ALKALOIDS OF *Peganum harmala*

M. V. Telezhenetskaya and S. Yu. Yunusov

UDC 547.944/945

Peganum harmala L. is a perennial herbaceous plant. No single opinion has been formulated up to the present time concerning the systematic position of this genus. Thus, in the last century it was assigned to the families Geraniaceae and Rutaceae, while Engler considers it to be in the family Zygophyllaceae and A. A. Takhtadzhyan isolates it in a family Peganaceae [1].

The genus *Peganum* includes six species growing in territories from the Mediterranean to Mongolia and in central America. In the USSR, two species of *Peganum* are found: *P. harmala* in the south-eastern European part in the republics of Central Asia and Transcaucasia, and in southern Kazakhstan [2], and *P. nigellastrum* in eastern Siberia [3].

P. harmala has been studied biologically, anatomically, and morphologically by N. N. Sharakhimov [1]. The plant forms a multistem bush 60 cm high with a tap root penetrating into the soil to a depth of 2-4 m and having numerous lateral branches. The size of the roots is somewhat greater than that of the epigeal part. Anatomorphologic features of the structure of the roots, stem, and leaves indicate an extreme adaptation of the plant to a dry hot climate. Growth begins at the end of March—beginning of April. Budding takes place at the end of April and flowering at the end of May. One of the biological features of *P. harmala* is the long duration of the flowering period: June-August. Fruit-bearing begins from the middle of July. The seeds ripen in the second half of July-August. A single bush forms 280-440 capsules with 1600-3700 seeds. At the end of the fruit-bearing phase the leaves, and then the stems, begin to dry up. Vegetation finishes in September-October. *P. harmala* multiplies by seeds and, in several cases, by root suckers.

There is no reliable information on the alkaloids of *P. nigellastrum*, but the alkaloids of *P. harmala* have been studied in detail.

Harmel peganum is popular in the folk medicine of the East and has been used since antiquity. Some local names of this plant are: mogil'nik, adraspan, isrik, yuzarlik, khazaraspand, ispandi, kharmal [harmal], belobok, bibik, garman', and mariam-sakmela.

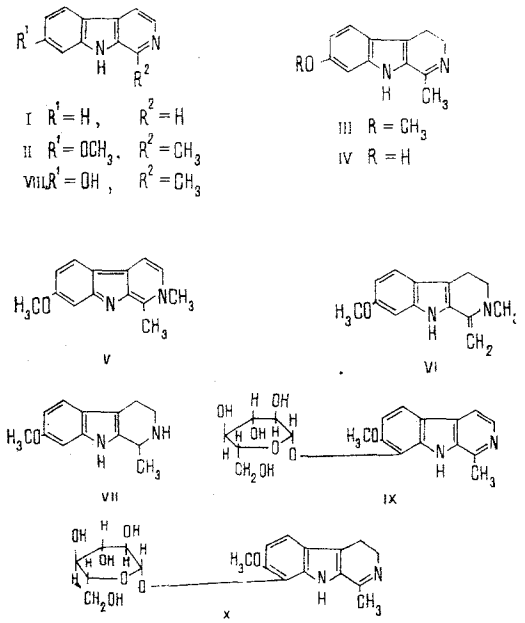
Harmel peganum is mentioned as a medical plant in the works of the celebrated medieval scientist Avicenna [4], and the sudorific, vermifuge, and narcotic action of the seeds have been described [5]. Baths of the herb are considered to be a good remedy for rheumatism, scabies, and skin diseases, and infusions and decoctions are taken internally for the common cold and malaria [6], and they also possess a sedative, anesthetic, antiinflammatory, and antiseptic action and are used in neurasthenia and nervous and epileptic attacks. An infusion of harmel peganum seeds is used together with flax seed in cases of asthma, and dyspnea, and the leaves are used for fomentations applied to swellings [7]. The smoke of the plant is used to fumigate dwellings for disinfection and for the treatment of catarrhal diseases. Special experiments have shown that the smoke possesses bacteriostatic properties in relation to the causative agents of typhoid fever, dysentery, and some other diseases [8]. The seeds yield a red dye for woollen fabric and an oil which is used in paint-making [5].

Alkaloids were first isolated from the seeds of *P. harmala* in 1841 by the Russian scientist F. Gebel', and they were called harmaline and harmalol. Then in 1847, another Russian scientist Zh. Fritche isolated a third alkaloid — harmine — from the seeds. However, the structures of these bases were shown only much later, in 1900-1920, thanks to the work of Fischer, Perkin, and Robinson. An account of the proof of the structure and the synthesis of these substances has been given in detail in monographs by A. P. Orekhov, T. A. Henry, Manske, and Boit [9]. Passages between harmine, harmaline, and harmalol have been effected. Harmine is obtained by the mild oxidation of harmaline. When harmaline is heated with hydro-

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 731-743, November-December, 1977. Original article submitted June 27, 1977.

0009-3130/77/1306-0613$07.50

chloric or phosphoric acid, it is converted into harmalol. The successive elimination from harmine of methoxy and methyl groups give norharmane, or β-carboline (I), which is the basis of these three alkaloids (Scheme 1).



Scheme 1

The structures of harmine, harmaline, and harmalol are illustrated by formulas (II-IV).

A feature of the carboline system is its capacity for forming anhydronium bases (V) by the action of alkali on alkyl halide derivatives. The alkylation of harmane was studied by Fischer, and then A. P. Orekhov and R. A. Konovalova [10] dealt with the alkylation of norharmine and harmaline. By the double alkylation of norharmaline in the reverse sequence they obtained two isomeric substances, as in the case of harmine, thereby showing that the methyl group at C-1 does not take part in the formation of anhydronium bases. In the case of harmaline, however, one and the same product was obtained. Consequently, in spite of the great similarity of structures II and III, the structures of methylharmine (V) and methylharmaline (VI) differ (see Scheme 1).

