

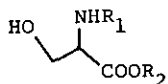
SYNTHESIS OF (+)-8-AZA-11-DEOXY-10-OXAPROSTAGLANDIN E<sub>1</sub>

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Abstract-----Synthesis of new oxazolidine prostanoids, racemic 8-aza-11-deoxy-10-oxaprostaglandin E<sub>1</sub>(10), starting from DL-serine(1) is described.

In recent years, chemical and biological interests have been developed in the synthesis of prostaglandin analogs, particularly heterocyclic prostaglandin analogs containing hetero-atoms in the five-membered ring.<sup>1</sup> Previously, we synthesized thiazolidine prostanoids, 8-aza-11-deoxy-10-thiaprostaglandin E<sub>1</sub> in both enantiomeric forms.<sup>2</sup> In this paper, we describe the synthesis of another type of the dihetero-analog, racemic 8-aza-11-deoxy-10-oxaprostaglandin E<sub>1</sub>(10) and the C-15 $\beta$  epimer(11), from DL-serine(1).

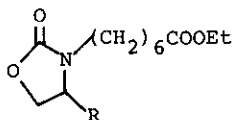
Hydrochloride of the amino ester(2), prepared from DL-serine(1), was treated with ethyl 7-oxoheptanoate<sup>3</sup> at pH 6, followed by catalytic hydrogenation, gave ethyl N-(6-ethoxycarbonylhexyl)-DL-serinate(3) in 50.5% yield. Subsequent cyclization of 3 with phosgene in toluene gave ethyl 7-(4-ethoxycarbonyl-2-oxo-3-oxazolidine)heptanoate(4) in 72.4% yield. Selective reduction of the ester function of the oxazolidine ring in 4 was achieved with sodium borohydride in ethanol, affording ethyl 7-(4-hydroxymethyl-2-oxo-3-oxazolidine)heptanoate(5) in 95.7% yield. The Pfitzner-Moffatt oxidation of 5 gave ethyl 7-(4-formyl-2-oxo-3-oxazolidine)heptanoate(6) in 73.8% yield, which on the Wittig reaction by means of dimethyl sodio-2-oxoheptylphosphonate in tetrahydrofuran gave ethyl 7-[4-(3-oxo-trans-1-octenyl)-2-oxo-3-oxazolidine]heptanoate(7). Reduction of 7 with sodium borohydride in ethanol gave a mixture of 8-aza-11-deoxy-10-oxaprostaglandin E<sub>1</sub> ethyl ester(8) and its C-15 epimer(9), which was separated by silica gel preparative plates to give the more polar isomer(8) and the less polar isomer(9) in 33.0% and 38.1% yield, respectively. The NMR spectra of 8 and 9 were essentially identical. Therefore, by analogy with the TLC behavior of previously



1,  $R_1=R_2=H$

2,  $R_1=H, R_2=Et$

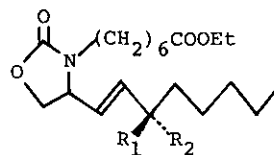
3,  $R_1=(CH_2)_6COOEt, R_2=Et$



4,  $R=COOEt$

5,  $R=CH_2OH$

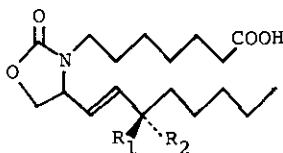
6,  $R=CHO$



7,  $R_1=R_2=O$

8,  $R_1=H, R_2=OH$

9,  $R_1=OH, R_2=H$



10,  $R_1=H, R_2=OH$

11,  $R_1=OH, R_2=H$

reported thiazolidine prostanoids,<sup>2</sup> 8 was tentatively assigned to the 15 $\alpha$ -hydroxy epimer and 9 to the 15 $\beta$ -hydroxy epimer. Hydrolysis of 8 with sodium hydroxide in aqueous ethanol gave 8-aza-11-deoxy-10-oxaprostaglandin E<sub>1</sub> (10) as crystals (mp 53-54°) in 98.7% yield. Similarly, hydrolysis of 9 gave the C-15 $\beta$  epimer (11) as semisolid (mp 56-58°) in 95.6% yield.

