both compounds, *i.e.*, 1.15 *vs.* 1.14 ppm. The constant W_H and δ would lead to the conclusion that there has been no change in the shielding of the C-1 methyl group, implying that the C-3 methyl group is equatorial in both cases. One would expect that an axial C-3 methyl would have strong interactions with the axial C-1 methyl and thus shift both the C-1 methyl and the C-3 methyl bands. The small differences in the δ values of the C-3 substituents between **1** and **3** (compound **1**, δ_H 1.53 and δ_{CH_3} 0.905; compound **3**, δ_H 1.42 and δ_{CH_3} 1.01) are attributed to differing effects from the β-phenethyl group.

Although it is tempting to assume that the downfield shift of the resonance of the C-3 methyl, which occurs between **1** and **3**, is indicative of a change from equatorial to axial conformation of this group, it is not possible to defend an inversion at C-3 using only this information. We, therefore, believe that the conformation at C-3 is the same in **1** and **3** (CH axial, CCH_3 equatorial).

The inversion of the hydrogen at C-3 in **3** may occur during the reaction of the C-3 anion with a proton.[2] The inversion of the hydrogen at C-2 in **1** may result from carbon–carbon cleavage between C-1 and C-2 of the resin acid molecule and a recombination during the reaction.[2] If this is the case, two more isomers could be formed. These isomers do not show up in the glpc analysis of the reaction mixture.

A comparison of the spectral data for **3** and the seco-dehydroabietate compound of Zinkel and Rowe[6] indicated that these compounds were apparently identical. Upon our isolation of **1**, however, a further more detailed comparison of the nmr spectra of **1** and the compound of Zinkel and Rowe showed the latter compounds to be identical. Zinkel, *et al.*, have confirmed this identity by glpc on DEGS and SE-30 columns[7] and concur with the assignment of structure **1**.

It was also found in the present work that methyl levopimarate refluxed in tri-*n*-butylamine for 5 hr gave the same four ring-opened compounds in 32.4% yield. No increase in yield was obtained on further refluxing.

Experimental Section[8]

Methyl 2α-[2′(*m*-Isopropylphenyl)ethyl]-1β,3α-dimethylcyclohexane Carboxylate (1).—Compound **1** was prepared by heating levopimaric acid with 105 mol % of potassium hydroxide for 3 days at 200° as described previously.[2] The compound of relative retention time 0.518 (methyl dehydroabietate, 1.0) was collected from a 10% Versamid 900 on Chromosorb W column (10 ft × 0.25 in. o.d. aluminum tubing F & M 500 instrument) run at 250°. Final purification was accomplished by very careful recollection from a 3.8% SE-30 Chromosorb W column (15 ft. × 0.25 in. o.d. aluminum column) at 200°. Analytical work was carried out on a 5% Versamid 900 on Chromosorb W (60–80 mesh) column (15 ft × 0.25 in. o.d. aluminum column) at 250°. Compound **1** was collected as a colorless oil which gave a single peak on both a Versamid 900 column (250°) and a 3.8% SE-30 column (at 200°). A 1:1 mixture of **2** and **1** was prepared and found to give two peaks on both a Versamid 900 and an SE-30 column. Compound **1** exhibits $[\alpha]^{25}D$ −13° (*c* 0.9, 95% EtOH); uv max (95% EtOH) 264 mμ (ε 284), 271 (253); ir (neat) 1725 (C=O), 1604 (aromatic), 1460 (CH_3), 1213, 1182, 1133 (isopropyl) 1112, 1048, 788 (*meta*-disubstituted aromatic); nmr ($CDCl_3$) δ 0.905 (d, 3, J = 7 Hz, C_3 CH_3), 1.15 (s, 3, C_1 CH_3), 1.245 (d, 6, J = 7 Hz, isopropyl CH_3), 1.41 (m, 2, C_2H CH_2), 1.53 (m, 1, C_3 **H**), 2.05 (t, 1, J = 4 Hz, C_2 **H**), 2.61 (t, 2, J = 9 Hz, C_6H_5 CH_2), 2.87 (quintet, 1, J = 7 Hz, *t*-**H** at isopropyl), 3.66 (s, 3, OCH_3), 7.02 largest peak (m, 4, aromatic **H**); mass spectrum (70 eV) *m/e* (relative intensity) 316 (15), 284 (15), 257 (3.9), 256 (3.2), 192 (7.9), 188 (6.3), 187 (39), 183 (7.9), 173 (3.2), 159 (3.2), 151 (7.9), 147 (15.8), 146 (100), 145 (3.9), 135 (3.9), 134 (28.3), 133 (45.6), 132 (3.9), 131 (14.2), 129 (3.2), 123 (18.9), 121 (3.2), 119 (7.1), 117 (18.9), 116 (7.1), 115 (5.5), 111 (7.9), 110 (3.2), 109 (12.6), 105 (11.8), 102 (3.2), 101 (45.6), 100 (3.2), 97 (3.2), 95 (11.8), 93 (6.3), 92 (23.6), 91 (25), 88 (3.2), 81 (11), 79 (5.9), 77 (3.9), 69 (8.7), 67 (7.9), 59 (3.9), 55 (14.2), 53 (3.2).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.72; H, 10.18. Found: C, 79.62; H, 10.23.

