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Amidines and Related Compounds. 6.[1] Studies on Structure–Activity Relationships of Antihypertensive and Antisecretory Agents Related to Clonidine

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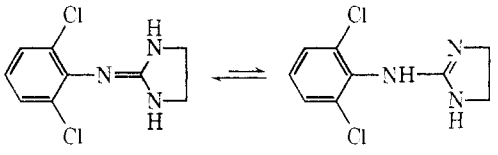
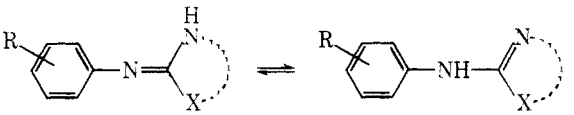
Correlations of antihypertensive and antisecretory activities with various structural modifications of the antihypertensive agent clonidine [2-(2,6-dichlorophenylimino)imidazolidine] are described. Eleven chemical classes of compounds containing an "amidine" moiety were prepared in this study. The antihypertensive activity of these compounds was evaluated in metacorticoid hypertensive rats and unanesthetized neurogenic hypertensive dogs following oral administration. Antisecretory activity was evaluated in fistula rats by measuring pH and volume of gastric secretion. Two compounds, 2-(2,6-dimethylphenylimino)imidazolidine and 2-(2,6-dichlorophenylimino)pyrrolidine, are particularly effective antisecretory agents with minimal antihypertensive activity.

Many cyclic amidines possess interesting biological properties particularly as antihypertensive agents.[2,3] The discovery of clonidine [2-(2,6-dichlorophenylimino)imidazolidine] as a centrally acting antihypertensive agent[4,5] with antisecretory activity[6] (reduction of gastric acidity) prompted us to initiate a broad investigation of structures containing an "amidine" moiety [the term "amidine" is used here to include the system –NHC(X)=N– in which X = C, N, O, or S]. In previous papers we reported the antihypertensive activity of a series of 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolines[7,8] and certain thioureas.[9] We now describe the structure–activity relationships (SAR) of other "amidines" related to clonidine. A particular objective of the present study was to develop selective antisecretory agents having minimal antihypertensive activity.



clonidine

Chemistry. The majority of compounds prepared for this study may be represented by the general structure I in which the dotted line denotes the variations involving either cyclic or open forms, ring size, or unsaturation. These compounds may exist in two tautomeric forms. ^1H and ^{13}C nmr spectral studies on representative examples suggest that except for 2-aminoimidazoles, -oxazoles, and -thiazoles the imino form is the predominant tautomer in cases where potential tautomerism exists.[10] For the convenience of SAR discussion, the compounds are grouped into five general structural types: (1) cyclic guanidines (Table I), (2) cyclic amidines (Table II), (3) 2-aminoimidazoles (Table III), (4) guanidines and amidines (Table IV), and (5) cyclic isoureas and isothioureas (Table V). Each type may be divided into different chemical classes.



I, imino form I, amino form

X = C, N, O, or S
R = H, Cl, CH_3, or CH_3O (mono or disubstituted)

With the exception of **1b**, **1i**, and **1j**, the imidazolidines and tetrahydropyrimidine (**1**, Table I) were prepared by method A. The appropriate *S*-methylphenylisothiuronium iodide was heated with the appropriate diaminoalkane. Treatment of **1a** with acetic anhydride under different conditions gave selectively the mono- or diacetylated products **1i** or **1j**. The structures of **1i** and **1j** are supported by nmr spectral data. The triplets at δ 3.42 and 3.96 in the spectrum of **1i** are due to the nonequivalent C-4 and C-5 protons, respectively. The alternative structure having the acetyl group on the exocyclic nitrogen atom is excluded by the absence of a four-proton singlet. The chemical shifts of the C-4 and the para aromatic protons (δ 6.80 q) also support the imino form.[10] In the spectrum of **1j**, the proton signals of the methyls (δ 2.30, s, 6 H) and the methylenes (δ 3.95, s, 4 H) are consistent with the assignment of the two symmetrical acetyl groups.

The pyrrolidines and piperidines (**2**, Table II) were prepared by method B: treatment of 2-pyrrolidinone or 2-piperidinone with $POCl_3$ followed by the appropriate aniline. Acetylation of **2d** gave **2i**. The position of the acetyl group in **2i** is assigned on the basis of nmr data: the chemical shift of the C-5 protons (δ 3.90 t) is similar to that of **1i** (δ 3.96) and **1j** (δ 3.95).

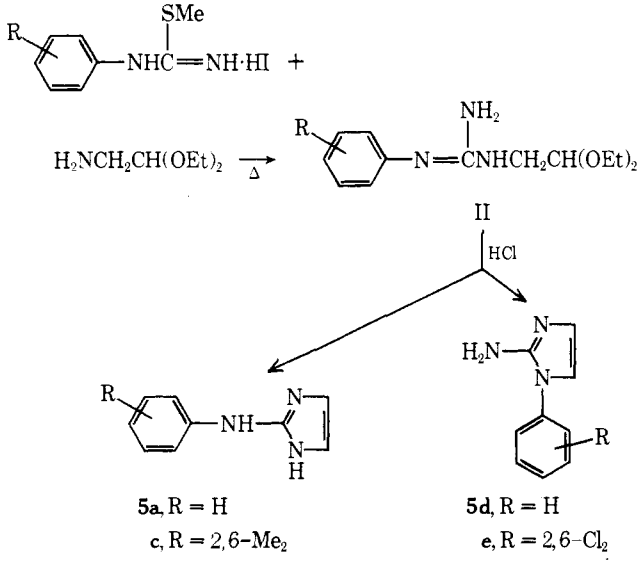
The pyrroline **3** was prepared by treatment of **2d** with MeI. The position of the *N*-methyl group in **3** was deduced from its different physical and spectroscopic properties in comparison with those of **2h** in which the methyl group is on the endocyclic nitrogen atom. In the nmr

spectrum, the C-5 proton signal of 3 (δ 3.76) appears at lower field than that of **2h** (δ 3.43) due to the anisotropic effect of the endocyclic imino bond.

The imidazolines (4) were prepared by method C. The appropriate phenylacetonitrile was heated with ethylenediamine mono-*p*-toluenesulfonate.

With the exception of **5b** the imidazoles (**5**, Table III) were prepared by method D: condensation of the appropriate *S*-methylphenylisothiuronium iodide with aminoacetaldehyde diethyl acetal followed by acid-catalyzed cyclization (Scheme I). It is interesting to note that cyclization of II (where R = H) gave a mixture of two products (**5a, 5d**), but with R being 2,6-Cl_2 or 2,6-Me_2 the reaction apparently led to a single product of one type or the other (*e.g.*, **5c** or **5e**). Compound **5b** was prepared from 2,6-dichlorophenylcyanamide and aminoacetaldehyde diethyl acetal followed by acid-catalyzed cyclization. Although this synthetic route is expected to involve the same guanidine intermediate II as in method D, no detectable amount of **5e** was found in the crude product by tlc analysis. The two types of cyclization products were distinguished by nmr analysis. The C-4 and C-5 imidazole proton signal of one type (**5a–c**) appears as a two-proton singlet whereas that of the other (**5d, 5e**) appears in the expected AB pattern.

