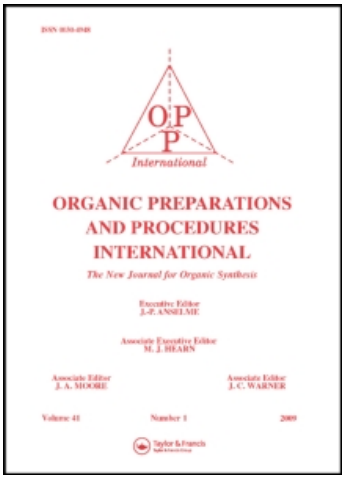

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SYNTHESIS OF 8-AZA-8,12-SECOPROSTAGLANDIN E_2

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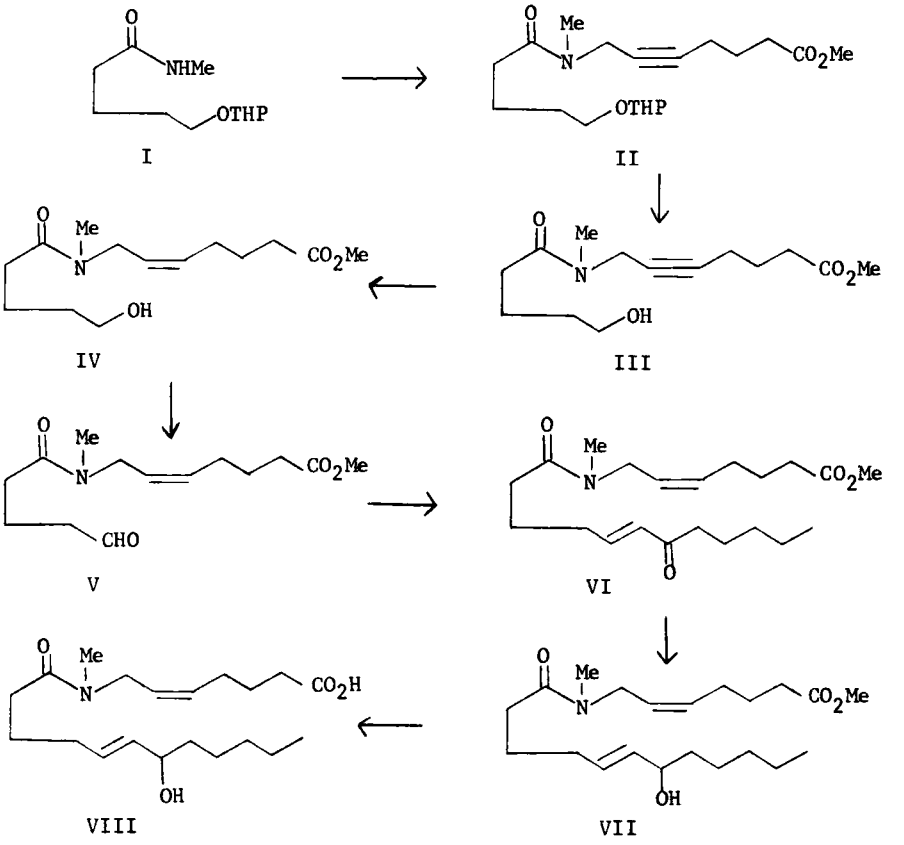
The synthesis of 8-aza-PGE_2 has been reported.[1] Recently, we described the synthesis and the antisecretory properties of 8-aza and 8-oxa-8,12-secoprostaglandin E_1.[2,3] Since 8-aza-PGE_2 has been shown to possess prostaglandin like activity, we were interested in synthesizing the 8-aza-8,12-seco-PGE_2 analog VIII to determine if this compound would possess agonistic properties or act as a prostaglandin antagonist.

Alkylation of the sodium salt of I[2] with methyl 7-bromo-5-heptynoate in THF gave II in 46% yield. Removal of the protecting group in II was effected with methanol in the presence of a catalytic amount of p-toluenesulfonic acid to afford an 84% yield of III after chromatography. Reduction of III with 5% Pd-$BaSO_4$ in methanol with H_2 in the presence of quinoline gave the cis-olefin IV in 93% yield. Oxidation of IV with Collins reagent[4] at 0^o in CH_2Cl_2 and subsequent chromatography on silica gel afforded a 55% yield of aldehyde V. Reaction of V with the lithium salt of dimethyl (2-oxoheptyl)phosphonate gave enone VI (78%) which was reduced in 88% yield to VII with $NaBH_4$ in methanol at -23^o. Saponification of VII and subsequent chromatography gave VIII in 75% yield.

