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BIOSYNTHESIS OF EVODIA ALKALOIDS.II. THE PARTICIPATION OF C_1-UNIT TO THE FORMATION OF INDOLOQUINAZOLINE ALKALOIDS.

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Previously, we proved by the isotope feeding experiment that the indoloquinazoline alkaloids of Evodia rutaecarpa Hook fil. et Thomson (Rutaceae) were biosynthesized from tryptophan, anthranilic acid and formic acid.[1)]

In the present communication, the result of our experiment is described to provide further evidence for the participation of C_1-unit to the biosynthesis of the indoloquinazoline alkaloids. From the fruits of E. rutaecarpa administered methionine-$^{14}CH_3$ (100 μCi) or sodium formate-^{14}C (250 μCi), radioactive evodiamine and rutaecarpine were isolated. The radioactivity was measured by the liquid scintillation counting method[2)] as shown in TABLE I.

TABLE I.

The Specific Radioactivity of the Alkaloids.

Alkaloids \ Precursors	Methionine-$^{14}CH_3$	Sodium Formate-^{14}C
	dpm./mmole x 10^{-4}	
Evodiamine	0.92	1.16
Rutaecarpine	1.50	0.87

The radioactive alkaloids obtained were degraded systematically as described in the previous report, and the radioactivities of the degradation products were measured as listed in TABLE II.

The result of degradation showed that the C_1-unit from methionine or formate was introduced into the 3-position of both alkaloids and into the N-methyl of evodiamine.

It should also be noted that the radioactivity is partly incorporated into the tryptophan portion of both alkaloids (25 and 17 % respectively) only on the administration of sodium formate-^{14}C.

TABLE II.

The Specific Radioactivities of the Degradation Products.

dpm./mmole x 10^{-4} (%)

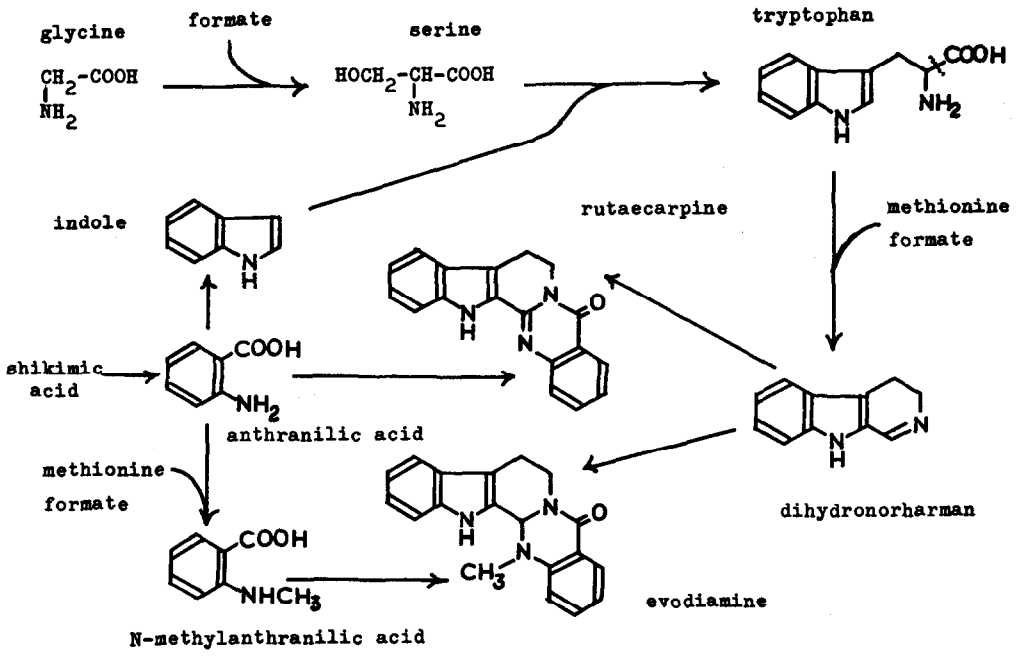
Precursors / Degradation Products	Methionine-$^{14}CH_3$	Sodium Formate-^{14}C
Evodiamine	0.92 (100.0)	1.16 (100.0)
Isoevodiamine	0.92 (100.0)	1.16 (100.0)
Tryptamine	0 (0)	0.20 (17.2)
CO_2 (3-C)	0.54 (58.7)	0.56 (48.3)
N-Methylanthranilic Acid	0.38 (42.4)	0.40 (34.5)
Rutaecarpine	1.50 (100.0)	0.87 (100.0)
Tryptamine-2-carboxylic Acid	1.24 (82.0)	0.87 (100.0)
Tryptamine	0 (0)	0.22 (25.3)
CO_2 (3-C)	1.49 (99.0)	0.60 (69.0)
Anthranilic Acid	0 (0)	0 (0)

