4,4-DIMETHYL-A-HOMOANDROSTANE DERIVATIVES* **

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Preparation of 17-substituted derivatives of 4,4-dimethyl-A-homo-4a-androsten-3-one and 4,4-dimethyl-A-homo-5-androsten-3-one is reported.

Our previous papers[1-5] dealt with preparation and conformational properties of some A-homocholestane derivatives. In the course of the continuing work we became interested in potential pharmacodynamic activity of compounds possessing a modified A-homo-androstane skeleton and we therefore prepared a series of compounds derived from 4,4-dimethyl-A-homo-4a-androsten-3-one and 4,4-dimethyl--A-homo-5-androsten-3-one.

17β-Benzoyloxy-4-androsten-3-one[6,7] (*I*) was treated with diazomethane to give the A-homo derivative *II* in 35% yield. Mass spectrum of the benzoate *II* proved the molecular weight 406 as required by the formula $C_{27}H_{34}O_3$. The infrared and ultraviolet spectroscopic data showed the compound *II* to be a non-conjugated ketone and suggested thus the structure of 17β-benzoyloxy-A-homo-4a-androsten-3-one. This structure was corroborated by the NMR-spectrum which revealed the presence of only one olefinic proton the corresponding signal being a triplet. On methylation with methyl iodide in the presence of potassium tert-butoxide, the non-conjugated ketone *II* furnished the 4,4-dimethyl derivative *III*. The mass spectrum confirmed the molecular weight of 434 as expected for the formula $C_{29}H_{38}O_3$. In the NMR-spectrum of this compound, in addition to the singlets of both angular methyls, two further signals of the 4-methyl groups appear as singlets. The fact that the only olefinic proton present appears as a singlet is also in agreement with the formula *III*. Alkaline hydrolysis of the latter substance gave the hydroxy derivative *IV* which also was characterized as the acetyl derivative *V*. Oxidation of the alcohol *IV* with chromium trioxide–pyridine complex yielded the dione *VI*.

Preparation of the 17α-ethinyl derivative required protection of the 3-keto group and ketalization was chosen for this purpose; however, treatment of the ketone *III*

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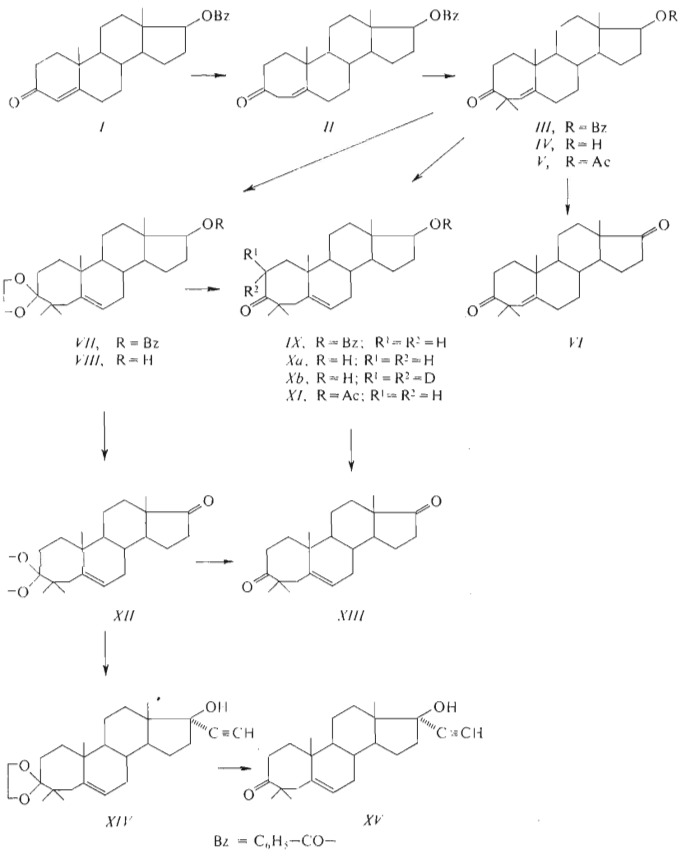
with ethylene glycol and *p*-toluenesulfonic acid in benzene led to a shift of the 4a,5--double bond into the 5,6-position to form the ethylenedioxy derivative *VII*. The same shift took place on heating the ketone *III* in benzene in the presence of *p*-toluene-



sulfonic acid. The resulting ketone *IX* can also be obtained on removal of the protective ketal grouping from the ethylenedioxy derivative *VII*. Structure of the compounds *VII* and *IX* as 4,4-dimethyl-A-homo-5-androstene derivatives was proved in the following manner: the NMR spectrum of the compound *IX* showed four singlets of the tertiary methyl groups and disclosed the presence of only one olefinic proton in the molecule. The doublet character of the signal can only be reconciled with the 5,6-position of the trisubstituted double bond. On alkali catalyzed methanolysis, the ketone *IX* yielded the alcohol *Xa* in which two protons can be replaced by deuterium.

