Thalictrum Alkaloids. IX.[1,2] The Isolation, Structural Elucidation, and Synthesis of *Thalisopavine*

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Evidence is presented for assignment of structure **5** to thalisopavine, a new phenolic alkaloid isolated from the roots of *Thalictrum dasycarpum* Fisch. and Lall. Elementary analysis and mass spectrometry supported a $C_{20}H_{23}NO_4$ empirical formula. Diazomethane methylation yielded O-methylthalisopavine (**6**). N-Methylation of **6**, followed by Hofmann degradation, gave N-methylisopavinemethine (**10**), characterized by direct comparison with a sample prepared from isopavine (**7**). Nmr and mass spectral analogies to amurensine (**8**) and amurensinine (**9**) favored assignment of structure **5** for thalisopavine. The structure was confirmed by total synthesis of (±)-thalisopavine by an unequivocal route similar to that used for the synthesis of (±)-isopavine (**7**). Other phenolic alkaloids isolated include (−)-norargemonine (**1**), (−)-bisnorargemonine (**2**), L-(+)-laudanidine (**3**), and corypalline (**4**).

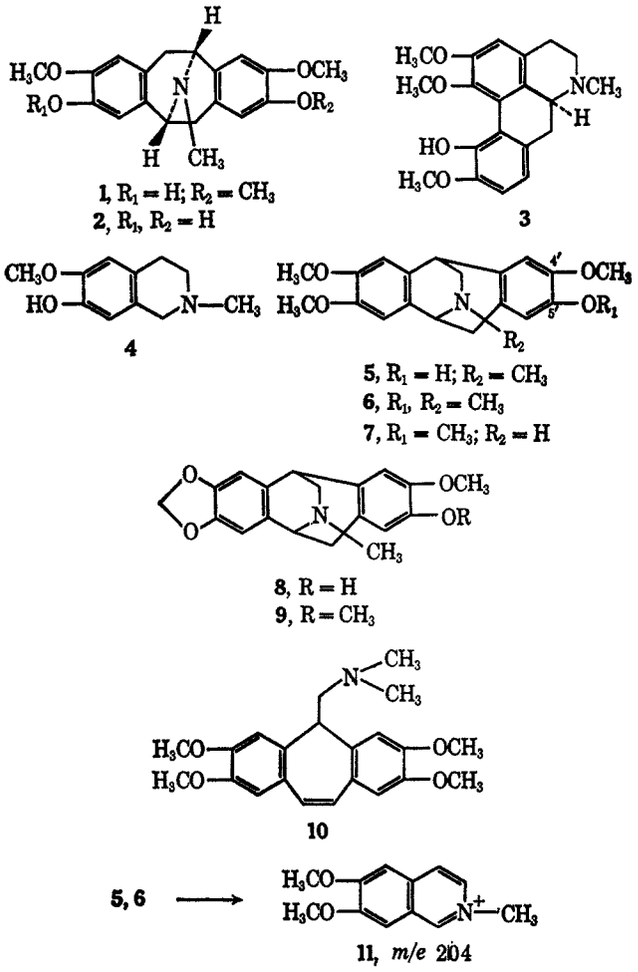
The genus *Thalictrum* has served as a uniquely profuse source of benzylisoquinoline, aporphine, pavine, bisbenzylisoquinoline, and dimeric benzylisoquinoline-aporphine alkaloids.[1] We now report the isolation, structural elucidation, and syntheses of the new phenolic isopavine alkaloid, thalisopavine (**5**). In addition, the isolation from *T. dasycarpum* of the phenolic alkaloids (−)-norargemonine (**1**), (−)-bisnorargemonine (**2**), L-(+)-laudanidine (**3**), and corypalline (**4**) is reported.

