PHENOL GLYCOSIDES OF THE COUMARIN SERIES

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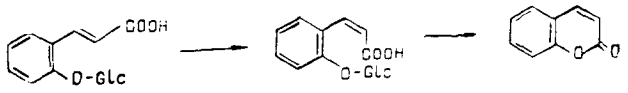
In this review, literature information on phenol glycosides of the coumarin series is systematized. Questions of the structural analysis of natural compounds by chemical and spectral methods are discussed. Facts are given about 63 phenyl glycosides of the coumarin series isolated from various plants.

Coumarins are lactones formed as the result of the cyclization of the cis form of ortho-hydroxycinnamic (coumarinic) acid [1, 2]. In plants, coumarins are found in the free form and in the form of glycosides. The fact that coumarins are found in the form of glycosides became known even in the last century. The first natural coumarins (daphnin (isolated in 1812), exculin, and fraxin) proved to be glycosides. Even unsubstituted coumarin is present in plants in the form of a glucoside of trans-ortho-hydroxycinnamic acid (1). Isomerization into the cis form and enzymatic hydrolysis of the β-glucosides of coumarinic acid (1a) so formed leads to coumarin (2) [1-3].



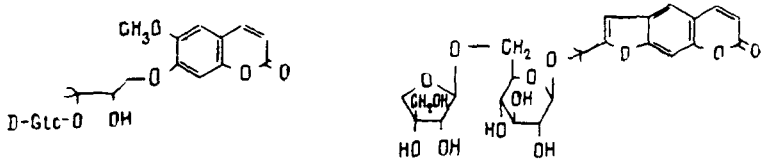
1 1a 2

Interest in the natural coumarins is due primarily to their high pharmacological activity. Among them have been detected compounds possessing photosensitizing, spasmolytic, anticoagulant, hypotensive, and antitumoral actions [4]. The results of investigations in the field of the chemistry of the coumarins have been generalized in monographs [3, 5] and review papers [6-9]. Information on individual representatives of this class and on plants containing coumarins can be found in handbooks [10-12] and the publications of Soviet and foreign scientists [13-15]. However, in the above-mentioned sources little attention has been devoted to coumarin glycosides. In recent years, a fairly large number of papers devoted to the isolation of glycosides of the coumarin series and to the study of their chemical structure and biological activity have been published.

Natural coumarin glycosides can be divided into two groups:

1. Phenol glycosides, the aglycons of which are hydroxycoumarins. This group includes all the compounds given in Table 1; and

2. Glycosides formed as the result of the glycosylation of alcoholic hydroxy groups in aliphatic side chains of coumarins. Representatives of this group of glycosides include obtusoside (3) [16], decuroside IV (4) [17], and analogous compounds.



The chemical properties and methods of establishing the structures of the compounds of the second group differ little from those of ordinary glycosides of aliphatic alcohols. For

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TABLE 1. Natural Phenol Glycosides of the Coumarin Series

