pregnane-3α,20β,21-triol 21-(*p*-toluenesulfonate) and the mixture was refluxed for 4 hr. An excess of ethyl acetate was added slowly and then 30 ml of 2 *N* hydrochloric acid was added. The ether phase was washed with water until neutral, filtered, and concentrated to dryness. Paper chromatography of an aliquot (system B, 2.5 hr) showed a principal product with the mobility of 5β-pregnane-3α,20β-diol (R_f 0.73) and a trace of material with the mobility of 5β-pregnane-3α,20β,21-triol (R_f 0.21). Crystallization from ethanol gave 39 mg (60%) of product, mp 234–235°, which did not depress the melting point of 5β-pregnane-3α,20β-diol; the infrared spectra of the two samples were identical. A second crop of crystals (7 mg, 11%), mp 230–233°, brought the yield to 71%. Aliquots of the crystals and mother liquor were chromatographed for 44 hr on paper impregnated with 30% propylene glycol in acetone and developed with cyclohexane. No 5β-pregnane-3α,20α-diol was detected in the crystals or mother liquor. Standard 5β-pregnane-3α,20β-diol moved 19.2 cm; 5β-pregnane-3α,20α-diol moved 11.6 cm.

5β-Pregnene-3α,20β-diol Diacetate (XVIII) from XIV. A. Acetylation.—A solution of 491 mg (1.00 mmole) of 5β-pregnane-3α,20β,21-triol 21-(*p*-toluenesulfonate) in 2.0 ml each of acetic anhydride and pyridine was heated on a steam bath for 6 min, cooled, and diluted with water. The mixture was extracted with chloroform and the chloroform solution was washed with dilute hydrochloric acid, dilute sodium hydroxide, and water and then taken to dryness *in vacuo*. It was not possible to obtain crysals from the product (XVI).

B. Treatment with Sodium Iodide.—A solution of the material in chloroform was evaporated to dryness *in vacuo;* 25 ml of acetic anhydride and 600 mg of sodium iodide were added. Ten milliliters of acetic anhydride was evaporated and then the solution was heated under reflux for 1 hr and concentrated almost to dryness. The residue was dissolved in chloroform and the solution was washed with water and concentrated to dryness *in vacuo*. Efforts to obtain crystals were not successful.

The residue was chromatographed in a 3.6-cm diameter column which contained 360 g of silica gel and 180 ml of *t*-butyl alcohol.[23] The product was eluted with 1% *t*-butyl alcohol in methylene chloride (11-ml fractions). Fractions 37–54 gave 408 mg of residue (XVII) which could not be induced to crystallize but which appeared to be homogeneous by chromatography on paper in system H for 24 hr.

C. Catalytic Deiodination.—Half of product XVII (204 mg) was dissolved in 20.0 ml of methanol and the solution was shaken in an atmosphere of hydrogen in the presence of 2.0 ml of dry ethyl morpholine and 400 mg of $Pd(CaCO_3)_x$[22] until uptake of hydrogen ceased (45 min). Then it was retreated with hydrogen and an additional 400 mg of catalyst. The solution was filtered and concentrated; the residue was taken into benzene and the solution was washed with water. The aqueous phase contained 0.315 mmole (82% of theory) of iodide ion. The residue from the organic phase was chromatographed on 90 g of silica gel plus 45 ml of *t*-butyl alcohol[23] in a 1.8-cm diameter column and eluted with 1% *t*-butyl alcohol in methylene chloride. Fractions (4.8 ml each) 24–42 gave 124 mg of residue which yielded crystals (114 mg, mp 112.5–113°) from aqueous alcohol. The product did not depress the melting point of authentic 5β-pregnane-3α,20β-diol diacetate (mp 112.5–113°); the infrared spectra of the two samples were identical.

5β-Pregnane-3α,20β-diol Diacetate (XVIII) from XV.—Acetylation of 5β-pregnane-3α,20β-diol, mp 234–235° (prepared from XIV by treatment with $LiAlH_4$), in acetic anhydride–pyridine yielded a product which melted at 111.5–112.5° (lit.[3] mp 112–113°) and which did not depress the melting point of 5β-pregnane-3α,20β-diol diacetate. Its infrared spectrum was identical with that of authentic 5β-pregnane-3α,20β-diol diacetate.

Registry No.—III, 7791-36-8; IV, 7791-37-9; V, 7791-38-0; VI, 7791-39-1; VIII, 7791-40-4; X, 7791-41-5; XII, 7791-42-6; XIV, 7791-43-7; XV, 80-91-1; XVIII, 6100-28-3.

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Synthesis of C-3 Ureido Steroids[1]

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3α-Ureido-5α-androstan-17-one, 3α-ureido-5β-androstan-17-one, and their 3β epimers have been synthesized. The stereospecific synthesis of the 3-aminoandrostan-17β-ols was first carried out. Carbamylation of the amino group was achieved with nitrourea or trichloroacetoisocyanate and oxidation of the 17β-hydroxy group afforded the 3-ureido-17-keto steroids. 3α-Ureido-5α-androstan-17-one was also prepared by an alternate route from the ethylene ketal of 3α-azido-5α-androstan-17-one.

In recent years there has been great interest in the biological activity of nitrogenous steroids from natural sources and from partial synthesis.[3] In general the nitrogen atom in the naturally occurring steroidal alkaloids is present as an alkamine which may vary from simple primary amine to complex tertiary amine. It was therefore interesting that an ureido steroid was isolated from human urine.[4] The compound was obtained after administration of 11β-hydroxy-Δ^4-androsten-17-one and was characterized as 3α-ureido-11β-hydroxy-Δ^4-androsten-17-one. It was subsequently demonstrated that the ureido steroid was formed at pH 5 from the allylic metabolite, 3α,11β-dihydroxy-Δ^4-androsten-17-one, and urea present in the urine.[5] In order to study the biological properties as well as chemical and physical properties of this novel type of steroids, the synthesis of the epimeric saturated 3-ureido-11-deoxy-17-keto steroids has been investigated.

