Bromination of 16-Keto Steroids. Conformation of Ring D

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The preparation of the two epimeric 15-bromo 16-ketones of the androstane series is described. Other new dibromo and tribromo 16-ketones are also described. The synthesis of some α-bromo Δ^{14}-16-ketones, as well as the various reactions and rearrangements of the ring-D bromo ketones, are also described. The infrared spectra of the new compounds and their bearing on the conformation of ring D in steroids are discussed.

Recent interest in the conformation of the ring D in steroids has resulted in several reports[3-5] dealing with the preparation and spectra of 17-bromo-16-keto steroids. The infrared, ultraviolet, and optical rotatory dispersion spectra of the epimeric 17-bromo 16-ketones have confirmed the assigned quasiaxial conformation to the 17α and quasi-equatorial conformation to the 17β bonds.[6] This paper is concerned with the preparation of other α-bromo 16-ketones and their reactions. The infrared spectra of the new compounds, in particular the 15-bromo derivatives, give pertinent information on the conformation of the 15α and 15β bonds and hence yield additional data on the conformation of ring D.

The starting material 3β-hydroxy-5α-androstane-16-one[7] on exchange reaction with isopropenyl acetate yielded a mixture of which the major part was the Δ^{16}-enol diacetate I, readily obtained by fractional crystallization. With bromine, I formed the 17α-bromo 16-ketone III[4] as the sole product. The mother liquors of I when similarly treated with bromine in carbon tetrachloride yielded additional III and a small amount of the isomeric 15β-bromo ketone IV; m.p. 196–198°, $[\alpha]^{27}D$ −162°. The ratio of III to IV was about 30:1 and the new isomer probably arises from a small amount of the isomeric enoldiacetate II which is present. The structure and stereochemistry of IV was obtained from the following reactions. Dehydrobromination of IV with γ-collidine yielded 3β-acetoxy-14-androstene-16-one (V), m.p. 165–167° readily distinguished by its ultraviolet absorption maximum $\lambda_{max}^{C_2H_5OH}$ 233 mμ. Further bromination of IV in acetic acid ceased after the uptake of an additional bromine atom to give the known 15β,17α-dibromoketone VI which was also obtained by further bromination of III. Finally, lithium aluminum hydride reduction of IV led to the known bromohydrin 15β-bromo-5α-androstane-3β,16β-diol.[5]

TABLE I[a]

	CCl_4 IR ν^{-}_{max} (cm.$^{-1}$)	$\Delta\nu^{-}$ (cm.$^{-1}$)
16-One	1746	...
17α-Bromo-16-one III	1754	+8
17β-Bromo-16-one VIII	1764	+18
15β-Bromo-16-one IV	1756	+10
15α-Bromo-16-one VII	1762	+16
15α,17β-Dibromo-16-one XI	1779	+33
15β,17α-Dibromo-16-one VI	1765	+19
17α,17β-Dibromo-16-one IX	1771	+25
15β,17α,17β-Tribromo-16-one X	1780	+34
15α,17α-Dibromo-16-one XII	1767	+21

[a] The infrared spectra were obtained successively on a carefully calibrated Perkin-Elmer 21 instrument using a calcium fluoride prism. The values are accurate to ± 1 cm.$^{-1}$.

The new bromo ketone IV was unchanged by standing with hydrobromic acid in acetic acid at room temperature. However, the same reagents at steam bath temperature for three hours resulted in partial epimerization of IV to the 15α-bromo 16-ketone VII, m.p. 200–203°, $[\alpha]D$ −105°. Reductive debromination of VII with hydrogen and catalyst gave 3β-hydroxy-5α-androstane-16-one, showing that no alteration at carbon-14 had occurred. Attempts to epimerize IV using hydrochloric acid instead of hydrobromic failed. This indicates that the epimerization does not proceed *via* simple enolization but that a debromination and rebromination mechanism suggested elsewhere[8] may also apply in this instance. Under alkaline conditions by which the 17α-bromo ketone III was epimerized to the 17β-bromo compound VIII,[5] IV was also rearranged to the 17β-bromo 16-ketone VIII.

