Oxidative Dimerization of Methyl (*E*)-4-Hydroxy-3,5-di-t-butylcinnamate with Potassium Ferricyanide

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The title compound on oxidation with alkaline potassium ferricyanide or 2,4,6-tri-t-butylphenoxyl gives a mixture of *threo*- and *erythro*-bisquinone methides (3) and (4) in the ratio 65 : 35 by coupling of C(β)-radical intermediates (2). The configuration of isomer (3) follows from its conversion into *trans*-3,4-bis-(4-hydroxy-3,5-di-t-butylbenzyl)tetrahydrofuran (10), which is also obtained from the diarylperhydrofurofuran (6). It is suggested that the non-stereospecific oxidative coupling of the phenol (1) is due to the bulky t-butyl groups impeding the formation of a dimeric reaction intermediate which would lead to exclusive *threo*-coupling as in other (*E*)-propenylphenol derivatives.

OXIDATION of (*E*)-propenylphenol derivatives has given C(β)-coupled dehydro-dimers with exclusively *threo*-configurations.[1] The existence of an intermediate 'tail-to-tail' complex involving association of the aromatic rings of phenoxyl radicals has been proposed to

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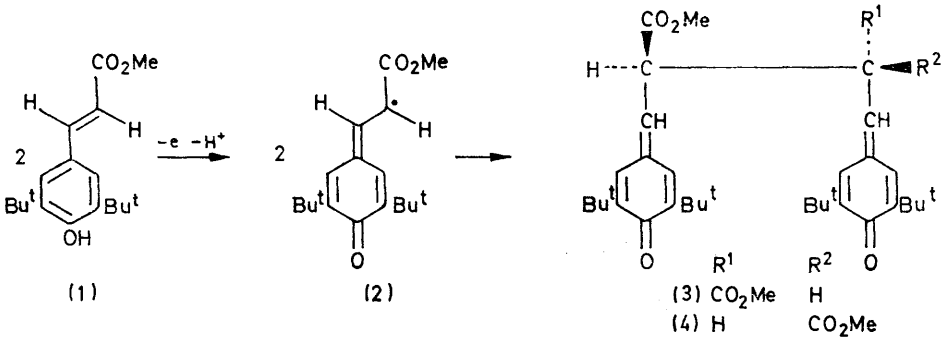
[1] K. V. Sarkanen and A. F. A. Wallis, preceding paper.

explain this stereospecificity.[1] We decided to investigate the effect of bulky ring substituents on the stereochemistry of the β–β oxidative coupling reaction. In this case the bulky substituents might impede the formation of the intermediate complex and thus the oxidation may lead to both *threo*- and *erythro*-products. The methyl (*E*)-cinnamate (1) containing two t-butyl groups was chosen for this study.

Müller *et al.*[2] have already shown that the phenol (1) on treatment with alkaline potassium ferricyanide in a two-phase benzene–water system gives the β–β-coupled bisquinone methide (3) and/or (4) of unspecified configuration. Repetition of this oxidation gave a mixture of the *threo*- and *erythro*-bisquinone methides (3) and (4). In an attempted separation on neutral alumina, the bisquinone methide mixture underwent a prototropic rearrangement to the bisphenol (7) in quantitative yield. This was not unexpected, since the oxidation of phenols analogous to (1) (CN or CHO instead of CO_2Me) has given bisphenols analogous to (7) rather than bisquinone methides.[3] The greater lability of methine protons α to the nitrile and formyl groups in comparison with the ester substituent allows the rearrangements to proceed spontaneously in these cases. Of the three possible isomers for the diene system of the bisphenol (7), two are symmetrical and one is unsymmetrical. Only the symmetrical isomers with the same stereochemistry about the double bonds are likely structures for (7) as each proton has the same chemical shift in both units.



The separation of isomers (3) and (4) was finally achieved by silica gel column chromatography. Hydrogenation of compound (3) in ethanol over 5% Pd–C gave the bisphenol (8), m.p. 107°, whereas the less abundant *erythro*-isomer (4) afforded (11), m.p. 171°, identical with the hydrogenation product described by Müller.[2] The dehydro-dimer (7) on hydrogenation yielded, after a slow uptake of hydrogen, a 1 : 1 mixture of bisphenols (8) and (11). The isomers were separated by crystallization of (11), and chromatography of the mother liquors. A stereochemical proof of configuration of isomers (3) and (4) is given by the following transformations.

