[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

The Reaction of Trimethylene Oxide with Amines[1]

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The reaction of trimethylene oxide with amines in aqueous solution at room temperature is very slow, contrary to a previous report. At elevated temperatures, however, good yields of 3-hydroxypropylamines are obtained, from both primary and secondary amines, except when the latter is sterically hindered. The reaction of trimethylene oxide with alkyl and aryl bromomagnesium amides seems to be a general method of preparing such amino alcohols and is less susceptible to steric hindrance. A lithium amide gave similar results in the one case tried.

One of the few reactions of trimethylene oxide which have been in the literature for some time is that with primary aliphatic amines. In 1937, Goldberg and Whitmore[3] indicated that the expected 3-alkylamino-1-propanols were formed when pure aqueous solutions of the reactants were allowed to stand at room temperature for 20 hours. These conditions would indicate that trimethylene oxide is approximately as reactive toward amines as ethylene oxide.

Since trimethylene oxide recently has been found to be much less reactive toward alcohols, phenols, thiols and thiosulfate in neutral or alkaline solution and also toward aromatic hydrocarbons in the presence of aluminum chloride,[4] the reaction with amines has been reinvestigated to check the possibility of a peculiarly high reactivity in this instance.

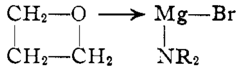
In our hands the Goldberg and Whitmore procedure for 3-butylamino-1-propanol gave less than 5% yield,[5] but when the temperature is raised to 150° in a sealed tube the reaction proceeded to give a 67% yield of the compound. Similar results were obtained with piperidine (60%) and with methylamine (45%) but the reaction failed with diisopropylamine, presumably because of steric hindrance. The reactivity of trimethylene oxide in the water-catalyzed reaction with amines, then, is seen to be much less than that of ethylene oxide.

Some attention was given to other methods of carrying out the reaction which would not require high pressure equipment. Acid catalysis was found to be ineffective in this reaction, in contrast to the experience in other reactions of this cyclic ether; presumably the added acid was tied up too completely by the amine. Basic catalysis also appeared ineffective.

The success of the Grignard reaction with trimethylene oxide[6] suggested that it would be advantageous to convert a primary or secondary amine to the corresponding bromomagnesium amide before attempted reaction with the cyclic ether. This method, the results of which are shown in Table I, proved to be applicable to both aliphatic and aromatic amines and was not noticeably subject to steric factors in the amine. Thus 3-diisopropylamino-1-propanol was obtained, whereas it is not formed by the alternative methods of making 1,3-aminoalcohols; *viz.*, (1) direct action of the amine and the oxide, (2) the reaction of the amine and trimethylene bromohydrin and (3) by the reaction of the amine with sodium and allyl alcohol.[7]

The bromomagnesium amides were formed by treating the amine with butylmagnesium bromide; with primary amines it was necessary to employ inverse addition and a large excess of amine to minimize formation of $RN(MgBr)_2$ compounds. The yields obtained in the trimethylene oxide reaction could doubtless be improved, as no attempt was made to determine optimum conditions. The use of a lithium amide was investigated in one case—1-piperidyllithium, from piperidine and butyllithium—with results practically identical with those from the corresponding bromomagnesium compound.

No reaction was obtained with sodamide under similar condition, possibly because of its insolubility or the lower coördinating ability of sodium with the cyclic ether. The bromomagnesium and lithium amides were soluble in diethyl ether, indicating coördination with the solvent. Addition of trimethylene oxide caused immediate precipitation of a solid, which is believed to be a complex, such as



Such complex formations may be a necessary first step in the reaction, as in the reaction with alkylmagnesium bromides, in order to polarize the cyclic ether. The fact that bromomagnesium diisopropylamide reacts quite well with trimethylene oxide whereas diisopropylamine does not, may be attributed to the complex formation, in which the amine nitrogen is held fairly close to a terminal carbon of the cyclic ether.

Experimental

Reaction of Trimethylene Oxide with Amines in Water Solution.—(A) Exact duplication of the procedure given by Goldberg and Whitmore[3] for the reaction of *n*-butylamine and trimethylene oxide at room temperature gave 0.2–0.7 g. (1–3.5%) of 3-butylamino-1-propanol, b.p. 84° (10 mm.), m.p. of hydrochloride, 114–115°. The reaction of trimethylene bromohydrin with butylamine under the same conditions gave a 38% yield. Treatment of diisopropylamine with trimethylene bromohydrin under these conditions, except that 7 days was allowed instead of 20 hours, gave no reaction; only starting materials were isolated. (B) A solution of 11.6 g. (0.2 mole) of trimethylene oxide, 29.2 g. (0.4 mole) of butylamine and 5 ml. of water were heated in a Carius tube at 150° for 18 hours. After the re-

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[1] Abstracted from the M.S. thesis of V. P. Gregory, Northwestern University, February, 1952.

