Experimental

All melting points are corrected. Elemental microanalyses were performed at the microanalytical laboratory of the National Institutes of Health, Bethesda, Md., or at Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

1-Methyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboximide.—To 90.5 g. (0.5 mole) of 7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride was added 150 ml. of a saturated aqueous solution of ammonia. After the vigorous reaction had subsided, the mixture was stirred and heated until homogeneous. The water was boiled off and the residue heated at 160–180° for 2 hr. On cooling the mass solidified to give a quantitative yield of product melting at 160–162°. On recrystallization from chloroform–ligroin, it melted at 161–162°.

4-Methyl-4,7-epoxyhexahydroisoindoline.—1-Methyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboximide (60 g., 0.3 mole) was placed in a Soxhlet apparatus and extracted overnight into a stirred solution of 25 g. of lithium aluminum hydride in 1.5 l. of absolute ether. The addition complex was decomposed by slow dropwise addition of water, and the mixture was stirred 4 hr. The inorganic precipitate was filtered, pressed tightly on the filter, and washed with two 100-ml. portions of ether. The ethereal filtrate and washings were dried over anhydrous sodium sulfate and filtered. The ether was stripped and the residue was distilled to yield 26 g. (56%) of product, b.p. 123–125° (35 mm.), $n^{25}D$ 1.4926.

Anal. Calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.26; H, 9.73; N, 8.98.

The **hydrochloride** was formed by bubbling anhydrous hydrogen chloride gas through an ether solution of the base, m.p. 148.5–149.5°. On recrystallization from methanol–ether, it melted at 150–151°.

Anal. Calcd. for $C_9H_{16}ClNO$: Cl, 18.69. Found: Cl, 18.81.

4-Methyl-4,7-epoxy-2-(2-cyanoethyl)hexahydroisoindoline.—4-Methyl-4,7-epoxyhexahydroisoindoline (19 g., 0.125 mole) was refluxed with a large excess of acrylonitrile (0.5 mole) for 2 hr. and the excess acrylonitrile was distilled. The residual oil was distilled under reduced pressure to give 24.5 g., 93%, of the compound, b.p. 158–160° (6 mm.).

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.79; N, 13.58. Found: C, 68.92; H, 8.54; N, 13.31.

The **methiodide** was obtained as a tacky yellow material by refluxing the base with a 10% excess of methyl iodide in ethyl acetate and diluting with ether. Vacuum drying for several days at room temperature gave a solid material, m.p. 156–157°, which on recrystallization from methanol–ether and methylene chloride–ether, melted at 165–166°.

Anal. Calcd. for $C_{13}H_{21}INO$: I, 36.45. Found: I, 36.56.

4-Methyl-4,7-epoxy-2-(3-amidoximinopropyl)hexahydroisoindoline Dihydrochloride.—To a solution of 14 g. of hydroxylamine hydrochloride in 300 ml. of absolute ethanol was added 41.2 g. (0.2 mole) of 4-methyl-4,7-epoxy-2-(2-cyanoethyl)hexahydroisoindoline. When a homogeneous solution was obtained, a solution of 4.6 g. (0.2 mole) of sodium in 150 ml. of absolute ethanol was added with stirring. The mixture was refluxed 3 hr. and let stand overnight. The next day, the mixture was filtered and gaseous hydrogen chloride bubbled in until precipitation was complete. After adding an equal volume of ether, mixing, and allowing the precipitate to settle, the product was filtered, washed with cold ethanol, and dried. It melted at 162–164° and on recrystallization from alcohol–ether at 163–165°.

Anal. Calcd. for $C_{12}H_{23}Cl_2N_3O_2$: C, 46.15; H, 7.37; Cl, 22.71. Found: C, 45.88; H, 7.01; Cl, 23.32.

Hypotensives. VI.[1] Disubstituted Alkylenediamines and Related Compounds

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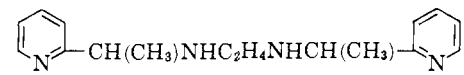
In an earlier report on studies of substituted alkylenediamines as diuretic agents we described a fleeting hypotensive action for some of the compounds.[3] These findings led directly to a related and orally effective adrenolytic agent, N,N′-bis[α-(2-pyridyl)ethyl]-ethylenediamine (I). The pharmacologic properties of



I

this material were the subject of a recent report by Halliday, *et al.*[4] Since compound I offered some promise, a structure–activity study was undertaken to determine the requirements for optimal activity. A few substituted alkylenediamines not closely related to the compounds discussed here are reported by Schusteritz, *et al.*,[5] and Short, *et al.*,[6] to possess adrenolytic or antihypertensive properties.

