

362. *Griseofulvin. Part XV.*¹ *Some Derivatives of the (l,d)-Stereoisomer of Griseofulvin.*

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(*l,d*)-7-Chloro-4 : 6 : 2'-trimethoxy-6'-methylgris-2'-en-3 : 4'-dione (I) has been degraded to (*l,d*)-7-chloro-4 : 6-dimethoxy-2'-methylgrisan-3 : 4'-dione (X) and (*l,d*)-7-chloro-4 : 6-dimethoxy-2'-methylgrisan-3-one (IX).

It has been shown¹ that griseofulvin (I) can be converted into a diastereoisomer in which the configuration at the spiran centre of asymmetry is inverted. According to the convention of Cahn *et al.*² griseofulvin and the above diastereoisomer were assigned the configurations (2*S* : 6'*R*) and (2*R* : 6'*R*) respectively, but for reasons stated previously¹ the configurations of these compounds are denoted in this and later papers by (*d,d*) and (*l,d*) respectively, the spiran centre being the first mentioned. (Configurations according to the convention of Cahn *et al.* are given in the Experimental part.)

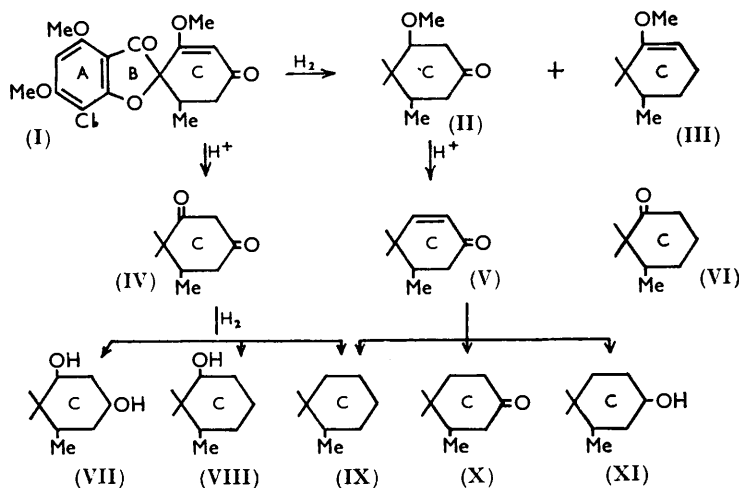
For comparison with synthetic racemates, described in subsequent papers, the (*l,d*)-stereoisomers of 7-chloro-4 : 6-dimethoxy-2'-methylgrisan-3 : 4'-dione (X) and 7-chloro-4 : 6-dimethoxy-2'-methylgrisan-3-one (IX) were required.

¹ Part XIV, MacMillan, preceding paper.

² Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.

The former was prepared from the (*l,d*)-diastereoisomer (I) by Mulholland's method.^{3,4} Hydrogenation in the presence of palladium-carbon gave a mixture of the (*l,d*)-dihydro-derivative (II) and (*l,d*)-7-chloro-4 : 6 : 2'-trimethoxy-6'-methylgris-2'-en-3-one (III).

Unlike the (*d,d*)-isomer,⁴ the (*l,d*)-compound (III) was not converted into the corresponding ketone (VI) by 80% acetic acid. Similar treatment⁵ of the (*l,d*)-ether (II) gave



dimorphic (*l,d*)-7-chloro-4 : 6-dimethoxy-6'-methylgris-2'-en-3 : 4'-dione (V) which on hydrogenation on palladium-carbon gave the required (*l,d*)-ketone (X) as the only isolable product.

Reduction of the (*l,d*)-dione (V) in the presence of Raney nickel gave the (*l,d*)-isomers of the ketone (X), the alcohol (XI), and 7-chloro-4 : 6-dimethoxy-2'-methylgrisan-3-one (IX). Reduction with Adams catalyst gave (*l,d*)-monoketone (IX) and -diketone (X) and an intractable alcoholic fraction. Previously, the (*d,d*)-monoketone (IX) had been obtained by hydrogenation of the (*d,d*)-trione (IV) with Adams catalyst. When a commercial Adams catalyst was used reduction of the (*l,d*)-trione (IV) gave the (*l,d*)-isomers of the diol (VII) and alcohol (VIII) but no monoketone (IX). With a catalyst prepared by Adams's method⁷ the (*l,d*)-monoketone was obtained but only in traces.

