Similarly, the sodium salt of N-benzylaniline failed to react with 4-fluorobenzonitrile or with 4-fluorobenzotrifluoride. When the anion of acetanilide was employed with 4-fluoroacetophenone or the 4-fluorobenzonitrile, no desired substitution products were obtained. It will be noticed from Table II that benzylamine reacted only with one molecule of p-fluorobenzonitrile, even though a 6:1 ratio of fluoro compound to amine was used. Again, the intermediate benzylaniline is too poor a nucleophile to effect further displacement. p-Difluorobenzene, p-bromofluorobenzene and 2,4-dibromofluorobenzene were recovered unchanged from attempted displacement reactions with piperidine in DMSO.

Experimental Section[8]

The following examples illustrate the experimental procedures.

4-Piperidinobenzonitrile.—A mixture of 3.4 g (0.04 mole) of piperidine, 4.84 g (0.04 mole) of 4-fluorobenzonitrile, 5.52 g (0.04 mole) of anhydrous potassium carbonate, and 50 ml of dimethyl sulfoxide was stirred and heated at 95° for 6 hr. The mixture was cooled and washed with water. After drying, the crude solid (6.7 g, mp 46–52°) was recrystallized from n-heptane–diethyl ether: yield 5.8 g (77%), mp 54–55°.

4-Piperidinoacetophenone. A.—A mixture of 3.06 g (0.036 mole) of piperidine, 4.14 g (0.03 mole) of 4-fluoroacetophenone,

4.14 g (0.03 mole) of anhydrous potassium carbonate, and 10 ml of dimethylformamide was stirred and heated at 95° for 6 hr. After cooling to room temperature, the reaction mixture was poured into 300 ml of ice-water, and 4-piperidinoacetophenone (4.71 g; 76.6% theory), mp 75–79°, was removed by filtration. Recrystallization from n-heptane gave 4.3 g of solid, mp 87–88°, which showed an infrared absorption spectrum identical with that of the crude product.

The aqueous solution was extracted with ether, the dried extract was evaporated, and to the oily residue water and pentane were added, causing crystallization of 0.23 g (4.3% yield) of 4-dimethylaminoacetophenone, mp 98–101°, which after crystallization from pentane melted at 104–105° and was identical (infrared spectra and mixture melting point) with the authentic sample (see below).

B.—Under the same conditions, but using 10 ml of dimethyl sulfoxide instead of dimethylformamide, filtration of the solid from water gave 5.82 g (94.6% theory) of 4-piperidinoacetophenone, mp 86–88°.

4-Dimethylaminoacetophenone.—Dimethylamine gas was passed through a solution of 4.14 g (0.03 mole) of 4-fluoroacetophenone in 100 ml of dimethyl sulfoxide kept at 80° for 5 hr, by which time absorption of the gas ceased. The solution was poured into 600 ml of water, and the product was filtered and air dried, yielding 5.0 g (96.3% theory) of solid, mp 102–104.5°. Crystallization from n-heptane gave long needles: mp 105–106°; ultraviolet absorption, $\lambda_{max}^{95\% \; EtOH}$ 240 mμ (ϵ 6800) and 332 mμ (ϵ 27,700); lit. mp 102–104° (Table II, ref c), 106°;[7] $\lambda_{max}^{95\% \; EtOH}$ 240 mμ (ϵ 6300) and 333 mμ (ϵ 28,200).[7,9]

(8) Melting points are corrected. Ultraviolet spectra were determined on a Beckman Model DK-2A ultraviolet spectrophotometer. Analyses were performed by Mr. Charles Pouchert of our Analytical Department.

(9) ϵ values quoted here (ref 7a) were read from the curve; ref 7b gives λ_{max}^{EtOH} 240.5 and 331.5 mμ. The same authors[7a,b] give, for the 3 isomer, mp 43°, λ_{max}^{EtOH} 241.7 (ϵ 22,400) and 360.5 mμ (ϵ 1800); and, for the 2 isomer, oil, λ_{max}^{EtOH} 267 mμ (ϵ 2200) and 349 mμ (ϵ 1800).

