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

BY RAPHAEL PAPPO,[2] BARRY M. BLOOM[3] AND WILLIAM S. JOHNSON

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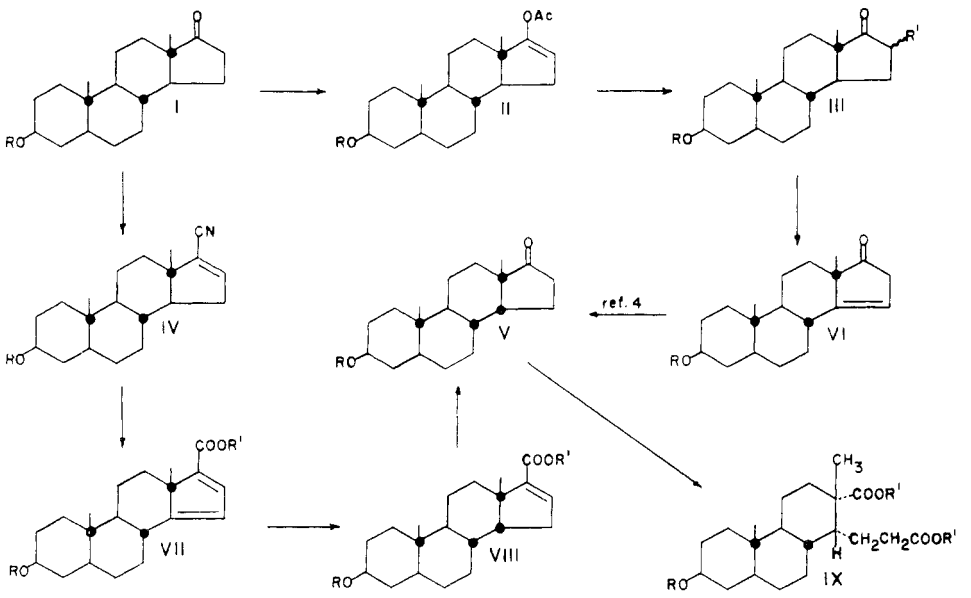
Bromination of the enol acetate II (R = Ac) of epiandrosterone acetate (I, R = Ac) gave a 16-bromo compound III (R = Ac, R′ = Br) which could be dehydrobrominated in only very poor yield to give the 14,15-dehydro compound VI (R = Ac). The previously known dienic acid VII (R = R′ = H) was readily converted 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).

(2) Merck and Co., Inc. (1952–1953) and Wisconsin Alumni Research Foundation (1953–1954) postdoctoral fellow. On leave of absence from the Weizmann Institute, Israel.

(3) National Research Council Postdoctoral Fellow, 1951–1952.



was abandoned in favor of the longer but stereochemically more certain course.

14-Isoepiandrosterone (V, R = H) and 3β-Acetoxy-14-isoetioallohomobilianic Acid (IX, R = Ac).—St. André and his collaborators[4] have prepared 14-isoepiandrosterone in the course of the proof of structure of the position of the hydroxyl group that was introduced into 5,6-dehydroepiandrosterone dibromide by the action of chromic anhydride. Debromination, followed by hydrogenation of the 5,6-double bond, then dehydration gave 14,15-dehydroepiandrosterone acetate (VI, R = Ac), thus showing that the hydroxyl in question was located at C_{14}. Catalytic hydrogenation of the 14,15-dehydro ketone afforded the 14-iso compound V (R = Ac). Although we were aware of the progress of this work before publication,[5] we elected to study another route, because at the time our work was initiated there was still doubt about the constitution of the St. André products. We hoped to devise a scheme which would afford material not only of unequivocal stereochemistry but in sufficient quantity for degradation to the acid IX (R = R′ = H).

Two approaches were examined. The first, which was unsuccessful, involved bromination of epiandrosterone acetate (I, R = Ac) followed by dehydrobromination to produce an authentic ring D dehydro compound with the expectation that the latter could be hydrogenated either as the 14,-15-dehydro isomer or the 14-iso-15,16-dehydro tautomer to give the desired product. Direct bromination was surprisingly difficult. In ether a mixture of mono- and dibromo compounds was produced, some of the former being separated as the 2,4-dinitrophenylhydrazone, m.p. 208°. In acetic acid, monobromination was favored, but the product was isolated in only 32% yield and appeared to be a mixture of C_{16}-epimers.

Bromination of the enol acetate II (R = Ac),[6] m.p. 176°, produced a single monobromo epimer III (R = Ac, R′ = Br), m.p. 174°, in 90% yield. Attempts to effect dehydrohalogenation with γ-collidine gave unpromising results. Considerable tarry material was produced, due probably in part to polymerization of the resulting sensitive cyclopentenone system. Chromatography of the tractable portion afforded in about 5% yield, crude 14,15-dehydro ketone VI (R = Ac), which after recrystallization melted at 152° alone or on admixture with the product of dehydration of the 14-hydroxy ketone.[7] Practical failure of the dehydrohalogenation approach[8] prompted us to examine another scheme.

Ruzicka and Plattner and their collaborators[9] have described the preparation of the dienic acid VII (R = Ac, R' = H) from epiandrosterone acetate (I, R = Ac). The cyanohydrin was dehydrated to give the unsaturated nitrile IV (R = Ac) which was brominated with N-bromosuccinimide and the resulting 15-bromo compound dehydrohalogenated, then hydrolyzed to convert the cyano to carboxyl. They also demonstrated that catalytic hydrogenation of the dienic ester VII (R = Ac, R′ = CH_3) gave substantial amounts of the 14-iso saturated compound. We, therefore, took advantage of this established route to an authentic 14-iso steroid. The excellent procedures of the Swiss workers gave the reported results in our

(4) A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica and C. R. Scholz, THIS JOURNAL, **74**, 5506 (1952).