The oxazolidine prostanoids had moderate bronchodilatory and hypotensive activities in anesthetized dogs at a dose of  $5 \times 10^{-5}$  g/kg, whereas 10 and 11 accelerated rabbit platelet aggregation induced by ADP or collagen at  $1 \times 10^{-6}$  M. The details of pharmacological study are now under investigation.

#### EXPERIMENTAL SECTION

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a HITACHI 260-30 spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained with a HITACHI R-24B spectrometer in deuteriochloroform with Me<sub>4</sub>Si as an internal standard. Mass (MS) spectra were recorded on a Shimadzu LKB-9000 instrument.

Ethyl N-(6-Ethoxycarbonylhexyl)-DL-serinate (3) A solution of hydrochloride of 2 (18.10 g, 107 mmol) in EtOH (360 ml) was stirred with ethyl 7-oxoheptanoate (18.40 g, 107 mmol) and triethylamine (11.0 ml) at room temperature. After 0.5 h the reaction mixture was hydrogenated in the presence of 10% Pd/C

(2.0 g). In 2.5 h 1900 ml of hydrogen (25°, 760 mmHg) was absorbed. The insoluble precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the extract was washed with saturated NaHCO<sub>3</sub> and saturated NaCl, then dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent in vacuo left an oil, which was purified by silica gel column chromatography using a mixture of CHCl<sub>3</sub> and EtOH (10:1) as an eluent to give 3 (15.61 g, 50.5%) as a pale yellow oil: IR (neat) 3400, 1735, 1190 cm<sup>-1</sup>; NMR δ 1.24(3H, t), 1.28(3H, t), 1.4(8H, br), 2.29(2H, t), 2.60(2H, br), 2.69(2H, s, disappeared with D<sub>2</sub>O), 3.21-3.49(1H, m), 3.60-3.82(2H, m), 4.14(2H, q), 4.21(2H, q); MS m/e 289(M<sup>+</sup>), 216 (base peak). Anal. Calcd. for C<sub>14</sub>H<sub>27</sub>NO<sub>5</sub>: C, 58.11; H, 9.41; N, 4.84. Found: C, 57.71; H, 9.42; N, 4.69.

Ethyl 7-(4-Ethoxycarbonyl-2-oxo-3-oxazolidine)heptanoate(4) To a stirred solution of 3 (11.56 g, 40 m mol) and pyridine (6.32 g, 80 m mol) in toluene (120 ml) was added phosgene (4.50 g, 45 m mol) in toluene (40 ml) dropwise under ice-cooling. The mixture was stirred for 0.5 h at the same temperature and the insoluble precipitate was filtered off. The filtrate was washed with saturated NaCl and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent in vacuo left an oil, which was purified by silica gel column chromatography using a mixture of benzene and AcOEt (4:1) as an eluent to give 4 (9.12 g, 72.4%) as a pale yellow oil: IR (neat) 1760, 1735 (shoulder), 1205 cm<sup>-1</sup>; NMR δ 1.24(3H, t), 1.31(3H, t), 1.4(8H, br), 2.30(2H, t), 3.30(2H, m), 4.15(2H, q), 4.28(2H, q), 4.40(3H, br); MS m/e 315(M<sup>+</sup>), 196 (base peak). Anal. Calcd. for C<sub>15</sub>H<sub>25</sub>NO<sub>6</sub>: C, 57.13; H, 7.99; N, 4.44. Found: C, 56.86; H, 8.05; N, 4.44.

Ethyl 7-(4-Hydroxymethyl-2-oxo-3-oxazolidine)heptanoate(5) To a stirred solution of 4 (8.58 g, 27 m mol) in EtOH (250 ml) was added NaBH<sub>4</sub> (1.24 g, 33 m mol) in a small portion under ice-cooling. The mixture was stirred for 1.5 h at the same temperature and concentrated in vacuo. The residue was extracted with AcOEt and the extract was washed with saturated NaCl, then dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent in vacuo left practically pure oily 5 (7.12 g, 95.7%), which was used without further purification. Purification by silica gel preparative plates using a mixture of CHCl<sub>3</sub> and EtOH (10:1) as a solvent system, gave an analytically pure oil: IR (neat) 3430, 1750 (shoulder), 1730, 1260 cm<sup>-1</sup>; NMR δ 1.25(3H, t), 1.4(8H, br), 2.30(2H, t), 3.20(2H, m), 3.55(1H, s, disappeared with D<sub>2</sub>O), 3.63(2H, br), 3.95(1H, m), 4.13(2H, q), 4.31(2H, m); MS m/e 273(M<sup>+</sup>), 196 (base peak). Anal. Calcd. for C<sub>13</sub>H<sub>23</sub>NO<sub>5</sub>: C, 57.12; H, 8.48; N, 5.13. Found: C,

56.78; H, 8.55; N, 5.04.

