of control) − (mean diameter of experimental)]/(mean diameter of control) × 100. The average mean score of the control animals for 72 experiments was 17.7 mm. Statistical analysis by Student's t test showed an inhibition of the PCA reaction of greater than 35% to be statistically significant at $p \leq 0.05$.

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Synthesis and Gastric Antisecretory Properties of an 8-Aza- and a 10-Oxa-8,12-secoprostaglandin

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The synthesis and gastric antisecretory properties of two novel 8,12-secoprostaglandin analogues, 8-aza-8,12-secoprostaglandin E_1 and methyl 10-oxa-8,12-secoprostaglandin E_1, are reported.

Recently the synthesis of 11,12-secoprostaglandins[2] and the synthesis of eicosatrienoic acid analogues[3] have been reported. Herein we describe the synthesis and the gastric antisecretory properties of two novel 8,12-secoprostaglandin analogues, 8-aza-8,12-secoprostaglandin E_1 (**9**) and methyl 10-oxa-8,12-secoprostaglandin E_1 (**14**).

Chemistry. Reaction of δ-valerolactone **1** with methylamine (Scheme I) afforded the alcohol amide **2**. Treatment of **2** with dihydropyran in the presence of an acid yielded the tetrahydropyranylamide **3**. Alkylation of the sodium salt of **3** with methyl 7-bromoheptanoate gave the tetrahydropyranyl ester **4**. Cleavage of the protecting group of **4** was smoothly accomplished with methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid, affording the alcohol ester **5**. Oxidation of **5** with Collins reagent[4] (Scheme II) gave the aldehyde **6**. Reaction of **6** with the lithium salt of dimethyl (2-oxoheptyl)-phosphonate afforded the enone **7**. Hydride reduction of **7** and subsequent hydrolysis of the alcohol ester **8** yielded the alcohol acid **9**.

Reaction of 1,3-propanediol (**10**) with 8-(methoxycarbonyloctanoyl) chloride (Scheme III) in the presence of pyridine gave the ester alcohol **11**. Oxidation of **11** with Collins reagent[4] afforded the aldehyde **12**. Reaction of **12** with the lithium salt of dimethyl (2-oxoheptyl)phosphonate yielded the enone **13**. Reduction of **13** with a methanolic sodium borohydride solution afforded the alcohol ester **14**.

Biological Activity. Compounds **8**, **9**, and **14** were found to be active in inhibiting gastric acid secretion. The procedure based on that of Lippmann[5] was used to assess the influence of the seco analogues on gastric acid secretion. These results are summarized in Table I.

Scheme I

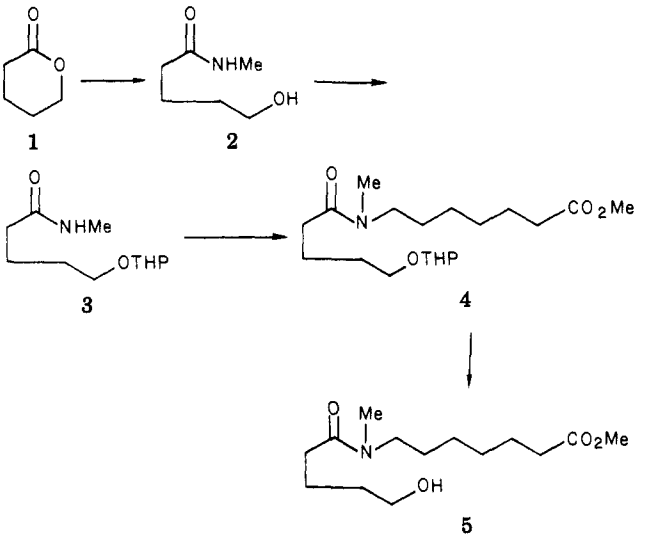

Table I. Effect on Gastric Acid Secretion in Rats[a]

	% change	
	volume	total acid
8	−21	−32
9	−25	−25
14	−25	−34
$PGF_{2\alpha}$	−37	−42
PGE_1	−74	−96

[a] Test dose, 3 mg/kg sc.

Experimental Section

NMR spectra were recorded on a Joelco Model C6OHL spectrometer at 60 MHz with Me_4Si as an internal standard. IR spectra were recorded on a Perkin-Elmer Model 337 spectrometer. Where the analyses are represented by symbols only, the values were found within ±0.4% of the theoretical values.

