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The Synthesis of Phosphates of Long-Chain ω-Hydroxyalkyl Esters of 11-Deoxyprostaglandin E_1

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Abstract—Di(*p*-methylbenzyl) phosphates of ω-hydroxyalkyl esters of 11-deoxyprostaglandin E_1 were synthesized from disubstituted 1,10-decane and 1,22-docosane derivatives for studying the permeability of bilayer membranes.

Key words: *decane, docosane, 11-deoxyprostaglandin E_1*

We described previously the synthesis of 11-deoxyprostaglandin E_1 ω-hydroxypentyl ester phosphate (**Ia**) [1]. Because of the importance of studying the permeability of bilayer membranes for compounds of this class, we synthesized analogous compounds bearing long chain esters with n = 10 (**Ib**) and 22 (**Ic**).

Diethyl esters of sebacic acid (n = 8) (**II**) and eicosanedicarboxylic (n = 20) acid (**III**) were used as starting compounds. They were reduced with lithium aluminum hydride to the corresponding α,ω-glycols (**IV**) and (**V**). It is worth mentioning that we failed to prepare monoesters of 11-deoxyprostaglandin E_1 from glycols (**IV**) and (**V**) using the procedures described in [1]. Therefore, glycols (**IV**) and (**V**) were converted into 1,10-dichlorodecane (**VI**) and 1,22-dichlorodocosane (**VII**) by treatment with thionyl chloride in pyridine and then into the corresponding iodides (**VIII**) and (**IX**) by the reaction of (**VI**) and (**VII**) with sodium iodide.

The interaction of (**VIII**) and (**IX**) with 11-deoxyprostaglandin E_1 potassium salt (**X**) resulted in 50 and 40% yields of ω-iodoalkyl esters (**XI**) and (**XII**), respectively, which were converted into esters (**XIII**) and (**XIV**) using silver salt of di(*p*-methylbenzyl) phosphate [1] (Scheme).

Deprotected (unstable) phosphates (**Ib**) and (**Ic**) can be obtained immediately before use by the treatment of dibenzyl esters (**XIII**) and (**XIV**) with dry hydrogen chloride in chloroform [1].

EXPERIMENTAL

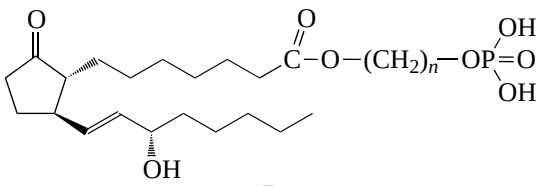
^{1}H NMR spectra were registered on a Bruker WH spectrometer (90 MHz) in $CDCl_3$ with hexamethyldisiloxane as an internal standard. Chemical shifts are given in ppm (δ scale) relative to Me_4Si.

The products were isolated and purified using column chromatography on silica gel 100/250 μm (Lachema, Czech Republic) in ethyl acetate–benzene. Compositions of reaction products were determined by TLC on Silufol plates (Czech Republic) in a 2 : 5 ethyl acetate–benzene system; the compound spots were visualized by spraying with 10% phosphomolybdic acid in ethanol, followed by heating.

In this work, we used diethyl sebacate (**II**) from Khimreaktivkomplekt (USSR), which was distilled before use, and silver salt of di(*p*-methylbenzyl) phosphate, which was obtained as described in [1].

Diethyl eicosanedicarboxylate (III). A solution of eicosanedicarboxylic acid (3.7 g, 10 mmol) and *p*-toluenesulfonic acid (0.5 g, 3.4 mmol) in absolute ethanol (20 ml) and benzene (15 ml) was refluxed using a Dean–Stark adapter for 2 h. The reaction mixture was cooled, diluted with ether, washed with water and saturated solutions of sodium carbonate and sodium chloride, dried with anhydrous sodium sulfate, and evaporated. Ester (**III**) (3.5 g, 82%) was obtained as crystals, mp 55–56°C (methanol); ^{1}H NMR: 1.1–1.8 (42H, m, CH_2 and CH_3), 2.22 (4H, t, J 7 Hz, CH_2), 4.02 (4H, q, J 7 Hz, CH_2O).

