

Sorbooses. II. Reaction Mechanism of Acetonization of 1,2-O-Isopropylidene- α -L-sorbopyranose¹

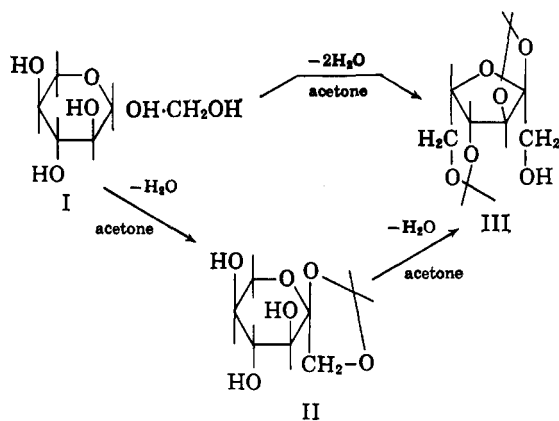
KANJI TOKUYAMA, ETSUKO HONDA, AND NOBUYUKI HŌKI

Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan

Received April 22, 1963

Acetonization of 1,2-O-isopropylidene- α -L-sorbopyranose (II) was studied kinetically. The reaction mechanism was proposed to be cyclic as follows: II \rightarrow [II]₂ \rightarrow diacetonized furanose (III) + L-sorbose (I), which in turn reverted to II.

The acetonization of L-sorbose (I) is a very important reaction for the production of 1-ascorbic acid. It has been known that the reaction in acetone solution without acids gave 1,2-O-isopropylidene- α -L-sorbopyranose (II)² and with acids gave 2,3:4,6-di-O-isopropylidene- α -L-sorbofuranose (III), along with 2,3-O-isopropylidene- α -L-sorbofuranose (IV) as a by-product.³ Recent results from our laboratory,⁴ which demonstrated the formation of the pyranoside (II) and its subsequent transformation into furanoside (III) during the acid-catalyzed acetonization of I, prompted us to investigate the reaction mechanism of the acid-catalyzed acetonization of II.



To determine the rate order of acid-catalyzed acetonization of the pyranoside (II), a convenient method might be titration of the acetone of III formed during the course of the reaction. However, several known methods^{5,6} gave poor results in our hands, because the loss of the acetonized sugars was too great on removal of the solvent from an alkaline solution. Thus we decided to use Karl Fischer's method⁷ of titrating water formed during the reaction. Although it appears that the formation of water due to dimerization of the solvent may disturb the titration, dimerization was only observed after the reaction of acetonization was over, as shown in Fig. 1. Therefore, reaction of the pyranoside (II) in acetone with a catalytic amount of sulfuric acid was followed successfully by the latter method. The results are shown in Fig. 1 and 2. Plots of concentration function $x/a(a-x)$ against time were linear as shown in Fig. 3, except that it showed a slight downward curvature at the final stage. Therefore, it was

(1) Part I: K. Tokuyama, M. Kiyokawa, and N. Hōki, *Bull. Chem. Soc. Japan*, **36** (11) (1963).

(2) H. Ohle, *Ber.*, **71**, 762 (1938).

(3) T. Reichstein, *Helv. Chim. Acta*, **17**, 3111 (1934).

(4) S. Sato, private communications.

(5) R. A. Kramarov, *Farmatsiya* (Sofia), **12**, 18 (1940).

(6) J. M. R. Romers and G. G. Trigo, *Chim. Ind. (Paris)*, **86**, 256 (1961).

(7) K. Fischer, *Z. angew. Chem.*, **48**, 394 (1935).

