Anal. Calcd. for $C_{18}H_{23}NO$: C, 80.25; H, 8.60. Found: C, 80.04; H, 8.58.

Adamantane-1-carboxaldehyde.—N-Methyl-N-phenyladamantane-1-carboxamide (32 g., 0.082 mole) was dissolved in 100 ml. of dry, redistilled tetrahydrofuran. The stirred solution was maintained at 0–5° with an ice bath. A slurry of 1.03 g. (0.027 mole) of $LiAlH_4$ in 50 ml. of dry redistilled tetrahydrofuran was added portionwise to the cooled, stirred solution through a cotton-stoppered dropping funnel with a large bore. The mixture was allowed to come to room temperature overnight with stirring. It was cooled in ice and decomposed by the dropwise addition of cold 6 *N* HCl. The strongly acidic aqueous mixture was extracted with three 300 ml. portions of ether. The combined ether extract was washed with water to remove acid and then dried over $MgSO_4$. An oil was obtained when the ether was removed under reduced pressure. Unreduced anilide (4 g.) was recovered from the oil when it was cooled in ice. The remaining oil was shown to be approximately a 50% mixture of anilide and aldehyde by comparing the relative infrared absorption intensities of the aldehyde and of the amide bands observed in the oil. Further attempts to separate the aldehyde from the anilide, including distillation, were fruitless. The oily mixture was used as such, yield 7 g. (presumably 3.5 g. of aldehyde, 26%). The aldehyde portion was characterized by converting it to 3-(adamantane-1)-6,7-dichloro-1,2,4-benzothiadiazine-1,1-dioxide (Table II).

1,2,4-Benzothiadiazine-1,1-dioxides (Table II). Method A. R = H, CH_3, C_2H_5.—The 2-aminobenzenesulfonamide (5 g.) was heated on the steam bath with excess formic acid according to the procedure of Park and Williams,[7] or with excess triethyl orthoformate, orthoacetate or orthopropionate according to Freeman and Wagner.[8] The reaction mixture was added to water or the excess reagent was distilled, and the resulting solid was recrystallized from dilute alcohol.

Method B. R is Other than H, CH_3, C_2H_5.—The 2-aminobenzenesulfonamide (5 g.) was treated with an equal molar amount of the mixed anhydride of the appropriate carboxylic acid and trifluoroacetic acid, and the resulting 2-N-acylaminobenzenesulfonamides were cyclized in NH_4OH according to the previously reported procedure.[9]

2,4-Dihydro-1,2,4-benzothiadiazine-1,1-dioxides (Table III).—The 2-aminobenzenesulfonamide (5 g.) was treated with an equal molar amount of the appropriate aldehyde in alcoholic-aqueous HCl according to previously reported procedures.[10] The products were recrystallized from dilute alcohol.

Pharmacology.—The compounds were tested in renal hypertensive rats prepared by the procedure described by Kempf and Page.[11] Systolic blood pressure was determined by the microphonic manometric method of Friedman and Freed.[12] Following the control blood pressure determination the compounds were administered by mouth to groups of three rats. Blood pressure readings were recorded hourly for 7 hr.

The results are reported in Tables II and III as the average percentage change in blood pressure from control over the 7 hr. observation period. Each figure represents the mean change in blood pressure for three animals resulting from an oral dose of 20 mg./kg. From past experience in this laboratory with known hypotensive agents a 5% blood pressure lowering is considered to be significant. Eight representative compounds from Tables II and III produced electrolyte retention in saline-loaded female rats. There did not seem to be a relationship between the intensity of electrolyte retention and this hypotensive activity.

Acknowledgments.—The biological activities of these compounds were determined by Drs. P. W. Willard and F. G. Henderson. The microanalyses were done by Messrs. William L. Brown, Howard Hunter, George Maciak, Alfred Brown, and David Cline.

(7) D. V. Park and R. T. Williams, *J. Chem. Soc.*, 1760, (1950).

(8) J. H. Freeman and E. C. Wagner, *J. Org. Chem.*, **16**, 815 (1951).

(9) C. W. Whitehead, J. J. Traverso, F. J. Marshall, and D. E. Morrison, *ibid.*, **26**, 2809 (1961).

(10) C. W. Whitehead, J. J. Traverso, H. R. Sullivan, and F. J. Marshall, *ibid.*, **26**, 2814 (1961).

(11) G. F. Kempf and I. H. Page, *J. Lab. Clin. Med.*, **27**, 1192 (1942).

(12) M. Friedman and S. C. Freed, *Proc. Soc. Exp. Biol. Med.*, **70**, 670 (1949).

Sympathetic Nervous System Blocking Agents. Derivatives of Guanidine and Related Compounds[1]

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A series of 84 derivatives of guanidine, including 2-amino-2-imidazolines, 2-amino-1,4,5,6-tetrahydropyrimidines, nitroguanidines, and aminoguanidines, has been prepared by standard methods. These compounds have been investigated for their ability to block the sympathetic nervous system, but without blocking the parasympathetic nervous system. Pharmacology and structure–activity relationships are discussed.

In our Laboratories for a number of years we have been interested in derivatives of guanidine both as chemotherapeutic agents and for their effects on the cardiovascular system. In this paper we wish to report our efforts to find an effective antihypertensive agent in this series of compounds.

With the discovery of the potent antihypertensive agent, guanethidine[2,3] [2-(octahydro-1-azocinyl)-ethyl]-guanidine sulfate, we were prompted to reinvestigate our series of compounds in comparison with guanethidine, and to synthesize others which might show this type of activity. Guanethidine differs from older antihypertensive agents in that it blocks the effects of stimulation of the sympathetic nervous system, as do the ganglionic blocking agents, but does not at the same time block the parasympathetic nervous system. Since parasympathetic blockade causes undesirable side effects such as constipation, dry mouth, urinary retention, and impaired visual accommodation, guanethidine maintains the advantages of the ganglionic blocking agents without many of their disadvantages.

Chemistry.—The guanidines described in Tables III–VII were prepared by standard methods. Method A is that of Rathke[4] and involves the reaction of a

(1) Portions of this work were presented before the Division of Medicinal Chemistry at the 141st National Meeting of the American Chemical Society, Washington, D.C., March, 1962.

(2) R. A. Maxwell, R. P. Mull, and A. J. Plummer, *Experientia*, **15**, 267 (1959).

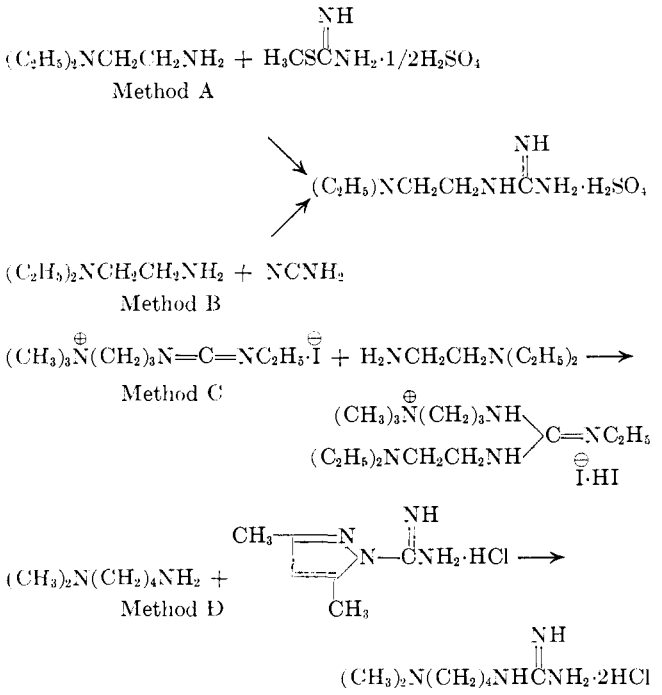
(3) R. P. Mull, M. E. Egbert, and M. R. Dapero, *J. Org. Chem.*, **25**, 1953 (1960).

(4) B. Rathke, *Ber.*, **14**, 1774 (1881).

