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A NOVEL PROCEDURE FOR THE AROMATIZATION OF RING A IN 19-NORTESTOSTERONE[1]

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Abstract—A convenient, 40% overall yield synthesis of 2,3,17β-triacetoxy-1,3,5(10)-estratriene is described, which involves epoxidation of 19-nortestosterone and subsequent acetylation, lead tetra-acetate acetoxylation of the so-formed 17β-acetoxy-4β,5-epoxy-5β-estran-3-one, and aromatization of ring A, by means of acidic alumina, of the resulting 2α and 2β epimers of 2,17β-diacetoxy-4β,5-epoxy-5β-estran-3-one.

In a previous communication[2] we reported that 3 - oxo - 4,5 - epoxy - steroids (**1**, Scheme 1) could be converted in good yield (of about 50%) to the corresponding 1,4 - dien - 2 - ol - 3 - ones **3b**, by acetoxylation with lead tetra-acetate followed by chromatography of the resulting 2α-acetoxy derivatives **2** on neutral alumina or silica gel (or treatment with base), when the latter products undergo O-acetyl and epoxide oxygen elimination.

The simplicity and efficiency of this procedure, which in normal steroids can lead only to the formation of the tautomeric system **3**, prompted us to investigate the possibility of applying the same transformation to 3 - oxo - 4,5 - epoxy - 19 - norsteroids, since in that case acetoxylation followed by eliminative rearrangement should result in the aromatization of ring A. The results obtained are described in the present paper.

When 17β - acetoxy - 4β,5 - epoxy - 5β - estran - 3 - one (**5**, Scheme 2), prepared in 66% yield by epoxidation of 19-nortestosterone **4** and subsequent acetylation of the 17β-hydroxyl group,[3,4] was treated with a 1.35 molar equivalent of lead tetra-acetate in glacial acetic acid at 80° for 5 h,[2] it underwent quantitative acetoxylation to give a mixture of the diastereomeric 2α- and 2β-acetoxy derivatives **6**. When a benzene solution of this epimeric mixture was introduced into an acidic alumina column and allowed to stand for 3 h, the desired transformation took place and, after chromatography, the catechol-type aromatic product **7** was obtained, which was (without further purification) directly acetylated to give 2,3,17β - triacetoxy - 1,3,5(10) - estratriene **8** in 60% yield with respect to **5**, and about 40% with respect to **4**.

7 (17β-OAc) was previously obtained in a lower overall yield (13%) by lead tetra-acetate acetoxylation of 19-nortestosterone acetate, selective hydrolysis of the newly formed 2α-acetate group and bismuth trioxide oxidation of the resulting 2α-ol.[5]

By repeated crystallization of the crude mixture of the 2α- and 2β-acetoxy compounds **6** (described above) from methanol, it was possible to separate and isolate (in 51% yield) that epimer **6a** in which the NMR signals for H-C(2) and H-C(4) appear at higher field, i.e. at δ 5.00 ppm (quartet, $J_{1e,2} = 7$ Hz, $J_{1a,2} = 12$ Hz) and δ 3.08 ppm (singlet), respectively. The other epimer **6b**, which was not separated and was analyzed only in admixture with **6a**, had NMR signals at δ 5.58 ppm (triplet, $J_{1e,2} = J_{1a,2} = 7$ Hz) for H-C(2) and at δ 3.26 ppm (singlet) for H-C(4). Although the position and coupling constants appear to indicate that hydrogen at C(2) is axial in epimer **6a** and equatorial in **6b**, because of the conformational flexibility of the C(1)-C(2)-C(3) chain in ring A,‡ it is not possible, from these NMR data, to assign with certainty the configuration at C(2) to the diastereomeric acetates **6a** and **6b**.§

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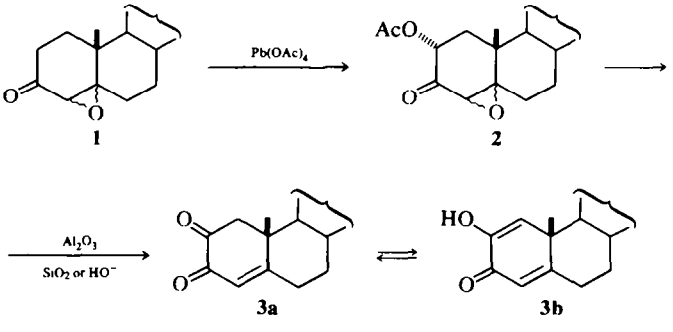
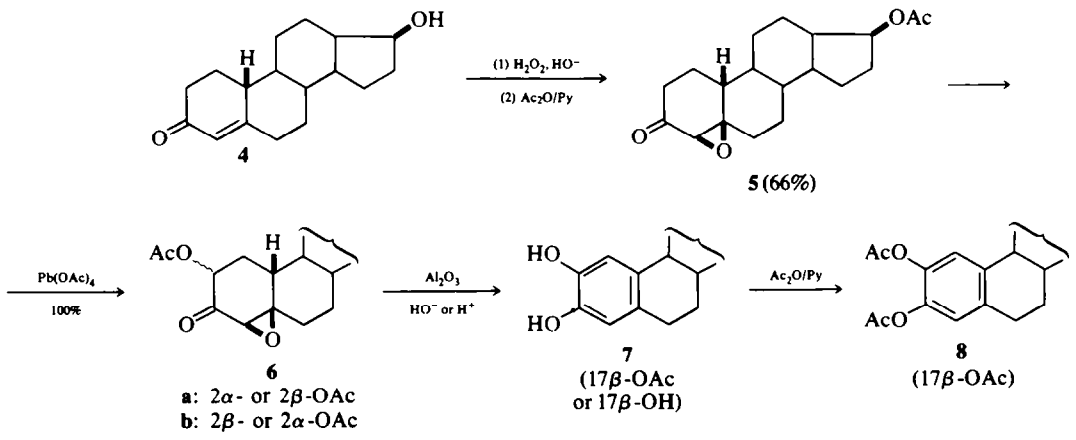
‡Similarly as in 4-unsaturated 3-oxo-steroids.[2]

