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

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

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

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

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

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

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

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

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

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

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

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

Acknowledgment. The authors thank Dr. Laura Mucchi for his aid in preparing some intermediates.

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

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

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

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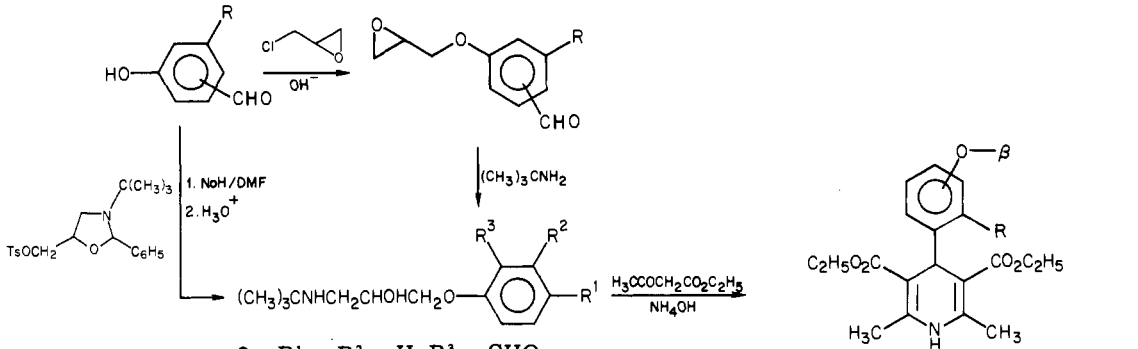
Scheme I

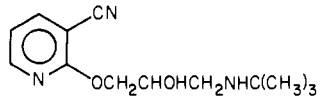


3a, $R^1 = R^2 = H$; $R^3 = CHO$
b, $R^2 = R^3 = H$; $R^1 = CHO$
c, $R^1 = CHO$; $R^2 = CH_3$; $R^3 = H$

4a, R = H; o-Oβ
b, R = H; p-Oβ
c, $R = CH_3$; p-Oβ
$\beta = CH_2CHOHCH_2NHC(CH_3)_3$

β-adrenergic blocking agents will inhibit the tachycardia due to the increased sympathetic stimulation which occurs as a result of the administration of a vasodilator drug.[1]

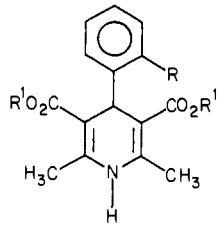
We have previously described our attempts to overcome the tachycardia liability of direct-acting peripheral vasodilators with compounds exemplified by 1 which were



1

designed to exhibit both vasodilating and β-adrenergic blocking properties.[2] Recently, other investigators have also reported on similar attempts to prepare such divalent compounds.[3]

In this paper, we describe model compounds related to the dihydrolutidine class of peripheral vasodilator, **2a,b**.



2a, $R = CF_3$; $R^1 = C_2H_5$
b, $R = NO_2$; $R^1 = CH_3$

Nifedipine (**2b**), the most widely studied member of this group, is believed to exert its cardiovascular actions, including vasodilation, by a direct effect on transmembrane calcium flux.[4] A combination of calcium antagonism and β-adrenergic blockade could, on theoretical grounds, be undesirable due to the potential adverse effect of two independent myocardial depressant actions. However, nifedipine has been reported to increase both heart rate and renin levels in hypertensive subjects, and these increases were inhibited by the coadministration of propranolol. In addition a cooperative effect on blood pressure was also observed.[5] Our specific approach to the introduction of β-adrenergic blocking activity into the dihydrolutidines was via the incorporation of the aminohydroxypropoxy moiety onto the 4-aryl substituent.

Table I. Comparative Effects on Arterial Pressure in Spontaneously Hypertensive Rats (SHR)

compd	dose, mg/kg	route[b]	no. of SHR	max. fall in MAP,[a] mmHg
4a	20	ip	2	15
	20	po	1	16
4b	20	ip	2	*c*
	5	po	2	17
4c	20	ip	2	*c*
	5	po	5	42 ± 5.8
	1.25	po	4	12 ± 2.5
2a	5	po	2	41
propranolol	5	po	8	7 ± 4
timolol	1.25	po	6	−1

[a] MAP = mean arterial pressure. [b] ip = intraperitoneal; po = per os. [c] Death.

