Journal of Organometallic Chem 177 (1979) 67—74

ON A SULFURATED GRIGNARD REAGENT EQUIVALENT TO THAT OF 2-CHLOROMETHYL-1,3-BUTADIENE NEW SYNTHESES OF IPSENOL (2-METHYL-6-METHYLENE-7-OCTEN-4-OL) AND OF (*E*)-β-FARNESENE ((*E*)-7,11-DIMETHYL-3-METHYLENE-1,6,10-DODECATRIENE) *

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(Received March 27th, 1979)

Summary

Experiments on the synthesis of (3-methylene-4-chloro)butylphenyl sulfide, which is the precursor of the corresponding Grignard reagent, are described With two typical electrophiles, namely isovaleraldehyde and geranyl chloride, this reagent provides the title terpenes in two further simple steps (oxidation to sulfoxides and thermolysis)

Introduction

It has been reported that Grignard or the analogous lithium reagents could not be prepared from 2-bromomethyl-1,3-butadiene [1] ***. The aim of our work was to find an organometallic species which might be a convenient analog of the isoprenyl carbanion (A), useful for the construction of some natural terpenes bearing a terminal isoprene unit. Our plan was to obtain a sulfurated organometallic reagent of type I or II, whose symmetrical allylic system would allow the utilization of various electrophiles The substituted methylenic sulfides (III) thus obtained could then be oxidized into the corresponding sulfoxides (IV) Finally, the thermolysis to afford the substituted isoprene compounds (V) would be facilitated by the presence of two allylic hydrogens.

We initially tried to obtain the lithio derivative (I) by a simple route. It is known that olefins of the general type $R(CH_3)C{=}CH_2$ can be metallated specifically on the methyl group by means of suitable bases [3] However, treatment

* Dedicated to Professor Henri Normant on the occasion of his 72nd birthday on 25th June 1979

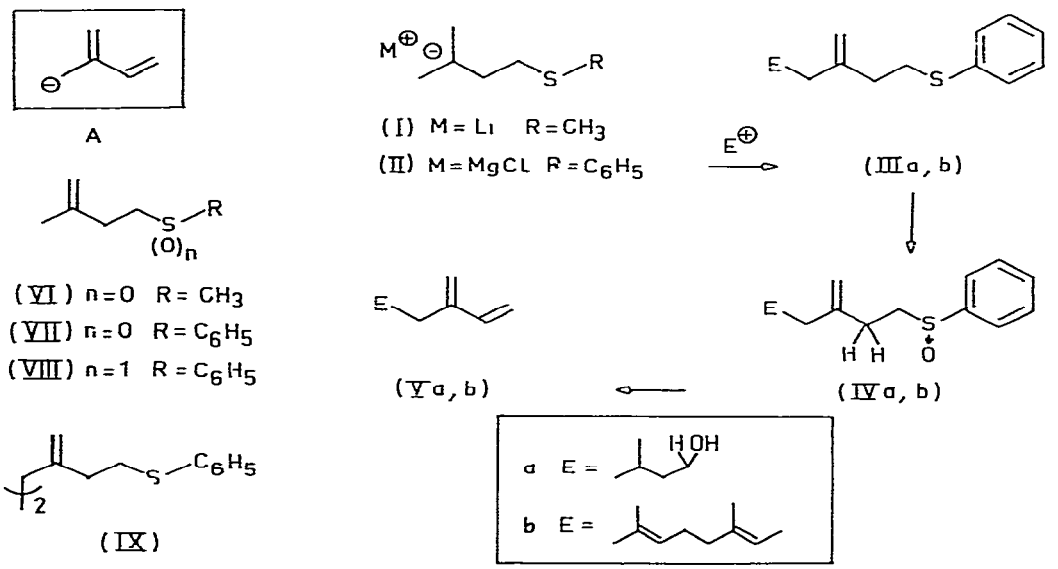
** Part of the doctoral thesis of E Guittet [22]

*** However this bromide could be treated with zinc in the presence of isovaleraldehyde to give ipsenol (Va) which is a pheromone of Ips paraconfusus [2]

of the methallylic sulfide (VI) * with n- or t-butyllithium under various reaction conditions lead to elimination of methanethiolate anion, which was trapped with n-octyl iodide to give methyl-n-octyl sulfide.

