Steroid Total Synthesis—Hydrochrysene Approach. XIV.[1] The Synthesis of *dl*-18-Norepiandrosterone and *dl*-18-Nortestosterone[2]

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The previously known furfurylidene derivative of II as the 3-acetate III was ozonolyzed to give the dibasic acid IV (R = H) which, after conversion to the dimethyl ester, was cyclized by the Dieckmann method. Hydrolysis and decarboxylation of the resulting β-keto ester afforded *dl*-18-norepiandrosterone (V) and the 13-iso compound VI. These two ketones were readily interconverted, and the position of equilibrium in dioxane–hydrochloric acid was estimated by infrared spectroscopy to be 50–75% in favor of the *cis* isomer. The ozonolysis of the 3-acetate of the previously known furfurylidene ketone VIII (R = Ac) gave the dibasic acid IX (R = H) which was converted to the dimethyl ester and cyclized. Hydrolysis and decarboxylation of the resulting β-keto ester afforded *dl*-3α-hydroxy-18-nor-5β-androstane (X. R = H) and the 13-iso compound XI (R = H). The position of equilibrium of these two ketones was estimated by infrared spectroscopy to be 60–65% in favor of the C/D *cis* isomer. The configuration of these substances was established by reduction experiments in pyridine–borane in acetic acid. Reduction of the C/D *trans* ketone, as the 3-acetate, followed by benzoylation, gave the acetate benzoate XII (R^1 = Ac, R^2 = COC_6H_5). Partial hydrolysis afforded the hydroxy benzoate XII (R^1 = H, R^2 = COC_6H_5) which, upon oxidation to the 3-keto compound XIII followed by bromination and dehydrobromination, gave *dl*-18-nortestosterone benzoate (XIV, R = COC_6H_5). Saponification of this material yielded *dl*-18-nortestosterone (XIV. R = H).

In view of the therapeutic importance of 19-nor steroidal hormones, there has recently been considerable interest in examining the 18-nor compounds. To date 18-nor-estrone,[3]-progesterone,[4] and -cortisone[5] have been prepared, but no representative of the male hormone series has been reported. We have already described[6] certain total syntheses of steroids embodying a common sequence for the elaboration of ring D involving, as key intermediates, the corresponding 18-nor-D-homo compounds. In the present study a similar sequence for the ring contraction was followed, but the methylation step was omitted. In this manner we have synthesized 18-norepiandrosterone (V) and 18-nortestosterone[7] (XIV. R = H), as well as some 13-iso compounds.

The stereoselective synthesis of the hydroxy ketone II, by reduction of the readily available tetracyclic ketone I with lithium and alcohol in ammonia followed by hydrolysis and finally catalytic hydrogenation, has already been reported.[8] In the present work the furfurylidene derivative[8] of II was acetylated with pyridine and acetic anhydride to give the furfurylidene ketone acetate III, m.p. 209–211°, which was ozonized in methylene chloride at −70° to yield 3β-acetoxy-18-nor etioallohomobilianic acid (IV. R = H), m.p. 275.5–277°. This acid was converted to the dimethyl ester IV (R = CH_3), m.p. 101–102°, by the use of diazomethane, and submitted to Dieckmann cyclization with potassium *t*-butoxide in benzene by the method employed in the epiandrostane series,[8] to yield a mixture of β-keto esters which was hydrolyzed and decarboxylated by heating in aqueous triethylene glycol. Chromatography on Florisil gave two crystalline epimers in the ratio of 7 to 3; the less preponderant isomer, m.p. 160–162°, was eluted before the major product, m.p. 148–149°. From the manner of synthesis, it is apparent that these isomers can differ only in configuration at C-13; therefore, one must be the C/D *cis* isomer VI and the other the C/D *trans* isomer V. Since the *cis* isomer would be expected to be less planar than the *trans* and therefore less strongly absorbed upon Florisil, the 162° isomer which was eluted first was tentatively assigned the *cis* configuration and the 149° material the *trans* configuration. Additional evidence for this assignment was obtained by comparison of the infrared spectra of these isomers with those of the epimeric pair in the 5β-androstane series (see below) for which there is chemical evidence for the assignment of configuration.

The ketones V and VI were equilibrated in dioxane and hydrochloric acid, and the infrared spectrum of the equilibrium mixture was compared with the spectra of synthetic mixtures in the 8–10-μ region. The position of the equilibrium was estimated to be 50–75% in favor of the *cis* isomer VII. In a study of the equilibration of the α-hydrindanone moiety in a number of fused-ring systems, by optical rotatory dispersion measurements, it has been found[9] that the position of equilibrium favored

(1) Part XIII, W. S. Johnson, D. S. Allen, Jr., R. R. Hindersinn, G. N. Sausen, and R. Pappo, *J. Am. Chem. Soc.*, **84**, 2181 (1962).

(2) A preliminary report of these findings has been published, *Tetrahedron Letters*, No. **8**, 11 (1960).

(3) K. H. Loke, G. F. Marrian, W. S. Johnson, W. L. Meyer, and D. D. Cameron, *Biochim. Biophys. Acta*, **28**, 214 (1958).

(4) R. Anliker, M. Müller, M. Perelman, J. Wohlfhart, and H. Heusser, *Helv. Chim. Acta*, **42**, 1071 (1959).

(5) L. Velluz, G. Amiard, R. Heymes, and B. Goffinet, *Compt. rend.*, **250**, 371 (1960).

(6) See ref. 1 and previous papers.

(7) Results of the biological tests of these compounds are to be reported elsewhere.

(8) W. S. Johnson, B. Bannister, and R. Pappo, *J. Am. Chem. Soc.*, **78**, 6331 (1956).

(9) J. F. Biellmann, P. Crabbé, and G. Ourisson, *Tetrahedron*, **3**, 303 (1958); J. F. Biellmann, D. Francetic, and G. Ourisson, *Tetrahedron Letters*, No. **18**, 4 (1960).

the *cis* isomer in every case, but varied from 60–99%.

18-Nortestosterone.—The A/B *cis* ketone VII was chosen as the starting point for the synthesis of 18-nortestosterone (XIV. R = H) rather than the A/B *trans* ketone because of the facility with which the $\Delta^{4,5}$-en-3-one system can be introduced into the former. The ring contraction sequence followed the same pattern as in the 18-norepiandrosterone series.