The nmr spectrum of **3** at 100 MHz showed δ 1.013 (d, 3, J = 5.5 Hz, C_3 CH_3), 1.14 (s, 3, C_1 CH_3), 1.235 (d, 6, J = 7 Hz, isopropyl CH_3), 1.42 (m, 2, C_2 CH_2), 1.42 (m, 1, C_3 **H**), <1.8 (definite position could not be found, C_2 **H**), 2.55 (t, 2, J = 7 Hz, $C_6H_5CH_2$), 2.86 (quintet, 1, J = 7 Hz, *t*-**H** at isopropyl), 3.64 (s, 3, OCH_3), 6.96 (m, 4, aromatic **H**).

Methyl Levopimarate Refluxed with Tri-*n*-butylamine.—Methyl levopimarate (0.8 g, 2.5 mmol) was dissolved with tri-*n*-butylamine (10 ml, 42 mmol) and refluxed (216°). After refluxing 5 hr, ether was added, the solution washed twice with aqueous acetic acid and with water five times, dried, and concentrated. The residue was analyzed by glpc (Versamid 900): methyl 9-(*m*-isopropylphenyl)-2,6-dimethyl-*cis*-6-nonenoate[2] (5.8%); mixture of **1** and methyl 9-(*m*-isopropylphenyl)-2,6-dimethyl-*trans*-6-nonenoate[2] (19.1%), **3** (1.75%), levopimarate–palustrate peak (39.8%), unknown (6.1%), dehydroabietate (19.5%), abietate (2.2%). The same composition was obtained on refluxing the sample for 10 hr.

Registry No.—**1**, 19556-80-0; **3**, 19556-81-1.

Acknowledgment.—The authors wish to thank Dr. Ludwig Bauer, of the University of Illinois, College of Pharmacy, Chicago, Ill., for the mass spectrum.

(6) See ref 2, footnote 9.

(7) In the course of communications with D. F. Zinkel, an interpretation of our data was called to our attention which resulted in the postulation of **3** for the compound from ref 2.

(8) The nmr spectra were obtained using a Varian HA-100 nmr spectrometer. Chemical shifts were measured in deuteriochloroform as a solvent relative to tetramethylsilane (TMS) as an internal standard, δ_{TMS} = 0 ppm.

Tumor Inhibitors. XXXVI.[1] Eupatin and Eupatoretin, Two Cytotoxic Flavonols from *Eupatorium semiserratum*[2]

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During a recent study of the cytotoxic constituents of *Eupatorium* species,[3] the isolation and characterization of two previously unreported flavonoids were described. Flavanoid K, mp 243–245°, and flavonoid L, mp 146–148°, which we designate, respectively, as eupatin and eupatoretin, were found to show moderate cytotoxicity against human carcinoma of the nasopharynx carried in cell culture (KB).[3] We report here structural studies leading to assignment of the 3,5,3′-trihydroxy-6,7,4′-trimethoxyflavone structure (**1**) for

(1) Part XXXV in the series: S. M. Kupchan, P. S. Steyn, M. D. Grove, S. M. Horsfield, and S. W. Meitner, *J. Med. Chem.*, **12**, 167 (1969).

