solutions and are reported in δ units relative to Me_4Si. Mass spectra were recorded on a Varian 112 S spectrometer by direct inlet.

The progress of all reactions and column chromatographs (silica gel G–Celite, 50:50 (v/v)) was monitored by TLC on E. Merck silica gel HF_{254} plates, visualized by spraying with 70% sulfuric acid followed by heating.

3-(Acetyloxy)-14α,15α-epoxy-5α-cholest-8-en-7-one (6). MCPBA (0.12 g) in dichloromethane (3 mL) was added to a solution of 3β-(acetyloxy)-5α-cholesta-8,14-dien-7-one (**5**) (0.3 g) in the same solvent (10 mL) dropwise over 30 min at 0 °C. The solution was washed with water, saturated $NaHCO_3$, and finally water, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed. Elution with 3% diethyl ether–hexane gave 3β-(acetyloxy)-14α,15α-epoxy-5α-cholest-8-en-7-one (**6**) (0.19 g). When crystallized from diisopropyl ether, **6** had the following properties: mp 122–123 °C; UV λ_{max} 246 nm (log ε 4.00); IR 1743, 1660, 1590 cm^{-1}; ^1H NMR δ 0.71 (s, 3 H, 18-CH_3; calcd[7] δ 0.73), 1.18 (s, 3 H, 19-φCH_3; calcd[7] δ 1.19), 2.00 (s, 3 H, OAc), 4.63 (m, 1 H, 15β-H; $w_{1/2}$ ca. 4 Hz), 4.75 (m, 1 H, 3α-H, $w_{1/2}$ ca. 20 Hz); mass spectrum *m/e* 456 (35%, M^+), 441 (100, M – CH_3).

Anal. Calcd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.21; H, 9.88.

Elution with 5% diethyl ether–hexane gave 3β-(acetyloxy)-15α-hydroxy-5α-cholesta-8(14),9(11)-dien-7-one (**7**): 0.06 g; mp 154 °C (from methanol); $[\alpha]^{23}_D$ +85°; UV λ_{max} 226, 318 nm (log ε 4.04, 3.41); IR 3485, 1740, 1670, 1628, 1580 cm^{-1}; ^1H NMR δ 0.82 (s, 3 H, 18-CH_3; calcd[7] δ 0.80), 1.06 (s, 3 H, 19-CH_3; calcd[7] δ 1.07), 2.04 (s, 3 H, OAc), 4.65 (m, 1 H, OH, $w_{1/2}$ ca. 7 Hz), 4.70 (m, 1 H, 3α-H, $w_{1/2}$ ca. 20 Hz), 4.83 (m, 1 H, 15β-H, $w_{1/2}$ ca. 12 Hz), 5.54 (dd, 1 H, 11β-H, J_{AX} = 3 Hz, J_{BX} = 7 Hz); mass spectrum *m/e* 456 (46%, M^+), 441 (100, M – CH_3).

Anal. Calcd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.50; H, 9.51.

When the reaction was worked up after standing for 24 h at 0 °C, dienone **7** was obtained in 65% yield.

3β,15α-Dihydroxy-9α,11α-epoxy-5α-cholest-8(14)-en-7-one (8). (a) From 3β-(Acetyloxy)-15α-hydroxy-5α-cholesta-8-(14),9(11)-dien-7-one (7). MCPBA (170 mg) in dichloromethane (4 mL) was added to a solution of **7** (300 mg) in the same solvent (20 mL) at 0 °C. After 2 h at room temperature, the usual workup yielded a pale yellow solid (300 mg), which, after chromatography, gave (eluted with 3% diethyl ether–hexane) pure epoxy ketone **8**: mp 140 °C; $[\alpha]^{23}_D$ +57°; UV λ_{max} 253 nm (log ε 3.97); IR 3430, 1725, 1680, 1610 cm^{-1}; ^1H NMR δ 1.01 (s, 3 H, 18-CH_3; calcd[7] 0.97), 1.15 (s, 3 H, 19-CH_3; calcd[7] δ 1.13), 3.42 (dd, 1 H, 11β-H, J_{AX} = 2 Hz, J_{BX} = 6 Hz), 4.45 (bs, 1 H, 15α-OH), 4.53 (m, 1 H, 15β-H, $w_{1/2}$ ca. 10 Hz), 4.65 (m, 1 H, 3α-H, $w_{1/2}$ ca. 20 Hz); mass spectrum *m/e* 472 (20%, M^+), 287 (100).

