able. Certainly, the possibility that this correlation might be only a fortuitous coincidence void of any physical significance—the number of compounds examined is small—cannot be excluded. If, however, the correlation is real, one might suggest that for system I either the contact electron-spin term in C^{13} is a dominant one undergoing changes which are proportional to those in the corresponding term in proton, or/and changes of other terms, *e.g.*, electron-orbital term, in C^{13} parallel those of the contact electron–spin term in proton.

Finally, it was interesting to observe that substitution of an atom of oxygen for an atom of carbon (methyl esters of C^{13}-carbonyl labeled acids) results in considerable decrease of C^{13}–proton coupling constant (Table I, $J_{C^{13}O-C-H} < J_{C^{13}C-C-H}$).

TABLE II

PROTON SPIN–SPIN COUPLING CONSTANTS (C.P.S.) IN ISOPROPYL GROUPS

Compound	$J_{H\cdot C\cdot C\cdot H}$	$\frac{J_{C^{13}C\cdot C\cdot H}}{J_{H\cdot C\cdot C\cdot H}} \times 100$
$(CH_3)_2CHCCH(CH_3)_2$ (O)	7.2	71
$(CH_3)_2CHC(OH)HCH(CH_3)_2$	6.7	67
$(CH_3)_2CHCH_2CH(CH_3)_2$	6.1	79
$(CH_3)_2CHCO_2H$	7.2	75
$(CH_3)_2CHCO_2CH_3$	7.3	79
$(CH_3)_2CHCH_2OH$	4.8	79
$(CH_3)_3CH$[a]	5.0	
$(CH_3)_3CHCH(CH_3)_2$[a]	5.5	
$(CH_3)_2CHCH_2CH_2CH_3$[a]	5.2	
$(CH_3)_2CHOH$[b]	6.1	
$(CH_3)_2CHBr$[b]	6.4	
$(CH_3)_2CHNH_2$[b]	6.1	

[a] Taken from J. A. Pople, W. G. Schneider and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N.Y., 1959, pp. 236–237. [b] Taken from A. A. Bothner-by, C. Naar-Colin and B. L. Shapiro, "NMR Spectra and Structure Correlations," Vol. II, Harvard University, 1958.

Experimental

Preparation of C^{13}-Labeled Compounds. a. Diisopropyl Ketone and its Derivatives.—Preparation of 2,4-dimethyl-3-pentanone-3-C^{13} and 2,4-dimethylpentane-3-C^{13} will be described elsewhere. Preparation of 2,4-dimethyl-3-pentanol-3-C^{13} has been recorded.[10]

b. Trimethylacetic acid-1-C^{13} and dimethylacetic acid-1-C^{13} were isolated as by-products from the addition of carbon dioxide-C^{13} to *t*-butyllithium and isopropyllithium, respectively, at −60°, during synthesis of di-*t*-butyl ketone and diisopropyl ketone. Their infrared spectra (carbonyl frequency) have been discussed.[11]

c. Methyl Dimethylacetate-1-C^{13} and Methyl Trimethylacetate-1-C^{13}.—One gram of C^{13}-carbonyl labeled acid was dissolved in anhydrous ether (10 ml.) and diazomethane[12] was added until the yellow color persisted. The ether was evaporated through a small fractionating column. Practically quantitative yields of the esters were obtained.

d. C^{13} and Deuterium Labeled Alcohols.—The deuterated and undeuterated C^{13}-labeled isobutyl and neopentyl alcohols were prepared by reduction of the corresponding acids in ether solutions with lithium aluminum deuteride and lithium aluminum hydride. Vapor phase chromatography and infrared spectroscopy were used to ascertain purity of all samples.

Measurements.—All spectra were taken with a model V4250A Varian Associates high resolution n.m.r. spectrometer, at 60 Mc., with the exception of those of diisopropyl ketone and diisopropylmethane which were measured at 40 Mc. Thin-walled Wilmad Glass Co. tubes were used in taking the spectra; no sample degassing was applied. Trimethylacetic acid (10% solution in carbon tetrachloride) and its anion (10% solution in dilute aqueous potassium hydroxide) were the only compounds whose spectra were taken in solution. Spin–spin coupling constants were measured using the standard side band technique,[13] the frequency counter being employed.

Acknowledgments.—The author acknowledges with pleasure the stimulating and helpful discussions with Professor M. T. Rogers and J. D. Graham. He is indebted to Mr. Graham for taking many of the n.m.r. spectra, and to Dr. E. B. Baker of Dow Chemical Co. for the spectra of the methyl esters.

(10) G. J. Karabatsos, *J. Org. Chem.*, **25**, 1409 (1960).
(11) G. J. Karabatsos, *ibid.*, **25**, 315 (1960).
(12) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 165.
(13) J. T. Arnold and M. E. Packard, *J. Chem. Phys.*, **19**, 1608 (1951).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILL.]

