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# Tumor Inhibitors. XLII.[1a] Thalidasine, a Novel Bisbenzylisoquinoline Alkaloid Tumor Inhibitor from *Thalictrum dasycarpum*[1b]

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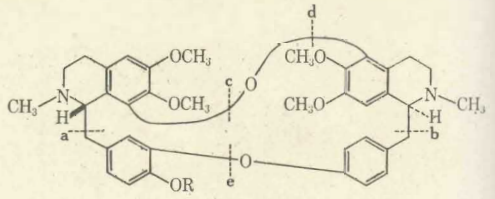
Evidence is presented for assignment of structure and configuration 1a to thalidasine, a new alkaloid tumor inhibitor from *Thalictrum dasycarpum*. Elemental analysis and molecular weight determination by mass spectrometry supported a $C_{39}H_{44}N_2O_7$ formula. Functional group analysis and nmr spectral evidence showed the presence of five O-methyl groups and two N-methyl groups. Cleavage in sodium–liquid ammonia afforded L-O-methylarmepavine (2a), L-1-(4′-hydroxybenzyl)-2-methyl-5-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3c), L-armepavine (3e), and L-1-(4′-methoxybenzyl)-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (2b). Permanganate oxidation of thalidasine yielded 2-methoxydiphenyl ether 4′,5-dicarboxylic acid (17). The mass spectrum of thalidasine showed a base peak corresponding to a doubly charged ion of *m/e* 213, supporting the unsymmetrical bisbenzylisoquinoline nature of the structure 1a. Thalfoetidine is shown to possess structure 1b, on the basis of evidence which includes interrelation with thalidasine.

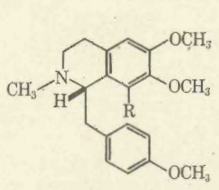
Thalidasine is a new alkaloid tumor inhibitor[3] from *Thalictrum dasycarpum* Fisch. and Lall from Wisconsin. In earlier communications, we have outlined the isolation[4] and structural elucidation[5] of thalidasine. It is the purpose of this paper to present, in detail, the elucidation of structure and configuration of thalidasine (1a). Thalidasine appears to be the first bisbenzylisoquinoline alkaloid recognized to contain a diphenyl ether terminus at C-5 and the first unsymmetrical bisbenzylisoquinoline recognized to contain a 20-membered ring.[6] Furthermore, the alkaloid thalfoetidine, from *T. foetida*,[7] is shown to possess structure 1b, on the basis of evidence which includes interrelation with thalidasine.

The molecular formula $C_{39}H_{44}N_2O_7$ was assigned for thalidasine on the basis of elemental analysis and molecular weight determination by mass spectrometry.[8] The nmr spectrum indicated the presence of two N-methyl groups ($\tau$ 7.38 and 7.75, 6 H), five methoxyl groups ($\tau$ 6.09, 6.13, 6.25, 6.50, and 6.73, 15 H), and nine aromatic protons ($\tau$ 2.46–3.70, 9 H).

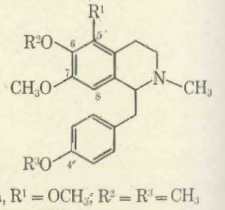
The most useful reaction in structural studies of dimeric alkaloids which possess diphenyl ether moieties has been cleavage by the action of metallic sodium in liquid ammonia.[9] Sodium–liquid ammonia reduction of thalidasine afforded, as principal products, L-(+)-O-methylarmepavine (2a) and a dihydroxydimethoxyisoquinoline (A), $C_{19}H_{23}NO_4$. The nmr spectrum of phenol A showed signals at $\tau$ 7.48 (3 H, $NCH_3$), 6.13, 6.45 (6 H, two $OCH_3$), 4.33 (1 H, C-8 H), 3.92 (2 H, two OH), and 3.08 and 3.35 (4 H, two doublets, $J$ = 8.5 Hz). The substitution pattern of phenol A was established by methylation with diazomethane to afford 1-(4′-methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (3a), characterized by direct comparison with the *dl* compound.[10] Analysis of the nmr spectrum of phenol A, in the light of correlations established for closely related compounds,[10–12] indicated that the signal at $\tau$ 6.45 corresponded to a C-7 methoxyl group, whereas that at $\tau$ 6.13 could be attributed equally well to a methoxyl group at either C-5 or C-6. These observations and the reactivity toward Gibbs reagent[13] limited the hypothetical alternatives for phenol A's structure to the 4′,6-diphenol 3b or the 4′,5-diphenol 3c.



