4,4-DIMETHYL-A-HOMOANDROSTANE EPOXIDES*

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The configuration of the oxygen-containing substituent in the position 3 of some 4,4-dimethyl--A-homo-4a-androstene derivatives was determined and their epimeric 4a,5-epoxides were prepared. The acid catalysed opening of the 4a,5-epoxide ring in epoxides *XV* and *XXIX* with the *trans*-orientation of the substituent in the position 3 and the epoxide ring afforded the products of $5(0)^n$ participation of the 3-substituent, *i.e.* 3,5-transannular epoxides *XVII* and *XXX*. 3,5--Transannular epoxides *XXII*, *XXXIV* and *XXXVI* were prepared as substances with a potential biological activity.

In our preceding papers we investigated the stereochemistry of epoxidation[1] and the direction of the opening of the 4a, 5-epoxide ring[2-4] under the conditions when both the S_N1 and the S_N2 mechanism worked in some 3-substituted 4,4-dimethyl-A-homocholestane derivatives as model compounds for the synthesis of the analogues of androgenous hormones. It was found that the oxygen-containing substituent in the position 3 can participate in the $5(0)^n$ way (for this notation see ref.[5]) in the opening of the 4a,5-epoxide ring, under formation of 3,5-transannular epoxides. This paper is devoted to the preparation and the properties of some 3,5-epoxy-4,4-dimethyl--A-homoandrostane derivatives with a potential antiandrogenous activity.

The reduction of 17β-acetoxy-4,4-dimethyl-A-homo-4a-androsten-3-one (I, ref.[6]) with sodium borohydride in ethanol afforded a chromatographically inseparable mixture of hydroxy derivatives *II* and *III* as the main product. They could be separated after their conversion to 3-benzoyloxy derivatives *IV* and *VII*. Alkaline saponification of the 17-acetoxy group in derivatives *IV* and *VII* with potassium hydrogen carbonate in boiling methanol gave hydroxy derivative *V* and *VIII* as the main products, in addition to small amounts of corresponding diols *VI* and *IX*. On oxidation with the chromium trioxide–pyridine complex hydroxy derivative *V* gave ketone *X*, while hydroxy derivative *VIII* gave ketone *XXIV*. Alkaline saponification of the 3-benzoyloxy group of derivatives *X* and *XXIV* with potassium hydroxide in boiling methanol gave hydroxy derivatives *XI* and *XXV*. The configuration of the hydroxy

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group in the position 3 of derivatives *VI*, *IX*, *XI* and *XXV* was determined on the basis of the benzoate rule[7,8]. According to this rule the $[M]_{D\ ester-alcohol}$ value should be more positive for 3β derivatives than for 3α derivatives. From Table I it follows that on the basis of the measured value of $[M]_{D\ benzoate-alcohol}$ β-configuration may be assigned to the 3-hydroxy group in derivatives *IX* and *XXV*, while substances *VI* and *XI* are 3α-hydroxy derivatives. The same conclusion was also drawn from the application of the benzoate sector rule[9]. Dreiding models indicate a negative Cotton effect for 3β-benzoyloxy derivatives and a positive Cotton effect for 3α-benzoyloxy derivatives, which is in agreement with the curves obtained for derivatives *V* and *VIII*.

In our preceding paper[1] we have found that the stereochemistry of the 3-substituted 4,4-dimethyl-A-homo-4a-cholestene derivatives is directed by steric effects and that the ester function in the position 3 prevents the attack of the reagent from that side of the cyclic system onto which it is oriented. A similar stereochemistry of epoxidation was also observed in 4,4-dimethyl-A-homo-4a-androstene derivatives *X* and *XXIV*. The chromatographically inseparable mixture of epimeric epoxides *XII* and *XIII*, formed on epoxidation of olefin *X* with 3-chloroperbenzoic acid in chloroform, afforded – after alkaline saponification – a mixture of epoxides *XIV* and *XV* in an about 1 : 1 ratio, while the chromatographically inseparable mixture of epoxides *XXVI* and *XXVII*, formed by similar epoxidation of olefin *XXIV*, gave, after alkaline saponification, a mixture of epoxides *XXVIII* and *XXIX* in about a 1 : 3 ratio. The assignment of the configuration to the 4a,5-epoxide ring in epoxides *XIV*, *XV*, *XXVIII* and *XXIX* was carried out on the basis of the IR and the ^{1}H NMR data. As it is evident from Table II the hydroxy group in the position 3 is bound

TABLE I

Molecular rotation differences of 3-hydroxy derivatives *VI*, *XI*, *IX* and *XXV* and their 3-benzoyloxy derivatives *V*, *X*, *VIII* and *XXIV* in chloroform

Compound	*VI*	*XI*	*IX*	*XXV*
$[M]_D$ (benzoate-alcohol)	−181	−300	−119	+100

TABLE II

$\nu_{(OH)}$-Vibrations of hydroxy derivatives *XIV*, *XV*, *XXVIII* and *XXIX* in chloroform

