pare the cytotoxicity of 3 with BrdUrd and experiments to demonstrate the incorporation of an isotopically labeled compound 3 into the DNA of hamster cells are in progress. The effect of the hypothetical methylphosphonate diester bond (in DNA) upon the biosynthesis, enzymatic repair, and physical properties of DNA remains to be investigated.

Acknowledgments. The authors are indebted to Mrs. Emily T. Best for excellent technical assistance. This investigation was supported in part by Public Health Service General Research Support to the Memorial Research Center (Grant No. FR-5541).

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Amidines.† 3.[1] Thioureas Possessing Antihypertensive Activity

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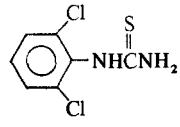
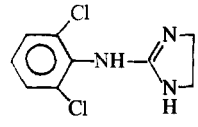
A series of 2- and 2,6-substituted phenylthioureas were found to have potent antihypertensive activity; the 2,6-dimethyl compound was particularly effective and had an unusually high ratio of efficacy to lethality (>1000). These compounds are orally active in the rat but not in the dog. Several potential metabolites were synthesized, one of which was active in both species.

In the course of an investigation into the potential antihypertensive activity of amidines,‡ we observed that the thiourea I was as potent (approx 1 mg/kg) in producing prolonged blood pressure depression as the clinically effective hypotensive agent 2-(2,6-dichloroanilino)-2-imidazoline§ (II) when administered orally to metacorticoid rats. Although II is reported to have a low incidence of side effects in man,[3a,b] in rats it has an efficacy:lethality (E:L)# of only 10, whereas I shows an E:L ratio of 50-200.

Further testing showed that I administered orally did not produce blood pressure lowering in either normotensive or neurogenic hypertensive dogs. The biological data (see Pharmacology Section) suggested that inactivity in the dog might be due to the failure of these thioureas to be converted to an active metabolite, rather than due to metabolic inactivation. The possibility of a species-specific metabolic activation and the unexpectedly large potency and high E:L ratio of I prompted the synthesis of related thioureas and several possible metabolites, and the investigation of their antihypertensive activity.



I



II

Chemistry. Highly hindered and weakly basic amines react poorly with alkali metal thiocyanates under the usual conditions for thiourea synthesis. It had previously been observed that the use of trifluoroacetic acid with NaOCN led to carbamylation in systems which were otherwise refractory.[4,5] When trifluoroacetic acid was used in the reaction of aryl amines with NaSCN, excellent yields of the monosubstituted thioureas were obtained. The 1,3-disubstituted thioureas were prepared by reaction of 2,6-dichlorophenyl isothiocyanate[6] with the appropriate amines.

The acetylthiourea **15** was more conveniently obtained

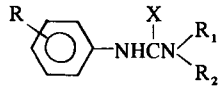
†We include in the term "amidines," those compounds containing the moiety N–C=X (X = C, N, O, or S).

‡A preliminary communication concerning active amidines is given by Loev, *et al.*[2]

§Catapres®.

#The term efficacy:lethality (E:L) is used in this paper to mean the ratio of the minimal oral dose producing lethality in the normal rat to that producing significant blood pressure depression in the metacorticoid hypertensive rat.

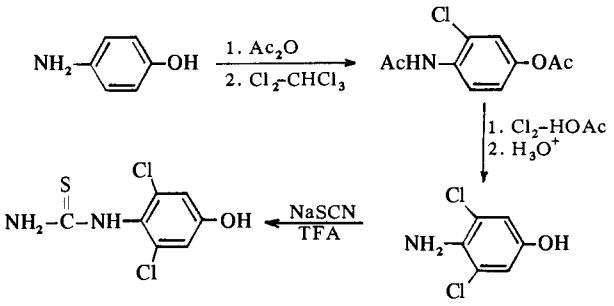
Table I. Chemical and Pharmacological Properties



