242. *Griseofulvin Analogues. Part II.*[1] *Some 3′-Alkylgriseofulvic Acids and Their Enol Ethers.*

By G. I. GREGORY, P. J. HOLTON, HILARY ROBINSON, and T. WALKER.

Several 3′-substituted griseofulvic acids (3′-methyl, -ethyl, -propyl, -allyl, and -benzyl) and their 2′- and 4′-enol ethers have been prepared. Further methylation of 3′-methylgriseofulvic acid gave the 3′,3′-dimethyl derivative, and a study of the by-products formed during the benzylation of griseofulvic acid led to the isolation of the 3′,3′-dibenzyl compound. Hydrogenolysis of the latter resulted in the cleavage of a carbon–carbon bond to give 3′-benzylgriseofulvic acid.

Griseofulvic acid underwent a Michael condensation with methyl vinyl ketone; methylation of the product led to 3′-(3-oxobutyl)griseofulvin and its isomer.

As part of a programme to produce structural modifications of the antifungal antibiotic griseofulvin (I), we undertook the preparation of analogues bearing an alkyl or a substituted alkyl group at position 3′. The modified griseofulvic acids (III; R = Me, Et, Pr^n, $CH_2{:}CH{\cdot}CH_2$, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2$, or $Ph{\cdot}CH_2$) and their corresponding isomeric pairs of ethers (VI and VII) are described in this paper. An example of this type, the 4′-butoxy-3′-butyl compound (VII; R = R′ = Bu^n), was isolated by Duncanson *et al.*[2] as a by-product of the *O*-butylation of griseofulvic acid (II) with diazobutane.

Treating salts of the simple cyclic β-diketones, cyclohexa-1,3-dione [3-7] and 5,5-dimethylcyclohexane-1,3-dione,[6,8] with alkyl, alkenyl, or benzyl halides leads to a mixture of *C*- and *O*-alkylated products. In alcoholic solutions containing 1 equivalent of a metal alkoxide (preferably [3] potassium methoxide in methanol), it has been shown [3,8] that the highest ratios of *C*- to *O*-alkylation are obtained with reactive alkyl halides and high concentrations of reactants. The use of a more polar medium, *e.g.*, water, aqueous acetone, or aqueous alcohols, has also been shown [3,4] to favour *C*- at the expense of *O*-alkylation.[9]

The corresponding *C*- and *O*-alkyl and dialkyl derivatives of griseofulvic acid (II) are represented by structures (III)—(VIII), where R = R′, and examples of each type have been isolated. Direct alkylation of the potassium salt of griseofulvic acid (II) with methyl iodide, allyl bromide, or benzyl bromide in water or aqueous acetone led to moderate yields of the triones (III; R = Me, $CH_2{:}CH{\cdot}CH_2$ or $Ph{\cdot}CH_2$). The 3′-methyl- and the 3′-benzyl-trione were purified by crystallisation or, better, by acid hydrolysis of their ethers (VI or VII) prepared as described below. The 3′-allyl-trione was not obtained pure.

An attempt to prepare 3′-propylgriseofulvic acid (III; R = Pr^n) by alkylating the potassium salt of griseofulvic acid directly with propyl iodide gave a low yield of the *C*-alkylated product with a high proportion of the ethers (IV and V; R = Pr^n), in accord with the finding [3,8] that the proportion of *C*- to *O*-alkylation decreases with increasing chain-length of the alkyl halide. A satisfactory method for preparing the 3′-propyl analogue (III; R = Pr^n) was hydrogenation of the 3′-allyl-trione (III; R = $CH_2{:}CH{\cdot}CH_2$) over a palladium-carbon catalyst.

The 3′-ethyl-trione (III; R = Et) was obtained by acid hydrolysis of the 4′-ether

---

[1] Part I, preceding paper.

[2] Duncanson, Grove, and Jeffs, *J.*, 1958, 2929.

[3] Stetter and Dierichs, *Chem. Ber.*, 1952, **85**, 61, 1061.

[4] Nazarov and Zav'yalov, *Zhur. obshchei Khim.* 1953, **23**, 1703; *Chem. Abs.*, 1954, **48**, 13,667; Nazarov, Zav'yalov, Burmistrova, Gurvich, and Shmonina, *Chem. Abs.*, 1956, **50**, 13,847; Nazarov and Zav'yalov, *Bull. Acad. Sci. U.S.S.R.*, 1957, 339.

[5] Friedmann and Robinson, *Chem. and Ind.*, 1951, 777.

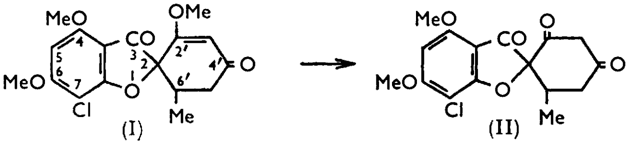
[6] Meek, Turnbull, and Robinson, *J.*, 1953, 811.

[7] Eskola, Auvinen, Hirvimies, Rinne, and Waris, *Suomen Kem.*, 1954, **27**, *B*, 88; *Chem. Abs.*, 1956, **50**, 5558.

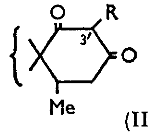
[8] Desai, *J.*, 1932, 1079.

[9] Cf. Kornblum, Berrigan, and Le Noble, *J. Amer. Chem. Soc.*, 1960, **82**, 1257.

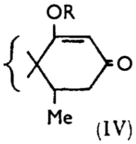
(VII; $R = R' = Et$), in turn isolated as a minor product after the alkylation of griseofulvic acid with ethyl iodide and potassium carbonate under anhydrous conditions. The neutral product was treated with Girard's reagent P to isolate the unsubstituted griseofulvin homologue[10] (IV; $R = Et$); crystallisation of the remainder gave the isomeric ether (V; $R = Et$), and chromatography of the mother-liquors yielded the isomeric ethyl ethers (VI and VII; $R = R' = Et$) of 3'-ethylgriseofulvic acid.