1,10-Decanediol (IV) and 1,22-docosanediol (V). Diester (**II**) (1.03 g, 4 mmol) or diester (**III**) 1.6 g, 3.7 mmol) was added to a stirred, ice-cooled suspen-



(**I**)

(a) n = 5; (b) n = 10; (c) n = 22

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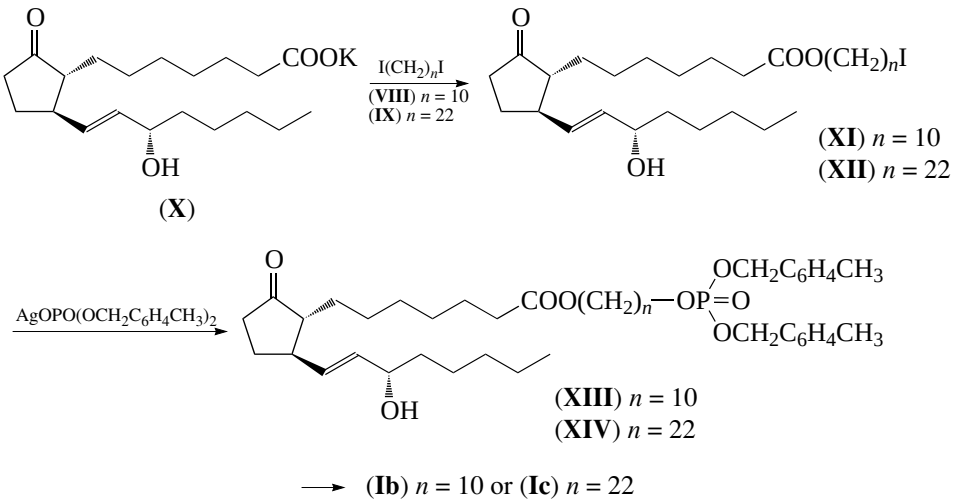

Scheme.

sion of lithium aluminum hydride (0.2 g, 5.26 mmol) in ether (20 ml). The mixture was refluxed for 1 h, cooled, treated with 10% ammonium chloride (2–3 ml), and evaporated to dryness. The dry residue was loaded into a Soxhlet apparatus, and glycol (**IV**) or (**V**) was extracted with benzene or toluene, respectively. After cooling, the respective crystals were precipitated from the benzene and toluene solutions:

Glycol (**IV**); 0.6 g (86%); mp 70–75°C (from benzene) (cf. lit. mp 72–75°C [2]).

Glycol (**V**); 1.2 g (86%); mp 104–105°C (from toluene) [3]); ^{1}H NMR: 1.0–1.7 (40H, m, CH_2), 3.55 (4H, t, *J* 6 Hz, OCH_2).

1,10-Dichlorodecane (VI) and 1,22-dichlorodocosane (VII). Thionyl chloride [0.6 ml for dichloride (**VI**) or 0.3 ml for dichloride (**VII**)] was added dropwise and stirred into a pyridine solution (0.16 ml) of diol (**IV**) (0.35 g, 2 mmol) or diol (**V**) (0.34 g, 1 mmol), respectively, cooled to 0°C, and the reaction mixture was kept for 1 h at room temperature. The mixture was then refluxed for 1 h, cooled, treated with water (2 ml), and extracted with ether. The extract was successively washed with water, sodium bicarbonate solution, and sodium chloride solution, dried with sodium sulfate, and evaporated to give dichloride (**VI**) (0.36 g, 83%) as a thick liquid; R_f 0.79; mp 15°C (cf. [4], mp 15.6°C), or dichloride (**VII**), (0.3 g, 87%), mp 63–64°C (acetone). ^{1}H NMR: 0.95–2.0 (40H, m, CH_2), 3.44 (4H, t, *J* 6 Hz, $ClCH_2$).

