32. S. S Popov and N. L. Marekov, Chem. Ind. (London), 655 (1971).
33. H. Inouye, S. Ueda, and Y. Nakamura, Chem. Pharm. Bull., 18, 1856 (1970).
34. L. Canonica, F. Polissoni, P. Manito, and G. Jommi, Tetrahedron, 16, 192 (1961).
35. J. Bricout, Phytochemistry, 13, 2819 (1974).
36. H. Onouye, S. Ueda, and Y. Nakamura, Chem. Pharm. Bull., 18, No. 10, 2043 (1970).
37. E. Stephanou K. Hostettmann, and A. Jacot-Guillarmod, Phytochemistry, 15, 330 (1976).
38. H. Wagner and K. Vasirian, Phytochemistry, 13, 615 (1974).
39. H. Inouye, and Y. Nakamura, Tetrahedron Lett., 47, 4919 (1968).
40. O. Sticher and B. Meier, Pharm. Acta Helv., 53, 40 (1978).
41. H. Inouye, T. Yoshida, S. Tobita, K. Tanaka, and T. Nishioka, Tetrahedron Lett., No. 28, 2459 (1970).
42. Y. Ikeshiro and Y. Tomita, Plant Med., 48, 169 (1983).
43. H. Inouye, S. Ueda, Y. Nakamura, K. Inouye, T. Hayano, and H. Matsumura, Tetrahedron, 30, 571 (1974).
44. J. H. Suhr, P. Arends, and B. Jensen, Phytochemistry 17, 135 (1978).
45. A. Kromayer, Arch. Pharm., 160, 27 (1982).
46. A. M. Verney, Riv. Ital. Essenze, Profumi, Piante Off., Aromi, Saponi, Cosmet., Aerosol., 55, (4), 232 (1973).
47. P. Manitto and U.M.Pagnoni, Gazz. Chim. Ital., 94, 229 (1964).
48. H. Inouye, T. Yoshida, Y. Nakamura, and S. Tobita, Tetrahedron Lett., 4429 (1968).
49. T. Kubota, and Y. Tomita, Tetrahedron Lett., No. 5, 176 (1961).
50. M. Koch, M. Plat. J. Le Men, and N. M. Janot, Bull. Soc. Chim. Fr., 403 (1964).

FLAVOLIGNANS AND OTHER NATURAL LIGNOIDS: PROBLEMS OF STRUCTURAL ANALYSIS

V. A. Kurkin and G. G. Zapesochnaya

UDC 547.9

In this review, literature information on natural lignoids — flavolignans, xanthonolignans, coumarinolignans, and neolignans — is systematized. Questions of the structural analysis of this group of natural compounds are discussed.

At the present time, a fairly large amount of factual material on the class of natural lignoids has accumulated, and therefore the necessity for its generalization has arisen. There are reviews in the literature on flavolignans, but, as a rule, they relate to structural investigations and the pharmacological properties of compounds from milk thistle [1-5]. It must be mentioned that recently information has begun to appear ever more frequently in the literature not only on flavolignans but also on other lignoids — coumarinolignans, xanthonolignans, and neolignans. As a result of this, even today in structural investigations of these compounds certain methodological approaches have arisen which are applicable to the whole class of lignoids.

A feature of the structural investigations of natural lignoids is the fact that the complete proof of their structure requires not only traditional spectral methods but also chemical transformations (cleavage, synthesis, the preparation of various derivatives). The difficulties up against which workers have come in determining the structures of such compounds are clearly demonstrated by the history of the first representative of the class of flavanolignins — silybin — the complete structure and absolute configuration of which were established only as the result of synthetic studies. This required the efforts of many scientists of various countries for more than 20 years [6-12].

In the present review, an attempt has been made to generalize information on all groups of lignoids in the light of the problems that scientists solve in the course of structural studies of compounds of this class.

All-Union Scientific-Research Institute of Medicinal Plants, Moscow. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 11-35, January-February, 1987. Original article submitted January 20, 1986.

0009-3130/87/2301-0007$12.50

CLASSIFICATION AND NOMENCLATURE. DISTRIBUTION IN NATURE

In the study of the literature on lignoids, workers come up against such difficulties as the absence of a single nomenclature. All natural lignoids can be divided into four large groups: I — flavolignans (flavano- and flavonolignans); II — xanthonolignans; III — coumarinolignans; and IV — neolignans.

Since in all four groups of compounds a common structural element is a coniferyl alcohol residue or another similar fragment, for convenience we may consider a classification and nomenclature that clearly show the component parts of the molecules and distinctly single out the side chain of the coniferyl alcohol residue [13] (see Table 2). Furthermore, each of these groups can be distinguished by the type of attachment of the coniferyl residue with the formation of various systems: a) 1,4-dioxanes; b) benzofurans; c) tricyclic ketones; d) cyclohexanoids; and e) ethers.

Table 1 gives the structures of natural lignoids, their physicochemical charactersitics, and their plant sources on the basis of this classification.

Table 1 shows that flavolignans are found in six families, the greater number of them (12 compounds) have been isolated from the fruit of milk thistle — *Silybum marianum* (L) Gaertn. (Asteraceae). The flavonoid moiety of the compounds of this group is represented by flavo-nones (eriodictyol), flavonols (taxifolin), flavones (luteolin, scutellarein, isoscutellarein, tricetin, tricin), and flavonols (herbacetin).

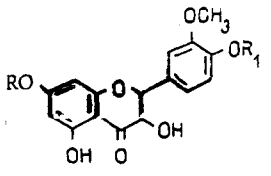
All the xanthonolignans were isolated from plants of the family Hypericaceae, while coumarinolignans have been found in four families (Table 1). It is interesting that all the compounds of these two groups contain a 1,4-dioxane ring in their structure.

The bulk of the neolignans has been isolated from plants of the family Lauraceae, compounds both with 1,4-benzodioxane and with dihydrobenzofuran structures having been found (Table 1).

FLAVOLIGNANS

Flavolignans — flavonoids containing in their molecule an additional C_6–C_3 fragment (mainly from coniferyl alcohol) — form a comparatively small new group of natural compounds. The first representative of the flavanolignans, silybin (1) was isolated by a number of authors from the fruit of the milk thistle [14, 26, 47].

The unusual nature of this compound initially led workers to incorrect structures. At first, Wagner et al. [47], on the basis of the results of the fusion of the substance with bromosuccinimide and pyridine hydrobromide, and also of the NMR spectra of silybin, its pentaacetate, and its trimethyl ether, proposed the structure of 3'-methyltaxifolin containing a $C_{10}H_{11}O_4$ residue in position 7 for this compound. Then Hänsel et al. [8] and Wagner et al. [48] proposed a chromandiol structure for silybin. The difference between the proposed structures consisted only in the fact that Hänsel et al. assigned a chromandiol residue to the 4'-OH group, while Wagner et al. considered the substition of the 7-OH or 4'-OH group by this residue to be equally probable.



Hänsel et al.(1967):

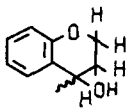
R = H; R_1 = Ø

Wagner et al.(1968):

a) R = H; R_1 = Ø

b) R = Ø; R_1 = H

Ø =



Pelter and Hänsel [12] continued the study of the structure of silybin, and on the basis of the NMR and mass spectra of the initial compound and its pentaacetate and pentamethyl ether established that silybin belonged to a new class of flavoglycans. The analysis of the signals of the aliphatic protons in the NMR spectra presented the greatest difficulty; these were distinguishable only in the pentamethyl ether and clearly showed the presence of the following system in the (1) molecule:

TABLE 1. Natural Lignoids and Their Distribution in Plants

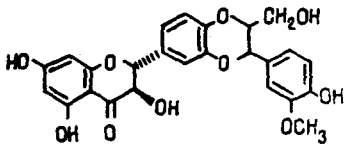
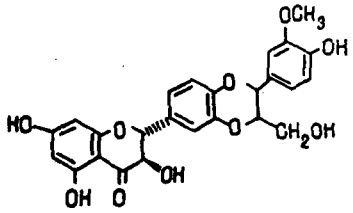
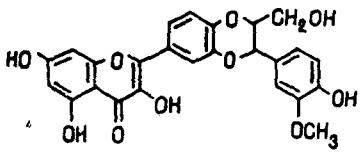
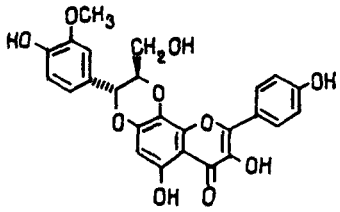
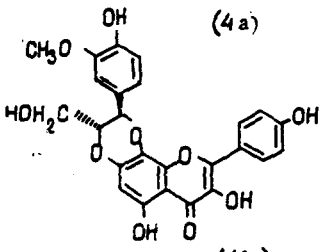
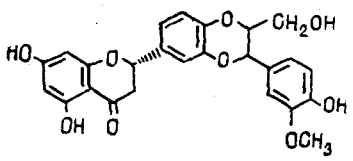
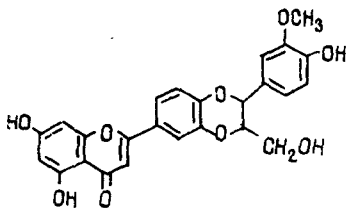
Structure of the compound	Name, constants, plant source
1	2
	1. Flavolignans a) 1,4-dioxanes 1. Silybin $C_{25}H_{22}O_{10}$, mp 164—168°, $[\alpha]_D$ +10,8°(acetone), Silybum marianum Gaertn. (Asteraceae), fruit [14]
	2. Isosilybin $C_{25}H_{22}O_{10}$, mp. 239—241°, $[\alpha]_D$ +16,9° (acetone), S. marianum, fruit [6, 15]
	3. 2,3-Dehydrosilylbin $C_{25}H_{20}O_{10}$, mp. 254—255°, S. marianum, fruit [16]
 (4a)	4. Rhodiolin $C_{25}H_{20}O_{10}$, mp. 235—237°, $[\alpha]_D$ ±0° (acetone) Rhodiola rosea L. (Crassulaceae), rhizomes [17]
 (4b)	
	5. Silandrin $C_{25}H_{22}O_9$, mp. 234—236°, $[\alpha]_D$ −42,7° Silybum marianum (white-flowered variety), fruit [14]
	6. Hydnocarpin $C_{25}H_{20}O_9$, mp 262-264° Hydnocarpus wightiana (Blume), Flacourticaceae, fruit [18]; Cassia absus L. (Fabaceae), fruit [19]

