product was digested with 25 ml. of boiling benzene which left a residue of 0.35 g. melting at 195–205°. Crystallization of the residue from glacial acetic acid furnished pure hexanitrobibenzyl, m. p. 213–215°. The benzene extract on cooling deposited 0.25 g. of impure pentanitrobibenzyl, m. p. 165–175°; mixed with pure pentanitrobibenzyl (m. p. 187–188°) the melting point was 175–180°.

**2,2',4,4'-Tetranitrostilbene** was prepared from 2,4-dinitrotoluene by treatment with iodine and potassium hydroxide in methanol and piperidine.[8] When 9.7 g. of tetranitrostilbene was added to a mixture of 100 g. of 90% nitric acid and 165 g. of 95% sulfuric acid and the reaction mixture was warmed on the steam-bath, the solid dissolved. Next 85 g. of 15% oleum was added, followed by a mixture of 45 g. of 15% oleum and 45 g. of 90% nitric acid. The solution was heated on the steam-bath for seven hours, left overnight at room temperature, and poured onto ice. The solid was washed with water and ethanol and dried; weight 3.3 g. Crystallization from 200 ml. of benzene furnished 3.2 g. of pure 2,2',4,4'-tetranitrobenzil, yield, 30%.

*Anal.* Calcd. for $C_{14}H_6N_4O_{10}$: C, 42.56; H, 1.54; N, 14.36. Found: C, 42.63; H, 1.53; N, 14.71.

2,2',4,4'-Tetranitrobenzil is a pale yellow solid which melts at 222–223° and is almost insoluble in the ordinary solvents. It is sparingly soluble in the higher-boiling solvents such as glacial acetic acid and toluene. When 0.5 g. of the benzil was dissolved in 20 ml. of boiling acetic acid and 15 ml. of 30% hydrogen peroxide was gradually added, the first additions caused a transient precipitation, while with the last additions most of the color of the solution disappeared. A further 5 ml. of 30% peroxide was added and the reaction mixture was concentrated on the steam-bath to a volume of about 1 ml. On cooling, this residue solidified to furnish 0.55 g. of 2,4-dinitrobenzoic acid, m. p. 181–182°, which did not lower the melting point of an authentic specimen of 2,4-dinitrobenzoic acid (182–183°).

Alkaline hydrogen peroxide on the benzil leads to 2,4-dinitrophenol. To a solution of 0.2 g. of the benzil in 100 ml. of methanol was added 5 ml. of 30% hydrogen peroxide and a solution of 0.85 g. of sodium in 50 ml. of methanol. The reaction mixture was kept at the boiling point while a small precipitate formed. (The precipitate was apparently sodium carbonate for it was inorganic and liberated carbon dioxide on treatment with hydrochloric acid.) The filtrate, after removal of the precipitate, was evaporated to dryness and the residue was dissolved in 7 ml. of water. On acidification with dilute hydrochloric acid, 0.1 g. of 2,4-dinitrophenol (m. p. 111°, mixed melting point with pure dinitrophenol 111–112°) was obtained.

Tetranitrobenzil treated exactly as described in the preceding paragraph save that the hydrogen peroxide was omitted, yielded a dark brown alkali-soluble solid, which resembled the complex products generally obtained by the action of alcoholic alkali on aromatic nitro compounds and from which no dinitrophenol or any other chemical individual could be isolated.

**Formation of a Quinoxaline from 2,2',4,4'-Tetranitrobenzil.**—When 0.2 g. of the benzil was suspended in 125 ml. of boiling ethanol and 0.18 g. of *o*-phenylenediamine hydrochloride and 0.2 g. of potassium acetate were added and the solution was boiled for four and a half hours, the benzil slowly dissolved and a sandy yellow precipitate of the quinoxaline formed. The solid was filtered and crystallized from toluene using Darco to remove some highly colored by-products. The yield of the pure quinoxaline, m. p. 278° dec., was 0.2 g.