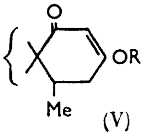
(I) (II)



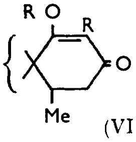
(III)



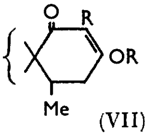
(IV)



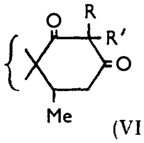
(V)



(VI)



(VII)



(VIII)

Further methylation of the potassium salt of 3'-methylgriseofulvic acid (III; $R = Me$) in aqueous acetone with methyl iodide gave a low yield of 7-chloro-4,6-dimethoxy-3',3',6'-trimethylgrisan-3,2',4'-trione (VIII; $R = R' = Me$). The corresponding lævorotatory 3',3'-dibenzyl-trione (VIII; $R = R' = Ph{\cdot}CH_2$) was isolated from the non-hydrolysable portion of the neutral fraction produced when the potassium salt of griseofulvic acid was treated with benzyl bromide in the presence of sodium iodide. These triones (VIII) were distinguished from the ethers (VI and VII) by low or negative optical rotations and an infrared band for a ketone at *ca.* 1730 cm.$^{-1}$, indicating some interaction between the 3- and the 2'-carbonyl groups (cf. a similar band in the spectra of 7-chloro-4,6-dimethoxy-6'-methylgrisan-3,2'-dione[11] and 7-chloro-4'-ethylenedioxy-4,6-dimethoxy-6'-methylgrisan-3,2'-dione[1]). The dibenzyl compound (VIII; $R = R' = Ph{\cdot}CH_2$) resisted acid hydrolysis, but underwent smooth hydrogenolysis of a *C*-benzyl group with palladium–carbon to give the 3'-benzylgriseofulvic acid (III; $R = Ph{\cdot}CH_2$). Previous examples of *C*-debenzylation have been recorded by Murin *et al.* and Jurd.[12]

Griseofulvic acid underwent a base-catalysed Michael condensation[4,13] with methyl vinyl ketone, to give the 3'-(3-oxobutyl)-trione (III; $R = CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2$), which was converted without purification into the methyl ethers (VI and VII; $R = CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2$, $R' = Me$) by diazomethane.

The 3'-substituted triones (III) were etherified either with the appropriate diazoalkane or with an alkyl halide in the presence of potassium carbonate; a mixture of ethers (VI and VII) was obtained and the 3',3'-disubstituted trione (VIII) was sometimes also detected as a fraction with a low or negative rotation and the expected infrared and ultraviolet characteristics. *O*-Alkylation with a diazoalkane was conveniently conducted in an acetone solution of the triethylamine salt of the trione (III). Similar results were obtained when, as described by Duncanson *et al.*,[2] a solution of the diazoalkane in toluene was added to a suspension of the 3'-alkyl-trione (III) in toluene.

In contrast to griseofulvin[10] and its homologous ethers (IV),[1] the 3'-alkyl analogues (VI) do not form derivatives with Girard's reagent P or T. We were, however, able to separate the isomeric ethers (VI and VII) by chromatography on acid alumina. Like the unsubstituted ethers[2] (IV and V), the 4'-ethers (VII) were eluted more easily than their

---

[10] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.

[11] Mulholland, *J.*, 1952, 3994.

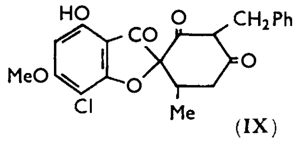
[12] Murin and Riedl, *Chem. Ber.*, 1959, **92**, 2030; Riedl and Nickl, *Chem. Ber.*, 1956, **89**, 1838; Jurd, *J. Amer. Chem. Soc.*, 1959, **81**, 4610.

[13] Bergmann, Ginsberg, and Pappo in " Organic Reactions," Wiley and Sons, New York, 1959, Vol. X, p. 179.

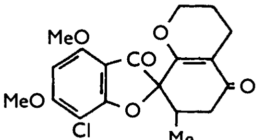
isomers (VI), and in several instances when the 3′-alkyl-trione to be *O*-alkylated was contaminated with griseofulvic acid the order of elution was (VIII), (VII), (VI), (V), and (IV). An exception was noted with the isomeric methyl ethers of 3′-(3-oxobutyl)griseofulvic acid, the 2′- being eluted before the 4′-ether. As expected, acid-catalysed[2] alkylation of the triones (III; R = Pr^n or Ph·CH$_2$) in methanol gave high yields of the 4′-ethers.

Treatment of 3′-benzylgriseofulvin (VI; R = Ph·CH$_2$, R′ = Me) with ethereal magnesium iodide under conditions used for the preparation of 7-chloro-4-hydroxy-6,2′-dimethoxy-6′-methylgris-2′-en-3,4′-dione from griseofulvin[1] resulted in demethylation in rings A and C, to give the 4-hydroxy-compound (IX).

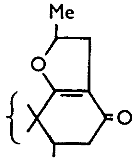
Attempts to prepare the 3′-allyl-trione (III; R = CH$_2$:CH·CH$_2$) by heating the 2′-allyl enol ether (IV; R = CH$_2$:CH·CH$_2$) in dimethylaniline under the conditions of the Claisen rearrangement[14] gave, instead, a mixture of unidentified neutral products, from which a 10% yield of an isomer, C$_{19}$H$_{19}$ClO$_6$, of the starting material was isolated. No absorption at 830—840 cm.$^{-1}$ was apparent in its infrared spectrum, indicating[15] the absence of a hydrogen atom on the ring C double bond and so favouring a 3′-alkylated ether; the infrared spectrum also favoured a 2′-enol ether, but the ultraviolet spectrum was ambiguous. Further, the same material was isolated when the 4′-allyl ether (V; R = CH$_2$:CH·CH$_2$) was refluxed with dimethylaniline. Structure (XI) is favoured over



(IX)



(X)



(XI)

TABLE 1.

Ultraviolet [$\lambda_{\max.}$ (mμ); $10^{-3}\varepsilon$ in parenthesis] and infrared absorption (cm.$^{-1}$) data for the isomeric enol ethers (VI and VII).