TABLE 1 (Continued)

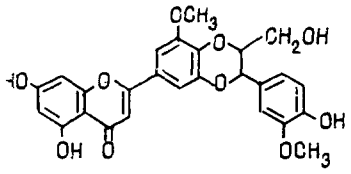
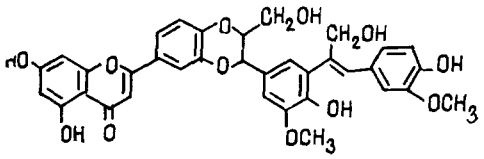
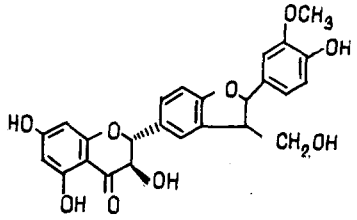
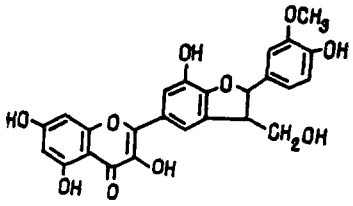
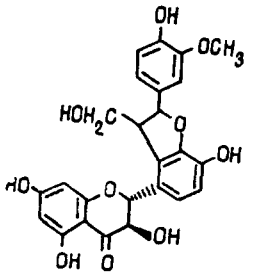
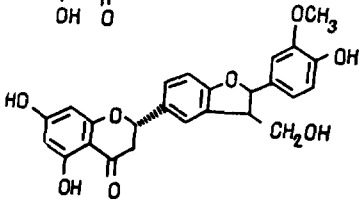
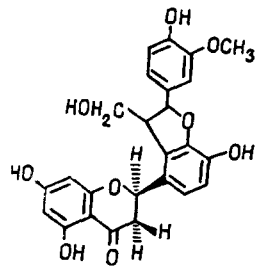
Structure of the compound	Name, constants, plant source
1	2
	7. Methoxyhydnocarpin $C_{26}H_{22}O_{10}$, Hydnocarpus wightiana, fruit [20]
	8. Hydnowightin $C_{35}H_{30}O_{12}$, mp. 239-241° $[\alpha]_D$ +40° (methanol) H.wightiana, fruit [21]
	b) Benzofurans
	9. Silychristin $C_{25}H_{22}O_{10}$, mp. 174-176° $[\alpha]_D$ +81,4° (pyridin), Silybum marianum, fruit [22]
	10. 2,3-Dehydrosilychristin $C_{25}H_{20}O_{10}$, mp. 275—277°, Silybum marianum, fruit [23]
	11. Isosilylchristin $C_{25}H_{22}O_{10}$, mp 155-157° $[\alpha]_D$ +245° (pyridine) Silybum marianum, fruit [24]
	12. Silyhermin $C_{25}H_{22}O_9$; isolated from the form of the pentaacetate from the fruit Silybum marianum (white-flowered variety): $C_{35}H_{32}O_{14}$, mp. 93-95° $[\alpha]_D$ +29,9° (chloroform)
	13. Neosilyhermin A $C_{25}H_{22}O_9$, $[\alpha]_D$ —99,0° (methanol) Silybum marianum (white-flowered variety fruit [13]

TABLE 1 (Continued)

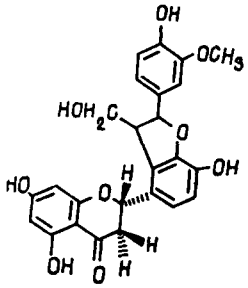
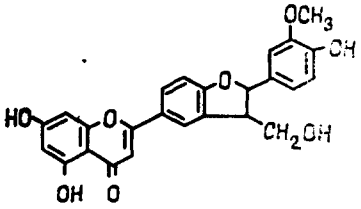
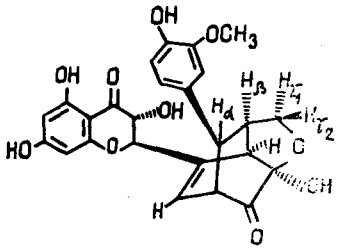
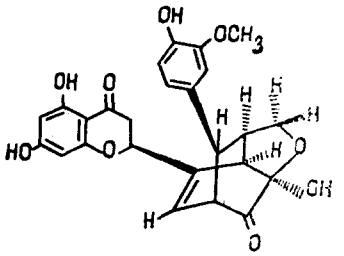
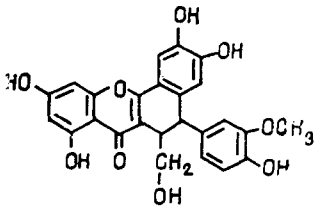
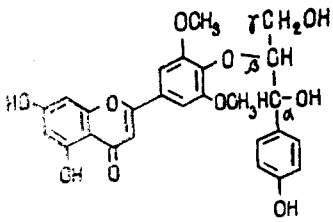
Structure of the compound	Name, constants, plant source
1	2
	14. Neosilyhermin B $C_{25}H_{22}O_9$; isolated from the form of the pentaacetate from the fruit of Silybum marianum (white-flowered variety): $C_{35}H_{32}O_{14}$, mp. 98-100° $[\alpha]_D$ +24.8° (chloroform)
	15. Isohydnocarpin $C_{25}H_{20}O_9$, mp. 238—240°, Hydnocarpus wightiana, fruit [25] Cassia absus, fruit [19]
	c) Tricyclic ketones 16. Silydianin $C_{25}H_{22}O_{10}$, mp. 189-191° $[\alpha]_D$ +218° Silybum marianum, fruit [26]
	17. Silymonin $C_{25}H_{22}O_9$, mp. 258—260°, $[\alpha]_D$ +127°, Silybum marianum (white-flowered variety) fruit [14]
	d) Cyclohexanol 18. Neohydnocarpin $C_{25}H_{20}O_9$, mp. 235-237° $[\alpha]_D$ —20,3° (methanol) Hydnocarpus wightiana, fruit [20]
	e) Ethers 19. Aegicin $C_{26}H_{24}O_{10}$, mp. 235—236°, $[\alpha]_D$ —4°, Aegilops ovata L. (Gramineae), whole plant [27]

TABLE 1 (Continued)

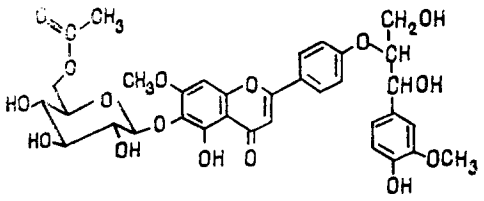
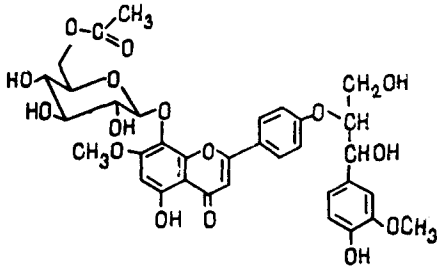
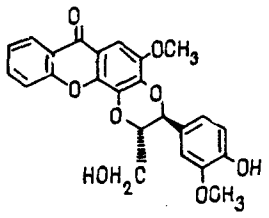
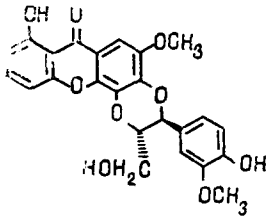
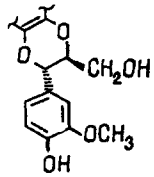
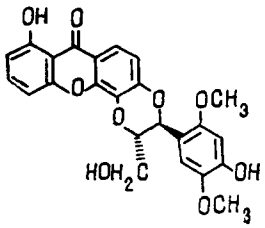
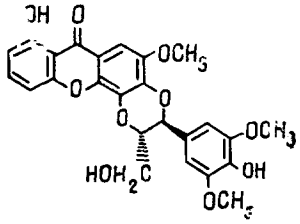
Structure of the compound	Name, constants, plant source
1	2
	20. Lignoside $C_{34}H_{36}O_{16}$, mp. 245-247° $[\alpha]_D$ −91,6° DMF Gratiola officinalis L. (Scrophulariaceae) herbage [28, 29]
	21. Isolignoside $C_{34}H_{36}O_{16}$, mp. 230-232° $[\alpha]_D$ −147,3° DMF Gratiola officinalis L. herbage [28, 29]
	II. Xanthonolignans a) 1,4-Dioxanes 22. Kielcorin $C_{24}H_{20}O_8$, mp 250-251° $[\alpha]_D$ ±0° Kielmeyera coriacea, Caraipa densiflora (Hypericaceae), roots [30]; Hypericum calycinum, H. androsaeum, H. maculatum, H. perforatum (Hypericaceae), roots [31]; H. ericoides, herbage [32]
 (23a)  (23b)	23. Cadensin A $C_{24}H_{20}O_8$, mp. 264-267° Caraipa densiflora roots [30]
	24. Cadensin B $C_{24}H_{22}O_{10}$, mp. 236-238° Caraipa densiflora roots [30]
	25. Cadensin C $C_{24}H_{22}O_{10}$; Vismia guaramirangae (Hypericaceae), roots [33] isolated in the form of the triacetate: $C_{30}H_{28}O_{13}$, mp. 210-214°