This disappointing result led us to undertake a longer but safer route to obtain the new Grignard reagent (II) ** The group R = C_6H_5 was chosen because it is known that phenylsulfinyl derivatives undergo the final elimination reaction at a temperature 70° C lower than that required for the corresponding methyl compounds [6]

SCHEME 1



Procedure

Preparation of the sulfide—chloride (XVI)

We examined three methods for obtaining the alcohol—sulfide (XV). The first route started with the easily accessible [7] sulfurated derivative (X) of Meldrum's acid, which was treated with excess of $LiAlH_4$ *** to give a 36% yield alcohol (XV) of 92% purity.

The second route utilized a procedure [9] previously described for the preparation of α-methylenic esters by reaction of the sodium enolate of the oxalo ester (XI) with gaseous formaldehyde. This afforded 53% of pure ester (XIV)

* At the outset of our work this sulfide was not known to be naturally occurring However Wilson et al. [4] have recently reported that this compound is one of the major scent constituents of red-fox urine. Other recently reported terpenoid sulfur compounds have been found to have a broad significance in mammalian olfaction.

** Grignard reagents from 3-bromopropyl- or 4-bromobutyl-phenyl sulfides have been recently reported [5]

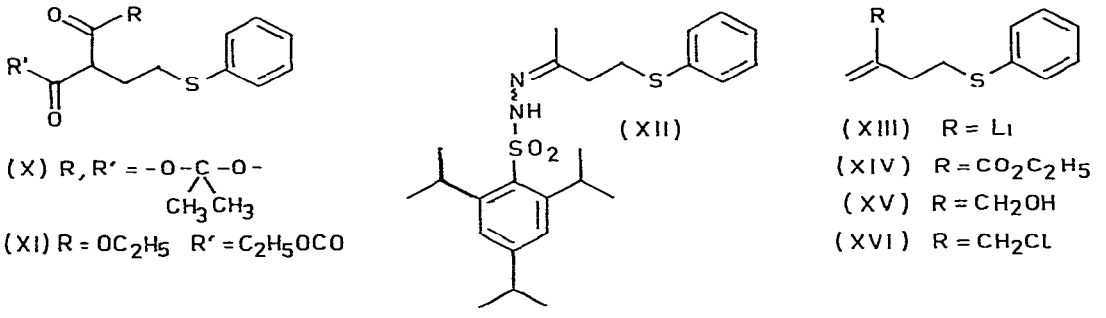
*** Using $LiAlH_4$ cyclic β-diketones have been reduced to allylic alcohols [8]

Selective reduction of the ester group was performed in 70% yield by using diisobutylaluminum hydride

The third and shortest route (overall yield 53%) was the reaction of paraformaldehyde with the new vinyllithium reagent (XIII), which was obtained from the readily accessible trisylhydrazone (XII) following a general procedure [10] recently described

The chloride (XVI) was then formed by a known method

SCHEME 2



Synthesis of ipsenol (Va)

Formation of the Grignard reagent (II) from the chloride (XVI) was most efficiently carried out with activated magnesium [11] * in THF Subsequent reaction with isovaleraldehyde gave the alcohol—sulfide (IIIa) ** in 43% yield The sulfoxide (IVa) obtained (yield 68%) after oxidation with *m*-chloroperbenzoic acid was heated in toluene to give 52% of the pure ipsenol (Va) ***

Synthesis of (E)-β-farnesene (Vb)

To test the reactivity of Grignard reagent II toward alkylating agents, geranyl chloride was chosen, as it could promote the linkage of two C_{10} and C_5 units, leading finally to (*E*)-β-farnesene which is a natural aphid alarm pheromone [14]

When this alkylation was carried out in THF—HMPA § using the reagent II prepared from magnesium turnings §§, a mixture (70/17/13) of the three compounds IIIb, VII and IX was obtained Chromatography on silica gel allowed the separation of only the bis-sulfide IX The oxidation was therefore carried out on an 8/2 mixture of sulfides IIIb and VII to afford the sulfoxides (IVb)

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* The use of magnesium turnings afforded smaller yields (28%) of compound IIIa and also some by-products (VII and IX)

