Thallium in Organic Synthesis. Part II.[1] Oxidation of Steroid Ketones by Thallium(III) Acetate

By **Giorgio Ortar** and **Aurelio Romeo,*** Centro di Studio per la Chimica del Farmaco del CNR, Istituto di Chimica Farmaceutica dell'Università, 00185 Rome, Italy

The action of thallium triacetate on several steroid ketones has been investigated. It was established that three distinct oxidation modes are involved, namely an acetoxylation, a dehydrogenation, and a rearrangement of the carbon skeleton.

OXIDATIONS of a variety of substrates by thallium(III) salts have been extensively investigated. Nevertheless, most of this work has been concerned with olefins as substrates and only a few papers deal with the oxythalliation of cyclic ketones.[2] There are only two reports of reactions of steroid substrates with thallium(III) salts, both involving olefin oxidations.[3] In Part I [1] we reported, together with results on a variety of steroidal αβ-unsaturated ketones, an example of ring contraction of cholestan-3-one, and we have now investigated the oxidation of a number of steroid ketones (1-, 2-, 4-, 6-, 7-, 11-, 12-, 17-, and 20-oxo-, and 3-oxo-Δ^5-derivatives) with thallium triacetate in hot acetic acid. Reactions generally gave complex mixtures and only major products were isolated. Yields are thus only moderate (*ca.* 30%). We found that three modes of reaction predominate in these oxythalliations, namely acetoxylation, dehydrogenation, and rearrangement of the carbon skeleton. The results are summarized in the Scheme.

The 1- and 7-ketones behaved similarly giving αβ-unsaturated ketones and ring-contracted products in comparable yields. Thus cholestan-1-one (1) [4] afforded cholest-2-en-1-one (2) [4,5] and A-norcholestane-1α-carboxylic acid (3) in 28 and 27% yield, respectively. Confirmation of the structure of (3) was obtained by converting it into the known A-norcholestan-1-one [4,6] *via* a Schmidt reaction. The carboxy-group was expected to have the α-configuration on mechanistic grounds, since oxythalliation should take place from the less hindered α-side of the molecule and proceed through the scheme postulated by Wiberg,[2d] or according to the modification proposed by McKillop and Taylor.[2e] In fact the methyl ester of (3) is different from methyl-A-norcholestane-1β-carboxylate obtained by Cava and Vogt.[4] The unsaturated ketone (2) probably arises from a thallium enolate [see (A)], since an equatorial 2α-Tl^{III} adduct is unsuitable for 1,2-elimination and a 2β-configuration, which would favour diaxial elimination, is unlikely because of steric opposition by the 10-methyl group.

In the same way 3β,17β-diacetoxyandrostan-7-one (6) [7] gave 3β,17β-diacetoxyandrost-5-en-7-one (8) [7] and 3β,17β-diacetoxy-B-norandrostane-6α-carboxylic acid (10) in 25 and 27% yield, and 3β-acetoxycholestan-7-one (7) [8] afforded 3β-acetoxycholest-5-en-7-one (9) [9] and 3β-acetoxy-B-norcholestane-6α-carboxylic acid (11) in 26 and 28% yield. Compounds (10) and (11) were identified on the basis of reaction pathway for the 1- and 3-ones.†

Oxidation of cholestan-2-one [10] (4) gave as major product (26% yield) an unexpected acetoxy-ketone different from the 1β-,[11] 3α-,[12] and 3β-[12] acetoxy-compounds and therefore considered to be the hitherto unknown 1α-acetoxycholestan-2-one (5). This assignment was supported by the following data: (*a*) the

† The shorter reaction time and the preference for ring contraction (83%) in the case of cholestan-3-one (in comparison with the 1- and 7-ones) may be due to the greater accessibility of the Δ^2-enol.

[1] Part I, A. Romeo and G. Ortar, *Tetrahedron*, 1972, **28**, 5337.

