Synthesis and Reactions of 17β-Oxygenated 16α,17-Cyclopropylandrostanes

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Addition of carbene to the enol ether and enol acetate derivatives of several 17-keto steroids has provided the corresponding 16α,17-cyclopropyl steroids (**f**). The cyclopropyl ethers (**f**, R = Me, Et) on treatment with iodine afforded the *D*-homo unsaturated ketones (**e**) which may be alternately synthesized by base treatment of the keto aldehyde (**j**) resulting from ozonolysis of the Δ^{16}-17-methyl steroids (**k**). The cyclopropyl alcohol **1f** (R, R′ = H), formed by hydrolysis of its acetate, was readily isomerized with base to the corresponding *D*-homo ketone **1g** (R′ = H) or oxidized with, *e.g.*, ferric chloride, to a mixture of the unsaturated ketone **1e** (R′ = H) and the 16,17a-diketone (**1i**, R′ = H; Z = O). The addition of dibromocarbene to the enol ether gave the unsaturated bromo ketone **1h** (R′ = Ac; X = Br) which was also prepared by bromination of the cyclopropyl ether **1f** (R = Et; R′ = Ac). The dehydroacetoxylation of 5-acetoxyandrostanes on alumina is also described.

17-Methyltestosterone represents an early synthetic modification of testosterone which has enjoyed considerable utility in human therapy, largely due to its oral potency.[1] Since analogs of methyltestosterone with a larger 17α substituent exhibit in most cases a decreased physiological activity,[1] attention was turned to synthesis of compounds, the 16α,17-cyclopropyl derivatives, in which a sterically less bulky C-17α substituent was present.

Synthesis of the Cyclopropyl Ethers.—Initial plans for preparation of 16α,17-cyclopropyl steroids[2] involved reduction of the dihalocarbene adduct[3] formed from an enol derivative of a 17-keto steroid. Accordingly, the enol ether **1c** (R = Et; R′ = Ac), prepared from its ketal by elimination of ethanol in refluxing cymene, was treated with bromoform and potassium *tert*-butoxide. The product was the bromo unsaturated ketone **1h** (R′ = Ac; X = Br; λ_{max} 257 mμ), whose structure was consistent with mechanistic considerations,[3] the single vinyl proton in its nmr (438 Hz) and its elemental analysis. Further characterization was achieved by acid-catalyzed hydrolysis of its C_3-acetate group. Supporting evidence for the bromo unsaturated ketone structure came from its hydrogenation to the known *D*-homoandrostane **1g** (R′ = H).[4] Proof of structure of the bromo ketone **1h** (R′ = Ac; X = Br) was accomplished by an alternate synthesis involving addition of 1 mol equiv of bromine to the unsaturated ketone **1e** (R′ = Ac; see below) followed by dehydrobromination.

Attempts to isolate the dibromocyclopropane **1d** (R′ = Ac; X = Br), the logical intermediate to the unsaturated bromo ketone **1h** (R′ = Ac; X = Br), or to obtain evidence for its existence in the product (tlc, halogen analysis) were unsuccessful. A similar instability is displayed in simpler cyclopentene derivatives.[3] An attempt was made to prepare the analogous dichloro derivative **1d** (R′ = Ac; X = Cl) by treatment of the enol ether **1c** (R = Et; R′ = Ac) either with ethylene oxide–chloroform (essentially neutral conditions)[5] or with sodium trichloroacetate–sodium methoxide.[3] Although the dichloro adduct **1d** (R′ = Ac; X = Cl) was more stable than the bromo analog (as indicated by halogen analysis of the total reaction product), it was too unstable to isolate. The product isolated was the unsaturated chloro ketone **1h** (R′ = Ac; X = Cl) which had an ultraviolet spectrum with a maxium (243 mμ) displaced hypsochromically, as expected, from that of the corresponding bromo ketone. Hydrolysis of the 3-acetate group was again accomplished with acid. An immediate lithium–ammonia reduction of the freshly isolated dichlorocarbene reaction product yielded small amounts of the dehalogenated cyclopropyl derivative **1f** (R = Et; R′ = H); the chief product, however, was the saturated *D*-homo ketone **1g** (R′ = H), presumably formed by reduction of the unsaturated chloro ketone **1h** (R′ = H; X = Cl).

Direct addition of methylene to the enol ether was easily accomplished by use of diethylzinc and methylene iodide.[6] The product obtained from the enol ether **1c** (R = Et; R′ = Ac) was a new compound spectrally very similar to the starting material. Unambiguous evidence of the presence of the additional methylene group was obtained only from the mass spectral data (M^+ 312). Methylenation was similarly run on the enol methyl ether **1c** (R = Me; R′ = Ac), formed again by elimination of alcohol from its ketal. Both cyclopropyl derivatives **1f** (R = Me or Et; R′ = Ac) were transformed to their respective 3-hydroxy and then 3-keto derivatives by saponification followed by chromic acid oxidation (Scheme I). The nmr spectra of the latter clearly showed the cyclopropyl protons as multiplets at 40–50 Hz. The formation of the 16,17-cyclopropyl group is postulated to occur by α-face attack at the 16,17 double bond as has been documented for other reagents (*e.g.*, halogens, peracid).[7] Additional evidence of this cyclopropyl configuration is given below.

Reactions of the Cyclopropyl Ethers.—The cyclopropyl ethers were relatively stable to aqueous acid in refluxing methanol. Acetic acid solutions of *p*-toluensulfonic acid (at reflux) or hydrobromic acid (room temperature) produced mixtures of the *D*-homo

(1) P. D. Klimstra in "The Chemistry and Biochemistry of Steroids," Vol. 3, IntraScience Chemistry Reports, IntraScience Research Foundation, Santa Monica, Calif., 1969, p 83.

(2) A number of steroidal cyclopropanes have appeared in the recent literature. For examples, see J. Levisalles, G. Teutsch, and I. Tkatchenko, *Bull. Soc. Chim. Fr.*, 3194 (1969); D. E. Evans, G. S. Lewis, P. J. Palmer, and D. J. Weyell, *J. Chem. Soc.*, 1197 (1968); A. J. Birch and G. S. R. Subba Rao, *Tetrahedron, Suppl.*, **7**, 391 (1966).

(3) The addition of dihalocarbenes to enol ethers has been described, *e.g.*, by W. E. Parham, R. W. Soeder, J. R. Throckmorton, K. Kuncl, and R. M. Dodson, *J. Amer. Chem. Soc.*, **87**, 321 (1965). See also ref 13, p 160, and a recent review by R. Barlet and Y. Vo-Quang, *Bull. Soc. Chim. Fr.*, 3729 (1969).

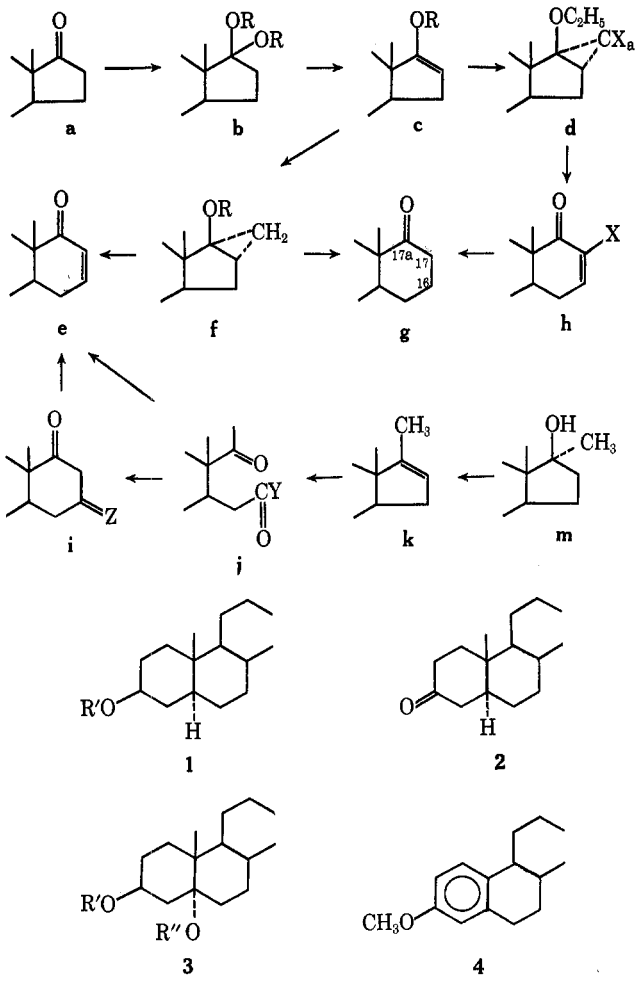
(4) A sample for comparison was prepared by hydrogenation of the Δ^5 derivative, in turn obtained by the synthesis of H. Heusser, P. Th. Herzig, A. Fürst, and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950), and kindly supplied by Dr. P. B. Sollman of these laboratories.

(5) F. Nerdel and J. Buddrus, *Tetrahedron Lett.*, 3585 (1965).

(6) J. Furukawa, N. Kabawata, and J. Nishimura, *Tetrahedron*, **24**, 53 (1968).

(7) See, *e.g.*, G. P. Mueller and W. F. Johns, *J. Org. Chem.*, **26**, 2403 (1961); N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Amer. Chem. Soc.*, **76**, 2943 (1954).

SCHEME I



ketone **1g** (R′ = Ac) and additional products, probably 16-methylandrostan-17-ones (**1a**, 16-Me; R′ = Ac); with the latter reagent the mixture also contained brominated by-products.[8,9]

The ready reaction of the cyclopropyl ethers with halogens was first seen in an attempt to introduce a double bond into the A ring of the cyclopropyl derivative **2f** (R = Me); when direct dehydrogenation with dichlorodicyanoquinone or selenium dioxide proved unpromising, the A ring enol acetate of the ketone **2f** (R = Et) was brominated under neutral conditions. The resulting product, after magnesium oxide dehydrohalogenation, yielded an unsaturated D ring ketone (**e**) in which the A ring enol acetate was still intact. To further explore this reaction of bromine with the cyclopropyl ether grouping, the saturated 3-acetate **1f** (R = Me; R′ = Ac) was brominated and the resulting unstable product dehydrobrominated. The product was the *D*-homo unsaturated ketone **1e** (R′ = Ac) as suggested by its spectra and supported both by mechanistic considerations[8,9] and its facile hydrogenation to the known saturated ketone **1g** (R′ = Ac). Saponification of its 3-acetate followed by oxidation to the corresponding 3-ketone **2e** further characterized the product.

(8) A comparable example of a cyclopropyl ether cleavage has been described by E. Wenkert and D. A. Berger, *J. Amer. Chem. Soc.*, **89**, 2507 (1967).

(9) Other examples have been described by E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, and G. Tosi, *ibid.*, **92**, 7428 (1970); R. E. Ireland, D. R. Marshall, and J. W. Tilley, *ibid.*, **92**, 4754 (1970).

The potential synthetic utility of this bromination reaction was limited by the rapid consumption of bromine in excess of 1 mol equiv, the excess resulting (after dehydrobromination) in formation of the unsaturated bromo ketone **1h** (R′ = Ac; X = Br). Iodine was seen to effect the same ring opening with minimal uptake of a second mole of halogen, thus giving a higher yield of the desired unsaturated ketone **1e** (R′ = Ac). The product was accompanied in this case by small amounts of the saturated *D*-homo ketone **1g** (R′ = Ac). In contrast to the cyclopropyl ether (**1f**, R = Et; R′ = Ac), the 17-acetate **1f** (R, R′ = Ac; see below) did not react with iodine.

A definitive structure proof of the unsaturated ketone **1e** was obtained by its synthesis from the ketoaldehyde **1j** (R′ = Ac; Y = H) *via* base-catalyzed cyclization.[10] The ketoaldehyde and the 17-ketone **1a** (R′ = Ac) were formed by direct ozonolysis of the olefin mixture resulting from phosphorous oxychloride dehydration of 17-methylandrostanediol 3-acetate (**1m**, R′ = Ac).

