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ALKALOIDS OF THALICTRUM—XXIII[1]

FOUR NEW APORPHINE-BENZYLISOQUINOLINE DIMERIC ALKALOIDS FROM *THALICTRUM REVOLUTUM*

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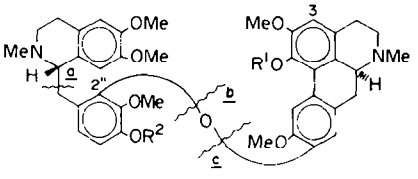
Abstract—Structures, based on physical and chemical methods, are proposed for four new aporphine-benzylisoquinoline dimers. Thalirevolutine (**1**) and thalirevoline (**2**) are related to fetidine (**5**); the latter is isomeric with fetidine bearing the phenolic group at C-4″, and the former is O-methylfetidine. Thalilutidine (**3**) is the C-6′ phenolic analogue of thalicarpine (**6**), while thalilutine (**4**) is the C-3 phenolic analogue of adiantifoline (**13**).

The alkaloid fraction from the roots of *Thalictrum revolutum* DC. (Ranunculaceae)—a perennial, indigenous to the eastern U.S.A.—was shown to possess hypotensive and antimicrobial activities, and on separation had previously yielded 15 alkaloids.[1] We wish to report additional work that has afforded 4 new aporphine-benzylisoquinoline dimers; thalirevolutine (**1**), thalirevoline (**2**), thalilutidine (**3**) and thalilutine (**4**). The first two belong to the fetidine (**5**)[2]-type, in which the benzyl unit is 2,3,4-trioxygenated, the third is related to thalicarpine (**6**),[3] and the fourth to adiantifoline (**13**),[4] both bearing the 2,4,5-trioxygenated benzyl pattern. The literature records at least fifteen examples of aporphine-benzylisoquinoline dimer alkaloids of which all but one are elaborated by *Thalictrum* species.[5]

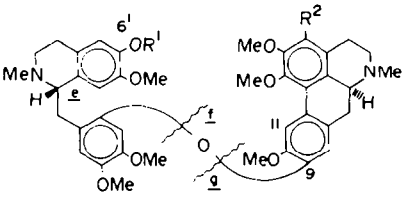
Thalirevolutine (**1**), m.p. 105–108°, was isolated from the mother liquor of a fraction containing predominantly thalicarpine (**6**) and showed physical properties (UV, IR, NMR and MS) in accord with a nonphenolic aporphine-benzylisoquinoline dimeric structure and isomeric with thalicarpine. The MS exhibited a weak molecular ion peak at *m/e* 696, and elemental analyses were in agreement with formula $C_{41}H_{48}N_2O_8$. The base peak at *m/e* 206 corresponded to ion fragment *a*, $C_{12}H_{16}NO_2$ and $KMnO_4$ oxidation of thalirevolutine (**1**) produced the known isoquinolone, N-methylcorydaldine† (**7**),[6] thus establishing the substitution pattern of the tetrahydroisoquinoline unit. Additional peaks in the MS at *m/e* at 355 (M-*b*-H), 340 (*b*) and 324 (c) indicated tetraoxygenated aporphine and benzylisoquinoline components as biogenetic precursors. The NMR spectrum contained a one-proton singlet at δ 8.16 ppm characteristic of H-11 protons of aporphines.

Cleavage of thalirevolutine (**1**) with Na/NH_3 yielded two major products; (*S*)-2,10-dimethoxyaporphine (**8**) characterized by direct comparison with an authentic sample, and a phenolic base **9**. The former is identical with the cleavage product reported for thalicarpine (**6**)[7] and originates from the 1,2,9,10-tetraoxygenated aporphine unit. The latter was different (TLC, IR and NMR) from 6′-hydroxylaudanosine, the corresponding cleavage product of thalicarpine, but showed a comparable MS fragmentation pattern. An AB quartet (δ_A 6.22 and δ_B 6.53 ppm) with J = 8.5 Hz in the NMR spectrum of **9** requires an *ortho*-dihydro benzylic system. A positive Gibbs' test[8] indicated a phenol with an unsubstituted *para* position, placing it, therefore, at position 2′ or 3′. Methylation of **9** with diazomethane formed 2′-methoxylaudanosine (**10**) with spectral properties in agreement with the assigned structure.

