from water (with charcoal treatment); yield, 0.3 g., m.p. 239–240° dec.

Anal. Calcd. for $C_7H_8ClN_3O_3$: C, 38.63; H, 3.71; Cl, 16.29; N, 19.31. Found: C, 38.47; H, 3.67; Cl, 16.33; N, 19.13.

N-(1H-2-Oxo-5-bromo-4-pyrimidinyl)-D,L-alanine (IVh).—The mixture of IVb (D,L-form, 1.0 g.) and N-bromosuccinimide (1.1 g.) in acetic acid (30 ml.) was kept for 20 min. at 80–100° and treated as above. The product (1.0 g.) was recrystallized from water (0.85 g.), m.p. 225–227° dec.

Anal. Calcd. for $C_7H_8BrN_3O_3$: C, 32.08; H, 3.08; Br, 30.49; N, 16.03. Found: C, 32.00; H, 3.19; Br, 30.43; N, 15.85.

1-(β-D-Ribofuranosyl)-4-methylthio-2-pyrimidinone (XIa).—2',3',5'-Tri-O-benzoyl-4-thiouridine[13] (X, R = OBz, R_2 = H, 11.5 g.) was dissolved in *N* sodium hydroxide (60 ml.), water (40 ml.), and ethanol (100 ml.) and stirred for 1 hr. Methyl iodide (14.2 g.) and more *N* sodium hydroxide (20 ml.) were added, and the mixture stirred for 30 min. After neutralization with acetic acid, the solution was evaporated *in vacuo*, and the residue dissolved in ethanol. The insoluble material was removed by filtration and discarded, and the filtrate concentrated to a sirup. This sirup was treated with ethanol and the solids which formed were discarded. The filtrate was again concentrated to a sirup and the treatment with alcohol was repeated. The final filtrate was concentrated to a sirup and triturated repeatedly with acetone. The acetone-insoluble sirup (4.5 g., crude XIa) was used in the following reactions.

N-(1-β-D-Ribofuranosyl-2-oxo-4-pyrimidinyl)-L-phenylalanine (XIIa).—The solution of XIa (2.7 g.), L-phenylalanine (2.0 g.), and sodium carbonate (0.56 g.) in water (12.5 ml.) was refluxed for 15 hr. After acidification with acetic acid, the solution was concentrated *in vacuo* and the residue dissolved in ethanol. The insoluble material was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in water, adjusted to pH 7.5, and applied to a column (Dowex I, formate, 2.5 × 16 cm. long). The column was washed with water which removed uridine and unchanged XIa. Formic acid (0.2 *M*) was used for elution. The eluate was collected in 100-ml. fractions. The ultraviolet absorbing fractions (measured at 290 mμ) containing product were combined and evaporated to dryness *in vacuo*, and the residue was dissolved in ethanol from which crystals were obtained (1.2 g.), m.p. 165–170° slow dec.

Anal. Calcd. for $C_{18}H_{21}N_3O_7 \cdot 1.5H_2O$: C, 51.67; H, 5.77; N, 10.04. Found: C, 51.90; H, 5.74; N, 10.26.

N-(1-β-D-Ribofuranosyl-2-oxo-4-pyrimidinyl)-L-tryptophan (XIIb).—The solution of XIa (3.2 g.), L-tryptophan (2.05 g.), and sodium carbonate (0.56 g.) in water (15 ml.) was refluxed for 6 hr. The solution was diluted with water, adjusted to pH 9, and applied to a column (Dowex I, formate, 2.5 × 16 cm.). After washing the column with water, the product was eluted with *N* formic acid. The combined eluate was evaporated *in vacuo* to a sirup which was treated with ether to remove formic acid. The residue was taken up in a small amount of water from which the precipitate separated (yield 2.0 g.) and recrystallized from water, m.p. 176–178° dec.

Anal. Calcd. for $C_{20}H_{22}N_4O_7 \cdot H_2O$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.37; H, 5.22; N, 12.36.

