[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Steroid Total Synthesis—Hydrochrysene Approach. X.[1] Total Synthesis of Testosterone

BY WILLIAM S. JOHNSON, BRIAN BANNISTER,[2] RAPHAEL PAPPO[3] AND J. E. PIKE[4]

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The *anti-trans*-dihydro ketal III, described in an earlier paper of this series, has been reduced by lithium and alcohol in ammonia to give, after hydrolysis, a mixture of the 13,14- (IV) and 16,17-(V) dehydro ketones. These have been hydrogenated to the ketal ketone VI, the configuration of which was established by acid hydrolysis to VII followed by reduction with lithium and alcohol in ammonia to yield, after acetylation, the perhydro diacetate VIII (R = Ac) of established configuration. The desired ketal ketone VI was also prepared directly from the ketal II of the tetracyclic ketone I, without isolation of intermediates. The angular methylation–ring contraction sequence was applied to VI. Condensation with furfuraldehyde afforded the furfurylidene ketone IX which, on methylation, yielded the expected mixture of C_{13}-epimeric homologs, X and XI. Selective ozonization did not proceed satisfactorily; therefore a new oxidation procedure was developed, utilizing alkaline hydrogen peroxide. The methylated furfurylidene derivatives thus treated gave, after esterification with diazomethane, the dimethyl esters XIII (R = CH_3) and XIV (R = CH_3). Cyclization by the Dieckmann method, followed by a pyrolytic decomposition of the resulting β-keto esters gave the ketal ketones XII and XV, respectively. The latter was reduced with sodium borohydride to XVI which on hydrolysis afforded *dl*-testosterone (XVII). This substance and its precursors XVI and XV were identified by infrared comparison with naturally derived *d*-substances. Preliminary resolution studies *via* the *l*-menthoxyacetate of *dl*-XVI are described. Additional compounds in the 18-nor-D-homosteroid series were prepared for physiological examination. These include *dl*-18-nor-D-homotestosterone XXI (R = H), the acetate and propionate.

The male hormone, testosterone, was isolated from testicular tissue by Laqueur and his collaborators[5] in 1935. Although only about 10 mg. of the pure hormone was isolated from 100 kg. of steer testes tissue,[6] this was sufficient for inferring the structure which was soon confirmed by partial synthesis.[7] Recently several formal totally synthetic pathways have been opened[8] including one from our own laboratory, *via* epiandrosterone.[9] The objective of the present study was to effect a direct total synthesis of testosterone by exploitation of approaches described in previous papers of this series.

The obvious route to totally synthetic testosterone from epiandrosterone[9] *via* transformations already known from partial synthetic studies[10] appeared to be not only circuitous but impractical. Moreover, since the starting tetracyclic ketone I already contained the α,β-unsaturated ketone ring A system of testosterone, the plan of removing (by reduction[9]) and then later reintroducing this structural feature appeared inelegant. We decided, therefore, to explore the possibility of protecting this functional system as the ethylene ketal II, a technique which has been applied so dramatically by Sarett and his collaborators[11] in the total synthesis of adrenal steroids.

The use of the ketal II appeared particularly promising, because before the work of Sarett had been published we had found that the A/B unsaturated ketal system was inert to the Wilds Nelson conditions of reduction with lithium and alcohol in liquid ammonia which, in this case, effected stereo-selective reduction of the styrene bond to give mainly the *anti-trans*-dihydro ketal III.[12] Since potassium proved to be better than lithium in a comparable case,[13] this modification was tried in the present study, but the dihydro ketal III was produced in about the same yield as with lithium.

The hope that the ketal system would in turn survive the vigorous lithium reduction conditions[9] was realized. The *anti-trans*-dihydro ketal III was thus converted to an oily product which was essentially transparent to ultraviolet light except for end absorption showing that the aromatic nucleus had been reduced. On addition of a drop of dilute hydrochloric acid to the spectral sample, a strong band appeared at 240 mμ due to the α,β-unsaturated ketone produced by hydrolysis of the ketal. Selective hydrolysis of the enol ether was effected with 0.1 *M* aqueous methanolic oxalic acid—conditions which were found not to affect either the ketal III, or the ketal of Δ^4-cholestenone. The ultraviolet spectrum of the product was unchanged, but a strong band appeared at 5.85 μ in the infrared region showing that a carbonyl group had been produced. These spectral data showed clearly that the oxalic acid treatment had afforded the primary (β,γ-unsaturated) ring D ketonic hydrolysis products without isomerization to the conjugated system.[14] Under these conditions the

(1) (a) Paper IX, R. Pappo, B. M. Bloom and W. S. Johnson, THIS JOURNAL, **78**, 6347 (1956); (b) a preliminary report of the present work has been published, W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, *ibid.*, **77**, 817 (1955).

(2) Postdoctoral project associate supported by the Wisconsin Alumni Research Foundation, 1952–1953; and the National Science Foundation, 1953–1954.

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(4) Postdoctoral project associate supported by G. D. Searle and Co.

(5) K. David, E. Dingemanse, J. Freud and E. Laqueur, *Z. physiol. Chem.*, **233**, 281 (1935).

(6) K. David, *Acta Brevia Neerland*, **5**, 85, 108 (1935).

(7) A. Butenandt and G. Hanisch, *Z. physiol. Chem.*, **237**, 89 (1935); L. Ruzicka, THIS JOURNAL, **57**, 2011 (1935), *et seq.*

(8) See paper I for summary, W. S. Johnson, *ibid.*, **78**, 6278 (1956).

(9) Paper VII, W. S. Johnson, B. Bannister and R. Pappo, *ibid.*, **78**, 6331 (1956).

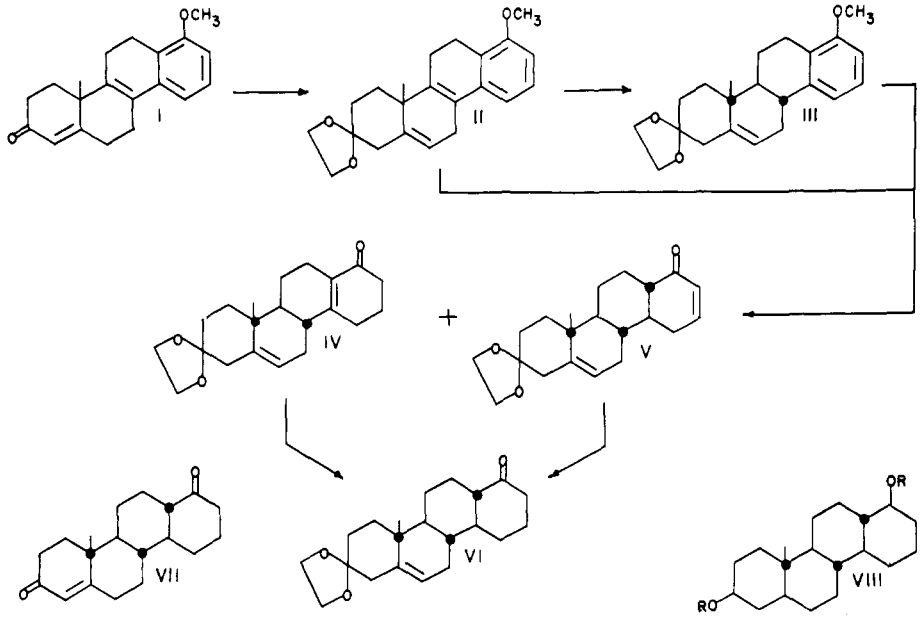
(10) The steps are summarized by H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann and R. Robinson, *J. Chem. Soc.*, 361 (1953).