***N*-Methyl-5-hydroxypentanamide (2).** Methylamine gas was passed slowly into δ-valerolactone (15 g, 0.15 mol) in 60 mL of dry THF under N_2 at 20 °C. After a pH of 9 was obtained, the reaction mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo and the resulting oil was heated [40 °C (0.1 mm)] for 1.5 h to afford 20 g (100%) of **2**: bp 130–135

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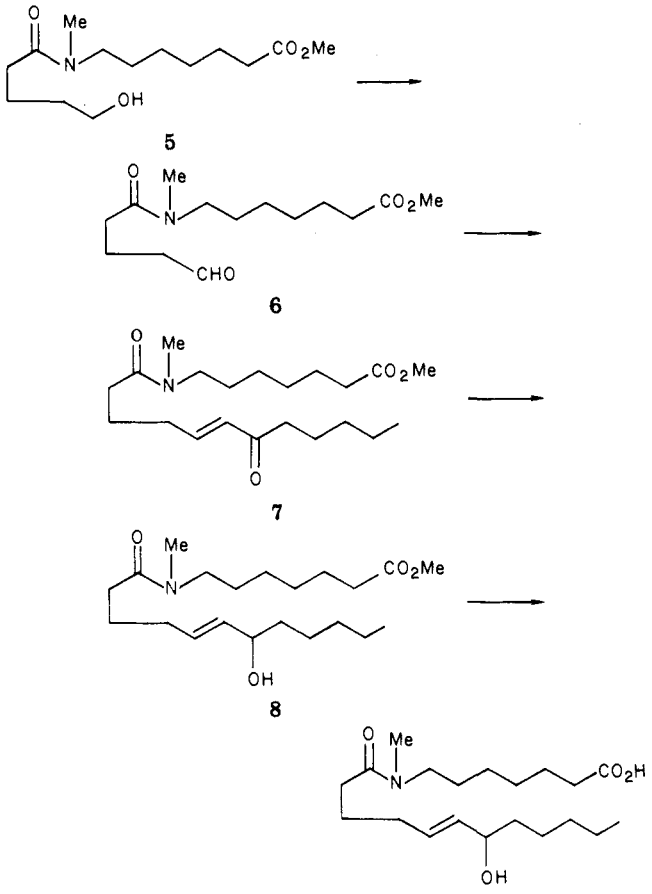
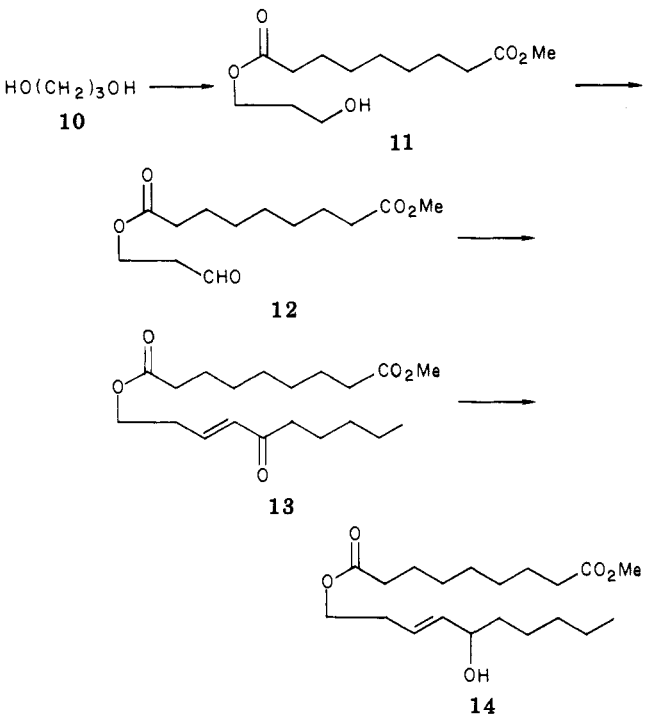
Scheme II



Scheme III



°C (0.015 mm); IR (film) 3350 (br) and 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.25–2.0 (m) and 2.02–2.42 (t, distorted) (6 H), 2.72 and 2.79 (s, 3 H, NCH_3), 3.30–3.95 (t, distorted, 3 H), 4.09–4.62 (s, br, 1 H), and 6.80–7.45 (s, br, 1 H). Anal. ($C_6H_{13}NO_2$) C, H, N.