Since the data suggested that thalirevolutine (**1**) was possibly a fetidine (**5**)-type dimer with the diphenyl ether located between C-9 of the aporphine and C-2″ of the benzylisoquinoline, a direct comparison was made between thalirevolutine (**1**) and O-methylfetidine prepared from fetidine (**5**)[2] with diazomethane. The two substances showed the same physical properties (TLC, UV, IR, NMR and CD), thus establishing the location of the diphenyl ether bridge and confirming the oxygenation pattern and the stereochemistry as *S,S*. In this connection, the CD spectra of thalirevolutine (**1**), thalicar-

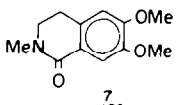


1, $R^1 = R^2 = Me$
2, $R^1 = Me$, $R^2 = H$
5, $R^1 = H$, $R^2 = Me$
11, $R^1 = Me$, $R^2 = Et$



3, $R^1 = R^2 = H$
4, $R^1 = Me$, $R^2 = OH$
6, $R^1 = Me$, $R^2 = H$
13, $R^1 = Me$, $R^2 = OMe$

†Prepared by $KMnO_4$ oxidation of thalicarpine.



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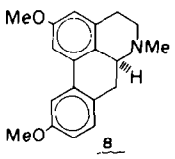

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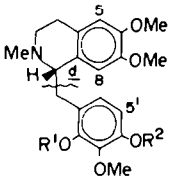

9, R^1 = H, R^2 = Me
10, R^1 = R^2 = Me
12, R^1 = H, R^2 = Et

pine (**6**)[9] and fetidine (**5**) are much alike with two negative maxima near 305 and 275 nm, and one positive maximum at about 234 nm; supporting identical stereochemistry and conformation. However, unlike 2,10-dimethoxyaporphine (**8**) which exhibited a CD curve expected for *S*-configuration,[10] the other Na/NH_3 cleavage product from thalirevolutine (**1**), the phenolic base **9**, exhibited a negative maximum at 285 nm expected for *R*-configuration. However, after methylation to (+)-2′-methoxylaudanosine (**10**) a change to two positive maxima at 285 and 232 nm resulted. This anomalous behavior is characteristic of 2′-hydroxybenzyltetrahydroisoquinolines, with reversal of sign also occurring after acetylation.[11] A similar change in sign of the Cotton effect curve was observed on protonation of the phenolic base.†

Thalirevoline (**2**), m.p. 123–125°, $C_{40}H_{46}N_2O_8$ (by elemental analyses and MS), the major alkaloid of the phenolic tertiary base fraction, showed a UV spectrum typical for aporphine-benzylisoquinoline dimers. The slight bathochromic and hyperchromic change under alkaline conditions was indicative of the presence of a phenolic group, and was supported by OH absorption in the IR spectrum. The NMR spectrum exhibited peaks for two N-methyls, six O-methyls and seven aromatic protons, one of which was upfield at δ 6.14, typical of H-8′, and another downfield at δ 8.17, diagnostic for H-11 of the aporphine. An AB quartet (J 8.5 Hz) with δ_A 6.56 and δ_B 6.68 is supportive of *ortho* aromatic protons. The latter observation would place thalirevoline (**2**) into the fetidine(**5**)-class. The MS peaks at *m/e* 206 (fragment *a*) and 340 (*b*) indicated, respectively, an isoquinoline unit with N-methyl and two O-methyls, and an aporphine with four oxygens, three of which are methoxyls. The phenolic group must reside, therefore, with the benzylic component.

Methylation of thalirevoline (**2**) with diazomethane produced thalirevolutine (**1**), thereby confirming the carbon skeleton, oxygenation pattern and stereochemistry of the former. The location of the phenolic group was established by Na/NH_3 cleavage of O-ethylthalirevoline (**11**) and isolation of 1 - (2′ - hydroxy - 3′ - methoxy - 4′ - ethoxybenzyl) - 2 - methyl - 6,7 - dimethoxy-tetrahydroisoquinoline (**12**) as one of the products; another was aporphine **8**. Thalirevoline (**2**) gave a negative Gibbs' test[8] and since the benzylic group contains the phenolic function (MS of **12** showed a peak at *m/e* 181 for fragment M-*d*), its location is most probably at C-4″.

