

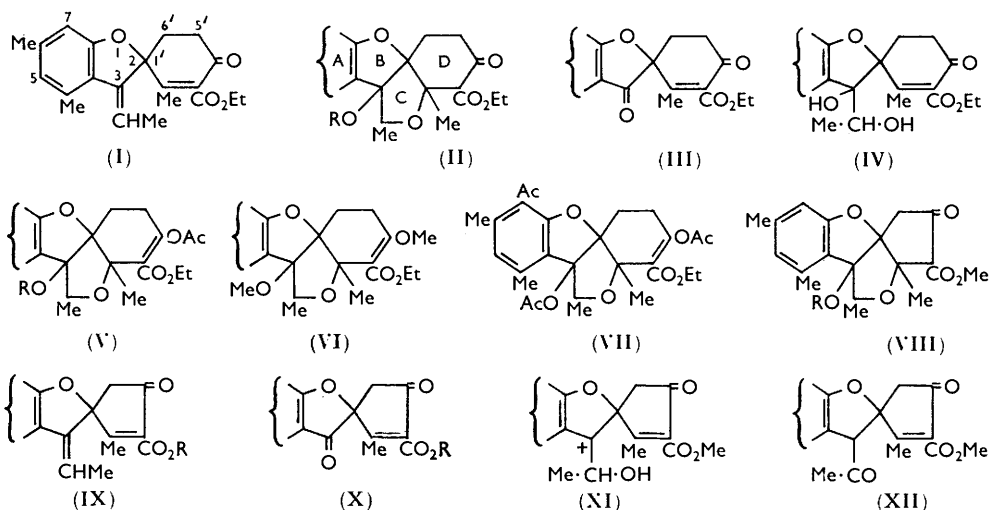
930. *Spirans. Part IV.*¹ *The Oxidation of 3-Alkylidenegrisens to Grisen-3-ones by Ruthenium Tetroxide.*

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3-Alkylidenegris-2'-ens are oxidised to grisen-3-ones by ruthenium tetroxide in a single operation which avoids the stable tetracyclic compounds produced by other oxidising agents.

OXIDATION of the 3-ethylidenegris-2'-en-4'-one (I) by osmium tetroxide leads to the tetracycle (II; R = H), ozone in methyl acetate giving the related ether (II; R = Me), as shown previously.^{1,2} While it has not proved possible to modify either these reactions or their products so that the further oxidation to the grisen-3-one (III) can be realised, it is now shown that ruthenium tetroxide effects the desired conversion in a single step. The reaction seems general though its efficiency, never high, is markedly affected by the nature of the substitution pattern. Chromium trioxide has a similar but very limited application.

Re-investigation of the ozonolysis of the 3-ethylidenegrisenone (I) has, in the main, confirmed the earlier results:^{1,2} in most solvents general degradation ensues, methyl acetate alone giving a distinctive tetracyclic product (II; R = Me). It has now been found that methanol may replace methyl acetate, but that the product is then entirely in the form of the oxo-ester whereas only the enol had been encountered before. The oxo-ester gives the appropriate infrared absorption bands at 1735 (ester) and 1695 cm^{-1} (cyclohexanone) and gives no ferric reaction: in warm alcohol it soon changes into the enol.

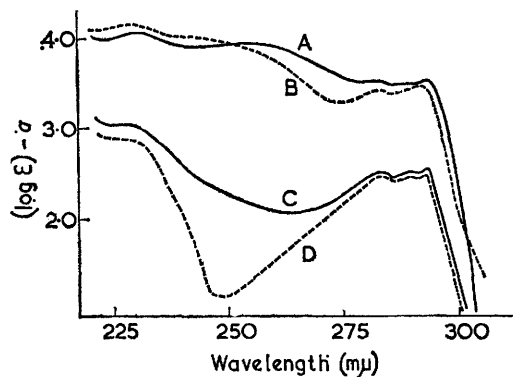


The glycol (IV) cannot be isolated after reaction of osmium tetroxide with the olefin (I) because of cyclisation by β -addition of one hydroxyl group to the $\alpha\beta$ -unsaturated ketonic system. If in the resulting tetracycle (II; R = H) this cyclisation could be reversed, thus opening ring c, the desired conversion into the required coumaran-3-one (III) might still be feasible. But the tetracycle is stable and no such reversal has been detected. Apparently there is no spontaneous ring-opening, for preliminary experiments with periodic acid, plumbic acetate, and zinc permanganate led, not to glycol fission, but only to complete disintegration. Nor could ring c be opened and kept open by acetylation or methylation. Thus, acetylation of compound (II; R = Me) by acetic anhydride and

¹ Part III, Dean, Deorha, Knight, and Francis, *J.*, 1961, 327.

² Dean, Francis, and Manunapichu, *J.*, 1958, 4551.

pyridine gives the enol acetate (V; R = Me) with ν_{\max} 1770 (vinyl acetate) and 1721 cm^{-1} ($\alpha\beta$ -unsaturated ester) but no ketonic absorption. Similarly, Kuhn methylation³ affords the enol ether (VI) which is not ketonic since it fails to react with borohydride or semicarbazide, but behaves as a vinyl ether in being readily hydrolysed by acids to the original enol. The infrared spectrum includes, not only the expected bands at 1712 ($\alpha\beta$ -unsaturated ester) and 1295 cm^{-1} (enol ether), but also one at 1672 cm^{-1} which, however, need not be attributed to (unreactive) carbonyl since olefinic bonds placed as in (VI) are known to have strong absorption near this point, though usually at a lower frequency.⁴ The ultraviolet spectrum (Figure) is appropriate to a spirocoumaran containing an isolated β -alkoxycrotonate chromophore (λ_{\max} \sim 245 $\text{m}\mu$; $\log \epsilon \sim 3$). With pyridine as catalyst, the tetracycle (II; R = H) could only be monoacetylated, the tertiary hydroxyl group in the vinyl acetate (V; R = H) being unreactive. With sulphuric acid as catalyst, the tertiary hydroxyl group was also esterified but the product appeared to contain yet a third acetyl group. As the third group seemed stable to hydrolysis and responsible for



