A New Method for the Preparation of Piperazines. III. Mechanism of Ring-closure Reactions with Elimination of Ester

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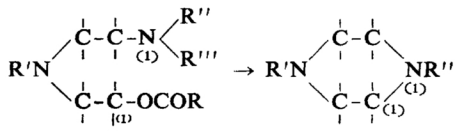
The new synthesis of piperazines proposed by the author in the preceding papers[1], consists in heating a compound A to obtain a piperazine-derivative B under elimination of an ester C, as can be seen from the following over-all Scheme 1;



[A] [B]

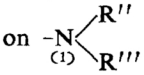
$$+ \mathrm{RCOOR'''} \qquad (1)$$

[C]

The compound A is an ester. It is generally accepted that the alkyl-ogygen bond in carboxylic acid ester of primary or secondary alcohols remains unattacked in hydrolysis or in other reactions in which these esters are concerned. However, esters of tertiary alcohols in some of their reactions may suffer the rupture of the alkyl-oxygen bond. For example, *tart*-butyl acetate, heated under reflux, is completely converted by dry hydrogen chloride into *tart*-butyl chloride and acetic acid, while *n*- and *sec*-butyl acetate undergo no reaction by the same treatment.

According to Eq. 1, however, the $C_{(1)}$–O bond should break up and the liberated acetoxyl group should combine with an alkyl group which comes out of $N_{(1)}$ to build up an ester molecule C, thus leaving a piperazine-ring system B.

The $-C-C_{(1)}-$ linkage in A may be regarded as an alkyl, so the piperazine-ring formation 1 may be considered to be a reaction which involves a replacement of R''' by $-C-C_{(1)}-$ grouping.

In other words, the ester part of A reacts as an alkylating reagent on  to drive out R'''.

In order to see the reactivities of alkyl acetates with tertiary amines, triethylamine and dimethylaniline were heated with *n*-butyl acetate under reflux for 20 hr.

However, no reaction could be observed and the starting materials were recovered unchanged. An attempt in an autoclave (at 280°C for 3 hr.) gave the same result.

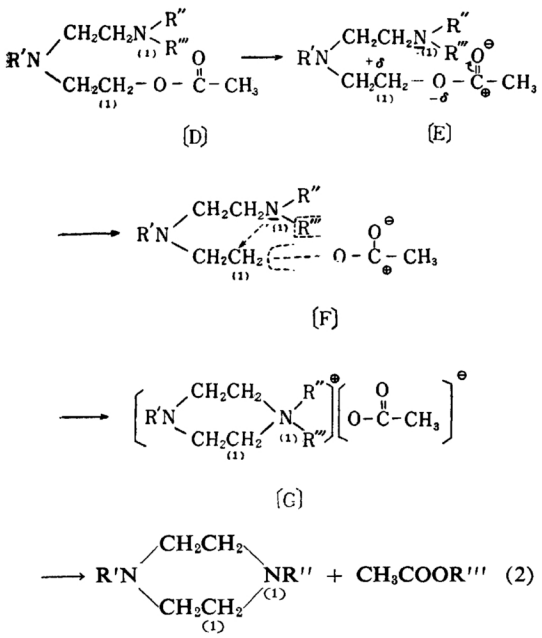
Even when *tert*-butyl acetate which has tendency to rupture at the alkyl-oxygen bond was used, reaction between the ester and triethylamine or dimethylaniline did not proceed.

In contrast to the very smooth progress of reaction 1 (R', R'', R''': CH_3), a ring-closure reaction for obtaining the same product by heating *N*, *N*, *N'*, *N'*-tetramethylethylenediamine and ethylenediacetate in an autoclave for 3 hr. at 280°C proved to be a failure.

In reaction 1 (R', R'', R'''; CH_3), the dialkylated amino group and the ester grouping are held in one molecule and are able to stay very close to each other on account of their special configuration. This proximity of the two groups is the most remarkable difference between the two cases of cyclization reaction and it seems to be plausible to attribute the cause of reaction 1 to the close situation of these groups.

The mechanism of the piperazine-ring formation might be written as follows;

1) K. Nakajima, This Bulletin, **34**, 651, 655 (1961).

