300–350 g which had been treated 5 days prior to sacrifice with 500 mg/kg Aroclor 1254. The S-9 fraction was prepared by centrifugation of the liver homogenate (25% in 0.15 M KCl) at 9000*g* for 15 min as described by Ames et al.[30] The S-9 fraction was filter sterilized at 4 °C using a 600-mL Millipore pressure filtration apparatus equipped with 0.45-μm Swinex filter (Millipore Corp., Bedford, Mass.). Each microsomal preparation was checked for sterility on nutrient agar prior to storage at −80 °C. The S-9 mix contained, per milliliter, 100 μmol of potassium phosphate buffer, pH 7.4; 8 μmol of $MgCl_2$; 1.65 μmol of KCl; 5 μmol of glucose 6-phosphate; 4 μmol of $NADP^+$; and 0.5 mL of S-9 fraction.

The procedure of Ames et al.[30] was employed in performing these assays. In summary, various concentrations of chrysenes in 50 μL of dimethyl sulfoxide (Me_2SO) were added to 0.1 mL of an overnight nutrient broth culture of the bacterial tester strain. After the addition of 200 μL of S-9 mix and 2 mL of molten top agar at 45 °C, the contents were mixed and poured on minimal glucose agar plates. Percent survivors for all compounds assayed was determined by employing dilutions of bacterial broth under identical conditions, with the exception that excess histidine was added to the top agar. No significant toxicity toward the bacteria was observed for the compounds assayed. All compounds were analyzed by high-pressure LC, GLC, and/or TLC prior to mutagenicity assays; in all cases, purity was greater than 99%.

Acknowledgment. This study was supported by National Cancer Institute Grant CA 12376. S.S.H. is a recipient of NCI Research Career Development Award 5K04 CA 00124. We thank Dr. Ronald G. Harvey for his generous gift of a sample of 5,6-dihydro-5-methylchrysene. We are indebted to Ms. Lorraine Tulley for mutagenicity assays.

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Synthesis and Biological Activity of Carboxyl-Terminus Modified Prostaglandin Analogues

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A series of PGE_2, 16,16-dimethyl-PGE_2, and $PGF_{2\alpha}$ analogues modified at the carboxyl terminus with tetrazole, amide, acylurea, imide, and sulfonimide functionalities was evaluated for uterine stimulant, bronchodilator, hypotensive, gastric antisecretory, and diarrheal activity. These compounds were prepared by modification of the Corey prostaglandin synthesis utilizing as a key step condensation of known hemiacetals with the ylide derived from the requisite substituted phosphonium salts. Structure–activity relationships suggest that a proton at the C-1 position appears necessary for agonist activity and the acidity of this proton has a relatively greater influence on activity than pendant steric bulk. Noteworthy are the tissue-selective bronchodilator activity of *N*-acetyl-PGE_2-carboxamide and the selectivity for uterine tissue of *N*-methanesulfonyl-PGE_2-carboxamide, 2-decarboxy-2-(tetrazol-5-yl)-16,16-dimethyl-PGE_2, *N*-acetyl-16,16-dimethyl-PGE_2-carboxamide, and *N*-methanesulfonyl-16,16-dimethyl-PGE_2-carboxamide.

Achievement of tissue selectivity and metabolic stability has emerged as a necessary requirement for the realization of the potential therapeutic utility of prostaglandins. In pursuit of this objective, numerous prostaglandin analogues modified in the *n*-amylcarbinol side chain or cyclopentane ring have been prepared.[1,2] One line of research pursued

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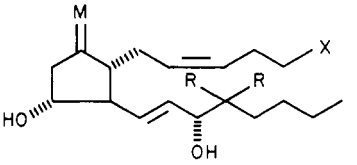
Table I. Structures and Biological Activities of Carboxyl-Terminus Modified Prostaglandin Analogues



compd	X	M	R	effects: uterine[a]	broncho-dilator[b]	blood pressure[c]	anti-secretory[d]	diar-rheal[e]
PGE_2	CH_2CO_2H	O	H	100	100	100 (−)	100	100
4a	CH_2CN_4H	O	H	100	65	10 (−)	35	50
4b	$CH_2CONHCOCH_3$	O	H	65	63	25 (−)	160	100
4c	$CH_2CONHCOC_6H_5$	O	H	67	87	10 (−)	40	83
4d	$NHCONHCOCH_3$	O	H	<0.1	25	<0.5	0	<5
4e	$CH_2CONHCONHC_2H_5$	O	H	0.2	28	0.5 (−)	0	27
4f	$CH_2CONHSO_2CH_3$	O	H	7	47	1 (−)	12	10
4g	$CH_2CONHSO_2C_6H_5$	O	H	3.1	28	<0.5	20	33
4h	CH_2CONH_2	O	H	0.6	28	10 (−)	0	10
$PGF_{2\alpha}$	CH_2CO_2H	α-OH	H	10		10 (+)		6.5
5a	CH_2CN_4H	α-OH	H	0.8		2.5 (−)		<5
5b	$CH_2CONHCOCH_3$	α-OH	H	30		<0.5		78
5c	$CH_2CONHCOC_6H_5$	α-OH	H	0.9		0.5 (+/−)		<5
5d	$NHCONHCOCH_3$	α-OH	H	<0.1		<0.5		<5
5e	$CH_2CONHCONHC_2H_5$	α-OH	H	<0.1		<0.5		<10
5f	$CH_2CONHSO_2CH_3$	α-OH	H	<0.1		<0.5		25
5g	$CH_2CONHSO_2C_6H_5$	α-OH	H	<0.1		<0.5		<10
5h	CH_2CONH_2	α-OH	H	<0.1		2.5 (+)		<5
16,16-PGE_2	CH_2CO_2H	O	CH_3	33	41	10 (−)	360[f]	5300
7a	CH_2CN_4H	O	CH_3	120	76	10 (−)	130[f]	2550
7b	$CH_2CONHCOCH_3$	O	CH_3	100	24	2.5 (−)	330[f]	1250
7f	$CH_2CONHSO_2CH_3$	O	CH_3	25	28	<0.5	220[f]	1350

[a] Spasmogenic effects (PGE = 100) on isolated guinea pig uterus. [b] Inhibition (PGE_2, 2.85×10^{-4} aerosol solution = 100) of histamine-induced bronchoconstriction in conscious guinea pigs. [c] Threshold dose (PGE_2, 0.1 μg/kg, iv = 100) for effect on blood pressure in anesthesized dogs (−, depressor; +, pressor). [d] Inhibition (PGE_2, 50 μg/kg, iv = 100) of pentagastrin-stimulated gastric acid secretion in anesthesized rats. [e] Intravenous induction of diarrhea in conscious mice (PGE_2 = 100). [f] Compounds were tested at 10 μg/kg. For details of the procedures used, see Experimental Section.

in our laboratories has been the relatively unexplored area of modification of the C_1 carboxyl terminus.[3] The synthesis and biological evaluation of a series of PGE_2 and $PGF_{2\alpha}$ analogues containing a variety of carboxylic acid surrogates differing in steric bulk and pK_a are the subject of this paper.

