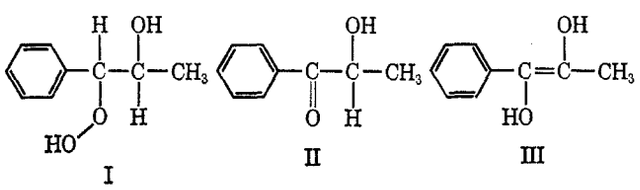
for cleavage to the observed products are available. The intermediate might decompose to give benzaldehyde and acetaldehyde. This possibility is eliminated since it has been shown that acetaldehyde is not produced in the system.

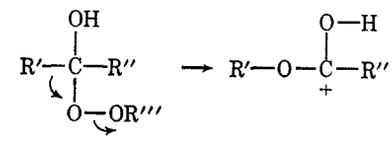
The production of the benzaldehyde and acetic acid as primary products requires that 2 moles of hydrogen peroxide are added to the system with the cleavage occurring during or after addition of the second mole of peroxide. Subsequent oxidation of the intermediate I can occur in two ways: (a) attack on a dehydrated product of I or (b) by a direct attack on the intermediate I. The intermediate could undergo intramolecular loss of water producing an α-hydroxy ketone (II). The α-hydroxy ketone could then react through the enediol III to give benzaldehyde and acetic acid.



I II III

Such a mechanism, however, could not account for the reactivity of 3-phenyl-2-butanone since the presence of the α-methyl group eliminates the possibility of forming an α-hydroxy ketone (II). The validity of the mechanism was also investigated by preliminary studies of 1-hydroxy-1-phenyl-2-propanone, the stable isomer of structure II which in alkali would give the same enediol III. The ketone, which has a second-order rate constant more than 20 times as high as that for benzaldehyde at 25°, rapidly consumes 2 moles of hydrogen peroxide. These results are inconsistent with the enediol being an intermediate.

Direct attack of the β-hydroxyhydroperoxide I by the nucleophilic hydroperoxide anion represents the most feasible mechanism of cleaving the ketone which is consistent with all of the experimental observations. The cleavage (eq 8) is considered to occur in a concerted manner in which the oxygen–oxygen bond and the carbon–carbon bond are broken concurrently with formation of the carbon–oxygen bond at the original carbonyl carbon. An analogous series of events are postulated to occur in the rearrangement of an α-hydroxyhydroperoxide in the Baeyer–Villiger reaction.



A requirement of the cleavage is that it be faster than the rate-determining step of the reaction. In addition to the Baeyer–Villiger reaction, many of the mechanisms of peroxide reactions involve intramolecular decomposition of peroxide intermediates. The driving force for these reactions, with the exception of the Dakin reaction,[2,26,27] is primarily the instability of the oxygen–oxygen bond. The presence of a strong nucleophile such as the hydroperoxide anion could assist this decomposition when there is a reactive site adjacent to the hydroperoxide. The polar hydroxyl group on the carbon adjacent to that containing the hydroperoxide makes the hydroxyl-containing carbon susceptible to attack by the nucleophile. Cleavage assisted by hydroperoxide anion would be expected to proceed at a faster rate than unassisted decomposition of the same intermediate.

Registry No.—*p*-Methoxyphenyl-2-propanone, 122-84-9; *p*-chlorophenyl-2-propanone, 5586-88-9; *p*-Hphenyl-2-propanone, 103-79-7; *p*-methylphenyl-2-propanone, 2096-86-8; 4-phenyl-2-butanone, 2550-26-7; 3-phenyl-2-butanone, 769-59-5; 3-methyl-3-phenyl-2-butanone, 770-85-4; *p*-chlorodeoxybenzoin, 1889-71-0; *p'*-chlorodeoxybenzoin, 6332-83-8; deoxybenzoin, 451-40-1.

(26) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 341.

(27) A. G. Davies, "Organic Peroxides," Butterworth and Co. (Publishers) Ltd., London, 1961, p 155.

Direct Methylenation of Steroidal α,β-Epoxy Ketones

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Condensation of 1,2α-epoxy-3-ketoandrostanes with formaldehyde led to their 4-methylene derivatives. The same reaction carried out with 4,5β-epoxy-3-ketoandrostanes gave the 2-methylene analogs. Opening of the two series of epoxides with halogen acids produced 2-halo-4-methylene-3-keto-1-enes and 4-halo-2-methylene-3-keto-4-enes, respectively.

The introduction of methylene groups into steroidal A-ring conjugated ketones has been achieved by various synthetic routes. For example, 2-methylene-Δ⁴-3-keto steroids[1] have been prepared by condensation of the 2-ethoxalyl-Δ⁴-3-keto derivatives with formaldehyde or chloromethyl methyl ether. Also 2-N-piperidinomethylene-Δ⁴-3-keto steroids[2] are converted by sodium borohydride reduction to the corresponding 2-methylen-Δ⁴-3β-ols, which upon allylic oxidation yield 2-methylene-Δ⁴-3-keto compounds. Recently Lunn[3] reported the direct introduction of a 4-methylene group into a Δ¹-3-keto steroid by condensation with paraformaldehyde.