1a, R = $CH_3$
b, R = H



2a, R = H
b, R = OH



3a, $R^1 = OCH_3$; $R^2 = R^3 = CH_3$
b, $R^1 = OCH_3$; $R^2 = R^3 = H$
c, $R^1 = OH$; $R^2 = CH_3$; $R^3 = H$
d, $R^1 = OCH_3$; $R^2 = R^3 = CH_2Ph$
e, $R^1 = H$; $R^2 = CH_3$; $R^3 = H$

(1) (a) Part XLI: S. M. Kupchan, J. E. Kelsey, M. Maruyama, J. M. Cassady, J. C. Hemingway, and J. R. Knox, *J. Org. Chem.*, **34**, 3876 (1969). This paper is also part X in our series entitled "Thalictrum Alkaloids." Part IX: S. M. Kupchan and A. Yoshitake, *J. Org. Chem.*, **34**, 1062 (1969). (b) This investigation was supported by grants from the National Heart Institute (HE-02952) and the National Cancer Institute (CA-04500), and a contract with Chemotherapy, National Cancer Institute, National Institutes of Health (PH 43-64-557).

(2) Author to whom inquiries should be directed: Department of Chemistry, University of Virginia, Charlottesville, Va. 22901.

(3) Thalidasine showed significant inhibitory activity against Walker intramuscular carcinosarcoma 256 in rats at 200 mg/kg. Tumor-inhibitory activity was assayed, under the auspices of the CCNSC, by the procedures described in *Cancer Chemotherapy Rept.*, **25**, 1 (1962).

(4) S. M. Kupchan, T.-H. Yang, M. L. King, and R. T. Borchardt, *J. Org. Chem.*, **33**, 1052 (1968).

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(6) Cissampareine was the first symmetrical bisbenzylisoquinoline recognized to contain a 20-membered ring [S. M. Kupchan, S. Kubota, E. Fujita, S. Kobayashi, J. H. Block, and S. A. Telang, *ibid.*, **88**, 4232 (1966)].

(7) N. M. Mollov and V. St. Georgiev, *Chem. Ind.* (London), 1178 (1966).

(8) The authors thank Professor A. L. Burlingame and Dr. H. K. Schnoes, University of California, Berkeley, for the mass spectral data and helpful discussions.

(9) M. Tomita, *Progr. Chem. Org. Nat. Prod.*, **9**, 175 (1952).

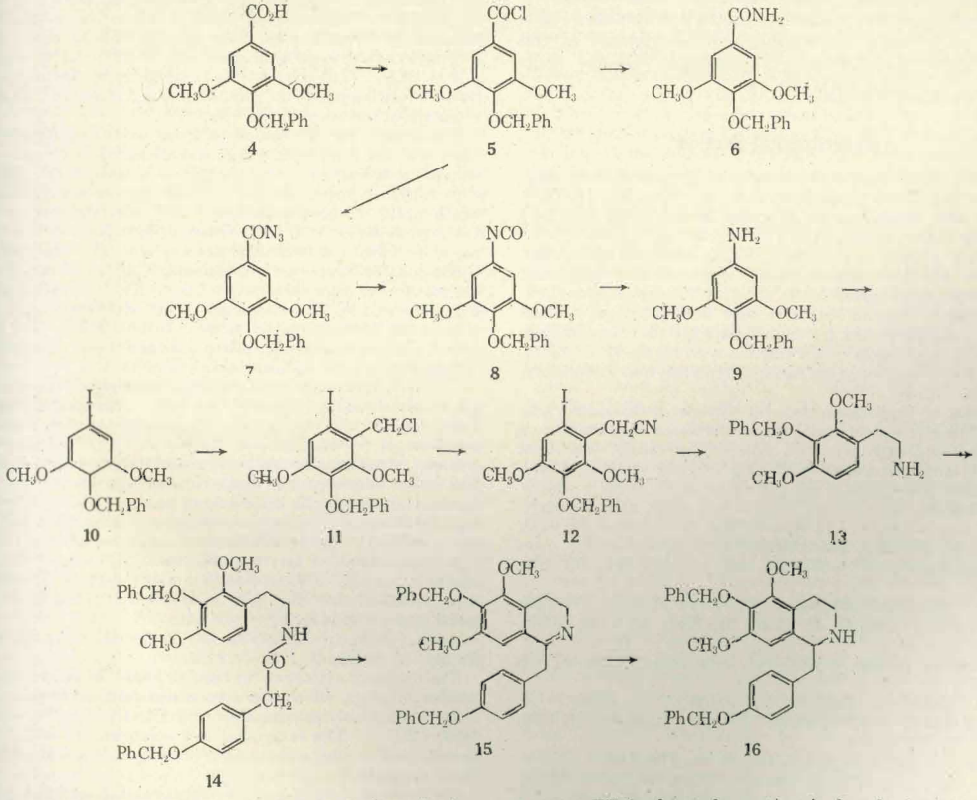
(10) S. Kubota, T. Masui, E. Fujita, and S. M. Kupchan, *J. Org. Chem.*, **31**, 516 (1966).