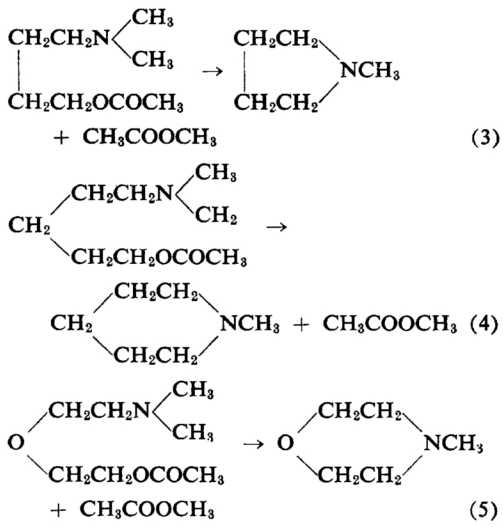


The first stage of the reaction mechanism is assumed to be the formation of a polarized state in the molecule D under the influence of heat as shown in E. In the second stage the union of $N_{(1)}$ and $C_{(1)}$ takes place and the carboxyl group is released as an anion. Then in the third stage the salt-like compound G thus formed is considered to be broken into a piperazine-derivative H and an ester CH_3COOR''' at that elevated temperature. The decomposition of G may be regarded as a similar type of reaction to the thermal decomposition of the quarternary ammonium halides, which was reported by Hofmann[2].

This assumption for the similiarity can be explained by the fact that ease in liberation of the alkyl group R''' is identical to that of Hofmann's reaction, as briefly refered to in preceding report[1].

On inspecting the reaction mechanism shown in Scheme 2, an important question naturally arises as to what kind of compounds having a disubstituted amino and an ester-grouping in suitable positions in the molecule can undergo cyclization in the same way as these described above.

In order to give an answer to this question, several trials have been made with 4-dimethylamino-*n*-butyl acetate, 5-dimethylamino-*n*-pentyl acetate and β-acetoxy-β'-dimethylaminodiethyl ether. They have successfully proved that these compounds also undergo similar ring-closure reaction at about 200°C with elimination of an ester, giving *N*-methylpyrrolidine (3), *N*-methylpiperidine (4) and *N*-methylmorpholine (5), respectively.



These reactions make it easy to suppose that β-acetoxy-β'-dimethylaminodiethyl sulfide may have the possibility of being converted into *N*-methylthiomorpholine under similar conditions.

Synthesis of the sulfide, however, has not yet been attained.

Experimental

***tert*-Butyl Chloride from *tert*-Butyl Acetate by Hydrogen Chloride.**—Dry hydrogen chloride was passed into *tert*-butyl acetate boiling in a flask fitted with a fractionating column, at such a rate that *tert*-butyl chloride formed distilled over at 50~60°C.

The reaction proceeded smoothly, leaving acetic acid in the reaction flask. *n*-Butyl and *sec*-butyl acetate remained intact by the same treatment.

***N*-Methylpyrrolidine from 4-Dimethylamino-*n*-butyl Acetate.**—*4-Dimethylamino-1-butanol.*—A mixture of 22 g. (0.2 mol.) of tetramethylene chlorohydrin and 50 g. of a 40% aqueous solution of dimethylamine was allowed to react in a bottle, plugged with a stopper holding a thermometer and an outlet tube connected to another bottle fed with water. By occasional shaking and timely cooling in water, the exothermic but moderate reaction was regulated so that no methylamine gas came to the bottle with water.

After adding 9 g. of powdered sodium hydroxide cautiously in small portions, the mixture was distilled. The crystals of sodium chloride which prevented the further distillation were removed by filtration and the filtrate was submitted to a careful fractionation. There was obtained about 15 g. of 4-dimethylamino-1-butanol as a colorless, viscous liquor boiling at 184°C.

Found: N, 11.82. Calcd. for $C_6H_{15}ON$: N, 11.95%.

4-Dimethylamino-n-butyl Acetate.—Twelve grams (0.12 mol.) of acetic anhydride was gradually

2) A. W. Hofmann, *Proc. Roy. Soc.*, **1860**, 10, 595.

added to 12 g. (0.12 mol.) of 4-dimethylamino-1-butanol with stirring and cooling in water. The reaction mixture was then dissolved in about 50 cc. of water and neutralized with sodium bicarbonate added in small portions until no more evolution of carbon dioxide was observed. The resultant solution was extracted with ether in a continuous extraction apparatus.

Distillation of the ether followed by a careful distillation in vacuo gave a 90~95% yield of the acetate.

Colorless liquid, b. p. 85°C/15 mmHg. Picrate, m. p. 126°C.

Found: N, 8.69. Calcd. for $C_8H_{17}O_2N$: N, 8.80%.