(11) See G. E. Arth, G. I. Poos and L. H. Sarett, THIS JOURNAL, **77**, 3834 (1955), and previous papers.

(12) Paper III, W. S. Johnson, E. R. Rogier, J. Szmuszkovicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharyya, B. M. Bloom, L. Stalmann, R. A. Clement, B. Bannister and H. Wynberg, *ibid.*, **78**, 6289 (1956).

(13) Paper V, W. S. Johnson, A. D. Kemp, R. Pappo, J. Ackerman and W. F. Johns, *ibid.*, **78**, 6312 (1956).

(14) *Cf.* the products produced in similar reductions, ref. 9.



model substane Δ^5-cholestenone[15] was isomerized to the Δ^4-compound in only 12% yield as demonstrated spectrophotometrically. Isomerization of the double bond without affecting the ketal system was achieved readily by adsorption on alkaline alumina as demonstrated by the appearance of strong absorption in the 240–250 mμ region. Purification by chromatography gave, in addition to considerable hydrogenolysis material, two crystalline ketones, one melting at 176°, λ_{max} 225 mμ, and the other (preponderant) melting at 143°, λ_{max} 246.5 mμ. The ultraviolet spectra clearly showed that these were the 16,17- and 13,14-dehydro ketones V and IV, respectively.[14]

Catalytic hydrogenation of V or of IV (in alkaline medium) could be carried out selectively without extensive reduction of the 5,6-double bond[16] to give a single ketone, m.p. 143°, which, except for end absorption, was transparent to ultraviolet light until treated with aqueous hydrochloric acid whereupon a strong band appeared at 240 mμ. This behavior demonstrated that the unsaturated ketal system was still intact and that the 143° ketone was correctly represented structurally by formula VI. A question remained, however, about the configuration of this substance at C_{14} and in turn C_{13}. This point was established by acid hydrolysis to give an α,β-unsaturated ketone VII, m.p. 147°, λ_{max} 240 mμ, which in turn was reduced with lithium and alcohol in ammonia and acetylated to give a diacetate, m.p. 170° identical (by mixed m.p.) with the diacetate VIII (R = Ac) of established configuration.[9] The configuration of the 143° ketone was thus firmly established as *anti-trans-anti-trans* (formula VI).

We next explored the possibility of producing the ketone VI from the ketal II without purification of intermediates. The reduction with potassium was followed immediately by lithium treatment without isolation of III. After the oxalic acid hydrolysis, the isomerization was effected by heating with alcoholic sodium acetate which appeared to be less deleterious to the alkali-sensitive 16,17-dehydro compound. The over-all yield of crude $\alpha\beta$-unsaturated ketones IV and V from II was 39%. The yield of the desired ketone VI from this total crude material was 47% and appeared to be attended by significant reduction of the 5,6-double bond. In one experiment the crude 13,14-dehydro ketone fraction from chromatography was selectively hydrogenated to VI in 84% yield. A fraction rich in the 16,17-dehydro ketone, in contrast, afforded VI in only 44% yield, the remainder of the product showing no appreciable absorption in the 240 mμ region after acidification indicating reduction of the 5,6-double bond. The selective hydrogenation step will require further study for proper refinement; however, the conditions described in the present report may be expected to give at least the lower yields.

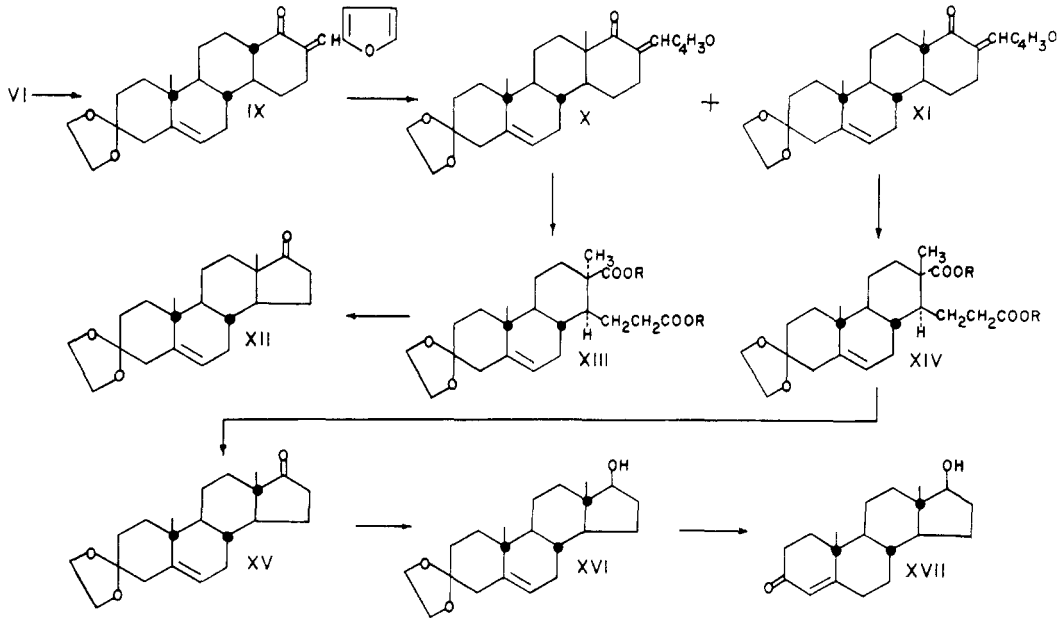
The angular methylation–ring contraction sequence for conversion of the α-decalone ring system into the 17-keto steroid ring moiety[9,17,18] was applied to the ketone VI; however, some major modifications were required to preserve the unsaturated ketal system. The condensation with furfuraldehyde proceeded readily to give an excellent yield of the furfurylidene derivative IX, m.p. 188°. The angular methylation step also proceeded normally to give two easily separable C_{13}-epimers. As in previous cases with furfurylidene derivatives,[9,18] the less preponderant isomer, m.p. 211°, λ_{max} 323 mμ, was also less soluble. The preponderant epimer melted at 188° and exhibited λ_{max} 327 mμ. The ratio of isomers and their spectral characteristics suggested[9] that they were the C/D *trans* (XI) and *cis* (X) epimers, respectively. These

(15) *Org. Syntheses*, **35**, 43 (1955).

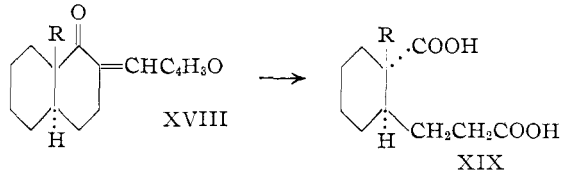
(16) *Cf.* for example the selective hydrogenation of 3β-hydroxypregna-5,16-diene-17-one to pregnenolone; A. Butenandt and J. Schmidt-Thomé, *Ber.*, **71**, 1487 (1938); **72**, 182 (1939).

(17) (a) W. S. Johnson, THIS JOURNAL, **65**, 1317 (1943); **66**, 215 (1944); (b) W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg and L. J. Chinn, *ibid.*, **74**, 2832 (1952).

(18) Paper VIII, W. S. Johnson, R. Pappo and W. F. Johns, *ibid.*, **78**, 6339 (1956).

