SYNTHESIS OF MONOMERIC 2-[(2-METHYL-2-PROPENOYL)OXY]ETHYL ESTERS OF PROSTAGLANDINS

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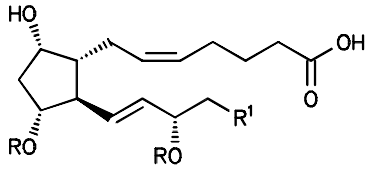
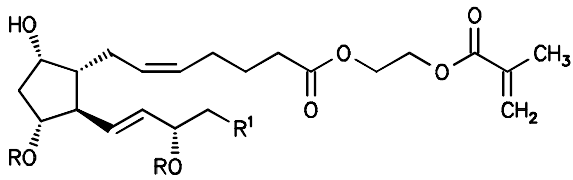
Prostaglandins (PG) and their synthetic analogues are indispensable in human medicine for curing many serious diseases[1]. However, their low stability, particularly in the drug forms, limits considerably their application in the current ambulant medical practice[2]. A prospective solution of this problem has been published recently[3] that consists in reversible anchoring of a prostaglandin E_1 analogue (Misoprostol) on a modified polybutadiene chain.

In the present communication we describe another possibility of anchoring the active substance, characterized by reversible immobilization of prostaglandins in the form of esters containing a monomeric (2-methyl-2-propenoyl)oxy group. As model compounds we have chosen 2-[(2-methyl-2-propenoyl)oxy]ethyl esters of PG $F_{2\alpha}$ (*IIa*), 11,15-bis(tetrahydro-2*H*-pyran-2-yl)-PG $F_{2\alpha}$ (*IIb*), (±)-16-(3-chlorophenoxy)-17,18,19,20-tetranor-PG $F_{2\alpha}$ (cloprostenol, *IIc*) and PG A_2 (*IId*). The monomeric esters *IIa–IId* were prepared by reaction of an alkali metal or triethylammonium salt of a prostaglandin of the $F_{2\alpha}$ or A_2 series (obtained from the corresponding PG *Ia–Id* and the corresponding alkoxide or triethylamine in anhydrous alcohol) with about 50% molar excess of 2-iodoethyl (*IIIa*) or 2-bromoethyl 2-methyl-2-propenoate (*IIIb*). The best yields (60–84%) of the monomers *IIa–IIc* were obtained with sodium or potassium salt of prostaglandins *Ia–Ic* and 2-iodoethyl ester *IIIa* in acetone–dimethyl sulfoxide or acetone–dimethylformamide at 40–45 °C. Whereas under identical conditions trimethylammonium salt of PG A_2 (*Id*) reacted with 2-iodoethyl ester *IIIa* to give the desired monomeric ester *IId* in relatively good yield (52%), the reaction with 2-bromoethyl ester *IIIb* afforded only 34% of the ester *IId*, even when the reaction was performed with 100% molar excess of *IIIb*, prolonged reaction time and higher temperature (50–55 °C). We also tried to prepare ester *IIa* by reaction of iodo ester *IIIa* with potassium salt of PG $F_{2\alpha}$, prepared in situ from the free acid *Ia* and freshly calcined potassium carbonate in anhydrous acetone. Heating at 40–42 °C for 16 h, followed by chromatography, afforded mainly the starting PG $F_{2\alpha}$ *Ia* (28%), R_F 0.11 (chloroform–methanol–acetic acid 90 : 8 : 2), the

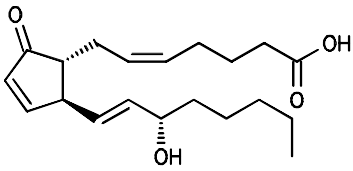


Ia–Ic

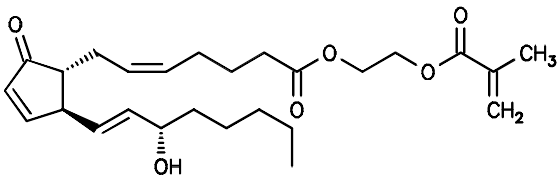


IIa–IIc

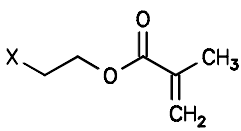
In formulae *I*, *II* : ***a***, R = H; R^1 = $CH_2CH_2CH_2CH_3$
b, R = THP; R^1 = $CH_2CH_2CH_2CH_3$
a, R = H; R^1 = 3-ClC_6H_4O



