TABLE II

PYROLYSIS OF ESTERS

| Ester[a] | Sample size, g. | Procedure used | Yield (%) olefins | Yield (%) alcohol |
|---|---|---|---|---|
| Me HP | 23.7 | A | 0[b] | 92[c] |
| *n*-Bu HP | 56 | A | 0[b] | 86[c] |
| *n*-Bu HP | 0.5 | B | 0[d] | 100[d] |
| *n*-Heptyl HP[e] | 6.0 | A | 9[d] | 91[d] |
| 4-Heptyl HP | 38.5 | A | 13[c] | 72 |
| *cis*-2MC HP | 8.5 | A | 0[d] | 86[c,f] |
| *trans*-2MC HP | 16.0 | A | 8[c] | 72[c] |
| *trans*-2MC HP | 0.5 | C | 0[d] | 100[d,g] |
| C HP | 6.0 | A | 0.4[d] | 99.6[d] (25[c]) |
| (−)-2-Octyl HP | 16.0 | A | 9 | 67[h] |
| $Bu_2P$ | 101.7 | A | 54[c] | 63[c] |
| $C_2P$ | 12.6 | A | 56[d] | 44[d] |
| $C_2P$ | 100.5 | A | 72[d] | 28[d] |
| EtHT | 6.7 | A | 28 max[i] | 72[c,j] |
| EtHA | 21.9 | A | 0[b] | Trace[d,k] |
| BuHM | 28 | A | 9 max[i] | 39[d,l,m] |
| $Bu_2M$ | 50 | A[m] | 10[c] | 13[c] |

[a] A = adipate, M = maleate, P = phthalate, T = tetrachlorophthalate, C = cyclohexyl, MC = 2-methylcyclohexyl. [b] Bromine solution unaffected. [c] Weighed product. [d] Relative amounts based on gas chromatography. [e] 4% of two other peaks, probably isomeric heptene and heptyl alcohol. [f] 4.5 g. phthalic anhydride in residue. [g] *trans*-2-Methylcyclohexanol (no *cis*). [h] $n^{20}D$ 1.4263, $[\alpha]^{20}D$ −8.8°, identical with original alcohol. [i] Bromine decolorized. [j] 17% of condensed distillate and the pot residue (m.p. 250–253° after recrystallization) is tetrachlorophthalic anhydride.[10] [k] Neut. equiv. 176 (theoretical for EtHA 174). Small volatile fraction of distillate is 5% ethanol, 70% probably $Et_2A$, 24 and 1% unknowns by gas chromatography. [l] 52% unknown, probably benzene and 9% $Bu_2M$ in condensate distillate. Pot residue is maleic anhydride. [m] Held at reflux 8 hr.

gave a sirup of neut. equiv. 137. This was used for the pyrolysis when further attempts at purification in the same manner proved fruitless. The material reacted with concentrated ammonia. Evaporation to dryness gave ammonium maleamate (20.6% nitrogen, calcd. for $C_4H_8O_3N_2$, 21.2%).[8]

**Pyrolysis of Esters.**—Three general procedures for the thermal decomposition of esters were used. A. Distillation at atmospheric pressure (see ref. 4). B. A sample was placed in a side-arm test tube, the mouth of the tube closed with a rubber stopper containing a stopcock, and the side arm with a rubber stopper only partially bored. The tube was evacuated, then the needle of a 5-ml. hypodermic syringe was inserted through the stopper into the side arm. The tube was heated until the syringe filled, and the sample was immediately injected into a gas chromatograph. C. Heating a sealed tube containing the sample.[9]

Details are given in Table II.

**Gas Chromatographic Analysis of Products.**—Most of the analyses were performed using a Beckman GC-2 gas chromatograph with an 8-ft. benzyl ether on firebrick column at 160°. Peak areas were determined with a planimeter, by counting squares, or by half-width and peak height measurements. Product identification was by comparison of retention time on any given day with known samples. In general, quantitative accuracy is limited chiefly by lack of proportionality of peak area with weight for dissimilar compounds, but for olefin–alcohol mixtures, the resulting error is less than 5%. A column of 6 ft. of benzyl ether and 6 ft of nitrophenyl ether was used for the analysis of methylcyclohexenes.

(8) We wish to thank Dr. Price Truitt, Denton, Texas, for this analysis.

(9) A sample of butyl hydrogen phthalate exploded on one occasion. Caution is suggested.

(10) Reported melting point of tetrachlorophthalic anhydride 256°; ref. *a* (Table I) p. 147.

