Cleavage of Proanthocyanidins with Thioglycollic Acid

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BROWN and his co-workers[1] have used thioglycollic acid to determine the mode of linkage in the tannin from common heather. Thioglycollic acid degradation of this tannin followed by methylation of the crude product with diazomethane led, after purification, to the *S*-benzylthioglycollate (I). Since thioglycollic acid is known to cleave benzylic ethers,[2] it was concluded that the condensed tannin was comprised of flavanoid units attached by C-4 benzylic ether linkages (II).

Consideration of this work led us to speculate that thioglycollic acid might be capable of cleaving tannins in which the structural units are linked by carbon–carbon bonds [*e.g.* (III)]. The recent isolation of numerous, natural, dimeric proanthocyanidins[3,4] [*e.g.* (IV)] strongly supports the suggestion that the most commonly occurring polymeric leucoanthocyanidins (condensed tannins which yield cyanidin on acid treatment) are composed of flavan-3-ol nuclei in which the acid-labile carbon–carbon bond from the 4-position of the one is linked to the 6- or 8-position of the other [*e.g.* (III)].[3,5] The condensed tannin is terminated by a catechin unit which lacks a hydroxy-group at C-4 and is incapable of further condensation. Although thioglycollic acid has not been reported to cleave carbon–carbon bonds it appeared that suitably activated carbon–carbon linkages should be readily capable of rupture with this reagent.

To test our hypothesis, the reactions of two model proanthocyanidin compounds, (V) and (VI), with thioglycollic acid have been studied. These compounds were initially synthesized and characterized by Geissman and Yoshimura,[6] and the preparation and extensive characterization of (V) have been investigated by Jurd and Lundin.[7]

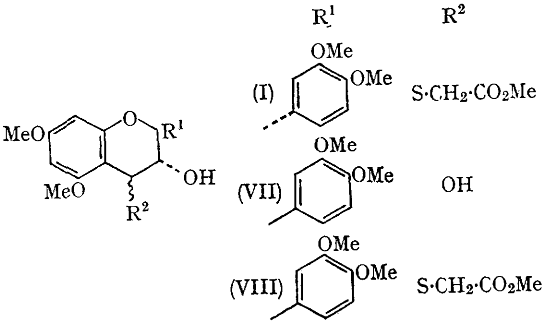
Both (V) and (VI) were prepared by the method of Geissman and Yoshimura in which the flavan-3,4-diol (VII) was condensed with equimolar amounts of phloroglucinol or (+)-catechin in aqueous 0·1N-hydrochloric acid–dioxan at 0°. In both preparations two major products were formed (believed to be epimeric at C-4)[6] with the isomer of higher R_F predominating on t.l.c. Compound (VII) was prepared by reducing 5,7,3′,4′-tetra-*O*-methyldihydroquercetin[8] with sodium borohydride to obtain the higher melting isomer (m.p. 205°, in agreement with Fujisë, *et al.*[9]).

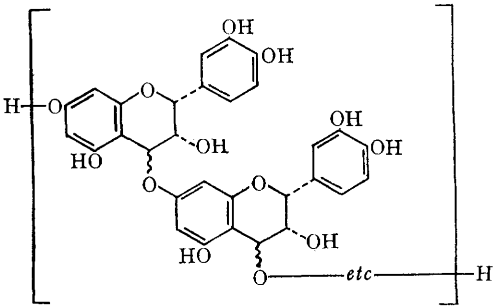
Prior to thioglycollic acid degradation of either (V) or (VI), the *S*-benzylthioglycollate (VIII) was prepared by heating flavan-3,4-diol (VII) under reflux with 25% aqueous thioglycollic acid for two hours followed by methylation with dimethyl sulphate and potassium carbonate in acetone under reflux. The predominant product (VIII) was isolated by preparative t.l.c. in chromatographically homogeneous form. Sublimation (150°/10^{-5} mm.) gave methyl *S*-(3-hydroxy-5,7,3′,4′-tetramethoxyflavan-4-yl)-thioglycollate (VIII) as an amorphous solid, $\nu_{\max}$ ($CHCl_3$) 3440 and 1735 cm.$^{-1}$, $\lambda_{\max}$ (EtOH) 277 (ϵ 4000). The n.m.r. spectrum was in accord with structure (VIII); τ 5·10 (d, C-2 methine proton, *J* 10·0 Hz) indicating that the 2,3-hydrogens are *trans*-diaxial; a determination of the 3,4-configuration could not be made. The compound analyzed for $C_{22}H_{26}O_8S$, and had a parent peak in the mass spectrum at *m/e* of 450, the calculated molecular weight. A much smaller quantity of the other, presumed, epimeric C-4 isomer was also formed in the reaction. This had a lower R_F value and after purification by preparative t.l.c. gave an identical u.v. and a similar i.r. spectrum.

