Tetrahedron Vol. 25, pp 4257 to 4264. Pergamon Press 1969. Printed in Great Britain

STEROIDS—XI*

ACTION OF HYDROGEN PEROXIDE ON 3-KETO-1,4,6-TRIENE STEROIDS

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(*Received in the UK* 24 *April* 1969; *Accepted for publication* 7 *May* 1969)

Abstract—Hydrogen peroxide oxidation of 17α-methyl-1,4,6-androstatrien-17β-ol-3-one yielded a mixture of two products, the major component of which was a lactonic acid (**3a**) with the same number of C atoms as the starting material, and the neutral minor component (**4a**) was a A-nor-steroid. Both products exist in the 2-oxasteroid form; their structures were elucidated by spectral methods and chemical degradation to the same 1,3-seco-2-nor-compound (**11a**). The H_2O_2-degradation, a combination of Bayer–Villiger reaction with epoxidation, is a simple method of synthesis of 2-oxasteroids.

OXIDATION of α,β-unsaturated steroidal ketones with hydrogen peroxide[1] yields either α-epoxy-ketones, or in the presence of a suitable catalyst, unsaturated lactones (the Bayer–Villiger reaction), which can undergo further degradation.[2]

In the present paper the results of the oxidation of 17α-methyl-1,4,6-androstatrien-17β-ol-3-one (**1**), with hydrogen peroxide under drastic conditions (room temperature, excess of the oxidant and alkali) are reported. In the course of the reaction the known[3] epoxide **2** was initially formed, and was further oxidized to the acid **3a** and the neutral product **4a**.

The reaction was carried out using 4·5 molar excess of hydrogen peroxide and 10 moles sodium hydroxide per mole of the ketone. During the first 4 hr there was clear TLC evidence of the formation of 1,2α-epoxy-3-keto-4,6-diene (**2**), and during further oxidation other polar products were formed. In a control experiment the epoxy-compound **2**[3] gave identical polar products when exposed to oxidation under similar conditions.

After 70 hr the mixture was concentrated and on acidification yielded an abundant precipitate, which partly dissolved in aqueous sodium hydrogen carbonate. Recrystallization of the insoluble matter gave a neutral product (**4a**), whereas the acidic product (**3a**) was obtained upon acidification of the aqueous solution and subsequent recrystallization. The latter product was a monocarboxylic acid with the titrimetric equivalent corresponding to the formula $C_{20}H_{26}O_4$. It can readily be esterified to the methyl ester (**3b**) which, in turn, can be acetylated to the monoacetate (**3c**).

The NMR spectrum of **3a** exhibits in the low-field region two one-proton singlets at τ 5·38 and τ 4·33 and a diprotonic singlet at τ 3·77. The latter two signals can readily be ascribed to the vinylic proton H-4 (τ 4·33) and the two protons H-6 and H-7 (τ 3·77), since they appear at very similar values 4·45 and 3·88 in the 3-keto-4,6-diene.[4] The reason the 3·77 signal is unsplit may be a fortuitous coincidence of the H-6 and H-7 resonances and the "virtual coupling" involving interaction with the H-8.

* Part X—see Ref. 5.

