711. *The Relative and Absolute Configurations of Catechins and* epi*Catechins.*

By A. J. Birch, J. W. Clark-Lewis, and A. V. Robertson.

The 3-hydroxyl groups in (+)-catechin and (−)-*epi*catechin 5 : 7 : 3′ : 4′-tetramethyl ether are of opposite configuration as reductive ring-opening and methylation gave enantiomorphous pentamethoxy-1 : 3-diarylpropan-2-ols. Epimerisation of catechins and *epi*catechins therefore results from inversion of the 2-aryl and not of the 3-hydroxyl group.[1] Prelog's atrolactic acid method [2] has been used to determine the absolute configurations of the catechins and *epi*catechins, the first of such determinations with flavan derivatives. Hydroxyl stretching frequencies of (+)-catechin and (−)-*epi*-catechin tetramethyl ethers indicate strong intramolecular hydrogen bonding of 3(a)-hydroxyl groups and hence the existence of these compounds in the preferred 2(a)aryl : 3(a)hydroxyl and 2(e)aryl : 3(a)hydroxyl conformations respectively.

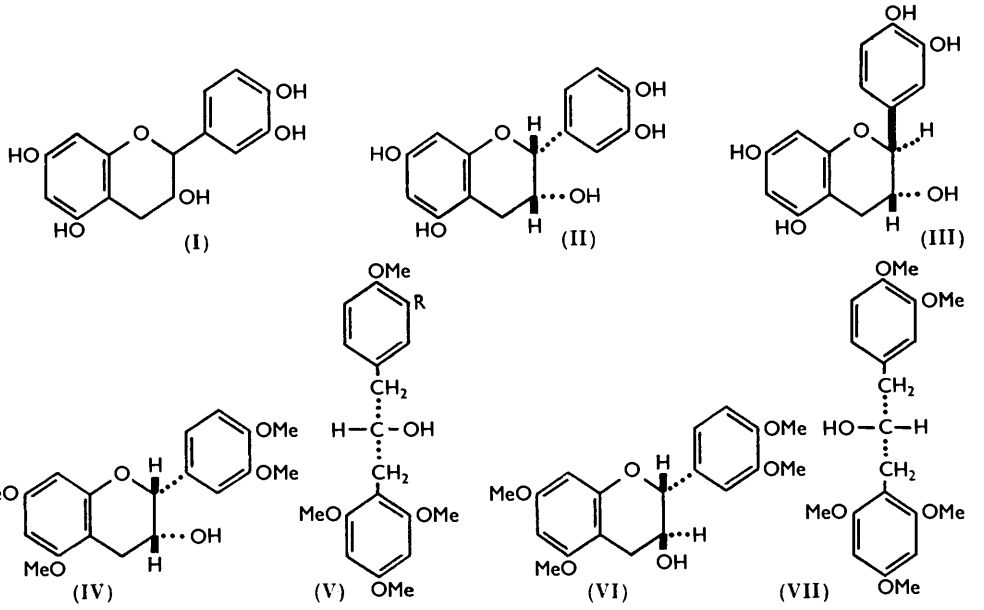
Catechin and *epi*catechin were shown to be 5 : 7 : 3′ : 4′-tetrahydroxyflavan-3-ols (I) in classical structural studies by Freudenberg and his school,[3] completed in 1925 [4] and reviewed by Mason.[5] Although the nature of the geometrical isomerism in these diastereoisomers was clear, it was not then possible to decide whether catechin or *epi*-catechin is the *cis*-compound (II), and evidence cited by Freudenberg [6] was later regarded as equivocal,[7] so that the question remained undecided.[8] Interpretation of Freudenberg's data in terms of modern stereochemical theory, however, establishes *epi*catechin as the *cis*- (II) and catechin as the *trans*-isomer (III), and reasons for these assignments were recently discussed in detail by King, Clark-Lewis, and Forbes,[9] and by Whalley.[10] Outstanding features of catechin stereochemistry, and particularly the relative and absolute configurations, have now been elucidated and are discussed below.

Epimerisation and racemisation of catechins occurs in hot aqueous solutions under a variety of conditions,[11, 12] and the resulting interconversions have been summarised by Freudenberg and Purrmann.[12] (+)-Catechin is thus partially converted into (+)-*epi*-catechin, and similarly (−)-*epi*catechin yields some (−)-catechin; these transformations clearly result from inversion at one only of the two asymmetric centres. Freudenberg [3, 13] assumed that epimerisation occurred by inversion of the 2-aryl group (*viz.*, II ⟶ III, and III ⟶ II) and we have proved this assumption correct.

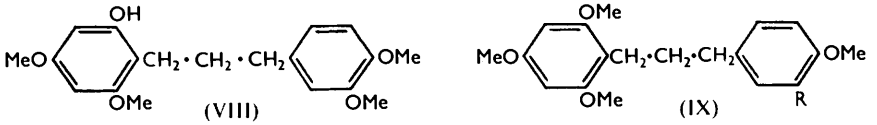
This was carried out by removing the asymmetry of the centre carrying the 2-aryl group. The C–O bond at this centre is of the benzyl ether type, and bonds of this type are usually smoothly reduced by sodium and ethanol in liquid ammonia, provided the rings do

