Some Reactions of Epichlorohydrin with Amines

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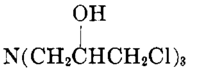
Certain reaction products of epichlorohydrin with ethylenediamine, ammonia, and diethylamine have been isolated and characterized. The chlorohydrin derived from diethylamine and epichlorohydrin is converted to an azetidinium salt on standing.

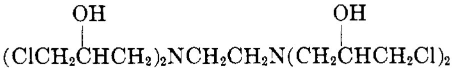
Because of our interest in epichlorohydrin as a cross-linking agent for polyamines, we undertook a study of the reactions of this versatile reagent with amines of varying functionality. We wish to report some new products derived from these reactions and new physical data and spectra for previously reported compounds.

Reaction of Epichlorohydrin with Ethylenediamine.—Since ammonia has been shown to react with three equivalents of epichlorohydrin to give I,[2,3] it was expected that ethylenediamine and four equivalents of epichlorohydrin might afford II under similar conditions. Although II may have been formed to some extent, III separated from the reaction mixture in moderate yield, as a finely divided solid which was insoluble in cold water and cold, neutral organic solvents. Variation in the order of addition of the reactants or in the amount of water or alcoholic solvent did not prevent separation of III before further reaction with epichlorohydrin could occur. The infrared spectrum of III was unusual in that the broad O–H absorption band expected for such an alcohol was not seen, presumably because of strong hydrogen bonding to nitrogen.[4]



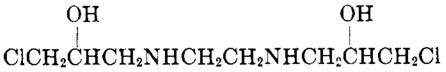
$N(CH_2\overset{OH}{C}HCH_2Cl)_3$

I



$(ClCH_2\overset{OH}{C}HCH_2)_2NCH_2CH_2N(CH_2\overset{OH}{C}HCH_2Cl)_2$

II

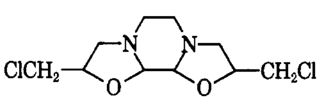


$ClCH_2\overset{OH}{C}HCH_2NHCH_2CH_2NHCH_2\overset{OH}{C}HCH_2Cl$

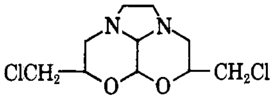
III

The reaction of III with nitrous acid gave a solid dinitrosamine. The presence of two secondary amino groups was thus demonstrated, and the possibility that III was an unsymmetrical, N,N-disubstituted ethylenediamine was excluded. The dinitrosamine had typical broad alcoholic OH absorption in the infrared region, and its proton nuclear magnetic resonance (n.m.r.) spectrum was consistent with the expected structure. Since the dinitrosamine was soluble in organic solvents, its molecular weight could be easily determined; the monomeric nature of III thus was confirmed. The possibility that III is a dimer or low polymer which depolymerized in the cold nitrosation mixture is remote. Structures can be written for polymers of the composition of III, joined through dioxane rings or other types of ether linkages, but to agree with the over-all composition, part of the chlorine would need to be ionic, and no significant quantity of ionic chlorine was found.

A tricyclic compound resulted from the reaction of III with aqueous glyoxal. Spectroscopic evidence favored 2,9-bis(chloromethyl)octahydrobisoxazolo[3,2-*a*:2′,3′-*c*]pyrazine (IV) over the isomer (V). Neither ring system has been reported previously.



IV

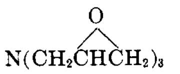


V

Reaction of Epichlorohydrin with Ammonia.—Although the reaction of 3 moles of epichlorohydrin with 1 of ammonia undoubtedly gives a mixture of products derived from different reactant ratios,[5] a solid 3:1 product (I) has been reported.[2,3] The solubility properties given for I[2] were similar to those found for III, but the isolation of the solid form apparently has not been reported since 1888.

Our preparations gave sirups, for the most part, but one solution crystallized spontaneously, although very slowly. The solid isolated was apparently identical with that obtained by Fauconnier.[2] Its molecular weight and spectra confirmed the structure I. The low water solubility of the solid, approximately 1%, must be caused by intermolecular hydrogen bonding in the solid.

The tris(epoxide) (VI) previously described as a liquid,[3,6] was obtained in crystalline form. Although the yield of solid directly from the crude product was not so high as might be desired, the pure product was obtained easily without a possibly hazardous[3] distillation.