R	R′	2′-Ethers (VI)					4′-Ethers (VII)				
		$\lambda_{\max.}$ ($10^{-3}\varepsilon$)			$\nu_{\max.}$[a]	$\nu_{\max.}$[b]	$\lambda_{\max.}$ ($10^{-3}\varepsilon$)			$\nu_{\max.}$[a]	$\nu_{\max.}$[b]
Me	Me	232 *	289	320	1704	1664	230 *	281·5	320	1695	1652
		(19·3)	(25·3)	(5·5)			(16·6)	(33·2)	(5·5)		
CH$_2$:CH·CH$_2$	Me	231 *	290	318 *	1704	1665	230 *	281·5	320 *	1692	1656
		(20·2)	(26·1)	(6·05)			(15·8)	(33·0)	(5·6)		
Ph·CH$_2$	Me	231 *	291	319	1704	1665	230 *	283	321 *	1695	1656
		(19·0)	(25·6)	(6·3)			(15·9)	(31·4)	(5·3)		
Ph·CH$_2$	Et	231 *	290	316 *	1706	1668	230 *	282·5	321 *	1694	1655
		(19·7)	(25·4)	(5·9)			(16·7)	(30·2)	(5·6)		
Ph·CH$_2$	Pr^n	232 *	291	320	1706	1668	230 *	283	322	1696	1654
		(18·0)	(25·3)	(5·75)			(16·8)	(33·1)	(5·2)		
Ph·CH$_2$	Bu^n	232 *	292	320	1705	1666	231 *	283	322	1694	1654
		(18·7)	(25·0)	(5·5)			(16·7)	(34·6)	(5·65)		
Ph·CH$_2$	CH$_2$:CH·CH$_2$	—	—	—	—	—	230 *	282·5	321	1690	1655
							(16·3)	(31·2)	(4·9)		
Ph·CH$_2$	Br[CH$_2$]$_3$	230 *	290	320	1710	1670	231	282·5	322 *	1696	1656
		(20·1)	(25·3)	(5·7)			(16·8)	(33·4)	(5·3)		
Et	Et	230 *	290	320	1706	1666	231 *	281	320 *	1694	1652
		(19·1)	(26·4)	(5·8)			(15·6)	(34·0)	(5·4)		
Pr^n	Me	230 *	290·5	321	1710	1668	230 *	281·5	320	1696	1654
		(19·4)	(26·2)	(6·1)			(16·4)	(34·4)	(5·6)		
Pr^n	Pr^n	232·5	289·5	321	1710	1668	231 *	283	320 *	1696	1654
		(20·2)	(25·0)	(5·9)			(15·3)	(36·1)	(5·25)		

* Inflexion. [a] C=O band. [b] C=C–C=O band.

---

[14] Tarbell in " Organic Reactions," Wiley and Sons, New York, 1944, Vol. II, p. 1.

[15] Part V, Page and Staniforth, *J.*, 1962, 1292.

the isomeric structure (X) both on evidence from the infrared spectrum and from *C*-Me analysis which gives a value approximately double that given by griseofulvin.

Ultraviolet and Infrared Spectra of the Isomeric Ethers (VI) *and* (VII).—The ultraviolet absorption spectra of the isomers (VI) and (VII) provide a well-defined means of identification (Table 1). For each pair of isomers the main absorption band of the 2′-ether (VI) occurs at a higher wavelength (~8 mμ) than that of its isomer, whereas the intensity of this band for the 2′-ether (VI) (ε ~25,000) is lower than that for its isomer (ε ~33,000). Less pronounced, but nevertheless consistent, trends are to be found in the intensities of absorption at *ca.* 231 mμ.

A comparison of the infrared spectra (bromoform solution) of isomers (VI) and (VII) reveals (Table 1) that bands at 1704—1708 (3-ketone) and 1664—1668 cm.$^{-1}$ (Δ^2-4′-ketone) for the 2′-enol ethers (VI) occur at a higher frequency (~12 cm.$^{-1}$) than the corresponding bands (1694—1696 and 1652—1656 cm.$^{-1}$) for the isomeric 4′-enol ethers (VII). The infrared spectra are discussed more fully in Part V of this series.[15]

Unlike the unsubstituted ethers (IV) and (V), in which the molecular rotation of the former is the greater, the isomeric 3′-alkyl enol ethers (VI) and (VII) show no consistent trend in optical rotation.

EXPERIMENTAL

M. p.s were taken in capillary tubes and are corrected. Unless otherwise stated, ultraviolet and infrared spectra were measured for solutions in ethanol and bromoform, respectively. Optical rotations refer to 0·8—1·2% solutions in acetone at 18—22°. Extracts in organic solvents were dried ($MgSO_4$) before evaporation. Aluminium oxide used for chromatography was Woelm acid alumina, of activity grade 2, obtained through L. Light Ltd., Colnbrook, Bucks.

7-*Chloro*-4,6-*dimethoxy*-3′,6′-*dimethylgrisan*-3,2′,4′-*trione* (III; R = Me).—A mixture of griseofulvic acid (II) (25·0 g.), potassium carbonate (5·1 g., 1 equiv.), methyl iodide (6·5 ml., 1·4 equiv.), acetone (140 ml.), and water (110 ml.) was heated under reflux for 4 hr. The acetone was removed under reduced pressure and the resulting solid was extracted in chloroform (3 × 150 ml.). Acidification of the aqueous phase led to the recovery of griseofulvic acid (2·9 g.), m. p. 255—256° (decomp.). The combined chloroform extracts were washed with N-sodium carbonate, the alkaline layer was acidified and extracted with chloroform, and the dried extracts were concentrated to 80 ml., giving the 3′-methyl-trione (III; R = Me) (8·1 g., 35% based on griseofulvic acid), m. p. 248—250·5°, $[\alpha]_D$ +404° (*c* 1·0 as Na salt in H_2O). The absence of a band at 860 cm.$^{-1}$ in the infrared spectrum (in Nujol) of this material indicated the absence of griseofulvic acid (II). A second crop (3·7 g.), m. p. 240—244·5°, was contaminated with griseofulvic acid.