Lithium aluminium hydride reduction of the ester (1) afforded the cinnamyl alcohol derivative (5). Oxidation of phenol (5) with 2,4,6-tri-t-butylphenoxyl in benzene [4] yielded the bicyclic dehydro-dimer (6) by direct crystallization of the reaction mixture. An attempt to isolate further reaction products was unsuccessful. The assignment of the aryl groups to the equatorial positions in the ring system of (6) is made on the basis of the similarity of the ring proton n.m.r. signals to those of the lignan sesamin.[5] Hydrogenolysis of compound (6) in methanol containing hydrogen chloride over palladium gave the diol (9) as an oil. As the bridgehead protons in (6) are necessarily *cis*, the diol (9) is the *threo*-isomer. Acid-catalysed dehydration of (9) with 0·1N-hydrogen chloride in boiling methanol afforded the crystalline *trans*-3,4-disubstituted tetrahydrofuran (10).

Reduction of the diester (11) with lithium aluminium hydride gave an oily diol (12), which on acid-catalysed dehydration gave the *cis*-tetrahydrofuran (13), m.p. 164°. Similar reactions of isomer (8) yielded the diol (9) and the same *trans*-tetrahydrofuran (10), m.p. 124°, as was obtained from the bicyclic compound (6). Thus (3) and (4) are the *threo*- and *erythro*-isomers, respectively.

The ratio of the *threo*- and *erythro*-bisquinone methides (3) and (4) formed in the oxidation of phenol (1) was estimated to be 65 : 35 by integration of the H(α) n.m.r. signals at δ 5·96 and 6·25, respectively. That the ratio of isomers is not that of an equilibrium mixture formed by epimerization at C(β) under the alkaline oxidation conditions was demonstrated by oxidation of the phenol (1) with 1 equiv. of 2,4,6-tri-t-butylphenoxyl in benzene [4] to give a mixture of (3) and (4) in the same ratio. The bisquinone methide sample, m.p. 159—163°, described earlier by Müller was evidently a mixture of isomers, which when hydrogenated gave the less abundant, but more easily crystallizable, *erythro*-diester (11).

Thus in contrast to the exclusive formation of *threo*-dimers from the β–β coupling of radicals derived from other (*E*)-propenylphenols, coupling of radicals (2) has indeed given a mixture of *threo*- and *erythro*-isomers. The non-stereospecificity in the coupling of radicals (2) may be attributed to the steric hindrance experienced between bulky t-butyl groups in the approach of aryl

[2] E. Müller, R. Mayer, H.-D. Spanagel, and K. Scheffler, *Annalen*, 1961, **645**, 53.

[3] E. Müller, H.-D. Spanagel, and A. Rieker, *Annalen*, 1965, **681**, 141.

[4] E. Müller and K. Ley, *Chem. Ber.*, 1954, **87**, 922.

