Prostaglandin Isosteres. 1. (8-Aza-, 8,10-Diaza-, and 8-Aza-11-thia)-9-oxoprostanoic Acids and Their Derivatives

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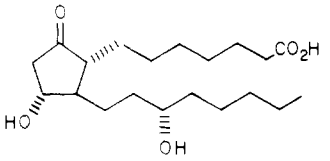
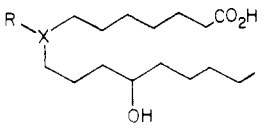
A series of novel (8-aza-, 8,10-diaza-, and 8-aza-11-thia)-9-oxoprostanoic acids has been synthesized and evaluated for their ability to mimic the E series prostaglandins in stimulating cAMP formation in the mouse ovary and in binding to the rat kidney plasma membrane prostaglandin receptor. 7-[2-(3-Hydroxyoctyl)-1,1,4-trioxo-3-thiazolidinyl]heptanoic acid markedly stimulates cAMP formation at reasonable pharmacological concentrations and avidly binds to the rat kidney prostaglandin receptor.

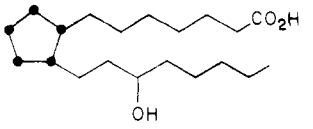
Recent publications from these laboratories have described the syntheses of novel 11,12-secoprostaglandins[1] and certain of their aza[2,4] and thia[3] isosteres typified by Ia–e which display prostaglandin-like activity, improved metabolic stability, oral efficacy, and tissue specificity. In this paper, we wish to describe a second class of PG analogues based upon isosteric substitution[5] of one or more PG ring carbon(s) and, where appropriate, the pendent oxygen function. This approach appeared to be especially attractive since the target PG isosteres, typified by structures 1, were expected to be more amenable to synthesis and are stereochemically less complex than the corresponding natural products. The synthesis and biological evaluation of a series of (8-aza-, 8,10-diaza-, and 8-aza-11-thia)-9-oxoprostanoic acids are the subject of this first paper.



PGE



Ia, R = CH_3CO; X = CH
b, R = CH_3CO; X = N
c, R = H_2NCO; X = N
d, R = CH_3SO_2; X = CH
e, R = CH_3SO_2; X = N

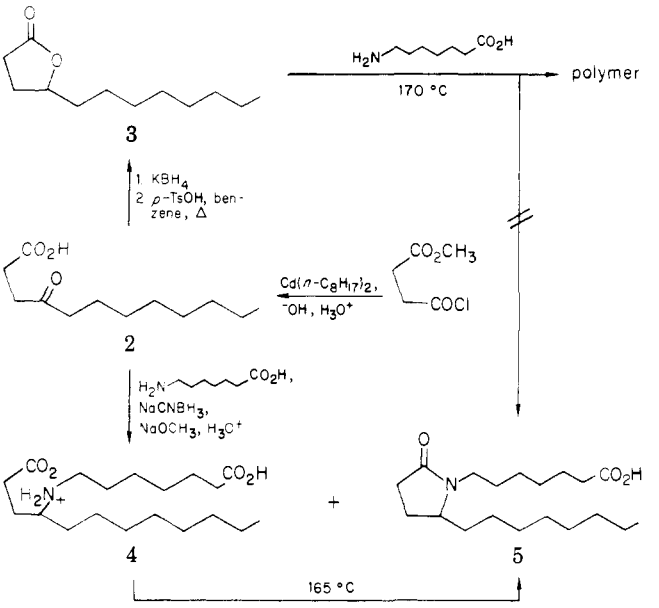


1 (• = positions for isosteric substitution)

Chemistry. Our prostanoic acid isosteres are tabulated in Table I. Racemic lactam **5** was synthesized as shown in Scheme I. Reaction of 3-methoxycarbonylpropionyl chloride[7] with (di-*n*-octyl)cadmium gave, after saponification, γ-keto acid **2**.[8] The latter was converted to lactone **3** in quantitative yield via reduction with potassium borohydride and subsequent acid-catalyzed lactonization of the intermediate γ-hydroxy acid. Attempts to condense **3** with 7-aminoheptanoic acid at elevated temperatures (e.g., ≥170 °C) failed to afford lactam **5**; instead, intractable polymers were obtained and this route to **5** was abandoned. Reductive amination of the sodium salt of **2** (generated in situ), using the Borch[9] method, proceeded smoothly to afford a readily separable mixture of amino diacid **4** and lactam **5** in 15 and 73% yield, respectively. The latter was formed from **4** during the work-up of the reaction mixture. Interestingly, **4**, upon liquification at 165 °C for a brief period, afforded analytically pure **5** in quantitative yield. Hence, the transformation **2** to **5** was effected in 88% overall yield.

Scheme II was used to prepare the 8,10-diaza compound **8b**. Amino ketone **7b** was generated from 1-chloro-2-decanone[10] using the procedure of Sheehan and Bolhofer.[11] Isocyanate **6** was readily prepared from 7-methoxycarbonylheptanoyl chloride[12] by the modified Curtius rearrangement[13] and condensed with **7b** to give the intermediate β-keto urea. This compound underwent concomitant acid-catalyzed cyclodehydration and ester interchange to provide ethyl ester **8a**. Saponification of the latter afforded **8b**. Attempts to convert **8b** to the

Scheme I



Scheme II

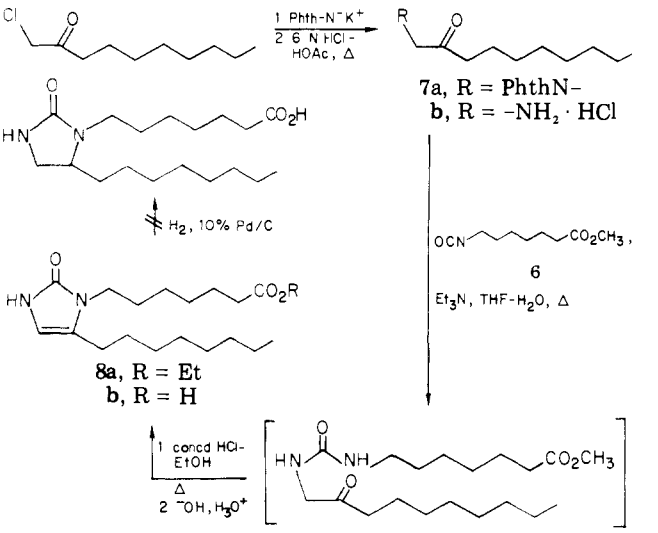
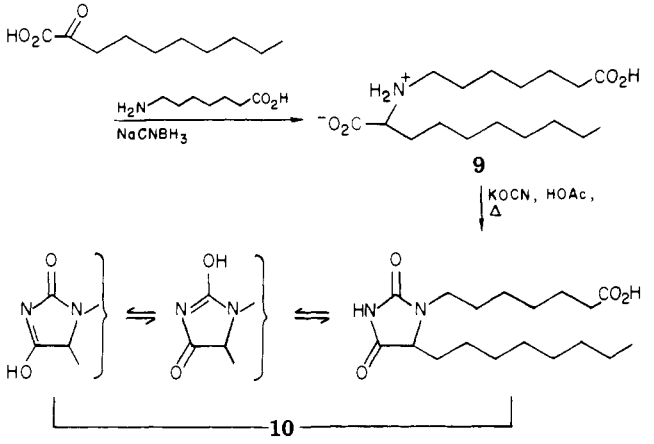