[2] (*a*) H. J. Kabbe, *Annalen*, 1962, **654**, 204; (*b*) S. Uemura, T. Nakano, and K. Ichikawa, *J. Chem. Soc. Japan*, 1967, **88**, 1111; (*c*) J. S. Littler, *J. Chem. Soc.*, 1962, 827; (*d*) K. B. Wiberg and W. Koch, *Tetrahedron Letters*, 1966, 1779; (*e*) A. McKillop, J. D. Hunt, and E. C. Taylor, *J. Org. Chem.*, 1972, **37**, 3381; (*f*) J. Salaun, B. Garnier, and J. M. Conia, *Tetrahedron*, 1974, **30**, 1423.

[3] B. Cocton and A. C. de Paulet, *Bull. Soc. chim. France*, 1966, **9**, 2947; A. McKillop, J. D. Hunt, F. Kienzle, E. Bigham, and E. C. Taylor, *J. Amer. Chem. Soc.*, 1973, **95**, 3635.

[4] M. P. Cava and B. R. Vogt, *J. Org. Chem.*, 1965, **30**, 3775.

[5] C. Djerassi, D. H. Williams, and B. Berkoz, *J. Org. Chem.*, 1962, **27**, 2205.

[6] H. P. Sigg and Ch. Tamm, *Helv. Chim. Acta*, 1960, **43**, 1402; B. Fuchs and H. J. E. Loewenthal, *Tetrahedron*, 1960, **11**, 199.

[7] K. Heusler and A. Wettstein, *Helv. Chim. Acta*, 1952, **35**, 284.

[8] O. Wintersteiner and M. Moore, *J. Amer. Chem. Soc.*, 1943, **65**, 1503.

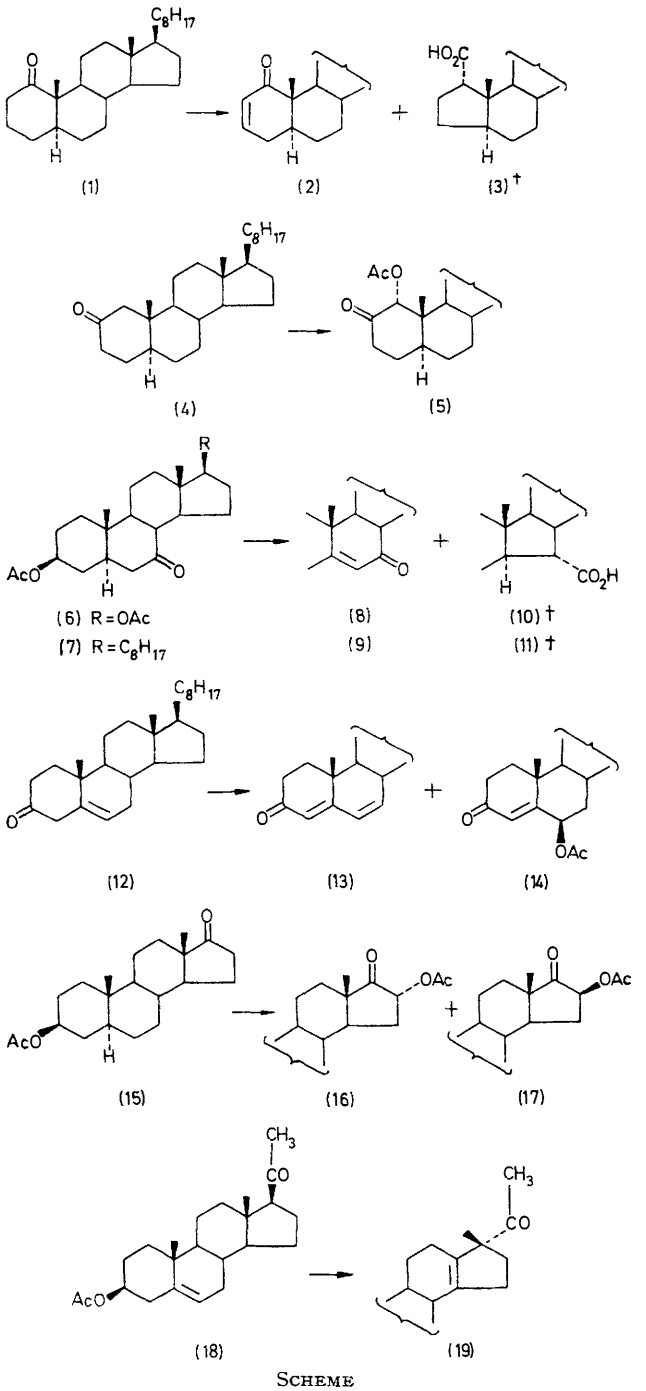
[9] W. G. Dauben and G. J. Fonken, *J. Amer. Chem. Soc.*, 1956, **78**, 4736.

