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OXIDATION OF STEROIDAL KETONES—VI

MECHANISM OF REACTION AND PROOF OF STRUCTURE OF RING A CONTRACTED ACID[1]

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Abstract—The mechanism of selenium dioxide–hydrogen peroxide oxidation of saturated steroidal-3-ketones was investigated with the use of 2,2,4,4-D_4-17β-hydroxy-5α-androstane-3-one. It was proven that formation of lactones II and III proceeds through a process analogous to Baeyer-Villiger oxidation. Formation of ring contracted acid (IV) was subject to a primary isotope effect with considerable C-D bond breakage in rate determining step. From this it was inferred that IV arises via enolization of the ketone. The ring A contracted acid retained essentially three D atoms, hence equilibration was excluded.

The structure of acid IV was proven.

RECENTLY we have described the oxidation of steroidal 3-ketones with hydrogen peroxide in the presence of catalytic amounts of selenium dioxide.[3–5] It was observed that in the case of steroidal ring A saturated 3-ketones,[4] either of the 5α or 5β series, a mixture of products consisting of lactones of type II and III and acids of type IV and V was obtained. Interestingly, Biellmann and Rajic,[6] Giroud *et al.*,[7] Hellman and Jerussi[8] using somewhat different conditions obtained only ring A contracted acids from the oxidation of 5α-cholestanone.

At the time of our earlier report we had not characterized fully the ring contracted acid. We now wish to report results of studies on the mechanism of the reactions and provide evidence in support of structure IV for the ring contracted acid.

Obviously, no single mechanism could provide a satisfactory explanation for the

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[3] E. Caspi and S. N. Balasubrahmanyam, *Experientia* **19**, 396 (1963); E. Caspi and S. N. Balasubrahmanyam, *J. Org. Chem.* **28**, 3383 (1963).

[4a] E. Caspi, Y. Shimizu and S. N. Balasubrahmanyam, *Tetrahedron* **20**, 1271 (1964); [b] E. Caspi and S. N. Balasubrahmanyam, *Tetrahedron Letters* 745 (1963).

[5] E. Caspi and Y. Shimizu, *J. Org. Chem.* **30**, 223 (1965).

[6] J. F. Biellmann and M. Rajic, *Bull. Soc. Chim. Fr.* 441 (1962).

[7] A. M. Giroud, A. Rassat, P. Witz and G. Ourisson, *Bull. Soc. Chim. Fr.* 3240 (1964).

[8] H. M. Hellmann and R. Jerussi, *Tetrahedron* **20**, 741 (1964).

simultaneous formation of lactones II and III, ring A contracted acids IV and 2,3-seco diacids (V). Different pathways have to be envisioned for each case. A process analogous to Baeyer–Villiger oxidation can be anticipated in the formation of the lactones. On the other hand, enolization might be implicated in the pathway leading to the ring A contracted acids.[9] Whether indeed enolization is involved in the rate determining step,[9] or if at all, cannot be predicted *a priori*. The seco acids of type V could arise from an intermediate 2,3-diketone or, what is less probable, from the oxidation of hydroxy-acid VI. Since the diacid V was usually formed in lesser amount, it will be omitted from further discussions.

The above assumptions on the possible mechanisms seemed to be amenable to critical evaluation with the use of 2,2;4,4-D_4-analog of I. Should Baeyer–Villiger oxidation be the mechanism by which the lactones were formed, the lactones would retain practically all the deuterium. Ring contractions, on the other hand, would be subject to a primary isotope effect if *enolization* is the rate determining step.

Our first objective was to establish the ratio of products formed on oxidation of Ia under standardized conditions of reaction. The oxidation was carried out essentially as previously described.[4a] To expedite separation of the products the entire reaction mixture was saponified then treated with diazomethane and the methyl esters were resolved by TLC[4a]. Saponification of the individual esters gave acids IV, V, VI and VII. The ratio of acids VI:VII:IV was 1·7:2·3:1. Since acids VI and VII must have originated from lactones II and III, it may be concluded that the ratio of lactones II and III to acid IV must be as above (1·7:2·3:1). The mechanism of the formation of both lactones (II and III) is most probably the same, and, therefore, they can be considered together. Thus, the overall ratio of products resulting from *oxygen insertion on either side of the* 3-*ketone to ring contraction* is 4:1.