The 4′-methyl enol ether (VII; R = R′ = Me) (0·5 g., prepared by method A as described below) in acetic acid (5·0 ml.) containing 2N-sulphuric acid (0·5 ml.) was heated on the steam-bath for 35 min. Dilution with ethyl acetate, extraction with 2N-sodium carbonate, and acidification gave the 3′-methyl-trione (III; R = Me) in an enol form, m. p. 267·5—270°, $[\alpha]_D$ +406° (*c* 1·0 as Na salt in H_2O), $\nu_{max.}$ (in Nujol) 2630 (bonded OH), 1705 (3-ketone), and 1576 cm.$^{-1}$ (bonded CO·C=C). Crystallisation from ethyl acetate–methanol gave another enol form of the 3′-methyl-trione (III; R = Me) (0·35 g., 73%), m. p. 271·5—272·5°, $[\alpha]_D$ +407° (*c* 1·0 as Na salt in H_2O), $\lambda_{max.}$ 283 mμ (ε 30,100) (1·49 × 10^{-5}M), $\lambda_{max.}$ (in 0·1N NaOH) 294 mμ (ε 61,100), $\nu_{max.}$ (in Nujol) 3300 (bonded OH), 1688 (bonded 3-ketone) and 1655 cm.$^{-1}$ (CO·C=C) (Found: C, 57·8; H, 4·9; Cl, 10·1. $C_{17}H_{17}ClO_6$ requires C, 57·9; H, 4·9; Cl, 10·1%). The infrared spectra of the two forms in tetrahydrofuran or in bromoform solution were identical.

7-*Chloro*-4,6-*dimethoxy*-3′,3′,6′-*trimethylgrisan*-3,2′,4′-*trione* (VIII; R = Me).—3′-Methylgriseofulvic acid (6·1 g.) in acetone (35 ml.) and water (25 ml.) containing potassium carbonate (1·2 g., 1 equiv.) was heated under reflux with methyl iodide (1·63 ml., 1·5 equiv.) for 4 hr. The acetone was removed *in vacuo* and the neutral fraction (3·3 g.) was isolated with ethyl acetate. This product, in acetic acid (16 ml.) containing 2N-sulphuric acid (3·3 ml.), was heated on the steam-bath for 35 min. The cooled mixture was poured into an excess of 2N-sodium carbonate, and the neutral fraction was extracted into ethyl acetate, evaporated and triturated with ether–ethanol. to give crystals (0·6 g.), m. p. 149—151°. Two crystallisations from ethanol gave the 3′,3′-*dimethyl-trione* (VIII; R = Me), double m. p. 128° and 150·5—152°, $[\alpha]_D$ +30°, $\lambda_{max.}$ 292 (ε 23,000), 324—328 mμ (ε 5500), $\nu_{max.}$ 1734 and 1706—1688 cm.$^{-1}$ (ketones) (Found: C, 58·5; H, 5·1; Cl, 9·6. $C_{18}H_{19}ClO_6$ requires C, 58·9; H, 5·2; Cl, 9·7%).

Ethylation of Griseofulvic Acid with Ethyl Iodide and Potassium Carbonate.—Griseofulvic acid (30 g.), anhydrous potassium carbonate (150 g.), and ethyl iodide (75 ml.) in anhydrous acetone (1·5 l.) were heated under reflux for 5·5 hr. The cooled and filtered mixture was evaporated *in vacuo*; the residue, in benzene (400 ml.), was washed with 2N-sodium carbonate and water and evaporated to a pale yellow foam (28·5 g.). This material and Girard's reagent P (15·0 g.) in ethanol (180 ml.) containing acetic acid (20 ml.) were heated under reflux for 45 min., cooled, poured into a solution of sodium hydrogen carbonate (1·75 l.), and extracted with ethyl acetate (4 × 300 ml.). The alkaline layer was acidified to pH 1 with 2N-hydrochloric acid, ethyl acetate (450 ml.) was added, and the mixture was stirred for 4 hr. The washed and dried ethyl acetate layer was evaporated *in vacuo*; crystallisation of the product from ethanol afforded colourless needles of 7-chloro-2′-ethoxy-4,6-dimethoxy-6′-methylgris-2′-en-3,4′-dione (IV; R = Et) (5·5 g., 17%), m. p. 206—207°, $[\alpha]_D$ +319° (*c* 0·59) (lit.,[16] m. p. 205—206°, $[\alpha]_D$ +316° in acetone).

The ethyl acetate extracts containing material not forming a Girard's P derivative were washed with water, dried, and evaporated *in vacuo* to a yellow foam (18·9 g.). Two crystallisations from ethanol gave 7-chloro-4′-ethoxy-4,6-dimethoxy-6′-methylgris-3′-en-3,2′-dione (V; R = Et) (11·9 g., 37%), m. p. 192—194°, $[\alpha]_D$ +218° (lit.,[16] m. p. 192—193°, $[\alpha]_D$ +214° in acetone). The mother-liquor from the first crystallisation was evaporated to dryness *in vacuo*, affording a yellow foam (5·9 g.) which was dissolved in benzene and adsorbed on alumina (350 g.). Elution with benzene containing 1% of ether gave a group of fractions which were combined (2·0 g.) and crystallised twice from ethanol, affording 7-*chloro*-4′-*ethoxy*-3′-*ethyl*-4,6-*dimethoxy*-6′-*methylgris*-3′-*en*-3,2′-*dione* (VII; R = R′ = Et) (0·69 g.), m. p. 185—186°, $[\alpha]_D$ +280° (Found: C, 60·7; H, 5·9; Cl, 9·0. $C_{20}H_{23}ClO_6$ requires C, 60·8; H, 5·9; Cl, 9·0%). The next two fractions (0·50 g.) were twice crystallised from ethanol, to give 7-*chloro*-2′-*ethoxy*-3′-*ethyl*-4,6-*dimethoxy*-6′-*methylgris*-2′-*en*-3,4′-*dione* (VI; R = R′ = Et) (0·17 g.), m. p. 133—139°, $[\alpha]_D$ +286° (Found: C, 60·2; H, 5·7; Cl, 9·3. $C_{20}H_{23}ClO_6$ requires C, 60·8; H, 5·9; Cl, 9·0%). Subsequent successive fractions consisted of the 4′- and the 2′-ethyl ether (V and IV; R = Et).

