161°, in 60 ml. of absolute ethanol was added cautiously to 600 ml. of ammonia, then 6.0 g. of lithium wire was added as rapidly as possible and the mixture was stirred until the blue color was discharged (about 45 minutes). The ammonia was evaporated, water and ether added, the aqueous layer extracted with ether and the combined organic layers washed thoroughly with water and dried over anhydrous sodium sulfate.

Evaporation of the solvent gave a colorless crystalline residue which was acetylated with 3.0 ml. of acetic anhydride in 6.0 ml. of pyridine. After 16 hr. at room temperature, ice was added and the mixture extracted with ether. The organic layers were washed with water, 2% hydrochloric acid, water, saturated sodium bicarbonate and dried over anhydrous sodium sulfate. Evaporation of the solvent gave, after trituration with a little ether, 0.639 g. of crude diacetate, m.p. 164–167°. Crystallization from methylcyclohexane, followed by sublimation at 161° (0.06 mm.) and recrystallization from the same solvent yielded 0.363 g. of colorless hexagonal prisms, m.p. 169.5–170°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.5; H, 9.67.

(b) From *dl*-13,14-Dehydro-18-nor-D-homoepiandrosterone.—A 0.140-g. sample of the unsaturated ketone III, m.p. 159–161°, was reduced as described in part (a) above with 30 ml. of ethanol, 270 ml. of ammonia and 3.0 g. of lithium wire. The product was converted to the diacetate as described above. A single crystallization of the crude product from methylcyclohexane gave 0.150 g. (82% yield) of colorless prisms, m.p. 169–170°, undepressed on admixture with the analytical sample described above.

dl-3β-17aβ-Dihydroxy-18-nor-D-homoandrostane (XIX, R = H).—A 0.178-g. sample of the diacetate XIX (R = Ac) was dissolved in 30 ml. of methanol, a solution of 0.15 g. of potassium hydroxide in 2 ml. of water was added and the mixture heated at reflux. After 2 hr., the solution was cooled, neutralized with acetic acid and concentrated at 50° under a stream of nitrogen. Water was added, the product extracted with chloroform and the organic layers washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.152 g. of crude colorless diol, m.p. 206–211°. Two recrystallizations from methyl ethyl ketone afforded fine colorless prisms, m.p. 210–211°.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.8; H, 10.9.

dl-18-Nor-D-homoandrostane-3,17a-dione (XX).[30]—The total crude product from the hydrogenation of 0.340 g. of the 13,14-dehydro ketone III, m.p. 158–160°, as described above, was dissolved in 20 ml. of acetic acid, then a solution of 0.185 g. of chromium trioxide in 0.6 ml. of water was added. After 16 hr. at room temperature 1 g. of sodium bisulfite was added, most of the solvent evaporated in a stream of nitrogen at steam-bath temperature, then 30 ml. of water was added, whereupon the insoluble bisulfite adduct of the diketone separated as a finely divided colorless precipitate. The suspension was diluted with an additional 100 ml. of water, extracted thoroughly with ether and the ether layers were discarded. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. The combined organic layers were washed with 5% sodium hydroxide, then with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.240 g. of crude colorless diketone, m.p. 137.5–145.7°. Trituration with ether, followed by three recrystallizations from methylcyclohexane, gave colorless prisms, m.p. 149–150.5°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.0; H, 9.91.

(30) After a preparation performed by H. Lemaire.

MADISON, WISCONSIN

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

Steroid Total Synthesis—Hydrochrysene Approach. VIII.[1] *dl*-3β,11β-Dihydroxyandrostane-17-one

BY WILLIAM S. JOHNSON, RAPHAEL PAPPO[2] AND WILLIAM F. JOHNS[3]

RECEIVED MAY 31, 1956

The modified lithium–ammonia–alcohol reduction procedure described in paper VII has been applied to the 11β-hydroxy compound II to give a mixture of 13,14- and 16,17-dehydro ketones III and IV. This mixture, which has been separated into the pure components, could be hydrogenated directly in alkaline solution to give a single dihydroxy ketone V. A procedure has been developed for carrying out the reduction of the 12-oxygenated precursor, as well as of the aromatic nucleus of II in a single step. Condensation of V with furfuraldehyde yielded the furfurylidene ketone VI (R = H), which as its ditetrahydropyranyl ether VI (R = —CHCH$_2$CH$_2$CH$_2$CH$_2$O) was angularly methylated to give, after acid hydrolysis, the C/D *cis* (VII, R = H) and C/D *trans* (VIII, R = H) epimers. The latter (less preponderant) isomer on acetylation, ozonolysis and esterification with diazomethane gave *dl*-dimethyl 3β,11β-diacetoxyetioallohomobilianate (XI, R = Ac, R′ = CH$_3$), the infrared spectrum of which was identical with that of naturally derived *d*-XI (R = Ac, R′ = CH$_3$). Dieckmann cyclization of the *dl*-compound, followed by hydrolysis and decarboxylation in aqueous dioxane at 200–210° afforded, after saponification to cleave the acetate residues, the *dl*-form of the natural product 3β,11β-dihydroxyandrostane-17-one (XIII, R = H). The infrared spectrum of the *dl*-diacetate XIII (R = Ac) was identical with that of authentic (naturally-derived) *d*-XIII (R = Ac). Similarly the 13-isofurfurylidene ketone VII (R = H) was converted to the dimethyl ester X (R = Ac, R′ = CH$_3$) and cyclized to give the 13-isosteroid XII (R = H). When the intermediary diacid X (R = Ac, R′ = H) was saponified to cleave the acetate residues, then acidified, the product was the lactonic acid IX. Since such a lactone was not produced from the epimeric diacid XI (R = R′ = H), these results provide proof for the configuration of these substances and in turn for the C$_{11}$-configuration of the natural 11-hydroxy steroids. A similar reduction study has been carried out with the A/B *cis*-11β-hydroxy compound XV (as well as its precursor). The resulting unsaturated ketones XVI and XVII were converted to XVIII, the configuration of which was proved by relating it to the A/B *trans* series (of established configuration) as follows. Selective Oppenauer oxidation of XVIII gave the hydroxy diketone XIX, which on treatment with one mole-equivalent of bromine followed by dehydrohalogenation gave a mixture of unsaturated ketones XX and XXI. The latter, on reduction with lithium and alcohol in ammonia, followed by acetylation gave a triacetoxy compound identical with that (XXII, R = Ac) produced by similar treatment of the A/B *trans*-compound V.

The previous paper of this series[1] contains a description of the reduction with lithium and alcohol in ammonia of the aromatic nucleus of 1-methoxy-8β-hydroxy-10a-methyldodecahydrochrysene (11-desoxy II) to yield, after acid treatment, a mixture of α,β-unsaturated ketones which on hydrogenation in alkaline solution afforded *dl*-18-nor-D-homo-

(1) Paper VII, W. S. Johnson, B. Bannister and R. Pappo, THIS JOURNAL, **78**, 6331 (1956).

(2) Wisconsin Alumni Research Foundation Postdoctoral Fellow, 1953–1954. On leave of absence from the Weizmann Institute, Israel.

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epiandrosterone[4] (11-desoxy V). This last substance was further converted by the C/D angular methylation–ring contraction sequence[5] into *dl*-epiandrosterone. The major objective of the present work was to apply this synthetic scheme to the 11β-hydroxy derivative II in the hope of effecting the total synthesis of 3β,11β-dihydroxyandrostane-17-one (XIII, R = H), a naturally occurring steroid that has been isolated from beef adrenal glands[6] and has also been found in human urine as a metabolite of compound "F."[7] The present paper includes an account of the details of this work[8] as well as some related, preliminary studies in the A/B *cis* stereochemical series.

The preparation of the diol II *via* the 11,12-dehydro compound I has been described.[9] Reduction of II by the vigorous lithium–ammonia–alcohol method[1] proceeded readily to give, after acid treatment, a mixture of the 13,14- and the 16,17-dehydro ketones III and IV, which was relatively insoluble and could be easily isolated in 69% yield simply by trituration of the crude reaction product. The 11β-hydroxy group thus appears to facilitate the desired reduction by inhibiting hydrogenolysis, for in its absence the yields are significantly lower.[1] The preponderant isomer, m.p. 277°, could be isolated from the mixture by fractional crystallization and was recognized as the 13,14-dehydro compound by its characteristic[1] intense maximum at 248 mμ. The companion isomer was partially separated by fractional crystallization and obtained pure as the diacetate, m.p. 205°; the λ_{max} 224.7 mμ showed it to be the 16,17-dehydro isomer. As in the 11-desoxy series,[1] catalytic hydrogenation in alkaline medium of both α,β-unsaturated ketones III and IV gave rise to the same product, namely, *dl*-3β,11β-dihydroxy-18-nor-D-homoandrostane-17a-one (V), m.p. 257°.