Scheme I

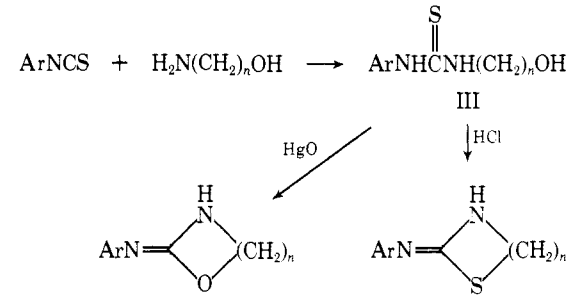


2-(2,6-Dichlorophenylamino)benzimidazole (**6b**) was prepared by condensing 2,6-dichlorophenyl isothiocyanate with *o*-phenylenediamine and cyclodesulfurization of the resulting thiourea **6a** with yellow mercuric oxide. Attempts to prepare **6b** from *o*-phenylenediamine and *S*-methyl-2,6-dichlorophenylisothiuronium iodide gave only intractable material.

The guanidines and amidines (**7, 8**, Table IV) were prepared by one of the following methods: the appropriate urea or amide was treated with $POCl_3$ followed by the appropriate aniline (method E); the appropriate urea was treated with $COCl_2$ followed by the appropriate aniline (method F); the appropriate phenylcyanamide, obtained from the corresponding phenylthiourea and $Pb(OAc)_2$, was treated with the appropriate aniline (method G); the appropriate *S*-methylphenylisothiuronium iodide was treated with the appropriate alkylamine (method H).

The oxa- and thiazolidines and tetrahydrooxazines and -thiazine (**9**, Table V) were prepared by one of the following methods (Scheme II): cyclodesulfurization of the requisite thiourea III with yellow HgO (method I) and

Scheme II



acid-catalyzed cyclodehydration of the appropriate thiourea III (method J).

The thiazole **10b** was obtained by treating 2,6-dimethylphenylthiourea with 1,2-dichloroethyl ethyl ether.

The benzothiazole **11** was prepared by treating phenyl isothiocyanate with 2,6-dimethylaniline and cyclization of the resulting thiourea by sulfuryl chloride.

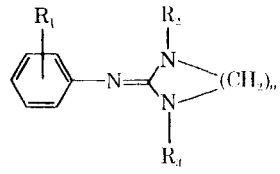
Pharmacological Methods and Results. Antihypertensive activity was evaluated in metacorticoid hypertensive rats[11a] and unanesthetized neurogenic hypertensive dogs[11b] following oral administration. In rats, the mean systolic blood pressures (control) of groups (four each) were determined (tail pulse) on three separate days prior to dosing. The test compound was generally administered to each group for two consecutive days and the systolic blood pressures were determined 5 and 24 hr after each dose. The lowest dose causing a decrease in mean systolic blood pressure which is less than or equal to the lower confidence limit (95%) of the control value in the same group is referred to as the *minimum effective dose* (MED). The statistical method for calculation of the confidence limits is based on a modification of Student's t test.[12]

In other experiments, trained dogs were used. Control values were determined from six systolic and diastolic pressure readings taken over a period of several weeks. The test compound was given by capsule to groups of two or three dogs on two consecutive days. Blood pressures were determined 3 hr after each dose by femoral arterial puncture. Mean arterial blood pressure (MBP) was calculated by adding one-third of the pulse pressure to the diastolic pressure. The lowest dose of a compound for which there is a statistically significant difference ($p \leq 0.05$) between control MBP and postdrug MBP is referred to as the MED.

The antihypertensive test results are summarized in Tables I–V. The MED (as previously defined) or its range is used whenever possible so that a comparison of the relative potencies of the compounds can be made. For inactive compounds the highest dose tested is indicated following NA (not active). In cases where the MED cannot be determined because of insufficient data, the symbols $\geq$ (equal to or greater than) and $\leq$ (equal to or less than) are used to show the probable MED.

The antisecretory activity of the compounds was evaluated in rats with permanent gastric fistulas.[13] A stainless steel cannula was implanted in the gastric rumen several weeks before an animal was used in drug studies. Male Charles River Farms rats fasted for 18 hr were used. The vehicle (control) was administered by gavage to rats with the cannula stoppered. After 45 min the cannula was unstoppered and gastric secretion collected for 2 hr. Then the cannula was restoppered and the test compound administered by gavage. Forty-five numutes later the cannula was unstoppered and a second 2-hr collection was made. Drug-induced changes in pH and volume of the se-

Table I. Cyclic Guanidines —Chemical and Pharmacological Testing Data



1

Compd	n	R_1	R_2	R_3	Antihypertensive act., mg/kg[a] Rat	Antihypertensive act., mg/kg[a] Dog	Antisecretory act., mg/kg[a] pH ~2	Antisecretory act., mg/kg[a] Δ vol ~50%	pK_a	Method[b]	Yield,[c] %	Mp or bp (mm), °C[d] Base	Mp or bp (mm), °C[d] Salt	Crystn solvent Base	Crystn solvent Salt	Formula[e]	Ref[f]
1a	2	2,6-Cl_2	H	H	≤0.1 ≤0.5	≤0.2	0.08	0.08	7.11	A	45	137–139[g]	308–311[g]	C_6H_6–hexane	Et_2O	$C_9H_9Cl_2N_3$	*h*
1b	2	H	H	H	NA 80	NA 20	(>50)	>50	9.30	*i*		136–137[j]		H_2O		$C_9H_{11}N_3$	*h*
1c	2	2-Me	H	H	≤0.1	0.1–0.2	0.4	NA 10	9.83	A	47	136–140	180–182	EtOAc	*t*-BuOH	$C_{11}H_{13}N_3 \cdot HCl$	*l*
1d	2	2,6-Me_2	H	H	>10 ≤40	NA 10	0.4	2	9.40	A	29	156–157[m]		EtOAc		$C_{11}H_{15}N_3$	*h*
1e	2	2,6-$(MeO)_2$	H	H	>20 ≤80	NA 5	50	>50		A	39	145–147	234–237	EtOAc	Et_2O	$C_{11}H_{15}N_3O_2 \cdot HCl$[n]	
1f	2	2,6-Cl_2	Me	H	≤10	2–4	10	2	6.17	A	12	85–88	303–305	2-PrOH–H_2O	2-PrOH–Et_2O	$C_{10}H_{11}Cl_2N_3 \cdot HCl$	*o*
1g	2	H	Me	Me	NA 80	NA 10				A	47	98–100[p] (0.2)				$C_{11}H_{15}N_3$[q]	*r*
1h	2	2,6-Cl_2	Me	Me	NA 40	NA 40	(>50)	50	5.23	A	17	81–83 152–154[p] (0.5)		Hexane–Et_2O		$C_{11}H_{13}Cl_2N_3$	
1i	2	2,6-Cl_2	Ac	H	≤0.5	5–10	10	2			53	165–168		EtOH		$C_{11}H_{11}Cl_2N_3O$	
1j	2	2,6-Cl_2	Ac	Ac	NA 80	NA 15	50	NA 50			47	113–115		EtOH		$C_{13}H_{13}Cl_2N_3O_2$	
1k	3	2-Cl, 6-Me	H	H	≤80	NA 20	50	>50	10.19	A	20	117–118[s]	238–239	CCl_4–hexane	MeOH–Et_2O	$C_{11}H_{14}ClN_3 \cdot HCl$[t]	*h*

