4,4-DIMETHYL-A-HOMOANDROSTANE EPOXIDES*

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Epimeric 3-hydroxy derivatives *II* and *III* were prepared on reduction of ketone *I* and then submitted to epoxidation. It was found that the $5(0)^n$ participation of the 3α-oxygenated substituent leads to the formation of 3α,5α-transannular epoxide *IX* both if the 5β,6β-epoxide *VIII* was opened with alkalies, or when the 5,6-double bond of the hydroxy derivative *III* was epoxidized, 3α,5α-Transannular epoxide *XI* was prepared as a substance with potential antiandrogenic activity.

In the preceding paper[1] we studied the stereochemistry of the epoxidation of the 5,6-double bond and the stereochemistry of the opening of the 5β,6β-epoxide ring in some 3-substituted 4,4-dimethyl-A-homocholestane derivatives. In this paper the results achieved were applied in the preparation of 3α,5α-transannular epoxide *IX* which is a substance with a potential antiandrogenic activity.

The reduction of the known[2] 17β-benzoyloxy-4,4-dimethyl-A-homo-5-androsten-3-one (*I*) with sodium borohydride in a dioxane–ethanol–ethyl acetate mixture afforded hydroxy derivatives *II* and *III* in an approximate 1 : 2 ratio, characterized as acetates *IV* and *V*. The probable configuration of the hydroxyl group in the position 3 of derivatives *II* and *III* was derived using the conformational disymmetry rule[3], while for the configuration determination of the hydroxyl group the difference of molecular rotations of the corresponding acetoxy derivative and hydroxy derivative was used instead of the molecular rotation difference $\Delta[M_D$ benzoate–alcohol]. The utilisability of $\Delta[M_D$ acetate–alcohol] for the determination of the configuration of secondary hydroxy group of triterpenes and steroids of the normal series was demonstrated earlier[4,5], and it was checked for steroids with a seven-membered ring A on substances with a known configuration of the 3-hydroxyl group. The $\Delta[M_D$ acetate–alcohol] value should be more positive for 3β-hydroxy derivatives than for 3α-hydroxy derivatives, which is in agreement with the values observed for $\Delta[M_D$ acetate–alcohol] (Table I). Hence, β-configuration may be tentatively assigned to the 3-hydroxy group of derivative *II* ($\Delta[M_D] = +125$) and α-configuration to the 3-hydroxy group of derivative *III* ($\Delta[M_D] = -88$) on the basis of the observed $\Delta[M_D$ acetate–alcohol] values.

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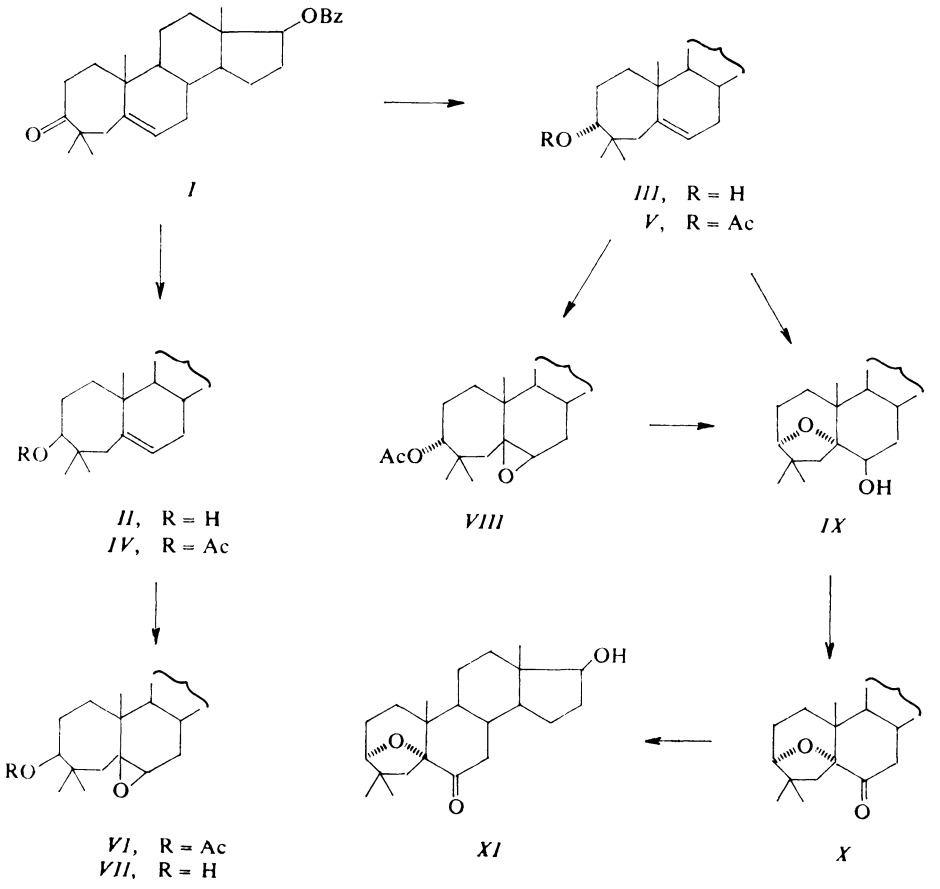
In the preceding paper[1] it was found that on epoxidation of the 5,6-double bond in 4,4-dimethyl-A-homocholestane derivatives only the products of an attack of the reagent from the β-side of the cyclic system are formed. A similar stereochemistry of epoxidation was also observed in 4,4-dimethyl-A-homo-5-androstene derivatives *II*, *IV* and *V*. Epoxidation of olefins *II*, *IV* and *V* with *m*-chloroperbenzoic acid in chloroform afforded epoxides *VI*, *VII* and *VIII*, in the ^{1}H NMR spectra of which the signal of the epoxide proton appears as a doublet with the coupling constant $J = 2$ Hz. This low value of the coupling constant is in agreement both with the earlier observed[1] coupling constant value for 5β,5β-epoxides of the 4,4-dimethyl-A-homocholestane series ($J = 1{\cdot}5$ Hz), and with the observation[6] that in 5β,6β-epoxides of the normal steroid series the interaction between the epoxide proton on $C_{(6)}$ and the 7β-proton gives the value for J about 2·1 – 2·7 Hz, while for 5α,6α-epoxides the coupling constant value is between 3·3 and 4·1 Hz.