$N(CH_2\overbrace{CHCH_2}^{O})_3$

VI

Reaction of Epichlorohydrin with Diethylamine.—The reaction products of secondary amines with epichlorohydrin, most probably of the structure R_2NCH_2-$CHOHCH_2Cl$, have been reported to cyclize to azetidinium salts[7,8] such as VII. Increases in ionic chlorine content of aminochlorohydrins have been noted by others[5,9] and have been attributed to quaternization

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[1] To whom communications should be addressed.

[2] A. Fauconnier, *Compt. rend.*, **107**, 115 (1888).

[3] J. B. McKelvey, B. G. Webre, and R. R. Benerito, *J. Org. Chem.*, **25**, 1424 (1960).

[4] For a discussion of hydrogen bonding in amine–epoxide products and infrared spectra of amino alcohols, see J. F. Harrod, *J. Polymer Sci.*, **1**, 385 (1963). It is possible that the presence of secondary amine groups in III and a 1:1 ratio of –OH groups to N atoms are somehow responsible for the atypical spectrum, especially the lack of a broad absorption band in the vicinity of 3400 cm.$^{-1}$.

[5] J. B. McKelvey, R. R. Benerito, R. J. Berni, and B. G. Burgis, *Textile Res. J.*, **33**, 273 (1963).

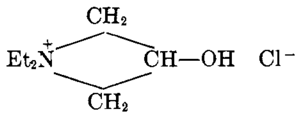
[6] K. Gerzon, J. E. Cochran, Jr., L. A. White, R. Monahan, E. V. Krumkalns, R. E. Scroggs, and J. Mills, *J. Med. Pharm. Chem.*, **1**, 223 (1959).

[7] L. Niemilowicz, *Monatsh.*, **15**, 118 (1894).

[8] R. Rothstein and K. Binovic, *Compt. rend.*, **236**, 1050 (1953).

[9] N. S. Drozdov and O. M. Cherntzov, *Zhur. Obschei Khim.*, **4**, 969 (1934); *Chem. Abstr.*, **29**, 2148 (1935).

reactions.[5] On the other hand, it has been suggested that the ionic chlorine-containing products (presumably including VII) are hydrochlorides of dioxanes,[10] since dioxanes have been obtained by base treatment of the salt reported to be VII.[8]



VII

We have re-examined the reaction of equivalent amounts of epichlorohydrin and diethylamine and found that the crude reaction mixture crystallized on standing. The purified solid product had an apparent molecular weight in water corresponding to the completely ionized salt of VII. In acetonitrile, on the other hand, the molecular weight appeared to be twice as great, corresponding to the unionized salt, as was the Rast molecular weight previously reported.[8]

Infrared and proton n.m.r. spectra clearly show VII to be a secondary alcohol. The infrared spectrum contains no band at 2800 cm.$^{-1}$ attributable to a -CH_2 group adjacent to a tertiary amine. A band at about 2600 cm.$^{-1}$, corresponding to a tertiary amine hydrochloride, is absent also. The proton n.m.r. spectrum showed a one-proton doublet (OH attached to a carbon having a single hydrogen), two nonequivalent ethyl groups, and a group of complicated multiplets centered at 5.5 τ and integrating to five protons. The nonequivalence of the ethyl groups is consistent with a four-membered ring having an asymmetric carbon atom opposite the nitrogen. The complex multiplet for the ring hydrogens is not unexpected since the hydrogens form an A_2B_2C system. Therefore, the only reasonable structure for the product appears to be VII.

Our data, then would confirm the azetidinium salt structure proposed by Rothstein and Binovic and fail to support the suggestion made by Heywood and Phillips[10] that these ionic chloride-containing products are simply dioxane dihydrochlorides.

Experimental[11]

1,1'-(Ethylenediimino)bis(3-chloro-2-propanol) (III).—To a mixture of 33 ml. (0.5 mole) of 98% ethylenediamine and 1 ml. of water was added in one portion 167 ml. (2.1 moles) of epichlorohydrin. The mixture was stirred efficiently and cooled in an ice bath to maintain the temperature at 28–32°. After 0.5 hr. the product began to separate. Two hours later the pasty mass was mixed with 1500 ml. of ice–water. The solid was collected on a suction filter and washed with water. After drying in a vacuum desiccator, the product amounted to 80 g. (65%) which melted at 105–112° dec. on further heating. Recrystallization from dimethylformamide raised the melting point to 135°.

In a number of other runs, where the order of addition and mole ratio of ethylenediamine to epichlorohydrin were varied, III was always obtained as a product. In one run where stirring was ineffective, the exothermic reaction was uncontrollable and the mixture decomposed somewhat violently.

