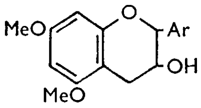
492. *Flavan Derivatives. Part II.* The Relative Configurations of Catechin and Epicatechin: 1,2-Rearrangement in the Reduction of the Diastereoisomers to the Same Enantiomorph of a Propan-1-ol.*

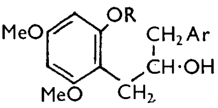
By J. W. CLARK-LEWIS.

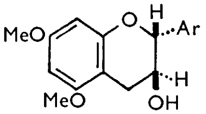
Reductive ring-opening of the heterocyclic ring in catechin and epicatechin tetramethyl ether with lithium aluminium hydride and aluminium chloride is accompanied by 1,2-rearrangement and gives a phenol which is converted by methylation into 2-(3,4-dimethoxyphenyl)-3-(2,4,6-trimethoxyphenyl)propan-1-ol. Formation of the same enantiomorph of this propan-1-ol from (+)-catechin and (—)-epicatechin tetramethyl ether confirms the relative configurations previously established for these diastereoisomers.

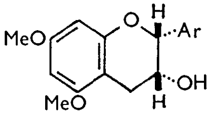
RELATIVE configurations in the catechin series of flavan derivatives (I) were determined by reductive ring-opening of the heterocyclic ring with sodium and liquid ammonia to the phenolic alcohol (II; R = H) which was converted by methylation into the propan-2-ol (II; R = Me). (+)-Catechin (III) and (—)-epicatechin tetramethyl ether (IV) thus gave enantiomorphous forms of the propan-2-ol (II) and this showed that the 3-hydroxyl group has opposite configurations in (+)-catechin and (—)-epicatechin.[1] This was soon confirmed by independent determinations of the absolute configurations of (+)-catechin by ozonolysis [2] and of (—)-epicatechin [1] by Prelog's atrolactic acid method.

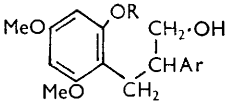
Reduction of both (+)-catechin and (—)-epicatechin tetramethyl ether with lithium aluminium hydride and aluminium chloride in tetrahydrofuran, followed by methylation, led however to the lævorotatory enantiomorph of an alcohol originally regarded [3] as the propan-2-ol (II; R = Me) but later shown to be the propan-1-ol (V; R = Me) formed by 1,2-rearrangement.[4] The structure of the propan-1-ol (V; R = Me) was established by synthesis as follows: condensation of 2,4,6-trimethoxybenzaldehyde with homoveratronitrile gave the *trans*-α-cyanostilbene (VI) accompanied by traces of the *cis*-isomer (*cis* and *trans* here refer to the relative positions of the aryl groups); both isomers resisted attempts to hydrolyse them, and an attempt to prepare the unsaturated acid by Oglialoro's modification of the Perkin reaction gave only *trans*-2,4,6,3′,4′-pentamethoxystilbene. Reduction of the cyanostilbene (VI) with sodium in liquid ammonia gave the saturated nitrile (VII) which was hydrolysed with alkali to the acid (VIII). Reduction of the acid with lithium

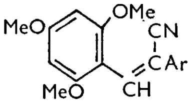

(I)

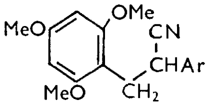

(II)

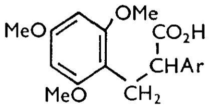

(III)

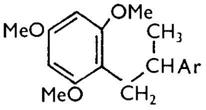

(IV)

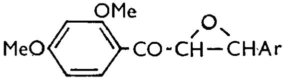

(V)


(VI)


(VII)


(VIII)


(IX)


(X)

Ar = 3,4-$(MeO)_2C_6H_3$

---

* Part I, *J.*, 1958, 2367.

[1] Birch, Clark-Lewis, and Robertson, *J.*, 1957, 3586.

