GLUCOSYLATION OF 5-ANDROSTEN-3β-OL DERIVATIVES CONTAINING BUTENOLIDE, FURAN OR UNSATURATED ESTER MOIETIES IN THE SIDE CHAIN*

Ivan ČERNÝ, Vladimír POUZAR, Pavel DRAŠAR, Miloš BUDĚŠÍNSKÝ and Miroslav HAVEL

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6

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3-O-(Tetra-O-acetyl-β-D-glucopyranosyl) derivatives *II*, *V*, *XV* and *XX* were prepared from 5-androstene-3β,17β-diol 17-benzoate (*I*), (20*R*)-3β-hydroxy-21-nor-5,22-choladien-(24 → 20)--olide (*IV*), 17β-(2-furyl)-5-androsten-3β-ol (*XIV*) and methyl (20*E*)-3β-hydroxy-5,20-pregnadiene-21-carboxylate (*XIX*), respectively, using tetra-O-acetyl-α-D-glucopyranosyl bromide and silver silicate. The furyl derivative *XIV* was obtained from methyl 3β-methoxymethyletienate • *VIII* by reaction sequence in which the key reactions were alkylation of the keto sulfoxide *IX* with bromoacetate, cyclization of the obtained product with sodium borohydride and reduction of the mixture of lactones *XI* and *XII* with diisobutylaluminium hydride. The unsaturated ester *XIX* was prepared from 3β-acetoxy-5-androstene-17β-carbaldehyde (*XVII*) by treatment with diethyl methoxycarbonylmethylphosphonate and deacetylation of the formed acetyl derivative *XVIII*. Deacetylation of the acetyl derivatives *II*, *XV* and *XX* afforded the glucosides *III*, *XVI* and *XXI*, respectively; the deacetylation of *V* was accompanied by opening of the lactone ring under formation of the methyl 21-nor-20-oxo-5-cholen-24-oate derivative *VI*.

In connection with investigation of cardiotonic activity of steroidal derivatives, we endeavoured to prepare derivatives in which the distribution of polar groups would resemble that in natural cardiac glycosides. Therefore, we set out to synthesize the corresponding glycosides of some of our steroidal models. Since the biological activity of cardiac glycosides is to a certain extent influenced by the attached carbohydrate moiety[1], the choice of a standard monosaccharide component was necessary. β-D-Glucosides seemed to be suitable sugar derivatives since they are easily accessible and their activities in the case of natural genins are comparable with those of glycosides with more complex sugar moieties[2]. Glycosylations of steroidal alcohols are usually effected by catalysts containing mercuric or silver salts[3]. Because of good results obtained with silver silicate in the synthesis of oligosaccharides[4], we decided to try this glycosylation catalyst in the steroid field.

For glycosylations we have selected the following 5-androsten-3β-ol derivatives:

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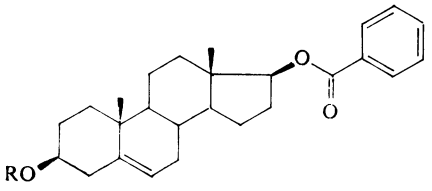
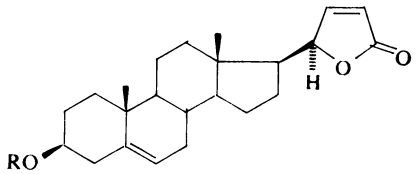
5-androstene-3β,17β-diol 17-benzoate (*I*), (20*R*)-3β-hydroxy-21-nor-5,22-choladien-(24 → 20)-olide (*IV*), 17β-(2-furyl)-5-androsten-3β-ol (*XIV*) and methyl (20*E*)-3β-hydroxy-5,20-pregnadiene-21-carboxylate (*XIX*). The easily accessible[5] benzoate *I* was chosen for study of experimental conditions of the glycosylations. In the 17β-position of the remaining three alcohols *IV*, *XIV* and *XIX* there are groups interesting from the point of the structure–activity relationships in cardiac glycoside models. The lactone *IV* has been prepared recently[6], its synthesis affording also the furyl



I, R = H
II, R = Ac_4-β-D-Glc
III, R = β-D-Glc



IV, R = H
V, R = Ac_4-β-D-Glc

derivative *XIII* as a side product. We developed also an independent synthesis of *XIII* in which carbon skeleton of the side chain was built making use of the reaction of alkyl bromoacetates with β-keto sulfoxides[7]. The starting methyl 3β-methoxymethoxyetienate[6] (*VIII*) on treatment with sodium salt of dimethyl sulfoxide gave the keto sulfoxide *IX*. Its sodium salt on reaction with ethyl bromoacetate was converted into the derivative *X*. The products *IX* and *X* are mixtures of configurational isomers at the sulfur atom or $C_{(22)}$ which was not separated. Sodium borohydride reduction of compound *X*, combined with cyclization, furnished a mixture of lactones *XI* and *XII* with the (20*R*)-isomer *XI* preponderating. Its crystallization afforded a product containing 90% of the isomer *XI* (according to its CD spectrum and those of authentic[6] *XI* and *XII*). The lactone mixture was reduced with diisobutylaluminium hydride[8] to give the furyl derivative *XIII* identical with an authentic sample[6]. Removal of the methoxymethoxy group was accomplished by action of hydrochloric acid in a benzene–methanol mixture. In the resulting 3β-hydroxy derivative *XIV* the furan ring was preserved as evidenced by an ABX system of aromatic protons $C_{(3')}$—H, $C_{(4')}$—H and $C_{(5')}$—H in its ^{1}H NMR spectrum as well as by the IR bands at 1 508 and 1 594 cm^{-1}. The unsaturated ester *XIX* was obtained by reaction of 3β-acetoxy-5-androstene-17β-carbaldehyde[9] (*XVII*) with diethyl methoxycarbonylmethylphosphonate[10] and deacetylation of the formed ester *XVIII* with sodium methoxide in methanol. The presence of the unsaturated ester group in *XVIII* was confirmed by ^{1}H NMR signals at δ = 6·97 and 5·78 due to the $C_{(20)}$—H and $C_{(21)}$—H protons, respectively, and by the corresponding constants $J_{20,21}$ = 16 and $J_{17,20}$ = 7·3 Hz.