Compound III was purified for analysis by recrystallization from dimethylformamide (about 30 ml. per gram, heated to 80°). Recovery was 50% and the melting point was 135–137°.

Anal. Calcd. for $C_8H_{18}Cl_2N_2O_2$: C, 39.19; H, 7.40; Cl, 28.93; N, 11.43; ionic Cl and oxirane oxygen, 0.0. Found: C, 39.27; H, 6.76; Cl, 28.22; N, 11.1; ionic Cl, 0.1; oxirane oxygen, <0.6.

The material is soluble in glacial acetic acid, trifluoroacetic acid, and dilute hydrochloric acid at room temperature; and in water, pyridine, dimethylformamide, dimethyl sulfoxide, and the monomethyl ether of ethylene glycol when heated on a steam bath. The proton n.m.r. spectrum of a trifluoroacetic acid solution was too broad to be useful; no other suitable solvent was found.

The infrared spectrum (mineral oil and halocarbon mulls) showed N-H at 3280 (sharp), OH····N at 3070 and 2720 (shoulder at 2650), and C-Cl at 733 cm.$^{-1}$.

Titration with perchloric acid in the monomethyl ether of ethylene glycol indicated an equivalent weight of 128. Two breaks at approximately equal volumes of titrant were obtained.

1,1'-[Ethylenebis(nitrosimino)]bis(3-chloro-2-propanol).—To a solution of 25 g. of III (0.1 mole) in a mixture of 50 ml. of concentrated hydrochloric acid and 175 ml. of water, cooled in an ice bath, was added a chilled solution of 21 g. (0.3 mole) of sodium nitrite in 75 ml. of water over a period of 6 min. while the mixture was held below 6°. The solution then was kept in an ice bath for 3.5 hr. The product, collected on a suction filter and washed with water, isopropyl alcohol, and ether, amounted to 3.5 g. and melted at 110–114°. The mother liquor deposited a second crop of 12.2 g. of pale yellow solid which melted at 110–111° (total, 51% yield).

Recrystallization from hot water gave bladed prisms which melted at 114–115°.

Anal. Calcd. for $C_8H_{16}Cl_2N_4O_4$: C, 31.69; H, 5.32; total Cl, 23.39; N, 18.48; mol. wt., 303.15. Found: C, 31.90; H, 4.84; total Cl, 23.34; ionic Cl, 0.6; N, 18.32; mol. wt., 290 (in acetonitrile).

The infrared spectrum showed OH at 3330 (broad), CH_2N-N=O at 1422 and 1390, and C-Cl at 687 cm.$^{-1}$. The n.m.r. spectrum in DMSO-d_6 had peaks at 4.87 (OH), 6.32 (CH_2Cl), and 5.83 τ (N-CH_2CH_2N); the remaining absorption was buried underneath these.

2,9-Bis(chloromethyl)octahydrobisoxazolo[3,2-*a*:2',3'-*c*]pyrazine (IV).[12]—A mixture of 2.5 g. (0.01 mole) of III, 2.0 g. of technical 30% aqueous glyoxal, and 4 ml. of water was stirred until the solid dissolved. An oil began to separate in a few minutes, followed by crystallization of the product, which was collected on a suction filter (after cooling) and washed with water and a small amount of isopropyl alcohol. The 1.8 g. (67%) of nearly colorless crystals melted at 99–101°.

Recrystallization from chloroform–hexane and from acetone gave prisms which melted at 130–132° dec.

Anal. Calcd. for $C_{10}H_{16}Cl_2N_2O_2$: C, 44.95; H, 6.08; Cl, 26.54; N, 10.49; mol. wt., 267.16. Found: C, 45.19; H, 5.77; Cl, 26.20; N, 10.78; mol. wt., 250 (in chloroform).

The infrared sprectrum showed cyclic C-O or C-N at 1040 and C-Cl at 715 cm.$^{-1}$. The 1040-cm.$^{-1}$ absorption is more typical of a five-membered than a six-membered cyclic ether, but this is not conclusive because of the complexity of the structure.

The proton n.m.r. spectrum ($CDCl_3$) had single peaks at 5.35 and 7.28 τ; the remaining absorption formed a complex pattern between 5.4 and 7.2 τ. Detailed analysis was not possible. The material may be a mixture of stereoisomers of IV (or possibly V[12]).

