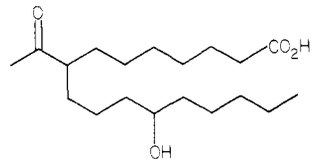
11,12-Secoprostaglandins. 6. Interphenylene Analogues of Acylhydroxyalkanoic Acids and Related Compounds as Renal Vasodilators

John B. Bicking,*[†] Charles M. Robb,[†] Edward J. Cragoe, Jr.,[†] Edward H. Blaine,*[‡] L. Sherman Watson,[‡] and Mary C. Dunlay[‡]

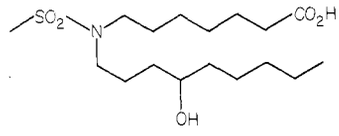
Merck Sharp & Dohme Research Laboratories and Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486. *Received June 1, 1982*

The synthesis is described of a series of interphenylene analogues of the modified 11,12-secoprostaglandins and their sulfonamide isosteres on which we have reported previously. The new compounds are formally derived from members of earlier series by replacement of segments of the methylene chains by phenylene units. Several of these compounds displayed renal vasodilatory activity on iv stat administration to anesthetized dogs. 4-(4-Acetyl-8-hydroxytridecyl)benzoic acid tested additionally in conscious dogs orally caused a significant increase in renal blood flow at 5 mg/kg.

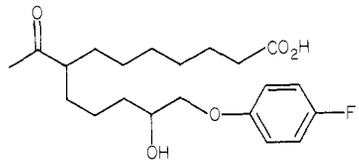
We have reported that structurally simplified 11,12-secoprostaglandins, such as members of a series of acylhydroxyalkanoic acids (e.g., **1**)[1] and of isoteric amides,[2]



1



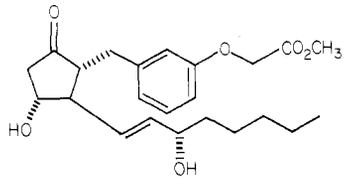
2



3

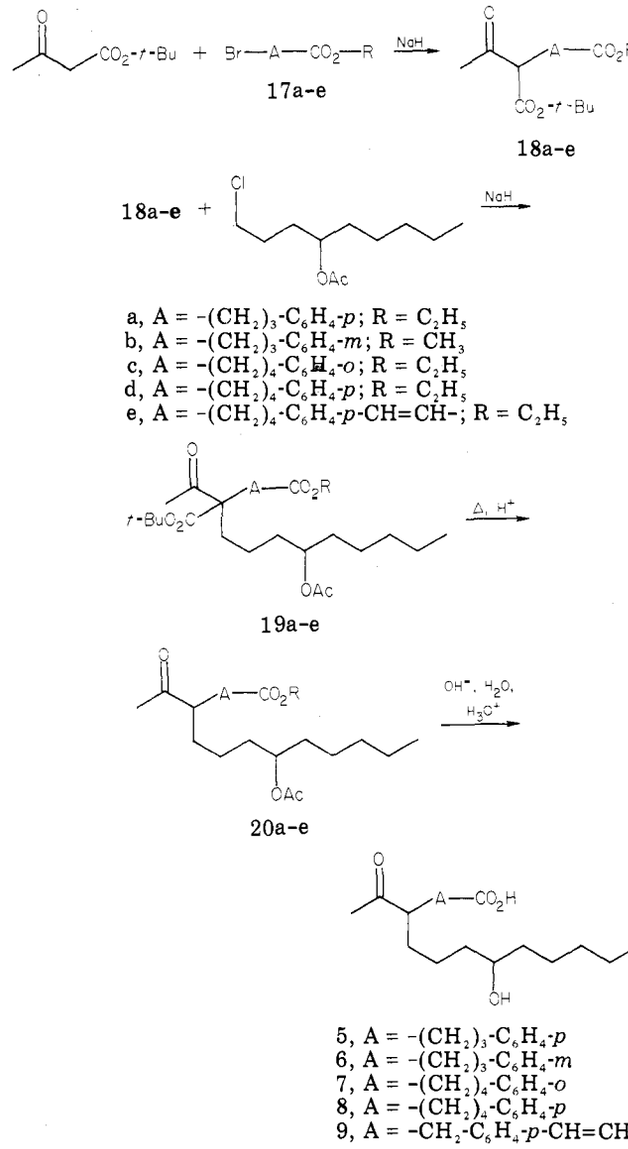
sulfones,[3] and sulfonamides (e.g., **2**),[4] show a number of the characteristic biological actions of the prostaglandins of the E series. Most recently, we reported[5] that analogues of **1** and **2** bearing terminal aryloxy groups (e.g., **3**) retain certain PGE_1-like actions, the most notable being inhibition of blood platelet aggregation.

The present paper is concerned with the synthesis and biological evaluation of further aryl-substituted analogues of **1** and **2** wherein phenylene groups replace methylene units of the carbon chain between the carboxy group and the acetyl or methylsulfonyl side chain. After this work was begun, Nelson, Nishizawa, and co-workers described analogues of PGE_1 and $PGF_{1\alpha}$ that contain phenylenoxy units in the carboxy chain.[6] The PGE_1 analogue, **4**, displayed a spectrum of activity similar to that of the natural substance and gave evidence of increased stability and specificity.



4

Scheme I



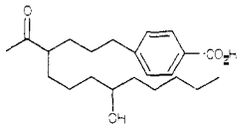
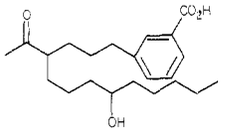
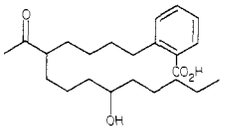
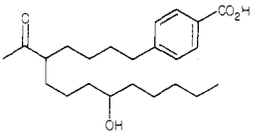
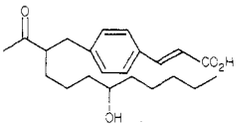
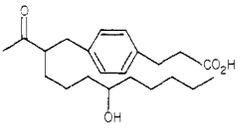
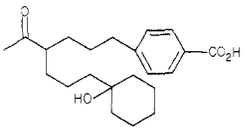
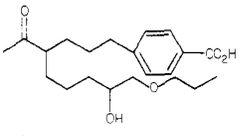
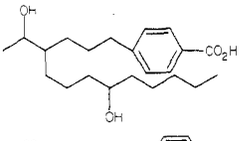
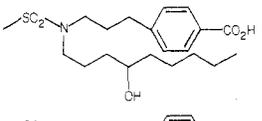
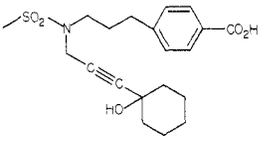
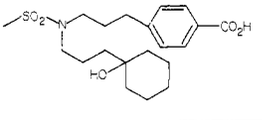
Chemistry. Compounds prepared for biological assay are listed in Table I. Their syntheses follow the general

[†] Merck Sharp & Dohme Research Laboratories.
[‡] Merck Institute for Therapeutic Research.

