Anomalous Reaction of Epichlorohydrin with Trimethylamine

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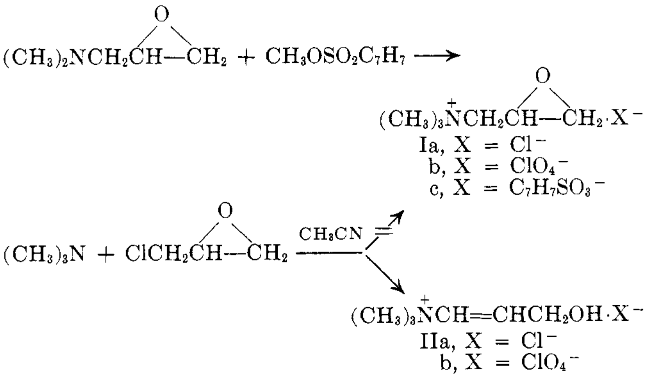
The reaction of epichlorohydrin and trimethylamine in acetonitrile does not give the expected product, N-(2,3-epoxypropyl)trimethylammonium chloride (Ia) but, instead, N-(3-hydroxy-1-propenyl)trimethylammonium chloride (IIa). Evidence is presented to show that Ia is a likely intermediate in the reaction, and that its rearrangement to IIa occurs readily in the presence of trimethylamine. The reaction has been extended to the long-chain amine, N,N-dimethyldodecylamine.

The preparation and reactions of epoxides which contain quaternary ammonium functions have been of recent interest.[1] These salts were readily prepared from tertiary glycidyl amines by alkylation with suitable agents. Thus, N-(2,3-epoxypropyl)trimethylammonium *p*-tosylate (Ic) was obtained in good yield from N-(2,3-epoxypropyl)dimethylamine and methyl *p*-tosylate. Since the glycidyl amine is not readily available, and must first be prepared from epichlorohydrin, an alternate procedure, the direct alkylation of trimethylamine with epichlorohydrin was considered. This reaction has led to an anomalous result, namely, the formation of the isomeric compound, N-(3-hydroxy-1-propenyl)trimethylammonium chloride (IIa).



Ia, X = Cl⁻
b, X = ClO₄⁻
c, X = C₇H₇SO₃⁻

IIa, X = Cl⁻
b, X = ClO₄⁻

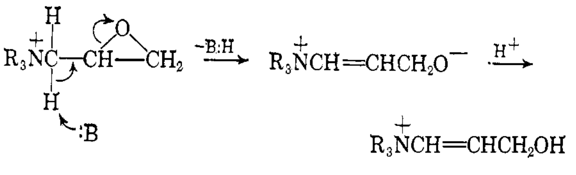
Although the reaction of epichlorohydrin with tertiary amines to produce epoxypropyl quaternary salts is mentioned in the literature,[2] including technical brochures, original references to the reaction with trimethylamine are very old and in them the products were not definitely characterized. Reboul[3] heated equal volumes of trimethylamine and epichlorohydrin in a sealed tube at 100° and reportedly obtained Ia as a viscous sirup. Somewhat later, Schmidt and Hartmann[4] in a similar reaction, but, using a 2:1 ratio of amine to epichlorohydrin, obtained a small amount of Ia; the chief product was the bis salt, 2-hydroxypropane-1,3-bis(trimethylammonium chloride) (III). The reaction of a long-chain tertiary amine with epichlorohydrin has also been reported to produce an epoxide salt, but without documentary proof.[5,6]

The reaction of epichlorohydrin and trimethylamine in acetonitrile was found to occur readily, under ambient conditions, to give good yields of a product consisting largely of the 3-hydroxy-1-propenyl salt (IIa) which is isomeric with epoxide Ia. The presence of a small amount of the epoxide was indicated by an epoxy oxygen analysis and by the n.m.r. spectrum of the product. The major product has not previously been reported in the literature nor have the properties of the expected epoxide. Although the elemental analysis of the product was consistent with Ia, an extremely low epoxy oxygen value and the presence of a strong hydroxyl band in the infrared spectrum indicated a product other than the unexpected compound.

