Tetrahedron Letters Vol. 21, pp 1685 - 1686 0040-4039/80/0422-1685$02.00/0

PROSTAGLANDINS VI[1] BASE-CATALYSED AUTOXIDATION OF α-HYDROXYCYCLOPENTANONES AND THE SYNTHESIS OF 9,10-DIKETOPROSTANOIC ACIDS

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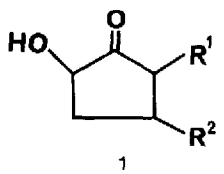
Summary. α-Hydroxycyclopentanones (1,3) are autoxidised to 1,2-cyclopentanediones (2) by molecular oxygen in alkaline solution. This oxidation procedure is used in the first synthesis of an 11-deoxy-9,10-diketoprostaglandin.

In the course of studies on 11-deoxyprostaglandins, we have recently shown that 2-alkyl-5--hydroxycyclopent-2-enones may be prepared from epoxides of 2-alkylcyclopent-2-enones and then elaborated to 11-deoxy-10-hydroxyprostaglandin derivatives (1a).[1,2]

We now wish to report our finding that α-hydroxyketones (1 and 3) undergo a base-catalysed autoxidation in the presence of molecular oxygen to give α-diketones (2). This reaction was first observed when the α-hydroxycyclopentanones (1,3) were simply allowed to stand at room temperature in aqueous ethanolic sodium hydroxide, although formation of the 1,2-diketone, which could be monitored by U.V. (enolate anion λ max ca. 300 nm.[3]), took place only slowly under these conditions and was shown (using 1d) to be incomplete after 47 hrs. However, when oxygen was passed through the reaction mixture, the oxidation was completed much more rapidly. Thus, bubbling oxygen for 2 hours through a solution of the 10-hydroxy-9-ketoprostanoic acid methyl ester (1a) (50mg) in methanol (10ml) containing 1M aqueous sodium hydroxide (1 drop) gave, after acidification (NaH_2PO_4) and ether extraction, the 9,10-diketoprostaglandin (2a) (34mg), which was purified by chromatography on silica gel (ethyl acetate-cyclohexane, 1/1) (9.4mg; 19%); λ max (EtOH) 262nm (ε max 12,340); λ max (EtOH + NaOH) 301nm (ε max c. 10,000); δ ($CDCl_3$) 1.9-2.5 (5H,m, .CH_2CO_2Me, .CH_2.C:C.OH and O:C.C<u>H</u> cis to side chain)2.72 (1H, dd J=16 and 6Hz, O:C.C<u>H</u> trans to side chain)3.15-3.45 (1H,m, HOC:CH.C<u>H</u>.CH:), 3.63 (3H, s, O<u>Me</u>), 3.9-4.25 (1H, m, C<u>H</u>OH), 5.27 (1H, dd J=15 and 9Hz, CH.C<u>H</u>: CH.CHOH) and 5.68 (1H, dd J=15 and 6Hz, CH:C<u>H</u>. CHOH). m/e 366 (M^+), 348 (M-H_2O), 316 (348-MeOH), 295 (m-C_5H_{11}), 277 (295-H_2O), 245 (277-MeOH).



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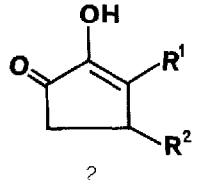

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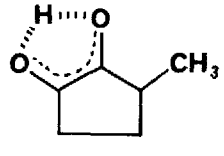

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a, $R^1 = (CH_2)_6CO_2CH_3$, $R^2 = CH{=}CH{-}C(OH)C_5H_{11}$ b, $R^1 = CH_3$, $R^2 = H$

c, $R^1 = (CH_2)_6CO_2CH_3$, $R^2 = H$ d, $R^1 = (CH_2)_6CO_2CH_3$ $R^2 = CH{=}CHC_5H_{11}$

The possibility of using this autoxidation as a preparative method was further investigated with the simple α-hydroxyketone (3)[4], which afforded the diketone (2b) in good yield using the following experimental procedure:-

α-hydroxyketone (3)[4] was shaken in an atmosphere of oxygen with ethanol (10ml) containing 1M aqueous NaOH solution (2ml). The mixture was evaporated in vacuo, the residue dissolved in water and acidified to pH4 with NaH_2PO_4. Ether extraction then gave the diketone (2b) (170mg; 77%), m.p. 104-6° (from ethyl acetate-light petroleum) (lit.[5] 104-5°).

This autoxidation was also shown to occur with α-hydroxycyclopentanones (1c, 1d) as observed by the λ max of ca 300nm, although here the products were not isolated.

Although several instances of base-catalysed autoxidations of ketones to α-diketones have been reported,[6] the only other base-catalysed autoxidations of α-hydroxyketones to α-diketones of which we are aware are the little known examples reported for the carotenoids.[7] Although many more examples are clearly required to evaluate the broad generality of this method, it seems that this remarkably simple procedure could well find preparative application in the oxidation of other α-hydroxyketones, especially where mild conditions are required.

ACKNOWLEDGEMENTS:

The authors would like to thank Miss S.E.M. Dye for technical assistance and Drs. B.J. Peart, M.L. Podmore and B.J. Slater for spectral measurements and helpful discussions.

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2. M.P.L. Caton, G. Darnbrough and T. Parker, Synth. Commun., 1978, 8, 155.
3. This is supported by the U.V. spectral data for 2-hydroxy-3-methylcyclopent-2-enone (2b). λ max (EtOH) 258nm (ϵ max 12,300); λ max (EtOH + NaOH) 297nm (ϵ max 9,100).
4. Prepared by catalytic hydrogenation (5% Pd/C) in ethanol of 2b; the isomeric constitution of the product was not established.
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(Received in UK 18 February 1980)