Chemistry. The Corey synthesis (Scheme I),[4] which is ideally suited to synthesize PGE_2 and $PGF_{2\alpha}$ analogues modified in either side chain, was used to prepare the analogues listed in Table I. Condensation of the optically active hemiacetal 1[5] with the ylide derived from the requisite phosphonium salts **2a–g** listed in Table II and sodium methylsulfinylcarbanide[6] in dimethyl sulfoxide gave the corresponding $PGF_{2\alpha}$ bis(tetrahydropyranyl) ethers **3a–g**. While ylides from phosphonium salts containing a δ ester functionality are known to undergo facile intramolecular acylation,[7] ylides having a δ carboxylic acid moiety undergo the expected Wittig reaction.[4] Consistent with these reports, the ylides containing a highly acidic moiety (**2a,f,g**) reacted smoothly with the hemiacetal 1, while ylides with less acidic groups (**2b–e**) appeared to undergo both reactions concurrently; thus, larger excesses of these ylides were necessary. Not unexpectedly, the ylide with a δ carboxamide moiety (**2h**) underwent exclusively intramolecular acylation. Therefore, compound **3h** (X = CH_2CONH_2) was prepared by treatment of $PGF_{2\alpha}$ 11,15-bis(tetrahydropyranyl) ether[5] with 1,1′-carbonyldiimidazole, followed by anhydrous ammonia. Hydrolysis of the tetrahydropyranyl ether protecting groups of **3a–h** with aqueous acetic acid at 40–45 °C afforded the $PGF_{2\alpha}$ analogues **5a–h**. Oxidation of **3a–h** with Jones reagent,[8] followed by hydrolysis of the crude product, provided the PGE_2 analogues **4a–h**. Preparation of the 16,16-dimethyl-PGE_2 analogues **7a,b,f** was carried out as described above, starting with the optically active hemiacetal **6**.[9]

Table II. pK_a of Phosphonium Salts $Ph_3P^+(CH_2)_3XBr^-$

compd	X	pK_a[a]
	CH_2CO_2H	5.19
2a	CH_2CN_4H	4.93
2b	$CH_2CONHCOCH_3$	∼12.9[b]
2c	$CH_2CONHCOC_6H_5$	∼12.9[b]
2d	$NHCONHCOCH_3$	[c]
2e	$CH_2CONHCONHCH_2CH_3$	[c]
2f	$CH_2CONHSO_2CH_3$	5.25
2g	$CH_2CONHSO_2C_6H_5$	5.12
2h	CH_2CONH_2	∼15.1[d]

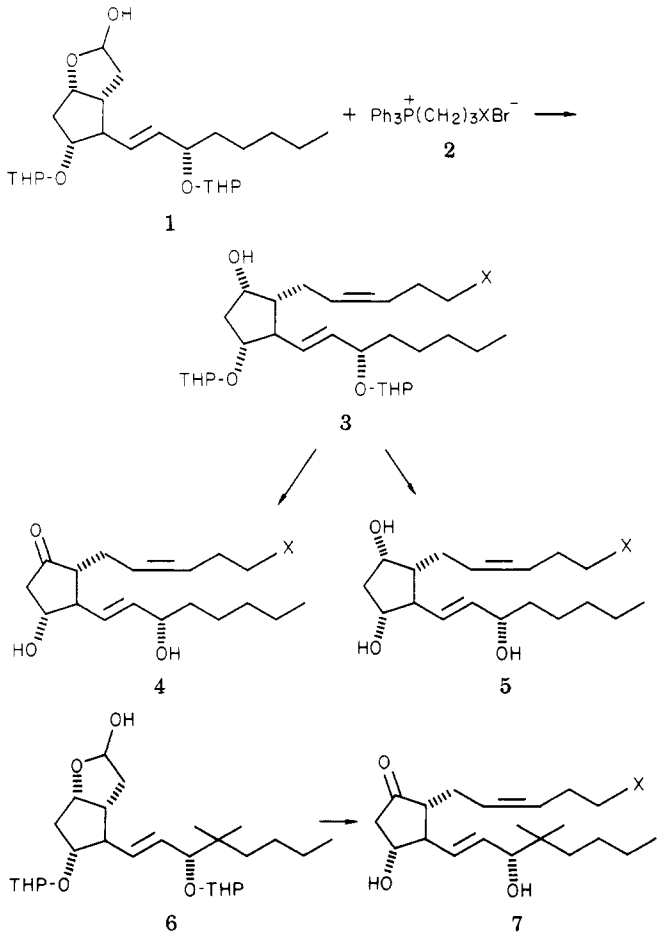
[a] Determined in 1:1 ethanol-water. [b] Based on pK_a of *N*-acetylacetamide; see J. T. Edward and K. A. Terry, *J. Chem. Soc.*, 3527 (1957). [c] pK_a unknown; see J. S. Fitz, *Anal. Chem.*, **24**, 674 (1952). [d] pK_a of acetamide; see G. E. K. Branch and J. O. Clayton, *J. Am. Chem. Soc.*, **50**, 1680 (1928).

Biology. Since PGE_2 and $PGF_{2\alpha}$ exhibit an array of pharmacological activities,[10] a variety of in vitro and in vivo tests was used to assess potency and selectivity of the analogues prepared.

The abortifacient activity of prostaglandins has been the subject of recent intense clinical investigation.[11] Because in humans this activity is ascribed to direct uterine stimulation, uterine stimulant effects of the analogues as a measure of potential abortifacient activity were determined on the isolated guinea pig uterus.

Prostaglandins of the E series inhibit gastric acid secretion in the rat,[12] dog,[13] monkey[14] and man,[15] and the accelerated healing of duodenal ulcers by prostaglandins in man has been attributed, at least in part, to inhibition

Scheme I



of hypersecretion of acid.[16] Consequently, antisecretory activity of the compounds was determined in anesthetized rats to assess potential antiulcer utility.

Intravenous administration of PGE_1 to normal volunteers and hypertensive patients has been reported to induce a fall in blood pressure.[17] In addition, upon intravenous administration, E prostaglandins are potent systemic blood-pressure depressor agents in the rat and dog, an effect attributed to direct vasodilatation.[18] Blood pressure effects were therefore determined following intravenous administration of the compounds to anesthetized dogs.

