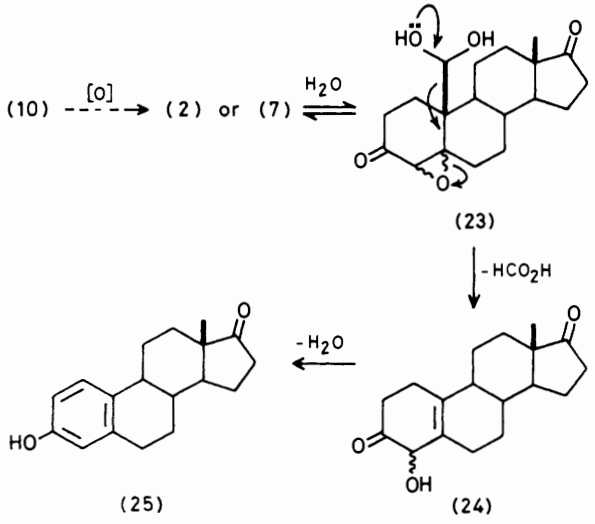
Acid- and Base-catalysed Reactions of 4β,5β- and 4α,5α-Epoxyandrostane-3,17,19-trione

By **Harold Mastalerz** and **Peter Morand,*** Department of Chemistry, University of Ottawa, Ottawa, Ontario, Canada K1N 9B4

The acid- and base-catalysed reactions of 4β, 5β- and 4α, 5α-epoxyandrostane-3,17,19-triones (2) and (7) have been examined to see if epoxide opening in these compounds would result in elimination of the C-10 substituent and the subsequent formation of estrone (25). However, the products obtained indicated that epoxide solvolysis or rearrangement concomitant with epoxide opening is the predominant mode of reaction under the conditions examined.

WE have been examining the reactions of steroidal epoxides in which the elimination of the C-10 substituent, in different oxidation states, is initiated by the opening of a 4β,5β-[1] or a 5β,6β-epoxide.[2] Our interest in this type of fragmentation reaction arose from the observation [3] that 4β,5-epoxy-19-hydroxy-5β-androst-4-ene-3,17-dione (1) was converted into estrone by placental microsomes. This suggested that the last oxidation step † in the biosynthesis of estrone (25) might involve an epoxidation (Scheme 1). It was thought that an A-ring



SCHEME 1

epoxide, either (2) or (7), could, in the form of an acetal (23), undergo elimination of the C-10 substituent to give an allylic alcohol (24) which, could, subsequently lose water to form estrone (25). Since the epoxy-aldehydes (2) and (7) would be in the desired oxidation state for their conversion into estrone, the possibility of such a transformation, aided by an acidic or basic catalyst, was examined.

RESULTS

Preparation of the Epoxides (2) *and* (7).—Since the reactions of both isomeric 4,5-epoxides were of interest, it was necessary to prepare the unknown 4α,5α-epoxide (7). In previous work,[6] it was shown that treatment of the 19-hydroxy-α, β-unsaturated ketone (11) with alkaline hydrogen peroxide affords the 4β,5β-epoxide (5) exclusively. We found that the 19-silyl ether (14) gave a mixture (1.3 : 1) of isomeric epoxides under these conditions. The two isomers were separable and, when individually oxidized to their corresponding 17-ketones and then desilylated, it was found that the material derived from the minor product of the epoxidation was identical with the known [7] 4β,5β-epoxide (1). The major product was therefore the 4α,5α-epoxide (8). Subsequent oxidation of the 19-hydroxy-epoxides (1) and (6) gave the 19-aldehydes (2) and (7) respectively.

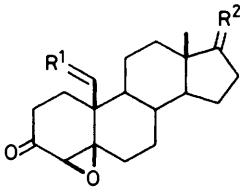
Acid-catalysed Reactions of the Epoxides (2) *and* (7).—It was found that relatively strong mineral acids were necessary to promote reaction of the epoxides (2) and (7) at a reasonable rate. The results obtained are listed in Table 1 and those features leading to the characterisation of the products are described below.