The proanthocyanidin (V) was treated with thioglycollic acid, with the same conditions used to prepare (VIII) from (VII), to obtain as the predominant product the *S*-benzylthioglycollate (VIII) synthesized by the independent route discussed. This compound was purified by preparative t.l.c. and was chromatographically identical, and had i.r., u.v., and n.m.r. spectra identical to those obtained for synthetic compound. Prior to methylation of the crude degradation products, the acidic reaction products were extracted with sodium hydrogen carbonate solution. Phloroglucinol was observed by two dimensional t.l.c. to be the major component of the non-hydrogen carbonate extractable material.

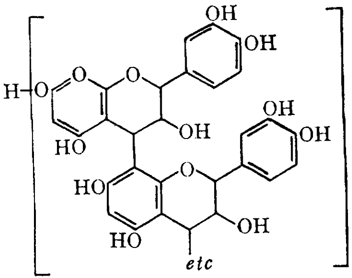
Similarly, the proanthocyanidin (VI) with catechin as the pendent ring, was degraded with thioglycollic acid; again, (VIII) was obtained as the predominant product. Purification by preparative t.l.c. gave a product which was chromatographically identical and had i.r. and u.v. spectra identical to those of the synthetic compound.

Our success in cleaving the model proanthocyanidin compounds with thioglycollic acid has led us to apply this technique as a structural tool in the degradation of tannin from western hemlock (*Tsuga heterophylla*), a condensed tannin believed to

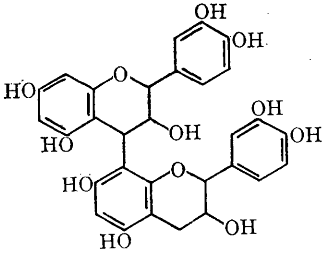




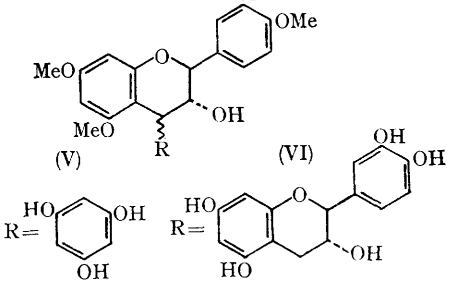
(II)



(III)



(IV)



(V) (VI)

have structural units linked by carbon–carbon bonds[9] as represented in (III).

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[1] M. J. Betts, B. R. Brown, P. E. Brown, and W. T. Pike, *Chem. Comm.*, 1967, 1110.

[2] B. O. Lindgren, *Acta Chem. Scand.*, 1950, **4**, 1365.

[3] T. A. Geissman and H. F. K. Dittmar, *Phytochemistry*, 1965, **4**, 359.

[4] K. Weinges and K. Freudenberg, *Chem. Comm.*, 1965, 11, 220; L. L. Creasy and T. Swain, *Nature*, 1965, **208**, 151; F. D. Monache, I. L. d'Albuquerque, F. Ferrai, and G. B. M. Bettolo, *Tetrahedron Letters*, 1967, 4211; K. Freudenberg, *Experienta*, 1968, **16**, 104.

[5] T. A. Geissman and N. N. Yoshimura, *Tetrahedron Letters*, 1966, 2669.

[6] L. Jurd and R. Lundin, *Tetrahedron*, 1968, **24**, 2653.

[7] H. L. Hergert, P. C. Coad, and A. V. Logan, *J. Org. Chem.*, 1956, **21**, 304.

[8] S. Fujise, K. Adachi, and S. Hishida, *J. Chem. Soc. Japan*, 1962, **83**, 1294.

[9] H. L. Hergert, 155th American Chemical Society Meeting, Abstracts, 1968, 21D.