

cator, then recrystallized from methanol to provide 4.6 g. (46%) of white needles, m.p. 111.5–112°.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.88; H, 6.80; N, 9.45. Found: C, 72.78; H, 7.18; N, 9.42.

Acid Hydrolysis of VIII.—To a solution of 1 ml. of concentrated sulfuric in 40 ml. of water was added 0.20 g. of 1,2-bis-[3-(3,4-dihydro-1,3,2H-benzoxazino)]-ethane. The solution which resulted on warming was distilled into a slightly saturated dilute alcohol solution of excess methone. The distillation was stopped when the distilland was about 3–5 ml. The yield of the formaldehyde methone derivative was 0.35 g. (88%), m.p. 188–189° (lit.¹⁰ m.p. 189°). The distillation residue was treated with 10% sodium hydroxide to pH 6–7 and filtered free of resinous-like material. Treatment of the filtrate with 2 ml. of 10% sodium carbonate followed by seeding and cooling produced a pale tan solid product of m.p. 117–122°. A mixture melting point with N,N' -bis-(*o*-hydroxybenzyl)-ethylenediamine was not depressed; the yield of recovered N,N' -bis-(*o*-hydroxybenzyl)-ethylenediamine was 0.16 g. (85%).

Reaction of N,N' -Bis-(*o*-hydroxybenzyl)-ethylenediamine I with Ketones. (A) **Acetone.**—A mixture of 1.0 g. (3.7 mmoles) of I and 15 ml. of acetone was refluxed for 1 hr. The reaction mixture was refrigerated and the crystalline product (0.8 g.) which formed was removed by filtration. A second crop of 0.3 g. was obtained after concentration of the mother liquor. Both crops were combined and recrystallized from absolute ethanol. The yield of 2,2-dimethyl-1,3-bis-(*o*-hydroxybenzyl)-imidazolidine was 0.9 g. (84%), white needles, m.p. 146.5°.

Anal. Calcd. for $C_{19}H_{24}N_2O_2$: N, 8.94. Found: N, 8.88.

This derivative was also prepared, in 90% yield (m.p. of crude product was 145.5°), at 50° in absolute ethanol in the same way as described previously for the isobutyraldehyde reaction in which a 1.6 *M* excess of acetone was used.

(B) **Methyl Ethyl Ketone.**—A solution of 6 g. (22 mmoles) of I in 50 ml. of methyl ethyl ketone was refluxed for 5 hr. The condenser used had a drying tube containing Drierite in its open

end. The reaction mixture was refrigerated and the resulting precipitate was filtered, rinsed with methyl ethyl ketone, and dried; 5.2 g., m.p. 129.5–135°. The crude product was purified by refluxing it in 30 ml. of fresh methyl ethyl ketone on a hot plate for 2.5 hr. The hot solution was filtered and crystallization was induced by cooling. The yield of 2-methyl-2-ethyl-1,3-bis-(*o*-hydroxybenzyl)-imidazolidine was 3.8 g. (53%); white prisms melting at 133–134°.

Anal. Calcd. for $C_{20}H_{28}N_2O_2$: N, 8.58. Found: N, 8.62.

(C) **Other Ketones.**—Condensation reactions of acetophenone, benzophenone, methyl ethyl ketone, and cyclohexanone with I were conducted in the same general manner as described for aromatic aldehydes. In the first three cases, the diamine reagent was recovered essentially unchanged. In the cyclohexanone reaction a solid product was obtained which melted slowly at 107–111°; a mixture melting point with I (m.p. 124°) was depressed. Recrystallization of this solid from anhydrous tetrahydrofuran gave a material of m.p. 103–107°. The cyclohexanone reaction was repeated using a benzene solution in which water formed in the reaction was removed as its benzene–water azeotrope. The product resulting when the theoretical amount of water was removed melted at 105.5–109.5°. Recrystallization from benzene–petroleum ether (b.p. 40–60°) or carbon tetrachloride gave products of lower melting points without improvement in the ranges (*e.g.*, 99.5–105.5°).

Acknowledgment.—We wish to thank the Dow Chemical Company for the N,N' -bis-(*o*-hydroxybenzyl)-ethylenediamine used in this research. The authors also wish to thank the Smith Kline and French Laboratories for testing the compounds listed in Table II for bacteriostatic, fungistatic, and antiviral activity. We are especially indebted to Dr. John R. E. Hoover, Miss M. Dolan, and colleagues—Microbiology Section, and Dr. Erling Jensen—Virology Section, of the SK and F Laboratories for their work in connection with the screening of these compounds.

(10) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 50.

Potential Antihypertensive Agents. Some Guanidine Derivatives

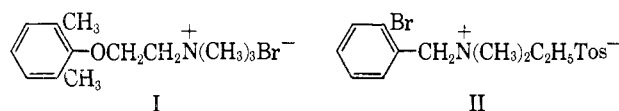
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2-(2,6-Xylyloxy)ethylguanidine sulfate is a potent hypotensive agent which acts by blocking the sympathetic nervous system. Related compounds have been synthesized and structure–activity relationships in the series have been investigated.

Treatment of hypertensive disorders has been revolutionized in recent years by the discovery and use of agents which inhibit the release of neurohormones from the postganglionic sympathetic nerve endings. The first compound discovered to have this effect was choline 2,6-xylyl ether bromide² (I), which effectively blocks transmission at peripheral sympathetic nerve terminals but suffers from muscarinic side-effects. Subsequently, bretylium (II) was developed and intensive investigation showed it to be selectively accumulated in postganglionic sympathetic nerve fibers^{3a} and to prevent the release of neurohormones from the sympathetic nerve endings following neural stimulation.^{3b} More recently guanethidine (III) was introduced for the treatment of hypertension. This com-



pound has been shown to exert its effect on the sympathetic nervous system by depleting the norepinephrine stores at the postganglionic sympathetic nerve endings.⁴



I, II, and III have certain common structural features. Each contains a strongly basic terminal group connected *via* a side chain to a carbocyclic or heterocyclic ring. These factors suggested that replacement of the poorly absorbed quaternary group of I by the guanidine residue might lead to compounds acting at the postganglionic sympathetic nerve fibers. 2-(2,6-Xylyloxy)ethylguanidine (IV) which is the guanidine analog

(4) R. Cass, R. Kuntzman, and B. B. Brodie, *Proc. Soc. Exptl. Biol. Med.*, **103**, 871 (1960).