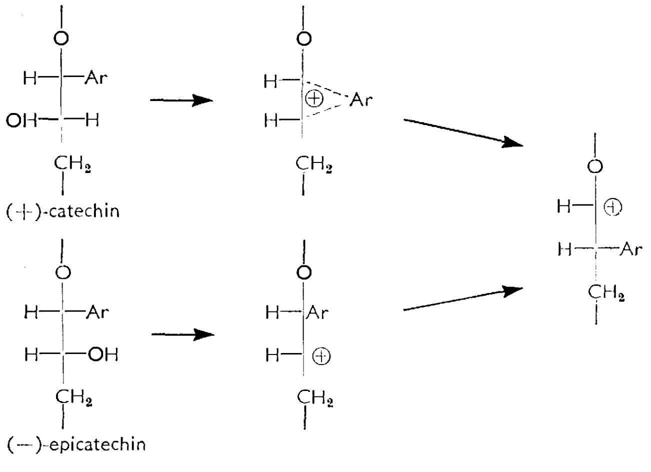
[2] Hardegger, Gempeler, and Züst, *Helv. Chim. Acta*, 1957, **40**, 1819.

[3] Brown and Somerfield, *Proc. Chem. Soc.*, 1958, 236.

[4] Clark-Lewis, *Proc. Chem. Soc.*, 1959, 388.

aluminium hydride gave the (±)-propan-1-ol (V; R = Me), and comparisons of infrared spectra established the structural identity of the (±)- and (—)-propan-1-ol.

Molecular rearrangement in the reduction of the (+)-catechin compound is unexceptional because its derivatives are prone to undergo 1,2-rearrangement, as occurs for example in the reaction of (+)-catechin tetramethyl ether with phosphorus pentachloride [5] and in the reaction of the 3-toluene-*p*-sulphonate with ethanolic potassium acetate,[6] which yield respectively 2-chloro- and 2-ethoxy-5,7,3′,4′-tetramethoxyisoflavan. These transformations are regarded as concerted rearrangements in which the aryl group migrates simultaneously with separation of the 3-substituent (OH or $O\cdot SO_2\cdot C_6H_4Me$-*p*) and results in inversion at the 3-position and in formation of a carbonium ion at the 2-position. In the reduction by lithium aluminium hydride and aluminium chloride the 2-carbonium ion similarly formed (see scheme) evidently reacts with the oxygen atom of a hydroxyl ion or an equivalent complex anion before fission of the heterocyclic ring. The resulting hemiacetal then undergoes fission and reduction to the phenolic propan-1-ol (V; R = H), which is converted by methylation into 2-(3,4-dimethoxyphenyl)-3-(2,4,6-trimethoxyphenyl)propan-1-ol (V; R = Me). Epicatechin tetramethyl ether 3-toluene-*p*-sulphonate undergoes an elimination reaction with hydrazine which is considered [7] to proceed by an E_2 mechanism, and formation of a 3-carbonium ion (and consequent rearrangement) has not previously been observed in the epicatechin series. Similar reduction of epicatechin tetramethyl ether presumably proceeds through the 3-carbonium ion which may be stabilised by interaction with the heterocyclic oxygen atom or may suffer inversion or racemisation. Nevertheless the configuration of the rearranged propan-1-ol will be determined by the configuration of the aryl group in the 2-position, and because this configuration is the same in (—)-epicatechin and in (+)-catechin the two compounds yield the same enantiomorph of the rearranged propanol. These sequences of reactions are indicated in the chart by Fischer projection formulæ drawn to show the absolute configurations, and from these it may be inferred that the propan-1-ol has the 2*S*-configuration.[8]



Some points of general interest were noted during synthesis of the racemic propan-1-ol: attempted hydrolysis of the *trans*-nitrile gave a mixture of *cis*- and *trans*-nitriles in which the latter predominated, and the *trans*-structure was assigned to the isomer with the higher absorption in the 330 mμ band. Reduction of the nitrile (VI) with sodium and boiling alcohol gave the propane (IX) which was also formed by gradual addition of sodium

---

[5] Drumm, MacMahon, and Ryan, *Proc. Roy. Irish Acad.*, 1923—24, **36**, *B*, 41, 1495; Freudenberg, Carrara, and Cohn, *Annalen*, 1925, **446**, 87.

[6] Clark-Lewis and Korytnyk, *J.*, 1958, 2367.

[7] King, Clark-Lewis, and Forbes, *J.*, 1955, 2948.

[8] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.

to a solution of the nitrile in liquid ammonia. Reduction of the cyanostilbene by lithium aluminium hydride unexpectedly gave the saturated nitrile (VII) accompanied by the trimer (triazine), but the nitrile (VII) was more conveniently obtained by adding the cyanostilbene rapidly to an excess of sodium dissolved in liquid ammonia.

