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# THALICTRUM ALKALOIDS—IV

## THREE NEW ALKALOIDS FROM *T. FENDLERI*: THALIDEZINE, THALIPORPHINE, AND PREOCOTEINE

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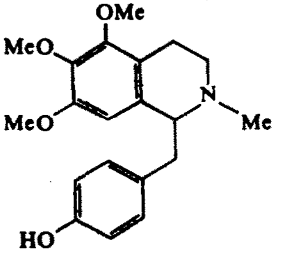
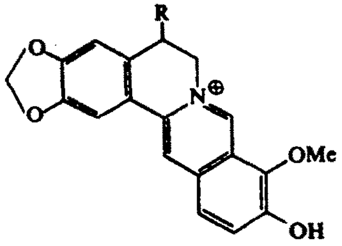
Abstract—The following new isoquinoline alkaloids have been isolated from *T. fendleri:* the bisbenzylisoquinoline thalidezine (IIIb), and the aporphines thaliporphine (XI) and preocoteine (XIV). Thaliporphine has been assigned a structure previously given to glaucentrine. The plant genus Thalictrum has a pronounced tendency to produce isoquinoline alkaloids possessing the trioxygenated moiety XIX.

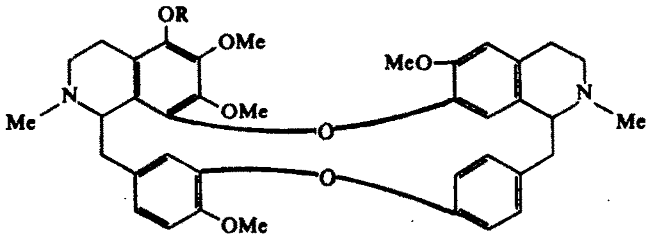
The isolation and characterization of three new alkaloids from *Thalictrum fendleri*, namely thalifendlerine (I),[2] thalifendine (IIa),[3] and thalidastine (IIb) have been reported.[3] Additionally, the known bisbenzylisoquinoline base hernandezine, which also occurs in *T. fendleri*, has been shown to possess the structure IIIa.[4]



I



IIa, R = H
IIb, R = OH



IIIa, R = Me
IIIb, R = H

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[1] Present address: Section of Biochemistry and Molecular Biology, Division of Biological Sciences, 14850, Cornell University, Wing Hall, Ithaca, New York.

[2] M. Shamma, M. A. Greenberg and B. S. Dudock, *Tetrahedron Letters* No. 40, 3595 (1965).

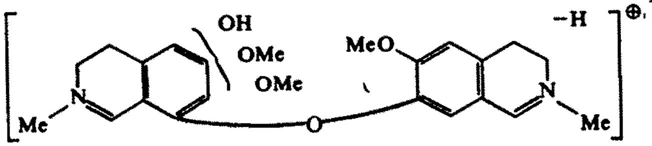
[3] M. Shamma and B. S. Dudock, *Tetrahedron Letters* No. 43, 3825 (1965).

[4] M. Shamma, B. S. Dudock, M. P. Cava, K. V. Rao, D. R. Dalton, D. C. DeJongh and S. R. Shrader, *Chem. Commun.* 7 (1966). This communication corresponds to paper III in the series Thalictrum Alkaloids.

In the course of studies on the alkaloids of *T. fendleri*, the new bisbenzylisoquinoline alkaloid, thalidezine, m.p. 158–159° (acetone), $[\alpha]_D$ 235° (Chf) has also been isolated. The UV spectrum exhibited $\lambda_{max}^{EtOH}$ 283 mμ (log ε 4·02), characteristic of a tetrahydroisoquinoline moiety, with a bathochromic shift in basic solution due to the presence of a phenolic group.

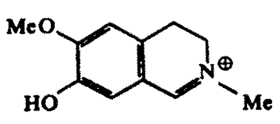
The NMR spectrum of thalidezine at 60 Mc showed absorption for four O–Me groups at 3·27, 3·37, 3·78 and 3·92 δ, and for two N–Me groups at 2·33 and 2·64 δ. One aromatic hydrogen absorption was situated relatively upfield as a singlet at 6·02 δ, while the remaining aromatic peaks overlapped in the region 6·12 to 7·5 δ.