The results of the first attempt at identification by n.m.r. were misleading in that the spectrum appeared to indicate the presence of two CH_2 groups in the molecule. The only structure compatible with this finding and other data is the highly improbable enolic form, $(CH_3)_3N^+CH_2CH(OH){=}CH_2{\cdot}Cl^-$, of acetonyltrimethylammonium chloride. The spectrum did confirm the presence of the OH group for the single proton resonance at τ 6.66; this shifted to the position of water resonance when a small amount of D_2O was added. It soon became apparent that the two protons appearing as a triplet at τ 3.66 are the olefinic protons of structure IIa, an instance in which two protons in completely different environments have essentially identical displacements in a magnetic field. The 3,5-dinitrobenzoate ester, on the other hand, gives an n.m.r. spectrum which is not only consistent with that of the hydroxy compound but which shows a normal separation of the olefinic protons. This has the appearance of an AB multiplet, each line of the doublet at higher field being split into a triplet.

Final confirmation of structure IIa for the product derived from its decolorization of permanganate and hydrogenation of the perchlorate salt (IIb) to N-(3-hydroxypropyl)trimethylammonium perchlorate.

The mechanism of formation of IIa from the reaction of epichlorohydrin and trimethylamine appears to proceed *via* the epoxide Ia as an intermediate. The latter may be formed by direct alkylation of the amine with the chloride or, alternatively, by a ring-opening step as is characteristic of reactions of epichlorohydrin with primary and secondary amines.[7] The rearrangement, occurring under catalysis by excess trimethylamine, may then proceed as follows.



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[1] D. M. Burness and H. O. Bayer, *J. Org. Chem.*, **28**, 2283 (1963).

[2] A. M. Paquin, "Epoxyverbindungen und Epoxyharze," Springer-Verlag, Berlin, 1958, p. 202.

[3] E. Reboul, *Compt. rend.*, **93**, 423 (1881).

[4] E. A. Schmidt and H. Hartmann, *Ann.*, **337**, 116 (1904).

[5] E. I. du Pont de Nemours and Co., Inc., British Patent 477,981 (March 30, 1936).

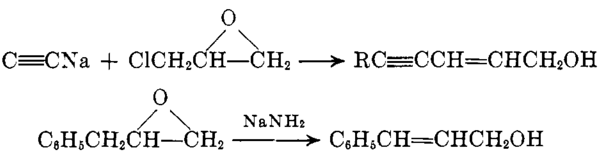
[6] When this work was substantially complete, Ia was made available in research quantities by Shell Chemical Co., to whom we are indebted for a sample. Details of their synthesis have not yet been published.

Confirmation of the intermediacy of the epoxide in this reaction was found in the ease and efficiency with which epoxides Ia and Ib rearranged under the reaction conditions to IIa and IIb. In one instance, a minor amount of the diquaternary salt, 2-hydroxypropane-1,3-bis(trimethylammonium perchlorate), was formed as a minor by-product. This probably arose from attack by trimethylamine on the terminal carbon of the epoxide ring, with resultant ring cleavage at this point.

The possibility that the chloride ion, when present in the reaction medium, may serve as the catalyst which promotes the rearrangement of Ia[8] may be discounted by the failure of Ia to rearrange to any appreciable extent in the absence of trimethylamine. In *refluxing* acetonitrile, a trace of the amine was detectable after 3 hr.; nevertheless, the bulk of the epoxide was recovered unchanged. Efforts to catalyze the rearrangement with triethylamine or triethylenediamine, under the usual ambient conditions, were notably unsuccessful. In the case of triethylamine, the increased steric requirement could be responsible; triethylenediamine is a considerably weaker base.

Although propylene oxide has recently been reported[9] to rearrange to allyl alcohol with a basic lithium phosphate catalyst, it underwent polymerization rather than rearrangement under the conditions of these reactions. Trimethylamine has previously been mentioned as a polymerization catalyst[10]; however, it was found that little reaction occurred at 25° in the absence of acetonitrile. Although other solvents have not been tried in the reactions under investigation, other highly polar solvents should also promote these ionic reactions.

The formation of an allylic alcohol in the reaction of epichlorohydrin with a basic reagent is not unique. Various workers[11-13] have found that epichlorohydrin and related compounds react with sodium acetylides to give such products. The rearrangement of the epoxide, benzylethylene oxide, to cinnamyl alcohol has been effected with a molar equivalent of sodamide in liquid ammonia.[11] Milder agents were ineffective.



An indication that the anomalous result obtained with trimethylamine is not unique and may be of considerable scope was found in the only other similar reaction attempted so far, *i.e.*, with dodecyldimethylamine. This reaction, which required more vigorous conditions than trimethylamine, resulted in an approximately 50% crude yield of a product which consisted largely of N-dodecyl-N-(3-hydroxy-1-propenyl)dimethylammonium chloride.

