Antituberculous Agents. II.[1] N,N′-Diisopropylethylenediamine and Analogs

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The preparation and antituberculous activity of some forty homologous alkylenediamines [$(C_nH_{2n+1}NH)_2(CH_2)_m$] is given along with a discussion of the structural features required for high activity. N,N′-Diisopropylethylenediamine (I) and its secondary (IV) and tertiary (V) butyl analogs displayed in mice about one-half the antituberculous activity of streptomycin.

In the course of general screening of compounds for antituberculous activity in mice, N,N′-diisopropylethylenediamine (I) was found[2a] to possess a high level of activity comparable to that of streptomycin. *In vitro* testing[2b] demonstrated a selective activity against mycobacteria with no appreciable activity against various Gram-negative and Gram-positive bacteria or against fungi. No activity was observed against various bacterial infections in mice.

Aliphatic polyamines such as spermine and spermidine[3] or substituted polymethylene-α,ω-diamines[4] and ethylenediamines[5] have been reported to have antimycobacterial activity but only *in vitro*. High toxicity but no antituberculous activity was observed in animals, which we have confirmed.[2a] In the earlier series of diamines, maximum activity was obtained when an unbranched alkyl or alkylene group of 12 to 18 carbons was present, giving a detergent type of structure. Detergency probably accounts for this activity *in vitro* which is non-specific and is reduced by the presence of protein. The authors[5] concluded that "the active compounds behaved as non-specific microbic poisons."

(1) Paper I. R. G. Wilkinson, R. G. Shepherd, J. P. Thomas and C. Baughn, *J. Am Chem. Soc.*, **83**, 2212 (1961).

(2a) Personal communication from J. P. Thomas and G. S. Redin of these Laboratories, whom we thank for permission to quote their unpublished data, determined by the method of M. Baker, M. Schlosser and H. J. White, *Ann. N. Y. Acad. Sci.*, **52**, 678 (1949).

(2b) Personal communication from M. Hauck and A. C. Dornbush of these Laboratories, whom we thank for permission to quote their unpublished data.

(3) J. G. Hirsch, "Ciba Foundation Symposium on Experimental Tuberculosis," Little Brown & Co., Boston, Massachusetts, 1955, p. 117.

(4) D. E. Ames and R. E. Bowman, *J. Chem. Soc.*, 1057 (1952).

(5) F. A. Barkley, G. W. Mast, G. F. Grail, L. E. Tenenbaum, F. E. Anderson, F. Leonard and D. M. Green, *Antibiotics and Chemotherapy*, **6**, 554–560 (1956).

The strikingly different structural requirements for activity in the present series, the very marked antimycobacterial specificity and the high activity *in vivo* demonstrated that the active structures discussed herein are of a new type. Analogs of N,N′-diisopropylethylenediamine were synthesized with variation of the length and branching of the alkylene chain and variation of the size, the branching and number of N-alkyl substituents.

Symmetrically disubstituted diamines were generally prepared by catalytic reductive alkylation[6] with the appropriate ketone or aldehyde, or by condensation of amines with an alkylene dihalide. Sodium borohydride gave satisfactory reductive alkylation of ethylenediamine with valeraldehyde whereas catalytic reduction with platinum oxide was unsuccessful. Previous mention[7] of reductive alkylation with sodium borohydride has involved only aromatic Schiff bases and the scope of this reduction is being examined. Condensation of an alkyl halide with ethylenediamine was not as generally useful a method as those mentioned above. N-Methylation of N,N′-dialkylethylenediamines by the Eschweiler-Clarke variation[14] of the Leuckart reaction proceeded rapidly and in high yield.

The unsymmetrically substituted ethylenediamines were made either by reductive alkylation of N-substituted ethylenediamines or by amination of N-substituted 2-chloroethylamine hydrochlorides.

Antituberculous activities are indicated in Tables I and II. The testing results on a large number of commercially available substituted alkylenediamines are not included since they showed no appreciable antimycobacterial activity.

N,N′-Diisopropylethylenediamine and its N,N′-di-*sec*-butyl and di-*tert*-butyl analogs were equally active against the otherwise fatal infection with *Mycobacterium tuberculosis* $H37R_v$ in mice. The median effective doses[2a] required for survival for at least 60 days were 180-200 mg./kg./day when given orally once a day, orally by drug-diet, subcutaneously or intraperitoneally. By the last two routes of administration, the activities were about one-half the activity of streptomycin. The diisopropyl compound was about one-half as toxic in mice as the di-*sec*-butyl and di-*tert*-butyl analogs, judging by body weight loss.[2a]

The following generalizations can be made about the antituberculous activity of N,N′-dialkylethylenediamines in mice. Highest activity was observed when the alkyl groups were isopropyl (I),

(6) W. S. Emerson, *Organic Reactions*, Vol. IV, 174–255 (1948).

