DERIVATIVES OF 5α-ANDROSTAN-3α- AND 3β-OL WITH ACRYLONITRILE SIDE CHAIN*

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Dedicated to Professor Alois Vystrčil on the occasion of his 70th birthday.

Aldehydes *I*—*III* were reacted with diethyl cyanomethylphosphonate and sodium hydride in 1,2-dimethoxyethane to give the respective pairs of unsaturated nitriles *IVa* and *Va*, *VIa* and *VIIa*, and *VIIIa* and *IXa* differing in configuration at the 20(21)-double bond. The pure isomers were obtained by chromatography on alumina, and the configuration at the double bond in them has been established on the basis of the coupling constants *J*(20, 21) in their ^{1}H NMR spectra. Nitriles *IVa*—*VIIa* and *IXa* were converted via the corresponding hydroxy derivatives into hemisuccinates *IVd*—*VIId* and *IXd*, and into β-D-glucosides *IVe*—*VIIe* and *IXe*.

Recently we have described the preparation of 5α-androstan-3α-ol and 5α-androstan-3β-ol derivatives containing acrylate side chain which were further converted into the corresponding hemisuccinates and β-D-glucosides[1]. The present paper describes the synthesis of analogous derivatives with acrylonitrile side chain. The side chain of this type was built using the reaction of 17β-formylandrostane derivatives with the Wittig–Horner reagent[2]. In contrast to preparation of compounds with acrylate side chain where the 20*E*-isomer was formed predominantly (about 70%), accompanied by only minor amounts (about 4%) of the 20*Z*-isomer[3], in this case the arising mixture of 20*E* and 20*Z* isomers contained considerable amounts (30 to 37%) of the latter. The preparation of the starting compounds, i.e. aldehydes *I*—*III* with the 3-OH group protected as tetrahydropyran-2-yl (THP) ether, has already been described[1]. Reaction of aldehyde *I* with the reagent prepared from diethyl cyanomethylphosphonate and sodium hydride in 1,2-dimethoxyethane afforded a mixture of unsaturated nitriles *IVa* and *Va*. These isomers, differing in configuration at the double bond 20(21), were separated by preparative chromatography on an alumina column which afforded the 20*Z*- and 20*E*-isomer in 33% and 50% yield, respectively.

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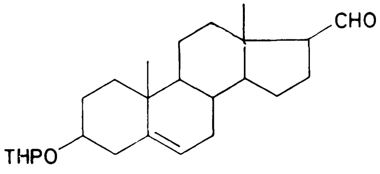
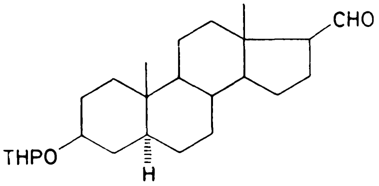


I



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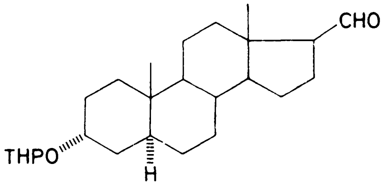
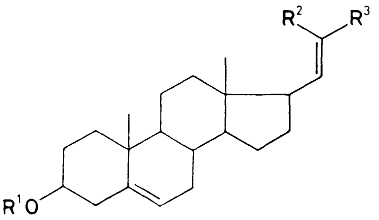
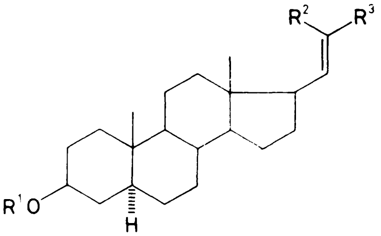


III

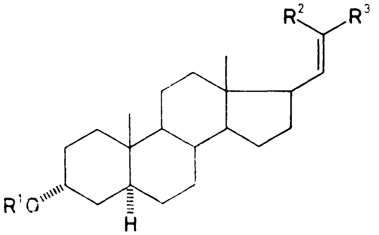
THP = tetrahydro-2*H*-pyran-2-yl



IV, R^2= CN ; R^3= H
V, R^2= H ; R^3= CN



VI, R^2= CN ; R^3= H
VII, R^2= H ; R^3= CN



VIII, R^2= CN ; R^3= H
IX, R^2= H ; R^3= CN

In formulae *IV*-*IX*: *a*, R^1= tetrahydro-2*H*-pyran-2-yl ; *b*, R^1= H

In formulae *IV*-*VII* and *IX*: *c*, R^1= $OCCH_2CH_2COOCH_2CH_2Si(CH_3)_3$; *d*, R^1= $OCCH_2CH_2COOH$
e, R^1= β-D-glucopyranosyl ; *f*, R^1= 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl

The configuration at the double bond was determined by ^{1}H NMR spectra: the coupling constant $J(20, 21)$ for the 20*Z*-isomer *IVa* is 10·5 Hz whereas for the 20*E*-isomer *Va* it amounts to 16·3 Hz. These values agree with those published for similar steroid derivatives[2].

Analogously, the aldehyde *II* was converted into nitriles *VIa* (37%) and *VIIa* (54%). In the case of the 3α,5α-derivative *III* we were not able to separate completely both isomeric nitriles *VIIIa* and *IXa* even by repeated chromatography. Nevertheless, small amounts of pure isomers have been obtained in pure form as evidenced by reversed phase HPLC (Table I). According to the ^{1}H NMR analysis, the reaction gave the 20*Z*- and 20*E*-isomers in the ratio 3 : 5 in an 80% overall yield.

