[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

# Light-catalyzed Organic Reactions. I. The Reaction of Carbonyl Compounds with 2-Methyl-2-butene in the Presence of Ultraviolet Light

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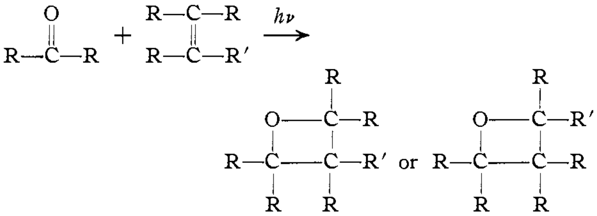
RECEIVED MARCH 3, 1954

The trimethylene oxides resulting from the ultraviolet irradiation of 2-methyl-2-butene with benzaldehyde, acetophenone and *n*-butyraldehyde were isolated and their structures investigated by identifying the carbonyl compounds formed by acid-catalyzed cleavage. The 2-methyl-2-butene–benzaldehyde product cleaved to form benzaldehyde and acetaldehyde, showing that the product was I. The 2-methyl-2-butene–acetophenone product was hydrolyzed to acetophenone and acetaldehyde. The product, therefore, was IV. The only carbonyl compound formed by the cleavage of the *n*-butyraldehyde–2-methyl-2-butene product was *n*-butyraldehyde. Although the structure was not definitely established, the cleavage in only one direction was best explained by assuming that the product was V. A radical mechanism for the formation of these compounds is advanced. The substituted trimethylene oxides reported here were not reduced by lithium aluminum hydride and did not react with phenyllithium.

## Introduction

Paterno[2] has reported that trimethylene oxides are formed when mixtures of tri- or tetrasubstituted olefins and aldehydes or ketones are exposed to sunlight.

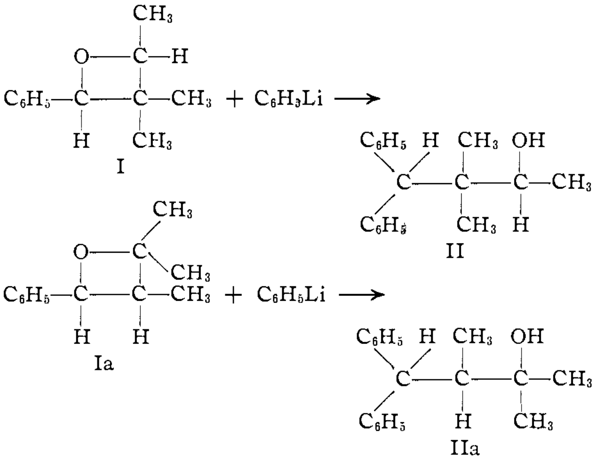


Since Kharasch[3] has shown that aldehydes react with monosubstituted terminal olefins in the presence of light or peroxides to form ketones, and because no general procedure has been developed for synthesizing highly substituted trimethylene oxides, it was of interest to reinvestigate Paterno's reaction and to determine the structures of the products obtained. Three substances, the products formed by ultraviolet irradiation of benzaldehyde with 2-methyl-2-butene, acetophenone with 2-methyl-2-butene and *n*-butyraldehyde with 2-methyl-2-butene, were prepared and investigated.

## Discussion

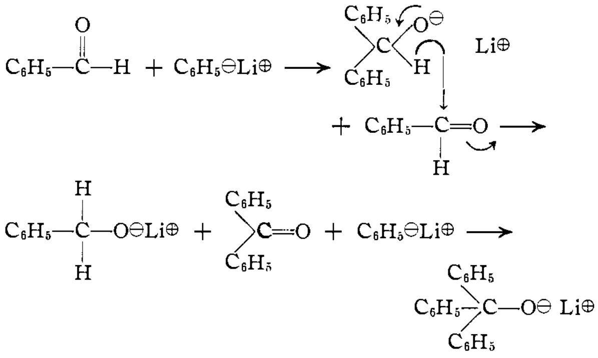
**Benzaldehyde–2-Methyl-2-butene Irradiation Product.**—The benzaldehyde–2-methyl-2-butene irradiation product (I) was obtained in pure form by repeated fractional distillation of the reaction mixture at low pressures.