(2) This investigation was supported by grants from the National Cancer Institute (CA-04500) and the American Cancer Society (T-275), and a contract with the Cancer Chemotherapy National Service Center (CCNSC), National Cancer Institute, National Institutes of Health (PH-43-64-557). C. W. S. was a N.I.H. Postdoctoral Fellow, 1967–1968.

(3) S. M. Kupchan, C. W. Sigel, R. J. Hemingway, J. R. Knox, and M. S. Udayamurthy, *Tetrahedron*, in press.

TABLE I

NMR SOLVENT SHIFT DATA FOR METHOXY GROUPS IN ETHYL ETHERS OF EUPATIN AND EUPATORETIN

	Benzene-d_6 (TMS)	$CDCl_3$ (TMS)[a]	Δ, ppm
Eupatin			
triethyl ether (**5**)	6.14	6.02	+0.10 ± 0.03 (C-6)
	6.52	6.02, 6.04 ± 0.03	+0.48 ± 0.03 (C-4′)
	6.69	6.07	+0.65 ± 0.03 (C-7)
Eupatoretin			
diethyl ether (**10**)	5.87	5.98	−0.15 ± 0.05 (C-5)
	6.18	6.00	+0.16 ± 0.05 (C-6)
	6.51	6.01, 6.02 ± 0.05	+0.49 ± 0.05 (C-4′)
	6.68	6.07	+0.66 ± 0.05 (C-7)
Quercetagetin			
hexamethyl ether (**3**)[b]	5.88	6.01	−0.13 (C-5)
	6.09	6.01	0.08 (C-6)
	6.20	5.96	0.24 (C-3)
	6.41	6.06	0.35 (C-3′)
	6.57	6.10	0.47 (C-4′)
	6.75	6.01	0.74 (C-7)

[a] The observed chemical shift (τ units) for each signal is given. The value used to calculate Δ is the mean of the two extremes. [b] See ref 6.

eupatin and the 3,3′-dihydroxy-5,6,7,4′-tetramethoxyflavone structure (**8**) for eupatoretin.

Elemental analysis for eupatin (**1**) supported the empirical formula, $C_{18}H_{16}O_8$. The ultraviolet absorption spectrum showed a peak at 366 mμ, indicative that it is a flavonol rather than a flavone. Acetylation afforded a triacetate (**2**), which exhibited three methoxyl and three acetate signals in its nmr spectrum, indicative that eupatin is a trihydroxytrimethoxyflavone.

Methylation of eupatin (**1**) with dimethyl sulfate furnished hexamethylquercetagetin (**3**), which was identified by direct comparison with an authentic sample.[4] The formation of **3** established the oxygenation pattern of eupatin. Methylation of eupatin with diazomethane afforded artemetin (**4**), characterized by comparison of its physical properties and those of its monoacetate with reported values.[5] These experiments established the presence of a hydroxyl at C-5 in eupatin.

Ethylation of eupatin with ethyl iodide afforded the triethyl ether (**5**). The nmr spectrum of this compound was determined in $CDCl_3$ and benzene-d_6 in order to utilize the chemical shift–structural correlations reported by Wilson, *et al.*[6] The solvent shifts observed for the three methoxy groups of eupatin are close to those reported for the C-6, C-7, and C-4′ methoxy groups of hexamethylquercetagetin (see Table I). Finally, the triethyl ether (**5**) was subjected to mild alkaline degradation. The acidic product (**6**) was identified by its melting point and nmr sectrum as the expected 3-ethoxy-4-methoxybenzoic acid. The neutral fraction afforded an acetophenone with physical properties identical with those reported for 2,2′-diethoxy-3′,4′-dimethoxy-6′-hydroxyacetophenone (**7**).[7] The base peak of its mass spectrum at *m/e* 225 corresponded to the loss of $CH_2OCH_2CH_3$ and confirmed the presence of a 2-ethoxyl group.[8]

The results of these structural studies firmly established that eupatin (**2**) possesses hydroxyl groups at C-3, C-5, and C-3′. On this basis the structure of eupatin could be assigned as 3,5,3′-trihydroxy-6,7,4′-trimethoxyflavone (**1**).

