

Reaction of N-Haloamide. VII.¹⁾ A Cleavage Reaction of Ether with
N,N-Dihalobenzenesulfonamide. (2).²⁾ Reactions of Tetrahydro-
furan with N,N-Dibromobenzenesulfonamide,
N-Bromosuccinimide, or Bromine. (1)

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The reactions of tetrahydrofuran with N,N-dibromobenzenesulfonamide, N-bromosuccinimide, or bromine were investigated and the same major product, *trans*-2-(4'-bromobutoxy)-3-bromotetrahydrofuran (3), was obtained.

A cleavage reaction of aliphatic ethers with N,N-dibromobenzenesulfonamide (1) was previously reported by us.⁴⁾ We have now attempted to apply this cleavage reaction to alicyclic ethers and the reaction of tetrahydrofuran with 1, that with N-bromosuccinimide and that with bromine were examined.

In appearance, the reaction of tetrahydrofuran with 1 occurred by the color change of initial yellow to deep red under the evolution of heat, and subsequent heating effected decolorization and the separation of the crystalline benzenesulfonamide in quantitative amount.

From the mother liquor obtained by the filtration of benzenesulfonamide, an oil (3), bp 116° (2 mmHg), C₈H₁₄O₂Br₂, was isolated in about 50% yield. Treatment of this oil with 2,4-dinitrophenylhydrazine gave an osazone (4), C₁₆H₁₄O₉N₈, which was identified with that converted from 2,3-dichlorotetrahydrofuran.²⁾

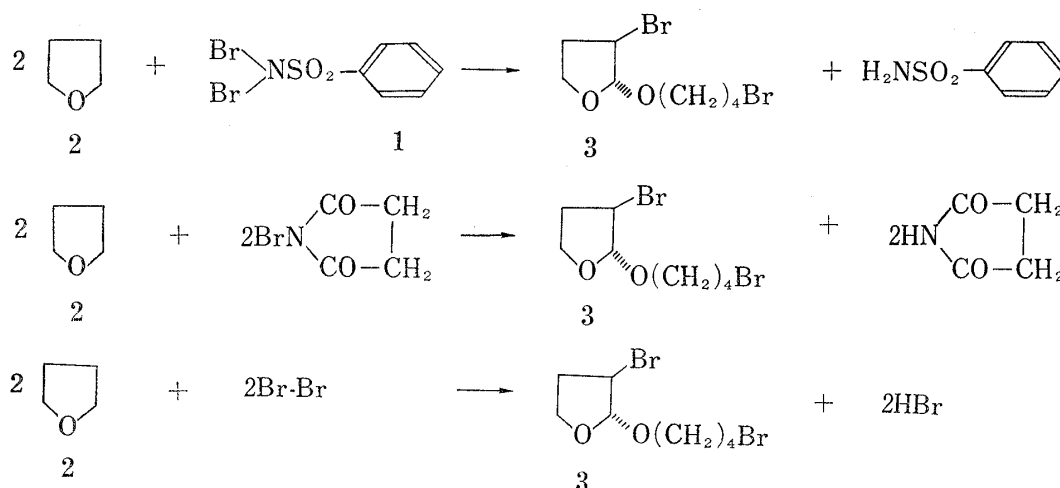


Chart 1

- 1) The title of the series, "Reaction of N-Halosulfonamide" is altered to "Reaction of N-Haloamide." Part VI: K. Otsuki, S. Takemura, K. Okamoto, and Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **16**, 1885 (1968).
- 2) Presented in part at the 16th Meeting of the Kinki Branch of the Pharmaceutical Society of Japan, 20th November, 1966.
- 3) Location: Kowakae, Higashi-Osaka, Osaka.
- 4) S. Takemura, Y. Ando, H. Terauchi, and Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **15**, 1331 (1967).

The nuclear magnetic resonance (NMR) spectrum of the oil (Fig. 1) was reasonable to give the structure **3**; a singlet at 4.8τ can be assigned to one proton in C-2, multiplet centered on 5.9τ with a magnitude of three protons to one proton in C-3 and two protons in C-4' of the side chain. A multiplet centered on 6.5τ is assignable to four protons in C-5 and C-1'.

