The benzylamino derivative was hydrogenated in AcOH over Pd-C at room temperature and pressure. The catalyst was filtered, the solvent was evaporated, and the residue was basified and distilled to give the product, **2-aminomethyl-2,3-dihydrobenzofuran,** bp 86° (0.01 mm), $n^{25}D$ 1.5575. *Anal.* ($C_9H_{11}NO$) C, H. The hydrogen maleate had mp 147° (from EtOH-Et_2O).

The primary amine was converted to the guanidine by a standard procedure (A, ref 1a). The product had mp 204–206° (from aqueous acetone). *Anal.* ($C_{10}H_{13}N_3O \cdot 0.5H_2SO_4$) C, H, N.

2-Guanidinomethylnaphthalene Tosylate (10).—2-Aminomethylnaphthalene (2.5 g) and guanidine tosylate (3.6 g) were heated together at 150°. NH_3 was evolved while the temperature of the reaction was raised to 190° over 45 min. When cold, the mixture was crystallized from H_2O and then EtOH to give the product, mp 198–200°. *Anal.* ($C_{12}H_{13}N_3 \cdot C_7H_8SO_3$) C, H, N.

Acknowledgment.—We wish to thank Mr. P. R. Wood for the microanalyses, Dr. C. R. Worthing and Mrs. S. M. Green for preparation of two of the compounds, and Messrs. P. Clement, B. Sneddon, and J. Zoro for their competent assistance. We also wish to thank Mr. K. Farrier for assistance with the pharmacology.

Sympathetic Nervous System Blocking Agents. IV. Synthesis of 2-(2-Methylthioethylamino)ethylguanidine Sulfate and Related Compounds[1,2]

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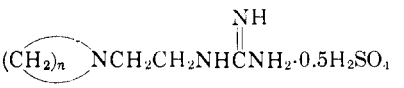
Received December 2, 1967

The reaction between N-(2-aminoethyl)aziridine and 2-methyl-2-thiopseudourea sulfate failed to give the expected 2-(1-aziridinyl)ethylguanidine sulfate (I, $n = 2$). The product isolated proved to be 2-(2-methylthioethylamino)ethylguanidine sulfate (V), and it caused an effective blockade of the sympathetic nervous system as determined by its effect on the nictitating membrane of the unanesthetized cat following oral administration. Eight homologs and analogs were prepared in order to study the structure–activity relationships in this series of compounds. The title compound proved to be the most active member of the series and was subjected to extensive pharmacological evaluation. The mechanism of formation of the title compound was studied. The reaction appears to proceed *via* 2-(1-aziridinyl)ethylguanidine followed by opening of the aziridine ring with methanethiol, rather than by a one-step intramolecular reaction.

The first guanidine reported to be effective in blocking the sympathetic nervous system was guanethidine[3] (I, $n = 7$). Lower homologs (I, $n = 4$–6) have been



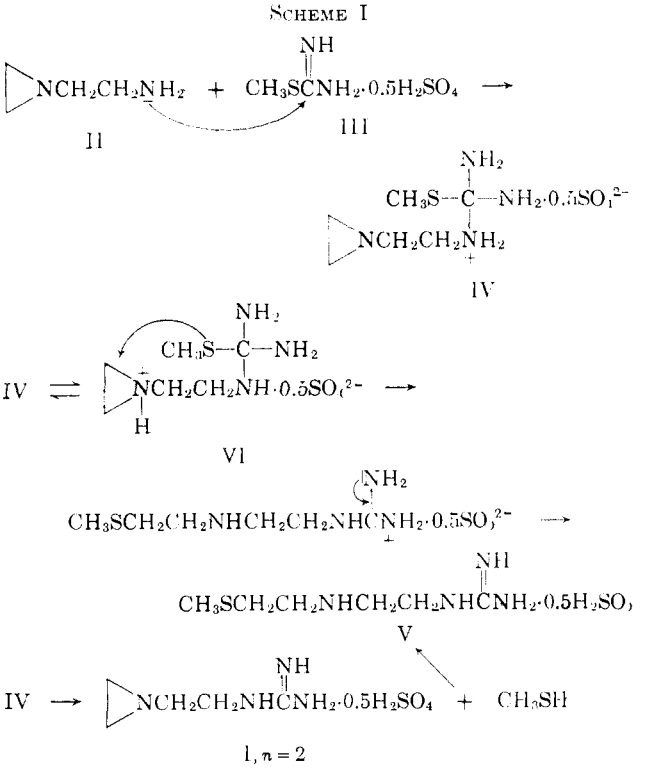
I

prepared,[4] but not those with $n = 2$, 3. We were interested in preparing the smallest homolog of the guanethidine series. Therefore, the reaction between N-(2-aminoethyl)aziridine (II) and 2-methyl-2-thiopseudourea sulfate (III) was investigated (Scheme I). The product of this reaction, however, was not the desired 2-(1-aziridinylethyl)guanidine sulfate (I, $n = 2$) but proved to be 2-(2-methylthioethylamino)ethylguanidine sulfate (V), on the basis of elemental analyses, ir, and nmr spectra. The same substance was obtained when N-(2-methylthioethyl)ethylenediamine (VII), obtained from II and methanethiol, was allowed to react with III.

VII

At first glance it seems logical that I ($n = 2$) did form, and then underwent ring opening to V by reaction with methanethiol. Indeed, the evolution of some

SCHEME I



I, $n = 2$

methanethiol during the course of this reaction was evident. On the other hand, the intermediacy of I ($n = 2$) is not essential to formation of V. One could visualize a concerted mechanism in which liberation of methanethiol does not occur. If I ($n = 2$) is actually an intermediate in this reaction then any other thiol present should compete with the methanethiol to open the aziridine ring. On the other hand if VI, or some-

(1) Paper III: J. H. Short and T. D. Darby, *J. Med. Chem.*, **10**, 833 (1967).

(2) Presented before the Division of Medicinal Chemistry at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

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

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

thing similar, represents an intermediate in the course of the reaction, then exogenous thiol should have no influence on the nature of the product.

