

1284. *The Synthesis of an Analogue of Griseofulvin*

By R. F. CURTIS, C. H. HASSALL, and D. W. JONES

Investigations of the oxidation of substituted 2,4'-dihydroxybenzophenones have established that the corresponding spirodienones are formed when bulky groups occupy the 6-position. Substitution in the 2'- or 6'-position also favours the intramolecular oxidative coupling reaction. The synthesis of (XIII), a biologically-active analogue of griseofulvin, has been achieved by controlled hydrogenation of the typical spirodienone(V).

RECENT studies¹⁻³ established that relatively small modifications of the structure of griseofulvin (I) may cause significant changes in antifungal activity. There is, therefore, reason to extend investigations of molecular structure-biological activity relationships in this series. Of the alternative synthetic routes to (\pm)-griseofulvin and its analogues,⁴ the procedure which simulated the biosynthetic pathway through 2,4'-dihydroxybenzophenone derivatives appeared to be the most convenient. Although there are several

¹ D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, 1963, **28**, 3344, and earlier Papers there cited.

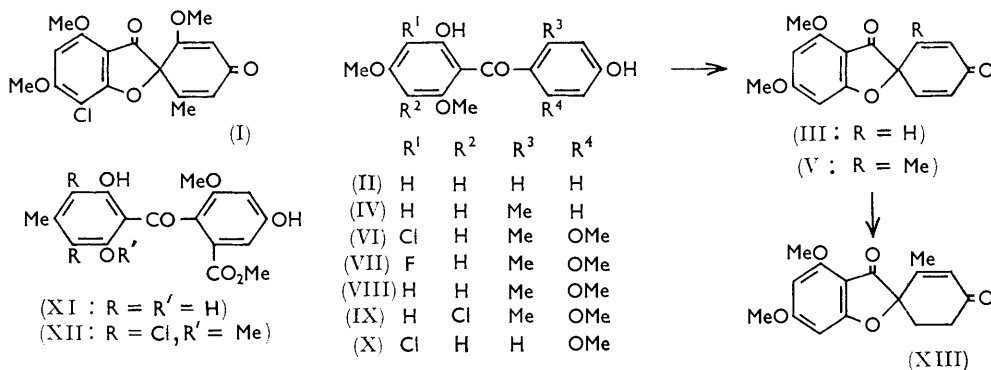
² S. R. Goodall, G. I. Gregory, and T. Walker, *J.*, 1963, 1610, and earlier Papers there cited.

³ M. Gerecke, E. Kyburz, C. v. Planta, and A. Brossi, *Helv. Chim. Acta*, 1962, **45**, 2241.

⁴ J. F. Grove, *Quart. Rev.*, 1963, **17**, 1; *Fortschr. Chem. org. Naturstoffe*, 1964, **22**, 203.

cases of oxidation of such substituted benzophenones, the scope of this procedure has not been defined. We have studied further examples, for this purpose, and in one typical case have completed the synthesis of a novel analogue of griseofulvin.

We have found that 2,4'-dihydroxybenzophenone,⁵ 2,4,4'-trihydroxybenzophenone,⁶ 2,2',4-trihydroxybenzophenone,⁷ and 2'-methyl-2,4,4'-trihydroxybenzophenone did not give the corresponding spirodienones on oxidation with potassium ferricyanide in alkali or with lead dioxide. This was in accord with a suggestion,⁸ based on a limited number of cases, that 2',6'-disubstitution was necessary for this intramolecular oxidation with "one-electron" oxidising agents. However, there were two cases in disagreement with this suggestion. 2,4'-Dihydroxy-4,6-dimethoxybenzophenone (II) could be oxidised to the corresponding spirodienone (III) with lead dioxide, although the yield was low. In the second case, the benzophenone (IV) was converted in good yield both by active lead dioxide



and by alkaline potassium ferricyanide into the corresponding spirodienone (V). This, together with the evidence that the 2,4'-dihydroxybenzophenone derivatives (VI),^{9,10} (VII),¹¹ (VIII),¹ (IX),¹ (X),¹ (XI),¹² and (XII)⁹ are known to be oxidised under these conditions, indicated that the presence of a bulky group in 6-position led to the formation of the corresponding spirodienones. Examination of Fischer-Taylor-Hirschfelder models showed that the presence of bulky 6-substituents, such as hydroxyl or methoxyl, in a 2,4'-dihydroxybenzophenone ensured a significant degree of non-planarity of the two benzene rings and this, presumably, favoured the intramolecular coupling reaction. Clearly, the occurrence of bulky substituents in the 2'- or 6'-position will have a similar effect. Differences in the ultraviolet absorption spectra¹³ of substituted benzophenones may be attributed to related steric effects.