Phenyllithium has been reported[4] to react with trimethylene oxide to give an 85% yield of 3-phenylpropanol. To prove the structure of the irradiation product, this reaction was applied to I. It was assumed that the phenyl anion would attack at the less substituted $\alpha$-carbon by analogy to the results obtained with ethylene oxides.[5] Two different alcohols II or IIa would be expected to be formed, depending on whether the irradiation product was I or Ia.



I II Ia IIa

Neither alcohol could be isolated from the reaction mixture. Chromatography resulted in the isolation of only biphenyl and a small amount of triphenylcarbinol. The latter compound was believed to have been formed by a Cannizzaro reaction of traces of benzaldehyde[6] either initially present or formed by the decomposition of I during the reaction.



Since reductions with lithium aluminum hydride are relatively unsusceptible to steric effects, the action of this reagent on I was investigated. It was assumed that the hydride ion would attack at the less substituted $\alpha$-carbon, as was found to be the case with ethylene oxides.[7] No detectable reaction took place even at 140°. Essentially all of the original trimethylene oxide was recovered.

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[1] Part of a program of research supported by a grant from the Godfrey L. Cabot Fund of M.I.T., Publication No. 36, M.I.T. Solar Energy Conversion Project.

[2] E. Paterno and G. Chieffi, *Gazz. chim. ital.*, **39**, 341 (1909).

[3] M. S. Kharasch, W. H. Urry and B. M. Kuderna, Jr., *J. Org. Chem.*, **14**, 248 (1949).

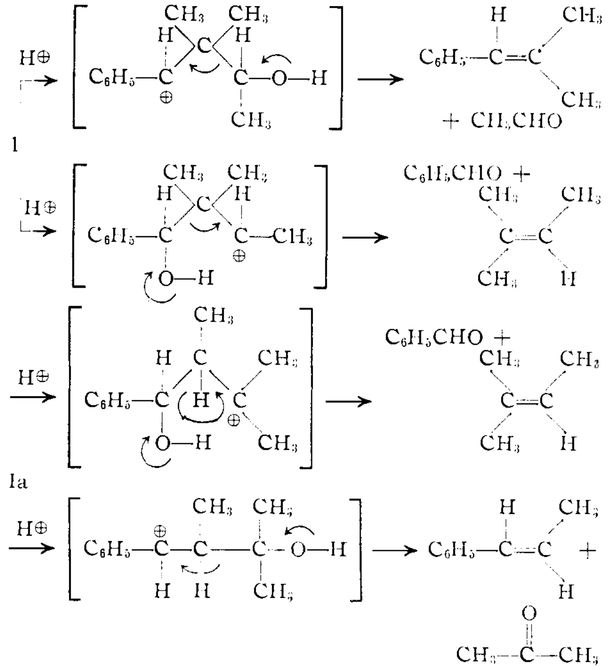
[4] S. Searles, THIS JOURNAL, **73**, 124 (1951).

[5] S. Cristol and R. F. Helmreich, *ibid.*, **74**, 4083 (1952).

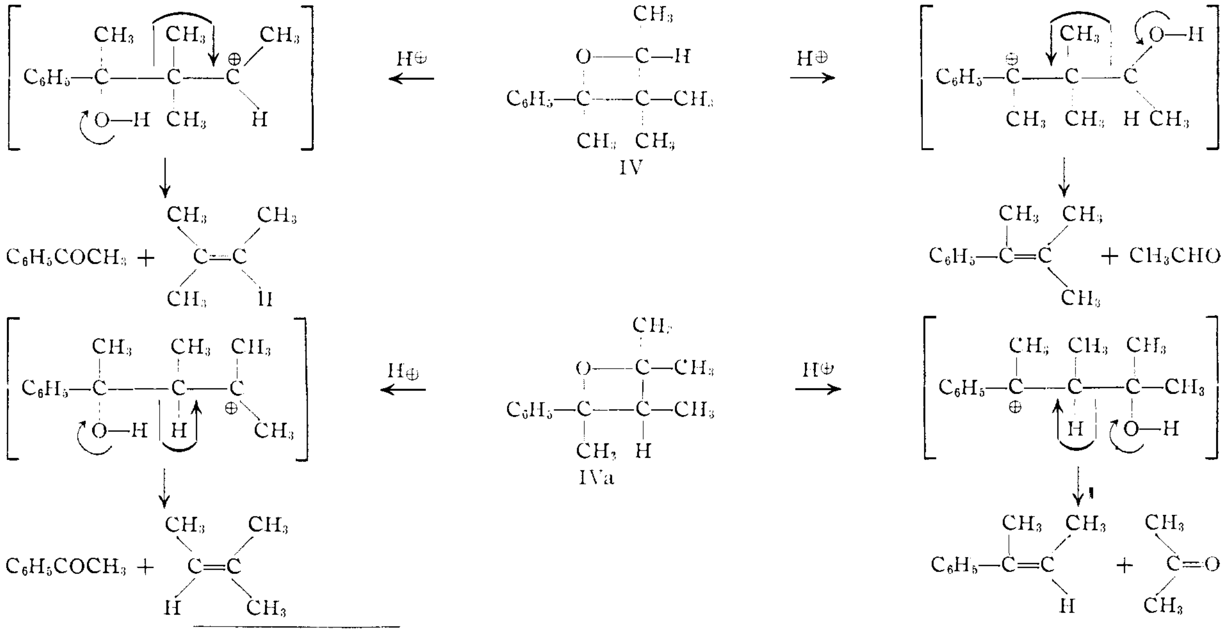
[6] Hg. Frey, *Ber.*, **28**, 2516 (1895).