Ultraviolet absorption spectra (in ethanol) of: (A) ethyl 6a-methoxy-3-oxo-5,11-dioxadibenzo[*a,d*]pentalene-4-carboxylate (II; R = Me; enolic form) ($a = 0$); (B) methyl 6a-methoxy-2-oxo-4,10-dioxabenzocyclopenta[*d*]pentalene-3-carboxylate (VIII; R = Me) ($a = 0$); (C) ethyl 3,6a-dimethoxy-5,11-dioxadibenzo[*a,d*]pentalene-4-carboxylate (VI) ($a = 1$); and (D) 6a-methoxy-3-oxo-5,11-dioxadibenzo[*a,d*]pentalene (II; R = Me; H for CO_2Et) ($a = 1$).

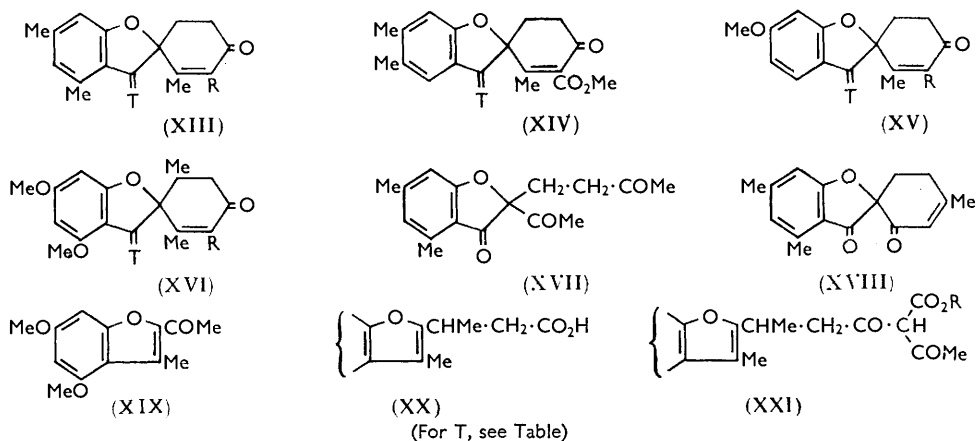
infrared absorption at 1689 cm^{-1} , and as the aromatic nucleus present is particularly subject to electrophilic substitution, the triacetyl derivative is considered to be the acetophenone (VII) or the isomer with acetyl at position 5.

While bases are known to open ring c, the reaction¹ seemed unsuitable for the present purpose, so the effect of acids was studied on a related tetracycle (VIII; R = H) available from an earlier study. Hydrogen chloride in methanol gave two compounds. One, a methyl ether which we believe to have structure (VIII; R = Me), is of interest since it cannot be obtained from the spiran (IX; R = Me) by ozonolysis in methyl acetate, the reaction being normal in the cyclopentene series and giving the expected coumaran-3-one (X; R = Me). The structural argument rests on analytical and spectroscopical evidence, especially the similarity of the ultraviolet spectrum to that of the corresponding grisan derivative (Figure). The other (and major) product appeared from analytical findings to be formed by dehydration of the tetracycle (VIII; R = H) or of the equivalent glycol. Theory predicting the loss of oxygen from the benzyl alcohol grouping to give an ion (XI), the product was allocated structure (XII). In support, the compound was found to absorb (in chloroform) at 1748 (ester), 1730 (cyclopentenone), and 1712 cm^{-1} (saturated ketone). The ultraviolet absorption [λ_{\max} \sim 220 and 280 $\text{m}\mu$ ($\log \epsilon$ 4.30, 3.43)] was consistent with the presence of a coumaran system as the major chromophore and, in particular, ruled out the presence of an acetophenone (grisan-3-one) chromophore. The compound afforded a mono-2,4-dinitrophenylhydrazone having λ_{\max} 373 $\text{m}\mu$ ($\log \epsilon$ 4.51) and (in mulls) ν_{\max} 1736 (ester) and 1709 cm^{-1} (saturated ketone), and was therefore formulated as a derivative of the unsaturated (cyclopentenone) carbonyl group rather than the other—which, as scale models show, is much the more hindered of the two.

³ Kuhn, Löw, and Trischmann, *Angew. Chem.*, 1955, **67**, 32; *Chem. Ber.*, 1955, **88**, 1492.

⁴ Bader, *Helv. Chim. Acta*, 1953, **36**, 215.

Because ruthenium tetroxide is a very vigorous oxidising agent—attacking benzene and pyridine with violence and converting ethers into esters—its applications have not been explored very far.^{5,6} It differs from the osmium analogue in that the complex formed with an olefin is unstable and at once decomposes by internal oxidation–reduction, giving carbonyl compounds and ruthenium dioxide. Consequently, the formation of glycols or their equivalents is unusual. For the preparation of grisen-3-ones (III) from 3-alkylidenegrisens (I) it appeared, therefore, that the advantage of complete avoidance of glycols and hence of tetracycles (II) might outweigh the disadvantage of general oxidation.