(7) J. H. Billman and A. C. Diesing, *J. Org. Chem.*, **22**, 1068 (1957); G. N. Walker and M. A. Moore, *J. Org. Chem.*, **26**, 432 (1961).

sec-butyl (IV) or *tert*-butyl (V). Without branching at the α-carbon, there was no appreciable activity as in the methyl, ethyl, *n*-propyl, *n*-butyl (II), isobutyl (III) or *n*-pentyl (VI) compounds. Activity dropped off rapidly when the secondary alkyl series (VII-IX, XII-XVI) was ascended but decreased more slowly in the tertiary alkyl series (V, X, XVII).

There was no activity when the two isopropyl groups were on the same nitrogen as in N,N-diisopropylethylenediamine or when only one such group was present as in N-isopropylethylenediamine. One compound with two different branched N-alkyl groups (XXVII) had high activity while the related compounds (XXVI, XXVIII, XXIX) were inactive.

Increasing the number of N-alkyl groups to three or to four lowered the activity, in most cases drastically. Thus, addition to (I) of one N-methyl group (XX) reduced activity by one-half while the presence of two N-methyl groups (XXI) led to inactivity as also occurred with the tertiary nitrogen analog, 1,4-diisopropylpiperazine (XXV). Diamines with three (XXII) or four (XXIII) isopropyl groups had only one-tenth the activity of I. Although activity was present in tetraethyl- and tetra-*n*-pentylethylenediamine (XXXI), the latter more active compound showed toxicity near the minimal effective dose.

Lengthening the alkylene chain to three or to four carbons gave inactive trimethylene (XXXVI, XXXVII) and tetramethylene (XXXVIII) analogs of the highly active I and V. Substitution of the ethylene chain with one methyl (XXXV) decreased activity three-fold whereas substitution on both carbons (XXXIX, XXXXI) led to inactivity. N,N′-Diacetylation of I as in XXIV removed activity. N-Substitution with long alkyl groups (XIX, XXXIII, XXXIV), reported[5] to be beneficial for *in vitro* antibacterial activity, produced no measurable activity *in vivo*.

The very selective activity connected with steric hindrance around the two nitrogen atoms suggests that the activity of these compounds may be associated with ability to form a specific type of metal chelate. Ability of antituberculous drugs to complex with metal ions is well known[8] but proof is still lacking that chelation is the key to their mechanism of action. Although no evidence in support of a mechanism of action is available for these diamines, chelation was employed as a working hypothesis in guiding the synthesis of analogs. A different type of chelate is formed by some of the active compounds

(8) M. B. Chenoweth, *Pharm. Revs.*, **8**, 57 (1956); W. O. Foye, *J. Pharm. Sci.*, **50**, 93 (1961).

TABLE

SYNTHESIS, PROPERTIES AND ANTIMYCOBACTERIAL

	Ethylenediamine	Method[a]	Reactants[b]	Catalyst[c] [H_2 press.,[c] (kg./cm.^{2})], % redn.	Time, hr. Temp. Solvent[c]
I[i]	N,N′-Diisopropyl-	A	6 R_2CO 1 ED	3 Pt-C 93 105%	4 50° none
II[j]	N,N′-Di-*n*-butyl-	A	2 RCHO 1 ED	3 PtO_2 3 40%	4 25° 400 EtOH
III[k]	N,N′-Diisobutyl-	A	2 RCHO 1 ED	1 PtO_2 3 85%	29 25° 400 EtOH
IV[l]	N,N′-Di-*sec*-butyl-	A	2 R_2CO 1 ED	1 Pt_2O 3 92%	21 25° 800 EtOH
V[m]	N,N′-Di-*tert*-butyl-	B	5 RNH_2 1 $C_2H_4Br_2$		72 50–100° 40 H_2O
I[n]	N,N′-Di-*n*-pentyl-	C	2 RCHO 1 ED 1.5 $NaBH_4$		3 80° 2000 EtOH
VII[o]	N,N′-Bis(2-pentyl)-	A	2 R_2CO 1 ED	18 Pt-C 62 89%	8 27–72° 400 EtOH
VIII	N,N′-Bis(3-pentyl)-	A	2 R_2CO 1 Ed	18 Pt-C 72 114%	4.5 20–65° 400 EtOH
IX	N,N′-Bis(3-methyl-2-butyl)-	A	2 R_2CO 1 ED	18 Pt-C 72 86%	8.5 30–101° 400 EtOH
X	N,N′-Bis(2-methyl-2-butyl)-	B	2 RNH_2 1 $C_2H_4Br_2$		40 80° 160 EtOH 20 H_2O
XI	N,N′-Dicyclopentyl-	A	2 R_2CO 1 ED	1.4 PtO_2 3 90%	94 30° 400 EtOH
XII[p]	N,N′-Bis(2-hexyl)-	B	2 RBr 1 ED		43 80° 500 EtOH 200 H_2O
XIII[q]	N,N′-Bis(4-methyl-2-pentyl)-	A	2 R_2CO 1 ED	18 Pt-C 62 90%	6 32–70° 400 EtOH
XIV[r]	N,N′-Bis(3,3-dimethyl-2-butyl)-	A	$(R_2C{=}NCH_2)_2$	2.5 PtO_2 3 60%	24 25° 500 EtOH

