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BIOSYNTHESIS OF SECOIRIDOID GLUCOSIDES†

Hiroyuki Inouye*, Shinichi Ueda and Yoshio Takeda

Faculty of Pharmaceutical Sciences, Kyoto University,
Sakyo-ku, Kyoto, Japan

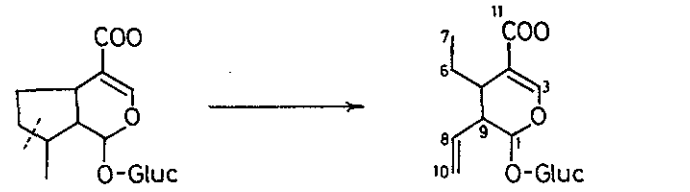
In the present review the biosynthetic pathways of sweroside, morroniside and oleuropein type secoiridoid glucosides through mevalonic acid (MVA), geraniol, deoxyloganin, loganin etc. are outlined. The biosynthesis of alkaloidal glucosides, which can be regarded as kinds of secoiridoids, is also briefly described.

I Introduction

At present, the number of substances regarded as secoiridoid glucosides is about thirty and that including alkaloidal glucosides amounts to more than fifty[1,2,3]. All of the compounds of this group have the carbon skeleton shown in the next page and are called under this name[4] because they are formed from an iridoid glucoside by the cyclopentane ring cleavage which will be described in the following.

† Dedicated to Professor Tsunematsu Takemoto on the occasion of his retirement.

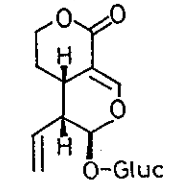
1 sweroside
2 morroniside
3 oleuropein
4 vincoside
5 secologanin
6 gentiopicroside
7 vindoline
8 loganin
9 swertiamarin
10 loganic acid
11 secologanic acid
12 secologanoside
13 foliamenthin
14 dihydrofoliamenthin
15 menthiafolin
16 ipecoside
17 ajmalicine
18 catharanthine
19 7-deoxyloganin
20 7-deoxyloganic acid
21 jasminin
22 gentioside
23 7-dehydrologanin
24 10-hydroxyloganin
25 phosphate of 24
26 10-tosyloxyloganin aglucone 1-O-methyl ether
27 10-tosyloxy-7-epiloganin aglucone 1-O-methyl ether
28 secologanin aglucone 1-O-methyl ether
29 secologanic acid aglucone 1-O-methyl ether
30 oxetane compound
31 sweroside tetraacetate
32 secologanoside tetraacetate dimethyl ester
33 7-dehydrologanin tetra-acetate
34 kingiside tetraacetate
35 bakankosin
36 secologanoside 11-methyl ester
37 amarogentin
38 amaroswerin
39 kingiside
40 oleoside
41 10-hydroxyoleoside
42 ligustroside
43 10-hydroxyligustroside
44 10-acetoxyligustroside
45 10-acetoxyoleuropein
46 8-epikingiside
47 aldehyde compound
48 alangiside
49 isovincoside
50 vincoside lactam
51 10-β-D-glucosyloxyvincoside lactam
52 cordifoline
53 deoxycordifoline
54 rubenine
55 desacetylipecoside



Iridoid glucosides — Secoiridoid glucosides

Chart 1

Secoiridoid glucosides are classified into (i) the sweroside (1)[5] type bearing a vinyl group at C-9, (ii) the morroniside (2)[6,7] type formed through the introduction of an oxygen function into the C-8 position of the vinyl side chain at C-9 and (iii) the oleuropein (3)[8] type having an ethylidene or a hydroxyethylidene side chain at C-9 and a carbonyl group in ester at



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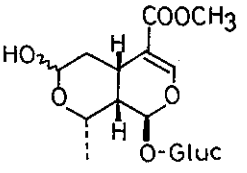

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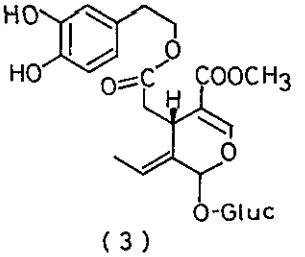

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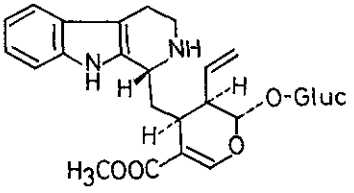

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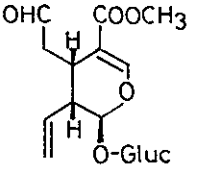

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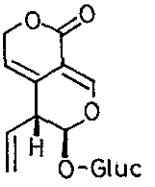


(6)

Chart 2

C-7. In addition, (iv) the alkaloidal glucosides, e.g., vincoside (4), formed by the Pictet-Spengler-type condensation of secologanin (5)[9,10,11] with phenethylamine, tryptamine or tryptophan could also be included in this group.

The study of secoiridoid glucosides has a long history. For example, a glucoside gentiopicroside (6) was found already in the last century[12]. But, most of them have been isolated since the latter half of the 1960's. The structure including the stereochemistry of substances in this group has also been throughly clarified for the first time in the past decade. One of the reasons for such rapid progress in the chemistry of the secoiridoid glucosides was the recognition that the non-tryptophan portion in each of the many indole alkaloids is of mevalonoid origin and is biosynthesized *via* the iridoid and secoiridoid glucosides. Accordingly, the biosynthetic studies of these glucosides have also made much progress recently, concurrently with those of the indole alkaloids.

Concerning the biosynthetic origin of the non-tryptophan portion of the indole alkaloids, besides the long standing phenylalanine hypothesis of Barger and Hahn[13,14], several new proposals, such as the prephenic acid[15], the terpenoid[16,17] and the acetate-malonate hypotheses[18] were presented at the beginning of nineteen sixties. This caused much confusion. However, within a few years since 1965, when Scott[19], Arigoni[20] and their associates recognized the incorporation of MVA into vindoline (7), a *Vinca* alkaloid, the incorporation of MVA or geraniol into various indole alkaloids was confirmed by several research groups[21-25].

