California, Riverside, provided the financial support for this study.[2] A.M. also thanks the Spanish Ministry of Education and Sciences for a Postdoctoral fellowship.

Registry No.—1, 67-97-0; **7**, 54473-74-4; **8**, 64242-58-0; **9**, 58028-00-5; **10a**, 26358-75-8; **10b**, 52032-63-0; **10c**, 56498-47-6; **10d**, 64265-01-6; **11a**, 64265-02-7; **11b**, 64252-59-1; **11c**, 64252-60-4; **12a**, 64252-61-5; **12b**, 64252-62-6; **13**, 64252-63-7; **14**, 53830-00-5; **15**, 64252-64-8; **16**, 52753-84-1; **17**, 21072-90-2; **18**, 5837-24-1; **19**, 21072-91-3; **20a**, 64265-03-8; **20b**, 64252-65-9; **21a**, 64252-66-0; **21b**, 64252-67-1; **21c**, 64265-09-4; **22a**, 35339-68-5; **22b**, 60008-81-3; **23**, 64252-54-6; **24a**, 64252-55-7; **24b**, 64252-56-8; **25**, 64252-57-9; **26a**, 50392-20-6; **26b**, 58699-24-4; **27b**, 58699-25-5; benzoyl chloride, 98-88-4; *p*-toluenesulfonylhydrazine, 1576-35-8.

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(2) This study was supported by USPHS Grants AM-16595 and AM-9012 and by a grant from the Intramural Research Fund of the University of California, Riverside, Calif.

(3) (a) Department of Chemistry; (b) Department of Biochemistry.

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Six New Bisbenzylisoquinoline Alkaloids from *Thalictrum rugosum*[1]

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The alkaloids thaligosidine (**1**), thaligosinine (**11**), thaligosine (**14**), thalirugine (**19**), thaliruginine (**29**), and thalirugidine (**32**) were isolated from the phenolic alkaloid fraction of *Thalictrum rugosum* Ait. roots. Their structures were advanced on the basis of spectral and chemical evidence.

The genus *Thalictrum* (family Ranunculaceae) has yielded well over 100 alkaloids biogenetically derivable from benzylisoquinoline precursors.[2] As part of a continuing study of alkaloids from *Thalictrum*, we report herein the isolation and structure determination of six new phenolic bisbenzyltetrahydroisoquinoline alkaloids from the roots of *Thalictrum rugosum* Ait. (*T. glaucum* Desf.). This source has already afforded over 20 alkaloids, of which seven have been characterized as bisbenzylisoquinolines.[3]

The residue obtained by extraction of the powdered roots

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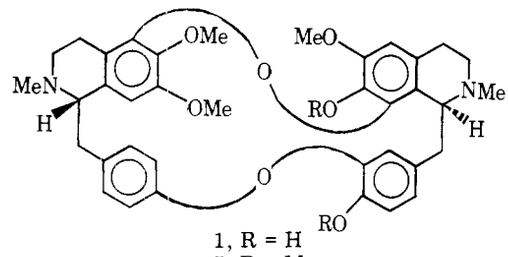
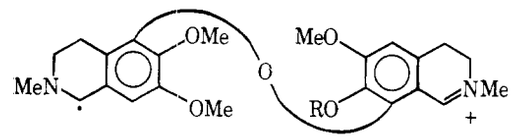
of *T. rugosum* was divided into the phenolic and nonphenolic tertiary alkaloid fractions by the usual solvent partition procedure, and the phenolic tertiary bases were chromatographed on silica gel and fractions thereof further purified to give the reported alkaloids.

Thaligosidine (1), obtained as colorless crystals, mp 175–177 °C, was assigned the composition $C_{37}H_{40}N_2O_7$ by high-resolution mass spectrometry, and the ^1H NMR spectrum clearly showed the presence of two *N*-methyls and three *O*-methyls along with nine aromatic protons. Two D_2O-exchangeable protons were assigned to two phenolic groups (vide infra). The UV spectrum exhibited a bathochromic shift in alkali. The IR spectrum showed hydroxyl absorption. The relatively intense molecular ion peak was suggestive of a bisbenzylisoquinoline structure with two diphenyl ethers,[4] and the peak at *m/e* 412 for fragment **2** supported a head to head arrangement as well as the placement of one phenolic group in an isoquinoline ring. Additional fragment peaks assigned to ions **3** and **4** supported the corresponding partial structures.

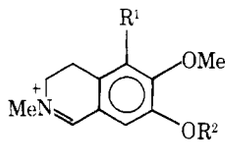
Methylation of thaligosidine (1) with diazomethane gave a methylated derivative **5** that showed two additional methoxy



1, R = H
5, R = Me
6, R = Et



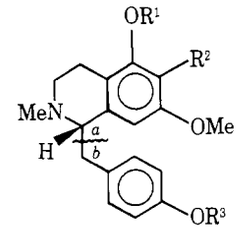
2, R = H
7, R = Et



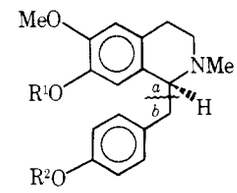
3, R^1 = H; R^2 = Me
4, R^1 = R^2 = H
8, R^1 = H; R^2 = Et
20, R^1 = OH; R^2 = Me
23, R^1 = OEt; R^2 = Me

peaks in the ^1H NMR spectrum and was identical with thalidasine (*S,S* configuration), previously isolated from this plant.[5] This conversion established the carbon skeleton, oxygenation pattern, and stereochemistry for thaligosidine (1). The location of the phenolic groups was determined from studies on *O,O*-diethylthaligosidine (**6**). The mass spectral peaks at *m/e* 440 and 220 for fragments **7** and **8**, respectively, confirmed the location of one phenolic group in an isoquinoline unit, and sodium–ammonia cleavage of **6** produced (*S*)-*N*-methyl-*O,O*-diethylcoclaurine (**9**)[6] and (*S*)-5-hydroxyarmepavine (**10**).[5] The nonphenolic product established the positions of the two phenolic groups.

