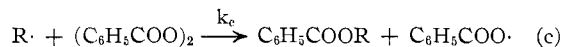
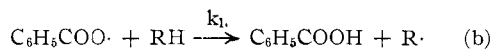


[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC COMPANY]

Products of the Reaction of Benzoyl Peroxide with Certain Ethers

BY W. E. CASS

The chain reaction steps (b) and (c) were postulated to account for the rapid decomposition of benzoyl peroxide in diethyl ether, diethyl Cellosolve and dioxane.



If such a chain mechanism is involved in these decompositions, the kinetic order^{1,1a} of the reactions will depend upon the nature of the chain initiating and terminating steps. However, if the chain length is appreciable, the chief products of the reaction should be those predicted by (b) and (c). In order to gain information on this point, a study has been made of the products of reaction of benzoyl peroxide in the above three solvents at about 40°. The main products of the reactions are listed in Tables I, II and III. The

TABLE I
PRODUCTS OF THE REACTION OF BENZOYL PEROXIDE WITH
DIETHYL ETHER AT 37°

Product	Approx. yield mole per mole peroxide dec.		
Carbon dioxide	0.20 ^a	0.25 ^b	0.19 ^c
Benzoic acid	.80 ^a	.78 ^d	
1-Ethoxyethyl benzoate (I)	.95 ^{a,b}	.84 ^d	

^a Calcd. from acidity of ether-free residue. (This calculation assumes that loss of carbon dioxide affects only the yield of benzoic acid.) ^b Calcd. from saponification equiv. of ether-free residue (acidic hydrolysis). ^c Determined by absorption in Ascarite. ^d Product actually isolated.

TABLE II
PRODUCTS OF THE REACTION OF BENZOYL PEROXIDE WITH
DIETHYL CELLOSOLVE AT 40°

Product	Approx. yield mole per mole peroxide dec.		
Carbon dioxide	0.19 ^a	0.17 ^b	0.22 ^c
Benzoic acid	0.81 ^a	0.77 ^d	
1-(2-Ethoxyethoxy)-ethyl benzoate (II) and 1,2-di- ethoxyethyl benzoate (III) ^e	1.02 ^{a,b}	0.80 ^d	

^a Calcd. from acidity of ether-free residue. (This calculation assumes that loss of carbon dioxide affects only the yield of benzoic acid.) ^b Calcd. from saponification equiv. of residue (acidic hydrolysis). ^c Determined by absorption in Ascarite. ^d Products actually isolated. ^e See discussion for relative yields.

(1) Cass, *This Journal*, **68**, 1976 (1946).

(1a) Recently, Nozaki and Bartlett have reported (*ibid.*, **68**, 1686 (1946)) results of extensive work on the kinetics of the decomposition of benzoyl peroxide in a large number of solvents. The kinetic treatment of these authors differs from that given in ref. 1 in that their elegant mathematical treatment includes that part of the benzoyl peroxide which disappears by spontaneous unimolecular decomposition as well as by a chain reaction. The general conclusions in both papers concerning the existence of a chain reaction and retardation by aromatic products are believed to be similar.

TABLE III
PRODUCTS OF THE REACTION OF BENZOYL PEROXIDE WITH
DIOXANE AT 40°

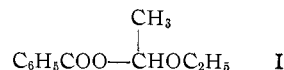
Product	Approx. yield mole per mole peroxide dec.	
Carbon dioxide	0.28 ^a	0.30 ^b
Benzoic and other acids	1.04 ^c	1.08 ^d
Dioxanyl benzoate (IV) and other acylals	0.68 ^{a,c}	0.37 ^e

^a Calcd. from saponification equiv. of solvent-free residue (acidic hydrolysis). ^b Determined by absorption in Ascarite. ^c Calcd. from acidity of residue. ^d Acid mixture actually isolated. ^e Actual yield of IV.

products formed, at least in the case of diethyl ether and diethyl Cellosolve, are those to be expected from (b) and (c) plus a certain amount of carbon dioxide.