***N*-Methyl-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]pentanamide (3).** To the amide alcohol **2** (15.1 g, 0.115 mol) and dihydropyran (11.5 g, 0.137 mol) in 125 mL of CH_2Cl_2 was added 11 drops of concentrated HCl. The reaction mixture was stirred at room temperature for 2.5 h, diluted with 100 mL of CH_2Cl_2, and extracted with 10% $NaHCO_3$ and brine. The organic solution was dried (Na_2SO_4) and concentrated in vacuo. Distillation of the oil gave 25 g (100%) of **3**: bp 146 °C (0.05 mm); IR (film) 1660 cm^{-1}; NMR (CCl_4) δ 1.10–2.45 (m, 12 H), 2.71–2.77 (s, 3 H, NCH_3), 3.06–4.10 (m, 4 H), 4.52 (s, 1 H), and 7.70–8.21 (s, br, 1 H). Anal. ($C_{11}H_{21}NO_3$) C, H, N.

Methyl 7-[*N*-Methyl-4-[(tetrahydro-2*H*-pyran-2-yl)-oxy]pentanamido]heptanoate (4). The tetrahydropyranylamide **3** (6.0 g, 0.0279 mol) in 10 mL of THF was added dropwise to a suspension of NaH (1.34 g, 0.0279 mol) in 50 mL of THF under N_2. The reaction mixture was stirred at room temperature for 2 h, refluxed for 30 min, and then cooled to room temperature. Methyl 7-bromoheptanoate (6.22 g, 0.0279 mol) in 10 mL of THF was added, and the reaction mixture was refluxed for 84 h. The solvent was removed in vacuo and the residue diluted with CH_2Cl_2 and extracted with 2% $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Chromatography of the oil on silica gel afforded 6.3 g (63%) of **4**: IR (film) 1740 and 1660 cm^{-1}; NMR (CCl_4) δ 1.0–1.95 (m, 18 H), 2.0–2.49 (m, 4 H), 2.81 and 2.94 (s, 3 H, NCH_3), 3.05–4.11 (m) and 3.58 (s) (9 H), and 4.48 (s, 1 H). Anal. ($C_{19}H_{35}NO_5$) C, H, N.

Methyl 7-(*N*-Methyl-5-hydroxypentanamido)heptanoate (5). *p*-Toluenesulfonic acid (829 mg) was added to the tetrahydropyranyl ester **4** (12.6 g, 0.0352 mol) in 200 mL of MeOH. The reaction mixture was stirred at 40 °C for 4 h. Solid $NaHCO_3$ (1.1 g) was added and stirring was continued for 30 min. The solvent was removed in vacuo and the residue dissolved in CH_2Cl_2. The organic solution was extracted with brine, dried ($MgSO_4$), and concentrated in vacuo. Chromatography on silica gel gave 7.0 g (73%) of **5**: IR (film) 3400 (br), 1735, and 1630 cm^{-1}; NMR (CCl_4) δ 1.05–1.95 (m, 12 H), 2.0–2.46 (m, 4 H), 2.81 and 2.94 (s, 3 H, NCH_3), 3.07–3.72 (m) and 3.62 (s) (7 H), and 4.17 (s, br, 1 H). Anal. ($C_{14}H_{27}NO_4$) C, H, N.

Methyl 7-(*N*-Methyl-4-formylbutanamido)heptanoate (6). Collins reagent[4] (46 g, 0.178 mol) in 500 mL of CH_2Cl_2 was added to the ester alcohol **5** (5.9 g, 0.0216 mol) in 1 L of CH_2Cl_2 at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 1.7 h. Powdered $NaHSO_4 \cdot H_2O$ (102 g) was added and stirring at 0 °C was continued for 20 min. The reaction solution was decanted and the residue washed with CH_2Cl_2. The organic solution was washed with 10% HCl, H_2O, 10% $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo. Chromatography of the oil on silica gel afforded 4.1 g (70%) of **6**: IR (film) 1745 and 1650 cm^{-1}; NMR (CCl_4) δ 1.05–2.74 (m, 16 H), 2.87 and 2.99 (s, 3 H, NCH_3), 3.10–3.56 (t, distorted, 2 H), 3.64 (s, 3 H), and 9.68 (s, 1 H). The aldehyde was not characterized further but subjected to the Wadsworth–Emmons reaction.

