A New Method for the Preparation of Piperazines. II. Preparation of N, N'-Disubstituted Piperazines

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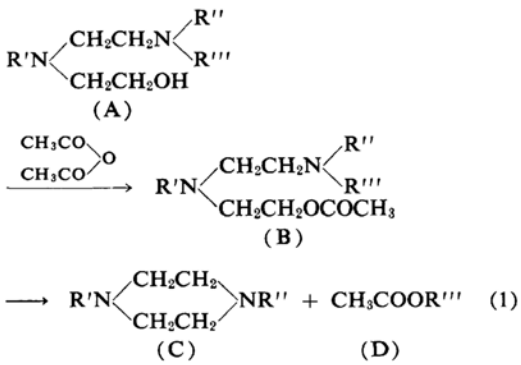
A new method for preparing piperazine derivatives has been proposed by the author in the preceding paper[1]. The present paper deals with the preparation of some *N*, *N'*-disubstituted piperazines by this method. The procedure consists in treating an *N*, *N'*, *N'*-trisubstituted *N*-β-aminoethylethanolamine of the general formula A with acetic anhydride to yield an *O*-acetyl derivative B, followed by heating at 200~300°C to split into the desired *N*, *N'*-disubstituted piperazine C, and an acetic ester D, as is seen in the following Scheme 1;



In the scheme, R' and R'' are alkyl, aralkyl, cycloalkyl or aryl group, whereas R''' is the same group as R'' or a lower alkyl, aralkyl or cycloalkyl group.

If R', R'' and R''' are chosen appropriately, it is possible to synthesize a variety of *N*, *N'*-disubstituted piperazines.

The properties of *N*, *N'*, *N'*-trisubstituted *N*-β-aminoethylethanolamines, which are used as the starting material, of their *O*-acetyl derivatives and of the end-products, *N*, *N'*-disubstituted piperazines are summarized in Tables I, II and III respectively.

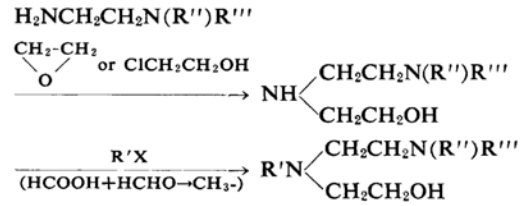
Many proposals have been made hitherto for the preparation of *N*, *N'*-disubstituted piperazines. Among the compounds of this series listed in Table III, *N*, *N'*-dimethyl-, *N*, *N'*-diethyl-, *N*, *N'*-di-*n*-propyl-, *N*-methyl-*N'*-phenyl, *N*-ethyl-*N'*-phenyl- and *N*, *N'*-diphenyl-piperazine are known.

The compounds I_1*, I_2, I_3 and I_4, where R', R'' and R''' are the same, are easily prepared through alkylation of *N*-β-aminoethylethanolamine.

The alkylation can be achieved by using alkyl halide, but the methylation is also readily accomplished with formic acid and formalin by the Eschweiler-Clarke procedure.

In the Experimental Part, the synthesis of *N*, *N'*, *N'*-trimethyl-*N*-β-aminoethylethanolamine (I_1) by the latter procedure and that of *N*, *N'*, *N'*-tri-*n*-butyl-*N*-β-aminoethylethanolamine (I_4) by the use of *n*-butyl bromide were examplified. The compounds, I_1, I_2, I_3 and I_4 are colorless oily liquids, the first two of which are miscible with water and the latter two are sparingly soluble in water.

As expressed in Scheme 2, the compounds I_5 to I_{11} were synthesized by the action of ethylene oxide or ethylene chlorohydrin on *N*, *N'*-disubstituted ethylenediamines, followed by the introduction of R' group.



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The preparation and properties of some of *N*-β-disubstituted aminoethylethanolamines have been shown in the preceding paper.

In the Experimental Part, the synthesis of (I_5) by the Eschweiler-Clarke procedure and that of (I_{10}) by the use of an alkyl halide have been illustrated.

The products thus obtained are colorless or yellowish oily liquids, sparingly soluble in water, with the exception of I_5 and I_6 which are freely soluble.

