aromatic), 8.68 (s, 1 H, pteridine ring); UV (0.1 N NaOH) λ_{max} 362 nm (ϵ 6502), 253 (36 800). Anal. ($C_{15}H_{13}N_5O_4$) C, H, N.

Preparation of 11-Oxahomofolic Acid (2). In an oven-dried round-bottom flask, a solution of 327 mg (1 mmol) of 11-oxahomopteroic acid in 50 mL of Me_2SO was treated with 35 mL of dry tetrahydrofuran. To this solution, 0.14 mL (1.25 mmol) of *N*-methylmorpholine was added and stirred closed for 15 min. To this reaction mixture, 0.131 mL (1 mmol) of freshly distilled isobutyl chloroformate was added and let stir for 20 min.

During this period, a solution of 480 mg (2 mmol) of diethyl-L-glutamic acid hydrochloride was made in 30 mL of Me_2SO containing 0.226 mL (2 mmol) of *N*-methylmorpholine. This solution was added to the flask containing the mixed anhydride and the coupling was allowed to proceed for 18 h. The reaction mixture was made 0.1 N with respect to sodium hydroxide by the proper addition of 1 N NaOH and hydrolyzed for 4 h. After dilution of the reaction mixture to ~500 mL with distilled water, the pH was adjusted to 7.3 and applied on a DEAE-cellulose column. The column was washed thoroughly with distilled water and eluted with a linear NaCl gradient as described before. Three products were eluted from the column. The least polar material was identified to be the monoethyl ester of 11-oxahomofolate (NMR) and the most polar compound was identified to be the desired final product. The compound which was eluted from the column possessing intermediate polarity was identified to be the starting pteroic acid analogue by comparison with an authentic sample. Rehydrolysis of the least polar material by 0.33 N NaOH in acetonitrile converted it to **2**. The pteroic acid analogue which was recovered from this reaction could be recycled to get additional amounts of **2**: NMR (TFA) δ 2–3 (C, 4 H, glutamic acid), 3.62, 4.6 (t, t, 4 H, ethylene bridge), 7.05, 7.83 (d, d, 4 H, aromatic), 8.95 (s, 1 H, pteridine ring); UV (0.1 N NaOH) λ_{max} 253 nm (ϵ 37 027), 362 (6976). Anal. ($C_{20}H_{20}N_6O_7$) C, H, N, O.

Stability Studies of Compounds 4, 8, and 9b. In a typical experiment, 50 mg of each of **4**, **8**, or **9b** were dissolved in 5 mL of trifluoroacetic acid and heated to 60 °C. To this solution, during a period of 20 min, 5 mL of 1.0 N HCl was added and the reaction mixture was evaporated to dryness. After drying under vacuum for a few hours, the residue was dissolved in 5 mL of ethyl acetate and tested for the presence of the respective starting materials and methyl *p*-hydroxybenzoate by TLC. Under these conditions, only the presence of methyl *p*-hydroxybenzoate was detected in the ethyl acetate layer.

To check the stability of these compounds under conditions which were employed for the dithionite reduction of **14**, each compound was subjected to these reduction conditions. After the addition of water, each reaction mixture was evaporated to dryness, dried under vacuum, and checked for the formation of methyl *p*-hydroxybenzoate. In each experiment, a clean single product was obtained, which was identified as methyl *p*-hydroxybenzoate.

Methods Used for Biological Testing. The preparation of 7,8-dihydro-11-oxahomofolic acid was carried out as described previously for the corresponding 11-thio analogue.[10] Catalytic reduction of 11-oxahomofolic acid gave a mixture of the diastereomers of the tetrahydro derivative, *d,l*-L-tetrahydro-11-oxahomofolic acid. The preparation of tetrahydro-11-oxahomofolic acid possessing the "natural" configuration at C^6 was carried out by substituting 7,8-dihydro-1-oxahomofolic acid for the natural substrate in the assay medium previously described for the assay of *L. casei*, DHFR,[21] and isolating the tetrahydro derivative thus formed after chromatography.

Dihydrofolate reductase,[21] thymidylate synthetase,[22] and microbiological assays[26] were carried out as described.

Acknowledgment. This investigation was supported by grants from the American Cancer Society (CH-53A) and National Institutes of Health (CA-10914 and CA-27101).

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Heterocyclic Analogues of the Antihypertensive β-Adrenergic Blocking Agent (*S*)-2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-cyanopyridine

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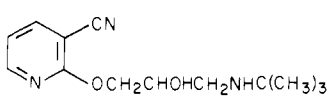
The syntheses of a series of isoelectronic analogues of (*S*)-2-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3-cyanopyridine (**1**) are described; included in this group are examples of thiazole, isothiazole, thiadiazole, pyrazine, and the structurally related naphthyridines. All of the compounds are similar to **1** in that they contain a cyano group ortho to the aminohydroxypropoxy side chain and meta to the nitrogen heteroatom. In addition, several related examples, having additional nuclear substituents and/or groups other than CN in the position adjacent to the aminohydroxypropoxy group, were prepared, and β-adrenoceptor antagonist activity and vasodilating potency were determined. Three compounds, thiazole **2** and isothiazoles **3** and **27**, effectively lowered mean arterial pressure in the SH rat at 5 mg/kg. Compounds **2**, **3**, and **27** increased iliac blood flow and exhibited β-adrenergic blocking properties in the dog.

An interest in the synthesis of compounds capable of lowering blood pressure by a vasodilating mode of action without inducing a concomitant increase in heart rate led to the discovery of (*S*)-2-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3-cyanopyridine (**1**).[1a] This compound lowered blood pressure acutely in the spontaneously hypertensive (SH) rat and was a potent nonselective β-adrenergic blocking agent in the anesthetized dog. In this latter species, a non-β-agonist type of vasodilator action was also indicated.