The oxidation by ruthenium tetroxide of the 3-ethylidenecoumaranospirocyclopentenone (IX; R = Et) was examined first, as the expected ketone (X; R = Et) had already been prepared (in *ca.* 35% yield) by ozonolysis.⁷ This ketone was indeed obtained, though only in *ca.* 7% yield. But when the method was applied to the 3-ethylidenegris-2'-en (I; H for CO₂Et), the desired grisen-3-one (III; H for CO₂Et) was formed in 16% yield whereas attempts to procure it by ozonolysis had repeatedly failed. Oxidation of the corresponding 3-methylenegris-2'-en gave the same product but in much lower yield, and the further results summarised in the Table confirm the finding that the reaction is best with fully alkylated olefins. Nevertheless, the yields do not rise above about 30% in spite of the fact that all oxidations were conducted so that a little of the starting material could be recovered. Acetone was detected as an oxidation product of the 3-isopropylidenegrisens, but ruthenium tetroxide rapidly attacks aldehydes, so neither formaldehyde nor acetaldehyde was detected in reactions which probably generated them.

Effect of substitution on ruthenium tetroxide oxidations.

3-Alkylidenegrisen	Yield (%) of grisen-3-one when T is		Grisen-3-one
	CH ₂	CMe ₂	
(XIII; R = H)	10	—	(XIII; R = H, T = O)
(XIII; R = CO ₂ Et)	0	—	(XIII; R = CO ₂ Et, T = O)
(XIV)	—	26	(XIV; T = O)
(XV; R = H)	—	19	(XV; R = H, T = O)
(XV; R = CO ₂ Me)	5	32	(XV; R = CO ₂ Me, T = O)
(XVI; R = H)	7	—	(XVI; R = H, T = O)
(XVI; R = CO ₂ Me)	3	—	(XVI; R = CO ₂ Me, T = O)

Direct oxidation of 3-alkylidenegris-2'-ens to grisen-3-ones is not confined to ruthenium tetroxide since chromium trioxide also converts the 3-methylenegrisen (XIII; R = H,

⁵ Berkowitz and Rylander, *J. Amer. Chem. Soc.*, 1958, **80**, 6682.

⁶ Djerassi and Engle, *J. Amer. Chem. Soc.*, 1953, **75**, 3838.

⁷ Dean, Halewood, Mongholsuk, Robertson, and Whalley, *J.*, 1953, 1250.

T = CH₂) into the ketone (XIII; R = H, T = O). But chromium trioxide failed to oxidise 3-ethylidene- or 3-isopropylidene-gris-2'-en similarly, so the poor yield in the one successful oxidation was not capable of improvement.

In earlier work, cyclisation of the triketone (XVII) had given a grisan derivative for which, for indirect reasons,⁸ expression (XVIII) was preferred to the alternative (XIII; R = H; T = O). This choice is now confirmed, since the grisan is isomeric, and not identical, with the coumaran-3-one (XIII; R = H, T = O) prepared by the ruthenium tetroxide method. Again, the grisen-3-one (XV; R = H, T = O) has already been reported by Dawkins and Mulholland⁹ who obtained it (in unstated yield) as an amorphous solid by ozonolysis, hydrolysis, and decarboxylation of the grisen (XV; R = CO₂Et, T = CH₂). The ruthenium tetroxide method gives a crystalline product otherwise apparently identical with that already reported.

The 2',6'-dimethylgrisens (XVI; R = H or CO₂Me, T = CH₂) were prepared by methods evolved previously.¹ 2-Acetyl-4,6-dimethoxy-3-methylbenzofuran (XIX) and ethyl bromoacetate in a Reformatsky reaction gave a crotonic acid, converted into the acid (XX) by hydrogenation. From the derived propionyl chloride and the appropriate alkyl acetoacetates the diketonic esters (XXI; R = Me and Bu^t) were made, and the grisans were obtained from these by cyclisation in sulphuric acid or by decarboxylation and cyclisation, as appropriate.

EXPERIMENTAL

Light petroleum refers to the fraction b. p. 60–80° unless another is specified. Infrared spectra are reported for mulls in paraffin except where a solvent is indicated. Ultraviolet spectra were determined in ethanol at concentrations between 10⁻³ and 10⁻⁴M.

Ethyl 2,3,4,4a,6,6a-Hexahydro-6a-methoxy-4a,6,7,9-tetramethyl-3-oxo-1H-5,11-dioxadibenzo-[a,d]pentalene-4-carboxylate (II; R = Me).—Ozonised oxygen was led into a solution of ethyl 3-ethylidene-4,6,2'-trimethyl-4'-oxogris-2'-en-3'-carboxylate (I) (0.05 g.) in methanol (100 ml.) at -80°. After 35 min., residual ozone was removed in a current of air and the solvent removed *in vacuo*, leaving a yellowish gum which, rapidly crystallised from methanol, afforded the 5,11-dioxadibenzopentalen-3-one as prisms (0.20 g.), m. p. 102°, devoid of a ferric reaction (Found, on a specimen fused *in vacuo*: C, 67.6; H, 7.5. C₂₂H₂₈O₆ requires C, 68.0; H, 7.3%). Repeated recrystallisation from methanol gave the enol, m. p. and mixed m. p. 136°, having a red ferric reaction.

