DIMERIC QUINOLINE ALKALOIDS

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The review is denoted to an analysis of the literature on the investigation of dimeric quinoline alkaloids, which are divided into four groups depending on the structures of the terpenoid moiety. The natural sources, structures, stereochemical features, possible biogenetic schemes of formation, and methods of synthesizing the alkaloids of this group are considered.

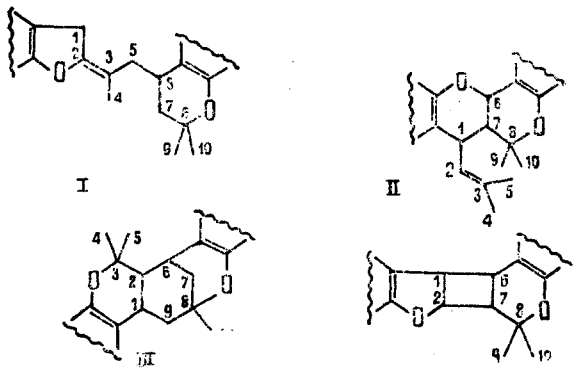
The dimeric quinoline alkaloids form a small group of natural compounds, the structural basis of which consists of two quinolone and one terpenoid fragments. The first representative of this group was discovered in 1978 [1]. Since this time, studies on dimeric quinoline alkaloids have appeared periodically in the literature, and by the time of writing this review the number of compounds of this group with established structures amounted to 15.

In the group of substances under consideration, the connection between the monomers is effected through a linkage of two prenyl units the presence of which is characteristic for natural compounds of the Rutaceae family and for quinoline alkaloids, in particular.

The aim of the present review is to generalize information on the structural studies of the dimeric quinoline alkaloids and to direct the attention of research workers to this unusual class of substances, since, on the one hand, different combinations of the prenyl units lead to a diversity of types of terpenoid structures in the molecules of the dimers, and, on the other hand, such dimers may be expected among any classes of natural compounds containing hemiterpenoid units. Such dimers have already been found among some of them [2-8], but the structure of the terpenoid moieties in their molecules differs from that of the terpenoid moiety of the quinoline dimers.

Dimeric quinoline alkaloids, like their monomeric precursors, are found only in plants of the Rutaceae family [9, 10]. They are all optically inactive. As a rule, they have high melting points. The absence of optical activity is not an indication of their artefactual nature, since they are isolated under exceptionally mild conditions – by extraction with low-boiling fractions of petroleum ether and rapid crystallization from concentrated solutions of the petroleum ether extract [11].

A common structural element of the quinoline dimers is a dimethyldihydropyrano-2-quinolone fragment. Depending on the structure of the terpenoid moiety, the following types of dimeric quinoline alkaloids are distinguished:



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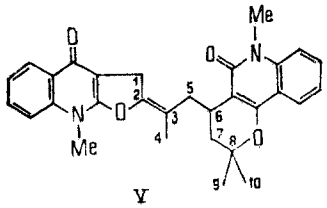
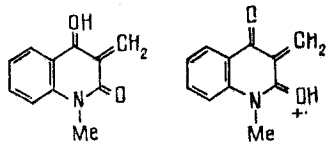
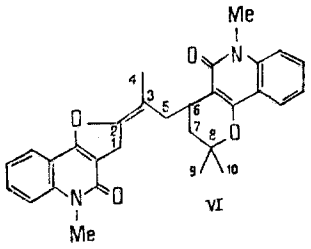
To the first type belong the alkaloids pteledimerine (V) and pteledimeridine (VI) isolated from a methanolic extract of the bark of Ptelea trifiliata roots [1, 2]. The two alkaloids have the same composition and close spectral properties but differ by the fact that in the IR spectrum of (V) there is an absorption band at 1550 cm^{-1} and in the UV spectrum of (VI) the long-wave absorption maximum at 328.5 nm undergoes a hypsochromic shift in an acid medium while the UV spectrum of (VI) does not change on acidification; in the PMR spectrum of (V) there is weak-field signal at 8.35 ppm which appears in a stronger field in the analogous spectrum of (VI). These differences are due to the fact that in pteledimerine there are 2- and 4-quinolone systems and in pteledimeridine only 2-quinolone systems [13-15]. Under the conditions of mass spectrometry, the two alkaloids give identical fragments with m/z 241 and 188. The ion with m/z 188 (VII) is characteristic in the mass spectra of all linear and angular N-methylisopropyldihydrofuranoquinolones [16, 17]. The fragmentation of the ion with m/z 241 corresponds to the breakdown of the molecular ion of M-methylflindersine (VIII) [18].



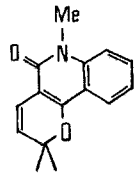
V



VII, m/z 188



VI

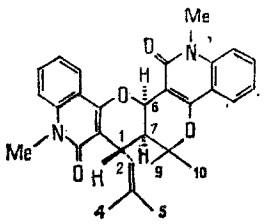


VII

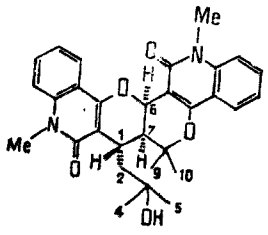
The structures of the terpenoid components on (V) and (VI) were established by analysis of their PMR spectra (Table 1). The alkaloids pteledimerine and pteledimeridine are structural isomers differing by the linear or angular linkage of the dihydrofuran ring and quinolone nucleus and represent a new type of linkage of hemiterpenoid units having no analogies among natural compounds.

