

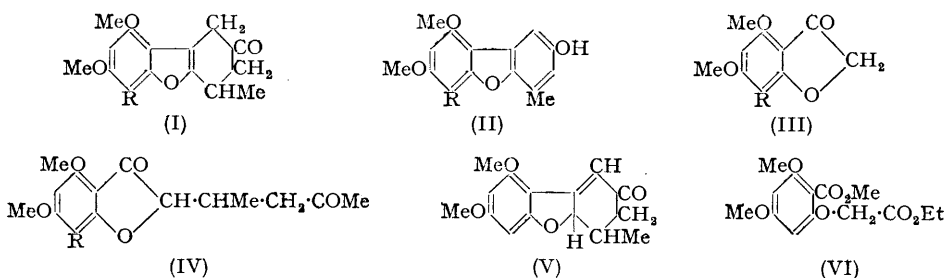
Griseofulvin. Part VIII. Syntheses of the Alkaline Rearrangement Products.*

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The (–)-ketone (I; R = Cl) and the phenol (II; R = Cl) have been synthesised, thereby confirming the structures proposed in Part IV (*J.*, 1952, 3977) for the products of alkaline hydrolysis and mercuric oxide oxidation of griseofulvin. The structures of the corresponding derivatives of dechloro-griseofulvin have also been verified by syntheses of the (±)-ketone (I; R = H) and the phenol (II; R = H); the methyl ether of the latter product has been made by two independent routes.

IN Part IV (*J.*, 1952, 3977) structure (I; R = Cl) was proposed for the ketone formed in the alkaline hydrolysis of griseofulvin, whilst the phenol, derived from it by aerial oxidation and also from griseofulvin by oxidation with alkaline mercuric oxide, was considered to be the dehydrogenation product (II; R = Cl). These conclusions have been confirmed by the syntheses of (–)-8-chloro-1:2:3:4-tetrahydro-5:7-dimethoxy-1-methyl-3-oxo-dibenzofuran (I; R = Cl) and the derived phenol (II; R = Cl), identical with the corresponding degradation products of griseofulvin. The structures proposed in Part VII* for the analogous derivatives of dechloro-griseofulvin have also been substantiated by syntheses of the (±)-form of (I; R = H) and the phenol (II; R = H). The crucial step in these syntheses involves ring closure of the ketone (IV) (cf. Panse, Shah, and Wheeler, *J. Indian Chem. Soc.*, 1941, 18, 453; Henecka, *Chem. Ber.*, 1949, 81, 197) and is thus essentially the last stage in the mechanism proposed in Part IV for the formation of (I; R = Cl) from griseofulvin.



In the griseofulvin series, 7-chloro-4:6-dimethoxycoumaran-3-one (III; R = Cl) was prepared from 2-chloro-3:5-dimethoxyphenol by ring closure of the intermediate ω:3-dichloro-2-hydroxy-4:6-dimethoxyacetophenone, and was condensed with pent-3-en-2-one, giving the Michael adduct (IV; R = Cl). Two racemates, arising from the creation of two centres of asymmetry, were isolated, each affording the (±)-form of (I; R = Cl) on ring closure with aqueous alkali. Resolution by means of (–)-menthyl *N*-aminocarbamate (Woodward, Kohmann, and Harris, *J. Amer. Chem. Soc.*, 1941, 63, 120) gave the (–)-form of (I; R = Cl), identical with the degradation product of griseofulvin. Regeneration of the ketone from the “(–)-menthydrazone” was difficult but was accomplished by hydrolysis in acetone with sulphuric acid.

Dehydrogenation of the (±)-ketone (I; R = Cl) by aerial oxidation as for the natural compound (Part II, *J.*, 1952, 3958) yielded the phenol (II; R = Cl). This and its methyl ether were identical with the phenol and methyl ether obtained from griseofulvin.

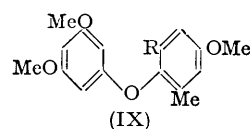
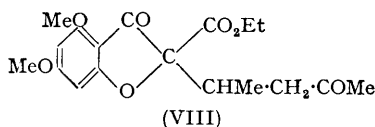
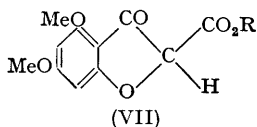
In the dechloro-series the intermediate Michael adduct (IV; R = H) was not isolated under the conditions employed. Condensation of 4:6-dimethoxycoumaranone (III; R = H) with pent-3-en-2-one gave directly the (±)-ketone (I; R = H) of which two

* Part VII, *J.*, 1953, 1697.

isomers were isolated. The α -isomer, m. p. 104°, which was the main product, did not depress the melting point of the natural compound, m. p. 100°, and both possessed identical infra-red spectra. Attempts to resolve the two isomers with (–)-menthyl *N*-aminocarbamate failed.