In the expectation that the stereochemistry of the halogen at C-17 would influence the bromination at C-15, the 17β-bromo 16-ketone VIII was treated with a molar equivalent of bromine in acetic acid and hydrobromic acid. The new α-

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(2) A portion of this work has been published in a preliminary note, J. Fishman, *Chem. & Ind.* (London), 1678 (1961).

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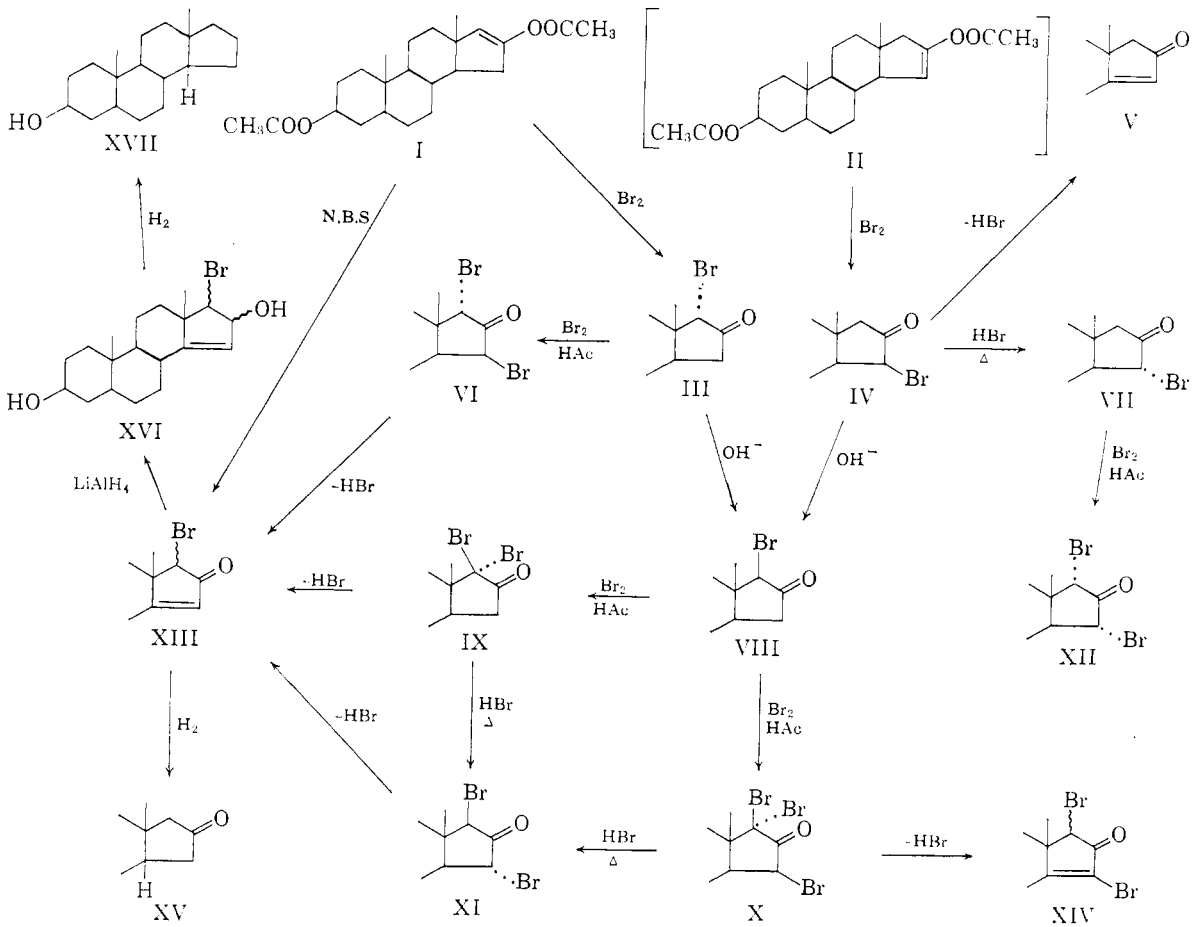


