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THE SYNTHESIS OF 19-HYDROXY-10α-TESTOSTERONE

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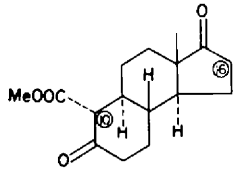
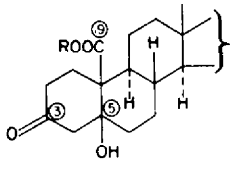
Abstract—The degradation of 19-norandrost-4-ene-3,17-dione (IV) to the tricyclic diketo-ester (I) is described. Michael condensation between I and methyl vinyl ketone in ethanolic sodium ethoxide yielded the 10α-carbomethoxy-ketol (XVIIIa), as well as the 10α-carboethoxy-ketol (XVIIIb). Dehydration of these ketols led to the corresponding Δ^4-3-ones (XIXa and XIXb), respectively. Reduction of either XIXa or XIXb with $LiAlH_4$ and subsequent oxidation with MnO_2 furnished 19-hydroxy-10α-testosterone (XXIIIa).

IN THIS paper we report the degradation of 19-norandrost-4-ene-3,17-dione (IV) to the tricyclic diketo-ester (I), and the Michael condensation between the latter substance and methyl vinyl ketone. It was anticipated that attack of the β-keto-ester (I) would occur at C-10,[1] although the stereochemical course of the reaction was uncertain. In any event, compounds of interest were expected to be formed, irrespective of whether attack of methyl vinyl ketone proceeded from the α or from the β-side at



I



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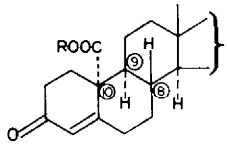

III

C-10. In the former case, a ketol of type II might have been produced, which contains the same oxygen substitution pattern at C-3, C-5 and C-19 as the cardiac aglycones of the strophanthidin type.[2] In the case of β-attack, dehydration of the product should lead to a 10α-ester (type III), which represents an unusual new modification of the normal steroid structure.

As already reported in preliminary form,[3] it was found in practice that the reaction under discussion gave rise only to 10α-esters (type III), which could be converted

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[1] This, however, is apparently not the case when the activating 10-carbomethoxy group is absent. Thus, it has been shown that a substance differing from I by possessing a 10-methyl instead of the 10-carbomethoxy group (and very probably also in stereochemistry) is attacked mainly at the C-16 position on condensation with 4-diethylaminobutan-2-one methiodide [R. H. Martin and Sir R. Robinson, *J. Chem. Soc.* 491 (1943); 1866 (1949)].

[2] See L. F. Fieser and M. Fieser, *Steroids* Chap 20. Reinhold, New York, N.Y. (1959).

[3] F. Sondheimer, R. Mechoulam and M. Sprecher, *Tetrahedron Letters* No. 22, 38 (1960).

simply to 19-hydroxy-10α-testosterone (XXIIIa). This represents the first synthesis 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 demonstration that certain 9β,10α-steroid hormone analogs (in which both the 9 and the 10 positions are inverted)[4] possess marked hormonal and anti-hormonal properties.[5] Since the appearance of our preliminary communication,[3] syntheses of other 10α-steroid hormone analogs,[6,7] as well as of 8α,10α-analogs[8] have been reported.[9] We now describe our work in detail.

19-Norandrost-4-ene-3,17-dione (IV)[10] on ozonolysis and subsequent oxidation with hydrogen peroxide yielded 80% of the diketo-acid (Va).[11] Esterification with diazomethane led to the corresponding methyl ester (Vb), the keto-groups in which were protected through conversion to the biscycloethylene ketal (VI) by means of ethylene glycol in the presence of *p*-toluenesulfonic acid. The bisketal (VI) was then subjected to Barbier-Wieland degradation.[12] Treatment with phenylmagnesium bromide furnished the diphenyl-carbinol (VII), which was dehydrated with boiling aqueous acetic acid (with concomitant removal of the ketal functions) to give the diketo-diphenyl-ethylene (VIII). The cleavage of the double bond in this compound by conventional means (e.g., with ozone or chromium trioxide in acetic acid) proceeded poorly. However, after some experimentation, it was found that the required reaction could be brought about smoothly through the action of sodium metaperiodate and a catalytic amount of ruthenium tetroxide,[13] whereby the nor-diketo-acid (IXa) was produced. The over-all yield from the diketo-acid (Va) was ca. 26%.

The nor-diketo-acid (IXa) exhibited IR spectral properties (Experimental), indicating it to exist in the acid form. This is in contrast to an analogous nor-keto-acid in the 19-methyl series, which has been shown to exist as the lactol.[12]

[4] P. Westerhof and E. H. Reerink, *Rec. Trav. Chim.* **79**, 771, 794, 1118 (1960); M. P. Rappoldt and P. Westerhof, *Ibid.* **80**, 43 (1961); A. Smit and P. Westerhof, *Ibid.* **82**, 1107 (1963).

[5] E. H. Reerink, H. F. L. Schöler, P. Westerhof, A. Querido, A. A. H. Kassenaar, E. Diczfalusy and K. G. Tillinger, *Nature, Lond.* **186**, 168 (1960); H. F. L. Schöler and A. M. de Wachter, *Acta Endocrinol.* **35**, 188 (1960); K. G. Tillinger and E. Diczfalusy, *Ibid.* **35**, 197 (1960).

[6] R. Wenger, H. Dutler, H. Wehrli, K. Schaffner and O. Jeger, *Helv. Chim. Acta* **45**, 2420 (1962).

[7] K. Heusler and J. Kalvoda, *Tetrahedron Letters* 1001 (1963).

[8] P. Westerhof and A. Smit, *Rec. Trav. Chim.* **80**, 1048 (1961).

