1016. *The Stereochemistry of Some Catechin Derivatives.*

By P. P. Mehta and W. B. Whalley.

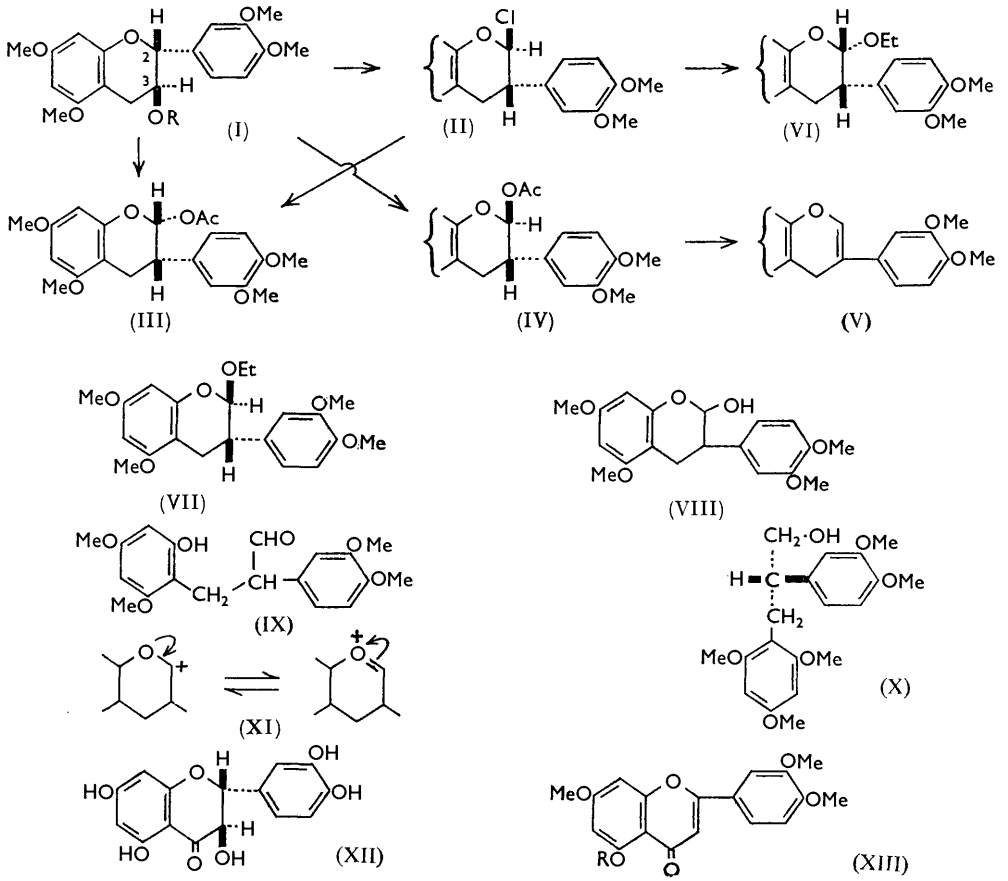
The solvolysis of the tetramethyl ether toluene-*p*-sulphonates of (+)-catechin and (±)-taxifolin has been investigated; the stereochemistry of various catechin derivatives has been clarified.

The action of phosphorus pentachloride on the tetramethyl ether (I; R = H) of (+)-catechin with the production of optically active 2-chloro-5,7,3′,4′-tetramethoxyisoflavan [1] (II) may be the first recorded example of a 1,2-shift involving neighbouring group participation and retention of optical activity. The conformational implications in the catechin series of this rearrangement have been discussed by us.[2,3] It was, therefore, of interest to investigate the solvolysis of the toluene-*p*-sulphonate (I; R = $SO_2 \cdot C_6H_4Me$) of this catechin ether.