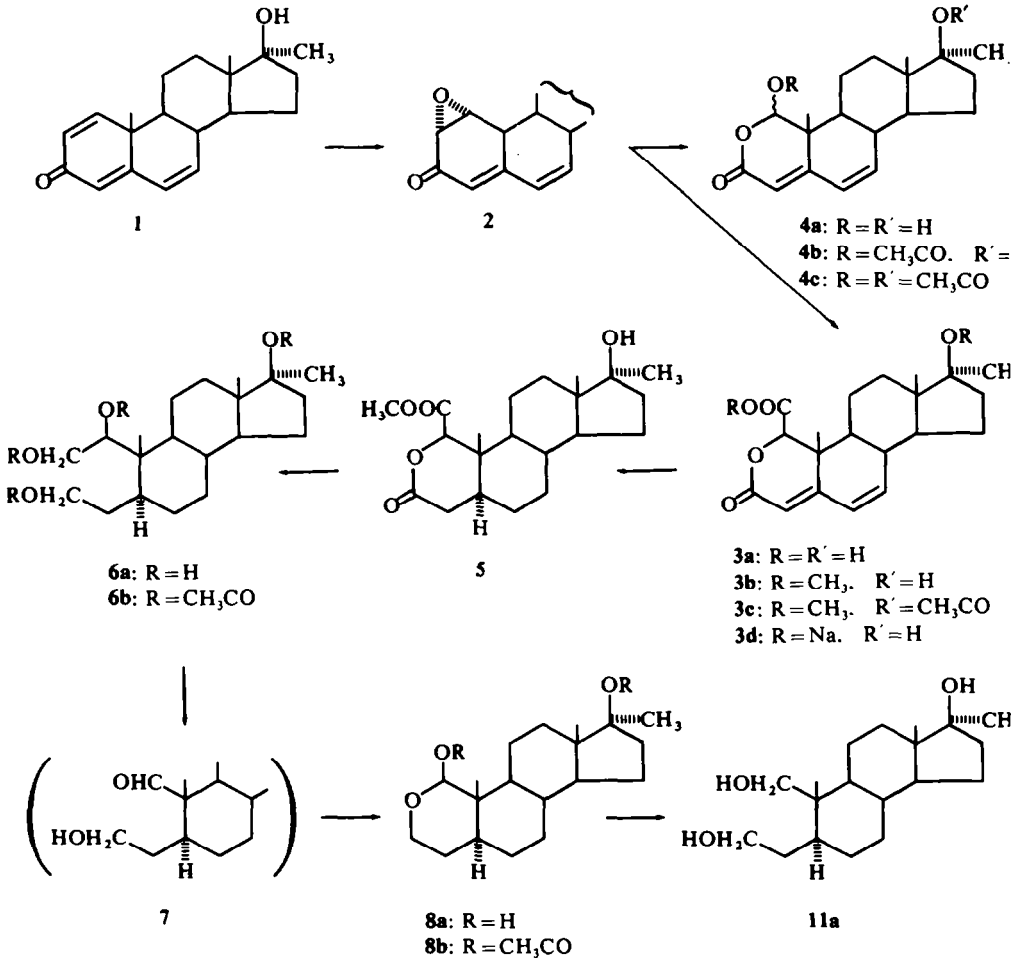
H-9 and H-14 protons. This situation is repeated in a series of derivatives and analogues[5] of **3a** and **4a**.

The assignment of the τ 3·77 signal is supported by the observation that when the overlapping of the H-6 and H-7 resonances is less close, as for instance in the spectrum of **3b** in $CDCl_3 + CF_3COOD$, a clear, though somewhat distorted AB-pattern occurs.

The singlet at τ 5·38 can be assigned to the H-1 proton in good agreement with the value expected for such an environment. The signal of the OH groups with a max at about τ 5 is very broad due to relatively slow exchange of the carboxyl, hydroxyl and water protons. On the other hand integration shows clearly that only one OH group is present in **3b**. Its signal at τ 7·97 moves downfield upon treating with trifluoroacetic acid and disappears in **3c**; hence, it can be ascribed to the C-17 OH.

IR spectra of **3a** and its derivatives confirm the proposed structure. The spectrum of **3a** exhibits a broad OH-band at 3300 cm^{-1} and a very broad structured band of the