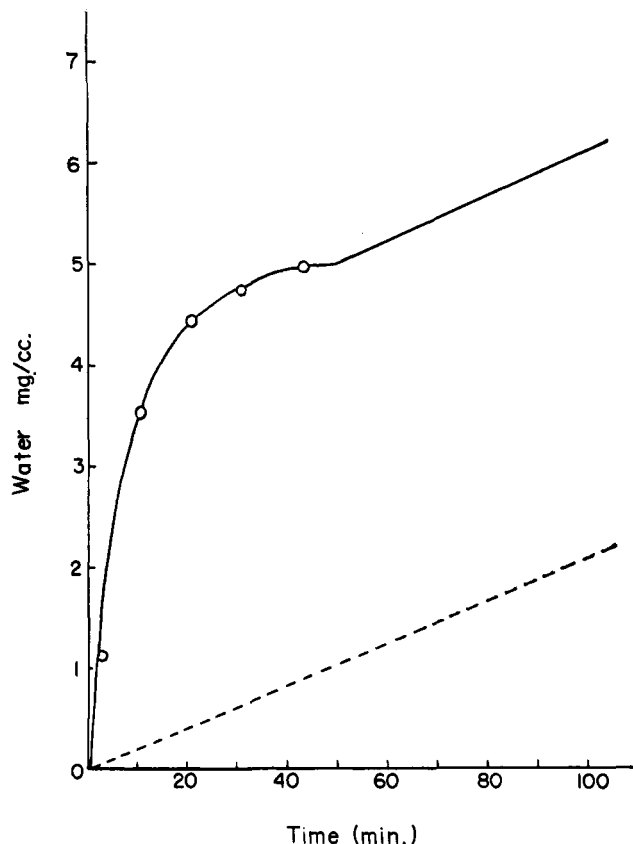


Fig. 1.—Increase of water in acid-catalyzed acetonization of II at 20°: II, 30.2, and sulfuric acid, 1.16 moles/l. ———, increase of the water; - - - -, increase of the water in absence of II.

considered that the reaction was second order and the rate was proportional to the square of the concentration of the reactant, II. The second order in pyranoside (II) suggests that two molecules of the pyranoside (II) participate in the sequence leading to the rate-determining step. Presumably the two molecules of the pyranoside (II) were converted into a dimer [II]₂. The rate constant also was found to be proportional to the concentration of sulfuric acid. These constants are shown in Table I.

Gas chromatographic investigations at the end of the reaction showed three products, II, III, and IV. Therefore, the reaction process was probably *via* a pathway of II \rightarrow III \rightarrow IV or II \rightarrow IV \rightarrow III.

The reaction rates of III \rightarrow IV and IV \rightarrow III in acetone with sulfuric acid were measured. They were carried out by titrating the water increase or decrease, but the reactions were too fast to allow measurements of the rates in the concentrated acid solution employed above. Since changes from III to IV and the reverse

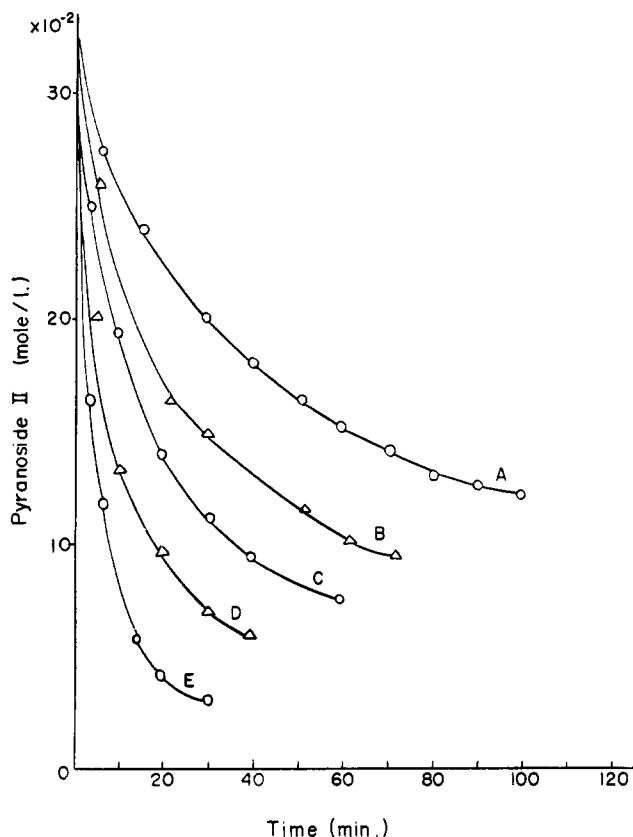


Fig. 2.—Decrease of II in acid-catalyzed acetonization of II at 30°: sulfuric acid (A) 0.44, (B) 0.58, (C) 0.74, (D) 0.85, and (E) 1.15 moles/l.