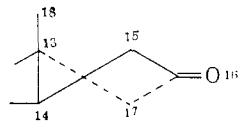
dibromo ketone obtained from this reaction, m.p. 168–170°, showed a band at 1412 cm.$^{-1}$ characteristic of a free α-methylene group in cyclopentanones and the compound was therefore formulated as the 17α,17β,-*gem*-dibromo ketone IX. Both the monobromo ketone VIII and the dibromo derivative IX on treatment with excess bromine in acetic acid yielded the same tribromo ketone, m.p. 179–181°, which on the basis of its preparation and infrared spectrum is best formulated as 3β-acetoxy-15β,17α,17β-tribromo-5α-androstane-16-one (X). This result is in contrast to the bromination of the epimeric 17α-bromo ketone III which does not proceed beyond the dibromo stage VI. When the 17-*gem*-dibromo ketone IX was refluxed in glacial acetic acid containing a few drops of hydrobromic acid a rearrangement occurred giving rise to a new α-dibromo ketone, m.p. 215–218°, which now lacked the methylene band at 1412 cm.$^{-1}$. Furthermore the carbonyl shift in the infrared was indicative of two quasiequatorial bromines, and the new compound must therefore be 15α,17β-dibromo ketone XI. Similar treatment of the tribromo ketone X proceeded with loss of bromine to give the same 15α,17β-dibromo ketone XI. Yet another isomeric α-dibromo 16-ketone was obtained by further bromination of the 15α-bromo 16-ketone VII. The new compound, m.p. 152–154°, was assigned the structure 15α,17α-dibromo 16-ketone XII, on the basis of the analytical and spectral data as well as the clearly established preference for 17α bromination.

In an attempt to prepare the 15β-bromo 16-ketone IV by a more efficient route the enol diacetate I was treated with *N*-bromosuccinimide. The product was a mixture which after separation on alumina yielded the 17α-bromo 16-ketone III and a new compound, m.p. 150–152°. The latter exhibited an ultraviolet maximum at 239 mμ which in addition to the analytical data was consistent with the structure 3β-hydroxy-17ξ-bromo-14-androstene-16-one XIII. This material proved to be identical with the collidine dehydrobromination product of the 15β,17α-dibromo ketone VI. In spite of the obvious correlation, the stereochemistry of the bromine at C-17 is undetermined since under the dehydrobrominating conditions used, rearrangements can occur particularly in the type of unsaturated system present. This was borne out by the collidine dehydrobromination at 15α,17β-dibromo ketone XI which yielded a compound identical with that obtained from the 15β,17α isomer VI. Similarly the dehydrobromination of the 17-*gem*-dibromo ketone IX was preceded by the shift of one C-17 bromine

to carbon-15 to also yield the same 14-dehydro compound XIII. Collidine dehydrobromination of the tribromo ketone X, gave a compound, m.p. 181–183°, which was clearly 3β-acetoxy-15,17ξ-dibromo-5α-androst-14-ene-16-one XIV. The ultraviolet absorption showed the expected bathochromic[9] shift to $\lambda_{max}^{C_2H_5OH}$ 262 mμ due to the bromine at C-15. The fused cyclopentenone system results in an essentially planar ring D with little if any conformational differences between the 17α and 17β bonds. Thus the apparent preference for one of these orientations may be due to the relative steric influence of the C-18 methyl group and the C-12 methylene group. Attempts to reduce the double bond in compound XIII and arrive at a saturated derivative resulted invariably in loss of bromine to give 3β-acetoxy-14β-androstan-16-one (XV), m.p. 145–148°. This compound was identical with that prepared by a totally different route in connection with another problem.[10] Lithium aluminum hydride reduction of the 17ξ-bromo-14-androstene-16-one (XIII) gave the rather unstable 17ξ-bromo-14-androstene-3β,16ξ-diol, (XVI). The latter on very brief hydrogenation in ethanol over 5% palladium-on-charcoal gave a product identified as 3β-hydroxy-14β-androstane (XVII), m.p. 142–144°, since it was identical with the Wolf-Kishner reduction product of 17-oxo-14β-androstane-3β-ol. It would appear that the hydrogenation of the double bond was preceded by hydrogenolysis of the allylic 16-hydroxy group. Since both the bromine and hydroxyl groups were probably lost prior to reduction of the double bond no conclusions about the stereochemistry of these substituents could be drawn from the stereochemistry of the reduction at C-14.[11]

