Prostaglandin Isosteres. 2. Chain-Modified Thiazolidinone Prostaglandin Analogues as Renal Vasodilators

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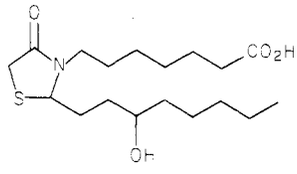
Chain modification of a thiazolidinone prostaglandin isostere has led to the production of 4-[3-[3-[2-(1-hydroxycyclohexyl)ethyl]-4-oxo-2-thiazolidinyl]propyl]benzoic acid (**5b**) which at 1 mg/kg po in the conscious dog causes a 70% increase in renal blood flow over control values with a duration of action exceeding 5 h. Preliminary testing indicates that **5b** has a relatively specific action on the vasculature of the kidney. The enantiomers of **5b** have been separated and the renal vasodilatory activity has been found to be entirely a property of the *R*-(+) enantiomer.

In our first paper in this series, we described the synthesis and biological evaluation of the 8-aza-11-thia-9-oxoprostanoic acid (**1**), a thiazolidinone prostaglandin



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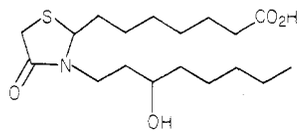
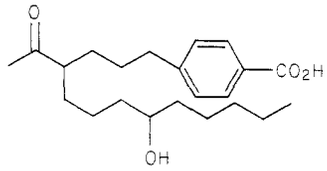


2a

isostere.[1] Compound **1** is qualitatively similar to PGE_1 in binding to the rat kidney prostaglandin receptor and in stimulating cAMP synthesis in the mouse ovary.

Subsequently, we prepared the isomeric thiazolidinone isostere **2a**. This compound not only displayed certain actions characteristic of the E prostaglandins in vitro but also caused a marked but transient increase in renal blood flow in the dog on oral administration.

Our concurrent studies on chain modification of the 11,12-secoprostaglandins indicated that replacement of the three methylene units nearest to the carboxy group by a *p*-phenylene group enhanced renal vasodilatory activity in this series. The formal cyclization of the terminal six carbon atom chain to give a cyclohexane ring is a further modification that has not proved to be activity enhancing in this regard but that potentially is capable of prolonging activity by blocking the metabolic oxidation of the chain hydroxy function. The renal vasodilatory activity of secoprostaglandins **3** and **4** that embody these modifications has been reported in a recent paper.[2]



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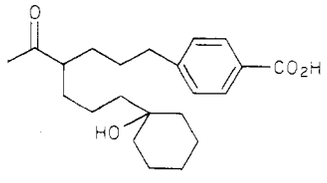

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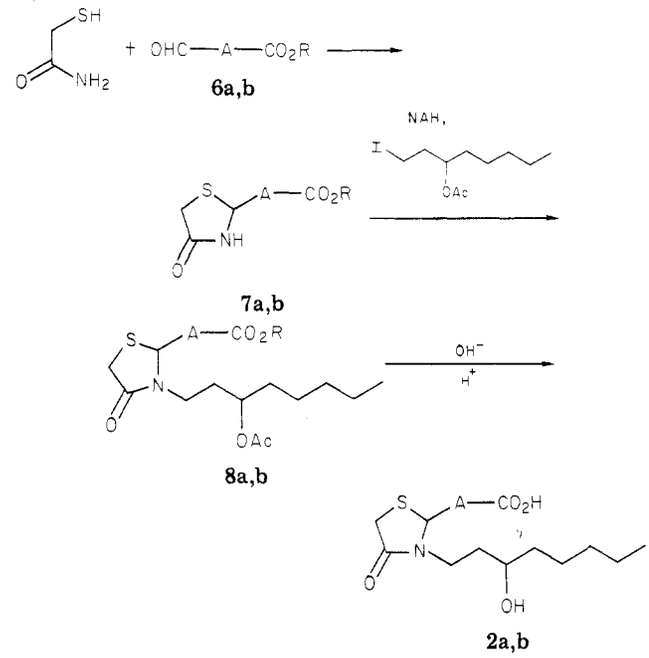
The systematic introduction of these two chain modifications into the structure of **2a** resulted in the preparation of the potent renal vasodilator **5b** and is the subject of this paper.

Scheme I[a]



[a] For compounds **2**, **6**, **7**, and **8a**, A = $-(CH_2)_6-$, R = CH_3; for compounds **2**, **6**, **7**, and **8b**, A = $-(CH_2)_3-C_6H_4-p$, R = C_2H_5.

Chemistry. Scheme I depicts the synthesis of **2a** and its interphenylene analogue **2b**. The condensation of aldehydes **6** with mercaptoacetamide gave thiazolidinones **7** bearing the esterified carboxy chains at their 2-positions. The thiazolidinones were converted to the anions with sodium hydride and N-alkylated with 3-acetoxy-1-iodooctane. The resulting diesters **8** were saponified to yield **2a,b**.

An alternate synthetic scheme (Scheme II) was used for the preparation of thiazolidinones **5a,b**, which incorporate a 2-(1-hydroxycyclohexyl)ethyl side chain. The alkylation route (Scheme I) had to be abandoned in these cases when the anions of thiazolidinones **7** failed to react with various hydroxy-protected derivatives of 1-(2-iodoethyl)cyclohexanol. The initial step of the alternate route involved

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(1) Smith, R. L.; Lee, T.-J.; Gould, N. P.; Cragoe, E. J., Jr.; Oien, H. G.; Kuehl, F. A., Jr. *J. Med. Chem.* **1977**, *20*, 1292.
(2) Bicking, J. B.; Robb, C. M.; Cragoe, E. J., Jr.; Blaine, E. H.; Dunlay, M. C.; Watson, L. S. *J. Med. Chem.*, preceding paper in this issue.

