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# BIOSYNTHESIS OF EVODIA ALKALOIDS.

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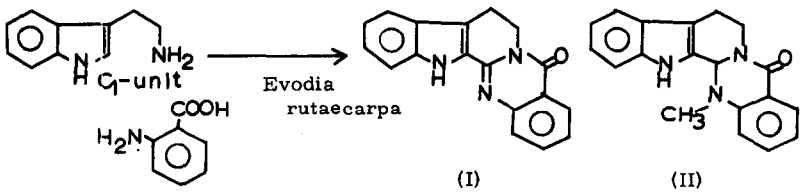
The Rutaceous plants contain quinoline, quinazoline or indoloquinazoline alkaloids which would be derived biogenetically from anthranilic acid or its metabolites[1]. As an example of the biosynthesis of Rutaceous alkaloids, we have proved that skimmianine, one of the furoquinoline alkaloids of Skimmia plant, is formed by the condensation of anthranilic acid with acetic acid[2]. In regard to this result, the indoloquinazoline alkaloid of Evodia rutaecarpa, such as rutaecarpine(I) and evodiamine(II), would also possibly be biosynthesized through the tryptophan-anthranilic acid metabolism pathway.

Schöpf and Steuer[3] synthesized rutaecarpine under the so-called physiological condition by the condensation of anthranilic acid with




5, 6-dihydro-4-carboline which was prepared from tryptamine and formic acid to suggest a possible biogenetic scheme of this type of alkaloids.

In the present paper, the result of our experiment is reported, in which tryptophan-3-$^{14}C$ (50μc, 0.3mg.), sodium formate-$^{14}C$ (100μc, 0.5mg.) and anthranilic acid-$^{3}H$ (20μc, 2.0mg.) were fed to the fruit of Evodia rutaecarpa by infiltration method. The alkaloids extracted from the fruits after feeding labelled compounds for 10 days, were purified in the form of the hydrochlorides. During the process of making the hydrochlorides, evodiamine was converted into alcohol-soluble isoevodiamine hydrochloride, which was separated from alcohol-insoluble rutaecarpine hydrochloride. The specific radioactivities of the alkaloids are summarized in Table I.

When the $^{14}C$-labelled precursors were administered to the unripe fruits, $^{14}C$ was much larger incorporated into rutaecarpine than into evodiamine, whereas tritium was incorporated almost equally into the both alkaloids when anthranilic acid-$^{3}H$ was fed into the ripe

fruits. Especially, it is noted that the incorporation of formate-$^{14}C$ into evodiamine was much less than that into rutaecarpine, in spite of the presence of N-methyl group in the molecule of evodiamine. Therefore, the result shown in Table I strongly suggested that the biosynthesis of rutaecarpine was markedly dominant in the unripe fruits of Evodia plant, while the formation of evodiamine was somewhat suppressed in the unripe fruits.

TABLE I.

The Incorporation of Precursors into Alkaloids. ( dpm/mmole. )

| Alkaloid / Precursor | Rutaecarpine (I) | Evodiamine (II) |
|---|---|---|
| Tryptophan-3-$^{14}C$ a) | $1.5 \times 10^6$ | $2.5 \times 10^4$ |
| Sodium formate-$^{14}C$ a) | $5.1 \times 10^4$ | $7.3 \times 10^3$ |
| Anthranilic acid-$^{3}H$ b) | $1.3 \times 10^4$ | $1.9 \times 10^4$ |

a) Administered to the unripe fruits.
b) Administered to the ripe fruits.

The radioactive alkaloids obtained by feeding tryptophan-3-$^{14}C$ were degraded by refluxing for several hours in alcoholic potash solution[4]. As the degradation products, tryptamine-2-carboxylic acid and anthranilic acid were obtained from rutaecarpine, and tryptamine and N-methyl anthranilic acid from isoevodiamine. Tryptamine-2-

carboxylic acid was further decarboxylated to tryptamine by heating with diluted hydrochloric acid. The specific activities of the degradation products are shown in Table II.

TABLE II.

The Specific Activities of Alkaloids and their Degradation Products.

| | Specific activity dpm/mmole (%) | | Specific activity dpm/mmole (%) |
|---|---|---|---|
| Rutaecarpine | $1.48 \times 10^6$ (100) | Isoevodiamine | $2.49 \times 10^4$ (100) |
| Tryptamine | $1.45 \times 10^6$ ( 98) | Tryptamine | $2.47 \times 10^4$ ( 99) |
| Anthranilic acid | 0 ( 0) | N-Methyl anthranilic acid | 0 ( 0) |

It was recognized that the most of the radioactivity of the alkaloids derived from tryptophan-3-$^{14}$C was localized in the tryptamine portion of the molecule without any randomization.

The degradation of the alkaloids was not carried out in the experiment feeding formate-$^{14}$C because of the low yield of the alkaloids. Further experiment is in progress to study the participation of $C_1$-unit to the biosynthesis of Evodia alkaloids.

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Reference

1) J. R. Price, Chemical Plant Taxonomy, Edited by T. Swain, p. 443, Academic Press (1963).
2) Biochem. Biophys. Res. Comm. in press.
3) C. Schöpf and H. Steuer, Ann., 558, 124 (1947).
4) Y. Asahina and S. Maeda, Yakugaku Zasshi, 416, 871 (1916); Y. Asahina and A. Fujita, ibid, 476, 863 (1921).