A procedure based on Lippmann's[5] was used to assess the influence of VIII on inhibiting gastric acid secretion in the rat. Compound VIII was shown to be approximately ½ as active as PGE_1 in decreasing the volume of

gastric acid secretion and 1/3 as active as PGE_1 in decreasing total acid. Compound VIII did not display any antihypertensive activity in the rat as determined by Grollman's procedure.[6]



EXPERIMENTAL

Methyl 7-[N-methyl-5-(tetrahydro-2H-pyran-2-yl) oxypentanamido]hept-5-ynoate (II).- The tetrahydropyranyl amide I[2] (5.99 g, 0.279 mol) in 50 ml of THF was added to a 50% suspension of NaH (1.34 g, 0.0279 mol) suspended in 75 ml of dried THF over a 15 min. period. The reaction mixture was stirred at room temperature for 1.5 hr. Methyl 5-heptynoate (6.11 g, 0.0279 mol) in 25 ml of THF was added and the reaction mixture was refluxed for 40 hr. The reaction mixture was cooled and concentrated in vacuo. The residue was poured into brine and extracted with CH_2Cl_2. The

organic solution was washed with brine, dried (Na_2SO_4) and concentrated in vacuo to afford an oil. The oil was chromatographed on silica gel G and elution with ether-hexane solutions and ether gave 4.5 g (66%) of II, NMR (CCl_4) δ 1.05-2.05 (m, 12H), 2.10-2.57 (m, 6H), 2.96 and 3.10 (s, 3H, NCH_3), 3.20-4.16 (m) and 3.68 (s) [9H] and 4.59 (s, br, 1H); ir (neat) 1740 and 1650 cm^{-1}.

Anal. Calcd for $C_{19}H_{31}NO_5$: C, 64.57; H, 8.84; N, 3.96.

Found: C, 64.42; H, 8.65; N, 3.98.

Methyl 7-(N-methyl-5-hydroxypentanamido)hept-5-ynoate (III).- A solution of II (4.5 g, 0.0128 mol) and p-toluenesulfonic acid (200 mg) in 35 ml of MeOH was stirred at room temperature for 3 hr. Solid $NaHCO_3$ (1.0 g) was added and stirring was continued for 15 min. The reaction mixture was filtered with suction. The residue was washed with MeOH and the filtrate concentrated in vacuo. The residue was dissolved in 250 ml of CH_2Cl_2 and the organic solution was washed with 10% $NaHCO_3$ (50 ml), brine (50 ml), dried ($MgSO_4$) and concentrated in vacuo to afford an oil. The oil was chromatographed on silica gel G and elution with methanol-ether solutions afforded 2.9 g (84%) of III, NMR ($CDCl_3$) δ 1.20-2.08 (m, 6H), 2.06-2.63 (m, 6H), 2.98 and 3.10 (s, 3H, NCH_3), 3.70 (s) and 3.90-4.85 (m) [5H] and 4.16 (m, br, 2H); ir (neat) 3435 (br), 1740 and 1645 cm^{-1}.

Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20.

Found: C, 62.49; H, 8.59; N, 5.22.

(Z)-Methyl 7-(N-methyl-5-hydroxypentanamido)hept-5-enoate (IV).- To a solution of III (3.41 g, 0.0127 mol) in 27 ml of MeOH was added 5% Pd-$BaSO_4$ (220 mg) and quinoline (160 mg). The resulting reaction mixture was reduced with H_2 at 1 atm. at room temperature. After one equivalent of H_2 was absorbed, the reaction mixture was filtered with suction and the residue was washed with CH_2Cl_2. The solvent was removed in vacuo to afford

3.2 g (93%) of crude IV which was used directly in the Collins oxidation reaction. Chromatography of a sample of crude IV on silica gel G and elution with ether-hexane solutions and ether afforded pure IV, NMR ($CDCl_3$) δ 1.43-1.97 (m, 6H), 2.0-2.52 (m, 6H), 2.59 (s, 1H, OH), 2.90 and 2.94 (s, 3H, NCH_3), 3.50-3.77 (m) and 3.69 (s) [5H], 3.99 (t, 2H) and 5.09-5.75 (m, 2H); ir (neat) 3425 (br), 1740 and 1645 cm^{-1}.

Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16.

Found: C, 62.17; H, 9.40; N, 5.07.

(Z)-Methyl 7-(N-methyl-4-formylbutanamido)hept-5-enoate (V). - To a solution of IV (2.2 g, 0.0081 mol) in 300 ml of CH_2Cl_2, cooled to 0° and under N_2, was added Collins reagent [$CrO_3 \cdot 2py$ (18.3 g, 0.071 mol)] in 200 ml of CH_2Cl_2 and the reaction mixture was stirred at 0° for 1.5 hr. Powdered $NaHSO_4 \cdot H_2O$ (36.5 g) was added all at once and stirring at 0° was continued for an additional 30 min. The reaction solution was decanted and the residue washed with CH_2Cl_2. The organic solutions were combined and washed with two 200 ml portions of 10% HCl, 200 ml of H_2O, two 350 ml portions of 10% $NaHCO_3$ and two 200 ml portions of brine, dried ($MgSO_4$) and concentrated in vacuo to afford 1.7 g of an oil. The oil was chromatographed on silica gel G and elution with ether-hexane solutions gave 1.2 g (55%) of the aldehyde V, NMR (CCl_4) δ 1.20-2.70 (m, 14H), 2.85 and 2.93 (s, 3H, NCH_3), 3.76 (s, 3H), 3.75-4.07 (m, 2H), 5.0-5.80 (m, 2H) and 9.96 (s, br, 1H). The aldehyde was not characterized further, but submitted directly to the Wadsworth-Emmons reaction.