Catalytic dehydrogenation of both isomers as described for the natural compound afforded the phenol (II; R = H). The phenol and its methyl ether were identical with the corresponding compounds obtained from dechlorogriseofulvin.

The two (\pm)-isomers of the ketone (I; R = H) do not seem to be dimorphs since both can be sublimed unchanged, and can be separated by chromatography and, although a mixture melts at an intermediate value, the “(–)-menthydrazones” depress each other’s melting point. Since both give (II; R = H) on dehydrogenation they must possess the dibenzofuran skeleton. Although similar, the infra-red spectra of both forms showed small differences as solids and in ethylene chloride; both reveal the presence of an unconjugated carbonyl group (at 1715 in the α - and at 1720 cm.⁻¹ in the β -form) thus eliminating the $\alpha\beta$ -unsaturated keto-structure (V) for one of the isomers. The ultra-violet spectra of both isomers are identical with that of the natural ketone (I; R = H) (cf. Part VII) and show that the ethylenic bond is internuclear. It is conceivable that the α - and the β -isomer correspond to the two forms of the cyclohexene ring where the carbonyl group is either above or below the plane of the double bond with respect to the methyl group. On the other hand the energy of the interconversion should be small and attempts to bring this about by sublimation or by heating the β -isomer at 130° failed.



The (\pm)- α -ketone (I; R = H) was also made by treatment of the ester (VIII) with aqueous alkali, thus affording a closer analogy with the postulated mechanism (Part IV) for the alkaline rearrangement of griseofulvin to (I; R = Cl). The ester (VIII) was prepared by Michael addition of pent-3-en-2-one to the ester (VII) which in turn was obtained by the action of sodium on (VI) (cf. von Auwers, *Annalen*, 1912, 393, 338). Although the intermediates (VII; R = Me and Et) in this series did not melt sharply, the non-methoxylated analogue of (VII; R = Et), which was prepared for comparison, behaved as expected and gave 1 : 2 : 3 : 4-tetrahydro-1-methyl-3-oxodibenzofuran and the corresponding phenol.

Ring closure of ketones of the type (IV) provides a convenient synthesis of dibenzofurans substituted in the 3-position and the method could be extended to the preparation of derivatives unsubstituted in that position by reduction of the carbonyl group in the intermediate tetrahydro-3-oxodibenzofuran before dehydrogenation.

Finally the methyl ether of the phenol (II; R = H) was synthesised by an independent route. 2-Chloro-5-methoxy-3-nitrotoluene, prepared from the 2-amino-compound (MacMillan, *J.*, 1952, 4019), was heated with 3 : 5-dimethoxyphenol in the presence of potassium carbonate and copper bronze giving the diphenyl ether (IX; R = NO₂). Reduction and ring closure of the amine (IX; R = NH₂), *via* the diazonium salt, afforded the required dibenzofuran.

EXPERIMENTAL

Some microanalyses are by Messrs. W. Brown and A. G. Olney. In chromatography B.D.H. alumina was either activated for 3 hr. at 250°/17 mm. (pH 10 alumina) or rendered alkali-free (Prins and Shoppee, *J.*, 1946, 498) and then activated in the same way (pH 4 alumina). Infra-red absorption spectra were determined on Nujol mulls with a Grubb-Parsons S 3A spectrometer through which dry air was continuously circulated.

7-Chloro-4 : 6-dimethoxycoumaranone (III; R = Cl).—(i) A mixture of 2-chloro-3 : 5-dimethoxyphenol (2.0 g.) (*J.*, 1952, 3967), chloroacetyl chloride (2.5 g.), and nitrobenzene (3.0 g.) was treated with powdered aluminium chloride (2.8 g.). After the mixture had been kept at

room temperature for 20 hr., ice-water (40 ml.) and concentrated hydrochloric acid (8 ml.) were added, and nitrobenzene was removed by steam-distillation. The non-volatile product was collected and washed with water and then with methanol and ether until dark impurities were removed. ω : 3-Dichloro-2-hydroxy-4:6-dimethoxyacetophenone remained as a pale yellow powder (1.7 g.) which crystallised from dioxan as pale yellow needles, decomp. 211° (Found: C, 45.6; H, 3.9; Cl, 26.4; OMe, 22.2. $C_{10}H_{10}O_4Cl_2$ requires C, 45.3; H, 3.8; Cl, 26.8; 2OMe, 23.4%). The infra-red spectrum showed absorption due to carbonyl at 1633 cm^{-1} and to bonded hydroxyl at ~ 2600 cm^{-1} .