The same series of transformations were carried out for the Δ^4 ketone and the aromatic derivative **4k** yielding respectively the unsaturated ketones **2e** (Δ^4) and **4e**. In the latter case, mild base treatment of the ketoaldehyde **4j** afforded a crystalline ketol **4i** (Z = β-OH). The β configuration assigned to the 16-hydroxyl group was suggested by the relatively sharp nmr signal of its 16 proton. With more vigorous treatment this ketol dehydrated to provide the unsaturated ketone **4e**, which in turn was hydrogenated to the known *D*-homoestrone derivative **4g**.[11]

Insertion of the Δ^4 Bond.—Since preliminary investigations of direct insertion of an A ring double bond into the saturated 3-keto steroid **2f** (R′ = Me) had proved unsuccessful (see above), an alternate path was investigated starting with a 5-oxygenated androstane. The C-5 oxygen was expected to withstand the conditions of the carbene insertion sequence and could, at an appropriate time, be eliminated to form the desired unsaturation. (An unprotected double bond would be attacked by carbene.) Accordingly, 3β,5α-dihydroxyandrostan-17-one (**3a**, R, R′, R″ = H)[12] was treated with ethyl orthoformate to effect ketal formation. The instability of the molecule in this reaction was seen from the formation of the 5-dehydro derivative (as its 3-formate), the 3-monoformate of the starting diolone, and a number of less tractable derivatives. Ethyl orthoformate reacted smoothly with the 3,5-diacetate **3a** (R′, R″ = Ac), however, to yield the diethyl ketal **3b** (R = Et; R′, R″ = Ac). Recrystallization of this ketal from methanol converted it to the 17β-ethoxy-17α-methoxy ketal, the structure being suggested by the nmr spectra, the probable mechanism of the alcohol exchange, and conversion of the mixed ketal in boiling cymene to the enol *ethyl* ether. The enol ether **3c** (R = Et; R′, R″ = Ac), prepared from the diethyl ketal in hot cymene, was methylenated to provide 70% of the desired 16,17-cyclopropyl derivative **3f** (R = Et; R′, R″ = Ac) by direct crystallization. This compound was converted with lithium aluminum hydride to the 3,5-diol **3f** (R =

(10) For a similar synthesis of *D*-homo unsaturated ketones, see W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961).

(11) M. W. Goldberg and S. Studer, *Helv. Chim. Acta*, **24**, 295E (1941).

(12) K. I. H. Williams, R. S. Rosenfeld, M. Smulowitz, and D. K. Fukushima, *Steroids*, **1**, 377 (1963).

Et; R′, R″ = H) or with base to the 5-monoacetate. Chromic acid oxidation of the latter followed by base treatment yielded the 17-etherified testosterone analog **2f** (R = Et; Δ^4) in good yield.

Cyclopropyl Alcohol Synthesis and Reactions.—The 17-hydroxy-16α,17-cyclopropane derivatives were synthesized by addition of carbene to the androstane enol acetate **1c** (R, R′ = Ac). The product was a new compound **1f** (R, R′ = Ac) whose structure was again most clearly shown by the mass spectrum (M^+ 388) in conjunction with the general similarity of both its ir and nmr spectra to those of starting material. A lower yield of product and higher return of starting material reflected the decreased reactivity of the double bond, a result of the greater electron-withdrawing power of the acetate group as compared to the ether.[13] Lithium aluminum hydride reduction or careful alkaline hydrolysis converted the diacetate to the diol **1f** (R, R′ = H). This structure was supported by the dual method of preparation and by reacetylation of the diol to the starting diacetate.

The isomerization of the diol **1f** (R, R′ = H)[14] with potassium hydroxide in aqueous methanol at room temperature provided in high yield the *D*-homo ketone **1g** (R′ = H) mixed with minor amounts of the isomeric 16-methylandrostanes (**1a**, 16-Me; R′ = H; vpc analysis). With *p*-toluenesulfonic acid in aqueous methanol at reflux the initial product was a mixture of the *D*-homo ketone **1g** (R′ = H) and 3-hydroxy-16α-methylandrostan-17-one (**1a**, 16α-Me; R′ = H) in a 2:3 ratio. With prolonged acid treatment racemization of the 16-methyl group occurred. The cyclopropyl diol also isomerized upon chromatography (alumina or silica gel) or upon standing in chloroform solution giving mixtures of the same three products. The vpc identification of the 16α-methylandrostane **1a** (16α-Me; R′ = H) as the initial isomerization product of the cyclopropyldiol affords evidence that the cyclopropyl ring is on the α face of the molecule, a simple cleavage of the 16′,17 bond giving the 16α-Me group.

The diol **1f** (R, R′ = H) underwent ready oxidation with several oxidants, including chromic acid–pyridine, chromic acid–acetone, and *N*-bromoacetamide. These reagents effected oxidation at both C-3 and in the D ring, whereas milder oxidants, such as ferric chloride, caused reaction only in the latter.[15] The chief pathway of all of these oxidations involved transformation of the cyclopropyl alcohol into the readily identified *D*-homo unsaturated ketone (**e**). In addition, the *D*-homo ketone, a product of acid-catalyzed isomerization, was formed. Another component of the oxidation product was suggested by its uv spectrum to be the 16,17a-diketone **2i** (Z = O).[16] An alternate synthesis of this diketone was effected by ruthenium tetroxide oxidation of the olefin **1k** (R′ = Ac)[17] to afford the acid **1j** (R′ = Ac; Y = OH), followed by esterification and base-catalyzed cyclization. Oxidation of the 3-hydroxyl group gave the same trione **2i** (Z = O) as obtained from oxidation of the cyclopropyl alcohol **1f** (R, R′ = H).

Selective hydrolysis of the diacetate **1f** (R, R′ = Ac) was successfully accomplished with aqueous bicarbonate. The desired 3-monohydroxy compound **1f** (R = Ac; R′ = H) was accompanied by a varying amount of diol **1f** (R, R′ = H) and the *D*-homo ketone **1g** (R′ = H). Oxidation of the 17-mono ester gave the 3-ketone **2f** (R = Ac) and this in turn was hydrolyzed to the 17-hydroxy derivative **2f** (R = H).

Insertion of the A ring unsaturation was accomplished by use of the C-5 acetate as described above. The enol triacetate **3c** (R, R′, R″ = Ac) was methylenated to give the cyclopropyl triacetate **3f** (R, R′, R″ = Ac) which was reduced with lithium aluminum hydride to provide the cyclopropyl triol **3f** (R, R′, R″ = H). Base treatment of the triacetate (or the corresponding 3,17-diol) caused ready formation of the *D*-homo ketone **3g** (R′ = H; R″ = Ac); the latter was acetylated to give the diacetate **3g** (R′, R″ = Ac) and was also converted by chromic acid oxidation followed by base treatment to the known unsaturated ketone **2g** (Δ^4).[18]

Bicarbonate hydrolysis of the triacetate **3f** (R, R′, R″ = Ac) afforded, by direct crystallization, the 3,17-diol **3f** (R, R′ = H; R″ = Ac) whose structure was confirmed by reacetylation to the starting triacetate. The mother liquors of this hydrolysis were analyzed by chromatography on acid-washed alumina and provided the desired 3-monohydroxy diacetate **3f** (R′ = H; R, R″ = Ac), the starting triacetate, and the *D*-homo ketone **3g** (R′ = H; R″ = Ac). In a later repetition of this experiment, alkaline alumina was used for the chromatography and yielded, instead of the 5-acetoxy compounds, the corresponding Δ^5 derivative **1f** (R = Ac; R′ = H; Δ^5). The corresponding unsaturated ketone **2f** (R = Ac; Δ^4) was obtained either by Oppenauer oxidation of this olefin or by chromic acid oxidation of the monoalcohol **3f** (R′ = H; R, R″ = Ac) to its ketone followed by dehydroacetoxylation on alumina. Subsequent bicarbonate treatment afforded the testosterone derivative of **2f** (R = H; Δ^4).

The elimination of the 5-acetate group on alkaline alumina was also seen in the chromatography of the 17-ethoxy derivative **3f** (R = Et; R′ = H; R″ = Ac). Similar treatment of the 17-ketone **3a** (R′ = H; R″ = Ac) afforded dehydroepiandrosterone, some starting material, and *ca.* 5% of androstenedione. The latter probably arose as the result of a slow aluminum alkoxide oxidation of dehydroepiandrosterone in a reaction analogous to the Oppenauer oxidation. The reaction of the 3,5-diacetate **3a** (R′, R″ = Ac) on alumina provided the same products but at a much slower rate; absence of the 3-acetate Δ^5 derivative of **1a** (Δ^5; R′ = Ac) indicates that hydrolysis of the 3-acetate group occurs before elimination of the 5-acetate. The 3-hydroxy Δ^4 derivative was not seen in any of the dehydroacetoxylations.

Cyclopropyl Estratrienes.—Both the enol ethyl ether and enol acetate of estrone methyl ether were prepared and treated with diethylzinc–methylene iodide to

(13) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 29.

(14) For a review of cyclopropanol chemistry, see C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968).

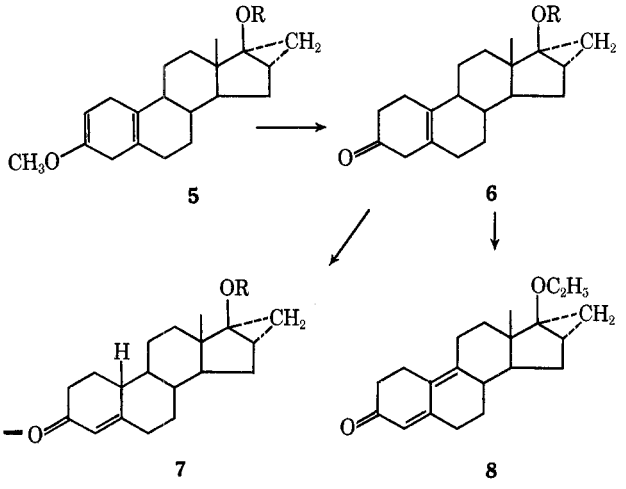
(15) Examples of cyclopropanol oxidation have been described by P. S. Venkataramani and W. Reusch, *Tetrahedron Lett.*, 5283 (1968), and S. E. Schaafsma, H. Steinberg, and Th. J. DeBoer, *Recl. Trav. Chim. Pays-Bas*, **85**, 73 (1966).

(16) For an alternate preparation of this material, see C. Thal and B. Gastambide, *Bull. Soc. Chim. Fr.*, 1222 (1966).

(17) F. Sondheimer, R. Mechoulam, and M. Sprecher, *Tetrahedron*, **20**, 2473 (1964); D. M. Piatak, H. B. Bhat, and E. Caspi, *J. Org. Chem.*, **34**, 112 (1969).

(18) M. W. Goldberg, J. Sice, H. Robert, and Pl. A. Plattner, *Helv. Chim. Acta*, **30**, 1441 (1947).

provide the corresponding cyclopropyl derivatives.[19] The ether **4f** (R = Et) was found to be stable to lithium–ammonia reduction, allowing preparation of the $\Delta^{5(10)}$- (**6**, R = Et) and Δ^{4}-3-keto-19-nor steroids (**7**) by standard acid hydrolysis. In addition, treatment of the $\Delta^{5(10)}$ compound (**6**, R = Et) with bromine in pyridine yielded the 4,9-dienone **8**; no reaction of the cyclopropyl ether group with bromine was seen in contrast to earlier bromination studies done in carbon tetrachloride (see above).



