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ALKALINE HYDROGEN PEROXIDE OXIDATION OF A-NORTESTOSTERONE: A NEW ROUTE TO 2-OXA-STEROIDS

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It has been observed that the alkaline hydrogen peroxide treatment of α,β-unsaturated ketones leads to the exclusive formation of epoxy ketones, without any evidence of Baeyer-Villiger products[1]. I wish to report herein the preparation of a 2-oxa-steroid[2] via alkaline peroxide oxidation of an A-norsteroid*. This represents to my knowledge, the first example of a Baeyer-Villiger product from an α,β-unsaturated ketone under these reaction conditions and also provides a route to heretofore undescribed 2-oxa-4-halo-4-dehydro steroids.

A-Nortestosterone[3] (I) was treated at room temperature with 30% hydrogen peroxide and 4N sodium hydroxide in methanol and the crude reaction product refluxed in glacial acetic acid saturated with hydrogen chloride. Chromatography of the product on neutral alumina

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*During the course of this investigation, the conversion of 2-oxo-A-norsteroids in both the 5α- and 5β-series via perbenzoic acid oxidation to 2-oxa-steroids has been reported. S. Hara, Chem. Pharm. Bull., 12, 1531 (1964).

(Activity V) afforded a chlorine-containing compound in low yield (5%), m.p. 238.5-240.5°[4]; $[\alpha]_D^{23}$ +145°; λ 5.80 (v.b.), 6.22 and 8.15 μ, which had the elementary composition $C_{20}H_{27}O_4Cl$ and hence could not be the expected product, 3-chloro-A-nortestosterone acetate (II). It was formulated as the 2-oxa-4-chloro-4-dehydro steroid III on the basis of the following evidence: (a) two protons appeared in the NMR spectrum as an AB quartet, τ 5.77 and 5.97, J = 11 c.p.s., consistent with a methylene group situated between an oxygen atom and an angular carbon atom bearing a methyl group; and (b) the UV spectrum exhibited a peak at λ 239 mμ (11,200).

In order to gain insight into the nature of the intermediate(s) leading to the formation of the 2-oxa-steroid, the epoxidation of I was repeated and the crude reaction product separated into neutral and acidic fractions.

Chromatography of the neutral fraction on silica gel afforded two components, The less polar compound was the expected product of epoxidation, 3β,5β-epoxy-A-norandrostane-2-one-17β-ol* (IV), $C_{18}H_{26}O_3$; $[\alpha]_D^{26}$ +102°; λ 2.83 and 5.77 μ; τ 9.22 (s, 18-Me), 8.82 (s, 19-Me), 6.87 (m, 3-H) and 6.39 (m, 17-H).

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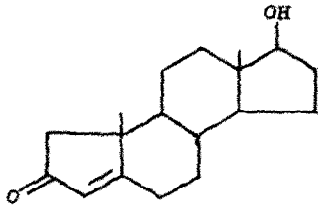
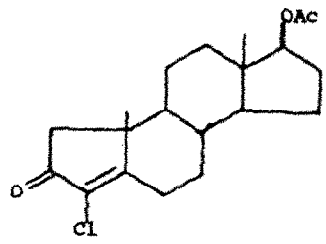
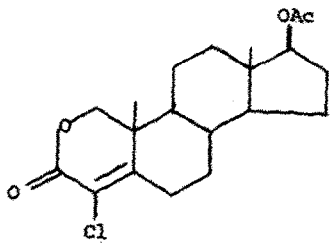
*Attack by peroxide to give the β-epoxide is based on analogy to the preferred β-side addition to the Δ^3-2-one system in A-norsteroids. For example: osmium tetroxide hydroxylation of I affords the 3β,5β-diol[5], cyanation of I affords 5β-cyano-A-nortestosterone[6], and catalytic hydrogenation of I gives the 5β-dihydro derivative[3].



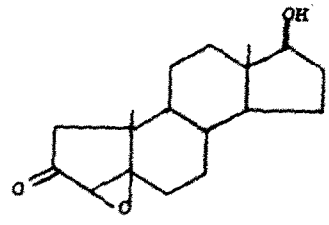
I



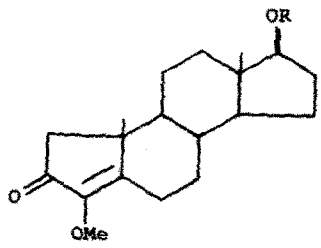
II



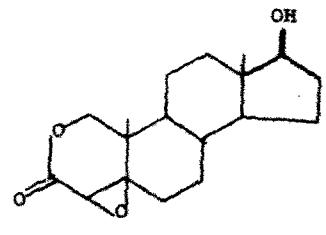
III



IV



V R = H
VII R = Ac



VI

The more polar component was identified as 3-methoxy-A-nortestosterone (V) by a comparison of its m.p., infrared, and NMR spectrum with an authentic sample[5].

The 2-oxa-3β,5β-epoxy ketone (VI) was obtained in 15% yield by chromatography of the acidic fraction on neutral alumina (Activity V), $C_{18}H_{26}O_4$; $[\alpha]_D^{23}$ +97°; λ 2.86 and 5.82 μ; τ 9.23 (s, 18-Me), 8.95 (s, 19-Me), 6.69 (s, 4-H), 6.33 (m, 17-H) and 6.00 (s, 2-methylene) Treatment of VI with glacial acetic acid saturated with hydrogen chloride afforded III.

In another experiment, I was epoxidized and the crude reaction product first treated in chloroform and ethanol with hydrogen chloride and then acetylated. Chromatography on silica gel afforded two compounds. The first to be eluted was 3-chloro-A-nortestosterone acetate (II), $C_{20}H_{27}O_3Cl$; $[\alpha]_D^{27}$ +26°; λ 5.80 and 6.13 μ; λ 246 mμ (13,400); τ 9.14 (s, 18-Me), 8.78 (s, 19-Me), 7.95 (s, 17-acetate) and 5.39 (m, 17-H). The more polar compound was characterized as 3-methoxy-A-nortestosterone acetate (VII), $C_{21}H_{30}O_4$; m.p. 144-145°; λ 5.78, 5.8 and 6.06 μ; λ 250 mμ (11,800).

In view of these findings, the formation of the 2-oxa-steroid VI may be envisioned as proceeding in the following manner: initial epoxidation of I leads to IV, which reacts either with methanol to give V or is further oxidized by hydrogen peroxide to VI.

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REFERENCES

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3. F. L. Weisenborn and H. E. Applegate, J. Am. Chem. Soc., 81, 1960 (1959).

4. Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were determined in chloroform on a Perkin-Elmer 411 polarimeter, infrared spectra on a Perkin-Elmer 21 spectrometer in pressed potassium bromide pellets, ultraviolet spectra on a Cary 11 spectrometer in ethanol and NMR spectra on a Varian A-60 in deuteriochloroform with tetramethylsilane as internal standard. Satisfactory analyses were obtained for all new compounds with cited empirical formulas.

5. S. D. Levine and P. A. Diassi, J. Org. Chem., 30, 0000 (1965).

6. S. D. Levine, unpublished observation.