In order to attempt to determine which course this reaction follows the reaction between II and III was run in the usual manner with the addition of ethanethiol. The product isolated proved to be about a 1:1 mixture of V and 2-(2-ethylthioethylamino)ethylguanidine sulfate (X, R = C_2H_5, $m = n = 2$). Identity and approximate ratio of the two substances were determined by nmr spectroscopy, and identity was confirmed by means of tlc.

Similar results were obtained when 2-ethyl-2-thiopseudourea sulfate (IX, R = C_2H_5) was allowed to react with II in the presence of methanethiol.

These observations tend to indicate that I ($n = 2$) is formed *in situ* followed by attack of the thiol on the aziridine ring to give the observed products. The above results would be meaningless, however, if either III or V underwent exchange with ethanethiol. Both III and V were allowed to stand in contact with ethanethiol at room temperature and at 55°. No exchange was evident in either experiment with V, but with III some exchange did take place at 55°, but none was evident at room temperature. Since the guanidine is prepared at room temperature, the intermediacy of I ($n = 2$) in this reaction seems well established.

This opening of the aziridine ring at room temperature is in contrast to the reaction of methanethiol with N-ethylaziridine and N-(2-aminoethyl)aziridine. In these two cases reaction does not occur at ambient temperature, but elevated temperatures must be employed.

The more facile ring opening of I ($n = 2$) is undoubtedly due to the fact that the aziridine nitrogen is partially protonated thus facilitating the attack of the methylthio anion. Thiols in general are acidic enough to protonate the aziridine nitrogen, thus facilitating ring opening, without addition of an acidic catalyst, although elevated temperatures are frequently required.

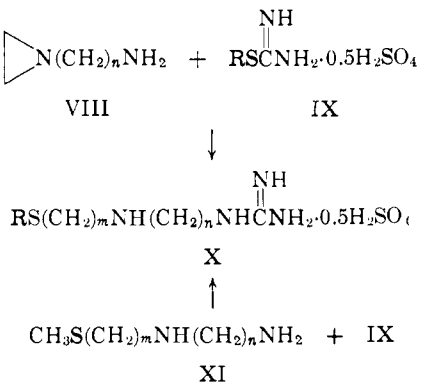
2-Methylpseudourea salts, as well as the thio analogs, may be used to prepare guanidines. Methanol instead of methanethiol is evolved. Methoxide anion is a poorer nucleophile than the methylthio anion; further, methanol is such a weak acid that it does not significantly protonate the aziridine nitrogen. An alcohol, therefore, will not open the aziridine ring in the absence of an acid catalyst, so we felt that the reaction between II and 2-methylpseudourea sulfate might produce the desired 2-(1-aziridinyl)ethylguanidine sulfate (I, $n = 2$). Several attempts to effect this reaction failed to lead to any single pure product.

The effectiveness of V in causing blockade of the sympathetic nervous system led us to prepare a number of homologs and analogs of V in order to attempt to draw some conclusions in regard to structure–activity relationships.

First we wished to determine the significance of the sulfur atom for activity. 2-Diethylaminoethylguanidine sulfate is also an effective adrenergic blocking agent.[5] This compound, guanethidine, and V possess in common a basic nitrogen atom separated from the guanidine moiety by two carbon atoms. This grouping

(5) J. H. Short, U. Biermacher, D. A. Dunnigan, and T. D. Leth, *J. Med. Chem.*, **6**, 275 (1963).

SCHEME II



is of undoubted importance, and the presence of the methylthio group may be of secondary importance. Analogs of V, wherein the methylthio group was replaced by hydrogen and by diethylamino, namely 2-ethylaminoethylguanidine sulfate and 2-(2-diethylaminoethylamino)ethylguanidine sulfate, were prepared and both proved to be inactive. The presence of the sulfur atom does, therefore, appear to be of real significance. The oxygen analog of V, 2-(2-methoxyethylamino)ethylguanidine sulfate, was active, but less so than V. The oxygen analog of V, as indicated above, could not be obtained from II and 2-methylpseudourea sulfate and was actually prepared from N-(2-methoxyethyl)ethylenediamine.

The reaction between 1-(3-aminopropyl)aziridine (VIII, $n = 3$) and IX (R = CH_3) produced a compound containing sulfur, and it is assumed to be 3-(2-methylthioethylamino)propylguanidine sulfate (X, R = CH_3; $m = 2$; $n = 3$) (Scheme II). The isomer of the last compound, 2-(3-methylthiopropylamino)ethylguanidine sulfate (X, R = CH_3; $m = 3$; $n = 2$), was prepared from N-(3-methylthiopropyl)ethylenediamine (XI, $m = 3$; $n = 2$). These isomers were equally active, but considerably less active than V.

A higher homolog, 3-(3-methylthiopropylamino)-propylguanidine sulfate (X, R = CH_3; $m = n = 3$), was prepared from N-(3-methylthiopropyl)-1,3-propanediamine (XI, $m = n = 3$), and it proved to be inactive.

The amines (XI, $m = 3$; $n = 2$ and XI, $m = n = 3$) required for the last two guanidines were prepared in four steps starting with the reaction between methanethiol and acrylonitrile to give 3-methylthiopropionitrile. The latter was reduced with $LiAlH_4$ to 3-methylthiopropylamine. The amine was allowed to react with glycolonitrile and acrylonitrile to give, respectively, 3-methylthiopropylaminoacetonitrile and 3-(3-methylthiopropylamino)propionitrile. Reduction of the nitriles with $LiAlH_4$ led to the desired diamines.

The reaction between N-(2-aminoethyl)aziridine (VIII, $n = 2$) and 2-ethyl-2-thiopseudourea sulfate (IX, R = C_2H_5), as indicated above, produced 2-(2-ethylthioethylamino)ethylguanidine sulfate (X, R = C_2H_5; $m = n = 2$). This homolog of V proved to be inactive.