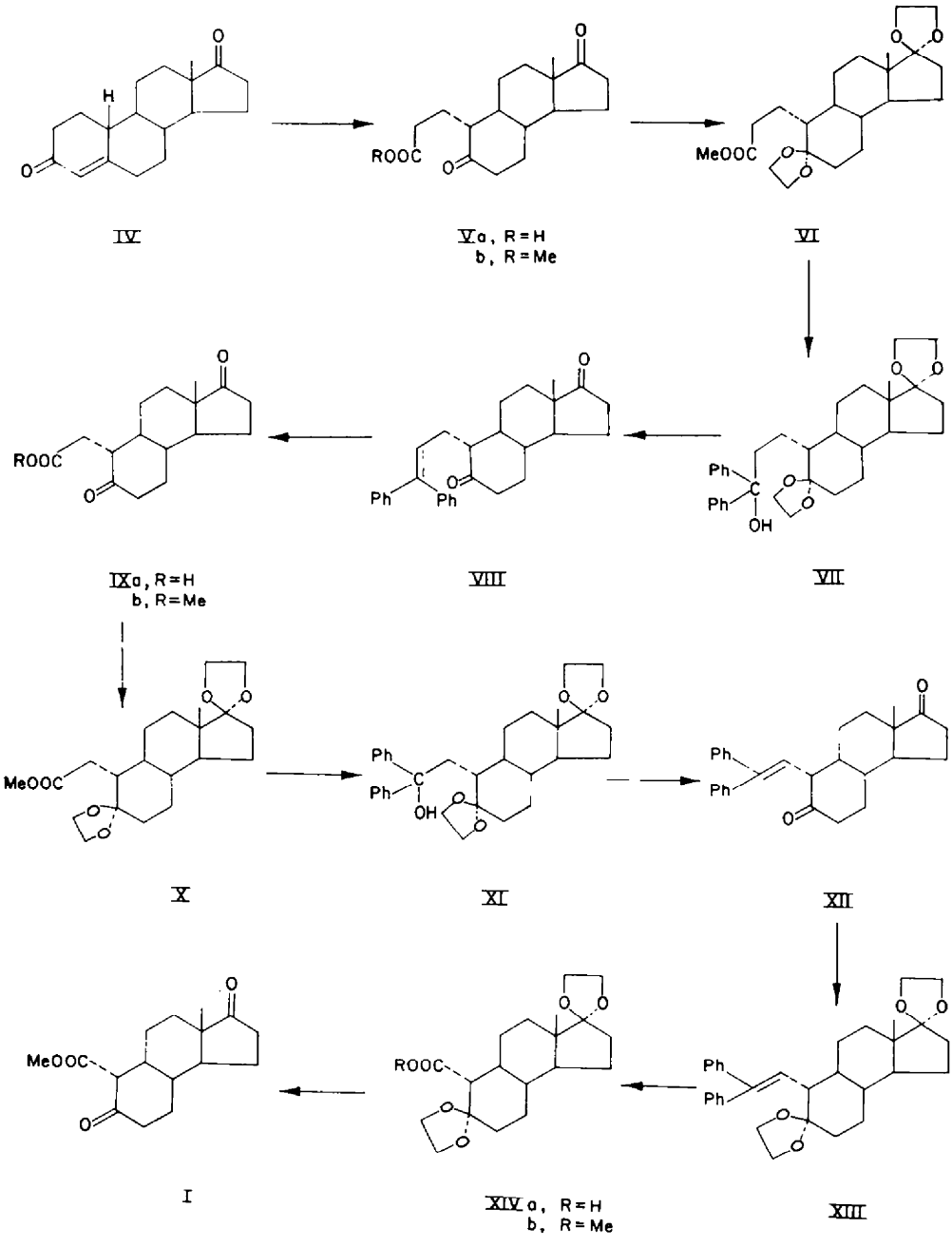
[9] See also the synthesis of a variety of 10α-, 9β,10α-, and 8α,10α-steroids in the ergostane series [J. Castells, E. R. H. Jones, G. D. Meakins, S. Palmer and R. Swindells, *J. Chem. Soc.* 2907 (1962), and earlier papers], the synthesis of certain 10α-substituted steroids [M. Torigoe and J. Fishman, *Tetrahedron Letters* 1251 (1963)], the synthesis of 10α-19-nor-steroids [R. E. Counsell, *Tetrahedron* **15**, 202 (1961), and references cited there], as well as of 9β,10α-19-nor-steroids [L. Velluz, G. Nominé, R. Bucourt, A. Pierdet and J. Tessier, *C.R. Acad. Sci., Paris* **252**, 3903 (1961); M. Legrand and J. Mathieu, *Bull. Soc. Chim. Fr.* 1679 (1961); J. A. Edwards, P. Crabbé and A. Bowers, *J. Amer. Chem. Soc.* **85**, 3313 (1963)].

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

[11] Similar oxidations have been carried out previously with other Δ^4-3-ones [see R. B. Turner, *J. Amer. Chem. Soc.* **72**, 579 (1950)] and 19-nor-Δ^4-3-ones [A. J. Birch, *Chem. & Ind.* 616 (1951); J. A. Hartman, A. J. Tomasewski and A. S. Dreiding, *J. Amer. Chem. Soc.* **78**, 5662 (1956)].

[12] See F. Weisenborn, D. C. Remy and T. L. Jacobs [*J. Amer. Chem. Soc.* **76**, 552 (1954)] for a related degradation in the 19-methyl series.

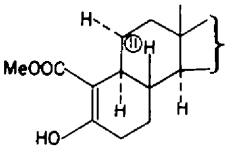
[13] See R. Pappo and A. Becker, *Bull. Res. Council Israel* **5A**, 300 (1956); S. Sarel and Y. Yanuka, *J. Org. Chem.* **24**, 2018 (1959); G. Stork, A. Meisels and J. E. Davies, *J. Amer. Chem. Soc.* **85**, 3419 (1963).



The sequence which had led from the diketo-acid (Va) to the diphenyl-ethylene (VIII) was then repeated with the nor-diketo-acid (IXa), and yielded successively the methyl ester (IXb), the diketal (X), the diphenyl carbinol (XI) and the diphenyl-ethylene (XII). Direct double bond cleavage in the last-mentioned compound would have given a β-keto-acid, which might have undergone decarboxylation. Substance XII was therefore converted first to the bisketal (XIII), which was then subjected to

the ruthenium tetroxide–sodium periodate oxidation. Esterification of the resulting bisnor-acid (XIVa) with diazomethane led to the methyl ester (XIVb), which was treated with aqueous sulfuric acid in boiling methanol in order to remove the ketal protecting groups. This procedure led to the desired bisnor-diketo-ester (I), the overall yield from the nor-diketo-acid (IXa) being ca. 30%.[14]

The 10-carbomethoxy grouping in the bisnor-diketo-ester (I) is assigned the equatorial α-configuration, since there is no reason why epimerization to the axial β-isomer should have occurred. It is of interest that this compound, though being a β-keto-ester, is not enolic. Thus, it showed no color with ferric chloride, it was recovered unchanged on treatment with acetic anhydride and pyridine, and the IR spectrum (in chloroform) showed bands at 5·75μ (ester and 17-one) and 5·85μ (5-one), but no hydroxyl band. This non-enolic character is presumably due to the fact that the enol (XV) would contain a *trans*-Δ^1-octalin system which is unfavored for energetic reasons,[15] and because of steric repulsion between the carbomethoxy group and the



XV

equatorial 11α-hydrogen atom.[16] Nevertheless, saponification of the diketo-ester (I) with potassium hydroxide in boiling methanol led to ca. 40% of the decarboxylated diketone (XVI), which was characterized as the dioxime. This reaction in addition yielded ca. 45% of the opened keto-diacid (XVIIa).[17] Treatment of this diacid with diazomethane gave the corresponding dimethyl ester (XVIIb), which was also obtained directly from the diketo-ester (I) by means of methanolic sodium methoxide at room temperature.

