

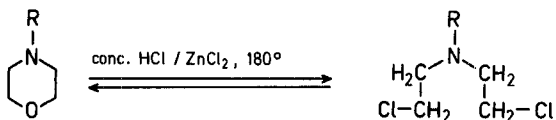
A New Route to Nitrogen Mustards

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Nitrogen mustards are among the relatively few types of compounds used in the treatment of neoplastic diseases. A vigorous search continues for more effective nitrogen mustards. The object of this research was to open the morpholine ring at the oxygen¹ atom with formation of the mustard moiety; an especially attractive idea since many morpholines are known and since the ring is quite stable and will withstand many transformations in other parts of the molecule.

We have now succeeded in opening the morpholine ring at the oxygen atom using a mixture of zinc chloride and conc. hydrochloric acid at 180°. Using N-phenylmorpholine we obtained, in one step, a very clean reaction product consisting of 50 % of the desired mustard and 50 % starting material as shown by physical properties and G.L.C. analysis:



Both compounds were prepared independently and the authentic samples matched the reaction products.

We found that essentially the same mixture resulted when a nitrogen mustard was used as the starting material. N,N-Bis-[2-chloroethyl]-aniline when heated at 180° gave a mixture of the morpholine and starting material. This provides a new and interesting method for preparing morpholine compounds.

The reaction was extended to several other morpholines. Using essentially the same experimental conditions, N-(4-bromophenyl)-morpholine, N-(4-methylphenyl)-morpholine, and N-(1-naphthyl)-morpholine gave respectively 68 %, 27 %, and 55 % of the corresponding mustard. All nitrogen mustards were prepared independently and the authentic samples matched the reaction products.

Attempts to extend this reaction to N-alkylmorpholines have thus far been unsuccessful. Although the N-alkylmorpholine undergoes reaction in each case no mustard could be isolated.

A typical cleavage experiment is described.

The Cleavage of N-(4-Bromophenyl)-morpholine: A solution of conc. hydrochloric acid (50 ml), zinc chloride (125 g, 0.915 mol), and N-(4-bromophenyl)-morpholine (5.0 g, 0.022 mol) was sealed in a Carius-tube and heated for 36 hr at 188°. The tube was cooled, broken, and the contents poured onto iced ammonium hydroxide. This was extracted with chloroform (100 ml), the extract dried, and the solvent removed. The residue was dissolved in benzene (8 ml) and eluted from a column of neutral alumina (80–200 mesh; 200 mm × 30 mm) with hexane; yield: 4.7 g (68 %) of 4-bromo-N,N-bis-[2-chloroethyl]-aniline; m.p. 72–73° (from petroleum ether). An I.R.-spectrum showed bands at 1271 cm⁻¹ (aromatic nitrogen) and 806 cm⁻¹ (p-substitution) but no band at 1124 cm⁻¹ (indicates loss of ether function).

C₁₀H₁₂BrCl₂N

calc. C 40.43 H 4.07 Br 26.91 Cl 23.87 N 4.10
found 40.69 4.10 27.09 23.65 4.07

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¹ It is well known that aliphatic ethers are easily cleaved by acids but this is not so for morpholine or its derivatives. R.L. BURWELL's excellent review [Chem. Rev. **54**, 615 (1954)] on the cleavage of ethers does not report a single case of the cleavage of the ethereal bond in morpholines.