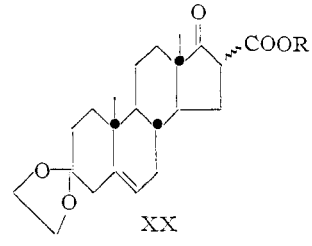


substances were cleanly separated by chromatography and isolated in 19 and 74% yields, respectively.



Attempts to effect selective ozonolysis of the *cis*-furfurylidene ketone X were unpromising and the desired product, isolated as the dimethyl ester XIII (R = CH_3), was obtained in 12% yield at best. We were thus prompted to search for another oxidative method. Since it is well known that alkaline hydrogen peroxide attacks α,β-unsaturated ketones, but not isolated olefinic bonds, we hoped to take advantage of this selectivity in a stepwise degradation. To our surprise, prolonged treatment with the reagent carried the oxidation beyond the point of the expected α,β-epoxide and afforded the desired dibasic acid directly. Preliminary experiments with *trans*-furfurylidene-1-decalone (XVIII, R = H) and with the *trans*-9-methyl homolog (XVIII, R = CH_3) gave substantial amounts of the known crystalline dibasic acids XIX (R = H) and XIX (R = CH_3) which were compared with authentic specimens. The insolubility of the tetracyclic compounds in the oxidizing medium precluded reaction under normal conditions even with a large proportion of methanol. This difficulty was overcome by use of vigorous agitation (preferably with a Waring blendor), and the compounds gradually dissolved in the alkaline medium. The products were easily purified by conversion to the dimethyl esters by treatment with diazomethane. The *cis* isomer X was thus converted into the dimethyl ester XIII (R = CH_3), m.p. 123° in 82% over-all yield. Similarly the *trans* epimer XI afforded the ester XIV (R = CH_3), m.p. 163°, in 92% yield.

Since it was desired to complete the formation of ring D without loss of the unsaturated ketal system, it was necessary to avoid the use of acidic conditions. Pyrolysis of the dibasic acid XIV (R = H) in the presence of barium hydroxide resulted in extensive decomposition, and the trace of distillate obtained exhibited absorption at 240 mμ indicating that the ketal had been cleaved at least partially under these conditions. Attention was then turned to utilization of the Dieckmann cyclization.



The β-keto esters XX and 13-iso-XX were formed readily by the potassium *t*-butoxide cyclization[9] of the esters XIV (R = CH_3) and XIII (R = CH_3), respectively. Preliminary attempts to saponify the ester group under mild conditions did not look promising, because of the not unexpected[19] ease with which the five-membered ring was opened. In another study[18] hydrolysis and decarboxylation of a similar system was effected by heating at 200° in aqueous dioxane. In a model experiment with the 3-ethylene ketal of testosterone these conditions effected complete hydrolysis of the ketal grouping; hence this approach was also abandoned.

Since the keto esters under consideration evolved gas slowly on melting, their decomposition in an inert solvent was studied. After one hour in refluxing *p*-cymene the crude keto ester from XIII (R = CH_3) was converted to material which no longer gave a color with alcoholic ferric chloride, and the desired ketone XII, m.p. 162°, was indeed isolated. This study in the 13-iso series has not yet been carried beyond the preliminary (and as yet incomplete) experiment, but this phase of the work is being continued.

(19) *Cf.* W. Dieckmann, *Ann.*, **317**, 27 (1901).

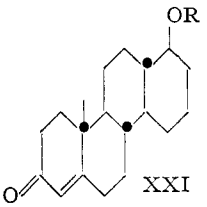
With preliminary success in the 13-iso series, our attention was turned immediately to the natural series. Heating the keto ester from XIV (R = CH_3) for 2 hours in *p*-cymene afforded crude *dl*-ethylenedioxy-5-androstene-17-one (XV), in 60% yield. The infrared spectrum of the pure material, m.p. 169°, was identical with that of authentic (naturally derived) *d*-XV.

The mechanism of the decarbomethoxylation described above is not clear. It occurred to us that the keto ester might actually be a product of ester exchange, namely, the *t*-butyl ester XX (R = *t*-butyl) which would be expected to decompose readily on heating to give the ketone, carbon dioxide and isobutylene.[20] This attractive hypothesis was invalidated by closer examination of the keto ester in the natural series which was obtained crystalline. Compositional analysis of a purified specimen, m.p. 167°, showed it to be the methyl ester XX (R = CH_3). On the chance that this substance had been fortuitously separated from the *t*-butyl ester during recrystallization, a methoxyl determination was performed on the total residues, and this result showed them to consist largely of methyl ester. We hope to give further study to the problem and to determine if the decomposition of the β-keto esters in *p*-cymene is a homolytic or heterolytic process. The fact that di-*p*-cymyl was isolated from the reaction mixture does not necessarily point to the former process, since it has been shown that this dimer is produced simply on distillation of *p*-cymene in air.[21]

Reduction of the ketal ketone XV with sodium borohydride gave *dl*-testosterone 3-ethylene ketal (XVI), m.p. 181°, which on acid hydrolysis afforded *dl*-testosterone (XVII), m.p. 169°. The infrared spectra of these two substances were identical with those of the corresponding naturally derived substances.

Preliminary resolution experiments have been performed through the *l*-menthoxyacetate of the *dl*-ketal XVI. The mixture of diastereoisomers was partially separated by a combination of chromatography and fractional crystallization. A specimen was isolated that melted at 159–160° alone or on admixture with authentic *d*-testosterone-*l*-menthoxyacetate 3-ethylene ketal prepared from naturally derived *d*-testosterone 3-ethylene ketal. Insufficient totally synthetic material was available for determining the specific rotation, but the infrared spectrum was indistinguishable from that of the authentic material. Saponification of this derivative[22] gave *d*-testosterone 3-ethylene ketal the hydrolysis of which to *d*-testosterone has been described.[23] The resolution study is receiving further attention.

As a continuation of our investigation of the physiologically active 18-nor-D-homo steroids,[9] additional members were prepared from intermediates in the present study. A synthesis of *dl*-18-nor-D-homoandrostenedione (VII) has already been reported above. Lithium aluminum hydride reduction of the ketal ketone VI followed by acid hydrolysis gave *dl*-18-nor-D-homotestosterone, (XXI, R = H), m.p. 173°. The acetate XXI (R = Ac), m.p. 183°, and the propionate



XXI

XXI (R = $COCH_2CH_3$), m.p. 150°, were also prepared. A convenient route to these testosterone analogs is by direct reduction of the 13,14-dehydro ketone IV with lithium and alcohol in ammonia, followed by acid hydrolysis of the ketal. Thus after acetylation the acetate XXI (R = H) was prepared from IV in 55% over-all yield.[24]

Acknowledgment.—We are grateful to the agencies named in footnotes 2–4 for supporting this work. We wish to thank Drs. A. L. Raymond and B. Riegel and their collaborators at G. D. Searle and Co. for providing us with supplies of intermediates for this study.