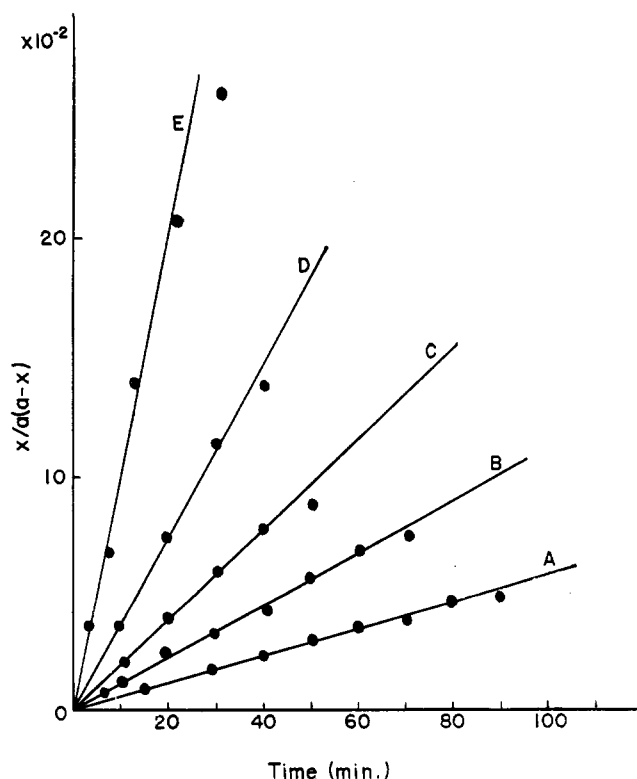


Fig. 3.—Values of concentration function against time at 30°: sulfuric acid (A) 0.44, (B) 0.58, (C) 0.74, (D) 0.85, and (E) 1.15 moles/l.

were considered to be very fast equilibria, they were not rate-determining steps in the total pathway. Since the total rate was second order by measurement of the

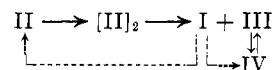
TABLE I

THE RATE CONSTANTS OF THE REACTION OF II \rightarrow III		
Reaction temp., °C.	Sulfuric acid, mole/l.	Rate constants $\times 10^{-4}$, l./mole sec.
20	0.45	0.68
20	0.58	1.27
20	0.72	2.00
20	0.89	4.50
20	1.16	12.17
30	0.44	1.00
30	0.58	1.83
30	0.74	3.43
30	0.85	6.50
30	1.15	17.17
40	0.45	2.00
40	0.59	3.83
40	0.73	5.83
40	0.86	11.37

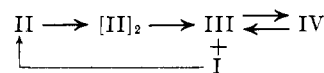
water, if the reaction process is assumed to be the pathway of II \rightarrow IV \rightarrow III, the reaction of II \rightarrow IV would be a second-order reaction in which water must be formed. However, the formation of water can not be expected during the course of II \rightarrow IV. Therefore, the reaction process of acetonization should be *via* the pathway of II \rightarrow III \rightarrow IV. In this pathway the reaction of II \rightarrow III is second order and the reaction of III \rightarrow IV reaches equilibrium very fast. As the reaction progresses, equilibrium will consume the water produced by the second-order reaction. This is why the plots of the concentration function showed a slight downward curvature on the final stage, as shown in Fig. 3.

The results of the reactions of III \rightarrow IV and IV \rightarrow III in slightly acid solution were shown in Fig. 4. They seem to be zero order at the initial stages, but further studies would be required for complete interpretation.

Thus the reaction process of acetonization of II is considered as the following.