Name and molecular formula	mp, °C $[\alpha]_D$, deg. (solvent)	Structure	Source (family) [literature]
1	2	3	4
1. Skimmin $C_{15}H_{16}O_8$	219–221; —79,8 (pyridine)	5	Skimmia japonica Thunb. (Rutaceae) [3,7,10,15]
2. Mahaleboside $C_{15}H_{16}O_8$	—36,2 (pyridine)	6	Prunus mahaleb L. (Rosaceae) [21]
3. Umbelliferone 7-O-α-D-glucoside $C_{15}H_{16}O_8$	219–220; +85 (pyridine)	7	Doronicum macrophyllum Fiscr. ex Horten (Asteraceae) [22]
4. Cichoriin $C_{15}H_{16}O_9$	214–216; —104,5 (dioxane)	8	Cichorium intybus L. (Asteraceae) [3,7,10,11,15]
5. Esculin $C_{15}H_{16}O_9$	204-205; —146 (methanol) (methanol)	9	Aesculus hippocastanum L. (Hippocastanaceae) [3,7,10, 11]
6. Daphnetin 8-O-β-D-glucoside $C_{15}H_{16}O_9$	197—198; +61,9 (water)	10	Gnidia polycephala Gligg. (Thymelaeaceae) [3,7,10,11]
7. Daphnin $C_{15}H_{16}O_9$	223–224; —114,7 (methanol)	11	Daphne odora Thunb. (Thymelaeaceae) [3,7,10,15]
8. Dauroside D (mulberroside B.) $C_{15}H_{16}O_9$	214–215; +108,5 (pyridine)	12	Haplophyllum dauricum (L.) G. Don. (Rutaceae) [18, 19,23]
9. Erioside $C_{15}H_{16}O_{10}$	350 (decomp.) —	13	Lasiosiphon eriocephalus Decen (Thymelaeaceae) [24]
10. Scopolin $C_{10}H_{18}O_9$	217–219 —	14	Scopolia japonica Maxim (Solanaceae) [3,7,10,11]
11. Magnolioside $C_{16}H_{18}O_9$	227; —28 (pyridine)	15	Magnolia macrophylla Michx. (Magnoliaceae) [25]
12. 6-β-D-Galactopyranosyloxy-7-methoxycoumarin $C_{16}H_{18}O_9$	—	16	Xeromphis spinosa Thunb. (Rubiaceae) [26]
13. Fraxin $C_{16}H_{18}O_{10}$	205; —85,5 (methanol)	17	Fraxinus excelsior L. (Oleaceae) [3,7,11,15]
14. Fraxetin 7-O-β-D-glucopyranoside $C_{16}H_{18}O_{10}$	164–166; —52,4 (dimethylformamide)	18	Haplophyllum obtusifolium Ledeb. (Rutaceae) [27]
15. Calycanthoside $C_{17}H_{20}O_{10}$	219—220; —42 (methanol)	19	Calycanthus occidentalis Hook et Arn. (Calycanthaceae) [28]
16. Eleutheroside B_1	218; +80 (methanol)	20	Eleutherococcus senticosus Rupr. et Makino (Araliaceae) [29]
17. Fraxidin 8-O-β-D-glucoside $C_{17}H_{20}O_{10}$	193–195; —49 (water)	21	Fraxinus excelsior L. (Oleaceae) [30]
18. Mandshurin $C_{17}H_{20}O_{10}$	182,5; —26,7 (methanol)	22	Fraxinus mandshurica L. (Oleaceae) [31,32]
19. Tomenin $C_{17}H_{20}O_{10}$	207 —	23	Prunus tomentosa L. (Rosaceae) [33,34]
20. 7-Glucosyloxy-4-methoxy-5-methylcoumarin $C_{17}H_{20}O_9$	246—248 —	24	Platymiscium praecox Mart. (Leguminosae) [35]
21. 7-β-Glucosyloxy-5,6-dimethoxycoumarin	129 (acetate) [sic]	25	Pelargonium reniforme (Geraniaceae) [36]

TABLE 1 (Continued)