[1] Birch, Robertson, and Clark-Lewis, *Chem. and Ind.*, 1956, 664.
[2] Prelog, *Helv. Chim. Acta*, 1953, **36**, 308; Prelog and Meier, *ibid.*, p. 320; Dauben, Dickel, Jeger, and Prelog, *ibid.*, p. 325; cf. "Progress in Stereochemistry," Butterworth, London, 1954, Vol. I, p. 198.
[3] Freudenberg, *Sci. Proc. Roy. Dublin Soc.*, 1956, **27**, 153.
[4] Freudenberg, Fikentscher, Harder, and Schmidt, *Annalen*, 1925, **444**, 135; for earlier work see refs. 3 and 5.
[5] Mason, *J. Soc. Chem. Ind.*, 1928, **47**, 269.
[6] Freudenberg, Fikentscher, and Harder, *Annalen*, 1925, **441**, 157; Freudenberg, Fikentscher, and Wenner, *ibid.*, **442**, 309; Freudenberg, Carrara, and Cohn, *ibid.*, 1926, **446**, 87.
[7] Freudenberg and Harder, *Annalen*, 1927, **451**, 213 (see footnote 3, p. 214); Hückel, Neunhoeffer, Gercke, and Frank, *ibid.*, 1930, **477**, 99 (see p. 159).
[8] Freudenberg and Harder, ref. 7; Freudenberg, Cox, and Braun, *J. Amer. Chem. Soc.*, 1932, **54**, 1913; Freudenberg and Oehler, *Annalen*, 1930, **483**, footnote, p. 141.
[9] King, Clark-Lewis, and Forbes, *J.*, 1955, 2949.
[10] Whalley, "The Stereochemistry of the Chromans and Related Compounds," Symposium on Vegetable Tannins, Cambridge, April, 1956, Society of Leather Trades' Chemists, Croydon, 1956, p. 151.
[11] Freudenberg, Böhme, and Purrmann, *Ber.*, 1922, **55**, 1734; Freudenberg and Purrmann, *Ber.* 1923, **56**, 1185.
[12] Freudenberg and Purrmann, *Annalen*, 1924, **437**, 274.
[13] Freudenberg and Oehler, *ibid.*, 1930, **483**, 140.

not carry free phenolic groups.[13a] (−)-*epi*Catechin tetramethyl ether (IV) was so reduced, and methylation of the resulting phenolic alcohol gave 1-(3 : 4-dimethoxyphenyl)-3-(2 : 4 : 6-trimethoxyphenyl)propan-2-ol with an excess of the (+)-enantiomorph * (V; R = OMe) (lævorotatory in EtOH, dextrorotatory in $CHCl_3$). Similar reduction of (+)-catechin tetramethyl ether (VI) and methylation gave the propan-2-ol with an excess of the (−)-enantiomorph * (VII) (dextrorotatory in EtOH, lævorotatory in $CHCl_3$). We infer that (+)-catechin and (−)-*epi*catechin tetramethyl ethers (and hence also the free phenols) have opposite configurations at position 3 so that (+)-catechin and (+)-*epi*catechin have the same configuration at this position, and therefore epimerisations of (+)-catechin to (+)-*epi*catechin and of (−)-*epi*catechin to (−)-catechin occur by inversion of the 2-aryl group. Conditions for reduction to the optically active propanols appear to be critical



and, for reasons which are not yet completely clear (see below), some reductions of the (+)-catechin compound (VI) gave only racemic propanol. Reduction to the phenolic alcohol was accompanied in each case by formation of the related propane (VIII), and after methylation the propanol (VII or V; R = OMe) was separated from the 1 : 3-diarylpropane (IX; R = OMe) by chromatography. The phenolic propane (VIII) had earlier been obtained by reduction of catechin [14] and *epi*catechin tetramethyl ethers [14b] with sodium and alcohol; its methyl ether (IX; R = OMe),[14] synthesised by Freudenberg,[15] was a key compound in structural investigations of the catechins.[5]



(−)-*epi*Afzelechin trimethyl ether [9] (X), which has the same configuration as (−)-*epi*-catechin tetramethyl ether (IV), was similarly reduced with sodium in liquid ammonia, and

* Prefixes (+) and (−) refer to the direction of rotation of the propanols in aprotic solvents.

[13a] Birch, Hughes, and E. Smith, *Austral. J. Chem.*, 1955, **7**, 83; Birch, E. Smith, and Speake, unpublished work.

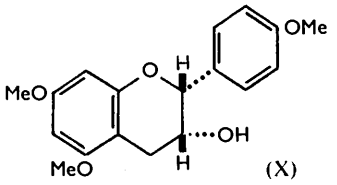
[14] (*a*) Kostanecki and Lampe, *Ber.*, 1907, **40**, 720; (*b*) Freudenberg and Cohn, *Ber.*, 1923, **56**, 2127.

[15] Freudenberg, *Ber.*, 1920, **53**, 1416.

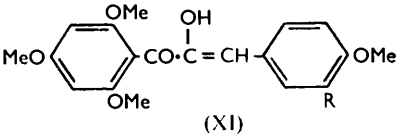
methylation of the phenolic products gave a mixture, separable by crystallisation, of the diarylpropane (IX; R = H) and diarylpropanol containing an excess of the (−)-enantiomorph (V; R = H) (lævorotatory in EtOH, $C_2H_2Cl_4$, and $CHCl_3$). As (−)-*epi*catechin tetramethyl ether (IV) gave the (+)-propanol (V; R = OMe) (dextrorotatory in $CHCl_3$ and $C_2H_2Cl_4$, lævorotatory in EtOH) it is now evident that the (−)-propanols (V; R = H) and (VII) have opposite configurations. Tacit assumption of the converse led us to incorrect conclusions [1] regarding the relative configurations of the catechins. It seems evident that no conclusions can be drawn in the diarylpropanol series by comparisons of the signs of rotation of different compounds at the D-line : rotational dispersion spectra may be more informative.*

The structures of the three optically active propanols (VII and V; R = OMe or H) were confirmed by the identity in each case of the infrared absorption spectrum of the active alcohol with that of its racemate synthesised from the appropriate 1 : 2-diketone. Condensation of ω-acetoxy-2 : 4 : 6-trimethoxyacetophenone with veratraldehyde and with *p*-anisaldehyde gave the two enolic diketones (XI; R = OMe or H) with infrared absorptions at 2·95—2·96 and 6·0 μ which are typical of enolic 1 : 2-diketones of this type.[16] Catalytic hydrogenation of the diketone (XI; R = OMe) gave the (±)-propan-2-ol which crystallised readily, but great difficulty was experienced in crystallising both the (−)-propanol (V; R = H) and its racemate obtained by reduction of the diketone (XI; R = H).