Anal. Calcd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.75; H, 9.60.

(b) From 3β-(Acetyloxy)-5α-cholesta-8,14-dien-7-one (5). Treatment of **5** (600 mg) in dichloromethane (20 mL) with MCPBA (590 mg) at 0 °C for 24 h gave, after the usual workup, the epoxy ketone **8** (0.4 g), identical with that described above.

3β,11α,15α-Trihydroxy-5α-cholestan-7-one (3). Catalytic hydrogenation of the epoxy ketone **8** (300 mg) with 10% Pd/C (150 mg) in ethanol (20 mL) plus pyridine (50 μL) at 25 °C and 1 atm was complete after 4 h. The catalyst was removed by filtration, and the solution was concentrated to give a residue (300 mg) which, after crystallization from methanol, was slightly impure on TLC: mp 103–105 °C; IR 3530, 3380, 1730 cm^{-1}; ^1H NMR δ 0.84 (s, 6 H), 0.92 (s, 6 H), 0.98 (d, 3 H), 2.02 (s, 3 H, OAc), 3.1–4.0 (2 m (overlapping), 2 H, 11β-H, 15β-H), 4.7 (m, 1 H, 3α-H); mass spectrum *m/e* 476 (4%, M^+), 458 (10, M – H_2O), 443 (5, M – H_2O – CH_3), 398 (11, M – H_2O – OAc), 345 (21, M – H_2O – side chain), 249 (100), 209 (64).

The product was dissolved in 5% methanolic potassium hydroxide and heated under reflux for 3 h. After the usual workup and crystallization from diethyl ether the triolone **3** was obtained (100% yield): mp 134 °C $[\alpha]^{23}_D$ +5°; IR 3610, 3450, 1695 cm^{-1}; ^1H NMR δ 0.72 (s, 3 H, 18-CH_3; calcd[7] δ 0.72), 1.21 (s, 3 H, 19-CH_3; calcd[7] δ 1.21), 3.60, 3.80, 4.00 (3 m (overlapping), 3 H, 3α-H, 11β-H, and 15β-H); mass spectrum *m/e* 434 (6%, M^+), 416 (9, M – H_2O), 398 (13, M – $2H_2O$), 303 (24, M – H_2O – side chain), 285 (11, M – $2H_2O$ – side chain), 209, (78), 208 (38), 207 (100); lit.[2] mp 117–120 °C; $[\alpha]^{23}_D$ +4.5°; all the other chemicophysical characteristics are identical.

Anal. Calcd for $C_{27}H_{46}O_4$: C, 74.59; H, 10.67. Found: C, 74.39; H, 10.50.

Acetylation of **3** (200 mg) in pyridine (5 mL) by treatment with acetic anhydride (2.5 mL) at room temperature for 10 h gave 3β,11α-bis(acetyloxy)-15α-hydroxy-5α-cholestan-7-one, which, when crystallized from acetone–hexane, was identical (melting point, optical rotation, NMR spectrum, and mass spectrum) with the compound described by Taylor and Djerassi.[2]

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Registry No. **3**, 71116-97-7; **5**, 63115-68-4; **6**, 71076-39-6; **7**, 71076-40-9; **8**, 71129-43-6; **9**, 71076-41-0; 3β,11α-bis(acetyloxy)-15α-hydroxy-5α-cholestan-7-one, 71116-98-8.