# Steroids. CCXIV.[1] 2α-Hydroxymethylandrostane Derivatives

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Hydrogenation of 2-hydroxymethylene-3-ketoandrostanes and their methyl ethers afforded the corresponding 2α-hydroxymethyl and 2α-methoxymethyl derivatives, respectively. Reduction of 2-hydroxymethylene-3-keto-androstanes with lithium aluminum hydride also yielded the corresponding 2α-hydroxymethyl-3-keto steroids as the major products accompanied by the 2-methylene-3β-ol and 2α-hydroxymethyl-3β-ol derivatives. Several of the compounds described were found to possess a high degree of pituitary depression activity.

Condensation of ketones with ethyl formate, followed by catalytic hydrogenation of the resulting α-hydromethylene ketones in methanol over a palladium–charcoal catalyst has been found to be a convenient method for the introduction of an α-methyl substituent into a ketone,[2-4] and one that has been used frequently in these laboratories. However, no example of the hydrogenation of a hydroxymethylene ketone, unattended by hydrogenolysis of the hydroxyl function, appears to have been recorded in the literature

We have observed that catalytic hydrogenation of 2-hydroxymethylene-3-keto-androstanes in aqueous methanol or tetrahydrofuran over a 5% palladium–charcoal catalyst affords 2α-methyl-3-keto derivatives and, in addition, the previously undescribed 2α-hydroxymethyl-3-keto derivatives. The 2α (equatorial) assignment for the latter de-

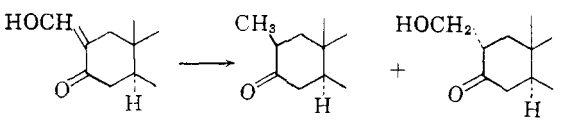



Figure 1

(1) Steroids. CCXIII. A. D. Cross, H. Carpio, and H. J. Ringold, in press.

(2) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **75**, 2567 (1953).

(3) H. J. Ringold, E. Batres, A. Halpern, and E. Necoechea, *ibid.*, **81**, 427 (1959).

(4) L. H. Knox, R. Villotti, F. A. Kincl, and H. J. Ringold, *J. Org. Chem.*, **26**, 501 (1961).

