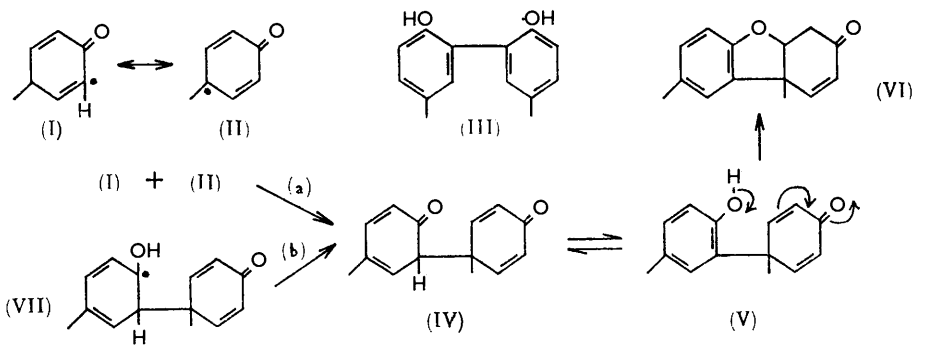
793. *Oxidative Pairing of Phenolic Radicals. Part I. The Total Synthesis of Griseofulvin.*

By A. C. Day, J. Nabney, and A. I. Scott.

Oxidation of synthetic 3-chloro-2,4′-dihydroxy-2′,4,6-trimethoxy-6′-methylbenzophenone (XVII) with potassium ferricyanide leads to (±)-dehydrogriseofulvin (XVIII) in 60% yield. Reduction of the latter with a rhodium–selenium catalyst gives, in addition to compound (XVII) and dihydrogriseofulvin, (±)-griseofulvin (XIX), which has been resolved by conversion into (+)-griseofulvic acid. Dehydrogenation of griseofulvin with selenium dioxide gives (−)-dehydrogriseofulvin which, with the benzophenone (XVII), has been isolated from *Penicillium patulum*.

It has been recognised for many years that oxidation of phenolic intermediates is an important step in the biogenesis of diverse types of natural product.[1-3] The generation of a radical from a phenol takes place under the influence of an oxidising agent of the required potential * for the removal of the phenolic hydrogen atom, or an electron from the corresponding phenoxide anion. The resultant phenoxyl radical may be stabilised by additional substituents (*e.g.*, 2,6-di-t-butyl) which prevent self-condensation. The phenolic radical owes its stability to contributions from *ortho*- and *para*-resonance forms (as I and II) which, in the case of lightly substituted phenols, can lead to dimeric and



polymeric products, either by symmetrical (*e.g.*, I ⟶ III) or non-symmetrical (I + II) carbon–carbon couplings. Oxygen–carbon and oxygen–oxygen coupling are rarer but authenticated processes.

In 1956 Barton and his co-workers [4] presented a unifying treatment of the oxidative

* Such an oxidant is defined as a one-electron transfer oxidising agent.

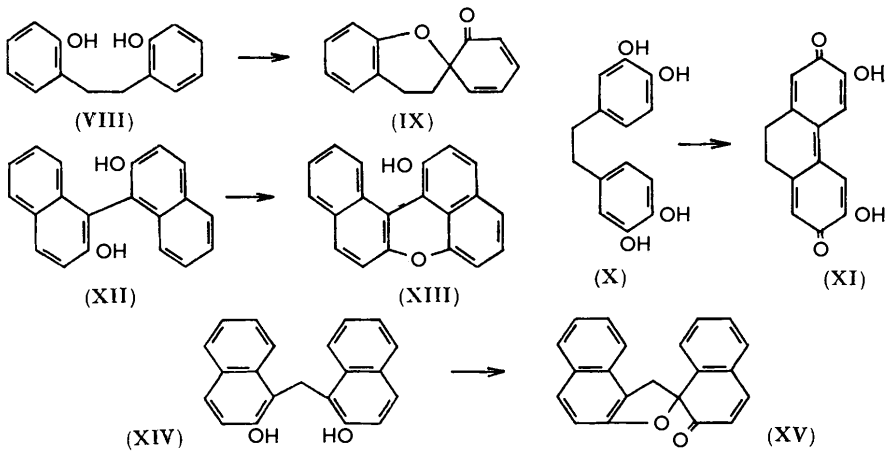
[1] Erdtman, *Research*, 1959, **3**, 63, and refs. cited.
[2] Robinson, " Structural Relations of Natural Products," Oxford University Press, Oxford, 1955.
[3] Freudenberg, *Nature*, 1959, **183**, 1152.
[4] Barton, Deflorin, and Edwards, *J.*, 1956, 530.

pairing of phenolic radicals based on the interpretation of the structure and genesis of Pummerer's ketone (VI), a product of the one-electron transfer oxidation of *p*-cresol. The mechanism of formation of this dimer can be regarded as the unsymmetrical carbon–carbon pairing of two *p*-tolyl radicals to give the intermediate (IV) (route a), whose tautomer (V) can undergo β-addition of the phenolic hydroxyl group to the dienone system (V ⟶ VI).*

The profound biogenetic implication of this concept was illustrated by a two-step synthesis of usnic acid *via* oxidative dimerisation of methylphloracetophenone. (For reviews see refs. 5 and 6.)

