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The Reaction of Lead Tetraacetate with 3β-Hydroxy Steroids

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It was found that the reaction of lead tetraacetate with 3β-hydroxy steroids of the 5α-series gave the corresponding 3β,19-oxido steroids. Only poor yields were obtained in the cases of 3β-hydroxy steroids having no substituent at C-5 (5α-H). Substitution at the 5α-position by an electronegative group such as halogen or acetoxyl enhanced the yield of the 3β,19-oxido compound. The best result was obtained when a steroid was heated with lead tetraacetate in benzene in the presence of calcium carbonate and a trace of benzoyl peroxide.

Keywords——steroids; lead tetraacetate; 3β,19-oxido steroids; steric mechanism; oxidation

Functionalization of non-activated carbon atoms in steroidal compounds has been extensively studied by many workers. The reaction of the 19-methyl group is of special interest, because this reaction is a key step in the synthesis of 19-norsteroids from steroids having a 19-methyl group. Conversion of 3β-acetoxy-5α-halo-6β-hydroxy compounds (I) into 6β,19-oxido compounds (II) by treatment with lead tetraacetate is typical of such reactions.[1,2] Similar reactions of 2β-hydroxy,[3] 4β-hydroxy[3-5] and 11β-hydroxy[4-6] compounds to give the corresponding oxido compounds were also reported. In all the examples described above, the stereochemical relationship of the 19-methyl and hydroxyl groups is 1,3-diaxial. Con-

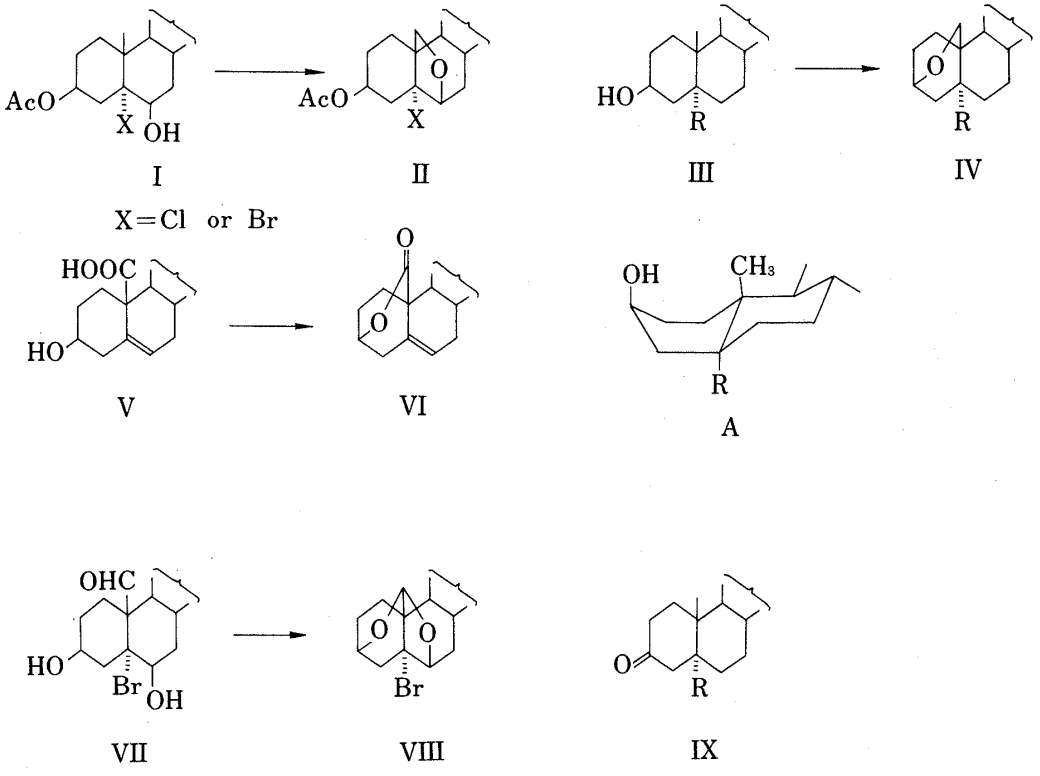

Chart 1

sequently, it can be concluded that such a free radical reaction is possible only when the two groups are stereochemically close.

Such a condition is also satisfied in 3β-hydroxy compounds of the A/B-trans series (III), if they can exist in an A-boat conformation (A). It was reported that 3β-hydroxy-19-oic acid[7] (V) and 3β,6β-dihydroxy-19-al[8] (VII) can be easily transformed into the lactone (VI) and the acetal (VIII), respectively. These results suggest that transformation of the chair conformation of the A-ring in 5α-steroids into the boat conformation is not difficult, even if the chair conformation is more stable. It has been reported by Barns *et al.*[9] and Cross *et al.*[10] that 5α-substituted-3-oxo steroids (IX) are distorted from the chair form on the basis of their optical rotatory dispersion and nuclear magnetic resonance (NMR) spectra. They explained this unusual conformation in terms of the dipole repulsion between the 5α-substituent and 3-oxo group. These observations, suggesting that a 5α-electronegative substituent would cause a conformational change from a chair to a distorted or boat-like conformation, prompted us to study the reaction of lead tetraacetate with 5α-substituted compounds. Thus, 5α,6β-dichloro-3β-hydroxyandrostan-17-one[11] (X) was treated with lead tetraacetate in benzene at reflux temperature to give a new compound in poor yield together with the 3-acetate (major product). In the NMR spectrum of the compound in question the signal of the 19-methyl group had disappeared and two doublets at δ 3.80 and δ 4.65 were observed. Its infrared (IR) spectrum did not exhibit any hydroxyl band. The molecular ion was observed at *m/e* 356 in its mass spectrum. These observations mean that this new compound can be formulated as 5α,6β-dichloro-3β,19-oxidoandrostan-17-one (XI). Some attempts were made to improve the yield by changing the solvent, and by carrying out the reaction in the presence or absence

