there was obtained 90 g. of the rearrangement product as yellowish leaflets from ethanol, m. p. 187°. In a like manner 13 g. of the butyroxy compound gave 9.6 g. of rearrangement product as yellowish leaflets from ethanol, m. p. 141°. *Anal.* (propionyl) Calcd. for $C_{13}H_{12}O_4$: C, 67.2; H, 5.18. Found: C, 67.2; H, 5.34. (butyryl) Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.7. Found: C, 68.1; H, 5.8.

2,6-Dihydroxypropiophenone and 2,6-Dihydroxybutyrophenone.—155 grams of the propionyl derivative treated with one liter of 12% aqueous sodium hydroxide for six hours on the steam-bath and in a nitrogen atmosphere gave, after cooling and acidification, 66 g. of 2,6-dihydroxypropiophenone, yellow needles from 25% aqueous methanol, m. p. 133.5°. By analogous treatment 16 g. of the butyryl derivative gave 9.4 g. of 2,6-dihydroxybutyrophenone as yellow needles from 25% aqueous methanol, m. p. 106°. *Anal.* (propiophenone) Calcd. for $C_9H_{10}O_3$: C, 65.1; H, 6.0. Found: C, 64.8; H, 6.0. (butyrophenone) Calcd. for $C_{10}H_{12}O_3$: C, 66.7; H, 6.7. Found: C, 66.9; H, 6.8.

Vicinal Propylresorcinol and Vicinal Butylresorcinol.—Clemmensen reduction of 36 g. of 2,6-dihydroxypropiophenone for six hours using 90 g. of amalgamated zinc, hydrochloric acid (180 cc. 12%) and with the addition of 15 cc. of concd. hydrochloric acid each hour gave, after separation, vacuum distillation and recrystallization from gasoline, 23 g. of vicinal propylresorcinol as white lustrous needles, m. p. 92.5°.

Using proportionate quantities, and continuing the reduction for seven hours, 60 g. of 2,6-dihydroxybutyrophenone yielded 44 g. of vicinal butylresorcinol as slender white needles from gasoline, m. p. 83°. *Anal.* (propyl) Calcd. for $C_9H_{12}O_2$: C, 71.1; H, 7.9. Found: C, 70.8; H, 8.0. (butyl) Calcd. for $C_{10}H_{14}O_2$: C, 72.3; H, 8.44. Found: C, 72.1; H, 8.5.

4-Methyl-7-caproyloxycoumarin.—4-Methyl-7-hydroxycoumarin (17 g.) was dissolved in dry pyridine (25 cc.) and the solution treated with caproyl chloride (35 g.). The whole was heated at the temperature of the steam-bath for ten minutes, cooled and poured into cold water (500 cc.) with good stirring. The solid was collected, washed, dried and recrystallized from methanol. It forms white prisms, m. p. 72°, yield 15.3 g. *Anal.* Calcd. for $C_{16}H_{18}O_4$: C, 70.0; H, 6.6. Found: C, 70.0; H, 6.9.

Summary

6- or β-substituted resorcinols are obtained easily in good yield whatever the nature of the substituting group. Moreover, methods are available for obtaining good yields of resorcinols substituted in the 5- or α-position. However, although some vicinal substituted resorcinols are known, up until the present no easy method has been exploited whereby substituents could be introduced into the resorcinol nucleus in the inaccessible 2-, γ- or vicinal position. Such a process is now described for obtaining vicinal alkyl resorcyl ketones and the corresponding vicinal alkyl resorcinols.

Chapel Hill, North Carolina
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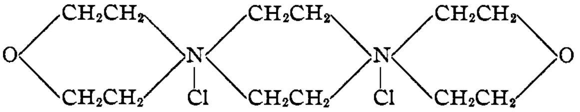
[Contribution from the Chemical Laboratory of Boston University]

Preparation and Polymerization of β-4-Morpholinoethyl Chloride

By J. Philip Mason and Harry W. Block[1]

