obtain a 0.20-g. sample of constant melting point, 207–209°, $[\alpha]D$ − 74°.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87; O, 16.55. Found: C, 74.70; H, 8.97; O, 16.41.

11α - Methyl - 17α - ethynyl - Δ⁴ - androsten - 11β,17β-diol - 3 - one (VIg).—By the perchloric acid procedure previously described 0.34 g. of Xe was hydrolyzed to provide 0.34 g. of oily crystals. Two crystallizations from acetone and one from ethyl acetate yielded 0.14 g. of analytically pure material, m.p. 240–242°, $[\alpha]D$ + 20°, λ_{max}^{EtOH} 242–244 mμ, log ε 4.15.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.70; H, 8.73.

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

Steroid Total Synthesis—Hydrochrysene Approach. Part XII.[1] An Alternative Route to Testosterone. The Synthesis of *l*-Testosterone and of *dl*-13-Isotestosterone

BY WILLIAM S. JOHNSON, WALTER A. VREDENBURGH AND J. E. PIKE

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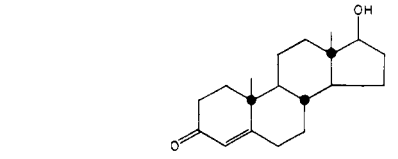
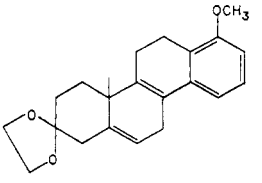
An alternative approach has been developed, which obviates some of the experimental difficulties attending the previous use of the ketal III in the first total synthesis of testosterone. The present synthesis involved the following steps. The hydroxy compound IV, available in three steps from the tetracyclic ketone II, was converted, by Birch reduction, into a mixture of α,β-unsaturated ketones V and VI, both of which could be hydrogenated to the same hydroxy ketone VII. The structure of this last substance was proved by conversion to the diketone and thence to the unsaturated diketone IX of established configuration. Condensation of the hydroxy ketone VII with furfural followed by methylation with potassium *t*-butoxide and methyl iodide gave a mixture of epimers X (R = αCH_3, R′ = H) and X(R = βCH_3, R′ = H), predominantly the former. The latter, as its acetate (R′ = Ac), was ozonized to give the diacid XI (R = H) which was converted, through a Dieckmann cyclization of the ester (R = CH_3), into *dl*-3α-hydroxyetiocholan-17-one (XII). This substance was oxidized to the diketone XIII, brominated and dehydrobrominated, to give *dl*-androstenedione (XIV). Phytochemical reduction afforded synthetic *d*-testosterone and *l*-androstenedione. The latter was converted by known methods into the hitherto unknown *l*-testosterone. *dl*-13-Isotestosterone was synthesized in connection with a continuation of the study of the previous approach to testosterone.

In a previous paper,[2] we described the total synthesis of testosterone (I) in ten steps from the readily accessible tetracyclic ketone II. The first step involved conversion to the ketal III in order to protect the sensitive ring A α,β-unsaturated ketone system which, in the last stage of the synthesis, was finally regenerated by hydrolysis. While this



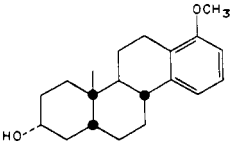
II



III

method of preserving the unsaturated ketone system provides a relatively short pathway to the desired objective, it suffers in that it limits the types of operations that can be performed on the intermediates. Thus mild acidic solvolytic conditions must be avoided, and all reactions that attack olefinic bonds, *e.g.*, hydrogenation and ozonization, must be performed selectively so as to minimize reaction with the double bond in ring B of the ketal III.

Another approach to the objective involves removal of the α,β-unsaturated ketone system of I by reduction of the A/B *cis*-saturated alcohol (*cf.* formula IV) then, at an appropriate later state, reintroduction of the unsaturated ketone residue by oxidation, bromination and dehydrobromination. Although less appealing intellectually, this more pedestrian approach has certain practical advan-



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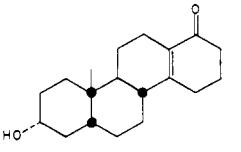

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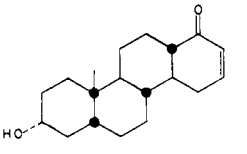

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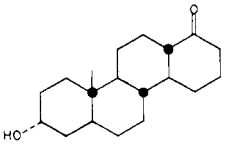
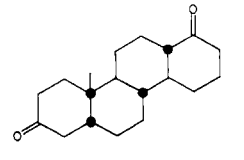
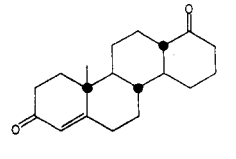


VII



VIII



IX

tages over that involving the ketal. The present paper describes our studies on this second scheme which, although adding to the number of steps required, has led to a better over-all yield than the

(1) Paper XI, W. S. Johnson, J. J. Korst, R. A. Clement and J. Dutta, THIS JOURNAL, **82**, 614 (1960).

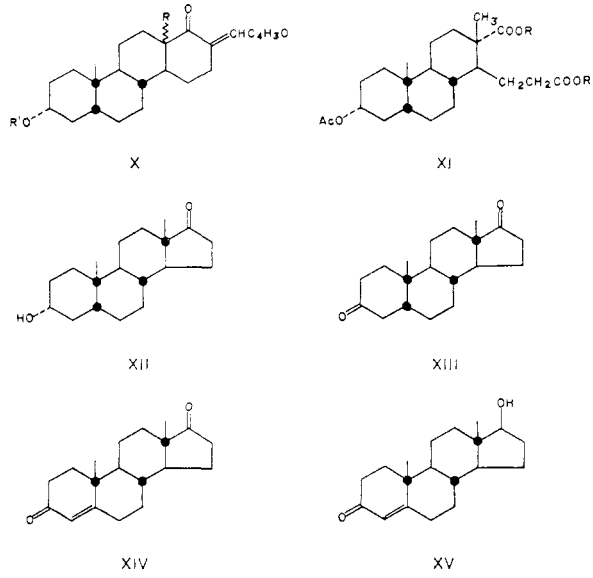
(2) Paper X, W. S. Johnson, B. Bannister, R. Pappo and J. E. Pike, *ibid.*, **78**, 6354 (1956).

first synthesis, and sufficient material has been prepared by this route for enzymatic resolution and full characterization of *l*- as well as *d*-testosterone.