Molecule-induced Homolytic Decompositions. I. Oxygen-18 Labeling Studies on the Reaction Yielding Cyclohexyl Acetate from Cyclohexene and Acetyl Peroxide[1]

BY J. C. MARTIN AND E. H. DREW

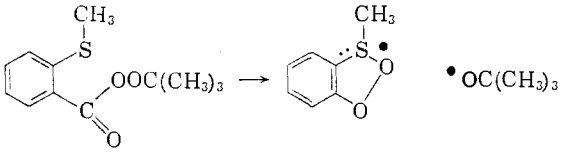
RECEIVED SEPTEMBER 6, 1960

The decomposition of acetyl peroxide in cyclohexene solution gives a small amount (~10%) of cyclohexyl acetate. This has been attributed[2] to a mechanism involving an addition of free acetoxy radicals to cyclohexene. To test the hypothesis that this product results instead from the operation of a molecule-induced decomposition in which cyclohexene attacks acetyl peroxide, we used O^{18}-tracer techniques to determine the disposition of the label in cyclohexyl acetate from the decomposition of carbonyl-labeled peroxide. The finding of 58% of the label in the carbonyl oxygen of the product acetate (42% in the saturated oxygen) serves to rule out the possibility that all of the product results from a process involving acetoxy radical. The demonstration of a dependence of labeling specificity on the availability of hydrogen atom donor molecules serves to confirm the postulated mechanism (mechanism II).

It has recently been shown[3,4] that suitable neighboring groups can bring about an anchimeric[5] acceleration of the homolytic cleavage of oxygen–oxygen bonds similar to the well-known accelerating effect of neighboring nucleophilic groups in

(1) Presented before the Division of Organic Chemistry at the 137th Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960.
(2) H. J. Shine and J. R. Slagle, *J. Am. Chem. Soc.*, **81**, 6309 (1959).
(3) J. C. Martin and W. G. Bentrude, *Chemistry & Industry*, 192 (1959); complete report in preparation.
(4) J. E. Leffler, R. D. Faulkner and C. C. Petropoulos, *J. Am. Chem. Soc.*, **80**, 5435 (1958).
(5) S. Winstein, C. R. Lindegren, H. Marshall and L. Ingraham, *ibid.*, **75**, 147 (1955).

ionization reactions. Most strikingly, it was shown[3] that the radical decomposition of *t*-butylperoxy *o*-methylthiobenzoate was faster by a factor of 2×10^4 (at 20°) than the corresponding reaction of the unsubstituted perbenzoate, an acceleration most easily explained by postulating the participation of neighboring sulfur in the decomposition step.



The large size of this acceleration made it seem likely to us that an intermolecular analog of this reaction, a participation of solvent in a homolytic peroxide bond cleavage, might be found. A search for such a reaction has been successful in that the work described in this present paper makes such a mechanism seem very probable for the reaction between cyclohexene and acetyl peroxide to give cyclohexyl acetate. In this case use has been made of isotopic labeling procedures rather than rate studies to establish this point.

Results and Discussion

Several reactions have been studied which appear, upon the basis of some experimental observation, to involve molecule-induced homolytic bond cleavages, reactions in which stabilization of the transition state for homolysis of a bond is furnished by the simultaneous formation of a bond to some other molecule in solution. In contrast with the large body of evidence for the ionic analogs of this reaction, nucleophilic displacements yielding ions from electrically neutral molecules, evidence for the free radical type of displacement is not extensive and has often been of an inconclusive nature.

Evidence has been cited to support the postulation of such a mechanism for the cleavage of covalent bonds joining atoms of various elements.

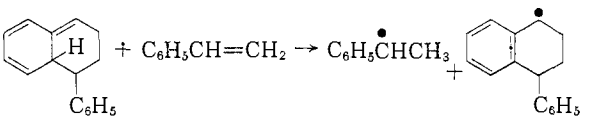
In order to explain the high rate of thermal initiation observed in the free-radical reaction of styrene with iodine, Fraenkel and Bartlett[6] postulated a mode of homolytic cleavage of an iodine–iodine bond involving reaction with one or two styrene molecules.

$$2C_6H_5CH{=}CH_2 + I_2 \longrightarrow 2C_6H_5\dot{C}HCH_2I$$

or

$$C_6H_5CH{=}CH_2 + I_2 \longrightarrow C_6H_5\dot{C}HCH_2I + I\cdot$$

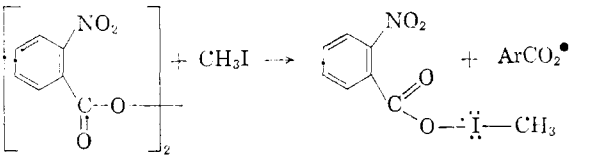
The thermal initiation of styrene polymerization may involve a similar reaction, three molecules of styrene reacting to give two free radicals.[7-9] Mayo (quoted by Hiatt and Bartlett[9]) has suggested a most attractive possibility for the step in which radicals are formed, involving a styrene molecule and a Diels–Alder type dimer of styrene. Here a C–H bond cleavage is assisted by simultaneous C–H bond formation in the transition state.



Walling and Chang[10] suggest a similar mechanism, involving cleavage of an O–H bond, to explain the increased rate of primary decomposition of *t*-butyl hydroperoxide in styrene as determined by a complete kinetic study of the reaction in this solvent.

