BIOSYNTHESIS AND METABOLISM OF SOME MATRINE ALKALOIDS IN *Goebelia pachycarpa*

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Information is given on the biosynthesis, metabolism, and interconversion of a number of matrine alkaloids isolated from *Goebelia pachycarpa*. The role of amino acids and other organic acids in the formation of these alkaloids is discussed.

The chemical structures of the alkaloids of various groups are extremely diverse, and, together with alkaloids of simple structure, successively more complicated structures are found going as far as high-molecular-weight polycyclic compounds [1, 2]. However, in spite of this diversity, the presence of the simplest heterocycles with pyridine, piperidine, and pyrrolizidine rings as the initial structural units in the molecules of these compunds is characteristic.

The alkaloids isolated from different plants differ in their structure, and it is therefore impossible to put forward a single hypothesis about their formation.

The elucidation of the routes of the biosynthesis of alkaloids is one of the urgent questions of the chemistry of natural compounds. The biosynthesis of alkaloids includes within itself such important processes as the decarboxylation and deamination of amino acids and diamines and also cyclization reactions. In the matter of the biosynthesis of alkaloids, various authors have expressed a number of hypotheses in which attempts have been made to connect the formation of alkaloids with the synthesis of proteins or carbohydrates [3-5]. It must be mentioned that up to the present time no deep analysis of the biosynthesis and mutual conversion of alkaloids has been given. And, in our opinion, the solution of precisely these questions would give useful information on the function of alkaloids in the plant organism. In this paper we consider questions of the biosynthesis and interconversions of the alkaloids of the matrine series in *Goebelia pachycarpa* Schrenk.

Isolation of Alkaloids Containing Matrine Skeletons

Alkaloids containing matrine skeletons have been isolated from the plants of two families: Leguminosae and Berberidaceae. The first representative of this group — matrine — was isolated in 1889 from *Sophora flavescens* Ait. It can exist in α-, β-, γ-, and δ- forms [1], but it is usually the α- form that is encountered in plants. Matrine is a strong monoacid base containing two ditertiary nitrogen atoms one of which is present in a lactam group, while the presence of the other has been shown by the preparation of sodium and potassium matrinates and other transformations [6, 7, 8, 9]. The reduction of matrine with lithium tetrahydroaluminate has given matridine [10, 11], and in 1961 it was obtained synthetically. The structure of matrine has been shown to be

At the present time, 30 alkaloids containing the matrine skeleton have been isolated and their structures have been demonstrated [2]: matrine, matrine N-oxide (ammothamnine), leontine, sophoronol, l-sophoridine, d-sophoridine, sophocarpine, sophoramine, isosophoramine, neosophoramine, sophocarpidine, (sophocarpine N-oxide), goebeline, leontalbine, leontalbinine, albertine, albertidine, albertamine, leontalbamine, leontismine, darvasine, darvasamine, darvasoline, isoleontalbine, lehmannine, 3α-hydroxysophoridine, sophorodine N-oxide, sophorbenzamine, 13,14-dehydrosophoridine, and 13,14-dehydrosophoridine N-oxide.

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Goebelia pachycarpa contains two groups of quinolizidine alkaloids: with matrine and with sparteine skeletons. The matrine groups differ from one another in their saturation, the presence of functional groups, and the conformation of the carbon–nitrogen skeleton. In solving the question of the formation of alkaloids derived from matrine in plants, the possible routes for the biosynthesis of the heterocyclic structures based on two condensed quinolizidine nuclei (systems) must be considered. On the other hand, the quinolizidine nucleus can be considered as two condensed piperidine rings.

Precursors of the Alkaloids

A number of workers have used various compounds, in addition to amino acids and diamines, with the aim of finding various precursors of the alkaloids: acetic acid [4], malic, oxalic, and tartaric acids [4], and carbohydrates. It was found that citric, oxalic, and tartaric acids do not take part in the biosynthesis of the quinolizidine alkaloids [13]. In view of this fact, we have suggested that if organic acids participate in the biosynthesis of the quinolizidine alkaloids the precursors must be compounds with structures close to lysine and its biological equivalent — cadaverine. If we take this as a starting point, then the most probable precursor of the alkaloids of *Sophora pachycarpa* must be considered to be glutaric acid, which, in addition to having a structure analogous to those of lysine and cadaverine, is also biologically linked with them [14]. To elucidate the interrelationship of the alkaloids with organic acids, the qualitative composition of the organic acids and the quantitative amount of citric acid in *Sophora pachycarpa* collected in the Bukhara province [15] in several phases of development have been studied. The quantitative composition of the di- and tricarboxylic acids has also been studied [16].

