302. *Griseofulvin Analogues. Part VII.*[1] *Replacements in the Aromatic Ring.*

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The two major products resulting from the reaction between griseofulvin or the 2′-chloro-derivative of griseofulvic acid and pyrrolidine are shown to be the isomeric 4,2′- and 6,2′-dipyrrolidin-1-yl derivatives. Treating the bisethylene ketal of griseofulvic acid with bases resulted in the replacement of the methoxy-group at position 4 only. These compounds were converted into analogues of griseofulvin by standard methods. Both methoxyl groups in ring A of the bisethylene ketal were replaced by methylthio-groups under basic conditions. However, griseofulvic acid salts, when treated with thiols in aqueous media under mild conditions, gave only norgriseofulvic acid. A third nucleophilic replacement was observed when the bisethylene ketal of griseofulvic acid was treated with methylmagnesium bromide, the 4-methoxy-group being replaced by a methyl group.

TREATMENT of griseofulvin (I; R = OMe) with ammonia in methanol leads to the replacement of the 2′-methoxy-group, to give griseofulvamine[2] (I; R = NH_2). We have found that methylamine readily gives the corresponding derivative (I; R = NHMe), whereas ethylamine gives only a low yield of the homologue (I; R = NHEt) and attempts to use higher aliphatic primary amines were unsuccessful, complex mixtures being obtained under forcing conditions. Similarly, though pyrrolidine readily gave the 2′-pyrrolidinyl derivative (I; R = C_4H_8N), no reaction occurred with piperidine or diethylamine even under forcing conditions. In contrast, treatment of isogriseofulvin (II; R = OMe) in methanol with a variety of amines readily gave the corresponding 4′-derivatives (see Tables 1 and 2). Some of these compounds were also obtained[3] from the 4′-chloro-compound (II; R = Cl).

We studied the products formed by dissolving 7,2′-dichloro-4,6-dimethoxy-6′-methylgris-2′-en-3,4′-dione (I; R = Cl) in pyrrolidine and leaving the solution at room temperature overnight. The mixture obtained was separated by chromatography on alumina into a less polar, pale yellow solid which showed a bright yellow fluorescence when a thin film chromatogram was viewed under ultraviolet light, and a white crystalline material, which absorbed when viewed under ultraviolet light, appearing as a brown spot on

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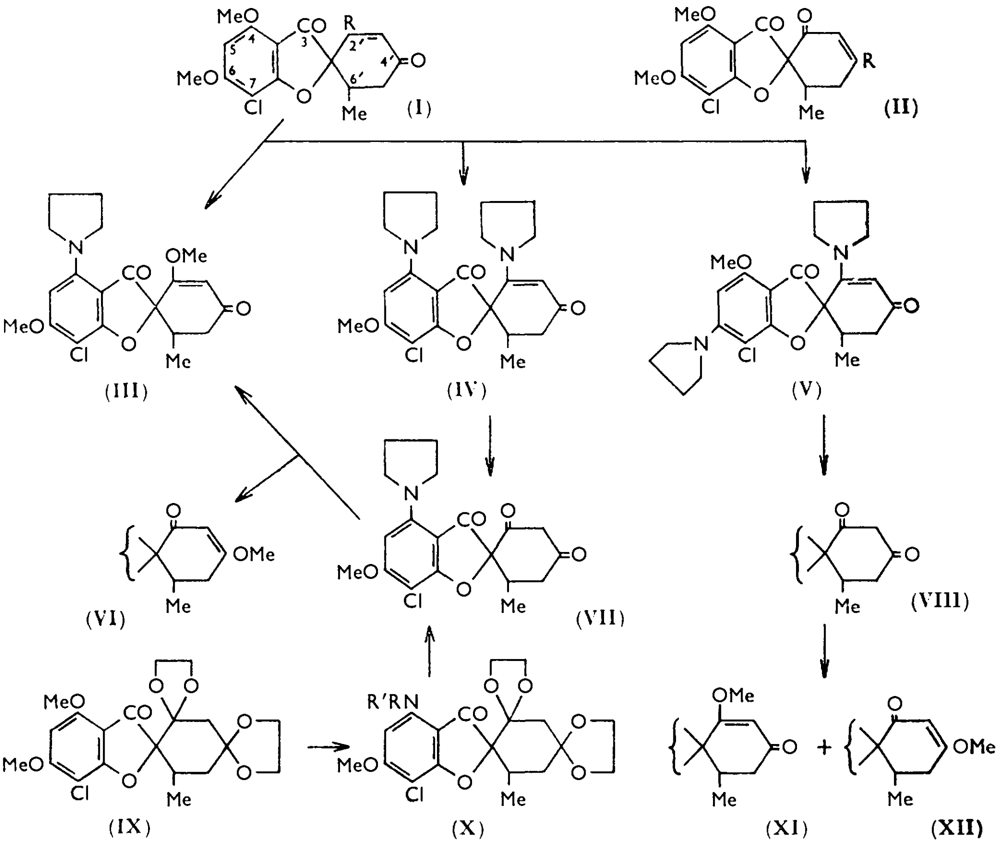
[1] Part VI, preceding paper.
[2] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.
[3] Stephenson, Walker, Warburton, and Webb, *J.*, 1962, 1282.

chromatography. Analysis suggested that they were isomers (IV and V) derived from the 2′-chloride (I; R = Cl) by replacement of one chlorine atom and one methoxy-group by pyrrolidinyl groups. Replacements of *o*- or *p*-methoxy-groups, suitably activated by an electron-withdrawing group (usually NO_2 or CN but in this instance the 3-ketone group), with amines have been previously reviewed.[4] The isomers showed absorption maxima at 376—379 and 343 mμ, respectively, suggesting, by analogy with the aminoacetophenones,[5] that the lower-melting one was formed by replacement of the 4-methoxy-group (*i.e.*, IV) and the other isomer by replacement of the 6-methoxy-group (*i.e.*, V). Support came from reactions with ethereal magnesium iodide under conditions that result in demethylation at position 4.[6] The crude product from the colourless isomer gave a strong ferric chloride test and showed the expected hydrogen bonding in its infrared spectrum: the yellow isomer gave no phenolic products.

The same isomers (IV and V) were obtained when griseofulvin was left in pyrrolidine overnight at room temperature, but their separation was complicated by the presence of the more easily eluted monopyrrolidinyl compound (III); its formation demonstrates the ease of substitution at position 4.



When the bisketal [6] (IX) of griseofulvic acid was dissolved in pyrrolidine a much slower

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[4] Bunnet and Zahler, *Chem. Rev.*, 1951, **49**, 273; Burwell, *ibid.*, 1954, **54**, 615; Wiles, *ibid.*, 1956, **56**, 329.

