PREPARATION OF (20*E*)-21-ETHOXYCARBONYL-14β,17α-PREGNA--5,20-DIEN-3β-YL HYDROGEN BUTANEDIOATE

Vladimir POUZAR and Ivan CERNY

Institute of Organic Chemistry and Biochemistry,
Academy of Sciences of the Czech Republic, 166 10 Prague 6, The Czech Republic

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The title compound *X* was prepared according to the recently published procedure[1,2] for preparation of analogous derivatives in the 5β-pregnane series, using the reaction sequence *I* → *II* → *III* → *IV* → *V* → *VI* → *VII* → *VIII* → *IX* → *X* (total yield 18%). The configuration at ring D centers (14β,17α) follows from the structure of the starting ketone[3] *I* and was also checked by comparing diol *IV* with the sample prepared by an independent route[4]. The epimeric purity at C-17 was carefully monitored during the whole synthesis by ^{1}H NMR spectra (singlet of 18-H_3).

EXPERIMENTAL

Melting points were determined on a micro melting point apparatus Boetius (Germany). Optical rotations were measured at 25 °C on a Perkin–Elmer 141 MC polarimeter. Infrared spectra were recorded on a UR-20 (Zeiss, Jena, Germany) spectrometer; wavenumbers are given 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 band widths (*W*) in Hz. All values were obtained by the first-order analysis. Column chromatography was performed on silica gel (60 – 120 μm) or on neutral alumina (Reanal, activity II), thin-layer chromatography on silica gel G according to Stahl (Woelm). Solutions in organic solvents were dried over anhydrous sodium sulfate and the solvents were evaporated in vacuo (about 2 kPa) on a rotary evaporator. Analytical samples were dried over phosphorus pentoxide at 40 °C/26 Pa for 12 h.

3β-Hydroxy-21-nor-14β,17α-pregn-5-en-20-oic Acid (*II*)

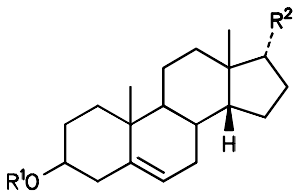
A solution of sodium hypobromite, prepared[5] from sodium hydroxide (3.7 g, 93 mmol), water (32 ml), bromine (3.8 g, 24 mmol), and dioxane (22 ml), was added over 5 min to a solution of ketone[3] *I* (2.55 g, 7.1 mmol) in a mixture of dioxane (90 ml) and water (30 ml), precooled to 8 °C. After stirring 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 and then acidified with concentrated hydrochloric acid (4.6 ml), diluted with water (80 ml) and set aside in a refrigerator overnight. The product was collected on filter, washed with water and dried over phosphorus pentoxide in vacuo, affording 1.96 g (87%) of acid *II*, m.p. 244 – 248 °C; $[\alpha]_D$ 0° (*c* 0.2, chloroform). Literature[6] gives m.p. 246 – 248 °C. IR spectrum (KBr): 3 500 – 2 500, 1 695 shoulder, 1 670 (COOH); 3 315 (OH).

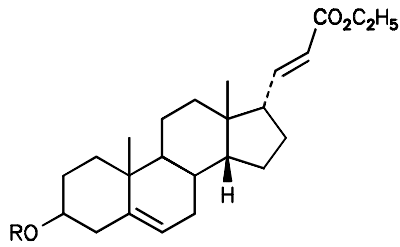
Methyl 3β-Hydroxy-21-nor-14β,17α-pregn-5-en-20-oate (*III*)

A stirred mixture of acid *II* (1.21 g, 3.8 mmol), anhydrous potassium carbonate (1.66 g, 12 mmol), acetone (14 ml), and dimethyl sulfate (0.75 ml, 7.9 mmol) was refluxed with stirring 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 acetone–light petroleum yielded 1.12 g (89%) of the methyl ester *III*, m.p. 153 – 154 °C; $[\alpha]_D$ –22° (*c* 0.3, chloroform). IR spectrum (chloroform): 3 610, 3 460 (OH); 1 725, 1 169 (COOR). ^{1}H NMR spectrum: 5.34 m, 1 H (H-6); 3.64 s, 3 H ($COOCH_3$); 3.53 m, 1 H, W ≈ 32 (H-3); 1.18 s, 3 H (3 × H-18); 0.97 s, 3 H (3 × H-19). For $C_{21}H_{32}O_3$ (332.5) calculated: 75.86% C, 9.70% H; found: 75.63% C, 9.81% H.

