of 0.33 *N* sulfuric acid was allowed to stand at room temperature for 48 hr, at which time no starting material remained. The product was recrystallized from methanol to yield 23 mg of **3β-(N-acetylureido)-5α-androstane-4β,5,17β-triol 17-monoacetate** (**12a**), mp 254–254.5°; $[\alpha]D$ 9.5° (ethanol); tlc, R_f = 0.21 (ethyl acetate); ir 3575, 3450, 3335, 3220, 3105, 1733, 1672, 1530, 1250 (br), 1050, 1028 cm^{-1}; nmr δ 0.77 (s), 1.13 (s), 2.03 (s), 2.10 (s), 3.50 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{24}H_{38}N_2O_6 \cdot {}^1/_2H_2O$: C, 62.72; H, 8.55; N, 6.10. Found: C, 62.48; H, 8.67; N, 6.06.

A solution of 56 mg of 3β-(N-acetylureido)-5α-androstane-4β,5,17β-triol 17-monoacetate (**12a**) in 1 ml of pyridine and 1 ml of acetic anhydride was allowed to stand for 5 days at room temperature. The reaction product was separated by a preparative thin-layer chromatogram of silica gel G in ethyl acetate–cyclohexane (7:3) to give 55 mg of **3β-(N-acetylureido)-5α-androstane-4β,5,17β-triol 4,17-diacetate** (**12b**). Recrystallization from methanol afforded diacetate **12b**, mp 233–234.5°; $[\alpha]D$ 15.7°; tlc, R_f = 0.22 (ethyl acetate–cyclohexane 7:3); ir 3600 (sh), 3490, 3300, 3150, 1745, 1720, 1695, 1548, 1505, 1245 (br), 1045, 1025 cm^{-1}; nmr δ 0.78 (s), 1.11 (s), 2.03 (s), 2.13 (s), 4.50 (m), 4.63 (t, J = 8 cps), and 4.97 ppm (m).

Anal. Calcd for $C_{26}H_{40}N_2O \cdot H_2O$: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.41; H, 7.99; N, 5.38.

Mixture (3:2) of 3β-(N-Acetylureido)-4β,5-oxido-5β-androstan-17β-ol Acetate (7b) and 3β-(N-Acetylureido)-4α,5-oxido-5α-androstan-17β-ol Acetate (8b).—A solution of 100 mg of the 3:2 mixture of 3β-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol acetate (**7b**) and its 4α,5α-epoxide isomer **8b** in 20 ml of acetone and 2.5 ml of 0.33 *N* sulfuric acid was kept at room temperature. After 16 hr, the 4α,5α-epoxide isomer had completely disappeared as judged by thin layer chromatography. After 48 hr, no evidence for the presence of the 4β,5β epoxide was obtained and the mixture was worked up as usual. Recrystallization from methanol afforded 49 mg of **3β-(N-acetylureido)-5α-androstane-4β,5,17β-triol 17-monoacetate** (**12a**), mp 256–257°. An additional 16 mg of **12a** was obtained from the mother liquor on preparative thin layer chromatography on silica gel G with ethyl acetate.

3β-Ureido-4α,5-oxido-5α-androstan-17β-ol Acetate (8a).—A solution of 12 mg of 3β-ureido-4α,5-oxido-5α-androstan-17β-ol acetate (**8a**) in 2 ml of acetone and 0.21 ml of 0.33 *N* sulfuric acid yielded a precipitate immediately. The mixture was allowed to stand for 48 hr. The starting material was recovered unchanged after neutralization with sodium carbonate solution.

Registry No.—**1a**, 20446-36-0; **1b**, 20446-37-1; **2a**, 20446-38-2; **2b**, 20446-39-3; **3a**, 20446-40-6; **3b**, 20446-41-7; **4a**, 17320-53-5; **4b**, 20446-43-9; **5**, 20446-44-0; **6b**, 20446-45-1; **7b**, 20446-46-2; **8a**, 20446-47-3; **10a**, 20446-48-4; **10b**, 20446-49-5; **11a**, 20446-50-8; **11b**, 20446-51-9; **11c**, 20446-52-0; **12a**, 20446-59-7; **12b**, 20446-53-1; **13a**, 20446-54-2; **13b**, 20446-55-3; **14**, 20446-56-4; Δ⁴-androstene-3β,17β-diol 17-monoacetate, 13903-65-6; 3α-hydroxy-4β,5-oxide-5β-androstan-17-one, 20446-58-6.

