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OXIDATIVE β-FRAGMENTATION OF 19-NOR-5α-ANDROSTANE-3β, 5, 17β-TRIOL 3, 17-DIACETATE[1]

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Abstract—The preparation of 19-nor-5α-androstane-3β,5,17β-triol 3,17-diacetate (**10**) is described. When this alcohol was treated with the mercuric oxide-iodine reagent, it underwent fragmentation of the C(5)–C(10) bond with formation of a new type of 10-membered ring containing 5,10-seco-steroidal compounds, i.e. (*Z*)-and (*E*)-19-nor-3β,17β-diacetoxy-5,10-seco-androst-1(10)-en-5-one (**11** and **12**), in 27 and 49% yield, respectively.

As previously reported,[2-4] alkoxy radicals **i** (Scheme 1), obtained from 5-hydroxy steroids such as **1** and **2**, readily undergo β-fragmentation involving scission of the C(5)–C(10) bond to give as final products (via the carbon radical intermediates **ii**) the diastereomeric *Z*- and *E*-1(10)-unsaturated 5,10-seco-steroidal 5-ketones **3** and **4**, in high yield.

These and subsequent investigations have shown: (1) that oxidative C(5)–C(10) β-fragmentation was a general process, which could be applied to various steroidal 5α- and 5β-hydroxy derivatives, such as **1** and **2** (Scheme 1), independently of the substituent at the C(17) position[5] or the presence[6] and orientation[7] of the 3-OAc group (although 5-OH substrates with modified[8] or substituted[9] ring *B* can give products other than 5,10-seco-ketones); and (2) that this type of fragmentation could be effected by various oxidative agents or methods (for example, with lead tetraacetate under thermal[2,3] or UV-photolytic[5,7] conditions, with mercuric oxide-iodine[4] or lead tetraacetate-iodine,[5,10] and with ceric ammonium nitrate[11]).

Since, in general, the direction of β-fragmentation in unsymmetrical alkoxy radicals can be rationalized in terms of the relative stability of the resulting C-centered free radical fragment (or moiety) and CO fragment (or moiety), as well as of steric and/or stereo-electronic factors,[12] it appears that in the case of 5-hydroxysteroids such as **1** and **2** (Scheme 1) the main factor controlling C(5)–C(10) bond cleavage is the stability of the tertiary C radical intermediate **ii**, bearing the angular 19-Me group at the C(10) radical center. Therefore, it is reasonable to assume that in 5-hydroxysteroid compounds the ease and direction of this fragmentation process should be, in general, strongly influenced by the presence or absence of Me substitution at C(10).† In order to establish the validity of such an assumption, in the present work a 19-nor-5-hydroxysteroid, i.e. 19-nor-5α-androstane-3β,5,17β-triol 3,17-diacetate (**10**), was prepared and subjected to oxidations which had been efficient to induce C(5)–C(10) bond cleavage in similar 19-Me systems.

RESULTS AND DISCUSSION

The 19-nor-5α-alcohol **10** was prepared according to the reaction sequence outlined in Scheme 2 (whereby all given yields refer to recrystallized products). The enol acetate **6**, obtained from 19-nor-androst-4-ene-3,17-dione (**5**) upon treatment with acetyl chloride and acetic anhydride, was reduced with sodium borohydride, and the resulting diol **7** was acetylated to give the diacetate **8**. This compound was converted stereospecifically with monoperphthalic acid to the 5α,6α-epoxide **9**. LAH reduction of this compound proceeded regioselectively, affording, upon acetylation, the desired final 19-nor-3β,5α,17β-triol 3,17-diacetate **10**.

Oxidations of **10** were carried out by methods previously used to effect fragmentation of the C(5)–C(10) bond in the analogous 19-methyl-5-hydroxysteroids of type **1** and **2** (Scheme 1), i.e. with lead tetraacetate alone under thermal conditions (28 hr) or UV-photolytic con-

