

[1,2-*a*]pyridine (0.094 mole) in 75 ml of EtOH was added a soln of 19.6 g of  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (0.28 mole) and 12 g of 95% NaOH (0.28 mole) in 120 ml of  $\text{H}_2\text{O}$ . After refluxing for 1.5 hr flaky crystals were obtained (14.4 g, yield 88%).

**3-Formylimidazo[1,2-*a*]pyridine Semicarbazone·HCl (Table I; 15).** **Method C.**—To 7.30 g of 3-formylimidazo[1,2-*a*]pyridine (0.05 mole) dissolved in 31.2 ml of 10% HCl was added a soln of 5.90 g of  $\text{H}_2\text{NNHCONH}_2\cdot\text{HCl}$  (0.053 mole) in 31.2 ml of 10% HCl and 10 ml of  $\text{H}_2\text{O}$ . A bulky ppt formed at once; it was filtered and dried (11 g, yield 92%).

**3-Formyl-6-bromoimidazo[1,2-*a*]pyridine Thiosemicarbazone·HCl (Table I; 22).** **Method D.**—To a soln of 1.12 g of 3-formyl-6-bromoimidazo[1,2-*a*]pyridine<sup>4</sup> (0.005 mole) in 10 ml of 10% HCl was added a soln of 0.478 g of  $\text{H}_2\text{NNHCSNH}_2$  (0.053 mole) in 3 ml of 10% HCl. After cooling overnight, the condensation product pptd as a bulky mass; it was filtered and dried (1.5 g, yield 90%).

**2-(*p*-Chlorophenyl)-3-formylimidazo[1,2-*a*]pyridine Guanyldrazone·2 HCl (Table I; 34).** **Method E.**—A soln of 12.8 g of 2-(*p*-chlorophenyl)-3-formylimidazo[1,2-*a*]pyridine (0.05 mole) in 1280 ml of boiling 10% HCl was filtered hot and added to a soln of 8.25 g of  $\text{H}_2\text{NNHC(=NH)NH}_2\cdot\text{H}_2\text{CO}_3$  (0.06 mole) in 50 ml of cold 10% HCl. Shiny white crystals pptd which were filtered after cooling (17.5 g) and which after recrystn from 3300 ml of 1% HCl gave 14.2 g (74%).

**3-[(Imidazo[1,2-*a*]pyridin-3-ylmethylene)amino]-5-morpholinomethyl-2-oxazolidone Dimaleate (Table I; 38).** **Method F.**—To a soln of 2.01 g of 3-amino-5-morpholinomethyl-2-oxazolidone (0.01 mole) in 20 ml of EtOH, 10 ml of  $\text{H}_2\text{O}$ , and 5 ml of 10% HCl was added a soln of 1.46 g of 3-formylimidazo[1,2-*a*]pyridine (0.01 mole) in 10 ml of EtOH and 5 ml of 10% HCl. The mixture was heated to 70° for 4 hr. The sep'd oil was extracted with  $\text{CHCl}_3$ , the solvent evapd, and the residue dissolved in 10 ml of EtOH and treated with 1.32 g of maleic acid in EtOH. On heating on a water bath **38**·dimaleate formed (1.6 g, yield 28%).

**2-Methyl-3-acetylimidazo[1,2-*a*]pyridine (Table II; 40).** **Method G.**—To a soln of 39.6 g of 2-methylimidazo[1,2-*a*]pyridine (0.3 mole) in 120 ml of  $\text{CS}_2$  was added, very slowly, 90 g of anhyd  $\text{AlCl}_3$  with external cooling. After stirring for 30 min at room temp the mixture was refluxed gently and 22.5 ml of  $\text{Ac}_2\text{O}$  was added drop by drop, in 30 min. After refluxing for 1 hr, the  $\text{CS}_2$  was evapd and the residue mixed with crushed ice, made alkaline with NaOH, and extracted with  $\text{CH}_2\text{Cl}_2$ . The soln was dried ( $\text{K}_2\text{CO}_3$ ) and evapd to dryness. The resulting oil was distd under vacuum. Starting product, (14.5 g), bp 92–100° (0.8 mm), and 15 g of the desired product, bp 126–130° (0.8 mm), were obtained. The oil was then crystd from ligroin giving 12 g of the pure product, yield 37% (based on recovered starting material).

**3-Acetylimidazo[1,2-*a*]pyridine (Table II; 39).** **Method H.**—

To a soln of 17.5 g of 2-aminopyridine (0.185 mole) in 20 ml of EtOH was added 15.2 g of 2-bromoacetoacetaldehyde (0.927 mole).<sup>7</sup> The exothermic reaction was moderated by cooling. The mixture was refluxed for 10 hr, the solvent evapd to dryness, and the residue mixed with  $\text{H}_2\text{O}$  and 20% NaOH and extracted with  $\text{Et}_2\text{O}$ . The soln was dried ( $\text{K}_2\text{CO}_3$ ) and evapd. The residue was distd, recovering first 9.6 g of 2-aminopyridine, and then the product, bp 128–130° (1.5 mm). The yield was 4 g (30%), based on 2-aminopyridine consumed.

**2-Methyl-3-acetylimidazo[1,2-*a*]pyridine (Table II; 40).** **Method H.**—A soln of 28.5 g of 2-aminopyridine (0.313 mole) in 20 ml of  $\text{Et}_2\text{O}$  was treated as indicated in the previous example with 28 g of crude 3-bromoacetylacetone<sup>8</sup> (0.156 mole). After evapg the solvent, the residue was distd to yield 14 g of 2-aminopyridine and 15 g of product, bp 125–135° (0.6 mm), mp 108–109°.

**3-Acetylimidazo[1,2-*a*]pyridine Semicarbazone (Table II; 44).** **Method I.**—To a soln of 20 g of 3-acetylimidazo[1,2-*a*]pyridine (0.125 mole) in 20 ml of  $\text{H}_2\text{O}$  was added a soln of 55.7 g of  $\text{H}_2\text{N-NHCONH}_2\cdot\text{HCl}$  (0.5 mole) in 100 ml of 10% NaOH (0.25 mole). The mixture was refluxed for 2 hr, made alkaline with  $\text{Na}_2\text{CO}_3$ , filtered, and washed with  $\text{H}_2\text{O}$  until neutral (21 g, yield 77%). The hydrochloride of this product hydrolyzes very easily.

**3-Acetyl-6-chloroimidazo[1,2-*a*]pyridine Thiosemicarbazone (Table II; 52).** **Method J.**—A soln of 2 g of 3-acetyl-6-chloroimidazo[1,2-*a*]pyridine (0.0103 mole), 1.87 g of  $\text{H}_2\text{NCSNHNH}_2$  (0.0206 mole), and 2.6 g of  $\text{H}_2\text{NCSNHNH}_2\cdot\text{HCl}$  (0.0206 mole) in 20 ml of  $\text{H}_2\text{O}$  and 20 ml of EtOH was refluxed for 2 hr, while still hot, the mixture was made alkaline with a satd soln of  $\text{Na}_2\text{CO}_3$ , and the ppt (2.8 g; yield 97%) was filtered and washed with  $\text{H}_2\text{O}$  until neutral.

**3-Acetylimidazo[1,2-*a*]pyridine Guanyldrazone (Table II; 54).** **Method K.**—A soln of 2 g of 3-acetylimidazo[1,2-*a*]pyridine (0.0125 mole) and 6.8 g of  $\text{H}_2\text{NNHC(=NH)NH}_2\cdot\text{H}_2\text{CO}_3$  (0.05 mole) in 75 ml of 1 N HCl was refluxed for 2 hr; the resulting soln was made strongly alkaline with 20% NaOH and cooled. The thick oil, which was obtained, solidified and was recrystd from  $\text{C}_6\text{H}_6$  and ligroin (1.5 g, yield 59%).

