and a void volume at 1.42 min. With the above concentrations, the radiopurity and chemical purity were consistently in excess of 90%, and the radioincorporation efficiency was in the 30 to 40% range. The reaction gave similar results at 10 and 100 times these concentrations, but at one-tenth this concentration the yields were drastically reduced.

Iodination of **7** to form **1m** and the direct synthesis of **1m**, when performed with ^{131}ICl in acetic acid but in the absence of perchloric acid, resulted in a maximum radioincorporation of 12%.

Acknowledgment. This work was supported by National Institute of Mental Health Grant MH36801-02; by the Director, Office of Energy Research, Office of Basic Energy Sciences, Biology and Medicine Division of the Department of Energy under Contract DE-AC03-76SF00098; and by the Donner Laboratory Schizophrenia Research Fund.

Registry No. **1a**, 90064-53-2; **1b**, 90064-54-3; **1c**, 90064-55-4; **1d**, 90064-56-5; **1e**, 90064-57-6; **1f**, 90064-58-7; **1g**, 90064-59-8; **1h**, 90064-60-1; **1i**, 90064-61-2; **1k**, 90064-67-8; **1l**, 90064-62-3; **1m** (unlabeled), 85563-10-6; **1m**·HCl (unlabeled), 90064-51-0; **1m**, 90064-52-1; **1n**, 90064-63-4; **1o**, 90064-64-5; **1p**, 90083-18-4; **1q**, 90064-65-6; **1r**·HCl (unlabeled), 42203-78-1; **1r**, 65756-98-1; **2a**, 51560-21-5; **2b**, 90064-46-3; **3a**, 90064-47-4; **3b**, 90064-48-5; **3c**, 7310-97-6; **4**, 90064-44-1; **5a**, 90064-49-6; **5b**, 90064-50-9; **6**, 14293-24-4; **7**, 67707-78-2; **7**·oxalate, 90064-45-2; *p*-dimethoxybenzene, 150-78-7; *N*-methylformanilide, 93-61-8; methanamine hydrochloride, 593-51-1; isopropylamine hydrochloride, 15572-56-2; cyclopropanemethanamine hydrochloride, 7252-53-1; hexanamine hydrochloride, 142-81-4; dodecanamine hydrochloride, 929-73-7; benzenemethanamine hydrochloride, 3287-99-8; hydrazine hydrochloride, 14011-37-1; hydroxylamine hydrochloride, 5470-11-1; aminoacetonitrile hydrochloride, 6011-14-9; 2-thioethanamine hydrochloride, 156-57-0; 2-methoxyethanamine hydrochloride, 18600-40-3; *N*,*N*-dimethyl-1,3-propanediamine hydrochloride, 77642-45-6; diethylamine hydrochloride, 660-68-4; *N*-methyl-2-propananine hydrochloride, 54565-61-6; *N*-methylhexananine hydrochloride, 42870-70-2; *N*-methylbenzenemethanamine hydrochloride, 13426-94-3; dimethylamine hydrochloride, 506-59-2.

Antihypertensives. *N*-1*H*-Pyrrol-1-yl-3-pyridazinamines

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The hypothesis that the side effects of hydralazine, such as mutagenicity and lupus erythematosus like syndrome, might be due to the $NHNH_2$ group prompted us to incorporate part of this moiety into a pyrrole ring. Therefore, we prepared a series of *N*-1*H*-pyrrol-1-yl-3-pyridazinamines and a limited number of *N*-1*H*-pyrrol-1-yl-1-phthalazinamines by reaction of 3-hydrazinopyridazines and 1-hydrazinophthalazines with γ-diketones. Most of these compounds, especially in the pyridazine series, showed moderate to strong antihypertensive activity in spontaneously hypertensive rats. The decrease in blood pressure generally had a slow onset after either oral or intravenous administration. *N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-6-(4-morpholinyl)-3-pyridazinamine hydrochloride (**30**) (MDL 899) showed no mutagenic activity in several tests and is now in clinical trials in patients.

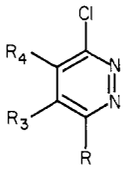
The pathogenesis of hydralazine-induced lupus erythematosus has been correlated with its rate of hepatic acetylation.[1] With the discovery of a novel urinary hydralazine metabolite in man, namely, 3-(hydroxymethyl)-*s*-triazolo[3,4-*a*]phthalazine, the hypothesis was advanced[2] that the functional alcoholic group might provide a handle for the formation of a covalent bond to a protein and, thus, to production of antibodies to the metabolite. The recently discovered mutagenic activity of hydralazine[3,4] could also be explained by the reactivity of the molecule itself. In particular, the high reactivity of the hydrazine moiety $NHNH_2$ for carbonyl groups might cause other chemical modifications, resulting in toxic effects. This hypothesis prompted us to incorporate the terminal NH_2 group of some antihypertensive 3-hydrazinoyridazines into a pyrrole ring. Therefore, we prepared a few *N*-1*H*-pyrrol-1-yl-3-pyridazinamines (VI, Scheme II) and tested them for their hypotensive and mutagenic activity. The discovery that three compounds (**29–31**) endowed with good antihypertensive activity were not mutagenic led us to develop this class. Some compounds having a phthalazine moiety instead of pyridazine were also prepared.

Chemistry. The last intermediates for the preparation of VI are hydrazino derivatives of general formula V (Table III)(Scheme I), where R represents a tertiary amino group. References[5,8] for those compounds already known are in Table IV. The new analogues were prepared starting from 3,6-dichloropyridazines I, which were reacted with secondary amines in the presence (method A) or absence (method B) of a solvent, to give 3-amino-6-chloropyridazines II (Table I). The substitution of the chlorine atom with hydrazine to give V was achieved by one of the following three procedures. In the first procedure, reaction with hydrazine hydrate as a solvent (method F, R_1 = H) was found to be useful only when the final product had a relatively low water solubility. In most cases, the isolation of V as the hydrochloride involved troublesome crystallizations in order to satisfactorily eliminate hydrazine hydrochloride, and the final yields were generally very low. In some cases, after elimination of the hydrazine hydrate, the residues containing the compounds V were used as such for the synthesis of VI. In the second procedure, compounds V were isolated as the benzalhydrazones III (Table II), which were easily hydrolyzed in dilute mineral acids when concomitant steam distillation of the benzaldehyde was carried out (methods C and E). In the third procedure, the hydrochlorides of II were reacted with *tert*-butyl carbazate in methylcellosolve, and after mild hydrolysis of the *tert*-butyl esters, the compounds V were isolated as the hydrazones III (method D). One compound, V-24, with a methyl on the hydrazino group (R_1 = CH_3) was prepared by methylation of the corresponding acetaldehyde hydrazone III-15, followed by hydrolysis of the resulting compound IV. The correct position of the R_1 methyl group was demonstrated by catalytic reduction to the aminopyridazine XI. The new intermediates V are reported in Table III.

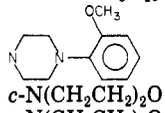
(1) B. N. La Du, H. G. Mandel, E. L. Way, "Fundamentals of Drug Metabolism and Drug Disposition"; William & Wilkins: Baltimore, 1971.
(2) H. Zimmer, R. Glaser, and J. Kokosa, *J. Med. Chem.*, 18, 1031 (1975).
(3) J. Tosk, J. Schmeltz, and D. Hoffmann, *Mutat. Res.*, 66, 247 (1979).
(4) C. R. Shaw, M. A. Butler, J. Thenot, K. D. Haegle, and T. S. Matney, *Mutat. Res.*, 68, 79 (1979).