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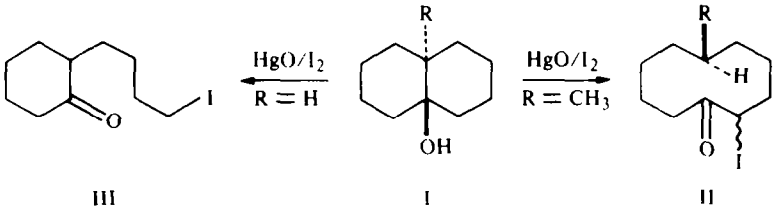
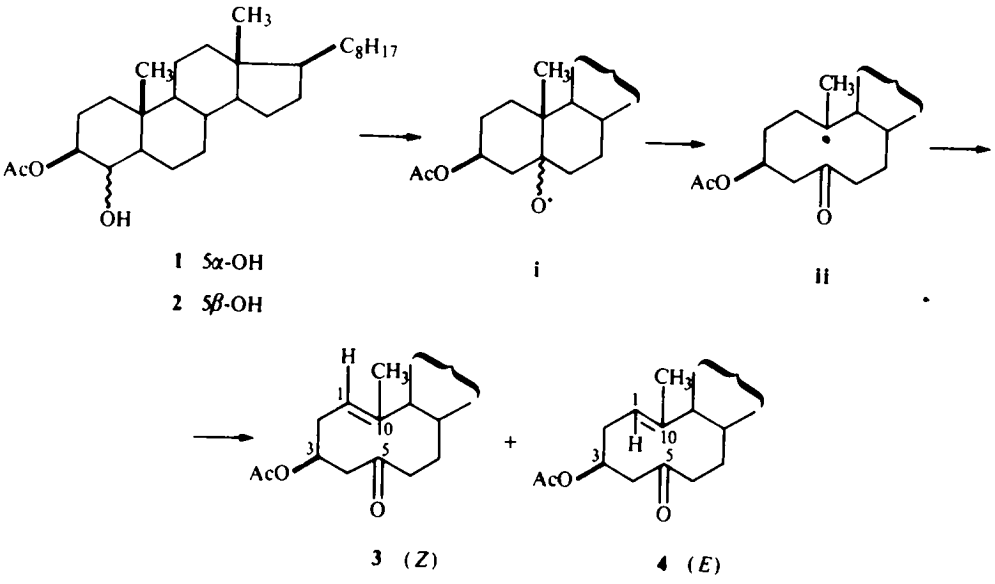
†Recently, it was reported[13] that the presence or absence of Me substitution at the ring-fusion site in the analogous decalinol system I had a dramatic impact on the direction of oxidative β-fragmentation (in the reaction with mercuric oxide-iodine); thus, the iodo-cyclodecanone derivative II was formed in high predominance when R=Me, while the substituted cyclohexanone III was produced exclusively when R=H.