The chloroacetophenone (1.7 g.) and crystalline sodium acetate (2.0 g.) were heated under reflux with ethanol (200 ml.) for 1 hr. Removal of the solvent *in vacuo* gave 7-chloro-4:6-dimethoxycoumaranone, which, after being washed with water, crystallised from dioxan in needles (1.2 g.), decomp. 210—220° (depending on crystal size and rate of heating) (Found: C, 52.6; H, 4.25; Cl, 15.5; OMe, 24.3. $C_{10}H_9O_4Cl$ requires C, 52.6; H, 4.0; Cl, 15.5; 2OMe, 27.1%). The 2:4-dinitrophenylhydrazone crystallised from nitrobenzene in red needles, decomp. 248° (Found: C, 47.4; H, 3.3; N, 13.5. $C_{16}H_{13}O_7N_4Cl$ requires C, 47.0; H, 3.2; N, 13.7%). The benzylidene derivative, prepared by saturating the coumaranone (100 mg.) and benzaldehyde (50 mg.) in acetic acid (15 ml.) with dry hydrogen chloride at 0° during 1 hr. and decomposing the red complex with water, crystallised from ethanol in almost colourless needles, m. p. 264—265° (Found: C, 64.1; H, 4.4. $C_{17}H_{13}O_4Cl$ requires C, 64.4; H, 4.1%).

(ii) A solution of 2-chloro-3:5-dimethoxyphenol (11.0 g.) and chloroacetonitrile (5.5 g.) in ether (80 ml.) containing 8% of fused zinc chloride was saturated with dry hydrogen chloride at 0° for 4 hr. After 15 hr. at 0°, the ether was decanted, and the solid was washed with ether by decantation and then freed from ether and hydrogen chloride *in vacuo* over potassium hydroxide. After the addition of water (150 ml.) the mixture was heated on the steam-bath for 1 hr., cooled, and filtered. Tarry impurities were removed by washing with ethanol and with ether. The residue was heated under reflux for 1 hr. with ethanol (1 l.) and crystalline sodium acetate (8 g.). On cooling, 7-chloro-4:6-dimethoxycoumaranone separated. It crystallised from dioxan (charcoal) in almost colourless needles (6.8 g.), decomp. 198—204°.

(\pm)-7-Chloro-4:6-dimethoxy-2-(1-methyl-3-oxobutyl)coumaranone (IV; R = Cl).—A solution of 7-chloro-4:6-dimethoxycoumaranone (7.0 g.) and pent-3-en-2-one (2.4 g.) in dry dioxan (500 ml.) was treated with ethanolic sodium ethoxide (3.1 ml.; 2N) at 30—33° and kept for 24 hr. at room temperature. Acetic acid (30 ml.) was added and the mixture was evaporated to dryness *in vacuo*. A solution of the residue in benzene was washed with water, dried, concentrated to 60 ml., and chromatographed on a column (12 \times 2.5 cm.) of pH 4 alumina. A band fluorescing yellow (or blue in some purer preparations) in ultra-violet light was eluted with benzene (100 ml.). Recovery gave an oil, trituration of which with methanol yielded a solid (5.7 g.), m. p. 125—155°. (Further elution gave a little unchanged starting material followed by yellow substances.) Fractional crystallisation from ethanol and from benzene gave the less soluble (\pm)- α -7-chloro-4:6-dimethoxy-2-(1-methyl-3-oxobutyl)coumaranone (1.8 g.), m. p. 167—172°; after sublimation *in vacuo* it crystallised from ethanol in needles, m. p. 172—173° (Found: C, 57.4; H, 5.3; Cl, 11.45; OMe, 20.2. $C_{15}H_{17}O_5Cl$ requires C, 57.6; H, 5.5; Cl, 11.3; 2OMe, 19.8%). The β -isomer (1.03 g., m. p. 129—140°) was sublimed *in vacuo* and recrystallised from methanol, forming needles, m. p. 139—141° (Found: C, 57.4; H, 5.6; Cl, 11.45%). Mixed fractions (0.8 g.) were recovered.

Both isomers were saturated to neutral permanganate and gave precipitates with Brady's reagent. Their infra-red spectra were very similar and showed absorption due to carbonyl at 1710 cm^{-1} and absence of hydroxyl groups.

(\pm)-8-Chloro-1:2:3:4-tetrahydro-5:7-dimethoxy-1-methyl-3-oxodibenzofuran (I; R = Cl).—(i) (\pm)- α -7-Chloro-4:6-dimethoxy-2-(1-methyl-3-oxobutyl)coumaranone (45 mg.) and sodium hydroxide (6 ml.; 0.5N) were heated under reflux in an atmosphere of nitrogen for 6 hr. After cooling, the (\pm)-ketone (I; R = Cl) (38 mg.; m. p. 157—159°) was collected, washed with water, and purified by passage of a solution in benzene through a short column of pH 4 alumina followed by crystallisation from methanol, giving long needles, m. p. 167—168°, depressed on admixture with starting material (Found: C, 61.0; H, 5.2; Cl, 12.1. $C_{15}H_{15}O_4Cl$ requires C, 61.1; H, 5.1; Cl, 12.0%).