On oxidation with a chromium trioxide–pyridine complex, the alcohol *Xa* was converted into the dione *XIII* which could also be prepared on removing the protective group from the ethylenedioxy derivative *XII*. Alkali catalyzed methanolysis of the benzoyloxy derivative *VII* furnished the alcohol *VIII* which on chromium trioxide–pyridine complex oxidation gave the ketone *XII*. Addition of acetylene in the presence of potassium tert-butoxide followed by removal of the ketal group converted the ketone *XII* into the 17α-ethinyl derivative *XV* (*via XIV*).

Pharmacodynamic properties of the compounds *IV*, *XIII* and *XV* are under investigation.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Unless stated otherwise, optical rotation were measured in chloroform. The infrared spectra were measured on a Zeiss UR 10 spectrophotometer and ORD measurements on a Jasco Model ORD/UV – 5. The NMR spectra were measured in deuteriochloroform on a Varian HA-100 apparatus using tetramethylsilane as internal standard. The identity of samples prepared by different routes was checked by mixture-melting point determination and by infrared spectra. The statement "worked up as usual" stands for: The solution was washed with 5% hydrochloric acid, 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*.

17β-Benzoyloxy-A-homo-4a-androsten-3-one (*II*)

An ethereal solution (60 ml) containing 1·65 g of diazomethane was added to a solution of 17β-benzoyloxy-4-androsten-3-one[6,7] (*I*) (3·3 g) in a mixture of benzene–ether (80 ml, 1 : 1) at 0°C. Aluminum chloride was added in catalytic amounts five times in five minutes intervales. After a further five minutes the reaction mixture was poured into water and the product isolated with ether as usual. The oily residue (3·5 g) yielded after chromatography on silica gel (400 g) in benzene 1·2 g of ketone *II*, m.p. 155–157°C which was crystallized from methanol, m.p. 158–159°C, $[\alpha]_D^{22}$ +86·2° (*c* 0·7). Mol. weight (mass spectrometry): 406. Infrared spectrum (tetrachloromethane): 1 279, 1 640 (ν(C=C)), 1 720(ν(C=O)) cm^{-1}. Ultraviolet spectrum (ethanol): λ_{max_1} 230 nm log ε 4·11; λ_{max_2} 261 nm, log ε 2·85; λ_{max_3} 274 nm, log ε 2·99. NMR: 0·96 (s, 3 H, 18-CH_3); 1·11 (s, 3 H 19-CH_3); 3·17 (broad triplet, 1 H, $C_{(4)}$—H); 4·85 (broad triplet, 1 H, $C_{(17)}$—H, J_{vic} = = 8 + 8 Hz); 5·19 (broad triplet, 1 H, $C_{(4a)}$—H, J_{vic} = 6 + 6 Hz); 7·30–7·60 (mt, 3 H, *m*- and *p*-arom. H); 7·95–8·15 (mt, 2 H, *o*-arom. H). For $C_{27}H_{34}O_3$ (406·5) calculated: 79·76% C, 8·43% H; found: 79·67% C, 8·53% H.

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

The ketone *II* (2 g) was added in nitrogen atmosphere to a stirred solution of potassium tert-butoxide (prepared from 0·90 g of potassium and 40 ml tert-butyl alcohol) at room temperature. When all material was dissolved, methyl iodide (3 ml) was added in several portions during 10 minutes. The mixture was stirred 1 hour, water was then added and tert-butyl alcohol was evaporated *in vacuo*. The residue was extracted with chloroform, the extract was washed with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (2·4 g) yielded after crystallization from methanol 1·5 g of the 4,4-dimethyl derivative *III*, m.p. 172–174°C, $[\alpha]_{22}^{D}$ +64·1° (*c* 0·7). Mol. weight (mass spectrometry): 434. Infrared spectrum (tetrachloromethane): 1 275, 1 707, 1 720 cm^{-1}. For $C_{29}H_{38}O_3$ (434·6) calculated: 80·14% C, 8·81% H; found: 80·06% C, 8·83% H.

