The Constitution and Stereochemistry of Terrein.

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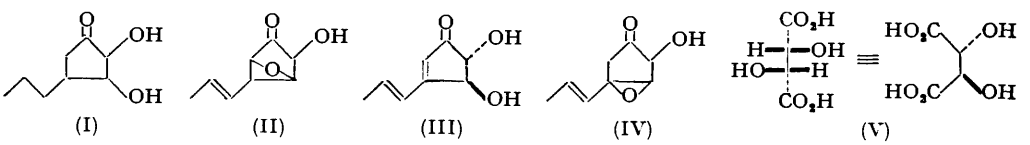
The constitution of the mould metabolite terrein has been elucidated. The stereochemistry of the molecule has been established by conversion into a derivative of (+)-tartaric acid.

The mould metabolite terrein was first isolated by Raistrick and Smith (*Biochem. J.*, 1935, **29**, 606). In an extensive and elegant contribution Raistrick and his collaborators (Clutterbuck, Raistrick, and Reuter, *ibid.*, 1937, **31**, 987) established that tetrahydroterrein, easily obtained by catalytic hydrogenation of terrein, had the constitution (I). Since terrein gives acetaldehyde on ozonolysis an ethylenic linkage must be placed in the *n*-propyl side chain. Of the various possible constitutions for terrein which remain, the interesting formula (II) was given preference. It seemed to us that the recorded chemical facts also made formula (III) and (IV) worthy of consideration. The former was one of the structures favoured by Raistrick *et al.*, but tentatively rejected on the grounds that terrein failed to react with maleic anhydride. However, one must note that the conjugated diene system of (III) would be deactivated towards dienophils of the usual type because of the conjugated carbonyl group.

With the very kind encouragement of Professor H. Raistrick, F.R.S., we have obtained additional evidence which confirms the correctness of (III). Terrein showed (in ethanol)



(I) (II) (III) (IV) (V)

$\lambda_{max.}$ 275 (ε 26,000) and 342 mμ (ε 130), a spectrum characteristic of conjugated dienones such as (III). In the infra-red region terrein exhibited maxima at 3620 and 3420 (hydroxyl), at 1700, 1640, and 1575 (·CO·C:C·C:C·, the CO being placed in a five-membered ring) and at 967 cm.$^{-1}$ (*trans*-CH:CH·), the spectrum being in complete agreement with formula (III).

That terrein contains two hydroxyl groups was demonstrated as follows. Terrein 2 : 4-dinitrophenylhydrazone (Clutterbuck, Raistrick, and Reuter, *loc. cit.*), which showed the ultra-violet absorption spectrum expected of a conjugated dienone derivative, gave a diacetate on treatment with pyridine and acetic anhydride at room temperature. 2 : 4-Dinitrophenylhydrazones are not, of course, acetylated on nitrogen under these conditions (see Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 5309). In the infra-red region (bromoform solution) the diacetate showed bands at 3350 (NH), 1742 and 1225 (acetate; strength of bands indicative of two acetate residues), and 967 cm.$^{-1}$ (*trans*-CH:CH·), in agreement with the assigned constitution. Both terrein and its 2 : 4-dinitrophenylhydrazone are stable in pyridine solution at room temperature.

On the basis, particularly, of the work already cited (Raistrick *et al.*, *loc. cit.*) and of the additional facts recorded above, the constitution (III) for terrein may be taken as established. The same conclusion has also been reached by Grove (personal communication; *J.*, 1954, 4693) on the basis, mainly, of spectroscopic evidence. We cordially thank Mr. J. F. Grove for sending us a copy of his manuscript.