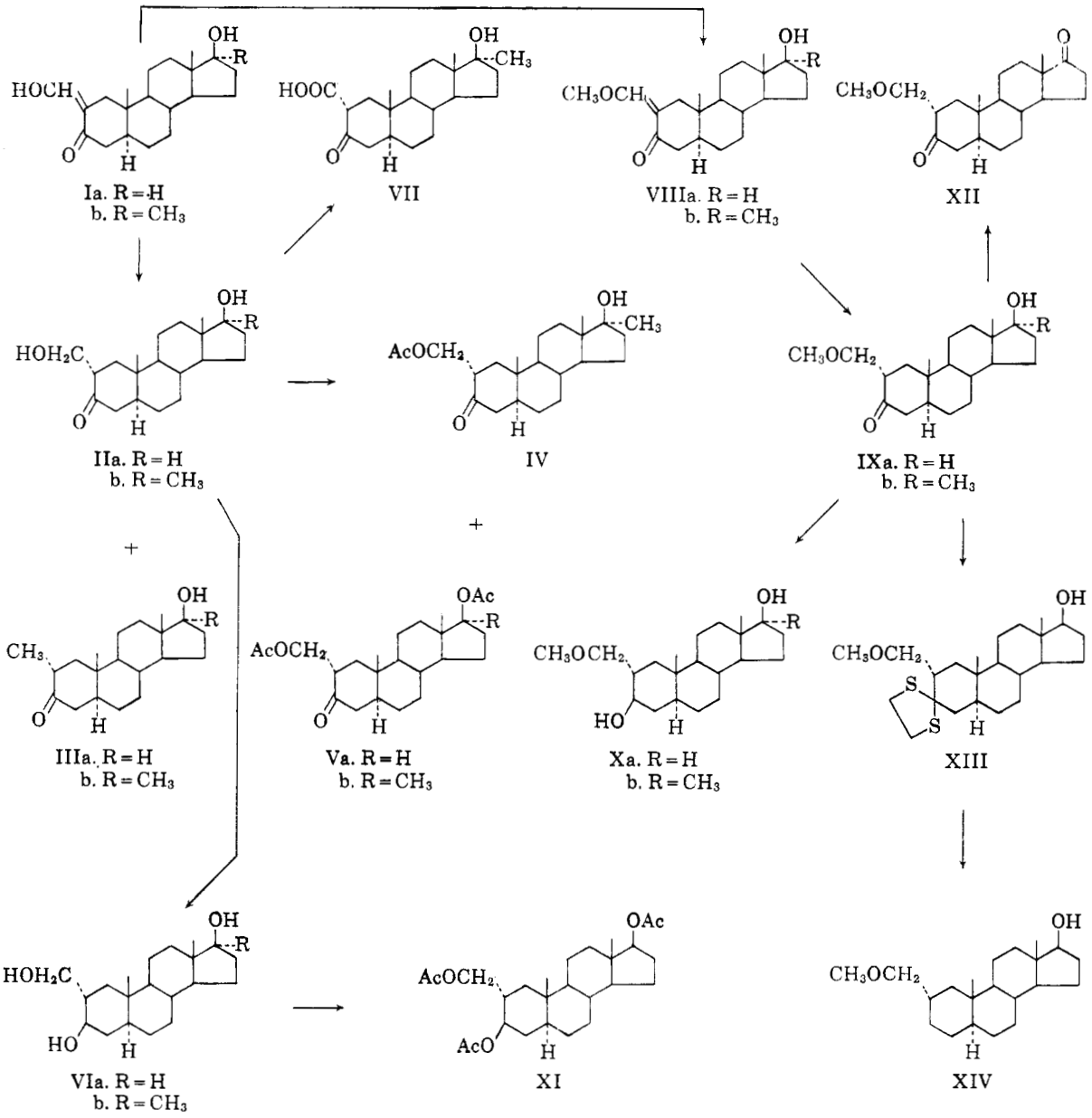



Figure 2

rivatives is inferred from their rotatory dispersions which are virtually the same as for dihydrotestosterone and 2$\alpha$-methyldihydrotestosterone. Equatorial methylation on either side of a 3-keto steroid does not significantly affect the amplitude of the dispersion curve relative to the parent 3-keto steroid. Axial methylation, while not altering the sign of the Cotton effect, does result in an increase in the amplitude of the dispersion curve.[5]

The ratios of the 2$\alpha$-methyl and 2$\alpha$-hydroxymethyl derivatives obtained is solvent dependent. Thus, Ringold and collaborators[3] obtained 2$\alpha$-methylandrostan-17$\beta$-ol-3-one (IIa), and 2$\alpha$,17$\alpha$-dimethylandrostan-17$\beta$-ol-3-one (IIIb) in 45–55% yields by hydrogenation of the corresponding hydroxymethylene derivatives (Ia and Ib) in methanol over a 10% palladium–charcoal catalyst. No other products were reported. In contrast, when the hydroxymethylene derivative (Ib) was hydrogenated over a 5% palladium–charcoal catalyst in aqueous methanol, the 2$\alpha$,17$\alpha$-dimethylandrostan-17$\beta$-ol-3-one (IIIb) was isolated in but 24% yield and the 2$\alpha$-hydroxymethyl-17$\alpha$-methylandrostan-17$\beta$-ol-3-one (IIb) in 53% yield. In tetrahydrofuran, Ib afforded a 79% yield of the 2$\alpha$-hydroxymethyl derivative (IIb) and 8% of impure IIIb. Catalytic hydrogenation of 2-hydroxymethylene-androstan-17$\beta$-ol-3-one (Ia) in tetrahydrofuran gave the 2$\alpha$-hydroxymethyl compound (IIa) in 50% yield. In these studies, the hydrogenation

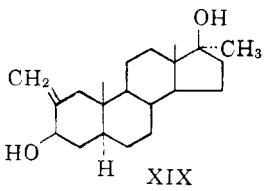
(5) C Djerassi, O. Halpern, V. Halpern, and B. Rineker, *J. Am. Chem. Soc.*, **80**, 4001 (1958).

products were isolated by direct crystallization or chromatography on silica gel and, regardless of solvent system, the 2α-methyl and 2α-hydroxymethyl derivatives were the sole isolable products.

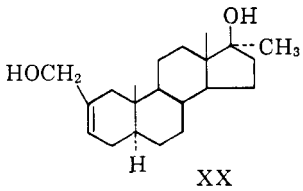
As would be expected of β-hydroxy ketones, these 2-hydroxymethyl-3-keto-androstane derivatives are sensitive to alkali and readily undergo elimination of water with formation of dimeric products (XIVa–b), presumably *via* the 2-methylene-3-keto derivative (XVa–b).[6,7] Thus, elution of 2α-hydroxymethylandrostan-17β-ol-3-one and 2α-hydroxymethyl-17α-methylandrostan-17β-ol-3-one from a column of alkaline alumina afforded in quantitative yields the dimeric products XVIa and XVIb, respectively.