[7] L. W. Trevoy and W. G. Brown, THIS JOURNAL, **71**, 1675 (1949).

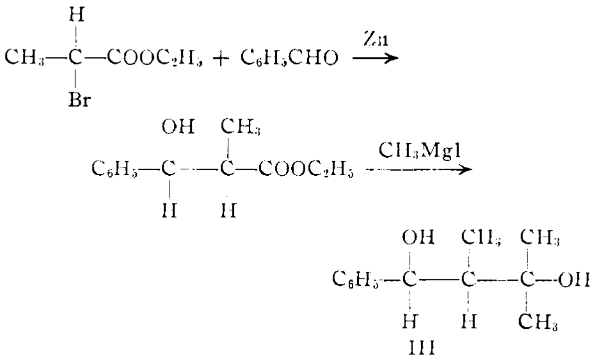
Di-tertiary-1,3-diols are known to undergo acid-catalyzed cleavage into ketones and olefins.[8] Since the reactions of unsubstituted trimethylene oxide are very susceptible to acid catalysis,[9] it was considered possible that highly substituted trimethylene oxides might cleave in the same manner as di-tertiary-1,3-diols, even if the $\alpha$-carbons were not completely substituted. Isomer I could cleave in two directions, forming acetaldehyde and benzaldehyde, as well as olefins. Isomer Ia should give olefins together with acetone and benzaldehyde.



The trimethylene oxides reported in this paper indeed were cleaved to olefins and carbonyl compounds by mineral acids.



Acetaldehyde and benzaldehyde were identified among the cleavage produces of I but no acetone was detected. Because the possibility existed that some Ia was also present but that it cleaved only in the direction giving benzaldehyde, 2,3-dimethyl-4-phenylbutane-2,4-diol (III), the diol corresponding to Ia, was synthesized. The cleavage of III under conditions identical with those employed for I resulted in the formation of acetone



Since the acetaldehyde was identified by its 2,4-dinitrophenylhydrazone, the possibility still remained that acetone was actually formed but that its 2,4-dinitrophenylhydrazone is more soluble in ethanol than is that of acetaldehyde. The acetone 2,4-dinitrophenylhydrazone might then have been left entirely in the mother liquor when the mixed 2,4-dinitrophenylhydrazones were recrystallized. A mixture of I and a small amount of III when cleaved under the same conditions gave a recrystallized 2,4-dinitrophenylhydrazone melting over a wide range. Hence, it was concluded that the irradiation product was entirely 1,2,2-trimethyl-3-phenyltrimethylene oxide (I).

**Acetophenone–2-Methyl-2-butene Irradiation Product.**—The acetophenone–2-methyl-2-butene irradiation product IV was obtained in pure form by fractional distillation under diminished pressure.

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(8) J. English and Brutcher, THIS JOURNAL, **74**, 4279 (1952).