N-(1-β-D-Ribofuranosyl-2-oxo-4-pyrimidinyl)-p-aminobenzoic Acid (XIII).—A mixture of XIa (5 g.), *p*-aminobenzoic acid (4.1 g.), and sodium carbonate (1.6 g.) in water (30 ml.) was refluxed for 3.5 hr. The solution was acidified with formic acid and the precipitate (*p*-aminobenzoic acid) was removed. Extensive hydrolysis of XIa to uridine was observed. The solution was adjusted to pH 9, applied to a column (Dowex I, formate 2.5 × 16 cm.), washed with water and 0.1 *N* formic acid, and eluted with *N* formic acid. The combined fractions containing the product were evaporated to a sirup and washed with ether. An amorphous solid was obtained from the residue which could not be crystallized; yield 1.4 g., m.p. 156–165° dec.

Anal. Calcd. for $C_{16}H_{17}N_3O_7$: C, 52.88; H, 4.72; N, 11.57. Found: C, 52,48; H, 4.75; N, 11.25.

1-(2-Deoxy-β-D-ribofuranosyl)-4-methylthio-5-methyl-2-pyrimidinone (XIb).—Compound X (R_2 = Me, R = H, 9.32 g.)[13] in *N* sodium hydroxide (40 ml.), ethanol (100 ml.), and water (70 ml.) was stirred for 1 hr. Methyl iodide (12 g.) and more *N* sodium hydroxide (20 ml.) were added and the mixture stirred for 30 min. After storage in the refrigerator overnight, needles separated and were collected. The filtrate was concentrated to a sirup and the sirup triturated with water from which additional needle crystals were obtained; total yield 4.9 g. (90%). One recrystallization from water afforded pure material, m.p. 176–178°.

Anal. Calcd. for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29; S, 11.78. Found: C, 48.49; H, 5.64; N, 10.22; S, 11.99.

N-[1-(2-Deoxy-β-D-ribofuranosyl)-5-fluoro-2-oxo-4-pyrimidinyl]-L-alanine (XIIc).—4-Thio-5-fluoro-2'-deoxyuridine (1.2 g.)[2] in *N* sodium hydroxide (6 ml.), water (20 ml.), and methyl iodide (1.5 g.) were stirred for 20 min. The solution was neutralized and evaporated to dryness. The residue was taken up in water (15 ml.), L-alanine (1 g.) and sodium carbonate (0.58 g.) were added, and the solution was refluxed for 2 hr. The reaction solution was applied to a column (Dowex I, formate, 2.5 × 16 cm.), washed with water, and eluted with 0.1 *N* formic acid. The fractions containing the product were combined and concentrated to a sirup, washed with ether, and the resulting crystalline residue was recrystallized from water; yield 0.7 g., m.p. 151–152° dec., $[\alpha]^{20}D$ −40° (*c* 0.54, *N* HCl).

Anal. Calcd. for $C_{12}H_{16}FN_3O_6$: C, 45.43; H, 5.08; F, 5.99; N, 13.24. Found: C, 45.14; H, 5.52; F, 6.16; N, 13.11.

Acknowledgments.—The authors wish to thank the Hoffmann-La Roche, Inc., Nutley, N. J., for the 5-fluorouracil and 5-fluoro-2'-deoxyuridine, and Miss Iris Wempen of this Institute for the 4-thio-5-fluoro-2'-deoxyuridine used in this study. The authors are indebted to Dr. George B. Brown of this Institute for helpful suggestions and continued interest.

Imidazolidines. III.[1a] 2-Substituted 1,3-Bis-(*o*-hydroxybenzyl)-imidazolidines[1b]

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N,N'-Bis-(*o*-hydroxybenzyl)-ethylenediamine (I) undergoes an equimolecular condensation with aldehydes and aqueous formaldehyde in alcohol solution to form imidazolidine derivatives. In contrast, paraformaldehyde reacts with I in benzene to form 1,2-bis-[3-(3,4-dihydro-1,3,2H-benzoxazino)]-ethane. Acetone forms a stable imidazolidine derivative of I. Reactions of I with other ketones are discussed. None of the compounds showed appreciable antibacterial, antifungal, or antiviral activity.

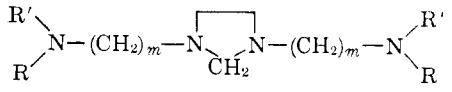
Our interest to investigate the condensation reactions of N,N'-bis-(*o*-hydroxybenzyl)-ethylenediamine (I) was essentially twofold. Other similarly substituted ethylenediamines, N,N'-bis-(*p*-methoxybenzyl)-,[2] N,N'-bis-

(1) (a) J. H. Billman, J. Y. C. Ho, and L. R. Caswell, *J. Org. Chem.*, **22**, 538 (1957). (b) Dow Research Fellow, 1959–1960. Taken from the Ph.D. thesis of L.C.D., Indiana University, 1961.

