mmoles) was reduced with $LiAlH_4$ (0.3 g, 8.0 mmoles) in 30 ml of tetrahydrofuran (THF) by refluxing for 24 hr. The yellow oil (quantitative yield) was converted to the **hydrochloride salt** (6 *N* HCl), mp 242° (from ethyl alcohol).

Anal. Calcd for $C_{24}H_{27}NO_2 \cdot HCl$: C, 72.6; H, 7.12; N, 3.52. Found: C, 72.5; H, 7.03; N, 3.86.

3-Ethylamino-1,1,3-triphenyl-1-propanol (17).—3-Acetamido-1,1,3-triphenyl-1-propanol (**16**, 20.0 g, 0.06 mole) was refluxed with $LiAlH_4$ (0.18 mole) in THF for 24 hr. The product was isolated by ether extraction and recrystallized from cyclohexane to yield 13.9 g (74%), mp 102°. Witting, *et al.*,[9] gave mp 104–105° for material obtained from the reaction of phenyllithium and 3-ethylimino-1-hydroxy-1,1-diphenylpropane.

3-(N-Ethylacetamido)-1,1,3-triphenyl-1-propanol (18).—Compound **17** (11.7 g, 0.037 mole) was heated for 2 hr at 50° with acetic anhydride (0.066 mole) and acetic acid (0.033 mole). The product crystallized from the hot mixture and was isolated and recrystallized from ethanol to yield 11.4 g (83%), mp 195°. An analytical sample, mp 197–198°, was obtained by further recrystallizations from ethanol.

Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.4; H, 7.29; N, 3.75. Found: C, 80.3; H, 7.31; N, 3.73.

3-(N,N-Diethylamino)-1,1,3-triphenyl-1-propanol (19).—Compound **18** (9.1 g, 0.025 mole) was refluxed overnight with $LiAlH_4$ in THF. The free base was isolated as a yellow oil in 93% yield. The **hydrochloride salt** was prepared with hot 6 *N* HCl and purified by recrystallization from dilute ethanol; mp 249° dec.

Anal. Calcd for $C_{25}H_{29}NO \cdot HCl$: C, 75.8; H, 7.64; N, 3.54. Found: C, 75.5; H, 7.87; N, 3.68.

Methyldiethyl-(3-hydroxy-1,3,3-triphenylpropyl)ammonium Chloride (20).—Base **19** (3.0 g, 8.4 mmoles), 3 ml (80 mmoles) of methyl iodide, and 10 ml of ethanol were heated for 4 hr at 100° in a steel bomb. The solution was concentrated, and the gum was triturated with isopropyl alcohol to give a solid. One recrystallization from isopropyl alcohol yielded the yellow iodide salt, 1.15 g, mp 185–187° dec. It was stirred for 3 hr with Dowex 2 (chloride) resin in 100 ml of methanol. The mixture was then filtered and concentrated, and the chloride salt was recrystallized from isopropyl alcohol–water. The analytical sample had mp 244–245.°

Anal. Calcd for $C_{26}H_{32}ClNO \cdot 0.5H_2O$: C, 74.5; H, 7.76; N, 3.34. Found: C, 74.8; H, 7.79; N, 3.28.

(9) G. W. Witting, H. J. Schmidt, and H. Renner, *Chem. Ber.*, **95**, 2377 (1962).

3-Amino-1,1-dimethyl-3-phenyl-1-propanol (21).—Ethyl 3-amino-3-phenylpropionate[3] (3.8 g, 0.02 mole) was refluxed with methylmagnesium bromide (3 *M* in ether, 27 ml, 0.08 mole) in ether overnight. The reaction was worked up and the resulting oil was stirred with 4 ml of 2.5 *N* NaOH for 1 hr and left at 25° in order to hydrolyze a small amount of starting ester. The alkaline mixture was extracted with ether, which was dried and concentrated to give 1.5 g (42%) of an oil which cystallized. This material showed no ester carbonyl in the infrared. An analytical sample, mp 75°, was prepared by recrystallization from butyl chloride.

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.7; H, 9.56; N, 7.81. Found: C, 73.6; H, 9.66; N, 7.84.

Biological.—For testing purposes, all aminopropanols were dissolved either in 0.1 *N* HCl or suspended (**6**, **16**, and **18**) by homogenizing with 0.1 *N* HCl and 2 drops of Tween 80. These solutions or suspensions were administered to male, albino mice (18–25 g) either intravenously *via* the tail vein (general behavioral screen, LD_{50}, MED_{50}) or intraperitoneally (tremor detector). The animals were periodically tested and observed in the behavioral screen at 3, 15, 30, and 60 min following injection. Two animals per dose level (0.1 log intervals) were used for LD_{50} determinations.

In the initial tremor-detector experiments carried out at 10 min postinjection and at a dosage of 25 mg/kg ip (expt 1) ten animals were used per compound and ten each for control (tremorine) and blank (0.1 *N* HCl). In expt 2 and 3 at 5, 15, and 45 min postinjection and at dosages of 25 and 15 mg/kg ip, five animals per compound for each of the time periods were used; four test compounds, tremorine, and a blank were evaluated each day for 5 days. The tremorine values at each time period are means of 50 mice. In expt 4, 15 mice per time period in a regimen of three mice per day for 5 days were used. The tremorine and blank controls were evaluated in ten mice per time period. In all experiments, a different group of animals was used for each time period to avoid acclimatization and no animal was used more than once. In expt 1–4, drug concentrations were adjusted for an injection of 0.5 ml/animal. In the antagonism studies, 0.2 ml of drug solution was administered.

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Aryloxyalkylaminoguanidines. Their Synthesis and Biological Properties[1]

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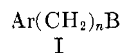
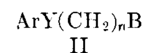
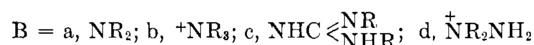
Proton magnetic resonance has been used to show that the products of guanylation of aryloxyethylhydrazines are (aryloxyethylamino)guanidines. Several such aminoguanidines containing chlorine and methyl substituents in the aromatic ring have been shown to possess adrenergic neuron blocking properties and to inhibit dopamine β-oxidase *in vitro*.

There is a striking similarity about certain features of the structure–activity patterns displayed by several series of compounds which affect the functioning of the adrenergic system. Thus, in a series of biologically







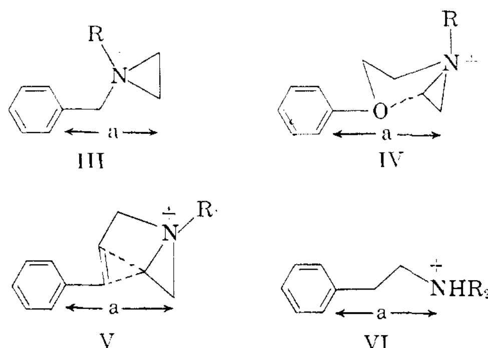
active bases of general formula I where extension of the chain by one methylene group leads to loss of activity, chain extension by introduction of a group Y (see II), where Y can represent O, S, NH, or CH=CH, frequently allows retention of activity.

(1) Presented in part before the Division of Medicinal Chemistry, 9th National Medicinal Chemistry Symposium of the American Chemical Society, Minneapolis, Minn., June 21–24, 1964. A preliminary report of some of this work has been published by J. Augstein and S. M. Green, *Nature*, **201**, 628 (1964).

(2) To whom enquiries should be addressed.

Illustration of this is found in the classical sympathomimetic effects of phenethylamine derivatives, which are virtually absent in 3-phenylpropylamine derivatives, yet found again in compounds of type IIa ($n = 2$).[3] Similarly, the well-known exercise[4] of introducing alkyl or aralkyl substituents into the amine group of Ia to produce α antagonists is effective in producing adrenolytic derivatives of phenethylamine,[5] and of the analogs IIa,[3,6] whereas the corresponding derivatives of 3-phenylpropylamine have only feeble adrenolytic properties.[7]

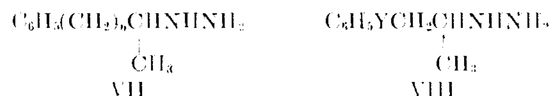
Belleau has suggested that the similarity of adrenergic blocking activity shown by N-benzyl- and N-(2-phenoxyethyl)-N-alkyl-2-haloethylamines (III and IV)[8] along with the significant activity of the N-(2-phenylpropenyl) analog V, when contrasted with the relative inactivity of the phenethyl and 3-phenylpropyl analogs,[9] can be explained by compounds IV and V folding in the manner indicated, such that the distance "a" between the aromatic ring and a positively charged



center approximates that found in the sympathomimetic amines (VI); in this way the molecule is able to "fit" the α-adrenergic receptor. Kinetic evidence was adduced in favor of this theory,[10] although it is not clear from Belleau's papers exactly what type of interaction (H bonding, dipole attraction, etc.) is represented by the dotted lines in IV and V.

