water. The ether layer was extracted two additional times with water. The combined water extract was extracted for two minutes with fresh ether, and the fresh ether was washed two additional times with water. The combined water extract was diluted to 25 ml. and analyzed spectrophotometrically for lithium thiophenolate.

2. **Reaction of *cis*- and *trans*-Bis-(phenylmercapto)-ethylene (I) with *n*-Butyllithium at Room Temperature.**—Anhydrous ether (950 ml.) was added to a dry 1-liter volumetric flask previously filled with nitrogen. A solution of *cis*- or *trans*-I (4.9×10^{-5} mole) in ether, and *n*-butyllithium (1.5×10^{-3} mole) in ether was added, and the total volume was made up to 1 liter. It was found that the reaction was complete (90% yield of lithium thiophenolate) by the time the first sample could be taken (one minute).

Attempts to obtain reliable kinetic data at 0° have not yet been successful.

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[CONTRIBUTION FROM FULMER LABORATORY, DEPARTMENT OF CHEMISTRY, THE STATE COLLEGE OF WASHINGTON]

The Mechanism of Base-catalyzed Acylative Decarboxylation[1,2]

BY GRANT GILL SMITH AND DENNIS M. FAHEY[3]

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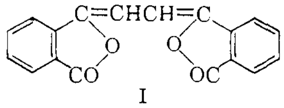
Examination of the reaction of *o*-chlorophenylacetic acid with acetic anhydride in the presence of pyridine reveals: first-order kinetics with respect to the acid in the presence of excess anhydride and base, the importance of anhydrous reaction conditions, and an isotope effect of 1.13 with acetic-1-C^{14} anhydride, but no isotope effect with *o*-chlorophenylacetic-1-C^{14} acid. The mechanism of base-catalyzed acylative decarboxylation is discussed.

Many acids with at least one α-hydrogen atom condense with acylating agents in the presence of a basic catalyst to yield ketones and carbon dioxide.

$$R'R''CHCOOH + R'''COX \xrightarrow{\text{base}} RR''CHCOR''' + HX + CO_2$$

Although it has been indicated recently[4] that the first described base-catalyzed acylative decarboxylation was in the late twenties,[5] as early as 1877 Gabriel and Michael[6] reported the isolation of I



I

from the reaction of succinic acid with phthalic anhydride in the presence of sodium acetate. The product I is the result of two acylations and decarboxylations, the diketone having been isolated as the double enol ester. Enol ester formation is common under such acylative conditions.[7]

Numerous studies of acylative decarboxylation of arylacetic acids have been made and several widely differing mechanisms have been proposed. In spite of the information accumulated, many critical facts concerning the mechanisms have not been reported. The purpose of this investigation was to better define the nature of the reaction with reaction kinetics, to investigate the effect of moisture and to determine the atoms involved in the rate-determining steps with the use of carbon-14.

Experimental[8]

Effect of Moisture on Acylative Decarboxylation. Reagents.—Acetic anhydride and pyridine were dried with phosphorus pentoxide and barium oxide, respectively, and freshly distilled in oven-dried (110°) glassware.

***o*-Chlorophenylacetic acid** was prepared according to the method described by Smith and Ott. Crystallization from 30% ethanol gave 63.8 g. (74.8%), m.p. 94.5–95.5°.[9] The *o*-chlorophenylacetic acid was stored in a vacuum desiccator.

Condensation Apparatus.—A 100-ml. three-necked flask was fitted with a Metroware spiral condenser as a nitrogen inlet, a thermometer adapted to the center neck, a Liebig condenser as a nitrogen outlet, and a glass-covered magnet for a stirrer. Only ground glass was used for the reaction vessel connections. The Liebig condenser was attached to a Dry Ice cold trap, a concentrated sulfuric acid wash bottle, a three-way stopcock, and weighed Ascarite tubes in series. The heat source was a Powerstat-regulated mantle.

Condensation of *o*-Chlorophenylacetic Acid.—In each run, 6.82 g. (40 mmoles) of the acid, 19 ml. (200 mmoles) of acetic anhydride and 29 ml. (360 mmoles) of pyridine were heated for four hours at 100°. This temperature was attained 20 minutes after heating was begun. The evolved carbon dioxide was swept into the weighed Ascarite tubes with nitrogen. The reaction was stopped by immersion of the reaction vessel in an ice-bath followed by the addition of approximately 45 ml. of ice-water. The decomposed mixture was poured into a solution of 4 g. of sodium hydroxide dissolved in 13 ml. of water in a separatory funnel, and the alkaline mixture was treated with a 50-ml. portion and two 25-ml. portions of ether. The ether extracts were combined, shaken for five minutes with a solution of 6 g. of sodium hydroxide dissolved in 54 ml. of water, washed with three 10-ml. portions of water, dried with anhydrous magnesium sulfate, and evaporated to a volume of about 25 ml. The solution was diluted to 50 ml. with absolute methanol in a volumetric flask, and 10-ml. aliquots were used for ketone analyses. The results are reported in Table I.

The remaining solutions not used for analysis were combined and evaporated. Evaporative distillation of part of this yielded *o*-chlorophenyl-2-propanone, $n^{20}D$ 1.5385, b.p. 100° (0.05 mm.).[10]

Anal. Calcd. for C_9H_9ClO: C, 63.8; H, 5.35. Found: C, 64.0; H, 5.4.

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[1] Presented before the Division of Organic Chemistry, 131st Meeting of American Chemical Society, Miami, Fla., April 8, 1957, p. 88-O.

[2] Abstracted from a thesis presented to the Graduate School of the State College of Washington by Dennis M. Fahey in partial fulfillment of the requirements for the Ph.D. degree, January, 1957.

[3] Research Corporation research assistant 1953–1954 and National Science Foundation Fellow 1954–1956.

[4] (a) G. H. Cleland and C. Nieman, THIS JOURNAL, **71**, 841 (1949); (b) S. Searles and C. J. Cvejanovich, *ibid.*, **72**, 3200 (1950); (c) C. S. Rondestvedt, Jr., B. Manning and S. Tabibian, *ibid.*, **72**, 3183 (1950); (d) J. A. King and F. H. McMillan, *ibid.*, **77**, 2814 (1955).

