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REARRANGEMENT OF 3,3-ETHYLENEDIOXY-ISOBORNYL TOSYLATE: AN EFFICIENT NEW SYNTHESIS OF 7-KETOCAMPHENE†

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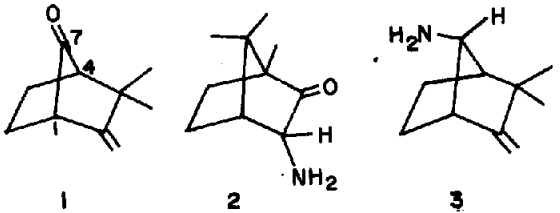
Abstract—A new efficient route to 7-ketocamphene, involving as the key-step, a solvolytic-type rearrangement of 3,3-ethylenedioxyisoborneol (via tosylate) is described. A side-reaction arising from acid-catalyzed fragmentation of 7,7-ethylenedioxycamphene was encountered and has been investigated further. A Baeyer–Villiger type oxidation with dioxane hydroperoxides in the presence of an acid has been noted.

In connection with another project, need arose for comparatively larger quantities of 7-ketocamphene (**1**). The known[1] procedure calls for reduction of α-aminocamphor (**2**) to 3-*endo*-aminoborneol/3-*endo*-aminoisoborneol, followed by rearrangement to 7-*anti*-aminocamphene (**3**), diazotisation and oxidation of the resulting 7-*anti*-hydroxycamphene. This sequence of reactions affords 7-keto-camphene in an overall yield of <15% from camphor. We now report a new‡ simpler route (Fig. 1) leading to **1** in over 60% yield from camphor.



1 **2** **3**

The key-step in the new sequence (Fig. 1) is rearrangement of 3,3-ethylenedioxyisoborneol (**5**), readily available[3] in high yield from camphorquinone (**4**),[4] to the required 7,7-ethylenedioxycamphene (**7**). Treatment of **5** with *p*-toluenesulphonyl chloride in pyridine at 88–90° (40 hr) gave a high yield of the corresponding tosylate (**6**), but no rearrangement took place.[5] However, in refluxing pyridine (56 hr), the desired 7,7-ethylenedioxycamphene (**7**; 55%) as was clear from the spectral characteristics of the product, together with the tosylate **6** (~20%) and unreacted isoborneol **5** (~10%), was formed. The same reaction, when carried out with methane sulphonyl chloride proved more sluggish, only ~10% of **7** having been formed after 24 hr at reflux.

In an effort to improve the yield of **7**, solvolytic-type rearrangement of the readily accessible tosylate **6** in alumina-matrix[6] was investigated. When **6** was adsorbed on Al_2O_3 and allowed to stand at room temp. (~30°) for 48 hr, **7** was formed to the extent of only 10–15%, balance being the unrearranged starting material. In a modification, aimed at hastening the reaction, **6** was stirred with Al_2O_3 in refluxing benzene; this resulted in a much improved yield (~70%) of **7**, together with a new product (~30%). This by-product is assigned structure **8** on the basis of its spectral characteristics. IR: COOR 1735, 1155 cm^{-1}; OH 3450, 1080 cm^{-1}; C=C 1666 cm^{-1}. PMR: two *tert* Me's (3H singlets at 1.01, 1.12 ppm), Me–C=C (3H, s, 1.67 ppm), $-COOCH_2\cdot CH_2OH$ (2H, m, 3.66–3.80 ppm), $-COOCH_2CH_2OH$ (2H, m, 4.11–4.23 ppm), $=C=CH\cdot CH_2$ (1H, bs, 5.3 ppm). Structure **8** was readily confirmed by its saponification to the known[1] **9**. Conceivably, **8** arises from the acid-catalyzed (at the Bronsted/Lewis acid sites of alumina[7]) fragmantation of the 7,7-ethylenedioxycamphene **7**, on the lines depicted in Fig. 2. If this indeed is the pathway to **8**, then it may be possible to suppress this reaction by suitably blocking the acid sites on alumina. In practice, addition of pyridine (20%, on alumina, ω/ω) to the reaction mixture resulted in an excellent yield (88%) of the required **7**.