Ethyl 7-(4-Formyl-2-oxo-3-oxazolidine)heptanoate(6) A mixture of 5 (5.46 g, 20 m mol), dicyclohexylcarbodiimide (12.38 g, 60 m mol), pyridine (1.62 ml, 20 m mol), trifluoroacetic acid (0.77 ml, 10 m mol), dimethyl sulfoxide (30 ml), and benzene (30 ml) was stirred for 14 h at room temperature. The insoluble precipitate was filtered off and the filtrate was washed with H<sub>2</sub>O and saturated NaCl, then dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent in vacuo left an oil, which was purified by silica gel column chromatography using a mixture of benzene and AcOEt (1:1) as an eluent to give 6 (4.00 g, 73.8%) as a colorless oil: IR (neat) 1750 (shoulder), 1730 cm<sup>-1</sup>; NMR  $\delta$  1.25(3H, t), 1.4(8H, br), 2.30(2H, t), 3.25(2H, br), 4.14(2H, q), 4.30(3H, br), 9.75(1H, s); MS m/e 271(M<sup>+</sup>), 196 (base peak). Anal. Calcd. for C<sub>13</sub>H<sub>21</sub>NO<sub>5</sub>: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.28; H, 8.09; N, 4.97.

Ethyl 7-[4-(3-Oxo-trans-1-octenyl)-2-oxo-3-oxazolidine]heptanoate(7) To a stirred suspension of 60% NaH (1.07 g, 26.8 m mol) in THF (200 ml) was added dimethyl 2-oxoheptylphosphonate (5.95 g, 26.8 m mol) in THF (200 ml) under ice-cooling and nitrogen atmosphere, and stirring was continued for 1 h at room temperature, additionally for 10 min at 50°. Then a solution of 6 (3.63 g, 13.4 m mol) in THF (50 ml) was added dropwise to the above mixture under ice-cooling, and stirring was continued for 1 h at room temperature under nitrogen atmosphere. The reaction mixture was concentrated in vacuo and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with saturated NaCl and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent in vacuo left an oil, which was purified by silica gel column chromatography using a mixture of benzene and AcOEt (9:1) as an eluent to give 7 (1.67 g, 34.0%) as a pale yellow oil: IR (neat) 1750, 1735 (shoulder), 1680, 1635 cm<sup>-1</sup>; NMR  $\delta$  0.90(3H, t), 1.24(3H, t), 1.4(14H, br), 2.29(2H, t), 2.60(2H, t), 3.20(2H, m), 4.00(1H, m), 4.12(2H, q), 4.40(2H, m), 6.27(1H, d, J=16 Hz), 6.69(1H, dd, J=16, 6 Hz); MS m/e 367(M<sup>+</sup>), 222 (base peak). Anal. Calcd. for C<sub>20</sub>H<sub>33</sub>NO<sub>5</sub>: C, 65.37; H, 9.05; N, 3.81. Found: C, 65.12; H, 9.08; N, 3.66.

8-Aza-11-deoxy-10-oxaprostaglandin E<sub>1</sub> Ethyl Ester(8) and Its C-15 Epimer(9) To a stirred solution of 7 (452 mg, 1.23 m mol) in EtOH (20 ml) was added NaBH<sub>4</sub> (56 mg, 1.48 m mol) under ice-cooling. The mixture was stirred for 40 min at the same temperature and quenched by addition of 10% HCl. Then the mixture was concentrated in vacuo and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with saturated NaCl and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent in vacuo

