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# 19-HYDROXY-10-ISOTESTOSTERONE

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WE wish to report the synthesis of 19-hydroxy-10-isotestosterone (XVII), the first example of a steroid hormone analog in which the 10-position, but no other asymmetric center, is inverted. This type of compound is of interest in view of the recent announcement that certain steroid hormone analogs in which both the 9- and the 10-positions are inverted possess interesting biological properties.[1]

19-Nor-$\Delta^4$-androstene-3,17-dione (I)[2] on ozonolysis

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[1] E.H. Reerink, H.F.L. Schöler, P. Westerhof, A. Querido, A.A.H. Kassenaar, E. Diczfalusy and K.C. Tillinger, Nature 186, 168 (1960); P. Westerhof and E.H. Reerink, Rec. Trav. Chim. 79, 771, 794 (1960).

[2] A.L. Wilds and N.A. Nelson, J. Amer. Chem. Soc. 75, 5366 (1953); C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, J. Amer. Chem. Soc. 76, 4092 (1954).

and subsequent oxidation with hydrogen peroxide[3] yielded the diketo-acid (II) [m.p. 179-181°; $[\alpha]_D$ + 72° (all rotations in chloroform). Found : C, 70.00; H, 8.01]. Esterification with diazomethane produced the corresponding methyl ester which with ethylene glycol and p-toluenesulfonic acid in boiling benzene gave the diketal (III) (m.p. 117-119°; $[\alpha]_D$ - 2°. Found : C, 66.67; H, 8.88). The latter was then subjected to a Barbier-Wieland degradation through treatment with phenylmagnesium bromide to yield the diphenyl-carbinol (IV) (m.p. 145-146°; $[\alpha]_D$ + 45°. Found : C, 76.13; H, 8.28), followed by boiling aqueous acetic acid and oxidation of the resulting diketo-diphenyl-ethylene (V) $\lambda_{max}^{EtOH}$ 250 mμ, ε 16,200) with ruthenium tetroxide and sodium periodate in aqueous acetone.[4] The nor-diketo-acid (VI) (m.p. 190-192°; $[\alpha]_D$ + 63°. Found : C, 69.25; H, 8.15) thus obtained appears to exist in the acid form (I.R. bands at 1730 and 1705 $cm^{-1}$), unlike an analogous nor-keto-acid in the 19-methyl series which exists as the lactol.[5]

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[3] See R.B. Turner, J. Amer. Chem. Soc. 72, 579 (1950); A.J. Birch, Chem. and Ind. 616 (1951); J.A. Hartman, A.J. Tomasewski and A.S. Dreiding, J. Amer. Chem. Soc. 78, 5662 (1956).

[4] S. Sarel and Y. Yanuka, J. Org. Chem. 24, 2018 (1959) and references quoted there.

[5] F.L. Weisenborn, D.C. Remy and T.L. Jacobs, J. Amer. Chem. Soc. 76, 552 (1954).

The sequence which had led from the diketo-acid (II) to the diphenyl-ethylene (V) was then repeated with the nor-diketo-acid (VI) and yielded successively the corresponding methyl ester (m.p. 99-100°; $[\alpha]_D$ + 66°. Found : C, 69.62; H, 8.01), the diketal (VII) (m.p. 143-145°; $[\alpha]_D$ - 2°. Found : C, 65.99; H, 8.45), the diphenyl-carbinol (VIII) (m.p. 139-140°; $[\alpha]_D$ + 99°. Found : C, 76.46; H, 8.04) and the diphenyl-ethylene (IX) (m.p. 197-200°; $[\alpha]_D$ + 213°; $\lambda_{max}^{EtOH}$ 250 mμ, ε 18,100. Found : C, 84.27; H, 7.67). Ethylene glycol and p-toluenesulfonic acid in boiling benzene converted (IX) to the diketal (X) (m.p. 194-195°; $[\alpha]_D$ + 83°; $\lambda_{max}^{EtOH}$ 250 mμ, ε 18,600. Found : C, 78.61; H, 7.89), the double bond of which was cleaved by the ruthenium tetroxide method.[4] Esterification of the product with diazomethane and subsequent cleavage of the ketal groupings with aqueous sulfuric acid in boiling methanol produced the dinor-diketo-ester (XI) (m.p. 148-150°; $[\alpha]_D$ + 77°. Found : C, 69.14; H, 7.96).