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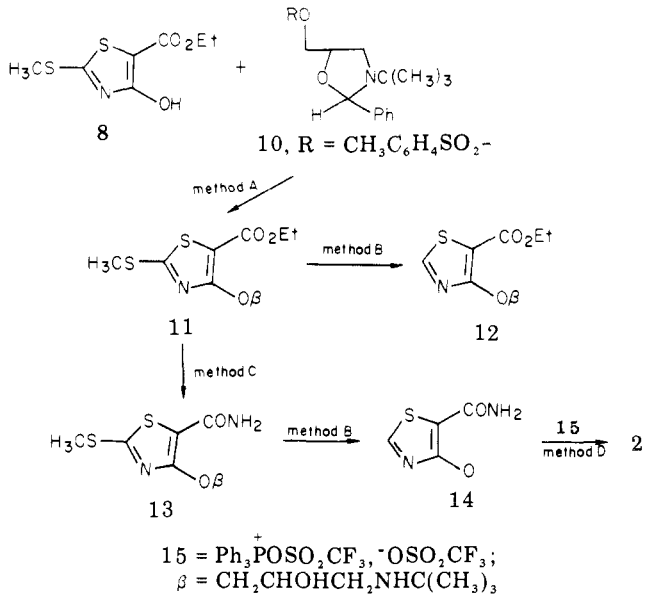
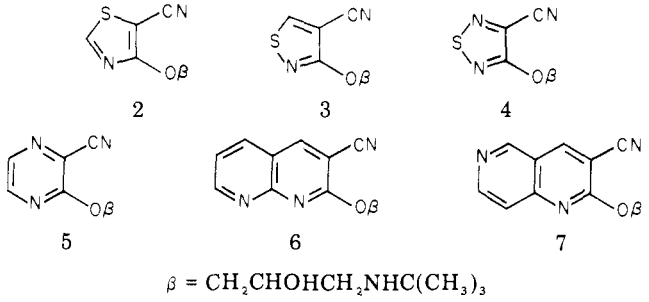
(1) (a) Baldwin, J. J.; Lumma, W. C.; Lundell, G. F.; Ponticello, G. S.; Raab, A. W.; Engelhardt, E. L.; Hirschmann, R.; Sweet, C. S.; Scriabine, A. *J. Med. Chem.* **1979**, *22*, 1284. (b) Unpublished results.

0022-2623/80/1823-0065$01.00/0

Scheme I



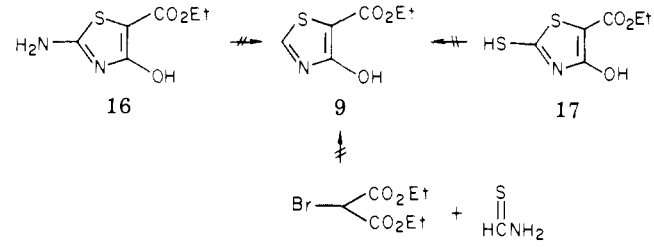
Structure–activity considerations indicated that a cyano group ortho to the β-adrenergic side chain and meta to the ring nitrogen was required for maximum antihypertensive activity. It was therefore of interest to incorporate these structural features into other nitrogen heterocycles and determine if the antihypertensive, vasodilating, and β-adrenergic blocking profile could be introduced. Specific isoelectronic analogues, namely, the thiazole **2**, isothiazole



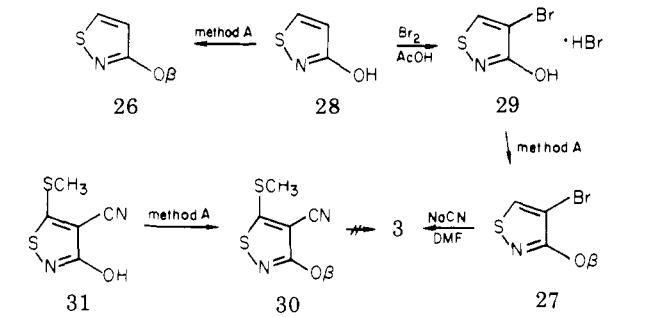
3, thiadiazole **4**, and pyrazine **5**, were chosen for study along with the structurally related naphthyridines **6** and **7**. The effect of additional nuclear substitution on antihypertensive activity was also determined for representative examples.

Chemistry. The thiazole **2** was prepared as outlined in Scheme I. Reaction of methyl dithiocarbamate[2] with diethyl bromomalonate yielded the 4-hydroxythiazole **8**; Raney nickel (EtOH, 15 h, room temperature) or aluminum amalgam (10% H_2O–THF, 0–4 °C)[3] failed to reductively desulfurize **8** to yield ethyl 4-hydroxythiazole-5-carboxylate (**9**). However, if the aminohydroxypropoxy side chain was first introduced through the reaction of **8** with the tosylate of (*S*)-3-*tert*-butyl-5-(hydroxymethyl)-2-phenyloxazolidine (**10**)[4] to give **11**, the desulfurization reaction (3 N HCl, Zn)[5] to yield **12** was successful. Alternatively, the ester **11** could be converted first to the amide **13** and then desulfurized to yield **14**. Finally,

Scheme II



Scheme III



dehydration of the amide using the triphenylphosphine oxide–triflic anhydride complex (**15**)[6] afforded the desired thiazole (**2**).

