The ether extracts were combined, washed with two 20-ml portions of cold water, and dried over magnesium sulfate. After the ether was removed under reduced pressure, the residue was recrystallized from 25 ml of petroleum ether (30–60°) to yield 1.7 g (84%) of 2,2-d_2-1-indanone (**5**), mp 39–40°. The nmr spectrum in the alicyclic region showed only one absorption peak at τ 6.90 corresponding to the protons in the 3 position of 1-indanone.

Preparation of 3-Chloropropiophenone-d_5 (6).—This compound was prepared in the same manner reported[25–27] for 3-chloropropiophenone. A solution of 26.6 g (0.21 mole) of 3-chloropropionyl chloride in 40 ml of benzene-d_6 was treated with 32 g (0.24 mole) of anhydrous aluminum chloride in 60 ml of dry carbon disulfide[27] and stirred for 75 min. The carbon disulfide was removed under reduced pressure and the dark residue was added to 500 g of cracked ice containing 50 ml of concentrated hydrochloric acid. The solid which separated was collected, dried, and recrystallized twice from a solution of 80% *n*-pentane and 20% *n*-heptane to yield 24.8 g (68%) of 3-chloropropiophenone-d_5 (**6**), mp 47.5–48.5° (lit[26,27] for 3-chloropropiophenone, mp 47–48°). The nmr spectrum showed no hydrogen absorption in the aromatic region. The ethylene region exhibited a typical A_2B_2 pattern.

Preparation of 2,2,4,5,6,7-d_6-1-Indanone (7).—3-Chloropropiophenone-d_5 (**6**) was cyclized in the manner reported[27] for the cyclization of 3-chloropropiophenone. A mixture of 1.7 g (0.0098 mole) of 3-chloropropiophenone-d_5 (**6**) and 20 g of sulfuric acid-d_2[28] was heated at 100° for 2.5 hr in a flask equipped with a magnetic stirrer and a reflux condenser fitted with a drying tube. The dark mixture was then cooled to room temperature and added to 150 g of cracked ice. The small amount of yellow solid that precipitated (0.1 g) was collected and washed with five 50-ml portions of cold water. The aqueous phase was extracted with four 50-ml portions of ether, and the combined ether extracts were washed with four 50-ml portions of water and dried over potassium carbonate. Removal of the ether left a yellow solid (0.6 g) which, when combined with the original solid and recrystallized from *n*-hexane containing a small amount of decolorizing charcoal, gave 0.45 g (35%) of 2,2,4,5,6,7-d_6-1-indanone (**7**),[29,30] mp 41–42° (lit.[27] for 1-indanone, mp 40–41°). The nmr spectrum showed only one absorption peak at τ 6.90 for the methylene hydrogens in the 3 position of 2,2,4,5,6,7-d_6-1-indanone (**7**). The 2,2,4,5,6,7-d_6-1-indanone (**7**) was converted to 4,5,6,7-d_4-1-indanone (**8**), mp 37–38°, in the manner previously described for the conversion of 1-indanone to 2,2-d_2-1-indanone (**5**), except that light water was used.

Preparation of 4,5,6,7-d_4-1-Indanone (8).—A mixture of 5.00 g (0.0287 mole) of 3-chloropropiophenone-d_5 (**6**) and 100 g of sulfuric acid-d_2 was stirred under a nitrogen atmosphere at 85° for 1 hr. The reaction mixture was cooled, added to cracked ice, and extracted with three 150-ml portions of ether. The combined ether extracts were washed with 50 ml of ice–water and dried over potassium carbonate. The ether solution was concentrated to 5 ml and chromatographed on 42–60 mesh alumina (Alcoa, Type F-1). Elution with 150 ml of petroleum ether (30–60°) gave 0.90 g (21%) of 4,5,6,7-d_4-1-indanone (**8**), mp 37–38°.

Registry No.—1-Indanone, 83-33-0; **1**, 716-28-9; **2**, 10036-00-7; **4**, 711-43-3; **5**, 10036-02-9; **6**, 10036-03-0; **7**, 10036-04-1; **8**, 10036-05-2.

Acknowledgment.—We thank Dr. Jo-Yun T. Chen of this division for the infrared measurements and interpretations and Mr. N. Duy for able assistance with nmr spectroscopy.

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[25] W. J. Hale and E. C. Britton, *J. Am. Chem. Soc.*, **41**, 845 (1919).

[26] J. B. Conant and W. R. Kirner, *ibid.*, **46**, 240 (1924).

[27] A. Rahman and A. E. Gastaminza, *Rec. Trav. Chim.*, **81**, 645 (1962).

[28] The carbon disulfide was dried over Molecular Sieves 4A.

[29] 98% D_2SO_4 of a minimum isotopic impurity of 99% deuterium.

[30] 2,2,4,5,6,7-d_6-1-Indanone (**7**) was also obtained in 53% yield by heating the reaction mixture for 1 hr at 100°.

The Alkaline Hydrogen Peroxide Oxidation of Phenyl-2-propanones[1a]

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The alkaline hydrogen peroxide oxidations of phenyl-2-propanones have been found to proceed by two competitive mechanisms. Product analyses and kinetic studies revealed the primary reaction to involve cleavage to a benzaldehyde and acetic acid. A slow competitive cleavage also occurs to produce the benzyl alcohol and acetic acid. A slow competitive cleavage also occurs to produce the benzyl alcohol and acetic acid which apparently result from the intermediate ester formed in a Baeyer–Villiger oxidation. The primary oxidation was found to be first order with respect to both oxidant and substrate. Hydroperoxide anion was shown to be the reactive peroxide species from studies of the effects of sodium hydroxide concentration and peroxide species concentration on reactivity. Evidence was found suggesting that the enol tautomer is the reactive substrate. The mechanism proposed involves attack of the hydroperoxide anion on the enol as the rate-determining step. Cleavage then is thought to occur by a concerted process with attack on the original carbonyl carbon atom by a second hydroperoxide anion.

The aromatic products obtained from the alkaline hydrogen peroxide oxidation of various lignin-related model compounds were recently investigated.[2] Ketones having a carbonyl group β to the ring, phenyl-2-propanones, reacted when either a hydroxyl or methoxyl substituent was present at the *para* position of the ring. When the carbonyl group was α to the ring, only the ketone having the hydroxyl substituent was reactive. From the unique reactivity of the phenyl-2-propanones and product analysis, Reeves suggested that oxidation of these ketones involved the ring-conjugated enol tautomer. Such a postulation is feasible since the enol content of pure phenyl-2-propanone is nearly 3%, 2×10^4 times as high as that for acetone.[3] The purpose of the present investigation was to determine the mechanism of the alkaline peroxide oxidation of the phenyl-2-propanones.