It is of interest that the β-keto-ester (XI) is not enolic (I.R. bands at 1730 and 1705 $cm^{-1}$ but no hydroxyl band; no color with ferric chloride; no reaction with acetic anhydride and pyridine), doubtlessly due to the $\Delta^{5(10)}$-trans (B/C)-system (steroid numbering) being energetically unfavored[6] and because of steric interaction in the enol between the carbomethoxy group

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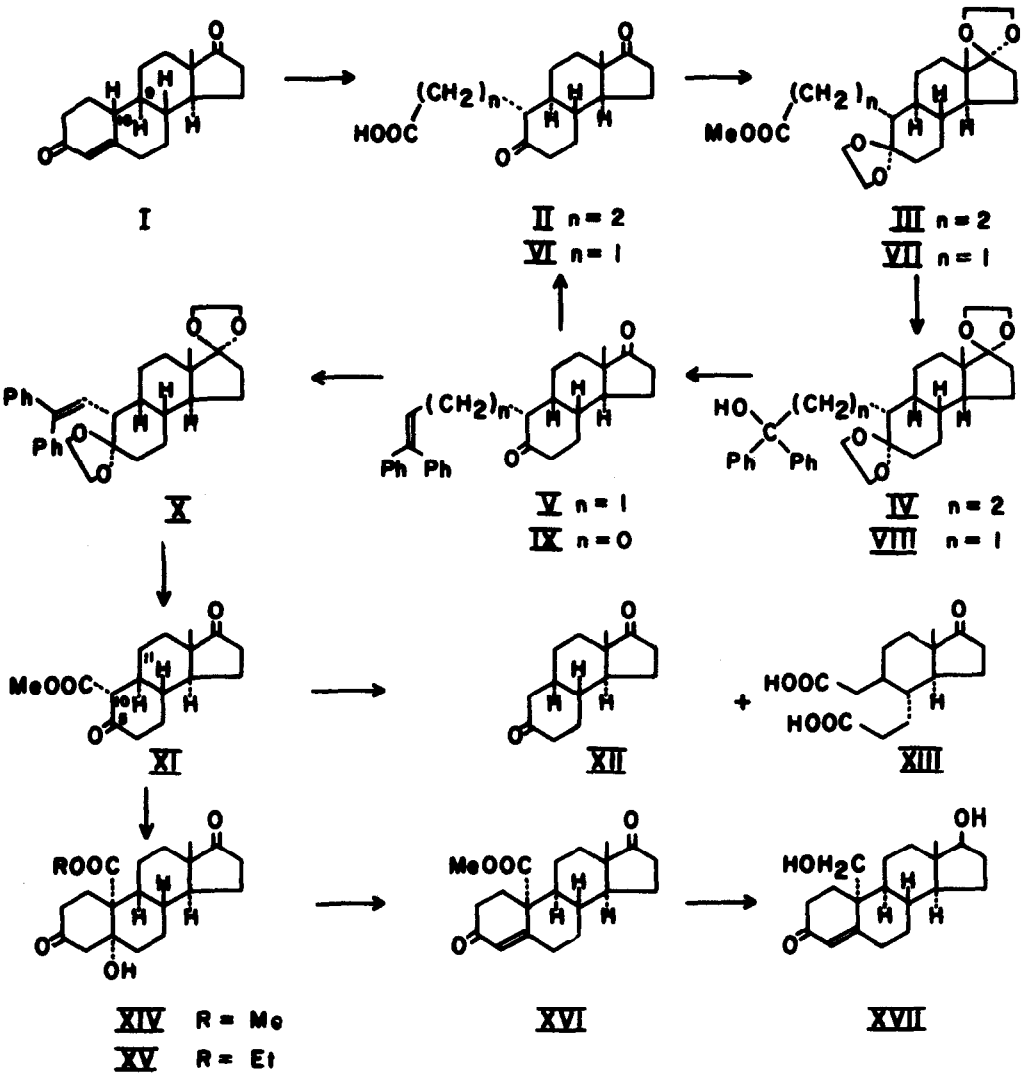
[6] See R.B. Turner, W.R. Meador and R.E. Winkler, J. Amer. Chem. Soc. 79, 4122 (1957).


