in aqueous 2 *N* NaOH and the pH was adjusted to 5 with acid to give VIb (0.7 g.), m.p. 237° dec. as the monohydrate, R_f 0.67 (solvent system: isoamyl alcohol–6 *N* ammonium hydroxide).

Anal. Calcd. for $C_{15}H_{13}I_2NO_4 \cdot H_2O$: C, 33.20; H, 2.75; I, 46.74. Found: C, 33.32; H, 2.77; I, 46.94.

The methyl ester Vc was hydrolyzed in comparable yield as described above to give the amino acid VIb as a white solid, m.p. 235° dec. There was no depression of melting point on admixture with an analytically correct sample prepared from the ethyl ester; the infrared spectra were identical.

Treatment of Vc with Hydriodic Acid.—Vc (200 mg.) was heated under reflux for 4 hr. with 47% aqueous hydriodic acid (3.0 ml.) and glacial acetic acid (3.0 ml.). The reaction mixture was poured into water (20 ml.) and the pH was adjusted to 4.5 with sodium acetate. The precipitate was treated with Norit A at 80° for 1 min. in 2 *N* aqueous HCl. Adjustment of the pH to 4.5 gave a white precipitate of 3-[3-(4-hydroxyphenoxy)-phenyl]-DL-alanine (15 mg., 17%), m.p. 239–240° dec. There was depression of melting point on admixture with a sample of VIb.

Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.54. Found: C, 65.76; H, 5.19.

3-[5-(3-Iodo-4-hydroxyphenoxy)-2,4-diiodophenyl]-DL-alanine (VIIb).—VIb (0.6 g., 1.1 mmoles) was iodinated as described in the preparation of VIIa. The crude product was dissolved in a mixture of 2 *N* NaOH (10 ml.) and ethanol (20 ml.). Adjustment of the pH to 5 gave a yellow precipitate which was removed by filtration. The volume of the filtrate was reduced one-half by evaporation. Addition of water (5 ml.) precipitated the amino acid (VIIb). This procedure was repeated four times to give VIIb (72 mg., 9%), m.p. 197–198° dec. as the hemihydrate, R_f 0.58 (solvent system: isoamyl alcohol–6 *N* ammonium hydroxide).

Anal. Calcd. for $C_{15}H_{12}I_3NO_4 \cdot 0.5H_2O$: C, 27.30; H, 1.99; I, 57.69. Found: C, 27.73; H, 2.28; I, 57.42.

Paper chromatography of the crude product showed traces of a slower moving impurity (R_f 0.30) which probably corresponds to the tetraiodinated derivative (VIIIb). This was removed during the purification procedure, and paper chromatography also showed the absence of the starting material VIb (R_f 0.67).

Lower 2′-Alkylthio Analogs and Derivatives of Griseofulvin *via* a Mercaptanolysis Reaction[1]

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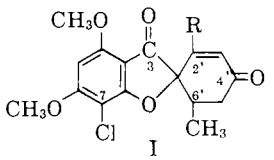
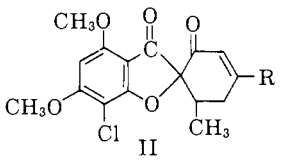
The synthesis of several homologous 2′,4′,4′-tris(alkylthio)-7-chloro-4,6-dimethoxy-6′-methyl-2′-grisen-3-ones by the acid-catalyzed reaction of griseofulvin with lower alkanethiols is described. A convenient route to the corresponding 2′-alkylthio analogs of griseofulvin is provided by the facile removal of the 4′-mercaptole group from the novel tris(alkylthio) derivatives. In a disk–plate assay against *Phoma*, the following biological activities *in vitro* are observed: 2′-methylthio and 2′-ethylthio analogs, as active as griseofulvin; 2′-ethoxy analog, more active than griseofulvin; 2′-*n*-propylthio, 2′-isopropylthio, and 2′-*n*-butylthio analogs, less active than griseofulvin; isogriseofulvin, 4′-alkylthio analogs, and tris(alkylthio) derivatives, inactive.

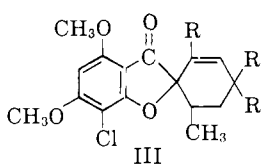
The therapeutic usefulness of griseofulvin (If) as an antifungal agent has stimulated considerable research into the relationship of structure and activity and towards discovering more effective analogs.[2] Recently, Stephenson, *et al.*,[3] prepared a number of 2′-alkylthio analogs of griseofulvin and 4′-alkylthio analogs of isogriseofulvin (IIf) by nucleophilic displacement of the chloro substituent with alkanethiols in 2′,7-dichloro-4,6-dimethoxy-6′-methyl-2′-grisene-3,4′-dione (Ig) and 4′,7-dichloro-4,6-dimethoxy-6′-methyl-3′-grisene-2′,3-dione (IIg), respectively. For the 2′-alkylthio analogs their synthesis starting from griseofulvin involved four steps: If → IIf → Ig → I (R = alkylthio). Our investigation of the direct acid-catalyzed reaction of griseofulvin with the lower alkanethiols (mercaptanolysis) as a synthetic route to the corresponding 2′-alkylthio analogs is reported below.



