473. *Flavan Derivatives. Part I. The Absolute Configuration of (+)-Dihydroquercetin.*

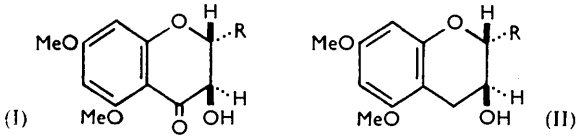
By J. W. Clark-Lewis and W. Korytnyk.

The *trans*-configuration is proved for (+)-dihydroquercetin and its racemate, and the absolute configurations of the two asymmetric centres in (+)-dihydroquercetin are shown to be identical with those in (+)-catechin. (+)-Catechin tetramethyl ether 3-toluene-*p*-sulphonate has been re-investigated; when heated with ethanolic potassium acetate it suffered a Wagner–Meerwein rearrangement to (+)-2-ethoxy-5 : 7 : 3′ : 4′-tetramethoxy*iso*flavan.

Considerable interest in the stereochemical relations of reduced flavan or dihydro-2-phenylbenzopyran derivatives is apparent from recent communications concerning catechins,[1-8] *leuco*anthocyanidins,[4,7,9-12] and dihydroflavonols.[4,7,13-15] Interconversions of these three classes of compound presumably occur in plant tissues, although details of

[1] King, Clark-Lewis, and Forbes, *J.*, 1955, 2948.
[2] Clark-Lewis, *Chem. and Ind.*, 1955, 1218.
[3] Roberts, *ibid.*, 1955, 631, 1551; 1956, 737.
[4] Whalley, " Chemistry of Vegetable Tannins," Soc. Leather Trades' Chemists, Croydon, 1956, p. 151.
[5] Freudenberg, *Sci. Proc. Roy. Dublin Soc.*, 1956, **27**, 153.
[6] Birch, Clark-Lewis, and Robertson, *J.*, 1957, 3586.
[7] Clark-Lewis, " Stereochemistry of Catechins and Related Flavan Derivatives," Symposium on Heterocyclic Chemistry, Canberra, September 1957, Chem. Soc. Spec. Publ., in the press.
[8] Hardegger, Gempeler, and Züst, *Helv. Chim. Acta*, 1957, **40**, 1819.
[9] King and Clark-Lewis, *J.*, 1955, 3384.
[10] King, *Sci. Proc. Roy. Dublin Soc.*, 1956, **27**, 87.
[11] Kulkarni and Joshi, *Chem. and Ind.*, 1954, 1456; 1956, 124.
[12] Bognár and Rákosi, *ibid.*, 1956, 188.
[13] Mahesh and Seshadri, *Proc. Indian Acad. Sci.*, 1955, **41**, *A*, 210.
[14] Gowan, Philbin, and Wheeler, " Chemistry of Vegetable Tannins," Soc. Leather Trades' Chemists, Croydon, 1956, p. 133.
[15] Kulkarni and Joshi, *J. Indian Chem. Soc.*, 1957, **34**, 217.

such transformations remain obscure.[16] In the laboratory both dihydroflavonols and flavan-3 : 4-diols can be converted into catechins by removal of the oxygen function from the 4-position, and the catechins [6,7] are therefore key compounds in stereochemical correlations of flavan derivatives. Correlation has shown that (+)-dihydroquercetin is stereochemically identical with (+)-catechin; this confirms the assignment [4,13] of the dihydroflavonol to the *trans*-series (2H : 3H *trans*) and establishes the absolute configurations of both asymmetric centres.



R = 3 : 4-$(MeO)_2C_6H_3$.

