Some Kinetic and Mechanistic Studies of the Dakin-West Reaction[1,2]

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A series of rate studies was carried out on the decarboxylation of a group of α-acylamino acids. The reactions were all found to be first order with respect to the acylamino acid, acetic anhydride, and pyridine. Oxazolones were found to react at the same rate as their respective parent acylamino acids. *N*-Methyl-5-pyrrolidone-2-carboxylic acid was found not to undergo the reaction. Mechanisms previously proposed are discussed. It was concluded that the oxazolone mechanism alone is in accord with the experimental facts under normal circumstances, and the possible rate-determining step is discussed.

The reaction of an α-amino acid **1** with acetic anhydride in the presence of pyridine to give α-acetamidoalkyl methyl ketones **2** was reported by Dakin and West in

$$\underset{\text{NH}_2}{\overset{|}{\text{RCHCOOH}}} + \text{Ac}_2\text{O} \xrightarrow{\text{Pyr}} \underset{\text{NHAc}}{\overset{|}{\text{RCHCOCH}_3}} + \text{CO}_2$$

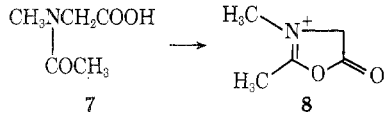
1 **2**

1928.[4] Prior to the beginning of the present work four types of mechanisms had been proposed for this reaction.

I. The first type of mechanism, the azlactone mechanism, was proposed by Dakin and West[5] and is generally the most favored one. According to this mechanism, the reaction proceeds through acylation of the amino acid, cyclization of the acylated product to an azlactone **4**, and reaction of the azlactone with base to give a resonance-stabilized carbanion,[6] which reacts with acetic anhydride to give the azlactone **5** of the acetamido-β-keto acid. Subsequent conversion of the azlactone to the acetamido ketone **6** and carbon dioxide follows. These steps are outlined in Scheme I, with some detailed elaborations; for a typical example, see hippuric acid (**3**). The first step of this mechanism is independently known to occur.[7] The second step is a proton transfer to give a resonance-stabilized carbanion. The third step is the reaction of the carbanion with a carbonyl group and displacement of a fairly good leaving group, acetate ion. The fourth–sixth steps involve reaction of the azlactone with 2 mol of carboxylic acid to yield the acylamino acid. Step seven, the decarboxylation of the keto acid, is the only irreversible step, and this step provides the driving force for the entire reaction.

Many saturated azlactones have been prepared[8,9] from α-amino acids. Those derived from leucine, phenylalanine, and aspartic acid all react with acetic anhydride and pyridine to give carbon dioxide and the same acetylamino ketone which is furnished by the amino acid itself.

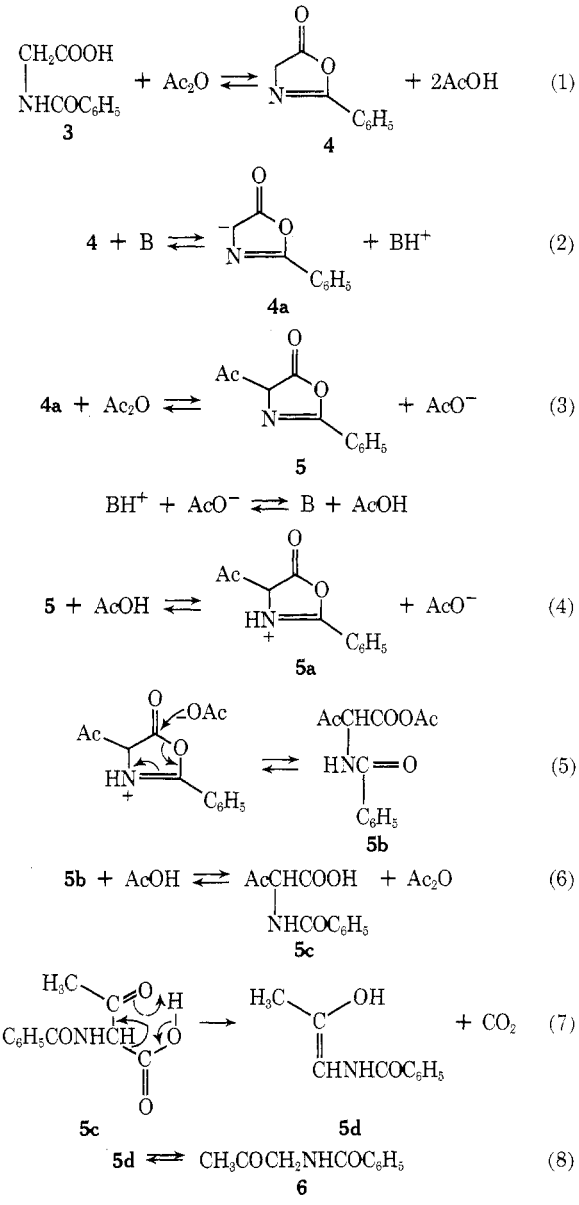
At one time the azlactone mechanism was challenged, because secondary amino acids such as *N*-acetylsarcosine[10] and similar compounds undergo the Dakin-West reaction. Several other mechanisms[10-12] were then put forth in an attempt to explain such reactions. In 1950, Cornforth and Elliott[13] suggested an oxazolonium cation intermediate **8** in an effort to explain the fact that acetylsarcosine (**7**) underwent the reaction. In other cases, oxazolonium cations were isolated and identified.[14-16]



