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REACTION OF 5α, AND 5β,3-KETO-STEROIDS WITH POTASSIUM SUPEROXIDE

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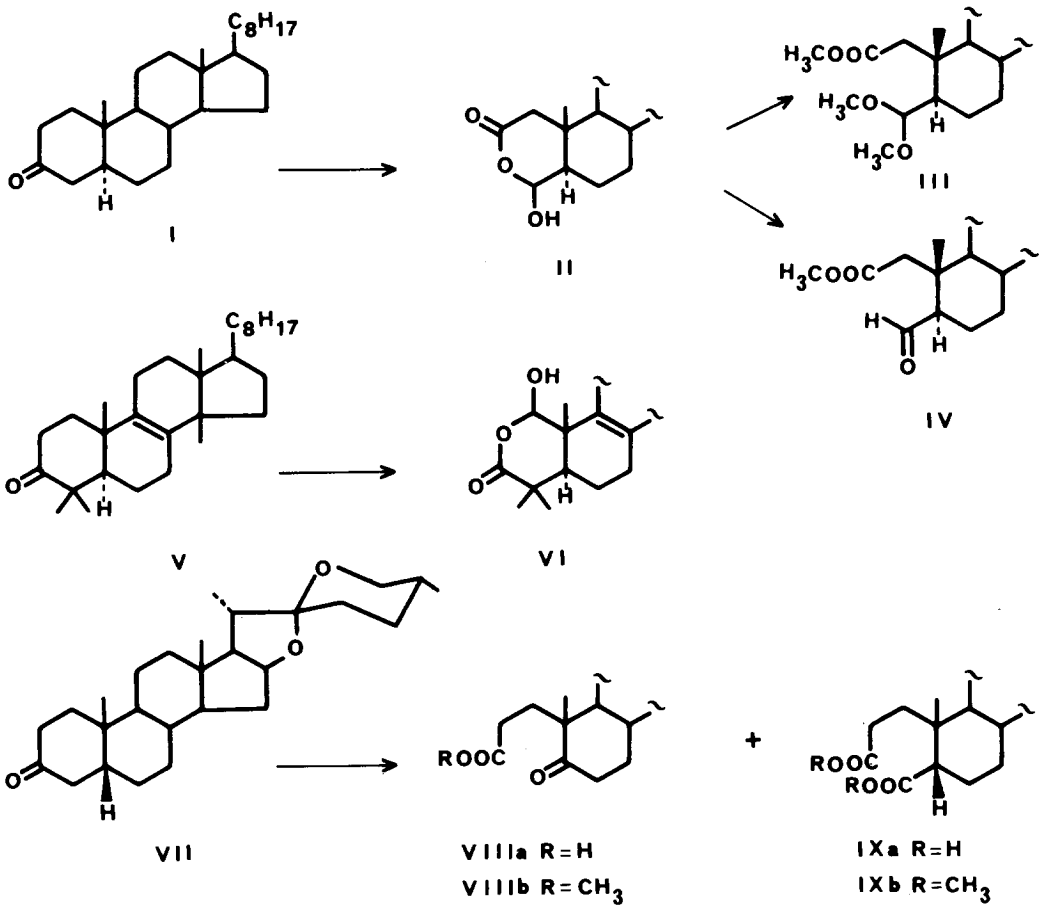
SUMMARY: A regiospecific behaviour is observed in the reaction of 5α and 5β-keto-steroids with potassium superoxide; so the 5α-cholestan-3-one (I) gave the lactol II and the 3-keto-smilagenin (VII) gave the keto-acid VIIIa and a small amount of the diacid IXa. The 3-keto-dihydrolanosterol (V) afforded the lactol VI.

The biochemistry of the superoxide ion is an area that has recently attracted considerable interest(1). Comparatively, its chemical reactivity has received little attention at least from the synthetic point of view (2).

The reactions of some carbonylic compounds have been described recently, e.g. α-keto, α-hydroxy, and α-halo-ketones, esters, and carboxylic acids (3) with the superoxide ion in which oxidative cleavage takes place. Although Lee-Ruff reports (2a) that isolated ketones are inert to $O_2^{\cdot}$ oxidation, it has been shown (4) that under catalytic phase transfer conditions it is possible to cleave monocyclic ketones to afford the diacid without loss of carbon atoms.

This communication describes the results of our investigation about the behaviour of this reagent with 5α, and 5β,3-keto-steroids in benzene in the presence of 18-crown-6 to give the oxidized compounds in which one carbon atom is lacking.