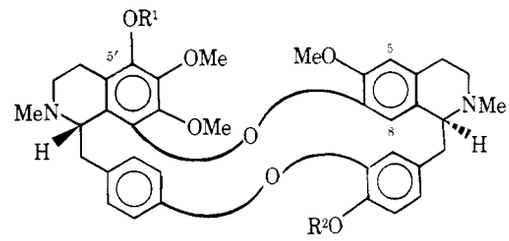
Thaligosinine (**11**), as colorless crystals, mp 233–234.5 °C (dec), with composition $C_{38}H_{42}N_2O_7$ from high-resolution mass measurement showed in the ^1H NMR spectrum two *N*-methyls, four *O*-methyls, and nine aromatic protons. A phenolic hydroxyl was supported by absorption in the IR and NMR spectra (in the latter, D_2O exchangeable), and by ob-



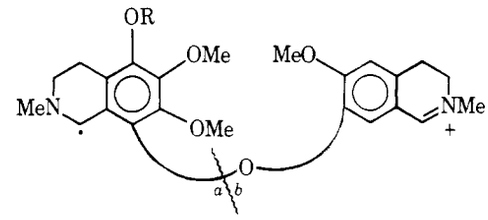
10, R^1 = R^3 = H; R^2 = OMe
18, R^1 = Et; R^2 = OMe; R^3 = H
35, R^1 = Et; R^2 = OMe, R^3 = Me
36, R^1 = Et; R^2 = H; R^3 = Me



9, R^1 = R^2 = Et
17, R^1 = H; R^2 = Me
24, R^1 = Et; R^2 = Me
31, R^1 = R^2 = Me



11, R^1 = Me; R^2 = H
12, R^1 = R^2 = Me
14, R^1 = H; R^2 = Me
16, R^1 = Et; R^2 = Me



13, R = Me
15, R = H

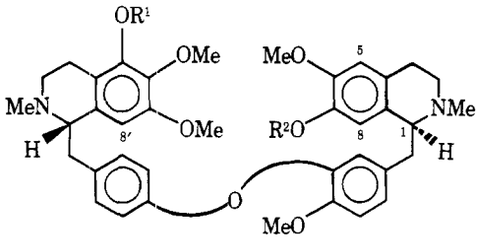
servation of a bathochromic shift in the UV spectrum with alkali. The *O*-methyl derivative was identical with thalrugosaminine (**12**) (*S,S* configuration) and established for thaligosinine the complete structure except for the phenolic hydroxyl position. Since the MS of thaligosinine (**11**) contains a peak at *m/e* 426 corresponding to fragment **13** and other peaks consistent with **13**, the phenolic hydroxyl must be with the benzylic ring.

Thaligosine (**14**), mp 143–145 °C, was found to have the same elemental composition as thaligosinine (**11**) and the NMR spectrum appeared similar; the major difference was in the location of one of the methoxyls. On treatment with diazomethane, thaligosine (**14**) was converted to thalrugosaminine (**12**), making thaligosine (**14**) a position isomer of thaligosinine (**11**). The phenolic group must be located in the tetraoxygenated isoquinoline ring, since the MS spectrum of **14** contains peaks at *m/e* 412, 222, and 192 corresponding to fragments **15**, **15a** + H and **15b** + H, respectively. *O*-Ethylthaligosine (**16**) on sodium–ammonia cleavage afforded two phenolic products **17** and **18**. The former is identical with a cleavage product from thalrugosaminine (**12**).[3a] The latter is new, for which the physical data (NMR, MS) support a structure in which the isoquinoline ring bears an ethoxy and two methoxy groups, and the benzylic ring contains a para phenolic hydroxyl. This compound is identical to one of the degradation products from thalirugine (**19**) for which location of the ethylated phenol was established (vide infra). Thaligosine (**14**) therefore has the phenolic group at the 5′-position and configuration *S,S*.

Thalirugine (**19**) was isolated as an amorphous solid and assigned a dimeric benzylisoquinoline structure on the basis of the number of protons in the NMR spectrum. The mass spectrum showed only very weak peaks above *m/e* 400 but the elemental analyses were consistent with the formula

$C_{38}H_{44}N_2O_7$ for which an apparent molecular ion at m/e 640 of 0.01% intensity was present. Such weak molecular peaks are observed for single diphenyl ether linked dimeric alkaloids.[4] The NMR spectrum contained peaks for two *N*-methyls, four *O*-methyls, ten aromatic protons, and two phenolic groups. Positive phosphomolybdic acid[7] and Gibbs'[8] tests supported a para unsubstituted phenol. Partial structures for the two isoquinoline portions in which one contains a phenolic and two methoxyl groups and the other a phenolic and one methoxyl were supported by ions in the mass spectrum at m/e 220 and 192 for fragments **20** and **4** (or their equivalent), respectively.

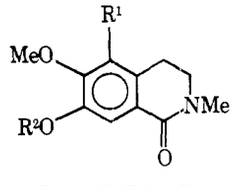
Methylation of thalirugine (**19**) with diazomethane gave a dimethyl derivative **21**, which substantiated the presence of



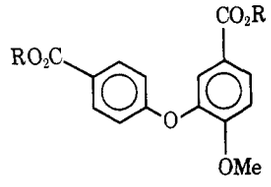
19, $R^1 = R^2 = H$
21, $R^1 = R^2 = Me$
22, $R^1 = R^2 = Et$
29, $R^1 = H$; $R^2 = Me$
30, $R^1 = Et$; $R^2 = Me$

two phenolic hydroxyls and their location in the isoquinoline rings, as did the diethyl derivative **22**. For the latter compound the intense mass spectral peaks at m/e 250 and 220 correspond to fragment ions **23** and **8**, respectively. Sodium in ammonia cleavage of *O,O*-diethylthalirugine (**22**) yielded a nonphenolic base **24** that was identical with a cleavage product from *O*-ethylthalrugosidine;[5] thus, one of the phenolic groups in thalirugine (**19**) is at position 7, and the configuration at C-1 *S*. The phenolic cleavage product was found to be identical with product **18** from *O*-ethylthaligosine (**16**); therefore, the other asymmetric center of thalirugine (**19**) is also *S*. The two cleavage products identified the nature of the oxygenation pattern for the individual benzylisoquinoline units of thalirugine (**19**). In addition, the phenolic group in the isoquinoline ring of **18** must be placed at position 5 if thalirugine is to give a positive Gibbs' test. It follows that thaligosine (**14**) must bear the phenolic hydroxyl at 5′.

Permanganate oxidation of *O,O*-diethylthalirugine (**22**) afforded three products, two isoquinolones **25**[9,10] and **26** and



25, $R^1 = H$; $R^2 = Et$
26, $R^1 = OEt$; $R^2 = Me$

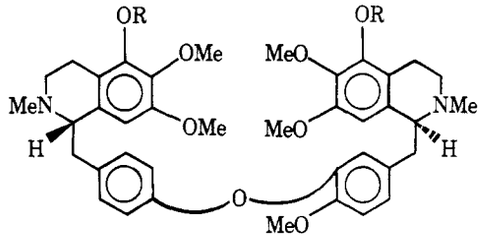


27, R = H
28, R = Me

diphenyl ether dicarboxylic acid **27**, each identified by direct comparison with known samples. 2-Methyl-5-ethoxy-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline (**26**) was prepared by oxidation of the diethyl ether product of **10**, a sodium–ammonia cleavage product from thalidasine (**5**).[11] The isoquinolones confirmed the phenol locations in the isoquinoline rings, and the diphenyl ether, also characterized as the diester **28**, established the point of attachment for the monomeric units of thalirugine (**19**).