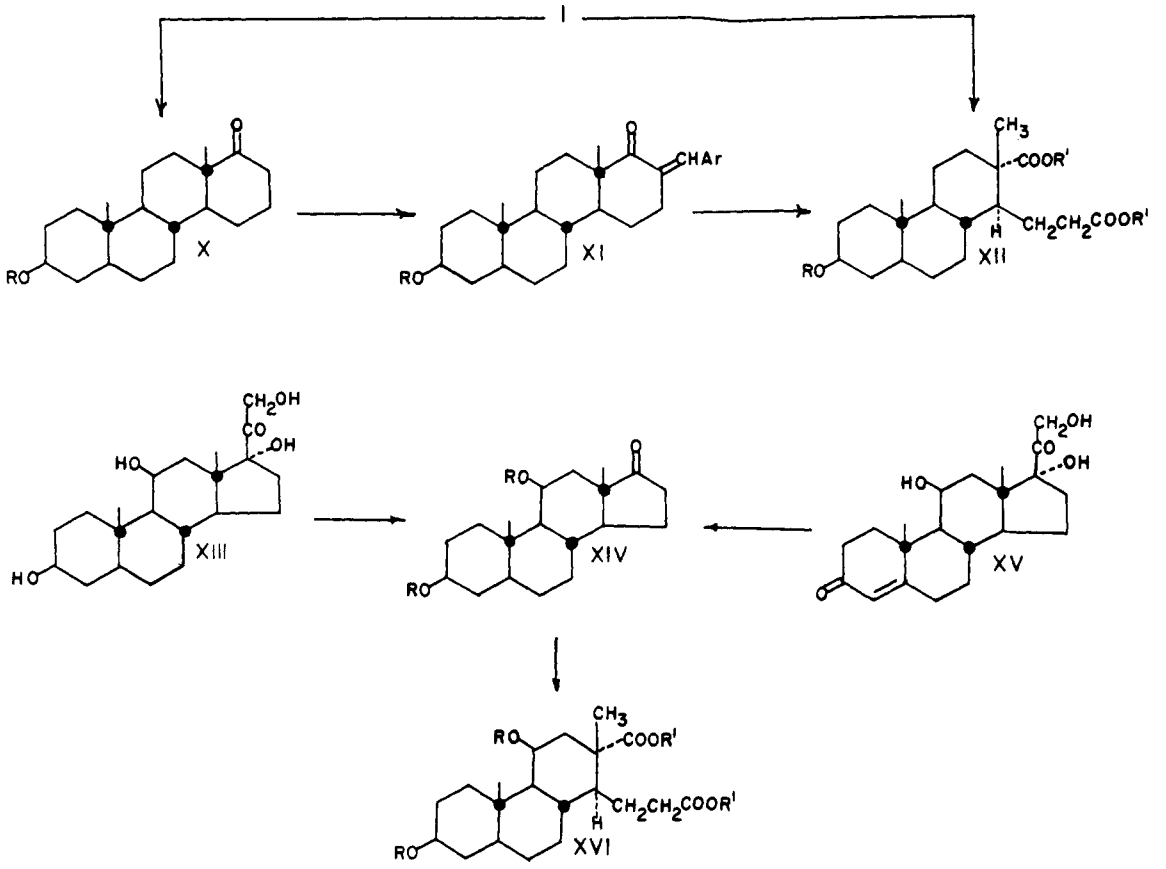
(5) Private communication from Dr. St. André to W. S. J.

(6) (a) N. S. Leeds, D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **76**, 2943 (1954); (b) J. Fajkos, *Czech. Chem. Communication*, **20**, 812, (1955).

(7) We are indebted to Dr. St. André for sending us a specimen of his material (see ref. 4).

(8) Since the present work was completed, H. J. Dauben, Jr., V. R. Ben and S. H. K. Chiang disclosed (Abstracts of the 123rd Meeting of the Am. Chem. Soc., Los Angeles, California, 1953, p. 9M) an excellent method for producing the cyclopentenone system by dehydrohalogenation of the ethylene ketal of the α-halo ketone. This method would undoubtedly be applicable to the present case, particularly since we have recently used the Dauben sequence most successfully in the synthesis of 14-isoestrone methyl ether from estrone methyl ether; W. F. Johns, Ph.D. Thesis, University of Wisconsin, 1955.

(9) (a) L. Ruzicka, Pl. A. Plattner, H. Heusser and J. Pataki, *Helv. Chim. Acta*, **29**, 936 (1946); (b) Pl. A. Plattner, L. Ruzicka, H. Heusser, J. Pataki and Kd. Meier, *ibid.*, **29**, 942 (1946); (c) Pl. A. Plattner, Kd. Meier, and H. Heusser, *ibid.*, **30**, 905 (1947).



hands. A minor improvement was made in the alkaline hydrolysis of the doubly unsaturated nitrile which was conducted in ethylene glycol, thus permitting the reaction to be carried out at atmospheric pressure. Selective acetylation of the resulting hydroxy acid VII (R = R′ = H) to the acetoxy acid by conventional methods is complicated by anhydride formation (VII, R = R′ = Ac), requiring a selective hydrolysis step.[9c] The yield of VII (R = Ac, R′ = H) by this method was 61%.[9c] In an effort to improve the acetylation a new method was developed. When the hydroxy acid was suspended in excess phenyl acetate and the mixture stirred with sodium hydride, a smooth ester exchange occurred with the 3-hydroxyl, and pure acetoxy acid VII (R = Ac, R′ = H), m.p. 268–269°, was isolated directly in 70% yield. The purest material previously obtained was reported to melt at 261.5–262.5°.[9c] To confirm the identity of our material, it was converted to the methyl ester melting at 150–151° in good agreement with the reported value of 150.5–151.5°.[9c]