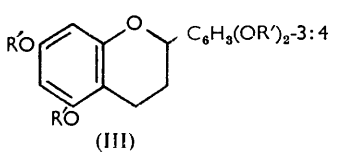
(+)-Dihydroquercetin (taxifolin) was first isolated [17] from the heartwood of Douglas fir and has since been obtained from the bark [18] and from other sources.[14] Methylation of (+)-dihydroquercetin by the acetone–potassium carbonate method already described for the (±)-compound [19] gave (+)-dihydroquercetin 5 : 7 : 3′ : 4′-tetramethyl ether (I), $[\alpha]_D$ −23·4°, which was converted by hydrogenation over Adams platinic oxide catalyst into (+)-catechin tetramethyl ether (II), $[\alpha]_D$ −9·8° (in $CHCl_3$), as noted in a preliminary communication.[20] The identity of the product with an authentic specimen prepared by methylation of (+)-catechin was established by mixed m. p. determination and by comparison of infrared absorption spectra (Nujol mulls and CCl_4 solutions). The absolute configurations of (+)-dihydroquercetin and (+)-catechin tetramethyl ethers are therefore identical, as shown in the formulæ (I) and (II), and the parent compounds may be described respectively as (2*R* : 3*R*)-5 : 7 : 3′ : 4′-tetrahydroxy-4-oxoflavan-3-ol and (2*R* : 3*S*)-5 : 7 : 3′ : 4′-tetrahydroxyflavan-3-ol according to Cahn, Ingold, and Prelog's method for specifying absolute configurations.[21]

After crystallisation of (+)-catechin tetramethyl ether (24%) the mother-liquors were evaporated and acetylation of the residue gave (±)-catechin tetramethyl ether 3-acetate (*ca.* 14%). Isolation of the (±)-catechin derivative indicated that the (+)-dihydroquercetin tetramethyl ether was optically impure. Recrystallisation of the latter from ethanol resulted in diminution of its specific rotation, but crystallisation of the 3-acetate from ethanol gave needles of (±)-dihydroquercetin tetramethyl ether 3-acetate and heavier rhombic crystals of the (+)-acetate, which was obtained with $[\alpha]_D$ +33·4° after several crystallisations. Shortage of material prevented completion of this purification process and there was insufficient for hydrolysis, so that the optical purities of the (+)-dihydroquercetin tetramethyl ether and its 3-acetate are not known. (+)-Dihydroquercetin and (+)-catechin show parallel changes in rotation on methylation and acetylation (see Table).

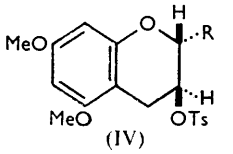
Compound	Specific rotation of (+)-catechin derivative	Specific rotation of (+)-dihydroquercetin derivative
Free phenol	$[\alpha]_{Hg}$ 0° in EtOH [22]	$[\alpha]_D$ +13° in EtOH [17]
	$[\alpha]_{Hg}$ +17° in 50% acetone [22]	$[\alpha]_D$ +46° in 50% acetone [17]
Tetramethyl ether	$[\alpha]_{Hg}$ −13·4° in $C_2H_2Cl_4$ [22]	—
	$[\alpha]_D$ −13·4° in $C_2H_2Cl_4$ [6]	—
	$[\alpha]_D$ −11·4° in $CHCl_3$	$[\alpha]_D$ −23·4° in $CHCl_3$
Tetramethyl ether 3-acetate	$[\alpha]_{Hg}$ +6·8° in $C_2H_2Cl_4$ [22]	$[\alpha]_D$ +33·4° in $CHCl_3$

[16] Swain and Bate-Smith, "Chemistry of Vegetable Tannins," Soc. Leather Trades' Chemists, Croydon, 1956, p. 109; Hillis, *ibid.*, p. 121; Bate-Smith, *ibid.*, p. 143; Hillis, *Austral. J. Biol. Sci.*, 1956, **9**, 263.
[17] Pew, *J. Amer. Chem. Soc.*, 1948, **70**, 3031.
[18] Kurth and Chan, *J. Amer. Leather Chemists' Assoc.*, 1953, **48**, 20; cf. ref. 19.
[19] Hergert, Coad, and Logan, *J. Org. Chem.*, 1956, **21**, 304.
[20] Clark-Lewis and Korytnyk, *Chem. and Ind.*, 1957, 1418.
[21] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.
[22] Freudenberg and Purrmann, *Annalen*, 1924, **437**, 274.