Stereoselective Synthesis of *cis*- and *trans*-2-(3,4-Dihydroxyphenyl)cyclobutylamine. Conformationally Restrained Analogues of Dopamine

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Due to our interest in the pharmacological activity of substituted 2-arylcylobutylamines, we have investigated methods of producing such compounds.[1] The report of a facile preparation of cyclobutanones[2,3] from aldehydes offered an attractive starting point for the preparation of 2-substituted cyclobutanone oximes and the conversion of such materials to *cis*- and *trans*-2-substituted cyclobutylamines. The conversion of 2-phenylcyclobutanone oxime to *trans*-2-phenylcyclobutylamine has been reported;[4] however, no successful method was found for the preparation of the cis isomer from the oxime. The cis isomer of 2-phenylcyclobutylamine was prepared by an alternate route.[4]

In this report, we present the synthesis of 2-(3′,4′-methylenedioxyphenyl)cyclobutanone oxime (**1**) and its stereoselective conversion to *cis*- and *trans*-2-(3′,4′-methylenedioxyphenyl)cyclobutylamine (**2** and **3**) (see Scheme I). The latter two compounds were transformed readily into conformationally restricted analogues of dopamine **4** and **5** and the ability of these compounds to bind to dopamine receptors has been previously reported.[5,6]

Results and Discussion

Our initial step in the synthetic scheme was the preparation of ketone **6** from piperonal (**7**). We first utilized the method of Trost and Bogdanowicz,[2,3] since it has been

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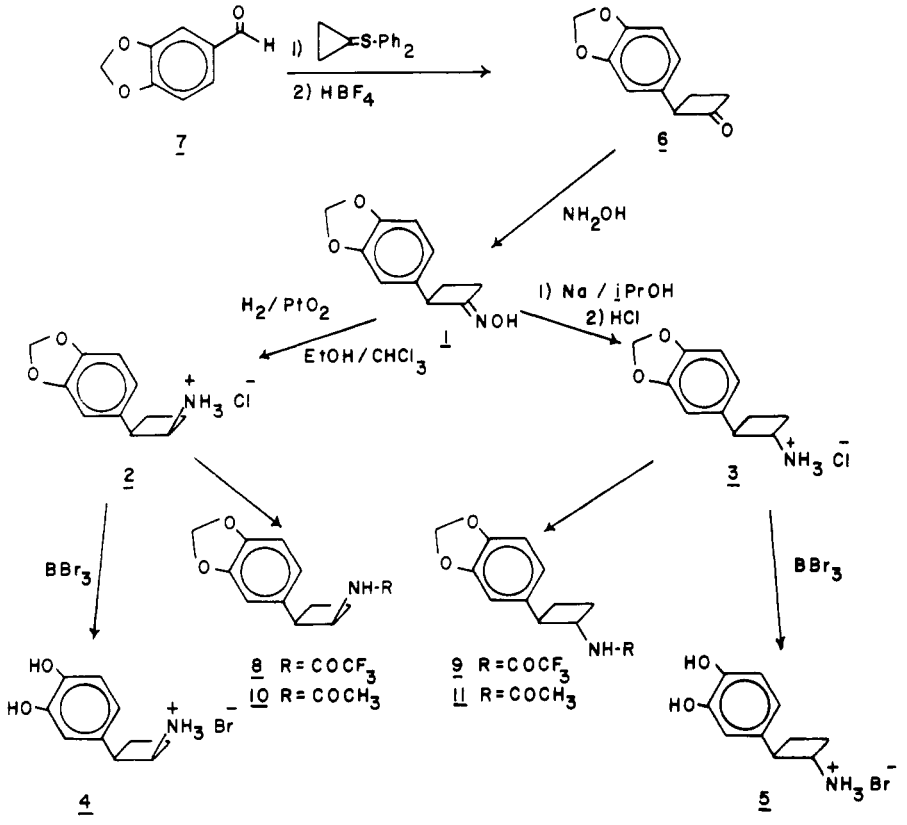
SCHEME I



reported[3] that the best yields of a variety of cyclobutanones could be achieved by reaction of an aldehyde or ketone with diphenylsulfonium cyclopropylide generated by the reaction of cyclopropyldiphenylsulfonium fluoroborate with potassium hydroxide in dimethyl sulfoxide. Although it was possible to prepare ketone **2** using the previously mentioned procedure,[3] we found better yields of **2** could be obtained using cyclopropyldiphenylsulfonium fluoroborate with potassium *tert*-butoxide in THF at ice bath temperature. The preparation of the oxime **1** could be carried out directly on the ketone/diphenyl sulfide mixture without purification of **2**. Using a basic solution, the oxime **1** remained in the aqueous layer and the byproduct, diphenyl sulfide, was conveniently removed with a ligroin wash. Acidification of the aqueous layer followed by $CHCl_3$ extraction afforded the oxime in 77% yield. Reduction of the oxime **1** with sodium in 2-propanol yielded the free base of the trans amine, which was isolated as the hydrochloride salt **3**.[7] We found an excellent procedure for converting the oxime **7** into the cis amine **2** using the procedure of Secrist and Logue[8] in which the reduction was carried out with platinum oxide in ethanol with $CHCl_3$ as the proton source.