With the ratio of products now established, we turned our attention to the preparation and oxidation of 2,2,4,4-D_4-17β-hydroxy-5α-androstan-17-one (Ic). The deuterated analog was prepared by refluxing a mixture of Ia with NaOD-D_2O in diglyme for 16 hr. The product was isolated by precipitation with water and recrystallization from aqueous methanol. The disappearance of the 1420 cm^{-1} band in the IR confirmed the replacement of the C-2 and C-4 protons with deuterium. The product Ic was analyzed for D by the combustion method and contained 3·58 atoms deuterium, indicating that about 90% of hydrogen was exchanged. It was thought that in view of possible enolization of Ic and ensuing loss of deuterium, it would be difficult to establish the relative amounts of mono, di, tri and tetra deuterated species mass-spectroscopically. Consequently, Ic was reduced with LAH in ether to the diol Id. Mass-spectroscopic analysis of Id revealed the following species (Table 1): Do 1·8%; D_1 1·1%; D_2 3·4%; D_3 19·4% and D_4 74·3%, hence the diol contained 3·63 atoms D. As expected LAH reduction of Ic to Id proceeded, without loss of tracer. The relatively good agreement of mass-spectroscopic and combustion results is evident.

Having defined the deuterium content of Ic, we proceeded with its *oxidation*. The oxidation and processing of the reaction mixture was carried out exactly as for the non-deuterated sample to yield acids VI, VII, V, and IV. In this instance, however, the ratio of acids VI:VII:V:IV was 6·4:8·2:1·5:1. For reasons discussed above,

[9] E. J. Corey and J. P. Schaefer, *J. Amer. Chem. Soc.* **82**, 918 (1960).

acids VI and VII will again be related to lactones II and III. Similarly, acid V will be omitted in further discussion. Thus, the overall ratio of lactones II and III to ring contracted acid IV is about 15:1, *markedly different* from the 4:1 ratio observed for non-deuterated ketone Ia. This large difference indicates that formation of IV was subject to a *primary isotope effect* with a considerable C—D bond breakage in the *rate determining step.* Mass-spectroscopic analysis of IV revealed the loss of 0·98 atom deuterium (Table 1). The distribution of species was Do 4·5%; D_1 2·7%; D_2 16·1%; D_3 76·7%, and as expected the D_4 species was absent. On this basis it is inferred that formation of IV proceeds through an enolization step. The fact that acid IV was predominantly trideuterated, and that only one atom deuterium was lost in its formation, eliminates the possibility of equilibration.

Acids VI and VII were analyzed by the combustion method and showed 3·50 and 3·49 atoms deuterium, respectively. It is apparent that *only* a small amount of deuterium, if any, was lost either in their formation, or during saponification. Mass-spectroscopically the following species were detected: acid VI; Do 0·1%; D_1 4·7%; D_2 11·5%; D_3 30·0%; D_4 53·7% and acid VII; Do 0·8%; D_1 1·6%; D_2 8·4%; D_3 27·1%; D_4 62·1%. The D content calculated from mass-spectroscopic analysis was 3·33 and 3·48 atoms, respectively, and in the case of VI it is somewhat lower than the results obtained by combustion method. A small loss of D from carbon 4 (which is α to the carboxyl) during the mass-spectroscopic analysis could account for the difference.

The evidence presented excludes the possibility of a primary isotope effect in the lactonization process. It may therefore be concluded that the lactones result from a process analogous to Baeyer–Villiger reaction.

Of incidental interest were certain equilibration and oxidation experiments carried out with D-acids VI and VII. When D acids VI and VII were first heated with aqueous acetic acid (1:1) and then the partially lactonized mixture was treated with base, no loss of deuterium occurred. On the other hand chromic acid–acetic acid oxidation resulted in a considerably greater than expected loss of tracer. It was anticipated that oxidation will remove the deuterium (about two atoms) from the hydroxyl bearing carbons. In actuality acids Ve and VIII retained only 0·86 and 0·98 D atoms respectively. A possible explanation for the loss of deuterium in excess of the expected about two atoms, might be chromic acid catalysed enolization of the carboxylic groups

