ethyl acetoacetate. Treatment of 20.9 g. (0.1 mole) of the product with 20 g. (0.104 mole) of cupric acetate in 400 ml. of water yielded a solid copper chelate (13.5 g.; 56%) which after cooling, filtration, and recrystallization from hexane melted at 143–146°.

Anal. Calcd. for $C_{12}H_{16}O_6Br_2Cu$: C, 30.0; H, 3.34; Cu, 13.13. Found: C, 30.54; H, 3.26; Cu, 13.07.

β-Iodoethyl acetoacetate. Forty-two grams (0.2 mole) of β-bromoethyl acetoacetate was dissolved in the smallest quantity of acetone capable of dissolving 60 g. (0.4 mole) of sodium iodide. After refluxing the solution for 3 hr., the mixture was poured into 1.5 l. of water and extracted with ether. The ether was removed under a nitrogen stream. The residue was rectified to yield 31.7 g. (62%) of product b.p. (10 mm.) 140–144°, b.p. (0.5 mm.) 83–85°, n_D^{25} 1.5151.

Anal. Calcd. for $C_6H_9O_3I$: C, 28.1; H, 3.52. Found: C, 28.21; H, 3.66.

The product gave a positive test for iodine[3] and had an infrared spectrum consistent with the structure of β-iodoethyl acetoacetate.

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Isomeric 16-Bromo-D-homo Steroids

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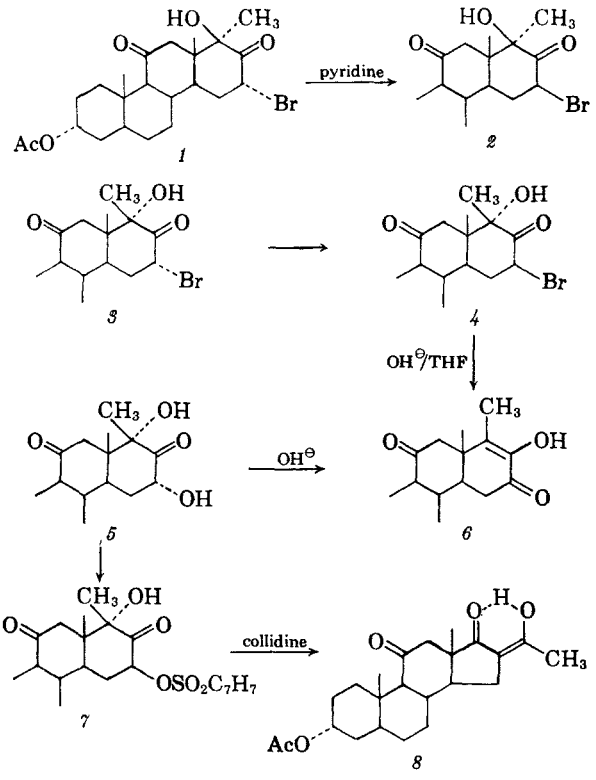
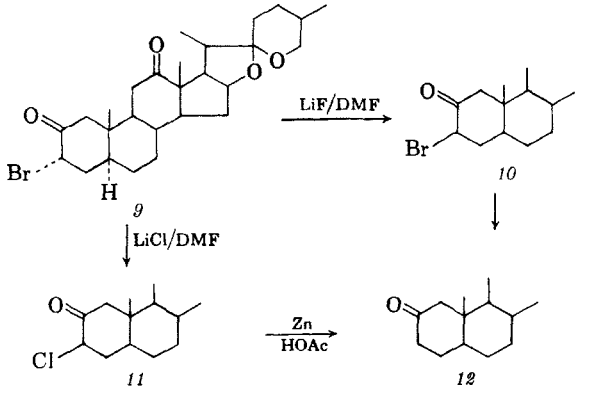
The primary monobromination products of 3α-acetoxy - 17a,β - hydroxy - 17a,α - methyl - 5β-androstane-11,17-dione and 3α-acetoxy-17a,α-hydroxy-17a,β-methyl-5β-androstane-11,17-dione[1] are respectively the axial 16α-bromo derivatives *1* and *3*. Both of these derivatives are labile and pass readily into the corresponding equatorial 16β-isomers *2* and *4* (see below). The axial configuration of *1* and *3* was ascertained in the case of the latter isomer, *3*, by bromination of the free diol, 3α-17a,α-dihydroxy-17a,β-methyl-5β-androstane-11,17-dione to a product possessing a single carbonyl band in the infrared at 5.86 μ; the latter is consistent with the combined absorption of the 11-carbonyl together with an unperturbed 16-axial (α) bromo-17-ketone function.[2] After isomerization of this product with hot pyridine, its infrared spectrum exhibited in addition to the 11-carbonyl absorption at 5.86 μ a new band at 5.76 μ indicating a 16 equatorial (β) bromo-17-ketone group.[2]