With the hope of introducing methylene groups (through their corresponding hydroxymethyl precursors) into steroidal A-ring epoxy ketones, the condensation of these ketones with aqueous formaldehyde was studied. This method had been utilized by Nogu-

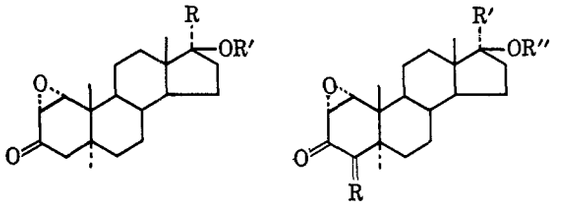
(1) D. D. Evans, D. E. Evans, G. S. Lewis, and P. J. Palmer, *J. Chem. Soc.*, 4312 (1963).

(2) J. A. Edwards, M. C. Calzada, and A. Bowers, *J. Med. Chem.*, **6**, 178 (1963).

(3) W. H. W. Lunn, *J. Org. Chem.*, **30**, 2925 (1965).

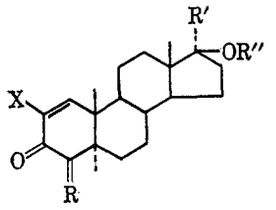
chi and Morita[4] to introduce hydroxymethyl groups directly onto C-21 steroidal carbon atoms. Thus, 1α,2α-epoxy-17β-hydroxy-5α-androstan-3-one (**1a**)[5] (Chart I) was refluxed in methanol with aqueous formaldehyde in the presence of sodium acetate. The crude reaction product was acetylated with acetic anhydride in pyridine and chromatographed. From the column 17β-acetoxy-1α,2α-epoxy-4-methylene-5α-androstan-3-one (**2a**) was eluted as a crystalline compound. The presence of a cisoid enone system[6] in a six-membered ring (A ring) was indicated for **2a** by its ultraviolet maximum at 234 mμ with a relatively low extinction coefficient of 5500. This was further verified by the nuclear magnetic resonance (nmr) spectrum showing an exocyclic methylene group at C-4, the two protons resonating as broad signals at 318 and 377 cps, values in good agreement with the resonance frequencies for a C-4 methylene group in a 3-keto Δ^1-steroid as reported by Lunn.[3] The intactness of the epoxide ring in **2a** was shown by the signals for the 1β- and 2β-hydrogens as a pair of doublets at 202 and 216 cps (J = 4 cps). In a similar manner the epoxide **1b**[7] was converted to 1α,2α-epoxy-17β-hydroxy-17α-methyl-4-methylene-5α-androstan-3-one (**2b**) in 30% yield using methanol as the solvent; changing the solvent to ethanol markedly increased the yield of **2b** to 74%. From the methanolic mother liquors of 2b, after chromatography, 1α,2α-epoxy-17β-hydroxy-17α-methyl-4ξ-hydroxymethyl-5α-androstan-3-one (**2c**) was obtained. Its nmr spectrum (deuterochloroform) showed two doublets at 198 and 218 cps (J = 4 cps) ascribed to the 1β- and 2β-hydrogens of the epoxide ring. The spectrum further showed a broad band at around 230 cps integrating for two protons and thus suggesting the direct introduction of a hydroxymethyl group into the molecule. This was confirmed by having another spectrum run in dimethyl sulfoxide; as would be anticipated[8] the signal due to the hydroxy proton of the primary alcohol was a triplet (separation equal to 5 cps), and was removed by dilution with deuterium oxide.

CHART I



1a, R = R′ = H
b, R = CH_3; R′ = H

2a, R = CH_2; R′ = H; R″ = Ac
b, R = CH_2; R′ = CH_3; R″ = H
c, R = $<^{CH_2OH}_{H}$; R′ = CH_3; R″ = H
d, R = $<^{CH_3}_{H}$; R′ = H; R″ = Ac



3a, R = CH_2; R′ = H; R″ = Ac; X = Cl
b, R = CH_2; R′ = CH_3; R″ = H; X = Cl
c, R = CH_2; R′ = CH_3; R″ = H; X = Br
d, R = CH_3; R′ = H; R″ = Ac; X = Cl

When **2c** was refluxed in methanol in the presence of formaldehyde and sodium acetate (the identical reaction conditions used for its formation from **1b**), it was completely converted to **2b** by the loss of the elements of water from the C-4 hydroxymethyl group. The reaction, therefore, between an epoxy ketone and formaldehyde may be regarded as a simple aldol condensation, the "aldol" in the present case being **2c**. As aldols are known to be dehydrated with extreme ease to the corresponding α,β-unsaturated carbonyl compounds, it is not surprising that in similar condensations with formaldehyde as presented in this paper, the only primary reaction products isolated were the "dehydrated" aldols, the exocyclic conjugated epoxy ketones.

