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The Reaction of Ketones with Peroxides in Alkaline Solution

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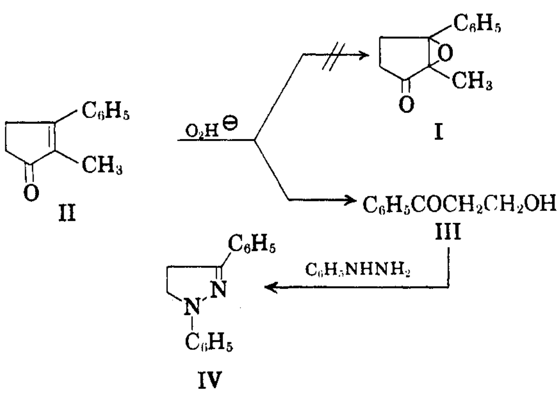
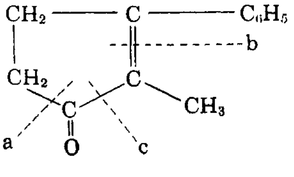
The reaction of 2-methyl-3-phenyl-2-cyclopentenone with alkaline hydrogen peroxide yielded β-hydroxypropiophenone. The cleavage of four ketones, butyrophenone, 2-pentanone, 2-octanone, and 2-methyl-3-hexanone, with sodium hydroperoxide was studied. A possible explanation for the results is suggested.

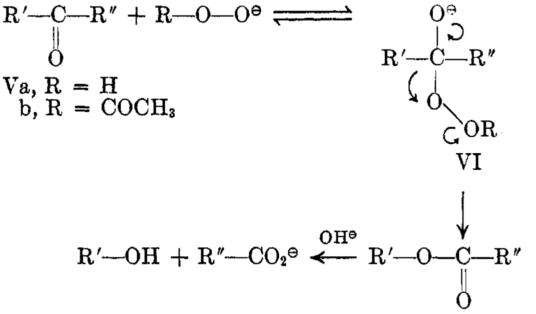
In an attempt to prepare 2,3-epoxy-2-methyl-3-phenylcyclopentanone (I) the corresponding unsaturated ketone II was treated with alkaline hydrogen peroxide. However, the product isolated from this reaction clearly was not the expected oxide I. The infrared and ultraviolet spectra of the product indicated the presence of conjugated carbonyl and hydroxyl functions; the composition of the material, $C_9H_{10}O_2$, established the loss of three carbon atoms in the reaction. These data suggested that the product was the previously unknown β-hydroxypropiophenone (III). This structural assignment was confirmed by treatment of the hydroxy ketone III with phenylhydrazine. The product, 1,3-diphenyl-2-pyrazoline (IV), was identical with an authentic sample prepared from β-dimethylaminopropiophenone and phenylhydrazine.



Since no other product was isolated the fate of the three carbon atoms lost in the reaction is unknown. The most reasonable course for the reaction involves cleavage of the unsaturated ketone II at positions designated as *a* and *b* in Figure 1. The carbon-carbon bond cleavage at position *a* can be likened to a Baeyer-Villiger reaction in which a ketone is cleaved in the presence of a peracid to yield an ester or, after hydrolysis, an alcohol and a carboxylic acid. A possible base-catalyzed counterpart of the Baeyer-Villiger reaction is illustrated in the accompanying equation.[1] Reaction of a ketone with the hydroperoxide anion Va to form the intermediate VI is in accord with the pronounced nucleophilic character of the hydroperoxide anion.[2]

FIGURE 1





The assumption of such a reaction path offers an explanation as to why the unsaturated ketone II underwent oxidative cleavage rather than base-catalyzed epoxidation. The first step in the epoxidation, the conjugate addition of the hydroperoxide anion to the unsaturated ketone II,[3] would be impeded by the presence of an α-alkyl substituent which would destabilize the intermediate carbonion.[4] In addition, the carbonyl group, being part of a five-membered ring, should be particularly reactive in carbonyl addition reactions. A combination of these factors could easily account for the fact that the predominant reaction with the ketone II is cleavage and not epoxidation. The relatively poor yields obtained in the epoxidation of other cyclic unsaturated ketones[5] is perhaps best attributed to this side reaction rather than a retrograde

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(1) A similar mechanism has been proposed for the Dakin reaction [J. Hine, *Physical Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 324].