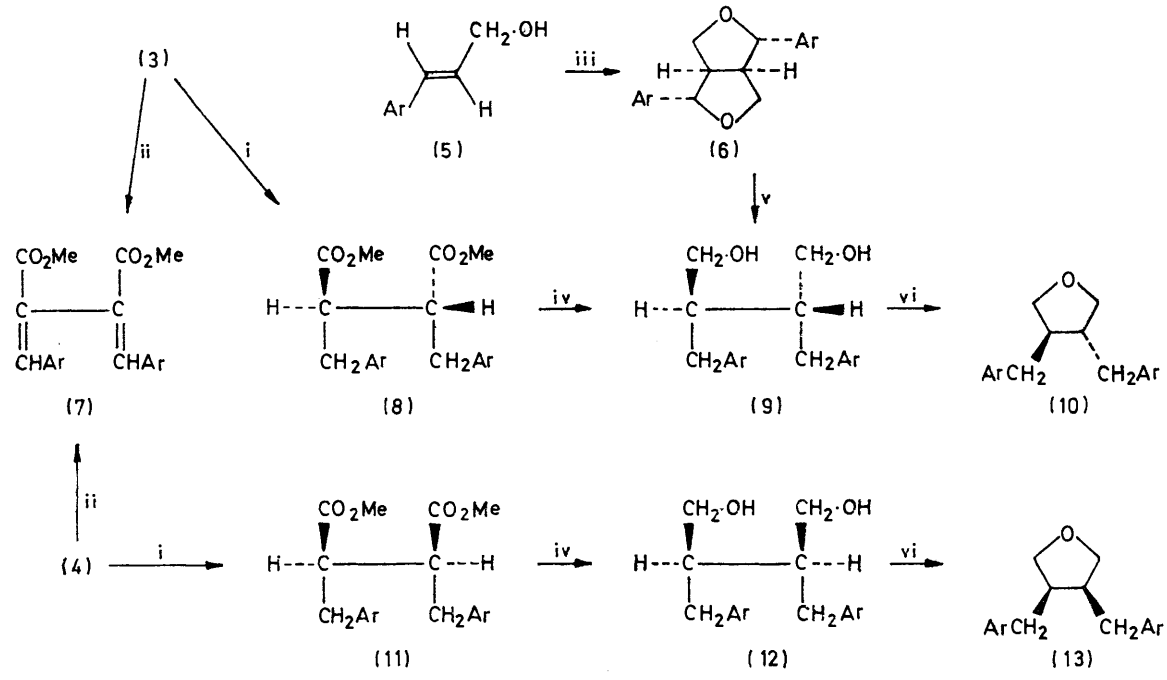
[5] K. Weinges, *Chem. Ber.*, 1961, **94**, 2522.

groups for complex formation which would lead exclusively to *threo*-products. Instead, the coupling process probably involves direct collisions of radicals (2). These results lend further, albeit indirect, support to the proposed existence of short-lived reaction intermediates in the coupling of phenoxyl radicals.[1]

EXPERIMENTAL

General experimental details are as given in the preceding paper.

Methyl (E)-4-*Hydroxy*-3,5-*di*-t-*butylcinnamate* (1).—The ester (1) was prepared by methylation (diazomethane) of



Ar = 3,5-(Bu^t)$_2$-4-HO·C$_6$H$_2$. Reagents: i, Pd-C/H$_2$; ii, Al_2O_3; iii, 2,4,6-tri-t-butylphenoxyl; iv, $LiAlH_4$; v, $PdCl_2$-H_2; vi, MeOH-HCl

quinone methide (3) (550 mg) which crystallized from hexane as *fine needles*, m.p. 161—163°, $\nu_{max.}$ 1740, 1632, 1619, 1258, and 883 cm^{-1}, δ 1·25 and 1·30 (each 18H, s, 2 × CMe$_3$), 3·74 (6H, s, 2 × CO$_2$Me), 4·32 [2H, q, *J* 8 and 2 Hz, 2 × H(β)], 5·96 [2H, q, *J* 8 and 2 Hz, 2 × H(α)], and 6·74 and 7·18 (8H, m, ring H) (Found: C, 74·6; H, 8·7%).

The ratio of isomers (3) and (4) in the crude oxidation mixture was estimated to be 65 : 35 by integration of the H(α) n.m.r. signals.

(b) *With* 2,4,6-*tri*-t-*butylphenoxyl*. To a stirred solution of the phenol (1) (1·0 g) in benzene (100 ml), a solution of the radical[4] in benzene (1·53%; 60 ml, 1 equiv.) was added during 30 min under nitrogen. The blue colour of the radical disappeared immediately. The solvent was evaporated off and the residue crystallized from hexane as yellow needles of isomers (3) and (4), m.p. 157—161°. By integration of the n.m.r. signals due to the CO$_2$Me groups a ratio [(3) : (4)] of 65 : 35 was estimated.

Rearrangement of Bisquinone Methides (3) *and* (4).—A mixture of isomers (3) and (4) (1·5 g) was adsorbed on alumina (80 g) (Woelm, grade III) in benzene. After 24 h the material was eluted with benzene and crystallized from hexane to give prisms of *dimethyl* 2,3-*bis*-4-*hydroxy*-(3,5-*di*-t-*butylbenzylidene*)*succinate* (7) (1·39 g), m.p. 169—170°, $\nu_{max.}$ 3638, 1722, 1630, 1250, 1208, 1159, and 1105 cm^{-1}, δ 1·35 (36H, s, 4 × CMe$_3$), 3·70 (6H, s, 2 × CO$_2$Me), 5·41 (2H, s, 2 × OH), 7·40 (4H, s, ArH), and 7·92 (2H, s, 2 × ArCH) (Found: C, 74·6; H, 8·9. $C_{36}H_{50}O_6$ requires C, 74·7; H, 8·7%).