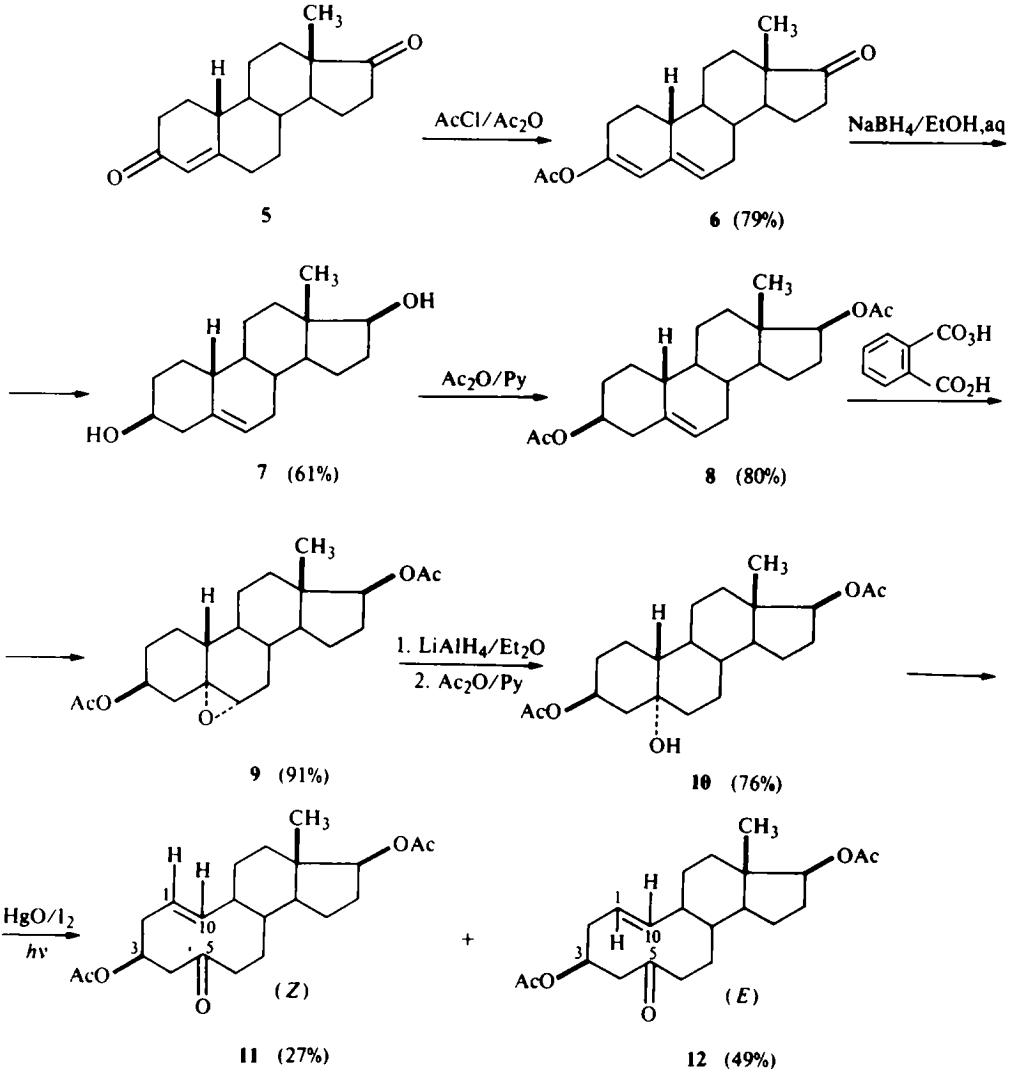


III I II



1 5α-OH
2 5β-OH

Scheme 1.



Scheme 2.

ditions (3 hr), with lead tetraacetate in the presence of iodine (6 hr), and with the mercuric oxide-iodine reagent (3 hr).† It was found that, in contrast to the 19-Me containing compound **1** (see above), the three procedures using lead tetraacetate were inefficient to induce β-fragmentation of the 19-nor-5α-ol **10**, and in all these cases only unchanged starting material (**10**) could be isolated in over 90% yield (the rest being a complex unresolvable mixture). However, in the reaction with mercuric oxide-iodine, the C(5)–C(10) bond of alcohol **10** was readily cleaved, when both the *Z* and *E* isomeric 19-nor-3β, 17β-diacetoxy-5, 10-seco-androst-1(10)-en-5-ones **11** and **12** (Scheme 2) were formed in about 27 and 49% yield, respectively.‡

The structures of the fragmentation products **11** and **12** were deduced on the basis of elemental microanalysis and spectral data, whereby UV and NMR analysis, similar to that described previously for the analogous *Z* and *E* stereoisomers of the "normal" (19-Me) 5,10-seco-steroidal series **3** and **4** (Scheme 1),[3,7,10,14] was applied to determine the stereochemistry around the double bond and the conformation of the 10-membered ring in these compounds (in soln). Thus, the UV spectrum of ketone **12** contained a short wavelength adsorption (λ_{max} 212 nm, ϵ 2800, in methanol, arising from photodesmotic transition[15]), characteristic of the (*E*)-cyclodecen-5-one system. As expected, this absorption was not present in the UV spectrum of the *Z* diastereomer **11**. In agreement with the *Z* configuration, in the ^{1}H NMR spectrum (at 360 MHz) of **11**, the signals of the protons H–C(1), H_α–C(3) and H–C(10) were located at ~5.43 ppm as an unresolvable multiplet, while those of H_α–C(4) and H_β–C(4) appeared as a $d \times d$ at 2.41 and 3.16 ppm, respectively (J_{gem} 16.5 Hz, $J_{3\alpha,4\alpha}$ 4.5 Hz, $J_{3\alpha,4\beta}$ 12 Hz). On the other hand, in the ^{1}H NMR spectrum (at 360 MHz) of the *E* isomer **12**, only H_α–C(3) and H–C(10) resonated as low as ~5.32 ppm (also as a complex multiplet), while the resonance of H–C(1), due to transannular shielding by the 5-keto grouping, was displaced upfield and located at 4.98 ppm, with a $d \times d \times d$ pattern ($J_{1,2\alpha}$ 4.5 Hz, $J_{1,2\beta}$ 11 Hz, $J_{1,10(trans)}$ 18 Hz). In the spectrum of this *E* isomer no signals between 2.7 and 4.5 ppm could be observed. Similar ^{1}H NMR parameters were obtained for the 19-Me containing 5,10-seco-5-ketones **3** and **4**,[3,7,10,14]§ as evident from the comparative data presented in Table 1. Therefore, using the same arguments in the present case, it follows that the conformations of the 10-membered ring in both *Z* compounds **3** and **11** in solution are very similar and correspond to **A** (Fig. 1), and that the conformation of the 10-membered ring in the *E* isomeric 19-nor-product **12** in solution closely resembles the main conformation in solution of the 19-methyl-seco-ketone **4**, both corresponding to **B** (Fig. 1).

