The Reaction of Enols with Superoxide Anion Radicals: Preparation of Tertiary α-Ketols

Carmen Betancor,[b] Cosme G. Francisco,[a] Raimundo Freire,*[a] and Ernesto Suárez[a]

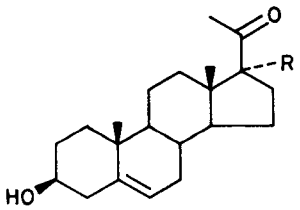
[a] *Instituto de Productos Naturales Orgánicos, C.S.I.C., Carretera La Esperanza 2, La Laguna, Tenerife, Spain*
[b] *Departamento De Química Orgánica, Universidad de La Laguna, Tenerife, Spain*

Pregnan-20-ones (**1**) and (**4**), and 3β-hydroxy-5α-cholestan-6-one (**7**) react with KO_2 and 18-crown-6 in benzene solution and under an oxygen atmosphere at 6—7 °C to give the corresponding α-hydroperoxides (**2**), (**5**), and (**8**) which after treatment with Ph_3P gives α-ketols (**3**), (**6**), and (**9**) in good yields.

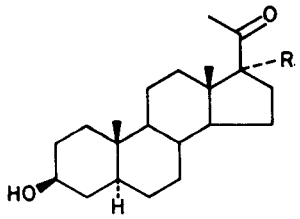
The development of direct methods for the synthesis of α-hydroxyketones, which are important intermediates in organic synthesis, has aroused much interest recently.[1] To achieve the transformation of ketones into a α-ketols different reagents have been used: lead tetra-acetate,[2] halogenating agents,[3] benzeneseleninic anhydride,[4] selenium dioxide,[1a] Vedejs' reagent,[1b] (diacetoxyiodo)benzene,[1c] and 2-sulphonyloxaziridine.[1d] The introduction of a 17-α-hydroxy group into 20-ketosteroids through direct oxygenation is an important reaction developed by Barton[5] and subsequently modified by Gardner *et al.*[6]

We report some extensions in our studies[7] on the reactivity of the superoxide anion O_2^- with steroid ketones; we herein describe an efficient two step procedure to transform the pregnan-20-ones (**1**) and (**4**), and 3β-hydroxy-5α-cholestan-6-one (**7**) into the corresponding α-ketols (**3**), (**6**), and (**9**). The intermediate hydroperoxides (**2**), (**5**), and (**8**), obtained by reaction with KO_2 and oxygen under pressure, were later reduced with Ph_3P to give the corresponding α-ketols (**3**), (**6**), and (**9**).

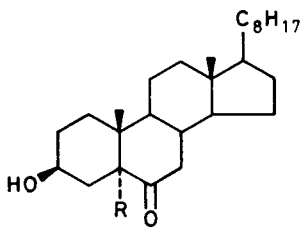
As displayed in Table 1, for the preparation of α-ketols the presence of the oxygen atmosphere under pressure was important in order to achieve better and faster reactions (compare entries 2, 3 and 5, 6), although it was not critical (see entry 2). A better yield and greater selectivity were observed when the reaction was carried out at 6—7 °C than at room temperature (entries 1, 2 and 6, 7). We also detected a better



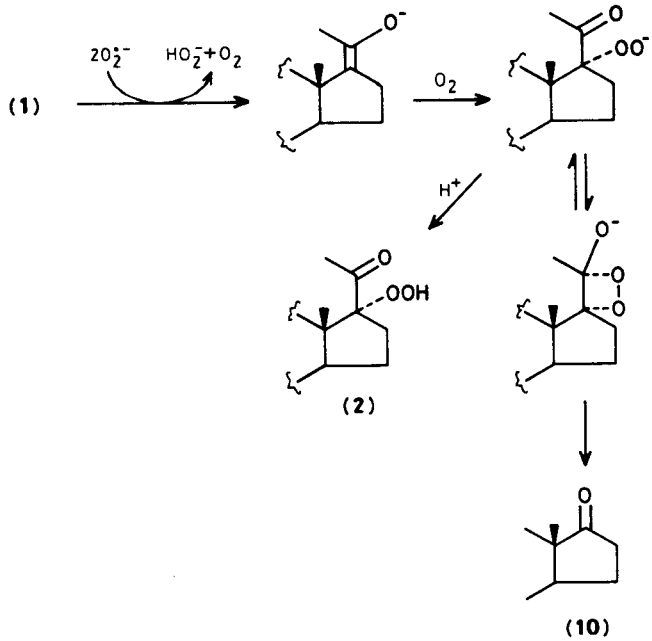
(**1**) R = H
(**2**) R = OOH
(**3**) R = OH



(**4**) R = H
(**5**) R = OOH
(**6**) R = OH



(**7**) R = H
(**8**) R = OOH
(**9**) R = OH



Scheme 1

Table 1. Reaction of ketones with potassium superoxide.

