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Steroid Series. XXIV.[1] Photolysis of 3α,5-Cyclo-6-oxo-17β-acetoxy-5α-androstan-19-oic Acid and 6-Oxo-17β-acetoxy-5α-androstan-19-oic Acid

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Irradiation of 3α, 5-cyclo-6-oxo-17β-acetoxy-5α-androstan-19-oic acid (**1**) in tertiary butyl alcohol yielded 4α-*tert*-butoxy-6,6-dihydroxy-17β-acetoxy-5α-androstan-19-oic acid 6,19-lactone (**2**) and 6-oxo-17β-acetoxyandrost-4-en-19-oic acid (**3**) in 50% and about 10% yields respectively. The former (**2**) was found to be formed by photochemical addition of tertiary butyl alcohol to the α, β-unsaturated ketone system in the latter (**3**). In connection with the mechanism of the above reaction, photolysis of 6-oxo-17β-acetoxy-5α-androstan-19-oic acid (**9**) in methanol and tertiary butyl alcohol is conducted to yield 5,6-secocarboxylic acid derivatives (**17**, **19**, **20**, **21**), and irradiation of methyl 3α, 5-cyclo-6-oxo-17β-acetoxy-5α-androstan-19-oate in tertiary butyl alcohol was also described yielding methyl 4α-*tert*-butoxy-6-oxo-17β-acetoxy-5α-androstan-19-oate (**4**) and methyl 6-oxo-17β-acetoxyandrost-4-en-19-oate (**14**).

Photochemistry of conjugated cyclopropyl ketones has been reported to involve (1) *cis-trans* isomerization,[3] (2) cleavage of cyclopropane ring resulting in the formation of γ, δ-unsaturated ketone,[4] and (3) dissociation of the better overlapped bond of cyclopropane ring with $n \rightarrow \pi^*$ excited ketone to form α,β-unsaturated ketones.[5]

Photolysis of steroidal conjugated cyclopropyl ketones was previously studied by several investigators[6,7] on 19-methyl series: for example 3α,5-cyclo-17β-acetoxy-5α-androstan-6-one upon irradiation in dioxane was reported to yield 17β-acetoxyandrost-4-en-6-one and dimeric product in 13—20% and 0.5% yields respectively, while in ethanol the same cyclopropyl ketosteroid was reported to give 17β-acetoxyandrost-4-en-6-one as a sole product.[7]

Our interest in photochemical behavior of 3α,5-cyclo-19-oxygenated steroid derivatives prompted us to undertake a photoreaction of 3α,5-cyclo-6-oxo-17β-acetoxy-5α-androstan-19-oic acid (**1**), which contains a carboxylic function in close proximity to the cyclopropyl ketone moiety.

A solution of 3α,5-cyclo-6-oxo-17β-acetoxy-5α-androstan-19-oic acid (**1**) in tertiary butyl alcohol was irradiated for 10—13 hours under argon gas using Hanovia high pressure mercury arc (200W) to yield 4α-*tert*-butoxy-6,6-dihydroxy-17β-acetoxy-5α-androstan-19-oic acid 6,19-lactone (**2**) and 6-oxo-17β-acetoxyandrost-4-en-19-oic acid (**3**) in 50% and about 10% yields respectively. The infrared (IR) spectrum of the lactol (**2**) shows absorption bands at 3360 and 1770 cm^{-1} due to a hydrogen bonded hydroxyl and a five membered lactone carbonyl groups respectively. The nuclear magnetic resonance (NMR) spectrum of the compound (**2**) exhibit-

1) Steroid Series Part XXIII: K. Kojima, R. Hayashi, and K. Tanabe, *Chem. Pharm. Bull.* (Tokyo), **18**, 1974 (1970).
2) Location: *1-2-58 Hiromachi, Shinagawa-ku, Tokyo.*
3) G. W. Griffin, E. J. O'Conell, and H. A. Hammond, *J. Am. Chem. Soc.*, **85**, 1001 (1963).
4) R. M. Roberts and R. G. Landolt, *J. Am. Chem. Soc.*, **87**, 2281 (1965); W. G. Dauben, L. Schutte, and R. E. Wolt, *J. Org. Chem.*, **34**, 1849 (1969).
5) J. N. Pitts, Jr. and I. Norman, *J. Am. Chem. Soc.*, **76**, 4815 (1954); W. G. Dauben and G. N. Shaffer, *Tetrahedron Letters*, **1967**, 4415; L. D. Hess and J. N. Pitts, Jr., *J. Am. Chem. Soc.*, **89**, 1973 (1967); O. L. Chapman, T. A. Rettig, A. A. Griswold, A. I. Button, and P. Fitton, *Tetrahedron Letters*, **1963**, 2049; O. L. Chapman, "Org. Photochemistry," Vol. I, p. 113.
6) R. Beugelman, *Bull. Soc. Chim. France*, **1967**, 224.
7) C. H. Robinson, O. Gnoj, and F. E. Carlon, *Tetrahedron*, **21**, 2069 (1965).

ed a nine proton singlet at τ 8.69 assignable to a tertiary butoxy group and a triplet-doublet signal (J=10, 3.5 cps) centered at τ 6.12 ascribable to 4β-proton.