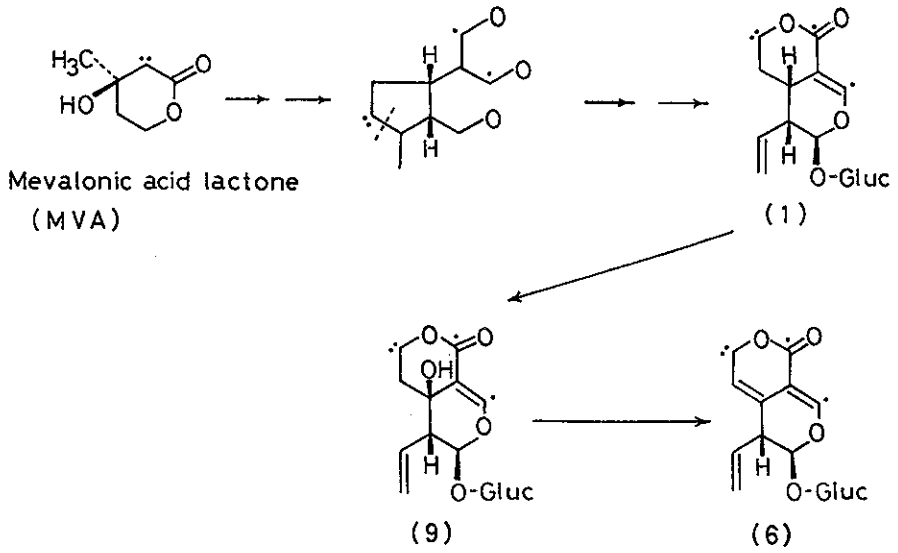
In 1966 Battersby[26] reported the incorporation of (carbo-^{3}H-methoxy)-loganin (8) into Vinca alkaloids. Further experiment of his group administering biosynthetically prepared (9-^{14}C)-loganin (8) securely established the key intermediacy of 8 for the biosynthesis of indole alkaloids[27]. Thus the compounds now known as the "secoiridoids" had come to be thought of as the more immediate intermediates of these alkaloids. Arigoni's work[28] using (10-^{14}C)-loganin (8) also afforded evidence for the validity of Battersby's conclusion.

On the other hand in the above mentioned hypothesis on the biosynthesis of indole alkaloids, the common biosynthetic pathway among glucosides such as gentiopicroside (6), swertiamarin (9) and these alkaloids was suggested[17] from the structural similarity of both groups of compounds. In 1967 Inouye[4], Coscia[29] and their associates first established, through the incorporation experiment of MVA to sweroside (1), swertiamarin (9) and gentiopicroside (6), that these substances also belong to the monoterpene.

Here we outline the subsequent progress in the biosynthetic studies of secoiridoid glucosides. Though, as described above, the studies of glucosides are inseparable from those of the indole alkaloids, this review especially focuses upon the secoiridoid glucosides.

II Proof of the precursorship of MVA, geraniol, 10-hydroxynerol etc. to the biosynthesis of secoiridoid glucosides

As mentioned above, Inouye and his associates[4] demonstrated that MVA was incorporated into sweroside (1) and swertiamarin (9) in Swertia japonica as well as gentiopicroside (6) in Gentiana triflora var. japonica. Through degradation of the radioactive glucosides it was further revealed that during the biosynthesis of these glucosides the randomization of the labeling between C-3 and C-11 occurred as in the case of several indole alkaloids[19-21] and plumieride[30]. Moreover, the formation sequence 1 → 9 → 6 was deduced from the comparison of the specific activities of sweroside (1) and swertiamarin (9) coexisting in the Swertia plant coupled with the observation of the structures of these three glucosides[4].



Mevalonic acid lactone (MVA)

(1)

(9)

(6)

Chart 3

Shortly before the publication of this work, Coscia and his associates[29] also reported the incorporation of MVA into gentiopicroside (6) in Swertia caroliniensis. Later, they further obtained the findings below by the administration of stereospecifically tritium-labeled MVA, that is, (4R,4-^{3}H)-, (4S,4-^{3}H)-, (2R,2-^{3}H)- or (2S,2-^{3}H)-MVA together with (2-^{14}C)-compound to the same plant followed by the chemical degradation of the radioactive loganic acid (10) and gentiopicroside (6) isolated from the plant.

a) Both pro-R hydrogens of the C-4 methylenes of two MVA molecules were retained in loganic acid (10), while both pro-S hydrogens disappeared.

b) Only one C-4 pro-R hydrogen of the two molecules of MVA was incorporated into gentiopicroside (6), while the C-4 pro-S hydrogen disappeared*.

c) Although the pro-2R hydrogen of MVA was retained at the C-3 and the C-7 positions of loganic acid (10), the pro-2S hydrogen was eliminated when 10 was formed.

On the basis of these findings, Coscia and his associates[31] inferred the steric course of the biosynthesis of gentiopicroside (6) from MVA as shown in Chart 4. They also isolated acidic glucosides such as loganic acid (10), secologanic acid (11) and

* This result gave a biochemical proof of the revised structure of gentiopicroside (6) presented by Inouye et al. cf. H. Inouye, T. Yoshida, Y. Nakamura and S. Tobita, Tetrahedron Letters, 1968, 4429 and reference 5b.

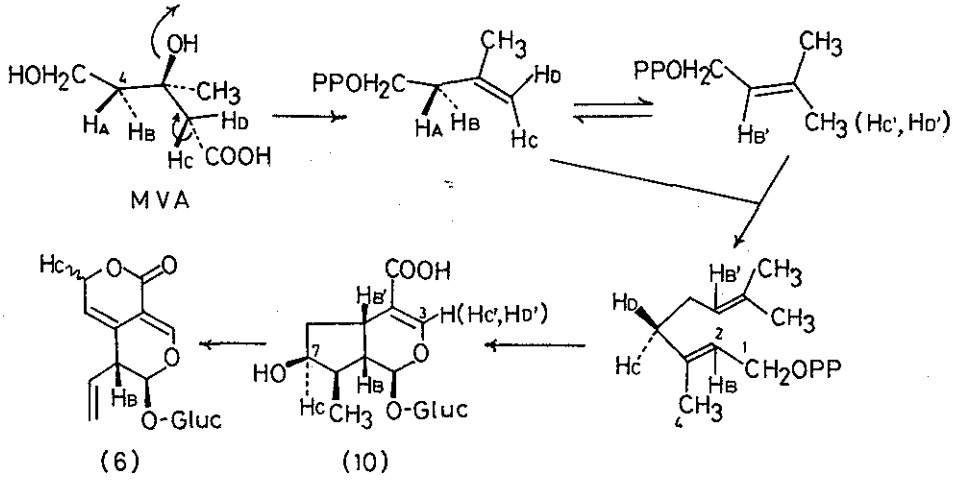


Chart 4

secologanoside (12) along with secologanin (5) from Vinca rosea and clarified, from the administration experiment of (2-^{3}H, 2-^{14}C)-MVA to this plant, that a tritium atom was retained on the C-3 and the C-7 positions of substances 5, 10 and 11[32].

Though the above studies provided evidences for the mevalonoid origin of the secoiridoid glucosides, the followings are concerned with the proof of the precursorship of acyclic monoterpenoids

Chart 5

such as geraniol for these glucosides.