In an earlier communication,[3] we reported the extraction of alkaloids from the roots of *T. dasycarpum* Fisch. and Lall from Wisconsin. The alkaloids were separated into nonquaternary phenolic, nonquaternary nonphenolic, and quaternary alkaloid fractions.[3] Attempts to separate the constituents of the nonquaternary phenolic bases by chromatography on a variety of absorbents were unsuccessful. Consequently, the mixture was fractionated first into two fractions (A and B) by buffer extraction at pH 6.0. Fraction A consisted mainly of alkaloids with R_f values higher than 0.4 upon tlc on silica gel with 30% methanol–chloroform, whereas fraction B consisted mainly of an alkaloid with R_f 0.39 and minor alkaloids with lower R_f values.

Chromatography of fraction A on silica gel, followed by preparative tlc on the same absorbent, gave (−)-norargemonine (**1**),[4-6] L-(+)-laudanidine (**3**)[7] (−)-bisnorargemonine (**2**),[6,8] and four unidentified minor alkaloids. Similar chromatographic separations of fraction B gave the new alkaloid, thalisopavine (**5**) [mp 211–212°, $[\alpha]^{25}D$ −210° ($CHCl_3$)], and (−)-norargemonine, (−)-bisnorargemonine, and the isoquinoline alkaloid, corypalline (**4**) (Chart I).[9,10]

The molecular formula $C_{20}H_{23}NO_4$ was assigned for thalisopavine on the basis of elemental analysis and the mass spectrum (M^+ *m/e* 341) of the alkaloid. The

CHART I



infrared (ir) spectrum indicated the presence of aromatic rings and a hydroxyl group. The ultraviolet (uv) absorption spectrum showed a maximum at 289 mμ (ε 11,500), and a bathochromic shift was observed upon the addition of sodium hydroxide, indicative of a phenolic benzyltetrahydroisoquinoline chromophore. The nmr spectrum showed signals at τ 7.52 for one N-methyl group, 6.14 for three O-methyl groups, 3.25 (2 H), 3.39 (1 H), and 3.46 (1 H) for four aromatic protons, 5.10 for one phenolic proton, and in the range between 6.20 and 7.40 for six aliphatic protons. On the basis of these observations, alternative pavine or

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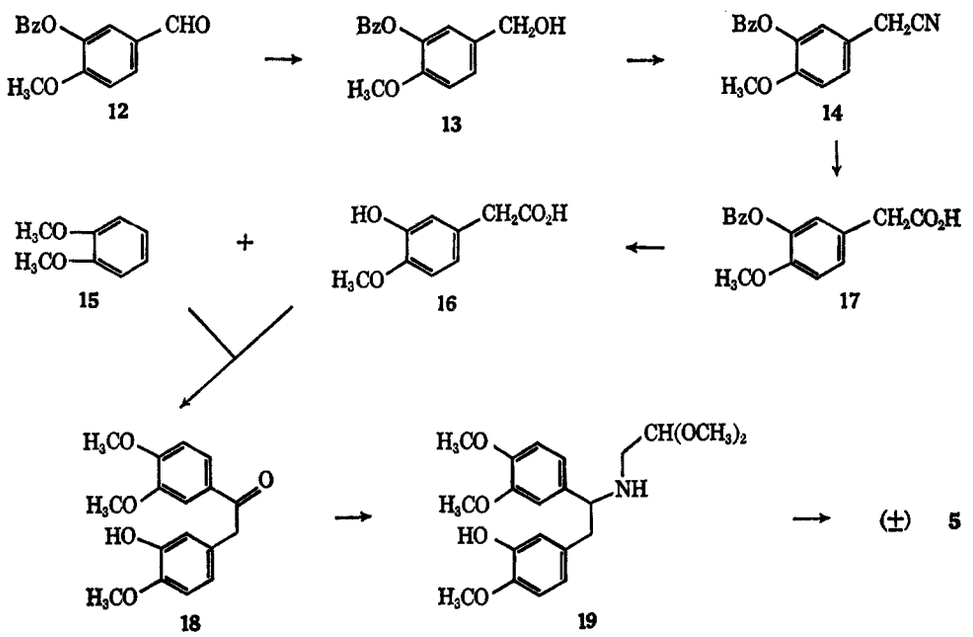
SCHEME I



isopavine[11] structures were initially considered for this alkaloid. The remarkable similarity of the nmr spectrum in the aromatic and aliphatic proton region to that of amurensine (**8**)[12,13] supported the view that thalisopavine has an isopavine skeleton and an oxygenation pattern similar to that of amurensine. Further evidence of this view was adduced from the experimental results which follow.