It is known[1] that the epoxide ring of 3α-acetoxy-5β,6β-epoxide of 4,4-dimethyl--A-homocholestane series is very easily opened under $5(0)^n$ participation of the 3α-oxygen substituent, under formation of 3α,5α-transannular epoxide, even when applying a mild alkaline saponification of the 3-acetoxy group. A similar course of the alkaline saponification was also observed in the case of 3α-acetoxy-5β,6β-epoxide *VIII* which reacted with potassium hydrogen carbonate in boiling methanol to give 3α,5α-transannular epoxide *IX* in a 61% yield. This is also the main product of epoxidation of olefin *III* with *m*-chloroperoxybenzoic acid in chloroform (93%). The formation of transannular epoxide *IX* under the conditions of epoxidation may be probably explained by $5(0)^n$ participation of the 3α-hydroxy group during acid catalysed cleavage of intermediary formed 5β,6β-epoxide. The $5(0)^n$ participation of the 3-oxygen substituent in acid catalysed opening of the epoxide ring under formation of 3,5-transannular epoxides was observed earlier in 4a,5-epoxides of 4,4-dimethyl-A-homocholestane series[10].

The oxidation of 6β-hydroxy group of transannular epoxide *IX* with the chromium trioxide–pyridine complex afforded ketone *X*, which gave after alkaline saponification of the 17β-benzoyloxy group the required hydroxy derivative *XI*. The results of the biological tests of derivative *XI* will be published later.

TABLE I

Molecular rotation differences $\Delta[M_D$ acetate–alcohol] for known 3-hydroxy derivatives and their acetoxy derivatives (in chloroform)

Compound	M_D	ΔM_D
4,4-Dimethyl-A-homo-4a-cholesten-3β-ol[7]	+193	+ 99
4,4-Dimethyl-A-homo-4a-cholesten-3β-ol 3-acetate[7]	+292	
4,4-Dimethyl-A-homo-4a-cholesten-3α-ol[7]	+180	− 53
4,4-Dimethyl-A-homo-4a-cholesten-3α-ol 3-acetate[7]	+127	
4,4-Dimethyl-A-homo-5-cholesten-3β-ol[7]	+ 77	+ 36
4,4-Dimethyl-A-homo-5-cholesten-3β-ol 3-acetate[8]	+113	
4,4-Dimethyl-A-homo-5-cholesten-3α-ol[7]	+ 77	−110
4,4-Dimethyl-A-homo-5-cholesten-3α-ol 3-acetate[8]	− 33	
4,4-Dimethyl-A-homo-4a-androstene-3β,17β-diol[9]	+130	+ 74
4,4-Dimethyl-A-homo-4a-androstene-3β,17β-diol 3,17-diacetate	+204	
4,4-Dimethyl-A-homo-4a-androstene-3α,17β-diol[9]	+160	−123
4,4-Dimethyl-A-homo-4a-androstene-3α,17β-diol 3,17-diacetate	+ 37	

