Acid-Catalyzed 1,5-Hydride Transfer

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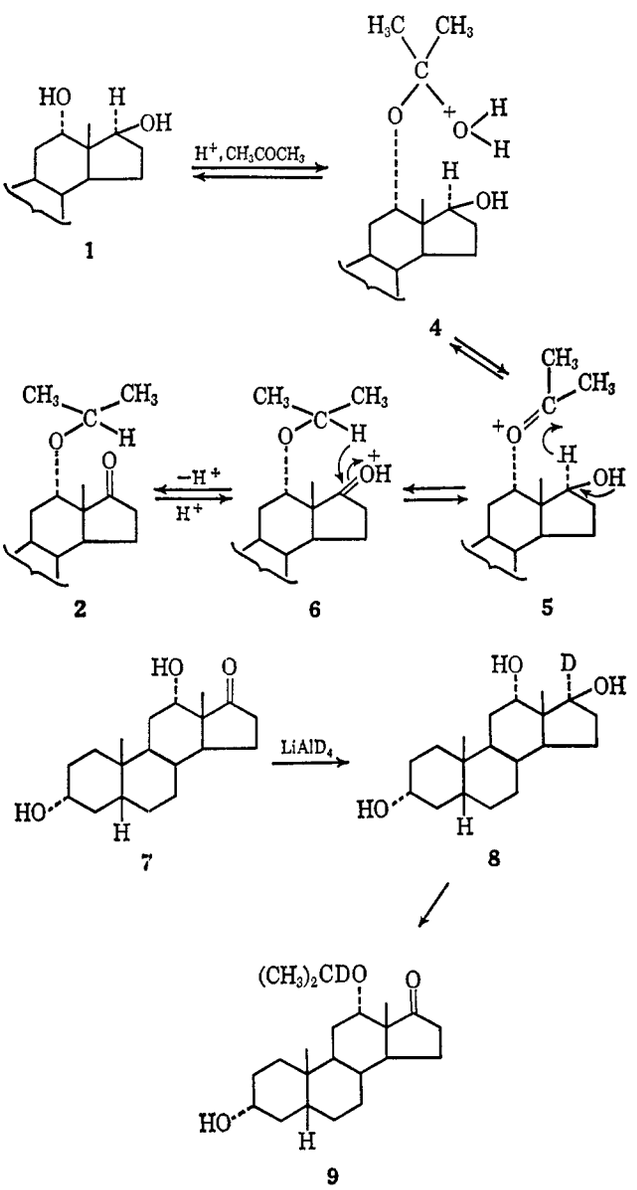
5β-Androstane-3α,12α,17β-triol (1) reacts with acetone to form 3α-hydroxy-12α-isopropoxy-5β-androstan-17-one (2) in a reversible, acid-catalyzed hydride transfer reaction. The corresponding deuterated analog (8) undergoes deuteride transfer to give 9. This reversible reaction has been utilized to protect the 12α- and 17β-hydroxyl groups in 1 during the synthesis of 12α,17β-dihydroxyandrost-4-en-3-one (14).

We have found that 5β-androstane-3α,12α,17β-triol (1)[1] (Scheme I) undergoes an acid-catalyzed hydride transfer reaction to produce 3α-hydroxy-12α-isopropoxy-5β-androstan-17-one (2) when treated with acetone containing a trace of perchloric acid or boron trifluoride. This reaction can be reversed by dissolving 2 in trifluoroacetic acid at room temperature. Alkaline hydrolysis of the resulting mixture of trifluoroacetate esters produces triol 1.

SCHEME I



(1) L. H. Sarett, *J. Am. Chem. Soc.*, **69**, 2899 (1947).

