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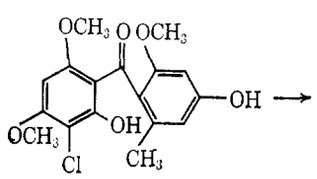
In 1957, Barton and Cohen,[1] in a classic paper speculating on the role of oxidative phenolic coupling in biogenesis, suggested that griseofulvin (3) arises biogenetically *via* oxidative ring closure of benzophenone 1 to dehydrogriseofulvin (2) followed by reduction.



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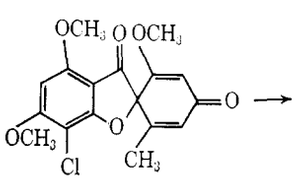

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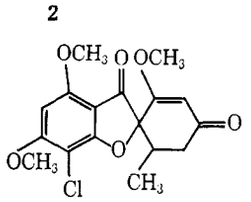
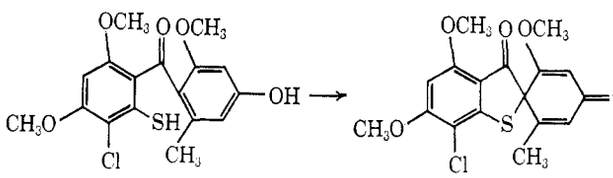


3

(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.

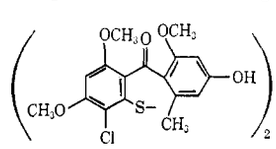
The position of the chlorine in 9 follows from its nmr spectrum in which the aromatic protons appeared as two doublets at δ 6.72 and 6.58 (J = 3 cps) consistent

(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*.

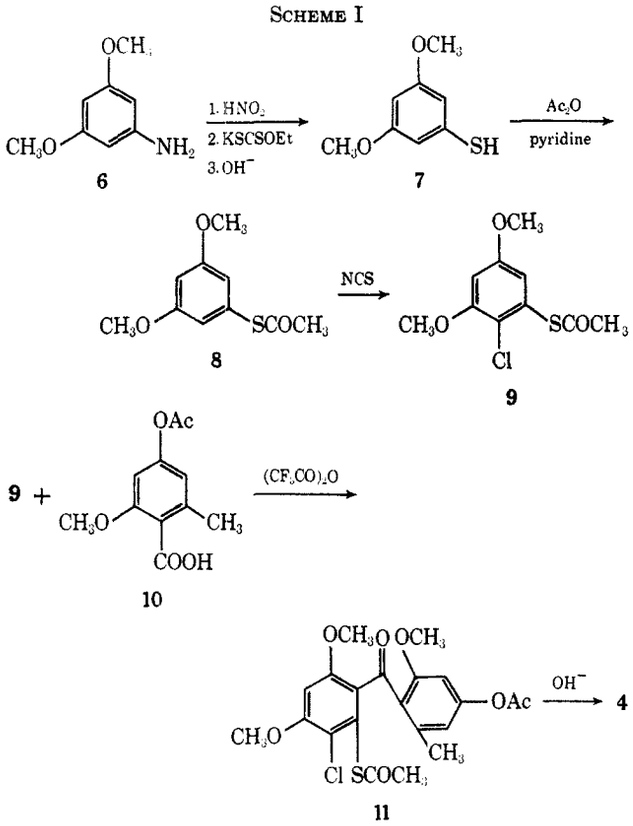
(9) D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Tetrahedron*, **19**, 1 (1963).

TABLE I[a]

	Aromatic proton	Vinyl proton	Aromatic methoxyls	Vinyl methoxyl	Vinyl methyl	Ring-B CH_2[b]
Dehydrogriseofulvin S analog **7**	6.37	6.18,[c] 5.71[d]	4.05, 4.00	3.65	1.90 (J = 1 cps)	
Dehydrogriseofulvin[e,g]	6.15	6.15, 5.59	4.04, 3.98	3.63	1.79 (J = 2 cps)	
Dehydrogriseofulvin C analog[f]	6.52	6.17,[c] 5.70[d]	4.07, 4.00	3.62	1.74 (J = 1 cps)	3.40, 3.32

[a] Chemical shift values are in parts per million from tetramethylsilane (internal standard). Solvent–$CDCl_3$. [b] H. Newman and R. B. Angier, *J. Org. Chem.*, **31**, 1462 (1966), Table I. [c] Triplet (J = <1 cps). [d] Doublet (J = <1 cps). [e] H. Newman and A. Durante, *J. Org. Chem.*, **31**, 2291 (1966). [f] B. H. Arison, *et al.*, *J. Amer. Chem. Soc.*, **85**, 627 (1963).