Experimental[14]

N-(3-Hydroxy-1-propenyl)trimethylammonium Chloride (IIa) and Derivatives.—A solution of 75 g. (0.81 mole) of epichlorohydrin (dried over Drierite) and 300 ml. of acetonitrile (Eastman Grade, dried over Drierite) in a flask equipped with stirrer, gas addition tube, and Dry Ice condenser was cooled to −20°, and 53 g. (0.90 mole) of anhydrous trimethylamine was passed in gradually. After 1.5 hr. at −10 to −20°, the solution was allowed to warm to 25°, and the temperature was maintained at 20–25° for 19 hr. Most of the trimethylamine was contained during this period by the condenser. The oil which gradually separated soon crystallized. The solid was removed and washed with acetonitrile and ether, 107-g. (87%) crude yield, m.p. 147–156°. A single recrystallization from *ca.* 400 ml. of absolute ethanol, with charcoal, and addition of ether to the cloud point produced 72 g. (58%) of a colorless, hygroscopic solid of m.p. 163–164° dec. A sample recrystallized further from absolute ethanol melted at 164–165° dec.

Anal. Calcd. for $C_6H_{14}ClNO$: C, 47.5; H, 9.3; Cl, 23.4; N, 9.2. Found: C, 47.2; H, 9.5; Cl, 23.6; N, 9.3.

An epoxy oxygen analysis indicated the possible presence of 9–10% of the epoxide Ia[15]; the infrared spectrum showed a strong hydroxyl absorption at 3.0.

The product failed to form a dinitrophenylhydrazone and failed to decolorize a solution of bromine in acetic acid. It did, however, decolorize aqueous permanganate, whereas the epoxide salt I gave a negative test with this reagent. The failure to react with bromine is in agreement with the result reported[16] with N-vinylpyridinium perchlorate.

The perchlorate salt (IIb), prepared from the chloride with concentrated aqueous sodium perchlorate, formed colorless plates of m.p. 181.5–183.5°. The n.m.r. spectrum of a 10% solution (w./v.) in acetonitrile shows a singlet at τ 6.76 (nine protons), two doublets at 5.82 (two protons), a triplet at 3.66 (two protons), and a triplet at 6.66 (one proton).

Anal. Calcd. for $C_6H_{14}ClNO_5$: S, 33.4; H, 6.5; Cl, 16.5; N, 6.5. Found: C, 33.7; H, 6.5; Cl, 16.8; N, 6.9.

An epoxy oxygen analysis indicated the possible presence of a small amount (0–2.5%) of Ib.[15]

The **3,5-dinitrobenzoate** was prepared from 1.5 g. of IIa and 2.3 g. of 3,5-dinitrobenzoyl chloride by boiling the solution for 5 min. in 60 ml. of nitromethane. Isolation of the ester and recrystallization from absolute ethanol–ether afforded 1.3 g. of nearly colorless crystals of m.p. 157.5–158° dec. The n.m.r. spectrum of a 5% solution (w./v.) in dimethyl sulfoxide shows a singlet at τ 6.65 (9 protons), a doublet at 4.93 (2 protons), a multiplet at 3.25 (2 protons), and three aromatic protons further downfield.

Anal. Calcd. for $C_{13}H_{16}ClN_3O_6$: C, 45.1; H, 4.6; Cl, 10.3; N, 12.15. Found: C, 45.3; H, 4.8; Cl, 10.2; N, 11.9.

N-(2,3-Epoxypropyl)trimethylammonium Perchlorate (Ib).—The tosylate salt[1] was converted to the perchlorate using sodium perchlorate in acetonitrile. After filtration of the sodium *p*-toluenesulfonate and removal of the solvent, the pure perchlorate was obtained from methanol in 87% yield, m.p. 132.5–133.5°.

Anal. Calcd. for $C_6H_{14}ClNO_5$: C, 33.4; H, 6.5; Cl, 16.5; N, 6.5. Found: C, 33.7; H, 6.2; Cl, 16.5; N, 6.9.

Acetonyltrimethylammonium Chloride and Perchlorate.—A solution of 50 g. of chloroacetone in 250 ml. of acetonitrile, held

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[7] *Cf.* S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. I, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 27.

[8] This possibility, suggested by Dr. Stanley Smith, of the University of Illinois, arises from known instances in which eliminations and rearrangements in acetonitrile and other polar organic solvents have been strongly catalyzed by halide ions. *Cf.* D. N. Kevill, P. H. Hess, P. W. Foster, and N. H. Cromwell, *J. Am. Chem. Soc.*, **84**, 983 (1962); R. P. Holysz, *ibid.*, **75**, 4432 (1953); H. W. Heine, M. E. Fetter, and E. M. Nicholson, *ibid.*, **81**, 2202 (1959).