(1) Bicking, J. B.; Robb, C. M.; Smith, R. L.; Cragoe, E. J., Jr.; Kuehl, F. A., Jr.; Mandel, L. R. *J. Med. Chem.* **1977**, *20*, 35.
(2) Jones, J. H.; Holtz, W. J.; Bicking, J. B.; Cragoe, E. J., Jr.; Mandel, L. R.; Kuehl, F. A., Jr. *J. Med. Chem.* **1977**, *20*, 44.
(3) Smith, R. L.; Bicking, J. B.; Gould, N. P.; Lee, T.-J.; Robb, C. M.; Kuehl, F. A., Jr.; Mandel, L. R.; Cragoe, E. J., Jr. *J. Med. Chem.* **1977**, *20*, 540.
(4) Jones, J. H.; Holtz, W. J.; Bicking, J. B.; Cragoe, E. J., Jr.; Mandel, L. R.; Kuehl, F. A., Jr. *J. Med. Chem.* **1977**, *20*, 1299.

0022-2623/83/1826-0335$01.50/0

Table I. Interphenylene Analogues of 11,12-Secoprostaglandins and Related Compounds

no.	structure	mp, °C	R_f[a]	yield, %	formula[b]
5		oil	0.45	15[c]	$C_{22}H_{34}O_4$
6		oil	0.45	26[c]	$C_{22}H_{34}O_4$[d]
7		oil	0.48	13[c]	$C_{23}H_{36}O_4$
8		oil	0.44	20[c]	$C_{23}H_{36}O_4$
9		87-92	0.40	9[c]	$C_{22}H_{32}O_4$
10		oil	0.44	88	$C_{22}H_{34}O_4$
11		oil	0.44	10[e]	$C_{22}H_{32}O_4$
12		oil	0.44	12[f]	$C_{21}H_{32}O_5$
13		oil	0.29	67	$C_{22}H_{36}O_4$
14		102-103 (from BuCl)	0.38	35[g]	$C_{20}H_{33}NO_5S$
15		120-121 (from benzene)	0.36	20[g]	$C_{20}H_{27}NO_5S$
16		128-129 (from CH_3CN)	0.36	65	$C_{20}H_{31}NO_5S$

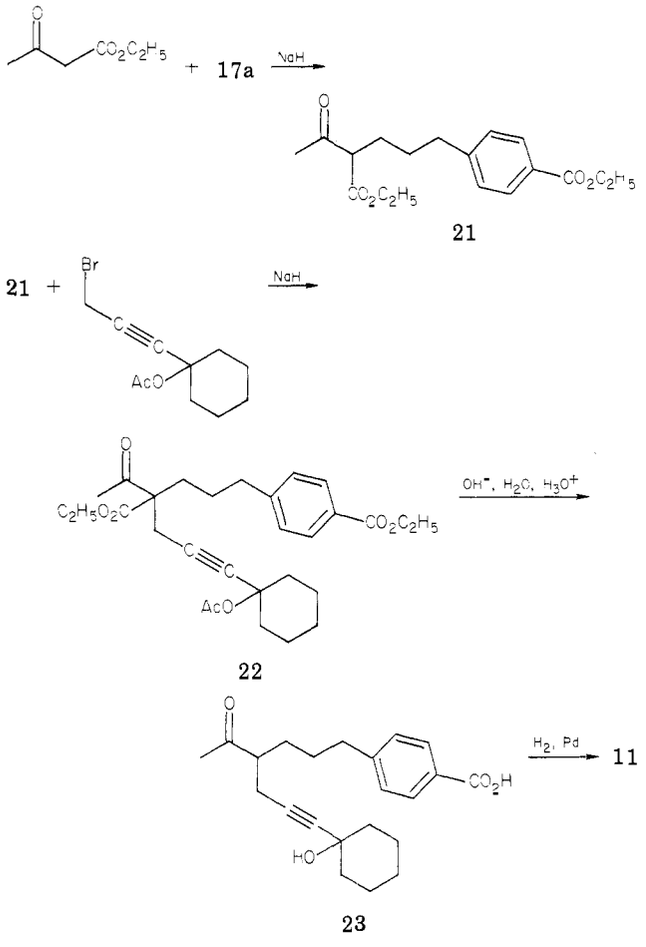
[a] Determined on SiO_2 plates with $CHCl_3$-CH_3OH-HOAc (95:4:1). [b] Compounds were analyzed for C and H, and for N when present. [c] Overall yield according to Scheme I. [d] C: calcd, 72.89; found, 71.57. [e] Overall yield, Scheme II. [f] Overall yield, Scheme III. [g] Overall yield, Scheme IV.

plan described in our earlier papers on the seco-prostaglandins.[1-5] Compounds **5–9** were prepared as shown in Scheme I. *tert*-Butyl acetoacetate was alkylated with alkyl bromides **17a–e** in order to introduce the eventual phenylene-containing carboxy-terminal moieties. The

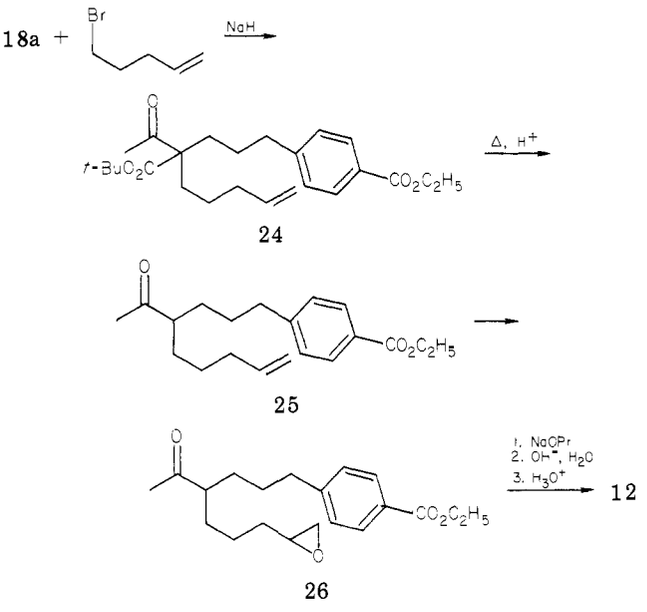
(5) Bicking, J. B.; Jones, J. H.; Holtz, W. J.; Robb, C. M.; Kuehl, F. A., Jr.; Minsker, D. H.; Cragoe, E. J., Jr. *J. Med. Chem.* **1978**, *21*, 1011.