To the second type of dimeric quinoline alkaloids belong paraensidimerines B (X) and D (IX), isolated from the heartwood sawdust of the Brazilian tree Euxylophora paraensis [11, 19, 20]. The assignment of the signals of the protons at the terpenoid moiety of paraensidomerine D (see Table 1) was made after the establishment of the structure of this alkaloid by x-ray structural analysis [11].

An analogous bisdihydropyrano-2-quinolone structure with cis-linkage of the dihydropyran rings was established for paraensidimerine B by spectral methods [19, 20].



IX



X

Extremely interesting are the dimeric alkaloids vepridimerines A-D detected in the bark of West African plants of the genus Vepris and Oricia [21] and paraensidimerines A, C, E, F, and G found in the heartwood of the Brazilian tree Euxylophora paraensis and belonging to the third type [20, 22].

TABLE 1. Dimeric Quinoline Alkaloids and Synthetic Analogs

Number of the structure, name, composition, M+, mp, °C (solvent), source	Details of the PMR spectra of the terpenoid			Literature
	working frequency of the instrument, MHz, solvent	protons	CS (δ, ppm; O – TMS, HMDS); number of protons; multiplicity (J, Hz)	
1	2	3	4	5
V. Pteledimerine $C_{20}H_{30}N_2O_4$, 482, 319–321 (acetone) Ptelea trifoliata L.		H-1 H-6 H-5 H-7 CH_3-4, CH_3-9, 10	3.44, 2H, s 3,21, m 2,16, 2H, d (5,4) 2,08, 2H, d (5,7) 1,85 s 1,54, 6H, s	1
VI. Pteledimeridine $C_{36}H_{30}N_2O_4$, 482, 340–342 (acetone) Ptelea trifoliata L.	90, $CDCl_3$	H-1 H-6 H-5 H-7 CH_3-4 CH_3-9, 10	3.71, 2H, s 3,14, m 2,23,2H, d (6) 2,15, 2H, d (6) 1,86, s 1,55, 6H, s	12
IX. Paraensidimerine D $C_{30}H_{30}N_2O_4$, 482, 264–265 (chloroform–methanol) Euxylophora paraensis Hub.	200, $CDCl_3$	H-6 H-2 H-1 H-7 CH_3-4, 5, 9, 10	5,56, d (3) 5,30, d (9) 3,92, d (9) 2,20, d (3) 1,94; 1,74; 1,70; 1,22	11,22
X. Paraensidimerine B $C_{30}H_{32}N_2O_5$, 500, 286–287 (chloroform–methanol) Exylophora paraensis Hub.	200, $CDCl_3$	H-6 H-1 H-7 H-2 CH_3-4, 5, 9, 10	5,54, d (4) 3,35, dd (6; 3) 2,45, d (4) 1,97, dd (15; 3), 1,8,2, dd (15; 6) 1,79; 1,39; 1,32; 1,22	11,19, 20
XII. Vepridimerine A $C_{34}H_{38}N_2O_8$, 602, 343–345, Vepris louisii	360	H-6 H-9$_{eq}$ H-1 H-2 H-7$_{ax}$ H-7$_{eq}$ H-9$_{ax}$	3,61, ddd (2,8; 2,7; 1) 3,10, ddd (14,2; 5,4; 2,2) 2.96, ddd (13,4; 6,1; 5,4) 2,16, dd (6,1; 1) 2,14, dd (13,7; 2,7) 1,70, ddd (13,7; 2,8; 2,2) 1,56, dd (14,2; 13,4)	21
XIII. Vepridimerine B $C_{34}H_{38}N_2O_8$, 602, 278–279, Vepris louisii, Oricia renieri	360	H-9$_{eq}$ H-6 H-1 H-7$_{ax}$ H-2 H-7$_{eq}$ H-9$_{ax}$	3,80, dd (14,6; 4,1) 3,20, ddd (3,4; 3,2 2,4) 2,59, ddd (12,9; 12,5; 4,1) 2,12, dd (13,5; 3,4) 1,55, dd (12,5; 3,2) 1,45, dd (13,5; 2,4) 1,39, dd (14,6; 12,9)	21
XIV. Vepridimerine C $C_{34}H_{38}N_2O_8$, 602, 272, Vepris louisii, Oricia renieri	360	H-6 H-9$_{eq}$ H-1 H-2 H-7$_{ax}$ H-7$_{eq}$ H-9$_{ax}$	3,58, ddd (2,7; 2,1) 3,26, ddd (14,4; 5,4; 2,2) 3,13, ddd (12,9; 6,8; 5,4) 2,15, dd (6,8; 1) 2,10, dd (13,6; 2,7) 1,71 ddd (13,6; 2,2; 2) 1.54, dd (14,4; 12,9)	21
XV. Vepridimerine D $C_{34}H_{38}N_2O_8$, 602, Oricia renieri	360	H-9$_{eq}$ H-6 H-1 H-7$_{ax}$	3,93, dd (14,4; 4,2) 3,16, ddd (3,5; 3,3; 2,5) 2,71, ddd (12,6; 12,6; 4,2) 2,13, dd (13,0; 3,3)	21

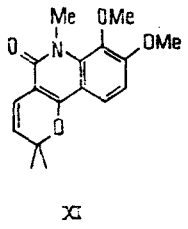
TABLE 1 (continued)

