[1,2-*a*]pyridine (0.094 mole) in 75 ml of EtOH was added a soln of 19.6 g of $NH_2OH \cdot HCl$ (0.28 mole) and 12 g of 95% NaOH (0.28 mole) in 120 ml of H_2O. 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 $H_2NNHCONH_2 \cdot HCl$ (0.053 mole) in 31.2 ml of 10% HCl and 10 ml of H_2O. 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[4] (0.005 mole) in 10 ml of 10% HCl was added a soln of 0.478 g of $H_2NNHCSNH_2$ (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 Guanylhydrazone·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 $H_2NNHC(=NH)NH_2 \cdot H_2CO_3$ (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 H_2O, 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 sepd oil was extracted with $CHCl_3$, 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 CS_2 was added, very slowly, 90 g of anhyd $AlCl_3$, with external cooling. After stirring for 30 min at room temp the mixture was refluxed gently and 22.5 ml of Ac_2O was added drop by drop, in 30 min. After refluxing for 1 hr, the CS_2 was evapd and the residue mixed with crushed ice, made alkaline with NaOH, and extracted with CH_2Cl_2. The soln was dried (K_2CO_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).[7] The exothermic reaction was moderated by cooling. The mixture was refluxed for 10 hr, the solvent evapd to dryness, and the residue mixed with H_2O and 20% NaOH and extracted with Et_2O. The soln was dried (K_2CO_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 Et_2O was treated as indicated in the previous example with 28 g of crude 3-bromoacetylacetone[8] (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 H_2O was added a soln of 55.7 g of $H_2NNHCONH_2 \cdot HCl$ (0.5 mole) in 100 ml of 10% NaOH (0.25 mole). The mixture was refluxed for 2 hr, made alkaline with Na_2CO_3, filtered, and washed with H_2O 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 $H_2NCSNHNH_2$ (0.0206 mole), and 2.6 g of $H_2NCSNHNH_2 \cdot HCl$ (0.0206 mole) in 20 ml of H_2O and 20 ml of EtOH was refluxed for 2 hr, while still hot, the mixture was made alkaline with a satd soln of Na_2CO_3, and the ppt (2.8 g; yield 97%) was filtered and washed with H_2O until neutral.

3-Acetylimidazo[1,2-*a*]pyridine Guanylhydrazone (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 $H_2NNHC(=NH)NH_2 \cdot H_2CO_3$ (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 C_6H_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 $NaBH_4$ (0.0115 mole) in 5 ml of H_2O in 5 min, keeping the temp at 10–15°. The soln was evapd to dryness and the residue recrystd from 30 ml of H_2O (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**, 14230*h* (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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A series of substituted aralkylaminoguanidines (I) was synthesized and evaluated for pharmacological activity. The compounds were prepared by catalytic reduction of the guanylhydrazones or by reaction of the aralkylhydrazines with either *S*-methylisothiouronium salts or cyanamide. A method of separating mixtures of I and II obtained by the reaction with *S*-methylisothiouronium 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, β-(2,6-dichlorophenyl)ethylaminoguanidine hydrochloride (**10**) and γ-phenylpropylaminoguanidine hydrochloride (**26**) proved of special interest as potentially

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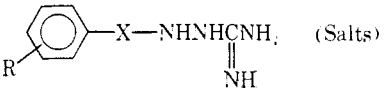
TABLE I