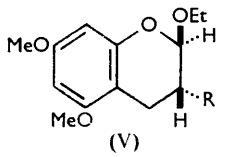
(+)-Dihydroflavonols theoretically could exist in *cis*- and *trans*-forms and yield *cis*- and *trans*-racemates, but racemisation of naturally occurring (+)-dihydroquercetin with acid [17] or with bases [23] yields a single racemate which is identical [23] with that obtained from quercetin by reduction with sodium dithionite.[17,24] This product is the *trans*-racemate, as shown by conversion of its tetramethyl ether [prepared from acid-racemised [17] (±)-dihydroquercetin] into (±)-catechin tetramethyl ether, and supported by the identity in infrared absorption of solutions of (+)- and (±)-dihydroquercetin tetramethyl ether. Distylin (from *Distylium racemosum*) is a naturally occurring form of *trans*-(±)-dihydroquercetin, as shown by its identity [25] with racemic Douglas-fir flavanone.



(III)



(IV)



(V)

R = 3 : 4-$(MeO)_2C_6H_3$. Ts = *p*-$C_6H_4Me{\cdot}SO_2$.

The central importance of catechins for elucidation of the stereochemistry of flavan derivatives prompted investigation of two possible (but unsuccessful) methods for confirming the established [6] configurations. Direct comparison of the configurations at the 2-positions of (+)-catechin and (−)-*epi*catechin would be achieved by removal of the oxygen function at the 3-position to yield the flavan (III; R′ = H or Me); (+)-catechin tetramethyl ether 3-toluene-*p*-sulphonate (IV) was accordingly treated with lithium aluminium hydride in the hope that alkyl–oxygen fission would ensue, but the toluene-*p*-sulphonate was unaffected. (+)-Catechin tetramethyl ether 3-toluene-*p*-sulphonate was found to be dimorphic (m. p.s 86—88° and 115—116°) and to have $[\alpha]_D$ +87·7° instead of the reported value (+22·7°),[26] which is apparently a miscalculation for 91·8°. Replacement of the toluene-*p*-sulphonyloxy-group by acetoxyl was attempted by heating the (+)-catechin derivative (IV) with alcoholic potassium acetate, as the desired replacement with Walden inversion would not only have confirmed the relative configurations of (+)-catechin and (−)-*epi*catechin but would also have provided a convenient source of the less easily accessible (−)-*epi*catechin derivatives. Reaction was incomplete in boiling solution and under more vigorous conditions (sealed tube) the product was (+)-2-ethoxy-5 : 7 : 3′ : 4′-tetramethoxy*iso*flavan (V), which previously had been obtained from the 2-chloro*iso*flavan resulting from the action of phosphorus pentachloride on (+)-catechin tetramethyl ether.[27-30] These rearrangements are of particular interest because they proceed with retention of optical activity, and it is clear that inversion occurs at the 3-position as a result of neighbouring-group participation (cf. Whalley [4]). The configuration at the 2-position is less certain, but the 2-ethoxy*iso*flavan is tentatively regarded as the *trans*-compound (V) formed by inversion at both centres, for which there are analogies in other cases of Wagner–Meerwein transformation.[31] The confirmation of configurations which we hoped to achieve with (+)-catechin tetramethyl ether toluene-*p*-sulphonate has since been provided by exhaustive ozonisation of (+)-catechin,[8] a method completely independent of that originally employed.[6]