As further investigations showed, the β-carboline system is present in complex indole alkaloids, and in the proof of this the rich material obtained in the study of the *P. harmala* alkaloids harmine, harmaline, and harmalol, was used.

Then another four alkaloids belonging to the β-carboline group were isolated from the seeds of *P. harmala*. Tetrahydroharmine (VII) [12], and harmol (VIII) [13] had been isolated previously from other plants. Ruine (IX) [14] and dihydroruine (X) [13] proved to be new glucoalkaloids (see Scheme 1) and they were both detected in an investigation of the metabolism of harmine in the plant. From its characteristic UV spectrum, ruine belongs to the β-carboline bases. The mass spectrum of the alkaloid and its tetraacetate contains ions characteristic both for hexopyranosides and for harmine, but 16 mass units higher. It follows from a comparison of the NMR spectra of harmine and ruine that the additional substituent in (IX) is present at C-8. Analysis of the NMR spectrum of ruine tetraacetate and a comparison of it with the spectra of acetylated hexosides led to the conclusion that the sugar had the β configuration. The acid hydrolysis of ruine gives glucose and an unstable aglycone. Dihydroruine and its tetraacetate are readily converted in the air to ruine and its tetraacetate. When callus tissues containing no alkaloids were fed with harmine, ruine was isolated. Correspondingly, feeding with harmaline gave dihydroruine. Experiments with labelled substances showed that the conversion takes place by direct hydroxylation and glycosylation.

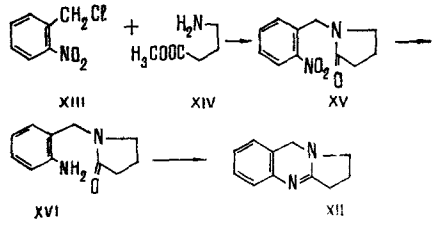
Späth isolated peganine (XI) from *P. harmala* in 1934 [9, 11, 54]. He established that vasicine, which had been isolated as long ago as 1888 from the Indian plant *Adhatoda vasica*, was identical with peganine. Successful work on the proof of the structure of this alkaloid

was performed in parallel by two groups of chemists under the leadership of Späth and Hanword. Peganine contains an alcoholic hydroxy group. It gives a readily hydrolyzed acetate derivative. Under the action of PCl_5, $POCl_3$, and $SOCl_2$ the hydroxy group is replaced by chlorine. The reduction of this substance have an oxygen-free derivative of peganine — deoxypeganine (XII). The formation from peganine of anthranilic acid, quinazolin-4-one, and 4-oxo-3,4-dihydroquinazol-3-ylacetic acid, and the stability of peganine to catalytic hydrogenation, has made it possible to suggest for peganine a tricyclic system consisting of condensed quinazoline and pyrrolidine nuclei. The correctness of the proposed formula was shown by the synthesis of deoxypeganine (XII).

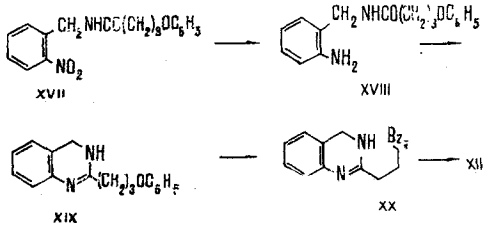
Späth et al. performed the synthesis of (XII) [9] by condensing o-nitrobenzyl chloride (XIII) with methyl γ-aminobutyrate (XIV) through the intermediate formation of N-o-nitrobenzylpyrrolidinone (XV) and N-o-aminobenzylpyrrolidinone (XVI), as shown in Scheme 2.

Simultaneously and independently, Hanword and Adams [15] synthesized deoxypeganine from γ-phenoxybutyric o-nitrobenzylamide [10] (XVII) by reducing it to the corresponding amine (XVIII), which was cyclized by heating to (XIX). Replacement of the phenoxy group of this by bromine gave 2-(γ-bromopropyl)-3,4-dihydroquinazoline (XX), the cyclization of which formed (XII) (Scheme 3).

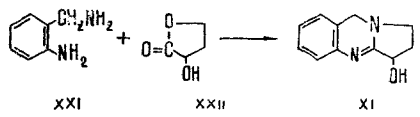
The position of the hydroxy group in peganine was established by synthesis. Späth obtained (XI) by condensing nitrobenzyl chloride with methyl γ-amino-α-hydroxybutyric acid in a similar manner to the preparation of (XII), and also more simply from o-aminobenzylamine (XXI) and α-hydroxybutyrolactone (XXII) (Scheme 4).



Scheme 2



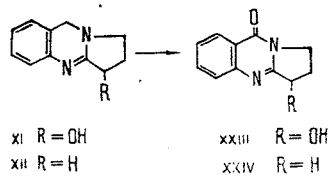
Scheme 3



Scheme 4

The position of the hydroxy group in peganine was determined simultaneously by Hanword et al. [16]. On oxidation, peganine (XI) and deoxypeganine (XII) formed oxo derivatives — vasicinone (XXIII) and deoxyvasicinone (XXIV), the structures of which were confirmed by synthesis [9, 11, 16]. When (XII) was treated with lead tetraacetate followed by mild hydrolysis, a product was obtained which was completely identical with (XXIII), and this established the structure of peganine as (XI), since lead tetraacetate can react only with an active methylene group (Scheme 5).