Diazomethane methylation of thalisopavine yielded O-methylthalisopavine (**6**), which showed an nmr signal (at τ 6.23) indicative of the presence of an additional methoxyl group and an ir spectrum indicative of absence of a hydroxyl group. When **6** was heated with an excess of methyl iodide, the methiodide was formed, which was smoothly degraded by the Hofmann method. The optically inactive Hofmann methine was shown to be identical with N-methylisopavinemethine (**10**) by direct comparison with a sample prepared from isopavine.[14]

The structural problem which remained at this point was the location of the free hydroxyl group in thalisopavine. The base peak in the mass spectrum of thalisopavine, at *m/e* 204, corresponded to the N-methylisoquinolinium ion **11**[13] and indicated that the hydroxyl group must be at C-4′ or C-5′. As noted earlier, the nmr signal for the nine methoxyl protons of thalisopavine (**5**) appeared as a singlet at τ 6.14, whereas the signal for the extra methoxyl group in O-methylthalisopavine (**6**) appeared at 6.23. It has been reported that the nmr signal corresponding to the C-4′ methoxyl group of amurensine (**8**) appears at τ 6.17, whereas the signal for the additional methoxy group (at C-5′) in amurensinine (**9**) appears at 6.22.[12] These facts and biogenetic analogy to amurensine supported location of the hydroxyl group at C-5′ in thalisopavine (**5**).

The structure of thalisopavine was confirmed by total synthesis of (±)-**5** by an unequivocal route similar to that used for the synthesis of (±)-isopavine (**7**).[11] 3-Hydroxy-4-methoxyphenylacetic acid (**16**)[15] was prepared by an improved procedure patterned on that used for the synthesis of 3,4-dihydroxyphenylacetic acid.[16] 3-Benzyloxy-*p*-anisaldehyde (**12**)[17] was reduced with sodium borohydride to 3-benzyloxy-4-methoxybenzyl alcohol (**13**),[18] and successive treatment with thionyl chloride and sodium cyanide gave 3-benzyloxy-4-methoxyphenylacetonitrile (**14**)[19] (Scheme I). Nitrile **14** was hydrolyzed to yield 3-benzyloxy-4-methoxyphenylacetic acid (**17**),[20] which, upon catalytic hydrogenolysis with palladium, was converted into 3-hydroxy-4-methoxyphenylacetic acid (**16**). Friedel–Crafts condensation of **16** and *o*-dimethoxybenzene (**15**) using polyphosphoric acid as condensation agent gave the key intermediate, 3′-hydroxy-3,4,4′-trimethoxydesoxybenzoin (**18**). Treatment of desoxybenzoin **18** with 2,2-dimethoxyethylamine generated the imine, which was hydrogenated to form the unstable acetal amine **19**. Acid-catalyzed ring closure, followed by N-methylation with formaldehyde and sodium borohydride afforded (±)-thalisopavine. The product was shown to be identical with natural thalisopavine, apart from optical activity, by ir, nmr, mass spectrometry, and mixed tlc comparisons.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus. Values of $[\alpha]_D$ have been approximated to the nearest degree. Uv spectra were determined on a Beckman Model DK-2A recording spectrophotometer. Ir spectra were determined on Beckman Models IR-5A and -9 recording spec-