(6) Nelson, N. A.; Jackson, R. W.; Au, A. T.; Wynalda, D. J.; Nishizawa, E. E. *Prostaglandins* **1975**, *10*, 795.

Scheme II



Scheme III



resulting dicarboxylic esters **18a–e** were alkylated with 1-chloro-4-acetoxynonane. Esters **19a–e** so produced were subjected to acid-catalyzed elimination–decarboxylation and saponification to yield **5–9**.

A route involving acid-catalyzed cleavage of the *tert*-butoxycarbonyl group is precluded for the synthesis of **11** in which an acylated propargylic alcohol is an intermediate and, likewise, undergoes a facile acid-catalyzed elimination. Accordingly, **11** was prepared via the sequential alkylations of ethyl acetoacetate as shown in Scheme II. The resulting dicarboxylic ester **22** was saponified and decarboxylated to yield the acetylenic acid **23**, which gave **11** on catalytic hydrogenation.

The method of preparation of **12**, an oxa analogue of **5**, is outlined in Scheme III. Epoxide **26** was obtained by reaction of *m*-chloroperbenzoic acid with olefinic ester **25** prepared by a conventional acetoacetic ester alkylation sequence. The epoxide was treated with sodium propoxide, and the resulting ester was saponified to yield **12**.

The sulfonamido acids **14** and **15** were prepared by sequential alkylations of methanesulfonamide (Scheme IV). The alkylation of methanesulfonamide with ethyl 4-(3-bromopropyl)benzoate (**17a**) under a variety of conditions produced a roughly 2:1 mixture of the monoalkylated and dialkylated sulfonamides. These were separated by column chromatography, and the monoalkylated product was carried on to **15**. Compounds **10**, **13**, and **16** in Table I were obtained, respectively, by reduction of **9** (H_2, Pd), **5** ($NaBH_4$), and **15** (H_2, Pt).

The preparations of alkylating agents **17a** and **17e** were conventional. The preparation of methyl 3-(3-bromopropyl)benzoate (**17b**) (Scheme V) began with the reaction of benzyloxyacetaldehyde with the ylide derived from phosphonium bromide **30**. Hydrogenolysis–hydrogenation of the product of this Wittig condensation (**31**) gave hydroxy ester **32**, which was treated with PBr_3 to produce **17b**. The key step in the synthesis of ethyl 4-(4-bromobutyl)benzoate (**17d**) (Scheme VI) was the alkylation by 2-(3-bromopropoxy)tetrahydro-2*H*-pyran of the dilithio derivative of *p*-toluic acid prepared by reaction of the acid with 2 equiv of lithium diisopropylamine. Simultaneous deprotection and esterification of the product with ethanol and acid gave hydroxy ester **33**, which was converted to **17d** by the action of PBr_3. Alkylating agent **17c** was prepared analogously from *o*-toluic acid.

The keto acids **5–10** and **12**, as obtained, consist of four stereoisomers presumably in equal parts; the hydroxy acid **13** consists of the eight possible stereoisomers probably in nearly equal amounts. Acids **11** and **14** are racemates; **15** and **16** are achiral entities. Separation of isomers was not attempted in any case, since our experience with the separated isomers of **1** and **2**[2,5] has suggested that biological activity is not strongly dependent on the configuration of the chiral centers in these flexible molecules.

The product acids that are not crystalline solids are extremely viscous oils that retain solvents tenaciously. Samples suitable for analysis and biological testing could be obtained in these cases only by being heated at 100 °C under high vacuum for 4–8 h.

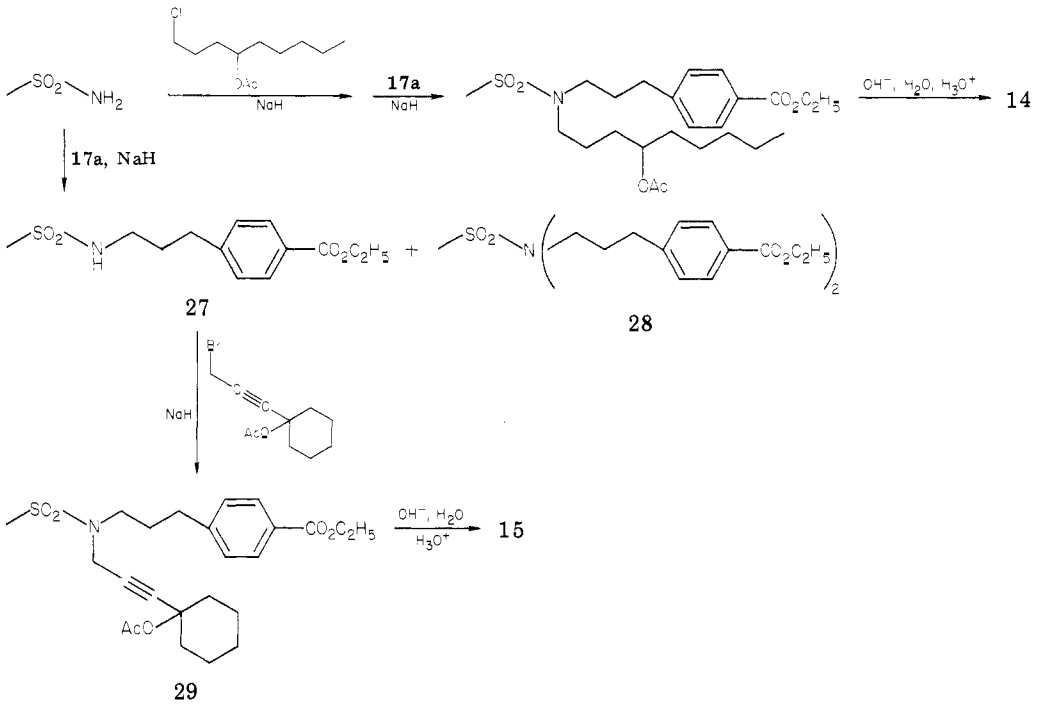
Biological Results and Discussion

A screening assay for renal vasodilatory activity is one of a group of assays to which our prostaglandin analogues have been submitted routinely. The basis for the inclusion of this screen is the series of observations that prostaglandins of the E, A, and D series increase renal blood flow in dogs and man.[7] This effect is observed most readily when the prostaglandins that are subject to rapid metabolic inactivation are infused directly into the renal artery. The detection of renal vasodilatory activity in prostaglandin analogues sufficiently stable for administration by clinically practicable routes would be the first step in the development of a new class of agents for the enhancement of renal blood flow.

