The Synthesis of the Ring-B Sulfur Analog of Epigriseofulvin

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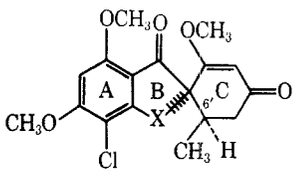
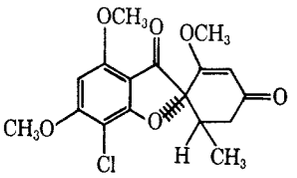
The synthesis of the ring-B thio analog **20** of epigriseofulvin is described.

We have previously described the synthesis of the ring-B carbon analog (**1**) of griseofulvin (**2**).[1] We report here on our attempt to synthesize the ring-B sulfur analog (**3**) of griseofulvin by a route which led instead to the ring-B sulfur analog (**20**) of epigriseofulvin (**2a**). Compound **20** proved to be stable under the conditions which converted epigriseofulvin to roughly a 1:1 mixture of it and griseofulvin.[2]



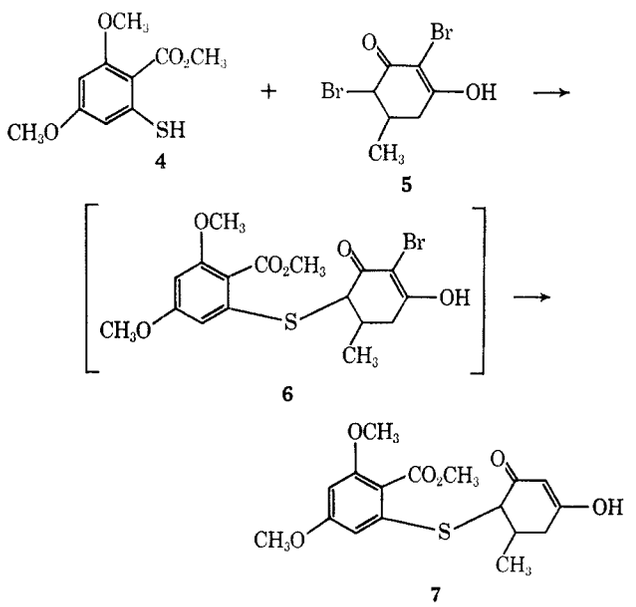
1, X = CH_2
2, X = O
3, X = S



2a

The key intermediate in our synthesis, 4-(2-carbomethoxy-3,5-dimethoxy)phenylthio-5-methyl-1,3-cyclohexanedione (**7**), was obtained from the condensation of 2-carbomethoxy-3,5-dimethoxybenzenethiol (**4**) and 2,4-dibromo-5-methyl-1,3-cyclohexanedione (**5**)[3] followed by debromination of the presumed adduct **6** (Scheme I).

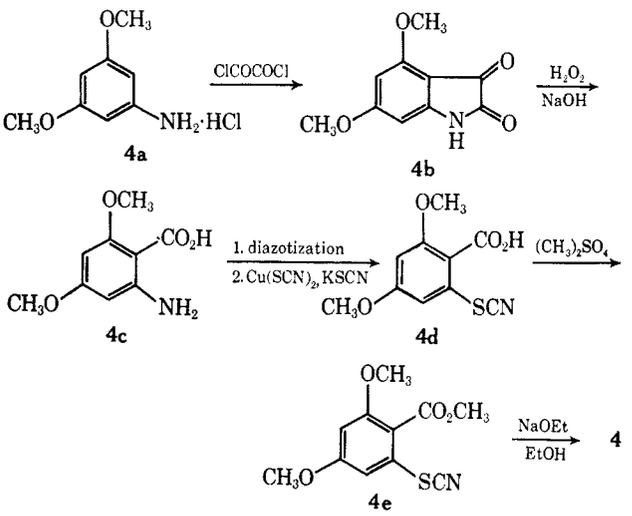
SCHEME I



4 **5** **6** **7**

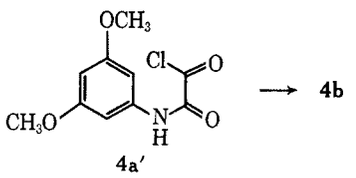
The thiol **4** was prepared in the following manner (Scheme II).

SCHEME II



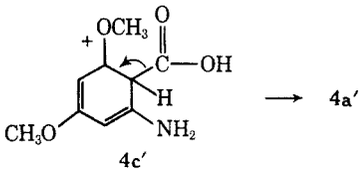
4a **4b** **4c** **4d** **4e**

Reaction of a neat mixture of the hydrochloride salt[4] of the commercially available[5] 3,5-dimethoxyaniline and oxalyl chloride at 165–170° for 1.5 hr gave the isatin **4b**. Formation of **4b** is presumed to proceed *via* intramolecular acylation of the initially formed oxamyl chloride **4a'**. The orientation of the two methoxyl groups *ortho* and *para* to the reaction center apparently activates the ring sufficiently toward electrophilic attack so that cyclization does not require the Lewis acid catalysis usually employed in isatin syntheses *via* intermediates of type **4a**[6] (see also below).



4a'

Conversion of isatin **4b** into the acid **4c** was effected with 30% peroxide in strong (33%) aqueous sodium hydroxide at 105°. The great susceptibility of the 2,4-dimethoxybenzene ring to electrophilic attack is again dramatically demonstrated by the ease with which **4c** decarboxylates in acid (within 1 hr at room temperature with dilute hydrochloric acid), presumably *via* the protonated species **4c'** (and its numerous canonical forms).



4c'

(1) H. Newman and R. B. Angier, *J. Org. Chem.*, **31**, 1462 (1966).

(2) An alternate approach to the synthesis of 1-thiogriseofulvin which we have investigated is described separately: H. Newman and R. B. Angier, *J. Org. Chem.*, **34**, 1463 (1969).

(3) The tautomeric form shown is done so arbitrarily.

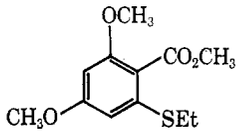
(4) The hydrochloride salt **4a** was used rather than its free base by analogy with the reported conversion of aromatic amine hydrochlorides to aryl oxamyl chlorides with oxalyl chloride: *Chem. Abstr.*, **22**, 4129 (1928).

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

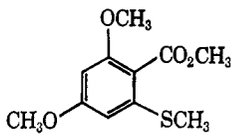
(6) W. S. Sumpter, *Chem. Rev.*, **34**, 393 (1944).

Conversion of **4c** into the thiocyanate **4d** was accomplished *via* diazotization and reaction of the diazonium salt with cupric thiocyanate–potassium thiocyanate. An attempt to introduce sulfur by allowing the diazonium salt to react with sodium disulfide[7] proved considerably less satisfactory. The thiocyanato acid **4d** was then methylated with dimethyl sulfate in aqueous sodium carbonate, and the methyl ester **4e** was transformed to the thiol **4** with ethanolic potassium hydroxide.

A minor side reaction (*ca.* 5%) in the conversion of **4e** into **4** was the formation of the ethyl thio ether **4f**, presumably arising from the reaction of **4** with the ethyl cyanate (EtOCN) generated from **4e** and ethoxide. Indeed, the conversion of **4e** into **4** with methanolic potassium hydroxide proceeded in poorer yield (55% *vs.* 79%) and led to the formation of considerably greater amounts (*ca.* 20%) of the methyl thio ether **4g**, in accord with the expected greater reactivity of methyl cyanate (CH_3OCN) toward nucleophiles.

