products (estimated 50% yield) but no uracil. However, a 0.6% yield of formaldehyde was obtained from this reaction by bubbling nitrogen into the solution throughout the heating period, passing the gases through a water trap (initial volume of 2 ml.) and assaying the trap solution with chromotropic acid.

After heating a sealed tube containing 0.004 *M* aqueous 5-hydroxymethyluridine at 100° for 65 hr., chromatograms revealed the formation of only traces of uridine and an unknown product. Using 0.002 *M* hydroxymethyluridine in 3 *N* HCl and a heating period of 24 hr., there was extensive breakdown to 5-HMU and three unknown compounds but no uridine or uracil. After heating sealed tubes containing 0.004 *N* 5-hydroxymethylcytosine in water solution or 0.002 *N* hydroxymethylcytosine in 0.1 *N* HCl at 100° for 24 hr., the breakdown products consisted of 5-HMU and unknown products but neither uracil nor cytosine. Sealed tubes containing 0.004 *M* aqueous solutions of 5-hydroxymethyl-6-methyluracil and the lactone of 5-hydroxymethylorotic acid (XII) were heated at 100° for 23 hr. By chromatography it was then estimated that about 40% of the first compound was degraded to 6-methyluracil, but none of the lactone was converted to orotic acid (XI) although much of it was hydrolyzed to XIII.

Paper Chromatography.—A filter paper sheet (Whatman No. 1, 20 × 22 cm.) was spotted 2.5 cm. from the edge and formed into a cylinder with the vertical edges of the sheet held nearly in contact by glass ringlets. The cylinder was then placed in a wide-mouth, half gallon fruit jar containing 50 ml. of solvent for ascending chromatography at a constant temperature of 28°. For two-phase solvent systems, the aqueous phase was placed in a 20-ml. beaker within the jar. Most of the pyrimidines were detected as dark spots on chromatograms held in front of an ultraviolet lamp (2537 Å.). Ribosides could generally be distinguished from other pyrimidine derivatives by their markedly lowered R_f values in the presence of borate,[28] employing *sec*-butyl alcohol saturated with 5% boric acid, and an inner beaker containing equal amounts of *sec*-butyl alcohol and 1.5 *N* ammonia.

Acknowledgment.—Valuable technical assistance has been provided by Philip Anthony, now at the University of Hawaii.

(28) I. A. Rose and B. S. Schweigert, THIS JOURNAL, **73**, 5903 (1951).

LOS ANGELES, CAL.
LONG BEACH, CAL.

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, LAKESIDE LABORATORIES, INC.]

Aminolysis and Hydrazinolysis Products of N-Methyl-3-chloropiperidine. Non-mercurial Diuretic Agents

BY JOHN H. BIEL, WALLACE K. HOYA AND HELEN A. LEISER

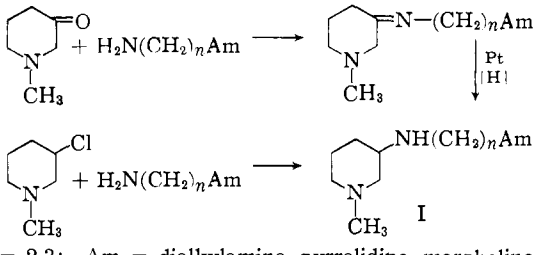
RECEIVED OCTOBER 15, 1958

The initial finding that maleic acid had diuretic properties in dogs prompted the synthesis of a number of maleic acid salts of alkylenediamine derivatives. This paper deals with the nature of the reaction products obtained from the aminolysis, hydrazinolysis of N-methyl-3-chloropiperidine, the unequivocal synthesis of N-(1-methyl-3-piperidyl)-N,N′-disubstituted alkylenediamines and N-(1-methyl-3-piperidyl)-N′-(w-aminoalkyl)-hydrazines, and the physiologic properties of the maleate salts. Optimum diuretic properties were obtained with the 2-pyrrolidylmethylethylenediamines. The isomeric 3-piperidyl derivatives and the isosteric hydrazines were considerably less potent. The more active diuretic agents also displayed pronounced blood pressure lowering effects in the dog.

The finding in our laboratories that the diuretic effect of maleic acid could be markedly enhanced when the acid was administered in the form of certain diamine salts[1] prompted the synthetic investigation of a variety of alkylene diamines.

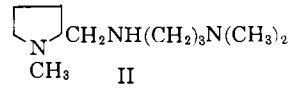
The present paper deals with the reaction of N-methyl-3-chloropiperidine with certain alkylene diamines as well as hydrazine, the nature of the reaction products and the pharmacologic properties of these new derivatives.

Two modes of preparation were employed in an effort to synthesize compounds of structure I

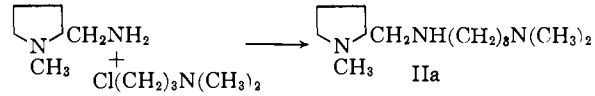


n = 2,3; Am = dialkylamino, pyrrolidino, morpholino, 4-methylpiperazino and *m*-chlorobenzylamino

Since the reaction products obtained from the condensation of 1-methyl-3-piperidone and 1-methyl-3-chloropiperidine with N,N-dimethylpropylenediamine were not identical as shown by their chemical and physiologic properties, we suspected that a ring contraction had occurred (in the case of the N-methyl-3-chloropiperidine reaction) to a pyrrolidylmethyl derivative (II). Such a phenomenon had been previously described by Reitsema[2] for N-ethyl-3-chloropiperidine, when the latter was allowed to react with such strongly basic nucleophilic agents as benzylamine and ammonia.



