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# ALKALOIDS OF THALICTRUM—X[1]

## TWO NEW ALKALOIDS FROM *T. MINUS* VAR. *ADIANTIFOLIUM*: NOROXYHYDRASTININE AND THALIFOLINE

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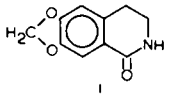
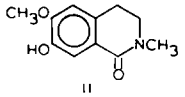
**Abstract**—Two new isoquinolone alkaloids, noroxyhydrastinine (I) and thalifoline (II) have been obtained from *T. minus* L. var. *adiantifolium* Hort. Characterization by physical methods and chemical synthesis have shown the former to be 6,7-methylenedioxy-1-oxo-1,2,3,4-tetrahydroisoquinoline and the latter to be 2-methyl-6-methoxy-7-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline.

THE plant genus *Thalictrum* has been shown to be a rich source of alkaloids of several different chemical types. These include members of the benzylisoquinoline,[2] benzyltetrahydroisoquinoline,[3] bis-benzyltetrahydroisoquinoline,[4] aporphine,[5] benzyltetrahydroisoquinoline-aporphine dimer[6] and protoberberine[3] class. We wish to report the characterization of two new alkaloids noroxyhydrastinine (I) and thalifoline (II), from *Thalictrum minus* L. var. *adiantifolium* Hort., which are isoquinolone derivatives and represent a new addition to the types of alkaloids obtained from *Thalictrum*. Noroxyhydrastinine (I) although known in the chemical literature[7] as an oxidation product of berberine (III) had previously not been found in natural sources. Thalifoline (II) had previously been obtained only as the ethyl ether derivative by permanganate oxidation of the O-ethyl ether of tetrahydrocolumbamine (isocorypalmine; IV).[8]




I

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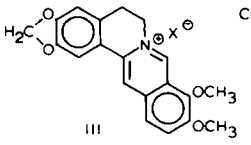


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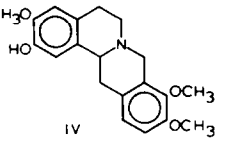



IV

The isolation of these alkaloids, as well as a number of others from this source will be presented elsewhere. Briefly, noroxyhydrastinine was obtained from the tertiary nonphenolic alkaloid fraction after chromatography on neutral alumina. The yield was 3·7 mg from 34 kg of dried roots. Thalifoline, was found to the extent of 5·2 mg from the same amount of starting material after chromatography of the tertiary

phenolic alkaloid fraction on silicic acid. These alkaloids were characterized entirely by physical methods with final proof made by direct comparison with known samples.

Noroxyhydrastinine (I) as pale yellow rosettes of needles, m.p. 182–183° (MeOH) showed a characteristic UV spectrum $\lambda_{max}$ 304 mμ (log ε 3·67), 261 (3·58) and 222·5 (4·31) unlike any previously observed for the thalictrum alkaloids and indicating more than just simple benzenoid absorption. No change was observed in the spectrum

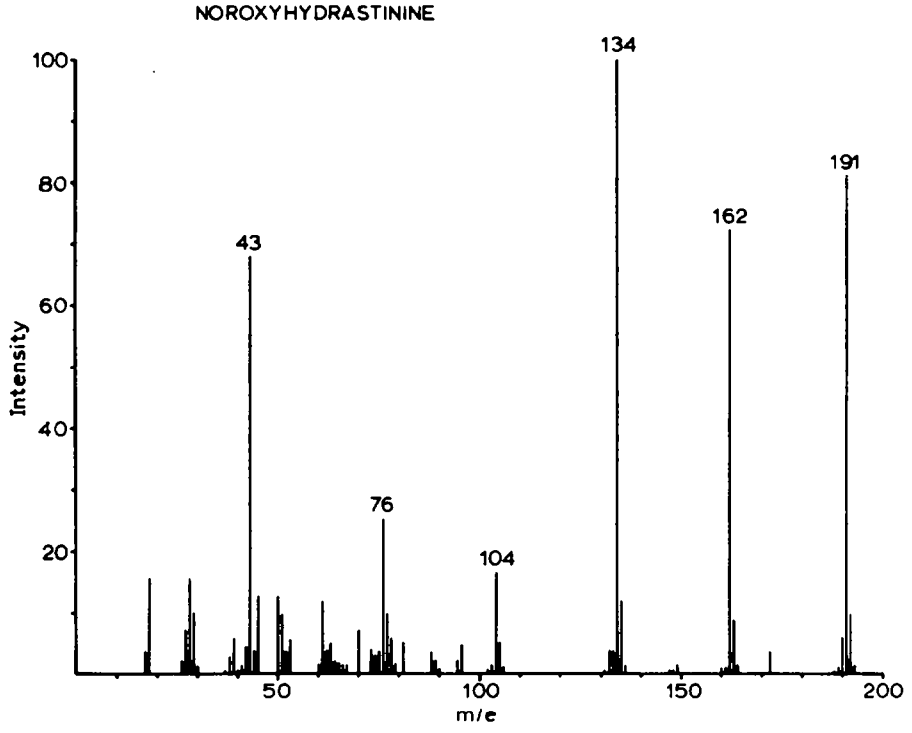
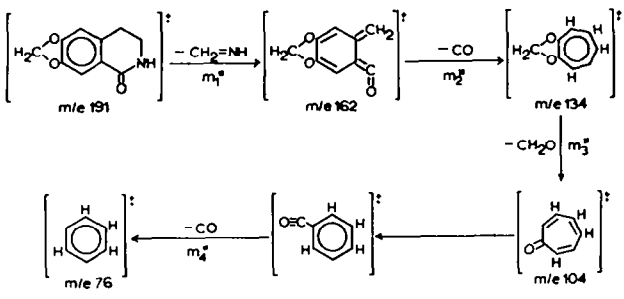