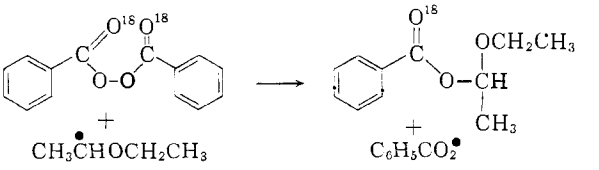
$$ROOH + CH_2{=}CHC_6H_5 \longrightarrow ROO\cdot + CH_3\dot{C}HC_6H_5$$

A kinetic argument was advanced by Leffler[4] to support the postulate that O–O bond cleavage in diacyl peroxides might occur with solvent participation. He has published results of an investigation of the decomposition reactions of various diacyl peroxides in solvents which might be expected to participate in the decomposition step. He presents evidence that this is occurring in the decomposition of bis-(*o*-nitrobenzoyl) peroxide in methyl iodide solvent. The reaction in this solvent is faster than in chloroform solution by a factor of 300. This increase in rate is attributed to the action of a molecule-induced decomposition involving an attack of methyl iodide on the peroxide molecule.



Another possible means for detecting the operation of such a mechanism in diacyl peroxide decompositions involves the investigation of products in which the bond formed in the transition state between the inducing molecule and an oxygen atom is preserved in the final product. Isolation of such a product from the decomposition of properly O^{18}-labeled peroxide makes possible the detection of a preference for attack on one or the other of the two oxygen atoms.

It is known that the radical-induced decomposition of benzoyl peroxide in diethyl ether[11-13] proceeds with such specificity, preferring attack on the saturated oxygen rather than the carbonyl, more than 70% of the reaction following this preferred path.



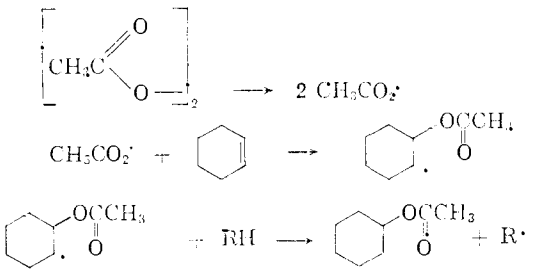
Similar results have been noted[13] for the attack of the cyclohexenyl radical and the triphenylmethyl radical on benzoyl peroxide, the attack being exclusively on the ether oxygen in the latter case.

(6) G. Fraenkel and P. D. Bartlett, *J. Am. Chem. Soc.*, **81**, 5582 (1959).
(7) K. E. Russell and A. V. Tobolsky, *ibid.*, **75**, 5052 (1953).
(8) F. R. Mayo, *ibid.*, **75**, 6133 (1953).
(9) R. R. Hiatt and P. D. Bartlett, *ibid.*, **81**, 1149 (1959).
(10) C. Walling and Y. Chang, *ibid.*, **76**, 4878 (1954).
(11) E. H. Drew and J. C. Martin, *Chemistry & Industry*, 925 (1959).
(12) D. B. Denney and G. Feig, *J. Am. Chem. Soc.*, **81**, 5322 (1959).
(13) W. von E. Doering, K. Okamoto and H. Krauch, *ibid.*, **82**, 3579 (1960).

It might be expected that a molecule-induced decomposition might show a similar specificity, attack occurring on one of the two oxygens preferentially.

The reaction chosen for study using this technique was the decomposition of acetyl peroxide in cyclohexene solvent. This reaction is known to produce appreciable amounts of cyclohexyl acetate in addition to the cyclohexenyl acetate which one might expect from the operation of a radical-chain induced decomposition. Shine[2] has postulated that the 10–15% of cyclohexyl acetate from this reaction results from the addition of free acetoxy radicals to the cyclohexene double bond. The resulting 2-acetoxycyclohexyl radical then abstracts hydrogen from the solvent to yield the observed product.

MECHANISM I



This mechanism calls for the acetoxy radical to exist in solution for a period of time sufficiently long for reaction with cyclohexene to occur. Previous work[14] on the decomposition of acetyl peroxide indicates that the acetoxy radical is very unstable. Rembaum and Szwarc[15] present evidence that C–C bond cleavage follows O–O bond cleavage almost immediately. Attempts to trap the acetoxy radical with iodine in moist carbon tetrachloride,[16] a technique which is successful in trapping benzoyloxy radicals from benzoyl peroxide,[17] have given completely negative results.

These data, with others of similar import, led us to doubt that cyclohexene was sufficiently efficient as a scavenger to trap acetoxy radicals as demanded by mechanism I.

In order to determine whether this reaction might not be an example of a molecule-induced decomposition, acetyl peroxide labeled with O^{18} in the carbonyl oxygens was decomposed in boiling cyclohexene. The resulting cyclohexyl acetate was found to have retained 58% of the label in the carbonyl oxygen with 42% in the saturated oxygen. The most straightforward interpretation of these results invokes the attack of cyclohexene on the saturated peroxidic oxygen to yield the intermediate 2-acetoxycyclohexyl radical as outlined in mechanism II.

