Reports

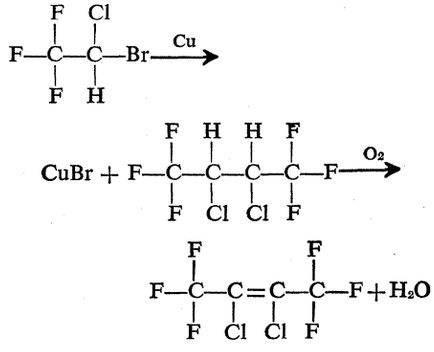
Impurity in Halothane Anesthetic

Abstract. *A halogenated butene has been isolated from commercially available halothane (Fluothane). Its concentration increases under the conditions in which halothane is commonly used in clinical work.*

Because of recent reports (*1*) of hepatic necrosis following the administration of halothane (2-bromo-2-chloro-1,1,1-trifluoroethane), and on request of the Subcommittee on the National Halothane Study of the Committee on Anesthesia of the National Academy of Sciences–National Research Council, an examination of this drug was undertaken for the presence of other halogenated compounds. Gas chromatographic analysis of halothane (hydrogen flame detector; di-isodecyl phthalate column; 70°C; helium flow 50 ml/min) showed the presence of a compound with a retention time of 35 seconds; halothane has a retention time of 75 seconds. The compound was present in each bottle of halothane that was examined, whether freshly opened or not. The average concentration in freshly opened bottles was approximately 0.01 percent. It was also shown, in a number of samples, that the concentration of this compound may increase under conditions in which halothane is used clinically. On one occasion it had increased to 0.1 percent during 5 days' use when the compound was stored continuously in a "copper kettle" vaporizer. Therefore a series of laboratory studies were undertaken to determine the conditions which would cause the concentration of this compound to increase.

Halothane, when refluxed in the presence of copper filings in an oxygen atmosphere, yielded an increased concentration. Heat further accelerated the reaction. In the absence of either copper or oxygen the concentration of the compound did not increase. Fractional distillation also yielded an increase of the compound, with radical enrichment observed, in the residual volume.

Identification of the compound was achieved by mass spectrometry following preparative gas chromatography with collection of the effluent under liquid nitrogen. The substance thus identified is 2,3-dichloro-1,1,1,4,4,4-hexafluorobutene-2, existing as the *cis* or *trans* isomer. Its boiling point is 67.8°C with a molecular weight of 232 (*2*). A feasible chemical mechanism of formation of the compound from halothane might be:



The pharmacologic properties of this compound have been only partially studied. Lu *et al.* noted that the compound produced convulsions at the point of anesthesia in two of four rats studied. All the rats had postanesthetic analgesia and died within 18 hours (*3*). This compound is closely related structurally to fluorocarbons of high toxicity. Clayton has shown that the presence of a double bond in the polyfluoroalkenes is associated with an increase in chemical activity and toxicity over that shown by the alkanes. In addition, the alkenes show an increasing toxicity with an increase in the number of chlorine atoms (*4*). However, since relationships between molecular configuration and toxicity are still obscure, investigations are currently under way to delineate the toxicity of this compound. A preliminary investigation in our laboratory has shown that it is acutely toxic to the dog when inhaled in anesthetic concentration. Delayed onset of anesthesia was followed by convulsions and death within 1 hour and 40 minutes. Another investigation has shown toxic symptoms in Wistar strain rats, after exposure for 4 hours to a 0.01-percent concentration. Severe degenerative changes were observed in the lung, liver, and kidney (*5*).

Of pertinent interest is a recent article (*6*) entitled "Halothane Hepatitis, an American Disease?" The wide use of copper vaporizers in this country as opposed to nickel-plated or glass vaporizers in many other countries may be significant.

Although the relative toxicity of 2,3-dichloro-1,1,1,4,4,4-hexafluorobutene-2 still remains to be established, a note of caution would include the suggestion that halothane be removed from the vaporizer at the end of each day's use to prevent a continuous concentration by evaporation and to further reduce to a minimum the time of contact within the copper container.

ELLIS N. COHEN
J. WELDON BELLVILLE
Department of Anesthesia, Stanford University, Stanford, California
HERBERT BUDZIKIEWICZ
DUDLEY H. WILLIAMS
Department of Chemistry, Stanford University

References and Notes

1. J. P. Bunker and C. M. Blumenfeld, *New Engl. J. Med.* **268**, 531 (1963).
2. A. I. Henne, J. B. Hinkamp, W. J. Zimmerschied, *J. Am. Chem. Soc.* **67**, 1906 (1945).
3. G. Lu, S. L. Johnson, M. S. Ling, J. C. Krantz, *Anesthesiology* **14**, 466 (1953).
4. J. W. Clayton, *J. Occupational Med.* **4**, 262 (1962).
5. M. B. Chenoweth, personal communication.
6. W. J. Heidenberg, I. S. Torio, J. Cebula, *Lancet* **1**, 1185 (1963).
7. Supported by contract PH43-63-65, National Institute of General Medical Sciences, and grant NB4167-01, National Institute of Neurological Diseases and Blindness.

21 August 1963

DDT and Dieldrin in Rivers: A Report of the National Water Quality Network

Abstract. *As a part of the water-quality surveillance activities of the National Water Quality Network at 101 sampling stations, insecticides were identified in 38 samples from ten rivers during the period May through December 1962. Both DDT and dieldrin were identified by infrared and gas chromatographic analysis of carbon adsorption extracts.*

Since the introduction of DDT as an insecticide during World War II, the use of organic pesticides has increased enormously. It has been estimated that more than 9000 commercial pesticide preparations are available in the United States (*1*). Such com-