7-*Chloro*-3′-*ethyl*-4,6-*dimethoxy*-6′-*methylgrisan*-3,2′,4′-*trione* (III; R = Et).—A mixture (1·8 g.) of the isomeric ethyl ethers of 3′-ethylgriseofulvic acid from the previous experiment in acetic acid (9 ml.) containing 2N-sulphuric acid (1·8 ml.) was heated on the steam-bath for 45 min. The mixture was diluted with ethyl acetate, and the acid was extracted in 2N-sodium carbonate. Acidification with concentrated hydrochloric acid gave a precipitate, crystallisation of which from acetic acid gave the *trione* (III; R = Et) (0·85 g., 51%), m. p. 217—218°, $[\alpha]_D$ +267°, $\lambda_{max.}$ 232 (ε 16,100), 282 (ε 31,600), and 320 mμ (ε 6000) (2·8 × 10^{-5}M), $\nu_{max.}$ (in Nujol) 1660 (bonded ketone) and 1634 cm.$^{-1}$ (bonded CO·C=C) (Found: C, 58·8; H, 5·3; Cl, 9·7. $C_{18}H_{19}ClO_6$ requires C, 58·9; H, 5·2; Cl, 9·65%).

3′-*Allyl*-7-*chloro*-4,6-*dimethoxy*-6′-*methylgrisan*-3,2′,4′-*trione* (III; R = $CH_2{:}CH{\cdot}CH_2$).—Griseofulvic acid (II) (26·8 g.) in water (46 ml.) containing potassium hydroxide (5·2 g., 85%, 1 equiv.) and copper powder [3] (0·10 g.) was stirred at room temperature for 5 hr. with allyl bromide (8·3 ml., 1·2 equiv.). A plastic, white, solid was gradually formed. The mixture was extracted with ethyl acetate; acidification of the aqueous layer gave griseofulvic acid (0·9 g.), m. p. 248—252° (decomp.). The organic layer was washed with 2N-sodium carbonate (3 × 100 ml.), and the combined washings were freed from ethyl acetate and carefully acidified with 2N-hydrochloric acid, to give crude 3′-allylgriseofulvic acid (15·9 g.), m. p. 162—168°, $[\alpha]_D$ +220°. Attempts to crystallise this from ethanol or acetic acid were not successful, there being some decomposition to neutral products. The infrared spectrum of the crude acid indicated the presence of <5% of griseofulvic acid. An attempt to obtain the 3′-allyl-trione by hydrolysing the pure 4′-methyl enol ether (VII; R = $CH_2{:}CH{\cdot}CH_2$, R′ = Me) (prepared as described below, see Table 2) failed.

Hydrogenation of the 3′-*allyl-trione.* The crude trione (3·5 g.) in ethyl acetate (200 ml.) was shaken with a 5% palladium–charcoal (0·15 g.) in hydrogen. Uptake (196 ml., at 22°/750 mm.) was complete after 6 hr. The catalyst was filtered off and the solvent removed *in vacuo*, to give the crude 3′-propyl-trione (3·5 g.). No attempt was made to purify this product.

---

[16] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3977.

Acid hydrolysis of the 4′-methyl enol ether (VII; $R = Pr^n$, $R' = Me$) in acetic acid containing 2N-sulphuric acid and crystallisation from chloroform gave the 3′-propyl-trione (III; $R = Pr^n$), m. p. 125—130°.

Benzylation of Griseofulvic Acid.—A solution of griseofulvic acid (170 g.) in water (250 ml.) containing 85% potassium hydroxide (33·0 g., 1 equiv.) and sodium iodide (75·5 g., 1 equiv.) was heated with copper powder (6·0 g.) and benzyl bromide (86 g., 1 equiv.) on a steam-bath for 100 min., cooled, and extracted three times with ethyl acetate. Griseofulvic acid (4·0 g.), m. p. 255—258° (decomp.), was recovered from the aqueous layer. The ethyl acetate extracts (A) were washed with N-sodium carbonate, the alkaline layer was acidified with 2N-hydrochloric acid, and the product was extracted with ethyl acetate (2 l.) (B). Insoluble material at this stage was griseofulvic acid (12·0 g.). The dried extract (B) was concentrated to *ca.* 500 ml., a mixture of the 3′-benzyl-trione (III; $R = Ph{\cdot}CH_2$) and griseofulvic acid (II) (16·2 g.), m. p. 216—232°, being obtained. Further concentration gave the *3′-benzyl-trione* (76·3 g., 40%) which, recrystallised from acetic acid, had m. p. 207—209°, $[\alpha]_D$ +192°, $\lambda_{max.}$ 230 (ε 16,200), 286—287 (ε 31,200), and 323 mμ (ε 5700), $\lambda_{max.}$ (in 0·1N-NaOH) 293·5 mμ (ε 49,100), $\nu_{max.}$ (in Nujol) 3300 (bonded OH), 1678 (bonded ketone), 1654 (CO·C=C), and 702 cm.$^{-1}$ (Ph) (Found, for a fused sample: C, 64·1; H, 4·8; Cl, 8·2. $C_{23}H_{21}ClO_6$ requires C, 64·4; H, 4·9; Cl, 8·3%). This trione was also obtained by the hydrolysis of its methyl enol ethers (VI and VII; $R = Ph{\cdot}CH_2$, $R' = Me$).