The only morpholinoethyl halide derivative which we have found described in the literature is β-4-morpholinoethyl bromide hydrobromide obtained by Prelog and Blozek[2] by heating triethanolamine hydrobromide with 64% hydrobromic acid in a sealed tube at 160°. Their yield was 25%. We have prepared β-4-morpholinoethyl chloride hydrochloride by treating β-4-morpholineëthanol hydrochloride with thionyl chloride, obtaining a yield of 63.5%, and also by treating β-4-morpholineëthanol with thionyl chloride, obtaining yields varying from 73 to 88%. Treatment of this hydrochloride with alkali yielded a colorless liquid, β-4-morpholinoethyl chloride. After standing for a few days, a solid appeared in the liquid, and the amount of solid increased slowly on standing. It was found that the formation of the solid could be accelerated by refluxing an alcohol solution of β-4-morpholinoethyl chloride. This solid was found to be a dimeric quaternary ammonium salt having the formula



and which can be named N,N′-dispiromorpholinopiperazonium dichloride or N,N′-di-[1,5-(3-oxapentylene)]-piperazonium dichloride. Knorr[3] previously had prepared β-chloroethyldimethylamine and had found that it polymerized on standing or on refluxing in alcohol solution to N,N′-tetra-

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[1] Taken from the thesis to be submitted by Harry W. Block to the faculty of the Graduate School of Boston University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Prelog and Blozek, *C. A.*, **29**, 4011 (1935).

[3] Knorr, *Ber.*, **38**, 3136 (1905); **39**, 1420 (1906).

methylpiperazonium dichloride. Knorr's proof of structure consisted in determining the decomposition products obtained when the compound was heated with concentrated potassium hydroxide solution. He obtained acetylene, symmetrical tetramethyldiaminoethane and dimethylaminoethanol. Knorr's quaternary piperazonium salt can decompose in two ways, (a) to yield acetylene and tetramethyldiamineëthane, and (b) to yield dimethylvinylamine which was apparently hydrated to form dimethylaminoethanol. If our compound is analogous to Knorr's compound, it should decompose on treatment with potassium hydroxide to yield (a) acetylene and 1,2-dimorpholinoethane and (b) β-4-morpholineëthanol. We have obtained both acetylene and 1,2-dimorpholineëthane, but did not obtain any morpholineëthanol. In this connection, we have tried, unsuccessfully, to make vinylmorpholine by the catalytic dehydration of β-4-morpholineethanol. It is, of course, possible that our quaternary piperazonium salt decomposes in only one way, to yield acetylene and 1,2-dimorpholinoethane.

When β-4-morpholinoethyl chloride was digested with absolute alcohol, the yield of N,N′-di-[1,5-(3-oxapentylene)]-piperazonium dichloride obtained after refluxing for forty-eight hours was about 34%, and the formation of the solid had practically ceased. Evaporation of the alcohol yielded a solid which was identified as the hydrochloride of β-4-morpholinoethyl ether. Since we obtained more of this solid than of the dimer, the reaction between β-4-morpholinoethyl chloride and the solvent alcohol proceeds more rapidly than the polymerization reaction.

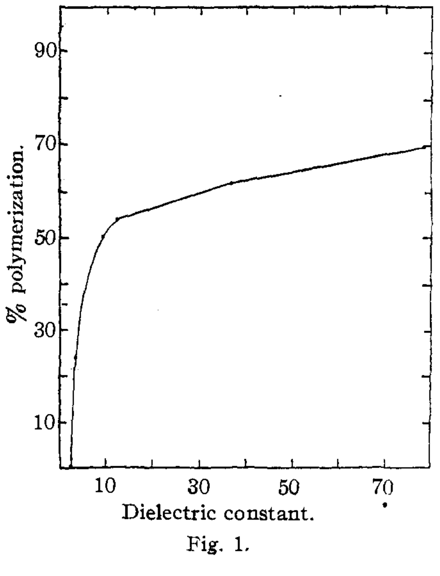

Fig. 1.

β-4-Morpholinoethyl chloride was then refluxed with separate portions of propyl alcohol, acetone and benzene. With propyl alcohol, a yield of 26.6% of the dimer was obtained after 218 hours of refluxing. β-4-Morpholinoethyl propyl ether hydrochloride was obtained after evaporation of the alcohol. Polymerization in acetone occurred very slowly, only 5% of the dimer being obtained after refluxing for a period of four months. There was no evidence of any reaction between β-4-morpholinoethyl chloride and acetone. A benzene solution of β-4-morpholinoethyl chloride was refluxed for one hundred eight hours without forming any trace of solid. At the end of this period, the benzene was distilled and 97% of the original β-4-morpholinoethyl chloride was recovered. In this connection, it is interesting to note that when benzene is used in place of ether for the extraction of β-4-morpholinoethyl chloride from the alkaline solution in which it is prepared, the β-4-morpholinoethyl chloride obtained does not form a solid as quickly as when ether is used for the extraction.