Enol Derivatives of Keto-ester (II; R = H or Me).—Silver oxide (0.53 g.) was added to dimethylformamide (6 ml.) containing methyl iodide (4 ml.) and the enol (0.20 g.), and the mixture shaken for 48 hr. The residue from filtration was washed with a little dimethylformamide, and the washings were combined with the filtrate before the addition of water (30 ml.) and ether (30 ml.). The mixture was treated with aqueous potassium cyanide until all silver salts had been removed, and the product was extracted into ether, washed with water, dried (MgSO₄), and recovered as a gum by evaporation. Purified by chromatography on silica from benzene, the gum solidified and then, when recrystallised from aqueous ethanol, supplied the enol ether (VI), *ethyl 1,2,6,6a-tetrahydro-3,6a-dimethoxy-4a,6,7,9-tetramethyl-4aH-5,11-dioxadibenzo[a,d]pentalene-4-carboxylate*, as needles (0.12 g.), m. p. 132°, insoluble in aqueous alkali and having no ferric reaction [Found: C, 68.6; H, 7.7; Alkoxy (as OMe), 22.8. C₁₉H₁₉O₃(OMe)₂·OEt requires C, 68.6; H, 7.5; alkoxy (as OMe), 23.1%]. Partial hydrolysis of this ether (0.20 g.) in boiling ethanol (5 ml.) with 2N-hydrochloric acid (1 ml.) for 10 min. gave a gum, isolated by dilution with water and collection into ether. Acids were removed by washing with aqueous sodium hydrogen carbonate and then with water, and the ethereal solution was then dried (MgSO₄) and concentrated. The residue was purified from methanol, giving the enol in prisms (0.07 g.), m. p. and mixed m. p. 136°, further identified by means of the infrared spectrum.

A suspension of the enol (0.50 g.) in acetic anhydride (5 ml.) containing pyridine (3 drops)

⁸ Dean and Manunapichu, *J.*, 1957, 3112.

⁹ Dawkins and Mulholland, *J.*, 1959, 2211.

was heated on the steam-bath for 10 hr., cooled, and diluted with water (50 ml.). The product was isolated by means of ether, freed from acid by means of sodium hydrogen carbonate in water, dried (MgSO_4), and recovered by evaporation as a gum which slowly crystallised. Purified from light petroleum, the solid gave the enol acetate (V; R = Me), *ethyl 3-acetoxy-1,2,6,6a-tetrahydro-6a-methoxy-4a,6,7,9-tetramethyl-4aH-5,11-dioxadibenzo[a,d]pentalene-4-carboxylate*, as needles (0.15 g.), m. p. 132°, λ_{max} . 283, 289, 292 $\text{m}\mu$ ($\log \epsilon$ 3.48, 3.50, 3.53) (Found: C, 66.9; H, 7.4; OAc, 9.7. $\text{C}_{22}\text{H}_{27}\text{O}_5 \cdot \text{OAc}$ requires C, 67.0; H, 7.0; OAc, 10.0%).

When the enol (0.50 g.) was treated with acetic anhydride (6.5 ml.) and sulphuric acid (3 drops) at room temperature overnight and the product isolated as in the previous experiment, there was obtained *ethyl 3-acetoxy-10(or 8)-acetyl-1,2,6,6a-tetrahydro-6a-methoxy-4a,6,7,9-tetramethyl-4aH-5,11-dioxadibenzo[a,d]pentalene-4-carboxylate* which crystallised from methanol in needles (0.14 g.), m. p. 169° (Found: C, 65.9; H, 6.8; OAc, 9.8. $\text{C}_{24}\text{H}_{29}\text{O}_6 \cdot \text{OAc}$ requires C, 66.1; H, 6.8; OAc, 9.1%).

Acetylation of Ethyl 2,3,4,4a,6,6a-Hexahydro-6a-hydroxy-4a,6,7,9-tetramethyl-3-oxo-1H-5,11-dioxadibenzo[a,d]pentalene.—Acetylations were conducted as in the foregoing experiments. With pyridine as the catalyst, the product was the enol acetate (V; R = H), *ethyl 3-acetoxy-1,2,6,6a-tetrahydro-6a-hydroxy-4a,6,7,9-tetramethyl-4aH-5,11-dioxadibenzo[a,d]pentalene-4-carboxylate*, separating from ethanol in needles, m. p. 167°, ν_{max} . 3448 (OH), 1742 (vinyl acetate), and 1724 cm^{-1} ($\alpha\beta$ -unsaturated ester), λ_{max} . 289 $\text{m}\mu$ ($\log \epsilon$ 3.52) (Found: C, 65.6; H, 6.6. $\text{C}_{22}\text{H}_{26}\text{O}_7$ requires C, 65.7; H, 6.5%). With sulphuric acid as the catalyst, the product was the triacetyl derivative (VII), *ethyl 3,6a-diacetoxy-10(or 8)-acetyl-1,2,6,6a-tetrahydro-4a,6,7,9-tetramethyl-4aH-5,11-dioxadibenzo[a,d]pentalene-4-carboxylate*, which formed diamond-shaped plates, m. p. 190°, from ethanol (Found: C, 64.7; H, 6.4; OEt, 9.2. $\text{C}_{25}\text{H}_{27}\text{O}_8 \cdot \text{OEt}$ requires C, 64.8; H, 6.4; OEt, 9.0%). This derivative had λ_{max} . 286 $\text{m}\mu$ ($\log \epsilon$ 3.58) and ν_{max} . 1748 (broad; vinyl acetate and alkyl acetate), 1723 ($\alpha\beta$ -unsaturated ester), and 1689 cm^{-1} (acetophenone).

