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ALKALOIDS OF JORDANIAN *THALICTRUM ISOPYROIDES*

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Key Word Index—*Thalictrum isopyroides*; Ranunculaceae; roots; aporphine alkaloids; dehydroaporphine alkaloids; oxoaporphine alkaloids; bisbenzylisoquinoline alkaloids.

Abstract—The isolation and identification of 12 alkaloids from an extract of the roots of *Thalictrum isopyroides* is described. The alkaloids isolated are the aporphines ocoteine (thalicmine), thaliporphine, preocoteine, *N*-methyllaurotetanine, delporphine, isoboldine, *N*-methylcassythine and magnoflorine, the dehydroaporphine, dehydroocoteine, the oxoaporphine, thalicminine, and the bisbenzylisoquinolines, thaligosinine and thalisopidine.

INTRODUCTION

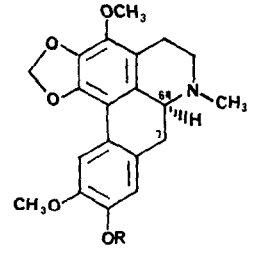
Thalictrum isopyroides (Ranunculaceae) is a perennial herb indigenous to temperate zones of the Soviet Union and the Middle East [1]. Extracts of the plant have been demonstrated to contain alkaloids which possess widely varying pharmacologic activities in different animals, including antiepileptic and sedative properties [2], plus hypotensive, skeletal muscle relaxant and uterotonic effects [3].

Although there are numerous references to the isolation and identification of various *Thalictrum* alkaloids [4–6], the alkaloids of *T. isopyroides* have not been exhaustively studied. In fact, all literature references to this species are concerned with the isolation, identification and pharmacology of alkaloids from *T. isopyroides* indigenous to various regions of the Soviet Union. To date, at least nine monomeric alkaloids and two dimeric alkaloids have been isolated from Soviet *T. isopyroides* including the isoquinolone, 6,7-dimethoxy-2-methyl-1,2-dihydroisoquinolin-1-one [7], the protoberberine, berberine [1], the protopine, cryptopine [8], the aporphines, ocoteine (thalicmine) [8], cabudine [9], thalisopynine (thalisopinine) [7] and magnoflorine [1], the dehydroaporphine, dehydroocoteine (dehydrothalicmine) [10], the oxoaporphine, thalicminine [8], and the bisbenzylisoquinolines, thalisopine [8] and thalisopidine [8].

This paper reports the isolation of 12 alkaloids from an extract of the roots of *T. isopyroides* indigenous to Southern Jordan. These alkaloids include the aporphines ocoteine (thalicmine, **1**), thaliporphine (**2**), preocoteine (**3**), *N*-methyllaurotetanine (**4**), delporphine (**5**), isoboldine (**6**), *N*-methylcassythine (**7**) and magnoflorine (**8**), the dehydroaporphine, dehydroocoteine (**9**), the oxoaporphine, thalicminine (**10**) and the bisbenzylisoquinolines, thaligosinine (**11**) and thalisopidine (**12**).

RESULTS AND DISCUSSION

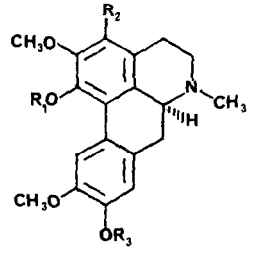
Roots of *T. isopyroides* from Jordan were dried, ground and extracted with ethanol. The extract was evaporated and the resulting residue stirred with tartaric acid solution and filtered. The insoluble residue was treated with ether, filtered and the filtrate partitioned with tartaric acid solution. The two tartaric acid solutions were combined, alkalinized with ammonium hydroxide and extracted first with ether (fraction A) and subsequently with chloroform (fraction B). Fractions A and B were combined because of