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Synthesis and Reactions of Isomeric 3-Acetamido-4,5-oxidoandrostan-17β-ol Acetates[1a]

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The *cis* and *trans* isomers of 3α- and 3β-acetamido-4,5-oxidoandrostan-17β-ol acetate have been synthesized. Dilute acid treatment of the isomeric pair of 3α-acetamido epoxides **4** and **5** afforded the same product, 3α-acetamido-4α,5β,17β-triol monoacetate **9a**, whereas the 3β-acetamido epoxides **7** and **8** yielded the 4β,5α,17β-triol monoacetate **10a**. Backside participation of the acetamido group in the opening of the *trans*-oxirane ring in the epoxides has been observed.

The backside neighboring-group participation of acylamino groups in substitution and addition reactions *via* an intermediate oxazolidine is well known.[2] However, the participation of the acylamino group in the opening of a vicinal oxirane ring has not been widely studied. In the present study, the synthesis and dilute acid treatment of the four isomers of 3-acetamido-4,5-oxidoandrostan-17β-ol acetate have been investigated.

The 3-acetamido-4,5 epoxides of the androstane series were prepared essentially in the same manner as those of the cholestane series described by Ponsold.[3] The *cis* epoxides, 3α-acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (**4**) and the 3β-acetamido-4β,5β-oxide **7**, were prepared from the corresponding 3-acetamido-Δ⁴-androsten-17β-ol acetates **3** and **6** with *m*-chloroperoxybenzoic acid. The configuration of the oxirane ring was verified by the doublet of the C-4 proton centered at δ 3.17 (J = 4 cps) and 3.08 (J = 4 cps) for **4** and **7** respectively.[4] The strong directive effect of the acylamino group on *cis* epoxidation of cyclic allylic derivatives have been amply noted.[2a,5] Similar effect of the ureido group has been reported in the previous paper.[6]

The *trans* epoxides, 3α-acetamido-4β,5-oxide-5β-androstan-17β-ol acetate (**5**) and 3β-acetamido-4α,5α-oxide **8**, were prepared from the 3β- and 3α-hydroxy-Δ⁴-androstene derivatives, respectively. Cyclic allylic alcohols are epoxidized stereoselectively to the *cis* oxides;[7] the C-3 hydroxyl group is then substituted by an azido group with epimerization *via* the intermediate methanesulfonoxy derivative. The preparation of 3α-azido-4β,5-oxido-5β-androstan-17β-ol acetate (**1a**)

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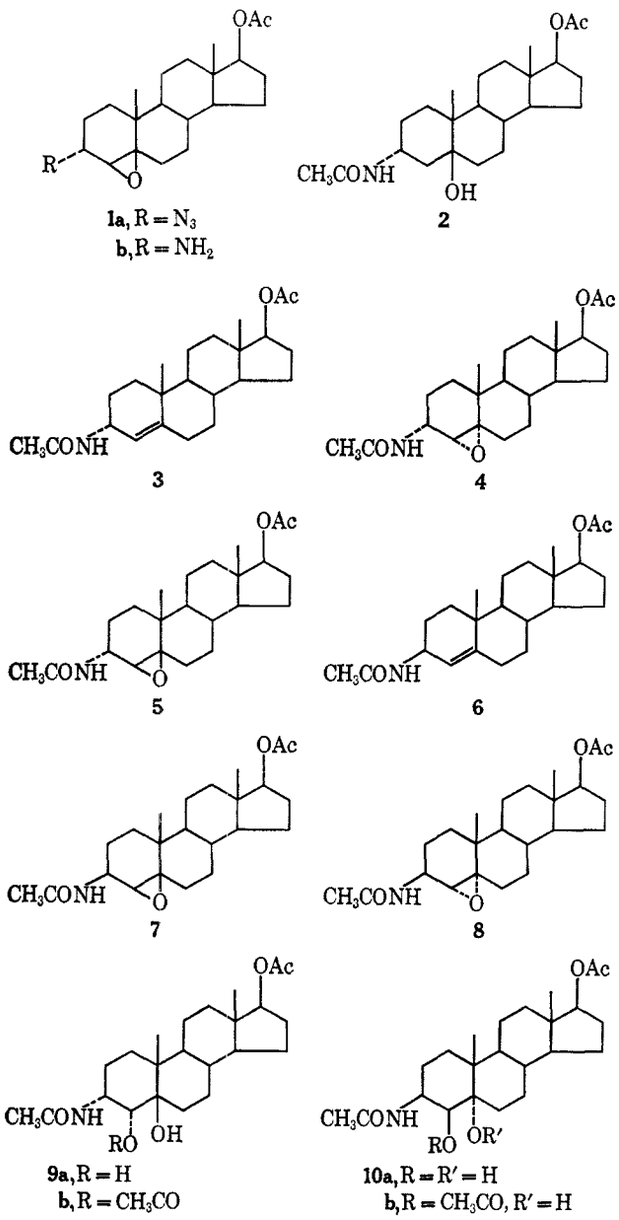