The quantitative determination of the free organic acids was carried out by a known method [17]. The results [16] show that the amount of glutaric acid is, on the whole, low throughout the vegetation period, and the maximum amount of it is present in the flowering period.

Our observations have shown that malic and citric acids, together with tartaric acid, make up the bulk of the sum of the di- and tricarboxylic acids throughout the vegetation period, while the amount of malic acid considerably exceeds that of citric acid in some phases. For example, at the end of vegetation the amount of malic acid was more than 70% of the combined sum of di- and tricarboxylic acids. It obviously accumulates mainly in the leaves, since after they have fallen the amount of malic acid in the plant material decreases sharply.

Fumaric acid was detected in the plant only in the stages of the ripening of the seeds and at the end of the vegetation period. This is possibly connected with its participation in the formation of aspartic acid, since the amount of this acid reaches a maximum at the end of seed ripening. Information on the dynamics of the accumulation of amino acids [8] and other organic acids and alkaloids during the vegetation process makes it possible to use the isotope method on a more concrete basis for studying the biosynthesis of the alkaloids.

The most convenient time of introducing radioactive lysine and cadaverine into a plant is the beginning of the phase of the maturity of the plant. As mentioned above, some of the possible precursors of the alkaloids are amino acids, and therefore the study of the dynamics of the accumulation of amino acids in the plant organism is of definite interest [19-25]. This has been confirmed by the inclusion of several labeled amino acids in the alkaloid molecules. In our experiments [18], we convinced ourselves that the amino acid lysine and its biologically equivalent cadaverine are actually included in the alkaloids of *Sophora pachycarpa*. But the specific activities of the latter were low, which obviously depends on the factor of the intensity of the synthesis of the alkaloids from amino acids in different phases of the development of the plant. The question naturally arises as to the optimum times of introducing labeled amino acids into the plant in order to obtain alkaloids with the greatest activity. To determine such times we investigated the quantitative compositions of the free amino acids in 14 samples of the epigeal part of *Goebelia pachycarpa* taken in different periods of development [18]. The amount of each amino acid in the mixture investigated was determined from the ratio of extractions of a standard solution and that under investigation. The results, which are given in [18] show that the amino acid composition of *G. pachycarpa* fluctuates widely, the amount of lysine gradually increasing during the budding period and decreasing towards the end of flowering. At the end of flowering, this amino acid accumulates and its amount reaches a maximum by the beginning of the ripening of the

fruit. In the fruit-bearing period, the amount of lysine falls sharply and it remains on a level until the end of the vegetation period. The dependence of the formation of alkaloids in plants on the carbohydrate metabolism is shown above all in the interrelationship of the nitrogen metabolism with the Krebs cycle [26], as a result of which a number of the amino acids necessary for the construction of the alkaloids are formed. Observations on the amounts of carbohydrates in the plants have shown their direct participation in the biosynthesis of the alkaloids [27].

In 1912, Trier showed that the initial substances for the biosynthesis of alkaloids are not only amino acids but also even simpler compounds [28]. Schoepf [29] proposed a scheme which envisaged the formation of alkaloids from carbohydrates via hydroxy acids with the participation of ammonia [29]. A possible participation of carbohydrates and organic acids in the biosynthesis of alkaloids has been shown by other workers [30, 31].

We have studied the qualitative composition of the carbohydrates of *G. pachycarpa* for the first time. During the investigation, in 19 samples of epigeal and underground parts at various periods of vegetation we detected nine carbohydrates. Of them seven were identified: sucrose, fructose, raffinose, glucose, arabinose, galactose, and maltose. Glucose and fructose were present in all the periods considered and these sugars apparently participate actively in the vital activity of the plants.