The ketone VII was prepared as previously described,[10] and the crude product was converted into the furfurylidene ketone VIII (R = H), m.p. 211.2–213.2°, which was in turn converted into the furfurylidene acetate VIII (R = Ac), m.p. 194–196°. Ozonolysis followed by acidic hydrogen peroxide oxidation gave the dibasic acid IX (R = H), m.p. 209–213°, which upon treatment with excess diazomethane gave the dimethyl ester IX (R = CH_3), m.p. 111–112°. Cyclization with potassium *t*-butoxide in benzene, followed by hydrolysis and decarboxylation of the β-keto ester in aqueous triethylene glycol at 170–190° gave a crude mixture of ketones X (R = H) and XI (R = H). Further purification by chromatography gave two components in a ratio of 1.5 to 8.5. The less preponderant isomer, m.p. 150–151°, was eluted first, and the major product, m.p. 113–114°, was eluted last. The 151° isomer could be obtained as the major product by selective crystallization under equilibrating conditions[11] from an acidic aqueous dioxane solution of the crude ketone mixture. The total yield of this conversion was 80%, and since the ketone mixture was obtained in 80% yield, the 151° isomer could be obtained in an overall yield of 64% from the diester IX (R = CH_3).

The infrared spectra of the two hydroxy ketones were very similar but showed significant differences in the 8–10-μ region; the spectrum of the 151° isomer exhibited a peak at 8.86 μ which is not present in that of the 114° isomer, while the latter spectrum showed a peak at 9.47 μ which was absent in the former. The two isomeric ketones were equilibrated in dioxane and hydrochloric acid, and by the intensity of these bands in the infrared spectra the position of equilibrium was estimated to be between 60–65% in favor of the 151° epimer which, as shown below, corresponds to the C/D *cis* isomer.

Treatment of the 151° isomer with excess acetic anhydride in pyridine gave a keto acetate, m.p. 144–145°, in 96% yield. Similar treatment of the 114° ketone gave a keto acetate, m.p. 116–117°, in 87% yield. Thus no isomerization occurred under these acetylation conditions. On the basis of a difference in reactivity of these keto acetates to reduction with pyridine borane as described below, the 114° isomer was assigned the *trans* (X. R = Ac) and the 151° isomer the *cis* (XI. R = Ac) configuration.

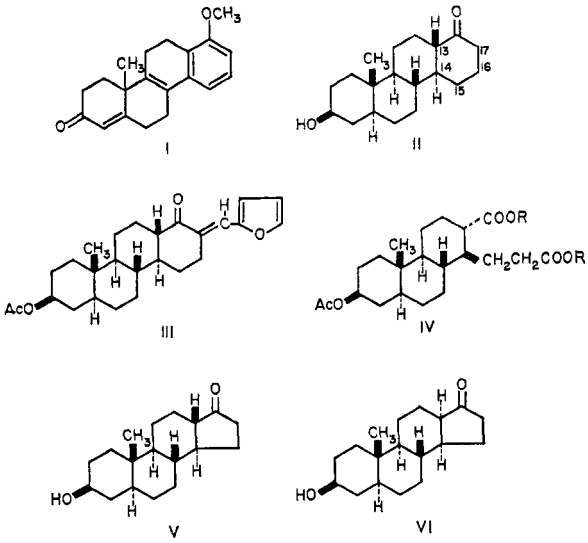

Figure 1

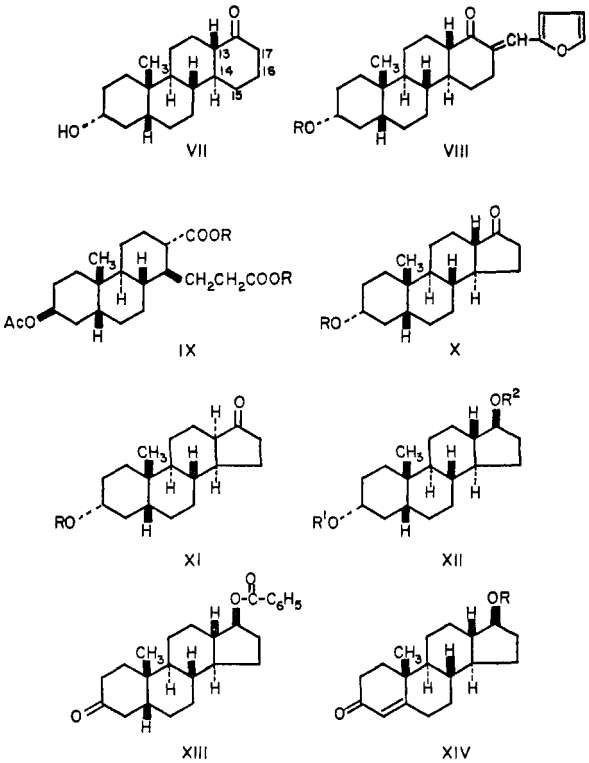

Figure 2

The next step of the proposed synthesis was to reduce selectively the 17-keto group, while retaining the 3α-acetate, and then to benzoylate to give the 3α-acetate 17β-benzoate. The 117° keto acetate, when treated with sodium borohydride in aqueous dioxane at 50°,[12] afforded, after benzoylation, the

(10) W. S. Johnson, W. A. Vredenburgh, and J. E. Pike, *J. Am. Chem. Soc.*, **82**, 3409 (1960).

(11) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *ibid.*, **74**, 4223 (1952).

(12) H. Heusser, P. Th. Herzig, A. Fürst, and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).

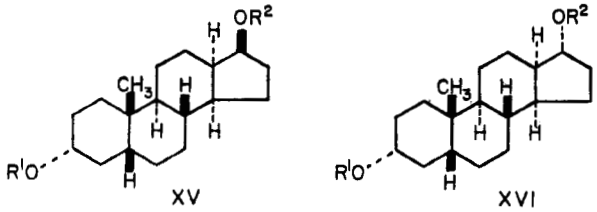

Figure 3

corresponding acetate benzoate XII (R^1 = Ac, R^2 = COC_6H_5), m.p. 144–145°, in a yield of 57%. The fact that the yield was only 57% may have been due to some hydrolysis of the acetate under the basic conditions of the reaction medium. In an effort to improve this yield, it was decided to try a reducing agent which would be effective under neutral or mildly acidic reaction conditions. The use of pyridine borane in a number of different solvents to reduce aromatic ketones in good yield has been described,[13] but these conditions did not effect reduction of aliphatic ketones in high yield. Pyridine borane in acetic acid has been suggested[14] as a reducing agent for carbonyl compounds having base-sensitive functional groups. To test the feasibility of these reaction conditions for selective reduction, a model compound, dehydroepiandrosterone acetate, was treated with a slight excess of pyridine borane in acetic acid at room temperature to give in 80% yield $\Delta^{5,6}$-androsten-3β,17β-diol-3-monoacetate.[15]

Treatment of the 117° keto acetate with pyridine borane in acetic acid yielded an oil which on reaction with benzoyl chloride gave the acetate benzoate XII (R^1 = Ac, R^2 = COC_6H_5) in 78% yield. When the 145° keto acetate was similarly treated with pyridine borane, the starting keto acetate was isolated unchanged. The inert keto acetate must, therefore, have the C/D *cis* configuration in which the 17-carbonyl group is axial to ring C and therefore more hindered than in the C/D *trans* ketone with the 17-carbonyl group equatorial to ring C.

