Fraction	Weight, g.	B.p., °C.	Press., mm.	$n^{26}D$
1	0.50	101–102	44	1.4582
2	2.10	101–103	40	1.4570
3	2.40	101–103	40	1.4590
	5.00 (83.5%) olefin B.			

The infrared spectra of fractions 1, 2 and 3 were identical.

Solvolysis of *t*-Butyldiisopropylcarbinyl *p*-Nitrobenzoate and Triisopropylcarbinyl *p*-Nitrobenzoate.—These two esters were solvolyzed as described above except that the triisopropylcarbinol ester was allowed to stand at 50° for four weeks instead of five days. The crude products obtained (olefins C and D) after removal of solvent were not purified further.

Perbenzoic Acid Oxidation of Olefin B.—The olefin (1.0 g., 0.00595 mole) was dissolved in 25 ml. of benzene and treated with 15.0 ml. of 0.465 *M* solution of perbenzoic acid (0.00698 mole) at 0°. After 36 hours a 1-ml. aliquot was run into an acetic acid solution of potassium iodide and the liberated iodine titrated with 0.100 *N* sodium thiosulfate (1.02 ml. of thiosulfate required; 83% reaction). After 86 hours a 1-ml. aliquot required 0.78 ml. of the thiosulfate solution (91% reaction).

The benzene solution was shaken with a solution of potassium iodide in dilute acetic acid, then with dilute thiosulfate, and finally with sodium bicarbonate solution. After drying over Drierite and removing solvent, there remained 0.900 g. of a colorless liquid whose infrared spectrum was very similar to the epoxide obtained from olefin A. The compound did not crystallize.

Ozonization of Olefin B.—One gram of the olefin was dissolved in 25 ml. of dry ethyl acetate, and ozone was bubbled through the solution at −60 to −70° for two hours. At the end of this period the solution contained excess ozone as indicated by the deep blue color. The ozone was removed by bubbling dry nitrogen through the solution. Palladium-on-strontium carbonate (0.150 g.) was then added and the mixture was stirred in an atmosphere of hydrogen at room temperature for four hours; no hydrogen uptake was observed.

The catalyst was removed by filtration and the solvent evaporated from the filtrate. The residue (0.60 g.) was an oil whose infrared spectrum indicated it to be largely the epoxide, but to contain a considerable quantity of a carbonyl compound as well. Chromatography on alumina was not effective in separating the mixture. Attempts to crystallize the mixture also failed.

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[CONTRIBUTION FROM THE WARNER-CHILCOTT RESEARCH LABORATORIES]

The Decarboxylative Acylation of α-Substituted Acids

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It is shown that the decarboxylative acylation of carboxylic acids having a suitable electron-attracting group in the α-position is a base-catalyzed condensation of an anhydride with the carbonyl group of the acylating agent. The scope and stoichiometry of the reaction have been further defined. Probable reaction sequences for the various acids undergoing the reaction are discussed.

It has been shown that carboxylic acids having certain electron-withdrawing groups attached to the α-position to the carboxyl group can be made to undergo a decarboxylative acylation reaction in the presence of an acylating agent and a base to give a compound in which the original carboxyl group is replaced by an acyl group. The types of electron-withdrawing groups are varied and there are in all probability at least two major routes by which this type of reaction takes place. The purpose of this paper is to clarify the mechanistic picture of these reactions.

Acids which have been shown to undergo this reaction are those which have the following groups attached to the α-positions: $-NH_2$,[1] $-NHR$,[2] $-NR_2$,[3] an aryl group,[1c,4] a heterocyclic group[5] and an aryloxy group.[6] Notable examples of acids which have failed to undergo this reaction are: α-aminoisobutyric acid, α-phenylpropionic acid,[4] diphenylacetic acid,[4] proline[7] and 5-pyrolidone-2-carboxylic acid.[7] It should especially be noted at this point that the acids which undergo this reaction are all acids which, under the reaction conditions employed, do not decarboxylate in the absence of the acylating agent; we believe that the scope of this reaction must, by definition, be limited to such reactions since there are a number of examples of acids which do decarboxylate under these conditions in the absence of the acylating agents and which in the presence of a carbonyl group may[8] (quinaldinic acid) or may not (trichloroacetic acid, *vide infra*) react with the carbonyl group at the time of decarboxylation.