After preliminary experiments with the benzoate *I*, the 3β-glucosylated 5-androsten-3β-ol derivatives were prepared using a 1·5 fold excess of 2,3,4,6-tetra-O-acetyl-α-D-

-glucopyranosyl bromide in 1,2-dichloroethane in the presence of a molecular sieve and silver silicate[11]. This procedure gave the acetylglucoside *II* as the sole product isolated in 68% yield. The presence of the β-D-glucopyranose moiety is seen in the ^{1}H NMR spectra (Table I). The region of the spectrum, corresponding to this moiety, was fully interpreted; the shifts of the $C_{(1')}$—H to $C_{(6'b)}$—H proton signals correspond to those in the spectrum of an analogous cholesterol derivative[12] and the coupling constants indicate a $^4C_1$(D) conformation in deuteriochloroform. The assignment of configuration at $C_{(1')}$ is based on the coupling constant $J_{1',2'} = 8{\cdot}0$ Hz and on the chemical shift of $C_{(1')}$—H ($\delta = 4{\cdot}60$); the values for steroidal α-glucosides are significantly different, *e.g.* for cholesteryl α-glucoside peracetate[12] $\delta = 5{\cdot}24$ and $J_{1',2'} =$

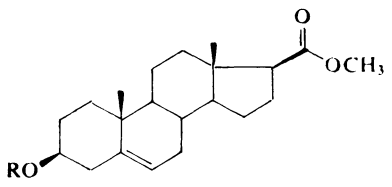
TABLE I

^{1}H NMR (200 MHz) Spectral parameters for the acetylated glucosides

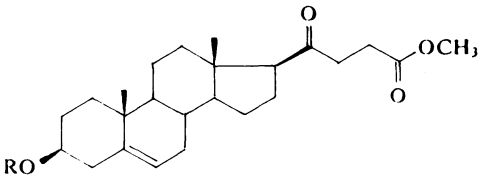
Compound[a]	*II*[b]	*V*[c]	*VII*[d]	*XV*[e]	*XX*[f]	*XXVI*[g]
$C_{(3)}$—H	3·48 m	3·49 m	3·49 m	3·49 m	3·49 m	—
$C_{(6)}$—H	5·37 m	5·35 bd	5·36 bd	5·37 m	5·36 bd	—
$C_{(18)}$—H	0·95 s	0·85 s	0·63 s	0·50 s	0·66 s	—
$C_{(19)}$—H	1·02 s	1·01 s	0·99 s	0·99 s	0·99 s	—
$C_{(1')}$—H	4·60 d	4·60 d	4·60 d	4·60 d	4·59 d	4·60 d
$C_{(2')}$—H	4·96 dd	4·96 dd	4·96 dd	4·96 dd	4·95 dd	4·97 m
$C_{(3')}$—H	5·21 dd	5·21 t	5·21 t	5·21 t	5·21 t	5·24 m
$C_{(4')}$—H	5·07 dd	5·07 t	5·07 dd	5·07 dd	5·07 dd	5·06 m
$C_{(5')}$—H	3·68 bd	3·68 ddd	3·68 m	3·68 ddd	3·65 ddd	3·66 ddd
$C_{(6'a)}$—H	4·26 dd	4·26 dd	4·26 dd	4·26 dd	4·26 dd	4·27 dd
$C_{(6'b)}$—H	4·11 dd	4·11 dd	4·11 dd	4·11 dd	4·11 dd	4·13 dd
$J_{6,7}$	—	4·6	4·6	—	4·8	—
$J_{1',2'}$	8·0	7·8	8·0	8·0	8·0	8·0
$J_{2',3'}$	9·4	9·6	9·4	9·4	9·4	—
$J_{3',4'}$	9·1	9·4	9·4	9·4	9·4	—
$J_{4',5'}$	9·6	9·5	9·6	9·6	9·6	—
$J_{5',6}$	4·6	4·9	4·8	4·8	4·8	5·1
$J_{5',6}$	2·6	2·6	2·6	2·6	2·6	1·8
$J_{6',6'}$	12·3	12·2	12·2	12·2	12·2	12·5