(1) To whom inquiries should be addressed.

(2) P. Hey and G. L. Willey, *Brit. J. Pharmacol.*, **9**, 471 (1954).

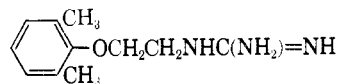
(3) (a) A. L. A. Boura, F. C. Copp, W. G. Duncoube, A. F. Green, and A. McCoubrey, *ibid.*, **17**, 265 (1960); (b) A. L. A. Boura and A. F. Green, *ibid.*, **14**, 536 (1959).

TABLE I
SYMPATHETIC BLOCKING ACTIVITY AND TOXICITY OF SUBSTITUTED GUANIDINES
ArXAlkNHC(NHR')=NR²

| Com- pound | Ar | X | Alk | R ¹ | R ² | Dose required to produce 50% coverage of the eye of the cat by the nictitating membrane (mg./kg. /sec.) | Time course, hr. | | LD ₅₀ , mice (mg./kg. P.o.) | LD ₅₀ , mice (mg./kg. S.c.) |
|---------------------|--|--------------------------------|-------------------------------------|---------------------------------|---------------------------------|--|------------------|---------------|---|---|
| | | | | | | | Onset | Dura- tion | | |
| IV | 2,6-(CH ₃) ₂ C ₆ H ₃ | O | (CH ₂) ₂ | H | H | 10 | 5 | >98 | >500 | 91 |
| V | C ₆ H ₅ | O | (CH ₂) ₂ | H | H | >50 | .. | .. | 750 | 250 |
| VI | <i>o</i> -CH ₃ C ₆ H ₄ | O | (CH ₂) ₂ | H | H | >50 | .. | .. | 375 | 125 |
| VII | <i>m</i> -CH ₃ C ₆ H ₄ | O | (CH ₂) ₂ | H | H | >50 | 5 | 24 | 750 | 375 |
| VIII | <i>p</i> -CH ₃ C ₆ H ₄ | O | (CH ₂) ₂ | H | H | >50 | .. | .. | 500 | 250 |
| IX | <i>o</i> -ClC ₆ H ₄ | O | (CH ₂) ₂ | H | H | >10 | .. | .. | 500 | 190 |
| X | <i>o</i> -BrC ₆ H ₄ | O | (CH ₂) ₂ | H | H | >50 | .. | .. | .. | .. |
| XI | <i>p</i> -CH ₃ OC ₆ H ₄ | O | (CH ₂) ₂ | H | H | >50 | .. | .. | 1000 | 250 |
| XII | <i>p</i> -ClC ₆ H ₄ | O | (CH ₂) ₂ | H | H | 24 | 24 | >48 | 250 | 95 |
| XIII | 2,4,6-(CH ₃) ₃ C ₆ H ₂ | O | (CH ₂) ₂ | H | H | >38 | .. | .. | .. | .. |
| XIV | 2,6-(CH ₃) ₂ -4-ClC ₆ H ₂ | O | (CH ₂) ₂ | H | H | 50 | 5 | >72 | 750 | 750 |
| XV | 2,6-(C ₂ H ₅) ₂ C ₆ H ₃ | O | (CH ₂) ₂ | H | H | 50 | 5 | 24 | .. | .. |
| XVI | 2,6-(<i>iso</i> -C ₃ H ₇) ₂ C ₆ H ₃ | O | (CH ₂) ₂ | H | H | >50 | .. | .. | >500 | 375 |
| XVII | 2,6-(CH ₃) ₂ C ₆ H ₃ | S | (CH ₂) ₂ | H | H | 10 | 2 | >72 | .. | .. |
| XVIII | C ₆ H ₅ | S | (CH ₂) ₂ | H | H | >50 | .. | .. | 750 | 375 |
| XIX | 2,6-(CH ₃) ₂ C ₆ H ₃ | NH | (CH ₂) ₂ | H | H | 10 | 24 | >48 | 750 | 250 |
| XX | 2,6-(CH ₃) ₂ C ₆ H ₃ | NCH ₃ | (CH ₂) ₂ | H | H | 10 | 2 | 48 | 375 | 190 |
| XXI | 2,6-(CH ₃) ₂ C ₆ H ₃ | NC ₂ H ₅ | (CH ₂) ₂ | H | H | >50 | .. | .. | 500 | 125 |
| XXII | C ₆ H ₅ | NCH ₃ | (CH ₂) ₂ | H | H | >35 | .. | .. | 375 | 188 |
| XXIII | α -C ₁₀ H ₇ | O | (CH ₂) ₂ | H | H | >50 | 24 | >48 | >2000 | 1500 |
| XXIV | β -C ₁₀ H ₇ | O | (CH ₂) ₂ | H | H | 50 | 30 | >48 | >500 | 250 |
| XXV | 2,6-(CH ₃) ₂ C ₆ H ₃ | O | CH(CH ₃)CH ₂ | H | H | 20 | 1 | 72 | 750 | 375 |
| XXVI | 2,6-(CH ₃) ₂ C ₆ H ₃ | O | (CH ₂) ₃ | H | H | 50 | 1 | 24 | 750 | 375 |
| XXVII | 2,6-(CH ₃) ₂ C ₆ H ₃ | O | (CH ₂) ₄ | H | H | >50 | .. | .. | 1000 | 375 |
| XXVIII ^a | 2,6-(CH ₃) ₂ C ₆ H ₃ | O | (CH ₂) ₂ | CH ₂ | CH ₂ | >50 | .. | .. | 1000 | 750 |
| XXIX | 2,6-(CH ₃) ₂ C ₆ H ₃ | O | (CH ₂) ₂ | C ₆ H ₅ | C ₆ H ₅ | >25 | .. | .. | 188 | 125 |
| XXX | 2,6-(CH ₃) ₂ C ₆ H ₃ | O | (CH ₂) ₂ | H | COC ₆ H ₅ | >50 | 5 | 24 | >2000 | .. |
| XXXI | 2,6-(CH ₃) ₂ C ₆ H ₃ | O | (CH ₂) ₂ | COC ₆ H ₅ | COC ₆ H ₅ | >50 | .. | .. | >2000 | >2000 |