[5] (a) P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, **74**, 689 (1927); (b) H. D. Dakin and R. West, *ibid.*, **78**, 91 (1928).

[6] S. Gabriel and M. Michael, *Ber.*, **10**, 1551 (1877).

[7] G. G. Smith, THIS JOURNAL, **75**, 1134 (1953).

[8] All melting points are corrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., or by Weiler and Strauss Laboratories, Oxford, England. All ketone derivatives were prepared by the methods of R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 170, 202.

[9] G. G. Smith and D. G. Ott, THIS JOURNAL, **77**, 2342 (1955), reported m.p. 94.5–95.5°.

[10] The value from evaporative distillation was difficult to compare with the values for distillation; R. T. Gilsdorf and F. F. Nord, *ibid.*, **74**, 1837 (1952), reported 103° (6 mm.).

TABLE I

EFFECT OF MOISTURE ON ACYLATIVE DECARBOXYLATION

Conditions	Carbon dioxide yield, %	Ketone yield, %
Anhydrous	46.9	47.1
Anhydrous	51.3	48.7
Anhydrous	50.5	49.0
Anhydrous + powdered glass	50.1	40.7[a]
Water, 0.15 ml.[b]	44.8	41.8
Water, 0.30 ml.[b]	32.8	32.2

[a] Extraction was incomplete because of emulsion formation. [b] The mole ratio of acid to anhydride to water was 1:5:0.21 in the first case and 1:5:0.42 in the second.

The semicarbazone was prepared, m.p. 184–185°.[11]

Anal. Calcd. for $C_{10}H_{12}N_3ClO$: C, 53.2; H, 5.4; N, 18.6; Cl, 15.7. Found: C, 53.5; H, 5.5; N, 18.5; Cl, 15.7.

The oxime was prepared, m.p. 120–122°.[12]

Anal. Calcd. for $C_9H_{10}NClO$: C, 58.8; H, 5.5; N, 7.6; Cl, 19.3. Found: C, 59.2; H, 5.6; N, 7.5; Cl, 18.8.

When the residue from the ether extract was diluted with 70% ethanol, 1.0 g. (*ca.* 4.5%) of 1,3-bis-(*o*-chlorophenyl)-2-propanone precipitated, m.p. 102.5–103.0°[13] after recrystallization from acetone–water (1:2) or petroleum ether (b.p. 30–60°).

Anal. Calcd. for $C_{15}H_{12}Cl_2O$: C, 64.5; H, 4.3; Cl, 25.4. Found: C, 64.5; H, 4.3; Cl, 25.6.

Analytical Procedure.—The method of Bryant and Smith[14] for determining ketones was found satisfactory for phenyl-2-propanone when a two-hour heating period was used (for example, two 10.0-meq. samples when analyzed gave results of 9.8 and 10.0 meq., respectively). Titrations were carried out by the use of a *p*H meter. The yields of ketone are reported in Table I.

Isotope Effect in Acylative Decarboxylation Using Acetic-1-C^{14} Anhydride.—After sweeping the apparatus[15] with nitrogen for 15 minutes, a mixture of 690.0 mg. (4.05 mmoles) of *o*-chlorophenylacetic acid,[16] 38.4 ml. (405 mmoles) of acetic-1-C^{14} anhydride[17] and 24.5 ml. (304 mmoles) of pyridine[16] was heated to 110.0° in 15 minutes and maintained at that temperature (±0.2° for run 8 and ±0.3° for runs 7 and 9). The carbon dioxide evolved in run 7 and 8 was collected in weighed Ascarite. In run 9, it was absorbed in 50 ml. of carbon dioxide-free 0.2 *N* sodium hydroxide solution; for counting, barium carbonate was precipitated from 5-ml. aliquots with 0.7 ml. of 1 *M* ammonium chloride solution and 0.6 ml. of 1 *M* barium chloride solution. The reaction was stopped by immersion of the vessel in an ice-bath, and nitrogen sweeping was continued for about 5 minutes.

The reaction mixture was treated with 30 g. of crushed ice, while it was still in the ice-bath, to decompose the anhydride. The resulting solution was poured into 140 ml. of ice-cooled 20% sodium hydroxide solution in a separatory funnel. The alkaline solution was extracted with 200 ml. of ether by shaking both together for five minutes; the ether extract was washed twice with 55 ml. of 20% sodium hydroxide solution, twice with 50 ml. of 6 *N* hydrochloric acid, and once with 25 ml. of water. After the ether extracts were dried over anhydrous magnesium sulfate, they were distilled in a modified sublimation apparatus and yielded from 0.3 to 0.5 g. of *o*-chlorophenyl-2-propanone-2-C^{14}, b.p. 90–100° (0.1 to 0.05 mm.). Two samples of the ketone from run 7 were radioanalyzed, and the remainder was converted to the oxime for purification (m.p. 119.5–120.0°) and further radioanalysis. Also two samples of the ketone from run 8 were radioanalyzed, and the remainder was converted to the semicarbazone for purification (m.p. 182.5–183.0°) and further radioanalysis. In run 9, the ketone itself was subjected to purification by recrystallization at Dry Ice temperature from ether–petroleum ether (b.p. 30–60°) (1:1) followed by preparation of the bisulfite compound, recovery, and evaporative distillation before radioanalysis; data are listed in Table IV.

In each run, the combined sodium hydroxide extracts were washed with 50 ml. of ether and acidified with 120 ml. of 12 *N* sulfuric acid. The organic acids were extracted with 80-, 70- and 60-ml. portions of ether, which were combined and dried with anhydrous magnesium sulfate. The ether and acetic acid were freed of unreacted *o*-chlorophenylacetic acid by distillation, at 18 mm. pressure, in order to compare the activity of the recovered acetic acid with that of the acetic anhydride used initially. After the distillate, which contained ether and acetic acid, was made basic with 25% sodium hydroxide solution, the ether and aqueous layers were separated. The ether layer was washed with a 50-ml. portion and a 25-ml. portion of water before being discarded. The aqueous washings and the basic solution were combined and evaporated. Samples of the dried sodium acetate were treated with concentrated sulfuric acid prior to radioanalysis to free them of carbon dioxide absorbed by the small excess of sodium hydroxide. When radioanalyzed after this treatment, the samples of sodium acetate had the same radioactivity (within the probable error of counting) as the anhydride, which had been used in the reaction. The increase (enrichment) of activity of the order of 13% of 0.005 would not be detectable, when allowing an accuracy of ±0.01 in the counting of the acetic anhydride and sodium acetate. The results are reported in Table IV.