1 R=CH_3

7 R=H

9 R=CH_3, 6a,7-dehydro-



2 R_1=R_2=H, R_3=CH_3

3 R_1=H, R_2=OCH_3, R_3=CH_3

4 R_1=CH_3, R_2=R_3=H

5 R_1=CH_3, R_2=OH, R_3=H

6 R_1=R_2=R_3=H

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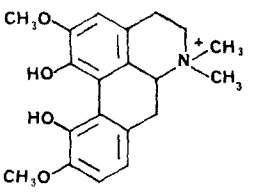
similar TLC behavior and the phenolic alkaloids (fraction C) separated from the nonphenolic alkaloids (fraction D) using well-established procedures [11]. Chromatography of the nonphenolic alkaloid fraction (fraction D) over silicic acid in petrol–chloroform (1:1) and elution with the same solvent afforded ocoteine (thalicmine, **1**), dehydroocoteine (**9**), thaliporphine (**2**) and thalicminine (**10**), while elution with chloroform gave thaligosinine (**11**). Ocoteine (**1**) was first isolated from *Ocotea puberula* (Lauraceae) in 1951 [12]. However, it was also isolated from *T. minus* about the same time and was named thalicmine [13]. Ocoteine was previously isolated from Soviet *T. isopyroides* [8] as well as other *Thalictrum* species including *T. fendleri* [14], *T. simplex* [15] and *T. strictum* [16]. The alkaloid is also known to occur in certain species of the genera *Cassytha*, *Nectandra* and *Phoebe* in the Lauraceae [17–19]. Ocoteine has been observed to act as a muscle relaxant [20], hypotensive [20, 21], antitussive [21] and hyperglycemic [22] in various animals. Dehydroocoteine (dehydrothalicmine, **9**) was first isolated from *T. isopyroides* in 1971 [10] and shortly thereafter from *Nectandra* and *Ocotea* species of the Lauraceae [17]. Dehydroocoteine has not been reported since then in any other plant nor other species of *Thalictrum* and was the first dehydroaporphine alkaloid reported in the genus *Thalictrum* [17–19]. Thaliporphine (**2**) was first isolated from *T. minus* in 1950 at which time it was called thalicmidine [13]. The same alkaloid was isolated in 1967 from *T. fendleri* and named thaliporphine [24, 25]. Since the structure of thalicmidine had not been unequivocally determined while that of thaliporphine had [24], the name thaliporphine was retained. Thaliporphine has also been isolated from *T. alpinum* [11] and *T. foetidum* [26] plus selected genera in the families Annonaceae [18, 19], Berberidaceae [18, 19], Euphorbiaceae [19], Fumariaceae [19], Lauraceae [17, 19], Magnoliaceae [18], Papaveraceae [17, 19] and Rutaceae [17]. Parenteral administration of thaliporphine to various animals produced respiratory disturbances and convulsions while the methiodide salt evoked a hypotensive response [27]. Thalicminine (**10**) was first isolated from *T. minus* in 1966 [28] and was subsequently isolated from *T. dioicum* [19], *T. isopyroides* [8], *T. simplex* [29] and *T. strictum* [30] as well as *Ocotea puberula* (Lauraceae) [17]. Thalicminine (**10**) produced respiratory stimulation and a brief hypotensive effect in animals at low doses while a higher dosage prolonged the hypnotic effect of chloral hydrate [31]. Thaligosinine (**11**) was first isolated from *T. rugosum* in 1978 [32] and this is only the second reported isolation of this alkaloid from nature. Thaligosinine was found to inhibit the growth of *Staphylococcus aureus* and *Mycobacterium smegmatis* in a standarized *in vitro* antimicrobial test [33].



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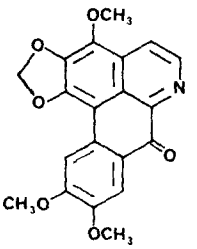

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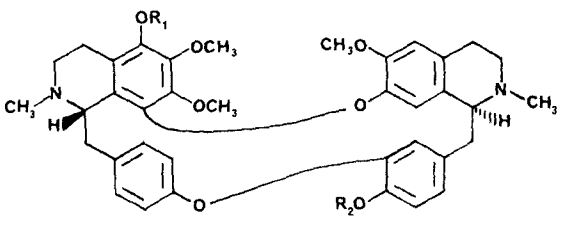

