608. *Griseofulvin. Part XI.** *4 : 6-Dimethoxy-2′-methylgrisan-3 : 4′-dione.*

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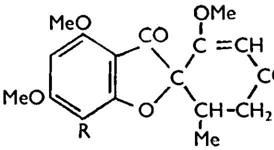
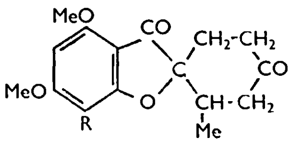
Dechlorogriseofulvin (I; R = H) has been degraded to 4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (II; R = H) which is not identical with the tricyclic spirandione, synthesised by Dean and Manunapichu.[1]

In connexion with the synthetic work described in the preceding paper,[1] dechlorogriseofulvin (I; R = H) was converted into 4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (II; R = H) by the method described by Mulholland[2] for degrading griseofulvin (I; R = Cl) to the dione (II; R = Cl).


(I)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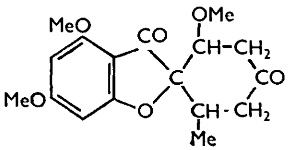
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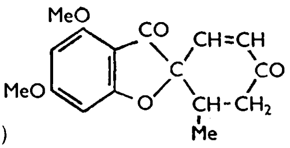
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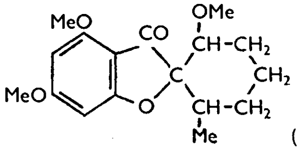
(V)

Dechlorogriseofulvin rapidly absorbed hydrogen in the presence of palladium–charcoal. Interruption of reduction when 1·3 mols. of hydrogen had been absorbed afforded the dihydro-derivative (III). In an experiment where dechlorogriseofulvin was allowed to absorb 2·6 mols. of hydrogen, the dihydro-derivative (III) was not isolated; instead, the hydrogenolysis product (V) and the unsaturated ketone (IV) were obtained. The latter product must have arisen from the dihydro-derivative (III) during working up, being readily obtained from it by treatment with acid. Hydrogenation of the unsaturated ketone (IV) with palladium–charcoal yielded the required 4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (II; R = H) which was distinct from the synthetic tricyclic spirandione described in the preceding paper by Dean and Manunapichu.[1]

Experimental

Microanalyses are by Messrs. W. Brown and A. G. Olney. M. p.s are corrected. In chromatography B.D.H. alumina was rendered alkali-free (pH 4) and activated for 3 hr. at 250°/15 mm. The infrared spectra were measured with a Grubb-Parsons S 3A spectrometer on "Nujol" mulls. The ultraviolet spectra were determined in ethanol with a Unicam S.P. 500 spectrophotometer.

Reduction of Dechlorogriseofulvin.—(*a*) Dechlorogriseofulvin (3·0 g.) in ethyl acetate (300 ml.) was shaken in hydrogen at room temperature and pressure in the presence of a catalyst prepared by heating palladium chloride (1·5 g.) and water (135 ml.) to the b. p., cooling the solution, and adding charcoal (2 g.). Reduction was stopped when 1·3 mols. of hydrogen had been absorbed (5 min.). Working up in the usual way yielded a gum (3·01 g.) which, in methanol, slowly deposited 4 : 6 : *6′-trimethoxy-2′-methylgrisan-3* : *4′-dione* (III) as prisms (1·49 g.), m. p. 167—168°, $[\alpha]_D^{20}$ −12° (*c* 0·91 in CHCl$_3$) (Found: C, 64·1, 64·15; H, 6·5, 6·3. $C_{17}H_{20}O_6$ requires C,

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* Part X, *J.*, 1956, 1956.

[1] Dean and Manunapichu, preceding paper.

[2] Mulholland, *J.*, 1952, 3994.

63·75; H, 6·3%). The infrared spectrum showed absorption bands at 1716 and 1692 cm.$^{-1}$ in the double-bond stretching region.

Recovery of the methanolic mother-liquors gave a gum (1·33 g.) which was chromatographed on alumina (12 × 1·5 cm.) from benzene, eluates fluorescing as follows in ultraviolet light: (1) blue; benzene eluted a gum (283 mg.); (2) dark blue; benzene eluted a gum (551 mg.) which gave a little crude dihydro-derivative (III) on trituration with ether; (3) pale blue; benzene–methanol (99 : 1) eluted a gum (466 mg.) which from methanol yielded dechlorogriseofulvin (9 mg.), m. p. and mixed m. p. 178—180°, and the dihydro-derivative (III) which was combined with that obtained from band (2) and crystallised from methanol in prisms (49 mg.), m. p. 167—168°.