In order to introduce a halogen atom into the A ring of these compounds, the opening of the conjugated epoxy ketones with halogen acids was then investigated. The reaction of the epoxide **2a** with a mixture of hydrochloric acid in acetic acid[7] was followed by spontaneous dehydration and led after chromatography to 17β-acetoxy-2-chloro-4-methylene-5α-androst-1-en-3-one (**3a**). No migration of the exocyclic double bond into the ring was observed. The two protons of the exocyclic methylene group at C-4 resonated at 318 and 373 cps and the enolic C-1 proton showed up as a sharp peak at 442 cps. In the same manner the opening of the epoxide **2b** with hydrochloric acid led to the chloride **3b**, while hydrobromic acid gave the bromide **3c**.

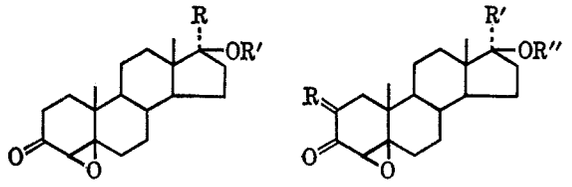
The reduction of **2a** with 5% palladium on charcoal yielded **2d** (a mixture of the 4-methyl epimers). The hydrochloric acid treatment of **2d** gave a single compound, **3d**, the 4-methyl group being now presumably in the more stable equatorial (α) configuration.

The protons on C-4 in a 1,2α-epoxy 3-ketone can be assumed to have the same electron density as the protons on C-2 in a 4,5β-epoxy 3-ketone. The latter ketones, when condensed with formaldehyde, should therefore lead to 2-methylene derivatives, in analogy to the former ones, which, as shown above, gave 4-methylene derivatives. This was indeed observed. When 4β,5β-epoxy-17β-hydroxyandrostan-3-one (**4a**)[9] (Chart II) was allowed to react with formaldehyde, 4β,5β-epoxy-17β-hydroxy-2-methyleneandrostan-3-one (**5a**), identified by its nmr spectrum (see Experimental Section) was the main reaction product. The condensation of the epoxide **4b**[10] in a similar fashion gave **5c**.

The only difference observed in the two series of reactions were the secondary condensation products obtained when 4,5β-epoxy 3-ketones were used as starting materials. Thus, from the mother liquors of **5a** one obtained **5d** (one hydroxymethyl group having been etherified by the solvent methanol). Similarly, the condensation of the epoxide **4b** with formaldehyde, in addition to **5c**, gave some **5e**. Chromatography of crude **5b** yielded the diacetate **5g** in addition to **5b**. These doubly substituted condensation products at C-2, obtained with the 4,5β-epoxy 3-ketones, are in

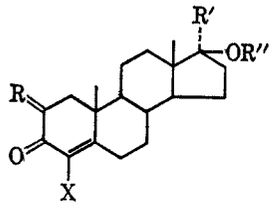
(4) S. Noguchi and K. Morita, *Chem. Pharm. Bull.*, **11**, 1235 (1963).
(5) W. M. Hoehn, *J. Org. Chem.*, **23**, 929 (1958).
(6) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 22.
(7) R. E. Counsell and P. D. Klimstra, *J. Med. Pharm. Chem.*, **5**, 477 (1962).
(8) O. L. Chapman, and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).
(9) B. Camerino, B. Patelli, and A. Vercellone, *ibid.*, **78**, 3540 (1956).
(10) H. J. Ringold, E. Batres, O. Mancera, and G. Rosenkranz, *J. Org. Chem.*, **21**, 1432 (1956).

CHART II

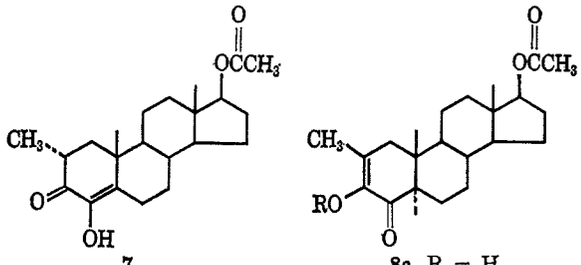


4a, R = R′ = H
b, R = CH_3; R′ = H

5a, R = CH_2; R′ = R″ = H
b, R = CH_2; R′ = H; R″ = Ac
c, R = CH_2; R′ = CH_3; R″ = H
d, R = $<^{CH_2OH}_{CH_2OCH_3}$; R′ = R″ = H
e, R = $<^{CH_2OH}_{CH_2OCH_3}$; R′ = CH_3; R″ = H
f, R = $<^{CH_3}_{H}$; R′ = H; R″ = Ac
g, R = $<^{CH_2OCCH_3}_{CH_2OCH_3}$; R′ = H; R″ = Ac