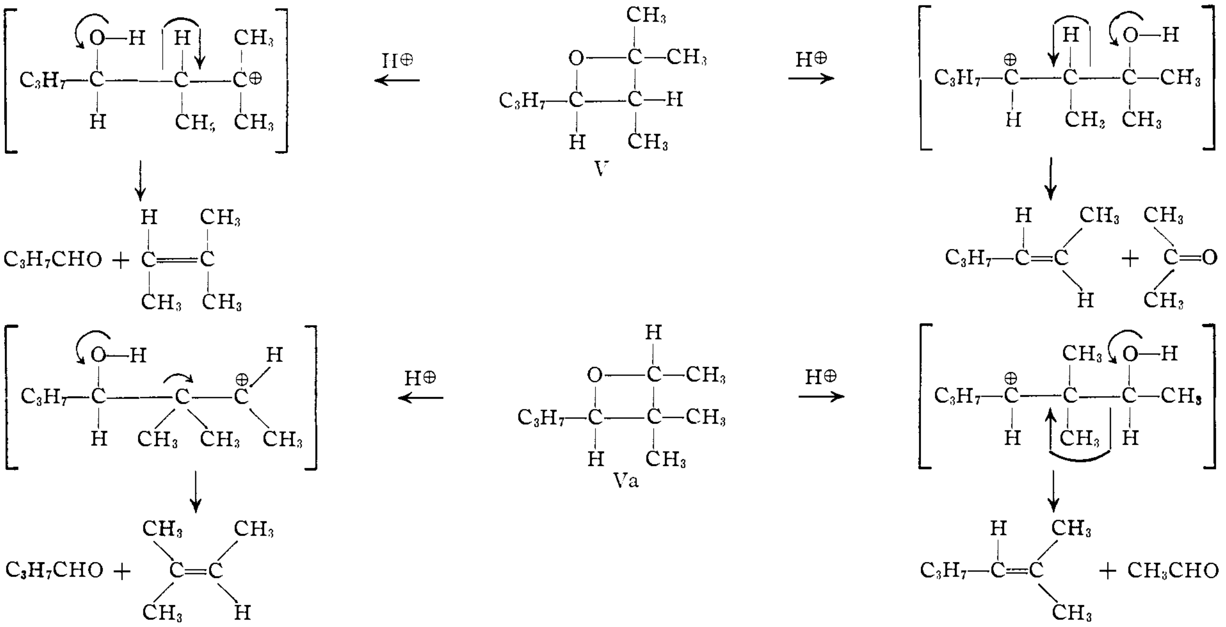
(9) S. Searles, *ibid.*, **73**, 4515 (1951).

When IV was cleaved under the same conditions employed for I, acetophenone and acetaldehyde were the only carbonyl compounds formed. This indicated that IV was entirely 1,2,2,3,4-tetramethyl-1-phenyltrimethylene oxide and that none of the isomer IVa, which would cleave to form acetone, was present.

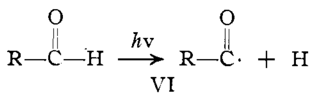
**n-Butyraldehyde–2-methyl-2-butene Irradiation Product.**—The *n*-butyraldehyde–2-methyl-2-butene irradiation product V was obtained in pure form by repeated fractional distillation under diminished pressure.

When subjected to acid-catalyzed cleavage conditions, *n*-butyraldehyde was the only carbonyl compound formed. Since both possible isomers, V and Va, could cleave to give *n*-butyraldehyde, the structure of the irradiation product could not be definitely established.

It is more difficult, however, to explain why cleavage should take place only in the direction giving *n*-butyraldehyde if the irradiation product were Va because, in this case, a secondary carbonium ion would be formed preceding cleavage in either direction. In the case of V, cleavage to form *n*-butyraldehyde involves an intermediate tertiary carbonium ion while cleavage in the other direction involves a secondary ion. Furthermore, the 2-methyl-2-butene, formed together with butyraldehyde, is a more stable olefin than 2-hexene (more hyperconjugation). It seems rather likely, therefore, that the irradiation product is 1,1,2-trimethyl-3-*n*-propyltrimethylene oxide (V).