The process of incorporating the aminohydroxypropoxy side chain via the tosylate of (*S*)-**10** has been previously shown to yield the stereochemically pure *S* isomer.[4] Although complex **15** was known to react with alcohols,[6] the stereochemical consequence of such an interaction with optically pure alcohols was unknown. Thus, the interaction of complex **15** with the β-blocking side chain was next investigated using (*S*)-2-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3-cyanopyridine (**1**) to assess its racemization potential. Compound **1** ($[\alpha]^{24}$ −11.87 in 1 N HCl) was allowed to react with complex **15**, under the identical condition used to prepare **2**, and after quenching, workup, and isolation the optical rotation was determined. The observed rotation ($[\alpha]^{24}$ −11.86 in 1 N HCl) indicated that the stereochemical integrity of the aminohydroxypropoxy side chain of **1** was retained after treatment with complex **15** and implied that in the dehydration of **14** to **2** no optical inversion occurred.

As previously indicated, an alternate approach to **2** could be visualized as proceeding through ethyl 4-hydroxythiazole-5-carboxylate (**9**). Attempts to prepare this potential intermediate are outlined in Scheme II. The reaction of thioformamide with diethyl bromomalonate, the reductive diazotization of ethyl 2-amino-4-hydroxythiazole-5-carboxylate (**16**), and the oxidative desulfurization[7] of ethyl 4-hydroxy-2-mercapto-5-carboxylate (**17**)[8] all failed to provide **9**.

Thiazoles **18**–**25**, found in Table I, were prepared by the general methods described in Scheme I from known 2,5-disubstituted 4-hydroxythiazoles.

The isothiazoles **26**, **27**, and **3** were prepared as outlined in Scheme III. Introduction of the aminohydroxypropoxy side chain was accomplished through the reaction of (*S*)-**10** (R = $CH_3C_6H_4SO_2$–) with 3-hydroxyisothiazole (**28**)[9] and 4-bromo-3-hydroxyisothiazole (**29**)[10] to yield **26** and **27**,

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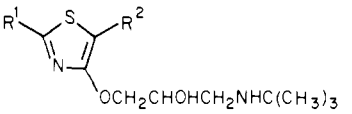
Table I. Thiazoles 18-25



compd	product R¹	product R²	method	% yield	formula	crystn solvent	mp, °C	anal.
(*S*)-18	4-C_5H_4N	H_3C-	A	10	$C_{16}H_{23}N_3O_2S$	C_6H_{14}	102-104	C, H, N[c]
(*S*)-19	C_6H_5-	H_3C-	A	6[a]	$C_{17}H_{24}N_2O_2S \cdot C_4H_4O_4$	*i*-PrOH-CH_3OH	174-176	C, H, N[d]
(*S*)-20	C_6H_5-	EtO_2C-	A	14[b]	$C_{19}H_{26}N_2O_4S \cdot C_4H_4O_4$	H_3CCN-Et_2O	165-167	C, H, N
(*S*)-21	C_6H_5-	$NH_2C(=O)$-	C	30[b]	$C_{17}H_{23}N_3O_3S \cdot C_4H_4O_4$	*i*-PrOH-Et_2O	184-185	C, H, N[e]
(*S*)-22	C_6H_5-	NC-	D	16[b]	$C_{17}H_{21}N_3O_2S \cdot C_4H_4O_4$	*i*-PrOH	204-206	C, H, N[f]
(*RS*)-23	H_3C-	$NH_2C(=O)$-	C	22[b]	$C_{12}H_{21}N_3O_3S \cdot C_4H_4O_4 \cdot 0.5H_2O$	*i*-PrOH-CH_3OH	177-178	C, H, N
(*S*)-24	H_3C-	$NH_2C(=O)$-	C	29[b]	$C_{12}H_{21}N_3O_3S \cdot C_4H_4O_4$	*i*-PrOH-Et_2O	161-163	C, H, N
(*S*)-25	H_3C-	NC-	D	47[b]	$C_{12}H_{19}N_3O_2S \cdot C_4H_4O_4$	*i*-PrOH-CH_3OH	172-174	C, H, N

[a] Chromatographed on silica gel. [b] Chromatographed on alumina. [c] Anal. Calcd for $C_{16}H_{23}N_3O_2S$: C, 59.78; N, 13.07; H, 7.21 Found: C, 59.46; N, 12.57; H, 7.26. [d] Anal. Calcd for $C_{17}H_{24}N_2O_2S \cdot C_4H_4O_4$: C, 57.78; N, 6.42; H, 6.46. Found: C, 57.34; N, 6.30; H, 6.43. [e] Anal. Calcd for $C_{17}H_{23}N_3O_3S \cdot C_4H_4O_4$: C, 54.18; N, 9.03; H, 5.85. Found: C, 53.73; N, 8.93; H, 5.86. [f] Anal. Calcd for $C_{17}H_{21}N_3O_2S \cdot C_4H_4O_4$: C, 55.25; N, 9.20; H, 5.74. Found: C, 55.75; N, 9.03; H, 5.71.

respectively. Nucleophilic displacement of the bromine of **27** by cyanide[11] yielded the isothiazole **3**. In addition, **30**, prepared from 4-cyano-3-hydroxy-5-(methylthio)isothiazole (**31**)[12] and (*S*)-**10** (R = $CH_3C_6H_4SO_2$-), failed to yield **3** under conditions used to successfully desulfurize the thiazoles **11** and **13**.

The synthesis of thiadiazole **4** involved the reaction of **10** (R = $BrC_6H_4SO_2$-)[13] in a suspension of $NaHCO_3$-DMF with 3-cyano-4-hydroxy-1,2,5-thiadiazole.[14]

Nucleophilic substitution of the halogen in 2-chloro-3-cyanopyrazine[15] by **10** (R = Na) gave the pyrazine **5**. In an analogous manner, naphthyridines **6** and **7** were prepared from the corresponding chloronaphthyridines on reaction with (*S*)-**10** (R = Na).

