The cell-free incubations were carried in five 25-ml conical flasks for 6 hr at 30° using 2.5 mg of substrate with similar specific activities (ratio 25.3:1), 1 mg of menadione, and 5 ml of enzyme solution per flask.[26] After extraction and preparative tlc as above, androsta-1,4-diene-3,17-dione product and unreacted starting material were eluted; conversion was 23%. They were diluted with appropriate carriers and crystallization to constant specific activities and ratios: product, 10.8:1, 10.7:1; substrate, 29.5:1, 30.8:1.

2. **A placental incubation**[22] was carried out with a 10,000 × g supernate preparation prepared in phosphate buffer using 200 μg of testosterone-1,2-t (sp activity 2.5 × 10^4 dpm ^3H and 944 dpm ^{14}C per μg, ratio 26.5) per 20 g wet weight of tissue. After incubation in air at 37° for 1 hr in the presence of an NADPH generating system, the mixture was extracted with ethyl acetate. The extract was chromatographed in the ligroin–propylene glycol paper system for 12 hr, and then in the toluene–propylene glycol systems without elution. The material in the estrone–testosterone and androstenedione areas were purified further by tlc. The $^3H/^{14}C$ ratios in dpm of the estrone were 8.2:1 after tlc in 20% ethyl acetate–benzene, 8.6:1 after a second crystallization, 8.1:1 after partition between KOH and toluene, and 8.3:1 after thin layer chromatography and two crystallizations of the acetate. The conversion to estrone was about 40%, as judged from the radioscans of the chromatograms.

The testosterone after tlc, reverse isotope dilution, and recrystallization showed $^3H/^{14}C$ ratios of 27.0:1, 27.7:1, and 28.0:1. The androstenedione material after tlc in 20% ethyl acetate–benzene followed by reverse isotope dilution and crystallization after $^3H/^{14}C$ ratios of 26.5:1, 25.8:1, and 26.5⁻1. Results in this and the preceding section are summarized in Table II.

Registry No.—I, 50-24-8; II, 898-84-0; tritium, 10028-17-8.

Acknowledgment.—We are grateful to Mrs. Cynthia E. Hay for skilled technical assistance.

Chemistry of 3-(N-Acetylureido)-4,5-oxidoandrostan-17β-ol Acetates[1a]

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Epoxidation of 3-ureido-Δ⁴-androsten-17β-ol derivatives **1a** and **6a** afforded exclusively the *cis*-4,5-oxido derivatives **2a** and **7a**, whereas the unsaturated N-acetylureido compounds yielded a mixture of oxides with predominant formation of the *cis* oxides. The *trans*-ureido oxides **3** and **8** were prepared from the *cis*-3-hydroxy 4,5-oxides **4** and **10**. The hydroxyl group was epimerized through the mesylates to the *trans*-azido oxides **5** and **11**. Reduction of the azides with hydrazine hydrate gave the amines which were converted into the ureides with nitrourea. Dilute acid-catalyzed treatment of the *cis*-3-(N-acetylureido) oxides **2b** and **7b** proceeded slowly to the *trans*-diaxial opened products **12** and **13**. Neighboring-group participation of the N-acetylureido group was realized in the acid treatment of the *trans* oxides **3** and **8**.

In continuation of the study on the chemistry of C-3 ureido steroids,[2,3] the synthesis of isomeric 3-ureido- and 3-(N-acetylureido)-4,5-oxidoandrostanes and the participation of the ureido group on ring opening of the epoxide have been investigated.

Epoxidation of 3α-ureido-Δ⁴-androsten-17β-ol acetate (**1a**) gave almost exclusively the *cis* product, 3α-ureido-4α,5-oxido-5α-androstan-17β-ol acetate (**2a**), whereas the 3α-N-acetylureido derivative **1b** gave the epimeric α- and β-epoxides **2b** and **3b** in a 2:1 ratio. The α-epoxide **2b** could also be prepared from 3α-ureido-Δ⁴-androsten-17β-ol (**1c**) and *m*-chloroperoxybenzoic acid followed by acetylation. The configuration of the epoxides was assigned on the basis of nmr spectrometric evidence.[4] The proton at C-4 in both **2a** and **2b** appeared as a doublet at δ 3.01 (J = 4.5 cps) indicating an epoxide ring *cis* to the substituent at C-3. In **3b** the C-4 proton appeared as a singlet at δ 2.85, demonstrating the *trans* relationship of the epoxide with the C-3α-N-acetylureido group. The stereoselective introduction of the epoxide *cis* to the C-3 ureido group can be ascribed to the hydrogen bonding between $-N^1H$ and the carbonyl group of the peracid directing the reagent from the *cis* face of the steroid nucleus. Henbest and Wilson[5] have proposed such a transition complex for the stereoselective epoxidation of cyclic allyl alcohols. It has also been found that cyclic allyl acetamido and benzamido groups have similar strong directive influence on epoxidation.[6,7] The formation of an appreciable amount of the *trans* epoxide from the 3α-N-acetylureido derivative **1b** may be in part due to steric hindrance of the *cis* face by the bulkier group as well as preferential hydrogen bonding of the reagent with the more acidic $-N^3H$ placing the peracid in a less favorable position for epoxidation; consequently a larger proportion of the *trans*-β epoxide **3b** could be formed.