TABLE I
NITRILES[f]

No.	Compound	B.p., °C.	Press., mm.	$n^{25}D$	Yield, %	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1.	4-Methyl-1-piperazine-acetonitrile[a]	113–114[b]	13		93	$C_7H_{13}N_3$			30.19			30.08
2.	4-Ethyl-1-piperazine acetonitrile[a,j]	133–137	15	1.4722	71	$C_8H_{15}N_3$	62.71	9.87	27.43	62.66	9.81	27.37
3.	3-Methyl-1-hexahydro-pyrimidineacetonitrile[a]	73	1.0	1.4741	76	$C_7H_{13}N_3$	60.40	9.41	30.19	60.47	9.66	30.09
4.	4-Methyl-1-homopiperazine-acetonitrile[a]	82–83	1.0	1.4809	88	$C_8H_{15}N_3$			27.43			27.41
5.	4-Diethylaminoethyl-1-piperazineacetonitrile[a,k]	178–182	2.0	1.4790	86	$C_{12}H_{24}N_4$	64.24	10.78	24.98	64.55	10.82	25.10
6.	4-Methyl-1-piperazine-propionitrile[c]	96–100	2.1[d]	1.4747	88							
7.	4-Methyl-1-homopiperazine-propionitrile[c]	117–121	1.3	1.4827	81	$C_9H_{17}N_3$	64.63	10.25	25.13	64.62	10.25	25.60
8.	4-Dimethylaminobutyronitrile[e]	74–76[f]	10	1.4250	45							
9.	5-Dimethylaminovaleronitrile[e]	94–95[g]	12	1.4310	67							
10.	6-Dimethylaminocapronitrile[h]	101–103[i]	15	1.4370	76	$C_8H_{16}N_2$	68.52	11.50	19.98	68.56	11.50	19.35
11.	N-(Diethylaminoethyl)-N-ethyl-aminoacetonitrile[a]	104	8.0	1.4470	94	$C_{10}H_{21}N_3$	65.53	11.55	22.92	65.87	11.27	23.16

[a] One mole of the appropriate amine and 1 mole of glycolonitrile in 500 ml. of benzene were heated under reflux until the theoretical amount of water was collected in a Dean–Stark separator. The solvent was removed and the residue was distilled. [b] M.p., 48–49°. [c] Prepared from the appropriate amine and acrylonitrile according to the procedure of L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **20,** 1693 (1955). [d] Recorded physical constants (Rice and Grogan, ref. *c*) are: b.p. 68–72° (0.3 mm.), $n^{20}D$ 1.4744. [e] One mole of the appropriate chloronitrile and 3 moles of dimethylamine in 300 ml. of ethanol was heated under reflux overnight. [f] The recorded b.p. is 44–47° (1.5 mm.), W. Huber, R. O. Clinton, W. Boehme, and M. Jacknian, *J. Am. Chem. Soc.*, **67,** 1618 (1945). [g] The recorded b.p. is 67–68° (3.0 mm.), J. M. Stewart, *J. Am. Chem. Soc.*, **76,** 3229 (1954). [h] Prepared by methylation of 6-aminocapronitrile according to the procedure of R. N. Icke, B. B. Wisegarver, and G. A. Alles, *Org. Syn.*, Col. Vol. III, p. 723. [i] The recorded b.p. is 94–96° (7.0 mm.), U.S. Patent 2,813,904, W. A. Lott and J. Krapcho (to Olin Mathieson Chemical Corp.), Nov. 19, 1957, *Chem. Abstr.*, **52,** 9197 (1958). [j] Preparation of 1-ethylpiperazine was carried out in the same manner as described in the Experimental section for 1-(2-diethylaminoethyl)-piperazine. The former has been described by W. S. Ide, E. Lorz, and R. Baltzly, *J. Am. Chem. Soc.*, **77,** 3142 (1955). [k] Preparation of 1-(2-diethylaminoethyl)-piperazine is described in the Experimental section. [l] After completion of the manuscript for this paper, R. P. Mull, R. H. Mizzoni, M. R. Dapero, and M. E. Egbert, *J. Med. Pharm. Chem.*, **5,** 944 (1962), reported compounds 1, 2, 4, and 5.



2-methyl-2-thiopseudourea salt with a primary or secondary amine. In general the primary amines were more reactive than the secondary amines. Many primary amines underwent reaction at room temperature while heating was usually required with the secondary amines. Indeed this difference in reactivity could be taken advantage of by obtaining monoguanyl derivatives from diamines containing a primary and a secondary amino function. Examples of such diamines are 2-(2-aminoethyl)-piperidine and 4-(2-aminoethyl)-piperidine. Proof of structure of the guanidine from the former was obtained by preparing it by catalytic reduction of 1-[2-(2-pyridyl)-ethyl]-guanidine sulfate. An exception was noted with 3-aminomethylpiperidine. Even at room temperature it reacted with 2-methyl-2-thiopseudourea sulfate to give the diguanyl derivative. Diethylenetriamine, when subjected to this procedure, reacted at both primary amino groups, but the secondary amino group did not react.

The reaction of cyanamide or substituted cyanamides with amines or ammonium salts (method B) was not, in our hands, a good general method for obtaining guanidines. Many guanidines readily prepared by method A were not accessible by method B. We found, however, that *t*-carbinamines (*i.e.*, derivatives of *t*-butylamine) failed to react with 2-methyl-2-thiopseudourea sulfate, but could be converted to the corresponding cyanamides and then allowed to react with ammonium salts to obtain the desired guanidines.[5] Again exceptions were noted. Menthanediamine, which contains two *t*-carbinamine groups, did react with 2-methyl-2-thiopseudourea sulfate to give the corresponding bisguanidine. Another exception was 2,2,4,6-tetramethylpiperidine which readily formed 1-guanyl-2,2,4,6-

(5) The guanidines obtained from these "hindered" amines were of special interest and are still under study. They will be reported in a future publication.

TABLE II

AMINES[e]

No.	Compound	M.p. or b.p., °C.	Press., mm.	$n^{25}D$	Yield, %	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1.	1-(2-Aminoethyl)-4-methylpiperazine[a]	76–77	6.0	1.4780	68							
	Trihydrochloride	242–244				$C_7H_{17}N_3 \cdot 3HCl$	33.28	7.98	16.64	33.37	7.98	16.87
	Secondary amine	140	0.8	1.4910	15	$C_{14}H_{31}N_5$	62.41	11.60	26.00	62.85	11.67	25.51
2.	1-(2-Aminoethyl)-4-ethylpiperazine[b]	118	12.5	1.4780	63	$C_8H_{19}N_3$	61.10	12.18	26.72	61.30	12.06	26.66
3.	1-(2-Aminoethyl)-3-methylhexahydropyrimidine[b]	78	5.0	1.4821	30	$C_7H_{17}N_3$	58.70	11.96	29.34	58.55	11.96	29.30
4.	1-(2-Aminoethyl)-4-methylhomopiperazine[a]	86–88	4.1	1.4850	63	$C_8H_{19}N_3$	61.10	12.18	26.72	60.73	11.87	27.21
	Trihydrobromide	222–223				$C_8H_{19}N_3 \cdot 3HBr$	24.02	5.54	10.51	24.22	5.64	10.71
	Secondary amine	158–162	0.6	1.4993	10	$C_{16}H_{35}N_5$	64.60	11.86	23.54	64.37	11.67	23.23
5.	1-(2-Aminoethyl)-4-(2-diethylaminoethyl)-piperazine[b]	126–130	2.0	1.4819	34	$C_{12}H_{28}N_4$	63.11	12.36	24.53	63.23	12.60	24.76
6.	1-(3-Aminopropyl)-4-methylpiperazine[a]	113	17	1.4796	81							
	Trihydrochloride	249–250				$C_8H_{19}N_3 \cdot 3HCl$	36.04	8.30	15.76	35.80	8.49	15.67
	Secondary amine	172	0.9	1.4923	46[c]	$C_{16}H_{35}N_5$	64.60	11.86	23.54	64.37	11.59	23.70
7.	1-(3-Aminopropyl)-4-methylhomopiperazine[a]	106–107	0.7	1.4860	76	$C_9H_{21}N_3$	63.11	12.36	24.53	63.17	12.43	24.49
	Trihydrobromide	147–148				$C_9H_{21}N_3 \cdot 3HBr$	26.11	5.84	10.15	25.89	5.92	10.12
	Secondary Amine	198	0.4	1.4992	8	$C_{18}H_{39}N_5$	66.41	12.08	21.52	66.34	12.30	21.66
8.	N,N-Dimethyl-1,4-butanediamine[a]	64	14	1.4386	69							
	Dihydrochloride	175.5–176				$C_6H_{6}N_2 \cdot 2HCl$	38.11	9.59	14.81	38.08	9.79	14.62
9.	N,N-Dimethyl-1,5-pentanediamine[a]	180–181	749	1.4403	78							
	Dihydrochloride	158–159				$C_7H_{18}N_2 \cdot 2HCl$	41.38	9.92	13.78	41.12	9.69	13.72
10.	N,N-Dimethyl-1,6-hexanediamine[a]	108–109[d]	32	1.4423	80							
	Dihydrochloride	142–143				$C_8H_{20}N_2 \cdot 2HCl$	44.23	9.74	12.89	44.73	9.79	12.48
11.	1,1,4-Triethyldiethylenetriamine[b]	122–126	27	1.4528	70	$C_{10}H_{25}N_3$	64.11	13.45	22.43	64.14	13.54	22.46

[a] Amines 1, 6, 8, and 9 were prepared by catalytic hydrogenation of the appropriate nitrile and are described by M. Freifelder in *J. Am. Chem. Soc.*, **82**, 2387 (1960). Amines 4, 7, and 10 were prepared by the same procedure. In all cases a small amount of secondary amine was obtained, and those secondary amines not described by Freifelder are characterized here. [b] Amines 2, 3, 5, and 11 were prepared by reduction of the appropriate nitrile with lithium aluminum hydride in diethyl ether. [c] In one run no ammonia was added to suppress secondary amine formation in order to see how high a yield of secondary amine could be obtained. [d] The recorded b.p. is 103–107° (23 mm.), U. S. Patent 2,813,904; see Table I, footnote *i*. [e] After completion of the manuscript for this paper, R. P. Mull, R. H. Mizzoni, M. R. Dapero, and M. E. Egbert, *J. Med. Pharm. Chem.*, **5**, 944 (1962), reported compounds 2, 4, and 5.