ARALKYLAMINOGUANIDINES



No.	R	X	Mp, °C	Method	Formula
1	H	CH_2	135–138	A[a]	$C_8H_{12}N_4 \cdot HNO_3$[b]
2	H	$(CH_2)_2$	145	A[a]	$C_9H_{14}N_4 \cdot HNO_3$[c]
3	H	$(CH_2)_2$	114–121	A	$C_9H_{14}N_4 \cdot HCl$
4	H	$(CH_2)_2$	109–111 dec	A	$C_9H_{14}N_4 \cdot H_2CO_3$
5	2-Cl	$(CH_2)_2$	158–160	B[a]	$C_9H_{13}ClN_4 \cdot HNO_3$[d,e]
6	3-Cl	$(CH_2)_2$	117–120	A	$C_9H_{13}ClN_4 \cdot HNO_3$
7	4-Cl	$(CH_2)_2$	144–146	B[d]	$C_9H_{13}ClN_4 \cdot HNO_3$
8	4-Cl	$(CH_2)_2$	192–195	C[d]	$C_9H_{13}ClN_4 \cdot 0.5H_2SO_4$
9	2,6-Cl_2	$(CH_2)_2$	190–192	A[a]	$C_9H_{12}Cl_2N_4 \cdot HNO_3$
10	2,6-Cl_2	$(CH_2)_2$	193–194	B[d]	$C_9H_{12}Cl_2N_4 \cdot HCl$
11	2,4-Cl_2	$(CH_2)_2$	161–163	A	$C_9H_{12}Cl_2N_4 \cdot HNO_3$
12	3,4-Cl_2	$(CH_2)_2$	147–150	A	$C_9H_{12}Cl_2N_4 \cdot HNO_3$
13	2-Br	$(CH_2)_2$	158–162	A	$C_9H_{13}BrN_4 \cdot HNO_3$
14	4-Br	$(CH_2)_2$	160–162	A	$C_9H_{13}BrN_4 \cdot HNO_3$
15	2-F	$(CH_2)_2$	131–134	A	$C_9H_{13}FN_4 \cdot HNO_3$
16	4-F	$(CH_2)_2$	123–124	B[d]	$C_9H_{13}FN_4 \cdot HNO_3$
17	2-Me	$(CH_2)_2$	153–154	A[a]	$C_{10}H_{16}N_4 \cdot HNO_3$
18	3-Me	$(CH_2)_2$	96–98	A	$C_{10}H_{16}N_4 \cdot HNO_3$
19	4-Me	$(CH_2)_2$	121–123	A[a]	$C_{10}H_{16}N_4 \cdot HNO_3$
20	2,6-Me_2	$(CH_2)_2$	179–183	A	$C_{11}H_{18}N_4 \cdot HNO_3$
21	2,4-Me_2	$(CH_2)_2$	112–115	A	$C_{11}H_{18}N_4 \cdot HNO_3$
22	2,4,6-Me_3	$(CH_2)_2$	184–185	A	$C_{12}H_{20}N_4 \cdot HCl$[f]
23	2-OMe	$(CH_2)_2$	129–132	A	$C_{10}H_{16}N_4O \cdot HNO_3$
24	4-OMe	$(CH_2)_2$	118–120	A[a]	$C_{10}H_{16}N_4O \cdot HNO_3$
25	H	$(CH_2)_3$	81–84	A	$C_{10}H_{16}N_4 \cdot HNO_3$
26	H	$(CH_2)_3$	123–125	A	$C_{10}H_{16}N_4 \cdot HCl$
27	2-Cl	$(CH_2)_3$	127	A	$C_{10}H_{15}ClN_4 \cdot HNO_3$
28	4-Cl	$(CH_2)_3$	126–129	A	$C_{10}H_{15}ClN_4 \cdot HNO_3$
29	2,6-Cl_2	$(CH_2)_3$	164–165	A	$C_{10}H_{14}Cl_2N_4 \cdot HNO_3$[g]
30	2,4-Cl_2	$(CH_2)_3$	124–126	A	$C_{10}H_{14}Cl_2N_4 \cdot HNO_3$
31	3,4-Cl_2	$(CH_2)_3$	140–142	A	$C_{10}H_{14}Cl_2N_4 \cdot HNO_3$
32	2-F	$(CH_2)_3$	78	A	$C_{10}H_{15}FN_4 \cdot HNO_3$[i,k]
33	4-F	$(CH_2)_3$	89–92	A	$C_{10}H_{15}FN_4 \cdot HNO_3$
34	2-Me	$(CH_2)_3$	126–129	A	$C_{11}H_{18}N_4 \cdot HNO_3$
35	4-Me	$(CH_2)_3$	120–122	A	$C_{11}H_{18}N_4 \cdot HNO_3$
36	4-OMe	$(CH_2)_3$	104–107	A	$C_{11}H_{18}N_4O \cdot HNO_3$
37	H	$CH{=}CHCH_2$	125–127	B	$C_{10}H_{14}N_4 \cdot HNO_3$
38	H	CH_2CHMe	218–219 dec	B[d]	$C_{10}H_{16}N_4 \cdot 0.5H_2SO_4$
39	H	CH_2CHMe	123–125	B[e]	$C_{10}H_{16}N_4 \cdot HCl$[l]
40	H	$(CH_2)_4$	129–131	A[a]	$C_{11}H_{18}N_4 \cdot HNO_3$