All the compounds described above contain a secondary amine function. We felt it was necessary to prepare a homologous tertiary amine to determine the importance of the secondary amine group. The necessary intermediate for the preparation of the N-ethyl homolog was 2-methylthiodiethylamine, which was

obtained by action of methanethiol on N-ethylaziridine. The yield was 81% when the reaction was effected at 100°. At 80° the yield was only 23% and none of the desired secondary amine was obtained when the reaction temperature was 60°.

The secondary amine was allowed to react with glycolonitrile and the nitrile was reduced, in turn, to N-ethyl-N-(2-methylthioethyl)ethylenediamine. The guanidine, which was prepared from this amine in the usual manner, proved to be less active than V, but about as active as the other active compounds.

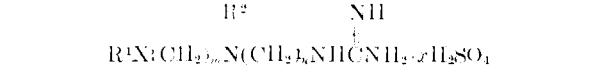
The following conclusions may therefore be made concerning structure–activity relationships of these compounds: (1) the methyl group is essential for activity; (2) sulfur may be replaced with oxygen, but a reduction in activity ensues; (3) either, but not both, ethylene groups may be replaced with a trimethylene group to give active compounds, but again activity is reduced; and (4) introduction of an alkyl group at the secondary amino nitrogen gives less active homologs.

The infrared spectra of the nine guanidines were determined. The only bands useful for identification purposes are a pair of strong bands between 1700 and 1600 cm^{-1}.

Pharmacology. Effect on the Cat Nictitating Membrane.—The nine guanidines were investigated for adrenergic neurone blocking activity by means of their effect on the nictitating membrane of the unanesthetized cat following oral administration in the manner previously described.[1,5] Four of the compounds (Table I, **2**, **7**–**9**) were inactive at 30 mg/kg. Four of them (**3**–**6**) caused a ++ prolapse lasting 24 hr after a 30-mg/kg dose. A 30-mg/kg dose of 2-(2-methylthioethylamino)ethylguanidine sulfate (**1**) caused a ++ prolapse lasting for 72 hr at 30 mg/kg while a ++ prolapse lasting for 26 hr followed administration of 10 mg/kg. Compound **1**, therefore, is about three times as active, on a milligram basis, as the other four active compounds. The data are summarized in Table I.

Table I

Effect of Guanidines on the Nictitating Membrane of the Cat



No.	R[a]	R^2	X	a	b	x	Dose, mg/kg	Effect on nictitating membrane[b]	Duration, hr
1	CH_3	H	S	2	2	0.5	30	++	72
							15	++	27
							10	−+	26
							5	−	24
							2	0	
2	C_2H_5	H	S	2	2	0.5	30	0	
3	CH_3	H	O	2	2	1	30	++	24
4	CH_3	C_2H_5	S	2	2	0.5	30	−+	24
							15	+	6
5	CH_3	H	S	2	3	1	30	++	24
							15	0	
6	CH_3	H	S	3	2	0.5	30	++	24
							15	0	
7	CH_3	H	S	3	3	1	30	0	
8	$(C_2H_5)_2$	H	N	2	2	1.5	30	0	
9	2-(Ethylamino)ethylguanidine sulfate						30	0	

[a] The degree of prolapse is indicated as follows: +, one-quarter of the eye covered by membrane; ++, one-half of the eye is covered.

Effect on Cat Blood Pressure.—The five compounds showing adrenergic neurone blocking activity were examined for their effect on mean arterial blood pressure of the anesthetized cat following intravenous administration in the manner previously described.[1]

The blood pressure responses were variable. The title compound (Table II, **1**) at 2 and 5 mg/kg along with **4** at 10 mg/kg caused an initial brief rise in blood pressure, followed by a prolonged decrease. The initial pressor response is presumed to be due to liberation of catecholamines from the adrenergic nerve endings. A similar pressor response is seen following intravenous injection of guanethidine, and is believed to be due to release of catecholamines.[6] In some cases only the pressor response occurred (**1** and **3** at 10 mg/kg) while in other cases only a depressor response was seen (**3**–**5** at 2 mg/kg and **5** at 10 mg/kg). Very little effect on blood pressure occurred following administration of **6**.

The pressor response to bilateral carotid artery occlusion was generally reduced, as expected, since this pressor response is mediated through the sympathetic nervous system.

The effects of these compounds on the response to a test dose of epinephrine varied. No uniform effect on the heart rate or respiration was observed.

These results are summarized in Table II.

Further studies were carried out only with V.

Symptomatology in Dogs.—The candidate drug (V) was given to two dogs at each of three dose levels, 12, 25, and 75 mg/kg for 14 days. The compound was placed in gelatin capsules, and the capsules were immersed for 10 sec in a 10% formaldehyde solution and then allowed to dry overnight. These "enteric-coated capsules" were placed inside the next larger size capsule and given to the dogs in a meat ball. The dogs were fed immediately. These precautions were taken to prevent the capsules from breaking down in the stomach which would result in immediate emesis. This method of dosing is used routinely in our laboratories for studying guanidine derivatives in both normotensive and hypertensive dogs. Reasonably uniform absorption from the intestine has been confirmed with labeled compounds.

The following observations were made: effect on pupil size, nictitating membrane, respiration, heart rate, and mucous membranes; evidence of CNS excitation; and GI disturbances. On the first day these observations were made at 0.5-hr intervals for 2.5 hr and then hourly for the rest of the day. On days 2–14 observations were made 3–6 hr after administration of the drug.

All dogs showed a + or ++ prolapse of the nictitating membrane which developed on day 2 and remained throughout the test period.

At 75 mg/kg emesis occurred after about half of the doses in spite of the precautions described above. Two episodes of diarrhea occurred with one dog and three

(6) J. W. McCubbin, Y. Kaneko, and I. H. Page, *J. Pharmacol. Exptl. Therap.*, **131**, 346 (1961); T. E. Gaffney, E. Braunwald, and T. C. Cooper, *Circulation Res.*, **10**, 83 (1962); D. C. Harrison, C. A. Chidsey, R. Goldman, and E. Braunwald, *ibid.*, **12**, 256 (1963); E. T. Alds, *Brit. J. Pharmacol.*, **26**, 162 (1966).