It we postulate the attack of cyclohexene to occur entirely on ether oxygen, yielding α-acetoxycyclohexyl radical with carbonyl label (I), then we may conclude that 58% of the reaction follows path A

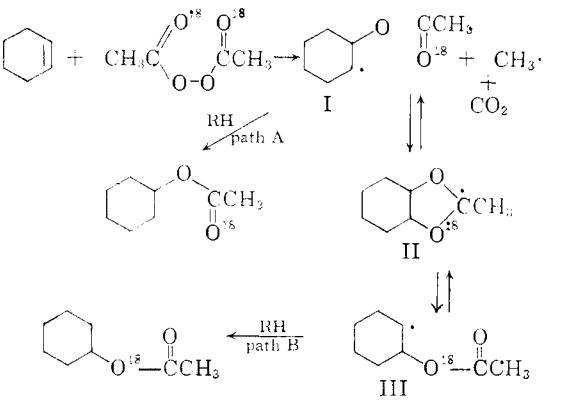
(14) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 491 ff.

(15) A. Rembaum and M. Szwarc, *J. Am. Chem. Soc.*, **77**, 3486 (1955).

(16) C. Walling and R. Hodgdon, *ibid.*, **80**, 228 (1958).

(17) G. Hammond and L. M. Soffer, *ibid.*, **72**, 4711 (1950).

MECHANISM II



and 42% of the reaction path B. This is equivalent to saying that in this medium 16% of the reaction proceeds directly by path A without going through II, while the 84% of the reaction which proceeds through II gives product with scrambled labeling. If, indeed, the scrambling of label which is observed results from the equilibration of radicals I and III through structure II, which may represent either an intermediate or a transition state, we see that the amount of equilibration might be expected to be a function of the life-time of the intermediate radical. Radical I can either give carbonyl-labeled product by a reaction (path A) with rate dependent on the concentration and nature of R–H or can undergo equilibration of label with a rate independent of R–H. As can be seen from an examination of the data in Table I, decreasing the concentration of R–H by dilution of the cyclohexene with three volumes of benzene had the predicted effect in yielding cyclohexyl acetate with more nearly statistical distribution of label (55.5% carbonyl-labeled and 44.5% ether oxygen labeled).

TABLE I

DISTRIBUTION OF THE LABEL IN CYCLOHEXYL ACETATE-O^{18}

Run	Total	Atom % excess oxygen-18 Ether-O	Carbonyl-O[a]	% of label[f] Ether-O	Carbonyl-O
I[b]	1.12	0.47	0.65	42.0	58.0
II[b]	1.13	.47	.66	41.6	58.4
III[c]	1.10	.49	.61	44.5	55.5
IV[d]	1.05	.37	.68	35.2 (33.0)[e]	64.8 (67.0)[e]

[a] By difference. [b] In cyclohexene. [c] In 75% benzene 25% cyclohexene. [d] In cyclohexene saturated with hydroquinone. [e] Calculated assuming cyclohexyl acetate-O^{18} contained 1.12 atom % excess oxygen-18, the value observed after more intensive purification. [f] Based on oxygen-18 analyses performed in duplicate; duplicate analyses gave identical results within the expressed number of significant figures.

Increasing the rate of reaction along path A relative to the rate of equilibration by saturating the solution with hydroquinone, a very good hydrogen atom donor in free-radical reactions, has the expected effect of producing an even greater specificity of labeling in the product cyclohexyl acetate, 67% of the label appearing in the carbonyl oxygen.

This allows us to say that at least 34% of the reaction between cyclohexene and acetyl peroxide to yield cyclohexyl acetate proceeds by a mechanism in which the two acetate oxygen atoms do not be-

come equivalent, a displacement on the peroxidic oxygen by cyclohexene being the most obvious possibility. The remaining 66% of the reaction may proceed either through the operation of a mechanism for equilibration such as is outlined in mechanism II, through the competing operation of a mechanism involving free acetoxy radical (such as mechanism I), or through the occurrence of equal amounts of displacement by cyclohexene on the carbonyl oxygen and on the peroxidic oxygen.

In runs with added hydroquinone the occurrence of a competing polar reaction,[18] which destroys acetyl peroxide by a route yielding no cyclohexyl acetate, made it difficult to get even the small amounts of product needed for mass spectrometric analysis. A further complication lay in the difficulty which we experienced in getting complete separation of the product ester from quinone, also formed in the reaction. By running the reaction on a larger scale and purifying the products by gas–liquid phase chromatography (g.l.p.c.) these difficulties were overcome.

It is important to show that the cyclohexyl acetate and cyclohexanol which we obtained by g.l.p.c. procedures were uncontaminated by cyclohexenyl acetate and cyclohexenol, respectively. It has been shown that the radical-chain induced decomposition of carbonyl-labeled benzoyl peroxide yields cyclohexenyl benzoate with 70% of the label in the carbonyl oxygen.[13] Contamination with the cyclohexenol derivatives in the present work would introduce grave uncertainties into our conclusions. With the g.l.p.c. support and packing used in this work it was found that, at the temperatures used, cyclohexenyl acetate was completely decomposed on the column to give products with much shorter retention times than cyclohexyl acetate. The cyclohexyl acetate was, therefore, in every case uncontaminated with cyclohexenyl acetate. Both the cyclohexyl acetate and cyclohexanol collected from the column were, in their infrared spectra, identical in all respects with authentic samples.

