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Yutaka Kuwada : A New Method for Preparation of Nitrogen Mustards.

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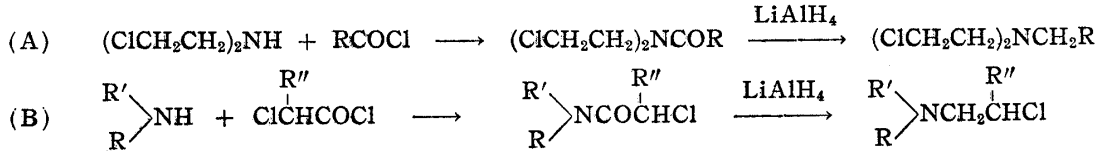
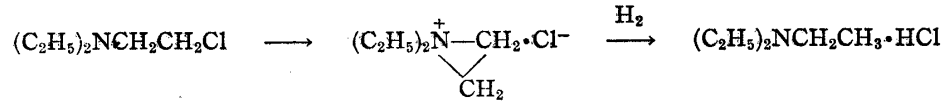
The usual process for preparing derivatives of nitrogen mustard requires chlorination of the corresponding hydroxyethyl intermediate at the final stage of synthesis. This drastic reaction is apt to result in the decomposition of the molecules of complicated structure or to yield a product chlorinated at an unexpected portion other than the 2-hydroxyethyl group. The following new process is able to avoid the final chlorination and is considered to be a useful method of preparing the derivatives of nitrogen mustard.



R, R′, R″=alkyl or 2-chloroethyl

As an exception, N-chloroacetyldiethylamine yielded triethylamine alone under quite similar condition. It has been known that the strongly basic mono-2-chloroethyl derivatives of tertiary amine such as the primary reduction product of this reaction, viz. 2-chlorotriethylamine, transformed far more promptly into its ethylenimmonium form in the reaction medium than the ordinary bis(2-chloroethyl) derivatives. This three-membered ring compound thus formed should be reduced successively by lithium aluminium hydride and yielded triethylamine as a reault.



If carbonamides are less soluble in ether, it would be better to use tetrahydrofuran or other suitable solvents as the reducing medium.

Experimental

Preparation of Substituted N,N-Bis(2-chloroethyl)carbonamides—Bis(2-chloroethyl)amine hydrochloride was dissolved in the smallest possible amount of water, added with 1 mol. equiv. of NaOH, and then extracted immediately with benzene. The extract was dried over anhyd. Na_2SO_4. The corresponding acyl chloride (1 mol. equiv.) was added dropwise slowly under ice-cooling to the benzene extract containing free bis(2-chloroethyl)amine (2 mol. equiv.) and then the mixture was boiled for 1 hr. on a water bath. After cool, the unreacted bis(2-chloroethyl)amine hydrochloride that precipitated was filtered off. The filtrate was distilled to remove benzene and the amide was usually obtained as an oily residue which was purified by distillation *in vacuo* or recrystallization of a solid.

N,N-Bis(2-chloroethyl)acetamide, b.p_{12} 150°.[1)]

N,N-Bis(2-chloroethyl)-2-chloroacetamide, b.p_8 167～169°.[2)]

N,N-Bis(2-chloroethyl)butanecarbonamide, b.p_8 148～149°.

N,N-Bis(2-chloroethyl)pentanecarbonamide (not completely purified)

N,N-Bis(2-chloroethyl)hexanecarbonamide, b.$p_{0.1}$ 190°. *Anal.* Calcd. for $C_{11}H_{21}ONCl_2$: C, 51.97; H, 8.33; N, 5.51. Found : C, 51.74; H, 7.92; N, 5.66.

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1) A. F. Childs, *et al.* : J. Chem. Soc., **1948**, 2174.

2) E. R. H. Johnes, W. Wilson : *Ibid.*, **1949**, 547.

N,N-Bis(2-chloroethyl)heptadecanecarbonamide, m.p. 135~136° (from EtOH). *Anal.* Calcd. for $C_{22}H_{43}ONCl_2$: C, 64.69; H, 10.61; N, 3.43. Found: C, 64.59; H, 10.60; N, 3.21.

The yield of the amide frequently decreased during purification because of its tendency to undergo molecular rearrangement,[3] yielding 2-chloro-2'-acyloxydiethylamine hydrochloride as the chief product. For this reason, it is recommended that the crude amide be reduced as such by $LiAlH_4$ without purification in majority of cases.