Reppe⁵⁾ obtained 3-chloro-2-(4'-chlorobutoxy)tetrahydrofuran by the direct chlorination of tetrahydrofuran; Lorette⁶⁾ also reported that 2,3-dichlorotetrahydrofuran reacted with tetrahydrofuran in the presence of Lewis acid giving the same product. The oil (**3**)

which we obtained is likely a bromo analog of the above compound in terms of a resemblance of the infrared spectra (IR) and the chemical behaviors, and additionally, as described below, the result of the direct action of bromine to tetrahydrofuran was similar to that of chlorine to it by affording the oil (**3**) as a major product.

On the steric structure of these products, no study has been presented yet and a conclusion was derived from the analysis of the NMR spectrum of **3**.

The tetrahydrofuran ring is nearly planar and considering the repulsion between adjacent bulky bromine and -OR groups, and when both groups exist in *trans*, the angle between C₂-H and C₃-H would be less than 120° . The coupling constant of said protons, in these case, would come to minimum value⁷⁾ and, therefore, no splitting would be observed. Thus, it is presumable that the substituents on the tetrahydrofuran ring of **3** would exist in *trans* by means of a singlet at 4.8τ assignable to the C₂ proton. On the above basis, the structure for **3** is proposed to be *trans*-2-(4-bromobutoxy)-3-bromotetrahydrofuran.

When N-bromo-N-methylbenzenesulfonamide instead of **1** is allowed to react with tetrahydrofuran, the similar appearance of the reaction process was observed and the formation of **3** was indicated by thin-layer chromatography (TLC).

Winkelmann⁸⁾ pointed out that the reaction of N-bromosuccinimide (NBS) with equimolar tetrahydrofuran gave a product which he presumed it as 2,3-dibromotetrahydrofuran. Our results of the reaction of N-bromobenzenesulfonamides with tetrahydrofuran suggest that NBS resembles in its reactivity. In experiments of both reactions of N-bromosulfonamides with tetrahydrofuran and NBS with that under the same conditions, it was shown that **3** was also a major product when NBS was used as reagent.

A temporary deep coloration observed during the reactions of N-bromosulfonamides with tetrahydrofuran and NBS with that was spectrometrically examined and the spectrum of the color was exactly identified with that of free bromine. Therefore, it seemed that these types of reactions may also occur by the action of free bromine with tetrahydrofuran on the analogy of the known reaction of chlorine with that giving 2-(4'-chlorobutoxy)-3-chlorotetrahydrofuran.

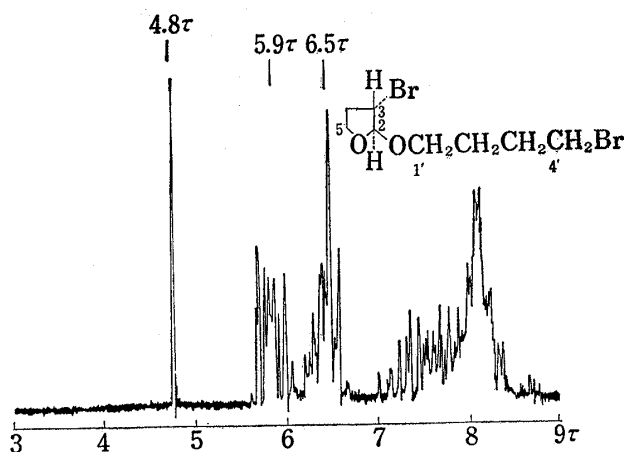


Fig. 1. Nuclear Magnetic Resonance Spectrum of *trans*-2-(4-bromobutoxy)-3-bromotetrahydrofuran (**3**) at 60 Mcps in Deutriochloroform (Internal Standard, TMS)

5) W. Reppe, *Ann.*, **596**, 1 (1955).

6) N.B. Lorette, *J. Org. Chem.*, **23**, 1990 (1958).

7) M.J. Karplus, *Chem. Phys.*, **30**, 11 (1959); M.J. Karplus, D.H. Anderson, *ibid.*, **30**, 6 (1959).

8) L. Horner and E.H. Winkelmann, "Neuere Methoden der Präparativen Organischen Chemie," III, 1957, p. 118.

The above presumption was confirmed by another experiment in which **3** was obtained under the mild reaction condition.

The liberation of bromine in the first step is unquestionable as N-bromoamides liberate their bromine when contacted with oxygen-containing substances such as ether.

