Mechanism of the Base-catalyzed Conversion of Acylamino Acids to Acylamido Ketones

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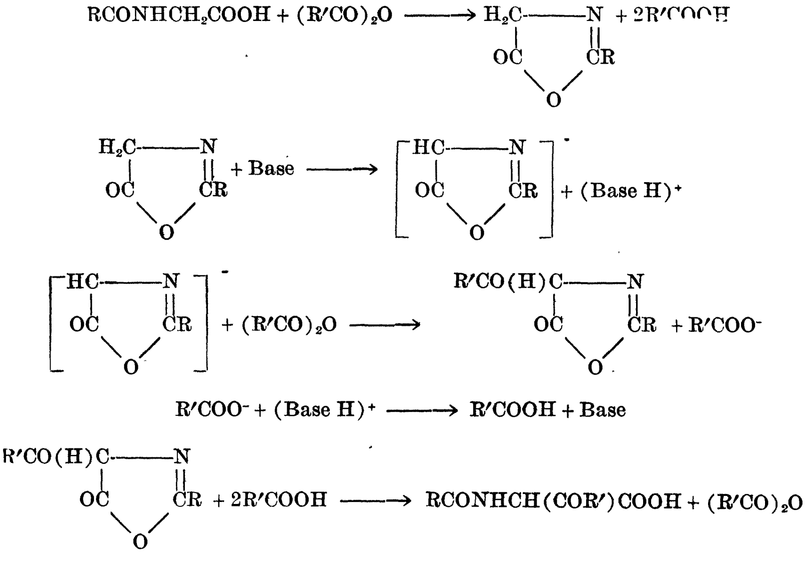
Recent studies (*6, 7*) of the base-catalyzed reaction of acylamino acids with acid anhydrides to form acylamido ketones

$$RCONHCH_2COOH + (R'CO)_2O \xrightarrow{\text{pyridine}} RCONHCH_2COR' + R'COOH + CO_2$$

have considerably extended the utility of the reaction. Methods have been described for obtaining excellent yields of ketone with many α-acylamino acids including acetylglycine (*7*) which at first was not believed to react, and many acid anhydrides including benzoic anhydride (*3*). It is also known that benzoyl fluoride may be substituted for the anhydride. In recent discussions of some of these discoveries (*1, 3*) a mechanism has been proposed for the reaction which involves acylation of an azlactone (oxazolone-5) as the essential or most likely intermediate. This mechanism is formulated as follows:



$$R'COO^- + (Base\ H)^+ \longrightarrow R'COOH + Base$$

$$RCONHCH(COR')COOH \longrightarrow RCONHCH_2COR' + CO_2$$

The first step of this mechanism is supported by the known conversion of α-amino acids to azlactones by anhydrides (*2*). Also, the Erlenmeyer azlactone synthesis and the formation of 4-ethoxymethylene-5-oxazolones are related reactions commonly accepted as involving azlactone intermediates. The acylation step offers a tempting comparison to other base-catalyzed acylations such as the Claisen and Perkin reactions.

The purpose of this report is to comment briefly on this mechanism in light of an observation made in this laboratory (*8*) that acetylsarcosine reacts, under the usual conditions of time and temperature, with acetic anhydride in the presence of pyridine with evolution of carbon dioxide to form N-methylacetamidoacetone.

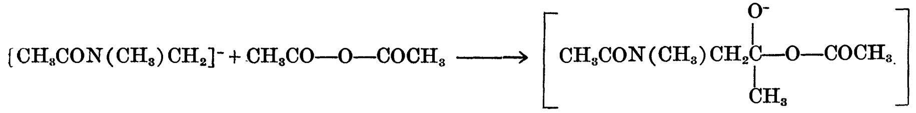
$$CH_3CON(CH_3)CH_2COOH + (CH_3CO)_2O \xrightarrow{\text{pyridine}} CH_3CON(CH_3)CH_2COCH_3 + CO_2 + CH_3COOH$$

This observation clearly indicates the insufficiency of the azlactone mechanism. Cyclization of acetylsarcosine to the azlactone is prevented by substitution of N—CH_3 for N—H. There is other evidence in the literature indicating that the azlactone mechanism is not sufficient, notably the report that phenylacetic acid reacts under these conditions with acetic anhydride (*4*).