The ^{1}H n.m.r. spectrum of the diosphenol (15) showed singlets for the 19-aldehyde proton (δ 10.13) and the enol proton (δ 6.45, exchangeable). Its u.v. ($\lambda_{max.}$ 278 nm) and i.r. (1 670 and 1 640 cm^{-1}) spectra were consistent with the assigned structure.

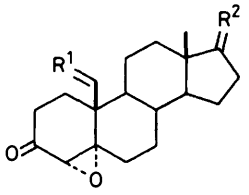
The mass spectrum (*m/z* 288, M^+) and elemental analysis obtained for compound (16) indicated that this material was derived from the epoxides (2) or (7) by a sequence involving loss of CO. Since there was only one signal in the downfield portion of its ^{1}H n.m.r. spectrum (δ 9.78, non-exchangeable) it was assigned the A-nor-aldehyde structure. The nature of the A/B ring junction remains uncertain, but by analogy with 1-hydrindanones,[8] *cis*-fusion is most likely.

The hemiacetal (17) was homogeneous according to t.l.c. analysis, but its ^{1}H n.m.r. spectrum indicated that it had been obtained as a mixture of epimers. The major epimer (*ca.* 80%) exhibited singlets ([$^2H_6$]acetone) at δ 2.75 (4α-H) and 5.25 (19-H) and the minor epimer (*ca.* 20%) at δ 2.04 (4α-H) and 4.90 (19-H). Oxidation of this mixture of epimers afforded a single lactone (19) ($\nu_{max.}$ 1 790 cm^{-1}) for which a singlet at δ 4.07 (4α-H) was observed in the ^{1}H n.m.r. spectrum. Treatment of the mixture of hemiacetals with methanol in the presence of acid afforded two separable epimeric acetals in a ratio of 2 : 1. Assuming that this ratio reflects their relative thermodynamic stability and that the latter quantity was largely determined by steric interactions between the methoxy-group and the axial hydrogen atoms of the A and B rings, the 19*S* structure (20) was assigned to the major epimer and the 19*R* structure (21) to the minor epimer.

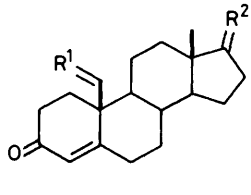
† Two alternative sequences have been proposed for this step. They involve a 2β-hydroxylation [4] of (10) and a Baeyer-Villiger-type oxidation [5] of the 10β-aldehyde group of (10) respectively.



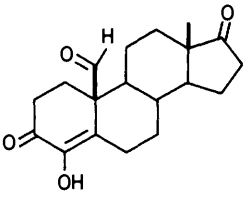
(1) R^1 = H, OH; R^2 = O
(2) R^1 = R^2 = O
(3) R^1 = H, $OSiMe_2Bu^t$; R^2 = H, β-OH
(4) R^1 = H, $OSiMe_2Bu^t$; R^2 = O
(5) R^1 = H, OH; R^2 = H, β-OH



(6) R^1 = H, OH; R^2 = O
(7) R^1 = R^2 = O
(8) R^1 = H, $OSiMe_2Bu^t$; R^2 = H, β-OH
(9) R^1 = H, $OSiMe_2Bu^t$; R^2 = O



(10) R^1 = R^2 = O
(11) R^1 = H, OH; R^2 = H, β-OH
(12) R^1 = H, OH; R^2 = H, β-OBz
(13) R^1 = H, $OSiMe_2Bu^t$; R^2 = H, β-OBz
(14) R^1 = H, $OSiMe_2Bu^t$; R^2 = H, β-OH



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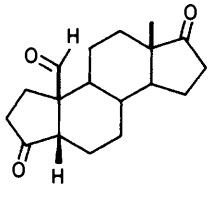

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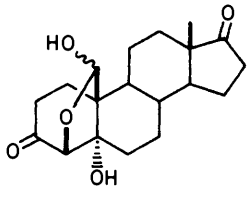

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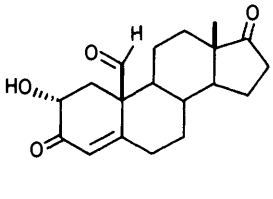