Spectral data (IR, ^1H NMR, and MS) for the intermediates and final products were consistent with the structural assignments. In the mass spectra, a parent ion was not always observed but instead a M - 15 ion was seen; this fragment has been ascribed to the loss of a CH_3 group from the *tert*-butyl moiety of the aminohydroxypropoxy side chain. In addition, the appearance of fragments at 57, 86, and 114 further confirmed the presence of this side chain.

Product yields, as listed in Table I and under Experimental Section, are based on analytically pure material, and no attempts were made to optimize reaction conditions.

Pharmacology. The antihypertensive activity of the heterocyclic analogues related to **1** was evaluated orally (po) in the SH rat;[16] the results obtained are shown in Table II. 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 a pharmacologic component other than β-adrenocepter blockade. The thiazole **2** lowered blood pressure from 26 to 42 mmHg at 0.312 to 5 mg/kg (po). Generally, introduction of substituents into the 2 position of the thiazole nucleus, as well as replacement of the cyano group by carboethoxy, carbamoyl, and methyl moieties, resulted in a decrease of antihypertensive activity, as indicated in Table II by compounds **11-13** and **18-25**. In a similar (SAR) study with **1**,[1a,b] replacement of the cyano group by other substituents or addition of substituents into the 4 and/or 6 position of **1** resulted in a decrease in antihypertensive activity. This observation is in accord with the similarity in biological properties between thiazole and pyridine analogues that has frequently been observed.[17]

In the isothiazole series, compound **3** lowered blood pressure 50 mmHg at 20 mg/kg. Replacement of the cyano group by bromine was allowed; this compound (**27**) was found to effectively lower blood pressure at 5 mg/kg. As in the thiazole series, introduction of a substituent into the 5 position, for example, **30**, completely abolished the antihypertensive response.

Thus, compounds **2**, **3**, and **27**, the examples which reduced blood pressure at 5 mg/kg, were further evaluated in the anesthetized dog (Table III) to assess their possible mechanism of action. Since all of the remaining examples exhibited only marginal antihypertensive activity as measured in the SH rat model, they were not subjected to a similar in-depth study. To determine if the antihypertensive response of **2**, **3**, and **27** might be due to vasodilating activity, the effect of administration of the compounds on blood flow was measured in the dog extremity. In order to establish the presence of dual components in the pharmacologic profile, the β-adrenergic blocking activity was determined in the dog by quantifying the shift in the isoproterenol dose-response curve.[4]

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Table II. Comparative Effect of Compounds on Arterial Pressure of Spontaneously Hypertensive Rats

compd	dose, mg/kg po[a]	no. of SHR	max fall in MAP,[b] mmHg ± SE
1	1.25	4	47 ± 5
	0.312	8	30 ± 4
	0.078	4	19 ± 2
2	20	1	37
	5	4	42 ± 1
	1.25	4	29 ± 11
	0.312	4	26 ± 8
	0.078	2	11
3	20	2	52
	5	1	27
4	5	2	9
5	20	2	8
6	20	4	28 ± 7
	5	2	22
7	20	2	22
11	20	2	15
12	20	2	9
13	20	2	11
18	20	1	41
	5	2	8
19	80	2	12
	20	2	17
20	20	3	10 ± 1
21	20	2	15
22	80	2	14
	20	2	9
	5	2	11
23	20	2	23
	5	2	30
	1.25	2	22
24	20	2	11
25	20	3	21 ± 3
26	20	3	22 ± 3
	5	2	26
	1.25	2	8
27	20	2	30
	5	2	41
30	20	4	15 ± 6
	5	2	3
hydralazine	2	4	40 ± 3
	1	6	30 ± 5
	0.5	4	15 ± 5
propranolol	20	5	14 ± 6
	5	8	7 ± 4
	1.25	6	12 ± 3
timolol	1.25	6	−1
	0.625	5	0
	0.312	6	3
1% methylcellulose[c]		6	10

[a] po = per os. [b] MAP = mean arterial pressure. [c] Drug vehicle.

Compounds **2**, **3**, and **27**, at a dose of 1600 μg, increased iliac blood flow; however, this vasodilating activity was partly attenuated by the prior administration of the β-adrenergic blocking agent, timolol. This result indicated that part, but not all, of the observed vasodilation could be due to β-sympathomimetic activity. As β-adrenergic blocking agents, compounds **2**, **3**, and **27** were similar to propranolol in potency and nonselective in their blockade; that is, the compounds exhibited similar effects on the β_1- and β_2-adrenergic receptors.

Although compounds **2**, **3**, and **27** appear to possess both vasodilating and β-adrenergic blocking activities, they do not exhibit a pharmacological profile superior to that observed for **1**.[1a]

Experimental Section

Spectral data were obtained with the following instruments: IR, Perkin-Elmer Models 137 and 257 infrared spectrophotometers; NMR, Varian T-60 using tetramethylsilane as internal standard; mass spectra, AEI MS-902; optical rotation measurements, Perkin-Elmer 141 polarimeter. 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. Silica gel 60 (E. Merck, Darmstadt) and aluminum oxide 90 (activity grade II, E. Merck, Darmstadt) were used for column chromatography. Silica GF plates (Analtech) were utilized for TLC and compounds containing the aminohydroxypropoxy side chain were eluted with 10% $CH_3OH/CHCl_3$ saturated with NH_3. Solutions were dried over Na_2SO_4 and concentrated to dryness using a Buchi rotary evaporator under water aspirator pressure (20 mm).