Entry	Substrate	Reagent[a]/mmol	Pressure/atm	Time/h	Temp/°C	% Yield
1	(**1**)	4/1.7	O_2 (1)	24	18	(**2**) (9), (**10**) (23)
2	(**1**)	4/1.7	Ar(1)	8	6—7	(**3**) (57)[b]
3	(**1**)	4/1.7	O_2 (8)	2.75	6—7	(**3**) (64)[b]
4	(**4**)	4/1.7	O_2 (8)	2.75	6—7	(**6**) (72)[b]
5	(**7**)	3/0.7	O_2 (1)	4	18	(**8**) (38), (**9**) (13)
6	(**7**)	3/0.7	O_2 (8)	2.5	18	(**8**) (50), (**9**) (10)
7	(**7**)	3/0.7	O_2 (8)	3.5	6—7	(**9**) (66)[b]

[a] KO_2/18-crown-6 per mmol of substrate. [b] After treatment with Ph_3P.

yield in the absence of the C-5 double bond in steroids (see entries 3 and 4).

In a typical procedure, 3β-hydroxy-pregn-5-en-20-one (**1**), 18-crown-6, and potassium superoxide (KO_2), in a 1:1.7:4 molar ratio, were dissolved in dry benzene–tetrahydrofuran, 8:1 (55 ml/mmol of steroid) and stirred under oxygen pressure (8 atm) in borosilicate Griffin–Worden pressure vessel (Kontes K-767100) at 6—7 °C until all the steroid had been essentially consumed (*ca.* 3 h). The reaction mixture was then acidified with 10% HCl and extracted with EtOAc. The organic phase was dried, concentrated, and crystallised (EtOAc/n-hexane) to yield (**2**). Reaction of hydroperoxide (**2**) with Ph_3P in CH_2Cl_2 for 3 h, concentration, and chromatographic purification, afforded the α-ketol (**3**).

The mechanism proposed in Scheme 1 is in agreement with the role of the oxygen; the required activation energy for the thermal decomposition of the intermediate cyclic peroxide is only attained when the reaction is realised at room temperature (entry 1). The hydroperoxide anion can be reduced *in situ* by an excess of O_2^- to an alkoxy anion as observed in Table 1 (entries 5 and 6) where the alcohol (**9**) is obtained. The versatile chemical behaviour of the superoxide anion is well known;[8] in the mechanism proposed in Scheme 1 it reacts as base, oxidant, and, eventually, as reducing agent (entries 5 and 6). It should be pointed out that the isolation of hydroperoxides (**2**), (**5**), and (**8**), that we had postulated earlier as intermediates for the reaction of several steroid ketones with superoxide ion, supports the previously proposed mechanism.[7]

This work was supported by the Investigation Programme of the Comisión Asesora de Investigación Científica y Técnica.

Received, 14th March 1988; Com. 8/01008K

References

1 (a) N. J. Hrib, *J. Chem. Soc., Chem. Commun.*, 1987, 1338; (b) E. J. Vedejs, D. A. Engler, and J. E. Telschow, *J. Org. Chem.*, 1978, **43**, 188; (c) S. J. Daum, *Tetrahedron Lett.*, 1984, **25**, 4725; R. M. Moriarty and K. Ch. Hou, *ibid.*, 1984, **25**, 691; (d) F. A. Davis, L. C. Vishwakarma, J. M. Billmers and J. Finn, *J. Org. Chem.*, 1984, **49**, 3243.

2 G. W. K. Cavill and D. H. Solomon, *J. Chem. Soc.*, 1955, 4426.

3 J. W. Kochi, *J. Am. Chem. Soc.*, 1955, **77**, 5274; C. Djerassi and C. R. Scholz, *ibid.*, 1948, **70**, 417; H. Mori, *Chem. Pharm. Bull.*, 1962, **10**, 429.

4 K. Yamakawa, T. Satoh, N. Ohba, R. Sakaguchi, S. Takita, and N. Tamura, *Tetrahedron*, 1981, **37**, 473.

5 E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1962, 1578.

6 J. N. Gardner, F. E. Carlon, and O. Gnoj, *J. Org. Chem.*, 1968, **33**, 3294.

7 E. Alvarez, C. Betancor, R. Freire, A. Martín, and E. Suárez, *Tetrahedron Lett.*, 1981, **22**, 4335; E. Alvarez, C. G. Francisco, R. Freire, R. Hernández, J. A. Salazar, E. Suárez, and C. Betancor, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1523.

8 For reviews see: E. Lee-Ruff, *Chem. Soc. Rev.*, 1977, **6**, 195; D. T. Sawyer and M. J. Gibian, *Tetrahedron*, 1979, **35**, 1471; D. T. Sawyer and J. S. Valentine, *Acc. Chem. Res.*, 1981, **14**, 393.