Thaliruginine (**29**) was obtained as an amorphous solid, $[\alpha]_D$ +104°, and exhibited spectral characteristics of a bisbenzylisoquinoline alkaloid with one diphenyl ether structure (weak molecular ion in MS). The NMR spectrum showed peaks for two *N*-methyls, five *O*-methyls, and ten aromatic protons. Treatment of thaliruginine (**29**) with diazomethane formed a monomethyl derivative **21** identical with the methylated product from thalirugine (**19**); thus, thaliruginine (**29**) is one of two *O*-methylthalirugines, and its MS with a peak at m/e 222 (**20**) supported a phenolic group in the trioxygenated isoquinoline ring. The positive Gibbs' test would place the phenolic group at position 5′. Confirmation of this assignment was made by the isolation of benzyl isoquinoline **18** on sodium–ammonium cleavage of *O*-ethylthaliruginine (**30**). The other cleavage product was (*S*)-*O*-methylarmepavine (**31**).

Thalirugidine (**32**), the third monoether-linked bisalkaloid, was assigned formula $C_{39}H_{46}N_2O_8$ on the basis of MS and elemental analyses. The NMR spectrum contained peaks for two *N*-methyls, five *O*-methyls, and nine aromatic protons, two of which were located at upfield positions, characteristic of H-8 and H-8′ protons. Two D_2O-exchangeable protons were from phenols and were supported by the preparation of di-*O*-methyl **33** and di-*O*-ethyl **34** derivatives. The MS of

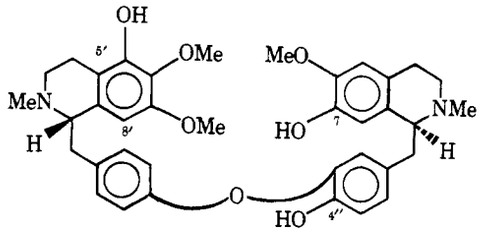


32, R = H
33, R = Me
34, R = Et

thalirugidine (**32**) and its derivatives, all with weak M^+ peaks, were in agreement with the location of a phenolic hydroxyl on each of the two trioxygenated isoquinoline rings. For example, peaks are present at m/e 222 for fragment **20** and m/e 250 for **23** of thalirugidine (**32**) and diethyl ether **34**, respectively.

Sodium–ammonia reductive cleavage of **34** gave (*S*)-5-ethoxy-4′,6,7-trimethoxy-*N*-methyltetrahydroisoquinoline (**35**) as the nonphenolic product and (*S*)-5-ethoxy-4′-hydroxy-6,7-dimethoxy-*N*-methyltetrahydroisoquinoline (**18**) as the phenolic product. The configuration was assigned on the basis of positive CD maxima at 282 and 230 nm for cleavage products **18** and **35**. Methylation converted **18** to **35**. Permanganate oxidation of *O,O*-diethylthalirugidine (**34**) formed 2-methoxy-4′,5-dicarboxy diphenyl ether (**27**) (identified as the dimethyl ester **28**) and provided the evidence for the location of the ether linkage. In addition, the isoquinolone **26** was also isolated. The CD spectrum of thalirugidine (**32**), with two positive maxima at 280 and 230 nm, is consistent with the *S,S* stereochemistry.

Five of the six new alkaloids, in this report, are derivable biogenetically from a hypothetical monoether-linked bisalkaloid **37** (northalirugine) formed by phenol coupling of (*S*)-northalifendlerine and (*S*)-*N*-methylcoclaurine. Intramolecular phenol coupling of **37** between the 5′-OH and the 8 position would yield thaligosidine (**1**), which on methylation



37

of both phenolic groups forms thalidasine (**5**). With phenol coupling between the 7-OH and the 8′ position, the precursor of thaligosinine (**11**) and thaligosine (**14**) would result. Only methylation, respectively, of the 5′-OH and the 4″-OH is required to the final products. Complete methylation gives thalrugosaminine (**12**). The remaining two alkaloids, thalirugine (**19**) and thaliruginine (**29**), are simple mono- and dimethylated products of the hypothetical precursor **37**. The sixth alkaloid, thalirugidine (**32**), is a monomethylated product of another hypothetical precursor formed from two (*S*)-northalifendlerines.

Experimental Section

Melting points are uncorrected. NMR spectra were determined in stated solvents with Me_4Si as an internal standard using Varian A-60A or Bruker HX-90E instruments and with chemical shifts (δ) reported in ppm and coupling constants (J) in Hz. IR and UV spectra were taken in $CHCl_3$ on a Beckman IR 4230 and in MeOH on a Cary 15 instrument, respectively. Mass spectra were obtained on an AEI MS-9 or DuPont 21-491 instrument by direct inlet probe at 70 eV. Optical rotations were measured on a Perkin-Elmer 241 photoelectric polarimeter and CD spectra in MeOH on a Durrum-Jasco ORD/UV-5 spectropolarimeter with Sproul Scientific SS-20 modification. TLC was performed on silica gel G (E. Merck) and column chromatography on silica gel PF254 (Brinkmann-EM) or alumina (Woelm) with stated solvents. Detection on TLC was with Dragendorff's spray reagent. Microanalyses were by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Roots of *T. rugosum* were collected from plants grown in the College of Pharmacy Medicinal Plant Garden. A voucher specimen is on file.

Extraction of *T. rugosum* Roots and Initial Partitioning. Ground roots (17.7 kg) were percolated to exhaustion with ethanol, and the extract was evaporated to dryness at reduced pressure and 40 °C, leaving 1.5 kg of residue. Suspension of the residue in 18 L of 2% aqueous citric acid and filtering gave a filtrate that was extracted with an equal volume of $CHCl_3$ and then brought to pH 9.0 with NH_4OH. The basic solution was extracted successively with Et_2O (35 L) and $CHCl_3$ (18 L), and the Et_2O fraction was extracted with 12 L of 5% NaOH. Evaporation of the Et_2O left 75 g of nonphenolic tertiary alkaloids, while from the $CHCl_3$ extract 11.6 g of alkaloidal residue remained. The NaOH solution was treated with solid NH_4Cl and the cloudy suspension was extracted with 30 L of Et_2O from which 39.2 g of phenolic tertiary alkaloids was obtained.

Chromatography of the Phenolic Tertiary Alkaloids. The crude phenolic tertiary alkaloid fraction (30 g) was separated on a column of silica gel (0.9 kg), collecting 0.5-L fractions for analysis. The eluting solvents were $CHCl_3$ (5 L) and the following mixtures of MeOH in $CHCl_3$: 2.5% (10 L), 5% (12 L), 7.5% (8 L), 10% (6 L), 15% (3 L), 20% (6 L), 40% (4 L), and 50% (4 L). Final column washes were made with 4 L of MeOH and 2 L of 5% HOAc in MeOH. The eluted fractions gave the alkaloids that follow.