TABLE 1 (Continued)

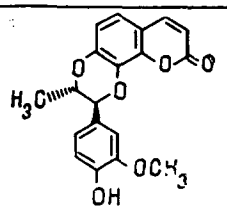
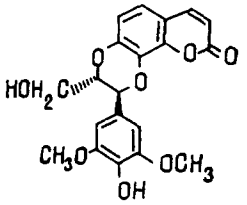
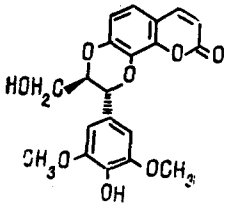
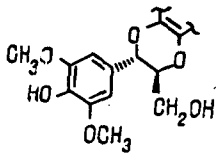
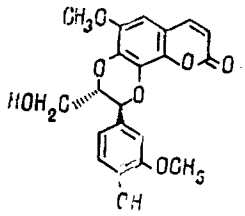
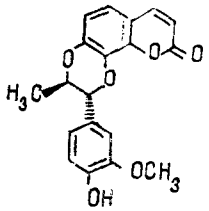
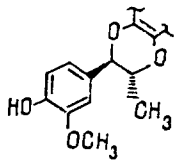
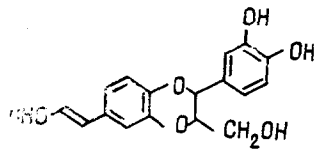
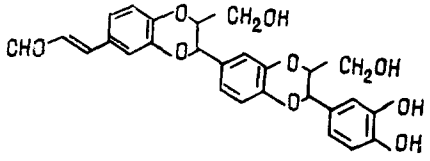
Structure of the compound	Name, constants, plant source
1	2
	III. Coumarinolignans a) 1,4-Dioxanes 26. Compound B $C_{20}H_{18}O_7$, mp. 245—248°, $[\alpha]_D$ —56°, Jatropha glandulifera (Euphorbiaceae), roots [34]
	27. Daphneticin $C_{20}H_{18}O_8$, mp. 235-238° $[\alpha]_D$ ±0° (pyridin) Daphne tangutica (Thymelaeaceae), stems and roots [35]
 (28 a)  (28b)	28. Aquillochin $C_{21}H_{20}O_9$, mp. 220°, Aquillaria agallocha (Thymelaeaceae), herbage [36]
	29. Cleomiscosin A $C_{20}H_{18}O_8$, mp. 247—249°, Cleome viscosa (Capparidaceae), fruit [37]
 (30 a)  (30b)	30. Propacin $C_{20}H_{18}O_7$, mp. 226—228°, Protium opacum (Burseraceae), bark [38]
	IV. Neolignans a) 1,4-Dioxanes 21. Americanin A $C_{18}H_{16}O_6$, mp. 246—247°, $[\alpha]_D$ +23,7°, Phytolacca americana (Phytolaccaceen), fruit [39, 40]
	32. Americanin B $C_{27}H_{24}O_9$, mp. 258—260°, $[\alpha]_D$ +1,7° (pyridin) Ph. americana, fruit [39]

TABLE 1 (Continued)

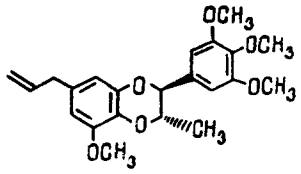
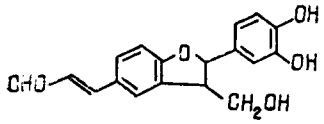
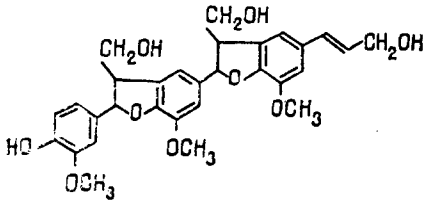
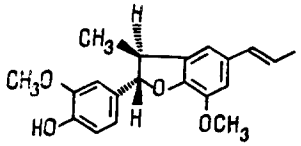
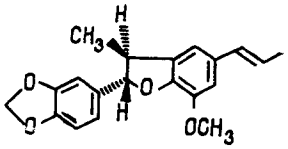
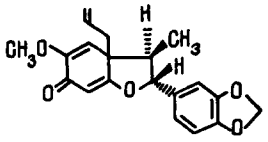
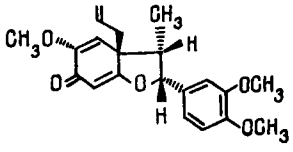
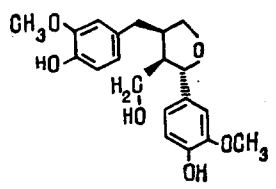
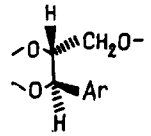
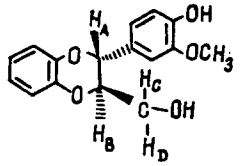
Structure of the compound	Name, constants, plant source
1	2
	33. Eusiderin $C_{22}H_{26}O_6$, mp. 94°, $[\alpha]_D$ −25,4°, Eusideroxylon zwageri (Lauraceae), bark [41]
	b) Benzofurans 34. Americanin D $C_{18}H_{16}O_6$, mp. 197—200°, Phytolacca americana, fruit [39]
	35. Herpetotriol $C_{30}H_{32}O_9$, mp. 175—176°, $[\alpha]_D$ −20°, Herpetospermum caudigerum (Cucurbitaceae) [42]
	36. Licarin A $C_{20}H_{22}O_4$, mp. 114—116°, Licaria aritu (Lauraceae), bark [43]
	37. Licarin B $C_{20}H_{20}O_3$, mp. 91—92°, Licaria aritu (Lauraceae), bark [43]
	38. Burchellin $C_{20}H_{20}O_5$, mp. 154—156°, Aniba burchelli (Lauraceae), bark [44]
	39. Porosin $C_{21}H_{26}O_5$, mp. 133-135°, Ocotea porosa (Lauraceae), bark [45]

TABLE 1 (Continued)

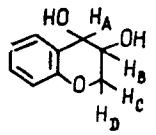
Structure of the compound	Name, constants, plant source
1	2
	40. Lariciresinol 4'-methyl ether $C_{21}H_{26}O_6$, mp. 125—127°, $[\alpha]_D$ +12,9° (chloroform) Turrea nilotica (Meliaceae), leaves [46]
	

Mass spectra showed the presence of fragments with m/z 180, 162, 137, and 124, which are characteristic for coniferyl alcohol. All this permitted these authors [12] to propose for silybin two possible structures (1 and 2) and to express the opinion that it was formed as the result of the oxidative coupling of taxifolin and coniferyl alcohol.

In the course of the synthesis of the cis and trans isomers of 1,4-benzodioxane (41) and of chroman-3,4-diol (42), the presence in a silybin of a 1,4-benzodioxane ring with substituents in the transoid position was confirmed [10].



(41)

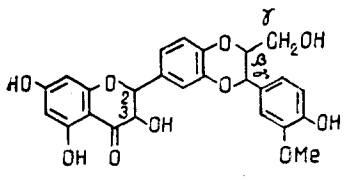


(42)

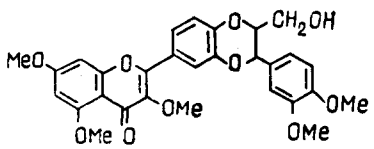
At the same time, it was shown that compounds (41) and (42) differed considerably with respect to their PMR spectra. Thus, the signal of the most descreened proton (H_A) appeared in the spectrum of (42) and of its diacetate in the form of a doublet (SSCC for the cis isomer 4 Hz, and for the trans isomer 3 Hz), and the signals of the H_B, H_C, and H_D protons formed a broad multiplet at 4.2-4.8 ppm, while for the model benzodioxane (41) and silybin (1), the H_A signal (trans form) appeared in the form of a doublet with J = 8 Hz (4.9 ppm), and the H_B and H_C/H_D protons formed two groups of signals in the stronger field (Table 2); the benzyl proton (H_A) of the cis isomer (41) resonated in the form of a doublet with a constant of 2-3 Hz.