The above observations concerning the polymerization of β-4-morpholinoethyl chloride suggested the possibility that the extent of polymerization was dependent upon the dielectric constant of the solvent. Consequently, a number of polymerizations were carried out in water, dioxane and mixtures of these solvents. The results are given in Table I and represented graphically in Fig. 1.

TABLE I

% Dioxane	Dielectric constant[a]	β-4-Morpholinoethyl chloride used, g.	Dimer,[b] g.	Dimer, %
100	2.2	5	0	0
93.6	4.4	5	1.2	24
85.0	9.0	5	2.5	50
80.0	12.0	5	2.7	54
47.0	37.0	5	3.1	62
0	78.6	7.6	5.3	69.7

[a] Kraus and Fuoss, THIS JOURNAL, **55**, 21 (1933).

[b] All mixtures refluxed for twenty-four hours.

It is to be noted that whenever water is present in the solvent, hydrolysis occurs, causing the formation of β-4-morpholineëthanol hydrochloride. In spite of this competing reaction, the evidence does indicate that, for this particular pair of liquids, the extent of dimerization of β-4-morpholinoethyl chloride is a function of the dielectric constant of the solvent. That no general conclusion can be drawn concerning the extent of dimerization and the dielectric constant is shown by the following facts: (a) absolute ether and benzene, with dielectric constants of 4.35 and 2.28, respectively, did not cause any dimerization in twenty to twenty-four hours; (b) acetone, with a dielectric constant of 21.3, caused only slight polymerization (5%) in four months; (c) ethyl alcohol and propyl alcohol, with dielectric constants of 25.8 and 22, respectively, yielded 34% (forty-eight hours of refluxing) and 22.6% (two hundred and twenty-eight hours refluxing), respectively, of polymer. However, when comparing the dimerization of β-4-morpholinoethyl chloride in alcohols and in dioxane–water mixtures, it should be remembered that our evidence indicates that dimerization proceeds faster than hydrolysis but slower than alcoholysis. The possibility that some relationship exists between the rate of dimerization and the dielectric constant of the solvent is being studied further, using solvents which do not react with β-4-morpholinoethyl chloride.

When it was first planned to make β-4-morpholinoethyl chloride, we intended to make the Grignard reagent, β-4-morpholinoethylmagnesium chloride, and to cause that to react with various carbonyl compounds. All of our attempts to make this Grignard reagent have proved unsuccessful. It is interesting to note that while β-4-morpholinoethyl chloride does not polymerize in absolute ether when the solution is refluxed for twenty-four hours, it does polymerize appreciably (10%) in a few hours in absolute ether solution when magnesium is present. The rate of polymerization is much slower than the rate of formation of most Grignard reagents. Inasmuch as other work in this Laboratory indicates that the chlorine in β-4-morpholinoethyl chloride is a fairly reactive chlorine, we are puzzled over the inability of this compound to form a Grignard reagent.

Experimental Part

β-4-Morpholinoethyl Chloride Hydrochloride. (A) **From β-4-Morpholineëthanol and Thionyl Chloride.**—Two moles (262 g.) of redistilled β-4-morpholineëthanol was dissolved in 200 cc. of chloroform[4] in a three-necked flask equipped with a mercury sealed mechanical stirrer, a reflux condenser and a dropping funnel. A gas absorption bottle was connected to the top of the condenser. By means of a water-bath the solution was warmed to 40°, while stirring, and a few drops of a solution of 2.75 moles (200 cc.) of thionyl chloride in 200 cc. of chloroform[4] was added. After the initial reaction had abated, the thionyl chloride solution was added dropwise at such a rate that the temperature of the reaction mixture did not rise above 55°. After the first thirty minutes, the thionyl chloride solution could be added at the rate of two drops a second. After the first hour, the thionyl chloride was added more rapidly and external heating was necessary to keep the reaction mixture at 50–55°. About two hours was required for the addition. After all of the thionyl chloride solution was added, the reaction flask was heated very slowly and intermittently, until the mixture refluxed smoothly and the refluxing was continued for an hour. After cooling, the white crystals were removed by filtration and recrystallized from one liter of absolute alcohol, using 20 g. of Norit to decolorize the solution; yield, 263.6 g. (70.9%). The alcohol filtrate was concentrated to a volume of about 100 cc. An additional 26 g. was obtained, making a total yield of 289.6 g. (78%), m. p. 182–182.5°.