The facile dehydrobromination of the 15-bromo-16-ketones is noteworthy since it is in contrast to the difficult dehydrobromination of the 16-bromo 17-ketones.[12] In that instance the formation of the highly strained *trans* fused planar cyclopentenone system is strongly resisted. The reluctant isomerization of the α-bromo 16-ketones in acid even when the bromine is quasiaxial is in marked contrast to the easy equilibration of the biaxial 16-halo 17-ketones. This difference can be readily accounted for by the lesser enolization of the 16-ketone, the reasons for which have already been discussed in connection with another problem.[13]

The infrared carbonyl absorptions of the various pertinent bromoketones are listed in Table I, together with the magnitude of the shift with respect to the unsubstituted 16-ketone. The 16 cm.$^{-1}$ shift in 15α-bromo-16-ketone VII reflects the pseudoequatorial nature of the 15α bond, while the 10-cm.$^{-1}$ shift of the 15β bromine in compound IV indicates the pseudoaxial nature of the 15β bond. These results, together with those obtained for the 17-bromo epimers,[3-5] fully substantiate the half-chair conformation for the ring D in 14α steroids with a ketone at C-16. The shifts encountered in the C-15 epimers show them to be slightly less axial and less equatorial than the 17α and 17β bromine, respectively. This can readily be explained by a small distortion in the half-chair form in that carbon-15 is less above the plane of carbons-13, -14, and -16 than carbon-17 is below.



This dissymetry could be the result of the nonbonded interaction of the C-18 methyl group with carbon-15. With the values of the shifts occasioned by the four possible isomeric α-bromines known, it is clear that the shifts in the di- and tribromo ketones are summations of the individual effects and that little, if any, bromine-bromine interaction occurs.

Experimental[14]

5α-Androst-16-ene-3β,16-diol Diacetate (I).—To a solution of 3 g. of 3β-hydroxyandrostane-16-one in 35 cc. of isopropenyl acetate was added 2 cc. of a catalyst solution (10 cc. of isopropenyl acetate containing 0.2 cc. of concd. sulfuric acid.) After the slow distillation, over 2.5 hr., of half the reaction volume an additional 35 cc. of isopropenyl acetate and 3 cc. of the catalyst solution were added and the slow distillation was continued for another 2 hr. The solution was cooled, diluted with ether, and washed with ice-cold 5% sodium bicarbonate solution and then with cold water. After drying and removing the solvent the residue was taken up in hot petroleum ether and filtered through 5 g. of alumina. The combined petroleum ether fractions were concentrated to a small volume to give upon cooling 1.88 g. of the enoldiacetate I, m.p. 114–118°.[4] A second crop of 0.15 g., m.p. 105–115° was obtained. The combined mother liquors were taken to dryness and the residue weighed 1.73 g.

3β-Acetoxy-17α-bromo-5α-androstane-16-one (III).—A solution of 1.8 g. of the enol diacetate I in 50 cc. of carbon tetrachloride was cooled in an ice bath, and a small amount of anhydrous potassium carbonate was added. The cold stirred solution was treated with a solution of bromine in carbon tetrachloride until an excess of bromine was present. Filtration and evaporation of solvent left a residue which was crystallized from methanol to give 1.1 g. of the 17α-bromo 16-ketone III; m.p. 172–174°, $[\alpha]^{29}D$ −49.