[9] Olin Mathieson Chemical Corp., British Patent 902,953; *Chem. Abstr.*, **58**, 13,794 (1963).

[10] C. S. Marvel and E. C. Horning, "Organic Chemistry," Vol. I, 2nd Ed., H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 771.

[11] L. J. Haynes, I. Heilbron, E. R. H. Jones, and F. Sondheimer, *J. Chem. Soc.*, 1583 (1947).

[12] C. F. Hiskey, H. L. Slates, and N. L. Wendler, *J. Org. Chem.*, **21**, 429 (1956).

[13] T. L. Jacobs, D. Dankner, and A. R. Dankner, *J. Am. Chem. Soc.*, **80**, 864 (1958).

[14] Melting points were taken in a capillary and are corrected. The method for epoxy oxygen determinations was an adaptation, by D. G. Bush of these laboratories, of one published by A. J. Durbetaki, *Anal. Chem.*, **28**, 2000 (1956). With quaternary salts, it has been found necessary to employ excess hydrogen bromide and to back-titrate after 30 min. with tetra-*n*-butylammonium hydroxide, using crystal violet as indicator. The n.m.r spectra were obtained on a Varian 60-Mc. dual purpose spectrometer, Model V-4302, using tetramethylsilane as an internal reference. The τ-values given are those of G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

[15] Although good accuracy is ordinarily obtained in these analyses, the values appear to run a bit high (0–2.5%) in the presence of the allylic hydroxyl group.

[16] I. N. Duling and C. C. Price, *J. Am. Chem. Soc.*, **84**, 578 (1962).

at 10°, was treated with 33 g. of gaseous trimethylamine. After 2 hr., the chloride was filtered and recrystallized from acetonitrile to give 36 g. of a colorless, hygroscopic solid of m.p. 155–157°. Conversion to the perchlorate in acetonitrile produced a colorless solid of m.p. 96–100° after recrystallization from 2-butanone.

Anal. Calcd. for $C_6H_{14}ClNO_5$: C, 33.4; H 6.5; Cl, 16.5. Found: C, 33.3; H, 6.4; Cl, 16.7.

Neither of these salts is reported in the literature.

N-(3-Hydroxypropyl)trimethylammonium Perchlorate and Tetraphenylboride. A. By Hydrogenation of IIb.—A solution of 4.3 g. of IIb in 90% aqueous methanol was hydrogenated at 25° and 45 p.s.i. using a platinum oxide catalyst; the theoretical amount of hydrogen was absorbed in 10 min. The solvent was removed and the residue was washed with ether to give 3.3 g. of crude product of m.p. 123–128° (melt not clear). Although the infrared spectrum compared favorably with that of the perchlorate prepared below, a troublesome impurity, indicated by bands in the spectrum at 3.7 and 10.2 μ to be trimethylammonium perchlorate, interfered with an attempted purification by recrystallization. The product thus was converted to the tetraphenylboride (TPB) salt, using aqueous sodium tetraphenylboron. After recrystallization from acetone, the TPB salt, consisting of colorless plates, melted at 228° dec. A mixture with the authentic compound, prepared as described in the next section, was not depressed, and the respective infrared and n.m.r. curves were identical.

B. By Quaternization of 3-Dimethylamino-1-propanol.—A sample of 3-dimethylamino-1-propanol (Eastman Practical Grade) was alkylated by methyl *p*-toluenesulfonate in benzene and converted to the perchlorate in acetonitrile. Recrystallization from methanol gave colorless plates of m.p. 163–164.5°.

Anal. Calcd. for $C_6H_{16}ClNO_5$: C, 33.1; H, 7.35. Found: C, 33.5; H, 7.3.

Conversion by aqueous sodium tetraphenylboron to the TPB salt resulted in a colorless solid of m.p. 229° dec.

Anal. Calcd. for $C_{30}H_{36}BNO$: C, 82.4; H, 8.2; N, 3.2. Found: C, 82.5; H, 8.6; N, 3.4.

