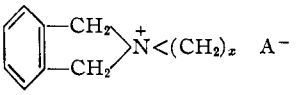
TABLE II

TRICYCLIC SPIROQUATERNARY SALTS  A⁻

Compounds 1, 3 and 5 were precipitated from a concentrated aqueous solution by the addition of isopropyl alcohol and ether. Compounds 2, 4 and 6 were dissolved in acetone and precipitated by the addition of water; when necessary, the solution was concentrated.

	x	A⁻	M.p., °C.	Yield, %	Formula	Analyses, % Calcd.	Found
1	6	Bromide	240–242[a]	44	$C_{14}H_{20}NBr$	C, 59.57; H, 7.15 N, 4.96; Br, 28.32	C, 59.33; H, 7.04 N, 4.88; Br, 28.56
2	6	Picrate	135–137		$C_{20}H_{22}O_7N_4$	N, 13.02	N, 12.85
3	7	Bromide	208–210	63	$C_{15}H_{22}NBr$	C, 60.80; H, 7.49 N, 4.73; Br, 26.98	C, 60.55; H, 7.70 N, 4.71; Br, 27.18
4	7	Picrate	135–137		$C_{21}H_{24}O_7N_4$	N, 12.61	N, 12.51
5	8	Bromide	204–206	60	$C_{16}H_{24}NBr$	C, 61.93; H, 7.80 N, 4.51; Br, 25.76	C, 62.20; H, 7.84 N, 4.49; Br, 25.82
6	8	Picrate	140–142		$C_{22}H_{26}O_7N_4$	N, 12.22	N, 12.18

[a] Melts with decomposition.

N,N,N',N'-Tetramethyl-4,4'-bipiperidinium Dibromide (III, R and R' = CH_3).—A solution of 4.0 g. of N,N'-dimethyl-4,4'-bipiperidine in 25 cc. of absolute ethanol in a pressure bottle was cooled and 9.5 g. of methyl bromide was added. After 24 hours at room temperature, the precipitate, 7.9 g. (100%) was filtered, dissolved in 25 cc. of water, the solution was treated with charcoal, filtered and the product precipitated with isopropyl alcohol; m.p. above 360°.

Anal. Calcd. for $C_{14}H_{30}N_2Br_2$: N, 7.26; Br, 41.39. Found: N, 7.21; Br, 41.58.

The dipicrate melted at 266–267° dec.

Anal. Calcd. for $C_{26}H_{34}O_{14}N_8$: N, 16.42. Found: N, 16.33.

4,4'-Bipiperidine.—This compound was obtained in 78% by hydrogenation of 4,4'-bipyridyl in the presence of platinum oxide.[12]

The dihydrochloride was obtained by the addition of ethereal hydrogen chloride to the base dissolved in methanol; m.p. above 360°.

Anal. Calcd. for $C_{10}H_{22}N_2Cl_2$: N, 11.62; Cl, 29.40. Found: N, 11.58; Cl, 29.26.

N,N - Tetramethylene - N',N' - tetramethylene - 4,4'-bipiperidinium Dibromide (IV, x = 4).—This hygroscopic compound was obtained in 48% yield by method B; m.p. 328–329° dec.

Anal. Calcd. for $C_{18}H_{34}N_2Br_2$: N, 6.39; Br, 36.46. Found: N, 6.40; Br, 36.44.

The dipicrate melted at 226–228°.

Anal. Calcd. for $C_{30}H_{38}O_{14}N_8$: N, 15.26. Found: N, 15.09.

N,N - Pentamethylene - N',N' - pentamethylene - 4,4'-bipiperidinium Dibromide (IV, x = 5).—By the use of method B, the yield of this compound was 40%; m.p. 356–357° dec.

Anal. Calcd. for $C_{20}H_{38}N_2Br_2$: N, 6.01; Br, 34.27. Found: N, 5.88; Br, 34.47.

