Monoester of Tetraethylene Glycol (I). This product was prepared by adding to the above solution Fluka tetraethylene glycol (31 g, 0.16 mol). The reaction mixture was left at 60 °C for 48 h in a thermostatic bath, then it was washed with water (2 × 50 mL), aqueous 0.1 N HCl (2 × 50 mL), water (2 × 50 mL), aqueous 0.1 N NaOH (2 × 50 mL), and water (2 × 50 mL), dried (anhydrous Na_2SO_4), filtered, and evaporated to dryness in vacuo. The product was then purified by extracting the residue with *n*-heptane (~250 mL) and drying to constant weight at 30 °C (0.1 mmHg): yield 14.8 g (80%). The product failed to crystallize. It could be distilled with some decomposition at 180–185 °C (0.01 mm).

Diesters of Poly(oxyethylene) of Molecular Weight 1000 and 2000 (II and III). Product II was prepared by adding to the above imidazolide solution Fluka poly(oxyethylene), M_r 1000 (19.2 g, 0.019 mol), and by following the same procedure as in the case of I: yield 19.8 g (75%). The product failed to crystallize. Product III was similarly prepared with Fluka poly(oxyethylene), M_r 2000 (38.4 g, 0.019 mol). The product was finally purified by dissolving in a small amount of chloroform and diluting with 5 volumes of a *n*-heptane/ether (2:1) mixture. The precipitate was filtered and dried to constant weight at 20 °C (0.1 mmHg): yield 40.10 g (88%); mp 25–30 °C.

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Azaprostaglandin Analogues. Synthesis and Biological Properties of 11-Azaprostaglandin Derivatives

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New nitrogen analogues of prostaglandins (**11**, **11a**, **12**, and **12a**) have been synthesized starting from a 4,5-disubstituted 2-pyrrolidinone nucleus (**5** and **5a**) containing one side chain and a suitable functionality for elaborating the second one. These analogues had no better activity than natural prostaglandins in vitro [guinea pig ileum and trachea, rat stomach fundus strip, uterus and portal vein, ADP-induced guinea pig platelet-rich plasma (PRP) aggregation]. They similarly lacked any interesting activity in vivo [anesthetized rat blood pressure, stress, and acetylsalycilic acid (ASA) induced gastric lesions in rat].

In the last few years, in the light of experience in the steroid field,[1] a multitude of prostaglandin analogues in which carbon atoms of the cyclopentane ring are substituted for hetero atoms have been synthesized, in the hope of obtaining interesting biological properties. Several laboratories have directed their attention toward the synthesis of γ-lactam analogues, and 8-aza, 9-aza, 10-aza, 11-aza, 12-aza, and 8,12-diaza analogues of the 11-deoxy-PGE_1 and PGE_2 series have been reported.[2]

As part of our continuing interest[3-5] in nitrogen analogues of prostaglandins, this paper reports the synthesis and biological behavior of new 11-azaprostaglandin analogues (**11**, **12**, **11a**, and **12a**).

Chemistry. The synthetic approach to the title compounds involves construction of a 4,5-disubstituted 2-pyrrolidinone nucleus containing an intact α-C_7 side chain and a suitable function for elaborating the second one. The key intermediate, **5**, was secured by two alternative pathways starting from the readily available diester **1**.[6] The ethoxide-ion catalyzed Michael addition of **1** with diethyl acetamidomalonate[7] proceeded with concomitant cyclization, giving a good yield of the disubstituted pyrrolidinone **2**. Stereoselective one-step decarboethoxylation of the geminal diester **2** was accomplished by heating in wet Me_2SO containing NaCl[8] to give **3** as sole product. The assigned trans disposition of the two side chains was based on the chemical shift of the C_{12} H and the vicinal coupling constant $J_{8,12}$ which is 5 Hz in full accord with the literature.[9] Compound **3b** was prepared starting from **1**, through the alternative sequence shown in Scheme I. Treatment of **3** and **3b** with an aqueous–methanolic potassium carbonate solution proceeded with hydrolysis of the more hindered ester with the probable assistance of the lactam moiety, as recently suggested for similar compounds,[10] affording the acid **5** which was reduced, by the mixed carboxylic–carbonic anhydride method,[11] with

