dichlorophenylacetonitrile (18.5 g, 0.1 mol) in a mixture of DMF–benzene (50 mL/150 mL), NaH (78%, 3.2 g, 0.1 mol) dispersion was added portionwise under N_2 atmosphere. After stirring for 1 h the mixture was cooled to 0 °C and 4-chlorophenoxymethyl chloride (17.7 g, 0.1 mol) was added over a period of 1 h. The mixture was stirred at room temperature for 2 h and then poured into H_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was triturated with MeOH giving a solid which was recrystallized from EtOH yielding 11 g (57%) of **90**, mp 172.8 °C.

The methanolic solution was evaporated in vacuo and the resultant residue crystallized from *n*-hexane to yield 5 g (37%) of **89**, mp 70 °C (lit.[4] 70–70.5 °C).

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4-Substituted Semicarbazones of Mono- and Dichlorobenzaldehydes as Antihypertensive Agents

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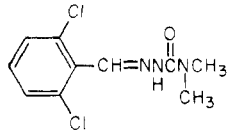
Twelve 4-substituted semicarbazone derivatives of *o*- and *p*-chloro- as well as 2,6-dichlorobenzaldehyde were synthesized and investigated for antihypertensive activity in spontaneously hypertensive rats. Several of the compounds synthesized (viz. **1**, **6**, **7**, and **15**) exhibited potent antihypertensive effects when orally administered. The same compounds were not hypotensive in the normotensive dog.

Several clinically effective antihypertensive drugs such as clonidine, guanabenz, guanoxabenz, and BS 100/141 possess a common molecular structural feature: a 2,6-dichlorobenzene moiety to which a basic nitrogen side chain is attached.[1]

In the course of our investigation into the potential antihypertensive activity of various 2,6-dichlorobenzaldehyde derivatives, we observed that semicarbazone **1** was a potent (5.0 mg/kg) antihypertensive agent when orally administered to spontaneously hypertensive rats[2] (SHR).



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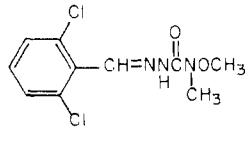
Further evaluation of **1** revealed it to be free of adverse side effects, such as ataxia, sedation, agitation, or tachycardia, at 10 or 5 mg/kg in the SHR. Semicarbazone **1** was toxic at 100 mg/kg in SHR due to a general depression of cardiovascular function.

Examination of the literature revealed that **2**, a close analogue of **1**, was claimed to be a potent antihypertensive agent with low toxicity.[3] These observations prompted



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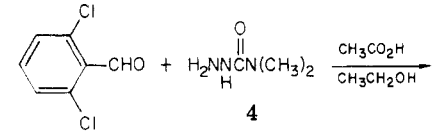
the synthesis of 11 related semicarbazones of **1** and the investigation of their antihypertensive activity.

Chemistry. The desired congeners of **1** were synthesized by two known general methods.[4] Method A involved the acid-catalyzed condensation of a chlorobenzaldehyde with a 4-methyl or dimethyl semicarbazide[5] to yield the semicarbazone. For example, **3** treated with **4** gave **1**. Method B involved the reaction of an amine (bp

method A



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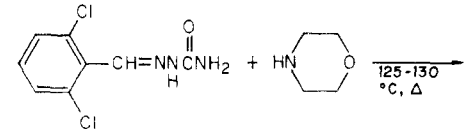
≥120 °C) with 2,6-dichlorobenzaldehyde semicarbazone[6] at 125–130 °C to yield the desired 4-substituted semicarbazone. For example, **5** treated with excess morpholine gave **6**. Table I lists the 12 synthesized semicarbazones and their method of preparation.

method B



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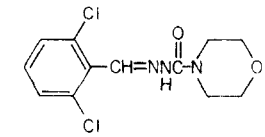

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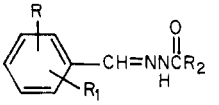
Biological Methods and Results. The semicarbazones were administered orally in two doses of 100 mg/kg each to spontaneously hypertensive rats (SHR). The second dose was given 24 h after the first dose. The mean arterial blood pressure (MABP) was measured at 4 h after the second dosing. All determinations were made in restrained, conscious animals by direct femoral puncture.[2]