SCHEME I



with their being *meta* oriented in an unsymmetrical environment.[10] (The symmetrical 4 analog would be expected to show a single two-proton peak.)

Depending on the catalyst and conditions employed, dehydrogriseofulvin (**2**) is reported to undergo either predominant hydrogenolysis to benzophenone **1** or predominant reduction to griseofulvin **3**.[3,9] The latter reaction course could be realized[9] (this was confirmed by us) by using a prepared Pd–C catalyst, in relatively large amounts and conducting the hydrogenation in a nonhydroxylic solvent. However, an attempt to convert **5** into the sulfur analog of griseofulvin under these conditions gave, instead, exclusive hydrogenolysis to benzophenone **4**.[11]

Experimental Section[12]

3,5-Dimethoxythiophenol (7).—To a stirred, cooled (ice–water) suspension of 37 g (0.24 mol) of 3,5-dimethoxyaniline[7] in 200 ml of water containing 50 ml of concentrated hydrochloric acid (0.6 mol) was added a solution of 16.6 g (0.24 mol) of sodium nitrite in 50 ml of water, the rate of addition being adjusted so as not to allow the reaction temperature to exceed 5°. The resulting red-purple, moderately thick solution of diazonium salt was added, over a 30-min period, to a stirred solution of 250 g (1.7 mol) of potassium ethyl xanthate in 200 ml of water at 85–90°. After cooling, the almost black reaction mixture was extracted with ether and the ethereal extracts were washed with dilute sodium hydroxide, water, dried, and evaporated. The crude xanthate (49 g) was heated under reflux in 200 ml of 90% ethanol containing 100 g of potassium hydroxide for 15 hr, the mixture extracted with ether (to remove any base insoluble material), and the basic aqueous phase acidified (concentrated hydrochloric acid). The water insoluble product which separated was extracted with ether and the ethereal extracts were washed, dried, and evaporated to yield a 23-g crude liquid residue. Distillation *in vacuo* from zinc dust gave 12.8 g (31%) of the thiophenol: bp 111° (0.1 mm); $n^{25}D$ 1.5830. The analytical sample was a colorless liquid: $n^{25}D$ 1.5834; λ_{max}^{film} 3.90 μ (–SH).

Anal. Calcd for $C_8H_{10}O_2S$ (170.18): C, 56.46; H, 5.92; S, 18.84. Found: C, 56.78; H, 5.99; S, 18.43.

3,5-Dimethoxythiophenol Acetate (8).—A cooled solution of 2 g (0.012 mol) of the thiophenol in 4 ml of dry pyridine was treated with 4 ml of acetic anhydride. The reaction mixture was kept at room temperature overnight, poured into ice water, and the product extracted with ether. The ethereal extracts were washed successively with cold dilute hydrochloric acid, cold water, aqueous bicarbonate, dried, and evaporated to yield 2.4 g (96%) of a colorless crystalline solid: mp 61–62.5°; λ_{max}^{Nujol} 5.85 μ.

Anal. Calcd for $C_{10}H_{12}O_3S$ (212.27): C, 56.58; H, 5.71; S, 15.11. Found: C, 56.40; H, 5.88; S, 14.80.

2-Chloro-3,5-dimethoxythiophenol Acetate (9).—To a solution of 7.8 g (0.037 mol) of 3,5-dimethoxythiophenol in 135 ml of dry benzene was added 5 g (0.037 mol) of N-chlorosuccinimide. The reaction mixture was stirred and irradiated for 23 hr with a 150-W G.E. projector lamp placed 4–6 in. from the side of the flask. The heat generated by the lamp raised the temperature of the reaction mixture to 77° and gave a homogeneous system. (N-Chlorosuccinimide is only partially soluble in benzene at room temperature.) The course of the reaction was followed by periodic testing of the reaction mixture for active halogen (starch–iodide paper). The test was still weakly positive after 18 hr, but was essentially negative after 21 hr. The orange solution was washed with water, dried, and evaporated to yield an oily solid residue which was heated and partially dissolved in a relatively small amount of ether and kept at room temperature overnight. The beige solid obtained (5.3 g) melted at 87–90° (softens *ca.* 84°). An additional 0.87 g, mp 81–86°, was isolated by concentrating the mother liquors giving a total yield of 6.2 g (68%). The analytical sample was obtained by partially dissolving a sample of the product in boiling ether and collecting after 1 hr at room temperature: mp 87–89.5° (softens 85°); λ_{max}^{Nujol} 5.90 μ.