The cyclopropyl alcohol **4f** (R = H) in this series was best prepared from its acetate **4f** (R = Ac) by treatment with methyllithium.[20] Potassium bicarbonate treatment of the cyclopropyl acetate yielded mixtures of the desired alcohol and the relatively insoluble *D*-homo ketone **4g**.[11] Attempts at purification gave additional amounts of *D*-homo ketone. The lability of the cyclopropyl alcohol **4f** (R = H) was also demonstrated by its ready conversion to the *D*-homo ketone in spectral grade chloroform. The instability of the 17-acetoxycyclopropane grouping in **4f** (R = Ac) to lithium–ammonia reduction was circumvented by use of the corresponding trimethylsilyl ether of the 17-alcohol **4f** (R = $SiMe_3$), prepared by treatment of the alcohol with hexamethyldisilazane and trimethylchlorosilane. Birch reduction of this ether followed by acid hydrolysis gave the nonconjugated unsaturated ketone **6** (R = H). Further acid treatment followed by acetylation gave the conjugated ketone **7** (R = Ac).

Experimental Section[21]

3β-Acetoxy-17-bromo-*D*-homoandrost-16-en-17a-one (1h, R′ = Ac; X = Br). Ketal Pyrolysis. Procedure A.—A solution of 70 g of 17,17-diethoxyandrostan-3β-ol acetate **1b** (R = Et; R′ = Ac)[22] in 300 ml of cymene was distilled to half-volume over a 5-hr period. The remainder of the solvent was then distilled *in vacuo*. The product, dissolved in 50 ml of pentane containing 1 ml of pyridine, crystallized slowly, yielding 26 g of the enol ether **1c** (R = Et; R′ = Ac): mp 93–95°; 5.80 μ; 52 (18,19-CH_3's), 256 Hz (m, 16-H).

Reaction of Dibromocarbene with the Enol Ether 1c (R = Et; R′ = Ac).—Potassium *tert*-butoxide (10 g) was added to a stirred solution of 24 g of the enol ether **1c** (R = Et; R′ = Ac) in 100 ml of benzene and 30 ml of *tert*-butyl alcohol at −5°.[3] Bromoform (8 ml) in 30 ml of benzene was then added dropwise over a 50-min period (T <5°). After an additional 10 min the solution was poured into water containing a slight excess of acetic acid. The product was isolated by benzene extraction[23] and then acetylated in pyridine–acetic anhydride (95°, 20 min). The acetate, isolated by benzene extraction, was purified by chromatography.[24] The bulk of the product was isoandrosterone acetate (12 g). Fractions (3.1 g) eluted with 1% ethyl acetate–benzene were recrystallized from methylene chloride–hexane to yield 2.2 g of the bromide **1h** (R′ = Ac): mp 227–230° dec; 5.78, 5.90 μ; 257 mμ (ε 5500); 49 (19-CH_3), 63 (18-CH_3), 121 (OAc), 438 Hz (m, 16-H).

Anal. Calcd for $C_{22}H_{31}BrO_3$: C, 62.42; H, 7.38. Found: C, 62.50; H, 7.39.

Bromination of the Cyclopropyl Ether 1f (R = Me; R′ = Ac). Procedure B.—To a well-stirred slurry of 5 g of anhydrous potassium carbonate in 30 ml of carbon tetrachloride containing 0.40 g of the methyl ether **1f** (R = Me; R′ = Ac) at 5° was added 2.2 mol equiv of bromine in carbon tetrachloride solution (0.17 M) over a 25-min period. The uptake of bromine was very fast. The mixture was diluted with ice water and extracted with ether (T <10°), yielding an unstable product which was dissolved in dimethylformamide. After 3 days the solution was diluted with water and the product isolated by benzene extraction. The semicrystalline residue was recrystallized from methylene chloride–methanol to yield 155 mg of the bromo ketone **1h** (R′ = Ac), mp 212–213°, identical spectrally with the compound prepared above.

Bromination of the Unsaturated Ketone 1e (R′ = Ac).—The unsaturated ketone **1e** (R′ = Ac; 0.20 g) in 8 ml of carbon tetrachloride was treated with 1.05 mol equiv of bromine (procedure B). After 5 min excess aqueous sodium bisulfite was added and the solution was extracted with methylene chloride. The crude bromine, 130 mg of lithium carbonate, and 5 mg of lithium chloride in 2 ml of dimethylformamide was allowed to stand at room temperature for 65 hr. The solution was diluted with water and the product isolated by methylene chloride extraction. The crystalline residue was recrystallized from methylene chloride–hexane to give 0.18 g of the bromo ketone **1h** (R′ = Ac), mp 213–214°, identical with the above sample.

3β-Hydroxy-17-bromo-*D*-homoandrost-16-en-17a-one (1h, R′ = H; X = Br). Procedure C.—*p*-Toluenesulfonic acid (0.20 g) was added to a boiling solution of the bromide **1h** (R′ = Ac) in 60 ml of methanol and 5 ml of water. After 16 hr half of the methanol was distilled and the solution was diluted with water. The resulting precipitate was collected on a filter, washed with water, and recrystallized from methylene chloride–hexane to yield 0.27 g of **1h** (R′ = H; X = Br): mp 222–224°; 2.73, 5.90 μ; 252 mμ (ε 5350); 48 (19-CH_3), 63 (18-CH_3), 437 Hz (m, 16-H).

Anal. Calcd for $C_{20}H_{29}BrO_2$: C, 67.99; H, 7.67. Found: C, 68.07; H, 7.85.

Attempted saponification of the 3-acetate group of **1h** led to loss of bromine.

3β-Hydroxy-*D*-homoandrostan-17a-one (1g, R′ = H).—A solution of 0.10 g of the bromide **1h** (R′ = H) in 20 ml of ethanol was hydrogenated[25] at atmospheric pressure in the presence of 100 mg of 5% palladium–charcoal catalyst. Although the first 1 mol equiv of hydrogen was taken up rapidly, the second required 3 hr. After removing the catalyst by filtration the solution was diluted with 5 ml of pyridine, concentrated to half-volume, and

(19) A recent patent (German Patent 1,240,078) records the preparation of the methyl ether **5f** (R = Me) and the acetate **5f** (R = Ac) by a similar route.

(20) C. H. DePuy, G. M. Dappen, K. L. Eilers, and R. A. Klein, *J. Org. Chem.*, **29**, 2813 (1964).

(21) We wish to thank Dr. J. W. Ahlberg and staff for the analyses and spectra reported. The infrared spectra (μ) were determined in chloroform, ultraviolet spectra (mμ) in methanol, and rotations in chloroform (1%). Nmr spectra (hertz) were determined in deuteriochloroform on a Model A-60 spectrometer, Varian Associates, Inc., using tetramethylsilane as an internal standard (Δν = 0). The mass spectra were determined on a Varian M-66 spectrometer; the relative intensities are recorded in parentheses after each mass peak.

(22) L. Caglioti, G. Cainelli, G. Maina, and A. Selva, *Gazz. Chim. Ital.*, **92**, 309 (1962).

(23) The isolation procedure used throughout this work involved dilution of the reaction mixture with water, extraction with an immiscible solvent, and washing with water and (if acidic) with aqueous bicarbonate solution. The extract was routinely dried over magnesium sulfate and the solvent removed under reduced pressure (T <50°).

(24) The chromatographies described in this section were uniformly run on a weight of Davison silica gel 60 times the weight of the compound involved. We thank Mr. R. T. Nicholson and staff for the competent execution of this work.

(25) We wish to thank Mr. W. M. Selby and staff for the hydrogenations described here.

diluted with water. The resulting precipitate was collected on a filter, washed with water, and recrystallized from aqueous ethanol to yield 60 mg of the alcohol 1g (R′ = H): mp 202–203°; 2.72, 5.82 μ; 48 (19-CH_3), 65 Hz (18-CH_3).

The comparison sample was made by hydrogenation of the Δ^5 derivative of 1g (R′ = H) over palladium–charcoal catalyst in ethanol solution. The reduction required 1.3 hr and yielded a product identical with that obtained above. (An earlier hydrogenation, run at 60 psi, caused overreduction, producing the corresponding 3,17-diol.)

3β-Acetoxy-17-chloro-*D*-homoandrost-16-en-17a-one (1h, R′ = Ac; X = Cl).—Sodium methoxide (3 g) was added to a stirred solution of 4 g of the ethyl ether 1c (R = Et; R′ = Ac) in 100 ml of ether at 5° followed by the rapid addition of 3 ml of ethyl trichloroacetate. After 3.5 hr the mixture was filtered through Super-Cel, water was added, and the product was extracted with ether. The semicrystalline residue was triturated with 1:1 ether–hexane to yield 1.8 g of the crude chloride 1h (R′ = Ac), mp 228–230°. Recrystallization from methylene chloride–hexane afforded the pure sample: mp 239–242°; 5.76, 5.89 μ; 243 mμ (ε 6800); 49 (19-CH_3), 63 (18-CH_3), 420 Hz (q, 16-H).

Anal. Calcd for $C_{22}H_{31}ClO_3$: C, 69.73; H, 8.24; Cl, 9.36. Found: C, 69.53; H, 8.06; Cl, 9.54.

Analysis of the crude reaction product showed 12.5% chlorine (calcd for $C_{24}H_{36}Cl_2O_3$, 15.8), but attempts to isolate a dichloro compound were unsuccessful. Longer treatment with sodium methoxide led to crude products exhibiting a methoxyl signal (226 Hz) in the nmr.

An alternate synthesis of the chloride 1h (R′ = Ac) involved heating a solution of 3 g of the ethyl ether 1c (R′ = Ac) and 20 mg of tetraethylammonium bromide in 5 ml of ethylene oxide and 10 ml of chloroform at 150° for 5 hr.[5] The solution was cooled, washed with water, dried, and concentrated yielding an oil which showed the spectral characteristics of impure unsaturated chloro ketone 1h ($E_{244\ m\mu}$ 3460; found, 10.12% Cl). Again no dichloro derivative was isolable.

Direct addition of the dichloro adduct 1d (R′ = Ac; X = Cl), as produced by the trichloroacetate reaction, to a solution of lithium metal in ammonia containing *tert*-butyl alcohol gave a product which was analyzed by successive chromatography, hydrolysis with aqueous acid, and rechromatography. It was seen to consist of minor amounts of the desired ethyl ether 1f (R′ = H) contaminated with larger amounts of isoandrosterone and *D*-homoisoandrosterone (1g, R′ = H).

3β-Hydroxy-17-chloro-*D*-homoandrost-16-en-17a-one (1h, R′ = H; X = Cl) was prepared from its 3-acetate 1h (R′ = Ac; X = Cl; procedure C) and was recrystallized from methylene chloride–hexane to yield the pure chloride 1h (R′ = H): mp 223–226°; 2.75, 5.87 μ; 244 mμ (ε 3740); 48 (19-CH_3), 63 (18-CH_3), 423 Hz (m, 16-H).

Anal. Calcd for $C_{20}H_{29}ClO_2$: C, 71.30; H, 8.68. Found: C, 70.98; H, 8.65.

Base treatment of the acetate 1h (R′ = Ac) led to loss of halogen.

17,17-Dimethoxyandrostan-3β-ol Acetate (1b, R′ = Ac; R = Me).—Five drops of concentrated sulfuric acid was added to a solution of 52 g of epiandrosterone acetate 1a in 500 ml of methanol and 50 ml of redistilled trimethyl orthoformate. The solution was heated at reflux for 10 min, 15 ml of pyridine was added, and the reaction was cooled. The resulting precipitate was collected on a filter, yielding 50 g of the methyl ketal 1b (R′ = Ac). Recrystallization of a portion from methylene chloride–methanol containing a trace of pyridine gave the pure product: mp 156–159°; 5.75 μ; 49 (18-CH_3), 52 (19-CH_3), 192.5, and 193.0 Hz (OCH_3).

Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 73.14; H, 10.36.

17β-Methoxy-16α,17-cyclopropanoandrostan-3β-ol Acetate (1f, R′ = Ac; R = Me). A. Pyrolysis.—The methyl ketal 1b (45 g, R′ = Ac) was boiled in refluxing cymene for 64 hr (procedure A). The product failed to crystallize but exhibited the proper spectral characteristics for the methyl ether 1c (R′ = Ac): 5.78 μ; 52 (18,19-CH_3's), 213 (OCH_3), 260 Hz (m, 16-H).