The relative configurations of the catechins having been thus established it remained to decide whether the *cis*-structure (II) and the *trans*-structure (III) represent respectively (−)-*epi*catechin and (−)-catechin, or their (+)-enantiomorphs. In principle this question might be resolved by examination of any one of the four optically active compounds, (+)- or (−)-*epi*catechin, (+)- or (−)-catechin, by the method for determining absolute configurations of alcohols developed by Prelog,[2] but in practice decisive evidence was obtained only with the *cis*-compounds. Reaction of methylmagnesium iodide with



(X)



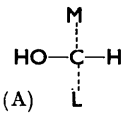
(XI)

(−)-*epi*catechin tetramethyl ether 3-phenylglyoxylate and hydrolysis of the ester gave atrolactic acid with $[\alpha]_D$ −16·4° (after three crystallisations) equivalent to a 43% excess of the (−)-isomer. The atrolactic acid obtained similarly from (−)-*epi*afzelechin 5 : 7 : 4′-trimethyl ether had $[\alpha]_D$ −30·4° (after three crystallisations) corresponding to an 81% excess of the (−)-isomer, thus confirming the steric identity of the *epi*afzelechin and *epi*catechin compounds already inferred.[9] Formation of (−)-atrolactic acid in these reactions indicates that the Fischer projection for the (−)-*epi*-compounds is (A), in which M is the group with CH_2, and L that with CHAr adjacent to position 3, and these absolute configurations are shown in the structural formulæ for (−)-*epi*catechin tetramethyl ether (IV) and (−)-*epi*afzelechin trimethyl ether (X). The stereochemistry of (−)-*epi*catechin (II), (−)-catechin (III), (+)-*epi*catechin (mirror image of II) and (+)-catechin (mirror image of III) is thus completely defined for the first time, and these formulæ agree with Freudenberg's recent conjecture.[3]

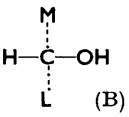
* Through the kindness of Dr. C. Djerassi (Wayne University) these have been examined. The curves for the alcohols from (−)-*epi*catechin tetramethyl ether and (−)-*epi*afzelechin trimethyl ether (in MeOH) are closely similar in shape and attain high positive values in the region of 300 mμ; the curve for the alcohol from (+)-catechin tetramethyl ether is enantiomeric. This result confirms the present conclusions on the identical configurations of the first two substances.

[16] Barnes and Pinkney, *J. Amer. Chem. Soc.*, 1953, **75**, 479.

(+)-Catechin tetramethyl ether (VI; Fischer projection B) was expected to yield the (+)-acid when examined by Prelog's method, but hydrolysis of the 3-atrolactate gave atrolactic acid with $[\alpha]_D$ −1·1° corresponding to a 3% excess of (−)-acid. The experiment was repeated with similar results and it was proved that the lævorotation of the acid was



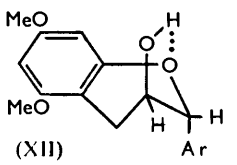
(A)



(B)

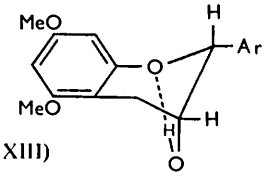
not caused by incomplete hydrolysis of the ester, by glycol formation,[17] or by contamination with lævorotatory (+)-catechin tetramethyl ether. In 3β-cholestanol phenylglyoxylate the ester group is flanked by two methylene groups and gave atrolactic acid with low optical activity, so that stereochemical inferences were considered inadvisable.[17] In the present case steric hindrance to reaction at the phenylglyoxylate carbonyl group due to the 2-aryl substituent is clearly much less in the *trans*- (catechin) than in the *cis*-series (*epi*-catechin), particularly in the diaxial *trans*-conformation where the proximate atoms are the 2(e)H and 4(quasi e)H. A low degree of asymmetric synthesis is therefore to be expected from (+)-catechin tetramethyl ether 3-phenylglyoxylate, and moreover from examination of models it seems to us plausible that slightly less hindrance should be offered from the side of the 2- than of the 4-position, which would account for the formation of (−)-atrolactic acid.

Several recent communications [18-20, 10] have dealt with possible conformations of flavan-3-ols, and a detailed analysis of the problem led Whalley [10] to conclude that the preferred conformations for catechins and *epi*catechins are probably those with 2(a)-aryl : 3(a)hydroxyl and 2(e)aryl : 3(a)hydroxyl arrangements of substituents respectively. The first decisive evidence supporting this conclusion is provided by the infrared absorptions of the hydroxyl groups of (+)-catechin and (−)-*epi*catechin tetramethyl ethers in carbon tetrachloride solution, measured and interpreted by Dr. A. R. H. Cole, which occur at 3594 and 3587 cm.$^{-1}$ respectively. These low hydroxyl stretching frequencies and the absence of a free hydroxyl band near 3630 cm.$^{-1}$ indicate strong intramolecular hydrogen bonding of axial hydroxyl groups, as postulated by Roberts.[18] (+)-Catechin tetramethyl ether (VI) and (−)-*epi*catechin tetramethyl ether (IV) therefore exist