Although excellent laboratory analogy is now available for those radical-pairing processes which result in dimeric and polymeric products of coupling (*e.g.*, usnic acid,[4] gossypol,[7] lignin [3]), the formation of C–C and C–O bonds by intramolecular radical pairing reactions, which has considerable relevance for the biogenesis of many systems, has not hitherto formed the basis of extensive experimental study (see, however, refs. 8 and 9). It is therefore the purpose of the present series to provide some experimental analogy for such intramolecular bond-making processes.

To this end we have synthesised several types of the precursors suggested by the concepts of the radical-coupling theory of biogenesis and have subsequently examined the effect of suitable oxidising agents on such progenitors. We cannot claim to have established the relationships which obtain between oxidant and substrate *in vivo*, but the experiments to be described in this and succeeding papers illustrate that the principles of intramolecular radical pairing can be applied successfully to intermediates of suitable structure under acceptably mild reaction conditions.



An early example [10] of intramolecular coupling is provided by the oxidation of 1,2-bis-*o*-hydroxyphenylethane (VIII) to the spiro-dienone (IX) with potassium ferricyanide—a result which augured well for the construction of the main features of several fungal

* It is implicit in Barton's description that in many cases it is not possible to distinguish between such a pairing process and an alternative mechanism involving substitution of the radical (II) into the nucleus of the phenol, followed by a second oxidation of the intermediate radical (VII) to the observed product (route b). We prefer to adopt the former convention as a working hypothesis throughout this series.

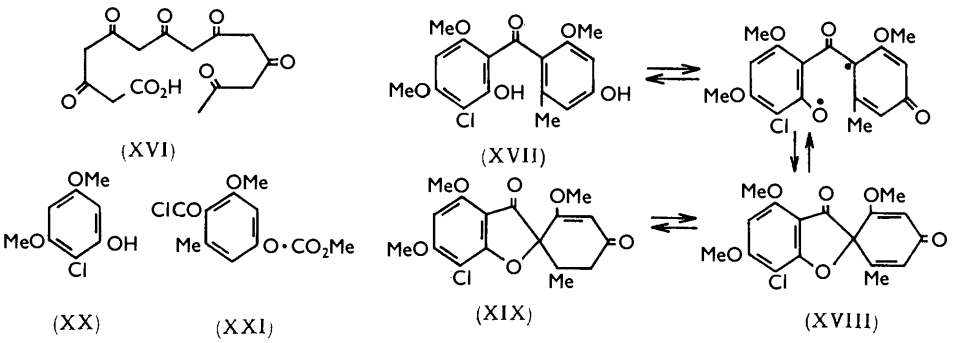
[5] Barton and Cohen in " Festschrift A. Stoll," Birkhauser, Basle, 1957, p. 117.
[6] Erdtman and Wachmeister, ref. 4, p. 114.
[7] Edwards, *J. Amer. Chem. Soc.*, 1958, **80**, 3798.
[8] Barton and Kirby, *Proc. Chem. Soc.*, 1960, 392.
[9] Brown, Clark, Ollis, and Veal, *Proc. Chem. Soc.*, 1960, 393.
[10] Fries and Brandes, *Annalen*, 1939, **542**, 48.

metabolites. Other relevant oxidations include the carbon-to-carbon coupling of the bisdihydroxyphenylethane (X) to the quinone (XI) [11] and the carbon–oxygen pairings of 2,2′-dihydroxy-1,1′-binaphthyl [12] (XII ⟶ XIII) and of bis-(2-hydroxy-1-naphthyl)-methane [13] (XIV ⟶ XV).

It is noteworthy that although these experiments (which we regard as useful models for coupling reactions) together with the oxidation of *p*-cresol and the successful synthesis of usnic acid, are indicative of the generality of such oxidations, the simplest model system relevant to at least two important categories of natural phenol failed to undergo oxidation.[14] The marked difference in the reactivity between these models and their congeners of natural substitutional pattern may be due to the effects of radical stabilisation or oxidation potential of the substance, to specificity of the one-electron transfer, or to a combination of these factors. Such considerations will form the basis of experiments to be described in this and later papers.

