REFERENCES

(1) Robinson, M., and Svedres, E., U. S. pat. 2,805,977.
(2) Robinson, M., and Swintosky, J., THIS JOURNAL, 48, 473(1959).
(3) McCabe, W., in "Chemical Engineer's Handbook," Perry, J., ed., 3rd ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1950, p. 1069.
(4) Stoyle, L., Ouellette, P., and Hanus, E., U. S. pat. 3,037,911.
(5) Stoyle, L., Ouellette, P., and Hanus, E., U. S. pat. 3,035,985.
(6) Schultz, T., and Talburt, W., U. S. pat. 2,929,722.
(7) Grevenstuk, A., and Hoogesteger, F., Union S. Africa pat. 611091.
(8) Scott, M., Lieberman, J., Maher, D., and Chow, F., "Spray Drying and Spray Congealing as Tools in the Preparation of Pharmaceutical Formulations," presented at First Annual Eastern Regional Meeting, Industrial Pharmacy Section, A. PH. A., New York, N. Y., November 1961.
(9) Marshall, W. R., Jr., "Atomization and Spray Drying," Chemical Engineering Progress Monograph Series, 50, No. 2, American Institute of Chemical Engineers, New York, N. Y., 1954.
(10) Fraser, R. P., and Eisenklam, P., *Trans. Inst. Chem Engrs.*, 34, 294(1956).
(11) Marshall, W. R., Jr., and Seltzer, E., *Chem. Eng. Progr.*, 46, 501(1950).
(12) Tate, R. W., and Marshall, W. R., Jr., *ibid.*, 49, 161, 226(1953).
(13) Duffie, J. A., and Marshall, W. R., Jr., *ibid.*, 49, 480(1953).
(14) Gretzinger, J., and Marshall, W. R., Jr., *A.I.Ch.E.J.*, 7 312(1961).
(15) Nelson, P. A., and Stevens, W. F., *ibid.*, 7, 80(1961)
(16) Ranz, W. E., and Hofelt, C., Jr., *Ind. Eng. Chem.*, 49 289(1957).
(17) Crosby, E. J., and Marshall, W. R., Jr., *Chem. Eng. Progr.*, 54, 56(1958).
(18) Friedman, S. J., Gluckert, F. A., and Marshall, W. R. Jr., *ibid.*, 48, 181(1952).
(19) Miro, A. R., and Otero, J. L., *Anales Fis. Quim (Madrid)*, 53F, 73(1957).
(20) Meyer, F. W., *Chem. Eng. Progr.*, 51, 528(1955).
(21) Wallman, H., and Blyth, H. A., *Ind. Eng. Chem.*, 43, 1480(1951).

Change of Ethylene Oxide Concentration During Gaseous Sterilization Process

By D. SATAS

The change of ethylene oxide concentration during the operation of laboratory and production sterilizers is reported. The rate of sorption is high at the beginning and decreases toward the end of a sterilization cycle.

ETHYLENE OXIDE (ETO) gas and its mixtures with carbon dioxide and fluorocarbons are widely used in the chemical sterilization of various pharmaceutical and hospital products. The principal use is for the sterilization of products which cannot be sterilized by steam without damage to their appearance or functionality. With an increasing utilization of heat-sensitive plastic materials, the importance of ETO as an efficient and economical sterilizing agent is growing.

This paper considers the change of ETO concentration during sterilization in laboratory and production size sterilizers, and discusses some of the experiences with a 10% ETO 90% CO_2 mixture at the Chicago Division of the Kendall Co.

Methods of ETO Analysis.—Chemical and infrared gas analyses were employed to assay the ETO concentration in the gaseous phase.

The reaction between epoxide compounds and hydrochloric acid to form the corresponding chlorohydrin was utilized to determine the ETO concentration (1). The reagent was prepared by dissolving 810 Gm. of $CaCl_2 \cdot H_2O$ and 95 ml. of concentrated HCl in 1400 ml. of water. Although several gas sampling techniques provided adequate accuracy, it was most convenient to bubble the gas slowly through gas washing bottles equipped with fritted glass cylinders and filled halfway with 150 ml. of reagent. Two wash bottles in series were used. At bubbling rates of 150–200 ml./minute and ETO concentrations of 10% or below, practically all ETO was absorbed in the first bottle. The gas flow rate was measured by a rotameter in series with the washing bottles. The amount of ETO absorbed was determined by titration of the excess acid with NaOH.