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

The benzoyloxy derivative *III* (400 mg) was dissolved in methanol (30 ml), aqueous solution of potassium hydroxide (10 ml, 2%) was added, the mixture was refluxed for 3 hours, concentrated to one third of the original volume, poured into water and the product extracted with chloroform. The extract was washed with water, dried with sodium sulfate and the solvent evaporated *in vacuo*. The residue (350 mg) yielded after crystallization from methanol 300 mg of the hydroxy derivative *IV*, m.p. 148–149°C, $[\alpha]_D^{22}$ +15·0° (*c* 0·7). Infrared spectrum (tetrachloromethane): 1053, 1068, 1706, 3620 cm^{-1}. For $C_{22}H_{34}O_2$ (330·5) calculated: 79·95% C, 10·37% H; found: 79·66% C, 10·62% H.

17β-Acetoxy-4,4-dimethyl-A-homo-4a-androsten-3-one (*V*)

The hydroxy derivative *IV* (265 mg) was acetylated with acetic anhydride (1 ml) in pyridine (2 ml) for 18 hours at room temperature. The usual work up gave 300 mg of the crude product which was crystallized from methanol to yield 235 mg of the acetate *V*, m.p. 146–147°C, $[\alpha]_D^{22}$ −12·0° (*c* 0·7). Infrared spectrum (tetrachloromethane): 1043, 1245, 1663, 1704, 1734 cm^{-1}. For $C_{24}H_{36}O_3$ (372·5) calculated: 77·37% C, 9·74% H; found: 77·27% C, 10·22% H.

4,4-Dimethyl-A-homo-4a-androsten-3,17-dione (*VI*)

The solution of the alcohol *V* (330 mg) in pyridine (8 ml) was added to a solution of chromium trioxide (240 mg)- pyridine (3 ml) complex. The mixture was allowed to stand at room temperature for 24 hours, diluted with ether and the ethereal extract was worked up as usual. The residue (300 mg) after evaporation and crystallization from methanol afforded 250 mg of the dione *VI*, m.p. 144–146°C, $[\alpha]_D^{22}$ +77·0° (*c* 0·7). Infrared spectrum (tetrachloromethane): 1707, 1742 cm^{-1}. For $C_{22}H_{32}O_2$ (328·5) calculated: 80·44% C, 9·82% H; found: 80·68% C, 10·04% H.

17β-Benzoyloxy-4,4-dimethyl-3-ethylenedioxy-A-homo-5-androsten (*VII*)

A mixture of the ketone *III* (800 mg), *p*-toluenesulfonic acid (80 mg), benzene (40 ml) and ethylene glycol (4 ml) was refluxed in a flask provided with a water separated for 24 hours. The reaction mixture was then poured into water. The benzene layer was separated and extracted with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (1·0 g) was chromatographed on silica gel in benzene–light petroleum (9 : 1). The first fraction furnished 600 mg of the 3-ethylenedioxy derivative *VII* m.p. 135–138°C

which was crystallized from methanol, m.p. 140–142°C, $[\alpha]_D^{22}$ +71° (*c* 0·7). Infrared spectrum (tetrachloromethane): 1029, 1086, 1095, 1275, 1582, 1603, 1720 cm^{-1}. For $C_{31}H_{42}O_4$ (478·65) calculated: 77·78% C, 8·85% H; found: 77·13% C, 8·83% H. The second fraction afforded the ketone *III* (125 mg), m.p. 171–173°C, (after crystallization from methanol), $[\alpha]_D^{22}$ +63° (*c* 0·7).

17β-Hydroxy-4,4-dimethyl-3-ethylenedioxy-A-homo-5-androsten (*VIII*)

To a solution of the benzoyloxy derivative *VII* (600 mg) in methanol (80 ml) solid potassium hydroxide (800 mg) was added. The mixture was refluxed for 8 hours, was then concentrated to the third original volume, poured into water and the product extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (600 mg) was chromatographed on silica gel (20 g) in benzene to yield 480 mg of the hydroxy derivative *VIII*, m.p. 165–168°C which was crystallized from heptane, m.p. 169–171°C. Infrared spectrum (tetrachloromethane): 3040, 3615 cm^{-1}. For $C_{24}H_{38}O_3$ (374·5) calculated: 76·96% C, 10·23% H; found: 76·65% C, 10·43% H.