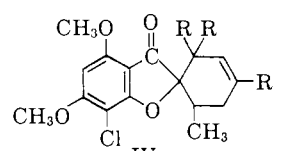
I



II



III



IV

a, R = CH_3S
b, R = C_2H_5S
c, R = n-C_3H_7S
d, R = i-C_3H_7S
e, R = n-C_4H_9S
f, R = CH_3O
g, R = Cl
h, R = C_2H_5O

When griseofulvin is shaken with an excess of methanethiol in the presence of small amounts of *p*-toluenesulfonic acid, a novel tris(methylthio) derivative crystallizes analytically pure in 70% yield from the reaction mixture shortly after the dissolution of If. Refluxing an acetone solution of the tris(methylthio) compound with the same catalyst results in the formation of pure 7-chloro-4,6-dimethoxy-6′-methyl-2′-methylthio-2′-grisene-3,4′-dione (Ia). Ethanethiol, 1-propanethiol, and 1-butanethiol also react with griseofulvin to give the corresponding tris(alkylthio) compounds, which can be converted in the same manner to the respective 2′-alkylthio analogs (Ib, Ic, and Ie). Two structures are possible for the tris(alkylthio) compounds (III or IV, R = alkylthio), in which two of the alkylthio groups are present as a mercaptole group. The assignment of structure III (R = alkylthio) to these compounds is discussed in a subsequent section.

In contrast to the alcoholysis of griseofulvin which usually forms substantial amounts of the 4′-alkoxy

(1) Presented in part at the 144th National Meeting of the American Chemical Society, Division of Medicinal Chemistry, Los Angeles, Calif., April, 1963.

(2) J. F. Grove, *Quart. Rev.* (London), **17**, 1 (1963).

(3) L. Stephenson, T. Walker, W. K. Warburton, and G. B. Webb, *J. Chem. Soc.*, 1282 (1962).

Table I

Optical Rotations[a] and Ultraviolet Maxima[b] of Methylthio Compounds

Compd.	$[\alpha]_D$,[c] deg.	M_D,[d] deg.	λ_{max}, mμ (log ε)		
Ia	+544[e]	+2010	230 (4.18)[f]	289.5 (4.61)	
IIa	+261	+964	230 (4.14)[f]	296 (4.60)	
IIIa	+218	+975	240 (4.24)	288 (4.35)	322 (3.72)[f]
Va	+530	+2040	240 (4.13)[f]	288 (4.57)	321 (3.81)[f]
VIa	+232	+935	240 (4.25)	288 (4.28)	322 (3.71)[f]
VIIa	+112	+416	[f]	289 (4.35)	322 (3.72)

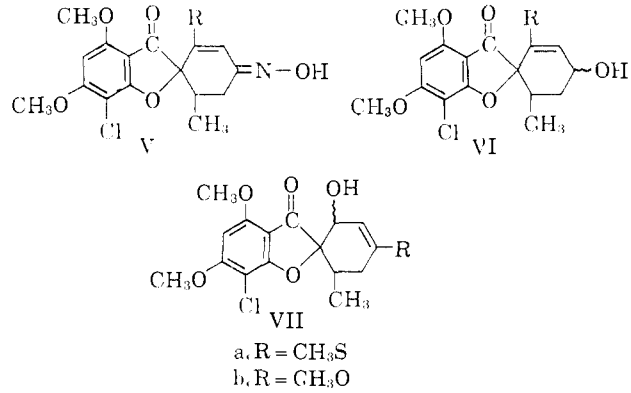
[a] In chloroform (*c* 1). [b] In ethanol. [c] Temperature: Ia and VIa, 23°; IIa, 26°; IIIa and VIIa, 23.5°; Va, 22°. [d] M_D for related methoxy compounds: If, +1190°[4b]; IIf, +759°[4b]; 7-chloro-2′,4,6-trimethoxy-6′-methyl-2′-grisen-3-one (III: 2′, R = CH_3O; 4′, R, R = H), +525° [T. P. C. Mulholland, *J. Chem. Soc.*, 3987 (1952)], +549°[7]; VIb, +582°[7]; VIIb, +373°.[7] [e] Ref. 3, $[\alpha]_D$ +500° (*c* 1, acetone) for Ia. [f] Inflection; 228 (4.39) and 235 (4.34) for VIIa.

analog, difficult to separate from the desired 2′-alkoxy analog,[4] the mercaptanolysis reaction followed by subsequent removal of the mercaptole group offers a convenient route to the lower 2′-alkylthio analogs, Ia–c and Ic. The utility of this method is limited to lower 1-alkanethiols, as compared to the wide variety of 2′-alkylthio and 2′-arylthio analogs possible by Stephenson's synthesis.[5]

Side products accompanying the tris(alkylthio) compound in the reaction mixture in the mercaptanolysis of griseofulvin include the 4′-alkylthio and 2′-alkylthio analogs. The yield of the tris(alkylthio) compound can be increased by employing larger amounts of alkanethiol and *p*-toluenesulfonic acid or by using a higher reaction temperature but is decreased as the alkanethiol increases in bulk. In the reaction of griseofulvin and 2-propanethiol, no tris(isopropylthio) compound is detected; the two characterized products of this reaction are IId and Id. The mercaptanolysis of isogriseofulvin, griseofulvinic acid, the 2′-methylthio analog, or the 4′-methylthio analog gives the same tris(methylthio) compound (IIIa) obtained from griseofulvin. The tris(ethylthio) compound (IIIb) is obtained when isogriseofulvin and ethanethiol are made to react. The tris(methylthio) derivative (IIIa) undergoes an acid-catalyzed exchange with either ethanethiol, 1-propanethiol, or 1-butanethiol to yield a product identical with the tris(alkylthio) compound obtained by direct reaction of griseofulvin and the alkanethiol. This exchange reaction, followed by removal of the mercaptole group, also can be used to prepare a higher 2′-alkylthio analog (*e.g.*, the 2′-*n*-butylthio analog).

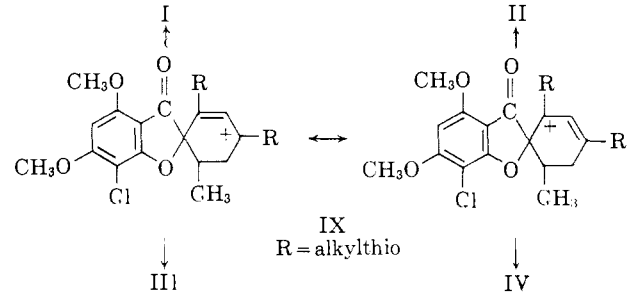
The methylthio analogs of griseofulvin oxime (Vb),[6] griseofulvol (VIb),[7] and isogriseofulvol (VIIb)[7] are prepared from Ia and IIa by methods described for the related methoxy compounds.

