SYNTHESIS OF (±)-8-AZA-11-DEOXY-10-OXAPROSTAGLANDIN E_1

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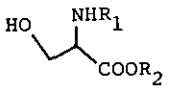
Abstract-----Synthesis of new oxazolidine prostanoids, racemic 8-aza-11-deoxy-10-oxaprostaglandin E_1(10), starting from DL-serine(1) is described.

In recent years, chemical and biological interests have beed developed in the synthesis of prostaglandin analogs, particularly heterocyclic prostaglandin analogs containing hetero-atoms in the five-membered ring.[1] Previously, we synthesized thiazolidine prostanoids, 8-aza-11-deoxy-10-thiaprostaglandin E_1 in both enantiomeric forms.[2] In this paper, we describe the synthesis of another type of the dihetero-analog, racemic 8-aza-11-deoxy-10-oxaprostaglandin E_1(10) and the C-15β epimer(11), from DL-serine(1).

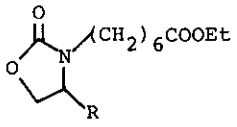
Hydrochloride of the amino ester(2), prepared from DL-serine(1), was treated with ethyl 7-oxoheptanoate[3] at pH 6, followed by catalytic hydrogenation, gave ethyl N-(6-ethoxycarbonylhexyl)-DL-serinate(3) in 50.5% yield. Subsequent cyclization of 3 with phosgene in toluene gave ethyl 7-(4-ethoxycarbonyl-2-oxo-3-oxazolidine)heptanoate(4) 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_1 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, $R_1=H$, $R_2=Et$

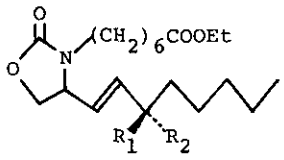
3, $R_1=(CH_2)_6COOEt$, $R_2=Et$



4, R=COOEt

5, $R=CH_2OH$

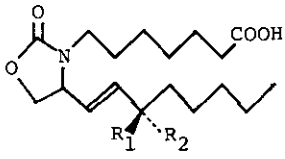
6, R=CHO



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,[2] 8 was tentatively assigned to the 15α-hydroxy epimer and 9 to the 15β-hydroxy epimer. Hydrolysis of 8 with sodium hydroxide in aqueous ethanol gave 8-aza-11-deoxy-10-oxaprostaglandin E_1(10) as crystals (mp 53 -54°) in 98.7% yield. Similarly, hydrolysis of 9 gave the C-15β 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 5×10^{-5} g/kg, whereas 10 and 11 accelerated rabbit platelet aggregation induced by ADP or collagen at 1×10^{-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_4Si 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 m mol) in EtOH (360 ml) was stirred with ethyl 7-oxoheptanoate (18.40 g, 107 m mol) 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_2Cl_2 and the extract was washed with saturated $NaHCO_3$ and saturated NaCl, then dried over Na_2SO_4. Removal of the solvent in vacuo left an oil, which was purified by silica gel column chromatography using a mixture of $CHCl_3$ 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^{-1}; 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_2O), 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^+), 216 (base peak). Anal. Calcd. for $C_{14}H_{27}NO_5$: 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_2SO_4. 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^{-1}; 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^+), 196 (base peak). Anal. Calcd. for $C_{15}H_{25}NO_6$: 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 $NaBH_4$ (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_2SO_4. 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 $CHCl_3$ and EtOH (10 : 1) as a solvent system, gave an analytically pure oil: IR (neat) 3430, 1750 (shoulder), 1730, 1260 cm^{-1}; 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_2O), 3.63(2H, br), 3.95(1H, m), 4.13(2H, q), 4.31(2H, m); MS m/e 273(M^+), 196 (base peak). Anal. Calcd. for $C_{13}H_{23}NO_5$: 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_2O and saturated NaCl, then dried over Na_2SO_4. 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^{-1}; NMR δ 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^+), 196 (base peak). Anal. Calcd. for $C_{13}H_{21}NO_5$: 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_2Cl_2. The extract was washed with saturated NaCl and dried over Na_2SO_4. 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^{-1}; NMR δ 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^+), 222 (base peak). Anal. Calcd. for $C_{20}H_{33}NO_5$: 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_1 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 $NaBH_4$ (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_2Cl_2. The extract was washed with saturated NaCl and dried over Na_2SO_4. 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 $CHCl_3$ 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 cm^{-1}; NMR δ 0.90(3H, t), 1.25(3H, t), 1.4(16H, br), 2.29(1H, s, disappeared with D_2O), 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(M^+), 172 (base peak). Anal. Calcd. for $C_{20}H_{35}NO_5$: 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 cm^{-1}; NMR δ 0.90(3H, t), 1.25(3H, t), 1.4(16H, br), 2.30(2H, t), 2.62(1H, s, disappeared with D_2O), 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(M^+), 196 (base peak). Anal. Calcd. for $C_{20}H_{35}NO_5$: 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_1(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 Na_2SO_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 cm^{-1}; NMR δ 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 D_2O); MS m/e 341 (M^+), 252 (base peak). Anal. Calcd. for $C_{18}H_{31}NO_5$: 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 $CHCl_3$ 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 cm^{-1}; NMR δ 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 D_2O); MS m/e 341(M^+), 196 (base peak). Anal. Calcd. for $C_{18}H_{31}NO_5$: C, 63.31; H, 9.15; N, 4.10. Found: C, 63.55; H, 9.37; N, 3.92.

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