In addition, X-ray studies of the *Z* and *E* isomeric

†For details see Experimental.

‡In the 19-Me series the same oxidative method applied to alcohol **1** afforded the *Z* and *E* diastereomeric 5,10-seco-5-ketones **3** and **4** (Scheme 1) in 10 and 63% yield, respectively.[4b]

§And also for analogous 19-methyl-5,10-seco-5-ketones of other steroidal series.

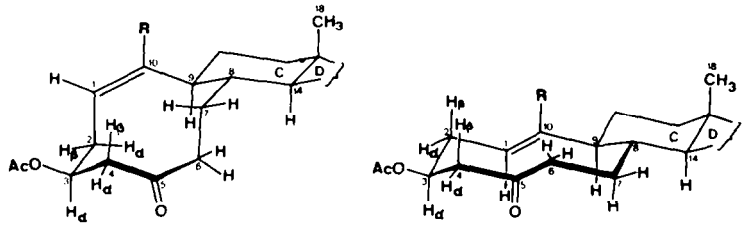
Table 1. ^{1}H NMR data (obtained in $CDCl_3$ at 360 MHz) for selected 10-membered ring protons in the 5,10-seco-5-ketones **3**, **4**, **11** and **12**

Protons	Z Compounds		E Compounds	
	3[a]	**11**	**4**[b]	**12**
	Chemical shifts (ppm/TMS)			
1	5.25 (m)	5.43 (m)	4.82 (d x d)	4.98 (d x d x d)
3α	5.39 (m)	5.43 (m)	5.35 (m)	5.32 (m)
4α	~2.14 (d x d)	2.41 (d x d)	c	c
4β	3.18 (d x d)	3.16 (d x d)	c	c
10	-	5.43 (m)	-	5.32 (m)
	Coupling constants J (Hz)			
1,2α			~5	4.5
1,2β			~11	11
1,10 (tr)			-	18
3α,4α	3.6	4.5		
3α,4β	11.8	12		
4α,4β (gem)	16.2	16.5		

[a] Coupling constants measured also in toluene-d_8

[b] Given data refer to the main conformation **B**–**4**[7,14]

[c] Signals masked by overlap with other resonances



A (*Z*) B (*E*)

3 (R=CH_3) **4** (R=CH_3)

11 (R=H) **12** (R=H)

Fig. 1. Conformations of the 10-membered ring (in solution and in the solid state) in the 5,10-seco-5-ketones **3**, **4** (main conformation in solution), **11** and **12**.

19-nor-5,10-seco-5-ketones **11** and **12** have established solid state structures in which the 10-membered ring conformations have also the forms **A** and **B**, respectively;[16] and previously, it was found by X-ray analysis that closely similar conformations of type **A** and **B** for the medium-sized ring exist in the solid state structures of the *Z* and *E* diastereomeric 19-Me containing seco-steroidal 5-ketones **3** and **4**, respectively.[10, 14]

The similarity in the spatial arrangements of C atoms in both the *Z* seco-compounds **3** and **11** and their *E* diastereomers **4** (in its main conformation) and **12**, respectively, is substantiated by comparison of the corresponding ^{13}C NMR spectra obtained for these products. Selected ^{13}C chemical shifts relevant for the conformational assignments are given in Table 2.