The three types of alkylthio compounds (I–III, R = alkylthio) derived from griseofulvin have characteristic optical rotations (Table I), ultraviolet spectra (Table I), infrared spectra (Table II), and n.m.r. spectra (Table III), which readily differentiate one type from another.[8]



Structure III (R = alkylthio) is preferred for the tris(alkylthio) derivatives rather than the alternate structure IV (R = alkylthio) for the following reasons.

(1) The mechanism of the acid-catalyzed reaction of griseofulvin and a lower alkanethiol to form the tris(alkylthio) compound probably is similar to the one postulated by Stephenson, *et al.*,[3] for the formation of the 4′-chloro analog (IIg) in the reaction of griseofulvin and phosphorus oxychloride. The initial product by such a mechanism should be the 4′-alkylthio analog, which in the presence of excess alkanethiol and catalyst would form the intermediate IX. The latter is probably



also involved in the acid-catalyzed demercaptolization of the tris(alkylthio) compound. Since the 2′-position is more hindered than the 4′-position,[2] removal of the mercaptole group from III (or IV) should lead only to I, agreeing with experimental observation. For the same reason, the further attachment of an alkylthio group to

(4) (a) L. A. Duncanson, J. F. Grove, and P. W. Jeff, *J. Chem. Soc.*, 2929 (1958); (b) J. F. Grove, J. MacMillan, T. P. C. Mulholland, and M. A. T. Rogers, *ibid.*, 3949, 3977 (1952).

(5) Over-all yields (starting from If) of 62, 75, 71, and 27% are realized for Ia-c and Ie, respectively, by the mercaptanolysis method as compared to over-all yields of 46, 29, 21, and 25%, respectively, for the same compounds by proceeding through Ig. The latter set of yields was calculated from data in ref. 3 based on a 75% yield for If → IIf [A. Brossi, M. Baumann, M. Gerecke, and E. Kyburz, *Helv. Chim. Acta*, **43**, 2071 (1960)] and a 95% yield for IIf → Ig.[4]

(6) (a) A. E. Oxford, H. Raistrick, and P. Simonart, *Biochem. J.*, **33**, 240 (1939); (b) A. Rhodes, S. Ball, and B. Boothroyd, British Patent 863,342 (1961).

(7) E. Kyburz, H. Geleick, J. R. Frey, and A. Brossi, *Helv. Chim. Acta*, **43**, 2083 (1960).

(8) (a) The optical rotations and infrared spectra of the 2′-alkylthio and 4′-alkylthio analogs synthesized *via* the mercaptanolysis reaction in general agree with those reported for these compounds by Stephenson, *et al.*,[3] and by J. E. Page and S. E. Staniforth [*J. Chem. Soc.*, 1292 (1962)]. Small differences in melting points remain unexplained. (b) The n.m.r. spectrum for Ia (Table III) agrees with that reported by G. F. H. Green, J. E. Page, and S. E. Staniforth [*ibid.*, 144 (1964)].

Table II

Infrared Absorption Bands[a] of Some Alkylthio Compounds

Compd.	R	—C=O bands, cm.⁻¹—		—C=C bands, cm.⁻¹—			
Id	i-C_3H_7S	1698[b]	1642	1610	1587[c]	1563	1504
IId	i-C_3H_7S	1689	1647[b]	1608	1585	1567[c]	1502
IIIa	CH_3S	1692		1608	1587		1502
IIIb	C_2H_5S	1692		1608	1587		1502
IIIc	n-C_3H_7S	1689		1608	1587		1502
Va	CH_3S	1692		1608	1587		1502
VIa	CH_3S	1686		1608	1587		1504

[a] In chloroform; Baird-Atomic, Inc. instrument for all infrared spectra except as noted otherwise. [b] Higher intensity peak of the two C=O bands. [c] Higher intensity peak of the two middle bands.

Table III

N.m.r. Bands (τ) of Methylthio and Ethylthio Compounds[a]

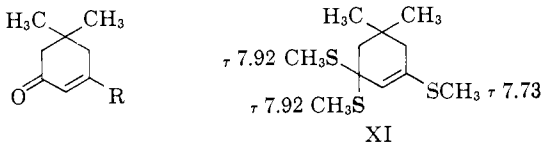
Compd.	5-H	3′-H[b]	—Aromatic CH_3O—		—CH_3 in alkylthio—		6′-CH_3
Ia	3.76	4.05	5.92	5.98	7.77	2′-CH_3S	9.05 d[c]
IIa	3.87	4.13 d[d]	5.98	6.13	7.62	4′-CH_3S	8.79 d
IIIa[e]	3.83	4.32	5.95	6.00	7.77	Tris-CH_3S	9.13 d
Ib	3.74	4.03	5.93	5.99	8.74 t[f]	2′-C_2H_5S	9.06 d
IIb	3.88	4.10 d[d]	6.00	6.13	8.63 t[f]	4′-C_2H_5S	8.98 d
IIIb[e]	3.86	4.05	5.98	6.03	8.74 t[f]	Bis-C_2H_5S	9.15 d
					8.80 t[f]	Mono-C_2H_5S	
VIa	3.82	4.13 d[g]	5.96	6.02	7.82	2′-CH_3S	9.13 d
VIIa	3.89	4.80 t[g]	6.00	6.08	7.72	4′-CH_3S	9.13 d

