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THE ACTION OF LITHIUM-ALUMINIUM HYDRIDE ON A DIENOL IN STEROID SERIE

A NEW CASE OF DOUBLE BOND REDUCTION

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Abstract—By treatment with LAH in boiling THF, androstane-4, 6-diene, 3β-ol 2 is slowly reduced to a mixture of androstenols 3a and 4. The reduction mechanism, as shown by deuteriation, involves an intramolecular hydride transfer, leading to an "allyl-lithium" intermediate.

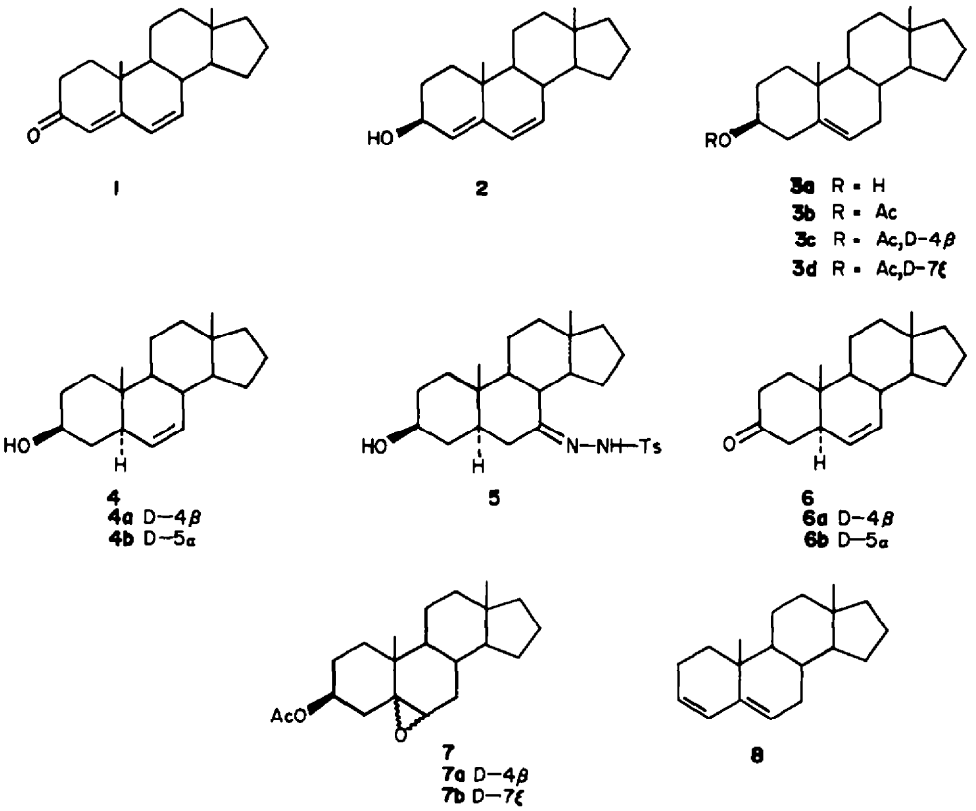
Androstane-4,6-diene,3β-ol 2, an intermediate in the synthesis of a compound intended to serve as a model for another investigation, was prepared by reduction of androstane-4,6-diene,3-one 1 by means of LAH in THF according to a literature procedure[1] requiring brief refluxing at the end of the reaction. The yield of pure dienol was only 75%, although the initial ketone has disappeared completely. Analysis of the mixture showed that three different products were formed in proportion depending on *the duration of heating.* A more precise investigation of the reduction was therefore undertaken.

1. RESULTS

The reduction of androstane-4,6-diene,3-one 1 by an excess of LAH in THF at room temperature gives the dienol 2 in nearly quantitative yield, if the reaction is stopped as soon as the initial ketone has disappeared.