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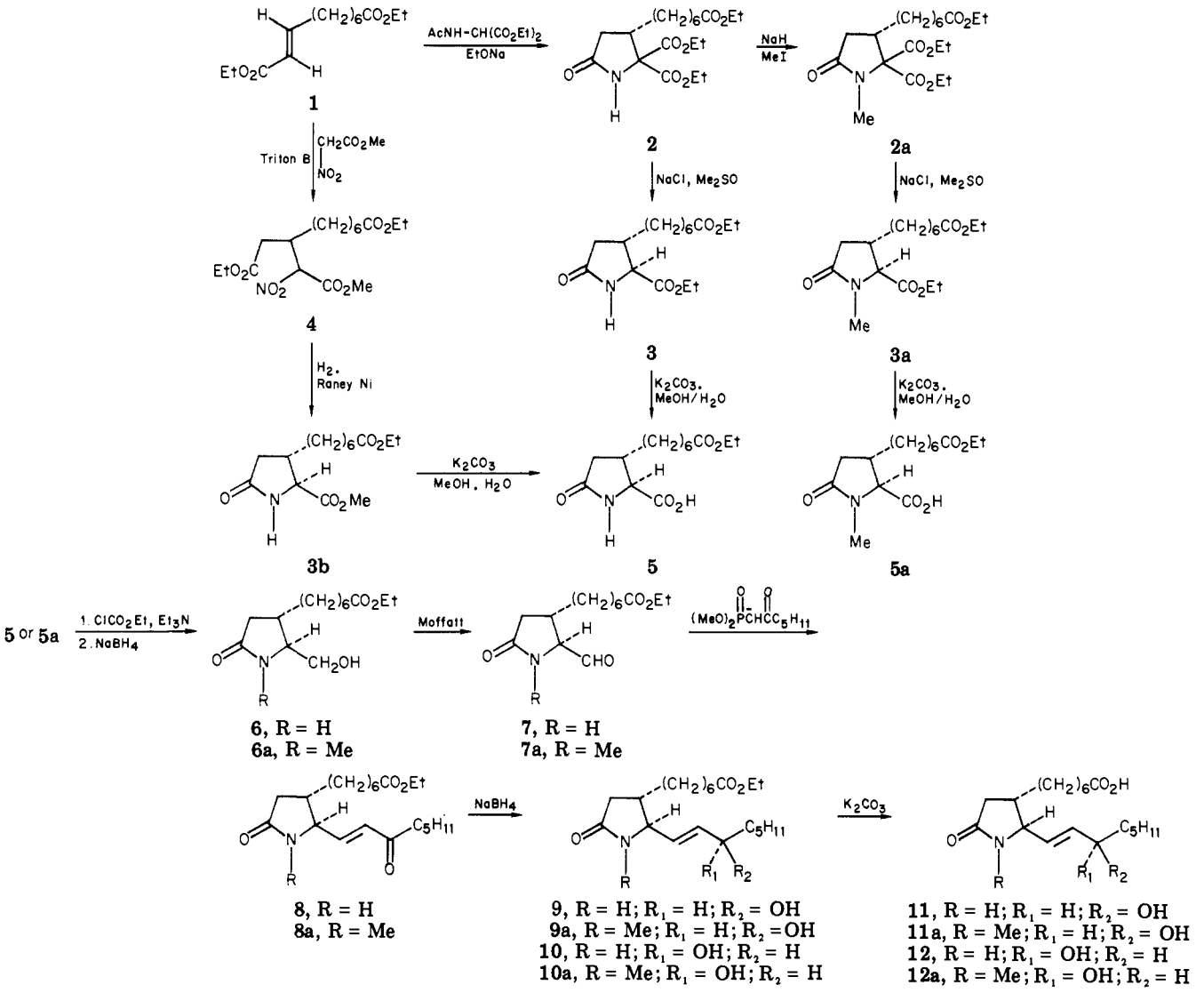
Scheme I



$NaBH_4$ to the primary alcohol **6**. Oxidation of **6** to the corresponding aldehyde **7** proved to be the crucial step. Better yields were obtained with the Moffatt oxidation procedure (Me_2SO, DCC, trifluoroacetic acid, pyridine, benzene),[12] the others being mainly destructive. The crude aldehyde **7** was converted to the enone **8** by reaction with the sodium salt of dimethyl 2-oxoheptylphosphonate in THF.[13] Reduction of **8** with sodium borohydride gave a 1:1 mixture of C_{15}-epimeric alcohols, which was separated by chromatography on silica gel into the more polar isomer **9** and the less polar **10**.[14] Saponification of the two ester-alcohols with methanolic potassium carbonate and subsequent acidification yielded the analogues **11** and **12** as white crystalline solids.