Number of the structure, name, composition, M^+, mp, °C (solvent), source	Details of the PMR spectra of the terpenoid			Literature
	working frequency of the instrument, MHz, solvent	protons	CS (δ, ppm; O – TMS, HMDS); number of protons; multiplicity (J, Hz)	
1	2	3	4	5
		H-2	1,57, dd (12,6; 3,5)	
		$H\text{-}7_{eq}$	1,44, dd (13,0; 2,5)	
		$H\text{-}9_{ax}$	1,34, dd (14,4; 12,6)	
XVI. Paraensidimerine A $C_{30}H_{30}N_2O_4$, 482, 311–312 (chloroform–methanol), Euxylophora paraensis Hub.	200, $CDCl_3$	H-6	3,69, m	11, 19, 22
		$H\text{-}9_{eq}$	3,20, ddd (13,9; 5,5; 2,4)	
		H-1	3,03, dd (12,5; 6,2)	
		H-2	2,22, d (7,8)	
		$H\text{-}7_{ax}$	2,21, dd (13,4; 2,5)	
		$H\text{-}7_{eq}$	1,75, dt (12,9; 2,7)	
		$H\text{-}9_{ax}$	1,62, t (13,5)	
XVII. Paraensidimerine C $C_{30}H_{30}N_2O_4$, 482, 210 (chlororform–methanol), Euxylophora paraensis Hub.	200, $CDCl_3$	$H\text{-}9_{eq}$	3,89, dd (14,7; 4,4)	11, 19, 22
		H-6	3,27, q (3,2)	
		H-1	2,63, td (12,6; 4,3)	
		$H\text{-}7_{ax}$	2,17, dd (13,6; 3,5)	
		H-2	1,63, dd (12,4; 3,5)	
		$H\text{-}7_{eq}$	1,48, dd (13,2; 4,9)	
		$H\text{-}9_{ax}$	1,45, t (12,7)	
XVIII. Paraensidimerine E $C_{30}H_{30}N_2O_4$, 482, 289–290 (chloroform–methanol) Euxylophora paraensis Hub.	200, $CDCl_3$	H-6	3,90, dd (5; 2)	11, 19, 20
		H-1	3,85, ddd (14; 11; 5)	
		H-2	3,56, d (11)	
		H-9	2,97, t (14,5)	
		H-7	2,27, dd (14; 2)	
		H-9	2,07, dd (15; 5)	
		H-7	1,63, dd (14; 5)	
XIX. Paraensidimerine F $C_{30}H_{30}N_2O_4$, 482, 310 (chloroform–methanol) Euxylophora paraensis Hub.	200, $CDCl_3$	$H\text{-}9_{eq}$	3,84, ddd (14; 4; 2)	19, 20
		H-6	3,77, td (3; 2)	
		H-1	2,79, td (12; 4)	
		H-2, 7_{ax}	2,35, m	
		$H\text{-}7_{eq}$	1,81, dt (13; 3)	
		$H\text{-}9_{ax}$	1,29, dd (14; 12)	
XX. Paraensidimerine G $C_{30}H_{28}N_2O_4$, 480, 280–281, Euxylophora paraensis Hub.	200, $CDCl_3$	H-9	7,60, t (2)	19, 20
		H-6	3,68, m	
		H-2	2,65, d (1,5)	
		H-7	1,99, dd (14; 3)	
		H-7	1,80, ddd (14; 4; 1)	
XXI. Isomer of paraensidimerine G (synthesized) $C_{30}H_{28}N_2O_4$ 480, 273–274 (chloroform–methanol)	200 $CDCl_3$	$H\text{-}9_{eq}$	4,12, d (20)	20
		H-6	4,10, d (3)	
		$H\text{-}9_{ax}$	2,79, d (20)	
		$H\text{-}7_{ax}$	2,08, dd (12; 3)	
		$H\text{-}7_{eq}$	1,86, dd (12; 3)	
XXII. Geijedimerine $C_{28}H_{28}N_2O_4$, 454, 205–207 (methanol) Geijera balansae	270, CD_3SOCD_3	$H\text{-}9_{eq}$	3,76, ddd (13; 4; 2)	30
		H-6	3,46, ddd (4; 3; 2)	
		H-1	2,57, td (13; 4)	
		$H\text{-}7_{ax}$	2,15, dd (13; 2)	
		H-2	2,06, dd (13; 3)	
		$H\text{-}7_{eq}$	1,71, ddd (13; 4; 2)	
		$H\text{-}9_{ax}$	1,30, t (13)	
XXIII. Dimethygeijedimerine (Obtained from XXII) $C_{30}H_{30}N_2O_4$, 482	270, $CDCl_3$	$H\text{-}9_{eq}$	4,07, ddd (13; 4; 2)	30
		H-6	3,77, ddd (4; 3; 2)	
		H-1	2,94, dd (13; 4)	
		$H\text{-}7_{ax}$	2,04, dd (13; 2)	
		H-2	2,02, dd (13; 3)	
		$H\text{-}7_{eq}$	1,82, ddd (13; 4; 2)	
		$H\text{-}9_{ax}$	1,29, t (13)	