Compound I and most of the analogs reported here were prepared by condensing 2 equiv. of a carbonyl compound with an alkylenediamine to afford symmetrical Schiff bases. Catalytic reduction of the crude Schiff bases usually proceeded in good yield to the expected products, which were isolated by distillation. A similar method was utilized by Lacoste[7] to prepare VI (Table I) and by Szabo[8] for the synthesis of related alkylenediamines. All of the compounds listed in Table I except IV, VII, VIII, and XIII, were prepared in this manner and converted to the indicated salts. Compound IV was isolated and purified as a salt since the base was thermally unstable. Compound VII was generated by addition of ethylenediamine to 2-vinylpyridine under acid catalysis. Compound VIII resulted from the catalytic reduction over platinum of the commercially available azine[9] in acetic acid followed by isolation and purification as the diacetate. Catalytic reduction of I over rhodium-on-alumina in the presence of acid provided XIII.

Another group of allied materials is listed in Table II. Displacement reactions on 2-(α-bromoethyl)pyridine[10] with *t*-butylamine, piperidine, trimethylamine, ethylenediamine, and 1-(*o*-methoxyphenyl)piperazine gave XIV, XV, XVI, XVII, and XVIII, respectively. The possibility of dehydrobromination of 2-(α-bromoethyl)-pyridine to 2-vinylpyridine followed by amine addition to the corresponding 2-(β-aminoethyl)pyridine was investigated. Piperidine was condensed with 2-vinylpyridine to afford XIX which was not identical with XV. Reductive aminations with 2-acetylpyridine and the appropriate amines were tried but found less satisfactory as a preparative route to some of these materials

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(6) J. H. Short, W. L. Chan, M. Freifelder, D. G. Mikolasek, J. L. Schmidt, H. G. Schoepke, C. Shannon, and G. R. Stone, Abstracts of Papers, 144th National Meeting, American Chemical Society, Los Angeles, California, April, 1963, p. 10-L.

(7) R. G. Lacoste, Ph.D. Thesis, Clark University, Worcester, Mass., 1957.

(8) J. L. Szabo, D. Hill, and W. F. Bruce, U. S. Patents 2,627,491, 2,739,981, and 2,876,236.

(9) Aldrich Chemical Co., Milwaukee, Wis.

(10) B. H. Walker, *J. Org. Chem.*, **25**, 1047 (1960).

Table

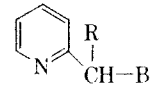
Symmetrical N,N′-Disubstituted Alkylenediamines,[a] A-Z-NH-Y-NH-Z-A