SCHEME I



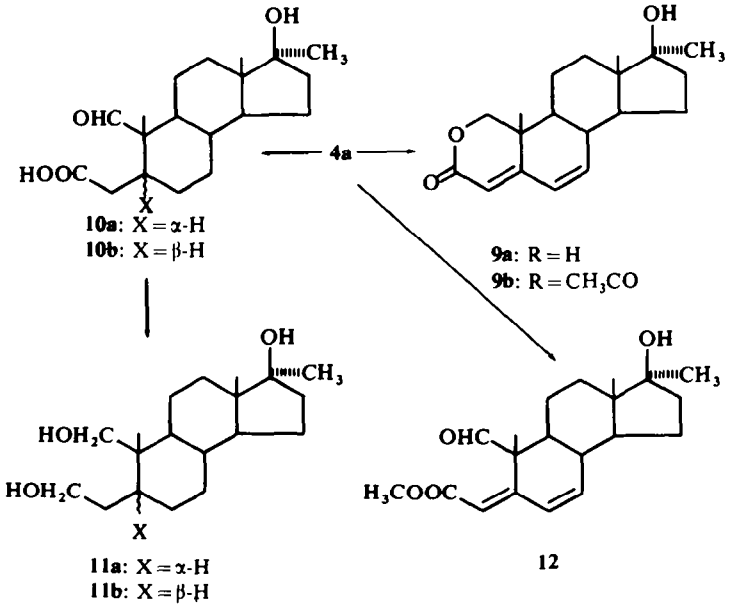
carboxyl group in the 3000–2400 cm^{-1} region. The latter band is absent in the spectra of **3b**, and **3c** and in the spectrum of sodium salt **3d**; in the spectrum of **3c** the former band is also lacking. The conjugated double bonds of **3a–3d** absorb at about 1620 and 1590 cm^{-1} (in the spectrum of **3d**—sodium salt of **3a**—the bands partly overlap with the $COO^{\ominus}$ absorption at 1610 cm^{-1}). The band at 1743 cm^{-1}, which is absent from the spectrum of **3d**, is also assigned to the carboxyl group; its high frequency may be explained by the presence of the electronegative O—C grouping in the α-position. The lactone carbonyl was identified by the very intense band at 1684 cm^{-1}, broadened on the low-frequency side because of H-bonding. Since there is no H-bonding with the carboxylic OH in **3b**, this band is shifted to higher wave numbers (1708 cm^{-1}). In UV spectrum of **3a–c** an absorption characteristic of diene lactones was observed (λ_{max} 273–274 nm, ε 19,000–21,000).

The proposed structures are confirmed by further reactions of **3b**. Its catalytic hydrogenation (H_2/Pt) yields the tetrahydroester **5**. Reduction of the tetrahydro ester **5** with LAH_4 gives the tetrol **6a** characterized as such and as the tetracetate (**6b**).

The stereochemistry of **6a** is believed to be identical with that of the product obtained in an analogous sequence of reactions[5] from 1,4,6-andro-statrien-17β-ol-3-one and unequivocally identified by mixture m.p. and TLC with the sample synthetized by Jeger *et al.*[6]

Oxidation of the α-glycol part of **6a** with KIO_4 yields the aldehyde **7**, which cyclized immediately to give the hemiacetal **8a**. The reaction of the latter with sodium borohydride affords a triol (**11a**), identical (by mixture m.p. and TLC) with that obtained from **4a**.

SCHEME II



Analytical data indicate that **4a** contains one C atom less than the starting compound **1**. However, **4a** is not a product of further degradation of **3a**, as it could not be obtained by oxidation of the latter.

The UV spectrum suggests a diene carboxyl derivative (λ_{max} 274 nm ε 22,100). In the IR spectrum the bands of the conjugated double bonds appear at 1616 and 1583 cm^{-1}, while the very strong band at 1680 cm^{-1} can be assigned to the lactol carbonyl. The NMR spectrum of **4a** resembles that of **3a** (singlets at τ 3·80—H-6, H-7; τ 4·40—H-4 and τ 4·65—H-1) except for the carboxyl proton resonance.

Acetylation in the cold yields a monoacetate **4b**, its H-1 resonance being shifted downfield by 1·02 ppm which is characteristic of a secondary alcohol. At an elevated temperature the tertiary OH group at the C-17 was also acetylated (**4c**). The lactol structure of **4a** was confirmed by its reduction with $NaBH_4$ to lactone **9a** (AB-quartet of the two C_1 protons at τ 5·82 and 6·03; $J=11$ c/s), which was acetylated to monoacetate **9b**. On the other hand, the lactol ring was opened using Ag_2O, and the silver salt was methylated to the aldehyde-ester **12**.

Catalytic hydrogenation of **4a** yields a mixture of 5α and 5β isomers (**10a*** or **10b** resp) from which only the 5β-isomer could be isolated by tedious column chromatography. Therefore, the total hydrogenation product without separation was reduced with LAH_4 to a mixture of 5α and 5β triols (**11a** and **11b** resp). A very thorough chromatography of this product gave the 5β-triol **11b** (ca. 80% yield) and a small amount (5%) of the 5α-isomeric triol **11a** identical with the compound obtained from the lactone acid **3a**.