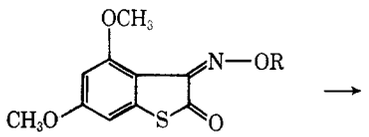


4f

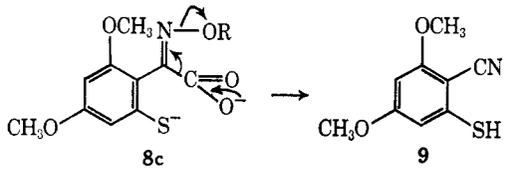


4g

One alternate route to **4** which we investigated involved the attempted conversion of **8** into **9**, a potential precursor of **4**, in base *via* decarboxylative elimination of the initially formed α-oximino acid **8c**. However,

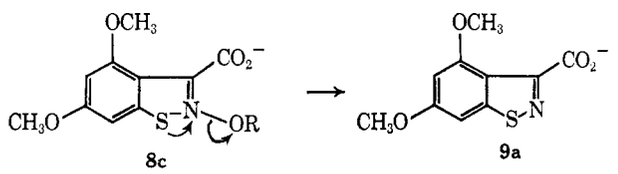


8a, R = H
b, R = Tos



8c **9**

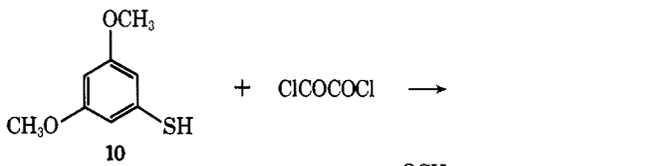
what was obtained instead, exclusively and in good yield, from both **8a** and **8b** was the 1,2-benzisothiazole **9a**, the result of intramolecular nucleophilic displacement of RO^- by mercaptide ion.



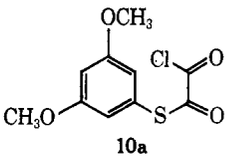
8c **9a**

The oximino ketone **8a** was obtained from the reaction of 3,5-dimethoxythiophenol (**10**)[2] with oxalyl chloride followed by oximation of the resulting dione **11**.

The conversion of **10** into **11** took place with extreme facility (room temperature, ≤2 hr) in very high (90%) yield on just mixing **10** and oxalyl chloride; no Lewis acid was required. In fact, a considerably inferior yield (27%) of **11** was obtained when the reagents were allowed to react in the presence of aluminum chloride (in carbon disulfide). Here again, as in the formation of the isatin **4b** above, intramolecular cyclization of the presumably first formed thioxalyl chloride **10a** is greatly

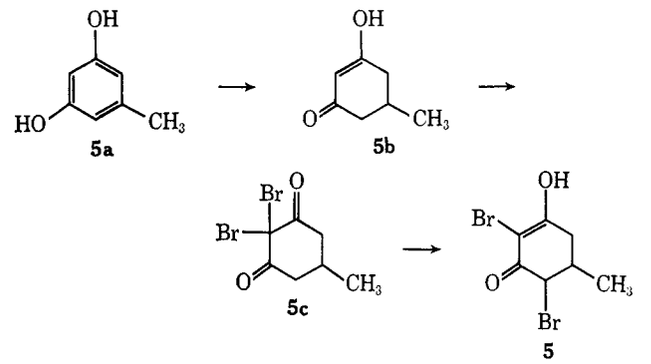


10 **11**



10a

facilitated as a result of the orientation of the methoxy substituents with respect to the reaction center. The 2,4-dibromo-1,3-cyclohexanedione (**5**) was prepared as follows.



5a **5b** **5c** **5**

Orcinol (**5a**) in 1 equiv of aqueous sodium hydroxide was hydrogenated over platinum oxide in a Parr shaker at room temperature to 5-methyl-1,3-cyclohexanedione (**5b**). (At the time this was done, literature procedures for the reduction of *m*-dihydroxybenzenes called for high-pressure conditions.[8] That low-pressure conditions were also effective was subsequently reported by Sircar and Meyers.[9]) Following the procedure of Schamp and DePooter,[10] **5b** was converted into the 2,2-dibromo derivative **5c**, which was then rearranged to the strongly acidic (bicarbonate-soluble) 2,4 isomer **5** with hydrogen bromide in dimethylformamide.

It was anticipated that the anion of the thiol **4** would preferentially displace the 4-bromo substituent of **5** in basic medium, the attack at the 2 position being disfavored for electrostatic reasons owing to anion formation. In fact, as already mentioned above, this result was realized. Thus, reaction of the thiol **4** and the dibromodione **5** in aqueous sodium carbonate followed by debromination of the resulting adduct, presumably **6**,

(7) C. F. H. Allen and D. D. MacKay, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley & Sons, Inc., New York, N. Y., 1943, p 580.

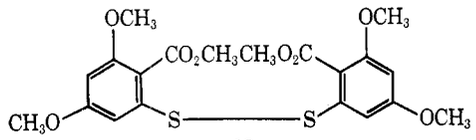
(8) *E.g.*, R. B. Thompson, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley & Sons, Inc., New York, N. Y., 1955, p 278.

(9) J. C. Sircar and A. I. Meyers, *J. Org. Chem.*, **30**, 3206 (1965).

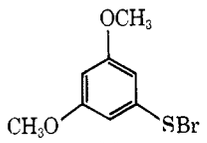
(10) N. Schamp and H. DePooter, *Bull. Soc. Chim. Belges*, **75**, 391 (1966).

with potassium iodide in aqueous acetic acid gave the desired **7** in 43% yield (see equation above). Its nmr spectrum, in which the absorption due to the methyl protons appeared as a fairly symmetrical triplet (at δ 1.08), indicated it to be roughly a 1:1 mixture of *cis–trans* isomers (RS *vs.* CH_3), the expected quadruplet (doublet for each isomer) appearing as a triplet owing to the fortuitous overlap of one of the signals of each doublet. (See Experimental Section for the complete spectrum.)

Along with **7** was obtained, in *ca.* 50% yield, 2-carbomethoxy-3,5-dimethoxyphenyl disulfide (**12**), which is presumed to arise from competitive attack of **4** on one



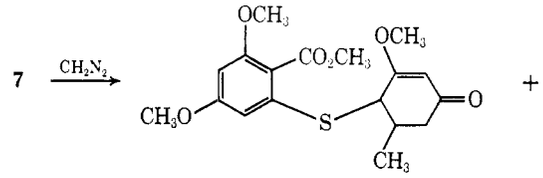
12



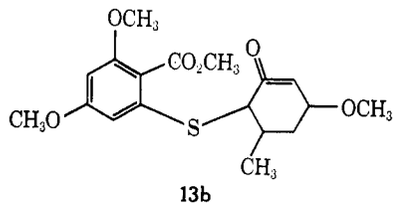
12a

of the bromines in **5** to give the sulfenyl bromide **12a** which then reacts with another molecule of **4**.[11]

The adduct **7** was methylated with ethereal diazomethane to give roughly a 1:1 mixture of the corresponding methyl ethers **13a** and **13b** as indicated by the two approximately equal intensity peaks at δ 3.72 and 3.68 due to the vinyl methoxyl protons in the two isomers in the nmr spectrum of the product. (See Experimental Section for the complete spectrum.[12]) Since **7** itself is a mixture of *cis–trans* isomers, the mixture of ethers consists of a total of four isomers.