^a XXVIII is [2-(2,6-xylyloxy)ethyl]amino-4,5-dihydroimidazole hydrochloride.

of I was prepared and shown to be as active as guanethidine when tested by its relaxant action on the nictitating



IV

membrane of the conscious cat and to have an activity comparable to that of guanethidine on the arterial blood pressure of anesthetized dogs.⁵ Clinical evaluation has shown the antihypertensive activity in man to be of the same order as that of guanethidine. The detailed pharmacology of this compound will be published elsewhere.

Numerous analogs of IV have been synthesized and evaluated for their activity in blocking the sympathetic nervous system (Table I).

Blockade of the Sympathetic Nervous System.—Each compound was administered by subcutaneous injection to conscious male or female cats at a dose level not exceeding 40% of the estimated LD₅₀ in mice. All compounds were either dissolved or suspended in a

vehicle of 5% acacia in distilled water and administered in a dose volume of 1 ml./kg. The animals were observed for relaxation of the nictitating membranes at hourly intervals for the first 6 hr. following the injection, then at 24 hr., and in some cases even longer periods of observation were employed. Relaxation of the nictitating membranes was taken as an indication of impairment of sympathetic nervous transmission.

Some of the more active compounds were further examined for their effects on the blood pressure of chloralose-anesthetized cats and pentobarbital-anesthetized dogs in the following manner.

(a) **Chloralose-Anesthetized Cats.**—In male and female cats anesthetized by intravenous injection of chloralose (80 mg./kg.), control responses were obtained to the intravenous injection of (–)-epinephrine, (–)-norepinephrine, and (±)-amphetamine, to bilateral carotid occlusion and to the stimulation of the ascending cervical sympathetic nerve. The compound under investigation was then injected intravenously at a dose level of 5 or 10 mg./kg. Between 3 and 5 hr. later, the control stimuli were repeated.

Intravenous injection of IV was accompanied by a rapid fall in blood pressure of short duration with a brief period of apnoea, followed by marked hypertension which persisted for 20 to 40 min. Simultaneously,

(5) During the final phases of this work, a publication by A. L. A. Boura, F. C. Coqui, A. F. Green, H. F. Hodson, G. K. Ruffell, M. F. Sim, E. Walton, and E. M. Grivsky (*Nature*, **191**, 1312 (1961)) referred to the adrenergic neurone blocking activity of this compound.

the nictitating membrane went into a sustained contraction which did not recover throughout the maximum period of 5 hr. used in these experiments. The hypertensive phase then gave way to a pronounced hypotension which was slow in onset, but of long duration (>5 hr.). During this hypotensive phase, the injection of amphetamine and the application of the bilateral carotid occlusion reflex stimulus no longer elicited a pressor response, whereas the pressor response to injected epinephrine and norepinephrine were potentiated. Compounds XX and XXIV produced qualitatively the same effect when similarly examined.

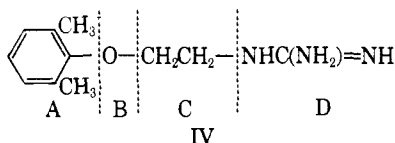
The hypertension has been demonstrated to be due to the release of endogenous sympathomimetic amines, for it is potentiated by the prior administration of pyrogallol, which inhibits catechol-O-methyl transferase. This technique was used by Wylie⁶ to show the pressor action of guanethidine to be due to the release of endogenous sympathomimetic amines.

Some cats were pretreated on each of 2 days with reserpine (2.5–5 mg./kg.) intraperitoneally. The intravenous injection of IV in the subsequently anesthetized animals produced little or no pressor response. This would appear to confirm that the hypertensive phase of the cardiovascular response to IV depends on the presence of endogenous sympathomimetic amines, which are depleted by treatment with reserpine.

(b) **Pentobarbital-Anesthetized dogs.**—The effects of these same compounds on the blood pressure of mongrel dogs, anesthetized by the intravenous injection of pentobarbital sodium (30 mg./kg.), were qualitatively similar to those in cats. Some dogs were pretreated with IV (10 mg./kg.) intravenously. Forty eight hours later the animals were anesthetized with pentobarbital sodium and the blood pressure was recorded. Saline-treated control animals exhibited a marked pressor response to intravenously injected tyramine or amphetamine, whereas the animals treated with IV showed a greatly reduced response. The slow intravenous infusion of 4 mg. of norepinephrine⁷ prior to tyramine or amphetamine injection, however, resulted in a normal response being obtained.

It is concluded, therefore, that the compounds under investigation as represented by IV, cause blockade in the sympathetic nervous system in a manner similar to that described for guanethidine⁴ which depletes the postganglionic sympathetic stores of their norepinephrine content.