17β-Benzoyloxy-4,4-dimethyl-A-homo-5-androsten-3-one (*IX*)

a) *p*-Toluenesulfonic acid (50 mg) was added to a solution of the ethylenedioxy derivative *VII* (50 mg) in methanol (5 ml). The mixture was allowed to stand at room temperature for 2 hours, concentrated to one third of the original volume, poured into water and the product taken up in ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (45 mg) afforded after crystallization from methanol 31 mg of the ketone *IX*, m.p. 221–223°C, $[\alpha]_D^{25}$ +45·1° (dioxane, *c* 0·06). Infrared spectrum (tetrachloromethane): 1274, 1700, 1716 cm^{-1}. NMR: 0·97 (s, 3 H, 18-CH_3); 1·03 (s, 3 H, 19-CH_3 or 4-CH_3); 1·07 (s, 3 H, 19-CH_3 or 4-CH_3); 1·12 (s, 3 H, 19-CH_3 or 4-CH_3); 4·86 (t, 1 H, $C_{(17)}$—H, J_{vic} = 8 + 8 Hz); 5·52 (broad d, 1 H, $C_{(6)}$—H, J_{vic} = 4 + ≦2 Hz); 7·35–7·65 (mt, 3 H, *m*- and *p*-arom. H); 7·95–8·15 (mt, 2 H, *o*-arom.H). For $C_{29}H_{38}O_3$ (434·6) calculated: 80·14% C, 8·81% H; found: 79·99% C, 8·83% H.

b) To a solution of the ketone *III* (310 mg) in benzene (15 ml) *p*-toluenesulfonic acid was added. The mixture was refluxed for 2 hours, poured into water, the benzene layer was separated and washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (300 mg) was chromatographed on silica gel (40 g) in benzene. The first fraction afforded after crystallization from methanol 70 mg of the ketone *III*, m.p. 172–173°C, $[\alpha]_D^{22}$ +64° (*c* 0·7). The second fraction afforded after crystallization from methanol 180 mg of the ketone *IX*, m.p. 220–222°C, $[\alpha]_D^{22}$ +44° (dioxane, *c* 0·7).

17β-Hydroxy-4,4-dimethyl-A-homo-5-androsten-3-one (*Xa*)

To a solution of the benzoyloxy derivative *IX* (600 mg) in methanol (30 ml) solid potassium hydroxide (500 mg) was added. The mixture was refluxed for 3 hours, concentrated to one third of the original volume, poured into water and the product extracted with ether. The ethereal extract was washed with water, dried with sodium sulfate and the solvent evaporated *in vacuo*. The residue (580 mg) afforded after crystallization from heptane 400 mg of the alcohol *X*, m.p. 146–147°C. Infrared spectrum (chloroform): 1654, 1692, 3610 cm^{-1}. For $C_{22}H_{34}O_2$ (330·5) calculated: 79·95% C, 10·37% H; found: 79·55% C, 10·22% H.

2α,2β-Dideutero-4,4-dimethyl-17β-hydroxy-A-homo-5-androsten-3-one (*Xb*)

A solution of deuterium oxide (1 ml) in dioxane (2 ml) was treated with sodium (10 mg), then a solution of the ketone *Xa* (12 mg) in dioxan (2 ml) was added under nitrogen atmospere and the mixture was refluxed under nitrogen for 2 hours. After concentrating the solution *in vacuo*, dioxane (4 ml) and deuterium oxide (1 ml) were added and the mixture was refluxed for 2 hours under nitrogen. This procedure was repeated once more, the residue was distributed between deuterium oxide and ether, the extract dried with sodium sulfate and the solvent evaporated *in vacuo*. After chromatography on silica gel (10 g, 10% of deuterium oxide) in benzene the residue yielded 8·6 mg of the deuterium compound *Xb*, m.p. 85–86·5°C. Mass spectrometry demonstrated the presence of two deuterium atoms in the molecule. Infrared spectrum (tetrachloromethane): 1660, 1696, 2225, 3615 cm^{-1}. NMR: 0·77 (s, 3 H, 18-CH_3); 1·01 (s, 3 H, 19- or 4-CH_3); 1·05 (s, 3 H, 19- or 4-CH_3); 1·11 (s, 3 H, 19- or 4-CH_3); 2·50 (broad doublet, 1 H, $C_{(1)}$—H, $J_{gem} = 13·5$ Hz); 3·65 (broad triplet, 1 H, $C_{(17)}$—H, $J_{17,16} = 8 + 8$ Hz); 5·48 (broad doublet, 1 H, $C_{(6)}$—H, $J_{6,7} = 5 + 2$ Hz).

17β-Acetoxy-4,4-dimethyl-A-homo-5-androsten-3-one (*XI*)

The hydroxy derivative *X* (100 mg) was acetylated with acetic anhydride (0·3 ml) in pyridine (1·2 ml) at room temperature for 18 hours. The usual work up gave 110 mg of the crude product which was crystallized from methanol, m.p. 176–178°C, $[\alpha]_D^{22}$ −21·4° (*c* 0·7). Infrared spectum (tetrachloromethane): 1246, 1660, 1737, 1704, 3030 cm^{-1}. For $C_{24}H_{36}O_3$ (372·5) calculated, 77·37% C, 9·74% H; found: 77·57% C, 9·81% H.