Aerosol administration of PGE_1 and PGE_2 causes bronchodilation in both healthy subjects[19] and in asthmatics,[20,21] although the therapeutic utility of PGE_1 and PGE_2 aerosols may be limited by upper airway irritation and coughing.[19,20] Since E prostaglandins also inhibit histamine-induced bronchospasm in the guinea pig,[22] bronchodilator activity of the PGE_2 analogues was determined in this model following aerosol administration.

Administration of prostaglandins in therapeutically useful doses is frequently accompanied by limiting gastrointestinal side effects, especially diarrhea. Intravenous injection of a variety of prostaglandins to mice has been found in our laboratories to provoke a reproducible occurrence of watery diarrhea, results which are consistent with those reported by Robert and co-workers in a rat assay.[23] Thus, this mouse model was used to determine diarrheal activity of the analogues.

Results and Discussion

A rational approach to overcome the lack of oral efficacy and the short duration of action of the natural prostaglandins is to design analogues resistant to metabolic inactivation. Examples of this approach are the 15- and 16-alkylprostaglandins which are resistant to C_{15} dehydrogenation, the primary mode of metabolic inactivation of the natural prostaglandins.[24] The relatively short half-life of 15(S)-methyl-$PGF_{2\alpha}$ (~2 min) in female subjects,[25] however, suggests that β-oxidation, another catabolic pathway, may significantly contribute to the metabolic inactivation of these prostaglandins. Consequently, one of our approaches to this problem has been to prepare analogues modified at the C_1 carboxyl terminus designed to be resistant to β oxidation. It was anticipated, in addition, that by varying the steric bulk and the pK_a (Table II) at the C_1 terminus, tissue selectivity might be achieved. Although susceptibility to β oxidation and duration of action were not specifically evaluated, the biological data summarized in Table I indicate that the goal of enhanced tissue selectivity has been, at least in part, realized.

The PGE_2-tetrazole analogue **4a**[26] exhibited a pharmacological profile qualitatively and quantitatively similar to that of PGE_2, which is not unexpected in view of the close similarity of the physical properties of the carboxylic acid and tetrazole moieties.[27] The nonacidic PGE_2-carboxamide **4h**, in contrast, displayed reduced overall pharmacological activity. Acylation of the amide group gave the PGE_2-imides **4b** and **4c**. These analogues are more acidic than the amide **4h** but possess significantly greater steric bulk around the acidic proton. The increased activities displayed by these compounds compared to those of **4h** suggest that biological activity is less sensitive to pendant steric bulk than to acidity. The potent bronchodilator activity of **4b** observed following aerosol administration to guinea pigs has been confirmed in man.[28] Replacement of the imide functionality by an acylated urea group, as in analogues **4d** and **4e**, resulted in a marked decrease in pharmacological activity. While the weak activity of **4e** suggests that factors other than the pK_a or pendant steric bulk are important, compound **4d** provides another example of the previously noted sensitivity of the activity of E prostaglandins to small changes at C-2.[29] Replacement of the pendant carbonyl of the imides **4b** and **4c** by a sulfone group provided the sulfonimides **4f** and **4g**, which have a pK_a similar to that of PGE_2. Although initial evaluation of the latter two analogues indicated weaker overall activity than exhibited by either PGE_2 or the imides **4b** and **4c**, further studies showed **4f** to have rat uterus stimulant effects in vitro and abortifacient activity in the guinea pig in vivo[30] comparable to that of PGE_2. The reduced hypotensive and diarrheal activity compared to abortifacient activity in vivo suggests this compound is a more selective abortifacient than PGE_2.

The activities of $PGF_{2\alpha}$ were found to be more sensitive to structural change at the C_1 terminus than those of PGE_2. With the exception of greater uterine stimulant and diarrheal potency of the $PGF_{2\alpha}$-methylimide **5b**, all other analogues (**5a,c–h**) were less potent than $PGF_{2\alpha}$. Since *N,N*-dimethyl-$PGF_{2\alpha}$-carboxamide is reported to be a $PGF_{2\alpha}$ antagonist,[31] the hypertensive activity of compound **5h** provides evidence for the importance of an acidic center at C-1 for agonist activity.

The 16,16-dimethyl-PGE_2 analogues **7a,b,f** were designed to be resistant to both β oxidation and C_{15} dehydrogenation. It was therefore gratifying to find that all three analogues exhibit potent activity in vivo. In addition, a comparison of the uterine stimulant and hypotensive and diarrheal effects of **7a,b,f** with those of 16,16-dimethyl-PGE_2 demonstrate that the former analogues are more

selective for uterine tissue and, thus, may be more selective abortifacient agents.

Experimental Section

Melting points were taken in open capillary tubes and are uncorrected. ^{1}H NMR spectra, obtained on a Varian T-60 spectrometer, were recorded in $CDCl_3$ unless otherwise noted, and data are reported as δ values with respect to Me_4Si. IR spectra, obtained on a Perkin-Elmer 237B spectrophotometer, were recorded in $CHCl_3$ unless otherwise noted, and data are reported in reciprocal centimeters. High-resolution mass spectra were obtained on an AEI-MS30 coupled with a DS-50 system. Titrations were run on a Metrohm E436 potentiograph.

Column chromatography was carried out on Mallinckrodt SilicAR CC-7 silica gel. Thin-layer chromatography (TLC) was used to monitor column fractions and to establish homogeneity of products. TLC was performed on EM Reagent silica gel 60F-254 plates (250-μm thick). Spots were located by spraying with vanillin in ethanol–phosphoric acid, followed by charring at 200 °C. A standard solvent system of 10% MeOH in CH_2Cl_2 was used for all products.

Chromatographed oils were prepared for analysis and biological testing by heating at 56 °C in vacuo for 8 h. When analyses are indicated only by the symbols of the elements, the analytical results obtained are within 0.4% of the theoretical values. Satisfactory high-resolution mass values were obtained for the peaks indicated.

Anhydrous $MgSO_4$ was used to dry organic extracts. Since optically active starting materials were employed, the absolute configuration of all chiral centers are identical with those found in the natural prostaglandins.

2-Decarboxy-2-(tetrazol-5-yl)-PGE$_2$ (4a) and -PGF$_{2\alpha}$ (5a). A solution of 5-bromovaleronitrile (55.5 g, 0.34 mol) and triphenylphosphine (65.0 g, 0.25 mol) in 150 mL of xylene was heated at reflux for 2.5 h and then was cooled. The resultant solid was collected by filtration, slurried with ethyl acetate, and dried to afford 102.4 g (96%) of the corresponding phosphonium salt as an off-white solid, mp 230–232.5 °C (lit.[32] mp 229–230 °C). A solution of this salt (102.4 g, 0.24 mol), sodium azide (23.6 g, 0.43 mol), ammonium chloride (19.3 g, 0.36 mol), and lithium chloride (322 mg) in 550 mL of DMF was heated under nitrogen at 130 °C for 18 h. The solution was concentrated and the resultant solid was triturated with $CHCl_3$. Concentration of the $CHCl_3$, followed by recrystallization of the crude product from EtOH–ether, provided 84.0 g (75%) of **2a** as a white solid: mp 212–213 °C; NMR δ 7.72 (15 H, m, C_6H_5), 3.66 (2 H, m, CH_2P), 3.18 (2 H, t, CH_2CN_4). Anal. ($C_{23}H_{24}N_4PBr$) C, H, N.