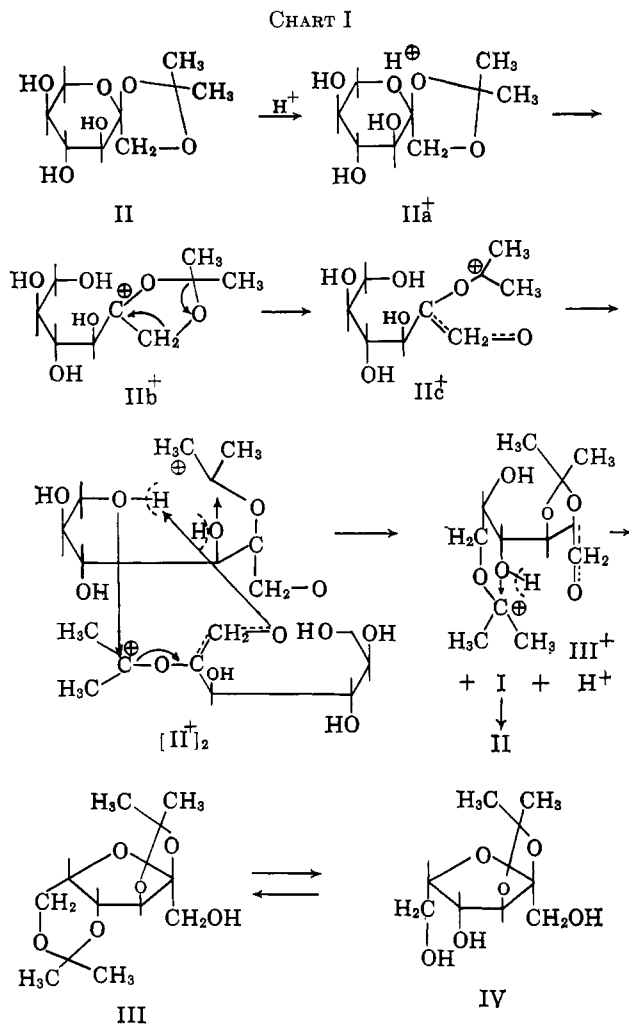
If this proposal is reliable, sorbose (I) must be detected during the course of the reaction. As expected, positive evidence was obtained by a Fehling's test of the reaction mixture. I also was noticed by paper partition chromatography of the reaction mixture. The rate of decrease of I in the reaction mixture by Bertrand's method⁸ was obtained as zero order as shown in Fig. 4. Because, if I is directly transformed into IV, the over-all rate of the reaction becomes zero order, which is inconsistent with the aforementioned results. The reaction process of acetonization of the pyranoside (II) was suggested by us as the following.



As indicated, acetonization of the pyranoside (II) is a cyclic pathway. When this cycle starts from I, the reaction is the same as acetonization of I. It also was found that acetonization of I does not take a simple pathway, such as I \rightarrow IV \rightarrow III.

Considering our reaction mechanisms, it may be expected that the furanoside (III) is prepared from the

(8) G. Bertrand, *Bull. soc. chim. France*, **35**, 1285 (1906).



pyranoside (II) in the absence of acetone. When I, II, III, or IV was allowed to stand in dioxane containing 2% of sulfuric acid for a long time, all solutions except that of IV exhibited the same absorption band at 280 μm . The bands disappeared by making the dioxane solutions alkaline and only the starting sugars were detected in the solutions. So, it seems likely that the absorption band at 280 μm is due to the protonated forms of the sugars. In the acidic dioxane solution with a higher concentration of the pyranoside (II), the solution turned from colorless to violet *via* pink, and labile crystals separated, which then polymerized to a black tar. The changes in ultraviolet absorption spectra of the solutions are shown in Fig. 5. In the first stage the absorption band at 280 μm appeared and then an absorption band at 225 μm appeared. The labile crystals exhibited both bands. If the reaction mixture was made alkaline at the stage that the second band at 225 μm appeared, I, II, III, and IV were identified. From these results it seems reasonable that the protonated form of the pyranoside (II^+) exhibits the first absorption band at 280 μm and the protonated form of the dimer $[\text{II}^+]_2$ exhibits the second absorption band at 225 μm . The labile crystals would be $[\text{II}^+]_2$, but it was too labile to be isolated in a pure state for further investigations. From the aforementioned, it may be considered that the pyranoside (II) is converted into the pyranoside ion (II^+) and then dimerized to $[\text{II}^+]_2$.