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TABLE I

FRACTIONATION OF PHENOLIC ALKALOIDS BY ABSORPTION CHROMATOGRAPHY

	Fractions	Flasks[a]	Main alkaloids isolated	R_f values[b]
Fraction A	1	12–51	(−)-Norargemonine (**1**)	0.55
	2	52–71	L-(+)-Laudanidine (**3**)	0.46
	3	72–106	(−)-Bisnorargemonine (**2**)	0.43
	4	107–123	Thalisopavine (**5**)	0.39
	5	124–148	Four alkaloids[c]	
	6	149–195		
Fraction B	1′	1–25	(−)-Norargemonine (**1**)	0.55
	2′	26–36	(−)-Bisnorargemonine (**2**)	0.43
	3′	37–51	Thalisopavine (**5**)	0.39
	4′	52–76	Corypalline (**4**)	0.35

[a] Each flask contained about 100 ml of solution. [b] Tlc. [c] These alkaloids have not yet been identified.

trophotometers. Nmr spectra were determined on a Varian A-60A spectrometer in deuteriochloroform solution with tetramethylsilane as the internal standard. We thank Dr. R. D. Brown and Dr. F. W. McLafferty of the Purdue Mass Spectrometry Center, supported under U.S. Public Health Service Grant FR-00354, for the mass spectral data. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. When organic solutions were dried, sodium sulfate was the drying agent; when organic solutions were evaporated to dryness, a rotary evaporator was used with reduced pressure. Tlc was conducted using silica gel F-254 plates (250 μ, pre-coated, abrasion resistant, E. Merck) and a developing solvent of 30% methanol–chloroform. Visualization was effected with Dragendorff reagent. Preparative plates (2 mm × 20 × 20 cm, precoated, E. Merck) were used in the same way, except that only borders were visualized, and the desired bands were scraped off with a spatula and extracted with 50% methanol–chloroform.

Partition of the Phenolic Alkaloid Mixture into Two Fractions by Buffer Extraction.—The phenolic alkaloid mixture (50.2 g) in chloroform (500 ml) was extracted with McIlvaine buffer solution (pH 6.0, triple strength, 6 l.). A gumlike material (1.6 g), insoluble in chloroform and buffer solution, was separated, and, after having been found to give a negative test with Dragendorff reagent, was discarded. The chloroform solution was washed with water, dried, and evaporated to dryness to give a greenish brown residue (29.4 g) (fraction A). The aqueous solution was combined with the washings, basified with potassium carbonate, and extracted with chloroform (2 l.). The chloroform solution was washed with water, dried, and evaporated to dryness to leave a light brown residue (17.2 g) (fraction B).

Preliminary Fractionation of Fractions A and B by Absorption Chromatography.—Fraction A (10.7 g) was chromatographed on silica gel (0.05–0.20 mm, E. Merck, 2 kg) with a mixture of methylene chloride–acetone–ethanol (3:2:1). The first eluate (1.5 l.) was evaporated to dryness to give a nonalkaloidal gummy material (1.46 g). The further eluate was separated into six fractions, after combination of like fractions as indicated by tlc. The results are summarized in Table I. The chromatography was completed by elution with methanol. The methanol solution was evaporated to dryness to leave material (1.37 g) which gave a negative test with Dragendorff reagent. Fraction B (1.463 g) was also chromatographed on silica gel (600 g) in the same manner as described above and separated into four fractions indicated in Table I. The last elution with methanol gave gummy nonalkaloidal material (451 mg).

(−)-Norargemonine (1).—Fraction 1 was evaporated to dryness to give a brown residue (1.195 g) which was essentially homogeneous on tlc. This residue (156 mg) was purified by preparative tlc (three plates). The main band gave a crystalline material (75 mg), which was recrystallized from acetone to yield colorless needles (34 mg), mp 239–242°, R_f 0.55. The melting point was not depressed by admixture with an authentic sample of (−)-norargemonine (**1**), and the uv, ir ($CHCl_3$), and nmr spectra, rotation, and tlc mobility were identical with those of the authentic sample.[21]

L-(+)-Laudanidine (3).—Fraction 2 was evaporated to give a brown residue (302 mg), which was shown by tlc to be a mixture of at least three alkaloids. The alkaloids were isolated by preparative tlc (six plates). The top band yielded (−)-norargemonine (**1**). The middle band gave crystals (37 mg) which were recrystallized from ethanol to give colorless prisms (25 mg), mp 181–182°, $[\alpha]^{28}D$ +87° (*c* 0.56, $CHCl_3$). This material was identified as L-(+)-laudanidine (**3**) by direct comparison with an authentic sample.[22] The melting point was not depressed by admixture with the authentic sample, and the ir and nmr spectra and mixed tlc were identical with those of the authentic sample. The third band was identified as (−)-bisnorargemonine (**2**) (see below).

