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C-10 SUBSTITUTED 19-NORSTEROIDS—VI

10α-METHYLSTEROIDS[1a,b]

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Abstract—The preparation of 17β-hydroxy-5α,10α-androstan-2-one IIa is described. Several aspects of the chemistry of the new compound are discussed. The conversion of IIa to the corresponding 3-keto derivative, 17β-hydroxy-5α,10α-androstan-3-one is also described.

IN THE great volume of steroid chemistry, steroids of the unnatural configuration at the ring junctures represented but an incidental chapter. This resulted primarily from the fact that those "unnatural" steroids which were available, largely as a by-product of total synthesis, were almost invariably physiologically less active than their natural counterparts. "Unnatural" steroids inverted at the difficultly accessible C-10 juncture were among the least explored. However, recently interest in the 10-iso compounds was quickened by the report that inversion at both C-9 and C-10 positions yielded 9β,10α steroid analogs[4] which possess valuable pharmacological properties.[4a] A significant alteration on these "retrosteroids" involved compounds where only the C-10 substituent was inverted to give the 9α,10α steroid structure. These 9-10 syn linked compounds were more difficult to obtain and only a few examples have been reported. Degradation and reconstitution of ring A in 19-nortestosterone led to 19-hydroxy-10α-testosterone,[5] and more significantly, photochemical rearrangement of 1-dehydrotestosterone acetate led to compounds which were converted to a variety of 10α-methylsteroids[6] including 10α-testosterone.[7]

[1a] Part IV: J. Fishman, *J. Org. Chem.* **28**, 1528 (1963); Part V: M. Torigoe and J. Fishman, *Tetrahedron Letters* 1251 (1963); [b] Some of the results in this communication were presented at the VI*th Pan-American Congress of Biochemistry and Pharmacology*, Mexico City, December 10 (1963).

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[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); See also J. Castells, E. R. H. Jones, G. D. Meakins, S. Palmer and R. Swindells, *J. Chem. Soc.* 2907 (1962) and preceding papers for ergostane derivatives; 9β,10α-19-norsteroids have also been reported, 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); J. M. H. Graves, G. A. Hughes, T. Y. Jen and Herchel Smith, *J. Chem. Soc.* 5488 (1964); [a] E. H. Reerink, H. F. L. Scholer, P. Westerhof, A. Querido, A. A. H. Kassenaar, E. Diczfalusy and K. G. Tillinger, *Nature, Lond.* **186**, 168 (1960); H. F. L. Scholer and A. M. deWachter, *Acta Endocrinol.* **35**, 188 (1960); K. G. Tillinger and E. Diczfalusy, *Ibid.* **35**, 197 (1960).

[5] F. Sondheimer, R. Mechoulam and M. Sprecher, *Tetrahedron Letters* No. 22 38 (1960); *Tetrahedron* **20**, 2473 (1964).

[6] S. Ganter, E. C. Utzinger, K. Schaffner, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **45**, 2403 (1962).

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

As reported in our previous communication,[1] we obtained the 10α-methyl-steroids, with the C-9 configuration unaltered, by a totally different route involving 1,4 Grignard addition to the $\Delta^{1(10)}$-2 keto unsaturated system.[8] This procedure, which represents substitution on a 19-nor structure, has the advantage of versatility since the Grignard reagent permits introduction of many 10α-alkyl substituents. Since the appearance of our initial report, there has appeared in the patent literature a similar sequence involving $\Delta^{5(10)}$-6-keto compounds,[9] which is reported to lead to 5β,10α-methylsteroids. In this paper we report in detail on our synthesis of the 10α-methylsteroids, and some of the aspects of chemistry of the 5α,9α,10α-2 ketone system.

Reaction of 2-oxo-5α-estra-1 (10)-ene-17β ol (Ia) with methyl Grignard in the presence of copper salts,[10] and separation of the ketonic fraction yielded about 70% of essentially pure 2-oxo-5α, 10α-androstane-17β-ol (IIa). No 10β product could be identified. The stereospecific nature of the reaction has been discussed by Mori[11] who suggests that it is due to the greater steric hindrance to 10β approach. The non-ketonic fraction from the Girard separation, resulted from 1,2 Grignard addition and subsequent dehydration; on the basis of the UV absorption the product can be formulated as the 2-methyl heteroannular diene (III). Treatment of the acetate of Ia with Grignard reagent yielded the 10α-methyl-17-acetate (Ia) but without any significant improvement in yield.