The corresponding *N*-methyl derivatives **11a** and **12a** were readily prepared by the same reaction sequence starting from **2a** obtained by alkylation of **2** with methyl iodide in the presence of sodium hydride in DMF. The better overall yield of this sequence is clearly accounted for by the protection of the amide function, particularly in the oxidation step.

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Results and Discussion

The 11-aza derivatives **11**, **11a**, **12**, **12a** in vitro had virtually no contracting activity on guinea pig ileum and rat stomach strip; they did not antagonize PGE_2- and $PGF_{2\alpha}$-induced contractions in the guinea pig ileum.

At concentrations from 2 to 8 × 10^{-6} g/mL they stimulated the rat uterus very little, showing about a hundredth and a thousandth the potency of PGE_2 and $PGF_{2\alpha}$, respectively. They always contracted guinea pig tracheal chain at concentrations from 1 to 4 × 10^{-6} g/mL in comparison to 1 to 4 × 10^{-7} g/mL for $PGF_{2\alpha}$ showing a $PGF_{2\alpha}$-like pattern, whereas PGE_2 induced relaxation. The derivatives enhanced rhythmic contractions and tone of rat portal vein at concentrations from 2 × 10^{-6} to 1 × 10^{-5} g/mL and were unable to inhibit ADP-induced aggregation in guinea pig PRP at 250 ng/mL. These derivatives showed a certain degree of antiulcer activity, being 30–60 times less potent than PGE_2 in protecting against gastric ulcers induced by stress or by ASA. In anesthetized rats these 11-aza analogues induced dose-dependent hypotension with 13–15 times less potency than PGE_2, with the exception of compound **11** which had a potency ratio of 0.13 (fiducial limits for $p = 0.95$, 0.10–0.17).

In conclusion, it can be inferred from these results that replacement of the normally functionalized five-membered ring of the PGs with a 2-pyrrolidinone nucleus did not result in any improvement in biological activities in com-

parison with natural prostaglandins, at least under our experimental conditions.

Experimental Section

Melting points (Tottoli apparatus) are uncorrected. ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R24 spectrometer using Me_4Si as internal standard. IR spectra were determined on a Perkin-Elmer Model 257; where analyses are indicated by symbols, values were within ±0.4% of the calculated ones. Thin-layer chromatography (TLC) was carried out on Merck precoated silica gel 60 F_{254} plates.

Pharmacology. Guinea pig (400–500 g) ileum[15] and trachea[16] and rat (250 g) portal vein,[17] uterus,[18] and stomach[19] were used. Tone variations were isotonically recorded by an isotonic transducer connected to a four-channel recorder Watanabe.

Antiaggregating activity of the 11-aza derivatives, at the final concentration of 250 ng/mL, was tested on guinea pig (350 g) PRP (platelet-rich plasma)[20] using ADP (0.4 μg/mL) as aggregating agent.

Rats (130–150 g) were subjected to restraint and cold according to a modification of the method of Takagi and Okabe[21] or given ASA (acetylsalycilic acid) (100 mg/kg orally)[22] 15 min after administration of the test compounds. Gastric ulcers were scored 1 h after stress and 2 h after ASA according to Osterloh.[23]

PGE_2 (800 μg/kg) and the four 11-aza derivatives were injected sc at a dose of 800 μg/kg immediately before stress and 2000 μg/kg 15 min before ASA in a volume of 0.2 mL/100 g of body weight.

Pressure recordings from rats (240 g), anesthetized with pentobarbital sodium (40 mg/kg ip), were made using a Statham pressure transducer connected to a four-channel Hewlett Packard polygraph.