3β-Acetoxy-15β-bromo-5α-androstane-16-one (IV).—The mother liquors from the crystallization of the 16-enol diacetate I (1.73 g.) were brominated as above. The crude product was chromatographed on 60 g. of alumina. Elution with 30% benzene in petroleum ether afforded an additional 750 mg. of the 17α-bromo 16-ketone III, m.p. 164–168°. Elution with 50% benzene gave 100 mg. of 3β-acetoxy-5α-androstane-16-one. The 15β-bromo 16-ketone IV eluted

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(10) J. Fishman and T. Nambara, *J. Org. Chem.*, in press.

(11) See *inter alia*, F. Sondheimer, S. Burstein, and R. Mechoulam, *J. Am. Chem. Soc.*, **82**, 3209 (1960).

(12) W. S. Johnson and W. F. Johns, *ibid.*, **79**, 2005 (1957).

(13) J. Fishman, *ibid.*, **82**, 6143 (1960).

(14) Melting points were determined on a hot-stage apparatus and arec orrected. Rotations were determined in chloroform. The microanalyses were performed by Spang Microanalytical Laboratory.

with benzene after recrystallization from methanol weighed 65 mg., m.p. 190–194°. The analytical sample melted 196–198°, $[\alpha]^{29}D$ −166°.

Anal. Calcd. for $C_{21}H_{31}O_3Br$: C, 61.31; H, 7.59. Found: C, 61.41; H, 7.64.

3β-Acetoxy-5α-androst-14-ene-16-one (V).—A solution of 10 mg. of IV in 1 ml. of γ-collidine and 0.75 ml. of dimethylformamide was refluxed for 20 min. It was then diluted with water and extracted with ether which was washed with cold 5% hydrochloric acid, then 5% sodium bicarbonate, and finally water. After drying and evaporating the solvent the residue was crystallized from petroleum ether, m.p. 165–167°. $\lambda_{max}^{C_2H_5OH}$ 233 mμ (ε 15,000), infrared carbonyl band at 1713 cm.$^{-1}$ in carbon tetrachloride.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 75.94; H, 9.41.

Lithium Aluminum Hydride Reduction of 3β-Acetoxy-15β-bromo-5α-androstane-16-one (IV).—An ethereal solution of 20 mg. of IV was reduced with lithium aluminum hydride in the usual manner. On work-up the product obtained was 15β-bromo-5α-androstane-3β,16β-diol, m.p. 176–178°; lit., m.p. 178–179°.[5]

The diacetate was obtained in the usual manner and was recrystallized from methanol m.p. 195–198°, lit., m.p. 198–199°.[5]

3β-Acetoxy-15α-bromo-5α-androstane-16-one (VII).—A solution of 40 mg. of 15β-bromo 16-ketone IV in 10 cc. of glacial acetic acid containing 4 drops of hydrobromic acid was heated on a steam bath for 4 hr. The reaction mixture was then diluted with water and extracted with ether which was washed with 5% sodium bicarbonate solution and water. After drying and evaporation of solvent the residue was chromatographed on 4 g. of neutral alumina. Elution with 30% benzene in petroleum ether afforded first 21 mg. of the 15α-bromo 16-ketone VII which crystallized from methanol as prisms, m.p. 200–203° $[\alpha]^{27}D$ −107.

Anal. Calcd. for $C_{21}H_{31}O_3Br$: C, 61.31; H, 7.59. Found: C, 61.14; H, 7.29.

Further elution with 30% benzene in petroleum ether gave 14 mg. of the 15β-bromo 16-ketone IV as needles from methanol, m.p. 192–196°.