The mass spectrum of thalidezine showed a molecular ion at *m/e* 639, pointing to the composition $C_{38}H_{42}O_7N_2$ suggestive of a bisbenzylisoquinoline system. Two of the most intense peaks in the spectrum were at *m/e* 411 and 192, and could be tentatively explained in terms of the cationic shards IVa and IVb indicated below:



*m/e* 411

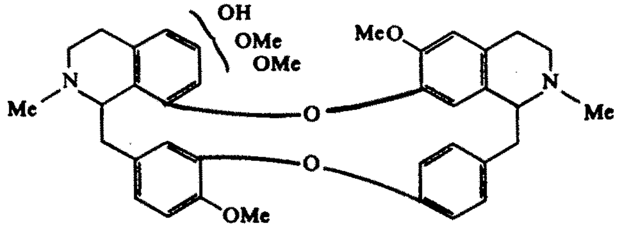
IVa



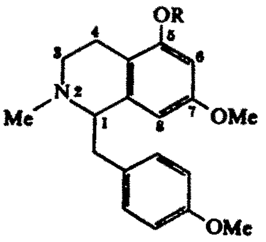
*m/e* 192

IVb

These data indicated the possibility that thalidezine is a demethylhernandezine corresponding to expression V, and indeed O-methylation of thalidezine with diazomethane gave hernandezine (IIIa).

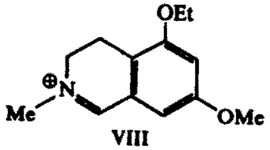


V

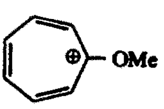


VI, R = Me

VII, R = Et



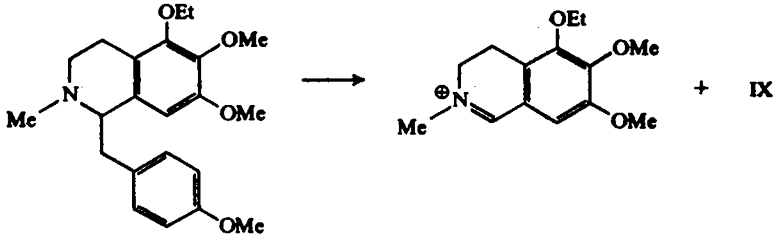
VIII



IX

The remaining problem was, therefore, the determination of the exact position of the phenolic function in thalidezine. For this purpose most of our limited supply of thalidezine was O-ethylated with diazoethane, and the resulting O-ethylthalidezine (M+ at *m/ε* 667, $C_{40}H_{46}O_7N_2$), m.p. 117–120°, reduced with sodium in liquid ammonia at −70°. It will be recalled that the sodium in liquid ammonia cleavage of hernandezine at −50° had yielded as the main non-phenolic product the trimethoxybenzylisoquinoline VI.[4] In the present case, from 107 mg of O-ethylthalidezine, and after repeated TLC on silica gel, a minor and a major non-phenolic compound were obtained. The minor non-phenolic compound VII was an oil weighing 3·6 mg. The mass spectrum of VII had a molecular ion at *m/ε* 341, in accordance with the formula $C_{21}H_{27}O_3N$. The base peak was at *m/ε* 220, representing the species VIII, and another important peak occurred at *m/ε* 121, representing the cation IX. Bearing this information in mind, the structure of the degradation product VII was conclusively indicated by the NMR spectrum of the compound run in $CDCl_3$ solution at 100 Mc. It will be remembered that in a benzylisoquinoline, the absorption at C-7 or C-8 will be shifted relatively upfield due to shielding by the benzylic aromatic ring.[5] For compound VII, the C-6 proton appeared as a doublet centered at 6·23 δ while the C-8 proton doublet was at 5·76 δ. The $J_{6,8}$ value is 2·5 c/s in accordance with a meta relationship between the two hydrogens. Additionally, the C-7 methoxyl group was at 3·54 δ while the MeO in the benzylic moiety appeared further downfield at 3·76 δ. The EtO showed up as a triplet at 1·38 δ and a quadruplet at 3·95 δ (J = 7 c/s), and finally the N-methyl group appeared at 2·45 δ.

The major non-phenolic product from the reductive cleavage was the oily benzylisoquinoline X, weighing 9·8 mg; with a molecular ion at *m/ε* 371 for $C_{22}H_{29}O_4N$, a base peak at *m/ε* 250, and another peak at *m/ε* 121 representing the ion IX. The C-7 MeO group appeared at 3·58 δ, with the remaining methoxyls at 3·78 and 3·83 δ; the C-8 proton was at 5·90 δ.