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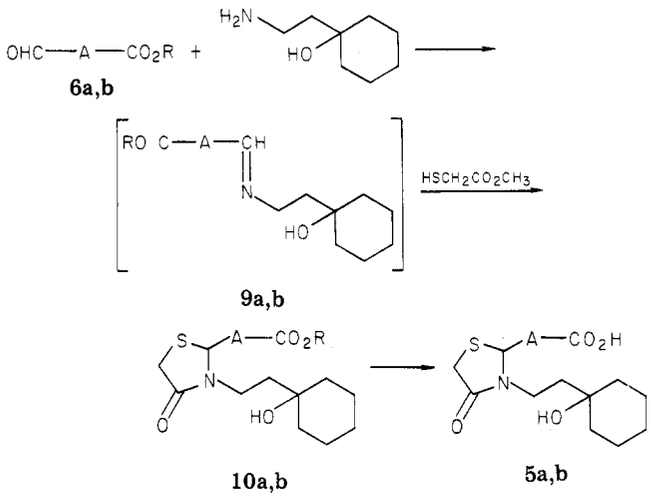
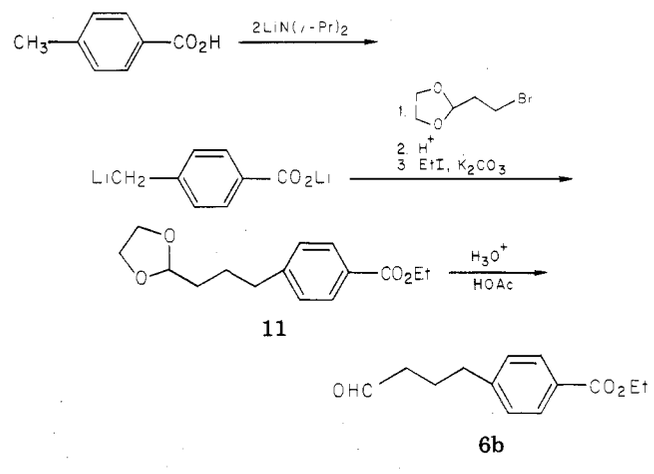
Scheme II[a]



[a] For compounds **5**, **6**, **9**, and **10a**, A = $-(CH_2)_6-$, R = CH_3; for compounds **5**, **6**, **9**, and **10b**, A = $-(CH_2)_3-C_6H_4-p$, R = C_2H_5.

Scheme III

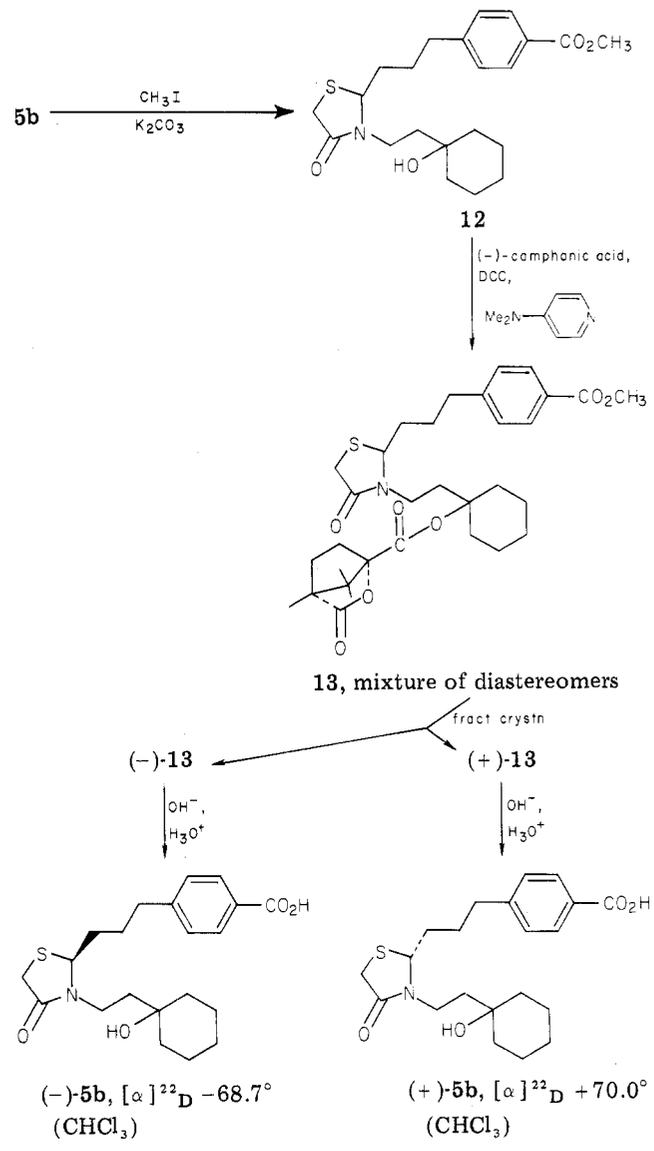


the condensation of aldehydes **6** with 1-(2-aminoethyl)-cyclohexanol to give the imines **9**. These reacted with methyl thioglycolate to give the appropriately 2,3-disubstituted thiazolidinones **10** by thiol addition to the imine double bond and subsequent amide bond formation. Saponification of the ester functions of **10** afforded **5a,b**.

The preparation of aldehyde **6b** is of interest. As shown in Scheme III, the dilithio derivative of *p*-toluic acid was alkylated with 2-(2-bromoethyl)-1,3-dioxolane. Subsequent esterification and acetal hydrolysis gave **6b** in 46% yield overall.

Thiazolidinones **2a** and **2b**, as obtained, must consist of two racemates, a fact reflected in the noncrystallinity of the samples. Compounds **5a** and **5b** with only one asymmetric center are single racemates and are crystalline. When **5b** was found to be a particularly potent renal vasodilator, we undertook its resolution in order to determine the degree of dependence of this biological activity on the configuration of the molecule. The obvious method for the resolution of **5b** appeared to be through the formation and subsequent separation of a diastereomer pair obtained either by salt formation between the carboxy group of **5b** and an optically active amine or by ester formation between the carboxy group and an optically active alcohol. A series of such pairs of salts and esters were prepared, but in no case could the diastereomers be separated by fractional crystallization or chromatographic methods. We then turned to resolution through diastereomer pairs ob-

Scheme IV



tained by acylation of the hydroxy group of **5b** by optically active acids. Experimentation along this line led to the practicable resolution procedure outlined in Scheme IV. In the key step, the methyl ester of **5b** was acylated with (1*S*)-(−)-ω-camphanic acid through the agency of *N*,*N*′-dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine.[3] The resulting mixture of diastereomeric diesters **13** was separable into its component diastereomers by fractional crystallization. These were separately hydrolyzed to yield the enantiomers (+)-**5b** and (−)-**5b**. Hydrolysis can be effected by simple saponification in aqueous media; however, a process that more efficiently cleaves the hindered camphanyl ester linkage employs the naked hydroxide ion in toluene solution obtained by complexation of solid KOH with dicyclohexyl-18-crown-6 in that solvent.[4]

X-ray diffraction experiments on enantiomer (+)-**5b** demonstrated that the absolute configuration at the asymmetric 2-position carbon atom of the thiazolidinone ring is *R*. Figure 1 is a perspective drawing of (+)-**5b** showing the conformation in the solid state, as well as the absolute configuration. Since renal vasodilatory activity has been shown to reside almost entirely in this enantiomer (vide infra), it is interesting that this configuration (*R*) is

(3) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.
(4) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.

