petroleum ether (b.p. 30–60°) gave 0.9 g. colorless needles, which after several recrystallizations from petroleum ether (b.p. 30–60°) melted 83–85.5°; λ_{max}^{KBr} 2.95 μ (OH); 7.57 μ, 11.65 μ, 11.90 μ ($N \rightarrow O$).

The residue from the petroleum ether extractions was recrystallized several times from methanol, to give 0.09 g. colorless crystals, m.p. 152.5–154.5°. This gave the ultraviolet absorption spectrum of a dioxide and is 2-hydroxymethyl-3,5,6-trimethylpyrazine-1,4-dioxide; λ_{max}^{KBr} 3.05 μ (OH); 7.62, 11.72 μ ($N \rightarrow O$).

Absorption spectra. The ultraviolet absorption spectra of compounds reported in this paper were obtained with a Beckman DU spectrophotometer, with 1.0-cm. cuvets. These are given in Table III.

Infrared absorption spectra were obtained with a Perkin-Elmer Model 21 recording spectrophotometer either as potassium bromide disks or in chloroform solution.[28]

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TABLE III

ULTRAVIOLET ABSORPTION SPECTRA[a]

Compound	λ_{max}, mμ	log ϵ	λ_{max}, mμ	log ϵ
2-Acetoxymethylpyrazine				
5-Methyl	271[b]			
	274	3.99		
6-Methyl	273	3.99		
3,5,6-Trimethyl	279	4.36		
4-Oxide	219	4.23	260	4.18
5-Methyl-4-oxide	215	4.03	264	4.00
5-Methyl-1,4-dioxide	232	4.11	300	4.04
5-Acetoxymethyl	269	3.84		
2-Hydroxymethylpyrazine				
5-Methyl	274	3.87		
6-Methyl	274	3.83		
3,5,6-Trimethyl	280	3.90		
5-Methyl-1,4-dioxide	232	4.10	300	4.00
3,5,6-Trimethyl-*N*-oxide	216	4.31	259	3.03
			296	3.77
3,5,6-Trimethyl-1,4-dioxide	238	4.52	299	4.34

[a] All spectra taken in distilled water. [b] 95% ethanol.

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[28] The authors are indebted to Dr. Oscar Auerbach and the Research Committee, Veterans Administration Hospital, East Orange, N. J., for continued loan of this instrument.

[CONTRIBUTION FROM THE DEVELOPMENT DEPARTMENT, UNION CARBIDE CHEMICALS COMPANY, DIVISION OF UNION CARBIDE CORPORATION]

A Novel Synthesis of Homopiperazine and Its Monomethyl Derivatives

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Homopiperazine has been synthesized in a yield of about 32% by a new method involving the catalytic reductive cyclization of *N*-(2-cyanoethyl)ethylenediamine. 1-, 2-, 5-, and 6-methylhomopiperazine, the four possible monomethylhomopiperazines, were prepared analogously. *N*-(2′-Aminoethyl)-1,3-propanediamine and its monomethyl derivatives were formed as co-products in 28 to 50% yields.

The intermediate cyano compounds were made by the interaction of the appropriate diamines and unsaturated nitriles.

Several derivatives of homopiperazine (1,4-diazacycloheptane) (I) have already been shown to have marked and desirable physiological activity.[1,2,3] Progress in finding new active compounds based on homopiperazine has, however, undoubtedly been hampered because of the relative inaccessibility of the base and its simple derivatives. Until very recently, the only methods published[4,5] for the preparation of homopiperazine involved the alkylation of the disodium salt of a *N*,*N*′-diarylsulfonylethylenediamine with a 1,3-dihalogenopropane followed by acid hydrolysis of the *N*,*N*′-diarylsulfonylhomopiperazine formed to homopiperazine. These syntheses are tedious and expensive and are, therefore, ill-suited for commercial production. A publication[6] which appeared last year after the work reported in this paper had been completed described the preparation of the cyclic amine (I) by the cyclodehydration of *N*-(2′-hydroxyethyl)-1,3-propanediamine by catalytic means or by pyrolysis of its hydrohalides. Over-all yields based on ethanolamine, the starting material, varied from 7.7 to 10.5% and from 7.4 to 19.2%, respectively.