6a, R = CH_2; R′ = H; R″ = Ac; X = Cl
b, R = CH_2; R′ = H; R″ = Ac; X = Br
c, R = CH_2; R′ = CH_3; R″ = H; X = Cl



7

8a, R = H
b, R = Ac

contrast with the condensation results of 1,2α-epoxy 3-ketones, where no double substitution at C-4 had occurred. This is undoubtedly due to different steric environments at C-2 and C-4 for the two corresponding series of compounds. Model studies show that in 4,5β-epoxy 3-ketones the A-ring is almost perpendicular to the plane of the other three rings and the C-2 atom is at the farthest point spatially from the rest of the molecule; furthermore true diaxial interaction[11] is involved only with the 9α-hydrogen. Thus, two hydroxymethyl groups can occupy the C-2 atom with no or only little steric strain. In 1,2α-epoxy 3-ketones on the other hand, the introduction of another hydroxymethyl group at C-4 would lead to strong steric inhibition due to diaxial interactions with the C-19 methyl group and the 6β-hydrogen.

The opening of the 2-methylene-4,5β-epoxy 3-ketones **5a–c** with halogen acids[9,10] led to the corresponding 2-methylene-4-halo Δ^4-3-ketones, **6a–c**. In the reaction leading to the formation of **6b**, according to its nmr spectrum, some isomerization of exocyclic double bond into the ring had occurred. Thus the nmr of **6b** showed in addition to the strong broad signals at 318 and 360 cps (the exocyclic methylene protons at C-2) a weak signal at 407 cps, attributed to the olefinic proton at C-1.

(11) For a general discussion on diaxial steric interactions, see W. Klyne, *Progr. Stereochem.*, **1**, 50 (1954).

Concurrent attempts to open the epoxide rings of the two reduced compounds **2d** and **5f**, the latter obtained by reduction from **5b**, and to convert them to their enolic hydroxy derivatives, were only partially successful. A sulfuric acid–acetic acid solution[12] of the epoxide **2d** gave an inseparable mixture of compounds. When epoxide **5f** was treated under identical conditions a mixture of two enols **7** and **8a**[13] was obtained. Compound **7** was less soluble and crystallized first from the reaction mixture. It showed in the nmr spectrum an enolic hydroxy band at 366 cps and the signals for a secondary methyl group at C-2 as a doublet at 67 and 73 cps. The secondary nature of the methyl substituent at C-2 established the position of the enolic hydroxy group at C-4. The C-2 methyl group of enol **7**, after the epoxide opening with strong acid, can be assumed to be now in the more stable equatorial (α) configuration. The second enol **8a**, which concentrated in the mother liquors, could be completely freed of enol **7** only upon conversion to its 3-acetate **8b**. Both **8a** and **b** showed the expected olefinic methyl signal at 112 and 108 cps, respectively.

Experimental Section[14]

17β-Acetoxy-1α,2α-epoxy-4-methylene-5α-androstan-3-one (2a).—To a solution of 19.9 g of the epoxide **1a**[5] in 400 ml of methanol was added 100 ml of 36–38% aqueous formaldehyde and 14.9 g of sodium acetate in 60 ml of distilled water. The reaction mixture was refluxed for 5 hr. It was cooled, neutralized with 9.9 ml of acetic acid, and concentrated to one-half of its volume. The residual liquid was diluted with water, and the product was filtered and redissolved in ether. It was washed with water, dried, and evaporated to yield 20.4 g of crude 17β-ol. This material was acetylated overnight at room temperature with 90 ml of acetic anhydride in 120 ml of pyridine. After dilution with water the 17β-acetate was filtered and chromatographed over 1.2 kg of silica.[15] The eluates obtained with 5% ethyl acetate in benzene were combined, evaporated, and triturated with ether. An ether-insoluble product was removed by filtration. The clear mother liquor was concentrated to dryness and crystallized from acetone–Skellysolve B to yield 8.8 g of crystals, mp 122–123°. Another recrystallization from the same solvent mixture gave the pure conjugated ketone **2a**: mp 125.5–6.5°; λ_{max} 5.77, 5.87, and 6.21 μ; λ_{max} 234 (ε 5500) mμ; Δν 49 (18 and 19-CH_3 groups), 122 (OAc), two doublets 200, 204 and 214, 218 (1,2-hydrogens), and two multiplets 318 and 377 (C=CH_2) cps; $[\alpha]_D$ +96°.

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.75; H, 8.45.

1α,2α-Epoxy-17β-hydroxy-17α-methyl-4-methylene-5α-androstan 3-one (2b).—To 32.0 g of the epoxide **1b**[7] in 625 ml of methanol was added 155 ml of 36–38% aqueous formaldehyde and 23.4 g of sodium acetate dissolved in 93 ml of water. The solution was refluxed for 5 hr, cooled, and neutralized with acetic acid. About one-half of the solvents were removed *in vacuo* and the residual liquid was poured into ice water. The solid product (27.6 g) was crystallized from methanol to yield 9.9 g (30% yield) of needles, mp 178–188°. One more recrystallization from methanol (Darco) produced the pure conjugated ketone **2b**: mp 194–196°; λ_{max} 2.74, 5.88, and 6.21 μ; λ_{max} 234 (5100) mμ;

(12) B. Camerino, R. Modelli, and B. Patelli, *Farmaco* (Pavia) *Ed. Sci.*, **13**, 52 (1958).