Compound	*XIV*	*XV*	*XXVIII*	*XXIX*
ν(OH), cm^{-1}	3 525	3 630	3 525	3 620

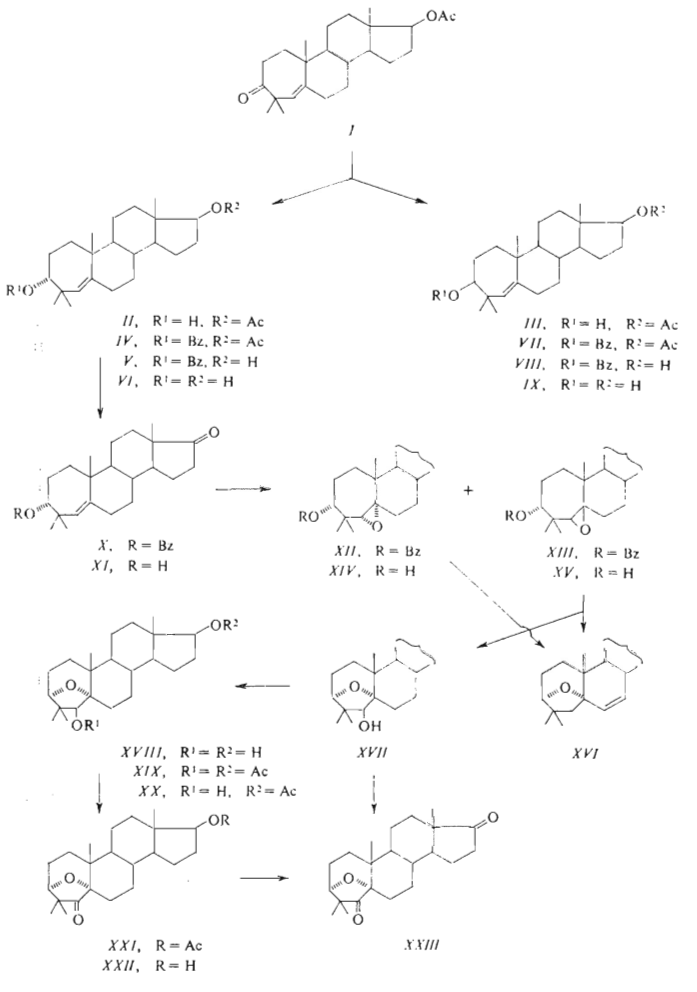
by a strong intramolecular hydrogen bond to the epoxidic oxygen atom in derivatives *XIV* and *XXVIII* and therefore these derivatives must possess the structure of 3α--hydroxy-4aα,5α-epoxide (*XIV*) and 3β-hydroxy-4aβ,5β-epoxide (*XXVIII*). In agreement with the splitting of the expected singlet of the 4a-epoxide proton in the ^{1}H NMR spectra of 3β-substituted 4aβ,5β-epoxides and 3α-substituted 4aα,5α-epoxides of 4,4-dimethyl-A-homocholestane series to a doublet (under the effect of long--range interaction between the protons on the carbon atoms $C_{(4a)}$ and $C_{(3)}$, ref.[1]), observed earlier, is also the character of the signals of the 4a-epoxide proton in the ^{1}H NMR spectra of epoxides *XIV*, *XV*, *XXVIII* and *XXIX* (Table III). Hence, on the basis of these data β-configuration was assigned to the 4a,5-epoxide ring in epoxides *XV* and *XXVIII* and α-configuration to the 4a,5-epoxide ring in epoxides *XIV* and *XXIX*.

Acid catalysed cleavage of the 4aβ,5β-epoxide ring in epoxide *XV* with hydrobromic acid in chloroform gave 3α,5α-transannular epoxide *XVII* as the main product in a 75% yield. As the by-product 6,7-unsaturated 3α,5α-transannular epoxide *XVI* is formed in 11% yield, probably by intramolecular cyclization of the intermediary formed 4a,6-diene (ref.[3]). It is also the main product of the acid catalysed cleavage of 3α-hydroxy-4aα,5α-epoxide *XIV*. Reduction of the 17-keto group in derivative *XVI* with lithium aluminium hydride gave hydroxy derivative *XXXVI*, which was characterized as acetoxy derivative *XXXVII*. 17-Keto derivative *XVII* was converted to diol *XVIII* on a similar reduction. After acetylation it afforded a mixture of diacetoxy and monoacetoxy derivatives *XIX* and *XX* in about a 1 : 6 ratio. Monoacetoxy derivative *XX*, when oxidized with the chromium trioxide–pyridine complex, gave ketone *XXI* which was submitted to alkaline hydrolysis, affording the required hydroxy derivative *XXII*. Oxidation of hydroxy derivatives *XVII* and *XXII* with the chromium trioxide–pyridine complex afforded the same diketone *XXIII*. Acid catalysed cleavage of the 4aα,5α-epoxide ring of epoxide *XXIX* with hydrobromic acid in chloroform gave 3β,5β-transannular epoxide *XXX*, which was reacted with lithium aluminium hydride, affording diol *XXXI*. Diol