(2) K. B. Wiberg, *J. Am. Chem. Soc.*, **75**, 3961 (1953); *J. Am. Chem. Soc.*, **77**, 2519 (1955).

(3) C. A. Bunton and G. J. Minkoff, *J. Chem. Soc.*, 665 (1949).

(4) For example, the epoxidation of both α-ethyl- and α-methyl-*trans*-benzalacetophenone is appreciably slower than the corresponding reaction with α-phenyl-*trans*-benzalacetophenone or *trans*-benzalacetophenone [H. O. House and D. J. Reif, *J. Am. Chem. Soc.*, in press, and earlier work cited therein]. Similarly, the conjugate addition of methoxide ion is inhibited by the presence of an α-alkyl substituent [J. E. Dubois and R. Luft, *Compt. rend.*, **242**, 905 (1956)].

(5) H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957).

aldol condensation as we had previously supposed.

The cleavage of ketones by alkaline hydrogen peroxide is not without precedent, the reaction having been observed previously with cyclohexanone,[6,7] cyclopentanone,[8,9] and one substituted cyclopentanone.[9] Related reactions include the cleavage of certain aromatic aldehydes[10] and of α-diketones.[11] In each of these previous examples the cleavage products are the same as those formed when the carbonyl compounds are treated with peracids. However, the reaction of one α-diketone with alkaline hydrogen peroxide has been found[12] to yield products different from those obtained when the diketone was cleaved with a peracid.[3] The interesting cleavage of certain α,β-unsaturated ketones recently reported by Southwick and coworkers[13] also represents a marked departure from the reaction to be expected with peracids and may be similar to the cleavage reported here.

Although the cleavage of the unsaturated ketone II at position *a* (Figure 1) bears a resemblance to the Baeyer-Villiger reaction, one point of difference is readily apparent. In previous studies[14–16] of the reaction of α,β-unsaturated ketones with peracids cleavage has invariably occurred at the bond joining the carbonyl group to the carbon-carbon double bond. Consequently, reaction of the unsaturated ketone II with a peracid would be expected to result in cleavage at position *c* (Figure 1). These considerations, which suggested that the base-catalyzed reaction of ketones with peroxides differed both in mechanism and direction of cleavage from the acid-catalyzed[17] reaction, prompted us to study the reaction of several simple ketones with peroxides in alkaline solution.

Butyrophenone reacted very slowly with sodium hydroperoxide in methanol solution at room temperature to form benzoic acid. Even after a reaction period of 118 hr. the bulk of the ketone was recovered, the yield of benoic acid being 5.8%. In an effort to increase the yield of cleavage products, the reaction was run at the boiling point of methanol. Under these conditions the reaction time was limited to about 2 hr. by the instability of the sodium hydroperoxide; the yield of benzoic acid was 11%. The necessity of base in the reaction was demonstrated by treatment of butyrophenone with a methanolic solution of hydrogen peroxide which contained no alkali. Only the unchanged ketone was isolated from the mixture. The amount of benzoic acid formed was estimated to be 0.3%.

The possible mechanism outlined previously for the base-catalyzed cleavage suggested that the reaction might be accelerated if the hydroxide ion (or water) eliminated from the intermediate VI were replaced by a more favorable leaving group. To explore this possibility butyrophenone was treated with sodium peracetate in methanol. As in a previous experiment the reaction time was limited by the instability[18] of sodium peracetate. However the reaction was definitely more rapid than the corresponding reaction with sodium hydroperoxide under comparable conditions, the yield of benzoic acid being 7.2% after a reaction time of 22 hr. at room temperature.

In no instance could butyric acid be detected in the reaction mixtures obtained from butyrophenone. Each of the alkaline reaction mixtures contained *n*-propyl alcohol; unfortunately the amounts of *n*-propyl alcohol were too small to permit reliable yield estimates. In one case, the reaction of the ketone with sodium hydroperoxide in boiling methanol, a small amount of propionic acid was also formed. This acid may have resulted either from further oxidation of propyl alcohol or by direct oxidation of the enolate anion derived from butyrophenone.[19] The absence of butyric acid in these experiments is in marked contrast to the results expected with peracids. Both acetophenone[20,21] and propiophenone[20] yield as major products the phenyl esters of the corresponding aliphatic acids when treated with peracids.[22]

To investigate the behavior of aliphatic ketones, 2-pentanone, 2-octanone, and 2-methyl-3-hexanone were treated with sodium hydroperoxide in boiling methanol. The neutral and acid components of the reaction mixtures were analyzed by vapor-phase chromatography. The results are outlined in Table I. The expected alcohols could be detected in each of the neutral fractions of the reaction mixtures;[23] however, reliable estimates of the quantities of the alcohols formed were not possible except in the case

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[6] S. W. Fox, E. H. Polak, M. W. Bullock, and Y. Kobayashi, *J. Am. Chem. Soc.*, **73**, 4979 (1951).