All attempts to dehydrohalogenate the isomeric bromo ketones *1–4* with either refluxing pyridine, collidine, or sodium acetate in acetic acid at 100° were unsuccessful. The products in all cases were essentially the respective equatorial isomers *2* and *4*. It is apparent that the rate of epimerization exceeds the rate of elimination wherein the equatorial bromides are geometrically unfavorable and the β-hydrogens probably less accessible for *trans*-elimination. This is doubtlessly an over-simplification since the epimeric 3-bromo-2-keto sapogenin derivatives *9* and *10* also resist dehydrohalogenation with refluxing pyridine or collidine. Treatment of *9* on the other hand with lithium chloride in dimethylformamide at 100° produced the 3β-chloro ketone *11* whereas lithium fluoride under the same conditions converted *9* to *10*.[3]





Treatment of *4* with hot aqueous alkali in tetrahydrofuran afforded the known diosphenol *6*, also formed from the diolone *5* under comparable

(1) N. L. Wendler, D. Taub, S. Dobriner, and D. K. Fukushima, *J. Org. Chem.*, **78**, 5027 (1956).

(2) R. N. Jones, D. A. Ramsey, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).

(3) R. R. Engle and C. Djerassi (Abstracts of the 134th Meeting of the American Chemical Society, September 1958, p. 15-0) have indicated unusual behavior in the dehydrohalogenation of a comparable 3-bromo-2-ketone.

conditions.[4] The *p*-toluenesulfonate derivative of the diolone *5*, namely *7*, likewise did not respond to elimination with refluxing collidine but suffered instead ring contraction to the 3-acetate derivative of the known β-diketone *8*.[5] The latter consequence was also indicated when *5* was treated with zinc dust in refluxing acetic acid.

EXPERIMENTAL

3α-Acetoxy-16α-bromo-17a,β-hydroxy-17a,α-methyl-5β-androstane-11,17-dione (1). A solution of 390 mg. of 3α-acetoxy-17a,β-hydroxy-17a,β-methyl-5β-androstane-11,17-dione in 10 cc. of chloroform was treated with 1 drop of 16% hydrogen bromide in acetic acid followed by 160 mg. of bromine in 5 cc. of chloroform. Bromine absorption was very slow and became complete only after several hours. Evaporation of the solvent and addition of ether caused crystallization. Recrystallization from ether afforded *1* as needles (wt. 150 mg.) m.p. 195–198°.

Anal. Calcd. for $C_{23}H_{33}O_5Br$: C, 58.85; H, 7.04; Br, 17.06. Found: C, 58.79; H, 7.07; Br, 16.96.

The mother liquors afforded 200 mg. of *2* (see below).

A 100-mg. sample of *1* in 10 cc. of pyridine was refluxed for 1 hr. At the end of this period the solvent was evaporated and the product crystallized from ethyl acetate to afford *3α-acetoxy-16β-bromo-17a,β-hydroxy-17a,α-methyl-5β-androstane-11,17-dione (2)*, m.p. 223–226°.

Anal. Found: C, 59.36; H, 7.40; Br, 16.92.

A small amount of pyridinium salt formation was also indicated.[6] The isomer *2* could also be isolated from the mother liquors of *1* and was the only isolated product when the original bromination was allowed to stand overnight before isolation.

3α-Acetoxy-16α-bromo-17a,α-hydroxy-17,a,β-methyl-5β-androstane-11,17-dione (3). A 390-mg. sample of 3α-acetoxy-17a,α-hydroxy-17a,β-methyl-5β-androstane-11,17-dione in 10 cc. of chloroform containing 1 drop of 16% hydrogen bromide in acetic acid was treated dropwise with 160 mg. of bromine in 5 cc. of chloroform at 0°. Bromination set in only after removal of the ice bath and was markedly more rapid than the corresponding formation of *1*, being complete within an hour. Removal of the solvent *in vacuo* and crystallization of the residue from ether afforded *3* as small prisms, m.p. *ca.* 125–130° (wt. 250 mg.)

Anal. Found: C, 59.20; H, 7.21; Br, 16.99.

This isomer, despite numerous attempts, was probably never obtained completely free of the 16β-isomer as adjudged by its low, uncertain melting point and the results of N.M.R. examination, showing multiple 18-methyl resonances.

A 200-mg. sample of *3* in 5 cc. of pyridine was refluxed for 1 hr. The product was precipitated by addition of water, extracted with ethyl acetate and crystallized from the same solvent to give *3α-acetoxy-16β-bromo-17a,α-hydroxy-17a,β-methyl-5β-androstane-11,17-dione 4*, m.p. 205–207°.

Anal. Found: C, 59.15; H, 7.03; Br, 16.82.