Nucleophilic Activity of the Phosphoryl Group. Oxygen-18 Transfer in Reactions of Phenyl Isocyanate with Labeled Phosphine Oxides[1a]

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The proposed mechanism for the formation of carbodiimides from isocyanates using phosphine oxide catalysts has been tested using phosphine oxides labeled with oxygen-18. With both triphenylphosphine oxide-O[18] and 3-methyl-1-phenyl-3-phospholene 1-oxide-O[18] the carbon dioxide formed is enriched in oxygen-18. As the reaction progresses, the oxygen-18 content of the carbon dioxide formed decreases rapidly toward normal isotopic distribution while the second-order rate remains constant. The results demonstrate facile phosphorus–oxygen bond cleavage in the cyclic intermediate or transition state formed between isocyanate and phosphine oxide and provide strong support for the proposed mechanism.

The formation of carbodiimides from aryl isocyanates under the catalytic influence of the phosphoryl group is a convenient method for the preparation of these compounds in high purity under mild conditions.[2a]

A kinetic study of the reaction led to a proposed mechanism involving formation of an intermediate phosphinimide (II) followed by reaction of II with a second molecule of isocyanate to form the carbodiimide and regenerate the catalyst.[2b] Formation of the phosphinimide is believed to occur through the transition state or intermediate I formed by nucleophilic attack on the isocyanate carbonyl by the polarized oxygen of the phosphine oxide followed by cleavage of the phosphorus–oxygen bond. Nucleophilic activity
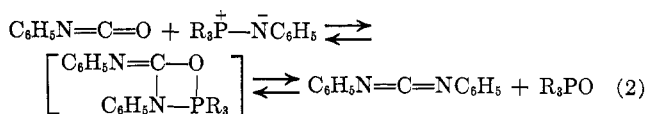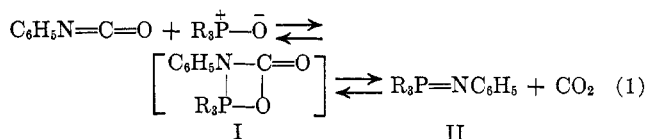
of the phosphoryl group has been well demonstrated[3] but cleavage of the very stable phosphorus–oxygen bond is less well documented. Although evidence is available that this type of cleavage can occur under mild conditions,[3c] establishment of this point to support the proposed mechanism was essential to further study of the reaction.

$$C_6H_5N{=}C{=}O + R_3\overset{+}{P}{-}\overset{-}{O} \rightleftharpoons$$

$$\left[\begin{array}{c} C_6H_5N{-}C{=}O \\ | \quad\quad | \\ R_3P{-}O \end{array}\right] \rightleftharpoons R_3P{=}NC_6H_5 + CO_2 \quad (1)$$

$$\text{I} \qquad\qquad\qquad \text{II}$$

$$C_6H_5N{=}C{=}O + R_3\overset{+}{P}{-}\overset{-}{N}C_6H_5 \rightleftharpoons$$

$$\left[\begin{array}{c} C_6H_5N{=}C{-}O \\ | \quad\quad | \\ C_6H_5N{-}PR_3 \end{array}\right] \rightleftharpoons C_6H_5N{=}C{=}NC_6H_5 + R_3PO \quad (2)$$

(1) (a) Presented at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965. (b) Taken from a portion of a thesis by J. M. in partial fulfillment of requirements for the M.S. Degree.

(2) (a) T. W. Campbell, J. J. Monagle, and V. S. Foldi, *J. Am. Chem. Soc.*, **84**, 3673 (1962); (b) J. J. Monagle, T. W. Campbell, and H. F. McShane, Jr., *ibid.*, **84**, 4288 (1962); (c) J. J. Monagle, *J. Org. Chem.*, **27**, 3851 (1962).