The possibility must be considered that the reaction yielding cyclohexyl acetate is not free radical but ionic.[19] We have been unable to devise any reasonable ionic mechanism which would be expected to yield cyclohexyl acetate. A most probable product in any ionic displacement process would be 1,2-diclohexanediol diacetate, a product which was not found.[2] The possibility that the greater specificity of labeling observed in the runs with added hydroquinone could be attributed to the action of hydroquinone as an acid catalyst for such a polar mechanism was ruled out by the observation that the rate of formation of cyclohexyl acetate is not increased by addition of hydroquinone. This was determined by following by infrared spectroscopy the concentration of acetyl peroxide in parallel runs, one containing hydroquinone and the other containing only cyclohexene and acetyl peroxide. The areas under the plots of concentration of acetyl peroxide *vs.* time for the two runs fell in the same ratio as the yields of acetate determined by vapor phase chromatography for the same runs.

It has been found[13,20] that the decomposition of carbonyl-labeled benzoyl peroxide in cyclohexene yields cyclohexyl benzoate in which the two oxygen atoms are essentially equivalently labeled.

The much greater specificity of labeling in the acetyl peroxide case could result from the operation of two factors: (a) The greater stability of the benzoyloxy radical favors the competing reaction which involves the addition of an acyloxy radical to cyclohexene with resulting dilution of specificity. As Doering has pointed out[13] the labeling in the product cyclohexyl benzoate is consistent with the exclusive operation of such a mechanism. (b) The equilibration of labeling in the intermediate 2-acyloxycyclohexyl radical would be favored in the benzoyl peroxide case by stabilization of the transition state for equilibration by resonance forms involving the aromatic ring.

An assessment of the relative importance of these two factors might possibly be made by observing the effect on the specificity of labeling when a very good hydrogen atom donor is added to the reaction mixture.

It is possible to envisage a great number of cases with more obvious sources of driving force for molecule-induced decompositions than the present one. We are undertaking an investigation of some of these cases applying the criterion, developed in this paper, of specificity of attack on labeled diacyl peroxides to establish the operation of a molecule-induced decomposition. There are also hydrogen atom donors, such as 9,10-dihydroanthracene, which might well be much more effective in this reaction than is hydroquinone. These will be used in an attempt to establish further details in the mechanisms of these reactions.

The results outlined in this paper allow us definitely to rule out the exclusive operation of mechanisms involving an intermediate free acetoxy radical. Our evidence does not, however, rule out the possibility that such a mechanism may be operating simultaneously with the mechanism which we have postulated. Earlier work[14–16] does make it seem unlikely, however, that acetoxy radicals would be trapped by reaction with cyclohexene before decarboxylating to methyl radicals and carbon dioxide.

Our results are consistent with the operation of mechanism II as the sole mechanism of this reaction and demand its operation, or the operation of a closely related mechanism, for at least 34% of the reaction.

Experimental[21]

Analyses for Oxygen-18.—The procedure and apparatus used for these analyses were those of Doering and Dorfman[22]

(18) Reference 14, p. 481.

(19) Such as Greene [F. O. Greene and W. W. Rees, *J. Am. Chem. Soc.*, **82**, 893 (1960)] has demonstrated in the reactions of phthaloyl peroxide with olefins. These reactions yield derivatives of glycols, not monoesters.

(20) Also demonstrated independently by D. B. Denney, private communication.

(21) We are indebted to Mr. Josef Nemeth, Mrs. Eula Ihnen and Mrs. Nancy Nielson for assistance with the oxygen-18 analyses upon which this work is based.

as modified by Denney and Greenbaum.[23] Duplicate analyses, run in each case gave results identical within the stated number of significant figures.

Acetic Acid-$CO^{18}O^{18}H$.—Acetyl chloride (337 g., 4.29 moles) was hydrolyzed with H_2O^{18} containing 1.67 atom % excess oxygen-18. The resulting acetic acid was distilled, reconverted to acetyl chloride by the action of thionyl chloride and hydrolyzed a second time with H_2O^{18} (1.67 atom % excess) to give 181 g. (301 moles) of labeled acetic acid (1.22 atom % excess oxygen-18 per oxygen), b.p. 111–116°.

Acetyl Chloride-$CO^{18}Cl$.—To 92 g. (1.53 moles) of labeled acetic acid (1.22 atom % excess oxygen-18)was slowly added 214 g. (1.80 moles) of thionyl chloride, with stirring and cooling. The temperature was gradually raised to 40° and maintained there until evolution of hydrogen chloride and sulfur dioxide ceased. The product was distilled and 105.6 g. (1.34 moles) of labeled acetyl chloride (1.10 atom % excess oxygen-18), b.p. 48–52°, was obtained (87%).