The detail of the experiments and the considerations concerning the mechanism of these reactions will be presented in later papers.

Experimental

Reaction of N,N-Dibromobenzenesulfonamide (1) with Tetrahydrofuran—When **1** (9.5 g, 0.03 mole) was added to a solution of tetrahydrofuran (4.3 g, 0.06 mole) in CCl_4 (40 ml), it dissolved in the solution — although **1** itself is insoluble in CCl_4 — and an exothermic reaction gently occurred when kept at room temperature. The mixture gradually turned orange to deep red and a large amount of crystals presumably unstable intermediate, separated out from the solution.

When the deeply colored mixture warmed at 50° for 1 hr, the solution rapidly changed to nearly colorless and colorless crystals appeared. After the mixture was refluxed for more 1 hr, the resulting crystals were collected, and they were identified with benzenesulfonamide (yield: 4.2 g) by mixed melting point determination and the comparison of IR spectra.

Isolation of 2-(4'-bromobutoxy)-3-bromotetrahydrofuran (3): After the removal of benzenesulfonamide, the mother liquor was chromatographed on a silica gel column eluting with CHCl_3 . The fractions which gave a spot in TLC were collected. The solvent was evaporated and the residual oil was purified by distillation *in vacuo* to give a colorless oil (**3**), bp 116° (2 mmHg); Yield, 4.6 g (54%). Molecular weight: Calcd. for 302.0. Found: 311.8 (Rast). *Anal.* Calcd. for $\text{C}_8\text{H}_{14}\text{O}_2\text{Br}_2$: C, 31.71; H, 4.66; Br, 52.91. Found: C, 31.70; H, 4.67; Br, 52.80. The NMR spectrum of **3** was shown in Fig. 1. IR $\nu_{\text{max}}^{\text{liquid}}$ cm^{-1} : 1093, 1065; 1020, 915.

2,3-Dioxotetrahydrofuran 2,4-Dinitrophenylosazone—The oil (**3**) was warmed with 2,4-dinitrophenylhydrazine in acidic ethanol solution to give orange crystals, mp 267° (decomp.) (EtOAc). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{14}\text{O}_9\text{N}_8$: C, 41.56; H, 3.05; N, 24.24. Found: C, 41.65; H, 3.14; N, 24.50. They were identified with the osazone obtained from authentic 2,3-dichlorotetrahydrofuran by IR spectral comparison and by a mixed fusion.

Reaction of N-Bromo-N-methylbenzenesulfonamide with Tetrahydrofuran—N-Bromo-N-methylbenzenesulfonamide (7.5 g, 0.03 mole) was added to tetrahydrofuran (2.2 g, 0.03 mole) in CCl_4 (20 ml). Any reaction did not occur at room temperature but, when the mixture was refluxed, the reaction started and the color of the mixture changed from yellow to deep red. After being refluxed for 1 hr, the mixture was allowed to stand overnight and refluxed for 1 hr to complete the reaction. Thus, an oil was afforded and it was identified with **3** on TLC.

Reaction of NBS with Tetrahydrofuran—NBS (35.6 g, 0.2 mole) was added to tetrahydrofuran (7.2 g, 0.1 mole) in CCl_4 (50 ml). When the mixture was warmed on a water bath the reagent gradually dissolved. The initial yellow color changed into orange to deep red during the course of the reaction. When the reaction mixture was refluxed for 9 hr, the mixture gently turned to nearly colorless and colorless crystals of succinimide were separated out, which were identified with the authentic sample by the mixed melting point determination. The yield was nearly quantitative. The filtrate free from crystals was treated by the same method as in the reaction of tetrahydrofuran with **1** and an colorless oil was obtained which was identified with **3** by the comparison of their IR spectra. Yield: 6.8 g, 45%.

Reaction of Bromine with Tetrahydrofuran—When bromine (4 g, 0.05 mole) in CCl_4 (40 ml) was added to tetrahydrofuran (7.2 g, 0.1 mole) and the mixture was allowed to stand for 10 min at room temperature, oil of a deep red color and having a greater density than CCl_4 was separated out. When refluxed for 1 hr, the reaction mixture was changed to nearly colorless. The solvent was removed and the residual oil was treated by the above-mentioned manner to give colorless oil, which was identified with **3** by the comparison of their IR spectra. Yield: 43%.