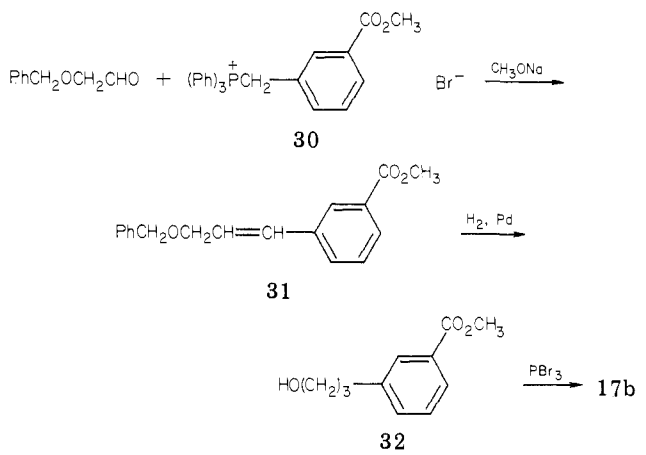
When compounds **5–8** and **10–16** were broadly screened, we found renal vasodilation to be the most noteworthy and

(7) Dunn, M. J.; Hood, V. L. *Am. J. Physiol.* **1977**, *233*, F 169.

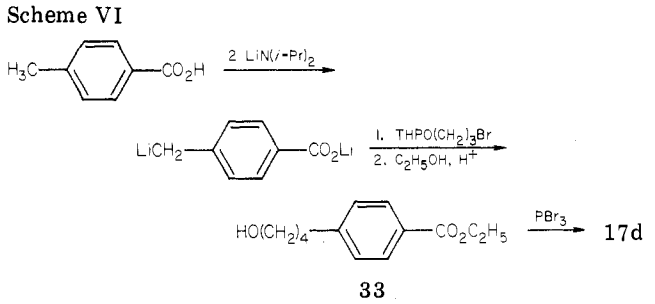
Scheme IV



Scheme V



Scheme VI



generally displayed activity detectable in this group of compounds. The effects of these analogues on the renal vasculature are reported in Table II in terms of the calculated changes produced in renal resistance (RR).

A detailed description of the experimental protocol is provided under Experimental Section. Briefly, our compounds were screened in anesthetized dogs that were prepared by placement of an electromagnetic blood flow transducer on one renal artery, the contralateral kidney having been removed. Because prostaglandins can also act as hypotensive agents, arterial blood pressure (BP) was monitored during the experiments. Two dogs were tested with each compound, except for time control studies in which three dogs were studied. After a 30-min period during which renal blood flow (RBF) and BP were monitored, 500 μg/kg of the test compound was injected iv, and monitoring of the variables was continued during the subsequent 30-min period. RR was calculated by dividing mean BP by mean RBF observed in the control and postinjection periods.

Table II. Effects of PG Analogues on Renal Resistance in Anesthetized Dogs

compd[a]	no. of dogs	renal resistance (RR)[b] control period[c]	drug period[c]	% change in RR
5	2	0.74 ± 0.22	0.39 ± 0.02	−47
6	2	0.86 ± 0.21	0.69 ± 0.19	−20
7	2	0.58 ± 0.09	0.69 ± 0.06	19
8	2	1.17 ± 0.10	1.38 ± 0.25	18
10	2	0.83 ± 0.26	0.94 ± 0.25	13
11	2	0.99 ± 0.14	0.57 ± 0.16	−42
12	2	1.04 ± 0.25	0.59 ± 0.16	−43
13	2	0.81 ± 0.23	0.66 ± 0.16	−19
14	2	0.75 ± 0.25	0.79 ± 0.20	5
15	2	0.62 ± 0.26	0.56 ± 0.16	−10
16	2	0.94 ± 0.26	0.87 ± 0.29	−7
placebo[d]	3	0.96 ± 0.11	1.10 ± 0.11	15

[a] A dose of 500 μg/kg in aqueous solution as the Na salt was given to each of two dogs by iv bolus injection. [b] Resistance was calculated by dividing mean arterial pressure by mean renal blood flow, which averaged 125 ± 2 mmHg and 189 ± mL/min, respectively, for all dogs studied during the control period. [c] Values are means ± SE for the 30-min pretreatment period and the 30-min posttreatment drug period. [d] Isotonic saline solution was given by iv injection.

We consider the calculated changes in RR to be the best measure of renal vasodilatory action, since RBF is affected not only by renal vasodilation or vasoconstriction but also by changes in BP that can result from a peripheral vasodilatory action of the test compounds. Actually, the changes in BP produced by this group of compounds were small; both increases and decreases were observed.

This screening assay identifies compounds **5**, **11**, and **12** as highly effective renal vasodilators producing 47, 42, and 43% decreases in RR, respectively, at the test dose of 500

Table III. Effects of Oral Administration of Compound 5 on Cardiovascular Parameters in the Conscious Dog

compd	dose, mg/kg, po	no. of dogs	observation period	mean renal blood flow,[a] mL/min ± SE	mean arterial blood pressure,[a] mmHg ± SE	mean heart rate,[a] beats/min ± SE
5	5	3	control[b]	111 ± 12	113 ± 10	64 ± 9
			0-1[c]	137 ± 27	116 ± 11	74 ± 11
			1-2[c]	194 ± 45	106 ± 7	73 ± 3
			2-3[c]	173 ± 24	97 ± 3	74 ± 8
			3-4[c]	139 ± 12	95 ± 6	64 ± 6
			4-5[c]	124 ± 7	106 ± 23	68 ± 8
placebo[d]		5	control[b]	111 ± 13	112 ± 6	88 ± 7
			0-1[c]	115 ± 13	111 ± 3	88 ± 7
			1-2[c]	116 ± 9	110 ± 5	88 ± 7
			2-3[c]	129 ± 8	114 ± 5	90 ± 9
			3-4[c]	122 ± 9	113 ± 6	86 ± 8
			4-5[c]	123 ± 10	115 ± 5	85 ± 8

[a] The variable was recorded at 2-min intervals. Data so obtained were averaged for the 30-min control period and for each of the 5-h of postdrug or postplacebo observation. [b] A 30-min pretreatment period. [c] Hours after drug or placebo administration. [d] Lactose capsule po. Time control experiments to determine the stability of the preparation under the experimental conditions.

μg/kg iv. Four analogues, **6**, **13**, **15**, and **16**, decreased RR to a lesser degree. RR was seen to increase after administration of **7**, **8**, **10**, and **14**. However, RR increased (15%) during the placebo postinjection period so that it is unlikely that any analogue of this latter group caused renal vasoconstriction.

Compound **5** was tested for activity or oral administration of 5 mg/kg in a similar protocol employing conscious dogs. RBF, BP, and heart rate (HR) were monitored during a 30-min control period and during a 5-h period after administration of **5**. Each variable was recorded at 2-min intervals. These data were averaged for the control period and for each hour of the posttreatment period to give the mean values recorded in Table III. Compound **5** is seen to cause a significant rise in RBF in the 2nd and 3rd hours following dosage. Its effects on BP and HR are small and nonsignificant in these experiments.