The structure of II was proved by treating 1-methyl-2-pyrrolidylmethylamine[2] with 3-dimethylaminopropyl chloride



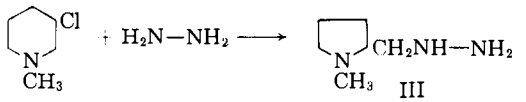
The identity of product II and IIa was established *via* the mixed melting points of the picrate and maleate salts and the similarity of their physiologic properties: While product I produced a 53% increase in the diuretic response with a 50 mg./kg. dose (oral, dog), products II and IIa produced a 300-330% diuresis increase at the same dose.

A similar ring contraction was observed when 1-methyl-3-chloropiperidine was treated with hy-

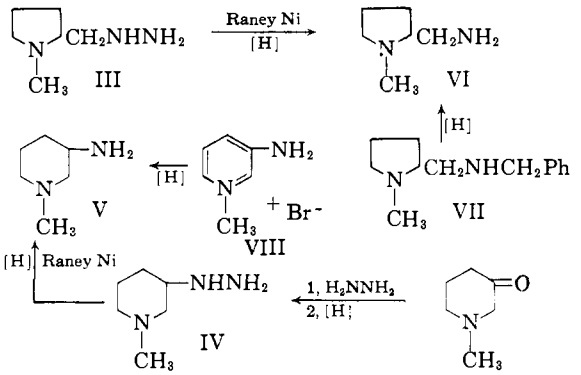
(1) R. R. Rowland and P. A. Nuhfer, unpublished report.

(2) R. H. Reitsema, THIS JOURNAL, **71**, 2041 (1949).

drazine in aqueous medium yielding the 1-methyl-2-hydrazinomethylpyrrolidine (III)



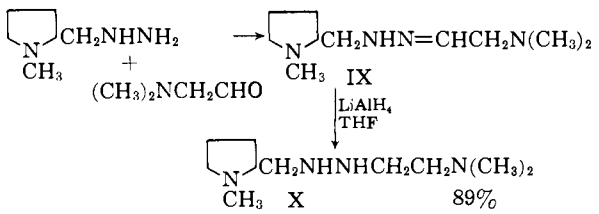
The structure of III was established both directly and indirectly



The mixed melting points of the maleate salts of V and VI were depressed. N-Methyl-2-pyrrolidylmethylamine prepared by either the catalytic cleavage of the 2-pyrrolidylmethylhydrazine III or the debenzylation of the N-benzyl derivative VII yielded identical maleate and picrate salts.

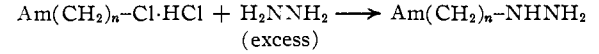
N-Methyl-3-aminopiperidine (V) was prepared either by the catalytic cleavage of the hydrazine derivative IV or the reduction of the methobromide salt of 3-aminopyridine (VIII).

1 - Methyl - 2 - pyrrolidylmethyl hydrazine was treated with dimethylaminoacetaldehyde (formed *in situ* by cleavage of the acetal with aqueous hydrochloric acid) to form the corresponding ethylidene compound IX which was then reduced with lithium aluminum hydride in tetrahydrofuran to the desired hydrazine derivative X

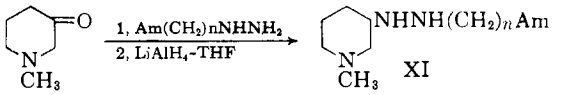


Catalytic reduction of compound IX with palladium or platinum oxide invariably resulted in the cleavage of the hydrazine bond to yield low boiling amines.

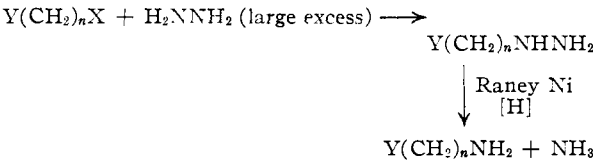
A number of the isomeric N-(1-methyl-3-piperidyl)-N′-(disubstitutedamino alkyl)-hydrazines (XI) were also prepared, in order to compare their effects with the corresponding pyrrolidylmethyl derivatives. Their synthesis was accomplished quite readily by producing the N,N-disubstituted aminoalkylhydrazines in good yield from the corresponding haloamines with a large excess (six molar) of hydrazine hydrate



The large excess of hydrazine is necessary to prevent the formation of *unsym.* disubstituted hydrazines. The aminoalkyl hydrazines were then allowed to react with 1-methyl-3-piperidone to form the Schiff base which was reduced in its crude form with lithium aluminum hydride in tetrahydrofuran

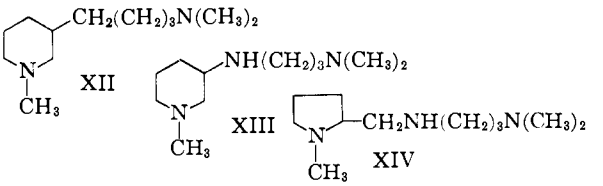


The hydrazinolysis of primary alkyl halides has proved in our hands a convenient means of obtaining monosubstituted alkyl hydrazines in good yield and of high purity. Such hydrazines are then readily cleaved with Raney nickel to yield the primary amines in excellent yields. Hence, this method lends itself to the facile preparation of primary amines with varying types of substituents on the alkyl chain



X = Cl, Br, I
Y = phenyl, hydroxy, 2° amino group
n = 2,3

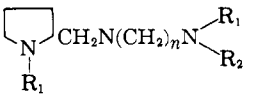
Structure–Activity Relationships.—The compounds were screened primarily for their oral diuretic activity in female dogs at a standard dose of 50 mg./kg. The data are summarized in Tables III and IV. Optimum diuretic properties were displayed by N-(1-methyl-2-pyrrolidylmethyl)-N′,-N′-diethylethylenediamine dimaleate (no. 3). Increasing the length of the chain or the bulkiness of the terminal amino group tended to decrease diuretic potency. Replacing the pyrrolidylmethyl with an isomeric 3-piperidyl ring (nos. 1 *vs.* 16 and 12 *vs.* 17) produced a sharp lowering of the diuretic effect. The isosteric replacement of CH_2 by NH to yield a hydrazine derivative (nos. 1 *vs.* 11) likewise reduced diuretic efficacy. Phillips[3] has previously reported on the potent hypotensive properties of 1 - methyl - 3 - (4′ - dimethylamino) - butylpiperidine (XII) in cats. The nitrogen isostere XIII prepared by us exhibited only a fleeting hypotensive effect when administered orally to dogs (10 mg./kg.)