left an epimeric mixture of 8 and 9, which was separated on silica gel preparative plates, developing 3 times with a mixture of  $\text{CHCl}_3$  and EtOH (30 : 1), to give 8 (150 mg, 33.0%) as a colorless oil and 9 (173 mg, 38.1%) as a colorless oil, at the lower and upper bands, respectively. 8: IR (neat) 3450, 1750 (shoulder), 1735  $\text{cm}^{-1}$ ; NMR  $\delta$  0.90(3H, t), 1.25(3H, t), 1.4(16H, br), 2.29(1H, s, disappeared with  $\text{D}_2\text{O}$ ), 2.30(2H, t), 3.14(2H, m), 3.96(2H, m), 4.13(2H, q), 4.37(2H, m), 5.61-6.08 (2H, m); MS m/e 369( $\text{M}^+$ ), 172 (base peak). Anal. Calcd. for  $\text{C}_{20}\text{H}_{35}\text{NO}_5$ : C, 65.01; H, 9.55; N, 3.79. Found: C, 64.67; H, 9.60; N, 3.68. 9: IR (neat) 3450, 1750 (shoulder), 1735  $\text{cm}^{-1}$ ; NMR  $\delta$  0.90(3H, t), 1.25(3H, t), 1.4(16H, br), 2.30(2H, t), 2.62(1H, s, disappeared with  $\text{D}_2\text{O}$ ), 3.14(2H, m), 3.96(2H, m), 4.13(2H, q), 4.37(2H, m), 5.61-6.08(2H, m); MS m/e 369( $\text{M}^+$ ), 196 (base peak). Anal. Calcd. for  $\text{C}_{20}\text{H}_{35}\text{NO}_5$ : C, 65.01; H, 9.55; N, 3.79. Found: C, 64.85; H, 9.69; N, 3.68.

8-Aza-11-deoxy-10-oxaprostaglandin E<sub>1</sub>(10) and Its C-15 Epimer(11) To a stirred solution of 8 (140 mg, 0.38 m mol) in EtOH (3 ml) was added 2 N NaOH (0.3 ml, 0.6 m mol) under ice-cooling. The mixture was stirred for 2 h at room temperature and concentrated in vacuo. The residue was acidified with 10% HCl and extracted with AcOEt. The extract was washed with saturated NaCl and dried over  $\text{Na}_2\text{SO}_4$ . Removal of the solvent in vacuo left practically pure crystalline 10 (128 mg, 98.7%), which on recrystallized from a mixture of *n*-hexane and AcOEt gave analytically pure 10 as colorless needles: mp 53-54°; IR (KBr) 3600-2500, 1750 (shoulder), 1730  $\text{cm}^{-1}$ ; NMR  $\delta$  0.89(3H, t), 1.4(16H, br), 2.33(2H, t), 3.13(2H, m), 3.82-4.56(4H, m), 5.60-6.08(2H, m), 6.32(2H, s, disappeared with  $\text{D}_2\text{O}$ ); MS m/e 341 ( $\text{M}^+$ ), 252 (base peak). Anal. Calcd. for  $\text{C}_{18}\text{H}_{31}\text{NO}_5$ : C, 63.31; H, 9.15; N, 4.10. Found: C, 63.25; H, 9.19; N, 4.06.

Similarly, hydrolysis of 9 (170 mg, 0.46 m mol) in EtOH (3.7 ml) with 2N NaOH (0.37 ml, 0.74 m mol) gave an oil, which was purified by silica gel preparative plates using a mixture of  $\text{CHCl}_3$  and EtOH (10 : 1) as a solvent system, gave 11 (150 mg, 95.6%) as a colorless semisolid: mp 56-58°; IR (KBr) 3600-2500, 1750 (shoulder), 1730  $\text{cm}^{-1}$ ; NMR  $\delta$  0.90(3H, t), 1.4(16H, br), 2.33(2H, t), 3.13(2H, m), 3.82-4.56(4H, m), 5.60-6.08(2H, m), 5.98(2H, s, disappeared with  $\text{D}_2\text{O}$ ); MS m/e 341( $\text{M}^+$ ), 196 (base peak). Anal. Calcd. for  $\text{C}_{18}\text{H}_{31}\text{NO}_5$ : C, 63.31; H, 9.15; N, 4.10. Found: C, 63.55; H, 9.37; N, 3.92.

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