Removal of the THP protecting group in position 3 afforded the hydroxy derivatives *IVb*–*IXb*. The hydroxy derivative *VIIb* has already been described[2], however, the reported melting point is different from that found by us (see Experimental). Their chromatographic separation is described in Table I. In the series of both THP derivatives and hydroxy derivatives, the particular 20*Z*-isomer exhibits shorter retention time than the corresponding 20*E*-isomer.

TABLE I

Retention times[a] (t_r) of nitriles *IVa*–*IXa* and *IVb*–*IXb* (for other conditions see Experimental)

Compound	Configuration	Solvent A t_r, min	Solvent B t_r, min
	THP derivatives		
IVa	20*Z*	14·46	11·46
Va	20*E*	16·84	15·94
VIa	20*Z*	15·56	13·48
VIIa	20*E*	18·21	18·57
VIIIa	20*Z*	16·29	14·92
IXa	20*E*	17·94	18·37
	Hydroxy derivatives		
IVb	20*Z*	5·13	4·42
Vb	20*E*	5·71	5·07
VIb	20*Z*	5·72	4·79
VIIb	20*E*	6·09	5·65
VIIIb	20*Z*	5·83	5·37
IXb	20*E*	5·83	5·89

[a] Solvent A: methanol–water (9 : 1), flow rate 1 ml min^{-1}, pressure 3·8 MPa; solvent B: ethanol–water (8 : 2), flow rate 1 ml min^{-1}, pressure 10·7 MPa.

The hydroxy derivatives *IVb–VIIb* and *IXb* were converted into the hemisuccinates *IVd–VIId* and *IXd*, using the known[4] procedure. Further we prepared[5,6] the β-D-glucosides *IVe–VIIe* and *IXe* which were then converted into the corresponding tetraacetates *IVf–VIIf* and *IXf*. The structure of the latter was con-

TABLE II

^{1}H NMR spectral parameters for glucoside tetraacetates. Measured on spectrometer Varian XL-200 (FT mode, 200 MHz) in deuteriochloroform, for other conditions see Experimental

Parameter	*IVf*	*Vf*	*VIf*	*VIIf*	*IXf*
			Steroid unit		
H-18 (3 H)	0·70 s	0·66 s	0·67 s	0·63 s	0·62 s
H-19 (3 H)	0·99 s	0·99 s	0·79 s	0·79 s	0·77 s
H-21 (1 H)	5·31 d	5·28 dd	5·30 d	5·26 dd	5·26 dd
H-20 (1 H)	6·41 t	6·69 dd	6·39 t	6·68 dd	6·68 dd
H-3 (1 H)	3·49 m[a]	3·48 m[a]	3·56 m[a]	3·55 m	3·91 m[b]
H-6 (1 H)	5·36 m	5·36 m	[c]	[c]	[c]
J(20, 21)	10·4	16·4	10·5	16·3	16·2
J(17, 20)	10·8	8·1	10·6	8·0	8·2
J(17, 21)	≈0	1·2	≈0	1·2	1·2
			Sugar unit		
H-1′ (1 H)	4·59 d	4·59 d	4·59 d	4·59 d	4·53 d
H-2′ (1 H)	4·96 dd	4·95 dd	4·94 dd	4·94 dd	5·00 dd
H-3′ (1 H)	5·21 t	5·21 t	5·20 t	5·20 t	5·21 t
H-4′ (1 H)	5·07 t	5·07 t	5·06 t	5·07 t	5·07 t
H-5′ (1 H)	3·68 ddd	3·67 ddd	3·68 ddd	3·67 ddd	3·66 ddd
H-6′a (1 H)	4·26 dd	4·26 dd	4·24 dd	4·26 dd	4·24 dd
H-6′b (1 H)	4·20 dd	4·11 dd	4·11 dd	4·11 dd	4·11 dd
J(1′, 2′)	8·1	8·0	8·0	7·9	7·8
J(2′, 3′)	9·4	9·4	9·4	9·5	9·4
J(3′, 4′)	9·4	9·3	9·4	9·3	9·3
J(4′, 5′)	9·5	9·6	9·4	9·6	9·7
J(5′, 6′a)	5·0	4·8	5·0	4·8	4·8
J(5′, 6′b)	2·6	2·6	2·6	2·6	2·6
J(6′a, 6′b)	12·2	12·0	12·2	12·1	12·2
OAc (3 H)	2·08 s	2·08 s	2·08 s	2·08 s	2·07 s
OAc (3 H)	2·05 s	2·05 s	2·04 s	2·04 s	2·03 s
OAc (3 H)	2·02 s	2·02 s	2·02 s	2·02 s	2·02 s
OAc (3 H)	2·00 s	2·00 s	2·00 s	2·00 s	2·01 s

[a] $W = 32$; [b] $W = 10$; [c] undeterminable value.

firmed by comparison of their ^{1}H NMR spectra (Table II) with those[1] of analogous derivatives with acrylate side chain.