Structure-Activity Relationships.—The biological results for sympathetic blocking activity revealed an interesting structure-activity pattern which may be expressed in terms of the various structural features (A, B, C, and D) of IV as follows



A.—For optimum activity, presence of the flanking methyl groups is essential. Analogous compounds with the 2,6-xylyl group replaced by phenyl, *o*-, *m*-, and *p*-tolyl, *o*-chloro, *o*-bromo, and *p*-methoxy substituents are

much less active (V, VI, VII, VIII, IX, X, and XI, respectively, Table I). The corresponding *p*-chloro compound XII is, however, more active than these latter compounds, but the trisubstituted compound XIV formed by introduction of a *p*-chloro substituent into structure IV is less active than either 2-(2,6-xylyloxy)ethylguanidine or 2-(*p*-chlorophenoxy)ethylguanidine. Increase in size of the flanking methyl groups to ethyl XV or isopropyl XVI causes a progressive decline in activity. Naphthalene analogs XXIII and XXIV also possess a moderate degree of activity, the α isomer being slightly the more active.

B.—Replacement of oxygen by sulfur in IV yields a compound of comparable activity, relaxation of the nictitating membrane being observed at 10 mg./kg. (XVII). As expected, unsubstituted 2-(phenylmercapto)ethylguanidine (XVIII) is much less active. Replacement of oxygen by NH in IV leads to an equally active compound (XIX). Methylation of this nitrogen atom causes only a slight drop (XX) in activity but the analogous compound containing an ethyl substituent is less active (XXI). *N*-Methylphenylaminoethylguanidine (XXII) is also less active.

C.—Introduction of a β -methyl substituent into structure IV causes no apparent reduction in activity (XXV). The structure containing an unbranched three-carbon chain is slightly less active (XXVI) and activity of the analogous *n*-butyl compound is of a very low order (XXVII).

D.—Alteration of the terminal guanidine group invariably leads to less active compounds. Cyclization of the terminal atoms into an imidazoline ring (XXVIII) or phenyl substitution on the terminal nitrogen atoms (XXIX) causes a fall in activity. Reduction of the basicity of the terminal nitrogen atoms by mono- and dibenzoylation also causes a decline in sympatholytic activity (XX and XXI, respectively). Boura, *et al.*,⁵ have reported that methylation of these nitrogen atoms is accompanied by loss of adrenergic neurone blocking activity.

The optimum structural requirements for blocking the sympathetic nervous system would, therefore, appear to be the 2,6-xylyl group linked *via* an oxygen, sulfur, or nitrogen atom to a two-carbon side chain, optionally containing a β -methyl substituent and terminating in an unsubstituted guanidine group.

Miscellaneous Structures.⁸—Numerous miscellaneous guanidines were prepared and evaluated for activity in a similar manner (Table II). 2-(Benzhydryloxy)ethylguanidine (XXXV) is inactive and phenothiazinylalkylguanidines with three-carbon side chains (XXXVI and XXXVII) including a 2-trifluoromethyl substituted derivative are also inactive.


Guanethidine analogs with the nitrogen atom outside the ring, *viz.* *N*-methylcyclooctylaminoethylguanidine sulfate (XXXII) and the cycloheptyl analog (XXXIII), also give evidence of causing blockade of the sympathetic nervous system. The presence of a heterocyclic ring is apparently not a prime requisite for activity with this structure. The bicyclic octahydroisindole XXXIV is also highly active, indicating that the bridging of guanethidine-like compounds is accompanied by retention of activity.

(6) D. W. Wylie, *Nature*, **189**, 490 (1961).

(7) J. H. Burn and M. J. Rand, *J. Physiol.*, **144**, 314 (1958).

(8) Structure-activity relationships among phenylalkylguanidines (bretylum analogs) will be published separately.

TABLE II
 SYMPATHETIC BLOCKING ACTIVITY AND TOXICITY OF MISCELLANEOUS GUANIDINES

| Compound | R | n | Dose required to produce 50% coverage of the eye of the rat by the nitroating membrane (mg./kg. s.c.) | Time course, hr.— | | LD ₅₀ , mice mg./kg.— | |
|----------|---|---|---|-------------------|----------|----------------------------------|------|
| | | | | Onset | Duration | P.o. | S.c. |
| III | (CH ₂) ₇ N | 2 | 10 | 4 | >48 | 1000 | 500 |
| XXXII | (CH ₂) ₂ CHN(CH ₃) | 2 | 50 | 5 | >24 | 750 | 375 |
| XXXIII | (CH ₂) ₆ CHN(CH ₃) | 2 | 20 | 4 | >24 | 500 | .. |
| XXXIV |  | 2 | 10 | 4 | >48 | >2000 | 1000 |
| XXXV | (C ₆ H ₅) ₂ CH- | 2 | >40 | .. | .. | 375 | 125 |
| XXXVI | 10-Phenothiazinyl | 3 | >40 | .. | .. | .. | .. |
| XXXVII | 2-CF ₃ -10-Phenothiazinyl | 3 | >50 | .. | .. | >2000 | 1500 |

Synthetic Methods.—The guanidine sulfates were prepared by the reaction of the appropriate amine with 2-methyl-2-thiopseudourea sulfate using water or aqueous ethanol as the solvent.⁹

Intermediate aryloxyethylamines were normally prepared from a substituted phenol by reaction with chloroacetonitrile in ethyl methyl ketone, using potassium carbonate as base,¹⁰ and reducing the nitrile so formed with lithium aluminum hydride in ether solution. Another method employed for the preparation of amine intermediates was a modified Gabriel synthesis, involving conversion of haloethers to corresponding phthalimides, followed by cleavage with hydrazine to yield the desired amine. Other amine intermediates were prepared by established methods described in the Experimental section.

Experimental¹¹

Amine Intermediates.—The appropriate phenols and thiophenols, most of which were available commercially, were etherified with chloroacetonitrile in ethyl methyl ketone, using potassium carbonate as base.¹⁰ The products, obtained by distillation, were generally contaminated with 5–10% of the starting phenols as shown by their infrared spectra. Since the derived amines were readily purified, refractionation of the nitriles was not attempted. 2-Bromophenoxyacetonitrile was obtained pure, crystallizing as colorless needles from hexane, m.p. 47–49°.