The absolute configuration of the ether has been defined as (I; R = H);[4,5] thus the toluene-*p*-sulphonate is represented by (I; R = $SO_2 \cdot C_6H_4Me$). Acetolysis of this sulphonate gave a mixture from which (2*R*,3*S*)- (III), m. p. 156°, $\nu_{max.}$ 1736 (OAc) and 1259 (OAc) cm.$^{-1}$, and (2*S*,3*S*)-2-acetoxy-5,7,3′,4′-tetramethoxyisoflavan (IV) m. p. 103°, $\nu_{max.}$ 1745 (OAc) and 1250 (OAc) cm.$^{-1}$, have been isolated. The former acetate is identical with that prepared by the action of potassium acetate upon the lævorotatory 2-chloro-isoflavan (II). That the difference between our two acetates is stereochemical is illustrated by their hydrolysis to the same (±)-2-hydroxy-5,7,3′,4′-tetramethoxyisoflavan (VIII). Since the isoflavans in the catechin series are derived by the well-established 1,2-migration of *trans*-groups,[2,3,6,7] C-3 may be assigned the (*S*)-configuration in compounds (III) and (IV). Collateral support is provided by reduction, with lithium aluminium hydride and

[1] Drumm, MacMahon, and Ryan, *Proc. Roy. Irish Acad.*, 1923—24, **36**, *B*, 41, 149.
[2] Whalley, Symposium on the Chemistry of Vegetable Tannins, Cambridge, April 1956, p. 151, Soc. Leather Trades' Chemists, Croydon, 1956.
[3] Whalley, "The Chemistry of Flavonoid Compounds," ed. Geissman, Pergamon Press, London, 1962, p. 441.
[4] Birch, Clark-Lewis, and Robertson, *J.*, 1957, 3586.
[5] Hardegger, Gempeler, and Züst, *Helv. Chim. Acta*, 1957, **40**, 1819.
[6] King, Clark-Lewis, and Forbes, *J.*, 1955, 2948.
[7] Clark-Lewis and Ramsay, *Proc. Chem. Soc.*, 1960, 359.

aluminium chloride, of a 2-acetoxy-5,7,3′,4′-tetramethoxyisoflavan of unspecified melting point to (2*S*)-2-(3,4-dimethoxyphenyl)-3-(2,4,6-trimethoxyphenyl)propan-1-ol (X).[7] Thus the two acetates differ only in their relative configurations at position 2. The complete, absolute stereochemical assignments are derived from their behaviour on pyrolysis. The acetate of m. p. 103° furnishes a high yield of 5,7,3′,4′-tetramethoxyisoflav-2-en (V), identical with the dehydrochlorination product of the 2-chloroisoflavan (II); consequently the 2-acetoxyl group and the 3-hydrogen atom are *cis* [8] in this acetate, which is thus defined as the (2*S*,3*S*)-form (IV). In the epimeric acetate, 2-acetoxy-group and the



3-hydrogen atom must be *trans*-oriented, as in (III). In agreement with this, the latter form (III) is stable [8] to pyrolytic conditions. The nuclear magnetic resonance (n.m.r.) spectrum of the isoflavene (V) confirms the presence of a 4-methylene group (singlet at 6·45 τ) and hence the accepted formula.

The 2-hydroxyisoflavan (VIII) furnishes an oxime [from the aldehydo-form (IX)] and an *O*-acetate [from the cyclic form (VIII)] (cf. Freudenberg *et al.*[9]). Since the infrared spectrum of (±)-2-hydroxy-5,7,3′,4′-tetramethoxyisoflavan is devoid of carbonyl absorption but shows strong hydroxyl absorption at 3472 cm.$^{-1}$ in a mull and in chloroform

[8] See, *e.g.*, Barton, *J.*, 1949, **2174**; Barton, Head, and Williams, *J.*, 1953, **1715**; Arnold, Smith, and Dodson, *J. Org. Chem.*, 1950, **15**, 1256.
[9] Freudenberg, Karimullah, and Steinbrunn, *Annalen*, 1935, **518**, 37.

solution this compound exists as the hemiacetal (VIII). Further support for the stereochemical assignments allocated to our acetates is provided by the acetate of (±)-2-hydroxyisoflavan (VIII). Its infrared spectrum (in $CHCl_3$) is identical with that of the (2*S*,3*S*)-compound (IV) (in $CHCl_3$), but differs from that of the (2*R*,3*S*)-acetate (III) (in $CHCl_3$). It follows that (±)-2-acetoxy-5,7,3′,4′-tetramethoxyisoflavan is stereochemically homogeneous and is the racemate of compound (IV). This conclusion is in agreement with the sharp m. p. of the (±)-acetate of (VIII) and with the identical, extremely characteristic crystalline form exhibited by compound (IV) and by the (±)-acetate (cf. the similar stereochemical homogeneity of the analogous dihydroflavanols [2,10,11]). In the acetate (IV) and its racemate it is possible for the 2-acetoxy and 3-phenyl groups (*i.e.*, the two bulky substituents) to be equatorial and therefore in a more stable conformation than that obtaining in the (2*R*,3*S*)-acetate where at least one substituent, probably the acetoxy-group, must be axial.