** Compound IIIa could also be obtained (yield 35%) by treatment of 2 6-dimethyl-6-hepten-4-ol first with 2 2 equiv of n-BuLi/TMEDA and then with iodomethylphenyl sulfide

*** Three previous syntheses of ipsenol have been carried out by linking two C_5 units [1 2 12] For other syntheses see ref 13

§ This solvent mixture has been recommended for the stereoselective alkylation of methallylmagnesium chloride with allylic chlorides [15]

§§ Use of the reagent II generated from activated magnesium yielded a crude product But examination by GLC (Se-30) showed the presence of a mixture (8/1/1) of three compounds, namely IIIb an unidentified compound which was probably 3 7-dimethyl-2 6-octadienylphenyl sulfide, and VII.

and (VIII) which were separated by preparative TLC. When heated neat in a distillation tube under vacuum, the sulfoxide IVb yielded the pure (*E*)-β-farnesene (Vb)* in 66% yield, 24% overall yield from the chloride XVI.

Conclusion

The above syntheses** show that the sulfurated Grignard derivative II can be used as a convenient reagent for introducing a terminal isoprene unit into electrophilic carbon centers in two simple steps.

Experimental

Δ³-Isopentenylmethyl sulfide VI

Crude 3-methyl-3-butenol tosylate was treated with thiourea in ethanol under reflux for 3 h. Evaporation of the solvent left a crude isothiouronium salt which was heated with sodium hydroxide (2.2 equiv.) in water under reflux for 1 h. The cold reaction mixture was then stirred with methyl iodide (1.5 equiv.) during 15 h. Usual work up and distillation gave compound VI (yield 32%) b.p. 82°C/130 mmHg, with IR, ^{1}H NMR and mass spectra comparable to those previously reported [4].

Trisylhydrazone, XII

The mixture of *syn* and *anti* isomers (NMR) with m.p. 103—105°C, obtained in 85% yield, by procedure A of ref. 10, was recrystallized from methanol to afford one isomer (yield 70%), m.p. 97—98°C. NMR ($CDCl_3$) δ 1.25 (d, *J* 7 Hz, 18H), 1.78 (s, 3H), 2.46 (t, *J* 8 Hz, 2H), 2.90 (h, *J* 7 Hz, 1H), 3.00 (t, *J* 8 Hz, 2H), 4.25 (h, *J* 7 Hz, 2H), 7.10—7.40 (m, 7H), 7.60 (s, 1H). IR (KBr) 3240, 2950, 2920, 2860, 1640, 1595, 1320, 1168, 1155, 745, 690, 660 cm^{-1}. mass spectrum (*m/e*, %): 460 (M^+), 204 (29), 189 (70), 161 (43), 131 (36), 123 (84), 110 (61), 105 (32), 91 (55), 85 (64), 70 (98), 55 (61), 45 (55), 43 (100), 41 (50).

Ethyl-2-methylene-4-(phenylthio)butanoate XIV

4-Phenylthiobutanoic acid was prepared (yield 52%) from butyrolactone and thiophenol [18] and then esterified (90%) with ethyl *ortho*-formate [19]. Following a general procedure [9], the oxalyl derivative XI was prepared (yield 68%). NMR ($CDCl_3$): δ 1.21 (t, *J* 7.5 Hz, 3H), 1.33 (t, *J* 7.5 Hz, 3H), 2.26 (t, *J* 6.75 Hz, 2H), 3.00 (t, *J* 6.75 Hz, 2H), 3.3—4.2 (m, 1H), 4.17 (q, *J* 7.5 Hz, 2H), 4.33 (q, *J* 7.5 Hz, 2H), 7.30 (bs, 5H). Next, using NaH as a base, the α-methylene ester XIV was prepared (yield 53%), b.p. 101°C/0.003 mmHg. IR 1710, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, *J* 7 Hz, 3H), 2.58 (t with fine struc-

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* The sulfoxide VIII is easily accessible by another straight-forward route and has been used as the starting material for a simple synthesis of (*E*)-hotrienol [16].

** For previous syntheses of β-farnesene see refs. 13a and 17.

*** The same overall yield can be obtained by thermolysis of a mixture of the two sulfoxides IVb and VIII to give β-farnesene and the unchanged sulfoxide VII which may be easily separated by chromatography.