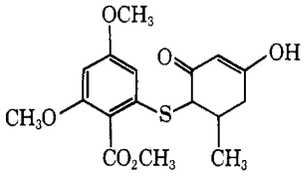


13a

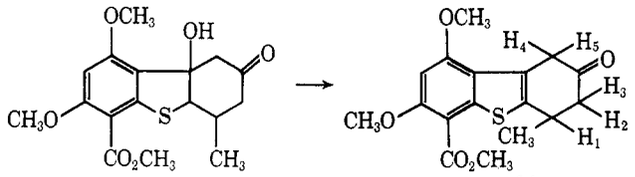


13b

An attempt to methylate **7** with methanolic hydrogen chloride gave a crystalline product whose nmr spectrum (see Experimental Section) is consistent with its formulation as the tricyclic structure **14** and which presumably arises by intramolecular alkylation of the activated aromatic ring by the β-dicarbonyl system.[1]

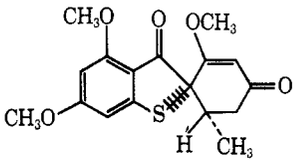


7



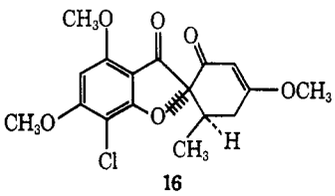
14

Treatment of the ether mixture **13a** and **13b** with methanolic sodium methoxide at reflux for 1.25 hr gave a new crystalline solid, A, which appears from its nmr spectrum to be a single substance and which is assigned structure **15** on the basis of the nmr spectral comparisons to be described below.

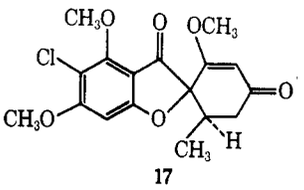


15

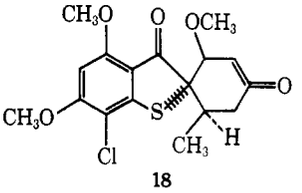
Chlorination of **15** with sulfuryl chloride in methylene chloride gave a two-component mixture (by tlc) which was separated by partition chromatography. Elemental analytical data indicated the minor component B (faster moving, *ca.* 25% of mixture) and the major component C to be isomeric monochlorination products of **15**. Their nmr spectra, along with those of griseofulvin (**2**), isogriseofulvin (**16**), epigriseofulvin (**2a**), 5-chloro-7-dechlorogriseofulvin (**17**), (+)-thio-



16

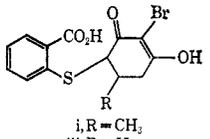


17

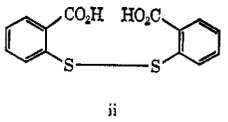


18

(11) (a) Unpublished observations in model systems suggest this side reaction to be the result of steric factors. Thus, it was observed that, whereas thiosalicylic acid reacts with **5** in aqueous sodium carbonate to give, in addition to the adduct i, the disulfide ii in *ca.* 25% yield, at best, only a trace amount of ii was formed along with adduct iii from the reaction of thiosalicylic acid and 2,4-dibromo-1,3-cyclohexanedione.[10] It would thus appear that the proximity of the C-5 methyl group to the reaction center in **5** sufficiently decreases the rate of nucleophilic displacement at C-4, so that mercaptide ion attack on bromine (either at C-2 or C-4; the data in hand do not permit a choice) can compete favorably. (b) An analogous sequence is



i, R = CH_3
iii, R = H



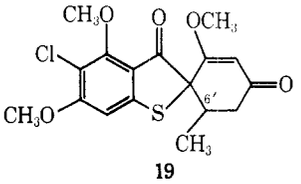
ii

presumably responsible for disulfide formation in the reaction of halogen-containing systems capable of anion stabilization, such as α-chloroacetate, phenacyl chloride, α-bromo amides, bromo nitromethane, etc. See H. Gilman, "Organic Chemistry," Vol. I, 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1943, p 854.

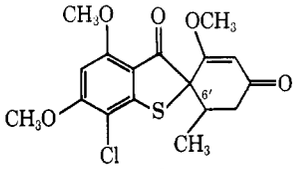
(12) The magnitude of the separation, 2.4 Hz, makes it improbable that a single methylated product formed and the two signals result from its being a *cis–trans* mixture (RS– *vs.* $-CH_3$), since only a single peak was observed in the nmr spectrum for the vinyl, aromatic methoxyl and carbomethoxyl protons, respectively.

griseofulvin (**18**) (obtained from the microbiological reduction[13] of dehydrothiogriseofulvin[2]), and the ring-B carbon analogs of griseofulvin and isogriseofulvin[1] are compared in Table I. (The spectrum of **15** is also included.)

As can be seen, the nmr spectra of components B and C are essentially identical except for the position of the aromatic proton. [The chemical-shift difference between these is seen to be similar to the difference between the corresponding protons in griseofulvin and 5-chloro-7-dechlorogriseofulvin (**17**).] B and C are therefore isomeric with respect to the position of the chlorine on the aromatic ring. It is also clear from Table I that the vinyl methoxyl proton resonances in griseofulvin, 5-chloro-7-dechlorogriseofulvin (**17**), (+)-thiogriseofulvin (**18**), and the ring-B carbon analog of griseofulvin virtually coincide with their counterparts in components B and C, whereas the vinyl OCH_3 signals in isogriseofulvin (**16**) and its ring-B carbon analog are distinctly different. Components B and C are therefore assigned the gross griseofulvinlike structures **19** and **20**, respectively.[14] The assignment of structure **20** to C follows from the coincidence of its aromatic proton chemical shift with that of thiogriseofulvin (**18**). The lower field absorption of aromatic protons in **19** parallels the lower field appearance of these protons in 5-chloro-7-dechlorogriseofulvin compared with griseofulvin.[16]



19



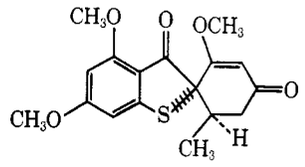
20

With regard to the configuration of the C-6′ methyl group in **19** and **20**, the *epi* (CH_3/C=O *trans*) arrangement is favored on the basis of the similarity of the $CHCH_2$ absorption pattern in **19** and **20** with the corresponding signal in epigriseofulvin (narrow multiplet with the major portion of the signal appearing as a singlet); it being quite different from the relatively broad multiplet observed for these protons in griseofulvin, 5-chloro-7-dechlorogriseofulvin (**17**), and, especially, (+)-thiogriseofulvin (**18**).

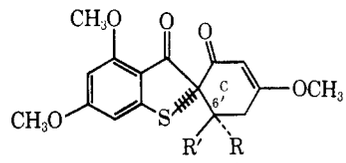
This conclusion is supported by a comparison of the chemical shift values of the C-6′ methyl protons in **20** and (+)-thiogriseofulvin (**18**) with their counterparts in epigriseofulvin and griseofulvin. Thus, although there is no correlation with respect to the absolute values of this signal in the two series (see Table I), the higher field appearance of this signal in **20** and epigriseofulvin relative to (+)-thiogriseofulvin and griseofulvin, respectively, suggests that the two pairs (**20** and epigriseofulvin and (+)-thiogriseofulvin and griseofulvin) are related configurationally.

It has been reported that treatment of either griseofulvin (**2**) or epigriseofulvin (**2a**) with 0.5 *M* methanolic sodium methoxide under reflux leads to the same equilibrium mixture of the two (*ca.* 1:1).[18] We found, however, that the *epi* thio analog **20** was recovered completely unchanged under these conditions.

The isolation of a single crystalline substance, **15** from the treatment of the ether mixture **13a** and **13b** with methanolic methoxide was rather surprising, since, *a priori*, four isomeric products, **15**, **21**, **22**, and **23**, could have formed. We therefore investigated the stability of isogriseofulvin, the griseofulvin derivative related to **22** and **23**, under the conditions used to form **15**, and



21



22, R′ = H; R = CH_3
23, R′ = CH_3; R = H

found that, in contrast to the behavior of griseofulvin,[18] it was transformed into a product mixture which no longer contains any absorption in the region δ 5.4 ± 0.2 characteristic of the vinyl hydrogen in β-hydroxy or alkoxy cyclohexenones, indicating a more profound change in ring C then just epimerization at the spiran junction. [Under more strongly basic conditions (2 *N* methanolic sodium methoxide), griseofulvin also undergoes more extensive changes.[18c]] The absence of two of the four possible isomers **21** and **22** is thus understandable. Additionally, the demonstrated instability of isogriseofulvin is further support for the gross griseofulvinlike structure assigned to **15** and, as a result, to **19** and **20**.