Experimental[25,26]

***anti-trans*-1-Methoxy-8-ethylenedioxy-10a-methyl-4b,5,7,-8,9,10,10a,10b,11,12-decahydrochrysene (III).**—A solution of 2.00 g. of the ketal II,[12] m.p. 119.5–121°, in 200 ml. of anhydrous ether was added to 400 ml. of liquid ammonia; then 3.0 g. of potassium metal was added with stirring in portions over a 5-minute period. After stirring for an additional 10 minutes, 120 ml. of ethanol was added dropwise over a 15-minute period, followed by 10 g. of ammonium chloride. The crude product was isolated from the reaction mixture as already described,[12] and crystallized from a small volume of ether to yield 1.54 g. (77% yield) of the crude *anti-trans*-ketal III, m.p. 140–145°. The purification of such material is already described.[12]

Reduction of the *anti-trans*-Ketal III.—A solution of 4.97 g. of the ketal III,[12] m.p. 148.5–149.5°, in 220 ml. of dry dioxane[27] was added to 750 ml. of liquid ammonia, then 450 ml. of absolute ethanol was added followed by a total of 23 g. of lithium wire, 800 ml. of additional ammonia and 300 ml. of additional ethanol. The rate of the addition of reagents was controlled so as to maintain the bronze phase as described elsewhere.[9] After all of the lithium had reacted (about 90 minutes), the ammonia was evaporated, water added, and the product extracted with ether. The ether layers were washed thoroughly with water (until neutral to litmus) and dried over anhydrous sodium sulfate. The oily residue obtained upon evaporation of the solvent was essentially transparent to ultraviolet light except for strong end absorption. This residue was dissolved in 260 ml. of methanol, a solution of 4.0 g. of oxalic acid dihydrate in 50 ml. of water added, the mixture left at room tempera-

(20) See, for example, D. S. Breslow, E. Baumgarten and C. R. Hauser, THIS JOURNAL, **66**, 1286 (1944).

(21) H. Pines, B. Kvetinskas and V. N. Ipatieff, *ibid.*, **77**, 343 (1955).

(22) Naturally derived material was used as a "relay" at this point.

(23) H. J. Dauben, Jr., B. Löken and H. J. Ringold, THIS JOURNAL, **76**, 1359 (1954).

(24) For reports on physiological action see ref. 1b and forthcoming publications by R. K. Meyer and Elva G. Shipley.

(25) Unless otherwise indicated, all new substances described in this section are racemic (*dl*) compounds. Melting points of analytical specimens are corrected for stem exposure. Ultraviolet absorption spectra were determined on a Cary recording spectrophotometer (model 11MS), 95% ethanol being employed as the solvent. Infrared spectra were determined on a Baird double beam infrared recording spectrophotometer, model B. Unless otherwise specified, carbon disulfide was used as the solvent.

(26) An arbitrary change from chrysene to steroid nomenclature has been invoked at the stage where the aromatic ring D becomes hydroaromatic.

(27) Purified by the procedure in L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, Mass., 1955, p. 284.

ture for 2 hours, then poured into an excess of 15% potassium bicarbonate solution. The mixture was extracted with ether, and the ether layers were washed thoroughly with water and dried over anhydrous sodium sulfate. The pale yellow oily residue obtained upon evaporation of the solvent absorbed strongly in the 5.85 μ (C=O) and 9.1–9.2 μ (ketal) regions. This residue was dissolved in 30 ml. of benzene, 70 ml. of petroleum ether (60–68°) added, and the solution mixed with 100 g. of Alcoa alkaline alumina (*p*H of aqueous slurry about 10) at room temperature. After 12 hours the material was eluted with ether. The total pale yellow oily residue obtained on evaporation of the combined filtrates absorbed strongly in the 240–250 mμ and 5.99–6.05 μ (C=C—C=O) as well as the 9.1–9.2 μ (ketal) regions. Low intensity bands appeared at 5.85 μ (C=O) and at 2.85–2.95 μ (OH contaminant).

The oily residue was chromatographed on 300 g. of alkaline alumina (Merck and Co.). Elution with 1:4 to 2:3 benzene–petroleum ether (60–68°) gave a total of 2.2 g. in three major fractions which apparently contained considerable hydrogenolysis material as shown spectrographically (*cf.* similar reductions[9]). These fractions have not been studied further. Elution with 3:4 benzene–petroleum ether (60–68°) gave a small (0.043 g.) intermediate fraction, which was followed by the crystalline 16,17-dehydro ketone fraction (0.338 g., m.p. 169–173°) eluted by 4:1 benzene–petroleum ether. This crystalline material absorbed strongly at 226 mμ and 6.0 μ (C=C—C=O). Recrystallization from diisopropyl ether, followed by sublimation at 170° (high vacuum), then two more recrystallizations from the same solvent, gave ***dl*-3-ethylenedioxy-18-nor-D-homoandrosta-5,16-diene-17a-one** (V), as colorless elongated prisms, m.p. 175–176°, λ_{max} 225 mμ (log ϵ 3.94); λ_{max} 6.0 μ (C=C—C=O), 9.1 μ (ketal).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.9; H, 8.55.

Further elution of the chromatographic column with 9:1 benzene–petroleum ether (60–68°) afforded a total of 0.590 g. of crystalline 13,14-dehydro ketone fraction, m.p. 138–141°, λ_{max} 246 mμ and 6.08 μ (C=C—C=O). Recrystallization from ether, followed by sublimation at 130° (high vacuum) and recrystallization again from ether gave ***dl*-3-ethylenedioxy-18-nor-D-homoandrosta-5,13-diene-17a-one** (IV), as colorless prisms, m.p. 142.8–143.2°, λ_{max} 246.5 mμ (log ϵ 4.13); λ_{max} 6.05 μ (C=C—C=O), 9.1–9.2 μ (ketal).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.9; H, 8.68.

***dl*-3-Ethylenedioxy-18-nor-D-homo-5-androstene-17a-one (VI). (a) From the 13,14-Dehydro Ketone IV Fraction.**—The mother liquor residues (0.460 g.) from the crystallization of the 13,14-dehydro ketone fraction described in the preceding section were dissolved in 100 ml. of 95% ethanol (distilled from Raney nickel) containing 0.1 g. of potassium hydroxide in 1 ml. of water, and hydrogenated over 0.100 g. of 10% palladium-on-carbon (American Platinum Works) at room temperature and an initial pressure of 38 p.s.i. Absorption of hydrogen ceased after 1 hour, the mixture was filtered, the filtrate concentrated, and the residue dissolved in ether, washed with water and dried over anhydrous sodium sulfate. The residue obtained upon evaporation of the solvent was washed through 60 g. of alkaline alumina (Merck and Co., Inc.). Evaporation of the filtrate gave 0.388 g. (84% yield) of crude ketone VI, m.p. 139–142°, which showed only end absorption of low intensity in the ultraviolet region. On the addition of dilute hydrochloric acid, a peak developed rapidly at 240 mμ. Repeated recrystallization from diisopropyl ether gave colorless plates, m.p. 142–143°, λ_{max} 5.86 μ (C=O), 9.0–9.2 (ketal).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.31; H, 9.15. Found: C, 76.7; H, 9.43.

(b) Directly from the Original Ketal II without Purification of Intermediates (Improved Isomerization Procedure).—A solution of 18.0 g. of 1-methoxy-8-ethylenedioxy-10a-methyl-5,7,8,9,10,10a,11,12-octahydrochrysene (II), m.p. 119.5–121°, in 1 l. of anhydrous ether was added to 2 l. of liquid ammonia; then 30 g. of potassium was added rapidly with stirring. After stirring for 10 minutes, 2 l. of absolute ethanol was added cautiously. When all the potassium had reacted, an additional 2 l. of liquid ammonia was added; then a total of 80 g. of lithium wire was introduced in portions with stirring over a 1.5-hour period along with additional ammonia to maintain the original volume. The metal was added at the rate necessary to maintain the bronze phase as described elsewhere in detail,[9] and the crude product was isolated as described above (reduction of III).