Experimental Section

All melting points were determined with N.B.S. calibrated total immersion thermometers. The melting points of the ketones and their semicarbazones all showed satisfactory agreement with literature values. Three ketones, deoxybenzoin (Matheson Coleman and Bell), 4-phenyl-2-butanone (K & K), and phenyl-2-propanone (K & K), were commercially available.

Phenyl-2-propanones.—Several of the phenyl-2-propanones were prepared by condensing the appropriate substituted benzaldehyde with nitroethane. The resulting nitropropene was

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[1] (a) A portion of a thesis submitted by D. D. Jones in partial fulfillment of the requirements of The Institute of Paper Chemistry for the degree of Doctor of Philosophy from Lawrence University, Appleton, Wis., June 1966. (b) To whom inquiries should be addressed.

[2] R. H. Reeves and I. A. Pearl, *Tappi*, **48**, 121 (1965).

[3] A. Gero, *J. Org. Chem.*, **19**, 1960 (1954).

then reduced to the oxime and hydrolyzed to the ketone.[4,5] Some of the ketones were prepared by a recent modification[6] of this procedure. The crude oils from these preparations were distilled on a Nester–Faust spinning-band distillation column. The ketones prepared by this procedure were 4-hydroxy-3-methoxyphenyl-2-propanone (pale yellow viscous oil, semicarbazone mp 157.2–157.8°), *p*-hydroxyphenyl-2-propanone (clear viscous oil which solidified, mp 39.7–40.6°, semicarbazone 211.8–212.5°), *p*-methoxyphenyl-2-propanone (pale yellow oil, semicarbazone mp 173.6–174.3°), *p*-methylphenyl-2-propanone (clear oil, semicarbazone mp 152.4–152.7°), and 3,4-dimethoxyphenyl-2-propanone (pale yellow oil, semicarbazone mp 175.2–176.2°). *p*-Chlorophenyl-2-propanone was prepared by the method of Overberger and Biletch.[7] The distilled product was a pale green oil which solidified on refrigeration, semicarbazone mp 190.2–190.8°. The preparation of *p*-nitrophenyl-2-propanone has also been described.[7] A low yield of light yellow-brown plates was obtained, mp 62.8–63.3°.

Related Ketones.—3-Phenyl-2-butanone was prepared by the sodium isopropoxide catalyzed methyl iodide alkylation of phenyl-2-propanone.[8] The product was isolated by preparative gas chromatography[9] giving a clear oil, semicarbazone mp 170.7–171.4°. 3-Methyl-3-phenyl-2-butanone was prepared by alkylation of phenyl-2-propanone with methyl iodide in the presence of potassium *t*-butoxide.[10] The clear oil was obtained by fractional distillation, semicarbazone mp 187.6–188.2°. The substituted deoxybenzoins were prepared by the method of Clark, *et al*, using the appropriate benzylmagnesium chlorides and benzamides.[11] The products, recrystallized from ethanol, were white flakes, *p*′-chlorodeoxybenzoin (mp 137.4–138.1°) and *p*-chlorodeoxybenzoin (mp 106.1–107.2°).

Product Analysis.—The same general procedures were used to determine the products from the oxidation of all the ketones, but the determinations were more comprehensive for some. To establish the stoichiometry of the reaction, a thorough analysis was made of the products obtained from oxidations of *p*-methoxyphenyl-2-propanone.

To minimize interference from the spontaneous decomposition of hydrogen peroxide, all vessels which contacted the solutions used in the oxidations were cleaned by an appropriate procedure.[12] All reagents were stored in polyethylene containers. The reaction vessel was a modified polyethylene wash bottle equipped with entries for a small condenser, a nitrogen line, and a sample line. Dry nitrogen was continuously introduced below the surface of the solution.

Before initiating an oxidation, the appropriate alkaline peroxide solution was prepared and the concentration of the hydrogen peroxide determined at selected intervals to obtain an estimate of peroxide decomposition. The alkaline peroxide solution was combined with the ketones, and the reaction allowed to proceed in a thermostated bath.

Gas chromatography was used extensively for both qualitative and quantitative determinations. The concentration of the two volatile aromatic products and residual ketone were determined by quantitative gas chromatography using internal standardization.[13] The response factors for the appropriate compounds were determined in comparison to a suitable internal standard under conditions similar to those for the quantitative determinations. An aliquot of the reaction mixture was quenched with sodium bisulfite and neutralized with sulfuric acid. A known amount of the internal standard was combined with the aliquot and the quantitative determinations made;[14] the comparative peak areas were determined by triangulation. The accuracy of this technique was estimated to be ±4%. The volatile aromatic products, *p*-methoxybenzaldehyde and *p*-methoxybenzyl alcohol, were collected on the preparative gas chromatograph and identified by comparison of their infrared spectra and gas chromatography retention times with those of knowns.

Acetic acid was a primary cleavage product of the oxidation. This compound was determined quantitatively using the Hy-FI gas chromatograph. An aliquot was quenched and acidified to pH 2–3, and the quantitative determinations were made using an appropriate amount of propionic acid as the internal standard. Knowing the response factor and the relative peak areas, determined by triangulation, the concentration of the acetic acid was determined with an accuracy of ±7%. The determinations were made using a 1/8 in. × 5 ft column packed with Carbowax 4000 TPA on acid-washed 60–80 Chromosorb W.

The aromatic acid produced by the oxidation was isolated from an aliquot of the reaction mixture. Most of the acid crystallized from the acidified reaction mixture on refrigeration. The remainder of the acid was isolated by a sodium bicarbonate extract and recrystallized from ethanol–water. The two fractions were combined to give the yield of the aromatic acid. The identity of the acid was established from its melting point and mixture melting point with authentic *p*-methoxybenzoic acid.

The residual hydrogen peroxide concentration was determined iodometrically.[15] The organic materials present in the reaction mixture were shown not to interfere with the titration.

Only the aromatic materials were investigated for the other ketones reacting by the same mechanism: the other substituted phenyl-2-propanones and three deoxybenzoins. To simplify the analyses, reaction conditions were modified so that the reaction went essentially to completion; *i.e.*, the aromatic acids were the primary products. The aromatic acids were isolated through a bicarbonate extract. The bicarbonate extract was extracted with ether to remove organic contaminants, and the aromatic acid was obtained by ether extraction from the acidified bicarbonate extracts. The isolated acids were characterized by their melting points.

For the two unsymmetrical deoxybenzoins, the products were two different aromatic acids. The yield of products was estimated using the average molecular weight of the two aromatic acids since they would be present in equimolar amounts as the reaction neared completion. The acids were identified by paper chromatography using a butanol–aqueous ammonia developer and an indicator, 4-(4-dimethylamino-1-naphthylazo)-3-methoxybenzene sulfonic acid for visualization. The residual aromatic materials from oxidations of the phenyl-2-propanones and deoxybenzoins were determined by quantitative gas chromatography using internal standardization. Reference materials were not available for *p*-methyl and *p*-chlorobenzyl alcohol. The unknowns were tentatively identified as the alcohols, since their retention times relative to the parent ketones were similar to those for which the alcohols were available.