Compd	R	R_1	R_2	X	Antihypertensive activity (po) Rat[a]	Dog[b]	E:L (rat)	Yield,[c] %	Mp, °C	Method	Formula	Analyses[d]
1 (I)	2,6-Cl_2	H	H	S	++++	NSA	50–200	38	157–159[e]	A	$C_7H_6Cl_2N_2S$	C, H, N
2	2,6-Me_2	H	H	S	++++	NSA	>1000<2000	71	205–207[f]	A	$C_9H_{12}N_2S$	C,[g] H, N
3	2,6-$(MeO)_2$	H	H	S	++++	NSA	>200<2000	47	188–190[h]	A	$C_9H_{12}N_2O_2S$	C, H, N
4	2,4,6-Cl_3	H	H	S		NSA		15	215–216	A	$C_7H_5Cl_3N_2S$	C, H, N, Cl
5	2,6-Cl_2-4-OH	H	H	S	NSA	++		45	202–204	A	$C_7H_6Cl_2N_2OS \cdot H_2O$	C, H, N, Cl
6	2-Me	H	H	S	++++	NSA	>200<2000	71	161–162[i]	A		
7	H	H	H	S	NSA		*j*		153–155[k]	*k*		
8	2,6-Cl_2	Me	H	S	+	NSA	>2.5	52	180 dec	B	$C_8H_8Cl_2N_2S$	C, H, N, Cl, S
9	2,6-Cl_2	Et	H	S	+	NSA	>2.5	57	178–179	B	$C_9H_{10}Cl_2N_2S$	C, H, N, Cl, S
10	2,6-Cl_2	Me	Me	S	+	NSA	>2.5	37	180–182	B	$C_9H_{10}Cl_2N_2S$	C, H, N, Cl, S
11	2-Me	Me	Me	S	±	++++	>1	39	136–139[l]	*l*		
12	2,6-Cl_2	H		SMe	+	+	>1	80	131–132	*m*	$C_8H_8Cl_2N_2S$	C, H, N, Cl
13	2,6-Me_2	Me		SMe	+++	NSA	>20<40	79	50–51	*n*	$C_{11}H_{16}N_2S$	C, H, N
14	[2,3]Benzo	H	H	S	NSA	NSA	*o*		193–195[p]	*p*		
15	2,6-Cl_2	Ac	H	S	NSA		*q*	49	218–219	*r*	$C_9H_8Cl_2N_2OS$	C, H, N, Cl, S
16	2,6-Cl_2	H	H	O	±	NSA	>2.5	55	225–227	*r*	$C_7H_6Cl_2N_2O$	C,[s] H, N
17	2,6-Me_2	H	H	SO_2	+++[±]	++	80	31	135 dec[t]	*t*	$C_9H_{12}N_2O_2S$	C, H, N
18	2,6-Me_2	H	H	SO_3	NSA			70	220 dec[u]	*u*	$C_9H_{12}N_2O_3S$	C, H, N
19	*z*				+	NSA	>1	68	187–188[v]	*v*		
20	*aa*				NSA	NSA			39–41	*w*		
21 (II)	*bb*				++++	++++	10		137–139[x]	*x*	$C_9H_9Cl_2N_3$	C, H, N, Cl[y]

[a]Metacorticoid hypertensive rat;[17] ++++, active at 1 mg/kg or less; +++, active at >1–5 mg/kg; +, active at >20<80 mg/kg; ±, barely active at 80 mg/kg; NSA, no significant activity at 80 mg/kg. [b]Neurogenic hypertensive dog;[18] ++++, active at 1 mg/kg or less; ++, active at 10 mg/kg; +, active at 20 mg/kg; NSA, no significant activity at 20 mg/kg. [c]Based on immediate precursor. [d]See footnote (##) to Experimental Section. [e]Lit. mp 156–158°.[6] [f]Dyson, *et al.*,[21] report mp 190°. [g]C: calcd, 59.96; found, 59.30. [h]Dyson and George[22] report mp 164.5°. [i]Hunter and Styles[23] report mp 160°. [j]Lethal at 5 mg/kg. [k]Eastman Organic Chemicals. [l]Lit. mp 138–139°.[16] [m]Zelle, *et al.*,[24] report HI salt. [n]Schwartzman and Corson[25] report HI salt. [o]Lethal at 0.5 mg/kg. [p]Neville and McGee[26] report mp 198°. [q]Lethal at 200 mg/kg. [r]See Experimental Section. [s]C: calcd, 41.00; found, 41.48. [t]Lit. mp 137–140° dec.[10] [u]Lit. mp 214–217° dec.[11] [v]Tung, *et al.*,[27] report mp 189–190°. [w]Aldrich Organic Chemicals. [x]Zelle, *et al.*,[24] report mp 130°. [y]Cl: calcd, 30.82; found, 30.01. [z]*S*-(α-Naphthylethyl)isothiourea. [aa]2,6-Dichloroaniline. [bb]2-(2,6-Dichloroanilino)-2-imidazoline.

Scheme I



by reaction of 2,6-dichloroaniline with acetyl isothiocyanate than by acetylation of the thiourea.

We considered sulfur oxidation products as potential metabolites, by analogy[7,8] with identified metabolites of certain thionamides.** The syntheses of the sulfur monoxide, dioxide, and trioxide derivatives of a few highly hindered thioureas have been described by Walters.[9-11] We prepared the dioxide and trioxide of 2,6-dimethylphenylthiourea, but were unable to prepare the monoxide of this thiourea nor any of these oxidation products from the 2,6-dichloro analog.

Another potential metabolite, 2,6-dichloro-4-hydroxyphenylthiourea, was prepared as shown in Scheme I.

The compounds prepared in the course of this study are listed in Table I.