[a] See Pharmacological Methods and Results in text. [b] The general synthetic method indicated for the compound is exemplified in the Experimental Section. Experimental procedures for those compounds without indication of synthetic method are described in the Experimental Section. [c] Based on immediate precursor. [d] Unless otherwise noted, the melting points (if known) are consistent with those reported in the literature (see reference in the Table). [e] The formula indicates the form in which the compound was tested. Unless otherwise noted, satisfactory elemental analyses for C, H, and N (within ±0.4% of calculated values) were obtained for the corresponding formula. [f] Literature references to the compounds are given. Because some were published after we had completed our work, the literature methods of preparation of certain compounds may not necessarily be the same as ours. [g] Lit. base mp 130°, HCl salt mp 305°. [h] K. Zeile, K. H. Hauptmann, and H. Stahle, U. S. Patent 3,202,660 (1965). [i] Method of S. R. Aspinall and E. J. Bianco, *J. Amer. Chem. Soc.*, 73, 602 (1951). [j] Lit. mp 122°. [k] W. Lehmann and H. Rinke, German Patent 842,065 (1952). [l] H. Najer, R. Giudicelli, and J. Sette, *Bull. Soc. Chim. Fr.*, 2114 (1961). [m] Lit. mp 143°. [n] C: calcd, 50.10; found, 50.58. [o] K. Zeile, K. H. Hauptmann, and H. Stahle, U. S. Patent 3,236,857 (1966). [p] Boiling point. [q] Lit. base mp 130°, HCl salt mp 305°. [r] Belgium Patent 632,578 (1963). [s] Lit. mp 133–135°. [t] Analyzed as the free base.

cretion were determined by comparing pre- and postdrug collections in the same group of rats.

The antisecretory testing results are summarized in Tables I–V. The potency of a compound is expressed in terms of the dose which elevated gastric pH by about 2 units. In our experience this corresponds to a decrease in titratable acidity of about 50%. For compounds with minimal activity (1–2 pH unit increase), the highest dose tested is shown in parentheses. Inactive compounds are shown with NA (not active) preceding the maximum dose tested. The effect on secretion volume is shown in terms of the lowest dose which produced a decrease of about 50%. Compounds causing a smaller effect are considered inactive (NA). Compounds which *increased* secretion volume are shown with a "+" preceding the smallest dose that produced a 50% change.

Structure-Activity Relationships (SAR). With respect to antihypertensive activity, **1c** is the most potent compound of type 1 (Table I). In this series, it appears that at least one ortho substituent in the phenyl ring is required for activity. However, the influence of the electronic effect of the substituents on activity is not certain. The fact that **1f** and 1i showed good activity whereas 1h and 1j failed to do so suggests that at least one *N*-hydrogen is required for activity. The same correlation was reported in another series of amidines.[7] Ring expansion appears to reduce potency. In the cyclic amidines‡ (2–4, Table II), **2b** is the most potent compound. Surprisingly, the dichloro analog **2d** failed to show activity in either species. Ring expanded modifications, 2l and **2m,** similarly showed poor activity. Many 2-benzylimidazolines (4) had been studied by other workers.[14] Our data show that the dimethyl analog **4e** is one of the most potent compounds tested in both species. The requirement of ortho substituents for activity is also true for aryl-2-aminoimidazoles (**5,** Table III). The dimethyl analog **5c** is the most potent compound in this series. Surprisingly, the 1-substituted imidazole **5e** is active in the dog. The benzimidazole analog **6b** showed poor activity. Particularly in the dog the arylguanidines (**7,** Table IV) generally had poor activity. The dichloro analog **7h** is the most potent compound in this series. In the amidines (**8**), only the dimethyl analog **8b** showed appreciable activity. The cyclic isoureas and isothioureas (**9–11,** Table V) generally demonstrated poor activity. The sulfur analogs are slightly more active than the corresponding oxygen analogs. The dimethyl congener **9g** (Bayer 1470), which has been claimed to possess various pharmacological activities,[15] is the most potent compound in this group.

On the basis of our testing of structurally modified clonidine derivatives, the following generalizations of SAR with respect to antihypertensive activity can be made: (1) replacement of one of the nitrogen atoms by a methylene group (*e.g.*, 2 or 4) gives compounds retaining much of the potency, while compounds with other hetero atoms (O or S) have greatly diminished effectiveness; (2) expanding or opening the imidazolidine ring diminishes potency; (3) aromatization of the imidazoline ring (imidazoles) affords slightly less potent compounds (**5**), but fusion with a benzene ring (**6b**) nearly abolishes activity; (4) ortho substitution in the phenyl ring appears to be an essential structural requirement for activity, but the influence of electronic effects is not clear; (5) although it is not possible to directly correlate activity with pK_a values, compounds with pK_a values significantly higher or lower than clonidine are much less potent or inactive.

Two measurements of antisecretory activity were made: a decrease in acidity (*i.e.*, an increase in pH) of the secretion and a reduction in volume of the secretion. As volume reduction data are often erratic, the following SAR discussion is based on the pH data only. In evaluating the potential of a compound with antisecretory activity as a clinically useful agent, minimal antihypertensive activity is desired. Compounds of interest should have a good separation of antihypertensive from antisecretory activity (AH/AS ratio§). However, due to the differences of conditions (*e.g.*, time of measurement and animal species) under which these data were obtained, only rough estimates of AH/AS ratios are possible.

Although clonidine (**1a**) is the most potent compound of type 1 (Table I), the dimethyl analog **1d** has a better AH/AS ratio. Among type 2 compounds (Table II), **2g** is the most potent, but the dichloro analog **2d** has a better separation ratio. Of all the amidines in this study, 4i is the most potent in decreasing the acidity of secretion. However, it also increases *basal* secretion volume and constricts peripheral blood vessels.& Compound 4e is quite potent but has an unfavorable AH/AS ratio. The most potent imidazole is **5b** (Table III); other members of this series did not show significant activity. The guanidines and amidines (Table IV) and the cyclic isoureas and isothioureas (Table V) have poor activity except for **7e** which is potent and has a favorable AH/AS ratio.

The overall SAR for antisecretory activity are similar to those previously described for antihypertensive activity. Compounds **1d** and **2d** appear to be the most effective antisecretory agents among which **1d** has the additional advantage of reducing secretion volume.

Experimental Section**

Method A. The appropriate arylisothiuronium iodide was heated with the appropriate ethylenediamine (2.2 mol equiv) to a temperature (130–165°) causing evolution of MeSH. After gas evolution ceased (30–120 min), heating was continued for another 30–60 min. The mixture was cooled and the residue dissolved in H_2O. After basifying the solution, it was extacted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried, and evaporated to dryness. The product in the residue was either purified by crystallization or distillation.

For preparation of **1b** and **1e**, the reaction was conducted in refluxing MeOH. The starting isothiuronium salt for 1e was prepared by refluxing the corresponding thiourea[9] with MeI.