The isolation of only one (**15**) of the two possible C-6′ epimers from the base treatment of the ether mixture **13a** and **13b** is consistent with our inability to epimerize **20** (under conditions which successfully epimerized epigriseofulvin) and indicates that either the *epi* configuration at C-6′ is by far the more stable in the ring-B thio series in contrast to the roughly equal stability of the two C-6′ configurations in the griseofulvin series, or that ring B in the thio series does not open under the conditions used, thereby preventing epimerization, in contrast to the behavior of epigriseofulvin. Given the roughly equal size of sulfur and oxygen,[19] it is not obvious why there should be so large a difference in the equilibrium constants in the two series, nor is it apparent why there should be any difference in the ability of ring B to open. Perhaps it is simply that **20** is too insoluble in the medium used (see Experimental Sec-

(13) W. Andres, *et. al.*, unpublished results.

(14) The higher field position of the vinyl OCH_3 protons in the griseofulvinlike compounds could be reasonably attributed to the location of the OCH_3 group in the shielding region of the anisotropic ring-B carbonyl,[15] a necessary consequence of the spiro junction between rings B and C.

(15) N. S. Bhacca and D. H. Williams, "Application of Nmr Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, p 27.

(16) The difference in chemical shift of the aromatic proton in B and C and the various griseofulvin derivatives would be expected, owing to the change in the aromatic ring substituent from oxygen to sulfur. The direction of the shift is also in accord with previous observations, being at higher field for the more electron-donating substituent.[17]

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

(18) (a) J. MacMillan, *J. Chem. Soc.*, 1823 (1959); (b) E. Kyburz and A. Brossi, *Chem. Ind.* (London), 86 (1965); (c) J. F. Grove, J. MacMillan, T. P. C. Mullholland, and M. A. T. Rogers, *J. Chem. Soc.*, 3977 (1952).

(19) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 44.

TABLE I[a]

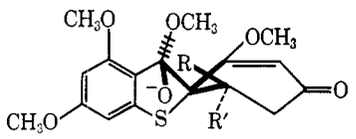
COMPARISON OF THE CHEMICAL-SHIFT VALUES OF THE VARIOUS PROTONS IN COMPONENTS B AND C AND VARIOUS GRISEOFULVIN DERIVATIVES

Compd	Aromatic proton	Vinyl proton	Aromatic methoxyls	Vinyl methoxyl	$CHCH_2$	CH_3
Component B	6.71	5.55	3.98, 3.97	3.65	3.1–2.3 (2.47)[b]	0.95 (d, J = 7 Hz)
Component C	6.27	5.50	4.00, 3.98	3.63	2.6–2.2 (2.45)[b]	0.95 (d, J = 6 Hz)
Griseofulvin[c]	6.15	5.51	4.04, 3.99	3.63	~2.7 (m)	0.98 (d)
Ring-B carbon analog of griseofulvin[d]	6.55	5.57	4.05, 4.00	3.63	2.8–2.1	0.88 (d)
Isogriseofulvin[c]	6.07	5.42	4.01, 3.90	3.78	~2.8 (m)	1.04 (d)
Ring-B carbon analog of isogriseofulvin[d]	6.41	5.45	4.00, 3.89	3.77	2.6–2.1	0.97 (d)
Epigriseofulvin[c]	6.15	5.58	4.03, 4.00	3.62	2.59[b] (m)	0.90 (d)
5-Chloro-7-dechloro griseofulvin[c]	6.46	5.59	4.16, 4.01	3.64	~2.7 (m)	0.96 (d)
Thiogriseofulvin[e]	6.27	5.60	4.02, 3.98	3.65	3.1–2.1 (br m)	1.12 (d, J = 6 Hz)
15	6.50 (d, J = 2 Hz) 6.22 (d, J = 2 Hz)	5.52	3.95, 3.90	3.67	3.0–2.7 (2.43)[b]	0.95 (d, J = 6 Hz)

[a] Chemical-shift values are in parts per million from tetramethylsilane (internal standard); solvent $CDCl_3$. [b] Major portion of the absorption. Appeared as a singlet. [c] B. H. Arison, N. L. Wendler, D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, and N. R. Trenner, *J. Amer. Chem. Soc.*, **85**, 627 (1963). [d] See ref 1. [e] See ref 13.

tion) and epimerization could be effected under more strongly basic conditions or in other solvents. This was not investigated further, since the desired thiogriseofulvin **18** was obtained by another route.[13]

If **15** represents the kinetic ring-closure product, of the ether mixture **13a** and **13b**, this could perhaps be due to steric factors; of the two immediate precursors, A of **15** and B of its C-6′ epimer, respectively (see diagram), the formation of B would be kinetically less favored because of the proximate *cis* relationship of the methyl and bulky (compared with the sulfur) tetrahedral carbon in ring B with its charged substituent and accompanying solvation shell.



A, R = H; R′ = CH_3
B, R = CH_3; R′ = H

Experimental Section

Melting points are uncorrected. Nmr spectra were determined in chloroform on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Magnesium sulfate was used for drying. The petroleum ether used boiled at 30–60°.

4,6-Dimethoxyisatin (4b).—The hydrochloride salt of the commercially available 3,5-dimethoxyaniline[5] was prepared by bubbling gaseous hydrogen chloride through an ethereal solution of the latter. The solid which separated was collected by filtration and washed well with ether. The hydrochloride (36 g) was obtained from 3,5-dimethoxyaniline (30 g).

A gray moist mixture of 60 ml (89 g, 0.7 mol) of oxalyl chloride and 36 g (0.19 mol) of 3,5-dimethoxyaniline hydrochloride (**4a**) prepared above (contained in a 1-l. flask open to the atmosphere) was stirred and heated at 165–170° (oil-bath temperature) for 1.5 hr. Hydrogen chloride was evolved and the color of the solid reaction mixture changed to green-yellow. The mixture was allowed to cool, methanol was added, and the resulting suspension was heated in boiling methanol and filtered while hot. The solid collected was washed with methanol and air dried overnight (the isatin was quite insoluble in methanol); yield 34 g (86%); mp 295–296° dec.

The analytical sample was obtained (inadvertently, see next paragraph) by dissolving a small portion (*ca.* 100 mg) of the product in 1 ml of 2 *N* sodium hydroxide and 1 ml of water [the solution was accompanied by the initial formation of a deep red color (sodium salt of the isatin) which faded to a pale red within 2–3 min (owing to ring opening to the isatoic acid sodium salt)][6] and treating the solution at 70° with *ca.* 20 drops (micropipet) of 30% hydrogen peroxide. After the vigorous foaming subsided, the solution was diluted with water and acidified with glacial acetic acid. The canary yellow solid which separated was collected, washed well with water, and dried at 100° *in vacuo* over phosphorous pentoxide for 8 hr; mp 292–295° dec (sample begins darkening at *ca.* 275°); λ_{max}^{Nujol} 3.00, 5.72 (s), and 5.88 μ (s).

Anal. Calcd for $C_{10}H_9O_4N$ (mol wt 207.18): C, 57.97; H, 4.38; N, 6.76. Found: C, 57.98; H, 4.79; N, 6.62.

It was our original intention to oxidize the isatin to its corresponding anthranilic acid **4c** (see below) by the procedure described. However, these conditions were not drastic enough and a simple purification was achieved instead.