0022-2623/84/1827-1077$01.50/0

Table I

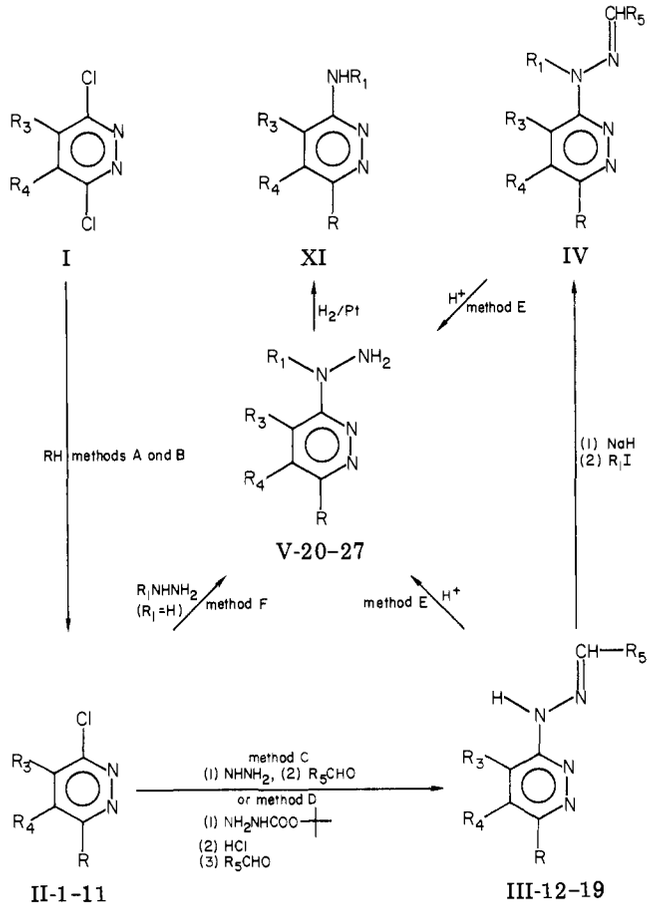


II

no.	R	R_3	R_4	mp or bp (mm), °C	crystn solvent	formula	anal.	method	yield, %
1	$N(CH_3)(CH_2CH_2OCH_3)$[a]	H	H	68–69	Et_2O	$C_8H_{12}ClN_3O$	C, H, Cl, N	A	65
2	$N(CH_2CH_2OCH_3)_2$	H	H	115–118 (0.4)[c]		$C_{10}H_{16}ClN_3O_2$[b]	C, H, Cl, N	B	41
3	$N(CH_2CH_2OC_2H_5)_2$	H	H	140 (0.2)		$C_{12}H_{20}ClN_3O_2$	C, H, Cl, N	B	77
4	c-NC_4H_8	H	H	130–132	H_2O	$C_8H_{10}ClN_3$	C, H, Cl, N	A	58
5	2,6-Me_2-c-$N(CH_2CH)_2O$	H	H	158–160	EtOH	$C_{10}H_{14}ClN_3O$	C, H, N[d]	A	53
6	4-OH-c-NC_5H_{10}	H	H	114–116	H_2O	$C_9H_{12}ClN_3O$	C, H, Cl, N	A	42
7		H	H	141–143	EtOAc	$C_{15}H_{17}ClN_4O$	C, H, Cl, N	A	70
8	c-$N(CH_2CH_2)_2O$	$(CH_2)_4$		129–130	EtOH	$C_{12}H_{16}ClN_3O$	C, H, Cl, N	B[e]	
9	c-$N(CH_2CH_2)_2O$	CH_3	CH_3	98–99	EtOH	$C_{10}H_{14}ClN_3O$	C, H, Cl, N	B[f]	69
10	c-$N(CH_2CH_2)_2O$	CH=CHCH=CH		149–152	EtOAc	$C_{12}H_{12}ClN_3O$	Cl, N	A	70
11	4-OH-c-NC_5H_{10}	CH=CHCH=CH		140–145	EtOAc	$C_{13}H_{14}ClN_3O$	C, H, Cl, N	A	30

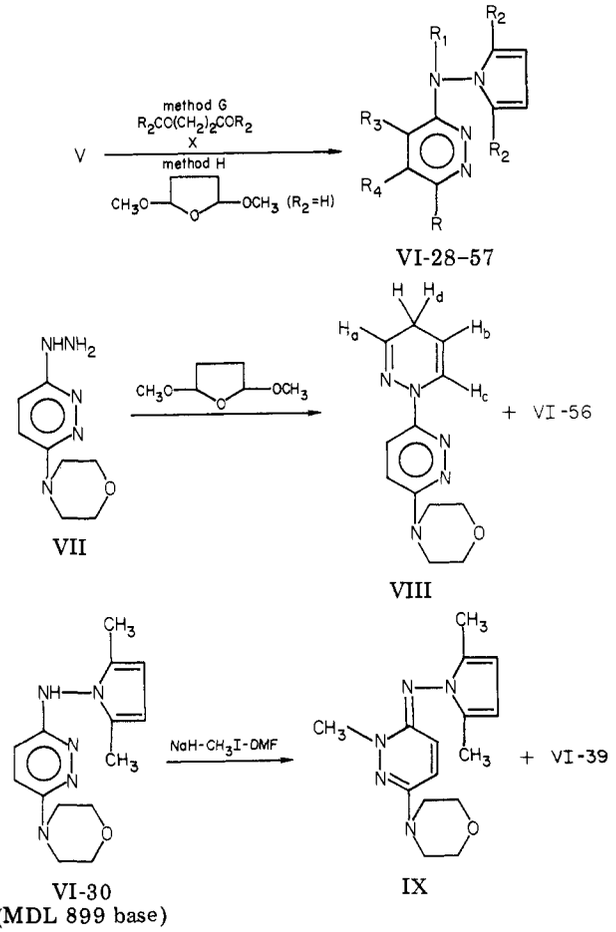
[a] For the preparation of *N*-methyl-*N*(2-methoxyethyl)amine, see W. R. Boon, *J. Chem. Soc.*, 307 (1947). [b] Hydrochloride: mp 131–132 °C (EtOAc). [c] Oil which solidified, mp 33–34 °C. [d] N: calculated, 18.45; found, 17.57. [e] For the preparation of 1,4-dichloro-5,6,7,8-tetrahydrophthalazine, see R. H. Horning and E. D. Amstatz, *J. Org. Chem.*, **20**, 707 (1955). [f] For the corresponding 3,6-dichloropyridazine, see E. Steck, R. P. Brundage, and L. T. Fletcher, *J. Am. Chem. Soc.*, **76**, 44 (1954).

Scheme I[a]



[a] RH = secondary amine. IV: R = c-$N(CH_2CH_2)_2O$; R_1 = R_5 = CH_3; R_3, R_4 = H. XI: R = c-$N(CH_2CH_2)_2O$; R_1 = CH_3; R_3, R_4 = H.