Hydrolysis.—The total crude enol ether (38.6 g.) from two identical runs was dissolved in 3 l. of methanol and 1 l. of ether; then a solution of 32 g. of oxalic acid dihydrate in 400 ml. of water was added. After 2 hours at room temperature, 100 ml. of 10% sodium hydroxide was added, followed by excess saturated potassium bicarbonate solution. The aqueous layer was extracted with benzene, and the combined organic layers washed with water and dried over anhydrous sodium sulfate.

Isomerization.—The total crude ketonic mixture obtained upon evaporation of the solvent was dissolved in 1 l. of absolute ethanol, 44 g. of anhydrous sodium acetate added, and the mixture heated at reflux. After 4 hours absorption at 242 mμ had reached a maximum, benzene and water were added, and the aqueous layer extracted with benzene. The combined organic layers were washed with saturated sodium bicarbonate solution, then with water and dried over anhydrous sodium sulfate. The pale yellow oil (37.5 g.) obtained on evaporation of the solvent was chromatographed on 1500 g. of Florisil. A large proportion of the material—including a 7-g. crystalline fraction showing only end absorption in the ultraviolet region (probably hydrogenolysis product)—was eluted in the early fractions as in the experiment on the reduction of III described above. The late 1:9 and the early 1:4 ether–benzene eluates yielded 4.01 g. of crude crystalline 16,17-dehydro ketone, λ_{max} 225 mμ. After an intermediate 1.25-g. fraction (λ_{max} 238 mμ) eluted with 1:4 ether–benzene, there was obtained by elution with the same solvent followed by 1:1 ether–benzene, a total of 8.30 g. of crystalline 13,14-dehydro ketone fraction, λ_{max} 244–246 mμ.

Hydrogenation.—A solution of 4.00 g. of the crude 16,17-dehydro ketone fraction in 250 ml. of absolute ethanol was hydrogenated over 0.500 g. of 6% palladium-on-strontium carbonate[28] at room temperature and an initial pressure of 38 p.s.i. After 1 hour gas absorption had ceased, the mixture was filtered and the filtrate evaporated leaving a crystalline residue, λ_{max} 247 mμ (low intensity).

The intermediate 1.25-g. fraction from the chromatogram was similarly hydrogenated in 125 ml. of ethanol over 0.200 g. of the catalyst. The crude product exhibited λ_{max} 247 mμ, showing that the 16,17-dehydro compound had been hydrogenated leaving the 13,14-dehydro isomer. This material was combined with the 8.30-g. 13,14-dehydro ketone fraction, dissolved in 420 ml. of ethanol containing 3.0 g. of potassium hydroxide in 3 ml. of water, and hydrogenated over 2.0 g. of 10% palladium-on-carbon (American Platinum Works) as described above. The reaction was interrupted after the absorption of approximately one mole-equivalent of hydrogen, the mixture filtered, the filtrate concentrated, and the concentrate taken up in benzene. The organic layer was washed with water until neutral to litmus, then dried over anhydrous sodium sulfate. The crystalline residue obtained upon evaporation of the solvent was essentially transparent in the ultraviolet region except for strong end absorption.

The two crude hydrogenation products described above were combined and crystallized from methanol to give a total of 6.4 g. of the ketone VI, m.p. 136–140°, suitable for formation of the furfurylidene derivative (see below). The poor yield at the catalytic hydrogenation step in this experiment as compared with the one above (part a) is probably due to some reduction of the 5,6-double bond as observed in the case described below.

(c) From the 16,17-Dehydro Ketone V. (Total Reduction of II with Lithium.)—In another experiment, 25 g. of the ketal II, m.p. 119–120°, was reduced directly with lithium essentially as described above for the reduction of the *anti-trans*-dihydro ketal III. Chromatography of the isomerized material on alkaline alumina gave, in order, the following α,β-unsaturated ketone fractions: 0.998 g. of material, m.p. 169–177°, λ_{max} 246 mμ, which may correspond to a stereoisomeric (at rings B/C) form of IV but has not been investigated further; 0.206 g. of fairly pure 16,17-

(28) See ref. 12, footnote 33.

dehydro ketone, m.p. 170–173°; 0.535 g. of an intermediate fraction; and 3.29 g. of 13,14-dehydro ketone, m.p. 139–143°.

A solution of 0.090 g. of the 16,17-dehydro ketone, m.p. 170–173°, in 20 ml. of 95% ethanol (distilled from Raney nickel) was hydrogenated over 0.020 g. of 10% palladium-on-carbon (American Platinum Works) at room temperature and an initial pressure of 38 p.s.i. The reaction was interrupted after approximately one mole-equivalent of hydrogen was absorbed, the mixture filtered and the filtrate evaporated. The oily residue still showed some absorption in the 226 mμ region. The material was readily purified by chromatography on Florisil to give 0.040 g. of the saturated ketone, m.p. 140–143°, alone or on admixture with the pure specimen described above. The early fraction of the chromatogram was an oily mixture which absorbed at 5.86 μ (C=O) and 9.2 μ (ketal) but was essentially transparent in the ultraviolet region even after acidification and therefore was presumably a mixture resulting from hydrogenation of the 5,6-double bond.

An attempt to improve the selectivity of the reduction by conducting the hydrogenation in alkaline solution (as described above) gave only a 50% yield of the desired ketone, m.p. 139–142°. In this experiment considerable material of high molecular weight was formed, perhaps due to polymerization of the unsaturated ketone by the alkali.

dl-18-Nor-D-homo-4-androstene-3,17a-dione (VII).—A solution of 0.100 g. of the ketal ketone VI, m.p. 139–141°, in 5 ml. of acetone, containing 0.03 g. of *p*-toluenesulfonic acid monohydrate and 2 drops of water was heated at reflux. After 1.5 hours, water was added, the mixture extracted with ether, and the organic layers washed thoroughly with water, then dried over anhydrous sodium sulfate. The crystalline residue obtained on evaporation of the solvent amounted to 0.081 g., m.p. 140–146°. Recrystallization from ether, again from petroleum ether (90–100°) and finally from diisopropyl ether gave colorless needles, m.p. 146.5–147.5°, λ_{max} 240 mμ (log ε 4.2); $\lambda_{max}^{CHCl_3}$ 5.86 μ (C=O), 6.05 (C=C—C=O) and 6.19 (conjugated C=C).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.5; H, 9.14.