Method B. 2-(2,6-Dimethoxyphenylimino)pyrrolidine (2f). To a stirred solution of 2-pyrrolidinone (8.7 g, 0.104 mol) in C_6H_6 (20 ml) was slowly added a solution of $POCl_3$ (8.0 g, 0.052 mol) in C_6H_6 (10 ml), keeping the temperature below 25°. After stirring

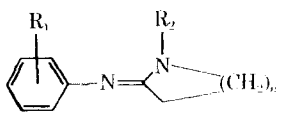
‡Antihypertensive activity of a series of cyclic amidines, including several described in the present paper, has been reported by Hershenson and Rozek (footnote *k* to Table II). These authors found antihypertensive activity for **2d** in the rat at 10 mg/kg po, whereas in our test it failed to show significant activity at 40 mg/kg po. Differences in time of blood pressure measurement (1, 2, 3, 4, and 24 hr in the reported study and 5 and 24 hr in ours) and method of measurement (direct cannulation *vs.* tail cuff) may account for the discrepancy. By the same token, **2k** was active in our experiments but considered as inactive in the previous report.

§The separation ratio AH/AS is the ratio of the antihypertensive minimum effective dose (MED) in the dog and the antisecretory MED which causes an increase of 2 pH units in the gastric secretion. A large ratio reflects a large separation of these two activities in favor of the antisecretory activity.

&Compounds **4g** (xylometazoline, Otrivin) and 4i (oxymetazoline, Afrin) are used as nasal decongestants and 4h (naphazoline, Privine) is used as a topical ocular vasoconstrictor. To our knowledge gastric antisecretory activity has not been previously reported for these compounds.

**Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by the Analytical Department of Smith Kline & French Laboratories. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. Nmr spectra were obtained on either a Varian T-60 or a Jeolco 60-MHz instrument (Me_4Si). pK_a values were provided by Mr. W. Hamill of these laboratories and were determined by potentiometric titration of the compounds in methyl cellosolve-H_2O (4:1) solution on a Sargent titrimeter Model D. The general synthetic methods are exemplified by either specific examples or general procedures.

Table II. Cyclic Amidines—Chemical and Pharmacological Testing Data



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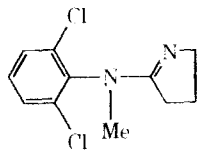

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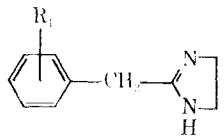


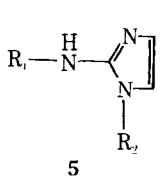
4

Compd	*n*	R_1	R_2	Antihypertensive act., mg/kg[a] Rat	Antihypertensive act., mg/kg[a] Dog	Antisecretory act., mg/kg[a] Δ pH ~2	Antisecretory act., mg/kg[a] Δ vol ~50%	pK_a	Method[b]	Yield,[c] %	Mp or bp (mm), C[d] Base	Mp or bp (mm), C[d] Salt	Crystn solvent Base	Crystn solvent Salt	Formula[e]	Ref[f]
2a	2	H	H	≤80	NA 20	(~50)	50	8.65	B	30	114–115	217–218	C_6H_6, ligroine	Et_2O	$C_{10}H_{12}N_2 \cdot HCl$[g]	*h*
2b	2	2-Cl	H	≤1	1–2	10	10	7.38	B	50	121–123	217–219	EtOAc	2-PrOH–Et_2O	$C_{10}H_{11}ClN_2 \cdot HCl$	*i*
2c	2	2-Me	H	≤1	2.5	10	10	8.86	B		125–135[h] (0.1)	163–164	EtOH–Et_2O		$C_{11}H_{14}N_2 \cdot HCl$	*i*, *k*
2d	2	2,6-Cl_2	H	NA 40	NA 8	2	NA 50	5.88	B	60	124–126 150–160[h] (0.25)		Cyclohexane		$C_{10}H_{10}Cl_2N_2$	*i*, *k*
2e	2	2,6-Me_2	H	≤10	2.5–5	10	10	9.02	B		122–126[h] (0.1)	188–189		EtOH–Et_2O	$C_{12}H_{16}N_2 \cdot HCl$	*i*, *k*
2f	2	2,6-$(MeO)_2$	H	~20–80	5–10	50	NA 50	9.66	B	36	114–115	203–204	EtOAc–hexane	EtOH–Et_2O	$C_{12}H_{16}N_2O_2 \cdot HCl$	
2g	2	2-Cl, 6-Me	H	~0.1–0.5	2–4	0.4	NA 2	7.50	B	30	137–140[h] (0.025)	221–222		EtOH–Et_2O	$C_{11}H_{13}ClN_2 \cdot HCl$	*i*
2h	2	2,6-Cl_2	Me	~40	NA 20	50	50	5.13	B	12		228–230		Me_2CO–Et_2O	$C_{11}H_{12}Cl_2N_2 \cdot HCl$	*i*
2i	2	2,6-Cl_2	Ac	NA 80	NA 8	50	NA 50			90	50–51				$C_{12}H_{12}Cl_2N_2O$	
2j	2	2,6-Me_2	Me	≤80	~5	(~30)	NA 30	7.9	B	26	95–135[h] (1.5)	187–190		2-PrOH MeOH	$C_{13}H_{16}N_2$·fumarate[i]	*i*
2k	2	3,4-Me_2	H	10–20	~5	10	NA 30		B	12	154–156	222–223	2-PrOH	EtOH–Et_2O	$C_{12}H_{16}N_2 \cdot HCl$	*i*
2l	3	2,6-Cl_2	H	~80	NA 10	30	NA 30		B	50	138–140	287–289		2-PrOH–Et_2O	$C_{11}H_{12}Cl_2N_2 \cdot HCl$[j]	*i*, *k*
2m	3	2,6-Me_2	H	~80	~10	NA 10	NA 10	9.38	B	26	~60, 115–128[h] (0.1)	190–192	H_2O	2-PrOH–Et_2O	$C_{13}H_{18}N_2 \cdot HCl$	*i*
3				40–80	NA 7.5	NA 2	NA 2	8.00		91		206–208		Me_2CO–ligroine	$C_{11}H_{12}Cl_2N_2 \cdot HCl$	
4a		H		NA 40		NA 100	NA 100								$C_{10}H_{12}N_2$[k]	*m*
4b		2-Cl		NA 10		NA 50	NA 50	9.35							$C_{10}H_{11}ClN_2 \cdot HCl$[l]	*n*
4c		2-Me				50	30	9.65	C	55	88–91	211–213	C_6H_6, hexane	EtOH	$C_{11}H_{14}N_2 \cdot HCl$[l]	*p*
4d		2,6-Cl_2		~40	~5	10	10	8.88	C	48	185–186		$CHCl_3$, hexane		$C_{10}H_{10}Cl_2N_2$[l]	*n*
4e		2,6-Me_2		0.5–1	~0.05	0.4	10	9.47	C	43	152–159	253–255		2-PrOH	$C_{12}H_{16}N_2 \cdot HCl$	
4f		2,4,6-Me_3				10	NA 10	9.78	C	44	154–156	273–276	C_6H_6	EtOH	$C_{13}H_{18}N_2 \cdot HCl$[m]	