In the case of the primary amino acids it has been suggested[1d,9] that an oxazolone is the compound which reacts with the acylating agent and in certain cases[10] an acylated oxazolone has been isolated previous to decarboxylation. This proposed route is probably correct because most of these compounds undergo the reaction more readily than do other types of acids.

Stoichiometric studies were carried out by Ron-

(1) (a) P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, **74**, 689 (1927); (b) **79**, 95 (1928); (c) H. D. Dakin and R. West, *ibid.*, **78**, 91 (1928); (d) **78**, 745 (1928).

(2) R. H. Wiley, *Science*, **111**, 259 (1950); R. H. Wiley and O. H. Borum, THIS JOURNAL, **72**, 1626 (1950).

(3) J. A. King and F. H. McMillan, *ibid.*, **73**, 4451 (1951).

(4) J. A. King and F. H. McMillan, *ibid.*, **73**, 4911 (1951).

(5) A. Burger and C. R. Walter, *ibid.*, **72**, 1988 (1950).

(6) G. G. Smith, *ibid.*, **75**, 1134 (1953).

(7) J. A. King and F. H. McMillan, *ibid.*, **74**, 2859 (1952).

(8) P. Dyson and D. Hammick, *J. Chem. Soc.*, 1724 (1937).

(9) G. H. Cleland and C. Niemann, THIS JOURNAL, **71**, 841 (1949).

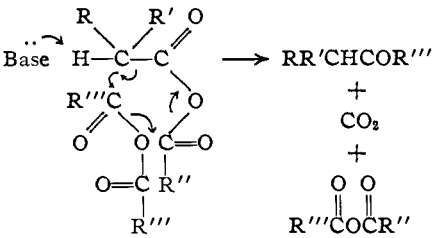
(10) J. Attenburrow, D. F. Elliott and G. F. Penny, *J. Chem. Soc.*, 310 (1948).

destvedt and co-workers[11] using limited amounts of acetic anhydride, in the presence of pyridine, on α-aminophenylacetic acid; they reported that the percentage of the theoretical amount of carbon dioxide evolved corresponded closely to the fraction of three moles of acetic anhydride used and concluded that the reaction is not complete unless three moles of acetic anhydride are used per mole of amino acid. We have found that α-aminophenylacetic acid in refluxing acetic anhydride without pyridine gave a mixture of α-acetamido-α-phenylacetone and 2,5-dimethyl-4-phenyloxazole; while we realized that this difference in behavior from other α-aminoacids was probably only one of degree, in that the greater acidity of the α-hydrogen atom permitted the reaction to take place with acetate ion functioning as the base, we preferred to use a more typical example and so we then chose as a substrate for stoichiometric study benzoylalanine which does not undergo the reaction with acetic anhydride alone. In a quantitative experiment benzoylalanine, when refluxed with pyridine and two moles of acetic anhydride, gave a 95% yield of α-benzamidoethyl methyl ketone and recovery of 0.96 mole of acetic anhydride, measured as acetanilide, showing there to have been the consumption of only one mole of acid anhydride in the conversion of the acylamido acid to the acylamido ketone. As further demonstration of this stoichiometry, we carried out quantitative experiments on the conversion of 2-phenyl-4-methyl-5-oxazolone to α-benzamidoethyl methyl ketone by heating it with pyridine, acetic acid and either one-half or one mole of acetic anhydride; we obtained a 96.5% yield of benzamido ketone in each case and recovered, measured as acetanilide, 68 and 86%, respectively, of the acetic anhydride put into the reaction mixture. As a final experiment we heated this oxazolone with pyridine and acetic acid alone and obtained a 74% yield of the benzamido ketone. We believe that this last reaction is made possible by a series of reversible anhydride–acid interchanges.

