A New Method for the Preparation of Piperazines. I. Preparation of N-Mono-alkyl(-aryl)-piperazines

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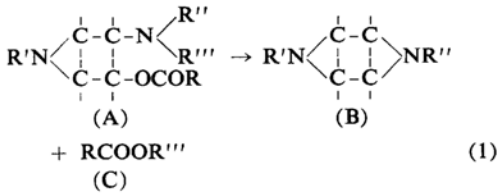
For the preparation of piperazine and its derivatives a number of methods have been proposed up to the present by several investigators[1]. Because of the complexity and the poor yield, these methods still leave much to be desired. Many trials, therefore, have been made by the present author to find out a new convenient route to these compounds. And, after all, it was found that a compound of the general formula A gives a piperazine derivative B under the elimination of an ester C, when it is heated at 200~300°C, according to the following Eq. 1.



(A) (B) (C) (1)

In this equation, R′ and R″ represent alkyl, aralkyl, cycloalkyl, aryl or acyl groups which are destined to remain in the molecule of B after the fission. R‴ also may be an alkyl, aralkyl or cycloalkyl group (equal to or lower than R″), but neither aryl nor acyl group, for these groups are incapable of being removed as a part of the ester C. RCO– in A and in C is an acyl group, but, in fact, it is restricted to the easily available acetyl.

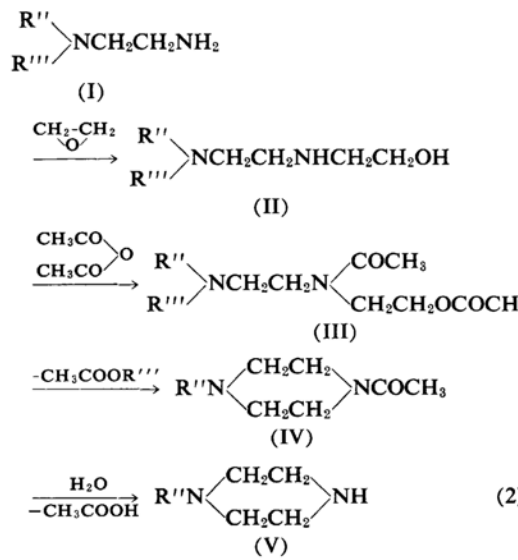
As can be seen from Eq. 1, this reaction seems to be quite a new type of reaction, i. e. the cyclization under the elimination of an ester*.

The actual procedure of this reaction consists in heating the compound A above 200°C, the conditions being arranged so that the ester C can be distilled over as it is formed during the heating, and in fractionating the resulting piperazine B under reduced pressure. Generally speaking from the data of the series of the experiments, the yields are fairly good.

The adequate selections of R′, R″ and R‴ in A make it possible to synthesize various compounds of piperazine-ring system.

As a part of synthetical works in the field of piperazines by the new route, synthesis of *N*-mono-alkyl(-aryl)-piperazines is dealt with in the present paper.

Synthesis of *N*-Mono-alkyl(-aryl)-piperazines.— The full course of synthesis of *N*-mono-alkyl-(-aryl)-piperazines (V) from *N*, *N*-disubstituted ethylenediamines (I) is represented by the following Eq. 2.

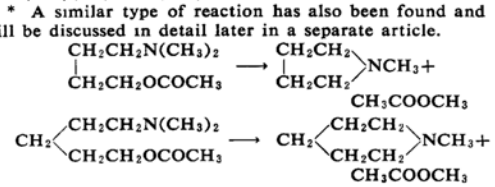


(I) (II) (III) (IV) (V) (2)

N, *N*-Disubstituted ethylenediamines (I)[2] are converted into *N*, *N*-disubstituted aminoethyl ethanolamines (II) by the action of ethylene oxide or ethylene chlorohydrin. In this reaction considerable quantities of *N*, *N*-disubstituted aminoethyl diethanolamines are formed, from which II can be isolated by fractionation under

1) D. S. Pratt and C. O. Young, *J. Am. Chem. Soc.*, **40**, 1428 (1918); W. B. Martin and A. E. Martell, ibid., **70**, 1817 (1948); T. S. Moore, H. Boyle and V. M. Thorne, *J. Chem. Soc.*, **1929**, 39; R. Baltzly, J. S. Buck, E. Lorz and W. Schön, *J. Am. Chem. Soc.*, **66**, 263 (1944), K. E. Hamlin et al., ibid., **71**, 2731 (1949); R. Baltzly, ibid., **76**, 1164 (1954); T. Ishiguro, E. Kitamura and M. Matsumura, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **73**, 1110 (1953); **74**, 1162 (1954); **75**, 1370 (1955).