However, the 2-pyrrolidylmethyl isomer of XIII (structure XIV) produced a 50% drop in blood pressure for a period of thirty minutes at the same dose level. It is interesting to note in this connection that some 3-(ω-aminoalkynyl)-piperidines prepared by us[4] only produced fleeting blood pressure effects, whereas the pyrrolidylmethyl-(ω-amino)-alkynes were potent blood pressure depressants

(3) A. P. Phillips, THIS JOURNAL, **76**, 2211 (1954).
(4) John H. Biel and F. DiPierro, *ibid.*, **80**, 4609 (1958).

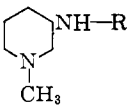
TABLE I

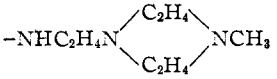


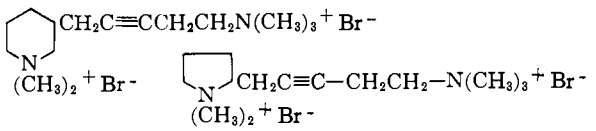
R_1	R_2	n	$N<^{R_1}_{R_2}$	B.p. °C.	B.p. Mm.	Yield, %	$n^{25}D$	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	H	3	$-N(CH_3)_2$	88–89	1.9	56.0	1.4661[a]	$C_{11}H_{25}N_3$	21.10	20.71
CH_3	CH_3	3	$-N(CH_3)_2$	107	4.7	52.6	1.4637[a]	$C_{12}H_{27}N_3$	19.70	19.53
CH_3	H	2	$-N(C_2H_5)_2$	99	2.3	64.6	1.4642[a]	$C_{12}H_{27}N_3$	19.70	19.32
CH_3	H	3	$-N(C_2H_5)_2$	120–122	4.0	64.2	1.4665	$C_{13}H_{27}N_3$	18.48	17.81
CH_3	H	2	$-N(CH_3)_2$	90	4.4	41.5	1.4630	$C_{10}H_{23}N_3$	22.68	21.45
CH_3	H	3	Morpholino	125–127	0.4	64.2	1.4875[a]	$C_{13}H_{27}N_3O$	17.41	17.05
CH_3	H	3	4-Methylpiperazino	154–155	2.4	55.0	1.4879[a]	$C_{14}H_{30}N_4$	22.02	21.54
CH_3	H	2	*o*-Cl-Benzyl methylamino	125–135	0.07	61.5	1.5244	$C_{16}H_{26}ClN_3$	14.20	13.88
CH_3	H	3	Pyrrolidino	142–143	6	61.1	1.4837	$C_{13}H_{27}N_3$	18.65	18.36
CH_3	H	0	4-Methylpiperazino	97–98	3.8	56.0	1.4820[a]	$C_{11}H_{19}N_3$	21.31	21.08

[a] $n^{20}D$.

TABLE II



R	B.p. °C.	B.p. Mm.	Yield, %	$n^{25}D$	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
$-NHC_2H_4N(CH_3)_2$	81–84	0.03	70.3	1.4782	$C_{10}H_{24}N_4$	20.97	20.61
$-NHC_2H_4NC_4H_8$	110–112	0.12	56.3	1.4992	$C_{12}H_{26}N_4$	18.57	18.50
	131–135	0.05	58.2	1.4978	$C_{13}H_{29}N_5$	27.40	27.78
$-(CH_2)_3N(CH_3)_2$	93	1.0	86.7	1.4711	$C_{11}H_{25}N_3$	21.10	20.56
$-NH_2$	88–90	1.8	34.2	1.4907	$C_6H_{15}N_3$	21.68	21.53



Some of the other pyrrolidylmethylethylenediamines (nos. 3, 4 and 6 in Table III) exhibited similar blood pressure lowering effects.

The 3-piperidylhydrazines (Table IV) had little, if any, effect on the dog blood pressure.

It would appear, therefore, that the diuretic effect of maleic acid can be markedly potentiated by administering it as a salt of certain pyrrolidylmethylethylenediamine derivatives. The isomeric 3-piperidyl derivatives and the isosteric hydrazines were markedly inferior as diuretic agents. Some of the more potent diuretic agents also displayed blood pressure lowering properties.

Experimental

1,1-Dimethyl-3-(N-methyl-2-pyrrolidylmethyl)-propylenediamine (II). Method A.—A mixture consisting of 33.85 g. (0.25 mole) of N-methyl-3-chloropiperidine, 25.7 g. (0.25 mole) of 3-dimethylaminopropylamine and 250 cc. of methylisobutylcarbinol was refluxed for 15 hours. The solvent was removed *in vacuo*. The residue was dissolved in 100 cc. of water, saturated with sodium hydroxide, and the product was isolated by extraction of the alkaline mixture with ether. The combined ether extracts were dried with potassium carbonate, and the product collected by distillation, b.p. 95° (2.2 mm.), yield 27 g. (68.5%), $n^{20}D$ 1.4661. *Anal.* Calcd. for $C_{11}H_{25}N_3$: N, 21.10. Found: N, 20.71.

