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OXIDATION OF THE α-KETOL AND ENONE DERIVATIVES OF CYCLOHEXANONE BY TETRAZOLIUM SALTS

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Abstract: A new red-ox reaction, leading to the respective keto derivatives from α-ketol and enone derivatives of cyclohexanone, is reported.

In our earlier papers[1-4] we have described new reaction of oxidation of isoprenoids with α-ketol or enone groups by compounds with thermodynamically reversible red-ox potentials. We found that, in one-step reactions, it is possible to obtain high yields of the respective steroid hydroxyacids as well as keto and hydroxy isoprenoid derivatives. When studying the mechanism of these reactions of oxidation of isoprenoids, the steric structure of the substrates was found to affect strongly the course of the processes and consequently the yields of the products.

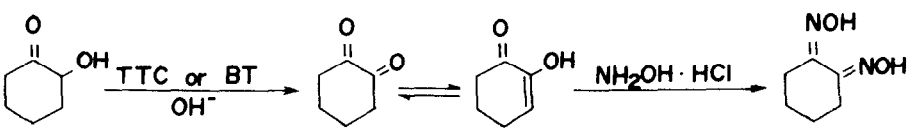
In the present paper, we report results concerning the oxidation of simple cyclic compounds containing an α-ketol or enone group, unhindered sterically by other substituents. As model compound we applied: Cyclohexane-2-ol-1-one (adipoin) - **1** ; Cyclohex-2-en-1-one - **2** ; 3-Methyl-cyclohex-2-en-1-one - **3** ; 5.5-Dimethyl-cyclohex-2-en-1-one - **4** . As oxidizers with reversible red-ox potential we used 2.3.5-triphenyltetrazolium chloride (TTC) and blue tetrazolium (BT). These compounds, hitherto known as analytic reagents e.g. in cytochemistry[5] have proved to be the most convenient oxidizers with respect to yield and relatively easy separation of coloured products of their reduction from the products of oxidation of the model compounds.

Oxidation of the α-ketol compound **1** : The compound **1** (8.8mmol) and the tetrazolium salt (9mmol of TTC or BT) were dissolved in hot ethanol (200ml) A stream of oxygen-free nitrogen was made to flow over the solution. A solution of KOH (3.5g) in water (10ml) was added (KOH concentration of the reaction solution: 0.3 normal). The mixture was maintained at 60°C for 15 min., a 30% solution of KOH in water (100ml) was then added, and the mixture cooled to ~5°C. The precipitated, coloured formazans (reduction products of tetrazolium salt) were removed by filtration. The filtrate was extracted with benzene and ether in order to remove formazan residues and traces of unreacted tetrazolium salt. The solution was then acidified by adding conc. hydrochloric acid and exhaustively extracted with chloroform. The combined chloroform

extracts were evaporated to dry, and the crude product 1a was subjected to purification in a chromatographic column (silica gel, ethanol-water 4:1) and crystallized from ethanol-ether.

Oxidation of the enone compounds 2 , 3 , 4 , (General Procedure) : 0.01 mole of the respective enone and 0.01 mole of tetrazolium salt (TTC or BT) were mixed in a reaction flask. The latter was blown through with oxygen-free nitrogen. Next, a 2N solution of KOH in 95% ethanol (200ml) was added. The solution was subjected to intense mixing with a magnetic stirrer and heated at boiling temperature for 20 min. On conclusion of the reaction, a 30% aqueous solution of KOH (30ml) was added and the mixture cooled to ~0°C. The precipitated formazans and water-insoluble compound 2c were removed by filtration. The filtrate was extracted with benzene to remove residual formazans and insoluble product 2c . The solution after benzene extraction was acidified by adding conc. hydrochloric acid and then extracted with CH_2Cl_2. The combined extracts were dried and evaporated to dry at ~1mm and 0°C yielding, respectively, the crude products 2a , 3a and 4a . Purification of 2a and 3a were achieved by sublimation, and of 4a in a chromatographic column (silica gel, $CHCl_3$-CH_2Cl_2). 2c was separated from the formazans in a column (silica gel, ether, twice).

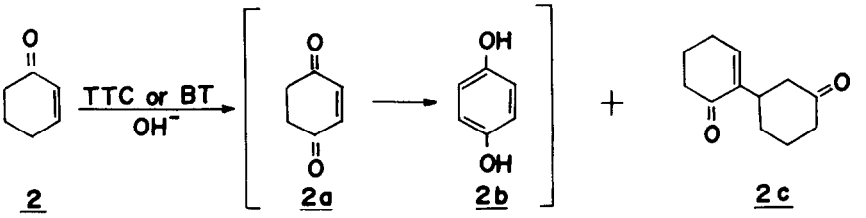
Under the condition applied by us in the oxidation of the α-ketol derivative 1 we obtained relatively high yields (65% for TTC, 72% for BT) of the respective di-ketone 1a , which exists exclusively in mono-enolic form. With hydroxylamine hydrochloride, in typical oxime-forming reaction, the isolated compound 1a gave the expected dioxime 1b .
We propose the obtaining of the di-ketone 1a from 1 by oxidation with tetrazolium salts as a new method of preparation, since the available literature states that 1a has hitherto been obtained from 2-chlorocyclohexanone by hydrolysis with water and oxidation with ferric chloride or by oxidation of cyclohexanone and trans-cyclohexane-1.2-diol[6].