The orientation of the newly introduced methyl group in IIa followed from its optical rotatory dispersion curve which was identical with that of a conventional 5β-3 ketone which has the same bicyclic environment.[12] Furthermore, in NMR the C-19 methyl resonance of IIa at 57 c/s, showed the typical broadening due to the 2-ketone.[13] The new compound was also shown to be identical with a 10α-2-keto-steroid obtained by Ganter *et al.*[6] and thus establishes the configuration of their product as 5α. It was of interest to explore some of the chemistry of the new compound with its unusual 5α,9α,10α stereochemistry and the possibility of changes in ring A conformation.

Reduction of the 2-ketone[15] might be expected to be subject to the competitive steric influence of C-10 methyl group on the α face, and of ring B on the β face.

Reduction with the bulky lithium aluminum tri t-butoxy hydride reagent gave exclusively one product which was assigned the axial 2α-hydroxy structure, VIIIa since the NMR spectrum of the diacetate showed the 2β proton resonance as a wide singlet (5 c/s at half-height) at 300 c/s typical of an equatorial proton.[14] Conversely, reduction with lithium and liquid ammonia, gave the equatorial 2β alcohol,[IXa] the diacetate of which in the NMR had a wide multiplet resonance (20 c/s at half-height) at 275 c/s, for the axial 2α proton.[14] The orientation of the alcohols VIIIa and IXa

[8] J. Fishman, *Chem. & Ind.*, 1556 (1958); J. Fishman and M. Tomasz, *J. Org. Chem.* **27**, 365 (1962).
[9] A. Bowers and O. Halpern U. S. Patent 3,148,185.
[10] A. Birch and R. Robinson, *J. Chem. Soc.* 501 (1943); H. Mori, *Chem. Pharm. Bull., Tokyo* **10**, 383 (1962), A. Birch, *Proc. Chem. Soc.* 356 (1962).
[11] H. Mori, *Chem. Pharm. Bull., Tokyo* **12**, 1224 (1964).
[12] C. Djerassi and W. Closson, *J. Amer. Chem. Soc.* **78**, 3761 (1956).
[13] N. S. Bhacca, J. E. Gurst and D. H. Williams, *J. Amer. Chem. Soc.* **87**, 302 (1965).
[14] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry* p. 79. Holden-Day, San Francisco (1964).
[15] W. G. Dauben, E. J. Blanz Jr., J. Jin, and R. A. Micheli, *J. Amer. Chem. Soc.* **78**, 3752 (1956).

can only be correct if ring A in the 5α,9α,10α 2-ketone is in an approximately chair conformation. That this is so is supported by the much larger downfield shift of the α 19 methyl group in the 2-hydroxy derivative (VIIIa; 74 c/s) compared with that in the epimeric compound (IXa; 60 c/s). This is only commensurate with a *cis* 2-hydroxy 19-methyl relationship in VIIIa and hence the orientation of the C-2 hydroxy group in VIIIa must be α, while that in IXa is β. These results confirm that ring A in the 5α,9α,10α structure is in the chair conformation, and also confirm the dominant steric influence of the C-19 methyl group in the reduction of IIa.

Since the chemistry of a cyclic ketone is intimately connected with the direction of enolization, the nature of the enol obtained from IIa was of primary interest. Reaction of 2-oxo-5α, 10α-androstane-17β-ol acetate (IIb) with acetic anhydride in the presence of perchloric acid[16] gave an enol diacetate which resisted crystallization. The NMR spectrum of the product showed the presence of 4 methyl groups, two from the acetates and two angular methyl resonances, with the discreet C-19 methyl proton resonance at 59 c/s shifted only slightly downfield. In addition the vinyl proton appeared as a poorly resolved triplet at 310 c/s, which was only consistent with a Δ^2-enol diacetate structure IV.[17]

When the enol acetylation of IIa carried out by exchange with isopropenyl acetate in the presence of *p*-toluensulphonic acid[18] the NMR of the product showed the presence of about 15% of the isomeric Δ^1 enol (V) characterized by the presence of an additional C-19 methyl resonance at 65 c/s.