Fig. 1

under acid or basic conditions although the latter caused an enhancement in the end absorption. The IR spectrum showed intense peaks at $\nu_{KBr}$ 3175, 3040 and 1670 $cm^{-1}$. The first two peaks were assigned to the associated N—H (*cis*) stretching vibration of a lactam while the latter was consistent with the position for the C=O stretching of a δ-lactam. A methylenedioxy group was suggested by the presence of peaks at 2800 $cm^{-1}$ (C—H stretching) and 925 $cm^{-1}$ (C—O stretching).

The mass spectrum (Fig. 1) of noroxyhydrastinine was most informative showing the molecular ion peak at *m/e* 191 (measured 191·0578 and calculated as 191·0582 for $C_{10}H_9NO_3$). The base peak was at *m/e* 134 and other intense peaks were found at *m/e* 162, 104, 76, and 43. A rationalization of the fragmentation pattern was developed by considering the other spectral evidence and the metastable ion peaks. The peak at *m/e* 43 (CONH) was consistent with the cyclic amide structure. Two other possible structures in which the methylenedioxy group position is changed could be proposed from this data.

FRAGMENTATION OF NOROXYHYDRASTININE




| Metastable Ions | Observed (m/e) | Calculated (m/e) |
|---|---|---|
| 1 | 137.4 | 137.4 |
| 2 | 110.8 | 110.9 |
| 3 | 80.7 | 80.7 |
| 4 | 55.6 | 55.5 |

A direct comparison of the isolated compound with noroxyhydrastinine prepared by the procedure of Perkin[7] from berberine chloride (III, X = Cl) showed the two to have the same IR and UV spectra and m.p. No m.p. depression was observed when a mixture melting point determination was made.

The second alkaloid, thalifoline (II), crystallized as colorless rods, m.p. 210–211° from methanol and exhibited a UV spectrum, $\lambda_{max}$ 302 mμ (log ε 3·77), 261 (3·87), 223·5 (4·41). A marked bathochromic shift was observed in the presence of 0·01N