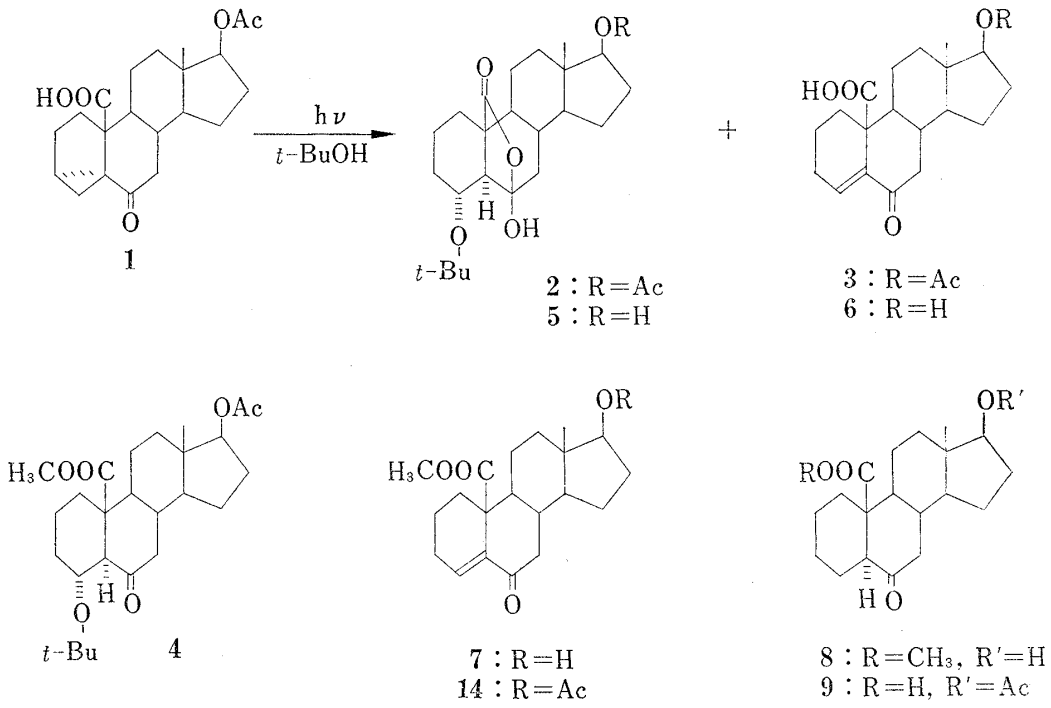


Chart 1

Treatment of the photoproduct (**2**) with etherial diazomethane gave a methyl ester, methyl 4α-*tert*-butoxy-6-oxo-17β-acetoxy-5α-androstan-19-oate (**4**). The IR spectrum of the ester (**4**) shows no absorption bands at 3360 and 1770 cm^{-1}, but a new six membered ring ketone was suggested by a strong band at 1738 cm^{-1} overlapped with that due to the ester carbonyl group. The NMR spectrum of the ester (**4**) exhibits a signal at τ 6.33 due to a carbomethoxy function. These data indicate the presence of a lactol moiety in the photoproduct (**2**).

The compound (**2**) in 10% ethanolic potassium hydroxide was heated at reflux and acidified with dilute hydrochloric acid yielding an oily 6-oxo-17β-hydroxyandrost-4-en-19-oic acid (**6**) along with 4α-*tert*-butoxy-6,6-dihydroxy-17β-hydroxy-5α-androstan-19-oic acid 6,19-lactone (**5**). The structure of the oily ketone (**6**) was characterized by its conversion into a crystalline methyl ester (**7**), which shows the infrared absorption bands at 1690 and 1621 cm^{-1}, and an ultraviolet absorption maximum at 237 mμ (ε=6680) due to an α,β-unsaturated ketone moiety.

Olefinic linkage in the ester (**7**) was catalytically hydrogenated with 5% palladium on charcoal to afford methyl 6-oxo-17β-hydroxy-5α-androstan-19-oate (**8**), which was identified with an authentic sample synthesized from the known 6-oxo-17β-acetoxy-5α-androstan-19-oic acid (**9**).[1] Thus the formation of α,β-unsaturated ketone (**6**) suggests that the tertiary butoxy function in the photoproduct (**2**) must be located at the C_4-position, beta to the 6-oxo function. These data unumbigously established the structure of the photoproduct (**2**) except the stereochemistry at the C_4-and C_5-positions, which was elucidated as follows.

The lactol (**2**) in acetic anhydride was treated with boron trifluoride etherate to yield a triacetate, 4α,6α,17β-triacetoxy-6β-hydroxy-5α-androstan-19-oic acid 6,19-lactone (**10**) in high yield. The NMR spectrum of the triacetate (**10**) shows a nine proton singlet at τ 7.98 due to three acetoxy functions. The cleavage reaction of tertiary butoxy ether[8] is known to involve

8) C. R. Narayanan and K. N. Lyer, *Tetrahedron Letters*, **1964**, 759.

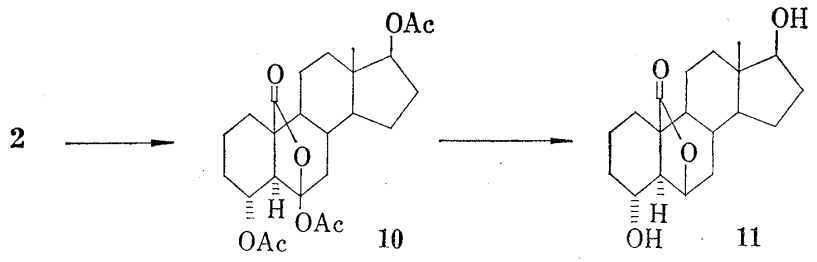


Chart 2

a fission of the bond between oxygen and tertiary butyl group resulting in the formation of more stable tertiary butyl cation. Therefore the configuration at the C_4-position must be retained in the above reaction conditions from the lactol (**2**) to the triacetate (**10**). Successive treatment of the triacetate (**10**) with excess sodium borohydride in aqueous ethanol, potassium hydroxide and conc. hydrochloric acid, without any separation of intermedial products, yielded 4α,6β,17β-trihydroxy-5α-androstan-19-oic acid 6,19-lactone (**11**)[9] in good yield. The IR spectrum of the lactone (**11**) shows absorption bands at 3420, 1772 and 1750 cm^{-1} due to a hydroxyl and γ-lactone groups respectively. The NMR and the results of the NMR spin decoupling of the lactone (**11**) are shown in Fig. 1. The C_4-proton was observed at τ 6.95 as triplet–doublet signal with coupling constant $J_{4a,3a}=J_{4a,5a}=9.5$ and $J_{4a,3e}=3.5$ cps respectively, which suggests the C_4-proton must be axial. Among the four stereoisomeric structures (A, B, C, D in Fig. 2)[10] for the lactone (**11**), two stereoisomers A and B are compatible with these data. Irradiation of the C_4-proton at its resonant frequency caused the C_5-proton doublet (τ 8.41, $J_{4a,5a}=9.5$ cps) to collapse into a singlet. On the other hand irradiation of the 6α-proton (doublet at τ 5.32, $J_{6\alpha,7\beta}=5$ cps)[11] did not cause the C_5-proton doublet to change, suggesting the dihedral angle between the C_5-and C_6-proton must be about 90°. Molecular model inspection indicates that the stereoisomer A in Fig. 2 is in better agreement with these results than the isomer B and hence stereochemical structure of the lactone (**11**) can be assigned as **11** in Chart 2.