Thus, a detailed analysis of the signals of the aliphatic protons in the PMR spectra of the above-mentioned compounds led to the unambiguous conclusion of the transoid configuration of the substituents in the 1,4-benzodioxane part of the silybin molecule.

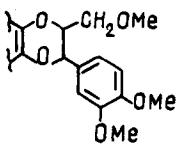
However, two more questions had to be answered: the positions of the substituents in the benzodioxane part of the molecule (i.e., structure 1 or 2) and the absolute configurations of the chiral centers C-α and C-β. The results of experiments on the cleavage of silybin [11] did not permit a choice to be made between the two possible structures. Only in the course of synthetic studies [7-9] was structure (1) shown reliably for silybin.



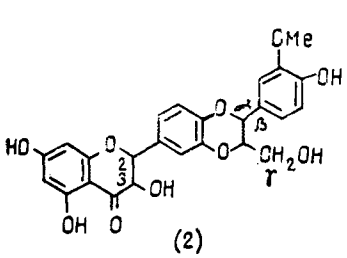
(1)



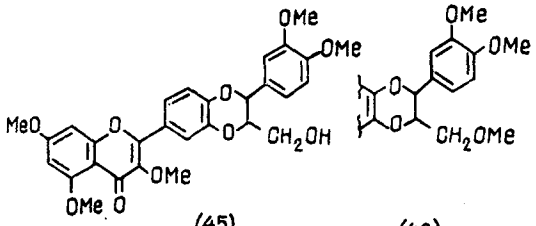
(43)



(44)



(2)



(45)

(46)

In this work, the tetra- and pentamethyl ethers of dehydrosilybin (43 and 44) and the analogous derivatives of its regio-isomer (45 and 46) were synthesized, and the corresponding derivatives were also obtained from natural silybin. These derivatives were not selected at random. On the one hand, the pentamethyl ether (44) is a well crystallizing and stable compound readily soluble in chloroform, and its signals are easily interpreted on comparative NMR spectroscopy. From another aspect, the endeavor to synthesize dehydro derivatives of silybin was due to the fact that this eliminated the stereochemical difficulties that were connected with the presence of two chiral centers in the flavanonol molecule (C-2 and C-3). The comparison showed that the natural tetra- and pentamethyl ethers of dehydrosilybin were identical, according to their PMR and IR spectra, with synthetic derivatives (43) and (44), respectively. So far as concerns their mass spectra, the fragmentations of the corresponding derivatives were very similar; however, when the spectra were recorded under the same temperature conditions the natural and synthetic derivative (44) had not only identical fragmentations but also identical relative peak intensities.

A study of the absolute configuration of silybin by comparing its circular dichroism (CD) spectra with the CD spectra of other flavanonols showed the 2R,3R configuration only for the flavanonol moiety: a negative Cotton effect in the short-wave region (295 nm) and a positive effect at 330 nm [3, 39]. Since the C-α and C-β asymmetric centers are not adjacent to a carbanol group, their contribution to the CD spectrum is insignificant, and the curve of the CD spectra is very similar to the curves of the 3R-flavanonols which did not permit Wagner [3] to draw any conclusions whatever.

On the basis of literature information, the hypothesis was put forward [7] that the pentamethyl ether (44), which is characterized by a considerable specific levorotation, had the αR,βR configuration. This conclusion was also applied to silybin.

However, its erroneousness was shown subsequently. Experiments on the mild dehydrogenation of silybin [6, 50], led to the optically inactive 2,3-dehydrosilybin. This investigation showed that natural silybin is a diastereoisomeric mixture of compounds with the same configuration at C-2 and C-3 and the opposite configurations at C-α and C-β: α-R,β-R and α-S, β-S. These conclusions were later confirmed by a brilliant 1-stage biomimetic synthesis of silybin (1) from taxifolin and coniferyl alcohol [6, 15, 31]. This gave a mixture of silybin and isosilybin (2) in a ratio of 57:43 (determined by the HPLC method). The isosilybin obtained was identical with the isosilybin isolated by preparative TLC from the fruit of the milk thistle [6]. On this basis, the authors concluded that the racemic silybin synthesized by Mishima et al. [51] was actually isosilybin.

These results were also confirmed by the hypothesis [11] that silybin is formed in the plant by the free-radical oxidative interaction of dihydroquercetin and coniferyl alcohol which may lead to a mixture of regio- and diastereoisomers.

The IR, UV, and ^{1}H and ^{13}C NMR spectra of silybin and of isosilybin are very similar and do not permit the type of isomerism to be determined. The structure of isosilybin was established definitively with the aid of the mild dehydrogenation of this compound in boiling pyridine [6], which gave dehydroisosilybin quantitatively. Dehydroisosilybin and dehydrosilybin were well separated by TLC, and thus excluded the possibility of diastereoisomerism at C-α and C-β between (1) and (2) which would have led to identical dehydroderivatives.

The same authors [6] report that in the measurement of the ^{1}H NMR spectra of the 2,3-dehydro derivatives (1) and (2) in benzene containing the minimum amount of pyridine to improve solubility, the signals of the H-α atom and of the methoxy group were split into two peaks of equal intensity with $\Delta\nu$ 1-2 Hz (100 MHz). On this basis, the authors [6] concluded that natural silybin and isosilybin formed a diastereoisomeric mixture with the 1:1 composi-

TABLE 2. Details of the PMR Spectra of Lignoids and Their Acetates (δ, ppm; J, Hz)

Compound	Solvent	Protons				Literature
		Ar–CH– (H-α)	–CH–CH_2– (H-β)	–CH_2O– (2H-γ)	–CH_3 (3H-γ)	
1	2	3	4	5	6	7
Silybin (1)	DMSO	4,88 (d, 8 Hz)	4,00—4,10 (m)	3,1—3,7 (2H, m)	—	11
Pentaacetate of (1)	$CDCl_3$	4,88 (d, 7 Hz)	4,25 (m)	3,96 (q, 5 and 10; H-γ_1); 4,36 (q, 3 Hz, H-γ_2)	—	11
The model benzodioxane (41)	$CDCl_3$	4,94 (d, 9 Hz)	4,01 (m)	3,53 (dd, 4 dd 13; H-γ_1); 3,80 (dd, 3 and 13; H-γ_2)	—	10
Dehydrosilybin (3)	C_5D_5N	5,36 (d 8 Hz)	4,36 (br. d)	3,7—4,1 (2H, m)	—	11
Pentaacetate of (3)	$CDCl_3$	4,97 (d, 7,5)	4,2—4,5 (m)	3,8—4 15 and 4,2—4,5 (2H, m)	—	11
Rhodiolin (4)	$(CD_3)_2CO$	5,27 (d, 8 Hz)	4,23 (m)	3,66 (dd, 4 and 12, H-γ_1); 4 00 (dd, 3 and 12, H-γ_2)	—	17
Pentaacetate of (4)	$CDCl_3$	5,10 (d, 8 Hz)	4,60 (3H, m)		—	17
Siladrin (5)	$(CD_3)_2CO$+ +CF_3CO_2D	5,03 (d, 8 Hz)	4,20 (m)	3,67 (1H, d, 6 Hz) 3,62 (1H, d, 4,5 Hz)	—	57
Tetraacetate of (5)	$CDCl_3$	4,98 (d, 8 Hz)	3,82—4,50 (3H, br. m)		—	57
Hydnocarpin (6) tetraacetate	$CDCl_3$	4,97 (d, 7,5 Hz)	4,18—4,50 (3H, m)		—	18
Silychristin (9)	$(CD_3)_2CO$+ +CF_3CO_2D	5,60 (d, 6,2 Hz)	3,50—4,00 (3H, m)		—	22
Pentaacetate (9)	$CDCl_3$	5,61 (d, 6 Hz)	3,60—3,95 (m)	4,38 (2H, d, 6,5 Hz)	—	22
Isosilychristin (11)	CD_3CN	5,62 (d, 2 Hz)			—	24
Hexaacetate of (11)	CD_3CN	5,82 (d, 2,5)	3,81—3,88 (m)	4,28—4,43 (q, q, 5 5 and 11,7 Hz)	—	24
Silyhermin (12) pentaacetate	$CDCl_3$	5,60 (d, 6 Hz)	3,8 (m)	4,36 (dd, 7,5 and 11, H-γ_1); 4,45 (dd, 5,5 and 11, H-γ_2)	—	13
Neosilyhermin A (13) pentaacetate	$CDCl_3$	5,66 (d, 3,5 Hz)	3,9 (m)	4,35 (dd, 7 and 11, H-γ_1); 4,40 (dd 5 and 11, H-γ_2)	—	13
Neosilyhermin B (14) pentaacetate	$CDCl_3$	5,72 (d, 3Hz)	3,8 (m)	4,28 (dd, 8,5 and 11, H-γ_1); 4,49 (dd, 4,5 and 11, H-γ_2)	—	13
Isohydnocarpin (15) pentaacetate	$CDCl_3$	5,65 (d, 6 Hz)	3,78 (m)	4,38 (2H, d, 6,5 Hz)	—	25
Silydianin (16)	$(CD_3)_2CO$	3,40 (m)	2,97 (m)	3,88 (1H, d, 8 Hz 4,32 (q, 3,5 and 8 Hz,	—	22
Silymonin (17)	$(CD_3)_2CO$	3,39 (d, 2,5)	2,87 (m)	3,87 (d, 8 Hz H-γ_1); 4,29 (d, 3 Hz, H-γ_2)	—	57
Neohydnocarpin (18) hexaacetate	$CDCl_3$	4,70 (s)	3,61 (m)	4 0—4 15 (2H, m)	—	21
Aegicin (19)	DMSO + +D_2O	4,82 (d, 5 Hz)	4,2 (dt)	3,4 (m)	—	27
Pentaacetate of (19)	$CDCl_3$	6,1 (d, 6 5)	4,64 (dt, 6 and 4)	3,91 (dd 4 and 12 Hz) 4,3 (dd, 4 and 12 Hz)	—	27
Kielcorin (22)	DMSO	5,06 (d, 8 Hz)	4,37 (dm, 8 and	3,85 (1H, m) 3,58 (dd 3 and 12,5 Hz)	—	30