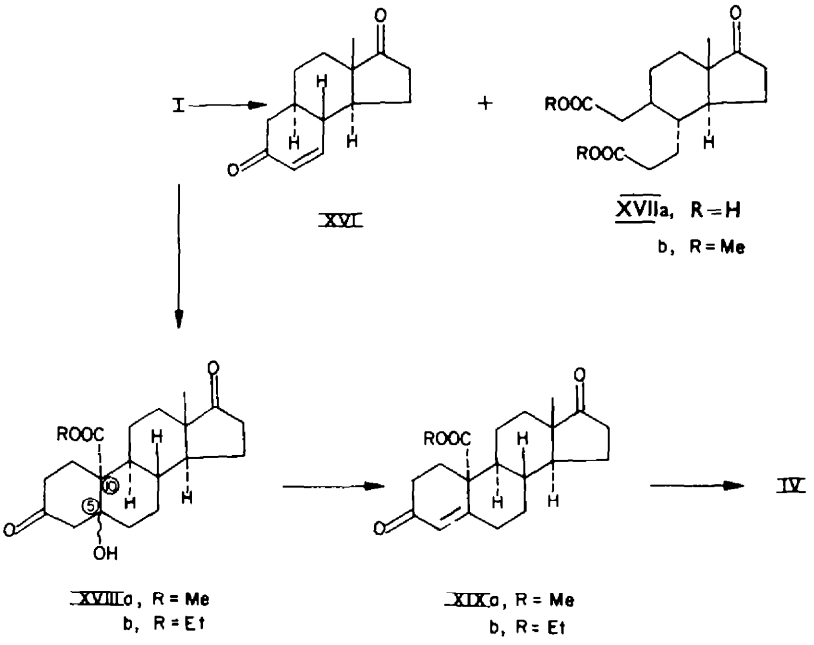
The Michael condensation between the diketo-ester (I) and methyl vinyl ketone was carried out in ethanolic sodium ethoxide at 0–20°. This reaction led to two apparently isomeric adducts as sole crystalline materials, in a total yield of ca. 30%. These substances, which could not be separated efficiently by chromatography on alumina or fractional crystallization, were at first thought to be C-10 stereoisomers. However towards the end of the investigation it became clear that the difference between the two compounds was trivial, one being the 10α-carbomethoxy-ketol (XVIIIa) and the other the corresponding ethyl ester (XVIIIb; formed by ester interchange). In agreement with the assigned structures, the molecular rotation values of

[14] The preparation of a bisnor-keto-ester which differs from I only in possessing a 17β-acetoxy instead of a 17-keto group, by a route resembling that described by us, has been reported very recently [E. Caspi and D. M. Piatak, *Experientia* **19**, 465 (1963)].

[15] See E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.* **77**, 2505 (1955); R. B. Turner, W. R. Meador and R. E. Winkler, *Ibid.* **79**, 4122 (1957).

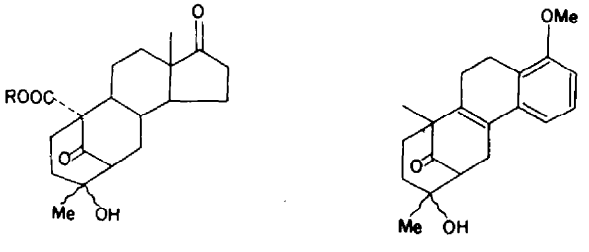
[16] For similar cases: [a] P. A. Stadler, A. Nechvatal, A. J. Frey and A. Eschenmoser, *Helv. Chim. Acta* **40**, 1373 (1957); [b] N. A. Nelson and R. N. Schut, *J. Amer. Chem. Soc.* **80**, 6630 (1958); [c] E. Wenkert and B. G. Jackson, *Ibid.* **81**, 5601 (1959); [d] G. Stork, P. Rosen and N. L. Goldman, *J. Amer. Chem. Soc.* **83**, 2965 (1961).

[17] For an analogous conversion of a steroidal β-keto-ester to a *seco*-diacid, see Ref. 16*b*.



the two substances were identical within experimental error (+134 for XVIIIa, +132 for XVIIIb), and the methyl ester (XVIIIa) was eluted from an alumina chromatography column after the ethyl ester (XVIIIb).

The 10α-configuration of the esters (XVIIIa and XVIIIb) follows from the experiments described below. The IR spectra of the two substances (which were very similar to each other) showed pronounced hydroxyl bands, indicating ketol rather than open 1,5-diketone formulations. The ketols appear to possess the structures XVIIIa and XVIIIb (stereochemistry at C-5 not determined) rather than the bridged-ring structures XXa and XXb of the type demonstrated for related ketols, such as XXI.[18] This follows from the fact that dehydration of the carbomethoxy-ketol (XVIIIa) with phosphorus oxychloride in pyridine at 90° led to the αβ-unsaturated ketone, XIXa



[18] See W. S. Johnson, J. J. Korst, R. A. Clement and J. Dutta, *J. Amer. Chem. Soc.* **82**, 614 (1960).

(see below), though only in poor yield.[19] On the other hand, bridged-ring ketols of type XXI under these conditions have been shown to give rise to $\beta\gamma$-unsaturated ketones with an unaltered carbon skeleton,[18] and repetition of the dehydration of the ketol (XXI, isomer a)[18] in our hands with phosphorus oxychloride–pyridine under the identical conditions used with the ketol (XVIIIa) gave no trace of $\alpha\beta$-unsaturated ketone.

The dehydration of the carbomethoxy-ketol (XVIIIa) was investigated under various conditions. The best results were achieved by use of *p*-toluenesulfonic acid in boiling benzene, whereby the 10α-carbomethoxy-Δ^4-3-one (XIXa) was obtained in ca. 60% yield.[20] From a preparative standpoint, it was found most convenient to carry out the dehydration of the mixed ketols (XVIIIa and XVIIIb) under these conditions, when the unsaturated methyl ester (XIXa) was the only crystalline transformation product to be isolated after chromatography. In agreement with the assigned structure, substance XIXa showed an UV maximum (in ethanol) at 242 mμ (ε 14,100) and IR bands (in chloroform) at 5·78 μ (ester and 17-one), as well as at 5·99 and 6·14 μ (Δ^4-3-one). The correctness of the carbon skeleton assumed for XIXa was confirmed by the fact that treatment with boiling methanolic potassium hydroxide smoothly led to 19-norandros-4-ene-3,17-dione (IV) in excellent yield.[21]

Reduction of the diketo-ester (XIXa) with lithium aluminum hydride in boiling tetrahydrofuran resulted in a product, showing hydroxyl but no carbonyl bands in the IR, which presumably consists of a mixture of the 3β,17β,19-triol (XXIIa) and the 3α,17β,19-triol (XXIIb).[22] The triol mixture was then oxidized directly with manganese dioxide in chloroform at room temperature, whereby 19-hydroxy-10α-testosterone (XXIIIa) was obtained in ca. 45% yield (based on XIXa).[23]

In accord with structure XXIIIa, the manganese dioxide oxidation product showed an IR spectrum indicative of the presence of an $\alpha\beta$-unsaturated ketone as well as of hydroxyl groups. However, the UV spectrum was somewhat anomalous, exhibiting a maximum (in ethanol) at 246 mμ (ε 13,800). By comparison, 19-hydroxytestosterone, the corresponding 10β-epimer,[24] shows a relatively normal UV maximum at 243 mμ,

[19] The poor yield in this reaction must be due to the fact that the product (XIXa) is attacked further under the experimental conditions employed, as was determined in a blank experiment with XIXa.