The CD curves of **3a**, **5** and **9a** yielded further proof of the structure of these compounds. The lactone acid **3a** shows three extrema: at λ 288·5 nm ($\Delta\varepsilon$ +10·30), λ 257 nm ($\Delta\varepsilon$ −6·94) and λ 208·5 nm ($\Delta\varepsilon$ +3·08). The lactone **9a** shows a positive effect at λ 286·5 nm ($\Delta\varepsilon$ +7·16) and a negative one at λ 254·5 nm ($\Delta\varepsilon$ −4·32).

The saturated lactone ester **5** exhibits a weak negative effect at λ 215 nm ($\Delta\varepsilon$ −1·19 dioxan) or λ 212·5 nm ($\Delta\varepsilon$ −1·05 ethanol) in good agreement with the observations of Klyne *et al.*[7] concerning 2-oxa-3-oxosteroids with 5 αH-configuration.

There are several possible mechanisms for the formation of the acid **3a**, the most probable being the following: the first oxidation step is the formation of the ketoepoxide **2**, which undergoes further oxidation similar to the Bayer–Villiger reaction to the lactone-epoxide **2A**. In the alkaline medium the latter rearranges through the ionic form **2B** to the α-hydroxyaldehyde **2C**. The addition of peroxide ion to the aldehydic carbonyl leads to the intermediate **2D**, from which a proton and a hydroxyl ion are eliminated yielding the dicarboxylate ion **2E**. Acidification leads to the δ-hydroxy acid, which cyclizes to the δ-lactonic acid **3a**.†

Similarly the formation of the neutral product **4a** can be explained by the same mechanism leading to **2D**. The latter intermediate loses formate ion thus producing the aldehydecarboxylate **2F**, which on acidification gives the lactol **4A**.

Alternatively the formation of the latter could also be explained by a different mechanism starting with the intermediate **2C** which in a strongly alkaline medium may undergo fragmentation to formaldehyde and the same aldehyde-carboxylate **2F**.

* The same compound was obtained in a different way by R. Pappo and C. J. Jung, *Tetrahedron Letters* 365 (1962).

† An alternative mechanism of the H_2O_2-oxidation of steroidal 3-keto-4,5-epoxides leading to saturated δ-lactonic acids has been given.[8]

SCHEME III

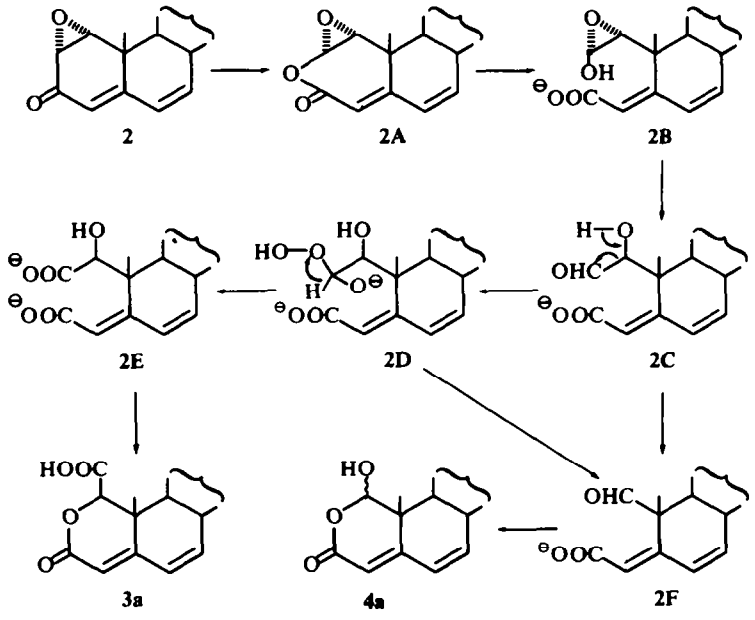


TABLE 1. IR ABSORPTION (cm^{-1}) AND NMR SIGNALS (τ-VALUES)