(11) M. Tomita, T. Shingu, K. Fujitani, and H. Furukawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 921 (1965).

(12) M. Tomita, T. Shingu, and H. Furukawa, *J. Pharm. Soc. Jap.*, **86**, 373 (1966).

(13) M. Tomita and Y. Kondo, *J. Pharm. Soc. Jap.*, **77**, 1019 (1957); H. Inouye, Y. Kanaya, and Y. Murata, *Chem. Pharm. Bull.* (Tokyo), **7**, 573 (1959).

The synthesis of *dl*-**3b** was undertaken to make possible a choice between the structural alternatives for phenol A. The recorded route to the intermediate 4-benzyloxy-3,5-dimethoxyaniline (**9**)[14] from 4-benzyloxy-3,5-dimethoxybenzoic acid[15] *via* **5** and **6** was found to give unsatisfactory yields. Hence, an alternative route was devised, which proceeded *via* Curtius degradation of azide **7** and afforded amine **9** in 66% overall yield from **4**. Conversion of **9** to **10** was effected as described previously,[14] and chloromethylation of **10** gave **11**. Treatment of **11** with aqueous potassium cyanide gave nitrile **12**, and reduction of **12** with lithium aluminum hydride afforded the iodine-free amine **13**, characterized as its oxalate salt. When **13** was acylated with 4-benzyloxyphenylacetyl chloride under Schotten–Baumann conditions, the phenylacetamide **14** was obtained. Ring closure with phosphoryl chloride under nitrogen, followed directly by sodium borohydride reduction, gave **16**. Methylation of **16** gave **3d**, and hydrogenolysis of the benzyl ether groups of **3d** with palladium on charcoal gave *dl*-**3b**. The spectral properties of *dl*-**3b** clearly *differed* from those of phenol A. Hence, phenol A was assumed to have structure **3c**, and thalidasine, an unprecedented diphenyl ether terminus at C-5. Evidence for both structures was adduced from the experimental results which follow.




Characterization of the *minor* phenolic products of reduction with sodium–liquid ammonia limited sharply the hypothetical structures which could be considered as likely possibilities. One minor phenolic cleavage product was characterized as L-(+)-armepavine (**3e**), indicative that cleavages d and e had occurred (as well as cleavage c). This view was confirmed by characterization of a second minor phenolic product as L-1-(4′-methoxybenzyl)-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (**2b**), identified by direct comparison with the *dl* compound.[16]

Permanganate oxidation of thalidasine resulted in oxidative cleavages a and b and yielded 2-methoxydiphenyl ether 4′,5-dicarboxylic acid (**17**), characterized by direct comparison with an authentic sample.[17] The nature of the oxidation product fixed the location of the termini of the diphenyl ether linkage as in **1a**, and thereby established that thalidasine belongs to the unsymmetrical bisbenzylisoquinoline group. With this information in hand, the previously established structures of cleavage products **2a**, **2b**, **3a**, and **3e** strongly supported assignment of structure **1a** for thalidasine. Furthermore, the fact that cleavage products from each of the tetrahydroisoquinoline moieties possess the L absolute configuration indicates the absolute configuration at the asymmetric centers of thalidasine to be as represented in **1a**.

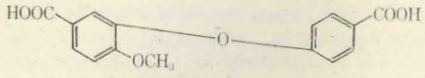
The most intense peak in the mass spectrum of thalidasine is a doubly charged ion (**18**) of *m/e* 213

(14) K. Freudenberg and W. Fuchs, *Chem. Ber.*, **87**, 1824 (1954).

(15) W. Bradley and R. Robinson, *J. Chem. Soc.*, 1553 (1928).

(16) A. Brossi and S. Teitel, *Helv. Chim. Acta*, **49**, 1757 (1966). We thank Dr. Brossi cordially for a sample of *dl*-**2b**.

(17) The authors thank Professor M. Tomita cordially for the authentic sample of 2-methoxydiphenyl ether 4′,5-dicarboxylic acid.



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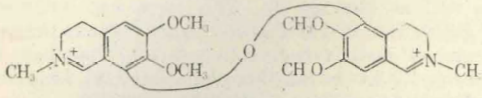

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($C_{24}H_{30}N_2O_5$), resulting from fragmentation at a and b. This type of fragmentation has been shown to be characteristic of alkaloids of the unsymmetrical bisbenzylisoquinoline type.[18-20]

Thalfoetidine's chemistry supports the structural features assumed earlier,[7] apart from the termini of the diaryl ether linkage connecting the tetrahydroisoquinoline moieties. Methylation of thalfoetidine[7,21] with diazomethane yielded O-methylthalfoetidine, and direct comparison has established the identity of the methylation product with thalidasine. Hence, thalfoetidine possesses structure **1b**.

## Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are corrected. Infrared spectra were determined on Beckman Model IR-5A and IR-9 recording spectrophotometers. Ultraviolet spectra were determined on a Beckman Model DK-2A recording spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian A-60A spectrometer using tetramethylsilane as internal standard. Specific rotations were determined on a Zeiss–Winkel polarimeter and are approximated to the nearest degree. Petroleum ether refers to the fraction with bp 60–68°. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

**Isolation of Thalidasine (1a).**—A solution of thalidasine oxalate[4] (120 mg) in water (10 ml) was made alkaline with ammonium hydroxide and extracted with ether. The extract was dried ($Na_2SO_4$) and evaporated to dryness to yield thalidasine as a pale yellow amorphous solid (83 mg): mp 105–107°; $[\alpha]^{27}D$ −70° (*c* 0.89, MeOH); uv $\lambda_{max}^{EtOH}$ 275 (ε 4560) and 282 mμ (ε 4530); nmr τ 7.38, 7.75 (6 H, 2 $NCH_3$), 6.09, 6.13, 6.25, 6.50, 6.73 (15 H, 5 $OCH_3$), and 2.46–3.70 (9 H, aromatic H); mass spectrum *m/e* 652 ($M^+$), 637, 621, 425, 411, 394, 379, 213, 204, and 190.

*Anal.* Calcd for $C_{39}H_{44}N_2O_7$: C, 71.76; H, 6.79; N, 4.29; 5 $OCH_3$, 23.77. Found: C, 72.20; H, 7.14; N, 4.14; $OCH_3$, 24.05.

**Thalidasine picrate**, crystallized from ethanol, showed mp 175–177°.

*Anal.* Calcd for $C_{39}H_{44}N_2O_7 \cdot 2C_6H_3N_3O_7$: C, 55.13; H, 4.54; N, 10.08; 5 $OCH_3$, 13.97. Found: C, 54.59; H, 4.98; N, 9.85; $OCH_3$, 14.87.

**Sodium–Liquid Ammonia Cleavage of Thalidasine (1a).**—A three-necked 1-l. flask was equipped with a mechanical stirrer, an equilibrated dropping funnel with a nitrogen gas inlet, and a nitrogen gas outlet on a dewar-type condenser. Ammonia (600 ml) was distilled into the flask through a trap containing potassium hydroxide. The temperature of the flask was maintained at −30 to −35° by the liquid ammonia under reflux. A small amount of metallic sodium sufficient to color the solution blue was added. A solution of thalidasine (0.55 g) in dried toluene (20 ml) was placed in the dropping funnel. The reaction was executed (under a nitrogen atmosphere) by adding small portions of the toluene solution and metallic sodium to the reaction vessel alternately so that the blue color of the reaction mixture was maintained. The reaction was stopped 30 min after all the toluene solution had been added to the mixture; the mixture maintained its blue color. About 1.75 g of sodium had been consumed in the reaction, which proceeded for a total of 3.5 hr. The reaction mixture was allowed to stand overnight in the hood to evaporate the solvent. The residual toluene solution was treated with 10% hydrochloric acid (20 ml) and ether (50 ml). The acid extract was made alkaline with ammonium hydroxide and extracted with ether (six 25-ml portions). The ethereal solution was extracted with 2.5% sodium hydroxide solution (six 4-ml portions), dried ($MgSO_4$), and evaporated to dryness to leave 198 mg of residue (fraction I). The sodium hydroxide solution was treated with an excess of ammonium chloride (5 g) and extracted with ether (eight 25-ml portions). The ethereal solution was dried ($MgSO_4$) and evaporated to dryness to leave 0.218 g of residue (fraction II).

**L-O-Methylarmepavine (2a) and L-1-(4′-Methoxybenzyl)-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (2b).**—A solution of fraction I (0.56 g) in ethanol was treated with a saturated solution of oxalic acid in ethanol and allowed to stand until precipitation was complete. The precipitate was collected and crystallized from acetone to give colorless plates (143 mg): mp 106–108°. Liberation of the free base in the normal way, followed by crystallization from ether–petroleum ether, gave L-O-methylarmepavine as needles: mp 61–62°; $[\alpha]^{26}D$ +99° (*c* 1.10, $CHCl_3$). The compound was identified by melting point, mixture melting point, tlc, mixture tlc, and ir and nmr spectral comparisons with an authentic sample.[22]

The filtrate from the oxalate salt was treated to liberate free base, and the residue (224 mg) was dissolved in benzene and chromatographed on alumina (50 g, Woelm, activity I). Elution with benzene–acetone mixtures and with chloroform gave residues which consisted largely of additional L-O-methylarmepavine (2a). Subsequent elution with 10% methanol–chloroform, 50% methanol–chloroform, and methanol gave a residue (27.2 mg) rich in a Gibbs-positive component. Chromatography on silica gel with chloroform and chloroform–acetone mixtures of increasing polarity, monitored by tlc on silica gel H, led to isolation of **2b** as a colorless oil (6.2 mg): $[\alpha]^{27}D$ +32° (*c* 0.40, $CHCl_3$). The compound was characterized by mixture tlc and ir and nmr spectral comparisons with an authentic sample of *dl*-**2b**.[16]