Sodium Acetate-$CO^{18}O^{18}Na$.—Sodium hydroxide pellets (53.6 g., 1.34 moles) were slowly added to 81.5 g. (1.36 moles) of labeled acetic acid (1.22 atom % excess oxygen-18). The slurry was stirred for 6 hours after which the mixture was heated to 160° (20 mm.) for 2 hours to remove water, leaving anhydrous labeled sodium acetate (100.4 g. 1.21 moles, 90%).

Acetic Anhydride-$CO^{18}O^{18}O^{18}C$.—To 60.5 g. (0.77 mole) of labeled acetyl chloride (1.10 atom % excess oxygen-18) was added 61.8 g. (0.75 mole) of labeled sodium acetate. The mixture was stirred for 4 hours at 40°. Sodium chloride was filtered from the liquid after the addition of 100 ml. of ether. After removal of the ether, the residue was distilled to give 60.7 g. (80%) of labeled acetic anhydride (1.20 atom % excess oxygen-18 per oxygen), b.p. 68.5–69° (51 mm.).

Acetyl Peroxide-carbonyl-O^{18}.—Acetyl peroxide-*carbonyl*-O^{18} was prepared according to the procedure described by Price and Morita.[24] To a solution of 10 g. (0.102 mole) of labeled acetic anhydride (1.20 atom % excess oxygen-18) in 50 ml. of ether cooled to 0° was added 12.5 g. (0.073 mole) of barium peroxide in 20 ml. of water with stirring. After stirring for 1 hour, the ether layer was separated, washed with 30 ml. of a 10% sodium bicarbonate solution, and dried over sodium sulfate. This procedure was repeated and the ether solutions combined. The solution was concentrated to 15 ml. at 10° under aspirator pressure, and acetyl peroxide-*carbonyl*-O^{18} was crystallized from the solution cooled in an acetone–Dry Ice-bath. Crystals (7.4 g., 62%) of labeled acetyl peroxide (1.14 atom % excess oxygen-18 per carbonyl oxygen) were obtained. After decanting the excess ether, the solvents used in the various decompositions were added to the crystalline labeled acetyl peroxide and the remaining traces of ether removed at 5° under reduced pressure. At no time was crystalline acetyl peroxide handled directly except for small samples used in the oxygen-18 determinations. The pyrolyses of these samples of acetyl peroxide, in the first step of the procedure for oxygen-18 analysis, were carried out satisfactorily on solutions of the crystalline peroxide in toluene. Attempts to pyrolyze the pure peroxide directly led inevitably to explosions. Even with samples of 1–2 mg., these explosions were violent enough to shatter the combustion tube.

Decomposition of Acetyl Peroxide-carbonyl-O^{18} in Cyclohexene. Run I.—In a typical run, a solution of 6.08 g. (0.052 mole) of acetyl peroxide-*carbonyl*-O^{18} (1.14 atom % excess oxygen-18 per carbonyl oxygen) in 100 ml. of cyclohexene was boiled gently under a nitrogen atmosphere. The decomposition was followed by the disappearance of the peroxide carbonyl absorption peaks at 1800 and 1825 cm.$^{-1}$ and the appearance of the acetate carbonyl absorption at 1740 cm.$^{-1}$ in the infrared spectra of aliquots. The decomposition was essentially complete after 19 hours. Cyclohexene was removed at aspirator pressure using a rotary solvent evaporator at room temperature. The residue was distilled, and the fraction distilling at 65–66° (15 mm.) was collected. Cyclohexyl acetate-O^{18} was isolated and purified by gas–liquid phase chromatography. An Aerograph instrument made by Wilkens Instrument and Research, Inc. and a Silicon 96 preparative scale column were used for the chromatography. At 155° and a flow rate of 2.58 l. of helium per hour, cyclohexyl acetate had a retention time of 16 minutes. Cyclohexyl acetate-O^{18} containing 1.12 atom % excess oxygen-18 (assuming all the label to be in one oxygen) was obtained. The infrared spectrum of this sample was identical in all respects with that of an authentic sample of cyclohexyl acetate. Cyclohexenyl acetate, either in the reaction mixture or in a pure sample, showed up as a broad peak at about 4 minutes retention time which was found on rechromatography to consist of acetic acid and a mixture of hydrocarbons.

Decomposition of Acetyl Peroxide-*carbonyl*-O^{18} in Benzene–Cyclohexene. Run III.—A solution of 4.1 g. (0.043 mole) of acetyl peroxide-*carbonyl*-O^{18} in 100 ml. of solvent (75% benzene–25% cyclohexene by volume) was boiled gently under a nitrogen atmosphere for 23 hours. After removal of the solvent, the residue was distilled and the fraction distilling at 65–67° (15 mm.) was collected. Cyclohexyl acetate-O^{18} was isolated and purified by g.l.p.c. Cyclohexyl acetate-O^{18}, 0.096 g., was obtained which contained 1.10 atom % excess oxygen-18 (assuming all the label to be in one oxygen). The infrared spectrum of this sample was identical in all respects with that of an authentic sample of cyclohexanol.