With the structure of the enol acetate (IV) established, we could proceed to subsequent reactions with confidence that substitution at C-3 would result. Titration of the enol diacetate (IV) with bromine in buffered acetic acid, gave a monobromoketone (VI) m.p. 123–126°. The orientation of the bromine at C-3 in the bromoketone (VI) was formulated as axial and β on the basis of physical data. The IR spectrum exhibited a carbonyl band at 1712 cm^{-1} which represents a 2 cm^{-1} shift consistent with an axial bromine.[19] In the NMR spectrum the 3α proton appeared as a doublet at 249 c/s, J 5·4, indicative of its equatorial nature; the C-19 methyl resonance was at 55 c/s, a 2 c/s upfield shift. The axial nature of the bromine and its β orientation are in agreement with a chair-like conformation for ring A in this compound. A consequence of this conformation should be instability of the axial 3β bromine due to steric interaction with the 6β hydrogen. This indeed proved to be the case. The bromoketone (VI), rearranged upon recrystallization to form the epimeric 3α-bromo-2-ketone (VII) m.p. 208–211°. The 3β proton resonance in the NMR spectrum of VII was now downfield at 285 c/s as a quartet (J a,a = 12·0 J a,e = 8·0) with both the coupling and the downfield shift typical of an axial proton* on carbon bearing a bromine.[20] The C-19 methyl proton resonance was also shifted downfield to 60 c/s,

* The possibility that the downfield shift of the axial proton in α-bromoketones may not be invariant has been suggested, Ref. 13.

[16] B. Berkoz, E. P. Chavez and Carl Djerassi, *J. Chem. Soc.* 1323 (1962).

[17] This result is somewhat different from that observed[7] with 5ξ-acetoxy -10α-methyl-2-ketone XIII, which gave a 2:1 mixture of Δ^2 and Δ^1 enolacetates under similar conditions.

[18] H. Vanderhaeghe, E. R. Katzenellenbogen, K. Dobriner and T. F. Gallagher, *J. Amer. Chem. Soc.* 74, 2810 (1952).

[19] R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* 74, 2828 (1952).

[20] A. Nickon, M. A. Castle, R. Harada, C. E. Berkoff, and R. O. Williams, *J. Amer. Chem. Soc.* 85, 2185 (1963).

supporting the α orientation of the bromine. The carbonyl absorption of VII in the IR showed a shift of 9 cm^{-1} which, while larger than that of the axial 3β bromine, is low compared with that to be expected from an equatorial bromine.[19] This raises the possibility of some conformational distortion of ring A, in the relatively more flexible ring A/B *cis* systems.

In an effort to arrive at 10α steroids bearing an oxygen function at C-3, 10α-methyl-2-ketone IIb was reacted at room temperature with lead tetraacetate in benzene in the presence of boron trifluoride etherate.[21] Chromatography on alumina gave only one product m.p. 170–173°, whose structure was assigned as 2-oxo-5α, 10α-androstane-3α, 17β-diol-diacetate (X). The NMR spectrum of this compound showed the presence of a quartet at 322 c/s, J a,a = 12·0, J a,e = 8·0, due to the 3β proton and quite similar to that exhibited by the 3α-bromoketone (VII). Although from the acetoxylation we isolated only one compound NMR analysis of the crude reaction product showed clearly the presence of an isomeric acetoxy compound with a C-19 methyl proton resonance at 64·5 c/s, and the C-3 proton resonance at 305 c/s as a quartet J a,e = 6, J e,e = 3. This compound to which we tentatively assign the axial 3β-acetoxy structure (XI) was not isolated since it epimerized completely to the more stable acetoxy ketone (X) on alumina or upon treatment with potassium acetate and acetic acid. In contrast, X was unchanged by adsorption on alumina, or on prolonged reflux in acetic acid with potassium acetate. That X was indeed the 2-ketone-3-acetoxy compound and not the isomeric 2-acetoxy-3-ketone was confirmed by zinc acetic acid deacetoxylation which yielded only the starting 2-ketone (IIb). In contrast the lead tetraacetate oxidation product of 5ξ-acetoxy-10α-methyl-2-ketone (XIII) is extremely easily converted[7] to a 2-acetoxy-Δ^4-3-ketone (XIV) presumably via a 2,5-diacetoxy-3-ketone intermediate. It is likely that in this instance the elimination of the 5-acetoxy group serves as the driving force for the rearrangement which may proceed via a concerted mechanism. However, when the 3α-acetoxy-2-ketone (X) was reduced with hydriodic acid,[22] a 70:30 mixture of 3-keto (XIIb) and 2-keto (Ib) compounds was obtained, from which the former could be obtained pure by fractional crystallization. In the NMR XIIb showed the expected downfield shift of the C-19 methyl proton resonance to 75 c/s. The hydrolysis product of XIIb, was also identical with 10α-dihydrotestosterone prepared by the lithium ammonia reduction of 10α-testosterone.[23]