4,6-Dimethoxy-2-aminobenzoic Acid (4,6-Dimethoxyanthranilic Acid) (4c).—To a heated (steam bath) deep red solution of 32.5 g (0.16 mol) of 4,6-dimethoxyisatin in 270 ml of 33% aqueous sodium hydroxide[20] contained in an oversized flask was added rapidly (5 min) 50 ml of 30% hydrogen peroxide with manual swirling. After *ca.* one-third of the peroxide was added, a vigorous exothermic reaction set in, accompanied by much foaming and fading of the deep red color. The reaction mixture was heated for an additional 10 min with swirling after all the peroxide was added, ice was added, and the mixture was brought to pH *ca.* 8 with concentrated hydrochloric acid, then acidified with glacial acetic acid. The solid which separated was collected, washed well with water, and air dried overnight; yield (pale brown solid) 17.4 g (55%); mp 137–138° dec with effervescence (softens *ca.* 135°).

The product obtained as described above from a smaller-scale run (0.3 g of isatin), mp 139–140° dec with effervescence (softens *ca.* 135°), was analyzed directly after drying at 100° *in vacuo* over phosphorous pentoxide for 1.5 hr.

Anal. Calcd for $C_9H_{11}NO_4$ (mol wt 197.18): C, 54.92; H, 5.62; N, 7.10. Found: C, 54.44; H, 5.62; N, 7.26.

The infrared spectrum of the compound showed a triplet in the NH region at 2.7, 2.9, and 3.1 μ and a peak at 5.96 μ (s) in the carbonyl region.

4,6-Dimethoxy-2-thiocyanatobenzoic Acid (4d).—Cupric thiocyanate, freshly prepared from 20 g of anhydrous cupric sulfate, and 28 g of potassium thiocyanate were mixed with 25 g of potassium thiocyanate in *ca.* 50 ml of water.

4,6-Dimethoxyanthranilic acid, **4c** (10 g, 0.05 mole), was diazotized by treating it, suspended in 25 ml of water and 10 ml of concentrated hydrochloric acid, with a solution of 3.45 g (0.05 mol) of sodium nitrite in 15 ml of water. The temperature of the reaction mixture was maintained below 0° by adding chopped ice. After the sodium nitrate solution was added (completed in *ca.* 2 min), the mixture was stirred (at $\leq 0°$) for approximately an additional 10 min to complete the diazotization (indicated by a negative starch–iodide test). The resulting dark brown-purple

(20) See F. N. Lahey, J. A. Lamberton, and J. R. Price, *Australian J. Sci. Res.*, **3A**, 155 (1950); *Chem. Abstr.* **46**, 4016e,f (1952).

solution of diazonium salt was poured into the copper thiocyanate–potassium thiocyanate mixture prepared above with stirring at room temperature, and the mixture was stirred at room temperature for 45 min. The addition of the diazonium salt to the thiocyanate mixture was accompanied by much frothing due to nitrogen evolution, which essentially ceased by the end of 30 min. The reaction mixture was filtered and the black solid obtained was extracted with aqueous bicarbonate by stirring at room temperature for 30 min. The mixture was filtered and the basic aqueous filtrate was acidified to yield a fine orange solid which was collected after *ca.* 1 hr at room temperature and washed with water. After air drying for *ca.* 1 hr, the solid was heated suspended in boiling methanol, collected by filtration, and dried for 3 hr. The beige-colored solid obtained (5.2 g, 43%) melted at 254–257° dec.

The analytical sample was prepared by reheating a sample of the product suspended in boiling methanol (in which it was only sparingly soluble); mp 262–264° dec; λ_{max}^{Nujol} 3.03 (m), 4.61 (w), and 5.91 μ (s).

Anal. Calcd for $C_{10}H_9NO_4S$ (mol wt 239.25): C, 50.20; H, 3.79; N, 5.86; S, 13.40. Found: C, 50.42; H, 3.92; N, 5.48; S, 13.18.

Methyl 4,6-Dimethoxy-2-thiocyanatobenzoate (4e).—To a well-stirred, largely homogeneous mixture of 19.1 g (0.08 mol) of 4,6-dimethoxy-2-thiocyanatobenzoic acid in 1 l. of 10% sodium carbonate was added 140 ml (190 g, 1.5 mol) of dimethyl sulfate. After the solution was vigorously stirred at room temperature for 12.5 hr, the orange solid present was collected, washed well with water, and air dried to constant weight during 25 hr; yield 14.3 g [*ca.* 90% based on unrecovered starting material (see below)], mp 138–142° (135°).

The analytical sample, mp 143–145°, was obtained from a similarly conducted smaller-scale (0.5 g) run after recrystallizing the crude product (mp 140–144°) from methanol; λ_{max}^{Nujol} 4.65 (weak, sharp) and 6.00 μ (strong, sharp). (Note the higher wavelength of the ester band compared to the acid.)

Anal. Calcd for $C_{11}H_{11}NO_4S$ (mol wt 253.28): C, 52.16; H, 4.38; N, 5.53; S, 12.66. Found: C, 52.49; H, 4.14; N, 5.65; S, 12.52.

Acidification of the basic aqueous filtrate from which the ester **4e** was separated yielded 4.3 g (23%) of starting acid **4d**, as indicated by infrared spectral comparison with an authentic sample.

Methyl 4,6-Dimethoxy-2-mercaptobenzoate (4). A.—Methyl 4,6-dimethoxy-2-thiocyanatobenzoate (4 g, 0.016 mol) was dissolved in 60 ml of *ca.* 1 *M* ethanolic potassium hydroxide by heating on the steam bath for 1.5 min. The resulting dark red-orange solution was kept at room temperature for 30 min, then poured into ice–water. The turbid mixture was extracted with ether and the clear basic aqueous phase was acidified. The solid which separated was collected after *ca.* 10 min and air dried to constant weight (*ca.* 2 hr) to give 2.9 g (79%) of methyl 4,6-dimethoxy-2-mercaptobenzoate as an orange-brown solid, mp 80–85°. (The product can be rendered colorless by percolating through alumina in ethylene chloride.) Its infrared spectrum was identical with that of the analytical sample obtained from the aluminum amalgam reduction of 2-carbomethoxy-3,5-dimethoxyphenyl disulfide (**12**) (see below).

Drying and evaporating the ethereal extracts gave 0.3 g of an orange oil. Its nmr spectrum was consistent with a mixture of predominantly (*ca.* 65%) 2-carbomethoxy-3,5-dimethoxyphenyl ethyl sulfide (**4f**) along with *ca.* 15% of 2-carbomethoxy-3,5-dimethoxyphenyl methyl sulfide (**4g**). The nature of the remainder of the mixture is not known; it is, perhaps, unreacted thiocyanato compound. The following absorptions appeared: δ 6.50 (d, 1, J = 3 Hz) and 6.33 (d, 1, J = 3 Hz) (both aromatic ring protons), 3.88 (s, 3, CO_2CH_3), 3.80 (unsymmetrical sharp d, 6, J = <1 Hz, aromatic OCH_3), 2.86 (q, *ca.* 1.3, J = 6 Hz, $ArSCH_2CH_3$), 2.42 (s *ca.* 0.45, $ArSCH_3$), and 1.25 *ca.* 1.3, J = 6 Hz, $ArSCH_2CH_3$). The yield of **4f** is thus *ca.* 5%.

B.—To a solution of 0.3 g (0.66 mmol) of 2-carbomethoxy-3,5-dimethoxyphenyl disulfide (**12**) (obtained as a by-product from the condensation of **4** and **5**, see below) in 10 ml of tetrahydrofuran–water (9:1) (commercial grade tetrahydrofuran was used) was added amalgamated aluminum foil prepared according to the procedure of Corey, *et al.*[21] After frequent swirling during the first 5 min, the reaction mixture was kept at room temperature for 80 min, methylene chloride was added, and the mixture was filtered. The colorless filtrate was dried and evaporated to yield 0.23 g of solid contaminated with some oily material. Trituration with ether furnished 0.19 g (63%) of pale yellow crystalline solid; mp 86–90 ° (82°); λ_{max}^{Nujol} 3.9 (w, SH) and 5.9 μ (s, CO_2CH_3).