We will now turn to the question of structure of acid IV. Evidence presented above indicates that ring contraction proceeds through *enolization.* It is more likely that the Δ^2-enol will predominate. This enol is then oxidized. The oxidation proceeds probably through the 2-selenoxy intermediate as proposed by Corey and Schaefer[9] for selenium dioxide oxidation of ketones. An enol-epoxide intermediate suggested by Sonoda and Tsutsumi[10] for selenium dioxide hydrogen peroxide oxidation of benzoin appears to be less likely.[8] It might be expected that the "oxidizing species" will approach the molecule, preferentially from the back-side resulting in a 2α-selenoxy[8] (or less probably, 2α,3α-epoxy intermediate). Concerted collapse of the "2α-intermediate" would then give the 2α-carboxylic acid. Obviously, should the alternative 3-enol also be formed a ring contracted 3α-carboxylic acid would be

[10] N. Sonoda and T. Tsutsumi, *Bull. Chem. Soc. Japan* **34**, 1006 (1961).

obtained. We have isolated acid IV, although small amounts of other acids were detected in the reaction mixtures.

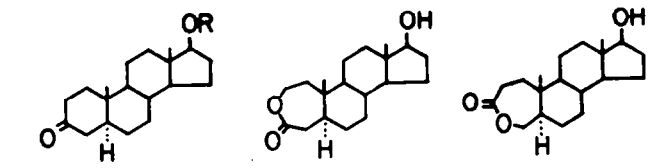
Identification of the acid IV required proof of position of attachment and of stereochemistry of the carboxylic moiety. For the projected chemical transformations required for structure determination a simpler synthesis of acid IV was needed. With this in mind, we turned our attention towards the Favorskii rearrangement of 17β-acetoxy-2α-bromo-5α-androstan-3-one. Indeed treatment of the 2α-bromo-3-ketone with sodium methoxide[11] gave the acid IVa as the major product. The acid IVa was isolated as the methyl ester-acetate IVb and was correlated to the acetoxy ester obtained from hydrogen peroxide–selenium dioxide oxidation of Ib. Three additional products were detected in the reaction mixture resulting from the Favorskii rearrangement, of which only the diacid Va was obtained in amount sufficient for characterization as the dimethyl ester acetate Vb.

Proof of the C–2 attachment of the carboxylic group[7] was obtained by the conversion of IVa to the diketone IXc. Treatment of IVa with methyl lithium and subsequent acetylation gave the A-nor-2α-acetyl product X. Baeyer–Villiger oxidation of X yielded the diacetate XIa. Saponification gave the 2α,17β-diol XIb which was oxidized to dione IXc. An authentic sample of the dione was prepared from dicarboxylic acid Va. The acid Va was pyrolysed with acetic anhydride to IXa, then saponified and IXb oxidized to IXc.

With the position of the carboxylic group established and in view of the fact that the acid resulted from Favorskii rearrangement of the 2α-bromo-3-ketone, it was considered very probable that the product has the 2α structure IV. Confirmation of the 2α-stereochemistry of the carboxyl was obtained by NMR spectroscopy. If the signal for the 19-methyl in 17β-acetoxy-A-nor-5α-androstan (XII) is used as the reference, 2β-substituents exert a greater deshielding effect on this methyl than their 2α-counterparts. These conclusions were derived from a detailed study of a number of A-nor-2-substituted steroids which will be published elsewhere. In summing up our observations on NMR spectra of A nor steroids, 2β-oxygen bearing substituents deshield the 19-methyl by about 12–15 c/s while the signal in 2α-substituted compounds is distinctly coupled (split or broadened[12,13]) and is deshielded only by about 2–6 c/s. The 19-methyl in 2β-substituted products was only insignificantly coupled. The 19-methyl in IVa and IVb is shifted downfield by 4 c/s and 2·5 c/s respectively from the resonance of this methyl in XII. Hence we can assign with certainty structure IV to the acid obtained by two routes: selenium dioxide–hydrogen peroxide oxidation and Favorskii rearrangements.

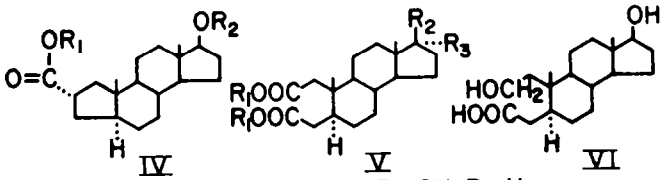
After the completion of our work, Jacques *et al.*,[14] have published an elegant study of NMR spectra and rotatory dispersion of A-nor steroids. Whenever the same compounds were investigated by the French workers and by us, the results were in good agreements. However, the French investigators have not reported the distinct and characteristic coupling of the 19-methyl in 2α-substituted-A-nor-5α-steroids.