The susceptibility of **7** to acid-induced fragmentation, as experienced above, was expected to vitiate the next step, viz. deketalisation of **7** to the required 7-ketocamphene (**1**). 7,7-Ethylenedioxycamphene (**7**) offers two sites for protonation. Preferential protonation at the ethylenedioxy moiety may be expected to give rise to the desired 7-ketocamphene (**1**), while protonation at the exocyclic olefinic bond may be expected to trigger the fragmentation reaction. In view of these considerations, exposure of **7** to a variety of acidic environments was investigated. Treatment of **7** with 1 to 4% HCl aq gave varying proportions of **1** and **8**. Interaction of **7** with $BF_3\cdot Et_2O$ led to the exclusive formation of **8**. Treatment with 2N and 6N H_2SO_4 in aq dioxane led solely to the formation of yet another product, which has been formulated as **10**; the basis for this structural assignment will be discussed later. Lactone **10** can arise from both **1** and **8**, the products of acid hydrolysis of ketal **7**. Whereas, unsaturated ester **8** can lactonise with or without the prior formation of acid **9**, 7-ketocamphene must, however, first fragment to the acid **9**. It may be noted that 7-ketocamphene (**1**) may be specially prone to

†MCR Communication No. 16.

‡A *probable* formation of 7-keto-camphene by acid-catalyzed rearrangement of chrysanthenone has also been reported.[2]

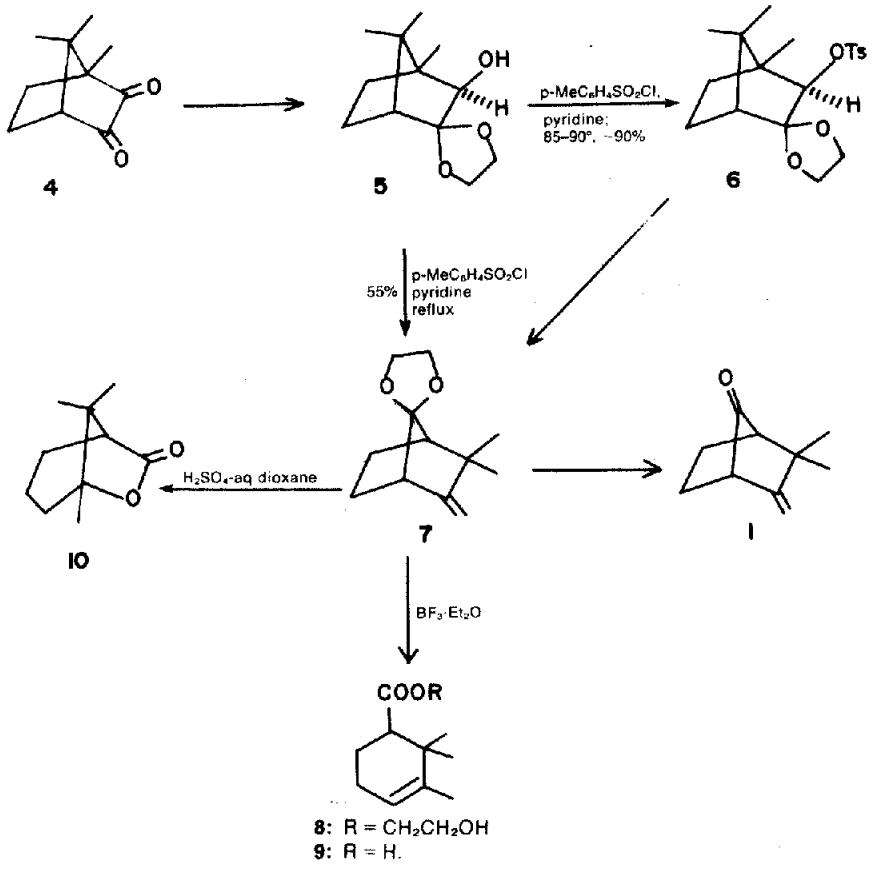


Fig. 1. 7,7-Ethylenedioxycamphene and its dekatalisation.