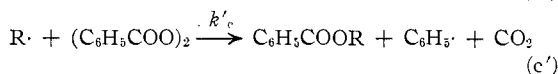
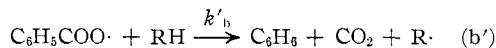
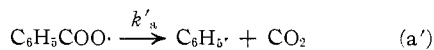
Discussion

Diethyl Ether.—With diethyl ether the product of step (c), $\text{C}_6\text{H}_5\text{COOR}$, proved to be 1-ethoxyethyl benzoate (I), an acylal.² The fact



that no 2-ethoxyethyl benzoate was obtained indicates that hydrogen was captured preferentially from the methylenic carbon of the ether. The fact that I was produced in practically quantitative yield indicates that there was little or no spontaneous decomposition under the experimental conditions of the ether radical, $\text{C}_2\text{H}_5\text{OCHCH}_3$, into acetaldehyde and an ethyl radical.

It will be noted that the postulated mechanism does not include equations to account for the carbon dioxide evolved. It appears that partial decarboxylation occurred at the expense of the benzoic acid. This decarboxylation could occur according to any of the following steps

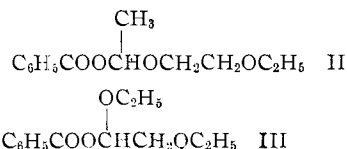


If the phenyl radical produced in steps (a') or (c') subsequently captures a hydrogen from the ether as does the benzoyloxy radical, it is impossible to decide on a kinetic basis which decarboxylation step is actually followed.

Diethyl Cellosolve.—Results with this solvent were similar to those obtained with diethyl ether. In this case the product, $\text{C}_6\text{H}_5\text{COOR}$, was a mixture of the isomeric acylals, 1-(2-ethoxyethoxy)-

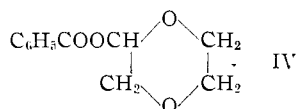
(2) Cf. Kurd and Green, *ibid.*, **63**, 2201 (1941).

ethyl benzoate (II) and 1,2-diethoxyethyl benzoate (III).



Hydrolysis of the mixture of these acylals produced acetaldehyde and ethoxyacetaldehyde. Nitrogen analysis of the mixture of 2,4-dinitrophenylhydrazones of these aldehydes indicated that II and III were obtained in a ratio of approximately 3 to 1.

Dioxane.—Results with dioxane were not so clean-cut as with the other two solvents. Benzoic acid and the expected acylal, dioxanyl benzoate (IV), were obtained, but the yields of these compounds were comparatively low.



Moreover, considerable amounts of higher molecular weight acids (at least in part substituted benzoic acids) and acylals were obtained. It is difficult to explain the formation of these higher molecular weight "by-products." They may result in part from termination processes, since the kinetics¹ indicated that termination was a more significant process for the reaction in dioxane than for the reaction in diethyl Cellosolve or diethyl ether; that is, dioxane exhibited a lower rate and higher order process.

Dioxanyl benzoate behaved similarly to the other acylals in ease of hydrolysis, but the aldehyde produced, presumably $\text{HOCH}_2\text{CH}_2\text{OCH}_2\text{CHO}$, actually yielded glyoxal osazones when treated with excess phenylhydrazine in aqueous acetic acid or 2,4-dinitrophenylhydrazine in dilute hydrochloric acid. It is assumed that the 2-hydroxyethoxyacetaldehyde underwent hydrolysis to glycolaldehyde in acidic solution and this gave glyoxal derivatives in the usual manner.

Experimental

Reactants were purified as previously described.¹

Diethyl Ether. (a) **Reaction.**—A 1-liter flask was fitted with a gas inlet tube and a bulb reflux condenser using glass joints. The top of the condenser was connected through a Dry Ice-acetone-cooled trap to a tared Ascarite tube. The Ascarite tube was protected from atmospheric contamination with a second Ascarite tube. In the flask was placed 24.5 g. (0.101 mole) of purified benzoyl peroxide and 500 ml. of anhydrous diethyl ether. After the system was swept with nitrogen, the solution was maintained at gentle reflux ($\sim 37^\circ$) using an electric mantle for one week. At the end of this time a second Dry Ice-acetone-cooled trap was inserted in the line and the system was swept with a slow stream of carbon dioxide-free nitrogen until the tared Ascarite tube reached constant weight (four hours). The residual solution was 0.0015 *M* in peroxide; since the initial peroxide concentration was about 0.19 *M*, reaction was considered essentially complete. The weight increase of the Ascarite

tube (0.865 g.) corresponded to 0.194 mole of carbon dioxide per mole of peroxide decomposed.