EXPERIMENTAL

Melting points were determined on a micro melting point apparatus Boetius (G.D.R.). Optical rotations were measured on a Perkin-Elmer 141 MC polarimeter at 25°C. IR spectra were taken on a Perkin-Elmer PE 580 spectrometer (wavenumbers in cm^{-1}). ^{1}H NMR spectra were obtained with a Tesla BS-497 (FT mode, 100 MHz) and a Varian XL-200 (FT mode 200 MHz) instruments at 23°C in deuteriochloroform with tetramethylsilane as internal standard, Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. All parameters were obtained by first-order analysis. Column chromatography was performed on silica gel (according to Pitra, 60—120 μm) or on neutral alumina (Reanal, activity II), thin-layer chromatography on silica gel G according to Stahl (Woelm). HPLC analysis was carried out on Spectra-Physics instruments: SP 8800 ternary gradient pump, SP 4290 integrator, SP 8450 uv/vis detector (detection at 230 nm), WINNER data station, Rheodyne 7125 syringe loading sample injector, 250 × 4 mm i.d. column packed with Separone Si C_{18} (Tessek Prague). Samples were applied as 1 mg/ml solutions (10 μl) in methanol-dichloromethane (1 : 1). Solutions in organic solvents were dried over anhydrous sodium sulfate and the solvents were evaporated in vacuo (about 2 kPa). Analytical samples were dried over phosphorus pentoxide at 40°C/26 Pa for 12 h.

(20*Z*)-3β-(2-Tetrahydropyranyloxy)-5,20-pregnadiene-21-carbonitrile (*IVa*) and (20*E*)-3β-(2-Tetrahydropyranyloxy)-5,20-pregnadiene-21-carbonitrile (*Va*)

Diethyl cyanomethylphosphonate (4·2 ml, 26 mmol) was added during 10 min under cooling (ice bath) in an argon atmosphere to a suspension of sodium hydride (625 mg, 26 mmol) in 1,2-dimethoxyethane (28 ml). The mixture was stirred at room temperature for 20 min and a solution of aldehyde[1] *I* (3·15 g, 8·15 mmol) in a mixture of 1,2-dimethoxyethane (15 ml) and benzene (15 ml) was added. After stirring at room temperature under argon for 4 h, the solvents were evaporated in vacuo and the residue was partitioned between ether and water. The aqueous phase was extracted with ether, the combined organic phases were washed with water (3×) and the residue was repeatedly chromatographed on a column of alumina (300 g) in light petroleum-ether (95 : 5). As a less polar compound we obtained nitrile *IVa* (1·11 g, 33%) m.p. 160 to 166°C (hexane-ether), $[\alpha]_D$ −180° (c 0·2, chloroform). IR spectrum (tetrachloromethane): 2 220, 1 618 (C=C—C≡N); 1 667 (C=C); 1 136, 1 114, 1 034, 1 025 (C—O). ^{1}H NMR spectrum (100 MHz): 6·41 t, 1 H (H-20, J(17, 20) = J(20, 21) = 10·5); 5·35 m, 1 H (H-6); 5·31 d, 1 H (H-21, J(20, 21) = 10·5); 4·70 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 1·01 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). For $C_{27}H_{39}NO_2$ (409·6) calculated: 79·17% C, 9·60% H, 3·42% N; found: 79·41% C, 9·83% H, 3·43% N.

The more polar product was nitrile *Va* (1·67 g, 50%), m.p. 153—158°C (hexane-ether), $[\alpha]_D$ −44° (c 0·2, chloroform). IR spectrum (tetrachloromethane); 2 225, 1 631 (C=C—C≡N); 1 668 (C=C); 1 136, 1 115, 1 034, 1 025 (C—O). ^{1}H NMR spectrum (100 MHz): 6·70 dd, 1 H (H-20, J(17, 20) = 7·7; J(20,21) = 16·3); 5·35 m, 1 H (H-6); 5·28 dd, 1 H (H-21, J(17, 21) = 1·0; J(20, 21) = 16·3); 4·71 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 1·02 s, 3 H (3 × H-19); 0·66 s, 3 H (3 × H-18). For $C_{27}H_{39}NO_2$ (408·6) calculated: 79·17% C, 9·60% H, 3·42% N; found: 79·37% C, 9·59% H, 3·42% N.

(20*Z*)-3β-(2-Tetrahydropyranyloxy)-5α-pregn-20-ene-21-carbonitrile (*VIa*) and (20*E*)-3β-(2-Tetrahydropyranyloxy)-5α-pregn-20-ene-21-carbonitrile (*VIIa*)

Nitriles *VIa* and *VIIa* were prepared from aldehyde[1] *II* (3·17 g, 8·15 mmol) according to the above-described procedure. Nitrile *VIa* (1·25 g, 37%) was obtained as the less polar compound m.p. 123–126°C (hexane), $[\alpha]_D$ −97° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 2 220, 1 620 (C=C—C≡N); 1 132, 1 115, 1 027 (C—O). ^{1}H NMR spectrum (100 MHz): 6·39 t, 1 H (H-20, *J*(17, 20) = *J*(20, 21) = 10·5); 5·29 dd, 1 H (H-21, *J*(17, 21) = 0·5; *J*(20, 21) = = 10·5); 4·70 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 0·81 s, 3 H (3 × H-19); 0·67 s, 3 H (3 × H-18). For $C_{27}H_{41}NO_2$ (411·6) calculated: 78·78% C, 10·04% H, 3·40% N; found: 78·73% C, 10·10% H, 3·29% N.

