MTX α-*tert*-Butyl Ester γ-Hydrazide (8). Hydrazine hydrate (0.5 mL) in MeOH (5 mL) was added to a solution of the diester 7 (0.52 g, 0.001 mol) in MeOH (15 mL), and the solution was kept at 4 °C for 3 days. After vacuum evaporation of most of the solvent, $CHCl_3$ was added with just enough MeOH to bring the solid into solution. Extraction with 5% $NaHCO_3$, evaporation of the organic layer, and purification of the residue by column chromatography on silica gel (9:1 $CHCl_3$–MeOH) gave a bright yellow powder: yield 0.33 g (60%): mp ~140 °C (foaming); IR (KCl) ν 1720 (ester C=O) cm^{-1}. Anal. ($C_{24}H_{32}N_{10}O_4 \cdot CH_3OH$) C, H, N.

MTX γ-Hydrazide (2). A solution of the γ-*tert*-butyl ester 8 (1.56 g, 0.003 mol) in 1 N HCl (25 mL) was kept at 50 °C (bath temperature) for 1 h, then cooled, and basified to pH >9 with 5% NaOH. Some unchanged starting material which came out of solution was collected and treated again with acid. The combined basic solutions were adjusted to pH ~8 with AcOH and NH_4OH and then freeze-dried. The product was purified by chromatographing it twice on a DEAE-cellulose column which was eluted first with 0.5% NH_4HCO_3 and then with 3% NH_4HCO_3: yield 0.64 g (45%). Anal. ($C_{20}H_{24}N_{10}O_4$) C, H, N.

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Antihypertensive Pyrrolo[1,2-*c*]quinazolines and Pyrrolo[1,2-*c*]quinazolinones

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The synthesis of a variety of pyrrolo[1,2-*c*]quinazolines and pyrrolo[1,2-*c*]quinazolinones is described. Several of these compounds have exhibited antihypertensive properties in the spontaneously hypertensive rat (SHR). Structure–activity comparisons have indicated that optimal activity is obtained in both the 2-carbethoxydihydroquinazoline series (C) and 2-carbethoxyquinazolinone series (D) when there is either a carbethoxy or cyanoethyl group at position 6 and no substitution in the benzene ring, while optimal activity is obtained in the 2-methylquinazolinone series (D) when both position 6 and the benzene ring are unsubstituted.

A variety of biological activities have been observed for compounds containing the quinazoline and quinazolinone ring systems.[1] For example, the quinazolinone alkaloids febrifugin[2] and vasicinone[3] were reported to possess antimalarial and bronchodilator activity, respectively. Other quinazolinones have been found to have diuretic,[4] antiinflammatory,[5] antimitotic,[6] antihistaminic,[7] and hypotensive[8] activities. In contrast, pyrrolo[1,2-*c*]quinazoline and pyrrolo[1,2-*c*]quinazolinone derivatives have received only limited attention.[9] This paper summarizes the synthesis and antihypertensive activity of such tricyclic quinazoline derivatives.

Synthesis. Substituted pyrrolo[1,2-*c*]quinazolines and pyrrolo[1,2-*c*]quinazolinones were prepared by condensing appropriate quinazolines[10] and quinazolinones[10] with α-halopyruvates (AHP) and α-halo ketones (AHK).

The general reaction sequence for the formation of the tricyclic products using α-halopyruvates (AHP) is shown in Scheme I (series A, compounds **1–5**; series B, compounds **6–14**; series D, compounds **35–49**). Catalytic or chemical reduction of series B affords the dihydro system (series C, compounds **15–22**). Chemical transformation of series C and D (e.g., Michael addition, formylation, and acylation) give series E (compounds **23–34**) and series F (compounds **50–57**), respectively.

The mechanism for the formation of compound **43** utilizing α-chloroacetone (AHK) proceeds by essentially the mechanism shown in Scheme I. The formation of the chlorine-containing byproducts **44** and **46** is the result of a secondary reaction between intermediate **43b** and AHK, as illustrated for **44** in Scheme II.

The formation of byproducts **36**, **37**, and **48** results when a quinazoline reacts with AHK by the alternate route as illustrated for **36** in Scheme III.

Within all series, we have executed further chemical transformations. For instance, treatment of bromo compound **15** with CuCN[11] gave three products: cyano compounds **8** and **17** and bromo product **6**. Hydrolysis of ester **12** gave acid **14**. Reaction of *N*-formyl compound **30** with diborane yielded the *N*-methyl product **31**, which was re-