[11] D. E. Evans, A. C. De Paulet, C. W. Shoppee and A. Winternitz, *J. Chem. Soc.* 1451 (1957).
[12] N. S. Bhacca, J. E. Gurst and D. H. Williams, *J. Amer. Chem. Soc.* **87**, 302 (1965).
[13] C. W. Shoppee, F. P. Johnson, R. Lack and S. Sternhell, *Tetrahedron Letters* 2319 (1964).
[14] J. Jacques, M. Minssen, D. Varech and J. J. Basselier, *Bull. Soc. Chim. Fr.* 77 (1965).



I a. R = H
b. R = Ac
c. R = H; 2,2,4,4-D_4
d. 3βOH instead of ketone; R = H

II III



IV a. R_1 = H; R_2 = H
b. R_1 = Me; R_2 = Ac
c. R_1 = Me; R_2 = H
d. R_1 = H; R_2 = H

V a. R_1 = H; R_2 = OH; R_3 = H
b. R_1 = Me; R_2 = OAc; R_3 = H
c. R_1 = H; R_2 = OAc; R_3 = H
d. R_1 = Me; R_2 = OH; R_3 = H
e. R_1 = H; R_2, R_3 = O

VI

EXPERIMENTAL[15]

2,2,4,4-D_4-17β-*Hydroxy*-5α-*androstan*-3-*one* Ic. Sodium (0·5 g) was dissolved with stirring in D_2O (99·8%, 10 ml) and dry diglyme (100 ml). Then 17β-hydroxy-5α-androstan-3-one (2·9 g) was added and the mixture was refluxed for 16 hr in an atm. of N_2. The reaction was terminated by dilution with water, and the obtained solid was collected (2·6 g). Recrystallization from MeOH gave Ic, ν_{max}^{KBr} 2200, 2080 (no 1420 band) cm^{-1}. The IR spectra of the deuterated and non-deuterated products differed in certain details.

2,2,4,4-D_4-3β,17β-*Dihydroxy*-5α-*androstane* (Id). A mixture of Ic (100 mg), ether (30 ml), and LAH was refluxed for 4 hr with exclusion of moisture. The reaction was terminated with acetone, poured on ice and acidified with 1N HCl. The phases were then separated, the ether solution was washed, dried and concentrated. The obtained solid was recrystallized from MeOH–ethyl acetate, λ_{max}^{KBr} 3500, 3200 (broad), 3180, 3100 cm^{-1}.

Oxidation of 17β-*hydroxy*-5α-*androstan*-3-*one* (Ia). A mixture of Ia (150 mg), SeO_2 (12 mg), *t*-butanol (8 ml) and H_2O_2 (50%, 0·4 ml) was refluxed for 7 hr. After dilution with water, the steroids were recovered with ether. The ether solution was washed with water, then dried, and reduced to a residue. The residue was dissolved in MeOH (10 ml), 1N NaOH (10 ml) was added, and the mixture was refluxed for 1 hr in an atm. of N_2. The solution was diluted with water and extracted with ether to remove neutral components. The aqueous phase was acidified with dil. HCl and extracted with ether. The ether was washed with saline, dried and concentrated. The crude residue was treated with ethereal diazomethane. Removal of the solvent left 134 mg of a mixture of esters. The mixture

[15] M.ps were determined on a hot stage and are corrected. IR spectra were taken in solids incorporated in KBr blotters. NMR spectra were determined in $CDCl_3$ or CD_3OD with tetramethylsilane as internal standard on a Varian spectrometer model V4300 B. Thin layer chromatographies (TLC) were performed on silica gel HF_{254} purchased from E. Merck, A. G. Darmstadt, Germany. Analyses by Else Beetz, Kronach, Germany. Mass spectroscopic analyses by Dr. R. Ryhage, Karolinska Institutet, Stockholm, Sweden. Deuterium determinations by combustion method by J. Nemeth, Urbana, Illinois.