The isomeric purity of the amines **2** and **3** was determined by conversion of the crude amine reduction products to trifluoroacetamides **8** and **9** and gas chromatographic analysis of the resulting trifluoroacetamides. It can be seen in Table I that catalytic reduction afforded good selectivity in the preparation of cis amine **2**, while reduction with sodium in 2-propanol was less selective in the preparation of the trans amine **3**. Reduction with diborane gave almost an equimolar amount of the cis and trans amines **2** and **3**.

Table I. Stereoselective Reduction of 2-(3′,4′-Methylenedioxyphenyl)cyclobutanone Oxime (1) to Amines 2 and 3 with Final Detection as Trifluoroacetamides 8 and 9

reduction method	ratio *trans*-9/*cis*-8
1. $H_2/PtO_2/EtOH/CHCl_3$	1/99
2. B_2H_6/diglyme	54/46
3. Na/*i*-PrOH	92/8

The stereochemical assignments for the two amines **2** and **3** were based on the routes of preparation and a study of the *N*-acetyl derivatives **10** and **11**. Reaction of **2** and **3** with pyridine and acetic anhydride yielded the desired amides **10** and **11**, respectively. It was observed that the methyl resonance of the cis acetamide (**10**) was shifted approximately 0.2 ppm upfield relative to the methyl group of the trans acetamide (**11**) (δ 1.95). The amine proton for **10** was also at a higher field (δ 5.15) as compared to the trans amide **11** (δ 5.75). The vicinal methine proton at C-1 of the trans amide **11** appeared at δ 4.46 or 0.26 ppm higher field than the vicinal methine proton at C-1 for the cis acetamide **10**. The shielding effect observed for functional groups cis to a phenyl ring in a four-membered ring system is consistent with earlier stereochemical assignments.[1,9-12]

Conversion of the amines **2** and **3** to the dopamine analogues **4** and **5** was readily accomplished with BBr_3 in CH_2Cl_2. The cis amine **4** was characterized as a hydrobromide salt while the trans amine **5** was isolated as a semihydrate hydrobromide salt. Both **4** and **5** gave a mo-

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lecular ion with chemical ionization mass spectroscopy at m/e 180.

Experimental Section

General. Melting points were determined in open capillaries on a Thomas Hoover UniMelt apparatus and are uncorrected. Infrared spectra were obtained on a Beckman 4230 spectrophotometer as potassium bromide disks (KBr).

Nuclear magnetic resonance spectra (NMR) were recorded either on a Varian A-60A NMR spectrometer (60 MHz) or on a Bruker HX-90E NMR spectrometer (90 MHz) in the pulse mode. The samples were prepared for NMR analysis using either $CDCl_3$ with Me_4Si as an internal standard or D_2O with DDS as an internal standard and run at approximately 25 °C.

Mass spectra were obtained with a Du Pont Model 21-491 double focusing mass spectrometer. Chemical ionization spectra were obtained at a source potential of 70 eV, with isobutane as the reagent gas.

Gas chromatographic analyses were run on a Hewlett-Packard 5710A gas chromatograph.