Failure of other workers to observe the formation of 2-hydroxymethyl-3-keto derivatives in the hydrogenation of hydroxymethylene ketones may be ascribed to their method of work-up, designed to afford the 2α-methyl-3-ketones. It was assumed that catalytic hydrogenation led initially to the formation of the thermodynamically unstable 2α-methyl (axial) derivatives and from the gross hydrogenation mixtures, the 2α-methyl compounds could be isolated only by chromatography on alkaline alumina.[3] Under such conditions, any 2-hydroxymethyl-3-keto derivatives would be converted to the high melting dimeric products (XVIa and XVIb) which can be eluted from alumina only with highly polar solvents.

Reduction of Ib with an excess of lithium aluminum hydride in ether at room temperature also afforded IIb in 45% yield accompanied by 2-methylene-17α-methylandrostan-3β,17β-diol (XIX)[8] in 15% yield and the triol (VIb) in 3.5% yield. The presence of any trace of XX[9] in the reduction prod-



XIX



XX

uct could not be detected. These results are in contrast to those obtained by Dreiding and Hartman in their study of the reduction of enolizable β-dicarbonyl compounds by lithium aluminum hydride.[10] They found that reduction of 2-hydroxymethylenecyclohexanone with an excess of lithium aluminum hydride in refluxing ether afforded a mixture of 2-methylenecyclohexanol, 1-cyclohexene-

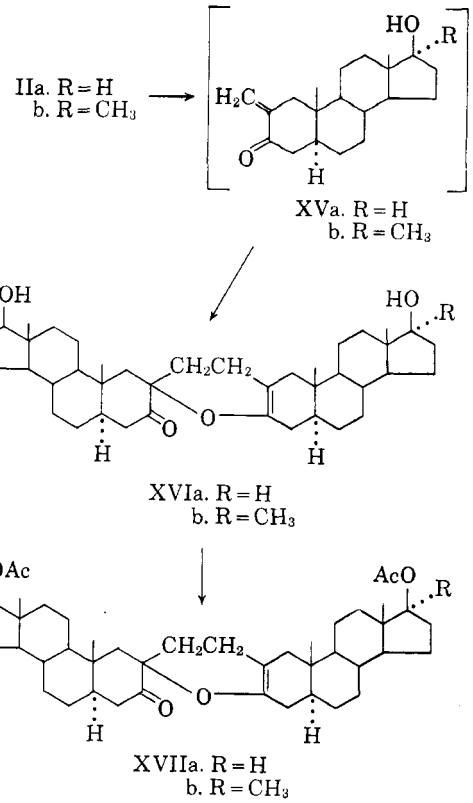


Figure 3

methanol, and 2-hydroxymethylcyclohexanol in a ratio of 5:2:1. Their interpretation of the formation of these products as involving hydride reduction of enolate ions and "normal" reduction of the un-enolized portion is one of several acceptable postulates. The differences in product formation and yields observed in the hydride reduction of 2-hydroxymethylenecyclohexanone and 2-hydroxymethylene-3-ketoandrostanes may be accounted for on the basis of differences in solubility of the intermediary enolate salts and aluminum hydride complexes.

Acetylation of IIa at room temperature readily afforded the diacetate (Va). Under similar conditions IIb gave a mixture of the mono- and diacetates (IV and Vb), readily separable by chromatography on silica gel.

Reduction of IIa and IIb with lithium aluminum hydride in ether or tetrahydrofuran gave the triols VIa and VIb, respectively. Acetylation of VIa readily afforded the triacetate (XI) but VIb gave only intractable oils.

The methoxymethylene ether (VIIIa) was readily obtained by refluxing Ia in methanol containing a catalytic amount of perchloric acid. Similar treatment of Ib yielded no crystalline product. However, treatment of Ib in methanol with ethereal diazomethane gave VIIIb in satisfactory yield. Hydrogenation of the ethers VIIIa and VIIIb in aqueous methanol or tetrahydrofuran afforded the saturated ethers IXa and IXb, which were reduced

(6) R. Mauli, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.* **82**, 5494 (1960).

(7) E. K. Dimroth, K. Resin, and H. H. Zetsch, *Ber.*, **73B**, 1399 (1940).