[23] Kurth, Hergert, and Ross, *J. Amer. Chem. Soc.*, 1955, **77**, 1621.
[24] Geissman and Lischner, *ibid.*, 1952, **74**, 3001.
[25] Kondo, *J. Fac. Agric. Kyushu Univ.*, 1951, **10**, 79, 101; *Chem. Abs.*, 1953, **47**, 4602.
[26] Freudenberg, Orthner, and Fikentscher, *Annalen*, 1924, **436**, 286.
[27] Drumm, *Proc. Roy. Irish Acad.*, 1923—1924, **36***B*, 41.
[28] Drumm, Carolan, and Ryan, *ibid.*, 1929, **39***B*, 114.
[29] Freudenberg, Carrara, and Cohn, *Annalen*, 1926, **446**, 87.
[30] Baker, *J.*, 1929, 1593.
[31] Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 510; Cram in Newman's "Steric Effects in Organic Chemistry," Wiley, New York, 1956, p. 255.

Experimental

(±)-*Dihydroquercetin* 5 : 7 : 3′ : 4′-*tetramethyl ether*, m. p. 169—170°, was prepared from (±)-dihydroquercetin (acid-racemised [17]) as described by Hergert, Coad, and Logan [19] (Found: C, 63·3; H, 5·68. Calc. for $C_{19}H_{20}O_7$: C, 63·3; H, 5·6%); the infrared absorption of the (±)-compound (in CCl_4) was indistinguishable from that of the optically active isomer described below, with OH and carbonyl absorption at 2·85 and 5·92 μ. A solution of the methyl ether (0·45 g.) in pyridine (4 c.c.) and acetic anhydride (4 c.c.) was kept at room temperature for 14 hr. and was then poured into water; the precipitated oil crystallised rapidly and recrystallisation from ethanol gave (±)-dihydroquercetin tetramethyl ether 3-acetate (0·43 g.) as needles, m. p. 184—185° (lit.,[19] m. p. 171—172°, from methanol, and [25] 186°), which had no observable rotation in chloroform.

(+)-*Dihydroquercetin* 5 : 7 : 3′ : 4′-*Tetramethyl Ether* (*Taxifolin Tetramethyl Ether*) (I).—(+)-Dihydroquercetin, after being dried over phosphoric oxide, had $[\alpha]_D^{18}$ +39·7° (2·5% in 50% aqueous acetone) (lit.,[17] +46°), and when methylated (5 g.) as for the (±)-compound [19] gave (+)-*dihydroquercetin tetramethyl ether* (*ca.* 3·0 g.), m. p. 165—168° after two crystallisations from ethanol, $[\alpha]_D^{16}$ −23·4° (2·3% in $CHCl_3$) (Found: C, 62·9; H, 5·75%). The optical purity of this product is unknown; recrystallisation of optically impure material from ethanol reduced the specific rotation; *e.g.*, material with $[\alpha]_D$ −20·3° had $[\alpha]_D$ −17·8° (1·2% in $CHCl_3$) after two crystallisations from ethanol. In a similar methylation partly racemised dihydroquercetin (9·25 g.), $[\alpha]_D^{18}$ +26·9° (2·8% in 50% aqueous acetone), gave the tetramethyl ether (5·32 g.) with $[\alpha]_D^{19}$ −9·9° (2·7% in $CHCl_3$). (+)-Dihydroquercetin tetramethyl ether (0·4255 g.), $[\alpha]_D^{18}$ −19·7° (2·4% in $CHCl_3$), was dissolved in acetic acid (10 c.c.) and the observed rotation (−0·29°) was unchanged after 15 days at room temperature (18—20°), $[\alpha]_D$ −6·8° (4·3% in AcOH).

