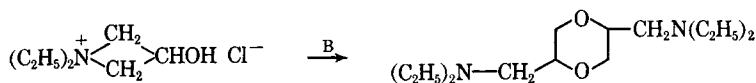


NOTES

The Reactions of Piperidine and Diethylamine with Epichlorohydrin

The reaction of epichlorohydrin with either primary or dissecondary amines can be used to produce polyhydroxyamines. The reactions of diethylamine and piperidine with epichlorohydrin were examined as models for these polymerizations to ascertain whether or not the regular 1,3-diamino-2-propanol structural unit is obtained. The expected reaction products were synthesized and unambiguous structure proofs obtained by means of proton magnetic resonance spectra. An analytical method using vapor phase chromatography for separation of isomeric diamino propanols was devised. We were then able to show that the reaction of two moles of piperidine with epichlorohydrin produces a single product, namely bis-1,3-(1-piperidyl)-2-propanol. The reaction of two moles of diethylamine with one mole of epichlorohydrin produces two products, namely bis-1,3-diethylamino-2-propanol and bis-2,3-diethylamino-1-propanol, the latter in minor amounts. In addition, the aminodiols expected from hydrolytic reaction were prepared and their VPC behavior examined. The aminodiols were demonstrated to be absent from the reaction products.

The reaction of piperidine with epichlorohydrin in ether was studied by Powell and Dehn who suggested the product, m.p. 149°C. to be the hydrochloride of 2,3-epoxypropyl piperidine. Prosdov and Chentzov observed that dimethylamine, diethylamine, and piperidine gave with epichlorohydrin aminochlorohydrins that could be dehydrochlorinated to epoxides or reacted directly with ammonia to tertiary amino-aminopropanols. The initial reaction was observed to give a second product, increasing with time, having ionizable chloride. Rothstein and Binovic treated epichlorohydrin with aqueous diethylamine and obtained 55% of 1-(diethylamino)-3-chloro-2-propanol, and small amounts (6-8%) of 1-diethylamino-2,3-epoxypropane, bis-1,3-(diethylamino)-propanol-2, and a water-soluble material having ionizable chloride. The latter was suggested to be an internal quaternary salt which, in the presence of base, was slowly converted to the (isolated) dioxane. The latter claim was disputed by Heywood and Phillips who ob-



served that, with piperidine, morpholine, or diethylamine and epichlorohydrin, the dihydrochloride of the dioxane was most likely the compound having ionizable chloride and that it could arise directly from the reaction mixture or from the action of acid on the epoxypropylamine. Gilman et al. had previously shown that diethylamine and epichlorohydrin reacted to the monochlorohydrin with a heat of reaction of 21 kcal./mole. This compound was converted quantitatively to the epoxide by concentrated alkali.

For our system, namely amine plus hydroxide ion with epichlorohydrin, the kinetic profile will be of the form shown in Figure 1. This is suggested by the results of Lidarik et al. for the analogous reaction of phenoxide and epichlorohydrin in the presence of base where a similar profile is observed.

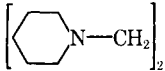
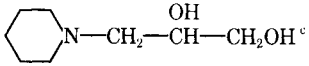
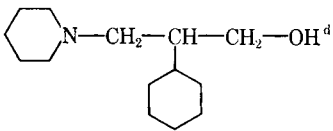
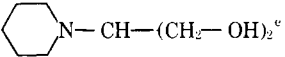
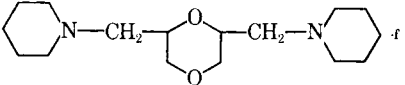
The reaction of two moles of piperidine with one mole of epichlorohydrin in the presence of one mole of sodium hydroxide (10% in water) yields exclusively bis-1,3-(1-piperidyl)-2-propanol. The same stoichiometry using diethylamine yields a mixture of bis-1,3-diethylamino-2-propanol and bis-2,3-diethylamino-1-propanol in the ratio of

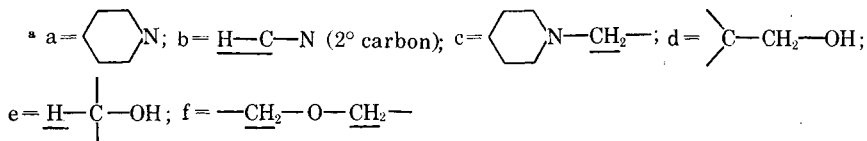
TABLE I. Chromatographic Data Using 5% 2M Carbowax on Haloport