The assigned structure for 2 is based on elemental analysis, the infrared spectrum (λ_{max}^{KBr} 2.86, 5.76 μ), molecular weight determination [calcd 348.5, found 348 (mass spectrum)],[2] and the nuclear magnetic resonance (nmr) spectrum. The protons of the two angular methyl groups (C-18 and C-19) appear as singlets at 0.917 and 0.767 ppm, respectively, which is in good agreement with the predicted positions (0.909 and 0.801 ppm) of these signals calculated by the method of Zuercher[3] for the corresponding C-14 alcohol. The signals for the methyl protons of the isopropoxyl group appear as doublets centered at 1.032 and 1.065 ppm (J = 7 cps). A satisfactory alkoxyl analysis for 2 was not obtained (calcd 16.95, found 2.61), probably because the hydride transfer reaction was faster than isopropoxyl cleavage under the acidic conditions of the assay.[4] However, reduction of 2 with lithium aluminum hydride afforded 12α-isopropoxy-5β-androstane-3α,17β-diol (3) which could not undergo the hydride transfer reaction and for which an acceptable alkoxyl value was found.[4]

A plausible mechanism which accounts for the reversible nature of the hydride transfer reaction involves formation of a protonated intermediate hemiketal 4. Elimination of water from 4 leads to oxonium ion 5, which is in equilibrium with a second oxonium ion (6) through a hydride shift. Loss of a proton from 6 affords 2, with each step in this series reversible.[5]

To obtain evidence supporting this intramolecular hydride transfer mechanism, we prepared 5β-androstane 3α,12α,17β-triol-17α-*d* (8) from 3α,12α-dihydroxy-5β-anrostan-17-one (7)[6] by lithium aluminum deuteride reduction.

Treatment of 8 with boron trifluoride in acetone furnished 3α-hydroxy-12α-(isopropoxy-2′-*d*)-5β-androstan-17-one (9). That deuterium transfer had occurred was clearly shown by the nmr spectrum of 9. Instead of the doublets at 1.032 and 1.065 ppm, which were observed in the spectrum of 2, only singlets were observed at these same positions. These signals were slightly broadened owing to the coupling with the adjacent deuterium atom, as would be expected.[7]

The nmr spectrum of the deuterated triol 8 in dimethyl sulfoxide solution exhibited two doublets centered at 4.20 and 4.50 ppm which were assigned to the

(2) We thank Dr. R. Breslow of Columbia University for this determination.

(3) R. F. Zuercher, *Helv. Chim. Acta*, **46**, 2054 (1963).

(4) A. Steyermark, *J. Assoc. Offic. Agr. Chemists*, **39**, 401 (1956).

(5) See R. B. Woodward, F. Sondheimer, and Y. Mazur, *J. Am. Chem. Soc.*, **80**, 6693 (1958); R. K. Hill and R. M. Carlson, *ibid.*, **87**, 2772 (1965).

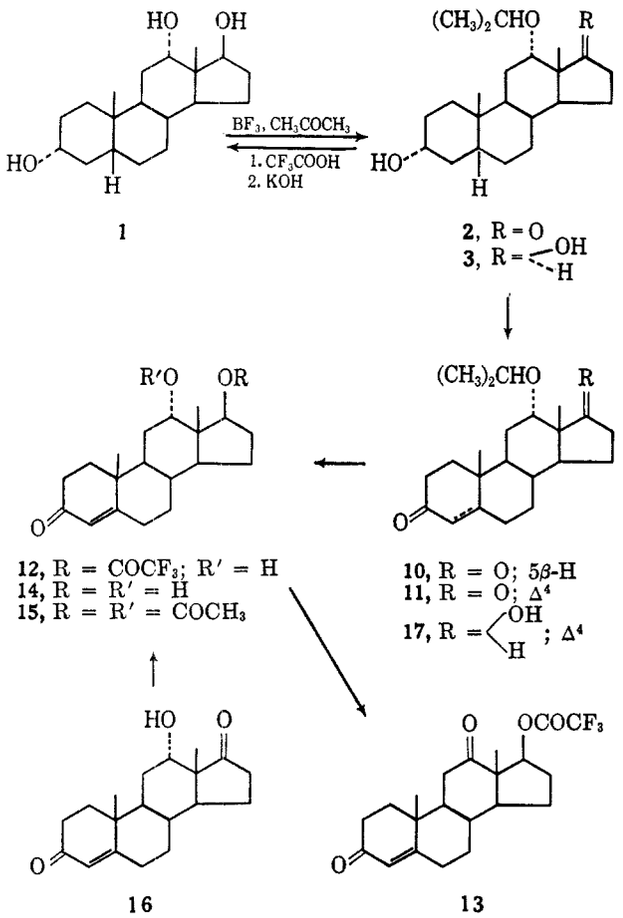
(6) W. J. Adams, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 1825 (1954).