If however, the reaction medium is refluxed, the dienol yield is observed to decrease. Two byproducts are formed, their yield increasing with refluxing time. This suggests that the dienol is their precursor. When the dienol was refluxed in the presence of an excess of LAH in THF, it disappeared slowly to give a mixture of two monoethylenic alcohols, which proved to be androst-5-ene,3β-ol 3a and (5α)-androst-6-ene,3β-ol 4. Thus for example, with 20 equivalents of hydride, all the dienol is consumed after 7 hr refluxing and the mixture contains 75% of alcohol 3a (isolated as its acetate 3b, the dienol and alcohol 3a having the same R_F on TLC).

The NMR spectrum of the other alcohol indicates the



1

2

3a R = H
3b R = Ac
3c R = Ac,D-4β
3d R = Ac,D-7ξ

4
4a D-4β
4b D-5α

5

6
6a D-4β
6b D-5α

7
7a D-4β
7b D-7ξ

8

Fig. 1.

presence of two olefinic protons forming an AB system (J_{AB} = 10.5 Hz) (the width of the two central lines at midheight is nearly 4 Hz). The chemical shifts of Me-18 and 19 are in agreement with values calculated by means of Zürcher increments on the basis of structure 4. In order to confirm this structure, compound 4 was prepared by treatment of the tosylhydrazone 5 of (5α)-androstane7-one,3β-ol with methyllithium in THF[2] (the lithium alcoholate formed being soluble in THF). The two products were identical.

At room temperature, the dienol in THF is reduced more slowly (25 hr) to a mixture of the same two monoenols, in similar ratio.

It is remarkable[10] that treatment of the dienol with a large excess of LAH *in ether* fails to induce any reduction, even after prolonged refluxing (Solvent effects for similar reductions[3,10]). In this solvent, reduction of the dienone gives the dienol exclusively.

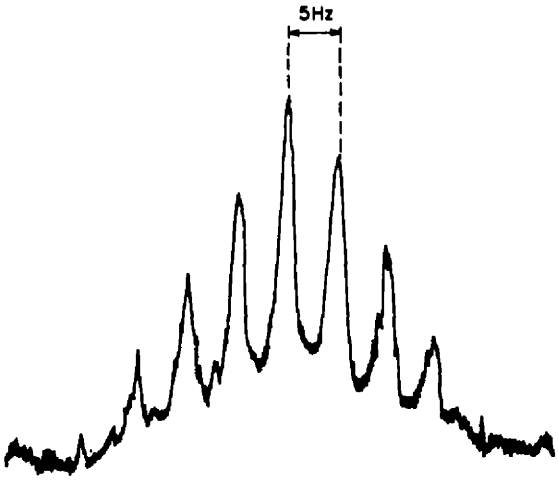


Fig. 2.

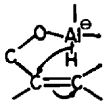
2. REDUCTION MECHANISM

2.1. *Stereospecificity of the introduction of hydride ion*

Very few cases of reduction of a double bond of a dienol such as 2 by LAH has been found in the literature. This phenomenon may be compared to the similar reactions of unsaturated alcohols such as propargylic,[4] cinnamic[5,6] and cyclopropenic[7] alcohols, or norbornadienols and norborneols.[8,9] Reduction of some simple aliphatic dienols have been recorded.[10]

The mechanism of these reductions was investigated, particularly by Franzus and Snyder[8] in the norbornane series and by Snyder[9] and Borden[11] in the cinnamic and propargylic series.

In all cases the introduction of the hydride ion is stereospecific and is interpreted as an intramolecular five center transfer from the alkoxyaluminohydride formed by reaction of LAH with the alcohol.



The new problem was investigated by the reduction of the dienol 2 with LAD in THF and hydrolysis of the complex with water. The two monoethylenic alcohol products were examined as follows:

(a) (5α)-*Androst-6-ene,3β-ol* **4a** exhibits a C-D vibration band in its IR spectrum and its mass spectrum shows the incorporation of one deuterium. The position of the deuterium in the skeleton was determined by chemical exchange. Oxidation of the deuteriated alcohol **4a** by silver carbonate on celite leads to (5α)-androst-6-ene,3-one **6a**. This ketone still contains a deuterium (mass spectrum) which is exchanged when the compound is refluxed in methanol in the presence of potassium hydroxide. Therefore the D atom is bonded to carbon 4.