*Anal.* Calcd. for $C_{20}H_{10}N_6O_8$: C, 51.9; H, 2.16; N, 18.2. Found: C, 51.8; H, 2.46; N, 17.88.

**Attempted Nitration of Tolan.**—When 0.5 g. of tolan was added slowly to 20 g. of 100% nitric acid cooled in an ice–salt-bath, the reaction was vigorous. Oxides of nitrogen were evolved and a dark brown solution resulted. After the reaction mixture had been kept in the ice–salt-bath for a half hour, it was poured onto ice and the sticky brown precipitate was removed, washed with water, and dried. Two crystallizations from ethanol removed most of the color from the product, but the material was still sticky and melted over the range from 120 to 180° with decomposition.

## Summary

Bibenzyl and 4,4'-dinitrobibenzyl can be nitrated to the 2,2',4,4'-tetranitro derivative readily and in good yield. The tetranitro compound is slowly nitrated by hot mixed acid to yield, first, the 2,2',4,4',6-pentanitro- and, second, the 2,2',4,4',6,6'-hexanitro-bibenzyl. 2,2'4,4'-Tetranitrostilbene is oxidized by mixed acid to the tetranitrobenzil, which undergoes a novel cleavage with alkaline hydrogen peroxide to furnish 2,4-dinitrophenol. Tolan furnished what is apparently polymeric material on attempted nitration.

FLUSHING, N. Y. RECEIVED AUGUST 11, 1949

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[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY AND FROM THE DEPARTMENT OF CHEMISTRY OF THE RICE INSTITUTE]

# Mechanism of the Reaction of Bis-β-chloroethyl Ether (β,β'-Dichlorodiethyl Ether) with Hydroxyl and Thiosulfate Ions[1]

BY PAUL D. BARTLETT* AND EDWARD S. LEWIS†

There is a structural analogy between bis-β-chloroethyl ether (β,β'-dichlorodiethyl ether) (I) and mustard gas (II).[2] The hydrolysis and displacement reactions of the latter[3–5] as well as of such "nitrogen mustards" as methylbis-β-chloroethylamine (III) and ethylbis-β-chloroethylamine[6,7] have been shown to proceed as a first-order reaction, controlled by the formation of a cyclic ethylene-sulfonium or ethylene-immonium ion. Although tertiary oxonium salts are formed far less readily[8] than either tertiary sulfonium or quaternary ammonium salts, there appeared to be a

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* Harvard University Ph.D., 1931; Faculty, 1934–.

† Harvard University Ph.D., 1947.

(1) This paper is based upon part of a thesis submitted by Edward S. Lewis for the degree of Ph.D. at Harvard University, May 10, 1947.

(2) L. H. Cretcher and W. H. Pittenger, THIS JOURNAL, **47**, 163 (1925).

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(6) P. D. Bartlett, S. D. Ross and C. G. Swain, *ibid.*, **69**, 2971 (1947).

(7) P. D. Bartlett, J. W. Davis, S. D. Ross and C. G. Swain, *ibid.*, **69**, 2977 (1947).

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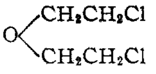
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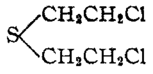
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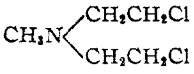

III

real possibility of oxygen participating in the displacement reactions of a β-chloroether, especially in view of the observation by Winstein and Buckles[9] of the role played by acetoxy groups in such reactions. The experiments here described were performed in the course of exploring the chemical basis of the great difference in physiological properties between the β-chloroethers on the one hand and the β-chlorosulfides and amines on the other.