Table I

Compd	Yield, %	R_f[a]	pK_a[b]	Formula[c]	Mouse ovary PG assay, fold increase in cAMP, concn in μg/mL: 1	25	100	Rat kidney receptor binding, μg equiv to 1 ng of PGE_1
5	88[d]	0.25 (A)	5.6	$C_{19}H_{35}NO_3$	0.7	8	13	8.3 ± 0.9 (n = 4)
8b[k]	14[e]	0.84 (B)	6.1	$C_{18}H_{32}N_2O_3$		5	9	19.6 ± 4.6 (n = 3)
10	68[f]	0.20 (A)	5.6, 9.2	$C_{18}H_{32}N_2O_4$		3	6	5.0 ± 0.5 (n = 4)
13b	47[g]	0.15 (A)	5.25	$C_{19}H_{35}NO_4$	0.9	8	18	4.6 ± 0.3 (n = 2)
19	30[h]	0.12 (C)		$C_{18}H_{33}NO_4S$	1.4	8	25	0.39 ± 0.08 (n = 3)
20	37[i]	0.24 (D)		$C_{18}H_{33}NO_6S$	5.2 ± 1.1 (n = 3)	27 ± 3 (n = 4)	37 ± 4 (n = 3)	0.06 ± 0.007 (n = 4)
25b	18[j]	0.13 (D)		$C_{20}H_{28}FNO_7S$		2	7	

[a] Determined on SiO_2 plates using the eluent designated in parentheses: A, $CHCl_3$-CH_3OH-HOAc (98:1:1); B, $CHCl_3$-CH_3OH-HOAc (8:1:1); C, $CHCl_3$-HOAc (50:1); D, $CHCl_3$-HOAc (25:1). [b] All values were determined in water except that for **5** which was determined in 30% EtOH. [c] All compounds were analyzed for C, H, and N. Analytical results are within 0.4% of the theoretical values. [d] Overall yield from keto acid **2**. [e] Overall yield from amino ketone **7b**. [f] Overall yield from amino diacid **9**. [g] Overall yield from keto acid **12**. [h] Overall yield from aldehyde 16. [i] Yield from thioether **19**. [j] Overall yield from aldehyde **23**. [k] Mp 87-88 °C.

Scheme III

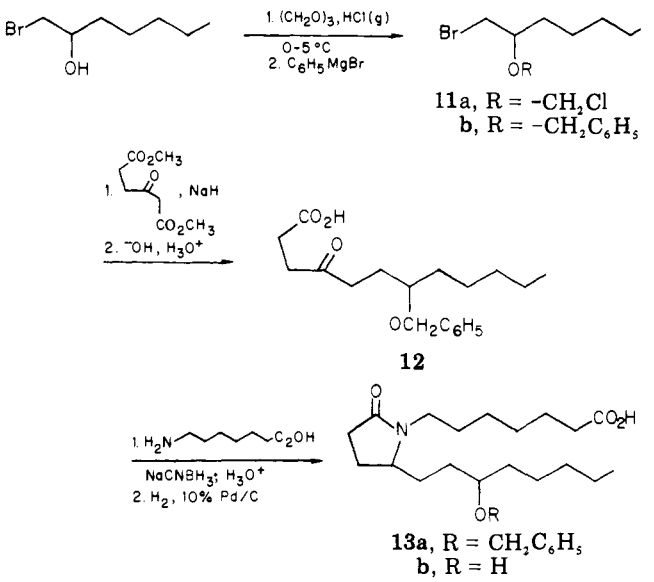


corresponding 1,5-disubstituted 4,5-dihydroimidazolidin-2-one via high-pressure catalytic hydrogenation proved futile;[14] **8b** was recovered unchanged.

Racemic hydantoin **10** was synthesized by the simple two-step route delineated in Scheme III. The success of the key step, preparation of amino diacid **9** via reductive amination[9] of 2-oxodecanoic acid,[15] proved to be predicated upon use of the starting α-keto acid rather than the corresponding sodium salt. When the latter was used, the amino triacid resulting from reaction of **9** with the starting α-keto acid and subsequent reduction became the major and only isolable product. A possible explanation for this observation is the fact that the sodium salt, unlike **9** itself, is soluble in the reduction medium. Conversion of **9** to the desired acid product **10** was accomplished in the classical manner.[16]

Elaboration of diastereomeric lactam **13** proceeded as indicated in Scheme IV, beginning with 1-bromo-2-heptanol[17] which was converted to chloromethyl ether **11a** with *s*-trioxane–hydrogen chloride. The latter proved to be relatively unstable and, accordingly, was treated immediately with phenylmagnesium bromide at 0 °C to provide benzyl ether **11b**.[18] Alkylation of the carbanion derived from dimethyl 3-oxoadipate[19] with bromide **11b** followed by saponification–decarboxylation gave γ-keto acid **12**. Reductive amination of **12** with 7-aminoheptanoic

Scheme IV

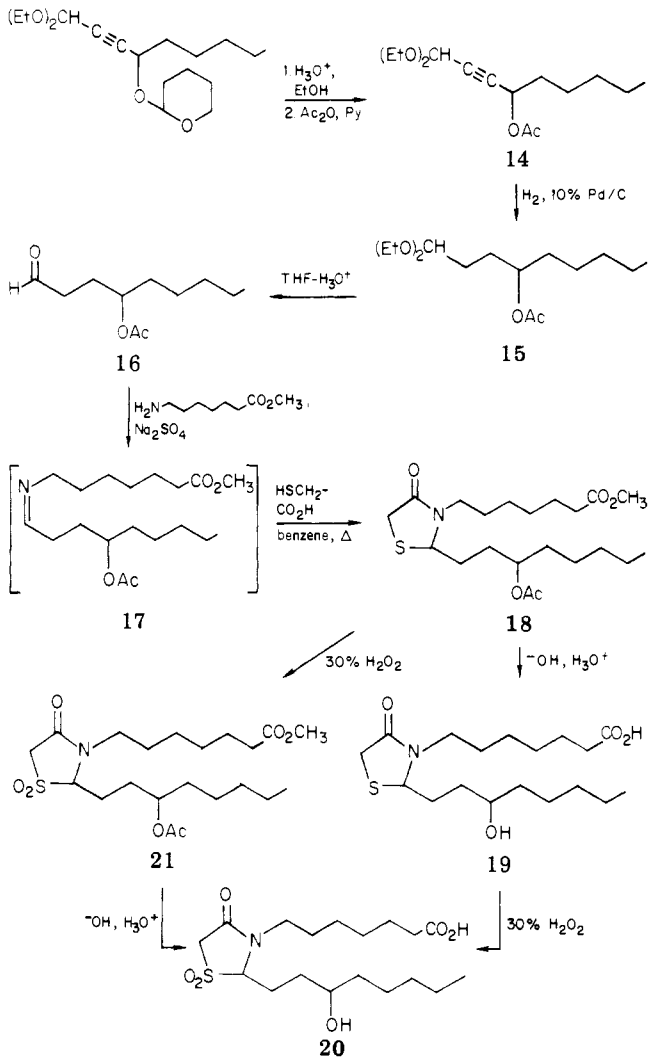


acid afforded **13a** which underwent smooth hydrogenolytic O-debenzylation to give target lactam **13b**.

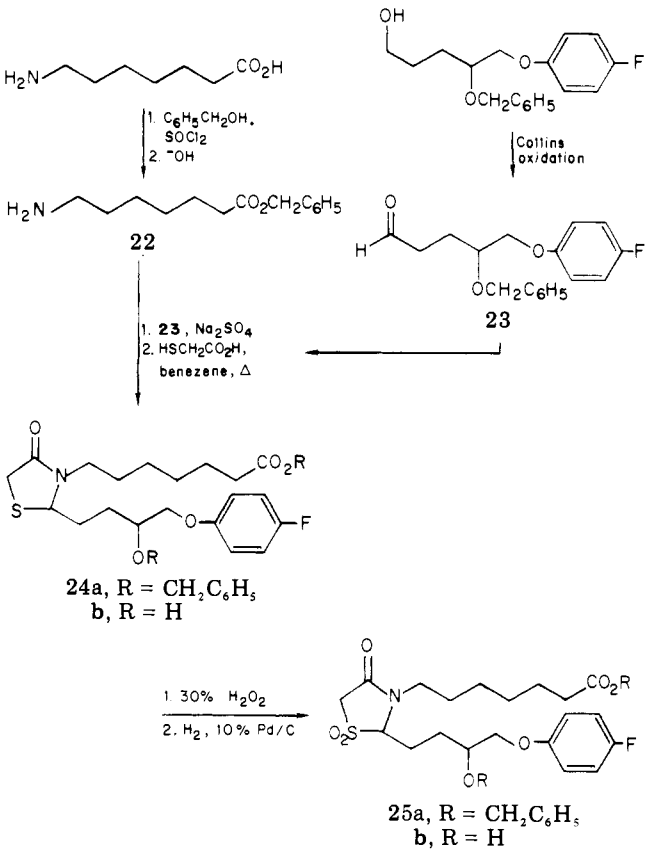
The 8-aza-11-thia-9-oxoprostanoic acids, **18–20**, are diastereomeric mixtures and were synthesized as shown in Scheme V. The sequence[21] beginning with 2-[[1-(3,3-diethoxy-1-propynyl)hexyl]oxy]tetrahydro-2*H*-pyran[20] and proceeding through **14** → **15** → **16** provided aldehyde **16**[22] in an overall yield of ~49%. Condensation of the latter with methyl 7-aminoheptanoate[23] in the presence of sodium sulfate gave imine **17** which underwent facile 1,2 addition with mercaptoacetic acid. Subsequent, thermally induced cyclodehydration of the intermediate thioether led to thiazolidinone **18** which, after saponification, afforded acid product **19**. Oxidation of **19** with 30% hydrogen peroxide under the usual conditions completed the synthesis of sulfone **20**. The alternate sequence, **18** → **21** → **20**, proved to be less satisfactory, in part due to the apparent susceptibility of the 1,1,4-trioxothiazolidine ring system to base-catalyzed degradation.

