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QUATERNARY ALKALOIDS OF *THALICTRUM FOLIOLOSUM*

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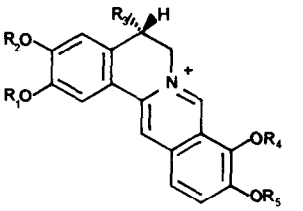
Key Word Index—*Thalictrum foliolosum*; Ranunculaceae; roots; quaternary alkaloids; protoberberine alkaloids; aporphine alkaloids, benzylisoquinoline alkaloids.

Abstract—The isolation and identification of eleven alkaloids from the quaternary alkaloid fraction of a root extract of *Thalictrum foliolosum* are described. The alkaloids isolated are the protoberberines thalifendine, palmatine, berberine, columbamine, jatrorrhizine, thalidastine and dehydrodiscretamine; the benzylisoquinolines rugosinone and tembetarine and the aporphines xanthoplanine and magnoflorine.

INTRODUCTION

Thalictrum foliolosum DC. (Ranunculaceae) is a tall perennial rigid herb indigenous to the tmperate Himalayas (5000–800 ft) and the Khasia hills (4000–6000 ft) of India. Extracts of the roots have been used by the natives as a tonic, febrifuge, diuretic, cathartic and collyrium for the improvement of eyesight as well as in the treatment of flatulence, jaundice and visceral obstructions [1, 2].

Although the literature is abundant with numerous chemical and phytochemical studies of various *Thalictrum* species [3–5], until recently the only references to previous work on *T. foliolosum* reported the isolation of the quaternary protoberberine alkaloids berberine (**1**), jatrorrhizine (**2**) and palmatine (**3**) [6] and the quaternary aporphine alkaloid magnoflorine (**4**) [7, 8] from extracts of the rhizomes. Then, in 1981, the isolation of the bisbenzylisoquinoline alkaloids thalrugosidine, thalrugosaminine, thalisopine (thaligosine) and thalirugidine, the protoberberine-derived alkaloid oxyberberine and the isoquinolone alkaloid noroxyhydrastinine from extracts of the roots of *T. foliolosum* was reported by our laboratories [9]. Finally, the reisolation of thalrugosidine, berberine, palmatine and magnoflorine as well as the isolation of the benzylisoquinoline alkaloid reticuline, the bisbenzylisoquinoline alkaloid thalidasine, the aporphine-benzylisoquinoline alkaloid thalicarpine and the novel aporphine alkaloid *N,O,O*-trimethylsparsiflorine from extracts of *T. foliolosum* rhizomes were reported in 1982 [10]. This paper is continuation of our earlier work [9] and reports the reisolation of berberine (**1**), jatrorrhizine (**2**), palmatine (**3**) and magnoflorine (**4**) from extracts of the roots of *T. foliolosum* as well as describing the isolation and identification of the quaternary protoberberine alkaloids thalifendine (**5**), columbamine (**6**), thalidastine (**7**) and dehydrodiscretamine (**8**), the benzylisoquinoline alkaloids rugosinone (**9**) and tembetarine (*N*-methylreticuline) (**10**) and the quaternary aporphine alkaloid xanthoplanine (**11**) from this same extract.



1 $R_1+R_2=CH_2$; $R_3=H$; $R_4=R_5=Me$

2 $R_1=R_4=R_5=Me$; $R_2=R_3=H$

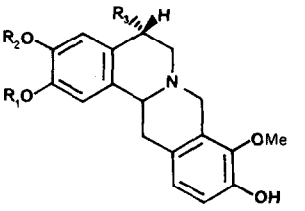
3 $R_1=R_2=R_4=R_5=Me$; $R_3=H$

5 $R_1+R_2=CH_2$; $R_3=R_5=H$; $R_4=Me$

6 $R_1=R_3=H$; $R_2=R_4=R_5=Me$

7 $R_1+R_2=CH_2$; $R_3=OH$; $R_4=Me$; $R_5=H$

8 $R_1=R_4=Me$; $R_2=R_3=R_5=H$



12 $R_1+R_2=CH_2$; $R_3=OH$

13 $R_1=Me$; $R_2=R_3=H$

RESULTS AND DISCUSSION

The ammoniacal solution remaining after the extraction of the non-quaternary bases (fraction B) [9] was acidified and the quaternary alkaloids precipitated with Mayer's Reagent. The precipitate was filtered by suction, washed with water, dissolved in methanol and passed through a column of anion exchange resin (Cl^-). The eluent was evaporated to afford the crude quaternary alkaloid chlorides which were adsorbed onto silicic acid