The dipicrate melted at 264–266°.

Anal. Calcd. for $C_{32}H_{42}O_{14}N_8$: N, 14.70. Found: N, 14.65.

(12) C. R. Smith, THIS JOURNAL, **50**, 1936 (1928).

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF ENTOMOLOGY OF THE UNIVERSITY OF CALIFORNIA, CITRUS EXPERIMENT STATION, RIVERSIDE]

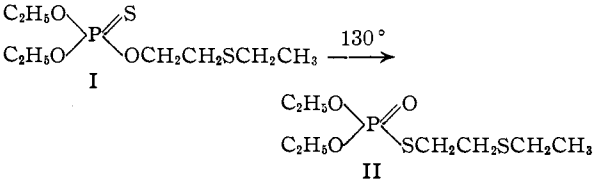
Isomerization of β-Ethylmercaptoethyl Diethyl Thionophosphate (Systox)[1-3]

BY T. R. FUKUTO AND R. L. METCALF

RECEIVED MARCH 20, 1954

The rearrangement of β-ethylmercaptoethyl diethyl thionophosphate to its isomer β-ethylmercaptoethyl diethyl thiophosphate has been investigated using P^{32}-labeled phosphate and paper chromatography and found to show first-order kinetics. The effect of solvents also has been investigated. Ethyl alcohol markedly increases the isomerization rate, chloroform to a lesser degree, while ethyl acetate, dioxane, methyl ethyl ketone, benzene and 2,2,4-trimethylpentane have little or no effect.

Recent reports[4,5] show that β-ethylmercaptoethyl diethyl thionophosphate (I, thiono isomer) isomerizes rapidly and cleanly to β-ethylmercaptoethyl diethyl thiophosphate (II, thiol isomer) at elevated temperatures.



I

II

Commercial Systox, a powerful systemic insecticide is a mixture of the two isomers. The physical and chemical properties of these isomers differ somewhat, and there are indications that the systemic activity and toxicity depend to a considerable ex-

(1) Paper No. 811, University of California Citrus Experiment Station, Riverside, Calif.

(2) Supported in part by generous grants from the U. S. Atomic Energy Commission, Contract AT (11-1) 34, Project 6, Dr. F. M. Turrell, Director; and from the Chemagro Corporation, New York, N. Y.

(3) Systox is the trade-name given by the Chemagro Corporation, New York, N. Y., for technical β-ethylmercaptoethyl diethyl thionophosphate.

(4) G. Schrader, "Die Entwicklung neur Insektizide auf Grundlage organischer Fluor und Phosphor-Verbindungen," Monograph No. 62, Angewandte Chemie, 1952.

(5) D. F. Heath, Paper presented to Third International Congress of Crop Protection, Paris, France, Sept., 1952.

tent on the relative amounts of the isomer. The solubility of I in water is approximately 20 p.p.m., as compared with 2,000 p.p.m. for II. I is considerably more stable to alkaline hydrolysis. Its half-life in 1 N sodium hydroxide is 75 minutes, compared with 0.85 minute for II. The concentrations of I and II required for 50% serum cholinesterase inhibition have been measured *in vitro* and found to be 10^{-5} and 3×10^{-6} M, respectively. This difference in cholinesterase inhibition is evident in the considerably greater mammalian and insect toxicity of II.[4] It would appear of interest from both practical and theoretical considerations to study the nature of this isomerization. Isomerizations similar to this have been described in the literature.[4-6] Trimethyl thionophosphate, diethyl *p*-nitrophenyl thionophosphate, diisopropyl *p*-nitrophenyl thionophosphate and ethyl *p*-nitrophenyl thionobenzenephosphonate all undergo similar types of isomerization. Analogous rearrangements in the carboxylic acid series also have been reported.[7] For example, γ-(2-methylpiperidino)-propyl thionobenzoate isomerizes rapidly and completely to the thiolbenzoate upon heating. Diphenyl thioncarbonate rearranges into the thiolcarbonate when heated at 280° for 90 minutes.