**2-Methyl-3-hydroxymethylimidazo[1,2-*a*]pyridine (Table III; 61).** **Method L.**—A soln of 3.7 g of 2-methyl-3-formylimidazo[1,2-*a*]pyridine (0.023 mole) in 37 ml of MeOH was cooled to 10° and added to a soln of 0.437 g of  $\text{NaBH}_4$  (0.0115 mole) in 5 ml of  $\text{H}_2\text{O}$  in 5 min, keeping the temp at 10–15°. The soln was evapd to dryness and the residue recrystd from 30 ml of  $\text{H}_2\text{O}$  (2.9 g, yield 77%).

(7) N. K. Kochetkov, E. E. Nifant'ev, and N. V. Molodtsov, *Zh. Obshch. Khim.*, **29**, 2330 (1959); *Chem. Abstr.*, **54**, 14230h (1960).

(8) D. F. Tavares, W. I. O'Sullivan, and C. R. Hauser, *J. Org. Chem.*, **27**, 1251 (1962).

## Aralkylaminoguanidines and Related Compounds

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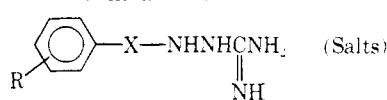
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A series of substituted aralkylaminoguanidines (I) was synthesized and evaluated for pharmacological activity. The compounds were prepared by catalytic reduction of the guanyldrazones or by reaction of the aralkylhydrazines with either *S*-methylisothiuronium salts or cyanamide. A method of separating mixtures of I and II obtained by the reaction with *S*-methylisothiuronium salts is described. Some of the aralkylaminoguanidines (I) possess adrenergic neurone blocking activity and produce a marked lowering of blood pressure in the hypertensive rat. Some structure-activity relationships are discussed.

During an investigation of compounds containing the hydrazino group, a series of new aralkylaminoguanidines was prepared. Some of these were found to possess

marked adrenergic neurone blocking activity similar in character to that of guanethidine. Amongst them,  $\beta$ -(2,6-dichlorophenyl)ethylaminoguanidine hydrochloride (10) and  $\gamma$ -phenylpropylaminoguanidine hydrochloride (26) proved of special interest as potentially

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TABLE I  
ARALKYLAMINO GUANIDINES

No.	R	X	Mp, °C	Method	Formula
1	H	CH <sub>2</sub>	135-138	A <sup>a</sup>	C <sub>8</sub> H <sub>12</sub> N <sub>4</sub> ·HNO <sub>3</sub> <sup>b</sup>
2	H	(CH <sub>2</sub> ) <sub>2</sub>	145	A <sup>a</sup>	C <sub>9</sub> H <sub>14</sub> N <sub>4</sub> ·HNO <sub>3</sub> <sup>c</sup>
3	H	(CH <sub>2</sub> ) <sub>2</sub>	114-121	A	C <sub>9</sub> H <sub>14</sub> N <sub>4</sub> ·HCl
4	H	(CH <sub>2</sub> ) <sub>2</sub>	109-111 dec	A	C <sub>9</sub> H <sub>14</sub> N <sub>4</sub> ·H <sub>2</sub> CO <sub>3</sub>
5	2-Cl	(CH <sub>2</sub> ) <sub>2</sub>	158-160	B <sup>a</sup>	C <sub>9</sub> H <sub>13</sub> ClN <sub>4</sub> ·HNO <sub>3</sub> <sup>d</sup>
6	3-Cl	(CH <sub>2</sub> ) <sub>2</sub>	117-120	A	C <sub>9</sub> H <sub>13</sub> ClN <sub>4</sub> ·HNO <sub>3</sub>
7	4-Cl	(CH <sub>2</sub> ) <sub>2</sub>	144-146	B <sup>a</sup>	C <sub>9</sub> H <sub>13</sub> ClN <sub>4</sub> ·HNO <sub>3</sub>
8	4-Cl	(CH <sub>2</sub> ) <sub>2</sub>	192-195	C <sup>d</sup>	C <sub>9</sub> H <sub>13</sub> ClN <sub>4</sub> ·0.5H <sub>2</sub> SO <sub>4</sub>
9	2,6-Cl <sub>2</sub>	(CH <sub>2</sub> ) <sub>2</sub>	190-192	A <sup>a</sup>	C <sub>9</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>4</sub> ·HNO <sub>3</sub>
10	2,6-Cl <sub>2</sub>	(CH <sub>2</sub> ) <sub>2</sub>	193-194	B <sup>d</sup>	C <sub>9</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>4</sub> ·HCl
11	2,4-Cl <sub>2</sub>	(CH <sub>2</sub> ) <sub>2</sub>	161-163	A	C <sub>9</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>4</sub> ·HNO <sub>3</sub>
12	3,4-Cl <sub>2</sub>	(CH <sub>2</sub> ) <sub>2</sub>	147-150	A	C <sub>9</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>4</sub> ·HNO <sub>3</sub>
13	2-Br	(CH <sub>2</sub> ) <sub>2</sub>	158-162	A	C <sub>9</sub> H <sub>13</sub> BrN <sub>4</sub> ·HNO <sub>3</sub>
14	4-Br	(CH <sub>2</sub> ) <sub>2</sub>	160-162	A	C <sub>9</sub> H <sub>13</sub> BrN <sub>4</sub> ·HNO <sub>3</sub>
15	2-F	(CH <sub>2</sub> ) <sub>2</sub>	131-134	A	C <sub>9</sub> H <sub>13</sub> FN <sub>4</sub> ·HNO <sub>3</sub>
16	4-F	(CH <sub>2</sub> ) <sub>2</sub>	123-124	B <sup>d</sup>	C <sub>9</sub> H <sub>13</sub> FN <sub>4</sub> ·HNO <sub>3</sub>
17	2-Me	(CH <sub>2</sub> ) <sub>2</sub>	153-154	A <sup>e</sup>	C <sub>10</sub> H <sub>16</sub> N <sub>4</sub> ·HNO <sub>3</sub>
18	3-Me	(CH <sub>2</sub> ) <sub>2</sub>	96-98	A	C <sub>10</sub> H <sub>16</sub> N <sub>4</sub> ·HNO <sub>3</sub>
19	4-Me	(CH <sub>2</sub> ) <sub>2</sub>	121-123	A <sup>a</sup>	C <sub>10</sub> H <sub>16</sub> N <sub>4</sub> ·HNO <sub>3</sub>
20	2,6-Me <sub>2</sub>	(CH <sub>2</sub> ) <sub>2</sub>	179-183	A	C <sub>11</sub> H <sub>18</sub> N <sub>4</sub> ·HNO <sub>3</sub>
21	2,4-Me <sub>2</sub>	(CH <sub>2</sub> ) <sub>2</sub>	112-115	A	C <sub>11</sub> H <sub>18</sub> N <sub>4</sub> ·HNO <sub>3</sub>
22	2,4,6-Me <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub>	184-185	A	C <sub>12</sub> H <sub>20</sub> N <sub>4</sub> ·HCl <sup>f</sup>
23	2-OMe	(CH <sub>2</sub> ) <sub>2</sub>	129-132	A	C <sub>10</sub> H <sub>16</sub> N <sub>4</sub> O·HNO <sub>3</sub>
24	4-OMe	(CH <sub>2</sub> ) <sub>2</sub>	118-120	A <sup>a</sup>	C <sub>10</sub> H <sub>16</sub> N <sub>4</sub> O·HNO <sub>3</sub>
25	H	(CH <sub>2</sub> ) <sub>3</sub>	81-84	A	C <sub>10</sub> H <sub>16</sub> N <sub>4</sub> ·HNO <sub>3</sub>
26	H	(CH <sub>2</sub> ) <sub>3</sub>	123-125	A	C <sub>10</sub> H <sub>16</sub> N <sub>4</sub> ·HCl
27	2-Cl	(CH <sub>2</sub> ) <sub>3</sub>	127	A	C <sub>10</sub> H <sub>15</sub> ClN <sub>4</sub> ·HNO <sub>3</sub>
28	4-Cl	(CH <sub>2</sub> ) <sub>3</sub>	126-129	A	C <sub>10</sub> H <sub>15</sub> ClN <sub>4</sub> ·HNO <sub>3</sub>
29	2,6-Cl <sub>2</sub>	(CH <sub>2</sub> ) <sub>3</sub>	164-165	A	C <sub>10</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>4</sub> ·HNO <sub>3</sub> <sup>g</sup>
30	2,4-Cl <sub>2</sub>	(CH <sub>2</sub> ) <sub>3</sub>	124-126	A	C <sub>10</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>4</sub> ·HNO <sub>3</sub>
31	3,4-Cl <sub>2</sub>	(CH <sub>2</sub> ) <sub>3</sub>	140-142	A	C <sub>10</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>4</sub> ·HNO <sub>3</sub>
32	2-F	(CH <sub>2</sub> ) <sub>3</sub>	78	A	C <sub>10</sub> H <sub>15</sub> FN <sub>4</sub> ·HNO <sub>3</sub> <sup>i,k</sup>
33	4-F	(CH <sub>2</sub> ) <sub>3</sub>	89-92	A	C <sub>10</sub> H <sub>15</sub> FN <sub>4</sub> ·HNO <sub>3</sub>
34	2-Me	(CH <sub>2</sub> ) <sub>3</sub>	126-129	A	C <sub>11</sub> H <sub>18</sub> N <sub>4</sub> ·HNO <sub>3</sub>
35	4-Me	(CH <sub>2</sub> ) <sub>3</sub>	120-122	A	C <sub>11</sub> H <sub>18</sub> N <sub>4</sub> ·HNO <sub>3</sub>
36	4-OMe	(CH <sub>2</sub> ) <sub>3</sub>	104-107	A	C <sub>11</sub> H <sub>18</sub> N <sub>4</sub> O·HNO <sub>3</sub>
37	H	CH=CHCH <sub>2</sub>	125-127	B	C <sub>10</sub> H <sub>14</sub> N <sub>4</sub> ·HNO <sub>3</sub>
38	H	CH <sub>2</sub> CHMe	218-219 dec	B <sup>d</sup>	C <sub>10</sub> H <sub>16</sub> N <sub>4</sub> ·0.5H <sub>2</sub> SO <sub>4</sub>
39	H	CH <sub>2</sub> CHMe	123-125	B <sup>d</sup>	C <sub>10</sub> H <sub>16</sub> N <sub>4</sub> ·HCl <sup>l</sup>
40	H	(CH <sub>2</sub> ) <sub>4</sub>	129-131	A <sup>a</sup>	C <sub>11</sub> H <sub>18</sub> N <sub>4</sub> ·HNO <sub>3</sub>

