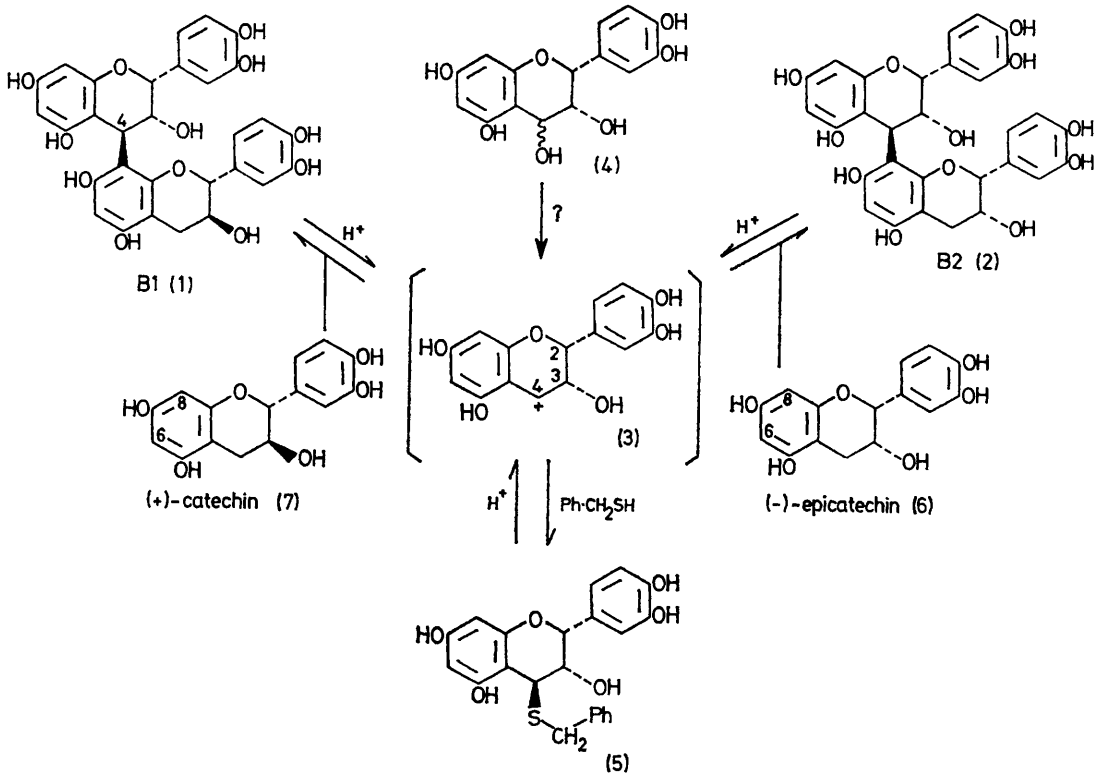
Biogenetically Patterned Synthesis of Procyanidins

By EDWIN HASLAM

(*Department of Chemistry, University of Sheffield, Sheffield* S3 7HF)

Summary The synthesis of the natural procyanidins B1 (**1**) and B2 (**2**) is described and the biogenetic implications of the mode of synthesis are discussed.

CHEMICAL[1] and recent biochemical[2] work has favoured a simulated acid-catalysed condensation of phenolic flavan-3,4-diols (**4**) and flavan-3-ols (**6**) and (**7**) as a mode of biogenesis of the dimeric procyanidins such as B1 and B2 (**1**)



and (**2**). The biogenetic arguments imply that condensation occurs between the 6 or 8 position of the resorcinol ring of the flavan-3-ol and the carbonium ion (**3**) derived from the flavan-3,4-diol. Further evidence to support this idea has now been obtained by the first synthesis of natural phenolic procyanidins by a method patterned on this process.