Hydrogenation of the threo-*Bisquinone Methide* (3).—Isomer (3) (500 mg) in absolute ethanol (50 ml) containing 5% Pd–C (20 mg) was hydrogenated at 1 atm. After 30 min, the yellow colour of (3) was no longer evident.

Further elution with benzene gave the (2RS,3SR)-bis-

the free acid.[6] Crystallization from methanol gave needles, m.p. 115—116° (lit.,[2] 115—116°), δ 1·45 (18H, s, 2 × CMe$_3$), 3·78 (3H, s, CO$_2$Me), 5·50 (1H, s, OH), 6·27 [1H, d, *J* 16 Hz, H(β)], 7·35 (2H, s, ArH), and 7·74 [1H, d, *J* 16 Hz, H(α)].

Oxidation of the Phenol (1).—(a) *With potassium ferricyanide*. The phenol (1) (3·0 g) in benzene (100 ml) was shaken with an aqueous solution (20 ml) containing potassium ferricyanide (8 g) and potassium hydroxide (3 g) for 15 min under nitrogen.[2] The organic layer was washed with water and dried. Evaporation afforded an orange solid (3·05 g), which on crystallization from light petroleum gave fine yellow needles (2·15 g), m.p. 158—161°. Adsorption of this on silica gel (200 g) and elution with benzene afforded (2RS,3RS)-*dimethyl* 2,3-*bis*-(4-*oxo*-3,5-*di*-t-*butyl*-*cyclohexa*-2,5-*dienylidenemethyl*)*succinate* (4) (260 mg) as needles (hexane), m.p. 154—156°, $\nu_{max.}$ 1740, 1630, 1616, 1260, and 880 cm^{-1}, δ 1·28 (36H, s, 4 × CMe$_3$), 3·70 (6H, s, 2 × CO$_2$Me), 4·29 [2H, q, *J* 8 and 2 Hz, 2 × H(β)], 6·25 [2H, q, *J* 8 and 2 Hz, 2 × H(α)], and 6·82 and 7·15 (8H, m, ring H) (Found: C, 74·6; H, 8·7. $C_{36}H_{50}O_6$ requires C, 74·7; H, 8·7%).

[6] T. H. Coffield, A. H. Filbey, G. G. Ecke, and A. J. Kolka, *J. Amer. Chem. Soc.*, 1957, **79**, 5019.

Filtration, evaporation, and crystallization from light petroleum gave fine needles of (2RS,3SR)-*dimethyl* 2,3-*bis*-(4-*hydroxy*-3,5-*di*-t-*butylbenzyl*)*succinate* (8) (320 mg), m.p. 105—107°, $\nu_{max.}$ 3640, 1738, 1239, and 1158 cm^{-1}, δ 1·40 (36H, s, 4 × CMe_3), 2·98 (6H, s, 2 × CH_2·CH), 3·57 (6H, s, 2 × CO_2Me), 5·07 (2H, s, 2 × OH), and 6·95 (4H, s, ArH) (Found: C, 74·6; H, 9·4. $C_{36}H_{54}O_6$ requires C, 74·2; H, 9·3%).

Hydrogenation of the erythro-*Bisquinone Methide* (4).—A solution of compound (4) (100 mg) in absolute ethanol (20 ml) was hydrogenated over 5% Pd–C. The product was crystallized from ethanol to give needles of the (2RS,3RS)-*isomer* (11) of (8) (70 mg), m.p. 170—171°, $\nu_{max.}$ 3640, 1735, 1238, 1158, and 880 cm^{-1}, δ 1·40 (36H, s, 4 × CMe_3), 2·65—3·10 (6H, m, 2 × CH·CH_2), 3·54 (6H, s, 2 × CO_2Me), 5·07 (2H, s, 2 × OH), and 6·94 (4H, s, ArH) (Found: C, 74·0; H, 9·3%).