Thalilutidine (**3**), a very minor alkaloid of the phenolic base fraction was obtained as an amorphous solid with physical properties suggestive of a phenolic aporphine-benzylisoquinoline dimer. The base peak at *m/e* 192 for fragment *e* in the MS placed the phenolic group in the isoquinoline part, and methylation of **3** with diazomethane gave thalicarpine (**6**), thus establishing for thalilutidine (**3**) the complete structure except for the exact location of the phenol. Since the NMR spectrum of thalilutidine (**3**) exhibits a methoxy peak at δ 3.55 and an aromatic proton at δ 6.13, characteristic of 7′-OMe and H-8′,[5d–f] the phenolic group must be at C-6′. Direct comparison of thalmelatine,[14] the 7′-phenolic analogue of thalicarpine (**6**), with thalilutidine showed them to be different.

Thalilutine (**4**) another very minor alkaloid from the phenolic tertiary base fraction was identified as a phenolic aporphine-benzylisoquinoline dimer with composition $C_{41}H_{48}N_2O_9$ from the physical data. The formula contains one oxygen more than thalicarpine (**6**) and the mass spectral peaks at *m/e* 356 and 340 for fragments *f* and *g*, respectively, place it with the aporphine unit. The large bathochromic shift in the UV spectrum under strong alkaline conditions support this assignment. Methylation of thalilutine (**4**) with diazomethane gave adiantifoline (**13**),[9] thus confirming the location of the extra oxygen, as well as carbon skeleton, oxygenated positions and stereochemistry (*S*, *S*). The presence of a methoxyl peak in the NMR spectrum of thalilutine at δ 3.98, considered characteristic of the C-10 position[5] forces location of the phenolic group at either C-1, -2 or -3. Acetylation of thalilutine (**4**) formed a monoacetate which exhibited chemical shifts for the aromatic protons very little different from those in the starting material or in adiantifoline (**13**). This would exclude C-1 as the phenol location, since thalictropine and thalictrogamine[5d] two aporphine-benzylisoquinoline alkaloids phenolic at C-1 showed large upfield shifts of 0.58 ppm for H-11 on acetylation. A decision could not be made between C-2 or -3, but the latter is preferred since *Thalictrum* alkaloids with trioxygenated isoquinoline units bear a phenolic group at the equivalent position or are apparently formed from such precursors. Availability of more material is necessary before a final resolution of this problem is possible.

The characterization of thalirevolutine (**1**) and thalirevoline (**2**) increases to four the total number of fetidine(**5**)-type dimeric alkaloids;—revolutopine, a diphenolic example (OH at C-7′ and C-4″) was recently reported from the tops of *T. revolutum*.[15] Thalilutine (**4**)

†The conclusions reached in Ref. 11 for stereochemical assignment have been revised; see Ref. 12. The reversal in sign of the CD maximum, reflecting a major change in conformation can be explained on the basis of the presence or absence of H-bonding between the 2′-hydroxyl and the tertiary nitrogen. With H-bonding the benzylic group is away from the isoquinoline ring forming a 7-membered ring as can be seen with Dreiding models; but in the absence of H-bonding the benzylic group can be located below the isoquinoline ring. NMR studies with compound **12** support this, as H-8 is moved 0.27 ppm upfield on protonation. This change is caused by shielding from the benzylic group no longer held by H-bonding and now free to rotate under H-8.[13] A similar high field shift of 0.51 ppm occurs in going from compound **9** to **10**, where the H-bonding is removed by O-methylation.

is the third adiantifoline(**13**)-type, while thalilutidine (**3**) adds to the growing list of the thalicarpine(**6**)-type numbering at least nine.

Thalirevolutine (**1**) and thalirevoline (**2**) possess hypotensive activity in normotensive rabbits. The latter also shows antibiotic activity agains *Mycobacterium smegmatis* at 100 μg/ml. The biological activity will be reported elsewhere.