**L-1-(4′-Hydroxybenzyl)-2-methyl-5-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3c) and L-Armepavine (3e).**—Fraction II (85 mg) was separated by thick layer chromatography on silica gel G with methanol–chloroform (9:1). After drying occurred, three bands could be discerned under ultraviolet light. The bands were separated and extracted with methanol. The methanol extract of the middle band yielded a solid residue (28 mg) which was crystallized from ether–petroleum ether (21 mg, mp 188–190°). Recrystallization from the same solvents yielded light brown cubes of **3c**: mp 194–196°; $[\alpha]^{27}D$ +51° (*c* 0.50, MeOH); uv $\lambda_{max}^{EtOH}$ 279 mμ (ε 2750); nmr τ 7.48 (3 H, $NCH_3$), 6.13, 6.45 (6 H, 2 $OCH_3$), 4.33 (1 H, C-8 H), 3.92 (2 H, 2 OH), and 3.08 and 3.35 (4 H, 2 d, $J$ = 8.5 Hz).

*Anal.* Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.36; H, 7.03; N, 4.32.

The methanol extract of the band of lowest $R_f$ yielded an oily residue (19 mg), which was crystallized from ether–petroleum ether to yield L-armepavine (**3e**): mp 122–125°; $[\alpha]^{27}D$ +99° (*c* 0.14, $CHCl_3$). The compound was identified by direct comparison with an authentic sample[22] (mixture tlc and ir and nmr spectral comparisons).

**Methylation of 3c to 1-(4′-Methoxybenzyl)-2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (3a).**—A solution of **3c** (45 mg) in methanol (3 ml) was treated with an excess of an ethereal solution of diazomethane, and the solution was allowed to stand for 3 days at room temperature. The solution was treated with a second charge of ethereal diazomethane on the third and fifth days of the 7-day reaction period. The solvent was evaporated and the residue was dissolved in benzene and chromatographed on neutral alumina (Woelm, activity I). Elution with 10% acetone–benzene gave a fraction enriched in a compound with the same tlc mobility as *dl*-**3a**.[10] Rechromatography by the same procedure yielded a chromatographically homogeneous product (8.4 mg) which showed the same tlc and mixture tlc as *dl*-**3a**. The ir spectrum in chloroform solution was superimposable upon that of the reference sample.

(18) M. Shamma, B. S. Dudock, M. P. Cava, K. V. Rao, D. R. Dalton, D. C. DeJongh, and S. R. Shrader, *Chem. Commun.*, 7 (1966).

(19) M. Tomita, T. Kikuchi, K. Fujitani, H. Kato, H. Furukawa, Y. Aoyagi, M. Kitano, and T. Ibuka, *Tetrahedron Lett.*, 857 (1966).

(20) D. C. DeJongh, S. R. Shrader, and M. P. Cava, *J. Amer. Chem. Soc.*, **88**, 1052 (1966).

(21) We thank Dr. Mollov cordially for a sample of thalfoetidine.

(22) S. M. Kupchan, B. Dasgupta, E. Fujita, and M. L. King, *Tetrahedron*, **19**, 227 (1963).

**Permanganate Oxidation of Thalidasine (1a).**—A solution of thalidasine (220 mg) in 2 *N* hydrochloric acid (26 ml) was adjusted with 10% sodium hydroxide solution to pH 6. To the stirred solution, 2% potassium permanganate solution (115 ml) was added gradually. The reaction mixture was kept at room temperature for 2.5 hr and then in a water bath at 70° for 30 min. The reaction mixture was cooled with ice, acidified with dilute sulfuric acid, and treated with sodium bisulfite to destroy the excess of potassium permanganate. The solution was extracted with ethyl acetate, and the ethyl acetate was extracted with 10% sodium hydroxide solution. Acidification with dilute sulfuric acid and extraction with ethyl acetate, drying ($Na_2SO_4$), and evaporation yielded a solid residue (174 mg). The solid was dissolved in 5% sodium carbonate solution, and the solution was washed with ether and acidified with 10% hydrochloric acid. The acidified solution was extracted with ether and the ethereal extract was dried ($Na_2SO_4$) and evaporated to dryness (residue, 132 mg). Crystallization from methanol yielded 2-methoxydiphenyl ether 2′,5-dicarboxylic acid (**17**, 5.2 mg): mp 295–297°. The melting point was not depressed by admixture of an authentic sample, and the ir spectrum in Nujol was superimposable upon that of the reference sample.[17]

**Methylation of Thalfoetidine (1b) to Thalidasine (1a).**—A solution of thalfoetidine (**1b**, 27 mg) in chloroform–methanol (1:1, 6 ml) was treated with an excess of an ethereal solution of diazomethane, and the solution was allowed to stand for 24 hr at room temperature. The solution was treated with two additional charges of ethereal diazomethane on the second and third days of the 3-day reaction period. The solvent was evaporated and the residue was dissolved in 2% hydrochloric acid solution and washed with ether. The aqueous solution was made alkaline with dilute sodium hydroxide solution and extracted with ether. The residue (20 mg) obtained upon evaporation of the ether was characterized as thalidasine (**1a**) by mixture tlc and ir and nmr spectral comparisons with an authentic sample.

