TABLE II

ANALYSIS OF THIOLACETATE ADDUCTS BY DESULFURIZATION

| Methylene-cyclohexene | Thiolacetate adducts | Alkane from desulfurization, *trans* to *cis* | Alkene hydrogenated | *trans* to *cis* | Lit. |
|---|---|---|---|---|---|
| 2-Methyl- | 73:27 | 74:26 | 1,2- and 2,3-Dimethylcyclohexene | 27:73 | 70–80% *cis*[a] |
| 3-Methyl- | 17:83 | 15:85 | 1,3-Dimethylcyclohexene | 26:74 | 70–80% *cis*[a] |
| 4-*t*-Butyl- | 91:9 | 88:12 | 4-*t*-Butyl-1-methylcyclohexene | 63:37 | 37% *cis*[b] |

[a] See ref. 12. [b] See ref. 14.

Washing with water removed excess phosphite. The dried hydrocarbon mixtures were compared chromatographically to authentic sample mixtures of known composition (column B at 100°) prepared by hydrogenation of the corresponding cyclohexenes over platinum in acetic acid. The chromatographic columns employed failed to separate the mixtures of thiols. The results are summarized in Table II.

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# Solvent Effects in the Base-Catalyzed Oxidation of Ketones to Mono- and Dicarboxylic Acids

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The base-catalyzed autoxidation of acetophenone and $C_5$ to $C_{12}$ cyclic aliphatic ketones was studied in hexamethylphosphoramide (HMPA) at 23.5 and 80°. The cyclic ketones were autoxidized to their corresponding dibasic acids in moderate to excellent yields in the presence of either potassium or sodium hydroxide. Evidence is presented which indicates that the choice of solvent for these reactions is a critical factor. The ease of oxidation with respect to the solvent was HMPA > *t*-butyl alcohol >>> water. Potassium and sodium hydroxide were equally effective catalysts but lithium hydroxide was extremely poor. Structural variations indicated that the ketone containing the most acidic $\alpha$-carbon–hydrogen bonds was most readily oxidized. These facts are consistent with a carbanion oxidation, and a mechanistic path involving formation of an unstable peroxy anion intermediate has been postulated. Results were obtained which indicate that the selectivity to acidic products can be controlled by the use of an HMPA–water mixture as the solvent medium.

The ability of alkali to accelerate the oxidation of ketones by molecular oxygen was first reported in the literature many years ago for ketones containing highly acidic $\alpha$-carbon–hydrogen bonds.[1–5] The base-catalyzed acceleration of the autoxidation of cyclic aliphatic ketones was initially reported by Harries[6,7] who found that carvone, an $\alpha,\beta$-unsaturated ketone, was autoxidized to a 1,3-diketone in the presence of hydroxide ion. The mechanism of the alkaline autoxidation of cyclic, $\alpha,\beta$-unsaturated ketones was subsequently studied in great detail by Treibs[8] who suggested that an unstable peroxide intermediate is initially formed and then decomposes to yield condensation products and hydrogen peroxide. The hydrogen peroxide subsequently reacts with the unsaturated ketone to form an epoxide which is unstable to base and decomposes to the observed products. Rigaudy[9] has found that certain enolizable ketones, such as 9-benzoylfluorene, do not oxidize under neutral conditions but in the presence of alkali a rapid reaction occurs which leads to the formation of scission products. The autoxidation of a variety of ketones under strongly alkaline conditions has been studied by Doering and Haines,[10] who used potassium *t*-butoxide in *t*-butyl alcohol and an oxygen pressure of 2 atm., and by Elkik,[11] who employed sodium *t*-pentoxide in benzene at room temperature as the reaction medium. Many reactions were exothermic and gave acidic products resulting from attack at the position $\alpha$ to the carbonyl group. However, Doering found that, even with the fairly basic system that he employed, certain structural limitations existed for these reactions. Cyclic aliphatic ketones such as cyclohexanone gave mainly tars and not the expected cleavage products.

From the above discussion, two fairly general conclusions can be made. First, the use of alkali metal hydroxides as catalysts for these reactions is limited to ketones having fairly acidic $\alpha$-carbon–hydrogen bonds, *e.g.*, $PhCH_2COPh$. Second, the base-catalyzed oxidation of cyclic aliphatic ketones to dicarboxylic acids does not proceed readily even in the presence of a strong base. Based on our previous studies on solvent effects in the anionic oxidation of sulfur compounds[12] it was felt that these limitations with respect to base and ketone could be overcome by the proper choice of solvent, *i.e.*, a solvent that was dipolar,

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(1) W. Miller and Rohde, *Ber.*, **25**, 2095 (1892).