1,1-Dimethyl-3-(N-methyl-2-pyrrolidylmethyl)-propylenediamine Dimethobromide.—To a solution of 15 g. (0.075 mole) of the base dissolved in 150 cc. of isopropyl alcohol was added 14.5 g. (0.15 mole) of methyl bromide. The precipitate was collected by filtration and recrystallized from 250 cc. (4:1) of isopropyl alcohol–ethanol; yield 8.5 g. (28.8%), m.p. 275–277° dec. *Anal.* Calcd. for $C_{13}H_{31}Br_2N_3$: Br, 41.13; N, 10.78. Found: Br. 40.99; N, 10.62.

1,1-Dimethyl-3-(N-methyl-2-pyrrolidylmethyl)-propylenediamine Trihydrochloride.—To a solution of 10.0 g. (0.05 mole) of free base dissolved in 200 cc. of acetone was added ethereal hydrochloric acid to *p*H 3. The solid was collected by filtration and was recrystallized several times from ethanol; yield 14.5 g. (94%), m.p. 199–200°. *Anal.* Calcd. for $C_{11}H_{28}Cl_3N$: Cl, 34.52; N, 13.61. Found: Cl, 34.16; N, 13.59.

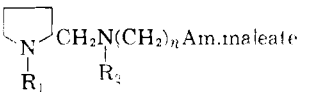
1,1-Dimethyl-3-(N-methyl-2-pyrrolidylmethyl)-propylenediamine Trimaleate (IIb).—To 17.4 g. (0.15 mole) of maleic acid dissolved in 125 cc. of ethanol was added 10 g. (0.05 mole) of free base diluted in 100 cc. of ethanol. The solution was heated to reflux to dissolve the solid, cooled to 25°, and collected by filtration; yield 24.7 g. (90.3%), m.p. 135–136°. *Anal.* Calcd. for $C_{23}H_{37}N_3O_{12}$: N, 7.67; neut. equiv., 91.26. Found: N, 7.58; neut. equiv., 90.7.

1,1-Dimethyl-3-(N'-methyl-2-pyrrolidylmethyl)-propylenediamine Tripicrate (IIc).—To 3.45 g. (0.015 mole) of picric acid dissolved in 50 cc. of ethanol was added 1 g. (0.005 mole) of base in 10 cc. of ethanol. A precipitate was collected by filtration and triturated several times in boiling ethanol; yield 4.25 g. (96%), m.p. 208–209°. *Anal.* Calcd. for $C_{29}H_{34}N_{12}O_{21}$: N, 18.95. Found: N, 18.76.

1,1-Dimethyl-3-(N-methyl-3-piperidyl)-propylenediamine (I).—To 0.1 g. of pre-reduced platinum in 25 cc. of ethanol in a Parr hydrogenator was added a solution consisting of 6.8 g. (0.06 mole) of N-methyl-3-piperidone, 6.15 g. (0.06 mole) of 3-dimethylaminopropylamine and 75 cc. of ethanol. The reduction occurred at 25° and 60 p.s.i. hydrogen in a period of 4 hours. The catalyst was removed by filtration and the product collected by distillation; b.p. 93° (1.0 mm.), yield 10.4 g., 86.9%, $n^{20}D$ 1.4711. *Anal.* Calcd. for $C_{11}H_{25}N_2$: N, 21.1. Found: N, 20.56.

1,1-Dimethyl-3-(N'-methyl-3-piperidyl)-propylenediamine Trihydrochloride (Ia).—To 2 g. (0.01 mole) of base dissolved in 50 cc. of anhydrous ether was added ethereal hy-

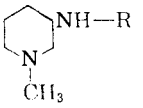
TABLE III

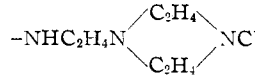


No.	R_1	R_2	n	Am	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found	Neut. equiv. Calcd.	Found	Oral diuretic activity, %[a]
1	CH_3	H	3	$-N(CH_3)_2$	135–136	90.3	$C_{23}H_{37}N_3O_{12}$	7.67	7.58	91.26	90.73	318
2	CH_3	CH_3	3	$-N(CH_3)_2$	108–110	93.5	$C_{24}H_{39}N_3O_{12}$	7.48	7.45	93.60	93.02	173
3	CH_3	H	2	$-N(C_2H_5)_2$	119–120	68.0	$C_{24}H_{39}N_3O_{12}$	7.48	7.39	93.60	91.35	334
4	CH_3	H	3	$-N(C_2H_5)_2$	116–117	84.4	$C_{25}H_{41}N_3O_{12}$	7.30	7.19	95.93	98.08	56
5	CH_3	H	2	$-N(CH_3)_2$								
6	CH_3	H	3	Morpholino	155–157	94.7	$C_{25}H_{39}N_3O_{13}$	7.13	7.04	98.27	97.92	188
7	CH_3	H	3	4-Methylpiperazino	113–115	71.0	$C_{29}H_{45}N_5O_{16}$	7.88	7.66	89.96	92.65	192
8	CH_3	H	2	*o*-Cl-benzyl methylamino	134–135	90.0	$C_{28}H_{38}ClN_3O_{12}$	6.52	6.61	107.35	105.80	0
9	CH_3	H	3	Pyrrolidino	140–142	95.5	$C_{25}H_{39}N_3O_{12}$	7.37	7.25	95.60	93.66	290
10	CH_3	H	0	4-Methylpiperazino	140–141	100.0	$C_{23}H_{35}N_3O_{12}$	7.70	7.65	90.92	90.20	201
11	R′–$CH_2NHNHC_2H_4N(CH_3)_2$[b]				103–104	25.0	$C_{20}H_{42}N_4O_{16}$	6.32	6.29	83.08	81.69	202
12	R′–CH_2NHNH_2[b]				91–92	88.3	$C_{14}H_{29}N_3O_8$	7.74	7.72	90.33	89.99	112
	Amisometradine (Rolicton)											182
	Maleic acid											177
	Chlormerodrin (Neohydrin)[c]											350

[a] Average 0.5 hour percentage increase in urinary volume for a 6-hour experimental period; dose = 50 mg./kg. (oral, dog). [b] R′ = 1-Methyl-2-pyrrolidylmethyl. [c] Dose = 9.0 mg./kg. (oral, dog).

