ALKALOIDS OF THALICTRUM XXXV.[1] NORTHALICARPINE, A NEW APORPHINE–BENZYLISOQUINOLINE DIMER, *N*-METHYLLAUROTETANINE AND THALFLAVIDINE FROM THE ROOTS OF *THALICTRUM REVOLUTUM*

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ABSTRACT.—Three alkaloids, northalicarpine (**1**), thalflavidine (**4**) and *N*-methyllaurotetanine (**5**) were isolated from the roots of *T. revolutum*. Northalicarpine (**1**), a new natural product, was characterized from spectral data and by conversion to thalicarpine (**2**). The location of the *N*-desmethyl position was proved by isolation of the phenolic isoquinoline base **3** after Na/NH_3 cleavage. Thalflavidine (**4**) and *N*-methyllaurotetanine (**5**) were identified from analysis of spectral data.

The plant *Thalictrum revolutum* DC (Ranunculaceae) has already yielded over 40 different alkaloids from all parts including roots, above-ground portion and fruit (see reference 1 and others therein). Additional plant material was extracted and the alkaloid fractions prepared, from which two compounds were isolated; both are new to this source and one is a new natural product.

The ether-soluble nonphenolic tertiary alkaloid fraction after chromatography on two columns yielded an amorphous but homogeneous base, northalicarpine, named, as will be shown, on the basis of its relationship to thalicarpine (**2**). Northalicarpine (**1**) exhibited an nmr spectrum with peaks for seven methoxyls and a down-field one-proton singlet at δ 8.26, characteristic of protons of C–11 of aporphines, along with six other aromatic protons, which immediately suggested it belonged to the aporphine-benzylisoquinoline dimers (2). The uv spectrum with absorption greater than 300 nm was suggestive of an aporphine moiety. That this alkaloid was not previously known was evidenced by the presence of only one *N*-methyl group from the nmr spectrum; all previously known examples contain two *N*-methyls (2). The mass spectrum with a weak but observable molecular ion at *m/e* 682 corresponded to formula $C_{40}H_{46}N_2O_8$, of which one of the oxygens was present as a diphenyl ether. The ir spectrum lacked hydroxyl absorption and the uv spectrum was unaffected by acid or base, thereby eliminating the presence of an alcoholic or phenolic group.

N-methylation of northalicarpine with formaldehyde and sodium borohydride gave thalicarpine (**2**) (3) identical by direct comparison of physical properties, including the cd spectrum (4), with those of a known sample. Thus, the only uncertainty remaining about northalicarpine was the location of the unmethylated nitrogen. The mass spectrum provided an indication by the presence of a very intense peak at *m/e* 192 which could be assigned to the fragment **1a** ($C_{11}H_{14}NO_2$), thereby locating the isoquinoline nitrogen as lacking the methyl. Cleavage of northalicarpine (**1**) with sodium/ammonia produced a phenolic base whose spectral properties agreed with 2'-hydroxy-4',5',6,7-tetramethoxybenzyltetrahydroisoquinoline (**3**) and confirmed the structure of northalicarpine as suggested by the mass spectrum. Northalicarpine (**1**) is, therefore, the first discovered *N*-desmethyl aporphine-benzylisoquinoline alkaloid.

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[1]For paper XXXIV see W.-N. Wu, W.-t. Liao, Z. F. Mahmoud, J. L. Beal and R. W. Doskotch ,*J. Nat. Prod.*, **43**, 472 (1980).