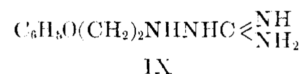
Comparison of the adrenergic neuron blocking agents of the quaternary ammonium or guanidine type reveals a similar picture. The activity which was found first for xylocholine (IIb, Y = O; $n = 2$; R = CH_3)[11] was found later in a series of benzyl quaternary ammonium compounds, *e.g.*, bretylium (Ib, $n = 1$; R = CH_3, CH_3, C_2H_5), whereas the homologous phenethyl quaternary compounds (Ib, $n = 2$) produced only weak effects.[12] More recently, the activity reported to be present in a series of benzylguanidines (Ic, $n = 1$), but not in homologous compounds (Ic, $n > 1$),[12-14] was also reported in certain compounds (see Discussion) of type IIc ($n = 2$ or 3).[15,16]

A somewhat similar structure–activity relationship has been observed for the hydrazine inhibitors of monoamine oxidase, in that the powerful *in vitro* inhibition displayed by benzylhydrazine and the phenethylhydrazine VII ($n = 1$) was considerably reduced in VII ($n = 2$),[17] yet found again in the series of compounds VIII, in which Y can represent O, S, or NH.[6]



It seemed to us that parallel behavior might be exhibited by the hydrazine inhibitors of dopamine β-oxidase. Thus, the good inhibition shown by benzylhydrazine (and O-benzylhydroxylamine) was reported to be lost on extending the chain by one carbon atom to give phenethylhydrazine and O-phenethylhydroxylamine[19] (but see later). Consequently, we tested 2-phenoxyethylhydrazine for inhibition of dopamine β-oxidase and were encouraged to find moderate activity, which was readily enhanced by *ortho* substituents (Table V).

In view of these considerations, it seemed possible that compounds derived from IX, by virtue of being isosteric with 3-phenoxypropylguanidines (IIc, Y = O, $n = 3$) might possess the interesting combination of adrenergic neuron blocking properties and the capacity of inhibiting dopamine β-oxidase.



Consequently, a series of compounds related to IX was synthesized and examined for their adrenergic neuron blocking properties, their inhibition of dopamine β-oxidase *in vitro*, and in the case of the more active compounds, for their cardiovascular effects in cats and dogs.

Chemistry.—The aminoguanidines were prepared by treatment of the appropriate aryloxyalkylhydrazine with S-methylisothiourea sulfate. This method could lead to compounds of type X (R = H) or XI, depending upon the site of guanylation. Previous reports[20]

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(4) E. J. Ariëns, A. M. Simonis, and J. M. van Rossum in "Molecular Pharmacology," Vol. I, E. J. Ariëns, Ed, Academic Press, London, 1964, p 215.

(5) E. J. Ariëns in Ciba Foundation Symposium, Adrenergic Mechanisms, J. and A. Churchill Ltd., London, 1960, pp 253, 264.

(6) J. Augstein, W. C. Austin, R. J. Boscott, S. M. Green, and C. R. Worthing, *J. Med. Chem.*, **8**, 356 (1965).

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(8) B. Belleau, *Can. J. Biochem. Physiol.*, **36**, 731 (1958).

(9) G. E. Ullyot and J. F. Kerwin in "Medicinal Chemistry," Vol. II, F. F. Blicke and C. M. Suter, Ed., John Wiley and Sons Inc., New York, N. Y., 1956, p 234.

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(14) (a) R. Fielden, A. L. Green, and G. L. Willey, *Brit. J. Pharmacol.*, **24**, 395 (1965); (b) R. Fielden and A. L. Green, *ibid.*, **24**, 408 (1965).

(15) (a) D. I. Barron, P. M. G. Bavin, G. J. Durant, I. L. Natoff, R. G. W. Spickett, and D. K. Vallance, *J. Med. Chem.*, **6**, 705 (1963); (b) D. I. Barron, I. L. Natoff, and D. K. Vallance, *Brit. J. Pharmacol.*, **25**, 534 (1965).

(16) W. E. Barrett, R. P. Mull, and A. J. Plummer, *Experientia*, **21**, 506 (1965).

(17) (a) J. H. Biel, A. E. Drukker, T. F. Mitchell, E. P. Sprengeler, P. A. Nuhfer, A. C. Conway, and A. Horita, *J. Am. Chem. Soc.*, **81**, 2805 (1959); (b) J. H. Biel, P. A. Huhfer, and A. C. Conway, *Ann. N. Y. Acad. Sci.*, **80**, 568 (1959).

(18) D. J. Drain, J. G. B. Howes, R. Lazare, A. M. Salaman, R. Shadbolt, and H. W. R. Williams, *J. Med. Chem.*, **6**, 63 (1963).

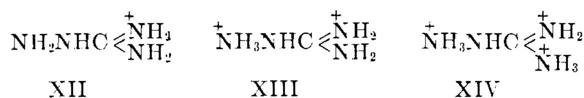
(19) (a) C. R. Creveling, J. B. van der Schoot, and S. Udenfriend, *Biochem. Biophys. Res. Commun.*, **8**, 215 (1962); (b) J. B. van der Schoot and C. R. Creveling, *Advan. Drug Res.*, **2**, 47 (1965).

(20) (a) J. E. Robertson, J. H. Biel, and F. DiPierro, *J. Med. Chem.*, **6**, 381 (1963); (b) E. G. Podrebarac, W. H. Nyberg, F. A. French, and C. C. Cheng, *ibid.*, **6**, 283 (1963); (c) J. H. Short, U. Biermacher, D. A. Dunnigan, and T. D. Leth, *ibid.*, **6**, 275 (1963); (d) C. Cipens and V. Grinsteins, *Zh. Obshch. Khim.*, **32**, 3811 (1962); *J. Gen. Chem. USSR*, **32**, 3739 (1962); (e) A. H. Greer and G. B. L. Smith, *J. Am. Chem. Soc.*, **72**, 874 (1950).

of the guanylation of hydrazine led us to expect products of type XI. In fact, we found that the products (listed in Table I) of our reactions were of type X, the assignment of structure being based on the nmr criteria discussed below.

By contrast, the only product isolated from a similar guanylation of benzylhydrazine was of type XI (**30**, Table II), while only mixtures could be isolated from guanylation of phenethylhydrazine.

Three compounds of type XI were prepared by the unambiguous method described recently,[21] and comparison of the nmr spectra with those of the products from the equivocal guanylation of the corresponding hydrazines provided a convenient method for distinguishing the isomers.



Aminoguanidine is a strong monoacidic base[22] (monocation XII); in strongly acid solution it forms diacid salts[23] (dication XIII). We determined the first pK_a of aminoguanidine itself as 11.97 ± 0.1 (25°) by potentiometric titration; the substituted compounds are not sufficiently soluble to reach the high concentration required for potentiometric measurement of bases of such high pK_a,[24] but they would be expected to lie in the same range. We measured the second pK_a of (benzylamino)guanidine as −3.2 ± 0.1 on the H_0 scale by the nmr method (see Experimental Section). Insufficient solubility precluded measurement of the (β-aryloxyethylamino)guanidines, but these compounds would be expected to have a second pK_a rather similar to that of the benzyl analog [*cf.* pK_a of $PhOCH_2CH_2NH_2$ and $PhCH_2NH_2$ = 9.36 ± 0.05 (20°) and 9.29,[25] respectively]. The addition of a third proton to an aminoguanidine, to produce a cation of type XIV, would require very high acidities. Guanidine has a first pK_a of 13.6 (which is changed but little on alkylation,[26] contrary to earlier conclusions) and a second pK_a at H_0 = −10.9.[27] The third pK_a of aminoguanidine would be expected to be at least several units more negative than −10.9.