The peganine isolated by Späth from the seeds of *P. harmala* was racemic. In 1936, A. D. Rozenfel'd and D. G. Kolesnikov isolated *l*-peganine from the flowers and stems of this plant

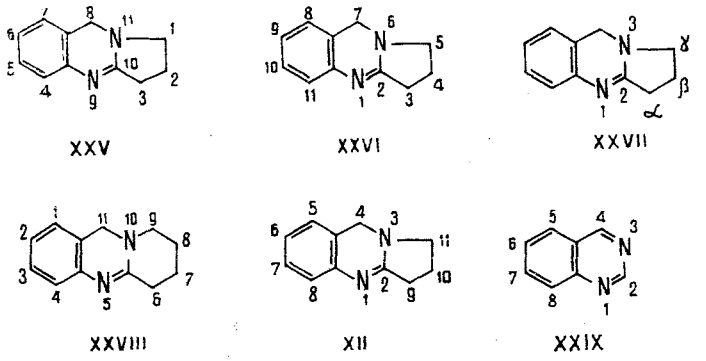


Scheme 5

[9]. The crystalline and the molecular structure and the absolute configuration of peganine are known. The pyrrolidine ring has the envelope conformation with the R configuration [17].

Very different systems of numbering are found for the quinazoline alkaloids in the literature. For example, Späth proposed the method illustrated by formula (XXV). It is used in Manske's monograph [9] and by some other authors [18]. The methods illustrated by formulas (XXVI) [19], (XXVII) [16], and (XXVIII) [20] are also found.

We shall make use of the numbering shown in formula (XII) [21, 55], since in this case it is more convenient to make a comparative analysis with the quinazoline derivatives (XXIX) (Scheme 6).



Scheme 6

In 1957, N. I. Koretskaya [22] isolated two new alkaloids from the epigeal part of *P. harmala*. He showed that they were vasicinone (XXIII) and deoxyvasicinone (XXIV) [23]. Both bases had been obtained previously in a study of the properties and the proof of the structure of peganine (vasicine) (XI), and had also been synthesized [9].

In 1969, from the epigeal part of *P. harmala* collected in various regions of Central Asia was isolated the new alkaloid deoxypeganine (XII) [24], obtained previously, as already mentioned, in the proof of the structure of peganine.

Siddiqui has isolated from the seeds of *P. harmala* a substance in the form of a hydriodide with mp 285°C. He suggested that this substance was deoxypeganine hydriodide [25], but gave no evidence to confirm this. The deoxypeganine hydriodide that we have obtained melts at 270°C with decomposition; Siddiqui's substance is probably not identical with (XII). The fact that deoxypeganine was isolated only in 1969, in spite of many years' work with this plant can be explained by two factors: the ease of oxidation of deoxypeganine to deoxyvasicinone by atmospheric oxygen on an alumina column, and by the high solubility of deoxypeganine in the majority of organic solvents. When the combined bases are separated, (XII) remains in the mother liquors.

The structures of the new alkaloids that we have isolated from *P. harmala* were elucidated mainly with the aid of spectral methods. The quinazoline alkaloids of this plant can be separated into two groups: the 3,4-dihydroquinazoline group (peganine (XI), deoxypeganine (XII), peganol (XXX) [26], peganidine (XXXI) [21], isopeganidine (XXXI) [27], and deoxypeganidine (XXXII) [28]), and the quinazolin-4(3H)-one group (vasicinone (XXIII), deoxyvasicinone (XXIV), and pegamine (XXXIII) [29]).

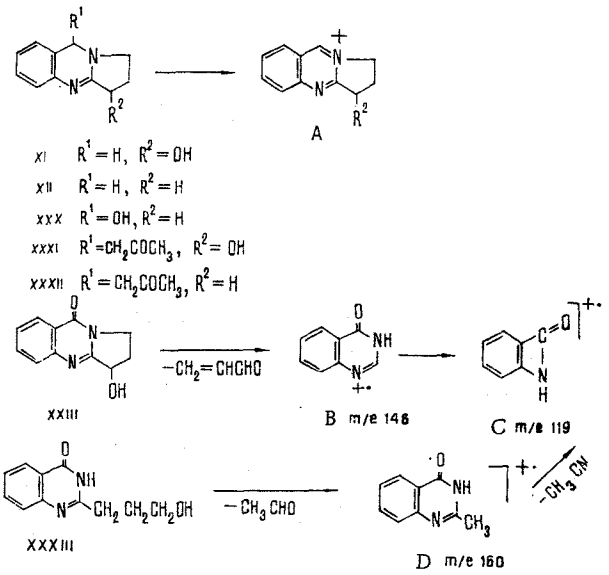
Characteristic for the UV spectra of the alkaloids of the 3,4-dihydroquinazoline group are two absorption maxima in the 220 and 300 nm regions [19, 21, 24, 27, 28]. The spectra of

the alkaloids of the quinazolin-4-one group are more complex: 226, 270, 303, and 316 nm [29-31].

The IR spectra of alkaloids of the peganine type show characteristic bands in the 1630-1585 and 1505-1460 cm^{-1} regions for a combination of C=C and CN bonds [32]. In the bases (XXXI) and (XXXII) an additional strong band of a C=O group appears at 1700-1710 cm^{-1}.

In the bases of the vasicinone group, in addition to the bands of C=C and C=N bonds there is a strong absorption band at 1640-1690 cm^{-1} [19, 31].

The mass spectrum of peganine has been discussed in detail by Bhatnagar and Popli [18]. The intensity of the molecular ion is ∿60%. The main peak is that of ion A (R^2 = OH) with m/e 187. The successive ejection of ethylene, carbon monoxide, and two HCN groups gives ions with m/e 131, 104, and 77 (Scheme 7).