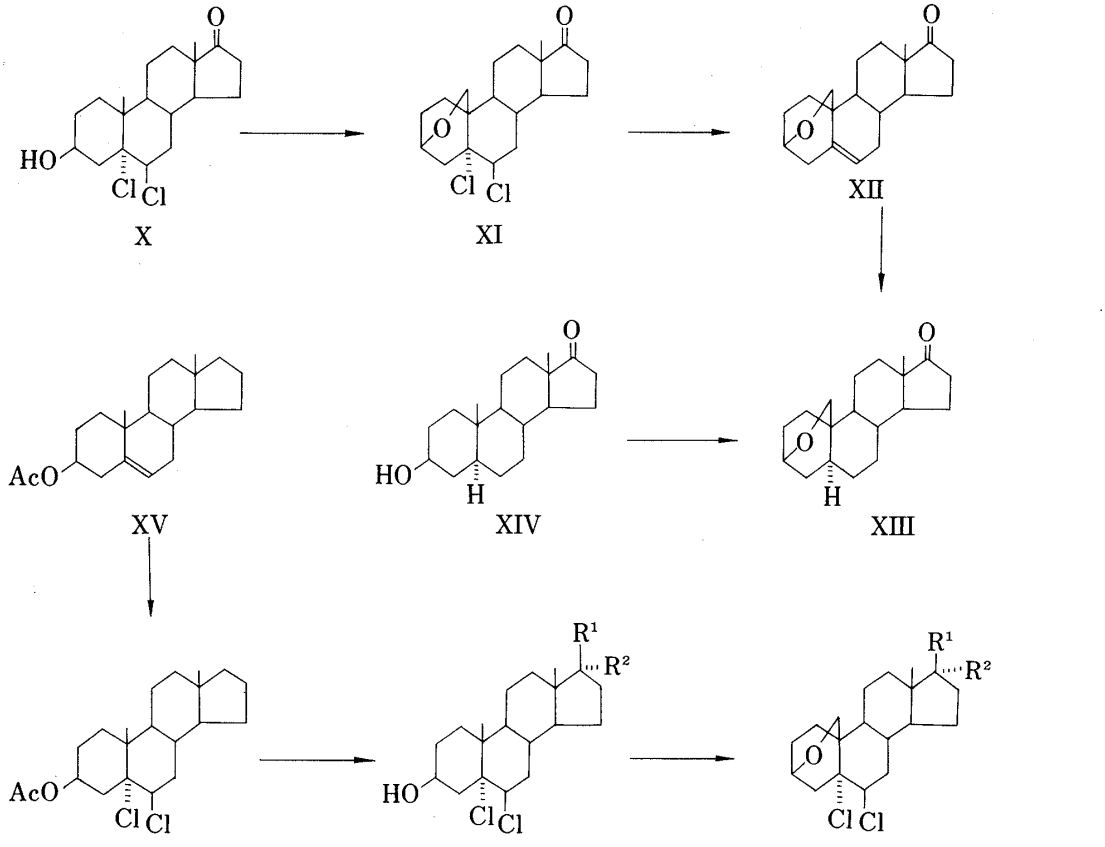

Chart 2

of calcium carbonate,[12] iodine[2] or benzoyl peroxide.[13] It should be noted that the presence of a small amount of benzoyl peroxide induced a marked increase in the yield, whereas a hypoiodate reaction with lead tetraacetate and iodine gave only an unsatisfactory result. The best result was obtained by reaction with lead tetraacetate in the presence of calcium carbonate and benzoyl peroxide. The yield reached 45% as determined by thin-layer chromatographic analysis. 5α,6β-Dichloroandrostan-3β-ol (XVII), 5α,6β-dichloro-3β-hydroxypregnan-20-one (XVIII) and 17α-acetoxy-5α,6β-dichloro-3β-hydroxypregnan-20-one (XIX) were treated with lead tetraacetate to give the corresponding 3β,19-oxido compounds (XX, XXI, and XXII) in reasonable yields, indicating that this reaction is a general one for 5α,6β-dichloro-3β-hydroxy steroids. In all cases, the corresponding 3-acetate was found as a by-product. XVII was synthesized from XV by a modification of the method reported by Cutler *et al.*[14]

In order to determine whether a 5α-unsubstituted 3β-hydroxy compound can be converted to a 3β,19-oxido compound or not, the reaction of 3β-hydroxy-5α-androstan-17-one (XIV)