(13) The corresponding 17α-methyl-17β-hydroxy analog of **8a** is described in French Patent 1,387,954 (1964).

(14) We wish to thank Dr. R. T. Dillon and staff for the analytical and spectral data reported here. The infrared spectra were determined in chloroform, ultraviolet spectra in methanol, rotations in chloroform (1%), and nmr spectra in deuteriochloroform (Δν = 0 cps with tetramethylsilane as an internal standard on a Varian A-60 spectrometer). The melting points were taken on a Fisher-Johns apparatus and are uncorrected. Skellysolve B refers to petroleum ether (bp 60–70°). Silica used was Davison 950 (60–200 mesh).

(15) We are grateful to Dr. E. G. Daskalakis and staff for the chromatographies reported.

$\Delta\nu$ 50 and 53 (angular CH_3 groups), 75 (17-CH_3), two doublets 201, 205 and 214, 218 (1,2-hydrogens), and two multiplets 318 and 377 (C=CH_2) cps; $[\alpha]D$ +94.5°.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.04; H, 9.08.

When the above reaction was repeated using 2B ethanol as the solvent, the yield of **2b** increased to 74%.

1α,2α-Epoxy-17β-hydroxy-17α-methyl-4ξ-hydroxymethyl-5α-androstan-3-one (2c).—The methanolic mother liquors of **2b** (see previous experiment) were distilled to dryness and chromatographed over 1.5 kg of silica. The crystalline fraction eluted with 40% ethyl acetate in benzene were combined and extracted with ether. The material which remained insoluble in ether was crystallized from acetone–Skellysolve B to yield the pure hydroxymethyl ketone **2c**: mp 176–178°; λ_{max} 2.74, 2.80 (shoulder), and 5.85 μ; $\Delta\nu$ 53 and 56 (angular CH_3 groups), two doublets 196, 200 and 216, 220 (1,2-hydrogens), and a multiplet 230 (CH_2OH) cps; $[\alpha]D$ +69°.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.40; H, 9.40.

Another nmr spectrum of **2c**, run in dimethyl sulfoxide, showed a triplet at 266, 271, and 276 cps, due to the hydroxy proton of the C-4 hydroxymethyl group. Exchange with deuterium oxide removed this triplet.

Conversion of 2c to b.—To a solution of 0.3 g of the hydroxy methyl ketone **2c** in 6 ml of methanol was added 1.5 ml of 36–38% aqueous formaldehyde and 0.23 g of sodium acetate in 0.9 ml of distilled water. After a 5-hr reflux period the solution was cooled, most of the methanol was removed with a stream of nitrogen, and the residue was diluted with water. The product isolated was the conjugated ketone **2b**, its ultraviolet, infrared, and nmr spectra being identical with the authentic material.

17β-Acetoxy-2-chloro-4-methylene-5α-androst-1-en-3-one (3a).—To a cooled solution of 0.5 g of the epoxide **2a** in 10 ml of acetic acid was added 1 ml of concentrated hydrochloric acid.[7] After standing at room temperature for 1 hr the reaction mixture was poured into stirred ice water and the crude product was separated by filtration. It was chromatographed over 40 g of silica. The fractions eluted with 1% ethyl acetate in benzene were combined and crystallized from acetone–Skellysolve B to yield 186 mg of the pure chloride **3a**: mp 133–134.5°; λ_{max} 5.77, 5.91, 6.15, and 6.25 μ; λ_{max} 258 (ϵ 7100) mμ; $\Delta\nu$ 49 and 57 (angular CH_3 groups), 122 (OAc), two multiplets 318 and 373 (C=CH_2), and 442 (1-H) cps; $[\alpha]D$ +5.5°.

Anal. Calcd for $C_{22}H_{29}ClO_3$: C, 70.10; H, 7.76; Cl, 9.41. Found: C, 69.92; H, 7.88; Cl, 9.84.

2-Chloro-17β-hydroxy-17α-methyl-4-methylene-5α-androst-1-en-3-one (3b).—An acetic acid solution of the epoxide **2b** (2.5 g) was treated with hydrochloric acid as in the previous example. The water-precipitated product (2.4 g) was chromatographed over 210 g of silica. The fractions eluted with 5% ethyl acetate in benzene were combined and crystallized from acetone–Skellysolve B to give 624 mg of pure chloride **3b**: mp 163–166°; $[\alpha]D$ −9°.

Anal. Calcd for $C_{21}H_{29}ClO_2$: C, 72.29; H, 8.38; Cl, 10.16. Found: C, 72.24; H, 8.35; Cl, 10.23.