[7] H. W. Heine and H. Jones, *J. Am. Chem. Soc.*, **73**, 1361 (1951).

[8] M. Fling, F. N. Minard, and S. W. Fox, *J. Am. Chem. Soc.*, **69**, 2466 (1947).

[9] W. W. Westerfeld, *J. Biol. Chem.*, **143**, 177 (1942).

[10] H. D. Dakin, *Am. Chem. J.*, **42**, 477 (1909).

[11] C. A. Bunton, *Nature*, **163**, 444 (1949).

[12] A. H. Blatt and A. W. Rytina, *J. Am. Chem. Soc.*, **72**, 403 (1950).

[13] P. L. Southwick, H. L. Dimond, M. S. Moores, and D. I. Sapper, *J. Am. Chem. Soc.*, **78**, 101 (1956).

[14] J. Boeseken and A. L. Soesman, *Rec. trav. chim.*, **52**, 874 (1933).

[15] N. Prilejaeff, *Bull. soc. chim. France*, [4] **41**, 687 (1927).

[16] J. Boeseken and J. Jacobs, *Rec. trav. chim.*, **55**, 786 (1936).

[17] S. L. Friess and A. H. Soloway, *J. Am. Chem. Soc.*, **73**, 3968 (1951).

[18] D. Swern, *Chem. Revs.*, **45**, 1 (1949).

[19] W. von E. Doering and J. D. Chanley, *J. Am. Chem. Soc.*, **68**, 586 (1946); W. von E. Doering and R. M. Haines, *J. Am. Chem. Soc.*, **76**, 482 (1954).

[20] S. L. Friess, *J. Am. Chem. Soc.*, **71**, 14 (1949).

[21] W. von E. Doering and L. Speers, *J. Am. Chem. Soc.*, **72**, 5515 (1950).

[22] A comprehensive study of this reaction, reported by M. F. Hawthorne at the Sixth Reaction Mechanisms Conference, Swarthmore College, Sept. 12–15, 1956, supported the previously reported (ref. 20 and 21) observations.

[23] The presence of methanol has no meaning since it was the reaction solvent.

TABLE I

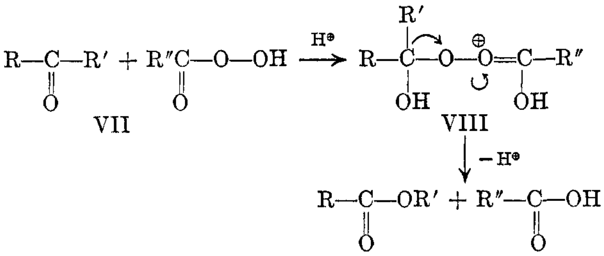
REACTION OF KETONES WITH SODIUM HYDROPEROXIDE IN BOILING METHANOL

Ketone	Recovered Ketone, %	Acidic Products (% Yield)
$C_6H_5COCH_2CH_2CH_3$[a]	80.8	$C_6H_5CO_2H$ (11.1%)[b]
$CH_3COCH_2CH_2CH_3$[c]	. . .	CH_3CO_2H (6.1%) + $CH_3CH_2CO_2H$ (1.6%) + $CH_3(CH_2)_2CO_2H$ (0.5%)
$CH_3CO(CH_2)_5CH_3$[c,d]	81	CH_3CO_2H (12%) + $CH_3(CH_2)_4CO_2H$ (1.6%) + $CH_3(CH_2)_5CO_2H$ (1.2%)
$CH_3CH\ CH_2COCH(CH_3)_2$[c]	82	$(CH_3)_2CHCO_2H$ (5.4%) + $CH_3(CH_2)_2CO_2H$ (1.9%)

[a] The yields were determined by isolation. [b] A small amount of propionic acid was also detected. [c] The yields were determined by vapor-phase chromatography. [d] The yield of *n*-hexyl alcohol from this reaction was estimated to be 8.8%.

of *n*-hexyl alcohol. It is apparent that the poor yields obtained in these reactions preclude the use of this reaction synthetically unless more favorable reaction conditions can be found.