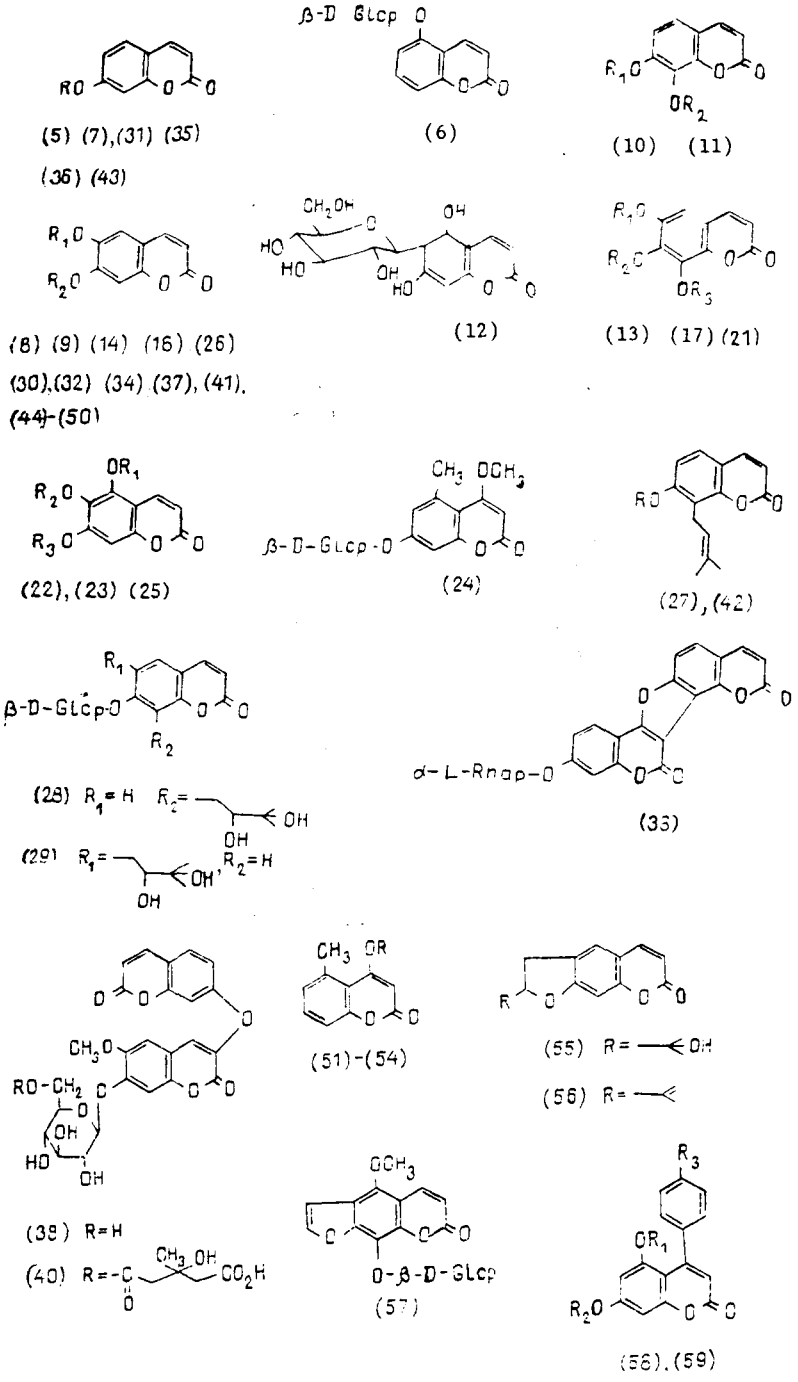
1	2	3	4
22. Scopoletin 7-O-β-(2',6'-diacetylglucopyranoside) $C_{20}H_{22}O_{11}$	178—179,5; —100 (methanol)	26	Viburnum suspensum (Caprifoliaceae) [37]
23 Vellein $C_{20}H_{24}O_8$	187,5—189 —	27	Velleia discophora T. Mucel (Goodeniaceae) [3,10,15]
24 8-(2',3'-Dihydroxy-3'-methylbutyl)-7-β-D-glucopyranosyloxycoumarin $C_{20}H_{26}O_{10}$	224—226 —	28	Phlojodicarpus sibiricus (M. Popov) Serg. (Apiaceae) [38]
25. (+)-Peucedanol-7-O-β-D-glucopyranoside $C_{20}H_{26}O_{10}$	205—205,5; —12,3 (methanol)	29	Seseli montanum L. (Apiaceae) [39]
26. Diospyroside $C_{20}H_{24}O_{13}$	249—250; —100 (dimethyl sulfoxide)	30	Diospyros sapota Roxb. (Ebenaceae) [40]
27 Umbelliferone β-D-apiosyl-(1 → 6)-β-D-glucopyranoside $C_{20}H_{24}O_{12}$	204—205; +169 (methanol-water)	31	Phlojodicarpus villosus (Turcz. ex Fisder et Meuer) Ledeb. (Apiaceae) [38]
28 Adicardin $C_{20}H_{24}O_{12}$	138—139; —121,3 (methanol)	31	Adina cordifolia (Roxb.) Brandis. (Rubiaceae) [41,42]
29. Baisseoside $C_{21}H_{26}O_{13}$	230—232, —166 (methanol)	32	Baissea leonensis [15,43]
30. Fabiatrin $C_{21}H_{26}O_{13}$	236—238; —140 (water)	33	Fabiana imbricata Ruiz et Pav. (Solanaceae) [44]
31. 7-α-L-Arabinopyranosyl-(1 → 2)-β-galactopyranosyloxy-6-methoxycoumarin $C_{21}H_{26}O_{13}$	—	34	Xeromphis spinosa Thumb. (Rubiaceae) [26]
32. Neohydrangin $C_{21}H_{28}O_{14}$	204; —190,9 (water)	35	Hydrangea paniculata Sieb. (Saxifragaceae) [3,45]
33. Dauroside A $C_{23}H_{28}O_{13}$	145—147; — 2,7 (methanol)	36	Haplophyllum dauricum (L.) G. Don. (Rutaceae) [46]
34 Dauroside C $C_{24}H_{30}O_{14}$	93—95 —	37	Haplophyllum dauricum (L.) G. Don. (Rutaceae) [47]
35. Eriocephaloside $C_{24}H_{18}O_{10}$	240	38	Lasiosiphon eriocephalus (Thymelaeaceae) [48]
36. Daphnorin $C_{25}H_{22}O_{12}$	204—205 — 78 (water)	39	Daphne mezereum L. (Thymelaeaceae) [5,7,49]
37. Rutarensin $C_{31}H_{30}O_{16}$	173—175 —	40	Ruta chalepensis (Rutaceae) [50]
38. Scopoletin 7-O-β-(6'-feruloyl-β-D-glucopyranoside) $C_{26}H_{26}O_{12}$	206—208; —110,5 (Pyridine)	41	Haplophyllum obtusifolium Ledeb. (Rutaceae) [27]
39. Osthenol 7-gentiobioside $C_{26}H_{34}O_{13}$	— 0 (methanol)	42	Glehnia littoralis Fr. Schmidt et Miq. (Apiaceae) [51]
40. Dauroside B $C_{30}H_{32}O_{14}$	143—150; 0 (pyridine)	43	Haplophyllum dauricum (L.) G. Don. (Rutaceae) [46]
41. Lariside $C_{21}H_{26}O_{13}$	155—156 —	44	Salsola laricifolia Turez. et Litw. (Chenopodiaceae) [52]
42 Hymexcelsin $C_{21}H_{26}O_{13}$	206; —116 (pyridine)	45	Hymenodictyon excelsum (Roxb.) Wall. (Rubiaceae) [53]
43. Haploperoside A $C_{22}H_{28}O_{13}$	212—213; —37 (methanol)	46	Haplophyllum perforatum (M. B.) Kar. et Kir. (Rutaceae) [54,55]
44. Haploperoside B $C_{24}H_{30}O_{14}$	222—224; —45 (methanol)	47	Haplophyllum perforatum (M. B.) Kar. et Kir. (Rutaceae) [20,56]