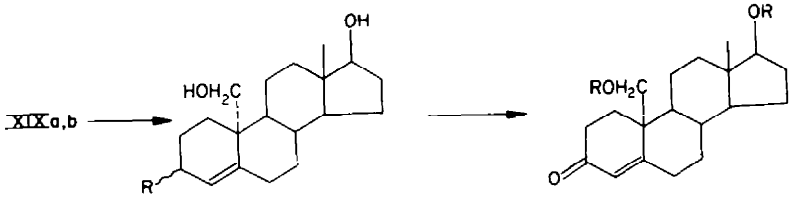
[20] The formation of the $\alpha\beta$-unsaturated ketone (XIXa) from the ketol (XVIIIa) by means of *p*-toluenesulphonic acid does not throw any light on the structure of this ketol, since the bridged-ring ketol (XXI, isomer a)[18] under the same conditions was found by us to give rise to the corresponding $\alpha\beta$-unsaturated ketone. The same transformation of XXI has already been reported to take place by heating with *p*-toluenesulphonic acid in butyl acetate and toluene [W. S. Johnson, J. Ackerman, J. F. Eastham and H. A. DeWalt, *J. Amer. Chem. Soc.* **78**, 6302 (1956)].

[21] After completion of this work, the synthesis of the 10β-epimer of XIXa was reported [H. Hagiwara, S. Noguchi and M. Nishikawa, *Chem. Pharm. Bull., Tokyo* **8**, 84 (1960); *Chem. Abstr.* **55**, 3653 (1961)]. The $[\alpha]_D$ value (+273° in dioxane) of the latter substance was completely different from from that of XIXa (−164° in chloroform), confirming the 10α-configuration of our substance.

[22] *Inter al.*, see W. G. Dauben, R. A. Micheli and J. F. Eastham, *J. Amer. Chem. Soc.* **74**, 3852 (1952).

[23] The $LiAlH_4$–MnO_2 sequence has been used previously for related transformations, e.g. for the conversion of androst-4-ene-3,17-dione to testosterone [F. Sondheimer, C. Amendolla and G. Rosenkranz, *J. Amer. Chem. Soc.* **75**, 5930 (1953)] and of androst-4-ene-3,11,17-trione to 11β-hydroxytestosterone [O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 2189 (1953)].

[24] M. Ehrenstein and K. Otto, *J. Org. Chem.* **24**, 2006 (1959); see also K. Heusler, J. Kalvoda C. Meystre, H. Ueberwasser, P. Wieland, G. Anner and A. Wettstein, *Experientia* **18**, 464 (1962); P. N. Rao and L. R. Axelrod, *J. Org. Chem.* **27**, 4694 (1962).



XXIIa, R = —OH
b, R = ---OH

XXIIIa, R = H
b, R = Ac

and other 19-hydroxy-10β-Δ⁴-3-ones have also been found to exhibit normal maxima at 242–243 mμ.[25] The bathochromic shift exhibited by XXIIIa appears to be associated with the 10α-Δ⁴-3-one grouping, since both 10α-testosterone (λ_{max}^{EtOH} 246 mμ)[6] and 6α-methyl-10α-progesterone (λ_{max}^{EtOH} 245 mμ)[7] have now been found to exhibit similar shifts. It is to be noted however that the 17,19-diacetate (XXIIIb), obtained by acetylation of XXIIIa, showed a normal UV maximum at 239 mμ.

The 10α-configuration of 19-hydroxy-10α-testosterone (XXIIIa), and hence of the precursors XVIIIa and XIXa, follows from several considerations. Firstly, the physical properties of substance XXIIIa differed from those of 19-hydroxytestosterone,[24] and direct comparison showed the two compounds not to be identical. Secondly, the molecular rotation difference (+988) in passing from 19-hydroxytestosterone[24] to XXIIIa is in good agreement with the corresponding difference in passing from the 10β- to the 10α-epimer in the case of testosterone (+939),[6] and 6α-methylprogesterone (+950).[7] Lastly, the optical rotatory dispersion (ORD) curve of XXIIIa (multiple negative Cotton effect, see Experimental for details) was very similar in shape to that of 10α-testosterone,[26,27] and essentially antipodal to that of testosterone.[28]

Finally, some experiments are reported which provide evidence that the ketol ethyl ester (XVIIIb) also belongs to the 10α-series. Dehydration of this substance with *p*-toluenesulfonic acid under the same conditions used with the ketol methyl ester (XVIIIa) led to the corresponding 10α-carboethoxy-Δ⁴-3-one (XIXb). The last mentioned compound, however, could not be crystallized, and was not isolated in pure form. It was converted by lithium aluminum hydride reduction and subsequent oxidation with manganese dioxide to 19-hydroxy-10α-testosterone (XXIIIa), identical with that obtained from the methyl ester (XIXa).

EXPERIMENTAL

M.ps are uncorrected. All chromatograms were carried out with Merck "acid-washed" alumina, unless otherwise stated. Rotations were determined at room temp in $CHCl_3$ solution, unless specified

[25] *Inter al.*, M. Ehrenstein, G. W. Barber, M. W. Gordon, P. T. Herzig and M. Dünnenberger, *J. Org. Chem.* **16**, 349 (1951); **17**, 713 (1952); **19**, 1758 (1954); **21**, 774, 783 (1956); A. S. Meyer, *Experientia* **11**, 99 (1955); A. Bowers, R. Villotti, J. A. Edwards, E. Denot and O. Halpern, *J. Amer. Chem. Soc.* **84**, 3204 (1962); B. Berkoz, E. Denot and A. Bowers, *Steroids* **1**, 251 (1963).

[26] The ORD curve of 10α-testosterone was kindly sent by Dr. K. Schaffner, who informed us that the signs of the ORD values given for this substance in publication[6] should be reversed.