In a typical experiment a solution of 5α-cholestan-3-one (I) (1 mmol) in dry benzene (5 ml) was added via syringe to a suspension of powdered potassium superoxide (5 mmol) in dry benzene (10 ml) containing 18-crown-6 (0.7 mmol) with stirring under inert atmosphere at room temperature. The resulting mixture was vigorously stirred for 7 hours and then cautiously poured into diluted HCl. The reaction was extracted with ethyl acetate and purified by chromatography to give the lactol II (50%) crystallized from methanol m.p. 151-155 ºC, $[\alpha]_D$ 17º ($CHCl_3$). The mass spectrum and analytical data established for II the molecular formula $C_{26}H_{44}O_3$. The IR spectrum ($CHCl_3$) showed bands of OH (3570 and 3370 cm^{-1}) and of carbonyl (1720 cm^{-1}) and the ^1H n.m.r.



spectrum displayed resonances "inter alia" at δ ($CDCl_3$) 5.6 (m, $W_{½}$ 18 Hz, H-C_4), 2.64 and 2.14 (AB, J 18 Hz, $2HC_1$). Methylation of II with methanolic-hydrogen chloride led to the methyl ester III as an amorphous substance [M^+ 464 m/z; ν_{max}($CHCl_3$) 1730 cm^{-1}; ^1H n.m.r. δ (C_6D_6) 4.44 (d, J 4 Hz, H-C_4), 3.41 (s, Me-O-C_2), 3.30 and 3.24 (s, 2 x Me-O-); 2.66 and 2.46 (AB, J 15 Hz, $2HC_1$); ^{13}C n.m.r. "inter alia" δ ($CDCl_3$) 172.3 (C_2), 106.9 (C_4)]. Chemical support for structure II was also obtained when this substance was methylated with CH_2N_2 to give the methyl ester IV, amorphous [M^+ 418 m/z; ν_{max}($CHCl_3$) 1720 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 9.90 (d, J 2 Hz, H-C_4), 3.66 (s, Me-O-), 6.6 (m, $W_{½}$ 4 Hz, 2H-C_2)]. In the ^1H.n.m.r. of IV the signal corresponding to the aldehydic proton is a doublet J 2 Hz, so this function must be in C_4, and leads to the conclusion that C_3 is lost.

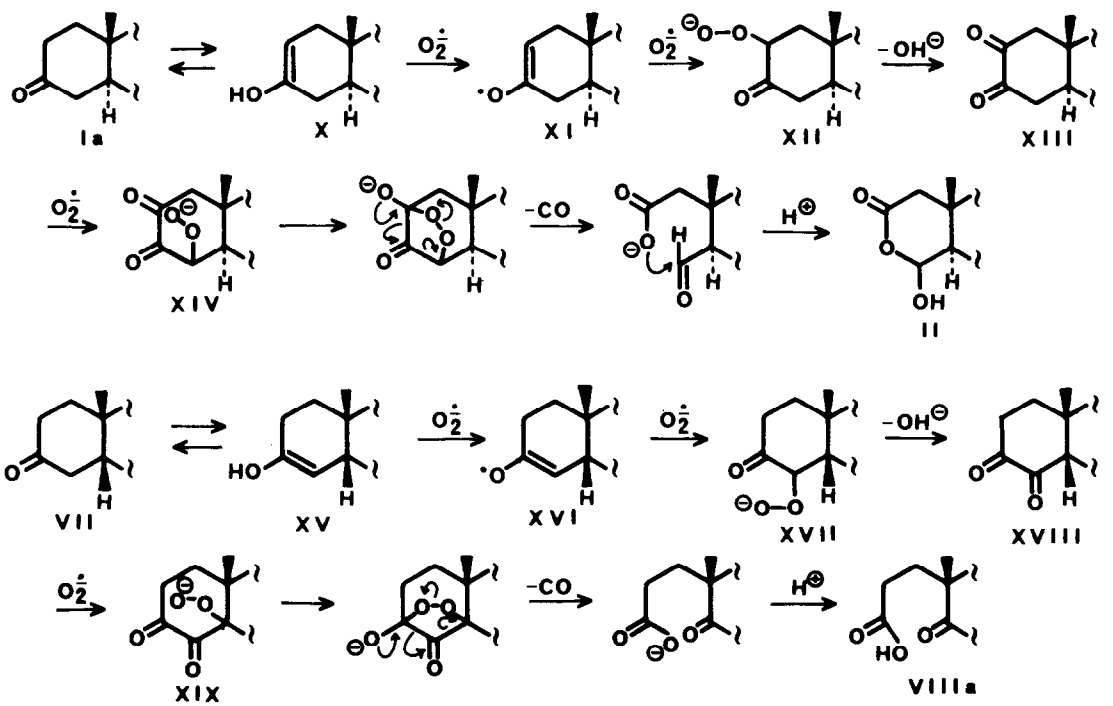
Reaction of 3-keto-dihydrolanosterol (V) with KO_2 under the same conditions (24 h), gives lactol VI (60%) identical in all respects with the compound obtained by autooxidation of V with O_2 in the presence of potassium t-butoxide, as described by R. Hanna and G. Ourisson (5).

