BIOSYNTHESIS OF SKIMMIANINE

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On the biosynthesis of quinine, a quinoline alkaloid in Chinchona plant, Kowanko and Leete (Kowanko and Leete, 1962) gave an experimental evidence for Goutarel's hypothesis (Goutarel et. al., 1953) that this alkaloid was derived biogenetically from the indole alkaloid such as chinchonamine. The biosynthesis of 2-n-alkyl-4-hydroxy-quinolines of Pseudomonas aeruginosa was also studied by Luckner and Ritter (Luckner and Ritter, 1965), who found that anthranilic acid and acetic acid were the precursors for the formation of 4-hydroxyquinoline derivatives.

Skimmianine (I) is a furoquinoline alkaloid isolated from Skimmia japonica and its structure has been established by Asahina (Asahina et. al., 1930) as 4, 7, 8-trimethoxy-2, 3-furoquinoline. The presence of a methoxyl group at C-4 in quinoline nucleus strongly suggests that skimmianine would be derived from anthranilic acid and acetic acid by the similar way as shown in the formation of the quinoline derivative in Pseudomonas.

In the present paper, some results of our experiments are described, in which the incorporations of anthranilic acid-^{3}H, acetate-2-^{14}C and DL-tryptophan-3-^{14}C into skimmianine in Skimmia plant are shown (Table I.). The labeled compounds were fed into the exised stems by the hydroponic method and the plants were cultured for 10 days after the administration of tracers. The permanganate oxidation of the radioactive

Table I.

Incorporation Ratios of Labeled Compounds to Skimmianine.

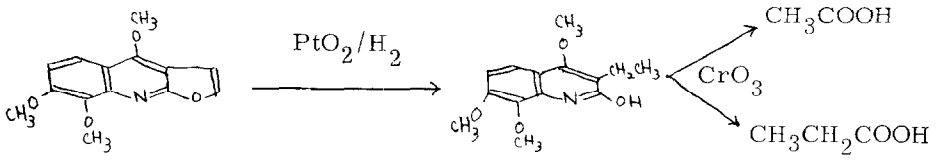
Precursor	Activity		Plants wt.	Skimmianine		
	Total	Spec.	fresh	Yield	Spec. Act.	Incorp. Ratio
	μC.	mC/mmole	g.	mg.	nC/mmole	%
Anthranilic acid-^{3}H	39	0.27	235	89	622	0.54(1.1*)
Sodium acetate-2-^{14}C	100	3.0	284	115	17.0	0.0076
DL-Tryptophan-3-^{14}C	50	33.7	292	120	0.336	0.00031

* The value indicates the incorporation ratio calculated except the loss of tritium by substitution of methoxyl groups to the benzene ring of skimmianine.

skimmianine which was derived from anthranilic acid-^{3}H afforded radioactive skimmianic acid (Asahina, 1930) which retained 96% of radioactivity of skimmianine. On the other hand, methyl iodide obtained from three methoxyl groups of skimmianine by the demethylation with hydrogen iodide was inactive. These results show that the radioactivity of anthranilic acid-^{3}H was incorporated entirely into the benzene ring of skimmianine.

Catalytic reduction of skimmianine with platinic oxide afforded 4, 7, 8-trimethoxy-2-hydroxy-3-ethylquinoline (II) (Ohta, 1953), which was further degraded to acetic acid and propionic acid by Kuhn-Roth oxidation (Fig. I.). These acids were then separated over a silica gel column and converted into 1-naphthyl amine derivatives to measure the radioactivities (Leete et. al., 1965) (Table II.).

Accordingly it seems reasonable to assume that anthranilic acid and acetic acid are the immediate precursors of the quinoline ring of



(I) (II)

Fig. I.

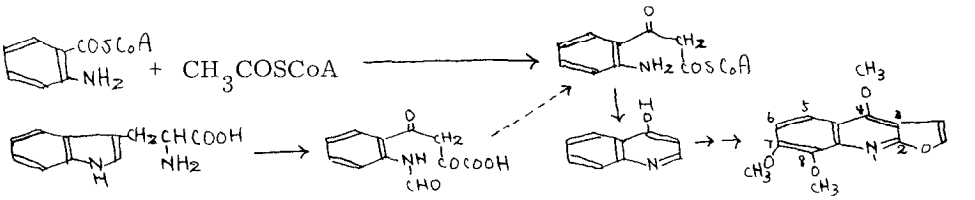
Degradation of Skimmianine Derived from Acetate.

Table II.

Radioactivities of Degradation Products of Skimmianine.

Precursor	Anthranilic acid-^{3}H		Na acetate-2-^{14}C		DL-Tryptophan-3-^{14}C	
Degradation product	Spec. Act.	Ratio	Spec. Act.	Ratio	Spec. Act.	Ratio
	dpm/mmole x 10^{6}	%	dpm/mmole x 10^{4}	%	dpm/mmole x 10^{2}	%
Skimmianine (I)	1.38	100	3.78	100	7 46	100
Reduction product (II)	---		3.74	99	7.50	101
Acetic acid	---		0.03	1	0	0
Propionic acid	---		3.38	89	7.83	105
Skimmianic acid	1.32	96	---		---	
Methyl iodide	0.001	1	---		---	

skimmianine in Skimmia plant. However, a possibility of tryptophan as another precursor could not be ruled out, since the radioactivity of DL-tryptophan-3-^{14}C is localized at C-3 of quinoline ring, though the incorporation ratio is very low. We propose therefore the following scheme as the possible pathway for the biosynthesis of skimmianine (Fig. II.).



Skimmianine (I)

Fig. II.

Biosynthetic Scheme of Skimmianine.

Summary

Skimmianine isolated from Skimmia plants fed with anthranilic acid -^{3}H, acetate-2-^{14}C and DL-tryptophan-3-^{14}C was shown to be radioactive. Degradation of the labeled skimmianine showed that the radioactivity was located in the benzene ring when anthranilic acid-^{3}H was administered, while it was located at the position 3 of quinoline nucleus when acetate-2-^{14}C or DL-tryptophan-3-^{14}C was used as the labeled precursors.

On the basis of these results, a scheme of the biosynthesis of skimmianine was proposed in which skimmianine was shown to be derived from anthranilic acid and acetate.

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