X *m/e* 371 *m/e* 250

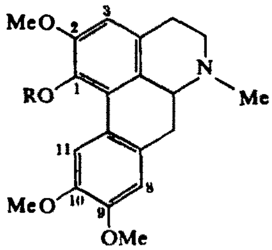
The isolation and characterization of the degradation product VII, together with the conversion of thalidezine into hernandezine, conclusively establish the structure of thalidezine as IIIb. Therefore, both hernandezine and thalidezine incorporate a thalifendlerine-like moiety in their structures, and it is safe to predict that in the years ahead several additional dimeric alkaloids derived from thalifendlerine analógs will be isolated and characterized.

The other two new alkaloids we have isolated from *T. fendleri* are aporphines. The first of these, thaliporphine, XI, melts 170–172° when recrystallized from methanol, and mass spectrometry indicated a molecular ion at *m/ε* 341 for the formula

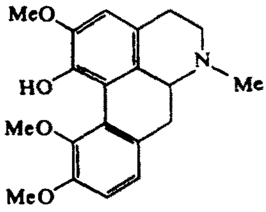
[5] D. R. Dalton, M. P. Cava and K. T. Buck, *Tetrahedron Letters* No. 31, 2687 (1965).

$C_{20}H_{23}O_4N$. The alkaloid exhibits a positive optical rotation in methanol,[6] and has $\lambda_{max}^{EtOH}$ 305, 280 and 220 mμ (log ε 4·12, 4·12 and 4·52) characteristic of a 1,2,9,10-tetrasubstituted aporphine. The presence of a phenolic function was indicated by a bathochromic shift upon the addition of base.

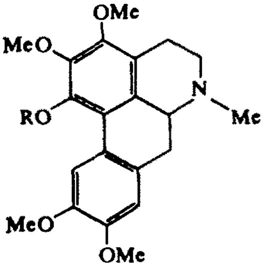
The use of NMR spectroscopy in the structural elucidation of aporphines revolves mainly around the fact that MeO groups at C-1 or at C-11 appear at higher fields (3·40–3·72 δ) than other MeO groups (3·72–3·90 δ), while at C-11 hydrogen is always located further downfield (7·57–8·10 δ) than the remaining aromatic protons (6·38–7·00 δ).[7] The NMR spectrum of thaliporphine at 60 Mc shows two superimposed MeO's at 3·89 δ, and one at 3·83 δ, one N–Me at 2·53 δ and three aromatic hydrogens at 6·51, 6·77 and 8·07 δ. The downfield aromatic absorption at 8·07 must be due to the presence of a C-11 hydrogen, while the absence of a relatively upfield MeO indicates that a phenolic function is at C-1. O-Methylation of thaliporphine with diazomethane yielded the known alkaloid glaucine (XII), so that thaliporphine can be considered to be 1-hydroxy-2,9,10-trimethoxyaporphine (XI). We were rather pleasantly surprised to isolate this aporphine from nature, since a few months earlier we had reported the synthesis of this same compound in our laboratory.[8] Indeed, spectral and TLC comparisons of the two materials proved them to be identical. Structure XI had originally been assigned in the literature to the alkaloid glaucentrine. This base has, however, been shown to correspond to corydine (XIII) so that the isolation and characterization of thaliporphine (XI) fills a "missing link" in aporphine chemistry.[8] It follows that the unnamed quaternary aporphine from *Fagara tinguassoiba* whose structural assignment has recently been reconsidered, corresponds to the N-methylthaliporphinium cation.[8,9]



XI, R = H
XII, R = Me



XIII



XIV, R = H
XVII, R = Me

The second new aporphine alkaloid we have found in *T. fendleri* is preocoteine (XIV). This alkaloid was obtained only in small amounts as an oil, but its uv spectrum showing $\lambda_{max}^{EtOH}$ 312, 302 and 278 mμ (log ε 4·22, 4·22, 4·16) is characteristic of a 1,2,3,9,10 pentasubstituted aporphine, and is close to that of the well characterized aporphine base ocoteine (XV) which shows $\lambda_{max}^{EtOH}$ 314, 302, 283, mμ (log ε 4·1, 4·2, 4·2) and which we have found also to be present in *T. fendleri*. Furthermore,

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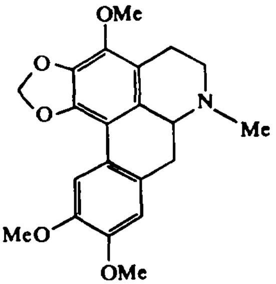
[6] Although thaliporphine is dextrorotatory, we are unable to obtain a reliable value for $[\alpha]_D$ because of the limited amount of material on hand.