TABLE IV



No.	R	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found	Neut. equiv. Calcd.	Found	Oral diuretic activity, %
13	$-NH-C_2H_4N(CH_3)_2$	103–104	31	$C_{20}H_{42}N_4O_{16}$	6.32	6.29	83.08	81.69	94
14	$-NHC_2H_4NC_4H_8$	107–108	39	$C_{28}H_{52}N_4O_{16}$	6.09	6.11	86.33	87.78	169
15		113–115	71	$C_{29}H_{45}N_5O_{16}$	7.88	7.66	89.96	92.65	107
16	$-(CH_2)_3N(CH_3)_2$	154–155	93	$C_{23}H_{37}N_3O_{12}$	7.67	7.53	91.26	88.58	53
17	$-NH_2$	108–109		$C_{14}H_{29}N_3O_8$	7.74	7.65	90.33	89.03	32
	Maleic acid								177
	Amisometradine (Rolicton)								182
	Chlormerodrin (Neohydrin)[a]								350

[a] Dose = 9.0 mg./kg. (oral, dog).

drochloric acid to *p*H 2. The solid was collected by filtration; yield 2.85 g. (92.3%), m.p. 233–235° dec. *Anal.* Calcd. for $C_{11}H_{28}N_3Cl_3$: N, 13.60; Cl, 34.46. Found: N, 13.52; Cl, 34.22.

1,1-Dimethyl-3-(N′-methyl-3-piperidyl)-propylenediamine Trimaleate (Ib).—To 3.5 g. (0.03 mole) of maleic acid dissolved in 30 cc. of ethanol was added a solution of 2 g. (0.01 mole) of the base in 30 cc. of anhydrous ether. The precipitate was collected by filtration; yield 5.15 g. (93.6%), m.p. 154–155°, mixed m.p. with IIb 134–140°. *Anal.* Calcd. for $C_{23}H_{37}N_3O_{12}$: N, 7.67; neut. equiv., 91.26. Found: N, 7.53; neut. equiv., 88.58.

1,1-Dimethyl-3-(N′-methyl-3-piperidyl)-propylenediamine Dimethobromide (Ic).—To 2 g. (0.01 mole) of base in 30 cc. of isopropyl alcohol was added 1.9 g. (0.02 mole) of methyl bromide. The solid was collected by filtration; yield 3.45 g. (88.5%), m.p. 237–238°. *Anal.* Calcd. for $C_{13}H_{31}N_3Br_2$: N, 10.78; Br, 41.13. Found: N, 10.35; Br, 40.68.

1,1-Dimethyl-3-(N′-methyl-3′-piperidyl)-propylenediamine Tripicrate.—To 3.45 g. (0.015 mole) of picric acid dissolved in 50 cc. of ethanol was added 1 g. (0.005 mole) of the base in 10 cc. of ethanol. A solid was collected by filtration; yield 4.1 g. (92.5%), m.p. 200–202°. The solid was suspended in boiling acetone and filtered; yield 2.4 g., m.p. 207°, mixed m.p. with IIc 204–207°. *Anal.* Calcd. for $C_{29}H_{34}N_{12}O_{21}$: N, 18.95. Found: N, 18.72.

1,1-Dimethyl-3-(N′-methyl-2-pyrrolidylmethyl)-propylenediamine. Method B (IIa).—A mixture consisting of 18.8 g. (0.165 mole) of 1-methyl-2-aminomethylpyrrolidine,[2] 9.75 g. (0.8 mole) of 3-dimethylaminopropyl chloride, 18 g. (0.12 mole) of sodium iodide and 50 cc. of ethanol was placed in a pressure bottle and the mixture heated to 100° for 4 hours. The salt was removed by filtration, water added to the filtrate and the latter saturated with solid potassium hydroxide. The oil was isolated by extraction of the alkaline mixture with ether. The combined extracts were dried with potassium carbonate and the product collected by distillation; b.p. 97–98° (0.25 mm.), yield 9.3 g. (58.4%), $n^{20}D$ 1.4649. *Anal.* Calcd. for $C_{11}H_{25}N_3$: N, 21.10. Found: N, 20.47.

1,1-Dimethyl-3-(N′-methyl-2-pyrrolidylmethyl)-propylenediamine Trimaleate.—To 3.5 g. (0.03 mole) of maleic acid dissolved in 30 cc. of ethanol was added 2 g. (0.01 mole) of base diluted in 30 cc. of anhydrous ether. The solid was collected by filtration and recrystallized from 50 cc. of boiling ethanol; yield 4.35 g. (80%), m.p. 140°, mixed m.p. with IIb 136–137°. *Anal.* Calcd. for $C_{23}H_{37}N_3O_{12}$: N, 7.67; neut. equiv., 91.26. Found: N, 7.57; neut. equiv., 89.02.