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Scheme I

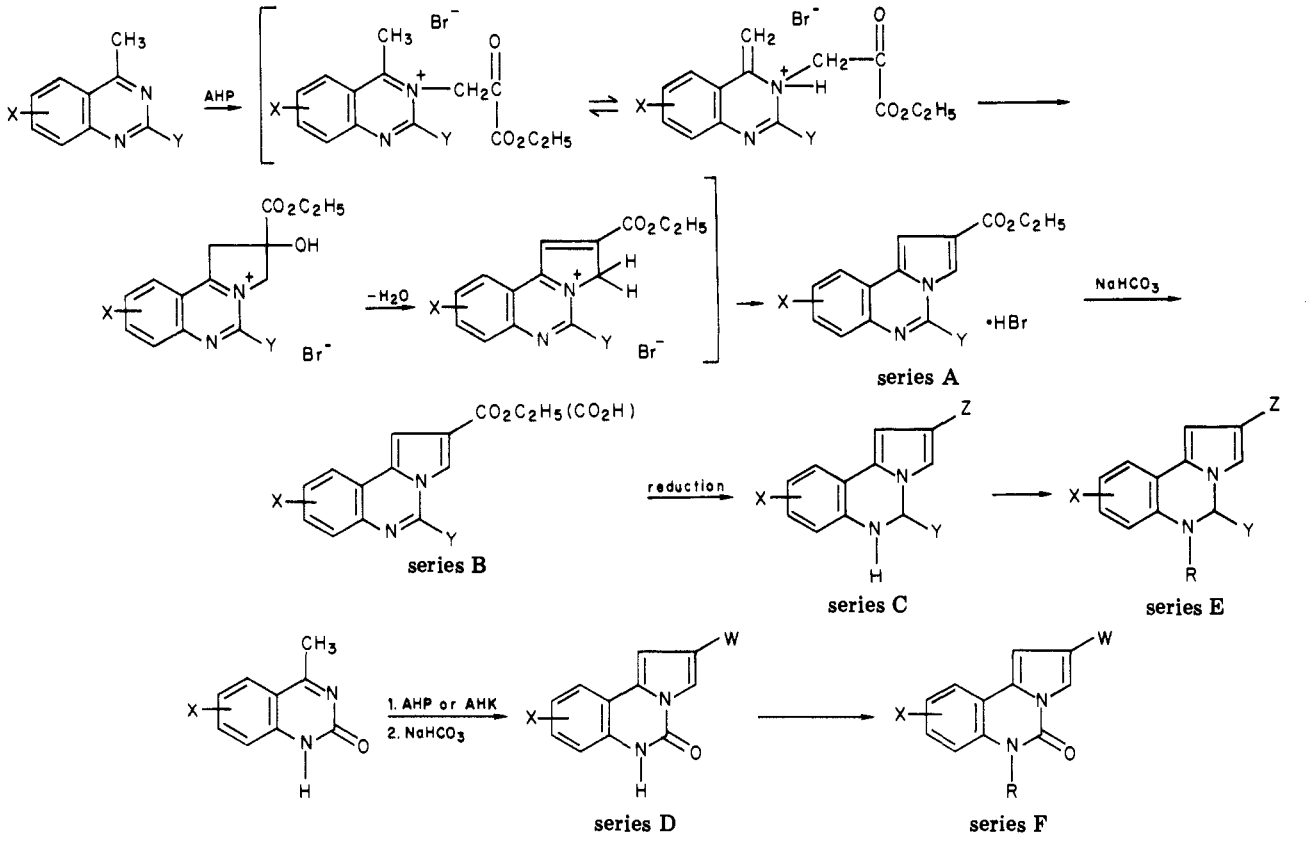
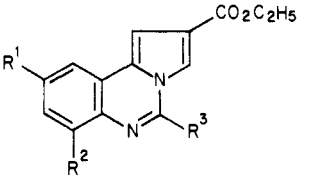


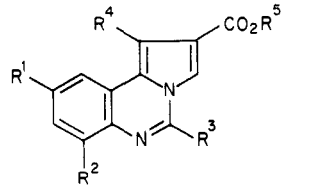
Table I



no.	R^1	R^2	R^3	mp, °C	yield, %	recrystn solvent[a]	formula	anal.
1	H	H	H	274-275	83.6	A	$C_{14}H_{13}BrN_2O_2$	C, H, N
2	Br	H	H	268-270	61.7	B	$C_{14}H_{12}Br_2N_2O_2$	C, H, N
3	Cl	H	H	>310	7.6	B	$C_{14}H_{12}BrClN_2O_2$	C, H, N
4	H	OCH_3	H	248-249	62.6	A	$C_{15}H_{15}BrN_2O_3$	C, H, N
5	H	H	CH_3	287-289	27.2	C	$C_{15}H_{15}BrN_2O_2$	C, H, N

[a] Recrystallization solvents: A = MeOH; B = CH_2Cl_2; C = EtOH.

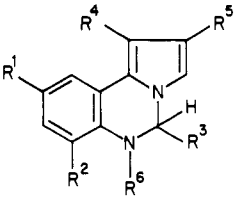
Table II



no.	R^1	R^2	R^3	R^4	R^5	mp, °C	yield, %	recrystn solvent[a]	formula	anal.
6	Br	H	H	H	C_2H_5	183-185	87.8	D	$C_{14}H_{11}BrN_2O_2$	C, H, N
7	Cl	H	H	H	C_2H_5	175-176	49.8	E	$C_{14}H_{11}ClN_2O_2$	C, H, N
8	CN	H	H	H	C_2H_5	264-266	14.3	F	$C_{15}H_{11}N_3O_2$	C, H, N
9	H	OH	H	H	C_2H_5	186-188	61.2	A	$C_{14}H_{12}N_2O_3$	C, H, N
10	H	OCH_3	H	H	C_2H_5	154-155	74.1	A	$C_{15}H_{14}N_2O_3$	C, H, N
11	H	H	CH_3	H	C_2H_5	113-116	47.1	E	$C_{15}H_{14}N_2O_2$	C, H, N
12	H	H	H	H	C_2H_5	138-139	83.6	A	$C_{14}H_{12}N_2O_2$	C, H, N
13	H	H	H	$CO_2C_2H_5$	C_2H_5	125-126	27.4	A	$C_{17}H_{16}N_2O_4$	C, H, N
14	H	H	H	H	H	323-325	30.5	A	$C_{12}H_8N_2O_2 \cdot 0.5H_2O$	C, H, N

[a] Recrystallization solvents: A = MeOH; D = EtOAc; E = 2-propanol; F = EtOAc/benzene.