and its isomer, 3β-azido-4α,5α oxide, in this manner has been described in the previous paper.[6] The azido groups were reduced with hydrazine hydrate in the presence of Raney nickel, and the amines acetylated to give 3α-acetamido-4β,5-oxido-5β-androstan-17β-ol acetate (**5**) and the 3β-acetamido-4α,5α oxide **8**. The *trans* configuration of the oxirane ring was verified by the singlet of the C-4 proton, δ 2.88, in both **5** and **8**.

3α-Amino-Δ⁴ steroids are formed in small amounts by lithium aluminum hydride reduction of the corresponding unsaturated oximes;[8] the β epimer is the major product. In order to prepare large quantity of 3α-acetamido-Δ⁴-androsten-17β-ol acetate (**3**) for the formation of the *cis* epoxide **4**, a stereoselective synthesis was conceived. 3α-Azido-4β,5-oxido-5β-androsten-17β-ol acetate (**1a**), an intermediate in the *trans* ureido and acetamido epoxides, was reduced with lithium aluminum hydride to the 3α-amino-5α-hydroxy derivative which was acetylated to give 3α-acetamido-5β-androstane-5,17β-diol 17-monoacetate (**2**). Dehydration of the 5β-hydroxyl group was achieved with thionyl chloride, leading to 3α-acetamido-Δ⁴-androsten-17β-ol (**3**). The appearance of a doublet centered at δ 5.27 (J = 5 cps) demonstrated that the unsaturation was at 4,5 and that the proton at C-3 was in the equatorial β orientation. The Δ⁴-3β-acetamido epimer **6** was prepared from testosterone oxime. Joska and Sorm[9] described the reduction of this oxime with zinc and acetic acid to a 3-amino-Δ⁴-androsten-17β-ol, but these authors did not assign the orientation of the 3-amino groups. In a recent study it was demonstrated that this reduction led to the Δ⁴-3β-amino epimer.[10] In the present study, the reduction product of testosterone oxime was acetylated and the product isolated as 3β-acetamido-Δ⁴-androsten-17β-ol acetate (**6**). The vinyl C-4 proton of **6** appeared as a narrow multiplet centered at δ 5.20, affording evidence of the 3α-axial proton.

Ponsold[8] recently synthesized the four isomers of 3-acetamido-4,5-oxido cholestane. The acid cleavage of the *trans* acetamido epoxides, 3β-acetamido-4α,5-oxido-5α-cholestane and 3α-acetamido-4β,5-oxido-5β-cholestane, in which participation by the acetamido group would be expected, was not studied. Instead, the author treated the corresponding crude amino epoxide derived from the hydrazine hydrate reduction of the 3-azido-4,5-oxidocholestanes with 10% perchloric acid in dioxane at reflux for 1 hr. The products were partially acetylated and reported to be 3β-acetamido-4ξ,-5ξ-dihydroxycholestane and 3α-acetamido-4ξ,-5ξ-dihydroxycholestane. The orientation of the hydroxyl groups was not assigned. When the two *cis* epoxides, 3β-acetamido-4β,5-oxido-5β-cholestane and 3α-acetamido-4α,5-oxido-5α-cholestane, were opened with 2% sulfuric acid in acetone at reflux for 1 hr, two different 3-acetamido-4ξ,5ξ-dihydroxycholestanes were obtained. The assignment of the orientation of the hydroxyl groups were also not made in these compounds.