Anal. Calcd. for $C_6H_{13}Cl_2NO$: total Cl, 38.10; ionic Cl, 19.05; N, 7.53. Found: total Cl, 38.28, 38.40; ionic Cl, 18.59, 18.74; N, 7.15, 7.26.

(B) **From β-4-Morpholineëthanol Hydrochloride.**—β-4-Morpholineëthanol hydrochloride was made by adding slowly 56.4 cc. (10% excess) of concentrated hydrochloric acid to 70 g. of β-4-morpholineëthanol with good cooling and stirring. After evaporating to dryness on a steam-bath under reduced pressure, the solid was dissolved in 200 cc. of water and the solution decolorized by two treatments with Norit. Evaporation of the colorless solution under reduced pressure gave a solid which was recrystallized twice from *n*-amyl alcohol (absolute ethyl alcohol can also be used); yield 62.9 g. (70.2%), m. p. 109–110° (softens at 100°). A second crop of 3.4 g. was obtained by concentrating the combined filtrates.

Anal. Calcd. for $C_6H_{14}ClNO_2$: Cl, 21.15. Found: Cl, 20.91, 20.90.

Since β-4-morpholineëthanol picrate has not been reported in the literature, it was analyzed for nitrogen. It melted at 126°.

Anal. Calcd. for $C_{12}H_{16}N_4O_9$: N, 15.60. Found: N, 15.65, 15.66.

Six-tenths of a mole (100.5 g.) of β-4-morpholineëthanol hydrochloride was suspended in 150 cc. of chloroform. A solution of 108 g. of thionyl chloride in 150 cc. of chloroform was added and the mixture digested on the steam-bath for one hour. Complete solution occurred, followed by the separation of some solid. The mixture was then cooled and filtered and the crystals washed with a little chloroform. Two recrystallizations from *n*-amyl alcohol (absolute alcohol can also be used) yielded 67.2 g. of β-4-morpholinoethyl chloride hydrochloride, m. p. 182°. An additional 2.3 g. was obtained by concentrating the amyl alcohol filtrates and recrystallizing from amyl alcohol. Only 1.4 g. of purified product was obtained from the chloroform filtrate. The total yield was 70.9 g. (63.5%).

β-4-Morpholinoethyl Chloride.—Three-fourths of a mole (139.5 g.) of β-4-morpholinoethyl chloride hydrochloride

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[4] When the amount of β-4-morpholineëthanol is considerably smaller, *e. g.*, 0.5 mole, the ratio of chloroform to reactants should be doubled in order to prevent the final reaction mixture from solidifying when cooled.

was dissolved in 150 cc. of water and 75 cc. of ether was added. To this mixture, 15% sodium hydroxide solution was added slowly until the aqueous solution was distinctly alkaline. The ether layer was removed and the aqueous solution was extracted with ten 50-cc. portions of ether. The combined ether extracts were dried over potassium hydroxide pellets. After distillation of the ether, the β-4-morpholinoethyl chloride distilled at 93–4° (12 mm.); yield, 95 g. (84.7%). In some later experiments, benzene was used instead of ether to extract the β-4-morpholinoethyl chloride. Five extractions with benzene were sufficient and the product could be kept for a longer period of time before polymerization was observed.

Anal. Calcd. for $C_6H_{12}ONCl$: Cl, 23.70; N, 9.36. Found: Cl, 23.48, 24.09; N, 9.39, 9.36.

β-4-Morpholinoethyl Chloride Picrate.—Since β-4-morpholinoethyl chloride reacts with both water and alcohol, the picrate was made by adding an excess of a saturated solution of picric acid in dry benzene to a solution of 1 cc. of β-4-morpholinoethyl chloride in 2 cc. of dry benzene. The precipitate, which formed immediately, was recrystallized from hot benzene in which it was soluble only to the extent of about 1.5%. However, it appears to be completely insoluble in cold benzene. It melted at 130°. Since the m. p. of β-4-morpholineëthanol picrate is 126°, a mixed melting point determination was made, m. p. 116°.