[a] Varian A60 instrument; tetramethylsilane = 10.0; 15% solution for Ia and IIIa, 30% solution for all others, in $CDCl_3$. [b] For Ic, 4.02; IIc, 4.08 d (J = 1.5 c.p.s.); IIIc, 4.04. [c] J = 6 c.p.s. for all 6′-CH_3. [d] J = 1.5 c.p.s. [e] As discussed in previous studies [M. Gerecke, E. Kyburz, C. v. Planta, and A. Brossi, *Helv. Chim. Acta*, **45**, 2241 (1962); B. H. Arison, N. L. Wendler, D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, and N. R. Trenner, *J. Am. Chem. Soc.*, **85**, 627 (1963); ref. 8b], the two 5′-protons and the single 6′-proton in If, IIf, and their analogs form a complex multiplet band (ABC system) in the n.m.r. spectrum. In IIIa these three protons appear in a more definitive pattern than in Ia or IIa. One 5′-proton in IIIa is located at τ 8.16 as a doublet (J = 11.5 c.p.s.), while the second 5′-proton doublet is found at τ 7.05 (J = 11.5 c.p.s.) as part of a compact region of bands (about τ 6.85 to 7.35) integrating for two protons (5′-H and 6′-H). The same pair of doublets is clearly seen in the n.m.r. spectrum of IIIb, although the one at τ 7.05 is partly hidden by the CH_2 bands of the ethylthio groups. It is of interest that the nonequivalent 3′-methylene protons of the 2′,4′-bisethylene ketal of griseofulvic acid are reported to be a pair of doublets (J = 11 c.p.s.) at τ 8.16 and 7.53.[8b] [f] J = 7.5 c.p.s. [g] J = 2 c.p.s.

IX should be at the less hindered 4′-position, resulting in structure III for the tris(alkylthio) compound.

(2) Replacement of the 4′-carbonyl group in If or the 2′-carbonyl group in IIf by a nonasymmetric tetrahedral carbon [as in If → 7-chloro-2′,4,6-trimethoxy-6′-methyl-2′-grisen-3-one (III: 2′, R = CH_3O; 4′, R, R = H)] or by an epimeric carbon pair (as in If → VIb or IIf → VIIb) results in a reduction in molar rotation by approximately one-half as seen in the following ratios of MD values (Table I): If/III (2′, R = CH_3O; 4′, R, R = H) = 2.3; If/VIb = 2.0; IIf/VIIb = 2.0. The same ratio holds for Ia/VIa (2.2) and IIa/VIIa (2.3). The molar rotation of the tris(methylthio) compound is consistent with structure IIIa (ratio of Ia/IIIa = 2.1) and not with IVa.

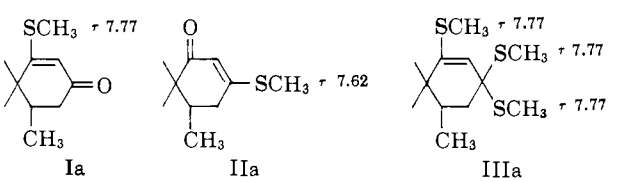
(3) Evidence from n.m.r. spectra (Table III) in support of structure III (R = alkylthio) is based on the following observations. (a) The n.m.r. band for the vinyl proton in IIa–c is a clean doublet (J = 1.5 c.p.s.) due probably to allylic coupling with a 5′-proton.[8b] In contrast, the 3′-proton in IIIa–c does not exhibit splitting into a narrow doublet, consistent with the assignment of structure III to the tris(alkylthio) compounds. (b) The change in going from the type of CH_3S group in Xa to that in the bis(methylthio) group in XI is reflected in the increase in chemical shift of τ 0.27, while the change in going from the CH_3S group in Xa to the monomethylthio group in XI is accompanied by the smaller increase of τ 0.08. Both kinds of changes in the type of CH_3S group are involved in going from Ia and IIa to the tris(methylthio) compound. The n.m.r. peak for CH_3S in Ia and IIa is located at τ 7.77



XI

Xa, R = CH_3S (τ 7.65)
b, R = C_2H_5S

and 7.62, respectively, while the CH_3S band in the tris(methylthio) compound appears as one sharp peak at τ 7.77. The single peak for the latter compound means that the 4′-CH_3S has moved upfield by τ 0.15, while the 2′-CH_3S is unchanged. This spectrum is compatible with structure IIIa for the tris(methylthio) compound but not IVa. The CH_3S group in the latter would be expected to appear in the n.m.r. spectrum at two locations, the bis(methylthio) peak upfield from τ 7.77 and the monomethylthio peak upfield from τ 7.62, with a larger increase in τ-value for the former peak than for the latter peak.



The alkylthio analogs and derivatives were tested for biological activity *in vitro* by a paper disk–agar plate assay. Table IV lists the zones of inhibition on a *Phoma* species plate for four different concentrations of the test compound. In this assay the following order of

TABLE IV

In Vitro ACTIVITY IN A DISK-PLATE ASSAY AGAINST *Phoma*

Compd.	R	Zone of inhibition (mm.) Concn. of compd., γ/ml. 5000	500	50	5
Ia	CH_3S	36[a]	39	34	21
Ib	C_2H_5S	39[a]	40	34	23
Ic	n-C_3H_7S	35	34	28	18
Id	i-C_3H_7S	27	26	22	17
Ie	n-C_4H_9S	26	24	20	NZ[b]
If[c]	CH_3O	45	40	33	20
Ih[c]	C_2H_5O	48	44	38	24
II	*d*	NZ	NZ	NZ	NZ
III	*e*	NZ	NZ	NZ	NZ
Va	CH_3S	36	33	21	NZ
Vb	CH_3O	41	34	21	NZ
VIa	CH_3S	33	28	NZ	NZ
VIb	CH_3O	40	27	NZ	NZ