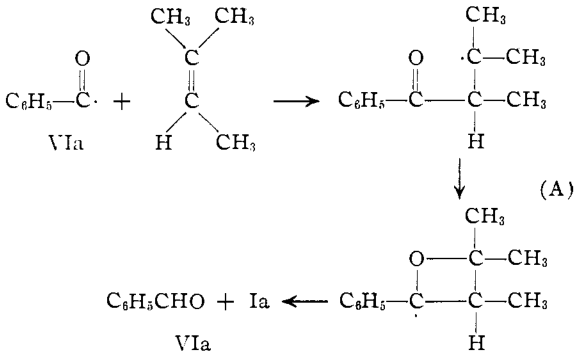


**Mechanism of Formation of Trimethylene Oxides.**—Kharasch[10] proposed that in the reaction of aldehydes with terminal olefins to form ketones it is the radical VI which attacks the olefin. If it is assumed that VIa is the species attacking 2-methyl-2-butene the isomer Ia instead of I would be expected to result. A reverse addition would produce a less stable secondary instead of a more stable tertiary radical intermediate.



$$\mathrm{R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}H \xrightarrow{h\nu} R{-}\overset{\overset{\displaystyle O}{\|}}{C}\cdot + H}$$

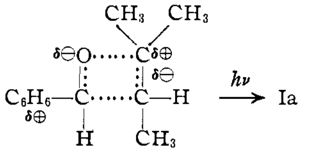
VI



(A)

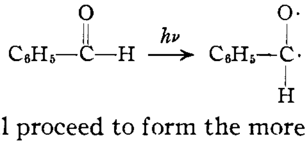
This mechanism, of course, would not explain the light-catalyzed reaction of ketones with olefins.

If the formation of the trimethylene oxide is assumed to arise from a simultaneous shift of electrons (either in pairs or singly) in the carbonyl and carbon–carbon double bonds, isomer Ia would again be expected to be formed because of the polarization of the reactants.



(B)

A mechanism which explains the formation of isomer I involves the diradical triplet state VII.



$$\mathrm{C_6H_5{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}H \xrightarrow{h\nu} C_6H_5{-}\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle O\cdot}{|}}{C}}\cdot}$$

VII

Addition will proceed to form the more stable intermediate VIII rather than IX.

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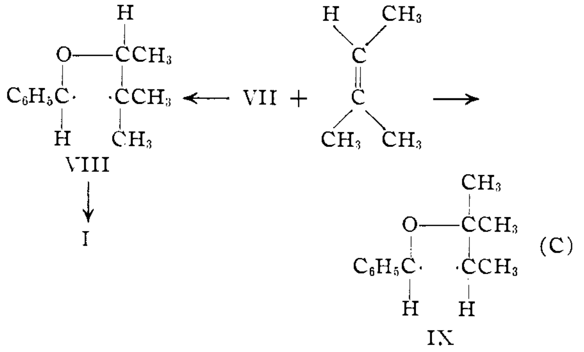
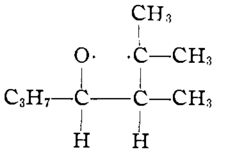
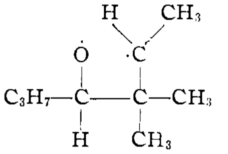
[10] M. S. Kharasch, W. H. Urry and B. M. Kuderna, Jr., *J. Org. Chem.*, **14**, 248 (1949).

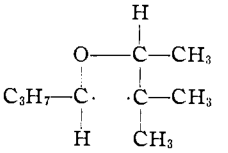


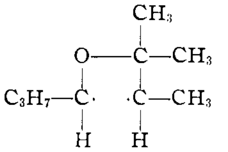
The same arguments apply to the mechanism of the formation of isomer IV from the irradiation of acetophenone with 2-methyl-2-butene.

V would be expected to be formed in the irradiation of butyraldehyde with 2-methyl-2-butene because biradical X might be more stable than the three other possible intermediates XI, XII and XIII.

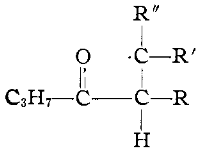

X

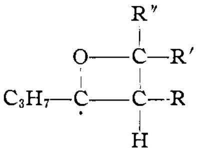

XI


XII


XIII

On the other hand, the formation of V can be explained with the Kharasch mechanism (mechanism A). Intermediate XIV can react either with butyraldehyde directly to give a ketone, or cyclize to XV, and then react with butyraldehyde to form a trimethylenoxide. Ketones are formed when R and R′ = H, a mixture of ketone and trimethylene oxide results when R = alkyl and R′ = H.[11]


XIV


XV

Finally when R, R′ and R″ are all alkyl substituents, only trimethylene oxides are formed. The fact that substituents stabilize small rings is well established in organic chemistry, but to our knowledge, no satisfactory explanation has been advanced.