(XII)

(+)-Catechin tetramethyl ether



(XIII)

(−)-*epi*Catechin tetramethyl ether

in the preferred conformations (XII and XIII; Ar = 3 : 4-dimethoxyphenyl). Weaker hydrogen bonding in the catechin compound (XII), indicated by the higher hydroxyl stretching frequency, is attributed to a tendency for conformational inversion.[21] Intramolecular hydrogen bonding of this type was first proposed in connection with R_F values by Roberts,[18] whose further conclusions however required modification.[10, 19, 20] The higher R_F value of catechin compared with that of *epi*catechin suggests that the former molecule is less compact; this may indicate [10, 19, 20] that catechin itself exists in the same

[17] Dauben, Dickel, Jeger, and Prelog, *Helv. Chim. Acta*, 1953, **36**, 325.
[18] Roberts, *Chem. and Ind.*, 1955, 631, 1551.
[19] Clark-Lewis, *ibid.*, p. 1218.
[20] Roberts, *ibid.*, 1956, 737.
[21] Kuhn, *J. Amer. Chem. Soc.*, 1954, **76**, 4323; Cole and Jefferies, *J.*, 1956, 4391.

conformation as its methyl ether (XII; Ar = 3 : 4-dimethoxyphenyl). A similar argument applies to gallocatechin which has a higher R_F value than *epi*gallocatechin.

The conclusions reached here concerning the relative and absolute configurations of catechins and *epi*catechins may be taken to apply generally to other members of this class of compound,[9,22] for example, to (−)-*epi*afzelechin, (+)-gallocatechin, and (−)-*epi*-gallocatechin, and to their stereoisomers which await discovery. The interesting uniformity [9] of the occurrence of these natural products in the forms (+)-catechin, (+)-gallocatechin, (−)-*epi*afzelechin, (−)-*epi*catechin, and (−)-*epi*gallocatechin is now seen to reside in the identity of their configurations at the 2-position, and all these compounds may be defined as (2*R*)-flavan derivatives according to the method for specification of absolute configuration proposed by Cahn, Ingold, and Prelog.[23] The sign of rotation, however, is (+) or (−) according to the configuration (3*S* or 3*R* respectively) of the 3-hydroxyl group (Table). The configurational prefixes *D* and *L* decided by the position of the hydroxyl group in the Fischer projections (A) and (B) have little significance when applied to catechins,[3,24] although it can be seen that (3*S*) corresponds to *L*-, and (3*R*) corresponds to *D*-configurations in Fischer projection formulæ written with the higher-numbered asymmetric carbon atom at the bottom. This fortuitous correspondence resulting from the arbitrary conventions involved (*e.g.*, for numbering) does not imply a relationship with the D- or L-series of amino-acids and carbohydrates, which can, however, be determined by comparison of the respective absolute configurations.

The reductions recorded above present some aspects of general interest. The formation of the propanes is unlikely to be due to direct hydrogenolysis since the hydroxyl groups are not in benzyl positions. It may be due to an alkali-catalysed elimination of a molecule of water, to produce the propene, and subsequent reduction of this made possible by conjugation of the double bond with a benzene ring. Alternatively, an elimination could occur *during* the reduction when an anionic charge is formed in the 2-position and could transfer to the hydroxyl group with formation of a conjugated double bond. The extent of the reaction would probably be related to the length of existence of the anion. The formation in some cases of optically inactive propanol may result from an alkali-catalysed opening of the heterocyclic ring to produce initially the propanone, which is then further reduced to the (±)-propanol. Similar ring-openings have been observed.[25] The variations in results are therefore probably related to details of the experimental work, in particular the presence or absence of ethanol, the speed with which the reduction is carried out, and the efficiency of the stirring. Strongly alkaline conditions and slow reactions are to be avoided.

Compound	Structure and absolute configuration
(+)-Catechin	(2*R* : 3*S*)-5 : 7 : 3′ : 4′-Tetrahydroxyflavan-3-ol
(+)-Gallocatechin	(2*R* : 3*S*)-5 : 7 : 3′ : 4′ : 5′-Pentahydroxyflavan-3-ol
(−)-*epi*Afzelechin	(2*R* : 3*R*)-5 : 7 : 4′-Trihydroxyflavan-3-ol
(−)-*epi*Catechin (II)	(2*R* : 3*R*)-5 : 7 : 3′ : 4′-Tetrahydroxyflavan-3-ol
(−)-*epi*Gallocatechin	(2*R* : 3*R*)-5 : 7 : 3′ : 4′ : 5′-Pentahydroxyflavan-3-ol
(+)-Propanol (V; R = OMe)	(2*S*)-1-(3 : 4-Dimethoxyphenyl)-3-(2 : 4 : 6-trimethoxyphenyl)propan-2-ol
(−)-Propanol (VII)	(2*R*)-1-(3 : 4)Dimethoxyphenyl)-3-(2 : 4 : 6-trimethoxyphenyl)propan-2-ol
(−)-Propanol (V; R = H)	(2*S*)-1-*p*-Methoxyphenyl-3-(2 : 4 : 6-trimethoxyphenyl)propan-2-ol

Experimental

Infrared measurements, except where otherwise noted, were made with a Grubb-Parsons S4 spectrometer equipped with a sodium chloride prism.

(−)-epi*Catechin* 5 : 7 : 3′ : 4′-*Tetramethyl Ether* (IV).—Methylation of (−)-*epi*catechin, $[\alpha]_D^{17}$ −60° (2% in EtOH) (lit.,[12] $[\alpha]_{578}$ −68·2°), with dimethyl sulphate and potassium carbonate in acetone gave the tetramethyl ether, m. p. 136—139°, $[\alpha]_D^{17}$ −55° (4% in $C_2H_2Cl_4$) (lit.,[12] m. p.