We therefore reasoned that the mono- and diprotonated forms of aminoguanidines should be accessible to measurement in trifluoroacetic acid and 90% aqueous sulfuric acid, respectively. The H_0 of 90% sulfuric acid is −8.92.[28] The H_0 values of trifluoroacetic acid have been studied by Randles and Tedder;[29] our measurements were made on solutions containing some 10% by weight of salt, and from their curve this would appear to correspond to an H_0 value of *ca.* −2. We made some measurements in tetrafluorodichloroacetone deuteriohydrate (FClA), the H_0 value of which we determined as 0.05. The near correspondence of results for the last two solvents indicated that large quantities of diprotonated forms did not exist in the trifluoroacetic acid solutions. This was confirmed by examination of the nmr spectra of four of the compounds in trifluoroacetic acid containing 10% w/w of water (Table III). The methylene protons in all four compounds showed only a slight upfield shift relative to their chemical shifts in the anhydrous acid, and in the case of **13** and **17** the shifts were now close to those found in FClA. Thus, we recommend that in future applications of this method, FClA or trifluoroacetic acid containing 10% w/w water be used as solvent.

Results of other nmr measurements are shown in Table IV. The signals listed were assigned to the CH_2N protons by comparison with the signals of the adjacent methylene groups. Of the compounds of known structure, the first three are simple guanidines which should exist in the monoprotonated form in both media; in agreement, the chemical shifts found are almost identical in trifluoroacetic acid and 90% sulfuric acid. The next four compounds of known structure are of type XI. Here the effect of protonation of the amino group on the CH_2 adjacent to nitrogen (Δ = 0.19 − 0.36 ppm) is significantly less than the corresponding effect for the four compounds of structure X (Δ = 0.61 − 1.04 ppm). This is as expected, for in compounds of type X the nitrogen adjacent to the methylene group is undergoing protonation, whereas in compounds of type XI, the second protonation is occurring at one atom further removed.

Twenty-two alkylaminoguanidines of ambiguous structure were also measured (Table IV). Application of the above criteria allows the indicated assignment of structure to type X or XI. For **11–13**, although they were prepared by the ambiguous method, structure X is the only reasonable assignment since they were different on melting point and infrared criteria from the isomeric compounds **26–28** of defined structure type XI. Insufficient quantities of **6**, **10**, **16**, and **21** remained to allow nmr measurements; their structures were assumed to be of type X, by analogy with the other products of this ambiguous reaction, and by application of a colorimetric spot test.[30]

The application of this method to a single isomer pair has already been reported[21] along with the supporting chemical evidence.

Biological Results.—Compounds were examined for their adrenergic neuron blocking potency by administering them subcutaneously at two dose levels to conscious cats, and observing the relaxation of the nictitating membrane after 20 hr[31] (Tables I and II).

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

(22) C. Hahn, E. Pribyl, E. Lieber, B. P. Caldwell, and G. B. L. Smith, *J. Am. Chem. Soc.*, **66**, 1223 (1944).

(23) J. J. Pitha, H. Hughes, Jr., and G. B. L. Smith, *ibid.*, **70**, 2823 (1948).

(24) A. Albert and E. P. Serjeant, "Ionisation Constants of Acids and Bases," Methuen and Co. Ltd., London, 1962, Chapter 4.

(25) H. K. Hall, Jr., *J Am. Chem. Soc.*, **79**, 5439 (1957).

(26) S. J. Angyal and W. K. Warburton, *J. Chem. Soc.*, 2492 (1951).

(27) G. Williams and M. L. Hardy, *ibid.*, 2560 (1953).

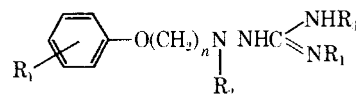
(28) M. J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.*, **85**, 878 (1963).

(29) J. E. B. Randles and J. M. Tedder, *J. Chem. Soc.*, 1218 (1955).

(30) It was found quite empirically that aminoguanidines (19 examples) known to be of type X (and also compounds **6**, **10**, and **16**) when applied (*ca.* 0.1 mg in 1 μl of MeOH) to a thin layer of silica, and sprayed with *p*-dimethylaminocinnamaldehyde reagent (a solution prepared by dissolving 1 g of reagent in 25 ml of concentrated HCl and diluting to 100 ml with MeOH) gave an immediate pink coloration. Aminoguanidines of type XI (**26–28**, **30**, **32**) gave no response to this reagent. The iodide ion in compounds **21–25** gave a brown coloration which made the test inapplicable.

(31) It is realized that activity in the nictitating membrane test is not always paralleled in other tests for adrenergic neuron blockade (see ref 14a).

TABLE I: ARYLOXYALKYLAMINOGUANIDINES



No.	% inhib of dopamine β-oxidase at 5 × 10⁻⁴ equiv/l.[a]	Effect on nm[b] 5 mg/kg	Effect on nm[b] 20 mg/kg	R_1	R_2	R_3	R_4	n	Mp, °C	Recrystn solvent[c]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	23	0	0	H	H	H	H	2	197–200	W	$C_9H_{14}N_4O\cdot 0.5H_2SO_4$	44.44	6.22	23.04	44.38	6.22	22.82
2	45	0	+	H	H	H	H	3	193–197	W	$C_{10}H_{16}N_4O\cdot 0.5H_2SO_4$	46.68	6.66	21.78	46.78	6.55	21.54
3	4	+	++	2-CH_3O	H	H	H	2	142–146	E	$C_{10}H_{16}N_4O_2\cdot 0.5H_2SO_4$	43.95	6.27	20.50	43.97	6.33	20.28
4	13	0	+	3-CH_3O	H	H	H	2	197–200	W	$C_{10}H_{16}N_4O_2\cdot 0.5H_2SO_4$	43.95	6.27	20.50	43.98	6.26	20.70
5	0	0	0	4-CH_3O	H	H	H	2	178–185	W	$C_{10}H_{16}N_4O_2\cdot 0.5H_2SO_4$	43.95	6.27	...	43.89	6.36	...
6	0	0	0	2-CH_3O	H	H	H	3	168–170	W	$C_{11}H_{18}N_4O_2\cdot 0.5H_2SO_4$	45.97	6.67	20.43	45.94	6.47	20.15
7	0	0	+	2-CH_3O	H	H	H	4	139–141	W	$C_{12}H_{20}N_4O_2\cdot 0.5H_2SO_4$	47.83	7.03	18.60	47.64	7.17	18.47
8	15	0	0	2-CH_3	H	H	H	2	193–195	W	$C_{10}H_{16}H_4O\cdot 0.5H_2SO_4$	46.68	6.65	21.87	46.63	6.65	22.18
9	52	0	0	2-Cl	H	H	H	2	192–194	W	$C_9H_{13}ClN_4O\cdot 0.5H_2SO_4$	38.92	5.08	20.18	38.76	4.83	20.05
10	37			2,3-Cl_2	H	H	H	2	198–199	W	$C_9H_{12}Cl_2N_4O\cdot 0.5H_2SO_4$	34.62	4.20		34.57	4.04	
11	79	0	++	2,4-Cl_2	H	H	H	2	222–224	M–W	$C_9H_{12}Cl_2N_4O\cdot 0.5H_2SO_4$	34.62	4.20	17.95	34.43	4.09	17.62
12	71	++	+++	2,5-Cl_2	H	H	H	2	187–188	M	$C_9H_{12}Cl_2N_4O\cdot 0.5H_2SO_4$	34.62	4.20	17.95	34.68	4.12	17.70
13	70	++	+++	2,6-Cl_2	H	H	H	2	210–214	W	$C_9H_{12}Cl_2N_4O\cdot 0.5H_2SO_4$	34.62	4.20	17.95	34.60	4.20	17.69
14	0	0	+	3,4-Cl_2	H	H	H	2	195–196	E–W	$C_9H_{12}Cl_2N_4O\cdot 0.5H_2SO_4$	34.62	4.20	17.95	34.32	4.21	17.95
15	25	0	+++	2,3-$(CH_3)_2$	H	H	H	2	212–214	W	$C_{11}H_{18}N_4O\cdot 0.5H_2SO_4$	48.70	7.06	20.65	48.53	6.92	20.70
16	7	0	0	3,5-$(CH_3)_2$	H	H	H	2	208–210	A	$C_{11}H_{18}N_4O\cdot 0.5H_2SO_4$	48.70	7.06	20.65	48.72	7.18	20.37
17	8	++	+++	2,6-$(CH_3)_2$	H	H	H	2	214–216	E–W	$C_{11}H_{18}N_4O\cdot 0.5H_2SO_4$	48.70	7.06	20.65	48.63	7.18	20.94
18	0	+	+	2,6-$(CH_3)_2$	H	H	H	3	182–184	W	$C_{12}H_{20}N_4O\cdot 0.5H_2SO_4$	50.51	7.42	19.64	50.30	7.45	19.40
19	0	++	+++[d]	2,6-$(CH_3)_2$	CH_3	H	H	2	222–224	W	$C_{12}H_{20}N_4O\cdot 0.5H_2SO_4$	50.51	7.42	19.64	50.75	7.49	19.55
20	0	0	0	2,6-$(CH_3)_2$	H	CH_3	H	2	167–168	E–Et	$C_{12}H_{20}N_4O\cdot C_{20}H_{18}O_8$[e]	61.72	6.15	9.00	61.56	6.19	8.84
21	0	0	0	2,6-$(CH_3)_2$	H	CH_3	CH_3	2	133–137	W	$C_{13}H_{22}N_4O\cdot HI$	41.27	6.13	14.81	41.30	6.25	14.52
22	9	+	+	2,6-$(CH_3)_2$	H	NH_2	H	2	157–159	E	$C_{11}H_{19}N_5O\cdot HI$	36.17	5.52	19.18	35.88	5.58	19.34
23	94	+	+	2,6-$(CH_3)_2$	H	NH_2	NH_2	2	144–146	W	$C_{11}H_{20}N_6O\cdot HI$	34.74	5.57	22.11	34.68	5.54	22.32
24	0	0	0	2-CH_3O	H	CH_3	H	2	150–152	E	$C_{11}H_{18}N_4O_2\cdot HI$	36.08	5.23	15.30	36.39	5.27	15.38
25	0	0	+	2-CH_3O	H	CH_3	CH_3	2	142–143	W	$C_{12}H_{20}N_4O_2\cdot HI$	37.90	5.57	14.73	38.17	5.49	15.02