I

ACTIVITY OF SUBSTITUTED ETHYLENEDIAMINES

Formula	B.p.° (mm.)[d] or m.p.°	Yield, %	Purif.,[f] ml./g.	Analyses Calcd. over Found C	H	N	Cl	Rel. act.[g] *in vivo*/ Inhib. concn.[h] *in vitro*
$C_8H_{20}N_2$	169–169.5 (760)	60		66.6	14.0	19.4		
				66.7	13.8	19.6		
·2HCl	258–259	97	0.3 H_2O	44.3	10.2	12.9	32.6	1.0
			3 EtOH	44.6	10.4	12.8	32.3	60
$C_{10}H_{24}N_2$	115–120 (17)	9		69.7	14.0	16.3		*ca.* 0.1
				69.8	14.0	16.1		>250i
$C_{10}H_{24}N_2$	94–97 (15)	70		69.7	14.0	16.3		*ca.* 0.1
				69.7	13.9	16.2		>250i
$C_{10}H_{24}N_2$	94–96 (17)	89		69.7	14.0	16.3		
				69.9	14.0	15.9		
·2HCl	199–201	98	2 EtOH	49.0	10.7	11.4	28.9	1.0
			4 Me_2CO	48.9	10.7	11.2	29.0	125
$C_{10}H_{24}N_2$	79–80 (14)	56						
·2HCl	281–282 gas	96	0.3 H_2O	48.1	10.7	11.4	28.9	1.0
			3 EtOH	48.4	10.7	11.2	28.6	500
$C_{12}H_{28}N_2$	134–136 (13)	42						
·2HCl	312 dec.	58	EtOH	52.7	11.1	10.2	26.0	<0.1i
				53.1	11.0	10.5	25.8	250
$C_{12}H_{28}N_2$	82.5–85 (3)	75				14.0		
						13.9		
·2HCl	150–154	85	3 EtOH	52.7	11.1	10.2	25.9	<0.03i
			4 Me_2CO	52.8	11.3	10.3	25.7	>250i
$C_{12}H_{28}N_2$	116–118 (15)	70		71.9	14.1	14.0		
				71.8	14.1	13.7		
·2HCl	173–174.5	95	2 EtOH	52.7	11.1	10.2	26.0	<0.1i
			4 Me_2CO	52.8	11.2	10.3	26.1	>250i
$C_{12}H_{28}N_2$	52–55 (1)	35						
·2HCl	217–220.5	71	6 EtOH	52.7	11.1	10.2	26.0	<0.1i
				52.3	11.1	10.4	25.8	>250i
$C_{12}H_{28}N_2$	110–115 (15)	48						
·2HCl	234 gas	94	1.5 EtOH	52.7	11.1	10.2	26.1	*ca.* 0.5
				53.1	11.2	9.9	25.6	>250i
$C_{12}H_{24}N_2$	146.5–148 (15)	90						
·2HCl	270–278 dec.	96	2 H_2O	53.5	9.7	10.4	26.3	*ca.* 0.1
			40 EtOH	53.3	9.8	10.4	26.3	250
$C_{14}H_{32}N_2$	138–142 (15)	23						
·2HCl	180.5–182.5	90	4 MeOH	55.8	11.4	9.3	23.5	<0.03i
			7 Me_2CO	55.6	11.6	9.4	23.5	500
$C_{14}H_{32}N_2$	93–95 (1)	70		73.6	14.1	12.3		
				73.6	14.5	12.1		
·2HCl	247–255.5	97	11 MeOH	55.8	11.4	9.3	23.5	0.03
				55.9	11.5	9.3	23.1	>250i
$C_{14}H_{32}N_2$	126–127.5 (16)	27						
·2HCl	290–291 dec.	70	4 H_2O	55.8	11.4	9.3	23.5	<0.1i
			6 EtOH	55.8	11.7	9.2	23.3	>250i

TABLE I

	Ethylenediamine	Method[a]	Reactants[b]	Catalyst[c] [H_2 press.[c]] kg./cm.^{2}), % redn.	Time, hr. Temp. Solvent[c]
XV	N,N'-Bis(4-heptyl)-	A	2 R_2CO 1 ED	18 Pt-C 72 111%	5.5 30–55° 400 EtOH
XVI[g]	N,N'-Bis(2-heptyl)-	A	2 R_2CO 1 ED	18 Pt-C 68 90%	4 30–81° 400 EtOH
XVII[f]	N,N'-Bis(2,4,4-trimethyl-2-pentyl)	B	5 RNH_2 1 C_2H_4B		8 100° 50 H_2O
XVIII-A[f,h]	N,N'-Bis(α-methylbenzyl)-	A	($R_2C{=}NCH_2$)$_2$	1 PtO_2 3 50%	20 25° 400 EtOH
XVIII B	N-(α-Methylbenzyl)-				
XIX[g]	N,N'-Didodecyl-	B	2 RNH_2 1 $C_2H_4Br_2$		264 110° 200 PrOH
XX[g]	N,N'-Diisopropyl-N-methyl-	B	4.6 i-$PrNH_2$ 1 R'Cl·HCl		2 75° 600 EtOH
XXI	N,N'-Diisopropyl-N,N'-dimethyl-	D	1 $(RNHCH_2)_2$ 2 CH_2O 4.8 HCOOH		3.5 100° none
XXII	N,N,N'-Triisopropyl-	A	3.5 Me_2CO 1 $R_2NC_2H_4NH_2$	1 PtO_2 3 90%	2 30° 250 EtOH
XXIII	N,N,N',N'-Tetraisopropyl-	B	2 R_2NH 1 $C_2H_4Br_2$		42 75° 180 EtOH 50 H_2O