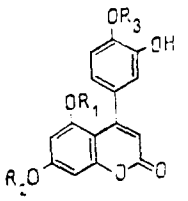
TABLE 1 (continued)

1	2	3	4
45. Haploperoside C $C_{21}H_{30}O_{14}$	155–157; −27.4 (methanol)	48	Haplophyllum perforatum (M. B.) Kar. et Kir. (Rutaceae) [55]
46. Haploperoside D $C_{22}H_{28}O_{13}$	249–251; −37.8 (dimethylformamide)	49	Haplophyllum perforatum (M. B.) Kar. et Kir. (Rutaceae) [55]
47. Haploperoside E $C_{21}H_{28}O_{17}$	175–177; −56.4 (dimethylformamide)	50	Haplophyllum perforatum (M. B.) Kar. et Kir. (Rutaceae) [55]
48. 4-β-D-Glucopyranosyloxy-methylcoumarin $C_{16}H_{18}O_8$	150 —	51	Ethulia conyzoides L. (Asteraceae) [57]
49. 5-Methyl-4-[α-L-rhamnopyranosyl(1→6)-β-D-glucopyranosyloxy]coumarin $C_{22}H_{28}O_{13}$	240–241; 79.4 (pyridine)	52	Gerbera jamesonii (Asteraceae) [58]
50. 4-β-D-Gentibiosyloxy-5-methylcoumarin $C_{22}H_{28}O_{13}$	—	53	Gerbera anandria (Asteraceae) [59]
51. 4-β-D-Cellobiosyloxy-5-methylcoumarin $C_{22}H_{28}O_{13}$	—	54	Gerbera anandria (Asteraceae) [59]
52. Rutarin (campesenin) $C_{20}H_{24}O_{10}$	143–144; −95.7 (pyridine)	55	uta graveolens L. (Rutaceae) [60,61]
53. (−)-9-β-D-Glucosyloxy-2-isopropenyl-2,3-dihydro-7H-furo[3, 2-g][1]benzopyran-7-one $C_{20}H_{22}O_9$	165, −60 (chloroform)	56	Apium graveolens L. (Apiaceae) [62]
54. 8-β-D-Glucosyloxy-5-methoxypsoralen $C_{18}H_{18}O_{10}$	230 —	57	Apium graveolens L. (Apiaceae) [62]
55. Serratin 7-O-β-D-glucoside $C_{21}H_{20}O_9$	166–168 —	58	Passiflora serratodigitata (Passifloraceae) [63]
56. 5-β-D-Galactopyranosyloxy-4',7-dimethoxy-4-phenyl coumarin $C_{23}H_{24}O_{10}$	217–221 —	59	Exostema caribaeum (Rubiaceae) [64]
57. 5-β-D-Glucopyranosyloxy-3',4',7-trihydroxy-4-phenylcoumarin $C_{21}H_{22}O_{11}$	—	60	Coutarea hexandra Jacq. (Rubiaceae) [65]
58. 5-β-D-Glucopyranosyloxy-3',4'-dihydroxy-7-methoxy-4-phenylcoumarin $C_{22}H_{22}O_{11}$	237–238 —	61	Coutarea hexandra Jacq. (Rubiaceae) [61]
59. 5-β-D-Galactopyranosyloxy-3',4'-dihydroxy-7-methoxy-4-phenylcoumarin $C_{22}H_{22}O_{11}$	228–231 —	62	Exostema caribaeum (Jacq.) Roem. et Schult. (Rubiaceae) [66]
60. 5-(6''-Acetyl-β-D-galactopyranosyloxy)-3',4'-dihydroxy-7-methoxy-4-phenylcoumarin $C_{24}H_{24}O_{11}$	215–220 —	63	Exostema caribaeum (Jacq.) Roem. et Schult. (Rubiaceae) [64]
61. 5-[D-Apiofuranosyl-(1 → 6)-β-D-glucopyranosyloxy]-3,4',7-trihydroxy-4-phenylcoumarin $C_{26}H_{28}O_{15}$	—	64	Coutarea hexandra Jacq. (Rubiaceae) [65]
62. 5-[β-D-Xylopyranosyl-(1→6)-β-D-glucopyranosyloxy]-3',4'-dihydroxy-7-methoxy-4-phenylcoumarin $C_{27}H_{30}O_{15}$	—	65	Coutarea hexandra Jacq. (Rubiaceae) [65]
63. Edgeworoside A $C_{33}H_{40}O_{13}$	208–209 —	66	Edgeworthia chrysantha Lindl. (Thymelaeaceae) [67]

this reason, they are not considered here, and in the present review we shall mainly discuss methods of isolation and the chemical and spectral properties of the phenol glycosides of the coumarin series.