The stereospecific synthesis of the isomeric C-3 amino 5α- and 5β-steroids was examined as a first stage in the synthesis of ureido derivatives. It is well known that cyclic oximes upon reduction with sodium and alcohol afford equatorial amines whereas axial amines are obtained by catalytic hydrogenation. The synthesis of 3β-amino-5α-androstan-17β-ol (Ia) and its 3α-amino epimer IIa from 3-oximino-5α-

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androstan-17β-ol by these methods has been reported.[6-9] In the present study the 3β-amine Ia was readily prepared by the reduction of the oxime with sodium and propyl alcohol, but in our hands catalytic hydrogenation of 3-oximino-5α-androstan-17β-ol with Adams catalyst in acetic acid yielded a mixture of epimeric amines with predominant formation of the equatorial 3β-amine. The 3α-amine IIa could not be readily separated from this mixture by methods which included fractional crystallization of the maleate salt.[10] This epimer was therefore synthesized from 3α-azido-5α-androstan-17-one (VI) which was obtained from 3β-toluenesulfonoxy-5α-androstan-17-one (V) by reaction with sodium azide in dimethyl sulfoxide.[11,12] Reduction with lithium aluminum hydride yielded 3α-amino-5α-androstan-17β-ol (IIa). The O,N-diacetyl derivative (IIb) was identical with that prepared from an authentic sample of IIa generously supplied by Dr. M. M. Janot.[13] In the 5β series the reduction of the 3-oximino derivative proceeded stereoselectively as expected. Treatment of 3-oximino-5β-androstan-17-β-ol with sodium and *n*-propyl alcohol afforded the equatorial 3α-amino-5β-androstan-17β-ol (IVa) in good yield while catalytic reduction of the oxime yielded the axial 3β-amino-5β-androstan-17β-ol (IIIa).

For characterization of amines Ia–IVa, the N,O-diacetyl derivatives (Ib–IVb) and the acetate salts (Id–IVd) were prepared. When the amines were recrystallized from acetone, the N-isopropylidene derivatives (Ic–IVc) formed spontaneously. The N-isopropylidene group was characterized by absorption[14] around 1670 cm^{-1}.

In the studies on the reductive amination of steroids, Schmidt and his colleagues obtained a 3-amino-5β-androstan-17β-ol by catalytic hydrogenation of a mixture of testosterone and benzylamine with palladium on charcoal.[10] The orientation of the 3-amino group was not established. The base was amorphous but the N-(*p*-methoxybenzylidene) derivative was crystalline: mp 143–145°; $[\alpha]_D$ +40.3°. In the present study 3β-amino-5β-androstan-17β-ol (IIIa) was the only one of the four stereoisomers that did not crystallize. The N-(*p*-methoxybenzylidene) derivative IIIe prepared from the base with anisaldehyde had the same physical constants as the compound described by Schmitt and co-workers.[10] It differed from the same derivative of the 3α-amino 5β-steroid IVe and is therefore 3β-amino-5β-androstan-17β-ol (IIIa).

Attempts to oxidize 3-aminoandrostan-17β-ol to the corresponding 17-ketone proved to be unfruitful without protection of the amino group. Although N-acetyl derivatives would be resistant to the required oxidation conditions, these derivatives were eliminated from consideration for a variety of reasons. Since the object of the investigation was the preparation of ureido steroids, the amino group could be protected by carbamylation which would then be on the path to the desired final product. Trichloroacetoisocyanate has recently been employed for the preparation of carbamates from alcohols[15] and the use of this reagent was investigated for preparation of N-substituted urea derivatives from amines. Treatment of 3β-amino-5α-androstan-17β-ol (Ia) with trichloroacetoisocyanate gave 3β-(N-trichloroacetylureido)-5α-androstan-17β-yl N-trichloroacetylcarbamate (XVIa) which was hydrolyzed with acid to 3β-ureido-5α-androstan-17β-yl carbamate (XVIb); the over-all yield from the free base was 50–70%. Methanolysis of the carbamate in the presence of sodium methoxide yielded the desired 3β-ureido-5α-androstan-17β-ol (VIIa). Trichloroacetoisocyanate proved to be an excellent reagent for the formation of the ureido group. However, the 17β-hydroxyl group was transformed to the carbamate which had to be removed. Since this procedure required several steps, the one-stage reaction of the acetate salt of the 3-aminoandrostan-17β-ols with nitrourea[16] was employed for preparation of the isomeric 3-ureidoandrostan-17β-ols (VIIa–Xa) in yields of 30–60%. The ureidohydroxy steroids were further characterized by the formation of the N-acetyl 17-acetates (VIIb–Xb). The 3-ureidoandrostan-17-ones (XI–XIV) were readily synthesized by oxidation of the corresponding 17β-hydroxy derivatives with Jones reagent (see Chart I).

An alternate synthesis of 3α-ureido-5α-androstan-17-one (XII) was also explored. The ethylene ketal of 3α-azido-5α-androstan-17-one (XVa) was prepared and the product was reduced with lithium aluminum hydride to yield 3α-amino-5α-androstan-17-one 17-ketal (XVb), isolated as the acetate salt. The salt was then treated with trichloroacetoisocyanate and the resulting trichloroacetylureido derivative was hydrolyzed with acid; 3α-ureido-5α-androstan-17-one (XII) was obtained in about 30% yield from XVa.

The orientation of the nitrogen function assigned from the mode of reduction was confirmed by nuclear magnetic resonance spectrometry. The axial proton at C-3 in the N-acetyl compounds, 3-acetamido derivatives (Ib and IVb), and the 3-N-acetylureido derivatives (VIIb and Xb) gave a signal that was broader and about 0.5 ppm farther upfield than that of the corresponding equatorial proton in IIb and IIIb, VIIIb and IXb. For example, 3β-acetamido-5α-androstan-17β-ol acetate (Ib) had a signal centered at $\delta = 3.62$ ppm (axial 3α proton), whereas the signal for the equatorial 3β proton in the 3α-acetamido derivative (IIb) was centered at $\delta = 4.12$ ppm. These differences in the chemical shifts of the axial and equatorial protons are in agreement with those found in the epimeric 3-acetoxy steroids[17] as well as in 17-acetamido steroids.[18] In addition the chemical shifts for the axial protons at C-3 of the acetamido and acetylureido derivatives in both the 5α and 5β series, which were centered at 3.62–