[a] Letters refer to procedures described under Experimental. [b] Reactants, given in mole ratios, are abbreviated in a manner which, from the structure of the product and the synthetic method, should make their structure obvious. ED is ethylenediamine; R'Cl·HCl is the alkyl- or dialkyl-aminoethyl chloride hydrochloride. [c] Amount of catalyst (g.) and volume of solvent (ml.) correspond to 1 mole of diamine. Pt/C is J. T. Baker & Co. 10% Pt-on-carbon. If desired to convert kg./cm.^{2} to atmospheres multiply by 0.97. [d] Boiling points (uncorr.) at pressure indicated. Melting points below 270° are corrected. [e] Yields of bases represent distillate of boiling point indicated; occasionally where hydrochloride salts were recovered from other fractions they are included. Yields of hydrochlorides (include second crops of high purity) are for conversion of base to salt. [f] Recrystallization from solvent pairs by dissolving in the more polar solvent and adding the less polar solvent, using the volumes given per g. of solute. Except in those cases involving fractional crystallization of isomers, two recrystallizations were sufficient to attain a constant m. p. A single solvent denotes recrystallization by heating and cooling. [g] Relative antimycobacterial activity[2a] (upper figure) against a lethal infection with *Mycobacterium tuberculosis* H37Rv in mice is based on dosages in the drug diet giving significant (4 days or more) prolongation of survival time, with (I) taken as the standard. Ratios based on preliminary evaluation data are labeled "*ca.* 0.2." Inactivity at the highest dose tested is indicated by <0.1, *etc.* [h] Minimal concentration (subject to ±2-fold variation) in mcg./ml.

(*continued*)

Formula	B.p.° (mm.)[d] or m.p.°	Yield,[e] %	Purif.[f] ml./g.	Analyses Calcd. over Found C	H	N	Cl	Rel. act.[g] *in vivo*/ Inhib. conen.[h] *in vitro*
$C_{16}H_{36}N_2$	126–129 (1.5)	62		74.9	14.2	10.9		
				74.6	14.1	10.8		
·2HCl	193.5–194.5	87	1 EtOH	58.3	11.6	8.5	21.5	*ca.* 0.2
			2 Me_2CO	58.7	11.7	8.4	21.1	60
$C_{16}H_{36}N_2$	113–116 (0.3)	78		74.9	14.2	10.9		
				75.1	14.3	10.8		
·2HCl	190–195	96	4 MeOH	58.3	11.6	8.5	21.5	<0.1i
			4 Me_2CO	58.6	11.5	8.7	21.4	30
$C_{18}H_{40}N_2$	118–120 (1.2)	41						
·2HCl	234–235.5	98	3 MeOH	60.5	11.8	7.9	19.9	*ca.* 0·5
				60.7	11.9	8.0	19.6	30
$C_{18}H_{24}N_2$	204–207 (12)	8						
(±)·2HCl	247–248.5	51	2 EtOH	63.3	7.7	8.2	20.8	<0.1i
			10 Me_2CO	63.1	7.9	8.2	20.6	250
meso·2HCl	295–295.5	46	25 EtOH	63.3	7.7	8.2	20.8	<0.1i
				63.7	7.9	8.2	20.8	250
(±)$C_{10}H_{16}N_2$	127–135 (12)	70						
·2HCl	257.5–260	97	25 MeOH	50.6	7.7	11.8	29.9	<0.06i
				50.6	7.5	11.8	29.9	
$C_{26}H_{56}N_2$	249–253	26	36 EtOH	66.5	12.4	6.0	15.1	<0.06i
·2HCl				66.8	12.4	6.2	15.0	>250i
$C_9H_{22}N_2$	174–179 (760)	53						
·2HCl·$^1/_4H_2O$	164–168	66	5 EtOH	45.8	10.5	11.9	30.1	*ca.* 0.5
			10 Me_2CO	45.7	10.7	12.0	29.9	>1000i
$C_{10}H_{24}N_2$	228–229	96	3 EtOH	49.0	10.7	11.4		<0.1i
·2HCl	gas			48.9	10.7	11.3		>250i
$C_{11}H_{26}N_2$	201–202.5 (760)	81		70.9	14.1	15.1		
				70.5	14.4	15.5		
·2HCl	118.5–120	100	1.5 EtOH	47.7	10.9	10.1	25.6	*ca.* 0.1
			7 Me_2CO	47.9	11.1	10.1	25.4	>1000i
$C_{14}H_{32}N_2$	110–115 (16)	16						
·2HCl	210.5–212.5	82	2 EtOH	55.8	11.4	9.3	23.5	*ca.* 0.1
			4 Me_2CO	55.6	11.4	9.3	23.1	>1000i