Table I. Effects of PG Analogues on Renal Blood Flow and Related Cardiovascular Parameters

compd	no. of dogs	dose, mg/kg po	observation period, h after dose	mean RBF,[a] mL/min ± SE	mean LAF,[b] mL/min ± SE	mean BP,[c] mmHg ± SE	mean HR,[d] beats/min ± SE
2a	4	5	control[e]	96 ± 14	413 ± 47	135 ± 10	86 ± 7
			0-1	181 ± 49	420 ± 43	123 ± 6	126 ± 10
			1-2	110 ± 18	424 ± 75	146 ± 16	79 ± 5
			2-3	110 ± 22	432 ± 64	140 ± 16	85 ± 7
			3-4	116 ± 28	427 ± 76	133 ± 13	82 ± 6
			4-5	111 ± 25	386 ± 73	132 ± 11	76 ± 4
2b	4	5	control[e]	150 ± 21	534 ± 100	122 ± 2	91 ± 10
			0-1	201 ± 82	546 ± 136	118 ± 5	103 ± 12
			1-2	241 ± 63	560 ± 174	108 ± 6	118 ± 7
			2-3	209 ± 33	625 ± 139	116 ± 8	107 ± 6
			3-4	183 ± 26	521 ± 152	116 ± 3	92 ± 10
			4-5	159 ± 31	510 ± 153	116 ± 3	84 ± 9
5a	2	1	control[e]	118 ± 8	366 ± 176	105 ± 15	76 ± 16
			0-1	97 ± 51	772 ± 450	59 ± 13	180 ± 9
			1-2	150 ± 68	742 ± 368	74 ± 6	185 ± 46
			2-3	199 ± 75	530 ± 252	92 ± 5	113 ± 26
			3-4	176 ± 40	510 ± 248	100 ± 4	94 ± 16
			4-5	160 ± 48	388 ± 196	104 ± 15	88 ± 22
5b	5	1	control[e]	140 ± 22	480 ± 90	110 ± 7	89 ± 8
			0-1	179 ± 25	486 ± 65	105 ± 10	122 ± 11
			1-2	211 ± 26	597 ± 109	89 ± 9	169 ± 22
			2-3	226 ± 25	521 ± 85	97 ± 8	144 ± 15
			3-4	233 ± 26	492 ± 89	101 ± 7	131 ± 14
			4-5	242 ± 26	477 ± 65	98 ± 5	136 ± 18

[a] RBF = renal blood flow. [b] LAF = lower aortic blood flow. [c] BP = arterial blood pressure. [d] HR = heart rate. [e] A 30-min predrug observation period.

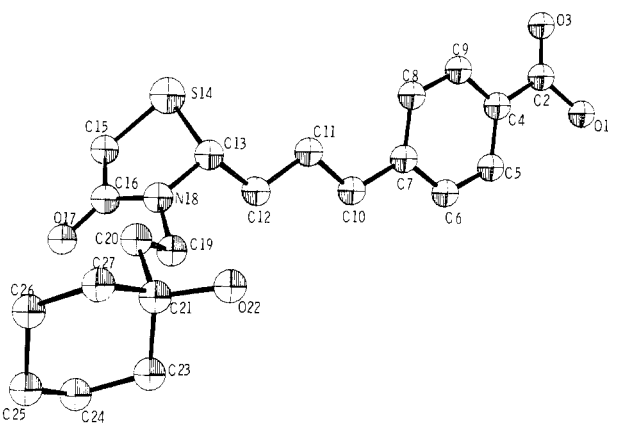


Figure 1. A perspective drawing of (+)-**5b** showing the conformation in the solid state as well as the absolute configuration. Hydrogens have been omitted for clarity.

the same as that at the corresponding 8-position of the natural prostaglandins. The five-membered ring in (+)-**5b** is best described as having a flattened half-chair conformation. In the crystal lattice, one intermolecular hydrogen bond of length 2.65 Å links O1–H1 to O22 (Figure 1), and another of length 2.76 Å links O22–H22 to O17.

Biological Results and Discussion

The preliminary testing of the effects of **2a,b** and **5a,b** on renal blood flow (RBF) and related cardiovascular parameters was performed in conscious dogs to which the compounds were administered orally. Details of the protocol have been described.[2] Mongrel dogs were prepared by placement of electromagnetic flow transducers on one renal artery and the lower aorta. A catheter was inserted into the aorta for the monitoring of blood pressure (BP) and heart rate (HR). After a 30-min control period during which RBF, lower aortic blood flow (LAF), BP, and HR were monitored, the test compounds were given orally and the variables were monitored for an additional 5 h. Each variable was recorded at 2-min intervals. These data were averaged for the control period and for each of the 5 hourly postdrug periods to give the mean values recorded in Table I.

Compound **2a** at 5 mg/kg po is seen to have caused a significant increase in RBF in the first hour after administration. This transient effect was accompanied by a moderate tachycardia. However, no effects on LAF or BP were seen, which suggests that **2a** has a relatively specific effect on the vasculature of the kidney.

Compound **2b**, the interphenylene analogue of **2a**, caused an increase in RBF at 5 mg/kg po comparable in magnitude to that caused by **2a** but sustained during the second and third hours after administration. Only modest changes were observed in the other variables. Compound **5a**, the terminally cyclized analogue of **2a**, at 1 mg/kg po raised RBF approximately to the same degree and for the same duration as did **2b** at 5 mg/kg po. A substantial increase in LAF also was observed with a concomitant fall in BP and rise in HR.

Although separate introduction of the two chain modifications did not appreciably enhance renal vasodilatory activity, the concurrent introduction of both modifications (to give **5b**) markedly increased both the degree and duration of this action. Compound **5b** at 1 mg/kg po increased RBF from the 1st through the 5th hour of observation to a maximum of 70% above the control value. A modest increase in LAF occurred during the 2nd and 3rd h; BP decreased with an associated tachycardia. The effect on the renal vasculature appeared to be more sustained than the peripheral effects, since RBF was at its maximum during the 5th hour of observation while the other variables had returned (LAF) or were returning to control values.

The strong renal vasodilatory activity of **5b** observed in these experiments has led to a further examination of the action of this compound. In Table II are presented the renal plasma flow responses of conscious dogs to varying iv doses of **5b** and its enantiomers. The details of the protocol employed are given under Experimental Section. The racemic **5b** is seen to produce large, dose-related increases in renal plasma flow over the dose range 0.05 to

Table II. Effects of **5b** and Enantiomers on Renal Plasma Flow in Conscious Dogs

compd	dose, mg/kg iv	no. of dogs	effective renal plasma flow,[a,b] mL/min: pretreatment[c]	effective renal plasma flow,[a,b] mL/min: posttreatment[d]	% change
5b	0.05	3	148 ± 16	240 ± 12	+62
	0.1	5	142 ± 18	216 ± 28	+52
	0.2	6	136 ± 11	322 ± 32	+137
(*R*)-(+)-**5b**	0.025	3	155 ± 25	239 ± 28	+54
	0.05	3	178 ± 16	289 ± 26	+62
	0.2	3	143 ± 10	292 ± 20	+104
(*S*)-(−)-**5b**	0.2	5	138 ± 6	146 ± 9	+6
	0.4	6	136 ± 9	147 ± 11	+8
	10.0	3	139 ± 9	151 ± 12	+9

[a] Values are means ± SEM. [b] Effective renal plasma flow was estimated from the renal clearance of *p*-aminohippurate. [c] Values are the averages of RPF determined in two 30-min pretreatment clearance periods. [d] Values are the averages of RPF in four 30-min posttreatment clearance periods.