Mustard gas is characterized by (1) rapid displacement of halogen compared to simple primary chlorides, (2) first-order kinetics, and (3) as a corollary of this, reaction with all displacing reagents at the same over-all rate. In contrast, previous work[10] has shown that bis-β-chloroethyl ether is much less reactive in hydrolysis and displacement than mustard gas. In the present work we find (1) that the rate of reaction of the ether with hydroxyl ion in 50% alcohol at 100° is only 1.2 times as great as for isoamyl chloride; (2) that the reaction of the ether with hydroxyl ion under these conditions, and the reaction with hydroxyl and thiosulfate ions in water at 100° are of the second order; and (3) that the reaction with thiosulfate ion is about eight times as fast as that with hydroxyl ion. Even at 100° the reactions with 1 *M* hydroxyl ion are not as fast as those of mustard gas at 25°.

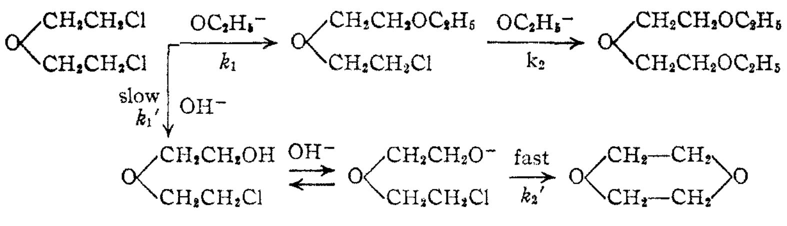
The fact that bis-β-chloroethyl ether shows no evidence of involvement of the oxygen in displacement reactions, with formation of an ethyleneoxonium ion, is in accord with the recent conclusion of Winstein, Grunwald and Ingraham[11] that there is no clear evidence that the methoxyl group assists in the ionization of *trans*-2-methoxycyclohexyl *p*-bromobenzenesulfonate.

We were not entirely successful in eliminating side reactions during the kinetic measurements. The reactions with thiosulfate appeared to be complicated by a slight amount of hydrolysis, and those with sodium hydroxide suffered from the fact that the attack of alkali on glass is rapid at 100°. Therefore the measurements with the base were all carried out with a considerable excess of base and the bimolecular nature of the reaction was established by comparing runs having different initial alkali concentrations. The mean deviation of the results, while precluding any great accuracy, was small enough to allow no doubt of the order of the reaction.

One result was found to vary from what might be expected of a displacement reaction of the $S_N2$ type. In the reaction with hydroxyl ion the change of medium from water to 50% alcohol, instead of being accompanied by an increased rate constant, resulted in a decrease from 0.030 to 0.017 l./mole min.[12] This is a very unusual behavior for a bimolecular displacement by an ionic reagent, and it therefore prompted a further inquiry into the effect of the change of medium.

In determining the rate constants no attempt was made to treat the reaction as a pair of successive reactions having different rate constants, as was necessary for accurate results in the case of mustard gas.[5] Actually we have a bifunctional compound undergoing two successive pseudounimolecular reactions with a reactant at constant concentration, with rate constants $2k_1$ and $k_2$. The approximation is made that each chlorine atom reacts independently with a rate constant $k$ and that the reacting material is present at a concentration twice that of the dichlorodiethyl ether molecules. If $k_1 = k_2$, this approximation yields a value of $k = k_1 = k_2$. If $k_2 >> k_1$ the kinetics will have the same form, but then the determined value of $k$ will be equal to $2k_1$ instead of to $k_1$ itself. If neither of these conditions is approached closely, the approximate equation will fail to fit the kinetics of the reaction.

One way in which the determined $k$ in 50% alcohol might be smaller than in water, while $k_1$ itself might be greater than in water, would be if in water $k_2 >> k_1$ while in alcohol $k_2 \cong k_1$. This might be so if the following reactions were the dominant ones in these respective media



According to this scheme the ethoxyl ion, being more powerfully nucleophilic than the hydroxyl ion, determines the product in 50% alcohol and this product, β-ethoxyethyl-β'-chloroethyl ether, can give only a second reaction which is quite like the first, $k_2 \cong k_1$. In the absence of alcohol, however, the first product is an alcohol, β-hydroxethyl-β'-chloroethyl ether, which yields enough alkoxide ion by interaction with hydroxyl ion to afford a rapid internal displacement with cyclization, so that $k_2' >> k_1'$.