[a] Measured in deuteriochloroform (tetramethylsilane as internal standard); further data: [b] 8·05 m and 7·50 m (5 H, phenyl), [c] 7·45 dd ($C_{(22)}$—H), 6·09 dd ($C_{(23)}$—H), 4·94 dd ($C_{(20)}$—H); $J_{17,20} = 10$, $J_{20,22} = 1{\cdot}4$, $J_{20,23} = 2{\cdot}0$, $J_{22,23} = 5{\cdot}7$, [d] 3·68 s (3 H, OCH_3), 2·50—2·77 m (5 H, $C_{(17)}$—H, $C_{(22)}$—H, $C_{(23)}$—H), [e] 7·31 dd ($C_{(5'')}$—H), 6·29 dd ($C_{(4'')}$—H), 6·00 dd ($C_{(3'')}$—H); $J_{3'',4''} = 3{\cdot}2$, $J_{4'',5''} = 1{\cdot}9$, $J_{3'',5''} = 0{\cdot}8$, $J_{17,3''} = 0{\cdot}9$, [f] 6·96 dd ($C_{(20)}$—H), 5·79 dd ($C_{(22)}$—H; $J_{20,22} = 15{\cdot}7$, $J_{17,20} = 8{\cdot}0$, $J_{17,22} = 1{\cdot}2$, [g] cholesteryl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (*XXVI*), taken from ref.[12] (100 MHz spectrum).

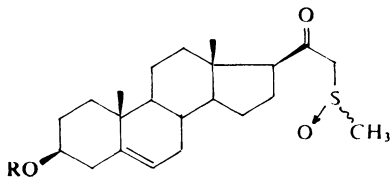
= 3·5 Hz. The glucosides *V*, *XV* and *XX* were obtained under the same conditions as the derivative *II* from the respective alcohols *IV*, *XIV* and *XIX*. Their ^{1}H NMR spectra (Table I) confirm the β-attachment of the sugar moiety as well as retention of all functional groups. The derivative *II* was deacetylated with a catalytic amount of sodium methoxide in methanol. Under these conditions the 17β-benzoyloxy group was not affected and the glucoside *III* was obtained. With derivative *V*, however, the methoxide destroyed the lactone ring and therefore milder conditions were sought. Even carrying out the reaction in triethylamine–methanol–water mixture, which had given good results in deacetylation of digitoxigenin glycosides[1], did not suppress



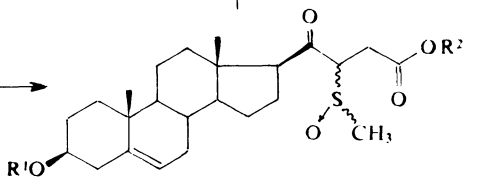
VIII, R = CH_3OCH_2
XXII, R = H



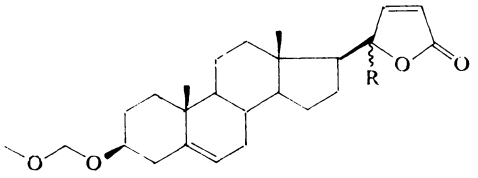
VI, R = β-D Glc
VII, R = Ac_4-β-D-Glc
XXV, R = Ac



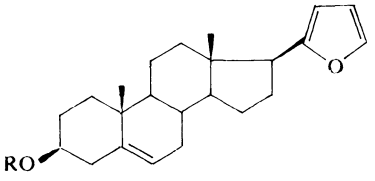
IX, R = CH_3OCH_2
XXIII, R = Ac



X, $R^1 = CH_3OCH_2$, $R^2 = CH_3CH_2$
XXIV, R^1 = Ac, $R^2 = CH_3$



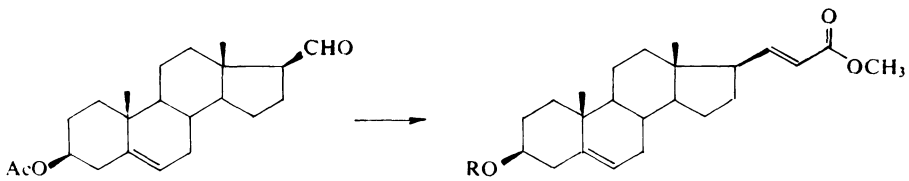
XI, R = αH
XII, R = βH



XIII, R = CH_3OCH_2
XIV, R = H
XV, R = Ac_4-β-D-Glc
XVI, R = β-D-Glc

the side reaction and the product *VI* did not exhibit any characteristic ^{1}H NMR signals or IR bands corresponding to the lactone ring. Structure of the product *VI* was proved after its acetylation with acetic anhydride in pyridine. The resulting acetyl glucoside *VII* was completely different from the starting acetyl glucoside *V*. The ^{1}H NMR spectrum of *VII* displayed a typical multiplet at $\delta = 2{\cdot}50-2{\cdot}77$ of the $C_{(22)}$—H and $C_{(23)}$—H protons of the saturated methyl γ-keto ester moiety and a three-proton singlet of the methyl group at $\delta = 3{\cdot}68$. To confirm the formation of such type of product, the lactone *IV* was subjected to conditions used for deacetylation of the acetyl glucoside *V* (triethylamine–methanol–water) and the product was acetylated with acetic anhydride in pyridine. The ^{1}H NMR spectrum of the obtained derivative *XXV* showed a multiplet at $\delta = 2{\cdot}60$ of a similar shape as in the case of compound *VII*. The structure of the keto ester *XXV* was proved by its independent synthesis. Methyl etienate[7] (*XXII*) was converted into the keto sulfoxide *XXIII* similarly as described for the derivatives *IX*. The obtained *XXIII* was treated with methyl bromoacetate to give the alkylated product *XXIV* which was reduced with amalgamated aluminium[13] to the keto ester *XXV*, identical with the product obtained from the lactone *IV*.