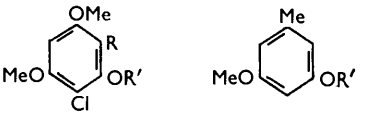
In this paper we consider griseofulvin, which represents an interesting combination of acetate and radical-pairing pathways of biogenesis.[15,16] The remarkable properties of griseofulvin as the " curling factor " [17] and more recently as an important oral antibiotic in the treatment of fungal diseases of man have been reviewed by Brian.[18]

Biogenetic dissection of the griseofulvin molecule into poly-β-ketone (XVI) and oxidation sequences was made by Barton and Cohen,[5] who suggested that a benzophenone (as XVII) derived from acetate could undergo C–O coupling of the derived diradical leading to dehydrogriseofulvin (XVIII) and hence to griseofulvin (XIX) by enzymic reduction. Tracer studies by Birch [19] have demonstrated that seven units of acetic acid are incorporated



into griseofulvin by head-to-tail condensation as summarised in expression (XVI). We therefore sought to provide some confirmation of the radical-pairing sequence by examining the oxidation of the benzophenone (XVII).

The required precursor (XVII) was synthesised by unexceptional methods [a] involving

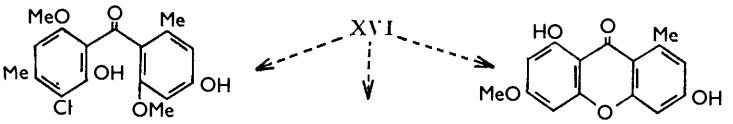


[a] Many attempts to achieve a synthesis of the benzophenone (XVII) by condensations of substituted phloroglucinolcarboxylic acids (as i) or nitriles as (ii) and orcinol derivatives (as iii) led only to recovery of starting materials or to decarboxylation of (i). Some of these efforts are described in the experimental section.

[11] Erdtman, *Annalen*, 1933, **505**, 195.
[12] Pummerer and Luther, *Ber.*, 1918, **51**, 1102.
[13] Pummerer and Cherbuliez, *Ber.*, 1914, **47**, 2987.
[14] Davidson, Nabney, and Scott, unpublished observations.
[15] Grove, Macmillan, Mulholland, and Rogers, *J.*, 1952, 3977; and numerous papers in that series.
[16] Oxford, Raistrick, and Simonart, *Biochem. J.*, 1939, **33**, 240.
[17] Brian, Curtis, and Hemming, *Trans. Brit. Mycol. Soc.*, 1946, **29**, 173; McGowan, *ibid.*, p. 188.
[18] Brian, *Trans. Brit. Mycol. Soc.*, 1960, **43**, 1.
[19] Birch, Massy-Westropp, Rickards, and Smith, *J.*, 1958, 360.

Friedel–Crafts interaction of 2-chloro-3,5-dimethoxyphenol [20] (XX) and *O*-methoxycarbonylverninoyl chloride [21] (XXI). Since the latter was extremely labile in moist air its solution in nitrobenzene had to be prepared and brought into reaction with the phenol as rapidly as possible. Brief alkaline treatment of the resultant methoxycarbonyl derivative gave 3-chloro-2,4′-dihydroxy-2′,4,6-trimethoxy-6′-methylbenzophenone (XVII) which was identical with the metabolite, griseophenone A, isolated from *P. patulum*,[22] and with the benzophenone obtained by degradation of griseofulvin by the following procedure.

Dehydrogenation of (XIX) with selenium dioxide in t-butyl alcohol–acetic acid gave (—)-dehydrogriseofulvin (XVIII), which was identical with the compound, m. p. 270—275°, isolated [22] from *P. patulum*. Hydrogenation of (XVIII) over a palladium or platinum catalyst or by hydrogen transfer from cyclohexene over palladium [23] (see Experimental) gave an almost quantitative yield of the benzophenone (XVII) by a process which represents the reversal of our projected synthesis and, furthermore, which allows of access to the benzophenone (XVII) from the readily available starting material, griseofulvin.



(XXIII) XVII (XXII)

The choice of this benzophenone for our first illustration of intramolecular coupling was governed by the expectation that the neutral product of such oxidation (XVIII), would be precipitated from an alkaline oxidation medium and would thus be protected from further degradative or polymerisation. In the event, addition of potassium ferricyanide (3 equivs.) to a solution of the benzophenone (XVII) in sodium carbonate solution in an inert atmosphere at 20° precipitated a neutral compound in 50—60% yield after 20 minutes. That this material had the desired structure was shown by its elemental analysis and light absorption, which were identical with those of (—)-dehydrogriseofulvin.