The drugs to be compared with standard PGE_2 were tested with at least two doses, chosen in order to obtain good centering, i.e., a nonsignificant difference between preparations.[24] When a drug was inactive, the dose was raised to a maximum of 20 μg/kg iv. Six animals were used for each dose. The potency ratio for each drug was statistically analyzed by analysis of covariance for a parallel line biological assay.[24]

PGE_2 and compounds 11, 11a, 12, and 12a dissolved in ethanol and stored at −20 °C were salified at the moment of use with 0.0019 M Na_2CO_3 (0.9 mL/1 mg of PG) and further diluted with saline; $PGF_{2\alpha}$ was diluted from the ethanolic stock solution at the moment of use with Tris buffer, pH 7.8. Noradrenaline bitartrate (Prodotti Gianni) and phenoxybenzamine hydrochloride (S.K.F.) were dissolved in distilled water.

Chemistry. Ethyl 5,5-Dicarbethoxy-2-oxo-4-pyrrolidineheptanoate (2). A mixture of diethyl acetamidomalonate (10.59 g, 48 mmol), diester 1 (11.7 g, 46 mmol), in anhydrous EtOH (140 mL) containing sodium (0.4 g, 17 mmol) was refluxed for 10 h. The cooled solution was concentrated in vacuo and H_2O (10 mL) was added. The oily product which separated was taken up in benzene (2 × 50 mL) and dried. The benzene extract was concentrated to about half its original volume, petroleum ether (20 mL) was added, and the mixture cooled at 0 °C. The precipitated solid was collected by filtration and dried to give 14 g (83%) of **2**: mp 75 °C; IR (KBr) 3200, 1755, 1740, 1708 cm^{-1}; NMR ($CDCl_3$) 1.25 (t, 3 H, J = 7 Hz), 1.3 (t, 6 H, J = 7 Hz), 4.13 (q, 2 H, J = 7 Hz), 4.25 (q, 4 H, J = 7 Hz), 7.41 ppm (s, 1 H). Anal. ($C_{19}H_{31}O_7N$) C, H, N.

Ethyl 5-Carbethoxy-2-oxo-4-pyrrolidineheptanoate (3). A mixture of the triester **2** (2.97 g, 8 mmol), NaCl (0.47 g, 8 mmol), and water (0.38 g, 16 mmol) in Me_2SO (20 mL) was refluxed for 2 h, diluted with H_2O (40 mL), and extracted with Et_2O. Evaporation of the washed (H_2O) and dried Et_2O extracts gave the diester **3** (2 g, 83%) as a colorless oil: IR ($CHCl_3$) 3320, 1740, 1720, 1690 cm^{-1}; NMR ($CDCl_3$) 1.2–1.4 (m, 6 H), 3.92 (d, 1 H, J = 4.5 Hz), 4–4.3 (m, 4 H), 7.4 ppm (br s, 1 H). Anal. ($C_{16}H_{27}O_5N$) C, H, N.

Ethyl 5-Carboxy-2-oxo-4-pyrrolidineheptanoate (5). The diester **3** (1 g, 3.5 mmol) in 95% EtOH (4 mL) was treated with K_2CO_3 (0.9 g, 6 mmol) in H_2O (12 mL) and held at room temperature for 6 h. Most of the solvents were evaporated in vacuo, and the mixture was acidified with dilute HCl, extracted with $CHCl_3$ (4 × 10 mL), and dried ($MgSO_4$). The usual workup left the half-ester **5** (0.6 g, 65%) as a solid: mp 99–100 °C (THF/hexane 1:3); IR ($CHCl_3$) 3300, 1725, 1670 cm^{-1}; NMR ($CDCl_3$) 1.25 (t, 3 H, J = 7 Hz), 3.85 (d, 1 H, J = 4.5 Hz), 4.2 (q, 2 H, J = 7 Hz), 7.3 (s, 1 H), 10.9 ppm (s, 1 H). Anal. ($C_{14}H_{23}O_5N$) C, H, N.