The above sequence represents a possible route to a variety of 10α-steroids, but has been superseded by a more versatile procedure reported in the following papers.

EXPERIMENTAL[24]

2-Oxo-5α,10α-androstan-17β-ol (IIa)

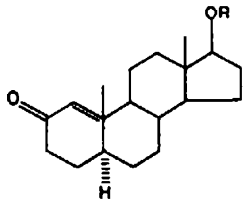
A 2·0 g sample of Ia was dissolved in 90 ml of purified tetrahydrofuran, and 1·0 g cupric acetate was added. Methyl Grignard reagent, prepared from 5·8 ml MeI and 2·2 g Mg, in 100 ml ether

[21] H. B. Henbest, D. N. Jones and G. P. Slater, *J. Chem. Soc.* 4472 (1961); J. D. Cocker, H. B. Henbest, O. H. Phillips, G. P. Slater and D. A. Thomas, *Ibid.* 6 (1965).

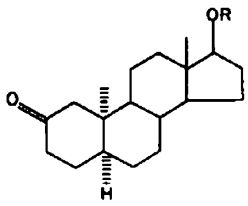
[22] W. Reusch, and R. LeMahieu, *J. Amer. Chem. Soc.* **86**, 3068 (1964); W. Reusch, R. LeMahieu and R. Guynn, *Steroids* **5**, 109 (1965).

[23] S. J. Halkes, Ph.D. Thesis, University of Leyden 1964. The authors would like to thank Dr. P. Westerhof for bringing this thesis to their attention.

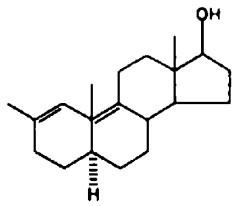
[24] M.ps. were determined on a Koffler block and are corrected. NMR Spectra were obtained in CCl_4 on a Varian A60 instrument. Values are given in c/s downfield from tetramethylsilane as an internal reference. Rotations were obtained in $CHCl_3$ unless otherwise stated. The IR spectra were run in KBr on a Beckman IR9 instrument. Analyses are by Spang Laboratory, Ann Arbor, Mich.



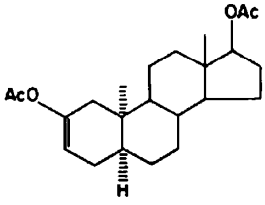
I
a R=H
b R=CH_3CO



II
a R=H
b R=CH_3CO



III



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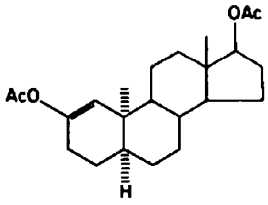
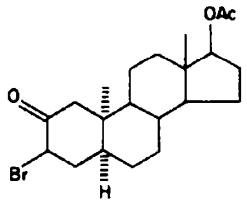
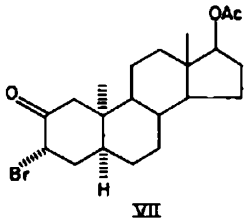


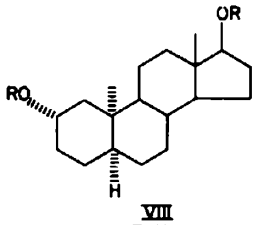
V



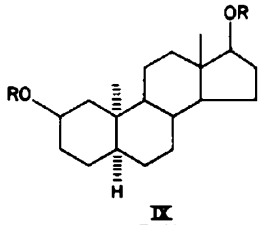
VI



VII



VIII
a R=H
b R=CH_3CO



IX
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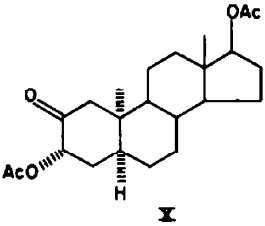
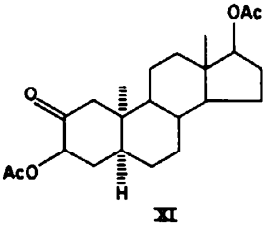
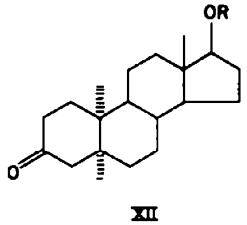
b R=CH_3CO