Anal. Calcd. for C₈H₆BrNO: C, 45.31; H, 2.85. Found: C, 45.59; H, 2.78.

The nitriles were reduced with excess lithium aluminum hydride in ether affording the derived amines which were purified by acid extraction and their identity was confirmed by infrared spectroscopy and equivalent weight determination. Relevant information on the new amines is recorded in Table VI. 2-Phenoxyethylamine,¹² 2-(*o*-tolxyloxy)ethylamine,¹³ 2-(*m*-tolxyloxy)ethylamine,¹³ 2-(*p*-tolxyloxy)ethylamine,¹³ 2-(*p*-methoxyphenoxy)ethylamine,¹⁴ 2-(*p*-chlorophenoxy)ethylamine,¹⁵ 2-phenylmercaptoethylamine,¹⁶ *N*-methyl-*N*-phenylethylenediamine,¹⁷ 2-(α -naphthoxy)ethylamine,¹⁸ 2-(β -naphthoxy)ethylamine,¹⁸ 2-benzhydryloxyethylamine,¹⁸ 3-(10-phenothiazinyl)propylamine,¹⁹ and

3-(2-trifluoromethyl-10-phenothiazinyl)propylamine^{20,21} have been previously reported.

The following preparation of 2-(2,6-xylyloxy)ethylamine is typical of the general synthetic procedure for the intermediate aminoethyl ethers.

Cyanomethyl 2,6-Xylyl Ether.—A mixture of 2,6-xylenol (241 g., 2.0 moles), anhydrous potassium carbonate (250 g.), and ethyl methyl ketone (350 ml.) was stirred and heated under reflux. A solution of chloroacetonitrile (140 ml.) in ethyl methyl ketone (150 ml.) was added during 1 hr., boiling and stirring being continued for a further 1 hr. The bulk of the solvent was removed under aspirator vacuum and the residue was diluted with ice-water, and extracted several times with ether. The ether extracts were washed with 20% sodium hydroxide solution and dried over anhydrous potassium carbonate. Distillation of the ether solution gave, after a small fore-run of xylenol, 240 g. of cyanomethyl 2,6-xylyl ether, b.p. 88–92° (0.5–1.0 mm.), *n*_D²⁰ 1.5138.

2-(2,6-Xylyloxy)ethylamine.—The nitrile (242 g., 1.5 moles) dissolved in dry ether (300 ml.) was added to a well stirred slurry of lithium aluminum hydride (75 g., 1.95 moles) in dry ether (600 ml.). After addition, the mixture was stirred and heated under reflux for 2 hr. It was cooled in an ice bath and well stirred, while 'wet ether' (1 l.) was added dropwise, followed by water (400 ml.). The mixture was filtered using "Hyflo" filter aid. The residue was thoroughly washed with ether, and the total ethereal filtrate combined, washed with brine, and exhaustively extracted with 2 *N* hydrochloric acid. The acid extracts were washed once with ether-petroleum ether (1:1), and made basic with 50% caustic soda solution which was extracted into ether. Distillation of the extract under nitrogen gave the aminoether (182 g.) as a colorless oil. The over-all yield of amine was 57%.

The other amine intermediates were prepared as follows, and are listed together with the relevant physical data in Table VI. Infrared spectra were used to confirm the identity of the nitriles prepared which were generally not refractionated.

2-(2,6-Xylyloxy)propionitrile.—2,6-Xylenol (24.4 g., 0.2 mole) was reacted with α -bromopropionitrile (39.4 g., 0.29 mole) in ethyl methyl ketone in the presence of potassium carbonate (26 g.) as described for the preparation of the analogous acetonitrile. The yield of 2-(2,6-xylyloxy)propionitrile was 15.2 g., b.p. 139–134° (17 mm.).

2-(2,6-Xylyloxy)propylamine.—Reduction of the foregoing nitrile (15.0 g., 0.085 mole) with lithium aluminum hydride (4.0 g., 0.11 mole) in ether, in the usual way yielded 2-(2,6-xylyloxy)propylamine (12.0 g.).

***N*-[3-(2,6-Xylyloxy)propyl]phthalimide.**—3-(2,6-Xylyloxy)propyl chloride²¹ (79.5 g., 0.4 mole), prepared in 85% yield from 2,6-xylenol and a large excess of trimethylene chlorobromide in the presence of excess potassium carbonate in ethyl methyl

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

(10) C. Djerasi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 1688 (1947).

(11) Melting points were recorded using an "Electrothermal" melting point apparatus comprising a gas-heated block and a thermometer calibrated for exposed stem.

(12) S. Gabriel and G. Eschenbach, *Ber.*, **30**, 810 (1897).

(13) D. Kablev, *Compt. Rend. Soc. Biol.*, **141**, 48 (1947).

(14) E. Kabane and J. Levy, *Bull. Soc. Chim. Biol.*, **27**, 582 (1945).

(15) R. L. Johns, T. P. Metcalfe, and W. A. Sexton, *Biochem. J.*, **45**, 113 (1949).

(16) S. Gabriel and J. Coburn, *Ber.*, **44**, 3632 (1911).