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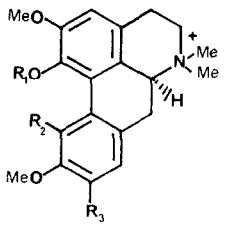
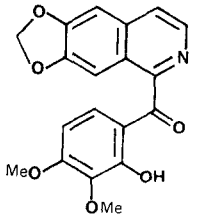


4 $R_1=R_3=H$; $R_2=OH$

11 $R_1=CH_3$; $R_2=H$; $R_3=OH$



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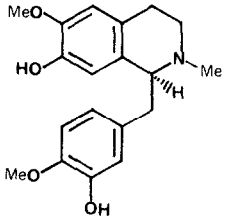

10 **14**$^+$ $MeCl$

and chromatographed over a column of silicic acid with chloroform–methanol–ammonium hydroxide (14:4:1) as the eluent. Four major fractions (Q-1, Q-2, Q-3 and Q-4) were obtained and each was rechromatographed in turn over silicic acid with chloroform–methanol mixtures as eluents. Chromatography of fraction Q-1 afforded palmatine chloride (**3**) and thalifendine chloride (**5**) while similar chromatography of fraction Q-2 gave rugosinone (**9**), palmatine chloride (**3**), berberine chloride (**1**), thalifendine chloride (**5**), columbamine chloride (**6**) (after prep. TLC), jatrorrhizine chloride (**2**), and a mixture of thalidastine chloride (**7**) and dehydrodiscretamine (**8**) (separated by prep. TLC). Chromatography of fraction Q-3 yielded xanthoplanine chloride (**11**) while that of fraction Q-4 afforded an incompletely characterized alkaloid (alkaloid A), tembetarine chloride (**10**) and magnoflorine chloride (**4**).

Berberine (**1**), jatrorrhizine (**2**), palmatine (**3**) and magnoflorine (**4**) have been isolated from numerous *Thalictrum* species (twenty-seven, twelve, eight and thirty subsp. respectively) [4–11], including *T. foliolosum* [6–8, 10]. Thalifendine (**5**) and columbamine (**6**) have likewise been isolated from many *Thalictrum* species (twelve and seven subsp. respectively) [4, 11] but this is the first reported isolation of these alkaloids from *T. foliolosum*. Thalidastine (**7**) has only been previously isolated from *T. fendleri* [12–14] and rugosinone (**9**) from *T. rugosum* [15, 16] and this is only the second reported isolation of these alkaloids from both the genus *Thalictrum* and as naturally occurring protoberberines. Rugosinone, a nonquaternary benzylisoquinoline alkaloid was apparently not separated along with other similar non-quaternary bases during the ordinary partitioning process [9] and remained with the water soluble alkaloids. Dehydrodiscretamine (**8**) was first isolated from *Corydalis tashiori* (Papaveraceae) in 1981 [17] and this is only the second reported isolation of this alkaloid and the first from the genus *Thalictrum* and the family Ranunculaceae. Xanthoplanine (**11**) has been found in *Hernandia* sp. (Hernandiaceae) [18] and *Fagara* sp. (Rutaceae) [18] while tembetarine (**10**) has been isolated from *Fagara* species [19] and *Zanthoxylum martinicense* (Rutaceae) [20]; however this is likewise the first reported isolation of these alkaloids in the genus *Thalictrum* or the Ranunculaceae. Various protoberberine alkaloids, including berberine, palmatine and jatrorrhizine have been shown to possess antimicrobial and uterine stimulant activity [21] while the isoquinoline alkaloid tembetarine has been found to exhibit hypotensive activity [22]. These biological activities may, in part, account for the use of *T. foliolosum* extracts as a medicinal.