(2) A. H. Salway and E. S. Kipping, *J. Chem. Soc.*, **95**, 166 (1909).

(3) V. Bogdanowska, *Ber.*, **25**, 1271 (1892).

(4) C. Graebe and E. Gfeller, *Ann.*, **276**, 12 (1893).

(5) C. Graebe and J. Jequier, *ibid.*, **290**, 199 (1896).

(6) C. Harries, *Ber.*, **34**, 2105 (1901).

(7) C. Harries and A. Stähler, *Ann.*, **330**, 264 (1904).

(8) (a) W. Treibs, *Ber.*, **63**, 2423 (1930); (b) *ibid.*, **64**, 2178 (1931); (c) *ibid.*, **65**, 163 (1932); (d) *ibid.*, **66**, 1483 (1933); (e) *ibid.*, **64**, 2545 (1931); (f) *ibid.*, **66**, 610 (1933); (g) *ibid.*, **65**, 1314 (1932); (h) *ibid.*, **68**, 1049 (1935).

(9) J. Rigaudy, *Compt. rend.*, **228**, 253 (1949).

(10) W. v. E. Doering and R. M. Haines, *J. Am. Chem. Soc.*, **76**, 482 (1954).

(11) E. Elkik, *Bull. soc. chim. France*, 933 (1959).

(12) (a) T. J. Wallace and A. Schriesheim, *Tetrahedron Letters*, **No. 17**, 1131 (1963), and references therein; (b) T. J. Wallace, H. Pobiner, and A. Schriesheim, *J. Org. Chem.*, **29**, 888 (1964); (c) T. J. Wallace, N. Jacobson, and A. Schriesheim, *Nature*, **201**, 609 (1964); (d) T. J. Wallace and A. Schriesheim, *Tetrahedron*, to be published.

aprotic, and stable to oxygen and any intermediate oxidation products.

## Results

The base-catalyzed oxidation of acetophenone and several cyclic aliphatic ketones was studied at 1-atm. pressure of oxygen at 23.5 and 80° in the dipolar solvent, hexamethylphosphoramide (HMPA). Initial studies on the effect of solvent and base on these reactions were carried out using acetophenone as a model compound. In all cases, the mole ratio of base/acetophenone was 3. These results are summarized in Table I. No oxidation occurred in KOH–water at 80° in 46 hr. Potassium *t*-butoxide was a more effective base in HMPA than in *t*-butyl alcohol at 23.5° with respect to both rate and yield of acid. Thus, HMPA was the solvent of choice for these reactions. The use of sodium or potassium hydroxide in place of potassium *t*-butoxide in HMPA at 23.5° resulted in an 11-fold decrease in the rate of oxidation and a substantial decrease in the yield of acid. No reaction was observed in the presence of lithium hydroxide at 23.5°. At 80°, the rate of oxidation with sodium and potassium hydroxide was about half of that observed with the butoxide at 23.5°. However, potassium *t*-butoxide at 23.5° was 543 times more effective than lithium hydroxide at 80°. As indicated in Table I, most reactions resulted in a ketone conversion of 90–100%. The nonacidic material was found to be polymeric and was assumed to result from enolate condensation reactions. This assumption was found to be true. In the presence of KOH at 80°, addition of 25 and 50 vol. % water resulted in a rapid decrease in the per cent conversion of acetophenone (98 to 38%) and a $10^2$ to $10^3$ decrease in the rate of oxidation but an increase in acid selectivity from 64 to 92% (see Table II).

Table I

Effect of Solvent and Base on the Oxidation of Acetophenone[a]

| Base–solvent | Temp., °C. | % yield[b] of benzoic acid | Moles of $O_2$[c] / mole of ketone min. × $10^3$ | Time, hr. |
|---|---|---|---|---|
| KO-*t*-Bu-*t*-$C_4H_9OH$ | 23.5 | 66 | 1.60 | 45 |
| KO-*t*-Bu–HMPA | 23.5 | 88 | 4.88 | 44 |
| KOH–HMPA | 80 | 62 | 2.14 | 44 |
| KOH–HMPA | 23.5 | 35 | 0.42 | 44 |
| NaOH–HMPA | 80 | 60 | 2.00 | 21 |
| NaOH–HMPA | 23.5 | 46 | 0.43 | 21 |
| LiOH–HMPA | 80 | 14 | 0.009 | 24.5 |
| LiOH–HMPA | 25.0 | .. | N.r. | 24.5 |
| KOH–$H_2O$ | 80 | .. | N.r. | 42 |

[a] Using 0.05 mole of acetophenone, 0.15 mole of base, and 1 atm. of oxygen pressure. [b] Theoretical moles of acid/initial moles of ketone × 100. Total ketone conversion, with the exception of LiOH, varied from 90 to 100%. [c] Calculated from the initial rates of oxygen consumption.