giving 100% inhibition[2b] of *Mycobacterium smegmatis* (ATCC607). Inactivity at the highest concentration tested is indicated by >250i, etc. [i] W. R. Boon, *J. Chem. Soc.*, 307 (1947), reported b.p. 169–171°, m.p. 250°. [j] F. B. Zienty, *J. Am. Chem. Soc.*, **68**, 1388 (1946), reported b.p. 110–111° (8 mm.). [k] Lit.[i] b.p. 212–214°. [l] Lit.[i] b.p. 210°, m.p. 187°. [m] Lit.[i] b.p. 196–198°, m.p. 275–280° dec. [n] J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, **68**, 1774 (1946), reported b.p. 165–175° (90 mm.) and b.p. 149° (26 mm.). G. N. Vyas and S. G. Dhopate, *Current Sci. (India)*, **25**, 356–7 (1956), report m.p. 305–310°. [o] R. A. Donia, J. A. Schotton, L. O. Bentz and G. F. P. Smith, *J. Org. Chem.*, **14**, 946 (1949), report b.p. 86–87° (2 mm.). [p] A lower boiling fraction (75–100°, 15 mm.) probably impure monoalkylated product was also isolated in about 30% yield. [q] J. L. Szabo and W. F. Bruce, U. S. Patent 2,739,981, March 27, 1956, reported b.p. 95–97°. [r] No reduction of the mixture of ketone and ethylenediamine occurred until the Schiff base was formed by the benzene azeotrope method. [s] Lit.[q] b.p. 125–127° (2 mm.). [t] Lit.,[12] 92% yield, b.p. 125–127° (2 mm.). [u] J. L. Szabo and W. F. Bruce, U. S. Patent 2,709,700, May 31, 1955, reported a superior reduction of the Schiff base in glacial acetic acid; however, they reported no yield or properties. [v] Linsker and Evans[11] reported 97% yield, m.p. 246–248° by a procedure we have found unsuccessful. [w] The crude intermediate β-(N-methyl-N-isopropylamino)ethyl chloride hydrochloride was prepared by the method of J. H. Biel, *J. Am. Chem. Soc.*, **71**, 1308 (1949).

TABLE

SYNTHESES, PROPERTIES AND ANTIMYCOBACTERIAL

	Name	Method[a]	Reactants[b]	Catalyst[c] [H_2 press.,[d] (kg./cm.^{2})], % redn.	Time, hr. Temp. Solvent[e]
XXIV	N,N′-Ethylenebis(N-isopropylacetamide)	E	1 $(RNHCH_2)_2$ 2.2 Ac_2O		0.5 110° no solv.
XXV	1,4-Diisopropylpiperazine	B	1 $(RNHCH_2)_2$ 1 $C_2H_4Br_2$		17 100° 80 H_2O
XXVI[n]	N-Propyl-N′-isopropylethylenediamine	B	2.1 n-$PrNH_2$ 1 R′Cl·HCl		48 80° 700 EtOH 50 H_2O
XXVII	N-*sec*-Butyl-N′-isopropylethylenediamine	B	1.1 EtMeCO 1 $RNHC_2H_4NH_2$	15 Pt-C 78 64%	3 30–90° 200 EtOH
XXVIII[n]	N-(1,1-Dimethylpropyl)-N′-isopropylethylenediamine	B	1.5 t-$AmNH_2$ 1 R′Cl·HCl		48 80° 700 EtOH 50 H_2O
XXIX[n]	N-Isopropyl-N′-phenylethylenediamine	B	9 $PhNH_2$ 1 R′Cl·HCl		18 80° 500 EtOH
XXX[n]	N-Isopropyl-N′,N′-di-n-pentylethylenediamine	B	1.2 R_2NH 1 R′Cl·HCl 1 NaOH		48 80° 750 EtOH 30 H_2O
XXXI	N,N,N′,N′-Tetra-n-pentylethylenediamine	B	2.5 R_2NH 1 $C_2H_4Br_2$		6 80° 500 EtOH 100 H_2O
XXXII[i]	N,N-Dibutyl-N′,N′-dimethylethylenediamine	B	5 n-Bu_2NH 1 R′Cl·HCl		24 80° 500 EtOH
XXXIII[j]	N,N,N′-Trimethyl-N′-nonylethylenediamine	B	1 RMeNH 1 R′Cl·HCl		30 80° 700 EtOH 250 H_2O
XXXIV[k]	N-Dodecyl-N,N′,N′-trimethylethylenediamine	B	2 RMeNH 1 R′Cl·HCl		3 140° 2000 xylene
XXXV	N^1,N^2-Diisopropyl-1,2-propanediamine	A	3 Me_2CO 1 $R(NH_2)_2$	8 Pt-C 103 87%	2.5 42–71° none
XXXVI	N,N′-Diisopropyl-trimethylenediamine	A	3 Me_2CO 1 $R(NH_2)_2$	18 Pt-C 103 118%	3.25 38–81° none