The (—)-propan-1-ol (V; R = Me) is lævorotatory in ethanol and in chloroform and thus differs from the propan-2-ol (II; R = Me) which was found to have opposite signs of rotation in these solvents.[1] A second synthesis to confirm the structure of the (±)-propan-2-ol has now been effected by reduction of the epoxide (X) successively to the 1,2-glycol and the propan-2-ol identical with that already described.[1]

EXPERIMENTAL

Ultraviolet light absorption measurements were made with an Optica recording spectrophotometer CF4. The absorption characteristics of solutions of the stilbenes changed rapidly when exposed to daylight, and solutions in 95% ethanol were therefore prepared and kept in the dark.

Reduction of (+)-*Catechin* 5,7,3′,4′-*Tetramethyl Ether*.—(+)-Catechin tetramethyl ether (2 g.), m. p. 142—143°, $[\alpha]_D^{25}$ $-15\cdot9°$ (2·9% in $C_2H_2Cl_4$), $[\alpha]_D^{25}$ $-11°$ (4·1% in $CHCl_3$), was added to a mixture of lithium aluminium hydride (0·5 g.) and aluminium chloride (3·5 g.) in boiling tetrahydrofuran (100 c.c.).[3] The mixture was boiled for 6 hr. before addition of ethyl acetate (10 c.c.) in ether (40 c.c.), and then acidified with 2N-sulphuric acid (30 c.c.). The aqueous layer was extracted with ether (3 × 25 c.c.) and the combined ethereal extracts were evaporated, and a solution of the residual yellow oil in benzene–ether (1 : 1, 30 c.c.) was extracted with 2N-sodium hydroxide. The phenolic material was extracted into ether and evaporation of the solution left a residue (1·81 g.) which was methylated by methyl sulphate–acetone–potassium carbonate (14 hr.) before isolation of the methylated products (1·69 g.), $[\alpha]_D$ $-11\cdot4° \pm 2\cdot0°$ (4·2% in EtOH), equivalent to 0·254 g. of propanol with $[\alpha]_D$ $-76°$. A benzene solution of this neutral material (1·69 g.) was added to a column of alumina (100 g.) deactivated with water (10 g.), and developed with benzene (700 c.c.) before elution of the propanol with benzene–ether (9 : 1) (500 c.c. in ten portions). Recrystallisation of the crystalline propanol residues from ethyl acetate–hexane gave (—)-2-(3,4-*dimethoxyphenyl*)-3-(2,4,6-*trimethoxyphenyl*)*propan*-1-*ol* (0·15 g.), m. p. 118—120°, $[\alpha]_D^{22}$ $-55°$ (1·9% in EtOH), raised by recrystallisation from ethanol to m. p. 125°, $[\alpha]_D^{21}$ $-76°$ (1·2% in EtOH) (Found: C, 66·3; H, 7·2. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%). The infrared absorption of the (—)-propan-1-ol (in CCl_4) was indistinguishable (2—11 μ) from that of the (±)-propan-1-ol described below, with max. at 3554, shoulder at 3586 cm.$^{-1}$ (OH), 3001 ± 1 (aromatic C–H), 2956 ± 2, 2942 ± 2, 2914 ± 5 and 2876 ± 5 cm.$^{-1}$ (C–H), and at 2836 ± 1 cm.$^{-1}$ (methoxyl C–H). The isomeric propan-2-ol [1] showed max. at 3576 ± 5 cm.$^{-1}$ (OH) and lacked the peak at 2876 cm.$^{-1}$.

Reduction of (—)-*Epicatechin* 5,7,3′,4′-*Tetramethyl Ether*.—When treated as described above for the (+)-catechin compound, (—)-epicatechin tetramethyl ether, m. p. 143°, $[\alpha]_D^{21}$ $-52°$ (3·8% in $C_2H_2Cl_4$), $[\alpha]_D^{21}$ $-40°$ (2% in $CHCl_3$), gave phenolic products (1·8 g.) which were converted into the methyl ethers (1·79 g.), $[\alpha]_D$ $-9\cdot3° \pm 0\cdot5°$ (in EtOH) [equivalent to the (—)-propanol (0·22 g.)]. Chromatography gave crystalline material (0·368 g.), $[\alpha]_D^{21}$ $-22°$ (1·5% in EtOH), raised by two crystallisations from ethanol to m. p. 124—125°, $[\alpha]_D^{21}$ $-75°$ (1·5% in EtOH). The propan-1-ol was identical with that from (+)-catechin (mixed m. p. and infrared).

