TABLE 3. NMR SPECTRUM OF N-METHYLCORYDALDINE (3)

Functional group	Chemical shift, δ	Protons
$-CH_2-C-$	2·89	2 (triplet)*
$>N-CH_3$	3·10	3 (singlet)
$-C-CH_2-$	3·50	2 (triplet)*
$-O-CH_3$	3·85	3 (singlet)
$-O-CH_3$	3·90	3 (singlet)
C-5 H	6·58	1 (singlet)
C-8 H	7·58	1 (singlet)

* J = 7 Hz

Isoquinolones can be considered to form a distinct group of alkaloids, and they probably originate in the plant by oxidation of benzylisoquinolines.[15] Known members of this group are doryanine (8),[5] 2-methyl-6,7-dimethoxyisoquinolone (7),[14] noroxyhydrastinine (9),[11] thalifoline (10),[11] thalactamine (11),[16] and now N-methylthalidaldine (2) and N-methylcorydaldine (3).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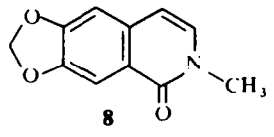
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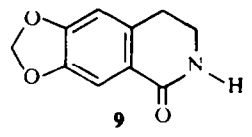
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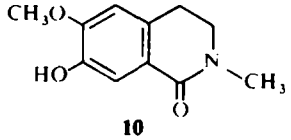
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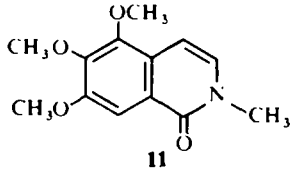
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EXPERIMENTAL

General procedures. UV absorbance measurements were made with a Cary Model 15 or a Hitachi Model 124 spectrophotometer. The IR spectra were recorded on a Perkin–Elmer 257 or a Beckman IR-5 instrument, with chloroform as the solvent. Mass spectra were obtained with a Nuclide 12-90-GI. 1 or an MS-9 spectrometer. The NMR spectra were measured at 60 MHz using a Varian A-60A model; the solvent was $CDCl_3$, and TMS the internal standard. M.ps are uncorrected. TLC was on Adsorbosil-1. All molecular weights were obtained through mass spectral measurements.

Plant extraction. T. fendleri growing wild near Tabiona, Utah, was harvested during the late summer

season. The whole plant was ground to a fine powder and 20 kg were extracted with hot MeOH. The solvent was evaporated to dryness leaving a thick viscous residue which was taken up in 3–5% AcOH, and then passed through a filter. The filtrate was extracted with chloroform to remove the acidic and neutral components. The aqueous acidic layer was made basic with conc ammonium hydroxide, and reextracted with chloroform and then with ether. The chloroform and ether fractions were combined and the solvent evaporated leaving a black, tarry residue containing about 15 g of crude alkaloid mixture.

Cellulose partition column chromatography.[7] Dry methanolic HCl (15 ml) was added to the crude alkaloid mixture. The excess methanolic HCl was rapidly evaporated under reduced pressure. The hydrochlorides were dissolved in 30 ml of the stationary phase solvent (water saturated with methyl ethyl ketone), and the soln added to 60 g dry cellulose powder. The mixture was shaken vigorously to break up the lumps, placed carefully on top of an equilibrated cellulose column, and then lightly tapped down. The chromatographic column had been made from 500 g of Whatman Chromedia CF 11 cellulose powder.[7]

Elution of the column was carried out with methyl ethyl ketone saturated with water. A total of 130 flasks each containing 125 ml of eluant was collected. The contents of the flasks were combined into 16 consolidated fractions on the basis of tlc R_f values as shown in Table 4.