II

ACTIVITY OF VARIOUS ALKYLENEDIAMINES

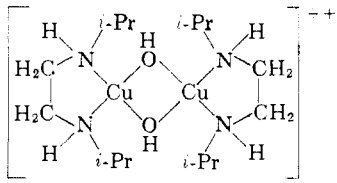
Formula	B.p.° (mm.)[d] or m.p.°	Yield,[e] %	Purif.[f] ml./g.	Analyses Calcd. over Found C	H	N	Cl	Rel. activ.[g] *in vivo*/ Inhib. concn.[h] *in vitro*
$C_{12}H_{24}N_2O_4$	107–109	73	5 Me_2CO	63.1	10.6	12.3		<0.1i
				63.3	10.6	12.2		>250i
$C_{10}H_{22}N_2$	199–204 (760)	39						
·2HCl	327	90	0.5 H_2O	49.4	10.0	11.5	29.2	<0.06i
			14 MeOH	49.4	10.0	11.3	28.9	>1000i
$C_8H_{20}N_1$	65–85 (12)	40						
·2HCl	214–216	89	2 MeOH	44.2	10.2	12.9	32.6	<0.03i
			4 Me_2CO	44.3	10.3	13.0	32.4	125
$C_9H_{22}N_2$	173–176 (760)	89		68.3	14.0	17.7		
				67.6	13.8	18.1		
·2HCl	219–221.5	83	3 EtOH	46.9	10.5	12.2	30.8	*ca.* 0.5
			4 Me_2CO	46.9	10.6	12.3	30.6	30
$C_{10}H_{24}N_2$	180–200 (760)	35						
·2HCl	325–326	60	1 H_2O	49.0	10.6	11.4	28.9	<0.03i
			5 EtOH	49.2	10.2	11.5	28.9	>250i
$C_{11}H_{18}N_2$	149–153 (15)	98						
·2HCl	160.5–163	65	4 EtOH	52.6	8.0	11.2	28.2	<0.03i
				52.5	8.1	11.5	28.4	>1000i
$C_{18}H_{34}N_2$	128–129 (5)	17		74.3	14.1	11.6		*ca.* 0.03
				73.8	13.8	11.7		250
$C_{22}H_{46}N_2$	150–153 (0.3)	87						
·2HCl	160–165	85	6 Me_2CO	63.9	12.2	6.8	17.1	*ca.* 0.2
				64.1	12.5	6.9	17.0	8
$C_{12}H_{28}N_2$	195–205 (760)	75						
·2HCl	204–205	93	1.5 MeOH	52.7	11.1	10.2	25.9	<0.1i
			10 Me_2CO	52.7	11.3	10.2	25.5	>250i
$C_{14}H_{32}N_2$	135–139 (11)	47						
·2HCl	267–267.5	97	8 MeOH	55.8	11.4	9.3	23.5	<0.1i
				55.8	10.9	9.5	23.5	60
$C_{17}H_{38}N_2$	128–138 (0.5)	31						
·2HCl	263–264.5	73	14 EtOH	59.4	11.7	8.2	20.6	<0.1i
				59.0	11.9	8.2	20.6	4
$C_9H_{22}N_1$	172–176 (760)	67		68.3	14.0	17.7		
				68.6	14.2	17.7		
·2HCl	169–179	85	2 EtOH	46.7	10.5	12.1	30.7	*ca.* 0.3
			3 Me_2CO	46.5	10.5	12.0	30.4	250
$C_9H_{22}N_2$	191–195 (760)	69		68.3	14.0	17.7		
				68.1	**14.2**	**17.5**		
·2HCl	299–302	96	2 MeOH	46.7	10.5	12.1	30.7	<0.03i
			2 Me_2CO	46.7	10.5	12.0	30.5	>1000i

TABLE II

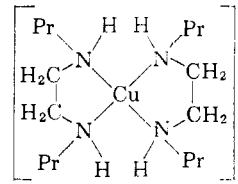
	Name	Method[a]	Reactants[b]	Catalyst[c] [H_2 press.[c] (kg./cm.^{2})]. % redn.	Time, hr. Temp. Solvent[c]
XXXVII	N,N′-Di-*t*-butyl-trimethylene-diamine	B	5 RNH_2 1 RBr_2		24 50–100° 100 H_2O
XXXVIII	N,N′-Diisopropyl-tetramethylene-diamine	A	3 Me_2CO 1 $R(NH_2)_2$	8 Pt-C 103 118%	4 35–75° none
XXXIX[f]	N,N′-Diisopropyl-2,3-butane-diamine	A	4.5 Me_2CO 1 $R(NH_2)_2$	2.5 PtO_2 3 95%	1.8 30° none
XXXX-A[m]	N,N′-Diisopropyl-2-butene-1,4-diamine	B	6 *i*-$PrNH_2$ 1 $C_4H_6Br_2$		0.5 40–80° 300 EtOH 30 H_2O
XXXX-B[m]	1,6,11-Triisopropyl-di-2-butenyl-enetriamine				
XXXXI	N,N′-Diisopropyl-1,2-*trans*-cyclo-hexanediamine	A	3 Me_2CO 1 $R(NH_2)_2$	18 Pt-C 93 49%	6.5 30–120° 200 EtOH