By the very excellence of its yields, the hydrogenolysis of the compound (XVIII) to the benzophenone (XVII) had now become the major obstacle to the final reductive step of the synthesis.[b] The many hydrogenations (see Experimental) which caused quantitative hydrogenolysis of the carbon–oxygen bond led us to examine the use of a rhodium catalyst.[24] (—)-Dehydrogriseofulvin was hydrogenated in ethanolic solution over rhodium–charcoal (5%) and the uptake stopped at 1·0 mole; removal of the alkali-soluble benzophenone (XVII) left a neutral residue (*ca.* 30%) which on chromatography afforded griseofulvin (8%). No other material of the same oxidation level as griseofulvin was encountered and we must assume that the hydrogenation of the dienone (XVIII) has followed a stereospecific course.

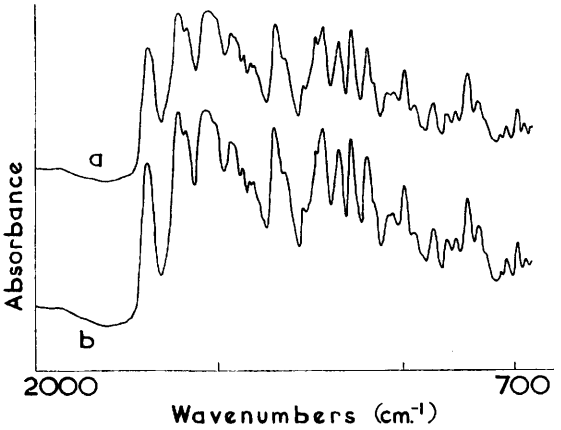
To obtain stereochemically homogeneous (±)-griseofulvin from the racemic dehydrocompound, the latter was now subjected to the hydrogenation conditions established above, but the total neutral material constituted only 2% of the hydrogenation product. We found the explanation of this result in the presence of traces of selenium in (—)-dehydrogriseofulvin, introduced in course of its preparation. Addition of selenium dioxide (3%) to rhodium–charcoal followed by prereduction to a selenium–rhodium catalyst now

[b] Experiments designed to circumvent direct hydrogenolysis by reduction with sodium borohydride and lithium aluminium hydride led to small yields of products whose spectra indicated profound changes in the spirodienone ring. These structures are now being studied; two are described in the Experimental Section.

[20] Grove, Macmillan, Mulholland, and Zealley, *J.*, 1952, 3967.
[21] Fischer and Hoesch, *Annalen*, 1912, **391**, 347.
[22] McMaster, Scott, and Trippett, *J.*, 1960, 4628.
[23] Cf. Braude, Linstead, and Jackman, *J.*, 1954, 3578.
[24] Trapnell, " Chemisorption," Butterworths, London 1955, p. 224.

provided the means of converting racemic dehydrogriseofulvin into a neutral product in 30% yield. Chromatography of this over alumina gave first (±)-dihydrogriseofulvin (10%), having identical light absorption with a sample of (—)-dihydrogriseofulvin prepared as described by Mulholland.[26] Later fractions afforded material (8%), whose infrared and ultraviolet spectra were identical with the data for naturally occurring griseofulvin (XIX). Further elution gave unchanged dienone (XVIII) (8—10%). From the alkaline extract of the hydrogenation a 70% yield of the benzophenone (XVII) could be isolated. Acidic hydrolysis of the racemate of griseofulvin (XIX) now gave (±)-griseofulvic acid.

Treatment of racemic griseofulvic acid with quinine methohydroxide [27] gave the quinine metho-salt which after several recrystallisations was identical (Fig.) with the salt from natural griseofulvic acid. Active griseofulvic acid was regenerated by passing a solution of the synthetic salt in methanol through a column of Amberlite-IR 120(H) resin. We thus obtained (+)-griseofulvic acid identical with an authentic sample.[16] The formal



(+)-Griseofulvic acid quinine metho-salt: (a) natural; (b) synthetic (as potassium chloride discs) (curve a has been displaced vertically).

total synthesis of griseofulvin is thus secured,[c] as the conversion of griseofulvic acid into griseofulvin has been described previously.[16]

The synthesis described above has considerable bearing on the biogenesis of the mould metabolites of *Penicillium patulum*, as isolation of the compounds (XVII), XVIII),[d] (XXII), and (XXIII) from this micro-organism [22] are in full accord with the postulated intervention of the hepta-β-ketone (XVI), which by various transformations of acceptable mechanism accounts for the presence of such compounds in the fermentation. Whether these represent by-products of the metabolism or true intermediates will only be determined by the appropriate tracer experiments now in hand.

Experimental

M. p.s were determined on a Kofler block. Ultraviolet spectra were measured in ethanol and infrared spectra in chloroform solution unless specified otherwise. Alumina for chromatography was neutralised and standardised according to the Brockmann scale. Silica gel for chromatography was supplied by Messrs. Hopkin and Williams. The phrase " in the usual

[c] The preliminary announcement of the completion of this work coincided with the conclusion [25] of a synthesis of the antibiotic by another route in the laboratories of Hoffman-La Roche (Basle). We are indebted to Dr. A. Brossi for kindly communicating his results to us before publication.