Preparation of sulfone **25b** was effected in an analogous manner (Scheme VI). Condensation of amino ester **22**,

Scheme V



Scheme VI



readily prepared from 7-aminoheptanoic acid as shown, with the aldehyde (**23**) resulting from Collins oxidation of 4-benzyloxy-5-(4-fluorophenoxy)pentanol[3] gave the intermediate imine. The imine was converted to thiazolidinone **24a** by reaction with mercaptoacetic acid and thence to sulfones **25a** and **25b** by treatment with 30% hydrogen peroxide and catalytic hydrogenation, respectively.

With exception of **8b**, the final products and intermediate esters are viscous oils, many of which are not amenable to purification by distillation. When necessary to achieve TLC homogeneity, these compounds were purified by column chromatography on silica gel. Frequently, they retained solvents tenaciously.[24] As a result, samples suitable for analysis and biological evaluation were desolvated at elevated temperatures (e.g., 100 °C) under high vacuum for extended periods. For this reason, elemental analyses generally were obtained only for the final products. Structural assignments for the intermediates were confirmed by NMR and IR spectroscopy. TLC analysis served to provide further evidence of their purity.

Biological Activity. Induction of cAMP formation in many types of cells by PGE's has been demonstrated.[25] The dose-related stimulation of cAMP formation by PGE_1 in the mouse ovary has been the basis for the primary assay used in these laboratories for the detection and measurement of prostaglandin-like activity.[26] In this assay, described in detail in the Experimental Section, mouse ovaries are initially incubated with [8-^{14}C]adenine to allow formation of intracellular [^{14}C]-ATP. Then, the test compound, along with the phosphodiesterase inhibitor theophylline, is added and incubation is continued. Reactions are ultimately terminated by addition of trichloroacetic acid and, subsequently, [^{14}C]-cAMP is isolated from the ovaries and measured. Results are expressed as fold increases in cAMP formation obtained by dividing the cAMP levels in treated ovaries by those levels in untreated ovaries.

Table II records the effectiveness of 7-[2-(3-hydroxyoctyl)-1,1,4-trioxo-3-thiazolidinyl]heptanoic acid (**20**) in stimulating cAMP formation which is compared with that of PGE_1, tetrahydroprostaglandin A_1, 8-acetyl-12-hydroxyheptadecanoic acid (Ia), and 8-methylsulfonyl-12-hydroxyheptadecanoic acid (Id). Compounds Ia and Id are representative 11,12-secoprostaglandins.[1,3] These data indicate that sulfone **20** raises cAMP levels markedly at reasonable pharmacological concentrations and, although less active than PGE_1 in this assay, **20** compares favorably with both tetrahydroprostaglandin A_1 and Id and is more active than Ia.

Demonstration that prostanoic acid isosteres not only express a characteristic action of the prostaglandins but are capable of interacting with prostaglandin receptors is imperative if these compounds are to be properly termed prostaglandin analogues in any biological sense. A prostaglandin receptor binding assay employing a binding fraction prepared from rat kidney plasma membrane was recently devised in these laboratories.[27a] In this assay, the test compound is allowed to compete with [^{3}H]-PGE_1 for binding to the receptors. Results are expressed herein as nanograms of test compound equivalent to 1 ng of cold PGE_1 in displacing [^{3}H]-PGE_1 from receptor binding sites. These data, also recorded in Table II, reveal that **20** avidly binds to the PGE_1 receptor, displaying a receptor affinity far greater than that displayed by either Ia or Id. The

Table II

Compd	Mouse ovary PG assay, fold increase in cAMP, concn in μg/mL									Rat kidney receptor binding, ng equiv to 1 ng of PGE_1
	0.01	0.05	0.1	1.0	10	25	50	100	200	
PGE_1	8 ± 1 (n = 3)	25 ± 3 (n = 3)	29 ± 5 (n = 3)	54 ± 5 (n = 27)	60 ± 5 (n = 3)	62 ± 4 (n = 4)		62 ± 5 (n = 3)		1
Tetrahydro-PGA_1				10	25	26	19			10[a]
Ia				2	11	14	16	23	16	833 ± 48 (n = 4)
Id			2	14	24	27		38		670[a]
20				5 ± 1 (n = 3)	23 ± 3 (n = 3)	27 ± 3 (n = 4)		37 ± 4 (n = 3)		60 ± 7 (n = 4)

[a] The PGE_1 receptor binding values recorded for tetrahydro-PGA_1 and Id were determined earlier in the rat lipocyte receptor binding assay.[1,3] The two receptor binding assays appear to yield comparable PGE_1 receptor binding values based upon the results obtained for test compounds evaluated to date in both assays.[27a]

decreased receptor affinity in comparing PGE_1 to **20** parallels the decreased potency of **20** toward cAMP stimulation in the mouse ovary as might be predicted.

With a relationship established between the biological activity of **20**, as well as that of 11,12-secoprostaglandins Ia and Id and that of the E series prostaglandins, evaluation of the series of (8-aza-, 8,10-diaza-, and 8-aza-11-thia)-9-oxoprostanoic acids for their ability to stimulate cAMP formation and to bind to the kidney PG receptor was appropriate. These data are tabulated in Table I. It should be noted that the composition and scope of this initial series of prostanoic acid isosteres were rationally determined on the basis of structure–activity relationships (SAR's) previously described for other analogue series.[1-3] In addition, since no meaningful relationship between stereochemistry and biological activity was observed in the 11,12-secoprostaglandin series,[1] no attempt was made either to separate or stereospecifically elaborate the various possible stereoisomers in the present series. Hence, compounds **5** and **10** are racemic and **13b**, **19**, **20**, and **25b** are diastereomeric mixtures.

Structure–Activity Relationships. Compounds **5**, **8b**, and **10** display comparable activities in both assay systems but of a magnitude higher than that which would be anticipated by comparison with 8-acetylheptadecanoic acid,[28] the corresponding carbon isostere in the 11,12-secoprostaglandin series. Hence, isosteric substitution of nitrogen in positions 8 and 10 may augment activity. Introduction of oxygen at position 11 (i.e., **8b** → **10**) appeared to contribute little, if any, to activity in either assay. Likewise, hydroxylation of **5** at position 15 to give alcohol **13b** resulted in a very modest increase in activity.

Replacement of the 11-methylene moiety of **13b** with a sulfur atom (**13b** → **19**) led to a marked increase in receptor binding and a slight increase in cAMP stimulation. However, the most dramatic increase in biological activity occurred upon conversion of thioether **19** to sulfone **20**, particularly from the standpoint of enhanced receptor binding. This result is in accord with the SAR's determined earlier for the 8-alkylthio(sulfinyl and sulfonyl)-12-hydroxyalkanoic acid series.[3] Finally, replacement of the terminal butyl group of **20** by the 4-fluorophenoxy group, a modification that markedly increases the luteolytic potency and specificity of $PGF_{2\alpha}$,[29] proved to be detrimental to cAMP stimulant activity as reflected by ether **25b**.