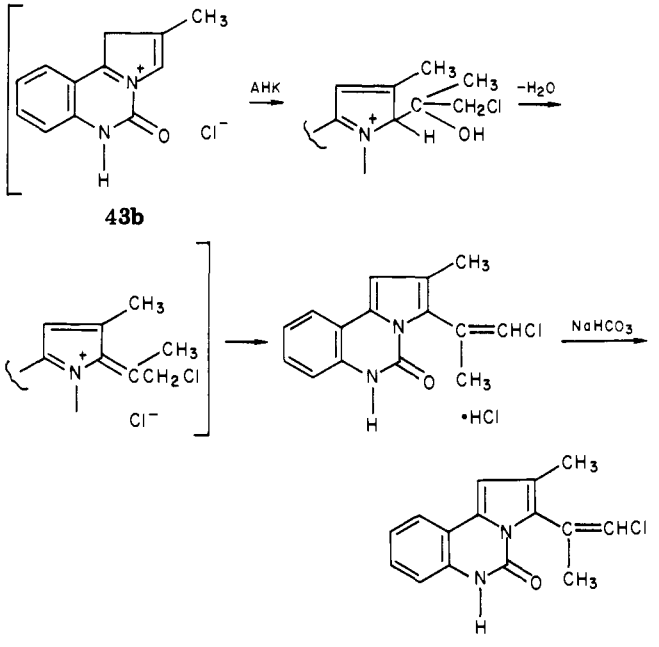
Table III



no.	R^1	R^2	R^3	R^4	R^5	R^6	mp, °C	yield, %	recrystn solvent[a]	formula	anal.
15	Br	H	H	H	$CO_2C_2H_5$	H	170-172	87.3	A	$C_{14}H_{13}BrN_2O_2$	C, H, N
16	Cl	H	H	H	$CO_2C_2H_5$	H	163-165	72.7	C	$C_{14}H_{13}ClN_2O_2$	C, H, N
17	CN	H	H	H	$CO_2C_2H_5$	H	228-230	16.1	G	$C_{15}H_{13}N_3O_2$	C, H, N
18	H	OCH_3	H	H	$CO_2C_2H_5$	H	131-133	65.1	A	$C_{15}H_{16}N_2O_3$	C, H, N
19	H	OCH_3	H	H	CH_2OH	H	137-138	53.8	A	$C_{13}H_{14}N_2O_2$	C, H, N
20	H	H	CH_3	H	$CO_2C_2H_5$	H	102-103	73.0	A	$C_{15}H_{16}N_2O_2$	C, H, N
21	H	H	H	H	CH_2OH	H	128-130	90.0	H	$C_{12}H_{12}N_2O$	C, H, N
22	H	H	H	H	$CO_2C_2H_5$	H	140-141	96.0	A	$C_{14}H_{14}N_2O_2$	C, H, N
23[b]	H	OCH_3	H	H	$CO_2C_2H_5$	$(CH_2)_2CN$	146-147	39.1	A	$C_{18}H_{19}N_3O_3$	C, H, N
24	H	H	H	H	$CO_2C_2H_5$	$(CH_2)_2CN$	102-104	44.0	A	$C_{17}H_{17}N_3O_2$	C, H, N
25	H	H	H	H	$CO_2C_2H_5$	$(CH_2)_2CO_2Et$	90-94	67.0	J	$C_{19}H_{22}N_2O_4 \cdot HCl$	C, H, N
26	Br	H	H	H	$CO_2C_2H_5$	$CO_2C_2H_5$	161-163	75.3	A	$C_{17}H_{17}BrN_2O_4$	C, H, N
27	H	OCH_3	H	H	$CO_2C_2H_5$	$CO_2C_2H_5$	172-174	73.9	A	$C_{18}H_{20}N_2O_5$	C, H, N
28	H	H	CH_3	H	$CO_2C_2H_5$	$CO_2C_2H_5$	125-127	84.0	A	$C_{18}H_{20}N_2O_4$	C, H, N
29	H	H	H	H	$CO_2C_2H_5$	$CO_2C_2H_5$	80-82	53.5	A	$C_{17}H_{18}N_2O_4$	C, H, N
30	H	H	H	H	$CO_2C_2H_5$	CHO	131-133	90.0	O	$C_{15}H_{14}N_2O_3$	C, H, N
31	H	H	H	H	$CO_2C_2H_5$	CH_3	82-84	81.6	A	$C_{15}H_{16}N_2O_2$	C, H, N
32	H	H	H	H	CH_2OH	CH_3	74-76	96.6	I	$C_{13}H_{14}N_2O$	C, H, N
33	H	H	H	H	CO_2H	$(CH_2)_2CO_2H$	234-236	80.0	A	$C_{15}H_{14}N_2O_4$	C, H, N
34	H	H	H	H	CH_3	$(CH_2)_3OH$	77-78	44.8	K	$C_{15}H_{18}N_2O$	C, H, N

[a] Recrystallization solvents: A = MeOH; C = EtOH; G = CH_3CN; H = EtOAc/hexane; I = ether; J = $CHCl_3$/hexane; K = pentane; O = acetone. [b] Calcd: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.04; H, 5.96; N, 13.09.

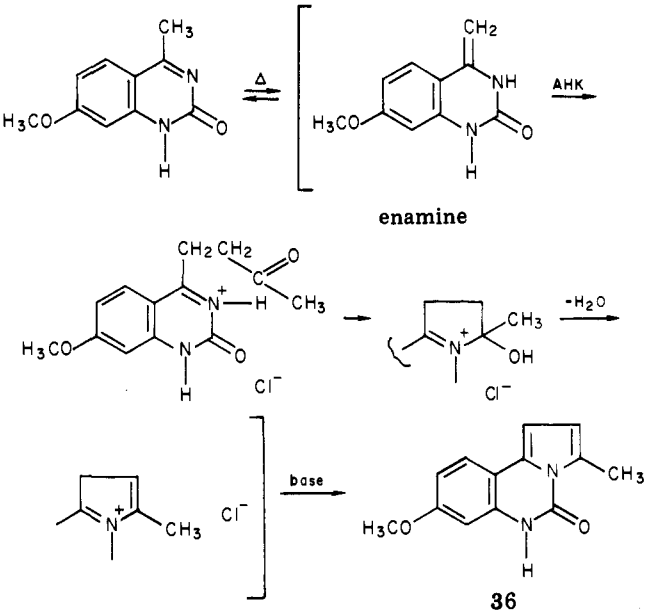
Scheme II



43b

44

Scheme III



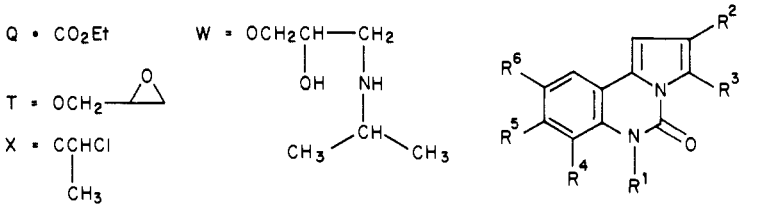
enamine

36

duced with $LiAlH_4$ to alcohol **32**. Bromination of **43** afforded bromo derivative **55**. Condensation of **40** with epibromohydrin gave epoxide **56**, which upon treatment with isopropylamine gave amino alcohol **57**. $LiAlH_4$ reduction of **52** gave alcohol **34**, while hydrolysis of diester **25** afforded diacid **33**.