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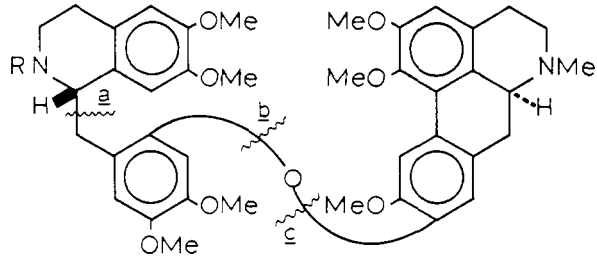
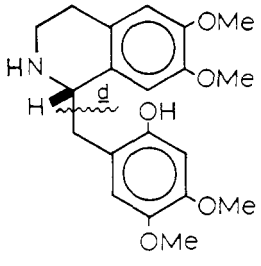
Thalflavidine (**4**), a phenanthrene alkaloid, was characterized on the basis of its spectral characteristics, in particular, the nmr spectrum which showed the presence of two *N*-methyls, two *O*-methyls, one methylenedioxy, three aromatic protons (one as a singlet and the other two as an AB quartet) and four methylene protons. The ir spectrum contained a carbonyl peak and the uv spectrum exhibited absorption beyond that of a simple benzenoid system, suggesting extended



1; R = H

2; R = Me



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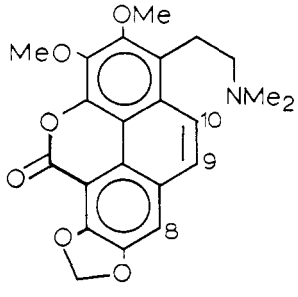

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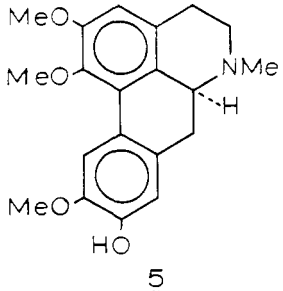

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conjugation as in polynuclear aromatics. The literature has recorded the properties of thalflavidine (**4**) from *T. flavum* L. (5), which are comparable to the alkaloid reported here. On that basis the structure has been accepted for our compound. *T. revolutum* is only the second reported source for thalflavidine.

N-Methyllaurotetanine (**5**), already reported from the tops of *T. revolutum* (6), was obtained from the ether-soluble phenolic alkaloid fraction and was identified by direct comparison of physical data with those from a known sample.

EXPERIMENTAL[3]

PLANT MATERIAL.—The roots of *Thalictrum revolutum* DC were harvested during the summers of 1974 and 1975 from two-year-old plants grown in the Ohio State University Medicinal Plant Garden from seeds obtained from Mr. Lloyd Spetzman, Botanist, of the U.S. Department of Agriculture. Voucher specimens are on file. The plant material was dried in a forced draft oven at 40° and powdered in a Wiley Mill.

EXTRACTION AND INITIAL ISOLATION PROCEDURE.—The powdered roots (8.6 kg) were percolated with ethanol at room temperature to exhaustion and the extract evaporated at reduced pressure to give 1 kg of residue. The residue was partitioned between 15 liters each of 2% aq. citric acid and chloroform, and the alkaloids contained in the citric acid solution were divided into the ether-soluble tertiary phenolic alkaloids (5.4 g), the ether-soluble tertiary nonphenolic alkaloids (29.3 g) and the chloroform-soluble tertiary alkaloids (2.4 g) by the procedure given in reference 7.

CHROMATOGRAPHY OF THE ETHER-SOLUBLE TERTIARY NONPHENOLIC ALKALOIDS.—The nonphenolic bases (29 g) were dissolved in a minimal volume of chloroform and added to a column of silica gel (900 g). Elution was accomplished with chloroform (2 liters) and mixtures of methanol in chloroform, 1% (11 liters), 2.5 (8), 5 (8), 10 (6), 20 (6) and 40 (2), then methanol (2 liters) and 5% HCl in methanol (2 liters). Effluent fractions of 500 ml were collected and evaporated and the residues were weighed and analyzed by tlc.