TABLE II

EFFECT OF GUANIDINES ON THE BLOOD PRESSURE OF ANESTHETIZED CATS

Compd[a]	Dose, mg/kg	Effect on mean arterial blood pressure[b,c]	Duration, min	Carotid occlusion[c,d] Before	Carotid occlusion[c,d] After	Epinephrine[c,e] Before	Epinephrine[c,e] After	Heart rate[c]	Respiration[c]
1	2.0	+17[f]	2	+10	+9	No change		0	0
		−40	180						
	5.0	+50[f]	10	+63	+12	No change		+	0
		−47	120						
	10.0	+40	22	+22	+3	+33	+16	0	0
3	2.0	−21	39	+16	+4	+14	+38	−	0
	10.0	+91[g]	4	+18	0	+48	+46	−	−
		+29	110						
4	2.0	−15	42	+59	+30	+19	+20	0	+
	10.0	+39[f]	8	+22	+10	+20	+50	+	−
		−14	114						
5	2.0	−17	32	+39	+10	+9	+14	−	0
	10.0	−51	94	+22	+6	+24	+20	−	0
6	2.0	−4	3	+39	+40	+20	+46	−	0
	10.0	+8	55	+50	+10	+48	+55	−	0

[a] The numbers refer to the compounds in Table I. [b] The mean arterial blood pressure is approximated by taking the sum of the diastolic and systolic pressures and dividing by 2. [c] + = increase, − = decrease, 0 = no change. [d] The effect of 25 μg of epinephrine on the blood pressure is measured before and after administration of the drug. [e] The effect on the blood pressure of 0.5 min of bilateral carotid artery occlusion is measured before and after administration of the drug. [f] An initial increase in blood pressure was followed by a decrease. [g] An initial large increase in blood pressure was followed by a prolonged smaller increase.

episodes with the other one. Both suffered a 20% weight loss. The only other adverse symptom seen was dryness of the nasal passages.

At 25 mg/kg one dog had two episodes of emesis and one of diarrhea. The other dog on 25 mg/kg and the two dogs on 12 mg/kg showed no abnormalities except for "dry nose" on days 11–14.

Effect on Hypertensive Dogs.—Studies in both renal and neurogenic hypertensive dogs were carried out with V in the manner previously described.[1] These dogs belong to a hypertensive colony maintained in our laboratories and each animal has been in the colony for at least 2 years. The control arterial blood pressures were obtained for 3 days before drug administration and the pressures were stable during this period. The control values given in Figures 1 and 2 correspond closely to other measurements made during the preceding year.

Single doses of 30 mg/kg of V given to both types of dogs did not cause an initial rise in blood pressure, as sometimes occurs with adrenergic blocking agents, but only a fall in blood pressure took place. The blood pressure was still significantly lower 24 hr later but had returned to control levels by 48 hr after administration of the substance. Diarrhea was observed in two of the four dogs.

A single oral dose of 5 mg/kg elicits at least a 15% decrease in blood pressure in both types of dogs.

Figure 1 shows the results of an 18-day study with two renal hypertensive dogs. The control blood pressure reading is indicated on day 0. A single dose of 20 mg/kg of V was administered on day 1. The dogs received a daily maintenance dose of 2.0 mg/kg on days 2–15 and 5.0 mg/kg on days 16–18. A significant reduction in blood pressure is evident, and no adverse side effects were seen.

A similar study was carried out on neurogenic hypertensive dogs and the results are shown in Figure 2. Results were more striking with the neurogenic dogs, as expected with this type of drug. Again no side effects were seen.

With four additional hypertensive dogs (two renal and two neurogenic), the results achieved with single daily oral doses were similar to those reported in detail in Figures 1 and 2. The compound has been administered a total of 106 times to the eight hypertensive dogs. The dose has ranged between 0.5 and 30 mg/kg. It causes a rapid onset of antihypertensive effect at 20 mg/kg, and the effect can be maintained with a daily dose as low as 2 mg/kg.

When guanethidine was studied in hypertensive dogs, similar results were seen, however diarrhea and emesis were common with guanethidine even at the lowest effective dose (5 mg/kg) in striking contrast to the lack of side effects seen with our compound. Guanethidine failed to show a significant effect on blood pressure at 2.0 mg/kg.

Toxicity Studies.—Acute toxicity studies were done in mice with V. The oral LD_{50} was found to be 1200 mg/kg, and the LD_{50} by the intravenous route was 93 mg/kg. The data are compiled in Table III.

The oral LD_{50} in rats was found to be 1850 mg/kg with a 95% confidence limit of 1560–2120 mg/kg. The intravenous LD_{50} was not determined in the rat.

The oral LD_{50} of guanethidine in rats is reported to be 1000 mg/kg while the intravenous LD_{50} is 23.1 mg/kg.[7]

Conclusions.—A new guanidine, 2-(2-methylthioethylamino)ethylguanidine sulfate (V), in animals, shows antihypertensive properties similar to those seen with guanethidine. It appears to have a somewhat better therapeutic index than guanethidine based on the oral LD_{50}'s in rats (1850 *vs.* 1000 mg/kg) and the minimum effective oral dose in hypertensive dogs (2.0 *vs.* 5.0 mg/kg). Further, at effective dose levels, V causes fewer side effects than does guanethidine.

(7) R. A. Maxwell, A. J. Plummer, F. Schneider, H. Povalski, and A. I. Daniel, *J. Pharmacol. Exptl. Therap.*, **128**, 22 (1960).