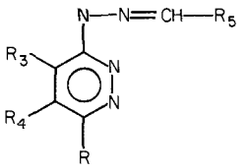
Scheme II



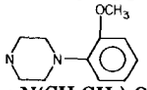
The preparation of *N*-1*H*-pyrrol-1-yl-3-pyridazinamines VI, substituted in the 2- and 5-positions of the pyrrole ring, was carried out by reaction of V with γ-diketones (method G) in acetic acid. Sodium acetate was added when the compounds were used either as salts or as crude products obtained through method F. The γ-diketones used were acetonylacetone and 3,6-octanedione.

(5) E. Bellasio, F. Parravicini, and E. Testa, *Farmaco, Ed. Sci.*, **24**, 919 (1969).

Table II

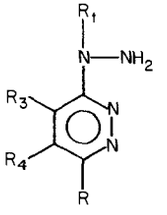


III

no.	R	R_3	R_4	R_5	mp, °C	crystn solvent	yield, % (method)	formula	anal.
12	$N(CH_3)(CH_2CH_2OCH_3)$	H	H	C_6H_5	154–155	EtOH	18 (C)	$C_{15}H_{19}N_5O$	C, H, N[a]
13	$N(CH_2CH_2OCH_3)_2$	H	H	C_6H_5	138–140	EtOH	32 (C), 44 (D)	$C_{17}H_{23}N_5O_2$	C, H, N
14	$N(CH_2CH_2OC_2H_5)_2$	H	H	C_6H_5	109–111	hexane	26 (C)	$C_{19}H_{27}N_5O_2$	C, H, N
15	c-$N(CH_2CH_2)_2O$	H	H	CH_3	181–183	EtOH	80 (C)	$C_{10}H_{15}N_5O$	*b*
16	c-$N(CH_2CH_2)_2O$	H	H	C_6H_5	281	EtOH	34 (D)	$C_{15}H_{17}N_5O$	C, H, N
17	c-$N(CH_2CH_2)_2S$	H	H	C_6H_5	245–250	EtOH	54 (C)	$C_{15}H_{17}N_5S$	C, H, N, S
18		H	H	C_6H_5	230–233	MeOH	39 (C)	$C_{22}H_{24}N_6O$	C, H, N
19	c-$N(CH_2CH_2)_2O$	$-(CH_2)_4-$		C_6H_5	186–188	*i*-PrOH	68 (C)	$C_{19}H_{23}N_5O$	C, H, N
20	c-$N(CH_2CH_2)_2O$	CH_3	H	C_6H_5	197–199	EtOH	30 (C)	$C_{16}H_{19}N_5O$	C, H, N

[a] C: calcd, 63.61; found, 62.70. [b] Anal. calcd for $C_{10}H_{15}N_5O$: C, 54.28; H, 6.38; N, 31.66. Found: C, 53.33; H, 7.04; N, 32.60.

Table III

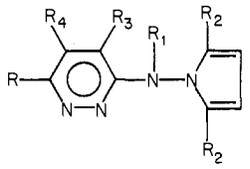


V

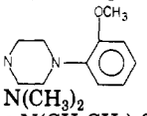
no.	R	R_1	R_3	R_4	mp, °C	crystn solv	yield, % (method)	formula	anal.
21	$N(CH_3)(CH_2CH_2OCH_3)$	H	H	H	219–221	$EtOH/Et_2O$	85 (E)	$C_8H_{15}N_5O\cdot 2HCl$	C, H, N
22	$N(CH_2CH_2OCH_3)_2$	H	H	H	198–200	$EtOH/Et_2O$	70 (E)	$C_{10}H_{19}N_5O_2\cdot 2HCl$	C, H, N, Cl
23	$N(CH_2CH_2OC_2H_5)_2$	H	H	H	181–183	*i*-PrOH	65 (E)	$C_{12}H_{23}N_5O_2\cdot 2HCl$	C, H, N
24	c-$N(CH_2CH_2)_2O$	CH_3	H	H	183–190	EtOH	85	$C_{19}H_{15}N_5O_2\cdot 2HCl\cdot H_2O$	C, H, N, Cl
25	c-$N(CH_2CH_2)_2NH$[a]	H	H	H	257	80% EtOH	20 (F)	$C_8H_{14}N_6\cdot HCl$	C, H, N, Cl
26	c-$N(CH_2CH_2)_2O$[b]	H	$-(CH_2)_4-$		148 dec	*i*-PrOH	84	$C_{12}H_{19}N_5O\cdot 2HCl\cdot C_3H_8O$	C, H, N, Cl
27	c-$N(CH_2CH_2)_2O$	H	CH_3	CH_3	172–176	*i*-PrOH	61 (F)	$C_{10}/H_{17}N_5O$	C, H, N

[a] Prepared from 3-chloro-6-(1-piperazinyl)pyridazine (7). [b] The compound crystallized with 1 mol of 2-propanol.