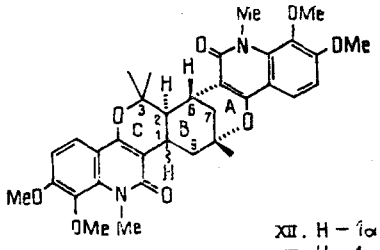
TABLE 1. (continued)

Number of the structure, name, composition, M+, mp, °C (solvent), source	Details of the PMR spectra of the terpenoid			Literature
	working frequency of the instrument, MHz, solvent	protons	CS (δ, ppm; 0 —TMS, HMDS); number of protons; multiplicity (J, Hz)	
1	2	3	4	5
XXIV. Heplodimerine $C_{28}H_{28}N_2O_6$, 486, 292—293 (ethanol) Haplophyllum foliosum Vved.	100, CF_3COOH	H-2 H-1 H-6 H-7 CH_3-9, 10	5.58, m 4.85, m 4.00, m 3.25, m 1.50, s 1.03, s	33
XXXVI. Vepridimerine E (synthesized) $C_{34}H_{38}N_2O_8$, 602, 287—288 (methanol)	360,	H-9_{eq} H-5 H-1 H-2 H-7_{ax} H-7_{eq} H-9_{ax}	3.80, ddd (13,8; 4,3; 3,0) 3.65, ddd (2,9; 2,4; 2,4) 2.84, ddd (12; 12; 4,3) 1.97, dd (12; 2,9) 1.93, dd (13; 2,4) 1.77, ddd (13; 3; 2,4) 1.17, dd (13,8; 12)	42
XXXIX. Dimer of N-methylflindersine (synthesized) $C_{30}H_{30}N_2O_4$, 482, 257—258 (methanol)	270	H-1 H-6 H-7 H-7 CH_3-4, 5, 9, 10	6.35, s 3.58, dd (10; 7) 2.24, dd (14; 7) 2.02, dd (14; 10) 1.96; 1.62; 1.54; 1.31	44

The vepridimerines have the same composition. Their structures were established on the basis of spectral characteristics. Thus, a study of the PMR spectrum of vepridimerine A showed that it was a dimer of the alkaloid veprisine (XI) which is present in the same plants as the dimers A-D [23, 24]. The two molecules are linked in such a way that, according to the ^{13}C NMR spectrum, the terpenoid fragment contains three tertiary methyl groups (24.77, 28.59, and 29.05 ppm), two methylene groups (32.23 and 39.48 ppm), three methine groups (26.20, 27.55, and 43.55 ppm), and two quaternary carbon atoms linked to oxygen atoms (76.83 and 78.95 ppm). The assignment of the signals of the protons of the terpenoid moiety (see Table 1) was made by experiments on the splitting of the signals of the coupled protons in the high-resolution PMR spectrum of vepridimerine A, as a result of which structure (XII) was established for this alkaloid.



XI



XII. H — 1α
XIII. H — 1β

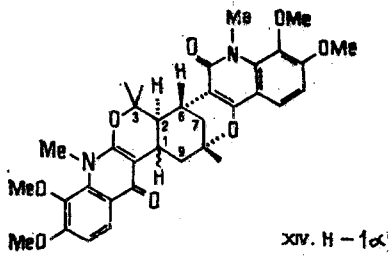
The value of the splitting constant between H-1 and H-2 (^3J = 6.1 Hz) indicates their cis-orientation. A study of the molecule showed that the cyclohexane ring B is present in the chair conformation, since in this case the H_{eq}-9 and H_{eq}-7 protons and the carbon atoms bearing them, C-9, C-8, and C-7, are present in a M-shaped arrangement, as a consequence of which a long-range spin-spin coupling constant between these protons is observed (^4J = 2.2 Hz) [25]. The H-6 and H_{eq}-9 protons experience the greatest influence of the carbonyl groups, and these signals appear at 3.61 and 3.10 ppm, respectively.

According to its spectral characteristics, vepridimerine B (XIII) has the same structure as the dimer A but a different stereochemistry. The large value of the splitting constant between the signals of the H-1 and H-2 protons (^3J = 12.5 Hz) indicates their trans-orientation. The assignment of the signals of the terpenoid moiety made in a similar way to that described above for (XII) is given in Table 1. A study of models allowing for the transposition of the H-1 and H-2 protons and the absence of a long-range splitting constant between the H_{eq}-9 and H_{eq}-7 protons showed that the cyclohexane ring must have the

boat conformation. Under these conditions, the greatest descreening resulting from the influence of the carbonyl groups is experienced by the H-6 and H_{eq}-9 protons the signals of which appear 3.20 and 3.80 ppm, respectively.

Like pteledimerine (V), vepridimerines C (XIV) and D (XV) contain 2- and 4-quinolone nuclei, as is shown by the weak-field signal of the aromatic proton present in the peri-position to the carbonyl group (8.06 ppm) [15] and the value of the chemical shift of the signal of the carbon atom of the carbonyl group (176.29 ppm) which is characteristic for 4-quinolones [26]. In dimer A (XII), the corresponding signals from the 2-quinolone fragment are observed at δ_H 7.69 and δ_C 164.33 ppm.

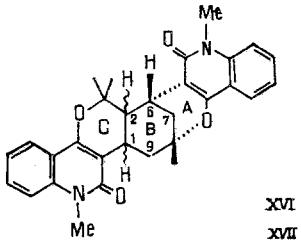
The values of the chemical shifts and splitting constants of the signals of the protons of the terpenoid moiety in the spectrum of vepridimerine C are close to those of (XII) (see Table 1), i.e., it has the same stereochemistry as vepridimerine A. The small difference in the chemical shifts ($\Delta\delta \approx 0.2$ ppm) observed for the H-1 and H_{eq}-9 signals gives grounds for assuming that the 4-quinolone nucleus is located in the left-hand part of the dimer C molecule.