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. Optical rotations were measured in chloroform. The infrared spectra were measured on a Zeiss UR 20 instrument in chloroform. The ^{1}H NMR spectra were measured on a Tesla B 476 instrument (60 MHz) 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 points determination and infrared spectra. The term „conventional work-up" means that the solution was washed with 5% hydrochloric acid, 5% aqueous potassium hydrogen carbonate solution and water, dried over sodium sulphate and the solvent evaporated in a vacuum. The crude products were chromatographed on preparative silica gel thin-layer plates (20 × 20 cm) in light petroleum–ether (9 : 1). The corresponding zones were combined, washed with ether and the solvent evaporated in a vacuum.

4,4-Dimethyl-A-homo-5-androstene-3β,17β-diol 17-Benzoate (*II*)

Sodium boro-hydride (300 mg) was added to a solution of 17β-benzoyloxy-4,4-dimethyl-A-homo--5-androsten-3-one (*I*), ref.[2] (600 mg) in a mixture of dioxane (10 ml), ethanol (23 ml) and ethyl acetate (2 ml). The mixture was allowed to stand at room temperature for 3 h, then poured into ice water and the excess hydride was decomposed with acetic acid. The product was extracted with ether and the extract washed with a 5% aqueous solution of potassium hydrogen carbonate and water, dried over sodium sulfate and the solvent was evaporated under reduced pressure. The residue (600 mg) was chromatographed on a silica gel column (60 g) in light petroleum–acetone (95 : 5). The corresponding less polar fractions were worked up, affording 200 mg of 3β-alcohol *II* which was crystallized from ethanol (150 mg), m.p. 203–204·5°C, $[\alpha]_D^{20} = +58°$ (*c* 0·5). Infrared spectrum: 3 630, 1 712, 1 238, 1 660 cm^{-1}. For $C_{29}H_{40}O_3$ (436·6) calculated: 79·77% C, 9·23% H; found: 79·49% C, 9·03% H.

4,4-Dimethyl-A-homo-5-androstene-3α,17β-diol 17-Benzoate (*III*)

The corresponding pooled more polar fractions after the separation of 3β-hydroxy derivative *II* from the preceding experiment were worked up to give 365 mg of 3α-hydroxy derivative *III* which was crystallized from methanol (316 mg), m.p. 169–171°C, $[\alpha]_D^{20} = +65°$ (*c* 0·5). Infrared spectrum: 3 618, 1 030, 1 711, 1 282, 1 660 cm^{-1}. For $C_{29}H_{40}O_3$ (436·6) calculated: 79·77% C, 9·23% H; found: 79·54% C, 9·28% H.

4,4-Dimethyl-A-homo-5-androstene-3β,17β-diol 3-Acetate, 17-Benzoate (*IV*)

Hydroxy derivative *II* (100 mg) was acetylated with acetic anhydride (0·2 ml) in pyridine (10 ml) overnight. The conventional work-up gave 100 mg of a crude product, which was crystallized from methanol to give 76 mg of acetoxy derivative *IV*, m.p. 162–164°C, $[\alpha]_D^{20} = +81°$ (*c* 0·5). Infrared spectrum: 1 714, 1 280, 1 660, 1 730, 1 263, 1 029 cm^{-1}. For $C_{31}H_{42}O_4$ (478·65) calculated: 77·78% C, 8·85% H; found: 77·62% C, 8·54% H.

4,4-Dimethyl-A-homo-5-androstene-3α,17β-diol 3-Acetate, 17-Benzoate (*V*)

Hydroxy derivative *III* (100 mg) was acetylated with acetic anhydride (0·2 ml) in pyridine (10 ml) overnight. The conventional work-up afforded 100 mg of crude product which was crystallized from methanol. Yield 80 mg of acetoxy derivative *V*, m.p. 162–164°C, $[\alpha]_D^{20} = +41°$ (0·5). Infrared spectrum: 1 719, 1 280, 1 258, 1 029, 1 653 cm^{-1}. For $C_{31}H_{42}C_4$ (478·65) calculated: 77·78% C, 8·85% H; found: 77·83% C, 8·75% H.