This compound, *4*, was recovered essentially unchanged after refluxing with collidine for 1 hr. or heating for a prolonged period of time with sodium acetate in acetic acid at 100°.

A 600-mg. sample of 3α-acetoxy-17a,α-hydroxy-17a,β-methyl-5β-androstane-11,17-dione was hydrolyzed with hot methanolic potassium hydroxide. Bromination of the hydrolyzed product (500 mg.) with 230 mg. of bromine in 30 cc. of chloroform provided a noncrystalline bromide, $\lambda_{max}^{CHCl_3}$ 5.86 μ (11C=O, 16αBr-17C=O). The latter was refluxed 1 hr. in pyridine (10 cc.); the product had $\lambda_{max}^{CHCl_3}$ 5.86 and 5.76 μ.

Formation of diosphenol 6. A solution of 200 mg. of *4* in 20 cc. of tetrahydrofuran containing 5 cc. of 10% aqueous potassium hydroxide was refluxed for 1 hr. Evaporation of the tetrahydrofuran followed by acidification of the aqueous residue precipitated the diosphenol *6*. The latter was extracted with ethyl acetate and crystallized from the same solvent, m.p. 277–281°; mixed melting point with authentic *6* not depressed. The infrared spectra of the two samples were the same.

3α-Acetoxy-16α-p-toluenesulfonoxy-17a,α-hydroxy-17a,β-methyl-5β-androstane-11,17-dione 7. A 400-mg. sample of 3α-acetoxy-16α,17a,α-dihydroxy-17a,β-methylandrostane-11,17-dione in 5 cc. of pyridine was treated with 220 mg. of *p*-toluenesulfonyl chloride at room temperature for 18 hr. The reaction product was precipitated with ice water, extracted with ether and crystallized from this solvent, m.p. 161–162°; 450 mg.

Anal. Calcd. for $C_{30}H_{40}SO_7$: C, 64.29; H, 7.14; S, 5.71. Found: C, 63.91; H, 7.07; S, 5.61.

Treatment of tosylate 7 with collidine. A solution of 100 mg. of *7* in 10 cc. of collidine was refluxed for 2 hr. At the end of this period the collidine was evaporated *in vacuo* and the residue extracted with ether. The ether extract was freed of traces of collidine with dilute aqueous hydrochloric acid. Concentration of the dried ether solution deposited crystals of *3α-acetoxy-16-acetyl-5β-androstane-11,17-dione (8)*. Recrystallization from ether gave material, m.p. 160–161°, $\lambda_{max}^{CH_3OH}$ 285 μ, ε 7,500.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.09; H, 8.25. Found: C, 70.62; H, 8.17.

Hydrolysis of *8* with dilute methanolic potassium hydride afforded *3α-hydroxy-16-acetyl-5β-androstane-11,17-dione*, m.p. 171–172°, identical with an authentic specimen[5] by mixed melting point and infrared comparison.

3α-Bromo-5α,22β-spirostane-2,12-dione 9 was prepared as previously described[7] and crystallized from acetone, m.p. 235–238°, $\lambda_{max}^{CHCl_3}$ 5.87 μ.

Anal. Calcd. for $C_{27}H_{39}O_4Br$: C, 63.90; H, 7.75; Br, 15.7 Found: C, 63.67; H, 7.60; Br, 15.68.

A 100-mg. sample of *9* was heated at 100° in 5 cc. of dimethylformamide containing 50 mg. of lithium fluoride for 1 hr. The solvent was evaporated *in vacuo* and the residue partitioned between ethyl acetate and water. Evaporation of the dried ethyl acetate layer and crystallization of the residue from acetone-ether afforded *3β-bromo-5α,22β-spirostane-2,12-dione 10*, m.p. 214–219°, $\lambda_{max}^{CHCl_3}$ 5.8 and 5.84 μ.

Anal. Found: C, 64.01; H, 7.59; Br, 15.73. Treatment of *10* with zinc in acetic acid as previously described[7] provided the 2-ketone *12*.

2β-Chloro-5α,22β-spirostane-2,12-dione 11. A solution of 500 mg. of the α-bromo ketone *9* in 14 cc. of dimethylformamide containing 278 mg. of lithium chloride was heated at 100° for 2 hr. The reaction mixture was cooled and the product precipitated with water, filtered and crystallized from methanol, m.p. 265–267° dec., $\lambda_{max}^{CHCl_3}$ 5.80 and 5.86 μ.

Anal. Calcd. for $C_{27}H_{39}O_4Cl$: C, 70.03; H, 8.49; Cl, 7.60. Found: C, 70.02; H, 8.50; Cl, 8.15.

A bromine analysis on the above material revealed the absence of this element.

Reduction of a 250-mg. sample of *11* in 20 cc. of refluxing acetic acid containing 2.5 g. of zinc dust for 1 hr. produced the 2-ketone *12* identical with an authentic sample.

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