Table III. Changes in Renal Vascular Resistance in Anesthetized Dogs after Infusion of PGE_2 and Injection of **5b** into the Renal Artery

compd	dose	*N*	% change in RR[a]
PGE_2[b]	10[c]	14	−13 ± 3
	60[c]	14	−29 ± 4
	110[c]	14	−35 ± 4
5b[d]	10[e]	4	−13 ± 4
	25[e]	5	−24 ± 4
	50[e]	5	−28 ± 9

[a] Calculated from the maximum decrease in renal resistance (RR) during each 10-min infusion period and the 180-min postinjection periods and the RR observed during the pretreatment period. [b] A stock solution of PGE_2 in EtOH–saline was diluted with saline so that an infusion rate of 1 mL/min delivered the indicated dose. [c] Nanograms per kilogram per minute infusion. [d] Administered as the Na salt in aqueous solution. [e] Nanograms per kilogram bolus injection.

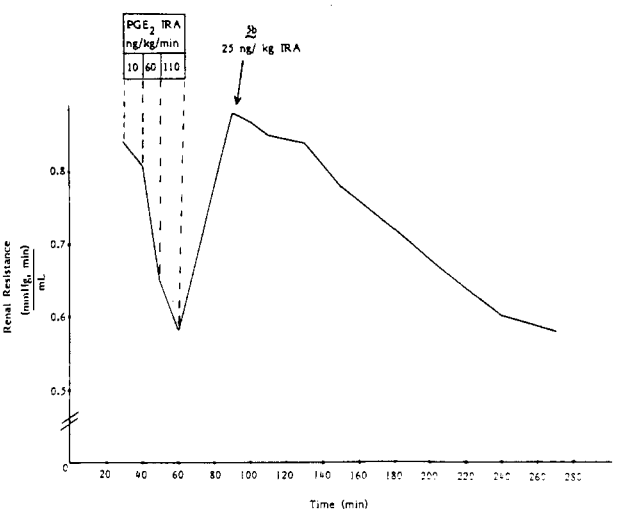


Figure 2. Changes in renal vascular resistance in a single anesthetized dog after infusion of PGE_2 and injection of **5b** into the renal artery (IRA).

0.2 mg/kg iv. This effect on the renal vasculature is entirely a property of the *R*-(+) enantiomer, which is seen to cause similar increases in renal plasma flow, while the *S*-(−) enantiomer is without significant activity.

A rigorous comparison of the effectiveness of the stable and long-acting **5b** relative to that of the rapidly metabolized and inactivated prostaglandin E_2 is difficult to make. Nevertheless, the data in Table III allow one to estimate the relative efficacies of the analogue **5b** and the natural substance in lowering renal vascular resistance (RR). Prostaglandin E_2 was infused into the renal arteries of 14 dogs at 10, 60, and 110 (ng/kg)/min each for 10 min in ascending order. After a 30-min recovery period during which RR returned approximately to pretreatment values, **5b** was injected into the renal arteries so that 4, 5, and 5 dogs received 10, 25, and 50 ng/kg of **5b**, respectively. Changes in RR were then determined for a subsequent 180 min. The maximum decreases in RR in each 10-min infusion period and in the postinjection period were used to calculate the percent changes in RR from pretreatment values. For clarity, we have shown in Figure 2 the response of the RR of an individual dog to the graded infusions of PGE_2 followed by bolus injection of 25 ng/kg of **5b** into the renal artery.

Clearly, single injections of 25 and 50 ng/kg of **5b** are capable of reducing RR to approximately the same extent as infusion of PGE_2 at 60 (ng/kg)/min. The estimate that **5b** and PGE_2 are roughly equal in potency seems reasonable when one takes into account the rapid metabolic deactivation of PGE_2.

In summary, the thiazolidinone prostaglandin analogue **5b** is a renal vasodilatory agent roughly equivalent in potency to the vasodilatory prostaglandins of the E series. Unlike the natural substances, it is chemically and metabolically stable and, as a result, is active on oral administration and has a long duration of action. At relatively high doses, **5b** exhibits peripheral vasodilatory effects, but these are of shorter duration than the renal vasodilation, suggesting that the compound may have a relative specificity for the renal vascular bed. The extensive pharmacological evaluation of **5b** and its *R*-(+) enantiomer is continuing preliminary to possible clinical trial. The results of these studies will be published elsewhere.

The use of renal vasodilators is indicated in a number of pathological conditions associated with increased renal resistance, e.g., hypertension,[5] congestive heart failure,[6] and acute renal failure.[7] Dopamine hydrochloride, given by iv infusion at low doses, reduces RR and increases RBF and has been used with benefit to patients with congestive heart failure and renal failure.[8] The ongoing development of dopamine prodrugs and dopaminergic agonists with improved pharmacological attributes is the subject of a recent review.[8] Progress in this area notwithstanding, a clear need exists for more effective renal vasodilators. It now appears that the pharmacological properties of **5b** are such as to allow for the first time the evaluation of a prostaglandin analogue as a clinically practical renal vasodilatory agent.

(5) Hollenberg, N. K.; Adams, D. F. *Am. J. Med.* **1976**, *60*, 773.
(6) Cannon, P. J. *N. Engl. J. Med.* **1977**, *296*, 26.
(7) Oken, D. E. *Kidney Int.* **1976**, *10*, S-94.
(8) Dolak, T. M.; Goldberg, L. I. *Annu. Rep. Med. Chem.* **1981**, *16*, 103.

Experimental Section

Chemical. Melting points were determined in open capillary tubes and are uncorrected, as are boiling points. ^1H NMR spectra were taken in $CDCl_3$ on either a Varian EM390 or a Varian SC-300 Superconducting NMR 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.

Column chromatography was carried out on silica gel (E. Merck, particle size 0.063–0.20 mm). Thin-layer chromatography (TLC) was used to monitor column fractions and to establish the purity of products. It was performed on Analtech silica gel GF plates (250-μm thickness). Spots were visualized both with iodine vapor and Mineral-Light exposure. Solutions in organic solvents were dried with $MgSO_4$.

Oily products were prepared for analysis and biological testing by being heated at 100 °C in oil pump vacuum for 4–6 h in order to remove the last traces of solvents. 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.