Previous studies of the reaction of peracids with ketones[17,20,21,24,25] have indicated that the cleavage reaction involves migration of an alkyl or aryl group to an electron-deficient oxygen atom as shown in the accompanying equation. These studies have



VII VIII

$$R{-}C({=}O){-}R' + R''C({=}O){-}O{-}OH \xrightarrow{H^{\oplus}} R{-}C(R')(OH){-}O{-}\overset{\oplus}{O}{=}C(OH){-}R'' \xrightarrow{-H^{\oplus}} R{-}C({=}O){-}OR' + R''{-}C({=}O){-}OH$$

further suggested that the migratory aptitudes of the groups R and R′ in the ketone VII are in the order: tertiary alkyl > secondary alkyl > phenyl > primary alkyl > methyl. This order has been rationalized by the assumption that the group which can better tolerate a positive charge in the transition state is the more favorable migrating group. The results of this study (Table I) indicate that the ease of cleavage (and migratory aptitude if the assumed mechanism is correct) of groups from ketones with alkaline peroxides is in the order: primary alkyl > secondary alkyl > methyl and phenyl. There is no compelling reason for the requirements of the migrating group to be similar in the base-catalyzed and acid-catalyzed reactions VI and VIII. The requirements of the migrating group in the base-catalyzed cleavage process represented by VI can be compared more appropriately with the requirements of the migrating group in the benzilic-acid rearrangement.[26] Presumably, the same migrating group requirements would also be applicable to the rearrangement of certain 1,3-dihalides.[27] These investigations as well as the results reported here all suggest that the migratory aptitudes to be expected in base-catalyzed rearrangements differ from the order established for the migration of groups to electron deficient atoms. The studies of certain substituted benzils[12,26] further imply that the migration of aryl groups is facilitated by electron-withdrawing substituents. One possible method for learning whether this implication is correct would be the reaction of various substituted benzophenones with sodium hydroperoxide. However, this study does not appear to be profitable because of the experimental difficulties arising from the very poor yields obtained. The question might also be answered by a study of the rearrangement of 2,2-diaryl-1,3-dihalopropanes as suggested by Schubert and Leahy.[27]

EXPERIMENTAL[28]

2-Methyl-3-phenyl-2-cyclopentenone (II). The unsaturated

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[24] W. von E. Doering and E. Dorfman, *J. Am. Chem. Soc.*, **75**, 5595 (1953).

[25] W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

[26] The migration of a phenyl group in the benzilic-acid rearrangement is retarded by a *p*-methyl or *p*-methoxyl group and accelerated by a *m*- or *p*-chloro substituent [for leading references see M. T. Clark, E. C. Hendley, and O. K. Neville, *J. Am. Chem. Soc.*, **77**, 3280 (1955); D. G. Ott and G. G. Smith, *J. Am. Chem. Soc.*, **77**, 2325 (1955)] whereas the reverse substituent effect is observed in symmetrical pinacol rearrangements and related reactions [W. E. Bachmann and F. H. Mosher, *J. Am. Chem. Soc.*, **54**, 1124 (1932); J. G. Burr, Jr., and L. S. Ciereszko, *J. Am. Chem. Soc.*, **74**, 5426, 5431 (1952)]. Unfortunately, these results are not definitive of migratory aptitudes since the results may be explained in terms of the concentrations of the two possible intermediates prior to rearrangement [see J. D. Roberts, C. R. Smith and C. C. Lee, *J. Am. Chem. Soc.*, **73**, 619 (1951)].

[27] W. M. Schubert and S. M. Leahy, Jr., *J. Am. Chem. Soc.*, **79**, 381 (1957). In this study no products were isolated which would correspond to the migration of a phenyl group. This might be taken (and was by the authors) to mean that the migration of a phenyl group is unfavorable in this kind of rearrangement.