(8) This product was identical in melting point and spectral properties with a sample of XIX prepared by an alternative route; J. A. Edwards, M. C. Calzada, and A. Bowers, *J. Org. Chem.*, in press.

(9) The allylic alcohol (XX) has been prepared from Ib by an alternative method. J. C. Orr, O. Halpern, and A. Bowers, *J. Med. Pharm. Chem.*, **V**, 409 (1962).

(10) A. S. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.*, **75**, 939 (1953).

with lithium aluminum hydride to the corresponding diols Xa and Xb, respectively. Oxidation of IXa gave the dione XII. With ethanedithiol, IXb afforded the ethylenethioketal (XIII) in excellent yield which was desulfurized to the 3-desoxy derivative (XIV) by refluxing with aged Raney nickel in methanol.

Oxidation of IIb in acetone with chromic acid gave the $\beta$-keto acid (VII) in low yield. On heating above its melting point, carbon dioxide was evolved with formation of 17$\alpha$-methylandrostan-17$\beta$-ol-3-one.

**Biological Activity.**—Compounds IIa and IIb were found to be highly active in inhibiting the pituitary function in the parabiotic rat assay,[11] being about three times as active as testosterone and methyltestosterone, respectively. The androgenic potency of IIa was only 10% as compared to testosterone. Detailed results of these studies will be reported elsewhere.

## Experimental[12]

**2$\alpha$-Hydroxymethyl-17$\alpha$-methylandrostan-17$\beta$-ol-3-one (IIb). (a) By Catalytic Hydrogenation of 2-Hydroxymethylene-17$\alpha$-methyldihydrotestosterone (Ib) in Aqueous Methanol.**—A suspension of Ib (20 g.) in 180 ml. of methanol (distilled from potassium hydroxide) and 20 ml. of water was hydrogenated over a 5% palladium–charcoal catalyst (6.0 g.) at an initial hydrogen pressure of 50 p.s.i. Reduction was complete in 30 min. as evidenced by a negative ferric chloride test with methanolic ferric chloride solution. The gross reduction product was isolated as a crystalline residue which was recrystallized twice from acetone to yield pure IIb, 5.6 g. (28%), m.p. 198–200°; $[\alpha]_D$ +19.7°.

*Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25; O, 14.35. Found: C, 75.60; H, 10.16; O, 14.30.

The mother liquors were absorbed from a benzene solution on silica gel (700 g.). Elution with benzene–ether (4:1) afforded 4.8 g. (24%) of 2$\alpha$,17$\alpha$-dimethyldihydrotestosterone (IIIb), m.p. 133–135°, raised to 154–155° by crystallization from acetone. Its infrared spectrum was identical with that of an authentic sample.[3] Further elution with ether gave an additional 4.9 g. of IIb, m.p. 185–187°, raising the yield of IIb to 53%.

(b) **By Catalytic Hydrogenation of Ib in Tetrahydrofuran.** A solution of 20 g. of Ib in tetrahydrofuran (200 ml.) was hydrogenated over 6 g. of a 5% palladium–charcoal catalyst at an initial hydrogen pressure of 50 p.s.i. One equivalent of hydrogen was absorbed in 6 hr. On working up the hydrogenation mixture, a crystalline residue was obtained, m.p. 186–189°, 13.9 g. (72.8%), after a single recrystallization from acetone. Chromatography of the mother liquor on silica gel afforded 0.92 g. of oil, 1.57 g. of a partially crystalline solid consisting of impure IIIb, and finally an additional crystalline fraction consisting of IIb, m.p. 190–192°, 1.0 g., after crystallization from acetone raising the yield of IIb to 78.5%.

(c) **By Reduction of Ib with Lithium Aluminum Hydride.**—A suspension of 2.0 g. of Ib in 200 ml. of dry ether was added in 15 min. to a stirred solution of 2.0 g. of lithium aluminum hydride in 300 ml. of dry ether. After stirring for an additional 1.5 hr., excess hydride was destroyed by addition of ethyl acetate. Saturated aqueous sodium sulfate (20 ml.) was added followed by sufficient anhydrous solid sodium sulfate to give a clear supernatant ether solution. The mixture was filtered, the salt cake washed thoroughly with ether, and the combined ether solution evaporated to dryness. The crystalline residue, 1.8 g., from acetone deposited 0.340 g. of the 2$\alpha$-hydroxymethyl derivative (IIb), m.p. 174–176°, raised to 188–190° by a further recrystallization from acetone, and identical infrared spectrum with the IIb obtained by catalytic hydrogenation of Ib.