Id



IId



IIIa, X = I
IIIb, X = Br

desired ester *IIa* (R_F 0.27, 17%) and further four compounds (R_F 0.16, 0.22, 0.40 and 0.49) the structure of which has not been so far determined. In order to suppress polymerization of the monomeric esters *IIa–IId*, *IIIa* and *IIIb* and to avoid formation of undesired products, the reaction was performed in an inert (nitrogen) atmosphere in the presence of catalytic amounts of octyl pyrocatechol as polymerization inhibitor. The reaction was monitored by TLC and was usually finished after 8–28 h. The monomeric esters *IIa–IId* were isolated from the reaction mixture by standard work-up procedure using column chromatography on silica gel in chloroform–methanol. The spectral characteristics (IR and ^{1}H NMR) and elemental analyses of the obtained substances were in accord with the assumed structure. On the basis of preliminary experiments we can expect that the monomers *IIa–IId*, as parts of three-dimensional biocompatible hydrogels prepared by copolymerization with 2-hydroxyethyl 2-methyl-2-propenoate[4,5] (HEMA), could be used in drug forms with controlled liberation of biologically active PG derivatives.

EXPERIMENTAL

The temperature data are uncorrected. Infrared spectra were recorded on a Nicolet 740 spectrometer in chloroform. Proton NMR spectra (δ, ppm; *J*, Hz) were taken on a Bruker 400 instrument in deuteriochloroform with tetramethylsilane as internal standard. TLC analyses were performed on 2.5 × 7.5 cm plates (Kieselgel G, Fluka, detection with 1% solution of cerium ammonium nitrate in 10% sulfuric acid).

Starting compounds. Prostaglandin $F_{2\alpha}$ (*Ia*), 11,15-bis(tetrahydro-2*H*-pyran-2-yl)-PG $F_{2\alpha}$ (*Ib*), prostaglandin E_2 and (±)-16-(3-chlorophenoxy)-17,18,19,20-tetranor-PG $F_{2\alpha}$ (*Ic*, cloprostenol) were obtained from Spolana works (Neratovice, Czech Republic), prostaglandin A_2 was prepared from prostaglandin E_2 according to a described procedure[6]. 2-Bromoethanol (b.p. 56–58 °C/2.7 kPa) was obtained from oxirane by treatment with hydrogen bromide[7], 2-iodoethanol (b.p. 84–85 °C/3.3 kPa was prepared by Finkelstein reaction[8] from 2-chloroethanol, 2-bromoethyl 2-methyl-2-propenoate (*IIIb*, b.p. 85–87 °C/1.9 kPa, ref.[9]) and 2-iodoethyl 2-methyl-2-propenoate (*IIIa*, b.p. 94–96 °C/1.9 kPa, ref.[9]) were synthesized by reaction of 2-methyl-2-propenoyl chloride with 2-bromoethanol and 2-iodoethanol, respectively, according to a described procedure[10].

2-[(2-Methyl-2-propenoyl)oxy]ethyl Ester of PG $F_{2\alpha}$ (*IIa*)