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[3] S. D. Goldberg and W. F. Whitmore, THIS JOURNAL, **59**, 2280 (1937).

[4] S. Searles, *ibid.*, **73**, 4515 (1951); **76**, 2313 (1954); S. Searles and C. F. Butler, *ibid.*, **76**, 56 (1954).

[5] No yields were given by Goldberg and Whitmore; it may be that their compounds were actually prepared by the reaction of the amines with trimethylene bromohydrin, which they mention without detail as an alternative method.

[6] S. Searles, THIS JOURNAL, **73**, 124 (1951).

[7] O. Hromatka, *Ber.*, **75B**, 131 (1952).

TABLE I

REACTION OF BROMOMAGNESIUM AMIDES WITH TRIMETHYLENE OXIDE

Amine	Mole of amine	Mole of Grignard reagent	Mole of $(CH_2)_3O$	Product, 1-propanol	Yield, %	B.p., °C.	Mm.	$n^{25}D$	Derivatives	Mp., °C.
Diethyl-	0.4	0.35	0.2	3-Diethylamino-[a]	38.2	62–64	11	1.4425	Methiodide	187[a]
Diisopropyl-	.18	.14	.12	3-Diisopropylamino-[b]	31.0	85–87	9	1.4447	Hydrochloride	111.6–112
									Picrate	132.5–133[d]
Piperidine	.4	.3	.2	3-(1-Piperidyl)-[e]	60.8	89	6	1.4750	Hydrochloride	154–155[e]
									Methiodide	133.8–134.5[e]
									Picrate	69.5–70[e]
Morpholine	.26	.25	.25	3-(4-Morpholyl)-[f]	20.6	107	9	1.4747	Hydrochloride	128.5–129.5[g]
									Methiodide	135–135.5[h]
									Picrate	135.5–136.5[f]
Aniline	.32	.16	.13	3-Anilino-	57.0	125–129	0.5	1.5687	Benzoatebenzamide	81.5–82[i]
N-Methylaniline	.4	.35	.2	3-(N-Methylanilino)-	52.9	120–122	1	1.5652	Hydrochloride	99.5–100.1
									Methiodide	129[k]
Stearyl-	.1	.05	.08	3-Stearylamino-[l]	34.0	65–66 m.p.				

[a] J. v. Braun, F. Jostes and H. Wagner, *Ber.*, **61**, 1426 (1928), reported b.p. 84° (20 mm.), methiodide m.p. 188°. [b] *Anal.* Calcd. for $C_9H_{22}NO$: C, 67.87; H, 13.29. Found: C, 67.95; H, 13.40. [c] *Anal.* Calcd. for $C_9H_{22}NOCl$: N, 7.16. Found: N, 7.29. [d] *Anal.* Calcd. for $C_{15}H_{24}N_4O_8$: N, 14.43. Found: N, 14.62. [e] Hromatka (ref. 7) reported b.p. 149° (68 mm.), hydrochloride m.p. 151°, methiodide m.p. 133–134°, picrate m.p. 69°. [f] Hromatka reported b.p. 143–145° (28 mm.), picrate m.p. 136–137°. [g] *Anal.* Calcd. for $C_7H_{16}NO_2Cl$: N, 7.71. Found: N, 7.35. [h] *Anal.* Calcd. for $C_8H_{18}NO_2I$: N, 4.88. Found: N, 5.20. [i] *Anal.* Calcd. for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.89; H, 6.00; N, 3.99; m.p. 95° also observed. [j] *Anal.* Calcd. for $C_{10}H_{16}NOCl$: N, 6.95. Found: N, 7.17. [k] J. v. Braun, E. Anton and K. Weissbach, *Ber.*, **63B**, 2847 (1930), reported m.p. 132°. [l] *Anal.* Calcd. for $C_{21}H_{45}NO$: C, 77.00; H, 13.85; N, 4.28. Found: C, 77.07; H, 13.62; N, 4.33.

action product was dried over potassium hydroxide pellets it was distilled to give 17.7 g. (67.6%) of 3-butylamino-1-propanol, b.p. 106–108° (16 mm.), $n^{25}D$ 1.4474, picrate m.p. 66–67°, hydrochloride m.p. 114–115° (reported[1]: b.p. 218–215° (atm.), *n* 1.4525 (temperature and wave length not stated), picrate m.p. 66–67°).