[a–h] These footnotes have the same meaning as in Table I. [f] G. F. Grail, L. E. Tenenbaum, A. V. Tolstoouhov, C. J. Duca, J. F. Reinhard, F. E. Anderson and J. V. Scudi, *J. Am. Chem. Soc.*, **74**, 1313 (1952), report b.p. 201°. [g] Lit.[i] b.p. 152–155° (18 mm.). [k] Lit.[i] b.p. 135–137° (2 mm.). [l] The *meso* isomer separated readily from the *dl* isomer using ethanol as solvent. [m] That the products of the reaction have the structures stated rather than that derived from an allylic rearrangement was supported by the absence in the infrared spectrum of their salts of the characteristic vinyl group absorption at 910 cm.$^{-1}$. The diamine (XXXX A) absorbed 1

as compared to various inactive diamines. Basolo and Murmann[9] found that N,N′-diisopropylethylenediamine forms a chelate of type A in water whereas less hindered ethylenediamines form only



A



B

type B chelates. The presence of a trimethylene or tetramethylene chain in certain analogs would prevent their forming either type.

(9) F. Basolo and R. K. Murmann, *J. Am. Chem. Soc.*, **76**, 214 (1954).

(*continued*)

Formula	B.p.° (mm.)[d] or m.p.°	Yield,[e] %	Purif.,[f] ml./g.	Analyses Calcd. and Found C	H	N	Cl	Rel. activ.[g] *in vivo*/ Inhib. concn.[h] *in vitro*
$C_{11}H_{26}N_2$	188–195 (200)	85						
·2HCl	>286°	77	0.5 H_2O	51.0	10.9	10.8	27.3	<0.2i
			75 EtOH	51.3	10.8	11.0	27.2	>1000i
$C_{16}H_{24}N_2$	208.5–218 (760)	67		69.7	14.0	16.2		
				69.4	14.1	16.0		
·2HCl	286.5–289 gas	97	0.4 MeOH	49.0	10.7	11.4	28.9	<0.03i
				49.1	10.8	11.4	28.5	>1000i
$C_{16}H_{24}N_2$	176–178 (760)	78		69.8	14.0	16.2		
				69.8	14.0	16.2		
(±)·2HCl	251–257	38	2 EtOH	48.9	10.7	11.4	28.9	<0.1i
			8 Me_2CO	49.1	10.6	11.8	28.7	>1000i
meso·2HCl	290–295 gas	54	>5 EtOH	48.9	10.7	11.4	28.9	<0.03i
				48.6	10.5	11.2	29.1	>1000i
$C_{16}H_{22}N_2$	70–85 (1)	18						
·2HCl	245–249	82	17 EtOH	49.4	9.9	11.5	29.1	<0.03i
			21 Me_2CO	49.1	9.9	11.2	28.8	>250i
$C_{17}H_{38}N_3$	120–160 (1)	37						
·3HCl	242.5–243.5	40	18 EtOH	52.0	9.8	10.7	27.1	<0.06i
			90 Me_2CO	51.8	9.9	10.4	26.7	>1000i
$C_{12}H_{26}N_2$	114–118 (18)	52						
·2HCl·0.5H_2O	256–258	96	3 EtOH	51.4	10.4	10.0	25.3	<0.06i
			5 Me_2CO	51.6	10.5	9.9	25.6	>250i

mole of hydrogen while the triamine (XXXX B) product absorbed 3 moles. This additional reduction of the triamine presumably is due to rapid initial hydrogenolysis of the substituted diallylamine to 1-isopropylamino-2-butene and N,N′-diisopropyl-2-butene-1,4-diamine which are then further reduced. [n] The R′Cl·HCl reagent, 2-isopropylaminoethyl chloride hydrochloride, was prepared by the procedure of A. C. Cope, H. R. Nace, W. R. Hatchard, W. H. Jones, M. A. Stakmann and R. B. Turner, *J. Am. Chem. Soc.*, **71**, 555 (1949).

Preparation of compounds designed to incorporate the features of type A chelate in a single diamine molecule led to the more active, less toxic (+)-N,N′-bis(1-hydroxy-*sec*-butyl)-ethylenediamine (ethambutol) reported in the following paper.[10]

Experimental

Most of these preparations were run on a scale from 0.1 to 0.5 mole. No attempt was made to obtain maximum yield where adequate product for testing was obtained.

Method A.—Catalytic reductive alkylation[6] usually was carried out with a ratio of 2 moles of the carbonyl compound per mole of diamine with conditions as indicated in the Tables. Although the choice of pressure and catalyst was arbitrary, with compound I an attempt to use lower pressure gave much less complete

(10) R. G. Wilkinson, M. Cantrall and R. G. Shepherd, *J. Med. Pharm. Chem.*, **5**, 835 (1962).

and slower reduction. In those cases where the Tables indicate a range of reduction temperatures, the higher temperature was used to complete a reduction which had leveled off at the initial temperature. In two instances (XIV, XVIII), no reduction occurred under the given conditions until the Schiff base had been formed by azeotropic distillation of the water.

The product was distilled after removal of the catalyst. In a few cases, a substantial portion of the product distilled as a water azeotrope (b.p. 96° for Compound I) from which it was recovered as the hydrochloride salt. This recovered salt was purified by recrystallization or conversion to the base with excess strong alkali, extraction with benzene and distillation.