The 151° ketone is therefore designated as the *cis* isomer XI (R = H) and the 114° ketone as the *trans* isomer X (R = H). Their acetates are accordingly XI (R = Ac) and X (R = Ac), respectively. It follows that the 117° keto acetate X (R = Ac) upon treatment with pyridine borane followed by benzoylation gave the acetate benzoate XII (R^1 = Ac, R^2 = COC_6H_5).

When the hydroxy ketone X (R = H) was reduced with lithium aluminum hydride, a diol, m.p. 196–197°, was obtained. Upon treatment of this diol with acetic anhydride in pyridine, a diacetate, m.p. 120–122°, was produced. This same diol was also obtained when the acetate benzoate XII (R^1 = Ac, R^2 = COC_6H_5) was saponified with potassium hydroxide in methanol. Therefore, both reducing agents afforded a 17-hydroxyl group with the same orientation. Since pyridine borane afforded the 17β-hydroxyl group upon reduction of dehydroepiandrosterone and since lithium aluminum hydride is known to give the 17β-hydroxyl upon reduction of a C/D *trans* 17-ketone,[16] it follows that the 17-hydroxyl in the 197° diol, as well as the 17-benzoyloxy group in the acetate benzoate XII (R^1 = Ac, R^2 = COC_6H_5), also has the β-configuration. The 197° diol, therefore, has the structure XII (R^1 = R^2 = H). An ancillary study was made of the configuration of the diols obtained by reduction of the hydroxy ketones X and XI (see below).

The next step in the proposed synthesis was to remove selectively the 3α-acetate of the acetate benzoate XII (R^1 = Ac, R^2 = COC_6H_5). Ruzicka, Wettstein, and Kägi[17] reported the selective hydrolysis of the 3β-acetate of $\Delta^{5,6}$-androsten-3β,17β-diol 3-acetate 17-benzoate using one equivalent of potassium hydroxide at room temperature. When this procedure was applied to the acetate benzoate, the diol XII (R^1 = R^2 = H) was obtained in 47% yield. Since these conditions proved to be too severe, potassium carbonate in aqueous methanol was employed. Under these conditions, the monobenzoate XII (R^1 = H, R^2 = COC_6H_5), m.p. 130–132°, was obtained in 73% yield (based on recovered starting material). Only a small amount of the diol XII (R^1 = R^2 = H) was isolated. Chromic acid oxidation of the monobenzoate XII (R^1 = H, R^2 = COC_6H_5) afforded the keto benzoate XIII, m.p. 139–140°, which, on treatment with bromine in acetic acid followed by dehydrobromination with lithium bromide in dimethylformamide, gave 18-nortestosterone benzoate (XIV. R = COC_6H_5), m.p. 151–152°. The ultraviolet spectrum, λ_{max} 234 mμ (log ϵ 4.43), was consistent with a superposition of the α,β-unsaturated ketone on the benzoate chromophore.

Hydrolysis of 18-nortestosterone benzoate (XIV. R = COC_6H_5) with potassium hydroxide in methanol[17] afforded 18-nortestosterone (XIV. R = H), m.p. 165–167°, λ_{max} 241 mμ (log ϵ 4.19).

Reduction of the C/D *cis* hydroxy ketone XI (R = H) with lithium aluminum hydride yielded two fractions in approximately equal amounts after chromatography. The diol which was eluted first melted at 151.5–152.5°, and further elution gave another diol, m.p. 181–182°. Upon treatment of these two diols with acetic anhydride in pyridine, the 182° diol gave a diacetate, m.p. 128–128.5°. The infrared spectrum of the crude reaction product of the 152.5° diol exhibited a strong peak at 2.90 μ

(13) R. P. Barnes, J. H. Graham, and M. D. Taylor, *J. Org. Chem.*, **23**, 1561 (1958).

(14) Technical Bulletin C-200, Callery Chemical Co.

(15) L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 1264 (1935).

(16) N. C. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishing Co., Inc., New York, N. Y., chap. 7, 1956 pp. 258–268.

(17) L. Ruzicka, A. Wettstein, and H. Kägi, *Helv. Chim. Acta*, **18**, 1478 (1935).

indicating partial acetylation. Attempts to crystalize this product failed, but upon chromic acid oxidation, the keto acetate XI (R = Ac) was obtained.

The possibility of epimerization of the *cis* ketone (R = H) to the *trans* ketone X (R = H) prior to reduction was ruled out by establishing the nonidentity of the 128.5° diacetate with the 122° isomer XII ($R^1 = R^2 =$ Ac) described above. The 152.5° diol and 182° diol are, therefore, derived from the C/D *cis* isomer, and are epimeric at C-17. On the basis of the results of the acetylation experiments, the 152.5° diol may be assigned the structure XV ($R^1 = R^2 =$ H) since, as may be seen from molecular models, the 17β-hydroxy group would be more hindered than the 17α-hydroxyl group of the structure XVI ($R^1 = R^2 =$ H) and therefore less readily acetylated. The 182° diol accordingly is assigned the structure XVI ($R^1 = R^2 =$ H).

As mentioned above, the position of equilibrium of the ketones V and VI was estimated approximately by infrared spectroscopy. A more accurate method of determining equilibria of this type has been employed[9] by the use of optical rotatory dispersion measurements. With the view to applying this technique in the present case, some preliminary attempts were made to resolve our compounds by enzymic reactions. Marcus and Talalay[18] have reported the microbiological oxidation of hydroxy steroids with *pseudomonas testosteroni* which contains an α-hydroxy steroid dehydrogenase (α-enzyme) and a β-hydroxy steroid dehydrogenase (β-enzyme). In preliminary experiments,[19] the diols XII ($R^1 = R^2 =$ H) and XVI ($R^1 = R^2 =$ H) were treated with the α- and β-enzymes. The results indicated that the C-3 hydroxy group was completely oxidized in both of these diols by the α-enzyme; however, the β-enzyme oxidized only one enantiomer of each of the diols at the C-17 hydroxy group. This approach, therefore, offers promise for the obtention of the optically active substances.

Experimental[20]

dl-**3β-Acetoxy-D-homo-18-norepiandrostane-17-furfuryliden-17a-one (III).**—To a mixture of 600 mg. of the furfurylidene derivative,[8] m.p. 206.5–209°, of the hydroxy ketone II and 15 ml. of dry pyridine was added 3 ml. of acetic anhydride. The mixture was stirred for 10 min. until it became clear, and then allowed to stand overnight at room temperature. The mixture was cooled in an ice bath, and water was added dropwise. The precipitate was filtered, washed with water, and dried. The yield was 598 mg. (89%) of pale yellow needles, m.p. 202.5–209.5°. Recrystallization from ethyl acetate–petroleum ether (b.p. 60–68°) gave a first crop, 507 mg. (76% yield), m.p. 209–211°, and a second crop, 57 mg. (9% yield), m.p. 207–209°. A sample of the first crop was washed through Florisil and recrystallized four times from ethyl acetate–petroleum ether (b.p. 60–68°) to give fine colorless needles, m.p. 210–212°, $\lambda_{max}^{CHCl_3}$ 5.78 μ (C=O), 5.98 μ (C=C—C=O), λ_{max} 324.5 mμ (log ϵ 4.3).