In previous papers we have described the stereoselective preparation of the *cis-anti-trans*-alcohol IV from the tetracyclic ketone II by the following steps: hydrogenation of the 4,5-(steroid numbering) double bond over palladium,[3] reduction of the keto group with lithium aluminum hydride,[3] and finally reduction of the 8,9-(styrene) double bond with potassium and alcohol in ammonia.[4] In the present work reduction of this product (IV) with lithium–ammonia–alcohol under vigorous conditions[5] afforded, after acid hydrolysis of the enol ethers, a mixture of the 13,14-dehydro ketone V, m.p. 137–138°, λ_{max} 248 mμ and the 16,17-dehydro ketone VI, m.p. 130–132°, λ_{max} 225 mμ, separable by chromatography. The former isomer was preponderant and on hydrogenation over palladium-on-carbon in the presence of a trace of potassium hydroxide was converted into *dl*-3-hydroxy-18-nor-D-homoetiocholane-17a-one (VII), m.p. 147–149°. This same substance was prepared from the 16,17-dehydro ketone VI by hydrogenation over palladium-on-strontium carbonate. For preparative purposes it was not necessary to separate the unsaturated ketones V and VI; moreover it was found that the potassium reduction of the 8,9-double bond and the lithium reduction of the aromatic nucleus could be carried out in sequence in the same reaction vessel without isolation of the alcohol IV. In this way it was possible to prepare the saturated ketone VII in over 50% over-all yield from 8,9-dehydro IV.

Before proceeding further we considered it desirable to prove the constitution of the saturated ketone VII by conversion to a substance of established configuration. Oxidation with Sarett reagent afforded the diketone VIII, m.p. 174.5–175°, which, it was hoped, could be selectively brominated at C_4.[6] Treatment of the diketone with 1 mole equivalent of bromine in dimethylformamide in the presence of *p*-toluenesulfonic acid, followed by dehydrohalogenation of the crude bromination product with lithium chloride in dimethylformamide[7] afforded, after purification, a substance, λ_{max} 240 mμ, shown, by mixed m.p. and infrared spectral comparisons, to be identical with the enedione IX of established configuration through its derivation from an intermediate in the total synthesis of testosterone.[2]

Attention was next turned to applying, to ketone VII, the angular methylation-ring contraction sequence as employed in the synthesis of *dl*-epiandrosterone.[5] Condensation with furfuraldehyde afforded the furfurylidene derivative X (R = β-H, R′ = H), m.p. 216.5–218°. This substance was converted by reaction with dihydropyran, into the



tetrahydropyranyl ether X (R = β-H, R′ = tetrahydropyranyl), which was treated with potassium *t*-butoxide and methyl iodide in *t*-butyl alcohol. Acid hydrolysis, to remove the tetrahydropyranyl group, followed by chromatography of the resulting mixture afforded, after crystallization, *dl*-17-furfurylidene-3α-hydroxy-D-homoetiocholan-17a-one (X, R = β-CH_3, R′ = H) in 18% yield and the 13-iso compound X (R = α-CH_3, R′ = H) in 68% yield. The former substance melted at 188.5–190.5°, λ_{max} 322.5 mμ, and the latter at 156–161° (after first melting at 104° and resolidifying), λ_{max} 326.2 mμ. The configurations of these epimers were assigned on the basis of the rule that, in such systems, the *cis* isomer is the preponderant product and exhibits in the ultraviolet spectrum a maximum at longer wave lengths than shown by the *trans* isomer.[8] That this assignment was correct was shown by the conversion of the less preponderant isomer to testosterone as described below.

The 190° furfurylidene derivative was converted into the acetate X (R = β-CH_3, R′ = Ac), m.p. 177–177.5°, which was transformed, by ozonization followed by treatment with hydrogen peroxide, into *dl*-3α-acetoxyetiohomobilianic acid (XI, R = H), m.p. 214–216°. The oily dimethyl ester XI (R = CH_3), prepared with diazomethane, was transformed by Dieckmann cyclization with potassium *t*-butoxide in benzene,[5] followed by hydrolysis and decarboxylation in the presence of acetic and hydrochloric acid, into *dl*-3α-hydroxyetiocholan-17-one (XII), m.p. 171–171.5°. The infrared spectrum of this material was identical with that of naturally-derived *d*-XII,[9] thus confirming the

(3) 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, THIS JOURNAL, **78**, 6289 (1956).

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

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

(6) *Cf.* the selective bromination at C_4 of etiocholane 3,17-dione; A. Ercoli and L. Mamoli, *Ber.*, **71**, 156 (1938).

(7) *Cf.* R. P. Holysz, THIS JOURNAL, **75**, 4432 (1953).

(8) W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood and E. T. Jones, *ibid.*, **80**, 661 (1958).

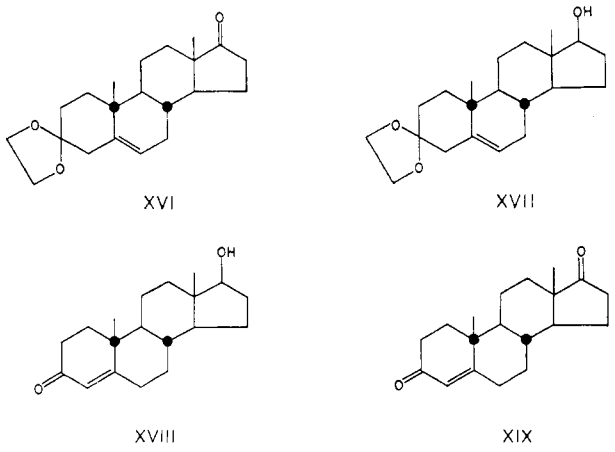
(9) Hydrogenation of the 4,5-double bond of androstenedione and of *d*-testosterone by methods described in the literature produces mixtures of the A/B *cis* and A/B *trans* isomers, and although the former is preponderant it was found, in our hands, extremely difficult to separate in a pure condition. L. Ruzicka, M. W. Goldberg and W. Bosshard, *Helv. Chim. Acta*, **20**, 541 (1937), reported that the hydrogenation of 17β-hydroxy-5-androsten-3-one benzoate over Raney nickel in dioxane gave only A/B *cis* products and suggested that the reduction proceeded through testosterone benzoate. We therefore carried out such a reduction of testosterone benzoate and, after treatment with chromium trioxide to oxidize any 3-hydroxy compound, 17β-hydroxy-

stereochemical assignments given to all substances up to this point in the synthesis.

The hydroxy ketone XII was oxidized by the Jones method[10] to *dl*-etiocholane-3,17-dione (XIII), m.p. 148.5–150.5°. This dione, on treatment in acetic acid solution with 1 mole equivalent of bromine,[6] followed by heating with lithium chloride in dimethylformamide, was in turn transformed into *dl*-4-androstene-3,17-dione (XIV), m.p. 129–130.5°. The infrared spectra of this substance and of its precursor XIII were indistinguishable from those of the corresponding naturally derived *d*-compounds.[9] The over-all yield of *dl*-androstenedione from the furfurylidene ketone X (R = β-CH_3, R′ = H) was 23%. A specimen of *dl*-androstenedione was converted, by the method described below for the *l*-enantiomer, into *dl*-testosterone which was identical with the specimen produced in the first synthesis.[2]

Phytochemical resolution of *dl*-androstenedione was effected by treatment with fermenting yeast medium according to the procedure of Mamoli and Vercellone.[11] The resulting mixture was easily separated by chromatography to yield, after recrystallization, *l*-androstenedione, m.p. 170–171.5°, $[\alpha]^{27}D$ −194 ± 2° (*c* 1.55 in $CHCl_3$), and *d*-testosterone, m.p. 153–154°, $[\alpha]^{26}D$ + 115 ± 1° (*c* 3.48 in $CHCl_3$). The melting point of the latter substance was undepressed on admixture with naturally derived *d*-testosterone, m.p. 154–155°, $[\alpha]^{26}D$ +115 ± 1.5° (*c* 3.173 in $CHCl_3$), and the infrared spectra of the two materials were identical. The yields of *l*-androstenedione and *d*-testosterone in the phytochemical step were 73 and 70%, respectively.