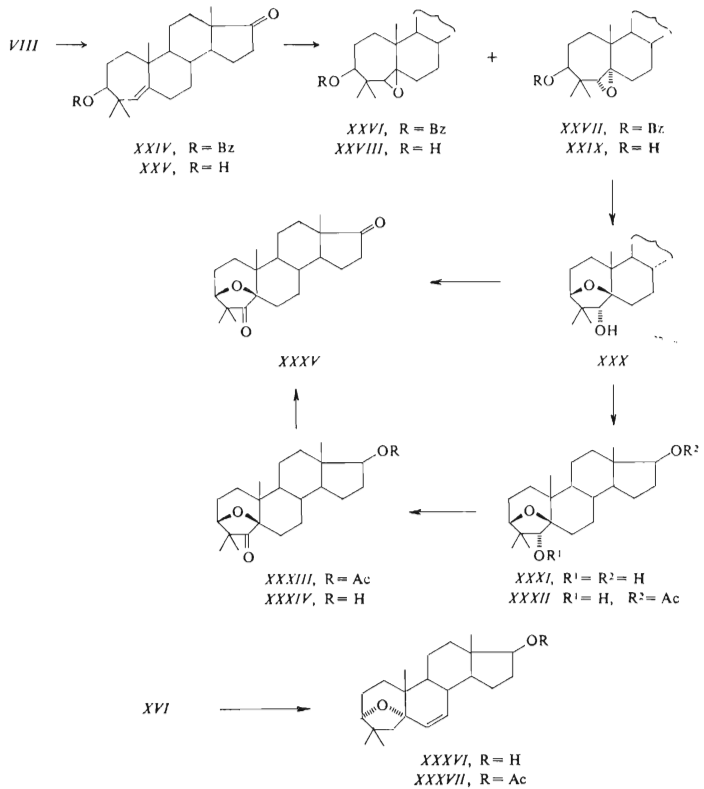
TABLE III

Characteristic parameters of ^{1}H NMR spectra of epoxides in deuteriochloroform

α-Epoxide	$C_{(4a)}$—H	β-Epoxide	$C_{(4a)}$—H
XIV	2·475 (d, J = 1·5 Hz)	*XV*	2·45 (s)
XXIX	2·43 (s)	*XXVIII*	2·50 (d, J = 1·5 Hz)


OAc
O
I
OR²
R¹O
II, R¹ = H, R² = Ac
IV, R¹ = Bz, R² = Ac
V, R¹ = Bz, R² = H
VI, R¹ = R² = H
III, R¹ = H, R² = Ac
VII, R¹ = Bz, R² = Ac
VIII, R¹ = Bz, R² = H
IX, R¹ = R² = H
RO
X, R = Bz
XI, R = H
XII, R = Bz
XIV, R = H
XIII, R = Bz
XV, R = H
OR¹
XVIII, R¹ = R² = H
XIX, R¹ = R² = Ac
XX, R¹ = H, R² = Ac
XVII
XVI
OR
XXI, R = Ac
XXII, R = H
XXIII

XXXI was acetylated to monoacetoxy derivative *XXXII*, which was oxidized to ketone *XXXIII* with chromium trioxide in pyridine. On alkaline saponification of the acetoxy group of derivative *XXXIII* the required hydroxy derivative *XXXIV* was obtained. Oxidation of hydroxy derivatives *XXX* and *XXXIV* with the chromium trioxide–pyridine complex gave the same ketone, *XXXV*. The results of biological tests of compounds *XVII*, *XXII*, *XXX*, *XXXIV* and *XXXVI* will be published later.



EXPERIMENTAL

The melting points were determined an a Kofler melting point apparatus and they not corrected. Optical rotations were measured in chloroform unless stated otherwise. The infrared spectra were measured on a Zeiss UR 20 apparatus in chloroform, unless stated otherwise. The CD spectra were measured on a Dichrographe II (Jouan-Roussel) instrument in dioxane. The ^{1}H NMR spectra were measured on a Tesla B 476 (60 MHz) instrument in deuteriochloroform. using tetramethylsilane as internal reference. Chemical shifts are given in ppm. The identity of the samples prepared in various ways was checked by mixture melting point determinations and infrared spectra. The term "conventional work-up" means: the ethereal extract was washed with 5% hydrochloric acid, 5% aqueous potassium hydrogen carbonate and water, then dried over sodium sulfate and the solvent was evaporated in vacuum. The crude products were chromatographed on preparative silica gel thin layers (20 × 20 cm) in light petroleum–ether (8 : 2), unless stated otherwise. The corresponding combined zones were washed with ether and the solvent was evaporated in a vacuum.

4,4-Dimethyl-A-homo-4a-androstene-3α,17β-diol 3-Benzoate, 17-Acetate (*IV*)

Sodium borohydride (180 mg) was added to a solution of 17β-acetoxy-4,4-dimethyl-A-homo--4a-androsten-3-one (*I*, ref.[6], 350 mg) in ethanol (15 ml) and the mixture was allowed to stand at room temperature for 6 h. It was poured into icy water and the product was extracted with ether. The extract was submitted to the conventional work-up, affording 350 mg of a crude product which was chromatographed on 6 silica gel coated plates. The combined, corresponding less polar zones were worked up, giving 300 mg of an inseparable mixture of hydroxy derivatives *II* and *III*. The corresponding combined more polar zones afforded 35 mg of an inseparable mixture of diols *VI* and *IX*. The mixture of hydroxy derivatives *II* and *III* was benzoylated with benzoyl chloride (0·6 ml) in pyridine (8 ml) overnight. The conventional work-up gave 300 mg of a crude product which was chromatographed on 7 silica gel thin-layer plates in light petroleum–ether (95 : 5), using double elution. The corresponding less polar zones were combined and worked up, giving 155 mg of derivative *IV*, which when crystallized from methanol (108 mg), had m.p. 183–185°C, $[\alpha]_D^{20} = -2°$ (*c* 0·5). Infrared spectrum (tetrachloromethane): 1 736, 1 247, 1 718, 1 276, 1 646 cm^{-1}. For $C_{31}H_{42}O_4$ (478·6) calculated: 77·78% C, 8·85% H; found: 77·28% C, 9·57% H.