At the present time, more than 60 phenol glycosides of the coumarin series have been described, and their physicochemical constants and sources are given in Table 1. The scheme gives their structural formulas. The information in Table 1 shows that coumarin glycosides are found in various families of higher plants and they are present most frequently in plants of the families Rutaceae, Rubiaceae, Apiaceae, Asteraceae, Oleaceae, and Thymelaeaceae. The number of biosides is 22, while haploperoside E is the only trioside of the coumarin series. Then other compounds are monosides. All the coumarin glycosides isolated, with the exception of dauroside D (12), are O-glycosides. Dauroside D, isolated from Haplophyllum dauricum (L.) G. Don. [18] is so far the only coumarin C-glycoside. This coumarin was later isolated by Japanese workers from Morus lhou and was called mulberroside B [19].





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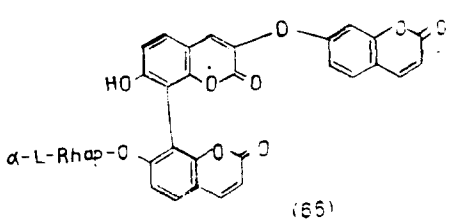

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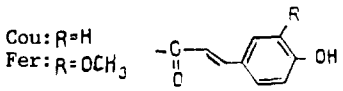


(5) R=β-*D*-Glcp
(7) R=α-*D*-Glcp
(31) R=3-*D*-Glcp^{6}←β-*D*-Api
(35) R=Glc←Glc
(36) R=β-*D*-Glcp^{6}←α-*L*-(4-OAc)-Rhap
(43) R=β-*D*-(2-Cou)-Glcp^{6}←α-*L*-Rhap

(10) R_1=H, R_2=β-*D*-Glcp
(11) R_1=β-*D*-Glcp, R_2=H

(8) R_1=H, R_2=3-*D*-Glcp
(9) R_1=β-*D*-Glcp, R_2=H
(14) R_1=CH_3, R_2=β-*D*-Glcp
(15) R_1=β-*D*-Glcp, R_2=CH_3
(16) R_1=β-*D*-Galp, R_2=CH_3
(26) R_1=CH_3, R_2=β-*D*-(2, 6 di-OAc)-Glcp
(30) R_1=H, R_2=β-*D*-Glcp^{6}←β-*D*-Api
(32) R_1=H, R_2=β-*D*-Glcp^{6}←α-*L*-Rhap
(33) R_1=CH_3, R_2=β-*D*-Glcp^{6}←β-*D*-Xylp
(34) R_1=CH_3, R_2=β-*D*-Galp^{2}←α-*L*-Arap
(37) R_1=CH_3, R_2=(β-*D*-Glcp^{6}←α-*L*-Rhap) OAc
(41) R_1=CH_3, R_2=β-*D*-(6-O-Fer)-Glcp
(44) R_1=CH_3, R_2=β-*D*-Glcp^{2}←β-*D*-Api

(45) R_1=CH_3, R_2=β-*D*-Glcp^{6}←β-*D*-Api
(46) R_1=CH_3, R_2=3-*D*-Glcp^{6}←α-*L*-Rhap
(47) R_1=CH_3, R_2=β-*D*-Glcp^{6}←α-*L*-(4-OAc)-Rhap
(48) R_1=CH_3, R_2=β-*D*-(2-OAc)-Glcp^{6}←α-*L*-Rhap
(49) R_1=CH_3, R_2=β-*D*-Glcp^{2}←α-*L*-Rhap
(50) R_1=CH_3, R_2=β-*D*-Glcp^{6}←α-*L*-Rhap
2^{A}
α-*L*-Rhap

(13) R=R_3=H, R_2=β-*D*-Glcp
(17) R_1=CH_3, R_2=H, R_3=β-*D*-Glcp
(18) R_1=CH_3, R_2=β-*D*-Glcp, R_3=H
(19) R_1=R_3=CH_3, R_2=β-*D*-Glcp
(20) R_1=R_3=CH_3, R_2=α-*D*-Glcp
(21) R_1=R_2=CH_3, R_3=β-*D*-Glcp

(22) R_1=R_3=CH_3, R_2=β-*D*-Glcp
(23) R_2=R_3=CH_3, R_1=β-*D*-Glcp
(25) R_1=R_2=CH_3, R_3=β-D-Glcp

