IRIDOIDS OF PLANTS OF THE GENUS *Gentiana* FROM THE FAMILY GENTIANACEAE

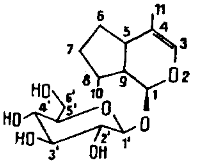
A. D. Bakuridze, T. D. Dargaeva,
G. G. Nikolaeva, A. V. Patudin,
and L. I. Brutko

UDC 615.322

The review contains the results of an analysis of the literautre on the study of plants of the genus *Gentiana*, family Gentianaceae Juss. The biological properties of the iridoid compounds are described. Their physicochemical constants are also given: the name of the substance, the melting point, the angle of rotation, details of the UV, IR and PMR spectra, and literature relating to them. The distribution of iridoid compounds in plants over the sections of the genus *Gentiana* is given in the form of tables, and the material is discussed correspondingly.

GENERAL CHARACTERISTICS OF THE IRIDOIDS

Iridoids form a homogeneous group of monoterpene compounds. They are characterized by a cyclopentanopyran ring structure (I) [1].



I

As can be seen from the general formula (I) in their chemical structure iridoid compounds have as a basis two cyclic nuclei: one of them is an α-pyran ring and the other a cyclopentane ring. A β-glucosyloxy group is attached in position 1, and between the C_3 and C_4 atoms there is a double bond forming a typical enol ether. In some cases there is also a double bond in the cyclopentane ring. Almost half the iridoid compounds contain one carbom atom C_{10} and C_{11} side chains which is in harmony with the biogenetic origin of these substances. These compounds are characterized by the presence of oxygen-containing functional groups in the aglycon in the form of hydroxy, alkoxy, and acyloxy or epoxide groups. The majority of iridoids are found in nature in the form of glycosides [2, 3].

Iridoids were first isolated in the middle of the XIXth century, but only in 1958 did Halpern et al. [4] propose the basic structure of the iridoids.

The intensive study of the iridoids began with the first half of the XXth century [5-9].

Numerous publications have been devoted to the study of the physicochemical properties of the iridoid compounds, their classification, their botanical distribution, their biosynthesis, their isolation and the determination of their structures [1, 3, 10-21]. The history of this study is also reflected in the various names that have been given to these compounds. Thus, they have been called "pseudoindicans" from the blue color they form in an acid medium; they have also been known as "aucubin glycosides." The name used at the present time — "iridoid glycosides" — is based on their link with the initial compound — iridodial, which was first described as a substance obtained from ants (*Iridomyrmex detectus*) [22].

BOTANICAL DISTRIBUTION

Iridoids have been detected as natural components in plants of the families Apocynaceae, Acanthaceae, Adoxaceae, Cornaceae, Caprifoliaceae, Daphniphyllaceae, Dipsacaceae, Eucommia-

---

All-Union Scientific-Research Institute of Pharmacy, Moscow. Translated from Khimiya Prirodnikh Soedinenii, No. 1, pp. 3-11, January-February, 1987. Original article submitted August 1, 1985; revision submitted September 4, 1986.

TABLE 1. Main Physicochemical Constants of Iridoid Compounds from Plants of the Genus *Gentiana* from the Family Gentianaceae