Since the conditions for reduction of the aromatic nucleus of II were similar to those previously employed for the preparation of II from the product of peracid oxidation of I,[9] it seemed desirable to attempt consolidation of the steps. Starting with *trans-anti-trans*-1-methoxy-8β-acetoxy-10a-methyldodecahydrochrysene each step—C_{12}-acetoxylation, dehydroacetoxylation (to give I as the acetate), performic acid oxidation and the lithium–ammonia–alcohol reduction—was carried out on the total crude products without purification. In this way the mixture of unsaturated ketones III and IV was produced directly, and catalytic hydrogenation of this mixture afforded the dihydroxy ketone V in 15% over-all yield.

The angular methylation–ring contraction sequence[5] as recently modified[1] was applied to the 11β-hydroxy compound V. Condensation with furfuraldehyde gave an excellent yield of the furfurylidene derivative VI (R = H), m.p. 229°, which was converted to the ditetrahydropyranyl ether VI (R = $-\underline{CHCH_2CH_2CH_2CH_2O}$) and methylated with potassium *t*-butoxide and methyl iodide. In contrast to previous cases,[1,5] appreciable (16%) starting furfurylidene derivative VI (R = H) was recovered after acid hydrolysis. Since conditions for exhaustive methylation were employed, it seems improbable that methylation was incomplete. It appears that the 11β-tetrahydropyranyloxy group hinders methylation at C_{13}, thus allowing the (ordinarily slow) O-methylation reaction to compete, the product giving rise on acid hydrolysis to starting material.[10] This view is supported by the fact that the crude methylation product exhibited strong secondary absorption at 310 mμ which disappeared after the acid treatment. The residual material from the methylation consisted mainly of a mixture of the angularly methylated isomers. Crystallization effected fairly complete separation of the less soluble (less preponderant) *trans* isomer VIII (R = H), most readily purified by acetylation with acetic anhydride and pyridine which gave the nicely crystalline 3-acetoxy-11-hydroxy compound, m.p. 269°. Further acetylation with isopropenyl acetate afforded the diacetate VIII (R = Ac), m.p. 258°, λ_{max} 322 mμ. Chromatography of the mother liquors from the *trans*-diol yielded a fraction rich in the 13-iso compound VII (R = H), which like its epimer was most readily purified by acetylation to give the diacetate VII (R = Ac), m.p. 243°, λ_{max} 329.5 mμ. The ratio of the resulting angularly methylated products, and the position of their principal maxima in the ultraviolet provided immediate evidence for the

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

(5) (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).

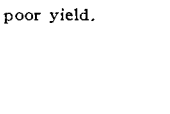
(6) T. Reichstein and J. von Euw, *Helv. Chim. Acta*, **21**, 1197 (1938); **24**, 879 (1941).

(7) A. D. Kemp, A. Kappas, I. I. Salamon, F. Herling and T. F. Gallagher, *J. Biol. Chem.*, **210**, 123 (1954).

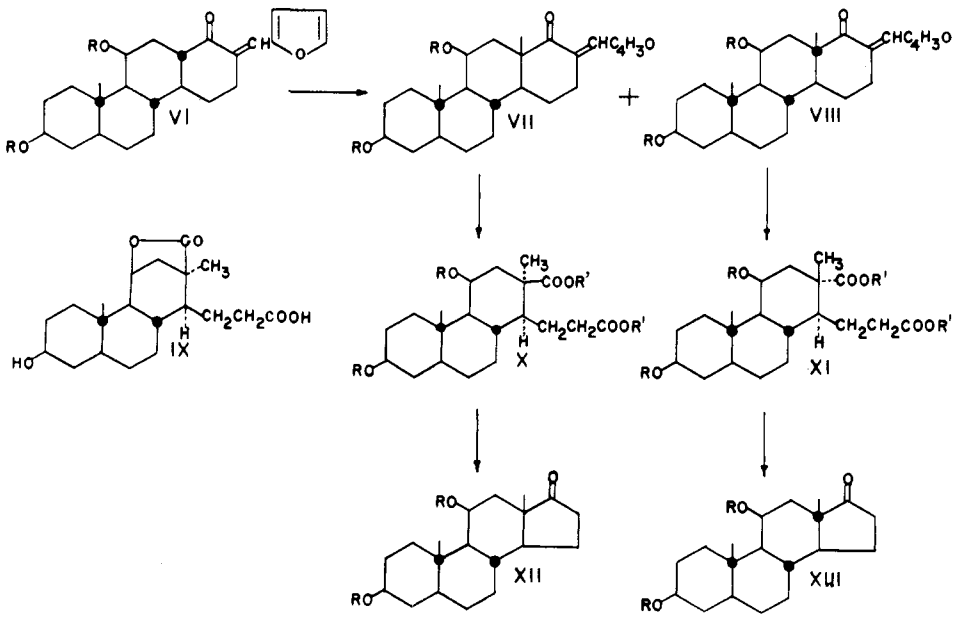
(8) A preliminary report has been published: W. S. Johnson, R. Pappo and A. D. Kemp, THIS JOURNAL, **76**, 3353 (1954).

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

(10) A precedent for this behavior has been found in our laboratories by R. J. Highet (Ph.D. thesis, University of Wisconsin, 1955). When methyl *p*-toluenesulfonate was employed in place of methyl iodide for the methylation of 2-benzylidene-1-decalone, the product was almost entirely the enol ether i. Acid hydrolysis of this unstable material regenerated the starting benzylidene ketone in poor yield.



i



configurations[1]. Unequivocal confirmation of these assignments followed from the experiments described below.

Ozonolysis of the 13-isodiacetate VII (R = Ac) gave the diacid X (R = Ac, R′ = H), which on esterification with diazomethane afforded the dimethyl ester X (R = Ac, R′ = CH_3), m.p. 144°. When the crude diacid X (R = Ac, R′ = H) was saponified to remove the acetate residues, the resulting product was a monobasic acid, m.p. 266°, which exhibited a strong band at 5.73 μ characteristic of a γ-lactone. This substance was, therefore, the lactonic acid IX, formed, undoubtedly, during the isolation (by acidification) of the saponification product. The epimeric dihydroxy diacid XI (R = R′ = H), on the other hand, is a stable substance which does not lactonize readily.[11,12] These combined results constitute conclusive evidence for the configurations of the angularly methylated epimers and, in turn, of the substances derived from them. Since the non-lactonizing epimer has been related to the natural steroids (see below) having the 11-hydroxyl group oriented in the "β" configuration, these results also provide direct, conclusive evidence for the configurations of the C_{11}-hydroxyl in the natural steroids.

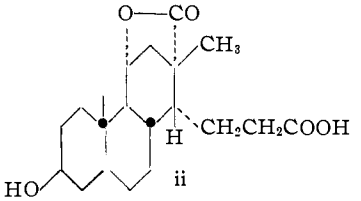
Ozonization of the *trans*-diacetate VIII (R = Ac) followed by esterification gave the dimethyl ester XI (R = Ac, R′ = CH_3) m.p. 133°, the infrared spectrum of which was identical with that of authentic (naturally derived) *d*-dimethyl ester. Dieckmann cyclization was effected with potassium *t*-butoxide in benzene.[1] In view of the well-known susceptibility of the 11β-hydroxy group of steroids to acid-catalyzed elimination,[13] it was considered necessary to avoid the usual acid treatment to effect hydrolysis and decarboxylation of the resulting keto ester. It was found that by using a modification of Meerwein's[14] method, *i.e.*, heating the crude cyclization product in aqueous dioxane at about 220°, the desired cleavage was realized without appreciably affecting the 11-hydroxyl group. *dl*-3β,11β-Dihydroxyandrostane-17-one (XIII, R = H), m.p. 251°, was thus obtained in 48% yield. Acetylation gave the *dl*-diacetate XIII (R = Ac), m.p. 217°, having an infrared spectrum indistinguishable from that of authentic (naturally-derived) *d*-XIII (R = Ac).[15]

Similarly the 13-isodimethyl ester X (R = Ac, R′ = CH_3) described above was cyclized and the resulting keto ester hydrolyzed and decarboxylated to give the 13-isodihydroxy ketone XII (R = H), m.p. 217°.