Attempted Rearrangement of 3β-Acetoxy-15β-bromo-5α-androstane-16-one IV.—**A.** A 5-mg. sample of the 15β-bromo 16-ketone IV was allowed to stand at room temperature for 66 hr. in glacial acetic acid containing a catalytic amount of hydrobromic acid. On work-up, the crude product was shown to be unchanged starting material by infrared spectra comparison and mixed melting point determination.

B. A solution of 5 mg. of IV in 2 cc. of glacial acetic acid containing 2 drops of concd. hydrochloric acid was heated on a steam bath for 4 hr. The crude product had a m.p. 190–196°, and its infrared spectrum showed it to be unchanged starting materal.

C. To a solution of 30 mg. of the 15β-bromo 16-ketone IV in 0.2 cc. of tetrahydrofuran and 1.3 cc. of ethanol was added 1.3 cc. of ethanol containing 10 mg. of sodium hydroxide. After standing at 18° for 20 min., the mixture was diluted with water and extracted with chloroform. The organic layer was washed with 5% hydrochloric acid and water. After drying the solvent was removed and the residue was acetylated with acetic anhydride in pyridine. The acetate was crystallized from methanol and exhibited a m.p. 200–206. Both by mixed melting point and infrared spectra comparison the product was identical with 3β-acetoxy-17β-bromo-5α-androstane-16-one (VIII).[5]

Reduction of 15α-Bromo-16-ketone VII.—A small sample of (11 mg.) of VII was hydrogenated in ethanol over 5% palladium on charcoal for 2 hr. The product obtained after work-up (7 mg.) was identical in all respects with 3β-acetoxy-5α-androstane-16-one.

Bromination of 3β-acetoxy-15β-bromo-5α-androstane-16-one (IV).—To a solution of 10 mg. of IV in 2 cc. of glacial acetic acid was added 10 mg. of bromine in 1 cc. of acetic acid and 2 drops of hydrobromic acid. After standing at room temperature for 2 days the solution was poured into ice water and the precipitate filtered off and recrystallized from methanol. The melting point was 210–214° and by mixed melting point and infrared spectra comparison it was identical with the 3β-acetoxy-15β,17α-dibromo-5α-androstane-16-one VI obtained from bromination of the 17α-bromo 16-ketone III.

3β-Acetoxy-17,17-dibromo-5α-androstane-16-one (IX).—A solution of 320 mg. of 3β-acetoxy-17β-bromo-5α-androstane-16-one (VIII)[5] in 20 cc. of glacial acetic acid was treated with 128 mg. of bromine. A few drops of 48% hydrobromic acid was added and the solution allowed to stand for 2 days at room temperature. Ice water was then added and the precipitate was filtered off. Crystallization from methanol gave 291 mg. of IX, m.p. 160–165°. The analytical sample obtained from methanol melted 168–170, $[\alpha]^{24}D$ −31.

Anal. Calcd. for $C_{21}H_{30}O_3Br_2$: C, 51.44; H, 6.17; Br, 32.60. Found: C, 51.66; H, 6.01; Br, 32.30.

3β-Acetoxy-15β-17,17-tribromo-5α-androstane-16-one (X). A. From VIII.—A solution of 100 mg. of VIII was brominated as above except that excess bromine (100 mg.) was used. The product crystallized from methanol and melted at 178–181°.

The analytical sample of 3β-acetoxy-15β,17,17-tribromo-5α-androstane-16-one (X) was obtained also from methanol; m.p. 179–182°, $[\alpha]^{26}D$ −49.

Anal. Calcd. for $C_{21}H_{29}O_3Br_3$: C, 44.31; H, 5.13; Br, 42.12. Found: C, 44.28; H, 5.00; Br, 41.96.

B. From IX.—When a small amount (10 mg.) of the 17-dibromo 16-ketone IX was treated with excess bromine as above, the product (7 mg.) obtained showed a m.p. 178–180° and was identical by infrared spectra comparison and mixed melting point with the tribromo ketone X obtained from VIII.