The NMR spectrum of deuteriated alcohol **4a** exhibits a change in the shape of the signal of the 3α proton of the non deuteriated compound. In the latter substance this signal is a well-resolved heptuplet, the lines being separated by 5 Hz (Fig. 2), on the basis of a first-order analysis and the assumption of the coupling constants with the equatorial C-2 and C-4 protons being 5 Hz and with the adjacent axial protons 10 Hz.

In the deuteriated compound **4a** this signal is a broadened quintuplet with three central lines of equal intensity, the line separation still being 5 Hz. This result can be explained only on the basis of the disappearance of axial–axial hydrogen coupling. *Hence the introduced* D *atom is in the* 4β-configuration.

(b) *Androst-5-ene,3β-ol*, isolated in the form of its acetate **3c**, is also monodeuteriated (IR, mass spectrometry). This acetate **3c** was converted into a mixture of epoxides **7a**, the NMR spectra of which are well known.[12] In particular the C-6 proton gives characteristic signal revealing coupling with the C-7 proton.

In the spectrum of the crude mixture these signals are not altered by the presence of deuterium, excluding the possibility of the latter being located at C-7β. Pyrolysis of the deuteriated acetate **3c** in quinolein affords non deuteriated androstane-3,5-diene **8** (IR, mass spectrometry), indicating that a molecule of deuteriated acetic acid has been eliminated. Since this elimination is generally accepted to be a *cis* elimination, it is probable that *the introduced* D *has the* 4β *stereochemistry*. Furthermore, the mass spectrum of the mixture of epoxy acetates exhibits a very intense peak at M-61 (elimination of a molecule of deuteriated acetic acid).

The introduction of a D atom at C-4β in the two hydroxylated products agrees with published results. Therefore the first stage would be an intramolecular transfer of a hydride ion, suggestive of the formation of an allyl carbanion, according to the following scheme:

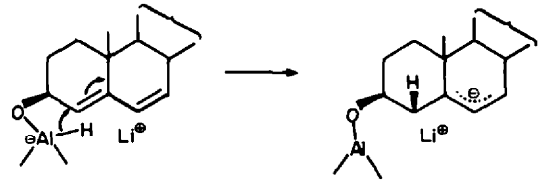


Fig. 3.

Thus the two monoethylenic alcohols can be derived from a single intermediate, differentiation occurring during hydrolysis.

This intermediate does not imply the formation of a C–Al bond, contrary to the suggestion of Franzus and Snyder[8] which, at least partially, should lead to a compound of 5β stereochemistry.

2.2. The lack of regio and stereospecificity on the introduction of the proton during hydrolysis

In order to study the nature of the introduction of the proton during hydrolysis, dienol **2** was reduced by LAH and hydrolysis carried out in heavy water. A deuterium was incorporated in the two alcohols obtained.

Monodeuteriated 5α-androst-6-ene,3β-ol **4b** exhibits an NMR spectrum which differs from that of the non-deuteriated product only by the appearance of the quadruplet for the two ethylenic protons. Each of the lines are thinly and clearly split (J = 1.8 and 2.1 Hz), making it possible to state *that the* D *atom was introduced at* C-5 (elimination of the homoallylic coupling for H-7 and the allylic coupling for H-6).

The ketone **6b**, obtained by oxidation of this alcohol with silver carbonate, was refluxed with potassium hydroxide under the above conditions. In this case the deuterium was retained, confirming the previous results.

Deuteriated androst-5-ene,3β-ol **3d** was examined in the form of epoxy acetates **7b** as above. In the NMR spectrum the 6β proton of the α epoxyde gives rise to a system of three lines of 1–2–1 intensity, the two external lines being separated by 4 Hz. in the non deuteriated compound **7**, this proton appears as a doublet (J = 4 Hz) caused by the coupling H-7β, the coupling with H-7α being practically[13] non existent.