[5] Grammaticakis, *Bull. Soc. chim. France*, 1953, **20**, 93; Grinter, Heibronner, Godfrey, and Murrell, *Tetrahedron Letters*, 1961, 771.

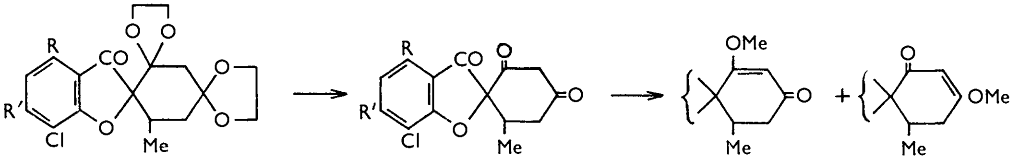
[6] Arkley, Attenburrow, Gregory, and Walker, *J.*, 1962, 1260.

reaction took place at 35°. Periodic chromatography showed the steady formation of a component with a bright blue-green fluorescence under ultraviolet light. After 10 days this component was isolated and purified by crystallisation. No appreciable amount of an isomer corresponding to (V) was detected. From the chromatographic behaviour and spectra of the product we concluded that the 4-methoxy-group of the bisketal had been replaced to give the base (X; $RR' = -[CH_2]_4-$). That the position of substitution in the bispyrrolidinyl compound (IV) and the bisketal (X; $RR' = -[CH_2]_4-$) is the same was confirmed when on acid hydrolysis each gave the same 4-pyrrolidinyl-trione (VII). Methylation of this gave a mixture of the isomers (III) and (VI) which were separated by chromatography. The more polar griseofulvin analogue (III) was identical with the compound obtained as a minor product by reaction of griseofulvin and pyrrolidine.

In a similar manner the 6,2′-bispyrrolidinyl isomer (V) was hydrolysed to the trione (VIII), whose methylation gave the isomers (XI) and (XII), which were separated by chromatography. These isomeric ethers underwent demethylation at position 4 to give phenolic products.

The 4-methoxy-group in the bisketal (IX) was also slowly replaced at room temperature by benzylamine, ethylamine, or diethylamine (the last two reactions were only studied by chromatography and ultraviolet absorption, no pure products being isolated). That the 4-methoxy-group was replaced was confirmed by the infrared spectrum of the benzyl derivative (X; $R = Ph{\cdot}CH_2$, $R' = H$) where strong hydrogen bonding between the $>NH$ group and the 3-ketone changed the frequency of the ketone group from 1696 to 1666 $cm.^{-1}$. Hydrogenolysis of the benzylamino-derivative gave the 4-amino-derivative (X; $R = R' = H$) which again showed hydrogen bonding in the infrared spectrum. Preliminary attempts to diazotise this amine and introduce halogens or a hydroxy-group at position 4 were unsuccessful.

Treatment of the bisketal (XIII; $R = R' = OMe$) with sodium methyl sulphide in t-butyl alcohol containing sodium t-butoxide gave, after chromatography, the bisalkylthio-derivative (XIII; $R = R' = SMe$). Acid hydrolysis to the griseofulvic acid analogue (XIV; $R = R' = SMe$) and subsequent methylation gave the isomeric ethers (XV and XVI; $R = R' = SMe$).

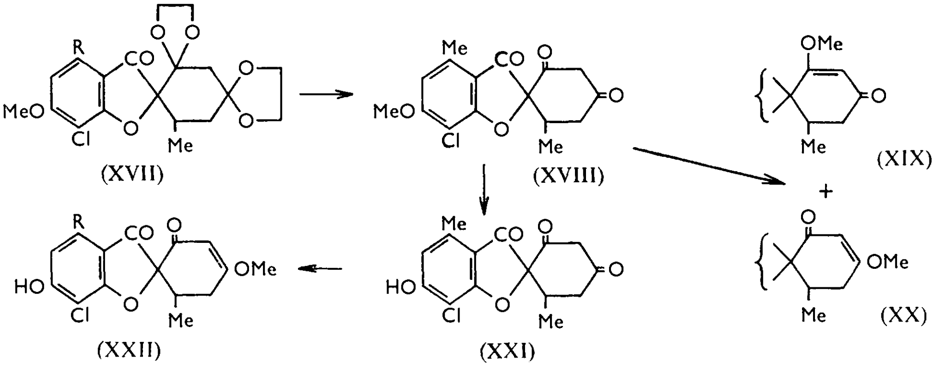


(XIII) (XIV) (XV) (XVI)

An unexpected result was obtained on treating griseofulvic acid (XIV; $R = R' = OMe$) in dimethylacetamide containing triethylamine and an excess of potassium hydroxide (3 mol.; no reaction with 1 mol.) with 4 mol. of methanethiol or ethanethiol. The optical rotation of the mixture at room temperature reached a maximum in 4—5 days and then isolation of the acidic fraction gave norgriseofulvic acid (XIV; $R = OMe$, $R' = OH$), in 64% yield, identified by comparison with an authentic specimen.[2,6] These mild conditions provide a much better yield of this important intermediate than does the previously described alkaline hydrolysis with the accompanying rearranged by-products. It is uncertain whether or not this reaction proceeds through the 6-alkylthio-analogue of griseofulvic acid with later replacement of the thio-group by hydroxyl. The reaction did not occur in purely aqueous solution. In view of the success [7] in replacing the aromatic methoxy-groups with ethoxy-groups in griseofulvic acid by means of 0·5N-sodium ethoxide, we treated griseofulvic acid under essentially anhydrous conditions with methanethiol in

[7] Macmillan, *J.*, 1959, 1823.

the presence of sodium with tetrahydrofuran or t-butyl alcohol as solvent, but these experiments also led to norgriseofulvic acid (XIV; R = OMe, R′ = OH), albeit in low yields.



(XVII) (XVIII) (XIX) (XX) (XXII) (XXI)

The third type of nucleophilic exchange reaction in ring A of griseofulvin was the replacement of an aromatic methoxy-group with an alkyl group by means of a Grignard reagent. Several examples of such replacements *ortho* and *para* to a hindred ketone have been described.[4,8-10] Treating the bisketal of griseofulvic acid (XVII; R = OMe) under mild conditions with methylmagnesium bromide in ether gave a new bisketal (XVII; R = Me) contaminated with some starting material. This product was not purified, but was hydrolysed to the corresponding triketone (XVIII), which gave a methoxyl analysis approximating to one group. Methylation of the crude acid and chromatography gave the ethers (XIX) and (XX) containing a methyl group attached at position 4. Later chromatographic fractions contained griseofulvin (I; R = OMe) and its isomer (II; R = OMe) arising from some unchanged bisketal (XVII; R = OMe); no sign of products was noted in which the 6-methoxy-group was replaced.