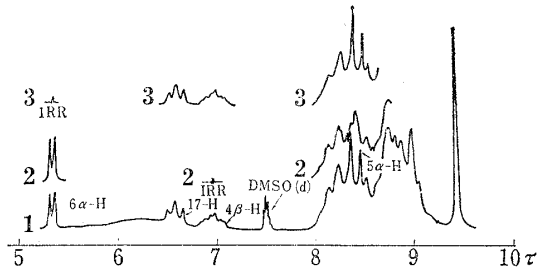
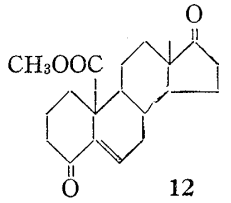


Fig. 1. 100 Mc NMR Spectrum of the Lactone (**11**) in d-DMSO (**1**), and Irradiation of the C_4-Proton (**2**) and the C_6-Proton (**3**)

9) Following chemical evidence confirmed that the lactone (**11**) has a 6,19-lactone and not a 4,19-lactone ring. Oxidation of the lactone (**11**) yielded 4,17-dioxo-6β-hydroxy-5α-androstan-19-oic acid 6,19-lactone, which upon treatment with refluxing ethanolic potassium hydroxide, followed by esterification afforded methyl 4,17-dioxoandrost-5-en-19-oate (**12**). Ultraviolet spectrum of the ester (**12**) shows an absorption maximum at 242 mμ (ε=6170) due to an α, β-unsaturated ketone chromophore. This ketone (**12**) was not identical with methyl 6,17-dioxoandrost-4-en-19-oate (**13**), derived from the known methyl 6-oxo-17β-hydroxyandrost-4-en-19-oate (**7**).



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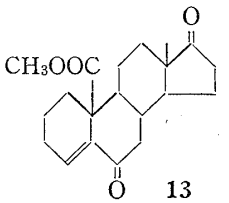

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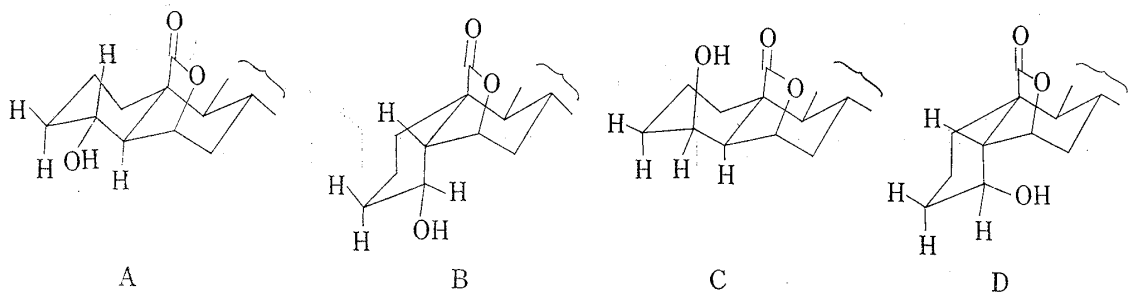
10) Molecular model of the isomers (A and B) or (C and D) indicates the similar relative configuration of the C_4-proton to the C_3- and C_5-protons respectively. The C_4-proton of the isomer C (the C_4-epimer of the isomer A), obtained by the reduction 4,17-dioxo-6β-hydroxy-5α-androstan-19-oic acid 6,19-lactone, was observed as a broad singlet signal (W $^1/_2$=8 cps) in the NMR spectrum. a=axial, e=equatorial.

11) 6α-Proton must be only coupled with 7β-proton.



A B C D

Fig. 2

As the configuration at the C_4-position is retained in the reaction sequence from the lactol (**2**) to the dihydroxylactone (**11**) *via* the triacetate (**10**), the configuration of the tertiary butoxy function in the lactol (**2**) was concluded to be also alfa.

The stereochemistry at the C_5-position of the photoproduct (**2**) might not always be the same as that of the diol (**11**) because of its formation through the intermedial 6-keto compound. It was finally established to be alfa since the C_4-proton signal of the compounds (**11**, **10** and **2**) exhibits the same pattern (triplet–doublet; **11**: τ 6.95, J=9.5, 3.5 cps; **10**: τ 5.08, J=10, 4.5 cps; **2**: τ 6.12, J=10, 3.5 cps) in the NMR spectrum. The presence of the intramolecular hydrogen bond (IR) in the compound (**2**) also supports this conclusion. From these results structure of the photoproduct (**2**) was established as shown in Chart 1.

Structure of another photoproduct (**3**) was established as cited below. Esterification of the compound (**3**) with diazomethane afforded a methyl 6-oxo-17β-acetoxyandrost-4-en-19-oate (**14**), which shows infrared absorption bands at 1680 and 1629 cm^{-1} and an ultraviolet absorption maximum at 244 mμ (ε=5500) due to an α,β-unsaturated ketone function, and was converted with 5% methanolic potassium hydroxide into the known methyl ester (**7**).