[a] See Experimental Section for details of procedure. For comparison with standard substances under these conditions see Table V. [b] nm = nictitating membrane; percentage of eye covered: 0 (<15%), + (15–30%), ++ (30–50%), +++ (>50%). On this scale guanethidine was rated ++ (5 mg/kg) and ++ (20 mg/kg). [c] A = acetic acid, E = ethanol, Et = ether, I = 2-propanol, M = methanol, W = water. [d] Activity of short duration only. [e] Di-p-toluoyl tartrate.

TABLE II: MISCELLANEOUS GUANIDINES AND AMINOGUANIDINES

No.	% inhib of dopamine β-oxidase at 5 × 10⁻⁴ equiv/l.[a]	Effect on nm[b] 5 mg/kg	Effect on nm[b] 20 mg/kg	Compd	Mp, °C	Recrystn solvent[c]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
26	52	0	0	1-Amino-1-[2-(2,4-dichlorophenoxy)ethyl]guanidine[e]	252–255	M	$C_9H_{12}Cl_2N_4O\cdot 0.5H_2SO_4$	34.62	4.20	17.95	34.71	4.44	17.98
27	56	0	0	1-Amino-1-[2-(2,5-dichlorophenoxy)ethyl]guanidine[e]	251–252	M–W	$C_9H_{12}Cl_2N_4O\cdot 0.5H_2SO_4$	34.62	4.20	17.95	34.51	4.13	17.76

28	14	+	+++[d]	1-Amino-1-[2-(2,6-dichlorophenoxy)ethyl]guanidine[f]	215	M							
29	16	0	+	Benzylaminoguanidine[g]	203–205	E–W	$C_8H_{12}N_4 \cdot C_7H_8O_3S$[h]	53.58	5.99	16.66	53.61	5.89	16.75
30	14	0	0	1-Amino-1-benzylguanidine[i]	270 dec	E–W	$C_8H_{12}N_4 \cdot 0.5H_2SO_4$	45.07	6.14	26.28	45.01	6.09	26.56
31	77	0	+	Phenethylaminoguanidine[j]	190–192	M	$C_9H_{14}N_4 \cdot C_7H_8O_3S$[h]	54.84	6.33	15.99	54.92	6.26	15.84
32	16	0	0	1-Amino-1-phenethylguanidine[e]	226–228	W	$C_9H_{14}N_4 \cdot C_7H_8O_3S$[h]	54.84	6.33	15.99	55.18	6.34	15.73
33	86	0	+	3-(2,6-Dichlorophenyl)propylaminoguanidine[k]	183–185	W	$C_{10}H_{14}Cl_2N_4 \cdot 0.5H_2SO_4 \cdot H_2O$	36.58	5.22	17.07	36.69	5.20	17.09
34		0	+	Phenethylguanidine[l]	176–178								
35		0	0	2,6-Dichlorophenethylguanidine[m]	164–166	M–W	$C_9H_{11}Cl_2N_3 \cdot C_7H_8O_3S$[h]	47.53	4.74	10.40	47.82	4.77	10.16
36a		+++	+++	2-(2,6-Dichlorophenoxy)ethylguanidine[n]	195–197	I							
37		0	++[d]	1-[2-(2,6-Dichlorophenoxy)ethyl]-1-methylguanidine[o]	283–285[p]	I–W	$C_{10}H_{13}Cl_2N_3O \cdot 0.5H_2SO_4$	38.59	4.53	13.51	38.31	4.31	13.60
38	21	+	+	2-(1,4-Benzodioxanyl)methylaminoguanidine[q]	195–200	W	$C_{10}H_{14}N_4O_2 \cdot 0.5H_2SO_4$	44.27	5.57	20.65	44.08	5.47	20.30

[a–d] See Table I. [e] Prepared by the method used for **28** in ref 21. [f] See ref 21. [g] Prepared by the method of W. G. Finnegan, R. A. Henry, and G. B. L. Smith [*J. Am. Chem. Soc.*, **74**, 2981 (1952)] who characterized the compound as the hydrochloride. [h] *p*-Toluenesulfonate. [i] Prepared by guanylation of benzylhydrazine with S-methylisothiourea sulfate. [j] Prepared *via* the method of *g* by hydrogenation of phenethylideneaminoguanidine hemisulfate, mp 203–204° (from 2-propanol–water). *Anal.* Calcd for $C_9H_{12}N_4 \cdot 0.5H_2SO_4$: C, 47.78; H, 6.24, N, 24.77. Found: C, 48.01; H, 6.31; N, 24.94. [k] Prepared by guanylation of 3-(2,6-dichlorophenyl)propylhydrazine (see Experimental Section) with S-methylisothiourea sulfate. [l] C. E. Braun, *J. Am. Chem. Soc.*, **55**, 1280 (1933), and ref 14. [m] Prepared from 2-(2,6-dichlorophenyl)ethylamine (see Experimental Section) and S-methylisothiourea sulfate. [n] See ref 39. [o] Prepared from N-methyl-2-(2,6-dichlorophenoxy)ethylamine, bp 92–94° (0.4 mm), $n^{25}D$ 1.5376 [P. Hey and G. W. Willey, *Nature*, **198**, 390 (1963), examined the anesthetic properties of this compound]; the amine was prepared by heating 2-(2,6-dichlorophenoxy)ethyl bromide with excess ethanolic methylamine. [p] Transition point 244–248°. [q] Prepared from 2-hydrazinomethyl-1,4-benzodioxane [G. B. Marini-Bettolo, R. Landi-Vittory, M. A. Jorio, F. Bovet-Nitti, and O. Orsingher, *Rend. Ist. Super Sanita*, **23**, 1110 (1960)] and S-methylisothiourea sulfate.