The analytical sample, mp 87.5–90°; was obtained by heating the product suspended in cyclohexane–ether.

Anal. Calcd for $C_{10}H_{12}O_4S$ (mol wt 228.27): C, 52.61; H, 5.30; S, 14.05. Found: C, 52.64; H, 5.57; S, 13.97.

4,6-Dimethoxybenzo[*b*]thiophene-2,3-dione (11). A.—Oxalyl chloride (1.5 ml) was added to 3,5-dimethoxythiophenol (1.7 g, 0.01 mol) at room temperature with stirring. An exothermic reaction set in accompanied by the evolution of hydrogen chloride, and within 5 min, the reaction mixture solidified. The mixture was kept at room temperature under vacuum (*ca.* 400 mm, laboratory vacuum line) for 17 hr to draw off the volatiles and then heated suspended in boiling methanol. The lime-colored solid was collected and washed with methanol; yield 2.1 g (*ca.* 90%), mp 209–214° dec. Its infrared spectrum was identical with that of product obtained according to the following alternate (inferior) procedure. (Essentially the same result was obtained after a 2-hr reaction time.)

B.—To a solution of 0.17 g (0.001 mol) of 3,5-dimethoxythiophenol in 0.4 ml of carbon disulfide was added 0.088 ml (0.13 g, 0.001 mol) of oxalyl chloride. The resulting golden yellow solution was treated with 0.2 g (0.0015 mol) of powdered anhydrous aluminum chloride at room temperature. A vigorous reaction set in; the reaction mixture turned brown-black. After *ca.* 2 min, water and ether were added, and the yellow solid which formed was collected by filtration, washed with water, and dried; yield 0.065 g (27%); mp 212–213° dec; λ^{Nujol} 5.78 (s) and 5.92 μ (s).

Anal. Calcd for $C_{10}H_8O_4S \cdot H_2O$ (mol wt 242.18): C, 49.59; H, 4.16; S, 13.21. Found: C, 49.22; H, 3.84; S, 13.13.

4,6-Dimethoxybenzo[*b*]thiophen-2-one 3-Oxime (8a).—A suspension of 4.6 g (0.02 mol) of **11** and 7.5 g (0.11 mol) of hydroxylamine hydrochloride in 75 ml of commercial grade absolute ethanol containing 50 drops (micropipet) of concentrated hydrochloric acid was heated under reflux for 2 hr, then poured into ice–water and agitated well to dissolve the unreacted hydroxylamine hydrochloride. The insoluble yellow solid was collected by filtration, washed, and dried to furnish 4.1 g (85%) of the oxime **8a**, mp 213–214°.

The analytical sample, obtained from heating in boiling ethanol, melted at 221–222° dec; λ_{max}^{Nujol} 3.2 (m) and 5.9 μ (s).

Anal. Calcd for $C_{10}H_9NO_4S$ (mol wt 239.25): C, 50.20; H, 3.79; N, 5.86; S, 13.40. Found: C, 50.64; H, 4.24; N, 5.77; S, 13.20.

4,6-Dimethoxy-3-carboxyl-1,2-benzisothiazole (9a). A.—A solution of 4.1 g (0.17 mol) of oxime **8a** in 65 ml of commercial grade ethylene glycol containing 6 g of potassium hydroxide was heated under nitrogen at 130–135° for 4 hr and poured into ice–water, and the aqueous solution was acidified. The yellow solid which separated was collected, washed well with water, and air dried overnight; yield 3.5 g (85%); mp 163–165 dec with effervescence. Recrystallization from methanol furnished the analytical sample; mp 170–171.5° dec with effervescence; λ_{max}^{Nujol} 5.80 (s) and 5.74 μ (medium shoulder).

Anal. Calcd for $C_{10}H_9NO_4S$ (mol wt 239.25): C, 50.20; H, 3.79; N, 5.86; S, 13.40. Found: C, 50.24; H, 4.28; N, 5.21; S, 13.20.

B.—The oxime **8a** (50 mg, 0.21 mol) was converted into its tosylate with tosyl chloride (70 mg, 0.37 mmol) in 2 ml of pyridine for 1.5 hr at room temperature. When poured into ice–water, the tosylate separated as a yellow-green solid which was collected and air dried for *ca.* 2 hr; yield 57 mg (68%); mp 162–166° dec. The tosylate was suspended in a mixture of *ca.* 2 mol of 2 *N* sodium hydroxide and 1 ml of methanol. The mixture was stirred at room temperature for 10 min, heated on the steam bath for 3 min, and filtered to separate insolubles, and the light yellow filtrate was acidified to yield 4,6-dimethoxy-3-carboxy-1,2-benzisothiazole (**9a**), identified by its infrared spectrum and its conversion into its methyl ester with ethereal diazomethane.

Methyl Ester of 9a.—A solution of 3 g (0.013 mol) of the acid **9a** in 20 ml of saturated methanolic hydrogen chloride was heated under reflux for 1.25 hr and poured into ice–water, and the organic product was extracted with ether. Drying and evaporating the ethereal extract furnished an oil which solidified on triturating with ether; yield (yellow solid) 1.85 g (58%); mp 110–116° (105°). Recrystallization from methanol furnished the analytical sample, mp 116.5–118.5°.

(21) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

Anal. Calcd for $C_{11}H_{11}NO_4S$ (mol wt 253.28): C, 52.16; N, 4.38; N, 5.53; S, 12.66. Found: C, 52.41; H, 3.99; N, 5.81; S, 12.71.

5-Methyl-1,3-cyclohexanedione (5b).—A solution of 25 g (0.2 mol) of orcinol (3,5-dihydroxytoluene) in 125 ml (0.25 mol) of 2 *N* sodium hydroxide was shaken in a hydrogen atmosphere with 5 g of platinum oxide in a Parr apparatus (initial pressure 30 lb). A 19-lb pressure drop took place over a 17-hr period [16 lb after 6 hr; calcd pressure drop (compound plus catalyst) 20 lb]. The catalyst was separated by filtration, and ice was added to the filtrate, which was then acidified with concentrated hydrochloric acid. The colorless solid which separated was collected and air dried for *ca.* 45 min; yield 23.5 g. The product was dissolved in methylene chloride and dried over magnesium sulfate for 5.5 hr, and the solvent was evaporated. The solid residue was triturated with ether containing a small amount of methylene chloride and the product was collected; yield 12.9 g (51%); mp 129.5–132° (lit.[22] mp 128°).

2,2-Dibromo-5-methyl-1,3-cyclohexanedione (5c).—The procedure of Schamp and DePooter[10] was followed. Bromine (4.5 ml, 0.09 mol) was slowly added to a vigorously stirred, ice-cold solution of 11.5 g (0.091 mol) of 5-methyl-1,3-cyclohexanedione and 8.5 g (0.11 mol) of sodium acetate in 100 ml of water and 10 ml of chloroform. The bromine was consumed almost as fast as it was added; the 2-monobromo derivative separated. After the bromine addition was complete, an additional 8.5 g (0.11 mol) of sodium acetate was added along with 80 ml of chloroform, and another 4.5 ml (0.09 mol) of bromine was added dropwise with vigorous stirring and cooling. The chloroform layer was separated, washed once with water, dried and charcoaled (single operation), and evaporated to give a colorless crystalline product which was triturated with petroleum ether and collected; yield 19 g (73%); mp 89–92° (86°); λ_{max}^{Nujol} 5.76 (m) and 5.85 μ (s).

Anal. Calcd for $C_7H_8Br_2O_2$ (mol wt 283.96): C, 29.61; H, 2.84; Br, 56.29. Found: C, 29.58; H, 3.02; Br, 56.39.