<sup>a</sup> The identical compound has also been prepared by method B. <sup>b</sup> The hydrochloride was described by W. G. Finnegan, R. A. Henry and G. B. L. Smith, *J. Amer. Chem. Soc.*, **74**, 2981 (1952). <sup>c</sup> The *p*-toluenesulfonate was described by Augstein, *et al.*<sup>3</sup> <sup>d</sup> The identical compound has also been prepared by method A. <sup>e</sup> The sulfate was described by Augstein, *et al.*<sup>3</sup> <sup>f</sup> Previously reported by Robertson, *et al.*<sup>5</sup> (mp 124-126°). <sup>g</sup> C: calcd 39.21; found, 40.01. <sup>h</sup> N: calcd 25.40; found, 25.82. <sup>i</sup> N: calcd 21.82; found, 22.30. <sup>j</sup> C: calcd 43.95; found, 44.37. <sup>k</sup> N: calcd 25.63; found, 26.61. <sup>l</sup> N: calcd 25.63; found, 26.14.

useful antihypertensive agents.<sup>1</sup> We now report the synthesis and properties of this series of aralkylaminoguanidines and related compounds.

**Chemistry.**—The aralkylaminoguanidines listed in Table I were prepared by two principal methods which are illustrated in Scheme I. Either the guanylhydrazones (Table II), prepared by condensation of aminoguanidine salts with appropriate aldehydes, acetals, or ketones, were catalytically hydrogenated (method A) or, alternatively, aralkylhydrazines (Table III) were treated with an *S*-methylisothiuronium salt (method B).

When the *S*-methylisothiuronium sulfate method was used, the products were usually found, on tlc, to be

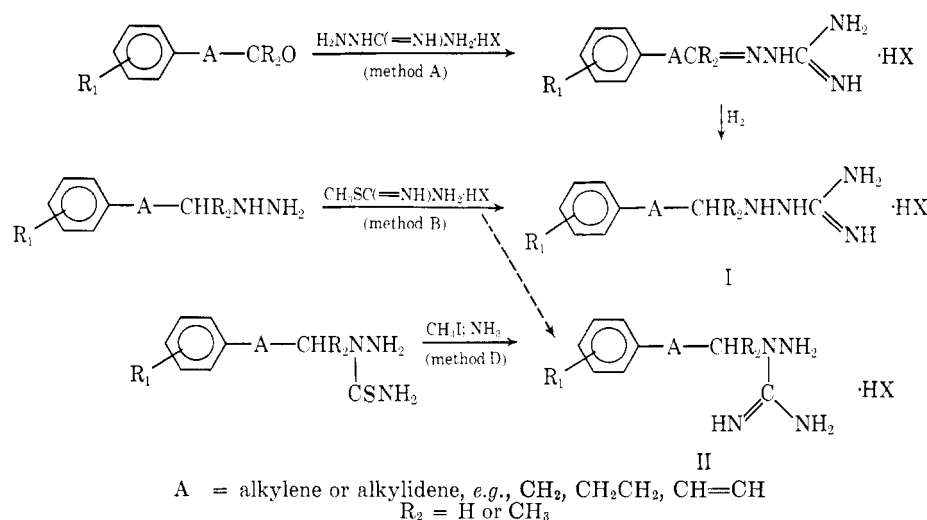
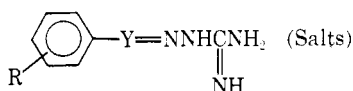
two-component mixtures. A partial separation by crystallization of the sulfates was achieved in three cases, namely with the  $\beta$ -(4-chlorophenyl)ethyl, the  $\beta$ -(2,4,6-trimethylphenyl)ethyl, and the cinnamyl compounds. Elemental analysis showed that in each case the minor component was isomeric with the aralkylaminoguanidine sulfate. The intensity of the spots obtained by tlc suggested that the reaction occurred preferentially on the unalkylated N, as it did in the case of the aryloxyalkyl analogs,<sup>1-3</sup> to give an aralkylaminoguanidine (I) as the major product of the reaction. The aralkylaminoguanidines gave a characteristic deep

(1) J. Augstein and S. M. Green, *Nature (London)*, **201**, 628 (1964), reported similar activity for certain aryloxyalkylguanidines while this work was in progress.

(2) J. Augstein, S. M. Green, A. R. Katritzky, and A. M. Monro, *J. Med. Chem.*, **8**, 395 (1965).

(3) J. Augstein, S. M. Green, A. M. Monro, T. L. Wrigley, A. R. Katritzky, and G. J. T. Tiddy, *ibid.*, **10**, 391 (1967).

