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10-HYDROPEROXY-19-NORSTEROIDS

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Steroidal hydroperoxides have been used principally in the past as synthetic intermediates (1). They are, for example, readily converted to alcohols. More recently, Nickon (2) has shown that α,β-epoxy ketones may be prepared from allylic alcohols stereospecifically via intermediary hydroperoxides. We wish now to report a new class of compounds (10-hydroperoxy-19-nor 3-keto Δ^4-steroids) which are not only of interest chemically, because of the unusual transformations they undergo, but also are of interest biologically because of their antifertility activity in animals as compared with norethynodrel (3).

In connection with another problem we had occasion to chromatograph 17α-methyl-17β-hydroxy-5-androstene-3-one (I) over silica gel. We obtained a mixture of substances more polar than I which was characterized as 6(α and β)-hydroperoxy-17α-methyl-17β-hydroxy-4-androstene-3-one (II) (positive starch iodide, re-

ducible to the 6(α and β)-hydroxy (III); upon chromic acid oxidation III gave the 6-ketone, which exhibited the typical spectroscopic absorptions for a 3,6-diketo-Δ^4 system both in methanolic as well as acidic or basic solutions). The formation of II had apparently occurred during the attempted purification of I over silica gel.

The transformation of a 3-keto-Δ^5 steroid to a 6(α and β)-hydroperoxy-Δ^4-3-keto steroid had been observed previously by Fieser. He has reported that in the presence of oxygen of the air, 5-cholesten-3-one is converted to 6(α and β)-hydroperoxy-4-cholesten-3-one (4). Accordingly, for comparison purposes, II was prepared by the aeration of a chloroform solution of I.

We were impressed with the relative facility with which I underwent this oxygenation reaction, and we felt that any system possessing unsaturation β,γ to a ketonic function (as in R'C=C-CH(R)-C(=O)-R") might be transformed under suitable oxygenation conditions to a γ-hydroperoxy-α,β-unsaturated ketone, R'-C(-O-OH)-C=C(R)-C(=O)-R".

We therefore applied this oxygenation reaction to several β,γ-unsaturated steroid ketones, and at this time we report our findings with the $\Delta^{5(10)}$-3-keto system.

A chloroform solution of 17α-ethinyl-17β-hydroxy-5(10)-estrene-3-one (IV) (5) at 45° was exposed to a fluorescent light source under an atmosphere of oxygen, producing 10β-hydroperoxy-17α-ethinyl-17β-hydroxy-4-estrene-3-one (V) (40% yield), m.p. 220-

222°;[1] $[\alpha]_D$ -28.2°; λ_{max}^{MeOH} 234-5 mμ(ε14,600); λ_{max}^{Nujol} 3.12, 4.75, 6.12 μ; positive starch-iodide test; (Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.70; H, 7.93. Found: C, 72.40; H, 8.13). The transformation to V may occur under a variety of conditions, that is, with or without the presence of radical generators such as benzoyl peroxide or azobis-isobutyryl nitrile, or it may occur also on suitable substrates such as silica gel as in the formation of II.

Proof of structure for V is as follows: Treatment of V with acetic anhydride in pyridine gave the 10β-acetoxy-peroxide VI, m.p. 138-139°; $[\alpha]_D$ +25.0°; λ_{max}^{MeOH} 233 mμ (ε14,400); λ_{max}^{Nujol} 2.98, 3.07, 4.73, 5.61 (-C=O of acetoxyperoxide), 6.02, 6.15, 8.24, 8.30 μ; (Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.97; H, 7.58). Brief hydrolysis of VI with aqueous methanolic potassium bicarbonate[2] regenerated V, thereby demonstrating that no rearrangements had occurred during esterification. Selective reduction of the hydroperoxide function with sodium iodide in a mixture of acetic acid, ethanol and ether (6) gave 17α-ethinyl-10β,17β-dihydroxy-4-estrene-3-one (VII), m.p. 255-262°; $[\alpha]_D$ -15.0°; $[\alpha]_D$ 0.0°(MeOH); λ_{max}^{MeOH} 234 mμ (ε13,700);

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[1] Melting points are uncorrected and were taken on a Fischer Johns apparatus. Unless otherwise noted, rotations are in dioxane at 25°.

