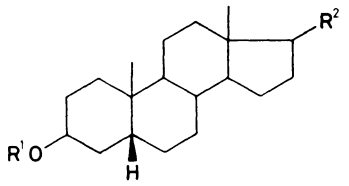
PREPARATION OF (20*E*)-21-ETHOXYCARBONYL-5β-PREGN-20-EN-3β-YL HYDROGEN BUTANEDIOATE

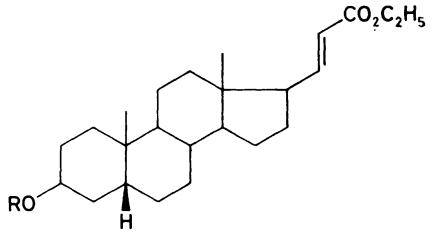
Vladimír POUZAR, Ivan ČERNÝ, Pavel DRAŠAR and Miroslav HAVEL

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

Received November 13, 1989
Accepted November 20, 1989

Title compound *X* was prepared according to the recently published[1] procedure for preparation of analogous derivatives of (20*E*)-21-methoxycarbonylpregna-5,14,20--trien-3β-yl hydrogen butanedioate, using this reaction sequence: *I* → *II* → *III* → → *IV* → *V* → *VI* → *VII* → *VIII* → *IX* → *X* (total yield 24%). Structures of all new compounds were confirmed by IR and ^{1}H NMR spectra and elemental analyses. Typical signal for 5β-pregnane derivatives with 3β-axial oxygen substituent is a multiplet of equatorial H-3α at δ 4·00–4·10 for free or at δ 5·10–5·13 for acylated hydroxyl with $W = 11-14$ Hz.





I, R^1 = Ac ; R^2 = $COCH_3$
II, R^1 = H ; R^2 = COOH
III, R^1 = H ; R^2 = $COOCH_3$
IV, R^1 = H ; R^2 = CH_2OH
V, R^1 = H ; R^2 = CH_2ODMTr
VI, R^1 = $OCCH_2CH_2COOTse$; R^2 = CH_2ODMTr
VII, R^1 = $OCCH_2CH_2COOTse$; R^2 = CH_2OH
VIII, R^1 = $OCCH_2CH_2COOTse$; R^2 = CHO

IX, R = $OCCH_2CH_2COOTse$
X, R = $OCCH_2CH_2COOH$

Tse = $CH_2CH_2Si(CH_3)_3$ DMTr = 4,4'-dimethoxytrityl

EXPERIMENTAL

Melting points were determined on a micro melting point apparatus Boetius (G.D.R.). Optical rotations were measured at 25°C on a Perkin–Elmer 141 MC polarimeter. Infrared spectra were recorded on UR-20 (Zeiss, Jena G.D.R.) spectrometer; wavenumbers in cm^{-1}. ^{1}H NMR spectra

were taken on a TESLA BS-476 (CW mode, 60 MHz) instrument at 23°C in deuteriochloroform with tetramethylsilane as internal standard, unless stated otherwise. Chemical shifts are given in ppm (δ-scale), coupling constants (J) and bandwidths (W) in Hz. All values were obtained by the 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). Prior to evaporation, solutions in organic solvents were dried over anhydrous sodium sulfate. Solvents were evaporated in vacuo (about 2 kPa). Analytical samples were dried over phosphorus pentoxide at 40°C/26 Pa for 12 h. Identity of samples prepared by different routes was checked by comparison of their IR and ^{1}H NMR spectra, thin-layer chromatography and mixture melting point determination.

3β-Hydroxy-5β-androstane-17β-carboxylic Acid (*II*)

A solution of sodium hypobromite (prepared[2] from sodium hydroxide (3·7 g, 93 mmol), water (32 ml), bromine (3·8 g, 24 mmol), and dioxane (22 ml)) was added during 5 min to a solution of ketone *I* (2·56 g, 7·1 mmol) in a mixture of dioxane (90 ml) and water (30 ml), precooled to +8°C. After stirring for 4 h at room temperature, a solution of sodium sulfite (0·9 g) in water (6·5 ml) was added, the mixture was refluxed for 15 min without stirring and then acidified with concentrated hydrochloric acid (4·6 ml), diluted with water (80 ml) and set aside in refrigerator overnight. The product was collected on filter, washed with water and dried over phosphorus pentoxide in vacuo, affording 2·03 g (90%) of acid *II*, m.p. 226–229°C; $[\alpha]_D$ +50° (*c* 0·2, chloroform). Literature[3] gives m.p. 226–228°C; $[\alpha]_D$ +36·8°. IR spectrum (KBr): 3 500–2 500, 1 713 (COOH); 3 500 (OH).