SCHEME I

TABLE II  
GUANYLHYDRAZONES

No.	R	Y	Mp, °C	Formula
41	H	CH <sub>2</sub> CH	157	C <sub>9</sub> H <sub>12</sub> N <sub>4</sub> ·HNO <sub>3</sub>
42	2-Cl	CH <sub>2</sub> CH	169–171 dec	C <sub>9</sub> H <sub>11</sub> ClN <sub>4</sub> ·HNO <sub>3</sub>
43	4-Cl	CH <sub>2</sub> CH	178–179	C <sub>9</sub> H <sub>11</sub> ClN <sub>4</sub> ·HNO <sub>3</sub>
44	2,6-Cl <sub>2</sub>	CH <sub>2</sub> CH	228–229 dec	C <sub>9</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>4</sub> ·HNO <sub>3</sub> <sup>a</sup>
45	2-F	CH <sub>2</sub> CH	154–156	C <sub>9</sub> H <sub>11</sub> FN <sub>4</sub> ·HNO <sub>3</sub> <sup>b</sup>
46	4-F	CH <sub>2</sub> CH	156–158	C <sub>9</sub> H <sub>11</sub> FN <sub>4</sub> ·HNO <sub>3</sub>
47	2-Me	CH <sub>2</sub> CH	183–184	C <sub>10</sub> H <sub>14</sub> N <sub>4</sub> ·HNO <sub>3</sub>
48	3-Me	CH <sub>2</sub> CH	104–108	C <sub>10</sub> H <sub>14</sub> N <sub>4</sub> ·HNO <sub>3</sub>
49	4-Me	CH <sub>2</sub> CH	169–172 dec	C <sub>10</sub> H <sub>14</sub> N <sub>4</sub> ·HNO <sub>3</sub>
50	4-OMe	CH <sub>2</sub> CH	157 dec	C <sub>10</sub> H <sub>14</sub> N <sub>4</sub> O·HNO <sub>3</sub>
51	H	CH <sub>2</sub> CMe	156	C <sub>10</sub> H <sub>14</sub> N <sub>4</sub> ·HCl <sup>c</sup>
52	4-F	CH <sub>2</sub> CH <sub>2</sub> CH	175–176	C <sub>10</sub> H <sub>13</sub> FN <sub>4</sub> ·HNO <sub>3</sub>
53	2-Me	CH <sub>2</sub> CH <sub>2</sub> CH	169–171 dec	C <sub>11</sub> H <sub>16</sub> N <sub>4</sub> ·HNO <sub>3</sub>
54	4-OMe	CH <sub>2</sub> CH <sub>2</sub> CH	145–147	C <sub>11</sub> H <sub>16</sub> N <sub>4</sub> O·HNO <sub>3</sub>
55	H	CH=CHCH	194–196 dec	C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> ·HNO <sub>3</sub>
56	2-Cl	CH=CHCH	212–215 dec	C <sub>10</sub> H <sub>11</sub> ClN <sub>4</sub> ·HNO <sub>3</sub>
57	4-Cl	CH=CHCH	219–220 dec	C <sub>10</sub> H <sub>11</sub> ClN <sub>4</sub> ·HNO <sub>3</sub>
58	2,4-Cl <sub>2</sub>	CH=CH	244 dec	C <sub>10</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>4</sub> ·HNO <sub>3</sub>
59	3,4-Cl <sub>2</sub>	CH=CH	233 dec	C <sub>10</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>4</sub> ·HNO <sub>3</sub>
60	4-CH <sub>3</sub>	CH=CH	208 dec	C <sub>11</sub> H <sub>14</sub> N <sub>4</sub> ·HNO <sub>3</sub>
61	H	(CH <sub>2</sub> ) <sub>3</sub> CH	107	C <sub>11</sub> H <sub>16</sub> N <sub>4</sub> ·HNO <sub>3</sub>

<sup>a</sup> C: calcd 35.08; found, 35.53. <sup>b</sup> C: calcd 42.02; found, 43.05. <sup>c</sup> N: calcd 24.71; found, 25.22.

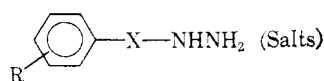
pink color with *p*-dimethylaminocinnamaldehyde reagent on tlc, whereas the isomers gave a yellow color.

It was assumed that the minor component isolated from these mixtures was the corresponding *N*-amino-*N*-aralkylguanidine sulfate (II). This was confirmed for the phenyl-, 4-chlorophenyl-, and 2-chlorophenylethyl compounds **82**, **83**, and **84** (Table IV), by unequivocal synthesis *via* the appropriate 2-( $\beta$ -arylethyl)thiosemicarbazide, as illustrated in Scheme I (method D). The corresponding  $\beta$ -(2,4,6-trimethylphenyl)ethyl and cinnamyl derivatives of type II (**85**, **86**) were isolated as minor components in the fractional crystallization of the aralkylaminoguanidines, **22** and **37** (Table I), prepared by condensation of the aralkylhydrazine with an *S*-methylisothiuronium salt.

It was also found that pure aralkylaminoguanidines I could be obtained from the reaction mixtures by iso-

lating their HNO<sub>3</sub> salts from aq or alcoholic solutions. The difference in solubilities between the isomeric nitrates was sufficient in nearly all cases to permit the isolation of pure aralkylaminoguanidine nitrates of type I by recrystallization. The nitrates could be obtained directly by treatment of aralkylhydrazines with *S*-methylisothiuronium nitrate in aq solution, or by conversion of the mixed sulfates into nitrates by means of hot Ba(NO<sub>3</sub>)<sub>2</sub> solution. Proof of the structure of many of these compounds was obtained by catalytic reduction of the guanylhydrazone nitrates, prepared by condensing the relevant aralkylaldehydes with aminoguanidine nitrate. In each instance, identity was established by mmp and tlc.

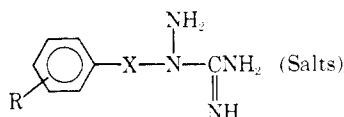
The reaction of cyanamide with  $\beta$ -(4-chlorophenyl)-ethylhydrazine (method C), employing the conditions previously described for the preparation of guanidines

TABLE III  
ARALKYLHYDRAZINES

No.	R	X	Mp, °C	Formula
62	H	CH <sub>2</sub>	158-160	C <sub>7</sub> H <sub>10</sub> N <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub>
63	H	(CH <sub>2</sub> ) <sub>2</sub>	169-171 dec	C <sub>8</sub> H <sub>12</sub> N <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub> <sup>a</sup>
64	2-Cl	(CH <sub>2</sub> ) <sub>2</sub>	169-173 dec	C <sub>8</sub> H <sub>11</sub> ClN <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub>
65	4-Cl	(CH <sub>2</sub> ) <sub>2</sub>	154-156 dec	C <sub>8</sub> H <sub>11</sub> ClN <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub>
66	3,4-Cl <sub>2</sub>	(CH <sub>2</sub> ) <sub>2</sub>	165-167 dec	C <sub>8</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub> <sup>b,c,d</sup>
67	2,4-Cl <sub>2</sub>	(CH <sub>2</sub> ) <sub>2</sub>	194-196 dec	C <sub>8</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub>
68	2,6-Cl <sub>2</sub>	(CH <sub>2</sub> ) <sub>2</sub>	171-173 dec	C <sub>8</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> · HCl
69	2-Me	(CH <sub>2</sub> ) <sub>2</sub>	187-189 dec	C <sub>9</sub> H <sub>14</sub> N <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub> <sup>e</sup>
70	3-Me	(CH <sub>2</sub> ) <sub>2</sub>	173-174 dec	C <sub>9</sub> H <sub>14</sub> N <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub>
71	4-Me	(CH <sub>2</sub> ) <sub>2</sub>	161-162 dec	C <sub>9</sub> H <sub>14</sub> N <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub> <sup>b</sup>
72	2,4-Me <sub>2</sub>	(CH <sub>2</sub> ) <sub>2</sub>	172-173	C <sub>10</sub> H <sub>16</sub> N <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub>
73	2,6-Me <sub>2</sub>	(CH <sub>2</sub> ) <sub>2</sub>	175-178 dec	C <sub>10</sub> H <sub>16</sub> N <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub>
74	2,4,6-Me <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub>	190 dec	C <sub>11</sub> H <sub>18</sub> N <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub>
75	2-F	(CH <sub>2</sub> ) <sub>2</sub>	156-157	C <sub>8</sub> H <sub>11</sub> FN <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub>
76	4-F	(CH <sub>2</sub> ) <sub>2</sub>	161-163	C <sub>8</sub> H <sub>11</sub> FN <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub>
77	2-Br	(CH <sub>2</sub> ) <sub>2</sub>	167-168	C <sub>8</sub> H <sub>11</sub> BrN <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub>
78	4-Br	(CH <sub>2</sub> ) <sub>2</sub>	170-175	C <sub>8</sub> H <sub>11</sub> BrN <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub> <sup>f</sup>
79	2-MeO	(CH <sub>2</sub> ) <sub>2</sub>	151-153	C <sub>9</sub> H <sub>14</sub> N <sub>2</sub> O · H <sub>2</sub> SO <sub>4</sub>
80	4-MeO	(CH <sub>2</sub> ) <sub>2</sub>	155-156	C <sub>9</sub> H <sub>14</sub> N <sub>2</sub> O · H <sub>2</sub> SO <sub>4</sub> <sup>b</sup>
81	H	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub>	146-148 dec	C <sub>10</sub> H <sub>16</sub> N <sub>2</sub> · H <sub>2</sub> SO <sub>4</sub> <sup>g</sup>