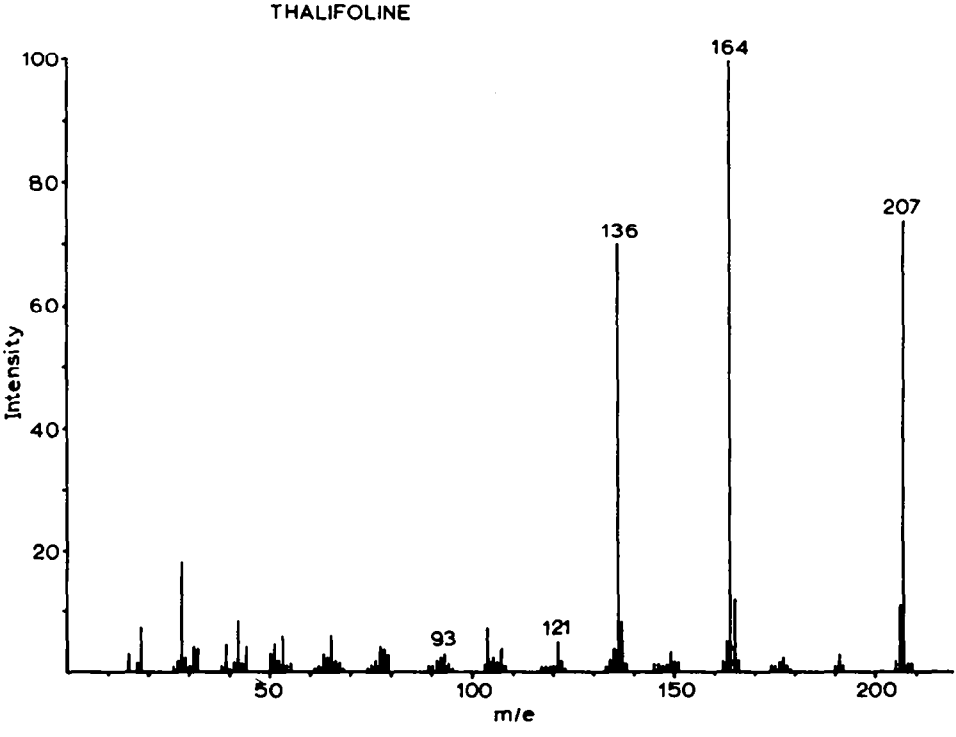
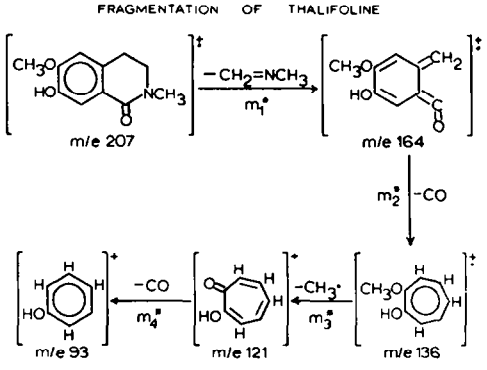



FIG. 2

methanolic KOH; $\lambda_{max}$ 330 mμ (log ε 3·65), 270 (3·73), 238 (4·40), but strong acid had no effect. The very close similarity of the UV absorption spectrum to noroxyhydrastinine suggested a structural analogue possessing a phenolic function. The IR absorption spectrum showed a broad band centered at $\nu_{KBr}$ 3150 $cm^{-1}$ (OH stretching) and a strong sharp band at 1640 $cm^{-1}$ (tertiary δ-lactam). The NMR sepctrum of thalifoline taken with the aid of a time averaging computer exhibited one N-Me peak at 3·27 δ, one O-Me peak at 4·03 δ and two one-proton singlets at 6·63 and 7·68 δ. The latter two peaks were assigned to *para* position aromatic protons because of the absence of any observed spin coupling.

The mass spectrum (Fig. 2) of thalifoline gave a molecular ion peak at *m/e* 207 (measured 207·0885 and calculated 207·0895 for $C_{11}H_{13}NO_3$) with the base peak at *m/e* 164. A rationalization of the fragmentation pattern was aided by the metastable ion peaks together with the other spectral data and resulted in II as a possible structure for thalifoline. The other possibility in which the methoxy and phenolic group is interchanged could not be ruled out. Lack of a sufficient supply of thalifoline prevented a chemical solution of this problem. Consequently, the synthesis of structure II and its direct comparison with the natural product was required for final proof of structure.

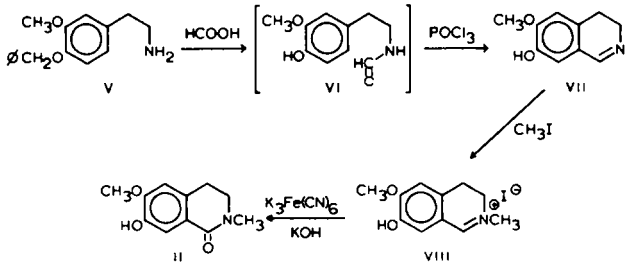
FRAGMENTATION OF THALIFOLINE



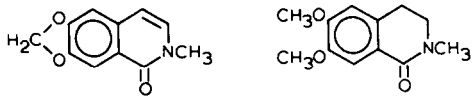

| Metastable Ions | Observed (m/e) | Calculated (m/e) |
|---|---|---|
| 1 | 129·9 | 129·9 |
| 2 | 112·8 | 112·8 |
| 3 | 107·7 | 107·7 |
| 4 | 71·5 | 71·5 |