Reduction of Substituted N,N-Bis(2-chloroethyl)carbonamides with $LiAlH_4$—A dried ether solution of a substituted N,N-bis(2-chloroethyl)carbonamide (1 mol. equiv.) was added dropwise from the dropping funnel into an ethereal solution of $LiAlH_4$ (1 mol. equiv.). The mixture was allowed to stand at room temperature with continuous stirring for 3 hr. after addition of the reagent was completed. After decomposing excess of the hydride with a small amount of water, the ether layer was separated and extracted with 10% HCl. The HCl layer was evaporated under reduced pressure and the reduction product was obtained as a solid hydrochloride. It was recrystallized from some adequate solvent if possible or else converted once to a crystalline picrate for further purification, from which its hydrochloride could be recovered. All the hydrochlorides were almost colorless and formed hygroscopic crystals. The yield of these amines reached more than 70%.

2,2'-Dichlorotriethylamine—Hydrochloride, m.p. 137~138°. Yield, 86%. Picrate, m.p. 100°. No melting point depression with the authentic sample.[4]

Tris(2-chloroethyl)amine—Hydrochloride, m.p. 110°.[4] Yield, 80%. Picrate, m.p. 131~132°.[4] *Anal.* Calcd. for $C_{12}H_{15}N_4Cl_3$: C, 33.24; H, 3.49; N, 12.92. Found: C, 33.19; H, 3.37; N, 12.85.

N-Amyl-bis(2-chloroethyl)amine—Hydrochloride, m.p. 83~84°.[5] Yield, 73%. Picrate, m.p. 83~84.[5] Picrylsulfonate, m.p. 153~154°. *Anal.* Calcd. for $C_{15}H_{22}O_8N_4Cl_2S$: C, 35.65; H, 4.39; N, 11.09. Found: C, 35.71; H, 4.35; N, 11.28.

N-Hexyl-bis(2-chloroethyl)amine—Hydrochloride, m.p. 63~65°.[6] Yield, 96%. Picrylsulfonate: m.p. 159~160°. *Anal.* Calcd. for $C_{16}H_{24}O_9N_4Cl_2S$: C, 37.00; H, 4.66; N, 10.79. Found: C, 37.29; H, 4.40; N, 10.29.

N-Heptyl-bis(2-chloroethyl)amine—Hydrochloride was very hygroscopic. Yield, 74%. Picrylsulfonate, m.p. 161~162°. *Anal.* Calcd. for $C_{17}H_{26}O_9N_4Cl_2S$: C, 38.28; H, 4.91; N, 10.51. Found: C, 38.42; H, 4.95; N, 10.53.

N-Octadecyl-bis(2-chloroethyl)amine—m.p. 86~87° (from EtOH and petr. ether). Yield, 70%. *Anal.* Calcd. for $C_{12}H_{45}NCl_2$: C, 66.97; H, 11.49; N, 3.55. Found: C, 66.61; H, 11.65; N, 3.46.

Reduction of N-chloroacetyldiethylamine—N-Chloroacetyldiethylamine[7] was reduced under similar conditions with $LiAlH_4$. Triethylamine hydrochloride: m.p. 245°(decomp.). Yield, 93%. *Anal.* Calcd. for $C_6H_{16}NCl$: N, 10.18. Found: N, 9.71. Picrate, m.p. 173°. *Anal.* Calcd. for $C_{12}H_{18}O_7N_4$: C, 43.63; H, 5.49; N, 16.96. Found: C, 43.53; H, 5.19; N, 16.99.

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Summary

Conditions for reduction of substituted N,N-bis(2-chloroethyl)carbonamides with lithium aluminium hydride into substituted N,N-bis(2-chloroethyl)amines were examined and the method was proved to be widely applicable for the preparation of the derivatives of nitrogen mustard.

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3) I. Aiko, K. Sawatari: Yakugaku Zasshi, **75**, 418(1955).
4) Y. Sakurai, M. Izumi: This Bulletin, **1**, 298(1953). Reported m.p. of the hydrochloride, 130~131°; Picrate, m.p. 136~137°.
5) Reported[4] m.p. of the hydrochloride, 79.5~80.5°; Picrate, m.p. 75~77°.
6) Reported (E. Wilson, M. Tishler: J. Am. Chem. Soc., **73**, 3635(1951)) hydrochloride, m.p. 82.2~82.8°.
7) F. L. Hahn, M. Loos: Ber., **51**, 1442(1918).