In order to prepare larger amounts of the *trans*-β epoxide **3**, the method employed by Ponsold[8] for the preparation of 3α-acetamido-4β,5-oxido-5β-cholestane was employed. The 4β,5β epoxide **4a** was stereoselectively introduced by *m*-chloroperoxybenzoic acid oxidation of Δ⁴-androstene-3β,17β-diol 17-monoacetate derived from testosterone acetate. Epimerization at C-3 was accomplished by mesylation to **4b** and treatment with sodium azide to give 3α-azido-4β,5-oxido-5β-androstan-17β-ol acetate (**5**). The α orientation of the azido group was demonstrated by the singlet at δ 2.88 due to the proton at C-4, indicating a *trans* relationship of the epoxide and the azido group.[4] Reduction of the azide with hydrazine hydrate in the presence of Raney nickel afforded the amine, which was converted to 3α-ureido-4β,5-oxide-5β-androstan-17β-ol acetate (**3a**) with nitrourea.[2] Attempts to form the N-acetyl derivative (**3b**) were unsuccessful.

(1) (a) This investigation was supported by a grant from the American Cancer Society and Grant CA-07304 from the National Cancer Institute, National Institutes of Health, U. S. P. H. S. (b) Visiting Scientist, 1966–1967. Institut de Chimie des Substances, Naturelles, Gif-sur-Yvette, France.

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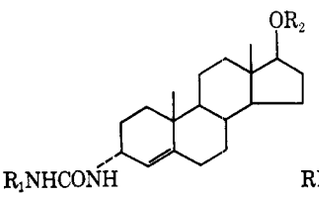
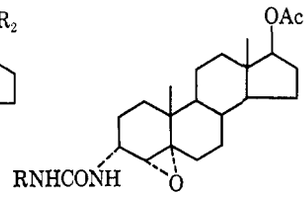
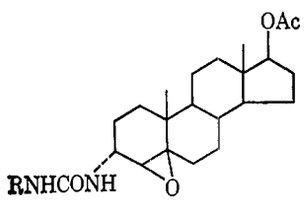


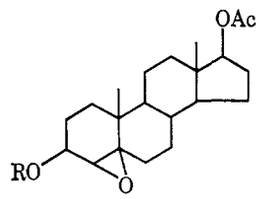
1a, $R_1 = H$, $R_2 = CH_3CO$
b, $R_1 = R_2 = CH_3CO$
c, $R_1 = R_2 = H$



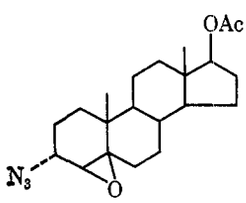
2a, R = H
b, $R = CH_3CO$



3a, R = H
b, $R = CH_3CO$



4a, R = H
b, $R = CH_3SO_2$



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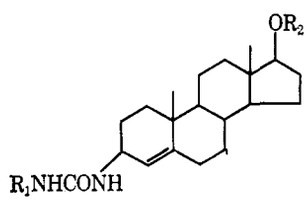
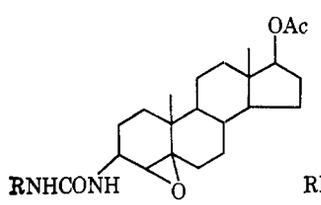
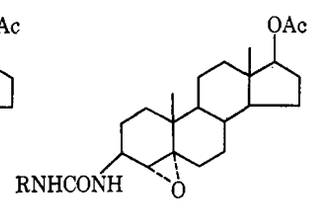


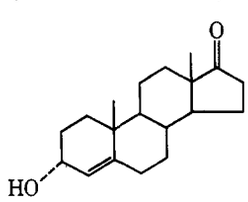
6a, $R_1 = R_2 = H$
b, $R_1 = R_2 = CH_3CO$



7a, R = H
b, $R = CH_3CO$



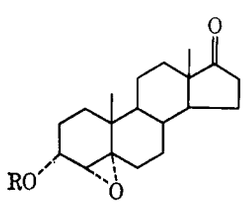
8a, R = H
b, $R = CH_3CO$



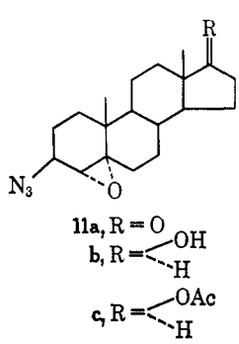
9

The 4,5 epoxides of the 3β-ureido derivatives were prepared in the same manner as the 3α epimers. The directive influence of hydrogen bonding between NH and the peracid was also evident for epoxidation of 3β-ureido-Δ⁴-androsten-17β-ol (**6a**). This yielded almost exclusively the *cis*-4β,5β epoxide despite the presence of the C-19 methyl group. The product was isolated as the N-acetylureido derivative **7b**. Only trace amounts of the *trans*-4α,5α epoxide **8b** was detected. Epoxidation of the 3β-(N-acetylureido)-Δ⁴-androsten-17β-ol acetate (**6b**) gave a higher proportion of the *trans* epoxide (*cis*:*trans*, 3:2) than that achieved with the 3α epimer **1b** in which the ratio was 2:1. This was probably due to the greater access of the peracid to the unsaturation from the less hindered α face in competition with the hydrogen bond assisted *cis*-β epoxide formation. The configuration of the oxirane ring in 3β-ureido-4β,5-oxido-5β-androstan-17β-ol acetate (**7a**), its N-acetyl derivative **7b**, and their 4α,5α epoxide isomers **8** was assigned by the splitting patterns of the C-4 protons.