Pharmacological Methods. Groups of four spontaneously hypertensive male rats (Charles-River or another suitable supplier) were used to evaluate the compounds for antihypertensive activity. Animals were given test compounds orally in suspension in the following vehicle: 30% PEG 200, 10% PEG 400, 10% EtOH, 50% pH 7.50 buffer (NaH_2PO_4, Na_2HPO_4) at the rate of 0.5 mL/100 g of body weight. Systolic blood pressure was recorded employing the tail-cuff technique at 2, 4, and 24 h after the first dose (100 mg/kg) and again 24 h later at 2, 4, and 24 h following the second dose (50 mg/kg). Prior to dosing, a control reading of the systolic blood pressure was recorded. The predose levels of blood pressure were compared statistically to each of the postdose levels utilizing the Student's *t* test (paired analyses). Compounds having a level of significance of $p \leq 0.05$ were regarded as active. Means plus or minus SE (standard error) are reported in all tables. Systolic blood pressure reduction equal to or

Table IV



no.	R¹	R²	R³	R⁴	R⁵	R⁶	mp, °C	yield, %	recrystn solvent[a]	formula	anal.
35	H	CH_3	H	H	OCH_3	H	233-235	11.6	A	$C_{13}H_{12}N_2O_2$	C, H, N
36	H	H	CH_3	H	OCH_3	H	238-240	10.2	A	$C_{13}H_{12}N_2O_2$	C, H, N
37	H	H	CH_3	H	OCH_3	OCH_3	256-258	2.0	A	$C_{14}H_{14}N_2O_3$	C, H, N
38	H	CH_3	H	H	OCH_3	OCH_3	237-239	5.7	C	$C_{14}H_{14}N_2O_3$	C, H, N
39	H	CH_3	H	OH	H	H	255-257	13.5	A	$C_{12}H_{10}N_2O_2$	C, H, N
40[b]	H	CH_3	H	H	H	OH	309-311	40.8	A	$C_{12}H_{10}N_2O_2 \cdot 0.5H_2O$	C, H, N
41[c]	H	CH_3	H	H	OCH_3	H	217-219	3.1	A	$C_{15}H_{16}N_2O_2$	C, H, N
42	H	CH_3	H	H			313-315	10.3	A	$C_{13}H_{10}N_2O_3$	C, H, N
43	H	CH_3	H	H	H	H	244-245	23.2	A	$C_{12}H_{10}N_2O$	C, H, N
44	H	CH_3	X	H	H	H	205-206	5.0	A	$C_{15}H_{13}ClN_2O$	C, H, N
45	H	H	CH_3	H	H	H	251-252	20.7	A	$C_{12}H_{10}N_2O$	C, H, N
46	H	CH_3	X	H	OCH_3	OCH_3	204-206	10.2	C	$C_{17}H_{17}ClN_2O_3$	C, H, N
47	H	CO_2Et	H	H	H	H	239-241	19.3	A	$C_{14}H_{12}N_2O_3$	C, H, N
48[d]	H	H	CH_3	OCH_3	H	H	190-192	21.9	L	$C_{13}H_{12}N_2O_2$	C, H, N
49	H	CH_3	H	OCH_3	H	H	198-200	43.8	L	$C_{13}H_{12}N_2O_2$	C, H, N
50	$(CH_2)_2Q$	CO_2Et	H	H	H	H	104-106	69.7	A	$C_{19}H_{20}N_2O_5$	C, H, N
51	$(CH_2)_2CN$	CO_2Et	H	H	H	H	191-193	80.0	G	$C_{17}H_{15}N_3O_3$	C, H, N
52	$(CH_2)_2Q$	CH_3	H	H	H	H	74-76	71.7	M	$C_{17}H_{18}N_2O_3$	C, H, N
53	$(CH_2)_2CN$	CH_3	H	H	H	H	161-163	50.0	C	$C_{15}H_{13}N_3O$	C, H, N
54	$(CH_2)_2Q$	CH_3	H	H	H	H	89-91	74.4	M	$C_{16}H_{16}N_2O_3$	C, H, N
55	H	CH_3	Br	H	H	H	>300	89.0	N	$C_{12}H_9BrN_2O \cdot H_2O$	C, H, N
56	H	CH_3	H	H	H	T	208-210	6.7		$C_{15}H_{14}N_2O_3$	C, H, N
57	H	CH_3	H	H	H	W	206-208	72.7	G	$C_{18}H_{23}N_3O_3$	C, H, N

[a] Recrystallization solvents: A = MeOH; B = CH_2Cl_2; C = EtOH; D = EtOAc; E = 2-propanol; F = EtOAc/benzene; G = CH_3CN; H = EtOAc/hexane; I = ether; J = $CHCl_3$/hexane; K = pentane; L = EtOAc/MeOH; M = petroleum ether; N = benzene; O = acetone. [b] Calcd: C, 64.57; H, 4.93; N, 12.54. Found: C, 65.03; H, 4.68; N, 12.55. [c] Calcd: C, 70.29; H, 6.29; N, 10.93. Found: C, 69.82; H, 6.28; N, 10.82. [d] Calcd: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.83; H, 5.53; N, 12.27.