The combined mother liquors were adsorbed on Florisil (60 g.). Elution with benzene–ether (4:1) afforded a crystalline product (XIX), 290 mg., m.p. 229–230° after crystallization from acetone, m.p. 229–230° in admixture with an authentic sample of 2-methylene-17$\alpha$-methylandrostan-3$\beta$,17$\beta$-diol,[3] and identical with the authentic sample by infrared spectroscopy. Further elution with benzene–ether (4:1) yielded an additional 0.550 g. of IIb, m.p. 190–192° after crystallization from acetone.

Finally, elution with ether afforded 70 mg. of the triol (VIb), m.p. 260–265° from methanol. Its infrared spectrum was identical with that of VIb obtained as described below by lithium aluminum hydride reduction of IIb.

**2$\alpha$-Hydroxymethyldihydrotestosterone (IIa.)**—A solution of Ia (20.0 g.) in tetrahydrofuran was hydrogenated over 6.0 g. of a 5% palladium–charcoal catalyst at an initial hydrogen pressure of 50 p.s.i. After 48 hr., an absorption of 0.9 molar equivalents of hydrogen was observed. The product was isolated as described above affording an oil that crystallized on digestion with ether affording 13.3 g. of IIa, m.p. 160–162°, raised to 190–192° by two recrystallizations from acetone (10.0 g., 50%); $[\alpha]_D$ +39°.

*Anal.* Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06; O, 14.98. Found: C, 74.63, H, 9.98, O, 15.30.

**Acetylation of 2$\alpha$-Hydroxymethyl-17$\alpha$-methylandrostan-17$\beta$-ol-3-one (IIb).**—A solution of IIb (5.0 g.) in a mixture of 25 ml. of pyridine and 15 ml. of acetic anhydride was set aside at room temperature for 72 hr. Precipitation in water and extraction with ether afforded an oil (5.3 g.) which was adsorbed on 250 g. of silica gel. The crystalline fractions eluted with benzene–ether (4:1) were combined and crystallized from methanol to give 0.68 g. of the diacetate (Vb), m.p. 168–170°, raised to 170–171° by a further recrystallization from acetone; $[\alpha]_D$ ±0°.

*Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15; O, 19.11. Found: C, 71.69; H, 9.30; O, 19.53.

The crystalline fractions obtained by further elution with benzene–ether (1:1) were combined (4.34 g.) and crystallized from acetone affording the monoacetate (IV), m.p. 130–131°, raised to 133–135° by a further recrystallization from acetone; $[\alpha]_D$ −13.8°.

*Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64; O, 17.00. Found: C, 73.22; H, 9.68; O, 17.25.

**2$\alpha$-Hydroxymethylandrostan-17$\alpha$-ol-3-one Diacetate (Va).**—A solution of 0.80 g. of IIa in 4 ml. of pyridine and 2.4 ml. of acetic anhydride was allowed to stand at room temperature for 65 hr. The crude product, m.p. 115–117°, was isolated by dilution with water and filtration. Crystallization from methanol afforded pure Va, m.p. 130–132°; $[\alpha]_D$ ±0°.

*Anal.* Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.60; H, 8.99.

**2$\alpha$-Hydroxymethyl-17$\alpha$-methylandrostan-3$\beta$,17$\beta$-diol (VIb).**—A solution of 5.0 g. of IIb in 150 ml. of dry tetrahydrofuran was added dropwise with stirring to a suspension of 5.0 g. of lithium aluminum hydride in 300 ml. of tetrahydrofuran. After 1 hr., excess reagent was destroyed by addition of ethyl acetate. Ether (1 l.) was added to the reaction mixture followed by saturated aqueous sodium sulfate and solid sodium sulfate, respectively. Filtration and evaporation yielded the triol (VIb), 4.56 g., m.p. 275–277°, raised to 280–282° by recrystallization from methanol, $[\alpha]_D$ −37°.

*Anal.* Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 75.12; H, 10.84.

(11) E. G. Shipley, "Methods in Hormone Research," Vol. II, R. I. Dorfman, ed., The Academic Press, New York, N. Y., 1962.

(12) Melting points are uncorrected. Rotations are in chloroform unless otherwise stated. We are indebted to Dr. J. Matthews for rotations and spectral data.

