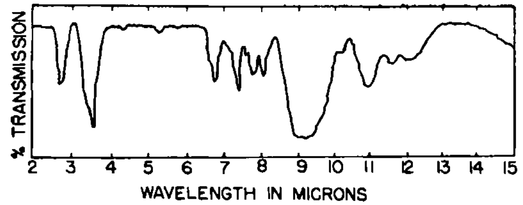

Fig. 6.—Infrared absorption of polyethylene glycol.

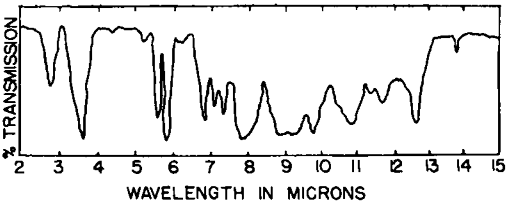

Fig. 7.—Infrared absorption of ethylene oxide polymerization products.

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

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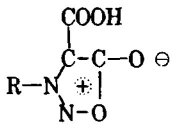
by introducing ring substituents other than short alkyl groups. This communication deals with the preparation and preliminary pharmacological study of two 3-alkylsydnone-4-carboxylic acids. A more detailed pharmacological evaluation and comparison with other sydnones is being published elsewhere (4).

Early attempts to prepare sydnone-4-carboxylic acids (I) included the oxidation of 3-phenyl-4-methylsydnone (5), the reaction of potassium cyanide with 3-phenyl-4-bromosydnone (6), and the reaction of carbon dioxide with the Grignard compound derived from 3-phenyl-4-bromosydnone (7). Kato and Ohta (8) successfully prepared the first sydnone-4-carboxylic acid—namely, 3-phenylsydnone-4 carboxylic acid. In their procedure they obtained the lithium compound by treating 3-phenyl-4-bromosydnone with *n*-butyl lithium. Subsequent treatment with carbon dioxide gave the acid.



(I)

We have modified this procedure slightly and have obtained the first reported 3-alkylsydnone-4-carboxylic acids—namely, the 3-isopropyl and the 3-*sec*-butyl acids. The two 4-bromosydnones were prepared by direct bromination of an acetic acid solution of the 3-alkylsydnones. The two bromosydnones were crystalline and stable compounds. Commercial *n*-butyl lithium in hexane was used to form the lithium compounds which were then carbonated *in situ* with dry ice. Both sydnone acids were crystalline and easily purified.

3-Isopropylsydnone-4-carboxylic acid as the sodium salt was studied along with other sydnones for their effects. A more detailed treatment of these findings will be published later (4). The 3-isopropylsydnone-4-carboxylic acid had only a moderate effect in raising urinary output and excretion rates of sodium, potassium, and chloride. The effect was less than for the alkyl and dialkylsydnones studied. There was no effect on the blood pressure of hypertensive rats compared with a moderate activity for the other sydnones tested. The acid was much less toxic than the other sydnones and produced none of the convulsions previously reported (1).

EXPERIMENTAL[1]

3-Isopropyl-4-bromosydnone.—A solution was prepared containing 5 Gm. of 3-isopropylsydnone (2) and 5 Gm. of fused sodium acetate in 40 ml. of glacial acetic acid. A 5-Gm. quantity of bromine was added to this with stirring and cooling. After 10 minutes, the solution was diluted with 400 ml. of water and extracted with ether. The ether solution was washed with sodium bicarbonate solution until neutral, then dried. The residue from the ether was crystallized from ethanol, m.p. 80 to 81.5°, yield 70%.

Anal.—Calcd. for $C_5H_7BrN_2O_2$: C, 28.98; H, 3.38; Br, 38.64; N, 13.52. Found: C, 29.00; H, 3.65; Br, 38.60; N, 13.48.

3-Isopropylsydnone-4-carboxylic Acid.—A solution of 10 ml. of *n*-butyl lithium (15% in hexane) was added dropwise to a suspension of 2 Gm. of 3-isopropyl-4-bromosydnone in 10 ml. of dry ether at −50° with stirring. After 30 minutes, the reaction mixture was poured over 5 Gm. of powdered dry ice. After all of the dry ice had sublimed, the solution was shaken with water. The aqueous phase was washed with ether and then acidified. The precipitate was filtered and crystallized from ethanol, m.p. 143–144°, yield 60%.

Anal.—Calcd. for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.28. Found: C, 42.01; H, 4.81; N, 16.25.

3-sec-Butyl-4-bromosydnone.—This compound was prepared as previously described. The material was crystallized from ethanol, m.p. 61 to 62.5°, yield 80%.

Anal.—Calcd. for $C_6H_9BrN_2O_2$: C, 32.58; H, 4.07; Br, 36.19; N, 12.67. Found: C, 32.74; H, 4.16; Br, 35.98; N, 12.80.

3-sec-Butyl-4-carboxylic Acid.—This compound was prepared as previously described. The material was crystallized from ethanol, m.p. 88–89°, yield 57%.

Anal.—Calcd. for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.67; N, 15.05. Found: C, 45.33; H, 6.04; N, 15.32.

REFERENCES

(1) Kier, L. B., Fox, L. E., Dhawan, D., and Waters, I. W., *Nature*, 195, 817(1962).
(2) Kier, L. B., and Dhawan, D., THIS JOURNAL, 51, 1136 (1962).
(3) *Ibid.*, 53, 83(1964).
(4) Fregly, M. J., Kier, L. B., and Dhawan, D., *J. Toxicol. Appl. Pharmacol.*, in press.
(5) Hashimoto, M., and Ohta, M., *Bull. Chem. Soc. Japan*, 31, 1048(1958).
(6) Kato, H., and Ohta, M., *ibid.*, 30, 210(1957).
(7) Ohta, M., and Kato, H., *J. Chem. Soc. Japan, Pure Chem. Sec.*, 78, 1653(1957).
(8) Kato, H., and Ohta, M., *Bull. Chem. Soc. Japan*, 32 283(1959).

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[1] All melting points are corrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.