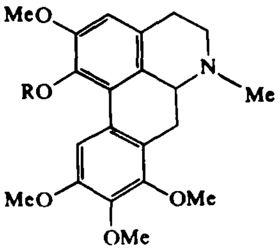
[7] I. R. C. Bick, J. Harley-Mason, N. Sheppard and M. J. Vernango, *J. Chem. Soc.* 1896 (1961).

[8] M. Shamma and W. A. Slusarchyk, *Tetrahedron Letters* No. 20, 1509 (1965).

[9] N. V. Riggs, L. Antonaccio and L. Marion, *Canad. J. Chem.* 39, 1330 (1961).

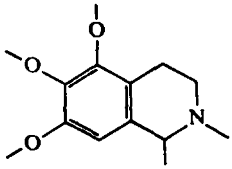


XV



XVI, R = H

XVIII, R = Me



XIX

the UV spectrum of preocoteine shows a bathochromic shift upon the addition of base so that the molecule must be phenolic.

The mass spectrum of preocoteine had a molecular ion at *m/ε* 371, corresponding to the formula $C_{21}H_{25}O_5N$. These data indicated that in analogy with ocoteine preocoteine is also pentaoxygenated but contains four MeO and one OH groups.

The NMR spectrum of preocoteine shows two superimposed MeO absorptions at 3·92 δ, and also at 3·88 δ, so that no MeO group is present either at C-1 or C-11. However, since all naturally occurring aporphines are substituted at C-1, the phenolic function must be placed at that position. The C-11 hydrogen was situated characteristically downfield as a singlet at 7·99 δ, while the C-8 hydrogen appeared also as a singlet at 6·74 δ.

In order to eliminate the possibility of preocoteine possessing the alternate structure XVI, the alkaloid was methylated with diazomethane to O-methylpreocoteine, intense molecular ion at *m/ε* 385 ($C_{22}H_{27}O_5N$). O-Methylpreocoteine (XVII) exhibited $\lambda_{max}^{EtOH}$ 311 (sh), 302 and 281 (log ε 3·98, 4·03 and 4·07), again characteristic of a 1,2,3,9,10-pentasubstituted aporphine, and different from the UV spectrum of an authentic sample of synthetic (±)-1,2,8,9,10-pentamethoxyaporphine (XVIII) kindly supplied to us by Dr. K. Hirai.[10] Compound XVIII showed $\lambda_{max}^{EtOH}$ 280 mμ (4·23) and 295 mμ (shoulder).

The paramount fact that can be derived from the present study of Thalictrum alkaloids is that this plant genus has a pronounced tendency to produce isoquinoline alkaloids possessing the trioxygenated moiety XIX. This tendency is exemplified by the isolation of such alkaloids as thalifendlerine (I), hernandezine (IIIa), thalidezine (IIIb), ocoteine (XV) and preocoteine (XIV) from *T. fendleri.*

Finally, a known benzylisoquinoline-aporphine alkaloid which we have also found in *T. fendleri* is thalicarpine (XX).[11]

## EXPERIMENTAL[12]

*Isolation of alkaloids.* Since the isolation of new alkaloids from *T. fendleri* is still in progress, the detailed description of the separation procedures will be presented in a separate paper. Briefly, however, the alkaloid extracts obtained from about 20 kg of dried whole plant were separated into

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[10] K. Hirai, *J. Pharm. Soc. Japan* **80**, 608 (1960); *Chem. Abstr.* **54**, 22696 (1960).

[11] S. M. Kupchan, K. K. Chakravarti and N. Yokoyama, *J. Pharm. Sci.* **52**, 985 (1963).

[12] All NMR spectra were run in $CDCl_3$ soln with TMS as an internal standard, using a Varian 60 or 100 Mc instrument. IR spectra were run in Chf soln using a Beckman IR-5A spectrometer. All m.ps. are uncorrected. TLC was accomplished on Adsorbosil-1, and column chromatograms on Baker neutral alumina.

tertiary and quaternary fractions. The tertiary alkaloids, as the hydrochloride salts (50 g), were subjected to partition chromatography on a cellulose column, using methyl ethyl ketone–water as the solvent system.

The following alkaloids as hydrochlorides were thus obtained in crude form: I (3·2 g); XV (200 mg); XII (5 mg); XIV (60 mg); XI (100 mg); IIIa (50 mg); XX (20 mg), and IIIb (300 mg).

*Preocoteine* (XIV). The crude preocoteine salt obtained above was converted to the free base and further purified first by column chromatography over neutral alumina, then by preparative TLC. The alkaloid was finally obtained as an oil which did not crystallize.