(+)-*Dihydroquercetin Tetramethyl Ether* 3-*Acetate*.—A solution of (+)-dihydroquercetin tetramethyl ether (0·40 g.), $[\alpha]_D^{18}$ −19·7° (in $CHCl_3$), in pyridine (1 c.c.) and acetic anhydride (1 c.c.) was kept for 5 hr. and then added to water. Crystallisation of the precipitated solid from ethanol gave crude product (0·35 g.) in rhombic crystals, m. p. 164—165° after softening at 159°, $[\alpha]_D^{18}$ +17·9° (1·7% in $CHCl_3$). Recrystallisation from ethanol gave a mixture of fine needles and larger rhombic crystals which were separated mechanically (swirling and filtering): the needles (0·066 g.) consisted of (±)-dihydroquercetin tetramethyl ether 3-acetate, m. p. 182—183° alone and when mixed with authentic material. The heavier rhombic crystals (0·258 g.), m. p. *ca.* 165°, $[\alpha]_D^{15}$ +22·9° (1·8% in $CHCl_3$), after two recrystallisations from ethanol and separation from further needle crystals of (±)-acetate, gave the (+)-*acetate* in rhombic crystals, m. p. 162—163°, $[\alpha]_D^{18}$ +33·4° (2·1% in $CHCl_3$) (Found: C, 62·5; H, 5·48; Ac, 10·5. $C_{21}H_{22}O_8$ requires C, 62·7; H, 5·51; Ac, 10·7%). Insufficient material remained for further recrystallisation, but the specific rotation (33·4°) was not exceeded in two subsequent experiments; the optical purity of this (+)-acetate is unknown.

(±)-*Catechin* 5 : 7 : 3′ : 4′-*Tetramethyl Ether from* (±)-*Dihydroquercetin Tetramethyl Ether*.—A suspension of platinic oxide (0·1 g.) in acetic acid was reduced by hydrogen for 3 hr. before introduction of a suspension of (±)-dihydroquercetin tetramethyl ether (1 g.) in acetic acid (*ca.* 20 c.c.). The mixture was shaken with hydrogen at room temperature and pressure until hydrogenation appeared to be complete (17 hr.) and the catalyst was removed at the centrifuge. Evaporation of the supernatant solution left a crystalline residue which, after recrystallisation from ethanol, gave a product (0·56 g.), m. p. 154—164°. This was acetylated with acetic anhydride–pyridine (1 : 1) for 14 hr. at room temperature; the crystalline product obtained by adding the acetylation mixture to water consisted of (±)-catechin tetramethyl ether 3-acetate which crystallised from ethanol in needles (0·28 g.), m. p. 134—135° raised to 135—136° by recrystallisation (lit.,[22] m. p. 134—135°) (Found: C, 64·9; H, 6·27; Ac, 9·8. Calc. for $C_{21}H_{24}O_7$: C, 64·9; H, 6·24; Ac, 11·1%). The infrared absorption (in CCl_4) of the (±)-acetate was indistinguishable from that of (+)-catechin tetramethyl ether 3-acetate but differed from that of (−)-*epi*catechin tetramethyl ether 3-acetate.

(+)-*Catechin* 5 : 7 : 3′ : 4′-*Tetramethyl Ether* (II) *from* (+)-*Dihydroquercetin Tetramethyl Ether* (I).—(+)-Dihydroquercetin tetramethyl ether (1 g.), $[\alpha]_D^{16}$ −23·4° (in $CHCl_3$), was hydrogenated over Adams catalyst as already described for the (±)-compound. Removal of the catalyst and evaporation of the solvent left an oil, $[\alpha]_D^{18}$ −5·6° (1·4% in $CHCl_3$), with infrared absorption (CCl_4 solution) closely similar to that of (+)-catechin tetramethyl ether except

for a band at 5·8 μ which was probably due to traces of acetic acid or an acetate as dihydroquercetin tetramethyl ether carbonyl absorption occurred at 5·92 μ. The oil crystallised from aqueous ethanol in needles (0·23 g., 24%), m. p. 138—140° raised by several crystallisations from aqueous ethanol to m. p. 140—141°, $[\alpha]_D^{18}$ −9·8° (1·6% in $CHCl_3$), which did not depress the m. p. of authentic (+)-catechin 5 : 7 : 3′ : 4′-tetramethyl ether, m. p. 141—142°, $[\alpha]_D^{23}$ −11·4° (4·5% in $CHCl_3$). The infrared absorption (CCl_4 and Nujol mull) of the product was indistinguishable from that of authentic (+)-catechin tetramethyl ether, but differed from that of (−)-*epi*catechin tetramethyl ether (in CCl_4).