(ii) The β -isomer (100 mg.) and sodium hydroxide (5.0 ml.; N) were heated under reflux in nitrogen for 35 min. The product (81 mg.) crystallised from methanol (charcoal) in needles, m. p. 168—169°, identical (mixed m. p., infra-red spectrum, and analysis) with the (\pm)-ketone obtained from the α -isomer above. It was unsaturated to neutral permanganate, and the infra-red spectrum, which showed absorption due to an unconjugated carbonyl group at 1722 cm^{-1} ,

was similar to but not identical with that of (-)-8-chloro-1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethoxy-1-methyl-3-oxodibenzofuran obtained from griseofulvin.

The 2 : 4-dinitrophenylhydrazones crystallised from nitrobenzene in red needles, decomp. 238° (Found : C, 53.4; H, 4.2; N, 11.8. $C_{21}H_{19}O_7N_4Cl$ requires C, 53.3; H, 4.0; N, 11.8%).

Resolution of (±)-8-Chloro-1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethoxy-1-methyl-3-oxodibenzofuran (I; R = Cl).—Condensation of the above (±)-ketone (3.0 g.) with (-)-menthyl *N*-aminocarbamate under the conditions described by Woodward *et al.* (*loc. cit.*) gave the “(-)-menthydrazone” (4.30 g.), decomp. *ca.* 190°, $[\alpha]_D^{21} - 24^\circ \pm 2^\circ$ (*c.* 0.70 in $CHCl_3$). Crystallisation from ethanol gave long silky needles and short rosettes. The former were more soluble at this stage and were concentrated by extraction of the mixture with small amounts of warm ethanol. Recrystallisation, assisted by seeding, gave the “(-)-menthydrazone” of (-)-8-chloro-1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethoxy-1-methyl-3-oxodibenzofuran (240 mg.) as long needles, decomp. *ca.* 175—180°, $[\alpha]_D^{19} - 59^\circ \pm 2^\circ$ (*c.* 1.14 in $CHCl_3$) (Found : C, 63.7; H, 7.5; Cl, 7.4. $C_{26}H_{35}O_5N_2Cl$ requires C, 63.4; H, 7.2; Cl, 7.2%). The same derivative, decomp. *ca.* 175—180°, $[\alpha]_D^{25} - 58^\circ \pm 2^\circ$ (*c.* 1.03 in $CHCl_3$) (Found : C, 63.6; H, 7.0; Cl, 7.0%), with identical infra-red spectrum was prepared from the griseofulvin degradation product.

The “(-)-menthydrazone” (64 mg.) in acetone (7 ml.) was hydrolysed by heating it under reflux for 5 hr. with 6*N*-sulphuric acid (0.6 ml.). After dilution of the mixture with water (5 ml.), and evaporation of most of the acetone at room temperature, the product was taken up in benzene. The water-washed extract was concentrated to 3 ml. and passed through a column (1 × 3 cm.) of pH 4 alumina. The material recovered by elution with benzene was chromatographed twice more on smaller columns, crystallised from methanol, sublimed *in vacuo*, and recrystallised from methanol, giving needles of (-)-8-chloro-1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethoxy-1-methyl-3-oxodibenzofuran (10 mg.), *m. p.* 136—138°, $[\alpha]_D^{19} - 23^\circ \pm 2^\circ$ (*c.* 0.76 in $CHCl_3$) (Found : C, 61.0; H, 5.1. Calc. for $C_{15}H_{15}O_4Cl$: C, 61.1; H, 5.1%). It was identical (mixed *m. p.* and infra-red spectrum) with the natural ketone, $[\alpha]_D^{21} - 21^\circ \pm 2^\circ$ (*c.* 0.79 in $CHCl_3$) obtained from griseofulvin.

The second diastereoisomer was not obtained pure. Fractions of short needles, but more soluble than crude fractions of the same appearance, were obtained : $[\alpha]_D^{19} - 7^\circ \pm 2^\circ$ (*c.* 1.21 in $CHCl_3$). Hydrolysis gave the partially resolved ketone, *m. p.* 143—148°, $[\alpha]_D^{18} + 4^\circ \pm 2^\circ$ (*c.* 0.87 in $CHCl_3$).