On examination of the constituents of Menyanthes trifoliata, Arigoni, Battersby and their groups[33,34] isolated foliamenthin (13), dihydrofoliamenthin (14) and menthiafolin (15) and established their structures. Thereby, Arigoni's group demonstrated, through the degradation of foliamenthin (13) isolated from the (4-^{14}C)-geraniol-fed plant, that the labeling was incorporated into the acyclic monoterpenoid and the secoiridoid portion at a ratio of 400 to 1 and that the latter portion was specifically labeled at C-10. In the same way, Battersby and his associates also clarified that (2-^{14}C)-geraniol was incorporated into the acyclic terpene and the secoiridoid portion of dihydrofoliamenthin

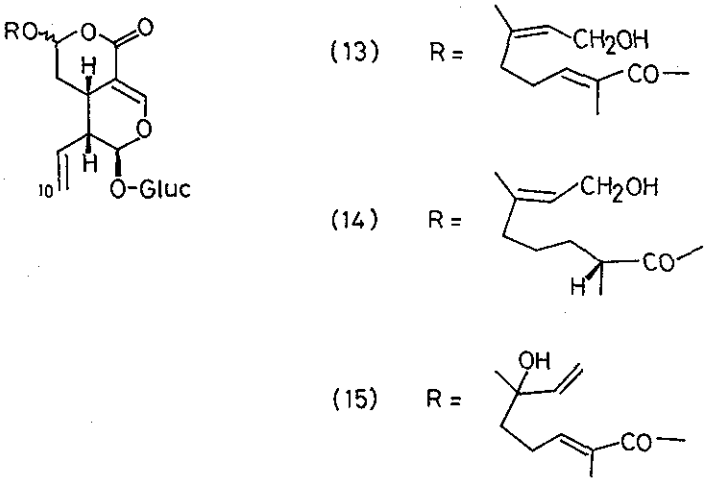


Chart 6

(14) at a ratio of 3 to 1*. Incidentally, the secoiridoid portion of these glucosides possesses a very interesting structure corresponding to the masked lactol form of secologanin (5), which is considered to be the first secoiridoid formed by the ring cleavage of the iridoid. By using secologanin (5) derived from foliamenthin (13), Battersby carried out several important studies concerning the biosynthesis of alkaloids, such as the synthesis of ipecoside (16) and vincoside (4) as well as the incorporation experiment into both alkaloidal glucosides[9,35,36]. These accounts are delineated in the section V. An additional fact about ipecoside (16) we wish to mention here is Battersby's finding that (2-^{3}H)-geraniol was incorporated in plants into 16 with retention of the labeling[37]. This experimental result indicated the retention of C-9 hydrogen of loganin (8) during the cleavage into the seco-type, a process we will describe in the next section.

As can be supposed from the occurrence of the 10-carboxyl derivative of nerol as in the esterified form in the molecule of foliamenthin (13), 10-hydroxy derivative of nerol (or that of geraniol) would be a possible biosynthetic intermediate coming

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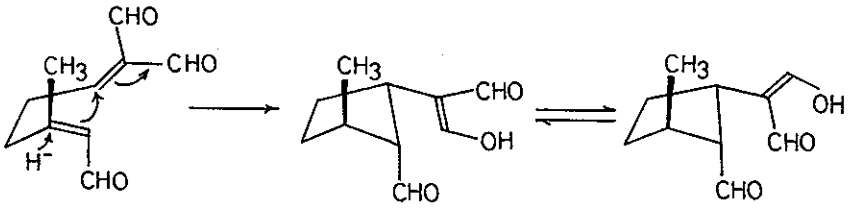
* Besides, on administration of (1-^{14}C)-geranyl pyrophosphate into Swertia caroliniensis, Coscia et al. recognized its incorporation into loganic acid (10) a possible precursor for gentiopicroside (6), but not into 6. They ascribed this unexpected result to a large pool of 6 in the plant used, causing the dilution of labeling. cf. C. J. Coscia and R. Guarnaccia, Chem. Commun., 1968, 138.

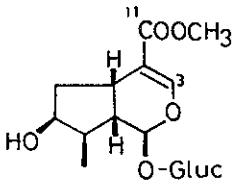
after geraniol. Research groups of Arigoni[38] and Battersby[39] carried out the administration experiments of ^{14}C or ^{3}H labeled 10-hydroxygeraniol, 10-hydroxynerol, 10-hydroxylinallol, 10-hydroxycitronellol, citronellol etc. to Vinca rosea. On the basis of the examination of the incorporation of these radioactive materials into loganin (8) and alkaloids such as ajmalicine (17), vindoline (7) and catharanthine (18), they clarified that 10-hydroxygeraniol or 10-hydroxynerol follows after geraniol (or nerol) in the biosynthetic sequences, while derivatives of linallol or citronellol described above could not be any biosynthetic intermediate. Particularly, Arigoni proposed the cyclization mechanism to iridoid as depicted in Chart 7 by considering the finding that nerol was incorporated into the above described substances more efficiently than geraniol coupled with the fact that the acyclic terpenic acid constituting foliamenthin (13) belongs to the nerol series. These findings are of great importance in disproving the heretofore accepted hypothesis[40] that the iridane skeleton is formed by the Michael-type addition of the oxocitronellal-type intermediate*.

Later, Coscia et al. demonstrated that cytochrome p-450 type

* Recently, Inouye et al. found that even in some iridoid glucosides whose 11 position is oxidized to the carboxyl level, the labeling of (2-^{14}C)-MVA was retained onesidedly at C-3. Thus, there still remain many problems unsolved on the cyclization mechanism. (H. Inouye, S. Ueda and S. Uesato, unpublished results.)

monooxigenase from Vinca rosea catalyzes the hydroxylation of geraniol and nerol at the C-10 position[41].





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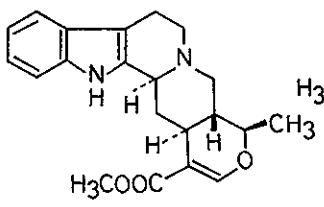

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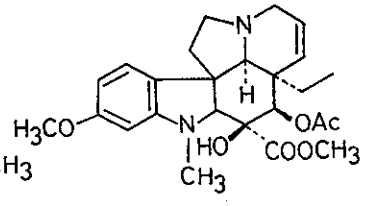

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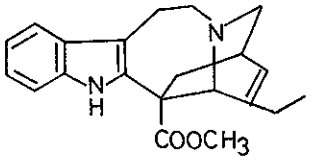

(18)

Chart 7

III Proof of the precursorship of iridoid glucosides such as 7-deoxyloganin (19), loganin (8) or the corresponding acids to the biosynthesis of secoiridoid glucosides and the consideration of the mechanism of cleavage of the cyclopentane ring of loganin (8)

On the basis of the presumption that 7-deoxyloganic acid (20)* could be the precursor of both iridoid and secoiridoid glucosides, which was derived from surveying structures of many iridoid glucosides, Inouye et al. carried out administration experiments with (10-^{3}H)-7-deoxyloganic acid (20) derived from asperuloside to several plants and recognized the effective incorporation of this substance into many iridoid and secoiridoid glucosides. Above all, the administration experiments with Lonicera japonica and Jasminum primulinum revealed that 20 was incorporated into loganin (8)[42] and jasminin (21)[43], respectively. These results first demonstrated that 7-deoxyloganic acid (20) is hydroxylated at C-7 to give loganic acid (10) and that 20 can also be a precursor of a secoiridoid glucoside jasminin (21).

Subsequently, Battersby et al.[44] recognized the conversion of (carbo-^{3}H-methoxy)-7-deoxyloganin (19), prepared through treatment of 7-deoxyloganic acid (20) with (^{3}H)-diazomethane, into loganin (8) and several indole alkaloids in Vinca rosea. They also succeeded in isolating 7-deoxyloganin (19) from this plant.