1-Chloro-3-octanol. 3-Chloropropanal (60.0 g, 0.648 mol) was added during 1 h to the Grignard reagent prepared from 1-bromopentane (97.8 g, 0.648 mol) and Mg (15.8 g, 0.648 mol) in Et_2O (250 mL). After an additional 1 h at reflux, the mixture was cooled to 5 °C and treated successively with saturated aqueous NH_4Cl and 6 N hydrochloric acid. The organic phase was separated, washed with H_2O, and dried. Distillation gave 34.9 g (33%) of product as a colorless liquid, bp 79 °C (0.2 mm). Anal. ($C_8H_{17}ClO$) H; C: calcd, 58.35; found 57.87.

3-Acetoxy-1-iodooctane. A mixture of 1-chloro-3-octanol (14.2 g, 0.086 mol) and Ac_2O (13.2 g, 0.129 mol) was heated at 95 °C for 1 h. The mixture was cooled and dissolved in 200 mL of Et_2O, and the solution was washed with 2% aqueous NaOH and H_2O and dried. Evaporation of the solvent gave 17.4 g (98%) of crude 1-acetoxy-1-chlorooctane, a colorless liquid. A solution of the acetate and NaI (64.5 g, 0.43 mol) in acetone (200 mL) was boiled at reflux with exclusion of light for 17 h. The reaction mixture was concentrated by vacuum distillation and treated with Et_2O (300 mL). Inorganic solids were removed by filtration. The organic filtrate was washed with dilute aqueous $Na_2S_2O_3$ and H_2O and dried. Distillation gave 15.5 g (62%) of the iodo compound as a yellow oil, bp 90–91 °C (0.1 mm). Anal. ($C_{10}H_{19}IO_2$) C, H.

Ethyl 4-[3-[2-(1,3-Dioxolanyl)]propyl]benzoate (11). Butyllithium (35 mL of a 2.29 M solution in hexane, 0.08 mol) was added to a solution of diisopropylamine (8.1 g, 0.08 mol) in THF (120 mL) and HMPA (10 mL) at 0 °C during 30 min. A partial solution/suspension of *p*-toluic acid (5.4 g, 0.04 mol) in THF (20 mL) was then added dropwise during 30 min at 0–5 °C, followed, after an additional 30 min, by 2-(2-bromoethyl)-1,3-dioxolane[9] (7.2 g, 0.04 mol) added dropwise in 30 min at 0–5 °C. The resulting solution was stirred for 30 min and then treated with H_2O and Et_2O. The aqueous layer was separated and acidified with 2 N hydrochloric acid. The crude acid product that separated was taken up in Et_2O, washed with H_2O, and dried. The Et_2O was evaporated. The residue was dissolved in DMF (50 mL) and treated with ethyl iodide (9.4 g, 0.60 mol) and K_2CO_3 (69 g, 0.5 mol). The resulting mixture was stirred at 25–27 °C for 16 h. Water and Et_2O were then added. The organic layer was washed with H_2O and dried. Distillation gave 5.8 g (55%) of the product ester as a colorless oil, bp 135–140 °C (0.05 mm). Anal. ($C_{15}H_{20}O_4$) C, H.

Ethyl 4-(4-Oxobutyl)benzoate (6b). A solution of **11** (47.6 g, 0.18 mol) and concentrated hydrochloric acid (3 mL) in H_2O (140 mL) and HOAc (290 mL) was stirred at 55–60 °C for 1.5 h. The solution was then cooled, diluted with H_2O, and extracted with Et_2O. The extract was washed with H_2O and saturated $NaHCO_3$ solution and dried. Evaporation of solvent at reduced pressure gave 39.9 g (~100%) of the crude aldehyde as a yellowish oil, which was used without purification in subsequent reactions: NMR δ 9.74 (1 H, t, J = 1 Hz, CHO).

Ethyl 4-[3-(4-Oxo-2-thiazolidinyl)propyl]benzoate (7b). A solution of **6b** (24.9 g, 0.113 mol), mercaptoacetamide (30.9 g, 0.339 mol), and *p*-toluenesulfonic acid monohydrate (250 mg) in benzene (300 mL) was heated at reflux for 2 h under a Dean–Stark device for separation of evolved H_2O. The solution was then cooled and treated with H_2O (600 mL). The organic layer was separated, washed with H_2O, and dried. The solvent was evaporated, and the residual solid was triturated with cyclohexane and recrystallized from BuCl to yield 16.8 g (51%) of product: white needles; mp 99–100 °C. Anal. ($C_{15}H_{19}NO_3S$) C, H, N.

Methyl 7-[3-(3-Acetoxyoctyl)-4-oxo-2-thiazolidinyl]heptanoate (8a). A solution of methyl 7-(4-oxo-2-thiazolidinyl)-heptanoate[10] (1.23 g, 5 mmol) and 3-acetoxy-1-iodooctane (1.73 g, 5.8 mmol) in DMF (5 mL) was added at 0–5 °C during 15 min to a stirred suspension of NaH (0.12 g, 5 mmol) in DMF (10 mL). The mixture was stirred at 0–5 °C for 3 h and then at 27 °C for 1 h. The mixture was diluted with H_2O and extracted with Et_2O. The extract was washed with 2 N hydrochloric acid and H_2O and dried. The solvent was evaporated to leave the crude product as a residual oil, which was purified by chromatography on 40 g of SiO_2 with elution by 1% CH_3OH in $CHCl_3$. There was obtained 1.5 g (72%) of **8a** as a colorless, viscous oil: TLC 1 spot, R_f 0.19 ($CHCl_3$–CH_3OH, 100:1); IR (neat) 1740 (ester CO), 1670 (lactam CO) cm^{-1}; ^1H NMR δ 3.54 (2 H, s, SCH_2CO), 4.70 (1 H, m, SCHN).

Ethyl 4-[3-[3-(3-Acetoxyoctyl)-4-oxo-2-thiazolidinyl]-propyl]benzoate (8b). This compound was prepared analogously to **8a** by the alkylation of **7b**. The colorless viscous oil was obtained in 54% yield: TLC 1 spot, R_f 0.21 (CH_3Cl–CH_3OH, 100:1).

7-[3-(3-Hydroxyoctyl)-4-oxo-2-thiazolidinyl]heptanoic Acid (2a). A solution of diester **8a** (0.97 g, 2.33 mmol) and 1.7 N aqueous NaOH (3 mL, 5.1 mmol) in CH_3OH (15 mL) was kept at 25 °C for 4 h. The solution was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified with 2 N hydrochloric acid. The separated oil was taken up in Et_2O, washed with H_2O, and dried. Evaporation of the solvent left the crude product as an oil, which was chromatographed on 15 g of SiO_2 with elution by $CHCl_3$–HOAc (25:1, v:v). There was obtained 0.33 g (40%) of **2a** as a pale yellow, viscous oil: homogeneous on TLC ($CHCl_3$–HOAc, 25:1) R_f 0.15; ^1H NMR δ 0.88 (3 H, t, CH_3), 2.73 (2 H, t, CH_2CO_2H), 3.54 (2 H, s, SCH_2CO), 4.68 (1 H, m, SCHN), 7.60 (2 H, br s, OH and CO_2H). Anal. ($C_{18}H_{33}NO_4S$) C, H, S; N: calcd, 3.90; found, 3.49.