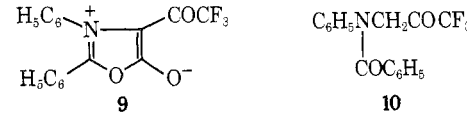
7 **8**

Singh and Singh[17] have observed that, when *N*-benzoyl-*N*-phenylglycine is treated with trifluoroacetic anhydride at room temperature, a mesoionic compound (**9**) is formed

Scheme I

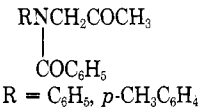


in good yield, which incorporates the trifluoroacetyl group. When subjected to the action of reluxing acetic anhydride, **9** undergoes decarboxylation with the formation of *N*-benzophenylaminotrifluoroacetone (**10**). However,



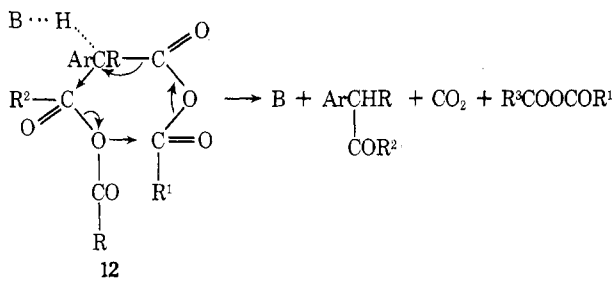
9 **10**

when cyclizations of *N*-acyl secondary amino acids were studied with acetic anhydride, the only products originally isolable in high yield were the "normal" products,[17] ketones **11**. Presumably the mesoionic systems carrying the acetyl group undergo cleavage more readily.[17] Huisgen and coworkers, during their studies of 1,3-cycloaddition reactions, also isolated a number of mesoionic oxazolones.[18,19]



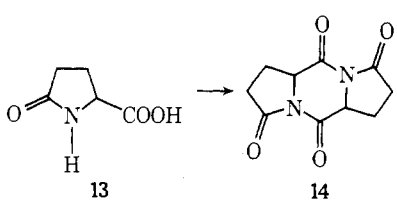
11, R = C_6H_5, *p*-$CH_3C_6H_4$

II. The second type of mechanism which was proposed for the Dakin-West reaction involves a base-catalyzed condensation between two anhydride molecules.[20] A cyclic intermediate **12** is involved. The main reason for this proposal was the fact that various assorted compounds other than α-amino acids with primary or secondary amino groups also undergo the same kind of reaction. Thus, if the amino group is tertiary, decarboxylation may occur. This requires some mechanism other than *via* the azlactone.[20] In addition, arylacetic acids such as phenylacetic acid undergo the same reaction.[4,21-23]



12

Until 1955 when King and McMillan[24] broadened their mechanism[20] there were a few acids known which failed to undergo decarboxylative acylation. Diphenylacetic acid was converted only to the anhydride, while proline was merely acetylated. 5-Pyrrolidone-2-carboxylic acid (**13**) also failed to decarboxylate, but rather dehydrated to a dimer (**14**). These failures were interpreted by King and McMillan[24] as showing steric hindrance to the formation of the six-membered ring intermediate of their proposed cyclic mechanism.



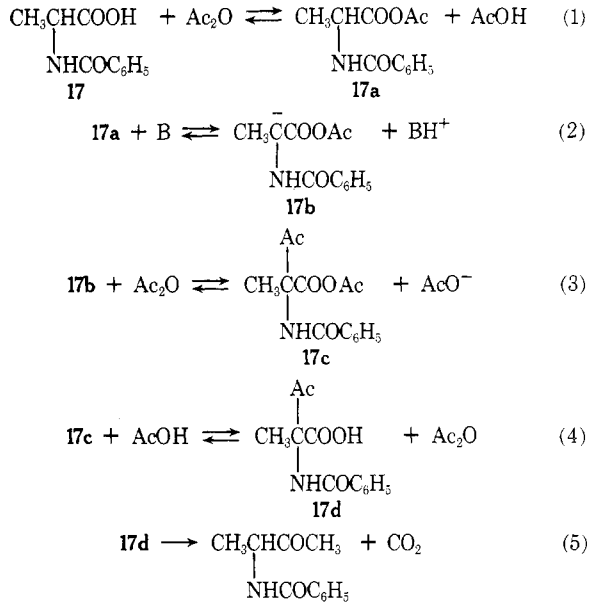
13 **14**

It was also known that amino acids without an α hydrogen failed to undergo the reaction. Since an α hydrogen is necessary in their mechanism, King and McMillan took the failure of such acids to show the reaction as evidence favoring their mechanism.