TABLE 4. CELLULOSE PARTITION COLUMN CHROMATOGRAPHY OF THE CRUDE ALKALOID MIXTURE

Fraction	Flask number	Alkaloid
1	0–12	N-Methylcorydaldine (3), N-methylthalidaldine (2), and tetrahydrothalifendine (1)
2–3	13–26	Thalifendlerine (5)
4–5	27–44	
6–8	45–59	Veronamine (4)
9–11	60–91	
12–13	92–101	Thalidezine[5]
14–16	102–130	

Isolation and purification of veronamine (4). Fraction 7 (Table 4) appeared as a dark brown oil. When chromatographed on a thin layer plate in a chloroform-acetone-methanol solvent system (7:3:1) and exposed to iodine vapors, an intense yellow spot appeared at R_f 0·5; in chloroform-methanol (9:2) R_f 0·72. The yield after the TLC separation was about 500 mg of amorphous veronamine, $[\alpha]_D$ – 145° (c 0·45 in MeOH); ORD (c 0·225 in MeOH) $[\alpha]_{350}$ – 622°, $[\alpha]_{288}$ – 2300° (trough), $[\alpha]_{273}$ – 970° (peak), $[\alpha]_{260}$ – 1600°.[17]

Color tests for veronamine.[18] Molish: violet ring; Ihl-Pechmann: greenish blue; Tauber benzidine: yellow.

Hydrolysis of veronamine (4). Veronamine (40·0 mg) was heated in 3% H_2SO_4 on a steam bath for 5 hr. The product was allowed to stand for two days at room temp after which it was neutralized with $Ba(OH)_2$, and the $BaSO_4$ filtered. The aqueous filtrate was extracted with chloroform, yielding 5, m.p. 177–178°, $[\alpha]_D$ – 108° (c 1·0 in MeOH); ORD (c 0·2 in MeOH) $[\alpha]_{350}$ – 650°, $[\alpha]_{288}$ – 3200° (trough), $[\alpha]_{273}$ – 1000° (peak), $[\alpha]_{260}$ – 2250°. The aqueous residue was concentrated under reduced pressure, dissolved in EtOH, and when purified by paper chromatography gave a material identical with authentic L-(–)-rhamnose, exhibiting an olive-brown color with the aniline oxalate spray.[19]

The apparent R_f values on paper chromatography for the L-(–)-rhamnose samples were as follows:

i-BuOH-1N NH_4OH (10:6)	0·46
n-BuOH-pyridine-water (6:4:3)	0·58
n-BuOH-EtOH-water (4:1:1)	0·40
Pyridine-EtOAc-glacial AcOH-water (5:5:3:1)	0·56

All the chromatograms were on Whatman W-1.

L-(–)-Rhamnose diethyldithioacetal. This material, m.p. 134–136°, was prepared as per Ref. 9. The mass spectrum has been recorded.[20]

Isolation of tetrahydrothalifendine (1), N-*methylthalidaldine* (2) *and* N-*methylcorydaldine* (3)

Fraction 1 from the cellulose partition chromatography (see Table 4) was placed on an alumina column and eluted with chloroform and small increments of MeOH until a 10% MeOH soln in chloroform was reached. The first alkaloids to come down were 3 and 2, followed by 1. TLC using ether–acetone (5:4) was used in the final purification stage of alkaloids 2 and 3, with the former moving more slowly. N-Methylcorydaldine (3) R_f 0·47 ether–acetone (5:4); N-methylthalidaldine (2) R_f 0·58 chloroform-methanol (9:1). Both alkaloids 3 and 2 were obtained as oils.

Tetrahydrothalifendine (1) exhibited $[\alpha]_{400}$ −600°, $[\alpha]_{306}$ −1650° (trough).

Reduction of thalifendine chloride (1a) *to* (±)-*tetrahydrothalifendine.* Reduction was carried out with Adams catalyst in EtOH at room temp. Tetrahydrothalifendine was obtained in nearly quantitative yield. The TLC R_f values, and UV, IR, and NMR spectra were identical with those of the optically active natural product.

Oxidation of (−)-*thalifendlerine* (5) *to* N-*methylthalidaldine* (2). A soln of thalifendlerine (50 mg) in 20 ml acetone was treated with 1% $KMnO_4$ in acetone (5 ml), and stirred at room temp for 4 hr. MeOH was added dropwise to decompose the excess permanganate. The mixture was filtered and evaporated to dryness. The residue was extracted with ether, washed with 5% K_2CO_3, 2% H_2SO_4, and water, and then dried over Na_2SO_4. Evaporation of the solvent yielded material identical with N-methylthalidaldine.

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