The acetyl glucosides *XV* and *XX*, containing 2-furyl and unsaturated ester groups, respectively, were smoothly deacetylated in triethylamine–methanol–water, yielding the corresponding glucosides *XVI* and *XXI*.



XVII

Ac = acetyl
Glc = glucopyranosyl

XVIII, R = Ac
XIX, R = H
XX, R = Ac$_4$-β-D-Glc
XXI, R = β-D-Glc

The silver-silicate catalyzed glucosylation represents thus a new method of preparation of steroidal glycosides. Its utilization for β-glucosylation of steroidal thiazoles will be the subject of our forthcoming publication[14]. The biological activity of the alcohols *XIV* and *XIX* and the corresponding glucosides *XVI* and *XXI* is under study and will be published in a separate communication.

EXPERIMENTAL

Melting points were determined on a Boetius block, optical rotations on a Perkin–Elmer 141 MC polarimeter in chloroform at 23–25°C. IR spectra were taken on a UR-20 (Zeiss, Jena) spectro-

photometer in chloroform or on a PE-621 (Perkin–Elmer) instrument in KBr pellets, wavenumbers are given in cm^{-1}. ^1H NMR spectra were measured on Tesla BS-467 (60 MHz) or Varian XL-200 (200 MHz) instruments in deuteriochloroform, with tetramethylsilane as internal standard, chemical shifts are given in δ-scale (ppm), coupling constants (J) and band widths (W) in Hz. All parameters were obtained by first-order analysis. ^1H NMR spectral data of compounds *II*, *V*, *VII*, *XV* and *XX* are given in Table I. Mass spectra were measured on an AEI-901 spectrometer, CD spectra on a Dichrographe II (Roussel-Jouan) instrument. Preparative chromatography was carried out on columns of silica gel (according to Pitra, 60–120 μm, from Service Laboratories of this Institute), thin-layer chromatography (TLC) was performed on silica gel G according to Stahl (Woelm). Spots were detected by spraying with sulfuric acid followed by heating. For HPLC a stainless steel column (250 × 4 mm) packed with Separon Si C_{18} (10 μm, Laboratory Instruments, Czechoslovakia) and a UVM-4 UV detector (Developmental Workshops, Czechoslovak Academy of Sciences, Prague) were used, with methanol–water as eluant (9 : 1). The fractions were detected at 230 nm. Solutions were dried over anhydrous sodium sulfate and taken down on a rotatory evaporator at bath temperature 40–50°C and pressure 2–2·5 kPa. Analytical samples were dried over phosphorus pentoxide at about 25 Pa. Sodium hydride in (50% suspension in paraffin oil was weighed and then washed with light petroleum. Reactions with organometalic reagents and glycosylations were performed under argon.

3β-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-5-androsten-17β-ol 17-Benzoate (*II*)

Powdered molecular sieve 4A (400 mg) and silver silicate[11] (300 mg) were added to a solution of the benzoate *I* (200 mg; 0·51 mmol) in 1,2-dichloroethane (2 ml) and the mixture was stirred in the dark for 20 min. A solution of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (320 mg; 0·78 mmol) in 1,2-dichloroethane (2 ml) was then added dropwise during 30 min and stirring was continued for 30 h. The catalyst was filtered off through Celite, washed with dichloromethane and the filtrate was washed twice with saturated potassium hydrogen carbonate solution and with water. After drying and evaporation of the solvent, the residue was chromatographed on a column of silica gel (25 g) in benzene–ether (20 : 1), affording 250 mg (68%) of the product *II*, m.p. 226–227°C (ethanol), $[\alpha]_D$ −5° (*c* 0·2, chloroform). IR spectrum: 1 044, 1 070, 1 254, 1 756 (CH_3COO—), 1 280, 1 712 (C_6H_5COO—). For $C_{40}H_{52}O_{12}$ (724·9) calculated: 66·28% C, 7·23% H; found: 66·34% C, 7·21% H.

3β-(β-D-Glucopyranosyloxy)-5-androsten-17β-ol 17-Benzoate (*III*)