2-Bromo-17β-hydroxy-17α-methyl-4-methylene-5α-androst-1-en-3-one (3c).—A solution of 1.0 g of the epoxide **2b** in 20 ml of acetic acid was cooled and treated with 2 ml of 48% aqueous hydrobromic acid. After a period of 1 hr at room temperature, ice water was added and the crude bromide **3c** was separated by filtration. It was chromatographed over 100 g of silica. The eluates collected with 5% ethyl acetate in benzene were combined and crystallized from acetone–Skellysolve B to yield 0.30 g of pure bromide **3c**: mp 152–154°; λ_{max} 2.74, 5.92, 6.15, and 6.27 μ; λ_{max} 264 (ϵ 6500) mμ; $\Delta\nu$ 53 and 58 (angular CH_3 groups), 74 (17-CH_3), two multiplets 318 and 373 (C=CH_2), and 460 (1-H) cps; $[\alpha]D$ −4°.

Anal. Calcd for $C_{21}H_{29}BrO_2$: C, 64.12; H, 7.43; Br, 20.32. Found: C, 64.36; H, 7.57; Br, 20.41.

17β-Acetoxy-2-chloro-4α-methyl-5α-androst-1-en-3-one (3d).—A solution of 4.0 g of the epoxide **2a** in 250 ml of methanol and 0.40 g of 5% palladium on charcoal was stirred in an atmosphere of hydrogen.[16] After 10 min the theoretical amount of hydrogen had been absorbed. The mixture was filtered and the filtrate was concentrated to dryness. The residue was crystallized from acetone–Skellysolve B to yield 3.23 g of **2d**. The nmr spectrum of **2d** showed that it was a mixture of the C-4 methyl epimers (two doublets at 65, 72 and 68, 75 cps). This mixture was dissolved in 70 ml of acetic acid. With slight cooling 7 ml of concentrated hydrochloric acid was added to the steroid solution. After standing for 4 hr at room temperature the solution was poured into stirred ice water. The product was separated by filtration and chromatographed over 300 g of silica. The fractions eluted with 1% ethyl acetate in benzene were combined, distilled to dryness, and crystallized from acetone–Skellysolve B to yield 1.77 g of crystals, mp 172–173°. A portion of it was recrystallized from the same solvent mixture to give the pure chloride **3d**: mp 177–178°; λ_{max} 5.77, 5.87, and 6.22 μ; λ_{max} 247.5 (ϵ 8400) mμ; $\Delta\nu$ 50 (18-CH_3), 67 (19-CH_3), doublet 68, 75 (4-CH_3), 123 (-OAc), and 437 (1-H) cps; $[\alpha]D$ +9°.

Anal. Calcd for $C_{22}H_{31}ClO_3$: C, 69.73; H, 8.25; Cl, 9.36. Found: C, 69.73; H, 8.31; Cl, 8.98.

4β,5β-Epoxy-17β-hydroxy-2-methyleneandrostan-3-one (5a) and 4β,5β-Epoxy-17β-hydroxy-2ξ-methoxymethyl-2ξ-hydroxymethylantrostan-3-one (5d).—The condensation of 59.0 g of the epoxide **4a**[9] with formaldehyde in methanol, according to the procedure outlined in the preparation of **2a**, gave 53.9 g of crude product. About one-half of this material (27 g) was chromatographed over 2.5 kg of silica. The crystalline fractions eluted with 15% ethyl acetate in benzene were combined and recrystallized from acetone–Skellysolve B to yield 6.85 g of pure **5a**: mp 150–152°; λ_{max} 2.75, 5.88, and 6.19 μ; λ_{max} 237 (ϵ 7900) mμ; $\Delta\nu$ 46 (18-CH_3), 71 (19-CH_3), 188 (4-H), and two multiplets 317 and 372 (C=CH_2) cps; $[\alpha]D$ +77°.

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.92; H, 8.94.

Compound **5d** was eluted from the column with 45% ethyl acetate in benzene. The eluates were combined, distilled to dryness and recrystallized from ethyl acetate–Skellysolve B to yield 1.15 g of pure **5d**: mp 153–156°; λ_{max} 2.75, 2.85, and 5.90 μ; $\Delta\nu$ 47 (18-CH_3), 69 (19-CH_3), 185 (4-H), 201 (OCH_3), 216 (OCH_2), and two doublets 190, 200 and 218, 228 (OCH_2) cps; $[\alpha]D$ +138.5°.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.49; H, 9.05.

When the reaction leading to **5a** and **d** was repeated using ethanol for the previously used solvent methanol, the yield of **5a** (after chromatography) was increased from 22 to 40%. No ethyl ether derivative corresponding to **5d** could be isolated.