XIV. H – 1α
XV. H – 1β

Similar arguments were used to prove the structure of vepridimerine D (XV) (see Table 1), which, like dimers A (XII) and B (XIII), forms a pair of stereoisomers with the dimer C (XIV) and differs from the latter by the configuration at C-1.

Another group of scientists [22] have established by x-ray structural analysis that paraensidimerines A and C have the heptacyclic structures (XVI) and (XVII) analogous to (XII) and (XIII), with the αα and βα stereochemistries at C-1 and C-2, respectively, i.e., they differ from vepridimerines A (XII) and B (XIII) only by the absence of four methoxy groups.



XVI H – 1α H – 2α
XVII H – 1β H – 2α
XVIII H – 1β H – 2β
XIX H – 1α H – 2β

It has been established by x-ray structural analysis that the cyclohexane ring in (XVI) has the chair conformation, and that in (XVII) the boat conformation. The PMR spectra of paraensidimerines A and C (assignment made independently of [21]) are close to those of vepridimerines A (XII) and (XIII), respectively (deviations within the range of 0.10-0.03 ppm; see Table 1).

As in (XII) and (XIII), the splitting constant of the H-1 and H-2 protons observed on measuring the PMR spectra of (XVI) ($^3J_{1,2}$ = 6 Hz) and (XVII) ($^3J_{1,2}$ = 12 Hz) in deuteropyridine [22] indicates their cis orientation in paraensidimerine A (XVI) and their trans orientation in paraensidimerine C (XVII)). Moreover, a long-range splitting constant between the H-7 and H-9 equatorial protons (^4J = 2 Hz) is observed only in the case of (XVI), since in (XVII), where the cyclohexene ring has the boat conformation, these protons are not arranged in the form of a M (or in a W configuration) [27].

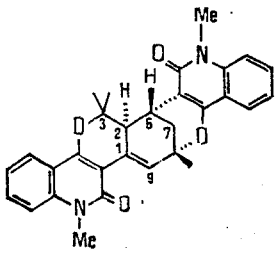
The type of dimerization with the formation of an ABC ring system (type III) under consideration is not new. Such a system has been obtained previously in the synthesis of 2,2-dimethylchromene dimers [28] and in the conversion of the alkaloid alfileramine – a dimer of a prenylated hordenine from Zanthoxylum punctatum Vahl (family Rutaceae) into isoalfileramine [8, 29]. Stereochemical features of the ABC tricyclic system presuppose the existence of four racemic isomers, since rings A/B can only be cis-linked, while rings B/C may be cis (αα and ββ) or trans (αβ and βα) [28]. All four isomers have been isolated from Euxylophora paraensis – dimers A (XVI) and C (XVII) have the αα- and αβ-configurations, while, on the basis of analysis of ^{1}H and ^{13}C NMR spectra, dimers E and F have the ββ and βα configurations relative to the C-2 and C-1 centers, respectively [structures (XVIII) and (XIX)].

A study of models has shown that in the case of dimer E (XVIII), with a chair-like conformation of the cyclohexane rings, the planes of the two quinolone ring systems are parallel and are present at a distance of 2.7 Å, i.e., they eclipse one another.

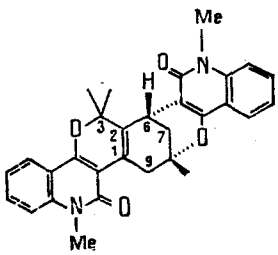
As models show, the cyclohexane ring B assumes the form of a flattened chair. This is confirmed by the values of the splitting constants between the protons at C-6, -2, -1, and -9 found experimentally (0, 11, 14, and 5 Hz), which agree with the assumption that the dihedral angles between H-6 and H-2 ≈ 90°, H-2 and H-1 ≈ 0, and H-1 and H-9 ≈ 0 and 120°, and that the carbon atoms in positions 6, 2, 1, and 9 are almost coplanar.

So far as concerns paraensidimerine F, cyclohexene ring B in XIX exists in the chair form, as is shown by the long-range splitting constant between the H-7 and H-9 equatorial protons and the large splitting constant between the H-1 and H-2 axial protons.

The composition of paraensidimerines G (XX) differs from that of the dimers A, C, E, and F by two hydrogen atoms. Its PMR spectrum shows the signals of only five protons from ring B, one of them being at 7.60 ppm. The presence of a double bond in ring B is confirmed by the ^{13}C NMR spectrum in which there are signals from quaternary (130.4 ppm) and methine (128.1 ppm) olefinic carbon atoms. The existence of a double bond between C-6 and C-7 does not permit the linkage of rings A/B at C-6 and C-8, and therefore linkage at C-1-C-9 remains for it. The absence of splitting between the H-2 and H-6 protons indicates their trans-orientation and a dihedral angle between them of ≈90°. Dimers A (XVI) and C (XVII) have the same orientation of these protons. On the oxidation of dimer C (XVII) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, dimer G is formed in quantitative yield. The oxidation of dimer A under analogous conditions gives dimer G (yield about 80%) and substance (XXI), isomeric with dimer G. The structure of (XXI) was established spectrally (^{1}H and ^{13}C NMR) [20].