Lithium Reduction of dl-18-Nor-D-homo-4-androstene-3,17a-dione (VII).—A solution of 0.051 g. of the diketone, m.p. 144–146°, in 10 ml. of absolute ethanol was added with stirring to 90 ml. of liquid ammonia, then 1.0 g. of lithium wire was added rapidly, and the deep-blue solution stirred for 20 minutes. An additional 3 ml. of ethanol was introduced to react with the last traces of metal, then the ammonia was evaporated, water and ether added, and the aqueous layer extracted with ether. The ether layers were washed throughly with water, dried over anhydrous sodium sulfate, the solvent evaporated, and the residue dissolved in benzene and washed onto a column of 2 g. of Florisil. Elution with 1:9 ether–benzene gave 0.044 g. of crude diol VIII (R = H) which was acetylated with 0.5 ml. of acetic anhydride in 1.0 ml. pyridine. After 12 hours at room temperature the crude **diacetate VIII (R = Ac)** was isolated as described in the preparation of 18-nor-D-homoepiandrosterone.[9] After passage of its benzene solution through a column of 2 g. of Florex, the eluate was evaporated and the crystalline residue recrystallized from methylcyclohexane to give colorless prisms, m.p. 167–169°. Sublimation at 165° (0.02 mm.) followed by recrystallization from the same solvent gave small prisms, m.p. 169.5–170°, undepressed on admixture with the authentic material of the same m.p.[9]

dl-3-Ethylenedioxy-17-furfurylidene-18-nor-D-homo-5-androstene-17a-one (IX).—A 2.25-g. sample of the ketone VI, m.p. 139–142°, was dissolved in 300 ml. of methanol, 50 ml. of 33% sodium hydroxide was added to the cooled solution, followed by 6.0 ml. of freshly distilled furfuraldehyde. After 10 hours at room temperature under nitrogen, the crystalline precipitate was separated and washed with 15% aqueous methanol, followed by 50% aqueous methanol until the filtrate was neutral to litmus. The product amounted to 2.57 g. (92% yield), m.p. 183–187°. Three recrystallizations from cyclohexane afforded tiny colorless platelets, m.p. 187–188.5°, λ_{max} 325 mμ (log ε 4.32).

Anal. Calcd. for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90. Found: C, 76.2; H, 7.89.

When a 6.40-g. sample of ketone, m.p. 136–140°, was condensed with furfuraldehyde as described above, the yield of furfurylidene ketone, m.p. 184–187°, was 6.72 g.

Angular Methylation.[17]—A 2.90-g. sample of the furfurylidene ketone IX, m.p. 184–187°, was added to a cooled (10°) solution of 2.7 g. of potassium in 80 ml. of anhydrous *t*-butyl alcohol under an atmosphere of nitrogen. Methyl iodide (15 ml.) was then added and after 1 hour at 10°, the mixture was allowed to stand at room temperature overnight. Most of the solvent was evaporated at 60° (10 mm.), water was added, and the mixture extracted with benzene. The benzene layers were washed thoroughly with water, and dried over anhydrous sodium sulfate. The viscous yellow oily residue obtained upon evaporation of the solvent was triturated with cyclohexane, which caused crystallization, to give 0.470 g. of crude **dl-3-ethylenedioxy-17-furfurylidene-D-homo-5-androstene-17a-one (XI)**, m.p. 201–205°. Several recrystallizations from cyclohexane, and finally once from methylcyclohexane gave 0.311 g. of pale yellow elongated plates, m.p. 210–211°, λ_{max} 323 mμ (log ε 4.35).

Anal. Calcd. for $C_{27}H_{34}O_4$: C, 76.74; H, 8.11. Found: C, 76.7; H, 8.16.

The residue obtained on evaporation of the mother liquors from the original trituration was crystallized from cyclohexane to give 1.23 g. of **dl-3-ethylenedioxy-13-iso-17-furfurylidene-D-homo-5-androstene-17a-one (X)** as pale yellow plates, m.p. 187–188.5°, λ_{max} 327 mμ (log ε 4.36). The m.p. was depressed to 160–166° on admixture with starting material.

Anal. Calcd. for $C_{27}H_{34}O_4$: C, 76.74; H, 8.11. Found: C, 76.75; H, 8.18.

Evaporation of the combined mother liquors from all of the crystallizations of both isomers gave 1.45 g. of brownish oil which was chromatographed on 100 g. of Florisil. The fraction eluted with pure benzene amounted to 1.00 g. of the 13-iso compound, m.p. 186–188°. Elution with benzene containing 2% ether gave an additional 0.262 g. of the C/D *trans* isomer, m.p. 208–210°. The total yield of methylated isomers was therefore 2.23 g. (74%) of *cis*- and 0.573 g. (19%) of *trans*-ketone.

In another methylation experiment with the 6.72 g. of furfurylidene derivative IX, m.p. 184–187°, the total crude product was chromatographed directly on 350 g. of Florisil. The C/D *cis* fraction (5.21 g. crystalline, λ_{max} 325.5 mμ) was eluted with 1 to 5% ether in benzene, and the C/D *trans*-isomer (1.31 g. crystalline, λ_{max} 323 mμ) with 5–20% ether in benzene. Recrystallization of the latter fraction from methanol gave 1.05 g. of material, m.p. 200–208°, suitable for the next step.

dl-Dimethyl 3-Ethylenedioxy-13-iso-etiohomo-5-bilienate (XIII, R = CH_3). (a) By Alkaline Peroxide Cleavage.—A 0.200-g. sample of the C/D *cis*-furfurylidene ketone X, m.p. 187–188°, was dissolved in 200 ml. of methanol, the solution was cooled, 10 g. of solid sodium methoxide added, and the mixture transferred to a Waring blendor with the aid of 50 ml. of methanol. Forty milliliters of 30% hydrogen peroxide was added, causing formation of a thick white precipitate, and stirring was commenced, the temperature rising quite rapidly to 48–50° which was maintained by the heat generated by the stirrer. After 4 hours, the mixture having become homogeneous, most of the solvent was removed at 50° in a stream of nitrogen, the residue diluted with water and washed thoroughly with ether. The aqueous phase was cooled to 0°, acidified with ice-cold 5% sulfuric acid, then quickly extracted with ether. These extracts were washed well with water, aqueous ferrous sulfate, water and dried over anhydrous sodium sulfate. The oil (0.160 g.) remaining upon evaporation of the ether was esterified with excess ethereal diazomethane to give (after evaporation of the ether) a pale yellow oil which crystallized on the addition of a drop of methanol; yield 0.164 g. (82%), m.p. 116–119°. Two recrystallizations from methanol gave colorless plates, m.p. 122–123°.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.6; H, 8.55.

(b) By Ozonolysis.—A solution of 0.100 g. of the furfurylidene derivative X, m.p. 187–188°, in 50 ml. of ethyl acetate was treated at −70° with 1.7 mole equivalent of ozone. Most of the solvent was removed at room temperature (10 min.), 2.5 ml. of 5% potassium hydroxide and 5 ml. of 30% hydrogen peroxide were added, and the mixture stirred

at room temperature for 2 hours, then washed thoroughly with benzene. The crude acid was isolated from the aqueous phase and esterified just as described above (part a). The crude dimethyl ester was chromatographed on 2 g. of Florex. The 1:1 benzene–petroleum ether (60–68°) eluate yielded 0.018 g. of oil which crystallized on standing. One recrystallization from ether gave 0.012 g. of colorless needles, m.p. 116–118°, undepressed on admixture with the analytical sample described above. The residues from the neutral (benzene washings) fraction yielded, on trituration with methanol, 0.050 g. of starting material, m.p. 185–187°.

When the oxidation was carried out using 1 mole-equivalent of ozone, only a trace of dimethyl ester, m.p. 117–119°, was isolated.

dl-**Dimethyl 3-Ethylenedioxyetiohomo-5-bilienate (XIV, R = CH$_3$).**—A 0.200-g. sample of the C/D *trans*-furfurylidene ketone XI, m.p. 208–210°, was oxidized just as described above for the *cis* isomer except that 250 ml. of methanol, 12 g. of sodium methoxide and 50 ml. of 30% hydrogen peroxide were used, and the stirring was continued for 6 hours (when the mixture became homogeneous). The crude ester amounted to 0.183 g. (92% yield), m.p. 160–163°, showing only end absorption in the ultraviolet region but developing a strong band at 240 mμ on acidification. Two recrystallizations from methanol gave colorless elongated flat prisms, m.p. 162.5–163.5°.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.5; H, 8.65.