17β-Acetoxy-4β,5β-epoxy-2-methyleneandrostan-3-one (5b) and 17β-Acetoxy-4β,5β-epoxy-2ξ-methoxymethyl-2ξ-acetoxymethylandrostan-3-one (5g).—One-half of the crude reaction product obtained from the preparation of **5a** (see above) was acetylated in 90 ml of pyridine with 70 ml of acetic anhydride. After standing overnight at room temperature the precipitated crystals of **5b** (12.4 g) were collected by filtration and washed with ether on the filter, mp 221–223° dec. A portion of it was recrystallized from acetone to give an analytical sample of **5b**: mp 225–227° dec; λ_{max} 5.76, 5.87, and 6.18 μ; λ_{max} 236 (ϵ 5900) mμ; $\Delta\nu$ 48 (18-CH_3), 71 (19-CH_3), 122 (OAc), 187 (4-H), and two multiplets 314 and 370 (C=CH_2) cps; $[\alpha]D$ +66.5°.

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.89; H, 8.52.

The mother liquor of **5b** was chromatographed over 1.4 kg of silica. The fractions eluted with 5% ethyl acetate in benzene furnished an additional amount of 1.4 g of **5b**. The fractions eluted with 10% ethyl acetate in benzene were combined and recrystallized from acetone–Skellysolve B to yield 4.2 g of **5g**, mp 123–125°. A sample recrystallized from the same solvent mixture furnished pure **5g**: mp 127–128.5°; $[\alpha]D$ +105.5°.

Anal. Calcd for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.54; H, 8.28.

4β,5β-Epoxy-17β-hydroxy-17α-methyl-2-methyleneandrostan-3-one (5c) and 4β,5β-Epoxy-17β-hydroxy-17α-methyl-2ξ-methoxymethyl-2ξ-hydroxymethylandrostan-3-one (5e).—The reaction of 27.95 g of the epoxide **4b**[10] with formaldehyde in methanol was carried out according to the method outlined in the preparation of **2a** and gave 25.1 g of crude product. This material was chromatographed over 2.5 kg of silica. The crystalline fractions eluted with 20% ethyl acetate in benzene were combined and recrystallized from ethyl ether to yield 8.21 g of pure **5c**: mp 152–153°; $[\alpha]D$ +54.5°. From the mother liquor a second crop of 2.35 g of **5c** was obtained, mp 145–147°.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.34; H, 9.42.

(16) Mr. W. M. Selby and staff kindly performed all hydrogenations described herein.

Further elution of the column with 50% ethyl acetate in benzene gave again crystalline eluates. These were combined and recrystallized from acetone–Skellysolve B to yield 4.3 g of pure **5e**: mp 147–149.5°; $[\alpha]_D$ +122.5°.

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.11; H, 9.18.

17β-Acetoxy-4β,5β-epoxy-2ξ-methylandrostan-3-one (5f).—A solution of 6.37 g of the epoxide **5b** in 1.3 l. of dioxane and 0.64 g of 5% palladium on charcoal were stirred at room temperature in an atmosphere of hydrogen. After 25 min the theoretical amount of hydrogen had been absorbed. The mixture was filtered and the filtrate concentrated to dryness. The solid residue was crystallized from methylene chloride–methanol to yield 5.28 g of pure **5f**: mp 211–213.5°; λ_{max} 5.78 and 5.92 (shoulder) μ; Δν 49 (18-CH_3), doublet 53, 61 (2-CH_3), 73 (19-CH_3), 122 (-OAc), and 187 (4-H) cps; $[\alpha]_D$ +72.5°.

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.32; H, 8.70.

17β-Acetoxy-4-chloro-2-methyleneandrost-4-en-3-one (6a).—To a slightly cooled solution of 6.0 g of the epoxide **5b** in 1 l. of acetone was added portionwise 100 ml of concentrated hydrochloric acid while keeping the reaction mixture below 20°.[10,11] After standing at room temperature for 45 min most of the acetone was removed *in vacuo* and the residual liquid diluted with ice water. The gummy precipitate was extracted with methylene chloride. It was washed with aqueous sodium bicarbonate, water, dried over sodium sulfate, and concentrated to dryness. The residue, upon crystallization from a small amount of ethyl ethyl ether yielded, 1.55 g of **6a** as needles. Recrystallization from acetone furnished an analytical sample of **6a**: mp 191–194°; λ_{max} 5.76, 5.94, 6.14, and 6.33 μ; λ_{max} 272 (ε 10,400) mμ; Δν 51 (18-CH_3), 68 (19-CH_3), 122 (OAc), and two multiplets 320 and 365 (C=CH_2) cps; $[\alpha]_D$ +111.5°.

Anal. Calcd for $C_{22}H_{29}ClO_3$: C, 70.10; H, 7.76; Cl, 9.41. Found: C, 69.77; H, 7.86; Cl, 9.74.