In order to elucidate the mechanism by which these thionophosphates rearrange to the thiophosphates, a kinetic study of the isomerization of I to II was undertaken. The difficulty in an investigation of this nature lies in the proper analysis of the isomeric mixture. This was overcome by the combined use of P^{32}-labeled thiono isomer and reversed-phase paper chromatography. On silicone-treated paper I and II can be separated very conveniently into two distinct zones with R_f values 0.07 and 0.75, respectively.[8] A graphic representation of a typical chromatogram is shown in Fig. 1. The relative amounts of the isomers can be determined by the total radioactivity present at each zone. By this method the rate of isomerization of I to II was determined at 59.5°, 78.2° and 95.0°. In order to study the effect of solvent on the isomerization, the rate in ethyl alcohol, chloroform, methyl ethyl ketone, dioxane, ethyl acetate, benzene and 2,2,4-trimethylpentane, at 37.2° also was measured.

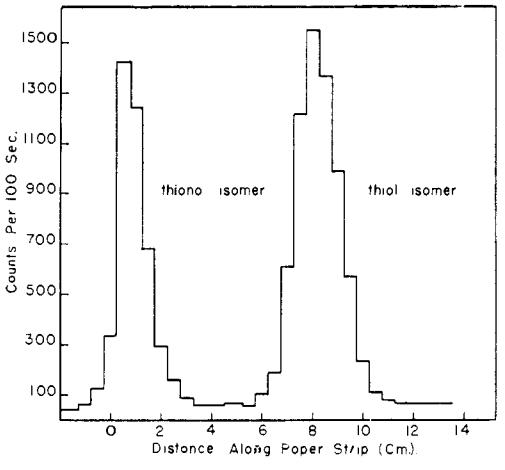


Fig. 1.—Typical chromatogram, showing thiono and thiol isomer zones.

Plots of time against log $1/f$ (f is the fraction of I in the mixture) gave straight lines over a range up to 60 to 70% isomerization and showed clearly that it is first order in nature. Typical plots are shown in Figs. 2 and 3, and it can be seen that the method is reliable. The values for the first-order rate of

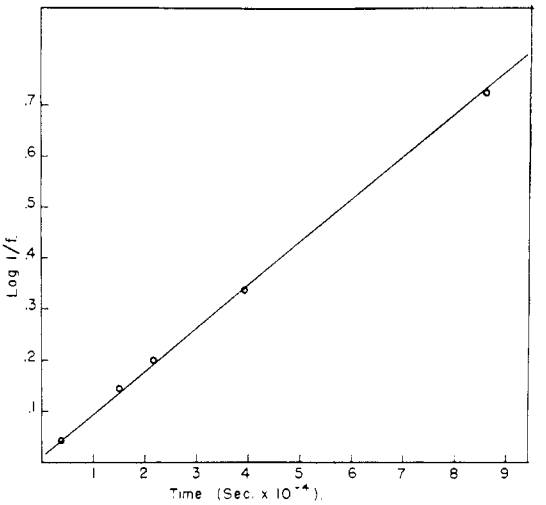


Fig. 2.—Rate of isomerization of thiono to thiol isomer at 95° (no solvent).

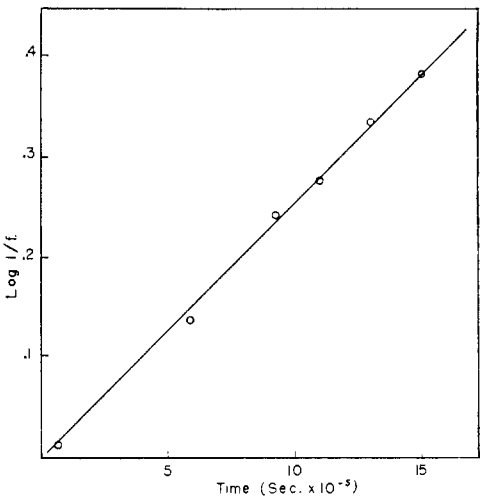


Fig. 3.—Rate of isomerization of thiono to thiol isomer in ethyl alcohol at 37.2°.