TABLE 2 (Continued)

Compound	Solvent	Protons				Literature
		Ar–CH– (H-α)	–CH–CH₂– (H-β)	–CH₂O– (2H-γ)	–CH₃ (3H-γ)	
1	2	3	4	5	6	7
Diacetate of (22)	$CDCl_3$	5.05 (br. d, 7,5)	4.05–4.60 (3H, m)		—	30
Cadensin C (25) triacetate	$CDCl_3$	5.0 (br. d. 7Hz)	4.05–4.60 (3H, m)		—	33
Compound B (26)	DMSO	4.70 (d, 7Hz)	4.30 (m)	–	1.20 (3H, d, 7)	34
Monoacetate of (26)	$CDCl_3$	4.70 (d, 7Hz)	4.20 (m)	—	1.30 (d, 7Hz)	34
Daphneticin (27)	DMSO	5.10 (d, 7,5Hz)	4.34 (m)	3.59 (2H, m)	—	35
Diacetate of (27)	DMSO	5.25 (d, 7,5)	4.79 (m)	4.22 (2H, m)	—	35
Aquillochin (28)	DMSO	5.05 (d, 8Hz)	4.1 (m)	3.5 (2H, m)	—	36
Diacetate of (28)	DMSO	4.88 (d, 8Hz)	4.31 (m)	4.03 (2H, m)	—	36
Propacin (30)	$CDCl_3$	4.70 (d, 7,5)	4.3 (m)	—	1.33 (d, 6, 5Hz)	38
Americanin A (31)	?	4.97 (d, 8Hz)	4.15 (m)	3.5 (2H, m)	—	40
Eusiderin (33)	$CDCl_3$	4.58 (d, 7Hz)	4.10 (m)	—	1.26 (d, 6Hz)	68
Americanin D (34)	?	5.69 (d 6Hz)	3.85 (m)	4.43 (2H, m, 7Hz)	—	39
Herpetotriol (35)	$CDCl_3$	6.14 (d, 6, 5)	4.00 (m)	4.22 (2H, m)		42
Licarin A (36)	$CDCl_3$	5.14 (d, 9, 2)	3.48 (dq), 6.7 and 9.2)	—	1.43 (d, 6, 7Hz)	43
Licarin B (37)	$CDCl_3$	5.04 (d 8,9)	3.39 (min, 8 Hz)	—	1.35 (d, 7Hz)	43
Burchellin (38)	$CDCl_3$	5.17 (d, 9,5)	2.88 (dq, 6.9 9.5)	—	1.16 (d, 6, 9Hz)	44
Porosin (39)	$CDCl_3$	5.89 (d, 5,4)	2.6 (m)	—	0.52 (d, 7,5Hz)	45
Lariciresinol 4'-monomethyl ether (40)	$CDCl_3$	4.81 (d, 6Hz)		3.8 (2H, m)	—	46
Diacetate of (40)	$CDCl_3$	4.79 (d, 6Hz)	2.5–3.0 (m)	4.18 (1H, dd, 7dd 10Hz); 4.36 (1H, dd, 7and10 Hz)	—	46

Symbols: s – singlet; d – doublet; t – triplet; q – quartet; quin – quintet; m – multiplet br. – broad signal; ? – solvent not given.

tion, which agrees with the zero specific rotation for the 2,3-dehydro derivatives of both regio isomers.

In recent years, liquid chromatography has been used successfully for studying the structure of the flavolignans [6, 15, 52-55]. On analysis by the HPLC method, silybin (sharp melting point, one TLC spot) issued in the form of a single peak if acidified mixtures of dioxane or acetonitrile were used as the mobile phase [6, 15, 52]. When mixtures containing methanol were used, silybin was separated into two peaks (A and B) [52] as in the case of another flavanolignin – isossilybin [6] but under these conditions the flavonolignan hydnocarpin gave only one peak [52]. On the basis of these results, the authors came to the conclusion that the flavanolignans silybin and isosilybin, unlike the flavonolignase, formed diastereoisomeric pairs that could be separated by the HPLC method only under the conditions of a reversed-phase process on C-18 with the mixture methanol–water–acetic acid (40:60:5) [52].

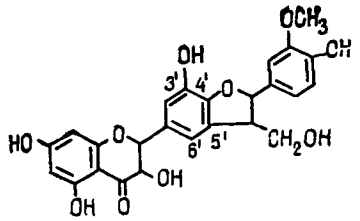
The flavolignans 3-21 belong to one of the five types of attachment of the aryl residue to the flavonoid molecule.

Among the 1,4-dioxanes, interest is presented by rhodiolin (4) and hydnowightin (8). Rhodiolin, isolated from the rhizomes of roseroot stonecrop, was the first example of the attachment of the coniferyl alcohol residue to ring A of a flavonoid (herbacetin). The relative configuration of the substituents in the dioxane fragment of (4) is transoid (Table 2), but the question of regio-isomerism in this part of the molecule remains open. In view of its zero specific rotation, it may be assumed by analogy with information in the literature for kielcorin (22) [50] and for the 2,3-dehydro derivatives of silybin and isosilybin [6] that rhodiolin is a mixture of enantiomers with the structure (4a) or (4b) [17].

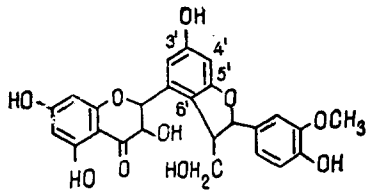
In hydnowightin (8), one coniferyl alcohol residue is attached to luteolin with the formation of a benzodioxane fragment, and a second in position 5 of the guaiacyl residue with the formation of a hydroxymethylstilbene structure. Sharma et al. [21] have proposed an unambiguous structure for compound (8), but here again two regio-isomers are possible. For example, in the course of synthetic studies [56, 57], the structure of hydnocarpin (6) was refined as 3-deoxydehydroisosilybin and not 3-deoxydehydrosilybin as was assumed previously [18].

Silychristin (9) and silydianin (16) are isomers of silybin and are among the main components of milk thistle [22]. The two compounds have the same molecular weight (M^+ 482) and their mass spectra contain fragments of coniferyl alcohol (Table 4) which are similar to the fragments of cinnamyl alcohol [58-60]. However, silydianin (16) differs from silybin and silychristin by the presence of an additional nonconjugated carbonyl group (IR spectrum). With the aid of x-ray structural analysis, and also of double resonance, an unambiguous structure has been proposed for silydianin [22 61]. The stereochemistry of this compound is simplified because of the presence of a rigid structure of the chiral tricyclic system. In addition to enantiomers of the cyclic system, only two stereoisomers relative to the α-C atom are possible. On the basis of the results of x-ray structural analysis the 2'R,αR absolute configuration is proposed for the tricyclic system in view of the 2R,3R configuration of the flavanonol series established with the aid of CD spectra.

Two structures were initially proposed for silychristin: 9a and 9b [62, 63].



(9a)



(9b)

In the course of supplementary investigations by the double resonance method of silychristin hexaacetate, the structure of the lateral phenyl residue and the position of attachment of the coniferyl alcohol residue in compound 9a were shown strictly [22]. A comparison of the chemical shifts of the C-α, C-β, and C-γ signals in the ^{13}C NMR spectra of silychristin, and anhydrosilychristin with the chemical shifts of the corresponding signals dihydrodiconiferyl alcohol and its anhydro derivative confirmed the correctness of structure (9a) [2, 62]. These conclusions were also confirmed by the ^1H NMR and mass spectra of anhydrosilychristin [64]. According to Wagner et al. [22], the relative configuration of the dihydrofuran ring of (9) is transoid. In the opinion of these authors, the absolute configuration of this part of the molecule can be decided only by comparing a number of derivatives with similar fragments in their molecules.

Definite interest is presented by silandrin (5) and silymonin (17), which are the main components of the white-flowered variety of milk thistle [14, 57, 65]. It has been shown on the basis of ^1H and ^{13}C NMR spectra that silymonin is 3-deoxysilydianin, and silandrin is 3-deoxysilybin or 3-deoxyisosilybin [54, 64]. The choice between the alternative structures for silandrin was made as the result of the synthesis of the trimethylether of silandrin chalcone from the neolignan americanin A (31) [54 65]. A comparison of this synthetic derivative with the trimethylether of silandrin chalcone obtained by the methylation of silandrin demonstrated their identity, which showed the structure of 3-deoxyisosilybin for (5). In the intermediate stages of the synthesis of the silandrin derivative from americanin A, an alcohol was formed

that had been obtained in the synthesis of isosilybin [9], and this permitted the authors [56, 57] to determine more accurately the assignment of the aryl and hydroxymethyl substituents in the structure of americanin A [40]. The CD spectra of dehydrosilandrin (positive bands at 319 and 245 nm) indicates that the benzodioxane ring of (5) has the Cα-R,Cβ-R or the Cα-S, Cβ-S absolute configuration [57].