It has been established that the 1,2-shifts which occur in the solvolysis of the toluene-*p*-sulphonates of various optically active *threo*- and *erythro*-3-phenylbutan-2-ols furnish products which substantially retain the *threo*- or *erythro*-configuration of the precursor.[12] However, solvolysis of the toluene-*p*-sulphonate (I; R = $SO_2{\cdot}C_6H_4Me$) yields appreciable quantities of both 2-epimers. We ascribe this to the distribution of the cationic charge from C-2 over the adjacent heteroatom, as in (XI), thereby causing the solvolysis, particularly with the relatively weak nucleophilic acetate anion, to be partially non-synchronous.

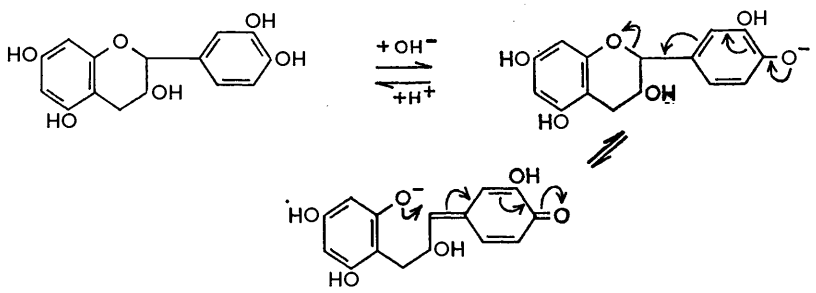
Our examination of the (−)-2-chloroisoflavan (II) [which readily crystallised (cf. Drumm *et al.*[1]), although Clark-Lewis and Korytnyk [11] and Baker [13] obtained oils] shows that it is a single compound and therefore stereochemically homogeneous. We define its absolute stereochemistry as (II). This is in agreement with, *inter alia*, its formation in almost 100% yield from the alcohol (I; R = OH) by a 1,2-shift involving the strongly nucleophilic chloride ion, with its high lævorotation, and with the production from it, by the action of potassium acetate in acetic acid, of the (2*R*,3*S*)-acetate (III) in very high yield. This result is strongly indicative of the chlorine displacement proceeding by an S_N2 mechanism with inversion at position 2.

Interaction [14] of the (−)-2-chloro-isoflavan (II) with alcohol gives (+)-2-ethoxy-5,7,3′,4′-tetramethoxyisoflavan (VI) in which the absolute configuration at position 3 and the general structure have been defined.[7] As in the formation of the (2*R*,3*S*)-acetate (III) from the chloride (II), production of an ether (VI) in high yield, together with the change in the sign of rotation from a high negative value to a high positive value, strongly support the view that ethanolysis proceeds by an S_N2 mechanism with inversion at position 2. We therefore formulate the (+)-2-ethoxyisoflavan as (VI) rather than (VII).[11] Ethanolysis of the toluene-*p*-sulphonate (I; R = $SO_2{\cdot}C_6H_4Me$) gives the same (+)-2-ethoxyisoflavan but in low yield (cf. Clark-Lewis and Korytnyk [11]), a result which does not necessarily conflict with the assignment (VI). Since the solvolysis of the sulphonate (I; R = $SO_2{\cdot}C_6H_4Me$) gives epimeric acetates (III) and (IV) it seems reasonable that ethanolysis should also furnish the epimeric derivatives (VI) and (VII), and that only one has been isolated from the complex products.