Table II

Effect of Added Water on Selectivity in the Oxidation of Acetophenone to Benzoic Acid[a]

| Vol. % of HMPA | % selectivity to benzoic acid | % conversion of acetophenone | Moles of $O_2$ / mole of ketone, min. |
|---|---|---|---|
| 100 | 64 | 98 | $2.14 \times 10^{-2}$ |
| 75 | 87 | 60 | $2.6 \times 10^{-4}$ |
| 50 | 92 | 38 | $5.0 \times 10^{-5}$ |

[a] Using 0.05 mole of acetophenone, 0.15 mole of KOH, and 75 ml. of solution, at 80°.

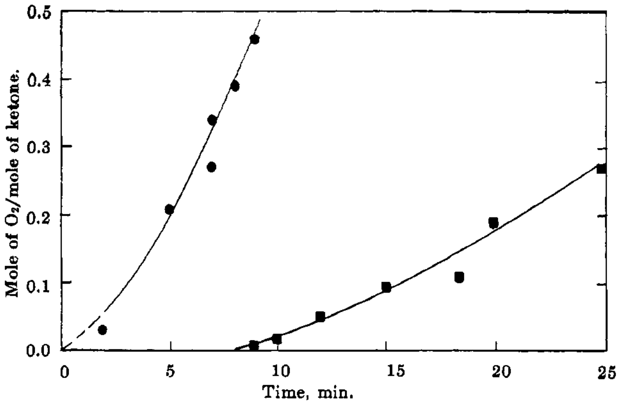


Figure 1.—Comparison of the reactivity of cyclohexanone and cyclododecanone in HMPA at 23.5° using a NaOH/ketone ratio of 3: ●, cyclohexanone; ■, cyclododecanone.

Studies on the autoxidation of $C_5$ to $C_{12}$ cyclic ketones to dibasic acids were carried out at 23.5 and 80° using a base/ketone ratio of 6. These results are summarized in Table III. In the presence of either sodium methoxide or sodium hydroxide, cyclohexanone and cyclopentanone were similar in reactivity and autoxidation of these cyclic compounds gave moderate to excellent yields of adipic and glutaric acids. Cycloheptanone and cyclododecanone were less reactive than the $C_5$ and $C_6$ cyclic ketones. The maximum yields of the corresponding diacids of these ketones were 40–44% after 20 hr. of oxidation in NaOMe–HMPA at 80°. The decrease in reactivity with increasing ring size is further demonstrated in Figure 1 where the moles of $O_2$ consumed/mole of ketone at 23.5° is plotted as a function of time for cyclohexanone and cyclododecanone. The oxidation of the isomeric tetralones proceeded readily in KOH–HMPA at 23.5° but it was impossible to make any definite conclusions about the products formed. In both cases, several acidic products were present but they were not readily separated. The initial rates of oxygen consumption for the tetralones along with that for acetophenone are shown in Table IV. The observed rates follow the expected ease of carbanion formation for this series of compounds.

Table III

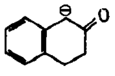
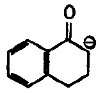
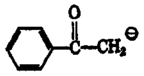
Summary of Base-Catalyzed Cyclic Ketone Oxidations[a]

| Ketone | Temp., °C. | Base | Acid (% yield) | Time, hr. |
|---|---|---|---|---|
| Cyclohexanone | 23.5 | NaOMe | Adipic (100) | 20 |
| Cyclohexanone | 80 | NaOMe | Adipic (>90) | 24 |
| Cyclohexanone[b] | 23.5 | NaOH | Adipic (94) | 78 |
| Cyclohexanone[b] | 80 | NaOH | Adipic (82) | 68 |
| Cyclohexanone[b] | 23.5 | NaOH | Adipic (81) | 24 |
| Cyclohexanone[b] | 80 | NaOH | Adipic (88) | 19 |
| Cyclopentanone | 23.5 | NaOMe | Glutaric (95) | 23 |
| Cyclopentanone | 80 | NaOMe | Glutaric (100) | 23 |
| Cyclopentanone[b] | 23.5 | NaOH | Glutaric (49) | 26 |
| Cyclopentanone[b] | 80 | NaOH | Glutaric (76) | 24 |
| Cycloheptanone | 23.5 | NaOMe | Pimelic (44) | 19 |
| Cycloheptanone | 80 | NaOMe | Pimelic (41) | 21 |
| Cyclododecanone | 80 | NaOMe | Dodecanedioic (40) | 21 |