l-Androstenedione was converted into *l*-testosterone by the procedure of Sondheimer, Amendolla and Rosenkranz[12] involving reduction by lithium aluminum hydride followed by selective oxidation of the allylic 3-hydroxyl group with manganese dioxide. *l*-Testosterone, thus obtained, melted at 152–153.5°, $[\alpha]^{26}D$ −112 ± 1.5° (*c* 2.501 in $CHCl_3$).



dl-**13-Isotestosterone.**—In our previous total synthesis of testosterone,[2] the step for the introduction of the angular methyl group at C_{13} yielded a mixture of epimers. The 13α-isomer of unnatural configuration was carried on through the synthesis up to the production of the 13-iso ketal XVI. In the present work this study was continued. Reduction of the ketal XVI with sodium borohydride afforded *dl*-13-isotestosterone 3-ethylene ketal (XVII), m.p. 152–154°, which on acid hydrolysis was converted into *dl*-13-isotestosterone (XVIII), m.p. 167.5–168°. An attempt to effect phytochemical reduction of the ketal XVI failed. Acid hydrolysis of XVI yielded *dl*-13-isoandrostenedione (XIX).

Acknowledgment.—We thank the following agencies for lending support to this work: The Institute of Arthritis and Metabolic Diseases, Public Health Service; The Wisconsin Alumni Research Foundation; The National Science Foundation, and The National Aniline Division of Allied Chemical and Dye Corporation for supporting W. A. V. with a fellowship.

Experimental[13]

Lithium–Ammonia–Ethanol Reduction. (a) Of the Tetrahydro Hydroxy Ether IV (Isolation of the 13,14-Dehydro Ketone V).—The reduction procedures described below in this section are fashioned after that developed for a stereoisomeric series.[5] The previous work should be consulted for details.

A solution of 2.40 g. of the hydroxy ether IV,[4] m.p. 156–157°, in 250 ml. of absolute ethanol was added cautiously with stirring to 700 ml. of liquid ammonia. Then 12 g. of lithium (in small portions), 400 ml. of additional ethanol and 300 ml. of ammonia were added so as to maintain the dissolved lithium as a bronze phase with a blue color at the surface of the dissolving metal.[5] After all of the metal had reacted, the ammonia was evaporated, water added and the mixture extracted with chloroform. The combined organic solutions were washed well with water, dried over anhydrous sodium sulfate and concentrated. The ultraviolet spectrum of the oily residue (2.4 g.) showed no anisole-type absorption.

A solution of this oil in 30 ml. of 95% ethanol and 25 ml. of 0.3 *N* hydrochloric acid was boiled under reflux in an atmosphere of nitrogen for 0.5 hr. Isolation of the organic material by chloroform extraction as described above (except that the washing with water was preceded by a washing with saturated potassium bicarbonate solution) afforded 2.4 g. of a pale yellow oil which, on standing with a little ether, gave 0.27 g. of crystalline material, m.p. about 125°. Recrystallization from ether raised the m.p. to 134.5–136°. The residual oily material (2.1 g.) was chromatographed on 65 g. of Florisil. The fraction eluted with 66% benzene in petroleum ether consisted of 0.12 g. of grease (from the surface of the lithium metal), and that eluted with up to 20% ether in benzene amounted to 0.73 g. of oil showing no significant absorption in the 220–250 mμ region of the ultraviolet spectrum. Elution with 20–50% ether in benzene afforded a total of 0.85 g. of crystalline fractions, all showing strong absorption in the 248 mμ region of the ultraviolet spectrum. Recrystallization from ether gave irregular rhombs, m.p. 136.5–138°, λ_{max}^{EtOH} 247 mμ (log ε 4.4), undepressed on admixture with the specimen of *dl*-3α-hydroxy-13,14-dehydro-18-nor-D-homoetiocholane-17a-one, m.p. 137–138°, isolated as a by-product in a previous study.[14]

For the purpose of preparing material on a larger scale for use in subsequent steps (see below), it was not necesssary to separate the mixture of α,β-unsaturated ketones which was produced as follows. A solution of 50.0 g. of the tetrahydro

etiocholan-3-one benzoate, m.p. 161–162.5°, was indeed readily isolated in 57% yield after four recrystallizations. This method provides ready access to the etiocholane series and afforded, by transformations described in the Experimental part, the material required for comparison purposes.

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(11) L. Mamoli and A. Vercellone, *Ber.*, **70**, 470 (1937); L. Mamoli, *ibid.*, **71**, 2278 (1938).

(12) F. Sondheimer, C. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5930 (1953).

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

(14) W. S. Johnson, R. Pappo and W. F. Johns, THIS JOURNAL, **78**, 6339 (1956).

hydroxy ether IV, m.p. 157–158.5°, in 2 l. of absolute ethanol was added to 4 l. of liquid ammonia; then 400 ml. of anhydrous tetrahydrofuran was introduced to dissolve some material that had precipitated. A total of 90 g. of lithium wire cut into 1-inch pieces was added with stirring over a 25-min. period. A bronze layer appeared after about two-thirds of the lithium was added and persisted for an hour afterward. When the blue color of the solution had disappeared, the ammonia was evaporated and the product isolated by benzene extraction (see above). The crude oily enol ether (54.6 g.) was dissolved in 500 ml. of absolute ethanol; then 100 ml. of water and 25 ml. of concentrated hydrochloric acid were added, and the solution heated under reflux (nitrogen atmosphere) for 1 hr. The product, isolated as described above, was crystallized from ether–petroleum ether to give 37.6 g. of colorless mixture of 13,14- and 16,17-dehydroketone, λ_{max} 245 mμ (log ε 3.98).

(b) Combined with the Potassium Reduction of the Styrene-type Precursor of IV (Isolation of the 16,17-Dehydroketone VI).—The direct reduction of 8,9(steroid numbering)-dehydro-IV with lithium–ammonia–alcohol under the conditions described in part a above gave only a 13% yield of the 13,14-dehydro ketone fraction. Since potassium has been shown to be better than lithium for the reduction of the styrene bond,[4] the following combined procedure was developed.

To a solution of 5.0 g. of 8,9-dehydro-IV,[3] m.p. 156–158°, in 200 ml. of anhydrous ether and 1 l. of liquid ammonia, was added with stirring 8.0 g. of potassium over a period of 20 min.; then 800 ml. of absolute ethanol was cautiously introduced with continued stirring. A further 400 ml. of ammonia was added; then 21 g. of lithium wire was introduced over a period of 1.5 hr. This reduction step, the isolation and hydrolysis of the enol ether, as well as the isolation of the final product were carried out essentially as described in part a. The crude product on standing with a little ether gave 0.79 g. of crystals which on recrystallization from ether yielded 0.36 g. of the 13,14-dehydro ketone, m.p. 136.5–138°.