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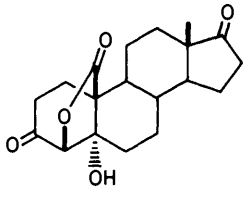

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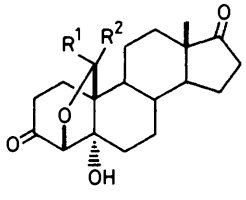
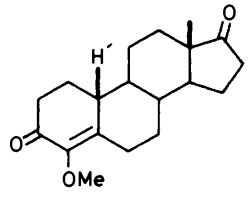


(20) R^1 = OMe; R^2 = H
(21) R^1 = H; R^2 = OMe



(22)

The 2α-hydroxy-compound (18) exhibited spectral properties which were in agreement with those reported [7] but differed in melting point and optical rotation. The observed differences are presumably due to the fact that the reported data is for the hydrate of (18) whereas the elemental analysis for the material obtained in this work did not indicate the presence of such a hydrate.

TABLE 1

Acid-catalysed reactions of 4β,5-epoxy-5β-androstane-3,17,19-trione (2) and 4α,5-epoxy-5α-androstane-3,17,19-trione (7)

		Yield of products (%)				
Epoxide	Conditions	(25)	(15)	(16)	(17)	(18)
(2)	conc. $HClO_4$ [a]	8	49	7	17	—
(2)	aq. $HClO_4$ [b]	3	—	—	82	—
(2)	aq. H_2SO_4 [c]	3	—	—	43	8
(7)	conc. $HClO_4$ [a]	17	29	17	13	—
(7)	aq. $HClO_4$ [b]	13	47	—	17	—
(7)	aq. H_2SO_4 [c]	12	47	—	26	—

[a] A solution of the steroid (180 mg) in tetrahydrofuran (6 ml) and perchloric acid (0.6 ml, 70%); 24 h. [b] A solution of the steroid (180 mg) in tetrahydrofuran (12 ml), water (3.6 ml), and perchloric acid (1.2 ml, 70%); 72 h. [c] A solution of the steroid (180 mg) in acetone (12 ml), water (3.6 ml), and conc. sulphuric acid (1.2 ml); 72 h.

Base-catalysed Reactions of the Epoxides (2) *and* (7).—Both of the epoxy–aldehydes (2) and (7) were found to give relatively complex mixtures of products when treated with methanolic potassium hydroxide. The major product (50%) isolated from the reaction mixture of the 4β,5β-epoxide (2) was the 19-nor-compound (22) ($\lambda_{max.}$ 255 nm, $\nu_{max.}$ 1675 and 1 610 cm^{-1}). The 4α,5α-epoxide (7) afforded three products of which two had very similar R_F values. From the mixture of the latter two products, a quantity of the 19-nor-compound (22) could be isolated in a pure form. The remainder of this mixture consisted of the 19-nor-compound (22) and the (19*R*)-acetal (21) according to t.l.c. and ^1H n.m.r. analysis. Including this unseparated material, the total yields of compounds (22) and (21) are 18 and 16%, respectively. The third product which was obtained (29%) was the (19*S*)-acetal (20).

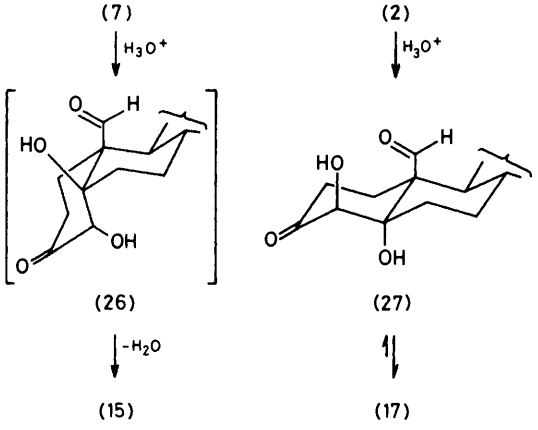
DISCUSSION

The nature of the compounds obtained from the acid-catalysed reactions of the epoxides (2) and (7) indicates that they are mainly derived *via* epoxide rearrangement or solvolysis. Elimination of the C-10 substituent as originally envisaged does not appear to be a major mode of reaction for these compounds and the origin of the estrone that was obtained remains obscure. The pos-

sibility that it was derived from one of the major isolated products was ruled out by the observation that both the hemiacetal (17) and the diosphenol (15) were recovered unchanged when subjected to the reaction conditions (aqueous perchloric acid).