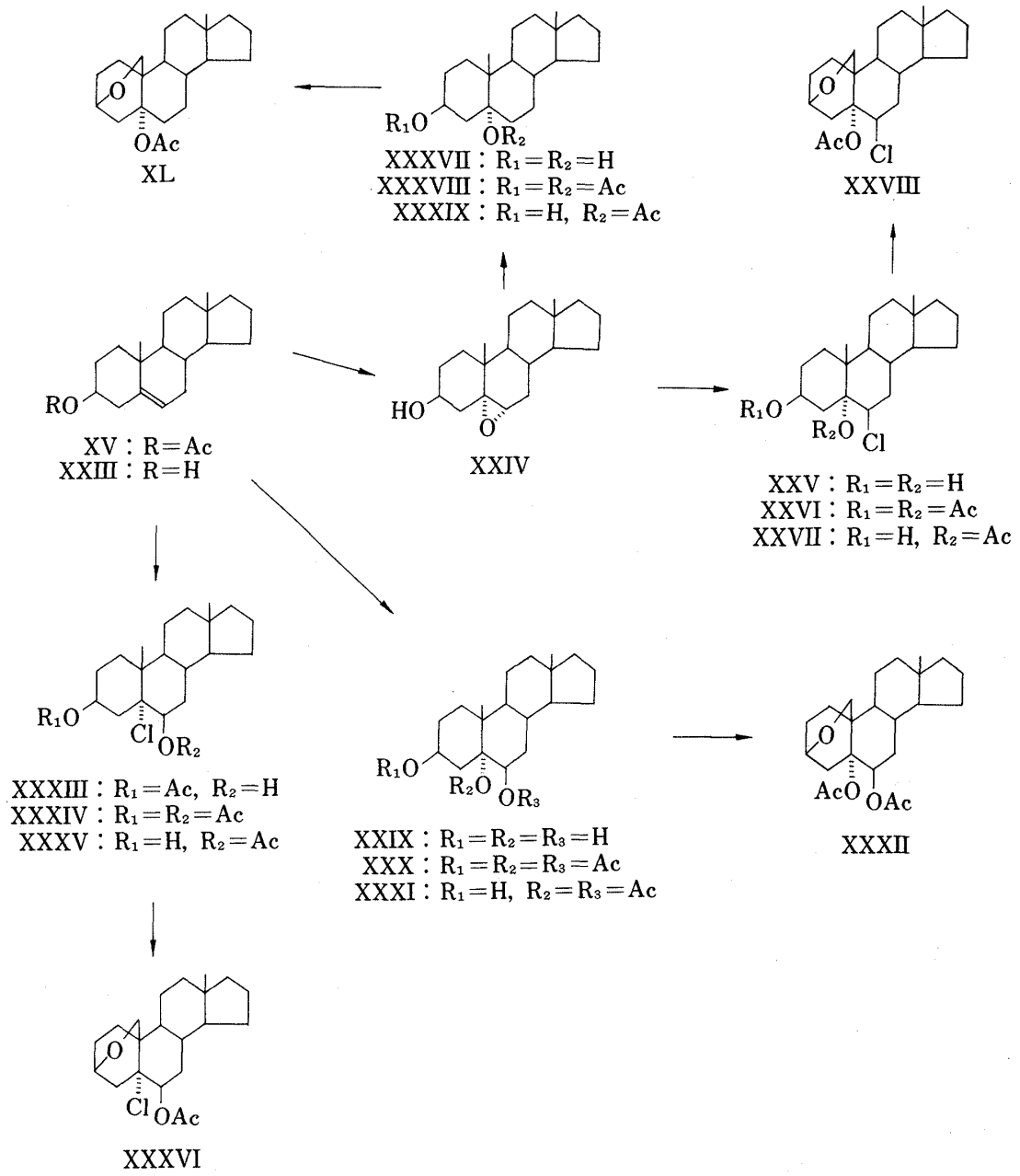

Chart 3

was carried out to give the 3-acetate as a main product, accompanied by a small amount (5%) of the 3β,19-oxido compound (XIII). The structure of the 3β,19-oxido compound (XIII) was easily established from its IR and NMR spectral data. This assignment was also supported by the transformation of XI into XIII; the reaction of XI with zinc dust and acetic acid provided XII, and hydrogenation over 5% palladium-charcoal then gave XIII.

Some 5α-substituted 3β-hydroxy compounds (XXVII, XXXI, XXXV, and XXXIX) were synthesized and treated with lead tetraacetate. These compounds were synthesized by a modification of the reported methods. Epoxidation of XXIII with monoperphthalic acid gave the α-oxide (XXIV), which was treated with hydrochloric acid[15] to afford the chlorohydrin (XXV). Acetylation of XXV with acetyl chloride and dimethylaniline, followed by partial hydrolysis, gave XXVII. Reduction of the α-oxide (XXIV) with lithium aluminum hydride gave the diol[16] (XXXVII), which was converted to its 5-acetate (XXXIX). 5α,6β-Diacetoxyandrostan-3β-ol (XXXI) was obtained by oxidation of XXIII with performic acid,[17] followed by acetylation and partial hydrolysis. Addition of hypochlorous acid[2] to XV gave the chlorohydrine (XXXIII), which, on acetylation and partial hydrolysis, gave the desired XXXV. 5α-Substituted 3β-hydroxy compounds (XXVII, XXXI, XXXV, and XXXIX) were treated with lead tetraacetate in the presence of calcium carbonate and benzoyl peroxide to give the corresponding 3β,19-oxido compounds (XXVIII, XXXII, XXXVI, and XL) in reasonable yields.

It should be pointed out that bond formation between the 3β-oxygen atom and 19-methyl group is possible only when the A-ring exists in the boat conformation (A). However, in the NMR spectra of 5α-substituted 3β-hydroxy compounds, signals of the 3α-proton were observed as multiplets having a very large half-bands width (20—25 Hz), indicating that the 3α-proton is axially oriented. Consequently, ring A in these compounds must have a chair conformation. On the other hand, 3β,19-oxido compounds, which must have ring A in the boat conformation, exhibit 3α-proton multiplets having a rather small half-band width (6—9 Hz) in their NMR spectra. It should be considered, therefore, that 5α-substituted 3β-hydroxy compounds have the boat conformation (A) only in an excited state. This conversion is considered to be made easier by the presence of a substituent at C-5. The very low yields of 3β,19-oxido compounds from 5α-unsubstituted compounds can be explained by the absence of such a substitutent at C-5.