The decarboxylative acylation of secondary amino acids has been postulated as proceeding through the analogous oxazolonium ion[12] and there is some evidence for the existence of such an ion.[13]

When tertiary amino acids undergo the reaction the tertiary amino ketone is not isolated but undergoes further reaction giving an N,N-disubstituted amide.[3] We have further extended this type of reaction by carrying out the reaction with N-benzyl-N-methylglycine, pyridine and acetic anhydride. The only product isolated was N-benzyl-N-methylacetamide; it was established that neither acetone nor isopropenyl acetate (conceivable additional products from this reaction) was present in the reaction mixture.

The constitution of the above mentioned tertiary amino acids as well as those acids having an aryl, heterocyclic or aryloxy group in the α-position requires that a different (from the oxazolone) and more generalized route be followed. Such a route has been suggested[4] as



The possibility for the simultaneous formation of the *quasi* six-membered ring as the proton is abstracted allows for easy disproportionation into the products actually obtained from the reaction.

It has been pointed out previously that α-phenylpropionic acid and diphenylacetic acid[4] do not undergo the decarboxylative acylation reaction and at the same time it was suggested that the possibility for the formation of the proposed *quasi* six-membered ring was dependent on a combination of electronic and steric factors. It has been reported similarly that neither proline nor 5-pyrrolidone-2-carboxylic acid[7] undergo the reaction; attempted construction with Fisher–Hirschfelder models of the spiro *quasi* six-membered ring intermediates for the last-mentioned compounds shows considerable hindrance to formation and we believe that this constitutes the reason for their failure to undergo the reaction.

This mechanism has been criticized[14] on the ground that it is based on negative evidence (*i.e.*, that acids not having an α-hydrogen atom have not been observed to undergo the reaction) and the Hammick reaction[3] has been cited as an example of an acid which must decarboxylate *before* the addition to a carbonyl group.

As we have stated above we are dealing here with a reaction involving a decarboxylation which does not take place in the absence of the acylating agent and this at once excludes consideration of the Hammick reaction in which this is not true. A correct mechanistic picture of this reaction must then include participation of the acylating agent prior to or, perhaps more accurately, simultaneously with the decarboxylation in a concerted action; *i.e.*, the bond between the α-carbon of the decarboxylating acid (now an anhydride) and the carbonyl group of the acylating agent must be forming as the carboxyl carbon is leaving and thus can the acylating agent serve as the *sine qua non* for the decarboxylation. The force allowing this acylating carbonyl group to approach the α-carbon is the possibility for the transformation of the α-carbon to a carbanion under the influence of the base. Such carbanion formation is not possible in those acids not having an α-hydrogen atom.

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Experimental[15]

Action of Acetic Anhydride and Pyridine on α-Aminoisobutyric Acid.—A mixture of α-aminoisobutyric acid (10.3 g., 0.10 mole), acetic anhyride (102 g., 1.00 mole) and pyridine (79 g., 1.00 mole) was refluxed 6.5 hours, during which time no carbon dioxide was evolved, and then fractionally dis-

(11) C. S. Rondestvedt, B. Manning and S. Tabibian, THIS JOURNAL, **72**, 3183 (1950).

(12) J. W. Cornforth and D. F. Elliott, *Science*, **112**, 534 (1950).

(13) J. L. O'Brien and C. Niemann, THIS JOURNAL, **72**, 5348 (1950).

(14) R. H. Wiley, *Science*, **114**, 448 (1951).

(15) Melting points and boiling points are uncorrected.

tilled at atmospheric pressure and cut into four fractions, b.p. 113–124°, 125–130°, 130–134°, 134–138°; there was no appreciable distillation residue. These are the same results reported as obtained[16] by the action of acetic anhydride alone on α-aminoisobutyric acid.

Treatment of Trichloroacetic Acid with Acetic Anhydride and Pyridine.—A mixture of trichloroacetic acid (16.3 g., 0.10 mole), acetic anhydride (100 cc.) and pyridine (100 cc.) was refluxed 2.5 hours, during which considerable carbon dioxide was evolved. The reaction mixture was distilled at atmospheric pressure through a 3-foot helix-packed vacuum-jacketed column to a vapor temperature of 113°. The distillate was extracted with three 10-cc. portions of methylene chloride, the combined extract was dried over magnesium sulfate and then fractionally distilled at atmospheric pressure through a one-foot wire-spiral column with a temperature gradient heated jacket to give 3.5 g. (33% yield) of chloroform, b.p. 56–60°, $n^{25}D$ 1.4403. The original pot-residue from which material volatile up to 113° had been removed was neutralized with aqueous sodium bicarbonate and extracted three times with 250-cc. portions of chloroform. Distillation of the dried extract through the 3-foot column gave no material boiling above 115° (atm.) and left a negligible tarry residue.