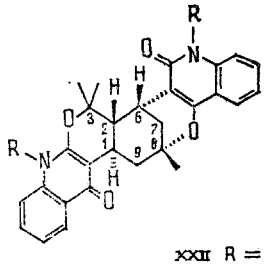
XX



XXI

The features presented above that were revealed in the determination and stereochemistry of dimeric alkaloids of the third group have been used successfully in proving of geijedimerine (XXII), isolated from the leaves of Geijera balansae Schintz. et Guill. growing in New Caledonia [30]. The presence in the mass spectrum of geijedimerine of the peak of the molecular ion with m/z 454 (82%) and the peaks of ions with m/z 228, 227, and 212 shows that it is a dimer of flindersine (XXVI) [31, 32], which is present in the same plant. Its structure was established by spectral methods (see scheme on following page).

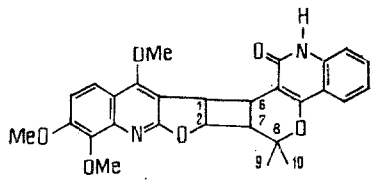
On the basis of the large splitting constant of the H-1 and H-2 protons (13 Hz) and the long-range constant spin-spin coupling between the H-7 and H-9 equatorial protons (^{4}J = 2 Hz), it was concluded that in (XXII) rings B/C are trans-linked, cyclohexane ring B has the chair conformation, and the axial proton at C-2 is β-oriented. Consequently, the stereochemistry of geijedimerine is identical with that of paraensidimerine F (XIX) from which it differs by the absence of N-methyl groups and by the presence of 2-quinoline



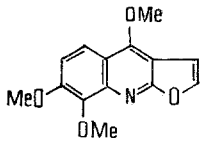
XXXII R = H
XXXIII R = Me

and 4-quinolone ring systems in place of two 2-quinolone systems. A comparative analysis of the PMR spectra of the N,N-dimethyl derivative of geijedimerine (XXIII) obtained from (XXII) and dimer F (XIX) (see Table 1) showed that the signals of the H-1 and H-9 protons in (XXIII) were shifted downfield ($\Delta\delta \approx 0.2$ ppm). Such a shift is characteristic for compounds in which ring C is linked to a 4-quinolone system [21].

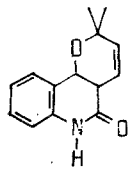
The alkaloid haplodimerine (XXIV) isolated from the fruit of Haplophyllum foliosum Vved. [XXXIII] belongs to the fourth type. Its structure was established by an x-ray investigation which showed that haplodimerine has the heptacyclic structure (XXIV) and consists of a dimer of skimmianine (XXV) and flindersine (XXVI), attached to one another through the double bonds of furan and dimethylpyran rings with the formation of an additional four-membered carbocycle. The dihydrofuranoquinoline and dimethyldihydropyrano-2-quinoline ring systems are cis-oriented relative to the plane of the cyclobutane ring. The dihydrofuran ring has the shape of a strongly flattened envelope, and the dimethyldihydropyran ring the "sofa" conformation with the departure of the C-8 atom from the plane of the other five atoms of this ring.



XXIV



XXV

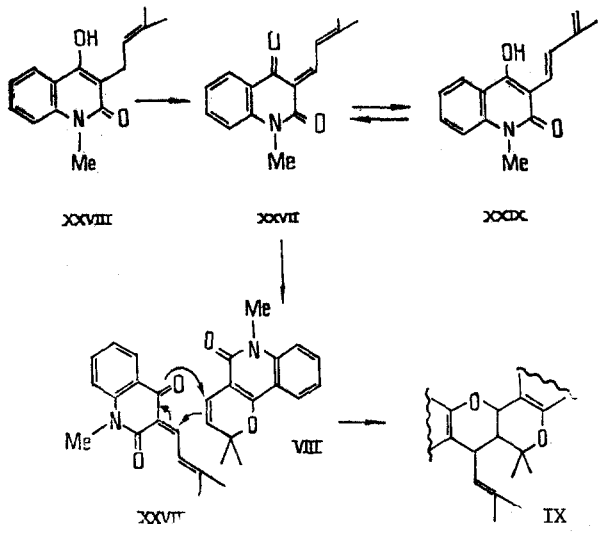


XXVI

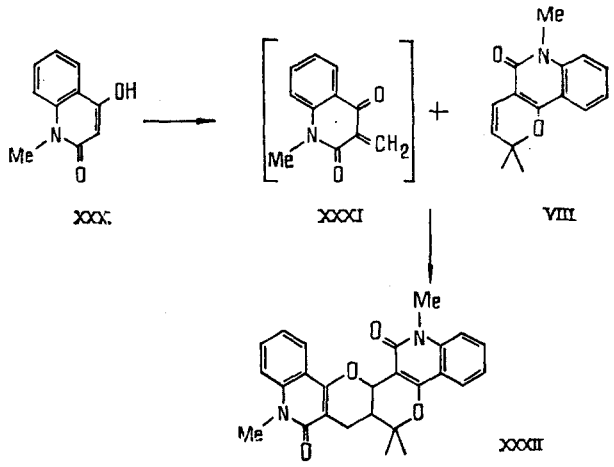
The behavior of haplodimerine under the conditions of mass spectrometry is interesting. The strongest peaks in its mass spectrum are those with m/z 259 (100%) and 212 (50%). The further fragmentation of the ion with m/z 259 resembles the breakdown of the molecular ion of skimmianine (peaks of ions with m/z 258, 256, 244, 230, 216) [34]. The ion with m/z 212 is a pyrylium cation formed as the result of the splitting out of a methyl radical from the molecular ion of flindersine with m/z 227 (15%). Such fragmentation is typical for substances containing a dimethylpyran ring [35]. In the spectrum of the deutero analog of haplodimerine a 1 m.u. shift is observed only for the fragments with m/z 227 and 212, each of which contains an NH group.