4-[3-[3-(3-Hydroxyoctyl)-4-oxo-2-thiazolidinyl]propyl]-benzoic Acid (2b). The basic hydrolysis of diester **8b** (3.1 g, 6.7 mmol) was conducted as in the preparation of **2a**. The crude product was chromatographed on 75 g of SiO_2 with elution by CH_3Cl–HOAc (25:1, v:v). There was obtained 1.1 g (42%) of **2b** as a colorless, viscous oil: homogeneous on TLC ($CHCl_3$–HOAc, 25:1) R_f 0.22; NMR δ 0.92 (3 H, t, CH_3), 3.60 (2 H, s, SCH_2CO), 4.72 (1 H, m, SCHN), 7.30 (2 H, d, J = 8 Hz, aryl 3- and 5-H), 8.08 (2 H, d, J = 8 Hz, aryl 2- and 6-H). Anal. ($C_{21}H_{31}NO_4S$) C, H, N, S.

2-(1-Hydroxycyclohexyl)acetonitrile.[11] Butyllithium (1.6 M solution in hexane, 125 mL, 0.2 mol) was added to a solution of diisopropylamine (20.2 g, 0.2 mol) in THF (280 mL) at 0 °C under N_2. The solution was cooled to −78 °C, and a solution of CH_3CN (8.2 g, 0.2 mol) in THF (10 mL) was added. The solution was stirred for 20 min at −78 °C and then was treated with cyclohexanone (19.6 g, 0.2 mol) and HMPA (15 mL). After an additional 45 min at −78 °C, the solution was allowed to warm to room temperature. Ether (100 mL) and H_2O (200 mL) were added, and the mixture was acidified with 3.5 N hydrochloric acid (140 mL). The organic phase was separated, washed with H_2O and 5% aqueous $NaHCO_3$, and dried. Evaporation of the solvents gave 23.6 g (85%) of the hydroxy nitrile as a pale yellow oil. It was used without purification in the following reaction: ^1H NMR δ 2.54 (2 H, s, CH_2CN), 2.64 (1 H, s, OH).

1-(2-Aminoethyl)cyclohexanol. A stirred suspension of lithium tetrahydridoaluminate (7.6 g, 0.2 mol) in Et_2O (200 mL) was treated with a solution of 2-(1-hydroxycyclohexyl)acetonitrile (25.0 g, 0.18 mol) in Et_2O (60 mL) dropwise during 1 h. The

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(10) Pennington, F. C.; Celmer, W. D.; McLamore, W. M.; Bogert, V. V.; Solomon, I. A. *J. Am. Chem. Soc.* **1953**, *75*, 109.

(11) The condensation of CH_3CN with cyclohexanone with $LiNH_2$ in NH_3 was reported by Ivanov, C.; Angelova, G. *C. R. Acad. Bulg. Sci.* **1966**, *19*, 739.

mixture was then stirred and boiled under reflux for 2 h and stirred at 25 °C for 16 h. The mixture was cooled in an ice bath and treated successively with H_2O (8.5 mL), 15% aqueous NaOH (8.5 mL), and H_2O (25 mL). The white precipitate was removed by filtration. The ether solution was concentrated to a residual oil. Distillation gave 13.3 g (52%) of the amino alcohol as a colorless oil: bp 85–87 °C (0.25 mm), n^{25}_D 1.4900 (lit.[12] bp 115–117 °C (10 mm), n^{25}_D 1.4950).

7-[3-[2-(1-Hydroxycyclohexyl)ethyl]-4-oxo-2-thiazolidinyl]heptanoic Acid (5a). Methyl 8-oxooctanoate[13] (17.2 g, 0.10 mol) was added dropwise during 20 min to a stirred solution of 1-(2-aminoethyl)cyclohexanol (14.3 g, 0.10 mol) in toluene (35 mL). The solution was boiled at reflux for 1 h under a Dean–Stark water separator. Additional toluene (35 mL), methyl thioglycolate (14.2 g, 0.134 mol), and triethylamine (2.5 g) were then added, and the solution was boiled under reflux for 21 h. The solution was cooled, washed with 2 N hydrochloric acid and H_2O, and dried. Evaporation of the solvent left 39 g of the methyl ester of **5a** as a viscous yellow oil. A solution of the crude ester and NaOH (8 g, 0.2 mol) in H_2O (100 mL) and CH_3OH (270 mL) was stirred at 25–27 °C for 16 h. Most of the CH_3OH was removed by vacuum distillation. The solution was diluted with H_2O and extracted with Et_2O. The aqueous solution was acidified with 2 N hydrochloric acid. The oily product was extracted with Et_2O and chromatographed on 500 g of silica gel. Elution with 1% CH_3OH in $CHCl_3$ gave 6.5 g (18%) of **5a** as a viscous oil, which crystallized, mp 80–83 °C. Anal. ($C_{18}H_{31}NO_4S$) C, H, N.

4-[3-[3-[2-(1-Hydroxycyclohexyl)ethyl]-4-oxo-2-thiazolidinyl]propyl]benzoic Acid (5b). A solution of ethyl 4-(4-oxobutyl)benzoate (167.2 g, 0.76 mol) and 1-(2-aminoethyl)-cyclohexanol (129.5 g, 0.91 mol) in toluene (500 mL) was boiled at reflux for 1 h under a Dean–Stark water separator. Additional toluene (500 mL), methyl thioglycolate (118.7 g, 1.12 mol), and triethylamine (30 mL) were then added, and the resulting solution was boiled at reflux for 21 h. The solution was cooled, washed with 2 N hydrochloric acid and H_2O, and dried. Evaporation of the solvent left 339 g of th ethyl ester of **5b** (**10b**) as a viscous orange oil. This crude ester was hydrolyzed as described in the preparation of **5a**. The crude acid solidified when precipitated. Recrystallization from CH_3CN–H_2O gave 133.7 g (45%) of **5b**: mp 147–148 °C; ^1H NMR δ 2.74 (2 H, t, CH_2Ph), 3.54 (2 H, s, SCH_2CO), 4.68 (1 H, m, SCHN), 6.98 (2 H, br s, OH and CO_2H), 7.24 (2 H, d, J = 8 Hz, aryl 3- and 5-H), 8.00 (2 H, d, J = 8 Hz, aryl 2- and 6-H). Anal. ($C_{21}H_{29}NO_4S$) C, H, N.