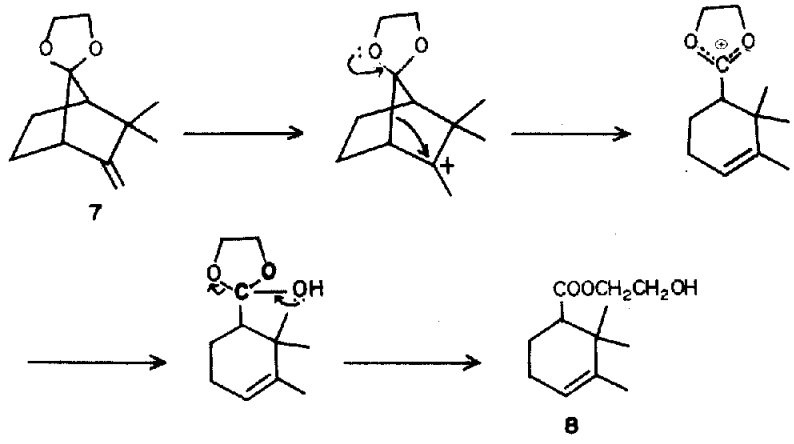
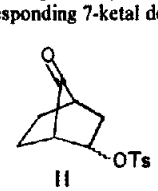


Fig. 2. Possible mechanism of acid-catalyzed fragmentation of 7,7-ethylenedioxycamphene.

†No fragmentation during solvolysis of **11** has been observed,[8,9] though the corresponding 7-ketal does fragment.[10]



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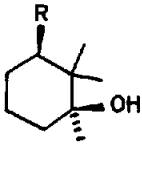
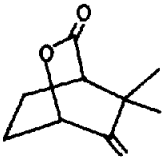
A similar fragmentation, followed by lactonisation has recently[11] been observed in the SbF_5-catalysed rearrangement of 3-*exo*-bromocamphor.

this type of fragmentation,† as the presence of an Sp^2 carbon at C-7 of bicyclo[2,2,1]heptane system would mean widening of the C(1)–C(7)–C(4) angle resulting in greater strain in the molecule.[8] After a series of protracted experiments to evaluate the effect of acid concentration on the above reactions, it was found that lower acid concentrations favour the formation of 7-ketocamphene, while higher acid concentrations favour fragmentation and lactonisation. It was finally found that the action of 0.7% perchloric acid in aq dioxane (42–46°, 56 hr) on **7** resulted in an excellent (95%) yield of the desired 7-ketocamphene (**1**).

That the new product obtained from the interaction of 7 and 2-6N H_2SO_4 in aq dioxane (*vide supra*) has the structure **10**, was essentially clear from its spectral characteristics, especially the presence of an absorption at 1767 cm^{-1} due to the lactone grouping in its IR spectrum and lack of olefinic protons and the presence of a 3H singlet at 1.21 ppm (CH_3–C–O) and 1H singlet at 2.10 ppm (CH·CO) in its PMR spectrum. The structure was further secured by its saponification to the hydroxyacid **12**. IR: OH 3584, 1106 cm^{-1}; CO_2H 1690, 920 cm^{-1}. **12** could be reconverted to the lactone **10** by treatment with methanesulphonyl chloride and pyridine or 6N H_2SO_4 aq. On LAH reduction **10** was converted to the diol **13**. CH_2OH (PMR: 2H, m, 3.39–3.85 ppm).



12: R = CO_2H
13: R = CH_2OH



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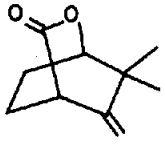

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While repeating the deketalisation of **7**, it was observed that whenever dioxane was contaminated with its hydroperoxides, the resulting 7-ketocamphene underwent some Baeyer–Villiger-type oxidation, leading to a mixture of lactones **14** and **15**. Indeed, **1** on treatment with 2N sulphuric acid in dioxane containing peroxides gave a mixture of **14**, **15** and **10** (~4:1:2 by PMR), which could be separated by chromatography into pure **14** and a mixture of **15** and **10**. The structures of **14** and **15** are based on their spectral characteristics (Experimental). It is noteworthy that under the reaction conditions, no epoxidation of the *exo*-cyclic olefinic bond of **1** took place. This is in contrast to the reaction of 7-ketocamphene (**1**) with peracetic acid in which epoxidation and Baeyer–Villiger-type oxidation products were formed in ratio (PMR) of ~4:1. The synthetic potential of dioxane hydroperoxides for selective Baeyer–Villiger-type oxidation is being explored.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Light petroleum refers to the fraction b.p. 60–80°. All solvent extracts were finally washed with brine and dried (Na_2SO_4).