(+)-Catechin may be epimerised to (+)-epicatechin, and (−)-catechin to (−)-epicatechin by dilute alkali,[15,16] a change which involves inversion at position 2.[17] We find that the alcohol (I; R = H) is not epimerised by the prolonged action of even

[10] Mahesh and Seshadri, *Proc. Indian Acad. Sci.*, 1955, **41**, *A*, 210.
[11] Clark-Lewis and Korytnyk, *J.*, 1958, 2367.
[12] See, *e.g.*, Cramm, *J. Amer. Chem. Soc.*, 1949, **71**, 3863.
[13] Baker, *J.*, 1929, 1593.
[14] Drumm, Ryan, and Carolan, *Proc. Roy. Irish Acad.*, 1929, **39**, *B*, 114.
[15] Freudenberg, Böhme, and Purrmann, *Ber.*, 1922, **55**, 1734.
[16] Freudenberg and Purrmann, *Annalen*, 1924, **437**, 274.
[17] Freudenberg, *Sci. Proc. Roy. Dublin Soc.*, 1956, **27**, 153.

concentrated alkali and hence it seems [3] that epimerisation at position 2 may proceed by the annexed process.



We have emphasised [2,3] that the ready 1,2-shifts, so characteristic of catechin and its derivatives require the 2-aryl group and the 3-substituent, which are *trans*-related in these compounds, to be axial, at least in the transition state. Further, this conformation may even be preferred in the ground state, although the available evidence is equivocal.[4,18] (+)-Taxifolin (XII) has the same absolute stereochemistry as (+)-catechin,[11] but exhibits reactions which clearly indicate the equatorial orientation of the bulky *trans*-2- and -3-substituents. Although the 4-carbonyl group in taxifolin may introduce complications, particularly by diminishing the stability of the 3-carbonium ion and thus reducing the value of comparisons between the catechin and the taxifolin series, it was of interest to examine the acetolysis of the toluene-*p*-sulphonate of (±)-tetra-*O*-methyltaxifolin. (±)-Taxifolin was employed in preference to (+)-taxifolin since the dihydroflavanols are easily racemised: further (±)-taxifolin belongs to the same stereochemical series as (+)-taxifolin.[2,14]

Acetolysis of the toluene-*p*-sulphonate of the inactive taxifolin ether was accompanied by extensive side-reactions, but the principal product was tetra-*O*-methyl-luteolin (XIII; R = Me), *i.e.*, elimination of the elements of toluene-*p*-sulphonic acid occurred without phenyl migration. The action of boiling quinoline on the ester produced 7,3′,4′-tri-*O*-methyl-luteolin, with demethylation at position 5.

Experimental

Acetolysis of the Toluene-p-*sulphonate of Tetra*-O-*methylcatechin* (I; R = H).—Methylation of (+)-catechin (5 g.) in boiling acetone (100 ml.) containing methyl sulphate (9 g.) and potassium carbonate (15 g.) was complete in 4 hr. The filtered solution was concentrated to half-volume under reduced pressure and diluted with N-sodium hydroxide (100 ml.). Purification of the crystalline precipitate from methanol gave the tetramethyl ether (4 g.) in needles, m. p. 143—144°, $[\alpha]_D^{24}$ −14° (*c* 7·4 in tetrachloroethane).

Prepared from this ether in almost quantitative yield by the method of Drumm *et al.*,[1] (2*S*,3*S*)-(−)-2-chloro-5,7,3′,4′-tetramethoxyisoflavan separated from light petroleum (b. p. 60—80°) in prisms, m. p. 113° (lit.,[1] 112°) (Found: C, 62·6; H, 6·1. Calc. for $C_{19}H_{21}ClO_5$: C, 62·6; H, 5·8%), $[\alpha]_D^{19}$ −124° (*c* 4·0 in $CHCl_3$).

Interaction of the tetramethyl ether (5 g.) and toluene-*p*-sulphonyl chloride (5 g.) in pyridine (25 ml.) at room temperature, during 3 days, gave the toluene-*p*-sulphonate (6·0 g.), which separated from methanol in stout prisms, m. p. 118°, or silky needles, m. p. 86°, $[\alpha]_D^{24}$ +80° (*c* 7·8 in tetrachloroethane) (cf. Clark-Lewis and Korytnyk [11]).

A solution of this toluene-*p*-sulphonate (3 g.) in acetic acid (25 ml.) containing anhydrous sodium acetate (5 g.) was heated on the steam-bath for 6 hr. The cooled solution was diluted with water until turbid. Next day the semi-crystalline precipitate was purified from methanol, to yield (2*R*,3*S*)-(+)-2-acetoxy-5,7,3′,4′-tetramethoxyisoflavan in needles (0·4 g.), m. p. 156°

[18] Clark-Lewis and Jackman, *Proc. Chem. Soc.*, 1961, 165.