Mass spectrometry proves the incorporation of the deuterium to be 100%. Hence it may be presumed that during hydrolysis, the deuterium is introduced at 7, but in *a non-stereospecific way.* About 50% of each isomer is obtained, the compound deuteriated at 7β being responsible for the central line of the observed triplet in NMR.

These results may be explained by assuming the common intermediate is an allyllithium (Fig. 3) for which the ionic character has been established on a simpler model.[14]

In such an intermediate, protonation can occur at the C-5 or C-7 position without regio or stereospecificity. Only thermodynamic control has any effect, the less stable 5β derivative being not obtained.

EXPERIMENTAL

M.ps were determined on a Köfler microhotstage and are not corrected. IR spectra were recorded on Perkin-Elmer 257 or 357 units. Rotary power was measured in chloroform by means of a Perkin-Elmer 141 electronic polarimeter. UV spectra were determined on a Shimadzu MPS 50-L. The NMR spectra were recorded on Jeol C-60H and 4H-100 spectrometers in deuteriated chloroform, unless indicated otherwise. Chemical shifts are expressed in ppm downfield from TMS = 0. Abreviations employed: s, singlet; d, doublet; q, quartet; m, multiplet.

Analytical and preparative TLC was carried out on silica plates impregnated with 7% of $AgNO_3$, eluted with pentane–ether mixtures. The mass spectra were recorded on a Varian Mat CH-5 spectrometer. Microanalysis were carried out by the Central Microanalysis Laboratory of the C.N.R.S., for which the authors are thankful. For all products characterized by formulas the analytical results agree there with to ±0.5% for the elements indicated.

Reduction of androstane-4,6-diene 3-one **1** *by* LAH *in* THF *with 15 min of reflux at end of reaction.* To a soln containing LAH (570 mg) in 10 ml THF, magnetically stirred, was added dropwise a soln of 1 g of **3** in 10 ml THF. When the dienone had disappeared completely, the mixture was refluxed for 15 min and then cooled and hydrolysed with 1 ml 15% NaOH and 3 ml distilled water. The mixture was filtered, dried over Na_2SO_4, and evaporated under vacuum. Chromatography of crude product (1 g, quantitative yield) on five fluorescent silica gel plates (HF 254), impregnated with *ca.* 7% of $AgNO_3$, and two elutions (eluant: pentane–ether 4/6) gave: R_f = 0.4: 60 mg of **4** (7%), m.p.: 161–162° (recrystallised from MeOH); IR (CCl_4) cm^{-1}: 3630 (νOH), 1640 (νC–C); NMR: 0.76 (3H, s, CH_3-18), 0.81 (3H, s, CH_3-19), 3.7 (1H, heptuplet, H-3α), 5.4 (2H, AB system, H-6 and H-7 olefinic): Analysis: $C_{19}H_{30}O$; R_f = 0.5: 750 mg of a mixture of androst-5-ene, 3β-ol and **2**. This mixture, analyzed by NMR, was acetylated with Ac_2O in pyridine, the two acetates are separated by TLC and two elutions (pentane–ether 9/1) leading to: R_f = 0.6: 120 mg of **3b** (15%); m.p.: 96–98° (identical to an authentic sample); R_f = 0.5: 700 mg of 3β-acetoxy, androstane-4,6-diene (78%) m.p.: 100–102°; IR (CCl_4) cm^{-1}: 1735 (νC–O acetate), 1640 (νC–C); NMR: 0.8 (3H, s, CH_3-18), 1.05 (3H, s, CH_3-19), 2.05 (3H, s, CH_3 acetate 5.7 (3H, m, H-4, H-6 and H-7 olefinic); UV (EtOH): λ max = 239 nm (ε = 24000) $\{\alpha\}_D^{20}$: 306° (*c*: 1.05).