4,4-Dimethyl-A-homo-4a-androstene-3α,17β-diol 3-Benzoate (*V*)

An aqueous solution of potassium hydrogen carbonate (480 mg, 3 ml H_2O) was added to a solution of derivative *IV* (480 mg) in methanol (50 ml) and the mixture was refluxed for 4 h. After concentration to one third of the original volume *in vacuo* the mixture was poured into water and the product was extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue (475 mg) was chromatographed on 10 silica gel thin-layer plates. The corresponding less polar zones were combined and worked up to give 400 mg of derivative *V*, which was crystallized from methanol (321 mg), m.p. 165–166°C, $[\alpha]_D^{20} = -5°$ (*c* 0·5). CD spectrum: $\Delta\varepsilon_{245} = +0{\cdot}58$ (terminal value). Infrared spectrum: 1 710, 1 280, 3 615 cm^{-1}. For $C_{29}H_{40}O_3$ (436·6) calculated: 79·77% C, 9·23% H; found: 79·26% C, 9·21% H.

4,4-Dimethyl-A-homo-4a-androstene-3α,17β-diol (*VI*)

The corresponding more polar zones after separation of derivative *V* in the preceding experiment were combined and worked up, affording 50 mg of diol *VI*, which was crystallized from heptane (31 mg), m.p. 179–181°C, $[\alpha]_D^{20} = +48°$ (*c* 0·5). Infrared spectrum: 3 615, 1 050, 1 020, 1 625 cm^{-1}. For $C_{22}H_{36}O_2$ (332·5) calculated: 79·46% C, 10·91% H; found: 78·90% C, 10·67% H.

4,4-Dimethyl-A-homo-4a-androstene-3β,17β-diol 3-Benzoate, 17-Acetate (*VII*)

The corresponding more polar zones after separation of benzoyloxy derivative *IV* (*vide supra*) were combined and worked up, affording 125 mg of derivative *VII* which was crystallized from methanol (89 mg), m.p. 147–149°C, $[\alpha]_D^{20} = +33°$ (*c* 0·5). Infrared spectrum (tetrachloromethane): 1 719, 1 275, 1 737, 1 249 cm^{-1}. For $C_{31}H_{42}O_4$ (478·6) calculated: 77·78% C, 8·85% H; found: 77·54% C, 8·73% H.

4,4-Dimethyl-A-homo-4a-androstene-3β,17β-diol 3-Benzoate (*VIII*)

An aqueous solution of potassium hydrogen carbonate (120 mg, 1 ml H_2O) was added to a solution of derivative *VII* (110 mg) in methanol (10 ml) and the mixture was refluxed for 2 h. After concentration to one third of the original volume the mixture was poured into water and the product was extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent was evaporated in a vacuum. The residue (110 mg) was chromatographed on 2 silica gel thin-layer plates, using double elution. The corresponding combined less polar zones afforded 88 mg of benzoyloxy derivative *VII* which was crystallized from methanol (49 mg), m.p. 184–186°C, $[\alpha]_D^{20} = +57°$ (*c* 0·5). Infrared spectrum: 3 615, 1 710, 1 280 cm^{-1}. CD spectrum: $\Delta\varepsilon_{245} = -0{\cdot}54$ (terminal value). For $C_{29}H_{40}O_3$ (436·6) calculated: 79·77% C, 9·23% H; found: 80·19% C, 9·15% H.

4,4-Dimethyl-A-homo-4a-androstene-3β,17β-diol (*IX*)

The corresponding combined more polar zones after the separation of derivative *VIII* in the preceding experiment were worked up, affording 12 mg of diol *IX* which was crystallized from ether–heptane (7 mg), m.p. 187–188°C, $[\alpha]_D^{20} = +39°$ (*c* 0·5). Infrared spectrum: 3 618, 1 020, 1 050, 3 070, 1 630 cm^{-1}. For $C_{22}H_{36}O_2$ (332·5) calculated: 79·46% C, 10·91% H; found: 78·93% C, 10·77% H.

3α-Benzoyloxy-4,4-dimethyl-A-homo-4a-androsten-17-one (*X*)

Chromium trioxide (300 mg) was added to a solution of derivative *V* (400 mg) in pyridine (20 ml) and the mixture was allowed to stand at room temperature overnight. The conventional work-up afforded 400 mg of a crude product which was crystallized from methanol, giving 318 mg of ketone *X* with m.p. 171–173°C, $[\alpha]_D^{20} = +64°$ (*c* 0·5). Infrared spectrum (tetrachloromethane): 1 743, 1 718, 1 275, 1 643 cm^{-1}. For $C_{29}H_{38}O_3$ (434·6) calculated: 80·14% C, 8·81% H; found: 79·89% C, 8·65% H.

3α-Hydroxy-4,4-dimethyl-A-homo-4a-androsten-17-one (*XI*)

Potassium hydroxide (90 mg) was added to a solution of ketone *X* (80 mg) in methanol (6 ml) and the mixture was refluxed for 1 h. It was poured into water and the product extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent

was evaporated in a vacuum. The residue (80 mg) was chromatographed on 2 silica gel thin-layer plates in light petroleum–ether (7 : 3). Corresponding zones were combined and worked up, affording 60 mg of derivative *XI* which was crystallized from ether–heptane. Yield 47 mg, m.p. 221–223°C, $[\alpha]_D^{20} = +175°$ (*c* 0·5). Infrared spectrum: 3 625, 1 018, 1 735, 1 638 cm^{-1}. For $C_{22}H_{34}O_2$ (330·5) calculated: 79·95% C, 10·37% H; found: 79·54% C, 10·06% H.

