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# THE BIOLOGICAL CONVERSION OF SWEROSIDE INTO GENTIOPICROSIDE AND VINDOLINE AND A BIOGENETIC ASPECT OF SOME INDOLE ALKALOIDS

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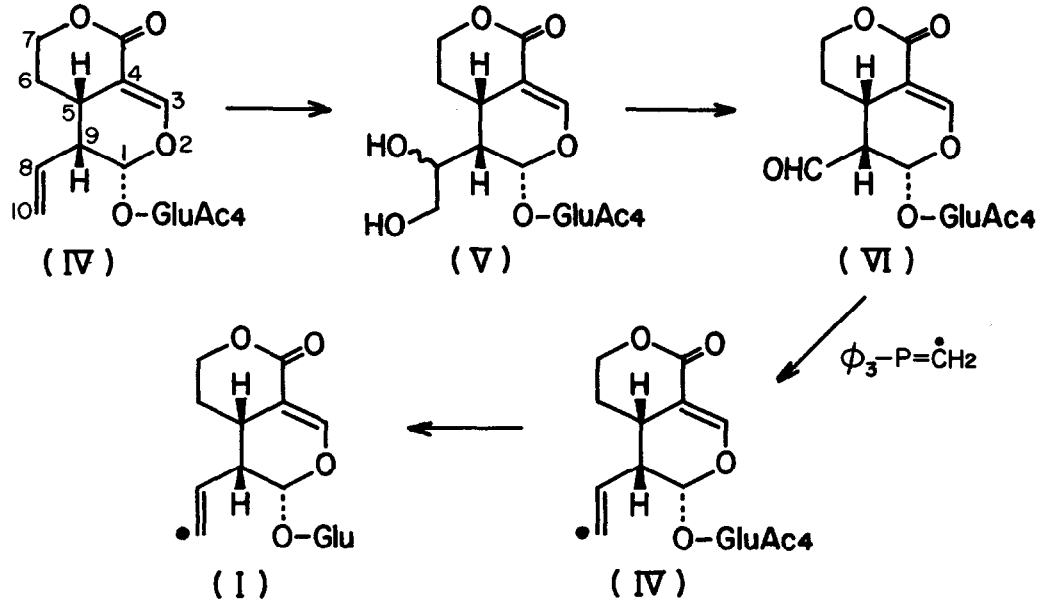
Recently we reported on the structure of sweroside (I)[1,2], a new bitter glucoside, which was isolated from Swertia japonica Makino along with swertiamarin (II)[3] and a tiny amount of gentiopicroside (III)[3]. Then the feeding experiment of mevalonic acid-2-$^{14}$C clarified that these secoiridoid glucosides[3] are of monoterpenoid origin from the iridoid[3,4].

Considering from the structure of sweroside (I), it is most likely that a series of the glucosides such as swertiamarin (II) and gentiopicroside (III) are biologically derived from this glucoside. The fact that the extent of the incorporation of mevalonate into (I) was about ten times greater than into (II) at the feeding experiment with Swertia japonica also supported the biosynthetic pathway of gentiopicroside (III) from sweroside (I) via swertiamarin (II)[3].

Although mevalonic acid[5], geraniol[6], and loganin[7] were proved to be incorporated into the non-tryptophan derived portion of the indole alkaloid, sweroside (I) (or its equivalent) is considered to be a closer precursor to the alkaloid. Accordingly, we synthesized 10-$^{14}$C-sweroside (I) by the route shown in Scheme 1 and administrated it to Gentiana scabra Bunge var. Buergeri Maxim. and Vinca rosea L. in order to examine the incorporation of the glucoside into gentiopicroside (III) and vindoline (VIII).

Osmium tetroxide oxidation of sweroside tetraacetate (IV) afforded glycol (V), $C_{24}H_{32}O_{15}$, m.p. 148-150°. This compound reacted with periodate to yield aldehyde (VI), $C_{23}H_{28}O_{14}$, amorphous powder. Wittig reaction of the compound (VI) with $^{14}C$-methylene triphenylphosphorane followed by Zemplén reaction produced 10-$^{14}C$-sweroside (I).