The phenylbutanones gave only volatile aromatic materials which were analyzed by quantitative gas chromatography.

Acetic acid was produced from oxidations of all the ketones except the deoxybenzoins. The presence of the product was shown using the Carbowax 4000 TPA column used for quantitative determinations.

Kinetic Measurements.—The kinetics of the oxidations were determined by following the hydrogen peroxide concentration. Since no direct method was available, an indirect, continuous system was devised. The reaction vessel, contained in a thermostated bath, was continuously sampled by a proportioning pump (Technicon Controls Corp., Chauncey, N. Y.) and the sample stream combined with an acidified titanium sulfate stream. The combined streams were passed to a Beckman microaperture flow cell, 97290, in a Cary Model 15 recording spectrophotometer. The intensity of the yellow complex resulting from the titanium sulfate reagent and hydrogen peroxide[16,17] was determined providing a continuous recording of hydrogen peroxide concentration as a function of time. The average deviation of the second-order rate constants determined using this technique was 4–5%.

To obtain an estimate of spontaneous decomposition, the concentration of an alkaline hydrogen peroxide solution was

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(4) I. A. Pearl and D. L. Beyer, *J. Org. Chem.*, **16**, 221 (1951).

(5) K. A. West and H. Hibbert, *J. Am. Chem. Soc.*, **65**, 1185 (1943).

(6) N. Rabjohn, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 573.

(7) C. G. Overberger and H. Biletch, *J. Am. Chem. Soc.*, **73**, 4880 (1951).

(8) C. M. Suter and A. W. Weston, *ibid.*, **64**, 534 (1942).

(9) All preparative chromatography utilized an Aerograph A-700 chromatograph using either a column packed with a 20% DEGS or Carbowax 20 M liquid phase on 60–80 Chromosorb W.

(10) A. Jonsson, *Acta Chem. Scand.*, **8**, 1203 (1954).

(11) M. T. Clark, E. C.Hendley, and O. K. Neville, *J. Am. Chem. Soc.*, **77**, 3280 (1955).

(12) The operation of a bench-scale peracetic acid generator (F. M. C. Corp) (New York, 1963).

(13) R. L. Pecsok, "Principles and Practices of Gas Chromatography," Chapman and Hall, Ltd., London, 1959, pp 136–150.

(14) A 1/8 in. × 5 ft column packed with 5% DEGS-20% Carbowax 20 M on 60–80 Chromosorb W was used on an Aerograph A-600B Hy-Fi gas chromatograph.

(15) B. D. Sulley and P. L. Williams, *Analyst*, **87**, 653 (1962).

(16) C. N. Satterfield and A. H. Bonnell, *Anal. Chem.*, **27**, 1174 (1955).

(17) D. F. Snell and C. T. Snell, "Spectrophotometric Methods of Analysis," Vol. IIa, D. Van Nostrand Co., Inc., Princeton, N. J., 1959, p 734.

followed for a minimum of 30 min under the conditions of the oxidation. The alkaline peroxide solution was then combined with the appropriate amount of substrate; the reaction vessel was replaced in the thermostated bath, controlled to within ±0.1°, and sampling was resumed immediately. The response of the flow system was good. Within 90 sec the absorbance was 98% of its maximum value. The oxidations were allowed to proceed for a minimum of 90 min. The oxidations were made using comparable quantities of reactants in 50% ethanol–water (v/v).

The kinetic data were evaluated using second-order rate expressions. For most of the oxidations the stoichiometry was $2A + B \rightarrow$ products, but for some it was $A + B \rightarrow$ products. The second-order rate constants were determined using the appropriate integrated expressions. The data were evaluated as paired points of absorbance *vs.* time using an IBM 1620II computer.

The initial rate procedure was used to determine the order of the oxidation with respect to the reactants. The concentration of one reactant was varied while the concentration of the other reactant was maintained constant (eq 1). The order of the

$$dA/dt = k_1 A^{n_A} B^{n_B} = k_2 A^{n_A} \qquad (1)$$

reaction with respect to the reactant being varied was determined using the logarithmic form of the expression (eq 2), assuming

$$\ln (\Delta A/\Delta t) = \ln k_2 + n_A \ln A \qquad (2)$$

$dA/dt \cong \Delta A/\Delta t$. The slope of the double logarithmic plot gives an estimate of n_A. For the initial rate approximation, only data from the first 10% of the reaction were used.

The deoxybenzoins were so insoluble that they completely precipitated in the flow lines making continuous analysis impossible. These oxidations were followed by taking aliquots at selected time intervals and determining the hydrogen peroxide concentration iodometrically.[15] Second-order rate constants were estimated by determining the slope of titer *vs.* time curves and using the initial rate approximation, $\Delta A/\Delta t = kAB$, where A and B are the initial concentrations of the reactants.

To study the effect of peroxide species concentration on reactivity, the hydrogen peroxide–hydroperoxide anion equilibria in 50% ethanol–water was studied spectrophotometrically. The molar absorptivity of undissociated hydrogen peroxide was determined using a pH 7 buffer and that of the hydroperoxide anion using 0.5 N NaOH. A correlation of hydroperoxide anion

$$H_2O_2 + OH^- \rightleftharpoons HO_2^- + H_2O \qquad (3)$$

as a function of total hydrogen peroxide in 50% ethanol–water was determined using the data shown in Table I.

TABLE I

HYDROPEROXIDE ANION CONCENTRATIONS OF ALKALINE PEROXIDE SOLUTIONS IN 50% ETHANOL–WATER[a]

Total H_2O_2 concn, M	HO_2^- concn, M
0.200	0.0798
0.160	0.0787
0.120	0.0757
0.080	0.0646
0.060	0.0522
0.040	0.0374
0.020	0.0191

[a] Added sodium hydroxide was constant at 0.08 M in all instances.

Results

Product Analysis.—The reaction conditions and yields of aromatic products are given in Table II for oxidations of the phenyl-2-propanones. Stoichiometry of the oxidations of phenyl-2-propanones were established by making a comprehensive study of *p*-methoxyphenyl-2-propanone. The yields of acetic acid from the two oxidations of *p*-methoxyphenyl-2-propanone (Table II) were 63 and 75 mole %. Including the residual ketone, the total recovery of acetic acid was 89 and 90%, comparable with that for the aromatics. Peroxide consumption was determined to be 53 and 62%. Calculated consumption on the basis of the products was 41 and 51%. The differences between the actual and calculated values were 20–25%, comparable to the estimated decomposition of 20% over the 4-hr period. The infrared spectra of the two volatile aromatic products were almost identical with those of *p*-methoxybenzaldehyde and *p*-methoxybenzyl alcohol. The isolated acid had a melting point of 183.0–183.9°; mmp 183.3–184.0° with authentic *p*-methoxybenzoic acid (mp 184.1–184.9°).