Of the possible monomethylhomopiperazines, only the 1- and 2-methyl compounds have been reported in the literature. 1-Methylhomopiperazine has been made (a) by the ring enlargement of 1-methyl-4-piperidone by a Schmidt-type rearrangement followed by lithium aluminum hydride reduction of the resulting homopiperazinone,[1,7,8] and (b) in poor yield by the catalytic cyclodehydration

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(1) A. H. Sommers, R. J. Michaels, Jr., and A. W. Weston, *J. Am. Chem. Soc.*, **76**, 5805 (1954).

(2) J. W. Reinertson and P. E. Thompson, *Antibiotics and Chemotherapy*, **5**, 566 (1955).

(3) P. Brookes, R. J. Terry, and J. Walker, *J. Chem. Soc.*, 3165 (1957).

(4) L. Bleier, *Ber.*, **32**, 1825 (1899).

(5) C. C. Howard and W. Marckwald, *Ber.*, **32**, 2038 (1899).

(6) Takeo Ishiguro and Masaaki Matsumura, *Yakugaku Zasshi*, **78**, 153 (1959); *Chem. Abstr.*, **53**, 13163 (1959).

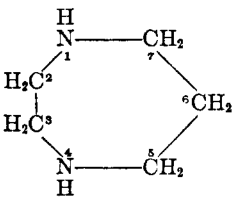
(7) J. G. Scruggs, Ph.D. dissertation, University of Michigan, 1956.

(8) P. S. Wadia and N. Anand, *J. Sci. Ind. Research* (*India*), **17B**, 31 (1958); *Chem. Abstr.*, **52**, 15549 (1958).

of *N*-(2′-hydroxyethyl)-*N*-methyl-1,3-propanediamine.[6] 2-Methylhomopiperazine has recently been prepared by the catalytic cyclodehydration of *N*-(2′-hydroxypropyl)-1,3-propanediamine.[9]

We wish to report a novel and simple synthesis of homopiperazine and the four possible monomethylhomopiperazines, *i.e.*, the 1-, 2-, 5-, and 6-methyl compounds, based on the reductive cyclization of *N* - (2 - cyanoethyl)ethylenediamine (II) and its methyl derivatives. The cyano compounds required were made by the interaction of the appropriate diamines and unsaturated nitriles most of which are cheap and readily available.

In the case of homopiperazine, the synthesis involves first the addition of acrylonitrile to ethylenediamine to form the cyanoethylated diamine (II) and then reductive cyclization of this compound with hydrogen and a nickel catalyst. Under optimum conditions for the cyclization, which include a hydrogenating pressure of 650 to 950 p.s.i.g. and a reaction temperature of 130°, homopiperazine was produced in a yield of about 32% based on acrylonitrile. The four monomethylhomopiperazines were prepared analogously.



I

$H_2NCH_2CH_2NHCH_2CH_2CN$
II

$H_2NCH_2CH_2NHCH_2CH_2CH_2NH_2$
III

$H_2NCH_2CH_2N(CH_3)CH_2CH_2CN$
IV

$CH_3NHCH_2CH_2NHCH_2CH_2CN$
V

N-(2′-Aminoethyl)-1,3-propanediamine (III) and its monomethyl derivatives were formed as coproducts in over-all yields of 28 to 50% based on the unsaturated nitriles.

Because of their thermal instability, the intermediate cyanoethylated diamine (II) and its monomethyl derivatives were prepared as residue products and converted into the corresponding homopiperazines without further purification.