Hydrogenation of dienic acids like VII in alcohol solution have been observed[10] to proceed readily to the perhydro stage without any apparent decrease in rate after the absorption of one mole equivalent of gas. Since the unsaturated acid VIII (R = Ac, R′ = H) promised to be more useful for the prosecution of the remainder of the synthesis, we attempted to selectively hydrogenate the dienic acid in a non-polar solvent (benzene) which was shown by Woodward, *et al.*,[11] to be effective in promoting preferential reduction of the terminal olefinic bond of a conjugated dienic ketone. These conditions were tried first with the acetoxy ester VII (R = Ac, R′ = CH_3); one mole-equivalent of hydrogen was absorbed selectively and the only product isolated (in about 60% yield) was the 14-iso ester VIII (R = Ac, R′ = CH_3), m.p. 141°. The corresponding ester in the natural series (14α hydrogen) is known and melts at 196°.[9a] Reduction of the dienic acid VII (R = Ac, R′ = H) proceeded similarly to give VIII (R = Ac, R′ = H), which was converted to the acid chloride and thence to the azide with sodium azide. Rearrangement by warming in toluene gave the isocyanate which was hydrolyzed with dilute acid (through the enamine) to give 14-isoepiandrosterone V (R = H) in 22% over-all yield from the dienic acid. The pure product melted at 168° and gave no m.p. depression on admixture with the St. André product[7] but gave a marked depression on admixture with epiandrosterone.

The dibasic acid IX (R = R′ = H) was prepared from V (R = H) by a general procedure[12] involving condensation with ethyl formate, conversion of the resulting hydroxymethylene derivative to the oxime (or disubstituted hydroxylamine),

(10) A. L. Wilds and M. Harnick, private communication.

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

(12) W. S. Johnson and W. E. Shelberg, *ibid.*, **67**, 1754 (1945). See also W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg and L. J. Chinn, *ibid.*, **74**, 2832 (1952), for application to estrone methyl ether.

followed by alkaline hydrolysis in the presence of hydroxylamine. The crude hydroxy acid thus obtained was acetylated by the phenyl acetate–sodium hydride method to give the acetoxy acid IX (R = Ac, R′ = H), m.p. 282–283°. Treatment with diazomethane gave the dimethyl ester IX (R = Ac, R′ = CH_3) as an oil.

D-Homoepiandrosterone Derivatives and Methyl 3β-Acetoxyetioallohomobilianate (XII, R = Ac, R′ = CH_3).—D-Homoepiandrosterone X (R = H) was prepared by the Tiffeneau ring enlargement of epiandrosterone acetate.[13] Alkaline-catalyzed condensation of the acetate X (R = Ac) with benzaldehyde[14] gave the 17-benzylidene derivative XI (R = H, Ar = C_6H_5), m.p. 197°. Similarly condensation of X (R = H) with furfuraldehyde yielded the furfurylidene derivative XI (R = H, Ar = C_4H_3O), m.p. 185°. Ozonization of the benzylidene acetate XI (R = Ac, Ar = C_6H_5), followed by treatment with hydrogen peroxide to cleave the ozonide, then with diazomethane, gave the acetoxy dimethyl ester XII (R = Ac, R′ = CH_3), m.p. 158°. This is essentially the method of Prins and Shoppee[13b] who first prepared this substance (m.p. 156°) by ozonolysis of the piperonylidene derivative XI (Ar = $C_7H_5O_2$). In the present work, we also prepared the acetoxydimethyl ester XII directly from epiandrosterone by application of the ring opening sequence[12] as in the 14-iso series described above.

3β,11β-Dihydroxyandrostane-17-one (XIV, R = H) and 3β,11β-Dihydroxyetioallohomobilianic Acid (XVI, R = R′ = H).—Reichstein[15] has prepared the dihydroxy ketone XIV (R = H) by cleavage of 3β,11β,17α,20,21-pentahydroxyallopregnane (substance "A") with lead tetraacetate or periodic acid. In the present investigation XIV (R = H) was produced readily in good yield by the oxidation of 3β,11β,17α,21-tetrahydroxyallopregnane-20-one (Reichstein's substance "V") (XIII) with sodium bismuthate.[16] The dihydroxy ketone XIV (R = H) was also obtained, but less readily, from 17α-hydroxycorticosterone (XV) by catalytic hydrogenation of the 4,5-double bond, followed by sodium borohydride reduction to give the pentahydroxy compound of Reichstein which was cleaved with periodic acid.[15]

The ring opening sequence[12] was applied, as in the cases described above, to the dihydroxy ketone XIV (R = H). Tetrahydrofuran was used instead of benzene in the formylation, because of insolubility of the ketone in the latter solvent. The highly polar nature of the products rendered them fairly water soluble and necessitated isolation by continuous extraction procedures. The dihydroxy diacid XVI (R = R′ = H) melted at 261° and the diacetoxy dimethyl ester XVI (R = Ac, R′ = CH_3) was obtained as a colorless oil.

Acknowledgment.—We are grateful to the concerns named in footnotes 2 and 3 for their assistance. We also wish to thank Drs. E. B. Hershberg and C. R. Scholz for gifts of epiandrosterone acetate, Dr. G. Rosenkranz for providing us with the tetrahydroxy ketone XIII and Dr. M. Tishler for contributing the 17α-hydroxycorticosterone (XV).

Experimental[17]

Direct Bromination of Epiandrosterone Acetate (I, R = Ac). (a) **In Ether.**[18]—A few drops of bromine in methylene chloride were added to a stirred solution of 4.00 g. of epiandrosterone acetate,[19] m.p. 115.5–117°, in 100 ml. of anhydrous ether. When the solution became colorless it was cooled to 5° and a total of 1.95 g. of bromine in 20 ml. of methylene chloride was added dropwise over a 3-hr. period. Water was added, the ether layer washed thoroughly with water and dried over anhydrous magnesium sulfate. The oily residue obtained on evaporation of the solvent was triturated with a large volume of petroleum ether (60–68°) to give 2.18 g. of colorless prisms, m.p. 147–157°. After standing several days the mother liquor yielded an additional 1.28 g., m.p. 127–158°.