Carbon-14 Determination.—Radioanalysis were performed as described earlier.[18]

Isotope Effect for Acylative Decarboxylation with *o*-Chlorophenylacetic-1-C^{14} Acid.—A mixture of 690.0 mg. (4.05 mmoles) of *o*-chlorophenylacetic-1-C^{14} acid,[19] 38.4 ml. (405 mmoles) of acetic anhydride[20] and 24.5 ml. (304 mmoles) of pyridine was subjected to the same conditions of reaction as for the reaction with acetic-1-C^{14} anhydride. The progress of the reaction was followed by weighing the evolved carbon dioxide in Ascarite tubes. Three runs were carried, respectively, to 81, 84 and 84% completion as measured by the carbon dioxide evolved after correction for the 8.2% of the carbon dioxide coming from other sources. (Table IV, footnote *c*). The ketone was isolated by the procedure described above.

The ketone, the oxime and the semicarbazone contained traces of activity which could not be removed. After the ketone had been purified by formation and washing of the bisulfite addition compound, it retained its original activity of 0.27 barium carbonate plate counts/sec. (uncorrected for self absorption). Multiple crystallization of the derivatives did not lower their activities (semicarbazone, 0.219 barium carbonate plate counts/sec., uncorrected for self-absorption). When the ketone was placed on a column of 20 g. of alumina and eluted with petroleum ether (b.p. 30–60°)–benzene (4:1), it retained its activity as did a sample of the oxime when put on either alumina or cellulose (Solka Floc) column and eluted with petroleum ether (b.p. 30–60°)–acetone (20:1). A sample of the acetic anhydride, which had been used, was radioanalyzed and found to be inactive. The radioactivity of the ketone and its derivatives indicated that 1.2–1.5% of the ketone retained the label of the starting acid. (The value of 1.5% was used for the calculations of the data recorded in Table IV.) Unreacted *o*-chlorophenylacetic-1-C^{14} acid was recovered from the residue, after

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[11] R. T. Gilsdorf and F. F. Nord, ref. 10, reported m.p. 174–176°.

[12] I. B. Johns and J. M. Burch, THIS JOURNAL, **60**, 919 (1938), reported 120°.

[13] J. A. King and F. H. McMillan, *ibid.*, **73**, 4911 (1951), reported m.p. 100.5–101.0°.

[14] W. M. D. Bryant and D. M. Smith, *ibid.*, **57**, 57 (1935).

[15] The same apparatus was used in the examination of the effect of moisture.

[16] *o*-Chlorophenylacetic acid and pyridine were purified as outlined under Reagents.

[17] Radioactive acetic anhydride was obtained by heating sodium acetate-1-C^{14} for two hours with freshly distilled acetic anhydride, which had been dried over phosphorus pentoxide; A. Fry, *ibid.*, **75**, 2686 (1953); S. Ruben, M. B. Allen and P. Nahinsky, *ibid.*, **64**, 3050 (1942). The acetic-1-C^{14} anhydride was distilled in oven-dried glassware and samples were radioanalyzed (Table II). Exchange was essentially quantitative, as would be expected from the solubility of sodium acetate in hot acetic anhydride; W. H. Perkin, *J. Chem. Soc.*, **21**, 181 (1868).

[18] D. G. Ott and G. G. Smith, THIS JOURNAL, **77**, 2325 (1955).

[19] *o*-Chlorophenylacetic-1-C^{14} acid was prepared by Dr. Edward Inamine (see ref. 9) by carbonation of the Grignard reagent, m.p. 95°.

[20] The acetic anhydride and pyridine were purified as outlined under Reagents. The same apparatus was used as described previously.

distillation of the ether and acetic acid, by dissolving it in 50 ml. of 5% sodium bicarbonate solution. This solution was washed twice with 25-ml. portions of ether, acidified with 12 *N* sulfuric acid, and extracted with three 30-ml. portions of ether. Evaporation of the ether left a crystalline product that was purified by alternate crystallizations from petroleum ether and water. After the melting point of the material had been raised to 95.0 ± 0.3°, samples were combusted between crystallizations, and the radioanalyses were averaged after the samples no longer increased in activity, but began to vary slightly in a random fashion. The recovered *o*-chlorophenylacetic-1-C^{14} acid, recovered from the three runs, averaged 22.85 ± 0.28 barium carbonate plate counts/sec. (uncorrected for self-absorption). The radioactivity of the original sample of *o*-chlorophenylacetic-1-C^{14} acid was 22.77 ± 0.38 barium carbonate plate counts/sec. (uncorrected for self-absorption) when treated in the same manner as the recovered acid. Calculations using equation 1 with the ratio $R = 22.85 \pm 0.28/22.77 \pm 0.38$ or 1.00 ± 0.03 indicated an isotope effect: $k_{12}/k_{14} = 1.00 \pm 0.02$.

Kinetics.—The reaction mixtures, which have been described above, were brought rapidly (10–15 minutes) to a reaction temperature between 110 and 111° and maintained at that temperature ±0.2° throughout reaction rate measurements. Runs 1, 2, 3 and 8 were followed to 77, 69, 81 and 79% completion based on the weight of carbon dioxide evolved [corrected for the 8.2% of the carbon dioxide coming from reactions other than the one being studied (Table IV, footnote *c*)]. The rate of reaction was followed by weighing the evolved carbon dioxide absorbed in Ascarite. Weighings were carefully spaced in order to obtain large increments of weight and to minimize weighing errors. Typical kinetic data are shown in Table II. *A* is the theoretical amount (in milligrams) of carbon dioxide expected from the reacting acid and *X* is the amount (in milligrams) evolved at time *t* (in minutes). The time of removal of the first Ascarite tube after the reaction temperature was reached was taken as zero time. A first-order plot of these data results in a straight line.