**2α-Hydroxymethylandrostan-3β,17β-diol (VIa).**—A solution of IIa (1.0 g.) in 200 ml. of dry ether was added in 15 min. to a suspension of 2.0 g. of lithium aluminum hydride in 150 ml. of dry ether. After stirring at room temperature for 1 hr., the mixture was worked up as described above. Two recrystallizations of the crude product from acetone afforded pure VIa, m.p. 245–246°; $[\alpha]_D$ +8°.

*Anal.* Calcd. for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.40; H, 10.68.

**2α-Hydroxymethylandrostan-3β,17β-diol Triacetate (XI).** — Acetylation of VIa (300 mg.) in pyridine–acetic anhydride under the usual conditions, and crystallization of the crude product from methanol afforded the triacetate (XI), m.p. 162–163°; $[\alpha]_D$ −23.5°.

*Anal.* Calcd. for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99; O, 21.40. Found: C, 69.71; H, 9.00; O, 21.66.

**2-Methoxymethylene-17α-methylandrostan-17β-ol-3-one (VIIIb).**—To a suspension of Ib (7.88 g.) in 100 ml. of ether containing a few drops of methanol, an ethereal solution of diazomethane was added until nitrogen ceased to be evolved and a permanent yellow color denoting excess diazomethane was observed. A few drops of pyridine were added and the solution evaporated affording a crystalline residue. Recrystallization from acetone containing a few drops of pyridine gave 4.5 g. of the enol ether (VIIIb), m.p. 175–178°, raised to 178–180° after two further recrystallizations from acetone–pyridine; $[\alpha]_D$ +10°.

*Anal.* Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; O, 13.85. Found: C, 76.01; H, 9.43; O, 14.30.

**2α-Methoxymethyl-17α-methylandrostan-17β-ol-3-one (IXb).**—Hydrogenation of VIIIb (10.0 g.) in 100 ml. of tetrahydrofuran over 3.0 g. of a 5% palladium–charcoal catalyst at an initial hydrogen pressure of 50 p.s.i. absorbed 1 molar equivalent of hydrogen. Isolation of the product and crystallization from acetone afforded 5.47 g. of the saturated ether (IXb), m.p. 175–184°. The analytical sample was obtained by two further recrystallizations from acetone, m.p. 186–189°; $[\alpha]_D$ −12°.

*Anal.* Calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41; O, 13.77. Found: C, 75.60; H, 10.50; O, 14.36.

**2-Methoxymethyleneandrostan-17β-ol-3-one (VIIIa).**—A mixture of 10.0 g. of Ia and 125 ml. of methanol containing a few drops of perchloric acid was heated under reflux for 2 hr. Concentration and cooling afforded 6.2 g. of the methyl ether (VIIIa), m.p. 200–205°; $[\alpha]_D$ +46.9°.

*Anal.* Calcd. for $C_{21}H_{32}O$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.47; H, 9.73; O, 14.78.

**2α-Methoxymethylandrostan-17β-ol-3-one (IXa).**—Hydrogenation of VIIIa (6.2 g.) in a mixture of 50 ml. of methanol and 5 ml. of water over a 5% palladium–charcoal catalyst resulted in an uptake of 1 mole of hydrogen. Crystallization of the hydrogenation product from acetone gave 2.9 g. of the saturated ether IXa, m.p. 175–180°; $[\alpha]_D$ +23.5°.

*Anal.* Calcd. for $C_{21}H_{34}O_3$: C, 75.86; H, 9.70; O, 14.4. Found: C, 75.57; H, 9.75; O, 14.78.

**2α-Methoxymethylandrostan-3β,17β-diol (Xa).**—A solution of IXa (1.0 g.) in 125 ml. of dry ether was added in 15 min. to a stirred suspension of 1.0 g. of lithium aluminum hydride in 100 ml. of ether. Stirring was continued for 1 hr. and the mixture worked as described above. Crystallization of the crude product, m.p. 155–160°, from acetone, afforded 0.88 g. of Xa, m.p. 192–195°, raised to 200–202° by a further recrystallization from acetone; $[\alpha]_D$ +13.1°.

*Anal.* Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78; O, 14.26. Found: C, 75.05; H, 10.75; O, 14.03.