An examination of the products under the conditions of our kinetic experiments confirmed the above course of the reaction. By distillation of the product of reaction of 71.5 g. (0.5 mole) of bis-β-chloroethyl ether with excess sodium hydroxide in water, there was obtained 35 cc. of the azeotrope, b. p. 87.5°, of dioxane and water.

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[9] S. Winstein and R. E. Buckles, THIS JOURNAL, **64**, 2780, 2787 (1942).

[10] H. Mohler and J. Hartnagel, *Helv. Chim. Acta*, **25**, 859 (1942).

[11] S. Winstein, E. Grunwald and L. L. Ingraham, THIS JOURNAL, **70**, 821 (1948).

[12] E. D. Hughes, *Trans. Faraday Soc.*, **36**, 608 (1941).

This was 92% of the amount of the same product recoverable from a solution of 39 g. (0.5 mole) of dioxane in the same volume (700 cc.) of water. In 50% ethanol no dioxane was observed in the product although a blank experiment showed that its presence in an amount equivalent to the starting material was easily detected. Diethyleneglycol diethyl ether, b. p. 185–187° (uncor.), $d^{20}_{20}$ 0.914, was isolated in the amount of 15% from the reaction product. While this recovery leaves much to be desired, coupled with the absence of dioxane it affords support of the proposed course of reaction. It follows that $k_1$ for reaction with hydroxyl ion in water is about 0.030/2 or 0.015; while $k_1'$ for reaction with ethoxyl ion in 50% alcohol is about 0.017 times the fraction $[(OH^-) + (OEt^-)]/(OEt^-)$. The rate of reaction with hydroxyl ion in 50% alcohol, which competes with the ethoxyl-ion reaction, must be slower than this over-all, but its specific rate constant cannot be estimated because of uncertainties as to the relative concentrations of hydroxyl and ethoxyl ions. The effect of changing medium upon the rate constant is not as anomalous as at first appeared.

## Experimental

Bis-$\beta$-chloroethyl ether from the Eastman Kodak Company was shaken with ferrous sulfate solution to remove peroxides, then dried and distilled in an atmosphere of nitrogen. The fraction boiling at 177–178° at atmospheric pressure was used for most runs, but a chlorine analysis showed it to be slightly impure.

*Anal.* Calcd. for $C_4H_8OCl_2$: Cl, 49.67. Found: Cl, 49.17 (by the Stepanov method).

A sample of this fraction was redistilled and a fraction boiling at 177.6–177.8° at 762.5 mm. was collected. This was used in Runs (3) and (4).

*Anal.* Calcd. for $C_4H_8OCl_2$: Cl, 49.67. Found: Cl, 49.53.

The runs at 100° are typified by Run (4) in which the procedure was as follows. A solution was made up at room temperature of 0.3725 g. of the chloroether in 1.020 *M* sodium hydroxide solution in a 100-cc. volumetric flask. After solution had been effected by a little shaking, 10-cc. portions were put into nine separate Pyrex test-tubes which were then sealed and heated in a wire gauze container in the steam cone. The temperature attained was determined to be within 0.1° of the boiling point of water at the prevailing atmospheric pressure which varied little from run to run. At suitable intervals a sealed tube was removed, plunged into cold water, opened and the entire contents titrated for chloride by the Volhard method after neutralization with nitric acid. In other runs the Mohr titration was used. The exact amount of chloroether present was determined by allowing the reaction to continue until no further change occurred in the concentration of chloride ion. The results are summarized in Table I.