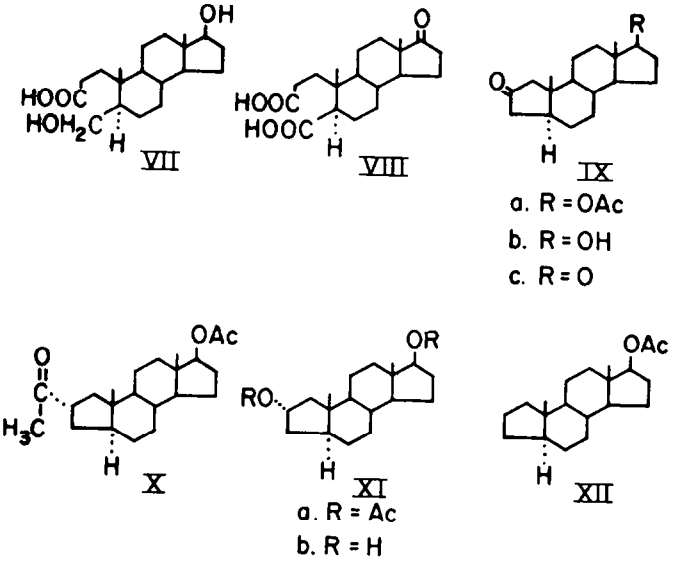


TABLE 1. D CONTENT OF SAMPLES INVESTIGATED

Sample	Method		
	Combustion	Mass spectroscopic	
	D-Atom	Calc. D-Atom	Species (in %)
Ic	3·58	—	
Id	—	3·63	D_0 1·8; D_1 1·1; D_2 3·4; D_3 19·4; D_4 74·3
IV	—	2·65	D_0 4·5; D_1 2·7; D_2 16·1; D_3 76·7
VI	3·50	3·33	D_0 0·1; D_1 4·7; D_2 11·5; D_3 30·0; D_4 53·7
VII	3·49	3·48	D_0 0·8; D_1 1·6; D_2 8·4; D_3 27·1; D_4 62·1
VI after equilibr.		3·45	D_0 1·4; D_1 3·0; D_2 12·3; D_3 29·3; D_4 54·0
VII after equilibr.		3·38	D_0 1·3; D_1 1·9; D_2 10·4; D_3 30·2; D_4 56·2
Ve		0·86	D_0 37·5; D_1 39·2; D_2 23·3
VIII		0·98	D_0 30·9; D_1 40·0; D_2 29·1

was resolved by TLC using chloroform–ethyl acetate (3:1) as solvent. Four zones were detected which upon elution gave: methyl ester of VI (39 mg); methyl ester of VII (53·0 mg); di-methyl ester Vd (13·7 mg), and methyl ester of IVc (23·2 mg). Total products recovered 128·9 mg. The compounds were identified by the comparison with previously described samples.[4a] The experiment was repeated several times and essentially similar ratios of products were obtained.

Oxidation of 2,2,4,4-D_4-17*β-hydroxy-5α-androstan-3-one* (Ic). The oxidation and processing of the D_4-Ic was carried out exactly as described above. TLC of the crude esters (117 mg) gave: methyl ester of VI (40 mg), methyl ester of VII (52·3 mg), di-methyl ester Vd (10·5 mg), and methyl ester IVc (6·3 mg). Total products recovered (109·1 mg). The experiment was repeated once more with essentially the same result.

Each ester was dissolved in MeOH (4 ml), then 1N NaOH (1 ml) was added, and the mixture was refluxed for 1 hr under N_2. The respective acids were isolated in the conventional manner and were analyzed for deuterium.

Equilibration of D-*acids* VI *and* VII. Both acids were treated identically. A mixture of the acid (40 mg), MeOH (1 ml), and 50% aqueous acetic (1 ml) was heated at 70° for 8 hr. The volatile components were removed in a stream of N_2. The residue was dissolved in 4 ml of 0·25N aqueous methanolic (1:1) NaOH and the solution was refluxed for 2 hr under nitrogen. The acids were recovered from the acidified and diluted mixture and were crystallized from MeOH.

17*β-Acetoxy* A *nor-5α-androstan-2-one* IXa. A solution of Ib (2·0 g) in glacial acetic acid (10 ml) was added to a solution of CrO_3 (3 g) in 80% aqueous acetic acid, and the mixture was heated at 60° for 2·5 hr.[16] The solution was cooled and the steroids were recovered with ether. After partitioning with a sat. $NaHCO_3$aq, the dicarboxylic acid Vc (1·62 g) was obtained.

