The Stereochemistry of Some Reactions of the Sesquiterpenoid Trichodermol

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Epoxidation of trichodermol and some derivatives gave the 9β,10β-epoxide although osmylation appeared to give the 9α,10α-glycol. Reduction of trichodermone with sodium borohydride gave 4-epitrichodermol. Elimination of the 4-hydroxy-group with phosphorus pentachloride afforded the Δ^3-olefin without rearrangement.

DURING the course of studies on the biosynthesis of the trichothecane antibiotics,[1] we investigated certain stereochemical aspects of the chemistry of trichodermol (roridin C) (1; R = α-H, β-OH).[2,3] These results are reported in this paper.

The Δ^9-double bond is readily epoxidized by *m*-chloroperbenzoic acid in chloroform. Thus trichodermol (1; R = α-H, β-OH), 4-epitrichodermol (1; R = β-H, α-OH), and trichothec-9-ene-4β,12β-diol [2] (2) each gave a single 9,10-epoxide. The epoxide ring was assigned the β-configuration on the basis of the n.m.r. spectrum (see Table 1). The coupling constant ($J_{10,11}$ 5·5 Hz) corresponds to a dihedral angle of *ca.* 40 or 125°.[4] Molecular models suggest the former with a β-oriented epoxide ring: an α-epoxide requires a dihedral angle of 70—80°. Thus epoxidation has occurred on the β-face of the

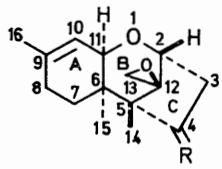
[1] B. Achilladelis, P. M. Adams, and J. R. Hanson, *J.C.S. Perkin I*, 1972, 1425.

[2] W. O. Godtfredsen and S. Vangedal, *Proc. Chem. Soc.*, 1964, 188; *Acta Chem. Scand.*, 1965, **19**, 1088; S. Abrahamsson and B. Nilsson, *Proc. Chem. Soc.*, 1964, 188.

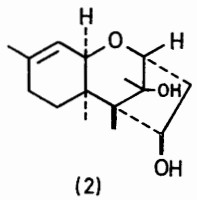
[3] J. Gutzwiller, R. Mauli, H. P. Sigg, and Ch. Tamm, *Helv. Chim. Acta*, 1964, **47**, 2234.

[4] N. Bhacca and D. Williams, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, p. 50.

molecule *trans* to the C-15 methyl group. In the verrucarol (12,13-epoxytrichothec-9-ene-4β,15-diol) series, where C-15 is hydroxylated, epoxidation affords [5]



(1)



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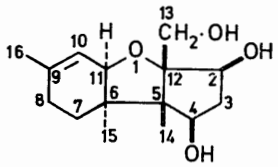

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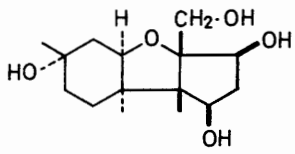

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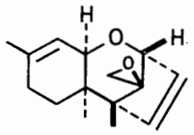

(5)

a mixture of α- and β-epimers. The β-epimer is the major product and here $J_{10,11}$ is 5·5 Hz; the α-epimer has $J_{10,11}$ 1·5 Hz. The C-15 oxygen function directs some epoxidation to the α-face by co-ordination with

TABLE 1

N.m.r. signals of some trichothecanes

	C-2	C-4	C-11	C-13	C-10	
Trichodermol (1; R = α-H, β-OH)	6·22	5·74	6·53	7·25	6·95	4·65
Dihydrotrichodermol	6·21	5·81	6·66	7·20	6·90	
Trichodermol epoxide	6·14	5·74	6·50	7·30	6·90	7·00
4-Epitrichodermol (1; R = β-H, α-OH)	6·36	5·82	5·82	7·16	6·99	4·58
9,10-Epoxy-4-epitrichodermol	6·25	5·75	5·75	7·30	6·90	6·90
Trichothec-9-ene-4β,12β-diol (2)	6·06	5·75	6·59	8·53		4·70
9β,10β-Epoxytrichothecane-4β,12β-diol	5·97	5·70	6·52	8·51		6·98

TABLE 2

Solvent shift n.m.r. data for trichodermone (1; R = O) and its 9α,10α-glycol

	Solvent	C-13	C-14	C-15	C-16
Trichodermone (1; R = O)	$CDCl_3$	7·07	6·76	9·18	8·26
	C_5D_5N	7·06	6·76	9·15	9·23	8·35
12β,13-Epoxy-9α,10α-dihydroxytrichothecan-4-one	$CDCl_3$	7·01	6·76	9·24	8·90	8·61
	C_5D_5N	6·94	6·70	9·14	8·63	8·36

the peroxy-acid. However the 9,10-glycol formed by osmylation of trichodermone (1; R = O) appeared to have α-stereochemistry on the basis of the solvent shifts in the n.m.r. spectrum (see Table 2). Thus introduction of a 9,10-dihydroxy group produces a big effect on the α-oriented 15-protons which is increased in deuteriopyridine. On the other hand there is little effect on the β-oriented 13-protons. The difference between these two reactions may be due to the influence of the allylic 11-oxygen bonding to the incoming peroxy-acid. Careful oxidation of the glycol with chromium trioxide gave a ketol ($\nu_{max.}$ 1705 cm^{-1}).