These preliminary demonstrations of renal vasodilatory activity in **5**, **11**, and **12** have caused us to regard the interphenylene secoprostaglandins as leads to the development of a clinically useful, orally active renal vasodilator. We have proceeded by building the structural features found in these compounds into other groups of prostaglandin analogues, particularly those in which heterocyclic rings replace the cyclopentane ring of the natural substances. The results of this work will be reported later.

Experimental Section

Chemical. Melting and boiling points are uncorrected. ^1H NMR spectra were taken on a Varian T-60 spectrometer in $CDCl_3$. Chemical shifts are reported as parts per million relative to Me_4Si as an internal standard.

Solutions in organic solvents were dried with $MgSO_4$. Column chromatography was carried out on silica gel (E. Merck, particle size 0.063–0.20 mm). We used thin-layer chromatography (TLC) to monitor column fractions and to establish the homogeneity of products. It was performed on Analtech silica gel GF plates (thickness 250 μm). Spots were located with iodine vapor. A standard solvent system was used for TLC of all acid products consisting of $CHCl_3$–CH_3OH–HOAc (95:4:1). A standard solvent system for TLC of esters was 2% CH_3OH in $CHCl_3$.

Compounds were prepared for analysis and biological testing by being heated at 100 °C under oil pump vacuum for 4–6 h. When analyses are indicated only by the symbols of the elements, the analytical results obtained for these elements are within 0.4% of the theoretical values.

Ethyl 4-(3-Bromopropyl)benzoate (17a). A mixture of 4-(3-bromopropyl)benzoic acid[8] (100.8 g, 0.41 mol), benzene (290 mL), ethanol (60 mL), and concentrated H_2SO_4 (1.4 mL) was boiled under a Dean and Stark constant water separator until the production of water ceased (23 h). The mixture was cooled, washed with water and 5% $NaHCO_3$ solution, and dried. The solvents were evaporated, and the residual oil was distilled at reduced pressure to afford 99 g (89%) of the ester as a colorless oil, bp 136–139 °C (0.05 mm). Anal. ($C_{12}H_{15}BrO_2$) C, H.

Methyl 3-(3-Bromopropyl)benzoate (17b). (a) Methyl 3-[3-(Benzyloxy)-1-propenyl]benzoate. [3-(Methoxycarbonyl)benzyl]triphenylphosphonium bromide[9] (38.8 g, 0.079 mol) and (benzyloxy)acetaldehyde[10] (11.9 g, 0.079 mol) were dissolved in CH_3OH (350 mL). The solution was stirred at room temperature while a solution of $NaOCH_3$, made by dissolving Na (1.91 g, 0.083 mol) in CH_3OH (40 mL), was added dropwise during 30 min. The solution was stirred for an additional 3.5 h. Most of the solvent was evaporated at reduced pressure. The residue was treated with H_2O, and the oil was taken up in Et_2O. The Et_2O solution was separated and evaporated, leaving a semisolid residue. Petroleum ether (bp 30–60 °C) was added, and the insoluble triphenylphosphine oxide was removed by filtration. The petroleum ether solution was evaporated, and the residue was distilled to give 15.5 g (70%) of the product as a colorless oil, bp 173–178 °C (0.2 mm). Anal. ($C_{18}H_{18}O_3$) C, H.

(b) Methyl 3-(3-Hydroxypropyl)benzoate. Methyl 3-[3-(benzyloxy)-1-propenyl]benzoate (15.2 g, 0.054 mol) and *p*-toluenesulfonic acid hydrate (0.5 g) were dissolved in EtOAc (75 mL) and hydrogenated over 2 g of a 5% Pd-on-charcoal catalyst at 27 °C and an initial pressure of 40 psi. The theoretical amount of hydrogen (0.11 mol) was absorbed in 2.5 h. The catalyst was removed by filtration, and the solvent was evaporated. The residue was taken up in Et_2O, washed with $NaHCO_3$ solution and H_2O, and dried. Evaporation of Et_2O gave 9.7 g (92%) of the hydroxy ester as a colorless oil: NMR δ 1.93 (2 H, m, CH_2CH_2Ph), 2.33 (1 H, s, OH), 2.73 (2 H, t, CH_2Ph), 3.60 (2 H, t, CH_2O), 3.85 (3 H, s, CH_3O).

(c) Methyl 3-(3-Bromopropyl)benzoate (17b). A solution of PBr_3 (4.9 g, 0.018 mol) in Et_2O (25 mL) was added to a solution of methyl 3-(3-hydroxypropyl)benzoate (9.6 g, 0.049 mol) in Et_2O (100 mL) during 30 min., The resulting mixture was stirred at 25–27 °C for 22 h. Th mixture was then added to H_2O (200 mL). The organic layer was separated, washed with $NaHCO_3$ solution and H_2O, and dried. Distillation gave 3.7 g (29%) of the bromo ester: colorless oil; bp 130–131 °C (0.2 mm). Anal. ($C_{11}H_{13}BrO_2$) C, H.

Ethyl 4-(4-Bromobutyl)benzoate (17d). (a) Ethyl 4-(4-Hydroxybutyl)benzoate. Butyllithium (140 mL of a 1.6 M solution in hexane, 0.224 mol) was added to a solution of diisopropylamine (22.6 g, 0.223 mol) in THF (200 mL) and HMPA (28 mL) at 0 °C during 30 min. A partial solution/suspension of *p*-toluic acid (15.1 g, 0.111 mol) in THF (50 mL) was then added

(8) Blicke, F. F.; Lillienfeld, W. M. *J. Am. Chem. Soc.* **1943**, *65*, 2281.

(9) Coombs, M. M.; Houghton, R. P. *J. Chem. Soc.* **1961**, 5015.

(10) Sabetay, S.; Mira, D. N. *C. R. Hebd. Seances Acad. Sci.* **1932**, *194*, 617; *Chem. Abstr.* **1932**, *26*, 2725.

dropwise during 30 min at 0–5 °C, followed, after an additional 30 min, by 2-(3-bromopropoxy)tetrahydro-2*H*-pyran[11] (24.9 g, 0.111 mol) added dropwise in 30 min at 0–5 °C. The solution was stirred for 30 min at 5 °C while the color faded from dark brown to light yellow. The solution was then treated with H_2O and Et_2O. The aqueous layer was separated and acidified with concentrated hydrochloric acid. The crude acid product that separated was taken up in Et_2O, washed with H_2O, and dried, and the solution was evaporated to yield 30 g of a residual oil. A solution of this oil and concentrated H_2SO_4 (1.2 mL) in ethanol (210 mL) was boiled under reflux for 18 h. The ethanol was evaporated at reduced pressure, and the residue was dissolved in Et_2O, washed with saturated $NaHCO_3$ solution, and dried. Distillation afforded 11.4 g (48%) of the hydroxy ester: colorless oil; bp 161 °C (0.2 mm); NMR δ 1.37 (3 H, t, CH_3), 2.23 (1 H, s, OH), 2.70 (2 H, t, CH_2Ph), 3.65 (2 H, t, CH_2OH), 4.33 (2 H, q, CH_2OCO), 7.20 (2 H, d, aryl H), 7.90 (2 H, d, aryl H). Anal. ($C_{13}H_{18}O_3$) C, H.