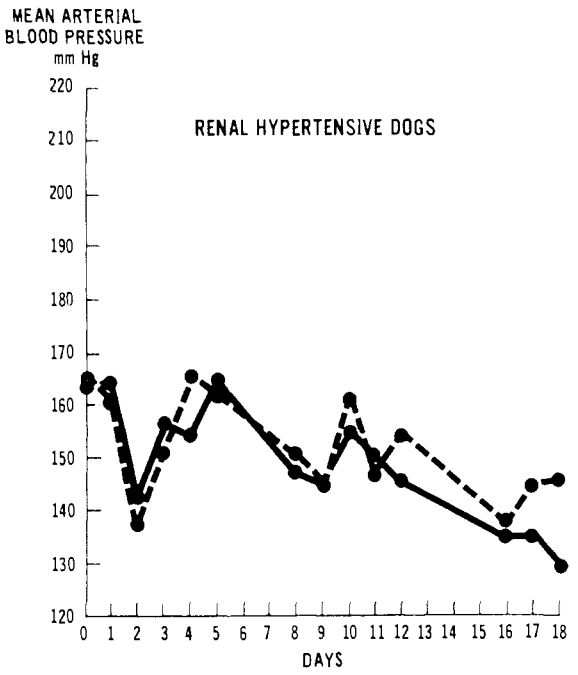


Figure 1.—The effect of 2-(2-methylthioethylamino)ethylguanidine sulfate (V) on two renal hypertensive dogs. The control blood pressure is recorded at day 0, and represents the average of three measurements taken on three different days. On day 1, 20 mg/kg of V was given, followed by 2.0 mg/kg on days 2–15, and then 5.0 mg/kg was given on days 16–18. Blood pressure measurements were made 4 hr after administration of the drug.

TABLE III

ACUTE TOXICITY STUDIES WITH V IN MICE

Oral[a]		Intravenous[b]	
Dose, mg/kg	Mortality ratio	Dose, mg/kg	Mortality ratio
1000	2/10	60	0/10
1200	5/10	70	0/10
1400	7/10	80	3/10
		90	4/10
1500	9/10	100	7/10
		110	10/10
2000	10/10	125	8/10

[a] Symptoms of toxicity: increased activity followed by decreased activity, fur ruffling, salivation, ataxia. The animals died quietly in 20 min to 5 days. Survivors were observed for 1 week. Calculated LD_{50} = 1200 mg/kg, 95% confidence limit = 1090–1320 mg/kg. Female Swiss-Webster (Wisconsin) mice weighing 16–22 g were used. The drug was administered as a 10% suspension in 0.5% methylcellulose. [b] At all doses excitement occurred. Convulsions occurred in some mice at the two lower dose levels. At higher doses convulsions were usually seen. Death occurred immediately. Calculated LD_{50} = 93 mg/kg, 95%, confidence limit = 86–100 mg/kg. Both male and female mice were used.

We therefore feel that these results clearly indicate that V should be investigated in the clinic.

Experimental Section[8]

N-(2-Methylthioethyl)ethylenediamine.—A solution of 86 g (1.0 mole) of N-(2-aminoethyl)aziridine and 62.5 g (1.3 mole) of methanethiol was heated at 100° for 18 hr in a bomb. The product, bp 99° (8 mm), was obtained after removal of a small amount of forerun. The yield of colorless oil was 114.5 g (85%), $n^{25}D$ 1.5042. *Anal.* ($C_5H_{14}N_2S$) C, H, N.

An experiment carried out at 60° produced an 81% yield of the diamine, while none was obtained at room temperature.

1-(3-Aminopropyl)aziridine.—Reduction of 96 g (1.0 mole) of 1-(2-cyanoethyl)aziridine was effected according to the procedure of Bestian.[9] The yield of colorless oil, bp 73–77° (40 mm), was 42 g (42%), $n^{25}D$ 1.4538. Bestian[9] reported bp 61–62° (19 mm). The reduction has also been effected with $LiAlH_4$.[10]

2-Ethyl-2-thiopseudourea Sulfate.—2-Ethyl-2-thiopseudourea hydrobromide[11] was converted to the sulfate salt with Ag_2SO_4 and was crystallized from MeOH–H_2O to give material melting at 225–226°, lit.[12] mp 202°. Identical material was obtained from thiourea and diethyl sulfate. *Anal.* ($C_3H_8N_2S \cdot 0.5H_2SO_4$) C, H, N.

3-Methylthiopropylamine.—A suspension of 11.4 g (0.3 mole) of $LiAlH_4$ in 200 ml of dry ether was stirred and cooled in an ice–salt bath. From a dropping funnel a solution of 40 g (0.4 mole) of 3-methylthiopropionitrile[13] in 200 ml of dry ether was added at such a rate that the temperature remained below 0°. Stirring was continued for 2 hr at 0° after the addition had been completed. The reaction mixture was decomposed by the dropwise addition of 12 ml of H_2O, 12 ml of 15% NaOH, and 36 ml of H_2O while the temperature was maintained at 0°. The solid was collected on a filter after being left at room temperature overnight. The solvent was removed and a colorless oil was obtained from the residue, bp 56–57° (8 mm), $n^{25}D$ 1.4906. The yield of amine was 15.6 g (38%). The recorded boiling point at atmospheric pressure is 169°.[14]

A portion of the amine was converted to the hydrochloride, and was crystallized from Me_2CO–EtOAc; mp 148.5–149.5°. *Anal.* ($C_4H_{11}NS \cdot HCl$) C, H, N.

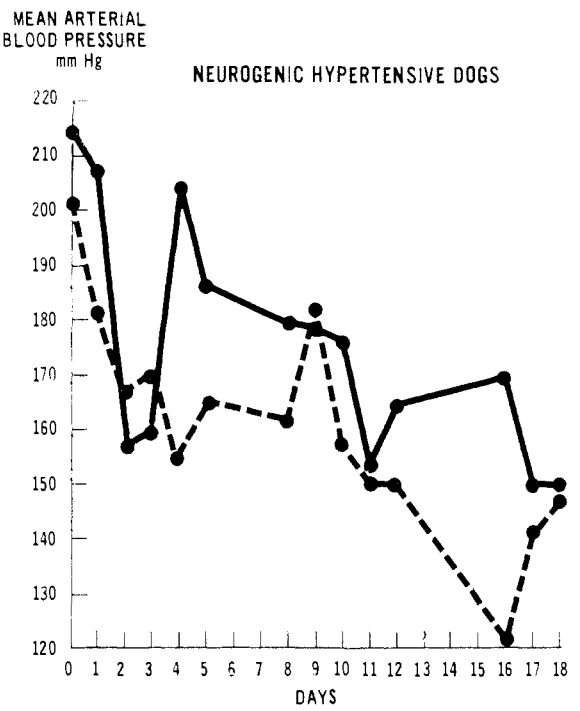


Figure 2.—The effect of 2-(2-methylthioethylamino)ethylguanidine sulfate (V) on two neurogenic hypertensive dogs. The control blood pressure is recorded at day 0 and represents the average of three measurements taken on three different days. On day 1, 20 mg/kg of V was given, followed by 2.0 mg/kg on days 2–15, and then 5.0 mg/kg was given on days 16–18. Blood pressure measurements were made 4 hr after administration of the drug.