The structures of these 4-methyl compounds rest on alkaline hydrolysis of the trione (XVIII) or its methyl ethers (XIX and XX) under conditions similar to those used to prepare norgriseofulvic acid.[6] The methoxyl value and ultraviolet absorption suggested that the acidic product was a mixture of the trione (XVIII) and the phenolic trione (XXI); methylation under acid-catalysed conditions [11] gave, as phenolic component, 7-chloro-6-hydroxy-4′-methoxy-4,6′-dimethylgris-3′-en-3,2′-dione (XXII; R = Me), whose ultraviolet spectra showed a bathochromic shift from 286·5 to 334 mμ with a concomitant increase in intensity on changing from acid to alkaline solution similar to that shown [2] by the compound (XXII; R = OMe) and related phenols. The neutral product of this methylation was the 4′-ether (XX) and arises from the triketone (XVIII) remaining in the unpurified acid (XXI). Treating the griseofulvin analogues (XIX) or (XX) with ethereal magnesium iodide failed to provide phenolic products, in accordance with the absence of a 4-methoxyl group.

EXPERIMENTAL

The general directions of Part VI [1] apply. Reaction mixtures were often assessed by thin-layer chromatography with Kieselgel G (E. Merck A.G., Darmstadt, Germany) as the absorbent spread on glass plates (5 × 20 cm., or 20 × 20 cm.); [12] 1 : 1 benzene–ethyl acetate was a satisfactory mobile phase and components were located by their fluorescence under ultraviolet light.

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[8] Gaertner, *Chem. Rev.*, 1949, **45**, 493; Kharasch and Reinmuth, " Grignard Reactions of Non-metallic Substances," Constable and Co., London, 1954, p. 231 *et seq.*

[9] Fuson and Shealy, *J. Org. Chem.*, 1951, **16**, 643; Fuson and Friedlander, *J. Amer. Chem. Soc.*, 1953, **75**, 5410.

[10] Fuson and Mehm Tin Mon, *J. Org. Chem.*, 1961, **26**, 756.

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

[12] Stahl, *Chem.-Ztg.*, 1958, **82**, 323; *Angew. Chem.*, 1961, **73**, 646.

Replacement of the 2'-Methoxy-group of Griseofulvin (I; R = OMe) *by Amines.*—Table 1 summarises the yields and properties of *products* obtained by treating suspensions of griseofulvin in methanol with four bases at room temperature for 24—48 hr. (except the pyrrolidine derivative which was formed by heating the mixture under reflux for 1 hr.). The reaction mixtures were evaporated *in vacuo* and the residues were crystallised from methanol or ethyl acetate.

TABLE 1.

Griseofulvamine (I; R = NH_2) and its homologues.

R	Yield (%)	M. p.	$[\alpha]_D$	$\lambda_{max.}$ † ($10^{-3}\varepsilon$)
NH_2 *	71	255—257°	+554°	287·5 (46·9)
MeNH	45	275—278	+571	287 (49·0)
EtNH	19	223·5—225·5	+517	287 (52·2)
C_4H_8N	40	268—269	+424	290 (43·8)

R	Found (%) C	H	N	Cl	Formula	Required (%) C	H	N	Cl
NH_2 *	—	—	—	—	$C_{16}H_{16}ClNO_5,H_2O$	—	—	—	—
MeNH	57·9	5·3	4·0	10·2	$C_{17}H_{18}ClNO_5$	58·0	5·2	4·0	10·1
EtNH	57·6	5·5	4·0	9·7	$C_{18}H_{20}ClNO_5,H_2O$	58·0	5·7	3·8	9·5
C_4H_8N	61·6	5·7	3·5	—	$C_{20}H_{22}ClNO_5$	61·3	5·7	3·6	—

* See also Grove *et al.*[2] The *N*-acetyl derivative has m. p. 253·5—256·5°, $[\alpha]_D$ +474°. † These spectra also show $\lambda_{max.}$ 235—237 (ε 13,400—14,400) and $\lambda_{infl.}$ ~322 mμ (ε ~6500).

TABLE 2.

Isogriseofulvamine (II; R = NH_2) and its homologues.

R	Time (hr.)	Temp.	Yield (%)	M. p.	$[\alpha]_D$	$\lambda_{max.}$ ($10^{-3}\varepsilon$)
NH_2	1·5	*ca.* 20°	89	321—322°	+359° (MeOH)	290 (51·0)
NHMe	24	*ca.* 20	67	288—294	+256 (pyridine)	290 (53·6)
$NHBu^n$	2	B. p.	58	192—193	+238	291 (49·5)
Et_2N	20	,,	52	283—286	+357	294 (45·5)
C_4H_8N	1	,,	88	251—252	+314	294·5 (53·7)
$C_5H_{10}N$	4·5	,,	82	190—194	+416	295 (45·5)
OC_4H_8N	2·5	,,	87	251—255	+379	294 (48·6)
$Et_2N{\cdot}CH_2{\cdot}CH_2{\cdot}NMe$	5	,,	75	192—195	+313	294 (54·1)
$OC_4H_8N{\cdot}CH_2CH_2{\cdot}NH,HCl$	3	,,	72	274—278	+266	290·5 (—)

R	Found (%) C	H	N	Cl	Formula	Requires (%) C	H	N	Cl
NH_2	54·9	5·2	3·8	9·9	$C_{16}H_{16}ClNO_5,CH_3{\cdot}OH$	55·2	5·5	3·8	9·6
NHMe	58·1	5·5	4·0	10·2	$C_{17}H_{18}ClNO_5$	58·0	5·2	4·0	10·1
$NHBu^n$	60·5	6·5	3·5	9·3	$C_{20}H_{24}ClNO_5$	61·0	6·2	3·6	9·0
Et_2N	60·3	6·0	3·3	9·0	$C_{20}H_{24}ClNO_5$	61·0	6·2	3·6	9·0
C_4H_8N	61·0	6·2	3·2	—	$C_{20}H_{22}ClNO_5$	61·3	5·7	3·6	—
$C_5H_{10}N$	62·0	6·3	3·3	8·7	$C_{21}H_{24}ClNO_5$	62·1	6·0	3·5	8·7
OC_4H_8N	59·4	5·6	3·2	8·7	$C_{20}H_{22}ClNO_6$	58·9	5·4	3·4	8·7
$Et_2N{\cdot}CH_2{\cdot}CH_2{\cdot}NMe$	61·4	7·0	6·0	7·9	$C_{23}H_{31}ClN_2O_5$	61·3	6·9	6·2	7·9
$OC_4H_8N{\cdot}CH_2{\cdot}CH_2{\cdot}NH,HCl$	54·2	6·1	5·4	14·1	$C_{22}H_{28}Cl_2N_2O_6$	54·2	5·8	5·7	14·5

Replacement of the 4'-Methoxy-group of Isogriseofulvin (II; R = OMe) *by Amines.*—Table 2 summarises the conditions used and the properties of the *products* when isogriseofulvin was treated with primary and secondary bases. The products either crystallised from the reaction mixtures or were isolated by concentration *in vacuo*, trituration with ether, and crystallisation from ethanol. The 4'-(2-morpholinoethylamino)-derivative was isolated as the sparingly soluble hydrochloride by shaking an ethyl acetate solution of the crude base with dilute hydrochloric acid and adjusting the aqueous layer to pH 5.