1,1-Dimethyl-3-(N′-methyl-2-pyrrolidylmethyl)-propylenediamine Tripicrate.—To 3.45 g. (0.015 mole) of picric acid dissolved in 50 cc. of ethanol was added 1 g. (0.005

mole) of the base in 10 cc. of ethanol. A precipitate was collected by filtration and triturated several times in boiling ethanol; yield 4.15 g. (93.5%), m.p. 209°, mixed m.p. with IIc 209°. *Anal.* Calcd. for $C_{29}H_{34}N_{12}O_{21}$: N, 18.95. Found: N, 18.90.

1,1-Dimethyl-3-(N'-formyl)-3-(N''-methyl-2''-pyrrolidylmethyl)-propylenediamine.—A mixture consisting of 17.32 g. (0.09 mole) of 1,1-dimethyl-3-(N-methyl-2-pyrrolidylmethyl)-propylenediamine and 13.37 g. (0.18 mole) of ethyl formate was refluxed for 5 hours. The excess ethyl formate and ethanol were removed by distillation. The product was collected by distillation, b.p. 122° (0.9 mm.), yield 10.72 g. (51.27%). *Anal.* Calcd. for $C_{12}H_{25}N_3O$: N, 12.32. Found: N, 12.57.

1,1-Dimethyl-3-(N'-methyl)-3-(N''-methyl-2-pyrrolidylmethyl)-propylenediamine.—To 2.91 g. (0.088 mole) of lithium aluminum hydride in 50 cc. of tetrahydrofuran at reflux was added a solution consisting of 10.1 g. (0.044 mole) of 1,1-dimethyl-3-(N'-formyl)-3-(N''-methyl-2-pyrrolidylmethyl)-propylenediamine and 25 cc. of tetrahydrofuran. The mixture was refluxed for 3 hours and the complex was decomposed with 13 cc. (40%) aqueous potassium hydroxide solution. The inorganic salts were removed by filtration, the filtrate was dried with potassium carbonate, and the product was collected by distillation, b.p. 107° (4.7 mm.), yield 4.7 g. (52.57%), $n^{20}D$ 1.4637. *Anal.* Calcd. for $C_{12}H_{27}N_3$: N, 19.70. Found: N, 19.53.

3-Substituted propionitriles were prepared by condensing acrylonitrile with the appropriate amine.[5]

3-Substituted propylamines were prepared by reducing the corresponding 3-substituted propionitrile with lithium aluminum hydride in tetrahydrofuran.[6]

N-Methyl-N-*m*-chlorobenzylaminoacetonitrile.—To a mixture consisting of 62.27 g. (0.41 mole) of N-methyl-N-*m*-chlorobenzylamine, 40.4 g. (0.40 mole) of triethylamine and 400 cc. of dry toluene at reflux was added 30.22 g. (0.40 mole) of chloroacetonitrile, and reflux was continued for 4 hours. The triethylamine hydrochloride was removed by filtration and the solvent was removed by distillation. The product was collected by distillation, b.p. 124–126° (0.4 mm.), yield 57 g. (73.2%). *Anal.* Calcd. for $C_{10}H_{11}ClN_2$: N, 7.19. Found: N, 7.16.

N-Methyl-N-(*m*-chlorobenzyl)-ethylenediamine.—To 11.4 g. (0.30 mole) of lithium aluminum hydride in 300 cc. tetrahydrofuran at reflux was added 57 g. (0.29 mole) of N-methyl-N-*m*-chlorobenzylacetonitrile. The mixture was refluxed for 2 hours and the complex was decomposed with 35 cc. (40%) of aqueous potassium hydroxide solution. The inorganic salts were removed by filtration. The filtrate was dried with potassium carbonate and the product was collected by distillation, b.p. 111–112° (1.6 mm.), yield, 43.7 g. (75%), $n^{25}D$ 1.5344. *Anal.* Calcd. for $C_{10}H_{15}N_2Cl$: N, 14.10. Found: N, 13.96.

N-(β-Dimethylaminoethyl)-hydrazine.—To 294 g. (5.0 moles) of 54.4% hydrazine was added 90 g. (0.84 mole) of β-dimethylaminoethyl chloride (freshly distilled) in 10 minutes. The solution began to reflux in 15 minutes, and refluxing was continued for one hour. The solution was saturated with sodium hydroxide and the product was isolated by extraction of the alkaline mixture with tetrahydrofuran. The combined tetrahydrofuran extracts were dried over potassium carbonate, and the product collected by distillation, b.p. 57–59° (7.3 mm.), yield 48.6 g. (53.6%), $n^{25}D$ 1.4541. *Anal.* Calcd. for $C_4H_{13}N_3$: N, 27.14. Found: N, 27.29.

N-(β-Dimethylaminoethylidenyl)-N'-(1-Methyl-2-pyrrolidylmethyl)-hydrazine.—To 100 cc. of concd. hydrochloric acid at 10° was added 32.25 g. (0.20 mole) of dimethylaminoacetal under a nitrogen atmosphere. After standing overnight at room temperature, the solution was concentrated to dryness with a 50° water-bath *in vacuo*. The residue was diluted to 200 cc. with water, neutralized to *p*H 7 with 55 cc. (10%) of sodium hydroxide solution, and 25.6 g. (0.20 mole) of N-methyl-2-pyrrolidylmethylhydrazine was added at 5°. The solution stood overnight at room temperature. It was saturated with sodium hydroxide and the product was isolated by extraction of the alkaline mixture with tetrahydrofuran. The combined tetrahydrofuran extracts were dried over potassium carbonate, and the product collected by distillation, b.p. 72–77° (0.03 mm.), yield 31 g. (78.9%), $n^{25}D$ 1.4895. *Anal.* Calcd. for $C_{10}H_{22}N_4$: N, 14.12. Found: N, 14.01.