Eupatoretin (**8**) was assigned the empirical formula $C_{19}H_{18}O_8$ on the basis of elemental analysis. The ultraviolet spectrum showed a strong absorption at 356 mμ, indicative of a flavonol structure. Acetylation afforded a diacetate (**9**), $C_{23}H_{22}O_{10}$, whose nmr spectrum established the presence of four methoxyl and two acetate groups in the molecule.

Methylation of eupatoretin with either dimethyl sulfate or diazomethane afforded a hexamethyl ether which was identical with hexamethylquercetagetin (**3**). Ethylation of eupatoretin afforded the diethyl ether (**10**). The nmr spectrum was measured in $CDCl_3$ and benzene-d_6 (see Table I). The solvent shifts for the four methoxy groups are close to those observed for C-5, C-6, C-7, and C-4′ methoxyl groups in the model compound hexamethylquercetagetin.[6]

Mild alkaline degradation of eupatoretin diethyl ether (**10**) afforded 3-ethoxy-4-methoxybenzoic acid (**6**) and the acetophenone (**11**), whose nmr spectrum established that it was an ethoxyhydroxytrimethoxyacetophenone. The mass spectrum of **11** showed a base peak at *m/e* 211 (M − $CH_2OCH_2CH_3$). Since this fragmentation defined the location of the ethoxyl, and the conversion of eupatoretin to hexamethylquercetagetin had established the substitution pattern, the structure of acetophenone **11** could be assigned as 2-ethoxy-2′,3′,4′-trimethoxy-6′-hydroxyacetophenone. Identification of the two degradation products located the two hydroxyl groups in eupatoretin at C-3 and C-3′. Thus the structure of eupatoretin is 3,3′-dihydroxy-5,6,7,4′-tetramethoxyflavone (**8**) (Scheme I).

Experimental Section

Melting points were determined with a Thomas–Hoover Unimelt apparatus and are corrected. Infrared spectra were determined on a Beckman IR-5A double-beam recording spectrophotometer. Ultraviolet spectra were determined on a Beckman DK2A recording spectrophotometer. Nmr spectra were determined on a Varian H-60A spectrometer.

(4) The authors cordially thank Professor T. R. Seshadri for the authentic sample for quercetagetin.

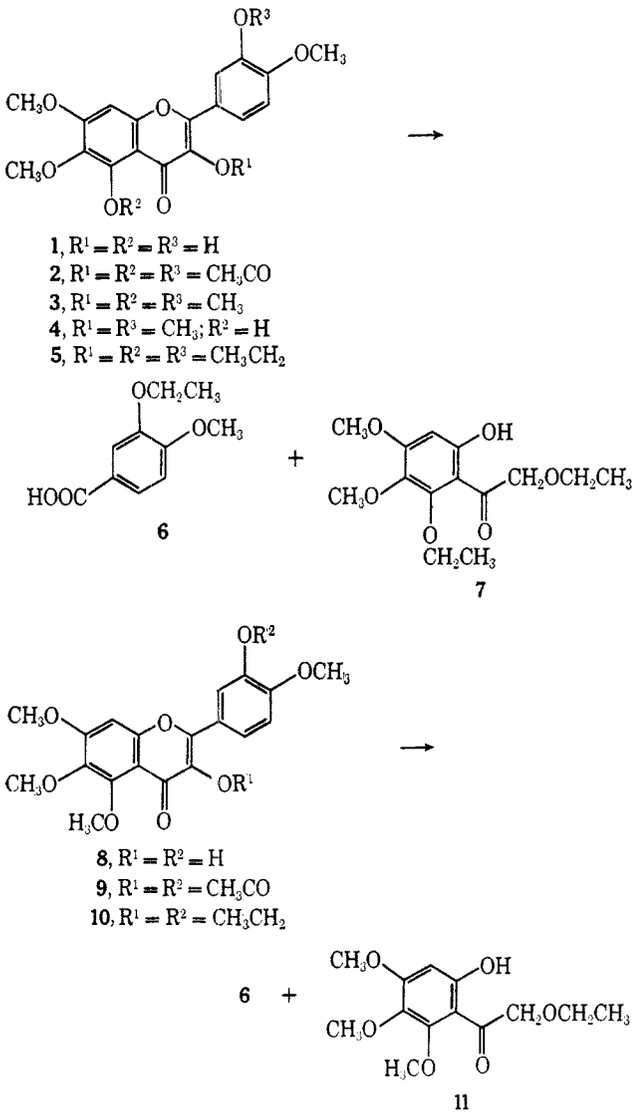
(5) Y. Mazur and A. Meisels, *Bull. Res. Council Israel*, **5A**, 67 (1955).