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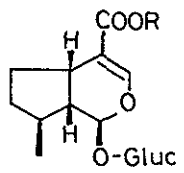
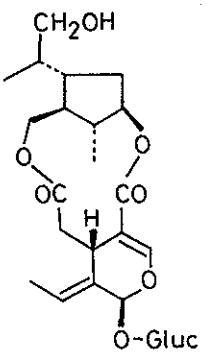
* Not having so far been found in the plant, 20 was later isolated from Physostegia virginiana (Labiatae). cf. H. Rimpler and B. von Lehmann, Phytochemistry, 1970, 9, 640.



(19) R = CH_3

(20) R = H



(21)

Chart 8

On the other hand, Coscia et al.[32] found the occurrence of loganic aicd (10) and secologanic acid (11) in Vinca rosea. They further demonstrated the incorporation of 10 biosynthetically prepared from (2-^{14}C)-MVA into loganin (8), secologanic acid (11) and secologanin (5) as well as the incorporation of labeled 8 into 11 in the same plant. From the results of these experiments, they supposed that the methylation of the C-11 carboxyl group would proceed reversibly at the stage after loganic acid (10)*.

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* Coscia et al. reported that a partially purified methyl transferase from Vinca rosea effectively converted loganic aicd (10) and secologanic acid (11) into loganin (8) and secologanin (5), respectively, while the enzyme did not convert 7-deoxyloganic acid (20) into 7-deoxyloganin (19). cf. K. M. Madyastha, R. Guarnaccia and C. J. Coscia, FEBS Letters, 1971, 14, 175; K. M. Madyastha, R. Guarnaccia, C. Baxter and C. J. Coscia, J. Biol. Chem., 1973, 248, 2497.

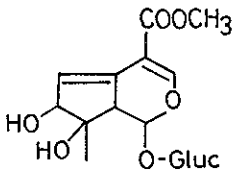
However, the results obtained by Battersby et al.[45] indicated no loss of radioactivity in the course of the conversion of doubly labeled (carbo-^{3}H-methoxy,7-^{3}H)-loganin (8) into indole alkaloids*. Anyway, it has thus been clarified that loganic acid (10) (or loganin (8)) is formed from 7-deoxyloganic acid (20) (or 7-deoxyloganin (19)). Thereby, the hydroxylation at C-7 proceeds stereospecifically with retention of the pro-2R hydrogen of MVA as was seen in the Coscia's experiment mentioned in the preceding section (see Chart 4).

The following are accounts of further experiments which established the precursorship of loganic acid (10) (or loganin (8)) for the biosynthesis of secoiridoid glucosides. As described in the introduction, Battersby's corroboration[26,27] of the incorporation of loganin (8) into indole alkaloids made the first, and the most important recognition on this subject, but we will not deal with this work further here. Coscia et al.[31] clarified in the work mentioned above that loganic acid biosynthetically prepared by the administration of (2-^{14}C;4R,4-^{3}H)-MVA to Swertia caroliniensis was directly incorporated into gentiopicroside (6). Inouye et al.[42a, 43b] and Gröger et al.[46] independently established that (10-^{3}H)- and (9-^{14}C)-loganin (8) were incorporated

* The results obtained by both groups are apparently inconsistent with each other. They are, however, practically compatible as, e. g., two per cent conversion of loganin (8) into secologanic acid (11) in Coscia's experiment is within the experimental error of Battersby's data.

into gentiopicroside (6) in Gentiana triflora var. japonica and G. petiolata, respectively. Inouye et al.[43b, 47] further reported the incorporation of (7-^{3}H)-loganin (8) into morroniside (2) in G. thunbergii and (10-^{3}H)-loganin (8) into jasminin (21) in Jasminum primulinum. Battersby et al.[9] clarified that the tritium of (7-^{3}H)-loganin (8) was retained at the C-7 position of secologanin (5) in Vinca rosea.

Here we also may mention of Popov's proposal[48] for the biosynthetic precursorship of gentioside (22), isolated along with gentiopicroside (6) from several Gentiana plants, to 6 based upon their finding of the reincorporation of radioactive 22 obtained by the incubation of the plant under $^{14}CO_2$ atmosphere into 6. The counterevidence to this proposal will be given afterwards.



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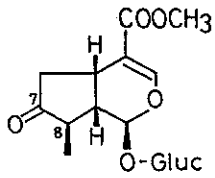


(23)

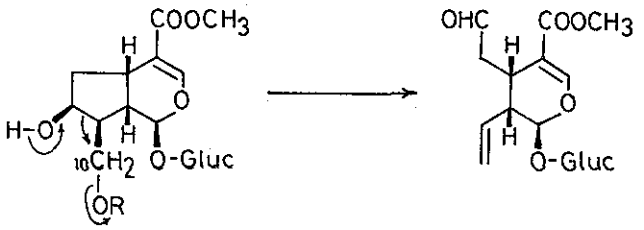
Chart 9

As described above, it has been clarified that 7-deoxyloganic acid (20) (or 7-deoxyloganin (19)) and loganic acid (10) (or loganin (8)) are biosynthetic key substances intervening between the acyclic terpenes and the secoiridoid glucosides. The next problem is the mechanism of the ring cleavage of loganin (8) giving rise to secologanin (5).

The ring cleavage could be considered to take place on one of

the following four types of substances: (i) 7-dehydrologanin (23), (ii) 7,8-dihydroxy compound such as gentioside (22), (iii) 10-hydroxyloganin (24) or (iv) loganin (8) itself.

The way through (i) is ruled out by the above mentioned fact that the tritium on C-7 of loganin (8) is retained in seco-iridoids[9,43b,47] or in indole alkaloids[49]. The counterevidence for the path through (ii) will be described later. The route through (iii) shown in Chart 10 was proposed by Battersby[50] in 1966 assuming that the ring cleavage would be caused through the facile elimination of the phosphorylated 10-hydroxy group of compound (25). Several attempts in our laboratory to convert



(24) R=H
(25) R=H_2PO_3

(5)

Chart 10

asperuloside or geniposide into the glucoside (24) have been unsuccessful. Though Tietze succeeded in 1973 in the total synthesis of this not easily obtainable substance[51], which opened up a way to the biosynthetic experiment, we have not yet received any report on the administration experiment using this substance. However, he reported that on alkali treatment of tosylates 26 and 27 derived from 10-hydroxyloganin aglucone-1-O-methyl ether and the 7-epi compound, only 27 underwent ring cleavage to give

secologanin-type substances 28 and 29, while 26 gave an oxetane-type substance (30)[52].