Attempts to find a better method of preparation of the (*l,d*)-monoketone (IX), by using as models the available (*d,d*)-ketones (V) and (X) failed. Wolff-Kishner reduction of the diketone (X) gave no crystalline products; and although the trimethylene dithioketals of (V) and (X) were obtained, fission did not take place on treatment with nickel (cf. ref. 9). The alcohol obtained by hydrogenation of the (*l,d*)-trione (IV) differed from the isomeric (*l,d*)-alcohol (XI) whose structure is shown by its formation from the (*l,d*)-dione (V); hence it is assigned the structure (*l,d*-VIII), analogous to the (*d,d*)-stereoisomer obtained⁶ from the (*d,d*)-trione (IV). Unlike the (*d,d*)-stereoisomer, the (*l,d*)-alcohol (VIII) could not be oxidised to the corresponding ketone with chromic acid.

The infrared spectra of the (*l,d*)-ketones (IX) and (X) in solution were distinct from those of their (*d,d*)-stereoisomers, and the m. p.s of mixtures of (*l,d*)- and (*d,d*)-forms were depressed. The relation between these compounds and synthetic racemates will be discussed later.

³ Mulholland, *J.*, 1952, 3987.

⁴ *Idem*, *J.*, 1952, 3994.

⁵ Riley, personal communication.

⁶ Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.

⁷ *Org. Synth.*, Coll. Vol. I, 1941, p. 463.

EXPERIMENTAL

M. p.s are corrected. Microanalyses are by Messrs. W. Brown and A. G. Olney. Absorption spectra (in ethanol) and alumina for chromatography were obtained as described previously.⁸ Unless otherwise stated, infrared spectra were determined for Nujol "mulls."

Hydrogenation of the (1,d) (i.e., 2R:6'R)-*Diastereoisomer* (I).—The compound (352 mg.) in ethyl acetate (30 ml.) was shaken in hydrogen at room temperature and pressure in the presence of a catalyst prepared by heating palladium chloride (300 mg.) and water (20 ml.) to the b. p., cooling the mixture, and adding charcoal (1.20 g.). Absorption (1.7 mol.) almost ceased after 7 min. Recovery of the product gave a gum (350 mg.) which was chromatographed in benzene (5 ml.) on alumina (20 × 2 cm.). Fluorescent bands were eluted in ultraviolet light: (i) Ether-light petroleum (b. p. 40–60°; 1:1) eluted a violet band, giving a solid (158 mg.). (ii) Ether-methanol (100:1) eluted a blue band, giving a solid (183 mg.).

Fraction (i) crystallised from benzene-light petroleum (b. p. 60–80°) in prisms, m. p. 183–184° of (1,d) (i.e., 2R:6'R)-7-chloro-4:6:2'-trimethoxy-6'-methylgrisan-2'-en-3-one (III), $[\alpha]_D^{25} + 39^\circ \pm 3^\circ$ (c 0.75 in acetone) (Found: C, 60.4; H, 5.7; OMe, 25.6. C₁₇H₁₉O₅Cl requires C, 60.3; H, 5.65; 3OMe, 27.5%), ν_{\max} 1709 (C=O) and 1675 cm.⁻¹ (weak, C=C). The compound did not react with Brady's reagent. Hydrolysis with 80% acetic acid⁴ failed to yield a diketone (VI).

Fraction (ii) crystallised from acetone-light petroleum in prisms of (1,d) (i.e., 2R:6'R)-7-chloro-4:6:2'-trimethoxy-6'-methylgrisan-3:4'-dione (II) which melted (loss of solvent) at ca. 100°, resolidified and remelted at 180–182°, $[\alpha]_D^{18} 0^\circ \pm 3^\circ$ (c 0.68 in acetone) (Found, for a sample dried at 100°: C, 57.6; H, 5.5; OMe, 24.9. C₁₇H₁₉O₆Cl requires C, 57.5; H, 5.4; 3OMe, 26.2%), ν_{\max} 1703, 1712 cm.⁻¹. The compound gave a precipitate with Brady's reagent.