EXPERIMENTAL

General. Methods and equipment used for UV, IR, ^1H NMR, MS, $[\alpha]_D$ and mp have been described elsewhere [9]. Silicic acid (100 mesh) (Mallinckrodt) was used for column chromatography and silica gel (silica gel $60GF_{254}$, E. Merck Reagents) for TLC and prep. TLC (0.5 mm). Amberlite IRA-401S(Cl) (Mallinckrodt) was used for ion-exchange chromatography. The solvent system $CHCl_3$–MeOH–NH_4OH (14:4:1) was used for TLC and spots were detected by spraying with Dragendroff reagent [23].

Plant material. The plant material used in this study was collected in the Western Himalayas (30.5° lat. and 78° long.) in June 1978 and identified by Mr. O. P. Misra, Central National Herbarium, Shibpur, West Bengal. A herbarium specimen is on deposit in the Department of Medicinal Chemistry, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, India.

Extraction and isolation. The extraction and separation of the non-quaternary alkaloids from the quaternary alkaloids has been described previously [9]. The ammoniacal solution remaining after the extraction of the non-quaternary alkaloids was acidified with 1% HCl and Mayer's Reagent [24] was added until precipitation was complete. The precipitate was filtered by suction, washed with H_2O, dissolved in MeOH (500 ml) and passed through a column of anion exchange resin (IRA-401S[Cl] (500 g). The column was rinsed with MeOH (200 ml) and the eluent and rinsing combined to afford a residue (310 g) of crude quaternary alkaloid chlorides. The mixture was adsorbed onto silicic acid (300 g) and most of this sample (250 g) chromatographed over silicic acid (1 kg) with $CHCl_3$–MeOH–NH_4OH (14:4:1) as the eluant. Four major fractions (Q-1, (5 l.), Q-2(20 l.), Q-3(14 l.) and Q-4 (12 l.) were obtained and each was rechromatographed in turn.

Palmatine (**3**). Chromatography of fraction Q-1 (280 mg) over silicic acid (30 g) (column A) in $CHCl_3$ and elution with $CHCl_3$–MeOH (98:2) (1.5 l.) afforded a yellow residue (49 mg) which was passed through a column of anion exchange resin (IRA-401S[I]) to afford palmatine iodide (**3**) (45 mg), mp 234–235° (MeOH), identical by direct comparison (UV, IR, mp, mmp, co-TLC) with an authentic reference sample [25].

Thalifendine (**5**). Elution of column A with $CHCl_3$–MeOH (93:7) (3 l.) afforded a dark yellow residue which upon treatment with MeOH gave thalifendine chloride (**5**) (75 mg), mp 230–231°

and iodide (IRA-401S[I]), mp 222–225° (MeOH) identical by direct comparison (UV, IR, mp, mmp, co-TLC) with an authentic sample [26].

Rugosinone (**9**). Adsorption of fraction Q-2 (26 g) onto silicic acid (60 g) (column B) and chromatography over silicic acid (400 g) in $CHCl_3$ and elution with $CHCl_3$ (900 ml) afforded a residue (175 mg) which was rechromatographed over silicic acid (5 g). Elution with $CHCl_3$ (250 ml) afforded an amorphous residue of rugosinone (**9**) (5 mg), mp 212–214°; UV λ_{max}^{MeOH} nm (log ε): 336 (sh) (3.90), 299 (4.06) and 234 (4.49); IR ν_{max}^{KBr} cm^{-1}: 1630, 1590, 1570, 1500, 1470, 1450, 1425, 1390, 1355, 1320, 1280, 1230, 1215, 1130, 1110, 1080, 1070, 1035, 1005, 965, 950, 860, 850, 780, 770, 730, 700 and 680; EIMS (probe) 70 eV *m/z* (rel. int.): 353 $[M]^+$ (29), 294 (71), 279 (23), 181 (16), 174 (43) and 172 (100) identical by direct comparison (UV, IR, MS, mp) with reference spectra and literature values [15, 16].

Berberine (**1**). Elution of column B with $CHCl_3$–MeOH (98:2) (2 l.) afforded additional palmatine chloride (280 mg). Elution with $CHCl_3$–MeOH (94:6) (12 l.) gave a yellow crystalline residue (8.5 g) which upon dissolution in MeOH (100 ml) and passage over IRA-4015(I) (100 g) gave berberine iodide (**1**) (6.5 g), mp 261–262° dec. (MeOH) identical by direct comparison (UV, IR, mp, mmp, co-TLC) with an authentic sample [26].