A general study like that described above was initiated with intermediates having the A/B rings *cis*- rather than *trans*-fused, because the products promised to be more useful for the eventual introduction of the 3-keto-Δ^4-system characteristic of the important 11-oxygenated steroids.[16] The modified lithium-in-ammonia reduction of the *cis-anti-trans*-diol XV,[9] followed by acid treatment, yielded the expected mixture of α,β-unsaturated ketones XVI and XVII. One isomer, m.p. 227°, was readily isolated in part by direct crystallization

(11) This work was carried out with the *d*-enantiomer and is described elsewhere (ref. 15).

(12) Under more vigorous acidic conditions the hydroxy acid XI (R = R′ = H) could possibly lactonize *via* an SN1 or SN2 reaction with inversion at C_{11} to form ii. This configuration would force ring C into the less favored boat conformation.



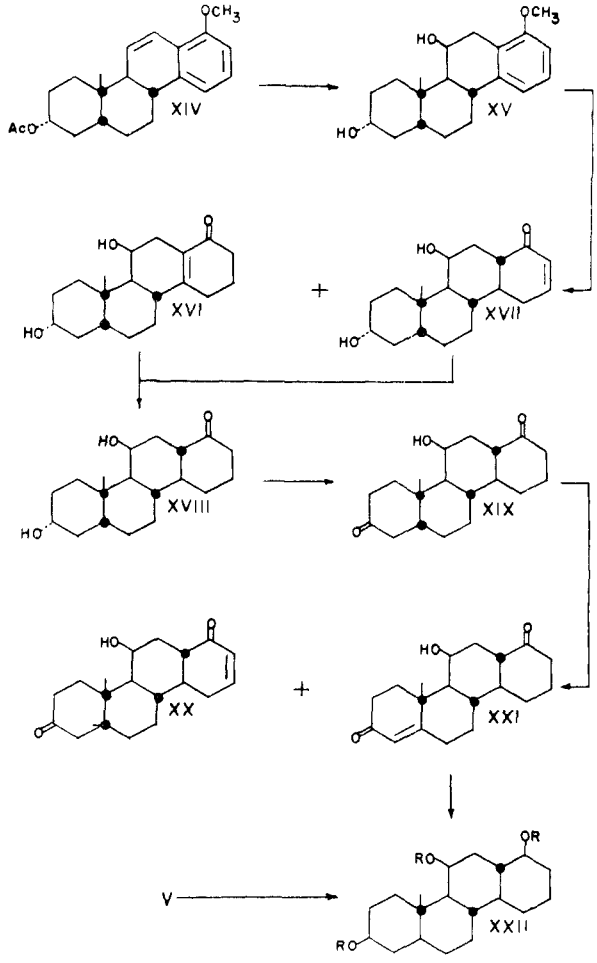
(13) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 408.

(14) H. Meerwein, *Ann.*, **398**, 242 (1913).

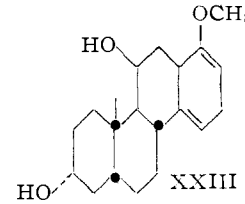
(15) Paper IX, R. Pappo, B. Bloom and W. S. Johnson, THIS JOURNAL, **78**, 6347 (1956).

(16) Reference 13, p. 262.

and completely by chromatography, the total yield being 63%. The ultraviolet absorption, λ_{max} 248 mμ, clearly showed[1] that this was the 13,14-dehydro compound XVI. Attempts to isolate a pure specimen of the 16,17-dehydro isomer were unsuccessful; however, its presence could be demonstrated spectrographically.



When the crude product of perbenzoic acid oxidation of the 11,12-dehydro compound XIV was reduced directly with lithium and alcohol in ammonia so as to combine the hydrogenolysis (to produce XV) and aromatic ring reduction steps as in the A/B *trans* series described above, the over-all yield of the mixture of α,β-unsaturated ketones was 37% from XIV. Other minor products isolated by chromatography included a small amount of the 11-desoxy-13,14-dehydroketone XVI (H in place of 11-OH), m.p. 138°, identified by compositional analysis, ultraviolet absorption spectrum (λ_{max} 248 mμ) and comparison with an authentic specimen.[17] This 138° unsaturated ketone evidently arose from some 11-desoxy XV produced in the hydrogenolysis step as in the *trans-anti-trans* series.[9] Also isolated was a small amount of an isomer of XVI, perhaps the 11α-epimer, m.p. 212°, λ_{max} 248 mμ. This substance could arise from 11-α XV produced in the hydrogenolysis step as in the *trans-anti-trans* series.[9]



In the reduction of the A/B *cis*-diol XV, the crude mixture of enol ethers (obtained before the acid treatment) could be crystallized. One of the isomers, m.p. 194°, was obtained pure. It was essentially transparent in the ultraviolet except for strong end absorption due to isolated olefinic bonds. On acid treatment it gave exclusively the 13,14-dehydro ketone XVI. These facts have been considered[1] as evidence for the preferred structure XXIII for the 194° enol ether.

Catalytic hydrogenation in alkaline medium of the pure 13,14-dehydro ketone XVI or of the mixture of XVI and XVII gave a saturated dihydroxy ketone, m.p. 185°. The configuration at C_3, C_5, C_8, C_9 and C_{10} of the precursor of XV, and hence of its progeny including the 185° ketone, has been established beyond reasonable doubt.[18] There is no certainty *a priori*, however, that the later steps involving (1) introduction of the C_{11}-hydroxyl group and (2) introduction of the C_{14} (and in turn the C_{13}) hydrogen, followed the same stereochemical course as in the A/B *trans* series. The experiments described below settle these points, serving as proof that the C_{11}-hydroxyl of all of these substances in the A/B *cis* series is oriented in the β-configuration and showing, moreover, that the 185° dihydroxy ketone is correctly represented by the "natural" configuration (formula XVIII).

Selective Oppenauer oxidation of the 185° dihydroxy ketone afforded the hydroxy diketone XIX, m.p. 195°, which on treatment with one mole-equivalent of bromine followed by dehydrohalogenation with lithium chloride in dimethyl formamide[19] yielded a mixture of α,β-unsaturated ketones XX and XXI, recognized by their characteristic λ_{max} at 228 and 240 mμ, respectively. The latter isomer, m.p. 233°, which was isolated by chromatography in 18% yield, was reduced completely with lithium and alcohol in ammonia to a trihydroxy compound which was converted to a nicely crystalline triacetate, m.p. 202°. This substance was identical (by mixed m.p. and infrared comparison) with material prepared by similar treatment of *dl*-3β,11β-dihydroxy-18-nor-D-homoandrostane-17a-one (V), the configuration of which has been established by conversion to a natural steroid as described above.

Acknowledgment.—We are indebted to the agencies named in references 2 and 3 for supporting this work. We also wish to thank the Sterling-Winthrop Research Institute for supplying generous amounts of intermediates.

(17) This substance was prepared in our laboratory by J. E. Pike in work to be described later, consisting of lithium-in-ammonia reduction of the *cis-anti-trans*-11-desoxy compound XV (H in place of 11-OH).

(18) Paper III, W. S. Johnson, E. R. Rogier, J. Szmuszkovicz, H. 1. Hadler, J. Ackerman, B. K. Bhattacharyya, B. M. Bloom, L. Stalmann, R. A. Clement, B. Banuister and H. Wynberg, THIS JOURNAL, **78**, 6289 (1956).

(19) The procedure of R. P. Holysz, *ibid.*, **75**, 4432 (1953).

Experimental[4,20]

Lithium Reduction of *trans-anti-trans*-1-Methoxy-8β,11β-dihydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (II).—A solution of 6.95 g. of the crude diol II,[9] m.p. 237–241°, in 500 ml. of tetrahydrofuran was passed through a column of Florex (25 g.), which was then eluted with 1.5 l. of tetrahydrofuran. The eluates were evaporated and the residue crystallized from 95% ethanol to give 6.16 g. of colorless diol, m.p. 238–241°.