Action of Acetic Anhydride on α-Aminophenylacetic Acid.—A mixture of *dl*-α-aminophenylacetic acid (15.1 g., 0.10 mole) and acetic anhydride (100 cc.) was refluxed 30 minutes and then fractionally distilled to give 3.0 g. (17% yield) of a fraction boiling at 135–144° (13 mm.) and 3.2 g. (17% yield) of a more viscous fraction boiling at 130–140° (0.25 mm.). The first fraction on redistillation furnished 1.5 g. of 2,5-dimethyl-4-phenyloxazole, b.p. 68–84° (0.2 mm.), $n^{25}D$ 1.5500; reported[17] b.p. 255–258° (atm.), $n^{25}D$ 1.5613; this material yielded an hydrochloride, m.p. 159–160° after two recrystallizations from alcohol.

Anal. Calcd. for $C_{11}H_{11}NO \cdot HCl$: Cl (ionic), 16.95. Found: Cl (ionic), 16.66.

The picrate of the 2,5-dimethyl-4-phenyloxazole melted at 130–131° after recrystallization from 95% alcohol; reported[17] m.p. 129.5–130.5°.

The higher boiling more viscous fraction was α-acetamido-α-phenylacetone and was crystallized from a little xylene; it melted, after recrystallization from the same solvent, at 98.5–99.5°; reported[18] m.p. 97–98°.

Action of Acetic Anhydride and Pyridine on Benzoylalanine.—A mixture of N-benzoyl-*dl*-alanine (19.3 g., 0.10 mole), acetic anhydride (100 cc.) and pyridine (100 cc.) was refluxed until carbon dioxide evolution ceased (about one hour) and excess reagents were removed by distillation under vacuum (bath 60–70°, pressure 1.5 mm.). The pot-residue spontaneously crystallized and melted, after recrystallization from carbon tetrachloride–Skellysolve B, at 69–70°; total weight of 3-benzamido-2-butanone 16.1 g. (85% yield).

Quantitative Reaction of Pyridine and Acetic Anhydride with Benzoylalanine.—A mixture of N-benzoyl-*dl*-alanine (19.3 g., 0.10 mole), acetic anhydride (20.4 g., 0.20 mole) and pyridine (100 cc.) was refluxed 40 minutes, during which 2040 cc. of carbon dioxide was evolved. The mixture was distilled without a column at 40 mm. pressure, bath below 120°, until no more distillate came over. The head, condenser and receiver were rinsed with pyridine, the rinsings being added to the distillate; there was then added to the distillate 18.0 g. of aniline (evolution of heat) and volatile substances were removed on the steam-cone under water-pump vacuum. Treatment of the residue with 50 cc. of water, followed by acidification with hydrochloric acid and chilling of the mixture gave 12.9 g. (0.096 mole, 96% yield) of acetanilide, m.p. 108–110°. The pot-residue from the original reaction mixture was then distilled to give 18.1 g. (95% yield) of methyl α-benzamidoethyl ketone, b.p. 105–116° (0.15 mm.), which crystallized in the receiver.

Action of Pyridine, Acetic Acid and Acetic Anhydride on 2-Phenyl-4-methyl-5-oxazolone.—2-Phenyl-4-methyl-5-oxazolone was prepared from N-benzoyl-*dl*-alanine with acetic anhydride in 84% yield by the procedure of Mohr and Stroschein,[19] b.p. 90–92° (0.2 mm.), $n^{25}D$ 1.5486; reported b.p. 80° (0.2–0.5 mm.).