Methyl 3β-Hydroxy-5β-androstane-17β-carboxylate (*III*)

A stirred mixture of acid *II* (2·02 g, 6·3 mmol), anhydrous potassium carbonate (2·63 g, 19 mmol), acetone (22 ml), and dimethyl sulfate (1·2 ml, 12·7 mmol) was refluxed for 4 h. After cooling, the mixture was diluted with dichloromethane–ether (350 ml, 1 : 1) and passed through a column of alumina (50 g), which was then washed with the same solvent mixture. Evaporation of solvents and crystallization of the residue from dichloromethane–light petroleum yielded 2·02 g (96%) of the methylester *III*, m.p. 130–132°C; $[\alpha]_D$ +54° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 615, 3 480 (OH); 1 724 (COOR). ^{1}H NMR spectrum: 4·10 m, 1 H (H-3, W = 11); 3·67 s, 3 H ($COOCH_3$); 0·96 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). For $C_{21}H_{34}O_3$ (334·5) calculated: 75·41% C, 10·25% H; found: 75·36% C, 10·37% H.

21-Nor-5β-pregnane-3β,20-diol (*IV*)

Sodium bis(2-methoxyethoxy)dihydroaluminate in benzene (3·5M solution, 6 ml) was added to methyl ester *III* (2·01 g, 6 mmol) in tetrahydrofuran (60 ml). The stirred mixture was refluxed under argon for 5 h, cooled to room temperature and decomposed with water. The formed precipitate was partitioned between chloroform–ethyl acetate (1 : 1) and dilute hydrochloric acid (1 : 4). The aqueous layer was extracted with chloroform–ethyl acetate mixture and the combined organic phases were washed with dilute hydrochloric acid, water, potassium hydrogen carbonate solution, and water. After removal of the solvent, the residue was crystallized from chloroform–ethyl acetate to give 1·41 g (77%) of diol *IV*, m.p. 216–218°C; $[\alpha]_D$ +16° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 620, 3 250 (OH). ^{1}H NMR spectrum ($CDCl_3$ and CD_3SOCD_3 mixture): 4·05 m, 1 H (H-3, W = 14); 3·62 m, 2 H (2 × H-20); 0·94 s, 3 H (3 × H-19); 0·60 s, 3 H (3 × H-18). For $C_{20}H_{34}O_2$ (306·5) calculated: 78·38% C, 11·18% H; found: 78·14% C, 10·97% H.

20-(Bis(4-methoxyphenyl)phenylmethoxy)-21-nor-5β-pregnan-3β-ol (*V*)

4,4′-Dimethoxytrityl chloride (1·12 g, 3·3 mmol) was added at 0°C to a solution of diol *IV* (920 mg, 3 mmol) in pyridine (15 ml). After stirring at room temperature for 24 h, the mixture was diluted with benzene (400 ml), washed with potassium hydrogen carbonate solution (2×), water (2×), dried over anhydrous potassium carbonate and taken down. The residue was co-evaporated with toluene to remove most of pyridine and chromatographed on a column of silica gel (100 g, pre-treated with ammonia vapours for 24 h). Light petroleum–benzene–triethylamine–ether (100 : 100 : 1 : 1) eluted non-polar impurities, and elution with the same solvent mixture (100 : 100 : 1 : 2) afforded 1·7 g (93%) of amorphous trityl derivative *V*; $[\alpha]_D$ +6° (*c* 2·5, dioxane). IR spectrum (tetrachloromethane): 3 623, 3 500 (OH); 1 610, 1 514 (aromatic system); 1 252, 1 228 (OCH_3). ^{1}H NMR spectrum (tetrachloromethane): 7·23 m, 9 H (9 × arom. H); 6·70 bd, 4 H (4 × arom. H, J = 9); 4·00 m, 1 H (H-3, W = 12); 3·72 s, 6 H (2 × OCH_3); 2·94 m, 2 H (2 × H-20); 0·93 s, 3 H (3 × H-19); 0·40 s, 3 H (3 × H-18). For $C_{41}H_{52}O_4$ (608·9) calculated: 80·88% C, 8·61% H; found: 80·64% C, 8·54% H.