7-*Chloro*-6-*methoxy*-6'-*methyl*-4,2'-*di*(*pyrrolidin*-1-*yl*)*gris*-2'-*en*-3,4'-*dione* (IV) *and* 7-*Chloro*-4-*methoxy*-6'-*methyl*-6,2'-*di*(*pyrrolidin*-1-*yl*)*gris*-2'-*en*-3,4'-*dione* (V).—(*a*) *From* 7,2'-*dichloro*-4,6-*dimethoxy*-6'-*methylgris*-2'-*en*-3,4'-*dione* (I; R = Cl). The enol chloride[3] (8 g.) was dissolved in pyrrolidine (80 ml.) with the evolution of some heat. After being kept at room temperature overnight the mixture was poured into an excess of dilute hydrochloric acid and extracted with ethyl acetate (3 × 250 ml.). The extracts were washed with water and aqueous sodium carbonate, dried, and evaporated to a yellow foam (5·1 g.). Chromatography of a benzene solution on alumina (500 g.; Grade H; methanol-washed and dried at 150° for 3 hr.) and elution with benzene gave a pale yellow component (2·6 g.) (R_F 0·28, yellow fluorescent spot under ultraviolet light) which was crystallised twice from ethanol–ether to give the *4,2'-dipyrrolidinyl compound* (IV) (1·1 g.), m. p. 236—237°, $[\alpha]_D$ +353°, $\lambda_{max.}$ 252 (ε 30,800), 295 (ε 35,100), and 376—379 mμ (ε 11,500), $\nu_{max.}$ 1680 (bonded C=O)* and 1612 (bonded CO·C=C) (Found: C, 62·1; H, 6·3; Cl, 8·3; N, 5·6. $C_{23}H_{27}ClN_2O_4,H_2O$ requires C, 61·6; H, 6·1; Cl, 7·9; N, 6·2%). When treated with magnesium iodide in ether [6] this isomer did not give a phenol.

The second component was eluted with benzene–ethyl acetate (9 : 1) as a foam (2·1 g.) (R_F 0·21, dark brown spot under ultraviolet light). It was crystallised from ethanol to give colourless needles of the *6,2'-dipyrrolidinyl isomer* (V) (1·3 g.), m. p. 252—253°, $[\alpha]_D$ +394°, $\lambda_{max.}$ 265 (ε 10,400) and 343 mμ (ε 45,000), $\nu_{max.}$ 1690 (C=O) and 1610 cm.$^{-1}$ (bonded CO·C=C) (Found: C, 61·8; H, 6·4; Cl, 8·0; N, 5·8; OMe, 7·2. $C_{23}H_{27}ClN_2O_4,H_2O$ requires C, 61·6; H, 6·1; Cl, 7·9; N, 6·2; OMe, 6·9%). Demethylation of this product with magnesium iodide–ether [6] gave a phenol (positive ferric chloride test and infrared evidence) which was not further characterised.

(*b*) *From griseofulvin* (I; R = OMe). Griseofulvin (20 g.) was dissolved in warm pyrrolidine (150 ml.) and left overnight at room temperature. The mixture was treated as above and the product (22 g.) in benzene was purified by chromatography to give (i) 7-*chloro*-6,2'-*dimethoxy*-6'-*methyl*-4-(*pyrrolidin*-1-*yl*)*gris*-2'-*en*-3,4'-*dione* (III) (0·2 g.), m. p. 226—228°, $\lambda_{max.}$ 249 (ε 40,500), 296 (ε 14,100), and 375 mμ (ε 10,000), identical (infrared spectra and chromatography) with a specimen described below, (ii) the 4,2'-dipyrrolidinyl compound (IV) (2·0 g.), m. p. 226—231°, $[\alpha]_D$ +345°, $\lambda_{max.}$ 252 (ε 29,300), 295 (ε 34,000), and 379 mμ (ε 11,200), and (iii) its 6,2'-pyrrolidinyl isomer (V) (2·2 g.), m. p. 246—249°, $[\alpha]_D$ +403°, $\lambda_{max.}$ 265 (ε 11,900) and 344 mμ (ε 51,000). The infrared spectra of these isomers were identical with those described above.

7-*Chloro*-2',4'-*bisethylenedioxy*-6-*methoxy*-6'-*methyl*-4-(*pyrrolidin*-1-*yl*)*grisan*-3-*one* (X; RR' = $-[CH_2]_4-$).—The 2',4'-bisketal [6] (IX) (10 g.) was dissolved in pyrrolidine (40 ml.; redistilled) with warming. The mixture was left for 10 days at *ca.* 35°. The product was isolated as described above and purified by two crystallisations from ethyl acetate, to give the *compound* (X; RR' = $-[CH_2]_4-$) (5·2 g., 54%), m. p. 271—274°, $[\alpha]_D$ −191°, $\lambda_{max.}$ 246·5 (ε 26,000), 294 (ε 11,700), and 365—368 mμ (ε 9300), $\nu_{max.}$ 1684 cm.$^{-1}$ (C=O) (Found: C, 59·0; H, 6·1; Cl, 7·6; N, 3·0. $C_{23}H_{28}ClNO_7$ requires C, 59·3; H, 6·1; Cl, 7·6; N, 3·0%).