Experiments are now under way in this Laboratory to establish the configurations of the trimethylene oxides formed by light-catalyzed reactions of carbonyl compounds with olefins.

## Experimental[12]

**1,2,2-Trimethyl-3-phenyltrimethylene Oxide** (I).—A 600-ml. mercury vapor illuminator[13] with an attached reflux condenser was flushed with nitrogen. Freshly distilled benzaldehyde (295 g., 2.78 moles) and 181 g. (2.58 moles) of 2-methyl-2-butene were placed in the illuminator. The arc electrodes were connected to a 9000-v., 30-ma. luminous tube transformer and the mixture irradiated for 48 hours, a slow stream of nitrogen through the mixture being maintained.

The unreacted 2-methyl-2-butene was removed under reduced pressure and the residue distilled through a 40-cm. glass helix packed column at 3.5 mm. The 80–84° fraction was redistilled through a semi-micro column at 0.2 mm. and the portion boiling at 44° collected, yield 46 g. (10%), $n^{25}_{D}$ 1.5018; principal infrared bands: 3.3, 3.42, 6.62, 6.8, 7.2, 7.25, 9.37, 9.95, 10.18, 13.5, 14.3.

*Anal.* Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.90; H, 9.12.

**Acid-catalyzed Cleavage of I.**—Compound I was added to 2,4-dinitrophenylhydrazine reagent containing 2% HCl. The precipitate which formed melted at 238–239° after recrystallization from ethanol–ethyl acetate. No depression of the melting point was observed when the precipitate was mixed with the 2,4-dinitrophenylhydrazone of benzaldehyde.

Glacial acetic acid (8 ml.), 2 ml. of water, 0.6 ml. of concentrated sulfuric acid and 2 g. of I were mixed together and distilled through a 7-cm. glass helix packed column. The distillate coming over up to 101° was collected in a flask immersed in a salt–ice freezing mixture. The distillate gave a precipitate with 2,4-dinitrophenylhydrazine melting at 147–153° after recrystallization from 95% ethanol which was identical with the derivative of acetaldehyde. The undistilled portion was diluted with 35 ml. of water and extracted with 35 ml. of pentane. The pentane solution was washed with sodium bicarbonate solution and then evaporated. The residue gave the semicarbazone of benzaldehyde melting at 221°.

**Ethyl 1-Methyl-2-phenyl-2-hydroxypropionate.**—Reagent 20–30 mesh granular zinc (40 g., 0.61 mole) was placed in the reaction flask. Fifteen ml. of a solution of 90.5 g. (0.50 mole) of ethyl α-bromopropionate and 65 g. (0.61 mole) of freshly distilled benzaldehyde in 80 ml. of dry benzene and 20 ml. of dry ether were run into the flask. The mixture was heated until the reaction began and the rest of the solution added at such a rate as to maintain boiling; 45 minutes were required for the addition. The mixture was heated for an additional 45 minutes, cooled in an ice-bath, and poured into 300 ml. of ice-cold 10% sulfuric acid solution with vigorous stirring. The acid layer was drawn off and the organic layer extracted twice with 50-ml. portions of ice-cold 5% sulfuric acid solution, washed successively with 25 ml. of cold 10% sodium carbonate solution, 25 ml. of cold 5% sulfuric acid solution and twice with 25 ml. of water. The combined acid extracts were extracted with two 50-ml. portions of ether and the ether washed with 25 ml. of 10% sodium carbonate solution and then with 25 ml. of water. The combined organic layers were dried over magnesium sulfate and the solvents removed. The residue was distilled through a Vigreux column at 5 mm. The fraction boiling at 144–150° was collected, yield 64 g. (62%).

**2,3-Dimethyl-4-phenylbutane-2,4-diol** (III).—Magnesium turnings (26.3 g., 1.08 moles) were placed in a 3-l. 3-necked flask to which were attached a dropping funnel, Dry Ice condenser, mercury-seal stirrer and gas inlet tube. Dry ether (150 ml.) was introduced and dry methyl bromide passed through the ether. When the reaction commended, another 260 ml. of ether was added. After 90 minutes, all the magnesium had reacted, and a water condenser was substituted for the Dry Ice condenser. The mixture was cooled in an ice-bath and ethyl 1-methyl-2-phenyl-2-hydroxypropionate (62.5 g., 0.30 mole) in 150 ml. of ether was added with stirring over a 45-minute period. Another 100 ml. of ether was added and the ice-bath removed. Stirring was continued for 21 hours. The mixture was then cooled in an ice-bath and 150 ml. of saturated ammonium chloride solu-

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(11) Unpublished results of D. Rosenthal.