TABLE II

Time, minutes	$(A - X)$, mg.	$\log (A - X)$
0	176.1	2.245
30	137.1	2.137
75	95.3	1.979
135	60.0	1.779
210	37.1	1.569

Results

Anhydrous Conditions Required.—Previous results have shown that a very large excess (*ca.* 100-fold) of acetic anhydride was necessary to effect acylation of arylacetic acids without a marked decrease in the rate of the reaction as it proceeded, thus demonstrating that small concentrations of free acid retards the reaction. Condensation of arylacetic acids with reagent grade acetic anhydride and pyridine using only a five- to tenfold excess of anhydride normally produced only about 70–75% of the theoretical amount of carbon dioxide. When enough water was added to remove less than one-twentieth of the anhydride used (Table I) the yield of carbon dioxide evolved in four hours was lowered by more than one-tenth, although the *o*-chlorophenylacetic acid to acetic anhydride ratio was essentially unchanged. Twice this quantity of water lowered the yield by one-third, yet four and one-half moles of acetic anhydride remained for each mole of *o*-chlorophenylacetic acid. This provided clear evidence that the anhydrous conditions are very important. A retarding effect of the same nature was observed by Attenburrow, Elliott and Penny[21] for the α-amino acids, although it was less marked, perhaps due to the greater stability of the oxazolone as an anhydride. Rapid diminution of the effective concentration of the anhydrides of *o*-chlorophenylacetic acid by pyridium salt formation has been credited as a major factor contributing to the lowering of the yield. (The stronger aryl acid would preferentially form the salt.) Acids are formed as the reaction proceeds or through hydrolysis when water is added.

Self-condensation of *o*-chlorophenylacetic anhydride does not adequately explain the low yield of carbon dioxide when only a five molar excess of acetic anhydride is present, since 4.5% yield of 1,3 - bis - (*o* - chlorophenyl) - 2 - propanone would account for less than 3% of the theoretically expected carbon dioxide.

The ketone analyses verified that weighing the evolved carbon dioxide absorbed in Ascarite was a reliable measure of the extent of reaction when pyridine was used as a catalyst.

Tracer Studies.—The labeled carboxyl carbon of the acetic anhydride served as a tracer to determine if carbon dioxide was evolved from the acylating agent. It was found that 8.2% of the evolved carbon dioxide came from the labeled carboxyl group of the acetic anhydride. About 1.5% of this could be attributed to an alternate path in which acetic anhydride was acylated by the *o*-chlorophenylacetic anhydride; the rest apparently arose from an independent reaction of acetic anhydride in pyridine. Argument is advanced below that this reaction is a self-condensation of the anhydride. A run made during the study of the isotope effect with acetic-1-C^{14} anhydride indicated a small amount of carbon dioxide came from these two reactants alone (see footnote *c*, Table IV).

A reaction between acetic anhydride and pyridine has been noted before by Nelson and Markham[22] who described a darkening of the mixture with the formation of tarry residue when the mixture was distilled. Fry[17] attributed the trace of radioactivity in the carbon dioxide evolved (during the reaction of 1,3-diphenylurea with acetic-1-C^{14} anhydride) to the self-condensation of the acetic-1-C^{14} anhydride in the presence of base, *i.e.*, to acylative decarboxylation. Dilution of the radioactivity in the carbon dioxide evolved by labeled alanine was noted by Rondestvedt, *et al.*,[4c] but it was considered to be due to a leaky system. In view of the evidence presented above, the diluting carbon dioxide undoubtedly came from the acetic anhydride; the amount was about that which would be expected from this source. This self-condensation of acetic anhydride is to be expected if the reacting species are anhydrides as has been assumed by many workers.[13,23] The self-condensation of phenylacetic anhydride was clearly established by King and MacMillan.[13] The fact that some of the *o*-chlorophenyl-2-propanone from the reaction of *o*-chlorophenylacetic-1-C^{14} acid and acetic anhydride actually came from acylation of the acetic

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[21] J. Attenburrow, D. F. Elliott and G. F. Penny, *J. Chem. Soc.*, 310 (1948).

[22] P. A. Nelson and A. E. Markham, THIS JOURNAL, **72**, 2417 (1950).

[23] (a) G. L. Buchanan and J. McArdle, *J. Chem. Soc.*, 2944 (1952); (b) D. S. Breslow and C. R. Hauser, THIS JOURNAL, **61**, 876 (1939).

anhydride is taken as further evidence that anhydrides are the reactants and that all of the theoretically expected interactions do occur.

Isotope Effect with *o*-Chlorophenylacetic-1-C^{14} Acid.—To trace the source of the carbon dioxide produced in the reaction and investigate the possibility of the decarboxylation as being involved in the rate-determining step labeled *o*-chlorophenylacetic acid was allowed to react with acetic anhydride and pyridine to greater than 80% completion. The isotope effect was calculated by comparing the radioactivity of the starting acid to the recovered unreacted acid. Since the reaction was shown to be first order in the acid, the isotope effect I, ($I = k_{12}/k_{14}$; k_{12} and k_{14} are the rate constants for the reaction of the unlabeled and labeled molecules) could be calculated from equation 1 in

$$I = \frac{\ln f}{\ln Rf} \qquad (1)$$

which f is the fraction of the reaction yet to be completed and R is the ratio of the activity of the recovered acid to that of the starting acid.[24] (Because only very minute quantities of carbon-14 were involved, the fraction of the reaction which was not complete at any given time could be represented as $f = C_t^{12}/C_0^{12}$.) In Table III are listed calculated values of R for isotope effects of various magnitudes calculated for 80, 85 and 90% completion of the reaction. The observed ratio of activities of starting acid to recovered acid, $R = 1.00 \pm 0.03$, indicated that there was no appreciable intermolecular isotope effect, $I = 1.00 \pm 0.02$ in the acylative decarboxylation of *o*-chlorophenylacetic-1-C^{14} acid with acetic anhydride. If the decarboxylation step or any step involving the carboxyl carbon of the arylacetic acid were rate-determining, the expected isotope effect would have to be about three times as great as the error of measurement permits.