Repeated recrystallization of the first crop from ether–petroleum ether (60–68°) gave material, m.p. 166–174°. The analysis (Found: C, 59.75; H, 7.79) indicated that this material was largely monobromo ketone contaminated with some of the dibromo compound. The contaminant was evidently removed in the preparation of the **2,4-dinitrophenylhydrazone** which was obtained from chloroform–absolute ethanol as rectangular, orange prisms, m.p. 205.5–208.5° dec.

Anal. Calcd. for $C_{27}H_{35}O_6N_4Br$: C, 54.82; H, 5.96. Found: C, 54.55; H, 5.92.

Recrystallization of the second crop material from ether–petroleum ether (60–68°) afforded colorless needles, m.p. 158.5–167°, which appeared to consist largely of dibromo ketone (Found: after sublimation at reduced pressure: C, 51.9; H, 6.17).

(b) **In Acetic Acid.**[20]—A 1.00-g. sample of epiandrosterone acetate,[19] m.p. 115–116°, was dissolved in 13 ml. of acetic acid; then 1 ml. of 48% hydrobromic acid was added, followed by a solution of 0.160 ml. of bromine in 10 ml. of acetic acid containing 0.5 ml. of 48% hydrobromic acid. The reaction was slow, and although the color was not discharged after 1 hr. at room temperature, the mixture was cooled and diluted with a solution of 1 g. of sodium hydroxide in a large volume of water. The crystalline precipitate was separated, washed with water and (after drying) recrystallized from methylcyclohexane to give 0.40 g. (32% yield) of crude 16-bromoepiandrosterone acetate, as colorless prisms, m.p. 165–168° dec. After recrystallization and sublimation at 120° (0.05 mm.), the m.p. was 166–168° dec.

Anal. Calcd. for $C_{21}H_{31}O_3Br$: C, 61.31; H, 7.60. Found: C, 61.2; H, 7.74.

When bromination was carried out essentially as described above except that anhydrous hydrogen bromide was employed, monobromide of comparable purity was obtained in only 12% yield.

3β,17-Diacetoxyandrostene-16 (II, R = Ac).[6]—The procedure of Moffett and Weisblat[21] for preparing enol acetates was employed. A solution of 5.00 g. of epiandrosterone, m.p. 172–174°, in 100 ml. of isopropenyl acetate containing 0.75 g. of *p*-toluenesulfonic acid monohydrate

(13) (a) M. W. Goldberg and R. Monnier, *Helv. Chim. Acta*, **23**, 376 (1940); (b) D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 494 (1946).

(14) *Cf.* W. S. Johnson, THIS JOURNAL, **65**, 1317 (1943).

(15) T. Reichstein, *Helv. Chim. Acta*, **19**, 402 (1936).

(16) An adaptation of the procedure of C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

(17) Unless otherwise indicated all melting points of analytical specimens are corrected for stem exposure. Ultraviolet absorption spectra were determined on a Cary recording spectrophotometer (model 11MS), 95% alcohol 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 used for mulls.

(18) By the procedure of A. L. Wilds, THIS JOURNAL, **64**, 1421 (1942).

(19) Prepared by catalytic hydrogenation of dehydroepiandrosterone acetate, m.p. 169–170.2°, over 30% palladium-on-strontium carbonate (ref. 39 of paper III) in 95% ethanol. H. Levy and R. P. Jacobsen, *J. Biol. Chem.*, **171**, 71 (1947), also obtained the high-melting modification, m.p. 116.5–117°.

(20) By the procedure of A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935).

(21) R. B. Moffett and D. I. Weisblat, THIS JOURNAL, **74**, 2183 (1952).

was distilled very slowly through a 20-cm. Vigreux column for 10 hr. More isopropenyl acetate was added as required so that the volume of the reaction mixture did not decrease below 50 ml. Excess solid sodium bicarbonate was added, the solvent removed at reduced pressure, ether and water added and the ether layer washed with water, then dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent was crystallized from methylcyclohexane to give 4.00 g. of colorless prisms, m.p. 174–176°. An additional 0.40 g., m.p. 170–172°, was isolated from the mother liquors.

A specimen from another run was recrystallized from ether to give colorless needles, m.p. 174–176°, $[\alpha]^{30}D$ +23 ± 3° (*c* 0.455 in $CHCl_3$). The analytical sample was sublimed at 150° (0.04 mm.). Since the present work was completed, Leeds, Fukushima and Gallagher[8a] reported the preparation of this enol acetate, m.p. 172°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.65; H, 9.18.

16-Bromoepiandrosterone Acetate (III, R = Ac, R′ = Br).—A solution of 0.051 ml. of bromine in 5 ml. of chloroform was added dropwise to a stirred solution of 0.374 g. of the enol acetate, m.p. 174–176° (described above), in 15 ml. of carbon tetrachloride at −15°. After about 5 minutes when 90% of the bromine solution had been added, the color persisted. The addition was stopped, the solvent removed at 10° under reduced pressure and the residue crystallized from methylcyclohexane to give 0.300 g. of colorless rods, m.p. 173–176°. An additional 0.070 g., m.p. 173–176°, was obtained from the mother liquors, making the total yield 90%. A sample, recrystallized from methylcyclohexane and sublimed at 130° (0.05 mm.), melted at 172–174° with slow darkening. Since the completion of the present work Fajkos[6b] reported the preparation of this product in 76% yield, m.p. 173–174°.

Anal. Calcd. for $C_{21}H_{31}O_3Br$: C, 61.31; H, 7.60. Found: C, 61.2; H, 7.78.