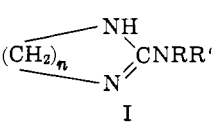
tetramethylpiperidine sulfate under the conditions of method A.

The reaction of a disubstituted carbodiimide with ammonia or an amine (method C) proved to be a satisfactory way of obtaining guanidines. The limitation of this method is the lack of availability of appropriate carbodiimides.

Formation of guanidines from 3,5-dimethyl-1-guanylpyrazole nitrate[6] and amines (method D) was found to be a useful procedure. The hydrochloride salt of this reagent was prepared and found to be as useful as the nitrate salt. Method D, however, appeared to have no great advantage over method A. For example, 1,1,-7,7-tetraethyldiethylenetriamine could not be converted to the desired guanidine by either method A or method D.

Use of method A was not limited to 2-methyl-2-thiopseudourea salt itself. Substituted derivatives of it could also be used to prepare guanidines. For example, N-methylthiourea, N-*n*-butylthiourea, N,N'-diethylthiourea, and N,N,N'-trimethylthiourea reacted with methyl iodide or dimethyl sulfate to form the corresponding S-methyl derivatives. They were then allowed to react with amines in the usual manner to obtain the expected guanidines.

A series of cyclic guanidines (I) was prepared for comparison with their non-cyclic analogs. To obtain



I

the 2-amino-2-imidazoline derivatives (I, $n = 2$), ethylenethiourea was converted to 2-methylthio-2-imidazoline hydrochloride and the latter allowed to react with amines in the manner of method A. It was interesting to note that this substance was more reactive toward amines than 2-methyl-2-thiopsueodurea sulfate. For example, both N,N,N'-triethylethylenediamine and 1,1,-7,7-tetraethyldiethylenetriamine formed the appropriate 2-amino-2-imidazolines with the former, while many unsuccessful attempts were made to obtain the guanidines with the latter.

The tetrahydropyrimidines (I, $n = 3$) were prepared in the same manner from 2-methylthio-1,4,5,6-tetrahydropyrimidine hydriodide.

(6) A. F. S. A. Habeeb, *Biochem. Biophys. Acta*, **34**, 294 (1959); *Can. J. Biochem. Physiol.*, **38**, 493 (1960).

Table III

Guanidines[a]

$$R^1R^2NC(=NR^3)NR^4R^5$$

No.	Compound[a] R¹	R²	R³	R⁴	R⁵	Salt	M.p., °C.	Method[b]	Empirical formula	Analyses, % Calcd. C	H	N	Found C	H	N
1	$(CH_3)_2NCH_2CH_2$					2HCl	178–178.5	A, D	$C_5H_{15}N_3 \cdot 2HCl$	29.57	7.94	27.59	29.39	8.32	27.61
2	$(C_2H_5)_2NCH_2CH_2$					H_2SO_4	280–281	A, B	$C_7H_{18}N_2 \cdot H_2SO_4$	32.80	7.87	21.86	32.65	7.78	21.71
						2HCl	141–142		$C_7H_{18}N_2 \cdot 2HCl$	36.40	8.70	21.20	36.72	8.84	24.27
3	$[(CH_3)_2CH]_2NCH_2CH_2$					$\frac{1}{2}H_2SO_4$	258–259	A	$C_9H_{22}N_2 \cdot \frac{1}{2}H_2SO_4$	45.93	9.85	23.81	45.71	9.84	24.01
4	$(CH_3)_2N(CH_2)_3$					H_2SO_4	259–261	A	$C_5H_{13}N_3 \cdot H_2SO_4$	29.71	7.49	23.12	29.66	7.89	23.08
5	$(C_2H_5)_2N(CH_2)_3$					H_2SO_4	255–257	A	$C_8H_{20}N_2 \cdot H_2SO_4$	35.54	8.20	20.73	35.67	8.24	20.56
6	$(CH_3)_2N(CH_2)_4$					2HCl	118–120	D	$C_7H_{18}N_2 \cdot 2HCl$	36.40	8.70	24.20	36.30	8.78	24.19
7	$(C_2H_5)_2N(CH_2)_4$					H_2SO_4	297–297.5	A	$C_9H_{22}N_2 \cdot H_2SO_4$	38.01	8.51	19.70	38.08	8.53	19.38
8	$(CH_3)_2N(CH_2)_5$					2HCl	139–139.5	D	$C_8H_{20}N_2 \cdot 2HCl$	39.29	9.01	22.85	39.60	9.03	23.02
9	$(CH_3)_2N(CH_2)_6$					2HCl	162–163	D	$C_9H_{22}N_2 \cdot 2HCl$	41.70	9.33	21.61	41.73	9.19	21.80
10	$(C_2H_5)_2NCH_2CH_2N(C_2H_5)CH_2CH_2$					3HI	[c]	A	$C_{11}H_{27}N_3 \cdot 3HI$	21.55	4.93	11.43	21.29	5.21	11.40
11	$(CH_3)_2NCH_2CH_2$	CH_3				H_2SO_4	280–281	A	$C_6H_{16}N_2 \cdot H_2SO_4$	29.74	7.49	23.12	30.06	7.79	23.08
12	$(C_2H_5)_2NCH_2CH_2$			CH_3		2HI	155–157	A[d]	$C_8H_{20}N_2 \cdot 2HI$	22.41	5.18	13.09	22.62	5.20	13.14
13	$(C_2H_5)_2NCH_2CH_2$	CH_3				H_2SO_4	265.5–266	A	$C_8H_{20}N_2 \cdot H_2SO_4$	35.54	8.20	20.72	35.27	8.16	20.82
14	$(C_2H_5)_2NCH_2CH_2$			n-C_3H_7		2HI	87–91	A[e]	$C_9H_{24}N_2 \cdot 2HI$	28.10	5.95	11.91	28.69	5.99	11.86
15	$(CH_3)_2NCH_2CH_2$	CH_3		CH_3		2HI	192–194	A[d]	$C_7H_{18}N_2 \cdot 2HI$	26.31	1.87	13.53	26.42	4.91	13.75
16	$(C_2H_5)_2NCH_2CH_2$		C_2H_5	C_2H_5		$(C_2H_2O_4)_2$[f]	112	A[g]	$C_9H_{26}N_2 \cdot C_2H_2O_4$	45.67	7.67	11.20	45.60	7.95	14.27
17	$(C_2H_5)_2NCH_2CH_2$		C_6H_{13}	C_6H_{13}		$(C_2H_2O_4)_2$[f]	178.5–179.5	C[h]	$C_{19}H_{38}N_2 \cdot C_2H_2O_4$	54.96	8.42	11.11	54.72	8.28	11.20
18	$(C_2H_5)_2NCH_2CH_2$		CH_3	CH_2	CH_3	2HI	130–132	A[i]	$C_{10}H_{24}N_2 \cdot 2HI$	26.33	5.71	12.28	26.11	5.81	11.90
19	$(C_2H_5)_3(CH_3)N^{\oplus}CH_2CH_2$					$I^{\ominus}HI$	158–159	A[j]	$C_8H_{21}IN_2 \cdot HI$	22.41	5.18	13.09	22.24	5.29	13.05
20	$(C_2H_5)_3N^{\oplus}CH_2CH_2$					$I^{\ominus}HI$	196–197	A[j]	$C_9H_{23}IN_2 \cdot HI$	24.44	5.47	12.68	24.17	5.78	12.73
21	$(CH_3)_2N^{\oplus}(CH_2)_3$		C_2H_5	CH_2		$I^{\ominus}HI$	211–212	C[k]	$C_{10}H_{25}IN_2 \cdot HI$	26.32	5.74	12.28	26.41	5.97	12.29
22	$(CH_3)_3N^{\oplus}(CH_2)_2$		C_2H_5	$(C_2H_5)_2NCH_2CH_2$		$I^{\ominus}HI$	175.5–177	C[k]	$C_{15}H_{36}IN_3 \cdot HI$	26.91	5.72	10.46	26.95	5.56	10.58
23	4-Methylpipecazinoethyl					3HCl	232–253	A	$C_8H_{18}N_2 \cdot 2HCl$	32.60	7.53	23.76	32.20	7.75	23.51
24	4-Ethylpiperazinoethyl					$2H_2SO_4$	237–238	A	$C_9H_{20}N_2 \cdot 2H_2SO_4$	27.33	6.37	17.71	27.35	6.52	17.74
25	4-Methylpiperazinoethyl			n-C_3H_7		3(C2H2O4)[f]	195–196	A[l]	$C_{22}H_{42}N_4 \cdot C_6H_6O_{12} \cdot H_2O$	40.83	6.67	13.23	40.78	6.40	13.11
26	4-Methylpiperazinopropyl					3HCl	242.5–243	A	$C_9H_{23}N_3 \cdot 3HCl$	35.01	7.84	22.69	34.90	7.80	22.72
27	3-Methylhexahydropyrimidinoethyl					HI	151–152.5	A	$C_8H_{19}N_2 \cdot HI$	30.68	6.44	22.37	30.55	6.49	22.36
28	4-Methylhomopiperazinoethyl					3HI	224–226	A	$C_9H_{21}N_3 \cdot 3HI$	18.53	4.11	12.61	18.60	4.43	12.02
						$2H_2SO_4$	218–219		$C_9H_{21}N_3 \cdot 2H_2SO_4$	27.33	6.37	17.71	27.11	6.10	17.69
29	4-Methylhomopiperazinopropyl					$2H_2SO_4$	264	A	$C_{10}H_{23}N_3 \cdot 2H_2SO_4$	29.33	6.65	17.10	29.46	6.79	17.29
30	4-(o-Methoxyphenyl)-piperazinoethyl					$\frac{1}{2}H_2SO_4$	246–248	A	$C_{13}H_{22}N_2O \cdot \frac{1}{2}H_2SO_4$	51.52	7.41	21.46	51.59	7.39	21.42
31	4-(Diethylaminoethyl)-piperazinoethyl					4HCl	240–241	A	$C_{18}H_{40}N_6 \cdot 4HCl$	37.50	8.23	20.19	37.42	8.06	20.00
32	2-(2-Pyridyl)-ethyl					H_2SO_4	264–264.5	A[f]	$C_8H_{12}N_2 \cdot H_2SO_4$	36.63	5.38	21.36	36.78	5.61	21.16
33	2-(2-Piperidyl)-ethyl					H_2SO_4	314–315	A[f, m]	$C_8H_{18}N_2 \cdot H_2SO_4$	35.81	7.51	20.88	35.83	7.27	20.83
34	2-(4-Pyridyl)-ethyl					H_2SO_4	248–249	A[f]	$C_8H_{12}N_2 \cdot H_2SO_4$	36.63	5.38	21.36	36.48	5.44	21.21
35	2-(4-Piperidyl)-ethyl					H_2SO_4	323 dec.	A[f]	$C_8H_{18}N_2 \cdot H_2SO_4$	35.81	7.51	20.88	35.82	7.61	21.19