1-Chloro-6-hydroxy-2 : 4-dimethoxy-8-methylidibenzofuran (II; R = Cl).—A suspension of (±)-8-chloro-1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethoxy-1-methyl-3-oxodibenzofuran (500 mg.) in sodium hydroxide (75 ml.; 2*N*) was heated under reflux in a stream of air for 6 hr. (*cf.* Part IV) and the mixture was worked up by the following improved method. After filtration of the hot mixture, the solid (286 mg.) which separated on cooling was collected and was dissolved in warm *N*-sodium hydroxide. The cooled, filtered solution deposited the sodium salt from which the free phenol (II; R = Cl) (115 mg.; *m. p.* 193—196°) was recovered by treatment with dilute hydrochloric acid. It crystallised from toluene (charcoal) in needles, *m. p.* 197—198° (Found : C, 61.6; H, 4.5; Cl, 12.1. Calc. for $C_{15}H_{13}O_4Cl$: C, 61.5; H, 4.5; Cl, 12.3%).

The methyl ether, obtained with methyl sulphate and sodium hydroxide, crystallised from ethanol in needles, *m. p.* 167—168° (Found : C, 62.6; H, 5.1; Cl, 12.3. Calc. for $C_{16}H_{15}O_4Cl$: C, 62.65; H, 4.9; Cl, 11.6%).

The synthetic phenol and its methyl ether were identical (mixed *m. p.* and infra-red spectra) with the corresponding compounds obtained from griseofulvin.

(±)- α - and β -1 : 2 : 3 : 4-Tetrahydro-5 : 7-dimethoxy-1-methyl-3-oxodibenzofuran (I; R = H).—A solution of 4 : 6-dimethoxycoumarone (18.5 g.) (Mulholland and Ward, *J.*, 1953, 1642) and pent-3-en-2-one (8.0 g.) in dry dioxan (450 ml.) was treated with ethanolic sodium ethoxide (7.85 ml.; 2*N*) at 20°. After 20 hr., acetic acid (40 ml.) was added and the mixture was evaporated to dryness *in vacuo*. A solution of the residual gum in ether (350 ml.) was filtered, washed with sodium hydrogen carbonate solution and then with water, dried ($CaCl_2$), treated with charcoal, and chromatographed on a column of pH 4 alumina (12 × 6.3 cm.). Fluorescent bands were eluted with ether in ultra-violet light : (i) A violet band, together with a little of the following band, and giving a solid (3.6 g.) on recovery. (ii) A blue band, giving a solid (8.2 g.) on recovery. Other bands remaining on the column were rejected.

The material from eluate (ii) was crystallised from methanol, sublimed *in vacuo* and recrystallised from methanol, giving (±)- α -1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethoxy-1-methyl-3-oxodibenzofuran (6.7 g.) as needles, *m. p.* 104° (Found : C, 69.6; H, 6.2; C-Me, 6.0. $C_{15}H_{16}O_4$ requires C, 69.2; H, 6.2; 1C-Me, 5.8%). The infra-red spectrum of the solid showed absorption due to a carbonyl group at 1715 cm^{-1} , and was identical with that of (-)-1 : 2 : 3 : 4-tetrahydro-

5 : 7-dimethoxy-1-methyl-3-oxodibenzofuran (m. p. 100°) obtained from dechlorogriseofulvin. A mixture showed no depression in m. p. The 2 : 4-dinitrophenylhydrazone crystallised from nitrobenzene in red needles, decomp. 234° (Found : C, 57.5; H, 4.7; N, 11.3. $C_{21}H_{20}O_7N_4$ requires C, 57.3; H, 4.6; N, 12.7%). The “(-)-menthydrazone” crystallised from ethanol in needles, decomp. 169—170°, $[\alpha]_D^{20} - 25^\circ$ (c, 1.0 in acetone) (Found : C, 68.3; H, 8.1; N, 6.6. $C_{26}H_{36}O_5N_2$ requires C, 68.4; H, 7.95; N, 6.1%); it could not be resolved by crystallisation from ethanol or benzene, and chromatography on pH 4 alumina led to recovery of the (\pm)-ketone.

Material recovered from the mother-liquors of crystallisation of the α -isomer was combined with the product from eluate (i). The mixture (3.7 g.) was sublimed *in vacuo* and then chromatographed again. The violet and the blue band were fractionally eluted with ether, and gave, on recovery, (i) 0.9 g., m. p. 88—89°, (ii) mixed fractions (1.5 g.), m. p. 88—89°, (iii) the α -isomer (0.3 g.), m. p. 101—103°.

The first fraction consisted of (\pm)- β -1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethoxy-1-methyl-3-oxodibenzofuran, which crystallised from methanol in prisms (0.62 g.), m. p. 90°, not changed by further crystallisation (Found : C, 69.2, 69.7; H, 6.2, 6.5; OMe, 22.6; C-Me, 5.15. $C_{15}H_{16}O_4$ requires C, 69.2; H, 6.2; 2OMe, 23.8; 1C-Me, 5.8%) A mixture with the α -isomer had m. p. 88—97°. The infra-red spectrum of the solid showed absorption due to carbonyl at 1720 cm^{-1} and was similar to, but not identical with, that of the α -isomer. Slight differences were also present in the infra-red spectra of the two isomers dissolved in ethylene chloride.