21-Nor-14β,17α-pregn-5-ene-3β,20-diol (*IV*)

Sodium bis(2-methoxyethoxy)dihydroaluminate in benzene (3.5 M solution, 4 ml) was added to methyl ester *III* (1.26 g, 3.8 mmol) in tetrahydrofuran (40 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 a chloroform–ethyl acetate mixture and the combined organic





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 = $COCH_2CH_2COOTse$; R^2 = CH_2ODMTr

VII, R^1 = $COCH_2CH_2COOTse$; R^2 = CH_2OH

VIII, R^1 = $COCH_2CH_2COOTse$; R^2 = CHO

IX, R = $COCH_2CH_2COOTse$

X, R = $COCH_2CH_2COOH$

DMTr = 4,4'-dimethoxytrityl

Tse = $CH_2CH_2Si(CH_3)_3$

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 yield 1.04 g (90%) of diol *IV*, m.p. 173 – 175 °C; $[\alpha]_D$ −28° (*c* 0.2, chloroform). Literature[4] gives m.p. 171 – 173 °C, $[\alpha]_D$ −33° (*c* 0.2, chloroform). IR spectrum (KBr): 3 280 (OH); 3 035, 1 673 (C=CH).

20-(Bis(4-methoxyphenyl)phenylmethoxy)-21-nor-14β,17α-pregn-5-en-3β-ol (*V*)

4,4′-Dimethoxytrityl chloride (1.12 g, 3.3 mmol) was added at 0 °C to a solution of diol *IV* (913 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 coevaporated with toluene to remove most of pyridine and chromatographed on a column of silica gel (100 g, pre-treated with ammonia vapors for 24 h). Light petroleum–benzene–triethylamine–ether (100 : 100 : 1 : 3) eluted nonpolar impurities, and elution with the same solvent mixture (100 : 100 : 1 : 8) afforded 1.6 g (88%) of amorphous trityl derivative *V*; $[\alpha]_D$ +2° (*c* 2.4, dioxane). IR spectrum (tetrachloromethane): 3 620, 3 340 (OH); 1 670 (C=C); 3 090, 3 070, 3 035, 1 607, 1 583, 1 508 (aromatic system). ^{1}H NMR spectrum (tetrachloromethane): 7.25 m, 9 H (9 × H-arom.); 6.70 bd, 4 H, J = 9 (4 × H-arom.); 5.24 m, 1 H (H-6); 3.73 s, 6 H (2 × OCH_3); 2.95 m, 2 H (2 × H-20); 1.05 s, 3 H (3 × H-19); 0.92 s, 3 H (3 × H-18). For $C_{41}H_{50}O_4$ (606.9) calculated: 81.15% C, 8.30% H; found: 80.97% C, 8.06% H.

20-Hydroxy-21-nor-14β,17α-pregn-5-en-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[7] (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 ester *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 the solvents, the residue was subjected to column chromatography on silica gel (200 g). Light petroleum–benzene–ether (10 : 10 : 1) eluted nonpolar impurities; the product was obtained on elution with light petroleum–benzene–ether (10 : 10 : 2). Yield 815 mg (70% from *V*) of oily *VII*; $[\alpha]_D$ −48° (*c* 0.5, chloroform). IR spectrum (chloroform): 3 625, 3 520 (OH); 1 725, 1 166 (COOR); 1 675 (C=C); 1 253, 860, 840 ($Si(CH_3)_3$). ^{1}H NMR spectrum (external lock): 5.35 m, 1 H (H-6), 4.58 m, 1 H (H-3); 4.16 m, 2 H, W = 17 ($O\mathbf{C}H_2CH_2Si$); 3.61 m, 2 H (2 × H-20); 2.58 s, 4 H ($OOCCH_2CH_2COO$); 1.08 s, 3 H (3 × H-18); 0.99 s, 3 H (3 × H-19); 0.03 s, 9 H ($Si(CH_3)_3$). For $C_{29}H_{48}O_5Si$ (504.8) calculated: 69.00% C, 9.58% H; found: 68.76% C, 9.76% H.