3α-Hydroxy-4,4-dimethyl-4aα,5-epoxy-A-homo-5α-androstan-17-one (*XIV*)

3-Chloroperbenzoic acid (230 mg) was added to a solution of olefin *X* (230 mg) in chloroform (15 ml) and the mixture was allowed to stand at room temperature for 30 min. It was poured into water and extracted with ether. The ethereal extract was washed with a saturated aqueous potassium carbonate solution, water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue (230 mg), representing a mixture of epoxides *XII* and *XIII* was dissolved in methanol (20 ml), potassium hydroxide (400 mg) was added and the mixture was refluxed for 8 h. After concentration to one third of the original volume *in vacuo* the mixture was poured into water and the product extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent was evaporated in a vacuum. The residue (215 mg) was chromatographed on 5 silica gel plates in light petroleum–ether (6 : 4). The corresponding combined least polar zones afforded 25 mg of the starting mixture of epoxides *XII* and *XIII*. The corresponding more polar zones were worked up, affording 85 mg of epoxide *XIV*, which when crystallized from methanol had m.p. 204–206°C, $[\alpha]_D^{20} = +78°$ (*c* 0·5). Infrared spectrum: 3 525, 1 738, 1 058, 1 003, 961, 951, 907 cm^{-1}. ^1H NMR spectrum: 0·875 (s, 3 H, 18-CH_3); 1·05 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 1·125 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 1·34 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 2·475 (d, 1 H, $C_{(4a)}$—H, J = 1·5 Hz); 3·30 (mt, 1 H, $C_{(3)}$—H). For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 75·72% C, 9·67% H.

3α-Hydroxy-4,4-dimethyl-4aβ,5-epoxy-A-homo-5β-androstan-17-one (*XV*)

The corresponding most polar zones after separation of epoxide *XIV* (*vide supra*) were combined and worked up, affording 105 mg of epoxide *XV* which was crystallized from aqueous methanol, m.p. 186–188°C, $[\alpha]_D^{20} = +86°$ (*c* 0·5). Infrared spectrum: 3 630, 1 738, 1 732, 955, 950 cm^{-1}, ^1H NMR spectrum: 0·875 (s, 3 H, 18-CH_3); 1·05 (s, 6 H, 19-CH_3 + $C_{(4)}$—CH_3 or $C_{(4)}$—CH_3 + + $C_{(4)}$—CH_3); 1·275 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 2·45 (s, 1 H, $C_{(4a)}$—H); 3·39 (mt, 1 H, $C_{(3)}$—H). For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 75·89% C, 9·68% H.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-androst-6-en-17-one (*XVI*)

a) Hydrobromic acid (1·1 ml, 48%) was added to a solution of epoxide *XV* (260 mg) in chloroform (16 ml) and the mixture was shaken for 30 min, then poured into water and the product extracted with ether. The extract was washed with a 5% aqueous potassium hydrogen carbonate solution and water, then dried over sodium sulfate and the solvent was evaporated under reduced pressure. The residue (250 mg) was chromatographed on 7 silica gel plates in light petroleum–ether (85 : 15; double elution). The corresponding less polar zones were combined and worked up, affording 28 mg of epoxide *XVI* which was crystallized from methanol, m.p. 141–143°C, $[\alpha]_D^{20} =$ $= +45°$ (*c* 0·5). Infrared spectrum: 1 736, 1 406, 1 652, 1 086, 1 010, 968 cm^{-1}. ^1H NMR spectrum: 0·77 (s 3H, 18-CH_3), 1·10 (s, 3H, 19-CH_3 or $C_{(4)}$—CH_3), 1·15 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 0·88 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 3·55 (mt, 1 H, $C_{(3)}$—H); 5·55 (dd, 1 H, $C_{(7)}$—H, J = = 1·5 + 10 Hz); 5·825 (d, 1 H, $C_{(6)}$—H, J = 10 Hz). For $C_{22}H_{32}O_2$ (328·5) calculated: 80·44% C, 9·82% H; found: 80·25% C, 9·64% H.

b) Hydrobromic acid (0·7 ml, 48%) was added to a solution of epoxide *XIV* (160 mg) in chloroform (10 ml) and the mixture was shaken for 5 h, then poured into water and the product extracted with ether. The extract was washed with a 5% potassium hydrogen carbonate solution and water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue (155 mg) was chromatographed on three preparative silica gel thin-layer plates. Corresponding zones were combined and worked up affording 148 mg of epoxide *XVI* which was crystallized from methanol, m.p. 141–143°C, $[\alpha]_D^{20} = +45°$ (*c* 0·5).

4aβ-Hydroxy-4,4-dimethyl-3α,5-epoxy-A-homo-5α-androstan-17-one (*XVII*)

The corresponding combined more polar zones after separation of epoxide *XVI* (see under *a*)) afforded 160 mg of epoxide *XVII* which was crystallized from methanol, m.p. 253–255°C, $[\alpha]_D^{20} = +52°$ (*c* 0·5). Infrared spectrum: 1 733, 3 630, 1 083, 1 010, 1 000 cm^{-1}. ^1H NMR spectrum: 0·84 (s, 3 H, 18-CH_3); 0·975 (s, 3 H, 19-CH_3 of $C_{(4)}$—CH_3); 1·075 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 1·12 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 3·575 (mt, 1 H, $C_{(3)}$—H). For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 75·89% C, 9·73% H.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-androstane-4aβ,17β-diol (*XVIII*)