Excess ether was removed under reduced pressure, first at line vacuum (30–40 mm.) and then for ten minutes at 0.3 mm. at 30–40°. There was thus obtained 28.9 g. of pasty residue. This residue contained 2.80×10^{-3} equiv. of acid per gram as determined by titration in acetone with 0.1 *N* sodium hydroxide using phenol red as indicator. (The end-point faded rapidly, indicating the presence of an easily hydrolyzable species.) This acidity corresponds to 0.80 equiv. of acid per mole of peroxide decomposed.

The pasty residue was hydrolyzed as follows: to a 1–1.5 g. sample in 20 ml. of acetone was added 25 ml. of 0.5 *N* hydrochloric acid. The mixture was heated one hour in an 80°-oven^{3,4} and then titrated with 0.5 *N* sodium hydroxide. This saponification indicated a total acidity of 6.10×10^{-3} equiv. per gram, corresponding to 1.75 equiv. of acylal plus acid or 0.95 equiv. of acylal per mole of peroxide decomposed. By evaporation and acidification of the solution from this hydrolysis, benzoic acid (m. p. 119.5–121°; mixed m. p. 120.5–121.5°; neut. equiv. 123) was recovered in 93% yield.

(b) **1-Ethoxyethyl Benzoate (I).**—A 24.5-g. portion of the above pasty residue was dissolved in 100 ml. of diethyl ether and stirred mechanically for ten minutes with a solution of 10 g. of sodium bicarbonate in 100 ml. of water.⁵ The ether layer was separated and the ether removed under reduced pressure. The residue was distilled (b. p. 63–65° at 0.3 mm.) through a 30-cm. unpacked, heated column. The yield of distillate was 14 g., corresponding to 0.84 mole of I per mole of peroxide decomposed.³ The colorless liquid thus obtained was slightly acidic ($\sim 1\%$ acid, calculated as benzoic) and was purified by dissolving in ether, washing with sodium bicarbonate solution and redistilling. The redistilled product was essentially neutral; b. p. 57–58° at 0.2 mm.; n_D^{25} 1.4868; d_4^{25} 1.042; *MR* 52.7 (calcd.), 53.6 (obsd.).⁴

Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_2$: C, 68.03; H, 7.27. Found: C, 68.0, 67.6; H, 7.60, 7.79.

Hydrolysis of I at 80° in 0.5 *N* hydrochloric acid indicated a saponification equivalent of 194 and 195 (calcd. 194). From the hydrolyzate, benzoic acid (m. p. 120–121.5°; mixed m. p. 121–122°; neut. equiv. 123) was recovered in 90% yield.

I was analyzed for aldehyde following the method of Iddles and Jackson.⁷ To a 0.5-g. sample of I in a 250 ml. g. s. flask was added 20 ml. of ethyl alcohol and 10 ml. of 2 *N* hydrochloric acid. The mixture was allowed to stand ten minutes at room temperature (hydrolysis complete) and then 200 ml. of 2,4-dinitrophenylhydrazine solution (4–5 mg. per ml. in 2 *N* hydrochloric acid) was added. The mixture was shaken for five minutes, cooled

(3) This procedure readily saponified the acylals. Experiments with ethyl benzoate, however, indicated that a normal ester is practically unaffected (<1% hydrolyzed) under these conditions. Benzoyl peroxide also was found to be practically unattacked under similar conditions.

(4) In several earlier experiments, alcoholic potassium hydroxide was used for these saponifications. Alkaline hydrolysis was abandoned for the following reasons: (a) generally high and less reproducible results were obtained, presumably because of the production of acidic material by the action of the alkali on the aldehyde produced by hydrolysis; (b) acidic hydrolysis was apparently specific for the acylal linkage (*cf.* ref. 3).