(b) Ethyl 4-(4-Bromobutyl)benzoate (17d). A solution of PBr_3 (6.0 g, 0.022 mol) in Et_2O (30 mL) was added to a solution of ethyl 4-(4-hydroxybutyl)benzoate (13.4 g, 0.06 mol) in Et_2O (130 mL) during 10 min. The resulting solution was boiled under reflux for 5 h. Workup as with **17b** and distillation gave 8.5 g (50%) of the bromo ester: colorless oil; bp 145–147 °C (0.15 mm). Anal. ($C_{13}H_{17}BrO_2$) C, H.

Ethyl 2-(4-bromobutyl)benzoate (17c) was prepared analogously to **17d** beginning with the alkylation of the dilithio derivative of *o*-toluic acid with 2-(3-bromopropoxy)tetrahydro-2*H*-pyran. **Ethyl 2-(4-hydroxybutyl)benzoate** was obtained in 25% yield: colorless oil; bp 140–142 °C (0.1 mm). Bromo ester **17c** was obtained in 58% yield: colorless oil; bp 122–124 °C (0.1 mm). Anal. ($C_{13}H_{17}BrO_2$) H; C: calcd, 54.75; found, 55.26.

Ethyl 4-(Bromomethyl)cinnamate (17e). A mixture of ethyl 4-methylcinnamate (93.5 g, 0.492 mol), *N*-bromosuccinimide (96.3 g, 0.541 mol), α,α′-azodiisobutyronitrile (1.0 g), and CCl_4 (400 mL) was boiled under reflux for 3 h. The mixture was cooled, and succinimide was removed by filtration. The filtrate was washed with 5% NaOH solution and H_2O and dried. Distillation gave 91.8 g (70%) of the bromo ester, bp 145–147 °C (0.1 mm). The product subsequently solidified. Recrystallization from petroleum ether (bp 30–60 °C) gave white crystals: mp 49–50 °C. Anal. ($C_{12}H_{13}BrO_2$) C, H.

Physical, analytical, and yield data for the acids **5–16** are listed in Table I. The method used for the preparation of acids **5–9** (Scheme I) is exemplified by the preparation of **4-(4-acetyl-8-hydroxytridecyl)benzoic acid (5).**

(a) Ethyl 4-[4-(*tert*-Butoxycarbonyl)-5-oxohexyl]benzoate (18a). *tert*-Butyl acetoacetate (23.7 g, 0.15 mol) was added during 30 min to a stirred suspension of NaH (4.0 g, 0.167 mol) in benzene (75 mL) and DMF (75 mL). Stirring was continued for 30 min. Ethyl 4-(3-bromopropyl)benzoate (**17a**; 40.7 g, 0.15 mol) was then added during 15 min, and the mixture stirred and heated at 100 °C for 5 h. The mixture was cooled and treated with 300 mL of water. The organic layer was diluted with Et_2O, washed with H_2O and brine, and dried. The solvents were removed by evaporation at reduced pressure to give 51.1 g of crude **18a** as an orange residual oil.

(b) Ethyl 4-[4-Acetyl-4-(*tert*-butoxycarbonyl)-8-acetoxytridecyl]benzoate (19a). Ester **18a** (51.1 g, 0.147 mol) was added during 30 min to a stirred suspension of NaH (3.9 g, 0.163 mol) in benzene (75 mL) and DMF (75 mL). Stirring was continued for 30 min. 1-Chloro-4-acetoxynonane[1] (36.0 g, 0.163 mol) and KI (500 mg) were added, and the mixture was heated at 100 °C for 64 h. Workup as with the preceding alkylation gave 78.0 g of crude **19a** as a red residual oil.

(c) Ethyl 4-(4-Acetyl-8-acetoxytridecyl)benzoate (20a). A solution of **19a** (78.0 g, 0.145 mol), *p*-toluenesulfonic acid (3 g), and Ac_2O (15 mL) in AcOH (300 mL) was heated at 100 °C for 4 h. The solution was then cooled and treated with 500 mL of water. The oily product was taken up in Et_2O, washed with H_2O and saturated $NaHCO_3$ solution, and dried. The solvent was evaporated at reduced pressure to yield 53.7 g of crude **20a**. Chromatography on 500 g of silica gel with elution by 1% CH_3OH in $CHCl_3$ gave 32.3 g (51%) of **20a** as a yellow oil: R_f 0.76. Anal. ($C_{26}H_{40}O_5$) C, H.

(d) 4-(4-Acetyl-8-hydroxytridecyl)benzoic Acid (5). A solution of **20a** (32.0 g, 0.074 mol) and NaOH (8.8 g, 0.22 mol) in methanol (320 mL) and water (50 mL) was heated at 60 °C for 18 h. Most of the methanol was distilled, and the residual solution was diluted with water and extracted with ether. The aqueous solution was acidified with concentrated hydrochloric acid. The precipitated oily product was taken up in ether and dried. Evaporation of the solvent left 20.1 g of crude **5**, which was chromatographed on 350 g of SiO_2 with 2% CH_3OH in $CHCl_3$ elution to yield 7.8 g (29%) of **5** as a colorless viscous oil: NMR δ 0.88 (3 H, t, CH_3CH_2), 2.05 (3 H, s, CH_3CO), 3.66 (1 H, m, CHOH), 6.82 (2 H, s, OH and COOH), 7.16 (2 H, d, aryl 3,5-H_2), 7.94 (2 H, d, aryl 2, 6-H).

Compound **6** was prepared analogously by the use of **17b** as the initial alkylating agent; **7** by the use of **17c**; **8** by the use of **17d**; and **9** by the use of **17e**. Compound **9** solidified after chromatography.

3-[4-(2-Acetyl-6-hydroxyundecyl)phenyl]propionic Acid (10). Compound **9** (2.6 g, 0.0072 mol) in EtOH (30 mL) was hydrogenated over 0.7 g of a 5% Pd-on-charcoal catalyst at 1 atmosphere and 27 °C. The theoretical amount of hydrogen was absorbed in 7 min. The catalyst was removed by filtration, the solvent was evaporated, and the residual oil was chromatographed on 45 g of silica gel with 2% CH_3OH in $CHCl_3$ elution. There was obtained 2.3 g (88%) of **10** as a colorless viscous oil.