[a] The smaller zone size at the high concentration was probably due to low solubility of the compound in the agar medium. [b] NZ = no zone of inhibition. [c] For twofold serial dilution the following inhibition zones (mm.) were observed for If and Ih, respectively: 50 γ/ml., 34 and 40; 25 γ/ml., 28 and 36; 12.5 γ/ml., 24 and 31; 6.3 γ/ml., 18 and 25; 3.1 γ/ml., NZ and 20; 1.6 γ/ml., both NZ. In a similar test Ia and Ib both gave inhibition zones down to 6.3 γ/ml. but none at 3.1 γ/ml. [d] R = CH_3S, C_2H_5S, n-C_3H_7S, i-C_3H_7S, n-C_4H_9S, and CH_3O. [e] R = CH_3S, C_2H_5S, n-C_3H_7S, and n-C_4H_9S.

decreasing biological activity is observed for I (R group given): C_2H_5O > CH_3O, CH_3S, C_2H_5S > n-C_3H_7S > i-C_3H_7S, n-C_4H_9S. Griseofulvin, the 2′-methylthio analog, and the 2′-ethylthio analog have approximately the same *in vitro* activity, while the 2′-ethoxy analog[4] is slightly more active.[9] Griseofulvin oxime, griseofulvol, and their alkylthio analogs are less active than the parent (4′-keto) compounds. Isogriseofulvin, its 4′-alkylthio analogs, and the tris(alkylthio) derivatives are inactive against *Phoma*. Like the corresponding 2′- and 4′-alkoxy analogs,[9a] both types of monoalkylthio analogs exhibit inhibitory activity on a *Botrytis alli* plate.

Experimental

Paper chromatography in Zaffaroni-type systems[10] was used to identify products, to check homogeneity, and to follow the course of reactions. Compounds were detected by their absorbance of ultraviolet light. The 2′-alkylthio or 2′-alkoxy analogs were also located as yellow zones on the paper chromatogram by treating the latter with isonicotinic acid hydrazide or as inhibition zones by bioautographing the sheet on a *Phoma* plate. The tris(alkylthio) derivatives appeared as orange fluorescent spots after exposing the paper chromatogram to ultraviolet light. Column chromatography was run using Merck acid-washed or neutral alumina and benzene solutions containing increasing amounts of methanol as developers. Specific rotations and ultraviolet spectra refer to chloroform solutions (*c* 1) and ethanol solutions, respectively. Melting points were determined in an electrically heated block (Culatti apparatus) using capillary tubes.

7-Chloro-4,6-dimethoxy-6′-methyl-2′,4′,4′-tris(methylthio)-2′-grisen-3-one (IIIa). A. From Griseofulvin.—A suspension of 63 g. (0.18 mole) of griseofulvin (If) and 3.6 g. of *p*-toluenesulfonic acid (TSA) in 300 ml. of methanethiol was shaken overnight in a sealed tube at room temperature. The solids dissolved on shaking and crystallization of IIIa began within an hour. After refrigerating the suspension for several hours, analytically pure IIIa was collected by filtration and washed with acetone and methanol, yield 56 g. (70%), m.p. 209–211°, $[\alpha]^{23}D$ +204°; m.p. 222–225° after recrystallization from chloroform.

Anal. Calcd. for $C_{24}H_{29}ClO_4S_3$: C, 51.05; H, 5.19; Cl, 7.93; S, 21.52. Found: C, 51.05; H, 5.32; Cl, 7.84; S, 21.40.

B. From Related Compounds.—Crystalline IIIa was prepared in a similar manner from the following compounds: (1) isogriseofulvin (IIf, 34%, m.p. 217–221°, $[\alpha]^{23}D$ +210°), (2) the 2′-methylthio analog (Ia, 90%, m.p. 221–223°, $[\alpha]^{23}D$ +211°, n.m.r. τ 7.77 singlet for CH_3S), (3) the 4′-methylthio analog (IIa, 59%, m.p. 221–223°, $[\alpha]^{22}D$ +210.5°, n.m.r. τ 7.77 singlet for CH_3S), and (4) the tris(ethylthio) compound (IIIb, 45%, m.p. 217–221°, $[\alpha]^{23.5}D$ +203°, n.m.r. τ 7.77 singlet for CH_3S). The reaction of griseofulvic acid (I or II, R = OH) and methanethiol gave a mixture of products (Ia, IIa, IIIa, and a new crystalline compound[11]), from which IIIa was recovered by column chromatography on acid-washed alumina (8%, m.p. 216–221°).

Anal. Found (range of values for the five preparations): C, 50.74–51.46; H, 5.28–5.43; S, 21.22–21.75.

7-Chloro-4,6-dimethoxy-6′-methyl-2′-methylthio-2′-grisene-3,4′-dione (Ia).—A mixture of 45 g. (0.10 mole) of IIIa and 1.125 g. of TSA in 2250 ml. of acetone was refluxed for 6 hr. The clarified solution was concentrated until a thick slurry of crystals formed. The analytically pure 2′-methylthio analog was collected by filtration, yield 32.6 g. (88%), m.p. 237–240°, m.p. 239–242° recrystallized from nitromethane (lit.[3] m.p. 251–253° from nitromethane).

7-Chloro-4,6-dimethoxy-6′-methyl-4′-methylthio-3′-grisene-2′,3-dione (IIa).—By using less catalyst (9.5 g. of TSA/mole of If) and a 5-hr. reaction time in the synthesis of IIIa, part A, the yield of IIIa was 56%. The 4′-methylthio analog was recovered from the mother liquor and purified by chromatography on an acid-washed alumina (17% yield). Recrystallization from ethanol afforded analytically pure IIa, m.p. 223–225° (lit.[3] m.p. 229.5–232.5°).