Chemistry. The dihydrolutidines, **4a–c**, prepared during this study are listed in Table I and were synthesized by the method developed by Hantzsch.[6] In this procedure an aldehyde, ammonia, and a keto ester are condensed to give the dihydropyridine. As indicated in Scheme I, the 3-(*tert*-butylamino)-2-hydroxypropoxy moiety was introduced onto the benzaldehyde derivatives, **3a–c**, prior to the condensation.

The racemic aryl aldehydes, **3a,b**, were prepared as previously described from the reaction of the appropriate hydroxybenzaldehyde with epichlorohydrin, followed by treatment of the intermediate epoxide with *tert*-butylamine.[2a] The aldehyde **3c** was prepared as the *S* isomer through reaction of 2-methyl-4-hydroxybenzaldehyde with the tosylate of (*S*)-2-phenyl-3-*tert*-butyl-5-(hydroxymethyl)oxazolidine.[2b] Optical purity of **3c** was determined

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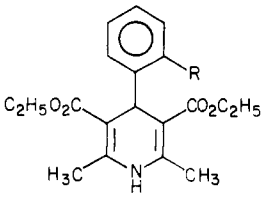
by NMR spectroscopy using the chiral shift reagent tris-[3-(heptafluorobutyryl)-α-camphorate]europium.[25] By this method, optical purity of the intermediate was found to be 99 ± 1%.

The aryl aldehydes, **3a–c**, on reaction with ethyl acetoacetate and aqueous ammonia in ethanol gave the dihydropyridines, **4a–c**, in moderate yield.

Discussion

The dihydrolutidines, **4a–c**, were evaluated for acute antihypertensive activity in the spontaneously hypertensive (SH) rat, of the Wistar–Okamoto strain, according to the method of Watson and Ludden.[7] In this model, the β-adrenergic blocking agents propranolol and timolol do not reduce arterial pressure following single oral administration; thus, any observed reduction in blood pressure may be ascribed to another pharmacologic component. β-Adrenoceptor blockade was determined in dogs as previously reported[2a] and was based on the inhibition of isoproterenol-induced tachycardia and hypotension as described under Experimental Section.

The structure–activity relationships among 4-aryldihydrolutidines, based on studies in dogs, have been described.[8] The unsubstituted 4-phenyl derivative **5a** low-



5a, R = H
b, R = CH_3

ered blood pressure >50 mmHg when administered by the intravenous (iv) route but was virtually inactive orally (po). The most potent compounds in the series were ortho-substituted derivatives, such as **5b** which lowered blood pressure >50 mmHg when administered at 5 mg/kg po. In-depth studies have been reported for the trifluoromethyl derivative, **2a**. As indicated in Table I, we have confirmed the oral activity of **2a** in the SH rat; this trifluoromethyl derivative effectively lowers mean arterial pressure when administered at 5 mg/kg po. Compound **2a** was also evaluated at 20 and 200 μg/kg ia in the anesthesized dog. It caused a dose-dependent reduction in mean arterial pressure and hindlimb perfusion pressure with a duration of action of at least 30 min. The onset of action was immediate, following intraarterial injection; the finding that systemic blood pressure was also reduced suggests that the compound reduced resistance in other vascular beds.

The introduction of the *tert*-butylamino-2-hydroxypropoxy side chain onto either the 2 or 4 position of the aryl ring, as in **4a,b**, yielded compounds with little acute antihypertensive activity as measured in the SH rat. The activity of **5a** has not been reported in the rat, but, since **2a** is effective in both rat and dog, species difference does not appear to be a likely explanation for the lack of activity found with **4a,b**.

The introduction of an ortho methyl group onto the inactive para isomer **4b** yielded compound **4c**, which was as potent in the SH rat as the trifluoromethyl derivative **2a** and was the most active member prepared in our study.