(6) R. G. Wilson, J. H. Bowie, and D. H. Williams, *Tetrahedron*, **24**, 1407 (1968).

(7) A. K. Kiang, K. Y. Sim, and J. Goh, *J. Chem. Soc.*, 6371 (1965).

(8) We thank Dr. R. D. Brown and Dr. F. W. McLafferty of Purdue Mass Spectrometry Center, supported under U.S. Public Health Service Grant FR-00354, for the mass spectral data.

SCHEME I



Eupatin (1).—The isolation of eupatin was reported previously.[3] Eupatin was crystallized from methanol as golden yellow rods: mp 243–245°; uv max (EtOH) 258 mμ (ε 22,100), 273 (15,500), 366 (23,200); ir ($CHCl_3$) 2.85, 3.07, 6.03 μ; nmr (DMSO) τ 2.33 (s, 1), 2.30 (m, 1), 2.93 (d, 1, J = 10 Hz), 3.18 (s, 1), 3.26 (s, 1), 6.05 (s, 3), 6.12 (s, 3), and 6.23 (s, 3).

Anal. Calcd for $C_{18}H_{16}O_8$: C, 60.22; H, 4.58. Found: C, 60.00; H, 4.48.

3,5,3′-Triacetoxy-6,7,4′-trimethoxyflavone (2).—A mixture of eupatin (0.10 g), acetic anhydride (2 ml), and pyridine (0.25 ml) was refluxed for 2 hr, cooled, and poured into ice water. The white insoluble material was filtered, dried, and crystallized from benzene–petroleum ether (bp 60–68°) to yield the triacetate (2) as a colorless powder (0.067 g): mp 219–221°; ir (Nujol) 5.65, 6.10 μ; nmr ($CDCl_3$) τ 2.33 (m, 2), 2.82 (d, 1, J = 10 Hz), 3.15 (s, 1), 6.03 (s, 3), 6.11 (s, 3), 6.15 (s, 3), 7.54 (s, 3), 7.67 (s, 6).

Anal. Calcd for $C_{24}H_{22}O_{11}$: C, 59.26; H, 4.56. Found: C, 59.23; H, 4.65.

3,5,6,7,3′,4′-Hexamethoxyflavone (3). **A.**—A solution of eupatin (0.10 g) in dry acetone (20 ml) was refluxed for 8 hr with potassium carbonate (2 g) and dimethyl sulfate (0.5 ml). The acetone was evaporated, distilled water was added, and the insoluble material was collected by filtration. Chromatography on alumina (Woelm, grade 1) and elution with 5% ethyl acetate–benzene followed by recrystallization from benzene–petroleum ether (bp 60–68°) afforded eupatin trimethyl ether (3, 45 mg) as colorless needles: mp 141–142°; uv max (EtOH) 242 mμ (ε 20,900), 251 sh (20,900), 266 sh (16,100), 333 (24,500); ir 6.15 and 6.21 μ. Admixture of an authentic sample of hexamethylquercetagetin (mp 141–142°) did not depress the melting point, and the uv and ir spectra were identical with those of the authentic sample.

B.—Eupatoretin (0.050 g) was methylated with dimethyl sulfate by the procedure used for eupatin. The product was crystallized from benzene–petroleum ether to give 0.027 g of pale yellow needles, mp 141–142°. The sample was shown by melting point, mixture melting point, and infrared spectroscopy to be identical with 3,5,6,7,3′,4′-hexamethoxyflavone (3) prepared from eupatin.