The β -form was not converted into the α -form when heated at 130° for 15 min. or when seeded during crystallisation with the α -form.

The “(-)-menthydrazone” crystallised from 90% ethanol in plates, decomp. 161—163°, depressed to 157—158° by mixture with the “(-)-menthydrazone” of the α -isomer, $[\alpha]_D^{19} - 24^\circ$ (c, 1.0 in acetone) (Found : C, 68.7; H, 8.1; N, 6.4%). The derivative could not be resolved by crystallisation.

3-Hydroxy-5 : 7-dimethoxy-1-methyldibenzofuran (II; R = H).—Dehydrogenation of (\pm)- α -1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethoxy-1-methyl-3-oxodibenzofuran (200 mg.) with 5% palladium-charcoal as described in Part VII (*loc. cit.*) gave the phenol (II; R = H) (76 mg.) which crystallised from benzene-light petroleum (b. p. 60—80°) in needles, m. p. 171—172° (Found : C, 70.1; H, 5.6. Calc. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.5%).

The methyl ether, prepared with methyl sulphate and sodium hydroxide and crystallised from methanol, had m. p. 117° (Found : C, 70.3; H, 6.0. Calc. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9%).

The phenol and its methyl ether were identical (mixed m. p. and infra-red spectra) with the corresponding compounds obtained from dechlorogriseofulvin.

Dehydrogenation of (\pm)- β -1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethoxy-1-methyl-3-oxodibenzofuran under the above conditions also gave 3-hydroxy-5 : 7-dimethoxy-1-methyldibenzofuran, identical (m. p. and mixed m. p., infra-red spectrum, and analysis) with material obtained from the α -isomer.

Ethyl 4 : 6-Dimethoxy-3-oxocoumaran-2-carboxylate (VII; R = Et).—Methyl 2-hydroxy-4 : 6-dimethoxybenzoate (1.0 g.) was heated under reflux with ethyl bromoacetate (0.70 g.) and potassium carbonate (0.70 g.) in acetone (7 ml.) for 6 hr. After filtration, recovery gave ethyl 2-methoxycarbonyl-3 : 5-dimethoxyphenoxyacetate (VI) (1.25 g.), crystallising from aqueous methanol in needles, m. p. 84° (Found : C, 56.4; H, 6.2. $C_{14}H_{16}O_4$ requires C, 56.4; H, 6.1%). On a larger scale it was necessary to wash the crude product with cold dilute sodium hydroxide to remove phenolic material, giving yields of about 80%.

A solution of this ester (17.3 g.) in dry benzene (100 ml.) was treated with powdered sodium (1.61 g.), and then heated under gentle reflux for 3 hr. An aqueous extract of the cooled mixture was treated with charcoal and acidified with concentrated hydrochloric acid at 0°. Recovery of the product in benzene (charcoal) gave a gum which crystallised (6.2 g.) under methanol. The crude product (21 g.) from 39.5 g. of starting material crystallised from ethanol in prisms (15.5 g.), m. p. 103—110°, of ethyl 4 : 6-dimethoxy-3-oxocoumaran-2-carboxylate (Found : C, 58.5; H, 5.2. $C_{13}H_{14}O_6$ requires C, 58.6; H, 5.3%). The ester could not be obtained with a sharp m. p. A specimen crystallised 5 times had m. p. 108—114° (Found : C, 58.1; H, 4.8%). It gave a green colour in ethanol with ferric chloride.

The *O*-acetate, obtained by heating the ester under reflux with acetic anhydride and sodium acetate, was purified by passage of a benzene solution through a short column of pH 4 alumina, and crystallised from ethanol in needles, m. p. 103—104° (Found : C, 58.2; H, 5.2. $C_{15}H_{16}O_7$ requires C, 58.4; H, 5.2%).

Ethyl 4 : 6-Dimethoxy-2-(1-methyl-3-oxobutyl)-3-oxocoumaran-2-carboxylate (VIII).—A solution of ethyl 4 : 6-dimethoxy-3-oxocoumaran-2-carboxylate (2.66 g.) and pent-3-en-2-one (0.84 g.) in benzene (25 ml.) was treated at 20° with ethanolic sodium ethoxide (0.83 ml.; 2N), and the mixture was set aside at room temperature for 24 hr.