III. A third type of mechanism was proposed by Wiley and Borum.[10,12] They suggested that the acylamino acid is first decarboxylated by the base to a carbanion. The carbanion then reacted with the acetic anhydride. However, since acylated amino acids do not react with base to give carbon dioxide, this mechanism can be ruled out.

IV. A fourth type of mechanism was proposed by Levene and Steiger[25] in 1928. Their mechanism suggested that the amino group and the enol form of the carboxyl group were acylated. An O → C migration of an acyl group then took place to give the β-keto acid which decarboxylated. This mechanism seems not to have been given further consideration until 1952, when Buchanan and McArdle[26] again proposed a similar mechanism. They noted that N-substituted amino acids underwent the reaction and suggested that either an oxazolonium ion must be an intermediate or else the nitrogen played no part in the reaction. In the latter event, the mechanism would be the same as that for phenylacetic acid and related compounds. They suggested that, for these, acylation of the enol form of the carboxyl group occurred, followed by an O → C migration and decarboxylation.

Scheme II



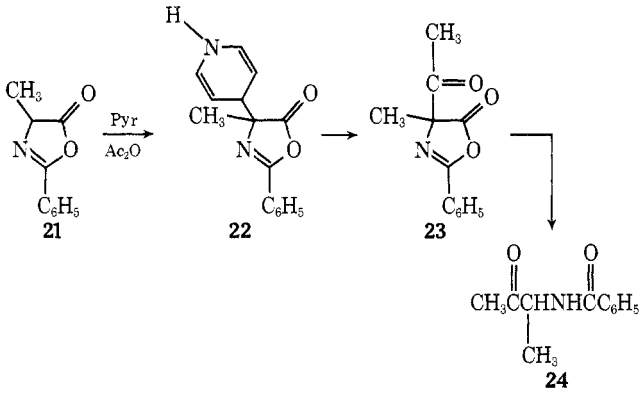
V. A fifth type of mechanism can also be proposed. This is an aldol-type condensation, closely related to the Perkin reaction, as was proposed earlier[27] for the acylative decarboxylation of arylacetic acids. Taking *N*-benzoylalanine as an example, a stepwise mechanism can be written (Scheme II). Obviously this mechanism can be generalized to all carboxylic acids but would be most effective in cases where the α position contained an activating (electron-withdrawing) substituent.

The first step is an acid-anhydride equilibrium,[28] as is step number 4. The second step is a proton removal from an activated methylene compound (anhydride) by base. The Perkin reaction is a particularly close analogy. The third step is an attack by a carbanion on a carbonyl group, and the fifth step is decarboxylation of a β-keto acid. These steps together constitute a reasonable mechanism for the Dakin-West reaction.

A stepwise aldol-type mechanism was first outlined by Dakin and West,[4,5] but they soon turned to the azlactone mechanism. The main objection to the simple aldol mechanism comes from the fact that the α-amino group does not directly participate, and it is known that, although other types of acids undergo a similar reaction, the α-amino acids as a class give much better yields of the Dakin-West product.

In 1968, after the present work had been completed, an important paper by Steglich and Hofle appeared, in which they described a reaction carried out on 4-methyl-2-phenyloxazolone.[29] The reaction was run under Dakin-West conditions, except at low temperature (28°), and followed with nmr. They were able to show that, as the reaction proceeded, the following series of discrete intermediates appeared and disappeared as a function of time. Unfortunately, they did no kinetic analysis of the data. The changes of concentration with time suggest that the reaction proceeds systematically from **21** → **22** → **23** → **24**, but

this is not necessarily so. Compound **22**, for example, may be a side product formed reversibly from **21** but at a rate faster than the rate of formation of **23**.



Discussion of Reaction Mechanisms Proposed Earlier. I. The azlactone mechanism originally proposed by Dakin and West is entirely consistent with the reaction of α-amino acids with primary amino groups and, with trivial modification, to secondary amino groups as well. It obviously does not explain the reaction on some nonamino acids which undergo decarboxylative acylation, but there is no real requirement that all of these compounds go by the same reaction mechanism.

II. The concerted cyclic mechanism proposed by King and McMillan is consistent with the reaction of tertiary amino acids, while the original Dakin–West mechanism is not. However, tertiary amino acids are clearly a special case; hence, although they react to give carbon dioxide, they do not give the anticipated amino ketone but rather give a resinous polymer and *N,N*-dimethylacetamide. Since the reaction products are different from those of the usual Dakin–West reaction, it is likely that the reaction proceeds by by a different mechanism.