C.—A solution of eupatoretin (0.20 g) in ethanol (90 ml) was treated with diazomethane (approximately 1 g) in ether at 0° for 2 hr. The product was crystallized from benzene–petroleum ether (bp 60–68°) to give colorless needles (0.115 g), mp 141–142°, which were shown to be identical with 3,5,6,7,3′,4′-hexamethoxyflavone (3) by melting point, mixture melting point, and infrared spectral comparison.

5-Hydroxy-3,6,7,3′,4′-pentamethoxyflavone (4).—A solution of eupatin (0.10 g) in methanol (50 ml) was treated with an excess of diazomethane in ether at 0° for 2 hr. The solvent was removed and the residue dissolved in chloroform. The chloroform was extracted several times with 3% potassium hydroxide solution. The alkaline extract was acidified and extracted with chloroform. The solution was dried ($MgSO_4$) and evaporated. The residue was crystallized from benzene–petroleum ether (bp 60–68°) to afford the pentamethoxyflavone (4) as pale yellow needles: mp 160–161° (lit.[5] mp 161°); uv max (EtOH) 255 mμ (ε 17,900), 274 (16,400), 346 (20,500); ir (Nujol) 6.00 μ.

3,5,3′-Triethoxy-6,7,4′-trimethoxyflavone (5).—A solution of eupatin (0.179 g), dry potassium carbonate (3 g), and ethyl iodide (3 g) in dry acetone (20 ml) was refluxed for 40 hr. After filtration, the solvent was evaporated and the residue was dissolved in ether, washed with water, and dried (Na_2SO_4). Evaporation of the solvent afforded 0.220 g of a pale yellow solid. Recrystallization from ethyl acetate–cyclohexane afforded yellow needles: mp 105–106°; uv max (95% EtOH) 242 mμ (ε 14,900), 250 sh (14,800), 265 sh (10,100), 233 (16,000); ir (KBr) 6.13, 6.18, 6.22 μ; nmr ($CDCl_3$) τ 2.23 (s, 1), 2.29 (m, 1), 3.0 (d, 1, J = 9 Hz), 3.21 (s, 1), 5.80 (q, 6, J = 7 Hz), 5.98 (s, 3), 6.00 (s, 3), 6.01 (s, 3), 8.46 (t, 6, J = 7 Hz), 8.65 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 64.68; H, 6.25.

Alkaline Degradation of 3,5,3′-Triethoxy-6,7,4′-trimethoxyflavone (5).—Triethyl ether 5 (0.120 g) in a mixture of 50% potassium hydroxide (30 ml) and ethanol (5 ml) was refluxed under nitrogen for 17 hr. The reaction mixture was cooled, acidified with 20% sulfuric acid, and extracted with ether (200 ml). The ethereal extract was washed with four 50-ml portions of 5% sodium bicarbonate, dried (Na_2SO_4), and evaporated to dryness to afford the acetophenone (7) as a yellow oil. Recrystallization from petroleum ether (bp 35–37°) afforded 20 mg of yellow prisms: mp 59–60° (lit.[7] mp 60–61°); uv max (95% EtOH) 235 mμ (ε 8500), 283 (11,400), 335 (3400); nmr ($CDCl_3$) τ −3.20 (s, 1), 3.74 (s, 1), 5.25 (s, 2), 5.78 (q, 2, J = 7 Hz), 6.12 (s, 3), 6.22 (s, 3), 6.33 (q, 2, J = 7 Hz), 8.55 (t, 3, J = 7 Hz), 8.69 (t, 3, J = 7 Hz); *m/e* (relative intensity) 284 (24), 226 (11), 225 (100), 197 (31).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 58.95; H, 7.07.

The bicarbonate extract was acidified with dilute hydrochloric acid and extracted with ether which was dried (Na_2SO_4) and evaporated *in vacuo* to afford a white solid (40 mg). Recrystallization twice from methanol–water gave 3-ethoxy-4-methoxybenzoic acid (6) as colorless needles, mp 162–163° (lit.[9] mp 163–164°).