The following instruments were used for spectral/analytical data: Perkin–Elmer infrared spectrophotometer, model 267; Perkin–Elmer, model R32 (90 MHz) NMR spectrometer; Varian Mat CH7 Mass spectrometer (70 eV, direct inlet system); Hewlett–Packard 5712A and 7624A gas chromatographs (Al columns, 180 cm × 0.6 cm; support, 60–80 mesh chromasorb W; carrier gas, H_2). All PMR spectra were recorded with 15–20% soln in CCl_4 (unless otherwise stated) with TMS as internal reference; signals are reported in ppm (δ); while citing PMR data the following abbreviations have been used: s, singlet; d, doublet; m, multiplet; bs, broad signal. While summarising mass spectral data, besides the molecular ion, ten most abundant ions (*m/e*) are reported with their relative intensities.

Silica gel for column chromatography (−100, +200 mesh) was washed with hot water till sulphate-free, dried, activated at 125–30° for 6–8 hr and standardised.[12] Tlc was carried out on SiO_2-gel layers (0.25 mm) containing 15% gypsum and activated at 110–115° (2 hr).

Reaction of 3,3-*ethylenedioxyisoborneol* (**3**) *with* p-*toluene sulphonyl chloride*

(i) *Formation of* 2-exo-*tosyloxy*-3,3-*ethylenedioxybornane.* A soln of **5**[3] (0.6 g) in 10 ml pyridine containing *p*-toluenesulphonyl chloride (1.7g) was heated at 88–90 for 40 hr. The mixture was cooled to room temp. (~30°) and poured onto crushed ice (30 g) when a crystalline ppt was formed which was filtered off washed with water, dried (5 torr/30°) and crystallised from light petroleum to give 0.91 g (88%) of **6**, m.p. 92–93°. IR (nujol); OTs 1352, 1178 cm^{-1}. PMR: *tert*-Me's singlets at 0.64, 0.79 1.06 ppm; ArMe; 3H, s, 2.45 ppm; O–CH_2–CH_2–O 4H, m, 3.70–3.91 ppm, CH OTs, 1H, s, 4.29 ppm; aromatic H's, 4H, m, 7.25–7.85 ppm (Found: C, 62.26; H, 6.97. $C_{19}H_{26}O_5S$ requires: C, 62.28 H, 7.15%).

(ii) *Dehydrative rearrangement of* **5**. A mixture of **5** (1.20 g) and *p*-toluenesulphonyl chloride (3.0 g) in 25 ml pyridine was refluxed for 56 hr. The mixture was cooled to room temp. and poured with stirring into ice-cold water (200 ml) and extracted with ether (50 ml × 3). The ether extract was washed and dried. Removal of solvent gave 1.1 g of a residue which was chromatographed over 40 g of neutral alumina/IIB (1.5 × 30 cm column).

Frac. 1	light petroleum	50 ml × 3	0.73 g,	essentially **7**
Frac. 2	C_6H_6	50 ml × 2	0.22 g,	essentially **6**
Frac. 3	5% EtOAc in C_6H_6	50 ml × 3	0.15 g,	unreacted **5**

Fraction 1 was distilled to yield **7**, b.p. 82–83°/8 mm (93% pure by glc, 10% Carbowax 20 M, 12'; 160°). IR (liq.): C=CH_2 3040, 1650, 875 CM^{-1}, ketal 1189, 1120, 1079, 1048 cm^{-1}. PMR: *tert*-Me's singlets at 1.08, 1.26 ppm; CH–C=CH_2, 1 H, d, 2.22 ppm, J = 3.5 Hz; O–CH_2 – CH_2–O, 4 H, m, 3.65–3.96 ppm, C=CH_2, two 1 H singlets at 4.58, 4.70 ppm. Mass: *m/e* 194 (M^+, 63%), 179 (41%), 152 (90%), 151 (20%), 113 (19%), 107 (67%), 99 (100%), 94 (52%), 93 (38%), 91 (48%). (Found: C, 73.95; H, 9.18. $C_{12}H_{18}O_2$ requires: C, 74.19; H, 9.34%).