In order to get a clearer picture of the effect of the acetamido group on the cleavage of the vicinal oxirane ring, the four isomers of 3-acetamido-4,5-oxido-androstan-17β-ol acetate were treated with 0.2 *N* sulfuric acid in acetone at room temperature (22°). 3β-Acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (**8**) and its *cis* isomer, 3β-acetamido-4β,5β oxide **7**, gave the same product, 3β-acetamido-5α-androstane-4β,5,17β-triol 17-monoacetate (**10a**). The β orientation of the C-4 hydroxyl group was assigned from the nmr spectra of the triol monoacetate **10a** and the 4,17-diacetate **10b**; the signals of the C-19 methyl protons appeared downfield at δ 1.08 and 1.10, respectively, consistent with the presence of a 4β substituent. 3α-Acetamido-4β,5-oxido-5β-androstan-17β-ol acetate (**5**) and its *cis* isomer, 3α-acetamido-4α,5α oxide **4**, also gave a single product, 3α-acetamido-5β-androstane-4α,5,17β-triol 17-monoacetate (**9a**). The chemical shifts of the C-19 methyl protons in **9a** and the 4,17-diacetate **9b**, δ 0.92 and 0.97 respectively, provided evidence for the α orientation of the substituent at C-4. The oxirane ring can open *trans* diaxially in two directions. Several factors influence the direction of the cleavage: backside participation by the vicinal acetamido group,[3] electronegativity of the acetamido group,[2c,11] and the greater stability of a tertiary car-

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bonium ion. The backside participation by the acetamido group is not possible in the *cis* epoxides **4** and **7**. The weakly electronegative acetamido group would destabilize the developing carbonium ion at C-4 in the transition state and the preferred opening would be at C-5 to give the products **9a** and **10a**. The opening of the oxirane ring in this direction would be further enhanced by the fact that the carbonium ion at C-5 is tertiary. In the *trans* epoxides **5** and **8**, the neighboring-group effect of the vicinal acetamido group on the opening of the epoxide ring through an oxazolidine intermediate is quite evident. Not only are **9a** and **10a** the expected products from backside participation, but the rates of cleavage of the *trans* epoxides are more than twice as great as those of the *cis* epoxides.

Experimental Section[12]

3α-Acetamido-Δ⁴-androsten-17β-ol Acetate (3).—A solution of 500 mg of 3α-azido-4β,5-oxido-5β-androsten-17β-ol acetate (**1a**)[6] in 200 ml of ether was added dropwise to 1.5 g of lithium aluminum hydride in 500 ml of ether. The mixture was refluxed overnight and the excess reagent destroyed with 10% sulfuric acid. The organic phase was washed with dilute acid. The aqueous phase was neutralized with base and extracted with ethyl acetate. The product was acetylated with acetic anhydride and pyridine and chromatographed on a thin layer of silica gel G in the system ethanol–ethyl acetate (1:19). The acetamido derivative, 240 mg, was eluted with methanol–methylene chloride. Recrystallization from acetone afforded **3α-acetamido-5β-androstane-5,17β-diol 17-monoacetate (2)**, mp 256–256.5°; $[\alpha]D$ 61.8°; tlc, R_f = 0.20 (methanol–ethyl acetate 1:9); ir 3400 (sh), 3340, 1735, 1675, 1650 (sh), 1555, 1250, 1033 cm^{-1}; nmr δ 0.80 (s), 0.93 (s), 1.95 (s), 2.03 (s), 4.05 (m), 4.63 (t, J = 9 cps).

Anal. Calcd for $C_{23}H_{37}NO_4$: C, 70.55; H, 9.53; N, 3.58. Found: C, 70.48; H, 9.29; N, 3.46.