Scheme 7

In the mass spectra of peganidine and isopeganidine, the intensity of the molecular ion is 10%. Yet again the strongest ion is A (R^2 = OH) with m/e 187.

In the mass spectra of 1,2-dihydroquinazolines having no hydroxy group at C-9 the strongest ion is that with m/e 171 (A, R^2 = H). The spectra of (XII) and (XXX) contain doubly charged ions from ion A. Ions with m/e 143, 116, and 89 are due to the successive loss of ethylene and of two HCN groups, the transitions being confirmed by metastable peaks.

Characteristic for the mass spectra of the quinazolin-4(3H)-ones is a 100% molecular ion. In the case of (XXIV), the $(M-1)^+$ ion has the same intensity. In the spectrum of vasicinone, however, apart from M^+ the strongest peaks are those of ions with m/e 146 and 119 having structures B and C [33] (see Scheme 7).

In pegamine (XXXIII), the main ion is D with m/e 160. By the loss of CH_3CN it is converted into ion C [29] (see Scheme 7).

In the NMR spectra of the alkaloids of the peganine group when there is no substituent at C-4 a two-proton singlet in the 4.5 ppm region for the C-4 methylene group is diagnostic [19, 34]. When there is a substituent at C-4, as in the case of (XXXI) and (XXXII), the C-4 methine proton appears in the form of a triplet in the 5.02-5.14 ppm region [28]. The chemical shifts of the other protons of the alkaloids of the peganine group in CF_3COOH are given below (the spectrum of deoxypeganidine was taken in $CDCl_3$):

Alkaloid	Structure	Aromatic	4	9	10	11	12	13
Peganine	XI	7.1-6.6 m	4.47 s	5.04 t	2.05 m 2.45 m	3.42 t		

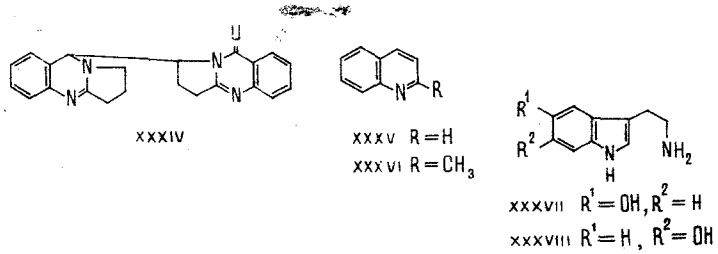
Alkaloid	Structure	Aromatic	4	9	10	11	12	13
Deoxypeganine	XII	7.0-6.5 m	4.45 s	2.75 t	2.02 m	3.46 t		
Peganidine	XXXI	7.1-6.6 m	5.02 t	5.02 t	2.02 m	3.73 m	3.07 d	1.86 s
					2.38 m	3.35 m		
Isopeganidine	XXXI	7.0-6.6 m	5.04 m	5.04 m	2.05 m	3.47 m	2.95 d	1.81 s
					2.45 m			
Deoxypeganidine	XXXII	7.2-6.9 m	5.14 t	3.42 m	2.00 m	3.42 m	2.76 m	1.95 s
					2.60 m			
Peganol	XXX	8.0-7.5		3.40 t	2.40 m	4.71 t		

In the NMR spectra of the alkaloids of the vasicinone group, the proton at C-5 is shifted downfield by approximately 0.5 ppm relative to the signals of the other aromatic protons. This paramagnetic shift is due to the anisotropic influence of the carbonyl group in the peri position [20]. The chemical shifts of the other protons of the alkaloids of the vasicinone group in CF_3COOH are given below:

Alkaloid	Structure	Aromatic	5	9	10	11
Vasicinone	XXIII	7.8-7.3 m	8.05 d	5.56 t	2.64 m	3.92 m
					2.21 m	4.32 m
Deoxyvasicinone	XXIV	7.8-7.3 m	8.00 d	3.43 t	2.29 m	4.2 t
Pegamine	XXXIII	7.95-7.4 m	8.15 d	3.00 t	2.14 m	4.21 m

Dipegine (XXXIV) [27], isolated from *P. harmala* is the first representative of bimolecular bases among the quinazoline alkaloids.

In addition to the β-carboline and quinazoline derivatives mentioned above, quinoline derivatives — quinoline itself (XXXV) and quinaldine (XXXVI) [27] — and indolylalkylamine derivatives — 5-hydroxytryptamine (XXXVII) and 6-hydroxytryptamine (XXXVIII) [13] (Scheme 8) — have also been isolated from *P. harmala*. The isolation of the latter base as a precursor of the β-carboline alkaloids is interesting.



Scheme 8

At the present time, the following alkaloids have been isolated from *P. harmala* (the Roman numerals correspond to the structures of the alkaloids given in the text):