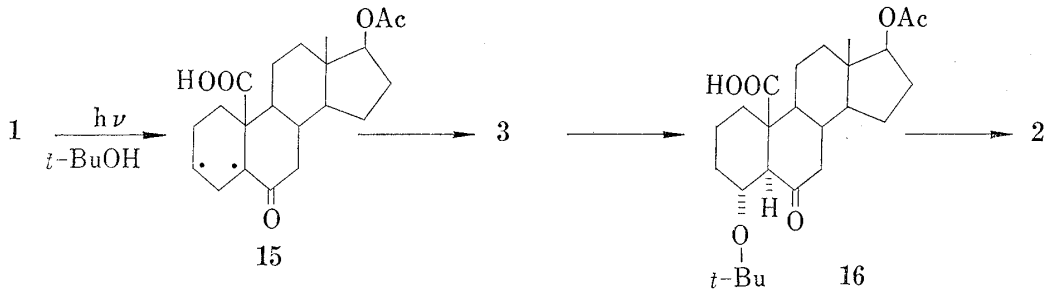


Chart 3

Mechanism of this photochemical reaction may be illustrated as shown in Chart 3. On photolysis of the cyclopropyl ketone (**1**) an initial cleavage of the better overlapped C_3-C_5 bond with 6-oxo function has taken place to form a diradical intermediate (**15**). The radical generated at the C_5-position must be less reactive than that at the C_3-position, since it is a tertiary radical and stabilized by 6-oxo group. Therefore 4α hydrogen radical, as suggested by Beugelman,[6] shifted to the more reactive C_3-position to yield the C_4-radical and then stabilized as 6-oxo-17β-acetoxyandrost-4-en-19-oic acid (**3**). Photochemical Michael addition of tertiary butyl alcohol to the α,β-unsaturated ketone (**3**) affords an intermediate tertiary butoxy carboxylic acid (**16**) and subsequent cyclizafon of carboxylic function in **16** to a lactol yielded 4α-*tert*-butoxy-6,6-dihydroxy-17β-acetoxy-5α-androstan-19-oic acid 6,19-lactone (**2**).

That the photoproduct (**2**) was formed photochemically *via* the intermediate α,β-unsaturated ketone (**3**)[12] was suggested from the following evidence. When α,β-unsaturated ketone

12) This was also supported by following the reaction mixture by measuring ultraviolet absorption at 237 mμ. The amount of α, β-unsaturated ketone (3) was found to reach at maximum after two hours' irradiation and then went to decrease gradually.

(**3**) and (**6**) in tertiary butyl alcohol was allowed to react at room temperature for 30 hours or heated at reflux for 12 hours, the starting material was recovered unchanged, while irradiation in tertiary butyl alcohol yielded the corresponding tertiary butoxy lactol (**2** and **5**). Photochemical addition[13] of alcohol to an α,β-unsaturated ketone chromophore has been reported by several workers to give adducts in a variety of yields depending upon alcoholic solvent used. For example cycloheptenone[14] gives the corresponding adduct in 86% in methanol and 50% yields in isopropyl alcohol respectively, while in tertiary butyl alcohol the adduct was obtained only in 3% yield. It is interesting that in our result described here the tertiary butyl alcohol adduct (**2**) was isolated in such a high yield, though accompanied by concommitant formation of a lactol ring.

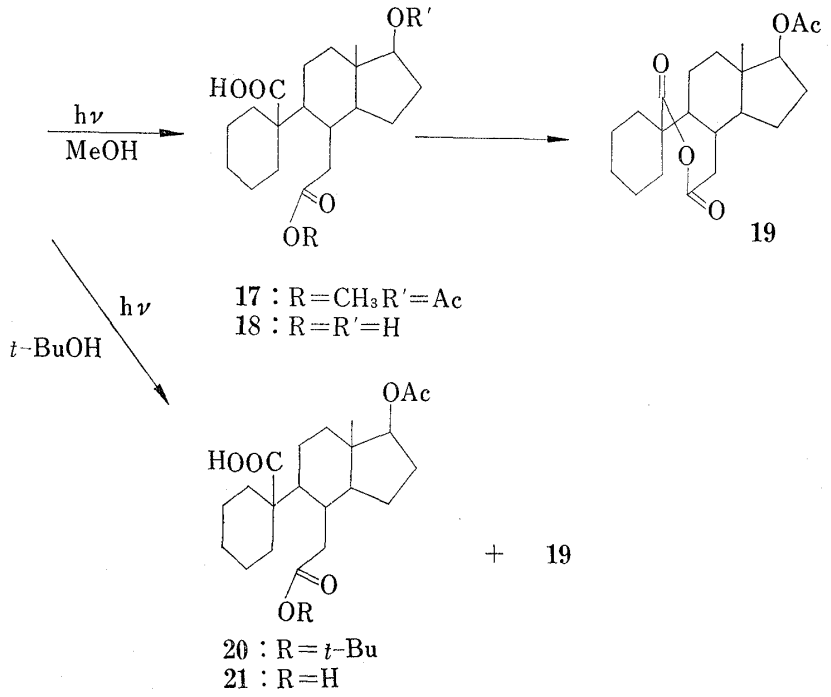


Chart 4

In order to investigate whether lactol ring can be formed in such a simple β-carboxy ketone as 6-oxo-17β-acetoxy-5α-androstan-19-oic acid (**9**), a solution of **9** in alcoholic medium was irradiated. Irradiation of the ketone (**9**) in methanol gave methyl 17β-acetoxy-5,6-secoandrostan-19-oic acid 6-oate (**17**) which was isolated in 67.5% yield. The IR spectrum of the ester (**17**) shows an absorption band at 1695 cm^{-1} due to a carboxyl group. The NMR spectrum exhibits a signal at τ 6.36 ascribable to carbomethoxy function. The ester (**17**) was hydrolysed with 10% methanolic potassium hydroxide to yield 17β-hydroxy-5,6-secoandrostan-6,19-dioic acid (**18**), which shows an infrared absorption band at 1707 cm^{-1} due to two carboxyl functions. Dicarboxylic acid (**18**) was converted by treatment with acetic anhydride in pyridine into 17β-acetoxy-5,6-secoandrostan-6,19-dioic acid anhydride (**19**), which exhibits absorption bands at 1789 and 1755 cm^{-1} due to anhydride carbonyl groups in the infrared spectrum. All these data supports the proposed structure of the methyl ester (**17**).