36	1-Methyl-2-piperidylmethyl	H_2SO_4	307–308	A	$C_8H_{18}N_4 \cdot H_2SO_4$	35.81	7.51	20.88	35.94	7.19	20.85
37	1-Ethyl-2-piperidylmethyl	H_2SO_4	292–292.5	A	$C_9H_{20}N_4 \cdot H_2SO_4$	38.28	7.85	19.85	38.18	7.90	19.79
38	2-(4-Imidazolyl)-ethyl	2HCl	214–216	A[n]	$C_6H_{11}N_5 \cdot 2HCl$	31.86	5.80	30.97	31.87	5.67	31.08
39	HO$(CH_2)_4$	$\frac{1}{2}H_2SO_4$	167–168	A	$C_8H_{18}N_3O \cdot \frac{1}{2}H_2SO_4$	33.32	7.83	23.32	33.48	8.12	23.41
40	HO$(CH_2)_6$	$\frac{1}{2}H_2SO_4$	135–136	A	$C_{10}H_{22}N_3O \cdot \frac{1}{2}H_2SO_4$	40.37	8.71	20.18	40.31	8.71	20.10
41	n-$C_{12}H_{25}$	$\frac{1}{2}H_2SO_4$	230.5	A	$C_{15}H_{29}N_3 \cdot \frac{1}{2}H_2SO_4$	56.48	10.93	15.20	56.62	10.67	15.03
42	2-Chlorobenzyl	$\frac{1}{2}H_2SO_4$	245.5–246.5	A	$C_8H_{10}ClN_3 \cdot \frac{1}{2}H_2SO_4$	41.29	4.77	18.06	41.00	4.86	17.87
43	4-Chlorobenzyl	$\frac{1}{2}H_2SO_4$	220–222	A	$C_8H_{10}ClN_3 \cdot \frac{1}{2}H_2SO_4$	41.29	4.77	18.06	41.54	4.78	17.71
44	2-(3,4-Dimethoxyphenyl)-ethyl	$\frac{1}{2}H_2SO_4$	176–177	A	$C_{11}H_{17}N_3O_2 \cdot \frac{1}{2}H_2SO_4$	48.51	6.66	15.43	48.62	6.48	15.44
45	Furfuryl	$\frac{1}{2}H_2SO_4$	212–213	A	$C_6H_9N_3O \cdot \frac{1}{2}H_2SO_4$	38.29	5.36	22.33	38.49	5.72	22.08
46	$C_{20}H_{39}$	$C_2H_2O_4$[f]	264.5–265.5	B[o]	$C_{21}H_{43}N_3 \cdot C_2H_2O_4$	71.28	9.62	10.84	71.05	9.68	11.06
47	2-(2,4-Dichlorophenylthio)-ethyl	HI	134–135	A	$C_9H_{11}Cl_2N_3S \cdot HI$	27.56	3.09	10.72	27.61	3.33	10.72

[a] R^2, R^3, R^5 are H unless indicated otherwise. [b] Methods A, B, C, and D are described in the Experimental section. [c] This substance is a glassy solid which did not crystallize. [d] Prepared from the appropriate amine and 1,2-dimethyl-2-thiopseudourea hydriodide, which was prepared as described by A. Lespagnol, E. Cuingnet, and M. Debaert, *Bull. Soc. Chim. France*, 387 (1960). [e] Prepared from the appropriate amine and 1-*n*-butyl-2-methyl-2-thiopseudourea hydriodide, which was prepared according to the procedure of G. W. Kirsten and G. B. L. Smith, *J. Am. Chem. Soc.*, **58**, 800 (1936). [f] $C_2H_2O_4$ is oxalic acid. [g] Prepared from diethylaminoethylamine and 1,3-diethyl-2-methyl-2-thiopseudourea hydriodide, which was prepared according to the procedure of W. G. Finnegan, R. A. Henry, and E. J. Lieber, *J. Org. Chem.*, **18**, 783 (1953). [h] Prepared from dicyclohexylcarbodiimide and diethylaminoethylamine. [i] 1,1,3-Trimethylthiourea, R. Singh, *J. Ind. Chem. Soc.*, **33**, 610 (1956), was converted to 1,1,2,3-tetramethyl-2-thiopseudourea hydriodide and the latter allowed to react with diethylaminoethylamine. [j] Prepared according to the procedure of A. Lespagnol, E. Cuingnet, and M. Debaert, *Bull. Soc. Chim. France*, 387 (1960). [k] Prepared from N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide methiodide. [l] The required amine has been described by M. Freifelder and G. R. Stone in *J. Org. Chem.*, **26**, 3805, 4757 (1961). [m] Compound 33 was also prepared by catalytic hydrogenation of 32, see Experimental section. [n] An aqueous solution of histamine dihydrochloride was neutralized with an equivalent amount of 50% sodium hydroxide solution, and then the reaction was run in the usual manner. [o] The amine component was dehydroabietylamine acetate. [p] $C_2H_4O_2$ is acetic acid. [q] After completion of the manuscript for this paper, R. P. Mull, R. H. Mizzoni, M. R. Dapero, and M. E. Egbert, *J. Med. Pharm. Chem.*, **5**, 944 (1962), reported compounds 23, 24, 26, 28, 30 and 31.