N-(β-Dimethylaminoethyl)-N'-(1-methyl-2-pyrrolidylmethyl)-hydrazine.—To 5.7 g. (0.15 mole) of lithium aluminum hydride in 100 cc. of tetrahydrofuran was added a solution consisting of 29.8 g. (0.15 mole) of N-(β-dimethylamino ethylidenyl)-N'-(1-methyl-2-pyrrolidylmethyl)-hydrazine and 100 cc. of tetrahydrofuran. The mixture was refluxed for 4 hours, and the complex was decomposed with 30 cc. (40%) of potassium hydroxide solution. The salts were removed by filtration, the filtrate dried with potassium carbonate and the product collected by distillation; b.p. 80° (0.03 mm.), yield 26.7 g. (88.9%), $n^{25}D$ 1.4794. Calcd. for $C_{10}H_{24}N_4$: N, 20.9. Found: N, 20.37.

Maleate Salt.—To 17.4 g. (0.15 mole) of maleic acid dissolved in 150 cc. of ethanol was added a solution of 10 g. (0.05 mole) of the free base in 50 cc. of ethanol. The solid was collected by filtration and recrystallized from hot ethanol; yield 8.3 g. (30%), m.p. 103–104° dec. *Anal.* Calcd. for $C_{26}H_{40}N_4O_{16}$: N, 6.32; neut. equiv., 83.08. Found: N, 6.29; neut. equiv., 81.69.

Ethanolamine (Reductive Cleavage of Hydroxyethylhydrazine with Raney Nickel).—A mixture consisting of 15.2 g. (0.20 mole) of hydroxyethylhydrazine, 2 g. of Raney nickel and 150 cc. of ethanol was subjected to hydrogenation in a Parr hydrogenator at 50° and 60 p.s.i. of hydrogen until the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration and the product collected by distillation, b.p. 169°, yield 9.9 g. (81.1%), $n^{25}D$ 1.4539. *Anal.* Calcd. for C_2H_7NO: N, 22.95. Found: N, 22.10.

N-Methyl-3-hydrazinopiperidine (IV).—To 36 g. (0.60 mole) of 54.5% aqueous hydrazine at 10° was added 13.8 g. (0.12 mole) of N-methyl-3-piperidone and the solution was allowed to stand at 25° overnight. It was saturated with sodium hydroxide and the product isolated by extraction of the alkaline mixture with tetrahydrofuran. The combined extracts were dried with potassium carbonate and the solvent removed by distillation; yield 14.15 g.

To 5 g. (0.13 mole) of lithium aluminum hydride in 100 cc. of tetrahydrofuran at reflux was added a solution of the above hydrazone dissolved in 100 cc. of tetrahydrofuran. The mixture was refluxed for 3 hours and the complex decomposed with 15 cc. (40%) aqueous potassium hydroxide solution. The inorganic salts were removed by filtration, the filtrate was dried with potassium carbonate, and the product collected by distillation, b.p. 88–90° (1.8 mm.), yield 5.3 g. (34.2%), $n^{25}D$ 1.4907. *Anal.* Calcd. for $C_6H_{15}N_3$: N, 21.68. Found: N, 20.53.

The dimaleate salt of the above hydrazine was prepared in ethanol in 72% yield, m.p. 108–109°. *Anal.* Calcd. for $C_{14}H_{23}N_3O_8$: N, 7.74; neut. equiv., 90.33. Found: N, 7.65; neut. equiv., 89.03.

Hydrogenation of IV.—A mixture consisting of 1.3 g. (0.01 mole) of N-methyl-3-hydrazinopiperidine, 1 g. of Raney nickel and 70 cc. of ethanol was placed in the Parr hydrogenator, and subjected to hydrogenation at 50° and 60 p.s.i. of hydrogen for 4 hours. The catalyst was removed by filtration and the filtrate refluxed to remove the ammonia. The dimaleate salt of the above base was prepared in 72% yield, m.p. 154–155°. *Anal.* Calcd. for $C_{14}H_{22}N_2O_8$: N, 8.08; neut. equiv., 86.55. Found: N, 7.96; neut. equiv., 85.75. Identity was established by a mixed melting point with an authentic sample of N-methyl-3-aminopiperidine dimaleate.

N-Methyl-2-pyrrolidylmethylhydrazine (III).—A mixture consisting of 38 g. (0.65 mole) of 54.5% aqueous hydrazine and 26.7 g. (0.20 mole) of N-methyl-3-chloropiperidine was refluxed for 3 hours. The solution was saturated with sodium hydroxide and the product isolated by extraction of the alkaline mixture with tetrahydrofuran. The combined extracts were dried with potassium carbonate and the product was collected by distillation, b.p. 78–79° (2.5 mm.), yield 17.5 g. (67.7%), $n^{25}D$ 1.4870. *Anal.* Calcd. for $C_6H_{15}N_3$: N, 21.68. Found: N, 21.08.

The dimaleate salt of the above hydrazine was prepared in ethanol in 88% yield, m.p. 91–92°. *Anal.* Calcd. for $C_{14}H_{23}N_3O_8$: N, 7.74; neut. equiv., 90.33. Found: N, 7.72; neut. equiv., 89.99.

Hydrogenation of III.—The above hydrazine was cleaved by a Raney nickel reduction as described previously; b.p.

(5) Joseph Corse, J. T. Bryant and H. A. Shonle, THIS JOURNAL, **68**, 1911 (1946).

(6) R. R. Nystrom and W. G. Brown, *ibid.*, **70**, 3738 (1948).

152–153° (760 mm.), yield 67.8%, $n^{20}D$ 1.4670. *Anal.* Calcd. for $C_6H_{14}N_2$: N, 24.52. Found: N, 24.75.