NORTHALICARPINE (**1**).—The residue (1.3 g) from fractions 53-55 of the ether-soluble tertiary nonphenolic alkaloids was rechromatographed on 65 g of neutral alumina with benzene (100 ml), benzene-chloroform (1:1, 600 ml), chloroform (800 ml) and 1% methanol in chloroform (250 ml) as eluents. The benzene-chloroform (1:1) effluent gave 1 g of thalrugosaminine first, followed by thaliglucinone (35 mg) in the early chloroform eluate: both alkaloids were previously reported from *T. revolutum* roots (8).

The late chloroform effluent afforded 72 mg of northalicarpine (**1**) as an amorphous solid: R_f 0.21 on tlc with silica gel G with benzene-acetone-ammonium hydroxide solution (10:10:0.3); $[\alpha]^{21}D$ +108° (*c* 0.25, MeOH; cd (C 4.4 x 10^{-3}M, MeOH) $[\theta]_{350}$ 0, $[\theta]_{304}$ −16,000, $[\theta]_{280}$ (min) −8,000, $[\theta]_{276}$ −25,000, $[\theta]_{256}$ 0, $[\theta]_{235}$ −171,000 and $[\theta]_{220}$ 0: uv λ max 314 nm (shld, log ε 3.97), 303 (shld, 4.08), and 282 (4.21) with no change with acid or base; ir ν max ($CHCl_3$) 3002, 2940, 2860, 2840, 2800, 1620, 1602, 1580, 1500, 1465, 1400, 1380, 1360, 1325, 1270, 1170, 1150, 1085, 1005, 880 and 850 cm^{-1}; nmr (60 MHz, $CDCl_3$) δ 2.50 (s, NMe), 3.72, 3.76, 3.83, 3.86, 3.93 (double intensity) and 3.95 (6s, 7 OMe), 6.61, 6.66 (quadruple intensity), 6.92 and 8.26 (H-11) (4s, 7 ArH); and ms *m/e* 682 (0.4%, M^+, $C_{40}H_{46}N_2O_8$), 490 (4, M-*a*), 341 (11, M-*b*+1), 340 (2, M-b), 325 (2, M-*c*+1), 324 (1, M-*c*), 206 (69), 192 (100, *a*), 177 (3), 176 (10) and 148 (5).

N-METHYLATION OF NORTHALICARPINE (**1**).—To 20 mg of northalicarpine (**1**) was added 2 ml of formaldehyde reagent (1 ml of 37% H_2CO in 100 ml MeOH) and the mixture stirred 1 hr at ambient temperature, then 75 mg of $NaBH_4$ was added and stirring continued 1 hr more. The solvent was evaporated and the residue was dissolved in 3 ml of 5% NaOH solution, then treated with excess NH_4Cl and extracted with ether (125 ml). The washed (H_2O) and dried (Na_2SO_4) ether extract, on evaporation, left 21 mg of solid that was purified on 2 g of neutral alumina (activity 1) with 50 ml each of benzene, benzene-chloroform and chloroform as eluents. The benzene-chloroform effluent gave 12 mg of the *N*-methylated product identified as thalicarpine (**2**) by direct comparison of physical data (tlc, uv, ir, nmr and cd) with those of a known sample from our collection (8).

Na/NH_3 CLEAVAGE OF NORTHALICARPINE (**1**).—Liquid NH_3 (10 ml) was condensed at −50° (dry ice-acetone) into a 100 ml 3-necked round-bottom flask fitted with a pressure-equalizing dropping funnel, a N_2 inlet tube, a Dewar-type condenser, and a magnetic stirrer. Na metal was added in finely divided form till a blue color persisted for 0.5 hr, requiring 100 mg, then 40 mg of northalicarpine (**1**) in 5 ml of dry tetrahydrofuran was added dropwise within 1 hr, and the reaction was allowed to proceed for an additional 2 hr. Excess NH_3 was evaporated at ambient temperature, and excess methanol was added to destroy any unreacted Na. After concentration of the reaction mixture to a few ml by evaporation, the contents were partitioned between 250 ml of 5% aq. NaOH and 150 ml of ether. The ether phase contained the nonphenolic products, and the aqueous phase was treated with excess NH_4Cl and extracted with ether to remove the phenolic products. The second ether extract was washed with water dried (Na_2SO_4) and evaporated to give 7 mg of a pale yellow solid. Chromatography on 1 g of silica gel with chloroform (10 ml), 1% (25 ml), 2% (25 ml) and 3% methanol in chloroform (10 ml) gave from the 2% methanl in chloroform effluent, 2.5 mg of the homogeneous but amorphous base, 2'-hydroxy-4',5',6,7-tetramethoxybenzyltetrahydroisoquinoline (**3**): R_f 0.52 on tlc with silica gel G and benzene-acetone-ammonium hydroxide solution (10:10:0.3); nmr (90 MHz,