Columbamine (**6**). Continued elution of column B with $CHCl_3$–MeOH (94:6) (3 l.) gave additional thalifendine chloride (**5**) (80 g). Further elution with $CHCl_3$–MeOH (94:6) (3 l.) gave a yellow residue (110 mg) which after prep. TLC and passage through IRA-401S (I) (40 g), afforded columbamine iodide (**6**) (40 mg), mp 222–225° (MeOH) identical by direct comparison (UV, IR, mp, mmp, co-TLC) with a reference sample [27].

Jatrorrhizine (**2**). Elution of column B with $CHCl_3$–MeOH (92:8) 11.5 l.) gave a reddish-brown residue which on treatment with MeOH afforded jatrorrhizine chloride (**2**) (600 mg). The salt was dissolved in MeOH (100 ml) and passed over IRA-401S(I) (50 g) to afford jatrorrhizine iodide (**2**) (585 mg), mp 219 220° (MeOH) identical by direct comparison (UV, IR, mp, mmp, co-TLC) with an authentic sample [25, 27].

Thalidastine (**7**). Elution of column B with $CHCl_3$–MeOH (80:20) (4.5 l.) afforded a residue (210 mg) which was separated by prep. TLC into two major bands. Treatment of the eluted (MeOH) upper band with MeOH gave a dark red amorphous residue (35 mg) of the thalidastine chloride (**7**), mp 232° dec.; $[\alpha]_D^{23}$ + 105° (MeOH; *c* 0.6); UV λ_{max}^{MeOH} nm (log ε): 425 (3.36), 350 (4.02), 273 (4.09) and 231 (4.15) with a bathochromic shift on addition of methanolic KOH to 476, 378 and 290 and a change to 285 on addition of a pinch of $NaBH_4$. Treatment of thalidastine chloride (25 mg) in MeOH (10 ml) with $NaBH_4$ (15 mg) and work-up in the usual manner [28] gave tetrahydrothalidastine (**12**) (20 mg) as an amorphous residue; ^1H NMR (60 MHz, $CDCl_3$, TMS): δ 3.80 (6H, *s*, 2OMe), 5.95 (2H, *s*, CH_2O_2), 6.73 (1H, *s*, ArH) and 6.81 (3H, *s*, ArH); EIMS (probe) 70 eV, *m/z* (rel. int.): 341 $[M]^+$ (21), 323 (23), 192 (100), 174 (33), 162 (20), 150 (31), 149 (45) and 135 (48) which was identical to reference tetrahydrothalidastine by direct comparison (IR) [12, 13].

Dehydrodiscretamine (**8**). Treatment of eluted (MeOH) lower band with MeOH gave a red amorphous powder (10 mg) of dehydrodiscretamine chloride (**8**), mp 205–206° dec; UV λ_{max}^{MeOH} nm (log ε): 434 (3.60), 346 (4.29), 273 (4.26), 263 sh (4.25), 237 sh (4.22) and 225 (4.28) with a bathochromic shift on addition of either 1 N $NaHCO_3$ (2 drops), or 1 N NaOH (2 drops) to 505 (3.60), 386 (4.50), 302 sh (4.10), 278 (4.23), 255 (4.20) and 235 sh (4.14); IR ν_{max}^{KBr} cm^{-1}: 1605, 1535, 1515, 1445, 1415, 1370, 1325, 1290, 1240, 1150, 1090, 1035, 1018, 975, 865 and 820 identical by direct comparison (UV, IR, mp, co-TLC) with reference [17]. Furthermore, treatment of dehydrodiscretamine chloride (3 mg) in MeOH (5 ml) with $NaBH_4$ (6 mg) and work-up in the usual manner [28] gave discretamine (**13**), EIMS (probe) 70 eV, *m/z* (rel. int.): 327 $[M]^+$ (13), 326 (12), 178 (75), 163 (13), 150 (38), 149 (70) and 135 (85).