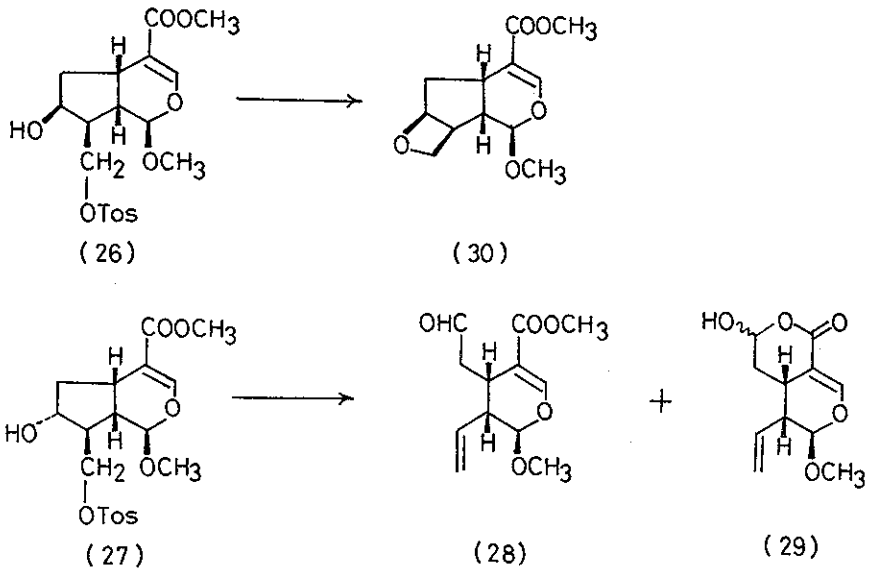


Chart 11

If the cleavage would occur through (iv), two ways could be expected: a radical fission or a cleavage initiated by the abstraction of a hydride on C-10. Lead tetraacetate oxidation of the four possible C-7 and C-8 stereoisomers of loganin aglucone-1-O-methyl ether attempting to convert them into the seco-type substances by Partridge et al.[53] revealed that these substances once underwent radical fission but the spontaneous recyclization hindered them from acquiring the desired seco-type substance.

Recently, Inouye et al. administered (7,8-$^{3}H_{2}$)-7-deoxyloganic acid (20) to Lonicera morrowii (containing secologanin (5)), Cornus officinalis (containing loganin (8) and morroniside (2)) and Gentiana thunbergii (containing morroniside (2)) and isolated

radioactive glucosides from these plants, respectively. Subsequently, secologanin (5) was converted into sweroside tetraacetate (31) and secologanoside tetraacetate dimethyl ester (32), while loganin (8) and morroniside (2) were converted into 7-dehydrologanin tetraacetate (33) and kingiside tetraacetate (34), respectively. Examination of the radioactivity in these substances revealed that the tritium labeling on C-7 and C-8 retained intact in all these glucosides 2, 5 and 8[54]. Hutchinson[55] also clarified that the tritium labeling on C-8 of (6,8-$^{3}H_{3}$)-loganin (8) was retained during the biosynthesis of an indole alkaloid camptothecin. All these results definitely exclude routes (i) and (ii). To decide the route between (iii) and (iv) on which the ring cleavage takes place is a problem for the future.

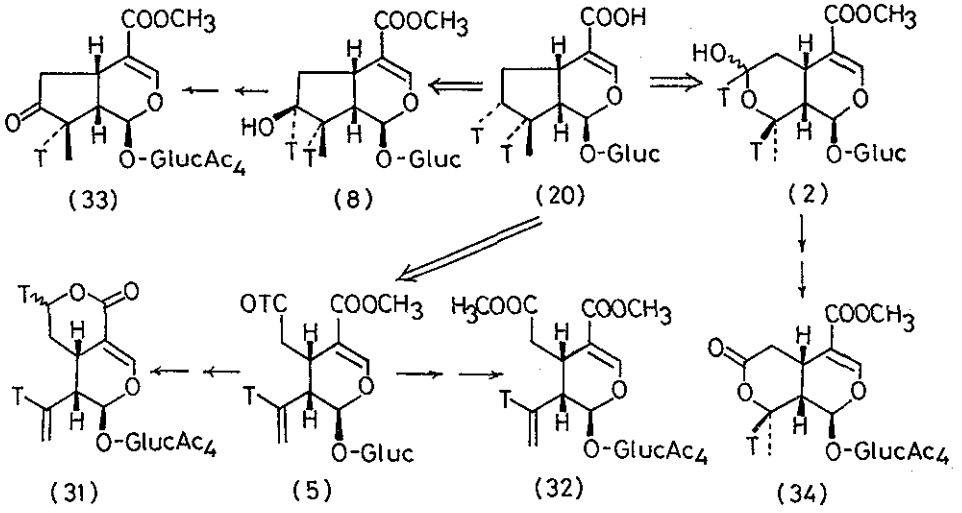


Chart 12

IV Consideration on the biosynthetic pathway of each group of glucosides at the later stage after formation of the secoiridoid skeleton

1. Sweroside-type glucosides

Besides 1, 5, 6, 9, 11, 12, 13, 14 and 15, various substances such as bakankosin (35)[56,57], secologanoside 11-methyl ester (36)[58], amarogentin (37), amaroswerin (38)[59], amaropanin[60], trifloroside[61], cantaleyoside[62] and centapicrin[63] also belong to this type. These glucosides are quite widely distributed in plants centering around Gentianaceae. The above described studies by Inouye et al. and Coscia et al. have already established the outline of the biosynthetic pathway of these substances.

Along with the confirmation of the incorporation of (10-^{14}C)-sweroside (1) prepared by the chemical modification of sweroside (1) into several alkaloids by administering this glucoside to several plants such as Vinca rosea, Inouye et al. recognized the incorporation of the same glucoside into gentiopicroside (6) in Gentiana scabra in a high percentage amounting to 40 %[64], They recently also succeeded in the chemical conversion of secologanin (5) into bakankosin (35) by reductive amination[57]. Although no report on the direct administration of secologanin (5) into the plant to examine the incorporation into glucosides of this type has so far appeared, there is no room to doubt the key intermediacy of secologanin (5) for the formation of this series of substances. Therefore, in view of the above described facts, it is evident that the biosynthetic pathway of this group of substances is that shown in Chart 13. Incidentally, the biogenesis