[3]For reagents, instruments and conditions used see paper XXXIII, W.-N. Wu, J. L. Beal and R. W. Doskotch, *J. Nat. Prod.*, **43**, 372 (1980).

$CDCl_3$) 2.72–3.42 (m, 6H, CH_2), 4.24–4.34 (d, H-1), 3.79, 3.81, 3.83 and 3.88 (4s, 4 OMe), 6.54 (s, 2H, H-5 and H-8), 6.47 and 6.64 (2s, H-3' and H-6'); and ms *m/e* 359 (1%, M^-, $C_{20}H_{25}NO_5$), 192 (100, *d*), 177 (3), 176 (5) and 167 (3, M-*d*).

The ether extract containing the nonphenolic products left a residue of 5 mg from which no pure constituent could be isolated.

CHROMATOGRAPHY OF THE ETHER-SOLUBLE PHENOLIC ALKALOIDS.—The phenolic bases (5.4 g) were chromatographed on 270 g of silica gel with chloroform (0.5 liter), 2.5% (2 liters), 5% (4 liters) and 10% methanol in chloroform as eluents. Effluent fractions of 10 ml were collected and handled as described for the nonphenolic alkaloids. From column fractions 23–25 was obtained, after rechromatography on silica gel, 20 mg of *N*-methyllaurotetanine (**5**), which was previously isolated from the tops (6). Identification was by comparison of physical data (tlc, uv, ir, nmr and cd) with those of an authentic sample.

THALFLAVIDINE (**4**).—The residue (1.3 g) from column fractions 27–46 of the ether-soluble phenolic alkaloids was chromatographed on 70 g of neutral alumina with $CHCl_3$ (1 liter), 1% (0.5 liter) and 2% methanol in chloroform as eluents. The early chloroform effluent gave a residue (10 mg) that from methanol afforded crystalline thalflavidine (**4**): mp 229–230° [lit. (5) mp 219–220°]; R_f 0.5 on tlc with silica gel and benzene-acetone-ammonium hydroxide solution (10:10:0.3); uv λ max 394 nm (log ϵ 3.92), 382 (3.91) and 295 (4.14) with no shift in 0.01N NaOH or HCl; ir ($CHCl_3$) ν max 1735 cm^{-1} (C=O); nmr (90 MHz, $CDCl_3$) δ 2.41 (s, NMe_2), 2.60, 3.30 (2m, 4H, CH_2), 4.05, 4.15 (2s, 2 OMe), 6.38 (s, OCH_2O), 7.57 (s, H-8), 7.69 and 7.92 (ABq, *J* 9.5, H-9 and H-10); and ms *m/e* 395 (85% M^+, $C_{22}H_{21}NO_6$), 364 (2, M–OMe), 351 (8, M–CO_2), 337 (13, M–CH_2NMe_2), 322 (8), 293 (5), 279 (10) and 58 (100, CH_2NMe_2). Identification was by interpretation of spectral characteristics and comparison with published values (5).

The later chloroform effluent gave 300 mg of thalirevoline, already reported from this plant (9). Identity was established by direct comparison with a known sample.

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