4,4-Dimethyl-3-ethylenedioxy-A-homo-5-androsten-17-one (*XII*)

A solution of the hydroxy derivative *X* (300 mg) in pyridine (6 ml) was added to a solution of chromium trioxide (300 mg)–pyridine (4 ml) complex. The mixture was allowed to stand at room temperature for 24 hours, diluted with ether and poured into water. The ethereal extract was worked up as usual. After crystallization from methanol the residue (300 mg) yielded 250 mg of the ketone *XII*, m.p. 152·5–154°C, $[\alpha]_D^{22}$ +101·7° (*c* 0·7). Infrared spectrum (tetrachloromethane): 1090, 1115, 1122, 1742, 3045 cm^{-1}. For $C_{24}H_{36}O_3$ (372·5) calculated: 77·37%C, 9·74% H; found: 77·87% C, 9·84% H.

4,4-Dimethyl-A-homo-5-androsten-3,17-dione (*XIII*)

a) *p*-Toluenesulfonic acid (50 mg) was added to a solution of the ethylenedioxy derivative *XII* (50 mg) in methanol (5 ml). The mixture was allowed to stand at room temperature for 2 hours, concentrated to one third of the original volume, poured into water and the product taken up in ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (42 mg) was preparatively chromatographed on one plate of silica gel (20 × 20 cm) in benzene. The corresponding zone was collected, eluted with ether and the solvent evaporated *in vacuo*. After crystallization from methanol the residue (31 mg) afforded the dione *XIII*, m.p. 140–141°C, $[\alpha]_D^{22}$ +29·7° (*c* 0·7). Infrared spectrum (tetrachloromethane): 1703, 1740 cm^{-1}. For $C_{22}H_{32}O_2$ (328·5) calculated: 80·44% C, 9·82% H; found: 80·53% C, 9·94% H.

b) A solution of the hydroxy derivative *X* (90 mg) in pyridine (2 ml) was added to a solution of chromium trioxide (60 mg)–pyridine (1 ml) complex. The mixture was allowed to stand at room temperature for 24 hours, diluted with ether, poured into water and the ethereal extract was

worked up as usual. The residue (80 mg) was preparatively chromatographed on two plates of silica gel (20 × 20 cm) in benzene. The corresponding zones were collected, eluted with ether and the solvent evaporated *in vacuo*. The residue (65 mg) was crystallized from methanol to yield 45 mg of the dione *XIII*, m.p. 140–142°C, $[\alpha]_D^{22}$ +28·5° (*c* 0·7).

4,4-Dimethyl-3-ethylenedioxy-17α-ethinyl-A-homo-5-androsten-17β-ol (*XIV*)

Resublimeed potassium tert-butoxide (200 mg) was added to a solution of the ketone *XII* (420 mg) in toluene (20 ml) and acetylene was passed into solution under stirring for 19 hours. The reaction mixture was then cooled to 0°C, neutralized with dilute sulfuric acid and the product was extracted with ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (400 mg) afforded after chromatography on silica gel (40 g) in benzene 340 mg of the ethinyl derivative *XIV*, m.p. 199–200·5°C, $[\alpha]_D^{22}$ −10·6° (*c* 0·7). Infrared spectrum (chloroform): 900, 1050, 1101, 1125, 3315, 3610 cm^{-1}. For $C_{26}H_{35}O_3$ (398·6) calculated: 78·35% C, 9·61% H; found: 78·52% C, 9·65% H.

4,4-Dimethyl-17α-ethinyl-17β-hydroxy-A-homo-5-androsten-3-one (XV)

p-Toluenesulfonic acid (300 mg) was added to a solution of the ethylenedioxy derivative XIV (300 mg) in methanol (30 ml) and the mixture was allowed to stand at room temperature for 2 hours. The reaction mixture was then concentrated to one third of the original volume, poured into water and the product extracted with ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated in vacuo. The residue (287 mg) afforded after crystallization from ligroin 200 mg of the ketone XV, m. p. 84–86°C, $[\alpha]_D^{22}$ −36·2° (c. 0·7). Infrared spectrum (tetrachloromethane): 1 048, 1 707, 3 310, 3 615 cm^{-1}. For $C_{24}H_{34}O_2$ (354·51) calculated: 81·31% C, 9·67% H; found: 80·92% C, 9·42% H.

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