Nitrile *VIIa* (1·81 g, 54%) was more polar, m.p. 134–137°C (hexane), $[\alpha]_D$ −15° (*c* 0·5, chloroform). IR spectrum (tetrachloromethane): 2 225, 1 632 (C=C—C≡N); 1 132, 1 115, 1 027 (C—O). ^{1}H NMR spectrum (100 MHz): 6·69 dd, 1 H (H-20, *J*(17, 20) = 7·8; *J*(20, 21) = 16·7); 5·25 dd, 1 H (H-21, *J*(17, 21) = 1·0; *J*(20, 21) = 16·7); 4·70 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 0·81 s, 3 H (3 × H-19); 0·62 s, 3 H (3 × H-18). For $C_{27}H_{41}NO_2$ (411·6) calculated: 78·78% C, 10·04% H, 3·40% N; found: 78·69% C, 10·02% H, 3·46% N.

(20*Z*)-3α-(2-Tetrahydropyranyloxy)-5α-pregn-20-ene-21-carbonitrile (*VIIIa*) and (20*E*)-3α-(2-Tetrahydropyranyloxy)-5α-pregn-20-ene-21-carbonitrile (*IXa*)

Nitriles *VIIIa* and *IX* were prepared from aldehyde[1] *III* (3·17 g, 8·15 mmol) according to the above-described procedure. The less polar fraction gave 90 mg (2·8%) of amorphous nitrile *VIIIa*, $[\alpha]_D$ −158° (*c* 1·1, chloroform). IR spectrum (tetrachloromethane): 2 220, 1 617 (C=C—C≡N); 1 134, 1 024, 1 008 (C—O). ^{1}H NMR spectrum (100 MHz): 6·39 t, 1 H (H-20, *J*(17, 20) = *J*(20, 21) = 10·6); 5·29 d, 1 H (H-21, *J*(20, 21) = 10·6); 4·60 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 3·89 m, 1 H (H-3); 0·78 s, 3 H (3 × H-19); 0·67 s, 3 H (3 × H-18). For $C_{27}H_{41}NO_2$ (411·6) calculated: 78·78% C, 10·04% H, 3·40% N; found: 78·63% C, 10·23% H, 3·22% N. An intermediary fraction 2·03 g (61%) contained a 45 : 55 mixture of *VIIIa* and *IXa* (according to ^{1}H NMR spectrum). Finally, pure nitrile *IXa* (534 mg, 16%) was obtained, m.p. 155–158°C (hexane), $[\alpha]_D$ +96° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 2 225, 1 632 (C=C—C≡N); 1 135, 1 024, 1 007 (C—O). ^{1}H NMR spectrum (100 MHz): 6·69 dd, 1 H (H-20, *J*(17, 20) = 7·8; *J*(20, 21) = 16·5); 5·25 dd, 1 H (H-21, *J*(17, 21) = 1·0; *J*(20, 21) = 16·5); 4·61 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 3·85 m, 1 H (H-3); 0·78 s, 3 H (3 × H-19); 0·62 s, 3 H (3 × H-18). For $C_{27}H_{41}NO_2$ (411·6) calculated: 78·78% C, 10·04% H, 3·40% N; found: 78·59% C, 10·32% H, 3·66% N.

General Procedure for Preparation of Hydroxynitriles *IVb*, *Vb*, *VIb*, *VIIb*, *VIIIb* and *IXb*

Concentrated hydrochloric acid (170 μl, 2 mmol) was added to a solution of protected nitrile (2 mmol) in a mixture of benzene (20 ml) and methanol (20 ml). After heating to 40°C for 1 h, the solvents were evaporated in vacuo, the residue was partitioned between dichloromethane and water and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with water, saturated aqueous solution of potassium carbonate, and water. The residue was chromatographed on a column of silica gel (60 g) in light petroleum–benzene–ether (40 : 40 : 20).

(20*Z*)-3β-*Hydroxy*-5,20-*pregnadiene*-21-*carbonitrile* (IVb). The protected nitrile *IVa* (820 mg) afforded 574 mg (88%) of hydroxy derivative *IVb*, m.p. 174–176°C (ether–hexane), $[\alpha]_D$ −41° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 610, 3 470 (O—H); 2 220, 1 617 (C=C—C≡N);

1 669 (C=C); 1 043 (C—O). ^{1}H NMR spectrum (100 MHz): 6·41 t, 1 H (H-20, J(17, 20) = = J(20,21) = 10·9); 5·36 bd, 1 H (H-6, J = 4·5); 5·32 dd, 1 H (H-21, J(17, 20) = 0·5; J(20, 21) = = 10·9); 3·53 m, 1 H (H-3, W = 36); 1·01 s, 3 H (3 × H-19); 0·71 s, 3 H (3 × H-18). For $C_{22}H_{31}NO$ (325·5) calculated: 81·18% C, 9·60% H, 4·30% N; found: 81·17% C, 9·61% H, 4·19% N.

(20E)-3β-*Hydroxy*-5,20-*pregnadiene*-21-*carbonitrile* (Vb). The protected nitrile *Va* (820 mg) gave 634 mg (97%) of hydroxy derivative *Vb*, m.p. 235—238°C (ether), $[\alpha]_D$ −22° (c 0·3, chloroform). IR spectrum (chloroform): 3 610, 3 470 (O—H); 2 225, 1 630 (C=C—C≡N); 1 669 (C=C); 1 045 (C—O). ^{1}H NMR spectrum (100 MHz): 6·74 dd, 1 H (H-20, J(17, 20) = 7·7; J(20,21) = 16·6); 5·35 bd, 1 H (H-6, J = 4·5); 5·27 dd, 1 H (H-21, J(17, 20) = 1·0; J(20, 21) = = 16·6); 3·51 m, 1 H (H-3, W = 36); 1·02 s, 3 H (3 × H-19); 0·66 s, 3 H (3 × H-18). For $C_{22}H_{31}NO$ (325·5) calculated: 81·18% C, 9·60% H, 4·30% N; found: 81·39% C, 9·51% H, 4·20% N.