Table V. Oral Antihypertensive Activity of Reference and Experimental Compounds in Spontaneous Hypertensive Rats[a]

compd	dose, mg/kg	ΔBP mean ± SE 2 h	ΔBP mean ± SE 4 h	ΔBP mean ± SE 24 h	dose, mg/kg	ΔBP mean ± SE 2 h	ΔBP mean ± SE 4 h	ΔBP mean ± SE 24 h
propranolol	100	18.7 ± 5.5	45.0 ± 9.8	32.5 ± 7.9	33	27.5 ± 6.3	28.7 ± 3.1	51.2 ± 4.7
clonidine	100[b]	36.0 ± 8.0	21.0 ± 13.9	9.0 ± 5.1	50[b]	45.0 ± 6.1	32.0 ± 8.0	16.0 ± 12.8
hydralazine	10	50.0 ± 11.7	62.5 ± 7.2	30.0 ± 9.8	5	61.2 ± 12.8	81.2 ± 14.6	47.5 ± 5.9
prazosin	25	56.2 ± 2.4	76.2 ± 8.7	41.2 ± 7.5	12.5	40.0 ± 5.0	48.2 ± 10.7	13.7 ± 3.1
7	100	17.5 ± 5.8	16.3 ± 8.5	5.0 ± 6.8	50	13.8 ± 8.9	31.3 ± 12.1	7.5 ± 5.2
8	100	11.6 ± 8.0	20.0 ± 7.6	20.0 ± 2.8	50	21.6 ± 7.3	33.0 ± 2.9	6.6 ± 10.9
24	100	13.8 ± 8.9	11.3 ± 8.0	1.2 ± 4.0	50	33.0 ± 21.6	38.0 ± 15.3	
29	100	6.2 ± 7.5	11.2 ± 8.5	20.0 ± 11.7	50	18.7 ± 6.6	42.5 ± 13.1	23.7 ± 7.2
31	100	29.0 ± 14.0		31.0 ± 16.7	50		26.0 ± 19.3	6.5 ± 13.7
41	100	6.0 ± 7.0	9.0 ± 4.0	15.0 ± 4.0	50	28.0 ± 8.0	31.0 ± 8.0	12.0 ± 6.0
43	100		39.0 ± 5.9	11.0 ± 5.9	50	46.0 ± 5.8		35.0 ± 5.6
44	100		27.0 ± 16.5	20.5 ± 5.8	50		30.0 ± 7.3	42.0 ± 7.8
51	100		2.0 ± 4.7	45.0 ± 2.2	50		19.0 ± 5.4	59.0 ± 2.8

[a] Four rats per dose. [b] In μg/kg.

greater than 35 mmHg was considered significant; compounds showing an average blood pressure lowering effect of between 25 and 35 mmHg were considered slightly active. The maximum antihypertensive response was generally observed at the 4-h measurement during the second dose (50 mg/kg). Compounds used as SHR standards were tested in the same system for comparison and are listed in Table V.

Structure–Activity Study. Of the 58 compounds described in this paper, 9 (compounds **7**, **8**, **24**, **29**, **31**, **41**, **43**, **44**, and **51**) had slight to significant activity in the SHR test (Table V). Significant activity was observed for the 2-carbethoxy derivatives **24**, **29**, and **51** (series C and D), while slight activity was noted for **31**. This suggests that substitution at position 6 is desirable for enhanced antihypertensive activity. When **24** and **29** were substituted on the benzene ring, the compounds were not active (**23** and **27**). In the 2-methylpyrroloquinazolinones (series D) only compounds **43** and **44** had significant activity. When **43** was substituted at position 6 (**52–54**) the compounds

were not active, while substitution in the benzene ring resulted in a less active compound (41). The activity of the 2-carbethoxypyrroloquinazolines 7 and 8 indicates that substitution on the benzene ring enhances the activity slightly in this series, since none of the unsubstituted products in series B showed activity. These SAR comparisons are considered valid, although in the absence of ED_{50} values no absolute conclusions can be drawn.

Experimental Section

The structures of all compounds were supported by their IR (Beckman IR-8) and ^1H NMR (Varian A-60, tetramethylsilane internal standard) spectra. Mass spectra were obtained on a Finnigan Model 1015-D mass spectrometer, and data reduction was accomplished with the System Industries Model 150 data system. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All compounds were analyzed for C, H, and N and were within 0.4% of calculated theoretical values unless otherwise indicated. Thin-layer chromatography (TLC) was performed on silica gel with a fluorescent indicator.

Starting Materials. Substituted acetophenones were prepared by known methods,[11] and were employed as starting materials for the synthesis of quinazolines and quinazolinones as described in the literature.[10]

General Preparation of 2-Carbethoxy-1*H*-pyrrolo[1,2-*c*]quinazolin-4-ium Bromides (1–5). 2-Carbethoxy-1*H*-pyrrolo[1,2-*c*]quinazolin-4-ium Bromide (1). A solution of ethyl bromopyruvate (32.76 g, 168 mmol) and 4-methylquinazoline[10] (15.61 g, 108 mmol) in dry ethanol (400 mL) was refluxed for 16 h, during which time a yellow precipitate formed. The reaction mixture was cooled, and the solid was isolated by filtration and dried. Crystallization from MeOH afforded a yellow solid (28.9 g, 83.6%): mp 274–275 °C; NMR (Me_2SO-d_6/Me_4Si) δ 9.00–9.50 (m, 1 H, 5-H), 7.25–8.50 (m, 5 H, 4-aromatic, 3-H), 5.45 (s, 2 H, 1-CH_2), 4.32 (q, J = 6.0 Hz, OCH_2CH_3), 1.37 (t, J = 6.0 Hz, OCH_2CH_3).

2-Carbethoxypyrrolo[1,2-*c*]quinazoline (12). A solution of ethyl bromopyruvate (3.2 g, 16 mmol) and 4-methylquinazoline (2.0 g, 14 mmol) in dry ethanol (150 mL) was refluxed for 2 h. During this time, a tan solid formed. Excess ethyl bromopyruvate was added (1.0 g), and the reaction mixture was refluxed overnight. The alcohol was removed in vacuo, and the residue was diluted with H_2O. Sodium bicarbonate was added until effervescence ceased, and the aqueous mixture was extracted with ether. The ether extracts were combined, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo to yield a tan solid. Crystallization from MeOH afforded a white solid (2.81 g, 83.6%): mp 138–139 °C NMR ($CDCl_3$/Me_4Si) δ 9.70 (s, 1 H, 5-H), 7.10–8.28 (m, 6 H, 4-aromatic, 3-H), 4.40 (q, 2 H, J = 6.0 Hz, OCH_2CH_3), 1.42 (t, 3 H, J = 6.0 Hz, OCH_2CH_3).