X



XI



XII
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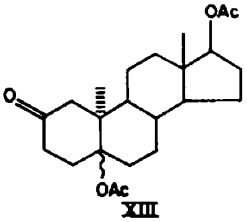
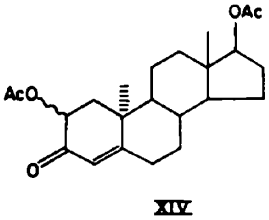
b R=CH_3CO



XIII



XIV

was then added dropwise at room temp with stirring. The reaction was stirred for another hr at room temp and then 50 ml 10% NH_4Cl was added. Extraction with ether which was washed with water, dried and evaporated gave an oil. The latter was refluxed for 1 hr with 2 g Girard's T reagent in 100 ml EtOH containing 10 ml acetic acid. The mixture was then cooled and poured in an excess Na_2CO_3aq and extracted with ether. The etheral layer after drying and evaporation gave 204 mg of an oil which absorbed strongly at 249 mμ in the UV and represented mainly *2-methylestra-1,9-dien-17β-ol* (III). The aqueous layer was acidified to pH2 with dil HClaq and after standing overnight was extracted with ether. After drying and evaporation the ether extract yielded a semicrystalline residue which was recrystallized from acetone–pet. ether to give 1·41 g *2-oxo-5α,10α-androstane-17β-ol* (IIa) m.p. 160–164°, undepressed on admixture with the sample obtained by other means.[6,25]

The analytical sample melted 162–165° $[\alpha]_D^{23}$ + 49°, ORD (c = ·04 in CH_3OH) α_{600} = +50°, α_{370} = +112°, α_{305} = −138°, α_{260} = +950. NMR—18 CH_3 at 46 c/s, 19 CH_3 at 57 c/s. (Found: C, 78·50; H, 10·40. Calc. for $C_{19}H_{30}O_2$: C, 78·59; H, 10·41%).

The acetate (IIb) was prepared in the usual manner. The analytical sample was obtained from acetone and melted 194–196°. (Found: C, 75·80; H, 9·88. Calc. for $C_{21}H_{32}O_3$: C, 75·86; H, 9·70%.)

2,17β-Diacetoxy-5α,10α-androst-2-ene (IV)

(a) A solution of 100 mg IIb in a mixture of 3 ml CCl_4 and 8 ml benzene was treated with 0·5 ml acetic anhydride and 1 drop 70% perchloric acid. After standing at room temp for 6 hr, 15 ml CCl_4 was added and the solution washed first with ice water and then with 5% $NaHCO_3$aq, and once again with water. The organic layer was dried and the solvent was removed. The residue was an oil which resisted crystallization, but was homogeneous on thin layer chromatography. The NMR spectrum showed 4 three proton singlets at 45 c/s (18 CH_3), 58 c/s (19 CH_3), 117 c/s (17-acetate) 122 c/s (2-acetate). The vinyl proton absorption was at 310 c/s as a poorly resolved triplet, J = 3 c/s.

(b) A solution of 100 mg IIb in 25 ml isopropenyl acetate containing 50 mg *p*-toluenesulphonic acid was gently refluxed for 8 hr. After distilling most of the isopropenyl acetate the residue was diluted with ether and washed to neutrality with cold 5% $NaHCO_3$aq. After drying and removing the solvent an oily residue remained. The NMR spectrum of the product showed in addition to the bands associated with IV a band at 65 c/s which integrated to 0·25 of the 19 CH_3 resonance at 58 c/s and 0·2 of the 18 CH_3 resonance at 45 c/s and was indicative of the presence of about 20% *2,17β-diacetoxy-5α,10α-androst-1-ene* (V).