Experimental

Melting points were determined on a Mettler FP21 melting point apparatus. Optical rotations were measured in chloroform solutions unless otherwise stated. NMR spectra were taken on a Hitachi R-20A spectrometer in deuteriochloroform solution with TMS as an internal reference unless otherwise stated. Preparative TLC were carried out on 20×20 cm plates with a 0.25 mm layer of Merck silica gel GF_{254}. IR spectra were taken on a Jasco IRA-1 spectrometer.

General Procedure for the Oxidation of 3β-Hydroxy Steroids with Lead Tetraacetate——A suspension of lead tetraacetate (freshly recrystallized from AcOH, washed with anhydrous ether and dried in a vacuum desiccator over KOH, 4.0 g), benzoyl peroxide (0.1 g) and $CaCO_3$ (2.0 g) in benzene (50 ml) was refluxed for 1 hr with vigorous stirring. A 3β-hydroxy steroid (1.0 g) was added and the mixture was refluxed overnight. H_2O was added and insoluble material was removed by filtration. The filtrate was washed with H_2O, and dried (Na_2SO_4), and the solvent was removed by evaporation. Purification was done by chromatography, TLC and recrystallization.

5α,6β-Dichloro-3β,19-oxidoandrostan-17-one (XI)——The product obtained from X by the general procedure was subjected to preparative TLC (benzene–Me_2CO (19: 1) was used as a developing system). The main fraction was recrystallized from Me_2CO to give XI (0.37 g), mp 181—183° as coloress needles. Further recrystallization from the same solvent afforded an analytical sample, mp 183.5—186°, $[\alpha]_D^{25}$ +71° (c=0.79). IR ν_{max}^{KBr} cm^{-1} 1740 (C=O). NMR δ: 0.88 (3H, s, 18-CH_3), near 3.80 (1H, m, 3α-H), near 4.65 (1H, m, 6α-H), 3.87 and 4.58 (2H, d, J=9.0 Hz, 19-CH_2). MS m/e: 356 (M^+). *Anal.* Calcd for $C_{19}H_{26}Cl_2O_2$: C, 63.86; H, 7.33. Found: C, 63.85; H, 9.19.

In experiments on oxidation with lead tetraacetate in the absence of a catalyst such as benzoyl peroxide, 3β-acetoxy-5α,6β-dichloroandrostan-17-one was obtained as a main product. In all oxidation experiments of 5-substituted compounds described below, the corresponding 3-acetates were obtained as by-products.

5α,6β-Dichloro-3β,19-oxidoandrostane (XX)——XVII (0.50 g) was treated with lead tetraacetate as described in the general procedure. The product was subjected to preparative TLC (benzene–MeOH (9: 1) was used as a developing system). The major fraction (0.12 g) was recrystallized from MeOH to give colorless prisms, mp 134.5—138°, $[\alpha]_D^{28}$ 0° ($c=0.80$). IR ν_{max}^{KBr} no hydroxy band. NMR δ: 0.71 (3H, s, 18-CH_3), 3.86 and 4.58 (2H, d, $J=9.0$ Hz, 19-CH_2) near 3.90 (1H, m, 3α-H), 4.62 (1H, t, $J=2.5$ Hz, 6α-H). *Anal.* Calcd for $C_{19}H_{28}Cl_2O$: C, 66.46; H, 8.22. Found: C, 66.11; H, 8.16.

5α,6β-Dichloro-3β,19-oxidopregnan-20-one (XXI)——The product obtained from XVIII by the general procedure was subjected to preparative TLC (benzene–Me_2CO (9: 1) was used as a developing system) to give XXI as an oily substance (0.30 g). NMR δ: 0.63 (3H, s, 18-CH_3), 2.10 (3H, s, 21-CH_3), 3.83 and 4.56 (2H, d, $J=9.0$ Hz, 19-CH_2), near 3.9 (1H, m, 3α-H), 4.61 (1H, t-like, 6α-H).

17α-Acetoxy-5α,6β-dichloro-3β,19-oxidopregnan-20-one (XXII)——XIX (0.60 g) was treated with lead tetraacetate as described in the general procedure. The product was chromatographed on alumina and material eluted by benzene–ether (9: 1) was subjected to preparative TLC (benzene–Me_2CO (9: 1) was used as a developing system). The main fraction (0.085 g) was recrystallized from Me_2CO to give XXII as colorless prisms, mp 186—190°, $[\alpha]_D^{25}$ −7° ($c=1.00$). IR ν_{max}^{KBr} cm^{-1} 1735 (OAc), 1710 (C=O). NMR δ: 0.65 (3H, s, 18-CH_3), 2.04 (3H, s, –OAc), 2.13 (3H, s, 21-CH_3), 3.84 and 4.57 (2H, d, $J=9.0$ Hz, 19-CH_2), 3.92 (1H, m, 3α-H), 4.65 (1H, t-like, 6α-H). *Anal.* Calcd for $C_{23}H_{32}Cl_2O_4$: C, 62.29; H, 7.27. Found: C, 62.28; H, 7.31.