Treatment of 5β-spirostan-3-one (3-keto-smilagenin) (VII) with KO_2 (2 h) afforded a mixture of acids that after methylation with CH_2N_2 was resolved by chromatography to give VIIIb (45%) and IXb (7%).

Compound VIIIb crystallized from methanol m.p. 105-107 ºC, $[\alpha]_D$ -48º ($CHCl_3$) [M^+ 446.106 m/z; ν_{max}($CHCl_3$) 1730 and 1700 (ester and ketone), 980, 920, 900, 865 cm^{-1}(25R-spirostan), ^1H n.m.r. δ ($CDCl_3$) 4.4 (m, $W_{½}$ 18 Hz, H-C_{16}), 3.66 (s, Me-O-), 1.12 (s, Me-C_{10}), 0.97 (d, J 6 Hz, Me-C_{20}), 0.84 (s, Me-C_{13}), and 0.79 (d, J 6 Hz, Me-C_{25})].

Compound IXb crystallized from benzene/n-hexane, m.p. 190-192 ºC, $[\alpha]_D$ -35º ($CHCl_3$). [M^+ 490.111 m/z, ν_{max}($CHCl_3$) 1735 (methyl ester), 980, 920, 900, 865 cm^{-1}(25R-spirostan), ^1H n.m.r. δ ($CDCl_3$) 4.4 (m, $W_{½}$ 18 Hz, H-C_{16}), 3.46 (m, $W_{½}$ 12 Hz, 2H-C_{26}), 3.65 (s, 2 x Me-O-), 0.96 (s, Me-C_{10}), 0.96 (d, J 6 Hz Me-C_{20}), and 0.77 (s, Me-C_{13})].

3- and 4-oxa-steroids have been previously synthesized by treatment of 3-keto-steroids with potassium t-butoxide in O_2 atmosphere (70-80 ºC, 5-6 atm) (6). Presumably the mechanism for this reaction with KO_2 is analogous to that proposed for the autooxidation of enolizable ketones in basic media (7). The different enolization of 3-keto-5α and 3-keto-5β-steroids to the positions 2 and 3 respectively (8) is well known. This explains in our case that the reaction of KO_2 with these substrates leads regioselectively to compounds II and VIIIa.



The abstraction, by superoxide ion, from enols X and XV of a H• gives the enol radicals XI and XVI, which on combination with another superoxide molecule lead to peroxianions XII and XVII that originate the 1,2-diketones XIII and XVIII (not isolables). Subsequent attack of the enolic form of the 1,2-diketones by the superoxide ion leads to peroxianions XIV and XIX that undergo rearrangement and elimination of C_3 and C_4 respectively to yield the products II and VIIIa.

The insertion of an atom of oxygen in the steroidal skeleton has been the subject of numerous studies (9). This reaction allows us an easy route to 3- and 4-oxa-steroids. The 3- and 4-oxa-steroids of androstanic type display pharmacological properties as antiandrogenic (10) and anabolic agents (11).

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REFERENCES

1. I. Fridovich, Acc. Chem. Res., 5, 321 (1972); A. M. Michelson, J. M. Mc Cord and I. Fridovich Eds., "Superoxide and Superoxide Dismutases". Academic Press, New York (1977).
2. (a). E. Lee-Ruff. Chem.Soc. Rev., 6,195 (1977).
(b). D. T. Sawyer and M.J. Gibian, Tetrahedron, 35, 1471 (1979).
3. J. San Filippo, Jr., Chuen-Ing Chern, and J.S. Valentine, J. Org. Chem. 41, 1077 (1976).
4. M. Lissel and E. V. Dehmlow, Tetrahedron Letters, 3689 (1978).
5. R. Hanna and G. Ourisson, Bull.Soc. Chim. France, 1945 (1961); ibid., 3742 (1967).
6. R. Sandmeier and C. Tamm, Helv. Chim. Acta, 56, 2238 (1973).
7. G. Rio, P-J- Cornu and R. Wagner, Bull. Soc. Chim. France, 587 (1961).
8. D. N. Kirk and H. P. Hartshorn, "Steroid Reaction Mechanism". Elsevier Publishing Company, Amsterdam, p. 161 (1968).
9. C. Djerassi Ed., "Steroid Reactions". Holden-Day Inc., San Francisco, p. 459 (1963).
10. A. Boris and M. Uskokovic, Experientia, 26, 9 (1970).
11. R. Pappo and C. J. Jung, Tetrahedron Letters, 365 (1962).

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