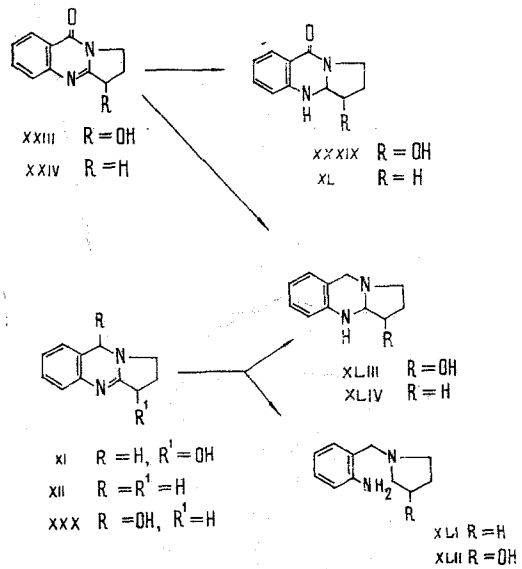
Alkaloid	Elementary Composition	mp, °C	Literature
Quinoline (XXXV)	C_9H_7N	Picrate, 201-202	27
Quinaldine (XXXVI)	$C_{10}H_9N$	Picrate, 187	27
5-Hydroxytryptamine (XXXVII)	$C_{10}H_{12}N_2O$		13
6-Hydroxytryptamine (XXXVIII)	$C_{10}H_{12}N_2O$		13
Deoxypeganine (XII)	$C_{11}H_{12}N_2$	86-87	24
Deoxyvasicinone (XXIV)	$C_{11}H_{10}N_2O$	110-111	23
l-Vasicinone (XXIII)	$C_{11}H_{10}N_2O_2$	203-204	23
dl-Vasicinone (XXIII)	$C_{11}H_{10}N_2O_2$	211-212	35
l-Peganine (XI)	$C_{11}H_{12}N_2O$	211-212	9
dl-Peganine (XI)	$C_{11}H_{12}N_2O$	198-199	9, 11
Peganol (XXX)	$C_{11}H_{12}N_2O$	178-180	26

Alkaloid	Elementary Composition	mp, °C	Literature
Pegamine (XXXIII)	$C_{11}H_{16}N_2O_2$	161	29
Harmol (VIII)	$C_{12}H_{10}N_2O$	319-321	13
Harmalol (IV)	$C_{12}H_{12}N_2O$	212	9
Harmine (II)	$C_{13}H_{12}N_2O$	257-258	9
Harmaline (III)	$C_{13}H_{14}N_2O$	250-251	9
Tetrahydroharmine (VII)	$C_{13}H_{16}N_2O$	199-200	12
Deoxypeganidine (XXXII)	$C_{14}H_{16}N_2O$	76-79	28
Peganidine (XXXI)	$C_{14}H_{16}N_2O_2$	189-190	21
Isopeganidine (XXXI)	$C_{14}H_{16}N_2O_2$	169-170	27
Ruine (XI)	$C_{19}H_{22}N_2O_7$	Tetraacetate, 195-196.5	14
Dihydroruine (X)	$C_{19}H_{24}N_2O_7$		13
Dipegine (XXXIV)	$C_{22}H_{20}N_4O$	221-223	27
Unidentified base	$C_{13}H_{16}N_2O_2$		12
Unidentified base		192	30

The difference between the 1,2-dihydroquinazolines and the quinazoline-4(3H)-ones is also shown in their reduction with sodium tetrahydroborate [36]. Vasicinone and deoxyvasicinone are reduced under more severe conditions, giving the dihydro products (XXXIX) and (XL) [55] in which the carbonyl group is retained, as is shown by the absorption bands in the IR spectrum in the 1620-1640 cm^{-1} region and the paramagnetic shift of the proton at C-5 due to the influence of the carbonyl group in the peri position on the NMR spectra of these compounds. It must be mentioned that the $LiAlH_4$ reduction of (XXIV) leads to the reduction both of the double bond and of the carbonyl group (XLIV) [23, 55], and 2,3-dialkyl-substituted and 2,3-diaryl-substituted dihydroquinazolines are reduced with cleavage of the 2-3 bond [37].

The 1,2-dihydroquinazolines deoxypeganine and peganol are reduced under very mild conditions, giving one and the same compound (XLI). The UV spectrum of the latter (λ_{max} 237, 288 nm) is close to that of aniline, and the IR spectrum shows the absorption bands of a primary amino group. Furthermore, the presence in the mass spectrum of ions with m/e 159, 106, and 70 shows that the cleavage of the bonds on reduction takes place at N_1—C_2, although 2,3-tetramethylenedihydroquinazoline, which is very close in structure to (XII), is reduced only to a dihydro derivative without ring opening [20].

The reduction of peganine gives both tetrahydro and dihydro products, (XLII) and (XLIII) with a predominance of the latter. Here the influence of the hydroxy group is obviously being shown (Scheme 9).

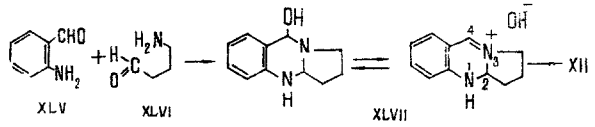


Scheme 9

The mass spectra of the tetrahydroquinazolines (XLIII) and (XLIV) and of the tetrahydroquinazoline-4-ones (XXXIX) and (XL) have been studied [38]. In both cases, the main directions of fragmentation are the elimination of the C_9—C_{10} chain with the subsequent splitting out of a methyleneimine radical and the formation of ions with m/e 146 [from (XLIII) and (XLIV)] and 160 [from (XXXIX) and (XL)] and the elimination of the C_9—C_{11} chain. In the decomposition of dehydropeganine and dehydrodeoxypeganine, migration of hydrogen to the uncharged fragment takes place during this process with the formation of the ion of a protonated quinazoline with m/e 131. In the decomposition of dihydrovasicinone and dihydrodeoxyvasicinone, hydrogen migrates to the charged fragment with the formation of protonated dihydroquinazoline-4-one with m/e 147.

The polarographic behavior of seven alkaloids of *P. harmala* has been investigated [39]. In the reduction of vasicinone and deoxyvasicinone, the products of the electrode reaction are the corresponding carbinols. The same compounds are obtained by the action of N-bromosuccinimide on peganine and deosypeganine followed by treatment with alkali as described by Marion [53].