TABLE III

VALUES OF ACTIVITY RATIO AND INDICATED ISOTOPE EFFECT

Extent of reaction, completion	Values of R for $I = 1.01$	Values of R for $I = 1.02$	Values of R for $I = 1.03$
80	1.016	1.032	1.048
85	1.019	1.038	1.057
90	1.023	1.046	1.070

Isotope Effect with Acetic-1-C^{14} Anhydride.—Comparison of the radioactivity of the *o*-chlorophenyl-2-propanone-2-C^{14} produced in the acylative decarboxylation reaction of *o*-chlorophenylacetic acid with acetic-1-C^{14} anhydride to the radioactivity of the acetic-1-C^{14} anhydride showed that there was a sizeable isotope effect—about 1.13 ± 0.01, Table IV. The marked isotope effect in this reaction gives strong indication that the labeled carbonyl group of the anhydride is involved in the rate-determining step of the reaction. In light of this, several possibilities must be considered which involve either bond formation or bond rupture at the labeled carbon atom, such as carbon–oxygen bond formation, carbon–carbon bond formation and carbon–oxygen bond rupture.

TABLE IV

ISOTOPE EFFECT WITH ACETIC-1-C^{14} ANHYDRIDE

Run	Compound	Barium carbonate plate counts/sec.[a]	Isotope effect k_{12}/k_{14}[b]
7	Acetic-1-C^{14} anhydride	8.58 ± 0.04	
	Sodium acetate-1-C^{14}	8.58 ± .04	
	Oxime of *o*-chlorophenyl-2-propane-2-C^{14}	1.60 ± .01	1.146 ± 0.010
8	Acetic-1-C^{14} anhydride	8.58 ± .04	
	Sodium acetate-1-C^{14}	8.58 ± .04	
	Semicarbazone of *o*-chlorophenyl-2-propanone-2-C^{14}	1.47 ± .04	1.126 ± 0.025
9	Acetic-1-C^{14} anhydride	10.57 ± .10	
	Sodium acetate-1-C^{14}	10.51 ± .09	
	o-Chlorophenyl-2-propanone-2-C^{14}	2.02 ± .04	1.129 ± 0.005
	Carbon dioxide	1.72 ± .04	8.2 ± .3[c]
Average isotope effect for 7, 8 and 9			1.13 ± .01

[a] Uncorrected for self-absorption. [b] These values were calculated as per the following example [allowing for 1.5% of the *o*-chlorophenyl-2-propanone produced by an alternate path (see Isotope Effect for Acylative Decarboxylation with *o*-Chlorophenylacetic-1-C^{14} Acid)] 1.60 plate counts/sec. × 9 carbons/carbonyl × 100/8.58 plate counts/sec. × (2 carbon/carbonyl) = 83.9%; 100.0 − (83.9 + 1.5) = 14.6 isotope effect or $k_{12}/k_{14} = 1.146$. [c] This is not an isotope effect, but the percentage of the evolved carbon dioxide coming from the labeled position of the acetic-1-C^{14} anhydride. It was equal to 13.8 mg. of carbon dioxide of which only 2.5 mg. came from the acylation of acetic anhydride by the *o*-chlorophenylacetic acid. The rest, 11.3 mg., was considered to be due to an independent reaction between acetic anhydride and pyridine; a blank run, with only these two reagents at 100°, yielded 7.4 mg. of carbon dioxide and confirmed this hypothesis.

Carbon–oxygen bond formation could arise from mixed anhydride formation. If this step was rate-determining it would have an intramolecular isotope effect.[25] There are at least two reasons for questioning this possibility: The exchange between an acid and an anhydride, facilitated by heat and base, is known to be rapid and reversible and little or no isotope effect would be expected. Secondly, the predicted value of 1.043, calculated by Raaen and Ropp[26] using the equation derived by Bigeleisen[27] is significantly smaller than the result obtained in this investigation.

There are many mechanisms that could account for a carbon–carbon bond formation in the rate-determining step. An intramolecular isotope effect would exist for an aldol-type condensation; the isotope effect for a carbon–carbon bond formation is known to be in the same order of magnitude as a carbon–carbon bond rupture. The largest calculated value for carbon-12 to carbon-14 bond rupture is twice that for the carbon-12 to carbon-13 bond rupture and is, therefore, 1.057.[28] This value is well confirmed by its excellent agreement with the intramolecular carbon-12 to carbon-14 bond formation isotope effect observed by Carrick and Fry[29] and with the accurately determined intramolecular carbon-12 to carbon-14 rupture isotope effect obtained by Yankwich, Promislow and

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(24) This equation is closely related to that used by R. W. Atree and W. H. Stevens, *Can. J. Research*, **B27**, 807 (1949), and is easily derived in the same manner.

(25) The term "intramolecular isotope effect" has been used to describe an isotope effect in which the reactant (the molecule in the ground state) passes immediately into two possible transition states differing only in the position of the label.

(26) V. F. Raaen and G. A. Ropp, *J. Chem. Phys.*, **21**, 1902 (1953).

(27) J. Bigeleisen, *ibid.*, **17**, 675 (1949).

(28) P. E. Yankwich and A. L. Promislow, THIS JOURNAL, **76**, 4648 (1954).

(29) W. L. Carrick and A. Fry, *ibid.*, **77**, 4381 (1955).

Nystrom[30] for malonic-1-C^{14} acid (1.054 ± 0.0046). Without data establishing whether or not the active methylene carbon is also involved in the rate-determining step, however, the possibility of carbon–carbon bond formation or an isotope fractionation in mixed anhydride formation or condensation of an anion with acetic anhydride cannot be presently excluded.

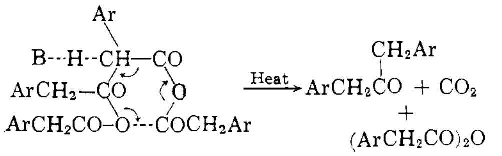
The isotope effect for carbon-oxygen bond rupture would be intramolecular for all the mechanisms to be considered. Predicted values for carbon-oxygen bond rupture have been calculated as 1.19 by Bigeleisen[31a] and 1.128 by Eyring and Cagle.[31b] Ropp, Weinberger, and Neville[32a] have reported the carbon–oxygen rupture intermolecular isotope effect in the dehydration of formic-1-C^{14} acid at zero degrees as 1.111 ± 0.0052; Stevens, Pepper and Lounsburg[32b] have reported a carbon–oxygen rupture as 1.16 ± 0.02 for the hydrolysis of ethyl benzoate.