Lithium aluminium hydride (80 mg) was added to a solution of ketone *XVII* (100 mg) in dioxane (5 ml) and the mixture refluxed for 1 h. The excess of the hydride was decomposed with a saturated solution of sodium sulfate and the mixture was filtered through a column of sodium sulfate. The filtrate was concentrated in a vacuum, affording 100 mg of a crude product which was crystallized from heptane. Yield, 69 mg of diol *XVIII*, m.p. 250–251°C, $[\alpha]_D^{20} = -5°$ (*c* 0·5). Infrared spectrum: 3 625, 1 080, 1 024, 1 010, 1 000 cm^{-1}. For $C_{22}H_{36}O_3$ (348·5) calculated: 75·81% C, 10·41% H; found: 75·34% C, 10·26% H.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-androstane-4aβ,17β-diol 4a,17-Diacetate (*XIX*)

Dihydroxy derivative *XVIII* (110 mg) was acetylated with acetic anhydride (0·4 ml) in pyridine (2 ml) overnight. The conventional work-up of the mixture gave 106 mg of crude product which was chromatographed on 2 silica gel plates. The corresponding less polar zones were combined and worked up, affording 15 mg of derivative *XIX* which was crystallized from aqueous methanol, m.p. 130–131°C, $[\alpha]_D^{20} = 0°$ (*c* 0·5). Infrared spectrum (tetrachloromethane)): 1 745, 1 241, 1 024, 1 056, 1 046 cm^{-1}. For $C_{26}H_{40}O_5$ (432·6) calculated: 72·19% C, 9·32% H; found: 72·01% C 9·16% H.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-androstane-4aβ,17β-diol 17-Acetate (*XX*)

The corresponding more polar zones after the separation of derivative *XIX* in the preceding experiment were combined and worked up, giving 90 mg of derivative *XX* which was crystallized from methanol, m.p. 238–240°C, $[\alpha]_D^{20} = 0°$ (*c* 0·5). Infrared spectrum (tetrachloromethane): 3 635, 1 738, 1 246, 1 023, 1 082, 1 046 cm^{-1}. For $C_{24}H_{38}O_4$ (390·5) calculated: 73·81% C, 9·81% H; found: 73·56% C, 9·76% H.

17β-Acetoxy-4,4-dimethyl-3α,5-epoxy-A-homo-5α-androstane-4a-one (*XXI*)

Chromium trioxide (50 mg) was added to a solution of derivative *XX* (100 mg) in pyridine (3 ml) and the mixture was allowed to stand overnight. The conventional work-up gave 97 mg of crude

product which was crystallized from methanol, affording 68 mg of ketone *XXI*, m.p. 192—194°C, $[\alpha]_D^{20} = -86°$ (*c* 0·5). Infrared spectrum: 1 725, 1 258, 1 741, 1 067, 1 042, 1 023, 1 002, 947 cm^{-1}. For $C_{24}H_{36}O_4$ (388·5) calculated: 74·19% C, 9·34% H; found: 74·08% C, 9·26% H.

17β-Hydroxy-4,4-dimethyl-3α,5-epoxy-A-homo-5α-androstan-4a-one (*XXII*)

Potassium hydroxide (50 mg) was added to a solution of derivative *XXI* (50 mg) in methanol (5 ml) and the mixture was refluxed for 1 h. After pouring it into water the product was extracted with ether and the extract washed with water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue (50 mg) was chromatographed on one silica gel plate in light petroleum–ether (7 : 3). The required zone was worked up, giving 40 mg of derivative *XXII* which was crystallized from heptane at 0°C. M.p. 130—132°C, $[\alpha]_D^{20} = -60°$ (*c* 0·5). Infrared spectrum: 1 745, 3 615, 1 066, 1 006, 951 cm^{-1}. For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 76·08% C, 9·77% H.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-androstane-4a,17-dione (*XXIII*)

a) Chromium trioxide (10 mg) was added to a solution of derivative *XVII* (20 mg) in pyridine (1 ml) and the mixture was allowed to stand at room temperature overnight. After the conventional work-up 20 mg of a crude product were obtained, which was chromatographed on one silica gel plate (10 × 20 cm). The required zone was worked up, affording 15 mg of diketone *XXIII* which was crystallized from methanol, m.p. 157—159°C. Infrared spectrum (tetrachloromethane): 1 744, 1 050, 1 004 cm^{-1}. For $C_{22}H_{32}O_3$ (344·5) calculated: 76·70% C, 9·36% H; found: 76·52% C, 9·23% H.

b) Chromium trioxide (15 mg) was added to a solution of derivative *XXII* (30 mg) in pyridine (1·5 ml) and the mixture was allowed to stand overnight. Conventional work-up gave 30 mg of crude product which was chromatographed on one silica gel thin-layer plate. The required zone was worked up, affording 23 mg of diketone *XXIII* which was crystallized from methanol, m.p. 157—159°C.

3β-Benzoyloxy-4,4-dimethyl-A-homo-4a-androsten-17-one (*XXIV*)

Chromium trioxide (100 mg) was added to a solution of hydroxy derivative *VIII* (120 mg) in pyridine (5 ml) and the mixture was allowed to stand overnight. The conventional work-up gave 120 mg of a crude product which was crystallized from methanol. Yield, 81 mg of ketone *XXIV*, m.p. 134—136°C, $[\alpha]_D^{20} = +138°$C (*c* 0·5). Infrared spectrum (tetrachloromethane): 1 743, 1 718, 1 275, 1 642 cm^{-1}. For $C_{29}H_{38}O_3$ (434·6) calculated: 80·14% C, 8·81% H; found: 80·24% C, 8·76% H.