A feature of these reactions which deserves some comment is the relationship between the products that were obtained and the epoxide configuration. Previous work [9] on the acid-catalysed reaction of α,β-epoxy-ketones has shown that there are three possible types of epoxide ring opening. Described as the α'-, α-, or β-modes of ring opening, they would correspond respectively to attack by a nucleophile at the 2-, 4-, or 5- positions of the epoxy-ketones (2) or (7). With aqueous perchloric acid, it would appear that both epoxides afford products derived predominantly from intermediates arising from the β-mode of epoxide opening (Scheme 2). In the case of the 4α,5α-epoxide (7), the intermediate diol (26) undergoes dehydration to give the observed diosphenol (15). The diol (27), originating from the 4β,5β-epoxide (2), can exist as a hemiacetal (17) which is stable under the reaction conditions. The differences encountered with aqueous sulphuric acid would, as has been previously noted,[9] illustrate the effect that the nature of the solvent and acid can have upon the course of these reactions.

With concentrated perchloric acid, approximately half the material obtained consisted of the diosphenol (15) and the A-noraldehyde (16). It seems most likely that these compounds arise *via* the acid-catalysed rearrangement of the epoxides (2) or (7). Although some of the diosphenol obtained from the 4α,5α-epoxide (7) may have originated *via* the dehydration of the intermediate solvolysis product (26) the fact that this epoxide afforded more of the A-nor-aldehyde (16) than did the isomeric 4β,5β-epoxide



SCHEME 2

(2), is consistent with the observations [10] of Collins on the boron trifluoride-catalysed rearrangement of 4α,5α- and 4β,5β-epoxycholestan-3-one.

Under basic conditions, both epoxides afforded products resulting from nucleophilic attack at the 4-position. Epoxide opening by methoxide followed by dehydration and a vinylogous *retro*-Claisen reaction would account for the formation of the methyl enol ether (22). In the case of the 4α,5α-epoxide (7), intramolecular attack by the conjugate base of the 19-methyl-hemiacetal to give the acetals (20) and (21) is also observed.

EXPERIMENTAL

Melting points were determined on a Hoover Uni-melt apparatus and are uncorrected. Optical rotations (chloroform solutions) were obtained on a Perkin-Elmer 141 polarimeter. U.v. spectra (methanol solutions) were recorded on a Bausch and Lomb Spectronic 600 instrument and i.r. spectra (chloroform solutions) on a Beckman 1R-8 spectrophotometer. ^{1}H n.m.r. spectra were obtained on a Varian T-60 spectrometer and unless otherwise stated, are of deuteriochloroform solutions with tetramethylsilane as internal standard. Mass spectra were obtained on a AEI MS9025 instrument. The light petroleum used was of boiling range 30—60 °C and throughout, ether refers to diethyl ether. Microanalyses were carried out by Galbraith Laboratories, Knoxville, TN, 37921, U.S.A.

General Procedures.—Work-up involved pouring the reaction mixture into water, extracting with dichloromethane, and washing the extracts with water. After drying with anhydrous sodium sulphate, the solvents were removed.

Chromatography refers to column chromatography on silica gel (Baker 60—200 mesh) using mixtures of ethyl acetate–hexane as eluant.