[22] Schmidt and Mayer, *Angew. Chem.*, 1956, **68**, 103.
[23] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.
[24] Compare discussion of camphor by Freudenberg and Lwowski, *Annalen*, 1955, **594**, 76.
[25] Birch and D. C. C. Smith, unpublished work.

153—154°, $[\alpha]_{578}$ −61·5°) (Found: C, 65·9; H, 6·4. Calc. for $C_{19}H_{22}O_6$: C, 65·9; H, 6·4%). Paper chromatograms (Bu^nOH–AcOH–H_2O) showed that the (−)-*epi*catechin (R_F 0·63) was free from (+)-catechin (R_F 0·75 on the same chromatogram); it presumably contained (±)-*epi*catechin (11%). The hydroxyl absorption of the tetramethyl ether occurred at 3587 cm.$^{-1}$; a 1 cm. layer of a dilute solution in carbon tetrachloride (*ca.* 1·7 mg./c.c.) was used, and measurements were made with a Grubb-Parsons S3A spectrometer equipped with a calcium fluoride prism.

(+)-*Catechin* 5 : 7 : 3′ : 4′-*tetramethyl ether* (VI), m. p. 143—144°, $[\alpha]_D^{20}$ −13·4° (10% in $C_2H_2Cl_4$) (lit.,[12] m. p. 143—144°, $[\alpha]_{578}$ −13·4°), was similarly prepared by methylation of (+)-catechin (Found: C, 65·9; H, 6·4%). Hydroxyl absorption occurred at 3594 cm.$^{-1}$ when examined under the same conditions as for the *epi*catechin analogue.

Reduction of (−)-epi*Catechin* 5 : 7 : 3′ : 4′-*Tetramethyl Ether* (IV) *by Sodium and Liquid Ammonia.*—Sodium (0·3 g., 2·2 equiv.) in small pieces was added to (−)-*epi*catechin tetramethyl ether (2·1 g.) in ethanol (25 c.c.) and liquid ammonia (400 c.c.). The solution was evaporated on a warm water-bath after the addition of ammonium chloride (2 g.), and the semisolid residue was treated with water (50 c.c.) and 2N-hydrochloric acid (10 c.c.) before extraction with chloroform. Removal of the chloroform left a gum (2·2 g.) which was dissolved in benzene (10 c.c.) and extracted with dilute aqueous sodium hydroxide (10 × 10 c.c.) to remove phenols completely, and evaporation of the benzene then gave *epi*catechin tetramethyl ether (0·65 g., 31% recovery), of m. p. 137—140° and $[\alpha]_D^{18}$ −54° (8% in $C_2H_2Cl_4$) after crystallisation from methanol. The alkaline extract (100 c.c.) was shaken for 1 hr. at room temperature with dimethyl sulphate (2 c.c.), and the excess of dimethyl sulphate was destroyed with aqueous ammonia before extraction of the solid product (1·4 g.) into ether. This material was separated by chromatography on acid-washed alumina into the 1 : 3-diarylpropane (IX; R = OMe) (0·38 g., 18%), which was eluted by benzene and crystallised from ethanol in needles, m. p. 88—89° (lit.,[15,26] m. p. 87—88°) (Found: C, 69·5; H, 7·6. Calc. for $C_{20}H_{26}O_5$: C, 69·3; H, 7·6%), and a gum (1·0 g.) which was eluted by benzene containing chloroform (10%) and when kept gave crystalline 1-(3 : 4-*dimethoxyphenyl*)-3-(2 : 4 : 6-*trimethoxyphenyl*)*propan*-2-ol (V; R = OMe) (0·25 g., 12%). Recrystallisation from *cyclo*hexane containing benzene (10%) or ethanol (10%) gave prisms, m. p. 87—88°, $[\alpha]_D^{18}$ +1·0° (8% in $CHCl_3$), $[\alpha]_D^{18}$ +0·6° (10% in $C_2H_2Cl_4$), $[\alpha]_D^{20}$ −1·7° (10% in EtOH) (Found: C, 66·3; H, 7·3; OMe, 41·7. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2; 5OMe, 40·1%). The infrared absorption spectrum of the active propanol in CCl_4 was identical with that of the (±)-propanol described below.

Reductions of (+)-*Catechin* 5 : 7 : 3′ : 4′-*Tetramethyl Ether* (VI) *by Sodium and Liquid Ammonia.*—(*a*) Reduction of the catechin compound (2·1 g.) as described above for the *epi*-catechin isomer gave recovered catechin tetramethyl ether (1·1 g., 52%), m. p. 143—144°, $[\alpha]_D^{24}$ −13·4°, the 1 : 3-diarylpropane (IX; R = OMe) (0·25 g., 12%), and a benzene–chloroform eluate (0·39 g., 18%) from which the diarylpropanol (VII) (0·17 g., 8%) separated. After recrystallisation the *propanol* had m. p. 87—88°, $[\alpha]_D^{21}$ −2·5° (4% in $CHCl_3$) (Found: C, 66·1; H, 7·3%). The reduction was repeated and gave the propanol (VII), $[\alpha]_D^{25}$ +1·0° (4% in EtOH). The infrared absorption spectrum of the propanol in CCl_4 was indistinguishable from that of the enantiomorph or that of the synthetic (±)-propanol described below.