To a solution of **2a** (2.7 g, 5.78 mmol) in 10 mL of Me_2SO was added 5.07 mL of a 2.17 M solution of sodium methylsulfinylcarbanide[6] in Me_2SO. To the resultant red ylide solution was added the hemiacetal 1[5] (845 mg, 1.93 mmol) dissolved in 5 mL of Me_2SO. The mixture was stirred under nitrogen at 45 °C for 1 h and then was poured onto ice water–ethyl acetate. The aqueous layer was acidified with 10% HCl and the acidified aqueous layer extracted with ethyl acetate. The combined organic extracts were dried and concentrated. Purification of the crude product by column chromatography using mixtures of ethyl acetate in $CHCl_3$ as eluants provided 810 mg (77%) of **3a** as a viscous, colorless oil: NMR δ 5.43 (6 H, br, CH=CH, OH, and NH), 4.70 (2 H, br, OCHO), 2.99 (2 H, t, CH_2CN_4).

Hydrolysis of **3a** (335 mg) in a 65:35 mixture of acetic acid–water (10 mL) under nitrogen at 40–45 °C for 3 h provided, after concentration and purification by column chromatography using mixtures of MeOH in $CHCl_3$ as eluants, 103 mg (45%) of **5a** as a viscous, colorless oil: NMR (CD_3OD) δ 5.46 (4 H, m, trans and cis CH=CH), 2.93 (2 H, t, CH_2CN_4); IR (CH_3CN) 3480 (OH and NH), 965 cm^{-1} (trans CH=CH); MS ($C_{20}H_{32}N_4O_2$, P – H_2O) calcd, 360.2525; found, 360.2463.

To a solution of **3a** (810 mg, 1.48 mmol) in 5 mL of acetone cooled to 0 °C under nitrogen was added 0.61 mL of Jones reagent.[8,33] The mixture was stirred for 3 min and then isopropyl alcohol (0.61 mL) was added. The mixture was diluted with ethyl acetate, washed with water, dried, and concentrated. Hydrolysis of the resultant crude product in acetic acid–water (65:35) for 20 h at 25 °C afforded, after concentration and purification by column chromatography using mixtures of ethyl acetate in $CHCl_3$ as eluants, 122 mg (22%) of **4a** as a viscous, colorless oil: NMR (CD_3OD) δ 5.63 (2 H, m, trans CH=CH), 5.39 (2 H, m, cis CH=CH), 2.92 (2 H, t, CH_2CN_4); IR (CH_3CN) 1732 (ketone C=O), 973 cm^{-1} (trans CH=CH); MS ($C_{20}H_{30}N_4O_2$, P – H_2O) calcd, 358.2368; found, 358.2398.

***N*-Acetyl-PGE$_2$-carboxamide (4b) and -PGF$_{2\alpha}$-carboxamide (5b).** A mixture of 5-bromovaleramide (100 g, 0.55 mol), acetic anhydride (62.4 g, 0.61 mol), and H_2SO_4 (5.4 g) was heated under nitrogen at steam bath temperature for 1.5 h, then was let cool, diluted with water, and filtered. The crude product was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$ and saturated NaCl, dried, and concentrated. Recrystallization from CH_2Cl_2–hexane provided 64.8 g (53%) of *N*-acetyl-5-bromovaleramide, mp 88–90 °C. A solution of *N*-acetyl-5-bromovaleramide (86 g, 0.39 mol) and triphenylphosphine (110 g, 0.42 mol) in 500 mL of xylene was heated at reflux for 3 h and then let cool. Recrystallization of the resultant oil from CH_2Cl_2–ethyl acetate provided 100 g (53%) of **2b** as an off-white solid: mp 161–162 °C; NMR δ 7.79 (15 H, m, C_6H_5), 3.68 (2 H, m, CH_2P), 2.80 (2 H, m, CH_2CO), 2.24 (3 H, s, $COCH_3$). Anal. ($C_{25}H_{27}NO_2PBr$) C, H, N.

To a solution of **2b** (2.9 g, 6.0 mmol) in 5 mL of Me_2SO was added 5 mL of a 2.3 M solution of sodium methylsulfinylcarbanide[6] in Me_2SO. A solution of the hemiacetal 1[5] (876 mg, 2.0 mmol) in 3 mL of Me_2SO was added to the red ylide solution, and the mixture was stirred under nitrogen for 20 h and then poured onto ice water–ethyl acetate. Isolation and purification as described above provided 689 mg (61%) of **3b** as a viscous, colorless oil: NMR δ 5.47 (4 H, m, trans and cis CH=CH), 4.70 (2 H, m, OCHO), 2.37 (3 H, s, $COCH_3$).

Hydrolysis of **3b** (108 mg, 0.19 mmol) and purification of the crude product as described above gave 42 mg (58%) of **5b** as a viscous, colorless oil: NMR δ 5.36 (4 H, m, trans and cis CH=CH), 3.97 (3 H, m, CHO), 2.33 (3 H, s, $COCH_3$); IR 1705 (imide C=O), 970 cm^{-1} (trans CH=CH); MS ($C_{22}H_{33}O_3N_2$, P – $2H_2O$) calcd, 359.2458; found 359.2590.

Oxidation[33] of **3b** (581 mg, 1.0 mmol), followed by hydrolysis and purification of the crude product as described above, provided 135 mg (36%) of **4b** as a white solid: mp 83–84 °C after recrystallization from ethyl acetate–hexane; IR 1685 and 1730 (imide C=O), 965 cm^{-1} (trans CH=CH); NMR δ 5.63 (2 H, m, trans CH=CH), 5.40 (2 H, m, cis CH=CH), 4.10 (2 H, m, CHO), 2.35 (3 H, s, $COCH_3$). Anal. ($C_{22}H_{35}NO_5$) C, H, N.