On the basis of all data presented, the mechanism of

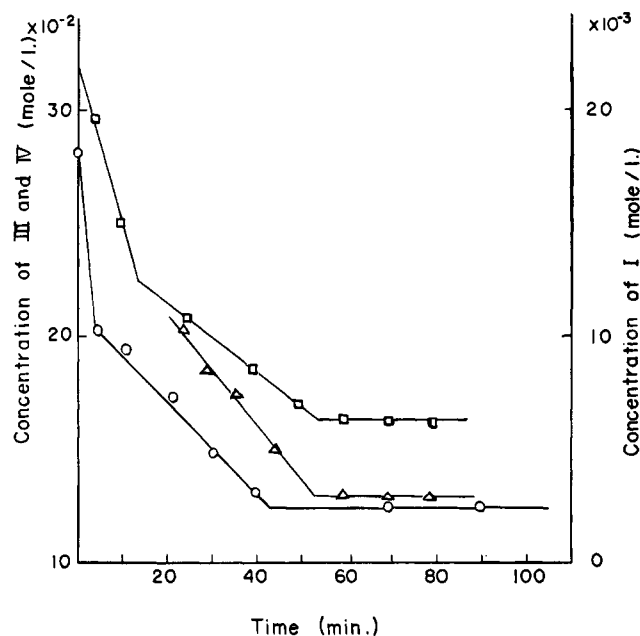


Fig. 4.—Results of the reactions of $\text{III} \rightarrow \text{IV}$, $\text{IV} \rightarrow \text{III}$, and $\text{I} \rightarrow \text{II}$ in acid solution. \circ — \circ —, decrease of III in the reaction of $\text{III} \rightarrow \text{IV}$ at 30° (sulfuric acid, 0.0078 mole/l.); \square — \square —, decrease of IV in the reaction of $\text{IV} \rightarrow \text{III}$ at 30° (sulfuric acid, 0.0080 mole/l.); \triangle — \triangle —, decrease of I in acetonization of II at 30° (sulfuric acid, 0.58 mole/l.).

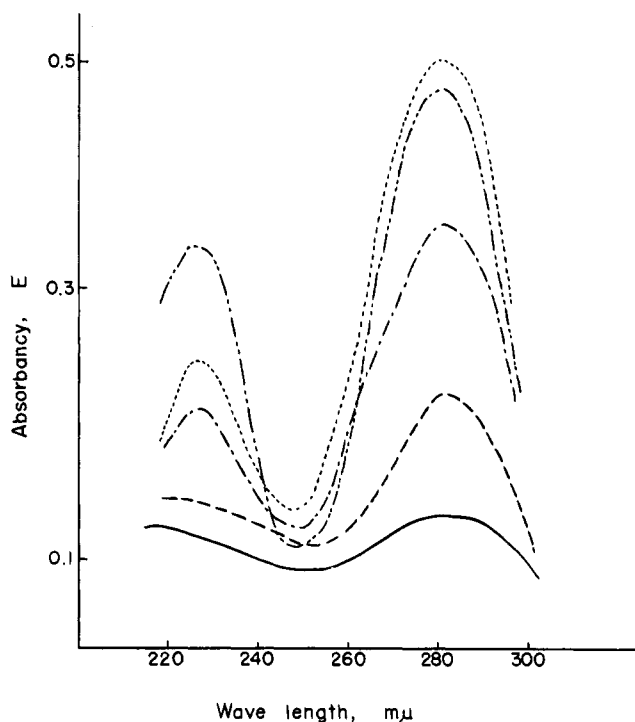


Fig. 5.—Changes in ultraviolet absorption spectra of the reaction mixture of II (0.10 g.), dioxane (1.86 g.), and sulfuric acid (0.038 g.) at 30°. —, after 11 min.; ---, after 22 min.; - · - · -, after 38 min.; · · · · ·, after 49 min.; - - - - -, after 60 min.

acetonization of the pyranoside (II) is summarized in Chart I.

