Tetrahedron Letters No. 11, pp. 497-500, 1962. Pergamon Press Ltd. Printed in Great Britain.

ANOMALOUS ENOLIZATION OF 3-KETO-5α-STEROIDS

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(Received 6 April 1962)

IT is generally admitted that the greater stability of Δ^2 - over Δ^3-5α-steroidal enes determines the Δ^2 structure of 3-keto-5α-steroid enol derivatives.[1,2] This structure was actually proved for cholestanone ethyl enol ether,[3] prepared by both pyrolysis of diethylacetal[4] and partial hydrogenation of cholestenone ethyl enol ether.[5]

Now we found that 3-keto-5α-steroid enol ethers with anomalous Δ^3-structure can be easily obtained by carrying out catalytical hydrogenation of Δ^4-3-ketone enol ethers in the presence of small amounts of an inorganic or organic base. Thus for instance, testosterone 17-acetate 3-ethyl enol ether [m.p. 130-132°,[6] $[\alpha]_D$ -145° (Di)] hydrogenated in tetrahydrofuran-methanol containing pyridine or sodium hydroxide in the presence of Pd over Al_2O_3 yielded 3-ethoxy-Δ^3-5α-androstene-17β-ol acetate (II), m.p. 111-114°, $[\alpha]_D$ +5° (Di).[7] Hydrogenation carried out in the same conditions, but in

[1] L.F. Fieser and M. Fieser, Steroids p. 276. Reinhold, New York (1959).

[2] In accordance with the role of the angular methyl group on this stability relationship, 19-nortestosterone was found to give a mixture of Δ^2- and Δ^3-enol acetates. Cf. R. Villotti, H.J. Ringold and C. Djerassi, J. Amer. Chem. Soc. 82, 5693 (1960).

[3] H.H. Inhoffen, W. Becker and G. Kölling, Liebigs Ann. 568, 181 (1950).

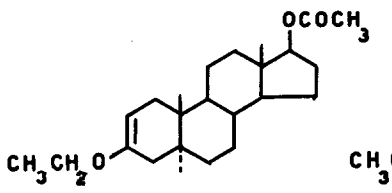
[4] A. Serini and H. Köster, Ber. Dtsch. Chem. Ges. 71, 1766 (1938).

[5] H.H. Inhoffen, G. Stoeck, G. Kolling and U. Stoeck, Liebigs Ann. 568, 52 (1950).

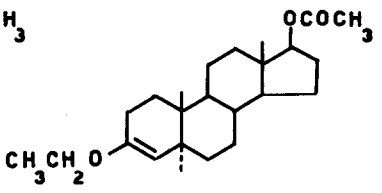
[6] Melting points uncorrected.

[7] W.V. Ruyle, A.E. Erickson, A. Lovell and E.M. Chamberlin, J. Org. Chem. 25, 1260 (1960), described the preparation of androstanolone ethyl enol ether by hydrogenation of testosterone ethyl enol ether in neutral medium and reported for the product the formula of Δ^3-enol. However, they supplied neither physical constants of the enol ether nor evidence of the double bond position.

the absence of bases, led regularly to 3-ethoxy-Δ^2-5α-androstene-17β-ol acetate (I), m.p. 132-134°, $[\alpha]_D$ +45° (Di).



I



II

Formation of Δ^3-rather than Δ^2-enol closely depends upon the presence of bases, nature of catalyst and solvent being markedly less important.

Enol ether II clearly differs from isomeric I by lower rotation[8] and shift of the -C=C- stretching band towards lower frequencies[1] (1671 from 1678 cm^{-1} in CCl_4).[9] Its structure was unequivocally proved. By reaction with N-bromosuccinimide in aqueous buffered acetone,[10] II yielded, after equilibration with hydrobromic acid,[11] 4α-bromo-5α-androstan-17β-ol-3-one acetate, m.p. 199-200° (dec.), $[\alpha]_D$ -19° (Chf),[12] which was dehydrobrominated with LiCl - Li_2CO_3 in dimethylformamide[13] to give testosterone acetate.

Enol ethers of type II readily regenerate the parent 3-ketone by acid hydrolysis,[14] while they are quite stable in neutral or alkaline medium, even by heating.

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[8] Cf. ref. 1, p. 177.

[9] We wish to thank Dr. C. Pedrali for determining infra-red spectra.

[10] Cf. H.J. Ringold, E. Batres, A. Bowers, J. Edwards and J. Zderic, J. Amer. Chem. Soc. 81, 3485 (1959).

[11] However, equatorial epimer was far prevalent in the raction product, as shown by rotation and infra-red data.

[12] J. Faikos and F. Sorm, Coll. Czech. Chem. Comm. 24, 3115 (1959).

[13] R. Joly, J. Warnant, G. Nominé and D. Bertin, Bull. Soc. Chim. Fr. 366 (1958).