A solution of the 6.16 g. of purified diol in 675 ml. of absolute ethanol was added to 1500 ml. of liquid ammonia, an additional 125 ml. of ethanol being used to complete the transfer. A total of 82 g. of lithium wire was then added over a 2-hr. period with stirring. The addition was carried out as described previously[1] so that the bronze phase was present and the solution verged on a blue color. During the second hour of addition a total of 1280 ml. of absolute ethanol and 1700 ml. of ammonia was added.

When all of the lithium had reacted, the ammonia was evaporated, water and chloroform were added and the aqueous layer extracted with chloroform. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The yellow gummy residue obtained upon evaporation of the solvent was essentially transparent in the ultraviolet except for intense end absorption. This product was dissolved in 275 ml. of 95% ethanol, 27.5 ml. of 35% hydrochloric acid and 5.5 ml. of water were added and the mixture heated at reflux under nitrogen. After 1 hr. the solvent was removed at 30° under reduced pressure and the residue dissolved in chloroform. The solution was washed with 10% potassium bicarbonate, then with water and dried over anhydrous sodium sulfate. The crystalline residue obtained upon evaporation of the solvent was triturated with hot chloroform leaving 2.60 g. of crystals, m.p. 274–275°. Evaporation of the triturate and treatment of the residue with methyl ethyl ketone gave an additional 1.50 g. of crystalline product, m.p. 266–275°. The total yield of α,β-unsaturated ketone mixture was thus 4.10 g. (69%), λ_{max} 247 mμ.

The combined crystalline fractions (4.10 g.) were triturated with hot methyl ethyl ketone. After cooling, there was obtained 3.17 g. of crude ***dl*-3β,11β-dihydroxy-13,14-dehydro-18-nor-D-homoandrostane-17a-one (III)**, m.p. 270–275°, λ_{max} 247.8 mμ (log ε 4.09). Material of comparable quality from another run was purified by repeated recrystallization from *n*-propyl alcohol, then from 95% ethanol and finally sublimed at 200° (0.01 mm.) to give colorless rectangular prisms, m.p. 276–277°, λ_{max} 248 mμ (log ε 4.14).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.8; H, 9.52.

The methyl ethyl ketone triturates were evaporated and the residue (0.750 g.) again triturated with a smaller volume of methyl ethyl ketone, giving 0.200 g., λ_{max} 230 mμ. The evaporation (of the triturate) and retrituration was then repeated twice again giving 0.230 g., λ_{max} 225 mμ and 0.043 g., λ_{max} 225 mμ. The last two fractions were combined and chromatographed on 2.3 g. of Florisil. The main fraction eluted with chloroform was recrystallized from methyl ethyl ketone to give 0.164 g. of crude, 16,17-dehydroketone IV, m.p. 214–234°, λ_{max} 225mμ. Since further recrystallization did not appear to effect purification, a specimen was acetylated with isopropenyl acetate and *p*-toluenesulfonic acid in acetone. ***dl*-3β,11β-Diacetoxy-16,17-dehydro-18-nor-D-homoandrostane-17a-one** was thus obtained, after three recrystallizations from 95% ethanol followed by sublimation at 195° (0.03 mm.), as colorless elongated prisms, m.p. 204–205°, λ_{max} 224.7 mμ (log ε 3.94).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.1; H, 8.23.

(20) The new substances described in this section are racemic compounds but the prefix "*dl*" has generally been omitted. Unless otherwise indicated, melting points of analytical specimens are corrected for stem exposure; those followed by "(vac.)" were determined in a capillary evacuated to <0.2 mm. Ultraviolet absorption spectra were determined on a Cary recording spectrophotometer (model 11 MS), 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. Nujol was employed for mulls.

***dl*-3β,11β-Dihydroxy-18-nor-D-homoandrostane-17a-one (V).** (a) **From the 13,14-Dehydro Ketone III.**—A solution of 3.17 g. of the crude dehydro ketone III, m.p. 270–275°, in 560 ml. of 95% ethanol (purified by distillation from Raney nickel) was treated with a solution of 0.36 g. of potassium hydroxide in 1 ml. of water and the mixture hydrogenated over 1 g. of 10% palladium-on-carbon (American Platinum Works) at room temperature and 46 p.s.i. initial pressure. After 1 hr. the gas uptake, which was approximately 1 mole-equivalent, had ceased. The mixture was filtered, the filtrate concentrated to a small volume, and acidified with a slight excess of acetic acid. On cooling there was obtained 2.24 g. (first crop), m.p. 252–253°, and after concentration 0.300 g. (second crop), m.p. 245–251°. The filtrate was diluted with water and extracted with chloroform. The organic layers were washed with water, 5% potassium bicarbonate solution, again with water and dried over anhydrous sodium sulfate. The semi-solid residue obtained upon evaporation of the solvent at reduced pressure was triturated twice with hot benzene to leave 0.300 g. of crystalline powder, m.p. 242–252°. The total yield of crystalline material was 89%.

A sample of the 252–253° fraction was recrystallized twice from methanol, once from methyl ethyl ketone and sublimed at 191° (0.01 mm.) to give colorless prisms, m.p. 256–257°.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.3; H, 9.92.

(b) **From 1-Methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,-7,8,9,10,10a,10b,11,12-dodecahydrochrysene without Purification of Intermediates.**—A 38.00-g. sample of the acetate,[18] m.p. 145–148°, was acetoxylated as previously described[9] with 62 g. of lead tetraacetate in 120 ml. of acetic acid. The resulting total crude 12-acetoxy compound was dehydroacetoxylated in 600 ml. of acetic acid at 95–105° for 15 hr., and 36.30 g. of the total crude 11,12-dehydro compound (amounting to 36.90 g.) was oxidized as previously described[9] in 55 ml. of benzene with 12.5 ml. of 35% hydrogen peroxide and 600 ml. of formic acid. The total crude product of oxidation amounted to 38.30 g. of dark oily material. A solution of 37.0 g. of this material in 1.2 l. of absolute ethanol was added to 2.4 l. of liquid ammonia. A total of 100 g. of lithium wire was added with stirring over a period of 2 hr., additional ethanol (450 ml. total) and ammonia (500 ml.) being introduced during the second hour at an appropriate rate (see details above for the reduction of II). The product was isolated as described in detail above, dissolved in 300 ml. of 95% ethanol, treated with 25 ml. each of 35% hydrochloric acid and water and heated at reflux for 1 hr. After 16 hr. at 5°, the mixture was treated as described above, and the crude product obtained on evaporation of the solvent was triturated with methyl ethyl ketone to give 6.45 g. of material, m.p. 235–270°, λ_{max} 247 mμ. Two additional crops, 0.250 g., m.p. 231–269°, and 0.320 g., m.p. 225–266°, were obtained from the mother liquors.

All of the above solid fractions were combined with 0.200 g. of material, m.p. 235–272°, similarly prepared in a pilot run. The total (7.22 g.) mixture of unsaturated ketones was hydrogenated in two (3.61-g.) portions, 520 ml. of 95% ethanol, 0.40 g. of potassium hydroxide in 2 ml. of water and 1.00 g. of 10% palladium-on-carbon (American Platinum Works) being used for each bath. The hydrogenation which was carried out at room temperature and 38 p.s.i. initial pressure had ceased after 45 minutes, approximately one mole-equivalent of gas having been absorbed. The combined batches were treated as described above (part a) to give after a combination of benzene trituration and fractional crystallizations from methanol and from dilute methanol a total of 4.75 g. of crude dihydroxy ketone V in fractions melting from 236–246° to 233–250°. Material of this quality was satisfactory for the next step, condensation with furfuraldehyde according to the procedure described below, affording furfurylidene derivative VI of satisfactory purity, m.p. 220–224°, in 88% yield.

***dl*-3β,11β-Dihydroxy-17-furfurylidene-18-nor-D-homoandrostane-17a-one (VI, R = H).**—A total of 2.84 g. (2.24 g., m.p. 252–253°, and 0.60 g., m.p. about 243–252°) of the dihydroxy ketone V was dissolved in 305 ml. of methanol, 5.7 ml. of freshly distilled furfuraldehyde was added to the cooled solution, followed by 45 ml. of 15% aqueous sodium hydroxide. After 1 hr. crystals began to form.

Two 100-ml. portions of water were added after an additional 35 minutes and after 15 hr. After cooling to 0–5° for 3 hr. the product was separated by filtration and washed with cold 1:1 methanol–water containing 2% acetic acid. The yield was 3.05 g. (86%), m.p. 222–227°. A sample was recrystallized from 95% ethanol, then from methyl ethyl ketone to give pale cream-colored micro prisms, m.p. 227–229°, λ_{max} 324 mμ (log ε 4.34).