(3) (a) H. J. Harwood and D. W. Grisley, Jr., *J. Am. Chem. Soc.*, **82**, 423 (1960); (b) R. G. Laughlin, *J. Org. Chem.*, **27**, 1005 (1962); (c) M. Green and R. F. Hudson, *Proc. Chem. Soc.*, 217 (1962).
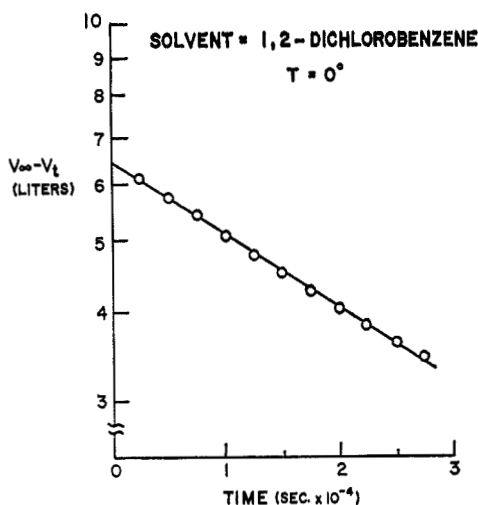
Figure 1.—First-order plot of the reaction of phenyl isocyanate in the presence of catalyst III.

This phosphorus–oxygen bond cleavage has now been confirmed by the reaction of phenyl isocyanate with phosphine oxides labeled with oxygen-18.

Experimental Section

Materials.—Phenyl isocyanate (Eastman) and *o*-dichlorobenzene (Baker Analyzed) were redistilled before use. Water containing 1.6 atom-% O^{18} was obtained from Liquid Carbonic Division of General Dynamics Corp. Bromine (Baker Analyzed) and triphenylphosphine (Matheson) were used as received.

Triphenylphosphine Oxide-O^{18}.—This compound was prepared by modification of the method of Halmann and Pinchas.[4] A solution containing 10 g (0.062 mole) of bromine in 100 ml of carbon tetrachloride was slowly added at room temperature to a solution of 16 g (0.061 mole) of triphenylphosphine in 300 ml of carbon tetrachloride. The resulting adduct was hydrolyzed *in situ* by the addition of 10 ml (0.56 mole) of water (1.6% H_2O^{18}) with vigorous stirring. The carbon tetrachloride was decanted from the precipitated phosphine oxide and the crude product was suspended in 500 ml of boiling water to remove the hydrobromic acid formed in the hydrolysis. Filtration of the cooled mixture followed by two sublimations gave 13.4 g (79%) of pure compound, mp 157–158° (lit. mp 158.5–159.5).[4]

3-Methyl-1-phenyl-3-phospholene 1-Oxide-O^{18} (III).—Hydrolysis of 52 g (0.21 mole) of 1,1-dichloro-3-methyl-1-phenyl-3-phospholene, prepared by the method of McCormack,[5] was carried out by the addition of 25 ml (1.39 moles) of water (1.6% H_2O^{18}) in a flask cooled in an ice bath. The resulting mixture was carefully neutralized to a pH of 6.5 with aqueous 30% sodium hydroxide solution. The neutralized solution was saturated with sodium chloride, then extracted with three 75-ml portions of chloroform. The combined chloroform extracts were concentrated and the residue was sublimed to yield 36.5 g (90%) of III, mp 64–67° (lit. mp 60–65° for unlabeled compound).[5] Portions of this compound used as a catalyst were distilled immediately prior to use (bp 174–175° (0.7 mm)).

Reactions of Phenyl Isocyanate with Labeled Phosphine Oxides.—The apparatus used consisted of a magnetically stirred 25-ml flask fitted with a small reflux condenser and attached to a gas sampling system consisting of several 125-ml evacuated sample bulbs. A manometer attached to the system was used to determine when the sample bulbs were filled. The sample bulbs were carefully dried, evacuated, and flushed with nitrogen several times before use.

A. Reaction with Triphenylphosphine Oxide-O^{18}.—Phenyl isocyanate (0.046 mole) and triphenylphosphine oxide-O^{18} (0.018 mole) were placed in the 25-ml flask. After the system was flushed with nitrogen, the flask was heated in an oil bath until carbon dioxide began to evolve at a convenient rate (135–145°). The reaction mixture was maintained at this temperature until two sample bulbs were consecutively filled.