(−)-Bisnorargemonine (2).—Upon evaporation of the solvent, fraction 3 gave a light brown residue (791 mg) which was shown by tlc to be a mixture of three components. The residue (81 mg) was subjected to preparative tlc (two plates). The top band was identified as L-(+)-laudanidine (**3**). The middle band gave a residue (46 mg) which was twice crystallized from ethanol to yield needles (27 mg), mp 244–246°. The alkaloid was shown to be (−)-bisnorargemonine by direct comparison with an authentic sample[15] by ir and nmr spectral comparisons, mixed tlc, mixture melting point, and rotation. The third band was not characterized.

Isolation of Thalisopavine (5) from Fraction 3′.—Fraction 3′ (see Table I) gave a light brown oil (256 mg) upon evaporation of the solvent. This oil was crystallized by the addition of ethanol, and recrystallization from the same solvent yielded thalisopavine (**5**, 118 mg) as colorless needles: mp 211–212°; $[\alpha]^{25}D$ −210° (*c* 0.21, $CHCl_3$); λ_{max}^{EtOH} 289 mμ (ϵ 11,500); $\lambda_{max}^{CHCl_3}$ 2.80, 6.21, 6.25 μ; nmr signals at τ 3.25 (2 H), 3.39 (1 H), 3.46 (1 H) (three singlets, four aromatic **H**), 5.10 (1 H, broad singlet, phenolic **OH**), 6.14 (9 H, singlet, three OCH_3), 7.52 (3 H, singlet, NCH_3); mass spectrum, M^+ *m/e* 341, base peak at *m/e* 204.

Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.70; N, 4.10. Found: C, 69.95; H, 6.91; N, 4.48.

Corypalline (4).—Fraction 4′ gave a residue (411 mg) which was shown by tlc to be a mixture of thalisopavine (**5**) and another alkaloid. After separation by preparative tlc (seven plates), the residue gave thalisopavine (**5**, 216 mg) from the higher band and a second crystalline material (59 mg) from the lower band. Recrystallization of the latter material from chloroform yielded needles (33 mg), mp 166–168°. This material was shown to be identical with an authentic sample of corypalline (**4**, N-methyl-7-hydroxy-6-methoxy-tetrahydroisoquinoline) by mixture melting point, mixed tlc, and ir spectral comparison.[23]

O-Methylation of Thalisopavine (5).—A solution of thalisopavine (**5**, 100 mg) in methanol (10 ml) and ether (20 ml) was treated with an excess of diazomethane in ether at room temperature for 24 hr. After decomposition of excess diazomethane with acetic acid (0.5 ml), the solution was evaporated to dryness to give an oily residue (100 mg), which was crystallized from ethanol to yield needles. Recrystallization of the needles from ethanol–ether gave O-methylthalisopavine (**6**, 71 mg) as color-

(21) We thank Professor T. O. Soine cordially for authentic samples of (−)-norargemonine and (−)-bisnorargemonine.

(22) We thank Professor M. Tomita cordially for an authentic sample of L-(+)-laudanidine.

(23) We thank Professor J. M. Bobbitt cordially for an authentic sample of corypalline. The work on the isolation and characterization of corypalline from *T. dasycarpum* was executed by Dr. W. R. Schleigh.

less needles: mp 91–92°; $\lambda_{max}^{CHCl_3}$ 6.23 μ, no hydroxyl absorption; nmr signals at τ 3.22 (2 H), 3.34 (1 H), 3.48 (1 H) (three singlets, four aromatic **H**), 6.13 (9 H, singlet, three OCH_3), 6.23 (3 H, singlet, OCH_3), 7.50 (3 H, singlet, NCH_3); mass spectrum, M^+ *m/e* 355, base peak at *m/e* 204.