[27] Other related systems which show rather similar multiple negative Cotton effect curves are (5S, 10R)-5-hydroxy-10-methyl-Δ¹⁽⁹⁾-2-octalone [C. Djerassi, J. Osiecki and W. Herz, *J. Org. Chem.* **22**, 1361 (1957)], (5S, 10R)-10-methyl-Δ¹⁽⁹⁾-2-octalone [C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.* **80**, 3986 (1958)] and 17β-hydroxy-9β,10α-androst-4-en-3-one (R. van Moorselaar, Ph.D. Thesis, p. 35). University of Leiden (1962).

[28] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6377 (1956).

otherwise. UV spectra were measured in 95% ethanol solution on a Cary model 14 recording spectrophotometer. IR spectra were determined in $CHCl_3$ solution (except those marked "KBr", which were measured as KBr pellets) on a Baird double-beam, or a Perkin–Elmer Infracord, recording spectrophotometer with NaCl optics. Analyses were carried out in our microanalytical laboratory under the direction of Mr. Erich Meier.

Diketo-acid (Va)

A solution of 12·5 g IV[10] in 310 ml ethyl acetate and 60 ml acetic acid was ozonized with a stream of 3% ozonized oxygen at −20° until an aliquot on IR examination no longer exhibited a band at 6·00 μ (ca. 4½ hr). A solution of 12·5 ml acetic acid, 10 ml H_2O_2aq (30%) and 25 ml water were added, and the mixture was allowed to stand for 16 hr at room temp. It was then diluted with water and extracted with ether. The ethereal solution was extracted several times with ice-cold 5% NaOHaq, and the combined alkaline extracts were acidified with conc. HClaq. Extraction with ether and ethyl acetate, drying, evaporation and crystallization from ethyl acetate–pentane afforded 10·7 g (80%) diketo-acid (Va), m.p. 176–180°. Further crystallization led to the analytical sample, m.p. 179–181°; $[\alpha]_D$ +72°; IR bands at 2·82 μ *et seq.* (hydroxyl of carboxyl), 5·78 μ (17-one) and 5·84 μ (5-one and carboxyl). (Found: C, 70·00; H, 8·01. $C_{17}H_{24}O_4$ requires: C, 69·83; H, 8·27%).

The reaction was repeated several times, a total of 63 g IV being converted to 53·7 g Va.

Diketal (VI)

An ethereal solution of diazomethane was added slowly to a solution of 53·7 g (Va) in acetone at 0° until the yellow colour of the reagent persisted. The solution was then allowed to stand for 20 min at room temp. Acetic acid was added dropwise until the excess diazomethane had been destroyed, and the solvents were then evaporated under red. press. The resulting oil (56·3 g), consisting of the methyl ester (Vb), could not be crystallized and was used directly for the next step; IR bands at 5·79 μ (ester and 17-one) and 5·83 μ (5-one).

A solution containing 56·3 g (Vb), 2 g *p*-toluenesulphonic acid monohydrate and 80 ml ethylene glycol in 2 l. benzene was boiled under reflux for 15 hr, the water being removed by azeotropic distillation by use of a Dean–Stark tube. The cooled reaction mixture was washed with sat. $NaHCO_3$aq, and then several times with water. The organic layer was dried and evaporated. Crystallization from methanol containing a trace of pyridine yielded the diketal (VI; 53·1 g; 73% from Va), m.p. 114–117°. A further purified sample showed m.p. 117–119°; $[\alpha]_D$ −2°; IR band at 5·78 μ (ester). (Found: C, 66·67; H, 8·88. $C_{23}H_{34}O_6$ requires: C, 66·98; H, 8·69%).

Diphenyl-carbinol (VII)

A solution of 53 g (VI) in 100 ml dry benzene and 700 ml dry ether was added dropwise during 1 hr to a solution of PhMgBr (prepared from 26·5 g Mg turnings and 125 ml bromobenzene in 400 ml ether), with stirring and ice-cooling. The mixture was stirred at room temp for 6 hr and then allowed to stand overnight. The mixture was cooled in ice, and sat. NH_4Cl aq was added slowly until the organic layer became clear. This layer was separated, and the precipitated Mg salts were washed well with ether. The combined organic extracts were then steam distilled, in order to remove biphenyl. Extraction with ether, drying, evaporation and crystallization from ether–pentane yielded 33·2 g diphenyl-carbinol (VII), m.p. 144–145°. Chromatography of the mother liquors on alumina (Alcoa activated, grade F-20), elution with benzene–ether (1:1), and crystallization from ether–pentane, furnished another 13·9 g (VII), m.p. 141–145° (total yield, 47·1 g; 68%). Further crystallization led to the analytical sample, m.p. 145–146°; $[\alpha]_D$ +45°; IR band at 2·93 μ (hydroxyl), no carbonyl bands. (Found: C, 76·13; H, 8·28. $C_{35}H_{42}O_5$ requires: C, 76·41; H, 8·16%).

Ruthenium tetroxide reagent

A mixture of 200 mg RuO_2[29] and 2 g powdered $NaIO_4$ was stirred in 100 ml water. An immediate reaction took place, gas was evolved and the solid components dissolved to give a yellow solution. A further 2 g $NaIO_4$ was then added. The yellow solution if allowed to stand in a closed vessel slowly covers the walls and stopper with a black deposit. During oxidation with this reagent, $NaIO_4$ should be added whenever the solution loses its yellow colour and turns black.

[29] Prepared according to E. Müller and K. Schwabe, *Z. Elektrochem.* **35**, 165 (1929). Inferior results were obtained with commercial material.

Nor-diketo-ester (IXb)

A solution of 6 g diphenyl-carbinol (VII) in 125 ml acetic acid and 4 ml water was boiled under reflux for 3 hr. Evaporation of the solvents under red. press. furnished the crude diketo-diphenyl-ethylene (VIII) as an oil which could not be crystallized; UV λ_{max} 250 mμ (ε 16,200); IR bands at 5·78 μ (17-one) and 5·84 μ (5-one), no hydroxyl band.

This material dissolved in 50 ml acetone was added to the above-described ruthenium tetroxide reagent (from 200 mg RuO_2), which was stirred magnetically. The mixture turned brown and then black. Water (50 ml) was added, followed by solid $NaIO_4$ (ca. 1 g) until the solution regained the yellow color. Stirring was then continued for another 6 hr, further additions of 1 g periodate being made whenever the black colour of RuO_2 appeared. Isopropyl alcohol (ca. 20 ml) was added, the black precipitate was removed by filtration and washed well with acetone. The combined filtrate and washings were evaporated almost to dryness under red. press., ethyl acetate and sat. NaClaq were added, and the organic layer was extracted with 5% NaOHaq. The basic solution was cooled in ice, acidified with conc. HClaq, and extracted with chloroform. This extract was washed with water, dried and evaporated. The resulting crude nor-diketo-acid (IXa) was used directly for esterification. A small sample after crystallization from chloroform–heptane showed m.p. 190–192°; $[\alpha]_D$ +63°; IR bands at 2·85 μ *et seq.* (hydroxyl of carboxyl), 5·78 μ (17-one) and 5·85 μ (5-one and carboxyl), no band at ca. 5·67 μ (γ-lactone).[12] (Found: C, 69·25; H, 8·15. $C_{16}H_{22}O_4$ requires: C, 69·04; H, 7·97%).