Rearrangement of the tosylate **6**

(i) *At room temperature.* The tosylate **6** (0.1 g) was adsorbed on a dry column of alumina (12 g, grade I) and allowed to stand at room temp. (~30°) for 48 hr. Elution with C_6H_6 gave 76 mg of a crude product, PMR of which indicated it to be a mixture of **6** and **7** (85:15).

(ii) *In refluxing* C_6H_6. A mixture of **6** (2.15 g) and alumina (10 g) in 15 ml of C_6H_6 was refluxed for 24 hr. It was cooled to room temp. and filtered. Alumina was washed with excess C_6H_6 (20 ml × 3). The solvent was removed from the combined organic extracts to get 0.75 g of **7**.

Alumina was further washed with 20% EtOAc in C_6H_6 (10 ml × 3). Removal of solvent furnished 300 mg of a yellow liquid (homogeneous on tlc, SiO_2-gel, EtOAc–C_6H_6, 5:95) which was found to be **8**.

(iii) *In refluxing benzene and in presence of pyridine.* A mixture of **6** (1.0 g) and alumina/I (10.0 g) in C_6H_6 (15 ml) and pyridine (2.0 g) was refluxed for 24 hr. It was worked up as usual to give 0.47 g of **7**.

Saponification of **8**

The hydroxyethyl ester **8** (50 mg) in 10 ml MeOH was mixed with 20% NaOH aq (15 ml) and the contents were refluxed for 12 hr. After dilution with water (50 ml), the mixture was acidified with 3N HCl and extracted with ether (30 ml × 3). The organic layer was washed and dried. Removal of solvent and crystallisation of the residue from light petroleum furnished 30 mg of **7**, m.p. 78.0–80° (lit.[1] m.p. 77.6–78.6°).

Hydrolysis of ketal **7**

(i) *Reaction of* **7** *with* 2N H_2SO_4-*formation of lactone* **10**. 7,7-Ethylenedioxycamphene (100 mg) was dissolved in 20 ml of 2N H_2SO_4 in aq dioxane (40:60, v/v) and stirred at room temp (~30°) for 6 hr. The mixture was neutralised with 5% $NaHCO_3$ aq (5 ml) diluted with water (50 ml) and extracted wither ether (10 ml × 3). The ether layer was washed and dried. Removal of solvent furnished a white solid which was crystallised from li ht petroleum to give 70 mg of **10**, m.p. 107–8° (sealed tube) (95% purity by glc, 5% carbowax 20M, 6', 170°). IR ($CHCl_3$): 3000,

2965, 2885, 1767, 1387, 1272, 1100, 946, 930, 879 cm^{-1}. PMR: *tert*-Me's 6H, s, 1.05; for other signals see text. Mass: *m/e* 168 (M^+ 0.6%), 140 (17%), 125 (11%), 124 (12%), 111 (15%), 109 (37%), 108 (20%), 97 (13%), 83 (16%), 82 (100%). (Found: C, 71.15; H, 9.41. $C_{10}H_{16}O_2$ requires: C, 71.39; H, 9.59%).

Saponification of **10**. The lactone **10** (50 mg) in 10 ml MeOH was mixed with 15 ml of 20% KOH aq. The mixture was refluxed for 12 hr, cooled to room temp. and diluted with water (25 ml). After acidification with 10N HCl (20 ml), it was extracted with ether (20 ml × 3) and the ether layer was dried. Removal of solvent gave 40 mg of **12**, m.p. 105° (light petroleum). PMR: Me's singlets at 1.06, 1.12 ppm, CH_3–C–OH, 3H, s, 1.19 ppm, $CHCO_2H$, 1H, bs 2.55 ppm (Found: C, 64.39; H, 9.53. $C_{10}H_{18}O_3$ requires: C, 64.49; H, 9.74%).

Lactonisation of hydroxy acid **12**. A soln of **12** (10 mg) in 3 ml pyridine containing $MeSO_2Cl$ (20 mg) was refluxed for 2 hr. It was worked up in the usual manner to get 8 mg of a product which was identical with **10** (m.m.p., tlc, IR, PMR).