In another run 1.05 g. of the furfurylidene ketone, m.p. 200–208°, was oxidized, using 1 l. of methanol, 27 g. of sodium methoxide and 50 ml. of 30% hydrogen peroxide. The mixture was agitated with a Vibro-Mischer (A. G. für Chemie-Apparatebau, Zürich, model E1), at room temperature. After 23 hours an additional 40 ml. of 30% hydrogen peroxide was added, then 50 ml. more after an additional 5 hours. After a total of 41 hours, the reaction mixture no longer exhibited absorption at 323 mμ, and the acidic material was isolated and esterified as described above in detail for the *cis* isomer. The crude crystalline ester (0.880 g.) was chromatographed on 30 g. of Florisil. A total of 0.575 g. of crystalline diester was eluted with 2–20% ether in benzene. (Late eluates contained 0.125 g. of oily material which was not further investigated.) Recrystallization from benzene–methanol containing a trace of pyridine gave 0.486 g. of pure colorless prisms, m.p. 162–163.5°.

Exploratory Alkaline Peroxide Oxidations. (a) Of *trans*-2-Furfurylidene-1-decalone.—Four grams of the furfurylidene derivative,[9] m.p. 113–114.5°, was suspended in 160 ml. of methanol, 8 ml. each of 8% sodium hydroxide and 30% hydrogen peroxide were added, and the mixture stirred slowly at room temperature. After 26 hours the mixture still exhibited strong absorption at 322 mμ; an additional 140 ml. of methanol, 20 ml. of 40% sodium hydroxide and 20 ml. of 30% hydrogen peroxide were added and the stirring continued for 3 days. Although the mixture still absorbed at 322 mμ, the crude products were isolated approximately as described above for the oxidation of X. The neutral fraction, isolated by continuous ether extraction, amounted to 0.532 g. and, on trituration with methanol, gave 0.400 g. of starting material, m.p. 110–114°.

The acidic fraction, also isolated by continuous ether extraction, was further separated into a bicarbonate-soluble fraction amounting to 2.48 g. of brown oil. Chromatography on Florex gave 0.21 g. of 2-furoic acid, m.p. 129–132°, on elution with benzene. Elution with 1:9 ethyl acetate–benzene gave 0.824 g. of crystalline *trans*-β-(2-carboxycyclohexyl)-propionic acid. Sublimation at 100° (0.05 mm.) gave material melting at 140–142° alone or on admixture with authentic material.[29] The bicarbonate-insoluble acidic fraction (0.28 g. of dark-brown oil) was soluble in dilute sodium hydroxide and may have contained 1,2-decalindione.

(b) **Of *trans*-9-Methyl-2-furfurylidene-1-decalone.**—A 0.610-g. sample of the furfurylidene derivative,[9] m.p. 110–111°, was dissolved in 60 ml. of methanol, a solution of 1.6 g. of sodium in 30 ml. of methanol was added followed by 20 ml. of 30% hydrogen peroxide, and the mixture stirred for 24 hours at room temperature. During this period an additional 10 ml. of hydrogen peroxide and 50 ml. of methanol were introduced. The products were isolated as described in part a above. The neutral fraction yielded, after crystallization from methanol, 0.295 g. of starting material, m.p. 110–111°. The bicarbonate-soluble fraction yielded 0.198 g. of *trans*-β-(2-carboxy-2-methylcyclohexyl)-propionic acid, m.p. 181–183°, undepressed on admixture with authentic material.[17a]

dl-**3-Ethylenedioxy-13-iso-5-androstene-17-one (XII).**[30]—A mixture of alcohol-free potassium *t*-butoxide (from 0.30 g. of potassium), 50 ml. of benzene and 0.590 g. of the 13-isodimethyl ester (XIII, R = CH$_3$), m.p. 121–122°, was stirred at reflux temperature for 8 hours, then at room temperature overnight. The mixture was chilled, acidified (to congo red) with ice-cold 5% sulfuric acid, and the organic layer washed with water, 10% potassium bicarbonate, water, then dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.538 g. of colorless oily β-keto ester which crystallized on cooling, m.p. 150–154° dec. This material gave a deep blue-green color with alcoholic ferric chloride.

A solution of 0.100 g. of the crude β-keto ester in 20 ml. of freshly distilled *p*-cymene was heated under gentle reflux in an atmosphere of nitrogen. After 60 minutes the solvent was removed at reduced pressure and the residue, which gave no coloration with ferric chloride, was purified by passage through a 1-g. column of Florex. Early benzene eluates contained di-*p*-cymyl, and the later fractions yielded 0.070 g. of crystalline ketone XII, m.p. 145–150°. Sublimation at 140° (0.01 mm.) gave material, m.p. 154–159°, which on crystallization from petroleum ether (60–68°) was obtained as colorless needles, m.p. 161–162.5°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.2; H, 9.15.

dl-**3-Ethylenedioxy-16-carbomethoxy-5-androstene-17-one (XX, R = CH$_3$).**[30]—A mixture of alcohol-free potassium *t*-butoxide (from 2.3 g. of potassium), 150 ml. of benzene and 0.476 g. of the diester XIV, m.p. 162–163.5°, was heated at reflux temperature with stirring. After 12 hours the solution was cooled, 4 ml. of glacial acetic acid added, and the mixture poured into excess aqueous potassium bicarbonate. The organic layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.381 g. of crystalline residue, m.p. 153–160° dec., which gave a deep purple color with alcoholic ferric chloride. This material was employed in the next step of the synthesis (see below). The acidic material recovered from the alkaline solution was esterified with diazomethane giving 0.107 g. of starting dimethyl ester.

Another cyclization experiment was carried out on 0.075 g. of crude diester, m.p. 145–160°, by the procedure described above. The crude keto ester (0.048 g.) was chromatographed on 2 g. of Florisil. The eluate yielded 0.036 g. of crystalline material, which was recrystallized from ether and again from petroleum ether (60–68°) to give colorless irregular rhombs, m.p. 164–167° dec.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.9; H, 8.7.

The total combined residues from the recrystallization mother liquors were triturated with ether and dried at the vacuum pump.

Anal. Calcd. for $C_{22}H_{29}O_4 \cdot OCH_3$: OCH_3, 7.99; Found: OCH_3, 7.1.

dl-**3-Ethylenedioxy-5-androstene-17-one (XV).**—A solution of 0.340 g. of the total crude keto ester (see above) in 100 ml. of freshly distilled *p*-cymene was heated under reflux (bath temperature 192–194°) in an atmosphere of nitrogen. After 2 hours the solution, which no longer gave a color with alcoholic ferric chloride, was concentrated at reduced pressure, and the residue chromatographed on 20 g. of Florisil. Elution with 1:1 benzene–petroleum ether (60–68°) gave 0.268 g. of crystalline material which after two recrystallizations from acetone–petroleum ether (60–68°) melted at 157–159°. The reported m.p. for di-*p*-cymyl is 156°.[21] After a small (0.016-g.) intermediate fraction, a total of 0.173 g. of crystalline ketone was eluted with 2–5% ether in benzene. Recrystallization from methanol containing some pyridine gave 0.152 g. of colorless

(29) Prepared by the method of A. J. Birch, R. Jaeger and R. Robinson, *J. Chem. Soc.*, 582 (1945).