To a solution of 786 mg of the crude 3α-acetamido derivatives **2** in 40 ml of pyridine maintained at 5° was added dropwise 0.5 ml of thionyl chloride. After 20 min, the reaction mixture was poured into ice–water, extracted with ethyl acetate, and washed with water. Evaporation of the solvent gave 839 mg of substance, which was purified by column chromatography using silica gel H. Elution with ethyl acetate–cyclohexane (7:3) yielded 397 mg of **3α-acetamido-Δ⁴-androsten-17β-ol acetate (3)**. Recrystallization from acetone–hexane gave the analytical sample of **3**, mp 152.5–153°; $[\alpha]D$ 132°; tlc, R_f = 0.18 (ethyl acetate–cyclohexane 7:3); ir 3280 (sh), 3255, 1735, 1663, 1635, 1555, 1528, 1250, 1045 cm^{-1}; nmr δ 0.83 (s), 1.03 (s), 1.98 (s), 2.03 (s), 4.30 (m), 4.63 (t, J = 9 cps), 5.27 (d, J = 5 cps).

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 74.37; H, 9.57; N, 3.61.

3α-Acetamido-4α,5-oxido-5α-androstan-17β-ol Acetate (4).—A solution of 256 mg of 3α-acetamido-Δ⁴-androsten-17β-ol acetate (**3**) and 250 mg of *m*-chloroperoxybenzoic acid in 270 ml of methylene chloride was kept at room temperature overnight. A single product, 255 mg, was obtained as judged by thin layer chromatography. Recrystallization from acetone–petroleum ether afforded 135 mg of **3α-acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (4)**, mp 169–170.5°; $[\alpha]D$ 61.1°; tlc, R_f = 0.25 (ethanol–ethyl acetate 1:19); ir 3398, 1732, 1682, 1520, 1253, 1080, 1040, 1030, 1012 cm^{-1}; nmr δ 0.83 (s), 1.08 (s), 1.98 (s), 2.03 (s), 3.17 (d, J = 4 cps), 4.25 (m), 4.63 (t, J = 9 cps).

Anal. Calcd for $C_{23}H_{35}NO_4$: C, 70.91; H, 9.06; N, 3.60. Found: C, 71.19; H, 8.79; N, 3.61.

3α-Acetamido-4β,5-oxido-5β-androstan-17β-ol Acetate (5).—3α-Azido-4β,5-oxido-5β-androstan-17β-ol acetate (**1a**) (1.0 g) was reduced with hydrazine hydrate in the presence of Raney nickel as previously described.[3,6] The crude 3β-amine **1b** had the following chemical shifts: δ 0.83 (s), 1.05 (s), 2.03 (s), 2.75 (s), 3.21 (s), 4.63 (t, J = 9 cps). The amine, 839 mg, was acetylated with acetic anhydride and pyridine to give 963 mg of **3α-acetamido-4β,5-oxido-5β-androstan-17β-ol acetate (5)**. Recrystallization from acetone–petroleum ether and methanol yielded **5**, mp 197–199.5°; $[\alpha]D$ 42.6°; tlc, R_f = 0.24 (ethanol–ethyl acetate 1:19); ir 3265, 3070, 1738, 1640, 1555, 1248, 1048, 1025 cm^{-1}; nmr δ 0.83 (s), 1.05 (s), 2.00 (s), 2.03 (s), 2.88 (s), 4.00 (br m), 4.63 (t, J = 9 cps).

Anal. Calcd for $C_{23}H_{35}NO_4$: C, 70.91; H, 9.06; N, 3.60. Found: C, 70.43; H, 9.00; N, 3.44.

3β-Acetamido-4β,5-oxido-5β-androstan-17β-ol Acetate (7).—Testosterone oxime was reduced with zinc and acetic acid[9] and the resulting 3β-amino-Δ⁴-androsten-17β-ol was acetylated with pyridine and acetic anhydride to give **3β-acetamido-Δ⁴-androsten-17β-ol acetate (6)**. Recrystallization from methanol yielded **6**, mp 236–237°; $[\alpha]D$ −1.8°; tlc, R_f = 0.19 (ethyl acetate–cyclohexane 7:3); ir 3295, 1735, 1642, 1548, 1245, 1043 cm^{-1}; nmr δ 0.80 (s), 1.05 (s), 1.98 (s), 2.03 (s), 4.30 (m), 4.63 (t, J = 9 cps), 5.20 (n m).