King and McMillan claim that their mechanism successfully explains the reaction of phenylacetic acid, and related compounds, and also the failure of hydrotropic acid and related compounds to undergo the reaction. The successes and failures cited seem consistent enough with the cyclic mechanism; however, they are also consistent with some of the other mechanisms as well, particularly with the aldol-type mechanism. The failure of hydrotropic acid to undergo the reaction can be explained on the basis of electron-donating ability of the methyl group counterbalancing the electron-withdrawing ability of the phenyl group and thus lowering the acidity of the α hydrogen. This could well prevent the reaction from occurring by the aldol-type mechanism.

Although proline was reported not to undergo the decarboxylative acylation in 1955,[4,5,30] Huisgen and coworkers[18] showed in 1964 in fact that the reaction did occur, and, since it can react *via* a mesoionic oxazolone intermediate, this is consistent with the Dakin–West mechanism. In the case of 5-pyrrolidone-2-carboxylic acid, the situation is a little different. This compound undergoes an alternative dimerization reaction (see later). It has been observed that only acids with at least one replaceable hydrogen on the α carbon undergo decarboxylative acylation, α-aminoisobutyric acid and α-amino-α-phenylpropionic acid being notable examples which fail to undergo the reaction.[20] While King and McMillan indicate that this is evidence for their mechanism, it is also consistent with the azlactone and aldol mechanisms as well.

There are two independent types of experiments which are not consistent with King and McMillans' mechanism. A study on decarboxylative acylation of arylacetic acids carried out by Smith and Fahey[27] shows no isotope effect when the carboxyl is labeled with ^{14}C in *o*-chlorophenylacetic acid. A cyclic mechanism indicates that such should be observed. We concluded that there is no convincing evidence for the occurrence of this mechanism in any case and evidence against it in the case of arylacetic acids.

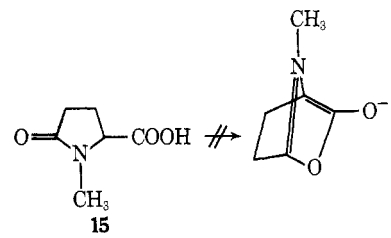
III. The carbanion mechanism proposed by Wiley has been severely criticized by several groups,[13,27] and it can be concluded that the lack of isotope effect with *o*-chlorophenylacetic acid-*1*-^{14}C acid rules out its occurrence in that particular case and makes it very unlikely that it occurs in any case.

IV. The rearrangement mechanism has been considered so superficially that it does not seem possible to draw any conclusions concerning it.[26]

V. The aldol mechanism proposed appears to be a generally applicable reaction mechanism, which can occur with any substituted acid which contains at least one α hydrogen but which probably does not occur except where other more favorable mechanisms are not possible. It seems to be the most reasonable mechanism in explaining decarboxylative acylation by nonamino aicds.

In 1950, Rondestvedt and coworkers[31] showed that the Dakin–West reaction did not go to completion unless 3 mol of acetic anhydride was used per mole of amino acid, based on the observed yield of carbon dioxide. In the same year, Searles and Cvejanovich[32] found that the reaction was first order with respect to the amino acid and the basic catalyst, by measuring the rate of evolution of carbon dioxide at 100° in a number of examples. They did not attempt to determine the order of the reaction to acetic anhydride. In 1955, King and McMillan[24] performed some stoichiometric studies and found that only 1 mol of acetic anhydride was consumed per mole of acylamino acid, indicating the work by Rondestvedt was incorrect. These were the only kinetic data available on the Dakin–West reaction when the present study was undertaken.

Plan of Attack. It seemed at the outset that the weight of the evidence favored the azlactone intermediate for the Dakin–West reaction and that the aldol mechanism obtained in cases where such an intermediate was not possible, but the reaction proceeded. A particular secondary amino acid was designed and synthesized in the present investigation, namely *N*-methyl-5-pyrrolidone-2-carboxylic acid. This acid is comparable with acetylsarcosine, benzoylsarcosine, proline, and other secondary amino acids which are known to undergo the Dakin–West reaction. It should therefore undergo the reaction if no other factors are involved. However, this acid (**15**) is so structured that the mesoionic oxazolone intermediate which would have to be formed would place double bonds at a bridgehead in a bicyclic system, in violation of Bredt's rule.[33] Therefore, if an azlactone is an essential intermediate for the Dakin–West reaction, this particular amino acid should not undergo the reaction.