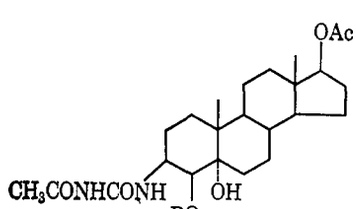
The *trans*-α epoxide, 3β-(N-acetylureido)-4α,5-oxido-5-androstan-17β-ol acetate (**8b**), could not be readily isolated from the 3:2 mixture (*cis*:*trans*) obtained from the epoxidation of unsaturated compound **6b**. Consequently, the synthesis of the *trans* epoxide **8** was undertaken by reactions analogous to those employed in the preparation of the *trans* epoxide of the 3α-ureide. The stereoselective introduction of the 4α,5α epoxide was achieved by the *m*-chloroperoxybenzoic acid treatment of 3α-hydroxy-Δ⁴-androsten-17-one (**9**) to yield 3α-hydroxy-4α,5-oxido-5α-androstan-17-one (**10a**). The *cis* configuration of the oxirane ring was verified by the doublet of the C-4 proton at δ 3.17 (J = 3.5 cps). Epimerization at C-3 was accomplished by formation of the mesylate **10b** and displacement with sodium azide to give 3β-azido-4α,5-oxido-5α-androstan-17-one (**11a**). The *trans* relationship was established from the chemical shift of the C-4 proton, a singlet at δ 2.92. The 17-carbonyl group of the azide **11a** was then reduced with sodium borohydride, and the alcohol **11b** was acetylated to give 3β-azido-4α,5-oxido-5α-androstan-17β-ol acetate (**11c**). The azido group in



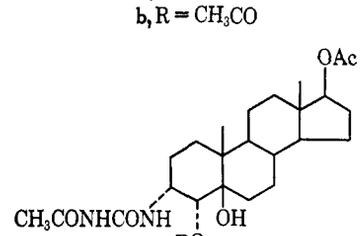
10a, R = H
b, $R = CH_3SO_2$



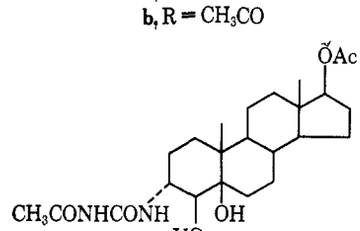
11a, R = O
b, R = OH, H
c, R = OAc, H



12a, R = H
b, $R = CH_3CO$



13a, R = H
b, $R = CH_3CO$



14

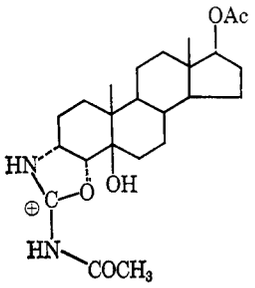
11c was next reduced with hydrazine hydrate to an amine, which was converted to 3β-ureido-4α,5-oxido-5α-androstan-17β-ol acetate (**8a**) with nitrourea. Although acetylation of the ureido group in the *cis* epoxy compounds proceeded readily, the preparation of the 3β-(N-acetylureido)-4α,5-oxido-5α-androstan-17β-ol acetate (**8b**) from the ureide **8a** was unsuccessful, just as in the epimeric *trans*-3α epoxide **3b**. The reaction lead to a variety of products which were not characterized.

The acid-catalyzed opening of isomeric 3-acetoxy-4,5-oxido steroids has been studied by several investigators, and the participation of the acetoxyl group has been demonstrated.[9-13] In the accompanying paper, participation of the 3-acetamido group in the opening of the vicinal epoxide ring is described.[14] In the present study, treatment of 3α-ureido-4β,5-oxido-5β-androstan-17β-ol acetate (**3a**) and the 3β-ureido-4α,5α-oxido isomer **8a** with dilute sulfuric acid in acetone resulted in precipitation of a salt, which prevented further reaction. Upon neutralization with base, starting material was recovered. Therefore, the ring opening of the 4,5-oxides of the N-acetylureido derivatives was examined. Dilute sulfuric acid in acetone afforded *trans* diaxial ring opening of 3β-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol acetate (**7b**) to 3β(N-acetylureido)-5α-androstane-4β,5,17-triol 17-monoacetate (**12a**) in 2 days at room temperature. The β orientation of the hydroxyl group at C-4 was assigned from the appearance of the C-19 methyl protons signals downfield at δ 1.13. This downfield shift of the C-19 methyl protons was also evident in the acetylated product **12b** and is consistent with the presence of a 4β-OR group.

Opening of the oxirane ring of the *cis* α isomer, 3α-(N-acetylureido)-4α,5-oxido-5α-androstan-17β-ol acetate (**2b**), required 16 days. The principal product was the *trans* diaxial product, 3α-(N-acetylureido)-5β-androstane-4α,5,17β-triol 17-monoacetate (**13a**).

trans diaxial opening of 4α,5α and 4β,5β oxides can occur in two directions, giving rise to 4β,5α-dihydroxy and 4α,5β-dihydroxy derivatives. The preferred opening would place the intermediate carbonium ion at the tertiary carbon, C-5, and thus the 4β,5β epoxide should give principally the 4β,5α dihydroxy derivative and the epimeric 4α,5α epoxide should give the 4α,5β-dihydroxy derivative. Both *cis*-N-acetylureido epoxides opened almost exclusively in the expected manner. Similar exclusive opening of *cis* oxides has been observed in the acetoxy and the acetamido series.