TABLE II

REACTION CONDITIONS AND PRODUCTS FOR OXIDATIONS OF PHENYL-2-PROPANONES[a]

Phenyl-2-propanone	Time, hr	Benzyl alcohol, mole %	Benzaldehyde, mole %	Benzoic acid, mole %	Total[b]
p-Methoxy[c]	4	16	21	25	88
	4	19	21	32	88
p-Chloro	4.5	6[d]	1	89	96
	4.5	6	1	87	94
p-H	7	8	3	80	92
	6.5	9	2	75	89
p-Methyl	6	10[d]	16	69	99
	9	7	6	79	93

[a] The conditions for the oxidations, unless otherwise noted, are approximately 0.1 M ketone, 0.40 M total hydrogen peroxide, and 0.40 M initial sodium hydroxide in 50% ethanol–water at 55°. [b] Total mole per cent recovery of aromatics including residual ketone. [c] Conditions were initial base 0.5 M and ketone 0.13 M at 45.0°. [d] Identification tentative since references were not available.

Product analysis indicated that the oxidation of *p*-methoxyphenyl-2-propanone is occurring by two different mechanisms: cleavage to the benzaldehyde and acetic acid and a much slower competitive cleavage to the benzyl alcohol and acetic acid. Subsequent oxidation of the benzaldehyde to the benzoic acid also occurs. The possibility of the entire oxidation proceeding through the alcohol was eliminated. By gas chromatography it was shown that the concentration of the alcohol continuously increased, whereas that of the aldehyde reached a maximum and decreased, characteristic of an intermediate. A comparison of alkaline hydrogen peroxide reaction rates showed that *p*-methoxybenzaldehyde reacted 50 times faster than *p*-methoxybenzyl alcohol at 45°.

The possibility that the initial product of the oxidation is acetaldehyde, with acetic acid being produced only in a consecutive reaction, was also investigated. An oxidation of phenyl-2-propanone was checked five times at 15-min intervals by gas chromatography, but no trace of acetaldehyde was found. The technique was sufficiently sensitive to detect the aldehyde at a concentration of less than 1 mole per cent of that of the original ketone. The alkaline peroxide oxidation of acetaldehyde was shown to be slower than that of the ketone; the aldehyde should have been detected if it were present.

The average recovery of aromatic materials was greater than 90% for the other phenyl-2-propanones presented in Table II. The reactions of these ketones are all comparable with those of *p*-methoxyphenyl-2-propanone, the primary reaction being cleavage to the aldehyde.

The experimental conditions for oxidations of the related ketones and the resulting products are presented in Tables III and IV. The only aromatic product obtained in quantity from oxidations of 4-phenyl-2-butanone and 3-methyl-3-phenyl-2-butanone were alcohols (Table III). Two primary products, acetophenone and α-phenethyl alcohol, were obtained from the oxidation of 3-phenyl-2-butanone.

Table III

Reaction Conditions and Products for Phenyl-2-butanones[a]

Ketone	Ketone concn, *M*	Time, hr	Alcohol[b]	Carbonyl product[c]	Residual ketone	Total
4-Phenyl-2-butanone	0.04	10	39	3	55	97[d]
3-Phenyl-2-butanone	0.11	28	18	42	40	100[e]
3-Methyl-3-phenyl-2-butanone	0.06	64	13	..	83	100[e]

[a] These are the results of duplicate oxidations; all averages agree within ±3%. The conditions for oxidations were total H_2O_2 = added NaOH = 0.4 *M;* 50% ethanol-water; 45.0° (except for 4-phenyl-2-butanone, 55.0°). [b] These alcohols are, respectively, phenethyl alcohol, α-phenethyl alcohol, and 2-phenyl-2-propanol. [c] These products are phenylacetaldehyde and acetophenone, respectively. [d] These estimates were made using internal standardization; response factors were determined for the alcohol and ketone. The total refers to mole per cent recovery of aromatic materials. [e] Estimates made using internal normalization. The total is necessarily 100%; the yields are weight percentages.

Table IV

Reaction Conditions and Products for the Deoxybenzoins[a]

Ketone	Ketone concn, *M*	H_2O_2 concn, *M*	NaOH concn, *M*	Aromatic acids	Total[b]
p-Chlorodeoxybenzoin	0.015	0.12	0.13	87	87
p′-Chlorodeoxybenzoin	0.010	0.11	0.11	85	87
Deoxybenzoin	0.023	0.22	0.22	76	86

[a] All oxidations at 55.0° in 70% ethanol-water; time, 4 hr, except deoxybenzoin (6 hr). All results represent average yields from duplicate oxidations. Agreement was within ±2% for figures except recovered ketone from deoxybenzoin oxidations. [b] Total mole per cent recovery including residual ketone.

The average recovery of aromatic materials from oxidations of the deoxybenzoins (Table IV) were 85–90% in all instances. Under the conditions utilized the only products of significance were aromatic acids.

Kinetics.—A series of investigations was made to determine the order with respect to reactants for oxidations of *p*-methoxyphenyl-2-propanone and phenyl-2-propanone. The effect of substrate was investigated by maintaining both added sodium hydroxide[18] and total hydrogen peroxide constant at 0.08 *M* and varying substrate concentration from 0.06 to 0.20 *M*. The effect of peroxide concentration was determined maintaining the substrate constant at either 0.06 or 0.10 *M* and varying the added base and total peroxide concentrations from 0.08 to 0.24 *M*. The data were evaluated as a double logarithmic plot of initial rate as a function of reactant concentration. The reaction was found to be first order with respect to both substrate and oxidant (Table V) for both phenyl-2-propanones; slopes of the initial rate plots were 0.99–1.04. The investigations of order with respect to oxidant were made using equimolar concentrations of hydrogen peroxide and sodium hydroxide. For the range of conditions being investigated, the ratio of hydroperoxide anion concentration to total peroxide would remain essentially constant.

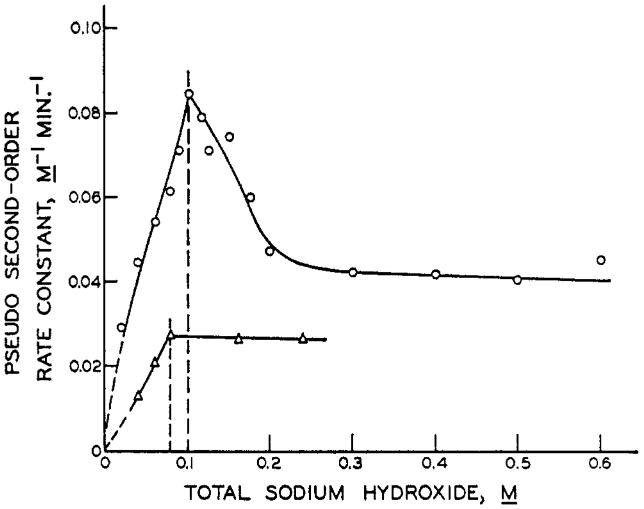

Figure 1.—Effect of added sodium hydroxide upon alkaline peroxide oxidations: ○ = *p*-methoxyphenyl-2-propanone, H_2O_2 = 0.10 *M;* △ = 4-phenyl-2-butanone, H_2O_2 = 0.08 *M;* discontinous lines, H_2O_2 = NaOH.