In compounds I_{12} and I_{13}, group R' is cyclohexyl. An attempt was made to introduce this by cyclohexyl bromide, but the formation of a considerable quantity of cyclohexene resulted in a low yield of I_{12} or I_{13}. In I_{14} and I_{15}, R' is a phenyl group.

I_{14} and I_{15} were therefore prepared from *N*-phenyl-*N*-β-aminoethylethanolamine.

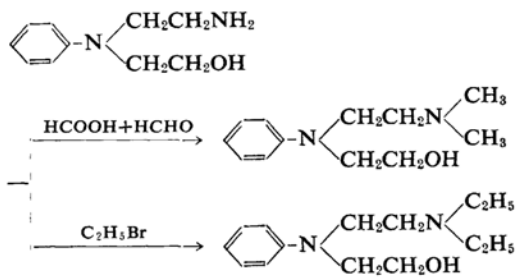
1) K. Nakajima, This Bulletin, **34**, 651 (1961).
* I_1 indicates compound 1 in Table I.

TABLE I. PROPERTIES OF $R'N\langle^{CH_2CH_2N(R'')R'''}_{CH_2CH_2OH}$

Comp. No.	R′	R″	R‴	Phys. form (color)	B. p., °C/mmHg 10	20	50	100	760	N, % Found	Calcd.	Picrate M. p. °C	Platinichloride Dec. p. °C	Pt, % Found	Calcd.
1	CH_3	CH_3	CH_3	Oily liq. (colorless)	84	100	122	142	206	19.15	19.16	229 (dec.)	215	34.75	35.08
2	C_2H_5	C_2H_5	C_2H_5	〃	115	130	154	174	237	15.09	14.88	*	227	32.75	32.61
3	n-C_3H_7	n-C_3H_7	n-C_3H_7	〃	142	157	180	199	266	12.30	12.16	164	227	30.39	30.47
4	n-C_4H_9	n-C_4H_9	n-C_4H_9	〃	162	180	204	225	295	10.31	10.28	*	220	28.35	28.59
5	CH_3	C_2H_5	C_2H_5	〃	90	110	134	155	225～226	15.98	16.08	218	215	33.39	33.40
6	n-C_3H_7	C_2H_5	C_2H_5	〃	117	135	159	180	250	13.70	13.85	163	225	31.80	31.87
7	n-C_4H_9	C_2H_5	C_2H_5	〃	129	158	170	192	262～263	12.63	12.95	66	215	31.26	31.15
8		C_2H_5	C_2H_5	〃	176	195	220	241	308	11.08	11.19	98	210	29.14	29.55
9	CH_3	n-C_4H_9	n-C_4H_9	〃	127	145	169	190	260	12.10	12.16	*	228	30.60	30.63
10	C_2H_5		CH_3	Syrupy (colorless)	179	190	216	235	305	12.54	12.60	130	red.		
11	CH_3		C_2H_5	〃	182	200	225	244	315	12.60	12.60	*	*		
12		CH_3	CH_3	〃	150	165	189	210	280	12.97	13.07	158	*		
13		C_2H_5	C_2H_5	〃	167	185	209	230	Ca. 290 (dec.)	11.21	11.56	*	190	30.10	29.91
14		CH_3	CH_3	〃	170	195	219	240	310 (dec.)	13.36	13.45	*	red.		
15		C_2H_5	C_2H_5	〃	180	197	222	242	313 (dec.)	11.60	11.85	115	red.		
16			$-CH_2-CH_2-OH$	Viscous (colorless)	264	282	311	330 (dec.)		9.24	9.33	141	147	27.45	27.47

* Not obtained in crystalline form.

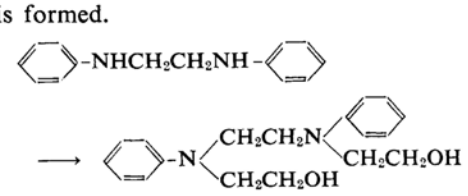
Key to abbreviation: Phys. form=physical form; liq.=liquid; dec. p.=decomposition point; red.=Platinichloride was reduced; mob. liq.=mobile liquid.