Action of Methanolic Hydrogen Chloride on Methyl 1,2,3,3a,5,5a-Hexahydro-5a-hydroxy-3a,5,6,8-tetramethyl-2-oxo-4,10-dioxabenzocyclopenta[d]pentalene-3-carboxylate.—This 4,10-dioxacyclopenta[d]benzo[a]pentalene derivative (1.0 g.) was heated under reflux with methanol (50 ml.) and concentrated hydrochloric acid (4 ml.) for 6 hr. The cooled solution was diluted with water (100 ml.) and repeatedly extracted with benzene. The extracts were washed with water, dried (MgSO_4), and concentrated, leaving an orange oil which crystallised from ethanol-light petroleum, giving *methyl 3-acetyl-4,6,2'-trimethyl-4'-oxocoumaran-2-spiro-1'-cyclopent-2'-ene-3'-carboxylate* (XII) as needles (0.20 g.), m. p. 153° (Found: C, 69.4; H, 6.2; OMe, 9.7. $\text{C}_{18}\text{H}_{17}\text{O}_4 \cdot \text{OMe}$ requires C, 69.5; H, 6.1; OMe, 9.5%). This diketone, which gave no ferric reaction, had λ_{max} . 280 $\text{m}\mu$ ($\log \epsilon$ 3.43), ν_{max} . (in CHCl_3) 1748 (ester), 1730 (cyclopentenone), and 1712 cm^{-1} (saturated ketone), and ν_{max} . (mull) 1730 (broad band; ester plus cyclopentenone) and 1712 cm^{-1} (saturated ketone). The *mono-2,4-dinitrophenylhydrazine* separated from ethanol-ethyl acetate in orange needles, m. p. 239° (Found: C, 59.3; H, 4.8; N, 11.0. $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_8$ requires C, 59.1; H, 4.8; N, 11.0%).

The mother-liquors from purification of the diketone contained a gum which was passed in benzene through a column of silica. One of the fractions furnished a solid which, when purified from methanol, afforded *methyl 1,2,3,3a,5,5a-hexahydro-5a-methoxy-3a,5,6,8-tetramethyl-2-oxo-4,10-dioxabenzocyclopenta[d]pentalene-3-carboxylate* (VIII; R = Me) as prisms (10 mg.), m. p. 159°, having a red-purple ferric reaction in ethanol [Found: OMe, 17.6. $\text{C}_{18}\text{H}_{18}\text{O}_5(\text{OMe})_2$ requires OMe, 17.2%]. This compound had λ_{max} . 229, 282, and 291 $\text{m}\mu$ ($\log \epsilon$ 4.15, 3.46, 3.50) and ν_{max} . 3125 (weak and very broad: enolic hydroxyl) and 1670 cm^{-1} (intense: chelated ester).

β -(6-Methoxy-3-methyl-2-benzofuryl)propionic Acid.—2-Formyl-6-methoxy-3-methylbenzofuran¹⁰ (13.5 g.) and malonic acid (13.5 g.) were heated together in pyridine (50 ml.) containing piperidine (1 ml.) until effervescence stopped. Pyridine was removed under reduced pressure and the residue crystallised from benzene and then from a large volume of ethanol, giving β -(6-methoxy-3-methyl-2-benzofuryl)acrylic acid as pale yellow needles (10.2 g.), m. p. 222° (Found: C, 67.0; H, 5.3; OMe, 13.7. $\text{C}_{12}\text{H}_9\text{O}_3 \cdot \text{OMe}$ requires C, 67.2; H, 5.2; OMe, 13.4%).

This acid (10.2 g.) was dissolved in 0.5N-aqueous potassium hydroxide (160 ml.) at 80°; Raney nickel (ca. 10 g.) was added and the mixture shaken at the same temperature under hydrogen

¹⁰ Foster, Robertson, and Healy, *J.*, 1939, 1594.

at 30 atm. for 6 hr. From the filtrate, dilute hydrochloric acid liberated a solid that crystallised from aqueous alcohol, giving the benzofurylpropionic acid in needles (8.5 g.), m. p. 143° (lit.,⁹ 137°) (Found: C, 66.6; H, 6.2; OMe, 13.4. Calc. for $C_{12}H_{11}O_3 \cdot OMe$: C, 66.7; H, 6.0; OMe, 13.2%).

Methyl 6-Methoxy-2'-methyl-3-methylene-4'-oxogris-2'-en-3'-carboxylate (XV; R = CO₂Me, T = CH₂).—This 3-methylenegrisenone, which was prepared from the foregoing benzofurylpropionic acid (8.0 g.) according to the method used previously for the corresponding ethyl ester,⁹ separated from methanol in faintly yellow needles (2.90 g.), m. p. 126°, λ_{max} . 216, 232, 259, and 315 m μ (log ϵ 4.36, 4.40, 4.18, 4.06), ν_{max} . 1730 and 1678 cm.⁻¹ [Found: C, 68.8; H, 5.8; OMe, 19.3. $C_{18}H_{12}O_3(OMe)_2$ requires C, 68.8; H, 5.8; OMe, 19.8%]. The 2,4-dinitrophenylhydrazone crystallised from ethanol-ethyl acetate in orange needles, m. p. 227° (Found: C, 58.4; H, 4.4; N, 11.1. $C_{24}H_{22}N_4O_8$ requires C, 58.3; H, 4.5; N, 11.3%).