***N*-Benzoyl-PGE$_2$-carboxamide (4c) and -PGF$_{2\alpha}$-carboxamide (5c).** A mixture of benzamide (7.26 g, 0.06 mol) and 5-bromovaleric acid chloride (11.9 g, 0.06 mol) was heated at 100 °C for 3 h and then let cool. The crude solid was triturated with ether and then recrystallized from CH_2Cl_2–hexane to provide 7.59 g (45%) of *N*-benzoyl-5-bromovaleramide as a tan solid, mp 118–120 °C. A solution of *N*-benzoyl-5-bromovaleramide (8.24 g, 0.03 mol) and triphenylphosphine (8.4 g, 0.03 mol) in 50 mL of xylene was heated at reflux for 5.5 h and then let cool. The xylene was decanted, and the oily product was triturated with ethyl acetate and then recrystallized from CH_2Cl_2–ethyl acetate to provide 9.4 g (58%) of **2c** as a white solid: mp 194–195 °C; NMR δ 7.66 (20 H, m, C_6H_5), 3.72 (2 H, m, PCH_2), 3.08 (2 H, t, CH_2CO). Anal. ($C_{30}H_{29}NO_2PBr$) C, H, N.

To a solution of **2c** (4.16 g, 7.6 mmol) in 8 mL of Me_2SO was added 7.5 mL of a 1.94 M solution of sodium methylsulfinylcarbanide[6] in Me_2SO. To the resultant red ylide solution was added a solution of the hemiacetal 1[5] (400 mg, 0.91 mmol) in 3 mL of Me_2SO. The mixture was stirred under nitrogen at 25 °C for 19 h. Isolation and purification as described above provided 242 mg (42%) of **3c** as a viscous, colorless oil: NMR δ 7.63 (5 H, m, C_6H_5), 5.51 (4 H, m, cis and trans CH=CH).

Hydrolysis of **3c** (100 mg, 0.16 mmol) and purification of the crude product as described above provided 10 mg (14%) of **5c** as a white solid: mp 110–111 °C after recrystallization from ethyl acetate–hexane; NMR δ 7.80 (5 H, m, C_6H_5), 5.45 (4 H, m, trans and cis CH=CH), 4.06 (3 H, m, CHO); IR (KBr) 1647 and 1620 (imide C=O), 970 cm^{-1} (trans CH=CH). Anal. ($C_{27}H_{39}NO_5$) C, H, N.

Oxidation[33] of **3c** (140 mg, 0.22 mmol), followed by hydrolysis and purification of the crude product as described above, afforded 8 mg (8%) of **4c** as a white solid: mp 108–109 °C after recrys-

tallization from ethyl acetate–hexane; NMR δ 7.73 (5 H, m, C_6H_5), 5.68 (2 H, m, trans CH=CH), 5.42 (2 H, m, cis CH=CH), 4.09 (2 H, m, CHO); IR 1690 and 1737 (imide C=O), 965 cm^{-1} (trans CH=CH). Anal. ($C_{27}H_{37}NO_5$) C, H, N.

***N*-Acetyl-2-aza-PGE$_2$-carboxamide (4d) and -PGF$_{2\alpha}$-carboxamide (5d).** To a solution of 3-bromopropylamine in 1,2-dichloroethane [prepared by treating a suspension of 3-bromopropylamine hydrobromide (32.8 g, 0.15 mol) in 65 mL of 1,2-dichloroethane with 21 mL of 40% KOH] was added a solution of acetyl isocyanate in 1,2-dichloroethane [distillate from reaction of acetamide (16.8 g, 0.28 mol) and oxalyl chloride (41.8 g, 0.33 mol)][34] until the addition was no longer exothermic. The mixture was stirred for 15 min and filtered to remove a white precipitate. Concentration of the filtrate, followed by recrystallization of the crude product from EtOH, provided *N*-acetyl-*N'*-(3-bromoprop-1-yl)urea weighing 7.94 g (24%), mp 120–121.5 °C. A solution of *N*-acetyl-*N'*-(3-bromoprop-1-yl)urea (5.57 g, 0.025 mol) and triphenylphosphine (7.87 g, 0.030 mol) in 100 mL of CH_3CN was heated at reflux for 48 h and then cooled. Collection of the resultant precipitate, followed by recrystallization from EtOH–ether, afforded 7.22 g (60%) of **2d** as a white solid: mp 243–245 °C; NMR δ 7.64 (15 H, m, C_6H_5), 3.46 (2 H, m, PCH_2), 2.05 (3 H, s, $COCH_3$). Anal. ($C_{24}H_{26}N_2O_2PBr$) C, H, N.

To a solution of **2d** (1.45 g, 3.0 mmol) in 4 mL of Me_2SO was added 4.4 mL of a 1.34 M solution of sodium methylsulfinylcarbanide[6] in Me_2SO. To the red ylide solution was added a solution of the hemiacetal **1**[5] (438 mg, 1.0 mmol) in 2 mL of Me_2SO. The mixture was stirred under nitrogen at 25 °C for 22 h and then poured onto ice water–ethyl acetate. Isolation and purification as above provided 265 mg (50%) of **3d** as a viscous, colorless oil: NMR δ 9.92 (1 H, s, CONHCO), 8.47 (1 H, m, NHCO), 5.43 (4 H, m, trans and cis CH=CH), 4.67 (2 H, br, OCHO), 2.10 (3 H, s, $COCH_3$).

Hydrolysis of **3d** (108 mg, 0.2 mmol) and purification of the crude product as described above gave 44 mg (56%) of **5d** as an off-white solid: mp 94–95 °C after recrystallization from ethyl acetate; IR 1690 (carbonyls), 965 cm^{-1} (trans CH=CH); NMR δ 9.59 (1 H, s, CONHCO), 8.36 (1 H, t, NHCO), 5.44 (4 H, m, trans and cis CH=CH), 4.05 (3 H, m, CHO), 2.10 (3 H, s, $COCH_3$). Anal. ($C_{21}H_{36}N_2O_5$) C, H, N.

Oxidation[33] of **3d** (265 mg, 0.50 mmol), followed by hydrolysis and purification of the crude product as described above, afforded 74 mg (38%) of **4d** as a white solid: mp 111–112 °C after recrystallization from ethyl acetate–hexane; NMR δ 9.66 (1 H, s, CONHCO), 8.43 (1 H, t, NHCO), 5.47 (4 H, m, trans and cis CH=CH), 4.04 (2 H, m, CHO), 2.12 (3 H, s, $COCH_3$); IR (KBr) 1709, 1689, 1667 (carbonyls), 967 cm^{-1} (trans CH=CH). Anal. ($C_{21}H_{34}N_2O_5$) C, H, N.