11 R_1=CH_3, R_2=H

12 R_1=R_2=H

13 R_1=R_2=CH_3

Chromatography of the phenolic alkaloid fraction (fraction C) over silicic acid in chloroform and elution with the same solvent afforded preocoteine (**3**), *N*-methyllaurotetanine (**4**), delporphine (**5**), isoboldine (**6**) and *N*-methylcassythine (**7**). Elution with chloroform–methanol (49:1) then gave thalisopidine (**12**). Preocoteine (**3**) was first isolated from *T. fendleri* in 1967 [24, 25] and subsequently from *T. strictum* some 10 years later [16]. It has not been isolated from any other species outside of the genus *Thalictrum* to date. *N*-Methyllaurotetanine (**4**) was first isolated from *Litsea citrata* (Lauraceae) in 1933 [23] and first reported as an alkaloid of *Thalictrum* species when it was isolated from *T. revolutum* in 1977 [34]. The alkaloid was subsequently isolated from *T. dioicum* [35] and *T. revolutum* [36] and is a constituent of numerous genera of the families Annonaceae [18, 19], Hernandiaceae [17, 19], Lauraceae [17, 19] Magnoliaceae [17, 18], Menispermaceae [19], Monimiaceae [17, 19], Papaveraceae [17, 19], Ranunculaceae [18] and Rhamnaceae [17]. Delporphine (**5**) was first isolated from *Delphinium dictyocarpum* (Ranunculaceae) in 1978 [37] and this is only the second reported occurrence of this alkaloid in nature. Isoboldine (**6**) was first reported as a constituent of *Nandina domestica* (Berberidaceae) in 1962 [17] and first found in the genus *Thalictrum* in *T. alpinum* in 1980 [11]. It has also been isolated from *T. foetidum* [26] and from numerous genera of the families Annonaceae [17–19], Berberidaceae [17], Hernandiaceae [19], Lauraceae [17–19], Leguminosae [17], Menispermaceae [17, 19], Monimiaceae [17, 19], Papaveraceae [17–19], Ranunculaceae [10], Rhamnaceae [18] and Symplocaceae [17]. *N*-Methylcassythine (**7**) was first described in the literature as a methylation product of cassythine [38] and to our knowledge, this is the first reported isolation of *N*-methylcassythine as a naturally occurring alkaloid. Thalisopidine (**12**) was first isolated from *T. isopyroides* in 1968 [8] and has not been isolated from any other plant to date.

The ammoniacal solution from which fractions A and B were removed was acidified to pH 3–4 with hydrochloric acid and ammonium reineckate solution added until

precipitation ceased. The precipitate was filtered by suction, washed with water, dissolved in methanol and passed through a column of anion exchange resin (chloride form). The column was rinsed with methanol and the eluent and rinsings combined and evaporated to afford a residue of crude quaternary alkaloid chlorides (fraction E). Chromatography of the crude quaternary alkaloid chlorides (fraction E) over silicic acid in chloroform and elution with chloroform–methanol (85:15) afforded magnoflorine chloride. Magnoflorine (**8**) has been isolated from at least twenty-five different species of the genus *Thalictrum* [17–19] as well as from *T. isopyroides* [1]. Other plant families that have served as a source of magnoflorine include the Annonaceae, Aristolochiaceae, Berberidaceae, Euphorbiaceae, Magnoliaceae, Papaveraceae, Ranunculaceae, Rhamnaceae and Rutaceae [17–19]. Magnoflorine was characterized pharmacologically as producing less curariform activity than roemerine (1,2-methylenedioxyaporphine) hydroxide and less hypotensive effects than *O*-methylisocorydine methiodide [39].

The limited distribution of many of the alkaloids described in this paper is of chemotaxonomic significance. In addition, the pharmacological activity of a number of these alkaloids may account for the use of species of the genus *Thalictrum* as indigenous medicinals.

EXPERIMENTAL

General. Mps are uncorr. UV spectra were obtained in MeOH and IR spectra in KBr pellets. ^{1}H NMR spectra were recorded at 60 MHz or 90 MHz in $CDCl_3$ with TMS as int. std; chemical shifts are reported in δ (ppm) units. Low-resolution MS were recorded on a quadrapole instrument. Silicic acid (100 mesh) (Mallinckrodt) was used for CC while silica gel (HF_{254}, Merck) was used for TLC. Alkaloids were visualized by spraying with Dragendorff reagent [40]. Dry Na_2SO_4 was routinely used for drying solvents and all solvents were evapd under red. pres. at 40°.