* A similar type of reaction has also been found and will be discussed in detail later in a separate article.



2) K. Nakajima, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **81**, 499, 961, 1131, 1477 (1960).

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

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. 1. (colorless)		80	97	118	135	205	21.02	21.19	200 (dec.)	214	35.67	35.99
2	C_2H_5	C_2H_5	〃		113	132	152	170	235	17.51	17.48	90	*		
3	n-C_3H_7	n-C_3H_7	〃		134	153	178	199	266	14.86	14.88	140	*		
4	i-C_3H_7	i-C_3H_7	〃		116	135	160	181	248	14.77	14.88	175	*		
5	n-C_4H_9	n-C_4H_9	Oily l. (colorless)		150	164	188	208	280	13.01	12.95	*	*		
6		CH_3	〃		168	186	210	230	302	14.14	13.98	*	*		
7			〃		220	236	264	286 (dec.)		10.32	10.44	193	212	28.78	28.76
8		CH_3	〃		182	199	222	244	317	14.33	14.42	153	*		
9		C_2H_5	Wh. sld. (colorless)	42	192	208	231	252	323	13.30	13.45	120	195	37.40	31.56

† uncorrected
* not obtained in crystalline form.
Key to abbreviation: Phys.=physical; mob. l.=mobile liquid; wh. sld.=white solid; dec. p.=decomposition point.

TABLE II. PROPERTIES OF $CH_3CON\langle^{CH_2CH_2N(R'')R'''}_{CH_2CH_2OCOCH_3}$

Comp. No.	R''	R'''	Phys. form (color)	B. p., °C/mmHg† 6	8	10	20	50	100	760	N, % Found	Calcd.	Picrate M. p. °C	Platinichloride Dec. p., °C	Pt, % Found	Calcd.
1	CH_3	CH_3	Oily l. (colorless)	140	147	152	170	188	205		13.05	12.95	185	167 (melt)	31.01	31.17
2	C_2H_5	C_2H_5	〃	164	174	180	192	212 (dec.)			11.52	11.47	*	*		
3	n-C_3H_7	n-C_3H_7	〃	182	189	194	210 (dec.)				10.27	10.28	195	198		
4	i-C_3H_7	i-C_3H_7	〃	170	176	182	194 (dec.)				10.12	10.28	220	*		
5	n-C_4H_9	n-C_4H_9	〃	189	296	202	216 (dec.)				9.30	9.33	*	209	19.50	19.30
6		CH_3	〃	192	203	210	227 (dec.)				9.89	9.90	*	*		
7			〃	240 (dec.)	250 (dec.)						7.75	7.95	*	*		
8		CH_3	〃	211	218	224	243	270	291 (dec.)		10.21	10.06	*	*		
9		C_2H_5	〃	216	224	232	251	274	295 (dec.)		9.51	9.58	*	*		

reduced pressure. Some physical properties of II are summarized in Table I.

The second stage is the acetylation of the secondary amino and hydroxyl group in II, which can be effected by two equivalent amounts of acetic anhydride. The reaction proceeds spontaneously with the evolution of heat, and the subsequent distillation under reduced pressure gives III almost in a quantitative yield.

Some physical properties of III are shown in Table II.

On the third stage, III is submitted to the thermal decomposition, which leads to IV and the ester. As outlined in the introduction, distillation of the ester formed during the heating, and subsequent vacuum-fractionation of IV remaining in the flask are the procedures sufficient to give a pure product for the present synthetic purpose.