[d] The syntheses of (XVII) and (XVIII) in the present work incidentally provide proof of structure of these metabolites of *P. patulum*.[22]

[25] Brossi, Baumann, Gerecke, and Kyburz, *Helv. Chim. Acta*, 1960, **43**, 1444.
[26] Mulholland, *J.*, 1952, 3987.
[27] Major and Finkelstein, *J. Amer. Chem. Soc.*, 1941, **63**, 1368.

way " refers to dilution with water, extraction with chloroform and/or ether, and washing successively with dilute sodium hydrogen carbonate solution, dilute sulphuric acid, and water followed by azeotropic removal of solvents and water on the steam-bath under reduced pressure, more chloroform being added when necessary. Light petroleum refers to the fraction, b. p. 60—80°.

3-Chloro-2,4,6-trimethoxybenzoic Acid.—This *acid*, prepared from the corresponding methyl ester,[28] formed needles (from chloroform), m. p. 188—190° (Found: C, 48·75; H, 4·4; Cl, 14·2. $C_{10}H_{11}ClO_5$ requires C, 48·7; H, 4·5; Cl, 14·4%). When the acid (150 mg.), orcinol dimethyl ether (150 mg.), zinc chloride (400 mg.), and phosphorus oxychloride (1 g.) were heated for 4 hr. at 70° and worked up in the usual way, chromatography over silica gel gave unchanged orcinol dimethyl ether and trimethylphloroglucinol as the sole isolable products, identified by m. p. and mixed m. p. Similar results were obtained by using polyphosphoric acid or anhydrous hydrogen fluoride and from experiments with the acid chloride in presence of aluminium chloride or stannic chloride.

3-Chloro-2-hydroxy-2',4,6-trimethoxy-4'-methoxycarbonyloxy-6'-methylbenzophenone.—2-Methoxy-4-methoxycarbonyloxy-6-methylbenzoic acid (100 mg.) was suspended in dry benzene (5 c.c.) and treated with oxalyl chloride (0·5 c.c.). Solution was complete after 4 hr. and, after a further 12 hr. at room temperature, solvent was removed under reduced pressure with careful exclusion of moisture. The residual crude acid chloride was dissolved in dry nitrobenzene ("AnalaR;" 10 c.c.) and 2-chloro-3,5-dimethoxyphenol (100 mg.) and aluminium chloride (50 mg.) were added rapidly. The resultant solution was kept at room temperature for 2 days then poured on ice (10 g.) and concentrated hydrochloric acid (1 c.c.). Isolation in ether gave the *benzophenone* (30 mg.) as pale yellow prisms (from aqueous ethanol), m. p. 129—130° (Found: C, 55·9; H, 4·6; Cl, 8·2. $C_{19}H_{19}ClO_8$ requires C, 55·55; H, 4·7; Cl, 8·6%).

3-Chloro-2,4'-dihydroxy-2',4,6-trimethoxy-6'-methylbenzophenone (XVII).—An ether–nitrobenzene solution (10 c.c.) of the foregoing methoxycarbonyloxy compound (30 mg.) was stirred for 1 hr. with sodium hydroxide solution (4N; 10 c.c.). Acidification of the alkaline layer and isolation in ether followed by chromatography over silica gel gave, on elution with benzene–ether (50 : 1), the *benzophenone* (25 mg.), m. p. 214—216°, $\lambda_{max.}$ 298 and 340 mμ (ε 17,400 and 5800), $\nu_{max.}$ 3330 (OH) and 1610—1615 cm.$^{-1}$ (bonded C=O) (Found: C, 57·8; H, 4·9; Cl, 10·2; OMe, 25·75. $C_{17}H_{17}ClO_6$ requires C, 57·9; H, 4·85; Cl, 10·1; 3OMe, 26·4%).