3β,19-Oxido-5α-androstan-17-one (XIII)——(a) From XII: A mixture of XII (0.135 g), 5% Pd-C (0.135 g) and EtOH (20 ml) was shaken in an H_2 atmosphere for 3 hr at room temperature under atmospheric pressure. After removal of the catalyst by filtration, the solvent was evaporated off. The residue was subjected to preparative TLC to give XIII (0.06 g). Recrystallization from MeOH gave an analytical sample as colorless needles, mp 165.5—168°, $[\alpha]_D^{25}$ +160° ($c=0.25$). IR ν_{max}^{KBr} 1745 (C=O). NMR δ: 0.82 (3H, s, 18-CH_3), 3.72 and 4.04 (2H, d, $J=9.0$ Hz, 19-CH_2), near 3.7 (1H, m, 3α-H). *Anal.* Calcd for $C_{19}H_{28}O_2$: C, 79.11; H, 9.78. Found: C, 79.23; H, 9.81.

(b) From XIV: The oxidation product of XIV (0.50 g) obtained by lead tetraacetate treatment as described in the general procedure was chromatographed on alumina. The material eluted by benzene was subjected to preparative TLC (benzene–Me_2CO (9: 1) was used as a developing system) to give XIV acetate (0.056 g) and XIII (0.025 g). The spectral data and TLC behavior of XIII obtained here were identical with those of the compound described above.

5α-Acetoxy-6β-chloro-3β,19-oxidoandrostane (XXVIII)——XXVII (0.50 g) was treated with lead tetraacetate as described in the general procedure. The product was chromatographed on Florisil, and the material eluted by benzene was subjected to preparative TLC (benzene–Me_2CO (97: 3) was used as a developing system). XXVIII was obtained as an oily material (0.073 g). NMR δ: 0.73 (3H, s, 18-CH_3), 2.05 (3H, s, –OAc), 3.84 (1H, m, 3α-H), 3.76 and 4.56 (2H, d, $J=9.0$ Hz, 19-CH_2), 5.19 (1H, t-like, 6α-H).

5α,6β-Diacetoxy-3β,19-oxidoandrostane (XXXII)——XXXI (1.5 g) was treated with lead tetraacetate as described in the general procedure, and the product was chromatographed on Florisil. The material eluted by benzene–ether (9: 1) (0.91 g) was subjected to preparative TLC (benzene–Me_2CO (9: 1) was used as a developing system) to give XXXII as an oily material. NMR δ: 0.70 (3H, s, 18-CH_3), 2.02 and 2.12 (6H, s, –OAc), 3.74 and 4.35 (2H, d, $J=9.0$ Hz, 19-CH_2), near 3.65 (1H, m, 3α-H), 5.87 (1H, t-like, 6α-H).

6β-Acetoxy-5α-chloro-3β,19-oxidoandrostane (XXXVI)——The product obtained from XXXV by the general procedure was subjected to preparative TLC (benzene–MeOH (9: 1) was used as a developing system). The main fraction (0.26 g) was recrystallized from MeOH to give XXXVI (0.14 g). Further recrystallization from the same solvent afforded an analytical samples as colorless needles, mp 125.5—127°, $[\alpha]_D^{25}$ −31° ($c=0.81$). IR ν_{max}^{KBr} cm^{-1} 1745 (C=O). NMR δ: 0.79 (3H, s, 18-CH_3), 2.14 (3H, s, –OAc), 3.85 and 4.33 (2H, d, $J=9.0$ Hz, 19-CH_2), near 3.85 (1H, m, 3α-H), 5.29 (1H, t, $J=2.5$ Hz, 6α-H). *Anal.* Calcd for $C_{21}H_{31}ClO_3$: C, 68.73; H, 8.51. Found: C, 68.63; H, 8.46.

5α-Acetoxy-3β,19-oxidoandrostane (XL)——XXXIX (0.80 g) was treated with lead tetraacetate as described in the general procedure. The product was chromatographed on Florisil, and the material eluted by benzene–ether (19: 1) was subjected to preparative TLC (benzene–Me_2CO (19: 1) was used as a developing system). The main fraction (0.12 g) was recrystallized from MeOH to give XL (0.073 g) as colorless prisms, mp 113—115°, $[\alpha]_D^{25}$ −26° ($c=1.03$). IR ν_{max}^{KBr} cm^{-1} 1725 (OAc). NMR: 0.67 (3H, s, 18-CH_3), 2.03 (3H, s, –OAc), 3.77 and 4.02 (2H, d, $J=9.0$ Hz, 19-CH_2). *Anal.* Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.89; H, 10.00.

3β-Acetoxy-5α,6β-dichloroandrostane (XVI)——A solution of chlorine in CCl_4 (0.055 g/ml, 25 ml) was added dropwise to an ice-cold solution of XV (5.0 g) in benzene (150 ml). Ether was added and the solution was washed with $Na_2S_2O_3$ solution and H_2O, and dried (Na_2SO_4). Removal of the solvent by evaporation and recrystallization of the residue from Me_2CO gave XVI (4.4 g), mp 157—158.5°. Further recrystallization from the same solvent afforded an analytical sample as colorless plates, mp 160—160.5°, $[\alpha]_D^{28}$ −68° ($c=1.44$). IR ν_{max}^{KBr} cm^{-1} 1745 (OAc). NMR δ: 0.75 (3H, s, 18-CH_3), 1.38 (3H, s, 19-CH_3), 2.03 (3H, s, –OAc), 4.35 (1H, q-like, 6α-H), 5.35 (1H, m, 3α-H). *Anal.* Calcd for $C_{21}H_{32}Cl_2O_2$: C, 65.11; H, 8.33. Found: C, 65.09; H, 8.26.