Anal. Calcd. for $C_{26}H_{34}O_4$: C, 76.06; H, 8.34. Found: C, 76.0; H, 8.4.

dl-**3β-Acetoxy-18-noretioallohomobilianic Acid (IV. R = H).**—A 507-mg. sample of the furfurylidene ketone acetate III (R = Ac), m.p. 209–211°, was dissolved in 75 ml. of methylene chloride and treated with ozone at −70° until a blue color persisted; the mixture was allowed to warm to room temperature, and the solvent was removed at reduced pressure. To the residue were added 70 ml. of glacial acetic acid, 3 ml. of water, 10 ml. of 30% hydrogen peroxide, and 3 drops of concentrated hydrochloric acid, and the mixture was let stand at room temperature overnight. The solvent was removed at reduced pressure, the residue dissolved in ethyl acetate, and the organic layer extracted with 10% potassium bicarbonate solution. The combined basic extracts were washed with ethyl acetate and acidified with 15% hydrochloric acid. The aqueous layer was extracted with ether, the combined extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 458 mg. (97% yield) of tan crystals, m.p. 261.3–269°. Crystallization from ethyl acetate yielded 390 mg. (83% yield), m.p. 272–273.5°, and a second crop, 15 mg., m.p. 259–266°. A sample of the first crop was recrystallized four times from ethyl acetate to give the dibasic acid IV (R = H) as colorless prisms, m.p. 275.4–277°, λ_{max}^{mull} 5.75 μ (C=O), 5.85 μ (C=O).

Anal. Calcd. for $C_{21}H_{32}O_6$: C, 66.28; H, 8.47. Found: C, 66.15; H, 8.5.

dl-**Dimethyl 3β-Acetoxy-18-noretioallohomobilianate (IV. R = CH_3).**—To a solution of 390 mg. of the aforementioned diacid, m.p. 272–273.5°, in methanol was added an excess of diazomethane in ether, and the mixture was then concentrated, filtered, and the solvent removed at reduced pressure. Trituration of the oily residue with petroleum ether (b.p. 60–68°) gave 356 mg. of the diester, m.p. 84–90°; and a second crop of 46 mg., m.p. 84–90°, was obtained after washing the mother liquors through Florisil; the total yield amounted to 96%. Five crystallizations from petroleum ether (b.p. 60–68°) afforded the diester VII as colorless plates, m.p. 101–102°, $\lambda_{max}^{CHCl_3}$ 5.80 μ (C=O).

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.3; H, 8.8.

dl-**18-Norepiandrosterone (V) and 13-Iso-18-norepiandrosterone (VI).**—The Dieckmann cyclization was conducted under essentially the same conditions as were employed in the epiandrostane series.[8] From 1.0 g. of the aforementioned diester, there was thus obtained 0.804 g. of an oil which gave a blue color with ferric chloride.

This oil was suspended in 200 ml. of triethylene glycol (Eastman Kodak Co., Yellow Label, distilled once under reduced pressure) and 8 ml. of water was added. The mixture, in a nitrogen atmosphere, was immersed in an oil bath preheated to 210°. Stirring was initiated, and the temperature of the bath dropped to 180–185° and was kept in this range for 10 min. The mixture was quickly cooled to room temperature, poured into water, and extracted with chloroform. The combined chloroform extracts were washed with water, dried over anhydrous sodium sulfate and the solvent was removed at reduced pressure to give 905 mg. of an oily residue.

A preliminary purification of this material was performed by washing it through 50 g. of Florisil with ether and 5% acetone–ether. The combined eluates afforded 495 mg. (73% yield) of a crude mixture of the two ketones V and VI. This mixture was chromatographed on 25 g. of Florisil which gave a crude separation of the two components. The early fractions eluted with 3% ether–benzene amounted

(18) P. I. Marcus and P. Talalay, *J. Biol. Chem.*, **218**, 661, 675 (1956).

(19) We wish to thank Dr. P. Talalay, Ben May Laboratories, University of Chicago, for performing and interpreting these experiments.

(20) All melting points are corrected for stem exposure.

to 177 mg. which was enriched in the C/D *cis* ketone VI, while the later fractions eluted with 3% ether–benzene fractions up to the 5% acetone–ether afforded 254 mg. enriched in the C/D *trans* ketone V. Each of these samples was purified by further chromatography. The first sample, after chromatography and recombination of the early 3% ether–benzene fractions followed by crystallization from ethyl acetate–petroleum ether (b.p. 60–68°), yielded 87 mg. of the C/D *cis* ketone VI, m.p. 137–159°. Repeated recrystallizations from ethyl acetate–petroleum ether (b.p. 60–68°) and finally from ethyl acetate afforded colorless irregular prisms, m.p. 160–162°, $\lambda_{max}^{CHCl_3}$ 2.92 μ (OH), 5.77 μ (C=O).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.1; H, 10.3.

The 254-mg. sample of enriched C/D *trans* ketone V was rechromatographed on Florisil. The later fractions eluted with 3% ether–benzene to ether were combined with the later fractions from the chromatogram described directly above and crystallized from ethyl acetate petroleum ether to give 240 mg. of the C/D *trans* ketone V, m.p. 137–147°. Six recrystallizations from the same solvent pair afforded colorless irregular prisms, m.p. 148–149°, $\lambda_{max}^{CHCl_3}$ 2.90 μ (OH), 5.75 μ (C=O).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.3; H, 10.2.

***dl*-3α-Acetoxy-D-homo-18-nor-5β-androstane-17-furfurylidene-17a-one (VIII. R = Ac).**—To a mixture of 3.50 g. of the furfurylidene ketone VIII (R = H),[10] m.p. 211.2–213.2°, in 87.5 ml. of pyridine, was added 17.5 ml. of acetic anhydride. The mixture was stirred in an atmosphere of nitrogen at room temperature in the dark. Within the first half hour, the mixture had become homogeneous and was allowed to stand overnight. The reaction mixture was then cooled in an ice bath and upon dropwise addition of 150 ml. of water a precipitate formed which was filtered and washed thoroughly with water. The dried, slightly yellow, crystalline material, m.p. 194–196°, amounted to 3.54 g. (91% yield). A sample was recrystallized three times from ethyl acetate–petroleum ether (b.p. 60–68°), washed through Florisil to remove the color, and recrystallized once from ethyl acetate–petroleum ether (b.p. 60–68°) to give colorless prisms, m.p. 195.2 196.8°, $\lambda_{max}^{CHCl_3}$ 5.80 μ (C=O), 5.98 μ (C=C—C=O), λ_{max} 325 mμ (log ϵ 4.3).

Anal. Calcd. for $C_{26}H_{34}O_4$: C, 76.06; H, 8.34. Found: C, 76.2; H, 8.3.