Table V

Kinetic Order with Respect to the Reactants

Ketone	Substrate reaction order	Oxidant reaction order
p-Methoxyphenyl-2-propanone	1.02 (0.98)[a]	1.04 (0.99)
Phenyl-2-propanone	0.99 (0.97)	1.01 (0.99)

[a] The values in parentheses refer to the correlation coefficients for the regression lines.

The effect of sodium hydroxide concentration was studied by varying the base concentration while maintaining initial reactant concentration at 0.06 (substrate) and 0.10 *M* (total hydrogen peroxide). A comparative study was made for 4-phenyl-2-butanone over a narrower range of base concentrations. The contrasting results of these investigations are shown in Figure 1 as a plot of the second-order rate constant as a function of added base. A result comparable with that for *p*-methoxyphenyl-2-propanone was obtained from a similar study of phenyl-2-propanone.

The effect of peroxide species on reaction rate was investigated by varying total peroxide concentrations from 0.02 to 0.18 *M* while maintaining constant added substrate at 0.065 *M* and base at 0.08 *M*. The hydroperoxide anion concentrations for these runs were determined from the correlation made from the data of Table I; the undissociated hydrogen peroxide was determined by difference. The results of the study are shown in Figure 2 as a double logarithmic plot of initial rate *vs.* peroxide species concentration.

Arrhenius activation energies were determined for two phenyl-2-propanones from integrated second-order rates at four temperatures between 26.5 and 65.0° using the logarithmic form of the Arrhenius equation (Figure 3). The thermodynamic activation parameters

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[18] All values representing sodium hydroxide concentrations refer to the total base added. The actual hydroxide ion concentration is dependent upon the equilibrium of the hydrogen peroxide system.

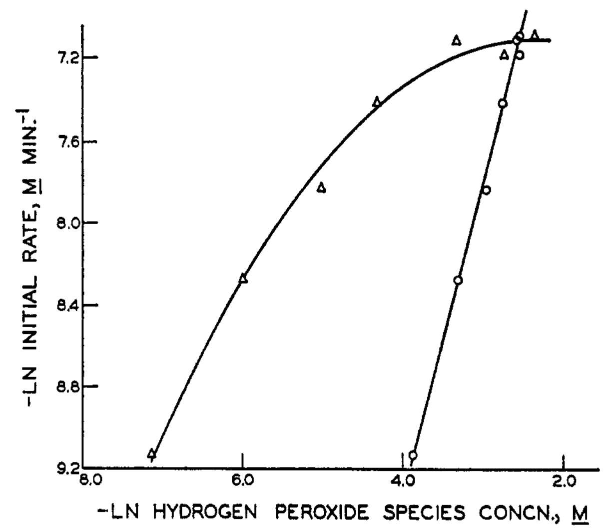

Figure 2.—Effect of peroxide species upon oxidations of phenyl-2-propanone: ○ = hydroperoxide anion; △ = undissociated hydrogen peroxide.

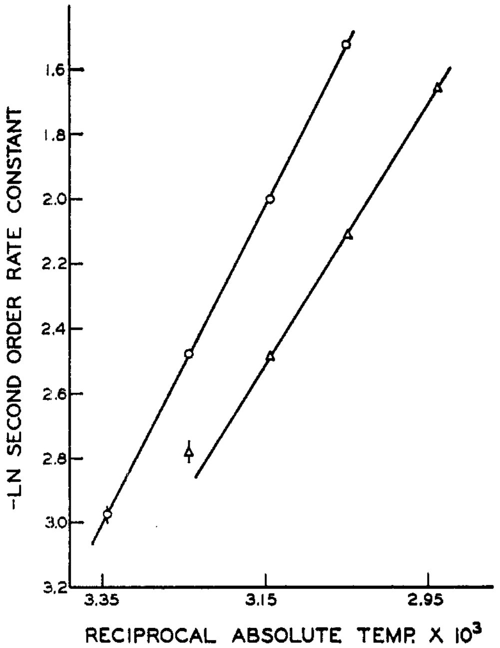

Figure 3.—Oxidations of phenyl-2-propanones (Arrhenius plots): ○ = phenyl-2-propanone; △ = *p*-methoxyphenyl-2-propanone.

at 45.0° presented in Table VI were calculated from transition state theory using the Arrhenius activation energy and second-order rate constants.

TABLE VI

ACTIVATION PARAMETERS FOR THE PHENYL-2-PROPANONES

Ketone	ΔH^*	ΔS^*
Phenyl-2-propanone	9 ± 2	−43 ± 6
p-Methoxyphenyl-2-propanone	7 ± 2	−49 ± 6

The effect of substituent on reactivity was studied for several substituted phenyl-2-propanones. The logarithms of their second-order rate constants are plotted as a function of the appropriate Hammett substituent constants in Figure 4. Three other phenyl-2-propanones with electron-releasing groups (*p*-hydroxy, *p*-dimethylamino, and 4-hydroxy-3-methoxy) were not included in the Hammett plot since the identified products accounted for considerably less than one-half of the reacted ketone, and second-order kinetics were not observed. Second-order kinetics adequately described the other phenyl-2-propanones (Figure 5).

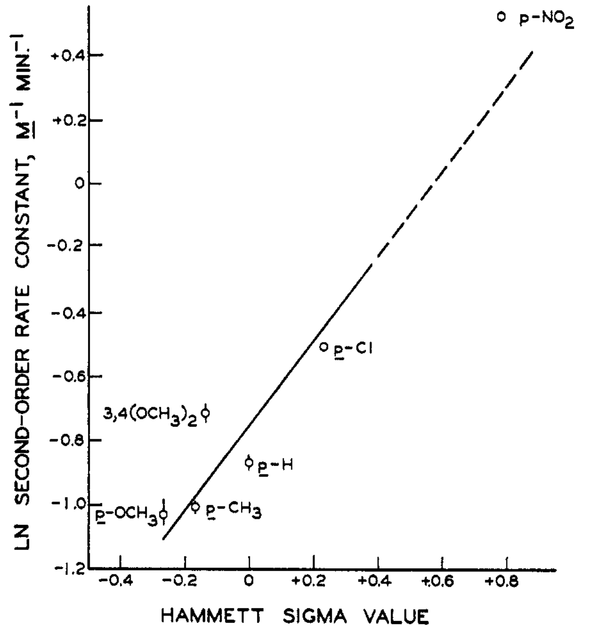

Figure 4.—Oxidation of phenyl-2-propanones (effect of substituents).