(*b*) Reduction of (+)-catechin tetramethyl ether (2·8 g.) with sodium (0·8 g., 4 equiv.), in an attempt to increase the yield of propanol, gave no recovered catechin but gave the propane (IX; R = OMe) (1·84 g., 66%) and the propanol (VII), which eventually crystallised (0·29 g., 10%) and after recrystallisation had no observable rotation (6% in $CHCl_3$, and 4% in $C_2H_2Cl_4$). Reduction under these conditions was repeated and the phenolic fraction, isolated in this instance before methylation, partially crystallised. Recrystallisation of this phenol from *cyclo*hexane–ethanol (10%) gave 1-(3 : 4-dimethoxyphenyl)-3-(2-hydroxy-4 : 6-dimethoxyphenyl)-propane (VIII) in prisms, m. p. 94—95° (lit.,[14b] m. p. 89—90°) (from carbon tetrachloride) (Found: C, 68·5; H, 7·4. Calc. for $C_{19}H_{24}O_5$: C, 68·6; H, 7·3%), which was converted by methylation into the propane (IX; R = OMe), m. p. and mixed m. p. 88—89°.

(*c*) Catechin tetramethyl ether (1·05 g.) was reduced with sodium (0·15 g., 2 equiv.) as described for the *epi*catechin compound except that ethanol was omitted. No catechin tetramethyl ether was recovered and, after methylation of the phenolic product (*ca.* 80%), the propane (IX; R = OMe) (0·19 g., 18%) and the propanol (VII) (0·25 g., 23%) were isolated. The recrystallised propanol was optically inactive (7% in $CHCl_3$).

[26] Drumm, O'Reilly, and Ryan, *Proc. Roy. Irish Acad.*, 1925, **37**, *B*, 19.

Reduction of (−)-epi*Afzelechin* 5 : 7 : 4′-*Trimethyl Ether* (X) *by Sodium and Liquid Ammonia.* —(*a*) (−)-*epi*Afzelechin 5 : 7 : 4′-trimethyl ether [9] (1·8 g.), m. p. 112—113°, $[\alpha]_D^{24}$ −63° (2% in EtOH), was treated with sodium (0·46 g.) and liquid ammonia as described above for the catechin compound (method *b*). The phenolic products failed to crystallise but, after methylation with dimethyl sulphate, fractional crystallisation gave 1-p-*methoxyphenyl*-3-(2 : 4 : 6-*trimethoxyphenyl*)*propane* (IX; R = H) (0·36 g., 20%), needles, m. p. 67—68° (from ethanol) (Found: C, 71·8; H, 7·6. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·6%), as the fraction more soluble in light petroleum, and 1-p-*methoxyphenyl*-3-(2 : 4 : 6-*trimethoxyphenyl*)*propan*-2-*ol* (V; R = H) (0·28 g., 15%) which was more soluble in ethanol and crystallised from light petroleum in needles, m. p. 77—78°, $[\alpha]_D^{24}$ −3·2° (18% in $C_2H_2Cl_4$) (Found: C, 68·6; H, 7·3. $C_{19}H_{24}O_5$ requires C, 68·7; H, 7·3%). Similarly (−)-*epi*afzelechin trimethyl ether (1·2 g.) was reduced with sodium (0·36 g., 4 g.-atoms/mole) and gave the propane (0·5 g., 42%), eluted from alumina with 7 : 3 benzene–light petroleum (b. p. 60—80°), and the crude propanol (0·35 g., 28%) eluted with 95 : 5 benzene–chloroform. After five crystallisations from light petroleum (b. p. 67—70°), the propanol (0·55 g.) had m. p. 77—78°, $[\alpha]_D^{23}$ −4·6° (5% in EtOH), −1·4° (5% in $CHCl_3$). The infrared absorption of the propanol in CCl_4 was indistinguishable from that of the synthetic (±)-propanol described below.

(*b*) Reduction of the *epi*afzelechin compound (2·4 g.) with sodium (0·38 g.) as described above for the *epi*catechin analogue gave recovered (−)-*epi*afzelechin trimethyl ether (0·88 g., 37%), $[\alpha]_D^{21}$ −63° (2% in EtOH), and a phenolic fraction which was methylated and then chromatographed on acid-washed alumina. Elution with 7 : 3 benzene–light petroleum gave the propane (IX; R = H) (0·41 g., 17%), and elution with 85 : 15 benzene–chloroform gave a gummy fraction (0·58 g., 23%). The propanol (V; R = H) is readily soluble in hydrocarbons and other solvents (except water).

ω-*Acetoxy*-2 : 4 : 6-*trimethoxyacetophenone.*—ω-Chloro-2 : 4 : 6-trimethoxyacetophenone [27] (15·2 g., 87%) was prepared from 1 : 3 : 5-trimethoxybenzene (12 g.) and chloroacetonitrile (6 g.). The required phloroglucinol trimethyl ether was conveniently obtained by methylation of anhydrous phloroglucinol (30 g.) in acetone (*ca.* 250 c.c.) containing anhydrous potassium carbonate (110 g.) with dimethyl sulphate (75 c.c., *ca.* 3·3 equiv.), which was added in three equal portions at intervals of 2 hr. to the stirred, warm suspension. After the mixture had been heated for 6½ hr. (total) the crude product (34 g., 85%) was isolated in two fractions, m. p.s 40—42° and 43—46°, raised to 53° by recrystallisation from ethanol (prisms) (Found: C, 64·1; H, 7·1; OMe, 55·1. Calc. for $C_9H_{12}O_3$: C, 64·3; H, 7·2; 3OMe, 55·4%). ω-Chloro-2 : 4 : 6-trimethoxyacetophenone (14 g.), anhydrous potassium acetate (20 g.), acetic acid (25 c.c.), and acetic anhydride (10 c.c.) were heated for 2 hr. before filtration of the hot solution from potassium chloride (3·3 g., 78%) and evaporation of the solution under reduced pressure. The oil obtained by adding water to the brown residue rapidly solidified (14·9 g., 97%; m. p. 103—105°), and recrystallisation from ethyl acetate or ethyl acetate–hexane gave ω-*acetoxy*-2 : 4 : 6-*trimethoxyacetophenone* in rhombic prisms, m. p. 111—112° (Found: C, 58·2; H, 6·0; OMe, 34·7; Ac, 16·1. $C_{13}H_{16}O_6$ requires C, 58·3; H, 6·0; 3OMe, 34·3; Ac, 16·3%). The crude material was suitable for chalcone condensations.