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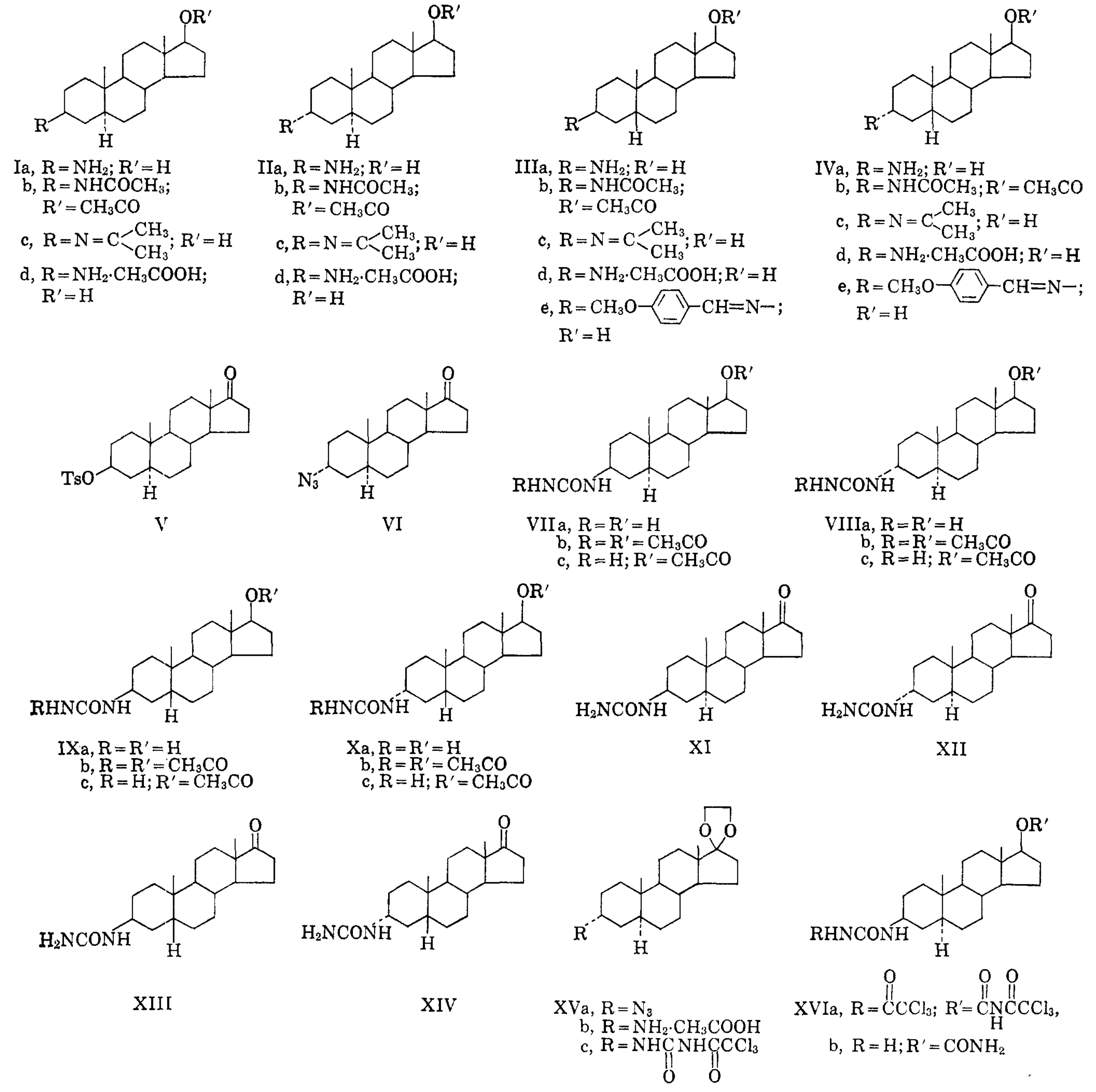
Chart I



3.78 ppm, agree well with that (multiplet between 3.33 and 4.16 ppm) found in O,N-diacetylfuntessine (3β-acetamido-5α-conan-12β-ol acetate)[19] for the axial 3α proton.

Experimental Section[20]

3β-Amino-5α-androstan-17β-ol (Ia).—A solution of 0.55 g of 3-oximino-5α-androstan-17β-ol, mp 213–214°, in 100 ml of *n*-propyl alcohol was treated, in portions, with a total of 10 g of sodium. After 7 hr at reflux, the solvent was evaporated under reduced pressure, water was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was washed with water and dried, and the solvent was evaporated. Crystallization from benzene afforded 0.3 g of **3β-amino-5α-androstan-17β-ol** (Ia): mp 170–171°; [α]D +12.0°; $\nu_{\max}^{\mathrm{KBr}}$ 3400 → 3170, 1598, 1075, 1064, 1050 cm^{-1}; vpc, rrt = 0.47 (SE30), 1.15 (QF1); TL-II, 0.50 (lit.[7] mp 167–169°, [α]D +11.1°).

The acetate salt Id was prepared by addition of acetic acid in ether to an alcoholic solution of Ia: mp 178–180°; [α]D +13.0° (ethanol); $\nu_{\max}^{\mathrm{KBr}}$ 3360 (br), 2600 (br), 2200 (br), 1625, 1540 (br), 1075, 1055, 1025, 1015, 660 cm^{-1} (lit.[7] mp 197–198°, [α]D +10.2°).

Recrystallization of Ia from acetone yielded **3β-(N-isopropylidenimino)-5α-androstan-17β-ol** (Ic): mp >280°; $\nu_{\max}^{\mathrm{KBr}}$ 3200 (br), 1670, 1085, 1055, 1030 cm^{-1}.

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[20] All melting points were determined on a micro hot stage and were corrected. Optical rotations were determined at 25° in chloroform unless otherwise stated. Nmr spectra were determined in deuteriochloroform on a Varian A-60 spectrometer with tetramethylsilane as internal reference. Values are given as δ in parts per million (ppm) (s = singlet, mbr = multiplet broad). Infrared spectra were determined on a Beckman IR-9 spectrophotometer (br = broad, s = small, → = series of bands). Thin layer chromatography on silica gel GF was carried out by the following systems: TL-I = methanol–ethyl acetate (1:9); TL-II = *n*-butyl alcohol–acetic acid–water (4:1:5), upper layer; TL-III = cyclohexane–ethyl acetate (7:3), and R_f values are given. Vapor phase chromatography (vpc) was carried out on the Barber Colman Model 5000 in 4 mm × 1.8 m glass columns packed with 100–140 mesh Gas Chrom-P coated with either SE-30 (3% by weight) or QF-1 (3% by weight) at 252°. The values are reported in relative retention times (rrt) to cholestane as reference. The retention times of cholestane were 5.8 min on SE-30 and 3.2 min on QF-1.