Conclusion

These preliminary results demonstrate that synthetically accessible prostanoic acid isosteres displaying prostaglandin-like biological activity can be designed and have encouraged us to continue this approach.

Experimental Section

Chemical. Melting points were determined in open capillary tubes and are uncorrected as are boiling points. ^1H NMR spectra were recorded in $CDCl_3$ on either a Varian A-60A or T-60 spectrometer. Chemical shifts are reported as δ values relative to Me_4Si as internal standard. IR spectra were taken on a Perkin-Elmer Infracord spectrophotometer and are expressed in reciprocal centimeters. pK_a values were determined by potentiometric titration in water, unless otherwise noted, using a Metrohm E 336 potentiograph.

Column chromatography was effected on silica gel (E. Merck, 0.063–0.20 mm mesh). Column fractions were monitored and product purity was established by thin-layer chromatography (TLC) on Analtech silica gel GF plates (250 μ thickness). Spots were visualized with both iodine vapor and Mineral-Light exposure.

All final products were homogeneous on TLC using the designated $CHCl_3$–CH_3OH–HOAc or $CHCl_3$–HOAc system (see Table I) as eluent. Satisfactory elemental analyses (within 0.4% of the theoretical values) were obtained for those compounds whose analyses are indicated only by the symbols of the elements. Solvents were removed in vacuo (water aspirator) using a rotary evaporator. Oily products were dried over P_2O_5 at 100 °C in vacuo (0.1–0.05 mm) for 6–12 h to remove the last traces of solvents prior to analysis and biological evaluation.

7-(5-Octyl-2-oxo-1-pyrrolidinyl)heptanoic Acid (5). (a) 4-Oxododecanoic Acid (2). To a cold (ice bath) solution of *n*-octylmagnesium iodide in ether (100 mL), generated in the usual manner from 1-iodooctane (48 g, 0.2 mol) and Mg turnings (4.86 g, 0.2 mol), was added $CdCl_2$ (19.6 g, 0.107 mol, dried in vacuo over P_2O_5 at 110 °C for 24 h *immediately prior to use*) portionwise over 5 min. The resulting clear solution was heated at reflux for 45 min, benzene (70 mL) was added, ether was removed by distillation, and additional benzene (70 mL) was added. Upon removal of the last traces of ether by distillation, a solution of 3-methoxycarbonylpropionyl chloride[7] (24.1 g, 0.16 mol) in benzene (30 mL) was added to the warm, vigorously stirred reaction mixture over 2 min. After the ensuing exothermic reaction had subsided, the thick reaction mixture was heated at reflux for 60 min, cooled to 0–5 °C, and cautiously treated with ice water (120 mL) followed by 20% H_2SO_4 (5 mL) with vigorous stirring. The phases were separated and the aqueous phase was extracted with benzene (200 mL). The combined organic extract was washed successively with water, 5% K_2CO_3, water, and saturated brine and dried over Na_2SO_4. Evaporation of the solvent gave crude **methyl 4-oxododecanoate** as a pale yellow oil: IR (neat) 1740 (ester CO) and 1710 cm^{-1} (ketone CO). The latter was saponified with KOH (16.83 g, 0.3 mol) in 90% CH_3OH (550 mL) for 5 h at reflux. Concentration of the reaction solution provided a viscous, oily residue which was dissolved in water (1 L). The solid which precipitated upon acidification of the cold aqueous solution with concentrated HCl (40 mL) was collected, washed with water, and dried to give 16 g (47%) of **2** as a white solid, mp 77–79 °C. Recrystallization from *n*-heptane afforded analytically pure **2** as glistening, colorless needles, mp 80–81 °C (sharp) (lit.[8] mp 77–78 °C).

(b) **4-(6-Carboxyhexylamino)dodecanoic Acid (4).**

$NaCNBH_3$ (2.52 g, 0.04 mol) was added portionwise over 5 min to a stirred solution of **2** (4.29 g, 0.02 mol), 7-aminoheptanoic acid (2.9 g, 0.02 mol), and $NaOCH_3$ (1.08 g, 0.02 mol) in anhydrous CH_3OH (200 mL) cooled in an ice bath. After standing at 20 °C for 7 days, the reaction solution was treated with concentrated HCl (20 mL) added dropwise over 15 min. The resulting fine slurry was stirred at 20 °C for 1 h and filtered. The collected inorganic cake was washed with CH_3OH (2 × 25 mL) and the washings were combined with the filtrate. Removal of the solvent left an oily residue which was triturated with CH_3OH (50 mL) and filtered to remove additional inorganic solids. Concentration of the filtrate afforded an oily residue exhibiting a ^1H NMR singlet at δ 3.67 ($-CO_2CH_3$), indicating that partial esterification had occurred. Hence, the latter was saponified with KOH (5.61 g, 0.1 mol) in 50% CH_3OH (100 mL) for 24 h at 20 °C. Evaporation of the reaction solution left a tacky residue which was dissolved in water (50 mL). Acidification of the cold aqueous solution with concentrated HCl (12 mL) provided a heterogeneous mixture which upon vigorous extraction with ether (100 mL) resulted in a clean phase separation (i.e., all solids dissolved). The aqueous phase was extracted with additional ether (3 × 50 mL) and the ethereal extracts were combined with the organic phase. Upon extraction of the combined organic extract with water (50 mL), precipitation of a white solid ensued. The precipitate was collected, washed with water and ether, and air-dried at 20 °C to give 0.55 g (8%) of **4** as a pale beige solid: mp 145–146 °C (sharp) with decomposition; IR (Nujol mull) 1715 (CO_2H), 1640 ($-^+NH_2-$), 1530, 1390 cm^{-1} (CO_2^-); R_f 0.13 (homogeneous, ninhydrin positive) on TLC (eluent system B).

The biphasic filtrate was placed in a separatory funnel and the phases were allowed to separate. Adjustment of the pH of the cold aqueous phase to approximately 3.5 with 2 N NH_4OH afforded additional **4** (0.5 g, 7%) as a pale beige precipitate, mp 145–146 °C (sharp) with decomposition, after work-up as above. Recrystallization from CH_3OH at −10 °C gave an analytical sample of **4** as tan needles (melting point and R_f unchanged) which underwent facile cyclodehydration to give lactam **5** upon drying in vacuo at 100 °C. This sample of **5** was found to be identical (via TLC, IR, and NMR) with authentic **5** prepared in step (c) below as well as **5** present in the organic phase of the biphasic filtrate (this isolation is described below).

(c) **7-(5-Octyl-2-oxo-1-pyrrolidinyl)heptanoic Acid (5).** Pulverized **4** (0.55 g, 1.63 mmol) was immersed in an oil bath maintained at 165 °C for 15 min. Chromatography of the resulting oil on silica gel (10 g) using $CHCl_3$ followed by $CHCl_3$–CH_3OH (98:2) as eluent afforded 0.54 g (100%) of **5** as a colorless oil: IR (neat) 1570–1630 cm^{-1} (peaks at 1730, 1690, and 1650); NMR 0.88 (3 H, t, CH_3) 2.32 (6 H, m, CH_2CH_2CO and CH_2CO_2H), 2.91 (H, m, CHN), 3.54 (2 H, m, CH_2N), and 10.13 (H, br s, CO_2H). Anal. ($C_{19}H_{35}NO_3$) C, H, N.

The organic layer of the biphasic filtrate from section (b) above was dried over Na_2SO_4. Evaporation of the solvent left a residual oil (5.6 g) which was eluted from a silica gel column (15 g) with $CHCl_3$ followed by $CHCl_3$–CH_3OH (98:2) to afford **5** as a colorless oil (4.8 g, 73% based upon starting γ-keto acid **2**) which was shown to be identical with authentic **5** via IR, NMR, and TLC comparison analysis. Hence, lactam **5** was obtained in 88% overall yield from **2**.