Experimental

Materials.—1,2-O-Isopropylidene- α -L-sorbofuranose (II), m.p. 142°, $[\alpha]^{20D} -85.2^\circ$ (*c* 1.503, water)²; 2,3,4,6-O-isopropylidene- α -L-sorbofuranose (III), m.p. 78°, $[\alpha]^{18.5D} -18.1^\circ$ (*c* 1.380, acetone)³; and 2,3-O-isopropylidene- α -L-sorbofuranose (IV),

m.p. 91°, $[\alpha]^{20D} +7.02^\circ$ (c 1.42, water),⁹ were prepared by the usual methods.

Kinetic Measurements of the Reactions of II \rightarrow III, III \rightarrow IV, IV \rightarrow III, and I \rightarrow II.—Sulfuric acid was weighed into 50 g. of acetone in a standard flask which was then placed in a thermostat at the appropriate temperature. To the solution was added about 0.4 g. of the water to keep the water in the solution constant, and then 5 g. of the sugars. (1) Samples (1 ml.) were titrated by Karl Fischer's method.⁷ The data are shown in Fig. 1, 2, 3, and 4, and Table I. (2) Samples (1 ml.) were titrated by Bertrand's method.⁸ The data are shown in Fig. 4 and Table II.

TABLE II

THE RATE CONSTANTS OF THE REACTION OF I \rightarrow II		
Reaction temp., °C.	Sulfuric acid, mole/l.	Rate constants $\times 10^{-5}$, mole/l. sec.
30	0.71	0.61
40	0.73	3.20

After the reactions were over, the solutions were poured into a saturated solution of sodium carbonate to make the solution alkaline, evaporated to dryness *in vacuo*, and extracted with acetone. Evaporation of the solvent gave a brown sirup. (1) II, III, and IV were obtained from the sirup prepared from the

(9) T. I. Temnikova and V. V. Sklyarava, *Zh. Prikl. Khim.*, **21**, 1131 (1954); *Chem. Abstr.*, **49**, 2952 (1955).

reaction of II \rightarrow III, and were detected by gas chromatography (conditions: column, 1.5 m. \times 6 mm. silicone 550 on Chrom-sorb.; temp., 200°; flow rate, hydrogen 100 ml./min.; retention times of the sugars: II, 13.25 min., III, 16.5 min., IV, 20.5 min.). (2) III and IV were obtained from the sirup prepared from the reactions of III \rightarrow IV and IV \rightarrow III, and were detected by gas chromatography.

The reaction of 0.1 g. of II, 0.038 g. of sulfuric acid, and 1.86 g. of dioxane was allowed to stand at 30°. The color of the solution changed from colorless to pink (after 30 min.) and then violet (after 1 hr.). After about 30 min., crystals started to form, which then polymerized to a black tarry product. After 1 hr., the reaction mixture was made alkaline, evaporated to dryness *in vacuo*, and extracted with chloroform. From the extract, II, III, and IV were detected by gas chromatography and, from the residue, I, II, III, and IV were detected by paper chromatography (*n*-BuOH-AcOH-H₂O, 4:1:5, ascending method). In order to reveal the position of the sugars, the paper was sprayed with 1 *N* hydrochloric acid, dried at room temperature, sprayed again with benzidine solution,¹⁰ and heated at 90–95° for 5–10 min. The sugars appeared as brown spots. The R_f values were I, 0.25; II, 0.65; III, 0.88; IV, 0.68.

Acknowledgment.—The authors are deeply grateful to Dr. Ken'ichi Takeda, Director, and Dr. Kaname Hamamoto, assistant director of this laboratory, for encouragement and advice throughout this work.