Thaligosidine (1). The residue (1.1 g) from fractions 28–31 was rechromatographed on 35 g of silica gel. The 1% MeOH in $CHCl_3$ eluates gave 230 mg of a residue that was crystallized from benzene to yield 180 mg of colorless crystalline thaligosidine (**1**): mp 175–177 °C; R_f 0.9 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.5); $[\alpha]_D^{20}$ −45° (*c* 0.26, MeOH); CD $[\theta]_{287}$ −19 000, $[\theta]_{268}$ +6700, $[\theta]_{242}$ +5490 and $[\theta]_{224}$ −31 800; UV λ_{max} 275 (log ϵ 3.72), 283 nm (3.72), and in 0.01 N NaOH 275 (3.75), 284 (3.76), and 310 nm (shld) (3.22); IR ($CHCl_3$) 3540 cm^{-1} (OH); NMR δ ($CDCl_3$) 2.25 and 2.66 (s, 2 NMe), 3.49, 3.75 and 3.86 (s, 3 OMe), 6.2–7.7 (m, 9 ArH), and 5.6 ppm (br, 2 OH, D_2O exchangeable), with benzene adduct showing peaks at δ ($CDCl_3$) 2.42 and 2.66 (s, 2 NMe), 3.43, 3.76, 3.85 (s, 3 OMe), 6.3–7.7 (m, 9 ArH), and 5.88 ppm (br, 2 OH); MS *m/e* 624.2849 (40%, M^+, $C_{37}H_{40}N_2O_7$ requires 624.2835), 412 (7, **2**), 411 (20, **2** − H), 206 (23, double ions of 412 and **3**), and 192 (100, **4**).

Anal. Calcd for $C_{37}H_{40}N_2O_7 \cdot {}^3/_2H_2O$: C, 68.24; H, 6.18; N, 4.30. Found: C, 68.50; H, 6.48; N, 3.81.

***O*-Methylation of Thaligosidine (1).** To 35 mg of thaligosidine (**1**) in 2.5 mL of MeOH was added ethereal diazomethane prepared from 1 g of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide. After 4 days, the residue remaining after evaporation of solvent was chromatographed on neutral alumina with PhH–$CHCl_3$ (1:1) to give 25 mg of a pale-yellow amorphous base showing identical properties (IR, UV, specific rotation, CD, NMR, and TLC) with authentic thalidasine (**5**) previously isolated form *T. rugosum*.[5]

***O,O*-Diethylthaligosidine (6).** To 140 mg of thaligosidine (**1**) in 10 mL of MeOH was added ethereal diazoethane generated from 2 g of *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine. After 5 days the reaction residue was chromatographed on neutral alumina with benzene as solvent. The crystalline residue on recrystallization from MeOH gave colorless needles: mp 198–200 °C; R_f 0.93 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.5); NMR δ ($CDCl_3$) 0.74 and 1.43 (2 t, J = 7, 2 OCH_2CH_3), 4.14 (q, J = 7, OCH_2CH_3) with another methylene quartet of ethoxy hidden in the methylene region, 2.24 and 2.62 (s, 2 NMe), 3.52, 3.74, and 3.87 (s, 3 OMe), and 6.2–7.6 (m, 9 ArH); MS (CI, isobutane) *m/e* 681 (100%, MH^+, $C_{41}H_{49}N_2O_7$ requires 681), EI *m/e* 680 (100%, M^+), 651 (11, M − Et), 440 (7, **7**), 439 (22, **7** − H), 220 (37, **8**), 206 (4, **3**) and 190 (10, **8** − EtH).

Anal. Calcd for $C_{41}H_{48}N_2O_7$: C, 72.33; H, 7.11; N, 4.12. Found: C, 71.94; H, 7.15; N, 4.09.

Na/NH_3 Cleavage of *O,O*-Diethylthaligosidine (6). To 20 mL of liquid NH_3 containing 150 mg of Na at below −50 °C was added dropwise in 0.5 h 8 mL of tetrahydrofuran solution containing 70 mg of **6**. The reaction was maintained for 2 h. The NH_3 was allowed to evaporate and the unreacted Na was decomposed with excess MeOH. The mixture was concentrated in vacuo to 2 mL, taken up in 250 mL of Et_2O, and extracted with 125 mL of 1 N NaOH to separate the products into phenolic and nonphenolic fractions.

From the washed (H_2O) and dried (Na_2SO_4) Et_2O extract was obtained 30 mg of an oil on evaporation that showed one spot, R_f 0.80, on TLC with PhH–Me_2CO–NH_4OH (20:20:0.6). Column chromatography on 2 g of neutral alumina with 100 mL of PhH–$CHCl_3$ (1:1) and 150 mL of $CHCl_3$ as eluents yielded 24 mg of **9** as an amorphous solid: NMR δ ($CDCl_3$) 1.31 and 1.38 (2 t, J = 7, 2 OCH_2CH_3), 3.76 and 3.98 (2 q, J = 7, 2 OCH_2CH_3), 2.51 (s, NMe), 3.82 (s, OMe), 6.09 (s, H-8), 6.55 (s, H-5), and 6.77 and 6.98 (AA′BB′ q, J_{AB} = 8.5, 4 ArH); MS (CI, isobutane) *m/e* 356 (75%, MH^+, $C_{22}H_{29}NO_3$ requires 355), 220 (100, a) and 135 (5, b); CD $[\theta]_{290}$ + 9100, $[\theta]_{272}$ −1700, and $[\theta]_{234}$ +47 000. This compound showed identical TLC behavior, UV, IR, and NMR spectra with that of the corresponding cleavage product prepared from *O,O*-diethylobamegine,[6] but the CD spectrum was antipodal ($[\theta]_{290}$ −9300, $[\theta]_{272}$ +1900, and $[\theta]_{234}$ −38 000).