The excellent agreement of the experimental value obtained in this study (1.13 ± 0.01) with these predicted values and reported experimental values has been accepted as evidence in support of the hypothesis that the observed isotope effect is a result of carbon–oxygen bond rupture in the rate-determining step recognizing that further configuration of this point awaits study with *o*-chlorophenylacetic-2-C^{14} acid.

Discussion

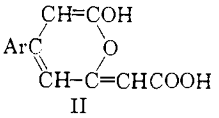
The mechanisms which have been reported for this reaction have been classified for convenience and are critically examined in the light of these data: the effect of anhydrous conditions, the absence of an isotope effect in the reaction with *o*-chlorophenylacetic-1-C^{14} acid and the very large isotope effect observed when acetic-1-C^{14} anhydride was used.

Cyclic Transition State.—A quasi six-membered ring was proposed by King and McMillan[4d,13] as a possible mechanism for the reaction of arylacetic anhydride with pyridine. This mechanism

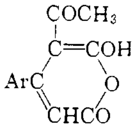


clearly illustrates their argument for carbon dioxide evolution as the driving force of the reaction. Carbon–carbon bond formation and cleavage occurring simultaneously with carbon–oxygen formation and cleavage, as is described by this proposed mechanism, would be expected to show an isotope effect with the label in the carbonyl group of the molecule. Since an isotope effect was not observed in the reaction using *o*-chlorophenylacetic-1-C^{14} acid (where a C^{12}–C^{14} bond rupture occurred) and a substantial one was observed with acetic-1-C^{14} anhydride (where a C^{14}–O bond rupture occurred) this mechanism is subject to serious criticism.

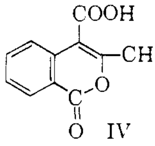
Because decarboxylation does not appear to be involved in the rate-determining step, the loss of carbon dioxide as the primary driving force is placed in question. In addition to the evidence from the isotope effect study, many acylations have occurred where decarboxylation was possible but did not occur under the conditions of the acylation. For an example: phthalylacetic acid was formed when phthalic anhydride was heated for ten minutes at 150° with acetic anhydride and potassium acetate.[6] King and McMillan[13] considered this as an exception to this reaction (which they have chosen to call decarboxylative-acylation). In light of the similarity of this reaction (and the three examples directly following) to the reaction of *o*-chlorophenylacetic acid, acetic anhydride and pyridine at 110°, as well as the isotope effect data, it seems logical to consider them as special examples of *acylative-decarboxylation* in which ring stabilization provides a substitute driving force, rather than to consider them as exceptions. King and McMillan accepted the identification of II report by Limaye and Bhave[33] as correct in their acylation of *β*-arylglutaconic anhydride and considered it also as an exception analogous to phthalylacetic acid. The identification of II as III by Gogte[34a] proves the analogy to be unjustified; Wiley and Smith[34b] have shown that *β*-alkylglutaconic anhydride undergoes acylation without decarboxylation. Another example where acylation occurred without decarboxylation was found in this Laboratory in the isolation of compound IV from the condensation of homophthalic acid with acetic anhydride in pyridine.[35]



II



III



IV

These examples serve to illustrate that although decarboxylation is possible it need not accompany acylation of anhydrides. The argument could be advanced that ring stabilization provides a substitute driving force in these reactions. Some compounds other than acids or acid derivatives having very reactive methylene groups undergo acylation under these conditions. For example, ethyl cyanoacetate[36] and *o*-cyanophenylacetonitrile[37] are acylated by acetic anhydride and sodium acetate although no carbon dioxide can be evolved. Here, too, these compounds may form products which are stabilized by ring formation since it is known that phenylacetonitrile possessing an active methylene group does not acylate under these conditions. Acylation not involving decarboxylation is under further investigation.

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[30] P. E. Yankwich, A. L. Promislow and R. F. Nystrom, This Journal, **76**, 5893 (1954).

[31] (a) J. Bigeleisen, *J. Phys. Chem.*, **56**, 823 (1952); (b) H. Eyring and F. W. Cagle, Jr., *ibid.*, **56**, 889 (1952).

[32] (a) G. A. Ropp, A. J. Weinberger and O. K. Neville, This Journal, **73**, 5573 (1951); (b) W. H. Stevens, J. M. Pepper and M. Lounsbury, *J. Chem. Phys.*, **20**, 192 (1952).

[33] D. B. Limaye and J. M. Bhave, *J. Univ. Bombay*, **2**, Pt. 2, 82 (1923); *C. A.*, **28**, 6128 (1934).

[34] (a) G. R. Gogte, *Proc. Indian Acad. Sci.*, 214 (1938); *C. A.*, **32**, 5389 (1938); (b) R. H. Wiley and Neston R. Smith, This Journal, **74**, 3893 (1952).

[35] G. G. Smith, C. J. W. DeLong and W. H. Wetzel, Abstract of Papers, Division of Organic Chemistry, 132nd Meeting of the American Chemical Society, New York, N. Y., Sept. 9, 1957 p. 19P.

[36] W. Dieckmann and F. Breesrt, *Ber.*, **37**, 3384 (1904).

[37] S. Gabriel and T. Posner, *ibid.*, **27**, 827 (1894).

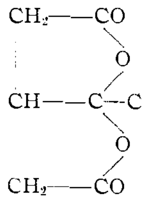
Decarboxylation Prior to Addition.—A mechanism involving base-catalyzed decarboxylation to a transitory carbanion was proposed by Wiley and Borum[38,39] and later modified by Wiley[40] to include the presence of an anion-accepting carbonyl as a driving force for decarboxylation. In such an S_N2 reaction one would predict an isotope effect in the decarboxylation steps but none was observed. It is difficult to picture any other rate-determining step for this mechanism.