thermal isomerization, k_1, at 59.5°, 78.2° and 95.0° are 3.7×10^{-7}, 3.7×10^{-6}, 2.2×10^{-5} sec.$^{-1}$, respectively. The Arrhenius plot of log k_1 *vs.* $1/T$, shown in Fig. 4 for the three determined rate constants, produced a good straight line; this indicates further the reliability of the method. The activation energy was calculated to be 28 kcal./mole.

The degree of isomerization at 37.2° in the different solvents is shown in Table I.

It appears from these data that ethyl alcohol and chloroform have an accelerating effect on the re-

(6) (a) R. L. Metcalf and R. B. March, *J. Econ. Ent.*, **46**, 288 (1953); (b) W. G. Emmett and H. A. Jones, *J. Chem. Soc.*, **99**, 713 (1911).

(7) (a) S. A. Karjala and S. M. McElvain, THIS JOURNAL, **55**, 2966 (1933); (b) A. Schönberg and L. V. Vargha, *Ber.*, **63**, 178 (1930); *Ann.*, **483**, 107 (1930).

(8) R. L. Metcalf and R. B. March, *Science*, **117**, 527 (1953).

TABLE I

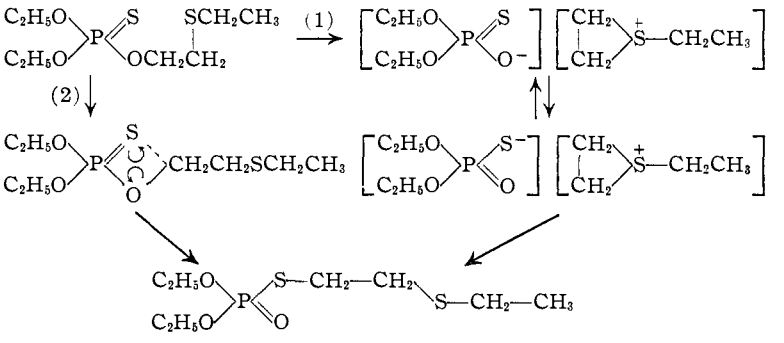
FIRST-ORDER RATE CONSTANTS k_1 FOR THE ISOMERIZATION OF THIONO TO THIOL ISOMER

Solvent	Temp., °C.	k_1, sec.$^{-1}$	Isomerization, % after 39 days
Ethyl alcohol	37.2	6.1×10^{-7}	56.0
Chloroform	37.2	8.0×10^{-8}	23.5
Methyl ethyl ketone[a]	37.2	.....	8.6
Dioxane[a]	37.2	.....	4.8
Ethyl acetate[a]	37.2	.....	4.3
Benzene[a]	37.2	.....	4.1
2,2,4-Trimethylpentane[a]	37.2	.....	1.8
None	37.2	1.8×10^{-8}[b]	6.0[b]
None	59.5	3.7×10^{-7}	..
None	78.2	3.7×10^{-6}	..
None	95.0	2.2×10^{-5}	..

[a] In these solvents the isomerization proceeded very slowly and the rate constants (k_1) were not calculated. The extent of isomerization after 39 days is given for comparison. [b] Calculated.

arrangement. The first-order constant k_1 in ethyl alcohol at 37.2° is greater than that at 59.5° without solvent. In dioxane, ethyl, acetate, benzene and 2,2,4-trimethylpentane, the rearrangement proceeds very slowly, and the constants were not calculated. From the activation energy, 28 kcal./mole, k_1, the rate of isomerization without solvent at 37.2° was calculated and found to be 1.8×10^{-8} sec.$^{-1}$, which gives a value of 6.0% isomerization after 39 days and is comparable to the figures given for methyl ethyl ketone, dioxane, ethyl acetate and benzene. The solvent 2,2,4-trimethylpentane appears to inhibit the isomerization to some extent.