§ The yields have not been optimized.

tuie, J 7 Hz, 2H), 3 08 (t with fine structuie, J 7 Hz, 2H), 4 20 (q, J 7 Hz, 2H), 5.55 (s. 1H), 6 22 (s, 1H), 7 28 (s, 5H), mass spectrum (m/e, %) 236 (M^+, 25), 191 (13), 127 (65), 123 (100), 110 (14), 109 (8), 99 (51), 81 (14), 77 (11), 45 (45)

2-Methylene-4-(phenylthio)butanol, XV

(A) The Meldrum's acid derivative X was prepared by the method of Danishesky and Singh [7], m p 96°C (ether) * (lit [7], m p 150—153°C) NMR ($CDCl_3$) δ 1 70 (s, 6H), 2 35 (td, J 6 Hz, 2H), 3 20 (t, J 7 Hz, 2H) 3 87 (t, J 6 Hz, 1H), 7 1—7 5 (m, 5H), mass spectrum (m/e, %) 280 (M^+, 35), 136 (64), 123 (100), 43 (95) Compound X (16 82 g) was treated with $LiAlH_4$ (7.5 g, 3 3 equiv.) in ether (1050 ml) under reflux for 21 h The usual work up gave a crude product (10 69 g) which was chromatographed on alumina Elutions with pentane containing increasing proportions of ether gave 4 2 g (36%) of alcohol XV (GLC, 97% purity) IR 3400, 3075, 2920, 1650, 1585, 1480, 1440, 1025, 900, 740, 690 cm^{-1}, NMR ($CDCl_3$) δ 2 34 (t, J 7 Hz, 2H), 2 55—3 15 (m, OH), 3 03 (t with fine structure, J 7 Hz, 2H), 4 03 (bs, 2H), 4 92 (bs, 1H), 5 08 (bs, 1H), 7 27 (m, 5H), mass spectrum (combined with GLC, m/e, %) 194 (M^+, 12), 123 (100), 110 (61), 45 (99)

(B) A solution of DIBAH in hexane (2 equiv) was transferred dropwise through a cannula into a stirred and cooled (—78°C) solution of ester XIV (7 92 g, 0 035 mol) in toluene (60 ml), taking care that the inside temperature did not exceed —60°C When the addition was complete, the reaction mixture was stirred at —78°C for 30 min and then hydrolyzed with a saturated solution of ammonium chloride The usual work up gave a crude product which was chromatographed on 240 g of silica gel Elution with petroleum ether/diethyl ether (4/6) gave the alcohol XV (4 51 g, 70%) (GLC, purity better than 95%)

(C) Following the general procedure [10], the trisylhydrazone XII was converted to the vinyllithium reagent XIII which was treated with dry *para*-formaldehyde (2 2 equiv) first at 0°C, then at room temperature for 2 h. The usual work up gave a mixture (GLC) of two compounds, which was separated by chromatography on silica gel Elution with pentane gave 3-butenylphenyl sulfide (20%) IR 3080, 1640, 1440, 990, 915, 740, 690 cm^{-1}, NMR ($CDCl_3$) δ 2 35 (td, J and J' 8 Hz, 2H), 2 98 (t, J 8 Hz, 2H), 5 03 (d, J 12 Hz, 1H), 5 05 (d, J 16 Hz, 1H), 5 86 (ddt, J 12, 16 and 8 Hz, 1H), 7.08—7 50 (m, 5H), mass spectrum (m/e, %)· 164 (M^+, 32) 123 (100), 45 (74) Elution with pentane/ether (7/3) gave the pure alcohol XV (yield 53%)

3-Methylene-4-chlorobutylphenyl sulfide, XVI

This chloride was prepared following the general procedure of ref 20, but with stirring at 0°C for 3 h The crude product was dissolved in methylene chloride and filtered through ten times its weight of silica gel, to afford the pure allylic chloride XVI (yield 82%) IR 1635, 900, 730, 680 cm^{-1}, NMR (CCl_4) δ 2 46 (t, J 8 Hz, 2H), 3 00 (t, J 8 Hz, 2H), 3 95 (s, 2H), 4 98 (s, 1H), 5 15 (s, 1H), 7 00—7 45 (m, 5H), mass spectrum (m/e, %) 214 (8), 177 (78), 123 (60), 110 (48), 109 (25), 45 (100)