Dehydrobromination of 16-Bromoepiandrosterone Acetate.—A solution of 2.00 g. of the bromo ketone, m.p. 172–174°, in 25 ml. of freshly distilled γ-collidine was heated at reflux under nitrogen. After 3 hr., the very dark red mixture containing precipitated salt was poured into excess 3 *N* hydrochloric acid and extracted with ether. The ether solution was separated from tarry material, washed with dilute hydrochloric acid, with water and dried over anhydrous magnesium sulfate. The oily residue (0.51 g.) obtained on evaporation of the ether was chromatographed on 15 g. of Florisil. The fraction eluted with 1:1 benzene–petroleum ether (65–68°) amounted to 0.095 g. of partially crystalline material. Crystallization from methylcyclohexane gave a product, m.p. 150–152°, undepressed on admixture with authentic 14,15-dehydroepiandrosterone acetate (VI, R = Ac),[4,7] m.p. 150–152.5°.

3β-Hydroxy-14,16-etioallocholadienic Acid (VII, R = R′ = H).—A solution of 5 g. of sodium hydroxide in 5 ml. of water was diluted with 30 ml. of ethylene glycol and the mixture boiled in an open stainless steel flask until the internal temperature reached 150–160°. At this point 1.00 g. of crude 3β-acetoxy-14,16-etioallocholadienonitrile,[9c] m.p. 134–145°, was added and the mixture heated at reflux under nitrogen. After 7 hr. the mixture was cooled, diluted with 700 ml. of water and extracted with ether. The aqueous (alkaline) layer was then acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.909 g. of acidic product. Recrystallization from acetone gave a first crop amounting to 0.453 g., m.p. 225–226° (reported[9c] 226–227°).

The hydrolysis was repeated on a 10-g. scale, and the crude reaction mixture was acidified without removing the neutral fraction. The total crude crystalline product isolated as described above was washed thoroughly with hot benzene to give 8.76 g. (94% yield) of material, m.p. 215–216°, suitable for use in the next step.

3β-Acetoxy-14,16-etioallocholadienic Acid (VII, R = Ac, R′ = H).—A 7.8-g. sample of the crude hydroxy acid, m.p. 215–216°, described above was dissolved in 25 ml. of phenyl acetate (dried by distillation at 14 mm. from sodium hydride) by warming at about 100°. The solution was cooled to 40–50°, 3 g. of sodium hydride added and the mixture cooled so as to maintain the internal temperature at about 40°. When the exothermic reaction had subsided (15 minutes), the mixture was stirred at room temperature. After 2.5 hr., an equal volume of benzene was added followed by 10 ml. of acetic acid (with cooling) and 30 ml. of water. When the exothermic reaction moderated, more benzene was added, followed by 10 ml. of 33% hydrochloric acid with stirring to complete the decomposition of the sodium hydride. Excess hydrochloric acid was then added, and the aqueous layer extracted with ether–benzene. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent was triturated with hot methylcyclohexane to give 6.2 g. (70% yield) of acetoxy acid, m.p. 268–269° (reported[9c] 261.5–262.5°). The methyl ester was prepared with diazomethane. After crystallization from methanol, the product melted at 150–151° (reported 148.5–150.5°[9a] and 150.5–151.5°[9c]), yield 61%.

Methyl 3β-Acetoxy-14-iso-16-etioallocholenate (VIII, R = Ac, R′ = CH_3).—A solution of 0.548 g. of the dienic ester (VII, R = Ac, R′ = CH_3), m.p. 150–151°, in 92 ml. of thiophene-free benzene (distilled from Raney nickel) was hydrogenated over 0.2 g. of prereduced 30% palladium hydroxide-on-strontium carbonate[22] at room temperature and an initial pressure of 38 p.s.i. After 1.75 hr. one mole-equivalent of hydrogen had been absorbed and the reduction was proceeding very slowly. After 2 hr., the shaking was stopped, the mixture filtered and the filtrate evaporated. Crystallization of the oily residue from methanol gave 0.330 g. of colorless elongated prisms, m.p. 134–135°. Two recrystallizations from methanol followed by sublimation at 130° (0.05 mm.) gave a specimen, m.p. 140.5–141.5°, λ_{max} 226 mμ (log ε 3.89).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.8; H, 9.02.

3β-Acetoxy-14-iso-16-etioallocholenic Acid (VIII, R = Ac, R′ = H).—A solution of 2.00 g. of the dienic acid, m.p. 268 269°, in 62 ml. of purified (see above) benzene was hydrogenated over 0.6 g. of prereduced 30% palladium hydroxide-on-strontium carbonate[22] as described in the preceding experiment. After the absorption of one mole-equivalent of hydrogen, the reaction was interrupted and the crude product isolated as described above. The oily residue was crystallized from methylcyclohexane to give 1.16 g. (58% yield) of material, m.p. 188–190°, suitable for use in the remainder of the synthesis. Recrystallization from acetone raised the m.p. to 206–212° and further recrystallizations did not improve the m.p. The ultraviolet spectrum suggested the presence of traces of starting dienic acid, which was, in fact, isolated from the mother liquor of the first crystallization—on standing a second crop of 0.25 g. was deposited, and this on recrystallization from acetone gave starting material, m.p. 261–265°.

A sample of the first crop material was esterified with diazomethane giving, after recrystallization from methanol, material, m.p. 135–136.5°, undepressed on admixture with the product of hydrogenation of the dienic ester described in the preceding experiment.