The residual oily material (5.2 g.) was chromatographed on 150 g. of Florisil. The earlier eluates of the α,β-unsaturated ketone fractions (see part a above) yielded 0.73 g. of crystalline material showing strong absorption at 225 mμ in the ultraviolet spectrum. The later fractions (λ_{max}^{EtOH} 248 mμ) amounted to 1.6 g., m.p. 123–130°, and on two crystallizations from ether gave 0.88 g. of the 13,14-dehydro ketone, m.p. 136–138°. The earlier fractions on crystallization twice from ether afforded 0.39 g. of the 16,17-dehydro ketone which was still contaminated with the 13,14-dehydro isomer as indicated by the ultraviolet spectrum, λ_{max}^{EtOH} 229 mμ. After rechromatography and recrystallization from petroleum ether pure ***dl*-3α-hydroxy-16,17-dehydro-18-nor-D-homoetiocholane-17a-one (VI)**, was obtained as colorless crystals, m.p. 130–132°, λ_{max}^{EtOH} 225 mμ.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.9; H, 9.93.

In a preparative run to produce the mixture of α,β-unsaturated ketones for use in succeeding steps (see below), the 8,9-dehydro-IV could be conveniently reduced on a 25-g. scale (12-l. equipment). The products from two such runs (23.45 and 20.5 g.) were combined and crystallized from ether–petroleum ether to yield 30.0 g. of crystalline mixture of α,β-unsaturated ketones, λ_{max}^{EtOH} 244 mμ.

***dl*-3α-Hydroxy-18-nor-D-homoetiocholane-17a-one (VII).**

(a) From the 16,17-Dehydro Ketone VI.—A 0.17-g. sample of the 16,17-dehydro ketone, m.p. 130–132°, in 15 ml. of absolute ethanol was hydrogenated in the presence of 0.05 g. of 6% palladium-on-strontium carbonate[15] at room temperature and atmospheric pressure. The reaction ceased in 1 hr. after the absorption of approximately 1 mole equivalent of hydrogen. The oil obtained after filtration and evaporation of the solvent was percolated through Florisil in benzene solution. The eluate, on crystallization from petroleum ether, afforded 0.12 g. of colorless irregular rhombs, m.p. 147–149°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.5; H, 10.25.

(b) From the 13,14-Dehydro Ketone V.—A 0.92-g. sample of the 13,14-dehydro ketone, m.p. 136–138°, in 150 ml. of absolute ethanol containing a solution of 1 g. of potassium hydroxide (85%) in 10 ml. of water, was hydrogenated over 0.3 g. of 10% palladium-on-carbon (American Platinum Works) at room temperature and an initial pressure of 2.7 atm. The reaction was interrupted after 1 mole equivalent of hydrogen was absorbed. The mixture was filtered, concentrated in a stream of nitrogen, diluted with water, and extracted with ether. The combined ethereal extracts were washed with dilute hydrochloric acid, saturated potassium bicarbonate solution, then water, and were finally dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent was chromatographed on 12 g. of Florisil. The fraction eluted with 10% ether in benzene was crystallized from petroleum ether to yield 0.75 g. of the saturated ketone VII, m.p. 147–149°.

(c) From the Mixture of α,β-Unsaturated Ketones.—A 25.0-g. specimen of the crude mixture of α,β-unsaturated ketones, λ_{max}^{EtOH} 244 mμ, obtained by direct crystallization as described above, in 500 ml. of absolute ethanol was hydrogenated over 1 g. of 6% palladium-on-strontium carbonate[15] as described above. After one hour, uptake of hydrogen had practically ceased; the mixture was filtered, and 3 g. of 10% palladium-on-carbon was added to the filtrate, followed by a solution of 5 g. of potassium hydroxide in 50 ml. of water. (Note that hydroxide should not be added until the 16,17-dehydro ketone, which is alkali sensitive, has been reduced.) The hydrogenation was then continued as described above (part b). The product, isolated as described above, after crystallization from ether amounted to 18.1 g., m.p. 120–125°. Material of this quality was used for the preparation of the furfurylidene derivative (see below). A sample, after recrystallization from petroleum ether, melted at 140–142°.

***dl*-18-Nor-D-homoetiocholane-3,17a-dione (VIII).**—A 0.12-g. sample of the hydroxy ketone VII, m.p. 147–149°, in 1.2 ml. of pyridine was treated with the complex from 0.12 g. of chromium trioxide and 1.2 ml. of pyridine. The mixture was allowed to stand overnight at room temperature, 7 ml. of water and 15 ml. of a 1:1 mixture of benzene–ether were then added, the mixture filtered, and the aqueous layer was extracted further with ether. The combined organic solutions were washed with water and dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent amounted to 0.11 g., m.p. 169–172°. A comparable specimen (kindly prepared by C. B. Abrahams), after repeated recrystallizations from petroleum ether, was obtained as colorless flat prisms, m.p. 174.5–175°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.3; H, 9.90.

***dl*-18-Nor-D-homo-4-androstene-3,17a-dione (IX).**—To 0.086 g. of the once-recrystallized dione VIII, m.p. 173–175°, dissolved in 3 ml. of dimethylformamide was added 0.06 g. of *p*-toluenesulfonic acid monohydrate. A solution of 0.047 g. of bromine in 3 ml. of dimethylformamide was added slowly over a period of 15 min., and the mixture was then allowed to stir for 1 hr. at room temperature. Water was added and the mixture extracted with 1:1 benzene–ether. The combined organic extracts were washed with water until neutral and dried over anhydrous magnesium sulfate. The crude crystalline bromo ketone, obtained on evaporation of the solvent, was dissolved in 20 ml. of dimethylformamide containing 0.60 g. of lithium chloride and the mixture was heated for 2 hr. at 100° in an atmosphere of nitrogen. The product was isolated by dilution with water and extraction as described above for the bromo ketone. The crude product, obtained on evaporation of the solvent, amounted to 0.095 g., m.p. 115–125°, λ_{max}^{EtOH} 240 mμ. This material was chromatographed on 3 g. of Florisil. Elution with benzene through 10% ether-in-benzene gave a total of 0.036 g. of fractions λ_{max}^{EtOH} 232–235 mμ. Further elution up to 50% ether in benzene afforded a total of 0.025 g. of crystalline material λ_{max}^{EtOH} 240 mμ, which on two recrystallizatons from ethanol gave colorless crystals, m.p. 142–143°, undepressed on admixture with the authentic enedione IX, m.p. 146.5–147.5°. The infrared spectra of the two specimens were identical.

***dl*-3α-Hydroxy-17-furfurylidene-18-nor-D-homoetiocholane-17a-one (X, R = β-H, R′ = H). (a) From Pure Hydroxy Ketone.**[16]—A 0.71-g. sample of hydroxy ketone VII, m.p. 147–149°, was dissolved in 25 ml. of absolute methanol, then 0.35 ml. of furfuraldehyde and 12 ml. of 33% aqueous so-

(15) See footnote 33 of ref. 3.