Sodium methoxide in methanol (0·05 ml; c 1 mol l^{-1}) was added to a solution of compound *II* (100 mg; 0·14 mmol) in methanol (10 ml). After standing for 48 h, solid carbon dioxide (about 100 mg) was added, the solution was taken down and the residue chromatographed on silica gel (10 g) in chloroform–methanol (10 : 1). Crystallization from ethanol gave 60 mg (78%) of the glucoside *III*, m.p. 259–261°C, $[\alpha]_D$ −8° (*c* 0·17, methanol). IR spectrum (KBr): 1 280, 1 719 (C_6H_5COO—), 1 011, 1 028, 1 047, 1 070, 1 081 (—O—), 3 365 (—OH). ^1H NMR spectrum (200 MHz, hexadeuteriodimethyl sulfoxide): 7·94–8·00 m (2 H, phenyl), 7·48–7·70 m (3 H, phenyl), 5·36 bd (1 H, $C_{(6)}$—H, $J_{6,7} \approx 4{\cdot}5$), 4·87 bd (1 H, OH, $J \approx 5{\cdot}5$), 4·85 d (1 H, OH, $J = 4{\cdot}8$), 4·68 t (1 H, $C_{(17)}$—H, $J_{17,16a} \approx 9{\cdot}0$, $J_{17,16b} = 7{\cdot}5$), 4·41 t (1 H, $C_{(6')}$—OH, $J_{OH,6'a} = 5{\cdot}7$, $J_{OH,6'b} = 5{\cdot}7$), 4·24 d (1 H, $C_{(1')}$—H, $J_{1',2'} = 7{\cdot}7$), 0·99 s (3 H, $C_{(19)}$—H), 0·92 s (3 H, $C_{(18)}$—H). For $C_{32}H_{44}O_8$ (556·7) calculated: 69·04% C, 7·97% H; found: 68·95% C, 7·97% H.

(20*R*)-3β-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-21-nor-5,22-choladien-(24 → 20)--olide (*V*)

The lactone *IV* (ref.[6]; 60 mg 0·17 mmol) in benzene (1 ml) and 1,2-dichloroethane (2 ml) was converted into the title compound *V* (90 mg; 78%) as described for *II*. M.p. 214–217°C, $[\alpha]_D$ −9° (*c* 0·11, chloroform). IR spectrum: 1 044, 1 249, 1 752 (—$OCOCH_3$), 1 169, 1 752, 1 789 (lactone). For $C_{37}H_{50}O_{12}$ (686·8) calculated: 64·71% C, 7·34% H; found: 64·91% C, 7·28% H.

Methyl 3β-(β-D-Glucopyranosyloxy)-21-nor-20-oxo-5-cholen-24-oate (*VI*)

A mixture of compound *V* (50 mg; 0·073 mmol), triethylamine (4 ml), methanol (4 ml) and water (0·2 ml) was stirred for 72 h. The solution was taken down, the residue dried and chromatographed on a preparative plate of silica gel (10 g) in chloroform–methanol (10 : 1), affording 35 mg (87%) of the glucoside *VI*, m.p. 230–232°C, $[\alpha]_D$ +13° (*c* 0·13, methanol). IR spectrum (KBr): 1 737 ($COOCH_3$), 1 703, 1 690 (C=O). ^{1}H NMR spectrum (200 MHz, 25% hexadeuteriodimethyl sulfoxide in deuteriochloroform): 5·34 bd (1 H, $C_{(6)}$—H, $J_{6,7} \approx 4{\cdot}5$), 4·70 d (1 H, OH, $J \approx 3$), 4·64 d (1 H, OH, $J \approx 2$), 4·48 d (1 H, OH, $J \approx 3{\cdot}5$), 4·34 d (1 H, $C_{(1')}$—H, $J_{1',2'} = 7{\cdot}9$), 3·94 t (1 H, $C_{(6')}$—OH, $J_{OH,4'a} \approx J_{OH,6'b} \approx 6{\cdot}0$), 3·64 s (3 H, —$OCH_3$), 0·99 s (3 H, $C_{(19)}$—H), 0·59 s (3H, $C_{(18)}$—H). For $C_{30}H_{46}O_9$ (550·7) calculated: 65·43% C, 8·42% H; found: 65·31% C, 8·20% H.

Methyl 3β-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-21-nor-20-oxo-5-cholen-24-oate (*VII*)

Glucoside *VI* (40 mg; 0·07 mmol) was acetylated with acetic anhydride (0·5 ml) in pyridine (2·5 ml) overnight. After cooling to 0°C, methanol (1 ml) was added and the solution was taken down. The residue was several times coevaporated with toluene and chromatographed on a preparative plate of silica gel (10 g) in benzene–acetone (10 : 1). Crystallization from ethanol gave 30 mg (57%) of *VII*, m.p. 119–121°C, $[\alpha]_D$ +13° (*c* 0·17, chloroform). IR spectrum: 1 044, 1 249, 1 752 (CH_3COO—), 1 172, 1 439, 1 742 (—$COOCH_3$), 1 706 (C=O). For $C_{38}H_{54}O_{13}$ (718·8) calculated: 63·49% C, 7·57% H; found: 63·50% C, 7·43% H.

(20*R* + 20*S*)-3β-Methoxymethoxy-21-nor-5,22-choladien-(24 → 20)-olide (*XI* + *XII*)