The anticipated backside participation of the neighboring ureido group was realized in the dilute acid treatment of the *trans* epoxides, 3β-(N-acetylureido)-4α,5-oxido-5α-androstan-17β-ol acetate (**8b**) and the corresponding 3α derivative **3b**; the starting epoxide disappeared rapidly in the reaction. 3α-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol acetate (**3b**) did not afford the expected 4α,5β-dihydroxy derivative **13a**, but yielded instead a compound which had a nmr spectrum consistent with 3α-(N-acetylureido)-5β-androstane-4β,5,17β-triol 17-monoacetate (**14**). The protons of the C-19 methyl group appeared relatively far downfield, δ 1.27, indicating that the hydroxyl groups at C-4 and 5 were both in the β orientation. The *cis*-β-diol could arise by the participation of the N-acetylureido group with the formation of a cyclic intermediate such as



In aqueous solution with an acetoxy or an acetamido group at C-3, analogous cyclic intermediates react with the solvent to afford the vicinial hydroxyl group *cis* to the neighboring group; that is, the epoxides are opened to the diols with inversion at C-4. However, in the case of the N-acetylureido group, hydration of the carbonium ion of the cyclic intermediate is superseded by attack of the solvent at C-4 to give the β-hydroxyl group, resulting in *cis* opening of the epoxide. It may be also postulated that a six-membered cyclic intermediate is formed by attachment of the acetylureido group at C-5α. Such an intermediate, by *cis* opening of the epoxide, could also give rise to the same product **14** in the manner proposed above.

The other *trans* epoxide, 3β-(N-acetylureido)-4α,5-oxido-5α-androstan-17β-ol acetate (**8b**), could not be prepared pure in sufficient amount for acid treatment. However, evidence of the participation of the N-acetylureido group was derived from the acid treatment of a 3:2 mixture (β:α oxide) with the *cis*-3β-(N-acetylureido)-4β,5β-oxide isomer. As measured by thin layer chromatography, the *trans*-α oxide disappeared within 16 hr, whereas the *cis*-β oxide required 48 hr for complete reaction. The sole product isolated and characterized was 3β-(N-acetylureido)-5α-androstane-4β,5,17-triol 17-monoacetate (**12a**) in 60% yield. However, since the pure *cis*-β oxide gave rise to this product in about 70% yield, the extent of formation of this product from the *trans*-α oxide could not be ascertained.

Experimental Section[15]

3α-Ureido-Δ⁴-androsten-17β-ol Acetate (1a) and 3α-(N-Acetylureido)-Δ⁴-androsten-17β-ol Acetate (1b).—A solution of 2.5 g of 3α-ureido-Δ⁴-androsten-17β-ol[3] (**1c**) in 90 ml of pyridine and 90 ml of acetic anhydride was allowed to stand at room temperature for 72 hr. It was poured into crushed ice containing 5% hydrochloric acid and extracted with methylene chloride. The extract was washed with base and water and dried, and the solvent was evaporated. The residue (2.8 g) showed four spots on chromatography on a thin layer of silica gel G in ethyl acetate–cyclo-

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(13) S. Julia and B. Furer, *Bull. Soc. Chim. Fr.*, 1114 (1966).
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(15) 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°.

hexane (7:3). The compounds were separated on a column of 300 g of silica gel G with the above solvent mixture at 30 ml per fraction. Fractions 13–22 afforded 1.47 g of **3α-(N-acetylureido)-Δ⁴-androsten-17β-ol acetate (1b)** which after recrystallization from methanol melted at 219–221°; $[\alpha]_D$ 163°; tlc, R_f = 0.42 (ethyl acetate–cyclohexane 7:3); ir 3295, 3242, 3110, 1738, 1693, 1660 (sh),1548, 1502, 1245, 1042 cm^{-1}; nmr δ 0.82 (s), 1.01 (s), 2.03 (s), 2.12 (s), 4.47 (m), 4.63 (t, J = 8 cps), and 5.33 ppm (m).

Anal. Calcd for $C_{24}H_{36}N_2O_4$: C, 69.19; H, 8.71; N, 6.72. Found: C, 69.26; H, 8.81; N, 6.85.

Two minor products were eluted from the column with the same solvent system and were discarded. Elution with methanol–ethyl acetate (1:9) yielded 830 mg of **3α-ureido-Δ⁴-androsten-17β-ol acetate (1a)**. Recrystallization from methanol gave **1a**, mp 208–211°; $[\alpha]_D$ 138° (ethanol); tlc, R_f = 0.07 (ethyl acetate–cyclohexane 7:3); ir 3500, 3350, 3290, 3220 (sh), 3080, 1733, 1678, 1645, 1605, 1580, 1550 (sh), 1248, 1045 cm^{-1}; nmr δ 0.82 (s), 1.00 (s), 2.02 (s), 4.05 (m), 4.63 (t, J = 8 cps), and 5.23 ppm (d, J = 5 cps).

Anal. Calcd for $C_{22}H_{34}N_2O_3$: C, 70.55; H, 9.15; N, 7.48. Found: C, 70.29; H, 8.87; N, 7.89.

3α-(N-Acetylureido)-4α,5-oxido-5α-androstan-17β-ol Acetate (2b) and Its 4β,5β Epimer (3b). A.—A solution of 218 mg of 3α-(N-acetylureido)-Δ⁴-androsten-17β-ol acetate (**1b**) and 220 mg of *m*-chloroperoxybenzoic acid in 15 ml of methylene chloride was stored at room temperature for 24 hr. It was washed with sodium carbonate solution and water and dried. Evaporation of the solvent and recrystallization of the residue from methanol–ethyl acetate afforded 59 mg of **3α-(N-acetylureido)-4α,5-oxido-5α-androstan-17β-ol acetate (2b)**, mp 274°; $[\alpha]_D$ 76.1°; tlc, R_f = 0.25 (ethyl acetate–cyclohexane 7:3); ir 3308, 3243, 3125, 1735, 1715, 1698, 1540, 1505, 1250 (br), 1048 cm^{-1}; nmr δ 0.80 (s), 1.05 (s), 2.02 (s), 2.08 (s), 3.01 (d, J = 5 cps), 4.30 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{24}H_{36}N_2O_5$: C, 66.64; H, 8.39; N, 6.47. Found: C, 66.78; H, 8.35; N, 6.55.