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

2-(3′,4′-Methylenedioxyphenyl)cyclobutanone (6). To a solution of piperonal (7; 2.0 g, 13.3 mmol) and cyclopropyldiphenylsulfonium fluoroborate (4.60 g, 14.6 mmol) in THF (50 mL) cooled to 0 °C there was added dropwise with stirring potassium *tert*-butoxide (1.80 g, 16.1 mmol) in a minimal amount of THF. After addition was complete the reaction was stirred an additional 0.5 h and quenched with 10 mL of 1 N fluoroboric acid. The solution was taken up in ether, washed with saturated bicarbonate and brine solution, and dried ($MgSO_4$). Filtration and concentration afforded an oil consisting of ketone 6 and diphenyl sulfide. Chromatography over silica gel with a 7% ether/ligroin mixture in a cold room afforded the ketone as an oil which solidified on cooling and was dried under reduced pressure (1.8 g, 71%): mp 44–46 °C; IR (KBr) 1781 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.72 (s, 3 H, Ar-H), 5.92 (s, 2 H, OCH_2O), 4.42 (t, 1 H, CH, J = 9 Hz), 2.8–3.4 (m, 2 H, $-COCH_2-$), and 2.0–2.8 (m, 2 H, $-CH_2-$). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.38; H, 5.40.

2-(3′,4′-Methylenedioxyphenyl)cyclobutanone Oxime (1). The oil obtained from the reaction of piperonal (7; 8.0 g, 53.3 mmol) with cyclopropyldiphenylsulfonium fluoroborate before chromatography was refluxed for 1 h with hydroxylamine hydrochloride (24.0 g, 345 mmol) in ethanol (200 mL) and 10% aqueous sodium hydroxide (300 mL, 750 mmol). The solution was cooled and extracted twice with 100-mL portions of ligroin which were back extracted with 50 mL of a 10% sodium hydroxide solution. The aqueous layers were combined, cooled to 10 °C with an ice bath, acidified to pH 5 with concentrated HCl, and extracted four times with 150-mL portions of chloroform, which were dried ($MgSO_4$). Filtration and concentration gave a heavy oil that crystallized on standing. Recrystallization from ethanol–water gave the oxime (8.3 g, 77%): mp 109–110 °C; IR (KBr) 3260 (OH), 1705 cm^{-1} (C=N); NMR ($CDCl_3$) δ 8.29 (s, 1 H, OH), 6.72 (s, 3 H), 5.90 (s, 2 H, OCH_2O), 4.32 (t, 1 H, CH, J = 8 Hz), 3.7–3.1 (m, 2 H, $-COCH_2-$), and 2.7–3.6 (m, 2 H, CH_2). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.49; H, 5.46; N, 6.85.

***cis*-2-(3′,4′-Methylenedioxyphenyl)cyclobutylamine Hydrochloride (2).** A suspension of 1 (2.0 g, 9.74 mmol), platinum oxide (240 mg, 1.1 mmol), and chloroform (2.0 mL, 16 mmol) in 180 mL of anhydrous ethanol was hydrogenated at 3 atm of hydrogen for 24 h. The solution was filtered through a Celite pad to remove the suspended platinum and concentrated to yield a white solid. Recrystallization from ethanol–ether yielded pure cis amine **2** (1.8 g, 79%): mp 247–248 °C dec; IR (KBr) 3200–2600 cm^{-1} (CH, NH); NMR (D_2O) δ 6.93 (s, 3 H), 5.99 (s, OCH_2O), 3.8–4.2 (m, 2 H, CH–CH), 2.2–2.7 (m, 4 H, CH_2CH_2-). Anal. Calcd for $C_{11}H_{14}NO_2Cl$: C, 58.03; H, 6.20; N, 6.15. Found: C, 57.94; H, 6.20; N, 6.13.

***trans*-2-(3′,4′-Methylenedioxyphenyl)cyclobutylamine Hydrochloride (3).** To a solution of 1 (2.0 g, 9.75 mmol) in anhydrous 2-propanol (150 mL) heated to reflux was added sodium (8.0 g, 350 mmol) in small pieces over a 1-h period. After the addition was complete the solution was refluxed an additional hour and cooled to room temperature. The resulting solid was acidified with 20% HCl and the solvent removed in vacuo. The residue was taken up in water, extracted with ether, basified with 40% sodium hydroxide, and extracted with methylene chloride. The methylene chloride was washed with brine and dried ($MgSO_4$). Filtration and concentration gave a colorless oil which was taken up in a minimal amount of anhydrous ether and treated with ethereal HCl to give the salt. Filtration gave the amine hydrochloride **3** (1.55 g, 70%) as a white solid. Three recrystallizations from ethanol–ether gave pure trans amine **3** (99.5% isomeric purity): mp 207–208 °C dec (lit.[7] mp 188–190 °C); IR (KBr) 3300–2600 cm^{-1} (CH, NH); NMR (D_2O) δ 6.93 (s, 1 H), 6.87 (s, 2 H), 5.96 (s, 2 H, OCH_2O), 3.4–4.0 (m, 2 H, CHCH), and 1.7–2.5 (m, 4 H, CH_2CH_2). Anal. Calcd for $C_{11}H_{14}NO_2Cl$: C, 58.03; H, 6.20; N, 6.15. Found: C, 57.97; H, 6.30; N, 6.06.