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Table II. Comparative Vasodilator and β-Adrenoceptor Blocking Activity in Anesthetized Dogs

compd	dose, μg/kg ia	no. of dogs	mean arterial pressure, mmHg					hindlimb perfusion pressure, mmHg					β-adrenoceptor blocking act. blockade of β-stimulation tachycardia		
			0 min	2 min	4 min	8 min	15 min	30 min	0 min	2 min	4 min	8 min	15 min	30 min	no. of dogs	dose, μg/kg iv	% antagonism
4a	200	2	158	160	161	161	157	158	192	121	137	172	177	197	2	1000	38
4b	200	2	160	160	160	162	160	153	186	182	187	196	201	204	1	1000	0
															2[a]	1334	0
4c	200	3	132	131	134	136	138	131	126	111	126	136	145	150	1	1000	0
2a	20	3	120	47	53	69	78	75	102	59	65	72	77	82			
	200	1	168	20	50	63	68	57	187	97	110	132	105	98			
propranolol															7	51 (35–86)[b]	50
timolol															8	2.4 (1.9–3.4)[b]	50

[a] In two separate experiments, compound **4b** was administered cumulatively and the degree of inhibition of isoproterenol-induced tachycardia was measured. These animals were not prepared for the measurement of hindlimb perfusion pressure. [b] Confidence limits.

All three compounds, **4a–c**, were devoid of potent β-adrenergic blocking activity; only **4a** exhibited marginal inhibition of isoproterenol-induced tachycardia in the dog.

In order to determine if the acute antihypertensive activity of **4c** was due to vasodilation, the compound was evaluated for its effect on hindlimb perfusion pressure in the dog.[2] Results of these studies, as seen in Table II, indicate that **4c**, unlike the standard **2a**, did not reduce hindlimb vascular resistance nor decrease mean arterial pressure. It is conceivable that **4c** is a peripheral vasodilator in the rat but not the dog. In SHR, vasodilators such as hydralazine reflexly increase heart rate. Since **4c** was devoid of β-adrenergic blocking activity, it was surprising to find that the compound did not increase HR in the rat. Thus, **4c** is either a unique vasodilator in the rat or another hypothesis relating to its mechanism of action in the rat must be entertained.

This study again indicates that the development of a useful bivalent agent cannot be achieved simply by combining pharmacophoric elements. The incorporation of an aminohydroxypropoxy moiety into an aryl ring does not guarantee the introduction of significant β-adrenoceptor antagonism. The balanced dual activity shown by **1** is not easily obtained and must result from an expression of the molecular structure as a whole and not from additive effects of the individual elements.

Experimental Section

Spectral data were obtained with the following instruments: IR, Perkin-Elmer Model 257 infrared spectrometer; NMR, Varian A-60 and T-60 using tetramethylsilane as internal standard. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses are within 0.4% of theoretical values when indicated by symbols of the elements. Solutions were dried over Na_2SO_4 and concentrated to dryness using a Buchi rotary evaporator under water aspirator pressure (20 mm).

4-[2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]phenyl]-3,5-dicarboethoxy-1,4-dihydrolutidine Hydrochloride (4a). A solution of ethyl acetoacetate (2.6 g, 0.02 mol), **3a**[2a] (2.5 g, 0.01 mol), EtOH (15 mL), and concentrated aqueous NH_3 (10 mL) was heated at reflux for 15 h. After the EtOH was removed under reduced pressure, the residue was treated with saturated Na_2CO_3 (50 mL) and extracted with $CHCl_3$ (3 × 50 mL). The organic layer was dried, filtered, and concentrated. The residual oil was treated with EtOH–HCl, concentrated, and crystallized from H_3CCN to yield 1.5 g (29%) of **4a**: mp 205–207 °C; ^1H NMR (Me_2SO-d_6) δ 1.1 (6 H, t), 1.4 (9 H, s), 2.3 (6 H, s), 2.6 (2 H, m), 4.0 (7 H, m), 4.9 (1 H, s, exch), 7.10 (4 H, m), 8.7 (1 H, br s, exch), 9.17 (2 H, s, exch); IR (Nujol) 3360, 3310, 1695, 1655, 1625 and 1585 cm^{-1}. Anal. ($C_{26}H_{38}N_2O_6 \cdot HCl$) C, H, N.