B. Methenylation. Procedure D.—Neat diethylzinc (12 ml) was added to a solution of the crude enol ether (32 g) in 230 ml of redistilled *n*-butyl ether, the whole procedure being carried out in a drybox under a slight positive pressure of nitrogen. As methylene iodide (20 ml) was added to the stirred solution dropwise over a 2-hr period, the temperature of the solution rose to 45°. After the reaction was stirred for an additional 16 hr, 50 ml of 2B ethanol was added followed by water and a slight excess of cold dilute hydrochloric acid. The product was extracted with ether. After removal of the solvent, the product crystallized and was recrystallized from methylene chloride–methanol to yield the pure adduct 1f (R = Me; R′ = Ac): 13.8 g; mp 129–130°; 5.80 μ; 38, 41, and 48 (m, cyclopropyl proton signals), 51 (19-CH_3), 60 (18-CH_3), 200 Hz (OCH_3).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.55; H, 9.97.

Chromatography of the mother liquors gave an additional 6.2 g of the same adduct eluted with 2% ethyl acetate–benzene. Elution with 30% ethyl acetate–benzene gave 4.2 g of crude material recrystallized from acetone–hexane to yield 2.3 g of the pure 3-ol 1f (R = Me; R′ = H), mp 192–194°, identical spectrally with the sample prepared below.

17β-Methoxy-16α,17-cyclopropanoandrostan-3β-ol (1f, R′ = H; R = Me). Procedure E.—A slurry of the methyl ether 1f (R′ = Ac, 12 g) in 0.6 l. of methanol and 100 ml of 10% aqueous potassium hydroxide was stirred at room temperature. The steroid dissolved within 15 min, followed by precipitation of the product. After 45 min the mixture was filtered and the precipitate was washed with water, yielding 10.6 g of the product: mp 195–196°; 2.76 μ; 49 (19-CH_3), 59 (18-CH_3), 198 Hz (OCH_3). Recrystallization of a portion of the product from methylene chloride–cyclohexane did not improve the melting point. The cyclopropyl signals in the nmr were similar to those seen in the spectrum of the parent acetate.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.30; H, 10.71.

This derivative was stable in boiling aqueous tetrahydrofuran containing *p*-toluenesulfonic acid. However, in boiling acetic acid containing *p*-toluenesulfonic acid, the known *D*-homo ketone 1g (R′ = Ac) was formed in 60% yield; the remainder of the product was a mixture of the epimeric 16-methylandrostanes (vpc analysis).

17β-Methoxy-16α,17-cyclopropanoandrostan-3-one (2f, R = Me).—The methyl ether 1f (R′ = H, 7.0 g) in 70 ml of pyridine was added to the Sarett reagent[26] prepared from 7 g of chromium trioxide. After 5 hr at room temperature the mixture was diluted with water and extracted with ether. The product was recrystallized from methylene chloride–methanol to yield 4.5 g of the pure ketone 2f (R = Me): mp 149–150°; 5.83 μ; 62 (18,19-CH_3's), 200 Hz (OCH_3). The complex cyclopropyl hydrogen pattern was seen in the nmr at 35–55 Hz.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.68; H, 10.21.

17β-Methoxy-16α,17-cyclopropanoandrost-2-en-3-ol Acetate (2f, Enol Acetate; R = Me). Procedure F.—A solution of 4.10 g of the ketone 2f (R = Me) and 1.0 g of *p*-toluenesulfonic acid in 50 ml of benzene and 50 ml of isopropenyl acetate was stirred at room temperature for 2 weeks. The product was extracted with ether and crystallized from aqueous methanol to give 3.9 g of the enol acetate. Further recrystallization from methanol gave 0.88 g of the pure material: mp 113–114°; 5.73 μ; 52 (19-CH_3), 62 (18-CH_3), 126 (OAc), 316 Hz (C_6H).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.91; H, 10.02.

A good yield of the 3-ketone (2f, R = Me) was produced by mild alkaline hydrolysis of this enol acetate.

The enol acetate was treated with 1.05 mol equiv of bromine (procedure B). The crude product displayed nmr signals for the enol acetate (126, 316 Hz) but lacked the methoxyl signal; the ir showed a 5.95-μ band, characteristic of an unsaturated ketone.

17β-Ethoxy-16α,17-cyclopropanoandrostan-3β-ol Acetate (1f, R = Et; R′ = Ac).—The ethyl ether 1c (R′ = Ac, 10.8 g) was methylenated (procedure D). The resulting crude product was recrystallized from methylene chloride–methanol to yield 7.8 g of pure adduct: mp 147–149°; 5.78 μ; 51 (19-CH_3), 61 (18-CH_3), 122 Hz (OAc).

Anal. Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23; OEt, 12.03. Found: C, 77.25; H, 10.30; OEt, 12.02.

Chromatography of the mother liquors afforded additional acetate 1b (R = Et; R′ = Ac) as well as its 3-hydroxy derivative (see below).

17β-Ethoxy-16α,17-cyclopropanoandrostan-3β-ol (1f, R = Et; R′ = H).—The acetate 1f (R = Et, 5.6 g) was saponified (proce-

(26) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

dure E) yielding 5.2 g of the corresponding alcohol. Recrystallization from acetone–hexane gave the pure material: mp 187–189°; 2.73 μ; 49 (19-CH_3), 59 Hz (18-CH_3). The nmr showed no clear cyclopropyl signals; $[\alpha]D$ +20°; mass spectrum (70 eV) *m/e* 332 (3), 315 (2), 298 (2).

Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.92. Found: C, 79.76; H, 10.62.

Treatment of this alcohol with aqueous *p*-toluenesulfonic acid in methanol effected no reaction. At room temperature hydrobromic acid in acetic acid produced the *D*-homo ketone (60%) and a mixture of 16α- (20%) and 16β- (10%) methylandrostanes (by vpc analysis).

17β-Ethoxy-16α,17-cyclopropanoandrostan-3-one (2f, R = Et).—The alcohol **1f** (R = Et; R′ = H; 2.8 g) in 30 ml of pyridine was treated with the Sarett reagent[26] from 3 g of CrO_3. After 5 hr the product was isolated by ether extraction and yielded, by recrystallization of the crude product from acetone–hexane, 1.43 g of the ketone **2f** (R = Et): mp 142–145°; 5.82 μ; 37, 42, 48, 51 (weak cyclopropyl bands), 62 Hz (18,19-CH_3's); $[\alpha]D$ +51°.

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 82.07; H, 10.38.

Oxidation of this ketone with selenium dioxide or with dichlorodicyanoquinone gave intractable mixtures.

17β-Ethoxy-16α,17-cyclopropanoandrost-2-en-3-ol acetate (3-enol acetate of 2f, R = Et) was prepared from 0.2 g of the ketone **2f** (R = Et) by use of procedure F. The product was crystallized from methylene chloride–methanol to yield 0.16 g of the enol acetate: mp 139–140°; 5.72 μ; 51 (19-CH_3), 61 (18-CH_3), 126 (OAc), 316 Hz (C_6H, m).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.48; H, 9.78.

3β,17β-Diacetoxy-16α,17-cyclopropanoandrostane (1f, R = Ac; R′ = Ac).—The enol acetate of isoandrosterone acetate[27] (29 g) was methylenated (procedure D). The crude extract deposited 9 g of crystals from ether which was recrystallized from acetone to yield the pure sample: mp 184–185°; 5.80 μ; 50 (19-CH_3), 55 (18-CH_3), 122 Hz (OAc); mass spectrum (70 eV) *m/e* 388 (1), 373 (10), 346 (100), 328 (40), 217 (40).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.24; H, 9.04.

Chromatography of the mother liquors yielded first the enol acetate **1c** (R, R′ = Ac). An additional 7.6 g of adduct **1f** (R, R′ = Ac) was obtained by elution with 5% ethyl acetate–benzene followed closely by 7.8 g of isoandrosterone acetate. In addition, 0.45 g of the 3-hydroxy 17-acetate **1f** (see below) was eluted at 30% ethyl acetate–benzene. The 3,17-diacetate was stable to iodine in carbon tetrachloride at room temperature for 20 hr.

16α,17-Cyclopropanoandrostane-3β,17β-diol (1f, R, R′ = H).—A mixture of 2 g of the diacetate **1f** (R, R′ = Ac) in 200 ml of methanol and 20 ml of 10% aqueous potassium hydroxide was stirred at room temperature for 1.5 hr. The mixture was diluted with water and filtered yielding 1.6 g of product. Recrystallization of a portion of this material from aqueous methanol gave the diol, mp 166–168°, as a hemihydrate: 2.95 μ (KBr); 50 (19-CH_3), 58 Hz (18-CH_3).

Anal. Calcd for $C_{20}H_{32}O_2 \cdot {}^1/_2H_2O$: C, 76.63; H, 10.61. Found: C, 76.65; H, 10.56.

The material was unstable to chromatography on alumina or silica. An alternate preparation of the diol was achieved in good yield by treatment of an ether solution of the diacetate with lithium aluminum hydride at room temperature overnight. Acetylation of the diol with acetic anhydride–pyridine at room temperature afforded the starting diacetate **1f** (R, R′ = Ac).

17β-Acetoxy-16,17-cyclopropanoandrostan-3β-ol (1f, R = Ac; R′ = H).—The diacetate **1f** (R, R′ = Ac) (1 g) in 70 ml of tetrahydrofuran was diluted with 140 ml of methanol and then with 60 ml of 1:1 water–saturated aqueous potassium bicarbonate solution. The mixture was stirred for 3 hr and was then diluted with water. The resulting precipitate was collected and chromatographed. Early fractions (eluted with 2% ethyl acetate–benzene) yielded 440 mg of crude starting material. Elution with 5% ethyl acetate–benzene gave 390 mg of the crude 17-monoacetate **1f** (R = Ac; R′ = H). Recrystallization from methylene chloride–hexane afforded the pure compound: mp 134–136°; 2.76, 5.74 μ; 50 (19-CH_3), 56 (18-CH_3), 122 Hz (OAc).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.49; H, 9.78.

Later fractions contained the D-homo ketone (ir, nmr analysis).

17β-Acetoxy-16,17-cyclopropanoandrostan-3-one (2f, R = Ac). Procedure G.—Jones reagent[28] (1.3 mol equiv of a 4 *N* chromic acid solution) was added dropwise over 2 min to a solution of 0.16 g of the alcohol **1f** (R = Ac; R′ = H) in 2 ml of acetone at 5°. After 15 min, excess 2-propanol was added and the reaction mixture was diluted with water. The resulting precipitate was separated and recrystallized from aqueous methanol to yield 60 mg of the ketone **2f** (R = Ac): mp 165–166°; 5.70, 5.76 μ; 57 (18-CH_3), 62 (19-CH_3), 121 Hz (OAc); mass spectrum (70 eV) *m/e* 344 (0.03), 329 (10), 312 (100), 287 (100), 284 (100), 233 (100).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.39; H, 9.43.

17β-Hydroxy-16,17-cyclopropanoandrostan-3-one (2f, R = H).—A slurry of the acetate **2f** (R = Ac, 0.25 g) in 5 ml of methanol containing 0.25 ml of 10% aqueous potassium hydroxide was stirred at room temperature for 3 hr. (The starting material dissolved after 1 hr.) The solution was diluted with water and the resulting precipitate was collected and recrystallized from aqueous acetone to yield 0.15 g of the hydroxy ketone **2f** (R = H): mp 131–134° (resolidifies, remelts at 174–204°); 2.82, 5.82 μ (KBr); 61 (18-CH_3), 63 Hz (19-CH_3).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.49; H, 10.05.

Isomerization of the 3,17-Diol 1f (R, R′ = H). A. Base Catalysis.—A solution of 0.10 g of the diol **1f** (R, R′ = H) in 5 ml of methanol containing 0.1 ml of 10% aqueous potassium hydroxide was boiled for 2 hr and then diluted with water. The resulting precipitate was collected and recrystallized from aqueous methanol to yield 76 mg of the *D*-homo ketone **1g** (R′ = H), mp 193–195°, identical spectrally with the known compound. The mother liquors contained a mixture of **1g** and the 16-methyl androstanes (vpc analysis).