(7) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 80.

two secondary hydroxyl protons at C-3 and C-12, and a singlet at 4.10 ppm which was assigned to the hydroxyl proton at C-17. These assignments were confirmed by deuterium exchange.[8]

The reversible nature of this hydride transfer reaction suggested that it might be used to protect the 12α- and 17β-hydroxyl groups of triol **1** (Scheme II) during

SCHEME II



its conversion to 12α,17β-dihydroxyandrost-4-en-3-one (**14**). Thus, N-bromoacetamide oxidation of **2** afforded 12α-isopropoxy-5β-androstane-3,17-dione (**10**), which was brominated with 1 molar equiv of bromine; the crude 4β-bromo derivative was dehydrobrominated[9] to produce 12α-isopropoxyandrost-4-ene-3,17-dione (**11**). Treatment of **11** with trifluoroacetic acid furnished a mixture of trifluoroacetate esters from which 12α,17β-dihydroxyandrost-4-en-3-one 17-trifluoroacetate (**12**) could be isolated by fractional crystallization. Chromium trioxide–pyridine oxidation of **12** to 17β-hydroxyandrost-4-ene-3,12-dione trifluoroacetate (**13**) (λ_{max}^{KBr} 5.65, 5.88, 5.96 μ) established the structure of **12** as the 17-trifluoroacetate ester. Alkaline hydrolysis of the mixture of esters remaining after **12** was isolated produced the desired product **14**. Acetylation of **14** afforded 12α,17β-dihydroxyandrost-4-en-3-one diacetate (**15**).

Diacetate **15** was also obtained from the known compound 12α-hydroxyandrost-4-ene-3,17-dione (**16**)[10] by the following method. Lithium aluminum hydride reduction of **16** gave a mixture of triols which was converted to a single dihydroxy ketone (**14**) by selective oxidation of the allylic alcohol function with dichlorodicyanoquinone.[11] Acetylation of **14** provided its diacetate **15**, which was more amenable to purification.

Reduction of 3,17-dione **11** with lithium aluminum hydride to a mixture of diols, followed by dichlorodicyanoquinone oxidation, gave 17β-hydroxy-12α-isopropoxyandrost-4-en-3-one (**17**), for which a satisfactory alkoxyl analysis was obtained.[4]

Experimental Section

Melting points are corrected. Specific rotations were measured in chloroform solution (1%) at 25°, ultraviolet spectra were recorded in 95% ethanol on a Cary-15 spectrometer, infrared spectra were obtained from potassium bromide disks on a Perkin-Elmer 21 spectrometer, and nmr spectra were obtained in deuteriochloroform or dimethyl sulfoxide solution (20%) with tetramethylsilane as an internal standard on a Varian A-60 spectrometer.

