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Authors

Fry, Arthur
Rapoport, Henry

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KETONES FROM AMINO ACIDS

Arthur Fry and Henry Rapoport

August 23, 1950

Berkeley, California

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A NOTE ON THE MECHANISM OF THE FORMATION OF ALPHA-ACYLAMINO
KETONES FROM AMINO ACIDS

by

Arthur Fry and Henry Rapoport

Radiation Laboratory and Department of Chemistry,
University of California, Berkeley (*)

August 23, 1950

ABSTRACT

The reaction of alanine-1-C¹⁴ and phenylalanine-1-C¹⁴ with acetic anhydride in the presence of pyridine has been studied, and the carboxyl group of the amino acid has been shown to be the exclusive source of the carbon dioxide involved.

(*) The work described in this paper was sponsored by the Atomic Energy Commission.

A NOTE ON THE MECHANISM OF THE FORMATION OF ALPHA-ACYLAMINO
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The mechanism of the conversion of α -amino acids to α -acylamino ketones and carbon dioxide by means of acetic anhydride in the presence of a base such as sodium acetate or pyridine has recently been the subject of several discussions (1,2,3,4,5). One of the proposed mechanisms is the con-

(*) After this paper was prepared for publication, Rondestvedt, Manning and Tabibian (J. Am. Chem. Soc., 72, 3183 (1950)) published a paper drawing the same conclusions by using alanine-1-¹⁴C.

(**) The work described in this paper was sponsored by the Atomic Energy Commission.

(1) Wiley and Brown, J. Am. Chem. Soc., 72, 1626 (1950).

(2) Wiley, Science, 111, 259 (1950).

(3) Cleland and Niemann, J. Am. Chem. Soc., 71, 841 (1949).

(4) Attenburrow, Elliott and Penny, J. Chem. Soc., 1948, 310.

(5) Wiley, Chem. Rev., 37, 401 (1945).

densation of one of the methyl groups of the acetic anhydride with the carboxyl group of the amino acid, solvolysis of the mixed anhydride so formed, followed by decarboxylation of the resulting β -keto acid (5). All of the other mechanisms lead to acetylation of the α -position of the amino acid, preceded by (1,2) or followed by (3) loss of carbon dioxide from its carboxyl group. It is evident that in the first mechanism mentioned the carbon dioxide evolved would come from the acetic anhydride, while in the latter case it would come from the carboxyl group of the amino acid.

The reaction has been carried out using alanine-1-C¹⁴ and phenylalanine-1-C¹⁴ with the results shown in Table I. In both cases the carbon dioxide evolved was found to have the same specific activity as the carboxyl group of the amino acid used. The 1-phenyl-2-acetamino-3-butanone obtained from the phenylalanine, and the semicarbazone of 3-acetamino-2-butanone obtained from alanine were found to be completely inactive after several recrystallizations.

It has thus been conclusively demonstrated that the carbon dioxide evolved in this reaction has its source exclusively in the carboxyl group of the amino acid. This same conclusion could be deduced from the results of Cleland and Niemann (3) and Wiley and Borum (6) who found that other anhydrides gave the acylamino ketone predicted by the second mechanism mentioned above rather than that predicted by the first.

(6) Wiley and Borum, J. Am. Chem. Soc., 70, 2005 (1948).

Table I

Activity in Disintegrations/min./mg.C.

Sample	Alanine	Phenylalanine
BaCO ₃ from combustion	$1.01 \pm 0.02 \times 10^4$	$9.4 \pm 0.2 \times 10^3$
Corresponding carboxyl group activity	$3.03 \pm 0.06 \times 10^4$	$8.45 \pm 0.2 \times 10^4$
BaCO ₃ from ninhydrin decarboxylation		$8.25 \pm 0.2 \times 10^4$
BaCO ₃ from reaction with acetic anhydride	$3.02 \pm 0.06 \times 10^4$	$8.2 \pm 0.2 \times 10^4$
Acetylated amino ketone or derivative	-0.6 ± 1.0	-0.3 ± 1.0

Experimental

Phenylalanine-1-C¹⁴ was prepared from glycine-1-C¹⁴ by the azlactone synthesis (7). Glycine-1-C¹⁴ and alanine-1-C¹⁴ were prepared by bromination and amination of labeled acetic and propionic acids by Dr. R. Ostwald of this laboratory (7).

(7) Calvin, Heidelberger, Reid, Tolbert and Yankwich, "Isotopic Carbon", John Wiley and Sons, Inc., New York, N.Y., (1949), p. 216, 223.

The reactions were carried out essentially as described by Dakin and West (8). The carbon dioxide was swept out by a nitrogen stream, collected in sodium hydroxide and precipitated as barium carbonate. After the evolution of carbon dioxide was complete, the reaction mixture was steam distilled to remove the pyridine and excess acetic anhydride, and the acylamino ketones were extracted into ether. The 1-phenyl-2-acetamino-3-butanone was recrystallized alternately from ether and xylene. The ether extract of the 3-acetamino-2-butanone from the alanine was evaporated over a small amount of water and one gram of the resulting yellow oil was warmed with a solution of one gram of semicarbazide hydrochloride and 1.5 g. of sodium acetate. The resulting semicarbazone was recrystallized several times from alcohol, M.P.-221-3°d. Anal. Calcd for $C_7H_{14}O_2N_4$: C, 45.2; H, 7.6; N, 30.1
Found: C, 45.5; H, 7.8; N, 30.3.

The activity of the 1-phenyl-2-acetamino-3-butanone and the semicarbazone of the 3-acetamino-2-butanone were determined by counting direct plates of about 30 mg. of material. The initial activity of the alanine and phenylalanine were determined by a modified Van Slyke-Folch combustion (9) and precipitation of the resulting carbon dioxide as barium carbonate. The activity of the carboxyl group of the phenylalanine was also determined by decarboxylation with ninhydrin (10) and collection of the resulting barium carbonate. The activities of the barium carbonate samples were determined by the procedure of Dauben, Reid and Yankwich (11).

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- (8) Dakin and West, J. Biol. Chem., 78, 91 (1928).
(9) McCready and Hassid, Ind. Eng. Chem. Anal. Ed., 14, 525 (1942).
(10) Van Slyke, MacFadyen and Hamilton, J. Biol. Chem., 141, 671 (1941).
(11) Dauben, Reid and Yankwich, Anal. Chem., 19, 828 (1947).

Acknowledgment: The authors wish to acknowledge the kind interest of Professor Melvin Calvin in this work.

Summary

The reaction of alanine-1-C¹⁴ and phenylalanine-1-C¹⁴ with acetic anhydride in the presence of pyridine has been studied, and the carboxyl group of the amino acid has been shown to be the exclusive source of the carbon dioxide evolved.