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

useful antihypertensive agents.[1] 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 guanylhydrazone salts (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*-methylisothiouronium salt (method B).

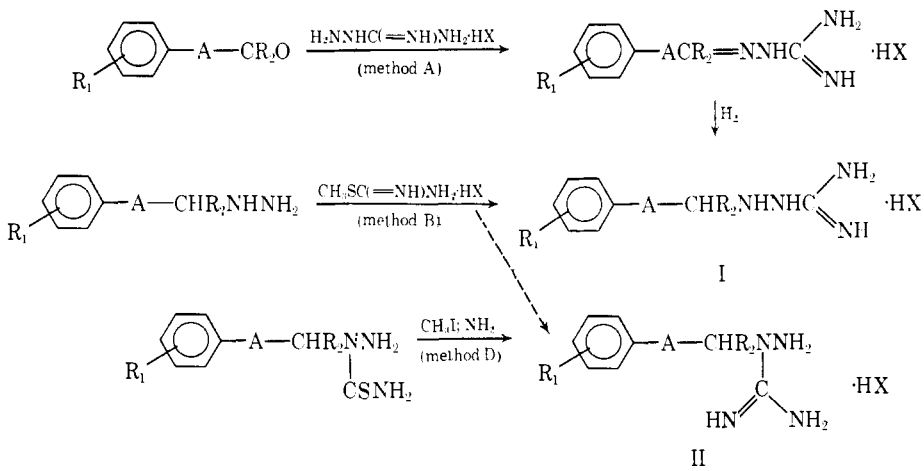
When the *S*-methylisothiouronium sulfate method was used, the products were usually found, on tlc, to be two-component mixtures. A partial separation by crystallization of the sulfates was achieved in three cases, namely with the β-(4-chlorophenyl)ethyl, the β-(2,4,6-trimethylphenyl)ethyl, and the cinnamyl 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,[1-3] to give an aralkylaminoguanidine (I) as the major product of the reaction. The aralkylaminoguanidines gave a characteristic deep