Ethyl 4-Hydroxy-2-(methylthio)thiazole-5-carboxylate (8). A mixture of methyl dithiocarbamate[2] (150.4 g, 1.4 mol), absolute EtOH (350 mL), and diethyl bromomalonate (336 g, 1.4 mol) was stirred at room temperature. After 0.5 h, the reaction became exothermic and the internal temperature rose to 55 °C. After stirring at room temperature overnight, the suspension was filtered and washed with Et_2O to yield **8** (191 g, 62%): mp 124–126 °C; ^1H NMR (Me_2SO-d_6) δ 1.2 (3 H, t), 2.65 (3 H, s), 4.15 (2 H, q), 9.1 (1 H, br s, exch); IR (Nujol) 1690 cm^{-1}; MS *m/e* 219 (M^+). ($C_7H_9NO_3S_2$) C, H, N.

(*S*)-Ethyl 4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-2-(methylthio)thiazole-5-carboxylate Maleate (11). Method A. Into a dry flask under N_2 was added **8** (20 g, 0.091 mol), DMF (200 mL), and NaH (50% oil dispersion, 5.0 g, 0.104 mol). After the mixture was stirred 15 min, a solution of the tosylate of (*S*)-**10**[4] (0.106 mol) in DMF (150 mL) was added at room temperature, and the solution was heated on a steam bath with mechanical stirring. After 15 h, the solution was cooled to 0–10 °C, poured into H_2O (1 L), and extracted with Et_2O. The organic layer was washed with H_2O and 1 N HCl (3 × 233 mL), and the acid layer was added to $NaOAc{\cdot}3H_2O$ (95 g, 0.7 mol).[23] After 5 h, the solution was extracted with Et_2O, basified with saturated Na_2CO_3, and extracted with $CHCl_3$. The organic layer was dried, filtered, and concentrated. The residue was chromatographed on alumina and the product eluted with $CHCl_3$. After evaporation of the solvent, the product was crystallized as the maleate salt from *i*-PrOH/Et_2O to yield **11** (8.8 g, 21%): mp 114–116 °C; ^1H NMR (Me_2SO-d_6) δ 1.2 (3 H, t), 1.25 (9 H, s), 2.7 (3 H, s), 3.15 (2 H, m), 4.25 (2 H, q), 4.4 (3 H, m), 6.3 (2 H, s, olefinic protons of maleate). Anal. ($C_{14}H_{24}N_2O_4S_2{\cdot}C_4H_4O_4$) C, H, N.

Thiazoles **18–20**, found in Table I, were prepared by this method from 4-hydroxy-5-methyl-2-(4-pyridyl)thiazole,[18] 4-hydroxy-5-methyl-2-phenylthiazole,[19] and ethyl 4-hydroxy-2-phenylthiazole-5-carboxylate.[20]

(*S*)-Ethyl 4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-thiazole-5-carboxylate Maleate Hemihydrate (12). Method B. To a solution of **11** (3.6 g, 0.01 mol) in 3 N HCl (20 mL) was added Zn dust (2.6 g) portionwise and with stirring. After 3.5 h at room temperature, the mixture was poured into saturated Na_2CO_3 and Super-Cel. The suspension was filtered and the pad washed with $CHCl_3$. The aqueous layer was extracted with $CHCl_3$, and the combined organic extracts were dried, filtered, and concentrated. The residue was chromatographed on silica gel and the product eluted with $CHCl_3$ saturated with NH_3. After evaporation of the solvent, the product was crystallized as the maleate salt from EtOH–Et_2O to yield **12** (0.4 g, 9%): mp 103–105 °C; ^1H NMR (Me_2SO-d_6) δ 1.3 (12 H, m), 3.2 (2 H, m), 4.25 (2 H, q), 4.4 (3 H, m), 6.05 (2 H, s, olefinic protons of maleate), 9.1 (1 H, s). Anal. Calcd for $C_{13}H_{22}N_2O_4S{\cdot}C_4H_4O_4{\cdot}0.5H_2O$: C, 47.76; N, 6.55; H, 6.36. Found: C, 48.14; N, 6.14; H, 6.30.

(*S*)-4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-5-carbamoyl-2-(methylthio)thiazole Maleate (13). Method C. A mixture of **11** (5.2 g, 0.015 mol), MeOH (90 mL), and liquid NH_3 (33 g) was heated at 100 °C in a sealed tube. After 24 h, the mixture was concentrated and the residue chromatographed on alumina. The product was eluted with $CHCl_3$ and crystallized as the maleate salt from *i*-PrOH to yield **13** (0.9 g, 14%): mp 180–182 °C; ^1H NMR (Me_2SO-d_6) δ 1.3 (9 H, s), 2.85 (3 H, s), 3.25 (2 H, m), 4.5 (3 H, m), 6.1 (2 H, s, olefinic protons of maleate).

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Table III. Comparative Effects of Compounds on Iliac Blood Flow and β-Adrenergic Blockade in Anesthetized Dogs

	increase in iliac blood flow, mL/min					blockade of isoproterenol-induced hypotension & tachycardia		
							est ED_{50}, μg/kg, iv	
compd	no. of dogs	dose, μg ia[a]	before timolol	dose, μg/kg iv[b]	after timolol	no. of dogs	MAP[c]	HR[d]
1	3	1600	98 ± 20	2000	90 ± 36	4	5.2 (3.5-8.1)[e]	1.5 (1.2-1.9)
	4	250		800	62 ± 19			
	4	64		800	38 ± 9			
2	4	1600	125 ± 29	1600	41 ± 8[f]	1	30	10
3	1	1600	22	2000	20	1	27	28
6	1	1600	0					
27	1	1600	31	1600	33	2	3	3
hydralazine	3	3200	53 ± 9					
	3	1600	66 ± 14					
	3	400	78 ± 12					
propranolol						7	19 (14-29)	51 (35-86)
timolol						8	1.3 (1.0-1.6)	2.4 (1.9-3.4)
acidified saline[g]	3	1.0 mL	5 ± 3		NT			

[a] ia, experimental compound administered intraarterially. [b] iv, timolol administered intravenously. [c] MAP, mean arterial pressure. [d] HR, heart rate. [e] Values in parentheses are the 95% confidence intervals. [f] Average of five dogs. [g] Drug vehicle used in iliac blood flow studies.