Concentration of the ethyl acetate extract (A) gave prisms of *2′-benzyloxy-7-chloro-4,6-dimethoxy-6′-methylgris-2′-en-3,4′-dione* (IV; $R = Ph{\cdot}CH_2$) (9·2 g.), m. p. 204—206°, $[\alpha]_D$ +202°, $\lambda_{max.}$ 236 (ε 23,200), 291 (ε 24,000), and 322 mμ (ε 4750) (Found: C, 64·1; H, 5·1; Cl, 8·3; OMe, 14·8. $C_{23}H_{21}ClO_6$ requires C, 64·4; H, 4·9; Cl, 8·3; OMe, 14·5%). This was also isolated in 10% yield when the triethylamine salt of griseofulvic acid was alkylated with ethereal phenyldiazomethane. Acid-catalysed alkylation[3] of griseofulvic acid with benzyl alcohol in the presence of toluene-*p*-sulphonic acid gave the isomeric *4′-benzyloxy-ether* (V; $R = Ph{\cdot}CH_2$), m. p. 184°, $[\alpha]_D$ +184°, $\lambda_{max.}$ 234·5 (ε 24,500), 264 (ε 24,600), 291 (ε 23,400), and 323 mμ (ε 6100) (Found: C, 64·6; H, 4·9; Cl, 8·1; OMe, 14·4%).

The ethyl acetate (A) mother-liquors were evaporated *in vacuo* and the resulting oil (103 g.) was hydrolysed in acetic acid (1 l.) containing 2N-sulphuric acid (100 ml.) on the steam-bath for 1 hr. Griseofulvic acid (32·7 g.), m. p. 261—263°, and an unidentified acid fraction (15·1 g,; froth) were isolated together with an oily neutral fraction (41·0 g.). This material (19 g.) in benzene (100 ml.) was chromatographed on alumina (800 g.). Early fractions eluted with benzene gave benzyl acetate, b. p. 213—216° (probably formed during the hydrolysis of the benzyl ethers); elution with benzene–ether (99 : 1) gave negatively rotating fractions containing *3′,3′-dibenzyl-7-chloro-4,6-dimethoxy-6′-methylgrisan-3,2′,4′-trione* (VIII; $R = Ph{\cdot}CH_2$) (5·0 g.), m. p. 146—149·5° (from ethanol), $[\alpha]_D$ −159°, $\lambda_{max.}$ 292 mμ (ε 21,800), infl. 322 mμ (ε 5190), $\nu_{max.}$ (in Nujol) 1730, 1706, and 1685 (C=O *), 704 and 700 cm.$^{-1}$ (Ph) (Found, for a fused sample: C, 69·2; H, 5·3; Cl, 6·7. $C_{30}H_{27}ClO_6$ requires C, 69·4; H, 5·2; Cl, 6·8%).

When the benzylation was carried out on griseofulvic acid (II) (44·2 g.) for 4·5 hr. but in the absence of sodium iodide, 3′-benzylgriseofulvic acid (III; $R = Ph{\cdot}CH_2$) (21·5 g.) was obtained together with unchanged griseofulvic acid (17·3 g.). The neutral fraction (12·5 g.) yielded the 2′-benzyl ether (IV; $R = Ph{\cdot}CH_2$), (2·15 g.), m. p. 204—206°, $[\alpha]_D$ +202°, and the 3′,3′-dibenzyl-trione (VIII; $R = Ph{\cdot}CH_2$) (1·2 g.).

Hydrogenolysis of the 3′,3′-dibenzyl-trione (VIII; $R = Ph{\cdot}CH_2$). The trione (1 g.) was shaken in methanol (40 ml.) and acetic acid (10 ml.) with 5% palladium–charcoal (0·5 g.) in hydrogen for 90 min. The catalyst was removed and the acidic fraction, isolated through its sodium salt and crystallised from acetic acid, yielded the 3′-benzyl-trione (III; $R = Ph{\cdot}CH_2$) (0·58 g., 70%), m. p. 206·5—207·5°, $[\alpha]_D$ +191°.

Demethylation of 3′-benzylgriseofulvin (VI; $R = Ph{\cdot}CH_2$, $R' = Me$). A mixture of benzene (10 ml.), ether (5 ml.), and magnesium turnings (0·8 g.) was warmed and treated with iodine (4 g.) during 30 min., then refluxed until the colour of iodine disappeared, diluted to 15 ml. with benzene, and filtered in an atmosphere of nitrogen. This solution (2·15 ml.) was added dropwise to a stirred and refluxing solution of 3′-benzylgriseofulvin (1 g.) in benzene (40 ml.). A yellow precipitate was formed rapidly. After 3 hr. the mixture was cooled and treated with 0·5N-sulphuric acid (11 ml.), the yellow colour being discharged. After dilution with water (50 ml.) the product was extracted in benzene and ethyl acetate, the combined extracts were shaken

* Ketonic C=O here and elsewhere.

with N-sodium carbonate (20 ml.) and with water; the yellow colour passed into the aqueous layer. Traces of solvents were removed *in vacuo*, the aqueous solution was acidified, and the solid (0·65 g.), m. p. 142—147°, was collected and dried. Successive crystallisations from aqueous acetic acid and ethanol gave *3′-benzyl-7-chloro-4-hydroxy-6′-methylgrisan-*3,2′,4′-*trione* (IX), m. p. 143—146°; $[\alpha]_D$ +205°, $\lambda_{max.}$ (in 0·1N-NaOH) 289 (ε 42,500) and 358 mμ (ε 7800), $\nu_{max.}$ (in Nujol) 3400 and 3200 (bonded OH), 1688 (bonded C=O), 1625 (bonded CO·C=C) and 695 cm.$^{-1}$ (Ph) (Found: C, 63·3; H, 4·8; Cl, 8·4; OMe, 7·7. $C_{22}H_{19}ClO_6$ requires C, 63·7; H, 4·6; Cl, 8·5; OMe, 7·5%).