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.44; N, 3.74. Found: C, 74.09; H, 9.26; N, 3.66.

A solution of 250 mg of 3β-acetamido-Δ⁴-androsten-17β-ol acetate (**6**) and 250 mg of *m*-chloroperoxybenzoic acid in 30 ml of methylene chloride was kept at room temperature overnight. A single product, 246 mg, was obtained as judged by thin layer chromatography. Recrystallization from ether–petroleum ether afforded 170 mg of **3β-acetamido-4,5-oxido-5β-androstan-17β-ol acetate (7)**, mp 127–129°; $[\alpha]D$ −9.4°, tlc, R_f = 0.34 (ethanol–ethyl acetate 1:19); ir 3300 (sh), 3260, 1738, 1655, 1635, 1545, 1248, 1045 cm^{-1}; nmr δ 0.82 (s), 1.03 (s), 1.98 (s), 2.03 (s), 3.08 (d, J = 4 cps), 4.40 (m), 4.63 (t, J = 9 cps).

Anal. Calcd for $C_{23}H_{35}NO_4$: C, 70.91; H, 9.06; N, 3.59. Found: C, 70.88; H, 9.37; N, 3.56.

3β-Acetamido-4α,5-oxido-5α-androstan-17β-ol Acetate (8).—Acetylation of the 3β amine[6] obtained by the reduction of 3β-azido-4α,5-oxido-5α-androstan-17β-ol acetate with hydrazine hydrate in the presence of Raney nickel afforded **3β-acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (8)**. Recrystallization from acetone–petroleum ether gave mp 229–233.5°; $[\alpha]D$ 13.1°; ir 3315, 1738, 1648, 1548, 1245, 1045, 1025, 535 cm^{-1}; nmr δ 0.82 (s), 1.13 (s), 2.00 (s), 2.03 (s), 2.88 (s), 4.00 (m), 4.63 (t, J = 9 cps).

Anal. Calcd for $C_{23}H_{35}NO_4$: N, 3.60. Found: N, 3.78.

Acid Treatment

3α-Acetamido-4α,5-oxido-5α-androstan-17β-ol Acetate (4).—A solution of 196 mg of 3α-acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (**4**) in 40 ml of acetone and 4 ml of 0.2 *N* sulfuric acid was kept at room temperature (22°) for 8 days, at which time approximately 20% of the starting material still remained as judged by thin layer chromatography. The reaction mixture was extracted with ethyl acetate and washed with dilute base and water. The extract was dried and the solvent was evaporated to give 190 mg of residue. Preparative thin layer chromatography on silica gel G in methanol–ethyl acetate (1:9) afforded 30 mg of starting material and 75 mg of a more polar product. Recrystallization of the latter from ethyl acetate afforded 63 mg of **3α-acetamido-5β-androstane-4α,5,17β-triol 17-monoacetate (9a)**, mp 268.5–271°, $[\alpha]D$ 48.8° (ethanol); tlc, R_f = 0.31 (methanol–ethyl acetate 1:9); ir 3630, 3365, 1740, 1655 (sh), 1630, 1245, 1045, 1025, 1015 cm^{-1}; nmr δ 0.78 (s), 0.92 (s), 1.95 (s), 2.03 (s), 3.67 (d, J = 3 cps), 4.17 (m), 4.63 (t, J = 9 cps).

Anal. Calcd for $C_{23}H_{37}NO_5$: C, 67.78; H, 9.53; N, 3.43. Found: C, 67.82; H, 9.27; N, 3.00.

Acetylation of 25 mg of 3α-acetamido-5β-androstane-4α,5,17β-triol 17-monoacetate (**9a**) with acetic anhydride and pyridine at room temperature for 2 days afforded 24 mg of 3α-acetamido-5β-androstane-4α,5,17β-triol 4,17-diacetate (**9b**). Recrystallization from acetone–petroleum ether yielded 15 mg of **9b**, mp 230–231°; ir 3450, 3330, 1738, 1715, 1645, 1550, 1270, 1250, 1045, 1039 cm^{-1}; nmr δ 0.80 (s), 0.97 (s), 1.90 (s), 2.03 (s), 2.15 (s), 4.50 (m), 4.63 (t, J = 9 cps), 5.17 (m).