20-Hydroxy-21-nor-5β-pregnan-3β-yl 2-(Trimethylsilyl)ethyl Butanedioate (*VII*)

A solution of hydroxy derivative *V* (1·4 g, 2·3 mmol) in benzene (11 ml) was added to 2-(trimethylsilyl)ethyl hydrogen butanedioate[4] (1·44 g, 6·6 mmol) and 4-dimethylaminopyridine (30 mg, 245 μmol) in pyridine (11 ml). N,N′-Dicyclohexylcarbodiimide (825 mg, 4 mmol) in benzene (6·5 ml) was added, the mixture was stirred at room temperature for 24 h, diluted with benzene (400 ml), washed twice with water, and filtered through an alumina column (100 g). The column was washed with benzene, the solvents were evaporated in vacuo and the residue was coevaporated with toluene in vacuo. Yield 2·3 g of crude *VI*, which was dissolved in benzene (180 ml), and heated to 65°C with silica gel (60 g) under argon 3 h. The content of the flask was washed with ether on a layer of silica gel and the product was eluted with ether. After evaporation of solvents, the residue was subjected to column chromatography on silica gel (200 g). Light petroleum–benzene–ether (10 : 10 : 1) eluted non-polar impurities; the product was obtained on elution with light petroleum–benzene–ether (10 : 10 : 2). Yield 860 mg (73% from *V*) of oily *VII*; $[\alpha]_D$ + 6° (*c* 1·8, chloroform). IR spectrum (chloroform): 3 620 (OH); 1 724 (COOR); 1 253, 860, 840 ($Si(CH_3)_3$). ^{1}H NMR spectrum (external lock): 5·12 m, 1 H (H-3, W = 14); 4·17 m, 2 H ($COOCH_2CH_2Si$, W = 17); 3·60 m, 2 H (2 × H-20); 2·59 s, 4 H ($OOCH_2CH_2COO$); 0·95 s, 3 H (3 × H-19); 0·62 s, 3 H (3 × H-18); 0·02 s, 9 H ($Si(CH_3)_3$). For $C_{29}H_{50}O_5Si$ (506·8) calculated: 68·83% C, 9·94% H; found: 68·65% C, 10·07% H.

(20*E*)-21-Ethoxycarbonyl-5β-pregn-20-en-3β-yl 2-(Trimethylsilyl)ethyl Butanedioate (*IX*)

Pyridinium chlorochromate (430 mg, 2 mmol) was added to a solution of hydroxy derivative *VII* (405 mg, 0·8 mmol) in dichloromethane (20 ml). After stirring at room temperature under argon for 2 h, the mixture was diluted with ether (40 ml) and filtered through an alumina column (20 g) which was then washed with ether. The combined filtrates were taken down in vacuo and the residue was coevaporated with toluene to remove pyridine. Yield 360 mg of crude aldehyde *VIII*. ^{1}H NMR spectrum (external lock): 9·78 bs, 1 H (H-20); 5·13 m, 1 H (H-3, W = 14); 4·18 m, 2 H ($COOCH_2CH_2Si$, W = 17); 2·62 s, 4 H ($OOCCH_2CH_2COO$); 1·00 s, 3 H (3 × H-19); 0·76 s, 3 H (3 × H-18); 0·07 s, 9 H ($Si(CH_3)_3$). Triethyl phosphonoacetate (0·6 ml, 3 mmol) was added under argon during 10 min to a suspension of sodium hydride (72 mg, 3 mmol) in 1,2-dimethoxyethane (4 ml). The mixture was stirred at room temperature for 20 min and then a solution of aldehyde *VIII* (353 mg, 0·7 mmol) in 1,2-dimethoxyethane (4 ml) was added. The mixture was stirred at room temperature in an argon atmosphere for 4 h and the