(*b*) Dechlorogriseofulvin (1·0 g.) in ethyl acetate (100 ml.) was hydrogenated as in (*a*) with a catalyst prepared from palladium chloride (0·5 g.), water (45 ml.), and charcoal (2·0 g.). Reduction was stopped when 2·6 mols. of hydrogen had been absorbed (40 min.). The crude product (1·0 g.), in benzene (40 ml.), was chromatographed on alumina (20 × 2·5 cm.); ether–light petroleum (b. p. 40—60°) (1 : 1) eluted as main band a gum (312 mg.) which crystallised from light petroleum (b. p. 80—100°) in prisms (210 mg.), m. p. 100—102°. Rechromatography on alumina and elution of the main band fluorescing bright blue gave 4 : 6 : 6′-*trimethoxy*-2′-*methylgrisan*-3-*one* (V), crystallising from light petroleum (b. p. 80—100°) in prisms, m. p. 110—111°, absorption at 1692 cm.$^{-1}$ in the double-bond stretching region (Found: C, 66·3; H, 7·3. $C_{17}H_{22}O_5$ requires C, 66·65; H, 7·2%).

The gums from subsidiary bands in the first chromatogram were combined and rechromatographed on alumina in benzene. Elution of the narrow band fluorescing blue with ether–methanol (99 : 1) afforded 4 : 6-*dimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* (IV) which crystallised from methanol in prisms (146 mg.), m. p. 149—151°, $[\alpha]_D^{20}$ +465° (*c* 0·95 in $CHCl_3$) (Found: C, 66·7; H, 5·7. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%), $\lambda_{max.}$ ~320, 288 mμ (log ε 3·81, 4·41 respectively). The infrared spectrum showed a fairly broad absorption band at 1695 cm.$^{-1}$ in the double-bond stretching region. The 2 : 4-*dinitrophenylhydrazone* crystallised from chloroform–light petroleum (b. p. 60—80°) in orange needles, m. p. 245—246° (Found: C, 56·5; H, 4·3. $C_{22}H_{20}O_8N_4$ requires C, 56·4; H, 4·3%).

4 : 6-*Dimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione*.—The dihydro-derivative (III) (1·25 g.) in methanol (125 ml.) was heated under reflux for 5 hr. with 7N-sulphuric acid (165 ml.). Removal of the methanol gave 4 : 6-dimethoxy-6′-methyl-gris-2′-en-3 : 4-dione which crystallised from methanol in prisms (1·1 g.), m. p. and mixed m. p. 149—151°.

4 : 6-*Dimethoxy*-2′-*methylgrisan*-3 : 4′-*dione*.—4 : 6-Dimethoxy-6′-methylgrisan-2′-en-3 : 4′-dione (200 mg.) in ethyl acetate (20 ml.) was hydrogenated as described above for dechlorogriseofulvin with a catalyst prepared from palladium chloride (200 mg.), charcoal (800 mg.), and water (12 ml.). Reduction ceased after 1 mol. of hydrogen had been absorbed (5 min.). The crude product recovered in the usual way crystallised from diethyl ether in prisms (168 mg.), m. p. 125—126°, of 4 : 6-*dimethoxy*-2′-*methylgrisan*-3 : 4′-*dione* (II; R = H), $[\alpha]_D^{20}$ +40° (*c* 1·1 in $CHCl_3$) (Found: C, 65·9; H, 6·3. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·25%), $\lambda_{max.}$ ~315, 284, ~232, ~225 mμ (log ε 3·77, 4·38, 4·05, 4·24 respectively). The infrared spectrum showed absorption bands at 1722 and 1694 cm.$^{-1}$ in the double-bond stretching region. The *semicarbazone* crystallised from methanol in needles, m. p. 185—190° (decomp.) (Found: C, 58·7; H, 6·0; N, 11·9. $C_{17}H_{31}O_5N_3$ requires C, 58·8; H, 6·1; N, 12·1%).

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