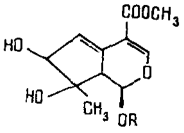
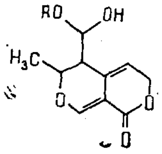
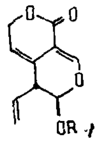
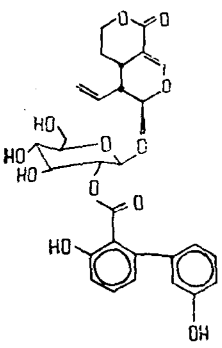
Name of the substance, composition, M^+	mp, °C	$[\alpha]_D^{20}$	UV spectrum, λ_{max}, nm	IR spectrum, ν_{max}, cm^{-1}	PMR spectrum δ, ppm; J, Hz	Literature
Iridoid glycosides with a C_9 side chain with a C_8-C_9 bond						
I. Iridoid A $C_{15}H_{24}O_{10}$, M^+364.1369	198—199	+10° $CHCl_3$	218	1650	1,24 (CH_3) 6,4(H-3)	1, 31
II. Gentioside  R = D-glucose $C_{17}H_{24}O_{11}$, M^+404.1318	191—192	—102° $CHCl_3$	209, 219, 243, 251, 260	1615, 1715	3,7 (OCH_3), 5,60(H-6), 7,40(H-3), 1,26(H-10)	1, 31
Simple secoiridoids						
III. Gentioflavoside  R = D-glucose $C_{16}H_{22}O_{10}$, M^+374.1213	126—128	—108° $CHCl_3$	210, 219, 243, 252, 269	1615, 1715	5,60 (H-6), 7,45 (H-3) 1,20 (d, CH_3)	1, 32
IV. Gentiopicroside  R = D-glucose $C_{16}H_{20}O_9$, M^+356.1107	122	$[\alpha]_D^{25}$ —216,6	C_2H_5OH 247, 255, 270	Nujol 3533, 3460, 3267, 1712, 1677, 1612, 931, 772	H_2O 5,69 (H-1) d, $J=3$, 7,49 (H-3) d, $J=1$, 6,13 (H-6) 5,00 (H-10)	33, 34, 35, 36
Secoiridoid glycosides with a phenolic moiety						
V. Amaropanin 	178	$[\alpha]_D^{26}$ —101,25	CH_3OH 210, 315, 240	KBr 3400, 1680, 1580, 1430, 980, 930, 890, 810, 783, 730	Acetone-d_6 7,33 (H-3) d, $J=2$; 2,6—2,8(H-5) (H-9); 5,33(H-1) d, $J=1,5$; 5,1—5,3(H-8), CH_2-10); 1,55—1,9 CH_2-6; 3,9—4,3 CH_2-7; 3,2—4,2, H-3′, 4′,5′;OH-3′,4′,6′; 4,34(H-1′) d, $J=8$; 5,2(H-2′) d, $J=8$; 2,58(H-5″) d, $J=8$	37, 38

TABLE 1 (Continued)

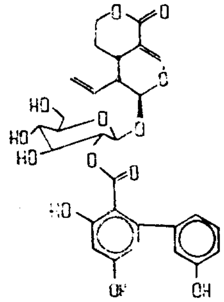
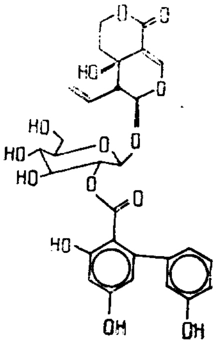
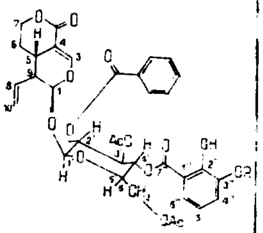
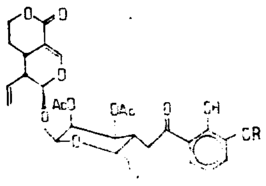
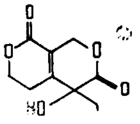
Name of the substance, composition, M$^+$	mp, °C	$[\alpha]_D^{20}$	UV spectrum, λ_{max}, nm	IR spectrum, ν_{max}, cm^{-1}	PMR spectrum δ, ppm; J, Hz	Literature
$C_{29}H_{30}O_{12}$, M$^+$570.1737						
VI. Amarogentin  $C_{29}H_{30}O_{13}$. M$^+$586.1686	229—230	$[\alpha]_D^{20}$ −116,6 CH_3OH	230, 266, 306	1655, 1580	See V. Differs from V by the presence of a signal at 9.2 ppm ($C_{5''}$−OH)	33, 35, 37, 38, 39, 40
VII. Amaroswerin  $C_{29}H_{30}O_{14}$, M+ 602. 1634	177—179	$[\alpha]_D^{20}$ −13 CH_3OH	CH_3OH 227, 271, 307	Nujol 1685, 1640, 1610, 995, 900	See V. Differs from V by the presence of signals at 9.2 ppm ($C_{5''}$ − OH) and at 7.33 ppm (H-3), and by a singlet due to the presence of an OH group at C_5	33, 39, 40
VIII. Scabraside  R = D-glucose $C_{40}H_{44}O_{20}\cdot 2H_2O$		$[\alpha]_D^{24}$ −152,3 CH_3OH	207, 230, 313	3420 (OH), 1740 (ester) 1/10 (C=O), 1620 (C=C) 1470 (aromatic series)	1,86 (2×OAc): 1,55—2,11 (2H, m, H-6); 2,62(1H, m, H-9); 3,46(1H, m, H-5); 3,48—3,85(2H, m, H-5′, H-5‴); 3,86—4,46(2H, m, H-6′, H-6‴); 4,60—5,00 (2H, m, H-7); 5,02—5,37(3H, m, H-8, H-10); 5,45 (1H, d, J=8, H-1′); 5,65(1H, t, J=8, H-2″);	42