***dl*-3α-Acetoxy-18-noretiohomobilianic Acid (IX. R = H).**—The ozonolysis was performed as described above for the 5α series. Thus from 1.00 g. of the aforementioned furfurylidene ketone acetate, m.p. 194–196°, there was obtained 921 mg. of a partially crystalline oil which upon trituration with ether and ethyl acetate yielded 771 mg. (83%) of colorless crystals, m.p. 209–213°. Recrystallization three times from ethyl acetate gave colorless prisms, m.p. 214.5–216°, λ_{max}^{mull} 5.75 μ (C=O), 5.85 μ (C=O).

Anal. Calcd. for $C_{21}H_{32}O_6$: C, 66.28; H, 8.47. Found: C, 66.2; H, 8.2.

***dl*-Dimethyl 3α-acetoxy-18-noretiohomobilianate (IX. R = CH_3)** was prepared by treatment of 647 mg. of the crude diacid, m.p. 209–213°, with excess diazomethane in ether. The crude product was washed through Florisil with ether and crystallized from petroleum ether (b.p. 60–68°) to give 597 mg. (86% yield) of diester, m.p. 110–112°. Repeated recrystallizations from petroleum ether (b.p. 60–68°) gave colorless irregular prisms, m.p. 111–112°, $\lambda_{max}^{CHCl_3}$ 5.78 μ (C=O).

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.5; H, 8.8.

3α-Hydroxy-18-nor-5β-androstan-17-one (X. R = H) and 3α-Hydroxy-13-iso-18-nor-5β-androstan-17-one (X. R = H).—The Dieckmann cyclization was carried out under essentially the same conditions as described in the epiandrostane series.[8] From 2.25 g. of the diester IX (R = CH_3), m.p. 110–112°, there was thus obtained 1.85 g. of a light yellow oil which produced a blue color with alcoholic ferric chloride.

This oil was suspended in 500 ml. of triethylene glycol, and 20 ml. of water was added. The mixture, in an atmosphere of nitrogen, was placed in an oil bath preheated to 220°. In 5 min. the temperature dropped to 170°, followed by a rise over 10 min. to 190°. The mixture was cooled rapidly to room temperature, water added, and the aqueous phase extracted with chloroform. The combined organic extracts were washed with water, dried over anhydrous sodium sulfate, and the solvent evaporated to give 2.10 g. of a light yellow oil.

A preliminary purification of this material was performed by washing it through 100 g. of Florisil with 3 l. of ether. This gave 1.22 g. (80% yield) of crude ketone mixture, which was chromatographed on 50 g. of Florisil. The C/D *cis* ketone XI (R = H) was eluted in the early 3% ether–benzene fractions and amounted to 337 mg. of crude crystalline material. These fractions were rechromatographed on 20 g. of Florisil to give 160 mg. in the early 3% ether–benzene fractions. Recrystallization from ethyl acetate–petroleum ether (b.p. 60–68°) gave 105 mg., m.p. 142–147°. A second recrystallization from the same solvent pair gave 80 mg., m.p. 146–150°, and four more recrystallizations gave colorless irregular prisms, m.p. 150–151°, $\lambda_{max}^{CHCl_3}$ 5.78 μ (C=O).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.2; H, 10.25.

The C/D *trans* ketone X (R = H) was eluted in the later 3% ether–benzene fractions and finally completely washed off of the column with ether. From the two chromatograms above a total of 840 mg. was obtained which was recrystallized from ethyl acetate–petroleum ether (b.p. 60–68°) to give 752 mg., m.p. 109–114°. Repeated recrystallizations from the same solvent pair gave colorless irregular prisms, m.p. 113–114°, $\lambda_{max}^{CHCl_3}$ 5.78 μ (C=O).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.3; H, 10.3.

Crystallization of the Ketone Mixture, X (R = H) and XI (R = H), under Equilibrating Conditions.—As in a reported procedure,[11] 450 mg. of the crude ketone mixture, obtained as described above, was dissolved in 9 ml. of dioxane, and 18 drops of concentrated hydrochloric acid was added, followed by a cautious addition of water to produce incipient cloudiness. This mixture was seeded with 2 mg. of finely powdered C/D *cis* ketone XI (R = H), m.p. 146–150°, and allowed to stand overnight at room temperature. By this time some crystallization had occurred, and the solution had become clear. More water was added to produce cloudiness, and this procedure was repeated periodically as crystallization continued, with subsequent loss of cloudiness. When finally the addition of water produced no further cloudiness, the mixture was refrigerated at 5° for 3 hr. The crystalline precipitate was separated, washed with water, and dried; it amounted to 352 mg., m.p. 138–144°. This was combined with 40 mg., m.p. 138–144°, which was obtained in a pilot experiment starting with 50 mg. of the mixture, and crystallized from ethyl acetate–petroleum (b.p. 60–68°) to give 341 mg., m.p. 142–147°. A second crystallization gave 327 mg., m.p. 145–148.5°.

The above aqueous dioxane solution was extracted with ether, the ether layers combined and washed with water until neutral, and dried over anhydrous sodium sulfate. Evaporation of the solvent left a residue which was combined with the residue from the recrystallizations conducted above. The resulting oil amounted to 140 mg. and was washed through Florisil with ether to give 100 mg. of an oil. This oil was dissolved in dioxane and crystallized after addition of water and hydrochloric acid, in the same manner as described above, to give 60 mg. of crystals, m.p. 142–147°. This amounted to a total of 401 mg. of the ketone XI (R = H) m.p. 142–147°, obtained from 500 mg. of the crude ketone mixture.

***dl*-3α-Acetoxy-13-iso-18-nor-5β-androstan-17-one (XI.**

R = Ac).—A 302-mg. sample of the hydroxy ketone XI (R = H), m.p. 145–148.5°, was dissolved in 9 ml. of dry pyridine, and 1.8 ml. of acetic anhydride was added. The mixture was allowed to stand overnight at room temperature and then cooled in an ice bath. Upon the dropwise addition of water, a precipitate formed and the crystals were separated, washed with water, and dried, yielding 335 mg. (96%), m.p. 140–143°. Repeated recrystallizations from ethyl acetate–petroleum ether (b.p. 60–68°) afforded colorless irregular prisms, m.p. 144–145°, $\lambda_{max}^{CHCl_3}$ 5.78 μ (C=O).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49. Found: C, 75.5; H, 9.55.

dl-3α-Acetoxy-18-nor-5β-androstan-17-one (X. R = Ac).—To a 500-mg. sample of the hydroxy ketone X (R = H), m.p. 109–114°, dissolved in 15 ml. of dry pyridine, was added 3.0 g. of acetic anhydride, and the mixture was allowed to stand at room temperature overnight. Water was then added, the aqueous mixture extracted with ether, and the combined organic layers washed with water and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left 570 mg. of a colorless oil which crystallized upon trituration with petroleum ether (b.p. 60–68°) to give 504 mg. (87% yield), m.p. 114–116°. Repeated recrystallization from petroleum ether (b.p. 60–68°) gave colorless prisms, m.p. 116–117°, $\lambda_{max}^{CHCl_3}$ 5.78 μ (C=O).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49. Found: C, 75.5; H, 9.6.