3α-Hydroxy-12α-isopropoxy-5β-androstan-17-one (2).—A suspension of 9.7 g (31.3 mmoles) of 5β-androstane-3α,12α,17β-triol (**1**)[1] in 600 ml of acetone was treated with 12 ml of boron trifluoride etherate and a clear solution was obtained in *ca.* 10 min. The solution was kept at room temperature for 2 hr and then poured into 300 ml of saturated sodium bicarbonate solution diluted with 300 ml of water. The acetone was removed by warming under reduced pressure and the aqueous residue was extracted with 600 ml of ether. The layers were separated and the extracts were washed with water and saturated salt solution and dried over powdered magnesium sulfate, then concentrated to dryness. Recrystallization of the residue from ether–pentane gave 5.85 g of title compound **2**, mp 138–148°. Two further recrystallizations from ether–pentane afforded 3.5 g of material which melted at 148–150°; its molecular weight was 348[2] (calcd 348.5). The analytical sample was prepared by recrystallization from acetonitrile: mp 150.5–152°; $[\alpha]_D$ +172.0°; λ_{max} 2.86, 5.76 μ; nmr ($CDCl_3$), *t*-CH_3 at C-18, 0.917 ppm, *t*-CH_3 at C-19, 0.767 ppm, two *sec*-CH_3, 1.032 and 1.065 ppm (J = 7 cps).

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.59; H, 10.27.

Reverse Hydride Transfer Reaction on 3α-Hydroxy-12α-isopropoxy-5β-androstan-17-one (2).—A solution of 0.40 g (1.14 mmoles) of **2** in 5 ml of trifluoroacetic acid was kept overnight at room temperature. Ether (200 ml) and 40 ml of 10% sodium carbonate solution were added and the layers were separated. The ether layer was washed with saturated salt solution, dried over powdered magnesium sulfate, and then concentrated to dryness. The clear, colorless, oily residue was hydrolyzed by dissolving it in 20 ml of methyl alcohol, adding 1.0 ml of 30% aqueous potassium hydroxide, and heating the solution under reflux for 30 min. The bulk of the methyl alcohol was removed by warming under reduced pressure and the residue was partitioned between 200 ml of methylene dichloride and 25 ml of water. The layers were separated and the organic layer was washed with saturated salt solution and dried over powdered magnesium sulfate, then concentrated to a small volume, and acetone was added. Upon cooling, 0.10 g of 5β-androstane-3α,12α,17β-triol (**1**) was obtained, mp 235–237°. Further concentration of the mother liquor afforded 0.10 g of a second crop, mp 236–237° (57% yield). A mixture melting point of either crop with a sample prepared previously,[1] mp 235–237°, was not depressed and the infrared spectra were identical.

12α-Isopropoxy-5β-androstane-3α,17β-diol (3).—To a stirred suspension of 3.0 g of lithium aluminum hydride in 300 ml of tetrahydrofuran was added dropwise a solution of 3.0 g (8.6 mmoles) of 3α-hydroxy-12α-isopropoxy-5β-androstan-17-one (**2**) in 300 ml of tetrahydrofuran and the mixture was heated under reflux for 18 hr. The excess hydride was decomposed by careful addition of 6 ml of water, the mixture was filtered through Celite, and the filter cake was washed with tetrahydrofuran. The filtrate was concentrated to dryness and the residue was crystal-

(8) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).
(9) R. Joly, J. Warnant, G. Nomine, and D. Bertin, *Bull. Soc. Chim. France*, 366 (1958).
(10) H. Reich, *Helv. Chim. Acta*, **28**, 863 (1945).
(11) E. Caspi and H. Zajac, *J. Chem. Soc.*, 586 (1964).

lized from ether–pentane to furnish 2.2 g (73% yield) of title compound **3**, mp 177–178°. One further recrystallization from ether–pentane afforded the analytical sample, mp 178–180°, $[\alpha]_D$ +78.7°.

Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93; PrO, 16.86. Found: C, 75.53; H, 11.04; PrO, 16.69.