2*R*,3*S*,4*S*-4-Benzylthioflavan-3,3′,4′,5,7-pentaol (**5**) is an acid-catalysed degradation product of both (**1**) and (**2**) formed by the stereospecific capture of the carbonium ion (**3**) by toluene-α-thiol.[3] Treatment of (**5**, 1·7 mM) in aqueous acidic dioxan (1N-HCl) in presence of (—)-epicatechin (**6**, 3·8 mM) at room temperature gave one predominant product isolated and identified[3] as procyanidin B2 [**2**, 25% based on (—)-epicatechin used] and two other isolable but minor products (8% in total). Chemical degradation[3] and ^{1}H n.m.r. analysis showed both of these latter products to be isomers of the dimer B2 (**2**) in which the interflavan bond is between ring A (C-6 or C-8) and C-4 of the two epicatechin units. One has been described previously[3] as a natural product procyanidin B5 and the remaining dimer has now also been obtained from natural sources (*Aesculus hippocastanum, Crataegus monogyna*). The identical pattern and quantitative distribution of procyanidin dimers based on (—)-epicatechin (**6**) was also produced by acid-catalysed equilibration of each of the individual dimers, such as B2 (**2**), with (—)-epicatechin (**6**) thus demonstrating that the synthesis is an equilibrium controlled process. Significantly this range of procyanidins formed synthetically is also identical both qualitatively and quantitatively to that found in the vegetative tissues of plants in which (—)-epicatechin (**6**) is the dominant flavan-3-ol.

Analogous results were obtained when (**5**) was treated similarly in the presence of (+)-catechin (**7**). Procyanidin B1 (**1**) was isolated as the major product (23%) along with two further dimers (*ca.* 10%) isomeric with B1 and linked similarly between C-6 or C-8 and C-4 in the two flavan nuclei. Likewise acid-catalysed equilibration of B1 with (+)-catechin (**7**) gave an identical range of products to that obtained from (**5**) and (**7**).

Although no flavan-3,4-diol of a type such as (**4**) has yet been identified in the procyanidin bearing vegetative tissues of a plant[3,4] these results nevertheless lend substantial support to the biogenetic arguments previously outlined. In particular they indicate that the chemical pattern of procyanidins formed in higher plants may be primarily under thermodynamic rather than enzymic control. This resemblance to lignin formation in plants suggests a possible biosynthetic relationship between the formation of these two groups of metabolites which is underlined by the observation[5] that procyanidins are found mainly in plants with a 'woody habit' of growth.

The nature of the structural and stereochemical differences between the two groups of procyanidins derived from (**5**) and (—)-epicatechin (**6**) and (+)-catechin (**7**) respectively has not yet been clarified in detail. However on the basis of the greater nucleophilic reactivity at C-8 as opposed to C-6 in flavan-3-ols [such as (**6**) and (**7**)][6] and knowledge of the solvolysis of carbonium ions related to (**3**) with a 2,3-*cis* stereochemistry[7] it now appears reasonable to formulate the major products from these two reactions as B1 (**1**) and B2 (**2**) with the 4-*S* absolute configuration. This conclusion was previously not possible on the basis of spectroscopic data alone.[3,4]

(*Received*, 17*th May* 1974; *Com.* 565.)

[1] T. A. Geissman and N. N. Yoshimura, *Tetrahedron Letters*, 1966, 2669; L. L. Creasey and T. Swain, *Nature*, 1965, **208**, 151; D. G. Roux and S. E. Drewes, *Biochem. J.*, 1964, **90**, 343; 1964, **92**, 555; 1965, **94**, 982; 1966, **98**, 493.
[2] D. Jacques and E. Haslam, *J.C.S. Chem. Comm.*, 1974, 231.
[3] R. S. Thompson, D. Jacques, E. Haslam, and R. J. N. Tanner, *J.C.S. Perkin I*, 1972, 1387.
[4] K. Weinges, W. Kaltenhauser, H.-D. Marx, E. Nader, J. Perner, and D. Seiler, *Annalen*, 1968, **711**, 184.
[5] E. C. Bate-Smith and N. H. Lerner, *Biochem. J.*, 1954, **58**, 126.
[6] K. Weinges, H.-D. Marx, and J. Perner, *Chem. Ber.*, 1970, **103**, 2344.
[7] M. J. Betts, B. R. Brown, and M. R. Shaw, *J. Chem. Soc.* (*C*), 1969, 1178; J. W. Clark-Lewis and L. R. Williams, *Austral. J.Chem.*, 1967, **20**, 2151; I. C. du Preez, D. Ferreira, and D. G. Roux, *J. Chem. Soc.* (*C*), 1971, **336**.