(5) During the sodium bicarbonate extraction, some of the acylal product probably underwent hydrolysis, resulting in a higher yield of benzoic acid and a decreased yield of the acylal.

(6) The observed molar refractions for the acylals were about one unit higher than the calculated values. This exaltation appears to be fairly general for esters of benzoic acid. For example, the exaltations for certain benzoates are as follows: ethyl, 0.8; *n*-propyl, 1.7; *i*-propyl, 0.5; 2-methoxyethyl, 0.9; 2-ethoxyethyl, 1.1; 2-butoxyethyl, 1.0 (calcd. from data in Hintruss and Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, New York, N. Y., 1941).

(7) Iddles and Jackson, *Ind. Eng. Chem., Anal. Ed.*, **6**, 454 (1934).

in ice and filtered. Acetaldehyde 2,4-dinitrophenylhydrazone was obtained in 96.5 and 97.5% yield; m. p. 157–159°. Recrystallized from ethyl alcohol, the derivative melted at 165–166° and showed no depression in a mixed melting point with an authentic sample of the acetaldehyde derivative (m. p. 165–166°).

(c) **Isolation of Benzoic Acid.**—The aqueous layer from the sodium bicarbonate extraction of the pasty residue (see above) was heated in an 80° oven to drive off ether and then acidified strongly with hydrochloric acid. The mixture was cooled and filtered, giving 8.1 g. of benzoic acid (m. p. 119–121°; mixed m. p. 120–121.5°; neut. equiv. 122). This yield corresponds to 0.78 mole of benzoic acid per mole of peroxide decomposed.⁵

Diethyl Cellosolve. (a) **Reaction.**—In an apparatus, similar to that described for diethyl ether, was placed 49.0 g. (0.202 mole) of benzoyl peroxide and 500 ml. of anhydrous diethyl Cellosolve. The system was swept with nitrogen and the flask kept in a 40° thermostat for one week. Carbon dioxide was not determined in this experiment, but in another check experiment was obtained in a yield corresponding to 0.218 mole per mole of peroxide decomposed. The final peroxide concentration of the solution was 0.0008 *M*, *i. e.*, reaction was essentially complete. Excess diethyl Cellosolve was removed under reduced pressure (bath temp. 50–60°) and the residue was finally heated for one hour under 0.2–0.5 mm. at 70–90°. The yield of pasty residue was 69.6 g. The acidity of the residue (2.35×10^{-3} equiv. per gram) corresponded to a yield of 0.81 equiv. of acid per mole of peroxide decomposed. Acid saponification of the residue as before^{3,4} indicated a total acidity of 5.32×10^{-3} equiv. per gram; this corresponds to 1.83 equiv. of acid and acylals or 1.02 mole of acylals per mole of peroxide decomposed. From the saponification, benzoic acid (m. p. 120.5–121°; mixed m. p. 121–121.5°, neut. equiv. 123) was recovered in 86% yield.

(b) **Isolation of Acylals II and III.**—A 58-g. portion of the above residue was dissolved in 200 ml. of diethyl ether and stirred for ten minutes with a solution of 18 g. of sodium bicarbonate in 200 ml. of water. The ether layer was separated and distilled as before. There was obtained 31.8 g. of distillate of b. p. 95–100.5° at 0.2 mm. (bath temp. 130–140°). This yield corresponds to 0.795 mole of acylals per mole of peroxide decomposed.⁵ The crude product (~1% acid, calculated as benzoic acid) was purified as before; b. p. 95–98° at 0.25 mm.; n_D^{20} 1.4839; d_4^{25} 1.051; *MR* 63.6 (calcd.), 64.8 (obsd.).⁶

Anal. Calcd. for $C_{13}H_{13}O_4$: C, 65.53; H, 7.62. Found: C, 65.5, 65.9; H, 7.59, 7.63.