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
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TABLE VI
 INTERMEDIATE AMINES R-ALK-NH₂

| R | Alk | B.p., °C. (mm.) | | Molecular formula | Equivalent weight | |
|--|-------------------------------------|------------------------|---------|--|--------------------|------------------|
| | | | | | Calcd. | Found |
| 2,6-(CH ₃) ₂ C ₆ H ₃ O | (CH ₂) ₂ | 100 | (1) | C ₁₀ H ₁₆ NO | 165.2 | 168.0 |
| 2-ClC ₆ H ₄ O | (CH ₂) ₂ | 150-153 | (18) | C ₈ H ₁₀ ClNO | 171.6 | 173.2 |
| 2-BrC ₆ H ₄ O | (CH ₂) ₂ | 67 | (0.02) | C ₈ H ₁₀ BrNO | 216.1 | 180 ^a |
| 2,4,6-(CH ₃) ₃ C ₆ H ₂ O | (CH ₂) ₂ | 100-101 | (0.25) | C ₇ H ₁₇ NO | 179.2 | 184.1 |
| 2,6-(CH ₃) ₂ 4-ClC ₆ H ₃ O | (CH ₂) ₂ | 261-262 ^{b,c} | | C ₁₀ H ₁₄ ClNO·HCl | 236.2 ^b | 236.5 |
| 2,6-(C ₂ H ₅) ₂ C ₆ H ₃ O | (CH ₂) ₂ | 95-100 | (0.5) | C ₁₂ H ₁₉ NO | 193.3 | 191.5 |
| 2,6-(iso-C ₃ H ₇) ₂ C ₆ H ₃ O | (CH ₂) ₂ | 104-106 | (0.3) | C ₁₄ H ₂₅ NO | 221.3 | 227.0 |
| 2,6-(CH ₃) ₂ C ₆ H ₃ S | (CH ₂) ₂ | 115-120 | (0.1) | C ₁₀ H ₁₅ NS | 181.2 | 183.7 |
| 2,6-(CH ₃) ₂ C ₆ H ₃ O | CH(CH ₃)CH ₂ | 126-128 | (13) | C ₁₁ H ₁₇ NO | 179.2 | 181.1 |
| 2,6-(CH ₃) ₂ C ₆ H ₃ O | (CH ₂) ₃ | 206-207 ^{b,c} | | C ₁₁ H ₁₇ NO·HCl | 215.7 | 218.2 |
| 2,6-(CH ₃) ₂ C ₆ H ₃ O | (CH ₂) ₄ | 93-94 | (0.25) | C ₁₂ H ₁₉ NO | 193.2 | 196.9 |
| 2,6-(CH ₃) ₂ C ₆ H ₃ NH | (CH ₂) ₂ | 75-80 | (0.05) | C ₁₀ H ₁₆ N ₂ | 82.1 | 83.5 |
| 2,6-(CH ₃) ₂ C ₆ H ₃ NCH ₃ | (CH ₂) ₂ | 80-88 | (0.071) | C ₁₀ H ₁₈ N ₂ | 89.2 | 87.5 |
| 2,6-(CH ₃) ₂ C ₆ H ₃ NC ₂ H ₅ | (CH ₂) ₂ | 85 | (0.06) | C ₁₂ H ₂₀ N ₂ | 96.2 | 100.3 |
| (CH ₂) ₆ CHNCH ₃ | (CH ₂) ₂ | 60 | (0.15) | C ₁₀ H ₁₂ N ₂ | 85.2 | 91.3 |
| (CH ₂) ₇ CHNCH ₃ | (CH ₂) ₂ | 75-76 | (0.1) | C ₁₁ H ₁₄ N ₂ | 92.2 | 97.1 |
|  | (CH ₂) ₂ | 148-150 | (15) | C ₁₀ H ₁₆ N ₂ | 84.1 | 89.1 |

^a Partial debromination occurred on reduction, but the derived guanidine sulfate was obtained pure. Data refer to the hydrochloride. ^c Melting point.

washings. The ether solution was then dried over calcium chloride and distilled, yielding an oil (39.8 g.), b.p. 104° (0.5 mm.).

4-(2,6-Xylyloxy)butylamine.—The nitrile (39.5 g., 0.21 mole) was reduced with lithium aluminum hydride (8.0 g., 0.21 mole) in dry ether in the usual way affording 32.0 g. of product.

N-[2-(2,6-Dimethylphenylamino)ethyl]phthalimide.—A mixture of 2,6-dimethylaniline (40.0 g., 0.33 mole) and β -bromoethylphthalimide (40.0 g., 0.16 mole) was heated on the steam bath for 20 hr. and then at 130° for 4 hr. The mixture was added to water and extracted with ether. The ether extracts were concentrated to low bulk and allowed to cool, depositing some high melting material (2.7 g.), probably 2,6-dimethyl-1,1-bisphthalimidoethylamine, which was removed by filtration. The filtrate was evaporated to dryness and the residual oil was dissolved in ethanol, filtered hot, and diluted with a few drops of water. On cooling, crystals were deposited (24.5 g., m.p. 45-55°). Two recrystallizations from aqueous ethanol finally afforded 20.5 g. of product, m.p. 66-69°.

Anal. Calcd. for C₁₃H₁₈N₂O₂: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.26; H, 6.28; N, 9.11.

N-(2,6-Dimethylphenyl)ethylenediamine.—The phthalimide (20.0 g., 0.07 mole) was dissolved in ethanol, treated with 100% hydrazine hydrate (4.0 g., 0.08 mole), and heated under reflux for 30 min. Phthalhydrazide was removed by filtration and the filtrate was concentrated, filtered, basified with 40% sodium hydroxide, and extracted with ether. The ether extracts were dried over potassium carbonate, concentrated, and distilled, yielding 7.0 g. of oil.

N-Methyl-N-(2,6-dimethylphenyl)ethylenediamine.—A suspension of 2,6-dimethylformanilide (25.0 g., 0.17 mole) and potassium carbonate (25 g.) in methyl ethyl ketone was stirred and refluxed for 1 hr. Chloroacetonitrile (13.3 g., 0.18 mole) was then added and the mixture refluxed for 4 hr. The mixture was cooled, filtered, and the solid washed with ethyl methyl ketone. The combined filtrates were concentrated *in vacuo* leaving an oil containing some solid. The solid was removed by filtration using a little benzene, and the filtrate was concentrated, yielding N-cyanomethyl-N-formyl-2,6-dimethylaniline as a brown oil. The oil (14.8 g., approx. 0.077 mole) was reduced directly with lithium aluminum hydride (6.28 g., 0.16 mole) in ether in the usual way followed by fractionation yielding 7.0 g. of product.