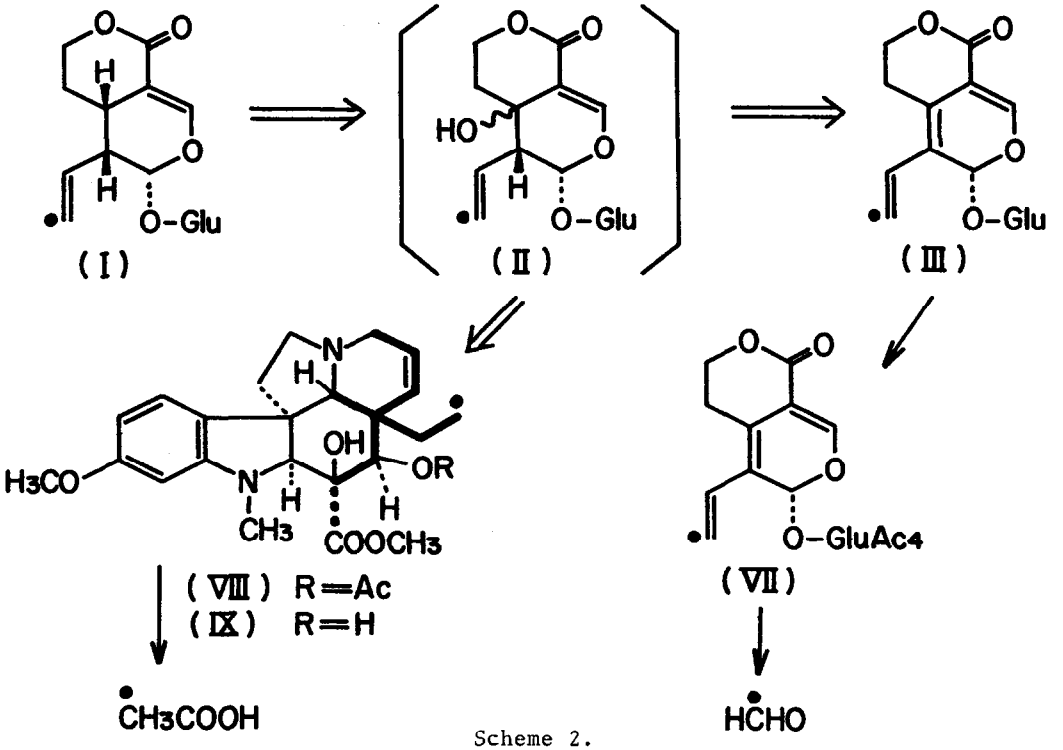



Scheme 1.

The 10-$^{14}C$-sweroside (I) (8,7 mg., $6,90\times10^5$ dpm/m mol) was administrated by the cotton wick method to Gentiana scabra plants at their flowering stage. Gentiopicroside (III) was isolated after four days by the usual method and was converted into its tetraacetate (VII), m.p. 142-143°. The specific activity of (VII) was $2,96\times10^3$ dpm/m mol (incorporation ratio 40 %). Ozonolysis of this compound yielded formaldehyde which was collected as its dimedone derivative, m.p. 191-193°, containing 98 % of the radioactivity of (III). The good and specific incorporation of 10-$^{14}C$-sweroside (I) into (III) established that sweroside (I) is an active precursor of gentiopicroside (III).

Foregoing radioactive sweroside (I) (26,4 mg., $1,38\times10^6$ dpm/m mol) was then administrated to the Vinca rosea plants by means of cotton wicks inserted into the stems. The plants were harvested after four days and vindoline (VIII) was

isolated as colorless needles, m.p. 177°. The specific activity of the vindoline (VIII) was $1,75\times10^5$ dpm/m mol (incorporation ratio 11 %). The alkaloid was then hydrolysed yielding inactive acetic acid and desacetylvindoline (IX) whose specific activity was the same as that of the original alkaloid (VIII). Kuhn-Roth oxidation of the desacetylvindoline (IX) yielded acetic acid having 96 % of the total activity in the vindoline (VIII). The result thus proved that sweroside (I) was actually incorporated into vindoline (VIII) in the Vinca rosea plant.