Table IV



VI

no.	R	R_1	R_2	R_3	R_4	mp or bp (mm), °C	yield, % (method)	formula	anal.	log P^a	$ED_{30}{}^b$
28	$N(CH_2CH_2OC_2H_5)_2$	H	CH_3	H	H	180 (0.2)	70 (G)	$C_{18}H_{29}N_6O_2$	C, H, N		2
29	$N(CH_2CH_2OCH_3)_2$	H	CH_3	H	H	112–114[c]	57 (G)	$C_{16}H_{25}N_5O_2$	C, H, N	2.06	2.7
30	c-$N(CH_2CH_2)_2O$	H	CH_3	H	H	260 dec[d]	61 (G)[p]	$C_{14}H_{19}N_5O$·HCl	C, H, N, Cl	1.94	3.9
31	$N(C_2H_5)_2$	H	CH_3	H	H	149–150[d]	29 (G)[r]	$C_{14}H_{21}N_5$	C, H, N	2.73	3.9
32	$N(CH_3)(CH_2CH_2OCH_3)$	H	CH_3	H	H	105–106[e]	52 (G)	$C_{14}H_{21}N_5O$	C, H, N	2.16	7
33	$N(CH_3)(CH_2CHOHCH_3)$	H	CH_3	H	H	139–140[c]	62 (G)[r]	$C_{14}H_{21}N_5O$	C, H, N	1.73	7.7
34	c-NC_5H_{10}	H	CH_3	H	H	185–187[c]	27 (G)[p]	$C_{15}H_{21}N_5$	C, H, N	3.13	10
35	$N(CH_2CH{=}CH_2)_2$	H	CH_3	H	H	135–136[e]	37 (G)[s]	$C_{16}H_{21}N_5$	C, H, N	1.70	11.4
36	c-$N(CH_2CH_2)_2O$	$COCH_3$	CH_3	H	H	162–168[f]	63[p]	$C_{16}H_{21}N_5O_2$·HCl	C, H, N, Cl	1.64	11.8
37	4-OH-c-NC_5H_{10}	H	CH_3	H	H	175–177[c]	28 (G)[o,t]	$C_{15}H_{21}N_5O$	C, H, N	1.70	12.6
38	c-$N(CH_2CH_2)_2O$	H	C_2H_5	H	H	186–189[d]	41 (G)[p]	$C_{16}H_{23}N_5O$	C, H, N	2.71	15.4
39	c-$N(CH_2CH_2)_2O$	CH_3	CH_3	H	H	119–122[g]	49 (G)[p]	$C_{15}H_{21}N_5O$	C, H, N	2.21	15.8
40	c-$N(CH_2CH_2)_2O$	CH_3	H	H	H	105–117[e,h]	50 (H)	$C_{13}H_{17}N_5O$	C, H, N	2	16.5
41	2,6-Me_2-c-N-(CHCH)$_2$O	H	CH_3	H	H	147–148[e]	45 (G)[o,t]	$C_{16}H_{23}N_5O$	C, H, N	2.59	18.5
42		H	CH_3	H	H	194–196[i]	51 (G)[o,t]	$C_{21}H_{26}N_6O$	C, H, N	3.61	~20
43	$N(CH_3)_2$	H	CH_3	H	H	165–167[e]	50 (G)[r]	$C_{12}H_{17}N_5$	C, H, N	2.18	~22
44	c-$N(CH_2CH_2)_2S$	H	CH_3	H	H	202–203[c]	50 (G)[r]	$C_{14}H_{19}N_5S$	C, H, N, S	*n*	~25
45	c-$N(CH_2CH_2)_2O$	H	CH_3	CH_3	H	196–198[c]	23 (G)[q]	$C_{15}H_{21}N_5O$	C, H, N	*n*	~26
46	c-$N(CH_2CH_2)_2NH$	H	CH_3	H	H	189–191[l]	18 (G)	$C_{14}H_{20}N_6$	C, H, N	1.44	30
47	c-$N(CH_2CH_2)_2O$	H	CH_3	$-(CH_2)_4-$		236–237[c]	62 (G)	$C_{18}H_{25}N_5O$	C, H, N	*n*	~33
48	4-OH-c-NC_5H_{10}	H	CH_3	CH=CHCH=CH		184–186[c]	40 (G)[o,t]	$C_{19}H_{23}N_5O$	C, H, N	*n*	~33
49	c-$N(CH_2CH_2)_2O$	H	CH_3	CH_3	CH_3	234–239[c]	57 (G)	$C_{16}H_{23}N_5O$	C, H, N	*n*	35
50	4-Me-c-$N(CH_2CH_2)_2N$	H	CH_3	H	H	180–182[c]	21 (G)[p]	$C_{15}H_{22}N_5$	C, H, N	1.94	~43
51	$N(CH_2\text{-}CHOHCH_3)_2$	H	CH_3	H	H	137–139[c]	40 (G)[r]	$C_{16}H_{25}N_5O_2$	C, H, N	1.55	~54
52	c-$N(CH_2CH_2)_2O$	H	CH_3	CH=CHCH=CH		205–209[m]	28 (G)[o,t]	$C_{18}H_{21}N_5O$	C, H, N	*n*	~91
53	$N(CH_2CH_2OH)(CH_2CHOHCH_3)$	H	CH_3	H	H	129–131[c]	40 (G)	$C_{15}H_{23}N_5O_2$	C, H, N	1.30	>100
54	c-NC_4H_8	H	CH_3	H	H	208–209[c]	42 (G)[o,t]	$C_{14}H_{19}N_5$	C, H, N	2.45	>100
55	$N(CH_2CH_2OH)_2$	H	CH_3	H	H	129–131[c]	39 (G)[p]	$C_{15}H_{23}N_5O_2$	C, H, N	1.06	>100
56	c-$N(CH_2CH_2)_2O$	H	H	H	H	228–229[c]	2 (H)	$C_{12}H_{15}N_5O$	C, H, N	*n*	>100
57	H	H	CH_3	CH=CHCH=CH		170–171[c]	15 (G)	$C_{14}H_{14}N_{14}$	C, H, N	*n*	

[a] P = partition coefficient, octanol–phosphate buffer, pH 7.4. [b] Oral dose in milligrams per kilogram produces a 30 mmHg drop of systolic blood pressure (calculated on the regression line). [c] EtOAc. [d] *i*-PrOH. [e] Et_2O. [f] *i*-PrOH–Et_2O. [g] Hexane. [h] Mixture of three crystalline forms melting at 105, 113 and 117 °C. [i] EtOH. [j] Deleted on revision. [l] CH_3CN. [m] Me_2CO. [n] Not determined. [o] Overall yield from the corresponding chloropyridazine or phthalazine. [p] For the corresponding hydrazino derivative V, see ref 5. [q] For the corresponding hydrazino derivative V, see ref 6. [r] For the corresponding hydrazino derivative V, see ref 7. [s] For the corresponding hydrazino derivative V, see ref 8. [t] The corresponding hydrazino derivative V was not isolated. [u] N: calcd. 20.75; found, 20.10.

Two compounds that were unsubstituted in the pyrrole ring were obtained by reaction of V with 2,5-dimethoxyfuran (method H) in ethanol, in the presence of hydrogen chloride. This reaction proceeded with fairly good yield to give compound VI-40 when we started from V-24, which has a CH_3NNH_2 group. In contrast, the reaction carried out on VII, which has an unsubstituted hydrazino group, gave only traces of the corresponding pyrrole derivative VI-56 and a slightly greater amount of the dihydropyridazine VIII. Compound VI-39 was also prepared by methylation of VI-30 in the presence of sodium hydride. In this case a derivative (IX) methylated on the pyridazine nitrogen was also formed.

Biological Activity. The antihypertensive activity of the compounds VI is reported in Table IV as the oral effective dose (ED_{30}) that produced a drop of 30 mmHg in spontaneously hypertensive rats.[9] No correlation between pharmacological activity and octanol–water partition coefficient was found. The amino group R is necessary for activity; a small number of *N*-1*H*-pyrrol-1-yl-3-pyridazines VI without this moiety, recently prepared and not reported in this paper, were shown to be inactive.[10] Also in the phthalazine series, compound VI-57, obtained from hy-

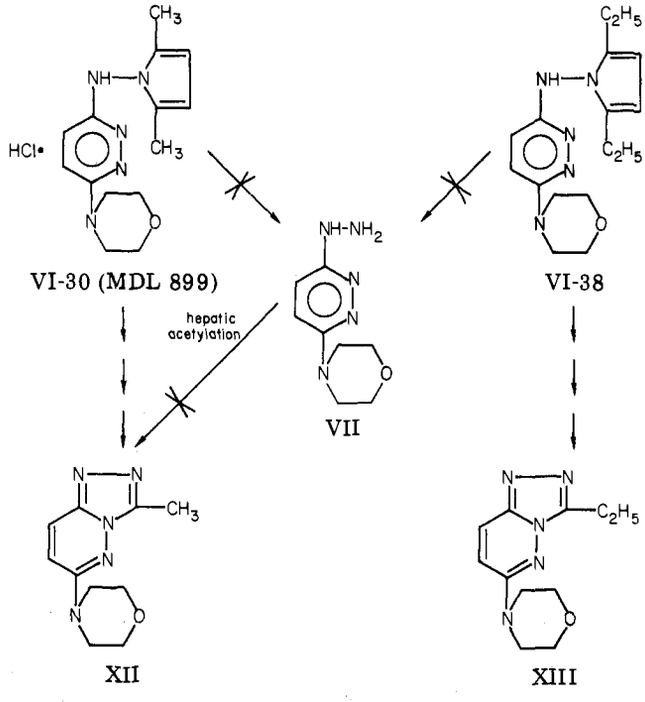
(6) E. Bellasio, A. Ripamonti, F. Parravicini, and E. Baldoli, *Farmaco, Ed. Sci.*, **27**, 581 (1972).
(7) G. Pifferi, F. Parravicini, C. Carpi, and L. Dorigotti, *J. Med. Chem.*, **18**, 741 (1975).
(8) P. L. Anderson, W. J. Houlikan, and R. E. Manning, German Offen. 2 062 107, 1970.
(9) K. Okamoto, K. Aoki, *Jpn. Circ. J.*, **27**, 282 (1963).
(10) E. Baldoli, unpublished results.
(11) V. Dezulian, personal communication.
(12) A Goldblatt, J. Linch, R. F. Hanzal, and W. W. Summerville, *J. Exp. Med.*, **59**, 347 (1934).
(13) B. P. Goldstein, F. Ripamonti, and F. Rodenghi, 12th Annual Meeting of the European Environmental Mutagen Society, Helsinky, June 20–24, 1982.
(14) A. Assandri, personal communication.
(15) R. A. Coburn and R. A. Carapellotti, *J. Pharm. Sci.*, **65**, 1505 (1976).
(16) H. Stetter, *Angew. Chem., Int. Ed. Engl.*, **15**, 639 (1976).