Recently, three new flavanolignins have been described for the white-flowered variety of milk thistle: silyhermin (12), neosilyhermin A (13) and neosilyhermin B (14), it having been possible to separate compounds (12) and (14) only in the form of their acetates, while (13) was obtained by preparative HPLC [13]. The absolute configuration only of the flavanonol moiety of compounds (12-14) has been established. It is interesting that (13) and (14) are diastereoisomers with, respectively, the 2R and 2S configuration at C-2, which has been confirmed by HPLC results and specific rotations [13].

Neohydrocarpin (18) is the only representative of the flavolignans in which the coniferyl alcohol is attached by two bonds to C 3 and C-6' of a flavonoid. The conclusion of the cis configuration of neohydrocarpin was made on the basis that the H-α signal appears in the PMR spectra of (18) and of its acetyl derivative in the form of a singlet (4.70 ppm) [21]. The question of the isomerism of the position of the substituents was solved with the aid of the ^{13}C NMR spectrum of (18), where (because of the influence of the carbonyl group in the peri position) the signal of the carbon atom of the hydroxymethyl group (C-γ) appeared in a weaker field than the analogous signals of other lignoids (Table 3).

An unusual type of attachment of the aryl residue has been found in aegicin (19) [27], lignoside (20), and isolignoside (21) [28, 29]. In all these compounds, the β-hydroxyls of the aryl residues are attached to the 4'-OH groups of the flavonoids with the formation of ether bonds, while lignoside and isolignoside each contains a 6-acetylglucose residue. The presence of an ether bond at Cβ-OH in aegicin (19) has been shown by a comparison of the NMR spectrum of the substance and its acetate (Table 3) with those of model compounds. The erythro configuration of aegicin follows from an analysis of the chemical shifts and the SSCCs of the signals of the aliphatic protons in the PMR spectra of the acetate (19) and of model threo- and erythro-1-phenylpropane-1,2,3-triols [27].

In concluding this section, we may note that the proposed mechanism [12] for the free-radical combination of a flavonoid and coniferyl alcohol has been confirmed not only in the course of a biomimetic synthesis of silybin and isosilybin [7, 8] but also in the biosynthesis of silybin (from taxifolin and coniferyl alcohol and of hydnocarpin (from luteolin and coniferyl alcohol) under the influence of horseradish peroxidase or a suspension of a milk thistle culture [66].

TABLE 3. Chemical Shifts of the Signals of Some Carbon Atoms in the ^{13}C NMR Spectra of Lignoids (δ, ppm)

Compound	Carbon atoms				Literature
	C-α	C-β	C-γ		
	(Ar-CH-)	(-CH-CH$_2$O-)	(-CH$_2$O-)	(-CH$_3$)	
Silybin (1)	75,72	77,89	60,09	—	15
Isosilybin (2)	75 70	78,01	60,05	—	15
Silandrin (5)	77,8	75,7	60,2		57
Hydnocarpin (6)	78,1	76,4	59,6	—	74
Methoxyhydnocarpin (7)	78,3	75,7	59,9	—	74
Hydnowightin (8)	77,8	76,1	59,8	—	74
Silychristin (9)	87 3	53,7	63,2	—	75
Isohydnocarpin (15)	87,9	52 8	62,9	—	74
Silydianin (16)	53,3	46,0	72,7	—	75
Silymonin (17)	53,1	46 1	72,7	—	57
Neohydnocarpin (18)	40,9	35,2	69,2	—	74
Aegicin (19)	73,1	86,9	60,8	—	27
Kielcorin (22)	76,4	77,8	59,8	—	30
Compound B (26)	80,6	73,7	—	17,3	34
Daphneticin (27)	77,8	79,9	60 7	—	35
Diacetate of (27)	77,2	75,5	62,7	—	35
Aquilochin (28) diacetate	73,03	75,02	62,34	—	36
Cleomiscoside A (29)	79,9	77,5	60,7	—	37
Diacetate of (29)	76,7	75,1	62 4	—	37
Americanin A (31)	76,1	78,1	60,1	—	39
Americanin B (32)	75,2	78,2	60,0	—	39
Eusiderin (33)	80,6	73,7	—	17,0	76
Americanin D (34)	87,5	52,9	63.0	—	39
Licarin A (36)	93,3	45,2	—	17,2	76
Burchellin (38)	90,9	49,5	—	8,3	76
Porosin (39)	87,2	42,5	—	11,6	76

PROBLEMS OF THE STRUCTURAL ANALYSIS OF NATURAL LIGNOIDS

In the matter of structural studies, great interest is presented not only by the flavolignans but also by other lignoids — xanthonolignans, coumarinolignans, and neolignans. All these compounds have a common structural element — a 1,4-dioxane or dihydrofuran system which is that part of the molecule the structural investigation of which presents the greatest difficulty. In synthetic investigations of flavolignans successful use has been made of model samples of neolignans (americanin A, eusiderin), which has enabled structures of silybin, isosilybin, and silandrin to be determined and the structures not only of hydnocarpin but also of the model compound itself, americanin A, to be determined more accurately. Furthermore, in the course of the systematic structural investigations of various lignoids, regular features appeared which are applicable to all this class of natural compounds. This relates, in particular, to such modern spectral methods as ^1H and ^{13}C NMR spectroscopy and mass spectrometry.

The details of the ^1H NMR spectra given in Table 2 for the aliphatic moieties of the 1,4-dioxanes indicate that a transoid position of the substituents in this part of the molecule for the compounds of all the groups (neolignans, and derivatives of flavonoids, xanthones, and coumarins) is clearly determined by the signal of the benzyl proton (H-α) with a constant of 6-8 Hz at ~5.0 ppm. A comparative investigation of model 1,4-benzodioxanes has shown that in their cis isomers the signal of the benzyl proton appears in the form of a doublet with a constant of 2-3 Hz [10, 67].

It was mentioned above that the answer to the question of regio-isomerism in the 1,4-dioxane ring is the greatest problem and it can be solved with the aid of additional synthetic studies. In an investigation of lignoids with the dihydrobenzofuran structure (compounds 9-15 and 34-39), the determination of the positions of the substituents in this part of the molecule does not present great difficulty since spectral characteristics (^1H and ^{13}C NMR) permit unambiguous conclusions to be drawn concerning regio-isomerism (Tables 2 and 3). However, in this case the determination of the relative configuration of the substituents in the dihydrofuran fragment is a matter of great complexity. cis and trans isomers have been described in the PMR spectrum of which the H-α doublet signals have SSCCs of from 2 to 9.5 Hz [69, 70].

A comparative investigation of model samples and natural neolignans has shown that in the NMR spectra of the cis isomers the signals of the H-β and CH_3-γ protons are present in a stronger field, while the H-α signal is in a weaker field [45, 71-73]. It follows from this that the values of the chemical shifts of the signals of the aliphatic protons have diagnostic value for determining the relative configurations of such systems. These results have also begun to be taken into account in the study of dihydrobenzofurans with hydroxymethyl groups, and, in particular, americanin D (34) [39] and the flavolignans of milk thistle [13]. For example, on the basis of the CS of the signal of the H-α proton the transoid configuration of the dihydrobenzofuran fragments has been established for americanin D, silychristin (9), isosilychristin (11), silyhermin (12), neosilyhermin A (13), and neosilyhermin B (14), although the compounds mentioned have considerably differing SSCCs for the H-α protons (from 2 to 6 Hz) (Table 2). However, no clear system for determining the relative configurations of such systems has yet arisen, all the more because contradictory results are not infrequently taken as starting points.

In our opinion, only a comparative study of model samples and natural dihydrofuran lignoids with hydroxymethyl groups will permit us to find parameters of PMR spectra for the unambiguous determination of a particular configuration.

Systematic investigations of lignoids by ^{13}C NMR spectroscopy [30, 74-76] have shown that compounds with 1,4-dioxane and 2,3-dihydrofuran structures are readily distinguished by this method. In particular, in all 1,4-dioxanes the chemical shifts of the C-α, C-β, and C-γ signals differ considerably from those of the corresponding signals of dihydrobenzofurans, in the spectra of which the C-α and C-γ ($-CH_2OH$) signals appear in the weaker field (+10-15 ppm and +2-3 ppm, respectively) and the C-β signal in the stronger field (−30 ppm) (Table 3). The signals of the CH_3 (γ) group appear at ~17 ppm in both systems. At the same time, it has been observed that the CS of this group has particular diagnostic value in the determination of the configuration and conformation of the molecule [76].