B. Reaction with 3-Methyl-1-phenyl-3-phospholene 1-Oxide-O^{18} (III).—Freshly distilled III (0.026 mole) was dissolved in 10 ml of dry 1,2-dichlorobenzene, placed in the 25-ml flask, and solidified at −78°. Phenyl isocyanate (0.046 mole) previously cooled to −20° was added and the system was flushed with nitrogen. The reaction flask was allowed to warm to 0–10° and three consecutive 125-ml gas samples were taken.

Comparison of O^{18} Transfer with Kinetics of Carbodiimide Formation.—The apparatus for kinetic runs consisted of a 125-ml, three-necked flask attached to a manometer, and two 100-ml gas burets in parallel. A three-way stopcock arrangement was used to switch burets. Dibutyl phthalate colored with a dye and previously saturated with carbon dioxide was used to fill the gas burets and leveling bulbs. The gas burets were maintained at constant temperature by means of a water jacket. An ice bath was used to maintain the reaction temperature at 0°. Both the reaction mixture and the ice bath were vigorously stirred by means of a magnetic stirrer.

To the reaction flask was added 100 ml of 1,2-dichlorobenzene containing 50 ml (0.46 mole) of phenyl isocyanate. The reaction mixture was stirred for 1 hr at 0°, during which time the system was flushed with nitrogen. A 10-ml aliquot of a solution of known concentration of III in 1,2-dichlorobenzene was then added from a pipet. When addition of the catalyst was completed, the timer was started and readings of time and evolved gas were taken about every 50 ml. The first 500 ml of evolved carbon dioxide was transferred, in 100-ml portions, from the burets into five consecutive sample bulbs for analysis.

Kinetic runs in 1,2-dichlorobenzene followed pseudo-first-order kinetics. Data were treated as follows. The pseudo-first-order rate constants k_1 were obtained graphically from the straight-line portions of log $(V_\infty - V_t)$ vs. time (see Figure 1). The value taken for V_∞ was the volume of 0.230 mole of carbon dioxide corrected to the temperature and pressure at which V_t was measured. Values of the second-order rate constant, k_2, were obtained by dividing k_1 by the catalyst concentration.

Analysis of Carbon Dioxide Samples.—Carbon dioxide samples were analyzed by Sinclair Research Laboratories using a Consolidated Electrodynamics mass spectrometer Model No. 21-102 at an excitation voltage of 70 v. The limits of error in the analysis were estimated to be ±1% relative to the amount of each component present. Tank carbon dioxide used as a standard showed a $CO^{16}O^{18}$ content of 0.41% in agreement with literature values.[6]

Results

According to the proposed mechanism, each molecule of carbon dioxide evolved in the reaction obtains one of its oxygen atoms from the phosphoryl group of the catalyst. Use of phosphine oxides labeled with oxygen-18 should therefore yield carbon dioxide which is initially enriched in oxygen-18. Also, since regeneration of phosphine oxide in the second step of the reaction would produce unlabeled catalyst which would repeat the catalytic cycle to yield carbon dioxide of normal oxygen-18 content, the oxygen-18 content of the carbon dioxide should drop rapidly to normal abundance.

To test this point, experiments were carried out using phenyl isocyanate and two representative catalysts, triphenylphosphine oxide and 3-methyl-1-phenyl-3-phospholene 1-oxide (III) labeled with approximately 1.6% oxygen-18.

III
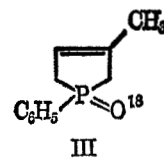
(4) M. Halmann and S. Pinchas, *J. Chem. Soc.*, 3264 (1958).

(5) W. B. McCormack, *Org. Syn.*, **43**, 73 (1963).

(6) "Handbook of Chemistry and Physics," R. C. Weast, Ed., 45th ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1964, p B-7.

Triphenylphosphine oxide was chosen because it shows the same kinetic behavior as the phosphine oxides previously studied.[7] In addition, Halmann and Pinchas[4] have demonstrated that its oxygen will not exchange with solvent water during isolation and purification. This assures the preparation of phosphine oxide of known O^{18} content.