5α,6β-Dichloroandrostan-3β-ol (XVII)——A solution of XVI (3.0 g) in MeOH (150 ml) and 35% HCl (7.5 ml) was refluxed for 1.5 hr and poured into H_2O. Precipitates were collected by filtration and dried.

Recrystallization from Me_2CO gave XVII (2.26 g), mp 162—166°. Further recrystallization from the same solvent afforded an analytical sample as colorless needles, mp 165.5—166°, $[\alpha]_D^{28}$ −67° (c=1.20). IR ν_{max}^{KBr} cm^{-1} 3320 (OH). NMR δ: 0.75 (3H, s, 18-CH_3), 1.37 (3H, s, 19-CH_3), near 4.3 (2H, m, 3α- and 6α-H). *Anal.* Calcd for $C_{19}H_{30}Cl_2O$: C, 66.08; H, 8.78. Found: C, 66.23; H, 8.84.

3β,19-Oxido-5-androsten-17-one (XII)——A mixture of XI (0.20 g) and Zn dust (0.20 g) in AcOH (10 ml) was stirred at room temperature for 2 hr. Zn cake was removed by filtration and the filtrate was poured into H_2O. The product was extracted with ether and the organic layer was washed with H_2O, 5% Na_2CO_3 and H_2O, and dried (Na_2SO_4). After removal of the solvent, the residue was recrystallized from MeOH to give XII (0.135 g), mp 152—157°. An analytical sample was obtained by further recrystallization from the same solvent as colorless needles, mp 161—165° $[\alpha]_D^{25}$ −17° (c=0.75). IR ν_{max}^{KBr} cm^{-1} 1725 (C=O). NMR δ: 0.87 (3H, s, 18-CH_3), 3.67 (1H, q, J=7.5 Hz, one proton of 19-CH_2) 3.91 (1H, d, J=7.5 Hz one proton of 19-CH_2), near 3.9 (1H, m, 3α-H), 5.5 (1H, m, 6-H).

5α,6α-Epoxyandrostan-3β-ol (XXIV)——XXIII (10.0 g) was added to an ice-cold solution of monoperphthalic acid in ether (0.062 g/ml, 700 ml) and the mixture was stirred until the steroid was dissolved completely. The solution was allowed to stand at room temperature for 2 days, washed with 5% $KHCO_3$ and H_2O, and dried (Na_2SO_4). Removal of the solvent by distillation gave a crystalline material, which was recrystallized from Me_2CO to afford XXIV (5.9 g), mp 156—158°. Further recrystallization from the same solvent afforded an analytical sample as colorless plates, mp 161.5—164.5°, $[\alpha]_D^{28}$ −87° (c=0.92). IR ν_{max}^{KBr} cm^{-1} 3400 (OH). NMR δ: 0.65 (3H, s, 18-CH_3), 1.06 (3H, s, 19-CH_3), 2.90 (1H, d, J=3.0 Hz, 6β-H), 3.7 (1H, m, 3α-H). *Anal.* Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.48; H, 10.35.

6β-Chloroandrostane-3β,5α-diol (XXV)——A solution of XXIV (10.0 g) in CH_2Cl_2 (600 ml) was shaken with 37% HCl (500 ml) for 20 min. The organic layer was washed with H_2O and dried (Na_2SO_4). Removal of the solvent by distillation gave a crystalline material (9.0 g), which was recrystallized from ether–petroleum ether to give XXV (7.3 g), mp 155—156.5°, $[\alpha]_D^{25}$ −43° (c=1.57). IR ν_{max}^{KBr} cm^{-1} 3330 (OH). NMR δ: 0.65 (3H, s, 18-CH_3), 0.86 (3H, s, 19-CH_3), 3.82 (1H, t-like, 6α-H), near 4.0 (1H, m, 3α-H). *Anal.* Calcd for $C_{19}H_{31}ClO_2$: C, 69.80; H, 9.55. Found: C, 69.73; H, 9.38.

6β-Chloro-3β,5α-diacetoxyandrostane (XXVI)——A solution of XXV (2.0 g) in Ac_2O (40 ml) and BF_3-etherate (0.6m l) was warmed on a steam bath for 2 min and allowed to stand at room temperature for 30 min. H_2O was added and the resulting precipitates were collected by filtration, washed with H_2O and dried. Recrystallization from MeOH gave XXVI (1.38 g), mp 163—166°. An analytical sample was obtained by further recrystallization from the same solvent as colorless needles, mp 162—164°, $[\alpha]_D^{25}$ −48° (c=1.36). IR ν_{max}^{KBr} cm^{-1}: 1750, 1735 (OAc). NMR δ: 0.74 (3H, s, 18-CH_3), 1.32 (3H, s, 19-CH_3), 2.00 and 2.07 (6H, s, –OAc), near 4.7 (1H, m, 3α-H), 5.1 (1H, t-like, 6α-H). *Anal.* Calcd for $C_{23}H_{35}ClO_4$: C, 67.72; H, 8.58. Found: C, 67.37; H, 8.82.

5α-Acetoxy-6β-chloroandrostan-3β-ol (XXVII)——A solution of XXVI (1.1 g) in MeOH (110 ml) and 10% H_2SO_4 (17.6 ml) was refluxed for 4 hr. Most of the solvent was removed by distillation and H_2O was added. The product was extracted with ether and the organic layer was washed with H_2O and dried (Na_2SO_4). The solvent was removed by distillation to afford a crystalline material, which was recrystallized from MeOH to give XXVII (0.70 g), mp 179—181°. An analytical sample was obtained by further recrystallization from the same solvent as colorless plates, mp 179—181°, $[\alpha]_D^{25}$ −43° (c=0.92). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1725 (OAc). NMR δ: 0.74 (3H, s, 18-CH_3), 1.30 (3H, s, 19-CH_3), 2.03 (3H, s, –OAc), near 3.7 (1H, m, 3α-H), 5.05 (1H, t-like, 6α-H). *Anal.* Calcd for $C_{21}H_{33}ClO_3$: C, 68.36; H, 9.02. Found: C, 68.54; H, 9.33.