Scheme 2.

Now, the carbon skeleton of the non-tryptophan derived portion of vindoline (VIII) is thought to be formed from the secoiridoid by fission of the bond between C-4 and C-5 and rearrangement of the three carbon unit to C-9 position.

When we assume swertiamarin (II) (or its equivalent) as an intermediate to the alkaloid, the formation of this structure would be explained i.e., by considering a route passing through a combination of cleavage of the glucoside

linkage, retroaldol and aldol condensation*1.

At any rate, this work together with other incorporation studies mentioned above[3-7] clarified that there must be a biosynthetic pathway of the indole alkaloids from mevalonic acid via geraniol, loganin, and sweroside (I) (or its equivalent).

On the contrary, it is easily supposed that some kind of indole alkaloids may be formed from loganin via another route, when their structures are considered.

The secoiridoids can be classified in two types according to the location of the double bond in their side chain, that is, sweroside- ($\Delta^{8,10}$) and oleuropein-type ($\Delta^{8,9}$)[8,9,*2], and there are many indole alkaloids in which the double bond is located at the corresponding position. For example, corynantheine, corynoxeine etc. have sweroside-type structure, while sarpagine, akuammicine etc. have oleuropein-type structure. The structural similarity between the glucosides and the alkaloids suggests that the biosynthetic route to both types of indole alkaloids would branch out at the stage of the cleavage of the cyclopentane ring of loganin. Accordingly, corynantheine etc. are presumably formed from sweroside-type glucosides; and sarpagine etc. from oleuropein-type glucosides in plant, and the converses do not happen.

Several indole alkaloids, for example, vindoline, on which we reported in this paper, strychnine, yohimbine, alstonine etc. are lacking in such characteristic double bond structure as mentioned above, so that it is not always easy to apply this hypothesis to them. It is, however, explained that among these alkaloids, yohimbine, reserpine, and the like or alstonine, alstonidine, and the like are formed from oleuropein-type precursor by the route shown in Scheme 3.

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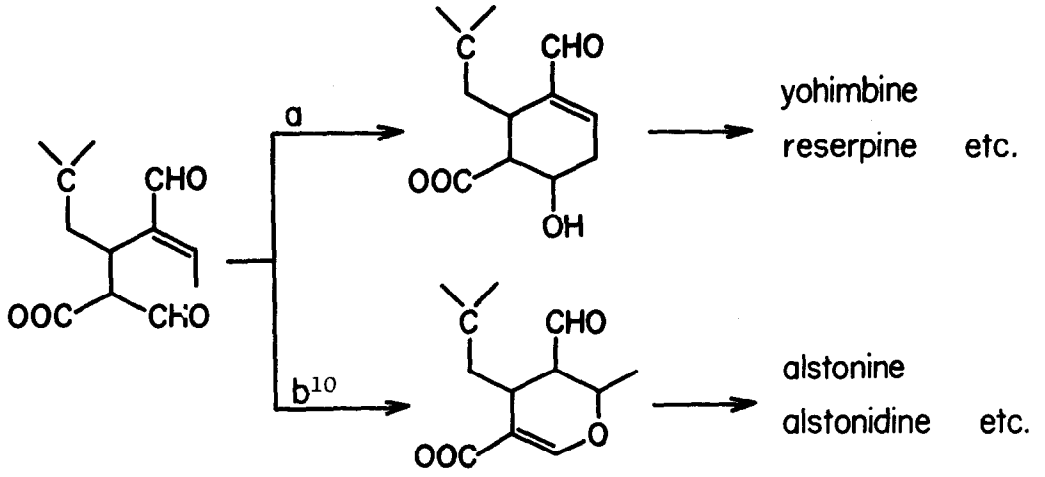
*1 Iboga alkaloids such as catharanthine could be formed in a similar way via swertiamarin (II) (or its equivalent).

*2 As the oleuropein-type glucosides so far isolated have their C-7 carbon oxidized to carboxyl, there remains a question whether the secoiridoid moiety of these glucosides actually lies on the route to the indole alkaloids or not.




Scheme 3.

The more detailed studies on the biosynthesis of these alkaloids will be published in the near future.

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