Catalytic hydrogenation of the dienone (V) in pentyl acetate or xylene gave no indication of hydrogenolysis, and when the uptake was limited to one mole of hydrogen the product (XIII) was obtained in 50% yield. This result was similar to that of Taub *et al.*¹⁰ who found that a spiro-enone could be obtained from the corresponding spirodienone by hydrogenation in non-hydroxylic solvents, whereas, in ethanol, hydrogenolysis to a benzophenone derivative predominated. Although two structures, (XIII) and (XIV), were possible for the enone derived from the compound (V), the former was evidently favoured,

⁵ F. F. Blicke and O. S. Weinkauff, *J. Amer. Chem. Soc.*, 1932, **54**, 1446.

⁶ A. Komarowsky and St. v. Kostanecki, *Ber.*, 1894, **27**, 1997.

⁷ H. Atkinson and I. M. Heilbron, *J.*, 1926, 2688.

⁸ A. I. Scott, *Quart. Rev.*, 1965, **19**, 1.

⁹ A. I. Scott, *Proc. Chem. Soc.*, 1958, 195; A. C. Day, J. Nabney, and A. I. Scott, *Proc. Chem. Soc.*, 1960, 284; *J.*, 1961, 4067.

¹⁰ D. Taub, C. H. Kuo, H. L. Slater, and N. L. Wendler, *Tetrahedron*, 1963, **19**, 1.

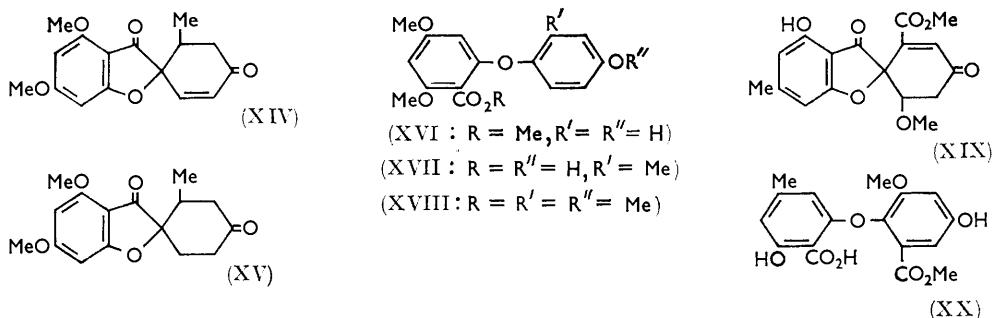
¹¹ D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, 1963, **28**, 2752.

¹² R. F. Curtis, C. H. Hassall, D. W. Jones, and T. W. Williams, *J.*, 1960, 4838.

¹³ E. J. Moriconi, W. F. O'Connor, and W. F. Forbes, *J. Amer. Chem. Soc.*, 1962, **84**, 3928.

as the 5'-ethylenic linkage was more accessible to association with the catalyst. The structure (XIII) was confirmed through the determination of the n.m.r. spectrum, which was kindly undertaken by Professor N. Sheppard. The assignments were facilitated by comparison with the spectra of the corresponding spirodienone (V) and the ketone (XV). The resonance of the 2'-methyl group in both the dienone (V) and the hydrogenation product (XIII) appeared as a very finely split doublet, τ 8.26, whereas the spectrum of the ketone (XV) included a doublet, τ 8.98 and 9.12, arising from interaction of the 2'-methyl group and the adjacent saturated system. The spectrum of the enone (XIII) included, as in the case of (XIV), a quadruplet centred at τ 7.55, which was attributed to $-\text{CH}_2-\text{CH}_2-$ resonances.

The spirodienones (III) and (V) were converted by acid-catalysed hydrolysis (or methanolysis) into the corresponding diphenyl ether derivatives (XVI) and (XVII), (or XVIII), respectively. This reaction is similar to the acid-catalysed hydrolysis of dechlorogodin (XIX) to asterric acid (XX).¹²



We are indebted to Dr. J. D. Levi for comparing the antifungal activities of griseofulvin and the compound (XIII). Griseofulvin was active in the "curling" test against *Botrytis allii* at a concentration approximately one hundredth of that of our synthetic compound, but spore germination of a strain of *Verticillium albo-atrum* was only five times more sensitive to inhibition by griseofulvin.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. Ultraviolet spectra were measured in ethanol and infrared absorption spectra in potassium bromide discs. N.m.r. spectra were determined in chloroform with a Perkin-Elmer 40 Mc. spectrometer using tetramethylsilane as an internal standard. Peak positions are recorded on the τ scale. Unless otherwise described alumina was Spence H, neutralised with dilute nitric acid, washed with water and methanol, dried in air, and activated at 110° for 12 hr. Thin-layer chromatography (system IV) was described in Part V.¹⁴