Anal. Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.4; H, 8.36.

The diacetate, prepared by the isopropenyl acetate–*p*-toluenesulfonic acid method was obtained as cream-colored micro-crystalline prisms, m.p. 246–248° from methanol.

Anal. Calcd. for $C_{28}H_{36}O_6$: C, 71.77; H, 7.74. Found: C, 71.6; H, 7.73.

Angular Methylation.—For the preparation of the ditetrahydropyranyl ether[21] VI(R = —CHCH$_2$CH$_2$CH$_2$CH$_2$O) chloroform was used instead of benzene as the solvent, because of the higher solubility of the furfurylidene derivative VI (R = H) in the former. Thus 2.34 g. of VI (R = H) suspended in 200 ml. of ethanol-free chloroform was treated with 20 ml. of dihydropyran and 0.100 g. of *p*-toluenesulfonic acid monohydrate. After 3 hr. at room temperature with stirring, 0.5 ml. of pyridine was added and the chloroform removed at 20° under reduced pressure. The residue was dissolved in 1:1 ether–benzene and washed with 10% potassium bicarbonate solution, then with water and dried over anhydrous sodium sulfate. The oily residue obtained on evaporation of the solvent was crystallized from petroleum ether (60–68°). The process was slow and was facilitated by seeding. The yield of ditetrahydropyranyl ether was 3.27 g., m.p. 162–165°, showing no absorption in the 3 μ region.

A solution of the ditetrahydropyranyl ether in 30 ml. of benzene was methylated with a solution of 8 g. of potassium in 230 ml. of *t*-butyl alcohol and 50 ml. of methyl iodide. The reagents were added in portions, approximately one-third of the *t*-butoxide solution being introduced first, followed by one-third of the methyl iodide. After 1.5 hr. the second third was added (in the same sequence), and after another 2.5 hr. the last of the reagents were added. After a total of 15 hr. (with stirring at room temperature) the solvents were removed at 20° under reduced pressure, water and ether were added and the aqueous layer extracted with ether. The gummy residue (λ_{max} 325 mμ, shoulder at 310 mμ) obtained on evaporation of the combined ether layers was dissolved in 250 ml. of methanol; then 50 ml. of water and 0.250 g. of β-naphthalenesulfonic acid were added and the mixture heated at reflux. After 2.25 hr., the mixture was cooled, neutralized with solid potassium bicarbonate, and the solvent was removed at 20–30° under reduced pressure. The residue was dissolved in chloroform, washed with water and dried over anhydrous sodium sulfate. The gummy residue obtained on evaporation of the solvent was triturated with methyl ethyl ketone to give 0.370 g. of starting material, m.p. 223–228°, λ_{max} 323.5 mμ. The residue from the mother liquors was crystallized from benzene giving several crops of material which apparently contained considerable *trans* isomer as indicated by the maximum at 322 mμ but which could not be purified readily by further crystallization. The combined crops (0.520 g.) were acetylated with 7 ml. of acetic anhydride and 22 ml. of pyridine at room temperature for 15 hr. Recrystallization of the crude product from methanol yielded 0.100 g. of ***dl*-3β-acetoxy-11β-hydroxy-17-furfurylidene-D-homoandrostane-17a-one**, m.p. 264–269°. An additional 0.162 g. of the same material, m.p. 265–269°, was isolated from the mother liquors by chromatography on 40 g. of Florisil and elution with 4:1 benzene–ether. Another sample of the acetate prepared from chromatographed dihydroxy compound (m.p. 244–255°) of another experiment was obtained as colorless needles, m.p. 268–269.5°, after recrystallization from methyl ethyl ketone and from toluene, λ_{max} 320.7 mμ (log ε 4.33); λ_{max}^{mull} 2.86 μ (OH), 5.88 (C=O), 5.99 (C=C—C=O).

Anal. Calcd. for $C_{27}H_{36}O_5$: C, 73.60; H, 8.24. Found: C, 73.3; H, 8.25.

(21) C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951).

The mother liquors, from which the 0.520 g. of crude *trans*-diol (see above) was separated, were chromatographed on 100 g. of Florisil. Elution with 4:1 benzene–ether gave 0.02 g. of crystalline material which appeared to be additional *trans*-compound VII (R = H) which was immediately followed by the *cis* (13-iso) fraction. The main portion of the latter was eluted with 3:2 to 1:1 benzene–ether, the total material amounting to 1.12 g. A center fraction was crystallized with difficulty, m.p. 120–123°, λ_{max} 327 mμ. The total crude *cis* fraction was acetylated with 80 ml. of isopropenyl acetate and 0.180 g. of *p*-toluenesulfonic acid monohydrate to yield after crystallization from 95% ethanol 0.675 g. of ***dl*-3β,11β-diacetoxy-17-furfurylidene-13-iso-D-homoandrostane-17a-one (VII, R = Ac)**, m.p. 230–242°, λ_{max} 329.5 mμ. A sample recrystallized from 95% ethanol and again from methanol was obtained as small colorless needles, m.p. 242–243°, λ_{max} 329.5 mμ (log ε 4.40); λ_{max}^{mull} 5.82 μ (C=O), 6.02 (C=C—C=O).

Anal. Cacld. for $C_{29}H_{38}O_6$: C, 72.17; H, 7.94. Found: C, 72.0; H, 7.68.

***dl*-3β,11β-Diacetoxy-17-furfurylidene-D-homoandrostane-17a-one (VIII, R = Ac)**.—A 0.262-g. sample of the monoacetate, m.p. 264–270°, obtained as described above was acetylated with 20 ml. of isopropenyl acetate and 0.045 g. of *p*-toluenesulfonic acid monohydrate at room temperature for 15 hr. The mixture was diluted with ether and washed with water, then with 10% potassium bicarbonate and dried over anhydrous sodium sulfate. The residue obtained upon evaporation of the solvent was dissolved in benzene and washed through a column of 1 g. of Florex with more benzene. The residue obtained on evaporation of the eluate was triturated with ether to give 0.234 g. of crude diacetate, m.p. 252–256°. Recrystallization from 95% ethanol and again from methanol afforded small pale yellow prisms, m.p. 256–258°, λ_{max} 322 mμ (log ε 4.33), λ_{max}^{mull} 5.82 μ (C=O), 5.98 (C=O—C=O).

Anal. Calcd. for $C_{29}H_{38}O_6$: C, 72.17; H, 7.94. Found: C, 72.5; H. 8.02.

Ozonolysis of the 13-Isodiacetate VII (R = Ac).—A solution of 0.500 g. of crude diacetate, m.p. 230–242°, in 125 ml. of ethyl acetate was treated with ozone at −70° until the blue color due to excess ozone appeared. The solvent was removed at 15–20° under reduced pressure, and 55 ml. of acetic acid was added followed by 1 ml. of 30% hydrogen peroxide in 6 ml. of water. After 19 hr. at room temperature, the solution was evaporated at 20–25° under reduced pressure. The crystalline residue, after trituration with water, then after drying with ether amounted to 0.48 g. of crude diacid X (R = Ac, R′ = H). Recrystallization from ethyl acetate afforded 0.300 g. of colorless prisms, m.p. 233–263° dec. The m.p. behavior, which was not improved by further recrystallization, is indicative of lactonization during heating with elimination of acetic acid. Treatment of the diacid in methanol with ethereal diazomethane gave ***dl*-dimethyl 3β,11β-diacetoxy-13-iso-etioallohomobilianate (X, R = Ac, R′ = CH$_3$)**, obtained from methylcyclohexane as colorless prisms, m.p. 143.5–144.5°, λ_{max}^{mull} 5.82 μ (ester C=O).

Anal. Calcd. for $C_{26}H_{40}O_8$: C, 64.98; H, 8.39. Found: C, 65.3; H, 8.56.

In another experiment 0.068 g. of crude diacetate, m.p. 225–231°, was ozonized as described above. The total residue from the hydrogen peroxide treatment was dissolved in 3 ml. of 10% sodium hydroxide, washed twice with ether and heated on the steam-bath for 3 hr. The solution was cooled with ice, acidified with 30% hydrochloric acid to *p*H 2 and the precipitate separated by centrifugation. Crystallization from methyl ethyl ketone gave 0.040 g. (82% yield) of ***dl*-3β,11β-dihydroxy-13-iso-etioallohomobilianic acid 11,17-lactone (IX)**, as colorless microcrystals, m.p. 262–265°. Recrystallization from the same solvent gave colorless elongated prisms, m.p. 264–266°, λ_{max}^{mull} 5.73 μ (γ-lactone), 5.88 (COOH).

Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63; neut. equiv., 350.4. Found: C, 68.4; H, 8.33; neut. equiv., 358.

***dl*-3β,11β-Dihydroxy-13-isoandrostane-17-one (XII, R = H)**.—A 0.300-g. sample of crude dimethyl ester (m.p. 137–138°) prepared in quantitative yield from diacid (R = Ac, R′ = H), m.p. 233–263°, was dissolved in 10 ml. of dry benzene and added to a suspension of alcohol-free

potassium *t*-butoxide[1] (from 0.700 g. of potassium) in 40 ml. of dry benzene. The mixture was heated at reflux for 4 hr. in an atmosphere of nitrogen. After 16 hr. at room temperature, the mixture was acidified with 1.3 ml. of acetic acid, washed with water, 10% potassium bicarbonate, water and dried over anhydrous sodium sulfate. The viscous, oily keto ester obtained on evaporation of the solvent amounted to 0.229 g. and gave an intense purple color with alcoholic ferric chloride.

A mixture of 0.190 g. of the crude keto ester, 8 ml. of pure dioxane, and 12 ml. of water was heated in a sealed tube at 200–210° for 35 minutes. The tube was cooled, opened and the solvent evaporated to give 0.156 g. of semi-solid residue which gave no color with alcoholic ferric chloride. This material was heated at reflux with 8 ml. of methanol and 2 ml. of 5% sodium hydroxide. After 3 hr., water was added and the mixture extracted thoroughly with ether. The organic layers were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.130 g. of crude product, m.p. 202–208°, resolidifying partially and remelting at 215°. Chromatography on 7.5 g. of Florisil gave on elution with 4:1 benzene–ether 0.100 g. (52% over-all yield) of dihydroxy ketone, m.p. 207–208°, resolidifying and remelting at 215°. Recrystallization from benzene gave 0.080 g. of colorless elongated prisms, m.p. 216–217°. Further recrystallization from methyl ethyl ketone and from benzene gave material having the same m.p., λ_{max}^{mull} 2.90 μ (OH), 5.81 (C=O).

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.3; H, 9.73.

***dl*-Dimethyl 3β,11β-Diacetoxyetioallohomobilianate (XI, R = Ac, R′ = CH_3).**—A solution of 0.234 g. of the diacetoxy-furfurylidene ketone VIII (R = Ac) in 80 ml. of ethyl acetate was ozonized at −70° as described above for the 13-iso epimer. After treatment with 0.6 ml. of 30% hydrogen peroxide and 5 ml. of water for 12 hr. at room temperature, 0.02 g. of platinum oxide was added and the mixture stirred for 3 hr. at room temperature. The mixture was filtered, extracted with ether and the ether extracts washed thoroughly with 5% potassium bicarbonate. The aqueous layers were acidified with dilute hydrochloric acid and extracted with 1:1 ethyl acetate–ether. The organic layers were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oily residue which crystallized on trituration with a small amount of ethyl acetate. The yield was 0.213 g. (97%), m.p. 210–227°. Recrystallization from ether gave 0.109 g., m.p. 227–231°.

Treatment of a methanolic solution of the 0.109-g. specimen of the diacid with ethereal diazomethane gave a crude diester which after trituration with hot diisopropyl ether amounted to 0.088 g., m.p. 131–133°. The residues from the mother liquors of the recrystallization of the diacid (see above) were similarly treated with diazomethane to yield an additional 0.058 g. of diester, m.p. 130–133°. The combined residues from the diisopropyl ether triturates were chromatographed on 5 g. of Florex. The fractions eluted with 20:1 to 10:1 benzene–ether were combined and triturated with petroleum ether (65–68°) to give 0.029 g. of additional diester, m.p. 127–132°. The total over-all yield of diester from the furfurylidene derivative was thus 0.175 g. or 75%. Repeated recrystallization from methylcyclohexane gave colorless prisms, m.p. 131.5–133°.

Anal. Calcd. for $C_{26}H_{40}O_8$: C, 64.98; H, 8.39. Found: C, 64.7; H, 8.12.

The infrared spectrum of this substance (as a supercooled film) was identical with that of the naturally derived *d*-compound[15] (as a liquid film).

***dl*-3β,11β-Dihydroxyandrostane-17-one (XIII, R = H).**—A solution of 0.140 g. of the dimethyl ester XI (R = Ac, R′ = CH_3), m.p. 131–133°, in 20 ml. of benzene was added to a suspension of alcohol-free potassium *t*-butoxide (from 0.350 g. of potassium) in 15 ml. of benzene. The mixture was heated at reflux for 4.5 hr., then stirred at room temperature for 15 hr. The isolation procedure was the same as that described above for the 13-iso epimer, and 0.102 g. of crude oily keto ester, giving an intense purple color with alcoholic ferric chloride, was thus obtained.

A mixture of the keto ester obtained above, 2 ml. of pure dioxane and 3 ml. of water was heated at 220–222° for 41 minutes and the product isolated as described above for the 13-iso series. The crude product was heated at reflux for 3 hr. with 12 ml. of methanol containing 7 ml. of 10% sodium hydroxide and the product isolated as in the 13-iso series. The 9:1 benzene–ether eluate from the chromatography was triturated with hot benzene to give 0.020 g. of dihydroxy ketone, m.p. 247–250.5°. Further elution with 4:1 to 1:1 benzene–ether gave, after trituration with benzene, an additional 0.009 g. of product, m.p. 242–247°. The later fractions eluted with 1:1 benzene–ether amounted to 0.018 g. and showed in addition to the 17-keto absorption at 5.84 μ, strong bands at 5.80 and 8.00 μ indicative of acetate. The triturates from the second fraction (see above) showed similar absorption. The two (incompletely saponified) fractions containing acetate were therefore combined and retreated with methanolic sodium hydroxide for 20 hr. at reflux. The bands at 5.80 and 8.00 μ were absent in the product which was purified as above by chromatography and trituration with benzene to give an additional 0.014 g. of dihydroxy ketone, m.p. 249–251.5°. The total yield was thus 0.043 g. or 48%. The analytical specimen was obtained from methyl ethyl ketone–ether as colorless microcrystalline prisms, m.p. 249–251.5°, λ_{max}^{mull} 2.98 μ (OH), 5.83 (C=O).

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.4; H, 9.61.

The diacetate XIII (R = Ac) was prepared[22] by stirring a mixture of 0.043 g. of dihydroxy ketone with 0.6 ml. of acetic acid, 0.08 ml. of acetic anhydride and 0.004 g. of *p*-toluenesulfonic acid monohydrate. After 24 hr. at room temperature, ice and water were added and the product—isolated by filtration and extraction of the filtrate with ether—triturated twice with ether and once with 95% ethanol to give 0.043 g., m.p. 215–216°. Recrystallization from methanol, from ethyl acetate and finally again from methanol gave colorless elongated prisms, m.p. 217–217.5°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.7; H, 8.97.

The infrared spectrum of this material was identical with that of authentic (naturally derived) *d*-XIII (R = Ac).[15]

***dl*-3α,11β-Dihydroxy-13,14-dehydro-18-nor-D-homoetiocholan-17a-one (XVI).** (a) From *cis-anti-trans*-1-Methoxy-8α,11β-dihydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,-10b,11,12-dodecahydrochrysene (XV).—A solution of 0.320 g. of the diol XV,[9] m.p. 189–191°, in 25 ml. of absolute ethanol was added to 50 ml. of liquid ammonia; then a total of 3.3 g. of lithium wire and 15 ml. of absolute ethanol were added to the mixture at the required rate (see details above) over a 45-minute period. The crude product was isolated as described above, dissolved in 10 ml. of 95% ethanol, 3 ml. of concentrated hydrochloric acid added and the mixture heated at reflux under nitrogen. After 1 hr., the solvent was evaporated at reduced pressure and the semi-solid residue crystallized from acetone to give 0.150 g. of unsaturated ketone, m.p. 222–225°. Recrystallization from acetone, then from ethyl acetate, gave colorless rods, m.p. 227–227.5°, λ_{max} 248 mμ (log ε 4.11).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.15; H, 9.38.