EXPERIMENTAL

All m.ps were taken in capillaries on a Thomas–Hoover Unimelt apparatus and are uncorrected. UV spectra were taken in MeOH on a Cary Model 15 Spectrophotometer; IR spectra were recorded on a Beckman Model 4230 instrument in $CHCl_3$ or in KBr pellets; NMR spectra were obtained on a Varian A-60A or Bruker HX-90E spectrometer in stated solvent with TMS as internal standard with chemical shifts reported as δ (ppm) values. Mass spectra were measured on A.E.I. Ms-9, MS-902 and DuPont 21-491 instruments. CD spectra were recorded on a Durrum–Jasco ORD-UV-5 spectropolarimeter with Sproul Scientific SS-20 modification in MeOH; and the specific rotation was taken on a Perkin–Elmer Model 241 photoelectric polarimeter.

The alkaloids were isolated from the ethanolic extract of the powdered dried roots of *Thalictrum revolutum* DC by the procedure reported in Ref. 1.

Thalirevolutine (**1**). The mother liquor residue (930 mg) of the thalicarpine fraction (see Ref. 1) was chromatographed on silica gel (40 g) with $CHCl_3$ and 1.2 and 5% mixtures of MeOH in $CHCl_3$. The 2% MeOH in $CHCl_3$ effluent yielded a residue that on crystallization from Et_2O gave 120 mg of **1**, m.p. 105–108° (Found: C, 70.00; H, 6.94; N, 3.76. Calc. for $C_{41}H_{48}N_2O_8 \cdot 1/2H_2O$: C, 69.76; H, 7.00; N, 3.97%). R_f 0.62 on TLC with silica gel G and C_6H_6–Me_2CO–NH_4OH (20:20:0.6); Uv λ_{max}270 nm shld (log ϵ 4.31), 280 (4.38), 302 (4.21) and 315 shld (4.10) with no change in acid or base; $[\alpha]_D^{20}$ + 134° (*c*, 0.1 MeOH) and CD $[\theta]_{300}$ −20,200, $[\theta]_{277}$ −26,100, $[\theta]_{240}$ +240,000; NMR ($CDCl_3$) δ 2.36 and 2.43 for 2 NMe groups, 3.59, 3.66, 3.78, 3.80, 3.87 (double intensity) and 3.96 for 7 OMe groups, and 7 ArH as singlets at 6.18, 6.42, 6.52, 6.57, 6.75 (2H) and 8.16 ppm; and MS peaks at *m/e* 696 (1%, M^+), 490 (7, M-*a*), 355 (12, M-*b*-H), 340 (10, *b*), 324 (7, *c*) and 206 (100, *a*).

$KMnO_4$ *Oxidation of thalirevolutine.* A 280 mg sample of **1** in 50 ml acetone was treated with 500 mg $KMnO_4$ over 1 hr while stirring at room temp. After an additional 5 hr of reaction, MeOH was added to consume excess reagent, and the precipitated MnO_2 collected by filtration. The filtrate was concentrated to a few ml, diluted with 25 ml H_2O, acidified with 1 N HCl and extracted with $CHCl_3$. The $CHCl_3$ residue (213 mg) was separated on a silica gel (6 g) column with the C_6H_6–$CHCl_3$ (1:1) fractions yielding 51 mg of **7** after crystallization from MeOH. The physical properties (m.p., TLC, UV, IR and NMR) were identical with authentic N-methylcorydaldine[6] on direct comparison; mixture m.p. undepressed.

Na/NH_3 *Cleavage of thalirevolutine* (**1**). A solution of 120 mg of **1** in THF was added dropwise over 1 hr to 20 ml NH_3 containing 130 mg Na maintained at −30 to −50° and stirred under N_2. After 2 hr of additional reaction the NH_3 was allowed to evaporate and excess Na removed by MeOH treatment. The mixture was concentrated to a few ml, mixed with 50 ml 5% NaOH and extracted with Et_2O (4 × 50 ml) to give 37 mg of nonphenolic bases. The aqueous solution was next treated with excess NH_4Cl and the cloudy mixture extracted with Et_2O (4 × 50 ml) to give 30 mg of phenolic bases after removal of Et_2O.