(16) This procedure is analogous to that described for the androstane series, ref. 5.

dium hydroxide solution were added. The mixture was allowed to stand in the dark, under nitrogen, at room temperature for 4 hr. The crystalline precipitate was separated by filtration, washed with aqueous methanol (until neutral) and finally with methanol, and dried. The crude product amounted to 0.86 g., m.p. 213–216°. Recrystallization twice from absolute ethanol afforded pale yellow needles, m.p. 216.5–218°, λ_{max}^{EtOH} 325 mμ (log ε 4.3).

Anal. Calcd. for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75. Found: C, 78.1; H, 8.63.

(b) **From Crude Hydroxy Ketone.**—A 21.7-g. specimen of crude once-crystallized hydroxy ketone VII, m.p. 120–125° (see above), was dissolved in 800 ml. of absolute methanol, then 12 ml. of freshly distilled furfuraldehyde and 360 ml. of 33% aqueous sodium hydroxide solution were added. The mixture was allowed to stand overnight in the dark under nitrogen at room temperature. The crude crystalline product, isolated as described above (part a), amounted to 21.0 g., m.p. 211–214°. A single recrystallization from absolute ethanol raised the m.p. to 216.5–218°.

Methylation of the Furfurylidene Ketone X (R = β-H, R′ = H).[16]—A 31.69.-g. sample of the crude furfurylidene ketone, m.p. 209–213°, was converted to the tetrahydropyranyl ether by treatment with a solution of 102 ml. of dihydropyran and 0.6 g. of *p*-toluenesulfonic acid monohydrate in 680 ml. of benzene. After stirring for 2 hr. at room temperature, under nitrogen, some furfurylidene ketone still remained undissolved; so an additional 200 ml. of benzene and 0.4 g. of acid catalyst were added. Within 2 min. the solution had become homogeneous, and after 3.5 hr. at room temperature the product was isolated essentially as previously described.[16] The crude pale yellow crystalline product, containing some polymeric dihydropyran, amounted to 51.2 g. This material was methylated without purification as described below.

A solution of 9.78 g. of the tetrahydropyranyl ether in 50 ml. of benzene was added, with stirring (nitrogen atmosphere), to a cooled (10–15°) solution of 5 g. of potassium in 180 ml. of *t*-butyl alcohol. An additional 50 ml. of benzene was used to aid in the transfer; 30 ml. of methyl iodide was then added and the mixture allowed to come to room temperature gradually with stirring. After 12 hr. the crude product, isolated essentially as previously described,[16] was hydrolyzed by heating under reflux for 1 hr. with 250 ml. of ethanol containing 30 ml. of water and 0.25 g. of *p*-toluenesulfonic acid monohydrate. The crude hydrolysate, isolated as previously described,[16] amounted to 6.97 g. of viscous yellow oil, which was chromatographed on 310 g. of Florisil. After elution of 0.31 g. of oil, a total of 4.95 g. of pale yellow crystalline material, λ_{max}^{EtOH} 326–327 mμ, was eluted with 1–3% ether in benzene. This material, on crystallization from isopropyl ether, gave 3.72 g. (first crop), m.p. 158–160°, and 0.51 g. (second crop), m.p. 144–160°, of ***dl*-3α-hydroxy-17-furfurylidene-13-iso-D-homoetiocholane-17a-one (X, R = α-CH_3, R′ = H).** Recrystallization of first crop material gave pale yellow microcrystals, m.p. 157–161°, which on recrystallization from methyl ethyl ketone–petroleum ether, was obtained in a polymorphic modification, m.p. 99–101°. Further crystallization from isopropyl ether gave pale yellow microcrystals, m.p. about 104° with resolidification and remelting at 156–161°, λ_{max}^{EtOH} 326.2 mμ (log ε 4.3); $\lambda_{max}^{CHCl_3}$ 2.94 μ (OH), 6.04 (C=C—C=O).

Anal. Calcd. for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: C, 78.2; H, 9.08.

Further elution of the column gave 0.22 g. of intermediate fractions, λ_{max}^{EtOH} 326–324.7 mμ, followed by a total of 1.3 g. of crystalline product λ_{max}^{EtOH} 323–324 mμ, eluted with 3–20% ether in benzene. This last fraction was crystallized from isopropyl ether to give 0.95 g. (first crop), of pale yellow crystals, m.p. 182–186°. The second crop (0.28 g.) was recrystallized from isopropyl ether–benzene to give 0.20 g. of pale tan crystals, m.p. 163–183°. Successive recrystallizations of first crop material from isopropyl ether, absolute ethanol, ethanol–isopropyl ether, and finally isopropyl ether, gave colorless microcrystals of ***dl*-3α-hydroxy-17-furfurylidene-D-homoetiocholane-17a-one** (X, R = β-CH_3, R′ = H), m.p. 188.5–190.5°, λ_{max}^{EtOH} 322.5 mμ (log ε 4.3); $\lambda_{max}^{CHCl_3}$ 2.94 μ (OH), 6.01 (C=C—C=O).

Anal. Calcd. for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: 78.3; H, 8.95.

A larger scale run, performed on 41.4 g. of crude tetrahydropyranyl ether, similarly yielded a total of 4.91 g. (18.5%) of X (R = β-CH_3, R′ = H), and 18.0 g. (68%) of X (R = α-CH_3, R′ = H).

***dl*-3α-Acetoxy-17-furfurylidene-D-homoeticholane-17a-one (X, R = β-CH_3, R′ = Ac).**—A solution of 0.753 g. of the C/D *trans*-furfurylidene ketone X (R = β-CH_3, R′ = H), m.p. 182–186°, in 14 ml. of pyridine was treated with 7 ml. of acetic anhydride. The mixture was allowed to stand overnight at room temperature, then most of the solvent was evaporated in a stream of nitrogen and the residue slowly added to excess cold saturated sodium bicarbonate solution, This mixture was extracted with benzene and the benzene layers were washed with water, saturated brine, and finally dried over anhydrous sodium sulfate. The residue obtained on evaporation of the benzene was freed of traces of pyridine by addition of a few ml. of toluene and evaporation. There remained 0.779 g. of yellow crystalline material, m.p. 169–174°, which, on crystallization from isopropyl ether, yielded 0.704 g. of pale yellow crystals, m.p. 176–178°. Two more recrystallizations from absolute ethanol afforded very pale yellow prisms, m.p. 177–177.5°, λ_{max}^{EtOH} 322.4 mμ (log ε 4.31); $\lambda_{max}^{CHCl_3}$ 5.82 μ (acetate C=O), 5.99 (C=C—C=O), 8.0 (acetate C—O).

Anal. Calcd. for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.8; H, 8.85.