α-(3,4-*Dimethoxyphenyl*)-β-(2,4,6-*trimethoxyphenyl*)*acrylonitrile* (VI).—Homoveratronitrile [9] (2·72 g.) and 2,4,6-trimethoxybenzaldehyde (3·0 g.) were heated on a steam-bath for 2 hr. with ethanol (75 c.c.) and sodium ethoxide (from 0·4 g. of sodium), and the product (4·86 g., 89%), m. p. 168—169°, was collected by filtration of the cold suspension. The sparingly soluble trans-*nitrile* crystallised from ethanol in pale yellow plates, m. p. 169—170° (Found: C, 67·5; H, 6·0. $C_{20}H_{21}O_5N$ requires C, 67·6; H, 6·0%), $\lambda_{max.}$ (Nujol, CaF_2 prism) 4·53 μ (CN peak), $\lambda_{max.}$ 247 (ε 18,000) and 349 mμ (ε 27,600). Evaporation of the filtrate left the more soluble cis-*nitrile*, which crystallised from methanol in pale yellow prisms, m. p. 163—164°, depressed to m. p. 144—146° by admixture with the *trans*-form (Found: C, 67·3; H, 6·0%), $\lambda_{max.}$ 4·56 μ (CN peak, Nujol, CaF_2 prism), $\lambda_{max.}$ at 247 (ε 20,600) and 340 mμ (ε 19,900). The nitriles resisted hydrolysis by alkali or acid; after being boiled for 24 hr. with methanolic 10% sulphuric acid recovered *trans*-nitrile was accompanied by the more soluble *cis*-nitrile.

---

[9] Haworth, Mavin, and Sheldrick, *J.*, 1934, 1423.

Reduction of the *trans*-nitrile (1·73 g.) with boiling ethanol (*ca.* 100 c.c.) and sodium (14 g.) gave 2-(3,4-dimethoxyphenyl)-1-(2,4,6-trimethoxyphenyl)propane [10] (0·78 g.), leaflets (from methanol), m. p. 108—109° (Found: C, 69·5; H, 7·8. Calc. for $C_{20}H_{26}O_5$: C, 69·3; H, 7·6%).

α-(3,4-*Dimethoxyphenyl*)-β-(2,4,6-*trimethoxyphenyl*)*propionitrile* (VII).—(*a*) The unsaturated nitrile (1·5 g.) was added to a solution of sodium (1 g.) in liquid ammonia (100 c.c.). After the blue colour had disappeared (*ca.* 5 min.) ammonium chloride (2·5 g.) was added and the solution was left to evaporate. The residue was washed with water, and recrystallisation from methanol gave the *propionitrile* (0·7 g., 47%) in prisms, m. p. 103° raised to 104—105° by recrystallisation from benzene–hexane (Found: C, 67·3; H, 6·5; N, 3·9. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·5; N, 3·9%). The cyanide showed CN absorption at 4·4 μ (Nujol).

When sodium (0·36 g.) was added in small pieces to the acrylonitrile (VI) in liquid ammonia it gave recovered nitrile (0·67 g.) and the propane (IX) (0·46 g.). Rapid addition of sodium (0·72 g.) in large pieces gave recovered nitrile (1·09 g.), the propane (0·5 g.), and the saturated nitrile (VII) (0·12 g.).

(*b*) A mixture of the unsaturated nitrile (2 g.), lithium aluminium hydride (0·32 g.), and tetrahydrofuran (100 c.c.) was boiled for 3 hr. and, when cold, was diluted with ether and shaken with 5N-sodium hydroxide. The ethereal layer was concentrated to small volume, diluted with methanol, and filtered from an unidentified substance (*triazine*?) (0·7 g.), m. p. 205—210° raised to m. p. 222—223° by recrystallisation from dimethylformamide [Found: C, 67·3, 67·0; H, 6·3, 6·3; N, 3·9. $(C_{20}H_{23}O_5N)_3$ requires C, 67·2; H, 6·5; N, 3·9%]. Evaporation of the filtrate to dryness and crystallisation of the residue (0·6 g.) from methanol gave a mixture of the unsaturated *cis*-nitrile and the propionitrile (*ca.* 0·3 g.).