6-Methoxycarbonylhexyl Isocyanate (6). 7-Methoxycarbonylheptanoyl chloride[12] was converted to isocyanate **6** in 82% yield using the procedure of Allen and Bell.[13] **6** was obtained as a colorless liquid: IR (neat) 2250 (NCO) and 1735 cm^{-1} (CO); NMR 2.32 (2 H, t, $CH_2CO_2CH_3$), 3.31 (2 H, t, CH_2N), and 3.67 (3 H, s, CO_2CH_3).

7-(5-Octyl-2-oxo-4-imidazolin-1-yl)heptanoic Acid (8b). (a) *N*-(2-Oxodecyl)phthalimide (7a). To a stirred suspension of potassium phthalimide (18.52 g, 0.1 mol) in dry DMF (100 mL) was added a solution of 1-chloro-2-decanone[10] (19.1 g, 0.1 mol). After stirring at 20 °C for 16 h, the reaction mixture was heated at 60 °C for 60 min, cooled, and partitioned between $CHCl_3$ (300 mL) and ice water (500 mL). Upon separation of the phases, the aqueous phase was extracted twice with $CHCl_3$. The combined organic extract was washed with water and saturated brine and dried over Na_2SO_4. Removal of the solvent left an oily residue which crystallized from ether–petroleum ether (1:3) to give 16.4 g (56%) of **7a** as colorless needles, mp 61–62 °C. Concentration of the mother liquors gave additional **7a** (7.6 g, 25%), mp 60.5–62 °C. Recrystallization from ether–petroleum ether (1:2) afforded an analytical sample of **7a** as colorless needles: mp 61–62 °C; NMR 0.88 (3 H, t, CH_3), 2.53 (2 H, t, CH_2CH_2CO), 4.49 (2 H, s, NCH_2CO), and 7.77 (4 H, m, aromatic H's). Anal. ($C_{18}H_{23}NO_3$) C, H, N.

(b) **1-Amino-2-decanone Hydrochloride (7b).** A suspension of phthalimide **7a** (24 g, 0.08 mol) in 6 N HCl–HOAc (1:1, 400 mL) was stirred and heated at reflux for 72 h, cooled to 0–5 °C, and filtered. Collected phthalic acid (7.2 g, 54%), mp 215–216 °C with decomposition, was washed with 5% HCl (2 × 50 mL). The combined filtrate and washings were concentrated in vacuo to a viscous sludge (approximately 50 mL in volume) which was dissolved in 20% CH_3OH (250 mL). Evaporation of the resulting solution left a tacky residue which, after drying azeotropically with benzene (200 mL), was dissolved in warm CH_3OH (50 mL). The resulting solution was diluted with ether to incipient turbidity and cooled in an ice bath whereupon 8.8 g (53%) of **7b** was deposited as colorless platelets, mp 169 °C (sharp) with decomposition. An additional 3 g (18%) of **7b**, mp 168–169 °C with decomposition, was obtained from the mother liquors. Recrystallization from CH_3OH–ether (1:3) provided analytically pure **7b** as glistening needles: mp 174–175 °C (sharp); R_f 0.13 (homogeneous, ninhydrin positive) on TLC (eluent system B); IR (Nujol mull) 1730 cm^{-1} (CO). Anal. ($C_{10}H_{22}ClNO$) C, H, N.

(c) **7-(5-Octyl-2-oxo-4-imidazolin-1-yl)heptanoic Acid (8b).** A solution of triethylamine (1.4 mL, 1 mmol) in THF (25 mL) was added dropwise over 45 min to a refluxing solution of isocyanate **6** (1.85 g, 1 mmol) and amino ketone **7b** (2.07 g, 1 mmol) in 95% THF (16 mL), providing a colorless suspension. After heating at reflux for an additional 1.5 h, the reaction mixture was cooled in an ice bath for 15 min and filtered to remove the precipitated white solid (1.7 g): mp 225–230 °C with decomposition; R_f 0.80 (trace) and 0.25 (major) on TLC with $CHCl_3$–CH_3OH (9:1) as eluent. Concentration of the filtrate gave additional white solid (0.4 g): mp 110–112 °C; R_f 0.80 (major) and 0.25 (minor) on TLC (same eluent). Both solids were ninhydrin negative.

A solution of the combined solids (2.1 g) in EtOH–concentrated HCl (25:1, 26 mL) was stirred and heated at reflux for 3 h and then concentrated to an oily residue which, upon trituration with ether (25 mL), afforded a fine slurry. The insoluble solid was collected, washed with ether, and dried at 60 °C to give triethylamine hydrochloride (0.9 g): mp 256–257 °C with decomposition [after recrystallization from EtOH–ether (2:1)]; NMR 1.32 (3 H, t, CH_3) and 3.24 (2 H, q, CH_2).

The filtrate was combined with the mother liquors from the white solids above and evaporated to an oily residue which was partitioned between ether and 5% HCl. The organic extract was washed with water and saturated brine and dried over Na_2SO_4. Evaporation of the solvent left a residual oil (3.45 g) which was applied to a silica gel column (30 g). After eluting impurities with $CHCl_3$, continued elution with $CHCl_3$ and $CHCl_3$–CH_3OH (49:1) afforded ethyl ester **8a** as a yellow oil (2.2 g, 62%): R_f 0.65 (homogeneous) on TLC with $CHCl_3$–CH_3OH (9:1) as eluent; IR (neat) 3300 (NH), 1745 (ester CO), and 1695 cm^{-1} (urea CO); NMR 0.88 (3 H, t, $CH_2CH_2CH_3$), 1.23 (3 H, t, J = 7 Hz, CH_3CH_2O), 2.28 (4 H, m, CH_2CO_2 and $HC{=}CCH_2$), 3.56 (2 H, m, CH_2N), 4.10 (2 H, q, J = 7 Hz, CH_3CH_2O), 5.97 (H, s, HC=C), and 10.30 (H, br s, NH).

A solution of ester **8a** (2 g, 5.67 mmol) and KOH (1 g, 17.8 mmol) in 90% CH_3OH (50 mL) was stirred at 20 °C for 90 h, acidified with HOAc (3 mL), and evaporated to a yellow oil which was partitioned between ether and 5% HCl. The organic extract was washed with 5% HCl and saturated brine and dried over Na_2SO_4. Evaporation of the dried extract left a residual semisolid which crystallized slowly from ether at 0 °C providing **8b** as a white solid (0.7 g, 22%), mp 81–87 °C. Recrystallization from ether afforded an analytical specimen of **8b** as colorless clumplets: mp 87–88 °C (slow); NMR 0.88 (3 H, t, CH_3), 2.31 (4 H, m, CH_2CO_2H and $HC{=}CCH_2$), 3.56 (2 H, m, CH_2N), 5.97 (H, s, HC=C), 10.02 (H, br s, NH), and 12.0 (H, br s, CO_2H). Anal. ($C_{18}H_{32}N_2O_3$) C, H, N.

7-(5-Octyl-2,4-dioxo-1-imidazolidinyl)heptanoic Acid (10). (a) 2-(6-Carboxyhexylamino)decanoic Acid (9). A magnetically stirred mixture of 7-aminoheptanoic acid (0.73 g, 5 mmol),

2-oxodecanoic acid[15] (0.93 g, 5 mmol), and $NaCNBH_3$ (0.63 g, 10 mmol) in CH_3OH (50 mL) was kept at 20 °C for 26 h. The resulting thick suspension was filtered and the collected solid was washed with CH_3OH (5 × 10 mL) and dried to give **9** as a pale tan solid (0.6 g, 38%), mp 217–218 °C (sharp) with decomposition. An analytical sample was prepared as follows. The tan solid (0.6 g) was dissolved in 2.5 N NH_4OH (60 mL) providing a clear solution which was adjusted slowly to pH 1 via dropwise addition of concentrated HCl. Precipitated solid was collected and dissolved in 1 N NH_4OH (25 mL). Adjustment of the resulting solution to pH 3 with 1 N HCl afforded pure **9** as a white solid: mp 226–227 °C (very sharp) with decomposition; R_f 0.27 (homogeneous, ninhydrin positive) on TLC (eluent system B); IR (KBr pellet) 1720 (acid CO), 1590, 1390 cm^{-1} (CO_2^-). Anal. ($C_{17}H_{33}NO_4$) C, H, N.