Table V. Effects of MDL 899 and Hydralazine, Given Intravenously, on Systolic Blood Pressure and Heart Rate in Conscious Renal Hypertensive Dogs[a]

	systolic blood pressure, mmHg, at the following times						
treatment	0 h	4 h	6 h	8 h	10 h	12 h	20 h
MDL 899, 1 mg/kg	190 ± 10	168 ± 8	150 ± 5	140 ± 7	147 ± 8	165 ± 5	187 ± 5
hydralazyne, 0.3 mg/kg	188 ± 7	135 ± 5	138 ± 2	148 ± 5	188 ± 7	190 ± 4	188 ± 7
P^b	NS	<0.01	< 0.05	NS	<0.01	<0.01	NS
	heart rate, beats/min, at the following times						
treatment	0 h	4 h	6 h	8 h	10 h	12 h	20 h
MDL 899, 1 mg/kg	80 ± 7	92 ± 10	100 ± 9	110 ± 7	107 ± 8	105 ± 7	105 ± 8
hydralazine, 0.3 mg/kg	78 ± 10	128 ± 12	140 ± 9	132 ± 8	125 ± 10	118 ± 6	115 ± 7
P^b	NS	<0.01	<0.01	<0.0	NS	NS	NS

[a] Mean plus or minus the standard error for four animals at each compound. [b] P = MDL 899 vs. hydralazine comparison by analysis of variance (F test).

Scheme III



dralazine and acetonylacetone, did not show any antihypertensive activity in rats either after intravenous or oral administration. Weak or moderate activity appeared in the analogues VI-48 and VI-52, which have basic groups. The most active compound of the series, VI-28, is an oil that did not form solid salts. Further pharmacological and toxicological evaluation was performed on compounds VI-29 and VI-30; the latter (MDL 899) was selected for its better therapeutic index. It oral LD_{50}'s in rats and mice are, respectively, 2250 and 660 mg/kg.[11]

Table V shows the effects of MDL 899 and hydralazine, give intravenously, on systolic blood pressure and heart rate in conscious renal hypertensive dogs.[12] As compared to hydralazine, the hypotensive effect of MDL 899 was evoked later ($p < 0.01$) but it lasted longer ($p < 0.01$); in addition, the increase in heart rate was significantly less ($p < 0.01$). No mutagenic activity of MDL 899 was observed[13] in the Ames test; gene conversion and point mutation tests in yeasts, including a host-mediated test in mice; and chromosomal aberration test in Chinese hamster. One of the most interesting results of the metabolic study in rats was that ~20% of the drug was transformed into the triazole derivative XII (Scheme III).[14] This seemed to indicate that the drug partially followed a metabolic pattern similar to that of hydralazine, although the precursor VII containing the $NHNH_2$ moiety was not detected in the urine. The hypothesis that the acetyl group necessary for the formation of the triazole ring might come from the pyrrole moiety and not from hepatic acetylation was supported by the discovery that the urine of rats treated orally with the analogue VI-38, which has two ethyls on the pyrrole ring, contained only the ethyltriazole compound XIII.[14]

Experimental Section

Melting points were taken in an oil bath and are uncorrected. Solvents were removed in vacuo on a Buchi rotavapor. IR spectra were registered with a Perkin-Elmer Model 137 spectrophotometer. NMR spectra were recorded on a Bruker WH-270 instrument. Chemical shifts are reported as δ units (part per million) with tetramethylsilane as internal reference (δ 0.00). All the reactions were carried out under nitrogen. Where analyses are indicated only by symbols of the elements, analytical results obtained are within 0.4% of the theoretical values.

Method A. 6-Chloro-3-[4-(2-methoxyphenyl)-1-piperazinyl]pyridazine (II-7). A mixture of 3,6-dichloropyridazine (14.9 g, 0.1 mol) and 1-(2-methoxyphenyl)piperazine (36 g, 0.2 mol) in C_2H_5OH (200 mL) was refluxed for 10 h. After evaporation of the solvent, the residue was triturated with H_2O, and the insolube material was filtered and crystallized from EtOAc: yield 21.5 g; NMR (Me_2SO-d_6) δ 3.08 (t, 4 H, $J_{CH_2CH_2}$ = 5.5 Hz, $CH_2NC_6H_3$) 3.74 (t, 4 H, CH_2N), 3.81 (s, 3 H, CH_3O), 6.9–7.2 (m, 4 H, phenyl protons), 7.48 (d, 1 H, $J_{H_4-H_5}$ = 10 Hz, H_5), 7.61 (d, 1 H, H_4).

Method B. 6-Chloro-*N*,*N*-bis(2-methoxyethyl)-3-pyridazinamine (II-2). To bis(2-methoxyethyl)amine (19 g, 0.14 mol) preheated at 135 °C was added portionwise under stirring over 10 min 3,6-dichloropyridazine (10.35 g, 0.07 mol). After the addition was complete, the mixture was kept at 145 °C for 30 min, cooled to room temperature, and diluted with EtOAc (100 mL). The solvent was washed with H_2O (3 × 20 mL), dried, and evaporated. The crude product (15 g) was purified by silica gel chromatography [500 g, mobil phase EtOAc–hexane (1:1)] and then by distillation: yield 6.9 g; bp 115–118 °C (0.4 mm). The product solidifed on standing: NMR ($CDCl_3$) δ 3.34 (s, 6 H, CH_3O), 3.63 (t, 4 H, J = 5.5 Hz, CH_2N), 3.78 (t, 4 H, CH_2O), 7.02 (d, 1 H, $J_{H_4-H_5}$ = 10 Hz, H_5), 7.18 (d, 1 H, H_4).