1,10-Diiododecane (VIII) and 1,22-diiododocosane (IX). A mixture of dichloride (**VI**) (0.36 g, 1.7 mmol) or dichloride (**VII**) (0.3 g, 0.8 mmol), acetone (10–20 ml), and sodium iodide (1 g) was heated in an autoclave at 125°C for 6–8 h. After cooling, the reaction mixture was diluted with ether, washed, and dried as described above. After evaporation, diiodide (**VIII**) (0.42 g, 62%) was obtained as a thick liquid, R_f 0.76, which was thickened and melted at 30°C (cf. lit. mp 30°C [5]), or diiodide (**IX**) (0.32 g, 71%), mp 66–68°C (acetone); ^{1}H NMR: 0.95–2.0 (40H, m, CH_2), 3.1 (4H, t, *J* 7 Hz, ICH_2).

11-Deoxyprostaglandin E_1 ω-iodo-*n*-decyl ester (XI) and ω-iodo-*n*-docosyl ester (XII). A solution of 11-deoxyprostaglandin E_1 (**X**) (0.34 g, 1 mmol) in 0.1 M potassium hydroxide (10 ml) in methanol was evaporated dry in a vacuum. The residue was dissolved in DMF (10–20 ml), and (**VIII**) (0.40 g, 1 mmol) or (**IX**) (0.56 g, 1 mmol) was added; the mixture was kept at room temperature for 1 day and evaporated. The residue was dissolved in ether, and the ether solution was washed, dried, and evaporated as described above. The residue was chromatographed on a silica gel column (20 g) to give a thick oily (**XI**); yield 0.3 g (50%); R_f 0.35; ^{1}H NMR: 0.81 (3H, t, *J* 7 Hz, CH_3), 1.0–2.4 (42H, m, CH_2 and CH), 3.1 (2H, t, *J* 7 Hz, ICH_2), 4.0 (3H, m, OCH_2 and H15), and 5.33 (2H, m, CH=CH) or a thick oily (**XII**); yield 0.31 g (40.4%); R_f 0.41; ^{1}H NMR: 0.81 (3H, t, *J* 7 Hz, CH_3), 1.0–2.4 (66H, m, CH_2 and CH), 3.1 (2H, t, *J* 7 Hz, ICH_2), 4.0 (3H, m, OCH_2 and H15), and 5.33 (2H, m, CH=CH).

11-Deoxyprostaglandin E_1 ω-hydroxy-*n*-decyl ester ω-di(*p*-methylbenzyl) phosphate (XIII) and ω-hydroxy-*n*-docosyl ester ω-di(*p*-methylbenzyl) phosphate (XIV). A mixture of (**XI**) (0.3 g, 0.5 mmol) or (**XII**) (0.31 g, 0.4 mmol) and silver salt of di(*p*-methylbenzyl) phosphate (0.2 g, 0.5 mmol) was refluxed in benzene (3–5 ml) for 5 h, cooled, and applied onto a silica gel column (20 g). After chromatography, phosphate (**XIII**) (0.15 g, 38%) was obtained as a thick, low mobile noncrystallizing oil; R_f 0.21; ^{1}H NMR: 0.81 (3H, t, *J* 7 Hz, CH_3), 1.0–2.4 (42H, m, CH_2 and CH), 3.8–4.1 (5H, m, OCH_2 and H15), 4.9 (4H, d, *J* 7.6 Hz,

$O\underline{CH_2}C_6H_4$), 5.50 (2H, m, CH=CH), and 7.01 (8H, m, C_6H_4). Phosphate (**XIV**) (0.13 g, 35%) was obtained as a thick, low mobile oil; R_f 0.23; ^{1}H NMR: 0.81 (3H, t, *J* 7 Hz, CH_3), 1.0–2.4 (66H, m, CH_2 and CH), 3.8–4.1 (5H, m, OCH_2 and H15), 4.93 (4H, d, *J* 7.6 Hz, $O\underline{CH_2}C_6H_4$), 5.50 (2H, m, CH=CH), and 7.01 (8H, m, C_6H_4).

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