The second-order rate constants for the alkaline peroxide oxidations of the phenyl-2-butanones at 45° were determined for comparison with those for phenyl-2-propanone. These results are presented in Table VII. The results of the kinetic investigations of the deoxybenzoins at 45.0° in 60% ethanol are given in Table VIII.

TABLE VII

REACTIVITY OF PHENYL-2-PROPANONE AND THE PHENYL-2-BUTANONES

Ketone	Av second-order rate constant,[a] M^{-1} min⁻¹
Phenyl-2-propanone	0.125
4-Phenyl-2-butanone	0.028
3-Methyl-3-phenyl-2-butanone	0.012
3-Phenyl-2-butanone	0.016[b]

[a] The constants are an average of two runs. The average deviation for the phenyl-2-butanones was 5%. [b] Average of three runs.

TABLE VIII

REACTIVITY OF DEOXYBENZOINS

Ketone	Average second-order rate constant,[a] M^{-1} min⁻¹
p-Chlorodeoxybenzoin	0.392
p'-Chlorodeoxybenzoin	0.490
Deoxybenzoin	0.150

[a] The constants are an average of two runs; the average deviation for the duplicates was 7%.

Discussion

Product Analysis.—The phenyl-2-propanones are cleaved in alkaline hydrogen peroxide by two mechanisms. The primary reaction is characteristic of the phenyl-2-propanones and involves cleavage to a benzaldehyde and acetic acid. The competitive cleavage to a benzyl alcohol and acetic acid has also been noted

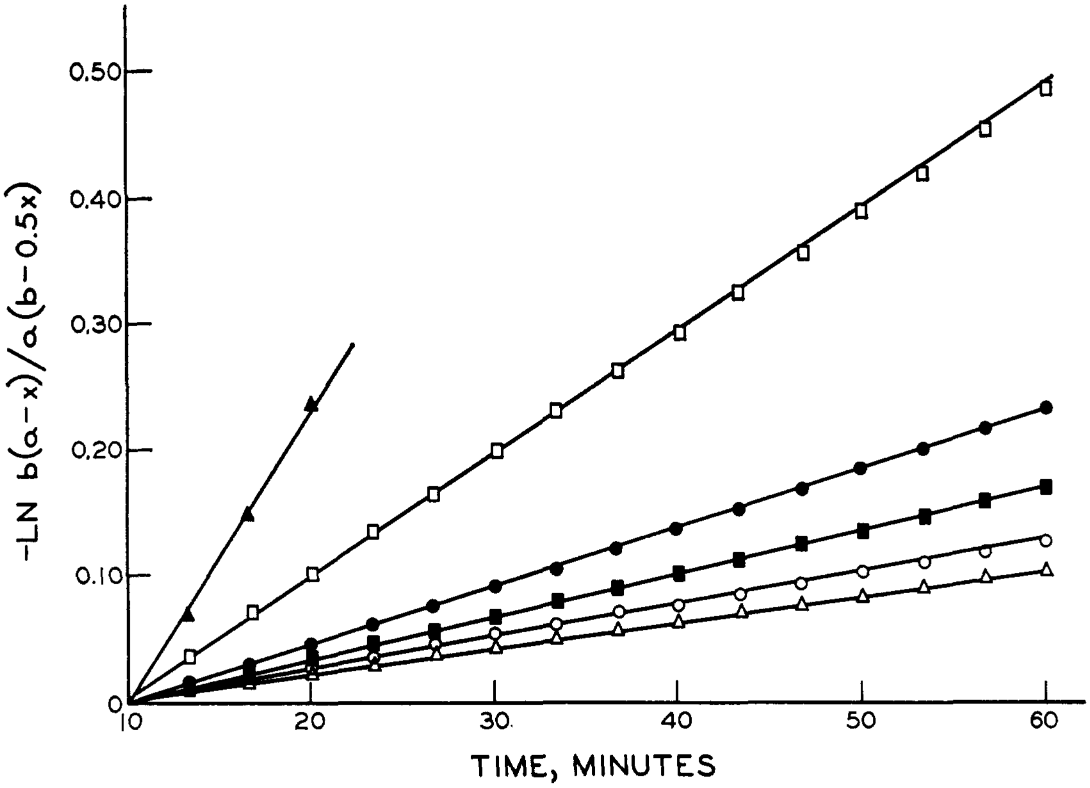

Figure 5.—Typical second-order reactions for some phenyl-2-propanones at 45°: ▲ = *p*-nitro-, □ = *p*-chloro-, ○ = *p*-H, ● = 3,4-dimethoxy, △ = *p*-methyl-, and ■ = *p*-methoxypropanones.

by others.[19] This reaction has been considered the alkaline analog of the Baeyer–Villiger oxidation of ketones by peroxy acids. The proposed mechanism involves attack at the carbonyl carbon by hydroperoxide anion, rearrangement to the ester, and hydrolysis to an alcohol and an acid. This work shows that those ketones which cannot form a ring-conjugated enol, 4-phenyl-2-butanone and 3-methyl-3-phenyl-2-butanone, react only by this mechanism.

Reaction Order.—The initial rate investigations (Table V) demonstrate that the oxidation is first order with respect to both oxidant and substrate. First-order kinetics with respect to the oxidant eliminates the possibility that enolization is the rate-determining step of the reaction. Enolization has frequently been shown to be rate-controlling in the oxidation of ketones.[20]

Sodium hydroxide concentration was found to have a significant effect on reactivity. For both *p*-methoxyphenyl-2-propanone and 4-phenyl-2-butanone (Figure 1), the reactivity increased with base concentration until the added base equalled that of total hydrogen peroxide. These results indicate that hydroperoxide anion is the reactive peroxide species: the hydroperoxide anion concentration would continually increase with the addition of base. A significant difference is noted between the two ketones in the presence of excess base. The reactivity of *p*-methoxyphenyl-2-propanone drops significantly in the presence of excess base suggesting that the reactive substrate is a neutral species and that its conversion to a negatively charged enolate ion decreases reactivity.[21]

The study of peroxide species concentration verified that hydroperoxide anion was the reactive peroxide species. A continuous increase in reactivity (Figure 2) was obtained with hydroperoxide anion, but reactivity was insensitive to undissociated hydrogen peroxide at higher peroxide concentrations. The slope of the plot for hydroperoxide anion was 1.4. The deviation from first-order dependence was in the direction expected considering the effect of base concentration on reactivity (Figure 1).

Effect of Substituents.—Although the data comprising the Hammett relationship (Figure 4) exhibit considerable scatter, they definitely indicate that electron-withdrawing substituents enhance reactivity. The relatively high, positive ρ value of 1.4 (correlation coefficient = 0.92) is consistent with attack of hydroperoxide anion on the enol tautomer. A similar effect was noted for the deoxybenzoins where a ρ value of 1.8 was calculated from the comparative reactivity of deoxybenzoin and the benzyl substituted ketone, *p*'-chlorodeoxybenzoin.