From the results described above, it follows that the presence of the 19-Me group in steroidal 5-alcohols does enhance cleavage of the C(5)–C(10) bond by β-fragmentation of the corresponding 5-alkoxy radicals, when compared to the analogous 19-nor-compounds, and that various oxidative reagents or methods, which are equally efficient (but not necessarily stereochemically equivalent[5]) when applied to 19-methyl-5-hydroxy derivatives, become selective in inducing β-fragmentation in 19-nor-steroidal systems. This difference in reactivity between mercuric oxide-iodine and lead tetraacetate (under various conditions) in the latter case (and probably the difference in stereochemical behaviour in the former case) is undoubtedly also due to factors dependent on the nature and mode of action of the oxidizing agents investigated,† but, on the basis of available evidence, it is not possible as yet to give a precise mechanistic rationalization of the results obtained.

†On the general mechanism of oxidative β-fragmentations see for example refs 4a and 12.

Table 2. ^{13}C NMR chemical shifts (ppm/TMS) of the 10-membered ring carbon atoms in the 5,10-seco-5-ketones **3**, **4**, **11** and **12**

Carbon atom	Z Compounds		E Compounds	
	3[a]	**11**[b]	**4**[a]	**12**[b]
1	123.9	126.7	120.4	122.9
2	34.0	39.6	28.6	29.2
3	74.4	73.4	70.6	70.3
4	47.7	48.5	40.7	40.7
5	-	206.6	210.5	212.4
6	42.7	44.9	39.6	39.4
7	28.6	29.5	27.5	28.3
8	38.2	42.4	36.8	39.8
9	54.9	48.8	41.7	40.1
10	138.8	138.0	142.5	139.0
14	56.5	50.3	50.3	44.8

[a] Measured in toluene-d_8 at 25.2 MHz[7,10,14]

[b] Measured in $CDCl_3$ at 25.2 MHz

EXPERIMENTAL†

All m.ps are uncorrected. Optical rotations were measured in $CHCl_3$ soln. ^1H NMR spectra were obtained at 100 MHz with a Varian HA-100 spectrometer and at 360 MHz with a Bruker HX-360 spectrometer; noise decoupled ^{13}C NMR spectra were recorded at 25.15 MHz on a Varian XL-100 spectrometer equipped with a Fourier transform accessory; solvent—$CDCl_3$, internal standard—TMS, room temp; chemical shifts are reported in ppm as δ values. IR spectra were determined on a Perkin–Elmer double-beam instrument, model 337. UV absorption spectra were recorded in MeOH with a Perkin–Elmer 137 UV spectrophotometer. Silica gel (0.05–0.2 mm) was used for preparative column chromatography. The separation of products was monitored by TLC on silica gel G (Stahl) with benzene–AcOEt (9 : 1, 8 : 2 or 7 : 3), detection being effected with 50% H_2SO_4 aq. Light petroleum refers to the fraction b.p. 40–60°.

Synthesis of 19-*nor*-5α-*androstane*-3β,5,17β-*triol* 3,17-*diacetate* (**10**)

3-*Acetoxy*-19-*nor*-*androsta*-3,5-*dien*-17-*one* (**6**). A mixture of **5** (5.16 g), Ac_2O (25 ml) and AcCl (30 ml) was refluxed overnight under N_2 and then evaporated to dryness *in vacuo*. The residue (6.07 g) was recrystallized from acetone-light petroleum to give **6** (4.72 g, 79.2%), m.p. 159–161°; $[\alpha]_D^{20}$ −96.3° (*c* = 1.03); IR (KBr): ν_{max} 1765, 1740, 1680, 1385, 1220, 1128, 928 cm^{-1}; UV: λ_{max} 235 nm (ε 18950); NMR (100 MHz): δ 0.88 (Me-18, s), 2.10 (AcO-3, s), 5.48 (H-6, m), 5.74 (H-4, m). (Found: C, 76.28; H, 8.13. Calc. for $C_{20}H_{26}O_3$: C, 76.43; H, 8.28%.)