(*E*)-Methyl 7-(*N*-Methyl-7-oxo-5-dodecenamido)heptanoate (7). A hexane solution of 2.29 M *n*-BuLi (5.66 mL, 0.01297 mol) was added with a syringe to dimethyl (2-oxoheptyl)-phosphonate (2.88 g, 0.01297 mol) in 75 mL of THF under N_2 at 0 °C, and the reaction mixture was stirred for 15 min. The aldehyde **6** (3.7 g, 0.01365 mol) in 25 mL of THF was added and stirring at 0 °C was continued for 4 h. The reaction mixture was diluted with brine and extracted with CH_2Cl_2. The organic solution was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Chromatography of the oil gave 3.5 g (70%) of **7**: IR (film) 1745 and 1650 cm^{-1}; NMR (CCl_4) δ 0.95 (t) and 1.10–2.04 (m) (19 H), 2.06–2.68 (m, 8 H), 3.04 and 3.92 (s, 3 H, NCH_3), 3.15–3.52 (t, distorted, 2 H), 3.69 (s, 3 H), 6.15 (d, $J_{13,14}$ = 16.5 Hz, 1 H), and 6.83 and 7.10 (t, $J_{13,14}$ = 16.5 Hz, $J_{12,13}$ = 7.5 Hz, 1 H). Anal. ($C_{21}H_{37}NO_4$) C, H, N.

(*E*)-Methyl 7-(*N*-Methyl-7-hydroxy-5-dodecenamido)-heptanoate (8). $NaBH_4$ (746 mg, 0.0196 mol) was cooled to −23 °C under N_2 and dry MeOH was added to obtain a clear solution. The enone **7** (2.4 g, 0.00654 mol) in 25 mL of MeOH was added and stirring was continued at −23 °C for 4 h. The reaction mixture was diluted with brine (400 mL) and extracted with CH_2Cl_2. The organic solution was extracted with brine, dried ($MgSO_4$), and concentrated in vacuo. Chromatography of the oil on silica gel gave 2.2 g (91%) of **8**: IR (film) 3425 (br), 1730, and 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (t, 3 H), 1.07–2.55 (m, 24 H), 2.90 and 2.96 (s, NCH_3), 3.08–3.60 (m), 3.68 (s, OCH_3) and 3.85–4.22 (m) (10 H), and 5.47–5.70 (m, 2 H). Anal. ($C_{21}H_{39}NO_4$) C, H, N.

(*E*)-7-(*N*-Methyl-6-hydroxy-4-dodecenamido)heptanoic Acid (9). A solution of the ester alcohol 8 (1.2 g, 0.00325 mol), MeOH (14 mL), NaOH (260 mg, 0.0065 mol), and H_2O (6 mL) was stirred at room temperature for 23.5 h. The reaction mixture was diluted with H_2O, extracted with CH_2Cl_2, acidified, and then extracted with CH_2Cl_2. The organic solution was extracted with H_2O, dried ($MgSO_4$), and concentrated in vacuo. Chromatography on silica gel gave 900 mg (78%) of **9**: IR (film) 3400 (br), 1725, and 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.10–2.55 (m, 24 H), 2.92 and 2.98 (s, 3 H, NCH_3), 3.04–4.35 (m, 3 H), 5.50–5.80 (m, 2 H), and 6.63 (s, br, 2 H, CO_2H and OH). On addition of D_2O, the resonance peak at δ 6.63 disappeared. Anal. ($C_{20}H_{37}NO_4$) C, H, N.

3-Hydroxypropyl 8-Methoxycarbonyloctanoate (11). 8-(Methoxycarbonyl)octanoyl chloride (11.1 g, 0.05 mol) in 15 mL of CH_2Cl_2 was added over 1.5 h to a solution of 1,3-propanediol (**10**) (15.2 g, 0.20 mol) and pyridine (7.9 g, 0.10 mol) in 350 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 16.5 h and extracted with 10% HCl and brine. The organic solution was dried ($MgSO_4$) and concentrated in vacuo. Distillation afforded 9.4 g (72%) of **11**: bp 132–142 °C (0.08 mm); IR (film) 3490 (br) and 1740 cm^{-1}; NMR (CCl_4) δ 1.12–2.01 (m, 12 H), 2.07–2.90 (m, 5 H), 3.32–3.83 (m) and 3.64 (s) (5 H), and 4.03 (t, 2 H). Anal. ($C_{13}H_{24}O_5$) C, H.