(12) Melting points are corrected and boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for analyses and infrared spectra, which were determined with a Baird double beam infrared recording spectrophotometer.

(13) M. S. Kharasch and H. N. Friedlander, *J. Org. Chem.*, **14**, 239 (1949).

tion added. The ether solution was decanted from the precipitate and the ether removed under reduced pressure. The yellow viscous residue was distilled from a Hickman still at 0.07–0.08 mm. The fraction boiling at 106–107° was collected, yield 40 g. (69%). The color in the distillate, resulting from splashing of the residue, was removed by redistillation at 0.08 mm., $n^{25}D$ 1.5182.

*Anal.* Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.43; H, 9.48.

**Acid-catalyzed Cleavage of 2,3-Dimethyl-4-phenylbutane-2,4-diol (III).**—Glacial acetic acid (8 ml.), 2 ml. of water, 0.6 ml. of concentrated sulfuric acid and 1.7 g. of III were mixed together and distilled through a 7-cm. glass helix packed column. The distillate coming over up to 98° was collected in a flask immersed in a salt–ice freezing mixture. The 2,4-dinitrophenylhydrazone of the distillate melted at 118–122° after two recrystallizations from 95% ethanol and gave a mixed m.p. with the 2,4-dinitrophenylhydrazone of acetone of 124–126°. When an acidified aqueous solution of the distillate and sodium nitroprusside was made alkaline with ammonia, a violet color appeared.

The undistilled portion was diluted with 35 ml. of water and extracted with 35 ml. of pentane. The pentane was washed with sodium bicarbonate solution and evaporated. The residue gave a semicarbazone melting at 220–221° identical with a benzaldehyde semicarbazone.

**Cleavage of a Mixture of I and III.**—A mixture of 1.1 g. of III and 2.0 g. of I was cleaved using the same procedure employed for III. The portion distilling up to 99° was collected. The 2,4-dinitrophenylhydrazone of the distillate melted at 121–144° after recrystallization from 96% ethanol.

**1,2,2,3-Tetramethyl-1-phenyltrimethylene Oxide (IV).**—A mixture of 43 g. (0.61 mole) of 2-methyl-2-butene and 56 g. (0.46 mole) of acetophenone was irradiated in a 120-cc. mercury vapor illuminator for 196 hours. The irradiation was discontinued every 24 hours and the tar on the coils removed. The excess 2-methyl-2-butene was removed and the unreacted acetophenone distilled off through a 23-cm. glass helix packed column at 70–72° (3.8 mm.). The residue was distilled through a semi-micro column at 0.05 mm. and the fraction boiling at 42° collected, $n^{25}D$ 1.5040, yield 3.8 g. (4.4%).

The infrared spectrum indicated the presence of small amounts of hydroxy and carbonyl compounds. These impurities were removed by passing a pentane solution of the product through a column of neutral alumina; principal infrared bands: 3.4, 6.0, 7.2, 7.3, 7.9, 9.38, 9.6, 11.15, 13.1, 14.3.

*Anal.* Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.71; H, 9.41.

**Acid-catalyzed Cleavage of IV.**—When IV was added to 2,4-dinitrophenylhydrazine reagent a precipitate formed which melted at 246° after recrystallization from ethanol–ethyl acetate. No m.p. depression was observed when this precipitate was mixed with the 2,4-dinitrophenylhydrazone of acetophenone.

Compound IV (2.0 g.) was then hydrolyzed by the same method employed for III. The portion distilling up to 99° was collected. The distillate was acetaldehyde which gave a precipitate with 2,4-dinitrophenylhydrazine reagent, m.p. 149–154° after recrystallization from 95% ethanol.