TABLE I

BIMOLECULAR RATE CONSTANTS FOR REACTION OF BIS-$\beta$-CHLOROETHYL ETHER WITH HYDROXYL AND THIOSULFATE IONS AT 100°

| Run | $(OH^-)$ | $(S_2O_3^=)$ | Conditions | $k_2$, l./mole min. |
|---|---|---|---|---|
| 1 | | 0.0501 | $H_2O$ | 0.25 |
| 2 | | 0.100 | $H_2O$ | .32 |
| 3 | 0.255 | | $H_2O$ | .030 |
| 4 | 1.020 | | $H_2O$ | .032 |
| 5 | 1.067 | | $H_2O$ | .034 |
| 6 | 0.534 | | $H_2O$ | .037 |
| 7 | .505 | | 0.50 *M* $NaNO_3$ added | .030 |
| 8 | .505 | | Isoamyl chloride in 50% EtOH | .014 |
| 9 | .505 | | 50% EtOH | .017 |

**Reaction of Bis-$\beta$-chloroethyl Ether with Sodium Hydroxide in Water.**—A solution of 60 g. (1.5 moles) of sodium hydroxide in 700 cc. of water was heated to nearly 100° inside the steam-bath. To this solution was added 71.5 g. (0.5 mole) of bis-$\beta$-chloroethyl ether with stirring. After the addition of all the chloroether the solution was maintained at steam-bath temperature overnight. It was cooled, neutralized with hydrochloric acid to *p*H 2, filtered to remove silica, and distilled through a 6 ft. column packed with glass helices. The distillation yielded a fraction of about 35 cc. boiling at 87.5° sharply. A solution of 39 g. (0.5 mole) of dioxane in 700 cc. of water, distilled through the same column, gave about 38 cc. of the same constant boiling mixture without an appreciable forerun.

**Reaction of Bis-$\beta$-chloroethyl Ether with Sodium Hydroxide in 50% Ethanol.**—A solution of 350 g. of absolute ethanol, 350 g. of water, 71.5 g. (0.5 mole) of dichlorodiethyl ether and 60 g. (1.5 moles) of sodium hydroxide was heated under reflux in the steam-bath. Because of the presence of ethanol the temperature was lower than 100°. After heating overnight the solution was cooled, neutralized to *p*H 2 and filtered and distilled as before. The distillation curve of this solution was flat at 78°, corresponding to 95% ethanol, then rose steeply to 98° at which temperature a two-phase distillate came over, containing water and some unreacted chloroether. After 5 cc. of the organic phase had come over, together with 50 cc. of water, the distillate was clear. The remaining material was distilled at 50 mm. pressure, giving a first fraction boiling from 44–48°, $n^{29}D$ 1.3479, and a second fraction $n^{24}D$ 1.3325 whose boiling point was not accurately determined because of superheating resulting from salt crystallized from the solution. The first fraction was saturated with sodium chloride and a lighter phase separated. This phase was dried and distilled, boiling at 185 and 187° (uncor.), $d^{20}_{20}$ 0.914. Diethyleneglycol diethyl ether has b. p. 188° and $d^{20}_{20}$ 0.909.[13] The total yield of this material after extraction of the aqueous solution with ether was 12 g. (15%). There may easily have been more than this which escaped isolation in the distillation with the large amount of water and alcohol.

To ascertain whether dioxane could have been detected in this solution, a mixture was made up containing 700 g. of 50% ethanol and 39 g. (0.5 mole) of dioxane. The distillation curve showed that dioxane could have been detected easily if formed in anything like this amount.

## Summary

Bis-$\beta$-chloroethyl ether ($\beta,\beta'$-dichlorodiethyl ether) though structurally analogous to mustard gas, does not undergo hydrolysis or displacement through a cyclic oxonium intermediate, as analogy might suggest. It reacts slowly, bimolecularly and at different rates with hydroxyl ion and thiosulfate ion at 100°. In water the product of reaction with sodium hydroxide is dioxane; in 50% alcohol the only observed product is diethylene glycol diethyl ether.

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[13] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, New York, N. Y., 1948.