(1,d) (i.e., 2S:6'R)-7-Chloro-4:6-dimethoxy-6'-methylgrisan-2'-en-3:4'-dione (V).—A solution of (1,d)-7-chloro-4:6:2'-trimethoxy-6'-methylgrisan-3:4'-dione (II) (1.409 g.) in 80% acetic acid (140 ml.) was heated under reflux for 15 hr. and evaporated to dryness *in vacuo*. Crystallisation of the residue from methanol gave needles, (i) m. p. 195–196° (632 mg.) and (ii) m. p. 188–192° (155 mg.), and a residue. Re-treatment of the residue with 80% acetic acid for 6 hr. and recovery gave a further crop of m. p. 189–194° (69 mg.). Crystallisation of the combined products from methanol and dilute methanol gave the (1,d)-dione (V) as needles, m. p. 196–198°. In the first two experiments the product had m. p. 166–167°, converted into the form of higher m. p. on melting and cooling or by seeded crystallisation. A mixture of the two forms had m. p. 196–198°, $[\alpha]_D^{21} - 148^\circ \pm 3^\circ$ (c 1.15 in acetone) (Found: C, 59.8; H, 4.7; OMe, 18.5. C₁₆H₁₅O₅Cl requires C, 59.5; H, 4.7; 2OMe, 19.2%), ν_{\max} 1708, 1685 cm.⁻¹ (low m. p.), or 1700, 1689 cm.⁻¹ (high m. p.). The compound was unsaturated to neutral permanganate and gave a precipitate with Brady's reagent.

Hydrogenation of (1,d) (i.e., 2S:6'R)-7-Chloro-4:6-dimethoxy-6'-methylgrisan-2'-en-3:4'-dione (V).—(i) *With a palladium catalyst*. A solution of the compound (495 mg.) in ethyl acetate (50 ml.) was shaken in hydrogen at room temperature and pressure in the presence of a catalyst prepared from palladium chloride (500 mg.), water (30 ml.), and charcoal (2.00 g.) as described above. Absorption (1.0 mol.) was complete in 1 min. The crude recovered product was chromatographed in benzene (50 ml.) on alumina (12 × 4 cm.) and a narrow blue-fluorescent band was eluted in ultraviolet light with benzene-methanol (100:1). The recovered gum (451 mg.) was twice sublimed at 10⁻⁴ mm. (bath, 120–140°), and the sublimate (374 mg.) crystallised from methanol in prisms, m. p. 168–170° of (1,d) (i.e., 2S:2'R)-7-chloro-4:6-dimethoxy-2'-methylgrisan-3:4'-dione (X), $[\alpha]_D^{22} - 30^\circ \pm 3^\circ$ (c 1.34 in acetone) (Found: C, 59.2; H, 5.4. C₁₆H₁₇O₅Cl requires C, 59.2; H, 5.3%). The infrared spectra in Nujol (C=O, 1709 cm.⁻¹; OH absent) and in chloroform (C=O, 1702 cm.⁻¹ broad) were distinct from the corresponding spectra of the (d,d)-isomer,⁸ and the m. p. of a mixture was depressed. The compound was saturated to neutral permanganate and gave a precipitate with Brady's reagent.

(ii) *With platinum oxide*. The compound (150 mg.) and platinum oxide (100 mg.) prepared by the Adams method⁷ in methanol (30 ml.) were shaken with hydrogen at room temperature and pressure until absorption nearly stopped (3.1 mol. in 40 min.). The recovered gum was chromatographed in benzene on alumina (17 × 2.3 cm.). Elution in ultraviolet light removed fluorescent bands: (i) Ether eluted a violet band, giving a solid (8 mg.), m. p. 128–144°. (ii) Ether-methanol (100:1) removed a blue band, giving a gum (118 mg.). (iii) Ether-methanol (100:3) eluted a blue band, giving a gum (11 mg.).

⁸ Mulholland and Ward, *J.*, 1954, 4676.

Fraction (i) crystallised from ether–light petroleum (b. p. 40–60°) in prisms, m. p. 149–153°, of (1,d)(i.e., 2S : 2'R)-7-chloro-4 : 6-dimethoxy-2'-methylgrisan-3-one (IX) identical (mixed m. p. and infrared spectrum) with material obtained by another method (see below), $[\alpha]_D^{20} -24^\circ \pm 3^\circ$ (*c* 0.55 in acetone) (Found: C, 61.7; H, 6.1. $C_{16}H_{19}O_4Cl$ requires C, 61.8; H, 6.1%). The infrared spectrum was distinct from that of the (*d,d*)-isomer obtained⁶ from griseofulvin and the m. p. of a mixture was depressed.