Irradiation of the acid (**9**) in tertiary butyl alcohol yielded also the corresponding 5,6-seco-tertiary butyl ester (**20**) in 25% yield along with dicarboxylic acid (**21**) and aforementioned anhydride (**19**). Structure of the photoproduct (**20** and **21**) was deduced from the evi-

13) T. Matsuura and K. Ogura, *Bull. Chem. Soc. Japan*, **40**, 945 (1967); P. D. Gardner and B. J. Ramey, *J. Am. Chem. Soc.*, **89**, 3949 (1967).
14) H. Nozaki, M. Kurita, and R. Noyori, *Tetrahedron Letters*, **1968**, 2025.

dence cited below. The NMR spectrum of the butyl ester (**20**) shows a nine proton singlet at τ 8.55 due to a tertiary butoxy group. Hydrolysis of the ester (**20**) yielded the known dicarboxylic acid (**18**). Treatment of the photoproduct (**21**) with acetic anhydride in pyridine afforded the anhydride (**19**) described above. These photochemical reactions are analogous to that of 6-oxo-19-methyl steroid.[15] In both cases however, the formation of lactol ring was not observed.

On the other hand irradiation in tertiary butyl alcohol of methyl 3α,5-cyclo-6-oxo-17β-acetoxy-5α-androstan-19-oate, which is impossible to form internal lactol ring, yielded methyl 4α-*tert*-butoxy-6-oxo-17β-acetoxy-5α-androstan-19-oate (**4**) in about 15% yield accompanied by methyl 6-oxo-17β-acetoxyandrost-4-en-19-oate (**14**).

The yield of the tertiary butoxy ether (**4**) is lower than that of the tertiary butoxy lactol (**2**) described in photolysis of the free carboxylic acid (**1**). Therefore the higher yield of the lactol (**2**) might be explained as follows: photochemical Michael addition of tertiary butyl alcohol to the intermediate α,β-unsaturated ketone (**3**) forms tertiary butoxy compound (**16**), whose tertiary butoxy function must prefer an equatorial conformation over an axial one due to its bulkiness. Then strong hydrogen bond was formed between tertiary butoxy group and 6α-hydroxyl function, which was generated through reaction of 6-ketone with 19-carboxyl function. The strong hydrogen bond thus formed will play an important role for stabilization and yield of the lactol (**2**).

Experimental

All melting points were uncorrected. The NMR spectra were recorded with Varian A-60 and/or HA 100 spectrometer (spin decoupling) in $CDCl_3$ solution unless otherwise stated and calibrated against internal tetramethylsilan. Chemical shifts were expressed in τ, s: singlet, d: doublet, t: triplet, br; broad. The IR spectra were taken with Hitachi Model EPI S-2.

Irradiations were conducted using Hanovia high pressure mercury arc (200 W) inserted into a water-cooled, quarz imersion probe. Stirring of the solution was effected by introduction of argon gas through a jet opening at the bottom of the apparatus and argon was continuously bubbled through the solution during irradiation.

Photolysis of 3α, 5-Cyclo-6-oxo-17β-acetoxy-5α-androstan-19-oic Acid (1)[1]——A solution of the compound (1:1.5 g) in *t*-BuOH (150 ml) was irradiated for 10—13 hr. Evaporation of the solvent under reduced pressure gave a syrupy residue which was chromatographed over silica gel. Elution with benzene–chloroform (1:1) gave a crystalline residue which was recrystallized from iso-Pr_2O to afford 918 mg of 4α-*tert*-butoxy-6, 6-dihydroxy-17β-acetoxy-5α-androstan-19-oic acid 6, 19-lactone (**2**), mp 181—182°. *Anal.* Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.89. Found: C, 69.20; H, 9.05. IR $\nu_{max}^{CCl_4}$ cm^{-1} (1.42×10^{-3}M): 3360 (OH), 1770 (γ-lactone), 1738 (OAc). NMR τ: 9.13 (3H, s, 18-CH_3), 8.69 (9H, s, *t*-Bu), 7.98 (3H, s, OAc), 6.12 (1H, t—d, J=10, 3.5 cps, 4β-H), 5.41 (1H, 17α-H). Further elution with chloroform gave 403 mg of a gummy residue (**3**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695, 1625), which was treated with diazomethane in ether. The gummy product obtained was chromatographed over silica gel. Elution with hexane–benzene (1:1) gave a crystalline substance which was recrystallized from iso-Pr_2O to afford 157 mg of methyl 6-oxo-17β-acetoxyandrost-4-en-19-oate (**14**) mp 126—128°. *Anal.* Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.44; H, 8.05. IR ν_{max}^{KBr} cm^{-1}: 1738 (sh), 1729 (OAc, $COOCH_3$), 1680 (6-CO), 1629 (C=C). NMR τ: 9.27 (3H, s, 18-CH_3), 7.98 (3H, s, OAc), 6.33 (3H, s, $COOCH_3$), 5.40 (1H, 17α-H), 3.39 (1H, t, J=3cps, 4-H). UV λ_{max}^{EtOH} mμ (ε): 244 (5500).

Methyl 4α-*tert*-Butoxy-6-oxo-17β-acetoxy-5α-androstan-19-oate (4)——To a solution of the compound (2:150 mg) in chloroform (0.5 ml) excess etherial diazomethane solution was added under ice–water cooling. After ten minutes (ice cooled) the reaction mixture was treated with acetic acid to decompose excess diazomethane and diluted with chloroform. The chloroform layer was washed with water and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave a gummy residue which was chromatographed over silica gel. Elution with benzene–chloroform (1:1) gave 124 mg of the ester (**4**) as an oily substance. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1738 (ester, ketone). NMR τ: 9.19 (3H, s, 18-CH_3), 8.75 (9H, s, *t*-Bu), 7.98 (3H, s, OAc), 6.33 (3H, s, $COOCH_3$), 6.06 (1H, t—d, J=9, 5 cps, 4β-H), 5.38 (1H, 17α-H).