2-Carbethoxy-9-cyano-5,6-dihydropyrrolo[1,2-*c*]quinazoline (17). Compound 15 (6.90 g, 0.021 mmol) and copper cyanide (7.73 g, 86 mmol) in DMF (500 mL) was heated at reflux for 16 h. The dark brown reaction mixture was cooled and then poured into concentrated NH_4OH (276 mL). The resulting mixture was extracted with CH_2Cl_2 (1800 mL), and the extract was washed with 2 N HCl (3 × 150 mL) and H_2O (3 × 150 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo yielded a light brown semisolid (4.55 g). The crude product was chromatographed on a SilicAR column (400 g) prepared in benzene. Elution with 2–4% EtOAc/benzene yielded 6 (0.30 g, 4.5%). Elution with 4% EtOAc/benzene yielded 8 (0.80 g, 14.3%). Elution with 6–8% EtOAc/benzene yielded 17 as an off-white solid (0.90 g, 16.1%). Recrystallization from CH_3CN afforded 17 as an off-white solid: yield 0.63 g; mp 228–230 °C; NMR (CF_3COOH/Me_4Si) δ 8.15 (d, 1 H, J = 2.0 Hz, 3-H), 7.50–7.90 (m, 3 H, 7-, 8-, 10-H), 7.30 (d, 1 H, J = 2.0 Hz, 1-H), 5.75 (s, 2 H, 5-H), 4.55 (q, 2 H, J = 7.0 Hz, 11-H), 1.55 (t, 3 H, J = 7.0 Hz, 12-H).

Pyrrolo[1,2-*c*]quinazoline-2-carboxylic Acid Hemihydrate (14). A solution of 12 (2.0 g, 8 mmol) and KOH (2.0 g, 36 mmol) in MeOH (20 mL) and H_2O (20 mL) was refluxed for 1 h. The methanol was removed under vacuum, and the resulting aqueous solution was acidified with HCl (10% aqueous). The resulting solid was filtered, washed (H_2O), and dried (Na_2SO_4) to yield 1.23 g of crude product. Crystallization from MeOH afforded 14 as an off-white solid: yield 0.54 g (30.5%); mp 323–325 °C; NMR (Me_2SO-d_6/Me_4Si) δ 9.20 (s, 1 H, 5-H), 7.20–8.50 (m, 6 H, 4-aromatic, 1-H, COOH).

2-Methylpyrrolo[1,2-*c*]quinazolin-5(6*H*)-one (43), 3-Methylpyrrolo[1,2-*c*]quinazolin-5(6*H*)-one (45), and 3-(2-Chloro-1-propenyl)-2-methylpyrrolo[1,2-*c*]quinazolin-5(6*H*)-one (46). A solution of chloroacetone (58.8 g, 635 mmol) and 4-methyl-2(1*H*)-quinazolinone (12.0 g, 66 mmol) in dry ethanol (1500 mL) was heated at reflux for 68 h. The reaction mixture was concentrated to dryness in vacuo to give a dark brown semisolid. This was slurried in H_2O and treated with excess $NaHCO_3$. The aqueous mixture was extracted with ether (4 × 200 mL) and $CHCl_3$ (4 × 200 mL). These combined extracts were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo to yield 24.4 g of a dark brown semisolid. The semisolid was chromatographed on a 2000-g SilicAR column prepared in benzene. Elution with benzene gave 46, which was crystallized from MeOH to give a colorless solid: yield 2.08 g (10.2%); mp 204–206 °C. Further elution with benzene gave 45, which was recrystallized from MeOH to give a colorless solid: yield 3.08 g (20.7%); mp 251–252 °C. Further elution with benzene gave 43, which was recrystallized from MeOH to give a colorless solid: yield 3.45 g (23.2%); mp 244–245 °C. 45: NMR (Me_2SO-d_6/Me_4Si) δ 9.10 (s, 1 H, NH), 7.60–8.00 (m, 1 H, 7-H), 6.90–7.40 (m, 3 H, 8, 9, 10-H), 6.78 (d, 1 H, J = 4.0 Hz, 1-H), 6.20–6.45 (m, 1 H, 2-H), 2.70 (s, 3 H, 3-CH_3). 43: NMR (Me_2SO-d_6/Me_4Si) δ 9.10 (s, 1 H, NH), 7.60–7.90 (m, 1 H, 3-H), 6.85–7.40 (m, 4 H, 7-, 8-, 9-, 10-H), 6.70 (d, 1 H, J = 2.0 Hz, 1-H), 2.15 (s, 3 H, 2-CH_3). 46: NMR ($CDCl_3$/Me_4Si) δ 7.20 (s, 1 H, 10-H), 6.55 (s, 1 H, 7-H), 6.20 (br s, 1 H, 1-H), 6.10 [s, 1 H, $C(CH_3)$=CHCl], 3.90 (s, 3 H, 8- or 9-OCH_3), 3.85 (s, 3 H, 8- or 9-OCH_3), 2.75 (s, 3 H, 2-CH_3), 2.15 [d, 3 H, J = 2.0 Hz, $C(CH_3)$=CHCl].

General Procedure for Catalytic Reductions. 2-Carbethoxy-5,6-dihydropyrrolo[1,2-*c*]quinazoline (22). Compound 12 (2.5 g, 10 mmol) was dissolved in MeOH (250 mL). Platinum oxide (0.5 g) was added, and the mixture was hydrogenated at 42 psi for 3 h. Filtration and removal of the solvent in vacuo yielded a colorless solid. Recrystallization from MeOH afforded colorless 22: yield 2.3 g (96%); mp 140–141 °C; NMR ($CDCl_3$/Me_4Si) δ 6.60–7.63 (m, 6 H, 4 aromatic, 1 H, 3-H), 5.09 (s, 2 H, 5-CH_2), 4.30 (q, 2 H, J = 6.0 Hz, OCH_2CH_3), 1.32 (t, 3 H, J = 6.0 Hz, OCH_2CH_3).