Ethyl 5-(Hydroxymethyl)-2-oxo-4-pyrrolidineheptanoate (6). Ethyl chloroformate (0.2 mL, 2 mmol) was added slowly at −10 °C to a stirred solution of the half-ester **5** (0.54 g, 1.9 mmol) and triethylamine (0.2 mL, 2 mmol) in THF (15 mL). Stirring was continued for 30 min at 0 °C, after which triethylammonium chloride was filtered and washed with THF (5 mL). The filtrate was added to $NaBH_4$ (0.2 g, 5 mmol) in H_2O (5 mL) at 0 °C and the reaction mixture was stirred for 4 h at room temperature. The mixture was cooled, and the excess of $NaBH_4$ was decomposed with dilute HCl and then extracted with $CHCl_3$ (4 × 15 mL). The extract was washed with $NaHCO_3$ solution and brine, dried, and concentrated in vacuo to provide 0.38 g (75%) of the alcohol **6**: mp 55–56 °C; IR (Nujol) 1740, 1680 cm^{-1}. Anal. ($C_{14}H_{25}O_4N$) C, H, N.

Ethyl 5-Formyl-2-oxo-4-pyrrolidineheptanoate (7). A mixture of the alcohol **6** (1.3 g, 4.3 mmol), N,N'-dicyclohexylcarbodiimide (2.96 g, 14 mmol), trifluoroacetic acid (0.43 mL), pyrrolidine (0.79 mL), Me_2SO (8.6 mL), and benzene (20 mL) was stirred for 18 h. After addition of Et_2O (25 mL), oxalic acid (1.26 g, 14 mmol) in CH_3OH (3 mL) was added carefully. The mixture was stirred for 1 h, then water was added, and the precipitated dicyclohexylurea was filtered. The organic layer was washed with $NaHCO_3$ solution and brine and dried, and the solvent was evaporated in vacuo to give the crude aldehyde **7**, which was used without further purification in the next step (0.9 g): NMR ($CDCl_3$) 9.6 ppm (d, 1 H, J = 2 Hz).

Ethyl 5-(3-Oxo-*trans*-1-octenyl)-2-oxo-4-pyrrolidineheptanoate (8). Dimethyl 2-oxoheptylphosphonate (1 g, 4.4 mmol) was dissolved in dry THF (35 mL) and treated with NaH (50% oil; 0.13 g, 5.4 mmol) at 0 °C for 10 min and then for 1 h at room temperature. A solution of the crude **7** (0.9 g) in THF (5 mL) was added dropwise with stirring at 0 °C and left to warm at room temperature. After 3 h the mixture was poured into ice–water and extracted with Et_2O (3 × 25 mL). The Et_2O solution was dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified on a silica gel column (eluent $Et_2O/CHCl_3$, 1:1), giving **8** as an oil (0.6 g, 34% from **6**): IR ($CHCl_3$) 3340, 1730, 1695, 1640, 980 cm^{-1}; NMR ($CDCl_3$) 0.9 (t, 3 H, J = 5.8 Hz), 1.25 (t, 3 H, J = 7 Hz), 3.81 (m, 1 H), 4.15 (q, 2 H, J = 7 Hz), 6.27 (d, 1 H, J = 16 Hz), 6.75 (dd, 1 H, J = 16 and 6 Hz), 7.15 ppm (br s, 1 H).

Ethyl 5-(3-Hydroxy-*trans*-1-octenyl)-2-oxo-4-pyrrolidineheptanoate (9 and 10). To a stirred solution of **8** (0.6 g, 1.6 mmol) in EtOH (5 mL) was added solid $NaBH_4$ (0.5 g, 13 mmol) portionwise at 0 °C. After 1 h, the mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 15 mL), and the ethereal extract was washed with brine, dried ($MgSO_4$), and evaporated in vacuo to provide 0.55 g (91%) of the epimeric alcohols **9** and **10**, which were separated by column chromatography on silica gel (eluent $CHCl_3$/benzene/MeOH, 17:1:0.1) to give 0.2 g of **9** and 0.3 g of **10** with similar spectroscopic properties: IR ($CHCl_3$) 3340, 1730, 1690, 980 cm^{-1}; NMR ($CDCl_3$) 5.7 ppm (m, 2 H).