Functional groups (IR)	4a	4b	4c	9a	9b
O—H	3250 3500	3550	—	3500	—
C=O lactol	1679	1720	1711	1690	1700–1720
C=O acetate	—	1740	1741	—	1700–1720
C=C	1583 1613	1595 1623	1591 1615	1590 1620	1595 1622
Position of protons (NMR)					
C_1—H	4·65	3·63	3·60	5·82 6·03 $J=11$ c/s	5·86 6·12 $J=9·7$ c/s
C_4—H	4·40	4·35	4·31	4·43	4·44
C_6, C_7—2H	3·80	3·81	3·80	3·88	3·88
C_1—$OCOCH_3$	—	7·91	7·90	—	—
C_{17}—$OCOCH_3$	—	—	8·02	—	8·04
18-CH_3	9·14	9·03	9·08	9·07	9·10
19-CH_3	8·91	8·76	8·74	8·82	8·86
20-CH_3	8·89	8·79	8·58	8·80	8·63

Our observation of the increase in yield of lactol **4a** with increasing pH of the reaction medium seems to support the latter hypothesis.

The results of the hydrogen peroxide oxidation of the propionate of 1,4,6-androstatriene-17β-ol-3-one were very similar to those described above. They are published in a Polish journal.[5]

TABLE 2. IR ABSORPTION (cm^{-1}) AND NMR SIGNALS (τ VALUES)

Functional groups (IR)	**3a**	**3b**	**3c**
O—H	3292	3550	—
C=O ester	1743	1755	1750
C=O acetate	—	—	1718
C=O lactol	1684	1708	1700
C=C	1618	1627	1618
Position of protons (NMR)			
C_1—H	5·48	5·40	5·40
C_4—H	4·40	4·42	4·38
C_6, C_7—2H	3·81	3·89	3·86
C_1—$COOCH_3$	—	6·24	6·28
C_{17}—$OCOCH_3$	—	—	8·04
18-CH_3	9·15	9·11	9·13
19-CH_3	8·91	8·80	8·70
20-CH_3	8·76	8·66	8·62

EXPERIMENTAL

All m.ps are uncorrected. All solvents used were analytical reagent grade and, if necessary, dried with Al_2O_3 before use. UV spectra were recorded in EtOH soln with an Unicam SP700 or SP500 and IR spectra with a Hilger 800 or Unicam SP200 spectrophotometer. NMR spectra were determined in $CDCl_3$ soln unless otherwise stated with a Varian V4391 60MC and with TMS as an internal standard. All chemical shifts are quoted in τ-values. The purity of all compounds described was monitored by m.ps and TLC. The specific rotations were measured with Perkin–Elmer 141 polarimeter at c ~ 1 in $CHCl_3$ unless indicated otherwise. Microanalyses were performed by our analytical laboratory (head: Mrs. Z. Celler, M.Sc.). The yields correspond to TLC-pure compounds. The spectroscopic data not presented in this part are given in the Tables.

Oxidation of 17α-*methyl*-1,4,6-*androstatriene*-17β-*ol*-3-*one* (**1**) *with hydrogen peroxide.* To 2·8 g **1** dissolved in 140 ml MeOH, 11 ml 4N NaOH and 11 ml 30% H_2O_2 were slowly added at 2–5°. The reaction mixture was left at this temp for 72 hr; 40 ml H_2O was then added and the soln concentrated *in vacuo* at room temp to 60 ml. The clear soln was acidified with 2N HCl (30 ml) and the abundant ppt filtered off, washed with cold water and partially dissolved in 15 ml sat NaHCO aq. The insoluble matter (440 mg) was washed neutral with water, dried in desiccator and recrystallized from $CHCl_3$–MeOH, yielding 17α-*methyl*-2-*oxa*-4,6-*androstadien*-1ξ,17β-*diol*-3-*one* (**4a**, 360 mg 12% yield, m.p. 265–270°). The analytical sample was obtained by further recrystallization, m.p. 268–272°, $[\alpha]_D^{20}$ +40·4 (DMSO). (Found: C, 71·50; H, 8·34. $C_{19}H_{26}O_4$ requires: C, 71·67; H, 8·23%). λ_{max} 274 nm (ε 22,100).