To elucidate the connection of lysine, cadaverine, glutaric acid, and carbohydrates with alkaloids, it was necessary to determine the amounts of alkaloids present in the various vegetation periods.

Localization and Dynamics of the Alkaloids

The localization of the alkaloids depends on the species of plant. They may be concentrated in the leaves, in the roots, in the fruit, in the seeds, or in the stems. An accumulation of alkaloids in individual parts of plants is still not a proof of their synthesis in those particular organs, and therefore the localization of the alkaloids must be considered in close connection with their biosynthesis.

The majority of workers tend to the opinion that the synthesis of alkaloids takes place in the roots, and this has been confirmed by experiments with grafts of an alkaloid-forming plant onto a stock not forming alkaloids [13, 32, 33].

The qualitative and quantitative compositions and localization of the alkaloids in shoots of *Goebelia pachycarpa* were first investigated by the present author and his colleagues [34]. It was shown that alkaloids with a matrine skeleton — matrine, matrine N-oxide, sophocarpine, sophocarpine N-oxide, and sophoramine — are localized mainly in the epigeal part of the shoots, while matrine N-oxide is present equally in the roots of the shoots. This is possibly explained by the special role of matrine N-oxide in oxidative processes of the metabolism of the shoot.

A quantitative determination of the matrine alkaloids showed that in the period of initial growth the main alkaloids are present in the epigeal and underground parts of the plants in approximately equal amounts in the period of vigorous flowering and fruit-bearing. The maximum synthesis and accumulation of them take place in the epigeal part. During this period the amount of matrine makes up 18.9% of the sum of the alkaloid. Beginning with the fruit-bearing period, the amount of matrine alkaloids gradually decreases, and the proportion of matrine falls to 8.7% of the sum of the alkaloids [35].

This has permitted the hypothesis that in the study of the biosynthesis of the alkaloids of *G. pachycarpa* it is best to introduce labeled lysine and its analogs into the plant in the period between the end of vegetation and the beginning of the ripening of the fruit, since it is precisely at this time that one may expect a vigorous synthesis of the matrine alkaloids from the above-mentioned precursors.

Biosynthesis of the Alkaloids

From the time when the structures of the alkaloids were first established, organic chemists began to draw up hypotheses concerning their biosynthesis. The beginning of the development of the question of the biosynthesis of alkaloids is Trier's hypothesis on a possible link between amino acids and alkaloids [28].

The classical work on the biosynthesis of alkaloids is that of Robinson [36], who confirmed and supplemented Trier's theoretical predictions concerning the synthesis of alkaloids from amino acids. The formation of alkaloids takes place in plants at the expense of amino acids with the participation of diamine oxidases.

A definite advance in this field was made by the investigations of Schoepf [29], who performed a number of syntheses of alkaloids under physiological conditions [29].

Let us dwell in more detail on matrine, since this alkaloid is the first representative of this type. All the alkaloids of the matrine series are, in our opinion, formed from the alkaloid matrine. As mentioned above, *Goebelia pachycarpa* contains two groups of quinolizidine alkaloids — those with matrine and those with sparteine skeletons.

At the present time, the following alkaloids have been isolated from this species of *Goebelia*: cytisine [7], pachycarpine [38-40], sophoramine [11], sophocarpine [39, 41, 42], matrine N-oxide [37, 39, 43], isosophoramine [44-46], matrine [39, 41], goebeline [47-50], sophocarpine N-oxide [51], N-methylcytisine [52, 53], pachycarpine N_1-oxide [54], pachycarpine N_{16}-oxide [54], sophorbenzamine [55], a base N_1 [47], and bases A_1, A_2, and A_4 [44].

Several opinions exist on the question of the formation of the quinolizidine alkaloids and, in particular, those with a matrine skeleton [19, 20, 56-58]. However, in all cases they start basically from two different hypotheses concerning the biosynthesis of the matrine alkaloids. According to the first hypothesis, the matrine skeleton is biosynthesized from three molecules of lysine, the lupinine skeleton being formed first. Then, via a number of intermediate products, it is converted into matrine (route A). According to the second hypothesis, the precursors of the matrine alkaloids are two molecules of Δ^1-piperidine, which, on reacting with glutaraldehyde, form tetrahydroanabasine. Subsequently the matrine alkaloids are formed (route B) [20].