Preparation of the Ethers (VI and VII).—(A) *Action of diazoalkane on the triethylamine salt of the trione* (III). The 3′-alkyl-trione (III) (10 mmoles) in "AnalaR" acetone (80 ml.) containing redistilled triethylamine (1·54 ml., 11 mmoles) was treated at room temperature for 15 min. with an excess of the ethereal diazoalkane (generated from the alkylnitrosourea and dried over potassium hydroxide). The excess of diazoalkane was destroyed with acetic acid, and the mixture was concentrated *in vacuo*. The residue in ethyl acetate was washed with N-sodium carbonate and water, dried, and evaporated. A benzene solution of the product was chromatographed on alumina, elution being with benzene, then benzene containing an increasing proportion of ether, and finally with benzene–methanol. In some cases the development was followed by viewing the column in ultraviolet light.[10] When this technique was unsatisfactory, fractions were evaporated, triturated with ether, and characterised by m. p. and ultraviolet spectrum. Suitable fractions were combined and crystallised from ethanol.

(B) *Alkylation of the triones* (III) *with diazoalkanes in toluene.*[2] A solution or suspension of the trione (10 mmoles) (passed through a 60-mesh sieve) in toluene (150 ml.) was treated with an excess of the diazoalkane prepared from the alkylnitrosourea in toluene. After 12—24 hr. the ethers were isolated as described above.

(C) *Alkylation of the triones* (III) *with an alkyl halide and potassium carbonate.*[1] The 3′-alkyl-trione (10 mmoles) in acetone (200 ml.) containing anhydrous potassium carbonate (0·1—0·2 mole) and the alkyl halide (11 mmoles; a larger excess was used in the case of volatile halides) was heated under reflux for 16—20 hr. The filtrate obtained after cooling was concentrated *in vacuo*, and the residue in ethyl acetate was washed with 2N-sodium carbonate and water, dried, evaporated, and purified by chromatography as described above.

Isomeric *ethers* thus prepared are listed in Table 2.

TABLE 2.

Isomeric enol ethers (VI and VII).

						Found (%)			Required (%)				Yield
	R	R	M. p.	$[\alpha]_D$	Formula	C	H	Cl	C	H	Cl	Method	(%)
VI	Me	Me	166·5—170·5°	+291°	$C_{18}H_{19}ClO_6$	58·7	5·2	9·6	58·9	5·2	9·7	A †	14
VII	,,	,,	249—250	+348	,,	58·7	5·5	9·7	,,	,,	,,	,,	22
VI	Allyl	Me	140·5—142·5	+264	$C_{20}H_{21}ClO_6$	60·7	5·45	9·0	61·1	5·4	9·0	A †	12
VII	,,	,,	169—170·5	+274	,,	60·7	5·3	9·2	,,	,,	,,	,,	26
VI	Ph·CH$_2$	Me	148—150	+278	$C_{24}H_{23}ClO_6$	64·6	5·5	7·8	65·0	5·5	8·0	A	13
VII	,,	,,	150—152	+224	,,	64·8	5·3	7·8	,,	,,	,,	,,	45
VI	Ph·CH$_2$	Et	152—153	+271	$C_{25}H_{25}ClO_6$	65·4	5·4	8·2	65·7	5·5	7·8	B (C)	21 (13)
VII	,,	,,	137·5—141·5	+218	,,	65·8	5·55	7·65	,,	,,	,,	,,	27 (49)
VI	Ph·CH$_2$	Pr^n	89	+248	$C_{26}H_{27}ClO_6,H_2O$	64·0	5·7	7·6	64·0	5·7	7·6	B	13
VII	,,	,,	112—113	+222	$C_{26}H_{27}ClO_6,\frac{1}{2}H_2O$	64·9	5·9	7·75	65·1	5·9	7·75		15
VI	Ph·CH$_2$	Bu^n	—	+225	$C_{27}H_{29}ClO_6$	—	—	—	—	—	—	—	3 (4)
VII	,,	,,	152—153·5	+220	,,	66·9	6·3	6·9	66·7	6·0	7·3	A (C)	10 (22)
VII	Ph·CH$_2$	Allyl	102—103	+205	$C_{26}H_{25}ClO_6,\frac{1}{2}H_2O$	65·3	5·5	7·2	65·3	5·7	7·4	C	22
VI	Ph·CH$_2$	Br·[CH$_2$]$_3$	—	+210	$C_{26}H_{26}BrClO_6$	56·8	5·0	21·6 *	56·8	4·8	21·0 *	C	10
VII	,,	,,	145—147	+197	$C_{26}H_{26}BrClO_6,H_2O$	55·4	4·8	20·2 *	55·0	5·0	20·2 *	,,	50
VI	Pr^n	Me	115—116	+284	$C_{20}H_{23}ClO_6$	60·6	5·9	8·7	60·8	5·9	9·0	A	10
VII	,,	,,	206—207	+305	,,	61·0	6·1	9·0	,,	,,	,,	,,	25
VI	Pr^n	Pr^n	106·5—107·5	+260	$C_{22}H_{27}ClO_6$	62·7	6·3	8·1	62·5	6·4	8·4	B	15
VII	,,	,,	148—149	+282	,,	62·3	6·5	8·2	,,	,,	,,	,,	22

* Total halogen (Br + Cl). † Triones contaminated with 10—20% of griseofulvic acid were used.

*7-Chloro-*4,6-*dimethoxy-*6′-*methyl-*3′-(3-*oxobutyl*)*gris-*2′-*en-*3,4′-*dione* (VI; R = $CH_3·CO·CH_2·CH_2$) *and its Isomer* (VII).—A solution of griseofulvic acid (20·0 g.) in methanol (100 ml.) containing triethylamine (10 ml., 1·2 equiv.) was treated with methyl vinyl ketone (9·6 ml., 2 equiv.) at room temperature. The optical rotation of the solution, initially +55·2°, fell to a constant value of +23·0° in 148 hr. The mixture was poured into water (1 l.) and extracted with ether (3 × 100 ml.). The aqueous layer was acidified with 2N-hydrochloric acid, and the yellow precipitate was extracted with ethyl acetate (3 × 300 ml.). Evaporation of the washed and dried extracts gave a froth (22·6 g.), $\lambda_{\max}$ (in 0·1N-NaOH) 291·5 mμ ($E^{1\%}_{1\,\text{cm.}}$ 957), $\nu_{\max}$ (in Nujol) 1704 (C=O) and 1654 cm.$^{-1}$ (CO·C=C), which was not purified.