Benzaldehyde [6-[Bis(2-methoxyethyl)amino]-3-pyridazinyl]hydrazone (III-13). (a) Method C. A mixture of II-2 (7 g, 0.029 mol), hydrazine hydrate (15 mL), and butanol (10 mL) was stirred at 98 °C for 48 h, cooled to room temperature, diluted with H_2O (150 mL), and evaporated to dryness. The residue was dissolved in H_2O (100 mL), and the unreacted starting material was extracted with toluene (2 × 75 mL). The aqueous phase was evaporated, and the residue was again dissolved in H_2O (50 mL). Benzaldehyde (7 mL) was added, and the mixture was heated on a steam bath for 30 min. After standing overnight, the suspension was slowly neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The solvent was dried and evaporated, and the residue was crystallized from C_2H_5OH: yield 3 g; NMR ($CDCl_3$) δ 3.36 (s, 6 H, CH_3O), 3.66 (t, 4 H, $J_{CH_2CH_2}$ = 5.5 Hz, CH_2N), 3.82 (t, 4 H, CH_2O), 7.12 (d, 1 H, $J_{H_4-H_5}$ = 10 Hz, H_5), 7.31 (dd, 1 H, J_{ortho} = 9 Hz, J_{meta} = 2.5 Hz, phenyl H_4), 7.40 (dd, 2 H, J_{ortho} = 9 Hz, phenyl H_3 and H_5), 7.67 (d, 1 H, H_4), 7.73 (dd, 2 H, phenyl H_2, H_6), 8.36 (s, 1 H, CH=N), 11.92 (br s, 1 H, NH).

(b) **Method D.** A mixture of II-2 hydrochloride (2 g, 7.1 mmol), *tert*-butyl carbazate (2.34 g, 17.7 mmol), and methylcellosolve (40 mL) was refluxed for 12 h. After evaporation of the solvent, the residue was suspended in 5% HCl (100 mL), heated at 50 °C for 10 min, and evaporated to dryness. The solid was dissolved in H_2O (100 mL) and neutralized with Na_2CO_3, and the unreacted starting material was extracted with toluene. The aqueous phase was evaporated to dryness. The residue was treated with H_2O (50 mL) and benzaldehyde (3 mL) and worked up as described in the previous preparation: yield 1.02 g.

Method E. 6-Hydrazino-*N*-methyl-*N*-(2-methoxyethyl)-3-pyridazinamine Dihydrochloride (V-21). A solution of III-12 (21 g) in 3% HCl (500 mL) was evaporated to dryness. The operation was repeated twice until the benzaldehyde was completely removed. The residue was crystallized from EtOH–Et_2O (1:1): yield 1.7 g; NMR (Me_2SO-d_6) δ 3.27 (s, 6 H, CH_3O and CH_3N), 3.58 (t, 2 H, $J_{CH_2CH_2}$ = 5.5 Hz, CH_2N), 3.88 (t, 2 H, OCH_2), 7.63 (d, 1 H, $J_{CH=CH}$ = 10 Hz, H_5), 8.03 (d, 1 H, H_4), 8.3–10.6 (br, 5 H, mobile H).

Method F. 3-Hydrazino-6-(1-piperazinyl)pyridazine Hydrochloride (V-25). A mixture of 3-chloro-6-(1-piperazinyl)-pyridazine[7] (5 g, 25 mol) and hydrazine hydrate (80 mL) was stirred at 80 °C for 10 h. The solution was cooled to 10 °C, and the precipitate (3 g of the starting material) was filtered off. The filtrate was evaporated to dryness, and the residue was crystallized twice from EtOH–H_2O (4:1): yield 1 g; NMR (Me_2SO-d_6) δ 3.17 (t, 4 H, J = 5.5 Hz, CH_2N), 3.62 (t, 4 H, CH_2N), 3.0–4.3 (br 5 H, mobile H), 7.05 (d, 1 H, $J_{H_4-H_5}$ = 10 Hz, H_4), 7.37 (d, 1 H, H_5).

Acetaldehyde Methyl[6-(4-morpholinyl)-3-pyridazinyl]-hydrazone (IV). To a stirred suspension of III-15 (9.95 g, 45 mmol) in anhydrous DMF (100 mL), was added at room temperature 55% NaH in mineral oil (2.38 g, 54 mmol). The mixture was heated at 55 °C for 30 min, and a solution of CH_3I (7.03 g, 49.5 mmol) in DMF (15 mL) was slowly added at 10 °C. The suspension was heated at 55 °C for 90 min, and then the solvent was distilled. The residue was dissolved in EtOAc, and the solution was washed with H_2O (3 × 50 mL). The organic solvent was dried and evaporated, and the crude IV was triturated with cyclohexane to give 8.3 g, mp 131–134 °C. An analytical sample was obtained by crystallization with $(C_2H_5)_2O$: mp 133–134 °C; NMR ($CDCl_3$) δ 2.22 [d, 3 H, J = 5.5 Hz, $CH_3(CH)$], 3.50 (t, 4 H, J = 5.5 Hz, CH_2N), 3.57 (s, 3 H, CH_3N), 3.90 (t, 4 H, CH_2O), 7.01 [q, 1 H, $CH(CH_3)$], 7.00 (d, 1 H, J = 10 hZ, H_5), 7.82 (d, 1 H, H_4). Anal. ($C_{11}H_{17}N_5O$) C, H, N.

***N*-Methyl-6-(4-morpholinyl)-3-pyridazinamine (XI).** A mixture of V-24 (1 g), acetic acid (55 mL), and PtO_2 (0.25 g) was hydrogenated under normal pressure (220 mL of H_2 absorbed over 10 h). The catalyst was filtered off, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (50 mL), washed with 5% $NaHCO_3$ and H_2O, dried, and evaporated. The crude product (0.1 g) was crystallized from EtOAc: yield 0.05 g; mp 196–198 °C (lit.[14] mp 195–197 °C).

Method G. (a) *N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-6-(4-morpholinyl)-3-pyridazinamine Hydrochloride (VI-30). To a stirred suspension of 3-hydrazino-6-(4-morpholinyl)pyridazine (VII,[5] 20 g, 0.102 mol) in CH_3COOH (100 mL) was added over 5 min acetonylacetone (14.05 g, 0.123 mol). The mixture was heated at 65 °C for 3 h and evaporated to dryness. The residual oil was suspended in H_2O, and the pH was adjusted to 8 with $NaHCO_3$. The insoluble material was filtered and crystallized from *i*-C_3H_7OH to give 17 g of the base: mp 189–191 °C. The hydrochloride was obtained by cautious addition of ethereal HCl to a hot solution of the base in C_2H_5OH: NMR (Me_2SO-d_6) δ 2.05 (s, 6 H, CH_3), 3.56 (t, 4 H, J = 4.5 Hz, CH_2N), 3.74 (t, 4 H, J = 4.5 Hz, CH_2O), 5.73 (s, 2 H, pyrrol H), 7.34 (br d, 1 H, J = 9.8 Hz, H_4), 7.95 (d, 1 H, J = 9.8 Hz, H_5), 3.5 (br, 1 H, NH), 10.5 (br, 1 H, HCl).