Anal. ($C_{12}H_{21}N_3O_3S_2 \cdot C_4H_4O_4$) C, H, N.

(*S*)-4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-5-carbamoylthiazole (14). Compound **13** (1.7 g, 0.005 mol), 3 N HCl (10 mL), and Zn dust (0.94 g) were allowed to react as described in method B. Extraction of the aqueous layer first with Et_2O gave recovered **13**; extraction with $CHCl_3$ yielded **14** (0.7 g, 48%): ^1H NMR ($CDCl_3$) δ 1.05 (9 H, s), 2.65 (2 H, m), 4.0 (1 H, p), 4.5 (2 H, m), 8.6 (1 H, s); MS *m/e* 286 (M - 15) and fragments 57, 86 and 114. This material was used in the next step without further purification.

(*S*)-4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-5-cyanothiazole Maleate (2). Method D. A solution of triflic anhydride (0.78 mL, 0.005 mol) in CH_2Cl_2 (10 mL) was added dropwise at 0–4 °C to a solution of triphenylphosphine oxide (1.42 g, 0.005 mol) in CH_2Cl_2 (10 mL). After 15 min, **14** (0.7 g, 0.0026 mol) was added and the mixture allowed to stir at room temperature. After 18 h, the solution was washed with saturated Na_2CO_3 and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated. The residue was chromatographed on silica gel and the product eluted with $CHCl_3$ saturated with NH_3. After evaporating the solution to dryness, the residue was crystallized as the maleate salt from *i*-PrOH to yield **2** (0.28 g, 29%): mp 168–170 °C; ^1H NMR ($CDCl_3$) δ 1.1 (9 H, s), 2.7 (2 H, m), 4.0 (1 H, p), 4.5 (2 H, d), 8.8 (1 H, s); IR (Nujol) 2225 cm^{-1}. Anal. ($C_{11}H_{17}N_3O_2S \cdot C_4H_4O_4$) C, H, N.

Control Experiment for Racemization Potential. As described for the preparation of **2**, triflic anhydride (0.32 mL, 0.002 mol) in CH_2Cl_2 (4 mL), triphenylphosphine oxide (0.56 g, 0.002 mol) in CH_2Cl_2 (4 mL), and **1** (0.5 g, 0.002 mol, $[\alpha]^{24}_D$ -11.87 in 1 N HCl) were allowed to react. After workup, **1** was recovered and the optical rotation determined. The observed rotation was $[\alpha]^{24}_D$ -11.86 in 1 N HCl.

Ethyl 2-Amino-4-hydroxythiazole-5-carboxylate (16). To a solution of thiourea (30.4 g, 0.4 mol) in absolute EtOH (250 mL) was added dropwise diethyl bromomalonate (100 g, 0.42 mol). After the addition was completed, the solution was heated at reflux for 2 h and stirred at room temperature overnight. The mixture was then concentrated to dryness and the residue covered with concentrated NH_4OH. The solid was filtered and crystallized from EtOH to yield **16** (20.3 g, 27%): mp 174–176 °C; ^1H NMR (Me_2SO-d_6) δ 1.2 (3 H, t), 4.15 (2 H, q), 5.0 (1 H, s, exch), 9.1 (2 H, br s, exch). Anal. ($C_6H_8N_2O_3S$) C, H, N.

Ethyl 4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-2-methylthiazole-5-carboxylate Maleate (32). As described in method A, ethyl 4-hydroxy-2-methylthiazole-5-carboxylate[20] (9.35 g, 0.05 mol), DMF (100 mL), NaH (57% oil dispersion, 2.5 g, 0.052 mol), and the tosylate of **10** (0.053 mol) in DMF (100 mL) were heated on a steam bath for 24 h with stirring. After workup, the residue was chromatographed on alumina and the product eluted with 25% C_6H_{14}–$CHCl_3$. The resulting residue was crystallized as the maleate salt from *i*-PrOH/Et_2O to yield **32** (4.7 g, 30%): mp 100–102 °C; ^1H NMR (Me_2SO-d_6) δ 1.35 (12 H, s and t), 2.65 (3 H, s), 3.1 (2 H, m), 4.2 (2 H, q), 4.35 (3 H, m), 6.0 (2 H, s, olefinic protons of maleate). This material was used in the next step without further purification. Similarly, the corresponding *S* isomer **33** was prepared in 20% yield from the tosylate of (*S*)-**10**.

(*S*)-3-[3-(*tert*-Butylamino)-2-hydroxypropoxy]isothiazole Maleate (26). As described in method A, **28**[9] (11.1 g, 0.1 mol), DMF (250 mL), NaH (50% oil dispersion, 5.0 g, 0.1 mol), and the tosylate of (*S*)-**10** (0.1 mol) in DMF (150 mL) were heated on a steam bath for 15 h. After workup, the residue was crystallized as the maleate salt from *i*-PrOH to yield **26** (19.8 g, 57%): mp 187–188 °C; ^1H NMR ($CDCl_3$) δ 1.1 (9 H, s), 2.8 (2 H, dd), 4.0 (1 H, p), 4.4 (2 H, d, *J* = 6 Hz), 6.6 (1 H, d, *J* = 4 Hz), 8.45 (1 H, d, *J* = 4 Hz). Anal. ($C_{10}H_{18}N_2O_2S \cdot C_4H_4O_4$) C, H, N.