Dimethyl sulfoxide (45 ml) was treated with sodium hydride (1·5 g; 62·5 mmol) at 65°C for 2 h. The mixture was cooled to room temperature and a solution of the ester *VIII* (ref.[6]; 2·36 g; 6·27 mmol) in tetrahydrofuran (25 ml) was added. After stirring for 2 h the mixture was poured into water, neutralized with solid ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water, dried and the solvent evaporated. The residue was dissolved in benzene, the solvent was again evaporated and the resulting crude keto sulfoxide *IX* (2·8 g) was dried at 25 Pa and used in the subsequent reaction. A sample for ^{1}H NMR spectrum was crystallized from light petroleum–benzene. ^{1}H NMR spectrum: 5·33 bd (1 H, $C_{(6)}$—H, $J_{6,7} = 3{\cdot}5$), 4·67 s (2 H, —OCH_2O—), 3·98 and 3·68 AB system (1·2 H, $C_{(21)}$—H,S (*R*)-isomer, $J_{gem} = -14{\cdot}4$), 3·88 and 3·70 AB system (0·8 H, $C_{(21)}$—H,S (*S*)-isomer, $J_{gem} = -14{\cdot}4$), 3·34 s (3 H, —OCH_3), 2·71 s (1·2 H, —SCH_3,S (*S*)-isomer), 2·69 s (1·8 H, —SCH_3,S (*R*)-isomer), 0·99 s (3 H, $C_{(19)}$—H), 0·66 s (3 H, $C_{(18)}$—H). A solution of the crude keto sulfoxide *IX* (2·7 g) in tetrahydrofuran (20 ml) was added with stirring to a suspension of sodium hydride (330 mg; 13·8 mmol) in tetrahydrofuran (5 ml). After the hydrogen evolution had ceased, the mixture was cooled (ice-salt bath) and ethyl bromoacetate (1·14 ml, 10·28 mmol) was added. The mixture was stirred for 2·5 h at room temperature, saturated ammonium chloride solution was added, the product was taken

up in ethyl acetate and the extract was washed with ammonium chloride solution, dried and taken down. The residue (product *X*) was dissolved in methanol (25 ml) and dichloromethane (5 ml), the solution was cooled to 0°C and sodium borohydride (260 mg; 6·87 mmol) was gradually added under stirring. After stirring for 2 h at 0°C the mixture was diluted with ethyl acetate (200 ml), washed with 2M-NaOH and saturated ammonium chloride solution and dried. The solvents were evaporated and the residue was chromatographed on a column of silica gel (50 g), affording 1·2 g (48% based on *VIII*) of a mixture of lactones *XI* and *XII* (85% *XI* and 15% *XII* according to HPLC). Recrystallization from benzene–ethanol gave 870 mg (35%) of the product containing 91% of the (*R*)-isomer *XI* according to CD spectrum, m.p. 190–195°C; CD spectrum (dioxane): 215 nm, $\Delta\varepsilon$ +11·83. ^{1}H NMR spectrum identical with that of the pure isomer *XI* (ref.[6]).

17β-(2-Furyl)-3β-methoxymethoxy-4-androstene (*XIII*)

A mixture of the lactones *XI* and *XII* (250 mg; 0·62 mmol) in tetrahydrofuran (5 ml) was cooled to −20°C and a solution of diisobutylaluminium hydride in toluene (1 ml, c 1·5 mol l^{-1}) was added under stirring. The stirring at −20°C was continued for 3 h, the excess hydride was decomposed with 10% sulfuric acid and the solution was left to warm to room temperature. Then it was poured into 10% sulfuric acid and extracted with ether. The organic layer was washed with 5% hydrochloric acid, water and saturated potassium hydrogen carbonate solution and dried. Chromatography of the residue on a column of silica gel (25 g) in benzene–ether (100 : 1) afforded 80 mg (34%) of the furyl derivative *XIII*, m.p. 108–109°C (ether–pentane); $[\alpha]_D$ −41° (*c* 0·2, chloroform). Its IR and ^{1}H NMR spectra were identical with those of an authentic sample[6].

17β-(2-Furyl)-5-androsten-3β-ol (*XIV*)

To a solution of the methoxymethoxy derivative *XIII* (800 mg; 2·1 mmol) in a mixture of benzene (40 ml) and methanol (40 ml) was added concentrated hydrochloric acid (0·4 ml). After warming to 40°C for 24 h, the solution was taken down, the residue was dissolved in chloroform, filtered through silica gel (10 g) and eluted with chloroform–methanol (50 : 1). Crystallization from ethanol gave 610 mg (86%) of the furyl derivative *XIV*, m.p. 161–163°C; $[\alpha]_D$ −50° (*c* 0·2, chloroform). IR spectrum: 1 045, 3 620 (—OH), 1 508, 1 594 (furan). ^{1}H NMR spectrum: 7·31 bd (1 H, $C_{(5')}$—H, $J_{5',4'} \approx 1{\cdot}5$), 6·30 dd (1 H, $C_{(4')}$—H, $J_{4',3'} \approx 2$, $J_{4',5'} \approx 1{\cdot}5$), 6·02 bd (1 H, $C_{(3')}$—H, $J_{3',4'} \approx 3$), 5·36 m (1 H, $C_{(6)}$—H, $W = 12$), 1·00 s (3 H, $C_{(19)}$—H), 0·50 s (3 H, $C_{(18)}$—H). For $C_{23}H_{32}O_2$ (340·5) calculated: 81·13% C, 9·47% H; found: 81·02% C, 9·44% H.

3β-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-17β-(2-furyl)-5-androstene (*XV*)

The furyl derivative *XIV* (400 mg; 1·17 mmol) was converted into the acetyl glucoside *XV* as described for *II*. Yield of *XV* 240 mg (30%), m.p. 209–210°C, $[\alpha]_D$ −27° (*c* 0·19, chloroform). IR spectrum: 1 252, 1 745, 1 755 (—$OCOCH_3$), 1 243, 1 506, 1 692 (furan). For $C_{37}H_{50}O_{11}$ (670·8) calculated: 66·25% C, 7·51% H; found: 66·20% C, 7·52% H.