***dl*-3α-Acetoxyetiohomobilianic Acid (XI, R = H).**[16]—Ozone, from a Welsbach ozonator, was passed into a solution of 0.280 g. of the aforementioned acetate X (R = β-CH_3, R′ = Ac), m.p. 176–178°, in 40 ml. of ethyl acetate at −70°. After 12 min. the solution turned blue in color, and the treatment was continued for an additional 5 min. The solvent was evaporated in a stream of nitrogen (without warming) and 40 ml. of glacial acetic acid was added to the oily residue followed by 1.5 ml. of water, 1 drop of concentrated hydrochloric acid and 4 ml. of 30% hydrogen peroxide. After standing overnight at room temperature, the clear solution was evaporated in a stream of nitrogen, and the acid isolated, essentially as already described,[16] through bicarbonate extraction. The crude acid obtained upon evaporation of the final ethyl acetate solution amounted to 0.260 g. of tan crystalline material, m.p. 190–210°. Recrystallization from isopropyl ether gave 0.187 g. of pale yellow crystals, m.p. 201–211°. Repeated recrystallizations from benzene–cyclohexane and finally from methyl ethyl ketone gave small colorless prisms, m.p. 214–216°.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 66.7; H, 8.62.

During the purification by recrystallization, on one occasion a form melting at 228.5–231° was encountered.

In an ozonization experiment on 2.51 g. of furfurylidene ketone X (R = β-CH_3, R′ = Ac), m.p. 176–177°, the total crude product amounted to 2.02 g. of slightly tan crystalline diacid, m.p. 202–210°. This material was satisfactory for use in the succeeding steps described below.

***dl*-3α-Hydroxyetiocholan-17-one (XII).**[16]—A solution of 1.77 g. of the crude diacid XI (R = H), m.p. 202–210°, in about 50 ml. of ethanol–benzene was treated with excess ethereal diazomethane. Concentration of the solution gave, after drying at reduced pressure, 1.84 g. of pale amber oily diester XI (R = CH_3), which was used directly in the Dieckmann condensation described below. All attempts to obtain the diester crystalline, even after preparation from purified diacid, m.p. 215–218°, have failed.

A solution of *t*-butyl alcohol-free potassium *t*-butoxide (from 1 g. of potassium) in benzene was prepared as previously described[16] and then a solution of the 1.84 g. of diester in 30 ml. of benzene was added. The mixture was heated at reflux with stirring (under nitrogen) for 8 hr., then allowed to stir at room temperature for an additional 10 hr. The mixture was diluted with 10% aqueous potassium bicarbonate solution, and the aqueous layer extracted with benzene. The combined benzene layers were washed with water, brine, and then dried over anhydrous sodium sulfate. Evaporation of the solvent left 1.43 g. of the crude β-keto ester as a pale amber oil which gave a dark green color with ferric chloride solution. This material was dissolved in 30 ml. of acetic acid, 10 ml. of concentrated hydrochloric acid and 2 ml. of water were added, and the solution heated at reflux under nitrogen for 1.5 hr. The solvent was removed at reduced pressure, the residue dissolved in 50 ml. of methanol, 20 ml. of 5% aqueous potassium hydroxide was added, and the mixture heated at reflux for 1 hr. under nitrogen. The crude product, isolated essentially as previously described[16] except

that benzene was used for the extractions, amounted to 1.02 g. of amber crystalline residue. Chromatography on 30 g. of Florisil gave in fractions eluted with 5–50% ether in benzene a total of 0.76 g. of yellow crystalline material which, on recrystallization from isopropyl ether, afforded 0.615 g. (first crop) of colorless crystals, m.p. 169–171° (with previous softening), and 0.059 g. (second crop), m.p. 160–167°. Rechromatography of the residue from the mother liquors on 3 g. of Florisil, followed by recrystallization, yielded an additional 0.012 g., m.p. 143–165°. A sample of the first crop material, after two recrystallizations from isopropyl ether, was obtained as colorless rods, m.p. 171–171.5°, $\lambda_{max}^{CHCl_3}$ 2.96 μ (OH), 5.83 (C=O). The infrared spectrum of this sample was superimposable on that of naturally derived, *d*-3α-hydroxyetiocholan-17-one, m.p. 150.6–151.2° (see below for preparation).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.5; H, 10.27.

***dl*-Etiocholane-3,17-dione (XIII).**—A solution of 0.093 g. of chromium trioxide in 1.5 ml. of water containing 0.4 ml. of concentrated sulfuric acid was added with stirring to a solution of 0.324 g. of the hydroxy ketone XII, m.p. 169–171°, in 20 ml. of acetone (distilled from potassium permanganate). The reaction mixture was cooled (0–5°) during the addition which required 15 min. After stirring for 1 hr. at room temperature the mixture was diluted with water, and extracted with ether and benzene. The combined organic layers were washed with water, then with saturated brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 0.336 g. of pale yellow solid, m.p. 128–135°. Two recrystallizations from isopropyl ether followed by one from methanol gave 0.276 g. of colorless prisms, m.p. 149–151°. The residues from the mother liquors, on chromatography on 3 g. of Florisil followed by crystallization from isopropyl ether, gave an additional 0.037 g., m.p. 131–150°.

A further recrystallization of the 149–151° material gave colorless prisms, m.p. 148.5–150.5°, $\lambda_{max}^{CH_2Cl_2}$ 5.87 μ (C=O), with a shoulder at 5.81 μ. The infrared spectrum of this material was identical with that of the naturally derived *d*-compound, m.p. 132–134° (see below for preparation).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.2; H, 9.95.

***dl*-4-Androstene-3,17-dione (XIV).**—The following procedure represents an adaptation of previously described methods for the bromination[17] and dehydrobromination[7] reactions. A solution of 0.149 g. of bromine in 1.58 ml. of glacial acetic acid was added dropwise with stirring to a solution of 0.255 g. of the diketone XIII, m.p. 149–151°, in 2.5 ml. of glacial acetic acid containing 0.083 ml. of a 0.14 *N* solution of hydrobromic in acetic acid. The reaction mixture was kept under nitrogen at room temperature during the addition which required 15 min., and then for a further 5-min. period after which 0.4 g. of sodium acetate was added. This mixture was diluted with water, extracted with benzene, and the benzene layers washed with water, 10% potassium bicarbonate solution, again with water, saturated brine, and finally dried over anhydrous sodium sulfate.

The pale yellow solid residue, m.p. 169–178°, obtained on evaporation of the solvent and drying at reduced pressure was dissolved in 4 ml. of anhydrous dimethylformamide, 0.071 g. of dry lithium chloride was added, and the mixture heated with stirring at 100° in an atmosphere of nitrogen for 2 hr. The cooled mixture was diluted with water, extracted with ethyl acetate, and the organic layers washed with water, saturated brine, and finally dried over anhydrous sodium sulfate. By recrystallizations from isopropyl ether and chromatographs on Florisil it was possible to isolate a total of 0.128 g. of *dl*-androstenedione in the following crops (note below that this substance has been encountered in two polymorphic modifications): 0.074 g., m.p. 135–138°, λ_{max}^{EtOH} 240 mμ (log ϵ 4.15); 0.020 g., m.p. 135–140°, λ_{max}^{EtOH} 240 mμ (log ϵ 4.15); and 0.034 g., m.p. 135–141°, λ_{max}^{EtOH} 240 mμ (log ϵ 4.11). In addition there was isolated, by rechromatography on alumina of the halogen-containing fractions that were less strongly adsorbed on Florisil, a total of 0.057 g. of material presumed to consist largely of the 4-chloro ketone produced by displacement of the bromine. A 0.229-g. sample of such chloro ketone fractions (accumulated from the present and a subsequent larger run), on further treatment with 0.123 g. of lithium chloride and 2 ml. of dimethylformamide at 100° for 2.5 hr., yielded, after recrystallizations and chromatography on alkaline alumina, 0.106 g. of *dl*-androstenedione, m.p. 139–143°, λ_{max} 240 mμ (log ϵ 4.06). This corresponds to an additional 0.026 g. of this material derived from the chloro ketone in the experiment described above, or a total yield of 0.154 g. (61%).