The nonphenolic bases showed three spots, R_f 0.43, 0.66 (major) and 0.85 on TLC with silica gel G and C_6H_6–Me_2CO–NH_4OH (20:20:0.6), and was chromatographed on silica gel with $CHCl_3$ to yield 10 mg of **8** (R_f 0.66), identical (TLC, UV, IR, NMR and CD $[\theta]_{271}$ −11,300 and $[\theta]_{238}$ +20,700) with authentic (*S*)-2, 10-dimethoxyaporphine[7] obtained from **6**.

The phenolic base fraction, with two spots R_f 0.46 (major) and 0.68 on TLC with the same system as for the nonphenolics, was chromatographed on a column of 2 g of silica gel with $CHCl_3$ and 1% MeOH in $CHCl_3$. The $CHCl_3$ eluates yielded 20 mg of phenolic base **9** as an amorphous solid; IR ($CHCl_3$) no distinct OH peaks; UV λ_{max} 282 nm (log ϵ 3.80) and unaffected by base; NMR ($CDCl_3$) δ 2.60 (s, NMe), 3.80, 3.83, 3.86 and 3.88 (4s, 4 OMe), 6.22 and 6.53 (AB q, *J* 8.5 Hz, H-5′ and H-6′), 6.49 (s, H-8) and 6.59 (s, H-5); Ms *m/e* 373 (6%, M^+, $C_{21}H_{27}NO_5$ requires 373), 206 (100, *d*), 191 (6, *d*-Me), 190 (16, *d*-Me–H) and 167 (4, M-*d*); and CD $[\theta]_{285}$ −6000 and $[\theta]_{234}$ +2800.

Methylation of 2′-hydroxylaudanosine (**9**). The base **9** (20 mg) was treated with excess CH_2N_2 in Et_2O for 10 days and the mixture still containing some starting material was separated on a silica gel column with $CHCl_3$. The amorphous product **10** (10 mg) was eluted first and showed: R_f 0.68 on TLC with silica gel G and C_6H_6–Me_2CO–NH_4OH (20:20:0.6); $[\alpha]_D^{21}$ +88.2° (*c*, 0.135 MeOH); CD $[\theta]_{285}$ +16,300 and $[\theta]_{232}$ +43,300; UV λ_{max} 255 (log ϵ 3.99), 281 (3.90); NMR ($CDCl_3$) δ 2.53 (s, NMe), 3.54 (s, C-7 OMe), 3.82 (s, 3 OMe), 3.85 (s, OMe), 5.98 (s, H-8), 6.55 (s, H-5), 6.53 and 6.63 (AB q, *J* 8.5 Hz, H-5′ and H-6′); and MS (C.I. isobutane) *m/e* 388 (83%, MH^+, $C_{22}H_{29}NO_5$ requires 387) and 206 (100, *d*).

Methylation of fetidine (**5**). To 39 mg of fetidine (CD $[\theta]_{305}$ −24,400, $[\theta]_{272}$ −14,600, $[\theta]_{234}$ +144,000) in 5 ml of MeOH was added ethereal diazomethane generated from 0.5 g *p*-toluenesulfonylmethylnitrosamide and 3 ml 0.1 N alcoholic KOH. After 5 days, the residue (40 mg) remaining upon removal of solvent was passed through a small column of alumina (3 g) in $CHCl_3$ and crystallized from Et_2O to give 32 mg of crystalline product identical (TLC, UV, IR, NMR and CD) with thalirevolutine (**1**).