5β-Androstane-3α,12α,17β-triol-17α-*d* (8).—To a stirred suspension of 0.68 g (16 mmoles) of lithium aluminum deuteride[12] in 50 ml of tetrahydrofuran was added dropwise a solution of 4.00 g (13.0 mmoles) of 3α,12α-dihydroxy-5β-androstan-17-one (**7**)[6] in 50 ml of tetrahydrofuran and the mixture was heated under reflux for 5 hr. The excess hydride was decomposed by careful addition of 1.4 ml of water in 5 ml of tetrahydrofuran and, after dilution with 100 ml of tetrahydrofuran, the mixture was filtered and the precipitate was washed with two 50-ml portions of the same solvent. The filtrate and washes were combined and concentrated to dryness, and the residue was recrystallized from methylene dichloride–acetone to produce 2.40 g (60% yield) of title compound **8**: mp 235–237°; nmr (dimethyl sulfoxide), OH at C-17, 4.10 ppm (singlet), two *sec*-OH, 4.20 ppm (J = 4 cps) and 4.50 ppm (J = 4 cps).[8]

3α-Hydroxy-12α-(isopropoxy-2′-d)-5β-androstan-17-one (9).—Treatment of 5β-androstane-3α,12α,17β-triol-17α-*d* (**8**) under the same conditions described above for the nondeuterated analog **1**, gave title compound **9** in 37% yield: mp 149–151°; nmr ($CDCl_3$), four unsplit CH_3, 0.767, 0.917, 1.032, and 1.065 ppm.

Anal. Calcd for $C_{22}H_{35}DO_3$: C, 75.60; H, 10.67. Found: C, 75.76; H, 10.72.

12α-Isopropoxy-5β-androstane-3,17-dione (10).—A solution of 36.0 g (0.103 mole) of 3α-hydroxy-12α-isopropoxy-5β-androstan-17-one (**2**) in 600 ml of *t*-butyl alcohol containing 25 ml of water, 25 ml of pyridine, and 17.8 g (0.131 mole) of N-bromoacetamide was kept overnight at room temperature in the dark and then poured into 4 l. of cold water containing 36 g of sodium sulfite. The aqueous mixture was extracted with three 1-l. portions of methylene dichloride and the combined extracts were washed with dilute hydrochloric acid, dilute sodium hydroxide, water, and saturated salt solution, and dried over powdered magnesium sulfate, then concentrated to dryness. Crystallization of the residue from ether–pentane containing a trace of methylene dichloride afforded 16.3 g of title compound **10**, mp 112.5–115°. A 3.0-g portion was recrystallized once from ether–pentane to give 2.1 g of analytically pure material, mp 113–115°, $[\alpha]_D$ +163.5°. An additional 11.7 g (77% total yield) of product, mp 113–116°, was obtained by saturation of the above aqueous layer with ammonium sulfate, re-extraction with methylene dichloride, combination of this extracted material with that from the two recrystallization mother liquors, and purification by chromatography on silica gel.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.33; H, 9.83.

12α-Isopropoxyandrost-4-ene-3,17-dione (11).—To a stirred solution of 25.5 g (73.5 mmoles) of 12α-isopropoxy-5β-androstane-3,17-dione (**10**) in 150 ml of acetic acid containing 1 drop of 30% hydrogen bromide in acetic acid was added dropwise 11.75 g (1 equiv) of bromine in 150 ml of acetic acid. The reaction mixture was at once poured into 2 l. of water and the bulk of the acid was neutralized by adding *ca.* 1.5 l. of 10% sodium carbonate solution. Ether was added, the layers were separated, and the organic layer was washed with water, saturated sodium bicarbonate solution, and saturated salt solution, and dried over powdered magnesium sulfate, then concentrated to dryness. The brown, viscous, oily 4β-bromo derivative (34 g), thus obtained, was used without further purification. The oil was dissolved in 250 ml of dimethylformamide and stirred with 22 g of lithium carbonate and 25 g of lithium bromide for 18 hr with heating on a steam bath. Ether and water were added and the layers were separated. The ether layer was washed with water and saturated salt solution and dried over powdered magnesium sulfate, then concentrated to dryness. The residue was recrystallized twice from methyl alcohol to furnish 11.0 g (43% yield) of title compound **11**, mp 161–162°. One further recrystallization from the same solvent afforded the analytical sample: mp 162–164°; $[\alpha]_D$ +222.1°; λ_{max} 240 mμ (ε 16,200).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.71; H, 9.36. Found: C, 76.86; H, 9.10.