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

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

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

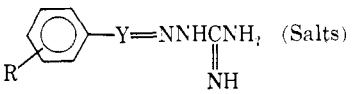
SCHEME I



A = alkylene or alkylidene, *e.g.*, CH_2, CH_2CH_2, CH=CH
R_2 = H or CH_3

TABLE II

GUANYLHYDRAZONES



No.	R	Y	Mp, °C	Formula
41	H	CH_2CH	157	$C_9H_{12}N_4 \cdot HNO_3$
42	2-Cl	CH_2CH	169–171 dec	$C_9H_{11}ClN_4 \cdot HNO_3$
43	4-Cl	CH_2CH	178–179	$C_9H_{11}ClN_4 \cdot HNO_3$
44	2,6-Cl_2	CH_2CH	228–229 dec	$C_9H_{10}Cl_2N_4 \cdot HNO_3$[a]
45	2-F	CH_2CH	154–156	$C_9H_{11}FN_4 \cdot HNO_3$[b]
46	4-F	CH_2CH	156–158	$C_9H_{11}FN_4 \cdot HNO_3$
47	2-Me	CH_2CH	183–184	$C_{10}H_{14}N_4 \cdot HNO_3$
48	3-Me	CH_2CH	104–108	$C_{10}H_{14}N_4 \cdot HNO_3$
49	4-Me	CH_2CH	169–172 dec	$C_{10}H_{14}N_4 \cdot HNO_3$
50	4-OMe	CH_2CH	157 dec	$C_{10}H_{14}N_4O \cdot HNO_3$
51	H	CH_2CMe	156	$C_{10}H_{14}N_4 \cdot HCl$[c]
52	4-F	CH_2CH_2CH	175–176	$C_{10}H_{13}FN_4 \cdot HNO_3$
53	2-Me	CH_2CH_2CH	169–171 dec	$C_{11}H_{16}N_4 \cdot HNO_3$
54	4-OMe	CH_2CH_2CH	145–147	$C_{11}H_{16}N_4O \cdot HNO_3$
55	H	CH=CHCH	194–196 dec	$C_{10}H_{12}N_4 \cdot HNO_3$
56	2-Cl	CH=CHCH	212–215 dec	$C_{10}H_{11}ClN_4 \cdot HNO_3$
57	4-Cl	CH=CHCH	219–220 dec	$C_{10}H_{11}ClN_4 \cdot HNO_3$
58	2,4-Cl_2	CH=CH	244 dec	$C_{10}H_{10}Cl_2N_4 \cdot HNO_3$
59	3,4-Cl_2	CH=CH	233 dec	$C_{10}H_{10}Cl_2N_4 \cdot HNO_3$
60	4-CH_3	CH=CH	208 dec	$C_{11}H_{14}N_4 \cdot HNO_3$
61	H	$(CH_2)_3CH$	107	$C_{11}H_{16}N_4 \cdot HNO_3$

[a] C: calcd 35.08; found, 35.53. [b] C: calcd 42.02; found, 43.05. [c] N: calcd 24.71; found, 25.22.

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

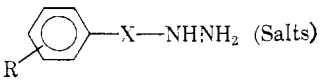
It was assumed that the minor component isolated from these mixtures was the corresponding *N*-amino-*N*-aralkylguanidine sulfate (II). This was confirmed for the phenyl-, 4-chlorophenyl-, and 2-chlorophenylethyl compounds **82**, **83**, and **84** (Table IV), by unequivocal synthesis *via* the appropriate 2-(β-arylethyl)thiosemicarbazide, as illustrated in Scheme I (method D). The corresponding β-(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*-methylisothiouronium salt.

It was also found that pure aralkylaminoguanidines I could be obtained from the reaction mixtures by isolating their HNO_3 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 conld be obtained directly by treatment of aralkylhydrazines with *S*-methylisothiouronium nitrate in aq solution, or by conversion of the mixed sulfates into nitrates by means of hot $Ba(NO_3)_2$ 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 β-(4-chlorophenyl)-ethylhydrazine (method C), employing the conditions previously described for the preparation of guanidines