From our point of view, the formation of matrine and of the other matrine alkaloids must be preceeded by the formation of matridine.

Unfortunately, so far it has not been possible to isolate the intermediate compounds in the biosynthesis of matridine.

The presence of anabasine in *Leontice alberti* Bgl. [59] indicates the possibility of the formation of the alkaloids of the matrine series through anabasine. Then the biosynthesis of the matrine alkaloids is preceded by the formation of the matridine skeleton. Information on the biosynthesis of alkaloids of the quinolizidine series [19, 24, 35, 60-62] permits us to consider lysine and cadaverine and their biological equivalents as possible precursors of the alkaloids of *Goebelia pachycarpa*.

We have performed a series of experiments to study the biosynthesis of the alkaloids. A number of the above-mentioned compounds labeled at carbon were introduced into a shoot. Experiments with 10- to 15-day shoots [54] showed that cadaverine was incorporated in several alkaloids of the plant. The cadaverine was synthesized by Leete's method [63] with some modifications [54].

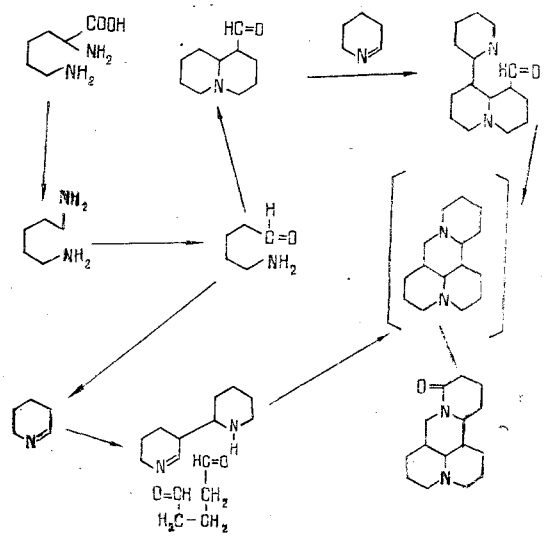


TABLE 1. Specific Radioactivities of the Alkaloids Isolated from Shoots

Compound	Activity, counts/min/mmole	% inclusion
[1,5-^{14}C]Cadaverine	$2.4 \cdot 10^7$	
10-15-day shoots		
Matrine	$3.72 \cdot 10^3$	0,015
Sophocarpine	$4.16 \cdot 10^3$	0,017
Sophoramine	$4.22 \cdot 10^4$	0,05
15-20-day shoots		
[1,5-^{14}C]Cadaverine	$6.25 \cdot 10^6$	
Matrine	$2.5 \cdot 10^4$	0,40
Matrine N-oxide	$5.6 \cdot 10^5$	8,88
Sophocarpine	$2.0 \cdot 10^4$	0,30
Sophocarpine N-oxide	$6.8 \cdot 10^4$	1,07
Sophoramine	$3.5 \cdot 10^4$	0,56

The total alkaloids were separated on a column of alumina and the individual bases were eluted with ethyl acetate. The alkaloids isolated were identified by comparing their R_f values and by mixed melting points. After the alkaloids had been identified, their specific radioactivities were determined.

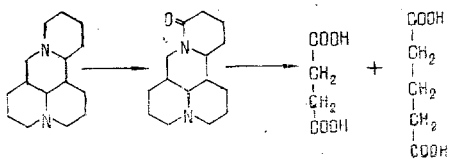
In view of the small weight of 10- to 15-day shoots and the correspondingly small yield of combined alkaloids, we were forced to modify the procedure for extraction and the separation of the individual alkaloids.

As can be seen from Table 1, the alkaloids were radioactive, which shows the participation of the [1,5-^{14}C]cadaverine in their formation. The greatest radioactivity was possessed by matrine and sophocarpine N-oxides. It is known that the N-oxides of the alkaloids are oxygen carriers and participate in the redox cycle [64, 65] and that they suppress the development of the causative agents of some diseases [66].