General Procedure for Michael Additions. Ethyl 2-Carbethoxy-5,6-dihydropyrrolo[1,2-*c*]quinazoline-6-propionic Acid Hydrochloride (25). Triton B (benzyltrimethylammonium hydroxide; 0.1 mL) was added dropwise to a suspension of 22 (0.8 g, 3.3 mmol) in ethyl acrylate (5 mL) at 0–5 °C. After an initial exotherm, the reaction mixture was refluxed for 72 h. The excess ethyl acrylate was distilled in vacuo to yield a dark brown semisolid (1.0 g). The residue was dissolved in $CHCl_3$ and chromatographed on a 50-g SilicAR column prepared in $CHCl_3$. The column was eluted with $CHCl_3$ to afford 0.75 g of an oily product. A solution of this oily product in ether (50 mL) was treated with excess HCl (g). A white solid formed immediately and was filtered, washed with ether, and air-dried. Rapid crystallization from cold $CHCl_3$/hexane afforded the desired product: yield 0.8 g (67%); mp 90–94 °C; NMR ($CDCl_3$/Me_4Si) δ 7.02–7.85 (m, 6 H, 4 aromatic, 1-H, 3-H), 5.58 (s, 2 H, 5-CH_2), 4.35 (q, 2 H, J = 7.0 Hz, 2-$COOCH_2CH_3$), 4.06 (q, 2 H, J = 7.0 Hz, 5-$CH_2CH_2COOCH_2CH_3$), 3.68 (t, 2 H, J = 7.0 Hz, NCH_2), 2.92 (t, 2 H, J = 7.0 Hz, NCH_2CH_2), 1.38 (t, 3 H, J = 7.0 Hz, 1-$COOCH_2CH_3$), 1.20 (t, 3 H, J = 7.0 Hz, $NCH_2CH_2OOCCH_2CH_3$).

2-Carbethoxy-5,6-dihydro-6-formylpyrrolo[1,2-*c*]quinazoline (30). Compound 12 (2.1 g, 8.6 mmol) was refluxed for 10 min with dry formic acid (20 g, 436 mmol) and then cooled in an ice bath. Water (300 mL) was added, and a solid (2.15 g) was collected by filtration. The solid was recrystallized from acetone to afford 30: yield 2.05 g (90%); mp 131–133 °C. NMR ($CDCl_3$/Me_4Si) δ 8.58 (s, 1 H, NCHO), 7.37 (d, 1 H, $J_{3,1}$ = 1.0 Hz, 3-H), 7.03–8.00 (m, 4 H, 4 aromatic), 6.91 (d, 1 H, $J_{1,3}$ = 1.0 Hz, 1-H), 5.68 (s, 2 H, 5-CH_2), 4.30 (q, 2 H, J = 7.0 Hz, $COOCH_2CH_3$), 1.30 (t, 3 H, J = 7.0 Hz, $COOCH_2CH_3$).

2-Carbethoxy-5,6-dihydro-6-methylpyrrolo[1,2-*c*]quinazoline (31). Diborane (60 mL of a 0.96 M solution in THF)

was added via a serum cap to a mixture of **30** (3.0 g, 11 mmol) in dry THF (150 mL). The mixture was allowed to stir under nitrogen at room temperature for 30 min, and excess diborane was carefully destroyed with MeOH (10 mL). The solvents were removed in vacuo to afford a yellow solid (2.4 g). Crystallization from MeOH yielded colorless **31**: yield 2.3 g (81.6%); mp 82–84 °C; NMR ($CDCl_3/Me_4Si$) δ 6.70–7.50 (m, 6 H, 4 aromatic, 1-H, 3-H), 4.30 (q, 2 H, J = 7.0 Hz, $COOCH_2CH_3$), 2.83 (s, 3 H, 6-NCH_3), 1.33 (t, 3 H, J = 7.0 Hz, $COOCH_2CH_3$).

2-(Hydroxymethyl)-6-methyl-5,6-dihydropyrrolo[1,2-*c*]quinazoline (32). A solution of ester **31** (27.92 g, 109 mmol) in ether (500 mL) was added to a slurry of $LiAlH_4$ (16.75 g, 442 mmol). The reaction mixture was stirred at ambient temperature for 1.5 h. To the reaction mixture was added dropwise and successively H_2O (17.0 mL), NaOH (17.0 mL of 15% aqueous solution) and H_2O (51 mL). The precipitate was filtered and washed with ether. After the solution was dried ($MgSO_4$), the solvent was removed in vacuo to yield **32** as a colorless solid: yield 22.56 g (96.6%); mp 74–76 °C; NMR ($CDCl_3/Me_4Si$) δ 6.30–7.58 (m, 6 H, 4 aromatic H, 1-H, 3-H), 4.80 (s, 2 H, 5-CH_2), 4.58 (s, 2 H, 1-H), 2.85 (s, 2 H, CH_2OH), 2.10 (s, 1 H, OH).

2-Carboxy-5,6-dihydropyrrolo[1,2-*c*]quinazoline-6-propionic Acid (33). A solution of the free base of **25** (2.75 g, 8 mmol) and KOH (4.0 g, 71 mmol) in MeOH (40 mL) and H_2O (40 mL) was refluxed for 4 h. The ethanol was removed under vacuum and the resulting aqueous solution was acidified with HCl (10% aqueous). The greenish solid which formed was filtered, washed (H_2O), and dried to yield 2.2 g of crude product. Crystallization from MeOH afforded **33**: yield 1.8 g (80%); mp 234–236 °C; NMR (Me_2SO-d_6/Me_4Si) δ 10.70–11.50 (m, 2 H, 2-COOH and 6-CH_2CH_2COOH), 6.70–7.70 (m, 6 H, 1-, 3-, 7-, 8-, 9-, 10-H), 5.16 (s, 2 H, 5-CH_2), 3.61 (t, 2 H, J = 6.5 Hz, 2′-H), 2.57 (t, 2 H, J = 6.5 Hz, 1′-H).