[14] Treatment of enol II (as well as enol I) with p-toluenesulphonic acid in methanol leads to androstanolone 17-acetate 3-dimethyl acetal, m.p. 143-144°, $[\alpha]_D$ +9° (Di). However the reaction occurs with hydrolysis and reacetalization. Ready formation of 3-keto-5α-steroid acetals in such conditions was also reported by M.M. Janot, X. Lusinchi and R. Goutarel, Bull. Soc. Chim. Fr. 2109 (1961).

Although it may be supposed that such derivatives can be intermediates in the formation of Δ^2-enol ethers by hydrogenation of $\Delta^{3,5}$-dienol ethers, we have been unable, until now, to obtain isomerization of Δ^3- to Δ^2-enol. However, bromination of II with bromine in carbon tetrachloride in the presence of K_2CO_3 [15] yielded 2α-bromo-5α-androstan-17β-ol-3-one acetate, m.p. 177-178° (dec.), $[\alpha]_D$ +32° (Chf),[16,12] identical with the product obtained by bromination (Br_2 or NBS) of enol I. Evidently bromination conditions caused bond migration.

Δ^3-Enol ethers are useful for the preparation of 4-substituted 3-keto 5α-steroids by reaction with electrophilic reagents.[17] Thus reaction of II with N-chlorosuccinimide[18] yielded 4α-chloro-5α-androstan-17β-ol-3-one acetate, m.p. 219-220°, $[\alpha]_D$ -14° (Chf).

Reaction of the same enol ether with perphtalic acid[19] gave 5α-androstan-4α, 17β-diol-3-one 17-acetate, m.p. 197-199°, $[\alpha]_D$ -9° (Chf), which after dehydratation *via* 4-tosylate afforded testosterone acetate. The 4-hydroxyl group proved to be equatorial, since the corresponding 4,17-diacetate, m.p. 196.5-197.5°, $[\alpha]_D$ -24° (Chf), remained unchanged after acid equilibration. By the same treatment, Δ^2-enol ether I afforded 5α-androstan-2α, 17β-diol-3-one diacetate, m.p. 200-201°, $[\alpha]_D$ +40.5° (Chf). M_D increments were in good agreement with the data reported for similar derivatives.[20]

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15 *Cf.* W.S. Johnson and W.F. Johns, *J. Amer. Chem. Soc.* 79, 2005 (1957).

16 *Elsevier's Encyclopaedia of Organic Chemistry* 14s, 2704s (1959).

17 Δ^3-Enolate anions of 5α-3-ketones suitable for 4-methylation were obtained by R.E. Schaub and M.J. Weiss, *Chem. & Ind.* 2003 (1961); *cf.* also G. Stork, P. Rosen and N.L. Goldman, *J. Amer. Chem. Soc.* 83, 2965 (1961).

18 *Cf.* H.J. Ringold, O. Mancera, C. Djerassi, A. Bowers, E. Batres, N. Martinez, E. Necoechea, J. Edwards, M. Velasco, C. Casas Campillo and R.I. Dorfman, *J. Amer. Chem. Soc.* 80, 6464 (1958).

19 *Cf.* J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Org. Chem.* 19, 1509 (1954) and L.L. Smith, J.J. Goodman, H. Mendelsohn, J.P. Dusza and S. Bernstein, *Ibid.* 26, 974 (1961).

20 K.L. Williamson and W.S. Johnson, *J. Org. Chem.* 26, 4563 (1961).

Comparable results were obtained by working on enol ethers derived from other parent steroids.

Thus from cholestenone ethyl enol ether[21] we obtained 3-ethoxy-Δ^3 cholestene, m.p. 64-67°, $[\alpha]_D$ +28° (Di), which on bromination with NBS yielded 4α-bromo-cholestan-3-one, m.p. 150-152°, $[\alpha]_D$ +2° (Chf).[22,23]

Likewise progesterone 3-cyclopentyl enol ether[24] gave 3-cyclopentyloxy-Δ^3-pregnene-20-one, m.p. 95-97°, $[\alpha]_D$ +75° (Di), from which 4α-bromo-5α-pregnane-3,20-dione, m.p. 194-195°, $[\alpha]_D$ +40° (Chf), was prepared.

However, the presence or the lack in the steroid nucleus of certain groups; as for instance 11-ketone or 10-methyl appear to play an important role in determining the structural composition of the products derived from partial hydrogenation of $\Delta^{3,5}$-dienol ethers. Further details will be given later.

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21 E. Schwenk, G. Fleischer and B. Whitman, J. Amer. Chem. Soc. 60, 1702 (1938).

22 R.M. Evans, J.C. Hamlet, J.S. Hunt, P.G. Jones, A.G. Long, J.F. Oughton, L. Stephenson, T. Walker and B.M. Wilson, J. Chem. Soc. 4356 (1956).

23 J. Malunowicz, J. Faikos and F. Sorm, Coll. Czech. Chem. Comm. 25, 1359 (1960).

24 A. Ercoli and R. Gardi, J. Amer. Chem. Soc. 82, 746 (1960).