Pyrolysis.—Pyrolysis was proposed by Wedekind[41] and Hurd and Thomas[42] for this reaction. Wedekind compared the reaction of phenylacetyl chloride with pyridine in moist solvent, yielding 1,3-diphenyl-2-propanone, to the dry distillation of calcium salts, but no pyridium salts were prepared to test the relationship. A related suggestion made by Bamberger[43] was that the decomposition of calcium salts to ketones may involve prior disproportionation to the acid anhydride and to calcium oxide so that the anhydride can react in the presence of the oxide as a basic catalyst. Neunhoeffer and Paschke[44] showed that the mechanism proposed by Bamberger is incorrect, particularly since water facilitates the reaction in some cases. More convincing proof was offered by Bigeleisen, Bothner-By and Friedman,[45] who demonstrated that the pyrolysis of barium adipate involves no isotopic fractionation when labeled with carbon-13 in a carboxyl group. The mechanism for barium adipate pyrolysis cannot be the same as for the base-catalyzed acylative decarboxylation of *o*-chlorophenylacetic acid with acetic anhydride in pyridine because a sizeable isotope effect is observed in this latter case.

Hurd and Thomas[42] described the "pyrolysis" of phenylacetic anhydride to 1,3-diphenyl-2-propanone in the presence of base as a simple pyrolysis with no indication of what part the base may play. It was recognized that without the base the ketone is not obtained and higher temperatures are required for pyrolysis to take place. It appears that base-catalyzed condensation of the anhydride is a better explanation.

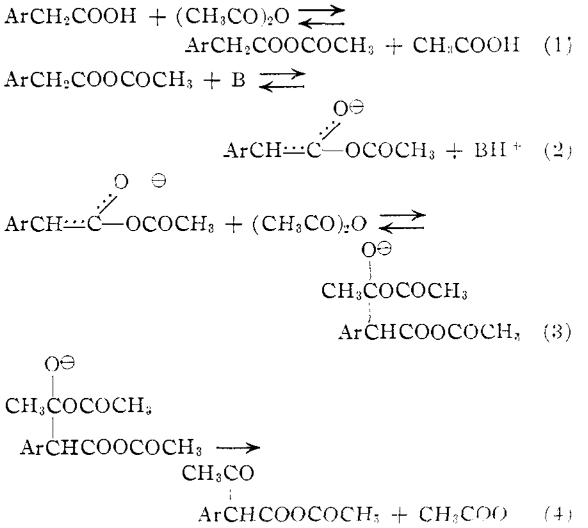
The question arises whether reactions forming ketones in agreement with Blanc's rule[46] may be base-catalyzed condensation of anhydrides. According to Blanc's rule, when a dicarboxylic aliphatic acid is heated with acetic anhydride and distilled, the ketone of one less carbon atom will form unless it is possible for a cyclic anhydride of five or six members to form.[46] Usually temperatures of at least 200° are required to cause the polymeric anhydride formed by acetic anhydride treatment to break up and form the ketone. Until it is demonstrated that a basic catalyst and an α-hydrogen are necessary, gross appearances are sufficient to warrant treatment of these ring closures as a different type of reaction. The possible relationship of reactions which comply with Blanc's rule deserves further study.

Alcohol-type Condensation.—The close resemblance of base-catalyzed acylative decarboxylation to the Perkin synthesis of cinnamic acid was recognized by the earliest workers[6,47–49] who simply assumed water split out. Fittig[50] recognized that the mechanism was inadequate since water could not split out when benzoic anhydride reacted with trisodium carballylate to yield V.


V

Later an aldol-type mechanisn similar to those generally given for the Perkin, Claisen and Knoevenagel condensation was suggested by Breslow and Hauser[23b] for the self-condensation of phenylacetic anhydride in the presence of sodium acetate. This same type of mechanism was evolved for the formation of acylamide ketones from α-amino acids by other workers.[4a,5b,21,51]

The mechanism proposed by Breslow and Hauser is now supported for the acylative decarboxylation reaction of arylacetic acids reacting with anhydrides in the presence of base with these data: (a) α-Hydrogens and a base are required. (b) For good yields, anhydrous conditions are necessary. (c) Condensation of *o*-chlorophenylacetic-1-C^{14} acid shows no isotope effect. (d) Condensation with acetic-1-C^{14} anhydride shows an isotope effect of 13%. (e) The reaction shows first-order kinetics with respects to the active methylene component. A possible stepwise mechanism which is in agreement with all facts known concerning base-catalyzed acylative decarboxylation is proposed as



$$\mathrm{ArCH_2COOH + (CH_3CO)_2O \rightleftarrows ArCH_2COOCOCH_3 + CH_3COOH} \quad (1)$$

$$\mathrm{ArCH_2COOCOCH_3 + B \rightleftarrows ArCH{\cdots}\overset{O^{\ominus}}{C}{-}OCOCH_3 + BH^+} \quad (2)$$

$$\mathrm{ArCH{\cdots}\overset{O\ \ominus}{C}{-}OCOCH_3 + (CH_3CO)_2O \rightleftarrows \begin{array}{c} O^{\ominus} \\ | \\ CH_3COCOCH_3 \\ | \\ ArCHCOOCOCH_3 \end{array}} \quad (3)$$

$$\mathrm{\begin{array}{c} O^{\ominus} \\ | \\ CH_3COCOCH_3 \\ | \\ ArCHCOOCOCH_3 \end{array} \longrightarrow \begin{array}{c} CH_3CO \\ | \\ ArCHCOOCOCH_3 \end{array} + CH_3COO} \quad (4)$$

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(38) R. H. Wiley and O. H. Borum, THIS JOURNAL, **72**, 1626 (1950).

(39) R. H. Wiley, *Science*, **111**, 259 (1950).

(40) R. H. Wiley, *ibid.*, **114**, 448 (1951).

(41) E. Wedekind, *Ber.*, **34**, 2070 (1901).

(42) C. D. Hurd and C. L. Thomas, THIS JOURNAL, **58**, 1240 (1936).

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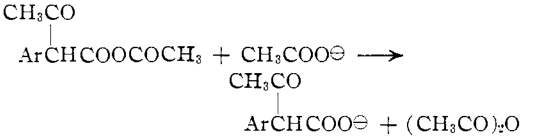
(48) J. Volhard, *Ann.*, **253**, 206 (1889).