***N*-Ethylcarbamoyl-PGE$_2$-carboxamide (4e) and -PGF$_{2\alpha}$-carboxamide (5e).**[35] A mixture of ethylurea (1.76 g, 0.02 mol) and 5-bromovaleric acid chloride (4.0 g, 0.020 mol) in 20 mL of benzene was heated at reflux for 2 h and then concentrated. Recrystallization of the crude product afforded 2.8 g (56%) of *N*-ethyl-*N'*-(5-bromovaleroyl)urea as a white solid, mp 95–97 °C. A mixture of *N*-ethyl-*N'*-(5-bromovaleroyl)urea (2.51 g, 10 mmol) and triphenylphosphine (2.62 g, 10 mmol) in 20 mL of toluene was heated at reflux for 20 h and then was let cool. The resultant solid was collected to provide 2.62 g (51%) of **2e** after crystallization from EtOH–hexane: mp 190–191 °C; NMR δ 7.74 (15 H, m, C_6H_5), 3.82 (2 H, m, PCH_2), 3.22 (2 H, q, NCH_2), 2.76 (2 H, t, $COCH_2$), 1.08 (3 H, t, CH_3). Anal. ($C_{26}H_{30}N_2O_2PBr$) C, H, N.

To a solution of **2e** (1.75 g, 3.4 mmol) in 3 mL of Me_2SO was added 4.0 mL of a 1.72 M solution of sodium methylsulfinylcarbanide[6] in Me_2SO. To the resultant red ylide solution was added a solution of **1**[5] (438 mg, 1.0 mmol) in 3 mL of Me_2SO. The mixture was stirred under nitrogen at 25 °C for 16 h and then poured onto ice water–ethyl acetate. Isolation and purification as described above afforded 387 mg (65%) of **3e** as a viscous, colorless oil: NMR δ 9.76 (1 H, s, CONHCO), 8.53 (1 H, t, CONH), 5.45 (4 H, m, trans and cis CH=CH), 4.71 (2 H, m, OCHO), 3.40 (2 H, q, NCH_2), 1.16 (3 H, t, CH_3).

Hydrolysis of **3e** (80 mg, 0.13 mmol) and purification of the crude product as described above provided 21 mg (38%) of **5e** as a viscous, colorless oil: NMR δ 5.40 (4 H, m, trans and cis CH=CH), 4.05 (3 H, m, CHO); IR (mull) 1680 (imide C=O), 965 cm^{-1} (trans CH=CH); MS ($C_{23}H_{36}N_2O_3$, P – $2H_2O$) calcd, 388.2723; found, 388.2789.

Oxidation[33] of **3e** (300 mg, 0.50 mmol), followed by hydrolysis and purification of the crude product as described above, gave 20 mg (9.5%) of **4e** as a crystalline solid: mp 87–88 °C after recrystallization from ethyl acetate–hexane; NMR δ 9.40 (1 H, m, CONHCO), 8.40 (1 H, m, NHCO), 5.58 (2 H, m, trans CH=CH), 5.33 (2 H, m, cis CH=CH), 3.99 (2 H, m, CHO); IR (KBr) 1767, 1745, 1718 and 1695 (carbonyls), 970 cm^{-1} (trans CH=CH). Anal. ($C_{23}H_{38}N_2O_5$) C, H, N.

***N*-Methanesulfonyl-PGE$_2$-carboxamide (4f) and -PGF$_{2\alpha}$-carboxamide (5f).** A mixture of methanesulfonamide (77 g, 0.81 mol) and 5-bromovaleric acid chloride (161 g, 0.81 mol) was heated at 85–90 °C for 1 h, then was let cool, and diluted with ethyl acetate (1200 mL). The solution was washed with water and saturated NaCl, dried, and concentrated to ca. 500 mL. Cooling the solution (0 °C) provided *N*-methanesulfonyl-5-bromovaleramide, weighing 163 g (52%), mp 97–98 °C. Heating a solution of *N*-methanesulfonyl-5-bromovaleramide (163 g, 0.42 mol) and triphenylphosphine (190 g, 0.72 mol) in 450 mL of xylene at reflux for 2 h provided, after collection of the crude product and recrystallization from acetone–ethyl acetate, 207 g (96%) of **2f**: mp 190–191 °C; NMR δ 7.68 (15 H, m, C_6H_5), 3.65 (2 H, m, CH_2P), 3.12 (3 H, s, CH_3), 2.80 (2 H, t, CH_2CO). Anal. ($C_{24}H_{27}NO_3SPBr$) C, H, N.

To a solution of **2f** (9.47 g, 18 mmol) in 12 mL of Me_2SO was added 25.6 mL of a 1.42 M solution of sodium methylsulfinylcarbanide[6] in Me_2SO. To this red ylide solution was added a solution of the hemiacetal **1**[5] (1.99 g, 4.5 mmol) dissolved in 6 mL of Me_2SO. The mixture was stirred under nitrogen at 25 °C for 20 h and then was poured onto ice water–ethyl acetate. Isolation and purification as described above provided 1.81 g (60%) of **3f** as a viscous, colorless oil: NMR δ 5.33 (4 H, m, trans and cis CH=CH), 4.68 (2 H, m, OCHO), 3.23 (3 H, s, SO_2CH_3).

Hydrolysis of **3f** (90 mg, 0.14 mmol) and purification of the crude product as described above gave 19 mg (32%) of **5f** as a white solid: mp 127–128 °C after recrystallization from ethyl acetate; NMR (CD_3OD) δ 5.46 (4 H, m, trans and cis CH=CH), 4.00 (3 H, m, CHO), 3.20 (3 H, s, SO_2CH_3); IR (KBr) 1733 (carbonyl), 975 cm^{-1} (trans CH=CH). Anal. ($C_{21}H_{37}NO_6S$) C, H, N.

Oxidation[33] of **3f** (1.7 g, 2.5 mmol), followed by hydrolysis and purification of the crude product as described above, gave 422 mg (39%) of **4f** as a white solid: mp 118–119 °C after recrystallization from acetone–hexane; NMR δ 5.57 (2 H, m, trans CH=CH), 5.30 (2 H, m, cis CH=CH), 4.05 (2 H, m, CHO), 3.24 (3 H, s, SO_2CH_3); IR (KBr) 1739 (carbonyls), 975 cm^{-1} (trans CH=CH). Anal. ($C_{21}H_{35}NO_6S$) C, H, N.

***N*-Benzenesulfonyl-PGE$_2$-carboxamide (4g) and -PGF$_{2\alpha}$-carboxamide (5g).** A solution of benzenesulfonamide (3.14 g, 0.02 mol) and 5-bromovaleric acid chloride (4.38 g, 0.022 mol) in 10 mL of CH_3CN was heated at reflux for 1.5 h and then was concentrated. Recrystallization of the crude product from CH_2Cl_2–hexane provided *N*-benzenesulfonyl-5-bromovaleramide weighing 5.39 g (84%), mp 95–97 °C. A solution of *N*-benzenesulfonyl-5-bromovaleramide (4.81 g, 15 mmol) and triphenylphosphine (5.89 g, 22 mmol) in 50 mL of CH_3CN was heated at reflux for 140 h. The mixture was concentrated, triturated with ether, and recrystallized from EtOH–hexane to provide 5.34 g (60%) of **2g**: mp 189–190 °C; NMR δ 7.65 (20 H, m, C_6H_5), 3.53 (2 H, m, PCH_2), 2.72 (2 H, m, CH_2CO). Anal. ($C_{29}H_{29}NO_3SPBr$) C, H, N.