7-Chloro-2′,4′,4′-tris(ethylthio)-4,6-dimethoxy-6′-methyl-2′-grisen-3-one (IIIb). A. From Griseofulvin.—A mixture of 21 g. (0.06 mole) of If, 1.20 g. of TSA, and 180 ml. of ethanethiol was heated at 65° in a sealed tube overnight with occasional shaking. The residue obtained from evaporating the solution was triturated with 25 ml. of ethanol. After refrigerating the mixture for 1 hr., crystalline IIIb was collected by filtration and washed with ethanol, yield 26 g. (89%), m.p. 139–144°. For analysis a sample was chromatographed on acid-washed alumina and recrystallized from ethanol, m.p. 166–167°, $[\alpha]^{26}D$ +172°, λ_{max} 288 mμ (log ε 4.35).

Anal. Calcd. for $C_{22}H_{29}ClO_4S_3$: C, 54.02; H, 5.98; Cl, 7.25; S, 19.67. Found: C, 54.03; H, 5.95; Cl, 7.27; S, 19.79.

Isogriseofulvin and ethanethiol, treated in the same manner, also yielded crystalline IIIb (79%), m.p. 165–167°, $[\alpha]^{22}D$ +177°.

B. From IIIa.—A mixture of 45 g. (0.10 mole) of IIIa, 3.0 g. of TSA, and 500 g. of ethanethiol kept 6 days at room temperature and worked up as described in the preceding section yielded 45.7 g. (93%) of crystalline IIIb, m.p. 140–144°. Recrystallization from ethanol gave analytically pure product, m.p. 168–170°, $[\alpha]^{22}D$ −180°.

Anal. Found: C, 54.14; H, 6.06; S, 19.57.

7-Chloro-2′-ethylthio-4,6-dimethoxy-6′-methyl-2′-grisene-3,4′-dione (Ib).—Ten grams (0.02 mole) of IIIb was treated with TSA (250 mg.) and acetone (500 ml.) as described for Ia to yield the crystalline 2′-ethylthio analog (6.6 g., 84%), m.p. 170–174°. Recrystallization from ethanol provided analytically pure Ib, m.p. 180–181°, $[\alpha]^{25}D$ +489°, λ_{max} 290 mμ (log ε 4.61) [lit.[3] m.p. 185–187°, $[\alpha]^{1}D$ +475° (*c* 1, acetone)].

(9) The 2′-ethoxy analog is approximately twice as active as griseofulvin against *Phoma*, paralleling the reported activity of these two compounds against *Botrytis alli*. *Cf.* (a) S. H. Crowdy, J. F. Grove, and P. McCloskey, *Biochem. J.*, **72**, 241 (1959); (b) M. Jackson, E. L. Dulaney, I. Putter, H. M. Shafer, F. J. Wolf, and H. B. Woodruff, *Biochim. Biophys. Acta*, **62**, 616 (1962).

(10) A. Zaffaroni, R. B. Burton, and E. H. Keutmann, *Science*, **111**, 6 (1950); T. M. Lees, P. J. DeMuria, and W. H. Boegemann, *J. Chromatog.*, **5**, 126 (1961).

(11) This compound, also observed in small amounts in paper chromatograms (blue fluorescent zone migrating slightly slower than IIIa) of the other reaction products of methanethiol in parts A and B, was isolated in low yield from a chromatographic fraction and tentatively identified as 7-chloro-4,6-dimethoxy-6′-methyl-4′,4′-bis(methylthio)grisan-2′,3-dione, m.p. 179–183°, $[\alpha]^{23}D$ 0°; λ_{max} 294.5 mμ (log ε 4.33); ν_{max} 1718 and 1689 cm.$^{-1}$ (KBr); n.m.r. (τ): 3.87 (5-H), no vinyl proton, 5.98 (CH_3O), 6.05 (CH_3O), 7.83 (CH_3S), 7.93 (CH_3S), and 9.03 d (CH_3) (J = 6 c.p.s.). T. P. C. Mulholland [*J. Chem. Soc.*, 3994 (1952)] reports λ_{max} 291 mμ (log ε 4.28) (methanol), ν_{max} 1728 and 1700 cm.$^{-1}$ (Nujol); Page and Staniforth[3] report ν_{max} 1726 and for 1696 cm.$^{-1}$ (CHBr$_3$) for 7-chloro-4,6-dimethoxy-6′-methylgrisan-2′,3-dione. *Anal.* Calcd. for $C_{18}H_{21}ClO_5S_2$: C, 51.85; H, 5.08; Cl, 8.5; S, 15.4. Found: C, 52.02; H, 5.28; Cl, 8.9; S, 14.8.

7-Chloro-4′-ethylthio-4,6-dimethoxy-6′-methyl-3′-grisene-2′,3-dione (IIb).—A suspension of 14.1 g. (0.04 mole) of If, 400 mg. of TSA, and 100 g. of ethanethiol agitated at room temperature for 4 hr. formed a mixture (Ib, IIb, and IIIb), from which crystalline IIb (3.6 g., 24%) was recovered by chromatography on acid-washed alumina. Recrystallization from ethanol afforded analytically pure product, m.p. 173–175°, $[\alpha]^{26}D$ +240°, λ_{max} 296 mμ (log ε 4.62) [lit.[3] m.p. 177–179°, $[\alpha]^{20}D$ +236° (*c* 1, acetone)].

7-Chloro-4,6-dimethoxy-6′-methyl-2′,4′,4′-tris(*n*-propylthio)-2′-grisen-3-one (IIIc). A. From Griseofulvin.—Griseofulvin (7.0 g., 0.02 mole), TSA (400 mg.), and 1-propanethiol (70 g.) reacted as described for IIIb, part A, to give 7.6 g. (72%) of crystalline IIIc, m.p. 99–101°. For analysis a sample was recrystallized from ethanol, m.p. 102–104°, $[\alpha]^{25}D$ +163°, λ_{max} 288 mμ (log ε 4.37).