TABLE III

ARALKYLHYDRAZINES

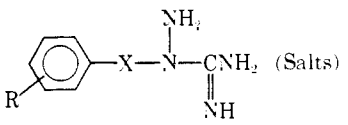


No.	R	X	Mp, °C	Formula
62	H	CH_2	158–160	$C_7H_{10}N_2 \cdot H_2SO_4$
63	H	$(CH_2)_2$	169–171 dec	$C_8H_{12}N_2 \cdot H_2SO_4$[a]
64	2-Cl	$(CH_2)_2$	169–173 dec	$C_8H_{11}ClN_2 \cdot H_2SO_4$
65	4-Cl	$(CH_2)_2$	154–156 dec	$C_8H_{11}ClN_2 \cdot H_2SO_4$
66	3,4-Cl_2	$(CH_2)_2$	165–167 dec	$C_8H_{10}Cl_2N_2 \cdot H_2SO_4$[b,c]
67	2,4-Cl_2	$(CH_2)_2$	194–196 dec	$C_8H_{10}Cl_2N_2 \cdot H_2SO_4$
68	2,6-Cl_2	$(CH_2)_2$	171–173 dec	$C_8H_{10}Cl_2N_2 \cdot HCl$
69	2-Me	$(CH_2)_2$	187–189 dec	$C_9H_{14}N_2 \cdot H_2SO_4$[d]
70	3-Me	$(CH_2)_2$	173–174 dec	$C_9H_{14}N_2 \cdot H_2SO_4$
71	4-Me	$(CH_2)_2$	161–162 dec	$C_9H_{14}N_2 \cdot H_2SO_4$[e]
72	2,4-Me_2	$(CH_2)_2$	172–173	$C_{10}H_{16}N_2 \cdot H_2SO_4$
73	2,6-Me_2	$(CH_2)_2$	175–178 dec	$C_{10}H_{16}N_2 \cdot H_2SO_4$
74	2,4,6-Me_3	$(CH_2)_2$	190 dec	$C_{11}H_{18}N_2 \cdot H_2SO_4$
75	2-F	$(CH_2)_2$	156–157	$C_8H_{11}FN_2 \cdot H_2SO_4$
76	4-F	$(CH_2)_2$	161–163	$C_8H_{11}FN_2 \cdot H_2SO_4$
77	2-Br	$(CH_2)_2$	167–168	$C_8H_{11}BrN_2 \cdot H_2SO_4$
78	4-Br	$(CH_2)_2$	170–175	$C_8H_{11}BrN_2 \cdot H_2SO_4$[f]
79	2-MeO	$(CH_2)_2$	151–153	$C_9H_{14}N_2O \cdot H_2SO_4$
80	4-MeO	$(CH_2)_2$	155–156	$C_9H_{14}N_2O \cdot H_2SO_4$[g]
81	H	$CH_2CH_2CH_2CH_2$	146–148 dec	$C_{10}H_{16}N_2 \cdot H_2SO_4$[a]

[a] The free base and the hydrochloride were first described by Votocek and Lemminger, *Coll. Czech. Chem. Commun.*, **4**, 271 (1932). [b] Previously reported by Hoffmann-La Roche, British Patent 864,108 (1961). [c] C: calcd 31.69; found, 32.20. [d] N: calcd 9.24; found, 9.75. [e] H: calcd 6.50; found, 6.00. [f] C: calcd 30.68; found, 31.46. [g] C: calcd 45.78; found, 45.07.

TABLE IV

N-AMINO-*N*-ARALKYLGUANIDINES



No.	R	X	Mp, °C	Method	Formula
82	H	$(CH_2)_2$	242–243	D	$C_9H_{14}N_4 \cdot 0.5H_2SO_4$
83	4-Cl	$(CH_2)_2$	262–264 dec	D[a]	$C_9H_{13}ClN_4 \cdot 0.5H_2SO_4$
84	2-Cl	$(CH_2)_2$	237–239	D	$C_9H_{13}ClN_4 \cdot 0.5H_2SO_4$[b]
85	2,4,6-Me_3	$(CH_2)_2$	272–274 dec	B	$C_{12}H_{20}N_4 \cdot 0.5H_2SO_4$
86	H	$CH{=}CHCH_2$	258–260 dec	B	$C_{10}H_{14}N_4 \cdot 0.5H_2SO_4$

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

from amines,[4] 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 β-(4-chlorophenethyl)aminoguanidine sulfate obtained by unequivocal synthesis from 4-chlorophenylacetaldehyde.