It is important to note that the first attempts have also been made at determining the isomerism of the position of the substituents in a 1,4-dioxane fragment with the aid of double ^{13}C-^1H heteronuclear magnetic resonance. Thus, the structure of cleomiscoside A (29) has been solved by a study of the spectrum of its diacetate: ^{13}C-^1H-spin coupling between the C-7 signal (136.9 ppm) and the H-β signal (4.1 ppm), and also between the C-8 (135.5 ppm) and H-α

TABLE 4. Some Characteristics of Fragments in the Mass Spectra of Lignoids

Compound	M	M−H₂O	M−X	M−Y	Y	Y−H₂O	Y−HCO	ArCH₂	ArH	Literature
	m/z (intensity, %)									
Silybin (1)	482 (70)	464 (26)	—	302 (5)	180 (96)	162 (28)	—	137 (100)	124 (57)	11
Dehydrosilybin (3)	480 (60)	462 (18)	302 (50)	—	180 (70)	162 (30)	151 (28)	137 (100)	124 (70)	11
Rhodiolin (4)	480 (16)	462 (1)	302 (100)	—	180 (56)	—	151 (17)	137 (88)	124 (48)	17
Silandrin (5)	466 (67)	—	288 (8)	—	180 (100)	162 (50)	—	137 (91)	124 (55)	57
Methoxyhydnocarpin (7)	491	476	316	314	180	162	—	137	124	20
Silychristin (9)	482 (19)	464 (47)	—	—	—	—	—	137 (45)	—	22
Isosilycristin (11)	482 (2,7)	464 (3,4)	—	—	—	—	—	137 (13)	124 (15,1)	22
Neosilyhermin A (13)	466 (3)	448 (18)	—	—	—	—	—	137 (35)	124 (23)	13
Isohydnocarpin (15)	464	—	—	284	180	162	—	137	124	25
Silydianin (16)	482 (3)	464 (2)	— (14)	302	180 (44)	—	—	137 (54)	124 (28)	22
Silymonin (17)	466 (1)	—	288 (2)	—	180 (11)	—	—	137 (8)	—	57
Kielcorin (22)	436 (3)	418 (5)	258 (78)	—	180 (86)	162 (37)	151 (15)	137 (100)	124 (100)	30
Cadensin A (23)	452 (39)	434 (7)	274 (100)	—	180 (68)	162 (11)	151 (6)	137 (71)	124 (32)	30
Cadensin B (24)	482 (8)	464 (2)	274 (100)	—	210 (48)	—	—	167 (42)	154 (19)	30
Daphneticin (27)	386 (6)	—	178 (100)	—	210 (50)	—	—	167 (60)	—	35
Aquillochin (28)	416 (25)	398 (5)	208 (52)	—	210 (100)	—	—	167 (66)	154 (26)	36
Cleomiscoside A (29)	386	—	208	—	180	—	—	—	—	37
Lariciresinol 4'-monomethyl ether (40)	374 (100)	—	—	—	194 (17)	—	165 (51)	151 (34)	—	43

Note: X=Ar—C≡C—CH₂—OH; Y=Ar—CH=CH—CH₂OH.

(5.03 ppm) signals [37]. The structure of another coumarinolignan — daphneticin (27) — has been solved similarly [35].

The structure of the xanthonolignan kielcorin (22) has been established by an original method [50]. In their investigation of this compound, Nielsen and Arends [50] succeeded in opening the 1,4-dioxane ring in the course of alkaline hydrolysis. The product so obtained differed strongly with respect to the chemical shift of the signal of the H-α proton (δ 5.46, d, J = 4 Hz) from its ethyl derivative (δ 4.98, d, J = 4 Hz — H-α), which was in agreement with the chemical shifts of the analogous signal for butane-1,3-diol and its methyl ether [50].

Mass spectrometry is also fairly informative in the structural analysis of the lignoids. The mass spectra of the substances (Table 4) show great similarities in the fragmentation of the lignoids. Thus, in the majority of mass spectra of these compounds there are peaks of ions with m/z 180, 162, 151, 137, and 124 which show the presence in the molecule of a coniferyl alcohol residue or of one of its derivatives. Analysis of the spectral information given in Table 4 permits the conclusions that the fragmentation of the flavonol derivative (4), the xanthone derivatives (22-24), and the coumarin derivatives (27-29) takes place with the formation of strong peaks of the (M — X) ions; similar peaks of ions with a low intensity are also given by the flavanones (5, 17), while in the case of the flavanols (1, 16) and the flavones (7, 15), the (M — Y) fragments — the quinoid forms of taxifolin and luteolin — appear. But flavones apparently occupy an intermediate position, since in one compound (7) the peak

of the (M − X) ion has also been recorded. All this clearly shows that mass spectroscopy will supplement other spectral methods used in structural studies.

A consideration of questions of the structural analysis of the lignoids also indicates that in the solution of the structures of such substances and, in particular, those compounds the molecules of which contain a 1,4-dioxane ring, not only spectral methods but also chemical transformations, including experiments on the synthesis and cleavage of the initial compounds and of model samples, are necessary.

THE BIOLOGICAL ACTIVITY OF THE NATURAL LIGNOIDS

The significance and the necessity for progress in the field of structural investigations of this class of compounds are due to the fact that many substances of this group and, in particular, the flavanolignans of milk thistle (silybin, silydianin, silychristin) possess antihepatotoxic activity [1, 3, 77], and preparations based on them (legalon, silibor, etc.) are being used successfully in medical practice for the treatment of diseases of the liver [78-81].

The use of the fruit of the milk thistle as a raw material in the pharmaceutical chemicals industry has initiated additional investigations on its composition. Hungarian scientists have studied the chemical composition of the flavanolignans of about 100 populations of milk thistle growing in various geographic zones of Europe [82]. It was found that the white-flowered variety differed considerably in its chemical composition from the lilac-flowered variety that is used in the preparation of drugs. Furthermore, differences were also found within the lilac-colored variety: "silybin" and "silydianin" races have been found [82-86]. Silydianin is the main component of the raw material from milk thistle grown in an experimental field of VNIIKhTLS [All-Union Scientific-Research Institute of the Chemical Technology of Medicinal Substances] (Kharkov) [84, 85], and it is used as the standard (VFS 42-1146-81) for the quality control of the raw material and the drug silibor. Silybin is the predominating component in milk thistle grown in the Moscow experimental base and the Kuibyshev and North Caucasus Zonal Experimental Stations of VILR [All-Union Scientific-Reserach Institute of Medicinal Plants] [86], and also of that cultivated in Bulgaria [87] and in Yugoslavia [88].

Reports have recently appeared of six new hepatoprotective components of milk thistle, and it has been shown that the 3-deoxy analogs of silybin, silydianiin and silychristin have the most pronounced biological activity [89]. In view of this, it is of interest to study the possibility of creating drugs on the basis of the raw material from the white-flowered variety of this plant, as well. It is interesting that other lignoids possessing antihepatotoxic activity have also been found — these are the neolignan americanin A [40] and the lignins of the Chinese magnolia vine [90]. Furthermore, an anticancer activity has been found for the neolignan 4'-methyllariciresinol [46] and for the coumarinolignan daphneticin [35]. All this indicates the promising nature of further investigations of natural lignoids.

LITERATURE CITED

1. G. Vogel, in: Flavonoids and Bioflavnoids, 1981, Akademiai Kiado, Budapest (1982), p. 461.
2. H. Wagner, in: Flavonoids and Bioflavnoids: Current Research Trends, Akademiai Kiado, Budapest (1977), p. 29.
3. H. Wagner, in: Recent Flavonoid Reserach, Akademiai Kiado, Budapest (1973), p. 51.
4. G. Vogel: in: New Natural Products and Plant Drugs with Pharmacological or Therapeutical Activity, Springer, New York (1977), p. 249.
5. M. Gabor, in: Flavonoids and Bioflavnoids, 1981, Akademiai Kiado, Budapest, (1982), p. 363.
6. A. Arnone, L. Merlini, and A. Zanarotti, J. Chem. Soc. Chem. Commun., 696 (1979).
7. R. Hänsel and A. Pelter, Chem. Ber., 108, 1482 (1975).
8. R. Hänsel and G. Schöpflin, Tetrahedron Lett., 3645 (1967).
9. R. Hänsel, J. Schulz, and A. Pelter, J. Chem. Soc. Chem. Commun., 195 (1972).
10. R. Hänsel, J. Schulz, and H. Rimpler, et al., Tetrahedron Lett., 4417 (1969).
11. A. Pelter and R. Hänsel, Chem. Ber., 108, 790 (1975).
12. A. Pelter and R. Hänsel, Tetrahedron Lett., 2911 (1968).
13. M. Fiebig and H. Wagner, Planta Med., 51, 310 (1984).
14. I. Szilágyi and P. Tétényi, Herba Hung., 17, 65 (1978).
15. L. Merlini, A. Zanarotti, and A. Pelter et al., J. Chem. Soc., Perkin Trans I., 775 (1980).