A specimen of the enedione, purified by repeated recrystallizations from isopropyl ether, was obtained as colorless prisms, m.p. 129–130.5°, λ_{max}^{EtOH} 240 mμ (log ϵ 4.18); $\lambda_{max}^{CHCl_3}$ 5.81 μ (C=O), 6.06 (C=C—C=O), 6.19 (C=C).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.7; H, 9.09.

The infrared spectrum of this material was identical with that of the naturally derived *d*-compound, m.p. 171.5–172.5°.[18] When the analytical sample was melted and then seeded with the fraction m.p. 135–138° (see above), it resolidified and remelted at 135–140°; thus the identity of the higher-melting polymorphic form was established.

***dl*-Testosterone.**—The reduction of 0.019 g. of *dl*-androstenedione, m.p. 135–140°, with 0.087 g. of lithium aluminum hydride in tetrahydrofuran was carried out essentially as described for the *d*-series,[12] except that the product was isolated by diluting the reaction mixture with water and extracting with benzene. The benzene layers were washed with water until neutral, then with saturated brine, and finally dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent was dissolved in 5 ml. of chloroform and stirred at room temperature with 0.093 g. of manganese dioxide for 14 hr.; then 0.08 g. of additional manganese dioxide was introduced and the stirring continued for 12 hr. more. Filtration and evaporation gave 0.029 g. of amber oil which was chromatographed on 1.5 g. of alkaline alumina. An intermediate fraction eluted with ether–benzene, on two recrystallizations from acetone gave colorless crystals, m.p. 166–168°, undepressed on admixture with the sample of *dl*-testosterone, m.p. 167–169°, from the first synthesis.[2]

Phytochemical Resolution of *dl*-4-Androstene-3,17-dione.—The published method[11] was used with slight modification. A solution of 0.219 g. of *dl*-androstenedione, m.p. 135–141°, in 22 ml. of 95% ethanol was added to a fermenting mixture of 25 g. of bakers' yeast, 50 g. of sucrose and 400 ml. of lake water. The mixture, from which air was excluded by a bubbling trap, was stirred slowly at room temperature for 48 hr., an additional 50 g. of sucrose being added after 24 hr. The mixture was extracted thoroughly with ether, with the aid of centrifugation to separate the yeast suspension, and the ether solutions were washed thoroughly with water until free of yeast, then with saturated brine, and finally dried over anhydrous sodium sulfate. The residue, obtained on evaporation of the solvent, was chromatographed on 25 g. of grade H-51 alkaline alumina. The fractions eluted with 5–10% ether in benzene amounted to 0.109 g. of crude crystalline *l*-androstenedione. Recrystallizations from isopropyl ether, then from methanol and twice again from isopropyl ether gave 0.069 g. of *l*-4-androstene-3,17-dione, m.p. 170–171.5°, λ_{max}^{EtOH} 240 mμ (log ϵ 4.18), $[\alpha]^{27}D$ −194±2° (*c* 1.55 in $CHCl_3$). The infrared spectrum was identical with that of naturally derived *d*-androstenedione, m.p. 171.5–172.5°, λ_{max}^{EtOH} 240 mμ (log ϵ 4.19), $[\alpha]^{26}D$ +194.8 ± 1° (*c* 2.064 in $CHCl_3$).[18] An additional 0.011 g. of the *l*-compound, m.p. 152–168°, was isolated from the mother liquors.

In the chromatogram described above, the *d*-testosterone fractions (total 0.077 g.) were eluted with 50% ether in benzene. Five recrystallizations from isopropyl ether gave 0.049 g. of testosterone, m.p. 153–154°, λ_{max}^{EtOH} 242 mμ (log ϵ 4.20), $[\alpha]^{26}D$ +115 ± 1° (*c* 3.477 in $CHCl_3$). The m.p. was not depressed on admixture with naturally derived *d*-testosterone, m.p. 154–155°, λ_{max}^{EtOH} 242 mμ (log ϵ 4.21), $[\alpha]^{26}D$ + 115 ± 1.5° (*c* 3.173 in $CHCl_3$). The infrared spectra of the two specimens were identical.

***l*-Testosterone.**—The procedure described above for the *dl*-series was used. A total of 0.071 g. of *l*-androstenedione, m.p. 170–171.5°, was reduced in two portions with a total of 0.134 g. of lithium aluminum hydride in a total of 14 ml. of tetrahydrofuran. The crude products were combined, dissolved in 8 ml. of chloroform, and stirred at room temperature for 14 hr. with 0.520 g. of freshly prepared[19] manganese

(17) H. L. Herzog, M. A. Jevnik, P. L. Perlman, A. Nobile and E. B. Hershberg, THIS JOURNAL, **75**, 266 (1953).

(18) Prepared by the Oppenauer oxidation of dehydroepiandrosterone, R. V. Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).

dioxide, then with an additional 0.310 g. of manganese dioxide for 9 hr., and a further 0.504 g. for 11 hr. (total time 34 hr.). The crude product, isolated by filtration and evaporation, was chromatographed twice on 2-g. portions of alkaline alumina. The fractions eluted with benzene to 2–3% ether-in-benzene amounted to 0.036 g. of crystalline material. Crystallization from isopropyl ether gave 0.031 g. of *l*-androstenedione, m.p. 153–165.5°, evidently formed by over-oxidation with manganese dioxide. The fractions eluted with 50% ether-in-benzene amounted to 0.023 g. Recrystallization from isopropyl ether gave 0.018 g. of *l*-testosterone, m.p. 147–151.5°.

The total recombined *l*-androstenedione fractions were retreated as above with 0.060 g. of lithium aluminum hydride, and the crude product thus produced was oxidized in 1.5 ml. of chloroform with 0.160 g. of manganese dioxide for 9 hr. The *l*-testosterone fraction isolated by chromatography as above amounted to 0.016 g. This specimen was combined with the 0.018 g. described above and chromatographed again rapidly on 1 g. of Florisil. Two recrystallizations of the product from isopropyl ether yielded 0.026 g. of *l*-testosterone as colorless prisms, m.p. 152–153.5°, λ_{max}^{EtOH} 242 mμ (log ε 4.19), $[\alpha]^{26}D$ −112±1.5° (*c* 2.501 in $CHCl_3$).