Anal. Calcd for $C_{10}H_{11}ClO_3S$ (246.73): C, 48.68; H, 4.50; S, 13.00. Found: C, 48.78; H, 4.62; S, 12.70.

The nmr spectrum of the product in deuteriochloroform showed two one-proton doublets at δ 7.72 (J = 3 cps) and 6.58 (J = 3 cps) (aromatic protons), two three-proton singlets at 3.90 and 3.82 (aromatic methoxyl), and a three-proton singlet at 2.47 (–$SCOCH_3$).

(10) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 96.

(11) The reduction of **5** to the sulfur analog of griseofulvin has been accomplished microbiologically (unpublished results with W. W. Andres, *et al.*). The details of this conversion will appear elsewhere.

(12) Melting points were taken in a Hershberg apparatus using a 3-in. immersion thermometer. Infrared spectra were determined either neat (liquids or oils) or in Nujol mulls (solids) on a Perkin-Elmer Infracord spectrophotometer. Nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Ultraviolet spectra were measured in methanol on a Cary 11MS spectrophotometer. Magnesium sulfate was used for drying. The petroleum ether used boiled at 30–60°.

4-Hydroxy-2'-mercapto-3-chloro-2,4',6'-trimethoxy-6-methylbenzophenone Diacetate (11).—A mixture of 4.4 g (0.018 mol) of **9** (above) and 4.0 g (0.018 mol) of isoeverninic acid acetate (**10**)[8,9] in 60 ml of trifluoroacetic anhydride was heated in a pressure bottle at 55–60° for 20 hr. The dark solution was evaporated *in vacuo*, the residue dissolved in methylene chloride, and the solution washed with aqueous bicarbonate, dried, and evaporated to yield a gummy residue which solidified on trituration with ether. The purple tinged colorless solid obtained, 2.8 g (34%), melted at 163–166°. Heating, partially dissolved, in boiling methanol furnished the analytical sample: mp 168–170°; λ_{max}^{Nujol} 5.67 (OAc), 5.87 (thioacetate), and 6.00 μ (ArCOAr); λ_{max}^{MeOH} 311 mμ (ϵ 7720), 242 sh (17,000), and 209 (50,000).

Anal. Calcd for $C_{21}H_{21}ClO_7S$ (452.91): C, 55.69; H, 4.67; S, 7.08. Found: C, 55.94; H, 5.09; S, 7.06.

Only partial conversion into **11** was realized when the reaction was conducted at room temperature.[13]

4'-Hydroxy-2-mercapto-3-chloro-2',4,6-trimethoxy-6'-methylbenzophenone (4).—Nitrogen was bubbled through a stirred suspension of 2.5 g (0.055 mol) of **11** in 40 ml of methanol at room temperature and 40 ml of 2 *N* aqueous sodium hydroxide was added in *ca.* 3 min. By the end of 10–15 min the reaction mixture was homogeneous. The nitrogen passage was terminated, and the flask stoppered and kept at room temperature for an additional 1.25 hr. Ice was added to the solution which was then acidified with cold, fairly concentrated hydrochloric acid. The practically colorless gum which separated solidified almost immediately and was collected after 15 min and air dried overnight; yield 2 g (99%); mp 195–199°. Recrystallization from aqueous methanol furnished the analytical sample: mp 198–199; λ_{max}^{Nujol} 290 and 6.33 μ. The latter band showed two inflections at 6.13 and 6.23 μ: λ_{max}^{MeOH} 300 mμ (ϵ 9250), 240 sh (21,300), and 210 (40,800).

Anal. Calcd for $C_{17}H_{17}ClO_5S$ (368.78): C, 55.36; H, 4.65; S, 8.70. Found: C, 55.05; H, 4.83; S, 8.43.

7-Chloro-2',4,6-trimethoxy-6'-methylspiro[benzo(*b*)thiophene-2(3H),1'-(2,5)-cyclohexadiene]-3,4'-dione (5).—A solution of 1.7 g (0.0046 mol) of **4** (above) in 150 ml of water containing 25 g of potassium carbonate was added dropwise, over *ca.* a 10-min period, to a stirred solution of 6 g (0.018 mol) of potassium ferricyanide in 75 ml of water. The solid which began separating almost immediately was collected after stirring for 1 additional hr and heated, suspended, in boiling ethanol: yield 1.3 g (77%); mp 235–238°. A portion of this product was again heated in boiling ethanol to furnish the analytical sample: mp 236–238°; λ_{max}^{Nujol} 5.90 and 6.02 μ; λ_{max}^{MeOH} 348 mμ (ϵ 4550), 306 (18.700) and 235 (43,300). The nmr spectrum is presented in Table I.