<sup>a</sup> The free base and the hydrochloride were first described by Votocek and Leminger, *Coll. Czech. Chem. Commun.*, **4**, 271 (1932).

<sup>b</sup> Previously reported by Hoffmann-La Roche, British Patent 864,108 (1961). <sup>c</sup> C: calcd 31.69; found, 32.20. <sup>d</sup> N: calcd 9.24; found, 9.75. <sup>e</sup> H: calcd 6.50; found, 6.00. <sup>f</sup> C: calcd 30.68; found, 31.46. <sup>g</sup> C: calcd 45.78; found, 45.07.

TABLE IV  
N'-AMINO-N'-ARALKYLGUANIDINES

No.	R	X	Mp, °C	Method	Formula
82	H	(CH <sub>2</sub> ) <sub>2</sub>	242-243	D	C <sub>9</sub> H <sub>14</sub> N <sub>4</sub> · 0.5H <sub>2</sub> SO <sub>4</sub>
83	4-Cl	(CH <sub>2</sub> ) <sub>2</sub>	262-264 dec	D <sup>a</sup>	C <sub>9</sub> H <sub>13</sub> ClN <sub>4</sub> · 0.5H <sub>2</sub> SO <sub>4</sub>
84	2-Cl	(CH <sub>2</sub> ) <sub>2</sub>	237-239	D	C <sub>9</sub> H <sub>13</sub> ClN <sub>4</sub> · 0.5H <sub>2</sub> SO <sub>4</sub> <sup>b</sup>
85	2,4,6-Me <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub>	272-274 dec	B	C <sub>12</sub> H <sub>20</sub> N <sub>4</sub> · 0.5H <sub>2</sub> SO <sub>4</sub>
86	H	CH=CHCH <sub>2</sub>	258-260 dec	B	C <sub>10</sub> H <sub>14</sub> N <sub>4</sub> · 0.5H <sub>2</sub> SO <sub>4</sub>

<sup>a</sup> The identical compound was also isolated from the mixture of products obtained by method B. <sup>b</sup> C: calcd 41.30; found, 40.66.

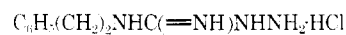
from amines,<sup>4</sup> gave a 60% yield of crude product, isolated as the bicarbonate, which was converted into the sulfate (8). This sulfate was shown to be identical, by mmp and tlc, with  $\beta$ -(4-chlorophenethyl)aminoguanidine sulfate obtained by unequivocal synthesis from 4-chlorophenylacetaldehyde.

In contrast with the report by Robertson, *et al.*,<sup>5</sup> that  $\beta$ -phenylisopropylhydrazine reacted with *S*-methylisothiuronium sulfate to give *N*-amino-*N*-( $\beta$ -phenylisopropyl)guanidine sulfate, we found that it proceeded in a strictly analogous manner to the unbranched aralkylhydrazines, to give  $\beta$ -phenylisopropylaminoguanidine sulfate (38) in 90% yield. This product was identical with the product obtained by catalytic hydrogenation of benzyl methyl ketone guanyldiazine hydrochloride (51), by mmp, ir, and tlc. We were not able to prepare the isomeric *N*-amino-*N*-( $\beta$ -phenylisopropyl)guanidine for comparison, but the 4-chlorophenethyl isomers (8 and 83, synthesized by unequiv-

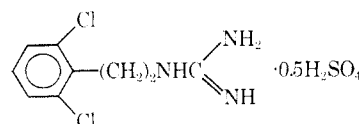
ocal methods C and D, respectively) exhibited significant differences both in mp and ir in the range 1580 to 1160 cm<sup>-1</sup>.

Finally, the third isomer of the parent compound of the series, *N*-amino-*N*'-phenethylguanidine hydrochloride (III), was prepared by condensation of phenethylamine with *S*-methylisothioureazide HI, followed by conversion into the HCl salt.

The guanidine IV was also synthesized for further studies of structure-activity relationships.



III



IV

The intermediate aralkylhydrazines shown in Table III were prepared by conventional methods from the corresponding aralkyl alcohols *via* their aralkyl chlorides. The alcohols were prepared either from the

(4) R. Fielden, A. M. Roe, and G. L. Willey, *Brit. J. Pharmacol. Chemother.*, **23**, 505 (1964).

(5) J. E. Robertson, J. H. Biel, and F. DiPierro, *J. Med. Chem.*, **6**, 381 (1963).

TABLE V

$  \begin{array}{c}  \text{R} \\    \\  \text{C}_6\text{H}_4 \\    \\  \text{X}-\text{NHNHCNH}_2 \\  \quad \parallel \\  \quad \text{NH}  \end{array}  $						
No.	X	R	Adrenergic block, cat ED <sub>50</sub> mg/kg iv	Hypertensive rat <sup>a</sup> mg/kg oral	Mouse Heart, NA % of control <sup>b</sup>	LD <sub>50</sub> mg/kg
1	CH <sub>2</sub>	H	0	100 ++	45	122 ip
3	(CH <sub>2</sub> ) <sub>2</sub>	H	2.0	100 +++	54	110 ip
				50 +		
5	(CH <sub>2</sub> ) <sub>2</sub>	2-Cl	3.5	100 +	56	220 ip
6	(CH <sub>2</sub> ) <sub>2</sub>	3-Cl	0	100 ++	56	
				50 +		
7	(CH <sub>2</sub> ) <sub>2</sub>	4-Cl	7.0	100 ++	12	66 ip
10	(CH <sub>2</sub> ) <sub>2</sub>	2,6-Cl <sub>2</sub>	3.0	100 +++	100	180 ip
				50 +++		900 oral
11	(CH <sub>2</sub> ) <sub>2</sub>	2,4-Cl <sub>2</sub>	0	50 0	15	
12	(CH <sub>2</sub> ) <sub>2</sub>	3,4-Cl <sub>2</sub>	0	100 +	12	
20	(CH <sub>2</sub> ) <sub>2</sub>	2,6-(CH <sub>3</sub> ) <sub>2</sub>	2.0	100 ++	71	105 ip
26	(CH <sub>2</sub> ) <sub>3</sub>	H	3.0	50 ++	57	120 ip
29	(CH <sub>2</sub> ) <sub>3</sub>	2,6-Cl <sub>2</sub>	2.0	100 +++	100	250 ip
				50 ++		2000 oral
				100 +++	25	180 ip
						3000 oral
	Guanethidine		2.0	100 +++		

<sup>a</sup> Decrease of systolic pressure 4 hr after oral administration: (0) no action; (+) 11–30 mm; (++) 31–50 mm; (+++) 51–80 mm. <sup>b</sup> 2–6 hr after ip injection of 50 mg/kg of compound.

substituted arylmagnesium bromides and ethylene oxide or, alternatively, from the substituted aralkyl-carboxylic acids by reduction with LAH.