Plant material used in this study was collected in the vicinity of Ros en Naqb, Jordan on April 20, 1982. A herbarium specimen has been deposited at the Department of Pharmacognosy, Faculty of Pharmacy, University of Jordan, Amman, Jordan.

Extraction and fractionation. Powdered, dried roots of *T. isopyroides* C.A.M. (2.27 kg) were extracted by percolation with EtOH (216 l.) and the solvent evapd to leave a residue (364 g). The residue was stirred with tartaric acid (1%) (4 l.) and filtered. The insoluble residue was treated with Et_2O (1 l.), filtered and the filtrate partitioned with tartaric acid (1%) (1 l.). The tartaric acid solns were combined, basified with NH_4OH to pH 8–9 and extracted first with Et_2O (5 l.) (× 3) to afford a brown oil (29.6 g) (fraction A) and then with $CHCl_3$ (5 l.) (× 3) to yield a dark brown oil (12.6 g) (fraction B). Fractions A and B were subsequently combined because of TLC similarity, dissolved in $CHCl_3$ (500 ml) and partitioned with NaOH (5%) (500 ml) (× 2). The alkaline soln was treated with solid NH_4Cl to pH 8–9 and partitioned with $CHCl_3$ (1 l.) (× 2). The $CHCl_3$ was evapd to an oily residue (7.3 g) (fraction C) of phenolic nonquaternary alkaloids. The $CHCl_3$ extract remaining from partitioning with NaOH was partitioned with H_2O (500 ml) (× 2) and evapd to a residue (24.9 g) (fraction D) of nonphenolic nonquaternary alkaloids.

Chromatography of fraction D. Fraction D was dissolved in petrol–$CHCl_3$ (1:1) (25 ml) and chromatographed over silicic acid (250 g) (column A) in the same solvent. Elution with petrol–$CHCl_3$ mixtures followed by $CHCl_3$ and $CHCl_3$–MeOH mixtures afforded various fractions which were collected (250 ml each) and combined according to TLC analysis (C_6H_6–MeOH–NH_4OH, 70:30:0.1).

Ocoteine (*thalicmine*, **1**). Elution of column A with petrol–$CHCl_3$ (1:1) (500 ml) afforded a solid residue (2 g) which, on treatment with MeOH, afforded ocoteine (thalicmine, **1**) as white rosettes (1.67 g), mp 140°; $[\alpha]_D^{23}$ +40° ($CHCl_3$; *c* 1.0), identical by direct comparison (UV, IR, ^{1}H NMR, MS, $[\alpha]_D$, mp) with an authentic sample and lit. data [17].

Dehydroocoteine (**9**). Continued elution of column A with petrol–$CHCl_3$ (1:1) (750 ml) afforded a solid residue (10.98 g). Chromatography of this residue over silicic acid (150 g) in petrol–$CHCl_3$ (2:1) and elution with the same solvent gave a residue (534 mg) which on treatment with MeOH furnished dehydroocoteine (**9**) as greenish-yellow needles (102 mg), mp 200–203°, identical by direct comparison (UV, IR ^{1}H NMR, MS, mp) with a sample prepared via the oxidation of ocoteine (**1**) in a standard fashion [41] and with lit. data [17].

Alkaloids A, B and C. Continued elution of column A with petrol–$CHCl_3$ (1:1) (500 ml) afforded a mixture of three incompletely characterized alkaloids, designated alkaloids A, B and C.

Thaliporphine (**2**). Continued elution of column A with petrol–$CHCl_3$ (1:1) (250 ml) yielded a residue (1.1 g), which on treatment with MeOH gave white needles of thaliporphine (**2**, 71 mg), mp 176–177°; $[\alpha]_D^{23}$ +44° ($CHCl_3$; *c* 1.0), identical by direct comparison (UV, IR, ^{1}H NMR, MS, $[\alpha]_D$, mp) with an authentic sample and lit. data [17].