6-(3-Hydroxypropyl)-2-methyl-5,6-dihydropyrrolo[1,2-*c*]quinazoline (34). $LiAlH_4$ (2.88 g, 76 mmol) was slurried in ether (250 mL) and to this was added a solution of **52** (5.5 g, 9 mmol) in ether (100 mL). The reaction mixture was stirred at room temperature for 0.5 h. Water (3.0 mL), NaOH (3.0 mL of 15% aqueous), and H_2O (9.0 mL) were added to the reaction mixture. The precipitate was filtered and washed with ether. The solvent was removed in vacuo and the residue crystallized from pentane to yield **34** as a pale yellow solid: yield 2.06 g (44.8%); mp 77–78 °C: NMR ($CDCl_3/Me_4Si$) δ 7.30–7.52 (m, 1 H, 7-H), 7.20 (d, 1 H, $J_{3,1}$ = 1.0 Hz, 3-H), 6.60–7.10 (m, 3 H, 8-, 9-, 10-H), 6.35 (s, 1 H, 3′-OH), 6.25 (d, 1 H, $J_{1,3}$ = 1.0 Hz, 1′-H), 4.92 (s, 2 H, 5-H), 3.72 (t, 2 H, J = 7.0 Hz, 3′-H), 3.35 (t, 2 H, J = 7.0 Hz, 1′-H), 2.15 (s, 3 H, 2-CH_3), 1.60–2.10 (m, 2 H, 2′-H).

3-Bromo-2-methylpyrrolo[1,2-*c*]quinazolin-5(6*H*)-one Hydrate (55). Bromine (1.6 g, 10 mmol) was added dropwise to a solution of **43** (2.0 g, 10 mmol) in CCl_4 (600 mL) at reflux. The reaction mixture was refluxed for 1 h, and the solvent was removed in vacuo to yield a dark solid residue (2.4 g). Trituration with MeOH (50 mL) and crystallization from benzene (500 mL) afforded **55** as an off-white solid: yield 2.05 g (89.0%); mp >300 °C: NMR (Me_2SO/Me_4Si) δ 11.28 (s, 1 H, NH), 7.53–7.80 (m, 1 H, 7-H), 6.93–7.27 (m, 3 H, 8-, 9-, 10-H), 6.87 (s, 1 H, C_1 H), 2.10 (s, 3 H, 2-CH_3).

9-(2′,3′-Epoxypropoxy)-2-methylpyrrolo[1,2-*c*]quinazolin-5(6*H*)-one (56). Compound **40** (6.10 g, 27 mmol), NaOH (1.28 g, 32 mmol), EtOH (409 mL), and H_2O (656 mL) were combined, and the resulting yellow solution was stirred at room temperature, protected from light with Al foil, under nitrogen for 3 h. Epibromohydrin (4.79 g, 35 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 40 h. During this time, a white solid formed. The reaction mixture was cooled to 0 °C, and the white solid was filtered, washed (H_2O), and dried to give 2 g of crude product. The crude product was chromatographed on a 175-g SilicAR column prepared in CH_2Cl_2. Elution with 1% $MeOH/CH_2Cl_2$ yielded **56** as a white solid: yield 0.49 g (6.7%); mp 208–210 °C: NMR (Me_2SO-d_6/Me_4Si) δ 11.76 (s, 1 H, N-H), 7.20–7.40 (m, 2 H, 3-H, 8-H), 7.08 (d, 1 H, $J_{7,8}$ = 9 Hz, 7-H), 6.88 (d, 1 H, $J_{8,10}$ = 3 Hz, 10-H), 6.73 (d, 1 H, $J_{1,3}$ = 2 Hz, 1-H), 3.83 (J/gem = 11 Hz, J_{vic} = 6 Hz), 4.30 (J_{gem} = 11 Hz, J_{vic} = 4 Hz, (AB quartet, 2 H, i), 3.23 (m, 1 H, ii), 2.71 (m, 2 H, iii), 2.18 (s, 3 H, 2-CH_3).

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9-[3′-(Isopropylamino)-2′-hydroxy-1′-propoxy]-2-methylpyrrolo[1,2-*c*]quinazolin-5(6*H*)-one (57). A solution of **56** (1.42 g, 5 mmol) in isopropylamine (50 mL) and acetonitrile (50 mL) was placed in a pressure bottle. The bottle was heated in an oil bath at 95 °C for 16 h. During this time, a white solid formed. It was filtered, washed (cold acetonitrile), and dried to give **57** as a white solid: yield 1.20 g (72.7%); mp 206–208 °C; NMR (CF_3COOH/Me_4Si) δ 7.55–8.20 (m, 4 H, 1-, 7-, 8-, 10-H), 7.20 (br s, 2 H, 2 NH), 5.30–5.80 (m, 2 H, 3-H), 4.70–5.10 (m, 1 H, 2′-H), 4.30–4.70 (m, 2 H, 1′-H), 3.50–4.10 (m, 3 H, 3′-, 5′-H), 2.80 (s, 3 H, 2-CH_3), 1.70 (d, 6 H, 5′-CH_3), 1.60 (br s, 1 H, OH).

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2-(Isoxazolylethenyl)phenoxypropanolamines: A New Class of β-Receptor Antagonists with Antihypertensive Activity

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The synthesis of a series of (*E*)-1-amino-3-[2-(2-isoxazolylethenyl)phenoxy]-2-propanols is described. These compounds were found to have β- and α-adrenergic blocking properties, as well as hypotensive and antihypertensive properties. The β-adrenoceptor antagonism of all these compounds was more pronounced than their α-sympatholytic and hypotensive activity. **3a** was 16 times more potent than labetalol in β-adrenergic receptor blockade and was effective in lowering blood pressure in acute trials on spontaneously hypertensive rats at a dosage of 15 mg/kg. Structure–activity considerations showed that antihypertensive potency was more sensitive to structural variations than β-adrenoceptor antagonistic activity. However, in general, those compounds having the most potent β-adrenoceptor blocking activity also lowered blood pressure most effectively.

β-Adrenoceptor antagonists alone[1-8] or in combination with peripheral vasodilators[5,6,9-12] are of great importance in antihypertensive pharmacotherapy. Combination of both these activities results in an enhancement of antih-

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