The one example of a compound containing a seven-membered ring, 2-(2-diethylaminoethylamino)-1,3-diaza-2-cycloheptene hydriodide [I, $n = 4$, R = H, R′ = $CH_2CH_2N(C_2H_5)_2$] was prepared from diethylaminoethylamine and 2-nitroamino-1,3-diaza-2-cycloheptene.

A series of aminoguanidines was prepared in order to determine what effect this variation in structure might have on activity. One method of obtaining the desired aminoguanidines would be by reduction of the corresponding nitro compounds. However, attempts to reduce four such nitroguanidines, in water at low pressure using a platinum catalyst, failed. The nitro groups were cleaved, and the corresponding guanidines were obtained.

Najer[7] has recently reported the preparation of aminoguanidines by reduction of nitroguanidines. When 1-(2-diethylaminoethyl)-3-nitroguanidine was subjected to reduction by Najer's method, it rapidly took up the required amount of hydrogen with no cleavage taking place. The product was isolated as a stable, crystalline oxalate salt, but elemental analyses were unsatisfactory.

An alternative procedure for obtaining the desired compound is the reaction of 2-diethylaminoethylamine with 2-methyl-2-thioisosemicarbazide hydriodide. This method was successful even though much work was required before an analytically pure salt was obtained. The dihydrochloride, dihydriodide, and dioxalate salts proved unsatisfactory, but finally a difumarate salt gave an adequate analysis.

Additional 1-amino-3-substituted-guanidines were prepared by this variation of method A. Another variation is the reaction of 2-diethylaminoethylhydrazine with 2-methyl-2-thiopseudourea sulfate to obtain 1-amino-1-(2-diethylaminoethyl)-guanidine sulfate.

Many of the amines required for the preparation of the guanidines were available from commercial sources. Others were prepared by reduction of the nitriles in Table I and are described in Table II, and the preparation of some of them is described in the Experimental section.

Pharmacology.—The effectivness of these compounds as sympathetic blocking agents was determined in unanesthetized cats. The candidate drugs were administered orally, and the degree and duration of the prolapse of the nictitating membrane were the criteria used to determine whether or not the desired activity was present. Since parasympatholytic agents and ganglionic blocking agents alter the pupillary responses of the eye, normal responses were taken as indications that the parasympathetic nervous system was not also being blocked.

When the candidate drugs failed to cause a prolapse of the nictitating membrane at an initial low dose level, dosage was increased as high as 30 mg./kg. Those substances which failed to show a response at that dose were classified as inactive. Of our 84 compounds, 16 showed activity; they are compared in Table VIII. The relative activity is obtained by dividing the average duration of prolapse in hours, observed in several experiments, by the dose in mg./kg., and then expressing this activity as a percentage of the activity of our most active compound (23).

(7) H. Najer, R. Giudicelli, and J. Sette, *Bull. Soc. Chim. France*, 561 (1992).

Table IV

N-Guanylheterocycles

NH

R—CNH$_2$

No.	Compound R	Salt	M.p., °C.	Method	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
48	Pyrrolidino	$^1/_2H_2SO_4$	>350	A	$C_5H_{11}N_3 \cdot {}^1/_2H_2SO_4$	37.02	7.46	25.91	36.82	7.31	25.78
49	2,2,4,6-Tetramethylpiperidino	$^1/_2H_2SO_4$	197–199	A	$C_{10}H_{21}N_3 \cdot {}^1/_2H_2SO_4$	51.70	9.55	18.09	51.90	9.88	18.08
50	2,6-Dimethylthiamorpholino	$^1/_2H_2SO_4$	240–242	A[a]	$C_7H_{15}N_3S \cdot {}^1/_2H_2SO_4$	37.81	7.26	18.91	37.89	7.19	18.73
51	2-Methyl-6-phenylmorpholino	$^1/_2H_2SO_4$	268.5–270	A	$C_{12}H_{17}N_3O \cdot {}^1/_2H_2SO_4$	53.71	6.76	15.66	53.46	6.51	15.86
52	4-Morpholinopiperidino	$^1/_2H_2SO_4$	279–280	A[b]	$C_{10}H_{20}N_4O \cdot {}^1/_2H_2SO_4$	45.96	8.16	21.44	45.85	8.32	21.60
53	4-Piperidinopiperidino	2HCl	294–295	A[c]	$C_{10}H_{22}N_4 \cdot 2HCl$	40.64	8.54	19.78	40.35	8.40	20.08
54	4-(2-Pyrrolidinoethyl)-piperidino	2HI	192–193.5	A[b]	$C_{12}H_{24}N_4 \cdot 2HI$	30.01	5.46	11.67	29.83	5.42	12.11
55	N-Phenylpiperazino	H_2SO_4	>300	A	$C_{10}H_{16}N_4 \cdot H_2SO_4$	43.70	6.00	18.53	43.49	5.99	18.22
56	N-Methylhomopiperazino	$^1/_2H_2SO_4$	274	A	$C_7H_{16}N_4 \cdot {}^1/_2H_2SO_4$	40.93	8.31	27.29	40.56	8.18	27.21

[a] The required amine, 2,6-dimethylthiamorpholine, was prepared according to the procedure of D. Harman and W. E. Vaughan, *J. Am. Chem. Soc.*, **72**, 632 (1950). In order to obtain the desired guanidine, the reactants were refluxed for 18 hr. [b] The required amine was prepared according to the procedure of M. Freifelder and G. R. Stone, *J. Org. Chem.*, **26**, 3807 (1961). [c] 4-Piperidinopiperidine dihydrochloride was neutralized with sodium carbonate, then refluxed for 18 hr. with 2-methyl-2-thiopseudourea sulfate.

Structure–Activity Relationships.—We found early in our work that 1-(2-diethylaminoethyl)-guanidine sulfate (Table III, 2) had the desired activity. Variations in this structure, however, led to decreased activity. The next higher homolog, 1-(3-diethylaminopropyl)guanidine sulfate (5), was less active, and 1-(4-diethylaminobutyl)-guanidine sulfate (7) was inactive.

Replacing the diethylamino group of (2) with dimethylamino resulted in an inactive compound (1). Homologous dimethylaminoalkylguanidines (4, 6, 8, and 9) were all inactive. Activity was observed with 1-(2-diisopropylaminoethyl)-guanidine sulfate (3), but it was less active than the diethylamino homolog.

In a study of the effect of additional alkyl substituents on the guanidine portion of the molecule, activity was maintained, but not increased, with 1-(2-diethylaminoethyl)-3-methylguanidine dihydriodide (12). Increasing the size of the 3-alkyl group (14) or increasing the number of alkyl groups (16–18) led to inactive compounds.

It is interesting to note that, although (12) is active, its isomer, 1-(2-diethylaminoethyl)-1-methylguanidine sulfate (13), is inactive. It appears that the nitrogen of the guanidine nucleus to which the side chain is attached must also bear a hydrogen atom if the compound is to be active. This could explain why none of the N-guanylheterocyclic compounds (Table IV) is active.

Quaternization of the side chain amino group (19–21) did not enhance activity. Compound 22, a guanidine containing two basic side chains, one of which is quaternized, did show weak activity. The activity of the latter appears to be due to ganglionic blockade and not to the desired activity.

We next turned our attention to the effect of the introduction of a second basic nitrogen into the side chain. For this purpose the piperazine nucleus was chosen, and 1-[2-(4-methylpiperazino)-ethyl]guanidine trihydrochloride (23) proved to be one of our most active compounds. Two homologs, 1-[2-(4-ethylpiperazino)ethyl]-guanidine disulfate (24) and 1-[3-(4-methylpiperazino)-propyl]-guanidine trihydrochloride (26), were both inactive. An isomer of (23), 1-[2-(3-methylhexahydropyrimidino)-ethyl]-guanidine hydriodide (27), was also inactive. Another homolog of 23, 1-[2-(4-methylhomopiperazino)-ethyl]-guanidine disulfate (28), was active, but less so than 23.

A compound containing a third basic nitrogen in the side chain, 1-[2-(4-diethylaminoethylpiperazino)-ethyl]-guanidine tetrahydrochloride (31), was inactive. No activity was observed with 1-[2-(N-diethylaminoethyl-N-ethylamino)-ethyl]-guanidine trihydriodide (10). The latter is a ring-opened analog of 23.

