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Formation of α-Amino-γ-Butyrolactone from *S*-Adenosylmethionine[1]

S-Adenosylmethionine has been recognized as a donor and precursor of several important biochemical groups (1). Homoserine and 5′-methylthioadenosine are derived from it on hydrolysis (2). Recently it has been observed in this laboratory that cell-free preparations of *Aerobacter* metabolize *S*-adenosylmethionine and accumulate a product which after paper chromatography gives a brown color with the ninhydrin spray (3). This compound is also formed by chemical splitting of *S*-adenosylmethionine in slightly acid solution. Attempts to identify it seemed warranted for a better understanding of the mechanism of degradation of the adenosyl sulfonium compound.

A sample of *S*-adenosylmethionine containing 15 μmoles/ml. was adjusted to pH 4. The solution was heated at 100° for 20 min. Aliquots were chromatographed on Whatman No. 1 filter paper using butanol, acetic acid, water (60:15:25, v/v) as the developer. The papers were examined for ultraviolet quenching reaction and sprayed with ninhydrin. Duplicates were treated with the chloroplatinate reagent. Sulfur and adenine were accountable only as 5′-methylthioadenosine. A small amount of homoserine was present, and a brown ninhydrin product which contained no adenine or sulfur was evident at R_f 0.34.

The main portion of the hydrolyzate was chromatographed in bands on Whatman No. 1 paper and the unknown material eluted. Since the compound appeared to be related to homoserine, the eluate was heated at 100° and aliquots were removed at intervals and chromatographed. Homoserine was found to accumulate as the other material disappeared in the course of the heat treatment.

The homoserine precursor was found also on hydrolysis of *S*-adenosylethionine (4), *S*-ribosylmethionine, and to a lesser degree from *S*-methylmethionine. Methionine and dimethyladenosylthetin do not yield this compound when treated similarly. Thus it became clear that the unknown homoserine precursor was derived from the amino acid moiety of the *S*-adenosylmethionine. Under the conditions of

[1] This work was performed under the auspices of the U. S. Atomic Energy Commission.

hydrolysis homoserine and 5′-methylthioadenosine either alone or in combination were not converted to the brown ninhydrin product.

A comparison of the unknown material with α-amino-γ-butyrolactone[2] showed the two compounds to be identical. This conclusion is based on their identical behavior in the hydrolysis to homoserine and on co-chromatography in six different solvent systems.

The mechanism of formation of the lactone may involve an unsaturated precursor as suggested by the earlier observations on the chemical (5) and biological breakdown (6) of sulfonium compounds. These reports indicate that under a variety of conditions unsaturated derivatives result as the main split products. The sequence of reactions in the degradation of the amino acid moiety of *S*-adenosylmethionine to homoserine possibly includes α-amino-β,γ-butenoic acid. This β,γ unsaturated acid would irreversibly cyclize to form α-amino-γ-butyrolactone by intramolecular addition. Heating of the lactone in solution results in its hydrolysis to homoserine:

$$\text{Adenine-ribose}-\overset{+}{\underset{\displaystyle CH_3}{S}}-CH_2CH_2CH(NH_2)COOH \rightarrow \text{Adenine-ribose-}SCH_3 + CH_2{=}CHCH(NH_2)COOH + H^+;$$

$$CH_2{=}CHCH(NH_2)COOH \rightarrow CH_2CH_2CH(NH_2)CO \rightarrow HOCH_2CH_2CH(NH_2)COOH.$$

The significance of these compounds as biological intermediates is under investigation.

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