Activation Parameters.—The observed low enthalpies of activation and large negative entropies of activation (Table VI) are consistent with the attack of a nucleophile upon unsaturated carbon. The values are comparable with those noted for the alkaline peroxide oxidation of benzil by hydrogen peroxide ($\Delta H^* = 4.4$

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[19] H. O. House and R. L. Wasson, *J. Org. Chem.*, **22**, 1157 (1957).

[20] W. A. Waters, "Mechanisms of Oxidation of Organic Compounds," Methuens and Co., Ltd., London, 1964, pp 90–99.

[21] Unfortunately, the acid ionization constants for phenyl-2-propanone and its *p*-methoxy derivative are not known. No difference could be detected in ultraviolet spectra of a pH 7 buffer solution and a 0.1 *M* sodium hydroxide solution of *p*-methoxyphenyl-2-propanone. Potentiometric titration also was unsuccessful. The possibility remains, however, that the enol concentration (estimated at about 1% in dilute solution[3]) is lowered in excess base by conversion to the enolate anion. The enol form is undoubtedly much more acidic than the keto form: C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 566; G. Schwarzenbach and E. Felder, *Helv. Chim. Acta*, **27**, 1701 (1944).

kcal/mole and $DS^* = -34.0$ eu).[22] There is also little difference in the activation parameters found for 4-phenyl-2-butanone ($\Delta H^* = 7.7$ kcal/mole and $\Delta S^* = -50$ eu).

Study of Related Ketones.—These ketones were studied to determine the effect of structure modification on products and reactivity. Two of the phenylbutanones reacted only by the alkaline Baeyer–Villiger reaction to give aromatic alcohols. The additional methylene group in 4-phenyl-2-butanone eliminates the possibility of ring-conjugated enolization and reaction by the mechanism characteristic of the phenyl-2-propanones. A similar effect was noted by replacing both of the α-hydrogens by methyl groups, *i.e.*, 3-methyl-3-phenyl-2-butanone. These ketones were considerably less reactive than phenyl-2-propanone (Table VII). The reduced reactivity of 4-phenyl-2-butanone (bearing the less hindered carbonyl group) also argues against rate-determining attack by the nucleophile on the carbonyl carbon of phenyl-2-propanone.

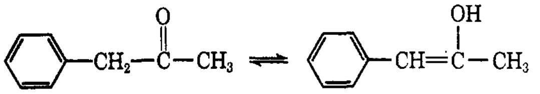
The oxidation of 3-phenyl-2-butanone, which can form a ring-conjugated enol, yielded the products expected from oxidation by both the primary and competitive mechanisms observed for the phenyl-2-propanones. However, the second-order rate constant for the oxidation of phenyl-2-propanone was 8.1 times as high as the corresponding constant for 3-phenyl-2-butanone (Table VII). This represents a significant difference in rate but is of the magnitude expected if the reaction involves the enol tautomer. Bunton[23] observed that the addition of a methyl group at the reaction site reduced the reactivity of alkaline hydrogen peroxide toward α,β-unsaturated ketones by a factor of 5.6. The presence of the bulky electron-releasing methyl group would decrease the reactivity of 3-phenyl-2-butanone in at least three ways: (a) steric inhibition, (b) electronic repulsion of the hydroperoxide anion, and (c) decrease in the enol content of the substrate.[24] The comparative study of products and reactivity of phenyl-2-propanone and the phenyl-2-butanones provides good evidence for proposing that the unique oxidation of the phenyl-2-propanones is occurring through the enol tautomer.

The relative reactivity of the deoxybenzoins which were studied (Table VIII) and the products formed are also consistent with the enol being the reactive form. Here again a ring-conjugated enol can be formed. The rate enhancement resulting from introduction of the *p*-chloro substituent roughly parallels that observed for the phenyl-2-propanones. There is only a small difference in the reactivity of the two chloro-substituted deoxybenzoins.

The similarity of the reactions of the deoxybenzoins and the phenyl-2-propanones offer some support for the hypothesis that the hydroperoxide anion does not attack the oxygen-bearing carbon of the enol. Such an attack would be expected to be severely hindered by substituting an α-phenyl group for an α-methyl group. The rate constants for reaction of phenyl-2-propanone (0.125 M^{-1} min^{-1}) and deoxybenzoin (0.150 M^{-1} min^{-1}) at 45° do not reveal any steric effect. Such a comparison of rates must be tempered with caution, however, since the enol content of deoxybenzoin is not known and the solvent systems for the kinetics of the two ketones were slightly different (50% ethanol *vs.* 60% ethanol).

Mechanism of the Oxidation.—On the basis of extensive product analysis and kinetic investigations of the phenyl-2-propanones and related compounds, a reaction mechanism for the primary reaction of the phenyl-2-propanones is postulated. The rate-determining step in the reaction (eq 6) involves attack of the enol tautomer by the hydroperoxide anion to give an intermediate β-hydroxyhydroperoxide anion which immediately picks up a proton from water. Such a suggestion requires the addition of a nucleophile to a carbon–carbon double bond, a situation which is usually considered to be unfavorable. Hydrogen peroxide will not attack isolated double bonds, but the reactivity of activated double bonds, α,β-unsaturated aldehydes, ketones, esters, etc., has been widely noted.[2,23,25] The enol tautomer is similar in some respects to the activated α,β-unsaturated systems. The inductive effect of the electron-withdrawing hydroxyl group could assist attack of the hydroperoxide anion on the unsaturated system.

$$H_2O_2 + OH^- \rightleftharpoons HO_2^- + HOH \qquad (4)$$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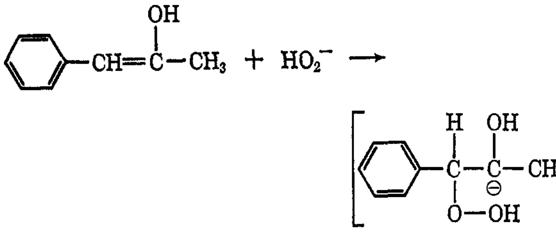
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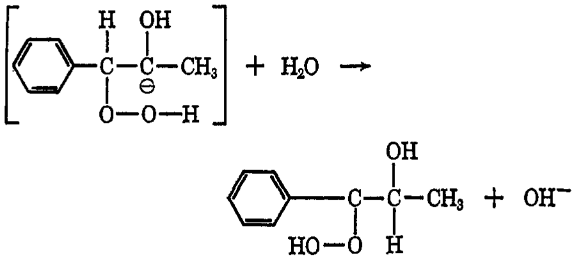
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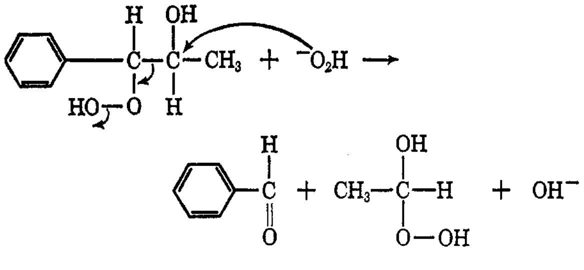
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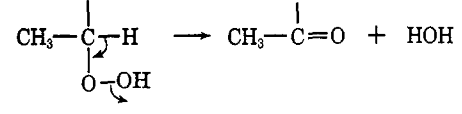
(9)

$$\mathrm{CH_3{-}\overset{OH}{\underset{O-OH}{C}}{-}H \longrightarrow CH_3{-}\overset{OH}{C}{=}O + HOH} \qquad (9)$$

Considering the pseudo-stable intermediate to be the β-hydroxyhydroperoxide I several possible routes

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[22] H. Kwart and N. J. Wegemer, *J. Am. Chem. Soc.*, **83**, 2736 (1961).