2,4-Dibromo-5-methyl-1,3-cyclohexanedione (5).—The procedure employed is essentially that of Schamp and DePooter.[10] Gaseous hydrogen bromide (6 g) was bubbled into commercial grade dimethylformamide (24 ml). 2,2-Dibromo-5-methyl-1,3-cyclohexanedione (26.2 g, 0.092 mol) was added and the mixture was heated at 55–57° (temperature of the reaction mixture) for 45 min. (During the initial stages of the reaction, the reaction flask had to be frequently removed from the oil bath in order to keep the temperature within these limits owing to the exothermicity of the reaction. Approximately 10 min was required for the reaction mixture, which was inserted into an oil bath preheated to 55–57°, to reach this temperature.) A color change (observed after *ca.* 35 min of heating) from orange-red to yellow accompanied the transformation. (Rigorous temperature control is essential to the success of the reaction.) After the solution had cooled for 30 min, it was poured onto ice, ether was added, and the mixture was made basic by the addition of solid sodium bicarbonate. The basic aqueous phase was separated, washed with ether, and, after adding ice, acidified with concentrated hydrochloric acid. The organic product was extracted with ether and the ethereal extracts were dried and charcoaled (single operation) and evaporated. Triturating the partially solid residue with ether gave a colorless solid which was collected and washed well with ether; yield 7.5 g (29%); mp 142–143.5° dec. (The crystalline product appeared quite insoluble in ether.)

Elemental analysis was performed on a sample, obtained (from another preparation) by recrystallization from aqueous acetic acid; mp 146–146.5° dec.

Anal. Calcd for $C_7H_8Br_2O_2$ (mol wt 283.96): C, 29.61; H, 2.84; Br, 56.29. Found: C, 30.34; H, 3.29; Br, 55.07.

The nmr spectrum of the product was consistent with its formulation as **5**, showing a broad one-proton absorption between δ 8.00–7.42, an unsymmetrical four-proton multiplet at δ 2.42, and a three-proton doublet at δ 1.22 (J = 5 Hz). These are assigned, respectively, to OH, proton on bromine-bearing carbon, C-4, C-5, and C-6 protons, and the C-5 methyl protons.

The compound showed absorption in the infrared both in the free and hydrogen-bonded OH region and at 6.1 (m) *ca.* 6.4 μ (s, broad).

4-(2-Carbomethoxy-3,5-dimethoxy)phenylthio-5-methyl-1,3-cyclohexanedione (7).—A solution of 3 g (0.13 mol) of 2-carbomethoxy-3,5-dimethoxyphenylthiol (**4**) in 40 ml of 10% sodium carbonate was prepared (some ether was added to facilitate dissolution) and treated, at room temperature, with a solution of 3.7 g (0.13 mol) of 2,4-dibromo-5-methyl-1,3-cyclohexanedione in 20 ml of 10% sodium carbonate. The mixture was shaken well during 5 min and then allowed to stand at room temperature for an additional 40 min. A solid, shown to be 2-carbomethoxy-3,5-dimethoxyphenyl disulfide (**12**) (see below), separated during this time. The mixture was then diluted with water and extracted with ether–methylene chloride. The basic aqueous phase was acidified and the virtually colorless gum which separated was extracted into ether. Drying and evaporating the ethereal extracts left a practically colorless opaque gum which was treated directly with 50 ml of aqueous acetic acid (1:1) and 3.8 g of potassium iodide at room temperature. Iodine was generated almost immediately. The mixture was manually swirled for 10 min, during which time a homogeneous system was produced, and then kept at room temperature for an additional 40 min. The reaction mixture was diluted with water, treated with cold aqueous sodium bisulfite to destroy the iodine present, and extracted with ether. The ethereal extracts were washed once with water and extracted with saturated aqueous sodium bicarbonate. The bicarbonate extracts were acidified and the practically colorless gum which formed was extracted into ether. Drying and evaporating the ethereal extracts left a nearly colorless oil which rapidly solidified on rubbing (glass rod) in ether. The colorless solid was collected and washed with ether (the product was quite insoluble in this solvent); yield 2 g (43%), mp 139–141°; λ_{max}^{Nujol} 3.7–3.9 (broad, weak), 5.70 (s), 6.20 (sh, m), and 6.26 μ (s).

Anal. Calcd for $C_{17}H_{20}O_6S$ (mol wt 352.40): C, 57.94; H, 5.72; S, 9.10. Found: C, 57.76; H, 5.89; S, 8.78.

The nmr spectrum of the product indicates a mixture of *cis–trans* isomers (RS *vs.* CH_3) showing the following absorptions: δ 7.87 (s, 1, not sharp), exchangeable, OH), 6.84–6.25 (m, 2, aromatic H), 5.47 (s, 1, exchangeable, vinyl H), 3.84 (unsymmetrical quadruplet with additional poorly resolved shoulders, 10, CO_2CH_3, aromatic OCH_3 (2) and C-4 H), 3.34–1.83 (broad m,[3] C_5 and C_6 H), and 1.08 (fairly symmetrical triplet with additional poorly resolved shoulders, 3, C-5 CH_3).

Evaporation of the ether–methylene chloride extract of the original basic reaction mixture (from the reaction of **4** and **5**), after drying and treating with Darco G-60, left a semisolid residue which gave a beige-colored solid on triturating with ether. Percolation of this product in methylene chloride through a short column of alumina followed by recrystallization from methanol gave analytically pure 2-carbomethoxy-3,5-dimethoxyphenyl disulfide (**12**); mp 115–117°; yield *ca.* 50%.

Anal. Calcd for $C_{20}H_{22}O_8S_2$ (mol wt 454.51): C, 52.85; H, 4.88; S, 14.11. Found: C, 52.93; H, 5.03; S, 13.95.

3-Methoxy-4-2-carbomethoxy-3,5-dimethoxy)phenylthio-5-methyl-Δ^2-cyclohexenone (13a) and 3-Methoxy-5-methyl-6-(2-carbomethoxy-3,5-dimethoxy)-phenylthio-Δ^2-cyclohexenone (13b).—A cooled suspension of 3.9 g (0.11 mol) of **7** was treated with an excess of ethereal diazomethane (from N-methyl-N-nitrosourea). After *ca.* 10 min, the excess diazomethane was destroyed with acetic acid, and the solution was diluted with ether, washed with aqueous sodium bicarbonate, dried, and evaporated to yield 3.65 g (90%) of the methylated product. Its nmr spectrum indicated it to be roughly a 1:1 mixture of **13a** and **13b**, showing the vinyl OCH_3 protons in the two isomers at δ 3.72 and 3.68 (singlets) and the methyl protons centered about δ 1.08 (two moderately broad doublets). The aromatic protons appeared between δ 6.83 and 6.33, the vinyl proton at δ 5.52 (broad singlet), the carbomethoxyl protons at δ 3.88 (singlet), and the aromatic OCH_3 protons at δ 3.84 (singlet). The signals at δ 3.80 and δ 2.75–2.17 account for the remaining protons.

The product was used directly without further purification.

Treatment of 7 with Methanolic Hydrogen Chloride. Formation of Methyl 4,7,8,9-Tetrahydro-1,3-dimethoxy-6-methyl-8-oxo-4-dibenzothiophenecarboxylate (14).—A solution of 400 mg (0.0011 mol) of **7** in 15 ml of saturated methanolic hydrogen chloride was kept at room temperature for 2.25 hr and poured into ice–water, and the colorless solid which formed was collected and washed with water. (The product filtered very slowly because of its fine particle size.) After being allowed to dry on the filter overnight, the solid was dissolved in boiling methanol and the methanolic solution was evaporated to leave an oily residue which solidified on trituration with ether. The colorless crystalline solid was collected and washed with ether; yield 40 mg (11%), mp 165–170° (163°); λ_{max}^{Nujol} 5.85 and 6.00 μ. Its nmr

(22) "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965.

spectrum, consistent with its formulation as **14**, showed the following absorptions: δ 6.42 (s, 1, aromatic H), 4.00 (s, 6, one of the aromatic OCH_3 and the carbomethoxyl H), 3.95 (s, 3, aromatic OCH_3), 3.83 (poorly resolved d, 2, H_4 and H_5, see numbering in diagram **14** in the discussion), 3.6–2.2 (m, 3, H_1, H_2, and H_3), and 1.42 (d, 3, J = 8 Hz, (methyl H).