Other reductions of androstane-4,6-diene,3-one. The other reductions of dienone **1** were carried out by following the above procedure, with variations in the refluxing time, and the solvent. Some results are given in the following Table:

Solvent	Reflux time (hr)	2	% 3a	4
THF	0	100	—	—
THF	0.5	60	31	9
THF	4	20	35	25
Ether	6	100	—	—

Reductions of androstane-4,6-diene,3β-ol **2** *by* LAH. The same procedure was followed as in the reductions of the dienone, the fraction containing the alcohol **3a** being acetylated in all cases after separation, either to eliminate the initial dienol, or to check its complete disappearance. Results obtained were as follows:

Solvent	Reaction time	2	3a	4
THF	25 hr at 18°C	0	80	20
THF	6 hr reflux	0	75	25
Ether	10 hr reflux	100	0	0

3β-Acetoxy,androst-5-ene,7-one. This ketone was obtained by allylic oxidation of androstenol acetate **3b** using Meuly's[15] method. Acetate **3b** (10 g) was dissolved in 130 ml dry benzene. To this, was added 250 ml AcOH and 90 ml Ac_2O, followed by portionwise additions of 18 g K_2CrO_4 at room temp. The reaction medium was stirred for 24 hr at 38° and then poured into 1 l. of water containing a little $NaHSO_3$. The mixture was extracted with ether (3 times) and washed with sat $NaHCO_3$ aq and then with water. The ether phase was dried over Na_2SO_4 and evaporated under vacuum. By recrystallization from a mixture of CH_2Cl_2 and MeOH, 5.66 g of ketone was obtained, m.p.: 178–180° (lit.: 179–180°[16]); IR (CCl_4) cm^{-1}: 1635 (νC–C), 1680 (νC–O conjugate), 1735 (νAcetate); NMR: 0.74 (3H, s, CH_3-18), 1.24 (3H, s, CH_3-19), 2.07 (3H, s, CH_3 of $CH_3CO_2^-$) 4.70 (1H, m, H-3α), 5.7 (1H, s, H-6 olefinic).

3β - Acetoxy(5α)androstane,7 - one. 3β - Acetoxy,androst - 5 - ene,7 - one (3 g) was hydrogenated in 100 ml cyclohexane over 0.8 g 5% Pd–C.[17]

The mixture was filtered, washed with EtOH, and crystallised from aqueous MeOH yielding 2.4 g (yield: 80%), m.p.: 133–135° (lit.: 130–132°[16]); IR (CCl_4) cm^{-1}: 1710 (νC–O), 1740 (νAcetate); NMR: 0.7 (CH_3-18), 1.1 (CH_3-19), 2.02 (CH_3 Acetate), 4.7 (H-3).

Tosylhydrazone **5**. 3β-Acetoxy(5α)androstane 7-one, (2.8 g) 1.66 g of *p*-toluensulfonylhydrazine, 100 ml EtOH and 2 ml conc H_2SO_4 were refluxed for 50 min. The soln was concentrated to 30 ml and the ppt collected by filtration and washed with ice cold EtOH, 850 mg of tosylhydrazone **6** were obtained (yield: 52%), m.p.: 219–220° (lit.: 226–229°[18]); IR (KBr) cm^{-1}: 3500 (νN–H), 1640 (νC–N), 1330, 1160 (SO_2), NMR (DMSO): 0.62 (3H, s, CH_3-18), 0.88 (3H, s, CH_3-19), 3.35 (1H, m, H-3α) 2.35 (3H, s, CH_3-φ).

(5α)*Androst-6-ene,3β-ol* **4**. To a soln of **5** (315 mg; 0.69 mmole) in 17 ml dry THF, cooled to 0°, was added a soln of 4 ml of MeLi (2N in ether). The mixture was stirred magnetically under N_2 for 48 hr, then cooled, diluted with ice cold water, acidified and extracted several times with ether. The ether phase was washed with 10% $NaHCO_3$ aq and with water and dried over Na_2SO_4. The product was purified on a silica gel column; 100 mg of **4** were obtained (yield: 30%), m.p.: 160–163° (recrystallised from MeOH). The product was identical with **4** (from reductions by LAH).