17β-(2-Furyl)-3β-(β-D-glucopyranosyloxy)-5-androstene (*XVI*)

The acetyl glucoside *XV* (120 mg; 0·18 mmol) was deacetylated as described for *VI*, affording, after chromatography and crystallization from methanol, the glucoside *XVI* (80 mg; 89%), m.p. 270–272°C, $[\alpha]_D$ −46° (*c* 0·28, methanol). IR spectrum (KBr): 1 011, 1 029, 1 054, 1 078 (—O—), 1 506, 1 520, 1 692 (furan), 3 445 (—OH). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 7·50 dd (1 H, $C_{(5')}$—H, $J_{5',4'} \approx 2$, $J_{5',3'} \approx 1$), 6·35 dd (1 H, $C_{(4')}$—H, $J_{4',3'} \approx 3$, $J_{4',5'} \approx 2$), 6·10 bd (1 H, $C_{(3')}$—H, $J_{3'4'} \approx 3$), 5·33 m (1 H, $C_{(6)}$—H), 4·23 bd (1 H, $C_{(1'')}$—H, $J_{1'',2''} \approx 7$),

0·94 s (3 H, $C_{(19)}$—H), 0·43 s (3 H, $C_{(18)}$—H). For $C_{29}H_{42}O_7$ (502·7) calculated: 69·30% C, 8·42% H; found: 69·03% C, 8·42% H.

Methyl (20*E*)-3β-Acetoxy-5,20-pregnadiene-21-carboxylate (*XVIII*)

Diethyl methoxycarbonylmethylphosphonate (5·89 g; 28 mmol) was added during 10 min to a stirred suspension of sodium hydride (670 mg; 20 mmol) in 1,2-dimethoxyethane (35 ml) at room temperature. After stirring for 20 min a solution of the aldehyde *XVII* (freshly prepared[9] from 2 g (5·77 mmol) of the corresponding alcohol) in 1,2-dimethoxyethane (35 ml) was added and the stirring was continued for 4 h. The solvent was evaporated and the residue was partitioned between water and ether. The ethereal layer was washed with water, dried and taken down. Chromatography on a column of silica gel (100 g) in benzene–acetone (100 : 1) afforded 1·07 g (48%) of the ester *XVIII*, m.p. 142—145°C, $[\alpha]_D$ −41° (*c* 0·26, chloroform). IR spectrum: 1 252, 1 715 (—$OCOCH_3$), 1 649 (C=C—CO—), 1 715 (—$COOCH_3$). ^{1}H NMR spectrum: 6·97 dd (1 H, $C_{(20)}$—H, $J_{20,21}$ = 16, $J_{20,17}$ = 7·3), 5·78 d (1 H, $C_{(21)}$—H, $J_{21,20}$ = 16), 5·38 bd (1 H, $C_{(6)}$—H, $J \approx 4$), 4·54 m (1 H, $C_{(3)}$—H, W = 35), 3·69 s (3 H, —$COOCH_3$), 2·01 s (3 H, —$OCOCH_3$), 1·02 s (3 H, $C_{(19)}$—H), 0·66 s (3 H, $C_{(18)}$—H). For $C_{25}H_{36}O_4$ (400·6) calculated: 74·96% C, 9·06% H; found: 75·24% C, 9·15% H.

Methyl (20*E*)-3β-Hydroxy-5,20-pregnadiene-21-carboxylate (*XIX*)

Sodium methoxide in methanol (2·7 ml; c 1 mol l^{-1}) was added dropwise to a stirred solution of the acetyl derivative *XVIII* (898 mg; 2·24 mmol) in benzene (20 ml) and methanol (50 ml). After standing overnight the methanol was evaporated, the solution diluted with ether, washed three times with water, dried and taken down. Crystallization from light petroleum–ether gave 650 mg (81%) of the ester *XIX*, m.p. 146—149°C, $[\alpha]_D$ −56° (*c* 0·16, chloroform). IR spectrum: 3 407, 3 605 (—OH), 1 649, 1 710 (C=C—$COOCH_3$). ^{1}H NMR spectrum: 6·97 dd (1 H, $C_{(20)}$—H, $J_{20,21}$ = 15·8, $J_{20,17}$ = 7·2), 5·77 d (1 H, $C_{(21)}$—H, $J_{21,20}$ = 15·8), 5·35 m (1 H, $C_{(6)}$—H, W = 12), 3·70 s (3 H, $COOCH_3$), 3·48 m (1 H, $C_{(3)}$—H, W = 35), 1·00 s (3 H, $C_{(19)}$—H), 0·65 s (3 H, $C_{(18)}$—H). For $C_{23}H_{34}O_3$ (358·5) calculated: 77·05% C, 9·56% H; found: 76·89% C, 9·58% H.

Methyl (20*E*)-3β-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-5,20-pregnadiene-21-carboxylate (*XX*)

The ester *XIX* (250 mg; 0·7 mmol) was glycosylated in benzene–1,2-dichloroethane (2 ml, 1 : 2) as described for the derivative *II*, affording 365 mg (76%) of *XX*, m.p. 195—197°C, $[\alpha]_D$ −19° (*c* 0·18, chloroform). IR spectrum: 1 044, 1 173, 1 252, 1 760 (—$OCOCH_3$), 1 439, 1 662, 1 716 (C=C—CO—). For $C_{37}H_{52}O_{12}$ (688·8) calculated: 64·52% C, 7·61% H; found: 64·28% C, 7·59% H.