B. Acid Catalysis.—A solution of 100 mg of the diol **1f** in 15 ml of acetone and 0.5 ml of water containing 30 mg of *p*-toluenesulfonic acid was boiled for 18 hr. (A similar treatment at room temperature effected no change.) The cooled solution was diluted with water and the resulting precipitate collected. The major component was readily identified as the *D*-homo ketone **1g** (R′ = H) by ir, nmr, and vpc. When methanol was used as solvent, after 2.5 hr at reflux, the reaction was half complete; the product contained 3β-hydroxy-16α-methylandrostan-17-one (28%) and the *D*-homo ketone **1g** (R′ = H; 18%) by vpc analysis. With a longer reaction time, the epimeric 16β-methylandrostane was formed.

Oxidation of 16α,17-Cyclopropanoandrostane-3β,17β-diol (1f, R, R′ = H). A. Ferric Chloride Oxidation.—A solution of 24 ml of 10% aqueous ferric chloride was added with stirring to a solution of 0.80 g of the diol **1f** (R, R′ = H) under a nitrogen atmosphere at 5°. After 20 min, the solution was diluted with water and the resulting precipitate was separated and washed with water. The material was dried and then purified by a short (five fraction) chromatogram, yielding 0.54 g of the pure unsaturated ketone **1e** (R′ = H), as indicated by ir, nmr, and uv analysis.

The yield of the 16,17a-diketone **1i** (R′ = H; Z = O) from these reactions varied from 2 to 15% and was most readily detected by its characteristic uv absorption (see below).

B. Chromic Acid Oxidation.—Jones reagent[28] (3 ml) was added dropwise to 1 g of the diol **1f** (R, R′ = H) in 50 ml of acetone at 5°. After 1.5 hr the solution was diluted with water. The resulting precipitate was dissolved in ether and stirred with 2% aqueous potassium hydroxide. The ether soluble portion yielded a crystalline residue which was recrystallized from methylene chloride–hexane to yield 0.18 g of the pure unsaturated ketone **2e**: mp 192–194°; 5.83, 5.96 μ; 223 mμ (ε 7550); 63 (18,19-CH_3's), 350 and 360 (16-H), 402–422 Hz (16,17-H's).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.22; H, 9.41.

The aqueous basic extract was acidified and the resulting precipitate was collected, yielding 0.12 g of the triketone **2i** (Z = O), identical with the material produced below.

(27) J. Fajkoš and F. Šorm, *Collect. Czech. Chem. Commun.*, **24**, 766 (1959).

(28) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

3β-Acetoxy-*D*-homoandrost-16-en-17a-one (1e, R′ = Ac).—The methyl ether **1f** (R = Me; R′ = Ac) (1 g) and 0.76 g of iodine were mixed in 50 ml of carbon tetrachloride resulting in the slow formation of a heavy purple oil. After 20 hr methylene chloride and excess aqueous sodium thiosulfate were added and the mixture was stirred for 3 hr at room temperature. The product was then isolated by methylene chloride extraction yielding an oil (found, 4.69% I). The product was stirred in 10 ml of dimethylformamide with 0.5 g of lithium carbonate and 0.01 g of lithium chloride. The material, extracted with benzene, was crystallized from methylene chloride–hexane to yield 0.43 g of the unsaturated ketone: mp 148–151°; 5.75, 5.93 μ; 222 (ε 7800) mμ; 51 (19-CH_3), 62 (18-CH_3), 123 Hz (OAc).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.31; H, 9.22.

Chromatography of the mother liquors showed the major impurity to be the known saturated ketone **1g** (ir, nmr, and vpc analysis). A similar halogenation procedure using bromine in carbon tetrachloride in the presence of anhydrous potassium carbonate was successful in producing the unsaturated ketone **1e** but the accompanying bromo derivative **1h** made iodine a superior reagent. Use of bromine in pyridine effected no reaction.

3β-Hydroxy-*D*-homoandrost-16-en-17a-one (1e, R′ = H). A. Dehydration. Procedure H.—Phosphorous oxychloride (35 ml) was added to a solution of 35.8 g of the acetate **1m** in 350 ml of pyridine. The mixture was stirred at ambient temperature overnight and was then poured into ice water with stirring. The product (preparation C) extracted with chloroform consisted of a 3:2 mixture of Δ^{16} (**1k**, R′ = Ac) to $\Delta^{17(20)}$ isomers (vpc analysis).

B. Ozonolysis. Procedure I.—A solution of 10 g of the crude olefin **1k**, as produced above, in 250 ml of methylene chloride and 3 ml of pyridine was treated with a stream of ozonized oxygen at −70° until a blue color appeared. Zinc dust (15 g) and 60 ml of acetic acid was added and the mixture was stirred for 1 hr in an ice bath. The mixture was filtered and the filtrate extracted with methylene chloride. The product was purified by chromatography. The 17-ketone **1a** (R′ = Ac, 3.0 g) was eluted at 10% ethyl acetate–benzene, followed by the amorphous ketoaldehyde **1j** (R′ = Ac; Y = H; 3.3 g): 3.68, 5.78, 5.84 μ (sh); 48 (19-CH_3), 65 (18-CH_3), 120 (OAc), 127 Hz ($COCH_3$).

C. Cyclization. Procedure J.—A solution of 2.6 g of the ketoaldehyde **1j** (R′ = Ac) in 250 ml of methanol and 50 ml of 10% aqueous potassium hydroxide was boiled under an atmosphere of nitrogen for 1 hr. The methanol solution was diluted with 100 ml of water, the methanol was distilled, and the resulting mixture was extracted with methylene chloride. The product was recrystallized from ether and from acetone–hexane to yield the unsaturated ketone **1e** (R′ = H): mp 182–184°; 2.76, 5.97 μ; 222 mμ (ε 8500); 48 (19-CH_3), 61 (18-CH_3), 349 and 361 (m, 16-H), 404–423 Hz (m, 17-H); mass spectrum (70 eV) *m/e* 302 (5), 274 (10), 256 (4).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.10; H, 10.29.

Saponification of the acetate **1e** (procedure E) also led to a good yield of the alcohol **1e**.

***D*-Homoandrosta-4,16-diene-3,17-dione (2e, Δ^4). A. Ozonolysis.**—A solution of 10 g of 17-methylandrosta-4,16-dien-3-one (**2k**, Δ^4) was ozonized (procedure I) using a total of 1.2 mol equiv of ozone. The product was chromatographed and yielded 3.1 g of amorphous ketoaldehyde which crystallized poorly on ether trituration as a solvate: 3.66 (w), 5.80, 5.98 μ; 68 (18-CH_3), 72 (19-CH_3), 128 (Ac), 344 Hz (C_6H).

B. Cyclization.—The ketoaldehyde **2j** (Y = H; Δ^4) was cyclized (procedure J) and the resulting product was purified by chromatography. The crystalline material (0.44 g) eluted with 5% ethyl acetate–benzene was recrystallized from acetone to give the dienedione as a hemiacetonate: mp 184–187°; 5.98 μ; 235 mμ (ε 20,000); 64 (18-CH_3), 72 (19-CH_3), 355 Hz (m, 15-H); mass spectrum (70 eV) *m/e* 298 (10), 256 (8), 175 (3), 124 (5).

Anal. Calcd for $C_{20}H_{26}O_2 \cdot {}^1/_2C_3H_6O$: C, 78.86; H, 8.93. Found: C, 79.23; H, 9.00.

When the unpurified ketoaldehyde was used in this cyclization an acidic portion was isolated by extraction. This material was recrystallized from acetone–hexane to yield **3,17-diketo-17-methyl-16,17-secoandrost-4-en-16-oic acid**: mp 207–210°; 5.83, 5.98 μ; 241 mμ (ε 16,200); 61 (18-CH_3), 72 (19-CH_3), 132 (Ac), 347 Hz (4-H); mass spectrum (70 eV) *m/e* 332 (2), 314 (1), 289 (5), 272 (1), 230 (1).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.17; H, 8.42.

3-Methoxy-*D*-homoestra-1,3,5(10),16-tetraen-17a-one (4e).—3-Methoxy-17α-methylestra-1,3,5(10)-trien-17-ol (**4m**) was dehydrated and ozonized (procedures H, I). The product was chromatographed and the crude ketoaldehyde **4j** (14 g of material eluted with 5% ethyl acetate–benzene) was treated in 150 ml of methanol with 15 ml of 5% aqueous potassium hydroxide at room temperature for 45 min. The product was isolated by benzene extraction and chromatographed. Early fractions (6.8 g) from the column were largely unreacted ketoaldehyde **4j** eluted at 2% ethyl acetate–benzene. Elution with 5% ethyl acetate–benzene gave fractions which were recrystallized from acetone–hexane (Darco) to give 1.83 g of **3-methoxy-*D*-homoestra-1,3,5(10)-trien-15β-ol-17a-one (4i, Z = β-OH, H)**: mp 177–179°; 2.81, 5.89 μ (KBr); 68 (18-CH_3), 215–240 (15α-H), 226 Hz (OMe). The ultraviolet spectrum showed only the A ring chromophore.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.60; H, 8.27.

The ketol **4i** (Z = OH, 0.75 g) was treated with base (procedure J) and yielded, by dilution of the reaction mixture with water, 0.62 g of the unsaturated ketone **4e**. Recrystallization from acetone–hexane gave 0.47 g of the pure material: mp 162–164°; 6.01 μ; 222 mμ (ε 15,700; enhanced uv due to the A ring chromophore); $[\alpha]_D$ −1°.

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.04; H, 8.07.

The same material was isolated by base treatment of the crude ketoaldehyde **4j** (Y = H) followed by chromatography. Hydrogenation of the unsaturated ketone proceeded readily to give in good yield the known saturated ketone **4g**.[11]

3β-Acetoxy-17-keto-17-methyl-16,17-secoandrostan-16-oic Acid (1j, R′ = Ac; Y = OH).—Sodium metaperiodate (12.5 g) in 125 ml of water was added to a suspension of 2.2 g of ruthenium dioxide (54%) in 500 ml of acetone.[17] A solution of 11 g of "preparation C" (the crude olefin **1k**, R′ = Ac) in 500 ml of acetone was added over a 30-min period. An additional 25 g of sodium metaperiodate in 150 ml of water was then added over a 1-hr period. After a total reaction time of 4 hr, the reaction was diluted with 50 ml of 2-propanol. The black precipitate was filtered and the filtrate was concentrated to 100 ml at T <20°. The remainder was diluted with saturated sodium chloride solution and extracted with ethyl acetate. The extract was washed twice with iced 2% potassium hydroxide solution. The basic washes were acidified and extracted in turn with ethyl acetate. The latter yielded 2.17 g of the crystalline acid which was further purified by recrystallization from ether–hexane to give the pure compound: mp 153–156°; 5.82 μ; 49 (19-CH_3), 64 (18-CH_3), 121 (OAc), 132 Hz (Ac).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.54; H, 8.92.

3β-Hydroxy-17-keto-17-methyl-16,17-secoandrostan-16-oic acid (1j, R′ = H; Y = OH) was prepared by saponification of the corresponding acetate (procedure E) and was crystallized from methylene chloride–hexane to yield the pure alcohol: mp 179–185°; 2.90, 5.85 μ (KBr); 46 (19-CH_3), 62 (18-CH_3), 130 Hz (Ac).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.37; H, 9.56.

3β-Hydroxy-17-keto-17-methyl-16,17-secoandrostan-16-oic Acid Methyl Ester (1j, R′ = H; Y = OMe).—The hydroxy acid **1j** (R′ = H; Y = OH; 0.90 g) was suspended in 250 ml of ether. Diazomethane, prepared from 2 g of *N*-nitroso-*N*-methylurea in 100 ml of ether, was added. The mixture was stirred 1 hr. (The starting material dissolved during this time.) The solvent was evaporated and the residue crystallized from methylene chloride–hexane to yield 0.67 g of the ester: mp 143–145°; 2.86, 5.76, 5.88 μ; 48 (19-CH_3), 61 (18-CH_3), 130 (Ac), 217 Hz (OMe).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.10; H, 9.88.