(10) R. H. Horrocks, *Nature*, **164**, 144 (1949).

Diacyl Peroxide-Olefin Reactions. Epoxidation of Tetramethylethylene by an Aroyl Peroxide¹

FREDERICK D. GREENE AND WALDEMAR ADAM

Department of Chemistry, Massachusetts Institute of Technology, Cambridge 39, Massachusetts

Received August 19, 1963

Reaction of *m,m'*-dibromobenzoyl peroxide and tetramethylethylene in benzene at 45° affords tetramethylethylene oxide (72%), *m,m'*-dibromobenzoic anhydride (75%), *m*-bromobenzoic acid (13%), and a small amount of allylic *m*-bromobenzoates. Oxygen-18 labeling experiments show that the tetramethylethylene oxide oxygen is derived exclusively from the peroxygen bond of the peroxide. From kinetic evidence, utilizing the stable free-radical galvinoxyl, it is concluded that the reaction proceeds by direct reaction between olefin and peroxide; contributions from free-radical chain processes are negligible.

Reaction between *m,m'*-dibromobenzoyl peroxide and *p,p'*-dimethoxy-*trans*-stilbene has been shown to afford a mixture of *meso*- and *d,l*-dihydroanisoin bis-*m*-bromobenzoates.² The reaction occurs principally *via* a nonchain, bimolecular reaction between peroxide and olefin. In this paper, evidence is presented for a direct reaction between this diacyl peroxide and a purely aliphatic olefin, tetramethylethylene, in which, in marked contrast to the cited case, the major course of the reaction is single oxygen atom transfer from peroxide to olefin.

Results

Products.—Tetramethylethylene and *m,m'*-dibromobenzoyl peroxide undergo a moderate reaction at 45° in benzene to give tetramethylethylene oxide (72%), *m,m'*-dibromobenzoic anhydride (75%), *m*-bromobenzoic acid (13%), and a neutral oil, assigned the composition of a mixture of the allylic esters, 2,3-dimethyl-but-3-ene-2-yl *m*-bromobenzoate and 2,3-dimethyl-but-2-ene-1-yl *m*-bromobenzoate on the basis

(1) This work was supported by the research program of the Atomic Energy Commission under Contract No. AT-(30-1)-905. Reproduction is permitted for any purpose of the United States Government.

(2) F. D. Greene, W. Adam, and J. E. Cantrill, *J. Am. Chem. Soc.*, **83**, 3461 (1961).

of the spectroscopic, hydrolytic, and hydrogenolysis data given in the Experimental section.

Kinetics.—Rate studies were conducted in benzene in the absence of oxygen. By use of olefin in excess, the rate of the peroxide-olefin reaction exceeded the rate of unimolecular decomposition of peroxide by more than 100-fold. The kinetic data are summarized in Table I.

TABLE I

REACTION OF *m,m'*-DIBROMOBENZOYL PEROXIDE (P) WITH TETRAMETHYLETHYLENE (TME) IN BENZENE AT 44.8°

Run no.	Reactants, $M \times 10^2$	$k_2 \times 10^5 M^{-1} \text{sec.}^{-1}$	$k_1 \times 10^5 \text{sec.}^{-1}$
	P TME	G ^a	P ^b G ^{a,c}
1	1.00 0	0	<i>d</i>
2	1.00 0	0.095	<i>e</i>
3	0 100	0.95	23.2
4	5.00 111	0	4.71
5	5.00 97	0	4.70
6	5.00 47	0	4.72
7	5.00 100	0.95	5.13
8	5.00 112	0.90	4.83
9	5.00 100	0	1.0 ^f
10	5.00 100	0	9.1 ^g

^a Galvinoxyl, see ref. 2 and 3. ^b Titrimetric. ^c Spectroscopic. ^d k_1 for peroxide decomposition = $1.84 \times 10^{-7} \text{sec.}^{-1}$. ^e $k_1 = 1.98 \times 10^{-7} \text{sec.}^{-1}$. ^f At 30.3°. ^g At 54.8°.