Acetylation of the amino alcohol (Ia) with acetic anhydride and pyridine at room temperature followed by crystallization from ethyl acetate gave **3β-acetamido-5α-androstan-17β-ol acetate** (Ib): mp 284–286°; [α]D 0°; $\nu_{\max}^{\text{KBr}}$ 3280, 3909, 1735, 1640 (br), 1576, 1560, 1265, 1260, 1240, 1050, 1035 cm^{-1}; nmr, δ = 0.80 (s, C-18 methyl protons and C-19 methyl protons), 1.98 (s, acetamido methyl protons), 2.05 (s, acetate methyl protons), 3.62 (mbr, C-3α proton) 4.64 (mbr, C-17α proton) and 6.01 ppm (mbr, imino proton); vpc rrt = 1.90 (SE 30); TL-II, 0.50 (lit.[7,21] mp 286–287°, [α]D 0°).

3β-Amino-5β-androstan-17β-ol (IIIa).—A solution of 0.3 g of 3-oximino-5β-androstan-17β-ol in 30 ml of acetic acid was hydrogenated with 0.7 g of Adams catalyst for 4 hr at room temperature. After filtration of the catalyst, the filtrate was evaporated to dryness and the residue was crystallized from ethanol to yield 0.1 g of **acetate salt IIId**: mp 170–173°; $\nu_{\max}^{\text{KBr}}$ 3370, 2800 → 2350, 2200 (br), 1635, 1520 (br), 1075, 1060, 1010, 685, 660, 620 cm^{-1}; TL-II, 0.50.

The acetate salt (IIId) was dissolved in aqueous alcohol, neutralized with base, and extracted with ether. The ethereal solution was washed with water and dried and the solvent was evaporated to give **3β-amino-5β-androstan-17β-ol** (IIIa), an amorphous base which could not be crystallized: [α]D +14.3°; $\nu_{\max}^{\text{KBr}}$ 3700 → 3070 (br), 1588 (br), 1075, 1050 (br), cm^{-1}; vpc, rrt = 0.42 (SE 30), 0.97 (QFI); TL-II, 0.50

Anal. Calcd for $C_{19}H_{33}NO \cdot 0.5H_2O$: C, 75.94; H, 11.41; N, 4.66. Found: C, 76.26; H, 10.81; H, 4.48.

3β-(N-Isopropylidenimino)-5β-androstan-17β-ol (IIIc) was prepared from IIIa with acetone: amorphous base; $\nu_{\max}^{\text{KBr}}$ 3420 (br), 1665 1075, 1055, 1040, 1020 cm^{-1}.

Acetylation of IIIa and recrystallization from ethyl acetate afforded **3β-acetamido-5β-androstan-17β-ol acetate** (IIIb): mp 197–198°; [α]D +29.3°; $\nu_{\max}^{\text{KBr}}$ 3400, 3350 (s), 1720 (br), 1680 (br), 1530, 1270, 1265, 1050, 1030 cm^{-1}; nmr, δ = 0.78 (s, C-18 methyl protons), 1.00 (s, C-19 methyl protons), 2.00 (s, acetamido methyl protons), 2.05 (s, acetate methyl protons), 4.28 (mbr, C-3α proton), 4.66 (mbr, C-17α proton) and 5.83 ppm (mbr, imino proton); vpc, rrt = 1.59 (SE 30); TL-I, 0.54.

Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.41; H, 10.02; N, 3.80.

A solution of 0.1 g of IIIa in 10 ml of ethanol was refluxed with 0.1 ml of anisaldehyde for 3 hr. The reaction mixture was evaporated *in vacuo* and the residue was dried under high vacuum at 100° for 1 hr. The residue was recrystallized from alcohol to afford crystalline **3β-[N-(*p*-methoxybenzyliden)imino]-5β-androstan-17β-ol** (IIIe): mp 140–142°; [α]D +38.7°; $\nu_{\max}^{\text{KBr}}$ 3440 (br), 3070, 3040, 1640, 1608, 1576, 1511, 1250, 1070 (s), 1055 (s), 1035, 830, 815 cm^{-1}; nmr, δ = 0.75 (s, C-18 methyl protons), 1.03 (s, C-19 methyl protons), 3.62 (m, C-3α proton), 3.83 (s, methoxymethyl protons), 6.96 and 7.75 (d, protons of benzene ring) and 8.30 ppm (s, methine proton) (lit.[10] mp 143–145°, $[\alpha]^{22}$D +40.3°).

3α-Amino-5β-androstan-17β-ol (IVa).—A solution of 1.0 g of 3-oximino-5β-androstan-17β-ol, mp 207–210° in 160 ml of *n* propyl alcohol was treated, in parts, with a total of 20 g of sodium. After refluxing for 7 hr the reaction mixture was worked up as for the 3β-amine (Ia). Crystallization of the residue from benzene afforded 0.56 g of **3α-amino-5β-androstan-17β-ol** (IVa): mp 179–182°; [α]D +16.6°; $\nu_{\max}^{\text{KBr}}$ 3340, 3190 (br), 1605, 1080, 1055, 1030, 1010 cm^{-1}; vpc rrt = 0.42 (SE 3;), 0.97 (QF 1); TL-II, 0.50.

Anal. Calcd for $C_{19}H_{33}NO$: C, 78.29; H, 11.41; N, 4.81. Found: C, 78.28; H, 11.44; N, 4.77.

The **acetate salt** (**IVd**) was prepared from IVa: mp 179–182°; $\nu_{\max}^{\text{KBr}}$ 3500 → 3010, 2800 → 2300, 2140 (br), 1635 (br), 1560 (br), 1075 (s), 1055, 1030 (s), 1015 (br), 665 cm^{-1}. Recrystallization of the amino alcohol from acetone yielded **3α-(N-isopropylidenimino)-5β-androstan-17β-ol** (IIIc): mp 240–241°; $\nu_{\max}^{\text{KBr}}$ 3225 (br), 1670, 1095, 1075, 1060, 1040, 1020, 1010 cm^{-1}.

Anal. Calcd for $C_{22}H_{37}NO$: C, 79.70; H, 11.25; N, 4.23. Found: C, 79.47; H, 11.49; N, 3.92.

Acetylation of IVa and recrystallization from ethyl acetate yielded **3α-acetamido-5β-androstan-17β-ol acetate** (IVb): mp 225–226°; [α]D +45.8°; $\nu_{\max}^{\text{KBr}}$ 3255, 3085, 1730, 1670 (s), 1650, 1550, 1245, 1045, 1025 cm^{-1}; nmr, δ = 0.78 (s, C-18 methyl protons), 0.95 (s, C-19 methyl protons), 1.97 (s, acetamido methyl protons), 2.05 (s, acetate methyl protons), 3.78 (mbr, C-3β proton), 4.63 (t, C-17α proton), 5.71 ppm (mbr, imino proton); vpc, rrt = 1.59 (SE 30); TL-I, 0.56.

Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73. Found: C, 73.29; H, 9.97; N, 3.74.

3α-[N-(*p*-Methoxybenzyliden)imino]-5β-androstan-17β-ol (IVe) was prepared from the amino alcohol (IVa) and anisaldehyde. Recrystallization from ethanol gave IVe: mp 214–216°; [α]D +43.7°; nmr, δ = 0.76 (s, C-18 methyl protons), 1.00 (s, C-19 methyl protons), 3.17 (mbr, C-3β protons) 3.85 (s, methoxy methyl protons), 6.90 and 7.72 (d, protons of benzene ring) and 8.28 ppm (s, methine proton); $\nu_{\max}^{\text{KBr}}$ 3240 (br), 1632, 1603, 1512, 1305, 1255, 1173, 1050 (s), 1045 (s), 1033, 1015 (s), 840, 818 (s) cm^{-1}.

3α-Amino-5α-androstan-17β-ol (IIa).—A solution of 10.0 g of 3β-tosyloxy-5α-androstan-17-one (V) in 300 ml of dimethyl sulfoxide was heated with 5.0 g of sodium azide at 100° for 3 hr. The reaction solution was then extracted with ether and the ethereal solution was washed with water and the solvent was evaporated. Recrystallization from ethanol yielded 4.8 g of **3α-azido-5α-androstan-17-one** (VI): mp 116–117°; [α]D +79.8°; $\nu_{\max}^{\text{KBr}}$ 2100, 2078, 1740 cm^{-1}; nmr, δ = 0.85 (s, C-18 methyl protons), 0.83 (s, C-19 methyl protons), and 3.92 ppm (sbr, C-3β proton); TL-III, 0.46.

A solution of 6.3 g of 3α-azido-5a-androstan-17-one (VI), in 3 l. of anhydrous ether was refluxed overnight with 12.6 g of lithium aluminum hydride. The ethereal solution was washed with water, dried, and evaporated to dryness. The residue was dissolved with alcohol and ethereal acetic acid was added to give after recrystallization from ethanol 6.0 g of **acetate salt IId**: mp 180–182°; $\nu_{\max}^{\text{KBr}}$ 3300 → 3000, 2700 (br), 2500 (br), 2140 (br), 1635, 1575, 1545, 1085, 1075 (s), 1060, 680, 660 cm^{-1}; TL-II, 0.50.

The acetate salt IId was dissolved in aqueous alcohol, neutralized with base, and extracted with ether. The ethereal layer was washed with water, dried, and evaporated to yield **3α-amino-5α-androstan-17β-ol** (IIa): mp 173–175°; [α]D +16.8°; $\nu_{\max}^{\text{KBr}}$ 3380 → 3180, 1588 (br), 1075, 1055 cm^{-1}; vpc, rrt = 0.47 (SE 30), 1.06 (QF 1); TL-II, 0.50 (lit.[7,10] mp 170–175°, [α]D +17.3°).

3α-(N-isopropylidenimino)-5α-androstan-17β-ol (IIc) was prepared by recrystallization of IIa from acetone: mp 171–174°; $\nu_{\max}^{\text{KBr}}$ 3300 (br), 1655, 1075, 1060, 1050, 1025 cm^{-1}. Acetylation of IIa and recrystallization from ethyl acetate gave **3α-acetamido-5α-androstan-17β-ol acetate** (**IIb**): mp 196–197°; [α]D +23.5°; $\nu_{\max}^{\text{KBr}}$ 3240 (br), 3060, 1740, 1630 (br), 1560, 1245 (br), 1025 (br), cm^{-1}; nmr, δ = 0.79 (s, C-18 methyl protons), 0.82 (s, C-19 methyl protons), 2.00 (s, acetamido methyl protons), 2.05 (s, acetate methyl protons), 4.12 (mbr, C-3β proton), 4.58 (C-17α proton), and 6.03 ppm (mbr, imino proton); vpc, rrt = 1.70 (SE 30); TL-I, 0.56 (lit.[7,10] mp 192°, [α]D +26°); the melting point of the N,O-diacetyl derivative IIb was not depressed on admixture with the derivative prepared from an authentic sample[13] of IIa. The infrared spectra of the samples were identical.

3β-Ureido-5α-androstan-17β-ol (VIIa), and 3β-Ureido-5α-androstan-17-one (XI). A.—A solution of 1.0 g of acetate salt Id in 100 ml of 50% ethanol was refluxed for 1 hr with 0.3 g of nitrourea.[16] The solution was concentrated under reduced pressure, made slightly alkaline, and extracted with chloroform. The chloroform layer was washed with water and dried, and the solvent was evaporated to dryness. The residue (0.99 g) was chromatographed on silica gel. Elution with 3–5% ethanol–ethyl acetate and recrystallization from ethanol afforded 0.6 g of **3β-ureido-5α-androstan-17β-ol** (VIIa): mp >280°; [α]D +11.3° (pyridine); $\nu_{\max}^{\text{KBr}}$ 3520, 3370 (br), 1675 (br), 1600, 1554, 1071, 1052, 1029 cm^{-1}; TL-I, 0.31.

Anal. Calcd for $C_{20}H_{34}N_2O_2$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.98; H, 10.27; N, 8.32.

B.—Into a solution of 0.12 g of Ia in 20 ml of anhydrous methylene chloride was added 2 ml of trichloroacetoisocyanate[15] dropwise. The solution was allowed to stand overnight at room temperature and the solvent was evaporated. Water was added and the precipitate was extracted with benzene. The benzene layer was dried and the solvent was evaporated. The residue was crystallized from petroleum ether–benzene yielding **3β-(N-trichloroacetylureido)-5α-androstan-17β-yl N-trichloroacetylcarbamate** (XVIa), mp 230–232°. A solution of the bistrichloroacetyl derivative (XVIa) in 30 ml of 3 *N* alcoholic hydrochloric acid was refluxed for 1.5 hr and the reaction mixture was extracted with chloroform. The chloroform layer was dried and

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(21) E. L. Foster and R. T. Blickenstaff, *J. Org. Chem.*, **31**, 1500 (1966).

evaporated to dryness, and the residue was recrystallized from ethanol to give 0.12 g of **3β-ureido-5α-androstan-17β-yl carbamate** (XVIb); mp 184–186°. A solution of 0.10 g of 3β-ureido-5α-androstan-17β-yl carbamate and 2.5 g of sodium methoxide in 50 ml of methanol was refluxed for 1.5 hr and the reaction mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried, and the solvent was evaporated. Recrystallization from ethyl acetate gave 0.06 g of **3β-ureido-5α-androstan-17β-ol** (VIIa): mp >250°; TL-I, 0.31; the infrared spectrum was identical with that synthesized by method A.