[10] U.S.P. 3,415,816 (*Chem. Abs.*, 1969, **70**, 58134h).

[11] T. Nakano, M. Hasegawa, and C. Djerassi, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 465.

[12] (*a*) H. B. Henbest, D. N. Jones, and G. P. Slater, *J. Chem. Soc.*, 1961, 4472; (*b*) K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, 1961, **26**, 4563.

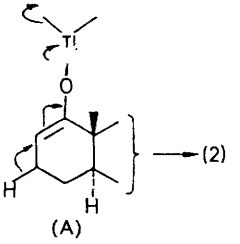
^{1}H n.m.r. spectrum showed the signal at δ 4.66 as a singlet broadened by coupling (*J* 2.5 Hz calculated from



SCHEME

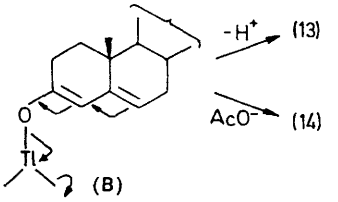
† Characterized as the methyl esters.

the peak width at half height) through the carbonyl group to the equatorial 3β-proton; [13] and (*b*) compound (5) was converted into cholest-1-ene [14] *via* Wolff–Kishner reduction. Since enolisation of 2-oxo-steroids has been observed to proceed towards C-3,[11,12,15] cholest-3-en-2-one and 3α-acetoxycholestan-2-one would have been the expected products (*via* thallium attack on the α-side or *via* a thallium enolate). In fact boron trifluoride-catalysed reaction of (4) with lead tetra-acetate gives the 3α-acetoxy-derivative.[12a,*] Migration of an



initially formed 3α-acetoxycholestan-2-one was excluded since this compound was largely unchanged when treated with thallium triacetate for 15 h at 80 °C. Further investigations are needed to clarify this point.

The easily enolised βγ-unsaturated ketone, cholest-5-en-3-one (12) reacted completely in 2 h (*cf.* a minimum of 15 h for the other ketones). Two products were obtained: cholesta-4,6-dien-3-one (13) [16] (23% yield) and 6β-acetoxycholesta-4-en-3-one (14) [17] (36% yield), both probably arising from the same thallium adduct [see (B)]. It must be emphasized that stereospecific axial 6β-acetoxylation is a normal reaction path, in contrast to the attack at C-4 that occurs with lead tetra-acetate to give 4α-acetoxycholest-5-en-3-one,[18] indicating greater tendency of lead adducts to decompose, with intramolecular donation of an acetoxy-group.[19]



The 4- and 6-ones, exemplified by cholestan-4-one and 3β-acetoxycholestan-6-one, both afforded complex reaction mixtures of about ten products, none predominant, which were not further examined.

The 11- and 12-ketones appeared to be unreactive towards thallium triacetate, probably on account of steric hindrance. Thus methyl 3α-acetoxy-12-oxocholanate (20),[20] 3β,17β-diacetoxy-5α-androstan-11-one

* The same product is obtained by carrying out the reaction without catalyst at 80 °C for 2.50 h.

[13] K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, 1961, **83**, 4623; N. S. Bhacca and D. H. Williams, 'Applications of N.m.r. Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field,' Holden-Day, San Francisco, 1964, p. 121.

[14] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1956, 3289.

[15] H. B. Henbest, G. D. Meakins, and G. W. Wood, *J. Chem. Soc.*, 1954, 800; C. Djerassi and T. Nakano, *Chem. and Ind.*, 1960, 1385.

[16] F. Sondheimer, C. Amendolla, and G. Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 5932.

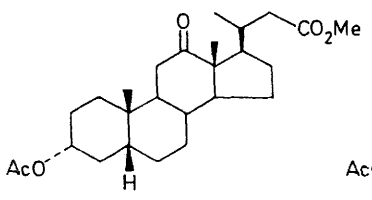
[17] L. F. Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4377.