This acid (III; R = $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2$) in acetone (300 ml.) containing triethylamine (7·7 ml., 1 equiv.) was treated with an excess of ethereal diazomethane. After 10 min. acetic acid was added, and the product (21·0 g.; foam) was isolated in the usual way. A portion (10 g.) of this material was chromatographed on silica gel (400 g.; Hopkin and Williams Ltd.; M.F.C. grade). Elution with benzene–ethyl acetate (1 : 1) gave the *2′-methyl enol ether* (VI; R = $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2$) (1·7 g.) which, crystallised twice from ethanol (yield, 0·64 g.), had m. p. 129·5—130·5°, $[\alpha]_D$ +259°, $\lambda_{\max}$ 290·5 (ε 25,800) and 321 mμ (ε 5650), $\nu_{\max}$ 1712 (C=O) and 1670 cm.$^{-1}$ (CO·C=C) (Found: C, 59·2; H, 5·3; Cl, 8·6. $C_{21}H_{23}ClO_7$ requires C, 59·65; H, 5·5; Cl, 8·4%). Further elution gave, successively, a mixture of the isomers (VI and VII; R = $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2$) (2·3 g.) and the *4′-methyl enol ether* (VII; R = $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2$) (3·5 g.) which, crystallised twice from ethanol (yield, 1·5 g.), had m. p. 187·5—190°, $[\alpha]_D$ +286°, $\lambda_{\max}$ 230 (ε 16,750), 282 (32,000), and 320 mμ (ε 5250), $\nu_{\max}$ 1700 (C=O), and 1650 cm.$^{-1}$ (CO·C=C) (Found: C, 59·4; H, 5·35; Cl, 8·5%).

2′-Allyloxy-7-chloro-4,6-dimethoxy-6′-methylgris-2′-en-3,4′-dione (IV; R = $CH_2{:}CH{\cdot}CH_2$).—Griseofulvic acid (30 g.), anhydrous potassium carbonate (90 g.), allyl bromide (23 ml.), and "Hi-drite" ($CaSO_4$) (20 g.; grade I obtained from Hi-drite Ltd., 2, Great Winchester Street, E.C.2.) in dry acetone (1·2 l.) was heated under reflux for 3 hr. The cooled mixture was filtered and the precipitate was washed with hot acetone (250 ml.). The gum obtained by evaporation of the combined acetone filtrates was dissolved in benzene, washed with 2N-sodium carbonate, recovered *in vacuo*, and heated in ethanol (250 ml.) containing acetic acid (25 ml.) with Girard's reagent P (15 g.) under reflux for 40 min. The cooled mixture was poured into sodium hydrogen carbonate solution (1 l.) and extracted with ethyl acetate. The aqueous layer was covered with ethyl acetate, acidified with 2N-sulphuric acid, and stirred overnight. The organic extract yielded a pale yellow solid (6·5 g., 19%) which crystallised from ethanol to give the *2′-allyl ether* (IV; R = $CH_2{:}CH{\cdot}CH_2$) (4·9 g., 15%), m. p. 175—177°, $[\alpha]_D$ +294°, $\lambda_{\max}$ 235 (ε 24,000), 290·5 (ε 25,900), and 320—324 mμ (ε 6060) (Found: C, 60·0; H, 4·9; Cl, 9·1. $C_{19}H_{19}ClO_6$ requires C, 60·2; H, 5·1; Cl, 9·4%). Chromatography of the unchanged material gave a negatively rotating oil (12·3 g.), $\lambda_{\max}$ 290 mμ ($E^{1\%}_{1\,\text{cm.}}$ 600), which was thought to be the 3′,3′-diallyl-trione (VIII; R = $CH_2{:}CH{\cdot}CH_2$). Subsequent fractions yielded the *4′-enol ether* (V; R = $CH_2{:}CH{\cdot}CH_2$) (4·3 g., 13%), m. p. 153—156°, also prepared in 76% yield by the esterification of griseofulvic acid with allyl alcohol in benzene containing toluene-*p*-sulphonic acid (cf. ref. 2), m. p. 156·5—159·5°, $[\alpha]_D$ +202°, $\lambda_{\max}$ 234 (ε 23,500), 263 (ε 22,500), 291 (ε 22,000), and 324 mμ (ε 5300) (Found: C, 60·0; H, 5·2; Cl, 9·3%).

Attempted rearrangement of the 2′- and 4′-allyl ethers (IV and V; R = $CH_2{:}CH{\cdot}CH_2$). The 2′-allyl ether (2·0 g.) in dimethylaniline (20 ml.) was heated under reflux in nitrogen for 30 min. The cooled mixture was diluted with ethyl acetate (150 ml.) and washed with N-sulphuric acid, water, and dilute sodium hydrogen carbonate. Evaporation gave a pale yellow foam (1·85 g.) which, crystallised successively from ethanol and acetone, gave a *substance* (perhaps X or XI) (0·20 g., 10%), m. p. 183—185°, $[\alpha]_D$ +278°, $\lambda_{\max}$ 234·5 (ε 15,100), 289 (ε 33,600), infl. 320 mμ (ε 6550), $\nu_{\max}$ 1706 (C=O) and 1650 cm.$^{-1}$ (CO·C=C) (Found: C, 60·1; H, 5·2; Cl, 9·3. $C_{19}H_{19}ClO_6$ requires C, 60·2; H, 5·1; Cl, 9·4%). Concentration of the mother-liquors gave a mixture which was not purified.

Rearrangement of the 4′-allyloxy-ether (5·0 g.) under the same conditions gave the same product (0·25 g., 5%), identified by mixed m. p. and infrared spectra, $[\alpha]_D$ +274° (*c* 0·71), $\lambda_{\max}$ 233·5 (ε 14,700), 287·5 (ε 31,700) and infl. 317 mμ (ε 5650). A Kühn–Roth *C*-Me determination with this material gave 5·1% (theory 7·9%) compared with 2·7% (theory 4%) for griseofulvin.

GLAXO LABORATORIES LTD., GREENFORD, MIDDLESEX.

[*Received, October* 19*th*, 1961.]