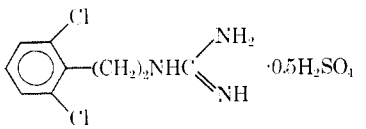
In contrast with the report by Robertson, *et al.*,[5] that β-phenylisopropylhydrazine reacted with *S*-methylisothiouronium sulfate to give *N*-amino-*N*-(β-phenylisopropyl)guanidine sulfate, we found that it proceeded in a strictly analogous manner to the unbranched aralkylhydrazines, to give β-phenylisopropylaminoguanidine sulfate (**38**) in 90% yield. This product was identical with the product obtained by catalytic hydrogenation of benzyl methyl ketone guanylhydrazone hydrochloride (**51**), by mmp, ir, and tlc. We were not able to prepare the isomeric *N*-amino-*N*-(β-phenylisopropyl)guanidine for comparison, but the 4-chlorophenethyl isomers (**8** and **83**, synthesized by unequivocal methods C and D, respectively) exhibited significant differences both in mp and ir in the range 1580 to 1160 cm^{-1}.

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*-methylisothiosemicarbazide HI, followed by conversion into the HCl salt.

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

$C_6H_5(CH_2)_2NHC(=NH)NHNH_2 \cdot HCl$

III



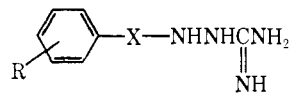
IV

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



No.	X	R	Adrenergic block, cat ED_{50} mg/kg iv	Hypertensive rat[a] mg/kg oral	Mouse Heart, NA % of control[b]	Mouse LD_{50} mg/kg
1	CH_2	H	0	100 ++	45	122 ip
3	$(CH_2)_2$	H	2.0	100 +++	54	110 ip
				50 +		
5	$(CH_2)_2$	2-Cl	3.5	100 +	56	220 ip
6	$(CH_2)_2$	3-Cl	0	100 ++	56	
				50 +		
7	$(CH_2)_2$	4-Cl	7.0	100 ++	12	66 ip
10	$(CH_2)_2$	2,6-Cl_2	3.0	100 +++	100	180 ip
				50 +++		900 oral
11	$(CH_2)_2$	2,4-Cl_2	0	50 0	15	
12	$(CH_2)_2$	3,4-Cl_2	0	100 +	12	
20	$(CH_2)_2$	2,6-$(CH_3)_2$	2.0	100 ++	71	105 ip
26	$(CH_2)_3$	H	3.0	50 ++	57	120 ip
29	$(CH_2)_3$	2,6-Cl_2	2.0	100 +++	100	250 ip
				50 ++		2000 oral
Guanethidine			2.0	100 +++	25	180 ip
						3000 oral

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

substituted arylmagnesium bromides and ethylene oxide or, alternatively, from the substituted aralkylcarboxylic 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 cotractionn 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.[6] 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 γ-phenylpropyl derivatives showed activities similar to that of guanethidine. β-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.*[3] 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[7]

The experimental procedures are illustrated by the following examples.

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

(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 ±0.4% of the theoretical values.

Aralkylaminoguanidines. Phenethylaminoguanidine Nitrate (2). Method A.—A solution of phenylacetaldehyde guanylhydrazone nitrate (11 g, 0.046 mole, **41**) in 90% aq AcOH (100 ml) at about 45° was shaken with H_2 and Adams' PtO_2 catalyst (0.25 g). When the theoretical quantity of H_2 had been absorbed, the catalyst was filtered off and the filtrate was diluted with *i*-Pr_2O. The white solid obtained on cooling was twice recrystd from EtOH–*i*-Pr_2O, giving fine colorless plates, mp 145° (5.1 g, 47%). *Anal.* ($C_9H_{14}N_4 \cdot HNO_3$) C, H, N, O.