3β-Hydroxy-4,4-dimethyl-A-homo-4a-androsten-17-one (*XXV*)

Potassium hydroxide (50 mg) was added to a solution of derivative *XXIV* (50 mg) in methanol (10 ml) and the mixture was refluxed for 6 h. After concentration to one third of the original volume in a vacuum the mixture was poured into water and the product extracted with ether. The extract was washed with water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue (50 mg) was chromatographed on one silica gel thin-layer plate in light petroleum–ether (7 : 3). The required zone was worked up, affording 35 mg of hydroxy derivative *XXV* which was crystallized from heptane, m.p. 171—173°C, $[\alpha]_D^{20} = +151°$ (*c* 0·5). Infrared spectrum: 3 625, 1 015, 1 733, 1 407, 1 654, 1 633 cm^{-1}. For $C_{22}H_{34}O_2$ (330·5) calculated: 79·95% C, 10·57% H; found: 79·68% C, 10·42% H.

3β-Hydroxy-4,4-dimethyl-4aβ,5-epoxy-A-homo-5β-androstan-17-one (*XXVIII*)

3-Chloroperbenzoic acid (150 mg) was added to a solution of olefin *XXIV* (150 mg) in chloroform (10 ml) and the mixture was allowed to stand at room temperature for 1 h. After pouring it into water, the mixture was extracted with ether and the extract was washed with a saturated aqueous potassium carbonate solution and water, then dried over sodium sulfate and the solvent was evaporated in a vacuum. The residue (150 mg), representing a mixture of epoxides *XXVI* and *XXVII*, was dissolved in methanol (15 ml), potassium hydroxide (160 mg) was added and the mixture refluxed for 2 h. After concentration to one third of the original volume in a vacuum the mixture was poured into water and the product extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue (145 mg) was chromatographed on 3 silica gel thin-layer plates in light petroleum–ether (7 : 3). The required combined least polar zones were worked up, affording 15 mg of the starting mixture of epoxides *XXVI* and *XXVII*. The corresponding combined more polar zones gave 35 mg of derivative *XXVIII* which was crystallized from heptane, m.p. 175–176°C. Infrared spectrum: 3 525, 1 735, 1 049, 1 006, 943 cm^{-1}. ^1H NMR spectrum: 0·87 (s, 3 H, 18-CH_3); 1·08 (s, 3 H, 19-CH_3 or $C_{(4)}$—H_3); 1·11 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 1·26 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 2·50 (d, 1 H, $C_{(4a)}$—H, J = 1·5 Hz); 3·33 (mt, 1 H, $C_{(3)}$—H). For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 76·01% C, 9·65% H.

3β-Hydroxy-4,4-dimethyl-4aα,5-epoxy-A-homo-5α-androstan-17-one (*XXIX*)

The corresponding combined most polar zones after the separation of derivative *XXVIII* from the preceding experiment were worked up, affording 90 mg of derivative *XXIX*, which was crystallized from methanol, m.p. 228–230°C, $[\alpha]_D^{20} = +62$ (*c* 0·5). Infrared spectrum: 3 620, 1 733, 1 052, 1 014, 960 cm^{-1}. ^1H NMR spectrum: 0·87 (s, 3 H, 18-CH_3); 1·00 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 1·08 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 1·26 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 2·43 (s, 1 H, $C_{(4a)}$—H); 3·375 (mt, 1 H, $C_{(3)}$—H). For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 76·08% C, 9·66% H.

4aα-Hydroxy-4,4-dimethyl-3β,5-epoxy-A-homo-5β-androstan-17-one (*XXX*)

Hydrobromic acid (1·2 ml) was added to a solution of epoxide *XXIX* (450 mg) in chloroform (36 ml) and the mixture was shaken for 20 min and poured into water. The product was extracted with ether and the extract washed with a 5% aqueous potassium hydrogen carbonate solution and water. After drying over sodium sulfate the solvent was evaporated in a vacuum. The residue (445 mg) was crystallized from methanol, affording 300 mg of epoxide *XXX*, m.p. 314–315°C, $[\alpha]_D^{20} = +94°$ (*c* 0·5). Infrared spectrum: 1 725, 3 440, 1 104, 1 087, 1 044, 1 015, 907 cm^{-1}. ^1H NMR spectrum (deuteriochloroform–dimethyl sulfoxide): 0·85 (s, 3 H, 18-CH_3); 0·94 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 1·09 (s, 6 H, 19-CH_3 + $C_{(4)}$—CH_3 or $C_{(4)}$—CH_3 + + $C_{(4)}$—CH_3); 3·56 (t, 1 H, $C_{(3)}$—H); 3·66 (s, 1 H, $C_{(4a)}$—H). For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 75·97% C, 9·64% H.

4,4-Dimethyl-3β,5-epoxy-A-homo-5β-androstane-4aα,17β-diol (*XXXI*)

Lithium aluminium hydride (100 mg) was added to a solution of ketone *XXX* (140 mg) in dioxane (10 ml) and the mixture was refluxed for 5 min. The excess of the hydride was decomposed with a saturated sodium sulfate solution and the mixture was filtered through a column of sodium sulfate. The filtrate was concentrated in a vacuum, affording 136 mg of a crude product which

was crystallized from methanol to give 100 mg of diol *XXXI*, m.p. 277–279°C, $[\alpha]_D^{20} = +43°$ (*c* 0·5, pyridine). For $C_{22}H_{36}O_3$ (348·5) calculated: 75·81% C, 10·41% H; found: 75·97% C, 10·36% H.