[18] L. F. Fieser and R. Stevenson, *J. Amer. Chem. Soc.*, 1954, **76**, 1728.

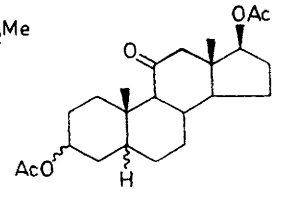
[19] E. J. Corey and J. P. Schaeffer, *J. Amer. Chem. Soc.*, 1960, **82**, 918.

[20] E. Schwenk, B. Riegel, R. B. Moffett, and E. Stahl, *J. Amer. Chem. Soc.*, 1943, **65**, 549.

(21),[21] and 3α,17β-diacetoxy-5β-androstan-11-one (22) [22] were largely unchanged after treatment for 38 h.*



(20)



(21) 3β-OAc, 5α-H
(22) 3α-OAc, 5β-H

In the case of 3β-acetoxyandrostan-17-one (15), the predominant reaction pathway observed was acetoxylation to give 3β,16α-diacetoxyandrostan-17-one (16) [23] and its 16β-epimer (17),[23] in similar yields (26 and 23%). Both acetoxy-ketones, treated with thallium triacetate under the same conditions as used for acetoxylation, were unchanged; both compounds must therefore arise from oxythalliation of the oxo-acetate (15), *via* a Δ^{16}-enolate. Neither ring contraction (as observed by Wiberg with cyclopentanone [2d]) nor dehydrogenation occurred, probably because of strain due to the unsaturated centre in the five-membered cyclic system.

Finally a Wagner–Meerwein type of rearrangement was found to occur predominantly with 3β-acetoxypregn-5-en-20-one (18). 3β-Acetoxy-17β-methyl-18-nor-17α-pregna-5,13-dien-20-one (19) was obtained as the major product † (30% yield), from attack on the more stable $\Delta^{17,(20)}$-enol, in contrast to the kinetically controlled acetoxylation at C-21 in the reaction with lead tetra-acetate.[24]

EXPERIMENTAL

Thallium triacetate was prepared by the method of Kochi and Bethea.[25] M.p.s were determined with a Kofler hot-stage apparatus. Optical rotations were taken at 20 °C with a Schmidt–Haensch polarimeter (1 dm cell). Where appropriate, identities of compounds were confirmed by comparison of i.r. spectra (KBr discs; Perkin-Elmer 521 grating spectrophotometer). ^{1}H N.m.r. spectra were measured for solutions in $CDCl_3$ (Me_4Si as internal standard) with a Varian HA-100 spectrometer. Preparative layer chromatography (p.l.c.) was carried out with Merck HF_{254} silica gel (layers 0.5 mm thick).

General Procedure for Oxidation of Steroidal Ketones with Thallium Triacetate.—A solution of the oxo-steroid (1 mmol) and thallium triacetate (3 or 4 mmol) in glacial acetic acid (1 ml for every 0.2 g of thallium triacetate) was heated with stirring at 80 °C. The oxidation was followed by t.l.c. The mixture was cooled, diluted with water, and extracted with ether three times, and the ether layers were washed to neutrality, dried (Na_2SO_4), and evaporated.

Oxidation of Cholestan-1-one (1).—The ketone (1) (802 mg) and the thallium salt (3.35 g) (molar ratio 1 : 4) in acetic acid (16.8 ml) reacted for 75 h. The residue from the ethereal extract was chromatographed on silica (p.l.c.) [elution with benzene–hexane (1 : 1)] giving unchanged cholestan-1-one (93 mg), cholest-2-en-1-one (2) (226 mg, 28%), m.p. 60° (from MeOH), $[\alpha]_D$ +128° (*c* 1.0 in $CHCl_3$), identical with an authentic sample,[4,5] and a crude acid (3) (185 mg, 27%) which was directly esterified with ethereal diazomethane. Chromatography of the crude ester (185 mg) on silica (p.l.c.) and extraction of the major band gave *methyl* A-*norcholestane-1α-carboxylate* (95 mg), m.p. 76.5—77° (from MeOH), $[\alpha]_D$ +85.5 (*c* 1.0 in $CHCl_3$) (Found C, 80.8; H, 11.55. $C_{28}H_{48}O_2$ requires C, 80.7; H, 11.6%).