Methyl 7-(N-methyl-7-oxo-5E-dodecenamido)hept-5Z-enoate (VI).- A hexane solution of 2.29 M n-Buli (1.7 ml, 0.00389 mol) was added with a syringe to dimethyl (2-oxoheptyl)phosphonate (865 mg, 0.00389 mol) in 35 ml of THF under N_2 at 0° and the reaction mixture was stirred at 0° for 25 min. Then a solution of V (1.1 g, 0.00410 mol) in 35 ml of THF was added all at

once and stirring at 0° was continued for 2.5 hr. The reaction mixture was diluted with ice-water and extracted with three 250 ml portions of CH_2Cl_2. The organic solutions were combined, washed with 50 ml of brine, dried ($MgSO_4$) and concentrated in vacuo to afford an oil. The oil was chromatographed on silica gel G and elution with ether-hexane solutions gave 1.1 g (78%) of enone VI, NMR (CCl_4) δ 0.98 (t, distorted) and 1.09-2.55 (m) [21H], 2.87 and 2.95 (s, 3H, NCH_3), 3.67 (s, 3H), 3.80-4.05 (m, 2H), 5.05-5.86 (m, 2H), 6.06 (d, 1H, $J_{13,14}$ = 16.1 Hz) and 6.96 and 6.70 (t, 1H, $J_{12,13}$ = 6.7 Hz, $J_{13,14}$ = 16.1 Hz); ir (neat) 1745, 1700 (shoulder) and 1650 (br.) cm^{-1}.

Anal. Calcd for $C_{21}H_{35}NO_4$: C, 69.01; H, 9.65; N, 3.83.
Found: C, 69.10; H, 9.51; N, 3.72.

Methyl 7-(N-methyl-7-hydroxy-5E-dodecenamido)hept-5Z-enoate (VII).- $NaBH_4$ (365 mg, 0.00961 mol) was cooled to -23° under N_2 and dry MeOH was added to obtain a clear solution. The enone VI (850 mg, 0.00233 mol) in 25 ml of MeOH was added all at once and the reaction mixture was stirred at -23° for 5 hr. The reaction mixture was diluted with 150 ml of brine and extracted with three 350 ml portions of CH_2Cl_2. The organic extracts were combined, washed with 100 ml of brine, dried ($MgSO_4$) and concentrated in vacuo to afford an oil. The oil was chromatographed on silica gel G and elution with ether-hexane solutions gave 750 mg (88%) of VII, NMR ($CDCl_3$) δ 0.90 (t, distorted, 3H), 1.10-2.59 (m, 21H), 2.92 (s, 3H), 3.69 (s, 3H), 3.70-4.25 (m, 3H), and 5.17-5.90 (m, 4H); ir (neat) 3424, 1730 and 1635 cm^{-1}.

Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81.
Found: C, 68.13; H, 9.89; N, 3.69.

7-(N-Methyl-7-hydroxy-5E-dodecenamido)hept-5Z-enoate (VIII).- A solution of VII (900 mg, 0.00245 mol), MeOH (20 ml), NaOH (125 mg, 0.00313 mol) and

H_2O (4 ml) was stirred at room temperature for 20 hr. The reaction was diluted with 10% $NaHCO_3$ (40 ml) and extracted with ether. The aqueous solution was cooled, acidified with conc. HCl and extracted with three 200 ml portions of CH_2Cl_2. The combined organic solution was washed with 100 ml of brine, dried ($MgSO_4$) and concentrated in vacuo to afford an oil. The oil was chromatographed on silica gel G and elution with ether-hexane solutions and ether gave 650 mg (75%) of VIII, NMR ($CDCl_3$) δ 0.90 (t, distorted, 3H), 1.10-2.65 (m, 20H), 2.91 and 2.95 (s, 3H, NCH_3), 3.80-4.30 (m, 3H), 5.10-5.97 (m, 4H) and 6.55 (s, br., 2H, CO_2H and OH); on addition of D_2O the resonance peak at 6.55 δ disappeared; ir (neat), 3400 (br.), 1725 and 1620 (br.) cm^{-1}.

Anal. Calcd for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96.

Found: C, 67.53; H, 9.88; N, 3.93.

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† Undergraduate Research Participant.

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