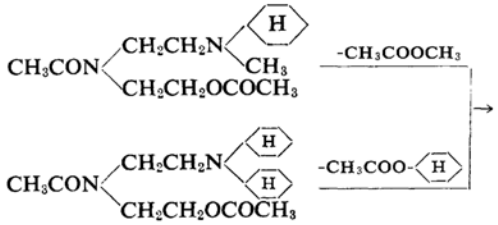
TABLE III. PROPERTIES OF $CH_3CON\langle^{CH_2CH_2}_{CH_2CH_2}\rangle NR''$

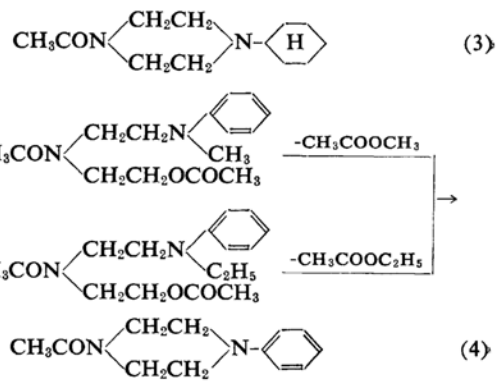
Comp. No.	R''	Phys. form (color)	M. p. °C	B. p., °C/mmHg† 10	20	50	100	760	N, % Found	Calcd.	Picrate M. p. °C	Platinichloride Dec. p., °C	Pt, % Found	Calcd.
1	CH_3	Mob. l. (colorless)						168	19.50	19.70	280 (dec.)	270	28.02	28.10
2	C_2H_5	〃		118	138	160	182	254	17.93	17.93	115	227	27.44	27.01
3	n-C_3H_7	〃		133	151	175	194	265	16.30	16.45	212 (dec.)	*		
4	i-C_3H_7	〃		124	146	171	193	263	16.27	16.45	*	*		
5	n-C_4H_9	〃		146	165	190	210	280	15.11	15.20	190 (dec.)	*		
6,7		Oily l. (colorless)		186	202	226	248	320	13.09	13.31	*	*		
8,9		Cryst. (colorless)	75	206	225	251	270	347	13.67	13.71	*	230	23.93	23.83

TABLE IV. PROPERTIES OF $HN\langle^{CH_2CH_2}_{CH_2CH_2}\rangle NR''$

Comp. No.	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	Mob. l. (colorless)			44	66	137	28.02	27.97	270 (dec.)	275	28.11	28.25
2	C_2H_5	〃		40	64	84	157	24.42	24.53	250 (dec.)	280	37.34	37.23
3	n-C_3H_7	〃	47	65	89	110	180	22.00	21.85	228	260	36.18	36.23
4	i-C_3H_7	〃	44	63	87	103	173	21.78	21.85	240 (dec.)	266	36.24	36.23
5	n-C_4H_9	〃	84	101	123	141	208	19.43	19.70	250 (dec.)	250	35.22	35.34
6,7		Oily l. (colorless)	116	135	158	177	248	16.45	16.65	225 (dec.)	260	33.40	33.76
8,9		Oily l. (yellowish)	139	154	178	180	272	17.30	17.27	150	259	33.99	34.10

As would be anticipated, β-(*N*-methyl-*N*-cyclohexylaminoethyl)-acetaminoethyl acetate (Table II, No. 6) and β-(*N*, *N*-dicyclohexylaminoethyl)-acetaminoethyl acetate (Table II, No. 7) give the same product, *N*-cyclohexyl-*N'*-acetyl-piperazine (Table III, No. 6, 7) under elimination of methyl acetate or cyclohexyl acetate respectively (Eq. 3). The same applies to the case of β-(*N*-methyl-*N*-phenylaminoethyl)-acetaminoethyl acetate (Table II, No. 8) and β-(*N*-ethyl-*N*-phenylaminoethyl)-acetaminoethyl acetate (Table II, No. 9), *N*-phenyl-*N*-acetyl-piperazine (Table III, No. 8, 9) being equally formed (Eq. 4).





Some physical properties of IV are shown in Table III.

The last stage is the de-acetylation of IV. It may be effected easily by heating the acetyl piperazines with an equal volume of 6 N hydrochloric acid under reflux for 2 hr. The *N*-mono-substituted piperazines thus prepared are a colorless liquid, readily soluble in water

with an exception of *N*-phenyl-piperazine.

Some physical properties of V are cited in Table IV.

The reaction mixture of II and acetic anhydride can conveniently be submitted to the thermal decomposition without isolation of the acetylated compounds.