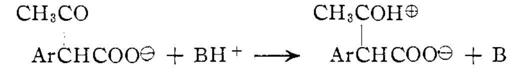
(49) J. Volhard, *ibid.*, **267**, 48 (1892).

(50) R. Fittig, *Ber.*, **30**, 2145 (1897).

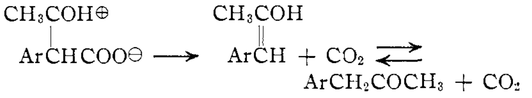
(51) H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 745 (1928).



$$\mathrm{Ar\overset{CH_3CO}{\overset{|}{C}}HCOOCOCH_3 + CH_3COO^{\ominus} \longrightarrow Ar\overset{CH_3CO}{\overset{|}{C}}HCOO^{\ominus} + (CH_3CO)_2O} \quad (5)$$



$$\mathrm{Ar\overset{CH_3CO}{C}HCOO^{\ominus} + BH^+ \longrightarrow Ar\overset{CH_3COH^{\oplus}}{\overset{|}{C}}HCOO^{\ominus} + B} \quad (6)$$

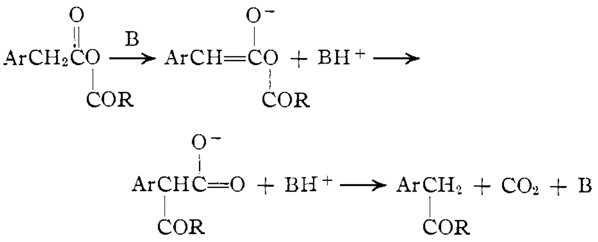


$$\mathrm{Ar\overset{CH_3COH^{\oplus}}{\overset{|}{C}}HCOO^{\ominus} \longrightarrow Ar\overset{CH_3COH}{\overset{\|}{C}}H + CO_2 \rightleftarrows ArCH_2COCH_3 + CO_2} \quad (7)$$

In this mechanism, anhydrides are the reactants and step 4, involving carbon–oxygen bond rupture, is the rate-determining step. The mechanism satisfies the requirements that the reaction be first order with respect to the active methylene component and that the effect of moisture is as described earlier. Step 5 contributes as a driving force because the anion of the strong β-keto acid will form rapidly in the presence of salts of weaker acids. Excess anhydride ensures anhydrous conditions and maintains a supply of reactants, and decarboxylation may act as a secondary driving force by removing some of the acid produced during the reaction. The decarboxylation of a β-keto acid was suggested early by Fittig[50]; King and McMillan[52] agree with Rondestvedt, *et al.*,[4c] on this point for the decarboxylation of acylated oxazolones. Based on a review by Brown[53] on the decarboxylation of β-keto acids in the presence of bases, the decarboxylation of β-keto acid zwitterion is proposed in step 7.

O to C Migration.—A number of O to C migrations have been described in the literature to explain the formation of C-acylated compounds. One of the early examples[54] described the formation of acetone from a sodium acetate–acetic anhydride complex. Fried[55] has pictured the C-acylation of β-arylglutamic anhydride with acetyl chloride and pyridine to proceed through an O-acyl derivative followed by an O to C migration. Such a reaction path is difficult to apply to the acylation of oxazolones resulting from amino acids with only one α-hydrogen although they are readily acylated in base.

A slightly modified O to C migration was proposed by Buchanan and McArdle[23a] for the acylative decarboxylation of arylacetic acids. This



$$\mathrm{ArCH_2\underset{COR}{\overset{O}{\overset{\|}{C}}}O \xrightarrow{B} ArCH{=}\underset{COR}{\overset{O^-}{\overset{|}{C}}}O + BH^+ \longrightarrow}$$

$$\mathrm{Ar\underset{COR}{C}H\overset{O^-}{\overset{|}{C}}{=}O + BH^+ \longrightarrow Ar\underset{COR}{C}H_2 + CO_2 + B}$$

mechanism was essentially presented by Levene and Steiger[56] earlier for the acylative decarboxylation of amino acids.

Many reactions are in accord with this mechanism such as the reaction of oxazolones with acetic acid in pyridine[13] and the numerous examples of intramolecular ring closure under the influence of acetic anhydride and base[57,58] though they might logically be described as proceeding by an aldol-type mechanism. An intramolecular O to C migration is in general agreement with the experimental evidence cited in this paper (first-order kinetics, proposed carbon–oxygen bond rupture as rate-determining).

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PULLMAN, WASH.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Cyclic Diketals of 1,2-Disubstituted *cis*-1,2-Dibenzoylethylenes[1]

BY ROBERT E. LUTZ AND MILLARD G. REESE[2]

RECEIVED JULY 18, 1958

Easily hydrolyzable cyclic diketals (2,5-dialkoxy-2,5-dihydrofurans) are produced by acid-catalyzed alcoholysis of *cis* but not *trans* disubstituted dibenzoylethylenes. Metathetical reactions at the 2- and 2,5-positions are described. Structural proof, mechanism of formation and facility of the *cis* cyclization reactions are considered. With absolute ethanolic hydrogen chloride *cis*- but not *trans*-dibromodibenzoylethylene underwent halogen displacement and cyclization to the 4-chloro-2-ethoxy-3-furanone. With acetic anhydride and sulfuric acid it gave the 4-bromo-2-acetoxy-3-furanone.

As a part of the study of *cis* addition cyclizations of unsaturated 1,4-diketones, this paper deals with the conversion of 1,2-disubstituted dibenzoylethylenes into 2,5-dialkoxy-2,5-dihydrofurans of the type IV which are cyclic diketals. The work stems from earlier studies[3] in which it had been shown that absolute ethanolic hydrogen chloride converts both *cis*- and *trans*-monochloro-

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[2] (a) National Science Foundation Postgraduate Fellow, 1956–(1957). (b) Some of the experiments reported here were carried out by Grover C. Helsley.

[3] R. E. Lutz and M. G. Reese, THIS JOURNAL, **81**, 127 (1959); *cf.* also references cited therein.