4,4-Dimethyl-5,6β-epoxy-A-homo-5β-androstane-3β,17β-diol 3-Acetate, 17-Benzoate (*VI*)

a) *m*-Chloroperbenzoic acid (100 mg) was added to a solution of acetoxy derivative *IV* (100 mg) in chloroform (5 ml) and the mixture was allowed to stand at room temperature for 1 h and poured into water. The product was extracted with ether and the extract washed with a saturated potassium carbonate solution and water, dried over sodium sulfate and the solvent was evaporated in a vacuum. The residue (100 mg) was chromatographed preparatively on 2 silica gel plates to give 89 mg of epoxide *VI*, which was crystallized from methanol (51 mg), m.p. 197—199°C. Infrared spectrum: 1 731, 1 260, 1 029, 1 713, 1 280 cm^{-1}. ^1H NMR spectrum: 0·89 (6 H, s, 18-CH_3 + 19-CH_3 or 18-CH_3 + $C_{(4)}$—CH_3); 2·05 (s, 3 H, $OCOCH_3$); 3·12 (d, 1 H, $C_{(6)}$—H, J = 2 Hz); 4·76 (center mt, 2 H, $C_{(3)}$—H + $C_{(17)}$—H). For $C_{31}H_{42}O_5$ (494·65) calculated: 75·27% C, 8·56% H; found: 75·45% C, 8·32% H.

b) Hydroxy derivative *VII* (50 mg) was acetylated with acetic anhydride (0·1 ml) in pyridine (5 ml) overnight. The conventional work-up afforded 50 mg of a crude product which was chromatographed preparatively on one silica gel thin-layer plate. The required zone was worked up to give 41 mg of acetoxy derivative *VI*, which was crystallized from methanol. Yield, 30 mg, m.p. 197—199°C.

4,4-Dimethyl-5,6β-epoxy-A-homo-5β-androstane-3β,17β-diol 17-Benzoate (*VII*)

m-Chloroperbenzoic acid (80 mg) was added to a solution of olefin *II* (80 mg) in chloroform (5 ml) and the mixture was allowed to stand at room temperature for 45 min. The mixture was worked up as in the preceding experiment (ad *a*)), affording 80 mg of a crude product which was crystallized from heptane. Yield, 46 mg of epoxide *VII*, m.p. 151—153°C, $[\alpha]_D^{20}$ = +30° (*c* 0·5). Infrared spectrum: 3 630, 3 615, 1 711, 1 280 cm^{-1}. For $C_{29}H_{40}O_4$ (452·6) calculated: 76·95% C, 8·91% H; found: 76·35% C, 8·67% H.

4,4-Dimethyl-5,6β-epoxy-A-homo-5β-androstane-3α,17β-diol 3-Acetate, 17-Benzoate (*VIII*)

m-Chloroperbenzoic acid (100 mg) was added to a solution of olefin *III* (100 mg) in chloroform (5ml) and the mixture was allowed to stand at room temperature for 1 h. The working up of the mixture as in the preceding experiment gave 100 mg of a crude product which was chromatographed on 2 preparative plates with silica gel thin layer. The corresponding required zones were worked up. Yield, 88 mg of epoxide *VIII* which was crystallized from methanol (48 mg), m.p. 178—180°C, $[\alpha]_D^{20}$ = 0° (*c* 0·5). Infrared spectrum: 1 714, 1 280, 1 730, 1 260, 1 030, 986, 960, 927 cm^{-1}. ^1H NMR spectrum: 0·90 (s, 9 H, 18-CH_3 + 19-CH_3 + $C_{(4)}$—CH_3 or 18-CH_3 + + $C_{(4)}$—CH_3 + $C_{(4)}$—CH_3); 0·96 (s, 3 H, 19-CH_3 or $C_{(4)}$—CH_3); 2·01 (s, 3 H, $OCOCH_3$); 3·13 (d, 1 H, $C_{(6)}$—H, J = 2 Hz); 4·45 (mt, 1 H, $C_{(3)}$—H); 4·79 (mt, 1 H, $C_{(17)}$—H). For $C_{31}H_{42}O_5$ (494·65) calculated: 75·27% C, 8·56% H; found: 75·70% C, 8·98% H.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-androstane-6β,17β-diol 17-Benzoate (*IX*)

a) *m*-Chloroperbenzoic acid (350 mg) was added to a solution of olefin *III* (350 mg) in chloroform (20 ml) and the mixture was allowed to stand at room temperature for 1 h. The same working up procedure as in the preceding experiment gave 350 mg of a crude product which was chromatographed preparatively on 7 silica gel thin-layer plates. The combined corresponding zones were worked up, giving 336 mg of the transannular epoxide *IX* which was crystallized from heptane (300 mg), m.p. 181—182·5°C, $[\alpha]_D^{20}$ = +7° (*c* 0·5). Infrared spectrum: 3 615, 1 711, 1 280 cm^{-1}. ^1H NMR spectrum: 0·94 (s, 6 H, 18-CH_3 + 19-CH_3 or 18-CH_3 + $C_{(4)}$— — CH_3); 1·10 (s, 6 H, 19-CH_3 + $C_{(4)}$—CH_3 or $C_{(4)}$—CH_3 + $C_{(4)}$—CH_3); 3·60 (center mt,