(*S*)-4-Bromo-3-[3-(*tert*-butylamino)-2-hydroxypropoxy]-isothiazole Maleate (27). As described in method A, **29**[10] (3.3 g, 0.013 mol), DMF (40 mL), NaH (50% oil dispersion, 1.2 g, 0.026 mol), and the tosylate of (*S*)-**10** (0.013 mol) in DMF (20 mL) were heated at 80 °C for 15 h. After workup, the residue was chromatographed on silica gel and the product eluted with $CHCl_3$ saturated with NH_3. The resulting residue was crystallized as the maleate salt from *i*-PrOH/Et_2O to yield **27** (1.8 g, 45%): mp 162–164 °C; ^1H NMR (Me_2SO-d_6) δ 1.4 (9 H, s), 3.1 (2 H, m), 4.35 (3 H, m), 6.0 (2 H, s, olefinic protons of the maleate), 9.0 (1 H, s). Anal. ($C_{10}H_{17}BrN_2O_2S \cdot C_4H_4O_4$) C, H, N.

(*S*)-3-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-4-cyanoisothiazole Maleate (3). Into a dried flask under N_2 was placed **27** (3.9 g, 0.013 mol), CuCN (4.3 g, 0.076 mol), and DMF (20 mL). The mixture was heated at reflux with stirring for 1 h. After the mixture was cooled, a solution of NaCN (2.7 g) in H_2O (8 mL) was added, the solution was cooled to 25 °C, and a second portion of NaCN (5.7 g) in H_2O (16 mL) was then added. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with 10% NaCN and H_2O, dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel and the product eluted with $CHCl_3$ saturated with NH_3. After the solvent was evaporated, the residue was further purified by thick-layer chromatography on silica gel plates (Analtech, 2 mm), eluting with $CHCl_3$ saturated with NH_3. The product band was removed, stirred with CH_3OH, filtered, and concentrated. The residue was crystallized as the maleate salt from *i*-PrOH/Et_2O to yield **3** (0.3 g, 6%): mp 171–172 °C; ^1H NMR ($CDCl_3$) δ 1.05 (9 H, s), 2.75 (2 H, dd), 4.0 (1 H, p), 4.25 (2 H, d, *J* = 4 Hz), 9.1 (1 H, s). Anal. ($C_{11}H_{17}N_3O_2S \cdot C_4H_4O_4$) C, H, N.

(*S*)-3-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-4-cyano-5-(methylthio)isothiazole Maleate Hemihydrate (30). As described in method A, 4-cyano-3-hydroxy-5-(methylthio)isothiazole[12] (**31**; 8.6 g, 0.05 mol), DMF (20 mL), NaH (50% oil dispersion, 2.5 g, 0.05 mol), and the tosylate of (*S*)-**10** (0.05 mol)

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in DMF (80 mL) were heated at 80 °C for 15 h. After workup, the residue was chromatographed on silica gel and the product eluted with $CHCl_3$ saturated with NH_3. The resulting residue was crystallized as the maleate salt from *i*-PrOH to yield **30** (6.3 g, 42%). An analytical sample was prepared by crystallization as the maleate salt from *i*-PrOH: mp 199–200 °C; ^1H NMR ($CDCl_3$) δ 1.15 (9 H, s), 2.7 (3 H, s), 2.9 (2 H, m), 4.0 (1 H, p), 4.25 (2 H, d, J = 4 Hz). Anal. ($C_{12}H_{19}N_3O_2S_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

3-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-4-cyano-1,2,5-thiadiazole Maleate (4). A suspension of 3-cyano-4-hydroxy-1,2,5-thiadiazole[14] (1.91 g, 0.015 mol) and $KHCO_3$ (1.51 g, 0.015 mol) in DMF (55 mL) was heated under N_2 at 80–85 °C with stirring. To this mixture was added the brosylate of **10**[13] (4.53 g, 0.01 mol). After it was heated at 90 °C for 14 h, the mixture was concentrated to dryness, triturated with $CHCl_3$, filtered, and concentrated to dryness. The residue was stirred for 2 h with 1 N HCl (40 mL) at 50–70 °C. After the solution was cooled, the aqueous layer was washed with Et_2O and the extracts were discarded. The acid layer was neutralized with saturated Na_2CO_3 solution and extracted with Et_2O. The organic extracts were dried, filtered, and concentrated. The residue was crystallized as the maleate salt from EtOAc to yield 4 (1.12 g, 30%): mp 150.5–151 °C; ^1H NMR ($CDCl_3$) δ 1.1 (9 H, s), 2.8 (2 H, m), 4.0 (1 H, p), 4.5 (2 H, d, J = 4 Hz); IR (KBr) 2260 cm^{-1}. Anal. ($C_{10}H_{16}N_4O_2S \cdot C_4H_4O_4$) C, H, N, S.

2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-cyanopyrazine Maleate (5). Method E. Into a dried flask under N_2 was placed **10** (4.7 g, 0.02 mol), DMF (50 mL), and NaH (50% oil dispersion, 1.04 g, 0.022 mol), and the mixture was stirred at room temperature. After the evolution of H_2 ceased, 2-chloro-3-cyanopyrazine[15] (2.93 g, 0.021 mol) was added and the mixture heated at 65–70 °C. After 18 h, the mixture was concentrated to dryness and partitioned between H_2O and $CHCl_3$. The organic layer was dried, filtered, and concentrated to dryness. The residue was treated with 2 N HCl (144 mL) and stirred for 18 h at room temperature. After workup, as described for the preparation of **4**, the residue was crystallized as the maleate salt from EtOAc to yield **5** (2.6 g, 83%): mp 158.5–159 °C; ^1H NMR (Me_2SO-d_6) δ 1.3 (9 H, s), 3.1 (2 H, m), 4.4 (3 H, m), 6.0 (2 H, s, olefinic protons of maleate), 8.5 (1 H, d, J = 2 Hz), 8.6 (1 H, d, J = 2 Hz). Anal. ($C_{12}H_{18}N_4O_2 \cdot C_4H_4O_4$) C, H, N.