The crude not-diketo-acid (IXa) was dissolved in 100 ml acetone, and excess ethereal diazomethane was added. The solution was allowed to stand at room temp for 30 min, and the excess reagent was then destroyed by the dropwise addition of glacial acetic acid. The solvents were removed under red. press., and the residue was chromatographed on alumina. Elution with benzene–ether (2:1), followed by crystallization from ethyl acetate–pet. ether, yielded 1·79 g IXb (53% over-all from VII), m.p. 94–95°. Further crystallization led to the analytical sample, m.p. 99–100°; $[\alpha]_D$ +66°; IR broad band at 5·80 μ (superimposed 5-one, 17-one and ester). (Found: C, 69·62; H, 8·01. $C_{17}H_{24}O_4$ requires: C, 69·83; H, 8·27%).

The reaction was repeated several times, a total of 47 g VII giving rise to 14·1 g IXb.

Diphenyl-carbinol (XI)

The nor-diketo-ester (IXb; 14 g) was converted to the diketal (X), exactly as described above for the diketal (VI). Substance X was used directly for the next step. A small sample on crystallization from methanol exhibited m.p. 143–145°; $[\alpha]_D$ −2°; IR band at 5·78 μ (ester). (Found: C, 65·99; H, 8·45. $C_{21}H_{32}O_6$ requires: C, 66·30; H, 8·48%).

The crude diketal (X) was allowed to react with PhMgBr, and the product was isolated, exactly as described above for the diphenyl-carbinol (VII). Chromatography on alumina (Alcoa activated, grade F-20) and elution with benzene–ether (1:1) furnished the diphenyl-carbinol (XI) as an oil, which crystallized on being seeded.[30] Crystallization from ether–pet. ether yielded 18·7 g (XI; 77% based on IXb), m.p. 135–138°. The analytical sample exhibited m.p. 139–140°; $[\alpha]_D$ +99°; IR band at 2·88 μ (hydroxyl), no carbonyl bands. (Found: C, 76·46; H, 8·04. $C_{32}H_{40}O_5$ requires: C, 76·16; H, 7·99%).

Diphenyl-ethylene diketal (XIII)

A solution of 16·2 g diphenyl-carbinol (XI) in 250 ml acetic acid and 5 ml water was boiled under reflux for 4 hr. Evaporation of the solvents under red. press. yielded the crude diketo-diphenyl-ethylene (XII), which was used directly for the next step. A small sample on crystallization from methanol showed m.p. 197–200°; $[\alpha]_D$ +213°; UV λ_{max} 250 mμ (ε 18,100); IR bands (KBr) at 5·75 μ (17-one) and 5·84 μ (5-one), no hydroxyl band. (Found: C, 84·27; H, 7·67. $C_{38}H_{50}O_4$ requires: C, 84·38; H, H, 7·59%).

The crude substance (XII) was transformed to the diketal (XIII), exactly as described above for the diketal (VI). Crystallization from methanol led to 11·5 g (XIII; 74% based on XI), m.p. 189–192°.

[30] Substance XI could not be induced to crystallize in early experiments. However in one case a chromatography fraction crystallized after being allowed to stand for 3 months, and this material was used for seeding.

A further purified specimen exhibited m.p. 194–195°; $[\alpha]_D$ +83°; UV λ_{max} 250 mμ (ε 18,600); IR no hydroxyl or carbonyl bands. (Found: C, 78·61; H, 7·89. $C_{32}H_{38}O_4$ requires: C, 78·98; H, 7·87%).

Bisnor-diketo-ester (I)

A solution of 585 mg diketal (XIII) in 25 ml acetone was added to a ruthenium tetroxide solution (prepared as described above from 150 mg RuO_2[29] and 3 g $NaIO_4$ in 50 ml water). The mixture was then stirred for 2 hr, during which time 2 g periodate was added in 500 mg portions. The reaction was terminated by the addition of isopropyl alcohol (ca. 20 ml). The mixture was filtered, and the precipitate was washed well with acetone. The combined filtrates were evaporated to dryness, and the residue was extracted with chloroform. The organic extract on being dried and evaporated yielded 410 mg crude bisnor-acid (XIVa) as an oil which was not purified further; IR bands at 2·84 μ *et seq.* (hydroxyl of carboxyl) and 5·83 μ (carboxyl).

The crude substance (XIVa) was dissolved in 50 ml acetone, and excess ethereal diazomethane was added. The solution was allowed to stand at room temp for 1 hr, when the excess reagent was destroyed by means of acetic acid. Evaporation of the solvents led to the crude ester XIVb [IR band (KBr) at 5·74 μ (ester)], which was subjected directly to ketal cleavage through 2 hr boiling with 20 ml methanol and 2 ml 10% H_2SO_4aq. The solution was cooled in ice, neutralized with $NaHCO_3$aq, and extracted well with ether. The organic layer was washed with water, dried and evaporated The residue (290 mg) was then chromatographed on alumina. Elution with benzene–ether (5:1), followed by crystallization from ethyl acetate–pentane, led to 173 mg bisnor-diketo-ester (I; 52% based on XIII), m.p. 140–145°. Further crystallization furnished the analytical sample, m.p. 148–150°; $[\alpha]_D$ +77°; IR bands at 5·75 μ (ester and 17-one) and 5·85 μ (5-one), no hydroxyl band. On slow heating, a double m.p. at 128–130° and 148–150° was observed. (Found: C, 69·14; H, 7·96. $C_{16}H_{22}O_4$ requires: C, 69·04; H, 7·97%). The substance gave no color with alcoholic $FeCl_3$, and was recovered unchanged after treatment with acetic anhydride and pyridine for 16 hr at room temp.

Base treatment of bisnor-diketo-ester (I)

(a) *potassium hydroxide.* A solution containing 83 mg (I) and 3·5 g KOH in 28 ml methanol and 7 ml water was boiled under reflux for 1 hr. Addition of water and extraction with ether yielded 26 mg (40%) oily diketone (XVI); IR bands at 5·76 μ (17-one) and 5·85 μ (5-one) [these bands were were of about equal intensity, unlike I in which the 5·75 μ band was more intense than the 5·85 μ band]. The diketone could not be crystallized, even after chromatography on alumina. It was characterized as the dioxime, which on crystallization from ethanol showed m.p. 202–204 . (Found: N, 11·11. $C_{14}H_{22}O_2N_2$ requires: N, 11·19%).

