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.

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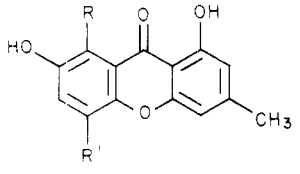
Pinselic acid and its methyl ester, pinselin, were first isolated by Munekata[1] in 1943 from the mold *Penicillium amarum* and were formulated, respectively, as 2,8-dihydroxy-6-methyl-9-oxo-9*H*-xanthene-1-carboxylic acid (**1**) and methyl 2,8-dihydroxy-6-methyl-9-oxo-9*H*-xanthene-1-carboxylate (**2**).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



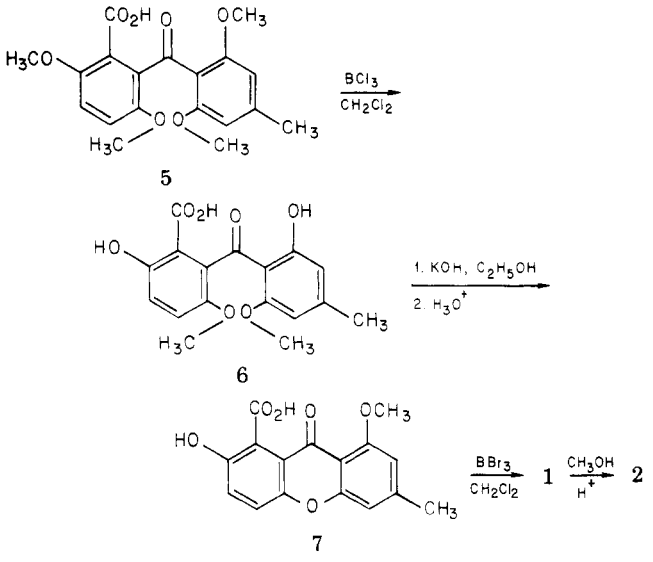
1, R = CO_2H; R′ = H
2, R = CO_2CH_3; R′ = H
3, R = R′ = H
4, R = H; R′ = CO_2CH_3

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.

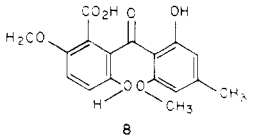
Since the location of the carboxyl group has been of primary concern in deciding the structure of pinselic acid, and thence pinselin, our synthetic methodology was devised in such a manner as not to leave any doubt regarding the regio relationship between the carboxyl and carbonyl groups upon the construction 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,

(1) (a) H. Munekata, *J. Agric. Chem. Soc. Jpn.*, **19**, 343 (1943); *Chem. Abstr.*, **45**, 8078 (1951); (b) *J. Biochem. Jpn.*, **40**, 451 (1953).
(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



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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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a methyl ester, identical in all respects with pinselin from natural sources.

As a further effort to confirm the identity of pinselin with that of cassiollin, compound **7** was methylated with diazomethane. The physical as well as spectral data of the fully methylated product were in full agreement with those of cassiollin dimethyl ether reported by Kulkarni and coworkers.[2]

Experimental Section

Melting points are uncorrected. Elemental analyses were carried out by the Australian Microanalytical Service, Parkville, Victoria, or the Microanalytical Laboratory of the University Chemical Laboratory, Cambridge, England. Infrared spectra were determined for KBr disks with a Beckman IR-10 spectrophotometer; ultraviolet spectra were obtained on a Unicam SP-800 spectrophotometer. NMR spectra were recorded on a JEOL 60HL instrument using Me_4Si as an internal standard. Mass spectra were taken on a Hitachi RMS-4 or on an AEI MS-9 spectrometer.