Treatment of trichodermol (1; R = α-H, β-OH) under conditions which would be expected to give trichodermol glycol (3) [2] also afforded a compound, $C_{15}H_{26}O_5$, which, whilst possessing the n.m.r. characteristics of the glycol,[2] lacked the olefinic 10-H resonance. On the other hand there was an additional singlet methyl resonance at τ 8·49 (in deuteriopyridine) and hence the compound was assigned the structure (4). Since the 15-H resonance is shifted to low field compared with that of trichodermol (1; R = α-H, β-OH) [τ 8·81 (*cf.* 9·15) in deuteriopyridine] the 9-hydroxy-group is assigned the α-configuration.

Trichodermol is readily oxidized to trichodermone (1; R = O).[2] Reduction of this ketone with sodium borohydride gave the epimeric 4-alcohol (1; R = β-H, α-OH) in which attack of the hydride has taken place from the less hindered β-face of ring C. In the n.m.r. spectrum of this alcohol, the 4-H resonance is partially obscured by the 11-H signal (see Table 1). However in the methanesulphonate the 4-H resonance appears as a quartet at τ 5·03 while the 3-protons resonate as a quartet and doublet at τ 7·40 and 7·64, respectively. The coupling constants ($J_{2,3}$ 0, $J_{2,3}$ 5, $J_{3,4}$ 10, and $J_{3,4}$ 5 Hz) correspond to approximate dihedral angles of 90, 45, 0, and *ca.* 125°.[4] Hence ring C is in an envelope conformation as in verrucarol.[6] There is a marked downfield shift of the 11-H resonance in the 4-epi-series (see Table 1) which can be ascribed to a transannular interaction between the C-4 oxygen function and the 11-proton. Both the methanesulphonates of trichodermol and 4-epitrichodermol were recovered unchanged after treatment with collidine under reflux for 1 h. However more prolonged treatment led to extensive decomposition. T.l.c. indicated the presence of the Δ^3-olefin amongst the products. Treatment of trichodermol with thionyl chloride in pyridine at −10° gave a dimeric sulphite, reduction of which with lithium aluminium hydride gave the diol (2). However treatment of trichodermol with phosphorus pentachloride in pyridine followed by chromatography on alumina gave the Δ^3-olefin (5). The n.m.r. spectrum showed that no rearrangement had occurred in the formation of this olefin (see Experimental section).

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage block apparatus. I.r. spectra were recorded on a Unicam SP 200 spectrometer as Nujol mulls. N.m.r. spectra were recorded on Varian A60A and HA 100 spectrometers in

[5] R. Achini and Ch. Tamm, *Helv. Chim. Acta*, 1968, **51**, 1712.
[6] A. T. McPhail and G. A. Sim, *J. Chem. Soc.* (*C*), 1966, 1394.

deuteriochloroform with tetramethylsilane as an internal standard. Rotations were determined in chloroform.

Epoxidations.—Trichodermol (1; R = α-H, β-OH) (200 mg) in chloroform (10 ml) was treated with *m*-chloroperbenzoic acid (200 mg) overnight. The solution was diluted with chloroform, washed with aqueous ferrous sulphate, water, and sodium hydrogen carbonate, and dried. Evaporation gave 9β,10β:12,13-*diepoxytrichothecan*-4β-*ol* (130 mg), needles, m.p. 209—211° (from ethyl acetate–light petroleum) $[\alpha]_D^{20}$ −20° (*c* 0·2) (Found: C, 67·9; H, 8·5. $C_{15}H_{22}O_4$ requires C, 67·65; H, 8·3%), $\nu_{max.}$ 3500 cm^{-1}, τ 9·27 (3H, s), 9·19 (3H, s), 8·68 (3H, s), 7·29 (1H, d, *J* 4·5 Hz), 7·00 (1H, d, *J* 5·5 Hz), 6·90 (1H, d, *J* 4·5 Hz), 6·51 (1H, dd, *J* 1·5 and 5·5 Hz), 6·14 (1H, d, *J* 5·5 Hz), and 5·71 (1H, m).