Acetylation of VIIa with acetic anhydride and pyridine was carried out at room temperature and the product was chromatographed on silica gel. The fraction eluted with 2% ethanol–methylene chloride yielded **3β-(N-acetylureido)-5α-androstan-17β-ol acetate** (VIIb): mp 280–284°; [α]D −3.7°; $\nu_{\max}^{\mathrm{KBr}}$ 3450, 3250 (br), 3120, 1740, 1700 (br), 1568, 1290 (s), 1245 (br), 1045 cm^{-1}; nmr, δ = 0.78 (s, C-18 methyl protons), 0.81 (s, C-19 methyl protons), 2.03 (s, acetate methyl protons), 2.11 (s, acetamido methyl protons), 3.75 (mbr, C-3α proton), and 4.67 ppm (t, C-17α proton); TL-I, 0.70.

Anal. Calcd for $C_{24}H_{38}N_2O_4$; C, 68.86; H, 9.15; N, 6.69. Found: C, 68.90; H, 9.24; N, 6.68.

The fraction eluted with 5% ethanol–methylene chloride yielded **3β-ureido-5α-androstan-17β-ol acetate** (VIIc): mp 236–239°; [α]D +2.7°; $\nu_{\max}^{\mathrm{KBr}}$ 3465, 3390, 3320, 3190, 1735, 1670, 1650, 1620, 1585, 1538, 1290 (s), 1267 (s), 1255, 1247, 1080 (s), 1048, 1033 cm^{-1}; TL-I, 0.35.

Anal. Calcd for $C_{22}H_{36}N_2O_3$: C, 70.17; H, 9.64; N, 7.44. Found: C, 69.94; H, 9.55; N, 7.28.

A solution of 0.2 g of VIIa in 300 ml of acetone was oxidized with 5 ml of Jones reagent[22] by stirring for 5 min at room temperature. After the addition of methanol, the product was extracted with chloroform. The chloroform was washed with water and dried, and the solvent was evaporated to yield 0.2 g of crude substance. Chromatography on silica gel, elution with 2% ethanol–methylene chloride, and recrystallization from ethyl acetate afforded 0.13 g of **3β-ureido-5α-androstan-17-one** (XI): mp 198–201°; [α]D +84.1°; $\nu_{\max}^{\mathrm{KBr}}$ 3275 (br), 1739, 1652 (br), 1600, 1548 (br) cm^{-1}; TL-I, 0.34.

Anal. Calcd for $C_{20}H_{32}N_2O_2 \cdot 0.52H_2O$: C, 70.34; H, 9.74; N, 8.20. Found: C, 70.54; H, 9.32; N, 7.94.

3α-Ureido-5β-androstan-17β-ol (Xa) and 3α-Ureido-5β-androstan-17-one (XIV).—A solution of 2.0 g of the acetate salt (IVd) in 200 ml of 50% alcohol was refluxed with 0.6 g of nitrourea for 1 hr and worked up in the same manner as in method A for VIIa. The product (1.8 g), was chromatographed on silica gel and elution with 5% ethanol–ethyl acetate gave 1.0 g of **3α-ureido-5β-androstan-17β-ol** (Xa): mp 258–161°, after recrystallization from ethanol; [α]D +57.2° (pyridine); $\nu_{\max}^{\mathrm{KBr}}$ 3460, 3340, 3200 (s), 3100 (s), 1662, 1640, 1605, 1555, 1090 (s), 1073, 1055, 1042 (s), 1027 (s), 1007 cm^{-1}; TL-I, 0.31.

Anal. Calcd for $C_{20}H_{34}N_2O_2$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.78; H, 10.15; N, 8.42.

The ureido alcohol (Xa) was acetylated and chromatographed on silica gel. Elution with 2% alcohol–methylene chloride afforded **3α-(N-acetylureido)-5β-androstan-17β-ol acetate** (Xb): mp 211–214°; [α]D +44.9°; $\nu_{\max}^{\mathrm{KBr}}$ 3290, 3250, 3150 (br), 1730, 1695, 1555, 1290 (s), 1260, 1252, 1227 (s), 1090 (s), 1075 (s), 1048, 1040, 1026 cm^{-1}; nmr δ = 0.79 (s, C-18 methyl protons), 0.95 (s, C-19 methyl protons), 2.05 (s, acetate methyl protons), 2.13 (s, acetamido methyl protons), 3.75 (mbr C-3β proton), and 4.67 ppm (t, C-17α proton); TL-I, 0.70.

Anal. Calcd for $C_{24}H_{38}N_2O_4$; C, 68.86; H, 9.15; N, 6.69. Found: C, 68.79; H, 9.18; N, 6.59.

Elution with 5% ethanol–methylene chloride gave **3α-ureido-5β-androstan-17β-ol acetate** (Xc): mp 138–140°; [α]D +40.2°; $\nu_{\max}^{\mathrm{KBr}}$ 3510, 3350 (br), 3200 (br), 3010 (br), 1735, 1660 (br), 1610 (br), 1545 (br), 1290 (s), 1240, 1220 (s), 1090 (s), 1075 (s), 1045, 1030 cm^{-1}; TL-I, 0.35.

Anal. Calcd for $C_{22}H_{36}N_2O_3 \cdot H_2O$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.10; H, 9.48; N, 6.86.

A solution of 0.20 g of Xa in 300 ml acetone was oxidized with 5 ml of Jones reagent. The product was chromatographed on silica gel. Elution with 2% ethanol–methylene chloride afforded 0.10 g of **3α-ureido-5β-androstan-17-one** (XIV): mp 196–199°, after recrystallization from ethyl acetate; [α]D +110°; $\nu_{\max}^{\mathrm{KBr}}$ 3420, 3400, 3260 (s), 3200 (s), 1730, 1690, 1655 (br), 1600 (s), 1530 (br) cm^{-1}; TL-I, 0.34.

Anal. Calcd for $C_{20}H_{32}N_2O_2$: C, 72.25; H, 9.70; N, 8.43. Found: C, 72.30; H, 9.76; N, 8.37.