Acid hydrolysis of the acylals as before indicated a saponification equivalent of 237 (calcd. 238). Benzoic acid (m. p. 120.5–121°; mixed m. p. 121–121.5°; neut. equiv. 126) was recovered in 87.5% yield from the saponification.

The presence of both II and III in the product was indicated by the formation of the 2,4-dinitrophenylhydrazones of acetaldehyde and ethoxyacetaldehyde formed by hydrolysis of the product. Quantitative analysis of 0.5-g. samples as before gave a mixture of 2,4-dinitrophenylhydrazones (m. p. 120–125°) in the following yields: 98 and 98.5% (acetaldehyde basis, *i. e.*, II) or 82 and 82.5% (ethoxyacetaldehyde basis, *i. e.*, III). When this mixture was recrystallized several times from ethyl alcohol, the acetaldehyde derivative was obtained (m. p. 163–164°; mixed m. p. 165–166°).

The presence of ethoxyacetaldehyde in the hydrolyzate was proved by the following experiment: a mixture of 5 g. of the acylal product, 20 ml. of methanol and 10 ml. of 2 *N* hydrochloric acid was allowed to stand ten minutes at room temperature. Water (20 ml.) was then added and the mixture slowly distilled from an oil-bath through a 30-cm. packed column until the top temperature reached 85°. The residue was treated with 200 ml. of 2,4-dinitrophenylhydrazine solution (4–5 mg. per ml. in 2 *N* hydrochloric acid) and the mixture was cooled and filtered. Benzoic acid was removed from the precipitate by washing with sodium bicarbonate solution. Recrystallized three

times from methanol, the derivative melted at 116–117°. (Ethoxyacetaldehyde 2,4-dinitrophenylhydrazone has m. p. 116–117°.⁸)

Anal. Calcd. for $C_{10}H_{12}O_5N_4$: N, 20.90. Found: N, 21.0, 20.8.

Nitrogen analysis of the original mixture of 2,4-dinitrophenylhydrazones obtained in the quantitative analysis indicated 23.8 and 23.9% N. From this result and the calculated values for the acetaldehyde and ethoxyacetaldehyde derivatives (25.00 and 20.90% N) it was calculated that the mixture consisted of 76 mole per cent. acetaldehyde derivative and 24 mole per cent. ethoxyacetaldehyde derivative.

(c) **Isolation of Benzoic Acid.**—The aqueous layer from the sodium bicarbonate extraction of the pasty residue was worked up for benzoic acid as before. There was obtained 15.8 g. of benzoic acid (0.77 mole per mole of peroxide decomposed⁵) of m. p. 120–120.5°, mixed m. p. 121–121.5° and neut. equiv. 123.

Dioxane. (a) **Reaction.**—A solution of 48.8 g. (0.202 mole) of benzoyl peroxide in 500 ml. of anhydrous dioxane (initial peroxide concentration 0.378 *M*) was maintained as before for three weeks at 40°. Carbon dioxide was obtained in 2.448-g. yield. Since the final peroxide concentration was 0.029 *M*, the extent of reaction was 92.4%, *i. e.*, 0.187 mole of peroxide had disappeared. Accordingly, 0.298 mole of carbon dioxide was obtained per mole of peroxide decomposed.

Excess dioxane was removed under reduced pressure, the residue finally being heated at 60–80° for one-half hour under 0.3 mm. The viscous residue (59.7 g.) was transformed into a semi-crystalline paste on cooling. The peroxide content of the residue was 4.81×10^{-4} equiv. per gram, corresponding to 93% reaction or 0.188 mole of peroxide decomposed. The acidity of the residue (3.28×10^{-3} equiv. per gram) indicated 1.04 equiv. of acid per mole of peroxide decomposed. Acid saponification of a sample of the residue as before indicated a total acidity of 5.41×10^{-3} equiv. per gram; this corresponds to a yield of 0.675 mole of acylal per mole of peroxide reacted. A mixture of acids was recovered from the saponification in 83.5% yield (based on equiv. wt.); m. p. 83–109°; mixed m. p. 107–118° with benzoic acid of m. p. 121–122°; neut. equiv. 149.5.