Cyanoethylation of *N*-methylethylenediamine yielded a product which analyses specific for aliphatic primary[10] and tertiary[11] amino groups showed to be a mixture of the isomers (IV) and (V) in the respective proportions of 73 and 27%. The isomer (IV) was separated in an almost pure state by distillation. Predominant formation of the tertiary amine (IV) may be a result of the secondary amino group of *N*-methylethylenediamine being more basic than the primary amino group.

The effectiveness of the following catalysts for the reductive cyclization was examined: commercial Raney nickel, Raney cobalt, copper chromite, Girdler G-49A catalyst,[12] and 5% palladium on carbon. Of these, only Girdler G-49A catalyst and Raney nickel proved capable of bringing about the desired cyclization. The former catalyst was much superior to the latter. Under identical reaction conditions, Girdler G-49A catalyst produced a 32% yield of homopiperazine; the yield with Raney nickel was but 4.8%.

An inert diluent was advantageous for the reductive cyclization, probably because dilution increases the likelihood of the intramolecular reaction which leads to the desired homopiperazine. Thus, catalytic reduction of the nitrile (II) without a diluent gave homopiperazine and coproduct triamine (III) in yields of 69 and 75%, respectively, of those obtained under comparable conditions when an amount of diluent (*t*-butyl alcohol) equal in weight to the cyano-compound (II) was employed. Furthermore, the weight of high-boiling nitrogeneous residue, which presumably consisted of high molecular weight amines, increased by 21%. *tert*-Butyl alcohol was the most satisfactory diluent examined. 2-Propanol and tetrahydrofuran gave inferior results.

Early reductive cyclization experiments were done by mixing the nitrile (II) with an equal weight of *t*-butyl alcohol, adding catalyst, and then hydrogenating the mixture. Later, it was discovered that gradual addition of the cyano compound (II) to a mixture of solvent and catalyst maintained at the desired temperature and pressure in the autoclave produced superior yields. Thus, when the nitrile (II) was fed to the auto clave over 3.3 hours the yield of homopiperazine was increased by about 33% over that secured by the earlier procedure.

A reaction temperature of 130° (with a Girdler G-49A catalyst concentration of 5% and a hydrogenating pressure of 650 to 950 p.s.i.g.) has been found to give the best yields of homopiperazine. The cyclization also proceeded at 115° but then the reaction was slow and unsatisfactory. Reaction

TABLE I

VARIATION OF THE YIELD OF HOMOPIPERAZINE WITH HYDROGENATING PRESSURE[a]

Hydrogenating Pressure, p.s.i.g.	Hydrogenation Time, Min.	Yield of Homopiperazine, %[b]
130–150	655	14.0
250–300	240	25.2
400–450	195	26.0
650–950	156	32.4

[a] Experiments listed were done by continuously feeding *N*-(2-cyanoethyl)ethylenediamine (200.0 g.) over 3.3 hours into a mixture of anhydrous *tert*-butyl alcohol (200.0 g.) and Girdler G-49A catalyst (20.0 g.) kept in a 3 l. stirred autoclave at 130° under the hydrogenating pressure quoted. [b] Based on acrylonitrile.

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[9] Takeo Ishiguro and Masaaki Matsumura, *Yakugaku Zasshi*, **79**, 302 (1959); *Chem. Abstr.*, **53**, 16147 (1959).

[10] F. E. Critchfield and J. B. Johnson, *Anal. Chem.*, **29**, 1174 (1957).

[11] F. E. Critchfield, G. L. Funk, and J. B. Johnson, *Anal. Chem.*, **28**, 76 (1956).

[12] Consists of reduced and stabilized nickel on a kieselguhr support and contains about 65% of nickel. It is sold by Girdler Catalysts, Chemical Products Division, Chemetron Corporation, Louisville, Ky.