Reduction of dl-3α-Acetoxy-18-nor-5β-androstan-17-one (X. R = Ac). (a) With Sodium Borohydride in Aqueous Dioxane.—A 100-mg. sample of the keto acetate X (R = Ac), m.p. 110–115°, was dissolved in 1.4 ml. of dioxane, a solution of 20 mg. of sodium borohydride in 1.4 ml. of a 1:1 dioxane–water mixture was added, and the solution was heated to 50° for 1 hr. A 15% solution of acetic acid in water was added dropwise to the cooled mixture. Water was then added, the aqueous mixture extracted with ether, and the combined ether extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 101 mg. of an oil which was dissolved in 2 ml. of pyridine and treated with 0.20 ml. of benzoyl chloride. After 0.5 hr. at room temperature, water was added, the mixture extracted with ether, the combined ether extracts were washed successively with water, 10% potassium bicarbonate, and water, and then dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 140 mg. of an oil which was washed through Florisil to give 120 mg. of an oil. Crystallization from methanol gave 76 mg., m.p. 140–144°. A sample was recrystallized three times from methanol to give **dl-18-nor-5β-androstan-3α,17β-diol 3-acetate 17-benzoate** (XII. R^1 = Ac, R^2 = COC_6H_5) as colorless plates, m.p. 144–145°, $\lambda_{max}^{CHCl_3}$ 5.80 μ (C=O), λ_{max} 229 mμ (log ϵ 4.2).

Anal. Calcd. for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.6; H, 8.7.

(b) **With Pyridine Borane in Acetic Acid.**—A solution of 75 mg. of pyridine borane (Callery Chemical Co.) in 2.5 ml. of glacial acetic acid was added to a solution of 252 mg. of the acetoxy ketone X (R = Ac), m.p. 114–116°, in 5 ml. of glacial acetic acid. The mixture was allowed to stand at room temperature in an atmosphere of nitrogen for 3 hr.; then 10 drops of 10% hydrochloric acid was added, followed in 5 min. by water. The aqueous mixture was extracted with ether, and the combined ether layers were washed with water, 10% potassium bicarbonate solution, and water, and dried over anhydrous sodium sulfate. The residue (257 mg.) obtained upon evaporation of the solvent was benzoylated as described in the preceding section, with 5 ml. of pyridine and 0.25 ml. of benzoyl chloride. The crude product on trituration with methanol gave 262 mg. (78% yield) of the acetate benzoate, m.p. 140–144°, undepressed on admixture with the sodium borohydride reduction product.

Other Reduction Experiments with Pyridine Borane.—A 100-mg. sample of dehydroepiandrosterone acetate, m.p. 166–170°, in 2 ml. of acetic acid was treated, as described above, with 30 mg. of pyridine borane in 1 ml. of acetic acid. The crude reduction product, isolated as described above, was triturated with petroleum ether (b.p. 60–68°) to give 80 mg. (80% yield) of $\Delta^{5,6}$-androsten-3β,17β-diol 3-monoacetate, m.p. 140–145°, reported,[15] 147–148°.

A 50-mg. sample of dl-3α-acetoxy-13-iso-18-nor-5β-androstan-17-one (XI, R = Ac), m.p. 140–143°, was treated with pyridine borane under the same reaction conditions as described above. The crude product amounted to 50 mg., m.p. 135–143°, undepressed on admixture with starting material. The infrared spectrum of the product showed no absorption in the hydroxyl region and was identical with that of starting material.

Reduction of dl-3α-Hydroxy-18-nor-5β-androstan-17-one (X. R = H) with Lithium Aluminum Hydride.—To a solution of 100 mg. of the hydroxy ketone X (R = H), m.p. 109–114°, in 33 ml. of tetrahydrofuran was added 330 mg. of lithium aluminum hydride. The mixture was stirred overnight at room temperature, then ethyl acetate was added, followed by methanol, water, and 10% hydrochloric acid. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with water, 10% potassium bicarbonate, again with water and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left 115 mg. of an oil which crystallized upon trituration with ether–petroleum ether (b.p. 60–68°) to give 100 mg., m.p. 141–151° with resolidification and remelting at 180–191°. Recrystallization from ethyl acetate–petroleum ether (b.p. 60–68°) gave 83 mg., m.p. 186–192°, with partial melting and resolidification at 171–178°. A sample was recrystallized once from ethyl acetate–petroleum ether (b.p. 60–68°) and three times from ethyl acetate to give **dl-3α,17β-dihydroxy-18-nor-5β-androstane** (XII. R^1 = R^2 = H) as colorless prisms, m.p. 196–197°, $\lambda_{max}^{CHCl_3}$ 2.78 μ (OH), 2.92 μ (OH). Satisfactory analytical data were not obtained for this compound.

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 76.4; H, 10.8.

A 60-mg. sample of this diol, m.p. 186–192°, was dissolved in 1.85 ml. of pyridine, and 0.4 ml. of acetic anhydride was added. The mixture was allowed to stand at room temperature for 3 hr., water was added, and the aqueous layer extracted with ether. The combined ether extracts were washed with water, dried over anhydrous sodium sulfate, and the solvent then evaporated to give 72 mg. of an oil that was chromatographed on Florisil. Elution with benzene gave 46 mg. of oily crystals, which upon recrystallization from methanol gave 35 mg. of the diol diacetate, m.p. 105–112°. Repeated recrystallization from ethanol–water gave **dl-3α,17β-diacetoxy-18-nor-5β-androstane** (XII). R^1 = R^2 = Ac) as colorless plates, m.p. 120–122°, $\lambda_{max}^{CHCl_3}$ 5.80 μ (C=O), 8.0 μ ($OCOCH_3$).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.3; H, 9.6.

Hydrolysis of the Acetate Benzoate XII (R^1 = Ac, R^2 = COC_6H_5). (a) With Methanolic Potassium Hydroxide.—A solution of 5.2 mg. of 85% potassium hydroxide in 1 ml. of methanol was added to a solution of 50 mg. of the acetate benzoate, m.p. 140–144°, in 9 ml. of methanol. The mixture was allowed to stand for 18 hr. at room temperature, then an additional 1.3 mg. of 85% potassium hydroxide in 0.25 ml. of methanol was added, and the mixture was allowed to stand for 24 hr. Water and acetic acid were added, the aqueous mixture extracted with ether, the combined ether layers washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave 48 mg. of an oil which crystallized on trituration with ethyl acetate–petroleum ether (b.p. 60–68°) to give 20 mg. (61% yield), m.p. 135–145°, with resolidification and remelting at 175–180°, alone or upon admixture with an authentic sample of the diol XII (R = H).