Similarly 4-epitrichodermol (1; R = β-H, α-OH) gave 9β,10β:12,13-*diepoxytrichothecan*-4α-*ol*, needles, m.p. 159—160° (from acetone–light petroleum), $[\alpha]_D^{20}$ +29° (*c* 0·09) (Found: C, 67·8; H, 8·5. $C_{15}H_{22}O_4$ requires C, 67·65; H, 8·3%), $\nu_{max.}$ 3440 cm^{-1}, τ 9·18 (3H, s), 8·91 (3H, s), 8·66 (3H, s), 7·5 (2H, m), 7·30 (1H, d, *J* 5 Hz), 6·90 (2H, d, *J* 5 Hz), 6·25 (1H, d, *J* 5 Hz), and 5·75 (2H, m). Similarly, trichothec-9-ene-4β,12-diol (2) gave 9β,10β-*epoxytrichothecan*-4β,12β-*diol*, prisms, m.p. 178—180° (from acetone–light petroleum), $[\alpha]_D^{20}$ −9° (*c* 0·16) (Found: C, 66·9; H, 9·0. $C_{15}H_{24}O_4$ requires C, 67·1; H, 9·0%), $\nu_{max.}$ 3300br cm^{-1}, τ 9·19 (3H, s), 9·03 (3H, s), 8·67 (3H, s), 8·51 (3H, s), 6·98 (1H, d, *J* 5 Hz), 6·52 (1H, dd, *J* 1·5 and 5 Hz), 5·97 (1H, d, *J* 5 Hz), and 5·70 (1H, dt, *J* 2·5 and 8 Hz).

12,13-*Epoxy*-9α,10α-*dihydroxytrichothecan*-4-*one.*— Trichodermone (1; R = O) (500 mg) in pyridine (10 ml) was treated with osmium tetroxide (500 mg) for 48 h at room temperature. Sodium hydrogen sulphite (2 g) in water (25 ml) and pyridine (5 ml) was added and the solution was stirred for 4 h. The solution was poured into water (150 ml) and the product was recovered in ethyl acetate. 12,13-*Epoxy*-9α,10α-*dihydroxytrichothecan*-4-*one* (330 mg) crystallized as needles, m.p. 210—212° (from acetone–light petroleum), $[\alpha]_D^{20}$ +38° (*c* 0·21) (Found: C, 63·7; H, 8·0%; *m/e* 282. $C_{15}H_{22}O_5$ requires C, 63·8; H, 7·85%; *M*, 282), $\nu_{max.}$ 3450sh, 3350br, and 1738 cm^{-1}, τ 9·24 (3H, s), 8·90 (3H, s), 8·61 (3H, s), 7·01 (1H, d, *J* 5 Hz), 6·76 (1H, d, *J* 5 Hz), 6·51 (1H, m), 6·30 (1H, m), and 5·97 (1H, m).

12,13-*Epoxy*-9α-*hydroxytrichothecane*-4,10-*dione.*— The glycol (100 mg) in acetone (2 ml) was treated with the 8N-chromium trioxide (0·2 ml) at 0° for 1 h. Methanol was added and the solvents were removed *in vacuo*. Water was added and the products were recovered in ethyl acetate and purified by p.l.c. (silica; 50% ethyl acetate–light petroleum) to give 12,13-*epoxy*-9α-*hydroxytrichothecane*-4,10-*dione* (14 mg), needles, m.p. 162—166° (from light petroleum), $[\alpha]_D^{20}$ −5° (*c* 0·2) (Found: C, 64·1; H, 7·2%; *m/e* 280. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·2%; *M*, 280), $\nu_{max.}$ 3300br, 1745, and 1705 cm^{-1}, τ [in $(CD_3)_2CO$] 9·20 (3H, s), 8·98 (3H, s), 8·00 (3H, s), 6·88 (1H, d, *J* 5 Hz), 6·70 (1H, d, *J* 5 Hz), 6·02 (1H, s), and 5·80 (1H, dd, *J* 1 and 4 Hz).

Apotrichothecane-2β,4β,9α,13-*tetraol* (4).—Trichodermol (1; R = α-H, β-OH) (500 mg) in 0·5N-sulphuric acid (50 ml) was heated under reflux for 2 h. The solution was neutralized with barium carbonate, the filtrate was evaporated to dryness, and the product was recrystallized from ethanol to give the *tetraol* (4) (230 mg) as very insoluble white prisms, m.p. 206—212° (Found: C, 62·6; H, 9·4%; *m/e* 286. $C_{15}H_{26}O_5$ requires C, 62·9; H, 9·15%; *M*, 286), $\nu_{max.}$ 3505 and 3330 cm^{-1}, τ (in C_5D_5N) 8·81 and 8·70 (both 3H, s), 8·49 (3H, s), 6·15 (1H, m), 5·90—5·40 (4H, m), and 5·19 (1H, s). P.l.c. of the residue [silica; in ethyl acetate–chloroform–acetic acid (15 : 5 : 1)] gave apotrichothec-9-ene-2β,4β,13-triol (3), m.p. 140—142° (lit.,[2] 143·5—144·5°), identified by its n.m.r. spectrum.[2]