4β - d,Androst - 6 - ene,3β - ol **4a** *and 4β - d,3β - acetoxy,androst - 5 - ene* **3c**. The reduction of **2** (1 g) by 1 g LAD in THF under 6 hr refluxing and subsequent hydrolysis with water produces the following compounds: (a) 100 mg of **4a** (13%), m.p.: 162–163°; I.R. (CCl_4) cm^{-1}: 2140 (νC–D); NMR: as **4** except for 3.7 (1H, quintuplet, H-3α); Mass spectrum: M: 275 *m/e*: 260, 257, 242, 163, 149, 135, 80. (b) 700 mg of 4β-d,androst-5-ene,3-ol (87%) identified as its acetate **3c**, m.p.: 97–99°.

5α - d,Androst - 6 - ene,3β - ol **4b** *and 7ξ - d,3β - acetoxy,androst - 5 - ene* **3d**. The reduction of **2** (1 g) by 1 g LAH in THF, refluxing period: 6 hr and subsequent hydrolysis with heavy water, produced the following substances: (a) 120 mg of **4b** (15%), m.p.: 162–163°; IR (CCl_4) cm^{-1}: 2140 (νC–D); NMR: identical with **4**, except at 5.55 ppm, the peaks of AB system are thin and clearly split (2 Hz); Mass spectrum: M: 275 *m/e*: 260, 257, 242, 162, 149, 135, 81. (b) 750 mg of 7ξd,androst-5-ene,3β-ol identified as its acetate **3d** m.p.: 97–99°.

(5α)*Androst-6-ene,3-one* **6**. A soln containing **4** (150 mg) and 3 g Ag_2CO_3 on celite in 45 ml of benzene was refluxed. The Ag_2CO_3 blackened after 15 min. The reaction, followed by TLC, was stopped after 2 hr of heating. The mixture was cooled, filtered through purified celite, which then is ringed with CH_2Cl_2. After evaporation of the solvent 150 mg of pure **6** were obtained, m.p.: 104–106° (recrystallized from purified acetone) (lit.: 100–103°); IR (CCl_4) cm^{-1}: 1715 (νC=O), 1643 (νC=C); NMR: 0.70 (3H, s, CH_3-18), 0.90 (3H, s, CH_3-19); Mass spectrum: M: 272 *m/e*: 257, 135, Analysis: $C_{19}H_{28}O$.

4β-d,(5α)Androst-6-ene,3-one **6a**. Compound **4a** (40 mg) in 15 ml benzene was oxidized by 1 g of Ag_2CO_3 on celite as described above. 30 mg of 4β-d(5α)androst-6-ene,3-one were isolated; IR (CCl_4) cm^{-1}: 2140 (νC–D), 1715 (νC=O), 1615 (νC=C); Mass spectrum: M: 273 (base peak) *m/e*: 258, 135.

5α-d,Androst-6-ene,3-one **6b**. The oxidation of 5α - d,androst - 6 - ene.3β - ol (40 mg) by Ag_2CO_3 (1 g) on celite in 15 ml benzene produced 30 mg of **6b**; Mass spectrum: M: 273 (base peak) *m/e*: 258, 135.

(5α)*Androst-6-ene,3-one* **6** *from* **6a**. A soln containing **6a** (30 mg) in 1 ml MeOH and 0.2 ml 2.5 N NaOH was refluxed for 1 hr. The cooled soln was taken up with ether, thoroughly washed with water, dried over Na_2SO_4 and then evaporated under reduced pressure, yielding 30 mg of **6**; Mass spectrum: M: 272 *m/e*: 257, 135.