Chromatography of the mother liquor on a thin layer of silica gel G with ethyl acetate–cyclohexane (7:3) yielded an additional 77 mg of the 4α,5α oxide **2b** and 70 mg of **3α-(N-acetylureido)-17β-acetoxy-4β,5-oxido-5β-androstane (3b)**. Recrystallization from methanol–ethyl acetate gave **3b**, mp 233.5–235.5°; $[\alpha]_D$ 38.8°; tlc, R_f = 0.37 (ethyl acetate–cyclohexane 7:3); ir 3290, 3250 (sh), 3135, 1735, 1700, 1545 (br), 1250, 1048, 1028 cm^{-1}; nmr δ 0.80 (s), 1.03 (s), 2.03 (s), 2.13 (s), 2.85 (s), 4.07 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{24}H_{36}N_2O_5$: C, 66.64; H, 8.39; N, 6.47. Found: C, 66.65; H, 8.13; N, 6.47.

B.—A solution of 50 mg of *m*-chloroperoxybenzoic acid in 3 ml of methylene chloride was added to 50 mg of 3α-ureido-Δ⁴-androsten-17β-ol in 3 ml of acetic acid. The mixture was stored at room temperature for 48 hr, and the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride, washed with sodium carbonate solution and water, and dried. The product was acetylated with pyridine and acetic anhydride overnight at room temperature. Chromatography of the acetylated mixture on a thin layer of silica gel G in ethyl acetate–cyclohexane (7:3) afforded 16 mg of **2b**, identical with the product described in method A.

3α-Ureido-4α,5-oxido-5α-androstan-17β-ol Acetate (2a).—A solution of 300 mg of 3α-ureido-Δ⁴-androsten-17β-ol acetate (**1a**) and 500 mg of *m*-chloroperoxybenzoic acid in 35 ml of methylene chloride was stored at room temperature overnight. As judged by thin layer chromatography, only a single product was obtained. The product (290 mg) was crystallized from methanol and from acetone–methanol to give 139 mg of **3α-ureido-4α,5-oxido-5α-androstan-17β-ol acetate (2a)**, mp 228–229.5°; $[\alpha]_D$ 79.6° (ethanol); tlc, R_f = 0.30 (methanol–ethyl acetate 1:9); ir 3430, 3340, 1740, 1678, 1658, 1625, 1592, 1550, 1245, 1048 cm^{-1}; nmr δ 0.82 (s), 1.05 (s), 2.02 (s), 3.01 (d, J = 4.5 cps), 4.21 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{22}H_{34}N_2O_4$: C, 67.66; H, 8.78; N, 7.18. Found: C, 67.66; H, 8.71; N, 7.08.

3α-Ureido-4β,5-oxido-5β-androstan-17β-ol Acetate (3a).—Testosterone acetate (10 g) was reduced with sodium borohydride in methanol at room temperature for 1 hr to give **Δ⁴-androstene-3β,17β-diol 17-monoacetate**; nmr δ 0.80 (s), 1.05 (s), 2.03 (s), 4.17 (m), 4.63 (t, J = 8 cps), 5.33 (br s). It was treated with an equal weight of *m*-chloroperoxybenzoic acid in 1 l. of methylene chloride at room temperature overnight to give **4β,5-oxido-5β-androstane-3β,17β-diol 17-monoacetate (4a)**, nmr δ 0.80 (s), 1.03 (s), 2.05 (s), 3.17 (d, J = 5 cps), 4.10 (m), and 4.66 ppm (t, J = 8 cps). The presence of a small amount of the 4α,5α epoxide was indicated by a singlet at δ 2.78.

A solution of 10 g of 4β,5-oxido-5β-androstane-3β,17β-diol 17-monoacetate (**4a**) and 7 ml of methanesulfonyl chloride in 130 ml of pyridine was allowed to stand at 5° for 3 hr. The mixture was poured into ice and extracted with methylene chloride. The extract was washed with water, sodium bicarbonate solution, and water, dried, and the solvent evaporated. Recrystallization from methanol afforded 11.6 g of **3β-methanesulfonoxy-4β,5-oxido-5β-androstan-17β-ol acetate (4b)**, ir 1733, 1360, 1242, 1175, 530 cm^{-1}; nmr δ 0.82 (s), 1.07 (s), 2.03 (s), 3.11 (s), 3.27 (d, J = 3.8 cps), 4.63 (t, J = 8 cps), and 5.18 ppm (m).

Anal. Calcd for $C_{22}H_{34}O_6S \cdot {}^1/_2H_2O$: C, 61.06; H, 8.20; S, 7.23. Found: C, 61.02; H, 8.10; S, 7.39.