Anal. Calcd for $C_{17}H_{15}ClO_5S$ (366.82): C, 55.66; H, 4.12; Cl, 9.67; S, 8.74. Found: C, 55.66; H, 4.41; Cl, 9.84; S, 863.

Attempted Reduction of 5 to the Ring-B Sulfur Analog of Griseofulvin.—A solution of 0.2 g (0.54 mmol) of **5** in a minimum of methylene chloride was prepared and diluted with 25 ml of ethyl acetate. The resulting solution was added to a suspension of 0.4 g of prereduced 10% Pd–C (prepared according to the procedure in ref 14) in 5 ml of ethyl acetate and the mixture was stirred under hydrogen at room temperature and atmospheric pressure until 10 ml of hydrogen was consumed (30 min) (0.54 mmol = 13.3 ml of H_2). The catalyst was separated by filtration through Celite and the filtrate evaporated to yield 0.18 g of a light yellow opaque gum which was separated into a base-soluble and base-insoluble fraction by dissolving in methylene chloride and extracting with cold dilute sodium hydroxide. The nmr spectrum of the base-insoluble fraction [isolated by drying and evaporating the methylene chloride solution (0.12 g, mp 237–240°)] was identical with that of pure **5**. The base-soluble material [obtained by acidifying the dilute sodium hydroxide extract and collecting the solid which separated (45 mg, mp 194–197°)] was identified by ir and thin layer chromatography as benzophenone **4**.

(13) As might have been anticipated, **8** proved more reactive. It was acylated by **10** in trifluoroacetic anhydride at a reasonable rate at room temperature.

(14) "Organic Syntheses, Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 687. (Darco-G-60 was the support employed.)

Registry No.—**4**, 19689-64-6; **5**, 19689-65-7; **7**, 19689-66-8; **8**, 19689-67-9; **9**, 19689-68-0; **11**, 19689-69-1.

Acknowledgment.—We thank Mr. L. Brancone and staff for the microanalyses and Mr. W. Fulmor and staff for the ultraviolet and nmr spectra.

A 1,4-Pyran Compound from Condensation of Pulegone and Ethyl Acetoacetate

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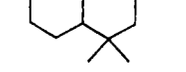
Received November 14, 1968

The zinc chloride catalyzed condensation of pulegone[1,2] with ethyl acetoacetate has been reported to yield two major crystalline compounds having mp 74–76°, proved[1,3] to possess structure **1**, and mp 37–39°, respectively.[1] Bicyclo[3.3.1]nonenone **2** was proposed as a possible structure for the compound of mp 37–39° in our early communication.[4] New chemical evidence and spectroscopic data now confirm that the compound of mp 37–39° is 2,4,4,7-tetramethyl-3-carbethoxy-5,6,7,8-tetrahydrobenzopyran[5] (**3**).



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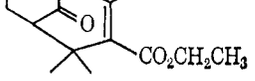

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In our earlier condensation experiments it was noticed that although the yield of enone **1** did not fluctuate appreciably, the yield of pyran ester **3** varied from 12 to 0% depending on the conditions of the condensation. It was shown that a prolonged heating of the reaction eventually gave only enone **1** and no pyran ester **3**. Shorter reaction time or milder reaction conditions did not improve the yield of pyran ester **3**, but also resulted in recovery of a substantial amount of the starting material. Under the condensation conditions pyran ester **3** was gradually rearranged to enone **1**. Pyran ester **3** is, therefore, formed by a kinetically controlled process and reversibly rearranges to the thermodynamically more stable enone **1**.

Elemental analysis and mass spectroscopy established the molecular formula of the compound of mp 37–39° as $C_{16}H_{24}O_3$. In the absence of a deep-seated rearrangement, two structures **2** and **3** can be formulated for the compound of mp 37–39°. The chemical transformations summarized in Scheme I would

(1) Y. L. Chow, *Acta Chem. Scand.*, **16**, 205 (1962).

(2) P. Barbier, *C. R. Acad. Sci., Paris*, **127**, 870 (1898); L. G. Jupp, G. A. R. Kon, and E. H. Lockton, *J. Chem. Soc.*, 1639 (1928).

(3) J. Wolinsky and M. A. Tyrell, *Chem. Ind.* (London), 1104 (1960).

(4) Y. L. Chow, *Tetrahedron Lett.*, 1337 (1964).

(5) Professor J. Wolinsky has independently proved that the compound of mp 37–39° has structure **3**. We thank Professor Wolinsky for calling our attention to his paper [J. Wolinsky and H. S. Hauer, *J. Org. Chem.*, **34**, 380 (1969); Abstract, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968].