It was also considered desirable to carry out some rate studies in order to find the reaction order with respect to not only the α-amino acid but also with respect to acetic anhydride and pyridine. In order to simplify the problem, α-acylamino acids were used in all rate studies. Further, it was desirable to compare the rates of azlactones which are proposed as reaction intermediates with those of the

Table I
Data for Determining the Order of Reaction with Respect to Acetic Anhydride[a]

Run	Substrate	Pyridine added, mol	Ac_2O molarity	Apparent k_1 ($\times 10^2$)	Rel Ac_2O molarity	Rel k_1
2[b]	Benzoylalanine	0.1	1.80	1.40 ± 0.04	1.00	1.00
1[b]	Benzoylalanine	0.1	3.08	2.90 ± 0.09	1.71	2.05 ± 0.13
4	Benzoylalanine	0.1	0.757	0.32 ± 0.04	1.00	1.00
23	Benzoylalanine	0.1	0.966	0.41 ± 0.04	1.28	1.30 ± 0.33
5	Benzoylalanine	0.1	1.060	0.51 ± 0.04	1.40	1.57 ± 0.37
3	Benzoylalanine	0.1	1.410	0.67 ± 0.04	1.86	2.07 ± 0.44
27	Acetamidophenylacetic acid	0.186	0.471	1.06 ± 0.04	1.00	1.00
28	Acetamidophenylacetic acid		0.790	1.71 ± 0.09	1.68	1.61 ± 0.17
29	Acetamidophenylacetic acid		1.006	2.37 ± 0.09	2.14	2.24 ± 0.18
30	Acetamidophenylacetic acid		1.300	2.48 ± 0.09	2.76	2.35 ± 0.19

[a] Reaction at 100° in 65 ml of *p*-dioxane as solvent, using 0.021 mol of substrate. [b] In these runs, 15 ml of dioxane was used as solvent.

Table II
Data for Determining the Order of Reaction with Respect to Pyridine[a]

Run	Substrate	Ac_2O added, mol	Pyridine molarity	Apparent k_1 ($\times 10^2$)	Rel pyridine molarity	Rel k_1
7	Benzoylalanine	0.160	0.583	0.48 ± 0.04	1.00	1.00
24	Benzoylalanine	0.160	0.695	0.55 ± 0.04	1.19	1.14 ± 0.21
8	Benzoylalanine	0.160	0.773	0.62 ± 0.04	1.32	1.29 ± 0.22
31	Acetamidophenylacetic acid	0.160	0.392	0.81 ± 0.04	1.00	1.00
32	Acetamidophenylacetic acid	0.160	0.583	1.04 ± 0.04	1.49	1.29 ± 0.13
33	Acetamidophenylacetic acid	0.160	0.696	1.43 ± 0.04	1.78	1.77 ± 0.16
34	Acetamidophenylacetic acid	0.160	0.774	1.47 ± 0.04	1.98	1.83 ± 0.16

[a] Reaction at 100° in 65 ml of *p*-dioxane solvent, using 0.021 mol of substrate.

acylamino acids themselves. Finally, it was desirable to be able to find out which step in the reaction was rate determining. To this end, hippuric acid (**3**), 2-phenyl-5-oxazolone (**4**), and 2-phenyl-4-(1′-hydroxyl)ethylidene-5-oxazolone (**5**) were examined. According to the oxazolone mechanism, the Dakin-West reaction of hippuric acid can be outlined as shown in Scheme I.

By comparing the rates of decarboxylation of hippuric acid (**3**), and the intermediates **4** and **5**, rate studies were carried out starting from steps 1, 2, and 4, respectively.

Results and Conclusions

The amino acid, *N*-methyl-5-pyrrolidone-2-carboxylic acid (**15**), was prepared. Although it is a known compound[34] there was no previous report of it having been submitted to the Dakin-West reaction conditions. Since it is the acylamino acid derivative of a secondary amino acid, it might be supposed that it would undergo the reaction. It cannot form the oxazolone intermediate, and so, if the amino acid does undergo the reaction, then the intermediate is not necessary in that case. The acid was in fact recovered from the reaction unchanged, even under forcing conditions, and it underwent disruption when the conditions were made still more vigorous. Hence the Dakin-West reaction apparently proceeds by a mechanism in the ordinary case which is impossible here and, explicitly, the azlactone mechanism.

The Dakin-West reaction was then studied kinetically. The reaction may be written as follows.

$$\mathrm{RCHCOOH} + \mathrm{Ac_2O} + \mathrm{Pyr} \longrightarrow \underset{\mathrm{NHCOR'}}{\overset{\mathrm{RCHAc}}{|}} + \mathrm{Pyr} + \mathrm{AcOH} + \mathrm{CO_2}$$
$$\mathrm{NHCOR'}$$

The reaction order with respect to acetic anhydride was determined by the method of initial rates, by varying the amount of acetic anhydride present with a range from 0.050 to 0.132 mol, while other concentrations were kept constant at 100° (Table I). The reaction order with respect to pyridine was similarly determined by varying the amount of pyridine over a range from 0.033 to 0.066 mol (Table II). Finally, the reaction order with respect to the α-acylamino acid was determined for two different amino acids, by varying the amount present while the molarities of the other reagents were kept constant. The order with respect to benzoylalanine (**16**) was determined using from 0.0110 to 0.0210 mol, and the order was similarly determined with respect to hippuric acid (**3**) over the range of

$$\underset{\mathrm{NHCOC_6H_5}}{\overset{\mathrm{CH_3CHCOOH}}{|}} \qquad \mathrm{C_6H_5CONHCH_2COOH}$$
16 **3**

0.0084 to 0.0168 mol at 121° (Table III). In every case, the reaction was first order with respect to each of the three reactants.