It would seem, therefore, since the isomerization is first order and is enhanced by the more polar solvents, that the rearrangement proceeds through an ionic type intermediate. Two possible first-order mechanisms can be suggested from the data obtained so far.



The first mechanism, which suggests a sulfonium ion intermediate, is analogous to that described for the reactions of sulfur and nitrogen mustards.[9] In this case the rate-determining step is the formation of the sulfonium ion. An intermediate of this nature explains the relative ease with which I and other, similar thionophosphate esters which contain a β-alkylmercaptoethyl moiety isomerize, as compared to simple trialkyl thionosphosphates which cannot proceed through the sulfonium ion. Further work on the nature of this rearrangement is in progress.

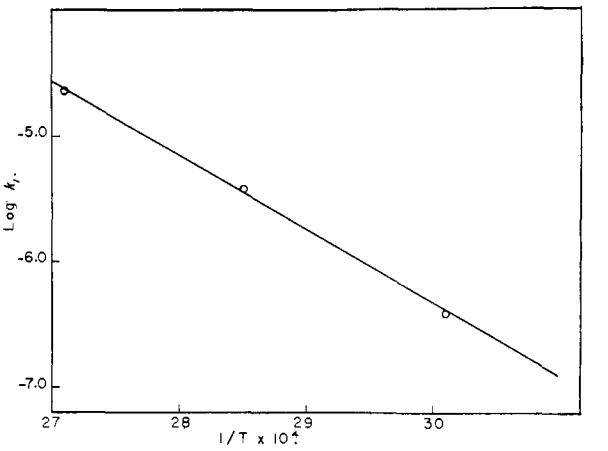


Fig. 4.—Arrhenius plot log k_1 *vs.* $1/T$.

Experimental

P^{32}-Phosphorus Thiochloride.—This compound was prepared according to the method described by Knötz,[10] using 6.5 g. of P^{32}-labeled phosphorus trichloride (10 mc., obtained from Tracerlab Inc., Boston, Mass.), 1.8 g. of sulfur and 0.18 g. of anhydrous aluminum chloride. The yield of phosphorus thiochloride, b.p. 60–63° (90 mm.), was 5.0 g., 62% of theoretical.

P^{32}-Diethoxythiophosphoryl Chloride.—This compound was prepared according to the procedure described by Schrader.[4] An ethanolic sodium ethylate solution was prepared by dissolving 1.39 g. of sodium in 25 ml. of absolute ethyl alcohol. This solution was added slowly to 5.0 g. of the labeled phosphorus thiochloride, the mixture being stirred with a mechanical stirrer and cooled in an ice–salt-bath during the addition. The mixture was then poured into 75 ml. of ice-water and extracted twice with methylene chloride. After the methylene chloride solution had been dried over calcium chloride and the solvent removed, the diethoxythiophosphoryl chloride was distilled, b.p. 74° (15 mm.). The yield was 5.0 g., 90% of theoretical.

P^{32}-β-Ethylmercaptoethyl Diethyl Thionophosphate (I).—The thiono isomer was prepared according to Schrader[4] by heating at 60° a mixture of 5.0 g. of diethoxythiophosphoryl chloride, 2.81 g. of β-hydroxyethyl ethyl sulfide,[11] 5.3 g. of anhydrous potassium carbonate, 0.106 g. of copper powder and 5 ml. of benzene. The product was not distilled. Chromatographic analysis showed that the radioactive constituent was 96.5% thiono isomer. The yield was 6.0 g., 88% of theoretical. The product had an initial activity of 2.42 counts per second per microgram.