In addition to work in the field of the chemistry of the β-carboline and quinazoline alkaloids, the biosynthesis of these alkaloids in *P. harmala* has become the object of detailed study. It is generally accepted that the β-carboline alkaloids are formed from tryptophan [40], and this has been confirmed by experiments with labelled atoms. Robinson put forward a hypothesis that peganine is formed from anthranilic acid and 3-hydroxy-Δ^1-pyrroline [41]. Groger and Mottes [42] have confirmed experimentally with the aid of [^{14}COOH]anthranilic acid introduced into a shoot of *P. harmala* that anthranilic acid is a specific precursor of peganine. Schopf and Oechler considered that o-aminobenzaldehyde and γ-amino-α-hydroxybutyraldehyde are probable precursors of peganine [43]. They performed the synthesis of deoxypeganine from o-aminobenzaldehyde (XLV) and γ-aminobutyraldehyde (XLVI) in accordance with Scheme 10.



Scheme 10

The transfer of two hydrogen atoms from N_1—C_2 in (XLVII) to N_3—C_4 takes place under the action of a platinum catalyst in an atmosphere of hydrogen.

Macholan [44] assumes that in addition to (XLVI) another precursor may be δ-amino-α-oxovaleric acid.

Ghosal [45] has put forward a hypothesis of a single route of the formation of quinazoline and furoquinoline alkaloids from anthranilic acid and ornithine. It has been shown with the aid of [2-^{14}C]ornithine that this compound is specifically included in peganine [35]. Ghosal criticized the Schopf—Oechler theory in view of the fact that aminobenzaldehyde has not so far been isolated from plants and there is no proof of the transfer of hydrogen from N_1—C_2 to N_3—C_4 in plant metabolism. However, later, Scursky showed that such a transition can be brought about in a plant [46]. On introducing 2,3-trimethylene-1,2-dihydroquinazolinium hydroxide (XLVII) into a pea shoot he isolated deoxypeganine (XII) and deoxyvasicinone (XXIV). This author considers that the hydroxylation of the deoxypeganine to peganine then takes place in the plant. The isolation of peganol (XXX) from the plant [26] may also be evidence in favor of the Schopf—Oechler scheme.

The question has been discussed of whether quinazolinones are first formed in the plant and these are then reduced to quinazolines, or, conversely, peganine and deoxypeganine are converted into vasicinone and deoxyvasicinone [46, 47]. Experiments by Liljergren with labelled ornithine [35] have shown that peganine, vasicinone, and deoxyvasicinone are formed simultaneously.

It is known that 3,4-dihydroquinazolines are readily oxidized to the corresponding quinazoline-4-ones, and the alkaloids of *P. harmala* behave similarly. The spontaneous oxidation of peganine and deoxypeganine to vasicinone and deoxyvasicinone has been reported [34, 42]. In view of this, doubt has been cast on the native nature of the latter. However, an investi-

gation of the fresh juice of the plant [48] has shown the presence of the same alkaloids as in the material obtained by the usual method.

There are a number of investigations on the dynamics of the accumulation of alkaloids in *P. harmala*. Thus, M. S. Shalyt [49] has determined the sum of the bases in the leaves, stems, and fruit of plants collected in various vegetation periods in the environs of Ashkhabad in 1944. According to his results, the amount of combined alkaloids in the stems increased with the development of the plant from 1.66% in the budding stage to 3.57% in the withering stage. The same change was observed for the leaves: 2.40% in the budding stage and 4.96% in the stage of the withering of the epigeal part.

Similar results have been obtained by N. V. Plekhanova in a study of harmal collected in Kirghizia in 1962-1963 [47]. The sum of the bases in the early period in the epigeal part was 1.98%, and in the fruit-bearing period 3.01%. These facts do not agree with the laws of the dynamics of the accumulation of alkaloids in plants established by S. Yu. Yunusov on the basis of many years' investigations [50]. The results of our investigations of the change in the combined bases of *P. harmala* collected in Uzbekistan (Dzhizak oblast) in 1968 are given below:

Date of Collection	Phase of Development	Total Alkaloids, %	Amount of Peganine, % of Total	Amount of Deoxypeganine, % of Total
April 11	Early stage	2.17	48	2.1
May 5	Budding	2.00	34	2.6
May 25	Flowering	1.95	0.9	Tr.

They show that as the plant develops the amount of combined alkaloids in the epigeal part falls. The amounts of peganine and deoxypeganine fall sharply in the flowering stage. Similar results have been obtained in a study of the plant collected in the Bukhara oblast in 1968 [51] in the phase of flowering and budding. The total amount of alkaloids fell from 2.30 to 1.86%. The amounts of peganine and deoxypeganine as percentages of the total fell from 41 to 0.12 to traces.

The dynamics of the accumulation of the alkaloids of the epigeal part of the plant collected in Kara Kalpak in 1972 has been considered [52]:

Date of Collection	Phase of Development	Total Alkaloids, %	Amount of Peganine, % of Total	Amount of Deoxypeganine, % of Total
May 4	Budding	3.10	82	3
June 4	Flowering—incipient fruit-bearing	1.74	53	7
July 4	Fruit-bearing	0.86	16	16
September 14	Withering of the epigeal part	0.36	--	--

The amount of combined alkaloids and of peganine in the epigeal part decrease as the plant develops, and the amount of deoxypeganine rises.

Thus, as for the majority of plants [50], the total alkaloids in the epigeal part of *P. harmala* falls by the moment of withering of the epigeal part to the minimum amount, which has accumulated in the fruit. The amount of alkaloids in the roots also changes during the vegetation period, but the available information does not give a complete picture. It must be mentioned that the roots of one-year plants of one period of vegetation and one section contained 3.32% of total alkaloids and those of old plants 1.68% [51].

We have determined the total bases of samples of *P. harmala* from various regions of Central Asia and the amounts of peganine and deoxypeganine in the total. As was to be expected [50], the total alkaloids and the ratios of the individual alkaloids to one another vary in accordance with the stage of development and the growth site.

