

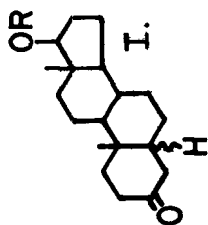
OXIDATION OF STEROIDAL KETONES I. SELENIUM DIOXIDE CATALYZED
HYDROGEN PEROXIDE OXIDATION OF RING A SATURATED 3-KETONES^{1a}

E. Caspi and S. N. Balasubrahmanyam^{1b}
Worcester Foundation for Experimental Biology
Shrewsbury, Massachusetts
(Received 9 February 1963)

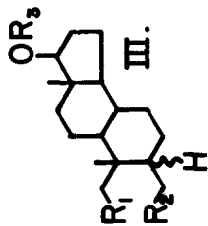
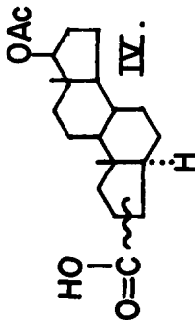
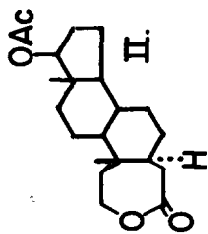
The selenium dioxide catalyzed reaction of hydrogen peroxide with saturated cyclic ketones has been shown to lead to carboxylic acids with a contracted ring.^{2,3} We have investigated this reaction for steroidal 3-ketones of 5 α and 5 β series. In our hands the major reaction was not ring contraction but Baeyer-Villiger oxidation.

The oxidation was carried out essentially as described by Payne and Smith² whereby the steroid was refluxed in tert. butanol containing hydrogen peroxide and catalytic amounts of selenium dioxide. On termination of the period of reflux (7 hr.), a large amount of water was added and the steroids were then recovered with a mixture of ether-methylene chloride (3:1). The products were then separated into acidic and neutral fractions with aqueous sodium carbonate.

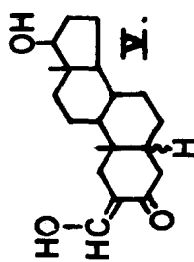
The model with A/B-trans junction, 17 β -acetoxy-5 α -androstan-3-one (Ia), gave a neutral material⁴ II, and two carboxylic acids, IIIa and IV. The lactone II, m.p. 240-241 $^{\circ}$, and the acid IIIa, m.p. 167-168 $^{\circ}$, were correlated by saponification to a common product viz. the dihydroxy acid IIIb m.p. 235-238 $^{\circ}$ (with change of crystalline form at ab. 200 $^{\circ}$). Oxidation of IIIa with chromic acid in acetone⁵ followed by saponification gave 17 β -hydroxy-2,3-seco-5 α -androstane-2,3-dioic acid (IIIc) m.p. 275-277 $^{\circ}$, identical with an authentic sample. The latter was prepared by permanganate-periodate oxidation⁶ of the hydroxymethylene derivative Va prepared from Ib. The condensation of Ib with ethyl formate in the presence of sodium hydride has been shown to lead to substitution⁷ at C-2. The



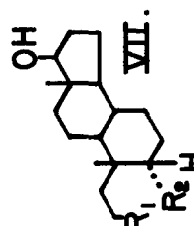
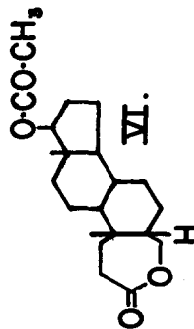
- a. 5 α ; R = COCH₃
 b. 5 α ; R = H
 c. 5 β ; R = COCH₃
 d. 5 β ; R = H



- a. 5 α ; R₁ = CH₂OH; R₂ = COOH;
 R₃ = CO·CH₃
 b. 5 α ; R₁ = CH₂OH; R₂ = COOH; R₃ = H
 c. 5 α ; R₁ = R₂ = COOH; R₃ = H
 d. 5 β ; R₁ = R₂ = CH₂OH; R₃ = H
 e. 5 β ; R₁ = R₂ = COOH; R₃ = H



- a. 5 α
 b. 5 β



- a. R₁ = COOH; R₂ = CH₂OH
 b. R₁ = R₂ = CH₂OH

second acidic product has been only partially identified as IV m.p. 214-215° on the basis of its composition (Found: C, 72.16, 72.27; H, 8.80, 9.22. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26), and acid equivalent (Found: 326. Calcd. for $C_{21}H_{32}O_4$: 348).