Fraction (ii) was sublimed *in vacuo* and crystallised from methanol and dilute methanol, giving the (*l,d*)-dione (X) as prisms (43 mg.), m. p. and mixed m. p. 168–170°.

Fraction (iii) contained alcoholic hydroxyl (infrared spectrum) but was intractable.

(iii) *With Raney nickel.* The compound (105 mg.) in ethanol (10 ml.) was shaken with hydrogen at room temperature and pressure in the presence of Raney nickel (*ca.* 0.5 g.) until 2 mol. were absorbed (5 min.). Chromatography of the recovered gum in benzene on alumina (24 × 1.2 cm.) and elution of fluorescent bands in ultraviolet light with ether–methanol (100 : 3) gave gums on recovery: (i) a violet band (16 mg.); (ii) a blue band (31 mg.); (iii) a blue band (17 mg.).

Fraction (i) was sublimed at 120–130°/10⁻⁴ mm. and chromatographed on alumina (20 × 0.5 cm.) in ether. Elution with ether removed a small blue fluorescent band, then a larger blue band. Recovery from the latter gave a gum (4 mg.) which crystallised from methanol, giving needles (0.6 mg.), m. p. 120–137°, raised to 140–146° by further recrystallisation and not depressed on admixture with the (*l,d*)-ketone (IX) (see above).

Fraction (ii) crystallised from methanol and dilute methanol in prisms (9 mg.) of the (*l,d*)-dione (X), m. p. and mixed m. p. 165–168°.

Fraction (iii) gave a solid (18 mg.) on trituration with ether. Recrystallisation from dilute methanol (needles) and from ethyl acetate–light petroleum (b. p. 60–80°) gave prisms of (1,d)(i.e., 2S : 2'R)-7-chloro-4'-hydroxy-4 : 6-dimethoxy-2'-methylgrisan-3-one (XI), m. p. 193–195° (Found: C, 59.3; H, 6.1. $C_{16}H_{19}O_5Cl$ requires C, 58.8; H, 5.9%), ν_{max} . 1697 (C=O), 3520 (OH) cm.⁻¹, λ_{max} . at 236, 286, 320 m μ (log ϵ 4.20, 4.32, 3.71 respectively). The compound did not react with Brady's reagent, and the m. p. was depressed on admixture with the isomeric (*l,d*)-alcohol (VIII) (see below).

(1,d)(i.e., 2R : 6'R)-7-Chloro-4 : 6-dimethoxy-6'-methylgrisan-3 : 2' : 4'-trione (IV).—A mixture of the (*l,d*)-diastereoisomer (I) (2.60 g.), ethanol (500 ml.), and 2N-hydrochloric acid (625 ml.) was heated under reflux for 5 hr. Most of the ethanol was evaporated *in vacuo*. The residual solution at 0° afforded a solid in 18 hr. This was dissolved in sodium hydrogen carbonate solution, and the solution was washed with ether and acidified with hydrochloric acid, giving the (*l,d*)-trione (IV) (1.65 g.), m. p. 215–216°, $[\alpha]_D^{20} +112^\circ$ (*c* 1.07 for the sodium salt in water). It was identical (infrared spectrum) with material obtained by MacMillan¹ by fractionation of a mixture of the (*l,d*)- and the (*d,d*)-trione.

Hydrogenation of (1,d)(i.e., 2R : 6'R)-7-Chloro-4 : 6-dimethoxy-6'-methylgrisan-3 : 2' : 4'-trione (IV).—The trione (1.00 g.) in acetic acid (150 ml.) was hydrogenated at room temperature and pressure in the presence of a platinum oxide catalyst prepared by the Adams method.⁷ Absorption (3 mol.) was complete in 6 hr. The recovered product was chromatographed on alumina (20 × 1.0 cm.), and fluorescent bands were collected in ultraviolet light, giving gums on recovery: (i) benzene, a pale blue band (10 mg.); (ii) benzene–methanol (100 : 1), a bright blue band (520 mg.); (iii) benzene–methanol (25 : 1), a violet band (316 mg.).