(20Z)-3β-*Hydroxy*-5α-*pregn*-20-*ene*-21-*carbonitrile* (VIb). The protected nitrile *VIa* (823 mg) furnished 616 mg (94%) of hydroxy derivative *VIb*, m.p. 174—176°C (ether), $[\alpha]_D$ −138° (c 0·2, chloroform). IR spectrum (chloroform): 3 610, 3 470 (O—H); 2 220, 1 617 (C=C—C≡N); 1 033 (C—O). ^{1}H NMR spectrum (100 MHz): 6·40 t, 1 H (H-20, J(17, 20) = J(20,21) = 10·7); 5·29 dd, 1 H (H-21, J(17, 20) = 0·5; J(20, 21) = 10·7); 3·60 m, 1 H (H-3, W = 32); 0·81 s, 3 H (3 × H-19); 0·68 s, 3 H (3 × H-18). For $C_{22}H_{33}NO$ (327·5) calculated: 80·68% C, 10·16% H, 4·28% N; found: 80·78% C, 10·40% H, 4·23% N.

(20E)-3β-*Hydroxy*-5α-*pregn*-20-*ene*-21-*carbonitrile* (VIIb). The protected nitrile *VIIa* (823 mg) afforded 600 mg (92%) of hydroxy derivative *VIIb*, m.p. 212—214°C (ether), $[\alpha]_D$ +34° (c 0·3, chloroform). Literature[2] gives m.p. 187—190°C. IR spectrum (chloroform): 3 610, 3 470 (O—H); 2 225, 1 629 (C=C—C≡N); 1 035 (C—O). ^{1}H NMR spectrum (100 MHz): 6·69 dd, 1 H (H-20, J(17, 20) = 7·8; J(20, 21) = 16·8); 5·26 dd, 1 H (H-21, J(17, 20) = 1·0; J(20, 21) = = 16·8); 3·59 m, 1 H (H-3, W = 32); 0·81 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{22}H_{33}NO$ (327·5) calculated: 80·68% C, 10·16% H, 4·28% N; found: 80·77% C, 10·23% H, 4·31% N.

(20Z)-3α-*Hydroxy*-5α-*pregn*-20-*ene*-21-*carbonitrile* (VIIIb). Reaction of the protected nitrile *VIIIa* (94 mg, 0·23 mmol) with corresponding amounts of reagents gave 61 mg (82%) of amorphous hydroxy derivative *VIIIb*, $[\alpha]_D$ −135° (c 1·0, chloroform). IR spectrum (chloroform): 3 618, 3 480 (O—H); 2 220, 1 617 (C=C—C≡N); 1 001 (C—O). ^{1}H NMR spectrum (100 MHz): 6·40 t, 1 H (H-20, J(17, 20) = J(20,21) = 10·6); 5·29 d, 1 H (H-21, J(20, 21) = 10·6); 4·04 m, 1 H (H-3); 0·78 s, 3 H (3 × H-19); 0·68 s, 3 H (3 × H-18). For $C_{22}H_{33}NO$ (327·5) calculated: 80·68% C, 10·16% H, 4·28% N; found: 80·38% C, 9·88% H, 3·97% N.

(20E)-3α-*Hydroxy*-5α-*pregn*-20-*ene*-21-*carbonitrile* (IXb). The protected nitrile *IXa* (823 mg) afforded 625 mg (96%) of hydroxy derivative *IXb*, m.p. 180—183°C (methanol–ether), $[\alpha]_D$ +37° (c 0·2, chloroform). IR spectrum (chloroform): 3 618, 3 480 (O—H); 2 225, 1 630 (C=C—C≡N); 1 003 (C—O). ^{1}H NMR spectrum (100 MHz): 6·68 dd, 1 H (H-20, J(17, 20) = 7·8; J(20, 21) = 16·6); 5·24 dd, 1 H (H-21, J(17, 20) = 1·2; J(20, 21) = 16·6); 4·03 m, 1 H (H-3); 0·78 s, 3 H (3 × H-19); 0·62 s, 3 H (3 × H-18). For $C_{22}H_{33}NO$ (327·5) calculated: 80·68% C, 10·16% H, 4·28% N; found: 80·42% C, 10·35% H, 4·45% N.

General Procedure for Preparation of Hemisuccinates *IVd*, *Vd*, *VId*, *VIId* and *IXd*

2-(Trimethylsilyl)ethyl hydrogen butanedioate[7] (415 mg, 1·9 mmol) and 4-dimethylaminopyridine (7 mg, 60 μmol) were added to a solution of the hydroxy derivative (1 mmol) in tetrahydrofuran

(4·5 ml). After addition of 0·5M solution of N,N′-dicyclohexylcarbodiimide in benzene (2·5 ml), the reaction mixture was stirred at room temperature for 6 h, diluted with light petroleum (10 ml) and set aside for 10 min. The separated N,N′-dicyclohexylurea was filtered off, washed with light petroleum, the filtrate was taken down in vacuo and the residue was chromatographed on a column of silica gel (35 g). Light petroleum–benzene–ether (50 : 49 : 1) eluted nonpolar impurities, light petroleum–benzene–ether (50 : 48 : 2) washed out the succinate. A solution of the succinate in tetrahydrofuran (10 ml) was stirred with 1M solution of tetrabutylamonium fluoride in tetrahydrofuran (2 ml) for 8 h at room temperature. The mixture was diluted with benzene (200 ml) and washed with 10% sulfuric acid (2×) and water (3×). Evaporation of the solvent and crystallization of the residue from hexane–dichloromethane (−78°C) afforded the hemisuccinate.