2 H, $C_{(3)}$—H + $C_{(6)}$—H); 4·81 (center mt, $C_{(17)}$—H). For $C_{29}H_{40}O_4$ (452·6) calculated: 76·95% C, 8·91% H; found: 76·67% C, 8·68% H.

b) An aqueous solution of potassium hydrogen carbonate (70 mg, 1 ml) was added to a solution of acetoxy derivative *V* (70 mg) in methanol (10 ml). The mixture was refluxed for 1 h and concentrated to one third of its volume in a vacuum. It was then poured into water and the product extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and evaporated in a vacuum. The residue (70 mg) was chromatographed on 2 preparative silica gel thin-layer plates and the corresponding zones were combined and worked up. Yield 39 mg of 3α,5α-transannular epoxide *IX* which was crystallized from heptane, m.p. 181—182·5°C, $[\alpha]_D^{20} = +7°$ (*c* 0·5).

17β-Benzoyloxy-4,4-dimethyl-3α,5-epoxy-A-homo-5α-androstan-6-one (*X*)

Chromium trioxide (150 mg) was added to a solution of hydroxy derivative *IX* (210 mg) in pyridine (5 ml) and the mixture was allowed to stand at room temperature overnight. The conventional work-up afforded 208 mg of a crude product which was crystallized from methanol, yield, 149 mg of ketone *X*, m.p. 194—195°C, $[\alpha]_D^{20} = 0°$ (*c* 0·5). Infrared spectrum: 1 714, 1 280 cm^{-1}. For $C_{29}H_{38}O_4$ (450·6) calculated: 77·30% C, 8·50% H; found: 77·21% C, 8·69% H.

4,4-Dimethyl-3α,5-epoxy-17β-hydroxy-A-homo-5α-androstan-6-one (*XI*)

Potassium hydroxide (200 mg) was added to a solution of benzoyloxy derivative *X* (210 mg) in methanol (20 ml) and the mixture was refluxed for 3 h. After concentration to one third of its volume in a vacuum the mixture was poured into water and the product was extracted with ether. The extract was washed with water, dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue (190 mg), was crystallized from heptane, yield, 132 mg of hydroxy derivative *XI*, m.p. 117—119°C, $[\alpha]_D^{20} = -48°$ (*c* 0·5). Infrared spectrum: 3 615, 1 717, 1 073, 1 057, 1 029, 1 009 cm^{-1}. For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 76·01% C, 9·54% H.

4,4-Dimethyl-A-homo-4a-androstene-3β,17β-diol 3,17-Diacetate

4,4-Dimethyl-A-homo-4a-androstene-3β,17β-diol[9] (100 mg) was acetylated with acetic anhydride (0·2 ml) in pyridine (10 ml) overnight. The conventional work-up afforded 98 mg of a crude product which was crystallized from methanol. Yield, 76 mg of the title diacetate, m.p. 146 to 148°C, $[\alpha]_D^{20} = +49°$ (*c* 0·5). Infrared spectrum (tetrachloromethane): 1 736, 1 245, 1 241 cm^{-1}. For $C_{26}H_{40}O_4$ (416·6) calculated: 74·96% C, 9·68% H; found: 74·76% C, 9·54% H.

4,4-Dimethyl-A-homo-4a-androstene-3α,17β-diol 3,17-Diacetate

4,4-Dimethyl-A-homo-4a-androstene-3α,17β-diol[9] (100 mg) was acetylated in the same manner as above. The conventional work-up gave 99 mg of a crude product, which was crystallized from methanol, affording 80 mg of the title diacetate, m.p. 180—182°C, $[\alpha]_D^{20} = +9°$ (*c* 0·5). Infrared spectrum (tetrachloromethane): 1 736, 1 248, 1 041 cm^{-1}. For $C_{26}H_{40}O_4$ (416·6) calculated: 74·96% C, 9·68% H; found: 74·81% C, 9·34% H.

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