Method G. (b) *N*-(2,5-Dimthyl-1*H*-pyrrol-1-yl)-6-(2-propenylamino)-3-pyridazinamine (VI-35). To a stirred suspension of 6-hydrazino-*N*,*N*-bis(2-propenyl)-3-pyridazineamine dihydrochloride was added over 15 min acetonyl acetone (3.42 g, 30 mmol), and the mixture was heated at 65 °C for 3 h. After distillation of the solvent, the residual oil was suspended in H_2O, neutralized with $NaHCO_3$, and extracted with EtOAc. The organic solvent was dried and evaporated. The resulting oil was purifed by chromatography on silica gel [260 g, mobil phase $CHCl_3$–C-H_3OH (9:1)]. Crystallization from $(C_2H_5)_2O$ gave 2.9 g of the pure compound: NMR ($CDCl_3$) δ 2.08 (s, 6 H, CH_3C), 4.07 (br d, 4 H, $J_{CH_2CH_2}$ = 5 Hz, CH_2N), 4.7–6.0 (m, 6 H, $2CH=CH_2$), 5.80 (s, 2 H, pyrrol H), 6.03 (d, 1 H, J_1 = 9.5 Hz, H_4), 6.73 (d, 1 H, H_5), 7.33 ns, 1 H, 1 H).

Method H. 6-(4-Morpholinyl)-*N*-1*H*-pyrrol-1-yl-3-pyridazinamine (VI-56). To a stirred solution of 3-hydrazino-6-(4-morpholinyl)pyridazine (VII,[5] 18 g, 90 mmol) in C_2H_5OH (130 mL) was slowly added at 20 °C a saturated solution of HCl in $(C_2H_5)_2O$ (45 mL). To the resulting suspension was then added dropwise over 20 min 2,5-dimethoxytetrahydrofuran (12 g, 90 mmol), and the mixture was heated at reflux for 6 h. The solvent was distilled, and the residue was dissolved in H_2O. After neuralization with $NaHCO_3$ (pH 8), the solution was extracted with $CHCl_3$ (4 × 100 mL). The solvent was dried and evaporated to give 13 g of any oily residue, which was chromatographed on silica gel [500 g, mobil phase $CHCl_3$–EtOAc, (4:1)]. After separation of VIII, the elution was continued with EtOAc, giving VI-56 (0.2 g): NMR ($CDCl_3$) δ 3.50 (t, 4 H, $J_{CH_2CH_2}$ = 5.5 Hz, CH_2N), 3.90 (t, 4 H, CH_2O), 6.27 (d, 2 H, $J_{H_2-H_3}$ = 2.5 Hz, pyrrol H_3), 6.32 (d, 1 H, $J_{H_4-H_5}$ = 10 Hz, H_4), 6.85 (d, 2 H, pyrrol H_2), 6.90 (d, 1 H, H_5), 7.65 (s, 1 H, NH).

3-(1,4-Dihydro-1-pyridazinyl)-6-(4-morpholinyl)pyridazine (VIII). The compound obtained by chromatography, as described in the previous preparation, was crystallized from EtOH: yield 1.5 g; mp 153–155 °C; NMR (for the attributions, see Scheme II) ($CDCl_3$) δ 2.94 (ddd, 2 H, J_{CH_2-Hc} = 0.5 Hz, $J_{CH_2-H_b}$ = 3 Hz, J_{CH_2-Ha} = 2.5 Hz, $=CCH_2C$), 3.50 (t, 4 H, $J_{CH_2CH_2}$ = 5 Hz, CH_2N), 3.85 (t, 4 H, CH_2O), 4.87 (ddt, 1 H, $J_{H_b-H_a}$ = 2.5 Hz, $J_{H_b-H_c}$ = 8 Hz, H_b), 6.78 (dt, 1 H, H_a), 6.99 (d, 1 H, $J_{H_4-H_5}$ = 10 Hz, H_5) 7.61 (d, 1 H, H_4), 7.66 (dt, 1 H, H_c). Anal. ($C_{12}H_{15}N_5O$) C, H, N.

***N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-*N*-methyl-6-(4-morpholinyl)-3-pyridazinamine (VI-39).** (a) 80% NaH in mineral oil (6.3 g, 0.21 mol) was added to a solution of VI-30 (31 g, 0.1 mol) in anhydrous DMF (250 mL). The suspension was stirred at 55 °C for 50 min, and then CH_3I (6.8 mL, 0.11 mol) was added at 10 °C over 10 min. The mixture was again heated at 55 °C for 1 h. The solvent was distilled, and the residue was suspended in H_2O and extracted with EtOAc. The solvent was dried and evaporated, and the crude product was chromatographed on silica gel [1200 g, mobil phase EtOAc–cyclohexane (1:3), 4000 mL; EtOAc–cyclohexane (1:2), 3000 mL]. The mixture of VI-39 and IX (16 g) thus obtained gave, after three crystallizations from hexane, 5 g of VI-39 (the mother liquors were combined and worked up as described below): NMR ($CDCl_3$) δ 2.01 (s, 6 H, $CH_3C=$), 3.48 (t, 4 *h*, $J_{CH_2CH_2}$ = 6.5 Hz, CH_2N), 3.63 (s, 3 H, CH_3N), 3.90 (t, 4 H, CH_2O), 5.87 (s, 2 H, pyrrol CH=C), 5.98 (d, 1 H, $J_{CH=CH}$ = 10 Hz, H_4), 6.90 (d, 1 H, H_5).

(b) Compound VI-39 was also obtained by reaction of V-24 with acetonylacetone (method G).

***N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2-methyl-6-(4-morpholinyl)-3(2*H*)-pyridazinimine (IX).** The combined hexane liquors of the previous preparation (a) were evaporated to dryness, and the residue was chromatographed on silica gel [500 g, mobil phase hexane–Et_2O (1:1)]: yield 2.2 g; mp 162–163 °C (from hexane); NMR ($CDCl_3$) δ 2.01 (s, 6 H, $CH_3C=$), 3.22 (t, 4 H, $J_{CH_2CH_2}$ = 6.5 Hz, CH_2N), 3.78 (s, 3 H, CH_3N), 3.83 (t, 4 H, CH_2O), 5.81 (s, 2 H, pyrrol CH=C), 6.28 (d, 1 H, $J_{CH=CH}$ = 10 Hz, H_4), 6.78 (d, 1 H, H_5).

***N*-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-*N*-[6-(4-morpholinyl)-3-pyridazinyl]acetamide Hydrochloride (VI-36).** To a stirred solution of VI-30 (6 g) in pyridine (12 mL) was slowly added over 20 min acetic anhydride (30 mL). The solution was heated at 110 °C for 1 h and then evaporated to dryness. The oil was dissolved in EtOAc (150 mL), and the organic solvent was washed with 3% $NaHCO_3$ and H_2O, dried, and evaporated. The residue (8 g) was chromatographed on silica gel [250 g, mobil phase cyclohexane–EtOAc (3:2)]. The resulting oil was dissolved in Et_2O (300 mL) and treated with ethereal HCl until complete precipitation. The product was crystallized from *i*-C_3H_7OH–Et_2O: yield 4.9 g; IR ν_{max} 1705 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 1.93 (s, 3 H, CH_3CO), 2.12 (s, 6 H, $2CH_3C$), 3.77 (s, 8 H, CH_2O and CH_2N), 5.85 (s, 2 H, pyrrol H), 8.07 (s, 2 H, H_4 and H_5), 10.62 (br s, 1 H, NH^+).