2-(2,6-Dimethoxy-4-methylbenzoyl)-3,6-dimethoxybenzoic Acid (5). A clear solution of 2,6-dimethoxy-4-methylphenyllithium[5,11] in ether–benzene was prepared by treating 6.1 g (0.04 mol) of 3,5-dimethoxytoluene in dry diethyl ether under nitrogen with 19.0 mL (0.04 mol) of 20% *n*-BuLi in hexane followed by addition of benzene. To a vigorously stirred suspension of 8.5 g (excess) of 3,6-dimethoxyphthalic anhydride in dry diethyl ether under nitrogen was added dropwise through a pressure-equalizing funnel the solution of the above phenyllithium reagent over 1.5 h. After further stirring for 1 h, the resulting brick-red colored mixture was decomposed with 200 mL of ice–water. Unreacted anhydride was removed by filtration and the separated aqueous layer was acidified with concentrated HCl. The gummy substance which was formed was taken up in $CHCl_3$. Repeated extraction of the $CHCl_3$ solution with 5% $NaHCO_3$ followed by acidification (HCl) of the combined aqueous extracts yielded a yellow precipitate upon refrigeration overnight. Two recrystallizations of this material from methanol afforded 2.4 g (17%, based on 3,5-dimethoxytoluene) of pure **5** as light yellow prisms: mp 220–221 °C; NMR ($CDCl_3$) δ 2.31 (s, 3 H, $ArCH_3$), 3.69 and 3.93 (s, 12 H, OCH_3), 6.42 (s, 2 H, 3′,5′-ArH), 6.95 (q, J = 9 Hz, 2 H, 4,5-ArH), 8.2 (s, 1 H, CO_2H); IR ν_{max} 3200–2500 (br, OH), 1700 (acid C=O), 1660 (ketone C=O) cm^{-1}; UV ($CHCl_3$) λ_{max} 240 (log ϵ 4.21), 285 (3.62), 324 (3.93) nm; MS m/e 360 (M^+), 316 ($M^+ - CO_2$), 315 ($M^+ - CO_2H$), 209, 179.

Anal. Calcd for $C_{19}H_{20}O_7$: C, 63.32 H, 5.59. Found: C, 63.00; H, 5.63.

Workup of the benzene–ether solution above yielded an additional small amount of impure **5**.

2-(2-Hydroxy-4-methyl-6-methoxybenzoyl)-3-methoxy-6-hydroxybenzoic Acid (6). Into a rapidly stirred suspension of 1.2 g (3.3 mmol) of **5** in 200 mL of dry CH_2Cl_2 at −78 °C was introduced 3.0 g (excess) of freshly prepared BCl_3. Stirring was continued at 0 °C for 1 h and at room temperature for 1.5 h. The resulting mixture was decomposed with ice–water and the organic solution obtained by phase separation was repeatedly extracted with 5% $NaHCO_3$. Acidification (HCl) of the combined extracts yielded a yellow precipitate which was recrystallized from aqueous methanol to give 0.9 g (82%) of **6** as light yellow needles: mp 177–178 °C; NMR (CD_3COCD_3) δ 2.33 (s, 3 H, $ArCH_3$), 3.50 and 3.73 (s, 6 H, OCH_3), 6.45 and 6.55 (s, 2 H, 3′,5′-ArH), 7.32 (q, J = 9.5 Hz, 2 H, 4,5-ArH); IR ν_{max} 3580 and 3460 (H-bonded OH), 3200–2500 (br, acid OH), 1670 (H-bonded acid C=O), 1630 (H-bond ketone C=O) cm^{-1}; MS m/e 332 (M^+), 301 ($M^+ - OCH_3$), 283 (301 − H_2O), 195, 194, 165.

Anal. Calcd for $C_{17}H_{16}O_7$: C, 61.45; H, 4.82. Found: C, 61.50; H, 4.77.

2-Hydroxy-6-methyl-8-methoxy-9-oxo-9*H*-xanthene-1-carboxylic Acid (7). A solution of 0.8 g (2.4 mmol) of **6** in 100 mL of 95% ethanol containing 2 g of KOH was refluxed under nitrogen for 3 h. The yellow potassium salt deposited was collected by filtration, washed with 95% ethanol, and transformed into crude acid **7** by adding into concentrated HCl. Purification of this material was best effected by conversion into a water-insoluble sodium salt in 10% Na_2CO_3 solution, which was then washed repeatedly with water and regenerated into **7** with concentrated HCl. Further recrystallization from chloroform–ethyl acetate gave 122 mg (17%) of analytically pure **7** as bright yellow needles, which decomposed at 250–252 °C and remelted at 290–291 °C: NMR (Me_2SO-d_6) δ 2.42 (s, 3 H, $ArCH_3$), 3.90 (s, 3 H, OCH_3), 6.86 and 6.97 (s, 2 H, 5,7-ArH), 7.47 (q, J = 9.5 Hz, 2 H, 3,4-ArH); IR ν_{max} 3000 (br, OH), 1660 (ketone C=O), 1630 (H-bonded acid C=O) cm^{-1}; UV ($CHCl_3$) λ_{max} 246 (log ϵ 4.27), 261 (4.29), 279 (4.18), 308 (3.87) nm; MS m/e 300 (M^+), 282 ($M^+ - H_2O$), 256 ($M^+ - CO_2$), 255 ($M^+ - CO_2H$), 254 (282 − CO), 226, 210, 197.