[28] All melting points are corrected and all boiling points are uncorrected. The ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, model 11 MS. The infrared spectra were determined either with a Baird, model B, or a Perkin-Elmer, model 21, double beam infrared recording spectrophotometer fitted with a sodium chloride prism. The microanalyses were performed by Dr. S. M. Nagy and his associates. The vapor-phase chromatographic analyses were obtained with a 8 mm. × 215 cm. column packed with di-(2-ethylhexyl) sebacate suspended on 50–80 mesh firebrick. The fractions from the chromatogram, eluted with helium, were detected with a thermal conductivity cell.

ketone, m.p. 49–50°, b.p. 90–91° (0.6 mm.) [lit.[29] m.p. 50–51°, b.p. 136–137° (6 mm.)], was obtained in poor yield by the base-catalyzed cyclization procedure of Koebner and Robinson.[29] In our hands the major product obtained from this reaction was β-benzoylpropionic acid. The unsaturated ketone II formed a 2,4-dinitrophenylhydrazone, m.p. 232–232.5° (lit.[29] 232–233°), in 95% yield. The infrared spectrum[30] of the unsaturated ketone has bands at 1695 cm.$^{-1}$ (conj. C=O in a 5-membered ring) and 1610 cm.$^{-1}$ (conj. C=C); the ultraviolet spectrum has maxima at 242 mμ (ϵ 1,500) and 279.5 mμ (ϵ 10,300).

Reaction of 2-methyl-3-phenyl-2-cyclopentenone (II) *with alkaline hydrogen peroxide.* A solution of 0.50 g. (0.0042 mole) of the ketone, 3 ml. (0.031 mole) of 30% aqueous hydrogen peroxide and 1 ml. (0.006 mole) of 6*N* aqueous sodium hydroxide in 20 ml. of methanol was stirred at room temperature (20–25°) for 4 hr. The reaction time was determined by measuring periodically the optical density of the reaction mixture at 279.5 mμ; after 4 hr. the optical density at 279.5 mμ had fallen to 1.8% of its initial value. However, the optical density of the reaction mixture at 240 mμ, examined several times during the reaction mixture, did not diminish in intensity. The reaction mixture was diluted with water and extracted with two 50-ml. portions of ether. After the combined extracts had been dried over magnesium sulfate and concentrated, the residual oil was crystallized from petroleum ether at Dry Ice temperatures. *β-Hydroxypropiophenone* separated as white crystals, m.p. 22–24°, yield 0.35 g. (58%). The infrared spectrum[31] of the product has bands at 3400 cm.$^{-1}$ (associated O—H) and 1690 cm.$^{-1}$ (conj. C=O); the ultraviolet spectrum has a maximum at 242 mμ (ϵ 10,000).

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 72.29; H, 6.99.

No acidic material was isolated from the alkaline aqueous solution from the reaction mixture.

A solution of 0.05 g. (0.00033 mole) of β-hydroxypropiophenone, 0.05 g. (0.00033 mole) of phenylhydrazine hydrochloride, and 0.1 g. of sodium acetate in 10 ml. of ethanol was refluxed for 30 min. The resulting cold solution deposited 0.05 g. (70%) of *1,3-diphenyl-2-pyrazoline* as light yellow needles, m.p. 150–152°. Recrystallization from ethanol sharpened the melting point of the pyrazoline to 151–151.5° (lit.[32] 151–153°). The material was shown to be identical with an authentic sample of pyrazoline, prepared as subsequently described, both by a mixed melting point determination and by comparison of the infrared spectra[33] of the two samples.

1,3-Diphenyl-2-pyrazoline (IV). A mixture of 2.13 g. (0.01 mole) of the hydrochloride of β-dimethylaminopropiophenone, 1.45 g. (0.01 mole) of phenylhydrazine hydrochloride, 2 ml. of 10% aqueous sodium hydroxide, 3 ml. of acetic acid, and 50 ml. of ethanol was boiled under reflux for 30 min. The pyrazoline separated from the cold solution as yellow needles, m.p. 148–152°, yield 1.6 g. (75%). Recrystallization from ethanol sharpened the melting point of the product to 151–151.5° (lit.[32] 151–153°).

Cleavage of butyrophenone with alkaline peroxides. Procedure A. A mixture of 14.8 g. (0.1 mole) of butyrophenone, 4 g. (0.1 mole) of sodium hydroxide,[34] 20 ml. (0.208 mole) of 30% aqueous hydrogen peroxide, and 100 ml. of methanol was boiled under reflux for 2 hr. at which time the solution gave a negative test for peroxides. After the bulk of the methanol had been distilled from the reaction mixture, the residue was diluted with water and extracted with ether. By the appropriate manipulations 11.95 g. (80.8%) of unchanged butyrophenone, b.p. 95–96° (6 mm.), n_D^{27} 1.5167, was recovered from the ether extract. The vapor phase chromatogram of the forerun from the distillation indicated the presence of *n*-propyl alcohol.