§If the rather large upfield shift of the axial hydrogen at C(2) in **6a** is due to shielding by the β-epoxide oxygen[6] (and not only to the fact that this hydrogen is axial), then epimer **6a** should have the 2-acetoxy group in the α-orientation.



1 **2** **3a** **3b**

Scheme 1.



Scheme 2.

As can be seen from Table 1, various reagents can effect aromatization of ring A in **6a**, the most efficient being acidic and neutral alumina. Potassium bicarbonate and silica gel were ineffective, although in the normal steroid series silica gel did produce the transformation **2→3** (Scheme 1).[2]

EXPERIMENTAL†

M.ps are uncorrected. Optical rotation was measured in $CHCl_3$ soln. NMR spectra were measured at 100 MHz with a Varian HA-100-D spectrometer in $CDCl_3$ soln, using TMS as internal standard; chemical shifts are reported in δ values; abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were determined on a Perkin–Elmer instrument, Model 337. UV absorption spectra were recorded in 95% EtOH with a Perkin–Elmer 137 UV spectrophotometer. The separation of products was monitored by TLC on silica gel G (Stahl) with benzene–EtOAc (9:1, 7:3 or 1:1), detection being effected with 50% H_2SO_4. Light petroleum refers to the fraction boiling at 40–60°.

Preparation of 17β - *acetoxy* - 4β,5 - *epoxy* - 5β - *estran* - 3 - *one* **5**. A soln of **4** (1.0 g) in MeOH (100 ml) was cooled to 5°, treated with 5.5 ml 4M NaOH and 5.5 ml 3% H_2O_2, and allowed to stand at 5° for 6 h. The mixture was acidified with AcOH (about 1 ml), concentrated *in vacuo* to 20 ml, diluted with H_2O and extracted with EtOAc. The organic layer was washed with $NaHCO_3$ aq, H_2O, dried over Na_2SO_4 and evaporated *in vacuo* to dryness to give 1.05 g of an oily residue (probably a mixture of 4α,5α- and 4β,5β - epoxyestran - 17β - ol - 3 - ones) which was acetylated with Ac_2O-pyridine at 20° for 24 h. After working up as usual, the product (1.2 g) was recrystallized from MeOH to give 800 mg (66%) of **5**, m.p. 108° (lit. 112°,[3] 104°[4]); $[\alpha]_D^{20} = +97° \pm 3°$ ($c = 2.0$)(lit. +102°,[3] +48°[4]); IR (KBr): ν_{max} 1738, 1710, 1240 cm^{-1}; NMR: δ 0.82 (Me-18, s), 2.01 (AcO, s), 3.02 (H-4, s), 4.62 (H-17, m) (Found: C, 72.15; H, 8.43. Calc. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.43%).

Lead tetra-acetate acetoxylation of **5** *and direct aromatization of the resulting mixture of the epimeric* 2α- *and* 2β-*acetates* **6**. A soln of **5** (4.32 g, 0.013 mol) and lead tetra-acetate (7.8 g, 0.0176 mol) in glacial AcOH (210 ml) and Ac_2O (2.1 ml) was stirred at 80° for 5 h. The mixture was poured into ice-cold H_2O and extracted with ether. The ether soln was washed with H_2O,

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Table 1. Aromatization of 2ξ,17β-diacetoxy-4β,5-epoxy-5β-estran-3-one (**6a**) under different reaction conditions

Run	Reagent, solvent temp., reaction time[a]	Yield (in %) of 2,3,17β-triacetoxy-1,3,5(10)-estratriene (8) Crude	Pure
1	Acidic Al_2O_3 (II) column, benzene, 20°, 3 hr	76	57
2	Neutral Al_2O_3 (II) column, benzene, 20°, 3 hr	70	47
3	5% Methanolic KOH, MeOH, N_2, 20°, 15 min	41	30
4	5% Methanolic KOH, MeOH, 20°, 15 min	31	22
5	1% Methanolic HCl, reflux, 4 h	16.5	-
6	6% Aqueous $KHCO_3$, benzene–methanol, 20°, 24 hr	0	-
7	SiO_2 column, benzene, 20°, 3 h	0	-

[a]100 mg of 6a, 5 ml of solvent and 5 ml or 5 g of reagent were used in runs 1–4 and 7. Run 5 was performed with 40 mg of 6a and 10 ml of reagent; run 6 with 30 ml of 6a dissolved in 5 ml of benzene–methanol (1:4 v/v) and 1 ml of reagent (for details see Experimental).