The mesylate (11 g) was treated with 41 g of sodium azide in 580 ml of dimethyl sulfoxide at 90° for 90 min. The solution was poured into ice and water, extracted with methylene chloride, washed with water, and dried. Evaporation of the solvent and trituration with methanol afforded 6.63 g of **3α-azido-4β,5-oxido-5β-androstan-17β-ol acetate (5)**, mp 139.5–141.5°. The analytical sample from methanol melted at 141–142°; $[\alpha]_D$ −4.9°; tlc, R_f = 0.36 (ethyl acetate–benzene 1:19); ir 2110, 1735, 1248, 1045, 1023, 1018 cm^{-1}; nmr δ 0.82 (s), 1.03 (s), 2.03 (s), 2.88 (s), 3.75 (t, J = 8 cps), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{21}H_{31}N_3O_3$: C, 67.53; H, 8.37; N, 11.25. Found: C, 67.42; H, 8.45; N, 11.31.

A mixture of 1.0 g of the azide in 2.4 ml of hydrazine hydrate in 40 ml of ethanol and a small amount of W-2 Raney nickel was refluxed for 10 min. It was cooled and filtered, most of the ethanol was evaporated, and the residue was dissolved in ethyl acetate and washed with water. A solution of 500 mg of the crude amine and 480 mg of nitrourea in 40 ml of 50% ethanol was refluxed for 7 hr. The solution was concentrated to half its volume, ethyl acetate was added, and the extract was washed with water, sodium carbonate solution, and water. Recrystallization of the product from ethyl acetate–methanol afforded **3α-ureido-4β,5-oxido-5β-androstan-17β-ol acetate (3a)**, mp 223.5–226°; $[\alpha]_D$ 38.9° (ethanol); tlc, R_f = 0.36 (methanol–ethyl acetate 1:3); ir 3620, 3462, 3362, 3290, 1735 (sh), 1716, 1660, 1650 (sh), 1615, 1558, 1540 (sh), 1267, 1250 (sh), 1045, 1023 cm^{-1}; nmr δ 0.80 (s), 1.00 (s), 2.02 (s), 2.85 (s), 4.05 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{22}H_{34}N_2O_4 \cdot CH_3OH$: C, 65.37; H, 9.06; N, 6.63. Found: C, 65.89; H, 9.01; N, 7.10.

The N-acetylureido derivative **3b** could not be obtained by treatment with acetic anhydride and pyridine. There were many products, but none had the mobility on a thin layer chromatogram of the desired product **3b**.

3β-(N-Acetylureido)-Δ⁴-androsten-17β-ol Acetate (6b).—A solution of 180 mg of 3β-ureido-Δ⁴-androsten-17β-ol (**6c**)[2] in 5 ml of pyridine and 5 ml of acetic anhydride was allowed to stand at room temperature overnight. The product was crystallized from methanol to give 131 mg of **3β-(N-acetylureido)-Δ⁴-androsten-17β-ol acetate (6b)**, mp 240–243°; $[\alpha]_D$ 2.3°; tlc R_f = 0.34 (ethyl acetate–cyclohexane 7:3); ir 3298, 3245, 3118, 1745, 1715, 1695, 1555, 1540 (sh), 1510, 1250, 1045, 1025 cm^{-1}; nmr δ 0.82 (s), 1.05 (s), 2.03 (s), 2.10 (s), 4.50 (m), 4.63 (t, J = 8 cps), and 5.21 ppm (nm).

Anal. Calcd for $C_{24}H_{36}N_2O_4$: C, 69.19; H, 8.71; N, 6.72. Found: C, 69.03; H, 9.11; N, 6.72.

3β-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol Acetate (7b).—A solution of 200 mg of 3β-ureido-Δ⁴-androsten-17β-ol (**6a**) and 200 mg of *m*-chloroperoxybenzoic acid in glacial acetic acid and 70 ml of methylene chloride was stored at room temperature overnight and then worked up as above for the 3α-epimer. The residue was acetylated with acetic anhydride in pyridine at room temperature for 4 days. The reaction mixture contained a small amount of a less polar product, R_f = 0.21, presumbably the 4α,5α oxide. Thin layer chromatography of the mixture on silica gel G in cylohexane–ethyl acetate (3:7) and recrystallization of the main product, R_f = 0.26, from methanol afforded 116 mg of **3β-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol acetate (7b)**, mp 246–248°; $[\alpha]_D$ −37.0° (chloroform); ir 3405 (sh), 3380, 3358, 3295, 1723, 1528, 1245, 1040 cm^{-1}; nmr δ 0.82 (s), 1.05 (s), 2.03 (s), 2.11 (s), 3.01 (d, J = 3.0 cps), 4.37 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{24}H_{36}N_2O_5$: C, 66.64; H, 8.39; N, 6.47. Found: C, 66.74; H, 8.18; N, 6.29.

A solution of 270 mg of 3β-(N-acetylureido)-Δ⁴-androsten-17β-ol acetate (**6b**) and 270 mg of *m*-chloroperoxybenzoic acid in 30 ml of methylene chloride was stored at room temperature overnight. Thin layer chromatography in cyclohexane–ethyl acetate (3:7) showed the presence of two products, R_f = 0.21 and 0.26, in relative yields of 2:3 respectively. The mixture was also verified by the relative intensities of the signals due to the C-4 protons in the nmr spectrum. The crude mixture could not be readily separated; only the *cis* oxide **7b** could be isolated in pure form.