Anal. Calcd. for $C_{25}H_{35}ClO_4S_3$: C, 56.52; H, 6.64; Cl, 6.68; S, 18.11. Found: C, 56.87; H, 6.88; Cl, 6.70; S, 18.28.

B. From IIIa.—A mixture of IIIa (11.25 g., 0.025 mole), TSA (750 mg.), and 1-propanethiol (153 g.) was treated as described for IIIb, part B, yielding crystalline IIIc, 8.9 g. (67%). Recrystallization from ethanol gave an analytically pure product, m.p. 96–99°, $[\alpha]^{22}D$ +170°.

Anal. Found: C, 56.63; H, 6.78; S, 18.34.

7-Chloro-4,6-dimethoxy-6′-methyl-2′-*n*-propylthio-2′-grisene-3,4′-dione (Ic).—The tris(*n*-propylthio) compound (IIIc, 1.5 g., 0.028 mole) was treated with TSA (37.5 mg.) and acetone (75 ml.) as described for Ia to form 1.1 g. (98%) of crystalline Ic. Recrystallization from ethanol gave analytically pure product, m.p. 160–162°, $[\alpha]^{24}D$ +481°, λ_{max} 290 mμ (log ε 4.60) [lit.[3] m.p. 166.5–168°, $[\alpha]D$ +459° (*c* 1, acetone)].

7-Chloro-4,6-dimethoxy-6′-methyl-4′-*n*-propylthio-3′-grisene-2′,3-dione (IIc).—A mixture of 3.52 g. (0.01 mole) of If, 100 mg. of TSA, and 25 ml. of 1-propanethiol on shaking at room temperature for 25 hr. afforded 1.4 g. (35%) of crystalline IIc. For analysis a sample was chromatographed on acid-washed alumina and recrystallized from ethanol, m.p. 160–161°, $[\alpha]^{25}D$ +228°, λ_{max} 296 mμ (log ε 4.64).

Anal. Calcd. for $C_{19}H_{21}ClO_5S$: C, 57.50; H, 5.33; Cl, 8.93; S, 8.08. Found: C, 57.51; H, 5.31; Cl, 9.02; S, 7.96.

7-Chloro-4,6-dimethoxy-6′-methyl-2′-isopropylthio-2′-grisene-3,4′-dione (Id).—Griseofulvin (3.53 g., 0.01 mole), TSA (200 mg.), and 2-propanethiol (30 g.) reacted as described for IIIb, part A, yielding crystalline IId, 1.45 g. (36.5%). The mother liquor was evaporated, and a benzene solution of the residue was chromatographed on acid-washed alumina (50 ml.). The 2′-isopropylthio analog was eluted from the column with 1% MeOH in benzene (813 mg., 20% yield, m.p. 172–176°) and recrystallized from ethanol, m.p. 174–176°, $[\alpha]^{24}D$ +460°, λ_{max} 291 mμ (log ε 4.58).

Anal. Calcd. for $C_{19}H_{21}ClO_5S$: C, 57.50; H, 5.33; Cl, 8.93; S, 8.08. Found: C, 57.42; H, 5.50; Cl, 9.15; S, 7.87.

7-Chloro-4,6-dimethoxy-6′-methyl-4′-isopropylthio-3′-grisene-2′,3-dione (IId).—When the reaction in the preceding section was run with 100 mg. of TSA for 3 days at room temperature, crystalline IId was recovered in 73% yield and recrystallized from ethanol, m.p. 188–190°, $[\alpha]^{25}D$ +244°, λ_{max} 296 mμ (log ε 4.61).

Anal. Calcd. for $C_{19}H_{21}ClO_5S$: C, 57.50; H, 5.33; Cl, 8.93; S, 8.08. Found: C, 57.17; H, 5.43; Cl, 8.94; S, 8.20.

2′,4′,4′-Tris(*n*-butylthio)-7-chloro-4,6-dimethoxy-6′-methyl-2′-grisen-3-one (IIIe).—A mixture of tris(methylthio) compound (IIIa, 4.5 g., 0.01 mole), TSA (300 mg.), and 1-butanethiol (30 ml.) was kept at 65° for 5 days and evaporated. A chloroform solution (100 ml.) of the residue was washed four times with 50-ml. volumes of *N* NaOH followed by water, dried, and evaporated to yield 4.9 g. (86%) of IIIe (glass); $[\alpha]^{25}D$ +149°; λ_{max} 289.5 mμ (log ε 4.42); ν_{max} 1704, 1616, 1592, and 1504 cm.$^{-1}$ (Perkin-Elmer).

Anal. Calcd. for $C_{28}H_{41}ClO_4S_3$: C, 58.66; H, 7.19; S, 16.78. Found: C, 58.08; H, 7.34; S, 16.42.

2′-*n*-Butylthio-7-chloro-4,6-dimethoxy-6′-methyl-2′-grisene-3,4′-dione (Ie).—Griseofulvin (3.52 g., 0.01 mole), TSA (200 mg.), and 1-butanethiol (35 g.), reacted as described for IIIb, part A, afforded 2.5 g. (44%) of IIIe after chromatography on acid-washed alumina (200 ml.). The product was treated with TSA and acetone as described for Ia, yielding 1.1 g. (61%) of crystalline Ie. Recrystallization from ethanol gave an analytically pure sample, m.p. 147–150°, $[\alpha]^{25}D$ +447°, λ_{max} 291 mμ (log ε 4.58) [lit.[3] m.p. 154.5–156.5°, $[\alpha]D$ +429° (*c* 1, acetone)].