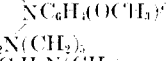
	A	Z	Y	Bases: B.p.,[c] °C. (mm.)	Bases: Formula	Bases: Calcd. N	Bases: Found N	Salts[b]: Acid	Salts: M.p., °C.	Salts: Yield, %[d]	Salts: Calcd., % C	Salts: Calcd., % H	Salts: Calcd., % N	Salts: Found, % C	Salts: Found, % H	Salts: Found, % N
I	2-Pyridyl	$CH(CH_3)$	C_2H_4	153–156 (0.25)	$C_{16}H_{22}N_4$	20.75	20.18	2 Fumaric	197–198	62	57.35	6.02	11.15	57.65	5.98	11.18
II	3-Pyridyl	$CH(CH_3)$	C_2H_4	176–180 (0.1)	$C_{16}H_{22}N_4$	20.75	20.52	2 Maleic	151–153	53	57.35	6.02		57.24	6.08	
III	4-Pyridyl	$CH(CH_3)$	C_2H_4	170–174 (0.05)	$C_{16}H_{22}N_4$	20.75	20.31	2 Maleic	145–147	63			11.15			11.01
IV	2-Pyrrolyl	CH_2	C_2H_4		$C_{12}H_{16}N_4$			2 HCl	315–320	14	49.48	6.92	19.24	49.37	7.04	19.09
V	2-Thienyl	$CH(CH_3)$	C_2H_4	143–150 (0.07)	$C_{14}H_{20}N_2S_2$	9.98	9.97	2 Maleic	155–156	21	S, 12.51		5.46	S, 12.21		5.56
VI	2-Pyridyl	CH_2	C_2H_4	151–158 (0.8)	$C_{14}H_{18}N_4$	23.12	23.02	2 Maleic	174–175	28	55.68	5.52	11.81	55.28	5.57	11.63
VII	2-Pyridyl	C_2H_4	C_2H_4	173–177 (0.2)	$C_{16}H_{22}N_4$	20.75	20.50	2 Maleic	172–173	13	57.35	6.02	11.15	57.46	6.11	11.22
VIII	2-Pyridyl	CH_2			$C_{12}H_{14}N_4$			2 CH_3CO_2H	124–126	15	57.47	6.63	16.76	57.68	6.86	16.75
IX	2-Pyridyl	$CH(CH_3)$	$(CH_2)_3$	165–168 (0.05)	$C_{19}H_{28}N_4$	17.93	17.20	2 Maleic	145–147	30	59.54	6.66	10.29	59.90	6.56	10.19
X	2-Pyridyl	$CH(CH_3)$	$CH_2CH(CH_3)$	140–145 (0.04)	$C_{17}H_{24}N_4$	19.70	19.71	2 Fumaric	151–153	16	57.85	6.29	10.85	58.13	6.24	11.02
XI	2-Pyridyl	$CH(CH_3)$	$(CHCH_3)_2$	160–163 (0.75)	$C_{18}H_{26}N_4$	18.74	18.47	2 Fumaric	172–174	9	58.93	6.46	10.56	58.85	6.46	10.48
XII	2-Pyridyl	$CH(CH_3)$	$CH(CH_2)_4CH$[c]	153–155 (0.005)	$C_{20}H_{28}N_4$	17.27	16.27	4 HCl	244–246	18	51.07	6.86	5.96	51.15	6.81	5.94
XIII	2-Piperidyl	$CH(CH_3)$	C_2H_4	140–143 (0.04)	$C_{16}H_{34}N_4$	19.83	19.13	4 Maleic	125–127	37	51.46	6.75	7.50	51.76	6.61	7.25

[a] All compounds listed except IV, VII, VIII, and XIII, were prepared by the method given in the Experimental section for compound I. [b] Salts were recrystallized from ethanol or ethanol-ether. [c] See ref. 14. [d] Over-all yield. [e] *trans*-1,2-Cyclohexylene. [f] See ref. 15.

Table II

2-(Aminoalkyl)pyridines



	B	R	Bases: B.p., °C./mm.	Bases: Formula	Bases: % N Calcd.	Bases: % N Found	Salts[a]: Acid	Salts: M.p., °C.[b]	Salts: Yield, %	Salts: Calcd., % C	Salts: Calcd., % H	Salts: Calcd., % N	Salts: Found, % C	Salts: Found, % H	Salts: Found, % N
XIV	$NHC(CH_3)_3$	CH_3	63–69 (0.03)	$C_{11}H_{18}N_2$	15.72	15.33	Maleic	124–125	28	61.20	7.53	9.52	61.16	7.60	9.37
XV	$N(CH_2)_5$	CH_3	84–90 (0.5)	$C_{12}H_{18}N_2$	14.72	14.60	Fumaric	142–145	48	62.73	7.24	9.15	62.80	7.18	9.07
XVI	$N(CH_3)_2$	CH_3		$C_9H_{14}N_2$			CH_3Br	189–191	58	Br, 32.60		11.43	Br, 32.87		11.39
XVII[c]	$NHC_2H_5NH_2$	CH_3	74–75 (0.07)	$C_9H_{12}N_2$	25.43	25.31	Fumaric	159–161	47	55.50	6.81	14.91	55.40	6.96	14.91
XVIII[d]		CH_3	168–175 (0.04)	$C_{18}H_{23}N_3O$	14.13	13.72	3 HCl	220–222	60	53.14	6.11	10.33	53.41	6.45	10.30
XIX	$CH_2N(CH_3)_2$	H	148–150 (17)	$C_{12}H_{18}N_2$	14.72	14.79	Fumaric	126–129	67	62.73	7.24	9.15	62.77	7.20	9.24
XX	$NHC_2H_4N(CH_3)_2$	CH_3	123–127 (0.14)	$C_{10}H_{25}N_3$	16.08	16.22	2 Maleic	138–141	25	58.40	7.14	8.51	58.55	7.19	8.42

[a] Salts were prepared and recrystallized from ethanol or ethanol-ether. [b] See ref. 14. [c] Over-all yield. [d] Prepared by the method described for XV. [e] Methobromide. [f] 4-(o-Methoxyphenyl)piperazine.

except in the case of 2-(octahydro-1-azocinyl)ethylamine which gave XX.