Fraction (i) was combined with the forerun (*a*) from rechromatography of fraction (ii) (see below) and purified by sublimation, chromatography, and crystallisation from methanol and ethanol, giving prisms (2 mg.), m. p. 153–155°, identified by the infrared spectrum and mixed m. p. as the (*l,d*)-monoketone (IX) (see above).

Fraction (ii) was chromatographed on alumina (15 × 1.0 cm.) in benzene and eluted with the same solvent, giving (*a*) a blue fluorescent forerun and (*b*) a broad light blue band. On recovery, band (*b*) gave a glass which was purified by sublimation followed by crystallisation from ethyl acetate–light petroleum (b. p. 40–60°) and from dilute methanol, giving prisms (230 mg.), m. p. 189–190°, of (1,d)(i.e., 2R : 6'R)-7-chloro-2'-hydroxy-4 : 6-dimethoxy-6'-methylgrisan-3-one (VIII), $[\alpha]_D^{22} -27^\circ \pm 3^\circ$ (*c* 0.45 in acetone) (Found: C, 58.95; H, 5.9. $C_{16}H_{19}O_6Cl$ requires C, 58.8; H, 5.8%), ν_{max} . 1695 (C=O), 3490 (OH) cm.⁻¹. The compound was saturated to neutral permanganate and did not react with Brady's reagent. The m. p. was depressed on admixture with the isomeric (*l,d*)-alcohol (XI) (see above). Attempts to oxidise the alcohol to the (*l,d*)-ketone (VI) with chromic acid as described⁶ for the (*d,d*)-isomer failed. At 30° no

oxidation occurred; at 60—100° the only isolable product was 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid.

Fraction (iii) was dissolved in water (300 ml.) by shaking at room temperature for 24 hr. The filtered solution was concentrated to *ca.* 30 ml. and cooled to 5—10°, giving prisms (280 mg.). Recrystallisation from ethyl acetate gave (1,d)(i.e., 2R : 6'R)-7-chloro-2' : 4'-dihydroxy-4 : 6-dimethoxy-6'-methylgrisan-3-one (VII) as needles, m. p. 213—215°, $[\alpha]_D^{19} +43^\circ \pm 3^\circ$ (*c* 0.50 in acetone) (Found: C, 56.4; H, 5.7. $C_{16}H_{19}O_6Cl$ requires C, 56.1; H, 5.55%), ν_{max} . 1695 (C=O) 3475, 3430, 3220 (OH) cm^{-1} .

Attempted Reduction of (d,d)(i.e., 2R : 2'R)-7-Chloro-4 : 6-dimethoxy-2'-methylgrisan-3 : 4'-dione (X).—A current of dry hydrogen chloride was passed through a mixture of the compound (325 mg.) and propane-1 : 3-dithiol (119 mg.) in chloroform (5 ml.) for 2 hr. at 0°. The solution was diluted with chloroform, washed with sodium hydroxide and water, dried, and evaporated, giving a glass (383 mg.). The solid (357 mg.; m. p. 210—212°) obtained by heating the glass with light petroleum (b. p. 40—60°) crystallised from methanol in prisms, m. p. 211—212° of (d,d)(i.e., 2R : 2'R)-7-chloro-4 : 6-dimethoxy-2'-methyl-3-oxogrisan-4'-one trimethylene dithioketal (Found: C, 54.8; H, 5.7; Cl, 8.5; S, 14.8; OMe, 14.4. $C_{19}H_{23}O_4S_2Cl$ requires C, 55.0; H, 5.6; Cl, 8.5; S, 15.5; 2OMe, 14.9%), ν_{max} . 1696 cm^{-1} (C=O).

Attempted fission of the ketal failed. An ethanolic solution containing a ten-fold excess of freshly prepared W6 Raney nickel was shaken for 2 hr. at room temperature, heated under reflux for 40 hr., and finally shaken in hydrogen for 48 hr., but in each case only starting material was recovered.

Attempted Reduction of (d,d)(i.e., 2R : 6'R)-7-Chloro-4 : 6-dimethoxy-6'-methylgrisan-2'-en-3 : 4'-dione (V).—Treatment of the above compound with propane-1 : 3-dithiol as described for the (*d,d*)-diketone (X) gave an intractable, unsaturated, sulphur-containing glass, insoluble in organic solvents, which was recovered (infrared spectrum) from attempts to split it by the above methods.

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