The alkaline aqueous layer was acidified with dil. HClaq and extracted well with ether. Evaporation of solvent and trituration with benzene led to 36 mg (43%) keto-diacid (XVIIa), m.p. 157–159°. The analytical sample showed m.p. 159–161°; $[\alpha]_D$ −92° (dioxane); IR bands at 2·84 μ *et seq.* (hydroxyl of carboxyl), 5·75 μ (17-one) and 5·83 μ (carboxyl; this band was more intense than 5·75 μ band, indicative of two carboxyls). (Found: C, 63·68; H, 7·90. $C_{15}H_{22}O_5$ requires: C, 63·81; H, 7·85%). Treatment of XVIIa in acetone with excess ethereal diazomethane for 1 hr at room temp furnished the crystalline diester (XVIIb); IR single carbonyl band at 5·76 μ (very strong, superimposed two esters and 17-one), no hydroxyl band.

The same two products (XVI and XVIIa) were obtained when the KOH treatment of I was carried out at room temp for 24 hr.

(b) *Sodium methoxide.* A solution of 19·4 mg (I) in 12 ml methanolic sodium methoxide (0·8 N) was allowed to stand at room temp for 22 hr. The solution was acidified with acetic acid, the solvent was evaporated under red. press., and the residue was diluted with benzene and water. The benzene layer was washed with $NaHCO_3$aq and water, and was then dried and evaporated. The resulting crystalline diester (XVIIb) showed an IR spectrum (strong band at 5·76 μ) identical in every respect with that of the diester described under (a).

10α-*Carbomethoxy-ketol* (XVIIIa) *and* 10α-*carboethoxy-ketol* (XVIIIb)

The diketo-ester (I; 1·306 g) was dissolved in 29·6 ml ethanolic sodium ethoxide (0·154 N), under N_2. The solution was allowed to stand for 75 min at room temp, and 1·45 ml methyl vinyl ketone (previously dried over K_2CO_3, $CaCl_2$, and again K_2CO_3, and then freshly distilled) was added. The reaction mixture was allowed to stand at ca. 0° in the refrigerator for 68 hr. It was then acidified

with acetic acid, the solvents were evaporated under red. press., and the residue was diluted with benzene and water. The benzene layer was washed with $NaHCO_3$aq and water, dried over $MgSO_4$, and concentrated to small volume under red. press. The resulting benzene solution was then chromatographed on 60 g alumina. A series of crystalline fractions (with very similar IR spectra) were eluted with benzene–ether (3:1) as far as ether–chloroform (2:1). Combination of these fractions yielded 465 mg (ca. 28%) of a mixture of the methyl ester (XVIIIa) and the ethyl ester (XVIIIb). The IR spectrum was almost identical to those of the pure components (see below).

This mixture (215 mg) on extensive rechromatography on alumina and recrystallization from ether–pet. ether was separated into 34 mg pure methyl ester (XVIIIa) and 52 mg pure ethyl ester (XVIIIb; methyl ester concentrated in tail fractions of chromatogram, ethyl ester concentrated in head fractions, although separation not clean-cut). The methyl ester (XVIIIa) showed m.p. 171–173·5°; $[\alpha]_D$ +38·6° ($[\phi]_D$ +134); IR bands (KBr) at 2·82 μ (hydroxyl), 5·78 μ (ester and 17-one) and 5·86 μ (3-one; this band less intense than 5·78 μ band). (Found: C, 68·80; H, 8·27. $C_{20}H_{28}O_5$ requires: C, 68·94; H, 8·10%). The ethyl ester (XVIIIb) showed m.p. 122–124 ; $[\alpha]_D$ +36·4° ($[\phi]_D$ +132); IR spectrum practically identical to that of XVIIIa. (Found: C, 69·77; H, 8·27. $C_{21}H_{30}O_5$ requires: C, 69·58; H, 8·34%).

10α-*Carbomethoxy*-Δ^4-3-*one* (XIXa)

A solution of 23 mg pure carbomethoxy-ketol (XVIIIa) and 6 mg *p*-toluenesulphonic acid monohydrate in 26 ml benzene was boiled under reflux for 2 hr, with azeotropic separation of water by means of a Dean–Stark tube. A further 6 mg *p*-toluenesulphonic acid were added, and boiling with separation of water was continued for a further 2 hr. The solution was cooled, and washed with 5% $NaHCO_3$aq and water. The dried benzene extract was evaporated under red. press., and the residue was chromatographed on 2 g alumina. A small amount of crystalline material (IR band at 5·80 μ, no unsaturated carbonyl band at ca. 6·0 μ or hydroxyl band) was eluted with benzene, but was not investigated further. The crystalline fractions eluted with benzene–ether (99:1 to 95:5) on crystallization from cyclohexane–benzene yielded 13 mg (60%) unsaturated methyl ester (XIXa), m.p. 146–148°; $[\alpha]_D$ −164°; ORD in dioxane (*c* 0·065): $[\alpha]_{700}$ −154°, $[\alpha]_{589}$ −212°, $[\alpha]_{380}$ −1254° (trough), $[\alpha]_{377.5}$ −1180° (peak), $[\alpha]_{375}$ −1340° (trough), $[\alpha]_{365}$ −1075° (peak), $[\alpha]_{360}$ −1231° (trough), $[\alpha]_{320}$ +2150° (peak, $[\alpha]_{280}$ −4260°; UV λ_{max} 242 mμ (ε 14,100); IR bands at 5·78 μ (17-one and ester), 5·99 and 6·14 μ (Δ^4-3-one), no hydroxyl band. (Found: C, 72·76; H, 7·92. $C_{20}H_{28}O_4$ requires: C, 72·70; H, 7·93%).

For preparative purposes, 195 mg unseparated mixed ketols (XVIIIa and XVIIIb) were dehydrated through 2 hr boiling with 40 mg *p*-toluenesulphonic acid monohydrate in 260 ml benzene, water being removed as before. The product was isolated as previously, and chromatographed on 10 g alumina. Benzene–ether (98:2 to 95:5) eluted crystalline fractions containing the unsaturated methyl ester (XIXa). The oily ethyl ester (XIXb) was eluted directly before, no clear-cut separation being achieved. Later fractions, eluted with ether to chloroform gave undehydrated starting material, which was recycled. Chromatography of the recycled material, and that of the earlier mixed ester fractions, followed by crystallization of the appropriate fractions from cyclohexane–benzene, yielded a total of 37 mg methyl ester (XIXa), m.p. 145–148°; $[\alpha]_D$ −167°. Identity with the above-described sample was established by mixture m.p. determination and IR spectral comparison.