Table III
Data for Determining the Order of Reaction with Respect to Benzoylalanine[a] and Hippuric Acid

Run	Benzoylalanine molarity	Apparent k_1 ($\times 10^2$)	Ratio of substrate molarity	Rel k_1
9	0.114	0.35 ± 0.04	1.00	1.00
10	0.149	0.48 ± 0.04	1.30	1.40 ± 0.32
3	0.218	0.67 ± 0.04	1.91	1.93 ± 0.39
25	0.298	0.83 ± 0.04	2.61	2.40 ± 0.45
	Hippuric acid molarity			
13	0.0924	1.66 ± 0.04	1.00	1.00
26	0.1482	2.56 ± 0.04	1.60	1.54 ± 0.07
12	0.1845	3.61 ± 0.09	2.00	2.18 ± 0.12
11	0.1845	3.84 ± 0.14	2.00	2.29 ± 0.15

[a] Reaction at 100° in 65 ml of *p*-dioxane containing 0.186 mol of pyridine and 0.132 mol of acetic anhydride.

$$\text{rate} = k(\text{acylamino acid})(\text{pyridine})(\mathrm{Ac_2O})$$

It was earlier established that the Dakin-West reaction is first order with respect to the catalytic base in the case of benzoylalanine,[32] and this observation was confirmed.

Table IV
Data for Determining the Relative Rates of Acylamino Acids and Their Oxazolones[a]

Run	Substrate	Molarity	Apparent k_1 ($\times 10^2$)	Ratio of substrate molarity	Rel rates
14	*N*-Benzoylphenylalanine (**17**)	0.220	0.32 ± 0.04	1.00	1.00
15	**18**[b]	0.220	0.35 ± 0.04	1.00	1.07 ± 0.30
16	*N*-Acetylphenylalanine (**19**)	0.220	0.25 ± 0.04	1.00	1.00
17	**20**[b]	0.217	0.28 ± 0.04	0.99	1.09 ± 0.38
18	**19**[c]	0.220	0.90 ± 0.04	1.01	1.15 ± 0.13
19	**20**[b,c]	0.217	0.78 ± 0.04	1.00	1.00
20	Hippuric acid (**3**)	0.187	0.60 ± 0.04	1.00	1.00
21	**4**[b]	0.185	0.65 ± 0.04	0.99	1.08 ± 0.16
	5[d]	0.215	0.71 ± 0.04	1.15	1.19 ± 0.17

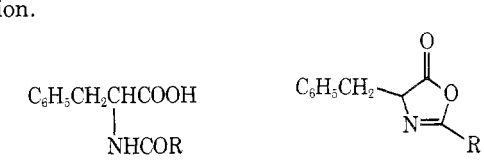
[a] At 100° in 65 ml of dioxane with 0.186 mol of pyridine and 0.106 mol of acetic anhydride. [b] With these oxazolones, a number of moles of acetic acid equal to the number of moles of substrate was added to the initial solution. [c] Using 65 ml of diglyme instead of dioxane as solvent. [d] Two moles of acetic acid per mole of substrate was added to the initial solution.

In the present work, the concentrations of both pyridine and acetic anhydride were very large and remained practically constant throughout each run; so the rate constant was calculated from the integrated form of the pseudo-first-order rate law (eq I) where V and V_∞ are the volumes

$$\log V_\infty/(V_\infty - V) = k_1 t/2.303 \qquad \text{(I)}$$

of carbon dioxide evolved at the time t and at infinite time, respectively. The constant k_1 was calculated from the data by the method of least squares. The correlation is poor between runs in which different amounts of dioxane were used as solvent, presumably due to the changes in the reaction medium. The reaction orders, on the other hand, are all unambiguously as stated.

Next, three sets of acylamino acids (**17**, **19**, **3**) and the corresponding azlactones (**18**, **20**, **5**) were separately synthesized and studied with respect to their reactions rates. The results (Table IV) showed that in each case the azlactone reacted at the same rate as did the respective parent acylamino acid, to within experimental error. This fact indicates that azlactone formation occurs in each case and that this step is not rate determining in the Dakin–West reaction.



17, R = C_6H_5 **18**, R = C_6H_5
19, R = CH_3 **20**, R = CH_3

The reaction mixture contains a number of acids and bases. The mechanism outlined in Scheme I is minimal with regard to these. It is likely that various acid and base processes are competing at various points in the reaction scheme.