2-Acetyl-4,6-dimethoxy-3-methylbenzofuran (XIX).—Sodium iodide (2 g.) in ethanol (20 ml.) was added to a mixture of 2-hydroxy-4,6-dimethoxyacetophenone (50 g.) and potassium carbonate (100 g.) in boiling ethyl methyl ketone (600 ml.). During 16 hr. monochloroacetone (32 ml.) was added gradually (2 ml. per hour). The hot solution was filtered, the inorganic salts were washed with hot ethyl methyl ketone, and the combined washings and filtrate and washings were evaporated to a viscous brown oil. This oil dissolved in boiling light petroleum (b. p. 40–60°), leaving a resin which was rejected: the pale yellow material remaining after distillation of the petroleum was taken up in ether and washed with dilute sodium hydroxide and then water. Evaporation of the ether left 2-acetyl-4,6-dimethoxy-3-methylbenzofuran crystallising from aqueous ethanol in needles (37 g.), m. p. 120° [Found: C, 66.4; H, 5.9; OMe, 26.7. $C_{11}H_9O_2(OMe)_2$ requires C, 66.7; H, 6.0; OMe, 26.5%].

β -(4,6-Dimethoxy-3-methyl-2-benzofuryl)butyric Acid (XX).—To a solution of 2-acetyl-4,6-dimethoxy-3-methylbenzofuran (20.0 g.) in benzene (dried over sodium; 400 ml.) containing ethyl bromoacetate (20.0 ml.) and heated under reflux was added zinc wool (etched with nitric acid and dried immediately before use; 10.0 g.). When heated and stirred for 6 hr., the mixture became scarlet: it was cooled, shaken with 2N-sulphuric acid to decompose the complex, and filtered. The organic layer was freed from acid by means of sodium hydrogen carbonate, dried (MgSO₄), and concentrated. A sample of the product was purified by chromatography from benzene on silica, to give ethyl β -(4,6-dimethoxy-3-methyl-2-benzofuryl)crotonate which separated from benzene in needles, m. p. 106° (Found: C, 67.2; H, 6.6. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%), λ_{max} . 230, 248, and 349 m μ (log ϵ 3.99, 4.04, 4.37), ν_{max} . 1695 cm.⁻¹.

The main part of the crude crotonic ester was boiled for 2 hr. with aqueous-ethanolic 2N-sodium hydroxide (200 ml.); unsaponifiable material was isolated with ether and identified as 2-acetyl-4,6-dimethoxy-3-methylbenzofuran (4.0 g.). Acidification of the alkaline solution afforded a powder which, when crystallised from pyridine-ethanol, gave β -(4,6-dimethoxy-3-methyl-2-benzofuryl)crotonic acid as yellow needles (12.5 g.), m. p. 208° [Found: C, 65.0; H, 6.0; OMe, 22.7. $C_{13}H_{10}O_3(OMe)_2$ requires C, 65.2; H, 5.8; OMe, 22.4%].

This crotonic acid (4.8 g.) in 2N-sodium hydroxide (160 ml.) containing Raney nickel (ca. 5 g.) was shaken in hydrogen (20 atm.) at room temperature for 6 hr. Isolated in the usual way, the product was purified from aqueous alcohol, supplying the butyric acid in needles (3.7 g.), m. p. 130° [Found: C, 64.8; H, 6.7; OMe, 22.1. $C_{13}H_{12}O_3(OMe)_2$ requires C, 64.7; H, 6.5; OMe, 22.3%].

Methyl 4,6-Dimethoxy-2',6'-dimethyl-3-methylene-4'-oxogris-2'-en-3'-carboxylate (XVI; R = CO₂Me, T = CH₂).—The foregoing butyric acid (3.0 g.) was converted into the acid chloride by means of phosphorus pentachloride (2.33 g.) in chloroform (30 ml.) and purified first by repeated distillation of added chloroform and then by being kept at 50°/15 mm. for 40 min. The product, in ether (70 ml.), was added to a suspension of the ethoxymagnesium derivative (2.0 g.) of methyl acetoacetate, also in ether (100 ml.). After being gently boiled for 3 hr., the mixture contained a magnesium complex which was decomposed *in situ* with dilute acetic acid. Evaporation of the ethereal layer then gave a red oil with an intense red ferric reaction; kept at 0° for 24 hr. in sulphuric acid monohydrate (15 ml.), this oil changed into a gum which was isolated by addition of ice and extracted in ether. Acids were removed by means of aqueous sodium hydroxide, then the ether was evaporated. The residue crystallised from methanol-light petroleum, to supply the *grisen-3'-carboxylate* as needles (0.05 g.), m. p. 169°, λ_{max} . 234, 241, 272, 281, and 308 m μ (log ϵ 4.51, 4.47, 4.26, 4.30, 3.89), ν_{max} . 1736 and 1678 cm.⁻¹ [Found: C, 67.1; H, 6.3; OMe, 25.9. $C_{17}H_{13}O_4(OMe)_3$ requires C, 67.0; H, 6.2; OMe, 26.0%].

4,6-Dimethoxy-2',6'-dimethyl-3-methylenegrise-2'-en-4'-one (XVI; R = H, T = CH₂).—The acid chloride (see above) from β-(4,6-dimethoxy-3-methyl-2-benzofuryl)butyric acid (5.0 g.) was condensed with the ethoxymagnesium derivative (4.7 g.) of t-butyl acetoacetate under the conditions specified in the preceding experiment. The yellow oil produced was warmed in toluene (75 ml.) containing toluene-*p*-sulphonic acid (0.25 g.) on a steam-bath until effervescence ceased, and then boiled for 1 hr. Removal of toluene by distillation (finally under reduced pressure) left an oil which was kept in sulphuric acid monohydrate (20 ml.) at 0° for 36 hr. Isolated by addition of ice and extraction in ether, the product was purified from light petroleum (b. p. 80—100°), giving the 3-methylenegrise as prisms (0.8 g.), m. p. 145°, λ_{max.} 234, 240, 271, 280, and 308 mμ (log ε 4.54, 4.47, 4.23, 4.27, 3.89), ν_{max.} 1672 (cyclohexenone C:O) and 1629 cm.⁻¹ (cyclohexenone C:C) [Found: C, 71.7; H, 6.9; OMe, 20.4. C₁₆H₁₄O₂(OMe)₂ requires C, 72.0; H, 6.7; OMe, 20.7%]. The 2,4-dinitrophenylhydrazone crystallised from benzene-ethanol in red needles, m. p. 247° (Found: C, 60.0; H, 5.0; N, 11.6. C₂₄H₂₄N₄O₇ requires C, 60.0; H, 5.0; N, 11.7%).

