The yield was 0.65 g., m.p. 269–271 dec., $[\alpha]^{25}D$ −21° (*c*, 4 in acetone). The infrared spectrum was slightly different from that of the racemic material when potassium bromide discs were used, but with acetone solutions the spectra were identical.

Anal. Calcd. for $C_{15}H_{12}O_6$: C, 62.50; H, 4.17. Found: C, 62.50; H, 4.31.

Tetraacetate from Optically Active Eriodictyol.—The above eriodictyol (0.200 g.) was dissolved in a mixture of 2.5 ml. of acetic anhydride and 1.0 ml. of pyridine and the solution allowed to stand 16 hr. It was then poured into water and allowed to stand overnight in the refrigerator. The crystals of eriodictyol tetraacetate which were recovered in nearly quantitative yield melted at 113–117°. Two crystallizations from ethanol yielded 0.230 g. of colorless needles, m.p. 120–122°, $[\alpha]^{25}D$ +11° (*c*, 4 in chloroform).

Bromination of 17-Oxo Steroids with Cupric Bromide[1]

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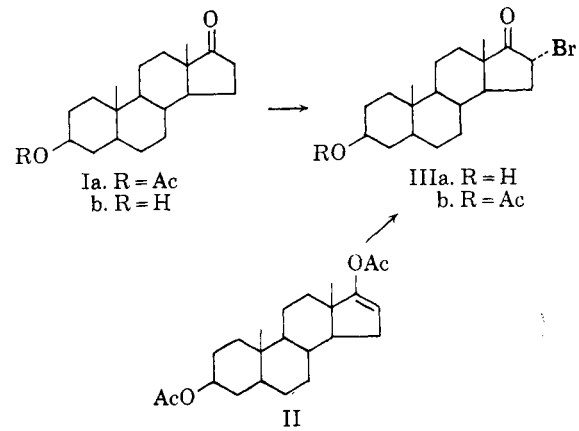
Formation of 16α-bromo-17-oxo-androstanes has been best achieved by bromination of the 17-enol acetates[2,3] since direct bromination of the 17-ketone has generally given poor results.[2,4] Kochi[5] has shown that aliphatic ketones can be halogenated with cupric halides. More recently, cupric bromide was reported to give excellent yields of α-bromocyclohexanones[6] and α-bromo aliphatic aldehydes.[7] In view of these results, it was felt that direct bromination of 17-ketosteroids might be readily achieved by the use of this reagent. This result has been attained, with some measure of success, in the formation of 16α-bromo-17-oxoandrostanes either directly from the 17-ketone or indirectly from the 17-enol acetate.

From 3β-acetoxy-5α-androstan-17-one (Ia) or 3β,17-diacetoxy-5α-androst-16-ene (II), 3β-hydroxy-16α-bromo-5α-androstan-17-one (IIIa) could be obtained in yields of 48% and 60%, respectively. Bromination of 3β-hydroxy-5α-androstan-17-one (Ib) was achieved to yield 59% of IIIa.

Saponification of the 3β-acetoxy group could be avoided by addition of a small amount of pyridine to the reaction. In this way, 3β-acetoxy-16α-bromo-5α-androstan-17-one (IIIb) was obtained from the 17-enol acetate, but the product was not easily purified nor was the yield large. An attempt



to prepare IIIb, retaining the 3β-acetoxy group, from Ia by using pyridine in the reaction was not successful. The infrared spectrum of the product after chromatography on silica gel indicated that there was no saponification, but even after recrystallization only a mixture was obtained. Fajkos[2] has shown that under the basic conditions of sodium borohydride reduction of 16α-bromo-17-ketones, epimerization of bromine occurs. It is possible that mixtures of the 16-epimers are being obtained under the mildly basic conditions in the presence of pyridine.

An attempt was made to form the 16,16-dibromo-17-ketone by using a larger amount of cupric bromide, but the only compound which could be isolated after chromatography was the monobromo ketone IIIa.