**Pharmacology. Methods.**—The aralkylaminoguanidines were tested for adrenergic neurone blocking activity by repeated stimulation of the peripheral trunk of the severed cervical sympathetic nerve of the cat and recording the contraction of the nictitating membrane. Table V shows the doses which reduce the contraction by 50%. The norepinephrine content in the mouse heart was determined 2 and 6 hr after ip injection of 50 mg/kg, using a spectrofluorimetric method.<sup>6</sup> The blood pressure in hypertensive nonanesthetized rats was measured in the tail by Riva-Rocci's procedure using a crystal or condenser microphone. Hypertension was produced by unilateral nephrectomy, implantation of a tablet of DOCA (25 mg), and addition of 1% NaCl and 5% sucrose to the drinking water.

**Structure-Activity Relationships.**—Only the aralkylaminoguanidines were found to exhibit adrenergic neurone blocking activity. Many of the corresponding guanylhydrazones showed only negligible autonomic effects.

Within the series of aralkylaminoguanidines themselves adrenergic neurone blockade was found to be strongly structure dependent (see Table V). The benzyl derivative (**1**) is inactive while many of the phenethyl and  $\gamma$ -phenylpropyl derivatives showed activities similar to that of guanethidine.  $\beta$ -Phenylisopropylaminoguanidine (**38**) had only about 20% of the adrenergic neurone blocking activity of the phenethyl homolog **3** and was inactive in the hypertensive rat. Table V further illustrates the influence of nuclear substitution on activity, as exemplified by Cl.

The 2,6-dichloro substituted derivatives (**10**, **29**) stand out from the series as adrenergic neurone blockers which do not cause any depletion of the norepinephrine

stores in the heart. This is in contrast to the action of guanethidine. In addition, these compounds, unlike guanethidine, do not give rise to diarrhea in mice.

The blood pressure lowering effects in the hypertensive rat do not run strictly parallel with the adrenergic neurone blocking effects. Compounds with little or no adrenergic neurone blocking action, *e.g.*, **1**, **6**, **7**, and **12**, still cause some lowering of blood pressure; however, these effects are weak compared with those produced by **10** and **29**.

Compounds **1** and **3**, as the tosylates, and **29**, as the sulfate, have previously been examined by Augstein, *et al.*<sup>3</sup> Using a different technique of evaluating sympathetic blockade these authors reported very weak activities for **3** and **29**, which are in marked contrast to our own findings. We are unable to offer any explanation at present for the discrepancy in results obtained by different methods of determining adrenergic neurone blockade.

The *N*-amino-*N*-aralkylguanidines (**82–86**) cause very marked pressor effects following iv injection. They produce no adrenergic blockade and are practically inactive in the hypertensive rat.

Compound **10**, having a more favorable oral absorption than **29**, was selected for full pharmacological and toxicological study and for clinical testing. The compound, when given in doses of between 50 and 225 mg to patients with essential hypertension, caused statistically significant lowering of blood pressure.

### Experimental Section<sup>7</sup>

The experimental procedures are illustrated by the following examples.

(7) Melting points were determined on an Electrothermal melting point apparatus using the maker's-supplied stem corrected thermometer. A heating rate of 2°/min from about 20° below the melting point was used. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within  $\pm 0.4\%$  of the theoretical values.

(6) A. H. Anton and D. F. Sayre, *J. Pharmacol. Exp. Ther.*, **138**, 360 (1962); *ibid.*, **145**, 326 (1964).

**Aralkylaminoguanidines. Phenethylaminoguanidine Nitrate (2).** **Method A.**—A solution of phenylacetaldehyde guanyldiazide nitrate (11 g, 0.046 mole, **41**) in 90% aq AcOH (100 ml) at about 45° was shaken with H<sub>2</sub> and Adams' PtO<sub>2</sub> catalyst (0.25 g). When the theoretical quantity of H<sub>2</sub> had been absorbed, the catalyst was filtered off and the filtrate was diluted with *i*-Pr<sub>2</sub>O. The white solid obtained on cooling was twice recrystd from EtOH-*i*-Pr<sub>2</sub>O, giving fine colorless plates, mp 145° (5.1 g, 47%). *Anal.* (C<sub>9</sub>H<sub>14</sub>N<sub>4</sub>·HNO<sub>3</sub>) C, H, N, O.

**Method B.**—A mixture of phenethylhydrazine (13.6 g, 0.1 mole) and *S*-methylisothiuronium sulfate (13.9 g, 0.05 mole) in H<sub>2</sub>O (25 ml) was heated on a steam bath until the evolution of MeSH ceased. The hot solution was treated with a hot solution of Ba(NO<sub>3</sub>)<sub>2</sub> (13.1 g, 0.05 mole) in H<sub>2</sub>O (50 ml) and stirred for 15 min. BaSO<sub>4</sub> was filtered off and washed (hot H<sub>2</sub>O and 94% EtOH). The crude crystalline product obtained from the combined filtrate and washings on cooling was recrystd from EtOH-*i*-Pr<sub>2</sub>O, giving fine colorless plates, mp 144–145° (8.1 g, 34%), undepressed on admixture with the product prepared by method A. *Anal.* (C<sub>9</sub>H<sub>14</sub>N<sub>4</sub>·HNO<sub>3</sub>) C, H, N, O.

**γ-Phenylpropylaminoguanidine Nitrate (25).** **Method A.**—A suspension of cinnamaldehyde guanyldiazide nitrate (39 g, 0.155 mole, **55**) in abs EtOH (1 l.) at 45° was hydrogenated with Adams' catalyst (0.5 g) until the uptake of H<sub>2</sub> ceased. The catalyst was filtered off and the filtrate was evaporated to dryness. The residual solid was recrystd from EtOH-*i*-Pr<sub>2</sub>O, giving clusters of white plates, mp 81–84° (23.7 g, 61%). *Anal.* (C<sub>10</sub>H<sub>16</sub>N<sub>4</sub>·HNO<sub>3</sub>) C, H, N, O: calcd, 18.80; found, 19.36.

**4-Chlorophenethylaminoguanidine Sulfate and N-Amino-N-4-chlorophenethylguanidine Sulfate.** **Method B.**—A mixture of 4-chlorophenethylhydrazine (17 g, 0.1 mole, base of **65**) and *S*-methylisothiuronium sulfate (13.9 g, 0.05 mole) in H<sub>2</sub>O (30 ml) was heated on a steam bath until the evolution of MeSH ceased. After removal of H<sub>2</sub>O *in vacuo* and azeotropic drying with *i*-PrOH, the crystalline residue was recrystd from *i*-PrOH-Et<sub>2</sub>O giving fine white needles, mp 182–190° (21.5 g). Extraction with hot abs EtOH left an insol product, which was filtered off and recrystd from hot H<sub>2</sub>O to give white plates, constant mp 263° dec (4.4 g, 17%). This compd was found to be identical, by mmp and tlc, with N-amino-N-4-chlorophenethylguanidine sulfate (**83**). *Anal.* (C<sub>9</sub>H<sub>13</sub>ClN<sub>4</sub>·0.5H<sub>2</sub>SO<sub>4</sub>) C, H, Cl, N, S, O: calcd, 12.23; found, 12.70.

The main product which sepd from the EtOH extract on cooling was recrystd from aq EtOH, yielding fine white needles of 4-chlorophenethylaminoguanidine sulfate, mp 182–187° (11.7 g, 45%) identical with **8**. Tlc of this material showed that it contained only traces of the isomer. *Anal.* (C<sub>9</sub>H<sub>13</sub>ClN<sub>4</sub>·0.5H<sub>2</sub>SO<sub>4</sub>) C, H, Cl, N, O, S.