TABLE 1 (continued)

Name of the substance, composition, M$^+$	mp, °C	$[\alpha]_D^{20}$	UV spectrum, λ_{max}, nm	IR spectrum, ν_{max}, cm^{-1}	PMR spectrum δ, ppm; J, Hz	Literature
					6,78(1H, t, J=8, H-5″); 7,25–7,95(8H, m, H-3, H-4″, H-6″ (benzoyl proton) 10,46 (1H, $C_{2''}$–OH).	
IX. Trifloroside  R = D-glucose $C_{35}H_{42}O_{20}$, +782.2269		$[\alpha]_D^{28}$ –122,8 CH_3OH	CH_3OH 249, 325	$CHCl_3$ 3350, 1750, 1705, 1625, 1470, 995, 910	See VIII. Differs from VIII by the presence of an additional signal of th 1-acetoxy group	41, 42, 43
Nonglycosidic iridoids of various structures						
X. Gentiolactone  $C_{10}H_{12}O_5$, M$^+$212.0684	119–120,5	$[\alpha]_D^{25}$ 0 CH_3OH	CH_3OH 22 230	KBr 1725–1715 (carbonyl group) 3500 (OH); 1600 (>C==C<)	$CHCl_3$ 1.0' (3H, t, H-4); 1,5–2.1 (2H, m); 3,6 (1H, s)	44

ceae, Gentianaceae, Globulariaceae, Hippuriadaceae, Hammaamelidaceae, Icacinaceae, Labiatae, Lentibulariaceae, Loasaceae, Loganiaceae, Lamiaceae, Meliaceae, Monotropaceae, Menyanthaceae, Montiniaceae, Myoporaceae, Orobanchaceae, Oleaceae, Redaliaceae, Plantaginaceae, Pyrolaceae, Rubiaceae, Saxifragaceae, Scrophulariaceae, Sarraceniaceae, Valerianaceae, and Verbenaceae. At the present time, about 250 iridoid compounds have been isolated from 300 plants belonging to these families.

BIOLOGICAL PROPERTIES OF IRIDOID COMPOUNDS

A pharmacological study of the iridoids isolated from various plants has confirmed that these compounds possess a fairly broad action spectrum.

Some iridoid compounds are similar in their biological action to antibiotics. Iridomyrmecin — an antibiotic produced by ants for their own protection — is a stronger insecticide than DDT. D(+)-Isoiridomyrmecin exhibits antimicrobial action, suppressing the growth of *Rhizopus*, *Penicillium*, and *Aspergillus*, although it shows no harmful influence on the multiplication and growth of *Staphylococcus*, and *Pseudomonas* [23]. Genipikin and genipikinic acid suppress the growth of Gram-positive and Gram-negative bacteria and the growth of the fungi *Trichophyton* and *Chlorella* [24]. Plumiericin — a compound also possessing antimicrobial activity — is used in various skin diseases [2, 11]. Aucubin is used in cases of dermatomycosis, in asthma, and in cases of ulcer of the digestive tract [25, 26]. The iridoid glycoside agnuside improves sexual function and at the same time exhibits a contraceptive effect [11]. Valepotriates are used as a sedative in vegetative disturbances [11].

Suzuki has found a diuretic property in *Catalpa* fruit which is due to the presence of iridoid compounds in them: catalposides and catalpol [27].

Verbenalin acts on the musculature of the uterus in a similar manner to ergotamine, raising its tonus and increasing the frequency of contractions [11]. Oleuropein and asperuloside possess hypotensive properties [11, 28].