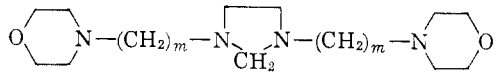
(2) (a) J. H. Billman, J. Y. C. Ho, and L. R. Caswell, *J. Org. Chem.*, **17**, 1375 (1952); (b) L. Veibel and I. B. Anderson, *Anal. Chim. Acta*, **15**, 15 (1956).

(*p*-chlorobenzyl)-,[1a] and N,N′-bis-(phenyl)-ethylenediamine,[3] have been found to be specific reagents for the detection and characterization of aldehydes as their corresponding solid imidazolidine derivatives. Of these, N,N′-bis-(*p*-methoxybenzyl)-ethylenediamine was the only one that formed a stable derivative with a ketone (acetone.)[2a,4] From this standpoint, it was of interest to determine the applicability of N,N′-bis-(*o*-hydroxybenzyl)-ethylenediamine as an aldehyde reagent and its reactivity toward ketones.

Since 1,3-disubstituted imidazolidines of the general structures II[5] and III[6] have been found to possess antifungal, antiviral, and antibacterial properties, it was of



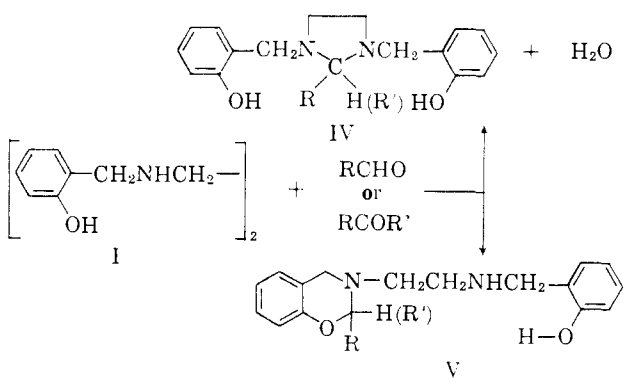
II



III

interest to determine if 1,2,3-trisubstituted imidazolidine derivatives of N,N′-bis-(*o*-hydroxybenzyl)-ethylenediamine would also possess similar antimicrobial properties.

A variety of aldehydes, aqueous formaldehyde, and acetone were found to condense equimolecularly with N,N′-bis-(*o*-hydroxybenzyl)-ethylenediamine (I) in alcohol solution to form solid derivatives in yields ranging from 41–91%. Although the imidazolidine structure IV was originally anticipated, it was also conceivable that derivatives might be 3,4-dihydro-1,3,2H-benzoxazines (V). In order to determine with certainty which product was formed, a study of the derivatives was made. First of all the condensation products were hydrolyzed with dilute mineral acids. Regeneration

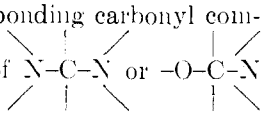


IV

I

V

R = H (aq.), alkyl
R′ = CH_3 (when R = CH_3)

of the diamine I and the corresponding carbonyl compound confirmed the presence of  or linkages as found in IV and V, respectively. It was hoped that differentiation of the two proposed structures might be accomplished by chemical conversions. Presumably, if the condensation products were imidazolidines of structure IV, then methylation of the phenolic functions should have given the same compound as would have been obtained from N,N′-bis-(*o*-methoxybenzyl)-ethylenediamine and the corresponding carbonyl compound. Attempts to methylate the condensation products were unsuccessful. However, some chemical evidence was found in support of the imidazolidines structure IV. *p*-Dimethylaminobenzaldehyde failed to condense with N-(*o*-hydroxybenzyl)-phenethylamine (VI) as it did with I under comparable reaction conditions. Also, even when identical experimental conditions were used with excess quantities of carbonyl compound and extended reaction times, the same derivatives with I were obtained as when equimolar quantities were employed. Presumably, benzoxazine of structure V would have reacted with a second mole of aldehyde to form a bisbenzoxazine.