(8) Melting points were determined in capillary tubes in a silicone oil bath, and are corrected. Nmr spectra were determined on a Varian A-60 spectrometer. Ir spectra were determined on a Perkin-Elmer Model 521 spectrometer. Where analyses are indicated only by symbols of the elements, analytical results for those elements are within ±0.3% of the theoretical values.

(9) H. Bestian, *Ann.*, **566**, 210 (1950).

(10) O. L. Salerni and R. N. Clark, *J. Med. Chem.*, **9**, 778 (1966).

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TABLE IV

NITRILES AND AMINES

$$CH_3X(CH_2)_mN(R^1)(CH_2)_nR^2$$

No.	X	m	n	R^1	R^2	Yield, %	Bp, °C (mm)	$n^{25}D$	Formula	Analyses
1	S	3	1	H	CN	58[a]	113–116 (0.3)	1.4960	$C_6H_{12}N_2S$	C, H, N
2	S	3	2	H	NH_2	40[b]	121–123 (12)	1.5006	$C_6H_{16}N_2S$	C, H, N
3	S	3	2	H	CN	82[c]	154–156 (10)	1.4930	$C_7H_{14}N_2S$	C, H, N
4	S	3	3	H	NH_2	68[b]	130–132 (10)	1.4996	$C_7H_{18}N_2S$	C, H, N
5	S	2	1	C_2H_5	CN	89[a]	123–125 (11)	1.4840	$C_7H_{14}N_2S$	C, H, N
6	S	2	2	C_2H_5	NH_2	91[b]	108–109 (11)	1.4890	$C_7H_{18}N_2S$	C, H, N
7	O	2	1	H	CN	59[a]	97–98 (12)	1.4324	$C_5H_{10}N_2O$	C, H, N
8	O	2	2	H	NH_2	6[b]	74–76 (10)	1.4436	$C_5H_{14}N_2O$	C, H, N

[a] The α-aminoacetonitriles were prepared from the appropriate amines and glycolonitrile as described in the Experimental Section. [b] The nitriles were reduced to the corresponding amines as described in the Experimental Section. [c] The nitrile was prepared by allowing equivalent amounts of acrylonitrile and 3-methylthiopropylamine to stand overnight at room temperature before distillation.

2-Methylthiodiethylamine.—A solution of 78 g (1.1 moles) of N-ethylaziridine and 72 g (1.5 moles) of methanethiol was heated in a bomb at 100° for 18 hr. Distillation gave 106 g (81%) of colorless oil, bp 50–52° (10 mm), $n^{25}D$ 1.4702. At 80° the yield was 23%, and no product was obtained at 60°. *Anal.* ($C_5H_{13}NS$) C, H, N.

Preparation of N-Substituted α-Aminoacetonitriles.—A solution of 0.3 mole of the appropriate amine and 25 g (0.3 mole) of 70% glycolonitrile in 150 ml of ethanol was heated under reflux for 4 hr. The solvent was filtered to remove a small amount of insoluble material. The solvent was removed from the filtrate and the residue was subjected to vacuum distillation to give the aminoacetonitriles as colorless oils. They are described in Table IV.

Reduction of Aminonitriles to Diamines.—Reduction of the aminonitriles was effected with $LiAlH_4$ in the manner described above for reduction of 3-methylthiopropionitrile except that the reaction was carried out in refluxing ether. The diamines are described in Table IV.

2-Ethylaminoethylguanidine Sulfate.—A solution of 8.8 g (0.1 mole) of N-ethylethylenediamine (Ames Laboratories) and 13.9 g (0.05 mole) of 2-methyl-2-thiopseudourea sulfate in 25 ml of H_2O was left at room temperature overnight. Addition of 2.8 ml (0.05 mole) of concentrated H_2SO_4 caused a white solid to precipitate which was crystallized from H_2O to give 10.5 g (45%) of the guanidine: mp 250–251°; ν_{max}^{Nujol} 1690 (s), 1630 (s) cm^{-1}. *Anal.* ($C_5H_{14}N_4 \cdot H_2SO_4$) C, H, N.

2-(2-Diethylaminoethylamino)ethylguanidine Sulfate.—A solution of 8.0 g (0.05 mole) of N^1,N^1-diethyldiethylenetriamine (Ames Laboratories) and 7.0 g (0.025 mole) of 2-methyl-2-thiopseudourea sulfate in 50 ml of 50% EtOH was left at room temperature for 3 days. The solution was taken to dryness after 2.8 ml (0.05 mole) of concentrated H_2SO_4 had been added. The residue was crystallized twice by dissolving in a large volume of boiling MeOH, concentrating the solution, and chilling. The yield of white crystalline solid was 8.5 g (48.8%); mp 206–207°; ν_{max}^{Nujol} 1652 (s), 1609 (s) cm^{-1}. *Anal.* ($C_9H_{23}N_5 \cdot 1.5H_2SO_4$) C, H, N.