Hydrogenation of the Dehydro-dimer (7).—The bisphenol (7) (1·2 g) was hydrogenated in absolute ethanol (100 ml) containing 5% Pd–C. After 36 h absorption ceased, the catalyst was removed, and the product crystallized from ethanol to give the *erythro*-bisphenol (11) (510 mg), m.p. 166—170° (recrystallized m.p. and mixed m.p. 170—171°). The mother liquor was evaporated and adsorbed on silica gel (120 g); elution with benzene gave more isomer (11) (40 mg). Continued elution with benzene gave the *threo*-bisphenol (8) (540 mg), needles (light petroleum), m.p. and mixed m.p. 105—107°. The ratio of CO_2Me n.m.r. signals of the crude product indicated a ratio [(8) : (11)] of 1 : 1.

(E)-4-*Hydroxy*-3,5-*di*-t-*butylcinnamyl Alcohol* (5).—A solution of the cinnamic ester (1) (5·0 g) in dry ether (300 ml) was added to a stirred suspension of lithium aluminium hydride (1·5 g) in ether (200 ml) under nitrogen at −10° during 2 h. The resulting yellow complex was decomposed with ammonium chloride solution, and the ether solution was washed with water and dried. Evaporation and crystallization from light petroleum gave the *cinnamyl alcohol* (5) (2·8 g), m.p. 82—84°, $\nu_{max.}$ 3640, 1239, 1156, and 965 cm^{-1}, δ 1·43 (18H, s, 2 × CMe_3), 4·30 (2H, d, *J* 5 Hz, CH_2·OH), 5·25 (1H, s, OH), 5·98—6·5 (2H, m, CH=CH), and 7·25 (2H, s, ArH) (Found: C, 77·7; H, 9·9. $C_{17}H_{26}O_2$ requires C, 77·8; H, 10·0%).

Oxidation of the Cinnamyl Alcohol (5).—A solution of 2,4,6-tri-t-butylphenoxyl [4] in benzene (1·38%; 73 ml, 1 equiv.) was added to a stirred solution of the phenol (5) (1·0 g) in benzene (100 ml) under nitrogen during 1 h. The solvent was evaporated off and the mixture on crystallization from light petroleum gave 1,4-*bis*-(4-*hydroxy*-3,5-*di*-t-*butylphenyl*)*perhydrofuro*[3,4-c]*furan* (6) as plates (330 mg), m.p. 174—175°, $\nu_{max.}$ 3640, 1339, 1237, 1157, and 1062 cm^{-1}, δ 1·45 (36H, s, 4 × CMe_3), 3·18 (2H, m, bridgehead H), 3·88 (2H, q, *J* 9·5 and 3·5 Hz, *ax*-CH_2·O), 4·32 (2H, q, *J* 9·5 and 7 Hz, *eq*-CH_2·O), and 7·20 (4H, s, ArH) (Found: C, 78·0; H, 6·7. $C_{34}H_{50}O_4$ requires C, 78·1; H, 9·6%). Chromatography of the remainder on silica gel gave no pure fractions.

Hydrogenolysis of the Dehydro-dimer (6).—The bicyclic compound (6) (140 mg) in methanol (40 ml) containing palladium chloride (100 mg) was hydrogenated at 1 atm for 2 h. After filtration and removal of the solvent, the resulting oil was adsorbed on silica gel (40 g). The column was first eluted with benzene, then with 20% ether–benzene to give (2RS,3SR)-2,3-*bis*-(4-*hydroxy*-3,5-*di*-t-*butylbenzyl*)-*butane*-1,4-*diol* (9) as an oil (95 mg), $\nu_{max.}$ 3640, 3240, 1318, 1236, 1152, 1120, and 1010 cm^{-1}, δ 1·40 (36H, s, 4 × CMe_3), 1·85 (2H, m, 2-, 3-H), 2·68 (4H, m, 2 × ArCH_2), 3·65 (6H, m, 2 × CH_2·O*H*), 5·05 (2H, s, 2 × OH), and 7·00 (4H, s, ArH) (Found: C, 77·4; H, 10·4. $C_{34}H_{54}O_4$ requires C, 77·5; H, 10·3%).