17β-Acetoxy-4-bromo-2-methyleneandrost-4-en-3-one (6b).—By following the procedure outlined for the preparation of the chloride **6a**, except substituting 48% hydrobromic acid for the hydrochloric acid, the opening of the epoxide **5b** (6.0 g) yielded, after crystallization from ethyl ether, 1.24 g of crystals of the bromide **6b**. Recrystillization from acetone gave an analytical sample of **6b**: mp 169–171°; λ_{max} 5.75, 5.92, 6.06 (shoulder), 6.26, and 6.35 μ; λ_{max} 273 (ε 8600) mμ; Δν 51 (18-CH_3), 78 (19-CH_3), 122 (OAc), and two multiplets 318 and 360 (C=CH_2) cps. The nmr spectrum showed further weak bands at 86 (19-CH_3), a doublet 115, 117 (2-CH_3), and 407 (1-H) cps, indicating that in a small amount of **6b** the exocyclic double bond had isomerized into the ring.

Anal. Calcd for $C_{22}H_{29}BrO_3$: C, 62.70; H, 6.94; Br, 18.97. Found: C, 62.75; H, 7.09; Br, 18.58.

4-Chloro-17β-hydroxy-17α-methyl-2-methyleneandrost-4-en-3-one (6c).—To a cooled solution of 2.0 g of the epoxide **5c** in 28 ml of acetone was added 2.8 ml of concentrated hydrochloric acid.[10,11] The solution was allowed to stand at room temperature for 30 min. It was then poured into stirred ice water. The solid was collected on a filter, washed well with water, and dried. The crude product (2.01 g) was chromatographed over 200 g of silica. The crystalline fractions eluted with 5% ethyl acetate in benzene were combined and recrystallized from acetone–Skellysolve B to yield 495 mg of pure chloride **6c**: mp 158–161°; $[\alpha]_D$ +121°.

Anal. Calcd for $C_{21}H_{29}ClO_2$: C, 72.29; H, 8.38; Cl, 10.16. Found: C, 72.28; H, 8.52; Cl, 10.24.

Acid Opening of the Epoxide 2d.—To a cooled solution of 0.5 g of the epoxide **2d** in 5 ml of acetic acid was added 2.1 ml of a solution of concentrated sulfuric acid in acetic acid (1:4, v/v).[12] The reaction mixture was stirred overnight at room temperature. It was poured into stirred ice water and the precipitate was filtered and washed with water. A thin layer chromatograph of this material showed a large number of very closely spaced compounds and no further attempt was made to separate this mixture into its components.

17β-Acetoxy-4-hydroxy-2α-methylandrost-4-en-3-one (7) and 3,17β-Diacetoxy-2-methyl-5α-androst-2-en-4-one (8b).—A cooled solution of 2.4 g of the epoxide **5f** in 24 ml of acetic acid was treated with 10 ml of a solution of concentrated sulfuric acid in acetic acid (1:4, v/v).[12] The reaction mixture was stirred overnight at room temperature. It was poured into ice water. The separated solid was collected on a filter, washed with water, and dried. The product (2.32 g) was chromatographed over 250 g of silica. The fractions eluted with 2% ethyl acetate in benzene were combined and evaporated to dryness to give 1.59 g of solids, a mixture of the enols **7** and **8a** as shown by its nmr spectrum. This material was recrystallized once from acetone–Skellysolve B, then twice from methanol to yield 260 mg of pure enol **7**: mp 192–195°; λ_{max} 275.5 (ε 11,900) mμ; Δν 50 (18-CH_3), doublet 67, 73 (2-CH_3), 72 (19-CH_3), 122 (-OAc), and 366 (4-OH) cps.

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.34; H, 8.67.

The mother liquor, retained from the acetone–Skellysolve B recrystallization of the mixture of enols **7** and **8a** in the previous example, was evaporated to dryness. It was recrystallized from a small amount of methanol to yield 400 mg of essentially pure enol **8a**. Its nmr spectrum showed a strong band at 355 cps (3-OH) and a weak band at 366 cps (4-OH of enol **7**). Enol **8a** was acetylated with 1.5 ml of acetic anhydride in 2.0 ml of pyridine. The water-precipitated product was recrystallized twice from methanol to give 260 mg of pure diacetate **8b**: mp 219–222°; λ_{max} 241 (ε 9700) mμ; Δν 48, 56 (angular CH_3 groups), 108 (2-CH_3), 122 (17-OAc), and 133 (3-OAc) cps.

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.93; H, 8.38.

Registry No.—**2a**, 10026-65-0; **2b**, 10026-66-1; **2c**, 10026-67-2; **3a**, 10026-68-3; **3b**, 10026-69-4; **3c**, 10026-70-7; **3d**, 7780-39-4; **5a**, 7780-40-7; **5b**, 7780-42-9; **5c**, 10026-58-1; **5d**, 7780-41-8; **5e**, 10026-59-2; **5f**, 10026-60-5; **5g**, 10026-57-0; **6a**, 10026-61-6; **6b**, 10026-62-7; **6c**, 10026-63-8; **7**, 10026-64-9; **8b**, 10039-04-0.

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