(27) R=β-*D*-Glcp
(42) R=β-*D*-Glcp^{6}←β-*D*-Glcp

(51) R=β-*D*-Glcp
(52) R=β-*D*-Glcp^{6}←α-*L*-Rhap
(53) R=β-*D*-Glcp^{6}←β-*D*-Glcp
(54) R=β-*D*-Glcp^{4}←β-*D*-Glcp

(58) R_1=H, R_2=β-*D*-Glcp, R_3=H
(59) R_1=β-*D*-Glcp, R_2=CH_3, R_3=OCH_3

(60) R_1 = β-*D*-Glcp, R_2 = R_3 = H
(61) R_1 = β-*D*-Glcp, R_2 = CH_3, R_3 = H
(62) R_1 = β-*D*-Galp, R_2 = CH_3, R_3 = H
(63) R_1 = β-*D*-(6-OAc)-Galp, R_2 = CH_3, R_3 = H
(64) R_1 = β-*D*-Glcp←^{6}β-*D*-Apf, R_2 = R_3 = H
(65) R_1 = β-*D*-Glcp←^{6}β-*D*-Xylp, R_2 = CH_3, R_3 = H

As a rule, the compounds found are glycosides of simple hydroxycoumarins. The aglycons of glycosides (55), (56), and (57) are derivatives of furocoumarin and of dihydrofurocoumarin. No phenol glycosides have been found in the pyranocoumarin series. Three bicoumarin glycosides (compounds 38, 39, and 40), one tricoumarin glycoside (66) and eight 4-phenylcoumarin glycosides (compounds 58-65) are known. The aglycon moieties of almost half the glycosides isolated are represented by umbelliferone (7-hydroxycoumarin), scopoletin (7-hydroxy-6-methoxycoumarin), esculetin (6,7-dihydroxycoumarin), and fraxetin (7,8-dihydroxy-6-methoxycoumarin) and its methyl ethers. The sugar moiety is most frequently attached to a hydroxy group in position 7 of the coumarin nucleus but it may also be located in position 4,5 , 6 or 8. The majority of the substances isolated (34 out of 63) are glucosides.

Carbohdyrate components of the glycosides under consideration are represented, apart from D-glucose, by D-galactose, L-rhamnose, and D-apiose, and, more rarely, by D-xylose and L-arabinose. Pentoses are found more rarely than hexoses. Eight disaccharides have been found as components of the coumarin glycosides, the most frequent among them being rutinose (6-O-α-L-rhamnopyranosyl-D-glucopyranose), gentiobiose (6-O-β-D-glucopyranosyl-D-glucopyranose), primeverose (6-O-β-D-xylopyranosyl-D-glucopyranose), and 6-O-β-D-apiosyl-D-glucopyranose

A new group of natural compounds has recently been formulated in the area of coumarin glycosides – their acylated derivatives. The first acylated glycoside, haploperoside B, was isolated in 1980 from Haplophyllum perforatum [20]. A number of acylated glycosides were subsequently detected in certain species of Haplophyllum A. Juss. Up to the present time, the structures of nine coumarin glycosides acylated in the carbohydrate moieties by acetic, 3-hydroxy-3-methylglutaric, p-coumaric, and ferulic acid residues have been established. The greatest interest is presented by glycosides (41) and (43), which are acylated by derivatives of trans-cinnamic acid (biogenetic precursors of the natural coumarins) and also the bicoumarin glycoside (40) acylated by 3-hydroxy-3-methylglutaric acid. In all the acylglycosides, esterification takes place at an alcoholic group of the carbohydrate moiety.

Investigations of recent years have shown that, apparently, coumarin glycosides are widely distributed in the vegetable kingdom. The fact that their number remained relatively low as a proportion of the total number of natural coumarins for many years is explained by the absence of modern methods for their detection and isolation.

ISOLATION

Coumarin glycosides, being polar compounds, are readily soluble in such polar organic solvents as ethanol, acetone, and methanol, and also in water. They are also extracted from the plant raw material by the above-mentioned solvents or mixtures of them [68, 69]. In some cases, alcoholic extracts are subjected to chromatography on a column without preliminary purification. Alcoholic and aqueous extracts usually contain, in addition to the coumarins, a large amount of carbohydrates, phenols, flavonoids, tanning substances, and other compounds which interfere with the separation and isolation of the coumarin glycosides. The primary extract is therefore frequently subjected to preliminary purification with the aid of eliminating ballast substances and separating extractive substances into groups of substances of similar polarity. Usually the concentrated alcoholic extract is diluted with water, the precipitate that has deposited is separated off by filtration, and the filtrate is extracted successively with organic solvents in order of increasing polarity – chloroform, ethyl acetate, and butanol [46, 52]. Coumarin glycosides pass into the ethyl acetate and butanol fractions, while the most polar compounds remain in the aqueous solution. As a rule, the separation of a particular fraction is carried out by column chromatography on silica gel or alumina, and more rarely on polyamide, cellulose, or Sephadex. The coumarins containing phenolic hydroxy groups are strongly absorbed by alumina, which hinders their elution from the column [6, 7]. To prevent this undesirable process it has been proposed to use acidic alumina [70]. In some cases, special adsorbents are used for the preliminary purification of particular fractions. For example, in the isolation of osthenol gentiobioside from the roots and rhizomes of Glehnia littoralis the butanol fraction of an alcohol extract was first chromatographed on activated carbon [51].