A seven step synthesis of compound II was developed beginning with vanillin which was converted to 3-methoxy-4-benzyloxy-β-phenethylamine[9] (V) via O-benzylvanillin[10] and 3-methoxy-4-benzyloxy-β-nitrostyrene[11] by known methods. The N-formyl derivative VI prepared by refluxing compound V in formic acid was not isolated but directly subjected to the Bischler–Napieralski reaction to give 6-methoxy-7-hydroxy-3,4-dihydroisoquinoline (VII). The reaction conditions were based on the procedures by Gulland and Virden[12] for a closely related substance, 6-methoxy-3,4-dihydroisoquinoline. The methiodide salt (VIII) of compound VII was converted to 2-methyl-6-methoxy-7-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline (II) by oxidation with alkaline potassium ferricyanide. The synthetic product (II) gave IR and UV spectra indistinguishable from that of the natural product thalifoline. In addition

there was no depression of the m.p. when the two were admixed, confirming the identity of compound II and thalifoline.




The discovery of noroxyhydrastinine (I) and thalifoline (II) in *Thalictrum minus* L. var. *adiantifolium* Hort. adds another class of alkaloids to the variety already elaborated by the genus *Thalictrum*. Two other substances closely related to the isoquinolones reported here are doryanine (IX)[13] isolated from *Doryphora sassafras* Endlicher (*Monimiaceae*) and N-methyl-6,7-dimethoxyisoquinolone (X)[14] obtained from *Hernandia ovigera* L. (*Hernandiaceae*). Since these compounds are minor constituents in sources that produce alkaloids derived from benzyltetrahydroisoquinoline units, their origin is most likely a result of biochemical oxidation of these major products. Indirect support for this hypothesis is available from the presence of hernandaline and compound X in the same plant and possibly resulting from the oxidation of the dimeric benzylisoquinolineaporphine dimer, thalicarpine[6] known to occur in the same species.[15] It should not be surprising, therefore, if alkaloids bearing the noroxyhydrastinine and thalifoline moities are later found to be present in *T. minus* var. *adiantifolium*.




## EXPERIMENTAL

IR spectra were taken in $CHCl_3$ soln (8–10%) or in a KBr pellet on a Perkin–Elmer Infracord Model 237. UV spectra were recorded in MeOH on a Cary Model 15 spectrophotometer. NMR spectra were obtained in $CDCl_3$ with TMS = O as internal standard and signals reported in $\delta$ units using a Varian A-60A spectrometer with a C-1024 time averaging computer. Mass spectra were recorded on an AEI MS9 double focusing instrument using a direct inlet system at an ionizing energy of 70 eV. M.ps were determined on a Fisher–Johns hot stage and were uncorrected. Microanalyses were by Mr. J. F. Alicino, Metuchen, N.J.

*Isolation of alkaloids.* A detailed isolation method for I and II will be presented in a separate paper along with the other alkaloids from *T. minus* var. *adiantifolium*. Briefly, the residue obtained from EtOH extraction of 34 Kg of dried powdered roots was separated into tertiary phenolic, tertiary nonphenolic and quaternary alkaloid fractions. Noroxyhydrastinine was obtained from the tertiary nonphenolic fraction after chromatography on alumina, while thalifoline came from the tertiary phenolic fraction after separation on silicic acid.

*Noroxyhydrastinine* (I). The crude column fraction obtained by elution with $CHCl_3$ yielded 3·7 mg of pale yellow rosettes of crystals (MeOH) m.p. 182–183° and a UV spectrum with $\lambda_{max}$ 304 mμ (log ε 3·67), 261 (3·58), 222·5 (4·31) and no shift on addition of acid or base. The IR spectrum in KBr showed $\nu_{max}$ 3175

and 3040 $cm^{-1}$ (N—H), 1670 $cm^{-1}$ ($\delta$-lactam C=O) and 925 $cm^{-1}$ ($OCH_2O$). The mass spectrum (Fig. 1) with $M^+$ peak at *m/e* 191 was measured 191·0578 and calculated at 191·0582 for $C_{10}H_9NO_3$.