The stereochemistry of terrein, both relative and absolute, has been elucidated as follows. The *trans*-configuration of the side-chain ethylenic linkage is shown by the infra-red data cited above. The *trans*-relation of the two hydroxyl groups, already made probable by the failure of terrein 2 : 4-dinitrophenylhydrazone to consume periodic acid, was proved by controlled ozonolysis of acetylated terrein. Conversion of the acidic product

into the di-*p*-bromophenacyl ester gave the di-*O*-acetyl-(+)-tartaric acid derivative identical with authentic material. The isolation of this derivative of (+)-tartaric acid (V) (Bijvoet, Peerdeman, and van Bommel, *Nature*, 1951, **168**, 271) proves that terrein has the stereochemistry already indicated in (III). It also, incidentally, provides further confirmation for the proposed constitution.

Experimental

Unless stated to the contrary, ultra-violet absorption spectra were determined in $CHCl_3$ with the Unicam S.P. 500 Spectrophotometer. Infra-red spectra were kindly determined by Messrs. Glaxo Laboratories using the same solvent unless stated to the contrary. Rotations were likewise determined in $CHCl_3$ solution.

Terrein 2 : 4-Dinitrophenylhydrazone Diacetate.—Terrein 2 : 4-dinitrophenylhydrazone (Clutterbuck, Raistrick, and Reuter, *loc. cit.*), $[\alpha]_D$ −619° (*c*, 0·06), $\lambda_{max.}$ 400 mμ (ε 33,700) (85 mg.), in acetic anhydride (1 ml.) and pyridine (2 ml.) was left at room temperature for 14 hr. Crystallisation of the product from ethyl acetate–methanol gave *terrein 2 : 4-dinitrophenylhydrazone diacetate*, m. p. 195—196°, $[\alpha]_D$ −613° (*c*, 0·53), $\lambda_{max.}$ 391 mμ (ε 38,700) [Found : C, 51·5; H, 4·3; Ac (determined by alkaline hydrolysis followed by distillation from aqueous sulphuric acid), 18·25. $C_{18}H_{18}O_8N_4$ requires C, 51·65; H, 4·35; Ac, 20·6%].

Di-p-bromophenacyl Di-O-acetyl-(+)-tartrate.—Di-*O*-acetyl-(+)-tartaric anhydride (216 mg.) in 50% ethanol (10 ml.) was neutralised with aqueous potassium hydroxide, and the solution refluxed with *p*-bromophenacyl bromide (556 mg.) for 2 hr. Crystallisation of the product from chloroform–methanol gave *di-p-bromophenacyl di-O-acetyl-(+)-tartrate*, m. p. 175—176°, $[\alpha]_D$ −9·3° (*c*, 2·46) (Found : C, 45·6; H, 3·2; Br, 25·8. $C_{24}H_{20}O_{10}Br_2$ requires C, 45·9; H, 3·2; Br, 25·4%). On crystallisation from methanol the ester melts (Köfler block) at 159—161° (plates) and then at 175—176° (needles).

Conversion of Terrein into Di-O-acetyl-(+)-tartaric Acid.—Terrein (250 mg.) was treated with acetic anhydride (1·0 ml.) and pyridine (2·0 ml.) for 14 hr. at room temperature. The resultant diacetate, which did not crystallise, was ozonised in carbon tetrachloride (100 ml.) at −20° for 2½ hr. (the optimum time was determined by preliminary experiments). The solution was warmed on the steam-bath for 30 min. and then titrated with aqueous 0·87N-potassium hydroxide (phenolphthalein) (3 equivs. required 5·6 ml.; consumed, 5·8 ml.). The aqueous layer was separated and hydrogen peroxide (30%; 2 ml.) added. After 10 min. the peroxide was destroyed by the addition of platinum. The filtered solution was evaporated *in vacuo* at pH 7 and the residue dissolved in 50% ethanol (20 ml.) and treated with *p*-bromophenacyl bromide (1·38 g.) as above. Crystallisation of the product from chloroform–methanol gave di-*p*-bromophenacyl di-*O*-acetyl-(+)-tartrate (54 mg.) identified by m. p., mixed m. p., rotation {$[\alpha]_D$ −8·7° (*c*, 2·24)} and infra-red spectrum. Crystallisation from methanol gave the second crystal form (plates; m. p. and mixed m. p.) referred to above.

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