Attention was next directed to the use of infrared spectroscopy in conjunction with a model compound. The use of infrared in the absence of a model compound was not feasible since both hypothetical structures, IV and V, have OH and/or NH functions which may be indistinguishable in the infrared. In the present study, it was possible to identify the N-H absorption band in N-alkyl substituted *o*-hydroxybenzylamine-type compounds (provided there were no other OH or NH functions elsewhere in the molecule). The model compound selected was N-(*o*-hydroxybenzyl)-phenethylamine, *o*-$HOC_6H_4CH_2NH(CH_2)_2C_6H_5$ (VI). When the infrared spectra of N,N′-bis-(*o*-hydroxybenzyl)-ethylenediamine (I), N,N′-bis-(*o*-methoxybenzyl)-ethylenediamine (VII), and the model compound VI were compared, all three compounds showed a distinct absorption band in the region of 2.9–3.05 μ. Since N,N′-bis-(*o*-methoxybenzyl)-ethylenediamine, (*o*-$CH_3OC_6H_4CH_2NHCH_2)_2$ (VII) has no OH function, this absorption band could be assigned to the N-H function which is present in all three compounds. The O-H absorption of I and VI were apparently shifted to higher wavelengths in or near the C-H absorption region and no definite assignment of this band was attempted.

The infrared spectra of the condensation products in question showed a broad absorption band beginning at 2.8 μ and extending throughout the C-H absorption region, λ_{max} *ca.* 3.5 μ. These spectra failed to show a discrete absorption band at 2.9 μ thereby showing that these molecules did not possess an N-substituted *o*-hydroxybenzylamine grouping as a part of their structure, and therefore, were not 3,4-dihydro-1,3,2H-benzoxazines (V). These spectra were, however, consistent with the alternate imidazolidine structure IV, the phenolic groups being responsible for that portion of the broad absorption band occurring in the O-H absorption region. This analysis was not applicable for the phenolic aldehyde derivatives of N,N′-bis-(*o*-hydroxybenzyl)-ethylenediamine. However, it was reasonable to assume that these aldehydes reacted in the same manner as other aromatic aldehydes since reaction conditions were essentially the same. The imidazolidine derivatives are summarized in Table I.

(3) H. W. Wanzel and W. Löchel, *Chem. Ber.*, **86**, 1463 (1953).

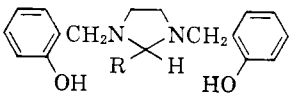
(4) 1,2-Bis-(benzyl)-ethylenediamine will react with acetone, but the scope of this reaction with other ketones was not established: W. F. Minor, D. A. Johnson, and L. C. Cheney, *J. Org. Chem.*, **21**, 528 (1956).

(5) J. O. Van Hook and W. E. Craig, U. S. Patent 2,675,387 (1954); *Chem. Abstr.*, **49**, 4729*b* (1955).

(6) W. E. Craig and J. O. Van Hook, U. S. Patent 2,675,381 (1954); *Chem. Abstr.*, **50**, 411*d* (1956).

TABLE I

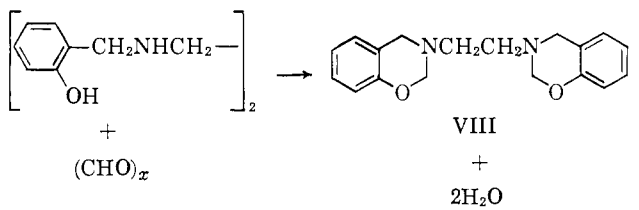
1,3-BIS-(*o*-HYDROXYBENZYL)-IMIDAZOLIDINES IV