Alkali Treatment of the Photoproduct (2)——A solution of the compound (2: 500 mg) in 10% KOH–EtOH (5 ml) was heated on a water bath at reflux for 8 hr. Then the cooled reaction mixture was acidified with dil. hydrochloric acid and extracted with chloroform. The extracts were thoroughly washed with water,

15) R. O. Kan (translated by M. Nakata), "Org. Photochemistry," Maruzen, 1968, p. 82.

dried over anhyd. Na_2SO_4 and evaporated to give 298 mg of a gummy residue which was chromatographed over silica gel. Elution with chloroform gave 37 mg of a crystalline product which was recrystallized from iso-Pr_2O to afford 4α-tert-butoxy-6,6-dihydroxy-17β-hydroxy-5α-androstan-19-oic acid 6,19-lactone (**5**), mp 216—217°. *Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.15; H, 9.18. IR ν_{max}^{KBr} cm^{-1}: 3530, 3330 (OH), 1755 (γ-lactone). NMR (d-DMSO) τ: 9.41 (3H, s, 18-CH_3), 8.84 (9H, s, *t*-Bu), 6.50 (1H, 17α-H), 6.40 (br, 4β-H). Subsequent elution with 0.5% MeOH–chloroform gave 163 mg of a mixture of the compound (**5**) and (**6**), and elution with 1—10% MeOH–chloroform gave 61 mg of 17β-hydroxyandrost-4-en-6-one (**6**) as an oily substance: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695 (6-CO, COOH), 1625 (C=C), which was characterized as its crystalline methyl ester (**7**) upon esterification with diazomethane in a usual way. Recrystallization from iso-Pr_2O gave a pure sample. mp 173—174°. *Anal.* Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.00; H, 8.43. IR ν_{max}^{KBr} cm^{-1}: 3310 (OH), 1730 (ester), 1690 (6-CO), 1621 (C=C). NMR τ: 9.31 (3H, s, 18-CH_3), 6.32 (3H, s, $COOCH_3$), 6.32 (1H, 17α-H), 3.36 (1H, t, J=3.5 cps, 4-H). UV λ_{max}^{EtOH} mμ (ε): 237 (6680).

Methyl 6-Oxo-17β-hydroxy-5α-androstan-19-oate (**8**)——(i) The compound (**7**; 61 mg) dissolved in MeOH (20 ml)was hydrogenated in the presence of 5% palladium on charcoal catalyst (100 mg). After the uptake of hydrogen ceased, the catalyst was removed by filtration. The filtrate was acidified with conc. hydrochloric acid (3 drops) and then warmed at 60—70° for 5 min. The cooled reaction mixture was diluted with water and extracted with chloroform. The extracts were washed with water and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave a crystalline residue which was recrystallized from iso-Pr_2O to afford 38 mg of the ketone (**8**) mp 199—200°. *Anal.* Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 72.15; H, 8.97. IR ν_{max}^{KBr} cm^{-1}: 3548 (OH), 1723 ($COOCH_3$, 6-CO).

(ii) 6-Oxo-17β-acetoxy-5α-androstan-19-oic acid (**9**; 100 mg) was treated with slightly excess etherial diazomethane (ice cooled) for 10 min. Then the reaction mixture was evaporated *in vacuo* to dryness and the crystalline residue was recrystallized from hexane–iso-Pr_2O to afford 63 mg of methyl 6-oxo-17β-acetoxy-5α-androstan-19-oate, mp 110—111°. *Anal.* Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 69.94; H, 8.69. IR ν_{max}^{KBr} cm^{-1}: 1720 ($COOCH_3$, OAc).

A solution of methyl 6-oxo-17β-acetoxy-5α-androstan-19-oate (30 mg) in 5% KOH–MeOH (3 ml) was allowed to stand at room temperature for 1 hr. The usual work-up gave the crude ester (**8**), which after recrystallization from iso-Pr_2O to afford 14 mg of a pure sample. mp 199—200°.

4α, 6α, 17β-Triacetoxy-6β-hydroxy-5α-androstan-19-oic Acid 6,19-Lactone (**10**)——A mixture of the photoproduct (**2**: 100 mg) in acetic anhydride (2 ml) and borontrifluoride etherate (3 drops) was allowed to stand in a refrigerator (0°) for 44 hr. The reaction mixture was diluted with ice–water to give a crystalline substance which was collected by filtration. Thus 79 mg of the pure triacetate (**10**) was obtained. Recrystallization from AcOEt–iso-Pr_2O gave a pure analytical sample. mp 220—222. *Anal.* Calcd. for $C_{25}H_{34}O_8$: C, 64.92; H, 7.41. Found: C, 64.82; H, 7.53. IR ν_{max}^{KBr} cm^{-1}: 1788 (γ-lactone), 1752 (OAc), 1740 (OAc). NMR τ: 9.22 (3H, s, 18-CH_3), 7.98 (9H, s, 3×OAc), 5.40 (1H, 17α-H), 5.08 (1H, t—d, J=10, 4.5 cps, 4β-H).

4α, 6β, 17β-Trihydroxy-5α-androstan-19-oic Acid 6, 19-Lactone (**11**)——Sodium borohydride (300 mg) was added portionwise to a stirred solution of the triacetate (**10**: 300 mg) in EtOH (15 ml) and water (4 ml). The resulting reaction mixture was further stirred at room temperature for one day, treated with acetic acid and made alkaline with 10% KOH–MeOH solution. This reaction mixture was subsequently heated at reflux for 50 min and then acidified with conc. hydrochloric acid. After heating on a water bath for 10 min, the reaction mixture was cooled to room temperature to give a crystalline precipitate which was collected by filtration, yielding 192 mg of the hydroxylactone (**11**). Recrystallization from AcOEt–iso-Pr_2O gave a pure analytical sample. mp 239—240°. *Anal.* Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.25; H, 8.85. IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 1772, 1750 (γ-lactone). NMR (d-DMSO) τ: 9.42 (3H, s, 18-CH_3), 8.41 (1H, d, J=9.5 cps, 5α-H), 6.95 (1H, t—d, J=9.5, 3.5 cps, 4β-H), 6.57 (1H, 17α-H), 5.32 (1H, d, J=5 cps, 6α-H). $[\alpha]_D^{dioxane}$ = −29.3°.