Catalyst III was chosen because it was one of the compounds used in the original mechanism study.[2b]

The first experiments were carried out using relatively large amounts of each catalyst to allow collection of sufficient carbon dioxide from *initial* reaction of phosphine oxide with isocyanate to establish unequivocally the presence or absence of carbon dioxide-O^{18} in greater than natural abundance. Results of duplicate experiments are shown in Table I. With both catalysts the O^{18} content of the carbon dioxide formed was well above normal abundance. As successive samples were taken, the amount of labeled carbon dioxide decreased slowly.

TABLE I

$CO^{16}O^{18}$ ANALYSES[a] FOR

$$2C_6H_5NCO \xrightarrow{R_3PO^{18}} CO_2 + C_6H_5N\!\!=\!\!C\!\!=\!\!NC_6H_5$$

Catalyst[b]	Moles of NCO/ mole of catalyst	Reaction interval, %	$CO^{16}O^{18}$,[c] %
$(C_6H_5)_3PO^{18}$	2.6	0–17	1.49
		17–36	1.32
III	1.8	0–15	1.56
		15–34	1.43
		34–53	1.37

a Results of duplicate runs. *b* Theoretical O^{18} content 1.6%. *c* Theoretical O^{18} content 1.8% (O^{18} content of phenyl isocyanate is 0.2%).

To relate the transfer of oxygen to the previous mechanism studies, the rate of decrease of carbon dioxide-O^{18} was determined in kinetic runs at 0°, using catalytic amounts of III in the presence of a large excess of phenyl isocyanate in *o*-dichlorobenzene. Under these conditions the reactions were pseudo first order as found previously, and the order and rate of the reaction were constant over at least 50% reaction (Figure 2).

Analysis of samples of carbon dioxide taken from the initial portions of the kinetic run showed that, in each case, the proportion of carbon dioxide-O^{18} dropped rapidly and, after approximately 6% reaction, the

TABLE II

$CO^{16}O^{18}$ ANALYSES FOR KINETIC RUN[a-c]

$$2C_6H_5NCO \xrightarrow{R_3PO^{18}} CO_2 + C_6H_5N\!\!=\!\!C\!\!=\!\!NC_6H_5$$

Reaction interval, %	$CO^{16}O^{18}$,[d] %
0–0.2	1.57
0.2–1.1	0.64
1.1–2.4	0.55
2.4–4.1	0.53
4.1–5.8	0.52

a Catalyst III. *b* Moles of isocyanate/mole of catalyst = 87. *c* Second-order rate constant = 4.8 × 10^{-4} l. mole^{-1} sec^{-1}. *d* Theoretical O^{18} content 1.8% (O^{18} content of phenyl isocyanate is 0.2%).
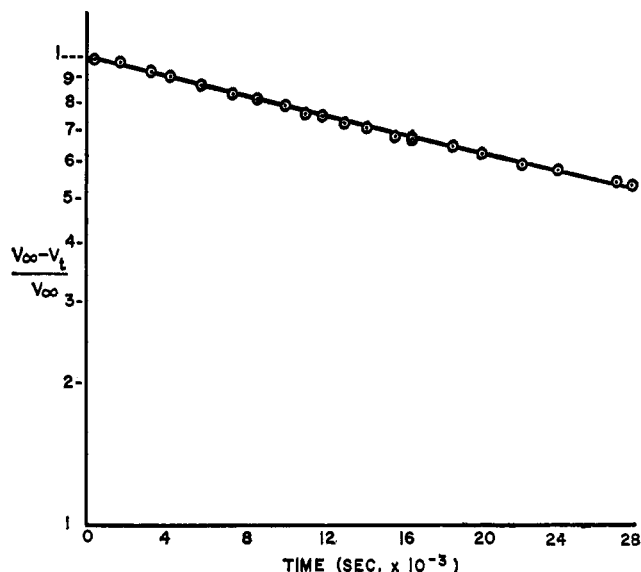

Figure 2.—Per cent reaction *vs.* time for reaction of phenyl isocyanate with catalyst III.

content of labeled carbon dioxide had dropped to 0.5%, very close to the value for natural abundance (0.4%).[6] The change in labeled carbon dioxide with increasing per cent reaction is shown in Table II.