Methyl (20*E*)-3β-(β-D-Glucopyranosyloxy)-5,20-pregnadiene-21-carboxylate (*XXI*)

The acetyl glucoside *XX* (140 mg; 0·2 mmol) was deacetylated as described for *VI*, yielding 90 mg (85%) of the glucoside *XXI*, m.p. 223—225°C (ethanol), $[\alpha]_D$ −32° (*c* 0·19, methanol). IR spectrum (KBr): 1 170, 1 438, 1 656, 1 722 (C=C—$COOCH_3$), 990, 1 016, 1 025, 1 037, 1 044, 1 074, 1 082, 1 170 (—O—), 3 360 (OH). ^{1}H NMR spectrum (200 MHz, 25% hexadeuteriodimethyl sulfoxide in deuteriochloroform): 6·91 dd (1 H, $C_{(20)}$—H, $J_{20,21}$ = 15·7, $J_{20,17}$ = 8·0), 5·77 dd (1 H, $C_{(21)}$—H, $J_{21,20}$ = 15·7, $J_{21,17}$ = 1·0), 5·34 bd (1 H, $C_{(6)}$—H, $J_{6,7} \approx 5$), 4·36 d (1 H, $C_{(1')}$—H, $J_{1',2'}$ = 7·6), 3·80 dd (1 H, $C_{(6')}$—H_a, $J_{6'a,6'b}$ = 11·8, $J_{6'a,5'}$ = 3·2), 3·76 s (3 H, OCH_3),

3·67 dd (1 H, $C_{(6')}$—H_b, $J_{6'b,6'a}$ = 11·8, $J_{6'b,5'}$ = 4·6), 3·58 bm (1 H, $C_{(3)}$—H), 1·00 s (3 H, $C_{(19)}$—H), 0·66 s (3 H, $C_{(18)}$—H). For $C_{29}H_{44}O_8$ (520·7) calculated: 66·90% C, 8·52% H; found: 66·92% C, 8·47% H.

Methyl 3β-Acetoxy-21-nor-20-oxo-5-cholen-24-oate (*XXV*)

A) The lactone *IV* (50 mg; 0·14 mmol) in a mixture of triethylamine–methanol–water (10 ml; 20 : 20 : 1) was stirred for 72 h. After evaporation and drying, the residue was dissolved in pyridine (3 ml), treated with acetic anhydride (0·1 ml) and set aside for 24 h. The mixture was worked up as described for *VII*, including the preparative TLC, to give 30 mg (50%) of the acetate *XXV* after crystallization from methanol. M.p. 138–142°C; $[\alpha]_D$ +14° (*c* 0·10, chloroform). The IR and ^{1}H NMR spectra were identical with those of the sample prepared by procedure *B*.

B) The ester *XXII* (ref.[9]; 1 g; 3 mmol) was treated as described for *X*, affording a mixture of keto sulfoxides which was acetylated with acetic anhydride (4·5 ml) in pyridine (15 ml) overnight. The mixture was poured into an ice–water mixture, extracted with ethyl acetate and the organic phase was washed with 5% hydrochloric acid, potassium hydrogen carbonate solution and water. Evaporation and drying gave 920 mg (73%) of a mixture of acetylated keto sulfoxides *XXIII* which was converted into the alkylated product *XXIV* as described for the derivative *XI*, using methyl bromoacetate (0·32 ml; 3·37 mmol) instead of ethyl bromoacetate. The obtained product *XXIV* was dissolved in tetrahydrofuran (60 ml), water (6 ml) was added, followed by amalgamated aluminium prepared[13] from aluminium foil (1 g). The mixture was refluxed for 2 h and filtered through silica gel (10 g) which was then washed with acetone. After evaporation, the residue was partitioned between ether and dilute ammonium sulfate solution, the organic phase was dried and evaporated. Column chromatography on silica gel (50 g) in benzene–ether (50 : 1) afforded 400 mg (42%) of the keto ester *XXV*, m.p. 142–145°C, $[\alpha]_D$ +17° (*c* 0·29, chloroform). IR spectrum: 1 032, 1 243, 1 735 (CH_3COO—), 1 669, 3 020 (C=C), 1 168, 1 437, 1 735 (—$COOCH_3$), 1 710 (C=O). ^{1}H NMR spectrum: 5·34 bd (1 H, $C_{(6)}$—H, $J \approx 4$), 4·58 m (1 H, $C_{(3)}$—H, $W = 40$), 3·65 s (3 H, $COOCH_3$), 2·60 m (4 H, $C_{(22)}$—H + $C_{(23)}$—H, $W = 10$), 1·99 s (3 H, CH_3COO—), 0·98 s (3 H, $C_{(19)}$—H), 0·60 s (3 H, $C_{(18)}$—H). Mass spectrum (*m/z*): 370 (M–60), 115 (CH_3O—$COCH_2CH_2CO$), 255 (M–60–115). For $C_{26}H_{38}O_5$ (430·6) calculated: 72·53% C, 8·90% H; found: 72·50% C, 8·97% H.

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