2-(2-Methylthioethylamino)ethylguanidine Sulfate from 1-(2-Aminoethyl)aziridine.—A solution of 43 g (0.5 mole) of 1-(2-aminoethyl)aziridine and 70 g (0.25 mole) of 2-methyl-2-thiopseudourea sulfate in 500 ml of H_2O was left at room temperature overnight. The solution was taken to dryness and the residue was crystallized from EtOH–MeOH (500:100 ml). The yield of white crystalline solid, melting at 170–171.5°, was 52 g (44.2%). Four recrystallizations from 95% EtOH raised the melting point to 178.5–179.5°; ν_{max}^{Nujol} 1678 (s), 1629 (s) cm^{-1}. *Anal.* ($C_6H_{16}N_4S \cdot 0.5H_2SO_4$) C, H, N.

2-(2-Methylthioethylamino)ethylguanidine Sulfate from N-(2-Methylthioethyl)ethylenediamine.—A solution of 13.4 g (0.1 mole) of N-(2-methylthioethyl)ethylenediamine and 13.9 g (0.05 mole) of 2-methyl-2-thiopseudourea sulfate in 50 ml of H_2O was left at room temperature overnight. The solution was taken to dryness and the solid was crystallized from 100 ml of 95% EtOH to give 18 g (80%) of material identical with that obtained above (determined by nmr, ir, and tlc); mp 179.5–180.5°. One recrystallization from 95% EtOH raised the melting point to 181–181.5°.

Reaction of 1-(2-Aminoethyl)aziridine with 2-Methyl-2-thiopseudourea Sulfate in the Presence of Ethanethiol.—To 7.0 g (0.025 mole) of 2-methyl-2-thiopseudourea sulfate in 25 ml of H_2O was added 6.2 g (0.1 mole) of ethanethiol. It was stirred while 4.3 g (0.05 mole) of 1-(2-aminoethyl)aziridine in 25 ml of MeOH was added during 2 hr. The reaction mixture did not evolve any heat. The solution was taken to dryness under reduced pressure at room temperature after standing overnight. The last traces of water were removed by adding 25 ml of benzene and taking to dryness. The residue was crystallized from 95% EtOH to give 9.0 g of material melting at 162–164°. Tlc showed two major spots which corresponded to authentic samples of 2-(2-methylthioethylamino)ethylguanidine sulfate and its ethyl homolog. The nmr spectrum (D_2O solution) had a singlet at 126.5 cps corresponding to the methyl group attached to the sulfur atom. A triplet is seen at 66, 74, 82 cps arising from the methyl group of the ethylthio moiety. The integration curve indicated approximately equal amounts of the two substances. The reaction was repeated using 2-ethyl-2-thiopseudourea sulfate and methanethiol. Again an equal mixture of the same two substances was obtained.

Reaction of 2-Methyl-2-thiopseudourea Sulfate with Ethanethiol.—A solution of 7.0 g (0.025 mole) of 2-methyl-2-thiopseudourea sulfate in 100 ml of H_2O was stirred with a magnet as a solution of 6.2 g (0.1 mole) of ethanethiol in 100 ml of MeOH was added dropwise during 1 hr. The clear colorless solution was left at room temperature overnight. The solution was taken to dryness on a rotary evaporator without heating. The residue was triturated with MeOH and the solid was collected on a filter. The yield was 6.4 g, mp 237–239°.

The nmr spectrum (D_2O solution) exhibited a single peak at 157 cps. There was no evidence of an ethyl group. Tlc also confirmed the identity of this material, and no spot corresponding to the ethyl homolog could be seen.

The reaction was run again, and the solution was heated at 55° for 4 hr. The nmr spectrum of the product had a singlet at 157 cps, a triplet at 75, 82.5, 90 cps, and a quartet at 178, 185, 193, 200 cps. The integration curve indicated about 3 parts of the methyl derivative to 1 part of the ethyl homolog. Tlc gave two spots which corresponded to authentic 2-methylthiopseudourea sulfate and its ethyl homolog.

Reaction of 2-(2-Methylthioethylamino)ethylguanidine Sulfate with Ethanethiol.—A solution of 7.4 g (0.033 mole) of 2-(2-methylthioethylamino)ethylguanidine sulfate and 6.2 g (0.1 mole) of ethanethiol in 40 ml of 50% MeOH was heated at 55° for 4 hr. The solution was taken to dryness and the residue was crystallized from 95% EtOH to give 7.4 g of material melting at 176.5–177.5°. Both nmr and tlc indicated that this substance was unchanged starting material, and that none of the ethyl homolog was present.

3-(2-Methylthioethylamino)propylguanidine Sulfate.—A solution of 10 g (0.1 mole) of 1-(3-aminopropyl)aziridine and 14 g (0.05 mole) of 2-methyl-2-thiopseudourea sulfate in 25 ml of H_2O was left at room temperature overnight. To the solution was added 2.8 ml (0.05 mole) of concentrated H_2SO_4. The solid which precipitated on chilling was recrystallized twice from 50% MeOH to give 20.3 g (70.5%) of white crystalline solid that

melted at 235.5–237°; ν_{max}^{Nujol} 1686 (s), 1633 (s) cm^{-1}. *Anal.* ($C_7H_{18}N_4S \cdot H_2SO_4$) C, H, N.

2-(2-Ethylthioethylamino)ethylguanidine Sulfate.—A solution of 7.0 g (0.082 mole) of 1-(2-aminoethyl)aziridine and 12.5 g (0.041 mole) of 2-ethyl-2-thiopseudourea sulfate in 20 ml of H_2O was left at room temperature overnight. The solvent was removed and the residue was crystallized from EtOH. The yield of white, crystalline solid was 10.2 g (52.3%): mp 151–152°; ν_{max}^{Nujol} 1670 (s), 1625 (s) cm^{-1}. *Anal.* ($C_7H_{18}N_4S \cdot 0.5H_2SO_4$) C, H, N.

2-(3-Methylthiopropylamino)ethylguanidine Sulfate.—A solution of 14.8 g (0.1 mole) of 2-(3-methylthiopropylamino)ethylamine and 13.9 g (0.05 mole) of 2-methyl-2-thiopseudourea sulfate in 25 ml of H_2O was left at room temperature overnight. The solvent was removed and the residue was crystallized from EtOH. The yield of white solid was 11.5 g (48.1%); mp 169–170°; recrystallization from EtOH raised the melting point to 173.5–174°; ν_{max}^{Nujol} 1683 (s), 1627 (s) cm^{-1}. *Anal.* ($C_7H_{18}N_4S \cdot 0.5H_2SO_4$) C, H, N.