**Dimer of 2-Methyleneandrostan-17β-ol-3-one Acetate (XVIa).**—A solution of 2.0 g. of IIa in 200 ml. of acetone was absorbed in a column of alkaline aluminum for 16 hr. The dimer, XVIa, m.p. 265–267°, was isolated quantitatively by elution with acetone. Acetylation with acetic anhydride in pyridine afforded the diacetate (XVIIa), m.p. 250–251°, and was identical by infrared spectroscopy with an authentic sample.[5]

**Dimer of 2-Methylene-17α-methylandrostan-17β-ol-3-one (XVIb).**—The crude product obtained as an oil by hydrogenation of Ib in methanol (distilled from potassium hydroxide) as described above, was absorbed on washed alumina (900 g.). The crystalline fractions eluted with benzene–ether (7:3) were pooled (15.4 g.) and crystallized from acetone to give the dimer (XVIb), 6.1 g., m.p. 220–225°. A further recrystallization from acetone afforded the analytical sample, m.p. 229–230°; $[\alpha]_D$ +29°.

*Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19; O, 10.11. Found: C, 79.35; H, 10.28; O, 10.45.

**Acetylation of XVIb.**—A mixture of 1.8 g. of XVIb, 4 ml. of dry pyridine and 12 ml. of acetic anhydride was heated for 3 hr. at steam-bath temperature. The product was isolated in the usual manner. Several recrystallizations from methanol gave the pure diacetate XVIIb, m.p. 215–217°; $[\alpha]_D$ +53°.

*Anal.* Calcd. for $C_{46}H_{68}O_6$: C, 77.05; H, 9.56; O, 13.39. Found: C, 77.35; H, 9.71; O, 12.97.

**2α-Hydroxymethylandrostan-3α,17β-diol (XVIII).**—A solution of 2.0 g. of IIa in 50 ml. of methanol was shaken with 1.0 g. of a 5% palladium–charcoal catalyst at 4 atm. for 40 hr. Isolation of the product and crystallization from methanol afforded XVIII, m.p. 252–254°; $[\alpha]_D$ −10.5°; no CO absorption in the infrared.

*Anal.* Calcd. for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63; O, 14.89. Found: C, 74.90; H, 10.96; O, 14.59.

When 2α-methyldihydrotestosterone was similarly treated, it was recovered quantitatively.

**2α-Methoxymethylandrostan-17β-ol-3-one Ethylenethioketal (XIII).**—To a solution of IXa (2.0 g.) in 15 ml. of glacial acetic acid, a mixture of 0.9 ml. of ethane dithiol and 0.9 ml. of boron trifluoride etherate was added.[13] After 30 min. at room temperature, the partially crystalline mixture was diluted with water, filtered, washed to neutrality, and dried, affording 2.80 g. of crude XIII, m.p. 212–215°. A sample recrystallized once from ethanol had m.p. 221–223°, $[\alpha]_D$ −14°.

*Anal.* Calcd. for $C_{21}H_{34}O_2S_2$: C, 65.92; H, 8.96; S, 16.76. Found: C, 66.21; H, 9.17; S, 16.90.

**2α-Methoxymethylandrostan-17β-ol (XIV).**—A mixture of 2.3 g. of XIII, 500 ml. of methanol, and 62 g. of aged Raney nickel was refluxed for 36 hr. Filtration of the catalyst and evaporation afforded a crystalline mixture, m.p. 133–135° after two recrystallizations from acetone; $[\alpha]_D$ +13°.

*Anal.* Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32; O, 9.98. Found: C, 78.33; H, 11.13; O, 9.97.

**17α-Methylandrostan-17β-ol-3-one-2-carboxylic Acid (VII).**—A solution of IIb, 1.5 g., in 75 ml. of acetone (distilled from potassium permanganate) at 0° was treated with 2 ml. of 8 *N* chromic acid in sulfuric acid.[14] After stirring at 0° for 5 min., water was added and the product isolated by filtration. The crude product (0.67 g., m.p. 125–217°) was recrystallized several times from acetone to yield the analytical sample, m.p. 190–192°.

*Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.37. Found: C, 72.30; H, 9.28; O, 18.55.

A sample of VII was maintained at 195–200° in an oil bath until evolution of carbon dioxide ceased. Crystallization of the residue from acetone afforded 17α-methyldihydrotestosterone, m.p. 189–191°, undepressed in admixture with an authentic sample. Its infrared spectrum was identical with that of the authentic specimen.

**2α-Methoxymethylandrostan-3,17-dione (XII).**—To a solution of 0.57 g. of IXa in 25 ml. of pure acetone 0.5 ml. of 8 *N* chromic acid was added. The crude product was isolated by dilution with water and filtration. Crystallization from methanol afforded the analytical sample, m.p. 147–148°, $[\alpha]_D$ −78°.

*Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.81; H, 9.70.

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