Preparation of the Trifluoroacetamides of 8 and 9 for Gas Chromatography Analysis. The crude reaction product of amine **2** and/or **3** (10 mg) was taken up in ethyl acetate (1 mL) to which was added trifluoroacetic anhydride (0.5 mL). The reaction was allowed to stand at room temperature for 15 min and then concentrated under a stream of argon. The amide was taken up in ethyl acetate and injected onto a 4 ft OV-101 column with the injection port at 240 °C, the flame ionization detector at 300 °C with a flow rate of 30 mL/min of helium, and the column at 170 °C; the retention time for the acetamide derived from the trans amine **9** was 10.2 min and that from the cis amine **8** was 7.4 min.

***cis*-2-(3′,4′-Dihydroxyphenyl)cyclobutylamine Hydrobromide (4).** To a suspension of **2** (1.10 g, 4.86 mmol) in methylene chloride cooled to −78 °C under argon there was added with stirring boron tribromide (3.5 g, 14.0 mmol). After the addition was complete the reaction was allowed to warm to room temperature and stir an additional 12 h. Addition of anhydrous methanol and removal of solvent in vacuo gave a white solid which was taken up in methanol–methylene chloride and crystallized in an ether chamber. Filtration under argon gave the catechol **4** (1.10 g, 87%), mp 248 °C dec, which gave a positive ferric chloride test: IR (KBr) 3400–2900 cm^{-1} (NH, OH); NMR (D_2O) δ 6.7–7.1 (m, 3 H), 3.7–4.2 (m, 2 H, CHCH), and 1.9–2.7 (m, 4 H, CH_2CH_2); mass spectrum (CI) m/e 180. Anal. Calcd for $C_{10}H_{14}NO_2Br$: C, 46.17; H, 5.42; N, 5.38. Found: C, 46.05; H, 5.60; N, 5.41.

***trans*-2-(3′,4′-Dihydroxyphenyl)cyclobutylamine Hydrobromide (5).** To a suspension of **3** (210 mg, 0.925 mmol) in methylene chloride (15 mL) cooled to −78 °C there was added dropwise boron tribromide (695 mg, 2.78 mmol). After addition was complete the solution was allowed to warm to room temperature and stir 18 h under argon. The reaction was quenched with methanol (3 mL) and the solvent was removed in vacuo. The white solid was filtered from methylene chloride/methanol to give the dihydroxy amine hydrobromide **5** as a hydroscopic solid (180 mg, 75%). Extended drying gave a tan hygroscopic solid, mp 123–125 °C, which analyzed as the hemihydrate, and gave a positive ferric chloride test: IR (KBr) 3600–2600 cm^{-1} (NH, OH); NMR (D_2O) δ 6.7–7.0 (m, 3 H), 3.3–4.0 (m, 2 H, CHCH), and 1.5–2.5 (m, 4 H, CH_2CH_2); mass spectrum via chemical ionization m/e 180. Anal. Calcd for $C_{10}H_{14}NO_2Br \cdot {}^1/_2H_2O$: C, 44.62; H, 5.62; N, 5.20. Found: C, 44.34; H, 5.56; N, 4.94.