Compounds **4b** and **4c** were prepared from **3b**[2a] and **3c**[2b] by essentially the same procedure as described for **4a**; the standard **2a** was synthesized by reported procedures.[8]

4-[4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]phenyl]-3,5-dicarboethoxy-1,4-dihydrolutidine (4b): yield 27%; mp 144–146 °C (H_3CCN); ^1H NMR (Me_2SO-d_6) δ 1.0 (9 H, s), 1.2 (6 H, t), 2.3 (6 H, s), 2.6 (2 H, m), 4.0 (7 H, m, 1 exch), 4.9 (1 H, s, exch), 7.0 (4 H, m), 8.8 (1 H, br s, exch); IR (Nujol) 3300, 3260, 3230, 1695, 1665, 1610, 1585 cm^{-1}. Anal. ($C_{26}H_{38}N_2O_6$) C, H, N.

(*S*)-4-[2-Methyl-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]-3,5-dicarboethoxy-1,4-dihydrolutidine (4c): yield 20%; sublimed 210–220 °C (0.2 mm) to yield a yellow glass, mp 65–75 °C; ^1H NMR ($CDCl_3$) δ 1.1 (9 H, s), 1.2 (6 H, t), 2.3 (6 H, s), 2.5 (3 H, s), 2.7 (2 H, m, 1 exch), 4.2 (7 H, m), 5.2 (1 H, s, exch), 5.7 (1 H, s, exch), 6.6 (2 H, m), 7.15 (1 H, d); IR (Nujol) 3440, 3300, 3220, 1680, 1660, 1620, 1555 cm^{-1}. Anal. ($C_{27}H_{40}N_2O_6$) C, H, N.

Pharmacology. Compounds were assessed for peripheral vasodilator activity in the following manner: Beagle or mongrel dogs of 6 to 13 kg of body weight and either sex were anesthetized with vinbarbital, 50 mg/kg iv. A cautery was used in all surgical procedures to minimize bleeding. An endotracheal tube was inserted and artificial respiration was routinely used. The animals were vagotomized. Mean arterial pressure, pulsatile arterial pressure, and heart rate were recorded from the left carotid artery using a Micron blood pressure transducer (Model MP15) and a Honeywell 1508B Visicorder recording system. Intravenous injections were made via the right jugular vein. The left iliac artery was isolated following a midline abdominal entry and cleared of connective tissue for a distance of approximately 5 cm. The animals were then allowed to stabilize for about 10 min, after which 5 mL of heparin sodium injection (Upjohn, 1000 units/mL) was administered iv. The cannula was filled with dextran (Abbott; 6% w/v in saline 0.9%). The iliac artery was then doubly cannulated with a silastic tubing circuit. The proximal end was inserted into the iliac artery and advanced toward the aorta. To complete the extracorporeal circuit, the distal end of the catheter was inserted into the same iliac artery in the opposite direction. A Holter roller pump (Model RE161) was interposed in the tubing circuit to maintain a desired flow rate. Beyond the pump the tubing circuit was fitted with two "t" tubes, 20 cm apart. The first "t" was fitted with a rubber stopper and attached to an inverted 250-mL Erlenmeyer flask filled with saline to dampen the pulsatile signal from the pump. The second "t" was fitted with a side-arm catheter, filled with dextran, and attached to a Statham transducer (Model P23Gb) to measure the changes in perfusion pressure. Perfusion pressure was set to approximate systemic arterial pressure. β-Adrenoceptor blocking activity was quantified in anesthetized dogs by determining the concentration of the compound which when administered cumulatively antagonized the positive chromotropic effects of isoproterenol, 0.5 μg/kg, iv.

Acknowledgment. The authors are indebted to P. K. Lumma for synthetic assistance, to K. B. Streeter for analytical data, to C. T. Ludden for determinations of antihypertensive activity in SH rats, and to T. H. Brunner for clerical assistance.