In terms of the above scheme, our rate study results (Table IV) showed that the formation of azlactone (step 1) is not rate determining. These results are consistent with the fact that azlactones are always formed under much more mild conditions than those used to carry out the Dakin–West reaction.[4,5,9,35-38]

Could step 2 or 3 in the above scheme be rate determining? In this case, an acylated azlactone, namely 2-phenyl-4-acetyl-5-oxazolone, was synthesized. Rate comparisons among the acylated azlactone **5**, the parent azlactone 5-oxazolone **4**, and the grandparent amino acid, hippuric acid (**3**), were carried out. Each of the three compounds was found to react at the same rate, to within experimental error. In this case the formation of acetylated azlactone is not the rate-determining step. This is consistent with the fact that the acetylated azlactone was synthesized under more mild conditions than commonly used for the Dakin–West reaction. Unfortunately, this is the only acetylated azlactone we were able to obtain.[39] Attempts to synthesize the analogous 2-methyl-4-acetyl-5-oxazolone from acetylglycine were not successful. We can only conclude that steps 2 and 3 of the above scheme can be eliminated as being the rate-determining step for the particular case of hippuric acid.

Further conclusions concerning the rate-determining step can be drawn from our general knowledge of organic chemistry. Step 4 is a proton transfer which is known to be fast. Step 6 is an acid–anhydride transfer step, similar to step 1. Since step 1 is not rate determining, it is unlikely that step 7 is rate determining. As for steps 5 and 7, either of these could be rate determining as far as the data from the present investigation are concerned.

In isotopic substitution work, Smith and Fahey[27] concluded that the rate-determining step in the case of arylacetic acids is that which corresponds to step 3 in our mechanism. It cannot be the rate-determining step in the case of hippuric acid; so the analogy here seems not to be a good one.

Searles and Cvejanovich[32] suggested that the rate-determining step is "the reaction of the basic catalyst with the acylamino acid or the azlactone derived from it." Again, at least in the case of hippuric acid, these steps cannot be rate determining.

Experimental Section

General Procedure Used for the Kinetic Studies. The reactions were carried out in a 50-ml or 100-ml flask placed in a well insulated oil bath controlled with a thermoregulator. The flask is equipped with a stirrer, a thermometer, and a water-cooled gas outlet tube. The temperature was 99.5–99.8°, constant to 0.05° in each run. A solution of 4.000 g of benzoylalanine in dioxane, pyridine, and acetic anhydride was used to determine acetic anhydride dependent pseudo-first-order rate constants. The standard experimental procedure was to add rapidly the liquid component used in the smallest quantity to the solution of the other components previously heated to 100° in the reaction flask, in order to minimize the time for temperature equilibration. Solid carbon dioxide was evaporated at room temperature through a drying tower and then added to the reaction flask during preheating to saturate the solution with carbon dioxide before the reaction commenced. Stirring was employed throughout each run, and the carbon dioxide evolved was measured over diethyl phthalate in a gas buret at atmospheric pressure. In a typical rate run, about 30 readings of the volume of carbon dioxide collected were taken at 3-min intervals over a period of 2 hr or about 2 half-lives. The rate of decarboxylation started to slow down about 3 hr after the reaction started. The total volume of carbon dioxide after 20 hr of reaction was used as V_∞.

General Information about Rate Run Data and Calculations. The integrated form of the pseudo-first-order rate law was used (eq I).[32] The rate constants were calculated using the "Least Squares Fit" program ($Y = MX + B$) by an IBM 7074 computer, where $X = t$ and $Y = \log V_\infty/(V_\infty - V)$. By comparing the rate law and the line $Y = MX + B$, it becomes $M = k_1/2.303$ or $k_1 = 2.303M$. ΔM and ΔB are the standard deviation in M and

B, respectively. The values in the "probable error in K_1" (with 95% confidence) in Tables I–IV were calculated from Δk_1's by the method of "Values of Fisher's *t*." [40] All the ΔM's which were less than 0.0001 were called 0.0001.

Reagents. Reagent grade acetic anhydride and pyridine were used without further purification. Dioxane was purified in the usual way.[41]

The amino acids used were purchased. Derivatives were prepared by standard methods. Melting points of the materials obtained in each case agreed with the literature and so we will list only the melting point obtained and the reference: *N*-benzoyl-α-*dl*-alanine, mp 163–164° (ref 42); *N*-benzoyl-β-phenyl-α-*dl*-alanine, mp 182.5–183.5° (ref 42); 2-phenyl-4-benzyl-5-oxazolone, mp 69–70° (ref 35); *N*-acetyl-β-phenyl-α-*dl*-alanine, mp 151.5–152.5° (ref 43); 2-methyl-4-benzyl-5-oxazolone, bp 110–118° (0.8 mm), n^{24}D 1.5129 (ref 44); 2-phenyl-5-oxazolone, mp 89–90° (ref 36, 45); 2-phenyl-4-acetyl-5-oxazolone, mp 194–195° (ref 45); 5-pyrrolidone-2-carboxylic acid, mp 180–183° (ref 46); methyl 5-pyrrolidine-2-carboxylate, bp 130–140° (0.7 mm) (ref 34); *N*-methyl methyl-5-pyrrolidone-2-carboxylate, mp 41–42° (ref 34); *N*-methyl 5-pyrrolidone-2-carboxylic acid, mp 143–145° (ref 34).