4-*Epitrichodermol* (1; R = β-H, α-OH).—Trichodermone (1; R = O) (300 mg) in dioxan (1 ml) and methanol (15 ml) was treated with sodium borohydride (400 mg) at room temperature for 1 h. The solution was treated with acetic acid and then poured into water and the product was recovered in ethyl acetate. 12,13-*Epoxytrichothec*-9-*en*-4α-*ol* (1; R = β-H, α-OH), (204 mg): needles, had m.p. 197—199° (from acetone–light petroleum), $[\alpha]_D^{20}$ +19° (*c* 0·53) (Found: C, 71·7; H, 8·9. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%), $\nu_{max.}$ 3420 cm^{-1}, τ 9·14 (3H, s), 8·92 (3H, s), 8·30 (3H, s), 7·16 (1H, d, *J* 4 Hz), 6·99 (1H, d, *J* 4 Hz), 6·36 (1H, d, *J* 5·5 Hz), 5·82 (2H, m), and 4·52 (1H, d, *J* 5·5 Hz). Prisms of the *methanesulphonate*, prepared with methanesulphonyl chloride in pyridine, had m.p. 130° (from acetone–light petroleum), $[\alpha]_D^{20}$ +28° (*c* 0·23) (Found: C, 59·7; H, 7·6. $C_{16}H_{24}O_5S$ requires C, 58·5; H, 7·4%), $\nu_{max.}$ 1675w and 1180 cm^{-1}, τ 9·00 (3H, s), 8·93 (3H, s), 7·64 (1H, d, *J* 5 Hz), 7·40 (1H, q, *J* 5 and 10 Hz), 7·14 (1H, d, *J* 4·5 Hz), 6·90 (3H, s), 6·85 (1H, d, *J* 4·5 Hz), 6·23 (1H, d, *J* 5 Hz), 5·85 (1H, d, *J* 5·5 Hz), 5·03 (1H, q, *J* 5 and 10 Hz), and 4·50 (1H, d, *J* 5·5 Hz).

Trichodermol Sulphite.—Trichodermol (500 mg) in pyridine (5 ml) was treated with thionyl chloride (0·75 ml) at −10° for 1 h. The solution was poured into ice-cold dil. hydrochloric acid and the product was recovered in chloroform. Needles of the *sulphite* (350 mg) had m.p. 194—195° (from acetone–light petroleum) (Found: C, 70·4; H, 8·3. $C_{30}H_{42}O_5S$ requires C, 70·0; H, 8·2%), $\nu_{max.}$ 1680w, 1210, and 1090 cm^{-1}, τ 9·22 (3H, s), 9·15 (3H, s), 9·10 (6H, s), 7·20 (2H, d, *J* 4·5 Hz), 6·88 (2H, d, *J* 4·5 Hz), 6·47 (2H, d, *J* 5 Hz), 6·17 (2H, d, *J* 5 Hz), 4·72 (2H, m), and 4·6 (2H, m).

Reduction of the Sulphite.—The sulphite (150 mg) in dioxan (1 ml) and ether (5 ml) was treated with lithium aluminium hydride (100 mg) at room temperature for 3 h. The solution was cautiously acidified and the product was recovered in chloroform. Trichothec-9-ene-4β,12-diol (2) (90 mg) crystallized from acetone–light petroleum as prisms, m.p. 146—147°, (lit.,[2] 147·5—148·5°), identified by its i.r. spectrum.

12,13-*Epoxytrichotheca*-3,9-*diene* (5).—Trichodermol (200 mg) in pyridine (5 ml) was treated with phosphorus pentachloride (500 mg) at 0° for 1 h. The solution was poured into ice–water, acidified with dil. hydrochloric acid, and the product was recovered in chloroform and chromatographed on alumina. Elution with light petroleum gave 12,13-*epoxytrichotheca*-3,9-*diene* (5) (38 mg), needles, m.p. 85—88° (from light petroleum), $[\alpha]_D^{20}$ −71° (*c* 0·2) (Found: C, 77·3; H, 8·4. $C_{15}H_{20}O_2$ requires C, 77·55; H, 8·7%), $\nu_{max.}$ 1675w, 790, and 720 cm^{-1}, τ 9·27 (3H, s), 9·13 (3H, s), 7·04 (1H, d, *J* 4·5 Hz, 13-H), 6·80 (1H, d, *J* 3·5 Hz, 13-H), 6·25 (1H, d, *J* 5 Hz), 5·94 (1H, d, *J* 2·5 Hz, 2-H), 4·60 (1H, d, *J* 5 Hz), 3·85 (1H, q, *J* 2·5 and 6 Hz, 3-H), and 3·6 (1H, d, *J* 6 Hz, 4-H).

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