(b) **With Potassium Carbonate to Produce *dl*-18-Nor-5β-androstan-3α,17β-diol 17-Benzoate (XII. R¹ = H, R² = COC_6H_5).**—To a solution of 200 mg. of the acetate benzoate, m.p. 140–144°, in 100 ml. of methanol cooled to 10–15°, was added 400 mg. of potassium carbonate dissolved in 8 ml. of water. The cloudy mixture was stirred for 10 min. until it became clear, and then was allowed to stand at room temperature for 2 hr. Acetic acid was added, the solvent evaporated under reduced pressure, water and ether were added, and the aqueous layer extracted with ether. The combined ether layers were washed with water and dried over anhydrous sodium sulfate. Removal of the solvent left 188 mg. which was chromatograped on 10 g. of Florisil and eluted with 1% ether–benzene to 2% ether–benzene to givd 26 mg. (13% yield) of starting material, m.p. 130–140°. The desired hydroxy benzoate was eluted with 2% ether–benzene to 5% ether–benzene and amounted to 130 mg. of oily crystals. Recrystallization from ethyl acetate–petroleum ether (b.p. 60–68°) gave 116 mg. of the hydroxy benzoate XII (R¹ = H, R² = COC_6H_5), m.p. 130–132° (73% yield based on recovered starting material, 64% conversion). Elution with 10% ether–benzene to 100% ether gave 23 mg. of oily crystals which appeared to be predominantly the diol. A sample of the hydroxy benzoate was recrystallized repeatedly from ethyl acetate–petroleum ether (b.p. 60–68°) to give clusters of colorless needles, m.p. 132–133°, $\lambda_{max}^{CHCl_3}$ 2.90 μ (OH), 5.82 μ (C=O), λ_{max} 229 mμ (log ε 4.2).

Anal. Calcd. for $C_{25}H_{34}O_3$: C, 78.47; H, 8.96. Found: C, 78.4; H, 9.0.

***dl*-18-Nor-5β-androstan-3-on-17β-ol Benzoate (XIII).**—The oxidation was performed with Jones reagent.[21] To 84 mg. of the hydroxy benzoateXII (R¹ = H, R² = COC_6H_5) m.p. 130–132°, dissolved in 12 ml. of acetone (distilled from potassium permanganate), at 10–15°, was added 0.12 ml. of Jones reagent (prepared by dissolving 2.67 g. of chromium trioxide in 2.3 ml. of concentrated sulfuric acid and diluting to 10 ml. of water). Previous to adding the Jones reagent, nitrogen was bubbled for a period of 10 min. through the reagent solution as well as the solution containing the substrate, and this procedure was continued after the reactants were mixed. The mixture was stirred magnetically and allowed to come to room temperature. After 10 min., water was added and the precipitate was collected, washed, and dried to give 71 mg. (85% yield) of the keto benzoate XIII, m.p. 135–138°. Five recrystallizations from ethyl acetate–petroleum ether (b.p. 60–68°) gave colorless prisms, m.p. 139–140°, $\lambda_{max}^{CHCl_3}$ 5.82 μ (C=O), λ_{max} 229 mμ (log ε 4.1).

Anal. Calcd. for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 78.7; H, 8.3.

***dl*-18-Nortestosterone Benzoate (XIV, R = COC_6H_5).**—The procedure of Holysz[22] for the bromination and dehydrobromination was modified according to conditions developed in our laboratories.[23] A 50-mg. sample of the keto benzoate XIII, m.p. 135–138°, was dissolved in 0.5 ml. of glacial acetic acid. To this was added with stirring (nitrogen atmosphere) 0.25 ml. of 0.07 *N* hydrogen bromide in acetic acid solution, followed by a dropwise addition of a solution of 20 mg. of bromine in 0.91 ml. of acetic acid. The addition was carried out at room temperature over a period of 10 min. during which time a white precipitate formed. After the addition was complete the mixture was stirred for 5 min., then 120 mg. of sodium acetate was added, and the mixture was stirred for an additional 2 min. Ethyl acetate was added, and the mixture was washed with water, 10% potassium bicarbonate solution, water, and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 62 mg. of partly crystalline material, to which were added 87 mg. of anhydrous lithium bromide (freshly dried at 180°, 10^{-3} mm.) and 1 ml. of dimethylformamide (distilled from phosphorus pentoxide). This mixture was heated at 100° in an atmosphere of nitrogen for 1.25 hr. Ethyl acetate was added, and the mixture was washed with water, then dried over anhydrous sodium sulfate.

Evaporation of the solvent under reduced pressure left 54 mg. of an oil which was chromatographed on 2.5 g. of Florisil. Elution with benzene gave fractions, totalling 20 mg., which gave a position Beilstein test. Elution with 1% ether–benzene to 5% acetone–ether afforded fractions amounting to 33 mg. (66%) which gave a negative Beilstein test. Recrystallization from ethyl acetate–petroleum ether (b.p. 60–68°) gave 24 mg., m.p. 142–147°. A sample was recrystallized four times from ethyl acetate–petroleum ether (b.p. 60–68°) and once from ethyl acetate to give colorless needles, m.p. 151–152°, $\lambda_{max}^{CHCl_3}$ 5.85 μ (C=O), 6.00 μ (C=C—C=O), λ_{max} 234 mμ (log ε 4.4).

Anal. Calcd. for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.3; H, 8.0.

The above fractions which gave positive Beilstein tests were combined with similar fractions from other experiments to give a total of 75 mg., and treated with lithium bromide in dimethylformamide as described above. An additional 21 mg. was thus obtained, after chromatography, in fractions which gave negative Beilstein tests. Crystallization from ethyl acetate–petroleum ether (b.p. 60–68°) gave 15 mg., m.p. 142–147°. This raised the total yield of *dl*-18-nortestosterone benzoate to 76%.

***dl*-18-Nortestosterone (XIV. R = H).**—A 30-mg. sample of *dl*-18-nortestosterone benzoate, m.p. 147–150°, was treated with 2 ml. of 2% potassium hydroxide in methanol at reflux in an atmosphere of nitrogen for 1.5 hr. After cooling, water was added, followed by acetic acid to neutralize the mixture. The aqueous mixture was extracted with ether, and the combined extracts were washed successively with water, 10% potassium bicarbonate solution, and water, and then dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left 22 mg. of an oil which was combined with 11 mg. of an oil that was obtained in a similar experiment starting with 15 mg. of *dl*-18-nortestosterone benzoate, m.p. 142–147°. The oil crystallized on trituration with ethyl acetate–petroleum ether (b.p. 60–68°) to give 22 mg. of slightly yellow prisms, m.p. 160–165°. Four recrystallizations from ethyl acetate afforded colorless, irregular prisms, m.p. 165–167°, $\lambda_{max}^{CHCl_3}$ 6.0 μ (C=C—C=O), 6.18 μ (C=C), λ_{max} 241 mμ (log ε 4.2).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 79.2; H, 9.6.