Experimental[8]

1. 3β-Hydroxy-16α-bromo-5α-androstan-17-one (IIIa).—A. 3β-Acetoxy-5α-androstan-17-one (Ia) (1.66 g., 0.005 mole) and cupric bromide (2.24 g., 0.01 mole) were dissolved in 250 ml. of methanol and the solution was refluxed for 24 hr. During this time a white precipitate formed and the solution lightened in color. The reaction mixture, after filtration, was evaporated *in vacuo* to a brown paste. To the paste were added 200 ml. of chloroform and 400 ml. of water, which mixture on shaking became almost colorless. The chloroform was separated and the aqueous layer was extracted twice more with 100-ml. portions of chloroform. The combined organic layers were dried over anhydrous magnesium sulfate and then evaporated *in vacuo* to yield white crystals. After two recrystallizations from acetone–heptane, there was obtained 800 mg. (48%) of IIIa as white needles, m.p. 155–156.5°; $[\alpha]^{27}D$ +60° (*c* 2.26) [reported values[9]: m.p. 164–165°; $[\alpha]^{20}D$ +52° (*c* 2.18)]. The infrared spectrum had bands at 3500 and 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{29}BrO_2$: C, 61.78; H, 7.79; Br, 21.64. Found: C, 61.56, 61.53; H, 7.78, 7.90; Br, 21.97, 22.19.

B. 3β-Hydroxy-5α-androstan-17-one (Ib) (2.90 g., 0.01 mole) and cupric bromide (4.48 g., 0.02 mole) were put into 400 ml. of methanol and the solution was refluxed for 24

(1) This work was supported by a grant from G. D. Searle & Co., Chicago, Illinois.

(2) J. Fajkos, *Collection Czech. Chem. Commun.*, **20**, 312 (1955).

(3) J. Fajkos and F. Sorm, *ibid.*, **24**, 766 (1959).

(4) Donnenberg, thesis, Danzig, p. 33 (1938); "Elsevier Encyclopedia of Organic Chemistry," Vol. 14, F. Radt, ed., Springer Verlag, Berlin, 1959, p. 2706s.

(5) J. K. Kochi, *J. Am. Chem. Soc.*, **77**, 5274 (1955).

(6) A. W. Fort, *J. Org. Chem.*, **26**, 765 (1961).

(7) C. E. Castro, *ibid.*, **26**, 4183 (1961).

(8) Melting points were taken on a Kofler block and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord 137 in chloroform solution. Optical rotations were measured in chloroform solution. The silica gel used for chromatography was grade 923 obtained from Davison Chemical Corp., Baltimore, Maryland. Elemental analyses were by Weiler & Strauss, Oxford, England.

(9) J. Fajkos, *Collection Czech. Chem. Commun.*, **23**, 1559 (1958).

hr. The work-up was identical to that in 1-A. The crude product, after two recrystallizations from chloroform–heptane, yielded 2.22 g. (59%) of IIIa as white needles, m.p. 161.5–163°. A mixture melting point with bromo ketone from 1-A showed no depression, and the infrared spectra were identical.

C. 3β,17-Diacetoxy-5α-androst-16-ene (II)[10] (1.87 g., 0.005 mole) and cupric bromide (2.24 g., 0.01 mole) were dissolved in 300 ml. of methanol. The solution was refluxed for 24 hr. After a similar work-up as in 1-A, white crystals were obtained which, after two recrystallizations from acetone–heptane, yielded 1.12 g. (60%) of IIIa as white needles, m.p. 156–157.5°; $[\alpha]^{27}D$ +60° (*c* 2.00). A mixture melting point with material from 1-A showed no depression, and the infrared spectra were identical.

D. 3β-Acetoxy-16α-bromo-5α-androstan-17-one (IIIb, see below) (600 mg.) was dissolved in a mixture of 10 ml. of 48% hydrobromic acid, 10 ml. of chloroform, and 40 ml. of methanol and the solution was stirred at room temperature overnight. After evaporation to one-half volume *in vacuo* at room temperature, the residue was poured into water and the resulting mixture was cooled in a refrigerator. The white crystals which had formed were separated by filtration, washed well with water, and dried *in vacuo* at 60°. After two recrystallizations from chloroform–heptane, there was obtained 540 mg. of IIIa as white needles, m.p. 158.5–159.5°; $[\alpha]^{26}D$ +50° (*c* 2.26). A mixture melting point with material from 1-A showed no depression, and the infrared spectra were identical.