3α-Hydroxy-4α,5-oxido-5α-androstan-17-one (**10a**).—A solution of 1.25 g of 3α-hydroxy-Δ⁴-androsten-17-one (**9**) and 1.25 g of *m*-chloroperoxybenzoic acid in 240 ml of methylene chloride was stored overnight at room temperature and worked up in the usual manner. Recrystallization of the product from ether–acetone afforded 876 mg of **3α-hydroxy-4α,5-oxido-5α-androstan-17-one** (**10a**), mp 128–129°, 136–137.5°; [α]D 174°; tlc, R_f = 0.37 (ethyl acetate); ir 3500, 1745, 1038 cm⁻¹; nmr δ 0.90 (s), 1.05 (s), 3.17 (d, J = 3.5 cps), and 3.95 ppm (m).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.29. Found: C, 74.20; H, 9.21.

From the mother liquor was obtained **3α-hydroxy-4β,5-oxido-5β-androstan-17-one**, mp 175.5–180.5°; tlc, R_f = 0.41 (ethyl acetate); ir 3460 (br), 1730, 1080, 1050 cm⁻¹; nmr δ 0.88 (s), 1.03 (s), 2.87 (s), and 3.97 ppm (t, J = 9 cps).

3β-Azido-4α,5-oxido-5α-androstan-17-one (**11a**).—A solution of 768 mg of 3α-hydroxy-4α,5-oxido-5α-androstan-17-one (**10a**) and 0.7 ml of methanesulfonyl chloride in 14 ml of pyridine was kept at 5° for 2.5 hr. The mixture was poured into ice and water and filtered. **3α-Methanesulfonoxy-4α,5-oxido-5α-androstan-17-one** (**10b**), 903 mg, could not be crystallized without decomposition. Its mobility on tlc was R_f = 0.26 (cyclohexane–ethyl acetate 1:1); ir 1745, 1365, 1175, 910 cm⁻¹; nmr δ 0.87 (s), 1.03 (s), 3.03 (s), 3.23 (d, J = 4 cps), and 5.05 ppm (m). The mesylate **10b** was treated with 2.9 g of sodium azide in 40 ml of dimethylsulfoxide at 90° for 90 min. The reaction product was recrystallized from methanol and the mother liquor chromatographed on a thin layer of silica gel G to afford 696 mg of **3β-azido-4α,5-oxido-5α-androstan-17-one** (**11a**), mp 129–129.5°; [α]D 138°; tlc, R_f = 0.39 (cyclohexane–ethyl acetate 7:3), R_f = 0.53 (cyclohexane–ethyl acetate 1:1); ir 2105, 1743, 1058, 1015 cm⁻¹; nmr δ 0.87 (s), 1.10 (s), 2.92 (s), and 3.72 ppm (t, J = 9 cps).

Anal. Calcd for $C_{19}H_{27}O_2N_3$: C, 69.27; H, 8.26; N, 12.76. Found: C, 69.28; H, 8.25; N, 12.76.

3β-Azido-4α,5-oxido-5α-androstan-17β-ol acetate (**11c**).—To a solution of 516 mg of 3β-azido-4α,5-oxido-5α-androstan-17-one (**11a**) in 30 ml of methanol was added 500 mg of sodium borohydride in 30 ml of methanol. Most of the methanol was removed *in vacuo* and the residue extracted with ethyl acetate. The product, 518 mg, was chromatographed on a thin layer of silica gel G in cyclohexane–ethyl acetate (1:1), and the major product was recrystallized from methanol to give **3β-azido-4α,5-oxido-5α-androstan-17β-ol** (**11b**), mp 106–107.5°; [α]D 66.0°; tlc, R_f = 0.41 (cyclohexane–ethyl acetate 1:1); ir 3330, 2100, 1075, 1057, 1035 cm⁻¹; nmr δ 0.77 (s), 1.10 (s), 2.92 (s), and 3.67 ppm (m).

Acetylation of 518 mg of the azide **11b** with acetic anhydride and pyridine and recrystallization from methanol afforded 479 mg of **3β-azido-4α,5-oxido-5α-androstan-17β-ol acetate** (**11c**), mp 149.5–150°; [α]D 49.7°; tlc, R_f = 0.46 (cyclohexane–ethyl acetate 7:3); ir 2480, 2195, 2100, 1745, 1250, 1048, 1045, 1022 cm⁻¹; nmr δ 0.82 (s), 1.10 (s), 2.03 (s), 2.90 (s), 3.73 (t, J = 9 cps), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{21}H_{31}N_3O_3$: C, 67.53; H, 8.37; N, 11.25. Found: C, 67.69; H, 8.10; N, 11.35.

3β-Ureido-4α,5-oxido-5α-androstan-17β-ol acetate (**8a**).—A mixture of 100 mg of 3β-azido-4α,5-oxido-5α-androstan-17β-ol acetate (**11c**), 0.5 ml of hydrazine hydrate, and a small amount of W-2 Raney nickel was stirred at room temperature for 1 hr. Most of the ethanol was removed, and the residue was extracted with ethyl acetate, affording 94 mg of **3β-amino-17β-acetoxy-4α,5-oxido-5α-androstane**. The product gave only one spot on thin-layer chromatography in the system *n*-butanol–acetic acid–water (4:1:5), R_f = 0.44. A solution of the 3β-amine and 150 mg of nitrourea in 24 ml of 50% ethanol was heated at 90° for 2 hr. The reaction mixture was worked up in the usual manner. Recrystallization from methanol–ether afforded 62 mg of **3β-ureido-4α,5-oxido-5α-androstan-17β-ol acetate** (**8a**), mp 121–125°, 207–213°; [α]D 21.5°; tlc, R_f = 0.34 (methanol–ethyl acetate 1:3); ir 3480, 3380, 3320 (sh), 1740, 1668, 1620, 1560, 1252, 1045, 1028 cm⁻¹; nmr δ 0.82 (s), 1.10 (s), 2.03 (s), 2.93 (s), 3.83 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{22}H_{34}N_2O_4 \cdot CH_3OH$: C, 65.37; H, 9.06; N, 6.63. Found: C, 65.65; H, 9.10; N, 6.96.