Method B.—A mixture of phenethylhydrazine (13.6 g, 0.1 mole) and *S*-methylisothiouronium sulfate (13.9 g, 0.05 mole) in H_2O (25 ml) was heated on a steam bath until the evolution of MeSH ceased. The hot solution was treated with a hot solution of $Ba(NO_3)_2$ (13.1 g, 0.05 mole) in H_2O (50 ml) and stirred for 15 min. $BaSO_4$ was filtered off and washed (hot H_2O and 94% EtOH). The crude crystalline product obtained from the combined filtrate and washings on cooling was recrystd from EtOH–*i*-Pr_2O, giving fine colorless plates, mp 144–145° (8.1 g, 34%), undepressed on admixture with the product prepared by method A. *Anal.* ($C_9H_{14}N_4 \cdot HNO_3$) C, H, N, O.

γ-Phenylpropylaminoguanidine Nitrate (25). Method A.—A suspension of cinnamaldehyde guanylhydrazone 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_2 ceased. The catalyst was filtered off and the filtrate was evaporated to dryness. The residual solid was recrystd from EtOH–*i*-Pr_2O, giving clusters of white plates, mp 81–84° (23.7 g, 61%). *Anal.* ($C_{10}H_{16}N_4 \cdot HNO_3$) 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*-methylisothiouronium sulfate (13.9 g, 0.05 mole) in H_2O (30 ml) was heated on a steam bath until the evolution of MeSH ceased. After removal of H_2O *in vacuo* and azeotropic drying with *i*-PrOH, the crystalline residue was recrystd from *i*-PrOH–Et_2O 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_2O 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.* ($C_9H_{13}ClN_4 \cdot 0.5H_2SO_4$) 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.* ($C_9H_{13}ClN_4 \cdot 0.5H_2SO_4$) 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 cyananide (17.9 g, 0.425 mole) in H_2O (100 ml) was heated on a steam bath for 8 hr. The product was pptd as the bicarbonate by addition of a solution of $NaHCO_3$ (9.3 g, 0.11 mole) in H_2O (*ca.* 200 ml). The solid (0.06 mole) was suspended in *n*-PrOH (100 ml) and treated with H_2SO_4 (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.* ($C_9H_{13}ClN_4 \cdot 0.5H_2SO_4$) 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_2O (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_2O, and recrystd from EtOH to give fine white needles, mp 154–155° (20.3 g, 53%). *Anal.* ($C_9H_{12}ClN_3S$) C, H, Cl, N, S.

4-Chlorophenethyl-*S*-methylisothiosemicarbazide 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*-PrO_2, the filtrate yielded a second crop, mp 170–175° (7 g, 12%). *Anal.* ($C_{10}H_{14}ClN_3S \cdot HI$) C, H, Cl, **I**, N, S.

***N*-Amino-*N*-(4-chlorophenethyl)guanidine Hydriodide.**—A suspension of 4-chlorophenethyl-*S*-methylisothiosemicarbazide·HI (29.7 g, 0.08 mole) in H_2O (250 ml) was warmed on a steam bath and treated at intervals with seven 5-ml portions of NH_3 (sp gr 0.880), after which the evolution of MeSH ceased. After removal of H_2O *in vacuo* and azeotropic drying with *i*-PrOH, the residue was recrystd twice from *n*-PrOH–*i*-Pr_2O, yielding flat white needles, mp 180–182° (18 g, 66%). *Anal.* ($C_9H_{13}ClN_3 \cdot HI$) 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_2O (100 ml) was stirred into a hot solution of Ag_2SO_4 (7.8 g, 0.025 mole) in H_2O (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_2O giving flat white needles, mp 262–264° dec. *Anal.* ($C_9H_{13}ClN_4 \cdot 0.5H_2SO_4$) 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_2O (4 l.) was added dropwise over 2.5 hr to a stirred suspension of LAH (200 g, 5.26 moles) in anhyd Et_2O (3 l.). The mixture was stirred for a further 2 hr and left overnight. H_2O (500 ml) was then added very slowly, followed by 5 *N* HCl (4). About half of the Et_2O was allowed to distil off during the acid addition. The Et_2O phase and three 150-ml Et_2O 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_2O (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_2O (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_2O phase and two 100-ml Et_2O 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_6H_6 (50 ml) was treated portionwise with $SOCl_2$ (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 cooled to about 250 ml, the residue was poured into cold 5 *N* NaOH (200 ml) and extracted with $CHCl_3$. The dried extract was distilled, yielding an oil (41.9 g, 81%), bp 132–135° (4 mm).