As observed by Edwards and Leete[3] in the biosynthesis of ajmaline, this would reasonably be accepted by the fact that the C_1-unit from formic acid or formaldehyde is directly incorporated into serine by the hydroxymethylation of glycine, and tryptophan is synthesized biologically from indole and serine.

The incorporation ratio of C_1-unit into evodiamine was unexpectedly lower than the rate expected, in spite of the existence of the N-methyl in the molecule. Thus, it would be incompatible to assume if N-methylation of rutaecarpine-type precursor leads evodiamine. But the above result would be explained by the incorporation of C_1-unit in the earlier stage of the biosynthesis forming N-methylanthranilic acid which subsequently condenses with dihydronorharman to afford evodiamine. In such a case, the radioactivity of C_1-unit which was administered to the plant would be diluted by the pre-existed non-labelled N-methylanthranilic acid.

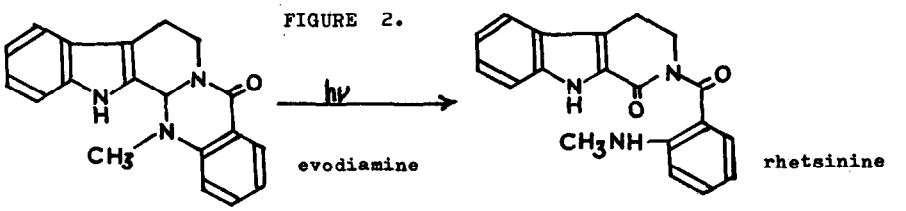
Conclusively, the biosynthesis of evodiamine and rutaecarpine in E. rutaecarpa is illustrated as follows :

FIGURE 1.



Rhetsinine, on the other hand, firstly isolated from the bark of Xanthoxylum rhetsa (Rutaceae) as a naturally occurring yellow alkaloid[4] has recently been found by us[5] in the fruits of E. rutaecarpa in a fairly good yield. Although this compound appears to be an intermediate of the biosynthesis of evodiamine, the natural occurrence of rhetsinine in the plant is now doubtful. We have confirmed that rhetsinine is readily formed from evodiamine by the irradiation of light in a short time.[5]

FIGURE 2.



We also have isolated three other alkaloids from the fruits of E. rutaecarpa as a result of the survey of alkaloids in the plant from the biogenetic interest, and elucidated the structure of one of them, named evocarpine, as N-methyl-4-quinolone substituted at 2-position by C_{13} long straight side chain containing one double bond in it.[6] The simultaneous occurrence of this unique type of quinolone alkaloid and indoloquinazolines in E. rutaecarpa seems to be interest from the biogenetic and chemotaxonomic points of view.

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4) R.H.F.Manske, The Alkaloids, Chemistry and Physiology, Vol.VIII, p.57 (1965) Academic Press, New York
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6) M.Yamazaki, The 24th. Annual Meeting of the Pharmaceutical Society of Japan, Kyoto (1967)

ADDENDUM During description of this manuscript, we received the paper in the latest arrived journal in which Tschesche and Werner[7] also reported the isolation of rhetsinine and evocarpine from the fruits of E. rutaecarpa. The latter quinolone alkaloid, evocarpine seems to be quite identical with our specimen on the basis of the chemical and spectral data.

7) R.Tschesche and W.Werner, Tetrahedron, 23, 1873 (1967)