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* Recrystallised from diethyl ether to constant m p

(5-Hydroxy-7-methyl-3-methylene)octylphenyl sulfide IIIa

A solution of XVI (3.7 g, 0.0173 mol) in THF (50 ml) was added dropwise (during 3 h) to a suspension in THF of activated magnesium (2 equiv.) prepared from magnesium bromide and potassium [11]. After stirring overnight the reaction mixture was filtered under argon. One fifth of this Grignard solution was cooled at −30°C and treated dropwise with isovaleraldehyde (2 equiv.). The solution was allowed to attain room temperature and was stirred at that temperature for 4 h. The usual work up gave a crude product which was chromatographed on silica gel (30 g). Elution with pentane afforded traces of compound (VII), followed by isovaleraldehyde. Further elution with pentane/ether (9/1) gave 0.44 g (48%) of the sulfide/alcohol IIIa. IR: 3480, 3080, 2960, 2930, 1640, 900, 740, 690 cm^{-1}; NMR ($CDCl_3$): δ 0.89 (d, *J* 5 Hz, 6H), 1.1—2.0 (m, 3H), 1.85 (bs, 1H), 2.0—2.33 (m, 2H), 2.38 (t, *J* 8 Hz, 2H), 3.06 (t with fine structure, *J* 8 Hz, 2H), 3.5—4.08 (m, 1H), 4.96 (s, 2H), 7.33 (m, 5H); mass spectrum (*m/e*, %): 264 (M^+), 246 ($M^+ - H_2O$), 123 (100), 110 (56), 69 (59), 45 (65), 43 (52).

(5-Hydroxy-7-methyl-3-methylene)octylphenyl sulfoxide, IVa

The general method [6] using a slight excess of *m*-chloroperbenzoic acid was followed, and the crude product was chromatographed on silica gel. Elution with pentane/ether (5/5) gave (5-hydroxy-7-methyl-3-methylene)octyl phenyl sulfone (yield 23%). IR: 3500, 3060, 2920, 2860, 1640, 1305, 1150, 895, 745, 690 cm^{-1}; NMR ($CDCl_3$): δ 0.89 (d, *J* 5.5 Hz, 6H), 1.1—2.0 (m, 3H), 2.12 (d, *J* 5 Hz, 2H), 1.9—2.23 (m, 1H), 2.25—2.70 (m, 2H), 3.10—3.53 (m, 2H), 3.55—4.07 (m, 1H), 4.8—5.0 (m, 2H), 7.4—8.2 (m, 5H). Elution with ether gave the sulfoxide—alcohol IVa (yield 68%). IR: 3400, 3070, 2950, 2920, 2860, 1640, 1035, 895, 747, 690 cm^{-1}; NMR ($CDCl_3$): δ 0.88 (d, *J* 5.5 Hz, 6H), 1.1—2.5 (m, 3H), 2.17 (d, *J* 6 Hz, 2H), 2.25—2.70 (m, 2H), 2.99 (t, *J* 7 Hz, 2H), 3.14 (bs, 1H), 3.42—4.1 (m, 1H), 4.93 (s, 2H), 7.42—7.9 (m, 5H). Mass spectrum (*m/e*, %): 186—185, 154, 136 (2), 121 (1), 110 (20), 85 (20), 69 (70), 68 (100), 67 (50).

2-Methyl-6-methylene-7-octen-4-ol (ipsenol), Va

A solution of the sulfoxide IVa (0.210 g) in toluene (10 ml) was heated at 120°C for 15 h and then chromatographed on a column of silica gel (5 g). Elution with pentane gave sulfurated by-products; further elution with pentane/ether (99/1) gave crude ipsenol, which was purified by distillation (0.060 g, 52%). The IR, UV and ^1H NMR spectra were comparable to those previously reported [1,2].