α-(3,4-*Dimethoxyphenyl*)-β-(2,4,6-*trimethoxyphenyl*)*propionic Acid* (VIII) *and* (±)-2-(3,4-*Dimethoxyphenyl*)-3-(2,4,6-*trimethoxyphenyl*)*propan*-1-*ol* (V; R = Me).—The propionitrile (0·13 g.) was boiled with a mixture of ethanol and aqueous 10N-sodium hydroxide for 6 hr., and the solution was then extracted with ether. Acidification of the alkaline aqueous solution gave the *propionic acid* (0·073 g., 53%) in needles, m. p. 146—147° raised to m. p. 148—149° by recrystallisation from aqueous methanol (Found: C, 63·4; H, 6·6. $C_{20}H_{24}O_7$ requires C, 63·8; H, 6·4%). Reduction of the acid (0·064 g.) in boiling ether (25 c.c.) for 1½ hr. with an excess of lithium aluminium hydride gave the (±)-*propan*-1-*ol*, which crystallised from hexane in needles (0·035 g., 57%), m. p. 108° depressed to 90—93° by admixture with the corresponding propane (Found: C, 66·3; H, 7·3. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%).

2,4,6,3′,4′-*Pentamethoxystilbene*.—Homoveratric acid (1 g.) and 2,4,6-trimethoxybenzaldehyde (1 g.) were submitted to Oglialoro's modification of the Perkin reaction as described for α-phenylcinnamic acid,[11] and the products were separated into an acidic fraction (homoveratric acid) and a neutral fraction of the stilbene which crystallised from methanol in needles (0·14 g.), m. p. 127—129° unchanged by two crystallisations from ethanol (Found: C, 68·8; H, 6·7. Calc. for $C_{19}H_{22}O_5$: 69·1; H, 6·7%), $\lambda_{max.}$ 243 (ε 19,000) and 334 mμ (ε 35,500), $\lambda_{min.}$ 265 mμ (ε 6500). Molho and Coillard [12] report m. p. 131° and max. at 332 mμ (ε 26,700).

3-(3,4-*Dimethoxyphenyl*)-1-(2,4,6-*trimethoxyphenyl*)*propane*-1,2-*diol*.—3-(3,4-Dimethoxyphenyl)-2,3-epoxy-1-(2,4,6-trimethoxyphenyl)propan-1-one [13] (1 g.) in ethanol was hydrogenated over Raney nickel at 100°/100 atm. for 6 hr., and the solution was filtered and then evaporated. The residue was chromatographed on alumina (100 g.) deactivated with water (10 g.), and then developed with benzene (500 c.c.) and with benzene–ether (9 : 1) (350 c.c.) before the same eluant (1050 c.c.) removed the *propane*-1,2-*diol* which crystallised from hexane in prisms (0·29 g.), m. p. 95—96° (Found: C, 63·3; H, 6·9. $C_{20}H_{26}O_7$ requires C, 63·5; H, 6·9%). Hydrogenolysis of the diol (0·158 g.) in ethanol (5 c.c.) over palladised charcoal at 100°/50 atm. for 12 hr. gave 1-(3,4-dimethoxyphenyl)-3-(2,4,6-trimethoxyphenyl)propan-2-ol,[1] which crystallised from hexane in prisms (0·1 g., 66%), m. p. and mixed m. p. 88—89°.

The author thanks Dr. W. G. C. Forsyth for supplying (—)-epicatechin, Dr. B. R. Brown for details of his reduction procedure, and Mr. A. G. Moritz for recording and discussing the infrared spectra.

UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA. [*Received, January* 18*th*, 1960.]

---

[10] Freudenberg and Harder, *Annalen*, 1927, **451**, 213.
[11] "Organic Reactions," Wiley, New York, 1942, Vol. I, p. 252.
[12] Molho and Coillard, *Bull. Soc. chim. France*, 1956, 78.
[13] Robertson, Suckling, and Whalley, *J.*, 1949, 1578.