P^{32}-β-Ethylmercaptoethyl Diethyl Thiophosphate (II).—Ninety-three milligrams of thiono isomer was heated in an open test-tube at 120–130° for 4 hours. Chromatographic analysis showed that the product had completely isomerized to the thiol isomer.

Paper Chromatography.—Tapered strips of paper, 19.0 cm. long, were dipped in a petroleum ether solution containing 5% of Dow Corning Silicone 550 fluid and allowed to dry. The developing solution used was prepared by taking the upper layer of a mixture consisting of (by volume) 10 parts 95% ethyl alcohol, 10 parts chloroform and 6 parts water. A mixture of P^{32}-labeled I and II was applied 2 cm. from the bottom of the paper strip and placed in a stoppered 8-inch test tube containing 2 ml. of the above solvent mixture. After the solvent had ascended to about 13 to 14 cm., the strip was removed and allowed to dry for

(9) (a) R. C. Fuson, E. C. Price and D. M. Burness, *J. Org. Chem.*, **11**, 475 (1946); (b) P. D. Bartlett and C. G. Swain, THIS JOURNAL, **71**, 1406 (1944); (c) P. D. Bartlett, S. D. Ross and C. G. Swain, *ibid.*, 1415 (1949).

(10) F. Knötz, *Osterr. Chem.-Ztg.*, **50**, 12809 (1949); *C. A.*, **43**, 9394 (1949).

(11) W. Steinkopf, J. Herold and J. Stohr, *Ber.*, **53**, 1007 (1920).

5 minutes. The radioactivity was determined by an end-window Geiger tube counter, the window of which was covered with a 1.5 mm.-thick aluminum disc in which was cut a slit 0.5 cm. wide and 3.0 cm. long. The dry paper strip was taped to an aluminum slide which fitted snugly against the disc and exposed 0.5 cm. of the entire width of the paper to the tube window. The paper strip was moved by 0.5-cm. increments under the Geiger tube, each position being counted for 100 seconds. In this manner, the zones for I and II were found at R_f values 0.07 and 0.75, respectively.[7] The relative amounts of isomers could then be determined quantitatively by summing the counts of all 0.5-cm. increments at the respective zones.

Determination of the rate of isomerization of I to II was carried out as follows: A small amount of P^{32}-labeled I was placed in a small standard-tapered test-tube and placed in a bath of appropriate temperature. The effect of solvent on the isomerization was studied in a similar manner, the solutions being made up to about 0.1 *M* in I. Since the isomerization followed first-order kinetics, it was not necessary to know the absolute concentrations. At various time intervals, samples were removed by a capillary pipet and transferred to the silicone-treated paper strips. Care was taken to deliver an amount such that the maximum count through the 0.5-cm. slit at any spot after development was not more than 25 counts per second. The strips were developed with the ethanol–chloroform–water mixture, the solvent front being allowed to rise to about 13 or 14 cm. After drying for 5 minutes the chromatograms were analyzed for activity in the manner described above, by moving the strip of paper by 0.5-cm. increment under the end-window Geiger tube (0.5 cm. slit); each increment was counted for 100 seconds. The following data (Table II) are typical of those obtained.

TABLE II

THERMAL ISOMERIZATION OF THIONO I TO THIOL II ISOMER AT 78.2°

Time, sec. × 10^{-4}	Total counts I	Total counts II	Ratio I/I + II	k_1, sec.$^{-1}$ × 10^6
0	4795	330	0.935	..
5.4	15850	4650	.773	3.5
8.3	1888	882	.682	3.8
14.0	3093	2407	.563	3.6
17.2	2360	2549	.481	3.9
22.7	4149	6725	.381	3.9

The methyl ethyl ketone and ethyl acetate were Eastman Kodak Co. white label grade, used without further purification. 2,2,4-Trimethylpentane was ASTM grade, used without further purification. Dioxane, chloroform and benzene were purified according to the methods described by Fieser,[12] b.p. 100–101°, 60° and 79°, respectively. The ethyl alcohol was U. S. Industrial Chemicals Co. absolute grade, used without further purification.