I
II n = 2
VI n = 1
III n = 2
VII n = 1
IV n = 2
VIII n = 1
V n = 1
IX n = 0
X
XI
XII
XIII
XIV R = Me
XV R = Et
XVI
XVII

and the 11α-hydrogen atom.[7] Nevertheless, saponification with potassium hydroxide in boiling methanol resulted in the decarboxylated diketone (XII) (dioxime : m.p. 202-204°. Found : N, 11.11) besides the dicarboxylic acid (XIII) [m.p. 159-161°; $[\alpha]_D$ + 92° (dioxane). Found : C, 63.68; H, 7.90].

Michael reaction of the β-keto-ester (XI) with methyl vinyl ketone in ethanolic sodium ethoxide at 0-20° led to the ketol methyl ester (XIV) (m.p. 171-173.5°; $[\alpha]_D$ + 39°. Found : C, 68.80; H, 8.27) and the corresponding ethyl ester (XV) (m.p. 122-124°; $[\alpha]_D$ + 36°. Found : C, 69.77; H, 8.27) as the only crystalline products isolated.[8] The methyl ester (XIV) on dehydration with p-toluenesulfonic acid in boiling benzene yielded the unsaturated ketone (XVI) (m.p. 146-148°; $[\alpha]_D$ - 164°; $\lambda_{max}^{EtOH}$ 242 mμ, ε 14,100. Found : C, 72.76; H, 7.92), which must possess the assigned carbon skeleton since 19-nor-$\Delta^4$-androstene-3,17-dione (I) was obtained smoothly on saponification with boiling methanolic potassium hydroxide.

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[7] For similar cases, see P.A. Stadler, A. Nechvatal, A.J. Frey and A. Eschenmoser, Helv. Chim. Acta 40, 1373 (1957); N.A. Nelson and R.N. Schut, J. Amer. Chem. Soc. 80, 6630 (1958); E. Wenkert and B.G. Jackson, J. Amer. Chem. Soc. 81, 5601 (1959).

[8] Experiments which point to the ketol structures (XIV) and (XV) rather than to the alternative bridged-ring formulations (W.S. Johnson, J.J. Korst, R.A. Clement and J. Dutta, J. Amer. Chem. Soc. 82, 614 (1960)) will be reported in the full paper.

Finally (XVI) was reduced with lithium aluminum hydride in boiling tetrahydrofuran and the product re-oxidized with manganese dioxide in chloroform,[9] whereby 19-hydroxy-10-isotestosterone (XVII) [m.p. 199.5-201°; $[\alpha]_D$ - 215°; $\lambda_{max}^{EtOH}$ 244-249 mμ (plateau), ε 13,800. Found : C, 75.17; H, 9.42] was formed. The identical compound resulted when the ketol ethyl ester (XV) was subjected to the same reaction sequence as described for the methyl ester (XIV). The 10-iso formulation for (XVII) follows from the optical rotatory dispersion curve (negative multiple Cotton effect; to be discussed in the full paper) and the non-identity with 19-hydroxytestosterone ($[\alpha]_D$ + 110°).[10] The unusual U.V. spectrum of (XVII) is presumably due to interaction between the 19-hydroxy and the $\Delta^4$-3-ketone groupings, since the corresponding diacetate showed a normal spectrum ($\lambda_{max}^{EtOH}$ 239 mμ).

All the compounds described showed I.R. spectra compatible with the assigned structures.

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[9] Method of F. Sondheimer, C. Amendolla and G. Rosenkranz, J. Amer. Chem. Soc. 75, 5930 (1953).

[10] M. Ehrenstein and K. Otto, J. Org. Chem. 24, 2006 (1959).

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