Method B: Alkylation of Amines Using an Alkyl Halide, Alkylene Dihalide or N-Substituted Aminoethyl Chloride Hydrochloride.–The general procedure was to mix the halo compound with an excess of the amine and solvent as indicated. The mixture was refluxed until either the salt of the product deposited to a large extent, or a sample of the reaction mixture indicated completion (little water-insoluble alkyl halide present or adequate ionic halogen by the silver halide test). Failures using this method were encountered in a few instances. Thus, both 2,3-dibromobutane or propylene dichloride when heated with *t*-butylamine and some ethanol in a bomb at 100° for 12–24 hr. gave no reaction. Similarly no product could be isolated when either dodecyl chloride or dodecyl bromide was heated with ethylenediamine for 3 to 5 hr. without solvent[11] and with a small amount of water.[12] The product (XIX) was finally obtained by reaction of dodecylamine with ethylene dibromide.

Attempted reaction of *t*-amyl bromide with ethylenediamine gave only the olefin and ethylenediamine dihydrobromide. This was not unexpected on the basis of the reported[13] readiness with which *t*-amyl bromide undergoes the elimination reaction. The alternative alkylation of *t*-amylamine went without difficulty.

In the reaction of 1,4-dibromo-2-butene with isopropylamine the low yield of the diamine (XXXXA) probably is due to a high local concentration of the dibromide when rapid mixing of the reagents gave an extremely vigorous reaction. Slow addition of the dibromide to a large excess of the amine probably would have been desirable.

Isolation of the products was accomplished by addition of concentrated alkali, extraction with benzene, usually drying the extract over solid NaOH, and then fractionally distilling.

Method C: Reductive alkylation using sodium borohydride previously[7] has been limited to aromatic Schiff bases. It was, however, found useful for aliphatic amines as in the following example.

To a mixture of 0.05 mole of ethylenediamine and 0.10 mole of valeraldehyde in 100 ml. of ethanol, small portions of sodium borohydride were added with stirring until 0.15 mole had been added during 45 min. The mixture then was boiled for 3 hr. prior to distillation of the ethanol. Addition of 15 ml. of 10 *N* NaOH followed by extraction with benzene (3 × 75 ml.) gave on fractional distillation a forerun of 2.21 g., b.p. 60–100° (12 mm.), which is probably partly the

(11) F. Linsker and R. L. Evans, *J. Am. Chem. Soc.*, **68**, 1432 (1946), reported a high yield under these conditions.

(12) N. Bortnick, L. S. Luskin, M. D. Hurwitz, W. E. Craig, L. J. Enner and J. Mirza, *J. Am. Chem. Soc.*, **78**, 4039 (1956), reported water in small amount to be a desirable catalyst for this type of condensation.

(13) E. D. Hughes, C. K. Ingold and A. D. Scott, *J. Chem. Soc.*, 1271 (1937).

monoamyl derivative. The main fraction (VI) distilled initially at 130–155° (12 mm.) and on redistillation 4.24 g. (42% of theor.) was obtained at 134–136° (13 mm.)

Method D: The Eschweiler-Clarke methylation[14] was used adding the diamine slowly to the mixture of formaldehyde and formic acid. Reaction was then completed by refluxing for 3.5 hr. The mixture was acidified with concentrated HCl and the solvent removed under reduced pressure. The residue was recrystallized from ethanol as indicated in the Table to give XXI.

Method E: Acetylation.—The addition of N,N′-diisopropylethylenediamine to excess acetic anhydride was accompanied by heat evolution. The mixture was refluxed for 30 min. and concentrated under reduced pressure to a solid. Two recrystallizations from acetone gave pure XXIV.

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(14) M. L. Moore, "Organic Reactions," Vol. V, 307 (1949).

Antituberculous Agents. III. (+)-2,2 -(Ethylenediimino)-di-1-butanol[1,2] and Some Analogs

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N-Hydroxyalkyl ethylenediamines have been synthesized by various methods as part of the further study of the antimycobacterial activity of analogs of N,N′-diisopropylethylenediamine. In these hydroxylated compounds an even higher structural selectivity has been observed along with a remarkable stereospecificity. Correlation of biological activity with the postulated ability to form a certain type of chelate is discussed. (+)-2,2′-(Ethylenediimino)-di-1-butanol is two to four times as active as streptomycin against human mycobacteria in mice.

In a series of diamines related to N,N′-diisopropylethylenediamine[3] high antituberculous activity *in vivo* was remarkably specific with

(1) A preliminary communication (Paper I) on this compound has been published by: R. G. Wilkinson, R. G. Shepherd, J. P. Thomas and C. Baughn, *J. Am. Chem. Soc.*, **83**, 2212 (1961).

(2) Biological data have been published by J. P. Thomas, C. Baughn, R. G. Wilkinson and R. G. Shepherd, *Am. Rev. Resp. Dis.*, **83**, 891 (1961).

(3) The study of these related compounds is reported (in Paper II) by R. G. Shepherd and R. G. Wilkinson, *J. Med. Pharm. Chem.*, **5**, 823 (1962).