The filtrate from the first crop of crystals (0·23 g.) was evaporated under reduced pressure and the residue, on acetylation with acetic anhydride and pyridine at room temperature, gave (±)-catechin tetramethyl ether 3-acetate (*ca.* 0·15 g.), m. p. and mixed m. p. 135—136°. Ester carbonyl absorption occurred at 5·72 μ (CCl_4 solution).

(+)-*Catechin* 5 : 7 : 3′ : 4′-*Tetramethyl Ether* (II) *from* (+)-*Catechin*.—A mixture of partly racemised (+)-catechin (11 g.), $[\alpha]_D^{24}$ +9·3° (0·9% in 50% aqueous acetone) (lit.,[22] $[\alpha]_{Hg}$ +17·1°), anhydrous potassium carbonate (25 g.), and dry acetone was heated to the b. p. before addition of dimethyl sulphate (13·2 c.c.) in three portions, and gentle boiling was maintained for 4 hr. (total). The suspension was filtered, the residue was washed with acetone, and the combined acetone filtrates were treated with a few drops of aqueous ammonia and evaporated on a steam-bath. Recrystallisation of the residue from methanol gave (+)-catechin tetramethyl ether (8·7 g.) in needles, m. p. 141—142°, $[\alpha]_D^{25}$ −11·2° (4·5% in $CHCl_3$), raised by recrystallisation to m. p. 142—143°, $[\alpha]_D^{23}$ −11·4° (4·5% in $CHCl_3$) and then to m. p. 143—144°, $[\alpha]_D^{22}$ −13·3° (4·3% in $C_2H_2Cl_4$) {lit.,[22] m. p. 143—144°, $[\alpha]_{Hg}$ −13·4° (3% in $C_2H_2Cl_4$)} (Found: C, 66·1; H, 6·25. Calc. for $C_{19}H_{22}O_6$: C, 65·9; H, 6·40%). The acetate [32] melted at 94—95°.

(+)-*Catechin Tetramethyl Ether* 3-*Toluene*-p-*sulphonate* (IV).—This was prepared from the foregoing methyl ether by Freudenberg, Orthner, and Fikentscher's method [26] and after three crystallisations from methanol had m. p. 86—88° and $[\alpha]_D^{21}$ +87·7° (6·1% in $C_2H_2Cl_4$) {lit.,[26] m. p. 86—87°, $[\alpha]_D^{14}$ +22·7° or, after recalculation, +91·8° (in $C_2H_2Cl_4$)}. The toluene-*p*-sulphonate crystallised from ethanol in plates, m. p. 114—116° raised to 115—116° by recrystallisation (Found: C, 62·4; H, 5·71. Calc. for $C_{26}H_{28}O_8S$: C, 62·4; H, 5·64%); crystallisation from methanol then gave needles, m. p. 86—88°, once more, and a mixture of the two sintered slightly at the lower temperature and melted at 110°. The toluene-*p*-sulphonate was recovered after being treated with lithium aluminium hydride under the conditions applied [33] to codeine toluene-*p*-sulphonate, and similar results were obtained with anhydrous dioxan as solvent in place of tetrahydrofuran.