(12) Volk Radiochemical Co., Skokie, Ill.

Reverse Hydride Transfer Reaction on 12α-Isopropoxyandrost-4-ene-3,17-dione (11).—A solution of 8.0 g (23.2 mmoles) of 12α-isopropoxyandrost-4-ene-3,17-dione (**11**) in 50 ml of trifluoroacetic acid was kept for 22 hr at room temperature and then poured into 250 ml of 10% sodium carbonate solution. Additional sodium carbonate solution was added until the mixture was alkaline, ether was added, and the layers were separated. The ether layer was washed with saturated salt solution, dried over powdered magnesium sulfate, and then concentrated to dryness. The sticky crystalline residue was recrystallized twice from methylene dichloride–ether to furnish 2.50 g of 12α,17β-dihydroxyandrost-4-en-3-one 17-trifluoroacetate (**12**), mp 213–216°. The residue from the combined mother liquors afforded 0.40 g of material, mp 205–212°, upon crystallization from ether–pentane. A further recrystallization from acetonitrile gave 0.28 g of **12**, mp 215–217°. The two crops were combined (2.78 g, 30% yield) and recrystallized from acetonitrile to produce the analytical sample (2.20 g): mp 218–219°; $[\alpha]_D$ +58.9°; λ_{max} 241 mμ (ε 16,500); λ_{max} 2.94 (OH at C-12), 5.60 ($OCOCF_3$ at C-17), 6.01 μ (conjugated CO at C-3).

Anal. Calcd for $C_{21}H_{27}F_3O_4$: C, 62.99; H, 6.80; F, 14.23. Found: C, 63.00; H, 6.58; F, 14.13.

All mother liquors were combined and concentrated to dryness to give 7.5 g of an oil which was dissolved in 500 ml of methyl alcohol, treated with 10 g of potassium hydroxide in 25 ml of water, and heated under reflux for 30 min. The solvents were removed by warming under reduced pressure and the residue was partitioned between 500 ml of methylene dichloride and 60 ml of water. The organic layer was separated, washed with water and saturated salt solution, dried over powdered magnesium sulfate, and concentrated to give 5.2 g of a brown oil which was chromatographed on 225 g of silica gel. Elution with 1:9 methylene dichloride–ether afforded 0.65 g of residue which was recrystallized from methyl alcohol to furnish 0.40 g of starting material **11**, mp 159–163°. Elution with 1:9 methyl alcohol–ether afforded, after two recrystallizations from ethyl acetate, 2.03 g of **12α,17β-dihydroxyandrost-4-en-3-one (14)**, mp 148–150°. One further recrystallization from the same solvent furnished the analytical sample: mp 150–152°; $[\alpha]_D$ +129.1°; λ_{max} 241 mμ (ε 16,300); λ_{max} 2.94 (OH at C-12 and C-17), 6.04 (conjugated CO at C-3), 6.21 μ (C=C).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.66; H, 9.10.