Infrared gas analysis is especially suitable for quick continuous determination of ETO and has been successfully used also by other workers (2). A known mixture of ETO and N_2 was used for calibration of the instrument. Such mixtures should be prepared carefully to assure their homogeneity. If any ETO is condensed in the calibration gas container, the discharge concentration will vary and might result in erroneous calibration of the instrument. For this reason, other more difficultly condensible gas mixtures (*n*-butane in N_2) can be used more conveniently for checking the analyzer once it has been calibrated with ETO.

ETO Changes in the Laboratory Sterilizer.—The change of ETO concentration in an 80-L. laboratory sterilizer manufactured by American Sterilizer Co.

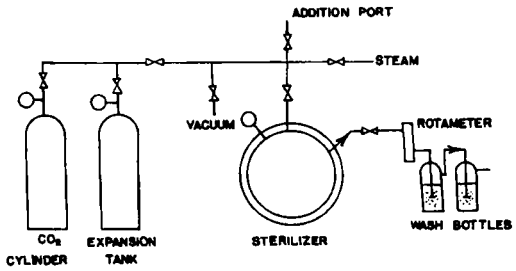

Fig. 1.—Schematic diagram of the equipment used for the laboratory sterilizer tests.

Received May 27, 1963, from the Kendall Co., Barrington, Ill.
Accepted for publication August 15, 1963.
The author is grateful to Mr. W. O. Elson and Dr. P. Laakso for support and helpful discussions.

was investigated under various conditions. A mixture of 10% ETO and 90% CO_2 was used for these experiments. Figure 1 shows the setup used for these tests. Liquid ETO is introduced through the addition port into evacuated sterilizer, and the proper amount of CO_2 is allowed to enter the sterilizer from the expansion tank. The rotameter and wash bottles are connected to the sterilizer for the assay of ETO concentration in the manner described above.

Figure 2 shows the change of ETO content in the sterilizer without a load at two different temperatures and two different water surface areas available for gas absorption. Water was introduced by placing pans of 10 to 70 sq. in. surface area into the sterilizer. The quantity of water was 1 L. in both cases.

The linearity of the curves suggests that the rate of ETO sorption is independent of ETO concentration in the gaseous phase and that the diffusion of ETO in water might be the rate-controlling step. The difference between curves A and B, however, cannot be attributed to the effect of temperature on ETO diffusivity in water. Increase of temperature might cause eddy diffusion in water and possibly some condensation of water on the cooler sterilizer surfaces, rendering the analysis of data difficult.

The sorption of ETO was sharply increased when a load of 8 lb. of cotton was placed in the sterilizer (Fig. 3). If the load is wetted with 100 ml. water, the ETO removal from the gas is further accelerated,

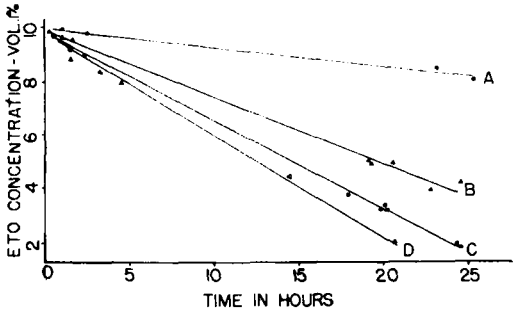

Fig. 2.—ETO removal in an empty laboratory sterilizer at different temperatures and available water surfaces for gas absorption. Key: (A) 80°F., 10 sq. in.; (B) 140°F., 10 sq. in.; (C) 80°F., 70 sq. in.; (D) 140°F., 70 sq. in. Total pressure 30 p.s.i.g.