In contrast to all the other dimeric quinoline alkaloids, the ring system in the haplodimerine molecule linked the quinoline nuclei consists of 7, and not 10 carbon atoms. However, provisionally haplodimerine can be assigned to the terpenoid quinoline dimers if it is considered that the biogenetic route of the formation of furanoquinoline alkaloids includes a hemiterpenoid unit from which a furan ring is formed as the result of the splitting out of three carbon atoms [36, 37]. Investigations to determine the structures of dimeric alkaloids have shown their affinity and have made it possible on the basis of structural correlations to suggest biogenetic schemes for their formation.

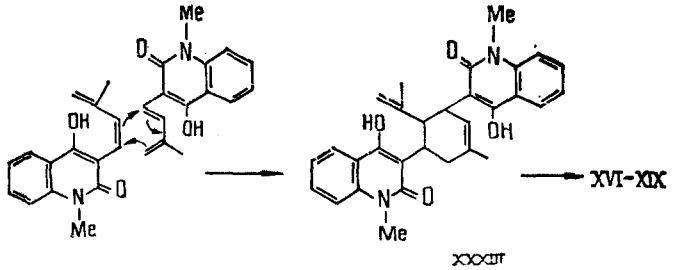
Thus, the alkaloids of the second type (paraensidimerines B and D) can be considered as Diels–Alder adducts between the alkaloid N-methylflindersine (VIII) as dienophile and the quinoline quinone methide (XXVII) as diene. The latter is formed by the oxidation of the C-prenylated quinolone (XXVIII) and is a precursor of the dimethylpyrano-2-quinolone alkaloids [38].



The model compound (XXXII) has been synthesized by a Diels–Alder reaction between (VIII) and the quinone methide (XXXI) obtained from (XXX) in the presence of dichlorodicyanobenzoquinone (XXXIX), confirming a possible route of the biosynthesis of the dimers (IX) and (X).

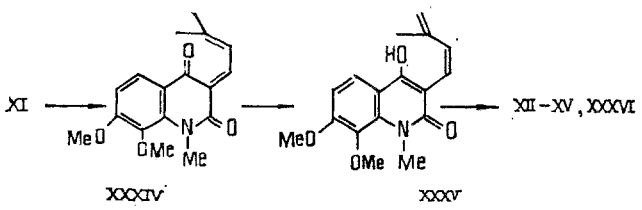


The formation of heptacyclic quinolone dimers of type (III) can be represented by the dimerization of the dehydroprenylated quinolone (XXIX) or its analogs as the result of cycloaddition in the manner of a Diels–Alder reaction [40]

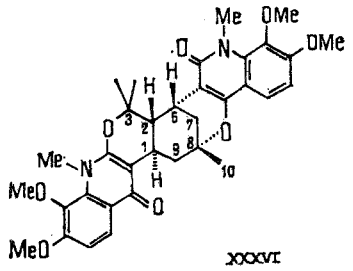


Compound (XXXIII) can then be cyclized by the formation of a ABC ring system (type III) through the presence in (XXXIII), on the one hand, of multiple bonds and, on the other hand, of hydroxy groups capable of interacting with the carbons of these bonds. The passage of the open forms into cyclic forms may be reversible, and in this case the processes of intramolecular addition—splitting out reactions are responsible for the existence of various tautomeric adducts [41] from which racemic stereoisomers can be formed. Biogenetic schemes for their formation are given in [22].

The synthesis of the vepridimerines A-D (XII-XV) has been effected by this scheme. The authors concerned [42] started from the possibility of the opening of the pyran ring in the thermal reaction of veprisine (XI) in the "cyclohexadiene → hexatriene" manner with the formation of a quinolone quinone methide (XXXIV) from which, under these conditions, as the result of a 1,7-sigmatropic shift, it is possible to obtain the required dehydroprenylated quinolone (XXXV).



By heating veprisine (XI) in a sealed tube at 200-220°C [42], a mixture of substances was obtained from which the alkaloids (XII-XV) were isolated together with a fifth dimer — vepridimerine E (XXXVI), the structure of which was established spectrally (^1H and ^{13}C NMR spectra).