The solid (A) (0.8 g.) was collected and the mother-liquor, after the addition of acetic acid (0.5 ml.), was evaporated to dryness *in vacuo*. The ether-washed residue (1.6 g.) was combined with (A) and crystallised from dioxan, giving 1.2 g., m. p. 173—181°. A sample (0.3 g.) in benzene (30 ml.) was chromatographed in benzene on a column of pH 4 alumina (2 × 20 cm.), and a band fluorescing blue in ultra-violet light was eluted with benzene containing 1% of methanol. The recovered product (0.25 g.), m. p. 174—180°, was crystallised several times from benzene and from benzene-light petroleum, giving needles of *ethyl 4 : 6-dimethoxy-2-(1-methyl-3-oxobutyl)-3-oxocoumaran-2-carboxylate*, m. p. 188—190° (Found: C, 61.3; H, 6.2. C₁₈H₂₂O₇ requires C, 61.7; H, 6.3%). The compound gave a precipitate with Brady's reagent.

Reaction with sodium hydroxide. The above ketone (200 mg.) was heated under reflux with sodium hydroxide (5 ml.; N) in an atmosphere of nitrogen for 30 min. An ethereal extract of the cooled mixture was treated with charcoal, dried, and evaporated. The pale yellow crystals (51 mg.), after sublimation *in vacuo* and crystallisation from methanol, had m. p. 104°, identical (mixed m. p. and infra-red spectrum) with (±)-α-1 : 2 : 3 : 4-tetrahydro-5 : 7-dimethoxy-1-methyl-3-oxodibenzofuran, already obtained by a different method (above).

Methyl 4 : 6-Dimethoxy-3-oxocoumaran-2-carboxylate (VII; R = Me).—*Methyl 2-methoxy-carbonyl-3 : 5-dimethoxyphenoxyacetate* was prepared in 80% yield as described for the ethyl ester (above) and crystallised from methanol in prisms, m. p. 105—107° (Found: C, 55.0; H, 5.7. C₁₃H₁₆O₇ requires C, 54.9; H, 5.7%).

Ring closure of the methyl ester (1.42 g.) was carried out by heating it under reflux for 1 hr. with sodium (0.135 g.) in benzene (15 ml.). Extraction of the mixture with water, acidification, and recovery of the product in ether (sodium hydrogen carbonate washing) gave *methyl 4 : 6-dimethoxy-3-oxocoumaran-2-carboxylate* (0.85 g.; m. p. 103—110°). A specimen crystallised from methanol in prisms, m. p. 117—121° (Found: C, 57.5, 56.6; H, 5.15, 4.95. C₁₂H₁₂O₆ requires C, 57.1; H, 4.8%). It gave a green colour in ethanol with ferric chloride. The *O-acetate* crystallised from ethanol in needles, m. p. 124—125° (Found: C, 57.5; H, 4.9. C₁₄H₁₄O₇ requires C, 57.1; H, 4.8%).

Ethyl 2-(1-Methyl-3-oxobutyl)-3-oxocoumaran-2-carboxylate.—A solution of ethyl 3-oxocoumaran-2-carboxylate (3.5 g.) (Friedlander, *Ber.*, 1899, **32**, 1869; von Auwers, *loc. cit.*) and pent-3-en-2-one (1.43 g.) in benzene (40 ml.) was treated with ethanolic sodium ethoxide (1.40 ml.; 2N) at 20°. Crystals, which separated, gradually dissolved. After 20 hr. the clear solution was acidified with acetic acid (2.0 ml.), and the mixture was evaporated to dryness *in vacuo*. An ethereal extract (200 ml.) of the residue was washed with water, dried, and passed through a column (3 × 1.5 cm.) of pH 4 alumina. Crystallisation of the recovered material from aqueous ethanol gave plates of the cyclised *ester* (2.4 g.), m. p. 94—95° (96—97° after recrystallisation) (Found: C, 66.4; H, 6.1; C-Me, 14.8. C₁₆H₁₈O₅ requires C, 66.2; H, 6.25; 3C-Me, 15.5%). It was saturated to neutral permanganate and gave a precipitate on warming with Brady's reagent.

Reaction with alkali. After the carboxylate (2.0 g.) had been heated with sodium hydroxide (50 ml.; N) under reflux in nitrogen for 1 hr., the mixture was steam-distilled. After cooling, 1 : 2 : 3 : 4-tetrahydro-1-methyl-3-oxodibenzofuran was filtered from the distillate, and crystallised from dilute ethanol in needles and plates (0.93 g.), m. p. 111° (Found: C, 78.2; H, 5.9. C₁₃H₁₂O₂ requires C, 78.0; H, 6.0%). The compound gave a precipitate with Brady's reagent and was unsaturated to neutral permanganate. The infra-red spectrum showed absorption due to an unconjugated carbonyl group at 1720 cm.⁻¹.