A solution of 5.8 g. (0.1 mole) of trimethylene oxide, 9 g. (0.1 mole) of piperidine and 2.5 ml. of water was heated at 145° for 15 hours and processed as described above to give 8.6 g. (60%) of 3-(1-piperidyl)-1-propanol, b.p. 96–98° (11 mm.), $n^{25}D$ 1.4738 (see Table I for comparison with reported properties).

Trimethylene oxide (49 g., 0.85 mole) was added to 250 ml. of 25% aqueous methylamine and heated in a glass-lined autoclave at 150° for 12 hours. Distillation, drying of the 160° fraction over barium oxide and redistillation through a 6-inch helices-packed Fenske column gave 34 g. (45%) of 3-methylamino-1-propanol, b.p. 54–58° (3 mm.), 155–158° (741 mm.), $n^{25}D$ 1.4370, d^{20}_4 0.940 (reported[8]: b.p. 74–77 (2.5 mm.), $n^{27}D$ 1.4418, *d* 0.9315).

(C) **Attempted Catalysis by Acid and Base.**—A solution of 18 g. of piperidine, 5.8 g. of trimethylene oxide and 1.0 g. of sulfuric acid was allowed to stand at room temperature two days. After neutralization by potassium carbonate, fractional distillation gave mainly starting materials and no 3-(1-piperidyl)-1-propanol could be detected. A solution that was similar except that it contained 0.2 ml. of concentrated hydrochloric acid was heated at 140° for three hours (sealed tube). Distillation gave 0.8 g. (5.6%) of 3-(1-piperidyl)-1-propanol, b.p. 75–85° (7.5 mm.), m.p. of hydrochloride, 150–151°. When a solution of the above amounts of piperidine and trimethylene oxide and 0.2 of 60% choline was allowed to stand at room temperature, no product was detected on distillation.

Reaction of Bromomagnesium Amides with Trimethylene Oxide.—A typical procedure starting with a secondary amine is the following: A solution of 13.2 g. (0.13 mole) of diisopropylamine in 50 ml. of ether was added to the butyl Grignard reagent prepared from 3.4 g. (0.15 g. at.) of magnesium turnings and 19.2 g. (0.14 mole) of *n*-butyl bromide in 100 ml. of ether under a nitrogen atmosphere. After the reaction mixture had stood several hours at room temperature, a solution of 6.9 g. (0.012 mole) of trimethylene oxide in 50 ml. of ether was added dropwise with stirring, causing immediate precipitation of a solid. After one hour of refluxing, 100 ml. of dry benzene was added, and the ether was stripped through a two-foot Vigreux column until the still-head temperature reached 70°. After cooling and hydrolysis with saturated ammonium chloride, the benzene layer was separated and the water layer extracted with four 50-ml. portions of ether. The solvent was distilled from the combined benzene–ether extracts, and the residue was dried over potassium hydroxide pellets and distilled under reduced pressure.

The procedure was modified when primary amines were used by adding the Grignard reagent to a large excess of amine in ether solution, except in the case of stearylamine, which was dissolved in benzene (100 ml. for 0.1 mole) before addition of the Grignard reagent. Upon addition of trimethylene oxide to this reaction mixture a heavy paste formed which prevented adequate stirring.

Reaction of 1-Piperidyllithium with Trimethylene Oxide.—A solution of butyllithium was prepared from 6.9 g. (1 g. at.) of lithium wire and 54.8 g. (0.4 mole) of *n*-butyl bromide in 200 ml. of anhydrous ether under a nitrogen atmosphere at −20°. After addition of 34 g. (0.4 mole) of piperidine at 0° the reaction mixture was allowed to come to room temperature during an hour and then 16.5 g. (0.29 mole) of trimethylene oxide in 50 ml. of ether was added. The rest of the procedure was the same as described for the bromomagnesium compounds. A yield of 22.9 (57%) of 3-(1-piperidyl)-1-propanol, b.p. 90–91° (6 mm.), $n^{25}D$ 1.4760, was obtained.

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