The NaOH solution was treated with NH_4Cl to pH 8–9 and extracted with Et_2O. The washed (H_2O) and dried (Na_2SO_4) Et_2O solution on evaporation gave 19 mg of a residue that showed two spots on TLC, R_f 0.6 (major) and 0.7, with PhH–Me_2CO–NH_4OH (20:20:0.6). Chromatography on silica gel (2 g) with $CHCl_3$, 2% and 4% MeOH in $CHCl_3$, yielded 12 mg of **10**, identical (TLC, UV, IR, NMR, MS, and CD) with the cleavage product from *O*-ethylthalrugosidine.[5]

Thaligosinine (11). The column fractions 28–31 that on rechromatography afforded thaligosidine (**1**) gave on elution with 2% MeOH in $CHCl_3$ 526 mg of an early fraction that crystallized from Et_2O to give white crystals of thalrugosine, mp 206–207 °C, already reported from this source.[5] The latter 2% MeOH in $CHCl_3$ effluents yielded 35 mg of a white crystalline solid that crystallized from Et_2O to give thaligosinine (**11**): mp 233–234.5 °C (dec); $[\alpha]_D^{21}$ −58.5° (*c* 0.316, MeOH); CD $[\theta]_{275}$ −13 000, $[\theta]_{242}$ −48 000, $[\theta]_{230}$ +100 000; UV λ_{max} 282 nm (log ϵ 3.90) and in 0.01 N NaOH 284 (4.11) and 307 nm (shld) (3.53); IR ($CHCl_3$) 3540 cm^{-1}; NMR δ ($CDCl_3$, 90 MHz) 2.51 and 2.56 (2 s, 2 NMe), 3.04, 3.40, 3.80, and 3.84 (4 s, 4 OMe), 6.36 (s, H-8), 6.47 (s, H-5), 6.5–7.5 (m, 7 ArH), and ~5.0 (br, OH, D_2O exchangeable); MS 638.3005 (100%, M^+, $C_{38}H_{42}N_2O_7$ requires 638.2992), 426 (15, **13**), 425 (37, **13** − H), 411 (34, **13** − Me), 236 (2, **13a**), 213 (97, double ion of **13**), 192 (31, **13b** + H), 191 (6, **13b**), and 190 (9, **13b** − H).

Methylation of Thaligosinine (11) to Thalrugosaminine (12). A 25-mg sample of **11** in 3 mL of MeOH was treated with excess ethereal diazomethane for 3 days. The product was chromatographed on 2 g of neutral alumina with PhH–$CHCl_3$ (1:1) to give 23 mg of a pale-yellow solid. Its TLC mobility and UV, IR, NMR, and CD spectra were identical with those of thalrugosaminine (**12**) earlier reported from this plant.[3a]

Thaligosine (14). The residue (1 g) from column fractions 32–34 was rechromatographed on 50 g of silica gel with $CHCl_3$ and 1, 2, 3, and 4% MeOH in $CHCl_3$. The 2 and 3% MeOH in $CHCl_3$ effluents gave a residue that from Et_2O gave 210 mg of thaligosine (**14**) as colorless crystals: mp 143–145 °C; R_f 0.33 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); $[\alpha]_D$ −109° (*c* 0.17, MeOH); CD $[\theta]_{287}$ +3200, $[\theta]_{272}$ −1200, $[\theta]_{240}$ −7980, $[\theta]_{225}$ +16 700; UV λ_{max} 282 nm (log ϵ 3.86) and in 0.01 N NaOH 282 (3.88) and 305 nm (shld) (3.64); IR ($CHCl_3$) 3520 cm^{-1} (OH); NMR δ ($CDCl_3$) 2.52 and 2.56 (2 s, 2 NMe), 3.08, 3.39, 3.78, and 3.95 (4 s, 4 OMe), 6.38 (s, H-8), 6.46 (s, H-5), 6.6–7.4 (m, 7 ArH) and 4.7 (br, OH, D_2O exchangeable); MS *m/e* 638 (89%, M^+, $C_{38}H_{42}N_2O_7$ requires 638), 637 (27, M − H), 623 (4, M − Me), 412 (25, **15**), 411 (92, **15** − H), 222 (14, **15a** + H), 206 (100, double ion of **15**) and 192 (30, **15b** + H).

Anal. Calcd for $C_{38}H_{42}N_2O_7 \cdot H_2O$: C, 69.49; H, 6.75; N, 4.27. Found: C, 69.35; H, 6.60; N, 4.17.

O-Methylation of Thaligosine (14). A 30-mg sample of **14** in 5 mL of MeOH was treated with excess ethereal diazomethane for 4 days. The product was chromatographed on 1.5 g of neutral alumina with 100 mL of chloroform as eluent and the homogeneous [TLC, R_f 0.5 with PhH–Me_2CO–NH_4OH (20:20:0.8)] material (23 mg) was identical (UV, IR, MS, NMR, and CD) with thalrugosaminine (**12**).[3a]

O-Ethylthaligosine (16). A 120-mg sample of thaligosine (**14**) in 5 mL of MeOH was treated with ethereal diazoethane prepared from 1.5 g of *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine. After 3 days the solvent was evaporated and the residue chromatographed on 6 g of neutral alumina with PhH–$CHCl_3$ (1:1) and $CHCl_3$ as eluents. The ethyl ether **16** as a homogeneous solid (110 mg) with R_f 0.47 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.6) was eluted with the latter solvent and showed: NMR δ ($CDCl_3$) 1.38 (t, J = 7, OCH_2CH_3), ~4.2 (q, J = 7, OCH_2CH_3, partially obscured), 2.50 and 2.55 (2 s, 2 NMe), 3.08, 3.38, 3.78, and 3.92 (4 s, 4 OMe), 6.39 (s, H-8), 6.45 (s, H-5), and 6.6–7.5 (m, 7 ArH); MS *m/e* 666.3316 (100%, M^+, $C_{40}H_{46}N_2O_7$ requires 666.3305).

Anal. Calcd for $C_{40}H_{46}N_2O_7 \cdot 0.5H_2O$: C, 71.09; H, 7.01; N, 4.15. Found: C, 71.45; H, 7.03; N, 4.14.

Na/NH_3 Cleavage of O-Ethylthaligosine (16). The ethyl ether **16** (105 mg) was dissolved in 6 mL of tetrahydrofuran and reduced with Na in NH_3 as described for **6**. The reaction mixture was separated into phenolic and nonphenolic fractions. Only unreacted starting material (5 mg) was obtained from the nonphenolic fraction. The phenolic fraction (57 mg) showed two major components on TLC, R_f 0.58 and 0.36 with PhH–Me_2CO–NH_4OH (20:20:0.6), and was separated on 3 g of silica gel.

The 1% MeOH in $CHCl_3$ eluent gave 13 mg of **17** as a yellow solid, identical (UV, IR, NMR, and CD) with one of the cleavage products from thalrugosaminine (**12**).[3a]

The 2% MeOH in $CHCl_3$ eluent gave 20 mg of **18** which crystallized from MeOH: mp 113–114 °C; $[\alpha]_D^{21}$ +103 (*c* 0.24, MeOH); CD $[\theta]_{284}$ +7300, $[\theta]_{230}$ +56 800; UV λ_{max} 283 nm (log ϵ 3.61); IR ($CHCl_3$) 3595 cm^{-1}; NMR δ ($CDCl_3$) 1.34 (t, J = 7, OCH_2CH_3), 4.05 (q, J = 7, OCH_2CH_3), 2.50 (s, NMe), 3.54 and 3.82 (2 s, 2 OMe), 5.87 (s, H-8), 6.62 and 6.88 (AA'BB' q, J_{AB} = 9, benzylic ring H), and 6.45 (br, OH, lost in D_2O); MS *m/e* 357.1946 (0.5%, M^+, $C_{21}H_{27}NO_4$ requires 357.1940, CI (isobutane) *m/e* 358 (10, MH^+), 250 (100, a), 107 (2, b).