solvent was removed in vacuo. The residue was partitioned between ether and water, the aqueous layer was extracted with ether and the combined organic phases were washed with water (2×), dried and evaporated. The residue was chromatographed on a column of silica gel (35 g) in light petroleum–benzene–ether (50 : 45 : 5) to give 253 mg (56% from *VII*) of oily product *IX*, $[\alpha]_D$ +22·5° (*c* 1·4, chloroform). IR spectrum (tetrachloromethane): 1 730 (C=O); 1 650 (C=C of unsaturated ester); 1 252, 862, 840 ($SiC(CH_3)_3$). ^{1}H NMR spectrum (external lock): 6·95 dd, 1 H (H-20, *J*(17, 20) = 7; *J*(20, 21) = 16); 5·76 d, 1 H (H-21, *J*(20, 21) = 16); 5·11 m, 1 H (H-3, *W* = 14); 4·18 q, 2 H ($COOCH_2CH_3$, *J* = 7); 4·16 m, 2 H ($COOCH_2CH_2Si$, *W* = 17); 2·61 s, 4 H ($OOCCH_2CH_2COO$); 1·28 t, 3 H ($COOCH_2CH_3$, *J* = 7); 0·97 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18); 0·06 s, 9 H ($Si(CH_3)_3$). For $C_{33}H_{54}O_6Si$ (574·9) calculated: 68·95% C, 9·74% H; found: 69·13% C, 9·77% H.

(20*E*)-21-Ethoxycarbonyl-5β-pregn-20-en-3β-yl Hydrogen Butanedioate (*X*)

Tetrabutylammonium fluoride in tetrahydrofuran (1M solution, 0·8 ml) was added to ester *IX* (230 mg, 0·4 mmol) in tetrahydrofuran (6 ml). After stirring for 5 h at room temperature, the mixture was diluted with benzene (200 ml), washed with 10% sulfuric acid, twice with water, and the solvents were evaporated. The residue was chromatographed on a column of silica gel (20 g) in dichloromethane–methanol (97 : 3) to give 165 mg (95%) of amorphous hemisuccinate *X*, $[\alpha]_D$ +26° (*c* 1·3, chloroform). IR spectrum (chloroform): 3 300–2 500 (COOH); 1 720 (C=O); 1 650 (C=C of unsaturated ester). ^{1}H NMR spectrum: 6·97 dd, 1 H (H-20, *J*(17, 20) = = 7; *J*(20, 21) = 16); 5·74 d, 1 H (H-21, *J*(20, 21) = 16); 5·10 m, 1 H (H-3, *W* = 12); 4·17 q, 2 H ($COOCH_2CH_3$, *J* = 7); 2·63 bs, 4 H ($OOCCH_2CH_2COO$); 1·28 t, 3 H ($COOCH_2CH_3$, *J* = 7); 0·95 s, 3 H (3 × H-19); 0·62 s, 3 H (3 × H-18). For $C_{28}H_{42}O_6$ (474·6) calculated: 70·86% C, 8·92% H; found: 70·75% C, 9·07% H.

Our thanks are due to Mrs Z. Ledvinová for optical rotation measurements and Dr S. Vašíčková for taking and interpretation of IR *spectra. We are also indebted to Mrs J. Jelínková and Mrs M. Snopková for measurement of* ^{1}H NMR *spectra. Elemental analyses were carried out in the Analytical Laboratory of this Institute (Dr V. Pechanec, Head).*

REFERENCES

1. Pouzar V., Černý I., Drašar P., Havel M.: Collect. Czech. Chem. Commun. *52*, 1803 (1987).
2. Staunton J., Eisenbraun E. J.: Org. Synth., Coll. Vol. *5*, 8 (1973).
3. Ruzicka L., Plattner P. A., Balla G.: Helv. Chim. Acta *25*, 65 (1942).
4. Pouzar V., Drašar P., Černý I., Havel M.: Synth. Commun. *14*, 501 (1984).

Translated by the author (V.P.).