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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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BOSTON UNIVERSITY]

Ethers and Amines from β-4-Morpholinoethyl Chloride

BY J. PHILIP MASON AND SAUL MALKIEL[1]

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 re sults 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).

Table I

Alcohol	Yield, %	B. p., °C.	Mm.	Neut. equiv. Calcd.	Neut. equiv. Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl (NaOR method)	75.9	104.0–105.8	(44)	145	145.7	9.66	9.65
Methyl (KOH method)[a]	64.8	105.3–107.3	(46)	145	145.2		
Ethyl	79.9	96.0–99.0	(17–19)[b]	159	159.9		
n-Propyl	82.2	120.0–123.0	(33)	173	172.5	8.09	8.07
i-Propyl	64.7	115.0–120.0	(34–35)	173	172.5	8.09	8.07
n-Butyl	81.3	134.5–137.5	(31)	187	186.2	7.49	7.48
s-Butyl	62.0	105.5–108.5	(7–8)	187	187.4	7.49	7.51
t-Butyl (20 min.)	58.8	114.0–119.0	(21–22)	187	187.0	7.49	7.48
t-Butyl (3 hr.)	53.5	113.0–116.0	(19)	187	186.3		
Morpholinoethyl[c]	66.2	178.0–180.5	(7)	122	122.1	11.48	11.47
Benzyl	67.8	196.0–202.0	(30–32)	221	220.4	6.33	6.30
Phenyl[d]	64.7	181.0–183.0	(21–22)	207	207.1	6.76	6.74

[a] 0.1 mole (5.6 g.) KOH dissolved in CH_3OH. [b] Cox and Carruthers (4a) report a b. p. 199.0–200.0° at 750 mm. and 80.0–81.0° at 10 mm. [c] M. p. of picrate, 175° (uncor.). Sand reported m. p. 123°. [d] 10 g. of C_6H_5OH dissolved in 50 cc. of 10% NaOH solution, and heated with 9.3 g. of β-4-morpholinoethyl chloride hydrochloride for 20 min.

Table II

β-4-Morpholinoethyl	Yield, %	B. p., °C.	Mm.	Nitrogen, % Calcd.	Nitrogen, % Found	Picrate M. p. (cor.), °C.	Picrate Nitrogen, % Calcd.	Picrate Nitrogen, % Found
Amine[a]	48.5	82	(6)[c]	21.54	21.59	188.0	19.05	19.27
Butylamine[b]	43.1	136–140	(20–21)	15.05	15.09	180.5	17.39	17.30
Aniline	57.3	186–188.5	(9)	13.59	13.68	179.4	16.87	16.79
Methylaniline	38.2	184–189	(9)	12.73	12.79	138–140.6	16.54	16.62
Morpholine	55.0	73[d]				234–237 (uncor.)[e]		

[a] Neut. equiv. calcd., 65. Found, 65.2. [b] Neut. equiv. calcd., 93. Found, 93.4. [c] Hultquist and Northey[7] report a b. p. of 204.5° at 768 mm. and 121–123° at 68 mm. [d] M. p. (uncor.); Knorr and Brownsdon,[6] m. p. 74°. [e] Knorr and Brownsdon,[6] m. p. 230–236°.

transferred to a 50-cc. Claisen flask whose side arm was well "vigreuxed" and was also packed with asbestos. After fractionation under reduced pressure, the high boiling fraction was dried over sodium and redistilled. The yield was 5.5 g. (76%) and the ether distilled at 105.3–107.3° (46 mm.).

The above procedure was used for the preparation of the ethyl, propyl, isopropyl, butyl, *s*-butyl, *t*-butyl, phenyl and benzyl ethers. All of the ethers were colorless mobile liquids possessing a strong ammoniacal odor. The methyl, ethyl, isopropyl, *s*-butyl and *t*-butyl ethers were soluble in water and typical organic solvents such as alcohol, ether and benzene. The butyl, benzyl and phenyl ethers were insoluble in water and soluble in the organic solvents just mentioned.

β,β′-Dimorpholinoethyl Ether.—Because of the high boiling point of β-4-morpholineëthanol (227°), 0.05 mole (7.5 g.) of β-4-morpholinoethyl chloride was added to 100 cc. of β-4-morpholineëthanol in which 0.05 mole (1.15 g.) of sodium had been dissolved. The mixture was heated to 200° in an oil-bath and kept at that temperature for twenty minutes. The separation and purification was carried out as described above. Dimorpholinoethyl ether is soluble in water and the above mentioned organic solvents.

β-4-Morpholinoethylamine.—To an excess of concentrated ammonium hydroxide (40 cc.) in a round-bottom flask was added 0.05 mole (7.5 g.) of freshly distilled β-4-morpholinoethyl chloride and sufficient water (45 cc.) to effect complete solution. A cork stopper was wired to the flask, which was then placed in an oven at 93–98° for five hours. After cooling, 80 cc. of 40% sodium hydroxide solution was added to the reaction mixture. The small upper layer was removed and the aqueous layer was extracted with three 25-cc. portions of ether. The ether solution was dried over Drierite, the ether removed by distillation and the residue distilled fractionally under reduced pressure. β-4-Morpholinoethylbutylamine was made by the same procedure, using 0.055 mole (4.0 g.) of *n*-butylamine. The results are given in Table II.