7-*Chloro*-6-*methoxy*-6'-*methyl*-4-(*pyrrolidin*-1-*yl*)*grisan*-3,2',4'-*trione* (VII).—(*a*) *From* 7-*chloro*-6-*methoxy*-6'-*methyl*-4,2'-*di*(*pyrrolidin*-1-*yl*)*gris*-2'-*en*-3,4'-*dione* (IV). A solution of the 4,2'-dipyrrolidinyl derivative (1·0 g.) in acetic acid (6 ml.) containing 2N-sulphuric acid (1 ml.) was heated on the water-bath for 1 hr. The mixture was diluted with water (200 ml.), and the yellow precipitate was isolated as a foam (0·9 g.) with ethyl acetate. This product (0·66 g.), which contained some neutral material, was dissolved in ethyl acetate and the acidic component was extracted with 2N-sodium carbonate solution. Acidification of the alkaline layer and extraction with ethyl acetate gave the crude acid (0·35 g.). Two crystallisations from ethanol gave the 4-(*pyrrolidin*-1-*yl*)-*triketone* (VII) (0·1 g.), m. p. 247—250°, $\lambda_{max.}$ (in 0·1N-NaOH) 248 (ε 30,200), 287 (ε 30,900), and 384 mμ (ε 11,200), $\nu_{max.}$ 1748 and 1720 (ketones), 1675 cm.$^{-1}$ (CO·C=C) (Found: C, 60·0; H, 5·7; Cl, 9·5; N, 3·2. $C_{19}H_{20}ClNO_5$ requires C, 60·4; H, 5·3; Cl, 9·4; N, 3·7%).

(*b*) *From the bisethylenedioxy-compound* (X; RR' = $-[CH_2]_4-$).—The 4-pyrrolidinyl-bisketal (5·2 g.) was refluxed in methanol (400 ml.) containing 2N-hydrochloric acid (60 ml.) and water (40 ml.) for 4·5 hr. The mixture was concentrated *in vacuo* to *ca.* 200 ml. and the resulting white solid was collected and dried (3·4 g.; m. p. 229—232°). A second crop (0·7 g.) was also obtained. These materials were combined and shaken with ethyl acetate and 2N-sodium carbonate. The aqueous layer was separated and acidified with 2N-hydrochloric acid, and the product was purified as described above, to give the 4-pyrrolidinyl-triketone (VII) (2·5 g., 61%), m. p. 252—254°, identified by comparison of infrared spectra with that of the authentic sample. The neutral product (1·4 g.) from this reaction was isolated from the ethyl acetate layer. Thin-film chromatography showed the presence of three components, none of which corresponded to the starting material.

* Ketonic C=O here and elsewhere.

7-Chloro-6,2′-dimethoxy-6′-methyl-4-(pyrrolidin-1-yl)gris-2′-en-3,4′-dione (III) *and 7-Chloro-6,4′-dimethoxy-6′-methyl-4-(pyrrolidin-1-yl)gris-3′-en-3,2′-dione* (VI).—The triketone (VII) (2·63 g.), suspended in acetone (300 ml.), was treated slowly, with stirring, at room temperature with an excess of ethereal diazomethane. The clear yellow solution was left for 15 min., then the excess of diazomethane was destroyed with acetic acid. The solution was evaporated *in vacuo* to a foam which was dissolved in ethyl acetate and washed with a solution of sodium hydrogen carbonate. The dried organic layer was evaporated to a foam (2·1 g.) which showed two well-separated components on a thin-layer chromatogram. No material was recovered by acidifying the alkaline layer. The product in benzene (20 ml.) was purified by chromatography on alumina (100 g.), the separation being followed by thin-layer chromatography. The less polar component was isolated by elution with benzene containing 5% v/v of ethyl acetate; trituration of combined fractions, and crystallisation from ethanol, gave the *6,4′-dimethoxy-4-pyrrolidinyl compound* (VI) (0·5 g.), m. p. 185—187°, $[\alpha]_D$ +212°, $\lambda_{max.}$ 250 (ε 42,600), 296 (ε 11,900), and 412 mμ (ε 10,400), $\nu_{max.}$ 1676 (C=O) and 1664 cm.$^{-1}$ (CO·C=C) (Found: C, 61·4; H, 6·0; Cl, 9·1; N, 3·2. $C_{20}H_{22}ClNO_5$ requires C, 61·3; H, 5·7; Cl, 9·1; N, 3·6%). Elution with 9 : 1 benzene–ethyl acetate provided the second component which was triturated with ether and crystallised from ethanol to give the *isomer* (III) (0·5 g.), m. p. 228—230°, $[\alpha]_D$ +292°, $\lambda_{max.}$ 250 (ε 40,000), 296 (ε 13,550), and 378 mμ (ε 10,100), $\nu_{max.}$ 1684 (C=O) and 1660 cm.$^{-1}$ (CO·C=C) (Found: C, 61·1; H, 6·0; Cl, 9·1; N, 3·5%).

7-Chloro-4-methoxy-6′-methyl-6-(pyrrolidin-1-yl)grisan-2′,3,4′-trione (VIII).—The 6,2′-dipyrrolidinyl derivative (V) (1·0 g.) in acetic acid (6 ml.) was heated with 2N-sulphuric acid (1 ml.) on the water-bath for 1 hr., then poured into water, and the product was isolated with ethyl acetate. Concentration of the dried extract gave a slightly yellow solid (0·2 g.), m. p. 236—239°, which was crystallised from ethanol to give the *triketone* (VIII) (0·18 g.), m. p. 239—241°, $[\alpha]_D$ +258° (*c* 0·7 in 2N-Na_2CO_3), $\lambda_{max.}$ 274 (ε 20,900) and 348 mμ (ε 37,200), $\nu_{max.}$ 1746 and 1718 (ketones) and 1680 cm.$^{-1}$ (CO·C=C) (Found: C, 60·4; H, 5·3; Cl, 9·4; N, 4·1. $C_{19}H_{20}ClNO_5$ requires C, 60·4; H, 5·3; Cl, 9·4; N, 3·7%). A second crop (0·25 g.), m. p. 225°, was also obtained.