According to the literature, some quinolizidine alkaloids are formed by various interconversions. Some workers [67] consider that saturated compounds are first formed which, on being subsequently oxidized, are converted into oxidized forms: sparteine—lupanine—hydroxylupanine.

Admitting such a possibility for the formation of the matrine alkaloids, we have suggested that the synthesis of the most saturated alkaloids of the matrine series takes place first. To prove the validity of this hypothesis, we used the isotope method. Biosynthetically obtained matrine was reduced to matridine with the aid of lithium aluminum hydride [54].

After purification and identification, the matridine was introduced into *G. pachycarpa*. After exposure for three days, the combined alkaloids were extracted from the experimental plants and the matrine was isolated; as in the first case, it contained radioactive ^{14}C atoms. When matrine was oxidized with chromium trioxide, succinic and glutaric acids were obtained.



The succinic acid contained one, and the glutaric acid two, radioactive atoms. This fully confirms the hypothesis of the possibility of the conversion of matridine into matrine in the plant.

The results of an experiment performed under similar conditions with [^{14}C]matrine completely confirmed the validity of our hypotheses and those found in the literature.

Alkaloid	Activity, pulses/min/mmole	%
Matrine	$5.68 \cdot 10^5$	
Matrine N-oxide	$1.58 \cdot 10^4$	2.80
Sophocarpine	$1.2 \cdot 10^4$	2.11
Sophocarpine N-oxide	$9.43 \cdot 10^3$	1.66

Judging from the proportion of the inclusion of matrine into the alkaloids mentioned, the transformation of matrine in the plant must be represented by the scheme given.

For a definitive answer to the question of the biosynthesis and metabolism of the alkaloids of the matrine series in *Goebelia pachycarpa* we have carried out far-reaching studies. The maximum synthesis and the maximum accumulation of alkaloids are observed in the epigeal part in the period of flowering and fruit-bearing [35]. A study of the percentage inclusions of labeled precursors into the matrine alkaloids showed that in the periods under consideration an intensive biosynthesis of alkaloids takes place [35]. On investigating the role of organic acids in the biosynthesis of alkaloids, we introduced [1,5-^{14}C]glutaric acid into the plant:

Compound	Incipient Ripening of the Seeds	
	Activity, pulses/min/mmole	% inclusion
[1,5-^{14}C]Glutaric acid	$2.4 \cdot 10^7$	—
Matrine	$1.98 \cdot 10^3$	0.08
Matrine N-oxide	$1.9 \cdot 10^2$	0.003
Sophocarpine	$1.2 \cdot 10^3$	0.006
Sophocarpine N-oxide	$5.24 \cdot 10^2$	0.002
Sophoramine	$9.7 \cdot 10^2$	0.004

The results of a determination of the radioactivities of the alkaloids isolated after feed supplementation showed that the percentage inclusion of the [1,5-^{14}C]glutaric acid in them was very low. Consequently, it is not a direct precursor of the alkaloids of *G. pachycarpa* at the beginning of the seed-ripening phase. While mentioning the phase of development during which the experiment was carried out, we should like to emphasize that the negative result in the experiments with isotopes must be interpreted with caution. In all probability, the small inclusion of glutaric acid into the alkaloids is connected with its active participation in the three-carbon cycle or in the transamination process which, in its turn, must undoubtedly lead to a marked dilution of the isotopic label.

Interconversion of the Alkaloids

The capacity of plants for transforming "foreign" alkaloids into new ones has been shown by Nowacki et al. [68], Nolbezzyk [69], and Neumann [70].

Some legumes containing quinolizidine alkaloids include tetrahydroanabasine and lupinine derivatives as minor components. Tetrahydroanabasine is considered as an intermediate compound between the products of the cyclization of cadaverine and a tetracyclic quinolizidine alkaloid of the matrine series. The results of a study of the biosynthesis of the quinolizidine alkaloids has permitted the following conclusion to be drawn: The starting point for the biosynthesis is lysine, which is decarboxylated to a diamine — cadaverine — and this is then converted into a cyclic compound. These first steps are known from the experiments of Schütte et al. [71] and of Nowacki et al. [72]. It is known that cyclization follows decarboxylation. The percentage transformation of cadaverine into alkaloids is higher than that of lysine [73]. Willamann et al. [74] isolated matrine from *L. angustifolus*, which made it possible to suggest a mutual conversion of matrine alkaloids into sparteine alkaloids.