Thalirevoline (**2**). The phenolic tertiary alkaloid fraction on chromatography on silica gel gave a fraction (1.2 g) which from Et_2O gave **2**, the major alkaloid, as colorless crystals; m.p. 123–125° (Found: C, 69.60; H, 6.90; N, 3.84. Calc. for $C_{40}H_{46}N_2O_8 \cdot 1/2H_2O$: C, 69.44; H, 6.85; N, 4.05%); R_f 0.4 on TLC with same system used for **1**; IR ($CHCl_3$) 3530 cm^{-1} (OH); UV λ_{max} 270 nm shld (log ϵ 4.31) 280 (4.40), 301 (4.24) and 310 shld (4.18), with change in 0.01 N NaOH (MeOH) to 283 (4.38), 300 (4.30) and 315 shld (4.30); $[\alpha]_D^{20}$ +95° (*c*, 0.1 MeOH) and CD $[\theta]_{300}$ −11,700, $[\theta]_{277}$ −12,800, $[\theta]_{240}$ +122,000; NMR ($CDCl_3$) δ 2.37 and 2.43 for 2 NMe groups, 3.56, 3.67, 3.80, 3.87 (double intensity) and 3.96 for 6 OMe groups, and 7 ArH at 6.14 (H-8′), 6.46, 6.52, 6.57, 8.17 (H-11) as singlets and an AB quartet (*J* 8.5 Hz) δ_A 6.56 and δ_B 6.68 ppm for H-5″ and H-6″; and MS *m/e* 682 (0.2%, M^+), 476 (4, M-*a*), 341 (12, M-*b*-H), 340 (13, *b*), 324 (5, *c*) and 206 (100, *a*). A positive phosphomolybdic acid test for phenol was obtained, and a negative Gibbs' test.[8]

Methylation of thalirevoline (**2**). A 70 mg sample of **2** in 5 ml MeOH was treated with ethereal diazomethane produced from 1 g of *p*-toluenesulfonylmethylnitrosamide. After 5 days the mixture was evaporated and the residue was chromatographed on neutral alumina and crystallized from Et_2O to give a crystalline product, m.p. 105–107°, identical (TLC, UV, IR, NMR and CD) with **1**.

Ethylation of thalirevoline (**2**). A 203 mg sample of **2** in 5 ml MeOH was treated with diazoethane generated from 2 g of N - ethyl - N′ - nitro - N - nitrosoguanidine and 5 ml 50% KOH. After 5 days the mixture residue was purified on a column of silica gel to give 120 mg of **11** as a homogeneous amorphous yellow solid; NMR ($CDCl_3$) δ 1.15 (t, *J* 7 Hz, OCH_2CH_3), 402 (q, *J* 7 Hz, OCH_2CH_3), 2 NMe at 2.38 and 2.44, 6 OMe at 3.58, 3.66, 3.81, 3.85, 3.87 and 3.95, 7 ArH at 6.21 (H-8′), 6.43, 6.53, 6.57 and 8.16 (H-11) as singlets and an AB quartet (*J* 9 Hz) δ_A 6.71 and δ_B 6.79 ppm.

Na/NH_3 *Cleavage of O-ethylthalirevoline* (**11**). Ethyl ether **11** (120 mg) in 10 ml of THF was reacted with Na/NH_3 and the products separated as described for **1**. The nonphenolic base fraction (39 mg) after chromatography on silica gel with $CHCl_3$ and 1% MeOH in $CHCl_3$ gave 12 mg of **8** identical (TLC, UV, IR, NMR and CD) with an authentic sample. The phenolic base fraction (22 mg) was purified on a silica gel (2 g) column with $CHCl_3$ to give 12 mg of **12** as a pale yellow amorphous solid; $[\alpha]_D^{21}$ +76.2° (*c*, 0.235 MeOH); CD $[\theta]_{286}$ −3470, $[\theta]_{238}$ +2670, and in ~0.01 N HCl (MeOH) $[\theta]_{275}$ +5000, $[\theta]_{228}$ +30,000; UV λ_{max} 280 nm (log ϵ 3.72) and in 0.01 N NaOH (MeOH) 281 (3.78); IR ($CHCl_3$) 3510 cm^{-1} (weak, OH); NMR ($CDCl_3$, 90 MHz) δ 1.34 (t, *J* 7.0 Hz, OCH_2CH_3), 4.07 (q, *J* 7.0 Hz, OCH_2CH_3), NMe at

2.58, 3 OMe at 3.77, 3.80 and 3.85, 4 ArH at 6.47 (H-8) and 6.58 (H-5) as singlets and an AB quartet (J 8.3 Hz) δ_A 6.21 and δ_B 6.51 ppm for H-5′ and H-6′, with change by addition of 1 drop of CF_3CO_2D to 0.3 ml sample sol. to δ 1.35 (t, J 7 Hz, OCH_2CH_3), 4.14 (q, J 7 Hz, OCH_2CH_3), NMe at 2.96, 3 OMe at 3.65 (C-7), 3.81 and 3.87; 4 ArH at 6.20 (H-8), 6.66 (H-5) as singlets and an AB quartet (J 8.3 Hz) δ_A 6.40 and δ_B 6.61 ppm for H-5′ and H-6′; and MS *m/e* 387 (2%, M^+), 206 (100, *d*), 191 (5, *d*-Me) and 181 (2, M-*d*). The AB spin system was established by spin-tickling experiments.