***cis*-*N*-Acetyl-2-(3′,4′-methylenedioxyphenyl)cyclobutylamine (10).** A solution of **2** (100 mg, 0.44 mmol), acetic anhydride (2 mL), and pyridine (2 mL) was stirred at room temperature for 16 h. The sample was concentrated in vacuo, taken up in chloroform, washed three times with 10% HCl, twice with 10% NaOH, and once with brine solution, and dried ($MgSO_4$). Filtration and concentration gave an oil which slowly crystallized on standing. Recrystallization from ether–ligroin gave the amide **10** as a white solid: mp 90–91 °C; IR (KBr) 3300 (NH), 1640 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.6–6.9 (m, 3 H), 5.96 (s, 2 H, OCH_2O), 5.15 (br s, 1 H, NH), 4.72 (m, 1 H, CHN), 3.65–3.90 (m, 1 H, CH), 1.8–2.6 (m, 4 H, CH_2CH_2), and 1.75 (s, 3 H, CH_3). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.95; H, 6.50; N, 5.97.

***trans*-*N*-Acetyl-2-(3′,4′-methylenedioxphenyl)cyclobutylamine (11).** A solution of **3** (100 mg, 0.44 mmol), acetic anhydride (2 mL), and pyridine (2 mL) was stirred at room temperature for 16 h. The sample was concentrated in vacuo, taken up in chloroform, washed three times with 10% HCl, twice with 10% NaOH, and once with brine solution, and dried ($MgSO_4$). Filtration and

concentration gave an oil which crystallized on standing. Recrystallization from ether–ligroin gave the amide **11** as a white solid: mp 132–133 °C; IR (KBr) 3295 (NH), 1650 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.71 (s, 3 H), 5.91 (s, 2 H, OCH_2O), 5.75 (br s, 1 H, NH), 4.46 (m, 1 H, CCHN), 3.23 (q, 1 H, J = 9 Hz), 1.5–2.5 (m, 4 H, $-CH_2CH_2-$), and 1.95 (s, 3 H, CH_3). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.79; H, 6.50; N, 5.93.

Acknowledgment. Support for part of this research project by the National Institutes of Health Research Grants No. NS14774 and NS09350 is gratefully acknowledged.

Registry No. **1**, 71749-90-1; **2**, 71718-49-5; **3**, 71718-50-8; **4**, 71718-51-9; **5**, 71718-52-0; **6**, 71718-53-1; **7**, 120-57-0; **8**, 71718-54-2; **9**, 71718-55-3; **10**, 71718-56-4; **11**, 71718-57-5; cyclopropyldiphenylsulfonium fluoroborate, 33462-81-6; diphenylsulfonium cyclopropylide, 29800-44-0.

Synthesis of Pinselic Acid and Pinselin

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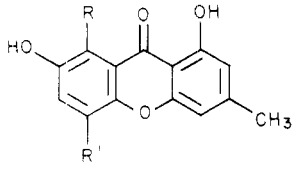
Pinselic acid and its methyl ester, pinselin, were first isolated by Munekata[1] in 1943 from the mold *Penicillium amarum* and were formulated, respectively, as 2,8-dihydroxy-6-methyl-9-oxo-9*H*-xanthene-1-carboxylic acid (**1**) and methyl 2,8-dihydroxy-6-methyl-9-oxo-9*H*-xanthene-1-carboxylate (**2**). The assignments of these structures were



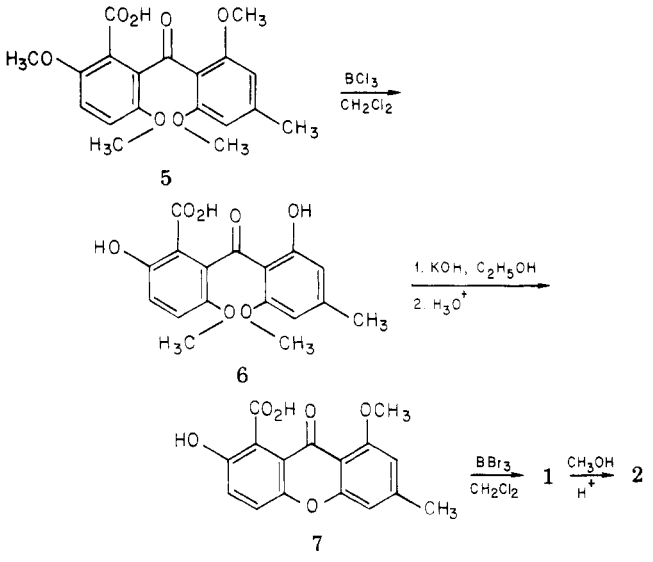
1, R = CO_2H; R′ = H
2, R = CO_2CH_3; R′ = H
3, R = R′ = H
4, R = H; R′ = CO_2CH_3

based mainly on the marked difficulties encountered in the interconversion of pinselin and pinselic acid, the decarboxylation of the latter into the known 1,7-dihydroxy-3-methyl-9*H*-xanthen-9-one (**3**), and certain other chemical properties.[1]