After separation of **4a** the combined alkaline filtrates were reacidified with 1N HCl, yielding 1·57 g **3a**. Recrystallization from $CHCl_3$–MeOH, repeated dissolving in $NaHCO_3$ and precipitation with HCl gave

1·360 g (42% yield) of pure 1-*carboxy*-2-*oxa*-17α-*methyl*-4,6-*androstadien*-17β-*ol*-3-*one*, **3a** m.p. 225–228°, $[\alpha]_D^{20}$ −0·2 (dioxan), λ_{max} 274 nm (ε 19,100). (Found: C, 69·04; H, 8·09. $C_{20}H_{26}O_5$ requires: C, 69·34; H, 7·57%).

Derivatives of **3a**. The methyl ester **3b** was obtained in 85% yield by treating **3a** with diazomethan or methanolic HCl. Recrystallization from aceton–hexane gave the pure **3b**, m.p. 198–200°, $[\alpha]_D^{20}$ −12·0, λ_{max} 274 nm (ε 21,200). (Found: C, 69·32; H, 8·19. $C_{21}H_{28}O_5$ requires: C, 69·97; H, 7·83%).

The acetate **3c** was produced by heating the ester **3b** with pyridine–Ac_2O on a water bath for 12 hr. The usual working up and chromatography on alumina yielded pure **3c** in 60% yield, m.p. 178–179°, $[\alpha]^2{}_D{}^0$ −4·0; λ_{max} 274 nm (ε 21,000). Oxidation of the epoxide **2** (1·4 g) under similar conditions yielded **3a** (680 mg, 43% yield) and **4a** (130 mg, 13% yield).

Catalytic reduction of **3b** *to* 1-*carbomethoxy*-2-*oxa*-17α-*methyl*-5α-*androstan*-17β-*ol*-3-*one* (**5**). Compound **3b** (328 mg) dissolved in 15 ml glacial AcOH were hydrogenated in the presence of Adams catalyst (44 mg). Filtration of the soln, evaporation of the solvent *in vacuo* and recrystallization from acetone–hexane gave 285 mg (87% yield) of crystalline **5**, m.p. 231–233°, $[\alpha]^{21}_D$ −22·0; no absorption in UV; IR: 1720 (lactone C=O), 1753 (ester C=O) and 3500 cm^{-1} (17—OH); NMR: 5·42 s (C_1—H), 6·22 s (ester CH_3), three singlets at 8·77, 8·88 and 9·13 (C_{18}-, C_{19}-, C_{20}-Me groups). (Found: C, 68·93; H, 9·22. $C_{21}H_{32}O_5$ requires: C, 69·20; H, 8·85%).

Reduction of lactone-ester **5** *to* 2,3-*secotetrol* **6a**. Compound **5** (194 mg) in 20 ml THF was slowly added to a suspension of LAH (130 mg) in 25 ml THF at room temp and the mixture refluxed for 4 hr. The standard working up gave **6** (123 mg, 67% yield), m.p. 246–247°, $[\alpha]_D^{20}$ −36·0 (dioxan); IR: broad max centred at 3350 cm^{-1}; NMR (DMSO): 6·1 s (C_{17}—OH), 5·6–6·0 m (C_1, C_2 and C_3—OH);* 6·2–6·9 diffuse m(—CH_2—OH and CH—OH); three singlets at 8·96, 9·20 and 9·30 (C_{18}-, C_{19}- and C_{20}-Me group protons). (Found: C, 70·03; H, 10·75. $C_{20}H_{36}O_4$ requires: C, 70·54; H, 10·66%).

The tetraacetate **6b** was obtained by refluxing **6a** with Ac_2O for 2 hr. The normal working up yielded **6b** in 70% yield, m.p. 123–124°$|\alpha|_D^{20}$ −29·0; IR: ν_{max} 1730–1740 cm^{-1} acetate (C=O); no OH absorption; NMR: 4·50 m (C_1—H); 5·80 m 4H (—CH_2OAc protons), 4CH_3-acetyl singlets at 7·92 (3H); 7·96 (6H); 8·03 (3H) and 3 skeletal Me singlets at 8·58, 9·16 and 9·20.