When the dialkylamino portion of the side chain was replaced with a pyridyl group, activity was noted with 1-[2-(4-pyridyl)-ethyl]-guanidine sulfate (34), but not with the isomer 1-[2-(2-pyridyl)-ethyl]-guanidine sulfate (32). The reverse held true with the corresponding piperidine analogs. While 1-[2-(4-piperidyl)-ethyl]-guanidine sulfate (35) was inactive, 1-[2-(2-piperidyl)-ethyl]-guanidine sulfate (33) was weakly active.

It was noted above that changing the ethyl groups of the active compound (2) to methyl groups resulted in an inactive compound. In the piperazine series, the reverse was true. The N-methyl derivative (23) was quite active while its ethyl homolog (24) was inactive. This effect was also noted in the piperidine series. 1-(1-Methyl-2-piperidymethyl)-guanidine sulfate (36) was active, but the ethyl homolog (37) failed to show activity.

Among a series of miscellaneous guanidines (39–47) from monoamines, 1-[2-(3,4-dimethoxyphenyl)-ethyl]-guanidine sulfate (44) possessed weak activity while 1-(2-chlorobenzyl)-guanidine sulfate (42) and 1-(4-chlorobenzyl)-guanidine sulfate (43) both showed a good level of activity.

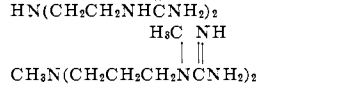
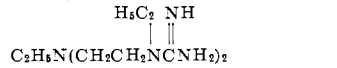
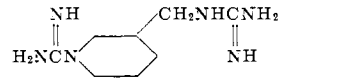
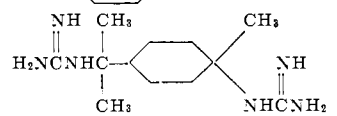
Only one active compound was found among a series of N-guanylheterocycles (Table IV). This further confirms the observation that guanidines from secondary amines are usually inactive. The exception was 1-guanyl-2,2,4,6-tetramethylpiperidine sulfate (49). Its activity, however, appears to be due to ganglionic blockade. That it is a ganglionic blocking agent is not surprising since it is closely related to pempidine (1,2,2,6,6-pentamethylpiperidine), a clinically useful ganglionic blocking agent.[8]

No active compound was found among the bisguanidines listed in Table V. The cyclic guanidines are given in Table VI, and the only member of this group to show the desired activity was 2-(2-diethylaminoethylamino)-2-imidazoline dioxalate (62). The amino- and nitroguanidines described in Table VII were uniformly inactive.

(8) M. Harington, P. Kincaid-Smith, and M. D. Milne, *Lancet*, 6 (1958 II).

TABLE V

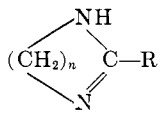
BIS-GUANIDINES

No.	Compound	Salt	M.p., °C.	Method	Empirical formula	Analyses, % Calcd. C	H	N	Found C	H	N
57		H_2SO_4	241–241.5	A	$C_6H_{17}N_7 \cdot H_2SO_4$	25.25	6.71	34.37	25.39	7.04	34.22
58		H_2SO_4	277–278	A	$C_{11}H_{27}N_7 \cdot H_2SO_4$	37.16	8.22	27.58	36.86	8.38	27.29
59		H_2SO_4	160.5–161	A	$C_{12}H_{29}N_7 \cdot H_2SO_4$	39.01	8.46	26.53	38.75	8.60	26.32
60		H_2SO_4	350–352	A[a]	$C_8H_{18}N_6 \cdot H_2SO_4$	32.42	6.81	28.36	32.50	7.05	28.51
61		H_2SO_4	242.5	A[b]	$C_{12}H_{26}N_6 \cdot H_2SO_4 \cdot {}^1/_2H_2O$	39.87	8.09	23.25	40.11	8.06	23.41

[a] 3-Aminomethylpiperidine was prepared according to the procedure of M. Freifelder and G. R. Stone, *J. Org. Chem.*, **26**, 3807 (1961). [b] The required amine is menthanediamine.

TABLE VI

CYCLIC GUANIDINES



No.	Compound R	n	Salt	M.p., °C.	Method[a]	Empirical formula	Analyses, % Calcd. C	H	N	Found C	H	N
62	$(C_2H_5)_2NCH_2CH_2NH$	2	$(C_2H_2O_4)_2$[b]	129–130[c]	A	$C_9H_{20}N_4 \cdot C_4H_4O_8$	42.85	6.64	15.38	42.92	6.94	15.35
			$(C_4H_4O_4)_2$[d]	167–168		$C_9H_{20}N_4 \cdot C_8H_8O_8$	49.03	6.78	13.46	49.24	6.94	13.53
63	$(CH_3)_2N(CH_2)_3NH$	2	$(C_4H_4O_4)_2$[d]	160.5–162	A	$C_8H_{18}N_4 \cdot C_8H_8O_8$	47.75	6.51	13.92	47.69	6.59	13.79
64	$(CH_3)_2N(CH_2)_3NH$	2	$(C_4H_4O_4)_2$[d]	146–147	A	$C_{10}H_{22}N_4 \cdot C_8H_8O_8$	50.22	7.03	13.02	50.34	7.28	13.00
65	$(C_2H_5)_2NCH_2CH_2N(C_2H_5)$	2	$(C_2H_2O_4)_2$[b]	160–160.5	A	$C_{11}H_{24}N_4 \cdot C_4H_4O_8$	45.91	7.19	14.28	46.04	7.49	14.37
66	$[(C_2H_5)_2NCH_2CH_2]_2N$	2	$(C_2H_2O_4)_3$[b]	145–147	A[e]	$C_{18}H_{38}N_8 \cdot C_6H_6O_{12}$	45.57	7.10	12.65	45.72	6.92	12.71
67	Morpholino	2	HCl	211–213	A	$C_7H_{13}N_3O \cdot HCl$	43.86	7.36	21.93	44.03	7.55	21.84
68	Morpholino	3	HI	119.5–120	A	$C_8H_{15}N_3O \cdot HI$	32.33	5.43		32.17	5.32	
69	$(C_2H_5)_2NCH_2CH_2NH$	3	2HI	148–148.5	A	$C_{10}H_{22}N_4 \cdot 2HI$	26.44	5.33	12.33	26.45	5.37	12.27
70	$(CH_3)_2N(CH_2)_3NH$	3	2HI	135–136	A	$C_9H_{20}N_4 \cdot 2HI$	24.56	5.04	12.73	24.86	5.06	12.84
			$(C_2H_2O_4)_2$[b]	157–158		$C_9H_{20}N_4 \cdot C_4H_4O_8$	42.85	6.64	15.38	43.02	6.50	15.34
71	4-Methylpiperazinopropyl	3	$(C_4H_4O_4)_3$[d]	157–158	A	$C_{12}H_{25}N_5 \cdot C_{12}H_{12}O_{12}$	49.05	6.34	11.92	48.91	6.54	11.78
72	$(C_2H_5)_2NCH_2CH_2NH$	4	HI	94–95	[f]	$C_{11}H_{24}N_4 \cdot HI$	38.83	7.40	16.47	38.68	7.60	16.69

[a] Compounds 62–67 were prepared from 2-methylthio-2-imidazoline hydrochloride (see Experimental), and compounds 68–71 were prepared from 2-methylthio-1,4,5,6-tetrahydropyrimidine hydriodide (A. F. McKay and W. G. Hatton, *J. Am. Chem. Soc.*, **78**, 1619 (1956). [b] $C_2H_2O_4$ is oxalic acid. [c] Boiling point (free base), 160–175° (1.5 mm.). [d] $C_4H_4O_4$ is fumaric acid. [e] Reactants refluxed in *n*-butyl alcohol overnight. [f] Prepared from 2-diethylaminoethylamine and 2-nitroamino-1,3-diaza-2-cycloheptene (A. F. McKay and G. F. Wright, *J. Am. Chem. Soc.*, **70**, 430 (1948).