3-(3-Methylthiopropylamino)propylguanidine Sulfate.—A solution of 22 g (0.135 mole) of 3-(3-methylthiopropylamino)propylamine and 19 g (0.068 mole) of 2-methyl-2-thiopseudourea sulfate in 35 ml of water was left at room temperature overnight. The solution was taken to dryness after 3.8 ml (0.07 mole) of concentrated H_2SO_4 had been added. The residue was crystallized twice from EtOH–H_2O to give 33.2 g (81.5%) of glistening white leaflets: mp 249–250°; ν_{max}^{Nujol} 1686 (s), 1635 (s) cm^{-1}. *Anal.* ($C_8H_{20}N_4S \cdot H_2SO_4$) C, H, N.

2-[N-Ethyl-N-(2-methylthioethyl)amino]ethylguanidine Sulfate.—A solution of 8.1 g (0.05 mole) of N-ethyl-N-(2-methylthioethyl)ethylenediamine and 7.0 g (0.025 mole) of 2-methyl-2-thiopseudourea sulfate in 10 ml of H_2O was left at room temperature overnight. To the solution was added 25 ml of 2,2-dimethoxypropane, and it was taken to dryness. The white solid which remained was collected and washed (Me_2CO). The yield was 7.0 g (57.5%); mp 70–71°; $\nu_{max}^{CHCl_3}$ 1660 (s), 1615 (sh) cm^{-1}. *Anal.* ($C_8H_{20}N_4S \cdot 0.5H_2SO_4$) C, H, N.

2-(2-Methoxyethylamino)ethylguanidine Sulfate.—A solution of 6.3 g (0.053 mole) of 2-(2-methoxyethylamino)ethylamine and 7.5 g (0.027 mole) of 2-methyl-2-thiopseudourea sulfate in 25 ml of H_2O was left at room temperature overnight. The solution was diluted with 100 ml of MeOH and 100 ml of acetone after 1.4 ml (0.025 mole) of concentrated H_2SO_4 had been added. Chilling caused 11.8 g (86%) of white, crystalline solid to precipitate: mp 254–255°; ν_{max}^{Nujol} 1684 (s), 1636 (s) cm^{-1}. *Anal.* ($C_6H_{16}N_4O \cdot H_2SO_4$) C, H, N.

Acknowledgments.—The microanalyses were provided by Mr. Orville Kolsto, Mr. Victor Rauschel, and staff of the Abbott Microanalytical Laboratory. The pressure reactions were carried out by Mr. Morris Freifelder and Mr. Daniel Dunnigan. Mr. William Washburn and his associates provided the infrared spectra. Evelyn Baker and her associates provided the tlc's. The nmr spectra were provided by Dr. Milton Levenberg and Ruth Stanaszek. We also wish to thank Messers. Harold Brondyk, Charles Shannon, and Leo Wiemeler for assisting with the pharmacological studies. Dow Chemical Company generously provided samples of 1-(2-aminoethyl)aziridine, 1-(2-cyanoethyl)-aziridine, and 1-ethylaziridine.

The Synthesis of Substituted Phenethylamines

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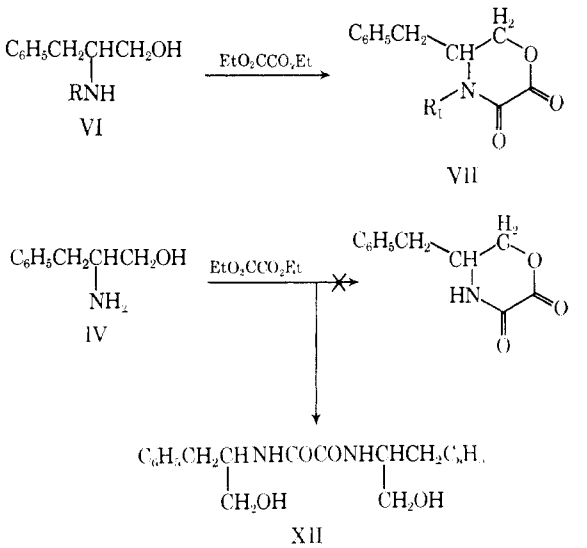
Received January 2, 1968

The methods of preparation and pharmacological data of a series of substituted β-phenethylamines are described.

2-Amino-3-phenyl-1-propanol (IV) was shown to possess significant analgetic activity in these laboratories. A number of compounds chemically related to this structure were prepared by the synthetic routes shown in Chart I and screened as to their analgetic, central nervous system, cardiovascular, and antiinflammatory effects.

Chemistry.—The reaction routes employed to obtain the compounds which were synthesized are found in Chart I. These compounds were derived from the *dl* form of compound I. Methods for the preparation of 2-amino-3-phenyl-1-propanol (IV),[1] ethyl 2-benzamido-3-phenylpropionate (Vb),[2] and 2-benzamido-3-phenyl-1-propanol (Xb)[3] have previously been described. 2-(*p*-Chlorobenzylamino)-3-phenyl-1-propanol (VIa) and the known 2-(benzylamino)-3-phenyl-1-propanol (VIb)[4] were synthesized by a $LiAlH_4$ reduction of Va and the known ester Vb.[4] The cyclic compounds, 5-benzyl-4-(*p*-chlorobenzyl)morpholine-2,3-dione (VIIa) and 4,5-dibenzylmorpholine-2,3-dione (VIIb), were prepared by the reaction of diethyl oxalate with VIa and VIb, respectively. The reaction of IV and diethyl oxalate yielded N,N′-bis(α-hydroxymethylphenethyl)oxamide (XII), while none of the expected product, 5-benzylmorpholine-2,3-dione, could be isolated. Apparently, under the conditions employed and based on the products isolated, the more hindered



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