2,4'-Dihydroxy-4,6-dimethoxy-6'-methylbenzophenone (IV).—4-Hydroxy-2-methylbenzoic acid¹⁵ in *n*-sodium hydroxide was treated with methyl chloroformate in the usual way, to give the 4-*O*-methoxycarbonyl derivative. This derivative (2.42 g.), m. p. 155–157° (from acetone), was heated under reflux with distilled thionyl chloride (40 ml.) for 1 hr. Excess reagent was removed under reduced pressure at 40° and the residual acid chloride was dissolved in dry benzene (30 ml.). 3,5-Dimethoxyphenyl benzoate¹⁶ (2.75 g.) and zinc chloride (2 g.) were added, and the mixture was heated under reflux for 3.5 hr. The solvent was decanted, washed with *n*-sodium carbonate, and distilled. The residual gum (3.9 g.) was boiled in aqueous ethanol (120 ml.; 1 : 1) and potassium hydroxide (10 g.) for 2 hr. After removal of the ethanol under reduced pressure the aqueous solution was worked up to give the product (IV) (2.2 g.), yellow needles from aqueous ethanol, m. p. 85° (Found: C, 66.9; H, 5.5; O, 27.9; OMe, 21.8; C-Me,

¹⁴ R. F. Curtis, P. C. Harries, C. H. Hassall, and J. D. Levi, *Biochem. J.*, 1964, **90**, 43.

¹⁵ F. Tiemann and C. Schotten, *Ber.*, 1878, **11**, 767.

¹⁶ J. Pollak, *Monatsh.*, 1897, **18**, 738.

5-5. $C_{16}H_{16}O_5$ requires C, 66.7; H, 5.6; O, 27.8; 2OMe, 21.5; 1C-Me, 5.2%, λ_{\max} 297 $m\mu$ ($\log \epsilon$ 4.22), ν_{\max} 1618 (H-bonded CO) and 1582 cm^{-1} (aromatic C=C), R_F 0.69 (red-purple). The compound gave a brown colour with ethanolic ferric chloride. The diacetate crystallised from light petroleum as prisms, m. p. 113° (Found: C, 64.3; H, 5.5; O, 30.0. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4; O, 30.1%).

4,6-Dimethoxy-2'-methylgris-2',5'-dien-3,4'-dione (V).—The preceding benzophenone (500 mg.) was dissolved in deaerated water (25 ml.) containing sodium carbonate (1.5 g.). Potassium ferricyanide (2 g.) in deaerated water (25 ml.) was added with vigorous stirring under nitrogen during 10 min. After a further 10 min. the solution was acidified and shaken with chloroform (2 × 25 ml.). The chloroform extract was washed with 2N-sodium carbonate (3 × 25 ml.), dried, and evaporated, to give a neutral product (330 mg.). This was purified by chromatography in benzene on alumina (Woelm, basic, grade III); the benzene eluate (200 ml.) was evaporated and the residue crystallised from chloroform-ether to give the product (V), prisms (250 mg.), m. p. 186–189° [Found: C, 66.9; H, 4.9; O, 28.3%; M (Rast), 334. $C_{16}H_{14}O_5$ requires C, 67.1; H, 4.9; O, 28.0%; M , 286], λ_{\max} 290 $m\mu$ ($\log \epsilon$ 4.47), ν_{\max} 1724 (C=O in spirocoumaran), 1667 (1,4-dienone), 1613 (enone), 1587 cm^{-1} (aromatic C=C). N.m.r. spectrum: τ 3.7 (quartet, aromatic and ethylenic protons); 6.12 (2OMe groups); 8.26 (doublet, $CH_3-C=CH-$). R_F 0.78 (yellow-brown). The compound gave no colour with ethanolic ferric chloride.

When the same benzophenone (130 mg.) in chloroform (20 ml.) was shaken with active lead dioxide (500 mg.) for 4 hr. and worked up by filtration and chromatography, the same dienone (V) (90 mg.) was obtained.