3β-Ureido-5β-androstan-17β-ol (IXa) and 3β-ureido-5β-androstan-17-one (XIII).—A solution of 1.4 g of acetate salt IIId in 140 ml of 50% alcohol was refluxed with 0.4 g of nitrourea for 1 hr, as above. The product (1.1 g) was chromatographed on silica gel. Elution with 5% ethanol–ethyl acetate and recrystallization from ethanol afforded 0.45 g of **3β-ureido-5β-androstan-17β-ol** (IXa): mp 246–248°; [α]D +23.5° (pyridine); $\nu_{\max}^{\mathrm{KBr}}$ 3480, 3362 (br), 3200, 1675, 1657, 1605, 1560 (br), 1073, 1058, 1041, 1018, 1005 cm^{-1}; TL-I, 0.23.

Anal. Calcd for $C_{20}H_{34}N_2O_2$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.71; H, 10.11; N, 8.20.

Acetylation of IXa and chromatography gave the O,N-diacetyl derivate (IXb) and the monoacetate IXc. The analytical sample of **3β-(N-acetylureido)-5β-androstan-17β-ol acetate** (IXb) melted at 258–261°: [α]D +15°; $\nu_{\max}^{\mathrm{KBr}}$ 3410 (s), 3320, 3240 (s), 3130 (br), 1737, 1706, 1660 (s), 1530 (br), 1500, 1255, 1245, 1225 (s), 1052 (s), 1035, 1027 cm^{-1}; nmr, δ = 0.78 (s, C-18 methyl protons), 1.00 (s, C-19 methyl protons), 2.05 (s, acetate methyl protons), 2.13 (s, acetamido methyl protons), 4.26 (mbr, C-3α proton), and 4.67 ppm (t, C-17α proton); TL-I, 0.70.

Anal. Calcd for $C_{24}H_{38}N_2O_4 \cdot 0.5H_2O$: C, 67.41; H, 9.19; N, 6.55. Found: C, 67.67; H, 8.91; N, 6.50.

The monoacetate (IXc), **3β-ureido-5β-androstan-17β-ol acetate**, melted at 209–212°; [α]D +13.3°; TL-I, 0.35; $\nu_{\max}^{\mathrm{KBr}}$ 3500 (s), 3440, 3330 (br), 3230 (br), 1735 (br), 1660 (br), 1615 (br), 1550 (br), 1285 (s), 1245, 1220 (s), 1090 (s), 1072 (s), 1045, 1030 cm^{-1}; TL-I, 0.35.

Anal. Calcd for $C_{22}H_{36}N_2O_3 \cdot 0.5H_2O$: C, 68.53; H, 9.65; N, 7.26. Found: C, 68.52; H, 9.81; N, 6.94.

An acetone solution 0.28 g of IXa was oxidized with Jones reagent and chromatography on silica gel gave 0.13 g of **3β-ureido-5β-androstan-17-one** (XIII) after recrystallization from ethyl acetate: mp 156–160°; [α]D +86.4°; $\nu_{\max}^{\mathrm{KBr}}$ 3460 (br), 3350 (br), 3220 (br), 1740, 1650 (br), 1605, 1550 (br), cm^{-1}; TL-I, 0.34.

Anal. Calcd for $C_{20}H_{32}N_2O_2 \cdot 0.5H_2O$: C, 70.34; H, 9.74; N, 8.20. Found: C, 70.69; H, 9.46; N, 8.50.

3α-Ureido-5α-androstan-17β-ol (VIIIa) and 3α-Ureido-5α-androstan-17-one (XII). **A.**—The ureido alcohol (VIIIa) was prepared from 5.0 g of acetate salt IId with nitrourea as above. Chromatography yielded 1.5 g of **3α-ureido-5α-androstan-17β-ol** (VIIIa): mp >260°; [α]D +16.8° (pyridine); $\nu_{\max}^{\mathrm{KBr}}$ 3480, 3425, 3310, 3195, 1660, 1632 (s), 1525, 1087, 1068 (s), 1058, 1030, 1010 (s) cm^{-1}; TL-I, 0.32.

Anal. Calcd for $C_{20}H_{34}N_2O_2$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.72; H, 10.11; N, 8.24.

Acetylation with acetic anhydride and pyridine afforded **3α-(N-acetylureido)-5α-androstan-17β-ol acetate** (VIIIb): mp 256–258°; [α]D +34.6°; $\nu_{\max}^{\mathrm{KBr}}$ 3460 (s), 3390 (s), 3282, 3242, 3130, 1735, 1695, 1548, 1505, 1290 (s), 1262 (s), 1245 (br), 1085 (s), 1075 (s), 1045 (s), 1032, 1015 (s) cm^{-1}; nmr, δ = 0.78 (s, C-18 methyl protons), 0.81 (s, C-19 methyl protons), 2.03 (s, acetate methyl protons), 2.13 (s, acetamido methy protons), 4.18 (mbr, C-3β proton), and 4.67 ppm (t, C-17α proton); TL-I, 0.70.

Anal. Calcd for $C_{24}H_{38}N_2O_4$: C, 68.83; H, 9.15; N, 6.69. Found: C, 68.83; H, 9.13; N, 6.64.

3α-Ureido-5α-androstan-17β-ol acetate (VIIIc) was also obtained: mp >260°; [α]D +12.8°; $\nu_{\max}^{\mathrm{KBr}}$ 3480, 3350 (br), 3210, 3090, 1735, 1645, 1613 (br), 1553, 1250, 1072 (s), 1030 cm^{-1}; TL-I, 0.35.

Anal. Calcd for $C_{22}H_{36}N_2O_3$: C, 70.17; H, 9.64; N, 7.44. Found: C, 70.35; H, 9.65; N, 7.48.

A solution of 0.29 g of VIIIa was oxidized with Jones reagent to yield 0.10 g of **3α-ureido-5α-androstan-17-one** (XII): mp 180–184°; [α]D +98.9°; $\nu_{\max}^{\mathrm{KBr}}$ 3600 → 3050, 1740, 1655 (br), 1600 (br), 1550 (br) cm^{-1}; TL-I, 0.34.

Anal. Calcd for $C_{20}H_{32}N_2O_2$: 3, 72.25; H, 9.70; N, 8.43. *Calcd.* For $C_{20}H_{32}N_2O_2 \cdot {}^{1}/_{3}H_2O$: C, 70.96; H, 9.72; N, 8.37. Found: C, 71.16, 71.44; H, 9.51, 9.48; N, 8.44.