19-*Nor*-*androst*-5-*ene*-3β,17β-*diol* (**7**). Compound **6** (4.50 g) was dissolved in 95% EtOH (2200 ml) and this soln, after cooling at 5°, was added to a soln of $NaBH_4$ (9 g) in 70% EtOH (225 ml). The mixture was kept at 5° for 2.5 hr, heated to boiling, treated with 5% NaOH aq (225 ml), and most of the solvent evaporated *in vacuo*. The residue was acidified with dil HCl and extracted with EtOAc. The organic layer was washed with water, sat. $NaHCO_3$ aq, sat NaCl aq, and dried over $MgSO_4$. Evaporation of the solvent afforded **7**[17,18] (3.66 g, 92.5%), m.p. 153–157°, which was recrystallized from EtOH (2.42 g, 61.2%), m.p. 164–166°; $[\alpha]_D^{20}$ +6.8° (*c* = 0.50); IR (KBr): ν_{max} 3400, 1077, 1058, 1035 cm^{-1}.

19-*Nor*-*androst*-5-*ene*-3β,17β-*diol diacetate* (**8**). Diol **7** (3.50 g) was acetylated with Ac_2O (50 ml) in dry pyridine (80 ml) at room temp for 16 hr. The mixture was poured on crushed ice–water (about 800 g) containing conc HCl (80 ml) with vigorous stirring, the ppt filtered off, thoroughly washed with water and air-dried, to give **8** (4.61 g, 98.8%), which was recrystallized from ether-light petroleum (3.74 g, 80.1%), m.p. 138.5°;[17,18] $[\alpha]_D^{20}$ −21.7° (*c* = 0.53); IR (KBr): ν_{max} 1755, 1750, 1245, 1038 cm^{-1}; ^1H NMR (100 MHz): δ 0.80 (Me-18, s), 1.96 and 1.98 (AcO-3 and AcO-17, two s), 4.52 (H-17, m), 4.65 (H-3, m), 5.52 (H-6, t). (Found: C, 73.34; H, 9.01. Calc for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95%.)

19-*Nor*-5,6α-*epoxy*-5α-*androstane*-3β,17β-*diol diacetate* (**9**). To a stirred soln of **8** (2.14 g) in dry ether (100 ml), monoperphthalic acid (1.30 g) in 35 ml ether was added, and the mixture was refluxed for 3 hr. After cooling, the ether soln was washed with $NaHSO_3$ aq, water, sat $NaHCO_3$ aq and water, dried over $MgSO_4$ and evaporated *in vacuo* to dryness, to afford **9**[18] (2.20 g, 98.6%), which was recrystallized from acetone-light petroleum (2.02 g, 90.6%), m.p. 146°; $[\alpha]_D^{20}$ −33.9° (*c* = 0.52); IR (KBr): ν_{max} 1745, 1735, 1245, 1072, 1040 cm^{-1}; ^1H NMR (100 MHz): δ 0.76 (Me-18, s), 2.02 (AcO-3 and AcO-17, s), 2.98 (H-6, d, *J* 4.5 Hz), 4.68 (H-17, m), 5.05 (H-3, m). (Found: C, 70.08; H, 8.61. Calc for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57%.)

19-*Nor*-5α-*androstane*-3β,5,17β-*triol* 3,17-*diacetate* (**10**). To a stirred suspension of LAH (2.4 g) in dry ether (240 ml) a soln of **9** (5.00 g) in dry ether (75 ml) was gradually added. The mixture was refluxed for 4 hr, cooled to 5°, treated successively with water (2 ml), 15% NaOH aq (2 ml) and water (6 ml), and evaporated *in vacuo* to dryness, whereupon traces of water were removed by distillation with added benzene. The diol thus obtained was acetylated with Ac_2O (80 ml) and pyridine (80 ml) at room temp for 12 hr and the mixture worked up as described, to give 19-*nor*-5α-*androstane*-3β,5,17β-*triol* 3,17-*diacetate* (**10**; 4.94g, 98.3%), which was recrystallized from acetone (3.81 g, 75.8%), m.p. 178°; $[\alpha]_D^{20}$ −4.0° (*c* = 0.56); IR (KBr): ν_{max} 3528, 1750, 1730, 1270, 1243, 1048, 1030 cm^{-1}; ^1H NMR (100 MHz): δ 0.80 (Me-18, s), 2.01 and 2.03 (AcO-3 and AcO-17, two s), 4.60 (H-17, q), 5.06 (H-3, m). (Found: C, 69.74; H, 8.97. Calc for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05%.)