Phase of Development	Date and Site of Collection	Total Alkaloids, %	Peganine, % of the Total	Deoxypeganine, % of the Total
Vigorous growth	April 18, 1967 UzSSR (Dzhizak oblast)	1.80	33	--
"	April 11, 1968	2.17	48	2.1
"	April 15, 1973	2.20	35	21.0
"	April 14, 1976	1.80	--	6.0
Budding	May 5, 1968	2.0	34	2.6
"	May 10, 1968 UzSSR (Bukhara oblast)	2.30	41	Tr.
"	May 4, 1972 KKASSR	3.10	82	3.0
Flowering	May 25, 1968 UzSSR (Dzhizak oblast)	1.95	0.9	Tr.
"	May 20, 1968 UzSSR (Bukhara oblast)	1.86	Tr.	Tr.
"	May 18, 1971 TSSR (Babadurmas)	2.31	1.5	21.0
"	May 30, 1974 KazSSR (Aksai)	2.82	47.0	10.0
"	May 22, 1976 KazSSR (Kyzylorda)	2.10	68.0	5.7
Flowering—incipient fruit-bearing	June 4, 1972 KKASSR	1.74	53.0	7.0
"	May 29, 1973 TSSR (Babadurmas)	1.83	11.0	18.0
Fruit-bearing	July 20, 1969 UzSSR (Bukhara oblast)	0.69	7.3	--
"	July 4, 1972 KKASSR	0.86	16.0	16.0

It is possible that, apart from ecological-geographical conditions, a role is also played here by the age of a perennial plant. The increased content of peganine in the total alkaloids of samples collected in Kara Kalpak must be noted. In samples from Turkmenia there is a larger amount of deoxypeganine than in samples from other sites. The large fluctuations in the amounts of deoxypeganine in the combined alkaloids of the plant collected in the Dzhizak oblast in the stage of vigorous growth over a number of years are probably due to the weather factor, and further investigations are necessary for definitive conclusions to be drawn.

LITERATURE CITED

1. N. N. Sharakhimov, "Harmal (*Peganum harmala* L.). Its biological characteristics and value as a drug," Author's Abstract of Candidate's Dissertation, Tashkent (1975).
2. Atlas of the Areas and Resources of Medicinal Plants of the USSR [in Russian], Vol. 34, Moscow (1976), p. 218.
3. Flora of the USSR [in Russian], Vol. 19, Moscow–Leningrad (1953), p. 146.
4. Abu Ali Ibn Sina [Avicenna], Canon of Medical Science [Russian translation], Book 2, Tashkent (1956).
5. V. S. Sokolov, Alkaloid-Bearing Plants of the USSR [in Russian], Moscow–Leningrad (1952), pp. 230, 288.
6. S. E. Zemlinskii, Medicinal Plants of the USSR [in Russian], Moscow (1958), p. 388.
7. V. P. Makhlayuk, Medicinal Plants in Folk Medicine [in Russian], Saratov (1967), pp. 98, 455.
8. P. K. Alimbaeva and A. V. Goncharova, Wild-Growing Medicinal Plants of Kirgisia [in Russian], Frunze (1971), p. 88; I. Isamukhamedov and N. Sharakhimov, in: The Pharmacology of Alkaloids and Their Derivatives [in Russian], Tashkent (1972), p. 187.