[Found: C, 65·1; H, 6·1; OMe, 21·7. Calc. for $C_{17}H_{12}O_3(OMe)_4$: C, 64·9; H, 6·2; OMe, 31·9%], $[\alpha]_D^{22}$ +196° (*c* 5·0 in $CHCl_3$). This compound was identical with a specimen prepared (quantitatively) by the action of potassium acetate and acetic acid on (−)-2-chloro-5,7,3′,4′-tetramethoxyisoflavan and had $[\alpha]_D^{21}$ +190° (*c* 3·0 in $CHCl_3$) {cf. Freudenberg *et al.*,[9] who record m. p. 151°, $[\alpha]_D^{17}$ +202° (in tetrachloroethane); also Drumm *et al.*[14]}. This compound distilled unchanged at 16 mm.; distillation at atmospheric pressure produced complete decomposition.

The filtrate remaining after separation of this acetate was again diluted until turbid with water. 24 Hours later the solid precipitate was purified from methanol, to give (2*S*,3*S*)-2-*acetoxy*-5,7,3′,4′-*tetramethoxyisoflavan* in characteristic, silky needles (0·3 g.), m. p. 103° [Found: C, 65·0; H, 6·3; OMe, 32·0. $C_{17}H_{12}O_3(OMe)_4$ requires C, 64·9; H, 6·2; OMe, 31·9%], $[\alpha]_D^{22}$ −14·6° (*c* 5·0 in $CHCl_3$). Slow distillation of this acetate at 16 mm. gave an almost quantitative yield of 5,7,3′,4′-tetramethoxyisoflav-2-en, identical with a specimen prepared by the action of pyridine on (−)-2-chloro-5,7,3′,4′-tetramethoxyisoflavan (Found: C, 69·1; H, 6·1. Calc. for $C_{19}H_{20}O_5$: C, 69·5; H, 6·1%).

Hydrolysis of the Diastereoisomeric Acetates.—Methanolic 50% w/w potassium hydroxide (8 ml.) was added to a warm solution of (2*R*,3*S*)-(+)-2-acetoxy-5,7,3′,4′-tetramethoxyisoflavan (1 g.) in methanol (30 ml.). 15 Minutes later the solution was diluted with water (25 ml.) and acidified with 2N-hydrochloric acid; purification of the semi-crystalline precipitate from methanol gave (±)-2-hydroxy-5,7,3′,4′-tetramethoxyisoflavan (0·6 g.) in needles, m. p. 103° (decomp.) [Found: C, 62·1; H, 6·5; OMe, 33·4. Calc. for $C_{15}H_{10}O_2(OMe)_4,H_2O$: C, 62·6; H, 6·6; OMe, 34·1%]. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave the anhydrous isoflavan in prisms, m. p. 134° [Found: C, 65·5; H, 6·4; OMe, 35·4. Calc. for $C_{15}H_{10}O_2(OMe)_4$: C, 65·9; H, 6·4; OMe, 35·8%]. Baker [13] records m. p. 133—134°.

(2*S*,3*S*)-2-Acetoxy-5,7,3′,4′-tetramethoxyisoflavan similarly gave the same (±)-2-hydroxy-5,7,3′,4′-tetramethoxyisoflavan.

Prepared by the pyridine method, the oxime formed prisms, m. p. 170°, from aqueous methanol (Found: C, 63·3; H, 6·4; N, 3·8; OMe, 34·2. Calc. for $C_{15}H_{11}NO_2(OMe)_4$: C, 63·1; H, 6·4; N, 3·9; OMe, 34·9%]. Freudenberg *et al.*[9] record m. p. 168°.

Prepared from (±)-2-hydroxy-5,7,3′,4′-tetramethoxyisoflavan by pyridine–acetic anhydride, the acetate separated from methanol in silky needles, m. p. 104° (Found: C, 65·1; H, 6·3. Calc. for $C_{21}H_{24}O_7$: C, 64·9; H, 6·2%). Freudenberg *et al.*[9] record m. p. 110°. The mixed m. p. with (2*S*,3*S*)-2-acetoxy-5,7,3′,4′-tetramethoxyisoflavan was *ca.* 90°.