A preliminary report by Halliday and co-workers on structure–activity relationships for the compounds described here has already appeared.[11] These materials were evaluated for hypotensive action in the normotensive anesthetized dog and rat and for adrenolytic effectiveness in the dog. In addition to the two reports mentioned,[4,11] other and more detailed descriptions of biological activities can be found elsewhere.[12] Furthermore, a summary publication on structure–activity relationships and mechanism of action of the more potent compounds will appear.[13] These studies reveal that a *sym*-N,N′-bis(2-pyridylalkyl)ethylenediamine skeleton is necessary for maximum adrenolytic potency. That is, all of the compounds listed in Table II in addition to II, III, IV, V, VIII, IX, and XIII, are substantially less adrenolytic than I at comparable doses. Compounds I, VI, and VII are of similar adrenolytic potency in that 10 mg./kg. (calculated as amount of base administered intravenously) usually reversed the pressor response to 2 γ/kg. of epinephrine in the normotensive anesthetized dog. Branching the ethylenediamine chain markedly increased adrenolytic potency. Compared to I, the branched compounds X and XI are roughly 2 and 10 times, respectively, more potent adrenolytic agents. Presently available data indicate that branching caused no changes in the quality of biological activity.

Experimental[14]

N,N′-Bis[α-(2-pyridyl)ethyl]ethylenediamine (I).—A mixture of 121 g. (1.0 mole) 2-acetylpyridine and 37 g. (0.50 mole) of 81% aqueous ethylenediamine in 400 ml. of benzene was heated at reflux for 5 hr. while 23 ml. of water was collected in a Dean–Stark apparatus. After cooling to room temperature, the precipitate was collected, washed with benzene, and dried. A mixture of this material and 0.4 g. of PtO_2 in 200 ml. of ethanol was reduced under 3 atm. (3.09 kg./cm.^{2}) of hydrogen. The catalyst was removed by filtration and the filtrate concentrated *in vacuo* to a sirup. Distillation provided 120 g. (89%) of product.

1,2-Bis(2-pyrrolylcarboxaldimino)ethane.—To a solution of 28 g. (0.29 mole) of pyrrole-2-carboxaldehyde in 100 ml. of benzene was added 12 ml. of 72% aqueous ethylenediamine. After heating at reflux with stirring for 8 hr., the mixture was cooled. The precipitate was collected, washed with benzene, and dried to afford 26.8 g. (87%) of product, m.p. 175–179°.

Anal. Calcd. for $C_{12}H_{14}N_4$: N, 26.15. Found; N, 26.18.

N,N′-Bis(2-pyrrolylmethyl)ethylenediamine Dihydrochloride (VI).—A mixture of 26.8 g. (0.125 mole) of the Schiff base and 0.3 g. of PtO_2 in 200 ml. of ethanol was reduced under 3 atm. (3.09 kg./cm.^{2}) of hydrogen. The catalyst was removed by filtration and excess ethereal hydrogen chloride was added to the cooled filtrate. The precipitate was collected and recrystallized from methanol to provide 6.7 g. (19%) of product.

N,N′-Bis[α-(2-pyridyl)ethyl]ethylenediamine[15] (VII).—A solution of 21 g. (0.20 mole) of 2-vinylpyridine, 6.1 g. (0.090 mole) of 88% aqueous ethylenediamine, and 12 g. (0.20 mole) of glacial acetic acid in 100 ml. of ethanol was heated at reflux for 6 hr. The reaction mixture was concentrated *in vacuo* and the residue was treated with excess aqueous sodium hydroxide. This mixture was extracted twice with tetrahydrofuran, and the combined and dried organic layers were distilled to afford 10.8 g. (46%) of product.

N,N′-Bispicolylhydrazine Diacetate (VIII).—A mixture of 21 g. (0.10 mole) of 2-pyridinealdazine,[9] 24 g. (0.40 mole) of glacial acetic acid, and 0.5 g. of PtO_2 in 200 ml. ethanol was reduced under 3 atm. of hydrogen. The catalyst was separated by filtration, and the filtrate was concentrated to dryness. Trituration of the residue with ether followed by recrystallization from acetonitrile afforded 4.9 g. (15%) of product.

N,N′-Bis[α-(2-piperidyl)ethyl]ethylenediamine (XIII).—A mixture of 27 g. (0.10 mole) of I, 66 ml. of 6 *N* hydrochloric acid, and 5 g. of 5% rhodium-on-alumina in 150 ml. of ethanol was reduced under 3 atm. of hydrogen. The catalyst was removed by filtration and the filtrate concentrated to a sirup which was treated with excess aqueous sodium hydroxide. This mixture was extracted with ether, then tetrahydrofuran, and the combined organic layers were dried over potassium carbonate. Distillation provided 20.1 g. (71%) of product.