Resolution of 5b. (a) Methyl 4-[3-[3-[2-(1-Hydroxycyclohexyl)ethyl]-4-oxo-2-thiazolidinyl]propyl]benzoate (12). A mixture of **5b** (10 g, 25.6 mmol), CH_3I (3.7 g, 26 mmol), K_2CO_3 (3.54 g, 25.6 mmol), and DMF (86 mL) was stirred at room temperature for 19.5 h. The mixture was then treated with H_2O (175 mL), and the product was extracted into Et_2O. The extract was washed with three 30-mL portions of saturated $NaHCO_3$ solution and dried. distillation of solvent at reduced pressure gave 10.55 g of **12**: light yellow oil; homogeneous on TLC (EtOAc–hexane, 7:3) R_f 0.4; IR ($CHCl_3$) 3400 (w), 1710 (s), 1660 (s), 1280 (s) cm^{-1}.

(b) Preparation of Methyl 4-[3-[3-[2-[1-[(1*S*)-ω-camphanyloxy]cyclohexyl]ethyl]-4-oxo-2-thiazolidinyl]propyl]-benzoate (13) and Separation of Diastereomers. *N,N'*-Dicyclohexylcarbodiimide (23.38 g, 113.52 mmol) in CH_2Cl_2 (180 mL) was added during 15 min to a solution at 0 °C of **12** (38.37 g, 94.6 mmol), (1*S*)-(−)-ω-camphanic acid (20.64 g, 104.1 mmol), and 4-(dimethylamino)pyridine (5.77 g, 47.3 mmol) in CH_2Cl_2 (180 mL). The mixture was stirred at room temperature for 22 h. Precipitated dicyclohexylurea was removed by filtration. The filtrate was washed with 0.1 N hydrochloric acid and H_2O and dried. Distillation of solvent gave crude **13** as a brown oily material. Chromatography on SiO_2 with elution by $CHCl_3$–CH_3OH (98:2, v/v) gave 55 g of the mixed diastereomers of **13** contaminated by *N*-(1S)-(−)-ω-camphanyl-*N,N'*-dicyclohexylurea. The isolation of the component diastereomers was carried out in the following manner.

(12) Stork, G.; Worrall, W. S.; Pappas, J. J. *J. Am. Chem. Soc.* **1960**, *82*, 4315.
(13) Rappoport, H.; Volcheck, E. J. *J. Am. Chem. Soc.* **1956**, *78*, 2451.

(1) Isolation of (−)-13. Product **13** was triturated with 300 mL of 1:1 EtOAc–hexane. The insoluble material (25 g) was collected on a filter. The filtrate containing the bulk of (+)-**13** and the acyldicyclohexylurea was set aside. The solid was recrystallized from EtOAc to constant melting point and optical rotation. There was obtained 8.85 g of (−)-**13**: mp 163–164 °C; $[\alpha]^{26}_D$ −47.3° (*c* 0.58, $CHCl_3$). Anal. ($C_{32}H_{43}NO_7S$) C, H, N.

(2) Isolation of (+)-13. Evaporation of solvents from the filtrate obtained from trituration of **13** mixed diastereomers gave 24 g of a residue consisting essentially of (+)-**13** and the byproduct acyldicyclohexylurea. This material was chromatographed on 700 g of silica gel. Elution with 30% EtOAc in hexane removed the acyldicyclohexylurea. Further elution with 40 to 60% EtOAc in hexane provided 15 g of (+)-**13**, which was recrystallized from EtOAc to constant optical rotation. There was obtained 10.55 g of pure (+)-**13**: mp 130–132 °C; $[\alpha]^{22}_D$ +37.2° (*c* 0.61, $CHCl_3$). Anal. ($C_{32}H_{43}NO_7S$) C, H, N.

^1H NMR analyses with the shift reagent Eu(fod)$_3$ of samples of (−)- and (+)-**13**, as obtained, indicated that each consisted of a single diastereomer.

(c) (+)-5b. Potassium hydroxide (finely crushed pellets) (3.83 g, 68.3 mmol) was added to toluene (100 mL) and the toluene boiled until 20 mL of distillate was collected in order to remove traces of H_2O. The mixture was cooled, treated with diastereomer (+)-**13** (4 g, 6.83 mmol) and dicyclohexyl-18-crown-6 (12.72 g, 34.2 mmol), and then stirred at 40 °C for 1 h. Water (80 mL) was added to the reaction mixture, and stirring at 40 °C was continued for 45 h.[14] The mixture was then cooled and poured into 1 N hydrochloric acid (200 mL). The aqueous layer was extracted with $CHCl_3$ (4 × 100 mL). The toluene layer and extracts were combined, washed with H_2O, and dried. Solvents were evaporated at reduced pressure. The residual oil was triturated with Et_2O to give 2.04 g of solid, which was recrystallized from MeOH to afford 1.1 g (40%) of (+)-**5b**: colorless crystals: mp 139.5–140.5 °C; $[\alpha]^{22}_D$ +70.0° (*c* 0.47, $CHCl_3$); R_f 0.26 ($CHCl_3$–CH_3OH, 9:1); IR and NMR spectra identical with those of **5b**. Anal. ($C_{21}H_{29}NO_4S$) C, H, N.

(d) (−)-5b. The hydrolysis of diastereomer (−)-**13** (4 g, 6.83 mmol) was carried out as described above. There was obtained 1.24 g (46%) of (−)-**5b**: colorless crystals; mp 140–141 °C (from MeOH); $[\alpha]^{22}_D$ −68.7° (*c* 0.47, $CHCl_3$). Anal. ($C_{21}H_{29}NO_4S$), C, H, N.

X-ray Diffraction Experiments. Crystals of (+)-**5b** formed as clear rectangular prisms with symmetry $P2_12_12_1$ and Z = 4 for a calculated density of 1.26 g/cm^3. The cell constants determined from ten well-centered reflections were a = 6.328 (1) Å, b = 7.204 (1) Å, and c = 45.280 (4) Å. Cu $K\alpha$ radiation (λ = 1.5418 Å) was used throughout the diffraction experiments. Of the 1706 unique reflections measured with $2\theta \leq 114°$ using an ω-scan technique, 1543 were observed ($I \leq 3\sigma I$). Initial coordinates for the majority of the non-hydrogen atoms were found by a multisolution tangent formula approach,[15] and the remainder was found by difference Fourier maps. Full-matrix least-squares refinements were used to minimize $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$. At the end of anisotropic refinement, one enantiomer had an unweighted residual of 0.082, while the other was refined to 0.088.[16] This difference is easily significant at the 0.005 level.[17] A careful remeasurement of ten enantiomorph-sensitive reflections and their Friedel pairs confirmed that the enantiomer with the lowest residual was indeed correct. Hydrogen atoms were added with fixed isotropic parameters, and final refinements gave an unweighted R factor of 0.042 for the observed reflections. Figure 1 is a labeled drawing showing the solid-state conformation and the correct absolute configuration of 1.[18] Tables containing the

(14) Hydroxide ion in toluene cleaves the camphanyl ester linkage. Subsequent addition of water serves to hydrolyze the liberated camphanic acid to the water-soluble 1-hydroxy-2,2,3-trimethylcyclopentane-1,3-dicarboxylic acid, which is readily separable from (+)-**5b**.
(15) Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M., MULTAN 78, 1978, University of York, York, England.
(16) Enraf-Nonius Structure Determination Package, 1980, Version 17.0.
(17) Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 502.

final fractional coordinates, temperature parameters, bond distances, and bond angles for 1 can be found in the supplementary material (see paragraph at the end of paper concerning Supplementary Material).