4g	2,6-Me_2, 4-*t*-Bu	≤5	*r*	2	NA 2	*l*	$C_{16}H_{24}N_2 \cdot HCl$[g]	*s*
4h	*l*	≤10		2	+0.4	*l*	$C_{14}H_{14}N_2$[g]	*m*
4i	2,6-Me_2, 3-OH, 4-*t*-Bu			0.08	+0.016	*u*	$C_{16}H_{24}N_2O \cdot HCl$[g]	*v*

[a-l]See corresponding footnotes to Table I. [g]No analyses. [h]H. Bredereck and K. Bredereck, *Chem. Ber.*, **94**, 2278 (1961). [i]H. Wollweber, R. Hiltmann, and K. Stoepel, U. S. Patent 3,563,994 (1971). [j]Boiling point. [k]F. M. Hershenson and L. F. Rozek, *J. Med. Chem.*, **14**, 907 (1971). [l]Supplied by Ciba Corp. [m]A. Sonn, U. S. Patent 2,161,938 (1939). [n]Supplied by Sahyun Laboratories. [o]J. A. Faust, L. S. Yee, and M. Sahyun, *J. Org. Chem.*, **26**, 4044 (1961). [p]C. Van der Stelt, A. B. H. Funke, H. M. Terstuger, and W. Th. Nauta, *Arzneim.-Forsch.*, **15**, 1251 (1965). [q]K. Zeile and H. Stahle, U. S. Patent 3,300,511 (1967). [r]Increase in MBP at 5 mg/kg dose. [s]A. Huene, U. S. Patent 2,868,802 (1959). [t]2-(α-Naphthylmethyl)-2-imidazoline. [u]Supplied by Schering Corp. [v]W. Fruhstorfer and H. Mueller-Calyan, German Patent 1,117,588 (1961).

Table III. 2-Aminoimidazoles—Chemical and Pharmacological Testing Data



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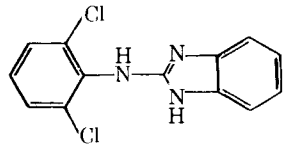
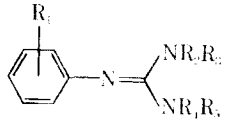


6b

Compd	R_1	R_2	Antihypertensive act., mg/kg[a] Rat	Antihypertensive act., mg/kg[a] Dog	Antisecretory act., mg/kg[a] + pH ~2	Antisecretory act., mg/kg[a] Δ vol ~50	pK_a	Method[b]	Yield,[c] %	Mp, °C[d] Base	Mp, °C[d] Salt	Crystn solvent Base	Crystn solvent Salt	Formula[e]	Ref[f]
5a	C_6H_5	H	≥80	NA 40	(>50)	NA 50	6.83	D	18	119–120	164–165	$CHCl_3$–hexane	MeOH	$C_9H_9N_3 \cdot C_6H_{13}NO_3S$[g]	
5b	2,6-$Cl_2C_6H_3$	H	>1 < 20	NA 4	2	NA 50		*h*		233–235[h]	279–281[h]	$CHCl_3$	2-PrOH	$C_9H_7Cl_2N_3 \cdot HCl$	*i*
5c	2,6-$Me_2C_6H_3$	H	5–20	≤1	10	10	7.31	D	20	236–238		$CHCl_3$–hexane		$C_{11}H_{13}N_3$	
5d	H	C_6H_5	NA 80	NA 20	50	NA 50		D	30	124–125[j]		C_6H_6–cyclohexane		$C_9H_9N_3$	*i*, *k*
5e	H	2,6-$Cl_2C_6H_3$	≥80	5–10	(>50)	NA 50	6.42	D	31	215–217		$CHCl_3$–hexane		$C_9H_7Cl_2N_3$	
6a	*l*		NA 80						90	189–192		EtOAc		$C_{13}H_{11}Cl_2N_2S$	
6b			≥40		NA 50	NA 50	4.84		76	265–267		MeCN		$C_{13}H_9Cl_2N_3$	

[a-l]See corresponding footnotes to Table I. [g]Cyclohexylsulfamate. [h]Lit. base mp 225–228°, salt mp 273–274°. [i]Belgium Patent 693079 (1967). [j]Lit. mp 117–121°. [k]B. A. Tertov and V. V. Burykin, *Khim. Geterotsikl. Soedin.*, 1, 180 (1969). [l]1-(2-Aminophenyl)-3-(2,6-dichlorophenyl)-2-thiourea.

Table IV. Guanidines and Amidines—Chemical and Pharmacological Testing Data



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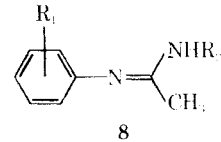
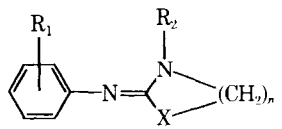


8

Compd	R_1	R_2	R_3	R_4	R_5	Antihypertensive act., mg/kg[a] Rat	Dog	Antisecretory act., mg/kg[a] pH -2	Δ vol -50%	pK_a	Method[b]	Yield,[c] %	Mp or bp (mm), °C[d] Base	Salt	Crystn solvent Base	Salt	Formula[e]	Ref[f]
7a	H	Me	H	Me	H	>80	NA 20	NA 50	NA 50		E	14	115–125	187–190	$CHCl_3$–hexane	EtOH	$C_9H_{13}N_3 \cdot C_4H_4O_4$[g]	*h*
7b	H	Me	Me	Me	Me	NA 80	NA 40	(>30)	+30		F	42	105[i] (0.7)				$C_{11}H_{17}N_3$[j]	*h*
7c	2-Cl	Me	H	Me	H	>80	NA 20	NA 50	NA 50	9.26	E	28	143–145		$CHCl_3$		$C_9H_{12}ClN_3$	
7d	2,6-Cl_2	H	H	H	H	>10 < 80	NA 20	50	10	8.39	G	85		243–244		2-PrOH	$C_7H_7Cl_2N_3 \cdot HCl$	*h*
7e	2,6-Cl_2	Me	H	H	H	>80	NA 10	>2	10		H	14	148–149	230–235[l]	$CHCl_3$		$C_8H_9Cl_2N_3$	*h*
7f	3,4-Cl_2	Me	H	H	H			50	+30		G	42		215–217		EtOH–Et_2O	$C_8H_9Cl_2N_3 \cdot HCl$[m]	*n*
7g	2,6-Cl_2	Me	Me	H	H	>40	NA 10	NA 2	2	7.73	H	70	78–80		Cyclohexane		$C_9H_{11}Cl_2N_3$	
7h	2,6-Cl_2	Me	H	Me	H	>20	>5	50	NA 50	8.14	E	16	113–114	148–151[l]	C_6H_6		$C_9H_{11}Cl_2N_3$	*n*
7i	2,6-Me_2	Me	H	H	H			10	NA 50	10.78	H	31		168–169		2-PrOH–Pr_2O	$C_{10}H_{15}N_3 \cdot HCl$	
7j	2,6-Me_2	Me	H	Me	H	NA 80	NA 20	NA 50	NA 50		E	50	105–107	240–242	C_6H_6	$CHCl_3$–hexane	$C_{11}H_{17}N_3 \cdot HCl$	
7k	2,6-Cl_2	Me	Me	Me	H	>80	>10 < 20	30	NA 30		F	53	102–105	185–188	Cyclohexane	2-PrOH	$C_{10}H_{12}Cl_2N_2 \cdot C_4H_4O_4$[k]	
7l[o]	2,6-Cl_2	Me	Me	Me	Me						F		78–80		Hexane		$C_{11}H_{14}Cl_2N_2$	
7m[p]	2,6-Me_2	2,6-Me_2-C_6H_3	H	H	H						E	8	263–266		MeOH		$C_{17}H_{22}N_2$[q]	*p*
8a	2,6-Cl_2	Me				>80	NA 20	NA 6			E	42	91–96		Hexane		$C_9H_{10}Cl_2N_2$	
8b	2,6-Me_2	Me				>1 < 10	20–40	(<10)	NA 10	8.79	E	16		215–217		MeOH–Et_2O	$C_{11}H_{16}N_2 \cdot HCl$	
8c	2,6-Me_2	2,6-Me_2-C_6H_3				>80	NA 20	NA 50	50			20	144–145	291–293	Et_2O	Me_2CO	$C_{19}H_{26}N_2 \cdot HCl$	