(20*Z*)-21-*Cyano*-5,20-*pregnadien*-3β-*yl hydrogen butanedioate* (IVd). Hydroxy derivative *IVb* (326 mg) afforded 495 mg of the succinate *IVc*. IR spectrum (tetrachloromethane): 2 220, 1 618 (C=C—C≡N); 1 735, 1 161 (COOR); 1 672 (C=C); 1 253, 861, 840 (Si—C). The succinate *IVc* was further converted into 316 mg (74%) of hemisuccinate *IVd*, m.p. 179—182°C, $[\alpha]_D$ −185° (*c* 0·2, chloroform). IR spectrum (chloroform): 3 500—2 500, 1 716 (COOH); 2 220, 1 616 (C=C—C≡N); 1 730 shoulder, 1 175 (COOR). ^1H NMR spectrum (100 MHz): 6·41 t, 1 H (H-20, *J*(17, 20) = *J*(20, 21) = 10·6); 5·31 d, 1 H (H-21, *J*(20, 21) = 10·6); 5·38 bd, 1 H (H-6, *J* = 4·5); 4·60 m, 1 H (H-3, *W* = 32); 2·65 s, 4 H ($OOCCH_2CH_2COO$); 1·03 s, 3 H (3 × H-19); 0·71 s, 3 H (3 × H-18). For $C_{26}H_{35}NO_4$ (425·6) calculated: 73·38% C, 8·29% H, 3·29% N; found: 73·27% C, 8·01% H, 3·10% N.

(20*E*)-21-*Cyano*-5,20-*pregnadien*-3β-*yl hydrogen butanedioate* (Vd). Hydroxy derivative *Vb* (326 mg) was converted into succinate *Vc* (474 mg). IR spectrum (tetrachloromethane): 2 225, 1 632 (C=C—C≡N); 1 737, 1 161 (COOR); 1 671 (C=C); 1 253, 861, 839 (Si—C). Succinate *Vc* afforded 280 mg (66%) of hemisuccinate *Vd*, m.p. 171—174°C, $[\alpha]_D$ −24° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 500—2 500, 1 717 (COOH); 2 225, 1 629 (C=C—C≡N); 1 730 shoulder, 1 175 (COOR). ^1H NMR spectrum (100 MHz): 6·70 dd, 1 H (H-20, *J*(17, 20) = 7·8; *J*(20, 21) = 16·5); 5·38 bd, 1 H (H-6, *J* = 4·5); 5·28 dd, 1 H (H-21, *J*(17, 21) = 1·0; *J*(20,21) = 16·5); 4·60 m, 1 H (H-3, *W* = 32); 2·64 m, 4 H ($OOCCH_2CH_2COO$); 1·03 s, 3 H (3 × H-19); 0·66 s, 3 H (3 × H-18). For $C_{26}H_{35}NO_4$ (425·6) calculated: 73·38% C, 8·29% H, 3·29% N; found: 72·67% C, 8·41% H, 3·15% N.

(20*Z*)-21-*Cyano*-5α-*pregn*-20-*en*-3β-*yl hydrogen butanedioate* (VId). Hydroxy derivative *VIb* (328 mg) afforded 497 mg of succinate *VIc*. IR spectrum (tetrachloromethane): 2 220, 1 619 (C=C—C≡N); 1 735, 1 165 (COOR); 1 253, 862, 840 (Si—C). The succinate *VIc* was converted into 296 mg (69%) of hemisuccinate *VId*, m.p. 151—154°C, $[\alpha]_D$ −111° (*c* 0·2, chloroform). IR spectrum (chloroform): 3 500—2 500, 1 716 (COOH); 2 220, 1 617 (C=C—C≡N); 1 716 (COOR). ^1H NMR spectrum (100 MHz): 6·40 t, 1 H (H-20, *J*(17, 20) = *J*(20, 21) = 10·6); 5·29 d, 1 H (H-21, *J*(20, 21) = 10·6); 4·72 m, 1 H (H-3, *W* = 32); 2·62 s, 4 H ($OOCCH_2CH_2.COO$); 0·82 s, 3 H (3 × H-19); 0·68 s, 3 H (3 × H-18). For $C_{26}H_{37}NO_4$ (427·6) calculated: 73·04% C, 8·72% H, 3·28% N; found: 72·87% C, 8·61% H, 3·05% N.

(20*E*)-21-*Cyano*-5α-*pregn*-20-*en*-3β-*yl hydrogen butanedioate* (VIId). Hydroxy derivative *VIIb* (328 mg) afforded 482 mg of succinate *VIIc*. IR spectrum (tetrachloromethane): 2 225, 1 631 (C=C—C≡N); 1 734, 1 162 (COOR); 1 252, 861, 838 (Si—C). Succinate *VIIc* was further converted into 313 mg (73%) of hemisuccinate *VIId*, m.p. 178—181°C, $[\alpha]_D$ +31° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 500—2 500, 1 718 (COOH); 2 225, 1 630 (C=C—C≡N); 1 718, 1 177 (COOR). ^1H NMR spectrum (100 MHz): 6·68 dd, 1 H (H-20, *J*(17, 20) = 7·8; *J*(20, 21) = 16·5); 5·26 dd, 1 H (H-21, *J*(17, 21) = 1·0; *J*(20, 21) = 16·5); 4·72 m, 1 H (H-3, *W* = 32); 2·63 m, 4 H ($OOCCH_2CH_2COO$); 0·83 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{26}H_{37}NO_4$ (427·6) calculated: 73·04% C, 8·72% H, 3·28% N; found: 72·75% C, 8·55% H, 3·30% N.