The N-acetyl derivative **8b** could not be derived by acetylation with acetic anhydride and pyridine.

Acid Treatment

3α-(N-Acetylureido)-4α,5-oxido-5α-androstan-17β-ol Acetate (**2b**).—A solution of 215 mg of 3α-(N-acetylureido)-4α,5-oxido-5α-androstan-17β-ol acetate (**2b**) in 43 ml of acetone and 5.4 ml of 0.33 *N* sulfuric acid was allowed to stand at room temperature (22°) for 16 days, at which time no starting material remained. The acetone was removed *in vacuo* and the residue was extracted with ethyl acetate. The extract was washed with dilute sodium carbonate and saline solutions and dried, and the solvent was evaporated. The product, 216 mg, was chromatographed on 30 g of Celite 545 with the system benzene–2,2,4-trimethylpentane (3:1) methanol–water (4:1). Elution with the upper phase afforded 110 mg of **3α-(N-acetylureido)-5β-androstane-4α,5,17β-triol 17-monoacetate** (**13a**), and 35 mg of a more polar product which could be derived from the monoacetate under the same acidic condition. Recrystallization of the triol monoacetate from acetone and methanol afforded 70 mg of **13a**, mp 171–176°; [α]D 20.3° (ethanol); tlc, R_f = 0.22 (ethyl acetate); ir 3470 (br), 3135, 3120, 1700 (br), 1550, 1250, 1028 cm⁻¹; nmr δ 0.78 (s), 0.93 (s), 2.03 (s), 2.10 (s), 3.70 (m), 4.17 (m), and 4.63 ppm (t, J = 8 cps).

Anal. Calcd for $C_{24}H_{38}N_2O_6 \cdot 1.5H_2O$: C, 60.35; H, 8.65; N, 5.87. Found: C, 60.21; H, 8.06; N, 5.75.

Acetylation of 70 mg of 3α-(N-acetylureido)-5β-androstane-4α,5,17β-triol 17-monoacetate (**13a**) with pyridine and acetic anhydride required 14 days at room temperature to go to completion. Chromatography on 20 g of Celite 545 in the system 2,2,4-trimethylpentane–benzene (5:3) and methanol–water (4:1) afforded 65 mg of the acetylated product. Recrystallization from acetone–petroleum ether gave 54 mg of **3α-(N-acetylureido)-5β-androstane-4α,5,17β-triol 4,17-diacetate** (**13b**), mp 222–225°; tlc, R_f = 0.36 (ethyl acetate); ir 3465, 3290, 3140, 1750, 1735, 1700, 1552, 1495, 1250–1225, 1030, 600 cm⁻¹; nmr δ 0.78 (s), 0.93 (s), 2.03 (s), 2.07 (s), 2.13 (s), 4.50 (m), 4.63 (t, J = 8 cps), and 5.01 ppm (m).

Anal. Calcd for $C_{26}H_{40}N_2O_7$: C, 63.39; H, 8.19; N, 5.69. Found: C, 63.61; H, 8.52; N, 5.31.

3α-(N-Acetylureido)-4β,5-oxido-5β-androstan-17β-ol Acetate (**3b**).—A solution of 103 mg of 3α-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol acetate (**3b**) in 20 ml of acetone and 2.5 ml of 0.33 *N* sulfuric acid was allowed to stand at room temperature for 48 hr. No starting material remained at this time as judged by thin layer chromatography. The reaction product (18 mg) was recrystallized from methanol and gave a product, mp 163–163.5°, with the same mobility on paper and thin layer chromatography as 3α-(N-acetylureido)-5β-androstane-4α,5,17β-triol 17-monoacetate. The product had [α]D −99° (ethanol), and the nmr spectrum was consistent with **3α-(N-acetylureido)-5β-androstane-4β,5,17β-triol 17-monoacetate** (**14**), nmr δ 0.80 (s), 1.27 (s), 2.03 (s), 2.13 (s), 3.80 (m), 4.43 (m), and 4.63 ppm (t, J = 8 cps); ir 3600–3100, 1736, 1613, 1587, 1250, 1105, 1045, 990 cm⁻¹.

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, 63.03; H, 8.40; N, 6.10.

After acetylation of the product **14** with acetic anhydride and pyridine at room temperature for 4 days, at least 80% of the starting material remained; there was insufficient acetylated material to isolate and characterize.

3α-Ureido-4β,5-oxido-5β-androstan-17β-ol Acetate (**3a**).—A solution of 50 mg of 3α-ureido-4β,5-oxido-5β-androstan-17β-ol acetate (**3a**) in 8 ml of acetone and 0.85 ml of 0.25 *N* sulfuric acid gave a precipitate almost immediately. The mixture was allowed to stand at room temperature for 5 days and filtered. The precipitate was insoluble in ethyl acetate and in acetone. The precipitate was treated with 5% sodium carbonate solution, extracted with ethyl acetate, and washed with water. The mobility of the product on tlc and the infrared spectrum were identical with that of the starting material.

3β-(N-Acetylureido)-4β,5-oxido-5β-androstan-17β-ol Acetate (**7b**).—A solution of 31 mg of 3β-(N-acetylureido)-4β,5-oxido-5β-androstan-17β-ol acetate (**7b**) in 6 ml of acetone and 0.74 ml

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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