A mechanism sufficiently comprehensive to explain this reaction is desirable and the following mechanism is accordingly suggested. The acylamino acid is first decarboxylated by the base to a carbanion. This reaction is to be expected of a carboxylic acid carrying an electrophilic group in the beta position.

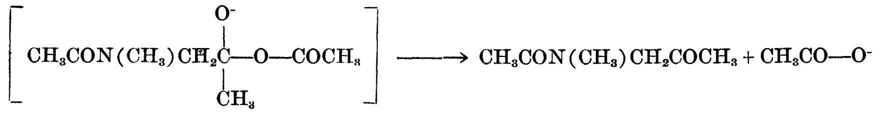
$$CH_3CON(CH_3)CH_2COOH \xrightarrow{\text{base}} [CH_3CON(CH_3)CH_2]^- + CO_2 + H^+$$

Both the acylamido and N-methylacylamido groups are apparently sufficiently electrophilic to promote this reaction. The anion formed then adds to the carbonyl group of the anhydride (or acyl halide) to give the anion shown:



$$[CH_3CON(CH_3)CH_2]^- + CH_3CO{-}O{-}COCH_3 \longrightarrow \left[CH_3CON(CH_3)CH_2\overset{O^-}{\underset{CH_3}{C}}{-}O{-}COCH_3\right]$$

This addition carbanion then loses the acetate ion to form the ketone



$$\left[CH_3CON(CH_3)CH_2\overset{O^-}{\underset{CH_3}{C}}{-}O{-}COCH_3\right] \longrightarrow CH_3CON(CH_3)CH_2COCH_3 + CH_3CO{-}O^-$$

or combines with a proton and loses acetic acid. The addition of a carbanion, formed by decarboxylation, to a carbonyl group has been previously observed (*9*).

An alternative mechanism regarded as less likely in view of the expected ease of loss of carbon dioxide, postulated as the first step in the preceding mechanism, is that the acylamino acid undergoes C-acylation as an active methylene compound. This can be visualized as proceeding through the intermediate

$$[CH_3CON(CH_3)CHCO_2H]^-$$

in which the carboxyl group may have been converted to a mixed anhydride, an anion, or an azlactone. This is merely a generalization of the previously stated azlactone mechanism. C-Acylation of active methylene compounds has long been known and is illustrated by formation of diacetoacetic ester from acetoacetic ester and acetyl chloride in the presence of sodium (*5*), or by rearrangement of β-acetoxycrotonic ester (*10*).

The mechanism proposed indicates that the reaction is more widely applicable than has been realized. Decarboxylation as a source of reactive carbanions represents a class of organic reactions hitherto unappreciated.

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The Pleistocene History of the Mississippi River

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The Mississippi River throughout about half its course now flows within an area that during Pleistocene time was invaded by the lobes of four continental glaciers in succession. The first (Missourian), second (Iowan), and third (Illinoian) came from an eastern quarter (Wapello Lobes); but the later invasions of the Illinoian, and the fourth (Wisconsin) glaciation (Mankato Lobes) spread out from the north (*2*).

The first three of these glacier invasions each caused a large displacement of the pre-Pleistocene Mississippi, whatever may then have been its position. During the deglaciation of each of these glaciers, which took place only during the warm summer months of each year, the upper course of the Mississippi River was marginal to a glacier lobe, and it carried vast quantities of cold meltwater, as well as the meteoric water from surface streams. During the winter months, however, these channels carried only the meteoric water of the surface streams, and so shrank to such moderate proportions as to expose a portion of the deposits on the bed to the fierce winds off the glacier and so yield a broad but thin surrounding apron of loess, now weathered (gumbotil).

From the Mankato lobes of the Late Illinoian and the Late Wisconsin glaciations, the periglacial land surface sloped outward, giving rise to many outward-flowing streams of meltwater that coalesced near the glacier front, and their floods formed plains of outwash, surrounding which were laid down heavy deposits of loess.

Displaced by the several glacier lobes, the courses of the marginal meltwater rivers within the states of Iowa and Missouri were as shown in Fig. 1; they are now revealed by deep trenches cut in the bedrock.

Approximately equal volumes of meltwater must have issued from the southern flanks of each of the four glaciers in southern Illinois, Indiana, and Ohio; but up to the present the courses of these streams have not been traced except in Ohio (*3*). The corresponding channels in Indiana and Illinois will probably be found soon by the ground-water geologists of both federal and state surveys in their now intensified search for aquifers within the region. Wherever these may later be discovered,