TABLE III

CHEMICAL SHIFTS (τ) OF ARYLOXYALKYLAMINOGUANIDINES IN CF_3CO_2H-H_2O (90:10)

No.[a]	CCH_2N
1	6.74
8	6.71
13	6.73
17	6.74

[a] See Table I.

TABLE IV

CHEMICAL SHIFTS (τ) OF ARYLOXYALKYL AND ARALKYL COMPOUNDS IN SEVERAL SOLVENTS

		CCH_2N			
Type	No.[a]	90% H_2SO_4	CF_3CO_2H	FClA[b]	Δ[c]
Known Structures					
IIc	36a	6.23	6.17	. . .	0.06
IIc	36b[d]	6.20	6.20	. . .	0.00
Ic	34	6.52	6.56	. . .	0.04
XI	32	~5.85	6.21	. . .	0.36
XI	26	~5.50	5.70	. . .	0.20
XI	27	5.52	5.71	. . .	0.19
XI	28	5.50	5.75	5.93	0.25
X	29	5.20	5.81	. . .	0.61
X	31	~6.0	6.62	. . .	0.62
X	17	5.70	6.54	6.72	0.84
X	19	5.64	6.68	6.89	1.04
Unknown Structures					
Assignment					
XI	30	4.90	5.20	5.30	0.30
X	1	5.57	6.60	. . .	1.03
X	2	5.92	6.65	. . .	0.73
X	3	~5.8	6.60	. . .	0.80
X	4	~5.45	6.60	. . .	1.15
X	5	~5.5	6.57	. . .	1.07
X	7	~5.8	6.55	. . .	0.75
X	8	5.70	6.59	. . .	0.89
X	9	~5.65	6.61	. . .	0.96
X	11	5.70	6.70	6.70	1.00
X	12	5.67	6.58	. . .	0.91
X	13	5.75	6.54	6.67	0.79
X	14	~5.79	6.58	. . .	0.79
X	15	5.70	6.60	. . .	0.90
X	18	~5.83	6.56	. . .	0.73
X	20	~5.73	6.54	. . .	0.81
X	22	~5.8	6.40	. . .	0.60
X	23	~5.8	6.41	. . .	0.61
X	24	~5.7	6.45	. . .	0.75
X	25	~5.7	6.45	. . .	0.75
X	33	~6.25	6.82	. . .	0.57
X	38	~5.90	6.83	. . .	0.93

[a] See Table I and II. [b] Tetrafluorodichloroacetone deuteriohydrate. [c] Difference in chemical shifts in 90% H_2SO_4 and CF_3CO_2H. [d] IIc (Ar = 2,6-xylyl, Y = O, n = 2, R = H).[15a]

A prerequisite for appreciable activity in compounds of type X was a two-carbon side chain and an *ortho* substituent (*cf.* **3–7**, **14**, **16**, and **18**). However, compounds containing only an *o*-chlorine or -methyl group were inactive (**8** and **9**) although good activity was observed for the 2,5- and 2,6-dichloro (**12** and **13**) and 2,3- and 2,6-dimethyl derivatives (**15** and **17**).

The introduction of additional amino or methyl groups into the aminoguanidine always reduced activity, except in the case of **19**.

The aminoguanidine **38**, related to guanoxan, displayed only marginal activity, despite the fact that the 2-guanidinoethyl homolog was equiactive with guan-

oxan,[32] thus indicating that the extra nitrogen is not acting as a simple "spacer" in this series.

Compounds of type XI were generally less active in causing adrenergic neuron blockade.

The structure-activity relationship for inhibition of dopamine β-oxidase by compounds of type X showed a somewhat different pattern. Some inhibition was displayed in the unsubstituted compounds **1** and **2**, but this was lost upon substitution by methyl or methoxyl (**3**–**8**). However, substitution by chlorine atoms in any position potentiated the inhibition considerably, resulting in compounds (**9**–**13**) more potent than O-benzylhydroxylamine.

This potentiation by chlorine substitution was also found in the few hydrazines which were tested (Table V). We found that the inhibitory properties of benzylhydrazine were not as powerful as claimed,[19a] and moreover that there was little diminution of inhibitory power on extending the carbon chain to two or three atoms. It can be seen that the introduction of two *o*-chlorine atoms into either 3-phenylpropylhydrazine or 2-phenoxyethylhydrazine led to a considerable enhancement of activity. It is interesting to note that this enhancement of activity on introduction of chlorine substituents was not observed in the O-benzylhydroxyamine series.[19b]

TABLE V

INHIBITION OF DOPAMINE β-OXIDASE BY HYDRAZINES

Compd	% inhib at 5×10^{-4} equiv/l.[a]
$C_6H_5CH_2ONH_2$	61
$C_6H_5CH_2NHNH_2$	46
$C_6H_5(CH_2)_2NHNH_2$	41
$C_6H_5(CH_2)_3NHNH_2$	47
$2,6\text{-}Cl_2C_6H_3(CH_2)_3NHNH_2$	69
$C_6H_5O(CH_2)_2NHNH_2$	32
$2,6\text{-}Cl_2C_6H_3O(CH_2)_2NHNH_2$	82

[a] See Experimental Section for details of procedure.

Compounds of type XI displayed a decrease in inhibitory powers when compared with their corresponding isomers X, this being most marked in the 2,6-dichloro derivative **28**. Notable is the powerful inhibition exhibited by **23**. Compound **38**, the amino homolog of guanoxan,[34] showed an inhibition comparable with that of 2-phenoxyethylaminoguanidine (**1**).

Compounds **12**, **13**, and **17** were examined further for their cardiovascular effects in cats and dogs. Experiments with the cross-perfused cat spleen indicated that the adrenergic neuron blocking properties of these compounds were due to inhibition of the release of the transmitter upon nerve stimulation. There was also an increase in the output of norepinephrine in the resting state, indicative of an ability to deplete tissue stores of catecholamines (see below).

Compounds **13** and **17** (5 mg/kg iv) potentiated the effects of norepinephrine and antagonized the pressor effects of tyramine in anesthetized cats and dogs. They produced little effect on the blood pressure of anesthetized cats, but raised that of dogs (5 mg/kg iv). Compound **12**, although somewhat similar, differed in that it potentiated the effects of tyramine and produced in anesthetized dogs sustained falls of blood pressure, preceded by a short pressor response.

(32) J. Augstein, S. M. Green, A. M. Monro, G. W. H. Potter, C. R. Worthing, and T. I. Wrigley, *J. Med. Chem.*, **8**, 446 (1965).

In conscious dogs with either neurogenic or nephrogenic hypertension, chronic oral administration of **12** (10 mg/kg) produced, after a latent period of 2–4 days, a fall in blood pressure of 30 mm, which persisted for 5–6 days after cessation of treatment. Compound **13** (20 mg/kg) led to slight and unreliable depression of the blood pressure; **17** (10 mg/kg) was slightly more effective in lowering the blood pressure. Compounds **13** and **17** caused some diarrhea and occasional vomiting, but these effects were absent with **12**.

The compounds were investigated for their ability to deplete tissue stores of catecholamines. Compounds **12** and **13** had little effect on levels in the brain, heart, spleen, and adrenals of the rat, even on chronic administration (20 mg/kg ip for 20 days). However, the corresponding tissues in the dog were considerably depleted by **13** after chronic oral administration (40 mg/kg for 6 weeks), although results were variable. Compound **17** caused a far more striking depletion in both the rat and the dog.

Compound **13** was also tested for inhibition of tyrosine hydroxylase obtained from beef caudate nucleus[33] and found to have no inhibitory powers at 10^{-5} equiv/l.

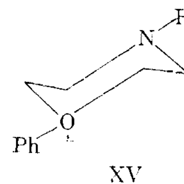
Finally, **13** was tested for inhibition of the synthesis of norepinephrine from ^{14}C-tyrosine in isolated guinea pig atria.[33] When administered (50 mg/kg ip) 0.5 hr before removal of the organ, almost complete inhibition was obtained. The rate of synthesis returned to normal within 6 hr. In animals treated with a single dose of **13**, only a slight depletion of endogenous norepinephrine was found 2 hr after administration, commensurate with a temporary loss of synthetic ability. Repeated administration of **13** caused a more profound depletion. This was taken as evidence that the compound was acting by enzyme inhibition and not by interfering with the entry of newly formed amine into storage sites.