14-Isoepiandrosterone (V, R = H).—A 2.00-g. sample of the crude unsaturated acid VIII (R = Ac, R′ = H), m.p. 185–190°, was dissolved in 12.5 ml. of pure thionyl chloride. After 15 hr. at 0°, then 1 hour at 20°, the excess reagent was evaporated at 15° under reduced pressure, the last traces being removed by repeated codistillation with benzene. The residual colorless crystalline acid chloride was dissolved in 80 ml. of purified dioxane[23] and 30 ml. of acetone, the mixture was cooled to 0°, then a solution of 2 g. of sodium azide in 12 ml. of water and 3 ml. of acetone was added. After 20 minutes at room temperature, the solution was diluted with cold water and extracted with ether. The ether layers were washed well with 10% potassium carbonate, then with water and dried over anhydrous sodium sulfate. The colorless solid obtained upon evaporation of the solvent was dissolved in 20 ml. of dry toluene and the toluene distilled at 20° under reduced pressure. More toluene was added and the distillation repeated to ensure removal of traces of moisture. The residue was dissolved in 30 ml. of dry toluene and the mixture heated on the steam-bath. After 10 minutes the evolution of nitrogen had subsided, and the solution was heated at reflux for an

(22) Footnote 39, paper III.

(23) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed. D. C. Heath and Co., Boston, Mass., 1941, p. 368.

additional 15 minutes. The oily residue obtained on evaporation of the toluene under reduced pressure crystallized on scratching.

The crude isocyanate obtained as described above was dissolved in 300 ml. of purified dioxane,[23] 30 ml. of 33% hydrochloric acid added, followed by 120 ml. of water and the mixture heated at reflux. After 6 hours, the solvent was evaporated and the residue heated at reflux for 1 hr. with 100 ml. of 5% sodium hydroxide in 1:2 aqueous methanol. Most of the methanol was removed at 30° under reduced pressure, water was added and the mixture extracted with ether–benzene. The organic layers were washed with water and dried over anhydrous magnesium sulfate. The partly crystalline residue obtained upon evaporation of the solvent was chromatographed on 40 g. of Florisil. The fraction eluted with 1:1 benzene–methylcyclohexane was recrystallized from methylcyclohexane to give 0.600 g. (37% yield) of 14-isoepiandrosterone, m.p. 162–164°. Two recrystallizations from methylcyclohexane followed by sublimation at 130° (0.05 mm.) gave colorless prisms, m.p. 166–168°, undepressed on admixture with a specimen prepared from 14-hydroxyepiandrosterone[4,7] (reported m.p. 161–164°).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.4; H, 10.78.

3β-Acetoxy-14-isoetioallohomobilianic Acid (IX, R = Ac, R′ = H).[24]—A 0.550-g. sample of 14-isoepiandrosterone, m.p. 162–164°, was treated with excess sodium methoxide and ethyl formate in benzene at room temperature overnight and the product isolated as previously described,[12] the alkali-soluble portion amounting to 0.567 g. (94% yield) of crude hydroxymethylene derivative, m.p. 193–194°.

The 0.567 g. of hydroxymethylene ketone was dissolved in 30 ml. of acetic acid, 0.500 g. of hydroxylamine hydrochloride added and the mixture stirred at room temperature. After 48 hr., the mixture was diluted with water and extracted with ether. The ether layers were washed with water, dried over anhydrous sodium sulfate and evaporated. The semi-solid residue was heated at reflux with 125 ml. of 5% potassium hydroxide and 0.125 g. of hydroxylamine hydrochloride in a steel flask. After 48 hr., the mixture was cooled, filtered and washed with ether. Acidification of the aqueous layer afforded a gummy precipitate which crystallized on scratching and was separated by filtration.

The crude hydroxy acid was acetylated with 50 ml. of phenyl acetate and 1.33 g. of sodium hydride as described above for the acetylation of the dienic acid VII (R = R′ = H). After stirring at room temperature for 3 hr. the product was isolated as described above and the crude oily product crystallized from ether to give 0.323 g. (46% yield), m.p. 270–275°. A sample twice recrystallized from methyl ethyl ketone and dried for 24 hr. at 0.05 mm. was obtained as small colorless blades, m.p. 282–283°.

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 66.75; H, 8.93.

The dimethyl ester was prepared from 0.040 g. of the diacid, m.p. 281–283°, by treatment with excess ethereal diazomethane. The crude oily product could not be crystallized; therefore it was evaporatively distilled twice at 130° (0.05 mm.) to yield 0.040 g. of colorless oil.

Anal. Calcd. for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07. Found: C, 68.0; H, 9.20.

The infrared spectrum of this specimen was indistinguishable from that of the totally synthetic racemic product, m.p. 98.5–100°.[25]

17-Benzylidene-D-homoepiandrosterone (XI, R = H, Ar = C_6H_5).—A solution of 0.202 g. of D-homoepiandrosterone acetate,[26] m.p. 124–126.5°, $[\alpha]^{29}D$ −42 ± 1° (*c* 1.045 in $CHCl_3$), in 6 ml. of methanol was treated with a solution of 0.103 g. of benzaldehyde in 2 ml. of methanol, followed by 2.2 ml. of 33% sodium hydroxide solution. The mixture was seeded and stored under nitrogen at room temperature for 3 days. The crystalline precipitate was separated and washed with dilute methanol followed by water. The yield of crude material, m.p. 189–196°, was 0.185 g. (81%). Repeated recrystallization from methanol gave colorless needles, m.p. 195.5–197.5°, λ_{max} 218 mμ (log ε 4.06), 283 (4.24); λ_{min} 240 (3.71). The material retained moisture tenaciously, even after drying for extended periods at 100° (0.1 mm.).

Anal. Calcd. for $C_{27}H_{36}O_2$: C, 82.60; H, 9.24. Found: C, 82.15; H, 9.39.