[a] Using 0.025 mole of ketone, 0.15 mole of base, and 75 ml. of HMPA. [b] Essentially the same results were obtained with KOH.

TABLE IV

EFFECT OF KETONE STRUCTURE ON THE RATE OF OXIDATION[a]

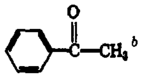
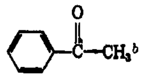
| Ketone | Moles of $O_2$[b] / mole of ketone min. |
|---|---|
|  | $2.0 \times 10^{-1}$ |
|  | $2.7 \times 10^{-2}$ |
|  | $4.2 \times 10^{-3}$ |

[a] In HMPA using 0.25 mole of ketone and a KOH/ketone ratio of 3, at 23.5°. [b] Calculated from the initial rates of oxygen consumption.

A few reactions have been selected at random to demonstrate oxygen balance between the millimoles of acid produced and the millimoles of oxygen consumed. These data are shown in Table V. The data indicate that each millimole of benzoic acid produced from acetophenone requires 2 mmoles of oxygen and that each millimole of dibasic acid produced from a cyclic ketone probably requires 1.75 mmoles of oxygen.

TABLE V

TYPICAL OXYGEN BALANCE FOR KETONE OXIDATIONS[a]

| Ketone (mmoles) | Base/solvent | Temp., °C. | Mmoles of acid formed | Mmoles of $O_2$ Calcd. | Found |
|---|---|---|---|---|---|
|  (50.0) | KOH/HMPA (50%)-$H_2O$ (50%) | 80 | 17.3 | 34.6 | 35.0 |
|  (25.0) | NaOH/HMPA | 23.5 | 22.7 | 45.4 | 46.6 |
| Cyclohexanone (26) | NaOH/HMPA | 80 | 21.2 | 37.1 | 37.4 |
| Cyclohexanone (25) | NaOH/HMPA | 23.5 | 20.0 | 34.0 | 35.3 |
| Cyclopentanone (26) | NaOMe/HMPA | 23.5 | 24.5 | 36.8 | 38.5 |

[a] Oxygen balance for the $C_7$ and $C_{12}$ cyclic ketones was poor. [b] The ratio of $CO_2$ to acid formed was close to unity.

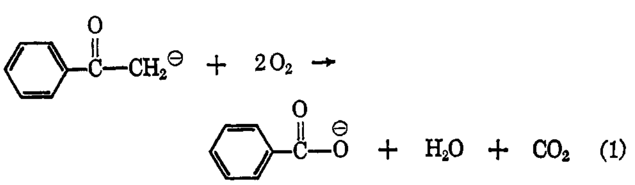
## Discussion

The present results are the first examples of the low-temperature autoxidation of cyclic ketones to dibasic acids in the presence of alkali. As shown in Table III, moderate to excellent yields of the diacids were obtained in either NaOMe–HMPA or NaOH–HMPA under mild conditions. Thus, it is anticipated that in the future the present technique should be a widely useful synthetic tool. The choice of solvent is, without doubt, the most critical factor. Ethereal solvents such as diethylene glycol dimethyl ether, though reasonably stable to oxygen and alkali at room temperature and below,[13,14] are readily autoxidized at 80°.[15] Dipolar solvents such as DMSO, DMF, and DMAC, which have been extensively used as solvents for carbanion reactions,[16] autoxidize at 80–100°, and in the case of DMSO condensation reactions with carbonyl compounds also occur.[17,18] DMF and DMAC probably behave in a similar manner. In the case of HMPA where all carbon–hydrogen bonds are $\beta$ to the dipolar group these side reactions are minimized.