TABLE II

METHYL-SUBSTITUTED *N*-(2-CYANOETHYL)ETHYLENEDIAMINES

Formula	B.P., Mm. and n_D^{20} or M.P.	Calcd., %			Found, %		
		C	H	N	C	H	N
$H_2NCH_2CH_2N(CH_3)CH_2CH_2CN$[a]	72/0.3; 1.4628	56.7	10.3	33.0	57.0	10.6	32.8[d]
$H_2NCH_2CH_2NHCH(CH_3)CH_2CN$	96.5/0.77; 1.4705	56.7	10.3	33.0	57.0	10.6	32.2
Dipicrate ($C_{18}H_{19}N_9O_{14}$)[b]	179–180			21.5			21.5
$H_2NCH_2CH_2NHCH_2CH(CH_3)CN$	77/0.2; 1.4635	56.7	10.3	33.0	56.5	10.6	33.4
Dipicrate ($C_{18}H_{19}N_9O_{14}$)[b]	187–188			21.5			21.7
$H_2NCH(CH_3)CH_2NHCH_2CH_2CN$ $H_2NCH_2CH(CH_3)NHCH_2CH_2CN$ } [c]	80.5/0.2; 1.4635	56.7	10.3	33.0	56.8	10.8	33.2

[a] Contained about 5% of the isomer $CH_3NHCH_2CH_2NHCH_2CH_2CN$. [b] Prepared in, and recrystallized from, ethanol. [c] Mixture of isomers. [d] Calcd.: NH_2, 12.6. Found: NH_2 [by the method of Critchfield and Johnson (ref. 10)], 11.9.

temperatures from 130 to 200° led to reduced yields of the cyclic amine (I).

The yield of homopiperazine depended on the hydrogenating pressure during the cyclization. This effect is summarized in Table I.

No attempt was made to find the best conditions for the reductive cyclization of the appropriate nitriles to the corresponding methylhomopiperazines. With one exception (the preparation of 1-methylhomopiperazine), the conditions used were those found optimum for the reductive cyclization of the cyano compound (II).

One possible way in which the reductive cyclization could take place is by cyclic deamination of the triamine (III). A nickel-catalyzed cyclic deamination of this type is, however, unlikely at a reaction temperature below 150°.[13] Positive proof that the reductive cyclization does not follow this path was provided by substituting the triamine (III) for the nitrile (II) in a reaction where conditions were otherwise optimum for the preparation of homopiperazine. Only unchanged triamine (III) could be isolated at the end of the reaction.

EXPERIMENTAL

N-(2-Cyanoethyl)ethylenediamine. Acrylonitrile (93.8 g., 1.77 moles) was gradually added with stirring and cooling to anhydrous ethylenediamine (425.0 g., 7.07 moles) kept under an atmosphere of dry nitrogen, the temperature of the mixture being maintained between 20° and 30° throughout the addition.

After being stirred for 15 min., the mixture was evaporated at a temperature below 70° under reduced pressure (30 to 5 mm.) in a current of dry nitrogen. This operation was continued until the residue no longer lost weight. Unchanged ethylenediamine (318.0 g.) was recovered and there remained *N*-(2-cyanoethyl)ethylenediamine (200.0 g., 99.8% yield) as a straw-colored oil, b.p. 106–108°/1.0 mm.

Anal. Calcd. for $C_5H_{11}N_3$: NH_2, 14.2; neut. equiv., 56.6. Found: NH_2 (by the method of Critchfield and Johnson[10]), 14.3; neut. equiv.,[14] 56.8.

This residual product was employed without further purification for the preparation of homopiperazine.

Methyl-substituted N-(2-cyanoethyl)ethylenediamines. The intermediate cyano compounds for the preparation of the monomethylhomopiperazines were made in a similar way from the appropriate diamine and unsaturated nitrile. Condensation of crotononitrile and ethylenediamine was effected at 50 to 60°. Methacrylonitrile and ethylenediamine were caused to react by adding the nitrile to the diamine over 3.75 hr. while the temperature of the reaction mixture was gradually raised from 10 to 86°; subsequently, the mixture was stirred at 100° for 0.5 hr. then refluxed for 3 hr. The methyl-substituted cyanoethylethylenediamines are listed in Table II.