Schmidt degradation [4] of the acid (3) (235 mg) gave A-norcholestan-1-one [4,6] (80 mg), m.p. 83.5—85° (from MeOH), $[\alpha]_D$ +11 (*c* 1.0 in $CHCl_3$), $\lambda_{max.}$ 5.79 μm (cyclopentanone C=O).

Oxidation of Cholestan-2-one (4).—The ketone (4) (734 mg) and the thallium salt (2.50 g) (molar ratio 1 : 3) in acetic acid (12.5 ml) were heated for 17 h. Chromatography of the residue from the ethereal extract on silica (p.l.c.) with benzene–ether (98 : 2) gave the major component (226 mg), which, rechromatographed as above, yielded finally 1α-*acetoxycholestan-2-one* (5) (190 mg, 26%), m.p. 149—150° (from MeOH), $[\alpha]_D$ +81.5 (*c* 1.0 in $CHCl_3$), $\lambda_{max.}$ 5.75, 5.85, 8.20, and 9.70 μm, δ 0.65 (3 H, s, 13-Me), 0.76 (3 H, s, 10-Me), 2.10 (3 H, s, 1α-OAc), and 4.66br (1 H, *J* 2.5 Hz, 1β-H) (Found: C, 78.25; H, 10.75. $C_{29}H_{48}O_3$ requires C, 78.3; H, 10.9%).

Wolff–Kishner reduction [26] of the ketone (5) (160 mg) gave an oil (132 mg) which was chromatographed on a column of neutral Woelm alumina (activity I; 15 g). Elution with light petroleum (b.p. 30—50°) afforded cholest-1-ene (80 mg), m.p. 67—68° (from acetone), $[\alpha]_D$ +12° (*c* 1.0 in $CHCl_3$), identical with an authentic sample.[14]

Oxidation of Cholest-5-en-3-one (12).—Compound (12) (513 mg) and thallium triacetate (1.62 g) (molar ratio 1 : 3), in acetic acid (8.1 ml) for 2 h, gave, after conventional work-up (537 mg of residue) and p.l.c. [benzene–ether (95 : 5) as eluant] cholesta-4,6-dien-3-one (13) (118 mg, 23%), m.p. 81.5—82° (from MeOH), $[\alpha]_D$ +30° (*c* 1.0 in $CHCl_3$), identical with a specimen obtained by oxidation of cholesterol with manganese dioxide,[27] and 6β-acetoxycholest-4-en-3-one (14) (183 mg, 36%), m.p. 102° (from MeOH), $[\alpha]_D$ +35° (*c* 1.0 in $CHCl_3$), identical with an authentic sample.[28]

Oxidation of 7-Ketones.—3β,17β-Diacetoxyandrostan-7-one (6) (320 mg) and thallium triacetate (1.04 g) (molar ratio 1 : 3) in acetic acid (5.2 ml) reacted for 24 h to give, after p.l.c. [benzene–ether (85 : 15) as eluant], starting material (73 mg), 3β,17β-diacetoxyandrost-5-en-7-one (8) (82 mg, 25%), m.p. 224.5—225° (from AcOEt) identical with an authentic sample,[7] and an acidic material (85 mg, 27%) which, esterified with ethereal diazomethane and

* The conformation adopted by the side chain in (20) may be important in preventing oxythalliation.

† Under these conditions a 5,6-double bond does not react appreciably.

[21] H. Heusser, K. Heusler, K. Eichenberger, C. G. Honegger, and O. Jeger, *Helv. Chim. Acta*, 1952, **35**, 295; A. Bowers and E. Denot, *J. Amer. Chem. Soc.*, 1960, **82**, 4956.

[22] L. H. Sarrett, *J. Amer. Chem. Soc.*, 1947, **69**, 2899; J. Warnant, R. Yoly, J. Mathieu, and L. Velluz, *Bull. Soc. chim. France*, 1957, 331; S. Libermann, D. K. Fukushima, and K. Dobriner, *J. Biol. Chem.*, 1950, **182**, 299.