Hofmann Degradation of O-Methylthalisopavine (6).—O-Methylthalisopavine (**6**, 65 mg) in methanol (10 ml) was refluxed with methyl iodide (2 ml) for 2 hr. Evaporation of the solvent and excess methyl iodide yielded a light brown residue (68 mg), which was dissolved in hot water (10 ml). The solution was shaken with moist silver oxide (from 1 g of silver nitrate) for 3 hr and then filtered. The clear filtrate and washings (30 ml) were treated with potassium hydroxide (30 g) and heated over a steam bath for 3 hr, whereupon a crystalline precipitate formed. This was extracted with chloroform and the chloroform solution was washed with water, dried, and evaporated to dryness to give a crystalline residue, mp 142–146°. Recrystallization from ethanol gave N-methylthalisopavinemethine (**10**, 21 mg) as colorless needles, mp 158–159°. The melting point was not depressed by admixture with an authentic sample of N-methylisopavinemethine. The ir and nmr spectra and mixed tlc were identical with those of the authentic sample.[14]

3-Benzyloxy-4-methoxybenzyl Alcohol (13).—Sodium borohydride (3 g) was slowly added to a solution of 3-benzyloxy-*p*-anisaldehyde[17] (15 g) in methanol (100 ml). The solution was stirred at room temperature for 5 hr and then evaporated to dryness to give a residue which was dissolved in chloroform. The chloroform solution was washed with water, dried, and evaporated to dryness to give a crystalline residue. Recrystallization from methanol gave 3-benzyloxy-4-methoxybenzyl alcohol (10.6 g) as colorless needles, mp 65–66° (lit.[18] mp 61°).

3-Benzyloxy-4-methoxyphenylacetonitrile (14).—Thionyl chloride (5 g) was added to a solution of 3-benzyloxy-4-methoxybenzyl alcohol (4.5 g) in anhydrous ether (100 ml) and the solution was refluxed for 4 hr. Evaporation gave an oily residue which was dissolved in ether. The ethereal solution was washed with 5% aqueous sodium carbonate solution and water, dried, and evaporated to dryness to give 3-benzyloxy-4-methoxybenzyl-chloride (4.4 g). The mixture of this chloride (4.4 g), sodium cyanide (8.8 g), and sodium iodide (7.7 g) in 2-butanone (100 ml) was refluxed for 12 hr. After cooling, the mixture was poured into ice–water (300 ml) and extracted with ether. The ethereal solution was washed with water, dried, and evaporated to dryness to leave 3-benzyloxy-4-methoxyphenylacetonitrile (4.2 g). Recrystallization from methanol gave colorless needles (4.0 g), mp 77–78° (lit.[19] mp 80°).

3-Benzyloxy-4-methoxyphenylacetic Acid (17).—3-Benzyloxy-4-methoxyphenylacetonitrile (1.5 g) in methanol (50 ml) and dioxane (40 ml) was refluxed with potassium hydroxide (20 g) in water (20 ml) for 25 hr. Evaporation left an oily residue which was dissolved in water (200 ml). The aqueous solution was washed with ethyl acetate, acidified with hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate solution was washed with water, dried, and evaporated to dryness to give a crystalline residue. Recrystallization from benzene yielded 3-benzyloxy-4-methoxyphenylacetic acid (1.4 g) as colorless prisms, mp 126–129° (lit.[20] mp 126–129°).

3-Hydroxy-4-methoxyphenylacetic Acid (16).—3-Benzyloxy-4-methoxyphenylacetic acid (670 mg) in methanol (30 ml) was hydrogenated with 30% palladium–carbon (300 mg) for 2 hr. After the catalyst was filtered, the solution was evaporated to dryness to leave a crystalline residue. Recrystallization from benzene yielded 3-hydroxy-4-methoxyphenylacetic acid (**16**, 311 mg), mp 129–130° (lit.[15] 130–131°).