7-Chloro-4,2′-dimethoxy-6′-methyl-6-(pyrrolidin-1-yl)gris-2′-en-3,4′-dione (XI) *and 7-Chloro-4,4′-dimethoxy-6′-methyl-6-(pyrrolidin-1-yl)gris-3′-en-3,2′-dione* (XII).—The 6-pyrrolidinyl-triketone (VIII) (1·07 g.) was dissolved in acetone (35 ml.) containing triethylamine (0·3 ml.) and treated with an excess of ethereal diazomethane (brownish precipitate). After 1 hr. at room temperature the excess of diazomethane was destroyed with acetic acid. The product was isolated in the usual manner as a pale yellow foam (0·66 g.). This and a similar product (total, 1·54 g.) were dissolved in benzene (30 ml.), filtered from traces of solid material, and chromatographed on alumina (100 g.). Elution was with 19 : 1 benzene–ethyl acetate, the separation being followed by thin-layer chromatography. The first group of fractions was combined, evaporated, triturated with ether, and filtered to give the *4′-ether* (XII) as a yellow solid (0·23 g.), m. p. 220—222° raised on crystallisation from ethanol to 225—226°, $\lambda_{max.}$ 254 (ε 22,800) and 345 mμ (ε 38,800), $\nu_{max.}$ 1670 (C=O) and 1660 cm.$^{-1}$ (CO·C=C) (Found: C, 61·2; H, 5·7; Cl, 8·9; N, 3·8. $C_{20}H_{22}ClNO_5$ requires C, 61·3; H, 5·7; Cl, 9·1; N, 3·6%). Further elution with 9 : 1 benzene–ethyl acetate provided the *2′-ether* (XI) (0·14 g.), m. p. 218—219°, $[\alpha]_D$ +357°, $\lambda_{max.}$ 252 (ε 21,200) and 342 mμ (ε 42,400), $\nu_{max.}$ 1692 (C=O) and 1654 cm.$^{-1}$ (CO·C=C) (Found: C, 60·1; H, 5·8; Cl, 8·8; N, 3·7. $C_{20}H_{22}ClNO_5,\frac{1}{2}H_2O$ requires C, 59·9; H, 5·8; Cl, 8·8; N, 3·5%). The 4′-ether (XII) was demethylated with magnesium iodide–ether to a phenol (purple ⟶ green colour with ferric chloride) which was not fully characterised.

4-Benzylamino-7-chloro-2′,4′-bisethylenedioxy-6-methoxy-6′-methylgrisan-3-one (X; R = CH_2Ph, R′ = H).—The bisketal (IX) (3·0 g.) in benzylamine (100 ml.) was kept at 35°. Aliquot parts, taken after 1, 2, and 16 days, were poured into an excess of 2N-hydrochloric acid; ethyl acetate extracts run on thin-layer chromatoplates showed the presence of a less polar component (bright blue-green fluorescence under ultraviolet light) and starting material (blue fluoresence). The bulk of the mixture was worked up after 3½ days by pouring it into water, acidification to pH ~6, and extraction with ethyl acetate. The organic layer was washed with aqueous sodium hydrogen carbonate, dried, and evaporated to a yellow foam (2·6 g.) This material in benzene (30 ml.) was fractionated on alumina (250 g.), the separation being followed by thin-layer chromatography. The group of fractions containing the least polar component was combined (0·43 g.) and crystallised from ether, giving the *4-benzylamino-compound* (X; R = CH_2Ph, R′ = H) (0·18 g.), m. p. 191—193° (from acetone–hexane), $[\alpha]_D$ −146°, $\lambda_{max.}$ 239 (ε 25,100), 247—250 (infl.) (ε 21,300), 284 (infl.) (ε 12,300), 293 (ε 17,250), and 361 mμ (ε 11,000), $\nu_{max.}$ 1666 cm.$^{-1}$ (bonded C=O) (Found: C, 62·0; H, 5·8; Cl, 7·1; N, 2·8. $C_{26}H_{23}ClNO_7$ requires C, 62·2; H, 5·6; Cl, 7·1; N, 2·8%).

4-*Amino*-7-*chloro*-2′,4′-*bisethylenedioxy*-6-*methoxy*-6′-*methylgrisan*-3-*one* (X; R = R′ = H).—The 4-benzylamino-derivative (X; R = CH_2Ph, R′ = H) (5·0 g.) in ethyl acetate (225 ml.) and ethanol (225 ml.) was shaken with hydrogen in the presence of 5% palladium–carbon (0·75 g.). Uptake of hydrogen became very slow after 125 ml. had been absorbed in *ca.* 2 hr. Acetic acid (150 ml.) was added and shaking was continued for a total of 20 hr. but no more hydrogen was absorbed. The catalyst was removed and the filtrate was concentrated to *ca.* 100 ml. and poured into an excess of 2N-sodium carbonate. The product, isolated as a foam (4·4 g.), showed the presence of starting material on thin-film chromatography. Further hydrogenation in ethanol–acetic acid (1 : 1; 200 ml.) and isolation as described above gave the crude amine (3·9 g.). Trituration with ether and two crystallisations from methanol gave the *amine* (X; R = R′ = H) (1·86 g., 45%), m. p. 248—249°, $\lambda_{max.}$ 224 (ε 21,600), 247·5 (ε 13,800), 289 (ε 18,600), and 355 mμ (ε 7200), $\nu_{max.}$ 1682 (C=O), 3500 and 3380 cm.$^{-1}$ (NH_2) (Found: C, 55·8; H, 5·4; Cl, 8·4; N, 3·3. $C_{19}H_{22}ClNO_7$ requires C, 55·4; H, 5·4; Cl, 8·6; N, 3·4%). Acetylation of the amine (1·8 g.) in pyridine (20 ml.) containing acetic anhydride (10 ml.) on the steam-bath for 20 hr. gave a buff product (1·7 g.), thin film chromatography of which showed the presence of a small proportion of the starting material. Crystallisation (charcoal) from ethanol gave 4-*acetamido*-7-*chloro*-2′,4′-*bisethylenedioxy*-6-*methoxy*-6′-*methylgrisan*-3-*one* (X; R = Ac, R′ = H) (0·52 g., 26%), m. p. 258—260°, $[\alpha]_D$ −118°, $\lambda_{max.}$ 241 (ε 27,250), λ (infl.) 245 (ε 26,500), λ (infl.) 291 (ε 17,250), $\lambda_{max.}$ 300 (ε 21,500), 335 (ε 7170), and 344 mμ (ε 7180), $\nu_{max.}$ 3350 (NH), 1702 (C=O), 1672, and 1528 cm.$^{-1}$ (CO·NH) (Found: C, 55·0; H, 5·4; Cl, 8·4; N, 3·0. $C_{21}H_{24}ClNO_8$ requires C, 55·6; H, 5·3; Cl, 7·8; N, 3·1%).