β-4-Morpholinoethylaniline.—A solution of 0.055 mole (5.2 g.) of aniline and 0.05 mole (7.5 g.) of freshly distilled β-4-morpholinoethyl chloride was heated under a reflux air condenser for two hours in an oil-bath at 200°. After cooling, the solution was treated with an excess of 40% sodium hydroxide solution and extracted three times with 25-cc. portions of benzene. The benzene solution was dried over Drierite, the benzene removed by distillation and the residue distilled using a fractionating column under reduced pressure. β-4-Morpholinoethylmethylaniline was made by the same procedure using 0.055 mole (5.5 g.) of methylaniline. When dimorpholinoethane was made by this procedure, a residue was left after distillation of the benzene. This was dissolved in hot ligroin, decolorized with Norit and recrystallized from ligroin. The results are given in Table II.

With the exception of dimorpholinoethane the amines are colorless liquids possessing an ammoniacal odor. The β-4-morpholinoethylamine and the β-4-morpholinoethylbutylamine are soluble in water and in the previously mentioned organic solvents. The β-4-morpholinoethylaniline and the β-4-morpholinoethylmethylaniline are viscous liquids, insoluble in water but soluble in the organic solvents. Dimorpholinoethane is a white, water soluble solid.

Summary

The β-4-morpholinoethyl ethers of methyl, ethyl, propyl, isopropyl, butyl, *s*-butyl, *t*-butyl, benzyl and β-4-morpholinoethyl alcohols and phenol have been prepared from β-4-morpholinoethyl chloride and the corresponding sodium alkoxide or phenoxide. β-4-Morpholinoethyl amines have been made by the interaction of β-4-morpholinoethyl chloride with ammonia, *n*-butylamine, aniline, methylaniline and morpholine.

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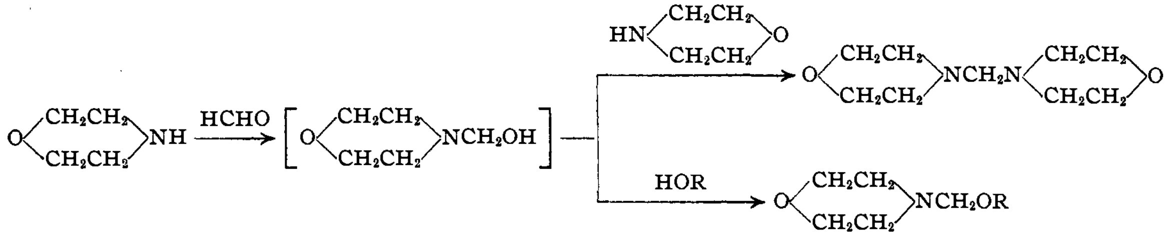
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF BOSTON UNIVERSITY]

4-Morpholinomethyl Alkyl Ethers and N-Substituted Morpholines

BY J. PHILIP MASON AND MORRIS ZIEF[1]

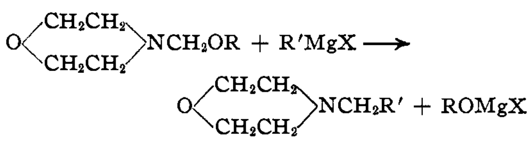
Dialkylaminomethyl alkyl ethers have been prepared by McLeod and Robinson[2] by the condensation of secondary amines with 40% aqueous formaldehyde solution and various alcohols. Stewart and Bradley[3] used paraformaldehyde instead of 40% aqueous formaldehyde solution. We have made a number of 4-morpholinomethyl alkyl ethers using the method described by Stewart and Bradley[3] with certain modifications.

(1) 

It will be seen from equation (1) that there are two reactions possible when the three reactants are mixed. In order to increase the yield of the ether, we used two equivalents of alcohol to one each of morpholine and formaldehyde.

Table I shows the percentage of morpholine converted into the 4-morpholinomethyl alkyl ether and dimorpholinomethane, together with the boiling points, nitrogen analyses and neutral equivalents. Increasing yields of ether were obtained with increasing molecular weight of the primary alcohols from methyl to *n*-propyl and *n*-butyl. This may be due to the fact that the ethers obtained from higher alcohols are hydrolyzed less readily than those from lower alcohols.[2] Evidence that the hydrogen of the water split off during the formation of the ether comes from the alcohol and the hydroxyl from the hypothetical 4-morpholinemethanol is found in the lower yields of ethers obtained when secondary and tertiary alcohols were used. Picrates of these ethers could not be obtained by the usual method because all of the ethers hydrolyzed to form morpholine, and morpholine picrate was the only compound obtained.

These ethers reacted readily with Grignard reagents (equation 2), as was expected from the work of McLeod and Robinson.[2] The results are reported in Table II.

(2) 

Experimental

4-Morpholinomethyl Ethyl Ether.—Fifteen grams of paraformaldehyde (equivalent to 0.5 mole of formaldehyde), 23 g. (0.5 mole) of absolute ethyl alcohol and 100 cc. of dry benzene were placed in a 500-cc. three-necked flask which was equipped with a mercury-sealed mechanical stirrer, a separatory funnel and a fractionating column attached to a condenser for distilling the ternary mixture. The flask was heated in a water-bath kept at 85°. A mixture of 43.5 g. (0.5 mole) of morpholine and 23 g. (0.5 mole) of absolute ethyl alcohol was dropped slowly into the reaction mixture, which was stirred continuously. During this addition, which was completed in one hour,

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[1] This material is taken from a thesis to be submitted by Morris Zief to the faculty of the Graduate School of Boston University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] McLeod and Robinson, *J. Chem. Soc.*, **119**, 1470 (1921).

[3] Stewart and Bradley, THIS JOURNAL, **54**, 4176 (1932).