Pharmacology. In 1950, Dawes and Fastier[12] observed that certain *iso*thioureas produced a reflex fall in blood pressure after iv administration to the *cat.* This activity was accompanied by respiratory distress and other toxic symptoms; the hypotensive activity was attributed to vagally mediated reflexes. The most potent compound reported (**19**, Table I) was found in our laboratories to produce marked toxic symptoms but *no* blood pressure depression in the metacorticoid hypertensive *rat.* Conversely, I produced a significant pressure drop without toxic symptoms when administered iv to the cat.

Foye and Anderson[13] reported the antihypertensive action of 1-methyl-3-phenethylthiourea in the dog and rat, but on retesting,†† these compounds showed no significant activity.

It is interesting to note that certain arylthioureas have potent and selective acute toxicities for rats;[14,15] thus α-naphthylthiourea (**14**) is a commercially used rodenticide.‡‡

A recent patent[16] describes three di- and trisubstituted phenylthioureas related to I as hypotensive agents active in the normotensive dog. The most potent compound reported (**11**) was prepared and found to be essentially devoid of antihypertensive activity in the metacorticoid hypertensive rat at doses 80 times those at which I is active. It was, however, orally active in the neurogenic dog.

In metacorticoid hypertensive rats,[17] a statistically significant decrease in blood pressure was observed 5, 24, 39, and 48 hr after a single dose of I (1 mg/kg po); it was not tested in normotensive rats. I produced prolonged (>90 min) blood pressure depression after iv administration of 5 mg/kg to the metacorticoid hypertensive rat; it was also active at 1 mg/kg iv in the cat. However, it was inactive at doses up to 5 mg/kg po in the normotensive dog, and up to 20 mg/kg po in the neurogenic hypertensive dog.[18]

When administered to metacorticoid rats pretreated with SK&F 525,[19] the activity of I was decreased (requiring 10 mg/kg for significant activity) and toxicity was increased (the E:L decreased to **1**). The mode of action in the rat, and reasons for inactivity in the dog have not yet been determined.

The testing results of the other thioureas and potential metabolites are summarized in Table I.

Structure–Activity Discussion. Examination of test results in the rat (see Table I) suggests that substantial antihypertensive activity requires a monosubstituted thiourea containing an ortho-substituted aromatic moiety. Only minimal activity is seen in thioureas containing additional substitution at N-3. However, where both nitrogen and sulfur are alkylated, as in **13**, significant activity is also observed.

The most potent thioureas are seen to be the 2,6-disubstituted methyl- (**2**), methoxy- (**3**), and chloro- (**1**) -phenylthioureas and the 2-monomethylphenylthiourea (**6**). The 2,6-dimethyl-substituted thioureas exhibit substantially increased potency as well as E:L when compared to all other compounds tested in the metacorticoid hypertensive rats. In the dog the relationship between structure and activity is not clear-cut, and there is no obvious correlation in antihypertensive activities between the rat and the dog; a number of compounds are active in the rat, but not in the dog, and *vice versa.*

Of the potential metabolites prepared, only **5**, the para-hydroxylation product, and **17**, the thiourea *S*-dioxide, exhibited significant activity in the neurogenic hypertensive dog; the latter compound was also very active in the rat. Compound **5** was subsequently identified as one of the metabolites in the rat and the dog.§§

Experimental Section##

General Methods for Preparation of Thioureas. A. A suspension of NaSCN (8.2 g, 0.10 mole) and the appropriate aromatic amine (0.05 mole) in anhyd PhH or $PhCH_3$ (30 ml) was treated at 45–50° dropwise with a soln of trifluoroacetic acid (8.0 g, 0.07 mole) in PhH or $PhCH_3$ (8 ml) over 2 hr. The reaction mixt was allowed to stir at 25° for 1 hr and if incomplete was refluxed an additional 1–3 hr. The suspension was cooled, filtered, washed with PhH and then H_2O, and recrystd.

B. The appropriate gaseous amine (0.12 mole) was bubbled through a stirred soln of 2,6-dichlorophenyl isothiocyanate (13.0 g, 0.064 mole) in $CHCl_3$ (100 ml) at 0° for 1 hr. The solvent was evapd, and the residue was triturated with ligroin and recrystd.

1-Acetyl-3-(2,6-dichlorophenyl)thiourea (15). A solution of **20** (15 g, 0.93 mole) in dry PhH (25 ml) was added to a refluxing soln of acetyl isothiocyanate[20] (0.15 mole) in dry PhH (150 ml). After 15 min refluxing, the suspension was filtered, washed with ligroin, and recrystd from THF–H_2O.

1-(2,6-Dichlorophenyl)urea (16). A stirred suspension of **20** (10 g, 0.06 mole) and NaOCN (8.1 g, 0.12 mole) in PhH (25 ml) at 25° was treated dropwise with a soln of trifluoroacetic acid (8.6 g, 0.075 mole) in dry PhH (20 ml). After 60 hr, the mixt was filtered, and the solid was washed with Et_2O and then H_2O and recrystd from EtOH.