Anal. Calcd. for $C_{12}H_{15}ClN_4O_8$: N, 14.80. Found: N, 14.85, 14.96.

Reactions of β-4-Morpholinoethyl Chloride in Ethyl Alcohol. (A) N,N'-Di-[1,5-(3-oxapentylene)]-piperazonium Dichloride.—Fifty grams of freshly distilled β-4-morpholinoethyl chloride was refluxed with 250 cc. of absolute alcohol. The precipitated solid was removed by filtration at one, two, four, four, twelve, twelve, twenty-four, and forty-eight hour intervals. The amount of solid formed during the last period of digestion was very small. The total weight of solid was 16.8 g. (34%). This solid was soluble in water, insoluble in organic solvents and did not melt. It was identified by the following data as N,N'-di-[1,5-(3-oxapentylene)]-piperazonium dichloride.

Anal. Calcd. for $C_{12}H_{24}Cl_2N_2O_2$: Cl, 23.70; N, 9.36. Found: Cl, 23.97, 23.76; N, 9.23, 9.16.

Sixteen grams of this dimer was dissolved in a solution of 32 g. of potassium hydroxide dissolved in 32 cc. of water in an Erlenmeyer flask fitted with a tube leading to an ammoniacal silver nitrate solution. The flask was heated on a steam-bath until all of the acetylene had been driven off. The precipitate of silver acetylide was filtered, and a small portion of it exploded when heated on the end of a spatula. A positive test for acetylene also was obtained when the gas was passed into a 1% solution of phenylmercuric bromide in 10% potassium hydroxide solution, using the procedure developed by Spahr, Vogt and Nieuwland.[5]

After all of the acetylene had been liberated, the solution was cooled and extracted first with 100 cc. of ether, followed by eight more extractions, using 50 cc. of ether for each extraction. These extracts were combined and dried over solid potassium hydroxide. The ether solution was concentrated to a volume of about 25 cc. Five grams of Norit was added to decolorize the solution and the colorless filtrate was evaporated to a volume of 15 cc. The ether solution was cooled to about −75° by placing it in a bath of dry-ice in methanol. The solid was filtered and washed with dry ether previously cooled to this temperature. In this way, 4.4 g. of solid was obtained. By concentrating the filtrate and washings to 5 cc. and then cooling to −75° (dry-ice in methanol) an additional 1.0 g. was obtained. The total yield was 5.4 g. (51%) and the solid melted at 71–72°. Recrystallization from ether solution by cooling in a bath of dry-ice and methanol yielded pure 1,2-dimorpholinoethane melting at 73.5°. Knorr[6] reported a melting point of 74° for 1,2-dimorpholinoethane and 230–236° for the picrate. Our picrate melted with decomposition at 234–236°.

Anal. Calcd. for $C_{10}H_{20}N_2O_2$: N, 13.99. Found: N, 14.23, 13.89.

β-4-Morpholinoethyl Ethyl Ether Hydrochloride.—Since only one-third of the β-4-morpholinoethyl chloride was accounted for as the dimer after refluxing with alcohol, the alcohol filtrate was distilled and the residue transferred to an evaporating dish, using a little alcohol to rinse out the flask. This residue was heated on the steam-bath for four hours. On cooling, the mass solidified and weighed 30.7 g. The solid was pulverized, divided into 6 g. portions and each portion extracted repeatedly with hot toluene. In this way, 12.8 g. of solid was extracted, leaving a resinous residue of 4.2 g. which was insoluble in toluene. Five grams of the solid extracted by toluene was recrystallized twice from 250 cc. of toluene. The weight of pure product was 3 g. and it melted at 138°. This solid was very soluble in water, ethyl alcohol and *n*-amyl alcohol, soluble in the hot solvents, acetone, dioxane, cellosolve, diethylene glycol, β,β'-dichlorodiethyl ether, benzene and toluene, but could be recrystallized satisfactorily only from the last two solvents. It was insoluble in ligroin, cyclohexane and ether. That this compound was β-4-morpholinoethyl ethyl ether hydrochloride was shown by analysis and mixed melting point determination with some β-4-morpholinoethyl ethyl ether hydrochloride prepared from β-4-morpholinoethyl ethyl ether. The picrate of our ether melted at 102–3°, the picrate from the commercial ether melted at 103° and a mixture of the two melted at 102°.