(−)-Dehydrogriseofulvin (XVIII).—A solution containing griseofulvin (12 g.) and selenium dioxide (19·2 g.) in t-butyl alcohol (500 c.c.) and acetic acid ("AnalaR;" 6 c.c.) was heated under reflux for 5 days in a nitrogen atmosphere.[29] Sodium acetate (20 g.) was then added and reflux maintained for 20 min. Removal of solvents under reduced pressure, extraction of the residue with boiling chloroform, washing with aqueous ammonium sulphide, and working up in the usual way gave a neutral product (17·8 g.) contaminated with selenium. This was heated under reflux for 30 min. in benzene (400 c.c.) containing freshly precipitated silver (4 g.), and the filtered solution chromatographed over alumina (Grade III; 300 g.) in benzene. Elution with benzene–ethanol (99 : 1; 1 l.) and recrystallisation from chloroform–ether (1 : 3) gave the required dehydro-compound (5·9 g.). Further purification was made by heating the dienone (100 mg.) for 1 hr. with Girard reagent P (350 mg.) in acetic acid (10 c.c.), then pouring the solution into ice-cold sodium hydroxide solution (2N; 10 c.c.), adjusting the pH to 6, and working up in the usual way. Dehydrogriseofulvin, thus freed from the starting material, was chromatographed over alumina and eluted with benzene–ethanol (99 : 1) to give needles (from chloroform–ether), m. p. 270—273° and 281—282° (rapid heating) [265—268°/274—276° (slow heating)] with a transition (to plates) at 245°, $[\alpha]_D$ −29° (*c* 0·80 in acetone); $\lambda_{max.}$ 238, 292, and 330 * mμ (ε 19,000, 34,000, and 5,500), $\nu_{max.}$ 1726 (coumaranone) and 1671 cm.$^{-1}$ (cyclohexadienone) (Found: C, 57·9; H, 4·5; OMe, 26·0. $C_{17}H_{15}ClO_6$ requires C, 58·2; H, 4·3; 3OMe 26·5%). Griseofulvin was recovered from solutions in boiling benzene and toluene containing chloranil or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone [30] after 7 days.

(±)-Dehydrogriseofulvin.—3-Chloro-2,4'-dihydroxy-2',4,6-trimethoxy-6'-methylbenzophenone (XVII) (3·0 g.) was dissolved in a warm solution of sodium carbonate (20 g.) in deærated distilled water (1·5 l.), and the solution stirred at room temperature in a nitrogen atmosphere

* This (erroneously) appeared as 350 mμ in a previous publication by Day, Nabney, and Scott.[31]

[28] Calam and Oxford, *J.*, 1939, 280.
[29] Cf. Meystre, Frey, Voser, and Wettstein, *Helv. Chim. Acta*, 1956, **39**, 734.
[30] Braude, Brooke, and Linstead, *J.*, 1954, 3569; Burn, Kirk, and Petrow, *Proc. Chem. Soc.*, 1960, 14.
[31] Day, Nabney, and Scott, *Proc. Chem. Soc.*, 1960, 284.

while a (deærated) solution of potassium ferricyanide (10 g.) in distilled water (1 l.) was added (1 hr.). Excessive foaming was avoided by use of silicone antifoam agent. Stirring was continued for a further 1½ hr. and the neutral fraction (1·75 g.; 60%) isolated in the usual way from chloroform. Chromatography over silica gel and elution with benzene–ethanol (49 : 1) gave (±)-*dehydrogriseofulvin* as needles (from chloroform–ether), m. p. 270—272°, whose infrared (potassium chloride disc) and ultraviolet spectra were identical with those reported above for the (−)-compound (Found: C, 58·1; H, 4·4. $C_{17}H_{15}ClO_6$ requires C, 58·2; H, 4·3%). Increasing the proportion of potassium ferricyanide (to 10 moles) or reducing the temperature (to 0°) or reaction time (to 20 min.) gave inferior yields (40—53%).

Reduction of (−)-*Dehydrogriseofulvin.*—(a) *With sodium borohydride.* A solution of sodium borohydride (435 mg.) in water (7 c.c.) was slowly added to a solution of (−)-dehydrogriseofulvin (1·0 g.) in methanol (70 c.c.). After 2 hr. at room temperature working up in the usual way gave a gum (810 mg.). Chromatography over silica gel and elution with benzene–ether (19 : 1) gave a fraction, m. p. 268—271° (decomp.) (from chloroform–ether), $[\alpha]_D$ +287° (*c* 0·85 in chloroform); $\lambda_{max.}$ 228, 292, and 323 mμ (ε 25,000, 19,000, and 5000); ν (potassium chloride disc) 1700 (coumaranone) and 1675 cm.$^{-1}$ (cyclohexenone) (Found: C, 59·1; H, 4·8; OMe, 18·8. Calc. for $C_{16}H_{15}ClO_5$: C, 59·5; H, 4·7; 2OMe, 19·2%). No depression in m. p. was obtained on admixture with an authentic sample of 7-chloro-4,6-dimethoxy-6′-methylgris-3′-en-3,2′-dione.