**4-Benzyloxy-3,5-dimethoxyaniline (9).**—A stirred solution of 4-benzyloxy-3,5-dimethoxybenzoyl chloride[15] (**5**, 9.25 g) in acetone at 5° was treated in portions with a solution of sodium azide (2.44 g) in water (10 ml). Ice and water were added, and the precipitated oil crystallized. After 30 min, filtration yielded the azide **7** (9.16 g): mp 70–71°; ir $\lambda_{max}^{Nujol}$ 4.65 $\mu$. A toluene (10 ml) solution of the azide (9.16 g) was heated under reflux for 1 hr. Evaporation of the toluene under reduced pressure left an oily residue of isocyanate **8** (12 g): $\lambda_{max}^{film}$ 4.41 $\mu$. The oily isocyanate was treated with benzene (20 ml) and 50% sodium hydroxide solution (36 ml), and the reaction mixture solidified upon swirling. The mixture was dissolved in water and extracted with ether. The ether extract was extracted with 5% hydrochloric acid. The first aqueous layer was acidified with 10% hydrochloric acid, basified with 20% sodium hydroxide, and extracted three times with ether. The combined ether extracts were extracted with a volume of 5% hydrochloric acid sufficient to dissolve the crystalline precipitate. The combined 5% hydrochloric acid extracts were basified with 20% sodium hydroxide solution and extracted three times with ether. The ethereal solution was washed, dried ($MgSO_4$), and evaporated to leave a crystalline residue of **9** (6.5 g): mp 69–70° (lit.[14] mp 69°).

**3,5-Dimethoxy-4-benzyloxyiodobenzene (10).**—The diazotization and replacement by iodine were carried out, as described earlier,[14] on 3.5 g of amine **9**, to yield a red oil which showed two spots on examination by tlc on silica gel using chloroform–benzene (3:1) and spraying with ceric sulfate solution. The higher $R_f$ and major product was the desired iodobenzene derivative. The red oil (4.4 g) was dissolved in petroleum ether (with difficulty, insoluble residue 0.45 g) and chromatographed on neutral alumina (Woelm, activity II, 200 g). Elution was continued with petroleum ether in fractions of 150 ml. Fractions 6–20 yielded homogeneous crystalline material (**10**), mp 53–60° (lit. mp 59°), and these were combined (2.4 g) and used in the next step.

**2,4-Dimethoxy-3-benzyloxy-6-iodobenzyl Chloride (11).**—A solution of **10** (1.0 g) and paraformaldehyde (0.80 g) in a mixture of glacial acetic acid (40 ml) and concentrated hydrochloric acid (5 ml) was stirred for 2.5 hr at room temperature. The reaction mixture rapidly became clear. Ice was added, and the reaction flask was left in an ice bath for 30 min. The white precipitate was collected by filtration, washed with water, and dried overnight. Recrystallization from petroleum ether afforded long needles (0.67 g): mp 70–71°. Recrystallization from the same solvent yielded needles (**11**): mp 71–71.5°; nmr $\tau$ 6.02, 6.19 (6 H, 2 $OCH_3$), 5.22 (2 H, $CH_2Cl$), 4.99 (2 H, $OCH_2Ph$), 2.86 (1 H, isolated aromatic H), and 2.45–2.70 (5 H, aromatic H).

*Anal.* Calcd for $C_{16}H_{16}ClIO_3$: C, 45.90; H, 3.85; Cl, 8.47; I, 30.32. Found: C, 45.79; H, 4.00; Cl, 8.55; I, 30.25.

**2,4-Dimethoxy-3-benzyloxy-6-iodobenzyl Cyanide (12).**—To a warm solution of potassium cyanide (2.70 g) in water (4 ml) was added dropwise a solution of **11** (1.95 g) in acetone (80 ml). The solution was then refluxed for 3 hr. The acetone was removed under reduced pressure, and the residue was dissolved in a mixture of ether and water. The layers were separated, and the aqueous layer was extracted three times with ether. The combined ether extracts were washed twice with water, dried ($MgSO_4$), and concentrated, to leave a viscous oil. The oil was dissolved in petroleum ether and chromatographed on neutral alumina (Woelm, activity II, 40 g). Benzene–petroleum ether (1:9, 2.4 l.) eluted a homogeneous product (1.70 g), which was crystallized from petroleum ether to yield **12** as needles: mp 66–67°; ir $\lambda_{max}^{Nujol}$ 4.46 $\mu$; nmr $\tau$ 6.19 (5 H, $OCH_3$ and $CH_2CN$), 6.02 (3 H, $OCH_3$), 5.00 (2 H, $OCH_2Ph$), 2.87 (1 H, isolated aromatic H), and 2.43–2.67 (5 H, aromatic H).