The crude acid was dissolved in acetic anhydride (10 ml) and refluxed for 3 hr. The solution was transferred to a sublimation apparatus, and the acetic anhydride was removed under red. press. The cold finger was then inserted, the pressure was reduced to 15 mm, and the residue was heated for 2·5 hr at 200–225°. During this time, almost all of the material sublimed and accumulated on the cold finger. The material was dissolved in MeOH (50 ml), 2N NaOH (10 ml) was added and the mixture was boiled for 1 hr in an atm. of N_2. Most of the MeOH was removed in a stream of N_2, then water was added and the mixture was extracted with ether. The ether solution was washed with saline, dried, and concentrated to yield a solid (800 mg). The solid was acetylated (pyridine–acetic anhydride 16 hr r.t.) to afford 780 mg of IXa as plates, m.p. 108–112° (rep.[16] 114–115°) ν_{max}^{KBr} 1730 cm^{-1}.

Upon acidification of the NaOH solution, acid Va (428 mg) was recovered.

17*β-Acetoxy*-A-*nor-5α-androstane* (XII). Zinc amalgam was prepared by agitating Zn moss (2 g) with a mixture of $HgCl_2$ (0·25 g), conc. HCl (0·15 ml) and water (2 ml) for 15 min at r.t. The amalgam was filtered, washed with water and 15% HClaq (2·5 ml). The amalgam was then added to a solution of IXa (100 mg) in MeOH (3 ml), and the mixture was refluxed for 45 hr. At intervals of about 6–8 hr, conc. HCl (0·5 ml) was added. The reaction mixture was cooled, diluted with water, and the steroid was recovered with ether. The ether solution was washed, dried, and reduced to yield a crystalline residue (98 mg). The residue was acetylated (pyridine–acetic anhydride, 16 hr r.t.) and after conventional workup XII (72 mg) was obtained m.p. 80–84°.

Recrystallization from aqueous MeOH gave long flat needles, m.p. 86·5–87·5°. λ_{max}^{KBr} 1725 cm^{-1}. NMR ($CDCl_3$) 4·62 (triplet), 2·0 (acetate), 0·78 (18-methyl), and 0·63 (19-methyl) ppm. (Found: C, 78·60; H, 10·42; Calc. for $C_{30}H_{52}O_2$: C, 78·89; H, 10·59%.)

Methyl 17*β-acetoxy*-A-*nor-5α-androstan-2α-oate* (IVb). To a mixture (stirred in an atm. of N_2) of Ia (2·09 g), glacial acetic acid (20 ml) and HBr (one drop of acetic acid saturated with HBr) a solution of Br_2 (1·056 g) in glacial acetic acid (5 ml) was added dropwise.[11] The uptake of bromine was very rapid, and the rate of addition was regulated to maintain a slight coloration. The pale yellow solution was left for 1·5 hr at r.t., then water was added, and the obtained solid was collected by filtration to give 2·12 g; m.p. 172–176. ν_{max}^{KBr} 1730 cm^{-1}.

A solution of the above bromide (475 mg) in ether (55 ml) was added dropwise to a cooled (ice bath) methanolic solution of MeONa[11] (1 g Na in 15 ml MeOH). After the addition of the bromide, the ice bath was removed, the temp was permitted to rise to 20°, and the mixture was stored for 10 hr. Then water was added, and the base insoluble components were removed with ether. The alkaline, aqueous phase was acidified with HCl and extracted with ether. The ether extract was washed dried and concentrated to yield a solid residue (301 mg).

The crude acids were esterified with ethereal diazomenthane. Removal of the ether left a syrup which was acetylated in the conventional manner. Upon processing of the reaction mixture, an oily residue was isolated and chromatographed on four 20 × 20 cm thin layer plates (TLC) using ethyl acetate–benzene (3:7) for resolution. Four zones were detected and were numbered 1–4 in decreasing order of mobility. Elution of zone 2 afforded IVb (108 mg), m.p. 76–82 identical to the sample previously obtained[4a] from SeO_2–H_2O_2 oxidation of Ia or Ib. Saponification of IVb gave the hydroxy acid IVa undistinguishable from the previously obtained product.[4a]

From zone 3 the diester acetate Vb (21 mg) was obtained and identified by comparison with an authentic sample.[4a]

The products from zones 1 and 4 were obtained in amounts insufficient for identification.

[16] T. Rull and G. Ourisson, *Bull. Soc. Chim. Fr.* 1573 (1958).