Oxidation of alcohols was effected with pyridinium chlorochromate buffered with sodium acetate according to the described procedure.[11]

Preparation of 19-*Dimethyl(t-butyl)silyloxy*17β-*hydroxyandrost*-4-*en*-3-*one* (14).—A solution of 19-hydroxy-3-oxoandrost-4-en-17β-yl benzoate (12) (12.2 g), dimethyl(t-butyl)silyl chloride (5.9 g, 1.2 equiv.), and imidazole (5.5 g, 2.5 equiv.) in dimethylformamide (50 ml) was left at room temperature for 24 h. Work-up followed by crystallization from acetone–water afforded 19-dimethyl(t-butyl)silyloxy-3-oxoandrost-4-en-17β-yl benzoate (13) (13.8 g, 88%), m.p. 132—133 °C (needles); δ 0.07 (s, Me_2Si), 0.85 (9 H, s, Bu^tSi), 1.00 (3 H, s, 18-Me), 3.90 (2 H, s, 19-CH_2), 4.90 (1 H, m, *W*/2 *ca.* 20 Hz, 17α-H), 5.70 (1 H, s, 4-H), and 7.3—8.2 (5 H, m, ArH). A solution of the benzoate (13) (13.7 g) in methanol (400 ml) and aqueous sodium hydroxide (30 ml, 10%) was heated at reflux for 10 h. Work-up followed by crystallization from ether–light petroleum afforded 19-*dimethyl(t-butyl)silyloxy*-17β-*hydroxyandrost*-4-*en*-3-*one* (14) (8.88 g, 81%), m.p. 139—140 °C (prisms), $[\alpha]_D$ + 111° (*c* 1.6); $\nu_{max.}$ 3 460 (OH), 1 660, and 1 620 cm^{-1} (α,β-unsaturated ketone); δ 0.03 (s, Me_2Si), 0.80 (s, 18-Me), 0.83 (s, Bu^tSi), 3.63 (1 H, m, 17α-H), 3.88 (s, 19-CH_2), and 5.82 (1 H, s, 4-H); *m*/*z* 418 (M^+) (Found: C, 71.7; H, 10.55. $C_{25}H_{42}O_3Si$ requires C, 71.77; H, 10.11%).

Epoxidation of 19-*Dimethyl(t-butyl)silyloxy*-17β-*hydroxyandrost*-4-*en*-3-*one* (14).—To an ice-cooled solution of the enone (14) (8.80 g) and hydrogen peroxide (60 ml, 30%) in methanol (400 ml) was added an aqueous solution of sodium hydroxide (20 ml, 10%). After 12 h, the solution was worked up and the residual oil was chromatographed on silica gel (600 g); elution was with ethyl acetate–hexane (1 : 19). This afforded 19-dimethyl(t-butyl)silyloxy-4α,5-epoxy-17β-hydroxy-5α-androstan-3-one (8) (3.21 g, 34%), m.p. 84—85 °C (needles from ether–light petroleum), $[\alpha]_D$ −14° (*c* 4.9); $\nu_{max.}$ 3 500 (OH) and 1 710 cm^{-1} (3-CO); δ *ca.* 0 (s, Me_2Si),

0.72 (s, 18-Me), 0.80 (s, Bu^{t}Si), 3.00 (1 H, s, 4β-H), and 3.72 (3 H, m, 17α-H and 19-CH_2); *m/z* 434 (M^+)(Found: C, 69.4; H, 10.0. $C_{25}H_{42}O_4Si$ requires C, 69.08; H, 9.74%); *19-dimethyl(t-butyl)silyloxy-4β,5-epoxy-17β-hydroxy-5β-androstan-3-one* (3) (2.50 g, 26%), m.p. 156—157 °C (needles from methanol), $[\alpha]_D$ +112° (*c* 2.1); $\nu_{max.}$ 3 500 (OH) and 1 710 cm^{-1} (3-CO); δ 0.10 (s Me_2Si), 0.92 (s, Bu^{t}Si), 2.85 (1 H, s, 4α-H), *ca.* 3.7 (m, 17α-H), and 3.85 (s, 19-CH_2); *m/z* 434 (M^+) (Found: C, 69.5; H, 10.25. $C_{25}H_{42}O_4Si$ requires C, 69.08; H, 9.84%); and starting material (14) (0.90 g, 10%).