Prostaglandin $F_{2\alpha}$ (*Ia*, 50 mg, 0.141 mmol) was converted into its potassium salt by treatment with methanolic potassium methoxide (0.45 ml of 0.315 M solution). This solution was mixed with 1 : 1 acetone–dimethylformamide mixture (8 ml) and octyl pyrocatechol (0.1 ml of 1% solution in acetone). A solution of 2-iodoethyl 2-methyl-2-propenoate (*IIIa*, 50 mg 0.21 mmol) in acetone (2 ml) was added under stirring in an atmosphere of nitrogen. The mixture was stirred at 40–45 °C and the reaction was monitored by TLC in chloroform–methanol–acetic acid (90 : 8 : 2). After 10 h the reaction mixture was diluted with water, the organic phase was separated and the aqueous one extracted with ethyl acetate (3 × 10 ml). The combined organic portions were washed with brine (5 ml), dried over magnesium sulfate, and the solvent was evaporated under diminished pressure on a rotatory evaporator. Chromatography of the residue (96 mg) on a column of silica gel (15 g; 10% methanol in chloroform) afforded lightly yellow oily product *IIa* (39 mg, 59%), R_F 0.27. For $C_{26}H_{42}O_7$ (466.6) calculated: 66.92% C, 9.07% H; found: 66.29% C, 9.18% H. IR spectrum: 1 153 (ester C–O); 1 636

(C=C); 1 727 (ester C=O); 2 858, 2 928, 2 957 (aliphatic CH); 3 350–3 500 (OH). ^{1}H NMR spectrum: 0.89 t, 3 H, J(19,20) = 7 (CH_3C); 1.96 s, 3 H (CH_3C=); 2.35 t, 2 H, J(3,2) = 7 (CH_2CO); 4.35 s, 4 H (OCH_2CH_2O); 5.25–5.65 m, 5 H (H-5, H-6 (*Z*), H-13, H-14 (*E*), 1 H in CH_2C); 6.15 s, 1 H (CH_2=C).

2-[(2-Methyl-2-propenoyl)oxy]ethyl Ester of 11,15-Bis(tetrahydro-2*H*-pyran-2-yl)-PG $F_{2\alpha}$ (*IIb*)

11,15-Bis(tetrahydro-2*H*-pyran-2-yl)-PG $F_{2\alpha}$ (*Ib*, 73 mg, 0.141 mmol) was converted into its sodium salt by treatment with methanolic sodium methoxide (0.47 ml of 0.30 M solution). This solution was mixed with a mixture of 2-butanone (6 ml) and dimethylformamide (2 ml), and octyl pyrocatechol (0.1 ml of 1% solution in acetone) was added under nitrogen. A solution of ester *IIIa* (50 mg, 0.21 mmol) in 2-butanone (2 ml) was added under stirring. After stirring at 40–45 °C for 8 h, the reaction mixture was worked up in the usual manner. Column chromatography afforded yellowish oily product (62 mg, 70%), R_F 0.23 (3% methanol in chloroform). For $C_{36}H_{58}O_8$ (634.8) calculated: 67.89% C, 9.50% H; found: 67.99% C, 9.31% H. IR spectrum: 1 160 (ester C–O), 1 638 (C=C); 1 740 (ester C=O); 2 859, 2 934 (aliphatic CH); 3 440–3 500 (OH). ^{1}H NMR spectrum: 0.82 t, 3 H, J(19,20) = 7 (CH_3C); 1.96 s, 3 H (CH_3C=); 2.35 t, 2 H, J(2,3) = 7 (CH_2CO); 4.35 s, 4 H (OCH_2CH_2O); 5.25–5.65 m, 5 H (H-5, H-6 (*Z*), H-13, H-14 (*E*), 1 H in CH_2C); 6.15 s, 1 H (CH_2=C).

2-[(2-Methyl-2-propenoyl)oxy]ethyl Ester of (±)-16-(3-Chlorophenoxy)-17,18,19,20-tetranor-PG $F_{2\alpha}$ (*IIc*)