3β-Acetoxy-17-keto-17-methyl-16,17-secoandrostan-16-oic acid methyl ester (1j, R′ = Ac; Y = OMe) was prepared by essentially the same procedure yielding crystalline material which was recrystallized from ether–hexane to give the pure compound: mp 127–129°; 5.76, 5.88 μ; 49 (19-CH_3), 62 (18-CH_3), 122 (OAc), 133 (Ac), 221 Hz (OMe).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.02; H, 9.51.

3β-Hydroxy-*D*-homoandrostane-16,17a-dione (1i, R′ = H; Z = O).—Sodium methoxide (0.10 g) was added to a solution of 0.45 g of the ester **1j** (R′ = H; Y = OMe) in 4 ml of anhydrous benzene. The mixture was stirred under nitrogen for 18 hr and was poured into a mixture of ice water and ether. The aqueous layer was separated and acidified with sodium dihydrogen phosphate. The resulting precipitate was separated and washed with water to give 380 mg of the diketone. Recrystallization from ethyl acetate gave the pure compound: mp 260–263°; 2.80, 2.96, 6.18 μ (KBr); 255 mμ (ε 16,800) [in 0.1 *N* KOH–MeOH, 282 mμ (ε 29,300)].

Anal. Calcd for $C_{20}H_{30}O_3$: C, 73.30; H, 8.95. Found: C, 73.40; H, 9.31.

The 3-acetate **1j** (R′ = Ac; Y = OMe) underwent a similar conversion in good yield to provide the same diketone (**1i**, R′ = H).

***D*-Homoandrostane-3,16,17a-trione (2i, Z = O).**—The 3-hydroxyl derivative **1i** (R′ = H; Z = O) was oxidized at 5° for 40 min with 1.7 ml of Jones reagent. The mixture was diluted with water and the resulting precipitate was separated. Recrystallization from aqueous methanol gave the pure sample: mp 292–295° dec; 5.82, 6.20 μ (KBr); in 0.1 *N* KOH–MeOH, 284 mμ (ε 24,700).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.69; H, 9.00.

3β,5α-Diacetoxyandrostan-17-one (3a, R′, R″ = Ac).—Acetic anhydride (2 ml) containing 0.40 g of *p*-toluenesulfonic acid was diluted with 20 ml of acetic acid and 20 ml of acetic anhydride. 3β,5α-Dihydroxyandrostan-17-one[12] (10.0 g) was then added. The mixture was stirred in a water bath at room temperature for 4 hr, was cooled to 5°, and was diluted with ice water. The resulting mixture was stirred at 5° for 1 hr and then filtered, washing the precipitate with water. The product was recrystallized from aqueous acetone to yield 11.4 g of the pure diacetate: mp 155–158°; 5.73 μ; 53 (18-CH_3), 64 (19-CH_3), 121 (OAc), and 123 Hz (OAc).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.72; H, 8.56.

3β,5α-Diacetoxyandrostan-17-one Diethyl Ketal (3b, R = Et; R′, R″ = Ac.) Procedure K.—To a slurry of 11.1 g of the diacetate **3a** (R′, R″ = Ac) in 15 ml of 2B ethanol, 15 ml of benzene, and 30 ml of triethyl orthoformate was added 0.4 ml of concentrated sulfuric acid. The mixture was stirred at room temperature for 2 hr and then treated with 2 ml of tetramethyl guanidine. The resulting colorless solution was diluted with water and the product extracted with benzene. Recrystallization of the product from ether–methanol gave 6.4 g of **17β-ethoxy-17-methoxyandrostane-3β,5α-diol diacetate** as a hemimethanolate: mp 176–177°; 5.78 μ; 52 (18-CH_3), 61 Hz (19-CH_3).

Anal. Calcd for $C_{27}H_{44}O_6 \cdot {}^1/_2CH_4O$: C, 68.71; H, 9.65. Found: C, 68.62; H, 9.38.

When the crude ketal was triturated with ether, the *diethyl* ketal **1b** (R = Et) crystallized (nmr analysis).

Reaction of Ethyl Orthoformate with 3β,5α-Dihydroxyandrostan-17-one (3a, R′, R″ = H).—The dihydroxy ketone **3a** (5 g) was treated with ethyl orthoformate (procedure K) yielding an amorphous product: 2.75, 5.80 (m) μ; the nmr showed many methyl group signals as well as a broad signal at 323 Hz for the C-6 vinyl proton and the C-3α proton. The product was then pyrolyzed in cymene (procedure A) and the resulting material chromatographed. **3β-Formyloxyandrost-5-en-17-one** was eluted at 5% ethyl acetate–benzene and recrystallized from ether. It had mp 145–147°; 5.75 μ; 53 (18-CH_3), 64 (19-CH_3), 324 and 328 (C_6H), 483 Hz (HCO_2).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.14; H, 8.88.

Elution of the column with 50% ethyl acetate–benzene gave 1.0 g of crude monoformate which recrystallized from acetone–hexane to yield **3β,5α-dihydroxyandrostan-17-one 3-formate**: mp 184–186°; 2.76, 5.76 μ; 52 (18-CH_3), 62 (19-CH_3), 483 Hz (HCO_2); $[\alpha]_D$ +56°.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.90; H, 9.03.

Later eluents afforded 0.2 g of the starting diolone **3a** (R′, R″ = H). The monoformate was also prepared by dissolving dehydroisoandrosterone in formic acid; after 1 hr at room temperature, addition of water gave the desired compound. A similar treatment of the diolone **3a** (R′, R″ = H) afforded in high yield its monoformate.

17β-Ethoxyandrost-16-ene-3β,5α-diol Diacetate (3c, R = Et; R′, R″ = Ac).—The diethyl ketal **3b** (R = Et; R′, R″ = Ac; 67 g) was boiled in cymene (procedure A) and afforded, by direct crystallization from methanol, 26 g of the enol ether, mp 130–135°. Recrystallization from methanol containing a trace of pyridine gave the pure product, mp 136–138°, 2.75 μ.

Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.79; H, 9.28.

17β-Ethoxy-16α,17-cyclopropanoandrostane-3β,5α-diol Diacetate (3f, R = Et; R′, R″ = Ac).—The enol ethyl ether **3c** (R′, R″ = Ac) was treated with methylene iodide (procedure D) yielding 18.5 g (72%) of the recrystallized (methylene chloride–methanol) cyclopropyl derivative: mp 194–197°; 5.78 μ; 61 (19-CH_3), 63 Hz (18-CH_3).

Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.09; H, 9.09.

17β-Ethoxy-16α,17-cyclopropanoandrostane-3β,5α-diol 5-Acetate (3f, R = Et; R′ = H; R″ = Ac).—A slurry of 1.40 g of the diacetate **3f** (R = Et) in 150 ml of methanol, 5 ml of water, and 5 ml of saturated aqueous potassium bicarbonate was stirred at room temperature for 8 hr. The solution was diluted with water and the product collected by filtration. The water-washed and air-dried precipitate was recrystallized from acetone–hexane to yield 1.05 g of the pure 3-hydroxy derivative: mp 203–205°; 2.75, 5.78 μ; 62 (18,19-CH_3's), 122 Hz (OAc); $[\alpha]_D$ +35°.

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.75; H, 9.99.

The same material was produced by boiling the diacetate in methanol containing aqueous potassium hydroxide for 2 hr.

17β-Ethoxy-16α,17-cyclopropanoandrostane-3β,5α-diol (3f, R = Et; R′, R″ = H). Procedure L.—A solution of 3.0 g of the diacetate **3f** (R = Et) in 200 ml of ether was added to a stirred slurry of 1.8 g of lithium aluminum hydride in 300 ml of ether over a 10-min period. After an additional 4 hr of stirring at room temperature, the solution was diluted cautiously and consecutively with 140 ml of ethyl acetate, 7 ml of water, and 2 ml of 10% aqueous potassium hydroxide. The resulting mixture was filtered through a mixture of magnesium sulfate and Super-Cel. The crystalline product, obtained by concentration of the filtrate, was recrystallized from acetone to give 1.8 g of the diol: mp 215–217°; 2.88 μ (KBr); 55 Hz (18,19-CH_3's) (DMSO-d_6); $[\alpha]_D$ +26°.

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.43; H, 10.60.

17β-Ethoxy-5α-acetoxy-16α,17-cyclopropanoandrostan-3-one (2f, R = Et; 5α-OAc).—A solution of 0.85 g of the 3-alcohol **3f** (R = Et; R″ = Ac) in 12 ml of pyridine was treated with the Sarett reagent[26] from 2.0 g of chromic acid at 5° for 10 min and at room temperature for 6 hr. The mixture was then diluted with water and the product isolated by ether extraction. Recrystallization of the material obtained from acetone gave 0.60 g of the ketone: mp 184–187°; 5.75, 5.82 μ (sh); 63 (18-CH_3), 73 Hz (19-CH_3).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.82; H, 9.12.

17β-Ethoxy-16α,17-cyclopropanoandrost-4-en-3-one (2f, R = Et; Δ^4).—A solution of 0.34 g of the 3-ketone **2f** (R = Et; 5α-OAc) in 50 ml of methanol, 5 ml of water, and 5 ml of saturated aqueous potassium bicarbonate was heated at reflux under an atmosphere of nitrogen for 16 hr. The solution was diluted with water and the methanol was distilled. The resulting precipitate was collected on a filter, washed with water, dried, and recrystallized from acetone–hexane to yield the unsaturated ketone: mp 166–168°; 5.98 μ; 241 mμ (ε 15,900); 63 (18-CH_3), 72 (19-CH_3), 343 Hz (4-H); $[\alpha]_D$ +125°.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.60; H, 9.66.

Androst-16-ene-3β,5α,17-triol Triacetate (3c, R, R′, R″ = Ac).—A solution of the dihydroxy ketone **3a** (6.5 g) in 200 ml of isopropenyl acetate containing 0.4 g of *p*-toluenesulfonic acid was distilled to half volume over an 18-hr period. The product, extracted from the cooled solution with ether, was dissolved in 1 l. of hexane and passed over a short chromatographic column containing 200 g of Florisil. The adsorbent was washed with 4 l. of 80% benzene–hexane, the solvent distilled, and the resulting crystalline material recrystallized from methanol to yield 4.4 g of the enol acetate: mp 152–153°; 5.75 μ; 53 (18-CH_3), 63 (19-CH_3), 118, 123, 128 (OAc's), 324–328 Hz (16-H).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.24; H, 8.50.

16α,17-Cyclopropanoandrostane-3β,5α,17β-triol Triacetate (3f, R, R′, R″ = Ac).—The enol acetate (**3c**, R, R′, R″ = Ac; 4.3 g) was methylenated (procedure D) to afford, by recrystallization from methylene chloride–methanol, 2.50 g of the adduct: mp 230–233°; 5.75 μ; 56 (18-CH_3), 62 (19-CH_3), 120 (OAc), 124 Hz (OAc); $[\alpha]_D$ +31°.

Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.76; H, 8.51.

Chromatography of the mother liquors afforded an additional adduct as well as smaller amounts of the starting enol acetate **3c** and the 17-ketone **3a**. The triacetate was also prepared by acetylation of the 5-monoacetate **3f** (R, R′ = H; R″ = Ac) with pyridine–acetic anhydride at room temperature.

16α,17-Cyclopropanoandrostane-3β,5α,17-triol (3f, R, R′, R″ = H).—The triacetate **3f** (0.28 g) was reduced with $LiAlH_4$ (procedure L) and yielded a crystalline residue which was recrystallized from acetone–ethyl acetate to give the triol (as a solvate with 1 mol equiv of ethyl acetate): mp 178–182°; 2.88, 5.73 μ (EtOAc); 52 (18-CH_3), 54 Hz (19-CH_3) (DMSO-d_6).

Anal. Calcd for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.60; H, 9.82.