Rearrangement of (+)-*Catechin Tetramethyl Ether* 3-*Toluene*-p-*sulphonate with Ethanolic Potassium Acetate*.—A solution of (+)-catechin tetramethyl ether 3-toluene-*p*-sulphonate (1 g.) and freshly fused potassium acetate in magnesium-dried ethanol (15 c.c.) was heated in a sealed tube at 135° for 48 hr. The cold solution was filtered from potassium toluene-*p*-sulphonate (0·367 g., 94·5%), then evaporation left a dark brown oil (0·67 g.), $[\alpha]_D^{18}$ +16·8° (0·8% in $C_2H_2Cl_4$), which was dissolved in a little methanol. Crystallisation gave (+)-2-ethoxy-5 : 7 : 3′ : 4′-tetramethoxy*iso*flavan (0·143 g.) in needles, m. p. 122—123° raised by two crystallisations to m. p. 123—124°, $[\alpha]_D^{20}$ +113·2° (1·1% in $C_2H_2Cl_4$) (Found: C, 67·6; H, 7·01; OAlk calc. as OMe, 39·8; *C*-Me, 3·9. Calc. for $C_{21}H_{26}O_6$: C, 67·4; H, 7·00; OMe, 41·4; *C*-Me, 4%); Drumm [27] reports m. p. 123°, and Drumm, Carolan, and Ryan [28] record $[\alpha]_D^{16}$ +119° (3·0% in $C_2H_2Cl_4$). The m. p. of the product was not depressed by admixture with the authentic specimen described below. A small quantity of unidentified material was obtained from the mother-liquors in needles (*ca.* 0·03 g.), m. p. 100—102°, $[\alpha]_D^{20}$ +14·9° (0·6% in $C_2H_2Cl_4$).

With methanolic potassium acetate the toluene-*p*-sulphonate (1 g.) similarly gave a brown oil (0·626 g.), $[\alpha]_D$ +34·3° (0·9% in $C_2H_2Cl_4$), from which no crystalline compound was isolated. With ethanolic potassium acetate under milder conditions (boiling for 11 hr.) conversion was incomplete and the toluene-*p*-sulphonate (20%) was recovered with $[\alpha]_D^{23}$ +84·4° ($C_2H_2Cl_4$).

(+)-2-*Ethoxy*-5 : 7 : 3′ : 4′-*tetramethoxy*isoflavan (V).—The intermediate 2-chloro*iso*flavan was not obtained crystalline when prepared according to Drumm's directions [27] (see also Baker [30]) and in subsequent work carbon disulphide was replaced by benzene. Phosphorus pentachloride (0·7 g.) was added to (+)-catechin 5 : 7 : 3′ : 4′-tetramethyl ether (1 g.) in dry (Na) benzene (20 c.c.) and the flask was immediately closed with a calcium chloride guard tube

[32] Freudenberg, Böhme, and Purrmann, *Ber.*, 1922, **55**, 1746.
[33] Rapoport and Bonner, *J. Amer. Chem. Soc.*, 1951, **73**, 2872.

and shaken. When the reaction appeared complete (5 min.) the reddish solution was stirred with aqueous sodium carbonate, and the organic layer was separated and washed twice with aqueous sodium carbonate, and then once with water. Benzene was removed by distillation under reduced pressure and the oily residue was heated under reflux with dry ethanol (10 c.c.) for 30 min. and then allowed to cool. (+)-2-Ethoxy-5 : 7 : 3′ : 4′-tetramethoxy*iso*flavan crystallised in needles (0·7 g.), $[\alpha]_D^{24}$ +119° (0·5% in $C_2H_2Cl_4$), m. p. 122—123° alone and when mixed with the compound prepared from (+)-catechin tetramethyl ether 3-toluene-*p*-sulphonate as already described.

2-Ethoxy-5 : 7 : 3′ : 4′-tetramethoxy*iso*flavan (0·5 g.), $[\alpha]_D^{24}$ +119°, was recovered after being heated in a sealed tube with potassium acetate (0·5 g.) and dry ethanol (8 c.c.) at 135° for 48 hr. The solution was diluted with water and extracted with chloroform; evaporation of the chloroform left a crystalline residue (0·5 g.), which was too dark for polarimetry. Recrystallisation of the residue from ethanol gave needles (0·389 g.), $[\alpha]_D^{24}$ +117° (0·9% in $C_2H_2Cl_4$), m. p. 123—124° alone and when mixed with the starting material.

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