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**Ethionamide.

††The compound is inactive in the metacorticoid hypertensive rat (up to 80 mg/kg po) and in the dog (at 10 mg/kg po).

‡‡ANTU.

§§B. Hwang and J. Weinstock, unpublished work, Smith Kline and French Laboratories, 1969–1970.

##Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Microanalyses were performed by the Analytical and Physical Chemistry Section of Smith Kline and French Laboratories. Where analyses are indicated only by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values.

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1-Substituted-3-aminoalkoxy-4,5-cycloalkylpyrazoles with Central Nervous System Depressant Activity

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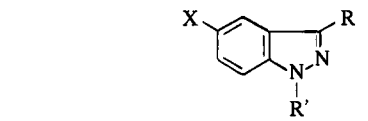
Various 1-substituted-3-aminoalkoxy-4,5-cycloalkylpyrazoles were prepared by alkylation of the 1-substituted-3-hydroxy-4,5-cycloalkylpyrazoles (**5**). The latter compounds were accessible by recently revealed procedures. The title compounds were prepared because of their relationship to Benzydamine (**1**), which has interesting antiinflammatory properties. The 1-aryl compounds, however, showed CNS depressant profiles, while the 1-benzyl compounds more analogous to **1** were devoid of both CNS and antiinflammatory activity. Thus, of the 1-aryl compounds, **8** and **14** showed marked depressant effects in the jiggle cage test at doses well separated from those that caused neurological deficit.

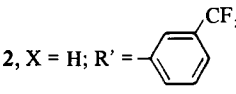
There is still clinical interest in the antiinflammatory properties of Benzydamine (**1**), 1-benzyl-3-[3-(dimethylamino)-propoxy]indazole, particularly as it is exceptionally well tolerated even in patients who already have a history of serious gastric disorders.[1] There is considerable interest generally in indazoles as potential antiinflammatory drugs, *e.g.*, **2**,[2] **3**,[3] **4**.[4] Therefore, as the related tetrahydroindazoles, *i.e.*, 1-substituted-3-alkoxytetrahydroindazoles, were undescribed, we chose to investigate them in the hope of encountering a new type of antiinflammatory compound. A recent account[5] of work on the tetrahydrocyclopentapyrazole system was based on somewhat similar reasoning, and this effort was, like ours, unsuccessful in the search for a novel antiinflammatory compound. We did, however, encounter quite a good level of selective CNS depression in the compounds which we now report.

Chemistry. Prior to our work,[6] a specific synthesis of 1-aryl(or alkyl)-3-hydroxy tetrahydroindazoles (**5**, $n = 2$) had not been described. However, an alternate route to these long-neglected isomers **5** of the well-investigated 2-aryl(or alkyl)pyrazolones **6** has recently been published.[7,8] All the 1-substituted-3-hydroxy-4,5-cycloalkylpyrazoles (**5**, $n = 1$, 2, and 3; R = aryl, benzyl) used in this investigation were generally prepared as described previously,[6] *i.e.*, by cyclization of appropriate *N*-substituted-2-chlorocycloalkene-1-carboxylic acid hydrazides (see Table I). O-Alkylation of **5b** ($n = 2$; R = $C_6H_5CH_2$) with 3-chloro-*N*,*N*-dimethylpropylamine to prepare the tetrahydro analog **18** of Benzydamine (**1**) proceeded well and without evidence of any competitive N-alkylation (see Table II).

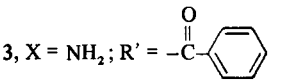
Pharmacology. The new compound **18** was devoid of



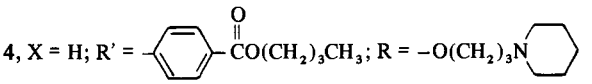
1, X = H; R' = $-CH_2-C_6H_4-$; R = $-O(CH_2)_3N(CH_3)_2$



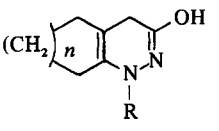
2, X = H; R' = 3-trifluoromethylphenyl; R = OH



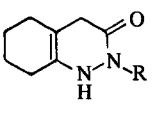
3, X = NH_2; R' = $-CO-C_6H_5$; R = H



4, X = H; R' = 4-$CO(CH_2)_3CH_3$-phenyl; R = $-O(CH_2)_3N$(piperidine)



5



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significant antiinflammatory properties (*e.g.*, in the carrageenin paw test) and was inactive in our preliminary CNS screen. However, in order to explore the structure-activity possibilities of this new molecule, the *N*-phenyltetrahydroindazole **5a** was prepared and O-alkylated with 3-chloro-