Ruthenium Tetroxide Reagent.—When prepared according to directions given by Berkowitz and Rylander,⁵ this reagent contained objectionable quantities of bromine. For the present study, hot *N*-aqueous potassium bromate was added drop by drop to a slowly distilling solution of ruthenium trichloride (1.0 g.) in 0.5*N*-hydrochloric acid (20 ml.). Collected in an ice-cooled receiver after passage through a water-cooled condenser, the yellow aqueous distillate contained bromine and ruthenium tetroxide partly in solution, partly as a red oil. The products were collected into carbon tetrachloride, wherefrom bromine was removed by means of aqueous sodium hydrogen carbonate. The solution was then washed with water, dried by shaking it with phosphorus pentoxide, and filtered through a compact pad of glass wool. For rough estimations of the amount of ruthenium tetroxide available, aliquot parts of the solution were treated with ethanol to reduce the reagent to the dioxide, which was washed with water, dried in air, and weighed. In general, the solution (40 ml.) contained about 0.35 g. of ruthenium tetroxide.

Ethyl 4,6,2'-Trimethyl-3,4'-dioxocyclopent-2'-ene-1'-spiro-2-benzofuran-3'-carboxylate (X; R = Et).—Ethyl 3-ethylidene-4,6,2'-trimethyl-4'-oxocyclopent-2'-ene-1'-spiro-2-benzofuran-3'-carboxylate⁷ (1.0 g.) in carbon tetrachloride (20 ml.) was treated slowly and with constant stirring at <5° with ruthenium tetroxide (0.5 g.), also in carbon tetrachloride. The mixture rapidly blackened, and after 1 hr. was filtered through Celite and evaporated to a viscous brown oil. Chromatography from benzene on silica gave a little (0.025 g.) of the original 3-ethylidenespirocoumaran, together with a second fraction which was eluted by ether in benzene (1:3) and when crystallised from light petroleum gave the 3,4'-dioxocoumaran as prisms (0.06 g.), m. p. 91—92° undepressed by admixture with an authentic specimen⁷ and further identified by means of the infrared spectrum. The compound had λ_{max.} 270 and 330 mμ (log ε 4.34, 3.70).

4,6,2'-Trimethyldioxogris-2'-en-3,4'-dione (XIII; R = H, T = O).—(i) Prepared by oxidation of the corresponding 3-methylenegrise-2'-en (0.50 g.) with ruthenium tetroxide (0.32 g.) according to the above method and purified by chromatography, this *diketone* crystallised from light petroleum in prisms (0.05 g.), m. p. 98°, λ_{max.} 268 and 329 mμ (log ε 4.31, 3.71) and ν_{max.} (in CHCl₃) 1701 (coumaran-3-one) and 1675 cm.⁻¹ (cyclohexenone C:O) (Found: C, 74.9; H, 6.3. C₁₆H₁₆O₃ requires C, 75.0; H, 6.3%). This compound gave a green colour with alkaline nitroprusside (coumaran-3-one) and a positive Zimmermann test for methylenecarbonyl but no ferric reaction. The 2,4-dinitrophenylhydrazone separated from ethanol-ethyl acetate in red needles, m. p. 225°, λ_{max.} 265 and 376 mμ (log ε 4.44, 4.51) (Found: C, 60.5; H, 4.7; N, 12.8. C₂₂H₂₀N₄O₆ requires C, 60.5; H, 4.6; N, 12.8%). (ii) The same grisendione (0.09 g.) was obtained by oxidising the corresponding 3-ethylidenegrise-2'-en (XIII; R = H, T = CHMe) (0.60 g.) with ruthenium tetroxide as in (i). (iii) The 3-methylenegrise (XV; R = H, X = CH₂) (1.0 g.) in acetic acid (15 ml.) at the b. p. was treated during 15 min. with a solution of chromium trioxide (3 g.) in acetic acid (21 ml.) containing water (9 ml.). Heating was continued for another 15 min., then the cooled mixture was diluted with much benzene and washed with plenty of water, dried (MgSO₄), and evaporated. The residual oil solidified when kept and then crystallised from light petroleum in prisms (0.15 g.), m. p. 98°, undepressed by a sample prepared as in (i).

Methyl 5,6,2'-Trimethyl-3,4'-dioxogris-2'-en-3'-carboxylate (XIV; R = CO₂Me, T = O).—Oxidation of methyl 3-isopropylidene-5,6,2'-trimethyl-4'-oxogris-2'-en-3'-carboxylate¹ (0.50 g.)

with ruthenium tetroxide by the standard method afforded the 3,4'-diketone as needles (0.12 g.), m. p. 171° (from methanol) (Found: C, 68.8; H, 5.9; OMe, 10.1. $C_{17}H_{15}O_4$ ·OMe requires C, 68.8; H, 5.8; OMe, 9.9%), λ_{\max} 264 and 338 $m\mu$ ($\log \epsilon$ 4.33, 3.78), ν_{\max} 730 ($\alpha\beta$ -unsaturated ester), 1706 (coumaran-3-one C:O), and 1678 cm^{-1} (cyclohexenone C:O). The 2,4-dinitrophenylhydrazine crystallised from ethanol-ethyl acetate in red needles, m. p. 279° (Found: C, 58.5; H, 4.7; N, 11.3. $C_{24}H_{22}N_4O_8$ requires C, 58.3; H, 4.5; N, 11.3%).