4, 17-Dioxo-6β-hydroxy-5α-androstan-19-oic Acid 6,19-Lactone——(i) A mixture of the compound (**11**: 282 mg) in pyridine (5 ml) and chromic anhydride (500 mg) in pyridine (20 ml) was allowed to stand at room temperature for 44 hr. The reaction mixture was diluted with water and extracted with chloroform. The combined chloroform extracts were washed with dil. hydrochloric acid, then water and dried over anhyd. Na_2SO_4. Evaporation of the solvent afforded a crystalline residue which was chromatographed over neutral alumina (G 111). Elution with chloroform gave a crystalline product which upon recrystallization from AcOEt–iso-Pr_2O gave 214 mg of 4,17-dioxo-6β-hydroxy-5α-androstan-19-oic acid 6,19-lactone mp 222—225°. *Anal.* Calcd. for $C_{19}H_{28}O_4$: C, 72.12; H, 7.65. Found: C, 71.57; H, 7.56. IR ν_{max}^{KBr} cm^{-1}: 1771 (γ-lactone), 1731 (4-and 17-CO). NMR τ: 9.12 (3H, s, 18-CH_3), 4.62 (1H, d, J=4.5 cps, 6α-H).

ii) To a solution of the isomer C (17 mg) in pyridine (1 ml), chromic anhydride (100 mg), dissolved in pyridine (3 ml), was added all at once. After 24 hr at room temperature the reaction mixture was treated as in the above experiment (i) and recrystallized from AcOEt–iso-Pr_2O to afford 13 mg of 4,17-dioxo-6β-hydroxy-5α-androstan-19-oic acid 6,19-lactone, mp 222—225°. From these results compound (**11**) and the lactone (C) are epimeric pairs.

Methyl 4,17-Dioxoandrost-5-en-19-oate (**12**)——4,17-Dioxo-6β-hydroxy-5α-androstan-19-oic acid 6, 19-lactone (170 mg) in 20% KOH–EtOH (15 ml) was heated under reflux for 2.4 hr. The reaction mixture

was diluted with water and washed with chloroform. The aqueous layer separated was acidified with dil. hydrochloric acid and then extracted with chloroform. The extract was washed with water and dried over anhyd. Na_2SO_4. Concentration of the solvent gave 81 mg of a crude product (almost pure in TLC) which, without further purification, was esterified with etherial diazomethane. The resulting reaction mixture was treated with acetic acid to decompose excess diazomethane and evaporated *in vacuo*. Then this crude product was chromatographed over neutral alumina (G 111). Elution with benzene gave a crystalline substance which was recrystallized from acetone–iso-Pr_2O to afford 16 mg of the compound (**12**). mp 192—194°. *Anal.* Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.88; H, 7.87. IR ν_{max}^{KBr} cm^{-1}: 1744 (17-CO), 1725 ($COOCH_3$), 1685 (4-CO), 1620 (C=C). UV λ_{max}^{EtOH} $m\mu$ (ε): 242 (6170).

Methyl 6,17-Dioxoandrost-4-en-19-oate (**13**)——A mixture of the compound (**7**: 210 mg) in pyridine (3 ml) and chromic anhydride (200 mg) in pyridine (8 ml) was allowed to stand at room temperature for 9.5 hr. After treatment of the reddish brown reaction mixture in a usual manner, the obtained crude product was chromatographed over silica gel. Elution with benzene afforded 116 mg of a colorless gummy residue which was crystallized from AcOEt–iso-Pr_2O to give 53 mg of the ketone (**13**) mp 147—150°. *Anal.* Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.82; H, 8.00. IR ν_{max}^{KBr} cm^{-1}: 1737 (17-CO), 1710 ($COOCH_3$), 1685 (6-CO), 1615 (C=C). UV λ_{max}^{EtOH} $m\mu$ (ε): 237 (6780).

Sodium Borohydride Reducion of 4,17-Dioxo-6β-hydroxy-5α-androstan-19-oic-Acid 6,19-Lactone——To a stirred solution of the titled compound (210 mg) in a mixture of EtOH (16 ml) and water (4 ml), sodium borohydride (210 mg) was added portionwise. After 4 hr's stirring at room temperature the reaction mixture was treated with acetic acid, then diluted with water and extracted with chloroform. The extract was washed with water and dried over anhyd. Na_2SO_4. Removal of the solvant gave a crude gummy residue which was chromatographed over neutral alumina (G 111). Elution with benzene–chloroform (4:6) gave a crystalline product which was recrystallized from AcOEt–iso-Pr_2O to afford 59 mg of the known dihydroxylactone (**11**). mp 239—240° and elution with 10% MeOH–chloroform gave a crystalline substance which was recrystallized from chloroform–AcOEt to yield 31 mg of 4β, 6β, 17β-trihydroxy-5α-androstan-19-oic acid 6,19-lactone (C) mp 236—238°. *Anal.* Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 70.66; H, 8.76. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1750 (γ-lactone). NMR (d-DMSO)τ: 9.42 (3H, s, 18-CH_3), 6.57 (1H, 17α-H), 6.13 (1H, br, s, $W^1/_2$= 8 cps, 4α-H), 5.38 (1H, d, J=4.5 cps, 6α-H). $[\alpha]_D^{dioxane}$ = +46°.

Hydrolysis of the Compound(**14**)——A solution of the compound (**14**:100 mg) in 5% KOH–MeOH (6 ml) was allowed at room temperature for 35 min. The reaction mixture was treated as usual and a gummy residue (83 mg) obtained was chromatographed over neutral alumina (G 111). Elution with 3% ether–benzene gave a crystalline substance which upon recrystallization from iso-Pr_2O afforded 29 mg of the hydroxy compound (**7**) partially hydrolyzed mp 173—174°.