N-*t*-Butyl-N-[α-(2-pyridyl)ethyl]amine (XIV).—*t*-Butylamine (53 g., 0.72 mole) and 14 g. (0.075 mole) of 2-(α-bromoethyl)-pyridine[10] in 100 ml. of ethanol were heated in a citrate bottle for 0.5 hr. at 100°. After cooling and removal of solvent by distillation, 4.2 g. (0.075 mole) of potassium hydroxide dissolved in 75 ml. ethanol was added, and the mixture was filtered to remove inorganic salt. The filtrate was concentrated and the residue was distilled to provide 4.5 g. (34%) of crude product.

N-[α-(2-Pyridyl)ethyl]piperidine (XV).—To a boiling solution of 34 g. (0.40 mole) of piperidine in benzene was added a solution of 8.8 g. (0.047 mole) of 2-(α-bromoethyl)pyridine in benzene over 0.5 hr. Heating at reflux was continued for an additional 3 hr. After cooling, the mixture was filtered and the filtrate was distilled to afford 7.3 g. (81%) of product.

[α-(2-Pyridyl)ethyl]trimethylammonium Bromide (XVI).—A solution of 47 g. (0.80 mole) of trimethylamine and 15 g. (0.080 mole) of 2-(α-bromoethyl)pyridine in 100 ml. ethanol was heated in a pressure bottle for 3 hr. at 100°. The solvent was evaporated and the residue was recrystallized from acetonitrile to provide 11.3 g. (58%) of material.

N-[β-(2-Pyridyl)ethyl]piperidine (XIX).—A solution of 21 g. (0.20 mole) of 2-vinylpyridine, 12 g. (0.20 mole) of glacial acetic acid, and 17 g. (0.20 mole) of piperidine in 85 ml. of ethanol was heated at reflux for 8 hr. The solvent was removed by evaporation and the residue was treated with excess aqueous potassium hydroxide. This mixture was extracted three times with ether. The combined and dried organic layers were concentrated and the residue was distilled to yield 29.5 g. (77%) of XIX.

N-[α-(2-Pyridyl)ethyl]-β-(octahydro-1-azocinyl)ethylamine (XX).—A solution of 15 g. (0.12 mole) of 2-acetylpyridine in 50 ml. of ethanol was added to a stirred solution of 19.5 g. (0.12 mole) of 2-(octahydro-1-azocinyl)ethylamine[16] in 100 ml. of ethanol during 10 min. An exothermic reaction ensued. After stirring for an additional 0.5 hr., 0.5 g. of PtO_2 was added, and the mixture was reduced under 3 atm. of hydrogen. The exothermic reduction was completed in 0.5 hr. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to a residue which was distilled to give 16.2 g. (52%) of product.

(11) R. P. Halliday, W. J. Kinnard, and J. P. Buckley, Abstracts of Papers, American Pharmaceutical Association Annual Meeting, Miami Beach, Florida, May 12–17, 1963.

(12) (a) R. P. Halliday, M.S. Thesis, University of Pittsburgh, 1960; (b) R. P. Halliday, Ph.D. Thesis, University of Pittsburgh, 1962.

(13) J. P. Buckley, personal communication.

(14) Melting points are corrected. Boiling points are uncorrected. Most analyses were performed under the direction of Mr. E. Kluchesky in the Analytical and Control Department, Lakeside Laboratories, Inc.

(15) A recent report suggests that this reaction affords the unsymmetrical product: E. Profft and S. Lojack, *Rev. Chim. Roumaine*, **7**, 405 (1963). *Index Chemicus*, **9**, 29485 (1963).

(16) R. P. Mull, M. E. Egbert, and M. R. Dapero, *J. Org. Chem.*, **25**, 1953 (1960).

3,6-Disubstituted Pyridazines[1]

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Since maleic hydrazide was first shown to regulate plant growth[2,3] there has been much interest in deriva-

(1) Contribution No. 228 from Research Center, United States Rubber Company.

(2) D. L. Schoene and O. L. Hoffmann, *Science*, **109**, 588 (1949).

(3) O. L. Hoffmann and D. L. Schoene (to U. S. Rubber Company), U. S. Patent 2,614,916 (Oct. 21, 1962).