6-Methoxy-2'-methylgris-2'-en-3,4'-dione (XV; R = H, T = O).—Oxidation of the 3-isopropylidenegrise derivative (XV; R = H, T = CMe₂) (0.33 g.) with ruthenium tetroxide as in the previous experiments led to a black oil which was chromatographed on silica. Elution with benzene returned the 3-isopropylidenegrise (0.10 g.), and with ether-benzene (1:9) supplied the 3,4'-diketone which formed needles (0.04 g.), m. p. 148°, ν_{\max} 1701, 1667 cm^{-1} , λ_{\max} 231, 271, and 319 $m\mu$ ($\log \epsilon$ 4.32, 4.22, 4.05), when crystallised from aqueous ethanol (Found: C, 69.6; H, 5.4; OMe, 12.1. $C_{14}H_{11}O_3$ ·OMe requires 69.8; H, 5.5; OMe, 12.3%). The 2,4-dinitrophenylhydrazine had m. p. 21° (lit.,⁷ 230°).

Methyl 6-Methoxy-2'-methyl-3,4'-dioxogris-2'-en-3'-carboxylate (XV; R = CO₂Me, T = O).—(i) The methyl 3-isopropylidene-6-methoxygrise carboxylate (XV; R = CO₂Me, T = CMe₂) (1.0 g.) in carbon tetrachloride was oxidised by ruthenium tetroxide in the standard way. After removal of the black precipitate by filtration, the clear solution was extracted several times with small quantities of water; the extracts were combined and treated with aqueous 2,4-dinitrophenylhydrazine hydrochloride. The solid which separated was purified from aqueous ethanol, giving acetone 2,4-dinitrophenylhydrazine in yellow needles, m. p. and mixed m. p. 128°. Manipulation of the carbon tetrachloride solution in the usual way afforded a crystalline mixture of two compounds; separated by chromatography on silica, this mixture gave the 3-isopropylidenegrise (0.23 g.) (eluted by benzene) and the methyl 3,4'-dioxogris-3'-carboxylate [eluted by benzene-ether (9:1)] which separated from methanol in needles (0.23 g.), m. p. 158° [Found: C, 64.8; H, 5.2; OMe, 19.8. $C_{15}H_{10}O_4$ (OMe)₂ requires C, 64.6; H, 5.1; OMe, 19.6%]. This compound had λ_{\max} 231, 273, and 319 $m\mu$ ($\log \epsilon$ 3.96, 3.96, 3.78), and ν_{\max} 1742 (ester), 1706 (coumaranone C:O), and 1672 cm^{-1} (cyclohexenone C:O). The 2,4-dinitrophenylhydrazine crystallised from ethanol-ethyl acetate in orange needles, m. p. 251°, having ν_{\max} 1724 ($\alpha\beta$ -unsaturated ester) and 1706 cm^{-1} (coumaranone C:O) (Found: N, 11.0. $C_{23}H_{20}N_4O_9$ requires N, 11.3%).

(ii) A reaction conducted as in (i) but with the corresponding 3-methylenegrise carboxylate (1.0 g.) resulted in unchanged material (0.14 g.) and the 3,4'-dioxogris-3'-carboxylate (0.04 g.) m. p. and mixed m. p. 158°. Formaldehyde could not be detected amongst the reaction products.

4,6-Dimethoxy-2',6'-dimethylgris-2'-en-3,4'-dione (XVI; R = H, T = O).—In the standard conditions, oxidation of the 2',6'-dimethyl-3-methylenegrise (XVI; R = H, T = CH₂) (0.50 g.) by ruthenium tetroxide led to the recovery of this olefin (0.06 g.) and of the 2',6'-dimethylgris-3,4'-dione which crystallised from aqueous methanol in prisms (0.03 g.), m. p. 196° [Found: C, 67.4; H, 6.3; OMe, 20.8. $C_{15}H_{12}O_3$ (OMe)₂ requires C, 67.5; H, 6.0; OMe, 20.5%], λ_{\max} 213, 286, and 315 $m\mu$ ($\log \epsilon$ 4.83, 4.71, 4.08), ν_{\max} 1700 and 1667 cm^{-1} .

Methyl 4,6-Dimethoxy-2',6'-dimethyl-3,4'-dioxogris-2'-en-3'-carboxylate (XVI; R = CO₂Me, T = O).—Obtained from the corresponding methyl dimethyl-3-methylenegrise-3'-carboxylate (1.0 g.) by oxidation with ruthenium tetroxide, the methyl 3,4'-dioxogris-3'-carboxylate separated from methanol in needles (0.03 g.), m. p. 157° [Found: C, 63.2; H, 5.9; OMe, 26.1. $C_{18}H_{11}O_4$ (OMe)₃ requires C, 63.3; H, 5.6; OMe, 25.8%], λ_{\max} 212, 287, and 316 $m\mu$ ($\log \epsilon$ 4.51, 4.42, 3.80), ν_{\max} (in CH₃l₃) 1736 (ester), 1706 (coumaran-3-one), and 1689 cm^{-1} (cyclohexenone).