Rechromatography of all *l*-testosterone residues from the mother liquors, followed by recrystallization from isopropyl ether, afforded an additional 0.018 g. of pale tan material, m.p. 147–153°.

Preparation of Comparison Substances. *d*-17β-Hydroxyetiocholan-3-one Benzoate.—A solution of 7.14 g. of *d*-testosterone benzoate,[20] m.p. 192.7–193.4°, in 55 ml. of purified dioxane was added to a mixture of 3 g. of W-2 Raney nickel and 20 ml. of dioxane that had been equilibrated by stirring with hydrogen at atmospheric pressure. Stirring with hydrogen was continued at room temperature and after 45 min. 1+ mole equivalents of gas was absorbed and the reaction had practically ceased. The residue obtained on filtration and concentration was dissolved in 50 ml. of glacial acetic acid, and 50 ml. of a 2% solution of chromium trioxide in acetic acid was added. After standing for 8 hr. at room temperature, the solution was concentrated at reduced pressure, water was added and the mixture extracted with ether. The ether layers were washed with 10% aqueous potassium bicarbonate, water, saturated brine, and finally dried over anhydrous sodium sulfate. The crystalline residue, obtained on evaporation of the solvent, amounted to 7.18 g., m.p. 146–156°. Recrystallization from isopropyl ether–petroleum ether followed by three recrystallizations from methanol gave 4.07 g. of material, m.p. 161–162.5°, of satisfactory quality for use in the succeeding steps. Further recrystallizations from methanol and then from absolute ethanol gave colorless rectangular prisms, m.p. 162–163°, λ_{max}^{EtOH} 229 mμ (log ε 4.16), $[\alpha]D$ +27.5° (*c* 0.977 in 95% ethanol).

Anal. Calcd. for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69. Found: C, 79.0; H, 8.46.

***d*-17β-Hydroxyetiocholan-3-one** was prepared by saponification of the aforementioned benzoate with refluxing methanolic potassium hydroxide under a nitrogen atmosphere for 18 hr. The crude product, isolated by conventional extraction procedures, was recrystallized once from isopropyl ether, then again from absolute ethanol to give readily pure material, m.p. 141–142.5°, reported[21] 139–140°.

For purposes of characterization, *d*-etiocholane-3α-17β-diol was produced from the aforementioned hydroxy ketone by conventional lithium aluminum hydride reduction in ether. A single crystallization of the crude product from ethyl acetate gave colorless crystals, m.p. 237–238°, reported[22] 236–236.5°. The diacetate, prepared for further characterization, melted at 124–126°, reported[22] 124.5–125.5°.

***d*-Etiocholane-3,17-dione.**—Oxidation of the aforementioned hydroxy ketone with Sarett reagent[23] gave a crude product which on one crystallization from isopropyl ether afforded colorless crystals, m.p. 132–134°, reported[24] 132–134°.

***d*-3α-Hydroxyetiocholan-17-one** was prepared by sodium borohydride reduction of the aforementioned dione according to a described procedure.[25] After chromatography and two recrystallizations from ethyl acetate this isomer was isolated as colorless prisms, m.p. 150.6–151.2°, reported[25] 151–152°.

***dl*-13-Isotestosterone. *dl*-13-Iso-4-androstene-3,17-dione (XIX).**—A solution of 0.071 g. of *dl*-3-ethylenedioxy-13-iso-5-androsten-17-one (XVI),[2] m.p. 157–162°, in 15 ml. of acetone containing 3 ml. of 4 *N* hydrochloric acid was allowed to stand for 36 hr. at room temperature. Most of the solvent was evaporated in a stream of nitrogen, water was added, and the mixture extracted with benzene. The combined organic layers were washed with water, 5% aqueous potassium bicarbonate solution, again with water, and saturated brine; then dried over anhydrous sodium sulfate. The pale yellow solid residue remaining upon evaporation of the solvent was crystallized from isopropyl ether to give 0.058 g. of pale yellow crystals, m.p. 183–186.5° with previous softening. This material was recrystallized from the same solvent, again from methanol, washed through a 0.5-g. alkaline alumina column to remove a trace of color, and finally recrystallized again from isopropyl ether to give colorless plates, m.p. 186–187°, λ_{max}^{EtOH} 240 mμ (log ε 4.19); $\lambda_{max}^{CHCl_3}$ 5.83 μ (C=O), 6.06 and 6.21 (C=C—C=O).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.8; H, 9.06.

***dl*-13-Isotestosterone 3-Ethylene Ketal (XVII).**—A solution of 0.50 g. of sodium borohydride in 10 ml. of water was added to a solution of 0.203 g. of the ketal ketone XVI,[2] m.p. 157–162°, in 100 ml. of methanol. The mixture was heated at reflux for 3 hr.; then an additional 0.50 g. of sodium borohydride was added and refluxing continued for 3 hr. more. The mixture was concentrated in a stream of nitrogen, diluted with water, and extracted with benzene. The combined organic layers were washed with water followed by saturated brine, and dried over anhydrous sodium sulfate. The crystalline residue obtained upon evaporation of the solvent was crystallized from isopropyl ether to give 0.149 g. of pale yellow crystals, m.p. 141–147°. Recrystallization from isopropyl ether, then again from ethyl acetate gave 0.071 g. of colorless crystals, m.p. 149.5–152°. A sample was recrystallized again from ethyl acetate giving rectangular plates, m.p. 152–154°, $\lambda_{max}^{CHCl_3}$ 3.0 μ (OH) 9.17 (ketal).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.8; H, 9.79.

Chromatography on alumina of the residues from the mother liquor of the 0.071-g. crop gave, after recrystallizations of appropriate fractions, a total of 0.061 g. of additional material, m.p. 148.5–152°. Other fractions were evidently mixtures, m.p. 87–141°, containing the 17α-epimer which was not isolated.

***dl*-13-Isotestosterone (XVIII).**—A 0.117-g. sample of the ketal XVII, m.p. 148.5–152.5°, was hydrolyzed just as described above for the ketal ketone XVI. The crude, pale yellow crystalline product was crystallized from isopropyl ether to give 0.091 g. of pale tan crystals, m.p. 161–166°. Recrystallization once from isopropyl ether–ethyl acetate, then twice from ethyl acetate gave 0.054 g. of colorless platelets, m.p. 167.5–168.2°, λ_{max}^{EtOH} 241 mμ (log ε 4.23); $\lambda_{max}^{CHCl_3}$ 2.98 μ (OH), 6.07 and 6.21 (C=C—C=O).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.2; H, 9.78.

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(19) O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

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

(21) A. Butenandt, K. Tscherning and H. Dannenberg, *Z. physiol. Chem.*, **248**, 305 (1937).

(22) L. Ruzicka, M. W. Goldberg and W. Bosshard, *Helv. Chim. Acta*, **20**, 541 (1937).

(23) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(24) T. Reichstein and A. Lardon, *Helv. Chim. Acta*, **24**, 955 (1941).

(25) E. Elisberg, H. Vanderhaeghe and T. F. Gallagher, THIS JOURNAL, **74**, 2814 (1952).