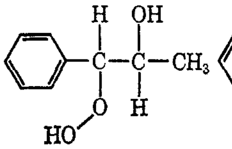
[23] C. A. Bunton and G. J. Minkoff, *J. Chem. Soc.*, 665 (1949).

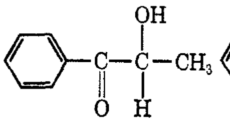
[24] J. B. Conant and A. F. Thompson, Jr., *J. Am. Chem. Soc.*, **54**, 4039 (1932); S. Zuffanti, *J. Chem. Ed.*, **22**, 230 (1945).

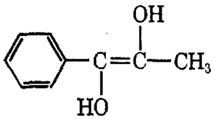
[25] J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).

for cleavage to the observed products are available. The intermediate might decompose to give benzaldehyde and acetaldehyde. This possibility is eliminated since it has been shown that acetaldehyde is not produced in the system.

The production of the benzaldehyde and acetic acid as primary products requires that 2 moles of hydrogen peroxide are added to the system with the cleavage occurring during or after addition of the second mole of peroxide. Subsequent oxidation of the intermediate I can occur in two ways: (a) attack on a dehydrated product of I or (b) by a direct attack on the intermediate I. The intermediate could undergo intramolecular loss of water producing an α-hydroxy ketone (II). The α-hydroxy ketone could then react through the enediol III to give benzaldehyde and acetic acid.

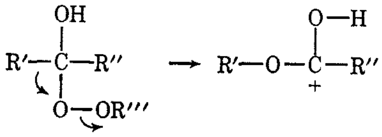

I


II


III

Such a mechanism, however, could not account for the reactivity of 3-phenyl-2-butanone since the presence of the α-methyl group eliminates the possibility of forming an α-hydroxy ketone (II). The validity of the mechanism was also investigated by preliminary studies of 1-hydroxy-1-phenyl-2-propanone, the stable isomer of structure II which in alkali would give the same enediol III. The ketone, which has a second-order rate constant more than 20 times as high as that for benzaldehyde at 25°, rapidly consumes 2 moles of hydrogen peroxide. These results are inconsistent with the enediol being an intermediate.

Direct attack of the β-hydroxyhydroperoxide I by the nucleophilic hydroperoxide anion represents the most feasible mechanism of cleaving the ketone which is consistent with all of the experimental observations. The cleavage (eq 8) is considered to occur in a concerted manner in which the oxygen–oxygen bond and the carbon–carbon bond are broken concurrently with formation of the carbon–oxygen bond at the original carbonyl carbon. An analogous series of events are postulated to occur in the rearrangement of an α-hydroxyhydroperoxide in the Baeyer–Villiger reaction.



A requirement of the cleavage is that it be faster than the rate-determining step of the reaction. In addition to the Baeyer–Villiger reaction, many of the mechanisms of peroxide reactions involve intramolecular decomposition of peroxide intermediates. The driving force for these reactions, with the exception of the Dakin reaction,[2,26,27] is primarily the instability of the oxygen–oxygen bond. The presence of a strong nucleophile such as the hydroperoxide anion could assist this decomposition when there is a reactive site adjacent to the hydroperoxide. The polar hydroxyl group on the carbon adjacent to that containing the hydroperoxide makes the hydroxyl-containing carbon susceptible to attack by the nucleophile. Cleavage assisted by hydroperoxide anion would be expected to proceed at a faster rate than unassisted decomposition of the same intermediate.

Registry No.—p-Methoxyphenyl-2-propanone, 122-84-9; p-chlorophenyl-2-propanone, 5586-88-9; p-H-phenyl-2-propanone, 103-79-7; p-methylphenyl-2-propanone, 2096-86-8; 4-phenyl-2-butanone, 2550-26-7; 3-phenyl-2-butanone, 769-59-5; 3-methyl-3-phenyl-2-butanone, 770-85-4; p-chlorodeoxybenzoin, 1889-71-0; p'-chlorodeoxybenzoin, 6332-83-8; deoxybenzoin, 451-40-1.

(26) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 341.

(27) A. G. Davies, "Organic Peroxides," Butterworth and Co. (Publishers) Ltd., London, 1961, p 155.

Direct Methylenation of Steroidal α,β-Epoxy Ketones

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Condensation of 1,2α-epoxy-3-ketoandrostanes with formaldehyde led to their 4-methylene derivatives. The same reaction carried out with 4,5β-epoxy-3-ketoandrostanes gave the 2-methylene analogs. Opening of the two series of epoxides with halogen acids produced 2-halo-4-methylene-3-keto-1-enes and 4-halo-2-methylene-3-keto-4-enes, respectively.

The introduction of methylene groups into steroidal A-ring conjugated ketones has been achieved by various synthetic routes. For example, 2-methylene-Δ^4-3-keto steroids[1] have been prepared by condensation of the 2-ethoxalyl-Δ^4-3-keto derivatives with formaldehyde or chloromethyl methyl ether. Also 2-N-piperidinomethylene-Δ^4-3-keto steroids[2] are converted by sodium borohydride reduction to the corresponding 2-methylen-Δ^4-3β-ols, which upon allylic oxidation yield 2-methylene-Δ^4-3-keto compounds. Recently Lunn[3] reported the direct introduction of a 4-methylene group into a Δ^1-3-keto steroid by condensation with paraformaldehyde.

With the hope of introducing methylene groups (through their corresponding hydroxymethyl precursors) into steroidal A-ring epoxy ketones, the condensation of these ketones with aqueous formaldehyde was studied. This method had been utilized by Nogu-

(1) D. D. Evans, D. E. Evans, G. S. Lewis, and P. J. Palmer, *J. Chem. Soc.*, 4312 (1963).

(2) J. A. Edwards, M. C. Calzada, and A. Bowers, *J. Med. Chem.*, **6**, 178 (1963).

(3) W. H. W. Lunn, *J. Org. Chem.*, **30**, 2925 (1965).