17β-Acetoxy-2α-acetyl-A-nor-5α-androstane (X). An ether solution of MeLi (1·6 mole 5 ml) was added to a vigorously stirred mixture of acid IVa (500 mg) ether–dioxan (1:1, 50 ml) at 80°. A white precipitate was formed immediately and the heating was continued for 8 hr. The reaction was terminated by addition of water and the product was recovered with ether. The ether solution was washed dried and concentrated to a residue (300 mg). The residue was acetylated in the conventional manner to yield upon processing a syrupy acetate. The acetate was chromatographed on four 20 × 20 cm TLC plates using benzene–ethyl acetate (4:1) for resolution. Elution of the plates gave a syrup which crystallized on trituration with MeOH (260 mg). A sample was crystallized from MeOH to yield X, m.p. 110–112°; ν_{max}^{KBr} 1735, 1705, 1248 cm^{-1}. (Found: C, 76·22; H, 9·89. Calc. for $C_{23}H_{34}O_3$: C, 76·26; H, 9·77%.)

2α,17β-Diacetoxy-A-nor-5α-androstane (XIa). To a stirred and cooled (ice bath) mixture of X (250 mg), anhydrous Na_2HPO_4 (700 mg) and CH_2Cl_2 (8 ml), a solution of trifluoroacetic anhydride (0·2 ml), H_2O_2 (90%, 0·2 ml) in dry CH_2Cl_2 (8 ml) was added dropwise during 15 min. The ice bath was removed and the stirring was continued for 3 hr at ambient temp. After addition of water, the phases were separated. The aqueous layer was extracted several times with CH_2Cl_2. The combined extracts were washed with water, an $NaHCO_3$aq, saline dried and concentrated to a syrupy residue (230 mg). Chromatography on three 20 × 20 cm TLC plates with benzene–ethyl acetate (4:1) gave a single zone. Upon elution of the plates XIa (200 mg) was obtained. A sample was crystallized from ethyl acetate–MeOH to a m.p. 127–130° (rep[14] 135–136°); ν_{max}^{KBr} 1740, 1730 (shoulder), 1248 cm^{-1}. (Found: C, 72·47; H, 9·27. Calc. for $C_{23}H_{34}O_4$: C, 72·89; H, 9·45%.)

The diacetate XIa (85 mg) was dissolved in 5% methanolic KOHaq (10 ml) and left for 16 hr at r.t. in an atm. of N_2. After the conventional workup, XIb (70 mg) was recovered. The diol was crystallized from acetate, m.p. 166–169°. ν_{max}^{KBr} 3500, 3300 (no carbonyl absorption), cm^{-1}.

A-Nor-5α-androstane-2,17-dione (IXc). A solution of XIb (12 mg) pyridine (0·2 ml) was added to a suspension of CrO_3 (12 mg) in pyridine (0·3 ml), and the mixture was left for 6 hr at r.t. The reaction was terminated by dilution with ethyl acetate, and the precipitated solid was removed by filtration over celite. The filtrate was washed with dil HCl, water, an $NaHCO_3$aq, saline and dried. Removal of the solvent gave the dione IXc (10 mg) which was crystallized from acetone–MeOH to m.p. 170°–172° (rep.[17] 171–173°). ν_{max}^{KBr} 1740 cm^{-1}. The same dione was obtained from oxidation of IXb.

NMR *spectra of esters* IVc and IVb. Ester IVc in $CDCl_3$, 41·0 (19-methyl), 43·5 (18-methyl), 221 (ester methyl) c/s. Half height width: 19-methyl, ca. 2·5 c/s; 18-methyl, ca. 2·0 c/s; ester methyl, ca. 1 c/s. (The 19 and 18 methyl overlap in part and the half height width are approximated.)

Ester IVb in $CDCl_3$, 43·0 (19-methyl); 48·0 (18-methyl); 122·0 (acetate) 220·5 (methyl ester) c/s. Half height width: 19-methyl-2 c/s, 18-methyl 1·5 c/s, acetate 1 c/s methyl ester ca. 1 c/s.

The acetate 12 in $CDCl_3$ 0·63 (19-methyl); 0·78 (18 methyl); 2·0 (acetate) ppm.

[17] M. Minssen and J. Jacques, *Bull. Soc. Chim. Fr.* 71 (1965).