7-*Chloro*-2′,4′-*bisethylenedioxy*-6′-*methyl*-4,6-*dimethylthiogrisan*-3-*one* (XIII; R = SMe).—To sodium wire (0·92 g., 40 mmoles), partially dissolved in dry redistilled t-butyl alcohol (100 ml.), was added methanethiol (2·2 ml., 1·9 g., 40 mmoles), and the mixture was warmed to aid dissolution of the sodium. The resulting colourless solution was treated with a suspension of the bisketal (XIII; R = R′ = OMe) (4·3 g., 10 mmoles) in t-butyl alcohol (25 ml.) to give a clear yellow solution which was heated under reflux for 5 hr. A precipitate appeared after *ca.* 30 min. but was not investigated. The mixture was acidified with 2N-hydrochloric acid, the excess of methanethiol was removed *in vacuo* and destroyed by passage through saturated aqueous potassium permanganate, and then the solid was extracted into ethyl acetate, to yield a yellow foam (3·3 g.). This product, redissolved in ethyl acetate (100 ml.), was washed with 2N-sodium carbonate and then obtained as a solid (1·6 g.), m. p. 216—223° (Found: S, 10·1%). Acidification of the alkaline layer gave a solid which was collected and dried (1·3 g.; m. p. 160—165°); this was not investigated. The neutral material, in benzene (50 ml.), was chromatographed on alumina (70 g.; Spence's grade H, methanol-washed). Elution with benzene and crystallisation from ethyl acetate gave the *bisalkylthio-derivative* (XIII; R = R′ = SMe) (0·42 g.), m. p. 243—245°, $[\alpha]_D$ −132°, $\lambda_{max.}$ 257·5 (ε 17,300), 277·5 (ε 5000), 321 (ε 20,200), and 355 mμ (ε 5700), $\nu_{max.}$ 1694 cm.$^{-1}$ (C=O) (Found: C, 52·1; H, 5·3; Cl, 7·9; S, 13·4. $C_{20}H_{23}ClO_6S_2$ requires C, 52·3; H, 4·9; Cl, 7·7; S, 14·0%). A similar experiment on a 50-g. scale gave a 12% yield of the product (XIII; R = R′ = SMe).

7-*Chloro*-6′-*methyl*-4,6-*dimethylthiogrisan*-3,2′,4′-*trione* (XIV; R = R′ = SMe).—The thioketal (XIII; R = R′ = SMe) (4·5 g.) was heated in acetic acid (30 ml.) containing 2N-sulphuric acid (4 ml.) under reflux for 45 min. A yellow precipitate began to separate after 30 min. After cooling, the pale yellow solid *triketone* (XIV; R = R′ = SMe) (3·5 g., 94%) was collected; it had m. p. 248—250°, $[\alpha]_D$ +439° (*c* 1·4 in 2N-Na_2CO_3), $\lambda_{max.}$ (in 0·1N-NaOH) 262 (ε 26,000), 277 (ε 28,200), 329 (ε 25,700) and λ (infl.) 370 mμ (ε 7350), $\nu_{max.}$ 1742 and 1690 (ketones), and 1648 cm.$^{-1}$ (CO·C=C) (Found: C, 51·7; H, 4·1; Cl, 9·3; S, 17·2. $C_{16}H_{15}ClO_4S_2$ requires C, 51·8; H, 4·1; Cl, 9·6; S, 17·3%).

7-*Chloro*-2′-*methoxy*-6′-*methyl*-4,6-*dimethylthiogris*-2′-*en*-3,4′-*dione* (XV; R = R′ = SMe) *and* 7-*chloro*-4′-*methoxy*-6′-*methyl*-4,6-*dimethylthiogris*-3′-*en*-3,2′-*dione* (XVI; R = R′ = SMe).—The triketone (XIV; R = R′ = SMe) (3·3 g.) in acetone (500 ml.) was treated during 20 min. with ethereal diazomethane until a yellow colour persisted. After 30 min. at room temperature acetic acid was added and the neutral product (3·0 g.) was isolated in the usual way. This mixture in benzene (30 ml.) was absorbed on alumina (150 g.) and eluted with 19 : 1 benzene–ethyl acetate. All fractions were submitted to thin-film chromatography and appropriate fractions were combined and triturated with ether, giving the pale yellow *4'-methyl ether* (XVI; R = R' = SMe) (1·12 g.), m. p. 161—163° (from EtOH), $[\alpha]_D$ +245°, $\lambda_{max.}$ 254 (ε 34,400), 326 (ε 26,400), and 370 mμ (ε 7250), $\nu_{max.}$ 1693 (C=O) and 1660 cm.$^{-1}$ (CO·C=C) (Found: C, 52·4; H, 4·5; Cl, 8·7; S, 16·3. $C_{17}H_{17}ClO_4S_2$ requires C, 53·1; H, 4·5; Cl, 9·2; S, 16·7%). Further elution gave a mixture of the two isomers and then a series of fractions from which the *2'-ether* (XV; R = R' = SMe) (0·43 g.) was isolated, having m. p. 202—203° (from ethanol), $[\alpha]_D$ +342°, $\lambda_{max.}$ 252 (ε 30,800), 326 (ε 27,200), and 371 mμ (ε 7800), $\nu_{max.}$ 1700 (C=O) and 1655 cm.$^{-1}$ (CO·C=C) (Found: C, 53·7; H, 4·2; Cl, 9·2; S, 16·45%).

Action of Methanethiol on Griseofulvic Acid (XIV; R = R' = OMe) *in the Presence of an Excess of Alkali.*—Griseofulvic acid (5·0 g., 15 mmoles), suspended in dimethylacetamide (100 ml.), was brought into solution by the addition of triethylamine (2 ml., 15 mmoles). Methanethiol (3·3 ml., 60 mmoles) was added and the optical rotation was observed over a period of 19 hr. No change occurred. 86% Potassium hydroxide (2·9 g., 45 mmoles) in water (5 ml.) was added and the optical rotation was observed to rise steadily for 96 hr.; it then had a maximum value (addition of 15 mmoles of potassium hydroxide did not result in a change of rotation). The mixture was diluted with water (200 ml.), acidified with 2N-hydrochloric acid (200 ml.), and concentrated *in vacuo*, the excess of methanethiol being trapped in potassium permanganate scrubbers. The white crystals obtained (2·7 g., 56%) were norgriseofulvic acid (XIV; R = OMe, R' = OH), m. p. 267—270° (decomp.), $[\alpha]_D$ +493° (*c* 0·8 in 2N-Na_2CO_3), $\lambda_{max.}$ (in 0·1N-NaOH), 285 (ε 29,400), and 322 mμ (ε 34,300); the infrared spectrum was identical with that of an authentic specimen. A large-scale experiment gave a 64% yield. Substitution of ethanethiol for methanethiol gave similar results. Only griseofulvic acid was isolated from control experiments carried out in the absence of a thiol.