A mixture of the oxazolone (18.8 g., 0.05 mole), acetic acid (3.0 g., 0.05 mole), acetic anhydride (2.6 g., 0.025 mole) and pyridine (50 cc.) was refluxed two hours, during which carbon dioxide was evolved. Fractional distillation of the reaction mixture yielded a fraction boiling up to 60° at 35–40 mm. and 9.2 g. (96.5% yield) of methyl α-benzamidoethyl ketone, b.p. 110–117° (0.2 mm.). To the first fraction there was added aniline (5.4 g., 0.06 mole) and the resultant mixture was evaporated on the steam-cone under water-pump vacuum; the remaining residue was treated with dilute hydrochloric acid then chilled and filtered to give 1.98 g. (0.0147 mole, 68% yield) of acetanilide, m.p. 108–110°.

The same quantities of oxazolone, acetic acid and pyridine, but with 5.2 g. (0.05 mole) acetic anhydride, were refluxed 90 minutes and then worked up as above but using 10.24 g. (0.11 mole) of aniline to give 5.78 g. (0.0428 mole, 86% yield) of acetanilide, m.p. 108–111°, and 9.2 g. (96.5% yield) of methyl α-benzamidoethyl ketone, b.p. 123–125° (0.2–0.3 mm.).

Action of Acetic Acid and Pyridine on 2-Phenyl-4-methyl-5-oxazolone.—A mixture of oxazolone (8.8 g., 0.05 mole), acetic acid (3.00 cc., 0.05 mole) and pyridine (50 cc.) was refluxed three hours, during which time 760 cc. of carbon dioxide was evolved. Fractional distillation of the reaction mixture gave 1.0 g. (11% recovery) of oxazolone, b.p. 88–92° (0.2 mm.), and 6.3 g. (66% yield) of methyl α-benzamidoethyl ketone, b.p. 112–115° (0.1 mm.), m.p. 62–65°.

A mixture of oxazolone (8.8 g., 0.05 mole), acetic acid (4.5 g., 0.075 mole) and pyridine (50 cc.) was refluxed 2.25 hours and then fractionally distilled to give a small amount of benzoic acid, b.p. 85–100° (0.15 mm.), m.p. 118–119°, m.m.p. with authentic sample 120–121°, followed by 7.1 g. (74% yield) of methyl α-benzamidoethyl ketone, b.p. 119–125° (0.1–0.2 mm.), m.p. 62–64.5°; there was a negligible pot-residue.

Reaction of N-Benzyl-N-methylglycine with Acetic Anhydride and Pyridine.—In a 500-ml. round-bottomed flask equipped with a reflux condenser with a means for collecting CO_2 over H_2O there was placed N-benzyl-N-methylglycine (17.9 g., 0.10 mole), acetic anhydride (100 ml.) and pyridine (100 ml.). This mixture was heated under reflux until CO_2 evolution ceased; this was about five hours and about 2400 ml. of gas was collected. The excess acetic anhydride and pyridine were removed under water-pump vacuum and the residue was distilled under oil-pump vacuum with no column giving 14.5 g. of material boiling at 114–121° (0.4–0.5 mm.), this was redistilled giving (a) 2.2 g., b.p. 95–97° (0.1 mm.); (b) 7.8 g., b.p. 97–99° (0.1 mm.); and (c) 1.0 g., b.p. 99–105° (0.1 mm.). Fraction b crystallized readily and melted at 42.5–44°. An authentic sample of N-benzyl-N-methylacetamide[20] melted at 43–44°. The mixed melting point was 42.5–44°.

In a similar reaction the reaction mixture was fractionated at atmospheric pressure through a column of about 50 plates; the lowest head temperature which could be maintained was 113°; when a small amount of acetone was added to the pot it was recovered easily at a head temperature of 56°. This demonstrates that acetone was not formed in the reaction. Isopropenyl acetate also cannot be present, since it boils at 96°.

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(16) P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, **93**, 581 (1931).
(17) R. H. Wiley, *J. Org. Chem.*, **12**, 43 (1947).
(18) S. Searles and G. J. Cvejanovich, THIS JOURNAL, **72**, 3200 (1950).
(19) E. Mohr and F. Stroschein, *Ber.*, **42**, 2521 (1909).
(20) E. L. Holmes and C. K. Ingold, *J. Chem. Soc.*, 1800 (1925).