TABLE 2. Iridoids and Plants of the genus *Gentiana* L.

Number of the iridoid from Table 1	Iridoid compound	Eugentiana Kusn.											
		Coelanthe D C.					Pneumonanthe Neck.				Aptera Kusn.		
		G. burseri	G. lutea	G. punctata	G. pannonica	G. purpurea	G. pneumonanthe	G. scabra	G. triflora	G. asclepiadae	G. cruciata	G. dahurica	G. macrophylla
1	Iridoid A		+	+						+			
2	Gentioside		+	+						+			
3	Gentioflavoside			+									
4	Gentiopicroside	+	+	+	+	+	+	+	+	+	+	+	+
5	Amaropanin			+	+	+		+	+				
6	Amarogentin	+	+	+	+	+		+	+				
7	Amaroswerin			+	+	+							
8	Scabraside							+	+				
9	Gentiolactone					+							
10	Trifloroside						+	+	+				

Number of the iridoid from Table 1	Iridoid compound	Eugentiana Kusn.					Gentianella Kusn.			
		Frigida Kusn.	Thylacites Griseb.		Cyclostigma Griseb.		Grossopetalum Froel		Endotricha Froel.	
		G. olgida	G. kochiana	G. klusii	G. verna	G. bavorica	G. ciliata	G. detonosa	G. germanica	G. campestris
1	Iridoid A									
2	Gentioside									
3	Gentioflavoside									
4	Gentiopicroside	+	+	+	+	+	+	+	+	+
5	Amaropanin	+								
6	Amarogentin									
7	Amaroswerin									
8	Scabraside									
9	Gentiolactone									
10	Trifloroside									

A secoiridoid — gentiopicroside, isolated from various species of plants of the genus *Gentiana* L. — possesses an antipyretic, analgesic, and cholagogic action [29]. In addition, an antiinflammatory action has been shown for gentiopicroside [30].

IRIDOIDS OF PLANTS OF THE GENUS *Gentiana* L., FAMILY Gentianaceae JUSS.

From the chemotaxonomic point of view, the presence of iridoid compounds is characteristic for plants of the following families: Apocynaceae, Labiatae, Loasaceae, Menyanthaceae, Oleaceae, Scrophulariaceae, Valerianaceae, Verbenaceae. The distribution of iridoids does not correspond to the botanical systematics of plants of the Gentianaceae family, but at the species level their presence sometimes links species and confirms a phylogenetic relationship. This relates to gentiopicroside in the genus *Gentiana* L.

We have made an attempt to generalize information of the presence of iridoid compounds for plants of the genus *Gentiana* L. (Gentianaceae Juss.). Until recently, 21 plants belonging to this genus had been studied for the presence of iridoids, and about 10 iridoid compounds had been isolated, the main physicochemical constants of these being given in Table 1. Compounds are classified on J. Letisia's scheme.

The sugar component of the known iridoid compounds isolated from plants of the genus *Gentiana* L., family Gentianaceae Juss., is D-glucose, the number and positions of its residues varying.

The distribution of iridoid compounds in plants of the gentian genus is given in Table 2.

As can be seen from Table 2, the presence of gentiopicroside is characteristic for all plants of the *Gentiana* genus studied.

The distribution of gentiopicroside in the vegetable kingdom is limited, and it is found only in plants of the Gentianaceae family.

Gentiopicroside (or gentiopicrin) was discovered in 1862 by Kromayer in the roots of *Gentiana lutea* L. [45]. Tanret determined a presumable structure, but a number of authors (Ashima, Korte, Canonica, and Pelizzoni) did not agree with such a structure [46]. A partial structure was proposed by Canonica and Pelizzoni and was modified by them in 1961. The absolute configuration was determined by Manitto and Pagnoni [47]. A reconsideration of the structure was carried out by Inouye in 1968 [48].

It must be mentioned that the *Coelanthe* and *Pneumonanthe* sections of the *Eugentiana* Kusn. subgenus have been studied in most detail, and the following, in addition to gentiopicroside, have been found in plants of these sections: iridoid A, belonging to the iridoid glycosides with a C-9 side chain, and gentioside, which belongs to the group with a C-10 side chain.