(+)-2-*Ethoxy*-5,7,3′,4′-*tetramethoxyisoflavan*.—A mixture of the tetramethyl ether toluene-*p*-sulphonate of (+)-catechin (3 g.), anhydrous sodium acetate (3 g.), and ethanol (25 ml.) was refluxed for 36 hr., cooled, and diluted with water until turbid. Next day the precipitate was recrystallised from alcohol, to yield 2-ethoxy-5,7,3′,4′-tetramethoxyisoflavan (0·5 g.) in needles, m. p. 125°, identical with a specimen kindly supplied by Dr. J. W. Clark-Lewis (Found: C, 67·2; H, 7·0. Calc. for $C_{21}H_{26}O_6$: C, 67·4; H, 7·0%), $[\alpha]_D^{22}$ +117° (*c* 0·5 in tetrachloroethane). Drumm *et al.*[14] record m. p. 119° and $[\alpha]_D^{16}$ +119° (in tetrachloroethane) for a specimen prepared from (−)-2-chloro-5,7,3′,4′-tetramethoxyisoflavan by the action of ethanol. The mother-liquors remaining after the isolation of this 2-ethoxyisoflavan gave the tetramethyl ether of (+)-catechin (*ca.* 0·2 g.), together with a mixed crystalline product (*ca.* 1 g.), m. p. *ca.* 90°.

Action of Alkali on the Tetramethyl Ether of (+)-*Catechin*.—A solution of the ether (1·5 g.) in alcohol (50 ml.) and 50% w/w aqueous potassium hydroxide (10 ml.) was refluxed for 72 hr. On cooling, unchanged ether (1·2 g.), m. p. 148°, $[\alpha]_D^{21}$ −15° (*c* 2·5 in tetrachloroethane), separated. Dilution of the mother-liquors with water gave a further quantity of the ether (0·2 g.), m. p. 144°, $[\alpha]_D^{21}$ −10° (*c* 2·0 in tetrachloroethane).

Solvolysis of the Toluene-p-*sulphonate of* (±)-*Tetra*-O-*methyltaxifolin*.—(+)-Taxifolin was racemised by boiling hydrochloric acid and then methylated by methyl sulphate–potassium carbonate in boiling acetone during 6 hr., to give (±)-tetra-*O*-methyltaxifolin, needles, m. p. 171-—172° (from methanol), $\nu_{max.}$ 1667 cm.$^{-1}$ (aromatic C=O). This (2·5 g.) with toluene-*p*-sulphonyl chloride (2·5 g.) in pyridine (25 ml.) at room temperature during 24 hr. gave the *toluene*-p-*sulphonate*, stout, very pale yellow prisms (2·0 g.), m. p. 163° (from methanol) [Found: C, 59·9; H, 5·0; OMe, 24·6. $C_{22}H_{14}O_5(OMe)_4$ requires C, 60·7; H, 5·1; OMe, 24·1%], $\nu_{max.}$ 1701 cm.$^{-1}$ (aromatic C=O).

A solution of this sulphonate (2 g.) in acetic acid (10 ml.) containing sodium acetate (1 g.) was heated on the steam-bath for 7 hr., then diluted with water (50 ml.). Crystallisation of

the precipitate from methanol or ethyl acetate gave unchanged ester (0·1 g.) and tetra-*O*-methyl-luteolin (0·1 g.), m. p. and mixed m. p. 192°. Further dilution of the hydrolysate with water (50 ml.) furnished more tetra-*O*-methyl-luteolin (0·2 g.).

A solution of the sulphonate (0·5 g.) in quinoline (2 ml.) was refluxed for 10 min., diluted with ether (50 ml.), freed from quinoline by extraction with 2N-hydrochloric acid, dried, and evaporated. The residue crystallised from methanol, yielding 7,3′,4′-tri-*O*-methyl-luteolin in pale yellow needles (0·1 g.), m. p. 159°, identical (m. p., mixed m. p., and infrared spectrum) with an authentic specimen and converted into tetra-*O*-methyl-luteolin.

Spectra.—Nuclear magnetic resonance spectra were determined in deuteriochloroform on a Varian A.60 Spectrophotometer. Infrared spectra were determined for paraffin mulls or chloroform solutions on a Perkin-Elmer model 21 spectrophotometer.

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