4,4-Dimethyl-3β,5-epoxy-A-homo-5β-androstane-4aα,17β-diol 17-Acetate (*XXXII*)

Dihydroxy derivative *XXXI* (300 mg) was acetylated with acetic anhydride (1 ml) in pyridine (5 ml) overnight. The conventional work-up gave 300 mg of a crude product, which was crystallized from methanol to afford 220 mg of derivative *XXXII*, m.p. 259–261°C, $[\alpha]_D^{20} = +23°$ (*c* 0·5). Infrared spectrum: 3 635, 1 728, 1 263, 1 051, 1 039, 1 012 cm^{-1}. For $C_{24}H_{38}O_4$ (390·5) calculated: 73·81% C, 9·81% H; found: 73·34% C, 9·47% H.

17β-Acetoxy-4,4-dimethyl-3β,5-epoxy-A-homo-5β-androstan-4a-one (*XXXIII*)

Chromium trioxide (40 mg) was added to a solution of derivative *XXXII* (90 mg) in pyridine (3 ml) and the mixture was allowed to stand overnight. The conventional work-up gave 88 mg of a crude product which was chromatographed on one silica gel plate. The required zone was worked up, affording 79 mg of ketone *XXXIII* which was crystallized from methanol, m.p. 150–152°C, $[\alpha]_D^{20} = +58°$ (*c* 1·0). Infrared spectrum (tetrachloromethane): 1 745, 1 248, 1 732, 1 052, 1 046, 1 028, 1 020 cm^{-1}. For $C_{24}H_{36}O_4$ (388·5) calculated: 74·19% C, 9·34% H; found: 74·39% C, 9·21% H.

17β-Hydroxy-4,4-dimethyl-3β,5-epoxy-A-homo-5β-androstan-4a-one (*XXXIV*)

Potassium hydroxide (100 mg) was added to a solution of derivative *XXXIII* (150 mg) in methanol (10 ml) and the mixture was refluxed for 1 h. After concentration to one third of its original volume in vacuo the mixture was poured into water and the product extracted with ether. The extract was washed with water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue (146 mg) was crystallized from methanol, affording 97 mg of derivative *XXXIV*, m.p. 274–276°C, $[\alpha]_D^{20} = +58°$ (*c* 0·5). Infrared spectrum: 1 741, 3 615, 1 042, 1 025 cm^{-1}. For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 76·02% C, 9·76% H.

4,4-Dimethyl-3β,5-epoxy-A-homo-5β-androstan-4a,17-dione (*XXXV*)

a) Chromium trioxide (15 mg) was added to a solution of derivative *XXX* (25 mg) in pyridine (1 ml) and the mixture was allowed to stand overnight. The conventional work-up gave 22 mg of a crude product which when crystallized from methanol afforded 11 mg of dione *XXXV*, m.p. 241–252·5°C, $[\alpha]_D^{20} = +112°$ (*c* 0·5). Infrared spectrum: 1 744, 1 732, 1 052, 1 023, 1 011 cm^{-1}. For $C_{22}H_{32}O_3$ (344·5) calculated: 76·70% C, 9·36% H; found: 76·44% C, 9·21% H.

b) Chromium trioxide (15 mg) was added to a solution of derivative *XXXIV* (25 mg) in pyridine (1 ml) and the mixture was allowed to stand overnight. The conventional work-up gave 24 mg of crude dione *XXXV* which was crystallized from methanol, m.p. 241–242·5°C, $[\alpha]_D^{20} = +112°$ *c* 0·5).

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-androst-6-en-17β-ol (*XXXVI*)

Lithium aluminium hydride (80 mg) was added to a solution of ketone *XVI* (160 mg) in dioxane (6 ml) and the mixture was refluxed for 15 min. The excess of the hydride was decomposed with a saturated aqueous sodium sulfate solution and the mixture was filtered through a small column of sodium sulfate. After evaporating the filtrate 154 mg of a crude product were obtained,

which was chromatographed on 3 silica gel thin-layer plates in light petroleum–ether (7 : 3). Corresponding combined zones were worked up, affording 144 mg of hydroxy derivative *XXXVI*, which was crystallized from heptane, m.p. 165–167°C, $[\alpha]_D^{20} = -74°$ (*c* 0·5). Infrared spectrum: 3 615, 3 060, 1 645, 1 084, 1 052, 1 010, 968 cm^{-1}. For $C_{22}H_{34}O_2$ (330·5) calculated: 79·95% C, 10·37% H; found: 79·90% C, 10·46% H.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-androst-6-en-17β-yl 17-Acetate (*XXXVII*)

Hydroxy derivative *XXXVI* (50 mg) was acetylated with acetic anhydride (0·2 ml) in pyridine (1 ml). The conventional work-up gave 50 mg of a crude product which was chromatographed on one silica gel plate. The required zone was worked up, giving 39 mg of derivative *XXXVII*, which was crystallized from methanol, m.p. 135–137°C. Infrared spectrum (tetrachloromethane): 3 030, 1 653, 1 743, 1 248, 1 045, 1 038, 1 019, 969 cm^{-1}. For $C_{24}H_{36}O_3$ (372·5) calculated: 77·37% C, 9·74% H; found: 77·24% C, 9·53% H.

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