Oxidative β-*fragmentation of alcohol* **10**

Oxidation with mercuric oxide-iodine. A mixture of **10** (3.207g), HgO (13.76 g) and I_2 (20.48 g) in CCl_4 (500 ml) was stirred and irradiated for 3 hr without heating with a 500 W tungsten lamp placed in a central water- and air-cooled jacket. It was then filtered, washed with 10% $Na_2S_2O_3$ aq, sat. $NaHCO_3$aq and water, dried over $MgSO_4$ and evaporated *in vacuo*, to give a pale oil (3.473 g), which was twice recrystallized from acetone-light petroleum affording (E)-19-*nor*-3β,17β-*diacetoxy*-5,10-*seco*-*androst*-1(10)-*en*-5-*one* (**12**; 1.015 g, 31.82%), m.p. 208–209°; $[\alpha]_D^{20}$ +51.8° (*c* = 1.05); IR (KBr): ν_{max} 1740, 1730, 1705, 1245, 1235, 1022 cm^{-1}; UV: λ_{max} 212 nm (ε 2800); ^1H NMR (360 MHz): δ 0.80 (Me-18, s), 2.00 (AcO-3 and AcO-17, s), 4.59 (H-17, t), 4.98 (H-1, *d* × *d*, $J_{1,10}$ 18 Hz, $J_{1,2\beta}$ 11 Hz, $J_{1,2\alpha}$ 4.5 Hz), 5.32 (H-10 and H-3, m) (see also Table 1). For ^1C NMR see Table 2. (Found: C, 70.21; H, 8.52. Calc for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57%.)

The mother liquor was evaporated to dryness *in vacuo* and the oily residue (2.458 g) chromatographed on silica gel (80 g). Benzene and benzene–ether (98 : 2) eluted a complex mixture (226 mg) which was not further investigated. Elution with benzene–ether (96 : 4) afforded (Z)-19-*nor*-3β,17β-*diacetoxy*-5,10-*seco*-*androst*-1(10)-*en*-5-*one* (**11**) (850 mg, 26.7%), which was twice recrystallized from acetone-light petroleum (265 mg, 8.31%), m.p. 159–160°; $[\alpha]_D^{20}$ +99.2° (*c* = 1.03); IR (KBr): ν_{max} 1750, 1740, 1705, 1250, 1235, 1020 cm^{-1}; ^1H NMR (360 MHz): δ 0.79 (Me-18, s), 2.00 (AcO-3 and AcO-17, s), 2.41 (H_α-4, *d* × *d*, J_{gem} 16.5 Hz, $J_{3\alpha,4\alpha}$ 4.5 Hz), 3.16 (H_β-4, *d* × *d*, J_{gem} 16.5 Hz, $J_{3\alpha,4\beta}$ 12 Hz), 4.65 (H-17, t), 5.43 (H-1, H-10 and H-3, m) (see also Table 1) For ^{13}C NMR see Table 2. (Found: C, 70.46; H, 8.48. Calc for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57%.)

Further benzene-ether (96:4) fractions gave an additional amount (555 mg, 17.4%) of the *E* product **12**, the total yield of **12** thus being 49.2%.

Attempted oxidations of **10** *using lead tetraacetate*

The thermal lead tetraacetate reaction was performed in boiling benzene with 1.25 molar equivs of lead tetraacetate and in the presence of 1.25 molar equivs of dry CaCO, for 28 hr.

The photolytic lead tetraacetate reaction was carried out in benzene soln with 3 molar equivs of lead tetraacetate and 3 molar equivs of $CaCO_3$, by irradiation with a high pressure mercury lamp Q 81 (Hanau) at room temp for 3 hr.

The lead tetraacetate-iodine reaction was performed in cyclohexane soln with about 4.5 molar equivs of lead tetraacetate and 1.7 molar equivs of I_2, by irradiation with a 500-W tungsten lamp at room temp for 6 hr.

In all these experiments, after the usual work-up of the mixture and recrystallization of the residue from acetone, starting alcohol **10** was recovered in over 90% yield.

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