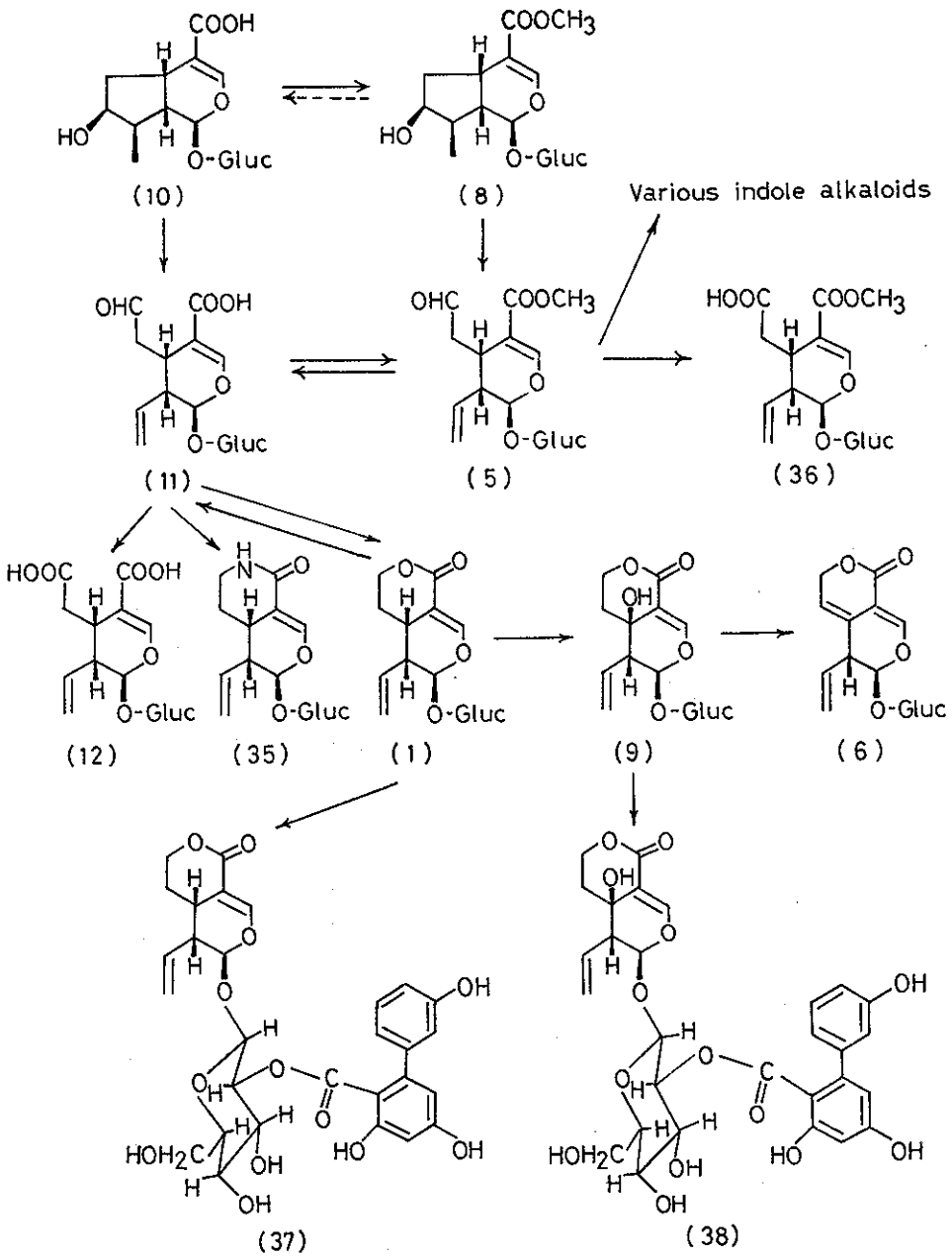
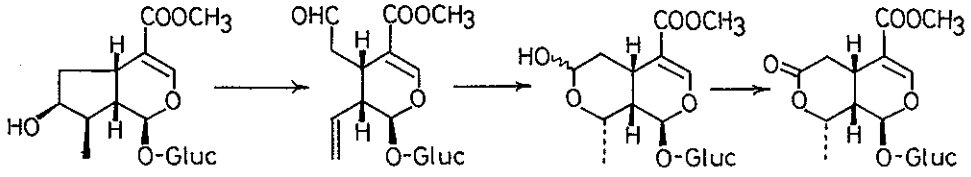

COOH
HO
O-Gluc
(10)
COOCH3
HO
O-Gluc
(8)
Various indole alkaloids
OHC
COOH
O-Gluc
(11)
OHC
COOCH3
O-Gluc
(5)
HOOC
COOCH3
O-Gluc
(36)
HOOC
COOH
O-Gluc
(12)
O-Gluc
(35)
O-Gluc
(1)
OH
O-Gluc
(9)
O-Gluc
(6)
OH
HO
OH
HOH2C
OH
OH
(37)
OH
HO
OH
HOH2C
OH
OH
(38)

Chart 13

of the diphenylcarboxylic acid moiety of amarogentin (37) and amaroswerin (38), (amaropanin and centapicrin being also their congeners), has been supposed to follow the route starting from m-hydroxybenzoic acid and malonate[59].

2. Morroniside-type glucosides

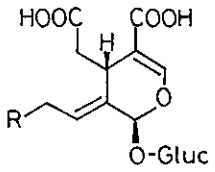
Both glucosides morroniside (2) and kingiside (39) were first isolated from Lonicera morrowii[6]. Afterwards, the former was isolated from several plants of the genera Gentiana[65], Cornus[66] etc. Comparison of the structures of both substances enabled us to suppose that the hemiacetal compound morroniside (2) first formed from secologanin (5) would be converted into kingiside (39) by the successive oxidation. Inouye et al.[43b,47] demonstrated the incorporation of (carbo-^{14}C-methoxy)-secologanin (5) into morroniside (2) in C. officinalis. Coupled with the fact described in section III that (7-^{3}H)-loganin (8) was incorporated into morroniside (2) in G. thunbergii, this result suggests the biosynthetic pathway of morroniside (2) and kingiside (39) can be represented as shown in Chart 14.



(8) (5) (2) (39)

Chart 14

3. Oleuropein-type glucosides



(40) R=H
(41) R=OH

Chart 15

Glucosides of this type comprise the oleoside (40)[8] or 10-hydroxyoleoside (41) moiety as the basic skeleton. Besides the above described oleuropein (3) and jasminin (21)[67], several glucosides such as nuezhenide[68], ligustroside (42), 10-hydroxy-ligustroside (43)[69], 10-acetoxyligustroside (44) and 10-acetoxy-oleuropein (45)[3] belong to this group. All these glucosides except jasminin (21) are the ester of p-hydroxy- or 3,4-dihydroxy-phenethyl alcohol. Up to now, they have been found only in the plants of the Oleaceae. On the basis of the finding obtained in the chemical correlation of oleuropein (3) with asperuloside establishing the absolute structure of the former, Inouye et al.[43] supposed, as a biosynthetic route for these glucosides, a direct Baeyer-Villiger-type oxidation of dehydrologanin (23) to give 8-epikingiside (46) followed by the dehydration yielding oleoside (40). Frequent occurrences of natural products which seem to be formed by the Baeyer-Villiger-type oxidation[70,71] coupled with the constant appearance of the 7-carboxyl structure in the oleoside-type glucoside also gave bases for this.