Renal Blood Flow Assays. (a) Conscious Dogs. Intravenous Administration (Table II). Trained conscious female mongrel dogs in the postabsorptive state were used. Tap water (500 mL) was administered orally 1–1.5 h prior to study. Venous catheters were inserted into one jugular and one saphenous vein for blood sampling and infusion of sodium *p*-aminohippurate (PAH). The renal clearance of PAH was used as an estimate of the effective renal plasma flow. The urinary bladder was catheterized, and the animal was placed in a modified Pavlov sling. A priming dose of PAH (8 mg/kg) was given iv, and a constant infusion of PAH [0.3 (mg/kg)/min] in isotonic NaCl solution was begun. After an equilibration period of 30–45 min, the bladder was emptied, and two 30-min control clearance periods were obtained. A single iv dose of the test compound as the Na salt in aqueous solution was then given and four additional 30-min clearance periods were taken. Heparinized blood samples for measurement of plasma PAH concentration were taken at the midpoint of each urine collection period. Concentrations of PAH in plasma and urine were measured by standard automated methods (Technicon Autoanalyzer).

(b) Anesthetized Dogs. Intrarenal Arterial Administration (Table III). Dogs were anesthetized with vinbarbital, an electromagnetic flow probe was placed around the left renal artery, and a catheter was inserted into the aorta for blood pressure measurement. After a 30-min pretreatment period during which saline was infused into the renal artery, PGE_2 was infused at 10, 60, and 110 (ng/kg)/min each for 10 min in ascending dose order. The dogs were allowed to recover for 30 min, and **5b** as the Na salt in aqueous solution was injected into the renal artery at 10, 25, or 50 ng/kg. All dogs (14) received the graded PGE_2 infusions, and 4, 5, and 5 dogs received 10, 25, and 50 ng/kg of **5b**, respectively. Renal blood flow and BP were recorded during the 10-min infusion periods and for 180 min after injection of **5b**. Renal resistances were calculated, and the maximum decrease in RR during each period was used to calculate the percent change from pretreatment RR.

(18) Johnson, C. K., ORTEP-II, ORNL-3794, 1970, Oak Ridge National Laboratory, Oak Ridge, TN.

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Registry No. (±)-8α,15α-**2a**, 84064-00-6; (±)-8α,15β-**2a**, 84064-01-7; (±)-8α,15α-**2b**, 84040-53-9; (±)-8α,15β-**2b**, 84040-54-0; (±)-**5a**, 84040-55-1; (+)-**5b**, 84040-56-2; (−)-**5b**, 84040-57-3; (±)-**5b**, 84064-02-8; (±)-**5b** Na salt, 84064-03-9; **6a**, 3884-92-2; **6b**, 72313-37-2; (±)-**7a**, 84040-58-4; (±)-**7b**, 84040-59-5; (±)-8α,15α-**8a**, 84040-60-8; (±)-8α,15β-**8a**, 84040-61-9; (±)-8α,15α-**8b**, 84040-62-0; (±)-8α,15β-**8b**, 84040-63-1; **9a**, 84040-64-2; **9b**, 84040-65-3; (±)-**10a**, 84040-66-4; (±)-**10b**, 84040-67-5; **11**, 72313-38-3; deethyl-**11**, 76865-45-7; (±)-**12**, 84040-68-6; (+)-**13**, 84040-69-7; (−)-**13**, 84064-04-0; CH_3CN, 75-05-8; 1-bromopentane, 110-53-2; (±)-1-chloro-3-octanol, 84040-70-0; (±)-3-acetoxy-1-chlorooctane, 84040-71-1; (±)-3-acetoxy-1-iodooctane, 84040-72-2; *p*-toluic acid, 99-94-5; 2-(2-bromoethyl)-1,3-dioxolane, 18742-02-4; 3-chloropropanal, 19434-65-2; cyclohexanone, 108-94-1; 2-(1-hydroxycyclohexyl)acetonitrile, 14368-55-9; 1-(2-aminoethyl)cyclohexanol, 39884-50-9.

Supplementary Material Available: Tables of fractional coordinates, temperature parameters, bond distances, and bond angles for (+)-**5b** (3 pages). Ordering information is given on any current masthead page.

Synthesis and Evaluation of 1- and 2-Substituted Fentanyl Analogues for Opioid Activity

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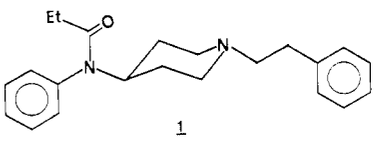
We synthesized fentanyl analogues that possess key groups common to the opioid peptides to investigate whether or not these two classes of compounds interact with common subsites on opioid receptors. The design of the analogues was based on the possibility of structural analogy between the two aromatic rings of fentanyl and the Tyr[1] and Phe[4] residues of the opioid peptides. The synthesized compounds showed very weak or no opioid activity as tested in the electrically stimulated longitudinal muscle of the guinea pig ileum or mouse vas deferens preparations. These results, together with those of reported studies, suggest that fentanyl and the opioid peptides interact with different subsites on either μ or δ receptors. Studies using the irreversible μ opioid receptor antagonist, β-funaltrexamine, indicate that fentanyl interacts preferentially with μ opioid receptors.

Fentanyl[1] (1) is the prototype of a series of analgesics known as the 4-anilidopiperidines. Compounds in the series are characterized by their potent analgesic properties. Structure–activity relationship studies of both fentanyl[1] and enkephalins[2] have suggested the possibility of analogies between them.[3] In the opioid peptides, the Tyr[1] and Phe[4] residues are important for opioid activity and probably interact with two complementary subsites on opioid receptors.[4,5] Since fentanyl (1) also contains two



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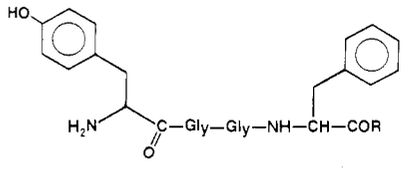

Opioid Peptides

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