*Thalifoline* (II). The 2% MeOH in $CHCl_3$ effluent fraction from chromatography of the tertiary phenolic alkaloids on silicic acid yielded 5·2 mg of colorless rods (MeOH), m.p. 210–211°. The UV spectrum exhibited $\lambda_{max}$ 302 mμ (log ε 3·77), 261 (3·87), 223·5 (4·41) and a bathochromic shift in 0·01N methanolic KOH to $\lambda_{max}$ 330 mμ (log ε 3·65), 270 (3·73), 238 (4·40). The IR spectrum showed a peak at $\nu_{max}$ 1640 $cm^{-1}$ (N-substituted $\delta$-lactam) and the NMR spectrum (140 scans) gave peaks at 3·27 ($NCH_3$), 4·03 ($OCH_3$) and two aromatic protons at 6·63 and 7·68 $\delta$. The mass spectrum (Fig. 2) with $M^+$ peak at *m/e* 207 was measured 207·0885 and calculated at 207·0895 for $C_{11}H_{13}NO_3$.

*Preparation of noroxyhydrastinine* (I). Oxidation of III (X = Cl) with alkaline $KMnO_4$ and the subsequent isolation procedure was performed according to Perkin.[7] The crystalline product m.p. 180–183° (MeOH), lit. 181–182° was undepressed when admixed with the isolated natural product and the UV and IR spectra were essentially identical. The NMR spectrum exhibited peaks at 6·02 (2H, $OCH_2O$), 6·69 (1H, Ar), 7·58 (1H, Ar) and a pair of triplets centered at 2·88 (2H) and 3·53 $\delta$ (2H) with $J$ = 7 c/s for —$CH_2CH_2$—.

*6-Methoxy-7-hydroxy-3,4-dihydroisoquinoline* (VII). Compound V[9] (10 gm) was refluxed with 10 ml 98% formic acid for 10 hr. The cooled reaction mixture was poured cautiously into 20 ml cold water and the resulting two phase mixture shaken 5 times with benzene. The dried ($Na_2SO_4$) benzene extract left a brown oil (16·6 gm) of crude VI after removal of solvent *in vacuo* at 40°.

While cooling in ice 25 ml of $POCl_3$ was added dropwise to VI and then the mixture refluxed for 45 min. Pet. ether (b.p. 30–60°, 50 ml) was added to the ice cold mixture, decanted and followed carefully by 50 ml of 10% HCl. The resulting soln was treated with conc. $NH_4OH$ to pH 7 shaken twice with benzene (100 ml) and the extraction procedure repeated at pH 8 and 9. The pooled and dried ($Na_2SO_4$) benzene extract on removal of solvent *in vacuo* at 40° left a crystalline mass (2·0 gm). Recrystallization from MeOH and then acetone gave long colorless needles of VII, m.p. 183·5–185°; IR, $\nu_{max}$ 3540 (OH) and 1635 $cm^{-1}$ (C=N). NMR spectrum showed peaks at 3·93 $\delta$ (3H, $OCH_3$) and two aromatic protons at 6·69 (s) and 6·90 (s). (Found: C, 67·6; H, 6·1; N, 7·8. $C_{10}H_{11}NO_2$ requires: C, 67·8; H, 6·3; N, 7·9%).

*6-Methoxy-7-hydroxy-3,4-dihydroisoquinoline methiodide* (VIII). Compound VII (300 mg) in 50 ml of warm acetone was treated with 0·8 ml MeI. Almost immediately a copious yellow ppt formed. After cooling in the freezer, the ppt was collected and washed with ether leaving 423 mg of the yellow crystalline VIII. An analytical sample, m.p. 211–212·5° was crystallized from MeOH. (Found: C, 41·5; H, 4·5; N, 4·3. $C_{11}H_{14}NO_2I$ requires: C, 41·4; H, 4·4; N, 4·4%).

*2-Methyl-6-methoxy-7-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline* (II). Compound VIII (289 mg) in 5 ml water was added dropwise over 30 min to 10 ml 10% KOH aq containing 1·54 gm $K_3Fe(CN)_6$ while cooling at 5–10°. Stirring in the cold continued another 30 min and after warming to room temp glacial AcOH was added to pH 5–6. The soln was extracted 5 times with ether (100 ml each time), pooled, dried ($Na_2SO_4$) and evaporated *in vacuo* to leave a yellow oil which formed feathery crystals (82 mg). Recrystallization from $CHCl_3$–pet. ether (b.p. 60–70°) gave a product, m.p. 208–211° having IR and UV spectra identical to that of II. A mixture m.p. of the two was undepressed.

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