Reactions	Products and ratios
$2 \text{ } \begin{array}{c} \text{C}_6\text{H}_{11}\text{N} \\ \\ \text{N}-\text{H} \\ \\ \text{O} \\ \\ \text{CH}_2-\text{CH}-\text{CH}_2\text{Cl} \end{array} + \text{NaOH}$	$\left[\begin{array}{c} \text{C}_6\text{H}_{11}\text{N} \\ \\ \text{N}-\text{CH}_2-\text{CHOH}^a \\ \\ \text{C}_6\text{H}_{11} \end{array} \right]_{100}$
$\begin{array}{c} \text{C}_6\text{H}_{11}\text{N} \\ \\ \text{N}-\text{H} \\ \\ \text{Br} \\ \\ \text{Br}-\text{CH}_2-\text{CH}-\text{CH}_2\text{OH} \end{array} \text{ (Excess)} + \text{NaOH}$	$\begin{array}{c} \text{C}_6\text{H}_{11}\text{N} \\ \\ \text{N}-\text{CH}_2-\text{CH}-\text{CH}_2\text{OH}^a \\ \\ \text{C}_6\text{H}_{11} \end{array} \sim \text{nil}$
$2 \text{ } \begin{array}{c} \text{O} \\ \\ \text{CH}_2-\text{CH}-\text{CH}_2\text{Cl} \end{array} + \text{NaOH}$	$[(\text{C}_2\text{H}_5)_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}-\text{CH}_2\text{OH}]_{19}$
$(\text{C}_2\text{H}_5)_2\text{NH} \text{ (Excess)} + \text{BrCH}_2-\text{CH}-\text{CH}_2\text{OH}$	$[(\text{C}_2\text{H}_5)_2\text{N}-\text{CH}_2-\text{CH}-\text{CH}_2\text{OH}]_{3}$
$\begin{array}{c} \text{O} \\ \\ \text{CH}_2-\text{CH}-\text{CH}_2 \\ \\ \text{N}-\text{CH}_2-\text{CH}-\text{CH}_2 \\ \\ \text{C}_6\text{H}_{11} \end{array} + \text{C}_2\text{H}_5\text{O}^-$	$\begin{array}{c} \text{OH} \\ \\ \text{CH}_2-\text{CH}-\text{CH}_2\text{OC}_2\text{H}_5 \\ \\ \text{C}_6\text{H}_{11} \end{array} \sim 100$
$\begin{array}{c} \text{O} \\ \\ \text{CH}_2-\text{CH}-\text{CH}_2 \\ \\ \text{N}-\text{CH}_2-\text{CH}-\text{CH}_2 \\ \\ \text{C}_6\text{H}_{11} \end{array} + \text{C}_3\text{H}_6\text{O}^e$	$\begin{array}{c} \text{OC}_2\text{H}_5^e \\ \\ \text{CH}_2-\text{CH}-\text{CH}_2 \\ \\ \text{C}_6\text{H}_{11} \end{array} \text{ (C}_3\text{H}_5)_2\text{N}-\text{CH}_2-\text{CH}-\text{CH}_2-\text{CH}-\text{CH}_2\text{OH}$

^a These pairs were shown to be easily separable in control experiments with synthetic mixtures; ^b b.p. 88°/1.2 mm. Hg $\eta_{30}^D = 1.4591$. Calculated for $\text{C}_{10}\text{H}_{21}\text{O}_3\text{N}$: C, 64.12%; H, 11.30%; N, 7.48%. Found: C, 64.17%; H, 11.08%; N, 7.36%; ^c the mixture had b.p. 60–80°/5 mm. Calc'd for $\text{C}_9\text{H}_{17}\text{O}_2\text{N}$: C, 61.67%; H, 12.08%; N, 7.99%; Found: C, 61.80%; H, 11.94%; N, 8.12%. Analyses by Galbreath Laboratories, Knoxville, Tenn.

TABLE II
Piperidine Derivatives: Chemical Shift, Relative to TMS in CCl₄ Solvent

Compound	Proton type ^a					
	a	b	c	d	e	f
	90	—	144	—	225	—
	91	—	146	215	233	—
	89	158	—	214	—	—
	91	158	—	214	—	—
	90	—	137-145	—	—	198-215



^b B.p. 120°C./1.5 mm. Hg, reported b.p. 328°C./760 mm.; 140°C./3 mm.; 130°C./25 mm.