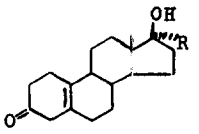
[2] Care must be taken with the saponification since the hydroperoxide in the presence of alkali undergoes an interesting rearrangement, which will be the subject of a future communication.

identical with the known compound (7) by comparison of infrared spectra, mixture melting point, rotation, and thin layer chromatography. Since iodide reduction of a hydroperoxy function to hydroxy is known to proceed by cleavage of the oxygen-oxygen linkage and not by cleavage of the carbon-oxygen bond, the stereochemistry of the 10-hydroperoxide V is established.

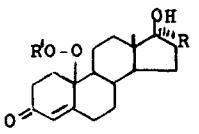
Similarly, 17β-hydroxy-5(10)-estrene-3-one (VIII) (8) was transformed to 10β-hydroperoxy-17β-hydroxy-4-estrene-3-one (IX), m.p. 181-185°; $[\alpha]_D$+51.0°; λ_{max}^{MeOH} 234 mμ (ε15,100); λ_{max}^{Nujol} 3.01, 3.13, 6.04μ; positive starch-iodide test; (Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.33; H, 8.70). Sodium iodide in acetic acid and ethanol gave the known 10β,17β-dihydroxy-4-estrene-3-one (X) (7), m.p. 196-206° (softens 187°); $[\alpha]_D$+68.1°; $[\alpha]_D$+77° (MeOH); λ_{max}^{MeOH} 234 mμ (ε14,400).

Also, 17α-chloroethinyl-17β-hydroxy-5(10)-estrene-3-one (XI) (9) was converted to 10β-hydroperoxy-17α-chloroethinyl-17β-hydroxy-4-estrene-3-one (XII).

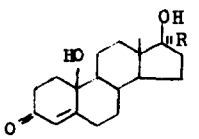
We are continuing our investigations of the hydroperoxidation of other β,γ-unsaturated ketones and of the chemistry of these novel steroid hydroperoxides.



IV, R = C≡CH
VIII, R = H
XI, R = C≡C-Cl



V, R = C≡CH; R' = H
IX, R = H; R' = H
XII, R = C≡C-Cl; R' = H
VI, R = C≡CH; R' = Ac



VII, R = C≡CH
X, R = H

REFERENCES

(1) See, for example (a) G.D. Schenck, Angew. Chem. 69, 579 (1957); (b) E.J. Bailey, J. Elks, and D.H.R. Barton, Proc. Chem. Soc. 214 (1960).

(2) A. Nickon, and W.L. Mendelson, J. Am. Chem. Soc. 85, 1894 (1963).

(3) The biological data will be reported by A. Watnick, J. Gibson, N. Vinegra, and S. Tolksdorf, Department of Endocrinology, Schering Corporation.

(4) (a) L.F. Fieser, T.W. Greene, F. Bischoff, G. Lopez, and J.J. Rupp, J. Am. Chem. Soc. 77, 3928 (1955); (b) L.F. Fieser, and M. Fieser, Steroids, Reinhold Publishing Corp., New York 1959, p. 235.

(5) F.B. Colton, U.S. Patent 2,725,389 (1955).

(6) A. Nickon, J.F. Bagli, J. Am. Chem. Soc. 83, 1498 (1961).

(7) J.P. Ruelas, J. Iriarte, F. Kincl, and C. Djerassi, J. Org. Chem. 23, 1744 (1958).

(8) A.J. Birch, and S.M. Mukherji, J. Chem. Soc. 2531 (1949).

(9) J.H. Fried, T.S. Bry, A.E. Oberster, R.E. Beyler, T.B. Windholz, J. Hannah, L.H. Sarett, and S.L. Steelman, J. Am. Chem. Soc. 83, 4663 (1961).