The ease of oxidation of acetophenone in KOH–HMPA and NaOH–HMPA in comparison with aqueous media is apparently due to decreased hydrogen bonding of the base in HMPA. This ultimately results in a higher concentration of carbanion which, in the presence of excess oxygen, is rapidly consumed. A comparison of the KO-*t*-Bu–HMPA and the KO-*t*-Bu-*t*-$C_4H_9OH$ systems also suggests this to be the case. The observed effect of ketone structure on the ease of oxidation (Table IV) is consistent with these conclusions since $\beta$-tetralone, which contains the most acidic $\alpha$-carbon–hydrogen bonds, was oxidized $10^2$ times as fast as acetophenone. The concomitant decrease in the rate of oxidation of acetophenone and increased selectivity to benzoic acid in HMPA with increasing concentration of water (Table II) indicates a stepwise decrease in the concentration of the carbanion. This in turn results in optimum acid selectivity since a decrease in the equilibrium concentration of the carbanion diminishes the amount of anion available for competing condensation reactions at any given time. In the presence of 50 vol. % of water, it would appear that all anions produced are consumed completely by oxygen.

The observed effect of alkali metal hydroxide on the ease of acetophenone oxidation in HMPA is consistent with previous findings for base-catalyzed racemization,[19] oxidation,[13] and elimination[20] reactions in polar solvents. In these previous studies, soluble alkali metal *t*-butoxides were employed. In the present case, the metal hydroxide–HMPA systems are heterogeneous. Thus, any definite conclusions based on previous studies would be fortuitous. However, the fact that sodium and potassium hydroxide are so much more effective than lithium hydroxide certainly suggests that solvent–cation interaction occurs more readily with $Na^+$ and $K^+$ than with $Li^+$. It should also be noted that this reactivity series is consistent with the results of Donoghue and Drago[21] who found that HMPA is capable of forming some unusual complexes with the larger, transition metal cations.

The stoichiometric findings indicate that the over-all reaction for acetophenone is given by eq. 1. For the



$$C_6H_5C(=O)CH_2^{\ominus} + 2O_2 \rightarrow C_6H_5C(=O)O^{\ominus} + H_2O + CO_2 \quad (1)$$

cyclic ketones the over-all reaction appears to be that shown in eq. 2. The exact path by which these re-

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(13) T. J. Wallace and A. Schriesheim, *J. Org. Chem.*, **27**, 1514 (1962).

(14) H. C. Gersmann, H. J. W. Nieuwenhuis, and A. F. Bickel, *Proc. Chem. Soc.*, 279 (1962).

(15) We have found that both diglyme and *p*-dioxane were rapidly autoxidized in the presence of KO-*t*-Bu at 80°. Although this finding was of interest, no attempt to isolate the products was made.

(16) A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962).

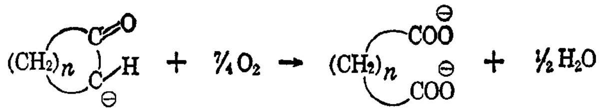
(17) M. Chaykovsky and E. J. Corey, *J. Org. Chem.*, **28**, 254 (1962).

(18) (a) H. D. Becker and G. A. Russell, *ibid.*, **28**, 1895 (1963); (b) G. A. Russell, *et al.*, *J. Am. Chem. Soc.*, **84**, 2652 (1962); (c) G. A. Russell and H. D. Becker, *ibid.*, **85**, 3406 (1963); (d) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965).

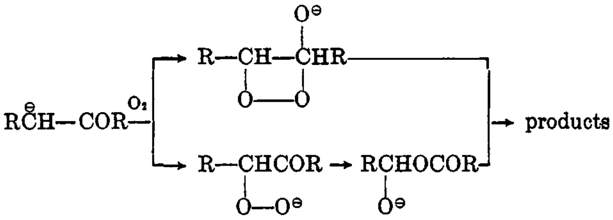
(19) D. J. Cram, *et al.*, *ibid.*, **81**, 5774 (1959).

(20) T. J. Wallace, J. E. Hofmann, and A. Schriesheim, *ibid.*, **85**, 2739 (1963).

(21) J. T. Donoghue and R. S. Drago, *Inorg. Chem.*, **1**, 866 (1963).