2-Hydroxy-3-cyano-1,8-naphthyridine (34). A mixture of 2-aminonicotinaldehyde[21] (2.44 g, 0.02 mol), ethyl 2-cyanoacetate (4.25 g, 0.04 mol), absolute EtOH (50 mL), and piperidine (0.5 mL) was stirred and heated at reflux. After 1 h, the solution was cooled and the precipitate filtered to yield **34** (2.5 g, 73%): mp >300 °C; IR (Nujol) 2230 and 1680 cm^{-1}; MS m/e 171 (M^+), 143 (M − 28), 116 (M − 55).

2-Chloro-3-cyano-1,8-naphthyridine (35). A mixture of PCl_5 (12.2 g, 0.06 mol), $POCl_3$ (44 mL), and **34** (2.3 g, 0.013 mol) was stirred and heated at reflux. After 1 h, the excess $POCl_3$ was distilled off under reduced pressure. The residue was treated with ice, neutralized with solid Na_2CO_3, and extracted with $CHCl_3$. The organic extracts were dried, filtered, and concentrated to dryness. The residue was sublimed at 140–150 °C at 0.2 mm to yield **35** (1.2 g, 81%): mp 273 °C; IR (Nujol) 2250 cm^{-1}; MS m/e 189 (M^+), 154 (M − 35), 127 (M − 62).

(*S*)-2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-cyano-1,8-naphthyridine (6). As described for method E, **35** (1.89 g, 0.01 mol), DMF (15 mL), NaH (50% oil dispersion, 0.5 g, 0.01 mol), and (*S*)-**10** (2.4 g, 0.01 mol) were stirred at room temperature for 18 h. After workup, as described in method A, the residue was crystallized from H_3CCN to yield **6** (0.85 g, 20%): mp 152–153 °C; ^1H NMR ($CDCl_3$) δ 1.15 (9 H, s), 2.75 (2 H, m), 4.15 (1 H, p), 4.75 (2 H, m), 7.5 (2 H, dd, J = 4 and 8 Hz), 8.1 (1 H, dd, J = 2 and 8 Hz), 8.5 (1 H, s), 9.1 (1 H, dd, J = 2 and 4 Hz); IR (Nujol) 2225 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.99; N, 18.65; H, 6.71. Found: C, 63.46; N, 18.53; H, 6.49.

(*S*)-2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-cyano-1,6-naphthyridine Dihydrochloride (7). As described for method E, 2-chloro-3-cyano-1,6-naphthyridine[22] (3.3 g, 0.017 mol), DMF (25 mL), NaH (50% oil dispersion, 0.85 g, 0.018 mol), and (*S*)-**10** (4 g, 0.017 mol) were stirred at room temperature for 18 h. After workup, as described in method A, the residue was chromatographed on silica gel and the product eluted with $CHCl_3$ saturated with NH_3. After the solvent was evaporated, the residue was crystallized as the hydrochloride salt from CH_3OH–*i*-PrOH to yield **7** (0.32 g, 5%): mp 215–217 °C; ^1H NMR (Me_2SO-d_6) δ 1.35 (9 H, s), 3.1 (2 H, m), 4.35 (1 H, p), 4.75 (2 H, d, J = 4 Hz), 8.2 (1 H, d, J = 6 Hz), 8.9 (1 H, d, J = 6 Hz), 9.4 (1 H, s), 9.7 (1 H, br s). Anal. ($C_{16}H_{20}N_4O_2 \cdot 2HCl$) C, H, N.

Pharmacology. Oral antihypertensive activity was estimated in SH rats as described by Watson and Ludden.[16]

The peripheral vasodilating activity was determined in adult mongrel dogs of either sex (8–13 kg body weight). The test animals were anesthetized with vinbarbital, 50 mg/kg iv. The trachea was cannulated and the vagi were cut. Systemic arterial pressure was recorded from the right carotid artery. The right iliac artery was exposed through a midline incision and a Micron blood flow transducer (3.0 mm) was secured around the artery. The left femoral artery was cannulated with PE 90 tubing and the tip of the catheter was advanced until it was positioned at the iliac bifurcation. Drug injections were made intraarterially through the catheter and the changes in blood flow were recorded. In each experiment, isoproterenol, 0.4 μg ia, was injected before and after timolol to assess the extent of β-adrenergic blockade. In all experiments, timolol whether administered at 320, 800, or 2000 μg/kg iv completely blocked the vasodilator response to isoproterenol, 0.4 μg ia.

To determine β-adrenergic blocking activity, mongrel dogs of either sex weighing between 8 and 13 kg were anesthetized with vinbarbital, 50 mg/kg iv; the vagi were cut and blood pressure was recorded through a femoral artery catheter. Drug injections were made through the femoral venous catheter. The trachea was cannulated but artificial respiration was used only if required. Heart rate was recorded electronically from the blood-pressure pulse. Isoproterenol was injected at 0.5 μg/kg iv, and the resultant hypotension and tachycardia were computed. Test compounds were administered cumulatively until nearly complete inhibition of isoproterenol effects was achieved.

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(23) This hydrolysis procedure for the oxazolidine moiety was worked out by Dr. W. C. Lumma, Jr., for compounds containing acid labile groups.