(b) **Dioxanyl Benzoate (IV).**—A 54.7-g. sample of the above pasty residue in 200 ml. diethyl ether was treated as before with a solution of 25 g. of sodium bicarbonate in 200 ml. of water. After separation of the ether layer and distillation of the ether, the residue was distilled under reduced pressure. There was thus obtained 13.2 g. of crude IV of b. p. 105–122° at 0.3 mm. This yield corresponds to 0.368 mole of acylal per mole of peroxide reacted.⁵ The residue (7.4 g.) from the distillation solidified to a glassy resin on cooling. This residue was assumed to contain higher acylals because it was saponifiable with alcoholic potassium hydroxide with the production of aldehyde gum. The crude distillate, which contained 5% acid (calcd. as benzoic), was purified as before. The redistilled product contained less than 0.5% acid (as benzoic); b. p. 108–110° at 0.3 mm.; n_D^{20} 1.5242; d_4^{25} 1.198; *MR* 52.1 (calcd.), 53.2 (obsd.).⁶

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 64.3, 64.2; H, 6.23, 6.04.

Acid hydrolysis of IV indicated a saponification equivalent of 208 (calcd. 208). Benzoic acid (m. p. 121–122°; mixed m. p. 121–122°; neut. equiv. 124) was recovered from the saponification in 87% yield.

Glyoxal 2,4-dinitrophenylsazone was obtained from IV as follows: to a 0.2-g. sample of IV was added 20 ml. of ethyl alcohol and 20 ml. of 2 *N* hydrochloric acid. After five minutes, 200 ml. of 2,4-dinitrophenylhydrazine solution (4–5 mg. per ml. in 2 *N* hydrochloric acid) was added and the mixture was placed in an 80° oven for two and one-half hours. The mixture was cooled and filtered and the precipitate was washed with water and then with

(8) Drake, Duval, Jacobs, Thompson and Sonnichsen, *THIS JOURNAL*, **60**, 73 (1938).

warm alcohol. The orange product (microscopic, hair-like crystals) was obtained in 87 and 89% yield, m. p. 320–328° (dec.). No depression was observed in a mixed melting point with a sample of this derivative prepared directly from glyoxal.

Anal. Calcd. for $C_{14}H_{10}O_8N_8$: N, 26.80. Found: N, 26.4, 26.5.

Glyoxal phenylosazone was obtained from IV in poor yield by the following procedure: a solution of 0.5 g. of IV, 10 ml. of glacial acetic acid and 20 ml. of water was heated to boiling and then let stand several minutes. Then 6 ml. of phenylhydrazine-acetic acid reagent (1 vol. of phenylhydrazine, 1 vol. of acetic acid and 2 vol. of water) was added and the reaction mixture was heated to boiling until a brown color developed (about two minutes). A solution of 50 ml. of water and 25 ml. of acetic acid was added and the mixture was cooled and shaken. The light brown product was filtered; m. p. 155–162°. Recrystallized from alcohol plus a little water the derivative was obtained as yellow-brown needles of m. p. 168–169°; a mixed melting point with an authentic sample of glyoxal phenylosazone (m. p. 169–172°) was 169–170°.

(c) **Isolation of Acids.**—A mixture of acids was isolated as before from the sodium bicarbonate extraction of the paste; yield, 29.8 g.; m. p. 76–93°; mixed m. p. (with benzoic acid) 85–107°; neut. equiv. 159. Since 0.187 equiv. of acids was obtained from an amount of residue originally containing only 0.18 equiv. of free acids, it was assumed that hydrolysis of acylals had occurred during the sodium bicarbonate extraction.⁵