Thalirugine (19). The residue (1.9 g) from fractions 38–44 was rechromatographed on 200 g of neutral alumina with $CHCl_3$ as eluent. The residue precipitated from Et_2O to give thalirugine (**19**) as a white amorphous solid: R_f 0.52 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); $[\alpha]_D^{20}$ +92° (*c* 0.25, MeOH); CD $[\theta]_{282}$ +6400, $[\theta]_{248}$ −3100, and $[\theta]_{226}$ +78 000; UV λ_{max} 280 nm (log ϵ 3.81) and in 0.01 N NaOH 280 (3.86), 285 (3.87), and 310 nm (shld) (3.45); IR ($CHCl_3$) 3520 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.43 and 2.49 (2 s, 2 NMe), 3.58 and 3.83 (2 s, 2 OMe), 3.78 (s, 2 OMe), 5.73 (s, H-8'), 6.38 (s, H-8), 6.47 (s, H-5), 6.6–7.2 (m, 7 ArH), and 5.50 (br, OH, D_2O exchangeable); MS *m/e* 640 (0.01%, M^+), 222 (100, **20**), 207 (35, **20** − Me), and 192 (83, **4**). Positive tests were obtained with phosphomolybdic acid[7] and Gibbs' reagents.[8]

Anal. Calcd for $C_{38}H_{44}N_2O_7 \cdot 0.5H_2O$: C, 70.24; H, 6.98; N, 4.31. Found: C, 70.11; H, 6.96; N, 4.27.

O-Methylation of Thalirugine (19) to 21. A 35-mg sample of **19** in 3 mL of MeOH was treated with excess ethereal diazomethane for 3 days. The residue after evaporation of solvent was chromatographed on 2 g of neutral alumina with $CHCl_3$ to yield derivative **21** as a pale yellow amorphous solid: R_f 0.75 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); $[\alpha]_D^{21}$ +105° (*c* 0.21, MeOH); CD $[\theta]_{282}$ +14 700 $[\theta]_{228}$ +76 600; NMR ($CDCl_3$) δ 2.48 and 2.51 (2 s, 2 NMe), 3.58, 3.63, 3.79, and 3.82 (4 s, 4 OMe), and 3.84 (s, 2 OMe), 5.93 (s, H-8'), 6.13 (s, H-8), 6.53 (s, H-5), and 6.6–7.2 (m, 7 ArH); MS *m/e* 668 (0.3%, M^+, $C_{40}H_{48}N_2O_7$ requires 668), 236 (100, $C_{13}H_{18}NO_3$, trimethoxylated isoquinoline fragment), and 206 (91, **3**).

O,O-Diethylthalirugine (22). A 200-mg sample of **19** in 5 mL of MeOH was treated with excess diazoethane generated from 2 g of *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine. After 5 days the reaction residue after solvent evaporation was chromatographed on 10 g of neutral alumina with 100 mL each of PhH, PhH–$CHCl_3$ (1:1), and $CHCl_3$ as eluents. A yield of 120 mg of a pale-yellow amorphous solid of diethyl ether **22** was obtained: R_f 0.85 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.6); NMR ($CDCl_3$) δ 1.34 (t, J = 7, 2 OCH_2CH_3), 3.82 and 4.05 (2 q, J = 7, 2 OCH_2CH_3), 2.47 and 2.49 (2 s, 2 NMe), 3.57, 3.81 (2 s, 2 OMe), and 3.78 (s, 2 OMe), 5.91 (s, H-8'), 6.16 (s, H-8), 6.51 (s, H-5), and 6.6–7.1 (m, 7 ArH); MS EI *m/e* 696 (0.3%, M^+, $C_{42}H_{52}N_2O_7$ requires 696), 476 (0.4, M − **8**), 446 (1, M − **23**), 250 (45, **23**), 220 (63, **8**), and 192 (100, **8** − CH_2CH_2), with CI (isobutane) *m/e* 697 (14, MH^+), 250 (85, **23**) and 220 (100, **8**).

Anal. Calcd for $C_{42}H_{52}N_2O_7 \cdot 2H_2O$: C, 68.83; H, 7.70; N, 3.82. Found: C, 68.98; H, 7.15; N, 3.95.

Na/NH_3 Cleavage of O,O-Diethylthalirugine (22). A 115-mg sample of **22** in 10 mL of tetrahydrofuran was added dropwise over 1 h to 25 mL of NH_3 containing Na. After an additional 2 h of reaction the products were separated into the phenolic and nonphenolic components by partitioning between Et_2O and 1 N NaOH.

From the ether fraction, 75 mg of a pale-yellow oil, R_f 0.85 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.6), was obtained. Chromatography on 4 g of silica gel with $CHCl_3$ and 1% MeOH in $CHCl_3$ gave the nonphenolic base **24** (47 mg), identical (UV, IR, NMR, MS, and CD) with a cleavage product from *O*-ethylthalrugosidine.[5]

The Naoh extract after treatment with solid NH_4Cl and Et_2O extraction gave the phenolic base fraction (35 mg). Chromatography on silica gel with 2 and 3% MeOH in $CHCl_3$ gave from the latter eluates 23 mg of product **18** that crystallized from MeOH, mp 114 °C, with R_f 0.6 on TLC using the same solvent as for **24**. This substance was identical (mmp, UV, IR, NMR, MS, and CD) with a cleavage product from *O*-ethylthaligosine (**16**).

$KMnO_4$ Oxidation of O,O-Diethylthalirugine (22). A 315-mg sample of **22** dissolved in 50 mL of Me_2CO was treated with 600 mg of $KMnO_4$ added portionwise in 1 h while stirring. After an additional 3 h of stirring the excess reagent was decomposed with MeOH, and the MnO_2 was removed by filtration. The filtrate was concentrated, mixed with 25 mL of H_2O, acidified with 5% HCl, and exhaustively extracted with $CHCl_3$. The residue (210 mg) from the washed (H_2O) and dried (Na_2SO_4) $CHCl_3$ extract was chromatographed on 10 g of silica gel with 50 mL of PhH and 100 mL each of PhH–$CHCl_3$ (1:1), $CHCl_3$, and 2.5, 5, and 10% MeOH in $CHCl_3$.