(30) The Dieckmann cyclization was carried out essentially as described in ref. 9.

rhombs, m.p. 163–166°. Further recrystallization raised the m.p. to 167–169°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.2; H, 9.06.

The infrared spectrum of this material was indistinguishable from that of authentic (naturally derived) *d*-XV. The latter material was prepared in excellent yield by the Sarett chromium trioxide–pyridine oxidation[31] of testosterone 3-ethylene ketal (see below). Crystallization from methanol containing a trace of pyridine gave elongated plates, m.p. 202–204°, which is in agreement with reported melting points.[23]

***dl*-Testosterone 3-Ethylene Ketal (XVI).**—A 0.116-g. sample of the crude ketone XV, m.p. 159–164°, was dissolved in 50 ml. of methanol, 15 ml. of water added followed by 0.50 g. of sodium borohydride, and the mixture heated at reflux temperature for 3 hours. An additional 0.50 g. of sodium borohydride was then introduced, and the heating continued for 3 hours longer. The solution was cooled, most of the methanol removed in a stream of nitrogen, water added, and the mixture extracted with benzene. The extracts were washed thoroughly with water and dried over anhydrous sodium sulfate. The solid residue obtained upon evaporation of the solvent was crystallized from methanol containing pyridine to give 0.106 g. (91% yield) of colorless needles, m.p. 178–180°. Further recrystallization from methylcyclohexane raised the m.p. to 180–181.5°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.9; H, 9.63.

The infrared spectrum of this material was indistinguishable from that of authentic (naturally derived) *d*-testosterone ketal. The latter specimen was prepared by a published procedure.[32] Crystallization from methanol containing a trace of pyridine gave colorless needles, m.p. 181–183°, reported[23] 182–183°.

***dl*-Testosterone (XVII).**—A 0.026-g. sample of the crude ketone XV, m.p. 159–164°, was reduced with a total of 0.20 g. of sodium borohydride in 10 ml. of methanol and 3 ml. of water just as described above. After heating for a total of 3.5 hours, the solution was cooled, 10 ml. of acetone and 0.7 ml. of 12 *N* hydrochloric acid dissolved in 2 ml. of water were added, and the mixture allowed to stand at room temperature. After 40 hours, water was added, the mixture extracted with benzene, and the organic layers washed with 2 *N* sodium hydroxide, water, then dried over anhydrous sodium sulfate. The oily residue left upon evaporation of the solvent crystallized on addition of a little ether. This material was chromatographed on 1.5 g. of Florisil. Elution with 10–50% ether in benzene gave a total of 0.016 g. of crystalline *dl*-testosterone. Recrystallization from methylcyclohexane gave 0.013 g. of colorless prisms, m.p. 162.5–164.5°. Further recrystallization from the same solvent gave material melting at 167.5–169°, λ_{max} 241 mμ (log ε 4.21).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.1; H, 9.69.

The infrared spectrum of this material was identical with that of *d*-testosterone.

Resolution Experiments.—The following represents only a preliminary study. A 0.086-g. sample of *dl*-testosterone ketal, m.p. 178–180°, was converted into the *l*-menthoxyacetate by treatment with *l*-menthoxyacetyl chloride[33] and pyridine at room temperature overnight, followed by retreatment of the unesterified portion (separated by chromatography) with *l*-menthoxyacetic anhydride and pyridine for 2 days at room temperature. A combination of chromatographies (on Florisil and on neutral alumina) and fractional crystallizations from methanol gave a small specimen of material (possibly the *ll*-diastereoisomer), m.p. 153–155°, depressed on admixture with the authentic *dl*-ester described below. This 155° substance has not been investigated further. Also isolated was a small specimen of crystalline material, m.p. 159–160°, undepressed on admixture with authentic (naturally derived) *dl*-ester. The infrared spectra of the two specimens were indistinguishable.

The authentic ***d*-3-ethylenedioxy-17-*l*-menthoxyacetoxy-5-androstene**, prepared from *d*-testosterone ketal,[32] m.p. 181–183°, was obtained from methanol as fine colorless needles, m.p. 159–160°, $[\alpha]^{28}D$ −62 ± 1° (*c* 3.80 in $CHCl_3$).

Anal. Calcd. for $C_{33}H_{52}O_5$: C, 74.96; H, 9.91. Found: C, 75.0; H, 9.97.

Saponification of the naturally derived *dl*-ester was effected by heating for 2 hours with methanolic potassium hydroxide in an atmosphere of nitrogen. Crystallization of the product from aqueous acetone gave material, m.p. 184.5–186°, undepressed on admixture with *d*-testosterone ketal. The hydrolysis of the ketal to testosterone has been described.[23]

***dl*-18-Nor-D-homotestosterone (XXI, R = H).**—A 0.288-g. sample of the ketal ketone VI, m.p. 139–141°, was dissolved in 60 ml. of anhydrous ether, 0.080 g. of lithium aluminum hydride in 75 ml. of ether added, and the mixture allowed to stand at room temperature. After 12 hours, excess cold 5% sulfuric acid was added and the aqueous layer extracted with ether. The crystalline residue obtained upon evaporation of the combined ether layers was dissolved in 15 ml. of acetone, 0.100 g. of *p*-toluenesulfonic acid monohydrate and 4 drops of water were added, and the mixture heated under reflux. After 1.5 hours, water was added, the mixture extracted with ether, and the organic layers washed thoroughly with water, then dried over anhydrous sodium sulfate. The oily residue obtained on evaporation of the solvent was chromatographed on 30 g. of Florisil. The major fraction (0.180 g.) eluted with 20–50% ether in benzene, melted over a wide range (polymorphism?) and consisted of a mixture of prisms and plates. The earlier portions (0.068 g.) of the major fraction melted at 171–173°. Sublimation at 155° (0.03 mm.) followed by crystallization from diisopropyl ether gave colorless plates, m.p. 172–173°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.2; H, 9.9.

The acetate prepared from 0.046 g. of the 171–173° material by the pyridine–acetic anhydride method was obtained after chromatography on Florex followed by two recrystallizations from diisopropyl ether as colorless prisms, m.p. 182–183°, λ_{max} 241 mμ (log ε 4.22); λ_{max} 5.80 μ (ester C=O), 6.0 (C=C—C=O).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.6; H, 9.38.

The yield in the preparation of the pure acetate described above was 0.042 g. (80%). The later portions (0.122 g., m.p. ranging from 146–172° to 156–172°) of the main fraction of the original chromatogram were also acetylated as above, yielding an additional 0.108 g. of acetate, m.p. 181–183°, undepressed on admixture with the analytical specimen.

This acetate was also prepared directly from 0.180 g. of the 13,14-dehydro ketone IV by reduction with 0.50 g. of lithium and 20 ml. of absolute ethanol in 200 ml. of ammonia by the standard procedure (see above). The crude product was hydrolyzed (with *p*-toluenesulfonic acid) and acetylated as described above to give, after two recrystallizations from diisopropyl ether, 0.100 g. (55% yield) of colorless prisms, m.p. 181–183°, undepressed on admixture with the analytical specimen described above.

The propionate was prepared from the 171–174° material using pyridine, propionic acid (to dissolve the hydroxy compound) and propionyl chloride. The yield of once-recrystallized (from diisopropyl ether) material, m.p. 148–151°, was 95%. Sublimation at 140° (0.05 mm.) followed by recrystallization from the same solvent gave colorless prisms, m.p. 149.5–150.5°.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.85; H, 9.41.

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