3,6-Octanedione (X, R_2 = C_2H_5). A mixture of propionic aldehyde (29 g, 0.5 mol), ethyl vinyl ketone (42 g, 0.5 mol), 3-

benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride[15] (13.5 g, 0.05 mol) and TEA (30.3 g, 0.3 mol) was stirred at 88 °C for 8 h. After cooling, the mixture was slowly poured into 10% H_2SO_4 (500 mL), and the resulting solution was extracted with $CHCl_3$. The solvent was washed with H_2O (2 × 100 mL), dried, and evaporated. The residue was distilled to give 34 g: bp 90–93 °C (11 mm); IR ν_{max} 1720 (C=O), 1140 (CO), 1075, 1038, 990 cm^{-1}.

Pharmacology. Oral Treatment. Groups of three male conscious spontaneously hypertensive rats (SHR) rats were used. The compounds, suspended in aqueous 0.5% methocel HC 90 Dow, were administered by gavage in a volume of 2 mL/kg. Systolic blood pressure (SBP) was recorded before and 2 and 4 h after treatment. The measurements were taken by the indirect tail-cuff method (W + W BP recorder, Electronic Basel) with a sensor and pressure cuff, after heating the rats for 20 min at 37 °C. Heart rate (HR) was calculated from the pressure tracing. Regression lines were plotted for the maximum fall in blood pressure vs. 1-g dose.

Intravenous Treatment. Groups of four conscious mongrel renal hypertensive dogs were used. The compounds were dissolved in distilled water and administered at 0.5 mL/kg. SBP and HR were measured in the tail by an indirect technique with the recorder already described.

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Registry No. 1, 89937-23-5; 2, 83491-12-7; 2·HCl, 83514-28-7; 3, 89937-24-6; 4, 66346-85-8; 5, 89937-25-7; 6, 89937-26-8; 7, 89937-27-9; 8, 89937-28-0; 9, 89937-29-1; 10, 89937-30-4; 11, 75848-36-1; 12, 89937-31-5; 13, 83491-13-8; 14, 89937-32-6; 15, 75842-13-6; 16, 76953-31-6; 17, 89937-33-7; 18, 89937-34-8; 19, 89937-35-9; 20, 37121-81-6; 21·2HCl, 75842-03-4; 22·2HCl, 75842-01-2; 23·2HCl, 75842-05-6; 24·2HCl, 75842-11-4; 25·HCl, 77510-12-4; 26·2HCl, 89937-36-0; 27, 89937-37-1; 28, 75848-33-8; 29, 75842-02-3; 30·HCl, 86703-02-8; 31, 75841-81-5; 32, 75842-04-5; 33, 89937-38-2; 34, 75841-90-6; 35, 75841-87-1; 36·HCl, 89937-39-3; 37, 75841-98-4; 38, 75841-80-4; 39, 75841-99-5; 40, 75842-12-5; 41, 89937-40-6; 42, 75842-08-9; 43, 75842-06-7; 44, 75842-00-1; 45, 89937-41-7; 46, 75841-93-9; 47, 89937-42-8; 48, 75848-35-0; 49, 89937-43-9; 50, 75841-91-7; 51, 75841-97-3; 52, 75841-86-0; 53, 75841-95-1; 54, 75841-89-3; 55, 75841-94-0; 26, 75842-10-3; 57, 89937-44-0; I ($R_3 = R_4 = H$), 141-30-0; IV (R = c-$N(CH_2CH_2)_2O$, $R_1 = CH_3$, $R_3 = R_4 = H$, $R_5 = CH_3$), 77510-10-2; V·2HCl (R = $(CH_2=CHCH_2)_2N$, $R_1 = R_3 = R_4 = H$), 28546-57-8; VII, 17259-72-2; VIII, 89937-45-1; IX, 89937-46-2; X ($R_2 = CH_3$), 110-13-4; X ($R_2 = C_2H_5$), 2955-65-9; XI (R = c-$N(CH_2CH_2)_2O$, $R_1 = CH_3$, $R_3 = R_4 = H$), 61472-02-4; $HN(CH_2CH_2OCH_3)_2$, 111-95-5; NH_2NHCO_2Bu-t, 870-46-2; C_2H_5CHO, 123-38-6; $C_2H_5COCH = CH_2$, 1629-58-9; 1-(2-methoxyphenyl)piperazine, 35386-24-4; 2,5-dimethoxytetrahydrofuran, 696-59-3.

Notes

Syntheses and Anthelmintic Activity of Alkyl 5(6)-(Substituted-carbamoyl)- and 5(6)-(Disubstituted-carbamoyl)benzimidazole-2-carbamates and Related Compounds[1]

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A number of alkyl 5(6)-(substituted-carbamoyl)- and 5(6)-(disubstituted-carbamoyl)benzimidazole-2-carbamates and related compounds have been synthesized, and their anthelmintic activity against various intestinal helminths of experimental animals have been evaluated. A large percentage of the compounds synthesized showed noteworthy activity against *Ancylostoma ceylanicum* and at higher doses against *Hymenolepsis nana* infections. Compared to the alkyl 5(6)-(substituted-carbamoyl)benzimidazole-2-carbamates, the disubstituted carbamoyl analogues were found to exhibit better anthelmintic activity. The most active compound of the series, namely, methyl 5(6)-[(*N*-2-pyridylpiperazino)carbamoyl]benzimidazole-2-carbamate (**90**), has been screened against intestinal helminths in higher animals and as a micro- and macrofilaricidal agent. Compound **90** has been identified as a broad-spectrum anthelmintic agent. Compound **90** has been identified as a broad-spectrum anthelmintic in view of its efficacy against *A. ceylanicum* (hamsters and dogs), *H. nana* (rats), *Nippostrongylus brasiliensis* (rats), *Syphacia obvelata* (mice), *A. tubaeformis* (cat), *Toxocara* spp. (cat), and *Litomosoides carinii* (cotton rat).

The incidence of helminth infections is alarmingly high in tropical and subtropical regions,[2,3] as a result of poor sanitation and lower standard of living. The nonavailability of minimal medical facilities for diagnosis of the specific helminth infection aggravates the situation even further. A research program was therefore initiated to obtain a broad-spectrum anthelmintic.

We report herein the syntheses and anthelmintic properties of alkyl 5(6)-(substituted- and -disubstituted-carbamoyl)benzimidazole-2-carbamates (**68–90**), 1,2-bis[[2-(carbomethoxyamino)-5-benzimidazolyl]carboxamido]-ethane and its phenyl derivature (**103** and **104**), bis[4-[[2-(carbomethoxyamino)-5-benzimidazolyl]carboxamido]phenyl] sulfide or sulfone (**105** and **106**) 1,4-bis-[[2-(carbomethoxyamino)-5-benzimidazolyl]carboxamido]benzene 1,4-bis[2-(carbomethoxyamino)-5-benzimidazolyl]carboxamido]benzene (**109**).

Chemistry. Nitration of 4-acetamidobenzoic acid with fuming HNO_3 at 0 °C furnished 4-acetamido-3-nitrobenzoic acid (**1**).[4] The reaction of **1** with $SOCl_2$ gave the

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(1) CDRI communication no. 3339.
(2) P. A. J. Janssen, *Prog. Drug. Res.*, 18, 191 (1974).
(3) B. B. Gaitonde and D. M. Renapurkar, *J Assoc. Physicians India*, 27, 129 (1979).

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