(b) *With lithium aluminium hydride.* To a solution of (−)-dehydrogriseofulvin (350 mg.) in tetrahydrofuran (100 c.c.) at −70° was added lithium aluminium hydride (100 mg.). The solution was stirred for 2 hr., then ethyl acetate and ice-water were added carefully and the mixture was worked up in the usual way. Chromatography over silica gel and elution with benzene–ether (9 : 1) gave plates (60 mg.; after recrystallisation from ethyl acetate–light petroleum), m. p. 168—169°, $[\alpha]_D$ 0° (*c* 1·0 in acetone); $\lambda_{max.}$ 234, 280, and 319 mμ (ε 27,400, 13,000, and 5400), $\nu_{max.}$ (Nujol) 1700 cm.$^{-1}$ (C=O) (Found: C, 60·75; H, 4·75; Cl, 10·45; OMe, 27·4. $C_{17}H_{17}ClO_5$ requires C, 60·75; H, 5·05; Cl, 10·45; 3OMe, 27·1%).

Catalytic Reduction of (−)-*Dehydrogriseofulvin.*—(a) *With palladium, platinum, or ruthenium.* The dienone (100 mg.) in ethanol (25 c.c.) was hydrogenated over the appropriate catalyst (20 mg.) until 1 mole had been absorbed (3—5 min.). The filtered, evaporated solution was separated into a neutral (<1 mg.) and a phenolic fraction. Recrystallisation of the phenolic fraction from aqueous ethanol gave an almost quantitative yield of the benzophenone (XVII), m. p. 214—216° identical with the synthetic material (see above). The same result was achieved with the following catalysts: Pd–C (5%); Pd–$BaSO_4$ (5%); PtO_2; Ru–C (5%). Replacement of ethanol by ethyl acetate gave an identical result. When uptake of hydrogen was stopped at 0·75 mole the neutral fraction (20—25%) was identified as starting material by m. p. and infrared spectrum.

(b) *By hydrogen transfer.* A solution of (−)-dehydrogriseofulvin (120 mg.) in *cyclo*hexene (5 c.c.) and tetrahydrofuran (20 c.c.) was heated under reflux over palladium black (25 mg.) with polarimetric control. After 24 hr. $[\alpha]_D$ had fallen to 0° and then remained constant for a further 100 hr. Removal of the catalyst by filtration and separation of neutral and phenolic fractions gave from the latter the benzophenone (XVIII) (115 mg.), identified by m. p. and infrared spectrum. No crystalline material was isolated from the neutral fraction.

(c) *With rhodium–charcoal.* (−)-Dehydrogriseofulvin (35 mg.) was hydrogenated in ethyl acetate (7 c.c.) over rhodium–charcoal * (5%; 10 mg.) until 1 mole of hydrogen had been consumed. Working up in the usual way gave a phenolic fraction (25 mg.) and a neutral fraction (10 mg.) which had $[\alpha]_D$ +310°. Recrystallisation of the neutral fraction from chloroform–ether gave needles of griseofulvin, m. p. and mixed m. p. 221°, $[\alpha]_D$ +350° (*c* 0·4 in acetone); $\lambda_{max.}$ 236, 291, and 324 mμ (ε 21,000, 22,000, and 5200); $\nu_{max.}$ (in chloroform) 1720 and 1675 cm.$^{-1}$.

Catalytic Reduction of (±)-*Dehydrogriseofulvin.*—(a) *With rhodium–charcoal.* (±)-Dehydrogriseofulvin (300 mg.) was hydrogenated in ethanol (90 c.c.) over rhodium–charcoal (5%; 200 mg.). After the consumption of 1 mole, the benzophenone (XVII) (270 mg.; 90%) was recovered with alkali, and the neutral fraction chromatographed on alumina (Grade III).

(i) Elution with benzene gave a mixture of dihydrogriseofulvin isomers, m. p. 200—215° (5 mg.) which on recrystallisation from ethyl acetate–light petroleum provided (±)-7-*chloro*-4,6,6′-*trimethoxy*-2′-*methylgrisan*-3,4′-*dione*, m. p. 216—219°; $\lambda_{max.}$ 230, 288, and 325 mμ (ε 12,000, 28,000, and 6200); $\nu_{max.}$ (potassium chloride disc) 1725 (coumaranone), 1700 cm.$^{-1}$

* Baker Platinum Company.

(cyclohexanone) (Mulholland gives $\lambda_{max.}$ 234, 288, and 323 mμ; and $\nu_{max.}$ 1725 and 1700 cm.$^{-1}$ for the optically active form) (Found: C, 57·5; H, 5·5. $C_{17}H_{19}ClO_6$ requires C, 57·5; H, 5·4%). (ii) Elution with benzene–ethanol (99 : 1) gave unchanged (±)-dehydrogriseofulvin (3 mg.; 1%), identified by m. p. and infrared spectrum.

(b) *With a rhodium–selenium catalyst: (±)-griseofulvin.* The following experiment represents the best of 39 runs. A solution of (±)-dehydrogriseofulvin (300 mg.) in ethanol (90 c.c.) was shaken with rhodium–charcoal (5%; 200 mg.) which had been pre-reduced in presence of selenium dioxide (5 mg.). After the consumption of 0·88 mole of hydrogen the neutral product was isolated in the usual way and chromatographed over alumina (Grade III).