4-[4-Acetyl-7-(1-hydroxycyclohexyl)heptyl]benzoic Acid (Scheme II) (11). (a) Ethyl 4-[4-Acetyl-4-(ethoxycarbonyl)-7-(1-acetoxycyclohexyl)-6-heptyn-1-yl]benzoate (22). Ethyl acetoacetate (13.0 g, 0.1 mol) was added during 30 min to a stirred suspension of NaH (2.6 g, 0.11 mol) in benzene (50 mL) and DMF (50 mL). Bromo ester **17a** (29.8 g, 0.11 mol) was then added during 15 min, and the mixture stirred and heated at 100 °C for 4.5 h. Workup as with **18a** above yielded 32 g of crude oily **ethyl 4-[4-(ethoxycarbonyl)-5-oxohexyl]benzoate (21).** Ester **21** (0.1 mol) was added to NaH (2.6 g, 0.11 mol) in benzene (50 mL) and DMF (50 mL). 1-Acetoxy-1-(3-bromo-1-propynyl)cyclohexane[1] (28.5 g, 0.11 mol) was added, and the mixture was heated at 100 °C for 3 h. Standard workup gave 49.5 g of crude **22** as a red-brown residual oil.

(b) 4-[4-Acetyl-7-(1-hydroxycyclohexyl)-6-heptyn-1-yl]benzoic Acid (23). A solution of ester **22** (49 g, 0.098 mol) and NaOH (24 g, 0.6 mol) in water (60 mL) and methanol (540 mL) was boiled under reflux for 4 h. Workup as in the preparation of **5** gave 35.6 g of a crude acidic product from which **23** was isolated by column chromatography on 530 g of SiO_2 with 4% CH_3OH in $CHCl_3$ as eluant. There was obtained 5.3 g of **23** as a yellow viscous oil: R_f 0.36; NMR δ 2.17 (3 H, s, CH_3CO), 7.24 (2 H, s, OH and COOH), 7.26 (2 H, d, aryl 3,5-H_2), 8.02 (2 H, d, aryl 2,6-H_2).

(c) 4-[4-Acetyl-7-(1-hydroxycyclohexyl)heptyl]benzoic Acid (11). Acetylene **23** (5.1 g, 0.014 mol) in EtOAc (55 mL) was hydrogenated over 2.0 g of a 5% Pt/C catalyst at 1 atm of pressure and room temperature. The theoretical amount of H_2 (0.028 mol) was absorbed in 25 min. The catalyst was filtered off, the solvent was evaporated, and the residual oil was chromatographed on 75 g of SiO_2 with 2% CH_3OH in $CHCl_3$ as eluant. There was obtained 3.7 g of **11** as a yellowish viscous oil.

4-(4-Acetyl-8-hydroxy-9-propoxynonyl)benzoic Acid (Scheme III) (12). (a) Ethyl 4-[4-Acetyl-4-(*tert*-butoxycarbonyl)-8-nonen-1-yl]benzoate (24). Alkylation of **18a** (49.3 g, 0.142 mol) with 5-bromo-1-pentene (23.2 g, 0.156 mol) and NaH (3.74 g, 0.156 mol) in benzene–DMF (100 °C, 21 h) and standard workup gave 59.7 g crude **24** as an orange residual oil: NMR δ 2.05 (3 H, s, CH_3CO), 2.67 (2 H, t, CH_2Ph), 4.8–5.2 (2 H, m, CH_2=), 5.5–6.0 (1 H, m, CH=).

(b) Ethyl 4-(4-Acetyl-8-nonen-1-yl)benzoate (25). Elimination–decarboxylation was carried out on crude **24** (59.5 g, 0.142 mol assumed) by the procedure and workup described for the preparation of **20a**. Column chromatography of crude **25** (40.7 g) on 600 g of SiO_2 with $CHCl_3$ elution gave 14.4 g (32%) of **25**: light yellow oil; R_f 0.74.

(c) Ethyl 4-(4-Acetyl-8,9-epoxynonyl)benzoate (26). A solution of **25** (14.4 g, 0.0454 mol) and *m*-chloroperbenzoic acid (8.6 g, 0.05 mol) in CH_2Cl_2 (100 mL) was kept at 27 °C. The

(11) Bohlmann, F.; Bornowski, H.; Herbst, P. *Chem. Ber.* **1960**, *93*, 1931.

progress of the reaction was followed by TLC of samples of the solution with 2% CH_3OH in $CHCl_3$ as the developing solvent. In 20 h the spot R_f 0.74 for **25** was replaced by a single spot R_f 0.60. The solution was washed with 5% aqueous NaOH solution and water and dried. Evaporation of solvent gave 14.0 g (93%) of **26** as a light yellow oil: NMR δ 2.10 (3 H, s, CH_3CO), 2.35–3.0 (6 H, m, CHCO, CH_2Ph, $CHOCH_2$); vinyl protons absent.

(d) 4-(4-Acetyl-8-hydroxy-9-propoxynonyl)benzoic Acid (12). Epoxide **26** (14.0 g, 0.042 mol) was added to a solution of Na (2.9 g, 0.126 mol) in 1-propanol (200 mL). The resulting solution was kept at 25 °C for 4 h. The solution was then treated with 25 mL of 10% aqueous NaOH solution and kept at 25 °C for 2 h. Most of the solvent was evaporated at reduced pressure. The residue was dissolved in 200 mL of water, and the solution extracted with ether and acidified with concentrated hydrochloric acid. Crude oily **12** obtained by ether extraction and evaporation weighed 16.4 g. It was chromatographed on 240 g of SiO_2 with 2% CH_3OH in $CHCl_3$ elution. There was obtained 6.0 g of **12** as a light yellow viscous oil: NMR δ 0.90 (3 H, t, CH_3CH_2), 2.10 (3 H, s, $CH_3C{=}O$), 3.25–3.55 (4 H, m, CH_2O), 3.76 (1 H, m, CHOH), 7.30 (2 H, d, aryl 3,5-H_2), 7.40 (2 H, s, OH and COOH), 8.0 (2 H, d, aryl 2,6-H_2).

4-[4-(1-Hydroxyethyl)-8-hydroxytridecyl]benzoic Acid (13). Compound **5** (7.3 g, 0.02 mol) and $NaBH_4$ (0.76 g, 0.02 mol) were dissolved in a solution of NaOH (1.2 g, 0.03 mol) in water (80 mL). The resulting solution was allowed to stand at 27 °C for 21 h. It was then acidified with concentrated hydrochloric acid. The oily acid that separated was taken up in ether, dried, and chromatographed on 100 g of silica gel with 4% CH_3OH in $CHCl_3$ elution. There was obtained 4.9 g (67%) of **13**: yellowish viscous oil; R_f 0.29.