***n*-Butyraldehyde-2-Methyl-2-butene Irradiation Product (V).**—A mixture of 196 g. (2.72 moles) of freshly distilled *n*-butyraldehyde and 174 g. (2.48 moles) of 2-methyl-2-butene was irradiated in a 600-cc. mercury vapor illuminator for 29 hours. The unreacted 2-methyl-2-butene was removed and most of the *n*-butyraldehyde distilled off through a 36-cm. glass helix packed column at atmospheric pressure. The residue was distilled through the same column at 22 mm. and the portion boiling at 59–61° collected, yield 23 g. (6.5%). This fraction was redistilled through a semi-micro column at 23 mm. (b.p. 62–64°), $n^{25}D$ 1.4178.

The infrared spectrum indicated the presence of small amounts of hydroxy and carbonyl compounds. These impurities were removed by passing a pentane solution of the product through a column of neutral alumina; principal infrared bands: 3.4, 6.8, 7.3, 9.5, 9.7, 10.4, 10.7, 11.6, 11.7.

*Anal.* Calcd. for $C_9H_{18}O$: C, 75.99; H, 12.76. Found: C, 75.79; H, 12.68.

**Acid-catalyzed Cleavage of V.**—Compound V was added to 2,4-dinitrophenylhydrazine reagent and the mixture allowed to stand for 10 minutes. The precipitate was filtered off and recrystallized twice from 95% ethanol, m.p. 120–121°, no m.p. depression when mixed with the 2,4-dinitrophenylhydrazone of *n*-butyraldehyde. The mother liquor was allowed to stand for 5 hours and the precipitate which formed recrystallized from 95% ethanol, m.p. 119–120°, no. m.p. depression when mixed with the 2,4-dinitrophenylhydrazone of *n*-butyraldehyde.

Compound V (2.0 g.) was hydrolyzed by the same method employed for III. No material distilled before *n*-butyraldehyde.

The completely precipitated 2,4-dinitrophenylhydrazone of V was dissolved in benzene and passed through a chromatography column filled with Florosil. All fractions melted at 120–121° after recrystallization from 95% ethanol and showed no m.p. depression when mixed with the 2,4-dinitrophenylhydrazone of *n*-butyraldehyde.

Cambridge, Mass.

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[Contribution from the Department of Agricultural Biochemistry, University of Minnesota]

# Spectrophotometric Study of the Reaction of Protein Sulfhydryl Groups with Organic Mercurials[1]

By P. D. Boyer

Received April 12, 1954

A procedure is described for the sensitive and rapid spectrophotometric measurement of the extent and rate of reaction of various organic mercury compounds, particularly *p*-mercuribenzoate, with sulfhydryl groups. The procedure with *p*-mercuribenzoate is based on the increase in absorbancy in the 250 mμ region accompanying mercaptide formation. The rate of reaction of the sulfhydryl groups of egg albumin and β-lactoglobulin is more rapid at *p*H 4.6 than at *p*H 7; the rate with egg albumin is markedly affected by the nature of the ions present. The reaction of *p*-mercuribenzoate with β-lactoglobulin at *p*H 4.6 in acetate buffer and with egg albumin at *p*H 7 in phosphate buffer follows the course of a second-order reaction. By variation of the experimental conditions three different types of sulfhydryl groups may be recognized in egg albumin.

Organic mercurial compounds are the most specific and sensitive reagents now available for reaction with sulfhydryl groups, and have been widely used in studies of the biochemical function of sulfhydryl groups since the pioneer researches of Hellerman with *p*-mercuribenzoate.[2] Quantitative studies of the reaction of *p*-mercuribenzoate

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[1] Supported in part by a grant from the National Science Foundation. Paper No. 3191, Scientific Journal Series, Minnesota Agricultural Experiment Station. A preliminary report was presented at the 123rd meeting of the Am. Chem. Soc., Los Angeles, March, 1953. The technical assistance of Mrs. Madelyn Ferrigan is gratefully acknowledged.

[2] (a) L. Hellerman, *Physiol. Revs.*, **17**, 454 (1937); *Cold Spring Harbor Symp. Quant. Biol.*, **7**, 165 (1939); (b) L. Hellerman, F. P. Chinard and V. R. Deitz, *J. Biol. Chem.*, **147**, 443 (1943). (c) The designation *p*-mercuribenzoate has been used herein for compounds in solution derived from added *p*-chloromercuribenzoate; the mercury compound in various solutions may be combined principally with hydroxyl or other anions instead of chloride ion.