The results of treatment of hypertensive patients with **13** have already been reported.[34]

Discussion

In dissussing our results, we have taken as the starting point Belleau's hypothesis of the conformational requirements for adrenergic blockade in the β-haloalkylamine series and adapted these ideas to the interpretation of the structure–activity relationships which exist among the adrenergic neuron blocking agents reported in this paper.

Belleau, in his interpretations of the adrenergic blocking properties of N-phenoxyethyl-β-haloalkylamines, depicted their conformation as IV, the dotted line being taken originally to imply a contribution from the canonical form XV.[8] The pK_a of anisole (-6.51[35])



XV

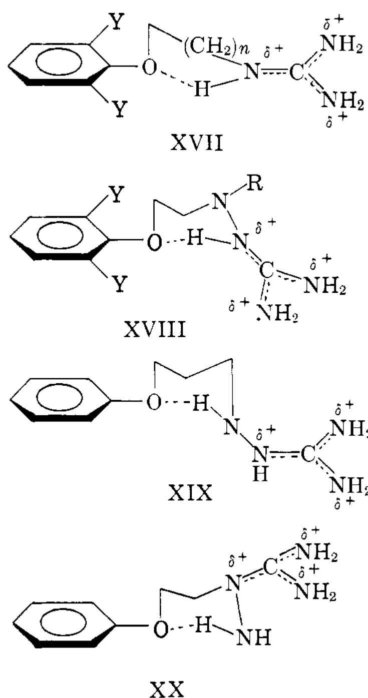
(33) S. P. Bagchi and P. L. McGeer, *Life Sci.*, **3**, 1195 (1964).

(34) T. D. V. Lawrie, A. R. Lorimer, S. G. McAlpine, and H. Reinert, *Brit. Med. J.*, **1**, 402 (1964).

(35) E. M. Arnett, C. Y. Wu, J. N. Anderson, and R. D. Bushick, *J. Am. Chem. Soc.*, **84**, 1674 (1962).

makes such a contribution appear unlikely. In a later paper,[10] the interaction was suggested to be electrostatic or to involve hydrogen bonding. Although the hydrogen atoms of the aziridinium ion would be somewhat acidic, and there is considerable evidence for the participation of acidic C–H groups in hydrogen bonding,[36,37] such bonding would be weak, and in aqueous solution any such effects would be slight due to the superior ability of water to act both as proton donor and acceptor. However, if one accepts the current concept that the immediate environment of a receptor site is largely nonpolar in nature[38] then hydrogen bonding of this type may play some part in controlling the conformation of the drug in the vicinity of the receptor.

The idea of an intramolecular hydrogen bond as suggested by Belleau for the aziridinium ions can be applied more readily to aryloxyalkylguanidines and aminoguanidines. Not only do N–H donor systems form stronger hydrogen bonds than do C–H systems, but, when the base is protonated (as are all those in question at physiological pH), then the donor properties of the N–H group are enhanced through the increased acidity of the proton.[36b] If it is assumed that in conformations XVII and XVIII the guanidino group is brought to the distance from the aromatic center required for effective adrenergic neuron blockade, then a possible explanation is available for the inactivity of ω-aralkylguanidines, for those compounds have no electron-rich group adjacent to the ring with which the guanidino group can form hydrogen bonds. If this concept has any validity, then methylation of N_I in XVII (Y = Cl) (**36a**)[39] should greatly diminish hydrogen bonding and so lead to loss of activity. The required homolog (**37**) was synthesized and found to have only marginal activity.



In 2-phenoxyethylaminoguanidines, the same distance between the aromatic ring and the guanidino group would be attained *via* conformation XVIII, utilizing the N–H of the guanidino group for hydrogen bonding. Support for this supposition comes from the activity of **19** (XVIII, Y = R = CH_3), the N-methyl homolog of **17**, in which methylation would not interfere with hydrogen bonding.

By following this line of argument one might expect that 3-phenoxypropylaminoguanidines of type XIX and 1-amino-2-phenoxyethylguanidines of type XX might show activity by virtue of being able to form hydrogen-bonded six-membered rings. However, the N–H group involved in each case is not part of the guanidino group, and not being protonated at physiological pH, will have a greatly reduced acidity and tendency to form hydrogen bonds. Furthermore, bonding of this sort would mean that the basic center of the guanidino group would be approximately one interatomic distance further removed from the aromatic ring. Thus, one might reasonably expect to find reduced activity with such compounds. This, in fact, was observed for the three pairs of isomeric aminoguanidines (*cf.* **11**, **12**, **13**, and **26**, **27**, **28**, respectively), while **18**, a 3-phenoxypropylaminoguanidine corresponding to an active 2-phenoxyethylaminoguanidine (**17**), was also found to have only slight activity. The lack of activity in **29**–**33** is explained by the absence of a suitable group adjacent to the aromatic ring with which the guanidino group can form a hydrogen bond.

Apart from the correlations described in the introduction, another striking similarity becomes apparent when one compares the structure–activity relationships of the compounds X discussed in this paper, with those of the 2-phenoxyethylguanidines (IIc, Y = O, n = 2)[15] and with those of the 2-phenoxyethylammonium and hydrazinium compounds (IIb and d, Y = O, n = 2). The series IIc and X both require two *ortho* groups in the aromatic ring for optimum activity; in series IIb the 2,4- and 2,5-dimethyl analogs are inactive as adrenergic neuron blocking agents,[40] in contrast to the well-known blocking activity of xylocholine (IIb, Ar = 2,6-xylyl; Y = O; n = 2);[11] the few hydrazinium compounds (IId) reported to be active, contain a 2,6-disubstituted aromatic ring.[12] The *ortho* groups in these examples may be methyl or chlorine [*e.g.*, in X (this paper), IIb,[41] IIc,[12,15] and IId[12]], but the introduction of larger alkyl groups (*e.g.*, in IIb[42] and IIc[15]) leads to reduced activity.

Another illustration of the significance of *ortho* groups to adrenergic neuron blockade is the fact that although 3-phenoxypropylguanidine is a powerful depleting agent with no adrenergic neuron blocking properties,[43] introduction of 2,6-dichloro[44] or dimethyl[15a]

(36) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco Calif., 1960: (a) p 197; (b) p 91; (c) p 90; (d) p 226; (e) p 202.

(37) R. West and C. S. Kraihanzel, *J. Am. Chem. Soc.*, **83**, 765 (1961); J. C. D. Brand, G. Eglinton, and J. F. Morman, *J. Chem. Soc.*, 2526 (1960).

(38) B. Belleau, *J. Med. Chem.*, **7**, 776 (1964).

(39) Burroughs Wellcome and Co., U. S. Patent 3,099,599 (July 30, 1963); *Chem. Abstr.*, **60**, 2824 (1964).

(40) R. Fielden, unpublished work, cited by R. Fielden, A. M. Roe, and G. L. Willey, *Brit. J. Pharmacol.*, **23**, 486 (1964).

(41) R. A. McLean, R. J. Geus, R. J. Mohrbacher, P. A. Mattis, and G. E. Ullyot, *J. Pharmacol. Exptl. Therap.*, **129**, 11 (1960).

(42) A. F. Green and A. L. A. Boura, unpublished work, cited in ref 12.

(43) G. Chen, C. R. Ensor, D. A. McCarthy, J. R. McClean, and A. Campbell, *J. Pharmacol. Exptl. Therap.*, **143**, 374 (1964); (b) A. L. Bartlet, *Brit. J. Pharmacol.*, **18**, 475 (1962).

(44) Parke, Davis and Co., French Patent 1788 M (March 26, 1962); *Chem. Abstr.*, **60**, 458 (1964).

substituents leads to compounds which cause adrenergic neuron blockade.