N-Methylpyrrolidine.—Sixteen grams (0.1 mol.) of 4-dimethylamino-*n*-butyl acetate was distilled slowly and carefully using a small Claisen flask, which is equipped with two thermometers, one being inserted in the liquid through the straight neck of the flask to read the internal temperature and the other fitted in the side neck to read the distillation temperature. When the internal temperature was raised to above 200°C, boiling commenced with the splitting into *N*-methylpyrrolidine and methyl acetate, both of which distilled over at 50~100°C as they were formed.

Redistillation of the distillate gave about 6 g. (about 75%) of pure *N*-methylpyrrolidine. *N*-Methylpyrrolidine is a well-known compound, a colorless liquid, b. p. 80~81°C. Picrate, m. p. 218°C.

N-Ethylpyrrolidine from 4-Diethylamino-*n*-butyl Acetate. — *4-Diethylamino-1-butanol.* — A mixture of 27 g. (0.25 mol.) of tetramethylene chlorohydrin and 36.5 g. (0.5 mol.) of diethylamine was boiled under reflux for 10 hr. The crystals of diethylamine hydrochloride, gradually formed during the heating, were filtered off and the filtrate was fractionally distilled. After a forerun of tetrahydrofuran (ca. 5 g.) formed in a side reaction 6, there was obtained about 15 g. of 4-diethylamino-1-butanol boiling at 208°C, as a colorless, viscous liquid.

$$HO(CH_2)_4Cl + HN(C_2H_5)_2 \rightarrow \begin{matrix} CH_2\text{-}CH_2 \\ | \quad | \\ CH_2 \quad CH_2 \\ \diagdown \quad \diagup \\ O \end{matrix} + (C_2H_5)_2NH\cdot HCl \qquad (6)$$

Found: N, 9.51. Calcd. for $C_8H_{19}ON$: N, 9.64%.

4-Diethylamino-n-butyl Acetate.—Obtained similarly as in the methyl derivative mentioned above. Colorless liquid, b. p. 98°C/12 mmHg.

Found: N, 7.31. Calcd. for $C_{10}H_{21}O_2N$: N, 7.48%.

N-Ethylpyrrolidine. — Obtained in the same way as in the methyl derivative above. Colorless liquid, b. p. 104~106°C. Picrate, m. p. 185°C.

N-Methylpiperidine from 5-Dimethylamino-*n*-pentyl Acetate.—On the whole, the actual procedure here is analogous to that of *N*-methylpyrrolidine.

5-Dimethylamino-1-pentanol.—A mixture of 24.5 g. (0.2 mol.) of pentamethylene chlorohydrin and 50 g. of a 40% aqueous solution of dimethylamine was allowed to react. After the reaction was completed the resultant homogenous solution was distilled until the internal temperature indicated 180°C. To the cooled mixture was added a concentrated solution of potassium hydroxide in methyl alcohol and the precipitate of potassium chloride was filtered off and the filtrate was distilled.

Colorless, viscous liquid, b. p. 205~206°C. Yield 21 g. (80%).

Found: N, 10.39. Calcd. for $C_7H_{17}ON$: N, 10.68%.

5-Dimethylamino-n-pentyl Acetate. — The procedure described in the case of the corresponding butyl derivative was also employed here.

Colorless oily liquid, sparingly soluble in water, b. p. 114°C/22 mmHg.

Found: N, 7.78. Calcd. for $C_9H_{19}O_2N$: N, 8.09%.

N-Methylpiperidine.—This compound was obtained by the slow distillation of 5-dimethylamino-*n*-pentyl acetate followed by the fractionation of the distillate, and was identified by comparison with the authentic sample.

Colorless liquid, b. p. 107°C.

N-Ethylpiperidine from 5-Diethylamino-*n*-pentyl Acetate. — *5-Diethylamino-1-pentanol.*—From 24.5 g. (0.2 mol.) of pentamethylene chlorohydrin and 30 g. (ca. 0.4 mol.) of diethylamine, about 25 g. (ca. 80%) of this compound was obtained as a colorless viscous liquid boiling at 127~130°C/22 mmHg.

Found: N, 8.75. Calcd. for $C_9H_{21}ON$: N, 8.80%.

5-Diethylamino-n-pentyl Acetate. — Colorless oil, sparingly soluble in water, b. p. 127°C/22 mmHg.

Found: N, 7.02. Calcd. for $C_{11}H_{23}O_2N$: N, 6.96%.

N-Ethylpiperidine. — The acetate above was split into *N*-ethylpiperidine and ethyl acetate at a temperature higher than 200°C. The reaction proceeded slowly but steadily. *N*-Ethylpiperidine is, of course, a well-known compound.