1,1',1''-Nitrilotris(3-chloro-2-propanol) (I).—A mixture of 278 g. (3 moles) of epichlorohydrin, 100 ml. of isopropyl alcohol, and 60 g. (1 mole) of 29% aqueous ammonia (each added in one portion) was stirred and maintained at 31–34° with cooling for 7 hr.

The solution, on storage in a refrigerator, deposited a white solid in 26% yield, which melted at 90–93°. The material was precipitated from dilute hydrochloric acid with potassium carbonate. The product (I) melted at 90–94°, lit.[2] m.p. 92–93°.

Anal. Calcd. for $C_9H_{18}Cl_3NO_3$: C, 36.69; H, 6.16; total Cl, 36.10; N, 4.76; mol. wt., 294.61. Found: C, 36.34; H, 6.01; total Cl, 35.77; ionic Cl, <0.01; N, 5.23; mol. wt., 301 (in acetonitrile).

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[10] D. L. Heywood and B. Phillips, *J. Am. Chem. Soc.*, **80**, 1257 (1958).

[11] Melting points were determined on a Fisher-Johns block and are uncorrected. Analyses were performed in these laboratories under the direction of Mr. R. Francel, Mr. J. Deonarine, and Mr. J. Robinson. Molecular weights were determined in a vapor pressure osmometer. Infrared spectra, as mineral oil and halocarbon mulls, were obtained on a Perkin-Elmer spectrophotometer, Model 21. Proton n.m.r. spectra were obtained on a Varian V4300B n.m.r. spectrometer operating at 56.4 Mc.; approximately 10% concentrations were employed in the solvents specified.

[12] Possibly 4,7-bis(chloromethyl)octahydro-5,6-dioxa-2a,8a-diazaacenaphthylene (V).

Although I is soluble in water to only about 1%, it dissolves in acetone to the extent of about 30 g. per 100 ml. of acetone.

The infrared spectrum showed broad OH at 3310, CH_2–N at 2865 (medium), CH–OH at 1050, and C–Cl at 700 cm.$^{-1}$. The n.m.r. spectrum (in DMSO-d_6) had peaks at 4.89 (OH, doublet), near 6.2 (HC $<$), 6.32 (CH_2Cl), and 7.42 τ (NCH_2, doublet).

One ammonia–epichlorohydrin reaction mixture, prepared as described for I, deposited a very small yield of a different solid which melted at 66–76°. This material has not been analyzed or identified; its infrared spectrum (mineral oil mull) was different from that of I, but showed OH at 3200, CH–OH at 1087 and 1067, and C–Cl at 730 and 695 cm.$^{-1}$.

Tris(2,3-epoxypropyl)amine (VI).—The reaction mixture from one mole of ammonia with three of epichlorohydrin, prepared as described for I, was cooled to 20°. A solution of 140 g. of sodium hydroxide (3.5 moles) in 200 ml. of water was added over a 7-min. period with stirring and cooling to maintain the mixture at 20–25°. After stirring for 50 min. at 20–25°, the layers were separated. The aqueous layer was extracted with ether, with addition of just enough water to dissolve the inorganic salt which had separated, and the combined ether and organic layers were dried with three successive portions of potassium hydroxide pellets and evaporated *in vacuo* from a bath at 45°.

The orange sirup partly crystallized when stored in a refrigerator. Extraction with several portions of boiling hexane gave several crops of a colorless solid (total, 18%) which melted in the vicinity of 45°.

The product was purified by recrystallization from methylcyclohexane (heated to 70°) and melted at 45–46°.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56; oxirane oxygen, 25.9; mol. wt., 185.22. Found: C, 58.73; H, 7.95; N, 7.0; oxirane oxygen, 24.2; Cl, <0.5; mol. wt., 169.0.

Although the analytical figures are not ideal, they show the chemical identity of the product with the liquids previously reported.[3,6]

The infrared spectrum showed NCH_2 at 2800 and epoxide group at 3600, 3000, and 857 cm.$^{-1}$.

1,1-Diethyl-3-hydroxyazetidinium Chloride (VII).—To a solution of 14.6 g. (0.2 mole) of diethylamine and 0.6 g. of water was added 18.5 g. (0.2 mole) of epichlorohydrin over a period of 10 min. The solution was then maintained at 28–30° with stirring for 6 hr.

The solution crystallized partly upon standing at room temperature or in a refrigerator. The solid was recrystallized from a mixture of acetonitrile (in which it is very soluble) and acetone and had m.p. 154–155°.