To a solution of **2g** (2.53 g, 4.3 mmol) in 3 mL of Me_2SO was added 5.05 mL of a 1.73 M solution of sodium methylsulfinylcarbanide[6] in Me_2SO. To this red ylide solution was added a solution of the hemiacetal **1**[5] (476 mg, 1.1 mmol) in 2 mL of Me_2SO. The mixture was stirred under nitrogen at 25 °C for 2.75 h and then poured onto ice water–ethyl acetate. Isolation and purification as described above provided 294 mg (40%) of **3g** as a viscous colorless oil: NMR δ 8.04 and 7.48 (5 H, m, C_6H_5), 5.32 (4 H, m, trans and cis CH=CH), 4.68 (2 H, m, OCHO).

Hydrolysis of **3g** (104 mg, 0.16 mmol) and purification of the crude product as described above provided 30 mg (38%) of **5g** as a viscous, yellow oil: NMR δ 7.97 and 7.47 (5 H, m, C_6H_5), 5.50 (2 H, m, trans CH=CH), 5.24 (2 H, m, cis CH=CH), 4.08 (3 H, m, CHO); IR 1720 (imide C=O), 965 cm^{-1} (trans CH=CH); MS

($C_{26}H_{35}NO_4S$, P - $2H_2O$) calcd, 457.2287; found, 457.2276.

Oxidation[33] of **3g** (175 mg, 0.26 mmol), followed by hydrolysis and purification of the crude product as described above, afforded 35 mg (28%) of **4g** as a viscous, colorless oil: NMR δ 7.97 and 7.49 (5 H, m, C_6H_5), 5.60 (2 H, m, trans CH=CH), 5.26 (2 H, m, cis CH=CH), 4.08 (2 H, m, CHO); IR 1730 (ketone C=O), 1720 (imide C=O), 965 cm^{-1} (trans CH=CH); MS ($C_{26}H_{35}NO_5S$, P - H_2O) calcd, 473.2236; found, 473.2224.

PGE_2- (4h) and $PGF_{2\alpha}$-carboxamide (5h). A solution of $PGF_{2\alpha}$ 11,15-bis(tetrahydropyranyl ether)[5] (792 mg, 1.5 mmol) and 1,1'-carbonyldiimidazole (486 mg, 3.0 mmol) in 10 mL of THF was heated at 60 °C for 45 min and then was let cool.[33] Anhydrous ammonia was added until saturation was achieved, and the mixture was stirred for 30 min and then concentrated. The residue was dissolved in ether, and the etheral solution was washed with water and saturated NaCl, dried, and concentrated. Purification of the crude product by column chromatography using 4% diethylamine in ethyl acetate as eluant afforded 544 mg (69%) of **3h** as a colorless oil: NMR δ 5.38 (4 H, m, trans and cis CH=CH), 4.62 (2 H, m, OCHO).

Hydrolysis of **3h** (111 mg, 0.21 mmol) and purification of the crude product as described above provided 37 mg (50%) of **5h** as a colorless, viscous oil: NMR δ 5.40 (4 H, m, trans and cis CH=CH), 4.05 (3 H, m, CHO); IR 1675 cm^{-1} (amide C=O); MS ($C_{20}H_{31}NO_2$, P - $2H_2O$) calcd, 317.2351; found, 317.2351.

Oxidation[33] of **3h** (200 mg, 0.38 mmol), followed by hydrolysis and purification of the crude product as described above, afforded 36 mg (27%) of **4h** as a colorless, viscous oil: NMR δ 5.63 (2 H, m, trans CH=CH), 5.36 (2 H, m, cis CH=CH), 4.10 (2 H, m, CHO); IR 1675 and 1735 (amide and ketone C=O), 965 cm^{-1} (trans CH=CH); MS ($C_{20}H_{31}NO_3$, P - H_2O) calcd, 333.2304; found, 333.2299.

2-Decarboxy-2-(tetrazol-5-yl)-16,16-dimethyl-PGE_2 (7a). To a solution of **2a** (750 mg, 1.61 mmol) in 5 mL of Me_2SO was added 1.44 mL of a 1.88 M solution of sodium methylsulfinylcarbanide[6] in Me_2SO. To this red ylide solution was added a solution of the hemiacetal **6**[7] (250 mg, 0.54 mmol) in 2 mL of Me_2SO. The mixture was stirred under nitrogen at 25 °C for 18 h and then poured onto ice water–ethyl acetate. Isolation and purification as described above provided 214 mg (69%) of 2-decarboxy-2-(tetrazol-5-yl)-16,16-dimethyl-$PGF_{2\alpha}$ 11,15-bis(tetrahydropyranyl ether) as a pale-yellow, viscous oil: NMR δ 5.45 (4 H, m, trans and cis CH=CH), 4.71 (2 H, m, OCHO), 3.00 (2 H, t, CH_2CN_4).

Oxidation[33] of this $PGF_{2\alpha}$ bis(THP ether), followed by hydrolysis and purification of the crude product as described above, gave 62 mg (42%) of **7a** as a viscous, colorless oil: IR 1735 (ketone C=O), 965 cm^{-1} (trans CH=CH); NMR δ 5.73 (2 H, m, trans CH=CH), 5.36 (2 H, m, cis CH=CH), 3.92 (2 H, m, CHO), 3.00 (2 H, t, CH_2CN_4); MS ($C_{22}H_{32}N_4O$, P - $2H_2O$) calcd 368.2576; found, 368.2635.

***N*-Acetyl-16,16-dimethyl-PGE_2-carboxamide (7b).** To a solution of **2b** (2.60 g, 5.36 mmol) in 20 mL of Me_2SO was added 5.45 mL of a 1.88 M solution of sodium methylsulfinylcarbanide[6] in Me_2SO. To the red ylide solution was added a solution of the hemiacetal **6**[7] (250 mg, 0.54 mmol) in 2 mL of Me_2SO. The mixture was stirred under nitrogen at 25 °C for 18 h and then poured onto ice water–ethyl acetate. Isolation and purification as described above afforded 226 mg (71%) of *N*-acetyl-16,16-dimethyl-$PGF_{2\alpha}$-carboxamide 11,15-bis(tetrahydropyranyl ether) as a pale-yellow oil: NMR δ 9.3 (1 H, s, CONHCO), 5.45 (4 H, m, trans and cis CH=CH), 4.71 (2 H, m, OCHO), 2.40 (3 H, s, $COCH_3$).