Oxidation of **6a** *with* KIO_4. To the soln of **6a** (100 mg) in 60 ml THF a soln of KIO_4 (100 ml) in 20 ml H_2O was added and the suspension stirred for 48 hr at room temp. The inorganic ppt was then filtered off, washed with MeOH, the combined filtrates concentrated *in vacuo* to ca. 30 ml and left in a refrigerator for 12 hr. The separated ppt was recrystallized from aqueous MeOH and yielded 71 mg of 2-*oxa*-17α-*methyl*-5α-*androstan*-1,ζ,17β-*diol*, (**8a**, 80%) m.p. 154–155°, $[\alpha]_D^{23}$ +2·5; IR: a broad max at 3400 cm^{-1} (OH); NMR: 5·20 s (C_1—H); 6·0–6·5 m (C_3-2H), 7·53 s (20H); three singlets at 8·83, 9·06 and 9·16 (skeleton Me groups); no aldehydic proton in offset region. (Found: C, 74·23; H, 10·59. $C_{19}H_{32}O_3$ requires: C, 73·98; H, 10·46%).

The diacetate **8b** was obtained in 80% yield by refluxing the above compound with Ac_2O for 2 hr, m.p. 148–155°, $[\alpha]_D^{23}$ +34·0; IR: 1720 cm^{-1} (broad signal of acetate–CO); no OH-absorption; NMR: 4·30 s (C_1—H), 6·30 m (C_3—2H), two 3H-singlets at 7·90 and 8·06 (acetate–CH_3); three 3H-singlets at 8·62, 9·0 and 9·20 (C_{18}-, C_{19}- and C_{20}-Me groups).

Reduction of the hemiacetal **8a** *to the triol* **11a**. The hemiacetal **8a** (45 mg) in 15 ml MeOH was treated with 40 mg KBH_4 at room temp, and the soln stirred for 12 hr. The solvent was partly removed *in vacuo* and the ppt recrystallized from ether–hexane, 34 mg (60% yield), m.p. 139–140°, $[\alpha]_D^{23}$ −42·0 (dioxan); IR: broad max at 3400 cm^{-1}; NMR (DMSO): 5·7–7·0 7H m (CH_2OH and 17-OH-protons) and three 3H-singlets at 8·95, 9·30 and 9·50. (Found: C, 73·20; H, 11·37. $C_{19}H_{34}O_3$ requires: C, 73·50; H, 11·04%).

Acetates of 2-*oxa*-17α-*methyl*-4,6-*androstadien*-1ζ,17β-*diol*-3-*one*. The 1-monoacetate **4b** was obtained in 85% yield by heating **4a** with Ac_2O–pyridine at room temp for 12 hr, m.p. 188–191° $[\alpha]_D^{20}$ +102·6°, λ_{max} 274 nm (ε 22,000). (Found: C, 69·43; H, 7·71. Calc. for $C_{21}H_{28}O_5$: C, 69·97; H, 7·83%). The diacetate **4c** was obtained (65% yield) from **4a** by refluxing with Ac_2O for 3 hr. Evaporation of the solvent *in vacuo* and recrystallization from acetone–hexane yielded pure **4a**, m.p. 203–205°, $[\alpha]_D^{23}$ +96·0; λ_{max} 274 nm (ε 21,500). (Found: C, 68·61; H, 7·56. Calc. for $C_{23}H_{30}O_6$: C, 68·63; H, 7·51%).

Catalytic reduction of **4a**. The lactol **4a** (267 mg in 50 ml MeOH) was hydrogenated in the presence of 75 mg Adams catalyst. After filtration through cellite and evaporation of the filtrate *in vacuo* the residue

* In all cases described in this paper the signals of the OH protons were identified by their downfield shift after acidifying the sample with CF_3COOH.