By employing mechanical stirring and extending the reaction period to 114 h, the yield of **9** was increased to 56%.

(b) **7-(5-Octyl-2,4-dioxo-1-imidazolidinyl)heptanoic Acid (10).** To a stirred solution of amino diacid **9** (6.05 g, 19.2 mmol) in glacial HOAc (65 mL) maintained at 20 °C was added KOCN (6.24 g, 76.8 mmol) in small portions over 45 min. The resulting clear solution was heated at reflux (steam bath) for 4 h, cooled, and slowly poured into stirred ice water (500 mL) providing a fine suspension. After stirring at 0–5 °C for 30 min, the suspension was filtered and the collected tacky solid was triturated with CH_3OH–ether (1:1, 200 mL) for 15 min at 20 °C. The insoluble solid (0.85 g), mp 212–213 °C (sharp) with decomposition, was collected and washed with ether (4 × 25 mL). Evaporation of the combined filtrate and washings provided an oily residue (6.5 g) which was chromatographed on silica gel (65 g). Elution with $CHCl_3$ followed by $CHCl_3$–CH_3OH (49:1) afforded 4.4 g (68%) of **10** as a pale yellow oil: IR (neat) 1780–1670 cm^{-1} (strong CO absorption); NMR 0.89 (3 H, t, CH_3), 2.36 (2 H, t, CH_2CO_2H), 2.65–3.87 (2 H, br m, CH_2N), 4.06 (H, t, ring CH), 9.60 (H, s, NH), and 10.31 (H, s, CO_2H). Anal. ($C_{18}H_{32}N_2O_4$) C, H, N.

7-[5-(3-Hydroxyoctyl)-2-oxo-1-pyrrolidinyl]heptanoic Acid (13b). (a) **1-Bromo-2-chloromethoxyheptane (11a).** A steady stream of HCl(g) was passed into a cold (0–5 °C) mixture of 1-bromo-2-heptanol[17] (29.3 g, 0.15 mol) and *s*-trioxane (4.5 g, 0.05 mol) contained in a conical flask for 6 h. The resulting biphasic mixture (two discrete liquid phases) was kept at 0–5 °C, treated with $CaCl_2$ (to remove aqueous phase), purged wtih a N_2 stream, and stored at 20 °C for 20 h. Rapid filtration of the dried, heterogeneous mixture through a dry, glass-fritted funnel (coarse porosity) provided a clear filtrate which was distilled immediately to give **11a** as a colorless liquid (21.9 g, 60%): bp 121–122 °C (13 mm); IR (neat) 1120 cm^{-1} (COC); NMR 0.90 (3 H, t, CH_3), 3.49 (2 H, d, CH_2Br), 4.0 (H, m, $CHOCH_2Cl$), and 5.62 (2 H, s, CH_2Cl).

(b) **1-Bromo-2-benzyloxyheptane (11b).** To a vigorously stirred, chilled solution (ice bath) of phenylmagnesium bromide in ether (50 mL), generated in the usual manner from bromobenzene (14.13 g, 0.09 mol) and Mg turnings (2.19 g, 0.09 mol), was added a solution of chloromethyl ether **11a** (21.9 g, 0.09 mol) in ether (50 mL) dropwise over 40 min. After standing an additional 15 h at ambient temperature, the reaction mixture was diluted with ether (100 mL), cooled to 0–5 °C, treated with ice water (50 mL) added dropwise over 10 min, and vigorously stirred for 10 min. The layers were separated and the aqueous phase was extracted with ether. The combined organic extracts were washed successively with water, 5% K_2CO_3, water, and saturated brine and dried over Na_2SO_4. Removal of the solvent afforded 25.6 g (100%) of 11b as a colorless liquid: NMR 0.90 (3 H, t, CH_3), 3.49 (3 H, m, CH_2Br and $CHOCH_2C_6H_5$), (2 H, t, $OCH_2C_6H_5$), and 7.37 (5 H, s, C_6H_5).

(c) **7-Benzyloxy-4-oxododecanoic Acid (12).** Dimethyl 3-oxoadipate[19] (15.8 g, 0.084 mol) was added dropwise over 60 min to a stirred suspension of 57% NaH in mineral oil (3.53 g, 0.084 mol) in dry benzene–DMF (1:1, 100 mL) at 20 °C. After an additional 30 min at 20 °C, bromide 11b (24 g, 0.084 mol) was added dropwise over 15 min and the resulting reaction solution was stirred and heated on the steam bath for 18 h. The cooled (ice bath) reaction mixture was partitioned between ice water (1.5 L containing 10 mL of concentratd HCl) and ether (3 × 500 mL). The organic extract was washed with water and saturated brine, dried over Na_2SO_4, and concentrated in vacuo to a yellow oil (29.8 g). A solution of the oil and KOH (12.3 g, 0.22 mol) in CH_3OH (200 mL) was stored at 20 °C for 22 h and then evaporated to an oily residue which was dissolved in water (200 mL). Acidification (accompanied by smooth CO_2 liberation) of the cold (ice bath) vigorously stirred aqueous solution with concentrated HCl (25 mL), added dropwise over 15 min, gave a heterogeneous mixture which was diluted with ether (200 mL) and vigorously stirred at ambient temperature for 30 min. After separating the phases, the aqueous phase was extracted with ether. The combined organic extract was washed with saturated brine, dried over Na_2SO_4, and concentrated. The residual oil (25.3 g) was chromatographed on silica gel (250 g). Elution with $CHCl_3$ gave 4.15 g (18%) of **12** as a viscous, pale yellow oil: R_f 0.28 (homogeneous) on TLC (eluent system A); NMR 0.88 (3 H, t, CH_3), 2.28–2.77 (6 H, m, $CH_2COCH_2CH_2CO_2H$), 3.50 (H, m, $CHOCH_2C_6H_5$), 4.47 (2 H, s, $OCH_2C_6H_5$), 7.32 (5 H, s, C_6H_5), and 10.27 (H, s, CO_2H). Anal.[24] ($C_{19}H_{28}O_4$) H; C: calcd, 71.22; found, 70.10.

Continued elution with $CHCl_3$ afforded 5.07 g (22%) of slightly impure **12** which was suitable for use in step (d) described below.

(d) **7-[5-(3-Benzyloxyoctyl)-2-oxo-1-pyrrolidinyl]heptanoic Acid (13a).** This compound, prepared analogously (except no $NaOCH_3$ was used) to pyrrolidinone **5** beginning with keto acid **12** and 7-aminoheptanoic acid, was obtained in 74% yield after chromatography on silica gel with $CHCl_3$–CH_3OH (98:2) elution as a pale yellow oil: R_f 0.25 (homogeneous) on TLC (eluent system A); NMR 0.90 (3 H, t, CH_3), 2.33 (6 H, m, CH_2CH_2CO and CH_2CO_2H), 2.98 (H, m, CHN), 3.53 (3 H, m, CH_2N and $CHOCH_2C_6H_5$), 4.55 (2 H, s, $OCH_2C_6H_5$), 7.36 (5 H, s, C_6H_5), and 9.0 (H, s, CO_2H).

(e) **7-[5-(3-Hydroxyoctyl)-2-oxo-1-pyrrolidinyl]heptanoic Acid (13b).** A magnetically stirred solution of ether **13a** (3.7 g, 8.57 mmol) in EtOH (100 mL) was hydrogenated at 24 °C and atmospheric pressure in the presence of 10% Pd/C (400 mg) until H_2 uptake ceased. The catalyst was collected and washed with EtOH (2 × 50 mL). Evaporation of the combined filtrate and washings in vacuo provided a colorless oil (3 g) which was applied to a silica gel column (15 g). Elution with $CHCl_3$ followed by $CHCl_3$–CH_3OH (49:1–19:1) gave 1.85 g (63%) of **13b** as a viscous, colorless oil: NMR 0.90 (3 H, t, CH_3), 2.33 (6 H, m, CH_2CH_2CO and CH_2CO_2H), 2.98 (H, m, CHN), 3.63 (3 H, m, CH_2N and CHOH), and 6.01 (2 H, s, OH and CO_2H). Anal. ($C_{19}H_{35}NO_4$) C, H, N.