1 1a 1b

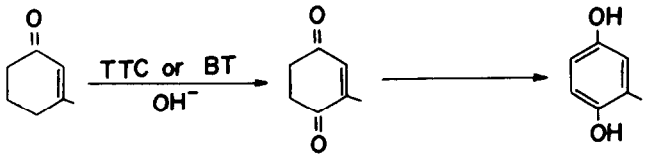
The use of a medium more strongly alkaline than that applied when oxidizing cyclic α-ketols has, by analogy with our previous studies[4], has enabled us to achieve oxidation of enone groups in 2 , 3 and 4 by tetrazolium salts. Similarly as in the case of isoprenoids, we found that a new ketonic function is introduced at the carbon γ relative to the ketone of the enone group.

As the chief products of oxidation of 2 we isolated mixtures of 2a and 2b with various stoechiometric ratios. Depending on the course of its isolation from the post-reaction mixture, the cyclohex-2-en-1.4-dion 2a underwent a transformation to hydroquinone 2b (joint yields of 2a and 2b : 73% for TTC, 81% for BT). The compound 2a , which is a tautomer of hydroquinone has according to the literature been hitherto described by Garbisch[7] only, who isolated 2a by multi-step synthesis from hydroquinone. The higher yield and relative stabilization of 2a were obtained by us in shorter reaction times and by lowering (down to ~0°C) the temperature of evaporation of the CH_2Cl_2 extracts. We moreover noticed that media of polar protic solvents accelerate the tautomerisation of 2a to 2b . As side-product of the oxidation reaction of 2 we isolated the compound 2c (yield ~15%) described in the literature, arisen by base-catalyzed dimerisation of the substrate 2 [8]. When applying longer reaction times and excess oxidizer (TTC or BT), TLC analysis of the post-reaction mixture showed total vanishing of 2a and, moreover, the presence of benzoquinone, possibly arisen by partial oxidation of hydroquinone 2b in the reaction medium.



2 2a 2b 2c

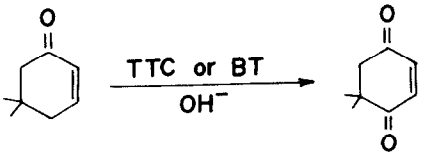
When oxidizing the 3-methyl-substituted cyclohexenone derivative 3 , no process of dimerisation of the above type was observed in the medium. The 3-methyl-cyclohex-2-en-1.4-dion 3a was more stable than its analog 2a and tautomerized more slowly to methylhydroquinone 3b (joint yields of 3a and 3b : 59% for TTC, 66% for BT). In this case too, protic solvents were found to accelerate the reaction 3a ⟶ 3b .



3 3a 3b

Elimination of tautomerisation to hydroquinone derivatives was achieved when oxidizing the compound 4 , where the carbon C-5 possessed a quaternary structure. As the only product of oxidation, the di-ketonic derivative 4a was isolated (yields: 47% for TTC, 51% for BT). The compound 4a is stable at room temperature; spectral and TLC analysis failed to detect any changes in 4a even after protacted storage.

However, the yield of 4a was lower than for its analogs 2a , 3a and their hydroquinone derivatives, maybe due to partial steric blocking of the oxidized carbon C-4 by two methyl groups at C-5.



4 4a

Investigation of the syntheses of other classes of oxygenated enone compounds, based on the results discussed above, is continuing in our laboratory.

Physical data for the oxidation products:

- their structure was confirmed by ^{1}H-NMR(δppm,TMS); IR(cm^{-1}); UV(in EtOH, λ_{max}),
- all compounds gave satisfactory elemental analysis (molecular formula),
- melting and boiling points are uncorrected.

1a m.p. 37.5-38.5°C; $C_6H_8O_2$ (112); UV: 265nm(logε=3.42); IR: in KBr, 1715-1725(α-diketone); NMR: in CD_3OD, 1.56-2.96(aliph.), 6.42(H-C-3 + OH).

2a m.p. 53°C; $C_6H_6O_2$ (110); UV: 234nm(logε=4.05), 353nm(logε=1.8); IR in CCl_4, 1685, 1605(C=O,C=C); NMR: in CCl_4, 2.84(aliph.), 6.6(2H,vinyl, J=8.3cps).

2c b.p. 157-161°C(2.2mm); $C_{12}H_{16}O_2$ (192); UV: 233nm(logε=3.9), 282nm(logε=2.01) IR: in $CHCl_3$, 1705(C=O), 1670(conj.C=O); NMR: in $CDCl_3$, 1.48-2.96(m,aliph.), 6.68(t,1H,vinyl,J=3.2cps).

3a m.p. 68-69°C; $C_7H_8O_2$ (124); UV: 242nm(logε=3.97), 356nm(logε=1.95); IR: in CCl_4, 1670,1595(C=O,C=C); NMR: in CCl_4, 2.25(s,3H,CH_3), 2.81(aliph.), 6.65(s,1H,vinyl).

4a m.p. 57°C; $C_8H_9O_2$ (137); UV: 232nm(logε=4.12), 351nm(logε=1.75); IR: in CC 1696, 1610(C=O,C=C); NMR: in CCl_4, 2.02(6H,2xCH_3), 2.79(aliphatic), 6.58(2H,vinyl,J=8.9cps).

2b and 3b melting points and spectral data identical with appropriate standard compounds.

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