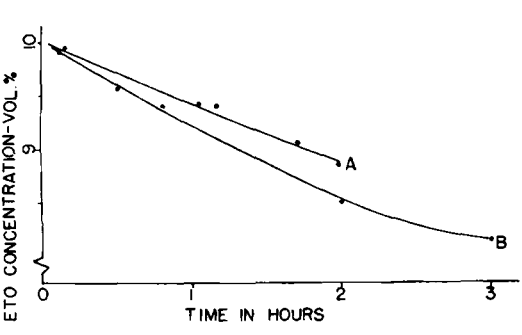

Fig. 3.—ETO sorption by cotton (8 lb.) in a laboratory sterilizer at 140°F., and 30 p.s.i.g. total pressure. Key: (A) dry load; (B) wetted with 100 ml. of water.

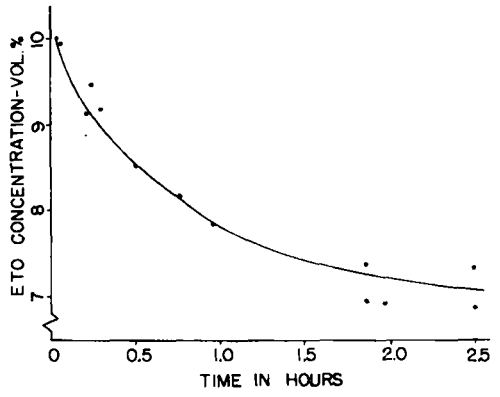

Fig. 4.—Change of ETO concentration in a laboratory sterilizer during a simulated sterilization cycle.

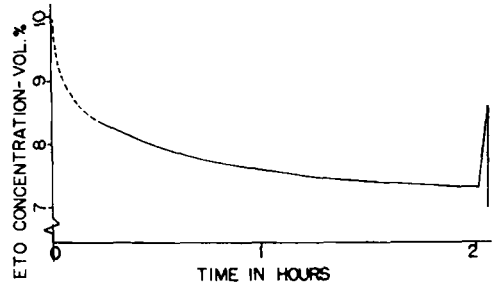

Fig. 5.—Typical ETO concentration change in a production sterilizer.

as evident from the differences between curves A and B.

The change of ETO concentration during a simulated sterilization cycle of a product containing cellulosic and plastic materials is shown in Fig. 4. Steam was introduced to preheat and humidify the load. Formation of fine condensate droplets increased the rate of ETO sorption and the amount of the gas absorbed by the load.

ETO Change in the Production Sterilizer.—Sterilizing gas can be introduced into the sterilizer either directly from a compressed gas cylinder or through auxiliary equipment designed to heat the gas. The ETO concentration change was followed in a 200-cu. ft. sterilizer by continuous infrared analysis as shown in a typical curve (Fig. 5). In this case, the gas was allowed to warm up in a jacketed expansion tank before introduction into the sterilizer. The sorption of ETO by the load of cellulosic and plastic material was faster than in the labora-

TABLE I.—CHANGE OF ETO CONCENTRATION IN STERILIZATION OF VARIOUS PRODUCTS

Product	Av. ETO Concn.—Vol. %: First Reading at the Start of Cycle	Av. ETO Concn.—Vol. %: At the End of Cycle	Difference Between Nominal 10% Concentration and Last Reading
Porous, fine cotton	7.6	6.1	3.9
Mixture of 1 and 3	7.9	6.3	3.7
Cotton gauge goods	8.1	7.0	3.0
Plastic and cellulosic materials	8.3	7.2	2.8
Heavy cotton goods	9.4	8.8	1.2

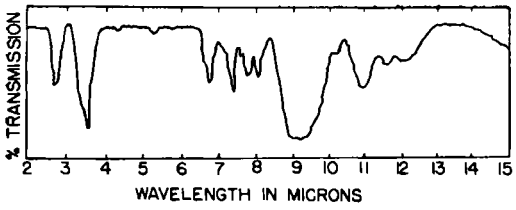

Fig. 6.—Infrared absorption of polyethylene glycol.

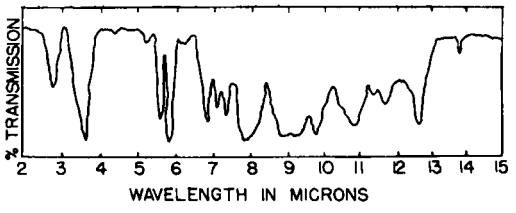

Fig. 7.—Infrared absorption of ethylene oxide polymerization products.

tory sterilizer. The first reading was invariably below the initial nominal 10% ETO concentration. The sudden increase in concentration at the ends of the cycles occurs during discharge, when the pressure drops from 30 p.s.i.g. to atmospheric, and some ETO is released by the load. Such a release was also observed by El Khishen in the fumigation of grain (4).