Xanthoplanine (**11**). Adsorption of fraction Q-3 (460 mg) onto silicic acid (6 g) and chromatography over silicic acid (95 g) (column C) with $CHCl_3$–MeOH (90:10) (9 l.) as eluent afforded a homogeneous solid of xanthoplanine chloride (**11**) (110 mg). The chloride salt was passed through IRA-401S (I) (25 g) in MeOH to afford xanthoplanine iodide (**11**) (105 mg), mp 190°, $[\alpha]_D^{26}$ + 53° (MeOH, *c* 0.28); λ_{max}^{MeOH} nm (log ε): 305 (3.71), 285 (3.71) and 222 (4.19); ^1H NMR (60 MHz, MeOH-d_4, TMS): δ3.07 (3H, *s*, N^+Me), 3.43 (3H, *s*, N^+Me), 3.69 (3H, *s*, C-2OMe), 3.90 (3H, *s*, C-10OMe) 6.86 (2H, *s*, H-3 and H-8) and 7.92 (1H, *s*, H-11); EIMS (probe) 70 eV, *m/z* (rel. int.): 356 $[M]^+$ (10), 297 (5) and 58 (100) identical by direct comparison with literature data [18, 29].

Alkaloid A. Adsorption of fraction Q-4 (20.5 g) onto silicic acid (60 g) and chromatography over silicic acid (250 g) (column D) in $CHCl_3$–MeOH (95:5) (6 l.) afforded a residue (40 mg). Prep. TLC of this residue gave an incompletely characterized base, alkaloid A (40 mg), mp 162–163° (MeOH).

Tembetarine (**10**). Elution of column D with $CHCl_3$–MeOH (90:10) (10 l.) afforded a white solid (4 g) which on treatment with MeOH gave tembetarine chloride (**10**) (1.5 g), mp 148–152°, $[\alpha]_D^{30}$ + 135° (MeOH, *c* 1.45); UV λ_{max}^{MeOH} nm (log ε): 287 (3.59) and 236 (3.85) with a bathochromic shift on addition 0.1 N methanolic KOH (2 drops) to 300 (3.60) and 255 (3.75); IR ν_{max}^{KBr} cm^{-1}: 1615, 1600, 1520, 1445, 1280, 1245, 1135, 1115, 1035, 995, 970, 925, 910, 870, 820 and 760; ^1H NMR (60 MHz, MeOH-d_4, TMS): δ3.11 (3H, *s*, N^+Me), 3.35 (1H, *s*, N^+Me), 3.82 (6H, *s*, 2OMe), 5.95 (1H, *s*, H-8), 6.48 (1H, *d*, *J* = 8 Hz, H-6'), 6.63 (1H, *s*, H-2'), 6.80 (1H, *s*, H-5) and 6.83 (1H, *d*, *J* = 8 Hz, H-5'). Dequaternization of tembetarine chloride with thiophenolate anion in an S_N2 fashion according to established procedures [30] afforded reticuline (**14**), characterized as its perchlorate salt mp, 199–200° (EtOH); $[\alpha]_D^{30}$ + 76° (EtOH, *c* 1.45); ^1H NMR (60 MHz, MeOH-d_4, TMS): δ 2.95 (3H, *s*, N^+Me), 3.88 (6H, *s*, 2OMe), 6.35 (1H, *s*, H-8), 6.64 (1H, *d*, *J* = 8 Hz, H-6'), 6.70 (1H, *s*, H-2'), 6.81 (1H, *s*, H-5) and 6.92 (1H, *d*, *J* = 8 Hz, H-5') and found to be identical by direct comparison (UV, IR, ^1H NMR, mp) to a reference sample and reference spectra [31].

Magnoflorine (**4**). Elution of column D with $CHCl_3$–MeOH (85:15) (15 l.) afforded a white solid (2.7 g) which on treatment with MeOH gave magnoflorine chloride. Passage of the chloride salt through IRA-401S(I) (100 g) in MeOH afforded magnoflorine iodide (**4**), mp 249–251° dec (MeOH); $[\alpha]_D^{26}$ + 199° (MeOH, *c* 0.35) identical by direct comparison (UV, IR, $[\alpha]_D$, mp, mmp) with a reference sample [26].

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