(2)

actions proceed cannot be absolutely defined. One possibility is the formation of a cyclic peroxide from the enolate of the α-carbanion[10]; the other is a peroxy anion intermediate.[11] Both intermediates would decompose to acidic and aldehydic products. The latter would be rapidly oxidized under the present conditions.[22] As Gersmann and co-workers[14] have recently isolated hydroperoxides as initial products in the autoxidation of ketones and esters at −5 to −75° in KO-*t*-Bu-*t*-$C_4H_9OH$–diglyme, the peroxy anion intermediate reaction path is the most probable course of reaction. The intermediate peroxy anions would be unstable under the present conditions and it is possible that they decompose by a four-centered intermediate which would be similar to that proposed by Doering.[10]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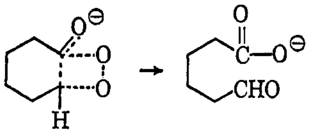

## Experimental Section

**Reagents and Starting Materials.**—Hexamethylphosphoramide (Monsanto Chemical Co.) and *t*-butyl alcohol (Matheson Coleman and Bell) were distilled under nitrogen over Linde-13X Molecular Sieves to remove any water that was present. A 10:1 volume ratio of sieve to solvent was employed. Potassium *t*-butoxide was obtained from the Mine Safety Appliance Co. as the sublimed white powder (98.5% pure). Lithium, sodium, and potassium hydroxides were obtained from the Baker Chemical Co. as reagent grade materials. With the exception of cyclododecanone, all ketones were obtained from either Columbia Organic Chemicals Co. or Matheson Coleman and Bell. The ketones were purified by distillation under reduced pressure through a 14-in. silvered column equipped with a tantalum-wire spiral. All distilled ketones gave only one peak when analyzed by gas chromatography. Cyclododecanone and its oxidation product, dodecanedioic acid, were Enjay Chemical Co. products. All materials were stored in a nitrogen drybox equipped with a moisture conductivity cell.

**Preparation of Reaction Mixtures and Actual Oxidation Experiments.**—All base–solvent systems were made up to the appropriate molarity in a nitrogen drybox. The alkali metal hydroxides were ground into powdered form before use. The desired ketone was then added to the reaction flask which was sealed and transferred to the oxidation apparatus. When alkali metal hydroxides were employed, the solvent–base systems were heterogeneous.

The reaction flask was a heavy-walled, Pyrex glass flask equipped with a ground-glass sealed side arm. The flask was attached to a water-cooled condenser which was attached to the source of oxygen. The oxygen was stored in a polyethylene gas balloon under 1-atm. pressure of oxygen. The oxygen flowed from the balloon through a wet-test meter with 10-ml. gradations and into a large drying tube filled with indicating Drierite before entering the glass reaction vessel containing the reaction mixture. In actual operation, the system was initially purged with oxygen through the reaction flask side arm, the side arm was sealed, and an equilibrium pressure was established. The reaction was then initiated by magnetic stirring at 1300 r.p.m. The volume of oxygen consumed as a function of time was determined from the wet-test meter which allows an estimation of the volume of gas consumed to within ±1 cc. With this method, a constant oxygen partial pressure of 1 atm. was maintained above the system. All reactions were allowed to proceed to completion, *i.e.*, till no apparent oxygen consumption was observed. This oxidation technique and its applications have been described in detail previously.[23]

**Quantitative Analysis for Reactants and Products.**—Analyses for the acidic materials were carried out according to the method of Pobiner, Wallace, and Hofmann.[24] Two techniques can be employed. One involves an extraction–ion exchange–infrared procedure for aliphatic products. The other is an extraction–ultraviolet procedure for aromatic products. Both rely on initial homogenization with water and subsequent extraction with cyclohexane to remove the starting material and nonacidic products. This removes any spectral interference with the determination of acidic products. These methods were accurate to within 95–99% for all products identified.

**Other Methods of Identification.**—In addition to the ultraviolet and infrared comparison to authentic samples, further proof for the formation of acidic products was obtained by isolation of the acid and determination of its melting point or by an infrared comparison of the isolated material to an authentic sample. In the case of α- and β-tetralone, several acidic products were formed but attempts to separate the acid mixtures were not successful.

**Acknowledgment.**—The authors are indebted to the Esso Research and Engineering Company for permission to publish this work and to Messrs. F. T. Fitzsimmons and J. I. Haberman who performed much of the experimental work.

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[22] Benzaldehyde and benzyl alcohol, which is a product of the Cannizzaro reaction, are oxidized to benzoic acid at an extremely rapid rate.

[23] T. J. Wallace, W. Bartok, and A. Schriesheim, *J. Chem. Educ.*, **40**, 39 (1963).

[24] H. Pobiner, T. J. Wallace, and J. E. Hofmann, *Anal. Chem.*, **35**, 680 (1963).