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5-(3-Hydroxy-*trans*-1-octenyl)-2-oxo-4-pyrrolidineheptanoic Acid (11 and 12). The hydroxy ester **9** (0.2 g, 5.4 mmol) in 95% EtOH (10 mL) was refluxed with 15 mL of an aqueous 10% solution of K_2CO_3 for 1 h. The solution was concentrated in vacuo, diluted with H_2O (5 mL), acidified with 2 N HCl, and extracted with $CHCl_3$ (4 × 15 mL). After the solution was dried, the solvent was removed in vacuo to give 0.14 g (76%) of **11** as a solid: mp 104–105 °C (after crystallization from THF/hexane, 1:5); IR ($CHCl_3$) 3340, 1700, 975 cm^{-1}. Anal. ($C_{19}H_{33}O_4N$) C, H, N. Saponification of **10** gave the acid **12** as a solid: mp 84–85 °C (65%); spectroscopic properties similar to **11**. Anal. ($C_{19}H_{33}O_4N$) C, H, N.

Ethyl 5,5-Dicarbethoxy-1-methyl-2-oxo-4-pyrrolidineheptanoate (2a). To NaH (50% oil, washed with hexane; 0.52 g, 10 mmol) in DMF (30 mL) was added a solution of **2** (3.71 g, 9 mmol) in DMF (10 mL) at 0 °C under nitrogen. After the solution was stirred at 50 °C for 1 h, CH_3I (8 g, 56 mmol) was added and the mixture was heated at 50 °C for 48 h. After the solvent was evaporated in vacuo, water was added to the residue and the precipitated oil was extracted with Et_2O (4 × 15 mL). The extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give an oil, which was purified by distillation at 0.01 mmHg to give 3.1 g (80%) of **2a**: bp 120–125 °C; IR (neat) 1735, 1680 cm^{-1}. Anal. ($C_{20}H_{33}O_7N$) C, H, N.

Ethyl 5-Carbethoxy-1-methyl-2-oxo-4-pyrrolidineheptanoate (3a). Decarboethoxylation of **2a** (2.5 g, 6.25 mmol) was carried out as described for **2**. After the usual workup, **3a** was obtained in an 84% yield after distillation at 0.01 mmHg: bp 130 °C; IR (film) 1735, 1690 cm^{-1}. Anal. ($C_{17}H_{29}O_5N$) C, H, N.

Ethyl 5-Carboxy-1-methyl-2-oxo-4-pyrrolidineheptanoate (5a). Partial hydrolysis of the diester **3a** (2.1 g, 6 mmol) according to the procedure described for **3**, gave 1.2 g (66%) of **5a** as a white solid: mp 72–73 °C (THF/hexane, 1:4); IR (Nujol) 1740, 1700 cm^{-1}. Anal. ($C_{15}H_{25}O_5N$) C, H, N.

Ethyl 5-(Hydroxymethyl)-1-methyl-2-oxo-4-pyrrolidineheptanoate (6a). Selective $NaBH_4$ reduction of the carboxy group of the half-ester **5a** was performed following the procedure described for **5**. The alcohol **6a** was obtained as an oil in a 75% yield: IR (neat) 3450, 1740, 1700 cm^{-1}. Anal. ($C_{15}H_{27}O_4N$) C, H, N.

Ethyl 5-Formyl-1-methyl-2-oxo-4-pyrrolidineheptanoate (7a). Moffatt oxidation of the alcohol **6a** (0.75 g, 2.6 mmol) according to the procedure described for **6** gave 0.52 g (69%) of the crude aldehyde **7a**, which was used without further purification in the next step: NMR ($CDCl_3$) 9.62 ppm (d, 1 H, J = 2.9 Hz).

Ethyl 1-Methyl-5-(3-oxo-*trans*-1-octenyl)-2-oxo-4-pyrrolidineheptanoate (8a). This compound, prepared analogously to **8** by Horner reaction of dimethyl 2-oxoheptylphosphonate (0.44 g, 1.8 mmol), NaH (50% oil; 0.054 g, 2.2 mmol), and the crude aldehyde **7a**, was obtained in a 73% yield after column chromatography on silica gel (eluent $Et_2O/CHCl_3$, 1:1) as an oil: IR ($CHCl_3$) 1735, 1685, 1640, 980 cm^{-1}; NMR ($CDCl_3$) 0.9 (t, 3 H, J = 5 Hz), 1.28 (t, 3 H, J = 7.4 Hz), 2.8 (s, 3 H), 3.65–3.85 (m, 1 H), 4.15 (q, 2 H, J = 7.4 Hz), 6.25 (d, 1 H, J = 16 Hz), 6.55 ppm (dd, 1 H, J = 8 Hz).