Rearrangement of N-(2,3-Epoxypropyl)trimethylammonium Salts. A. Using Trimethylamine with the Perchlorate.—A solution of 5 g. of Ib in 37 g. of acetonitrile was treated briefly with trimethylamine. (All materials were dried *via* anhydrous calcium sulfate.) Within a very few minutes, colorless crystals began to separate. After 16 hr. at 25°, the mixture was filtered, producing 4.35 g. (87% yield) of crude IIb, m.p. 166–168° dec.; the infrared spectrum was a close match with that of pure IIb obtained from the reaction product of epichlorohydrin with trimethylamine. Attempted recrystallization from methanol failed to raise the melting point to that of the pure compound, perhaps owing to a persistent impurity which was isolated in 0.2-g. yield by fractional crystallization, m.p. 322° dec. This proved to be 2-hydroxypropane-1,3-bis(trimethylammonium perchlorate); the infrared spectrum was compatible with this structure.

Anal. Calcd. for $C_9H_{24}Cl_2N_2O_9$: C, 28.8; H, 6.4; Cl, 18.9; N, 7.5. Found: C, 29.0; H, 6.1; Cl, 19.1; N, 7.3.

B. Using Trimethylamine with the Chloride.—A suspension of 7.4 g. of Ia (Shell Chemical Co.) in 85 ml. of acetonitrile was treated as in A. The colorless product weighed 6.75 g. (91% yield), m.p. 157–161°; the infrared spectrum was identical with that of the product obtained directly from the reaction of epichlorohydrin and trimethylamine in acetonitrile.

A 3-g. sample of Ia (m.p. 138.5–141°) in 25 ml. of acetonitrile was stirred without added catalyst for 18 hr. at 25°. A nearly quantitative recovery of the unchanged epoxide (m.p. 137–140.5°) was achieved. When such a solution containing 2.5 g. of Ia was heated at reflux for 3 hr., a slight odor of trimethylamine developed and 92% of the original material was recovered in two crops: (1) 1.75 g. of m.p. 115–125°, and (2) 0.55 g. of m.p. 133–138°. The infrared spectra of both fractions were essentially identical with that of Ia, although crop 1 was shown to contain small amounts of IIa and another unknown contaminant.

C. Attempted with Other Catalysts.—Small-scale experiments using triethylamine or triethylenediamine as catalysts in reactions with Ib under the conditions used in A failed to produce any crystalline product, although the infrared spectra of the solutions indicated the presence of small amounts of hydroxy compound. After 3 days, a solution containing 2% triethylenediamine contained a very small crop of crystals.

In another experiment, equivalent amounts (*ca.* 20 mole % based on the epoxide) of trimethylamine and triethylamine (in a little methanol) were added to separate solutions of Ib in acetonitrile. After 41 hr., the trimethylamine-catalyzed reaction had produced a 50% yield of crude IIb, and 28% of unchanged Ib was recovered from the filtrate. The triethylamine-catalyzed reaction failed to produce crystals; removal of the solvent left a crystalline residue which was shown by its infrared spectrum to contain a very small amount of IIb. By recrystallization of the material from methanol, 75% of pure Ib was recovered. It is obvious that triethylenediamine and triethylamine are less effective catalysts for this rearrangement.

N-Dodecyl-N-(3-hydroxy-1-propenyl)dimethylammonium Perchlorate.—A mixture of 21.4 g. (0.1 mole) of N-dodecyldimethylamine and 9.3 g. (0.1 mole) of epichlorohydrin in 75 ml. of acetonitrile was stirred under reflux for 10 hr. (After 15 min., solution was complete.) On cooling, the reaction mixture deposited 15.2 g. (50% yield) of a colorless, hygroscopic solid, which showed a definite CH_2OH peak in the infrared. Reaction with sodium perchlorate in acetonitrile produced the perchlorate which melted at 57–70° (from ethyl acetate). There was no change in melting point on repeated recrystallization. The n.m.r. spectrum closely resembled that of IIb, confirming the structure indicated.

Anal. Calcd. for $C_{17}H_{36}ClNO_5$: C, 55.2; H, 9.7; Cl, 9.6. Found: C, 54.9; H, 9.6; Cl, 9.7.

Reaction of Propylene Oxide in the Presence of Trimethylamine. A. Neat.—Propylene oxide (Eastman Grade, 38 g.) was treated briefly with anhydrous trimethylamine and allowed to stand at 25–30° for 70 hr. The mixture during this period became slightly yellow and the index of refraction (n^{25}_D) increased from 1.3633 to 1.3642, indicating only a slight degree of reaction.

B. In Acetonitrile.—A solution of 40 g. of propylene oxide and 10 g. of acetonitrile was treated as in A. The solution soon developed an amber color. After 70 hr., the solution was a deep red-brown and the n^{25}_D had increased from 1.3586 to 1.3739. Removal of the solvent left 8.2 g. of red oil, n^{25}_D 1.4565, which was indicated by the infrared spectrum to be a polyether.

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