*Anal.* Calcd for $C_{17}H_{16}INO_3$: C, 49.89; H, 3.94; I, 31.01; N, 3.42. Found: C, 50.00; H, 4.01; I, 31.08; N, 3.30.

**2-(2,4-Dimethoxy-3-benzyloxyphenyl) ethylamine (13).**—A solution of **12** (1.09 g, 0.0027 mol) in ether (45 ml) was added dropwise at room temperature under nitrogen to a stirred slurry of lithium aluminum hydride (0.65 g, 0.0085 mol) in ether (230 ml). Stirring was continued for 30 min and the solution was refluxed for 2 hr. The reaction mixture was cooled in ice, and water (10 ml) was added cautiously, followed by 20% sodium hydroxide solution (10 ml) and water (10 ml). The separated ether layer was decanted. The aqueous layer was extracted twice with ether and the ethereal extracts were combined and extracted three times with 5% hydrochloric acid. The acid solutions were basified with 20% sodium hydroxide solution (with cooling) and extracted with ether. The combined ether extracts were washed twice with water and dried ($MgSO_4$). Evaporation left a colorless oil (0.67 g) which was dissolved in ether (20 ml) and treated with oxalic acid dihydrate (0.35 g) in methanol (3 ml) dropwise with stirring. The precipitated white solid was collected by filtration (0.68 g, mp 150–152°). Recrystallization from methanol afforded small needles of the oxalate salt of **13**: mp 149–152°.

*Anal.* Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.37; H, 5.97; N, 3.72.

The oxalate was dissolved in 5% sodium hydroxide solution and extracted three times with ether. The combined ether extracts were washed twice with water, dried ($MgSO_4$), and evaporated to leave **13** as a colorless oil (0.49 g): nmr $\tau$ 6.17, 6.23 (6 H, 2 $OCH_3$), 5.02 (2 H, $OCH_2Ph$), 3.17, 3.45 (2 H, d, $J$ = 8 Hz), and 2.45–2.78 (5 H, aromatic H).

**N-(2,4-Dimethoxy-3-benzyloxyphenylethyl)-4′-benzyloxyphenylacetamide (14).**—To a mixture of **13** (0.21 g, 0.00073 mol) in ether (12 ml) and 5 *N* sodium hydroxide solution (4 ml) was added dropwise with stirring a solution of 4-benzyloxyphenylacetyl chloride[23] (0.36 g, 0.0014 mol) in ether (8 ml). Stirring was continued for a further 15 min and fine needles were precipitated from the mixture. The organic solvents were removed under reduced pressure, and the residue was extracted three times with chloroform. The combined chloroform extracts were washed with 5% hydrochloric acid and twice with water and dried ($MgSO_4$). Evaporation left an oily residue, which was readily crystallized from ether (0.29 g, mp 113–115°). Recrystallization from methanol gave feathery needles of **14**: mp 120–121°; nmr $\tau$ 6.52 (2 H, $COCH_2Ph$), 6.22 (6 H, 2 $OCH_3$), 5.00 (4 H, 2 $OCH_2Ph$), 3.28, 3.48 (2 H, d, $J$ = 9 Hz, aromatic H), and 2.88 and 3.12 (4 H, 2 d, $J$ = 9 Hz, aromatic H).

*Anal.* Calcd for $C_{32}H_{33}NO_5$: C, 75.12; H, 6.50; N, 2.74. Found: C, 75.01; H, 6.57; N, 2.77.

***dl*-1-(4′-Benzyloxybenzyl)-5,7-dimethoxy-6-benzyloxy-1,2,3,4-tetrahydroisoquinoline (16).**—A solution of **14** (0.40 g) in dry toluene (3.9 ml) was treated with phosphoryl chloride (1.0 ml) and the solution was maintained at 85–90° under nitrogen for 1–5 hr. The reaction mixture was allowed to cool and was poured onto ice and neutralized with 5% sodium bicarbonate solution. The mixture was extracted five times with ether; the ether was washed twice with water, dried ($MgSO_4$), and evaporated. The residual brown gum was dissolved (under nitrogen) in methanol (10 ml) and treated with sodium borohydride (80 mg) in portions over 10 min. The solution was stirred for 1 hr and the methanol