3′-Hydroxy-3,4,4′-trimethoxydesoxybenzoin (18).—To a mixture of 3-hydroxy-4-methoxyphenyl acetic acid (**16**, 200 mg) and *o*-dimethoxybenzene (**15**, 300 mg, J. T. Baker Chemical Co.), polyphosphoric acid (3 g) was added at 100–115° with mechanical stirring, and heating was continued for 5 min. After cooling, the reaction complex was decomposed with ice–water and extracted with chloroform. The chloroform solution was washed with 5% sodium carbonate to remove the starting carboxylic acid (**16**) and then extracted with 5% sodium hydroxide. The alkaline solution was acidified with hydrochloric acid and extracted with chloroform. The chloroform solution was washed with water, dried, and evaporated to dryness to give a yellowish residue (74 mg). This residue was purified by preparative tlc on silica gel with chloroform. The main band (R_f 0.3), upon elution with 50% methanol–chloroform, gave crystals which were recrystallized from methanol to yield the desoxybenzoin (**18**, 25 mg): mp 112–113°; λ_{max}^{EtOH} 229 mμ (ε 28,700), 278 (17,300), 320 (12,700); $\lambda_{max}^{CHCl_3}$ 2.80 (OH), 5.99 (conjugated ketone), 6.25 μ (aryl ring); nmr signals at τ 2.42 (2 H, singlet, two aromatic **H**), 3.09–3.25 (4 H, multiplets, four aromatic **H**), 4.30 (1 H, broad singlet, phenolic **OH**), 5.88 (2 H, singlet, benzyl **H**), 6.07, 6.10, and 6.15 (9 H, singlet, three OCH_3).

Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.41; H, 6.01.

N-(2,2-Dimethoxyethyl)-1-(3,4-dimethoxyphenyl)-2-(3-hydroxy-4-methoxyphenyl)ethylamine (19).—A mixture of the deoxybenzoin (**18**) (270 mg) and 2,2-dimethoxyethylamine (300 mg) was heated under nitrogen from 105 to 125° for 40 min, and the excess amine was slowly distilled off to leave a brown gum (345 mg). A solution of this gum in methanol (20 ml) was shaken at 25° with platinum oxide (50 mg) and hydrogen, absorption of gas (11 ml) being completed in 15 hr. Evaporation of the filtered solution left a residue which was dissolved in ether. The ethereal solution was shaken with 1 *N* hydrochloric acid, and the aqueous layer was quickly made alkaline and extracted with chloroform. The chloroform solution was washed with water, dried, and evaporated to give the diphenylethylamine (**19**) as a pale yellow gum (184 mg). This material was found to be unstable in air but homogeneous on tlc and positive to Dragendorff reagent, and its ir spectrum showed absorption bands at 2.85 (OH, NH) and 6.29 μ (aryl ring), and absence of carbonyl and C=N absorptions.

(±)-Thalisopavine.—A solution of acetal **19** (150 mg) was treated with chilled 83% sulfuric acid (10 ml) and allowed to stand at room temperature for 7 hr. The reaction mixture was worked up for base in the usual way but with exclusion of carbon dioxide, and a light brown gum (78 mg) was obtained. A solution of this gum in methanol (10 ml) was stirred with 38% formaldehyde (2 ml) at room temperature for 40 min. Sodium borohydride (1.5 g) was added portionwise and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated to leave a residue which was dissolved in water and extracted with chloroform. The chloroform solution was washed with water, dried, and evaporated, to yield a brown gum (62 mg). This material was purified by silica gel column chromatography and preparative tlc in the same way as natural thalisopavine (**5**), to yield (±)-thalisopavine (15 mg) as colorless needles, mp 172–173°. The ir (in chloroform), nmr, and mass spectra and the mixed tlc were identical with those of thalisopavine isolated from *T. dasycarpum*.

Registry No.—**5**, 18927-72-5; (±) **5**, 18927-73-6; **6**, 18944-92-8; **18**, 18929-89-0.