The ETO consumption varied with different products as summarized in Table I. ETO consumption appears to be related to the surface area of the product rather than the weight. The products which exhibited the highest rate of sorption initially, as shown by the decrease of ETO concentration from the initial 10% to the value given by the first reading (second column Table I), also consumed more ETO during the sterilization.

Polymerization Products of ETO.—ETO polymerization products, an oily viscous fluid of dark brown, are found in the expansion tank where the ETO–CO_2 mixture is stored at about 140° F. The residue was analyzed by the infrared method, and the spectra are similar to that of polyethylene glycol (Figs. 6 and 7). The additional bands at 5.5, 5.7, and 14 μ could be attributed to ethylene carbonates. The results agree with other reports (5, 6).

Summary and Discussion.—The rate of ETO sorption is rapid at the start of a sterilization cycle and decreases after 30 minutes to 1 hour. An increase of moisture content increases the rate of sorption as well as the amount of ETO removed from the gas by the product. The absorbed gas does not remain in the load, but a part is released when the pressure in the sterilizer decreases.

If the sterilization takes place *via* diffusion of ETO in the aqueous phase to bacteria as suggested by Mayr (3), then the rate of ETO absorption, most of which is probably dissolved by water in the load, and the amount of ETO removed from the gaseous phase, become a measure of the process efficiency. The removal is facilitated by forced diffusion and increased moisture content. Too much moisture, however, might cause a nonuniform distribution of ETO in the aqueous solution throughout the load, since a portion of ETO might be removed by the condensate on the outside of packages before the gas actually reaches the sterilization site. The importance of relative humidity in the vicinity of the spores and the danger of stripping the gas of ETO before the spores are reached has also been emphasized by Opfell and co-workers (7). An excessive amount of moisture would also decrease the ETO concentration in the aqueous phase, and thicker water film would hinder the diffusion of the sterilizing agent.

REFERENCES

(1) Siggia, S., "Quantitative Organic Analysis *via* Functional Groups," John Wiley & Sons, Inc., New York, N. Y., 1954, pp. 157–158.
(2) Perkins, J. J., and Lloyd, R. S., "Recent Developments in the Sterilization of Surgical Materials," The Pharmaceutical Press, London, 1961, p. 78.
(3) Mayr, G., *ibid.*, p. 96.
(4) El Khishen, S. A., *J. Sci. Food Agr.*, 1961, 71.
(5) Baize, T. H., *Ind. Eng. Chem.*, 53, 903(1961).
(6) Sokol, M., *Bull. Parenteral Drug Assoc.*, 15 (No. 6), 28 (1961).
(7) Opfell, J. B., Hohmann, J. P., and Latham, A. B., THIS JOURNAL, 48, 617(1959).

Notes

Synthesis of 3-Alkylsydnone-4-carboxylic Acids

By LEMONT B. KIER*, DEVINDRA DHAWAN, and MELVIN J. FREGLY

The synthesis of the first of the alkylsydnone carboxylic acids is reported. A brief review of the effects of 3-isopropylsydnone-4-carboxylic acid on urinary output and blood pressure is included.

DURING THE COURSE of our studies on structure-activity relationships, the authors have made a number of 3-alkylsydnones (1, 2) and 3,4-dialkylsydnones (3) in an effort to determine the effect of ring substituents on physical parameters and biological action. A significant influence on partition coefficient and convulsive activity by the 3-alkyl group of the monosubstituted sydnones (2) was noted. The influence of two alkyl groups on the sydnone ring, however, did not follow any predictable or readily apparent pattern in the compounds studied.

In an effort to learn more about the influence of ring substitution, we have begun a program of studying the effect on biological activity produced

Received June 27, 1963, from the Department of Pharmaceutical Chemistry, College of Pharmacy, University of Florida, Gainesville.
Accepted for publication August 8, 1963.
* Present address: College of Pharmacy, Ohio State University, Columbus.