7-[2-(3-Hydroxyoctyl)-4-oxo-3-thiazolidinyl]heptanoic Acid (19). (a) **4-Acetyloxy-1,1-diethoxy-2-nonyne (14).** A solution of 2-[[1-(3,3-diethoxy-1-propynyl)hexyl]oxy]tetrahydro-2*H*-pyran[20] (62.49 g, 0.2 mol) in EtOH–12.5% H_2SO_4 (100:3, 206 mL) was kept at 20 °C for 4 h and then poured into ice water. The resulting heterogeneous mixture was extracted several times with ether. The combined organic extract was washed with water, dried over Na_2SO_4, and concentrated to a residual oil which was dried azeotropically with benzene. A solution of the oil (57.24 g) in pyridine (63.3 g, 0.8 mol) was treated with acetic anhydride (22.5 g, 0.22 mol) and stored at 20 °C for 15 h. The reaction solution was diluted with ether, washed with 1 N HCl, water, 5% $NaHCO_3$, and water, and dried over Na_2SO_4. Distillation provided 14 (40 g, 74%) as a colorless liquid: bp 98–113 °C (0.5 mm); NMR 0.88 (3 H, t, 9-CH_3), 1.20 (6 H, t, CH_3CH_2O), 2.05 (3 H, s, CH_3CO), 3.70 (4 H, q, CH_3CH_2O), 5.34 [H, s, $C{\equiv}CCH(OEt)_2$], and 5.54 (H, t, CHOAc). Anal. ($C_{15}H_{26}O_4$) C, H.

(b) **4-Acetyloxy-1,1-diethoxynonane (15).** A solution of alkyne 14 (40 g, 0.15 mol) in EtOAc (175 mL) was hydrogenated in a Parr apparatus (50 psi) in the presence of 10% Pd/C (0.5 g) at 24 °C until H_2 uptake ceased. The catalyst was collected and washed with EtOAc. Distillation of the combined filtrate and washings afforded 34 g (83%) of **15** as a colorless liquid: bp 84–85 °C (0.03 mm); NMR 4.54 [H, m, $CH(OEt)_2$] and 4.98 (CHOAc). Anal. ($C_{15}H_{30}O_4$) H; C: calcd, 65.65; found, 65.00.

(c) **4-Acetyloxynonanal[22] (16).** A mixture of diethyl acetal **15** (10 g, 36.4 mmol) in THF–30% H_2SO_4 (5:1, 120 mL) was stirred at 20 °C for 5.5 h and then partitioned between ether and ice water. The organic extract was washed with saturated aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and distilled to give **16** (5.75 g, 76%) as a pale yellow liquid: bp 67–69 °C (0.05 mm); NMR 2.58 (2 H, t, CH_2CHO), 4.95 (H, m, CHOAc), and 10.0 (H, d, CHO).

(d) Methyl 7-[2-(3-Acetyloxyoctyl)-4-oxo-3-thiazolidinyl]heptanoate (18). To methyl 7-aminoheptanoate[23] (0.8 g, 5.1 mmol), freshly liberated from the corresponding hydrochloride, cooled in an ice bath was added aldehyde **16** (1.03 g, 5.2 mmol) dropwise with stirring. After warming to 25 °C, the oily reaction mixture was treated with Na_2SO_4 (0.5 g), kept at 25 °C for 20 min, and filtered. The inorganic filter cake was washed with $CHCl_3$ (3 × 2 mL). Concentration of the combined filtrate and washings left methyl **7-[*N*-(4-acetyloxynonylidenyl)amino]heptanoate (17)** as a pale yellow oil: IR (neat) 1740 (ester CO) and 1660 cm^{-1} (C=N); NMR 0.90 (3 H, t, CH_3), 2.03 (3 H, s, CH_3CO), 3.37 (2 H, t, CH_2N), 3.63 (3 H, s, CO_2CH_3), 4.94 (H, m, CHOAc), and 7.66 (H, t, CH=N).

A solution of the oily imine **17** and mercaptoacetic acid (0.46 g, 5 mmol) in benzene (30 mL) was refluxed in a Dean Stark apparatus for 15 h. Removal of the solvent afforded an oil which was chromatographed on silica gel (50 g). Elution with $CHCl_3$ gave 0.86 g (41%) of **18** as a pale yellow oil: NMR 0.91 (3 H, t, CH_3), 2.03 (3 H, s, CH_3CO), 3.48 (2 H, s, SCH_2CO), 3.66 (3 H, s, CO_2CH_3), and 4.60–5.14 (2 H, br m, CHOAc and SCHN). Anal. ($C_{21}H_{37}NO_5S$) C, H, N.

(e) 7-[2-(3-Hydroxyoctyl)-4-oxo-3-thiazolidinyl]heptanoic Acid (19). A turbid mixture of diester **18** (785 mg, 1.89 mmol) in CH_3OH–2.5 N NaOH (3:1, 8 mL) was stirred at 20 °C for 15 h. After removing the solvents in vacuo below 50 °C, the tacky residue was acidified with 2 N HCl and extracted with ether. The organic extract was washed with water, dried over $MgSO_4$, and evaporated to an oily residue. Chromatography on silica gel (20 g) using $CHCl_3$ followed by $CHCl_3$–HOAc (50:1) as eluent provided **19** as a viscous, pale yellow oil (494 mg, 73%): IR (neat) 1720 (acid CO) and 1670 cm^{-1} (lactam CO); NMR 0.90 (3 H, t, CH_3), 2.34 (2 H, t, CH_2CO_2H), 3.48 (2 H, s, SCH_2CO), 4.77 (H, m, SCHN), and 7.10 (2 H, s, OH and CO_2H). Anal. ($C_{18}H_{33}NO_4S$) C, H, N, S.

7-[2-(3-Hydroxyoctyl)-1,1,4-trioxo-3-thiazolidinyl]heptanoic Acid (20). To a stirred mixture of thioether **19** (1.27 g, 3.53 mmol) and ammonium molybdate (0.1 g, catalyst) in 80% CH_3OH (20 mL) maintained below 20 °C (ice bath cooling) was added *cautiously* 30% H_2O_2 (1.5 mL, 15 mmol). Stirring at 20 °C was continued for 64 h; then the reaction mixture was diluted with ice water and extracted with $CHCl_3$. The organic extract was washed with water (until peroxide free as determined by KI–starch paper) and dried over $MgSO_4$. Removal of the solvent left an oily residue which was applied to silica gel (20 g). Elution with $CHCl_3$–HOAc (25:1) provided **20** as a viscous oil (510 mg, 37%): IR (neat) 1730–1660 (strong CO absorption), 1330, 1130 cm^{-1} (SO_2); NMR 0.90 (3 H, t, CH_3), 3.78 (2 H, s, SO_2CH_2CO), 4.58 (H, t, SO_2CHN), and 7.15 (2 H, s, OH and CO_2H). Anal. ($C_{18}H_{33}NO_6S$) C, H, N.

Alternatively, sulfone **20** was prepared from diester **18** in 11% yield via oxidation of **18** with 30% H_2O_2 using essentially the same procedure described above to give **methyl 7-[2-(3-acetyloxyoctyl)-1,1,4-trioxo-3-thiazolidinyl]heptanoate (21)** [NMR 2.03 (3 H, s, CH_3CO), 3.68 (3 H, s, CO_2CH_3) and 4.96 (H, m, CHOAc)], followed by saponification of the latter in the usual manner and chromatographic purification on silica gel to afford **20** which was shown to be identical with an authentic sample.