[a–f] See corresponding footnotes to Table I. [g] Fumarate. [h] See footnote *b* to Table II. [i] bp 87–89° (0.3 mm). [j] No analyses. [k] Netherlands Patent 7,207,269 (1971). [l] HCl salt. [m] N: calcd, 16.53; found, 16.06. [n] N. S. Johary, S. S. Guha, and P. C. Guha, *Curr. Sci.*, 31, 184 (1952). [o] Obtained in low yield; insufficient for testing. [p] Obtained unexpectedly in an attempt to prepare 7i by method E. [q] C: calcd, 76.35; found, 75.65. Mass spectrum: m/e 267 (M^+). [r] A. Lenquist, J. Puska, and S. Bekassy, *Finn. Chem. Lett.*, 42, 225 (1968); *Chem. Abstr.*, 70, 115280 (1969).

Table V. Cyclic Isoureas and Isothioureas—Chemical and Pharmacological Testing Data



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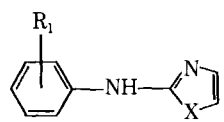

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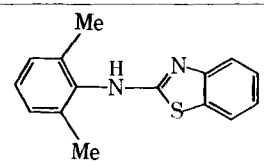

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Compd	n	X	R_1	R_2	Antihypertensive act., mg/kg[a] Rat	Antihypertensive act., mg/kg[a] Dog	Antisecretory act., mg/kg[a] + pH ~2	Antisecretory act., mg/kg[a] Δ vol ~50%	pK_a	Method[b]	Yield,[c] %	Mp, °C[d] base (salt)	Crystn solvent Base	Crystn solvent Salt	Formula[e]	Ref[f]
9a	2	O	2,6-Cl_2	H	NA 80	≥20	NA 50	NA 50		I	50	135–165 (198–201)	$CHCl_3$–hexane	EtOH	$C_9H_8Cl_2N_2O\cdot HCl$	*g*
9b	2	S	2,6-Cl_2	H	≥80	NA 20	NA 50	NA 50	5.82	J	62	184–185	C_6H_6		$C_9H_8Cl_2N_2S$	*h*
9c	2	S	2,6-Me_2	H	<80	NA 8	10	≥50		J	86	106–108	Cyclohexane		$C_{11}H_{14}N_2S$	*i*
9d	3	O	2,6-Cl_2	H	≥80	≥20	50	NA 50		I	67	184–185	$CHCl_3$–hexane		$C_{10}H_{10}Cl_2N_2O$	
9e	3	O	2,6-Me_2	H	NA 80	NA 20	50	+50	8.40	I		130–132	C_6H_6–cyclohexane		$C_{12}H_{16}N_2O$[j]	*k*
9f	3	S	2,6-Cl_2	H	NA 80	NA 20	NA 50	NA 50	4.62	J	29	168–172 (239–241)	C_6H_6	Et_2O	$C_{10}H_{10}Cl_2N_2S\cdot HCl$[g]	*l*
9g	3	S	2,6-Me_2	H	≤20	≥10	10	NA 10	7.19	J		135–137			$C_{12}H_{16}N_2S$[g]	*l*
9h	3	S	2,6-Me_2	Ac	NA 80	NA 40	50	≥50			18	64–66	2-Pr_2O		$C_{14}H_{18}N_2OS$	
10a		O	2,6-Me_2		NA 80	NA 20	(>50)	NA 50		*m*	25	119–123	Hexane		$C_{11}H_{12}N_2O$	*n*
10b		S	2,6-Me_2		NA 80	NA 20					75	153–156	EtOH		$C_{11}H_{12}N_2S$	
11					≥80	NA 40					40	214–216	EtOH		$C_{15}H_{14}N_2S$	

[a-f] See corresponding footnotes to Table I. [g] H. Wollweber, R. Hiltmann, and W. Stendel, German Patent 1,963,192 (1971); *Chem. Abstr.*, **75**, 118302b (1971). [h] L. Toldy, P. Sohar, K. Farago, I. Toth, and L. Bartalits, *Tetrahedron Lett.*, 2167 (1970). [i] G. Sagner and O. Behner, U. S. Patent 3,651,053 (1972). [j] No analyses. [k] H. Najer, P. Chaprier, and R. Giudicelli, *Bull. Soc. Chim. Fr.*, 611 (1959). [l] See ref 15. [m] See footnote *n*. [n] H. Najer, R. Giudicelli, and J. Menin, *Bull. Soc. Chim. Fr.*, 2052 (1960).

at 25° for 5 hr, a solution of 2,6-dimethoxyaniline (8.0 g, 0.052 mol) in C_6H_6 (10 ml) was added and the mixture was refluxed for 18 hr. The C_6H_6 solution was decanted from the oily residue and was replaced with a fresh portion of C_6H_6. The mixture was basified (2.5 *N* NaOH) and stirred. The C_6H_6 extract was washed with H_2O, dried, and evaporated to dryness. The product was isolated by crystallization.

For preparation of **2c-e,g,j,m** by this method, the products were isolated by distillation and the bases (oil) were converted to crystalline salts.

Method C. 2-(2,6-Dimethylbenzyl)-2-imidazoline (4e). A mixture of 2,6-dimethylphenylacetonitrile[16] (2.1 g, 14.5 mmol) and ethylenediamine mono-*p*-toluenesulfonate was heated at 190° for 2 hr when the evolution of NH_3 ceased (indicated by pH paper). The cooled mixture was dissolved in H_2O and basified with 10 *N* NaOH. The free base of **4e** (1.2 g, 43%) solidified (in some cases, extraction with Et_2O was necessary). It was converted to the HCl salt by treatment with ethereal HCl.