7-Chloro-2',6-dimethoxy-4,6'-dimethylgris-2'-en-3,4'-dione (XIX) *and 7-Chloro-4',6-dimethoxy-4,6'-dimethylgris-3'-en-3,2'-dione* (XX).—A suspension of magnesium turnings (8·0 g.) in dry ether (50 ml.) was treated with methyl bromide (25 g.) in dry ether at such a rate that the ether gently boiled. The mixture was heated under reflux for 90 min. and then filtered through kieselguhr under an atmosphere of dry nitrogen. To the resulting clear solution was slowly added a solution of the bisketal (XVII; R = OMe) (25·0 g.) in dry tetrahydrofuran (200 ml.). An initial orange cloudy solution gave way to a clear red solution as the addition was completed. The mixture, kept in a warm (*ca.* 50°) water bath, slowly (20—30 min.) became green. After 1 hr. the clear solution was treated with water (100 ml.), cooling being necessary to control the vigorous reaction. Subsequently 2N-hydrochloric acid (100 ml.) was added and the mixture was extracted with ethyl acetate (4 × 150 ml.). The organic extracts were combined, washed with 2N-sodium carbonate and water, dried, and evaporated to give a yellow solid (21·2 g.), m. p. 179—182°. Thin-film chromatography showed that this ketal (XVII; R = Me) (R_F 0·28) was still contaminated with a little unchanged starting material (XVII; R = OMe) (R_F 0·15).

The crude bisketal (XVII; R = Me) (15 g.) in acetic acid (100 ml.) containing 2N-sulphuric acid (15 ml.) was heated for 1 hr. on the steam-bath. The mixture was poured into water (500 ml.) and basified with 40% sodium hydroxide solution. The brown gum was extracted with ethyl acetate (3 × 150 ml.) and ether (100 ml.), and the aqueous alkaline layer was acidified with 2N-hydrochloric acid to give a buff precipitate of the *triketone* (XVIII) (7·2 g.), m. p. 210—215°, $\lambda_{max.}$ (in 0·1N-NaOH) 288 mμ ($E_{1\,\text{cm.}}^{1\%}$ 1196), $\nu_{max.}$ 1746 and 1695 cm.$^{-1}$ (ketones) (Found: OMe, 10·6. $C_{16}H_{15}ClO_5$ requires OMe, 9·7%). The neutral fraction was isolated as a dark red gum and was treated again as above, to furnish a further sample of the triketone (XVIII) (1·64 g.), m. p. 215—217° (Found: OMe, 10·4%).

This triketone (6·5 g.) in acetone (200 ml.) was treated with an excess of ethereal diazomethane and kept for 30 min. at room temperature. The excess of methylating agent was destroyed with acetic acid and the mixture was evaporated to a low volume, diluted with ethyl acetate, and shaken with saturated sodium hydrogen carbonate solution. Evaporation of the dried organic layer left a foam (5·9 g.) which was purified by chromatography from benzene on alumina (250 g.). Elution with benzene gave, after trituration with ether, the *4'-methyl ether* (XX) (0·93 g.), m. p. 213—216° (from ethanol), $[\alpha]_D$ +218° (*c* 0·6), $\lambda_{max.}$ 230·5 (ε 20,900), 262·5 (ε 17,700), 288 (ε 17,700), λ (infl.) 320 mμ (ε 7550), $\nu_{max.}$ 1696 (C=O) and 1658 cm.$^{-1}$ (CO·C=C) (Found: C, 60·6; H, 5·4; Cl, 10·5; OMe, 18·3. $C_{17}H_{17}ClO_5$ requires C, 60·6; H, 5·1; Cl, 10·5; OMe, 18·4%). Subsequent elution with benzene gave a mixture of isomers (XIX and XX) (0·8 g.) as indicated by thin-film chromatography. By use of 9 : 1 benzene–ethyl acetate the more polar *isomer* (XIX) was eluted and triturated with ether (1·27 g.), m. p. 165—166° (from ethanol), $[\alpha]_D$ +352°, $\lambda_{max.}$ 236·5 (ε 24,300), 288 (ε 21,600), and λ (infl.) 316 mμ (ε 8500), $\nu_{max.}$ 1708 (C=O) and 1656 cm.$^{-1}$ (CO·C=C) (Found: C, 60·2; H, 5·3; Cl, 10·7; OMe, 18·5%). Later fractions (0·43 g., total) eluted with ethyl acetate and 99 : 1 ethyl acetate–methanol contained isogriseofulvin (II; R = OMe) and griseofulvin (I; R = OMe) severally.

Alkaline Hydrolysis of the Ethers (XIX *and* XX).—The mixed ethers (0·6 g.) from the previous experiment were heated under nitrogen with 0·5N-sodium hydroxide (100 ml.) for 5 hr. The mixture was extracted with ethyl acetate, and the alkaline layer was freed from traces of ethyl acetate, filtered, and acidified to pH 1. The resulting solid was extracted into ethyl acetate, and the organic layer was washed, dried, and evaporated to a yellow solid (0·35 g.), considered to be a crude sample of the phenolic triketone (XXI), m. p. 120—130°, $\lambda_{max.}$ 273 mμ ($E^{1\%}_{1\,cm.}$ 279), $\lambda_{max.}$ (in 0·1N-NaOH) 287 ($E^{1\%}_{1\,cm.}$ 673) and 332 mμ ($E^{1\%}_{1\,cm.}$ 537) (Found: OMe, 5·0%), $\nu_{max.}$ 3500 (OH) and 1695 cm.$^{-1}$ (C=O).

This acid (0·3 g.) was heated in dry methanol (10 ml.) containing 2,2-dimethoxypropane (2 ml.) and toluene-*p*-sulphonic acid (18 mg.) for 5 hr. The bulk of the solvent was removed *in vacuo* and the residue was poured into 2N-sodium carbonate. Extraction with ethyl acetate gave the 4′,6-dimethoxy-compound (XX) (97 mg.), identified by infrared and ultraviolet spectra and thin-plate chromatography. The alkaline layer was freed from ethyl acetate and acidified with 2N-hydrochloric acid. Isolation with ethyl acetate gave a foam (0·14 g.) that crystallised from methanol as rods of *7-chloro-6-hydroxy-4′-methoxy-4,6′-dimethylgris-3′-en-3,2′-dione* (XXII) (63 mg.), m. p. 232—233°, $[\alpha]_D$ +251°, λ (infl.) 235 (ε 13,300), $\lambda_{max.}$ 259·5 (ε 12,500), 286·5 (ε 16,700), and λ (infl.) 317 mμ (ε 7500), $\lambda_{max.}$ (in 0·1N-NaOH) 259 (ε 16,400), 283 (ε 22,700), and 333 mμ (ε 31,600), $\nu_{max.}$ 3500 (OH), 3185 (bonded OH), 1697 (C=O), and 1660 cm.$^{-1}$ (CO·C=C) (Found: C, 59·5; H, 4·6; Cl, 11·0. $C_{16}H_{15}ClO_5$ requires C, 59·5; H, 4·7; Cl, 11·0%)

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