Cloprostenol (*Ib*, 59 mg, 0.141 mmol) was converted into its potassium salt by treatment with methanolic potassium methoxide (0.45 ml of 0.315 M solution). This solution was mixed with a 1 : 1 mixture (8 ml) of acetone and dimethylformamide, and octyl pyrocatechol (0.1 ml of 1% solution in acetone) was added under nitrogen. A solution of ester *IIIa* (50 mg, 0.21 mmol) in acetone (2 ml) was added under stirring. After stirring at 35–45 °C for 15 h, the reaction mixture was poured into a water–ice mixture (10 ml) and the aqueous phase was extracted with chloroform (3 × 15 ml). The combined extracts were washed with brine (5 ml), dried over magnesium sulfate and the solvent was evaporated. Column chromatography of the residue (71 mg) on silica gel (20 g, eluent 5% methanol in chloroform) afforded yellowish oily product (63 mg, 84%), R_F 0.43 (10% methanol in chloroform). For $C_{28}H_{37}ClO_8$ (537.1) calculated: 62.62% C, 6.94% H, 6.60% Cl; found: 62.15% C, 7.05% H, 7.12% Cl. IR spectrum: 1 163 (ester C–O); 1 598 (arom. C=C); 1 638 (C=C); 1 720 (ester C=O); 2 871, 2 932, 3 014 (aliphatic and aromatic CH); 3 400–3 450 and 3 598 (OH). ^{1}H NMR spectrum: 1.95 s, 3 H (CH_3C=); 2.36 t, 2 H, J(2,3) = 7 (CH_2CO); 4.35 s, 4 H (OCH_2CH_2O); 5.30–5.80 m, 5 H (H-5, H-6 (*Z*), H-13, H-14 (*E*), 1 H in CH_2=C); 6.15 s, 1 H (1 H in CH_2=C); 6.70–7.00 m, 4 H (3-ClC_6H_4O).

2-[(2-Methyl-2-propenoyl)oxy]ethyl Ester of PG A_2 (*IId*)

Procedure A: Prostaglandin A_2 (*Id*, 152 mg, 0.454 mmol) was converted into its triethylammonium salt by treatment with methanolic triethylamine (1.3 ml of 0.35 M solution). This solution was mixed under nitrogen with a 2 : 1 mixture (15 ml) of acetone and dimethyl sulfoxide, and octyl pyrocatechol (0.1 ml of 1% solution in acetone). A solution of 2-iodoethyl ester *IIIa* (164 mg 0.682 mmol) in an acetone–dimethyl sulfoxide mixture (2 : 1, 4 ml) was added under stirring. The mixture was heated at 40–45 °C for 10 h and then worked up in the usual manner. Column chromatography on silica gel afforded lightly yellow oily product (106 mg, 52%), R_F 0.31 (3% methanol in chloroform). For $C_{26}H_{38}O_6$ (446.6) calculated: 69.92% C, 8.58% H; found: 69.42% C, 8.37% H. IR spectrum: 1 163 (ester C–O); 1 595 (CH=CH–C=O); 1 638 (C=C); 1 722, 1 738 (ester and ring C=O); 2 858, 2 930, 2 956 (aliphatic CH); 3 440–3 500 (OH). ^{1}H NMR spectrum: 0.89 t, 3 H, J(19,20) = 7 (CH_3C); 1.95 s,

3 H (CH_3C=); 2.37 t, 2 H, *J*(3,2) = 7 (CH_2CO); 4.35 s (OCH_2CH_2O); 5.30–5.70 m, 5 H (H-5, H-6 (*Z*), H-13, H-14 (*E*), 1 H in CH_2=C); 6.15–6.40 m, 2 H (1 H in CH_2=C, 1 H in C=CHC=O); 6.85 d, 1 H (CH=CC=O).

Procedure B. A solution of triethylammonium salt of prostaglandin A_2, prepared from *Id* (100 mg, 0.299 mmol) in a mixture of acetone (10 ml) and dimethyl sulfoxide (4 ml), was mixed with octyl pyrocatechol (0.1 ml of 1% solution in acetone). 2-Bromomethyl 2-methyl-2-propenoate (*IIIb*; 115 mg, 0.598 mmol) was added, the mixture was stirred at 50–55 °C under nitrogen for 28 h and then worked up as described in procedure *A*. The yellowish product (46 mg; 34%) had the same R_F and spectral characteristics as a standard.

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