$NaHCO_3$ aq and H_2O, dried over Na_2SO_4 and evaporated *in vacuo* to dryness. Although appearing as a single spot on TLC, the residue (5 g, 100%) consisted of a mixture of 2α- and 2β-acetoxy products **6** (IR: ν_{max} 1725–1750, 1235–1245 cm^{-1}), as evident from the double signals in its NMR spectrum: δ 0.82 and 0.84 (Me-18, two s), 2.02 (AcO-17, one s), 2.08 and 2.11 (AcO-2, two s), 3.08 and 3.26 (H-4, two s), 4.62 (H-17, one t), 5.00 and 5.58 (H-2, q and t, respectively).

Part of this crude mixture **6** (500 mg), dissolved in benzene (5 ml), was introduced into a chromatography column of acidic Al_2O_3 II (15 g), allowed to stand for 3 h, and then chromatographed. Benzene eluted unchanged **6** (50 mg, 10%), and methanol gave a complex mixture (35 mg, 7%). The fractions eluted with 1% methanolic HCl were neutralized with solid $NaHCO_3$, the inorganic salt separated by filtration on a Celite mat and the filtrate evaporated *in vacuo* to dryness. The residue, i.e. the aromatic 2,3-dihydroxy product **7** (305 mg, 72%), was acetylated with Ac_2O-pyridine at 20° for 12 h to give, after the usual work-up, 371 mg (70%) of 2,3,17β - triacetoxy - 1,3,5(10) - estratriene **8**, which was recrystallized from MeOH (318 mg, 60%), m.p. 168° (lit.[5] 168–169°); $[\alpha]_D^{20} = +40° \pm 2°$ ($c = 0.53$) (lit.[5] +52.3°); IR (KBr): ν_{max} 1774, 1724, 1500, 1245, 1205 cm^{-1}; UV: λ_{max} 270 ($\epsilon = 1700$), 278 nm ($\epsilon = 1550$); NMR: δ 0.83 (Me-18, s), 2.05 (AcO-17, s), 2.28 (AcO-2 and AcO-3, one s), about 2.85 (two H adjacent to the aromatic ring A, m), 4.71 (H-17, m), 6.88 and 7.07 (H-1 and H-4, two s). (Found: C, 69.62; H, 7.15. Calc. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30%).

2ξ,17β - *Diacetoxy* - 4β,5 - *epoxy* - 5β - *estran* - 3 - *one* **6a**. Part of the crude mixture **6** (2.0 g), obtained as described above, was twice recrystallized from MeOH to give the pure epimer **6a** (1.02 g, 51%), m.p. 204–206°; $[\alpha]_D^{20} = +53° \pm 3°$ ($c = 2$); IR (KBr): ν_{max} 1752, 1740, 1726, 1243, 1232 cm^{-1}; NMR: δ 0.84 (Me-18, s), 2.03 (AcO-17, s), 2.11 (AcO-2, s), 3.08 (H-4, s), 4.62 (H-17, t), 5.00 (H-2, q). (Found: C, 67.54; H, 7.53. $C_{22}H_{30}O_6$ requires: C, 67.67; H, 7.74%).

Aromatization experiments with **6a** (see Table 1 for reaction conditions and results). Runs 1 (acidic Al_2O_3 II), 2 (neutral Al_2O_3 II) and 7 (SiO_2) were performed as indicated in Table 1, the working up of the reaction mixtures being effected as described above (for aromatization of **6**). Runs 3 (5% methanolic KOH, N_2), 4 (5% methanolic KOH) and 6 (6% aqueous $KHCO_3$) were carried out according to Table 1. The resulting soln was neutralized with AcOH, diluted with H_2O and extracted with ether. The ether extracts were dried (Na_2SO_4) and evaporated *in vacuo* to dryness, and the oily residue was acetylated with Ac_2O-pyridine at 20° for 12 h. After the usual work-up, the products were chromatographed on 3–5 g silica gel (0.20–0.05). Benzene–EtOAc (95:5) eluted **8** (in runs 3 and 4), which was recrystallized from MeOH, m.p. 168°. In run 5 (1% methanolic HCl), performed as indicated in Table 1, the resulting soln was diluted with H_2O and extracted with ether. The ether layer was washed with $NaHCO_3$ aq and H_2O, dried (Na_2SO_4) and evaporated *in vacuo* to dryness. Acetylation and chromatography (on SiO_2) were carried out as described above (for runs 3, 4 and 6).

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