Thalicminine (**10**). Continued elution of column A with petrol–$CHCl_3$ (1:1) (1.5 l.) afforded a dark orange residue (851 mg), which on treatment with MeOH gave thalicminine (**10**, 587 mg) as a red-orange needles, mp 275° dec., identical by comparison with lit. data (UV, IR, MS, mp) [17] and conversion to ocoteine (thalicmine, **1**) [28].

Thaligosinine (**11**). Elution of column A with $CHCl_3$ (500 ml) afforded a grey crystalline residue (3.21 g), which on treatment with MeOH yielded thaligosinine (**11**) (637 mg) as white needles, mp 233–234°; $[\alpha]_D^{23}$ −125° (MeOH; *c* 1.0); UV λ_{max}^{MeOH} nm (log ε): 283 (3.93) and 235 (sh) (4.44); IR ν_{max}^{KBr} cm^{-1}: 1510, 1460, 1420, 1365, 1355, 1325, 1290, 1275, 1255, 1215, 1170, 1120, 1060, 1040, 1030, 985, 970, 940, 885, 830 and 810; ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.49 (3H, *s*, NMe), 2.55 (3H, *s*, NMe), 3.04 (3H, *s*, OMe), 3.35 (3H, *s*, OMe), 3.78 (3H, *s*, OMe), 3.82 (3H, *s*, OMe), 6.38 (1ArH, *s*, H-8), 6.42 (1ArH, *s*, H-5) and 6.6–7.6 (7ArH, *m*); EIMS (probe) 70 eV *m/z* (rel. int.): 638 $[M]^+$ (3), 426 (15), 425 (25), 411 (23), 213 (100), 190 (21) and 174 (77); identical by comparison with lit. data (UV, ^{1}H NMR, MS, mp) [32] and conversion to thalrugosaminine (**13**) [42] via methylation with CH_2N_2 [43].

Chromatography of fraction C. Fraction C (7.3 g) was dissolved in petrol–$CHCl_3$ (1:3) (10 ml) and chromatographed over silicic acid (150 g) (column B) in the same solvent. Elution with petrol–$CHCl_3$ mixtures followed by $CHCl_3$ and $CHCl_3$–MeOH mixtures afforded various fractions which were collected (500 ml each) and combined according to TLC analysis (C_6H_6–MeOH–NH_4OH, 70:30:0.1).

Preocoteine (**3**). Elution of column B with $CHCl_3$ (1 l.) afforded a dark residue (130 mg) which on treatment with MeOH ultimately deposited preocoteine (**3**) (26 mg) as an amorphous base, darkening on exposure to air, $[\alpha]_D^{25}$ +16° (MeOH; *c* 1.1), identical by comparison (UV, IR, ^{1}H NMR) with authentic spectra [24, 25] and lit. data [17].

N-*Methyllaurotetaine* (**4**). Continued elution of column B with $CHCl_3$ (2 l.) yielded a residue (153 mg) which was rechromatographed over silicic acid (5 g) in petrol–$CHCl_3$ (3:1). Elution with the same solvent (25 ml) followed by $CHCl_3$ (25 ml) afforded a residue (79 mg), which on treatment with MeOH furnished white crystals of *N*-methyllaurotetanine (**4**, 17 mg), mp 235–236° (HBr salt) (Me_2CO); $[\alpha]_D^{23}$ +87° (MeOH; *c* 0.54), identical by direct

comparison (UV, IR, ^{1}H NMR, MS, $[\alpha]_D$, mp) with an authentic sample and lit. data [17].

Delporphine (**5**). Continued elution of column B with $CHCl_3$ (500 ml) afforded a residue (130 mg) which was rechromatographed over silicic acid (15 g) in petrol–$CHCl_3$ (1:1). Elution with petrol–$CHCl_3$ (1:2) (250 ml), (1:4) (250 ml), (1:7) (250 ml) and (1:9) (250 ml), followed by combination of these eluants yielded a residue (35 mg), which on treatment with MeOH furnished delporphine (**5**, 9 mg), mp 114–115°; $[\alpha]_D^{23}$ + 70° (MeOH; *c* 0.1); identical by comparison with lit. data (UV, ^{1}H NMR, MS, $[\alpha]_D$, mp) [18, 37, 44].