Benzyl 7-Aminoheptanoate (22) Hydrochloride. To a stirred suspension of 7-aminoheptanoic acid (14.5 g, 0.1 mol) in benzyl alcohol (150 mL) cooled in an ice bath was added dropwise $SOCl_2$ (73 mL, 1.0 mol) over 60 min. The resulting reaction solution was heated on a steam bath for 2.5 h and then stored at 20 °C for 18 h whereupon the clear solution was diluted slowly with ether (1.5 L) to incipient turbidity and kept at −30 °C for 1.5 h. The deposited white solid was collected, washed with ether, and crystallized from ether–EtOH (9:1, 1 L) at 10 °C to give 22.4 g (83%) of **22** hydrochloride as glistening, colorless platelets, mp 88–89 °C. Recrystallization from ether–EtOH (4:1) provided an analytical sample: mp 89–90 °C; NMR 2.39 (2 H, t, CH_2CO_2), 3.13 (2 H, t, $CH_2^+NH_3$), 4.90 (3 H, s, $^+NH_3$), 5.10 (2 H, s, $OCH_2C_6H_5$), and 7.35 (5 H, s, C_6H_5). Anal. ($C_{14}H_{22}ClNO_2$) C, H, N.

Benzyl 7-Aminoheptanoate (22). A solution of **22**·HCl (2.18 g, 8 mmol) in water (25 mL) was treated with 5 N NaOH (2 mL) at 20 °C. The liberated amine was quickly extracted into $CHCl_3$. The organic extract was dried over $MgSO_4$ and concentrated in vacuo below 40 °C to give **22** in quantitative yield as a pale yellow liquid (1.88 g) [NMR 2.72 (2 H, t, CH_2NH_2) and 2.97 (2 H, s, NH_2)], which was used immediately in step (b) described below.

7-[2-[4-(4-Fluorophenoxy)-3-hydroxybutyl]-1,1,4-trioxo-3-thiazolidinyl]heptanoic Acid (25b). (a) 4-Benzyloxy-5-(4-fluorophenoxy)pentanal (23). A solution of 4-benzyloxy-5-(4-fluorophenoxy)pentanol[3] (3.04 g, 0.01 mol) in CH_2Cl_2 (2 mL) was added to a vigorously stirred suspension of Collins reagent in CH_2C_2 (150 mL), freshly generated from CrO_3 (6 g, 0.06 mol) and pyridine (9.49 g, 0.12 mol) in the usual manner. Stirring was continued for 15 min at 20 °C; then the resulting suspension was filtered and the collected black precipitate washed with ether. The filtrate and washings were combined, washed with 5% NaOH, 5% HCl, and 5% $NaHCO_3$, and dried over $MgSO_4$. Evaporation of the dried extract afforded 2.83 g (94%) of **23** as a pale yellow oil: IR (neat) 1730 cm^{-1} (CHO); NMR 9.74 (H, br s, CHO).

(b) Benzyl 7-[2-[3-Benzyloxy-4-(4-fluorophenoxy)butyl]-4-oxo-3-thiazolidinyl]heptanoate (24). This compound, prepared analogously to thiazolidinone **18** beginning with amino ester **22** and aldehyde **23**, was obtained in 27% yield after chromatography on silica gel as a viscous, pale yellow oil: R_f 0.28 (homogeneous) on TLC ($CHCl_3$); NMR 2.34 (2 H, t, CH_2CO_2), 3.50 (2 H, s, SCH_2CO), 4.44–4.88 [3 H, m, containing doublets at 4.54 and 4.77 (J = 12 Hz), SCHN and $CHOCH_2C_6H_5$], 5.10 (2 H, s, $CO_2OCH_2C_6H_5$), 6.63–7.17 (4 H, m, 4-F-C_6H_4), and 7.30 (10 H, s, C_6H_5). Anal. ($C_{34}H_{40}FNO_5S$) C, H, N.

(c) Benzyl 7-[2-[3-Benzyloxy-4-(4-fluorophenoxy)butyl]-1,1,4-trioxo-3-thioazolidinyl]heptanoate (25a). Oxidation of thioether **24** using 30% H_2O_2 as described for the preparation of sulfone **20** afforded **25a** in 88% yield as a pale yellow oil: NMR 3.68 (2 H, s, SO_2CH_2CO).

(d) 7-[2-[3-Hydroxy-4-(4-fluorophenoxy)butyl]-1,1,4-trioxo-3-thiazolidinyl]heptanoic Acid (25b). Hydrogenolysis of ether–ester **25a** using the procedure described for the preparation of **13b** followed by chromatography on silica gel using $CHCl_3$–HOAc (25:1) as eluent gave **25b** in 75% yield as a pale yellow, viscous oil: IR (neat film) 1770–1670 (strong CO absorption), 1330, 1130 cm^{-1} (SO_2); NMR 2.32 (2 H, t, CH_2CO_2H), 3.60–4.30 [6 H, m, containing singlets at 3.80 and 3.90, CH_2O, CHOH, SO_2CH_2CO, and CH_2N (1-H)], 4.61 (H, t, SO_2CHN), 6.67–7.10 (4 H, m, 4-F-C_6H_4), and 7.30 (2 H, s, OH and CO_2H). Anal. ($C_{20}H_{28}FNO_7S$) C, H, N.

Biological. Mouse Ovary Prostaglandin Assay.[26] Virgin femal mice over 70 days old (Charles River CD-1) are killed and the ovaries dissected and denuded of adhering fatty tissue. Three ovaries are weighed (15–25 mg) and placed in 2 mL of aerated Krebs–Ringer phosphate buffer, pH 7.2, containing 1 μCi of [8-^{14}C]adenine. The tissues are incubated 60 min at 37 °C with moderate agitation to cause a pool of intracellular [^{14}C]-ATP to accumulate.

The following additions are then made: 0.2 mL of 0.05 M theophylline in 0.15 M NaCl and the test compound in 0.1 mL of Me_2SO. The ovaries are incubated again at 37 °C for 30 min. The reactions are terminated by the addition of 0.4 mL of 10% trichloroacetic acid, and 50 μL of a nucleotide mixture solution[30] is added to facilitate recovery of the labeled nucleotides. The incubation mixture is transferred to a glass homogenizer and the ovarian tissue is homogenized into the acidified incubation solution. The homogenate is centrifuged 1000g for 5 min and the [^{14}C]-cAMP is isolated from the supernatant fluid as described by Humes and co-workers[30] including the final paper chromatography step.

Rat Kidney Prostaglandin Receptor Binding Assay.[27a] This assay, based upon displacement of [^{3}H]-PGE_1 from a kidney plasma membrane binding fraction prepared from Sprague–Dawley male rats (120–150 g) according to the method of Fitzpatrick and co-workers,[31] is carried out essentially in the same manner as the previously reported rat lipocyte PGE_1 binding assay[32] which has been described in detail. In the title assay, appropriate concentrations of the test compound were incubated with 0.4 ng of [^{3}H]-PGE_1 and 125 μg of the rat kidney plasma membrane binding preparation[27b] for 60 min at 37 °C. Each sample was then treated with 1 mL of 0.01 M Tris HCl–saline (pH 7.5) buffer and the membrane-bound [^{3}H]-PGE_1, collected by millipore filtration (HAWP 02500 filters, Millipore Corp.). After rinsing with 1.5 mL of the Tris buffer, the amount of

membrane-bound [^{3}H]-PGE$_1$ was determined in methyl cellosolve–aquasol (1:6) with a Packard liquid scintillation counter. Duplicate experiments were run on each test compound at each of three concentrations.

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11,12-Secoprostaglandins. 4. 7-(*N*-Alkylmethanesulfonamido)heptanoic Acids

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A series of 7-(*N*-alkylmethanesulfonamido)heptanoic acids has been prepared which represents an extension of our 8-aza-11,12-secoprostaglandin studies. The compounds mimic the natural prostaglandins in that they markedly stimulate cAMP formation in the mouse ovary assay.

Previous papers[1-3] in this series have described a group of 11,12-secoprostaglandin analogues that mimic the action of the natural prostaglandins in that they stimulate cAMP formation in the mouse ovary PG assay.[4] Some of these