3β-Acetoxy-15α,17β-dibromo-5α-androstane-16-one (XI). A. From 17,17-Dibromo Ketone IX.—A solution of 150 mg. of IX in 15 cc. of glacial acetic acid containing 4 drops of 48% hydrobromic acid was heated on the steam bath for 2 hr. It was then poured into cold water and the white precipitate was filtered off and washed well with water. Crystallization from methanol gave 50 mg. of white needles, m.p. 200–210°. Another crystallization from methanol gave the analytical sample of XI, m.p. 215–218°, $[\alpha]^{25}D$ −134.

Anal. Calcd. for $C_{21}H_{30}O_3Br_2$: C, 51.44; H, 6.17; Br, 32.60. Found: C, 51.32; H, 6.24; Br, 31.96.

B. From Tribromo Ketone X.—An identical treatment of 20 mg. of the 15β,17,17-tribromo 16-ketone X gave 6 mg. of needles from methanol, m.p. 215–218°, identical with XI by mixed melting point and infrared spectra comparison.

3β-Acetoxy-15α,17α-dibromo-5α-androstane-16-one (XII).—To a solution of 10 mg. of 15α-bromo 16-ketone VII in 2 cc. glacial acetic acid containing 1 drop of hydrobromic acid was added 4.8 mg. of bromine. After standing overnight at room temperature the colorless solution was poured into ice water and the product was filtered off. Crystallization from dilute methanol gave irregular plates; m.p. 152–155°, $[\alpha]^{28}D$ −11.

Anal. Calcd. for $C_{21}H_{30}O_3Br$: C, 51.44; H, 6.17. Found: C, 51.17; H, 6.24.

3β-Acetoxy-17ξ-bromo-5α-androst-14-ene-16-one (XIII). A. From 5α-Androst-16-ene-3β,16-diol Diacetate (I).—A 500-mg. sample of the enol diacetate I was dissolved in 20 cc. of carbon tetrachloride and 4 cc. of solvent were distilled. To the remaining solution 300 mg. of *N*-bromosuccinimide were added and the mixture was brought to reflux by two photospot lamps. After 5 min. of reflux the cooled mixture was filtered, the filtrate was washed with 5% sodium bicarbonate and water, dried, and evaporated. The reddish residue was chromatographed on 40 g. of neutral alumina. Elution with 1:1 petroleum ether–benzene gave 150 mg. of the 17α-bromo 16-ketone III, m.p. 168–172. The benzene eluates weighed 136 mg. and upon crystallization were found to be identical with 3β-acetoxy-5α-androstane-16-

one, m.p. 112–114°. Finally elution with 2:1 benzene–petroleum ether gave 106 mg. of crystals of XIII which were recrystallized from petroleum ether and melted at 148–150°.

The analytical sample was obtained from the same solvent; m.p. 150–152, $[\alpha]_D$ +110, $\lambda_{max}^{C_2H_5OH}$ 238 mμ (ε 12,000).

Anal. Calcd. for $C_{21}H_{29}O_3Br$: C, 61.61; H, 7.14; Br, 19.5. Found: C, 61.48; H, 7.24; Br, 19.4.

B. From 15β,17α-Dibromo 16-Ketone VI.—A solution of 50 mg. of VI in 6 cc. collidine and 4 cc. dimethylformamide was refluxed for 15 min. It was then diluted with ether which was then washed with dilute hydrochloric acid and water. The residue remaining after drying and evaporating the solvent was crystallized from petroleum ether to give needles, m.p. 146–150°, identical in all respects with the 3β-acetoxy-17ξ-bromo-5α-androst-14-ene-16-one (XIII).

C. From 15α,17β-Dibromo 16-Ketone XI.—A small amount (15 mg.) of XI was dehydrobrominated as above. The product (6 mg.) was identical by mixed melting point with XIII. The infrared spectrum confirmed this identity, except in that a persistent impurity was also present as shown by a small carbonyl band at 1764 cm.$^{-1}$.