16. M. Bandopadhyay, N. P. Pardeshi, and T. R. Seshadri, Ind. J. Chem., 10, 808 (1972).
17. G. G. Zapesochnaya and V. A. Kurkin, Khim. Prir. Soedin., 23, (1983).
18. K. R. Ranganathan, and R. T. Seshadri, Tetrahedron Lett., 3481 (1973).
19. I. Kostova and S. Rangaswami, Ind. J. Chem., 15 B, 764 (1977).
20. K. R. Ranganathan and T. R. Seshadri, Ind. J. Chem., 12, 993 (1974).
21. D. K. Sharma, K. R. Ranganathan, and M. R. Parthasarathy, et al., Planta Med., 37, 79 (1979).
22. H. Wagner, O. Seligmann, M. Seitz, D. Abraham, and J. Sonnenbichler, Naturforschung, 31 B, 876 (1976).
23. T. Takemoto, S. Ikegawa, and K. Nomoto, Yakugaku Zasshi, 95, 1017 (1975).
24. M. Kaloga, Naturforschung 36 B, 262 (1981).
25. K. R. Ranganathan and T. R. Seshadri, Ind. J. Chem., 12, 888 (1974).
26. B. Janiak and R. Hänsel, Planta Med., 8, 71 (1960).
27. R. Cooper, H. E. Gottlieb, and D. Lavie, Isr. J. Chem., 16, 12 (1977).
28. L. I. Borodin, V. I. Litvinenko, and N. V. Kurinnaya, Khim. Prir. Soedin., 437 (1969).
29. L. I. Borodin, V. I. Litvinenko, and N. V. Kurinnaya, Khim. Prir. Soedin., 43, 62 (1970).
30. J. F. Castelao (Jr.), O. R. Gottlieb, R. A. De Lima, A. A. L. Mesguita, and H. F. Gottlieb, Phytochemistry, 16, 735 (1977).
31. L. Merlini, A. Zanarotti, A. Oelter, M. O. Rochefort, and R. Hansel, J. Chem. Soc. Chem. Commun., 695 (1979).
32. M. Luz Cardona and E. Seoan, Phytochemistry, 21, 2759 (1982).
33. F. Delle Monache, M. Marguina Mac-Quhae, G. Delle Monache, G. B. Marini Bettolo, and R. Alves de Lima, Phytochemistry, 22, 227 (1983).
34. M. R. Parthasarathy and K. Pardha Saradhi, Phytochemistry, 23, 867 (1984).
35. Z. Lin-Gen, O. Seligmann, and H. Wagner, Phytochemistry, 22, 617 (1983).
36. P. Bhandari, P. Pant, and R. P. Rastogi, Phytochemistry, 21, 2147 (1982).
37. A. B. Ray, S. K. Chattopadhyay, C. Konno, and H. Hikino, Tetrahedron Lett., 21, 4477 (1980).
38. B. Das Gracas, M. Zoghbi, N. R. Roque, and O. R. Gottlieb, Phytochemistry, 20, 180 (1981).
39. W. S. Woo, and S. S. Kang, Tetrahedron Lett., 21, 4255 (1980).
40. W. S. Woo, S. S. Kang, H. Wagner, and V. M. Chari, Tetrahedron Lett., 3239 (1978).
41. J. J. Hobbs and F. E. King, J. Chem. Soc., 4732 (1960).
42. J. Favre-Bonvin, M. Kaouadji, and A. M. Mariotte, Tetrahedron Lett., 4111 (1978).
43. C. J. Aiba, R. G. Campos Correa, and O. R. Gottlieb, Phytochemistry, 12, 1163 (1973).
44. O. Araujo Lima and O. R. Gottlieb, Phytochemistry, 11, 2031 (1972).
45. C. Aiba, R. Braz Filho, and O. R. Gottlieb, Phytochemistry, 11, 413 (1973).
46. S. M. Hussein Ayoub and D. G. Kingston, J. Nat Prod. (Lloydia), 47, 875 (1984).
47. H. Wagner, L. Hörhammer, and R. Münster, Naturwissenschaften, 52, 305 (1965).
48. H. Wagner, L. Hörhammer, and R. Münster, Arzneim-Forsch. (Drug Res.), 18, 688 (1968).
49. W. Gaffield and A. C. Waiss, Jr., J. Chem. Soc. Chem. Commun., 29 (1968).
50. H. Nielsen and P. Arends, Phytochemistryc 17, 2040 (1978).
51. H. Mishima, M. Kurabayashi, and K. Hirai, Sankyo Kenyusho Nempo., 23, 70 (1971); Chem. Abstr., 77, 5413m (1972).
52. G. Tittel and H. Wagner, in: Flavonoids and Bioflavonoids, Akademiai Kiado, Budapest (1982), p. 299.
53. G. Tittel and H. Wagner, J. Chromatogr., 135, 449 (1977).
54. G. Tittel and H. Wagner, J. Chromatogr., 153, 227 (1978).
55. V. Quercia and N. Pierini, Fitoterapia, 51, 297 (1980).
56. S. Antus, O. Seligmann, and H. Wagner, in: Flavonoids and Bioflavonoids, 1981, Akademiai Kiado, Budapest (1982), p. 147.
57. I. Szilagyi, P. Teteny, S. Antus, O. Seligmann, V. M. Chari, M. Seitz, and H. Wagner, Planta Med., 43, 121 (1981).
58. H. Schwarz, C. Koppel, and F. Bohlmann, Org. Mass Spectrom., 7, 881 (1973).
59. C. Koppel and H. Schwarz, Org. Mass Spectrom., 11, 101 (1976).
60. G. G. Zapesochnaya, and V. A. Kurkin, Khim. Prir. Soedin., 723 (1982).
61. D. J. Abraham, S. Takagi, R. D. Rosenstein, and R. Shiono et al., Tetrahedron Lett., p. 2675 (1970).
62. R. Hänsel, M. Kaloga, and A. Pelter, Tetrahedron Lett., 2241 (1976).
63. H. Wagner, O. Seligmann, L. Horhammer, M. Seitz, and J. Sonnenbichler, Tetrahedron Lett., 1895 (1971).
64. H. Wagner, V. M. Chari, M. Seitz, and J. Riess-Mauerer, Tetrahedron Lett., p. 381 (1978).
65. I. Szilágyi, P. Tétényi, S. Antus, O. Seligmann, V. M. Chari, and M. Seitz, in: Flavonoids and Bioflavnoids, 1981 Akademiai Kiado, Budapest (1982), p.345.

66. R. Schrall and H. Becker, Planta Med., 32, 27 (1977).
67. A. R. Martin, S. K. Mallick, and J. K. Caputo, J. Org. Chem., 39, 1808 (1974).
68. L. Merlini and A. Zanarotti, Tetrahedron Lett., 3621 (1975).
69. C. Aulin-Erdtman and Y. Tomita Acta Chem. Scand., 17, 535 (1963).
70. C. H. Ludwig, B. J. Nist, and J. L. McCarthy, J. Am. Chem. Soc., 86, 1186 (1984).
71. C. J. Aiba, M. A. De Alvarenga, O. C. Castro, A. M. Giesbrecht, O. R. Gottlieb, and F. M. Pagliosa, Phytochemistry, 16, p. 741 (1977).
72. C. J. Aiba, J. B. Fernandes, O. R. Gottlieb, and J. G. S. Maia, Physochemistry, 14, 1597 (1975).
73. C. J. Aiba, O. R. Gottlieb, M. Yoshida, J. C. Mourao, and H. E. Gottlieb, Phytochemistry, 15, 1031 (1976).
74. M. R. Parthasarathy, K. R. Ranganathan, and D. K. Sharma, Phytochemistry, 18, 506 (1979).
75. V. M. Chari, H. Wagner, and Neszmélyi, in: Flavonoids and Bioflavonoids; Current Research Trends, Akademiai Kiado, Budapest (1977), p. 49.
76. E. Wenkert, H. E. Gottlieb, O. R. Gottlieb, M. O. da S. Pereira, and M. D. Formiga, Phytochemistry, 15, 1547 (1976).
77. G. Hahn, H. D. Lehman, M. Kürten, H. Uebel, and G. Vogel, Arzneim.-Forsch. (Drug Res.), 18, 698 (1968).
78. G. Gross and W. Haase, Medizinische Welt, 22, 1350 (1971).
79. M. D. Mashkovskii, Drugs [in Russian], Moscow, Part 1 (1984) p. 516.
80. G. Poser, Arzneim.-Forsch. (Drug. Res.), 21, 1209 (1971).
81. R.-D. Schopen, O.-K. Lange, C. Panne, and E. I. Kirnberger, Medizinische Welt, 20, 888 (1969).
82. G. Stieber, I. Szilágyi, and P. Tétényi, Herba Hung., 16, 55 (1977).
83. Deutsche Artneibuch [German Pharmacopoeia], 8th edn. (DAB 8), Akademie-Verlag, Berlin (1981), p. 481.
84. V. V. Belikov, and N. T. Obolentseva, in: Fourth All-Union Symposium on Phenolic Compounds: Abstracts of Lectures. Section 2 [in Russian], Tashkent (1982), p. 12.
85. V. V. Belikov Rast. Resur., 21, 350 (1985).
86. L. T. Bondarenko, A. A. Kir'yanov, and M. E. Perel'son, Khim.-Farm. Zh., 14, 57 (1980).
87. M.Simova and T. Pangarova, Farmatsiya (Sofia), 30, 39 (1980).
88. Z. Kalodjera, D. Brikic, and J. Metricic, Farm. Vestn. (Ljubljana), 32, 335 (1981).
89. H. Hikino, Y. Kiso, H. Wagner, and M.Fiebig, Planta Med., 50, 248 (1984).
90. H. Hikino, Y. Kiso, H. Taguchi, and Y. Ikeya, Planta Med., 50, 213 (1984).