4-[3-[*N*-(4-Hydroxynonyl)methanesulfonamido]propyl]-benzoic Acid (14). *N*-(4-Acetoxynonyl)methanesulfonamide[4] (9.0 g, 0.032 mol) was added during 15 min at 27 °C to a suspension of NaH (0.84 g, 0.035 mol) in benzene (16 mL) and DMF (16 mL). Stirring was continued for 15 min. Bromide **17a** (9.6 g, 0.035 mol) was then added, and the mixture and heated at 90 °C for 3 h. Workup in the usual manner gave 15.0 g of the crude ethyl ester of **14** as a yellow viscous oil. The ethyl ester was added to a solution of NaOH (4.0 g, 0.1 mol) in H_2O (18 mL) and CH_3OH (160 mL). The resulting solution was boiled under reflux for 2 h. Methanol was evaporated, and the residue was diluted with water and acidified with concentrated hydrochloric acid to precipitate **14** as a solid. Recyrstallization from BuCl gave 8.7 g of **14**.

4-[3-[*N*-[3-(1-Hydroxycyclohexyl)-2-propyn-1-yl]-methanesulfonamido]propyl]benzoic Acid (15). (a) Ethyl 4-(3-Methanesulfonamidopropyl)benzoate (27) and *N*,*N*-Bis[3-[4-(ethoxycarbonyl)phenyl]propyl]methanesulfonamide (28). Methanesulfonamide (6.7 g, 0.07 mol) was added to a suspension of NaH (1.8 g, 0.075 mol) in benzene (50 mL) and DMF (50 mL). The mixture was heated and stirred at 90 °C for 2.5 h. It was then cooled, treated with **17a** (19.0 g, 0.07 mol), and heated at 90 °C for 28 h. Standard workup gave 19.2 g of an oily product, which was chromatographed on 260 g of SiO_2 with 2% CH_3OH in $CHCl_3$ elution. A forerun was obtained consisting of the pure bisalkylated product **28**: 4.7 g of light yellow oil; R_f 0.56. Anal. ($C_{25}H_{33}NO_6S$) C, H, N. A second fraction was taken consisting of the pure monoalkylated product **27**: 7.0 g of light yellow oil, R_f 0.30. Anal. ($C_{13}H_{19}NO_4S$) C, H, N.

Ethyl 4-[3-[*N*-[3-(1-Hydroxycyclohexyl)-2-propyn-1-yl]-methanesulfonamido]propyl]benzoate (29). Ester **27** (6.9 g, 0.024 mol) was added to NaH (0.6 g, 0.025 mol) in benzene (20 mL) and DMF (20 mL). 1-Acetoxy-1-(3-bromo-1-propynyl)-cyclohexane[2] (6.2 g, 0.024 mol) was added, and the mixture was heated at 60 °C for 1 h. Standard workup gave 11.2 g of crude **29** as an orange residual oil.

4-[3-[*N*-[3-(1-Hydroxycyclohexyl)-2-propyn-1-yl]-methanesulfonamido]propyl]benzoic Acid (15). Hydrolysis of ester **29** by the method described for the preparation of **14** provided 5.4 g of crystalline **15**.

4-[3-[*N*-[3-(1-Hydroxycyclohexyl)propyl]methanesulfonamido]propyl]benzoic Acid (16). Acetylene **15** (4.4 g, 0.011 mol) dissolved in AcOEt (50 mL) was hydrogenated at 27 °C over 1 g of a 5% Pt-on-charcoal catalyst in a Parr apparatus at an initial pressure of 44 psi. When 0.022 mol of hydrogen had been absorbed (5 min), the catalyst was removed by filtration, and the solvent was evaporated to leave the product as a white solid. Recrystallization from CH_3CN gave 2.9 g of **16**.

Renal Blood Flow Assays. (a) Anesthetized Dogs. Intravenous Administration. Male or female mongrel dogs weighing 14.5–34 kg were anesthetized with vinbarbital (60 mg/kg) and artifically respired with positive pressure ventilation. Via bilateral retroperitoneal incisions, the right kidney was removed and the left renal artery was dissected free of adjacent tissue for placement of a noncannulating electromagnetic flow transducer (Carolina Medical Electronics). A femoral artery and vein were catheterized with 19-gauge polyvinyl chloride tubing for blood-pressure measurement and intravenous injections, respectively. The dogs were allowed to recover from the surgical intervention for at least 30 min before any experimental observations were made. Mean renal blood flow (RBF) and mean arterial blood pressure (BP) were recorded with a digital system (Digitec) sampling each variable at 1-min intervals. A 30-min control period was followed by an intravenous injection of 500 μg/kg of a test compound (in aqueous solution as the Na salt), and the variables were monitored for a subsequent 30 min postinjection period. Renal resistance was calculated by dividing the mean BP by the mean RBF.

(b) Conscious Dogs. Oral Administration. Female mongrel dogs averaging 15 kg in body weight were anesthetized with thiopental sodium (12 mg/kg), and an endotracheal tube was inserted. Surgical anesthesia was maintained with a halothane–oxygen mixture delivered via a positive pressure respirator. A midline laparotomy was performed and one renal artery (usually the left) was dissected free of adhering connective tissue. An electromagnetic blood flow transducer (Micron Instruments or Statham Electronics) was placed around the renal artery close to its origin from the aorta. A second blood flow transducer was placed around the lower aorta 1–2 cm cephalad from the iliac bifurcation. The wire leads from the flow transducers were tunneled subcutaneously to exit between the shoulders. A polyvinyl chloride catheter for measurement of BP was inserted into the aorta via an iliac artery with its tip lying distal to the aortic flow probe. The abdominal incision was closed in layers, and after recovery from anesthesia, the flow transducer leads and catheter were protected by a sponge pad covered by a nylon jacket. All animals were allowed to recover from surgery for at least 3 days before being used in any experiment.

The conscious dogs prepared in this manner were kept in their transport cages during the studies reported here. The experimental protocol consisted of an initial 30-min control period before treatment, followed by a 5-h posttreatment observation period. The test compound was administered orally in a gelatin capsule. The outputs from the blood flow meters and the blood pressure transducer (Micron Instruments) were displayed on a cathode ray oscilloscope, and the data were recorded digitally at 2-min intervals on a PDP 8 minicomputer. These data were averaged for the predrug control period and for each of the 5 h of postdrug observation. The zero flow base line was established electronically for both the renal and aortic blood flow transducers and was checked at 30-min intervals during the course of each experiment.

Acknowledgment. We thank Mr. K. B. Streeter and his staff for elemental analyses and Mr. W. R. McGaughran and Ms. J. S. Murphy for NMR spectra. We are indebted to Drs. R. L. Smith and T.-J. Lee for helpful advice.