Homopiperazine. Anhydrous *t*-butyl alcohol (200.0 g.) and Girdler G-49A catalyst[12] (20.0 g.) were added to a 3-l., stainless steel, autoclave fitted with a stirrer. The air was replaced by hydrogen and then the pressure in the autoclave was increased to 700 p.s.i.g. by the addition of hydrogen. The autoclave and its contents were heated to 130° whereupon *N*-(2-cyanoethyl)ethylenediamine (200.0 g., 203 cc.) was introduced therein by a proportioning pump at the rate of 1 cc. per min. (29.6% per hour), this rate being maintained throughout the addition. Absorption of hydrogen took place smoothly and regularly and was complete at the end of the feed period. During the reaction the temperature was kept at 130° and the hydrogenating pressure at 650 to 950 p.s.i.g. These conditions were maintained for 1.5 hr. after all the cyano compound had been added.

The reaction product was filtered through a kieselguhr-coated filter, the residue washed with *t*-butyl alcohol (2 × 50 g.), and the washings combined with the filtrate. Distillation of the mixture at atmospheric pressure (750 mm.) at a reflux ratio of 3:1 through a column having an efficiency of about 10 theoretical plates afforded homopiperazine (57.3 g., 32.4% yield based on acrylonitrile) as a fraction of b.p. 169° which on cooling formed colorless platelets, m.p. 43° (lit. b.p. 168–170°,[4,6] 167°/764 mm.[5]; m.p. 42°[5,6]). The homopiperazine had the following boiling points at reduced pressures: 92°/50 mm. and 60°/10 mm.

Anal. Calcd. for $C_5H_{12}N_2$: neut. equiv., 50.1. Found: neut. equiv.,[14] 50.5.

N-(2'-Aminoethyl)-1,3-propanediamine. Distillation at reduced pressure of the residue from the foregoing preparation of homopiperazine gave the triamine (86.8 g., 41.9% yield based on acrylonitrile). Properties of this amine are given in Table IV.

Monomethylhomopiperazines. With the exception of 1-methylhomopiperazine, the methylhomopiperazines were prepared in the same way as that described for homopiperazine. The 1-methyl compound was made as follows.

Anhydrous *t*-butyl alcohol (125.0 g.), *N*-(2-cyanoethyl)-*N*-methylethylenediamine (125.0 g.), and Girdler G-49A catalyst[12] (12.5 g.) were added to a 3-l., stainless steel, autoclave fitted with a stirrer. The air was replaced by hydrogen and then the pressure in the autoclave was increased to 700 p.s.i.g. by the addition of hydrogen. The

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(13) H. Adkins, *The Reaction of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts*, University of Wisconsin Press, Madison, Wis., 1937, p. 55.

(14) Determined by titration with perchloric acid in acetic acid.

TABLE III

THE MONOMETHYLHOMOPIPERAZINES AND THEIR PICRATES[a]

Position of Methyl Group	Yield, %[b]	B.P./Mm. and n_D^{20} or M.P.	Formula	Analyses					
				Calcd., %			Found, %		
				C	H	N	C	H	N
1	16.8	164/754; 1.4769	$C_6H_{14}N_2$			24.5			24.4[g]
Dipicrate		245 dec.[c,d]	$C_{18}H_{20}N_8O_{14}$			19.7			19.3
2	8.3	175–175.5/752[e]; 1.4802[f]	$C_6H_{14}N_2$	63.1	12.4	24.5	62.7	12.7	24.2
Dipicrate		278 dec.	$C_{18}H_{20}N_8O_{14}$			19.7			19.9
5	38.7	175–175.4/745; 1.4843	$C_6H_{14}N_2$	63.1	12.4	24.5	63.2	12.2	24.5
Dipicrate		256 dec.	$C_{18}H_{20}N_8O_{14}$			19.7			19.9
6	20.6	181–181.3/755; 1.4869	$C_6H_{14}N_2$	63.1	12.4	24.5	62.9	12.4	24.5
Dipicrate		255–256 dec.	$C_{18}H_{20}N_8O_{14}$			19.7			19.5