2β-Bromo-17β-acetoxy-5α,10α-androstan-2-one (VI)

A 120 mg sample of IV was dissolved in 4 ml of a buffered solution (0·5 g sodium acetate, 40 ml acetic acid, 10 ml CCl_4) and 400 mg Br_2 in 4 ml of the same solution was added dropwise with stirring. After stirring for 15 min at room temp 15 ml CCl_4 was added and the organic solution was washed with cold water, 5% $NaHCO_3$aq and finally water again. The organic layer was dried and evaporated and the residue recrystallized once from MeOH to give 60 mg crystals of VI m.p. 123–128°. Further recrystallization increased greatly the m.p. range. The NMR spectrum of VI showed three 3 proton singlets at 45 c/s (18 CH_3), 55 c/s (19 CH_3) and 117 c/s (17 acetate). A one proton doublet appeared downfield at 249 c/s J = 6·2 c/s. The IR spectrum showed carbonyl absorption at 1712 cm^{-1}. (Found: C, 61·28; H, 7·68. Calc. for $C_{21}H_{31}O_3Br$: C, 61·43; H, 7·55%).

3α-Bromo-17β-acetoxy-5α,10α-androstan-2-one (VII)

A 35 mg sample of VI was dissolved in 5 ml acetic acid containing 3% HBr and was left at room temp for 3 hr. After the usual workup and crystallization from MeOH 22 mg VII m.p. 208–211° were obtained. The analytical sample melted at 211–213° $[\alpha]_D^{24}$ + 86°. The carbonyl absorption in the IR was at 1719 cm^{-1}. The NMR spectrum showed the 18 CH_3 singlet at 45 c/s and the 19 CH_3 resonance at 60 c/s. The C-3 proton was a quartet downfield at 284 c/s. J a,a = 12·0 J a,e = 8. (Found: C, 61·07; H, 7·52. Calc. for $C_{21}H_{31}O_3Br$: C, 61·43; H, 7·55%).

5α,10α-Androstane-2α,17β-diol (VIIIa)

A 100 mg sample of IIa dissolved in 20 ml purified tetrahydrofuran was treated with 110 mg lithium aluminum tri t-butoxyhydride in 10 ml tetrahydrofuran. After refluxing for 3 hr, ice water

[25] The mixed m.p. comparison was obtained through the courtesy of Dr. H. Wehrli.

was added, and the mixture was extracted with ether. The organic layer was washed with water and evaporated to leave an oily residue which was recrystallized from acetone–pet. ether to give 68 mg VIIIa as needles m.p. 192–195°. The analytical sample melted at 195–198°. The NMR spectrum exhibited 3 protons singlets at 43 c/s (18 CH_3) and 74 c/s (19 CH_3). (Found: C, 77·84; H, 11·14. Calc. for $C_{19}H_{32}O_2$: C, 78·03; H, 11·03%.)

The diacetate VIIIb was obtained in the usual manner and crystallized from pet. ether, m.p. 128–131°. The analytical sample melted at 131–133°. $[\alpha]_D^{24}$ + 17°. NMR-3 proton singlets at 44 c/s (18 CH_3), 67 c/s (19 CH_3), 6 proton singlet at 117 c/s (2α and 17β acetates), 2β proton at 300 c/s (5 c/s at half-height). (Found: C, 72·96; H, 9·33. Calc. for $C_{23}H_{36}O_4$: C, 73·36; H, 9·64%.)

5α,10α-*Androstane*-2β,17β-*diol* (IXa)

A solution of 100 mg IIa in 5 ml tetrahydrofuran was added to 30 ml liquid ammonia in a 3-neck flask equipped with stirrer and Dewar condenser. Into the stirred mixture 40 mg Li ribbon were introduced and the stirring was continued for 5 min. The blue colour was discharged by the addition of EtOH, and the ammonia was evaporated on the steam bath. The residue was extracted with CH_2Cl_2 which was washed to neutrality, dried and evaporated to give an oil which was crystallized from acetone–pet. ether to give 56 mg of prisms m.p. 214–217°. In the NMR the 18 CH_3 and 19 CH_3 resonances appeared at 43 c/s and 60 c/s respectively. (Found: C, 78·21; H, 10·90. Calc. for $C_{19}H_{32}O_2$: C, 78·03; H, 11·03%.)