5α-d,Androst-6-ene,3-one **6b**. When **6b** (30 mg) were treated as above, the starting product (**6b**) was recovered quantitatively, mass spectrum: M: 273 *m/e*: 258, 135.

3β - Acetoxy,5,6 - epoxy,androstane **7**. 3β - Acetoxy,androst - 5 - ene (160 mg) were dissolved in 1.2 ml distilled CH_2Cl_2 and treated overnight at 0° with 140 mg (1.4 equivs) *m*-chloroperbenzoic acid, 10 ml distilled $CHCl_3$ was added to dissolve the ppt. Then 25 ml ether was added, the mixture washed with water, with $NaHSO_3$ aq, Na_2CO_3 aq and finally with water and then dried over Na_2SO_4. Evaporation of the solvent produced 180 mg of a crystalline epoxide mixture (yield: 90%); NMR: 0.60 (3H, s, CH_3-18), 0.90 (CH_3-18,β-epoxide), 1.00 (CH_3-19,α-epoxide), 1.92 (3H, S, CH_3 acetate), 2.08 and 2.3 (H-4); 2.82 (d, H-6β), 3 (d, H-6α), 4.8 (1H, m, H-3α); Mass spectrum: M: 232 *m/e*: 272, 135.

4β - d,3β - Acetoxy,5,6 - epoxy,androstane **7a**. Compound **3c** (160 mg) was converted into 180 mg of 4β - d,3β - acetoxy,5,6 - epoxy,androstane by the above procedure; IR (CCl_4) cm^{-1}: 2140 (νC–D), 1250 (epoxide); NMR: 0.60 (3H, s, CH_3-18), 0.94 (CH_3-19, β-epoxide), 1.02 (CH_3-19, α-epoxide), 1.95 (3H, s, CH_3 acetate), 2.82 (d, H-6β), 3 (d, H-6α), 4.8 (1*H*, *m*, *H*-3α); Mass spectrum: M: 333 *m/e*: 272 (M-61), 254, 135.

7ξ - d,3β - Acetoxy,5,6 - epoxy,androstane **7b**. This product was prepared from **3d** as described above; IR (CCl_4) cm^{-1}: 2140 (νC–D), 1250 (νepoxide); NMR: 0.6 (3H, s, CH_3-18), 0.95 (CH_3-19, β-epoxide), 1.03 (CH_3-19, α-epoxide), 1.95 (3H, s, CH_3 acetate), 2.82 (t, H-6β), 4.8 (1H, m, H-3α), Mass spectrum: M: 333 *m/e*; 273 (M-60), 255, 135.

Androstane-3,5-diene **8** *and pyrolysis of 3β-acetoxy,androst-5-ene* **3b**. A soln containing 3β-acetoxy,androst-5-ene (200 mg) in 4 ml quinoline was refluxed under a N_2 for 24 hr (b.p.: 240°). The mixture was cooled diluted with ether, washed with water, 5% HCl, and water, dried over $NaSO_4$ and evaporation under vacuum. 160 mg of crude product (yield: 76%) was obtained, which was chromatographed on two silica gel plates impregnated with *ca.* 7% of $AgNO_3$ (eluant: pentane–ether: 8/1). The following substances were obtained: $R_F = 0.95$: 30 mg of androstane-3,5-diene (oil); Mass spectrum: M: 256; NMR: 0.74 (CH_3-18), 0.95 (CH_3-19), 5.6 (m, wide, 3 olefinic protons) $R_f = 0.55$: 120 mg of starting acetate identified by comparison with an authentic sample.

Androstane - 3,5 - diene **8** *and pyrolysis of 4β - d,3β - acetoxy,androst - 5 - ene* **3c**. The pyrolysis of **5c** (100 mg) in 2 ml quinoline gave 88 mg of crude product, from which the following compounds were isolated: (a) 21 mg of **8**, identical with the product obtained from pyrolysis of **3b** (IR, Mass spectrum) and (b) 65 mg of starting deuteriated acetate (m.p., spectral characteristics).

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