(i) Elution with benzene gave (±)-7-chloro-4,6,6′-trimethoxy-2′-methylgrisan-3,4′-dione (30 mg.), m. p. and mixed m. p. 216—219°. (ii) Elution with benzene–ethanol (99 : 1) gave first (±)-*griseofulvin* (24 mg.), m. p. 217—222°. Recrystallised from chloroform–ether this formed needles, m. p. 227—230°; $\lambda_{max.}$ 236, 291, and 324 mμ (ε 21,000, 22,000, and 5500); $\nu_{max.}$ (in chloroform) 1720 and 1675 cm.$^{-1}$. The infrared spectrum (potassium chloride disc) was identical with that of (+)-griseofulvin (Found: C, 57·8; H, 5·1. $C_{17}H_{19}ClO_6$ requires C, 57·9; H, 4·85%). Later eluates gave starting dienone (30 mg.), identified by m. p. and mixed m. p. The phenolic fraction gave the benzophenone (XVII) (210 mg.).

(±)-*Griseofulvic Acid* [(±)-7-*Chloro*-4,6-*dimethoxy*-2′-*methylgrisan*-3,4′,6′-*trione*].—A hot saturated solution of (±)-dehydrogriseofulvin (500 mg.) in ethanol (150 c.c.) was rapidly cooled and hydrogenated over rhodium–charcoal (5%; 330 mg.) and selenium dioxide (8 mg.). After the absorption of 1 mole of hydrogen (3 min.) the neutral product (206 mg.) was isolated in the usual way. When this (740 mg.) was heated for 30 min. on the steam-bath with acetic acid (5 c.c.) containing sulphuric acid (2N; 1 c.c.) the fraction (219 mg.) soluble in sodium carbonate solution had m. p. 230—240° and $\nu_{max.}$ 1695 cm.$^{-1}$. Recrystallised from aqueous methanol (±)-*griseofulvic acid* formed needles, m. p. 238—241° (decomp.); $\lambda_{max.}$ 236 and 289 mμ (ε 17,800 and 29,500); $\nu_{max.}$ (potassium chloride disc) 1695 (coumaranone and cyclohexanone), 1650 (C=C of enol), and 1605 cm.$^{-1}$ (β-diketone C=O) (Found: C, 56·2; H, 4·4; Cl, 10·3. $C_{16}H_{15}ClO_6$ requires C, 56·7; H, 4·5; Cl, 10·5%). The infrared spectra of (±)- and (+)-griseofulvic acids were identical.

Quinine Metho-salt of (+)-Griseofulvic Acid.—(a) *From (+)-griseofulvic acid.* Quinine methohydroxide solution (0·41N; 7·2 c.c.; 1 equiv.) was added to a suspension of (+)-griseofulvic acid (1·0 g.) in ethanol (12·5 c.c.). Dissolution was completed by gentle warming; then evaporation gave the salt (1·46 g.), m. p. 151—161°. Further concentration gave more salt (0·35 g.). After three recrystallisations from aqueous ethanol the quinine metho-salt formed a *dihydrate* as needles, m. p. 161—163°, $[\alpha]_D$ +69·5° (*c* 2·62 in ethanol) (Found: C, 62·05; H, 6·1; Cl, 4·8; N, 4·1. $C_{37}H_{41}ClN_2O_6,2H_2O$ requires C, 62·3; H, 6·4; Cl, 5·0; N, 3·9%).

(b) *From (±)-griseofulvic acid.* When the racemic acid (146 mg.) was treated with quinine methohydroxide solution (0·26N; 1·69 c.c.; 1 equiv.) and the solution processed as above, the resultant salt had m. p. 161—163° after several crystallisations from aqueous ethanol, undepressed on admixture with the authentic salt, $[\alpha]_D$ +67·5° (*c* 0·41 in ethanol). The infrared spectra (Fig.) of the salts were identical.

Regeneration of Synthetic (+)-Griseofulvic Acid.—The quinine metho-salt was dissolved in aqueous methanol (60%) and passed through a column of Amberlite IR-120 (H). The liberated (+)-griseofulvic acid formed prisms, m. p. 255—258° (from aqueous methanol), $[\alpha]_D$ +393° (*c* 0·31 as sodium salt in aqueous methanol), identical with authentic griseofulvic acid ($[\alpha]_D$ +399° as sodium salt in aqueous methanol) (Found: C, 57·0; H, 4·7; Cl, 10·3. Calc. for $C_{16}H_{15}ClO_6$: C, 56·7; H, 4·5; Cl, 10·5%).

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