Androstane-3β,5α,6β-triol (XXIX)——A solution of XXIII (16.7 g) in HCOOH (170 ml) was warmed at 80° for 30 min. When it had cooled, 30% H_2O_2 (20 ml) was added and the mixture was allowed to stand overnight. Hot H_2O (600 ml) was added and the precipitates were collected by filtration and washed with H_2O. MeOH (300 ml) and 25% NaOH (20 ml) were added and the mixture was refluxed for 10 min. After most of the MeOH had been removed by distillation, H_2O was added the resulting precipitates were collected by filtration, washed with H_2O and dried. Recrystallization from Me_2CO afforded XXIX (11.7 g), mp 215—217°. Further recrystallization from the same solvent afforded an analytical sample as colorless needles, mp 219—223°, $[\alpha]_D^{25}$ −30° (c=1.12, EtOH). IR ν_{max}^{KBr} cm^{-1} 3400 (OH). NMR (DMSO) δ: 0.67 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3). *Anal.* Calcd for $C_{19}H_{32}O_3$: C, 73.08; H, 10.46. Found: C, 73.95; H, 10.45.

3β,5α,6β-Triacetoxyandrostane (XXX)——A solution of XXIX (5.0 g) and *p*-TsOH (5.0 g) in AcOH (440 ml) and Ac_2O (75 ml) was allowed to stand for 3 days, then poured into H_2O. Precipitates were collected by filtration, washed with H_2O and dried. Repeated recrystallization twice from MeOH afforded an analytical sample as colorless needles, mp 164—171°, $[\alpha]_D^{28}$ −47° (c=1.33). IR ν_{max}^{KBr} cm^{-1} 1740 (OAc). NMR δ: 0.74 (3H, s, 18-CH_3), 1.21 (3H, s, 19-CH_3), 1.99 (9H, s, –OAc), 5.86 (1H, t-like, 6α-H), 4.75 (1H, m, 3α-H). *Anal.* Calcd for $C_{25}H_{28}O_6$: C, 69.09; H, 8.81. Found: C, 69.17; H, 8.87.

5α,6β-Diacetoxyandrostan-3β-ol (XXXI)——A solution of XXX (1.0 g) in MeOH (100 ml) and 10% H_2SO_4 (16 ml) was refluxed for 4 hr and a half of the MeOH was removed by distillation. H_2O was added and the product was extracted with ether. The organic layer was washed with H_2O and dried (Na_2SO_4). The solvent was removed by evaporation and the residue was subjected to preparative TLC to give XXXI (0.85 g). Recrystallization from Me_2CO–hexane gave colorless needles, mp 175—177°, $[\alpha]_D^{25}$ −70° (c=0.87). IR ν_{max}^{KBr} cm^{-1}: 3520 (OH), 1735, 1720 (OAc). *Anal.* Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.76;

H, 9.50.

3β-Acetoxy-5α-chloroandrostan-6β-ol (XXXIII)——A solution of CaClO (8.0 g) in H_2O (300 ml) was added to a solution of XV (5.0 g) in ether (80 ml). AcOH (6.1 ml) was added and the solution was stirred at room temperature for 30 min. Ether and CH_2Cl_2 were then added and the solution was washed with 5% Na_2CO_3 and H_2O, and dried (Na_2SO_4). The solvent was evaporated off and the residue was recrystallized from ether–hexane to give XXXIII (1.82 g), mp 196—199°. An analytical sample was obtained by further recrystallization from Me_2CO–hexane to give colorless plates, mp 198—199°, $[\alpha]_D^{21}$ −55° (c=0.84). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1710 (OAc). NMR δ: 0.71 (3H, s, 18-CH_3), 1.30 (3H, s, 19-CH_3), 2.02 (3H, s, –OAc), 3.95 (1H, m, 6α-H), near 5.30 (1H, m, 3α-H). *Anal.* Calcd for $C_{21}H_{33}ClO_3$: C, 68.36; H, 9.02. Found: C, 68.40; H, 8.87.

5α-Chloro-3β,6β-diacetoxyandrostane (XXXIV)——A solution of XXXIII (1.0 g) in C_5H_5N (10 ml) and Ac_2O (10 ml) was allowed to stand at room temperature overnight, and then poured into H_2O. Precipitates were collected by filtration, washed with H_2O and dried. Recrystallization from MeOH gave XXXIV (0.99 g), mp 181.5—184°. Further recrystallization from the same solvent afforded an analytical sample as colorless needles, mp 184—186°, $[\alpha]_D^{28}$ −83° (c=1.02). IR ν_{max}^{KBr} cm^{-1}: 1750, 1738 (OAc). NMR δ: 0.71 (3H, s, 18-CH_3), 1.27 (3H, s, 19-CH_3), 2.01 and 2.09 (6H, s, –OAc), near 5.3 (1H, m, 3α-H), 5.1 (1H, t-like, 6α-H). *Anal.* Calcd for $C_{23}H_{35}ClO_4$: C, 67.72; H, 8.68. Found: C, 67.20; H, 8.60.