(7,11-Dimethyl-3-methylene)-6,10-dodecadienylphenyl sulfide IIIb

The Grignard reagent II was prepared under argon by dropwise addition of the chloride XVI (2 g) dissolved in THF (16 ml) to a stirred and heated (30°C) mixture of THF (2 ml) and fine magnesium turnings (1.14 g, 5 equiv.), activated with a few drops of 1,2-dibromoethane. After stirring at room temperature overnight, the mixture was decanted. The clear solution was transferred through a cannula and found by titration to be ca. 0.297 *M*. Freshly prepared geranyl chloride [20] (0.560 g) was dissolved in THF (5 ml) and HMPA (5 ml),

cooled to 0°C and treated dropwise with 9 ml of the above Grignard solution. After stirring at room temperature overnight, the reaction mixture was poured into iced aqueous ammonium chloride and extracted with three portions of pentane. The usual work up gave a crude product (1.2 g) which was chromatographed on a column of silica gel (6 g). Elution with pentane gave first 0.81 g of a mixture of the two sulfides IIIb and VII (estimated by NMR 8/2). These sulfides were not separated by preparative thin layer chromatography, mass spectrum with GLC coupling (FFAP 5%, 2 m, 150°C +10°C/min) for VII: 178 (M^+ - 29), 149 (12), 123 (100), 110 (23), 45 (56), for IIIb: 314 (M^+), 123 (89), 93 (42), 81 (37), 69 (100), 41 (68). The yield for IIIb is estimated as ca. 48%. Further elution with pentane/ether (9/1) gave a fraction (0.150 g) which crystallized in cold pentane to afford the dimer (IX), m.p. 41—42°C. IR: 1640, 880, 730, 680 cm^{-1}, NMR (CCl_4): δ 2.13 (s, 4H), 2.30 (t, J 8 Hz, 4H), 2.95 (t, J 8 Hz, 4H), 4.78 (s, 4H), 7.00—7.45 (m, 10H). mass spectrum (*m/e*, %): 354 (M^+), 244, 231, 177, 123 (100), 74, 45.

(7,11-Dimethyl-3-methylene)-6,10-dodecadienylphenyl sulfoxide, IVb

A mixture (8/2) of the two sulfides IIIb and VII (0.55 g) was dissolved in methylene chloride and treated with one equivalent of *m*-chloroperbenzoic acid at —78°C. After 20 min, TLC analysis showed complete disappearance of the starting material. The mixture of sulfoxides (0.57 g) was chromatographed on a preparative thin layer of silica gel, using two elutions with methylene chloride/ether (97/3). The first compound eluted was the pure sulfoxide IVb (0.380 g, 37% overall yield from the chloride XIV). IR: 1640, 1045, 890, 740, 690 cm^{-1}, ^1H NMR ($CDCl_3$, 250 MHz): δ 1.58 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 1.94—2.16 (m, 8H), 2.20—2.55 (m, 2H), 2.80—3.02 (m, 2H), 4.78 (s, 1H), 4.83 (s, 1H), 5.00—5.16 (m, 2H), 7.44—7.70 (m, 5H), ^{13}C NMR ($CDCl_3$): 145.9 (s), 143.6 (s), 135.3 (s), 130.9 (s), 130.6 (d), 128.9 (d), 124.1 (d), 123.2 (d), 110.8 (d), 55.5 (t), 39.7 (t), 36.2 (t), 28.3 (t), 26.8 (t), 26.3 (t), 25.7 (q), 17.8 (q), 16.2 (q), mass spectrum (*m/e*, %): 330 (M^+), 204, 177, 135 (23), 123 (23), 110, 107 (20), 93 (35), 81 (31), 69 (100). The second compound was identified (by IR and NMR) as Δ^3-isopentenylphenyl sulfoxide (VIII) [16].

7,11-Dimethyl-3-methylene-1-(E)-6,10-dodecatriene (β-farnesene), Vb

Pure sulfoxide IVb (0.290 g) was placed in a distillation tube under 1.5 mmHg and heated in an oil bath at 140°C. The distillate collected in the flange (0.128 g, 66% yield) was pure β-farnesene with IR, ^1H- and ^{13}C-NMR and mass spectra comparable to those previously reported [17b,21].

Acknowledgments

The authors gratefully acknowledge support of this work by the C.N.R.S., and by the D.G.R.S.T. through Grant No. 76.7.0361.

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