Anal. Calcd. for $C_8H_{18}ClNO_2$: Cl, 18.12; N, 7.16; mol. wt., 195.6. Found: Cl, 18.01, 18.06; N, 6.80, 7.02; mol. wt. (acetic acid), 195.5, 198.5.

Picrate.—Calcd. for $C_{14}H_{20}N_4O_9$: N, 14.43. Found: N, 14.46, 14.65.

Reactions of β-4-Morpholinoethyl Chloride in Propyl Alcohol.—Twenty-one grams of freshly distilled β-4-morpholinoethyl chloride was refluxed with 100 cc. of *n*-propyl alcohol. Filtrations were made at two, twelve, thirty-six, sixty, and one hundred and eight hour intervals. At the end of 218 hours, a total of 5.6 g. (27%) of N,N'-di-[1,5-(3-oxapentylene)]-piperazonium dichloride was obtained. This was identified by decomposition with 50% sodium hydroxide solution as described above.

The propyl alcohol was distilled from the filtrate and

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(5) Spahr, Vogt and Nieuwland, THIS JOURNAL, **55**, 2465 (1933).

(6) Knorr, *Ber.*, **35**, 4472 (1902).

the residue transferred to an evaporating dish, which was heated to remove the last trace of solvent. When cooled, the entire mass solidified; weight, 21.5 g. The pulverized solid was extracted repeatedly with hot toluene, and the toluene solution was decolorized with Norit. In this way, 10.5 g. of β-4-morpholinoethyl propyl ether hydrochloride was obtained. When recrystallized from toluene and dried, it melted at 130–131°.

Anal. Calcd. for $C_9H_{20}ClNO_2$: C, 51.54; H, 9.61; Cl, 16.91; N, 6.68. Found: C, 51.14, 51.65; H, 10.13, 10.20; Cl, 17.02, 17.12; N, 6.80, 6.82.

Reactions of β-4-Morpholinoethyl Chloride in Acetone.—Twenty grams of freshly distilled β-4-morpholinoethyl chloride was dissolved in 100 cc. of acetone and the solution refluxed. A solid formed very slowly, only 1 g. being obtained after refluxing for four months. During this period acetone was added frequently because of evaporation losses. The solid was identified as N,N′-di-[1,5-(3-oxapentylene)]-piperazonium dichloride by decomposition with 50% sodium hydroxide as described above.

The acetone was removed from the filtrate by distillation and the remaining liquid (3.7 g.) distilled at 91–2° (12 mm.). This corresponds to the b. p. of β-4-morpholinoethyl chloride. The liquid gave a precipitate with alcoholic silver nitrate solution only when heated, which is characteristic of β-4-morpholinoethyl chloride. The loss of β-4-morpholinoethyl chloride during the digestion can be accounted for by assuming that it was carried off by evaporation along with the acetone during the long period of refluxing.

Digestion of β-4-Morpholinoethyl Chloride in Benzene.—Twenty grams of freshly distilled β-4-morpholinoethyl chloride was refluxed for one hundred and eight hours with 100 cc. of benzene. No solid formed. The benzene was removed by distillation and the residue distilled at 91° (12 mm.). The distillate weighed 19.4 g. It was proved to be β-4-morpholinoethyl chloride by analysis for chlorine and nitrogen.

Digestion of β-4-Morpholinoethyl Chloride in Ether.—Three and eight-tenths grams of freshly distilled β-4-morpholinoethyl chloride was refluxed for twenty hours with 50 cc. of absolute ether. No solid appeared. After removal of the ether by distillation, 3.0 g. of β-4-morpholinoethyl chloride, b. p. 87° (7 mm.), was obtained.

Digestion of β-4-Morpholinoethyl Chloride in Dioxane.—Six grams of freshly distilled β-4-morpholinoethyl chloride was refluxed for twenty-four hours with 50 cc. of pure dioxane. Only the slightest trace of solid formed. After removal of the dioxane by distillation, 5.8 g. of β-4-morpholinoethyl chloride was recovered, b. p. 93° (12 mm.).

