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OXIDATION OF STEROIDAL KETONES I. SELENIUM DIOXIDE CATALYZED HYDROGEN PEROXIDE OXIDATION OF RING A SATURATED 3-KETONES[1a]

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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 5α and 5β 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 Smith[2] 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, 17β-acetoxy-5α-androstan-3-one (Ia), gave a neutral material[4] II, and two carboxylic acids, IIIa and IV. The lactone II, m.p. 240-241°, and the acid IIIa, m.p. 167-168°, were correlated by saponification to a common product viz. the dihydroxy acid IIIb m.p. 235-238° (with change of crystalline form at ab. 200°). Oxidation of IIIa with chromic acid in acetone[5] followed by saponification gave 17β-hydroxy-2,3-seco-5α-androstane-2,3-dioic acid (IIIc) m.p. 275-277°, identical with an authentic sample. The latter was prepared by permanganate-periodate oxidation[6] 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 substitution[7] at C-2. The

a. 5α ; R=COCH$_3$
b. 5α ; R=H
c. 5β ; R=COCH$_3$
d. 5β ; R=H

a. 5α ; R$_1$=CH$_2$OH; R$_2$=COOH; R$_3$=CO·CH$_3$
b. 5α; R$_1$=CH$_2$OH; R$_2$=COOH; R$_3$=H
c. 5α; R$_1$=R$_2$=COOH; R$_3$=H
d. 5β; R$_1$=R$_2$=CH$_2$OH; R$_3$=H
e. 5β; R$_1$=R$_2$=COOH; R$_3$=H

a. 5α
b. 5β

a. R$_1$=COOH; R$_2$=CH$_2$OH
b. R$_1$=R$_2$=CH$_2$OH

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 17β-acetoxy-5β-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 diborane[8] gave the triol VIIb, m.p. 177-181°, distinctly different from the triol IIId, 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 methoxide[9] led to the known 2-hydroxymethylene ketone Vb, m.p. 153-157° (reported[9] 152-158°). Ozonization of Vb gave the dicarboxylic acid IIIe, m.p. 228-230°, which was reduced with diborane to the triol IIId.

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 IIId 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 5α- and 5β- 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.

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