Oxidation[33] of this $PGF_{2\alpha}$ bis(THP ether), followed by hydrolysis and purification of the crude product as described above, provided 13 mg (8%) of **7b** as a viscous, colorless oil: IR 1710 and 1740 (imide and ketone C=O), 975 cm^{-1} (trans CH=CH); NMR δ 5.64 (2 H m, trans CH=CH), 5.37 (2 H, m, cis CH=CH), 3.91 (2 H, m, CHO), 2.32 (3 H, s, $COCH_3$); MS ($C_{24}H_{37}NO_4$, P - H_2O) calcd, 403.2723; found, 403.2717.

***N*-Methanesulfonyl-16,16-dimethyl-PGE_2-carboxamide (7f).** To a solution of **2f** (835 mg, 1.61 mmol) in 2 mL of Me_2SO was added 1.42 mL of a 1.91 M solution of sodium methylsulfinylcarbanide[6] in Me_2SO. To a red ylide solution was added a solution of the hemiacetal **6**[7] (250 mg, 0.54 mmol) in 2 mL of Me_2SO. The mixture was stirred for 17 h and then poured into ice water–ethyl acetate. Isolation and purification as described above gave 249 mg (73%) of *N*-methanesulfonyl-16,16-dimethyl-$PGF_{2\alpha}$-carboxamide 11,15-bis(tetrahydropyranyl ether) as a tan oil: NMR δ 5.45 (4 H, m, trans and cis CH=CH), 4.68 (2 H, m, OCHO), 3.26 (3 H, s, SO_2CH_3).

Oxidation[33] of this $PGF_{2\alpha}$ bis(THP ether), followed by hydrolysis and purification of the crude product as described above, provided 70 mg (38%) of **7f** as a viscous, colorless oil: IR 1720 (imide C=O), 1737 (ketone C=O), 970 cm^{-1} (trans CH=CH); NMR δ 5.61 (2 H, m, trans CH=CH), 5.40 (2 H, m, cis CH=CH), 4.06 (2 H, m, CHO), 3.30 (3 H, s, SO_2CH_3); MS ($C_{23}H_{37}NO_5S$, P - H_2O) calcd, 439.2393; found, 439.2362.

Test for Uterine Stimulant Activity. Nulliparous female guinea pigs (300–400 g) which were not in estrus were sacrificed by cervical dislocation. The uteri were removed and suspended in a 2-mL tissue bath containing modified Krebs solution at 37 °C, and uterine contractions were measured with a linear-motion transducer (Phipps and Bird, Model ST-2). Tissues were allowed to stabilize for 20–30 min and were then exposed to PGE_2 or analogues, washed, and allowed to return to base line condition. All determinations are an average of responses for at least three individual tissues to each concentration of a drug. Potency of analogues was estimated from concentration–response curves compared to that for PGE_2 obtained with the same tissue. Data presented in Table I are the relative potency of analogues, with the PGE_2 response defined as 100.

Test for Effect on Blood Pressure. Mongrel dogs of either sex, 7–10 kg body weight, were anesthetized with sodium pentobarbital, 35 mg/kg iv. Femoral artery blood pressure was measured either with a mercury manometer and recorded on smoked paper or with a transducer (Statham, Model 23b) and recorded with a physiograph (Narco Biosystems, Model 4). PGE_2 and analogues were dissolved in ethanol (ca. 1 mg/mL) and then diluted with saline, and aliquots of these were administered into a femoral vein. A standard dose of PGE_2 (0.1 μg/kg) was administered to each animal before administration of analogues. Data for analogues found in Table I are the relative (PGE_2 = 100) minimum effective dose causing a reproducible change in blood pressure of greater than 10 mm in at least two PGE_2-responsive dogs.

Test for Bronchodilator Activity. The effect of PGE_2 analogues on histamine-induced bronchoconstriction was studied in conscious female Reed–Willet guinea pigs, 200–250 g, fasted 18–24 h, by a modification of the method of Van Arman, Miller, and O'Malley.[36] Drugs were dissolved in 90% ethanol at a concentration of 0.28 mM and nebulized for 1 min into an 8 × 8 × 12 in. Plexiglas container via a Vaponephrine nebulizer (Vaponephrine Co., Edison, N.J.) by compressed air, 6.5 psi. Animals inhaled the drug for the 1-min nebulization period and the subsequent minute and were then placed into another Plexiglas chamber of the same dimensions into which a 0.2% aqueous solution of histamine dihydrochloride had been nebulized for the prior minute. At the end of 1 min, the respiratory status of the animal was scored as follows: 0, normal breathing; 1, slightly deeper breathing; 2, labored breathing; 3, severely labored breathing and ataxia; 4, unconscious. The sums of scores for groups of eight animals were compared with those for animals exposed to solvent alone and the difference was expressed as percent protection. Data presented in Table I are the relative activity of analogues compared with the response for PGE_2 (defined as 100) determined in a group of eight animals with each analogue.

Test for Gastric Antisecretory Activity. The procedure of Ghosh and Schild[37] for continuous recording of pH was modified to monitor drug-induced pH changes in the anesthetized rat. Gastic pH changes were followed with a Heath pH recording electrometer (Model EV-20-11) attached to a Heath recorder (Model EU-20B). Gastric acid secretion was stimulated with pentagastrin (8.3 μg/mL) (Pentavlon-Ayerst) through an indwelling catheter in the femoral vein at an infusion rate of 1.2 mL/h. PGE_2 and analogues were administered iv (50 μg/kg) through a cannula in the jugular vein after pH levels of gastric fluid had reached a stable base line. The stomach was perfused with saline (37 ± 1 °C) at 2.9 mL/min with a Harvard two-channel peristaltic pump. Data found in Table I are expressed as a percent of the PGE_2 effect on pH of the gastric effluent (potency ×

duration) in the same animal where the corresponding PGE_2 response is defined as 100.

Test for Diarrheal Activity. Each of six adult male mice (25–40 g) were given analogues or PGE_2, 0.1, 0.3, 1.0, or 3.0 mg/kg, iv, or 0.9% sodium chloride solution, 0.1 mL, iv; they were placed in separate containers for 30 min, at which time they were removed and the feces examined. The occurrence of diarrhea was scored as plus or minus, as determined by the appearance of nonpelleted feces. Potency of analogues was estimated from concentration–response curves compared to that for PGE_2 obtained in a separate group of six animals. Data presented in Table I are the relative potency of analogues with PGE_2 defined as 100.

Acknowledgment. We thank Dr. J. W. Constantine for the dog blood pressure, mouse diarrhea, and guinea pig uterus data, Dr. P. F. Moore for the bronchodilator data, Dr. L. A. Hohnke for the rat gastric antisecretory data, Mr. E. G. Andrews for expert chemical assistance, Dr. E. B. Whipple and Mr. R. Ware for the high-resolution mass spectra, and Mr. T. J. Toolan and his staff for elemental analyses.

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