Preparation of 4α,5-Epoxy-5α-androstane-3,17,19-trione (7).—The 17-alcohol (8) (1.61 g) was oxidized to afford crude 19-dimethyl(t-butyl)silyloxy-4,5α-epoxy-5α-androstane-3,17-dione (9) (1.59 g); $\nu_{max.}$ 1 735 (17-CO) and 1 710 cm^{-1} (3-CO); δ 0.05 (s, Me_2 Si), 0.87 (s, Bu^{t}Si and 18-Me, 3.08 (1 H, s, 4β-H), and 3.87 (2 H, s, 19-CH_2). The crude dimethylsilyl ether (9) (1.50 g) was taken up in tetrahydrofuran (5 ml) and a solution of tetrabutylammonium fluoride (5 ml of a 1M solution in tetrahydrofuran) was added. After 4.5 h, the reaction was worked up. Chromatography afforded *4α,5-epoxy-19-hydroxy-5α-androstane-3,17-dione* (6) (0.84 g, 74%), m.p. 228—230 °C (needles from methanol), $[\alpha]_D$ +28° (c 3.4); $\nu_{max.}$ 3 450 (OH), 1 740 (17-CO), and 1 710 cm^{-1} (3-CO); δ 0.89 (3 H, s, 18-Me), 3.13 (1 H, s, 4β-H), 3.98 (2 H, q, δ_A 4.04, δ_B 3.90, J_{AB} 11 Hz, 19-CH_2); *m/z* 318 (M^+) (Found: C, 71.7; H, 8.4. $C_{19}H_{26}O_4$ requires C, 71.67; H, 8.23%). Oxidation of the 19-alcohol (6) (2.12 g) afforded *4α,5-epoxy-5α-androstane-3,17,19-trione* (7) (1.34 g, 62%), m.p. 206—208 °C (plates from methanol), $[\alpha]_D$ −16° (*c* 2.2); $\nu_{max.}$ 1 720 cm^{-1} (3-CO, 17-CO, 19-CO); δ 0.90 (3 H, s, 18-Me), 3.17 (1 H, s, 4β-H), and 9.98 (1 H, s, 19-H) (Found C: 71.6; H, 7.55. $C_{19}H_{24}O_4$ requires C, 72.12; H, 7.65%).

Preparation of 4α,5-Epoxy-5β-androstane-3,17,19-trione (2).—The 17-alcohol (3) (1.04 g) was oxidised to afford crude 19-dimethyl(t-butyl)silyloxy-4β,5-epoxy-5β-androstane-3,17-dione (4) (1.00 g); $\nu_{max.}$ 1 735 (17-CO) and 1 710 cm^{-1} (3-CO); δ 0.10 (s, Me_2Si), 0.92 (s, Bu^{t}Si and 18-Me), 2.90 (1 H, s, 4α-H), and 3.88 (2 H, q, δ_A 3.97, δ_B 3.79, J_{AB} 10 Hz, 19-CH_2). The crude dimethylsilyl ether (4) (1.00 g) in tetrahydrofuran (4 ml) was treated with tetrabutylammonium fluoride (4.8 ml of a 1M solution in tetrahydrofuran) for 5 h. Work-up followed by chromatography afforded 4β,5-epoxy-19-hydroxyandrostane-3,17-dione (1) (0.45 g, 59%) which was identical with authentic material. Oxidation of the 19-alcohol (1) (3.48 g) afforded *4β,5-epoxy-5β-androstane-3,17,19-trione* (2) (3.12 g, 90%), m.p. 196—197 °C (prisms from methanol), $[\alpha]_D$ +222° (*c* 3.9), $\nu_{max.}$ 1 725 cm^{-1} (3-CO, 17-CO, 19-CO); δ 0.93 (3 H, s, 18-Me), 3.02 (1 H, s, 4α-H), and 9.83 (1 H, s, 19-H) (Found: C, 71.95; H, 7.55. $C_{19}H_{24}O_4$ requires C, 72.12; H, 7.65%).

Acid-catalysed Reactions of the 4β,5β- and 4α,5α-Epoxides (2) *and* (7).—The reaction conditions together with the yields of products that were obtained are included in Table 1. The compounds obtained exhibited the following properties.

(*i*) Estrone (25) was characterised (t.l.c. and ^1H n.m.r.) as its 3-acetate when obtained in a yield of more than 5%, otherwise, its identity was inferred from its t.l.c. behaviour, namely, R_F and characteristic colour when visualised by spraying with ethanolic sulphuric acid followed by heating.