3β-Acetoxy-15,17,-dibromo-5α-androst-14-ene-16-one (XIV).—A 100-mg. sample of the tribromo ketone X in 8 cc. of collidine and 5 cc. of dimethylformamide was refluxed for 15 min. The reaction was worked up in the manner described above to give a reddish oil which was chromatographed on alumina. Elution with 50% benzene in petroleum ether gave 67 mg. of crystals which were recrystallized from methanol to give m.p. 180–183°.

The analytical sample melted at 182–184°, $[\alpha]^{25}_D$ +84, $\lambda_{max}^{C_2H_5OH}$ 262 mμ (ε 10,000).

Anal. Calcd. for $C_{21}H_{28}O_3Br_2$: C, 51.66; H, 5.78. Found: C, 51.52; H, 5.74.

3β-Acetoxy-5α,14β-androstane-16-one (XV).—A 100-mg. sample of the 17ξ-bromo-5α-androst-14-ene-16-one XIII was hydrogenated in ethanol over 5% palladium-on-charcoal. Within 10 min. 12 ml. of hydrogen was taken up. The catalyst was filtered off, the solvent was evaporated, and the residue crystallized from dilute methanol to show a melting point 144–148°. The material was identical in all respects with 3β-acetoxy-5α,14β-androstane-16-one (XV) obtained by a different route.[10]

17ξ-Bromo-5α-androst-14-ene-3β,16ξ-diol (XVI).—A 100-mg. sample of 3β-acetoxy-17ξ-bromo-5α-androst-14-ene-16-one (XIII) was dissolved in ether and treated for 1 hr. with lithium aluminum hydride at 0°. The conventional work-up gave 64 mg. of prisms from petroleum ether–acetone, m.p. 145–148° with decomposition.

Anal. Calcd. for $C_{19}H_{29}O_2Br$: C, 61.79; H, 7.91. Found: C, 61.37; H, 8.17.

14β-Androstane-3β-ol (XVII). A. From 17ξ-Bromo-5α-androst-14-ene-3β,16ξ-diol (XVI).—A 50-mg. sample of VI in ethanol was hydrogenated over 5% palladium-on-charcoal for 5 min. After filtering off the catalyst and evaporating the solvent the residue was crystallized from petroleum ether to give needles, m.p. 148–150°.

The analytical sample of XVII melted 148–150°.

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.17; H, 11.34.

B. From 3β-Acetoxy-5α,14β-androstane-17-one.—A 10-mg. sample of 3β-acetoxy-5α,14β-androstane-17-one was reduced by the Huang-Minlon procedure. The product obtained was recrystallized from petroleum ether as needles, m.p. 148–151°, identical in all respects with the 5α,14β-androstane-3β-ol obtained in method A.

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Bromination of Phenolic Steroids. I. Substitution of Estrone and 17β-Estradiol in Ring A[1]

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Both the 2- and 4-bromo as well as the 2,4-dibromo derivatives of estrone and 17β-estradiol have been synthesized and characterized. Conditions which produce exclusively one isomer in high yield are described.

Although phenols are brominated smoothly in high yield, this reaction has not been systematically applied to the phenolic steroids. Girard[2] prepared a monobrominated equilenin, but did not determine its structure. Marrian and Haslewood[3] found that the methyl ethers of estrone (I) and estriol consumed one mole of bromine in iodine number titrations (using BrI) forming monobromo compounds of undetermined structure. Woodward[4] synthesized 2,4-dibromoestradiol (IV) in 68% yield by treating estradiol (II) with *N*-bromoacetamide in alcohol. Recently, Tomson and Horwitz[5] synthesized 2- and 4-bromoestrone methyl ethers from the previously described nitro compounds[6] *via* the Sandmeyer reaction. We wish to report experiments which now enable one to brominate I and II in either the 2- or 4-position in high yield and purity. In addition, the 2,4-dibromo compound may be obtained in high yield with little substitution in the nonaromatic rings.

Aromatic dibromination occurs with *N*-bromosuccinimide (NBS) in refluxing chloroform, in

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