Thalilutidine (**3**). A column fraction (550 mg) of the phenolic tertiary alkaloids was rechromatographed on 20 g of silica gel using $CHCl_3$ and 1, 2, 3, 4 and 5% MeOH and $CHCl_3$ as eluents. From the 2% MeOH in $CHCl_3$ fraction, 88 mg of a homogeneous amorphous solid was obtained; R_f 0.42 on TLC with the system used for **1**; $[\alpha]_D^{20}$ +74.2° (*c*, 0.11 MeOH) and CD $[\theta]_{306}$ −13,900, $[\theta]_{274}$ −16,100, $[\theta]_{238}$ +180,000; UV λ_{max} 280 nm (log ϵ 4.38) and 304 shld (4.21) with shift in 0.01 N NaOH (MeOH) to 280 (4.36) and 300 shld (4.29); IR ($CHCl_3$) 3540 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.47 and 2.48 for 2 NMe, 6 OMe at 3.55, 3.70, 3.78 (double intensity), 3.88 and 3.92, 7 ArH at 6.13 (H-8′), 8.17 (H-11) and five between 6.5–6.7, and D_2O exchangeable OH at 5.1 ppm; and MS *m/e* 682 (1%, M^+, $C_{40}H_{46}N_2O_8$ requires 682), 490 (6, M-*e*), 340 (8, *f*), 324 (3, *g*) and 192 (100, *e*). A positive phosphomolybdic acid test for phenol was obtained with this compound.

Methylation of thalilutidine (**3**). A sample (28 mg) of **3** in 5 ml of MeOH was treated with excess ethereal diazomethane for 2 days. After purification of the reaction residue on a column of silica gel with 1% MeOH on $CHCl_3$, and crystallization from MeOH, colorless needles, m.p. 123° identical (TLC, UV, IR, NMR and CD) with **6** were obtained. A mixture m.p. was not depressed.

Thalilutine (**4**). Rechromatography of a column fraction (193 mg) of the phenolic tertiary alkaloids on 10 g of silica gel with $CHCl_3$ and MeOH in $CHCl_3$ in increasing polarity gave 100 mg of a homogeneous amorphous solid from the 2% MeOH in $CHCl_3$ eluate. The product, (**4**) showed: R_f 0.44 on TLC with the same system used for **1**; $[\alpha]_D^{20}$ +92° (*c*, 0.175 MeOH), CD $[\theta]_{307}$ −15,900, $[\theta]_{276}$ −19,300, $[\theta]_{239}$ +198,000; UV λ_{max} 282 nm (log ϵ 4.40), 303 shld (4.28) and 312 shld (4.23), with shift in 0.01 N NaOH (MeOH) to 288 (4.30), 313 (4.31) an 330 shld (4.23); IR ($CHCl_3$) 3530 cm^{-1}; NMR ($CDCl_3$) δ 2.48 and 2.49 for 2 NMe, 7 OMe at 3.58 (C-7′), 3.76 (C-1), 3.78 (double intensity, C-4″ and C-5″), 3.83 (C-6′), 3.94 (C-2) and 3.98 (C-10), a D_2O exchangeable OH at 5.65, and 6 ArH as singlets at 6.21 (H-8′), 6.53, 6.56, 6.58, 6.63 and 8.00 (H-11) ppm; and MS *m/e* 712 (0.01%, M^+, $C_{41}H_{48}N_2O_9$ requires 712), 506 (0.4, M-*e*), 372 (0.4, M-*g*), 356 (0.5, *f*), 340 (2.5, *g*) and 206 (100, *e*). A positive phosphomolybdic acid test for phenol was obtained.