3α-Acetamido-4β,5-oxido-5β-androstan-17β-ol Acetate (5).—A solution of 32 mg of 3α-acetamido-4β,5-oxido-5β-androstan-17β-ol acetate (**5**), in 5 ml of acetone and 0.5 ml of 0.2 *N* sulfuric acid was kept at room temperature (22°) overnight, after which time

(12) Melting points were determined on a micro hot stage and are corrected. Nmr spectra were obtained on a Varian A-60 instrument in deuteriochloroform with tetramethylsilane as internal standard; the chemical shifts are given in δ ppm. Optical rotations were determined in chloroform at 24° unless otherwise stated. Infrared spectra were determined on a Beckman IR-9 spectrophotometer in potassium bromide dispersion; br = broad, sm = small, sh = shoulder. Thin layer chromatography, tlc, was carried out on a 250-μ layer of silica gel GF at 24°.

no starting material remained. The reaction mixture, 26 mg, was recrystallized from ethyl acetate to give **3α-acetamido-5β-androstane-4α,5,17β-triol 17-monoacetate** (**9a**) identical with that obtained from the *cis*-3α-acetamido-4α,5α oxide **4**.

3β-Acetamido-4β,5-oxido-5β-androstan-17β-ol Acetate (**7**).—A solution of 168 mg of 3β-acetamido-4β,5-oxido-5β-androstan-17β-ol acetate (**7**) in 25 ml of acetone and 2.5 ml of 0.2 *N* sulfuric acid at room temperature for 4 days, after which time no starting material remained. Recrystallization of the reaction product, 160 mg, from methanol–ethyl acetate gave 88 mg of **3β-acetamido-5α-androstane-4β,5,17β-triol 17-monoacetate** (**10a**), mp 290° dec, subl; $[\alpha]_D$ −15.6° (ethanol); tlc, R_f = 0.30 (methanol–ethyl acetate 1:9); ir 3430, 3355, 1730, 1716, 1648, 1632, 1523, 1250, 1038, 1023, 960, 945 cm^{-1}; nmr δ 0.75 (s), 1.08 (s), 1.87 (s), 1.98 (s) (deuteriochloroform and dimethyl sulfoxide-d_6).

Anal. Calcd for $C_{23}H_{37}NO_5$: C, 67.78; H, 9.53; N, 3.43. Found: C, 67.52; H, 9.22; N, 3.47.

Acetylation of 48 mg of 3β-acetamido-5α-androstane-4β,5,17β-triol 17-monoacetate (**10a**) with acetic anhydride and pyridine at room temperature for 3 days afforded 48 mg of **3β-acetamido-5α-androstane-4β,5,17β-triol 4,17-diacetate** (**10b**). Recrystallization from acetone–petroleum ether afforded **10b**, mp 312–313°; $[\alpha]_D$ −30.0° (ethanol); tlc, R_f = 0.58 (methanol–ethyl acetate 1:3); ir 3508, 3330, 1745, 1722, 1660, 1553, 1268, 1233, 1045, 1025 cm^{-1}; nmr δ 0.78 (s), 1.10 (s), 1.90 (s), 2.01 (s), 2.03 (s), 4.63 (br m), 5.02 (d, J = 4 cps).

Anal. Calcd for $C_{25}H_{39}NO_6$: C, 66.78; H, 8.74; N, 3.11. Found: C, 66.88; H, 8.89; N, 3.22.

3β-Acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (**8**).—A solution of 11 mg of 3β-acetamido-4α,5-oxido-5α-androstan-17β-ol acetate (**8**) in 5 ml of acetone and 0.5 ml of 0.2 *N* sulfuric acid was kept at room temperature (22°) for 24 hr, after which time no starting material remained. Recrystallization from acetone–petroleum ether gave **3β-acetamido-5α-androstane-4β,5,17β-triol 17-monoacetate** (**10a**), mp 300° dec, subl. The product was identical with that obtained by the dilute sulfuric acid treatment of the corresponding *cis*-3β-acetamido-4β,5β oxide **7**.