4,6-Dimethoxy-2'-methylgris-2'-en-3,4'-dione (XIII).—The dienone (V) (100 mg.) in sulphur-free xylene (previously shaken for 4 hr. with palladium-charcoal) was shaken with 10% palladium-charcoal (12 mg.) in an atmosphere of hydrogen. After an induction period (75 min.), absorption commenced and was stopped when 1 mol. (8 ml.) had been absorbed. Catalyst was removed and the residue was purified by chromatography on alumina (6 g.). Elution with benzene (80 ml.) gave the dione (XV) (33 mg.), prisms from benzene-light petroleum (b. p. 60–80°), m. p. 146–148°, undepressed with authentic material (see below).

Further elution with benzene (570 ml.) gave the product (XIII) (50.2 mg.), m. p. 154–157°. Recrystallisation from benzene-light petroleum (b. p. 60–80°) gave needles, m. p. 158–159° (Found: C, 66.5; H, 5.5; O, 28.9. $C_{16}H_{16}O_5$ requires C, 66.7; H, 5.6; O, 27.7%), λ_{\max} 285 $m\mu$ ($\log \epsilon$ 4.37), ν_{\max} 1709 (C=O in spirocoumaran) and 1672 cm^{-1} (conjugated C=O). N.m.r. spectrum τ 3.90 (complex series, aromatic and ethylenic protons); 6.12 (2 OMe groups); 7.55 (quartet, $-CH_2-CH_2-$); 8.26 (doublet, $CH_3-C=CH-$). R_F 0.74 (pale blue).

4,6-Dimethoxy-2'-methylgris-3,4'-dione (XV).—The dienone (V) (100 mg.) in purified isopentyl acetate was shaken with 10% palladium-charcoal (12 mg.) under hydrogen. After an induction period, hydrogen uptake (2 mol., 16 ml.) was complete in 15 min. Catalyst was removed, solvent evaporated, and the residue recrystallised from chloroform-ether to give the product (XV), prisms, m. p. 149–150° [Found: C, 65.7; H, 6.3; O, 27.8%; M (Rast), 330. $C_{16}H_{18}O_5$ requires C, 66.2; H, 6.3; O, 27.6%; M , 290], λ_{\max} 282 $m\mu$ ($\log \epsilon$ 4.36), ν_{\max} 1724 (C=O in spirocoumaran) and 1695 cm^{-1} (conjugated C=O). N.m.r. spectrum: τ 3.9 (quartet, aromatic protons); 6.10 (2 OMe groups); 7.3–8.5 (complex series, CH_2 groups); 8.98 and 9.12 ($CH_3-CH<$). R_F 0.78 (mauve).

2-Carboxy-4'-hydroxy-3,5-dimethoxy-2'-methyldiphenyl Ether (XVII).—The dienone (V) (50 mg.) in glacial acetic acid (10 ml.) and water (0.1 ml.) was allowed to stand for 18 hr. Solvent was removed under reduced pressure and the residue was worked up in the usual way to give the product (XVII) (39 mg.), prisms from ethyl acetate-light petroleum (b. p. 60–80°), m. p. 173° (Found: C, 63.3; H, 5.5; O, 31.1. $C_{16}H_{16}O_6$ requires C, 63.2; H, 5.3; O, 31.5%), λ_{\max} 280 $m\mu$ ($\log \epsilon$ 3.52), ν_{\max} 1712 cm^{-1} (aromatic CO_2H). R_F 0.56 (yellow).

3,4',5'-Trimethoxy-2-methoxycarbonyl-2'-methyldiphenyl Ether (XVIII).—The dienone (V) (50 mg.) in dry methanolic hydrogen chloride (2% w/v; 16 ml.) was allowed to stand for 12 hr. After removing the solvent the residue crystallised from benzene-light petroleum (b. p. 60–80°), to give the product (XVIII), needles (37 mg.), m. p. 142° (Found: C, 64.7; H, 6.2; O, 29.1. $C_{18}H_{20}O_6$ requires C, 65.0; H, 6.1; O, 28.9%), λ_{\max} 280 $m\mu$ ($\log \epsilon$ 3.54), ν_{\max} 1706 cm^{-1} (aromatic CO_2Me).