Phosphorus oxychloride–pyridine dehydrations

(a) *Of ketol* (XVIIIa). Phosphorus oxychloride (1 drop) was added to a solution of 5 mg ketol (XVIIIa) in 5 drops dry pyridine, and the mixture was heated at 90° for 2½ hr. The mixture was cooled, diluted with benzene, and washed successively with dil. HClaq, Na_2CO_3aq, and water. The dried extract on evaporation yielded material, which contained the αβ-unsaturated ketone (XIXa) since it showed IR bands at 5·99 and 6·15 μ. Chromatography on alumina produced fractions exhibiting UV λ_{max} 242 mμ, indicative of XIXa. The yield of XIXa was however less than 10%, estimated spectroscopically. In a blank experiment, pure XIXa was subjected to these dehydration conditions, and was found to be largely destroyed.

(b) *Of bridged-ring ketol* (XXI, *isomer a*).[18] The ketol (XXI, isomer a;[18] 10 mg) was subjected to dehydration with phosphorus oxychloride–pyridine, and the product was isolated, exactly as described above for XVIIIa. Chromatography on alumina, and spectral examination of the fractions,

demonstrated that only the reported dehydration products[18] and no trace of $\alpha\beta$-unsaturated ketone[20] had been formed.

Treatment of XXI (isomer a) with *p*-toluenesulphonic acid in boiling benzene, as used for the preparation of XIXa from XVIIIa (see above), led to the reported $\alpha\beta$-unsaturated ketone[20] in ca. 30% yield.

19-*Norandrost*-4-*ene*-3,17-*dione* (IV) *from methyl ester* (XIXa)

A solution of 6 mg (XIXa) in 3 ml 10% methanolic KOH containing a few drops of water was boiled under reflux for 1 hr, in N_2. Addition of water and isolation with ether yielded 5 mg crystalline material, m.p. 167–170 , which was almost pure dione (IV). One crystallization from cyclohexane furnished pure IV, m.p. 170–172°; $[\alpha]_D$ +135°. There was no m.p. depression on admixture with an authentic sample (m.p. 169–171°; $[\alpha]_D$ +137°),[10] and the IR spectra were identical.

19-*Hydroxy*-10α-*testosterone* (XXIIIa) *and diacetate* (XXIIIb) *from methyl ester* (XIXa)

Lithium aluminium hydride (200 mg) was added to a solution of 28 mg XIXa in 20 ml dry tetrahydrofuran, and the mixture was boiled under reflux for 4 hr. The mixture was cooled, diluted with ether, and hydrolyzed by the careful addition of sat. Na_2SO_4aq. The organic layer was separated, and the aqueous layer was extracted well with ether. The combined organic extracts were washed with sat. NaClaq, and were then dried and evaporated. The residue, presumably consisting of a mixture of the triols (XXIIa and XXIIb), showed IR bands at 2·90 μ (strong, hydroxyl), but no carbonyl bands.

The manganese dioxide used for the oxidation was prepared according to Mancera *et al.*,[23] and was then aged through ca. 3 months standing in a stoppered bottle.[31] The MnO_2 (600 mg) was added to a solution of the mixed triols in 60 ml chloroform, and the mixture was shaken at room temp for 68 hr. The solid was removed by filtration, and washed well with warm chloroform. The combined filtrates were evaporated to dryness, whereby an oily residue was obtained containing ca. 50% Δ^4-3-one (UV examination). This material, dissolved in a little ether, was chromatographed on 2·5 g alumina. The fractions eluted with ether–methanol (95:5) on crystallization from acetone furnished 11·4 mg (44%) 19-hydroxy-10α-testosterone (XXIIIa), m.p. 196–199°. Further crystallization led to the analytical sample, m.p. 199·5–201°; $[\alpha]_D$ −215° (chloroform containing ca. 20% ethanol, for solubility reasons); ORD in dioxane (*c* 0·057): $[\alpha]_{700}$ −112°, $[\alpha]_{589}$ −231°, $[\alpha]_{372.5}$ −1849° (trough), $[\alpha]_{362.5}$ −1649° (peak), $[\alpha]_{357.5}$ −1678 (trough), $[\alpha]_{320}$ +372° (peak), $[\alpha]_{275}$ −2340°; UV λ_{max} 246 mμ (ε 13,800); IR bands at 2·90 μ (hydroxyl) and 6·02 μ (Δ^4-3-one; this band appears at 6·09 μ in KBr). (Found: C, 75·17; H, 9·42. $C_{19}H_{28}O_3$ requires: C, 74·96; H, 9·27%). There was a depression in m.p. on admixture with 19-hydroxytestosterone (m.p. 201–203°, $[\alpha]_D$ + 110°),[24] and the IR spectra were distinctly different.

The 17,19-diacetate (XXIIIb), prepared by acetylation of XXIIIa with acetic anhydride in pyridine for 24 hr at room temp, proved to be an oil. It showed ORD in dioxane (*c* 0·084): $[\alpha]_{700}$ −190°, $[\alpha]_{589}$ −252°, $[\alpha]_{372.5}$ −1545° (trough), $[\alpha]_{362.5}$ −1438° (peak), $[\alpha]_{357.5}$ −1472° (trough), $[\alpha]_{317.5}$ +152° (peak), $[\alpha]_{282.5}$ −1105°; UV λ_{max} 239 mμ; IR bands at 5·79 and 8·03 μ (acetate) and 6·02μ (Δ^4-3-one, this band less intense than 5·79 μ band, indicative of two acetoxy groups), no hydroxy band.

19-*Hydroxy*-10α-*testosterone* (XXIIIa) *from ketol ethyl ester* (XVIIIb)

The ketol ethyl ester (XVIIIb; 25 mg) was dehydrated with *p*-toluenesulphonic acid in boiling benzene, exactly as described above for the corresponding methyl ester (XVIIIa). Chromatography on 2 g alumina and elution with benzene–ether (99:1 to 98:2) yielded 15 mg unsaturated ester (XIXb) as an oil which could not be crystallized; $[\alpha]_D$ −145°; IR bands at 5·77 μ (ester and 17-one), 5·99 and 6·14 μ (Δ^4-3-one), no hydroxyl band. The UV spectrum [λ_{max} 242 mμ (ε 11,200)] indicated ca. 80% purity.

The ester (XIXb) was reduced with $LiAlH_4$ and then oxidized with MnO_2, exactly as reported

[31] Use of freshly prepared MnO_2 resulted in considerable oxidation of the 17-hydroxyl group to the 17-one, and the yield of XXIIIa was therefore much reduced [cf. I. T. Harrison, *Proc. Chem. Soc.* 110 (1964)].

above for the methyl ester (XIXa). Chromatography on alumina and crystallization from acetone then gave XXIIIa in ca. 25% yield. It showed m.p. 199–201°, and was shown to be identical with the substance obtained from XIXa through mixture m.p. determination and comparison of IR spectra.

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