Interests in the structures of pinselin and pinselic acid were rekindled recently by the works of Kulkarni[2] and Moppett[3] on cassiollin. The last-named substance, isolated from the acid-hydrolyzed extracts of *Cassia occidentalis* Linn, was originally described as methyl 2,8-dihydroxy-6-methyl-9-oxo-9*H*-xanthene-4-carboxylate (**4**)[2] but was later found to be spectrally identical with pinselin by UV, IR, NMR, and MS.[3] We now report the total synthesis of pinselic acid and pinselin, which unambiguously confirms structures **1** and **2** for these natural products.

Since the location of the carboxyl group has been of primary concern in deciding the structure of pinselic acid, and thence pinselin, our synthetic methodology was devised in such a manner as not to leave any doubt regarding the regio relationship between the carboxyl and carbonyl groups upon the construction of the xanthone system. The reaction sequence employed is outlined in Scheme I.

Scheme I



Reaction of 3,6-dimethoxyphthalic anhydride[4] with 2,6-dimethoxy-4-methylphenyllithium[5] gave 2-(2,6-dimethoxy-4-methylbenzoyl)-3,6-dimethoxybenzoic acid (**5**). Selective demethylation[6] of **5** with BCl_3 resulted in the removal of two methyl groups, giving a diphenolic compound in good yield. The mass spectrum of this product, which showed prominent peaks at m/e 195, 194, and 165 and the absence of peaks at 181 and 179, suggested that each benzene ring retained one methoxy group. These data, coupled with the general behavior of BCl_3 toward polymethoxylated aromatic carbonyl compounds,[6,7] allowed structure **6** for the demethylation product[8] of **5**. Heating of **6** in 2% ethanolic KOH solution[9] gave the insoluble dibasic salt of **7**, which was acidified to 2-hydroxy-8-methoxy-6-methyl-9-oxo-9*H*-xanthene-1-carboxylic acid (**7**). Demethylation[10] of **7** with BBr_3 in CH_2Cl_2 afforded pinselic acid in 60% yield. The synthetic product obtained in this manner gave spectral data consistent with structure **1** and exhibited physical properties which agreed well with those of natural pinselic acid reported by Munekata.[1] Esterification of synthetic pinselic acid with methanol gave, in low yield as expected,

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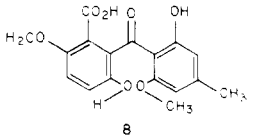
(2) B. S. Ginde, B. D. Hosangadi, N. A. Kudav, K. V. Nayak, and A. B. Kulkarni, *J. Chem. Soc. C*, 1285 (1970).
(3) C. E. Moppett, *Chem. Commun.*, 423 (1971).
(4) V. C. Farmer, N. F. Hayes, and R. H. Thomson, *J. Chem. Soc. C*, 3600 (1956).
(5) R. Adams, H. Wolff, C. K. Cain, and J. H. Clark, *J. Am. Chem. Soc.*, **62**, 1770 (1940).
(6) F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Lett.*, 4153 (1968).
(7) D. H. R. Barton, L. Bould, D. L. J. Clive, P. D. Magnus, and T. Hase, *J. Chem. Soc. C*, 2204 (1971).
(8) The formation of isomer **8** under these conditions was considered to be unlikely. However, even if **8** had been formed, the sequential



8

cyclization and demethylation reactions as described in the synthetic scheme would still ultimately lead to structure **1**.
(9) B. S. Au-Yeung, T. L. Chan and S. W. Tam, *Aust. J. Chem.*, **28**, 657 (1975).
(10) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968).

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