Reactions of β-4-Morpholinoethyl Chloride in Water.—Seven and six-tenths grams of freshly distilled β-4-morpholinoethyl chloride was refluxed with 50 cc. of water for twenty-four hours. The solution was then evaporated to dryness. The dry solid was pulverized and extracted three times with 10-cc. portions of hot *n*-amyl alcohol. The insoluble residue was washed three times with ether to remove adhering amyl alcohol. It weighed 5.3 g. (70%) and was identified as N,N′-di-[1,5-(3-oxapentylene)]-piperazonium dichloride by decomposing it with 50% sodium hydroxide solution and testing for acetylene with ammoniacal silver nitrate solution.

The *n*-amyl alcohol extracts were combined and concentrated to a volume of 10 cc. When cooled, a solid precipitated. When recrystallized from *n*-amyl alcohol, washed with ether and dried, 2.6 g. of solid was obtained which melted at 110°. This was identified as β-4-morpholineëthanol hydrochloride by means of a mixed melting point determination (109°) with some known β-4-morpholineëthanol hydrochloride. The weight of β-4-morpholineëthanol hydrochloride obtained is equivalent to 2.2 g. of β-4-morpholinoethyl chloride and accounts for 29% of the original chloride.

Reactions of β-4-Morpholinoethyl Chloride in Dioxane–Water Mixtures.—Five grams of freshly distilled β-4-morpholinoethyl chloride was refluxed for twenty-four hours in 50 cc. of the dioxane–water mixtures listed in Table I. A solid separated in each case except when the 47% dioxane–water solution was used. However, all mixtures were treated in the same way. After evaporation to dryness, the solids were extracted three times with 10-cc. portions of hot, 95% ethyl alcohol to remove β-4-morpholineëthanol hydrochloride. The insoluble N,N′-di-[1,5-(3-oxapentylene)]-piperazonium dichloride was washed with ether, dried and weighed. The results are given in Table I and Fig. 1.

Behavior of β-4-Morpholinoethyl Chloride on Standing and when Heated.—Fifty grams of freshly distilled β-4-morpholinoethyl chloride was placed in a tightly stoppered Erlenmeyer flask and stored in a dark closet. At the end of three months, 1.3 g. of solid was removed by filtration. At the end of an additional three months, 0.75 g. of solid was obtained. The remaining liquid was identified as β-4-morpholinoethyl chloride since it distilled at 92° (13 mm.) and left no residue. The solid was identified as N,N′-di-[1,5-(3-oxapentylene)]-piperazonium dichloride by the procedure described above.

Twenty-one grams of freshly distilled β-4-morpholinoethyl chloride was placed in a large test-tube in a flask of water which was heated on a steam-bath. The temperature of the water in the flask was 86° and the heating was continued for one week. When cold, the mixture was filtered and 1.2 g. of solid was obtained. This was identified as N,N′-di-[1,5-(3-oxapentylene)]-piperazonium dichloride and the remaining liquid distilled at the boiling temperature of β-4-morpholinoethyl chloride.

β-4-Morpholinoethyl Chloride and Magnesium.—Freshly distilled samples of β-4-morpholinoethyl chloride were added to magnesium in absolute ether, benzene and anisole. Even after adding iodine and refluxing for some time, no color test[7] indicating the presence of a Grignard reagent could be obtained. The use of activated catalysts[8,9] failed to cause the formation of any Grignard reagent. In some of these experiments, a white solid appeared. To determine the nature of the white solid, 9.5 g. of magnesium and 5 cc. of absolute ether were placed in a three-necked flask equipped with a mercury-sealed mechanical stirrer, a dropping funnel and a reflux condenser. At the top of the reflux condenser was placed a drying tube containing anhydrone. The flask was warmed on a steam-bath until the ether was refluxing and then a

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(7) Gilman and Schulze, This Journal, **47**, 2002 (1925).

(8) Gilman, Peterson and Schulze, *Rec. trav. chim.*, **47**, 19 (1928) [*C. A.*, **22**, 1134 (1928)].