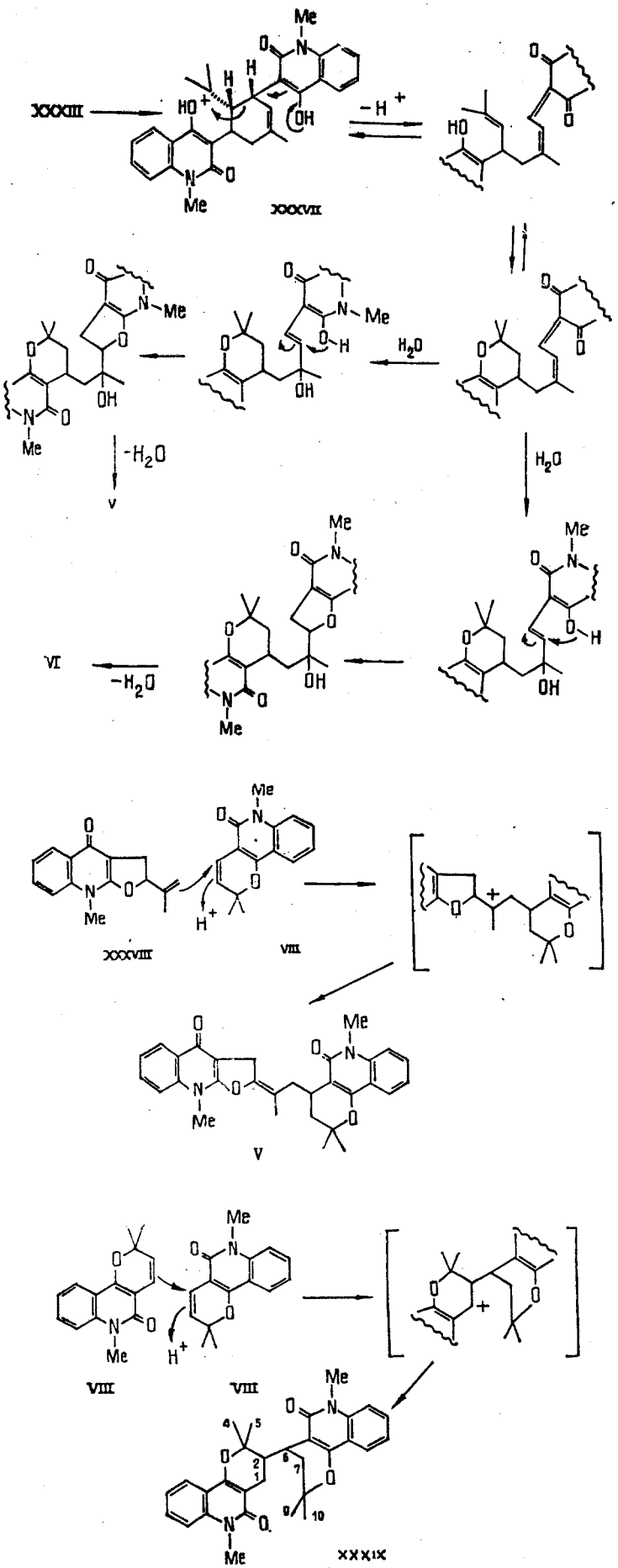
The simple preparation of vepridimerines from veprisine, which had been synthesized previously [23, 43], represents the first complete synthesis of heptacyclic dimers with a new unusual skeleton (see scheme on following page).

The conversion of veprisine (XI) into heptacyclic dimers under thermolysis conditions is not an argument in favor of the suggestion that dimeric alkaloids are not native, since the prolonged heating of (XI) under the conditions of extraction of the alkaloids from the plant left veprisine unchanged.

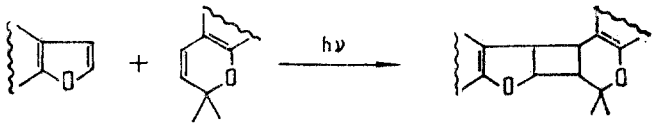
Possible schemes for the biosynthesis of the dimers (V) and (VI) from (XXXIII) by acid-catalyzed reactions have been given in [22]. The protonated form (XXXVII), on undergoing a retro-Michael reaction, can give (V) and (VI).

Another possible mechanism of the biosynthesis of dimers (V) and (VI) by the addition of the olefin (XXXVIII) to N-methylflindersine in the presence of an acid has been proposed [44] which is based on the combined presence in the plant Ptelea trifoliata of N-methylflindersine [18] and analogs of the olefin (XXXVIII) [45, 46] together with (V) and (VI) (see scheme on following page).

As a confirmation of this biosynthetic pathway of the dimers, (XXXIX) has been synthesized from N-methylflindersine (VIII) by heating it with formic or trifluoracetic acid [44] (see scheme on following page). The dimerization of N-methylflindersine can be regarded as acid-catalyzed addition in accordance with the Markovnikov rule through the formation of the most stable carbocation.


XXXIII
XXXVII
-H+
H2O
-H2O
V
VI
XXXVIII
VIII
V
VIII
VIII
XXXIX

The biogenetic pathways of the formation of the alkaloids of type (IV) can be represented as the photocycloaddition of aromatic compounds with the formation of cyclobutane dimers [47, 48].



XXV XXVI XXIV

Photochemical cycloaddition is a common and almost the only method of obtaining compounds of very diverse nature containing a four-membered carbocycle from unsaturated substances [49, 50].

The biological activity of the dimeric quinoline alkaloids has not yet been studied. There is information only on the cytotoxicity of vepridimerine A [42]. However, the prospect of the discovery of new types of dimeric alkaloids with unusual structures of the terpenoid component and interesting stereochemistry is that attractive force that is responsible for the undiminished interest in the chemistry of terpenoid dimers and the investigation of methods for their synthesis [51].

The search for dimers bound by a terpenoid component is promising in plants of those families where natural compounds containing hemiterpenoids constituents (or fragments) are found.

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