3β,5α-Dihydroxy-*D*-homoandrostan-17a-one 5-Acetate (3g, R′ = H; R″ = Ac).—The triacetate (1 g) was treated with base (procedure E) yielding 0.75 g of crystals which were recrystallized from aqueous methanol to give the pure material: mp 207–210°; 2.75, 2.79, 5.84 μ; 60 (19-CH_3), 66 (18-CH_3), 122 Hz (OAc).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.68; H, 9.26.

A similar treatment of the diol **3f** (R, R′ = H; R″ = Ac) with base gave the same D-homo ketone (**3g**, R′ = H; R″ = Ac).

3β,5α-Diacetoxy-*D*-homoandrostan-17a-one (3g, R′, R″ = Ac) was prepared from the monoacetate **3g** (R′ = H; R″ = Ac) with pyridine–acetic anhydride at 95°. The product was recrystallized from acetone–hexane to yield the diacetate: mp 142–143°; 5.75, 5.83 μ; 61 (19-CH_3), 66 (18-CH_3), 120 (OAc), 124 Hz (OAc).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.61; H, 8.51. Found: C, 71.85; H, 8.91.

5α-Acetoxy-*D*-homoandrostane-3,17a-dione (2g, 5α-OAc).—The alcohol **3g** (R′ = H; R″ = Ac) was oxidized with Jones reagent[28] (procedure G) and furnished, by dilution of the reaction mixture with water, 0.54 g of the diketone (**2g**, 5α-OAc). Recrystallization from aqueous acetone gave the pure material: mp 180–181°; 5.78 μ; 67 (18-CH_3), 72 (19-CH_3), 118 Hz (OAc).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.40; H, 9.14.

Treatment of this compound in aqueous methanol with potassium bicarbonate afforded in good yield the known unsaturated diketone (**2g**, Δ^4).

16α,17-Cyclopropanoandrostane-3β,5α,17-triol 5-Acetate (3f, R, R′ = H; R″ = Ac).—Saturated potassium bicarbonate solution (10 ml) and 10 ml of water were added to a solution of 1 g of the triacetate **3f** (R, R′, R″ = Ac) in 150 ml of methanol. The mixture was stirred at room temperature for 7.5 hr and the methanol was then evaporated in a stream of nitrogen (T <35°). The mixture was diluted with water and the resulting precipitate was separated, dried, and recrystallized twice from acetone–cyclohexane to afford 0.51 g of the diol as a hemiacetonate: mp 173–178°; 2.98, 5.80 μ; 53 (18-CH_3), 58 (19-CH_3), 118 Hz (OAc); $[\alpha]_D$ +29°.

Anal. Calcd for $C_{22}H_{34}O_4 \cdot {}^1/_2C_3H_6O$: C, 72.09; H, 9.53. Found: C, 71.81; H, 9.71.

The mother liquors were chromatographed on acid-washed alumina. Fractions eluted with 20% ethyl acetate–benzene were combined and recrystallized from ether–hexane to yield 0.11 g of **16α,17-cyclopropanoandrostane-3β,5α,17-triol 5,17-diacetate (3f, R, R″ = Ac; R′ = H)**: mp 179–181°; 2.78, 5.79 μ; 53 (18-CH_3), 57 (19-CH_3), 117 and 119 Hz (OAc); $[\alpha]_D$ +29°.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.19; H, 9.03.

In a similar experiment the mother liquors were chromatographed on alkaline alumina (Merck). The chief product was eluted, after a 2-day interval, with 5% ethyl acetate–benzene and recrystallized from methylene chloride–hexane to yield pure **16α,17-cyclopropanoandrost-5-ene-3β,17-diol 17-acetate (1f, Δ^5; R = Ac; R′ = H)**: mp 118–126°; 2.75, 5.72 μ; 55 (18-CH_3), 62 (19-CH_3), 120 (OAc), 320 Hz (m, C_5 H); mass spectrum (70 eV) m/e 344 (1), 326 (2), 302 (10), 284 (5).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.34; H, 9.61.

5α,17β-Acetoxy-16α,17-cyclopropanoandrostan-3-one (2f, R = Ac; 5α-OAc).—The alcohol **3f** (R, R″ = Ac; R′ = H; 6 g) was oxidized with Jones reagent[28] (procedure G) and afforded, after recrystallization of the product from methylene chloride–methanol, 2.87 g of the ketone (as a hemimethanolate): mp 170–177°; 5.75 μ; 57 (18-CH_3), 72 (19-CH_3), 118 (OAc), 120 Hz (OAc).

Anal. Calcd for $C_{24}H_{34}O_5 \cdot {}^1/_2CH_4O$: C, 70.30; H, 8.67. Found: C, 70.68; H, 8.62.

3β,5α-Dihydroxyandrostan-17-one 5-Acetate (3a, R′ = H; R″ = Ac).—A solution of 2 g of the diacetate **3a** in 70 ml of methanol containing 5 ml of saturated aqueous potassium bicarbonate and 5 ml of water was heated at reflux for 0.5 hr. Water was added, the methanol was distilled, and the resulting precipitate was collected. Recrystallization of this material from aqueous methanol and then methylene chloride–hexane gave the monoacetate: mp 152–157°; 2.75, 5.75 μ; 52 (18-CH_3), 62 (19-CH_3), 122 Hz (OAc); $[\alpha]_D$ +73°.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.30; H, 9.43.

Dehydroacetoxylation of 3a (R′ = H; R″ = Ac) on Alumina.—A solution of 0.29 g of the monoacetate **3a** (R′ = H; R″ = Ac) in benzene was put on 20 g of alumina (Merck). After 5 days elution with 10% ethyl acetate–benzene gave 20 mg of androstenedione. Elution with 30% ethyl acetate–benzene gave 0.26 g of dehydroisoandrosterone contaminated with 10% of the starting 5α-acetate (ir, nmr, tlc analysis).

17β-Acetoxy-16α,17-cyclopropanoandrost-4-en-3-one (2f, R = Ac; Δ^4). A. Oppenauer Oxidation.—A solution of 0.40 g of the alcohol **1f** (R = Ac; R′ = H; Δ^5) and 1 ml of redistilled cyclohexanone in 60 ml of toluene was distilled to a volume of 50 ml. Aluminum isopropoxide (0.45 g) in 3 ml of toluene was added to this boiling solution over a 2-min period. After 15 min more the solution was cooled and excess Rochelle salts solution was added. The mixture was steam distilled for 0.5 hr resulting in the precipitation of a crystalline product. Separation of this material followed by recrystallization from methylene chloride–hexane gave the ketone: mp 208–211°; 5.72, 6.01 μ; 239 mμ (ε 16,500); 57 (18-CH_3), 70 (19-CH_3), 121 (OAc), 343 Hz (4 H).

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.95; H, 8.47.

The same reagent converted the diacetate **3f** (R, R″ = Ac; R′ = H) to **2f** (R = Ac; Δ^4) using a 3-hr reflux period.

B. Dehydroacetoxylation.—The ketone **2f** (2.6 g, R = Ac; 5α-OAc) was dissolved in 250 ml of benzene and adsorbed on a chromatographic column of 260 g of alumina (Merck). After 1 hr, the steroid was eluted with 20% ethyl acetate–benzene and recrystallized from methylene chloride–hexane to yield 2.0 g of the pure unsaturated ketone **2f** (R = Ac; Δ^4), identical with the material prepared above.

17β-Hydroxy-16α,17-cyclopropanoandrost-4-en-3-one (2f, R = H; Δ^4).—The acetate **2f** (R = Ac; Δ^4; 0.90 g) was hydrolyzed according to procedure E for 2.5 hr. The product (0.78 g) was recrystallized from aqueous acetone and had mp 101–111°; 2.72, 6.00 μ; 62 (18-CH_3), 73 (19-CH_3), 344 Hz (C_4 H).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.93; H, 9.52.

3-Methoxy-17β-ethoxy-16α,17-cyclopropanoestra-1,3,5(10)-triene (4f, R = Et).—The diethyl ketal of estrone methyl ether (**4b**, 65 g), prepared by ketalization of the 17-ketone (procedure K), was boiled in cymene for 46 hr (procedure A). The resulting enol ether (amorphous) was methylenated (procedure D) without purification, yielding, by crystallization from methanol, 32 g of the adduct **4f**: mp 88–90°; no carbonyl absorption in the ir; no selective uv absorption beyond that of the aromatic A ring absorption; 62 (18-CH_3), 227 Hz (OMe); $[\alpha]_D$ +84°; mass spectrum (70 eV) m/e 326 (5), 311 (1), 298 (1), 218 (3), 174 (3), 147 (3).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.92; H, 9.45.

The mother liquors consisted mainly of the adduct **4f** (R = Et) and *ca.* 20% of the starting 17-ketone as shown by chromatographic analysis.

3-Methoxy-17β-ethoxy-16α,17-cyclopropanoestra-2,5(10)-diene (5, R = Et). Procedure M.—A solution of 23 g of the adduct

4f (R = Et) in 400 ml of tetrahydrofuran was added to 800 ml of ammonia and 400 ml of *tert*-butyl alcohol. Lithium rod (5 g) was added portionwise over a 10-min period. After a total of 40 min, excess solid ammonium chloride was added to decolorize the solution. The ammonia was distilled, water was added, and the solvents were steam distilled. The cooled aqueous mixture crystallized on cooling and the product was collected on a filter. Recrystallization of this material from methylene chloride–methanol gave 19.2 g of the product: mp 93–95°; 5.89 (m), 6.01 μ (m); no selective uv absorption; 61 (18-CH_3), 212 Hz (OCH_3); $[\alpha]_D$ +94°; mass spectrum (70 eV) *m/e* 328 (2), 204 (1), 146 (3).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.55; H, 9.71.

17β-Ethoxy-16α,17-cyclopropanoestr-5(10)-en-3-one (6, R = Et). Procedure N.—The reduction product **5** (R = Et; 5.0 g) was stirred in 95% aqueous acetic acid. The crystals dissolved in 15 min. After 25 min, the solution was diluted with water and the resulting precipitate was separated by filtration. Recrystallization of the product from aqueous methanol gave 4.0 g of the unsaturated ketone: mp 94–98°; 5.80 μ; no selective uv absorption; 62 Hz (18-CH_3); $[\alpha]_D$ +174°.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.24; H, 9.64.

17β-Ethoxy-16α,17-cyclopropanoestra-4,9-dien-3-one (8).—The unconjugated ketone (3 g) from the preceding experiment in 30 ml of pyridine at 5° was treated with 4.0 g of pyridinium bromide perbromide. After 15 min the mixture was diluted with water and the resulting dibromide was separated by filtration and displayed a band at 5.00 μ. The dibromide was dissolved in 50 ml of pyridine and after 1 hr the solution was diluted with water and extracted with benzene. The semicrystalline residue was recrystallized from ether–hexane (Darco) to yield 2.2 g of the dienone **8**: mp 102–104°; 6.00 μ; 304 mμ (ε 20,700); 72 (18-CH_3), 342 Hz (C_4 H); $[\alpha]_D$ −160°.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.95; H, 8.67.

17β-Ethoxy-16α,17-cyclopropanoestr-4-en-3-one (7, R = Et). Procedure O.—A solution of 1.4 g of the dihydroaromatic ether (**5**, R = Et) in 30 ml of methanol, 6 ml of water, and 2.4 ml of concentrated hydrochloric acid was allowed to stand at room temperature for 2 hr. The resulting mixture was diluted with water and filtered. The insoluble material was recrystallized from aqueous acetone to yield 1.25 g of the unsaturated ketone **7** (R = Et): mp 130–133°; 5.99 μ; 239 mμ (ε 11,600); 65 (18-CH_3), 350 Hz (4 H); $[\alpha]_D$ +71°.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.91; H, 9.42.