**4-Chlorophenethylaminoguanidine Sulfate (8).** **Method C.**—A solution of 4-chlorophenethylhydrazine·HCl (20.7 g, 0.1 mole; **65**·HCl) and cyanamide (17.9 g, 0.425 mole) in H<sub>2</sub>O (100 ml) was heated on a steam bath for 8 hr. The product was pptd as the bicarbonate by addition of a solution of NaHCO<sub>3</sub> (9.3 g, 0.11 mole) in H<sub>2</sub>O (ca. 200 ml). The solid (0.06 mole) was suspended in *n*-PrOH (100 ml) and treated with H<sub>2</sub>SO<sub>4</sub> (1.65 ml, 0.03 mole) in *n*-PrOH (25 ml) with swirling. The product crystallized on concentration and cooling, and recrystallization from aq EtOH gave white plates, mp 192–195° (9.6 g, 37%). *Anal.* (C<sub>9</sub>H<sub>13</sub>ClN<sub>4</sub>·0.5H<sub>2</sub>SO<sub>4</sub>) C, H, Cl, N, O.

**N-Amino-N-aralkylguanidines. Method D. 4-Chlorophenethylthiosemicarbazide.**—A solution of 4-chlorophenethylhydrazine·HCl (33 g 0.16 mole) in H<sub>2</sub>O (100 ml) was mixed with KCNS (19.1 g, 0.2 mole) and the solution was evapd to dryness. The residue was suspended in *n*-PrOH (150 ml) and refluxed for 30 min. The KCl was filtered off and the filtrate was refluxed for a further 3 hr. The crystalline solid which formed on cooling was filtered off, washed with *i*-Pr<sub>2</sub>O, and recrystd from EtOH to give fine white needles, mp 154–155° (20.3 g, 53%). *Anal.* (C<sub>9</sub>H<sub>12</sub>ClN<sub>3</sub>S) C, H, Cl, N, S.

**4-Chlorophenethyl-S-methylisothiiosemicarbazide Hydriodide.**—A suspension of 4-chlorophenethylthiosemicarbazide (36.8 g, 0.16 mole) in abs EtOH (500 ml) was mixed with MeI (22.8 g, 0.16 mole) in abs EtOH (200 ml). The mixture was warmed slowly to 40°, left for 72 hr at room temp, and finally refluxed for 2 hr. Concentration *in vacuo* gave heavy prisms, constant mp 174–177° (48.7 g, 82%). On dilution with *i*-Pr<sub>2</sub>O, the filtrate yielded a second crop, mp 170–175° (7 g, 12%). *Anal.* (C<sub>10</sub>H<sub>14</sub>ClN<sub>3</sub>SI) C, H, Cl, I, N, S.

**N-Amino-N-(4-chlorophenethyl)guanidine Hydriodide.**—A suspension of 4-chlorophenethyl-S-methylisothiiosemicarbazide·HI

(29.7 g, 0.08 mole) in H<sub>2</sub>O (250 ml) was warmed on a steam bath and treated at intervals with seven 5-ml portions of NH<sub>3</sub> (sp gr 0.880), after which the evolution of MeSH ceased. After removal of H<sub>2</sub>O *in vacuo* and azeotropic drying with *i*-PrOH, the residue was recrystd twice from *n*-PrOH-*i*-Pr<sub>2</sub>O, yielding flat white needles, mp 180–182° (18 g, 66%). *Anal.* (C<sub>9</sub>H<sub>13</sub>ClN<sub>4</sub>·HI) H, Cl, N, C: calcd, 31.73; found, 30.94; I: calcd, 37.26; found, 38.35.

**N-Amino-N-(4-chlorophenethyl)guanidine Sulfate (83).**—A solution of the hydriodide (17 g, 0.05 mole) in hot H<sub>2</sub>O (100 ml) was stirred into a hot solution of Ag<sub>2</sub>SO<sub>4</sub> (7.8 g, 0.025 mole) in H<sub>2</sub>O (700 ml). The pptd AgI was filtered off and the filtrate was evaporated almost to dryness. The damp residue was crystallized from aq EtOH and twice from H<sub>2</sub>O giving flat white needles, mp 262–264° dec. *Anal.* (C<sub>9</sub>H<sub>13</sub>ClN<sub>4</sub>·0.5H<sub>2</sub>SO<sub>4</sub>) C, H, Cl, N, O, S.

**Aralkylhydrazines. 2,6-Dichlorophenethanol.**—A solution of 2,6-dichlorophenylacetic acid (734 g, 3.58 moles) in anhyd Et<sub>2</sub>O (4 l.) was added dropwise over 2.5 hr to a stirred suspension of LAH (200 g, 5.26 moles) in anhyd Et<sub>2</sub>O (3 l.). The mixture was stirred for a further 2 hr and left overnight. H<sub>2</sub>O (500 ml) was then added very slowly, followed by 5 N HCl (4). About half of the Et<sub>2</sub>O was allowed to distil off during the acid addition. The Et<sub>2</sub>O phase and three 150-ml Et<sub>2</sub>O extracts of the aq phase were combined, dried, and distd to give an oil (655.1 g, 96%), bp 146–152° (12 mm).

**2,6-Dimethylphenethanol.**—2-Bromo-*m*-xylene (151 g, 0.815 mole) in dry Et<sub>2</sub>O (150 ml) was added dropwise over 2 hr with stirring, to a gently refluxing suspension of clean Mg turnings (21.4 g, 0.88 mole) in dry Et<sub>2</sub>O (400 ml). The mixture was refluxed for a further 5 hr, then left overnight. Ethylene oxide (36 g, 0.815 mole) was then added dropwise to the cooled mixture so that the internal temp was kept below –10°. On completion of the addition the mixture was allowed to reach 20° over 4 hr. Concentrated HCl (100 ml, 1 mole) was then added over 45 min with stirring.

The Et<sub>2</sub>O phase and two 100-ml Et<sub>2</sub>O extracts of the aq phase were combined, dried, and distilled, giving an oil, bp 160–163° (43 mm) (54.1 g, 44%).

**2,6-Dimethylphenethyl Chloride.**—A mixture of the above alcohol (54.1 g, 0.36 mole) in dry C<sub>6</sub>H<sub>6</sub> (50 ml) was treated portionwise with SOCl<sub>2</sub> (60.5 g, 0.51 mole). After standing at room temp for 30 min the mixture was heated for 30 min on a steam bath and then distd giving the chloride (53.2 g, 88%), bp 117–127° (12–15 mm).

**2,6-Dimethylphenethylhydrazine.**—A mixture of 2,6-dimethylphenethyl chloride (53.2 g, 0.32 mole), hydrazine hydrate (125 g, 2.5 moles), and *n*-PrOH (1 l.) was heated at reflux for 40 hr. The mixture was coned to about 250 ml, the residue was poured into cold 5 N NaOH (200 ml) and extracted with CHCl<sub>3</sub>. The dried extract was distilled, yielding an oil (41.9 g, 81%), bp 132–135° (4 mm).

**Guanyldiazones. 2,6-Dichlorophenylacetaldehyde.**—This was prepared by CrO<sub>3</sub> oxidation of 2,6-dichlorophenethanol by the method of Shumeiko<sup>8</sup> or by reduction of 2,6-dichlorophenylacetone nitrile by the method of Van Es and Staskun,<sup>9</sup> low-melting solid, bp 104–108° (2 mm); semicarbazone, mp 215°. *Anal.* (C<sub>8</sub>H<sub>6</sub>Cl<sub>2</sub>N<sub>3</sub>O) C, H, Cl, N, O: calcd, 6.50; found, 7.03.