The dimaleate salt of the above base was prepared in ethanol in 98% yield, m.p. 140°. A mixed melting point with the dimaleate salt of VI showed no depression. *Anal.* Calcd. for $C_{14}H_{22}N_2O_8$: N, 8.08; neut. equiv., 86.55. Found: N, 7.95; neut. equiv., 86.41.

The dipicrate salt of the above base was prepared in ethanol in 96% yield, m.p. 192.5°. A mixed melting point with the dipicrate salt of VI showed no depression. *Anal.* Calcd. for $C_{18}H_{20}N_8O_{14}$: N, 19.56. Found: N, 19.46.

N-Methyl-3-aminopiperidine.—An alcoholic solution containing 96.0 g. (0.50 mole) of 3-aminopyridine methobromide was reduced with Raney nickel catalyst (five teaspoonfuls) at 2,000 p.s.i. of hydrogen and 175° in a steel bomb. The catalyst was removed by filtration and the filtrate concentrated to one-third its original volume. The residue was treated with the calculated amount of sodium methoxide and the sodium bromide removed by filtration. The filtrate was subjected to a fractional distillation and the product collected at 163–165°, yield 27.7 g. (48.6%), $n^{20}D$ 1.4699. *Anal.* Calcd. for $C_6H_{14}N_2$: N, 24.56. Found: N, 24.13. The dimaleate salt melted at 154–155°, mixed m.p. with IV dimaleate gave no depression.

N-(β-Dimethylaminoethyl)-N′-(1-Methyl-3-piperidyl)-hydrazine.—To 23.5 g. (0.23 mole) of β-dimethylaminoethylhydrazine in 75 cc. of methanol was added 25.7 g. (0.23 mole) of freshly distilled N-methyl-3-piperidone in 25 cc. of methanol. The solution was refluxed for 10 minutes and the methanol removed by distillation. The residue was dissolved in 25 cc. of tetrahydrofuran and reduced with 8.62 g. (0.23 mole) of lithium aluminum hydride, dissolved in 150 cc. of tetrahydrofuran. The mixture was refluxed with stirring for 3 hours and the complex decomposed by the addition of 15% aqueous potassium hydroxide to the cold reaction mixture. The inorganic salts were removed by filtration and the filtrate dried with potassium carbonate. The product was collected by distillation *in vacuo*, b.p. 81–84° (0.03 mm.), yield 32 g. (70%).

MILWAUKEE, WISC.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

The Mesomorphic State: The Mesomorphic 4,4′-Di(n)alkoxybenzalazines

BY WILFRID G. SHAW[1] AND GLENN H. BROWN

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A homologous series of azines of *p-n*-alkoxybenzaldehydes and related benzalazine compounds were synthesized and their mesomorphism analyzed. Mesomorphism of these compounds in terms of even and odd series, pairing of transition points, and bonding forces is discussed in relationship to transition temperature *versus* alkoxy chain length. X-Ray diffraction patterns were obtained for the nematic and liquid structures for anisaldazine and several of its dialkoxy homologs. The small differences found between the mesomorphic and liquid diffraction patterns are discussed. Several additional substituted alkoxybenzalazines were synthesized only one of which exhibited mesomorphism.

It is well known that a large number of organic compounds exhibit the mesomorphic state. An extensive review of the structure and the properties of the mesomorphic state may be found in a recent article.[2] It can be generally stated that compounds exhibiting mesomorphism have molecules that are elongated, and in some cases flattened as well, and which possess one or more polar groups. This shape of the molecules favors a parallel alignment to one another, like a bundle of pencils. In the crystalline state of a mesomorphic substance, the molecules lie parallel to one another and are held together by attraction through the polar groups as well as by the unspecific van der Waals attraction. When the solid is heated, the weaker bonds break first, leaving the solid with some degree of relative movement before sufficient thermal energy has been acquired to overcome in any great degree the tendency for them to set themselves parallel to one another. Thus, the system becomes fluid but remains birefringent because of the preferred orientation of some of the molecules.

On the basis of the swarm hypothesis, first proposed by Bose,[3,4] the molecules in the nematic structure are not oriented in the same direction throughout the whole medium but are grouped in aggregates or swarms. The molecules in the swarm lie parallel or approximately so, but in a direction that is random to the molecules of other swarms in the medium. From this point of view the nematic structure resembles a mass of small crystals rather than a single crystal, but with this difference, owing to the mobility of the molecules, the swarms do not remain static but are continually exchanging molecules with one another and with the optically isotropic liquid; the arrangement of the swarms is not a rigid one and is subject to mechanical deformation.

Almost all of the compounds that form the mesomorphic state can be classified as forming the smectic or nematic structure. The smectic structure is stratified, the molecules being arranged in layers with their long axes approximately normal to the planes of the layers. In the nematic structure the only restriction on the arrangement of the molecules is that the molecules preserve a parallel or nearly parallel orientation.

The lower homologs of the 4,4′-di(*n*)alkoxybenzalazines show only the nematic structure while the higher homologs exhibit both the smectic and the nematic structures. These structural modifications are exhibited by homologous series of other compounds. For example, investigations of the homologous series of *p*-substituted mono- or di- alkyl-(and alkoxy) compounds, *e.g.*, the azoxy-, azo- and azomethine-phenol ethers,[5,6] have shown that the lowest members of the series have only a nematic structure, and as the chain length increases the smectic structure appears, while at still

(1) This paper was abstracted from a portion of the Ph.D. thesis of Wilfrid G. Shaw, University of Cincinnati, 1957; Dreyer Foundation Fellow 1955–1956; present address: Standard Oil Co. (Ohio) Research Laboratory, Warrensville Heights, Ohio.

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