trans-3,4-*Bis*-(4-*hydroxy*-3,5-*di*-t-*butylbenzyl*)*tetrahydrofuran* (10).—A solution of the *threo*-diol (9) (80 mg) in methanol (50 ml) containing 10N-hydrochloric acid (0·5 ml) was refluxed for 16 h. The solvent was removed and the residue adsorbed on silica gel (30 g). Elution with benzene gave the *trans*-tetrahydrofuran (10) (45 mg), which crystallized from light petroleum as *needles*, m.p. 123—124°, $\nu_{max.}$ 3640, 1360, 1318, 1237, 1152, and 888 cm^{-1}, δ 1·40 (36H, s, 4 × CMe_3), 2·0—2·4 (2H, m, 2-, 3-H), 2·58 (4H, m, 2 × ArCH_2), 3·48 (2H, q, *J* 8 and 6·5 Hz, 2-, 5-H_a), 3·88 (2H, q, *J* 8 and 6 Hz, 2-, 5-H_b), 5·0 (2H, s, 2 × OH), and 6·86 (4H, s, ArH) (Found: C, 80·1; H, 10·1. $C_{34}H_{52}O_3$ requires C, 80·3; H, 10·3%).

Reduction of the Diester (11).—The *erythro*-diester (11) (280 mg) in dry ether (25 ml) was added to a suspension of lithium aluminium hydride (100 mg) in ether (50 ml) at 0° under nitrogen. The solution was stirred for 4 h, and the product was decomposed with ammonium chloride solution. After washing with water, the ethereal solution was dried and distilled and the residue was an oil, identified as (2RS,3RS)-2,3-*bis*-(4-*hydroxy*-3,5-*di*-t-*butylbenzyl*)*butane*-1,4-*diol* (12) (240 mg), δ 1·40 (36H, s, 4 × CMe_3), 2·07 (2H, m, 2-, 3-H), 2·55 (4H, m, 2 × ArCH_2), 3·37 (4H, unresolved d, 1-, 4-H), 3·93br (2H, s, 2 × OH), 5·04 (2H, s, ArO*H*), and 6·95 (4H, s, ArH) (Found: C, 77·3; H, 10·5. $C_{34}H_{54}O_4$ requires C, 77·5; H, 10·3%). The diacetate crystallized from methanol as *needles*, m.p. 155—156°, $\nu_{max.}$ 3640, 1740, 1236, 1155, and 1038 cm^{-1}, δ 1·40 (36H, s, 4 × CMe_3), 1·99 (6H, s, 2 × OAc), 2·25 (2H, m, 2-, 3-H), 2·58 (4H, m, 2 × ArCH_2), 4·08 (4H, d, *J* 5 Hz, 1-, 4-H), 5·03 (2H, s, 2 × OH), and 6·91 (4H, s, ArH) (Found: C, 74·6; H, 9·5. $C_{38}H_{58}O_6$ requires C, 74·7; H, 9·6%).

cis-3,4-*Bis*-(4-*hydroxy*-3,5-*di*-t-*butylbenzyl*)*tetrahydrofuran* (13).—The *erythro*-diol (12) (150 mg) in methanol (50 ml) containing 10N-hydrochloric acid (0·5 ml) was heated under reflux for 18 h. Removal of the solvent, adsorption on silica gel (40 g), and elution with benzene gave the *cis*-tetrahydrofuran (13) (90 mg), which crystallized from light petroleum as *prisms*, m.p. 173—174°, $\nu_{max.}$ 3640, 1362, 1319, 1235, 1153, and 885 cm^{-1}, δ 1·40 (36H, s, 4 × CMe_3), 2·35—2·90 (6H, m, 3-, 4-H and ArCH_2), 3·70 (4H, m, 2-, 5-H), 5·00 (2H, s, 2 × OH), and 6·90 (4H, s, ArH) (Found: C, 79·9; H, 10·2. $C_{34}H_{52}O_3$ requires C, 80·3; H, 10·3%).

Conversion of the threo-*Diester* (8) *into the* trans-*Tetrahydrofuran* (10).—The *threo*-diester (8) (300 mg), treated with lithium aluminium hydride as for isomer (11), afforded the *threo*-diol (9) as an oil (272 mg). Dehydration of diol (9) with methanolic 0·1N-hydrochloric acid gave the *trans*-tetrahydrofuran (10) (120 mg), m.p. and mixed m.p. 123—124°.

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