Eupatoretin (8).—The isolation of eupatoretin was reported previously.[3] Eupatoretin was crystallized from benzene to give bright yellow needles: mp 146–148°; uv max (EtOH) 255 mμ (ε 20,500), 356 (23,400); ir ($CHCl_3$) 2.96, 6.15, and 6.22 μ; nmr ($CDCl_3$) τ 2.26 (m, 2), 3.05 (d, 1, J = 9 Hz), 3.23 (s, 1), 5.96 (s, 3), 6.03 (s, 3), 6.05 (s, 3), 6.08 (s, 3).

Anal. Calcd for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85. Found: C, 60.81; H, 4.52.

3,3′-Diacetoxy-5,6,7,4′-tetramethoxyflavone (9).—Eupatoretin (0.16 g) was acetylated in the same manner as for the preparation of eupatin triacetate. The product was crystallized from benzene–petroleum ether (bp 60–68°) to afford 0.11 g of a colorless powder: mp 145–147°; uv max (EtOH) 235 mμ (ε

(9) I. Heilbron, "Dictionary of Organic Compounds," Eyre and Spottswoode, London, 1965.

28,300), 263 (25,000) 316 (31,000); ir ($CHCl_3$) 5.68, 6.14, and 6.21 μ.

Anal. Calcd for $C_{23}H_{22}O_{10}$: C, 60.26; H, 4.84. Found: C, 59.96; H, 5.16.

3,3'-Diethoxy-5,6,7,4'-tetramethoxyflavone (10).—Eupatoretin diethyl ether was prepared in the same manner as for eupatin triethyl ether. The product was crystallized from ethyl acetate–cyclohexane to yield 0.160 g of light yellow prisms: mp 119–120°; uv max (95% EtOH) 242 mμ (ϵ 17,000), 249 sh (13,000), 264 sh (13,000), 233 (18,800); ir (KBr) 6.10, 6.24 μ; nmr ($CDCl_3$) τ 2.19 (s, 1), 2.28 (m, 1), 3.0 (d, 1, J = 9 Hz), 3.24 (s, 1), 5.80 (q, 2, J = 7 Hz), 5.91 (q, 2, J = 7 Hz), 5.98 (s, 3), 6.01 (s, 3), 6.02 (s, 3), 6.07 (s, 3), 8.49 (t, 3, J = 7 Hz), 8.66 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09. Found: C, 64.27; H, 6.10.

Alkaline Degradation of 3,3'-Diethoxy-5,6,7,4'-tetramethoxyflavone (10).—Alkaline degradation of 10 (0.120 g), using the same conditions as for eupatin triethyl ether, gave an acid and a neutral material. The acid was recrystallized from methanol–water to yield needles (0.030 g) of 3-ethoxy-4-methoxybenzoic acid (6), mp 163–164° (lit.[9] mp 164–165°). The neutral material was crystallized from petroleum ether (bp 35–37°) to afford 0.035 g of the acetophenone 11 as colorless needles: mp 60–61°; uv max (95% EtOH) 235 mμ (ϵ 5600), 283 (11,800), 334 (4750); ir (KBr) 6.15, 6.25 and 6.32 μ; nmr ($CDCl_3$) τ −3.02 (s, 1), 3.73 (s, 1), 5.30 (s, 2), 5.95 (s, 3), 6.08 (s, 3), 6.20 (s, 3), 6.32 (q, 2, J = 7 Hz), 8.68 (t, 3, J = 7 Hz); *m/e* (relative intensity) 270 (16), 212 (11), 211 (100), 196 (12), 69 (6).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.94; H, 6.70.

Registry No.—**1**, 19587-65-6; **2**, 19587-66-7; **5**, 19587-67-8; **7**, 4324-56-5; **8**, 19587-69-0; **9**, 19598-22-2; **10**, 19598-23-3; **11**, 19598-24-4.