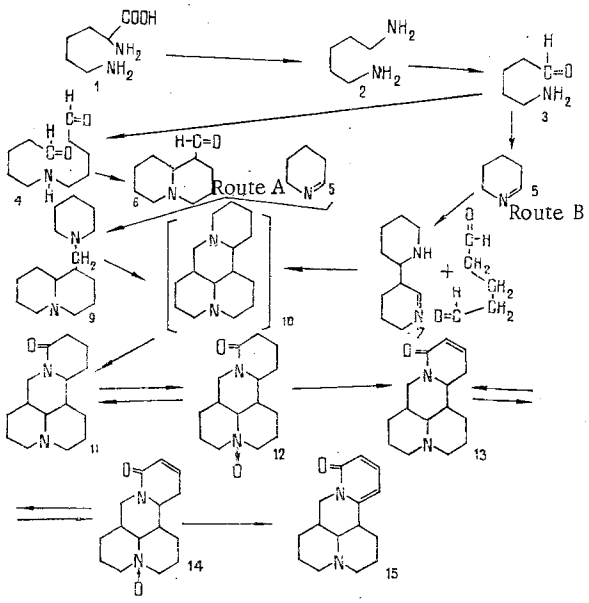
The results of our numerous investigations on the dynamics of the alkaloids and results from the literature indicate an undoubted biogenetic link between these groups of alkaloids. Characteristic for the plants studied is a high diversity of the alkaloids of the matrine group. A qualitative study has shown that such alkaloids as matrine, sophocarpine, and matrine N-oxide can be isolated from plants at practically any stage of development, beginning with the seeds and ending with the withered shoots at the end of the vegetation period. The amount of matrine in the total alkaloids is a maximum at the beginning of budding and the end of vegetation. In the early stages of development, the primary synthesis of matrine from lysine takes place, and the accumulation of matrine at the end of the vegetation period obviously takes place mainly through secondary synthesis. Attention is attracted by the fact that the amount of matrine alkaloids decreases in strict correspondence with the increase in the amount of pachycarpine and, conversely, with a decrease in the amount of pachycarpine,

the amount of matrine alkaloids rises. Such a relationship can be explained not only by interconversion of these alkaloids but also by a predominating process of the synthesis of one or other alkaloid in the different phases of the vegetation of the plant. It has been found that in all cases the amount of sophocarpine and sophoramine increases or decreases in accordance with the increase or decrease in the amount of matrine. This fact, and also the similarity of the structures of these alkaloids, has enabled us to suggest a capacity of the matrine alkaloids for interconversion. We assume that in *Goebelia pachycarpa* the first step is the synthesis of the most saturated alkaloid — matrine — which, subsequently undergoing oxidation, gives the less saturated forms. To elucidate this important question, we studied the biosynthetic links of some matrine alkaloids. The plants were fed with biosynthesized matrine and sophocarpine, and the alkaloids isolated were studied.

The results obtained after exposure for three days showed that matrine is converted successively into matrine N-oxide and sophocarpine by 7.15% and 5.1%, respectively. Sophocarpine is converted into sophocarpine N-oxide and sophoramine by 4.8% and 3.15%, respectively.

The results obtained after the oxidation of the isolated alkaloid show that their interconversions take place without intramolecular rearrangements [35].

The combination of facts given above permits us to put forward the following scheme for the biosynthesis of the matrine alkaloids in *Goebelia pachycarpa*:



Thus literature information and the results of our own investigations permit us to consider lysine and cadaverine as possible precursors of the alkaloids of *Goebelia pachycarpa*.

For a more far-reaching investigation of the alkaloids of the matrine series, feeding with suggested precursors must be carried out in the period of the incipient ripening of the seeds.

In an analysis of the results obtained it was established that, in their interconversion, the alkaloids of the matrine series do not undergo intramolecular rearrangements.

The finding of the alkaloids lupinine and anabasine together with alkaloids of the matrine series gives grounds for considering that the synthesis of the alkaloids takes place by two routes — A and B.

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