N-Methylmorpholine from β-Acetoxy-β'-dimethylaminodiethyl Ether.—*β-Hyroxy-β'-dimethylaminodiethyl Ether.*—The ether was prepared by the reaction of 2 mol. proportions of ethylene oxide on 1 mol. proportion of aqueous solution of dimethylamine.

In 110 g. (1 mol.) of a 40% aqueous solution of dimethylamine was absorbed ethylene oxide, generated by dropping a solution of 80 g. (2 mol.) of sodium hydroxide in 160 cc. of water onto a boiled mixture of 200 g. (2.5 mol.) of ethylene-chlorohydrin and 100 cc. of water under reflux. The reaction between ethylene oxide and dimethylamine is exothermic.

Suitable control of the dropping rate of the sodium hydroxide solution and occasional water-cooling were applied in order to bring the ethylene oxide entirely into action. The gain in weight of the reaction mixture was about 90 g. and indicated that in this way about 2 mol. of ethylene oxide could be generated and be made to enter into the reaction.

To the brown and viscous mixture was added portion-wise about 60 g. of anhydrous potassium

3) I. G. Farfen Ind., D. R. P. 432803; *Chem. Zentr.*, **1926**, II. 1693.

carbonate. Then there were formed two layers, of which the upper was separated and distilled fractionally. There was obtained about 15 g. of β-dimethylamino ethyl alcohol (b. p. 130~135°C) and about 50 g. of β-hydroxy-β'-dimethylamino-diethyl ether (b. p. 205°C).

Found: N, 10.68. Calcd. for $C_6H_{15}O_2N$: N, 10.52%.

β-Acetoxy-β'-dimethylaminodiethyl Ether. — Acetic anhydride (26 g. 0.25 mol.) was added dropwise to 35 g. (0.2 mol.) of β-hydroxy-β'-dimethylaminodiethyl ether with cooling in water.

After heating to boiling under reflux and subsequent cooling to room temperature, the mixture was dissolved in about 100 cc. of water, neutralized with about 30 g. of sodium bicarbonate added in small portions and extracted with ether in a continuous extractor. Distillation of the ether followed by fractionation of the residual liquid under reduced pressure gave almost a quantitative yield of β-acetoxy-β'-dimethylaminodiethyl ether as a colorless liquid boiling at 132°C/50 mmHg or 110°C/30 mmHg.

N-Methylmorpholine.—Distillation of β-hydroxy-β'-dimethylaminodiethyl ether, carried out slowly and carefully at atmospheric pressure, gave a mixture of methyl acetate and *N*-methylmorpholine in a good yield.

The *N*-methylmorpholine was identified by an authentic sample.

Colorless liquid, b. p. 215~216°C. Picrate m. p. 220°C. Chloroplatinate, m. p. 225~226°C.

N-Ethylmorpholine from β-Acetoxy-β'-diethylaminodiethyl Ether.—The procedure employed was substantially analogous to that of the methyl derivative.

*β-Hydroxy-β'-diethylaminodiethyl Ether**.—Obtained by the action of ethylene oxide on β-diethylaminoethyl alcohol in equimolecular proportions, or on an aqueous diethylamine solution in mole proportions of 2 to 1. Colorless, viscous oily liquid, b. p. 142°C/52 mmHg.

Found: N, 8.57. Calcd. for $C_8H_{19}O_2N$: N, 8.69%.

β-Acetoxy-β'-diethylaminodiethyl Ether.—Colorless oily liquid, b. p. 143~145°C/42 mmHg.

Found: N, 6.60. Calcd. for $C_{10}H_{21}O_3N$: N, 6.89%.

Chloroplatinate, yellow plates from concentrated solution, decomposed at 174°C.

Found (for chloroplatinate): Pt, 24.00. Calcd. for $(C_{10}H_{21}O_3N)_2 \cdot H_2PtCl_6$: Pt 23.90%.

N-Ethylmorpholine.—Obtained by a slow distillation of the above ether. The formation of *N*-ethylmorpholine proceeded very slowly but in an excellent yield. Colorless liquid, b. p. 139°C. Picrate, m. p. 190°C. Chloroplatinate, orange-yellow needles, m. p. 198°C. These data were identified with the authentic samples.

The auther wishes to express his heartfelt thanks to Professor Dr. Ryozo Goto, Kyoto University for his encouragement and numerous suggestions throughout this work.

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* Preparation by the action of mono-sodium compound of ethylene glycol on diethyl-(β-chloroethyl)-amine had been known; Bayer & Co., D. R. P. 398010; *Chem. Zentr.*, 1924, II. 1399.