In the Experimental Part, synthesis of *N*-(β-diethylaminoethyl)-*N*-cyclohexylethanolamine (I_{13}) is cited.

The next step of this piperazine-synthesis is the formation of *O*-acetyl compounds from the *N*, *N*′, *N*′-trisubstituted *N*-β-aminoethylethanolamines with acetic anhydride. By the careful fractional distillation of the reaction mixture under reduced pressure the *O*-acetyl derivatives are obtained in an almost theoretical yield. However, the distillation must be carried out under fairly low pressure, say 10 mmHg, in order to obtain the *O*-acetyl compounds in a pure form, because they have a tendency to undergo decomposition over 200°C to piperazine derivatives. For any practical purpose. the *O*-acetyl compounds need not be isolated. The yields of piperazines are 70 to 95 per cent.

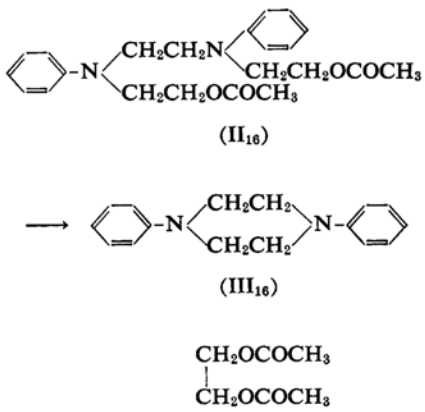
In the preparation of the compounds III_1 to III_{15} from the corresponding *O*-acetyl compounds, methyl acetate or ethyl acetate is formed. From II_{16}, however, ethylene diacetate is formed.

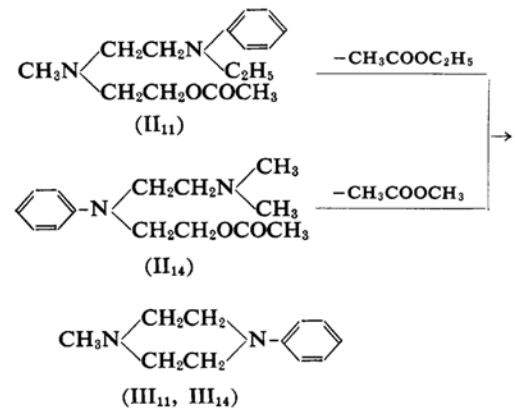


(I_{16})

TABLE II. PROPERTIES OF $R'N(CH_2CH_2N(R'')R''')(CH_2CH_2OCOCH_3)$

Comp. No.	R'	R''	R'''	Phys. form (color)	M. p. °C	B. p., °C/mmHg 10	20	50	100	760	N, % Found	Calcd.	Picrate M. p. °C	Platinichloride Dec. p. °C	Pt, % Found	Calcd.
1	CH_3	CH_3	CH_3	Oily liq. (colorless)		102	119	140	159	Ca. 220 (dec.)	14.58	14.88	263	222	32.49	32.62
2	C_2H_5	C_2H_5	C_2H_5	〃		125	142	166	186	Ca. 230 (dec.)	12.11	12.16	141	224	30.35	30.47
3	n-C_3H_7	n-C_3H_7	n-C_3H_7	〃		148	167	191	210	Ca. 256 (dec.)	10.22	10.28	134	222	28.35	28.59
4	n-C_4H_9	n-C_4H_9	n-C_4H_9	〃		167	185	209	230	229 (dec.)	8.80	8.91	125	223	26.90	26.93
5	CH_3	C_2H_5	C_2H_5	〃		104	124	148	170	240 (dec.)	13.10	12.95	163	166	31.23	31.16
6	n-C_3H_7	C_2H_5	C_2H_5	〃		127	146	169	190 (dec.)		11.50	11.46	105	208	29.70	29.82
7	n-C_4H_9	C_2H_5	C_2H_5	〃		128	157	180	202 (dec.)		10.71	10.89	125	222	29.40	29.19
8		C_2H_5	C_2H_5	〃		180	200	225	(dec.)		9.32	9.58	132	220	27.80	27.78
9	CH_3	n-C_4H_9	n-C_4H_9	〃		156	172	195	216	(dec.)	10.11	10.23	149	233	28.70	28.59
10	C_2H_5		CH_3	Viscous (colorless)		196	215 (dec.)				10.59	10.60	98	red.		
11	CH_3		C_2H_5	〃		190	210 (dec.)				11.09	10.60	132	221	28.96	28.94
12		CH_3	CH_3	〃		142	160	184	205	(dec.)	10.72	10.93	Ca. 290	215	29.20	29.28
13		C_2H_5	C_2H_5	〃		170	190	214	235 (dec.)		9.77	9.85	185	210	28.01	28.11
14		CH_3	CH_3	〃		195	219	240 (dec.)			11.36	11.19	*	red.		
15		C_2H_5	C_2H_5	〃		240	250 (dec.)				10.12	10.06	160	232		
16			$-CH_2CH_2OCOCH_3$	Cryst. (colorless)	76	(243/3 mmHg dec.)					7.20	7.29	140	202	24.80	24.56