17β-Hydroxyandrost-4-ene-3,12-dione Trifluoroacetate (13).—A solution of 1.33 g (3.3 mmoles) of 12α,17β-dihydroxyandrost-4-en-3-one 17-trifluoroacetate (**12**) in 8 ml of pyridine was added to 2.36 g of chromium trioxide in 25 ml of pyridine. The mixture was kept overnight at room temperature, diluted with hot benzene and filtered through Celite, and the filter cake was rinsed with two portions of hot benzene. The filtrate and washes were combined, diluted with ether, and washed with water, 2 *N* hydrochloric acid, 2 *N* sodium hydroxide, water, and saturated salt solution, dried over powdered magnesium sulfate, and then concentrated to dryness to give *ca.* 0.5 g of white, crystalline residue. The aqueous washes were reextracted with methylene dichloride to furnish an additional 0.33 g of crystalline material. Chromatography of the total product on silica gel and elution with methylene dichloride–ether–pentane (20:25:55) afforded (after recrystallization from acetone–hexane) 0.25 g (19% yield) of the title compound **13**: mp 216–218°; $[\alpha]_D$ +141.0°; λ_{max} 238 mμ (ε 16,700); λ_{max} 5.65 ($OCOCF_3$ at C-17), 5.88 (CO at C-12), 5.96 (conjugated CO at C-3), 6.19 μ (C=C).

Anal. Calcd for $C_{21}H_{25}F_3O_4$: C, 63.30; H, 6.33; F, 14.31. Found: C, 63.22; H, 6.08; F, 14.19.

12α,17β-Dihydroxyandrost-4-en-3-one Diacetate (15). A. From 12α,17β-Dihydroxyandrost-4-en-3-one (14).—A 0.90 g. sample of 12α,17β-dihydroxyandrost-4-en-3-one (**14**) prepared above was acetylated with acetic anhydride and pyridine and the product recrystallized from ether–pentane to give 0.67 g (58% yield) of 12α,17β-dihydroxyandrost-4-en-3-one diacetate (**15**), mp 192–195°, and undepressed upon admixture with a sample, mp 191–194°, described below; the infrared spectra of the two samples were identical.

B. From 12α-Hydroxyandrost-4-ene-3,17-dione (16).—A solution of 1.70 g (5.62 mmoles) of 12α-hydroxyandrost-4-ene 3,17-dione (**16**)[10] in 175 ml of tetrahydrofuran was added dropwise to a stirred suspension of 1.70 g of lithium aluminum hydride in 175 ml of tetrahydrofuran and the mixture heated under reflux for 5 hr. Water (3.5 ml) was added dropwise, the insoluble material was removed by filtration through Celite, and the fil-

trate was concentrated to dryness. The viscous, oily residue was dissolved in 25 ml of dioxane, treated with 1.65 g (7.3 mmoles) of dichlorodicyanoquinone, and stirred for 2 hr at room temperature. The precipitate which had formed was removed by filtration and washed with several portions of dioxane and the combined filtrate and washings concentrated to dryness. The residue was dissolved in methylene dichloride, washed with 2 *N* sodium hydroxide and water, and dried over powdered magnesium sulfate, then evaporated to dryness, and the oily residue was chromatographed on silica gel. Elution with 5% methanol in ether afforded 0.93 g of oil which was shown by thin layer chromatography on silica gel G (1:9 methanol–ether) to be mainly 12α,17β-dihydroxyandrost-4-en-3-one (**14**), but which could not be induced to crystallize from ethyl acetate. Acetylation of the crude oil with acetic anhydride and pyridine and purification of the product by recrystallization from ether–pentane containing a trace of methylene dichloride gave 0.60 g of **12α-17β-dihydroxyandrost-4-en-3-one diacetate** (**15**), mp 191–194°. The analytical sample was prepared by recrystallization from acetone–hexane: mp 194–196°; $[\alpha]D$ +130.2°; λ_{max} 240 mμ (ε 17,300); λ_{max} 5.73, 5.77, and 7.92 ($OCOCH_3$ at C-12 and C-17), 6.00 (conjugated CO at C-3), and 6.19 μ (C=C).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.84; H, 8.10.