After standing several months the m.p. of this specimen was 192–203° with softening at 190°. This behavior may be due to partial (geometric) isomerization about the benzylidene double bond of the type encountered in similar structures.[25]

17-Furfurylidene-D-homoepiandrosterone Acetate (XI, R = Ac, Ar = C_4H_3O).—A 0.068-g. sample of crude D-homoepiandrosterone, m.p. 186–191° (prepared by saponification of the acetate),[26] was dissolved in 2 ml. of methanol; then 6 drops of 33% aqueous sodium hydroxide was added, followed by 0.1 ml. of furfural. After 3 hr. at room temperature, the crystalline precipitate was separated, washed thoroughly with dilute methanol and dried. This crude product was acetylated with 2 ml. of isopropenyl acetate and 0.02 g. of *p*-toluenesulfonic acid monohydrate in 5 ml. of benzene. After 3.5 hr. at reflux (nitrogen atmosphere), the crude product was isolated in the conventional manner and purified by dissolution in benzene and filtration through a small column of acid-washed activated alumina. The pale yellow solid isolated from the eluates melted at 183–185°. Two recrystallizations from petroleum ether (90–100°) gave pale yellow prismatic needles, m.p. 184.5–185° (transparent crystals becoming opaque at 100–113°, or after long standing at room temperature), λ_{max} 322.5 mμ (log ε 4.33).

Anal. Calcd. for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.4; H, 8.54.

The infrared spectrum of this compound was indistinguishable from that of the totally synthetic *dl*-substance, m.p. 192–192.5°.[27]

Dimethyl 3β-Acetoxyetioallohomobilianate (XII, R = Ac, R′ = CH_3). (a) By Degradation of Epiandrosterone.[24]—The hydroxymethylene derivative was prepared as described above for the 14-iso compound. From 2.32 g. of epiandrosterone, m.p. 175.5–176.5°, alcohol-free sodium methoxide (from 0.50 g. of sodium), 50 ml. of benzene and 15 ml. of ethyl formate, there was thus obtained 2.47 g. of crude hydroxymethylene ketone, m.p. 208–214° dec. The pure material is reported[28] to melt at 223–225.5° dec.

A 2.41-g. sample of the crude hydroxymethylene ketone was partially dissolved in 100 ml. of glacial acetic acid and 1.0 g. of hydroxylamine hydrochloride added. After shaking for 24 hr., 1 l. of water was added and the tan precipitate separated by filtration; yield 2.26 g., m.p. 120–140° dec.

Two grams of the above crude product was heated at reflux with 400 ml. of 5% potassium hydroxide containing 0.55 g. of hydroxylamine hydrochloride. After 32 hr., the product was isolated as described in the 14-iso series. The crude acid in methylene dichloride was esterified with excess ethereal diazomethane and the crude product chromatographed on 40 g. of acid-washed activated alumina. The 1:3 benzene–chloroform eluate amounted to 1.22 g. of colorless oil which could be induced to crystallize from methanol at low temperature. The crystalline portion (0.125 g.) melted poorly (72–79°) with previous softening and evolution of gas indicating tenacity for solvent; hence this substance was not investigated further.

The 1.02 g. of residual oil hydroxy ester was acetylated in benzene with isopropenyl acetate and *p*-toluenesulfonic acid. The crude product obtained after trituration with methanol was recrystallized from the same solvent to give 0.54 g., of colorless prisms, m.p. 153.5–161°, $[\alpha]^{30}D$ −21 ± 1° (*c* 0.300 in $CHCl_3$) or −16.5 ± 1° (*c* 0.685 in acetone). Sublimation at 155° (0.02 mm.) gave material, m.p. 154–158.5°, reported[13b] 155–156°.

Anal. Calcd. for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07. Found: C, 67.9; H, 8.99.

The infrared spectrum of the material was identical with that of the totally synthetic *dl*-compound, m.p. 136–137°.[27]

(24) An adaptation of procedures described in ref. 12.

(25) Paper VI, W. S. Johnson, E. R. Rogier and J. Ackerman, THIS JOURNAL, **78**, 6322 (1956).

(26) Prepared from epiandrosterone acetate by the procedure of Prins and Shoppee, ref. 13b.

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

(28) L. Ruzicka, V. Prelog and J. Battegay, *Helv. Chim. Acta*, **31**, 1296 (1948).

(b) **By Ozonolysis of the Benzylidene Derivative (XI, R = Ac, Ar = C_6H_5).**—A solution of 0.050 g. of the benzylidene acetate, m.p. 153–155° (prepared by acetylation of the hydroxy compound described above with isopropenyl acetate), in 5 ml. of ethyl acetate was ozonized at 0°. After 0.024 g. of ozone was introduced, 2 ml. of acetic acid, 0.5 ml. of water and 0.2 ml. of 30% hydrogen peroxide were added and the mixture allowed to stand at room temperature overnight. The mixture was evaporated, the residue dissolved in methylene dichloride and excess ethereal diazomethane added. The solution was washed with saturated sodium bicarbonate, then with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent and trituration with methanol–ether gave 0.021 g. of diester, m.p. 155–160°, undepressed on admixture with the specimen prepared as described in part a above.

3β,11β-Diacetoxyandrostane-17-one (XIV, R = Ac).[16]—A solution of 0.900 g. of 3β,11β,17α,21-tetrahydroxyallopregnane-20-one (Reichstein's substance V),[15] m.p. 230–232°, in 100 ml. of 50% aqueous acetic acid was stirred at room temperature with 18 g. of sodium bismuthate (80% purity) for 30 minutes. The mixture was then cooled to 0°, neutralized with cold 3 *N* potassium hydroxide to *p*H 6.5 and continuously extracted with ether at 5° for 12 hr. The ether layer was dried over anhydrous sodium sulfate and evaporated to give 0.640 g. of crude 3β,11β-dihydroxyandrostane-17-one. Crystallization from 95% ethanol gave 0.300 g. (first crop), m.p. 231–234°, and 0.160 g. (second crop), m.p. 227–234°, making the total yield 61%. The reported m.p. for the pure compound is 235–238°.[15] A specimen was converted to the monoacetate according to the described procedure,[29] and the m.p. was 227–230°, reported[29] 230–231°.