On the respective administration of (8-^{3}H)-8-epikingiside (46)

and (8-^{3}H)-kingiside (39) to Jasminum primulinum they first found that the incorporation of both substances into jasminin (21) was equal. On the simultaneous administration of (carbo-^{14}C-methoxy)-8-epikingiside (46) and (carbo-^{3}H-methoxy)-kingiside (39) in Olea europaea, they further recognized that both 46 and 39 were also incorporated into oleuropein (3) retaining intact ^{3}H/^{14}C ratio of the substrates. These results are incompatible with the expectation that the biosynthesis would proceed stereospecifically and hence almost excluded the possibility of the intermediacy of 8-epikingiside (46) for the biosynthesis of oleoside-type glucosides. However, subsequent experiment administering (carbo-^{14}C-methoxy)-secologanin (5) to the same plant showed that this substance was incorporated into oleuropein (3) more effectively than epikingiside (46) or kingiside (39). From the above described results, it is most probable that oleoside-type substances are

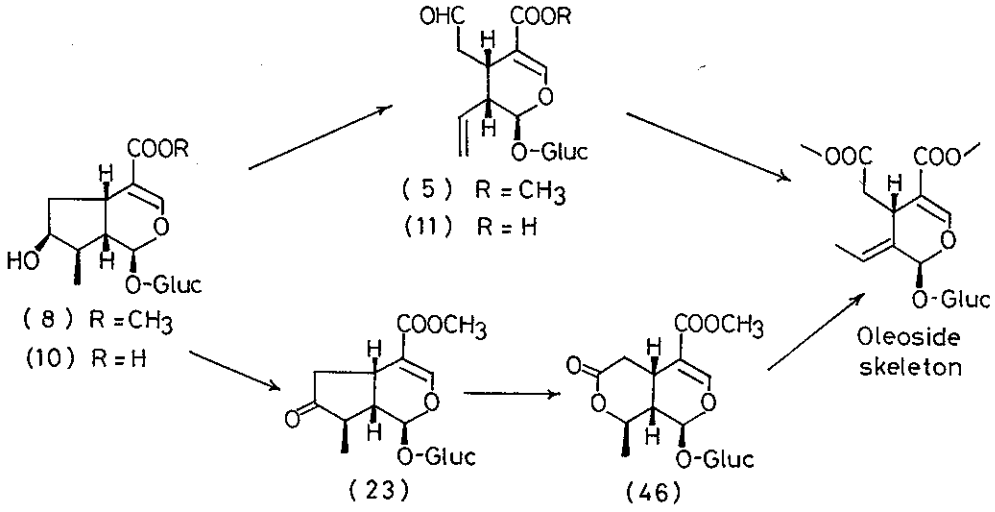


Chart 16

rather biosynthesized via secologanin (5) than 8-epikingiside (46)[43].

Though the 10-hydroxyoleoside-type glucosides were isolated since 1972 after finishing the above described experiment, Inouye et al.[72] recently isolated the 10-aldehyde compound (47) from Ligustrum japonicum which is also belonging to the Oleaceae. The biogenesis of this substance could be rationalized by assuming the epoxidation of the secologanoside (12) type substance* followed by the opening of the epoxide ring and a hydride transfer to yield the aldehyde (47). On this assumption, the formation of the 10-hydroxyoleoside-type glucoside could be explained by the cleavage of the epoxide ring followed by the deprotonation and that of the oleoside-type substance by the cleavage of the same epoxide ring to the opposite direction followed by dehydration. Stereochemical considerations require the epoxide ring to assume the configuration shown in Chart 17 to attain the 8-10 double bond of oleoside- and 10-hydroxyoleoside-type configuration at the final steps of the respective reactions.

Though much work, such as the administration experiment with the epoxide for the corroboration of the proposed biosynthetic pathway remains to be done, it is thus most likely that the

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* Secologanoside (12) or its methyl ester (36) could be subjected to epoxidation, possibly after esterification of the 7-carboxyl group with phenethyl alcohol.

biosynthetic route to oleoside- and 10-hydroxyoleoside-type glucosides also passes through secologanin (5) and secologanoside methyl ester (36) (or secologanic acid (11) and secologanoside (12)).

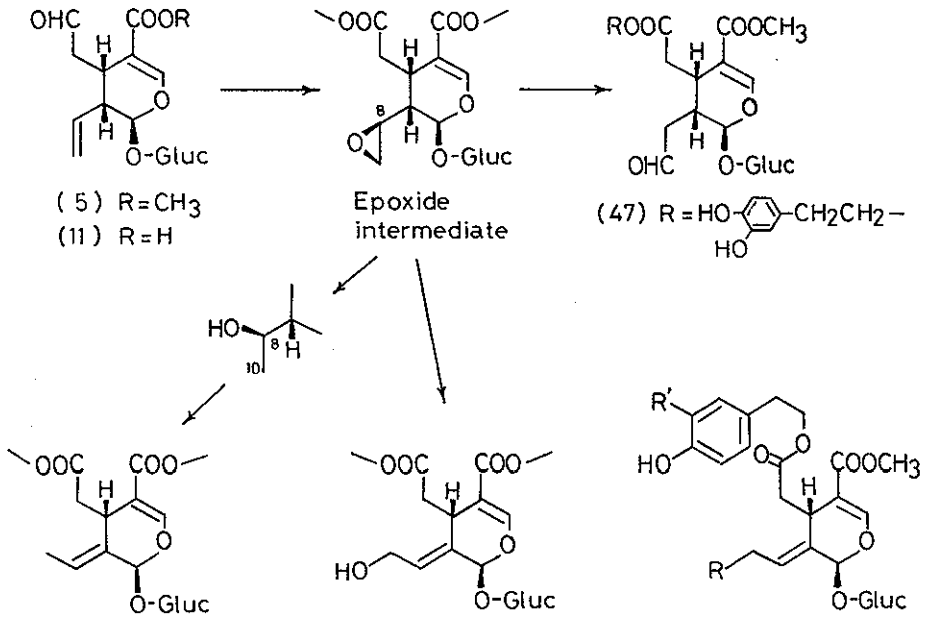


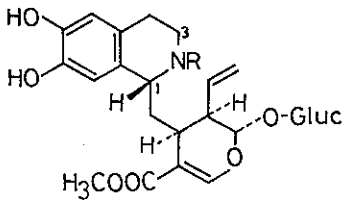
Chart 17

V Consideration on the biosynthetic pathway of the alkaloidal glucosides bearing a secoiridoid skeleton

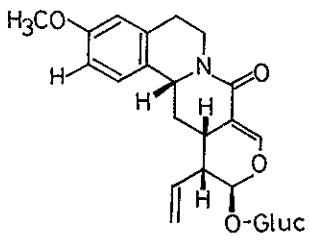
As these glucosides should preferably be dealt with in the realm of the successively formed indole alkaloids, they will be only briefly reviewed here.

A total of more than twenty glucosides of this type may be classified into the isoquinoline and the indole series. However, those belonging to the former are only ipecoside (16)[73] which was found from Cephaelis ipecacuanha (Rubiaceae) as a first example of the alkaloidal glucoside of this series, and alangiside (48)[74] isolated from Allangium lamarckii (Alangiaceae). Indole series glucosides are further classified into two groups according to the structure of the non-terpenoid portion being tryptamine or tryptophan. Those which belong to the tryptamin series are vincoside (4)[36], isovincoside (strictosidine) (49)[36,75], vincoside lactam (50)[76], 10-β-D-glucosyloxyvincoside lactam (51)[77], cadambine[78], isodihydrocadambine[79], palinine[80] etc., occurring in the Apocynaceous plants of the genera Vinca and Rhazya as well as the Rubiaceous plants of the genera Anthocephalus, Palicourea etc., while the tryptophan series substances are cordifoline (52)[81], desoxycordifoline (53)[82], rubenine (54)[83], 5α-carboxy-strictosidine[84], 3α,5α- and 3β,5α-tetrahydrodesoxycordifoline lactam[85], desoxycordifoline lactam[86], macrolidine[87] etc., most of which have been isolated from the plants of the genus Adina (Rubiaceae).