17β-Hydroxy-12α-isopropoxyandrost-4-en-3-one (**17**).—To a stirred suspension of 3.45 g of lithium aluminum hydride in 300 ml of tetrahydrofuran was added dropwise a solution of 3.45 g (10.0 mmoles) of 12α-isopropoxyandrost-4-ene-3,17-dione (**11**) in 300 ml of tetrahydrofuran and the mixture heated under reflux for 18 hr. Water (7 ml) was added cautiously; the precipitate was removed by filtration through Celite and washed with tetrahydrofuran. The combined filtrate and washings were concentrated to dryness to furnish a white, crystalline residue which was dissolved in 50 ml of dioxane and treated with 3.0 g (13 mmoles) of dichlorodicyanoquinone. The resulting solution was stirred for 3 hr at room temperature and the precipitate which formed during that time was collected and washed with dioxane. The filtrate and washings were combined and concentrated under reduced pressure at <50°; the residue was dissolved in methylene dichloride, washed with 2 *N* sodium hydroxide and water, dried over powdered magnesium sulfate, then concentrated to dryness. The red, oily residue was crystallized from ether–pentane to produce 2.2 g of material, mp 94–99°. Two further recrystallizations from the same solvent mixture afforded 1.57 g (45% yield) of title compound **17**: mp 93–96°; $[\alpha]D$ +125.8°; λ_{max} 243 mμ (ε 14,800); λ_{max} 3.00 (OH at C-17), 5.96 (conjugated CO at C-3), 6.19 μ (C=C).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; PrO, 17.05. Found: C, 76.14; H, 9.80; PrO, 17.38.

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17β Alkylation of a 17-Keto Steroid by Alkylmagnesium Halides

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The reaction of a 12α-hydroxy-17-keto steroid with methylmagnesium bromide to give both epimeric 17-methyl derivatives and with allylmagnesium bromide to give only the 17β-allyl derivative is described. Chemical evidence for the configurations of these products is presented.

Grignard addition to a 17-keto steroid generally affords the 17β-hydroxy-17α-alkyl derivative as the only product isolated.[1] However, in the large-scale preparation of 17α-methyltestosterone involving the addition of methylmagnesium bromide to dehydroepiandrosterone, a small amount of the 17β-methyl isomer was isolated.[2]

We have found that addition of methylmagnesium bromide to 3α,12α-dihydroxy-5β-androstan-17-one (**1**)[3] afforded both the 17α- and 17β-methyl isomers (**2** and **3**), respectively, and the 17α-methyl isomer predominated. Unexpectedly, addition of allylmagnesium bromide to **1** furnished the **17β-allyl derivative 14** in 81% yield as the only product isolated. This paper reports the proof of structure for these products and some related transformations.

Treatment of 3α,12α-dihydroxy-5β-androstan-17-one (**1**) with excess methylmagnesium bromide in ether–tetrahydrofuran at reflux temperature for 40–96 hr afforded the 17α-methyl derivative **2** in 34–46% yield and the 17β-methyl derivative **3** in 4–15% yield. The best yield of both derivatives was obtained by crystallization of **2** from acetone followed by acetylation of the residue from the mother liquor and chromatography to give 17α-methyl-5β-androstane-3α,12α,17β-triol 3,12-diacetate (**4**) and, finally, hydrolysis of the noncrystalline chromatography fractions to a mixture from which **3** could be separated by crystallization.

The configuration at C-17 in products **2** and **3** was determined by preparation of the corresponding diacetates, **4** and **5**, respectively, followed by hydrolysis of each diacetate in aqueous methanolic potassium hydroxide at reflux temperature for 30 min. In the case of the 17α-methyl diacetate **4**, only the 3α-acetoxy group was hydrolyzed under the reaction conditions, and the 12α-monoacetate **6** was obtained. Resistance to hydrolysis by a 12α-acetate because of the hindrance provided by a 17α-methyl substituent has been encountered in other steroid derivatives.[4] Both acetoxy groups of the 17β-methyl diacetate **5** were hydrolyzed under the same conditions and triol **3** was formed. Hydrolysis of the 12α-acetate in **5** should be even faster than that of the 3α-acetate, since the 17α-hydroxyl group bears a 1,3-diaxial relationship to the 12α-substituent and thus can assist in its hydrolysis.[5]

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