Decomposition of Acetyl Peroxide-*carbonyl*-O^{18} in Cyclohexene with Hydroquinone. Run IV.—A mixture of 13 g. (0.11 mole) of acetyl peroxide-*carbonyl*-O^{18}, 6.6 g. (0.06 mole) of hydroquinone and 200 ml. of cyclohexene was boiled gently for 4 hours under a nitrogen atmosphere. Cyclohexene was removed, the residue distilled and the fraction boiling at 63–68° (15 mm.) collected. Cyclohexyl acetate-O^{18} was isolated and purified by gas–liquid phase chromatography; however, great difficulty was experienced in eliminating an impurity judged from its color and retention time to be benzoquinone. By passing the cyclohexyl acetate-O^{18} through a polypropylene glycol column at 110° and a flow rate of 3.16 l. of helium per hour, most of this impurity was eliminated and cyclohexyl acetate-O^{18} containing 1.05 atom % excess oxygen-18 was obtained. However, it was found that polar column packings such as Carbowax caused some equilibration of the label (the cyclohexanol obtained contained 0.45 atom % excess oxygen-18); therefore, after passing the cyclohexyl acetate-O^{18} twice through a Silicone 96 column, only the amount needed for oxygen-18 analysis was passed through the glycol column. The remainder was hydrolyzed to cyclohexanol and then separated from the quinone by distillation and gas–liquid phase chromatography as described below. The infrared spectrum of this sample was identical in all respects with that of an authentic sample of cyclohexanol.

Reduction of Cyclohexyl Acetate-O^{18} with Lithium Aluminum Hydride. Run I.—To a slurry of 0.5 g. (0.013 mole) of lithium aluminum hydride in 50 ml. of ether was added 0.46 g. (0.003 mole) of cyclohexyl acetate-O^{18} (1.12 atom % excess oxygen-18) in 25 ml. of ether. The mixture was stirred for 4 hours after which 10 ml. of water was slowly added producing a white solid. To this mixture was added 30 ml. of 10% sulfuric acid producing two homogeneous layers. The aqueous layer was extracted with three 25-ml. portions of ether; the ether extracts and the ether layer were combined and dried over sodium sulfate. Ether was removed and the residue distilled. Cyclohexanol, b.p. 70° (15 mm.), was obtained and purified by g.l.p.c. techniques. Using the Silicone 96 preparative scale column at 150° and a flow rate of 2.58 l. of helium per hour, cyclohexanol had a retention time of 12 minutes and contained 0.47 atom % excess oxygen-18. The infrared spectrum of this sample was identical in all respects with that of an authentic sample of cyclohexanol.

Hydrolysis of Cyclohexyl Acetate-O^{18} with Potassium Hydroxide. Run IV.—Since only small quantities of cyclohexyl acetate-O^{18} were obtained in runs III and IV, hydrolysis was used as the method of degradation. In a typical run (run IV), 0.050 g. (0.00035 mole) of cyclohexyl acetate-O^{18} (1.05 atom % excess oxygen-18) was added to a solution of 0.025 g. (0.00045 mole) of potassium hydroxide in 10.0 ml. of ethanol at room temperature. After 1 hour, the liquid product was flash-distilled at 80° (0.1 mm.) and cyclohexanol containing 0.37 atom % excess oxygen-18 was isolated from it by g.l.p.c. techniques. The infrared spectrum of this sample was identical in all respects with that of an authentic sample of cyclohexanol.

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

(23) D. B. Denney and M. A. Greenbaum, *ibid.*, **79**, 979 (1957).

(24) C. C. Price and H. Morita, *ibid.*, **75**, 3686 (1953).

Relative Yields of Cyclohexyl Acetate.—Two parallel reactions were run under the conditions described for run IV except that the hydroquinone was omitted from one of the reaction mixtures. The concentration of acetyl peroxide was followed by infrared spectroscopy on aliquots withdrawn at frequent intervals, observing the carbonyl absorptions at 1800 and 1825 cm.$^{-1}$. A plot of these concentrations *vs.* time gave a curve for each compound. The areas under these curves were, after 19 hours, found to be in the ratio of 5:1, the smaller area being for the reaction with added hydroquinone. After 19 hours, 0.005-ml. aliquots of each reaction mixture were introduced into a Carbowax g.l.p.c. column at 130°. Careful reproduction of the conditions of introduction of sample, etc., gave plots from which the relative concentrations of cyclohexyl acetate could be determined for the two reaction mixtures. The ratio of the areas of the peaks corresponding to the ester (retention time 13 min. at a flow rate of 2.58 l. of helium per hour) was 8:1, the smaller concentration being evidenced for the run with added hydroquinone.

Acknowledgment.—This work was sponsored by the Office of Ordnance Research, U. S. Army.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA, LINCOLN 8, NEBR.]