Photolysis of the α,β-Unsaturated Ketone(**3**)——A solution of the compound (**3**:150 mg) in dry *t*-BuOH (20 ml) was irradiated for 13 hr. After evaporation of the solvent *in vacuo* the crude product was purified by silica gel column chromatography. Elution with benzene–chloroform (1:1) gave a crystalline residue, which upon recrystallization from iso-Pr_2O afforded 31 mg of the lactol (**2**) mp 180—181°.

Photolysis of the α,β-Unsaturated Ketone (**6**)——A solution of the compound (**6**: 329 mg) in dry *t*-BuOH (140 ml) was irradiated for 2 hr. Removal of the solvent gave a crystalline residue which was recrystallized from iso-Pr_2O to give 267 mg of the lactol (**5**) mp 216—217°.

Photolysis of 6-Oxo-17β-acetoxy-5α-androstan-19-oic Acid (**9**)[1]——(i) A solution of the ketone (**9**: 1.7 g) in absolute MeOH (170 ml) was irradiated for 6 hr. The solvent was evaporated *in vacuo* to give a syrupy residue which was chromatographed over silica gel. Elution with benzene–chloroform (1:1) afforded 1.247 g of a crystalline product, which upon recrystallization from iso-Pr_2O gave methyl 17β-acetoxy-5,6-secoandrostan-19-oic acid 6-oate (**17**) mp 147—148°. *Anal.* Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 67.15; H, 8.53. IR ν_{max}^{KBr} cm^{-1}: 1731 ($COOCH_3$), 1695 (COOH). NMR τ: 9.21 (3H, s, 18-CH_3), 7.96 (3H, s, OAc), 6.36 (3H, s, $COOCH_3$), 5.38 (1H, 17α-H).

(ii) A solution of the compound (**9**:1.5 g) in dry *t*-BuOH (150 ml: freshly distilled with Na) was irradiated for 7 hr. Evaporation of the solvent gave a gummy residue which was chromatographed over silica gel. Elution with benzene–chloroform (6:4) gave 93 mg of 17β-acetoxy-5,6-secoandrostan-6,19-dioic acid anhydride (**19**) recrystallized from iso-Pr_2O. mp 184—185°. *Anal.* Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.62; H, 8.25. IR ν_{max}^{KBr} cm^{-1}: 1789, 1755 (anhydride), 1738 (OAc). NMR τ: 9.15 (3H, s, 18-CH_3), 7.95 (3H, s, OAc), 5.33 (1H, 17α-H). Elution with benzene–chloroform (1:1) afforded 451 mg of *tert*-butyl 17β-acetoxy–5,6-secoandrostan-19-oic acid 6-oate (**20**) as an oily substance. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester), 1700 (COOH). NMR τ: 9.21 (3H, s, 18-CH_3), 8.55 (9H, s, *t*-Bu), 7.95 (3H, s, OAc), 5.38 (IH,17α-H). Further elution with benzene–chloroform (1:1) gave 234 mg of 17β-acetoxy 5,6-secoandrostan-6,19-dioic acid (**21**) as an oily product. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (OAc), 1700 (COOH). NMR τ: 9.22 (3H, s, 18- CH_3), 7.98 (3H, s, OAc), 5.38 (1H, 17α-H).

17β-Hydroxy-5,6-secoandrostan-6,19-dioic Acid (**18**)——(i) The ester (**17**: 325 mg) in 10% KOH–MeOH (10 ml) was heated under reflux for 9 hr and was allowed to stand at room temperature overnight. Then additional amount of 10% KOH–MeOH (5 ml) was added and heated again at reflux for additional 2 hr. The cooled reaction mixture was diluted with water, acidified with acetic acid and extracted with

chloroform. Chloroform layer was washed with water, dried over ahnyd. Na_2SO_4 and evaporated *in vacuo* to give a gummy residue which was crystallized from AcOEt to afford 269 mg of the diacid (**18**) mp 217—218°. *Anal.* Calcd. for $C_{19}H_{30}O_2$: C, 67.43; H, 8.94. Found: C, 67.19; H, 8.91. IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 1707 (COOH).

(ii) A mixture of the ester (**20**: 220 mg) in dioxane (15 ml) and 10% sulfuric acid (15 ml) was warmed on water bath for 8 hr. The reaction mixture was diluted with water and extracted with chloroform. The extract was washed with water, dried over anhyd. Na_2SO_4 and then evaporated. The crude product was purified by column chromatography of silica gel. Elution with chloroform–3% MeOH/chloroform gave 86 mg of a crystalline substance which was recrystallized from AcOEt to afford the diacid (**18**) mp 217—218.°

17β-Acetoxy-5,6-secoandrostane-6,19-dioic Acid Anhydride (**19**)——(i) A mixture of the diacid (**18**: 135 mg) in pyridine (2 ml) and acetic anhydride (0.5 ml) was maintained at room temperature overnight. Removal of the solvent *in vacuo* gave a crystalline residue which was recrystallized from iso-Pr_2O to afford 84 mg of the anhydride (**19**) mp 184—185°.

(ii) A solution of the compound (**21**: 72 mg) in pyridine (1 ml) and acetic anhydride (0.5 ml) was allowed to stand at room temperature overnight. The similar treatment as described avove gave 32 mg of the the anhydride (19) recrystallized from iso-Pr_2O.

Photolysis of Methyl 3α,5-Cyclo-6-oxo-17β-acetoxy-5α-androstan-19-oate——A solution of methyl 3α,5-cyclo-6-oxo-17β-acetoxy-5α-androstan-19-oate (630 mg) in dry *t*-BuOH (160 ml) was irradiated for 10.5 hr. After evaporation of the solvent a gummy residue obtained was chromatographed over silica gel. Elution with benzene–chloroform (1:1) gave a crystalline residue which was recrystallized from iso-Pr_2O to afford 43 mg of the α,β-unsaturated keton (**14**) mp 126—128°. Continuous elution with the same solvent afforded 110 mg of the *tert*-butoxy adduct (**4**) as an oily sustance.

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