R	M.p., °C.	Purified product % Yield	Formula	% Nitrogen Calcd.	% Nitrogen Found
3-Methoxy-4-hydroxyphenyl	151.2–152.5	71	$C_{24}H_{26}N_2O_4$	6.89	7.19
3,4-Methylenedioxyphenyl	131–132	74	$C_{24}H_{24}N_2O_4$	6.93	6.80
p-Methoxyphenyl	151–151.5[a]	72	$C_{24}H_{26}N_2O_3$	7.18	7.00
p-Nitrophenyl	143–144.5	64	$C_{23}H_{23}N_3O_4$	10.37	10.27
3,4-Dimethoxyphenyl	151.5–152.5	76	$C_{25}H_{28}N_2O_4$	6.66	6.91
p-Hydroxyphenyl	155–157.5	43	$C_{23}H_{24}N_2O_3$	7.45	7.26
H	110.5–111	92[b]	$C_{17}H_{20}N_2O_2$	9.85	9.49[c]
o-Hydroxyphenyl	149–150.5 dec.	60	$C_{29}H_{24}N_2O_3$	7.45	7.49
2-Phenylethenyl	131.5–132.5[a]	58	$C_{25}H_{26}N_2O_3$	7.31	7.26
p-Dimethylaminophenyl	152.3–152.5	73	$C_{25}H_{29}N_3O_2$	10.40	10.26
2-Propyl	107.5–108.5	78	$C_{20}H_{26}H_2O_2$	8.58	8.67
3-Furyl	166–168 dec.	91	$C_{21}H_{22}N_2O_3$	7.99	7.99
m-Hydroxyphenyl	165–167 dec.	67	$C_{23}H_{24}N_2O_3$	7.45	7.36
Phenyl	169–170	90	$C_{23}H_{24}N_2O_2$	7.77	7.99

[a] Purified material melted lower than crude product. [b] Per cent recovery from methanol. [c] Calcd.: C, 71.82; H, 7.09. Found: C, 71.46; H, 7.33.

Unlike aqueous formaldehyde and other aldehydes, paraformaldehyde underwent a bimolecular condensation with N,N′-bis-(*o*-hydroxybenzyl)-ethylenediamine in benzene to form 1,2-bis-[3-(3,4-dihydro-1,3,2H-benzoxazino)]-ethane (VIII) in a 46% yield. The structure of this derivative was based on its elemental analysis, its infrared and ultraviolet spectra, and its



acid hydrolysis products. This derivative possessed no NH or OH absorption in the infrared and its ultraviolet spectrum was similar to that of homologous methylene-bis-(3,4-dihydro-1,3,2H-benzoxazine), which is the condensation product of aqueous formaldehyde and *o*-hydroxybenzylamine,[7] both having λ_{max} 275 mμ (log ε 3.7). When VIII was hydrolyzed with dilute sulfuric acid the regenerated formaldehyde was recovered (as its methone derivative) in 88% yield, along with N,N′-bis-(*o*-hydroxybenzyl)-ethylenediamine in 85% yield based on the assigned structure VIII.

N,N′-Bis-(*o*-hydroxybenzyl)-ethylenediamine (I) reacted with pure acetone or with acetone in ethanol to form a stable imidazolidine in high yield. Methyl ethyl ketone, acetophenone, and benzophenone failed to condense under similar conditions. Cyclohexanone forms a solid derivative in methanol and in benzene under water removal conditions. However, the material could not be purified by recrystallization from several solvents or solvent mixtures. The imidazolidine derivative of methyl ethyl ketone was prepared by refluxing I with the preceding ketone for 5 hr. Attempted recrystallization of this derivative from 95% alcohol resulted in complete hydrolysis; however, purification was achieved by recrystallization from methyl ethyl ketone.

(7) F. W. Holly and A. C. Cope, *J. Am. Chem. Soc.*, **66**, 1875 (1944).

Construction of molecular models of actual and hypothetical ketone imidazolidine derivatives of I disclosed considerable steric interactions between the benzyl groups situated in the 1- and 3-positions and the substituents in the 2-position. These steric interactions increase on going from the acetone condensation product (2,2-dimethyl derivative) to those of higher ketones. As a consequence, the ketone derivatives of I probably have higher energies which may be related to some of the difficulties of preparation and purification.

In view of the anomalous reaction of N,N′-bis-(*o*-hydroxybenzyl)-ethylenediamine with paraformaldehyde and its facile condensation reaction with acetone, this diamine reagent does not appear to be as practical or as specific an aldehyde reagent as some previously studied diamines.[1a,2,3]

Table III summarizes the bacteriostatic and fungistatic activities of the compounds tested. None of the compounds showed appreciable activity as antibacterial, antifungal, or antiviral agents.

The compounds in Table II were tested in tissue culture systems (roller tube) against the viruses indicated. None showed any protective activity at concentrations up to the levels where host cell toxicity was encountered.