9. A. P. Orekhov, The Chemistry of the Alkaloids [in Russian], Moscow (1955), p. 565; T. A. Henry, The Plant Alkaloids, 4th ed., J. A. Churchill, London (1949); R. H. F. Manske and H. L. Holmes, The Alkaloids: Chemistry and Physiology, Academic Press, New York, Vol. II (1952), p. 393; H. G. Boit, Ergebnisse der Alkaloid-Chemie bix 1960, Berlin (1961), pp. 491, 741.
10. R. A. Konovalova and A. P. Orekhov, Zh. Obshch. Khim., 6, 487 (1936).
11. S. Johne and D. Groger, Pharmazie, 25, 22 (1970).
12. H. Kutlu and H. Amal, Chem. Abstr., 68, 112167 (1968).
13. E. McKenzie, L. Nettleship, and M. Slaytor, Phytochemistry, 14, 273 (1975).
14. L. Nettleship and M. Slaytor, Phytochemistry, 10, 231 (1971).
15. W. E. Hanword and R. Adams, J. Am. Chem. Soc., 57, 921 (1935).
16. R. S. Morris, W. E. Hanword, and R. Adams, J. Am. Chem. Soc., 57, 951 (1935).
17. K. Szulzewsky, E. Hohne, S. Johne, and D. Groger, J. Prakt. Chem., 318, 463 (1976).
18. A. K. Bhatnagar and S. P. Popli, Indian J. Chem., 4, 291 (1966).
19. R. R. Arndt, S. H. Eggers, and A. Jordaan, Tetrahedron, 23, 3521 (1967).
20. J. S. Fitzgerald, S. R. Johns, J. A. Lamberton, and A. H. Redcliffe, Aust. J. Chem., 19, 151 (1966).
21. Kh. N. Khashimov, M. V. Telezhenetskaya, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 599 (1969).
22. N. I. Koretskaya, Zh. Obshch. Khim., 27, 3361 (1957).
23. N. I. Koretskaya and L. M. Utkin, Zh. Obshch. Khim., 28, 1087 (1958).
24. Kh. N. Khashimov, M. V. Telezhenetskaya, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 456 (1969).
25. S. Siddiqui, Pakist. J. Sci. Ind. Res., 5, 207 (1962).
26. M. V. Telezhenetskaya, Kh. N. Khashimov, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 849 (1971).
27. B. Kh. Zharekeev, Kh. N. Khashimov, M. V. Telezhenetskaya, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 264 (1974).
28. B. Kh. Zharekeev, M. V. Telezhenetskaya, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 279 (1973).
29. Kh. N. Khashimov, M. V. Telezhenetskaya, R. V. Rashkes, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 453 (1970).
30. A. Chatterjee and M. Ganguly, Phytochemistry, 7, 307 (1968).
31. D. L. Liljegren, Phytochemistry, 7, 1299 (1968).
32. M. Ikram, M. E. Ehsanul Huq, S. A. Warsi, and V. Ahmad, Pakist. J. Sci. Ind. Res., 8, 76 (1965).
33. V. N. Plugar', T. T. Gorovits, N. Tulyagonov, and Ya. V. Rashkes, Khim. Prirodn. Soedin., 250 (1977).
34. S. Johne, D. Groger, and M. Hesse, Helv. Chim. Acta, 54, 826 (1971).
35. D. R. Liljegren, Phytochemistry, 10, 2661 (1971).
36. B. Kh. Zharekeev, M. V. Telezhenetskaya, Kh. N. Khashimov, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 679 (1974).
37. S. R. Pakrashi and A. K. Chakravarty, J. Org. Chem., 37, 3143 (1972).
38. Ya. V. Rashkes, M. V. Telezhenetskaya, V. N. Plugar', and S. Yu. Yunusov, Khim. Prirodn. Soedin., 378 (1977).
39. E. K. Dobronravova, M. V. Telezhenetskaya, and T. T. Shakirov, Khim. Prirodn. Soedin, 363 (1976).
40. E. Leete, in: Biogenesis of Natural Compounds, ed. P. Bernfeld, 2nd ed., Pergamon Press, Oxford (1967), p. 953.
41. R. Robinson, The Structural Relations of Natural Products, Clarendon Press, Oxford (1955).
42. D. Groger and K. Mottes, Arch. Pharm., 293, 1049 (1960).
43. C. Schopf and F. Oechler, Ann. Chem., 523, 1 (1936).
44. L. Macholan, Collection Czech. Chem. Commun., 24, 550 (1959).
45. S. Ghosal, Sci. Cult., 30, 142 (1964).
46. L. Scursky, Collect. Czech. Chem. Commun., 30, 2080 (1965).
47. N. V. Plekhanova and S. T. Aktanova, in: A Study of the Flora of Kirgizia for Alkaloid-Bearing Capacity [in Russian], Frunze (1965), p. 57.
48. A. I. Botbaev, N. V. Plekhanova, and E. V. Nikitina, Izv. Akad. Nauk KirgSSR, No. 2, 52 (1974).
49. Y. A. Adylov, Poisonous and Alkaloid-Bearing Plants of Uzbekistan [in Russian], Tashkent (1970), p. 118.

50. S. Yu. Yunusov, Izv. Akad. Nauk UzSSR, N. 4, 11 (1948); Khim. Prirodn. Soedin., 104 (1966); Jubilee Collection Devoted to the 25th Anniversary of the UzSSR [in Russian] (1950), p. 223; Chemistry in Uzbekistan [in Russian], Tashkent (1965), p. 58.
51. Kh. N. Khashimov, M. V. Telezhenetskaya, N. N. Sharakhimov, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 382 (1971).
52. D. Kurbanov and B. Kh. Zharekeev, Khim. Prirodn. Soedin., 685 (1974).
53. L. Marion, Can. J. Chem., 45, 1447 (1967).
54. E. Späth, F. Kuffner, and N. Platzer, Ber., 68, 497 (1935).
55. R. Landi Vittory and F. Gatta, Gazz. Chim. Ital., 99, 59 (1969).

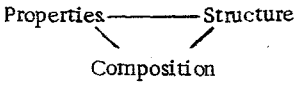
THE TECHNOLOGICAL CLASSIFICATION OF ALKALOIDS AND METHODS OF OBTAINING THEM FROM PLANTS

Kh. N. Aripov

UDC 547.94+615.45+615.32

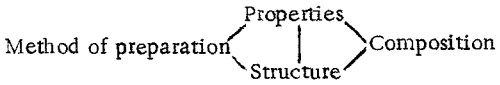
About 100 individual alkaloids are produced on the industrial scale [1]. In spite of this, there is no acceptable classification and systematization of the technology of the alkaloids that would lead to a generalization of all the experience accumulated in this field. In our opinion, this situation is due to the fact that insufficient attention has been devoted to the connection of the method of obtaining alkaloids with their structure, composition, and properties.

Academician B. M. Kedrov, generalizing methodological questions of chemistry, has put forward the scheme



[2], in which chemical technology does not have its due reflection. At the same time, from hydrogen to kurchatovium, from methane to protein, in all cases the method of preparation depends on the composition, structure, and properties. It is impossible to find even one example where the above-mentioned parameters of the compound being isolated has not been taken into account in technology.

On the basis of literature information and our own experiments on the development of a technology for producing the alkaloids of *Vinca erecta* we consider the following scheme to be the most correct:



since as the properties, composition, and structure of a substance become known so is the method for its preparation developed.

In order to find a parameter which to some extent would give a quantitative characterization of the main properties of an alkaloid and at the same time would be accessible to direct measurement, we have begun the study of the behavior of alkaloids in heterogeneous systems consisting of chloroform and buffer solutions, since the main processes of alkaloid tec nology do in fact involve heterogeneous systems: extraction, sorption, liquid–liquid extraction, etc. [3].

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 743-753, November-Decem ber, 1977. Original article submitted May 24, 1977.

 0009-3130/77/1306-0624$07.50