The aqueous, alkaline layer was concentrated and acidified. Benzoic acid, identified by a mixed melting point with an authentic sample, separated as white needles, m.p. 120.5–122.5°, yield 1.35 g. (11.1%). After the aqueous mother liquor had been extracted with ether, the extract was dried over magnesium sulfate and concentrated. Examination of the residual solution by vapor phase chromatography indicated the presence of a small amount of propionic acid; no butyric acid could be detected.

Procedure B. The same mixture of reagents as used in procedure A was stirred at room temperature for 118 hr., diluted with water and worked up as previously described. The yield of benzoic acid was 0.712 g. (5.8%) and the recovered butyrophenone amounted to 9.8 g. (66%). *n*-Propyl alcohol could be detected in the neutral fraction. The acidic residue, after removal of the bulk of the benzoic acid, was neutralized and treated with α,*p*-dibromoacetophenone. The infrared spectrum[30] of the resulting crude organic material has bands at 1705 and 1730 cm.$^{-1}$ attributable to the *p*-bromophenacyl ester of benzoic acid but lacks the absorption bands at 1715 and 1755 cm.$^{-1}$ found in the spectrum of the *p*-bromophenacyl ester of butyric acid.

As a control experiment a solution of 14.8 g. (0.1 mole) of butyrophenone and 20 ml. (0.208 mole) of 30% aqueous hydrogen peroxide in 100 ml. of methanol was stirred for 116 hr. The recovered butyrophenone amounted to 12.87 g. (86.9%). Since no benzoic acid could be isolated, the acid fraction was neutralized and treated with α,*p*-dibromoacetophenone. The infrared spectrum[30] of the resulting organic material indicated the presence of a small amount (estimated yield 0.3%) of the *p*-bromophenacyl ester of benzoic acid in the recovered α,*p*-dibromoacetophenone (C=O band at 1690 cm.$^{-1}$).

Procedure C. To a cold solution of 28 g. (0.7 mole) of sodium hydroxide in 200 ml. of methanol was added, dropwise and with stirring, 30 ml. of a solution of 0.2 mole of peracetic acid in acetic acid. The temperature was kept below 20° throughout the addition. The resulting mixture was treated with 14.8 g. (0.1 mole) of butyrophenone and then stirred at room temperature for 22 hr. The reaction mixture, which no longer gave a positive test for peroxides, was worked up as previously described. The yield of benzoic acid was 0.872 g. (7.2%) and the recovered butyrophenone amounted to 10.96 g. (74.2%). As in former cases *n*-propyl alcohol could be detected in the reaction mixture but butyric acid could not be detected.

Cleavage of the aliphatic ketones. The aliphatic ketones listed in Table I were all cleaved according to procedure A used for butyrophenone. The neutral and acidic fractions were weighed and then analyzed by vapor phase chromatography. The products listed in Table I were identified by demonstrating that their retention times corresponded to those of authentic samples of the various components. For the purpose of the yield estimates listed in Table I the response factors for the various components of the mixtures were all assumed to be unity.

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(29) A. Koebner and R. Robinson, *J. Chem. Soc.*, 566 (1941).

(30) Determined in chloroform solution.

(31) Determined in carbon tetrachloride solution.

(32) T. L. Gresham, J. E. Jansen, F. W. Shaver, and R. A. Bankert, *J. Am. Chem. Soc.*, **71**, 2807 (1949).

(33) Determined as a suspension in a potassium bromide pellet.

(34) It was found advantageous to prepare the sodium hydroperoxide from a methanolic solution of sodium hydroxide rather than by the usual technique of adding aqueous sodium hydroxide. Apparently the additional water introduced by the use of an aqueous solution facilitates decomposition of the sodium hydroperoxide, since the peroxide content of the reagent prepared with aqueous sodium hydroxide had fallen almost to zero at the end of 24 hr. at room temperature [see H. O. House and D. J. Reif, *J. Am. Chem. Soc.*, **76**, 6525 (1955)]. However, the reagent prepared as described here retained an appreciable peroxide content even after 5 days at room temperature.