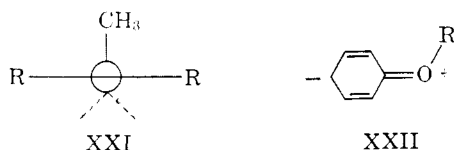
Speculating on the function of these *ortho* groups, we measured the ultraviolet spectra of several of our compounds (Table VI).[45] The 2,6-disubstituted compounds **13**, **17**, and **28** absorbed at shorter wavelengths and markedly lower intensities than isomeric disubstituted derivatives. Similar data have been reported for substituted anisoles,[46] the hypochromic effects of two *ortho* substituents being attributed to steric inhibition of resonance. The conformations of anisoles have been discussed in terms of sp^3-hybridized oxygen atoms,[47] and it was concluded that conformation XXI, with the methyl group twisted well out of the plane of the aromatic ring, was favored for *ortho*-disubstituted anisoles (in the diagram the horizontal line represents the section of the benzene ring and dotted lines indicate lone electron pairs). Similar conclusions were reached by means of Kerr constant and dipole moment studies[48] on *ortho*-substituted anisoles. It has been pointed out

TABLE VI

ULTRAVIOLET SPECTRA OF 2-ARYLOXYALKYLAMINOGUANIDINES[45]

No.[a]	λ_{max}, mμ	ε
10	277	1720
11	285	2130
12	280	2480
13	272	430
15	271	1140
16	273	1220
17	264	310
26	283	1990
27	279	2190
28	271	350
1	270	1730
2	271	1510
8	271	1900
9	274	1930

[a] See Table I.



that the strain in such compounds can also be relieved by bond bending,[49] although no attempt was made to assess this effect in the compounds in this paper. In general, it seems reasonable to assume that the presence of two *ortho* substituents in aryloxyalkyl derivatives leads to a considerable displacement of the α-carbon atom from the plane of the aromatic ring.

A corollary to this steric inhibition of resonance is that in the compounds in question the oxygen atom will be more basic in character, for the partial positive charge which occurs in the oxygen atom in the absence of *ortho* substituents (by contribution from canonical forms such as XXII) will obviously not arise when resonance is inhibited. Increased basicity in hydrogen bond acceptors leads to stronger hydrogen bonds,[36a] a pertinent reference in this context being the report[50] of the increase in energy of the O H···O bond between phenols and various ethers in the series PhOPh < PhOEt < Et_2O. Further evidence[51] for increased basicity in the *ortho*-disubstituted derivatives is available from nmr studies in strong acid which indicate that, whereas 2,3- and 3,5-dimethylanisoles were protonated in the 4 position, 2,6-dimethylanisole was protonated on the oxygen atom.

An increase in the hydrogen bond acceptor properties of the oxygen atom would obviously facilitate interactions of the type postulated for XVII–XX, although the significance of such interactions in aqueous solution and at the site of action must be subject to the same considerations as applied earlier to the phenoxyethylaziridinium ions.

An additional consideration is that the electron density at the oxygen atom may critically affect the interaction of the aromatic portion of the drug molecule with its binding site. Although in the case of catecholamines this interaction has been labeled "charge-transfer,"[52] and later "π-bonding,"[53] it is probably safe to say that the interaction is some function of the π-electron system, probably involving hydrophobic interactions.[54] In compounds of type II there is some conjugation of the nonbonding electrons of the hetero atoms with the aromatic π electrons, resulting in a certain amount of delocalization; in effect, the π cloud has been extended in length. It can be envisaged that a site which binds a phenyl group might alternatively accept a phenoxy group, in which case it is reasonable to suppose that small changes in the electron density on the oxygen atom might give rise to subtle, yet critical, changes in the orientation of the bound phenoxy group.

It seems reasonable to suggest, therefore, that the *ortho* groups in ω-aryloxyalkylamino derivatives enhance the biological activity of the unsubstituted compounds by forcing the α-carbon atom out of the plane of the aromatic ring, leading to decreased resonance and increased basicity of the oxygen atom. This may result in either a facilitated mechanism for bringing the basic group of the side chain to the requisite distance from the aromatic center for pharmacological activity, or an electron distribution (or perhaps simply an over-all molecular shape) which permits more effective binding of the drug molecule at its site of action.

Further support for the suggestion that the *ortho* substituents function in this way (and not perhaps by increasing the π basicity of the ring or critical hydrophobic interactions) is found in the fact that the presence of the *o*-chlorine atoms in **35** does not alter the known inactivity of phenethylguanidine **34**;[14] neither

(45) Owing to the uncertainty which attends measurements in methanol approaching 210 mμ, we have only recorded the secondary bands (λ_{max} *ca.* 275 mμ), although the compounds all show more intense absorption near 220 mμ. The secondary bands have been shown to give a good indication of steric inhibition of resonance.[46,47]

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do such substituents give rise to activity in **33**. These results affirm the notion that *ortho* substituents are only effective in enhancing activity when the α atom of the side chain is a hetero atom with a lone pair of electrons.

Experimental Section[55]

Aryloxyalkyl bromide intermediates were prepared by the methods described in the literature.[6,18,21,56] The following compound is novel.

2-(2,3-Dichlorophenoxy)ethyl bromide, bp 98–106° (0.1 mm), mp 55° (from ethanol), was prepared by an analogous method.[56c]

Aryloxyalkylhydrazines were prepared by reaction of the appropriate aryloxyalkyl bromide and hydrazine in boiling ethanol by the method of Gabriel.[57] The products often underwent partial decomposition during distillation, resulting in boiling points over a wide range. Those hydrazines not already reported [56,58] are listed in Table VII. The 2,3-dichloro- and 2,3-dimethylphenoxyethylhydrazines were used in the crude state without distillation.

TABLE VII

R-C$_6$H$_4$-O(CH$_2$)$_n$NHNH$_2$

R	n	Bp, °C (mm)
2-CH$_3$O	3	120–121 (1.75)
2-CH$_3$O	4	142–166 (3)
2-Cl	2	143–144 (2)
2,6-(CH$_3$)$_2$	3	130–155 (2.5–5)
3-(2,6-Dichlorophenyl)-propylhydrazine hydrochloride		Mp 157° (from methanol–ether)

N-Benzyl-N-methyl-2-(2,6-dimethylphenoxy)ethylamine.—N-Benzyl-2-(2,6-dimethylphenoxy)ethylamine[21] was methylated by the procedure of Clarke, *et al.*,[59] to give the tertiary amine in 87% yield, bp 132–137° (0.15 mm), n^{25}D 1.5425.

N-Methyl-2-(2,6-dimethylphenoxy)ethylamine.—The above tertiary amine was hydrogenated in acetic acid over Pd–C at atmospheric pressure at 70°, to give the required secondary amine in 55% yield, bp 134–136° (19 mm), n^{25}D 1.5078.

N-Methyl-N-nitroso-2-(2,6-dimethylphenoxy)ethylamine.—The above secondary amine was nitrosated by the procedure previously described for N-benzyl-2-(2,6-dimethylphenoxy)ethylamine[21] to give the nitrosamine in 61% yield, bp 146–148° (0.6 mm), n^{25}D 1.5271. The infrared spectrum showed strong absorption at 1480–1460 cm^{-1} and no N–H absorption.

1-[2-(2,6-Dimethylphenoxy)ethyl]-1-methylhydrazine.—The nitrosamine was reduced with LiAlH$_4$ in ether in the usual manner, to give the hydrazine in 65% yield, bp 82–84° (0.15 mm), n^{25}D 1.5186.

Anal. Calcd for C$_{11}$H$_{18}$N$_2$O: C, 68.00; H, 9.34; N, 14.42. Found: C, 67.89; H, 9.24; N, 14.44.

2-(2,6-Dichlorophenyl)ethylamine.—2,6-Dichlorophenylacetonitrile[60] (9.3 g, 0.05 mole) in dry tetrahydrofuran (25 ml) was stirred under nitrogen and treated dropwise with diborane (0.1 mole) in dry THF (200 ml). After 1 hr excess diborane was destroyed with ethanol, and the reaction mixture was treated with HCl to precipitate the hydrochloride of the product. This was filtered and recrystallized from 2-propanol to give 5.1 g (53%), mp 275–280° dec.

Anal. Calcd for C$_8$H$_9$Cl$_2$N·HCl: C, 42.42; H, 4.45; N, 6.18. Found: C, 42.38, H, 4.43; N, 6.04.