The diacetate IXb, prepared with acetic anhydride and pyridine, after the usual workup crystallized from pet. ether with m.p. 135–137°. The analytical sample exhibited the same m.p. $[\alpha]_D^{24}$ + 35°. NMR 3 proton singlets at 45 c/s (18 CH_3), 64 c/s (19 CH_3) 116 and 117 c/s (2β and 17β acetates), 2α proton at 285 c/s (20 cps wide at half-height). (Found: C, 73·00; H, 9·70. Calc. for $C_{23}H_{36}O_4$: C, 73·36; H, 9·64%.)

2-*Oxo*-5α,10α-*androstane*-3α,17β-*diol diacetate* (X)

To a solution of 200 mg IIb in 10 ml benzene and 0·5 ml MeOH, 270 mg freshly crystallized lead tetraacetate and 1 ml freshly distilled BF_3-etherate was added. After stirring for 2½ hr at room temp the reaction mixture gave a negative starch-iodide paper test, and was poured into 75 ml ether. The ether was washed with $NaHCO_3$aq and water, dried and evaporated to give an oily residue. The NMR spectrum of this product in $CDCl_3$ showed the presence of methyl group proton singlets at 46·3, 47·5 (18 CH_3), 59, 64·5 (19 CH_3), 122 (17 acetate), 130 (3α and 3β acetates). Two downfield quartets were present at 306 (3α proton) Ja,e = 6, Je,e = 3 and 321 (3β proton) Ja,a 12, Ja,e — 8. Chromatography of the product on alumina and elution with benzene gave 140 mg of X m.p. 168–172° which was recrystallized from acetone–pet. ether to raise the m.p. to 175–178°. The NMR spectra of the other fractions did not show the presence of the other isomer XI.

The crude product from an identical reaction was refluxed with 700 mg of acetic acid for 18 hr, and the solvent was removed *in vacuo*. The residue was taken up in water and extracted with $CHCl_3$ which after drying and evaporation gave a product which could be crystallized from pet. ether–acetone to give 124 mg of 2-oxo-5α,10α-androstane-3α,17β-diol diacetate (X) m.p. 170–174°. NMR-3 proton singlets at 46·3 (18 CH_3) 59 (19 CH_3), 122 (17 acetate) 130 (3 acetate) 1 proton quartet at 321 c/s J = 12, 8 (3β proton). (Found: C, 71·02; H, 8·73. Calc. for $C_{23}H_{34}O_5$: C, 70·74; H, 8·78%.)

Deacetoxylation of X

A 20 mg sample of X was refluxed in 3·5 ml acetic acid containing 0·2 ml acetic anhydride and 1·8 g Zn dust for 24 hr. The Zn was filtered off and washed with EtOH. The filtrate was evaporated *in vacuo* and the residue taken up in water and extracted with ether. The ether was washed with $NaHCO_3$aq, water, dried and evaporated. The product crystallized from acetone–pet ether m.p. 180–185°, identical in all respects (IR, mixed m.p, NMR) with 2-oxo-5α,10α-androstane-17β-ol acetate (IIb).

3-*Oxo*-5α,10α-*androstane*-17β-*ol* (XIIa)

A 40 mg portion of X was dissolved in 10 ml acetic acid and 0·25 ml HI (52%) was added. The mixture was refluxed for 1 hr and then excess 5% NaOHaq containing $NaHSO_3$ was added and the aqueous mixture was extracted with ether which was washed with water and evaporated. The NMR spectrum of the crude crystalline product showed angular methyl proton resonance at 74 and 59 c/s in a 7:3 ratio.

Recrystallization from acetone–pet. ether gave XIIb m.p. 170–174°. NMR 3 proton singlets at 46·3 (18 CH_3) 75·4 (19 CH_3), 122 (17 acetate). (Found: C, 75·64; H, 9·63. Calc for $C_{21}H_{32}O_3$: C, 75·86; H, 9·70%.)

Hydrolysis of 20 mg XIIb in 5% methanolic KOH gave after the usual workup 12 mg of 3-oxo-5α,10α-androstan-17β-ol m.p. 178–180° from acetone–pet. ether $[\alpha]_D^{24}$ −11°. (Lit. reports[23] m.p. 177·5–179° $[\alpha]_D^{24}$ −10°.)

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