Anal. Calcd for $C_{17}H_{18}O_5S$ (mol wt 334.38): C, 61.13; H, 5.43; S, 9.60. Found: C, 60.46; H, 6.05; S, 9.04.

2′,4,6-Trimethoxy-6′-methylspiro{benzo[*b*]thiophene-2(3H),-1′-[2]cyclohexene}-3,4′-dione (15).—A solution of 3.62 g (0.011 mol) of the ether mixture **13a** and **13b** in 37 ml of *ca.* 1 *M* sodium methoxide in methanol (prepared from sodium and commercial absolute methanol) was heated under reflux for 70 min. The dark green solution was poured into ice–water and the mixture was extracted with ether–methylene chloride. The organic extracts were washed with water, dried, and evaporated to yield a yellow foam which rapidly crystallized on trituration with ether. The ivory-colored crystalline solid was collected and washed with ether; yield 1.51 g (41%); mp 230–238.5° (223°) (essentially the same melting point was obtained after drying at 80° *in vacuo* for 1.5 hr); λ_{max}^{Nujol} 5.93, 6.03, 6.23, and 6.38 μ. (See Table I in the discussion for the nmr spectrum.)

Anal. Calcd for $C_{17}H_{18}O_5S$ (mol wt 334.38): C, 61.13; H, 5.43; S, 9.60. Found: C, 60.90; H, 5.60; S, 9.52.

Thin layer chromatography on silica gel G using benzene–ethyl acetate (1:1) as the developing solvent gave a single spot detected with uv light; R_f *ca.* 0.4.

The residue (light yellow foam) obtained upon evaporating the ethereal mother liquor was examined by nmr. The vinyl proton region was virtually transparent from δ 4–6. This excludes (except in perhaps trace amounts) the presence of any of the tricyclic products **21**, **22**, and **23** and starting materials **13a** and **13b**.

5-Chloro- and 7-Chloro-2′,4,6-trimethoxy-6′-methylspiro-{benzo[*b*]thiophene-2(3H),1′-[2]cyclohexene}-3,4′-dione (19 and 20), the Ring-B Sulfur Analogs of 5-Chloro-7-dechloroepigriseofulvin and Epigriseofulvin, Respectively.—A solution of 200 mg (0.6 mmol) of **15** in 7 ml of methylene chloride was treated with 0.049 ml (0.082 g, 0.6 mmol) of sulfuryl chloride (delivered through a microsyringe) at room temperature. A test for positive halogen, performed immediately after adding the sulfuryl chloride, with potassium iodide paper was negative. After 10 min at room temperature, the solution was evaporated and the pale yellow residual gum was triturate with ether to give a crystalline solid which was collected and washed with ether; yield 207 mg, mp 235–263° dec. The product showed two spots (R_f *ca.* 0.3 and 0.5) on thin layer chromatography on silica gel G using benzene–ethyl acetate (1:1) for development. Partition chromatography of 190 mg of this material on Celite 545 using heptane–ethyl acetate–Methyl Cellosolve–water (70:30:17:4) separated the two components. (Some solubility difficulties were encountered with the slower moving component.)

The faster moving component (43 mg) melted at 228–232° after being heated in boiling methanol and drying at 80° *in vacuo*. Its nmr spectrum (see Table I in Discussion section) indicated it to be the 5-chloro derivative of **15**; λ_{max}^{Nujol} 5.92, 6.05, 6.21, and 6.35 μ; λ_{max}^{MeOH} *ca.* 360 (plateau, ϵ 3800), 287 (ϵ 16,500), 258 (ϵ 50,000), 250 sh (ϵ 44,000), and 230 sh mμ (ϵ 22,000).

Anal. Calcd for $C_{17}H_{17}ClO_5S$ (mol wt 368.84): C, 55.35; H, 4.65; Cl, 9.61; S, 8.69. Found: C, 55.11; H, 4.63; Cl, 89.6; S, 8.44.

The slower moving component (143 mg) melted at 268–271° after being heated suspended in boiling methanol, recrystallized from ethyl acetate–methylene chloride, and dried at 80° *in vacuo*. Its nmr spectrum (see Table I in discussion) indicated it to be the 7-chloro derivative of **15**; λ_{max}^{Nujol} 5.95, 6.05, 6.23, and 6.34 μ (the peak profile in the carbonyl region in the two chloro analogs was different); λ_{max}^{MeOH} *ca.* 345 (plateau, ϵ 4000), 306 (ϵ 13,000), 248 (ϵ 31,000), and 231 (ϵ 33,000).

Anal. Calcd for $C_{17}H_{17}ClO_5S$ (mol wt 368.84): C, 55.35; H, 4.65; Cl, 9.61; S, 8.69. Found: C, 55.37; H, 4.72; Cl, 9.62; S, 8.44.

Treatment of Isogriseofulvin (16) with Methanolic Sodium Methoxide.—Isogriseofulvin (**16**)[23] (500 mg) was heated under reflux in 10 ml of 0.5 *M* methanolic sodium methoxide for 1 hr and the solution was poured into ice–water. The organic product was extracted once with methylene chloride and once with ether and the combined organic extracts were dried and evaporated to yield 0.35 g of a colorless foam which did not crystallize on trituration with ether. The nmr spectrum of this material showed the following absorptions: δ 6.12 (singlet), two peaks centered about δ 5.03 ± 0.05 (distance from peaks to the center), two peaks centered about δ 4.63 ± 0.03, two peaks centered about δ 3.97 ± 0.01, four peaks centered about δ 3.67 ± 0.12 (distance from the outermost lines), δ 3.2–2.6 (multiplet), and what looked like two doublets in the saturated CH_3 region centered about δ 1.08 and 0.83. Approximate relative ratios of the various absorptions were 1:1:0.5:8:7:5:4 (the last number represents the total absorption in the CH_3 region).

Treatment of 20 with Methanolic Sodium Methoxide.—A suspension of 49 mg of **20** in 0.5 ml of *ca.* 1 *M* methanolic sodium methoxide and 0.5 ml of commercial grade absolute methanol was heated under reflux for 2 hr. After another hour at room temperature, ice–water was added and the solid was collected, washed well with water, and dried *in vacuo* at 80° for 1 hr; yield 38 mg; mp 265–269°. The nmr spectrum of this material was indistinguishable from that of **20**.

Under essentially these same conditions, we found that griseofulvin was converted into roughly a 1:1 mixture of it and epigriseofulvin, as indicated by the melting point[18b] and nmr spectrum of the product isolated.

Registry No.—**4**, 21544-80-9; **4b**, 21544-81-0; **4c**, 21577-57-1; **4d**, 21544-82-1; **4e**, 21544-83-2; **5**, 21544-84-3; **5c**, 21544-85-4; **7**, *cis*, 21537-85-9; **7**, *trans*, 21537-86-0; **8a**, 21544-86-5; **9a**, 21544-87-6; **9a** (methyl ester), 21544-88-7; **11**, 21544-89-8; **12**, 21544-90-1; **13a**, 21544-91-2; **13b**, 21544-92-3; **14**, 21544-93-4; **15**, 21537-87-1; **19**, 21537-88-2; **20**, 21537-89-3.

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(23) J. F. Grove, J. MacMillan, T. P. C. Mulholland, and M. A. T. Rogers *J. Chem. Soc.*, 3949 (1952).