LAH reduction of lactone **10**. Lactone **10** (50 mg) was reduced with LAH (20 mg) in 20 ml of ether. After usual work up, 40 mg of **13**, m.p. 114° (light petroleum-benzene) was obtained. IR ($CHCl_3$): 3600, 3380, 2925, 1370, 1255, 1010, 995 cm^{-1}. PMR: *tert*-Me's singlet at 0.92, 1.01 ppm; CH_3–C–OH, 3H, s, 1.20 ppm, $-CH_2OH$, 2H, m, 3.39–3.85 ppm (Found: C, 69.32; H, 11.55. $C_{10}H_{20}O_2$ requires: C, 69.72; H, 11.70%).

(ii) *Reaction of* **7** *with* BF_3·Et_2O. BF_3·Et_2O (0.1 ml) was added to a stirred soln of **7** (20 mg) in 20 ml anhydrous ether at 0°. The mixture was stirred for additional 30 min, diluted with water (30 ml) and extracted with ether (20 ml × 3). The ether layer was washed and dried. Removal of solvent furnished 12 mg of **8** which was homogeneous by tlc. Mass: *m/e* 212 (M^+, 17%), 151 (20%), 150 (44%), 123 (44%), 122 (62%), 108 (18%), 107 (100%), 96 (36%), 93 (19%), 91 (18%). (Found: C, 67.97; H, 9.18. $C_{10}H_{20}O_3$ requires: C, 67.89; H, 9.50%).

(iii) *Reaction of* **7** *with* $HClO_4$. A soln of **7** (100 mg) and 70% $HClO_4$ (0.3 ml) in 30 ml of aqueous dioxane (40:60, v/v) was stirred at 42–46° for 56 hr. The mixture was cooled to room temp., neutralised with 5% $NaHCO_3$ aq (20 ml) and extracted with ether (25 ml × 3). The ether layer was washed with brine (10 ml × 3) and dried. Careful removal of solvent furnished the desired **1** in almost quantitative yield (75 mg), m.p. 70–71° (lit.[1] m.p. 55–66°). IR ($CHCl_3$): C=O 1750, 1772 cm^{-1}† lit.[1] IR ($CHCl_3$) C=O 1754 cm^{-1}. PMR: *tert*-Me's singlets at 1.09, 1.24 ppm; C≡C–CH, 1H, d, 2.45 ppm, J = 4.0 Hz; C=CH_2, 1H singlets at 4.80, 4.88 ppm.

†The splitting of C=O stretching absorption of the carbonyl group in such systems due to Fermi resonance has been recognised.[13]

Baeyer–Villiger oxidation of 7*-ketocamphene*

7-Ketocamphene (25 mg) was stirred in 30 ml of 5% H_2SO_4 in aqueous dioxane (40:60, v/v) containing some dioxane hydroperoxides, for 6 hr and worked up in the usual manner. The PMR of the residue indicated it to be mixture of **14**, **15** and **10**. Column chromatography of the product on silica gel (5 g) using benzene and 2% EtOAc in benzene as eluants, provided a mixture of **10** and **15** and pure **14**.

Compound **14**, m.p. 76° (light petroleum/benzene). IR ($CHCl_3$): C=O 1750 cm^{-1}, C=C 3062, 1650, 910 cm^{-1}, PMR: *tert*-Me's singlets at 1.15, 1.22 ppm, –CH–OCO, 1H, d, 4.76 ppm, J = 3.5 Hz; C=CH_2, 1H singlets at 4.95 and 5.09 ppm. Mass: *m/e* 166 (M^+, 16%), 138 (21%), 122 (52%), 109 (23%), 107 (100%), 95 (39%), 94 (21%), 93 (48%), 91 (37%), 79 (59%). (Found: C, 72.04; H, 8.36. $C_{10}H_{14}O_2$ requires: C, 72.26; H, 8.49%).

Compound **15**, PMR (deduced from that of mixture of **10** and **15**): O–COCH–C=CH_2, 1H, bs, 3.07 ppm, –CH–O–CO, 1H, bs, 4.12 ppm; C=CH_2, 1H singlets at 4.88, 5.02 ppm.

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