N-Ethyl-N-(2,6-dimethylphenyl)ethylenediamine.—2,6-Dimethylacetanilide (50 g., 0.1 mole) was dissolved in dry dimethylformamide (350 ml.). The mixture was stirred under nitrogen while sodium hydride (13.6 g., 0.31 mole) of 54% dispersion in paraffin oil was added portionwise, the temperature being maintained below 40° with the aid of a cold water bath. After addition, the reaction mixture was maintained at 40° for 2 hr. and then cooled during the addition of chloroacetonitrile (24 g., 0.32 mole). The mixture was allowed to stand overnight

at room temperature and filtered. The filtrate was concentrated *in vacuo* and the residue was dissolved in chloroform and washed with water. The dried chloroform solution was concentrated *in vacuo* and the residue was refluxed with dry ether (200 ml.) for 2 hr. Unreacted 2,6-dimethylacetanilide (14.2 g.) was removed by filtration and the filtrate was cooled and reacted with lithium aluminum hydride (15.2 g., 0.39 mole) in ether, in the normal manner. The crude amine was purified by acid extraction and basification of the acid extracts with sodium hydroxide, followed by extraction with ether. The ether extracts were dried over potassium carbonate, and concentrated, and the product was distilled; yield, 19.3 g. Attempts to make 2,6-dimethylacetanilide react with chloroacetonitrile under the conditions used for the alkylation of the formanilide derivative were unsuccessful.

(N-Methyl-N-cycloheptyl)acetonitrile.—N-Methylcycloheptylamine²² (15.0 g., 0.13 mole), prepared from cycloheptanone and ethanolic methylamine by reductive alkylation²³ using platinum oxide in ethanol, was alkylated with chloroacetonitrile (10.7 g., 0.14 mole) in toluene, in the presence of anhydrous potassium carbonate (36.2 g.). The nitrile (14.3 g.), b.p. 74-77° (0.4 mm.), n_D^{20} 1.4789, was isolated by fractionation.

(N-Methyl-N-cycloheptyl)ethylenediamine.—(N-Methyl-N-cycloheptyl)acetonitrile (10.0 g., 0.06 mole) was reduced with lithium aluminum hydride (2.7 g., 0.07 mole) in ether in the usual way, yielding the diamine (7.9 g.).

(N-Methyl-N-cyclooctyl)acetonitrile.—N-Methylcyclooctylamine²⁴ (17.0 g., 0.12 mole) was alkylated with chloroacetonitrile (10.0 g., 0.13 mole) in toluene yielding the nitrile (16.3 g.), b.p. 100-102° (0.1 mm.), n_D^{20} 1.4858.

(N-Methyl-N-cyclooctyl)ethylenediamine.—(N-Methyl-N-cyclooctyl)acetonitrile (16.3 g., 0.09 mole) was reduced with lithium aluminum hydride (3.9 g., 0.10 mole) in ether in the usual way, yielding the diamine (12.8 g.).

2-(Octahydroisoindolyl)acetonitrile.—Octahydroisoindole^{25, 26} (11.6 g., 0.09 mole) was alkylated with chloroacetonitrile (8.0 g., 0.11 mole) in toluene, yielding the nitrile (7.5 g.), b.p. 132-135° (14 mm.), n_D^{20} 1.4881.

2-(Octahydroisoindolyl)ethylamine.—Reduction of the foregoing nitrile (7.0 g., 0.04 mole) with lithium aluminum hydride (1.94 g., 0.05 mole) in ether, followed by fractionation yielded 2-(octahydroisoindolyl)ethylamine (5.0 g.).

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(25) (a) L. M. Rice and C. H. Crogan, *J. Org. Chem.*, **20**, 1687 (1944); (b) A. Dumet, R. Ratouis, P. Cadine, and A. Wilhelmot, *Bull. Soc. Chim. France*, 906 (1956).

Guanidine Sulfates.—The following example is illustrative of the general method used to prepare the guanidine sulfates listed in Tables III and V.

2-(2,6-Xylyloxy)ethylguanidine Sulfate.—2-Methyl-2-thiopseudourea sulfate (157.7 g., 1.21 moles) was dissolved in water (300 ml.) and 2-(2,6-xylyloxy)ethylamine (200 g., 1.21 moles) was added. A vigorous reaction occurred, accompanied by the formation of methyl mercaptan (trapped in a cooled mixture of aqueous sodium hydroxide and hydrogen peroxide.). The aqueous solution was boiled for 2 hr. and then cooled. The solid which separated was filtered, washed with ice-cold water and dried. Two recrystallizations from methanol-isopropyl alcohol followed by drying *in vacuo* at 125° for 6 hr., yielded 195 g. of pure anhydrous salt, m.p. 234–236°.

2-[2-(2,6-Xylyloxy)ethyl]amino-4,5-dihydroimidazole Hydroiodide.—2-(2,6-Xylyloxy)ethylamine (15.0 g., 0.091 mole) was added to a solution of 2-methylmercapto-4,5-dihydroimidazole hydroiodide²⁶ (22.2 g., 0.091 mole) in ethanol (100 ml.). The solution was heated under reflux for 2 hr., the evolution of methyl mercaptan being completed during this time. After cooling, the solution was concentrated to low bulk and left at –10° for 48 hr. The crystals deposited (16.1 g.) were recrystallized twice from isopropyl alcohol-ether, affording 11.6 g. of product, m.p. 116–119°.