II_{11} and II_{14} give the same product with liberation of ethyl acetate and methyl acetate respectively. This is also the case with II_{10} and II_{15}.

In the Experimental Part, preparations of *N, N'*-dimethylpiperazine (III_1), *N*-methyl-*N'*-phenylpiperazine (III_{14}), and *N, N'*-diphenylpiperazine (III_{16}) have been cited.

Table III. Properties of R'N(CH$_2$CH$_2$)$_2$NR''

Comp. No.	R'	R''	Phys. form (color)	M. p. °C	B. p., °C/mmHg 10	20	50	100	760	N, % Found	Calcd.	Picrate M. p. °C	Platinichloride Dec. p. °C	Pt, % Found	Calcd.
1	CH_3	CH_3	Mob. liq. (colorless)				40	62	132	29.51	24.53	280 (dec.)	Ca. 270	37.25	37.23
5	CH_3	C_2H_5	〃			36	61	82	151～153	21.70	21.85	255 (dec.)	248	36.35	36.26
9	CH_3	n-C_4H_9	〃		62	81	105	126	196	18.03	17.93	Ca. 240 (dec.)	280	38.45	34.46
12	CH_3		Oily liq. (colorless)		111	131	155	196	246	15.42	15.37	224 (dec.)	257	33.00	32.95
{11 {14	CH_3		Viscous (yellowish)	35	133	150	175	196	266	15.80	15.90	Ca. 210	245	32.99 33.10	33.29
2	C_2H_5	C_2H_5	Oily liq. (colorless)		37	56	80	101	171～173	19.77	19.70	Ca. 250 (dec.)	263	35.32	35.34
6	C_2H_5	n-C_3H_7	〃		52	76	94	115	188	19.82	19.93	235	225	34.45	34.46
7	C_2H_5	n-C_4H_9	〃		76	95	119	140	210	16.24	16.45	230	260	33.50	33.63
8	C_2H_5		〃		150	170	194	208	278	13.40	13.71	147	260	31.63	31.77
13	C_2H_5		〃		134	152	177	197	268	14.12	14.27	220	258	32.03	32.18
{10 {15	C_2H_5		Viscous (yellowish)		150	170	144	215	285	14.62	14.72	164	245	32.52 32.57	32.51
3	n-C_3H_7	n-C_3H_7	Oily liq. (colorless)		74	93	117	138	207～209	16.47	16.45	258 (dec.)	275	33.70	33.63
4	n-C_4H_9	n-C_4H_9	〃		99	127	152	173	243	14.17	14.12	245 (dec.)	Ca. 280	32.05	32.08
16			Cryst. (colorless)	163	226	242	266	288	(dec.)	11.75	11.76	192	245	30.09	30.10

Experimental

N,N',N'-Trimethyl-N-β-aminoethylethanolamine (I_1).—To a mixture of 52 g. (0.5 mol.) of N-β-aminoethylethanolamine and 350 g. of 80% formic acid, heated under reflux, was added 175 g. of formalin (30%) dropwise from a dropping funnel.

A vigorous reaction set in with the evolution of carbon dioxide.

When the addition of formalin was complete, the reaction mixture was boiled under reflux until no more gas was evolved (about 6 hr.). After an addition of 150 ml. of hydrochloric acid (approx. 6 N), the solution was evaporated to dryness under reduced pressure on a steam bath.