Methylation of thalilutine (**4**). A sample (50 mg) of **4** in 5 ml MeOH was treated with excess ethereal diazomethane for 3 days. The reaction residue was purified on a 2 g column of silica gel, and the 1% MeOH in $CHCl_3$ eluate gave 25 mg of a crystalline product, m.p. 144–145° from EtOH, identified as **13**[9] by comparison of TLC, UV, IR, NMR and CD with that of an authentic sample. Mixture m.p. was not depressed.

Acetylation of thalilutine (**4**). A 3 mg sample of **4** was dissolved in 2 drops each of Ac_2O and Pyr. Next day the mixture was treated with 0.5 ml MeOH–H_2O (1:1) and evaporated to dryness, then redissolved in 0.5 ml toluene and again evaporated. The residue (3.1 mg) showed R_f 0.58 on silica gel G with solvent system used for thalilutine, IR ($CHCl_3$) 1760 cm^{-1} (acetate C=O), and NMR ($CDCl_3$, 90 MHz) δ 2.36 for acetate, 2.49 for 2 NMe, 7 OMe at 3.56, 3.75, 3.78 (double intensity), 3.83 and 3.91 (double intensity) and 6 ArH as singlets at 6.16 (H-8′), 6.49, 6.58 (double intensity), 6.63 and 8.02 ppm (H-11).

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REFERENCES

[1]Part XXII: W.-N. Wu, J. L. Beal and R. W. Doskotch, *Lloydia* in press.
[2]M. P. Cava and K. Wakisaka, *Tetrahedron Letters* 2309 (1972).
[3]M. Tomita, H. Furukawa, S.-T. Lu and S. M. Kupchan, *Chem. Pharm Bull.* **15**, 959 (1967).
[4]R. W. Doskotch, J. D. Phillipson, A. B. Ray and J. L. Beal, *J. Org. Chem.* **36**, 2409 (1971).
[5]For a summary through 1971, [a]M. Shamma, *The Isoquinoline Alkaloids*, pp. 232–244. Academic Press, New York (1972); and additional reports by, [b]N. M. Mollov, P. P. Panov, L. N. Thuan and L. N. Panova, *Compt. rend. l'Acad. bulgare Sci.* **23**, 1243 (1970); [c]N. M. Mollov and L. N. Thuan, *Ibid.* **24**, 601 (1971); [d]M. Shamma and J. L. Moniot, *Tetrahedron Letters* 775 (1973); [e]M. Shamma, S. S. Salgar and J. L. Moniot, *Ibid.* 1859 (1973); [f]M. Shamma and J. L. Moniot, *Ibid.* 2291 (1974); [g]M. Shamma, J. L. Moniot, S. Y. Yao, G. A. Miana and M. Ikram, *J. Am. Chem. Soc.* **95**, 5742 (1973).
[6]M. Shamma and M. A. Podczasy, *Tetrahedron* **27**, 727 (1971).
[7]S. M. Kupchan and N. Yokoyama, *J. Am. Chem. Soc.* **86**, 2178 (1964).
[8]F. E. King, T. J. King and L. C. Manning, *J. Chem. Soc.* 563 (1957).
[9]R. W. Doskotch, P. L. Schiff and J. L. Beal, *Tetrahedron Letters* 4999 (1968).
[10a]J. C. Craig and S. K. Roy, *Tetrahedron* **21**, 395 (1965). [b]K. Kotera, Y. Hamada and R. Mitsui, *Ibid.* **24**, 2463 (1968).
[11]N. S. Bhacca, J. C. Craig, R. H. F. Manske, S. K. Roy, M. Shamma and W. A. Slusarchyk, *Ibid.* **22**, 1467 (1966).
[12]J. Kunitomo, K. Morimoto, K. Yamamoto, Y. Yoshikawa, K. Azuma and K. Fujitani, *Chem. Pharm. Bull.* **19**, 2197 (1971).
[13]G. Fraenkel, M. P. Cava and D. R. Dalton, *J. Am. Chem. Soc.* **89**, 329 (1967).
[14]N. M. Mollov and H. B. Dutschewska, *Tetrahedron Letters* 2219 (1964).
[15]J. Wu, J. L. Beal, W.-N. Wu and R. W. Doskotch, *Heterocycles* **6**, 405 (1977).