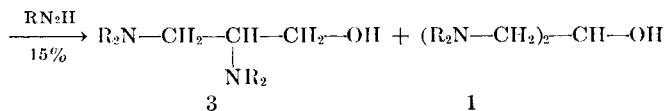
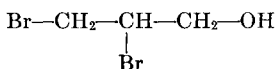
^c M.p. 79.5–80.5°C., reported m.p. 83°C.

^d B.p. 123–125°C./0.75 mm., reported b.p. 130–140°C./1 mm.

^e B.p. 122–125°C./1 mm., reported 150–151°C./3 mm.

^f M.p. 101–103°C., reported 101–104°C.

19:1. The intermediate glycidylamines, their hydrolysis products, the amino propanediols, and the bis(alkylamino)dioxanes were shown to be absent by a comparison of g.l.c. retention times (5% 2M Carbowax on Haloport). The bis-1,3-alkylamino-2-propanols were prepared using the model reaction and the isomeric bis-2,3-alkylamino-propanols were prepared by condensation of excess amine with 2,3-dibromo-1-propanol. The latter reaction yields both products in the ratio of 3:1, a result not previously noted and consistent with observations on the reaction of amines with other halohydrins.



In related experiments, the reaction of *N*-2,3-epoxypropylpiperidine with sodium ethoxide in ethanol gave a single product (by g.l.c.) presumably 3-(1-piperidyl-2-hydroxy-

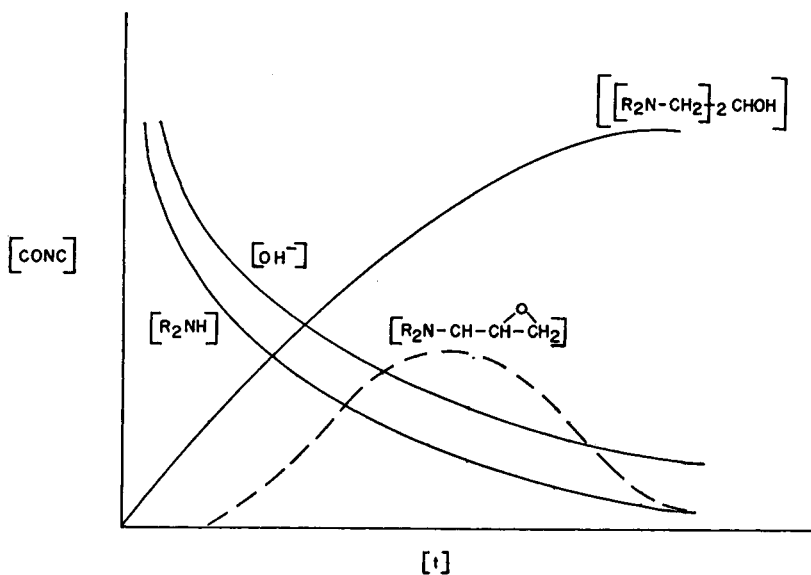


Figure 1.

propyl) ethyl ether. Sodium ethoxide with 2,3-epoxypropyl diethylamine gave a 9:1 mixture of two isomeric products, not separable by simple distillation. The major product was assigned the structure 3-diethylamine-2-hydroxypropyl ethyl ether and the minor product assigned the isomeric structure derived by substitution at the secondary carbon. Table I summarizes our g.l.c. data for these reactions.

Schemes for unambiguous synthesis of diaminopropanols and aminopropanediols are defeated by the internal rearrangement common to nitrogen mustards. For example, Cromwell and Hassner observed the complete interconvertibility of 1,3-dichloro-2-aminopropane and 1,2-dichloro-3-aminopropane, the latter predominating at equilibrium. However, we were able to correlate the chemical shift of protons in NMR spectra with structural assignments as given to achieve an internally consistent scheme (Table II). It was further observed that the bis-1,3-alkylamino-2-propanols had lower retention times than the isomeric 2,3-substituted -1-propanols. From the products of the reaction of amines with epichlorohydrin we may reasonably infer that polymers derived from related amines, e.g., piperazine, ethylamine, with epichlorohydrin have reasonable structural regularity with the expected 1,3-diamino-2-propanol unit predominant but not exclusive. The side reactions of hydrolysis and branching, found with epichlorohydrin and phenoxide ion, were not observed.

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