was crystallized from aqueous MeOH yielding 226 mg of a mixture of **10a** and **10b** m.p. 150–173°; IR: 1700–1740 (aldehyde and carboxyl C=O) and 3500 cm^{-1} (OH); NMR (DMSO): 1H 0·62 s (CHO) and three 3H-singlets at usual τ-values. (Found: C, 70·90; H, 9·43. Calc. for $C_{19}H_{30}O_4$: C, 70·77; H, 9·38%). A total of 73 mg of this hydrogenation product was chromatographed on silica gel. Initial elution with $CHCl_3$–AcOH (100:1) afforded 15 mg of **10a** (from aq. acetone) m.p. 155–165° (dec) $[\alpha]_D^{23}$ −21·2 (dioxan); IR: 1703 (aldehyde C=O), 1719 (carboxyl C=O), 2702 (aldehyde C—H stretching) and 3485 cm^{-1} (OH). (Found: C, 70·83; H, 9·57. Calc. for $C_{19}H_{30}O_4$: C, 70·77; H, 9·38%). Further elution with the same solvent yielded a mixture of both 5α- and 5β-isomers; the final eluates contained pure **10b**; 23 mg from aq. acetone, m.p. 180–190° (dec), $[\alpha]_D^{20}$ +21·0. (Found: C, 70·75; H, 9·07. $C_{19}H_{30}O_4$ requires: C, 70·77; H, 9·38%).

LAH_4 *reduction of* **10a, b***-mixture.* A THF soln of **10a, b** (113 mg in 20 m THF) was reduced with 600 mg LAH in 20 ml THF. After standard work up, the oily reaction product was crystallized from ether–acetone, yielding 66 mg of pure **11b**, m.p. 197–198°, $[\alpha]_D^{23}$ +8·0 (dioxan); IR: 3250 cm^{-1} (OH); NMR (DMSO): 5·5–6·0 m (3H-OH), 6·5–6·8 m (4H-CH_2OH) and 8·95, 9·10 and 9·30 (three 3H-singlets of C_{20}-, C_{19}- and C_{18}-methyls).

The remaining semi-solid product was chromatographed on silica gel. The initial elution with $CHCl_3$-AcOH (100:1) produced additional amounts of **11b** (14 mg, total yield of **11b** 80 mg 80%); the last fractions contained 6 mg of **11a**, m.p. 137·5–139°; $[\alpha]_D^{23}$ −42·0 (dioxan). Mixture m.p. and TLC showed this product to be identical with **11a**, obtained through degradation of the lactone-acid **3a**.

$NaBH_4$ *reduction of the lactol* **4a**. The lactol **4a** (115 mg) was dissolved in 40 ml MeOH, 40 ml water and 1 ml 0·5N NaOH, and subsequently 87 mg $NaBH_4$ in 2 ml water was added. The soln was left over night at room temp, the organic solvent removed *in vacuo*, and the residue recrystallized from acetone–hexane yielding 92 mg **9a** (85% yield), m.p. 218–222°; $[\alpha]_D^{20}$ + 15·6; λ_{max} 272 nm (ε 20,000). (Found: C, 75·40; H, 8·48. $C_{19}H_{26}O_3$ requires C, 75·46; H, 8·67%).

The acetate **9b** was produced in 60% yield by heating **9a** on a water bath with pyridine–Ac_2O for 2 days, m.p. 162–165°, $[\alpha]_D^{23}$ +36·0; λ_{max} 272 nm (ε 20,700). (Found: C, 73·12; H, 8·15. $C_{21}H_{28}O_4$ requires: C, 73·22; H, 8·19%).

Ring cleavage of the lactol **4a**. The lactol **4a** (194 mg), 30 ml MeI and 792 mg Ag_2O were refluxed for 1·5 hr. After cooling the inorganic matter was removed, washed with 50 ml CH_2Cl_2, the combined filtrates evaporated to dryness *in vacuo* and the residue recrystallized from aq acetone to give 86 mg (40%) of **12**, m.p. 132–134°; $[\alpha]_D^{20}$ −118·0; λ_{max} 273 nm (ε 20,100); IR: 1603 (C=C), 1615 (C=C), 1700–1720 (aldehyde C=O and ester C=O), 2700 (aldehyde C—H-stretching), 3500–3600 cm^{-1} (OH); NMR: 0·42 s (CHO), 3·90 s (2H, C_6—H and C_7—H), 4·32 s (C_4—H), 6·35 s (ester Me) and 8·56, 8·80 and 9·06 (three 3H singlets of C_{18}-, C_{19}- and C_{20}-Me groups). (Found: C, 72·61; H, 8·49. $C_{2(}H_{28}O_4$ requires: C, 72·26; H, 8·49%).

Acknowledgement—We are very much indebted to Dr. G. Snatzke (University of Bonn) for measuring the CD and for discussion of the curves.

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