6β-Acetoxy-5α-chloroandrostan-3β-ol (XXXV)——A solution of XXXIV (0.80 g) in MeOH (80 ml) and 10% H_2SO_4 (15 ml) was refluxed for 3 hr, and poured into H_2O. Precipitates were collected by filtration, washed with H_2O and dried. Recrystallization from Me_2CO–hexane gave XXXV (0.59 g), mp 173—177°. Further recrystallization from the same solvent gave an analytical sample as colorless needles, mp 179—180.5°, $[\alpha]_D^{28}$ −92° (c=0.99). IR ν_{max}^{KBr} cm^{-1}: 3530, 3460, 3390 (OH), 1750 (OAc). NMR δ: 0.72 (3H, s, 18-CH_3), 1.25 (3H, s, 19-CH_3), 2.08 (3H, s, –OAc), near 4.3 (1H, m, 3α-H), 5.1 (1H, t-like, 6α-H). *Anal.* Calcd for $C_{21}H_{33}ClO_3$: C, 68.36; H, 9.02. Found: C, 68.40; H, 9.06.

Androstane-3β,5α-diol (XXXVII)——A mixture of XXIV (0.50 g), lithium aluminum hydride (0.75 g) and THF (15 ml) was refluxed for 5 hr and stirred at room temperature overnight. H_2O was added to decompose excess reagent, and the mixture was poured into dilute HCl. The product was extracted with BuOH–ether (1: 2), and dried (Na_2SO_4). Evaporation to dryness *in vacuo* gave crude XXXVII (0.45 g) as a crystalline material. Recrystallization from Me_2CO afforded colorless plates (0.35 g). An analytical sample was obtained by further recrystallization from the same solvent. mp 197.5—199°, $[\alpha]_D^{25}$ −8° (c=0.85). IR ν_{max}^{KBr} cm^{-1}: 3400, 3300 (OH). NMR (DMSO) δ: 0.65 (3H, s, 18-CH_3), 0.86 (3H, s, 19-CH_3), near 4.1 (1H, m, 3α-H). *Anal.* Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.17; H, 11.38.

5α-Acetoxyandrostan-3β-ol (XXXIX)——A solution of XXXVII (3.3 g) in AcCl (42 ml), dimethylaniline (33 ml) and $CHCl_3$ (600 ml) was refluxed for 6 hr then allowed to stand at room temperature overnight. Most of the solvent was removed by distillation and H_2O was added. The product was extracted with ether and the organic layer was washed with 10% HCl and H_2O, and dried (Na_2SO_4). The solvent was removed by distillation to give an oily substance which was chromatographed on Florisil (60 g) to obtain XXXVIII (2.5 g, not pure). IR ν_{max}^{KBr} cm^{-1}: 1740 (OAc). NMR δ: 0.69 (3H, s, 18-CH_3), 1.01 (3H, s, 19-CH_3), 1.98 and 2.06 (6H, s, –OAc), near 4.8 (1H, m, 3α-H).

A solution of crude XXXVIII (1.8 g) and KOH (7.2 g) in MeOH (180 ml) was stirred for 15 min at room temperature and neutralized with 10% HCl. Removal of most of the solvent by distillation afforded a crystalline material, which was recrystallized from Me_2CO to give XXXIX (1.26 g), mp 158—160°. An analytical sample was obtained by further recrystallization from the same solvent as colorless needles, mp 159—160°, $[\alpha]_D^{25}$ +12° (c=0.96). IR ν_{max}^{KBr} cm^{-1} 3380 (OH), 1725 (OAc). NMR δ: 0.69 (3H, s, 18-CH_3), 0.98 (3H, s, 19-CH_3), 2.02 (3H, s, –OAc), near 3.7 (1H, m, 3α-H). *Anal.* Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.23; H, 10.59.

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References and Notes

1) A Bowers, R. Villotti, J.A. Edwards, E. Denot, and O. Halpern, *J. Am. Chem. Soc.*, **84**, 3204 (1962).
2) H. Ueberwasser, K. Heusler, J. Kalvoda, Ch. Meystre, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 344 (1963).
3) K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **45**, 2575 (1962).
4) K. Heusler, *Tetrahedron Lett.*, **1964**, 3975.
5) K. Heusler, J. Kalvoda, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 352 (1963).
6) J. Kolvoda, K. Heusler, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 618 (1963).
7) B. Berkoz, E. Denot, and A. Bowers, *Steroids*, **1**, 251 (1963).
8) M. Akhtar and D.H.R. Barton, *J. Am. Chem. Soc.*, **86**, 1528 (1964).
9) C.S. Barnes and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1962 (1962).
10) A.D. Cross and I.T. Harrison, *J. Am. Chem. Soc.*, **85**, 3223 (1963).

11) H. Mori and J. Yamada, *Chem. Pharm. Bull.*, **11**, 1418 (1963).
12) R.M. Moriarty and T.D. D'Silva, *J. Org. Chem.*, **28**, 2445 (1963).
13) K. Tanabe, R. Takasaki, K. Sakai, R. Hayashi, Y. Morisawa, and T. Hashimoto, *Chem. Pharm. Bull.*, **15**, 15 (1967).
14) F.A. Cutler, Jr., L. Mandell, D. Shew, J.F. Fisher, and J.M. Chemerda, *J. Org. Chem.*, **24**, 1621 (1959).
15) J.S. Mihina, *J. Org. Chem.*, **27**, 2807 (1962).
16) Pl. A. Plattner, H. Heusser, and M. Feurer, *Helv. Chim. Acta*, **32**, 587 (1949).
17) L.F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **71**, 3938 (1949).