Reduction of *dl*-3α-Hydroxy-13-iso-18-nor-5β-androstan-17-one (XI. R = H) with Lithium Aluminum Hydride.—To 150 mg. of the hydroxy ketone, m.p. 142–147°, dissolved in 50 ml. of tetrahydrofuran (distilled from lithium aluminum hydride) was added 450 mg. of lithium aluminum hydride. The mixture was stirred overnight at room temperature; then ethyl acetate was added to decompose the excess lithium aluminum hydride, followed by methanol and water, and finally 5% hydrochloric acid. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed successively with water, 10% potassium bicarbonate solution, and water, then dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave 157 mg. of a yellow oil which was chromatographed on 7 g. of Florisil. Elution with 2% ether–benzene to 3% ether–benzene gave 74 mg. which, upon trituration with ethyl acetate–petroleum ether (b.p. 60–68°), afforded 58 mg. of a diol, m.p. 150–152°. Repeated recrystallization from the same solvent pair gave ***dl*-3α,17β-dihydroxy-13-iso-18-nor-5β-androstane** (XV. R¹ = R² = H) as colorless prisms, m.p. 151.5–152.5°, $\lambda_{max}^{CHCl_3}$ 2.78 μ (OH), 2.92 μ (OH).

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 78.1; H, 11.0.

(21) *Cf.* C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.* **21**, 1547 (1956).

(22) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

(23) P. J. Krapp, Ph.D. dissertation, University of Wisconsin, 1961.

Elution with 3% ether–benzene to 100% ether gave 73 mg. which, upon trituration with ethyl acetate–petroleum ether (b.p. 60–68°), yielded 60 mg. of a diol, m.p. 175–181°. Repeated recrystallization from ethyl acetate afforded *dl*-**3α,17α-dihydroxy-13-iso-18-nor-5β-androstane** (XVI. $R^1 = R^2 = H$) as colorless prisms, m.p. 181–182°, $\lambda_{max}^{CHCl_3}$ 2.78 μ (OH), 2.92 μ (OH).

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.1; H, 11.0.

In another experiment starting with 150 mg. of the hydroxy ketone, m.p. 135–140°, 48 mg. of the diol XV ($R^1 = R^2 = H$), m.p. 146–150°, and 56 mg. of the diol XVI ($R^1 = R^2 = H$), m.p. 170–178°, were obtained after chromatography.

A 48-mg. sample of the diol XV ($R^1 = R^2 = H$), m.p. 146–150°, was treated with 0.30 ml. of acetic anhydride in 1.4 ml. of pyridine for 3 hr. at room temperature, followed by the addition of water and extraction of the aqueous phase with ether. The combined ether extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure left 58 mg. of an oil which would not crystallize, $\lambda_{max}^{CH_2Cl_2}$ 2.80 μ (OH), 5.8 μ (C=O), 8.1 μ ($OCOCH_3$).

The oil was dissolved in 8 ml. of acetone, and 0.07 ml. of Jones reagent (prepared as described above) was added at 10–15°. The mixture was stirred for 10 min. during which time the temperature rose to room temperature. Water was then added, the aqueous mixture extracted with ether, the combined ether layers washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 55 mg. of an oil which was chromatographed on 2.5 g. of Florisil. Elution with 10% petroleum ether–benzene to 2% ether–benzene gave 44.5 mg. of crude oily crystals which, on recrystallization from petroleum ether (b.p. 60–68°), gave 15 mg. of the crude keto acetate XI (R = Ac), m.p. 120–140°. Further recrystallization from petroleum ether (b.p. 60–68°) afforded 8 mg., m.p. 135–143°, alone or upon admixture with an authentic sample of the keto acetate XI (R = Ac). The infrared spectra of the two samples were identical.

To 56 mg. of the diol, m.p. 170–176°, dissolved in 1.57 ml. of pyridine was added 0.34 ml. of acetic anhydride. The mixture was allowed to stand at room temperature for 3 hr. and then water was added, followed by extraction of the aqueous layer with ether; the combined ether layers were washed with water and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave 69 mg. of an oil which was chromatographed on 3.5 g. of Florisil. Elution with benzene gave 48 mg. of oily crystals, which on recrystallization from methanol yielded 25 mg., m.p. 120–126°. Four recrystallizations from methanol gave *dl*-**3α,17α-diacetoxy-13-iso-18-nor-5β-androstane** (XVI. $R^1 = R^2 = Ac$) as colorless plates, m.p. 128–128.5°, $\lambda_{max}^{CHCl_3}$ 5.78 μ (C=O), 8.0 μ ($OCOCH_3$).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.6; H, 9.55.

Equilibration Experiments.—The C/D *cis* and *trans* ketones VI and V in the A/B *trans* series and the C/D *cis* and *trans* ketones XI (R = H) and X (R=H) in the A/B *cis* series were equilibrated in the following manner.

A 4-mg. sample of the ketone was dissolved in 0.5 ml. of dioxane, 1 drop of concentrated hydrochloric acid and 2 drops of water were added. The mixture was allowed to stand at room temperature for 12 hr. Water was then added and the aqueous mixture was extracted with chloroform. The combined chloroform extracts were washed with water, 10% potassium bicarbonate solution, water, and dried over anhydrous sodium sulfate. Evaporation of the solvent left an oily residue which was dissolved in chloroform to give a 10% solution. The infrared spectrum of this solution was compared with the spectra of synthetic mixtures of the pure epimers. All the spectra were determined using 10% chloroform solutions and the intensities of characteristic bands in the 8.5–10.0-μ region were used for analysis. The equilibrium position of ketones VI and V thus was estimated to be between 50 and 75% in favor of the ketone VI. The position of the equilibrium of the ketones XI (R = H) and X (R = H) was estimated to be between 60 and 65% in favor of the ketone XI (R = H).

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α-Halo Ketones. II.[1] Rearrangement, Reduction, Elimination, and Displacement in the Reaction of Pyridines with 2α-Bromocholestan-3-one

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The reactions of a bromo ketone, 2α-bromocholestan-3-one (**1**), with pyridine, β-picoline, γ-picoline, 2,4-lutidine, 2,6-lutidine, and γ-collidine have been examined. The structures and amounts of the major products have been determined, and the paths by which they are formed have been circumscribed. Reported discrepancies in the reactions of **1** with 2,4-lutidine, 2,6-lutidine, and γ-collidine have been resolved.

Although the reaction of α-halo ketones with various pyridines has been widely used to introduce unsaturation into conjugation with carbonyl groups,[3] the reaction often yields a mixture of products over which there is disagreement in some cases. The ordinary course of the reaction, dehydrohalogenation and displacement, is often apparently accompanied by varying amounts of reduction and double bond rearrangement. In many cases the reduction and double bond migration are questionable since no evidence has been provided that the halo ketone was free from unhalogenated ketone or isomeric halo ketone. For a closer study

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