3-(3 : 4-*Dimethoxyphenyl*)-1-(2 : 4 : 6-*trimethoxyphenyl*)*propane*-1 : 2-*dione* (XI; R = OMe). —Potassium hydroxide (4 g.) in water (4 c.c.) was added to ω-acetoxy-2 : 4 : 6-trimethoxyacetophenone (4 g.) and veratraldehyde (2·8 g.) in methanol (40 c.c.), and the solution was heated on a steam-bath for 3 hr. before being poured into water. The suspension was acidified with hydrochloric acid and extracted with chloroform, and the chloroform was removed after washing of the extract with aqueous sodium hydrogen carbonate and water. The oily residue from the evaporation was dissolved in a little ethyl acetate and diluted to incipient turbidity with hexane. Next day the deposit (2·55 g., 45%), m. p. 144—146°, was collected, and recrystallisation from methanol (*ca.* 80 c.c.) gave the *diketone* (XI; R = OMe) in pale yellow prisms (1·6 g.), m. p. 155—157° unchanged by recrystallisation in needles from aqueous acetone (Found: C, 64·3; H, 6·1; OMe, 41·0. $C_{20}H_{22}O_7$ requires C, 64·5; H, 5·9; 5OMe, 41·5%). Infrared absorptions were typical of enolised 1 : 2-diketones of this type: [16] OH absorption at 2·9 μ (in CCl_4) and 2·95 μ (in Nujol); >CO absorption at 5·98 μ (in CCl_4) and 6·0 μ (in Nujol). The compound was too sparingly soluble in carbon tetrachloride to afford optimum absorption curves.

[27] Freudenberg, Fikentscher, and Harder, *Annalen*, 1925, **441**, 168.

3-p-*Methoxyphenyl*-1-(2 : 4 : 6-*trimethoxyphenyl*)*propane*-1 : 2-*dione* (XI; R = H).—ω-Acetoxy-2 : 4 : 6-trimethoxyacetophenone (3·2 g.) and *p*-anisaldehyde (1·45 c.c.) were heated with aqueous-methanolic potassium hydroxide (3·2 g.), and the crude product (2·4 g.) was isolated as described above for the veratraldehyde analogue, and then washed with methanol to remove coloured impurities. Crystallisation from methanol (80 c.c.; charcoal) gave the diketone in pale yellow prisms (0·95 g.), m. p. 153° unchanged by recrystallisation in needles from aqueous acetone (lit.,[28] m. p. 144—145°) (Found: C, 65·9; H, 6·1; OMe, 36·6. Calc. for $C_{19}H_{20}O_6$: C, 66·3; H, 5·9; 4OMe, 36·0%). Infrared absorptions in Nujol: OH at 2·96 and >CO at 6·0 μ.

(±)-1-(3 : 4-*Dimethoxyphenyl*)-3-(2 : 4 : 6-*trimethoxyphenyl*)*propan*-2-*ol*.—The diketone (XI; R = OMe) (0·6 g.) in ethanol (100 c.c.) was hydrogenated over Raney nickel (W4; *ca.* 0·6 g.) at 90—130° with hydrogen at 1000 lb./sq. in. for 6 hr. The filtrate from catalyst was evaporated under reduced pressure, and last traces of ethanol were removed by continuing the evaporation after the addition of benzene. The residue was dissolved in benzene (2—3 c.c.), and after the addition of a little hexane the (±)-*propanol* (0·5 g., 86%) crystallised in colourless prisms, m. p. 87—88° unchanged by recrystallisation (Found: C, 66·3; H, 7·3. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%). A carbon tetrachloride solution showed hydroxyl absorption at 2·75 μ and the absorption curve, recorded from 2 to 11·5 μ, was identical with curves obtained with the (−)- and the (+)-propanol (VII and V; R = OMe).

(±)-1-p-*Methoxyphenyl*-3-(2 : 4 : 6-*trimethoxyphenyl*)*propan*-2-*ol*.—The diketone (XI; R = H) (0·6 g.) was hydrogenated as described for the pentamethoxy-diketone, and evaporation of the solvent left a viscous residue of the propanol. This was chromatographed on alumina and eluted with benzene (50 × 18 c.c.) and 9 : 1 benzene–chloroform (50 × 18 c.c.). The residues from the first 20 benzene–chloroform fractions solidified (m. p. *ca.* 60°) after several days, and solutions in carbon tetrachloride showed hydroxyl absorption at 2·77 μ, and the absorption curve (2—11·5 μ) was identical with that of the (−)-propanol (V; R = H) obtained from (−)-*epi*afzelechin trimethyl ether. The (±)-propanol crystallised in needles, m. p. 66°, by spontaneous evaporation of the carbon tetrachloride solution, but a satisfactory recrystallisation has not been achieved. The (±)-propanol dissolves readily in hexane, *cyclo*hexane, carbon tetrachloride, and other solvents except water.