2-Formylethyl 8-Methoxycarbonyloctanoate (12). Collins reagent[4] (30.1 g, 0.117 mol) was added to the ester alcohol **11** (5.3 g, 0.0204 mol) in 1.5 L of CH_2Cl_2 at 0 °C under N_2. Stirring was continued for 1 h at 0 °C. Processing was carried out as described for **5**. Thus there was obtained 3.4 g (65%) of **12**: IR (film) 1740 and 1715 cm^{-1}; NMR (CCl_4) δ 1.14–2.06 (m, 10 H), 2.12–2.60 (m, 4 H), 2.73 and 2.76 (t, 2 H), 3.64 (s, 3 H), 4.40 (t, 2 H), and 9.90 (s, 1 H).

(*E*)-5-Oxo-3-decenyl 8-Methoxycarbonyloctanoate (13). A hexane solution of 2.29 M *n*-BuLi (6.3 mL, 0.0145 mol) was added to dimethyl (2-oxoheptyl)phosphonate (3.2 g, 0.0145 mol) in 70 mL of THF at 0 °C under N_2. The reaction mixture was stirred for 15 min at 0 °C. The aldehyde **12** (3.6 g, 0.0140 mol) in 20 mL of THF was added and stirring at 0 °C was continued for 1.5 h. Processing was carried out as described for **6**. Thus there was obtained 3.4 g (69%) of **13**: IR (film) 1740, 1700, 1675 (d), and 1635 cm^{-1}; NMR (CCl_4) δ 0.94 (t, 3 H), 1.09–1.90 (m, 19 H), 1.94–2.77 (m, 8 H), 3.62 (s, 3 H), 4.15 (t, 2 H), 6.05 (d, $J_{13,14}$ = 15.8 Hz, 1 H), and 6.68 (sextet, $J_{12,13}$ = 6.8 Hz, $J_{13,14}$ = 15.8 Hz, 1 H). Anal. ($C_{20}H_{34}O_5$) C, H.

(*E*)-5-Hydroxy-3-decenyl 8-Methoxycarbonyloctanoate (14). The enone **13** (1.9 g, 0.00537 mol) in 20 mL of MeOH was added over a 15-min period to a solution of $NaBH_4$ (0.407 g, 0.0107 mol) in MeOH at −40 °C under N_2, and stirring was continued at −40 °C for 3.5 h. The reaction mixture was diluted with Et_2O and general processing and chromatography on silica gel afforded 1.6 g (84%) of **14**: IR (film) 3500 (br) and 1740 cm^{-1}; NMR (CCl_4) δ 0.91 (t) and 1.07–1.09 (m) (21 H), 2.0–2.54 (m, 6 H), 2.80 (s, br, 1 H), 3.63 (s, 3 H), 3.77–4.32 (m) and 4.06 (t) (3 H), and 5.05–5.85 (m, 2 H). Anal. ($C_{20}H_{36}O_5$) C, H.

Rat Gastric Secretion Assay. Male rats, 160–210 g, were randomly divided into groups of six animals each and fasted for 48 h previous to the experiment, water being available ad libitum during this period. Animals were anesthetized with ether, the abdomen was opened through a midline incision, and the pylorus was ligated. Test compounds were diluted from stock solutions so as to administer a dose of 1.5 mg/kg in a volume equivalent to 1 mL/kg. Subcutaneous injections were applied immediately after surgery and again 2.0 h later, so that a total dose of 3 mg/kg was administered. Dilutions were made with a phosphate buffer (pH 7.4) as recommended by Lee and co-workers,[6] in order to ensure adequate stability of the drugs at the subcutaneous depot. Each compound was tested in six rats; an additional control group received only the vehicle. Four hours after pyloric ligation the animals were killed with ether, the cardiacs were ligated, and the stomach was removed. The volume of gastric secretion was measured and the contents centrifuged at 5000 rpm for 10 min. Total acid in the supernatant was titrated against 0.1 N NaOH solution at pH 7.0 and the amount expressed in milliequivalents.

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