*Thaliporphine* (XI). The crude thaliporphine hydrochloride from the cellulose column was converted to the free base and rechromatographed over neutral alumina. Final purification was achieved by preparative TLC. Colorless crystals of thaliporphine crystallized from MeOH, m.p. 170–172°. The natural thaliporphine was shown to be identical to synthetic (±)-1-hydroxy-2,9,10-trimethoxyaporphine in terms of essentially identical UV, NMR, and mass spectra, as well as $R_f$ TLC comparisons.

*Thalidezine* (IIIb). The very impure thalidezine hydrochloride was converted to the free base and chromatographed over neutral alumina. The early fraction, eluted with Chf, contained IIIa and XX. The late fraction eluted with Chf–MeOH contained IIIb.

Repeated preparative TLC gave crystalline thalidezine, m.p. 158–159° (acetone), $[\alpha]_D^{25}$ 235° (Chf$_a$).

*Hernandezine* (IIIa) *and thalicarpine* (XX). The early fraction from the neutral alumina chromatography of the crude thalidezine (see above) contained IIIa and XX. Preparative TLC separated these 2 compounds. Hernandezine was recrystallized from MeOH, m.p. 158°, and the UV spectrum showed $\lambda_{max}^{EtOH}$ 283 m$\mu$ (log $\epsilon$ 3·90) with no shift on addition of base. This isolated material was shown to be identical to an authentic sample in terms of IR, UV, and mass spectra and TLC. The small amount of thalicarpine that was isolated was shown to be identical with authentic thalicarpine by TLC.

O-*Methylpreocoteine* (XVII). Preocoteine (5 mg) was dissolved in 10 ml MeOH and treated with excess ethereal diazomethane for 40 hr at 0°. Since TLC indicated that there was still starting material, the reaction mixture was again treated with excess ethereal diazomethane for 84 hr at 0°. The crude product was placed on a preparative 8″ × 8″ TLC plate which was developed using Chf–acetone (1:1). In this manner 3 mg of oily O-methylpreocoteine was obtained.

O-*Methylthaliporphine* (XII). Thaliporphine was treated with excess ethereal diazomethane at 0° for 24 hr. The reaction product, obtained in quantitative yield was shown to be identical to glaucine by means of superimposable UV and mass spectra and comparison of TLC $R_f$ values.

O-*Methylthalidezine* (IIIa). Thalidezine was O-methylated quantitatively with excess ethereal diazomethane in the manner described above. O-Methylthalidezine and hernandezine were proven to be identical through comparison of UV, NMR, and mass spectra, as well as TLC $R_f$ values.

O-*Ethylthalidezine.* Thalidezine (107 mg) was dissolved in 10 ml MeOH and treated with excess ethereal diazoethane (prepared by base hydrolysis of N-ethyl-N-nitrosourea). The reaction was allowed to proceed for 66 hr at 0°. The solvent was removed leaving 110 mg of a yellow solid, m.p. 117–120°, whose thin layer $R_f$ values differed from thalidezine. The IR spectrum of the reaction product showed the absence of a phenolic absorption at 2·8 $\mu$. The mass spectrum showed a molecular ion peak at $m/\varepsilon$ 667, corresponding to the formula $C_{40}H_{46}O_7N_2$.

*Sodium in liquid ammonia cleavage of* O-*ethylthalidezine.* Approximately 20 ml of dry liquid ammonia (distilled from Na) was collected at −70° in a 100 ml 3-neck flask. About 20 mg Na metal was added. Subsequently, 107 mg O-ethylthalidezine dissolved in 5 ml anhyd THF and 4 ml anhyd ether was added slowly from a 10 ml addition tube. More Na was added at intervals during the addition of the O-ethylthalidezine. The blue soln was allowed to stand for a ½ hr at −70°, and then the ammonia was allowed to escape. The orange solid remaining was distributed between Chf and $H_2O$. The Chf layer was dried ($Na_2SO_4$), filtered and evaporated. A TLC of the residue (nonphenolic fraction, 50 mg) in Chf:MeOH (90:10) showed it to be a complex mixture containing a major spot. This material was separated from the rest of the mixture by preparative TLC and, after elution from the Adsorbosil-1, weighed 20 mg. TLC of this material showed it to be a mixture. It was further purified by preparative TLC to give 9·8 mg of X and 3·5 mg of VII.

*Acknowledgements*—The authors are indebted to the National Institutes of Health for grant GM-10608-4, and to the National Science Foundation for a special departmental grant for the purchase of a Varian A-60 NMR unit and a Nuclide mass spectrometer.