Chromatography of the residue from the mother liquors of the acetone crystallization on 15 g. of Florisil gave on elution with 1:1 ether–petroleum ether (65–68°) 0.012 g. of a crystalline fraction which appeared to be mainly starting material. Later fractions eluted with 1:1 ether–chloroform afforded an additional 0.045 g. of unsaturated ketone, m.p. 220–225°, making the total yield 0.195 g. or 63%. The 16,17-dehydro ketone XVII was contained in fractions immediately preceding the 13,14-dehydro isomer as evidenced by the λ_{max} at 235 mμ; however, attempts to prepare a pure specimen by rechromatography of the appropriate fractions or by acetylation followed by chromatography failed.

(b) From *cis-anti-trans*-1-Methoxy-8α-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b-decahydrochrysene (XIV) with Isolation of the Enol Ether XXIII.—To a solution of 126.3 g. of the 11,12-dehydro compound XIV,[9] m.p. 136–140°, in 600 ml. of benzene at 5° was added 1100 ml.

(22) By the procedure of E. P. Oliveto, C. Gerold, L. Weber, H. E. Jorgensen, R. Rausser and E. B. Hershberg, THIS JOURNAL, **75**, 5486 (1953).

of 0.393 *M* perbenzoic acid[23] in benzene. After 24 hr. at 5°, 25 g. of benzoic acid was added and the solution allowed to stand for an additional 24 hr. at 5°. The solution was washed twice with 5% potassium hydroxide, then with water and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 175 g. of crude monobenzoate.

A solution of 66.3 g. of the monobenzoate in 1.8 l. of absolute ethanol was added to 3.6 l. of anhydrous ammonia; then a total of 85 g. of lithium and 500 ml. of ammonia was added at the required rate (see details above) over a 90-minute period. The crude product, isolated as described above, was crystallized from benzene–petroleum ether (65–68°) to give 16.37 g. (first crop), m.p. 165–177°, and 1.24 g. (second crop), m.p. 172–181°. From this mixture of enol ethers, a single isomer. ***dl*-3α,11β-dihydroxy-17a-methoxy-18-nor-D-homo-14.17-etiocholadiene (XXIII)**, was isolated by several recrystallizations from benzene, from acetone and finally from ethyl acetate as colorless prisms, m.p. 193–194°, λ_{max} 2.90 μ (OH), 5.96 and 6.10 (C=O). This material was essentially transparent in the ultraviolet except for end absorption.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.4; H, 9.53.

The average yield of crystalline enol ether mixture for three similar reductions was 35%.

A solution of 41.48 g. of crude crystalline enol ether mixture (m.p. above 165°) in 1.2 l. of 95% ethanol containing 300 ml. of water and 75 ml. of concentrated hydrochloric acid was heated at reflux under nitrogen. After 1 hr. the solution was concentrated under reduced pressure, to remove most of the alcohol, then extracted with chloroform. The organic layers were washed with water, saturated sodium bicarbonate, again with water and dried over anhydrous sodium sulfate. Concentration of the solution and trituration of the concentrate with ether gave 25.33 g. (first crop), m.p. 203–218° (λ_{max} 248 mμ), and 3.11 g. (second crop), m.p. 178–190° (λ_{max} 248 mμ). Additional α,β-unsaturated ketone mixture, m.p. 195–205° (λ_{max} 238 mμ), containing appreciable 16,17-dehydro isomer XVII was obtained in 19% yield by similar acid treatment of the residue from the mother liquors from which the enol ether mixture was crystallized. The over-all yield from XIV of material suitable (m.p. over 195°) for the hydrogenation step (see below) was 37%.

Recrystallization of a sample of the first crop material from absolute ethanol afforded a specimen m.p. 222–225°, undepressed on admixture with the analytical sample described above.

(c) **From XIV without Purification of Intermediates.**—A solution of 3.10 g. of crude monobenzoate (obtained from 2.22 g. of 11,12-dehydro compound XIV, m.p. 140–144°, as described above) in 180 ml. of absolute ethanol was added to 360 ml. of liquid ammonia; then a total of 21 g. of lithium was added at the required rate (see details above) over a period of 1 hr. The total crude enol ether, isolated as described above, was heated at reflux with 300 ml. of 95% ethanol, 75 ml. of water and 25 ml. of concentrated hydrochloric acid. After 1 hr. the solution was evaporated to dryness under reduced pressure and the residue triturated with ether to give 0.470 g. (first crop), m.p. 212–216°, and 0.050 g. (second crop), m.p. 204–208°. Chromatography of the residues from the mother liquors on 50 g. of Florisil afforded on elution with ether an additional 0.110 g. of unsaturated ketone fraction, m.p. 205–212°, making the total yield of material suitable for the next step 32%.

From earlier fractions eluted with 8:2 ether–petroleum ether (65–68°) there was obtained 0.112 g. (6% yield) of ***dl*-3α-hydroxy-13,14-dehydro-18-nor-D-homoetiocholan-17a-one** (XVI with H in place of 11-OH), m.p. 133–135°. Recrystallization from ether gave colorless plates, m.p. 137–138°, λ_{max} 248 mμ (log ε 4.10).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.3; H, 9.94.

There was no m.p. depression observed on admixture of this material with an authentic specimen prepared by the direct route.[17]

Later 1:1 ether–chloroform eluates from the chromatogram gave 0.89 g. of what is presumed to be ***dl*-3α,11α-dihydroxy-13,14-dehydro-18-nor-D-homoetiocholan-17a-one** (11 α-epimer of XVI), m.p. 202–208°. Two recrystallizations from ethyl acetate gave colorless prisms, m.p. 211–212°, λ_{max} 248 mμ (log ε 4.18).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.9; H, 9.25.

A large depression of the m.p. was observed on admixture of this material with pure XVI.

Acid Hydrolysis of Pure *dl*-3α,11β-Dihydroxy-17a-methoxy-18-nor-D-homoetiochola-14,17-diene (XXIII).—A solution of 0.055 g. of the enol ether XXIII, m.p. 192–194°, in 12 ml. of absolute ethanol containing 3 ml. of water and 0.75 ml. of concentrated hydrochloric acid was heated at reflux. After 1 hr. the solution was concentrated under reduced pressure, water was added and the mixture extracted with chloroform. The extracts were washed with saturated sodium bicarbonate, with water and dried over anhydrous magnesium sulfate. The colorless oily residue obtained upon evaporation of the solvent was crystallized from acetone to give 0.040 g. of the 13,14-dehydroketone, m.p. 214–217°. Recrystallization from ethyl acetate gave 0.035 g., m.p. 219–221°, λ_{max} 248 mμ (log ε 4.10). The total semi-crystalline residues from the combined mother liquors exhibited λ_{max} 247 mμ (log ε 3.95) showing that little, if any, 16,17-dehydro compound was present.

***dl*-3α,11β-Dihydroxy-18-nor-D-homoetiocholan-17a-one (XVIII).**—A solution of 0.255 g. of the 13,14-dehydro ketone XVI, m.p. 212–216°, in 25 ml. of absolute ethanol (distilled from Raney nickel) containing 2 ml. of 10% potassium hydroxide was hydrogenated over 0.04 g. of 10% palladium-on-carbon (American Platinum Works) at room temperature and atmospheric pressure. The uptake of hydrogen, which was one mole-equivalent, ceased after 20 minutes. The mixture was filtered, the filtrate evaporated under reduced pressure and the residue taken up in chloroform and washed with water. The residue obtained upon evaporation of the solvent was crystallized from ether–ethyl acetate to give 0.163 g. of saturated ketone, m.p. 179–182°. An additional 0.036 g. of material, m.p. 178–181°, was obtained by chromatography of the residues from the mother liquors on 5 g. of Florisil and elution with ether, making the total yield 77%. Repeated recrystallization of a specimen of the first crop material from acetone gave colorless rods, m.p. 184–185°.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.5; H, 9.85.

In a larger run, 41.50 g. of the crystalline mixture of unsaturated ketones, m.p. above 195°, was hydrogenated in 400 ml. of absolute ethanol containing 10 ml. of 10% potassium hydroxide over 5 g. of the same catalyst at room temperature and an initial pressure of 50 p.s.i. The reduction was complete in 35 minutes, and the yield of crystalline product was 27.94 g. (first crop), m.p. 169–173°, and 1.23 g. (second crop), m.p. 168–175°. Both crops were sufficiently pure for preparation of the furfurylidene derivative which will be described in a subsequent publication.