Experimental

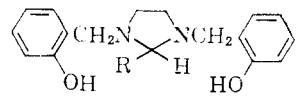
Melting points were taken in open capillaries and are corrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Infracord as potassium bromide disks. Microanalyses were performed by Miss J. Dickey of the Chemistry Department of Indiana University and/or Midwest Microlab, Inc., Indianapolis, Indiana.

Materials. (A) **Aldehydes.**—Either reagent grades of aldehydes were used or they were purified by distillation or by recrystallization from appropriate solvents. Exceptions were veratraldehyde and cinnamaldehyde for which practical grades were used.

(B) **Ketones.**—Acetone and methyl ethyl ketone were purified by distilling from potassium permanganate, drying with anhydrous potassium carbonate, and redistilling, b.p. 56° and 78.5–79°, respectively. Commercial grades of other ketones were used.

TABLE II

SUMMARY OF ANTIVIRAL ACTIVITY



R	Inactive in TC Test[a]
3-Methoxy-4-hydroxyphenyl	1, 2, 3, 4
3,4-Methylenedioxyphenyl	1, 2, 3, 4
4-Nitrophenyl	1, 2, 3, 4
3,4-Dimethoxyphenyl	1, 2, 3
2-Phenylethenyl	1, 2, 3
2-Furyl	1, 2, 3, 4
3-Hydroxyphenyl	1, 2, 3, 4

[a] Virus and all combinations used: (1) Adenovirus 4, HeLa; (2) Herpes simplex, HeLa; (3) Mumps, HeLa; (4) Influenza PR8, dog kidney.

purified by successive recrystallization from 50% isopropanol and petroleum ether (b.p. 40–60°), m.p. 59–60°.

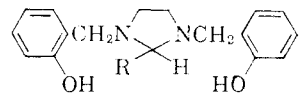
Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.96; H, 8.05; N, 9.32. Found: C, 72.44; H, 8.23; N, 9.42.

N-(*o*-Hydroxybenzyl)-phenethylamine (VI).—N-(*o*-Hydroxybenzylidene)-phenethylamine was prepared in a 90% yield from salicylaldehyde and phenethylamine following a procedure similar to that of Shepard and Tickner[9]; lemon yellow crystals, m.p. 42–43° (from ethanol) (lit.[9] m.p. 45.5°).

The Schiff's base was reduced in the same manner as described in the preceding experiment. After removal of the catalyst, the reaction mixture was acidified and concentrated. N-(*o*-Hydroxybenzyl)-phenethylamine was then precipitated with 15% sodium hydroxide as an oil which solidified on cooling. The yield of crude product was quantitative, light tan solid, m.p. 47–49°. Recrystallization from dilute methanol (Darco) provided light tan plates, m.p. 51–52°. The hydrochloride salt was precipitated from ether solution,[9] m.p. 129–130° (lit.[9] m.p. 130°).

TABLE III

SUMMARY OF BACTERIOSTATIC AND FUNGISTATIC ACTIVITIES BY AGAR DIFFUSION METHOD *in vitro* ANTIBACTERIAL[a]/ANTIFUNGAL



Zone size in mm.[b]

R	Concn. mg./ml.	*Pseudomonas aeruginosa*	*Escherichia coli*	*Proteus vulgaris*	*Staphylococcus aureus*	*Diplococcus pneumoniae*	*Klebsiella pneumoniae*	*Trichosporon mentagrophytes*	*Candida albicans*
3-Methoxy-4-hydroxyphenyl	20	0	(22)	0	0	15	(16)	18	0
3,4-Methylenedioxyphenyl	20	0	0	0	0	0	0	(21)	0
p-Methoxyphenyl	20	0	(18)	0	0	(24)	(14)	(20)	0
	2	0	0	0	0	(21)	(14)	0	0
	0.4	0	0	0	0	(17)	(14)	0	0
p-Nitrophenyl	20	0	0	0	0	13	0	15	0
3,4-Dimethoxyphenyl	20	0	(19)	(18)	16	17	11	18	0
p-Hydroxyphenyl	20	0	0	0	0	25	11	22	0
	2	0	0	0	0	15	(14)	0	0
o-Hydroxyphenyl	20	13	0	0	0	20	(17)	(21)	0
	2	0	0	0	0	17	0	0	0
2-Phenylethenyl	20	0	(21)	0	0	18	(15)	35	14
p-Dimethylaminophenyl	20	0	0	0	0	(19)	(11)	(18)	0
2-Furyl	20	0	0	0	0	0	0	0	0
For comparison, chloramphenicol shows the following zones	20	21	30	31	28	42	46		
	2	14	24	21	22	35	34		
	0.4	0	0	15	(16)	23	24		

[a] Parentheses ( ) indicate zone of partial inhibition.