Popov and Marakov [31] were the first to isolate from *G. asclepiadae*, *G. lutea* , and *G. Punctata* iridoid A and gentioside, which are precursors in the biosynthesis of gentiopicroside in these plants.

The presence of amarogentin, amaroswerin, and amaropanin (secoiridoid glycosides with phenolic moieties) is characteristic for the majority of the plants of these sections that have been studied.

Inouye and Nakamura [39] isolated amarogentin and amaroswerin from *Swertia japonica*.

Kariyone and Matsushima [10] isolated swertiamarin from *S. japonica*. Its structure was determined by Kubota and Tomita [49] but was modified by Koch [50] and its stereochemistry was determined by Inouye et al. [48].

The other species of plants of the gentian genus have so far been little studied for the presence of iridoid compounds.

LITERATURE CITED

1. L. J. El-Naggar and S. L Beal, J. Nat. Prod., 43, 649 (1980).
2. J. M. Bobbit and K. P Segebarth, in: Cyclopentenoid Terpene Derivatives (ed. W. I. Taylor and A. R. Battersby), Marcel Dekker, New York (1969), pp. 1-145.
3. S. R. Jensen, B. J. Nielsen, and R. Dahlgren, Bot. Notiser, 128, 148 (1975).
4. O. Halpern, H. Schmid, and A. Einleitung, Helv. Chim. Acta, 1109 (1958).
5. R. Haensel, Planta Med. Suppl., 61, (1966).
6. E. C. Bate-Smith and T. Swain, Comparative Phytochemistry, Academic Press, London (1966), p. 159.
7. D. Groeger and P. Simehen, Pharmazie, 22 316 (1967).
8. T. W. Bentley, R. A. Johnstone, and J. Grimshaw, J. Chem. Soc., 2234 (1967).
9. O. Sticher, Pharma. Acta, Helv., 44, 453 (1969).
10. V. Plouvier and J. Favre Bonvin, Phytochemistry, 10, 1697 (1971).
11. G. Buchbauer, Oesterr. Apoth. Ztg. 28, 173 (1974).
12. O. Sticher and U. Junod-Busch, Pharm. Acta Helv., 50, 127 (1975).
13. W. G. Van Der Sluis and R. P. Labadie, Pharmaceutisch Weekblad, 113, 21 (1978).
14. P. Kooiman, Acta Bot. Neerl, 18, 124 (1969).
15. P. Kooiman Acta Bot. Neerl 19, 329 (1970).
16. P. Kooiman, Acta Bot. Neerl 21, 417 (1972).
17. R. Hegnauer and P. Kooiman, Planta Med. 33, 1 (1978).
18. L. Jahodar, Farm. Obz., 47, 353 (1978).
19. H. Rimpler, Planta Med., 33, 313 (1978).
20. H. Inouye, S. Ueda, S. Uesato, and K. Kobayashi, Chem. Pharm. Bull., 26, 3384 (1978).
21. H. Inouye, S. Ueda, S. Uesato, and K. Kobayashi, Chem. Pharm. Bull., 26, 3384 (1978).
22. L. M. Roth and T. Eisner, Annu. Rev. Entomol., 7, 107 (1962).
23. Chem. Abstr., 59, 7902 (1963).
24. W. H. Tallent Tetrahedron 20, 1781 (1964).
25. R. Hegnauer, Pharm. Acta Helv., 41, 577 (1966).
26. R. Hansel, Dtsch. Apoth. Ztg., 106, 1761 (1966).
27. Y. Suzuki, Chem. Abstr., 62, 15300 (1965).
28. R. P. Knott and R. S. McCutcheon, J. Pharm. Sci., 50, 963 (1961).
29. A. Yoshinobu, K. Sadako, Y. Massaji, and T. Yaichiro, Yakugaku Zasshi, 99, 1047 (1979).
30. H. Teruaki and K. Michinori Ch. A. 61 K31/70, 27 Feb. 1979. Appl. 77/89 951, 26 Jul. 1977.
31. S. Popov and N. Marekov, Phytochemistry, 10, 3077 (1971).

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.