TABLE VII

NITRO- AND AMINO-GUANIDINES

No.	Compound R[1]	R[2]	Salt	M.p., °C.	Method	Empirical formula	Analyses, % Calcd. C	H	N	Found C	H	N
73	$(CH_3)_2NCH_2CH_2$	NO_2	HCl	214.5–216.5	[a]	$C_5H_{13}N_5O_2 \cdot HCl$	28.40	6.67	33.10	28.19	6.75	32.97
74	$(C_2H_5)_2NCH_2CH_2$	NO_2		117–119	[a]	$C_7H_{17}N_5O_2$	41.36	8.43	34.47	41.28	8.75	34.61
75	$(CH_3)_2N(CH_2)_3$	NO_2	HCl	149.5–151.5	[a]	$C_8H_{15}N_5O_2 \cdot HCl$	31.93	7.16	31.05	31.69	7.05	30.85
76	$(C_4H_9)_2N(CH_2)_3$	NO_2	HCl	128–130	[a]	$C_{12}H_{27}N_5O_2 \cdot HCl$	46.51	9.11	22.60	46.23	8.86	22.95
77	H	$N{=}C(CH_3)C_2H_5$	HNO_3	143.5–145.5	[b]	$C_5H_{12}N_4 \cdot HNO_3$	31.42	6.85	36.62	31.65	6.92	36.67
78	H	$N{=}CHC_6H_5$	HNO_3	159.5–161.5[c]	[b]							
79	H_3C	NH_2	HI	120–122[d]	[e]							
80	n-C_4H_9	NH_2	HI	53–54[f]	[e]							
81	$(CH_3)_2NCH_2CH_2$	NH_2	$(C_2H_2O_4)_2$[g]	128–128.5	[e]	$C_5H_{15}N_5 \cdot C_4H_4O_8$	33.22	5.89	21.53	33.12	5.89	21.31
82	4-Methylhomopiperazinopropyl	NH_2	$(C_2H_2O_4)_3$[g]	110	[e]	$C_{10}H_{24}N_6 \cdot C_6H_6O_{12}$	38.55	6.07	16.86	38.42	6.45	16.29
83	$(C_2H_5)_2NCH_2CH_2$	NH_2	$(C_4H_4O_4)_2$[i]	134.5–135.5	[e]	$C_7H_{19}N_5 \cdot C_8H_8O_8$	44.43	6.71	17.27	44.35	7.06	17.10
84	[j]		H_2SO_4	270–270.5	[h]	$C_7H_{19}N_5 \cdot H_2SO_4$	30.98	7.80	25.82	30.90	7.84	25.94

[a] The nitroguanidines were prepared by "Procedure II" described by A. F. McKay, *J. Am. Chem. Soc.*, **71**, 1969 (1949). [b] A suspension of aminoguanidine bicarbonate and the carbonyl compound was heated until solution was effected; nitric acid was added, and the solution chilled to obtain the product. [c] The recorded m.p. is 156–158°, F. L. Scott, D. G. O'Donovan, and J. Reilly, *ibid.*, **75**, 4054 (1953). [d] The recorded m.p. is 121–122°, G. W. Kirsten and G. B. L. Smith, *ibid.*, **58**, 801 (1936). [e] Prepared from the appropriate amine and 2-methyl-2-thioisosemicarbazide hydriodide, M. Freund and T. Paradies, *Ber.*, **34**, 3114 (1901). [f] The recorded m.p. is 51–52°. For reference, see footnote *d*. [g] $C_2H_2O_4$ is oxalic acid. [h] Prepared from 2-methyl-2-thiopseudourea sulfate and diethylaminoethylhydrazine. Synthesis of the latter is described in the Experimental. [i] $C_4H_4O_4$ is fumaric acid. [j] Compound is 1-amino-1-(2-diethylaminoethyl)-guanidine sulfate.

TABLE VIII

COMPARATIVE PHARMACOLOGICAL ACTIVITY

No.[a]	Dose, mg./kg.	Duration, hr.	Comparative activity[c]
2	15	48	90
	30	60	
3	15	7	10
	30	8	
5	15	48	60
	30	48	
12	15	32	40
	30	48	
21[b]	15	0	1
	30	3	
22[b]	15	5	15
	30	8	
23	15	48	100
	30	96	
28	15	30	40
	30	48	
33	15	0	15
	30	46	
34	15	0	15
	30	48	
36	15	8	20
	30	32	
42	15	22	30
	30	48	
43	15	26	40
	30	48	
44	15	0	1
	30	3	
49[b]	15	24	30
	30	32	
62	15	96	40
	30	6	

[a] The numbers in this column refer to the compounds in Tables III–VI. [b] The activity of this compound appears to be due to ganglionic blockade. [c] For explanation, see section on Pharmacology.

Experimental[9]

3,5-Dimethyl-1-guanylpyrazole Hydrochloride.—To a refluxing solution of 240.3 g. (2.4 moles) of acetylacetone in 336 ml. of 50% aqueous ethanol was added, in small portions, 132.6 g. (1.2 moles) of aminoguanidine hydrochloride. After the addition had been completed, refluxing was continued for 2 hr. The solution was allowed to stand overnight and then was diluted with ether, causing a yellow oil to precipitate. The oil slowly solidified to give 86.1 g. (40.5%) of white, slightly hygroscopic solid melting at 136.5–138°.

Anal. Calcd. for $C_6H_{10}N_4$·HCl: C, 41.26; H, 6.35. Found: C, 41.14; H, 6.55.

1-Ethyl-2-piperidylmethylamine.—A mixture of 24 g. (0.085 mole) of 2-pyridinealdoxime ethiodide,[10] 200 ml. of 2-methoxyethanol, 75 ml. of water, and 4.5 g. of 5% rhodium on alumina was hydrogenated at room temperature and 2.8 kg./cm.^{2} The catalyst was filtered and the solution was stripped. The residual oil was dissolved in 50 ml. of water, made alkaline with 50% sodium hydroxide solution, and extracted with three 100 ml. portions of benzene. The benzene was dried over Drierite. After removing the drying agent and solvent, the residue was subjected to vacuum distillation. The material boiling at 104–120° (25 mm.) was collected and redistilled to obtain 3.6 g. (30%) of colorless oil, which boiled at 79–89° (15 mm.), n^{25}D 1.4760.

An attempt to carry out the hydrogenation in acetic acid over platinum catalyst failed.

Anal. Calcd. for $C_8H_{18}N_2$: C, 67.55; H, 12.76; N, 19.70. Found: C, 67.44; H, 13.15; N, 19.48.

1-Methyl-2-piperidylmethylamine.—This compound was prepared in the same manner as was its ethyl homolog. The yield of colorless liquid, b.p. 83–86° (22 mm.), n^{25}D 1.4724, was 3.2 g. (13%).

Anal. Calcd. for $C_7H_{16}N_2$: C, 65.57; H, 12.58; N, 21.85. Found: C, 64.96; H, 12.10; N, 22.55.

1-Carbethoxy-4-(2-diethylaminoethyl)-piperazine.—A solution of 86 g. (0.5 mole) of 2-diethylaminoethyl chloride hydrochloride, 79 g. (0.5 mole) of 1-carbethoxypiperazine, and 53 g. (0.5 mole) of sodium carbonate in 1.0 l. of 50% ethanol was heated under reflux overnight. The solution was stripped and the residue was extracted with benzene. The benzene was filtered and the filtrate was stripped. Distillation of the residue gave 71.5 g. (59%) of colorless oil, b.p. 174–176° (15 mm.), n^{25}D 1.4712.

Anal. Calcd. for $C_{13}H_{27}N_3O_2$: C, 60.66; H, 10.57; N, 16.33. Found: C, 60.87; H, 10.50; N, 16.53.

1-(2-Diethylaminoethyl)-piperazine.—A solution of 41.5 g. (0.24 mole) of 1-carbethoxy-4-(2-diethylaminoethyl)-piperazine in 180 ml. of concd. hydrochloric acid diluted with 120 ml. of water was heated under reflux for 24 hr. The solution was stripped, and the residue was treated with liquid ammonia. After the ammonia had evaporated, the residue was triturated with ether. The inorganic material was separated by filtration; the ether was evaporated, and the residue was distilled to obtain 30.5 g. (66%) of colorless oil, b.p. 122–126° (13 mm.), n^{25}D 1.4760.

A **picrate** was prepared and recrystallized twice from acetone, m.p. 242–242.5°.

Anal. Calcd. for $C_{28}H_{32}N_{12}O_{28}$: C, 38.53; H, 3.70; N, 19.26. Found: C, 38.79; H, 3.98; N, 19.42.

2-Methyl-2′-phenyldiethanolamine.—To a stirred mixture of 360 g. (3 moles) of styrene oxide and 12 ml. of water was added dropwise 405 g. (5.4 moles) of 1-amino-2-propanol. During the addition the temperature was maintained at about 30° by means of an ice bath. Upon removal of the ice bath the temperature rose rapidly to 145°. After the exothermic reaction had ceased, the reaction mixture was heated on the steam bath for 1 hr., allowed to stand overnight at room temperature, and then distilled to obtain 434 g. (74%) of pale yellow, viscous oil, b.p. 169–173° (1.1 mm.), n^{25}D 1.5386.

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.79; N, 7.17. Found: C, 67.91; H, 8.61; N, 7.34.