N-[2-(2,6-Xylyloxy)ethyl]-N',N''-diphenylguanidine Hydrochloride.—2-(2,6-Xylyloxy)ethylamine (3.8 g., 0.023 mole) was added to a solution of N,N'-diphenyl-S-methylisothiourea²⁷ (5.5 g., 0.023 mole) in xylene (30 ml.). The mixture was heated under reflux for 24 hr. and then evaporated to dryness *in vacuo*. The residue crystallized slowly at 0° and was finally recrystallized from petroleum ether (60–80°) affording 3.6 g. of material, m.p. 90–94°.

The hydrochloride was prepared using isopropyl alcoholic hydrogen chloride and was recrystallized from isopropyl alcohol-ether, m.p. 163–166°.

N-[2-(2,6-Xylyloxy)ethyl]-N'-benzoylguanidine. A.—2-(2,6-Xylyloxy)ethylamine (8.5 g., 0.052 mole) was added to a solution of N-benzoyl-S-methylisothiourea²⁸ (10.0 g., 0.052 mole) in chlorobenzene (100 ml.). The solution was heated under reflux for 24 hr. and concentrated to an oil which gradually crystallized. Recrystallization from aqueous ethanol followed by recrystallization from benzene-petroleum ether afforded 7.5 g. of the guanidine, m.p. 111–114°.

Anal. Calcd. for C₁₃H₂₁N₃O₄: C, 69.42; H, 6.80; N, 13.49. Found: C, 69.26; H, 6.91; N, 13.34.

The hydrochloride was prepared using isopropyl alcoholic hydrogen chloride, and was recrystallized from isopropyl alcohol-ether, m.p. 162–164°.

(26) S. R. Aspinall and E. J. Bianco, *J. Am. Chem. Soc.*, **73**, 602 (1951).

(27) W. Will, *Ber.*, **14**, 1489 (1881).

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B.—2-(2,6-Xylyloxy)ethylguanidine sulfate (20.0 g., 0.04 mole) was suspended in ethanol (500 ml.) and an ethanolic solution of sodium ethoxide, prepared from 1.8 g. of sodium, was added with stirring. The mixture was stirred for 1 hr., filtered, and then concentrated *in vacuo* to yield the free base, 2-(2,6-xylyloxy)ethylguanidine (17.0 g.) as a viscous yellow oil. Ethyl benzoate (13.0 g., 0.085 mole) was added and the mixture heated on the steam bath for 45 min. The product was dissolved in benzene, filtered, and diluted with petroleum ether (60–80°), yielding the crude monobenzoyl derivative which was recrystallized twice from aqueous ethanol, finally affording 2.8 g., m.p. 113.5–115.5°. The melting point was undepressed on admixture with a sample from the first preparation and identical infrared and ultraviolet spectra (λ_{\max} 262 m μ (ϵ_{\max} 27,673)) were obtained.

N-[2-(2,6-Xylyloxy)ethyl]-N',N''-dibenzylguanidine. A.—2-(2,6-Xylyloxy)ethylamine (3.3 g., 0.02 mole) was added to a solution of N,N'-dibenzoyl-S-methylisothiourea²⁸ (6.0 g., 0.02 mole) in xylene (20 ml.). The solution was heated under reflux for 8 hr. and then cooled. Crystals were deposited which were filtered and recrystallized from benzene-petroleum ether (60–80°) affording 5.1 g. of product, m.p. 147–148°.

B.—2-(2,6-Xylyloxy)ethylguanidine sulfate (10.0 g., 0.02 mole) was suspended in 20 ml. of 10% sodium hydroxide solution and then rapidly stirred during the addition of 5.5 g. (0.04 mole) of benzoyl chloride. Stirring was continued for 1 hr. and the solid formed was recrystallized from ethanol followed by further recrystallization from benzene-petroleum ether (60–80°), finally affording 2.9 g. of the product, m.p. 147–149°. The melting point was undepressed on admixture with a sample from the previous experiment and identical infrared and ultraviolet (λ_{\max} 253 m μ (ϵ_{\max} 31,033), 277 m μ (ϵ_{\max} 26,272)) spectra were obtained.

In a previous experiment in which an excess of sodium hydroxide was used, the major product from the Schotten-Baumann reaction was the benzoate salt of 2-(2,6-xylyloxy)ethylguanidine, m.p. 147–148°.

Anal. Calcd. for C₁₇H₁₇N₃O·C₆H₅COOH: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.4; H, 6.77; N, 12.65.

An authentic sample of 2-(2,6-xylyloxy)ethylguanidine benzoate which was prepared from 2-(2,6-xylyloxy)ethylguanidine free base (made from sulfate and sodium ethoxide in ethanol) and benzoic acid, had m.p. 148–149°. There was no depression of melting point on admixture of these samples and infrared and ultraviolet (λ_{\max} 262 m μ (ϵ_{\max} 22,673)) spectra were identical.

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Benzo[b]thiophene Derivatives. IV.¹ The Preparation and Pharmacological Activity of Compounds Related to Serotonin and Gramine

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A number of derivatives of benzo[b]thiophene related to serotonin and gramine have been prepared and tested for pharmacological activity on a variety of smooth muscle preparations and on intact animals. Antihistamine, antiacetylcholine, antiserotonin, and in some cases spasmogenic properties have been demonstrated. The replacement of the indole ring system by the benzo[b]thiophene system in the compounds studied leads to a reduction in agonistic activity and to the emergence of variable nonspecific antagonistic properties to serotonin, acetylcholine, and histamine.

The application of the concept of bioisosterism to the preparation of pharmacologically active substances, which antagonize or mimic the active parent com-

pounds, has proved fruitful in several fields of pharmacological endeavor.² While the isosteric replacement

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(2) H. L. Friedman in "Influence of Isosteric Replacements upon Biological Activity," Symposium on Chemical-Biological Correlation, Natl. Acad. Sci., Natl. Research Council, Publication No. 206, Washington, D. C., 1951, p. 295.