To the resulting solid, was added 200 g. of 30% sodium hydroxide solution.

The solution was extracted with ether using a continuous extraction apparatus, until no more volume diminution of the aqueous layer was observed. After the removal of the ether, the residue was distilled fractionally. From the etherial solution there was obtained by the fractinal distillation 58～64 g. of I_1, a colorless oily liquid, b. p. 206°C, in an 80% yield.

This compound is readily miscible with water, alcohol, acetone and benzene; d_4^{20} 0.9044. The hydrochloride is colorless crystals, m. p. 187°C.

N,N',N',-Tri-n-butyl-N-β-aminoethylethanolamine (I_4).—In a three-necked flask equipped with a reflux condenser, a thermometer and a dropping funnel, was placed 52 g. (0.5 mol.) of N-β-aminoethylethanolamine, and heating was commenced.

When the temperature rose to about 100°C, 37 g. (0.25 mol.) of n-butyl bromide was carefully added from the dropping funnel.

When the addition was complete, the temperature of the reaction mixture was raised to about 180°C, and then the mixture was allowed to stand to cool. A hot solution of 14 g. of potassium hydroxide in 30 ml. of methyl alcohol was poured in, shaking well. The crystals of potassium bromide were separated by filtration, and washed with a small amount of methyl alcohol.

From the filtrate methyl alcohol and water were distilled off. The distillation was discontinued when the temperature of the residue in the flask reached 150°C.

This procedure was repeated twice, using 18.5 g. (0.125 mol.) of n-butyl bromide and 7 g. (0.125 mol.) of potassium hydroxide in 30 ml. of methyl alcohol the first time, and 10 g. of n-butyl bromide and 8 g.

of potassium hydroxide in 20 ml. of methyl alcohol in the second. I_4 was purified by distillation under reduced pressure. There was obtained about 110 g. of I_4 (approx. 80%) as a colorless oily liquid, b. p. 162°C/10 mmHg or 180°C/20 mmHg.

Almost the same yields were obtained with I_2 and I_3 in a manner similiar to that described above.

N-Methyl-N-(β-diethylaminoethyl) ethanolamine (I_5). — Forty grams (0.25 mol.) of N-(β-diethylamino-ethyl)ethanolamine was mixed with 40 g. of formic acid (80%). With boiling under reflux, 25 g. of formalin was added dropwise.

The reaction was carried out in the same manner as in I_1. The yield of I_5, b. p. 225~226°C, was 35 g. (80%).

Similarly, N-methyl-N-(β-di-n-butylaminoethyl)-ethanolamine (I_9) could be prepared from N-(β-di-n-butylaminoethyl)ethanolamine.

N-Ethyl-N-(β-methylamino-ethyl) ethanolamine (I_{10}). —In a pressure vessel, 22 g. (0.5 mol.) of ethylene oxide dissolved in 50 ml. of methyl alcohol was added to 76 g. (0.5 mol.) of N-methyl-N-phenyl-ethylenediamine and the mixture was allowed to stand until an exothermal but not violent reaction was complete.

Fractional distillation of this reaction mixture under reduced pressure gave about 30 g. of N-(β-methylanilinoethyl)ethanolamine, boiling at 182°C/10 mmHg, 199°C/20 mmHg, or 317°C/760 mmHg. From the fore-run of the distillation, about 20 g. of unchanged starting material, N-methyl-N-phenyl-ethylenediamine, was recovered (b. p. 124°C/10 mmHg, 142°C/20 mmHg, 257°C/760 mmHg). From the after-run, about 40 g. of N-(β-methylanilino-ethyl)-diethanolamine was obtained in the form of colorless oily liquid boiling at 208°C/10 mmHg or 231°C/20 mmHg.

For the purpose of preparing I_{10}, a mixture of 19.5 g. (0.1 mol.) of N-(β-methylanilino-ethyl)-ethanolamine and 11 g. (0.1 mol.) of ethyl bromide was heated under reflux.

After completion of the vigorous reaction, the reaction mixture was neutralized by adding a sodium hydroxide solution using phenolphthalein as the indicator. The oily layer was separated and distilled under reduced pressure.