Other aldehydes were prepared similarly or by other appropriate methods, *e.g.*, Perkin reaction, hydrolysis of the glycidate,<sup>10</sup> or hydrolysis of the benzylmagnesium halide with triethyl orthoformate.<sup>11</sup>

**2-Fluorophenylacetaldehyde Diethyl Acetal.**—2-Fluorobenzyl bromide (485.9 g, 2.57 moles) in anhyd Et<sub>2</sub>O (400 ml) was added dropwise over 3.5 hr to a stirred suspension of Mg turnings (68.6 g, 2.83 moles) in anhyd Et<sub>2</sub>O (1070 ml). The mixture was stirred for a further hour and left overnight. Triethyl orthoformate (381 g, 2.57 moles) was added over 1 hr, the mixture was refluxed for 6 hr, and allowed to cool overnight. The pptd Mg salts were decompd by adding ice-cold dil HCl to the stirred mixture at 0°, and the combined Et<sub>2</sub>O layer and two Et<sub>2</sub>O extracts were washed with cold H<sub>2</sub>O until neutral, dried, and distilled, giving the acetal (247.3 g, 46%), bp 112–118° (12 mm).

**2,6-Dichlorophenylacetaldehyde Guanyldiazide Nitrate (44).**—A solution of 2,6-dichlorophenylacetaldehyde (183.2 g, 0.971

(8) A. K. Shumeiko, *J. Appl. Chem. USSR*, **14**, 93 (1941).

(9) T. van Es and B. Staskun, *J. Chem. Soc.*, 5775 (1965).

(10) I. G. Farben, German Patent 591,452 (1934).

(11) Laboratoires Dausse, French Patent 1,327,160 (1963).

mole) in warm EtOH (250 ml) was run into a stirred solution of aminoguanidine nitrate (134 g, 0.975 mole) in 500 ml of H<sub>2</sub>O and 750 ml of EtOH. A ppt was formed almost immediately. The suspension was warmed to about 70° to complete the reaction, then allowed to cool to room temp overnight. The ppt was filtered off, washed (H<sub>2</sub>O, a little EtOH, and Et<sub>2</sub>O), and suspended in 1.8 l. of H<sub>2</sub>O. This stirred suspension was warmed at 80° for 30 min and filtered hot to give the guanyldiazotone, mp 228–229° dec, yield 213 g (72%). *Anal.* (C<sub>9</sub>H<sub>10</sub>Cl<sub>2</sub>N<sub>4</sub>·HNO<sub>3</sub>) H, N, O. C: calcd, 35.08; found, 35.53.

The other guanyldiazotones in Table II were prepared similarly.

**N-Amino-N'-phenethylguanidine Hydrochloride.**—*S*-Methylisothiosemicarbazide·HI (44.3 g, 0.19 mole) was suspended in a mixture of abs EtOH (100 ml) and phenethylamine (23.5 g, 0.193 mole) and heated under gentle reflux until MeSH was no longer evolved. Removal of the EtOH *in vacuo* gave an orange-brown oil which was taken up in *n*-PrOH and diluted with Et<sub>2</sub>O. A small crimson ppt was rejected. The filtrate was treated

with ethanolic HCl to give a fine white crystalline solid, mp 140–146°, yield 38.7 g. (90%). Three recrystallizations from EtOH gave fine pale-cream plates, mp 156–157° (10.1 g). *Anal.* (C<sub>9</sub>H<sub>11</sub>N<sub>4</sub>·2HCl) C, H, Cl. N: calcd, 22.31; found, 22.78.

**2,6-Dichlorophenethylguanidine Sulfate.**—A mixture of 2,6-dichlorophenethylamine<sup>12</sup> (24 g, 0.125 mole), *S*-methylisothiouronium sulfate (17.7 g, 0.063 mole), 93% EtOH (50 ml), and H<sub>2</sub>O (25 ml) was heated on a steam bath until the evolution of MeSH ceased. On cooling, a solid, mp 255–258°, crystd; yield 12.7 g. Trituration, first with hot H<sub>2</sub>O, then with hot EtOH, gave a fine white powder, mp 258–260°, yield 10.4 g. *Anal.* (C<sub>9</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>3</sub>·0.5H<sub>2</sub>SO<sub>4</sub>) C, H, Cl, N, O, S.

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(12) *β*-(2,6-Dichlorophenyl)ethylamine·HCl, mp 283–286° was prepared by catalytic reduction of 2,6-dichlorophenylacetonitrile, bp 134° (4 mm).

## Synthesis and Norepinephrine Depleting Activity of Some Metaraminol Ethers

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A series of ethers of (1*R*,2*S*)- $\alpha$ -(1-aminoethyl)-*m*-hydroxybenzyl alcohol (metaraminol) has been prepared. These compounds deplete the mouse heart of norepinephrine. The more potent members, *e.g.*, the ethyl and cyclopropylmethyl ethers, exhibited acute pressor effects in the dog while the *m*- and *p*-chlorobenzyl ethers of metaraminol were found to produce norepinephrine depletion without significant acute pressor action. Evidence is presented to show that the ethers are dealkylated *in vivo* to metaraminol.

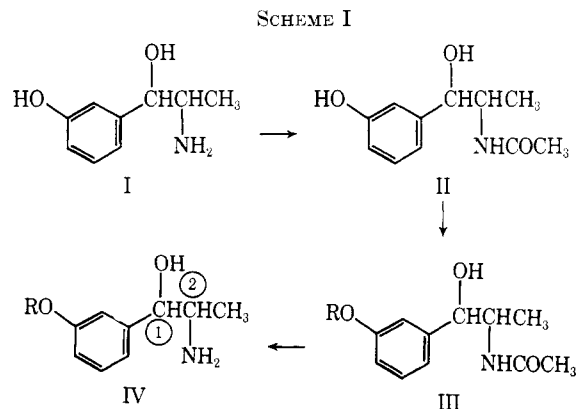
Metaraminol (I), (–)-erythro, appears to possess the attributes of a nearly ideal substitute adrenergic transmitter.<sup>1,2</sup> Thus metaraminol has a high intrinsic ability to enter and displace the normal transmitter norepinephrine from storage sites within the adrenergic neuron; it is released during stimulation of the sympathetic nervous system; it is not a substrate for monoamine oxidase; and it possesses considerably less transmitter potential than norepinephrine.

Crout<sup>2</sup> has reported that metaraminol has a significant antihypertensive effect in a few subjects given the drug orally in small dosages over several days. However, administration of metaraminol under certain conditions can produce acute pressor effects which makes testing of the compound for therapeutic utility precarious. The amino acid  $\alpha$ -methyl-*m*-tyrosine, which is metabolized to metaraminol in animals,<sup>3</sup> has also been reported to be effective in lowering the blood pressure of hypertensive patients when administered intravenously.<sup>4</sup> However, the amino acid was not effective

after oral administration. In addition central nervous system effects have been observed with  $\alpha$ -methyl-*m*-tyrosine which have discouraged further clinical trials.

It seemed desirable, therefore, to develop other derivatives of metaraminol which would be susceptible to metabolic conversion into the phenolic amine without causing acute cardiovascular effects.

**Chemistry.**—The ethers reported in Table I were prepared from metaraminol (I), (–)-erythro, by the route outlined in Scheme I. The acetyl intermediates



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(1) For leading references to the substitute transmitter hypothesis, see: I. J. Kopin, *Annu. Rev. Pharmacol.*, **8**, 377 (1968); C. A. Stone and C. C. Porter, *Advan. Drug Res.*, **4**, 71 (1967).

(2) J. R. Crout, *Circ. Res.*, **18**, 19, Suppl., **1**, 120 (1966).

(3) A. Carlsson and M. Lindquist, *Acta Physiol. Scand.*, **54**, 87 (1962); P. A. Shore, D. Bushfield, and H. S. Alpers, *J. Pharmacol. Exp. Ther.*, **146**, 194 (1964).

(4) D. Horwitz and A. Sjoerdsma, *Life Sci.*, **3**, 41 (1964); H. J. Holtmeier, A. vonKlein-Wisenberg, and F. Marongiu, *Deut. Med. Wochenschr.*, **91**, 198 (1966).

III were usually not isolated, but were hydrolyzed directly to the optically active ethers IV with NaOH.