(12) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 358.

RIVERSIDE, CALIFORNIA

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE VETERANS HOSPITAL AND THE DEPARTMENT OF CHEMISTRY MUNICIPAL UNIVERSITY OF WICHITA]

The Synthesis of Dimethyl-(α-hydroxy-β-propiothetin) Hydrochloride and Related Compounds

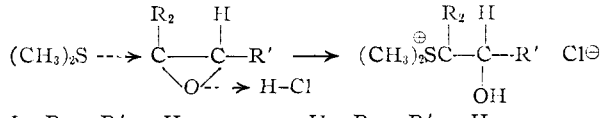
BY N. F. BLAU, J. W. JOHNSON AND C. G. STUCKWISCH

RECEIVED APRIL 8, 1954

Dimethyl-(α-hydroxy-β-propiothetin) hydrochloride has been synthesized through several routes. The reaction of dimethyl sulfide with epoxides has been studied. The acid-catalyzed reaction of dimethyl sulfide with β-lactones has been extended to β-butyrolactone.

As part of a continuing study of sulfonium compounds as potential lipotropic agents, we have investigated the synthesis of dimethyl-(α-hydroxy-β-propiothetin) hydrochloride (IIb).

In view of the earlier synthesis of dimethyl-β-propiothetin hydrochloride[1] by the reaction of dimethyl sulfide and hydrogen chloride with β-propiolactone, the nucleophilic displacement reaction of dimethyl sulfide on glycidic acid seemed particularly inviting. Bartlett and Small[2] have pointed out the resemblance between nucleophilic displacement reactions upon epoxides on the one hand and



Ia, R = R′ = H
b, R = H, R′ = CO_2H
c, R = H, R′ = $CO_2C_2H_5$
d, R = CH_3, R′ = CO_2CH_3

IIa, R = R′ = H
b, R = H, R′ = CO_2H
c, R = H, R′ = $CO_2C_2H_5$
d, R = CH_3, R′ = CO_2CH_3

β-propiolactone on the other. The present paper describes the reaction of dimethyl sulfide and hydrogen chloride on ethylene oxide (Ia), potassium glycidate (Ib), ethyl glycidate (Ic) and methyl β,β-dimethyl glycidate (Id). In all instances the corresponding sulfonium compounds were obtained, but the yields (10 to 20%) were much lower than with β-propiolactone. In the case of ethyl glycidate it was shown that epoxide ring cleavage by hydrogen chloride is a competing reaction. This is probably true for all the epoxides tried. The use of sulfuric acid or *p*-toluenesulfonic acid did not improve the yields.

The yield of potassium glycidate was improved by substituting methyl alcohol for ethyl alcohol[3] as the solvent.

β-Chlorolactic acid and ethyl β-chlorolactate gave unsatisfactory yields of the corresponding β-methylmercapto compounds when refluxed with an ethanol solution of sodium methylmercaptide.[4] β-Iodolactic acid and dimethyl sulfide failed to yield the dimethyl-(α-hydroxy-β-propiothetin) hydroiodide under a variety of conditions.

Acknowledgment.—The authors thank Dr. J. W. Dubnoff, Kerckhoff Laboratories of Biology, California Institute of Technology, for ascertaining the biochemical activity of a sample of crude racemic

(1) N. F. Blau and C. G. Stuckwisch, THIS JOURNAL, **73**, 2355 (1951).

(2) P. D. Bartlett and G. Small, Jr., *ibid.*, **72**, 4867 (1950).

(3) W. Freudenberg, *Ber.*, **47**, 2027 (1914).

(4) Koelsch encountered similar difficulties in the reaction of ethyl β-chlorolactate with potassium xanthate and sodium hydrosulfide, THIS JOURNAL, **52**, 1105 (1930).