Method D. (a) 2-Phenylaminoimidazole (5a) and 2-Amino-1-phenylimidazole (5d). A stirred mixture of *S*-methylphenylisothiuronium iodide (65 g, 0.22 mol) and 2-aminoacetaldehyde diethyl acetal (35.1 g, 0.264 mol) was heated at 100–110° for 3.5 hr. The mixture was cooled, made alkaline (NaOH), and extracted with CH_2Cl_2. The extract was washed with H_2O, dried, and evaporated to a red oil (69.5 g) which was treated with concentrated HCl (147 ml) and heated at 90° for 30 min. The solution was chilled, basified with NaOH, and extracted with CH_2Cl_2. The extract was washed with H_2O, treated with activated C, filtered, and dried. Evaporation of the solvent gave a brown oil (26.2 g) which gradually solidified. This material was indicated by tlc analysis (silica GF, MeOH) to contain two major components: A, R_f 0.65; B, R_f 0.82. These two components were separated by dry column chromatography,[17] eluting the column (Grade II alumina) with EtOAc and extracting the fractions with MeOH. Component A (9.5 g) was identified as **5d** by nmr analysis and its melting point which was in agreement with the reported value. Component B (6.3 g) was characterized as **5a** by nmr analysis.

(b) 2-(2,6-Dimethylphenylamino)imidazole (5c) was prepared by the same procedure. The appropriate isothiuronium salt and acetal were heated at 160° to give the guanidine intermediate (II, R = 2,6-Me_2, Scheme I) which was isolated as a solid. The analytical sample, recrystallized from cyclohexane, had mp 74–77°. *Anal.* ($C_{15}H_{25}N_3O_2$) C, H, N. This material underwent cyclization in concentrated HCl to give only a single component **5d** (tlc analysis).

Method E. 1-(2-Chlorophenyl)-2,3-dimethylguanidine (7c). A solution of 1,3-dimethylurea (10 g, 0.114 mol) in C_6H_6 (50 ml) was treated slowly with $POCl_3$ (18.3 g, 0.12 mol) in C_6H_6 (15 ml), keeping the temperature below 25°. After the mixture was stirred for 5 hr at 25°, a solution of 2-chloroaniline (15.7 g, 0.12 mol) in C_6H_6 (50 ml) was slowly added and the mixture was refluxed for 18 hr. The C_6H_6 was decanted and the residue dissolved in hot H_2O. The cooled aqueous solution was washed with C_6H_6 and basified with 2.5 *N* NaOH. The precipitated oil gradually solidified on cooling and trituration. The mixture was filtered and the residue washed with Et_2O. Recrystallization gave 6.2 g of **7c**.

Method F. 1-Phenyl-2,3-tetramethylguanidine (7b). A solution of 1,3-tetramethylurea (58 g, 0.5 mol) in toluene (75 ml) was added slowly to a stirred solution of $COCl_2$ (60 g, 0.6 mol) in toluene (100 ml) under N_2, keeping the temperature below 25° by external cooling. The chloroformamidinium chloride gradually precipitated. The mixture was stirred for 18 hr. The supernatant liquid containing unreacted $COCl_2$ was decanted and replaced with a fresh portion of anhydrous toluene. The procedure was repeated twice with caution to avoid exposing the hygroscopic salt to moisture. A solution of aniline (18.6 g, 0.2 mol) in MeCN (50 ml) was added and the mixture was shaken repeatedly. A viscous oil was formed. The mixture was heated at 40° for 1 hr and at 60° for 2 hr. The solvent was evaporated and the residue was dissolved in H_2O (100 ml). The aqueous solution was basified and extracted with Et_2O. The extract was washed with brine, dried, and evaporated to dryness to give **7b** (16 g) which was isolated by distillation.

Method G. 2,6-Dichlorophenylguanidine (7d). To a suspension of 2,6-dichlorophenylthiourea[9] (10 g, 0.045 mol) in boiling H_2O (80 ml) was added a solution of KOH (25.2 g, 0.45 mol) in boiling H_2O (70 ml) and then a solution of $Pb(OAc)_2$ (17.5 g, 0.054 mol) in boiling H_2O (80 ml). The mixture was refluxed for 10 min, cooled, and filtered. The filtrate was acidified with AcOH to precipitate a solid material which was recrystallized from MeCN to give 6.75 g (80%) of 2,6-dichlorophenylcyanamide, mp 132–135°. *Anal.* ($C_7H_4Cl_2N_2$) C, H, N.

To a solution of the above cyanamide (5 g, 27 mmol) in a mixture of MeOH (25 ml) and THF (10 ml) cooled to −70° was added liquid NH_3 (15 ml). The mixture was heated in a steel bomb at 100° for 5 hr. After the solvents and NH_3 were evaporated, the solid residue was dissolved in a mixture of Et_2O and 2-PrOH. Treatment of the solution with ethereal HCl and recrystallization of the precipitate gave 5.5 g of **7d.**

Method H. 1-(2,6-Dichlorophenyl)-2-dimethylguanidine (7g). An aqueous solution of dimethylamine (90 ml, 25% solution) and *S*-methyl-2,6-dichlorophenylisothiuronium iodide (20 g, 55 mmol) was heated in a steel bomb at 160° for 2 hr. The cooled mixture was extracted with Et_2O. The extract was washed with H_2O, dried, and evaporated to dryness. Crystallization of the residue from cyclohexane gave 9.0 g of **7g.**

Method I. 2-(2,6-Dichlorophenylimino)tetrahydro-1,3-oxazine (9d). A mixture of 2,6-dichlorophenyl isothiocyanate (15 g, 0.07 mol, see **6a** for preparation) and 3-aminopropanol (6 g, 0.08 mol) in EtOAc (50 ml) was refluxed for 45 min. Concentration of the solution gave 19.4 g (99%) of 1-(2,6-dichlorophenyl)-3-(3-hydroxypropyl)thiourea, mp 125–128°.

To a stirred solution of the above thiourea (7.4 g, 27 mmol) in C_6H_6 (400 ml) and EtOH (200 ml) was added yellow HgO (80 g) in portions. The mixture was refluxed for 45 min and filtered. Evaporation of the filtrate and recrystallization of the solid residue gave 4.3 g of **9d.**

Method J. 2-(2,6-Dimethylphenylimino)thiazolidine (9c). A solution of 1-(2,6-dimethylphenyl)-3-(2-hydroxyethyl)thiourea[18] (12 g, 0.054 mol) in concentrated HCl (25 ml) was heated at 90° for 45 min. The cooled mixture was basified with 10 *N* NaOH and the precipitated gummy residue was extracted with Et_2O. The extract was washed with brine, dried, and evaporated to dryness. The oily residue solidified on cooling and was recrystallized.

1-Acetyl-2-(2,6-dichlorophenylimino)imidazolidine (1i). A solution of **1a** (5.0 g, 21.8 mmol) in C_6H_6 (100 ml) was treated with Ac_2O (2.42 g, 24 mmol) at 25° for 18 hr. The insoluble material was removed by filtration. The filtrate was washed with $NaHCO_3$ solution and H_2O. Evaporation of the solvent left a solid residue which was recrystallized.

1,3-Diacetyl-2-(2,6-dichlorophenylimino)imidazolidine (1j). A solution of **1a** (5.0 g, 21.7 mmol) in Ac_2O (15 ml) was heated at 100° for 2 hr. The mixture was poured into ice-H_2O and the precipitate was filtered and recrystallized.

1-Acetyl-2-(2,6-dichlorophenylimino)pyrrolidine (2i). A solution of **2d** (3.0 g, 13.1 mmol) in Ac_2O (6 ml) was kept at 25° for 18 hr and then poured into ice-H_2O. The precipitate was filtered, washed with H_2O, dried, and recrystallized.