Registry No.—**2**, 20429-62-3; **3**, 20429-63-4; **4**, 20445-48-1; **5**, 20429-64-5; **6**, 20588-73-5; **7**, 20429-66-7; **8**, 20429-67-8; **9a**, 20429-68-9; **9b**, 20429-69-0; **10a**, 20429-70-3; **10b**, 20429-71-4.

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Polar and Steric Effects in Acyl Phosphate Monoanion and Dianion Reactions

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The rate constants for hydrolysis of a series of aliphatic acyl phosphates have been determined at 60°. Complete pH–rate profiles for three of the derivatives, isobutyryl, trimethylacetyl, and 3,3-dimethylbutyryl phosphate, were obtained as well as the monoanion and dianion hydrolytic rate constants for isovaleryl phosphate. The values of ΔS^* were uniformly close to zero, consistent with the postulated unimolecular mechanism of hydrolysis of acyl phosphates. A decrease in the rate of hydrolysis was observed for the monoanion and dianion reactions as steric bulk and electron donation in the acyl group, as measured by the Taft σ^* constants, were increased. Second-order rate constants for reaction of pyridine with the monoanions and dianions were also correlated with σ^* constants. The ρ^* for k_{pyr} (monoanion) was +2.0 and for k_{pyr} (dianion) was +6.1. Imidazole and morpholine did not catalyze the hydrolysis of trimethylacetyl phosphate or 3,3-dimethylbutyryl phosphate.

Detailed mechanistic studies of acyl phosphate dianion,[2-4] monoanion,[2-4] and acid-catalyzed[5] hydrolysis reactions have been carried out. Acetyl phosphate monoanion and dianion hydrolysis takes place with unimolecular decomposition to metaphosphate,[4] but reaction with various nucleophiles can be observed.[3,4] Various tertiary amines and pyridine will attack at phosphorus, but imidazole and primary amines attack at the carbonyl group. There seems to be no relationship between the pK_a of the attacking amine and the position of attack.[6] As a consequence, it was thought that steric influences might be of extreme importance in these reactions. A study of the effects of increased steric size of the acyl group in acyl phosphate reactions was therefore undertaken.

Experimental Section

Materials.—Dilithium acetyl phosphate was purchased from CalBiochem Corp. and was used without further purification. All of the remaining aliphatic acyl phosphates were prepared by the method of Lipmann and Tuttle,[7] and isolated as the disodium salts as previously reported.[5] β-Chloropropionyl phosphate was analyzed as the disilver salt. *Anal.* Calcd for $C_3H_4ClO_5PAg_2$: C, 8.96; H, 1.00; P, 7.70. Found: C, 8.79; H, 0.89; P, 7.53. The acyl phosphates were stored in a desiccator at −4°, and fresh samples were prepared periodically.

Dioxane was purified by the method of Fieser[8] and was stored frozen. Deuterium oxide (99.8%) was obtained from Bio-Rad Laboratories. The remainder of the chemicals were reagent grade.

Kinetic Measurements.—The hydroxamic acid assay was used exclusively for the kinetic runs as described by Di Sabato and Jencks.[4] All rates were run in duplicate to at least 75% completion, with less than 5% deviation between the two rate constants in all cases. Each run was initiated by adding the acyl phosphate to the preequilibrated buffer solution making it approximately 2×10^{-3} *M* in acyl phosphate. Rate constants did not change when the acyl phosphate concentration was varied 50%. At appropriate time intervals, aliquots were removed and introduced into the hydroxylamine solution. The resulting mixture was then stoppered and shaken. Development time for complete formation of the hydroxamate was experimentally determined for each compound. At least nine points were employed for a rate determination, and infinity points were taken at ten half-lives. Temperature was controlled to ±0.1° by a Princo thermoregulator in a stirring-water bath. Pseudo-first-order rate constants (k_{obsd}) were calculated with an Oliuetti-Underwood Programma 101 using a computer program designed to calculate a least-

(1) This study represents part of the work to be submitted by D. R. Phillips in partial fulfillment of the requirements for the Ph.D. degree, University of Southern California.

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