(−)-epi*Catechin Tetramethyl Ether* 3-*Phenylglyoxylate*.—(−)-*epi*Catechin tetramethyl ether (2·5 g.) was esterified by reaction with phenylglyoxylyl chloride[29] (1·2 g., 1 mol.) according to the general procedure described by Dauben, Dickel, Jeger, and Prelog.[17] The 3-*phenylglyoxylate* (1 g., 30%) crystallised from ethanol in needles, m. p. 174—175° (after softening at 170°) unchanged by recrystallisation, $[\alpha]_D^{20}$ −29·2° (3% in $CHCl_3$) (Found: C, 67·3; H, 5·6. $C_{27}H_{26}O_8$ requires C, 67·8; H, 5·5%).

(+)-*Catechin Tetramethyl Ether* 3-*Phenylglyoxylate*.—The ester (1·55 g., 95%) was prepared from the (+)-catechin compound (1·2 g.) as described above for the epimer except that phenylglyoxylyl chloride (2·3 g., 4 mol.) was used to improve the yield, and the excess of acid was removed by washing with aqueous sodium hydrogen carbonate. The crude product was chromatographed on acid-washed alumina, and the ester was eluted with benzene and finally with benzene–chloroform (25%). Recrystallisation from ethanol gave the *phenylglyoxylate* in needles, m. p. 106—107° unchanged by recrystallisation, $[\alpha]_D^{20}$ +4·4° (4% in $CHCl_3$) (Found: C, 67·4; H, 5·3%).

(−)-*Atrolactic Acid from* (−)-epi*Catechin Tetramethyl Ether* 3-*Phenylglyoxylate*.—The phenylglyoxylate (0·7 g.) in dry benzene–ether was added dropwise to methylmagnesium iodide (4 mol.) in ether; a white precipitate appeared immediately and remained after 5 hours' boiling under reflux. The suspension was acidified with dilute acetic acid, and the organic layer was washed with water before evaporation under reduced pressure. The residue of atrolactate was dissolved in methanol–benzene containing potassium hydroxide (5%) and next day the solution was boiled under reflux for 4 hr. The solvent was removed under reduced pressure and an aqueous solution of the residue was exhaustively extracted with ether to remove *epi*catechin tetramethyl ether (*ca.* 0·5 g.). The aqueous layer was acidified and extraction of the solution with ether gave atrolactic acid (0·16 g.) contaminated with dark viscous material which was insoluble in light petroleum. Two recrystallisations from light petroleum gave atrolactic acid, needles, m. p. 85—93°, $[\alpha]_D^{20}$ −16·4° (2% in EtOH), containing 43% excess of the (−)-isomer.

[28] Hutchins, Motwani, Mudbhatkal, and Wheeler, *J.*, 1938, 1882.
[29] *Org. Synth.*, Coll. Vol. III, p. 114; Kharasch and Brown, *J. Amer. Chem. Soc.*, 1942, **64**, 329.

(−)-*Atrolactic Acid from* (+)-*Catechin Tetramethyl Ether* 3-*Phenylglyoxylate*.—The (+)-catechin phenylglyoxylate (1·35 g.) was converted into the atrolactate and then hydrolysed as described above for the epimer. Two recrystallisations of the crude acid (0·28 g.) from light petroleum gave atrolactic acid hemihydrate, m. p. 85—90°, $[\alpha]_D^{21}$ −1·1° (28% in EtOH), containing 3% excess of the (−)-acid (Found : C, 61·8; H, 6·3. Calc. for $C_9H_{10}O_3,\frac{1}{2}H_2O$: C, 61·7; H, 6·3%). The experiment was repeated, because of the low optical activity, with (+)-catechin tetramethyl ether 3-phenylglyoxylate (3·7 g.) which gave similar results, and some possible sources of error were eliminated : hydrolysis was proved to be complete by quantitative recovery of catechin tetramethyl ether by exhaustive extraction with ether (no residue from the sixth extract), and contamination of the atrolactic acid with the lævorotatory catechin methyl ether was thus precluded. Contamination of the recrystallised atrolactic acid with the related glycol is precluded by elementary analysis (above), and the neutral fraction extracted by ether was shown by chromatography on alumina to consist only of catechin tetramethyl ether which was eluted with benzene and then with benzene containing increasing quantities of ether, the last traces being removed by benzene–ether (1 : 1). Ether (used in isolating the glycol [17]) removed nothing further from the column; the insolubility of the initial Grignard adduct probably prevented glycol formation from *epi*catechin and catechin atrolactates.

(−)-epi*Afzelechin trimethyl ether* 3-*phenylgloxylate* was prepared as described for the (+)-catechin analogue and crystallised from ethanol in needles, m. p. 123—124°, $[\alpha]_D^{20}$ −32·0° (5% in $CHCl_3$) (Found : C, 69·2; H, 5·4. $C_{26}H_{24}O_7$ requires C, 69·6; H, 5·4%). (−)-*epi*-Afzelechin trimethyl ether (1·0 g.) and phenylglyoxylyl chloride (2·1 g.) produced crude ester (1·35 g., 95%).

(−)-*Atrolactic Acid from* (−)epi-*Afzelechin Trimethyl Ether* 3-*Phenylglyoxylate*.—The ester (1·1 g.) was treated with methylmagnesium iodide (the initially insoluble Grignard adduct redissolved rapidly in this case), and the atrolactate was hydrolysed as described for the (−)-*epi*catechin analogue. Three crystallisations of the crude acid (0·13 g.) gave atrolactic acid, m. p. 107—111°, $[\alpha]_D^{20}$ −30·4° (5% in EtOH), containing 81% excess of the (−)-isomer. Recrystallisation of atrolactic acid, usually omitted,[2] was necessary in the present investigation because solutions of the crude acid were too dark for polarimetric examination.

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