(9) Underwood and Gale, This Journal, **56**, 2118 (1934).

solution of 26.4 g. of freshly distilled β-4-morpholinoethyl chloride in 30 cc. of absolute ether was added slowly. The mixture was refluxed for one hour, allowed to stand overnight and refluxed for three hours the next day. After filtration, the white solid was dissolved in 10 cc. of water. Evaporation to dryness yielded 2.8 g. which was purified by dissolving in water, decolorizing with Norit, evaporating to 5 cc. and adding alcohol and ether to precipitate the solid. It was identified as N,N′-di-[1,5-(3-oxapentylene)]-piperazonium dichloride by decomposition with 50% sodium hydroxide solution as described above.

Summary

β-4-Morpholinoethyl chloride hydrochloride has been prepared from β-4-morpholineëthanol and also from β-4-morpholineëthanol hydrochloride.

The free base has been obtained and has been found to polymerize on standing. When refluxed with benzene, ether, dioxane, or acetone, it either does not polymerize or polymerizes extremely slowly. When refluxed with alcohols or water, it not only polymerizes but also reacts with the solvent. In dioxane–water solutions, the rate of polymerization appears to be related to the dielectric constant of the solvent.

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Ethers and Amines from β-4-Morpholinoethyl Chloride

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The preparation of β-4-morpholinoethyl chloride has been described by Mason and Block.[2] They found the chlorine in β-4-morpholinoethyl chloride to be fairly reactive because hydrogen chloride is removed when the chloride is refluxed with alcohol or water. Since the chlorine in β-chloro ethers is known to be quite unreactive toward some reagents,[3] we considered it worth while to investigate the reactivity of the chlorine in β-4-morpholinoethyl chloride toward a number of reagents which react with alkyl halides.

This communication describes the preparation of a number of ethers and amines. Two ethers of this series have been reported previously, namely, the ethyl ether[2,4] and the propyl ether.[2] Sand[5] reported a melting point of what he thought might be the picrate of β,β′-dimorpholinoethyl ether. He was doubtful about it, however, and we have shown that his picrate was actually the picrate of β-4-morpholinoethanol. Two of the amines have been reported in the literature, namely, dimorpholinoethane[6] and β-4-morpholinoethyl amine.[7]

The method used for the preparation of the ethers was essentially a Williamson synthesis. Since β-4-morpholinoethyl chloride polymerizes on standing, we used the more stable, solid β-4-morpholinoethyl chloride hydrochloride. The results are given in Table I.

The β-4-morpholinoethyl amines were made simply by heating the amine with freshly distilled β-4-morpholinoethyl chloride. The results are given in Table II. Swallen and Boord[3] obtained β-ethoxyethylaniline (no yield given) from β-chloroethyl ether and aniline after heating for ten hours.

Experimental

β-4-Morpholinoethyl Methyl Ether.—To 100 cc. of methanol in a 500-cc. wide-mouth Erlenmeyer flask was added 0.1 mole (2.3 g.) of metallic sodium. After all the sodium had dissolved, sufficient glass wool was added to cover the bottom of the flask. In an underwriter's extraction thimble was placed 0.05 mole (9.3 g.) of β-4-morpholinoethyl chloride hydrochloride. An underwriter's coil condenser was used in the top of the flask. The β-4-morpholinoethyl chloride hydrochloride dissolved in the condensed methanol and as soon as it reached the sodium methoxide solution a precipitate of sodium chloride appeared. About fifteen minutes was required for complete extraction of the β-4-morpholinoethyl chloride hydrochloride. The reaction mixture was refluxed for an additional five minutes and the excess methanol was removed as completely as possible by distillation. When the residue was cool, 100 cc. of 30% sodium hydroxide solution was added. After separation of the two layers, the aqueous solution was extracted with three 25-cc. portions of ether. The ether extracts and the original upper layer were combined and dried over Drierite. The ether and alcohol were removed by distillation and the residue was

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(1) Abstracted from a thesis to be submitted by Saul Malkiel to the faculty of the Graduate School of Boston University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Present address: Massachusetts College of Osteopathy, Boston, Mass.

(2) Mason and Block, THIS JOURNAL, **62**, 1443 (1940).

(3) Swallen and Boord, *ibid.*, **52**, 651 (1930).

(4) (a) Cox and Carruthers, U. S. Patent 2,023,872; (b) Wilson, U. S. Patent 2,128,887.

(5) Sand, *Ber.*, **34**, 2906 (1901).

(6) Knorr and Brownsdon, *ibid.*, **35**, 4470 (1902).

(7) Hultquist and Northey, THIS JOURNAL, **62**, 447 (1940).