* The diosphenol (15) and the A-nor-compound (16) were found to elute together on a silica gel column. The fraction containing these two compounds was rechromatographed on basic alumina (activity V). The A-nor-compound (16) was eluted with dichloromethane–hexane (1 : 1) and the diosphenol (15) with dichloromethane.

(*ii*) *4-Hydroxyandrost-4-ene-3,17,19-trione* * (15), m.p. 188—189 °C (prisms from dichloromethane–light petroleum), $[\alpha]_D$ +320° (*c* 1.7), $\lambda_{max.}$ (methanol) 278 nm (ε 11 000); $\nu_{max.}$ 3 420 (OH), 1 730 (17-CO), 1 670, and 1 640 cm^{-1} [CO–C(OH)=C]; δ 0.90 (3 H, s, 18-Me), 6.45 (1 H, s, exchangeable), and 10.13 (1 H, s, 19-H); *m/z* 316 (M^+) (Found: C, 72.65; H, 7.65. $C_{19}H_{24}O_4$ requires C, 72.12; H, 7.65%).

(*iii*) A-*Nor-5β-androstane-3,17,19-trione* * (16), m.p. 145—147 °C (needles from ether–light petroleum), $[\alpha]_D$ −231° (*c* 2.9), $\nu_{max.}$ 1 735 cm^{-1} (3-CO, 17-CO, and CHO); δ_H 0.97 (3 H, s, 18-Me), 9.78 (1 H, s, 19-H); δ_C 220.4 and 215.1 (3-CO and 17-CO), and 203.1 (19-CHO); *m/z* 288 (M^+) (Found: C, 75.35; H, 8.65. $C_{18}H_{24}O_3$ requires C, 74.97; H, 8.39%).

(*iv*) *4,19-Hemiacetal of 4β,5-dihydroxy-5α-androstane-3,17,19-trione* † (17), m.p. 238—240 °C (needles from dichloromethane–light petroleum; $\nu_{max.}$ (KBr disc) 3 440 (OH) and 1 725 cm^{-1} (3-CO and 17-CO); δ ([$^2H_6$]acetone) 0.90 (1 H, s, 18-Me), 2.75 (s) and 2.04 (s) (*ca.* 5 : 1, 1 H, 4α-H), 4.90 (s) and 5.25 (s) (*ca.* 1 : 5, 1 H, 19-H) (Found: C, 68.2; H, 7.95. $C_{19}H_{26}O_5$ requires C, 68.24; H, 7.84%).

(*v*) *2α-Hydroxyandrost-4-ene-3,17,19-trione* (18), † m.p. 217—219 °C (needles from dichloromethane–light petroleum), $[\alpha]_D$ +302° (*c* 0.9) (lit.,[7] m.p. 205—209 °C, $[\alpha]_D$ +242°); $\nu_{max.}$ 3 500 (OH), 1 730 (17-CO and -CHO), 1 680, and 1 630 cm^{-1} (α,β-unsaturated ketone); δ 0.90 (3 H, s, 18-CH_3), 4.13 (1 H, q, *J* 6 and 14 Hz, 2β-H), 6.02 (1 H, s, 4-H), and 10.0 (1 H, s, 19-H) (Found: C, 71.8; H, 7.8. $C_{19}H_{24}O_4$ requires C, 72.12; H, 7.65%).

5-Hydroxy-3,17-dioxo-5α-androstane-19,4β-carbolactone (19).—The hemiacetal (17) (80 mg) was oxidized. Work-up followed by crystallization from dichloromethane–light petroleum afforded the *lactone* (19) (52 mg, 65%), m.p. 264—265 °C, $[\alpha]_D$ +23° (*c* 2.4); $\nu_{max.}$ 3 450 (OH), 1 790 (γ-lactone), and 1 735 (3-CO and 17-CO); δ 1.00 (3 H, s, 18-Me) and 4.07 (1 H, s, 4α-H) (Found: C, 68.45; H, 7.4. $C_{19}H_{24}O_5$ requires C, 68.65; H, 7.28%).