Attempted Dakin-West Reaction of Acetic Anhydride and Pyridine with *N*-Methyl-5-pyrrolidone-2-carboxylic Acid (15). A mixture of 0.43 g of **15**, 5 ml of pyridine, and 5 ml of acetic anhydride was heated on a steam bath overnight. No carbon dioxide was evolved. The reaction mixture turned brown and was distilled at 29–32° (8 mm). The distillate was colorless, gave a negative DNP test, and gave ir and nmr spectra identical with those of an authentic mixture of 5 ml of pyridine, 5 ml of acetic anhydride, and 1 drop of acetic acid. The residue from the distillation was dissolved in water and extracted with ether. The ether layer was evaporated to dryness and left no residue. After removal of the water from the aqueous layer, the solid residue weighted 0.42 g, and it gave ir and nmr spectra identical with those of an authentic sample of acid **15**. The melting point and mixture melting point with authentic acid were 143–144°.

Reaction of Acetic Anhydride and Pyridine with Acid 15 at 130° for 1 Hr. A solution of 1.02 g of acid **15**, 10 ml of pyridine, and 20 ml of acetic anhydride was refluxed in an oil bath for 1 hr. The reaction temperature stayed at 130–131° for the reaction period. No carbon dioxide was evolved. The reaction mixture was worked up as described in the previous paragraph. The starting acid **15** was recovered almost quantitatively and gave ir and nmr spectra identical with those of an authentic sample.

Reaction of Acetic Anhydride and Pyridine with Acid 15 at 130° for 15 Hr. A solution of 1.04 g of acid **15**, 10 ml of pyridine, and 45 ml of acetic anhydride was stirred and heated in an oil bath for 15 hr. The reaction temperature stayed at 130–132° over the period. Only a negligible amount of gas was evolved (<5 ml) which was collected and let pass through a saturated solution of barium hydroxide. No precipitate nor even cloudiness was formed. The reaction mixture was distilled, and the distillate was found to contain acetic anhydride, pyridine, and some acetic acid. The residual black oil resisted all efforts of distillation, crystallization, and sublimation. When chromatographed over Woelm activated neutral alumina, the same viscous black oil came down the column when eluted with aqueous acetone. After removal of the solvent, it showed all its stubborn characteristics as before chromatography. It gave a negative DNP test. Ir showed broad peaks at 2970, 2925, 1723, and 1673 cm^{-1} and one sharp peak at 1823 cm^{-1}.

Isolation of Products. To verify the course of reaction in all the rate studies, the ketonic product was isolated. In most cases this was done by removal of volatile products and solvent by distillation, neutralization of the residue with sodium bicarbonate solution, followed by extraction with ether, and distillation or crystallization from the appropriate solvent. In every case the expected product was obtained, regardless of whether dioxane or diglyme or no solvent was used. From *N*-benzoylalanine (**16**) and acetic anhydride was obtained 3-benzamido-2-butanone, bp 130–140° (1 mm) in 34–91% yield [reported[32] bp 138–142° (1 mm) in 65–88%]. This ketone can be crystallized from carbon tetrachloride–petroleum ether to give material with mp 68–69° (reported[24] mp 69–70°). The 2,4-dinitrophenylhydrazone forms yellow needles from alcohol, mp 198–199° (reported[37] mp 198–199°). From *N*-benzoylphenylalanine (**17**) and acetic anhydride, and also from 2-phenyl-4-benzyl-5-oxazolone (**18**), acetic anhydride, and 1 mol of acetic acid, was obtained 1-phenyl-2-benzamido-3-butanone, in 90 and 86% yield, respectively: mp and mmp 113–114° (reported[32] mp 113.5–114°; 78% yield). From *N*-acetylphenylalanine (**19**) and also from 2-methyl-4-benzyl-5-oxazolone (**20**) with acetic anhydride and 1 mol of acetic acid, there was obtained 1-phenyl-2-acetamidobutanone in 50–52 and 30–40% yield, respectively: mp 98–99° (reported[4] mp 98–99°). Hippuric acid (3), 2-phenyl-5-oxazolone (4), and 2-phenyl-4-(1′-hydroxyl)ethylidene-5-oxazolone (**5**) all reacted with acetic anhydride and 0, 1, or 2 mol of acetic acid, respectively, to give *N*-benzamidoacetone in 19–45% yield, mp 82–84° (reported[37] mp 84°).

Registry No.—**3**, 495-69-2; **4**, 1199-01-5; **5**, 37127-06-3; **15**, 7211-55-4; **16**, 1205-02-3; **17**, 2901-76-0; **18**, 5874-61-3; **19**, 2901-75-9; **20**, 5469-44-3; acetamidophenylacetic acid, 29633-99-6.

References and Notes

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