Ethyl 5-(3-Hydroxy-*trans*-1-octenyl)-1-methyl-2-oxo-4-pyrrolidineheptanoate (9a and 10a). Reduction of the enone **8a** (0.4 g, 1 mmol) with $NaBH_4$ (0.3 g, 8 mmol) as described for **9** and **10** gave a mixture of the epimeric alcohols **9a** and **10a**, which were separated by column chromatography on silica gel (eluent $CHCl_3$/benzene/MeOH, 17:1:0.1) to provide 0.13 g of **9a** and 0.2 g of **10a**, with similar IR and NMR data: IR ($CHCl_3$) 3340, 1730, 1685, 975 cm^{-1}.

5-(3-Hydroxy-*trans*-1-octenyl)-1-methyl-2-oxo-4-pyrrolidineheptanoic Acid (11a and 12a). Both epimeric alcohols **9a** and **10a** were transformed into the corresponding acids **11a** and **12a**. Hydrolysis was carried out as described for **9** and **10**, giving rise quantitatively to the acid **11a**, mp 152–153 °C (THF/hexane, 1:2), and **12a**, mp 70–72 °C (THF/hexane, 1:2) with similar spectroscopic properties: IR ($CHCl_3$) 3400, 1710, 1685, 975 cm^{-1}. Anal. ($C_{20}H_{35}O_4N$) C, H, N.

Diethyl 3-(Carbethoxymethyl)-2-nitrodecanedioate (4). A solution of methyl nitroacetate (4.4 g, 37 mmol), α,β-unsaturated diester **1** (4.5 g, 20 mmol), and methanolic Triton B (10 mL) was heated at 60 °C for 24 h. Water (40 mL) was added, the mixture was neutralized with CH_3CO_2H, extracted with EtOAc (5 × 20 mL), and dried ($MgSO_4$), and the solvent was removed. The residue was distilled at 100 °C (0.01 mm) to give **4** (4.2 g, 68%) as a pale yellow oil: IR (neat) 1760, 1730, 1560 cm^{-1}; NMR ($CDCl_3$) 1.22 (m, 6 H), 3.82 (s, 3 H), 4.15 (m, 4 H), 5.45 (d, 1 H, J = 7 Hz). Anal. ($C_{17}H_{29}O_8N$) C, H, N.

Ethyl 5-Carbomethoxy-2-oxo-4-pyrrolidineheptanoate (3b). A solution of **4** (2.1 g, 5.6 mmol) in EtOH was hydrogenated in the presence of Raney Nickel at 50 atm at room temperature for 8 h. The catalyst was filtered off and the solvent removed in vacuo. TLC (SiO_2; Et_2O/petroleum ether, 1:1) showed a mixture of cyclized product **3b** and some uncyclized material.

The latter was readily transformed into **3b** by heating in benzene solution for 1 h. The benzene solution was filtered through a pad of Florisil. Removal of the solvent left the diester **3b** (1.2 g, 75%), which was hydrolyzed to **5** as described for the diester **3**.

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Approaches to Vasodilating/β-Adrenergic Blocking Agents: Examples of the Dihydrolutidine Type

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The aminohydroxypropoxy moiety has been incorporated into the dihydrolutidine class of vasodilators. In the spontaneously hypertensive rat, one of these, (*S*)-4-[2-methyl-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]-3,5-dicarboethoxy-1,4-dihydrolutidine (**4c**), exhibited antihypertensive activity on the order of the standard 4-[2-(trifluoromethyl)phenyl]-3,5-dicarboethoxy-1,4-dihydrolutidine (**2a**). This antihypertensive activity could not be explained in terms of a vasodilating effect, as determined in the dog. In this latter model, **2a** decreased both mean arterial and hindlimb perfusion pressures.

Peripheral vascular resistance is abnormally high in most patients with essential hypertension. Although direct-acting peripheral vasodilator drugs lower resistance, these agents produce side effects which are a consequence of their action, i.e., reflex cardiac stimulation due to baroreceptor activation. This reflex response then limits the fall in pressure by causing vasoconstriction, tachycardia, and an increase in cardiac output. It has been found that

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