(20*Z*)-21-*Cyano-5α-pregn-20-en-3α-yl hydrogen butanedioate* (IXd). Hydroxy derivative *IXb* (328 mg) gave 460 mg of succinate *IXc*. IR spectrum (tetrachloromethane): 2 225, 1 632 (C=C—C≡N); 1 735, 1 154 (COOR); 1 252, 859, 836 (Si—C). The succinate *IXc* was further converted into 215 mg (50%) of hemisuccinate *IXd*, m.p. 137—140°C, $[\alpha]_D$ +41° (*c* 1·2, chloroform). IR spectrum (chloroform): 3 500—2 500, 1 715 (COOH); 2 225, 1 629 (C=C—C≡N); 1 715 (COOR). ^1H NMR spectrum (100 MHz): 6·69 dd, 1 H (H-20, *J*(17, 20) = 7·5; *J*(20, 21) = 16·6); 5·26 dd, 1 H (H-21, *J*(17, 21) = 1·1; *J*(20, 21) = 16·6); 5·05 m, 1 H (H-3, *W* = 10); 2·66 m, 4 H ($OOCCH_2CH_2COO$); 0·79 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{26}H_{37}NO_4$ (427·6) calculated: 73·04% C, 8·72% H, 3·28% N; found: 72·95% C, 8·63% H, 3·15% N.

General Procedure for Preparation of Glucosides *IVe*, *Ve*, *VIe*, *VIIe*, and *IXe*

A dry mixture of hydroxy derivative (1 mmol), silver silicate[5] (1·4 g) and ground molecular sieve 4A (2 g) was stirred in vacuo (10 Pa) 4 h. The flask was then filled with argon under slight overpressure (about 5 kPa) and 1,2-dichloroethane (20 ml) was injected through a septum. The mixture was stirred at room temperature for 20 min and then a solution of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (500 mg, 1·2 mmol) in 1,2-dichloroethane (3 ml) was added through the septum. After stirring at room temperature for 20 h, the catalyst was filtered through a column of silica gel (layered with Celite). The column was washed with chloroform–ether (4 : 1), and the combined organic phases were washed with 5% aqueous sodium hydrogen carbonate solution and water. The solvents were evaporated, the residue was dissolved in methanol (30 ml) and 5% solution of sodium methoxide (5 drops) was added. The mixture was stirred at room temperature for 3 h and neutralized with dry ice (about 300 mg). After evaporation, the residue was chromatographed on a column of silica gel (Silpearl, 40 g) in chloroform–methanol (9 : 1). Unless stated otherwise, the product was further purified by crystallization.

(20*Z*)-3β-(β-D-*Glucopyranosyloxy*)-5,20-*pregnadiene*-21-*carbonitrile* (IVe). Hydroxy derivative *IVb* (325 mg) was converted into 401 mg (82%) of amorphous glucoside *IVe*, $[\alpha]_D$ −132° (*c* 1·0, chloroform). IR spectrum (KBr): 3 410 (OH); 2 215, 1 621 (C=C—C≡N); 1 670 (C=C); 1 073, 1 022 (C—O). For $C_{28}H_{41}NO_6$ (487·6) calculated: 68·97% C, 8·47% H, 2·87% N; found: 68·68% C, 8·23% H, 2·50% N.

(20*E*)-3β-(β-D-*Glucopyranosyloxy*)-5,20-*pregandiene*-21-*carbonitrile* (Ve). Hydroxy derivative *Vb* (325 mg) gave 341 mg (70%) of glucoside *Ve* (after crystallization from chloroform–methanol), m.p. 281—284°C, $[\alpha]_D$ −46° (*c* 1·3, chloroform). IR spectrum (KBr): 3 420 (OH); 2 220, 1 628 (C=C—C≡N); 1 666 (C=C); 1 074, 1 053; 1 026 (C—O). For $C_{28}H_{41}NO_6$ (487·6) calculated: 68·97% C, 8·47% H, 2·87% N; found: 68·72% C, 8·33% H, 3·01% N.

(20*Z*)-3β-(β-D-*Glucopyranosyloxy*)-5α-*pregn*-20-*ene*-21-*carbonitrile* (VIe). Hydroxy derivative *VIb* (327 mg) afforded 311 mg (63%) glucoside *VIe* (after crystallization from chloroform–methanol), m.p. 295—300°C, $[\alpha]_D$ −90° (*c* 1·3, chloroform). IR spectrum (KBr): 3 450, 3 380 shoulder (OH); 2 220, 1 620 (C=C—C≡N); 1 077, 1 047, 1 027 (C—O). For $C_{28}H_{43}NO_6$ (489·7) calculated: 68·68% C, 8·85% H, 2·86% N; found: 68·95% C, 9·02% H, 3·03% N.

