β-ALANINE: A PRECURSOR OF QUINOLINIC ACID*

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Previous work has shown the existence of several pathways of quinolinic acid synthesis from 3-hydroxyanthranilic acid (Hankes and Henderson, 1957), anthranilic acid (Hankes, 1958), and O-amino-acetophenone (Hankes, 1958). Work with tobacco root cultures (Dawson, 1960) has shown that β-alanine-2-C^{14} is incorporated into nicotine in the proportions of 40% in the pyridine ring and 60% in the pyrrolidine portion. It was considered of interest to determine whether animals were capable of converting β-alanine into quinolinic acid, a direct precursor of nicotinic acid (Hankes and Segel, 1957).

Experimental

β-Alanine-2-C^{14} was obtained commercially and checked for purity chromatographically and radioautographically. It was administered in doses of 1.78 mg per mouse, 4 mg per rat, and 4 mg per guinea pig. The respiratory $C^{14}O_2$ and urine were collected for 12 hours. The urine was analyzed for quinolinic acid by microbiological assay (Henderson, 1949) and the quinolinic acid was isolated by column chromatography (Henderson and Hirsch, 1949).

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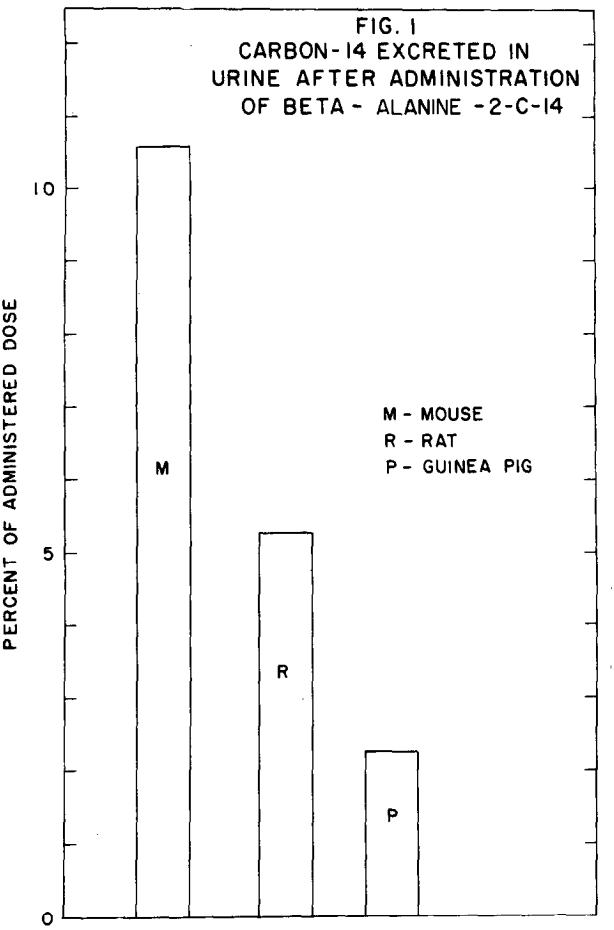
Results and Discussion

When β-alanine-2-C^{14} was administered to mice, rats and a guinea pig, C^{14}-labeled quinolinic acid was excreted in the urine. The $C^{14}O_2$ data showed that the mouse was able to



metabolize the β-alanine at a much faster rate than the rat or the guinea pig, as indicated by $C^{14}O_2$ excretion. Fig. 1 shows that the mouse also excreted a larger percentage of the administered C^{14} activity in the urine than either the rat or guinea pig. Table I shows that all animals were able to convert the β-alanine to quinolinic acid. Failure to obtain $C^{14}O_2$ by decarboxylation of quinolinic acid in the two position showed that the C^{14} activity was either in the three

position carboxyl group or in the pyridine ring of the quinolinic acid isolated from the urines.

TABLE I

Urinary Quinolinic Acid from β-Alanine-2-C^{14}

Animal	Mouse	Rat	Guinea Pig
Carbon-14 administered μc	36.84	44.07	46.76
QUINOLINIC ACID			
Q-Acid excreted, mMole	0.0004	0.0005	0.0012
Sp. Activity of excreted Q-acid, μc/mMole	1.96	1.74	1.01
Ratio = Sp.Act. of excreted Q-acid / Sp.Act. of admin. β-alanine =	0.197	0.175	0.101
Sp. Act. of admin. β-Alanine	996.532 μc/mMole		

The conversion of labeled 3-hydroxyanthranilic acid to labeled glutaric acid and labeled acetate (Gholson, Hankes and Henderson, 1960) indicated this as the pathway for the metabolism of 3-hydroxyanthranilic acid to acetate via 1-amino-4-formyl-1, 3-butadiene-1,2-dicarboxylic acid. The observation (Pihl and Fritzon, 1955) that C^{14}-labeled β-alanine is converted to C^{14}-labeled acetate coupled with the observation that β-alanine is converted to quinolinic acid suggests that the pathway for the formation of acetate from 3-hydroxyanthranilic acid via *cis*-glutaconic acid (Gholson, Sanders and Henderson, 1959) is reversible - at least as far as 1-amino-4-formyl-1,3-butadiene-1,2-dicarboxylic acid.

On the other hand, the failure of acetate-1-C^{14} to label glutarate (Rothstein and Miller, 1954) and the failure of glutaric-1,5-C^{14} (Rothstein and Miller, 1954) to label *trans*-glutaconic acid would tend to refute this theory. However,

endogenously formed glutaconic acid is undoubtedly the cis isomer which could be formed from acetate via glutaric acid and the cis form of glutaconic acid is the product expected from 3-hydroxyanthranilic acid metabolism.

In view of the above observations the data presented suggests the existence of another pathway for the synthesis of limited quantities of quinolinic acid from β-alanine-2-C^{14}.

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