2-Methyl-6-phenylmorpholine.—To 1.0 l. of 70% sulfuric acid was added dropwise, with stirring, 434 g. (2.22 mole) of 2-methyl-2′-phenyldiethanolamine. During the addition the temperature was maintained at 10–20°. The mixture was then heated for 4 hr. on the steam bath and allowed to stand overnight at room temperature. It was poured on to cracked ice and made alkaline with 40% sodium hydroxide solution. An oil separated, was taken up in benzene, and dried over magnesium sulfate. After removal of solvent and drying agent, distillation gave a colorless oil, which boiled at 132–134° (9.0 mm.), n^{25}D 1.5344. The yield was 261 g. (67%).

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.46; H, 8.25; N, 8.01.

A **hydrochloride** salt was prepared and after two recrystallizations from methanol–acetone melted at 153–154°.

Anal. Calcd. for $C_{11}H_{15}NO$·HCl: C, 61.82; H, 7.55; N, 6.56. Found: C, 61.99; H, 7.54; N, 6.57.

2-Diethylaminoethylhydrazine and 1,1-Bis(2-diethylaminoethyl)-hydrazine.—A solution of 48 g. (1.5 mole) of 95% hydrazine in 250 ml. of ethanol was heated under reflux while 68 g. (0.5 mole) of diethylaminoethyl chloride was added. Refluxing was continued for 4 hr. Most of the alcohol was removed under reduced pressure, and a solution of 33 g. of 85% potassium hydroxide dissolved in the minimum volume of ethanol was added. The solid which formed was filtered and washed with ethanol. The filtrate was diluted with ether and the solid which formed was removed. The filtrate was stripped and the residue was distilled to obtain 32 g. (49%) of 2-diethylaminoethylhydrazine which boiled at 69–71° (7.0 mm.), n^{25}D 1.4570. Recorded[11] physical constants are: b.p. 76–77° (9.0 mm.), n^{32}D 1.4590. A second product, boiling at 125–127° (7.0 mm.), n^{25}D 1.4585, was obtained in 13 g. yield.

Anal. Calcd. for $C_{12}H_{30}N_4$: C, 62.60; H, 13.04; N, 24.34. Found: C, 62.84; H, 12.82; N, 25.08.

The higher boiling material differed from 1,2-bis(2-diethylaminoethyl)-hydrazine, prepared according to a known procedure.[12] It is presumed to be 1,1-bis(2-diethylaminoethyl)hydrazine.

(9) Melting points are corrected.

(10) E. J. Poziomek, B. E. Hackley, Jr., and G. M. Steinberg, *J. Org. Chem.*, **23**, 714 (1958).

(11) A. Ebnöther, E. Jucker, A. Lindenmann, E. Rissi, R. Steiner, R. Süess, and A. Vogel, *Helv. Chim. Acta*, **42**, 540 (1959).

(12) J. H. Biel, H. E. Drukker, and T. F. Mitchell, Jr., *J. Am. Chem. Soc.*, **82**, 2205 (1960).

2-Methylthio-2-imidazoline Hydrochloride.—A mixture of 209.5 g. (2.05 moles) of ethylenethiourea, 120 ml. (2.36 moles) of methyl chloride, and 250 ml. of methanol was heated in a stainless steel bomb at 100° for 3 hr. The reaction mixture was filtered to obtain 196 g. of material melting at 166–169°. The filtrate was diluted with ether to obtain an additional 92.5 g. of product, m.p. 161–166°. Total yield was 288.5 g. (92%).

Anal. Calcd. for $C_4H_8ClN_2S$: C, 31.47; H, 5.94; N, 18.35. Found: C, 31.29; H, 6.05; N, 18.11.

Preparation of Guanidines.—The following are generalized procedures.

Method A.[4]—Equimolar amounts of the amine and 2-methyl-2-thiopseudourea sulfate in water, or the amine and 2-methyl-2-thiopseudourea hydriodide[13] in ethanol, were heated under reflux for 2 hr. or allowed to stand at room temperature overnight. In most cases one equivalent of acid was added; the solution was stripped, and the solid was recrystallized from an appropriate solvent.

Method B.—Equimolar amounts of the amine and cyanamide in water were heated under reflux for 6 hr. Acid was added and the solution was worked up in the manner described for method A.

Method C.—The method is essentially that of Raiford and Daddow.[14] When the reaction was run in benzene, however, it was heated under reflux for 30 hr. If the amine was low boiling, the reaction was carried out in a bomb and an excess of the amine was used as the solvent.

(13) A. Lespagnol, E. Cuingnet, and M. Debaert, *Bull. Soc. Chim. France*, 387 (1960).

(14) L. C. Raiford and W. T. Daddow, *J. Am. Chem. Soc.*, **53**, 1552 (1931).

Method D.—The procedure was based on the one described by Scott, O'Donovan, and Reilly,[15] using ethanol as the solvent.

1-[2-(2-Piperidyl)-ethyl]guanidine Sulfate.—A solution of 20.4 g. (0.078 mole) of 1-[2-(2-pyridyl)-ethyl]-guanidine sulfate (Table III, 32) in 150 ml. of water was hydrogenated over 5% rhodium on alumina at 2.8 kg./cm.^{2} Uptake was complete in 3 hr. The catalyst was removed and the solution was taken to dryness. The residue was recrystallized from aqueous ethanol to give 20.7 g. (88%) of white, crystalline solid (Table III, 33).

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(15) F. L. Scott, D. G. O'Donovan, and J. Reilly, *ibid.*, **75**, 4053 (1953).

Studies on Methylglyoxal Bis(guanylhydrazone)[1] Analogs. I. Homologs of Methylglyoxal Bis(guanylhydrazone)[2]

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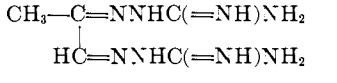
Investigation of different methods leading to the synthesis of alkylglyoxals was conducted. The method used in the preparation of ethylglyoxal *via* 2-butyne-1,4-diol is of only limited applicability. The reaction of Grignard reagents with dialkoxyacetylpiperidine provides the most convenient route to alkylglyoxals. The procedure utilizing ethyl diethoxyacetoacetate gives substituted glyoxals in relatively good yield. Use of dichloromethyl alkyl ketones as precursors is limited because of the poor yields of the dichloroketones. The preparation of all the theoretically possible methylated aminoguanidines bearing a free N-amino group has been studied. Condensation of these substituted aminoguanidines with methylglyoxal, together with the condensation of aminoguanidine with alkyl glyoxals, furnish all the necessary compounds for the phase I (homologs) study in the methylglyoxal bis(guanylhydrazone) series.

A recent report indicated that methylglyoxal bis(guanylhydrazone)[1] (I), prepared by Freedlander and French,[3] produced the first significant remissions in

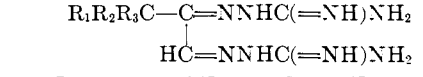


I

adult acute myelocytic leukemia.[4] This drug, however, is quite toxic.[5] These facts necessitated a systematic synthesis and investigation of compounds related to I in an attempt to prepare derivatives with better therapeutic indices. Studies on the synthesis of various compounds related to I have thus been undertaken.

The synthesis of the homologs of I can be divided into two areas: (1) homologs of the methylglyoxal moiety, and (2) homologs of the guanylhydrazone moiety.

Area 1—Homologs of the Methylglyoxal Moiety.—This area includes compounds in which the hydrogen atom(s) of the methyl group in I is (are) replaced by an alkyl group(s)



II.	$R_1 = CH_3$; R_2, R_3 = H
III.	R_1, $R_2 = CH_3$; R_3 = H
IV.	R_1, R_2, $R_3 = CH_3$
V.	$R_1 = CH_3(CH_2)_2$; R_2, R_3 = H
VI.	$R_1 = CH_3(CH_2)_3$; R_2, R_3 = H
VII.	$R_1 = CH_3(CH_2)_4$; R_2, R_3 = H
VIII.	$R_1 = CH_3(CH_2)_{14}$; R_2, R_3 = H

Although selenium dioxide is an outstanding agent

(1) The "Chemical Abstracts" name for this compound is 1,1'-[(methyl)-ethanediylidenedinitrilo]diguanidine.

(2) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service Contract SA-43-ph-3025.

(3) B. L. Freedlander and F. A. French, *Cancer Research*, **18**, 360 (1958).

(4) F. Freireich and E. Frei, III, *Proc. Am. Assoc. Cancer Res.*, **3**, 319 (1962).

(5) (a) W. Regelson, O. Selawry, and J. F. Holland, *Proc. Am. Assoc. Cancer Res.*, **3**, 352 (1962); (b) M. E. Tidball and D. P. Rall, *ibid.*, **3**, 367 (1962).