***dl*-11β-Hydroxy-18-nor-D-homoetiocholan-3,17a-dione (XIX).**—A modification of the procedure described by Sarett, *et al.*,[24] for selective oxidation by the Oppenauer method was followed. A solution of 0.220 g. of the dihydroxy ketone XVIII, m.p. 175–179°, in 20 ml. of toluene and 5 ml. of cyclohexanone was dried by distilling off 10 ml. of the toluene. A solution of 0.70 g. of aluminum *t*-butoxide in 15 ml. of dry toluene was next added slowly to the boiling mixture over a 5-minute period. The solution was then heated at reflux under nitrogen for 1 hr., cooled, treated with excess dilute hydrochloric acid and the aqueous layer extracted with benzene. The combined organic layers were washed with saturated sodium bicarbonate, then the solvents and excess cyclohexanone were removed by steam distillation (for about 1 hr.). The residue was extracted with benzene, and the extracts were dried over anhydrous magnesium sulfate. The colorless oily residue obtained upon evaporation of the solvent was chromatographed on 10 g. of Florisil. Elution with 4:6 ether–petroleum ether gave 0.160 g. of crude hydroxy diketone, m.p. 180–190°. Repeated recrystallization from acetone gave colorless plates, m.p. 193–195°.

(23) Freshly prepared according to D. Swern in Adams, "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 393.

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

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.1; H, 9.24.

dl-11β-Hydroxy-18-nor-D-homoandrost-4-ene-3,17a-dione (XXI).[19]—A solution of 0.035 g. of bromine in 3 ml. of redistilled dimethylformamide was added slowly over a 20-minute period at room temperature to 0.068 g. of the hydroxy diketone XIX, m.p. 193–195°, dissolved in 2 ml. of dimethylformamide. A total of 0.035 g. of *p*-toluenesulfonic acid monohydrate was also added in portions during this period. After 45 minutes the bromine color had disappeared, water was added and the solution was extracted with ether. The ether layers were washed with dilute sodium thiosulfate, then thoroughly with water and dried over anhydrous magnesium sulfate. The colorless oil (0.080 g.) obtained upon evaporation of the solvent under reduced pressure was dissolved in 20 ml. of dimethylformamide, 0.51 g. of lithium chloride added, the solution heated at 110° for 2 hr., cooled, diluted with water and extracted with ether. The organic layer was washed thoroughly with water and dried over anhydrous magnesium sulfate. The semi-solid residue (0.060 g., λ_{max} 237 mμ) obtained upon evaporation of the solvent was chromatographed on 10 g. of Florisil. Elution with 8:2 ether–petroleum ether gave a 0.040-g. fraction which on trituration with ether afforded 0.032 g. of crystals, m.p. 179–186°. Recrystallization from methanol and again from ethyl acetate gave material, m.p. 190–193°, which because of the low extinction coefficient (log ε 3.45) of the maximum at 228 mμ and because of the low percentage of carbon and high percentage of hydrogen (Found: C, 74.7; H, 9.35), appeared to consist of 16,17-dihydrohydroxy diketone XX contaminated with starting material XIX. This material has not been investigated further.

Elution of the column with chloroform gave a 0.023-g. fraction which on recrystallization from acetone afforded 0.012 g. of the 4,5-dehydro compound XXI, m.p. 226–230°. Recrystallization from methanol, then from acetone–petroleum ether (65–68°) and finally from acetone gave 0.009 g. of colorless prisms, m.p. 231–233°, λ_{max} 240 mμ (log ε 4.21).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.45; H, 8.58.

dl-3β,11β,17aβ-Trihydroxy-18-nor-D-homoandrostane (XXII, R = H).—A solution of 0.054 g. of the A/B *trans*-dihydroxy ketone V, m.p. 244–248°, in 5 ml. of absolute ethanol was added to 50 ml. of liquid ammonia and stirred while a total of 0.7 g. of lithium was introduced over a 30-minute period. After a total of 45 minutes, when the blue color had disappeared, the product was isolated as described above (reduction of II), benzene being employed for extraction. The crude semi-solid residue was triturated with ether to give 0.040 g. of the triol, m.p. 244–249°. Further treatment of the mother liquor residue with ethyl acetate yielded an additional 0.010 g., m.p. 248–252°, making the total yield 93%. Two recrystallizations from methyl ethyl ketone gave colorless plates, m.p. 249–251° (depressed to 220–240° on admixture with starting material).

Anal. Calcd. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.9; H, 10.36.

dl-3β,11β,17aβ-Triacetoxy-18-nor-D-homoandrostane (XXII, R = Ac). (a) From Authentic Triol XXII (R = H).[22]—A solution of 0.035 g. of the crude triol, m.p. 244–249°, of the preceding experiment in 2 ml. of acetic acid and 0.4 ml. of acetic anhydride containing 0.020 g. of *p*-toluenesulfonic acid monohydrate was allowed to stand overnight at room temperature. Water and chloroform were added and the organic layer washed with saturated sodium bicarbonate, then dried over anhydrous magnesium sulfate. The residue (0.038 g.) obtained on evaporation of the solvent was chromatographed on 3 g. of Florisil. Elution with ether gave 0.035 g. of material, m.p. 193–199°. Recrystallization from acetone, then from petroleum ether (65–68°) and finally from methanol gave colorless prisms, m.p. 201–203°.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.1; H, 8.61.

(b) From the Unsaturated Hydroxy Diketone XXI.—A solution of 0.005 g. of XXI, m.p. 231–233°, in 5 ml. of absolute ethanol was added to 50 ml. of liquid ammonia; then a total of 0.7 g. of lithium was added with stirring over a 30-minute period. After the blue color was discharged, the product was isolated as described above (reduction of V) and acetylated, as described in the preceding experiment, with 2 ml. of acetic acid, 0.4 ml. of acetic anhydride and 0.020 g. of *p*-toluenesulfonic acid monohydrate. The crude product (0.006 g.) eluted from Florisil with ether, was recrystallized twice from petroleum ether (65–68°) to give 0.004 g. of triacetate, m.p. 200–202°, undepressed on admixture with the analytical specimen described above. The infrared spectra of the two specimens were identical.

MADISON, WISCONSIN

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

Steroid Total Synthesis—Hydrochrysene Approach. IX.[1] Preparation of Comparison Substances by Partial Synthesis

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RECEIVED MAY 31, 1956

Bromination of the enol acetate II (R = Ac) of epiandrosterone acetate (I, R = Ac) gave a 16-bromo compound III (R = Ac, R′ = Br) which could be dehydrobrominated in only very poor yield to give the 14,15-dehydro compound VI (R = Ac). The previously known dienic acid VII (R = R′ = H) was readily converted to the acetoxy acid (R = Ac, R′ = H) by an ester exchange with phenyl acetate and sodium hydride. Selective hydrogenation of this compound in benzene solution afforded the 14-iso unsaturated acid VIII (R = Ac, R′ = H) which on Curtius degradation and hydrolysis of the enamine gave 14-isoepiandrosterone (V, R = H) identical with material prepared by the hydrogenation of VI (R = H).[4] Conversion of V (R = H) to the 16-hydroxymethylene derivative, followed by condensation with hydroxylamine and finally alkaline hydrolysis, gave the desired hydroxy diacid IX (R = R′ = H). D-Homoepiandrosterone X (R = H) was converted to the benzylidene (XI, R = H, Ar = C_6H_5) and furfurylidene (XI, R = H, Ar = C_4H_3O) derivatives. The acetate of the former on ozonolysis gave the known acetoxy diacid XII (R = Ac, R′ = H), which was also prepared from epiandrosterone by the ring opening sequence *via* the hydroxymethylene derivative (see above). The known dihydroxy ketone XIV (R = H) has been prepared by sodium bismuthate oxidation of Reichstein's substance "V" (XIII). It was also obtained by degradation of 17α-hydroxycorticosterone XV. Application of the ring-opening sequence (see above) to XIV (R = H) afforded the dihydroxy diacid XVI (R = R′ = H).

This paper contains an account of our work on the partial synthesis of substances required for comparison with the totally synthetic products described in previous papers of this series. It is noteworthy that, since our objective was to produce small specimens of good purity and unequivocal identity, particular attention was not generally given to the matter of obtaining the best yields, and in some instances the more direct approach

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

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