The diacetate was prepared as follows[30]: A solution of 0.020 g. of the dihydroxy ketone, m.p. 227–233°, in 1 ml. of acetic acid and 0.30 ml. of acetic anhydride containing 0.002 g. of *p*-toluenesulfonic acid was allowed to stand at room temperature for 20 hr. The precipitate obtained on dilution with water was separated by centrifugation, washed with water and dried; yield 0.024 g., m.p. 145–151°. Successive recrystallizations from 95% ethanol, methylcyclohexane and methanol gave colorless hexagonal prisms, m.p. 153.5–155°, reported[29] 154–156°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.25; H, 8.68.

The infrared spectrum of this specimen was identical with that of the totally synthetic compound, m.p. 217–217.5°.[1]

3β,11β-Dihydroxyandrostane-17-one was also prepared from 17α-hydroxycorticosterone (XV). The latter substance (3.4 g.) was hydrogenated in 95% ethanol solution over a total of 0.60 g. of 10% palladium-on-carbon at 30–40 p.s.i. and room temperature. The total crude product from this reaction was then reduced in 150 ml. of methanol with 3.1 g. of sodium borohydride in 30 ml. of water. The total crude product (fairly water-soluble) was oxidized with periodic acid as described by Reichstein[15] to give a total of 0.448 g. of crude dihydroxy ketone, m.p. 229–234°. Recrystallization from ethyl acetate afforded 0.312 g. of material, m.p. 236–237.2°.

The yields of the above experiment, which was tried only once, could undoubtedly be improved. An attempt to reduce 17α-hydroxycorticosterone with lithium and alcohol in ammonia directly to the pentahydroxy compound did not look promising.

3β,11β-Dihydroxyetioallohomobilianic Acid (XVI, R = R′ = H).[24]—The formylation procedure[12] was modified because of the insolubility of the dihydroxy ketone in benzene. A solution of 0.540 g. of 3β-11β-dihydroxyandrostane-17-one, m.p. 227–235°, and 5 ml. of dry ethyl formate in 65 ml. of tetrahydrofuran (dried by distillation from lithium aluminum hydride) were added at 0° to a suspension of alcohol-free potassium *t*-butoxide[27] (from 2.5 g. of potassium) in 125 ml. of anhydrous tetrahydrofuran. The mixture was stirred under nitrogen for 3 hr. at 0°, then for 15 hr. at room temperature and finally acidified with 5 ml. of acetic acid. The solvent was evaporated at 15–20° under reduced pressure, water was added and the suspension continuously extracted with ether for 5 hr. The ether solution was dried over anhydrous sodium sulfate and evaporated to give 0.654 g. of crystalline residue, which was completely soluble in 2% aqueous sodium hydroxide and gave an intense purple color with alcoholic ferric chloride. The weight of the product, which is in excess of the theoretical amount for the 16-formyl derivative, suggests that ester exchange may have occurred also to give the formate at C_3.

The crude hydroxymethylene derivative (0.754 g.) obtained as described above from 0.640 g. of dihydroxy ketone was dissolved in 50 ml. of glacial acetic acid, 0.337 g. of powdered hydroxylamine hydrochloride added and the mixture stirred at room temperature. After 36 hr., 0.5 g. of sodium acetate was added, most of the solvent evaporated at 25–30° under reduced pressure, water added and the suspension continuously extracted with ether for 4 hr. The crude residue obtained upon evaporation of the ether was heated at reflux with 140 ml. of 5% potassium hydroxide for 48 hr. The solution was then continuously extracted with ether for 15 hr. and the ether phase discarded. The aqueous solution was acidified with dilute sulfuric acid to *p*H 2[31] and again continuously extracted at 15° with ether for 2.5 hr. The ether phase was dried over anhydrous sodium sulfate and evaporated to give 0.676 mg. of crude diacid. (Continuous extraction for an additional 19 hours afforded 0.100 g. of material which was insoluble in the usual solvents and was discarded.) Crystallization from ether slowly deposited material which, after washing with methyl ethyl ketone, amounted to 0.107 g., m.p. 253–256°. Repeated recrystallization from methyl ethyl ketone gave colorless elongated prisms, m.p. 258–261°, λ_{max}^{mull} 2.82 μ (OH); 5.81; (*t*-RCOOH); 5.90 (COOH).

Anal. Calcd. for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75. Found: C, 65.0; H, 8.73.

Dimethyl 3β,11β-Diacetoxyetioallohomobilianate (XVI, R = Ac, R′ = CH_3).—The mother liquor residues (0.565 g.) from the ether crystallization of the dihydroxy diacid (see above) were dissolved in methanol and treated with excess ethereal diazomethane for 5 minutes. The residue obtained upon evaporation of the ether was acetylated (as above) with 6 ml. of acetic acid, 1.2 ml. of acetic anhydride and 0.06 g. of *p*-toluenesulfonic acid monohydrate. After 15 hr. at room temperature, water was added and the mixture extracted with ether. The organic layers were washed with 10% potassium bicarbonate, with water and dried over anhydrous sodium sulfate. The oily residue obtained upon evaporation of the solvent was chromatographed on 33 g. of Florex. The colorless oily fractions eluted with 9:1 to 4:1 benzene–ether amounted to 0.234 g. of practically pure dimethyl ester as shown by comparison of the infrared spectrum with that of the pure specimen described below.

A specimen of the crystalline dihydroxy diacid, m.p. 253–256°, was methylated and acetylated as described directly above to give an additional 0.120 g. of oily product. Chromatography yielded 0.080 g. of purer material. A center cut from this chromatogram was evaporatively distilled at 130° (0.03 mm.) to give a colorless oil.

Anal. Calcd. for $C_{26}H_{40}O_8$: C, 64.98; H, 8.39. Found: C, 65.3; H, 8.30.

The infrared spectrum (liquid film) of this material and the totally synthetic *dl*-compound, m.p. 131.5–133°,[1] were identical.

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(29) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 817 (1937).

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

(31) It should be noted that lactonization did not occur; *cf.* the 13-iso series, ref. 1.