Anal. Calcd. for $C_7H_{16}ClNO$: Cl, 21.40; mol. wt., 165.67. Found: ionic chlorine, 21.4; apparent mol. wt., 76 (in water), 162 (in acetonitrile).

The infrared spectrum (mineral oil mull) showed OH absorption at 3200 cm.$^{-1}$ (in addition to that attributed to a small amount of water).

The proton n.m.r. spectrum in DMSO-d_6 showed two ethyl groups whose methylene groups gave two overlapping quartets at 6.4 τ. The remaining spectrum consisted of a five-proton group of complicated multiplets centered at 5.5, and a one-proton doublet (OH) at 2.94 τ, splitting equal to 6.0 c.p.s. The doublet was easily exchanged upon the addition of deuterium oxide, and almost disappeared with sufficient deuterium oxide.

1,1-Diethyl-3-hydroxyazetidinium Picrate (VIII).—A crude diethylamine–epichlorohydrin product was treated with alcoholic picric acid in the hope of stabilizing the chlorohydrin intermediate as a picrate salt. Instead, an azetidinium picrate crystallized slowly from the solution, m.p. 223–226°.

Anal. Calcd. for $C_{13}H_{18}N_4O_4$: C, 43.57; H, 5.06; N, 15.64; Cl, 0.00. Found: C, 43.97; H, 5.07; N, 15.47; Cl (total), none.

Treatment of VII with picric acid gave VIII which melted at 223–227°.

Anal. Found: C, 44.07; H, 5.01; N, 16.12; Beilstein test, negative.

The proton n.m.r. spectrum (DMSO-d_6) was virtually identical with that of the chloride (except, of course, for picrate protons); the OH proton was shifted to $\sim$3.8 τ.

Acknowledgment.—The authors wish to thank Mr. Norman Colthup for interpretation of infrared spectra and Dr. John Lancaster for interpretation of proton n.m.r. spectra. We also wish to thank Professor Gilbert Stork for helpful discussions.

A New Synthesis of β,β-Diarylethylamines[1]

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A number of new β,β-diarylethylamines have been prepared by the reaction between β-phenylethanolamines and aromatic nucleophiles in acid solution. The amines included β-phenylethanolamine, *o*-, *m*-, and *p*-octopamine, *p*-sympatol, norepinephrine, and normetanephrine. The nucleophiles included phenol, catechol, guaiacol, resorcinol, phloroglucinol, β-naphthol, anisole, 4-hydroxycoumarin, and indole.

In the course of work on the biochemistry of octopamine [norsympatol, norsynephrine, α-(amino methyl)-4-hydroxybenzyl alcohol], it was desirable to seek a synthesis that might allow a convenient laboratory preparation of larger amounts than are practical with the usual methods. Hinsberg[2] had reported a synthesis which involved the Baeyer reaction of phenol and an amino acetal. With 1 mole of acetal for each mole of phenol he claimed that octopamine was formed, (eq. 1), and with 2 moles of phenol, β,β-bis(4-hydroxyphenyl)ethylamine (eq. 2).

$$C_6H_5OH + H_2NCH_2CH(OC_2H_5)_2 + HCl + H_2O \longrightarrow 4\text{-}HOC_6H_4CHOHCH_2NH_3^+\,Cl^- + 2C_2H_5OH \quad (1)$$

$$2C_6H_5OH + H_2NCH_2CH(OC_2H_5)_2 + HCl \longrightarrow (4\text{-}HOC_6H_4)_2CHCH_2NH_3^+\,Cl^- + 2C_2H_5OH \quad (2)$$

Repetition of these reactions in the manner described gave a product which had the reported properties but which was found to contain no octopamine when subjected to analysis by paper chromatography. Furthermore, when authentic octopamine was treated with hydrochloric acid under the conditions used by Hinsberg, it was completely destroyed. The condensation between 2 moles of phenol and 1 mole of amino acetal did yield a product with the properties of the bis(hydroxyphenyl)ethylamine described by Hinsberg. However, paper chromatographic examination of the compound showed that it contained at least three major byproducts which could not be removed completely by recrystallization.

Despite the lack of success in preparing pure β,β-bis(4-hydroxyphenyl)ethylamine from amino acetal and phenol it seemed possible that condensation of octop-

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(2) O. Hinsberg, German Patent 373,286 (March 5, 1923); *Friedländers Fortschr. Teerfarben fabr.*, **14**, 1278 (1923); *Ber.*, **56**, 852 (1923).