The Synthesis of the Ring-B Sulfur Analog of Dehydrogriseofulvin

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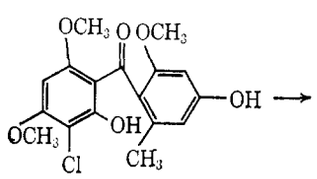
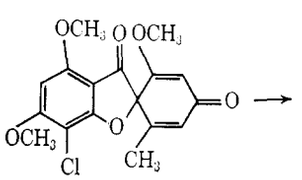
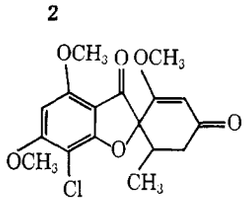
In 1957, Barton and Cohen,[1] in a classic paper speculating on the role of oxidative phenolic coupling in biogenesis, suggested that griseofulvin (3) arises biogenetically *via* oxidative ring closure of benzophenone 1 to dehydrogriseofulvin (2) followed by reduction.



1



2

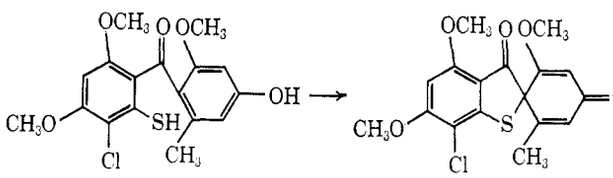


3

(1) D. H. R. Barton and T. Cohen, "Festschrift A. Stoll," Birkhauser, Basle, Switzerland, 1957, p 117.

A laboratory analogy for the oxidative ring closure was first provided in 1958 by Scott, who accomplished the transformation of 1 to 2 in alkaline medium in the presence of potassium ferricyanide.[2] This coupling reaction was subsequently employed by Scott, *et al.*, in their total synthesis of griseofulvin[3] and in the total synthesis of griseofulvin and a number of its analogs described by Taub, *et al.*[4]

We report here the application of this reaction to the mercapto analog 4 of benzophenone 1 which was thus transformed into 5, the ring-B sulfur analog of dehydrogriseofulvin 2.[5]



4 5

In Table I the chemical shift values of the various protons in 5 are compared with their counterparts in dehydrogriseofulvin 2 and the ring-B carbon analog of dehydrogriseofulvin 6 (-CH_2- in place of the ring oxygen in 1). As can be seen, with the exception of the aromatic protons, the chemical shift values of the various corresponding protons are essentially superimposable.

The different chemical shift values observed for the aromatic proton in the three compounds would be expected as a result of the ring substituent change from sulfur to oxygen to methylene. The increase in shielding observed with increasing electron-donating ability of the substituent attached to the aromatic ring (O > S > -CH_2-, resulting in an increase in ring electron density) is in accord with earlier observations made on monosubstituted benzenes.[6]

Benzophenone 4 was synthesized according to Scheme I. The commercially available[7] 3,5-dimethoxyaniline (6) was converted *via* its diazonium salt into 3,5-dimethoxythiophenol (7), which was, in turn, acetylated and chlorinated with N-chlorosuccinimide to give 9. Acylation of 9 with isoeverninic acid acetate (10) in trifluoroacetic anhydride[8,9] gave the diacetylated benzophenone 11 which was hydrolyzed to 4.

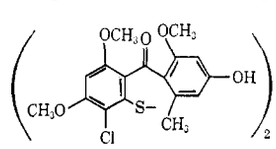
The position of the chlorine in 9 follows from its nmr spectrum in which the aromatic protons appeared as two doublets at δ 6.72 and 6.58 (J = 3 cps) consistent

(2) A. I. Scott, *Proc. Chem. Soc.*, 195 (1958).

(3) A. C. Day, J. Nabney, and A. I. Scott, *ibid.*, 284 (1960); *J. Chem. Soc.*, 4067 (1961).

(4) D. Taub, S. Kuo, and N. L. Wendler, *J. Org. Chem.*, **28**, 3344 (1963), and earlier papers cited there.

(5) At best, the formation of any disulfide i took place to only a very minor extent, and it is interesting that the rate influencing parameters in 4 com-



i

bine to cause intramolecular carbon–sulfur bond formation to dominate over the normally extremely rapid sulfur–sulfur bond-forming reaction.

(6) P. L. Corio and B. P. Dailey, *J. Amer. Chem. Soc.*, **78**, 3043 (1956).

(7) Aldrich Chemical Co., Milwaukee, Wis.

(8) See Table I, footnote *e*.

(9) D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Tetrahedron*, **19**, 1 (1963).