[a] The picrates were prepared in, and recrystallized from, water. [b] Over-all, based on the unsaturated nitriles. [c] Ref. 6, m.p. 242–243° dec. [d] Ref. 7, m.p. 233–234°. [e] M.p. 28°. [f] Value determined at 30°. [g] Calcd.: tertiary-amino N, 12.3. Found: tertiary-amino N [by the method of Critchfield, Funk, and Johnson (ref. 11)], 12.3.

TABLE IV

N-(2′-AMINOETHYL)-1,3-PROPANEDIAMINE AND MONOMETHYL DERIVATIVES

Formula	Yield, %[a]	B.P./Mm. and n_D^{20} or M.P.	Analyses					
			Calcd., %			Found, %		
			C	H	N	C	H	N
$H_2NCH_2CH_2NHCH_2CH_2CH_2NH_2$	41.9	72/1.0; 1.4805	51.2	12.9	35.9	51.6	13.5	35.0
Tripicrate ($C_{23}H_{24}N_{12}O_{21}$)[b]		228–229 dec.			20.9			21.0
$H_2NCK_2CH_2NHCH(CH_3)CH_2CH_2NH_2$	27.9	69.3–69.4/1.0; 1.4777	54.9	13.1	32.0	54.7	13.1	32.1
Tripicrate ($C_{24}H_{26}N_{12}O_{21}$)[b]		182–183			20.5			20.1
$H_2NCH_2CH_2NHCH_2CH(CH_3)CH_2NH_2$	47.1	75–76/1.0; 1.4880	54.9	13.1	32.0	55.0	12.7	31.9
Tripicrate ($C_{24}H_{26}N_{12}O_{21}$)[b]		184–185			20.5			20.9
$CH_3NHCH_2CH_2NHCH_2CH_2CH_2NH_2$ $H_2NCH_2CH_2N(CH_3)CH_2CH_2CH_2NH_2$ [c]	40.5	62–65.5/1.1	54.9	13.1	32.0	54.8	13.5	31.8
$H_2NCH(CH_3)CH_2NHCH_2CH_2CH_2NH_2$ $H_2NCH_2CH(CH_3)NHCH_2CH_2CH_2NH_2$ [c]	48.2	73–75/1.0; 1.4737	54.9	13.1	32.0	54.6	13.3	31.9

[a] Over-all, based on the unsaturated nitriles. [b] Prepared in, and recrystallized from, ethanol. [c] Mixtures of isomers.

autoclave and its contents were heated to 130° and kept at this temperature at a hydrogenating pressure of 600 to 950 p.s.i.g. until uptake of hydrogen had ceased and thereafter for 3 hours. Working up of the product by the method given for homopiperazine afforded 1-methylhomopiperazine.

The monomethylhomopiperazines and their picrates are listed in Table III.

Methyl-substituted N-(2′-aminoethyl)-1,3-propanediamines. These triamines (see Table IV) were isolated by distillation at reduced pressures of the residues from the foregoing syntheses of the monomethylhomopiperazines.

Attempted cyclic deamination of N-(2′-aminoethyl)-1,3-propanediamine. This experiment was done in the same way as that described for the reductive cyclization of *N*-(2-cyanoethyl)ethylenediamine in the presence of Girdler G-49A catalyst excepting that an equal weight of *N*-(2′-aminoethyl)-1,3-propanediamine (200.0 g.) was substituted for the cyanoethylethylenediamine. Uptake of hydrogen was negligible during the reaction.

Distillation of the product afforded only unchanged *N*-(2′-aminoethyl)-1,3-propanediamine (191.5 g.), b.p. 70–74°/1.0 mm.

Anal. Calcd. for $C_5H_{15}N_3$: neut. equiv., 39.1. Found: neut. equiv.,[14] 39.7.

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