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[24] J. D. Cocker, H. B. Henbest, G. H. Philips, G. P. Slater, and D. A. Thomas, *J. Chem. Soc.*, 1965, 6.

[25] J. K. Kochi and T. W. Bethea, *J. Org. Chem.*, 1968, **33**, 75.

[26] H. Heymann and L. F. Fieser, *J. Amer. Chem. Soc.*, 1951, **73**, 5252.

[27] F. Sondheimer, C. Amendolla, and G. Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 5932.

[28] L. F. Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4377.

purified further by p.l.c., gave *methyl* 3β,17β-*diacetoxy*-B-*norandrostane*-6α-*carboxylate* (50 mg), m.p. 133—134° (from light petroleum), $[\alpha]_D$ −26° (*c* 1.0 in $CHCl_3$) (Found: C, 68.5; H, 8.65. $C_{24}H_{36}O_6$ requires C, 68.55; H, 8.65%). Similarly 3β-*acetoxycholestan*-7-*one* (7) (888 mg) and thallium triacetate (3.31 g) (molar ratio 1 : 4) in acetic acid (16.5 ml) for 39 h yielded, after p.l.c. [benzene–ether (9 : 1)] 3β-acetoxycholest-5-en-7-one (9) (229 mg, 26%), m.p. 151—152° (from MeOH), identical with an authentic sample,[9] and crude 3β-acetoxy-B-norcholestane-6α-carboxylic acid (11) (254 mg, 28%) which esterified, and rechromatographed (p.l.c.) gave the *methyl ester* (150 mg), m.p. 125—125.5° (from MeOH), $[\alpha]_D$ −78° (*c* 1.0 in $CHCl_3$) (Found: C, 75.8; H, 10.55. $C_{30}H_{50}O_4$ requires C, 75.9; H, 10.6%).

Oxidation of 3β-*Acetoxyandrostan*-17-*one* (15).—The ketone (15) (0.67 g), treated with thallium triacetate (3.40 g) (molar ratio 1 : 4) in acetic acid (17 ml) for 20 h, gave, after p.l.c. (several runs from benzene), 3β,16α-diacetoxyandrostan-17-one (16) (171 mg, 26%), m.p. 186—187° (from MeOH), and the 16β-epimer (17) (157 mg, 23%), m.p. 156—158° (from light petroleum), both identical with authentic samples.[23] Each epimer (26 mg) was largely unchanged after treatment for 18 h with thallium triacetate (0.13 g) at 80 °C.

Oxidation of 3β-*Acetoxypregn*-5-*en*-20-*one* (18).—The ketone (18) (2.15 g) and thallium triacetate (8.60 g) (molar ratio 1 : 3) in acetic acid (43 ml) reacted for 15 h. The residue from the ethereal extract was saponified with methanolic 5% sodium hydroxide at room temperature for 2 h. The residue from ethyl acetate extraction was chromatographed on a column of deactivated (grade II) Woelm neutral alumina (100 g) [elution with CH_2Cl_2–AcOEt (9 : 1)] to afford crude 3β-*hydroxy*-17β-*methyl*-18-*nor*-17α-*pregna*-5,13-*dien*-20-*one* (0.77 g, 30%), m.p. 147—148° (from di-isopropyl ether), $[\alpha]_D$ +30° (*c* 1.0 in $CHCl_3$), identical with an authentic sample.[29] Acetylation of 0.20 g of this compound (Ac_2O–pyridine) gave the 3β-*acetoxy-derivative* (19) (0.22 g), m.p. 131—132°, $[\alpha]_D$ +32° (*c* 1.0 in $CHCl_3$), δ 1.02 (3 H, s, 10-Me), 1.17 (3 H, s, 17β-Me), 2.03 (3 H, s, 3β-OAc or 20-Me), 2.05 (3 H, s, 20-Me or 3β-OAc), 4.6 (1 H, m, 3α-H), and 5.4 (1 H, m, C=CH) (Found: C, 77.5; H, 9.15. $C_{23}H_{32}O_3$ requires C, 77.5; H, 9.05%).

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