The PhH–$CHCl_3$ (1:1) eluates gave first, after crystallization from MeOH, 36 mg of yellow needles of isoquinolone **25**: mp 120–121 °C; R_f 0.72 on TLC with PhH–Me_2CO (1:1); UV, IR, NMR, and MS identical with those of a synthetic sample[9] of 6-methoxy-7-ethoxy-*N*-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline.[10]

The later PhH–$CHCl_3$ (1:1) eluates gave 30 mg of isoquinolone **26** as a pale-yellow oil: R_f 0.66 on TLC with the same solvent as used for **25**; UV λ_{max} 296 (log ϵ 3.48), 270 (shld) (3.88), 260 (3.96), 253 (shld) (3.92), and 216 nm (4.52); IR ($CHCl_3$) 1645 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.35 (t, J = 7, OCH_2CH_3), 4.06 (q, J = 7, OCH_2CH_3), 2.92 and 3.51 (2 A_2B_2 t, J = 6, CH_2CH_2), 3.12 (s, NMe), 3.90 (s, 2 OMe), and 7.44 (s, H-8); MS *m/e* 265.1320 (100%, M^+, $C_{14}H_{19}NO_4$ requires 265.1314), 250 (3, M − Me), 236 (9, M − Et), 222 (33, M − CH_2NMe), and 194 (35, 222 − CO). This compound was identical (TLC, UV, IR, NMR, and MS) with 5-ethoxy-6,7-dimethoxy-*N*-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline produced by $KMnO_4$ oxidation of the *O*-ethylated cleavage product **10** from authentic thalidasine (**5**).[11]

From the 5 and 10% MeOH in $CHCl_3$ fractions, 100 mg of a white solid was obtained that exhibited the same TLC characteristics as 2-methoxy-4',5-dicarboxy diphenyl ether (**27**) prepared from the corresponding dialdehyde[12] by Ag_2O oxidation. Treatment of both samples with diazomethane afforded diester **28**, mp 79–80 °C, with identical TLC mobility, IR and NMR spectra, and an undepressed mmp.

Preparation of O,O-Diethyl 10 and $KMnO_4$ Oxidation. Diphenol **10** (120 mg) obtained by Na/NH_3 cleavage[11] of thalidasine (**5**, 300 mg) in 5 mL of MeOH was treated with excess ethereal diazoethane. After 12 days the solvent was evaporated and the residue chromatographed on 5 g of neutral alumina with PhH (200 mL) and PhH–$CHCl_3$ (4:1, 100 mL). From the latter eluate, 80 mg of the diethyl ether of **10** as a yellow heavy oil was obtained: R_f 0.86 on TLC with PhH–Me_2CO–NH_4OH (10:10:0.1); UV λ_{max} 278 nm (log ϵ 3.77) and unchanged by acid or base; NMR ($CDCl_3$) δ 1.34 and 1.38 (2 t, J = 7, 2 OCH_2CH_3), 3.98 and 4.05 (2 q, J = 7, 2 OCH_2CH_3), 2.50 (s, NMe), 3.57 and 3.82 (2 s, 2 OMe), 5.91 (s, H-8), and 6.77 and 6.97 (AA'BB' q, J_{AB} = 9, 4 ArH); MS *m/e* 385 (0.2%, M^+), 250 (100, **23**), 221 (1, **23** − Et), 220 (8, **23** −Et-H) and 135 (2, M − **23**).

A 70-mg sample of *O,O*-diethyl-**10** was dissolved in 25 mL of Me_2CO, and 150 mg of $KMnO_4$ was added during 1 h while stirring. After reacting an additional 3 h the excess reagent was destroyed by 10 mL of MeOH. The mixture was filtered and the filtrate concentrated to 3 mL. Addition of 10 mL of H_2O and acidification with 0.1 N HCl produced a white precipitate that was removed by filtration. The filtrate was extracted with 150 mL of $CHCl_3$, and the extract after washing (H_2O) and drying (Na_2SO_4) left, on evaporation, 40 mg of a pale-yellow oil. It was chromatographed on 2 g of neutral alumina with PhH (50 mL). The 30 mg of heavy oil was identified by spectral evidence to be isoquinolone **26**, identical (TLC, UV, IR, NMR, and MS) with the corresponding oxidation products from *O,O*-diethylthalirugine (**22**) and *O,O*-diethylthalirugidine (**34**).

Thaliruginine (29). From the same column separation that gave thaligosine (**14**), the 3 and 4% MeOH in $CHCl_3$ eluates gave 260 mg of thaliruginine (**29**) as a white amorphous solid: R_f 0.65 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); $[\alpha]_D^{20}$ +104° (*c* 0.16, MeOH); CD $[\theta]_{287}$ +14 500, $[\theta]_{252}$ −2100, $[\theta]_{230}$ +93 000; UV λ_{max} 281 nm (log ϵ 3.90) and in 0.01 N NaOH 281 (3.97) and 309 nm (shld) (3.09); IR ($CHCl_3$) 3520 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.48 and 2.50 (2 s, 2 NMe), 3.57, 3.61, 3.78, 3.80 and 3.83 (5 s, 5 OMe), 5.71 (s, H-8), 6.11 (s, H-8′), 6.53 (s, H-5′), 6.6–7.2 (m, 7 ArH), and 5.4 (br, OH, D_2O exchangeable); MS *m/e* 654 (0.8%, M^+), 222 (68, **20**), 206 (100, **3**), and 192 (26, **3** − Me). Thaliruginine gave positive tests with phosphomolybdic acid[7] and Gibbs' reagent.[8]

Anal. Calcd for $C_{39}H_{46}N_2O_7 \cdot H_2O$: C, 69.62; H, 7.19. Found: C, 69.32; H, 6.86.

O-Methylation of Thaliruginine (29) to 21. A 40-mg sample of **29** in 5 mL of MeOH was treated with excess ethereal diazomethane for 3 days to give 35 mg of derivative **21**, identical (TLC, UV, IR, NMR, and CD) with the methylated product of thalirugine (**19**).

***O*-Ethylthaliruginine (30).** A 100-mg sample of **29** in 5 mL of MeOH was treated with excess ethereal diazoethane. The product was chromatographed on 5 g of silica gel PF 254 using 100 mL each of $CHCl_3$ and 1% MeOH in $CHCl_3$ as eluents to yield 80 mg of **30** as an amorphous pale-yellow solid: R_f 0.8 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); NMR ($CDCl_3$) δ 1.34 (t, J = 7, $OCH_2\mathbf{CH_3}$), 4.05 (q, J = 7, OCH_2CH_3), 2.48 and 2.50 (2 s, 2 NMe), 3.58, 3.62, 3.78, 3.80, and 3.82 (5 s, 5 OMe), 5.92 (s, H-8′), 6.13 (s, H-8), 6.58 (s, H-5), and 6.6–7.2 (m, 7 ArH); MS *m/e* 682 (0.2%, M^+, $C_{41}H_{50}N_2O_7$ requires 682), 250 (95, **23**), and 206 (100, **3**).