A method has been described for isolating glycosides by extracting the raw material with hot water, after which the aqueous extract was treated with ether or chloroform and the residue after the elimination of the solvent was chromatographed with the aim of isolating individual substances [68]. In each concrete case, the method of treating the primary extract depends on the features of the plant under investigation.

It must be stated that the isolation of coumarin glycosides from plant raw materials is a complex problem because of their lability, the presence of compounds with similar properties in the raw material, and the existence of considerable amounts of accompanying substances in the majority of coumarin-bearing plants.

METHODS OF ESTABLISHING STRUCTURES

The assignment of a particular compound to the coumarin glycosides is made on the basis of the characteristic blue fluorescence in solutions and on TLC plates in UV light and the results of IR, UV, and PMR spectroscopy, and also the results of acid hydrolysis.

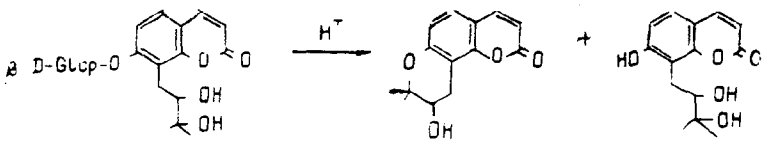
The sugar moiety does not absorb in the UV region of the spectrum and therefore the spectra of the glycosides differ little from the spectra of the corresponding coumarins. The use of UV spectroscopy in structural investigations of coumarins has been discussed in review papers and monographs [71, 72].

Characteristic for the PMR spectra of the coumarins and their glycosides are the resonance signals of the protons of the α-pyrone ring (H-3 and H-4), which appear in the weak field in the form of two one-proton doublets linked with one another in the manner of an AB system with a typical vicinal coupling constant ^3J = 9.5-10.0 Hz [72-74]. The H-3 signal usually appears in the 6.0-6.4 ppm region, while the H-4 signal appears at 7.4-8.1 ppm (Table 2). It has been established that the chemical shifts of the signals of the above-mentioned protons depend on the presence or absence of a substituent at C-5, on the nature of the solvent in which the spectrum is recorded, and on other factors [74, 75]. In the PMR spectra of the glycosides, the anomeric protons resonate in the 4.8-6.1 ppm region, i.e., in a weaker field than the other protons of the sugar moiety (see Table 2). The chemical shift of the signal of the anomeric proton is substantially affected by the nature of the sugar residue, the position of its attachment of the aglycon, and the configuration of the glycosidic bond. Characteristic for the spectra of rhamnosides and rutinosides is the presence of the signal of a methyl group at 0.92-1.45 ppm.

In addition to the vicinal coupling, long-range spin-spin coupling between the protons of the coumarin nucleus is observed [72, 73, 76]. Information on the long-range spin-spin coupling constants is of interest for structural analysis. The identification of the position of the carbohydrate residue in the molecule of dauroside D was made on the basis of the observation of a long-range interaction between the H-4 and H-8 protons in a double-resonance experiment [18].

Coumarin O-glycosides, in contrast to coumarin C-glycosides, are readily hydrolyzed by acids with the formation of aglycons (hydroxycoumarins) and free monosaccharides. The isolation and identification of the hydroxycoumarins are carried out by the usual methods and present no difficulties. In proving their structures, instrumental methods have determinative value at the present time [72, 74, 80].

In cases where the aglycon of a glycoside is the labile 6,7,8-trihydroxycoumarin (as, for example, in the case of erioside (13) [24]), it is difficult to isolate it in the native form from the reaction products. In such cases, acid hydrolysis is carried out after the preliminary methylation of the free phenolic hydroxy groups of the glycoside. The hydrolysis of glycosides containing a 2,3-dihydroxy-3-methylbutyl side chain in the ortho position with respect to the glycosylated hydroxy group leads to the formation, together with the native aglycon, of the product of its cyclization – a pyranocoumarin. The acid hydrolysis of glycoside (28) gave two aglycons: lomatin (67) and 8-(2',3'-dihyroxy-3'-methylbutyl)-7-hydroxycoumarin (68) [38].