(20*E*)-3β-(β-D-*Glucopyranoxy*)-5α-*pregn*-20-*ene*-21-*carbonitrile* (VIIe). Hydroxy derivative *VIIb* (327 mg) gave 328 mg (67%) of glucoside *VIIe* (after crystallization from ether–methanol), m.p. 265—278°C (decomposition), $[\alpha]_D$ +6° (*c* 1·0, chloroform). IR spectrum (KBr): 3 415 (OH); 2 220, 1 628 (C=C—C≡N); 1 075, 1 027 (C—O). For $C_{28}H_{43}NO_6$ (489·7) calculated: 68·68% C, 8·85% H, 2·86% N; found: 68·65% C, 8·81% H, 2·63% N.

(20*E*)-3α-(β-D-*Glucopyranosyloxy*)-5α-*pregn*-20-*ene*-21-*carbonitrile* (IXe). Hydroxy derivative *IXb* (327 mg) afforded 330 mg (67%) of glucoside *IXe* (after crystallization from ether–methanol), m.p. 200–203°C (decomposition), $[\alpha]_D$ +2° (*c* 1·1, chloroform). IR spectrum (KBr): 3 420 (OH); 2 225, 1 630 (C=C—C≡N); 1 077, 1 040, 1 020 (C—O). For $C_{28}H_{43}NO_6$ (489·7) calculated: 68·68% C, 8·85% H, 2·86% N; found: 68·53% C, 9·06% H, 3·00% N.

General Procedure for Preparation of Glucoside Tetraacetates *IVf*, *Vf*, *VIf*, *VIIf* and *IXf*

A solution of the glucoside (0·2 mmol) in mixture of pyridine (1 ml) and acetic anhydride (2 ml) was allowed to stand overnight at room temperature. The mixture was coevaporated with toluene (3×) under diminished pressure, the residue was dissolved in ether, the solution filtered through Celite and the solvent evaporated in vacuo. The product was purified by crystallization.

(20*Z*)-3β-(2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)-5,20-*pregnadiene*-21-*carbonitrile* (IVf). Glucoside *IVe* (97 mg) afforded 97 mg (74%) of acetate *IVf* (after crystallization from ether–light petroleum), m.p. 105°C, $[\alpha]_D$ −127° (*c* 2·5, chloroform). IR spectrum (tetrachloromethane): 2 220, 1 618 (C=C—C≡N); 1 762, 1 745 shoulder, 1 222, 1 040 (CH_3COO); 1 670 (C=C). ^1H NMR spectrum (200 MHz): see Table II. For $C_{36}H_{49}NO_{10}$ (655·8) calculated: 65·94% C, 7·53% H, 2·14% N; found: 66·08% C, 7·44% H, 2·07% N.

(20*E*)-3β-(2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)-5,20-*pregnadiene*-21-*carbonitrile* (Vf). Glucoside *Ve* (97 mg) gave 103 mg (79%) of acetate *Vf* (after crystallization from ether–light petroleum, m.p. 264–266°C, $[\alpha]_D$ −20° (*c* 1·6, chloroform). IR spectrum (tetrachloromethane): 2 225, 1 634 (C=C—C≡N); 1 764, 1 740 shoulder, 1 225, 1 031 (CH_3COO); 1 670 (C=C). ^1H NMR spectrum (200 MHz): see Table II. For $C_{36}H_{49}NO_{10}$ (655·8) calculated: 65·94% C, 7·53% H, 2·14% N; found: 65·77% C, 7·34% H, 1·99% N.

(20*Z*)-3β-(2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)-5α-*pregn*-20-*ene*-21-*carbonitrile* (VIf). Glucoside *VIe* (98 mg) afforded 84 mg (64%) of acetate *VIf*, (after crystallization from ether–light petroleum), m.p. 150–152°C, $[\alpha]_D$ −69° (*c* 1·6, chloroform). IR spectrum (tetrachloromethane): 2 220, 1 618 (C=C—C≡N); 1 763, 1 745 shoulder, 1 225, 1 041 (CH_3COO). ^1H NMR spectrum (200 MHz): see Table II. For $C_{36}H_{51}NO_{10}$ (657·8) calculated: 65·73% C, 7·81% H, 2·13% N; found: 65·61% C, 8·02% H, 1·97% N.

(20*E*)-3β-(2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)-5α-*pregn*-20-*ene*-21-*carbonitrile* (VIIf) Glucoside *VIIe* (98 mg) gave 92 mg (70%) of acetate *VIIf* (after crystallization from methanol), m.p. 270–272°C, $[\alpha]_D$ +14° (*c* 2·0, chloroform). IR spectrum (tetrachloromethane): 2 225, 1 635 (C=C—C≡N); 1 764, 1 740 shoulder, 1 220, 1 042 (CH_3COO). ^1H NMR spectrum (200 MHz): see Table II. For $C_{36}H_{51}NO_{10}$ (657·8) calculated: 65·73% C, 7·81% H, 2·13% N; found: 65·54% C, 8·04% H, 1·87% N.

(20*E*)-3α-(2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)-5α-*pregn*-20-*ene*-21-*carbonitrile* (IXf). Glucoside *IXe* (98 mg) afforded 90 mg (68%) of acetate *IXf* (after crystallization from chloroform–ether–light petroleum), m.p. 227–228°C, $[\alpha]_D$ 0° (*c* 0·9, chloroform). IR spectrum (tetrachloromethane): 2 225, 1 629 (C=C—C≡N); 1 755, 1 235 (CH_3COO). ^1H NMR spectrum (200 MHz): see Table II. For $C_{36}H_{51}NO_{10}$ (657·8) calculated: 65·73% C, 7·81% H, 2·13% N; found: 66·03% C, 7·57% H, 2·08% N.

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