Na/NH_3 Cleavage of *O*-Ethylthaliruginine (30). A 60-mg sample in 5 mL of tetrahydrofuran was reacted with Na/NH_3, and the products were worked up as described for compound **22**. From the nonphenolic fraction, 11 mg of (*S*)-*O*-methylarmepavine (**31**) was obtained and identified by direct comparison (TLC, UV, IR, NMR, and CD) with an authentic sample. The phenolic fraction gave 10 mg of crystalline **18** which was identified by comparison (mmp, TLC, UV, IR, NMR, and CD) with an authentic sample.

Thalirugidine (32). The residue (360 mg) from column fraction 37 was rechromatographed on 16 g of silica gel with $CHCl_3$ and 2, 4, 8, and 10% MeOH in $CHCl_3$ as eluents. From the 2% MeOH in $CHCl_3$ eluate, 55 mg of thalirugidine (**32**) was obtained as a white amorphous solid: R_f 0.60 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); $[\alpha]_D^{20}$ +112° (*c* 0.19, MeOH); CD $[\theta]_{280}$ +7200, $[\theta]_{230}$ +98 500; UV λ_{max} 278 nm (log ϵ 3.82) and in 0.01 N NaOH 281 nm (3.94); IR ($CHCl_3$) 3530 cm^{-1}; NMR ($CDCl_3$) δ 2.48 and 2.51 (2 s, 2 NMe), 3.61, 3.63, 3.85 (3 s, 3 OMe) and 3.81 (s, 2 OMe), 5.76 and 5.79 (2 s, H-8 and H-8′), 6.6–7.2 (m, 7 ArH), and 5.1 (br, 2 OH, D_2O exchangeable); MS *m/e* 670 (1.4%, M^+), 222 (100, **20**), 221 (3, **20** − H), 220 (3, **20** − 2H), 207 (3, **20** − Me), 206 (8, **20** − Me − H), 192 (8, 220 − CO), and 178 (2, 206 − CO).

Anal. Calcd for $C_{39}H_{46}N_2O_8$: C, 69.83; H, 6.91; N, 4.18. Found: C, 69.78; H, 7.18; N, 4.15.

***O,O*-Dimethylthalirugidine (33).** Thalirugidine (**32**, 20 mg) in 2 mL of MeOH was treated with excess diazomethane for 3 days to give 15 mg of a pale-yellow amorphous solid; R_f 0.83 on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8); $[\alpha]_D^{20}$ +53° (*c* 0.21, MeOH); CD $[\theta]_{285}$ +8700, $[\theta]_{230}$ +42 000; UV λ_{max} 278 nm (log ϵ 3.96); NMR ($CDCl_3$) δ 2.47 and 2.50 (2 s, 2 NMe), 3.59, 3.61, 3.79 (3 s, 3 OMe) and 3.83 (s, 4 OMe), 5.93 and 5.98 (2 s, H-8 and H-8′), and 6.6–7.2 (m, 7 ArH); MS *m/e* (M^+ not observed), 236 (100, isoquinoline fragments).

***O,O*-Diethylthalirugidine (34).** A 130-mg sample of **32** in 5 mL of MeOH was treated with diazoethane for 5 days. The reaction residue was chromatographed on 6 g of silica gel using 1% MeOH in $CHCl_3$ as eluent, to give 120 mg of the diethyl ether **34** as an amorphous solid: $[\alpha]_D^{20}$ +44° (*c* 0.17, MeOH); CD $[\theta]_{282}$ +5700, $[\theta]_{230}$ +30 500; NMR ($CDCl_3$) δ 1.33 (t, J = 7, 2 $CH_2\mathbf{CH_3}$), 4.03 (q, J = 7, 2 $\mathbf{CH_2}CH_3$), 2.45 and 2.47 (2 s, 2 NMe), 3.58, 3.60, 3.77 (3 s, 3 OMe), 3.81 (s, 2 OMe), 5.92 and 5.96 (2 s, H-8 and H-8′), and 6.6–7.2 (m, 7 ArH); MS *m/e* 726 (0.5%, M^+, $C_{43}H_{54}N_2O_8$ requires 726), 250 (100, **23**), 235 (8, **23** − Me), 234 (7, **23** − Me − H), 221 (4, **23** − Et), 220 (17, **23** − Et − H), 206 (11, 234 − CO), and 192 (7, 220 − CO).

Na/NH_3 Cleavage of *O,O*-Diethylthalirugidine (34). The diethyl ether **34** (105 mg) in 10 mL of tetrahydrofuran was reductively cleaved with 150 mg of Na in ammonia, and the products were divided into phenolic and nonphenolic bases. The nonphenolic fraction (50 mg) as a yellow oil showed two spots, R_f 0.86 (major) and 0.91, on TLC with PhH–Me_2CO–NH_4OH (20:20:0.8). Chromatography on 2.5 g of silica gel PF 254 with 50 mL of PhH–$CHCl_3$ (1:1) and 100 mL of $CHCl_3$ gave 18 mg of **35**, the major base, as a colorless oil. It showed TLC mobility and UV, IR, NMR, and CD spectra identical with the corresponding cleavage product from thalidezine[13] or isothalidezine.[14] The minor product **36**, obtained as a yellow oil (8 mg), showed identical TLC characteristics and UV, IR, and NMR spectra as those for a cleavage by-product from thalidezine.[13]

The phenolic fraction (38 mg) contained one component, R_f 0.36 on TLC with system used for the nonphenolics. Chromatography on 2 g of silica gel PF 254 with 100 mL each of 1 and 2% MeOH in $CHCl_3$ afforded a crystalline residue (26 mg) that was recrystallized from MeOH to give colorless rosettes of **18**, mp 113–114 °C, identical (TLC, UV, IR, NMR, and CD) with a sample from *O*-ethylthaligosine (**16**).

Methylation of **18** with diazomethane gave **35**.

$KMnO_4$ Oxidation of *O,O*-Diethylthalirugidine (34). Compound **34** (50 mg) in 10 mL of Me_2CO was treated with 150 mg of $KMnO_4$. After stirring for 3 h, the workup as reported for the oxidation of **22** yielded 8 mg of isoquinolone **26** and the diphenyl ether diacid **27**. Both were compared directly (the latter as the dimethyl ester **28**) with known samples by TLC and UV, IR, and NMR spectra. Compound **28** also showed no depression of the mmp.

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Registry No.—**1**, 64252-82-0; **6**, 64252-83-1; **9**, 3423-12-9; **10**, 16623-60-2; **10** diethyl ether, 64235-37-6; **11**, 64235-38-7; **14**, 22226-72-8; **16**, 64235-39-8; **18**, 64235-40-1; **19**, 64235-41-2; **21**, 64215-90-3; **22**, 64215-91-4; **25**, 2651-56-1; **26**, 64215-92-5; **28**, 5566-15-4; **29**, 64215-93-6; **30**, 64215-94-7; **32**, 64215-95-8; **33**, 64215-96-9; **34**, 64215-97-0; **35**, 64281-58-9; **36**, 64281-59-0.

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