2. **3β-Acetoxy-16α-bromo-5α-androstan-17-one (IIIb).**—A. 3β,17-Diacetoxy-5α-androst-16-ene (II) (1.87 g., 0.005 mole) and cupric bromide (2.24 g., 0.01 mole) were dissolved in 300 ml. of methanol. Pyridine (850 mg.) was added, causing an immediate heavy green precipitate. The mixture was refluxed for 24 hr. at which time the solution had become light green and a black precipitate had formed. After filtration, the solution was evaporated to a paste, which was taken up in chloroform and water and shaken. The organic layer was separated and the aqueous solution was extracted twice more with chloroform. After being combined and dried, the organic extract was evaporated *in vacuo* to a mixture of green glass and crystals. This residue was chromatographed on 100 g. of silica gel. Elution with 5% ether in benzene yielded a white solid from which, after two recrystallizations from chloroform–heptane, there was obtained 834 mg. (44%) of IIIb as white plates, m.p. 166–167°; $[\alpha]^{27}D$ +41° (*c* 2.69) [reported values[9]: m.p. 171–172°; $[\alpha]^{20}D$ +38° (*c* 2.14)]. The infrared spectrum had bands at 1750, 1725, and 1250 (br.) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{31}BrO_3$: C, 61.31; H, 7.60; Br, 19.43. Found: C, 61.41, 61.43; H, 7.62, 7.70; Br, 19.44, 19.18.

B. 3β-Hydroxy-16α-bromo-5α-androstan-17-one (IIIa) (510 mg.) was dissolved in 15 ml. of pyridine and 5 ml. of acetic anhydride. After standing at room temperature for 24 hr., the solution was poured into a large volume of water. The resulting white solid was collected by filtration, dried, and recrystallized twice from methanol to yield IIIb (266 mg.) as white plates, m.p. 164–165°; $[\alpha]^{25}D$ +42° (*c* 2.47). A mixture melting point with the 3β-acetoxy bromo ketone from 2-A showed no depression, and the infrared spectra were identical.

3. **Attempted Preparation of 3β-Hydroxy-16,16-dibromo-5α-androstan-17-one.**—3β-Hydroxy-5α-androstan-17-one (1.45 g., 0.005 mole) and cupric bromide (4.48 g., 0.02 mole) were dissolved in 200 ml. of methanol and refluxed for 24 hr. The usual work-up afforded white crystals which were chromatographed on 70 g. of silica gel. Only one compound was eluted, with 25% ether in benzene. After recrystallization twice from acetone–heptane, 1.20 g. of white needles was obtained, m.p. 160–161°; $[\alpha]^{25}D$ +60° (*c* 2.80). A mixture melting point with (IIIa) prepared above showed no depression and the infrared spectra were identical.

(10) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2941 (1954).

Chromic Acid Oxidation of Organoboranes. A Convenient Route to 6-Keto Steroids

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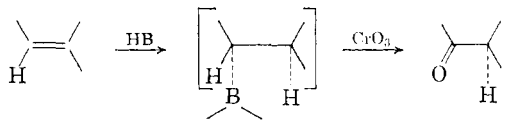
A conventional route to 6-keto steroids from Δ^5-compounds is *via* nitration with fuming nitric acid.[1] The reagents involved and the critical nature of the reaction[2] make this method unsuitable for large scale work. A recent report by Brown and Garg[3] of a one-step procedure for converting olefins to ketones, and the fact[4] that diborane reduces



esters comparatively slowly, prompted us to investigate the scope of this method to obtain 6-keto steroids, from their 3β-acetoxy C-5 unsaturated progenitors.

Using a modified hydroboration procedure, 3β,20β-diacetoxypregn-5-ene (I) was converted into monoketone (III, 48%)[5] and diketone (IV, 14%). The structure of ketone III was confirmed by its independent[6] synthesis from I, *via* nitration by concentrated nitric acid and sodium nitrite, followed by treatment with zinc and acetic acid. The structure of diketone IV was established by its conversion to 20β-acetoxy-5α-pregnane (VII).

3β-Acetoxy-17α-methyl-17β-carbomethoxyandrost-5-ene (II) on treatment with diborane, followed by oxidation with chromium trioxide, gave monoketone (V, 34%)[5] and diketone (VI, 14%). The structure of compounds V and VI are supported by their elemental analysis and their infrared spectra. When a tenfold excess of reagents was used either in the ether–diglyme medium or in dry tetrahydrofuran, excessive destruction of acetate groups was observed. From two such experiments with diacetate (I), 5α-pregnan-3,6,20-trione was isolated in

(1) (a) A. Bowers, M. B. Sanchez, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 3802 (1959). (b) C. E. Anagnostopoulos and L. F. Fieser, *ibid.*, **76**, 532 (1954).

(2) See footnote 12 and 24 in ref. 1a.

(3) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2951 (1961).

(4) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1135 (1957).

(5) Yields are based on recovered starting material.

(6) Recently a synthesis of ketone III was independently reported by D. H. R. Barton *et al.*, *J. Am. Chem. Soc.*, **83**, 4076 (1961).