2-(Methyl-2,6-dichlorophenylamino)-1-pyrroline (3). A solution of **2d** (4.5 g, 19.6 mmol) in MeOH (80 ml) was refluxed with MeI (1.3 ml) for 18 hr. The solvent was evaporated and the residue crystallized from 2-PrOH-Et_2O to give 6.8 g of HI salt (mp ~155°). The aqueous solution of this material was basified (10 *N* NaOH) and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$), and filtered. The filtrate was treated with ethereal HCl to precipitate 5.0 g of **3** · HCl.

1-(2-Aminophenyl)-3-(2,6-dichlorophenyl)thiourea (6a). A solution of 2,6-dichloroaniline (25 g, 0.154 mol) in $CHCl_3$ (140 ml) was added dropwise to a refluxing solution of $CSCl_2$ (25 g, 0.218 mol) in $CHCl_3$ (80 ml) during 1.5 hr. The evolved HCl was trapped by NaOH solution. The mixture was refluxed for 18 hr (the reaction was incomplete after 6 hr as indicated by ir analysis of an aliquot). The HCl salt of the aniline was removed by filtration and the filtrate evaporated to dryness. Unreacted 2,6-dichloroaniline was removed by distillation at 75° (3–4 mm). The product, 2,6-dichlorophenyl isothiocyanate, was collected at 106–109° (1.5–1.7 mm). The oil solidified to give 7.4 g (24%) of the product, mp 39–42°.

A solution of *o*-phenylenediamine (2.16 g, 20 mmol) in EtOAc (20 ml) at 55° was treated with 2,6-dichlorophenyl isothiocyanate (4.08 g, 20 mmol). The reaction temperature rose to 65°. After being stirred for 5 min, the product began to crystallize. The mixture was kept at 65° for 30 min, cooled, and filtered. The residue was washed with Et_2O to give 5.6 g of **6a.**

2-(2,6-Dichlorophenylamino)benzimidazole (6b). To a stirred and refluxing solution of **6a** (4.9 g, 15.7 mmol) in EtOH (450 ml) was added yellow HgO (20 g). Two additional portions of HgO (20 and 10 g each) were added 15 and 45 min after the initial reaction. Heating was continued for another 30 min when the reaction was completed. The progress of the reaction was monitored by treating an aliquot of the supernatant liquid with fresh HgO.

Completion of the reaction was indicated by the absence of a black color (HgS). The reaction mixture was cooled and filtered. The filtrate was evaporated to dryness and the residue was dissolved in boiling MeCN (100 ml). Insoluble material was removed by filtration. The filtrate was concentrated and cooled to give 3.3 g of crystalline **6b**.

N,N'-**Bis(2,6-dimethylphenyl)acetamidine (8c).** A solution of 2,6-dimethylaniline (50 g, 0.41 mol) in THF (50 ml) was treated slowly with Ac_2O (102 g, 1 mol). The mixture was stirred for 10 min and poured into ice-H_2O. The precipitated material was filtered, washed with H_2O, and recrystallized from EtOH to give 51 g (76%) of *N*-(2,6-dimethylphenyl)acetamide, mp 180–181°.

A solution of the above amide (50 g, 0.31 mol) in $CHCl_3$ (300 ml) at 0° was treated slowly during 20 min with $POCl_3$ (56.3 g, 0.37 mol) in $CHCl_3$ (70 ml). The mixture was stirred at 25° for 4 hr, treated with an excess of $MeNH_2$, and heated in an autoclave at 140° for 18 hr. Solvent was evaporated and the residue dissolved in H_2O. The aqueous solution was basified and extracted with $CHCl_3$. The extract was treated with activated C, filtered, and evaporated to a brown oil which crystallized on standing. A small sample, recrystallized from Et_2O, had mp 144–145°; the nmr spectrum of this material was consistent with **8c**. The remaining material was converted to the HCl salt by treatment with ethereal HCl. Recrystallization of the salt (45 g) from EtOH–Et_2O and Me_2CO gave 7.3 g of **8c** · HCl.

3-Acetyl-2-(2,6-dimethylphenylimino)tetrahydro-1,3-thiazine (9h). A solution of **9g** (10 g, 52.5 mmol) in Ac_2O (35 ml) was kept at 25° for 48 hr and then poured into ice-H_2O to decompose the excess Ac_2O. The mixture was extracted with C_6H_6 and the extract was washed with H_2O, $NaHCO_3$ solution, and brine and dried. Evaporation of the solvent left a viscous oil which slowly crystallized. After washing the residue with hexane, it was recrystallized to give 2.5 g of **9h**.

2-(2,6-Dimethylphenylamino)thiazole (10b). To a stirred and refluxing suspension of 2,6-dimethylphenylthiourea[9] (12 g, 66 mmol) in H_2O (50 ml) was added dropwise 1,2-dichloroethyl ethyl ether (10 g, 70 mmol). After 2 hr, the cooled mixture was basified (NaOH). The product was filtered and recrystallized from EtOH to give 10.1 g (75%) of **10b**.

2-(2,6-Dimethylphenylamino)benzothiazole (11). To a chilled solution of phenyl isothiocyanate (20 g, 0.148 mol) in EtOAc (60 ml) was added slowly 2,6-dimethylaniline (24.9 g, 0.21 mol). The mixture was refluxed for 25 min. The precipitated product, 1-(2,6-dimethylphenyl)-3-phenylthiourea (mp 203–205°), was collected by filtration (34.9 g, 91%).

A suspension of the above thiourea (25 g, 0.097 mol) in C_6H_5Cl (175 ml) was treated slowly with sulfuryl chloride[19] (17 g, 0.126 mol), keeping the reaction temperature below 50°. The mixture was maintained at 50° for 2.5 hr. The precipitated solid material was filtered, washed with C_6H_6, and dissolved in H_2O. After basifying the aqueous solution with NH_4OH, the precipitated product was filtered and recrystallized to give 10.35 g of 11.

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Notes

Synthesis and Biological Actions of Fragmented Derivatives of Tetrahydroisoquinolines

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Appropriately substituted tetrahydroisoquinolines have shown a variety of pharmacological actions including lipolytic,[1-4] bronchial relaxant,[5] and hypotensive activity.[3] In continuing our investigations of tetrahydroisoquinolines as agonists[1,2] and antagonists[6,7] in adrenergic systems we have initiated a program in determining the relationship of chemical structure to the production of biological actions. One portion of this program involves delineating the importance of an intact tetrahydroisoquinoline ring system for adrenergic activity with a goal toward the development of selective and/or potent β-adrenergic stimulants. This report is concerned with the modification of 1-benzyl-6,7-dihydroxytetrahydroisoquinoline (1) which is known to possess β-adrenergic activity.[1,2,8] The analogs prepared in this study may be considered tetrahydroisoquinolines in which the bond between C_4 and the aromatic ring is broken, as shown in 2. Modifications were also made in the catechol portion of the structure. It had been shown previously that elimination of either the 6- or 7-hydroxy group in 1 greatly reduced the bronchodilator activity.[8] In order to examine the importance of aromatic ring substitution in the fragmented derivative series, the