3-Methoxy-17β-acetoxy-16α,17-cyclopropanoestra-1,3,5(10)-triene (4f, R = Ac).—The enol acetate of estrone methyl ether[29] (30 g) was methylenated (procedure D). The product was taken up in 200 ml of methanol containing 20 ml of saturated aqueous potassium bicarbonate and 20 ml of water. After 15 min the solution deposited a crop of crystals. The mixture was diluted with water and filtered. The dried crystals were triturated with ether to remove estrone methyl ether (16 g). A portion (14 g) of the ether soluble material was chromatographed and the crude adduct (3.1 g), eluted at 5% ethyl acetate–benzene, was recrystallized from ether–methanol to yield 1.77 g of the adduct: mp 95–96°; 5.72 μ; 57 (18-CH_3), 122 Hz (OAc); $[\alpha]_D$ +54°; mass spectrum (70 eV) *m/e* 340 (10), 298 (10), 228 (3), 213 (2), 186 (2), 173 (3).

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.52; H, 8.26.

3-Methoxy-16α,17-cyclopropanoestra-1,3,5(10)-trien-17-ol (4f, R = H).—A solution of methyllithium in ether (1 *M*, 4.5 ml) was added to a solution of 0.80 g of the acetate **4f** (R = Ac) in 24 ml of ether at 5° over a 10-min period.[20] After an additional 10 min the reaction was poured into a stirred suspension of excess boric acid in 50 ml of water. A semicrystalline product, obtained by ether extraction, was recrystallized from ether–hexane to yield 0.46 g of the pure alcohol **4f** (R = H): mp 115–130°; 2.78 μ (KBr); 60 Hz (18-CH_3); mass spectrum (70 eV) *m/e* 298 (5), 228 (1), 213 (1), 186 (1), 173 (1).

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.61; H, 8.92.

Spectral grade chloroform was sufficiently acidic to cause transformation of the cyclopropyl alcohol **4f** (R = H) to the *D*-homo ketone **4g**, as demonstrated by the ensuing ir spectrum.

In other runs with methyllithium, under less carefully controlled conditions, the *D*-homo ketone **4g** contaminated the product so that crystallization and purification could not be effected. When attempts were made to use potassium hydroxide or potassium bicarbonate (all at room temperature) the chief product obtained was the *D*-homo ketone **4g**. This material was identical spectrally with the known compound.[11]

3-Methoxy-17β-trimethylsilyloxy-16α,17-cyclopropanoestra-1,3,5(10)-triene (4f, R = $SiMe_3$).—Hexamethyldisilazine (15 ml) was added to a stirred solution of 1.5 g of the alcohol **4f** (R = H) in 150 ml of pyridine followed by the addition of 7.5 ml of trimethylsilyl chloride. The reaction mixture was stirred at room temperature for 2 hr and then poured into ice water. The resulting precipitate was separated, washed with water, dried, and recrystallized from hexane to yield the pure silyl ether: mp 112–114°; 58 Hz (18-CH_3).

Anal. Calcd for $C_{23}H_{34}O_2Si$: C, 74.54; H, 9.25. Found: C, 74.87; H, 9.17.

3-Methoxy-17β-trimethylsilyloxy-16α,17-cyclopropanoestra-2,5(10)-diene (5, R = $SiMe_3$).—The silyl ether **4f** (R = $SiMe_3$; 1.5 g) was reduced as in procedure M. The product crystallized from pentane to yield 0.71 g of the reduced compound: mp 111–113°; 58 Hz (18-CH_3).

Anal. Calcd for $C_{23}H_{36}O_2Si$: C, 74.14; H, 9.74. Found: C, 74.06; H, 9.80.

17β-Hydroxy-16α,17-cyclopropanoestr-5(10)-en-3-one (6, R = H).—The dihydroaromatic ether **5** (R = $SiMe_3$) was treated according to procedure N and yielded a crystalline product which was recrystallized from aqueous methanol to yield the product: mp 137–148°; 5.83 μ; 58 Hz (18-CH_3).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.31; H, 9.22.

17β-Acetoxy-16α,17-cyclopropanoestr-5(10)-en-3-one (6, R = Ac) was prepared by acetylation of the corresponding alcohol at room temperature with pyridine–acetic anhydride. The product was recrystallized to give the pure material: mp 137–140°; 5.74, 5.82 μ.

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.52; H, 8.70.

Attempts to produce the 4,9-diene from this material with bromine in pyridine led to unstable mixtures containing only a little of the desired material (uv analysis).

17β-Acetoxy-16α,17-cyclopropanoestr-4-en-3-one (7, R = Ac).—Hydrolysis of **5** (R = H) according to procedure O followed by acetylation afforded the conjugated ketone: mp 115–117°; 5.70, 5.98 μ.

Anal. Found: C, 76.88; H, 8.64.

Registry No.—**1b** (R′ = Ac; R = Me), 29172-54-1; **1c** (R = Et; R′ = Ac), 29172-55-2; **1e** (R′ = Ac), 29172-56-3; **1e** (R′ = H), 29172-57-4; **1f** (R′ = Ac; R = Me), 29172-58-5; **1f** (R′ = H; R = Me), 29172-59-6; **1f** (R = Et; R′ = Ac), 29172-60-9; **1f** (R = Et; R′ = H), 29172-61-0; **1f** (R = Ac; R′ = Ac), 29172-62-1; **1f** (R, R′ = H), 29172-63-2; **1f** (R = Ac; R′ = H), 29172-64-3; **1f** (Δ^5; R = Ac; R′ = H), 29172-65-4; **1g** (R′ = H), 26729-16-8; **1h** (R′ = Ac; X = Br), 29172-67-6; **1h** (R′ = H; X = Br), 29172-68-7; **1h** (R′ = Ac; X = Cl), 29172-69-8; **1h** (R′ = H; X = Cl), 29172-70-4; **1i** (R′ = H; Z = O), 10458-94-3; **1j** (R′ = Ac; Y = OH), 29172-72-3; **1j** (R′ = Ac; Y = OH), 29172-73-4; **1j** (R′ = H; Y = OH), 29172-74-5; **1j** (R′ = H; Y = OMe), 29172-75-6; **1j** (R′ = Ac; Y = OMe), 29172-76-7; **2e**, 29172-77-8; **2e** (Δ^4), 29172-78-9; **2f** (R = Me), 29172-79-0; **2f** (enol acetate, R = Me), 29172-80-3; **2f** (R = Et), 29172-81-4; **2f** (3-enol acetate; R = Et), 29172-82-5; **2f** (R = Ac), 29172-83-6; **2f** (R = H), 29172-84-7; **2f** (R = Et; 5α-OAc), 29172-85-8; **2f** (R = Et; Δ^4), 29172-86-9; **2f** (R = Ac; 5α-OAc), 29172-87-0; **2f** (R = Ac; Δ^4), 29162-95-6; **2f** (R = H; Δ^4), 29162-96-7; **2g** (5α-OAc), 29162-97-8; **2i** (Z = O), 29162-

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98-9; **3a** (R′, R″ = OAc), 29246-51-3; **3a** (R′ = H; R″ = Ac), 29162-99-0; **3b** (R = Et; R′, R″ = Ac), 29163-00-6; **3c** (R = Et; R′, R″ = Ac), 29163-01-7; **3c** (R, R′, R″ = Ac), 29163-02-8; **3f** (R = Et; R′, R″ = Ac), 29246-52-4; **3f** (R = Et; R′ = H; R″ = Ac), 29163-03-9; **3f** (R = Et; R′, R″ = H), 29163-04-0; **3f** (R, R′, R″ = H), 29163-05-1; **3f** (R, R′ = H; R″ = Ac), 29163-06-2; **3f** (R, R″ = Ac; R′ = H), 29163-07-3; **3g** (R′ = H; R″ = Ac), 29163-08-4; **3g** (R′, R″ = Ac), 29163-09-5; **4f** (R = Et), 29163-10-8; **4f** (R = Ac), 29163-11-9; **4f** (R = H), 29163-12-0; **4f** (R = $SiMe_3$), 29163-13-1; **4i** (Z = β-OH, H), 29163-14-2; **5** (R = Et), 29163-15-3; **5** (R = $SiMe_3$), 29163-16-4; **6** (R = Et), 29163-17-5; **6** (R = H), 29246-53-5; **6** (R = Ac), 29163-18-6; **7** (R = Et), 29163-19-7; **7** (R = Ac), 29163-20-0; **8**, 29163-21-1; 3,-17-diketo-17-methyl-16,17-secoandrost-4-en-16-oic acid, 29163-22-2; 3β-formyloxyandrost-5-en-17-one, 29163-23-3; 3β,5α-dihydroxyandrostan-17-one 3-formate, 29246-54-6.

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A New Approach to the Synthesis of Nucleosides of 8-Azapurines (3-Glycosyl-*v*-triazolo[4,5-*d*]pyrimidines)[1]

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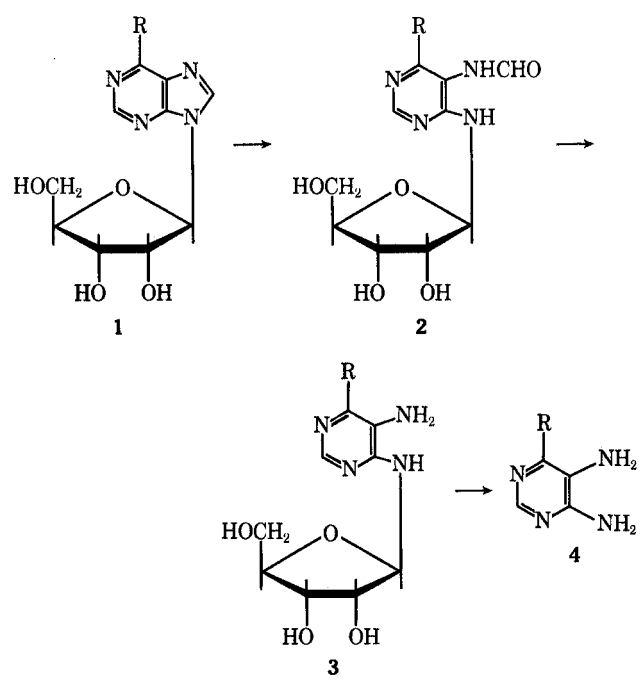
The four isomeric ribosyl derivatives of 8-azahypoxanthine (*v*-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one) have been prepared from appropriately protected derivatives of 6-chloro-9-β-D-ribofuranosylpurine by means of basic cleavage of the imidazole ring of the nucleosides followed by removal of the formyl group from the 5-amino group, closure of the triazole ring with nitrous acid, and then removal of the sugar-protecting groups.

It has been known for some time that certain purines suffer attack by aqueous base at C_2 or C_8, resulting in opening of the pyrimidine[2] or imidazole[3] ring. It appeared to us that these reactions might have synthetic utility, especially in the preparation of 2-[4] and/or 8-azapurine (imidazo[4,5-*d*]-*v*-triazine and *v*-triazolo-[4,5-*d*]pyrimidine) nucleosides difficult to prepare by other methods. For example, the synthesis of 8-azainosine *via* 8-azaadenosine by conventional procedures[6,7] presents difficulties, particularly in the preparation of large amounts of material. One approach to this problem might be to open the imidazole ring of an appropriately substituted purine nucleoside and cyclize the resultant 5-amino-4-glycosylaminopyrimidine with nitrous acid. The possibilities of this route were therefore surveyed.

Inosine (**1**, R = OH), a likely candidate for this route, is quite stable to base,[8] and, although it can be labilized by alkylation at N_7,[9] this approach did not appear promising.[10] Adenosine (**1**, R = NH_2) is completely converted to other compounds in 2 hr by aqueous base at 100°.[11] The only ring-opened product that could be isolated, however, was 4,5,6-triaminopyrimidine (**4**, R = NH_2).[8] Brown and coworkers found that purine ribonucleoside (**1**, R = H)[3] and purine ribonucleotide[12] are extremely sensitive to base, giving rise to sugar-containing pyrimidines that are converted finally to 4,5-diaminopyrimidine (**4**, R = H) (Scheme I). In-

SCHEME I



vestigations in this laboratory[13] and by Brown and coworkers[3] showed that, although 6-chloropurine reacts with aqueous base to give hypoxanthine,[14] nucleosides of 6-chloropurine undergo ring opening under milder

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