(C) **Amine Reagents.**—N,N'-Bis-(*o*-hydroxybenzyl)-ethylenediamine was provided by the Dow Chemical Company. The other reagents were prepared as described later.

N,N'-Bis-(*o*-methoxybenzyl)-ethylenediamine (VII).—To a stirred refluxing solution of 30 g. (0.22) of *o*-methoxybenzaldehyde in 45 ml. of methanol was added a solution of 6.8 g. (0.11 mole) of 98% ethylenediamine over a period of 40 min. Successive concentrations of the reaction mixture, and subsequent cooling, provided crops of 10.2 and 4.1 g. of crude 1,2-bis-(*o*-methoxybenzylideneamino)-ethane. These when combined and recrystallized from methanol yielded 11.9 g. (37%), m.p. 114.5–115.2° (lit.[8] 115.5–116.5°).

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: N, 9.45. Found: N, 9.53.

A mixture of 11 g. (0.037 mole) of 1,2-bis-(*o*-methoxybenzylideneamino)-ethane, 1 g. of platinum oxide, and 70 ml. of absolute ethanol was reduced at room temperature in a low-pressure Parr hydrogenator. The catalyst was removed by filtration and the filtrate was treated with a solution of 11 ml. of concentrated hydrochloric acid in 60 ml. of ethanol. When the solution was cooled the N,N'-bis-(*o*-methoxybenzyl)-ethylenediamine dihydrochloride precipitated as white plates, yield 10.9 g. (79%), m.p. 179.5–182°. The free amine was recovered from its aqueous salt solution by precipitation with 10% sodium hydroxide and

Aldehyde Imidazolidine Derivatives IV of N,N'-Bis-(*o*-hydroxybenzyl)-ethylenediamine (I).—To a hot saturated solution of 6.0 g. (0.022 mole) of I in 75 ml. of methanol was added an equimolar quantity of the aromatic aldehyde (or aqueous formaldehyde) dissolved in a minimum amount of warm methanol (liquid aldehydes were added directly). The reaction mixture was refluxed for 1 hr. The derivatives of benzaldehyde and furfural precipitated shortly after refluxing was commenced; the derivatives crystallized on cooling to room temperature or after variable periods of time in a refrigerator and were purified by recrystallization from methanol or absolute ethanol.

The isobutyraldehyde derivative of I was prepared by slowly adding the aldehyde to a saturated solution of I in absolute ethanol at 55°. The product crystallized after concentration and subsequent cooling of the reaction mixture.

1,2-Bis-[3,-(3,4-dihydro-1,3,2H-benzoxazino)]-ethane (VIII).—To a hot saturated solution of 10 g. (0.037 mole) of N,N'-bis-(*o*-hydroxybenzyl)-ethylenediamine in 50 ml. of thiophene-free benzene was added 2.0 g. (0.067 mole) of paraformaldehyde and the reaction mixture was refluxed for 8 min., filtered while hot, and the filtrate evaporated. The resulting viscous residue solidified and was completely freed of solvent in a vacuum desic-

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(9) N. A. Shepard and A. A. Tickner, *ibid.*, **38**, 385 (1916).

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°).

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Potential Antihypertensive Agents. Some Guanidine Derivatives

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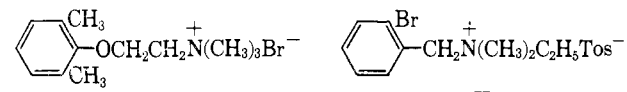
2-(2,6-Xylyloxy)ethylguanidine sulfate is a potent hypotensive agent which acts by blocking the sympathetic nervous system. Related compounds have been synthesized and structure–activity relationships in the series have been investigated.

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 bromide[2] (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 compound 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

$$(CH_2)_7NCH_2CH_2NHC(NH_2)=NH$$

III

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

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