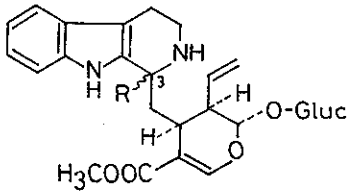
Among these alkaloidal glucosides, only ipecoside (16), vincoside (4) and isovincoside (49) have been precisely examined,



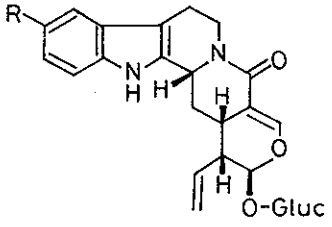
(16) R = Ac
(55) R = H



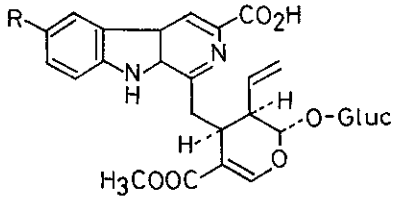
(48)



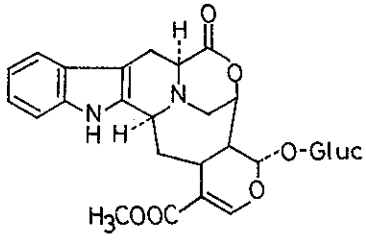
(4) R = β-H
(49) R = α-H



(50) R = H
(51) R = β-D-glucosyloxy



(52) R = OH
(53) R = H



(54)

Chart 18

especially by Battersby and his colleagues on the biosynthetic pathway. Therefore, this section deals with topics centering on these three alkaloids.

The structure of ipecoside (16) suggests that this substance should be biosynthesized by the Pictet-Spengler-type condensation of 3,4-dihydroxyphenethylamine (dopamine) with secologanin (5). Actually, through the administration experiments with (2-^{14}C)-geraniol, (carbo-^{3}H-methoxy)-loganin (8), (9-^{14}C,carbo-^{3}H-methoxy)-loganin (8), (7-^{3}H)-loganin (8), (carbo-^{3}H-methoxy,6-$^{3}H_2$)-secologanin (5), (3-^{14}C)-desacetylipecoside (55) etc., it was revealed that secologanin (5) biosynthesized by way of the route described above is converted into desacetylipecoside (55), the N-acetylation of which terminates the biosynthesis of ipecoside (16)[37,88].

On the other hand, vincoside (4) and isovincoside (49) were first obtained synthetically by the condensation of secologanin (5) with tryptamine. The occurrence of both alkaloids in Vinca rosea was then demonstrated by the dilution analysis and they were finally isolated from the plant[36]. Almost simultaneously with this work, isovincoside (strictosidine) (49) was isolated also from Rhazya stricta by Smith[75].

The problem of the configuration at C-3 of these alkaloidal glucosides, which once caused confusion and is one of the crucial points in considering the biosynthesis of indole alkaloids successively formed, was solved independently by three main groups, Battersby et al.[73b], Smith et al.[89] and Brown et al.[90], working on the alkaloidal secoiridoid glucosides. Though it is quite

obvious that vincoside (4) and isovincoside (49) are biosynthesized by the condensation of secologanin (5) with tryptamine, the incorporation of (7-^{3}H)-loganin (8) into both vincoside (4) and isovincoside (49) was actually confirmed by Battersby et al. They also clarified by the administration of (carbo-^{3}H-methoxy)-vincoside (4) and isovincoside (49) to Vinca rosea that only vincoside (4) having 3β hydrogen could be the precursor of the Corynanthe, Aspidosperma and Iboga type alkaloids[36]. This fact means that the conversion of the configuration at C-3 of vincoside (4) takes place during the transformation of 4 into these three types of indole alkaloids. As the C-3 proton of vincoside (4) originated in the C-7 proton of loganin (8), these findings, in the light of evidence from the incorporation experiments of (7-^{3}H)-loganin (8) into several alkaloids, urged them to conclude that the process should be going on with retaining the C-3 proton[49]. They also established that during the biosynthesis of cephaeline and emetine from desacetylipecoside (55), the C-1 proton of the latter was retained under inversion of configuration in the former two substances[37]. Recently, Brown et al.[91] found during a synthesis of Corynanthe type alkaloids that an inversion of the configuration at C-3 occurred with retention of hydrogen and furnished a suggestion on the mechanism of the in vivo reaction.

On the other hand, Hutchinson et al.[55] recently reported that, contrary to the three major groups of indole alkaloids, isovincoside (49) a 3α hydrogen bearing glucoside is incorporated into camptothecin.

Many excellent reviews on the biosynthetic pathway of several indole alkaloids formed successively from vincoside (4) are available[92-95].

VI Conclusion --- Problems remaining unsolved

As described above, we have understood the outline of the biosynthetic pathway of the secoiridoid glucosides. However, problems such as the detailed mechanism of the cyclization of acyclic monoterpene to iridoid *via* hydroxynerol, the process of the ring cleavage of loganin (8) to secologanin (5) and the formation process of oleoside and 10-hydroxyoleoside type glucosides after cyclopentane ring cleavage remain unsolved. Even if the entire biosynthetic sequences are clarified, studies on the enzymatic level on each biosynthetic step would be required, following those that have already been undertaken.

Iridoid and secoiridoid glucosides as well as indole alkaloids are widely distributed in many dicotyledons, especially in the sympetalous plants. As far as we know, among the various plants so far examined no genus other than *Cornus* and *Davidia** contain secoiridoid glucosides (including indole alkaloids) together with iridoid glucosides in a highly oxidized state such as

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* Although Jensen et al. reported the co-occurrence of substances belonging to both groups in the monotypic *Davidia* plant, no details have been made available. cf. S. R. Jensen, B. J. Nielsen, *Botaniska Notiser*, 1975, *128*, 148.

asperuloside, geniposide etc. In these cases, however, co-occurrences of both types of substances in the same genus have been reported. We have already established that loganin (8) can be a precursor of iridoid glucosides such as asperuloside[42b]. Worthy of interst, therefore, is the fact that, in spite of having the common precursor (8), the iridoid glucosides comprising a highly oxidized cyclopentane ring scarcely coexist in the same genus or species of plant with the secoiridoids and the indole alkaloids. These findings remind us of the relevant results pointed out before in a footnote that, on administration of (2-^{14}C)-MVA, almost equal distribution of labeling between C-3 and C-11 has been observed in all the secoiridoids and the indole alkaloids biosynthesized through loganin (8), while such randomization of labeling does not occur in some iridoid glucosides such as asperuloside. Exclusive occurrence of both groups of substances in a plant could be a phenomenon closely related with such a biosynthetic mechanism, the elucidation of which would be a remaining intriguing problem also from a point of view of chemosystematics featured by substances of the iridoid and secoiridoid series.

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