2,4'-Dihydroxy-4,6-dimethoxybenzophenone (II).—4-Methoxycarbonyl benzoic acid (1.8 g.) was heated under reflux with thionyl chloride (30 ml.) for 1 hr. Excess reagent was removed and the residual acid chloride was dissolved in anhydrous benzene (30 ml.). 3,5-Dimethoxyphenyl

benzoate¹⁶ (2.5 g.) and zinc chloride (2 g.) were added, and the mixture was heated under reflux (3.5 hr.). The product was worked up as described above for the benzophenone (IV), to give the *product* (II) (0.86 g.) as long yellow needles (from dilute aqueous ethanol), m. p. 135—145°. Recrystallisation from chloroform–light petroleum (b. p. 60—80°) gave yellow needles, m. p. 151—152° (Found: C, 65.8; H, 5.4; O, 29.2; OMe, 22.2. C₁₅H₁₄O₅ requires C, 65.7; H, 5.2; O, 29.2; 2 OMe, 22.6%), λ_{\max} 290 m μ (log ϵ 4.14), ν_{\max} 1631 (H-bonded CO) and 1610 cm.⁻¹ (aromatic C=C). R_F 0.69 (red-purple). The compound gave a red-brown colour with ethanolic ferric chloride.

4,6-Dimethoxygris-2',5'-dien-3,4'-dione (III).—Freshly prepared lead dioxide (15 g.) was added to the benzophenone (II) (1 g.) in purified chloroform–ether (1 : 1 v/v; 300 ml.) and the mixture was shaken for 14 hr. Lead dioxide was removed, washed with ether, and the filtrate evaporated under reduced pressure. The residue (280 mg.) was recrystallised from chloroform and then benzene to give the *product* (III) as very pale yellow microcrystals (117 mg.), m. p. 142° (Found: C, 66.3; H, 4.5. C₁₅H₁₂O₅ requires C, 66.2; H, 4.4%), λ_{\max} 249, 277 m μ (log ϵ 4.18, 4.05), ν_{\max} 1724 (C=O in spirocumarane), 1667 (1,4-dienone), 1615 (enone), 1585 cm.⁻¹ (aromatic C=C).

When the benzophenone (II) (250 mg.) was oxidised with potassium ferricyanide, as described for the benzophenone (IV), only starting material (210 mg.) was recovered.

4'-Hydroxy-3,5-dimethoxy-2-methoxycarbonyl-diphenyl Ether (XVI).—The preceding spiro-dienone (III) was subjected to preparative thin-layer chromatography (system IV). Recovery from the thin-layer plates gave the *product* (XVI) as small prisms [from chloroform–light petroleum (b. p. 60—80°)], m. p. 130° (Found: C, 63.2; H, 5.2; OMe, 32.1. C₁₆H₁₆O₆ requires C, 63.2; H, 5.3; 3 OMe, 32.1%), λ_{\max} 282 m μ (log ϵ 3.49), ν_{\max} 1709 (aromatic CO₂Me) and 1667 cm.⁻¹ (H-bonded CO₂Me). R_F 0.72 (orange-yellow).

2,4,4'-Trihydroxy-2'-methylbenzophenone.—4-Hydroxy-2-methylbenzoic acid¹⁵ (0.7 g.) and resorcinol (0.7 g.) in tetrachlorethane (15 ml.) were treated with gaseous boron trifluoride (increase in weight, 0.5 g.) under anhydrous conditions. The mixture was stirred on a steam-bath for 4 hr., cooled, and shaken with 2N-sodium hydroxide. The alkaline extract was acidified and worked up, to give a yellow oil which was purified by chromatography over deactivated alumina and eluted with ethyl acetate. The major fraction gave 2,4,4'-trihydroxy-2'-methylbenzophenone (0.31 g.), yellow needles from ethanol, m. p. 167—168° (Found: C, 68.6; H, 5.5; O, 26.1; C-Me, 6.3. C₁₄H₁₂O₄ requires C, 68.8; H, 5.0; O, 26.2; 1C-Me, 6.2%), λ_{\max} 285, 325 m μ (log ϵ 4.39, 4.30), ν_{\max} 1623 (H-bonded CO) and 1587 cm.⁻¹ (aromatic C=C). R_F 0.56 (blue-purple). The compound gave a red-brown colour with ethanolic ferric chloride.

When the benzophenone (1 g.) in ether (100 ml.) or ether–chloroform (100 ml.; 1 : 1) was shaken with various amounts of freshly prepared lead dioxide (up to 16.0 g.) for 100 hr., no compounds corresponding to spirodienones or diphenyl ethers could be detected on thin-layer chromatograms.

Attempted Oxidation of Other Benzophenones.—2,4'-Dihydroxybenzophenone (R_F 0.72; yellow-brown), 2,4,4'-trihydroxybenzophenone (R_F 0.54; mauve), and 2,2',4-trihydroxybenzophenone (R_F 0.65; mauve) were oxidised with lead dioxide under the same conditions as above for 54 hr. Only starting material could be detected by thin-layer chromatography.

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DEPARTMENT OF CHEMISTRY, UNIVERSITY COLLEGE,
SINGLETON PARK, SWANSEA.

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