4′-*n*-Butylthio-7-chloro-4,6-dimethoxy-6′-methyl-3′-grisene-2′,3-dione (IIe).—A mixture of 3.52 g. (0.01 mole) of If, 100 mg. of TSA, and 100 ml. of 1-butanethiol on shaking overnight at room temperature formed 0.92 g. (22%) of crystalline IIe. For analysis a sample was chromatographed on acid-washed alumina and recrystallized from ethanol, m.p. 146–147°, $[\alpha]^{25}D$ +244°, λ_{max} 296 mμ (log ε 4.61).

Anal. Calcd. for $C_{25}H_{33}ClO_5S$: C, 58.46; H, 5.64; Cl, 8.63; S, 7.80. Found: C, 58.62; H, 5.75; Cl, 8.54; S, 7.70.

7-Chloro-4,6-dimethoxy-6′-methyl-2′-methylthio-2′-grisene-3,4′-dione Oxime (Va).—The literature preparation of griseofulvin oxime[6b] was used to convert Ia (6.29 g., 0.017 mole) to Va, yield 6.5 g. (99%). For analysis the product was chromatographed on neutral alumina, recrystallized from benzene (solvate, m.p. 102–108°), and dried to remove solvent.

Anal. Calcd. for $C_{17}H_{18}ClNO_5S$: C, 53.19; H, 4.73; Cl, 9.24; N, 3.65; S, 8.35. Found: C, 53.27; H, 4.88; Cl, 9.07; N, 3.68; S, 8.56.

7-Chloro-4′-hydroxy-4,6-dimethoxy-6′-methyl-2′-methylthio-2′-grisen-3-one (VIa).—The sodium borohydride method for the preparation of griseofulvol[7] was used to reduce Ia (1.5 g., 0.04 mole) to VIa. Crystallization of VIa resulted, when the reaction solution was adjusted to pH 6, yield 1.17 g. (78%). For analysis the product was recrystallized from methanol, m.p. 102–108° (solvate).

Anal. Calcd. for $C_{17}H_{19}ClO_5S \cdot CH_3OH$: C, 53.66; H, 5.75; Cl, 8.80; S, 7.96. Found: C, 53.47; H, 5.78; Cl, 8.65; S, 8.19.

7-Chloro-2′-hydroxy-4,6-dimethoxy-6′-methyl-4′-methylthio-3′-grisen-3-one (VIIa).—The sodium borohydride method for the preparation of isogriseofulvol[7] was employed to reduce IIa (2.0 g., 0.054 mole) to VIIa, yield 1.14 g. (57%). For analysis the product was recrystallized from methanol, m.p. 211–213°; ν_{max} 1701, 1616, 1597, and 1506 cm.$^{-1}$ (Perkin-Elmer).

Anal. Calcd. for $C_{17}H_{19}ClO_5S$: C, 55.06; H, 5.16; S, 8.65. Found: C, 54.82; H, 5.24; S, 8.70.

5,5-Dimethyl-1,1,3-tris(methylthio)-2-cyclohexene (XI).—A mixture of dimedone (5.2 g., 0.037 mole), TSA (900 mg.), and methanethiol (70 ml.) was shaken overnight and evaporated. A chloroform solution (100 ml.) of the residue was washed with water, dried, and evaporated to give an oil, which crystallized on cooling, yield 3.24 g. (35%). For analysis a sample was recrystallized from petroleum ether (b.p. 30–60°), m.p. 75–77°; λ_{max} 236 mμ (log ε 4.00) and 252 mμ (log ε 4.03); n.m.r. (τ): 4.75 (vinyl H), 7.73 (mono-CH_3S), 7.92 (bis-CH_3S), 8.02 d (CH_2) (J = 1.5 c.p.s.), 8.07 (CH_2), 8.93 (CH_3).

Anal. Calcd. for $C_{11}H_{20}S_3$: C, 53.17; H, 8.11; S, 38.72. Found: C, 52.78; H, 8.07; S, 39.05.

5,5-Dimethyl-3-methylthio-2-cyclohexen-1-one (Xa).—Treating XI with acetone and TSA as described for Ia formed an oil, which on cooling yielded crystalline X, m.p. 34–37°; λ_{max} 290 mμ (log ε 4.32); ν_{max} 1645 cm.$^{-1}$ (Perkin-Elmer); n.m.r. (τ): 4.17 (vinyl H), 7.65 (CH_2 and CH_3S), 7.73 (CH_2), and 8.93 (CH_3).

Anal. Calcd. for $C_9H_{14}OS$: C, 63.48; H, 8.29; S, 18.83. Found: C, 63.19; H, 8.33; S, 18.77.

3-Ethylthio-5,5-dimethyl-2-cyclohexen-1-one (Xb).—A mixture of dimedone (3.5 g., 0.025 mole), TSA (600 mg.), and ethanethiol (40 ml.) was kept at 65° overnight and evaporated. The product was worked up as described for XI (incorporating a 5% $NaHCO_3$ wash) to give an oil, which crystallized on cooling, yield 3.2 g. (70%); m.p. 18°; $n^{24}D$ 1.5442; λ_{max} 292 mμ (log ε 4.27); ν_{max} 1639 cm.$^{-1}$ (Perkin-Elmer); n.m.r. (τ): 4.12 (vinyl H), 7.00 q (CH_2 in CH_3CH_2S) (J = 7.5 c.p.s.), 7.67 (CH_2), 7.73 (CH_2), 8.65 t (CH_3 in CH_3CH_2S) (J = 7 c.p.s.), and 8.93 (CH_3).[12]

Anal. Calcd. for $C_{10}H_{16}OS$: C, 65.17; H, 8.75; S, 17.40. Found: C, 64.70; H, 8.78; S, 17.49.

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(12) Attempts to synthesize 1,1,3-tris(ethylthio)-5,5-dimethyl 2-cyclohexene were not successful because of the rapid loss of ethanethiol from the reaction product to form Xb during purification.