Discussion of Results

With both phosphine oxides tested the results clearly establish that the carbon dioxide which is formed in the reaction obtains one of its oxygen atoms from the phosphoryl group.

Under the conditions of the kinetics experiments, the transfer of oxygen is extremely rapid. In reactions requiring approximately 8 hr for half-reaction, the carbon dioxide-O^{18} content drops to 0.5% within 7 min. The first-order dependence of the rate on phosphine oxide and isocyanate, respectively, and the constancy of the rate after essentially complete transfer of the labeled oxygen indicate that the phosphoryl oxygen is being transferred in the rate-controlling step (1) in the reaction and that the catalyst is being regenerated in a rapid reaction. These results are completely consistent with the proposed mechanism.[2b]

The results also provide evidence, similar to that of Green and Hudson,[3c] that the phosphorus–oxygen bond of the phosphoryl group can cleave under unexpectedly mild conditions considering the strength of this bond.[8]

With this additional substantiation of the mechanism involving nucleophilic activity of the phosphoryl group, the reaction of isocyanates with phosphoryl compounds offers a convenient method for a study of the factors controlling this activity. This study is now in progress.

This type of activity, plus the possibility of cleavage of the phosphorus–oxygen bond under mild conditions, may also require reappraisal of the mechanisms of many reactions, including biochemical processes, in which the possibility of participation by the phosphoryl group has been largely ignored. This area is now being explored.

Finally, in view of the variety of phosphoryl deriva-

(7) J. J. Monagle and D. A. Jones, Jr., unpublished work.

(8) A. F. Bedford and C. T. Mortimer, *J. Chem. Soc.*, 1622 (1960).

tives which react with isocyanates,[2c] the reaction may offer a convenient method to follow reactions of phosphorus compounds in which phosphoryl oxygen is being added or removed. Applications to several problems of this type are under study.

# Hydrolysis and Autoxidation of N-Benzoylleucomethylene Blue

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Hydrolysis of N-benzoylleucomethylene blue in 0.5 M sulfuric acid is a first-order reaction ($k_{50} = 29.3 \times 10^{-7}$ sec^{-1}), which is unaffected by, and independent of, the concurrent autoxidative development of methylene blue. N-Benzoylleucomethylene blue in aqueous sulfuric acid reacts with oxygen in a 1:0.5 molar ratio to form methylene blue and benzoic acid. After an induction period, the methylene blue formation follows first-order kinetics ($k_{50} = 30.0 \times 10^{-7}$ sec^{-1}). The rate constant for color production is independent of substrate concentration and oxygen pressure as well as of added methylene blue, benzoic acid, sodium chloride, mannitol, or ethanol. Color production becomes faster when the acid concentration is increased. p-Nitrobenzoylleucomethylene blue autoxidizes more slowly, p-methoxybenzoylleucomethylene blue more rapidly, than unsubstituted N-benzoylleucomethylene blue. All the data for autoxidation are consistent with a slow hydrolysis of N-benzoylleucomethylene blue to leucomethylene blue, followed by a more rapid oxidation of leucomethylene blue to methylene blue. The available data offer no support for participation of hydrogen peroxide in the oxidative stages. Several oxidants other than oxygen can convert N-benzoylleucomethylene blue to methylene blue without preliminary hydrolysis.
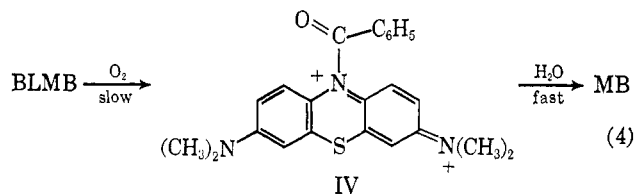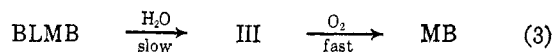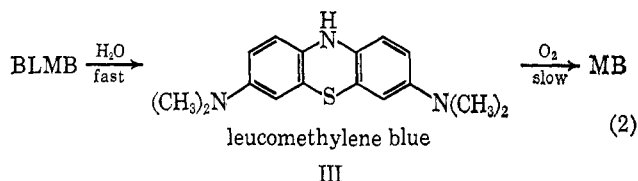
A colorless, acid solution of N-benzoylleucomethylene blue (BLMB, I) becomes blue on exposure to air. We have examined this process both qualitative and quantitatively and are now reporting the results. Equation 1 summarizes the over-all process. Benzoic acid is formed, as shown by its isolation. The color is that of methylene blue (MB, II), which may be isolated as the solid perchlorate salt and also identified by its absorption spectrum. Oxygen is required; no color develops in its absence.