3-(2,6-Dichlorophenyl)propan-1-ol.—The Grignard reagent formed in dry ether from 2,6-dichlorobenzyl chloride (18.35 g, 0.1 mole) and Mg (2.43 g) was stirred vigorously at 0° while treated slowly with ethylene oxide (8.8 g, 0.2 mole) in ether (20 ml). The reaction mixture was stirred for 1 hr during which time a solid formed. Dilute H$_2$SO$_4$ (2 *N*, 200 ml) was added with stirring, and the organic layer was separated. The aqueous layer was extracted with ether, and the combined organic phases were dried and evaporated. Distillation of the residue yielded the product (29.3 g, 48%), bp 110–116° (0.6 mm), n^{25}D 1.5558, ν_{max} 3330 cm^{-1}.

3-(2,6-Dichlorophenyl)propyl Bromide.—Phosphorus tribromide (25.7 g, 0.095 mole) was added over 15 min to 3-(2,6-dichlorophenyl)propan-1-ol (38.9 g, 0.19 mole) stirred vigorously at −5°. The mixture was stirred 0.5 hr at room temperature, and 0.5 hr at 60°, and then was cooled and worked up with water and ether. The ethereal layer was washed with NaHCO$_3$, dried, and evaporated. The residue was distilled to give the product (24 g, 47%), bp 122–126° (0.8 mm), n^{25}D 1.5748. The infrared spectrum showed no hydroxyl absorption.

Aryloxyalkylaminoguanidines (Table I) were prepared from the appropriate substituted hydrazine and S-methylisothiourea sulfate by the method described recently,[21] using water, ethanol, or a mixture of those two as solvent. Compounds **20–25** were prepared by use of the appropriate N-substituted derivative of S-methylisothiourea. The products were recrystallized until their melting points were constant, which procedure resulted in low yields (10–50%), so it is possible that isomeric compounds were present in the mother liquors. The nmr spectra indicated that the products isolated contained negligible quantities of isomers.

Nmr Measurements.—The spectra of solutions of substituted aminoguanidines in H$_2$SO$_4$ (Analar), trifluoroacetic acid (Analar), and tetrafluorodichloroacetone deuteriohydrate (FClA) were measured on a Perkin-Elmer 40-Mc spectrometer. The FClA was prepared according to the method of Lukalle.[61] The chemical shifts were measured with respect to tetramethylammonium sulfate (TMAS) (τ_{CH_3} = 6.81)[62] in H$_2$SO$_4$ and trifluoroacetic acid (TFA), and to (CH$_3$)$_4$Si (τ_{CH_3} = 10.0) in FClA. It was thought that the chemical shift of TMAS might be different in 90% H$_2$SO$_4$ from the value in TFA so the chemical shift of TMAS was measured in the above two solvents with respect to benzene and cyclohexane as external references.[63] The chemical shift was found to be insensitive to change of solvent

pK_a Measurements.—The first pK_a of aminoguanidine was determined by potentiometric titration using a Beckman Zeromatic pH meter.[24] The second pK_a of benzylaminoguanidine sulfate was determined using nmr. The chemical shift difference between the methylene protons and TMAS was measured in a series of H$_2$SO$_4$ solutions of various H_0 values and the pK_a was determined from the relationship

$$pK_a = H_0 + n \log \frac{\tau_D - \tau}{\tau - \tau_M}$$

where τ_D, τ_M, and τ represent the chemical shift of the methylene protons in the dication, monocation, and in the mixture, respectively, and n is a constant.

Enzyme Inhibition.—The activity of dopamine β-oxidase, prepared from bovine adrenal medulla by the method of Levin, *et al.*,[64] was assayed by fluorimetric estimation of norepinephrine[65] formed from dopamine in 30 min at 37°, in a solution containing catalase, ascorbate, and fumarate.[64b] The activity of the inhibitors was estimated by determining the activity of the enzyme after preincubation with the test substance for 15 min before addition of the substrate.

(55) Melting points were taken on an Electrothermal Apparatus, series 1A or on a Kofler micro hot stage, and are corrected. Ultraviolet spectra were measured on an Ultracord Model 137, intensities at λ_{max} being checked on a Unicam SP 500 instrument. Infrared spectra of liquids were obtained as thin films on a Perkin-Elmer Infracord 137 instrument.

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The inhibition by O-benzylhydroxylamine under these conditions was slightly lower than that reported by Creveling, *et al.*,[19] presumably through use of dopamine instead of tyramine as substrate in our studies.

The effect of **13** on the synthesis of norepinephrine from tyrosine in isolated guinea pig atria was investigated by the method of Merrills and Offerman.[66]

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New Antihypertensive Aminoalkyltetrazoles

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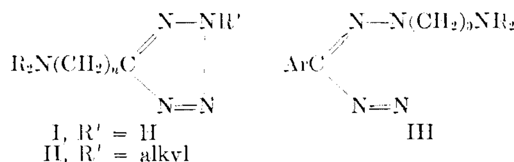
A series of 5-dialkylaminoalkyltetrazoles, 2-substituted 5-dialkylaminoalkyltetrazoles and 5-aryl-2-(3-dialkylaminopropyl)tetrazoles was prepared from the corresponding nitrile. These compounds showed varying degrees of antihypertensive activity; the 5-[2-(4-aryl-1-piperazinyl)ethyl]tetrazoles were the most active in experimental animals.

The antiadrenergic action of 1-phenylpiperazine and 1-phenyl-4-methylpiperazine were first mentioned by Bovet and Bovet-Nitti.[2] Numerous papers have since been published on the adrenergic blocking effects of 4-substituted 1-arylpiperazines.[3]

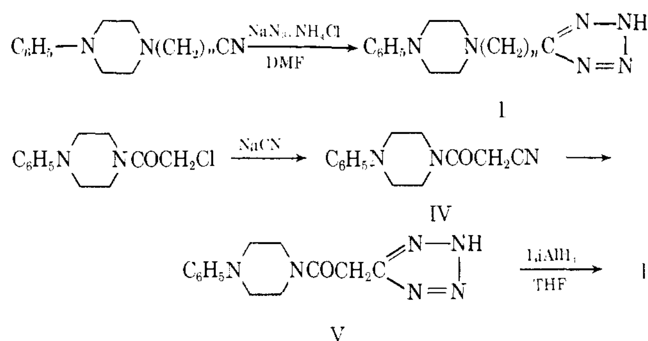
Some pharmacological activities of 1-aryl-5-dialkylaminomethyltetrazoles[4] and 5-aryl-1-alkyltetrazoles[5] have been reported. The chemistry of 2-dialkylaminoalkyl-5-aryltetrazoles[6] and 1-dialkylaminoethyl-5-aryltetrazoles[6] was described, but no pharmacological screening was carried out. These findings led us to prepare 5-dialkylaminoalkyltetrazoles (I), 2-substituted 5-dialkylaminoalkyltetrazoles (II), and 5-aryl-2-[3-dialkylaminopropyl]tetrazoles (III) for pharmacological screening as potential antihypertensive agents.



Some of the 5-[ω-(4-phenyl-1-piperazinyl)alkyl]tetrazoles were reported in a recent patent.[7]

Compounds of type I were prepared in high yield by reaction of the appropriate nitrile with hydrazoic acid according to Finnegan, *et al.*[8] (Scheme I). However, when $n = 1$ or 2, the yield of I was always less than 50% and 1-phenylpiperazine was obtained in *ca.* 50% yield.

SCHEME I



Alternatively, 1-phenyl-4-cyanoacetylpiperazine (IV) with hydrazoic acid gave 1-phenyl-4(5-tetrazolylacetyl)-piperazine (V) which was then reduced with lithium aluminum hydride to give I. The yield was 40% starting with IV.

Alkylation of 5-alkyltetrazoles is known to take place predominantly at position 2.[6] Therefore, the reaction of I (sodium salt) with an appropriate alkyl halide gave 2,5-disubstituted tetrazoles (II). Similarly, 5-aryl-2-substituted tetrazoles (III) were prepared from 5-aryltetrazoles and an alkyl halide (Scheme II).

Pharmacology.—Pharmacological tests in animals have shown that most of the compounds of this series

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