Experimental

***N*-(β-Diethylaminoethanol)-aminoethanol (Table I. No. 2).**—Ethylene oxide, generated by dropping 150 g. of 33% sodium hydroxide solution from a pressure-compensated dropping funnel upon a boiling mixture of 100 g. of ethylene chlorohydrin and 50 g. of water under reflux, is passed in a solution of 116 g. (1 mol.) of *N*,*N*-diethylethylenediamine in about 80 g. of methyl alcohol. Contineous shaking and cooling by cold water facilitate the absorption of ethylene oxide in the reaction mixture.

The gain of weight of the reaction mixture will be 44～50 g., and indicates that about one mole of ethylene oxide thereby can be brought into the reaction.

By distillation under atmospheric pressure, about 60 g. of *N*,*N*-diethylethylenediamine (b. p. 150～165°C) is recovered, and by fractionation under reduced pressure, about 50 g. of *N*-β-diethylaminoethylethanolamine, b. p. 113°C/10 mmHg, or 130°C/20 mmHg, and about 40 g. of *N*-β-diethylaminoethyldiethanolamine, b. p. 165°C/10mmHg, or 184°C/20 mmHg are obtained.

Ethylene chlorohydrin may be used instead of ethylene oxide as follows. Forty grams of ethylene chlorohydrin (0.5 mol.) is gradually added from a dropping funnel onto 116 g. (1 mol.) of *N*,*N*-diethylethylenediamine heated under reflux, thereby the reaction proceeds immediately at the rate of addition of the ethylene chlorohydrin. When the addition is complete, the reaction mixture is heated up to 200°C and maintained at this temperature for a while. Owing to the separation of hydrochloride of *N*,*N*-diethylethylenediamine, the reaction mixture is solidified. A hot solution of 30 g. (approx. 0.5 mol.) of potassium hydroxide in 80 cc. of methyl alcohol is gradually added to the reaction mixture with stirring. The precipitate of potassium chloride is removed by filtration and washed with a small quantity of methyl alcohol. After methyl alcohol has been removed from the filtrate and washings, 75 g. of *N*,*N*-diethylethylenediamine is recovered. The residual liquid is submitted to distillation under reduced pressure, whereby 45～50 g. of *N*-β-diethylaminoethylethanolamine and 25～30 g. of *N*-β-diethylaminoethyldiethanolamine are obtained.

***N*-(β-Diethylaminoethyl)-acetaminoethyl Acetate (Table II, No. 2).**—This compound can be obtained by addition of 23 g. (0.22 mol.) of acetic anhydride to 13 g. of *N*-β-diethylaminoethylethanolamine. Acetic acid and an excess of acetic anhydride are distilled off and the residue is distilled under reduced pressure, the expected acetate is collected at 175～177°C/10 mmHg, as a colorless oily liquid —yield 20～21 g. (about 90%).

The practical procedure in this piperazine-synthesis can be carried out so that the reaction mixture of *N*-β-disubstituted-aminoethylethanolamine and acetic anhydride is directly submitted to the thermal decomposition, the isolation of the acetylated compounds being omitted. The techniques here required are quite the same as in use of pure acetates isolated.

***N*-Ethyl-*N'*-acetyl-piperazine (Table III, No. 2).**—Twenty grams of *N*-β-diethylaminoethylacetaminoethyl acetate is heated in a Claisen flask, with a thermometer inserted through the straight neck so deep in the liquid as to read the internal reaction temperature and another thermometer fixed in the side neck of the flask. When the internal temperature reaches up above 250°C, the liquid turns brown in color and the boiling begins with the decomposition into *N*-ethyl-*N'*-acetyl-piperazine and ethyl acetate, which distills over as it is formed.

When the thermal decomposition is complete, the internal temperature is practically settled to a constant, i. e. 250～260°C.

On distillation, pure *N*-ethyl-*N'*-acetyl-piperazine comes over at 252～256°C as a colorless liquid—yield about 7 g. (Ca. 80%).

***N*-Ethyl-piperazine (Table IV, No. 2).**—*N*-Ethyl-*N'*-acetyl-piperazine (5 g.) is heated with 5 cc. of 20% hydrochloric acid under reflux for 2 hr. After the excess of hydrochloric acid has been distilled off, the resulting solution is made alkaline with a sodium hydroxide solution, and extracted with ether in a continuous extractor. The ether layer is dried over anhydrous sodium sulfate, the ether is removed, and the residue is distilled. About 3 g. of pure *N*-ethyl-piperazine is obtained as a colorless liquid b. p. 155～157°C—yield about 90%.

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