$$+ \ 0.5O_2 \longrightarrow$$

BLMB

I

$$+ \ C_6H_5COOH \quad (1)$$

MB

II
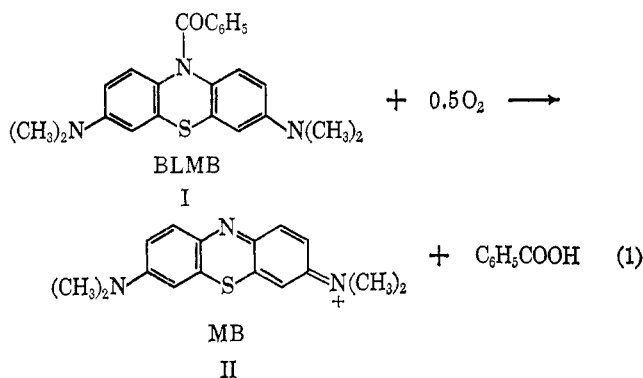
The stoichiometry of eq 1 was arrived at by finding the BLMB:methylene blue and the oxygen:methylene blue ratios. The former, determined by comparing the amount of BLMB starting material with the maximum intensity of color produced, is 1:1. The latter, determined by following oxygen absorption manometrically and color formation spectrophotometrically, is 1:2.

We considered three sequences for the conversion of BLMB (I) to methylene blue (II). Equation 2 shows how BLMB might first be hydrolyzed to leucomethylene blue (III) in a relatively fast step, which is followed by a rate-determining reaction of leucomethylene blue with oxygen. Equation 3 has the same sequence but with hydrolysis slow and autoxidation fast. Equation 4 has oxygen reacting directly with BLMB in a

rate-determining step to form an intermediate such as benzoylmethylene blue (IV), which would be expected to hydrolyze very rapidly to give the observed prod-

$$BLMB \xrightarrow[\text{fast}]{H_2O}$$

$$\xrightarrow[\text{slow}]{O_2} MB$$

leucomethylene blue

III

$$(2)$$

$$BLMB \xrightarrow[\text{slow}]{H_2O} III \xrightarrow[\text{fast}]{O_2} MB \quad (3)$$

$$BLMB \xrightarrow[\text{slow}]{O_2}$$

$$\xrightarrow[\text{fast}]{H_2O} MB$$

IV

$$(4)$$

ucts.[1] Comparison of the hydrolysis of BLMB in the presence and absence of air, as well as comparison of the rates of BLMB hydrolysis and methylene blue production, enabled a choice to be made between these three alternatives.

Hydrolysis of BLMB.—Hydrolysis of BLMB in 0.5 M sulfuric acid at 50° was followed with the help of an isotope-dilution procedure. The necessary radioactive BLMB was prepared by benzoylating the Grignard derivative of leucomethylene blue with carbonyl-labeled benzoyl chloride. In the absence of oxygen, the hydrolysis over 3 half-lives showed good first-order kinetics, with a rate constant of 26.5 (± 3) $\times$ 10^{-7} sec^{-1} (99% confidence level). A series of runs was also performed with oxygen present and, therefore, with methylene blue color developing simultaneously. Some of the runs were simply the continuation of the

(1) The formation of benzoylmethylene blue (IV) from BLMB is analogous to the formation of reactive, electron-deficient intermediates from hydroquinone precursors in oxidative phosphorylation. *Cf.* D. M. Brown, *Advan. Org. Chem.*, **3**, 138 (1963).