There was obtained about 18 g. of I_{10}, as a colorless oily liquid boiling at 179°C/10 mmHg or 190°C/20 mmHg in an 80% yield.

N-(β-Diethylamino-ethyl)-N-cyclohexylethanolamine (I_{13}). — A mixture of 18 g. (0.1 mol.) of N-(β-aminoethyl)-N-cyclohexylethanolamine (a colorless oily liquid, b. p. 162°C/10 mmHg, 181°C/20 mmHg, or 295°C/760 mmHg), and 11 g. (0.1 mol.) of ethyl bromide was heated under reflux. After a vigorous reaction had subsided, the cooled reaction mixture was made alkaline with 30% sodium hydroxide solution using phenolphthalein as the indicator.

The oily product that separated was shaken with an equal volume of water**, and distilled fractionally.

About 18 g. of I_{13} was obtained as acolorless oily liquid, boiling at 167°C/10 mmHg or 185°C/20 mmHg.

** There is no appreciable difference between the boiling point of the starting material and that of I_{13}. But the former is miscible with water at any proportion, and the latter is sparingly soluble in it. The separation depends upon this difference of solubility.

N, N'-(Bis-β-hydroxxethyl)-N, N'-diphenyl-ethylenediamine (I_{16}).—To 42 g. (0.2 mol.) of N,N'-diphenylethylenediamine was added 18 g. (0.4 mol.) of ethyleneoxide dissolved in 50 ml. of methyl alcohol. After being stored in a refrigerator for two days, the mixture was distilled. At 264°C/10 mmHg or 282°C/20 mmHg. I_{16} was distilled off quantitatively as a colorless and strongly viscous liquid. The melting point of its picrate was 141°C, and that of its platinichloride 147°C.

N-Methyl-N-(β-dimethylamino-ethyl) aminoethyl Acetate (II_1).—Acetic anhydride (12.5 g.) was added to 14.5 g. (0.1 mol.) of I_1. By fractional distillation of the mixture, II_1 was obtained at 119°C/20 mmHg, or 140°C/50 mmHg as a colorless oily liquid. The yield was 17 g. (approx. 90%).

N,N'-Dimethylpiperazine (III_1).—II_1 was placed in a Claisen flask equipped with a thermometer inserted through the straight neck to indicate the internal temperature and another thermometer fixed in the side neck to detect the distilling temperature.

Distillation was carefully carried out. At the beginning, the temperature of the content remained at about 206°C, the boiling point of II_1. As the decomposition of II_1 proceeded, the internal temperature gradually fell, and the distillation of the methyl acetate began. After the theoretical amount of methyl acetate had distilled over, N,N'-dimethyl-piperazine was collected at 110~140°C.

Redistillation gave the pure product boiling at 130~132°C. The yield was 90% or greater.

N-Ethyl-N'-phenylpiperazine (III_{15}).—A reaction mixture of 25 g. (0.1 mol.) of N-(β-diethylamino-ethyl)-N-phenylethanolamine (I_{15}) and 12 g. (0.12 mol.) of acetic anhydride was distilled in the same manner as in the preceding example.

After acetic acid formed and the excess acetic anhydride had distilled out, the temperature of the content increased gradually, reaching 300°C at one time. But as the decomposition proceeded, the internal temperature fell somewhat and ethyl acetate began to distill off at 80~100°C. After completion of the decomposition, the resulting brown liquid was purified by vacuum distillation. This purification furnished about 15 g. of III_{15} in an 80% yield as a yellowish viscous liquid.

N, N'-Diphenylpiperazine (III_{16}). — Acetic anhydride (25 g.; ca. 0.24 mol.) was added to 30 g. (0.1 mol.) of I_{16}. The reaction mixture was submitted to distillation in the same manner as in the preceding example with the object of decomposing it into III_{16} and ethylenediacetate, which distilled out 180~190°C. The residual material was further distilled under reduced pressure. Recrystallization of the solidified distillate from methyl alcohol afforded about 18 g. of III_{16} in colorless crystals, m. p. 163°C. The yield was about 80% of the theory.

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