Anal. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.00. Found: C, 63.78; H, 4.26.

Pinselic Acid (1). To a rapidly stirred suspension of 60 mg (0.20 mmol) of **7** in 30 mL of dry CH_2Cl_2 was introduced 0.4 mL (excess) of BBr_3 in one lot. After stirring at room temperature for 2 h, the resulting mixture was poured into ice–water. The organic layer separated was repeatedly extracted with 5% $NaHCO_3$ and the combined extracts were acidified with concentrated HCl. Upon standing at 0–5 °C overnight, a yellow precipitate was formed. Recrystallization of this substance from chloroform–hexanes gave 34 mg (60%) of **1** as golden yellow needles which sintered at 194–195 °C and remelted[12] at 252–253 °C: NMR (Me_2SO-d_6) δ 2.40 (s, 3 H, $ArCH_3$), 6.68 and 6.92 (s, 2 H, 5,7-ArH), 7.25 (q, J = 9.5 Hz, 2 H, 3,4-ArH); IR ν_{max} 3000 (br, OH), 1645 (H-bonded ketone C=O), 1630 (H-bonded acid C=O) cm^{-1}; UV ($CHCl_3$) λ_{max} 253 (log ϵ 3.84), 275 (3.84), 297 (3.38), 326 (3.35, 412 (3.21) nm; MS m/e 286 (M^+), 269 ($M^+ - OH$), 268 ($M^+ - H_2O$), 242 ($M^+ - CO_2$), 241 ($M^+ - CO_2H$), 240 (268 − CO), 212 (240 − CO), 184 (212 − CO), 156 (184 − CO).

Anal. Calcd for $C_{15}H_{10}O_6$: C, 62.93; H, 3.50. Found: C, 62.61; H, 3.65.

Pinselin (2). A solution of 10 mg (0.035 mmol) of synthetic pinselic acid (**1**) and a small crystal of *p*-toluenesulfonic acid in 5 mL of methanol was refluxed for 12 h. The residue obtained after evaporation of solvent was taken up in acetone and deposited on a silica gel preparative thin-layer plate. On elution with benzene–methanol (99:1) the yellow band collected at R_f 0.1 was extracted with benzene to afford 1.5 mg (14%) of yellow crystals of **2**, mp 226–227 °C, undepressed on admixture with authentic pinselin from a natural source. The infrared spectrum of synthetic pinselin was superimposable upon that of the natural product.

Methyl 2,8-Dimethoxy-6-methyl-9-oxo-9*H*-xanthene-1-carboxylate (Pinselin Dimethyl Ether). To a suspension of 40 mg (0.13 mmol) of **7** in 50 mL of dry diethyl ether was added a large excess of ethereal diazomethane and the mixture was left at 0 °C for 7 days. The residue on solvent evaporation was dissolved in 100 mL of diethyl ether, washed successively with 2% NaOH and water, and dried over $CaCl_2$. Removal of solvent in vacuo gave a crude product which was purified by chromatography on a preparative silica gel plate, developed with chloroform, to afford 25 mg (57%) of the fully methylated product as yellow prisms (from benzene), mp 223–224 °C (reported melting point for cassiollin dimethyl ether:[2] 222–223 °C). Both the NMR and IR spectra of this product agreed well with those reported for cassiollin dimethyl ether.[2]

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Registry No. 1, 476-53-9; 2, 479-67-4; 5, 71646-98-5; 6, 71607-17-5; 7, 71607-18-6; methyl 2,8-dimethoxy-6-methyl-9-oxo-9*H*-xanthene-1-carboxylate, 65489-48-7; 3,5-dimethoxytoluene, 4179-19-5; 3,6-dimethoxyphthalic anhydride, 14597-12-7.

(11) For a general procedure for the lithiation of methoxybenzenes, see also G. Wittig and U. Pockels, *Ber. Dtsch. Chem. Ges. B*, **72**, 89 (1939).

(12) Pinselic acid was previously noted[1b] to possess this similar property: it decomposed at 195–200 °C and remelted at 250–252 °C. However, the hydrolysis product of cassiollin, which may now be also regarded as pinselic acid, was reported[2] to melt at 213–215 °C. Nonetheless, both these substances were found[1,2] to undergo decarboxylation to give **3**.