The oxidation of the 17 β -acetoxy-5 β -androstan-3-one (Ic) gave the lactone VI, m.p. 219-222°, as a single product. Saponification of VI gave the 3,4-seco-dihydroxy acid VIIa, m.p. 194-195°, which, on attempted acetylation with acetic anhydride-pyridine reverted to VI. Reduction of VIIa with diborane⁸ gave the triol VIIb, m.p. 177-181°, distinctly different from the triol IIIId, m.p. 169-172° (m.p., mixed m.p. infrared spectra and retention times in g.l.c.).

Treatment of Id with ethyl formate in the presence of alcohol-free sodium methoxide⁹ led to the known 2-hydroxymethylene ketone Vb, m.p. 153-157° (reported⁹ 152-158°). Ozonization of Vb gave the dicarboxylic acid IIIIe, m.p. 228-230°, which was reduced with diborane to the triol IIIId.

Oxidation of Ic with hydrogen peroxide can proceed only by scission of either the 2,3 or 3,4 bonds. Since the derived triol VIIb has now been shown to be different from IIIId the lactone must have the structure VI.

It was found that secondary hydroxy groups are not affected under the conditions of reaction. The syrupy residue isolated from oxidation of Id on treatment with base gave a single product, VIIa.

Recently Hara et al.¹⁰ have shown that perbenzoic acid oxidation of 5 α - and 5 β - 3-ketones yields mixtures of lactones with an oxygen atom inserted on either side of the 3-oxo group. With the commonly used peracids it would seem that the reaction proceeds in a rather indiscriminate manner.^{11,10} Under the nearly neutral conditions we have employed, the direction of attack is more substrate dependent,¹² and hence leads to formation of single compounds in the main. For example, for A/B-trans junction the 2,3-bond and for A/B-cis junction the 3,4-bond are cleaved. Also the method offers advantages in terms of time and ease of processing.

REFERENCES

- 1a. This work was supported by U. S. Public Health Grants CA-4663 and A-5326.
- b. Post doctoral fellow 1961-1962.
2. C. Payne and C. W. Smith, J. Org. Chem. 22: 1680 (1957).
3. C. F. Biellman and M. Rajic, Bull. Soc. Chim. 441 (1962).
4. Analytical and spectroscopic data consistent with the assigned structures were obtained.
5. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc. 39 (1946).
6. R. U. Lemieux and E. von Rudlof, Can. J. Chem. 33: 1710 (1955).
M. E. Wall and S. Serota, J. Org. Chem. 24: 741 (1959).
7. H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, J. Am. Chem. Soc. 81: 427 (1959).
8. G. R. Pettit and T. R. Kasturi, J. Org. Chem. 26: 4557 (1961).
9. R. O. Clinton, R. L. Clarke, F. W. Stonnes, A. J. Manson, K. F. Jennings and D. K. Phillips, J. Org. Chem. 27: 2800 (1962).
10. S. Hara, N. Matsumoto and M. Takeuchi, Chem. and Ind. 2086 (1962).
11. V. Prelog, L. Ruzicka, P. Meister and P. Wieland, Helv. Chim. Acta 28: 618 (1945).
L. Ruzicka, V. Prelog and P. Meister, Helv. Chim. Acta 28: 1651 (1945).
12. J. Meinwald and E. Frauenglass, J. Am. Chem. Soc. 82: 5235 (1960).