Table I. Semicarbazones of *o*- and *p*-Chloro- and 2,6-Dichlorobenzaldehyde



Compd	R	R_1	R_2	Formula	Mp, °C	Method	Yield, %	Analyses
1	2-Cl	6-Cl	$N(CH_3)_2$	$C_{10}H_{11}Cl_2N_3O$	187–188	A	70	C, H, Cl, N
5[a]	2-Cl	6-Cl	NH_2	$C_8H_7Cl_2N_3O$	219.5–221	A	73	C, H, Cl, N
6	2-Cl	6-Cl	c-$N(CH_2CH_2)O$	$C_{12}H_{13}Cl_2N_3O_2$	219.5–220.5	B	6.2	C, H, Cl, N
7	2-Cl	6-Cl	$NHCH_3$	$C_9H_9Cl_2N_3O$	139–140	A	57	C, H, Cl, N
8[b]	2-Cl	6-Cl	$NHCH_2C_6H_5$	$C_{15}H_{13}Cl_2N_3O$	199–200	A	55	C, H, Cl, N
9[c]	2-Cl	6-Cl	NHC_6H_5	$C_{14}H_{11}Cl_2N_3O$	196–197.5	A	74	C, H, Cl, N
10[d]	2-Cl	6-Cl	$NHCH_2C_6H_3$-2,6-F_2	$C_{15}H_{11}Cl_2F_2N_3O$	224–225	B	1.0	C, H, Cl, F, N
11	2-Cl	6-Cl	c-$N(CH_2CH_2)_2N$-CH_3	$C_{13}H_{12}Cl_2N_4O$	223–224.5	B	20	C, H, Cl, N
12	2-Cl	6-Cl	$N(CH_2CH_2CH_3)_2$	$C_{14}H_{19}Cl_2N_4O$	162.5–163.5	B	15	C, H, Cl, N
13	2-Cl	6-Cl	$NCH_3(C_6H_{11})$	$C_{15}H_{19}Cl_2N_3O$	221–223	B	24	C, H, Cl, N
14	2-Cl	H	$N(CH_3)_2$	$C_{10}H_{12}ClN_3O$	198–200	A	25	C, H, Cl, N
15	4-Cl	H	$N(CH_3)_2$	$C_{10}H_{12}ClN_3O$	161.8–162.2	A	74	C, H, Cl, N

[a] Reference 5. [b] 4-Benzyl semicarbazide was prepared according to ref 8. [c] 4-Phenyl semicarbazide was prepared according to "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 450. [d] 2,6-Difluorobenzylamine was prepared from the corresponding nitrile by low-pressure hydrogenation over 5% Pd/C in the presence of excess HCl.

Table II. Antihypertensive Semicarbazones of Chloro- and Dichlorobenzaldehyde

Compd	*n*	MABP,[a] mmHg	Dose, mg/kg	% decrease in MABP from control value
1	1	Toxic	100	
1	4	89 ± 4.8	10	46
1	1	114	5	31
6	2	145 ± 10.0	100	13
7	2	113 ± 12.5	100	32
15	2	140 ± 10.0	100	16
Control	60	166 ± 3		
Guanabenz	20	123 ± 4.0	25	26
Clonidine	6	96 ± 3.0	0.5	43

[a] Mean arterial blood pressure ± standard error of mean.

The antihypertensive activity of the active semicarbazones in this series is shown in Table II.

When 1 was administered in gelatin capsules to dogs, no effect on blood pressure was observed after a single dose of 5 or 10 mg/kg. Ataxia was recorded at 10 mg/kg, which prevented testing at higher doses.

Semicarbazones **1**, **6**, **7**, and **15** decreased the MABP of SHR from 16 to 46%. Some interesting structure–activity relationships were observed. Unsubstituted semicarbazone **5** was inactive at 100 mg/kg. However, **1**, the dimethyl congener of **5**, lowered the MABP by 46% at 10 mg/kg and by 31% at 5 mg/kg. Compound **7**, the monomethyl congener of **5**, was as active as **1** only at 20 times the dose level. Interestingly, **14**, the *o*-chloro congener of **1**, was inactive whereas the *p*-chloro congener **15** decreased the MABP by 16%. Semicarbazone **6** was the only active congener which did not possess a nitrogen methyl group.

In conclusion, semicarbazone **1** is a potent antihypertensive drug in the SHR model. On a weight basis, **1** is more potent than guanabenz but less potent than clonidine. Semicarbazone **1** differs structurally from clonidine or guanabenz by possessing a nonbasic side chain attached to a 2,6-dichlorobenzene moiety.

The lack of hypotensive activity of **1** in the normotensive dog precludes further development of **1** as an antihypertensive drug.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by the Microanalytical Group of Lederle Laboratories.[7] All chemicals were of reagent grade.

2,6-Dichlorobenzaldehyde 4,4-Dimethylsemicarbazone (1) (Method A). A solution of 9.33 g (0.053 mol) of 2,6-dichlorobenzaldehyde and 5.5 g of 4,4-dimethyl semicarbazide[5] in 100 mL of absolute ethanol and 1.0 mL of glacial acetic acid was heated at reflux for 6.0 h and then cooled to room temperature. The solvent was removed under aspirator pressure and the residual solid crystallized from 250 mL of ethyl acetate. The colorless crystals were isolated by filtration, washed with ice-cold ethyl acetate, and then dried to yield 9.7 g (70%) of colorless crystals, mp 187–188 °C. Anal. ($C_{10}H_{11}Cl_2N_3O$) C, H, Cl, N.

4-Morpholinecarboxylic Acid 2,6-Dichlorobenzylidenehydrazide (6) (Method B). A solution of 9.0 g (0.039 mol) of **5** in 50 mL of morpholine was heated at 125–130 °C for 30.0 h and then cooled. After removal of excess amine under aspirator pressure, the residual solid was twice crystallized (charcoal) from ethyl acetate to yield 0.73 g (6.2%) of colorless crystals, mp 219.5–220.5 °C. Anal. ($C_{12}H_{13}Cl_2N_3O_2$) C, H, Cl, N.

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