Guanylhydrazones. 2,6-Dichlorophenylacetaldehyde.—This was prepared by CrO_3 oxidation of 2,6-dichlorophenethanol by the method of Shumeiko[8] or by reduction of 2,6-dichlorophenylacetonitrile by the method of Van Es and Staskun,[9] low-melting solid, bp 104–108° (2 mm); semicarbazone, mp 215°. *Anal.* ($C_8H_9Cl_2N_3O$) 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,[10] or hydrolysis of the benzylmagnesium halide with triethyl orthoformate.[11]

2-Fluorophenylacetaldehyde Diethyl Acetal.[11]—2-Fluorobenzyl bromide (485.9 g, 2.57 moles) in anhyd Et_2O (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_2O (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_2O layer and two Et_2O extracts were washed with cold H_2O until neutral, dried, and distilled, giving the acetal (247.3 g, 46%), bp 112–118° (12 mm).

2,6-Dichlorophenylacetaldehyde Guanylhydrazone 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_2O 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_2O, a little EtOH, and Et_2O), and suspended in 1.8 l. of H_2O. This stirred suspension was warmed at 80° for 30 min and filtered hot to give the guanylhydrazone, mp 228–229° dec, yield 213 g (72%). *Anal.* ($C_9H_{10}Cl_2N_4 \cdot HNO_3$) H, N, O. C: calcd, 35.08; found, 35.53.

The other guanylhydrazones 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_2O. 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.* ($C_9H_{14}N_4 \cdot 2HCl$) C, H, Cl. N: calcd, 22.31; found, 22.78.

2,6-Dichlorophenethylguanidine Sulfate.—A mixture of 2,6-dichlorophenethylamine[12] (24 g, 0.125 mole), *S*-methylisothiouronium sulfate (17.7 g, 0.063 mole), 93% EtOH (50 ml), and H_2O (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_2O, then with hot EtOH, gave a fine white powder, mp 258–260°, yield 10.4 g. *Anal.* ($C_9H_{11}Cl_2N_3 \cdot 0.5H_2SO_4$) C, H, Cl, N, O, S.

Acknowledgment.—The authors wish to thank Dr. H. Lehner and his staff for the microanalyses and ir spectra.

(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*)-α-(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.

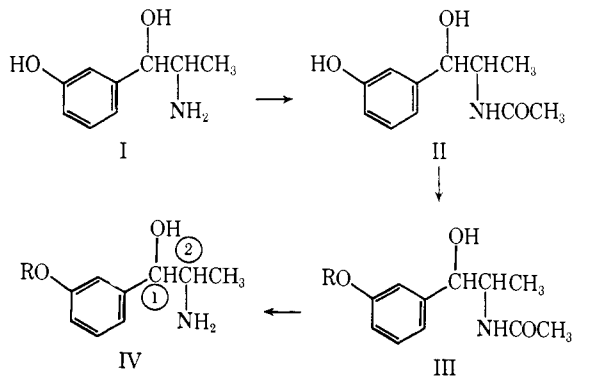
Metaraminol (I), (−)-erythro, appears to possess the attributes of a nearly ideal substitute adrenergic transmitter.[1,2] Thus metaraminol has a high intrinsic ability to enter and displace the normal transmitter norepinephrine from storage sites within the adrenergic neuron; it is released during stimulation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

Crout[2] 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 α-methyl-*m*-tyrosine, which is metabolized to metaraminol in animals,[3] has also been reported to be effective in lowering the blood pressure of hypertensive patients when administered intravenously.[4] However, the amino acid was not effective after oral administration. In addition central nervous system effects have been observed with α-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

SCHEME I



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

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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.*, **I**, 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).