B.—A solution of 4.8 g of 3α-azido-5α-androstan-17-one (VI) in 450 ml of benzene was refluxed overnight with 4.5 ml of ethylene glycol and 0.3 g of *p*-toluenesulfonic acid. The benzene layer was washed with water and 10% potassium hydroxide, the solution was dried, and the solvent was evaporated. The

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[22] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2555 (1953).

residue 4.4 g was chromatographed on basic alumina and the fraction eluted with 3% ethyl acetate in cyclohexane gave 3.2 g of **3α-azido-5α-androstan-17-one 17-ethylene ketal** (XVa), after recrystallization from methanol: mp 162–165; ν_{max}^{KBr} 2113, 2085, 1170, 1122, 1110 cm^{-1}; nmr δ = 0.80 (s, C-18 methyl protons), 0.83 (s, C-19 methyl protons), and 3.92 ppm (C-3β proton plus ethylene ketal protons).

A solution of 3.2 g of the azido ketal XVa in 3 l. of anhydrous ether was treated with 3.2 g of lithium aluminum hydride under reflux overnight. The product (2.5 g) was isolated as the acetate salt of **3α-amino-5α-androstan-17-one 17-ethylene ketal** (XVb): mp 130–133°; TL-II, 0.50. To a solution of 1.0 g of the acetate salt (XVb) in 20 ml of methylene chloride was added 1.0 g of trichloroacetosiocyanate. The reaction mixture was allowed to stand overnight at room temperature. After evaporation of the solvent, the residue was extracted with benzene, which was washed with water and dried, and the solvent was evaporated. The residue was recrystallized from ethyl acetate to yield 0.83 g of **3α-(N-trichloroacetylureido)-5α-androstan-17-one 17-ethylene ketal** (XVc); mp 220–225°. A solution of 0.6 g of 3α-trichloroacetylureido derivative XVc in 7.0 ml of 1 *N* alcoholic hydrochloric acid was refluxed for 1.5 hr. The solution was extracted with chloroform at pH 8. The chloroform layer was dried and evaporated to dryness, and the residue (0.5 g) was crystallized from ethyl acetate to give **3α-ureido-5α-androstan-17-one** (XII): mp 184–186°; TL-II, 0.34; the infrared spectrum was identical with that synthesized by method A.

Registry No.—Ia, 2426-52-0; Id, 7794-95-8; Ic, 7794-96-9; Ib, 2426-33-7; IIId, 7794-98-1; IIIa, 7794-99-2; IIIc, 7795-00-8; IIIe, 10028-42-9; IVa, 4215-18-3; IVd, 7795-02-0; IVb, 7795-03-1; IVe, 7795-04-2; VI, 7795-05-3; IId, 7795-06-4; IIa, 2436-47-7; IIb, 2603-32-9; VIIa, 7795-09-7; XVIa, 7795-10-0; XVIb, 7795-11-1; VIIb, 7795-12-2; VIIc, 7795-13-3; XI, 7795-14-4; Xa, 7795-15-5; Xb, 7795-16-6; Xc, 7795-17-7; XIV, 7795-18-8; IXa, 7795-19-9; IXb, 7795-20-2; IXc, 10060-16-9; XIII, 7795-22-4; VIIIa, 4271-67-4; VIIIb, 7795-24-6; VIIIc, 7795-25-7; XII, 7795-26-8; XVa, 7795-27-9; XVb, 7795-28-0; XVc, 7795-29-1.

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Spectral Properties and Reactions of 3β-Hydroxy-21-formyl-22-oximinopregn-5-en-20-one[1]

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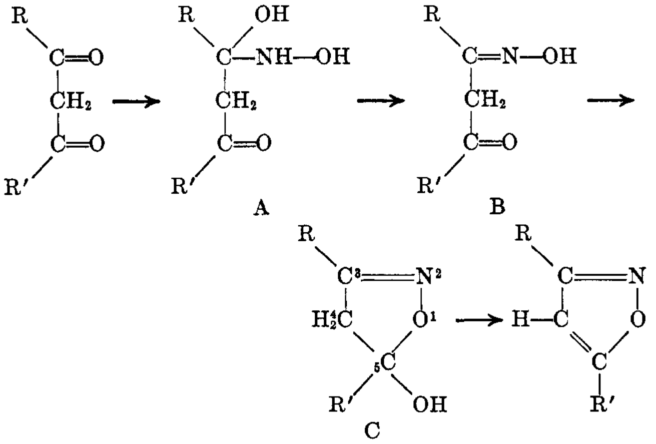
The reaction of 3β-hydroxy-21-formylpregn-5-en-20-one sodium enolate (**7**) with hydroxylamine hydrochloride, in ethanol–water, gave 3β-hydroxy-21-formyl-22-oximinopregn-5-en-20-one (**8**), as shown by its spectral and chemical characteristics. An attempted Beckmann rearrangement resulted in 3β-chloro-17β-(5-isoxazolyl)-5-androstene (**9**) as the sole product; this reaction seems to indicate that the formation of a nitrogen–oxygen bond is involved in the synthesis of the isoxazole ring.

The reaction of β-dicarbonyl compounds with hydroxylamine give rise to isoxazole derivatives, which are postulated to be formed according to the sequence shown below.



We reported earlier[3] that the reaction of 3β-hydroxy-21-formylpregn-5-en-20-one (**1**) with hydroxylamine hydrochloride in acetic acid yielded a mixture of 17β-(5-isoxazolyl)-5-androsten-3β-ol acetate (**2**) and 17β-(3-isoxazolyl)-5-androsten-3β-ol acetate (**3**). Treatment of this mixture with base allowed the isolation of 17β-(3-isoxazolyl)-5-androsten-3β-ol (**4**) and of 3β-hydroxy-21-cyanopregn-5-en-20-one sodium enolate (**5**). When β-ketoaldehyde **1** was treated with hydroxylamine hydrochloride in acetic acid buffered with sodium acetate, only 17β-(5-isoxazolyl)-5-androsten-3β-ol (**6**) was obtained; isoxazole **6** was also the only product when 3β-hydroxy-21-formylpregn-5-en-20-one sodium enolate (**7**) was treated with hydroxylamine in acetic acid (see Scheme I).

There have been reports on the isolation of 5-hydroxy-Δ^2-isoxazoline derivatives of type C as intermediates in the synthesis of 3,4- and 4-5-dialkyl-substituted isoxazoles.[4] We were unable, however, to find any mention of intermediates isolated in the preparation of 5-alkyl monosubstituted isoxazoles. We wish to report on the isolation, characterization, and chemical reactivity of an intermediate of type B, an

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