Isoboldine (**6**). Continued elution of column B with $CHCl_3$ (1.5 l.) yielded a residue (67 mg), which on treatment with MeOH afforded white crystals of isoboldine (**6**, 4 mg), mp 126–127°; $[\alpha]_D^{23}$ + 55° (EtOH; *c*, 0.2); identical by direct comparison (UV, IR, ^{1}H NMR, MS, $[\alpha]_D$, mp) with an authentic sample [45].

N-*Methylcassythine* (**7**). Continued elution of column B with $CHCl_3$ (1 l.) yielded a residue (23 mg), which on treatment with MeOH afforded *N*-methylcassythine (**7**, 19 mg) as white crystals, mp 215–216° (dec.); $[\alpha]_D^{23}$ + 23° ($CHCl_3$; *c* 0.3); identical by comparison with lit. data (UV, ^{1}H NMR, MS, $[\alpha]_D$, mp) and conversion to cassythine via treatment with HCHO–HCO_2H in the usual fashion [46].

Thalisopidine (**12**). Elution of column B with $CHCl_3$–MeOH (49:1) (1.5 l.) afforded a solid resiude which crystallized from MeOH as white needles of thalisopidine (**12**, 45 mg), mp 209–210°; $[\alpha]_D^{23}$ − 140° ($CHCl_3$; *c* 0.5) and $[\alpha]_D^{23}$ − 135° (EtOH; *c* 0.4) UV λ_{max}^{MeOH} nm (log ε); 285 (3.86) and 234 (sh) (4.25); IR ν_{max}^{KBr} cm^{-1}: 2940, 1605, 1590, 1505, 1460, 1430, 1370, 1325, 1285, 1275, 1255, 1215, 1205, 1165, 1115, 1090, 1025, 1000, 965, 950, 880 and 825; ^{1}H NMR (60 MHz, $CDCl_3$): δ2.49 (3H, *s*, NMe), 2.53 (3H, *s*, NMe), 3.03 (3H, *s*, OMe), 3.37 (3H, *s*, OMe), 3.76 (3H, *s*, OMe), 6.35 (1ArH, *s*, H-8), 6.42 (1ArH, *s*, H-5) and 6.58–7.3 (7ArH, *m*); EIMS (probe) 70 eV, *m/z* (rel. int.): 624 $[M]^+$ (1), 412 (4), 411 (4), 397 (5), 206 (66) and 174 (100); identical by comparison with lit. data (UV, ^{1}H NMR, MS, mp) [8] and conversion to thalrugosaminine (**13**) [42] via methylation with CH_2N_2 [43].

Magnoflorine (**8**). The alkaline soln remaining after removal of fraction A (Et_2O) and fraction B ($CHCl_3$) was acidified to pH 3–4 with HCl and treated with ammonium reineckate (Reinecke Salt) soln (1%) until pption ceased. The resulting ppt was filtered by suction, washed with H_2O, dissolved in MeOH (100 ml) and passed through a column of anion exchange resin (IRA-401S [Cl]) (300 g). The column was rinsed with MeOH (500 ml) and the eluent and rinsing combined to afford a residue (25.2 g) of crude quaternary alkaloid chlorides. The crude chlorides were treated with MeOH (200 ml), filtered and the filtrate evapd to leave a dark brown residue (20.1 g). This residue was adsorbed onto silicic acid (25 g) and chromatographed over silicic acid (150 g) in $CHCl_3$. Elution with $CHCl_3$ (500 ml) and $CHCl_3$–MeOH (9:1) (500 ml) afforded non-alkaloidal fractions. Elution with $CHCl_3$–MeOH (17:3) (500 ml) afforded a residue (7.4 g) which was rechromatographed in a similar manner over silicic acid (100 g). Elution of this second column with the same solvents as before afforded, from the $CHCl_3$–MeOH (17:3) eluent, a light brown residue (2.83 g) of magnoflorine chloride, which was converted to magnoflorine iodide by passage over anion exchange resin (iodide form; 50 g) in MeOH (100 ml). Magnoflorine iodide (420 mg) crystallized as white prisms, mp 248°; $[\alpha]_D^{23}$ + 198° (MeOH; *c* 0.4), identical to an authentical reference sample [47] by direct comparison (UV, IR, MS, $[\alpha]_D$, mp, mmp).

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