Benzoic acid was separated from the acid mixture by steam distillation. A 24.5-g. sample of the acids was steam distilled, keeping the volume at about 100 ml. Two distillate fractions were collected. The first fraction (800 ml.) on cooling yielded 6.7 g. of impure benzoic acid (m. p. 117–120°; mixed m. p. 119–121°; neut. equiv. 125). The second fraction (300 ml.) gave 0.7 g. of less pure benzoic acid (m. p. 110–117°; mixed m. p. 116–120°; neut. equiv. 127). On cooling the residue from the

steam distillation, 8.6 g. crude acids was obtained (m. p. 100–120°; mixed m. p. with benzoic acid 85–97°; neut. equiv. 215). This acid mixture was dissolved in dilute sodium hydroxide solution, treated with decolorizing charcoal and precipitated with hydrochloric acid. The product thus obtained (m. p. 117–138°; mixed m. p. with benzoic acid 100–110°) was recrystallized twice from dilute alcohol and once from water, giving a small amount of product of m. p. 180–185° (the melt was not clear until 250–260°). This product was proved to contain *p*-substituted benzoic acid by oxidation by boiling for about ten minutes in alkaline solution with excess potassium permanganate. The acid obtained from the oxidation was practically insoluble in water and alcohol, did not melt up to 310° and had neut. equiv. 85. It was identified as terephthalic acid (neut. equiv. 83) by its dimethyl ester of m. p. 139–140° (lit. m. p. for dimethyl terephthalate 140°).

Summary

A study has been made of the products of the reaction of benzoyl peroxide with excess diethyl ether, diethyl Cellosolve and dioxane at about 40°. With diethyl ether and diethyl Cellosolve the chief products are carbon dioxide, benzoic acid and acylals, *i. e.*, benzoates of the radicals derived from the respective ethers by loss of methylenic hydrogen. With dioxane the above products are obtained and also considerable amounts of higher molecular weight acids and acylals. These results have been interpreted as being in general agreement with a postulated chain mechanism for the decomposition of benzoyl peroxide in these solvents.

SCHENECTADY, N. Y. RECEIVED SEPTEMBER 26, 1946

CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY DENTAL SCHOOL, AND DEPARTMENT OF PHARMACOLOGY, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL]

Dialkylaminoalkyl Esters of 4,4'-Stilbenedicarboxylic and 4,4'-Dibenzyl-dicarboxylic Acid^{1,2,3}

BY L. S. FOSDICK AND K. F. URBACH

A great number of structurally unrelated compounds are known to produce local anesthesia. No single grouping has been observed to explain this effect although certain substitutions and structural characteristics are known to influence it. For example, Kamm¹ in considering certain derivatives of *p*-aminobenzoic acid has observed that local anesthetic activity is destroyed if the double bond conjugation between the carbonyl group and the aromatic nucleus is interrupted. This suggests that one of the structural characteristics influencing local anesthetic activity is the existence of double bond conjugation between

the carbonyl group and the aromatic nucleus in this type of anesthetic. In support of this hypothesis are the observations of Shriner⁵ on the vinylogy of *p*-aminobenzoic acid derivatives, the observations on the activities of *p*-amino and *m*-aminomandelic acid esters^{6,7} and the studies by Whitacre⁸ on the interrelationship between type of linkage of the ester carbonyl group to the aromatic ring and local anesthetic activity.

In addition, Gilman⁹ has pointed out that ethylenic linkages in positions other than between the carbonyl group and the aromatic nucleus increase local anesthetic activity.

This suggests that double bond conjugation, in general, plays a marked role in local anesthetic activity of a given compound. In support of this

(1) Presented before the Division of Medicinal Chemistry at the American Chemical Society meeting, September 12, 1946.

(2) A part of this material is taken from the thesis of Mr. Urbach submitted at Northwestern University Graduate School. Present address, Department of Pharmacology, Northwestern University Medical School.

(3) This work has, in part, been done under a grant from the Alford Fund.

(4) Kamm, *THIS JOURNAL*, **42**, 1030 (1920).

(5) Shriner and Keyser, *ibid.*, **60**, 286 (1938).

(6) Fosdick and Wessinger, *ibid.*, **60**, 1465 (1938).

(7) Fosdick and Calandra, *ibid.*, **63**, 1101 (1941).

(8) Whitacre, *Anesthesia and Analgesia*, **18**, 112 (1939).

(9) Gilman and Pickens, *THIS JOURNAL*, **47**, 245 (1925).