Elimination Reactions of α-Halogenated Ketones. IV.[1] Elimination–Substitution Reactions with α-Bromo-*p*-phenylisobutyrophenone

BY NORMAN H. CROMWELL AND PATRICK H. HESS

RECEIVED SEPTEMBER 23, 1960

The acyclic tertiary α-haloketone, α-bromo-*p*-phenylisobutyrophenone, has been found to react with morpholine to give the substitution product, α-morpholino-*p*-phenylisobutyrophenone, and with a stronger base with similar steric demands, piperidine, to produce the elimination–addition product, β-piperidino-*p*-phenylisobutyrophenone. The α-amino- and β-amino-*p*-phenylisobutyrophenones were synthesized for comparison purposes by independent means. Silver nitrate was shown to react with the α-bromoketone II to give mainly the Favorski rearrangement acid, 2-(4-biphenylyl)-2-methylpropanoic acid. A discussion of the reactivity of II compared with that of the previously studied[1] alicyclic α-haloketone, 4-biphenylyl 1-bromocyclohexyl ketone, is given.

Introduction.—In general α-halogenated ketones of the primary and secondary type (RCHXCOR', R = H, alkyl or aliphatic-aromatic or aromatic) are expected to give substitution rather than elimination reactions with various nucleophilic reagents under ordinary conditions. Although these substitution reactions have been found almost certainly to be bimolecular reactions, showing second-order kinetics,[2] there has been no general agreement as to the nature and geometry of their transition states.[3]

Several groups of investigators have studied the reactions of tertiary α-haloketones ($R_2CBrCOR$) with bases and reported a variety of products[4] including α,β-unsaturated ketones.

Previous investigations in this Laboratory have shown that tertiary α-haloketones of an alicyclic type (*e.g.*, 2-bromo-2-benzyl-1-tetralones[5] and 2-bromo-2-benzyl-1-indanones[6]) are readily dehydrobrominated with amines or various other reagents, such as alcoholic sodium methoxide, sodium hydroxide, silver nitrate, etc., to give excellent yields of α,β-unsaturated ketones. Also tertiary α-haloketones of the α-halocyclohexylarylketone type are known to react with silver nitrate[1,7] or amines[1] to produce good yields of 1-cyclohexenylarylketones. The silver nitrate reaction also gives some Favorski rearrangement acid[1,7] with these compounds.

The acyclic tertiary α-bromoketone, α-bromoisobutyrophenone, has been reported to react with ammonia, methylamine and dimethylamine to product the α-amino-,[8] α-methylamino-[9] and α-dimethylaminoisobutyrophenones,[10,11] respectively. Tertiary amines such as triethylamine have been found to dehydrobrominate α-bromoisobutyrophenone to give α-methylacrylophenone.[12] Cope and Graham[13] treated α-bromoisobutyrophenone with alcoholic silver nitrate to produce a 58% yield of the Favorski rearrangement product, α-phenylisobutyric acid.

Drake and McElvain,[14] in studying the rates of reaction of bromoesters with piperidine, found that ethyl α-bromoacetate and ethyl α-bromopropionate both react quite rapidly by bimolecular substitution to give an α-amino product, whereas ethyl α-bromoisobutyrate reacts much slower to give a β-amino product, presumably by a slow bimolecular elimination reaction followed by a rapid addition of piperidine.

To obtain a better insight into the chemistry of tertiary α-haloketones in connection with our studies of the mechanism of the elimination reactions,[1] it seemed important to investigate more thoroughly the behavior of an acyclic tertiary α-bromoketone with various amines.

Results.—For the current studies we chose the known α-bromo-*p*-phenylisobutyrophenone (II). This acylic tertiary α-haloketone reacted with mor-

(1) For paper III in this series, see N. H. Cromwell and Patrick H. Hess, *J. Am. Chem. Soc.*, **82**, 136 (1960).

(2) (a) R. S. Pearson, *et al.*, *ibid.*, **74**, 5130 (1952); (b) D. L. Brebner and L. C. King, *ibid.*, **75**, 2330 (1953).

(3) For a brief general discussion see E. L. Eliel in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 103.

(4) See B. Tchoubar, *Bull. soc. chim. France*, **10**, 1363 (1955), for an excellent review of the reactions of α-halogenated ketones with nucleophiles and ref. 1 for a brief mention of the products.

(5) (a) A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, **80**, 901 (1958); (b) N. H. Cromwell, R. P. Ayer and P. W. Foster, *ibid.*, **81**, 130 (1959).

(6) N. H. Cromwell and R. P. Ayer, *ibid.*, **81**, 133 (1959).

(7) (a) C. L. Stevens and E. Farkas, *ibid.*, **74**, 618 (1952); (b) **74**, 5352 (1952).

(8) H. Larramona, *Compt. rend.*, **232**, 849 (1951).

(9) C. Mannich and H. Budde, *Arch. Pharm.*, **271**, 51 (1933).

(10) T. Thompson and T. S. Stevens, *J. Chem. Soc.*, 1932 (1932).

(11) E. Eidebenz, *Arch. Pharm.*, **280**, 49 (1942).

(12) C. L. Stevens and B. V. Etting, *J. Am. Chem. Soc.*, **77**, 5412 (1955).

(13) A. C. Cope and E. S. Graham, *ibid.*, **73**, 4702 (1951).

(14) W. V. Drake and S. M. McElvain, *ibid.*, **56**, 697 (1934).