Dehydrogenation of the ketone (200 mg.) with 30% palladium-charcoal followed by sublimation gave 3-hydroxy-1-methyl-dibenzofuran (108 mg.), m. p. 147—148°, needles from benzene-light petroleum (b. p. 60—80°) (Found: C, 78.6; H, 5.0. C₁₃H₁₀O₂ requires C, 78.8; H, 5.1%).

2-Chloro-5-methoxy-3-nitrotoluene (cf. Ullmann, *Ber.*, 1896, **29**, 1878).—The hydrochloride of 2-amino-5-methoxy-3-nitrotoluene (3.0 g.) (MacMillan, *J.*, 1952, 4019), preparing by pouring a solution in concentrated hydrochloric acid (12 ml.) over ice (15 g.), was diazotised with sodium nitrite (1.5 g.) in water (4.0 ml.). After 10 min. the diazonium solution was added (vigorous reaction) with stirring to a mixture of copper bronze and precipitated copper (1 : 1; 4.0 g.) moistened with concentrated hydrochloric acid, stirring being continued for 3 hr. Steam-distillation, and ether-extraction of the distillate, gave an oil which was chromatographed in benzene (30 ml.) on alumina (pH 10; 15 × 1 cm.); elution of the broad yellow band with

benzene and recovery yielded the chloro-compound which, after sublimation at 100° and 10 mm., crystallised from benzene–light petroleum (b. p. 60–80°) in yellow needles (3.0 g.), m. p. 69° (Found: C, 48.0; H, 3.8; Cl, 17.2; N, 6.7. $C_8H_8O_3NCl$ requires C, 47.8; H, 4.0; Cl, 17.6; N, 6.7%).

4 : 3' : 5'-Trimethoxy-2-methyl-6-nitrodiphenyl Ether (IX; R = NO₂) (cf. Dunlop and Tucker, *J.*, 1939, 1945).—The above chloro-compound (1.5 g.), 3 : 5-dimethoxyphenol (705 mg.), potassium carbonate (630 mg.), and copper bronze (15 mg.) were intimately mixed and heated at 170° until evolution of carbon dioxide had ceased (barium hydroxide trap). After recovery of the excess of chloro-compound by steam-distillation, the residue was extracted with benzene, and the concentrated extract passed through a column of pH 4 alumina (25 × 1 cm.). Elution of the lower broad yellow band with benzene and recovery gave the diphenyl ether, crystallising from benzene–light petroleum (b. p. 60–80°) in buff needles, m. p. 107° (Found: C, 60.6; H, 5.4; N, 4.6. $C_{16}H_{17}O_6N$ requires C, 60.2; H, 5.4; N, 4.4%).

The recovered chloro-compound (180 mg.) was used again and the process repeated three times, giving a total of 1.8 g. of the product.

6-Amino-4 : 3' : 5'-trimethoxy-2-methyldiphenyl ether (IX; R = NH₂).—The above nitro-compound (440 mg.) in ethyl acetate (25 ml.) was shaken with Raney nickel (1.0 g.) in an atmosphere of hydrogen (2 hr.) at room temperature and pressure. Removal of the catalyst and solvent afforded the amine as an oil which, after passage through a column of alumina (pH 10; 10 × 0.7 cm.) and elution of the broad yellow band with benzene, crystallised from aqueous ethanol in needles (300 mg.), m. p. 96° (Found: C, 66.1; H, 6.25; N, 4.8. $C_{16}H_{19}O_4N$ requires C, 66.4; H, 6.6; N, 4.8%).

3 : 5 : 7-Trimethoxy-1-methyldibenzofuran.—The above amine (500 mg.) in concentrated hydrochloric acid (10 ml.) was diazotised at 0° with sodium nitrite (200 mg.) in water (1.25 ml.), and the diazonium solution was added dropwise to boiling 50% sulphuric acid (10 ml.). After the addition was complete, the mixture was heated under reflux for 2 hr., cooled, diluted with water, and extracted with benzene. The dried, water-washed benzene extract was concentrated to 50 ml. and passed through a column of alumina (pH 10; 15 × 1 cm.) which removed dark strongly adsorbed impurities. Elution of the colourless region with benzene and recovery gave the required dibenzofuran (ca. 10 mg.), which, after several recrystallisations from ethanol, was obtained in prisms, m. p. 115–116°, identical (mixed m. p. and infra-red spectrum) with the methyl ether of the phenol obtained from dechlorogriseofulvin by mercuric oxide oxidation; the m. p. (140–148°) of the picrate was undepressed on mixture with the picrate of the natural methyl ether.

In a small-scale trial run, a trace of a basic compound, m. p. ca. 58°, of unknown structure was isolated from the benzene-extracted mixture but was not obtained in the large-scale experiment.

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