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was removed under reduced pressure. The reaction was again worked up under nitrogen. The residue was treated with water and 5% ammonium hydroxide (2 ml) and extracted five times with ether. The combined ether extracts were washed twice with water, dried ($MgSO_4$), and evaporated. The brown gummy residue (346 mg) was separated by tlc on silica gel HF preparative plates developed in methanol. The dark bands with $R_f$ *ca.* 0.5 (seen under ultraviolet light) were cut out and extracted with methanol (300 ml) at room temperature with stirring for 1 hr. The silica gel was collected by filtration and treated with warm methanol in the same way for an additional 1 hr. The combined filtrates were evaporated under reduced pressure to leave a light brown, homogeneous gum (0.20 g). Recrystallization from ether–petroleum ether afforded small needles (**16**): mp 89–92°; uv $\lambda_{max}^{MeOH}$ 276 ($\epsilon$ 3830) and 282 m$\mu$ ($\epsilon$ 3750); nmr $\tau$ 6.12, 6.25 (6 H, 2 $OCH_3$), 4.92, 4.97 (4 H, 2 $OCH_2Ph$), 3.55 (1 H, C-8 **H**), and 3.88 and 3.08 (4 H, 2 d, $J$ = 8 Hz, aromatic **H**).

*Anal.* Calcd for $C_{23}H_{23}NO_4$: C, 77.55; H, 6.71; N, 2.83. Found: C, 77.45; H, 6.65; N, 2.75.

*dl*-1-(4′-Benzyloxybenzyl)-5,7-dimethoxy-6-benzyloxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**3d**).—A solution of **16** (0.16 g) in methanol (10 ml) was treated with formalin (5 ml). The mixture was stirred for 3.5 hr at room temperature and gradually became clear. The reaction mixture was cooled in ice and an excess of sodium borohydride (0.75 g) was added in portions while the temperature of the reaction mixture was kept below 40°. After the addition was complete, the solution was stirred for 1 hr at room temperature. The organic solvents were removed under reduced pressure and the residue was treated with water and 5% ammonium hydroxide and extracted five times with ether. The combined ether extracts were washed twice with water, dried ($MgSO_4$), and evaporated. The residue crystallized upon standing overnight, and was recrystallized from ether–petroleum ether to yield **3d** (106 mg): mp 83–86°; nmr $\tau$ 7.49 (3 H, $NCH_3$), 6.19, 6.55 (6 H, 2 $OCH_3$), 4.97, 5.02 (4 H, 2 $OCH_2Ph$), 4.14 (1 H, C-8 **H**), 3.90 and 3.19 (4 H, 2 d, $J$ = 9 Hz, benzylic Ph **H**), and 2.63 (10 H, benzyl ether Ph **H**).

The oxalate salt, mp 165–169°, showed $\lambda_{max}^{MeOH}$ 277 ($\epsilon$ 3360) and 283 m$\mu$ ($\epsilon$ 3310).

*Anal.* Calcd for $C_{35}H_{37}NO_8$: C, 70.10; H, 6.22; N, 2.34. Found: C, 70.21; H, 6.21; N, 2.40.

*dl*-1-(4′-Hydroxybenzyl)-2-methyl-5,7-dimethoxy-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (**3b**).—A solution of **3d** (95 mg) in absolute ethanol (9 ml) was hydrogenated over 30% palladium on charcoal catalyst (50 mg) for 13 hr. The catalyst was removed by filtration and washed with warm ethanol. The filtrate was evaporated to dryness under reduced pressure and the residual yellow green gum (61 mg) was crystallized from dichloromethane–petroleum ether (yield 37 mg). Recrystallization from the same solvents gave **3b** as pale yellow needles: mp 148–151°; uv $\lambda_{max}^{EtOH}$ 281 m$\mu$ ($\epsilon$ 3200); nmr $\tau$ 7.43 (3 H, $NCH_3$), 6.15, 6.47 (6 H, 2 $OCH_3$), 5.18 (2 H, 2 OH), 4.23 (1 H, C-8 **H**), and 3.11 and 3.29 (4 H, 2 d, $J$ = 8.5 Hz, benzylic Ph **H**).

*Anal.* Calcd for $C_{19}H_{23}NO_4 \cdot {}^1/_3CH_2Cl_2$: C, 66.78; H, 6.86; N, 4.03. Found: C, 67.00; H, 6.81; N, 4.00.

**Registry No.**—**1a**, 21899-44-5; **1a** picrate, 21927-69-5; **2b**, 21899-45-6; **3b**, 16687-92-6; **3c**, 16623-60-2; **3d**, 21899-48-9; **3d** oxalate, 21899-49-0; **7**, 21882-87-1; **11**, 21882-88-2; **12**, 21882-89-3; **13**, 21882-90-6; **13** oxalate, 21882-91-7; **14**, 21882-92-8; **16**, 21899-61-6.