Formation of the Mixed 19-Acetals of the 4,19-Hemiacetal of 4β,5-Dihydroxy-5α-androstane-3,17,19-trione (17).—A solution of compound (17) (190 mg) in methanol (10 ml) containing concentrated hydrochloric acid (3 drops) was heated at reflux for 11 h. The solution was poured into water and extracted with dichloromethane. The extracts were washed with a saturated aqueous solution of sodium hydrogen carbonate and then water, and dried (Na_2SO_4). Chromatography afforded (19R)-*5-hydroxy-19-methoxy-4β,19-oxido-5α-androstane-3,17-dione* (21) (48 mg, 24%), m.p. 254—257 °C (decomp.) (needles from dichloromethane–light petroleum), $[\alpha]_D$ −2° (*c* 2.5); $\nu_{max.}$ 3 420 (OH) and 1 730 cm^{-1} (3-CO and 17-CO); δ 0.90 (3 H, s, 18-Me), 3.43 (3 H, s, 19-OMe), 3.75 (1 H, s, 4α-H), 4.92 (1 H, s, 19-H) (Found: C, 69.07; H, 8.15. $C_{20}H_{28}O_5$ requires C, 68.94; H, 8.10%) and the (19*S*)-*isomer* (20) (102 mg, 51%), m.p. 252—255 °C (decomp.) (needles from dichloromethane–light petroleum), $[\alpha]_D$ +104° (*c* 2.8); $\nu_{max.}$ 3 440 (OH) and 1 725 cm^{-1} (3-CO and 17-CO); δ 0.88 (3 H, s, 18-Me), 3.50 (3 H, s, 19-OMe), 3.63 (1 H, s, 4α-H), and 5.27 (1 H, s, 19-H) (Found: C, 69.1; H, 8.25. $C_{20}H_{28}O_5$ requires C, 68.94; H, 8.10%).

Reactions of the Epoxides (2) *and* (7) *with Methanolic Potassium Hydroxide*.—To a solution of the epoxide (200 mg) in methanol (30 ml) under nitrogen was added a methanolic

† The hemiacetal (17) and the 2α-alcohol (18) were found to be eluted together on a silica gel column. The fraction containing these two components was rechromatographed on basic alumina (activity V). The 2α-alcohol (18) eluted with dichloromethane and the lactol (17) with dichloromethane–methanol (99 : 1).

solution of potassium hydroxide (4.5 ml, 0.28M, 2 equiv.). The mixture was heated at reflux for the specified period of time after which it was worked up and chromatographed.

The 4α,5α-epoxide (7) (12 h of reflux) afforded *4-methoxy-estr-4-ene-3,17-dione* (22) (24 mg, 13%), m.p. 154—156 °C (needles from dichloromethane–light petroleum), $[\alpha]_D$ +124° (*c* 6.0); $\lambda_{max.}$ (methanol) 255 nm (ε 14 000); $\nu_{max.}$ 1 735 (17-CO), 1 675, and 1 610 cm^{-1} (CO–C(OMe)=C); δ 0.93 (3 H, s, 18-CH_3), 3.60 (3 H, s, 4-OMe) (Found: C, 75.1; H, 8.55. $C_{19}H_{26}O_3$ requires C, 75.46; H, 8.64%); a mixture (42 mg) whose ^1H n.m.r. spectrum was consistent with a 1 : 3 mixture of the 4-methoxy-compound (22) (5%) and the (19*R*)-acetal (21) (16%); and lastly, the (19*S*)-acetal (20) (63 mg, 29%) which was identical (t.l.c. and ^1H n.m.r.) with material obtained previously.

The 4β,5β-epoxide (2) (43 h of reflux) afforded the 4-methoxy-compound (22) (95 mg, 50%).

We thank Dr. J. Redpath of Organon Laboratories, Newhouse, Scotland, for a generous gift of 19-hydroxy-3-oxo-androst-4-en-17β-yl benzoate and the Ontario government and the National Research Council of Canada for graduate scholarships (to H.M.). Financial support for this work from the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

[2/136 *Received*, 25*th January*, 1982]

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