(20*E*)-21-Ethoxycarbonyl-14β,17α-pregna-5,20-dien-3β-yl 2-(Trimethylsilyl)ethyl Butanedioate (*IX*)

Pyridinium chlorochromate (430 mg, 2 mmol) was added to a solution of hydroxy derivative *VII* (404 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*.

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 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 270 mg (59% from *VII*) of product *IX*, m.p. 52 – 54 °C, $[\alpha]_D$ +20° (*c* 1.3, chloroform). IR spectrum (tetrachloromethane): 1 734 (COOR); 1 720 shoulder, 1 654 (C=CCOOR); 1 254, 860, 840 ($Si(CH_3)_3$). ^{1}H NMR spectrum (external lock): 6.93 dd, 1 H, *J*(17,20) = 7, *J*(20,21) = 16 (H-20); 5.78 d, 1 H, *J*(20,21) = 16 (H-21); 5.38 m, 1 H (H-6); 4.62 m, 1 H, *W* = 32 (H-3); 4.18 m, 2 H, *W* = 17 ($O\mathbf{CH}_2CH_2Si$); 4.17 q, 2 H, *J* = 7 ($COO\mathbf{CH}_2CH_3$); 2.58 s, 4 H ($OOCCH_2CH_2COO$); 1.27 t, 3 H, *J* = 7 ($COOCH_2\mathbf{CH}_3$); 0.99 s, 6 H (3 × H-18 and 3 × H-19); 0.04 s, 9 H ($Si(CH_3)_3$). For $C_{33}H_{52}O_6Si$ (572.9) calculated: 69.19% C, 9.15% H; found: 68.92% C, 8.97% H.

(20*E*)-21-Ethoxycarbonyl-14β,17α-pregna-5,20-dien-3β-yl Hydrogen Butanedioate (*X*)

Tetrabutylammonium fluoride in tetrahydrofuran (1 M 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 crystallized from light petroleum–dichloromethane to give 135 mg (71%) of hemisuccinate *X*, m.p. 130 – 133 °C, $[\alpha]_D$ +24° (*c* 1.0, chloroform). IR spectrum (chloroform): 3 300 – 2 500, 1 716 (COOH); 1 716 (COOR); 1 716, 1 650 (C=CCOOR). ^{1}H NMR spectrum: 6.92 dd, 1 H, *J*(17,20) = 8, *J*(20,21) = 16 (H-20); 5.77 d, 1 H, *J*(20,21) = 16 (H-21); 5.37 m, 1 H (H-6); 4.68 m, 1 H, *W* = 32 (H-3); 4.18 q, 2 H, *J* = 7 ($COO\mathbf{CH}_2CH_3$); 2.63 bs, 4 H ($OOCCH_2CH_2COO$); 1.27 t, 3 H, *J* = 7 ($COOCH_2\mathbf{CH}_3$); 0.99 s, 6 H (3 × H-18 and 3 × H-19). For $C_{28}H_{40}O_6$ (472.6) calculated: 71.16% C, 8.53% H; found: 71.33% C, 8.74% H.

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REFERENCES

1. Pouzar V., Cerny I., Drasar P.: Collect. Czech. Chem. Commun. *58*, 2963 (1993).
2. Pouzar V., Cerny I., Drasar P., Havel M.: Collect. Czech. Chem. Commun. *55*, 1635 (1990).
3. Plattner P. A., Heusser H., Serge A.: Helv. Chim. Acta *31*, 249 (1948).
4. Cerny I., Budesinsky M., Drasar P., Pouzar V.: Collect. Czech. Chem. Commun. *59*, 2691 (1994).
5. Staunton J., Eisenbraun E. J.: Org. Synth., Coll. Vol. *5*, 8 (1973).
6. Heusser H., Frick N., Plattner P. A.: Helv. Chim. Acta *33*, 1260 (1950).
7. Pouzar V., Drasar P., Cerny I., Havel M.: Synth. Commun. *14*, 501 (1984).