28 67 68

TABLE 2. Chemical Shifts of the Protons of the α-Pyrone Ring and of the Anomeric Protons of Coumarin Glycosides (δ, ppm; J, Hz)

Compound	Solvent	Proton*			Literature
		H-3	H-4	H-1'	
1. Skimmin (5)	Py—d_5	6,14 (10,0)	7,45 (10,0)	5,50 (7,0)	77
2. Esculin (1)	DMSO-d_6	6,27 (10,0)	7,87 (10,0)	**	78
3. Scopolin (14)	CD_3OD DMSO-d_6	6,25 (9,5)	7,87 (9,5)	**	78
4. Fraxin (17)	Py—d_5	6,05 (9,5)	7,45 (9,5)	5,52 (7,0)	32
5. Erioside (13)	DMSO-d_6	5,68 (10,0)	7,76 (10,0)	**	24
6. Fraxidin 8-O-β-D-glucoside (21)	Py - d_5	6,35 (9,8)	7,62 (9,8)	6,05 (8,5)	79
7. Lariside (44)	Py—d_5	6,34 (9,5)	7,70 (9,5)	5,60 (7,5)	52
8. Magnolioside (14)	DMSO-d_6	6,23 (10,0)	7,83 (10,0)	**	78
9. Scopoletin 7-O-(2',6'-diacetyl-β-D-glucopyranoside) (26)	Py—d_5	6,30 (9,8)	7,63 (9,8)	5,43 (8,5)	37
10. Dauroside D (12)	Py - d_5	6,04 (10,0)	7,90 (10,0)	5,56 (9,5)	18
11. Hymexcelsin (45)	DMOSO-d_6	6,13 (9,5)	7,73 (9,5)	5,12 (4,75)	53
12. Cichoriin (8)	Py—d_5	6,10 (9,7)	7,53 (9,7)	5,50 (7,0)	32
13. Mandshurin (22)	Py—d_5	6,10 (9,7)	7,67 (9,7)	5,60 (6,0)	32
14. (+)-Peucedanol 7-O-β-D-glucopyranoside (29)	D_2O	6,23 (9,5)	7,58 (9,5)	4,90 (9,6)	39

*The signals of the H-3, H-4, and H-1' protons appear in the form of doublets.

**The values of the chemical shifts are not given in the literature.

The enzymatic cleavage of the glycosides is the mildest method of obtaining the aglycons, permitting the avoidance of the formation of byproducts and artefacts.

If the aglycon contains two or more phenolic hydroxy groups, the necessity arises for determining the position of attachment of the carbohydrate residue. This question is solved by bringing in both chemical and spectral methods. The chemical method consists in methylating the free phenolic hydroxy groups of the initial glycoside followed by hydrolysis and identification of the partially methylated hydroxycoumarin formed. As a result of acid hydrolysis of the product of the methylation of diospyroside (30) scopoletin was obtained, which unambiguously showed the attachment of the carbohydrate residue to the hydroxyl in the C-7 position [40].

The position of a free phenolic hydroxyl in the initial glycoside can be established by a study of UV spectra taken with the addition of diagnostic reagents [72].

Paper and thin-layer chromatographies and, in recent years, also GLC, have been used in the identification of the free monosaccharides in the hydrolysis products of a glycoside [51, 64, 65].

The determination of the sequence of monosaccharide units in biosides is achieved by studying the products of partial acid hydrolysis, and also the mass spectra of the peracetates and permethylates of the glycosides. The presence in the spectrum of the acetate of dauroside A (36) of intense peaks of ions with m/z 273 (100%), 213 (13), and 153 (13) enabled the nature of the terminal sugar residue to be established as L-rhamnose [46]. However, this method is unsuitable for biosides containing monosaccharides identical in composition. In such cases, recourse is had to the methods of exhaustive methylation. Hakomori's method of methylation has been used to prove the structures of the carbohydrate moieties of biosides (31), (42), (45), (46), and (49) and of the trioside (50). The permethylates obtained were hydrolyzed with the formation of incomplete ethers of monosaccharides, which were identified by the methods of TLC and GLC. It must be mentioned that in the Hakomori methylation of coumarin glycosides, mixtures of substances are frequently formed as a result of the opening of the lactone ring of the coumarin in the alkaline medium [24, 36].

The configurations of the glycosidic bonds are determined with the aid of PMR results on protonic spin-spin coupling constants, the calculation of molecular rotations, and the results of enzymatic hydrolysis. In the overwhelming majority of coumarin glycosides (32 out of 34) the aglycon is linked to the carbohydrate moiety by a β-glycosidic bond.

Coumarin acylglycosides differ from their nonacylated analogs by higher chromatographic mobilities, by the presence of bands of ester groups in the IR spectra, and by the signals of acyl residues in PMR spectra. The mild alkaline hydrolysis of the acylglycosides leads to the saponification of the acyl residues with the formation of the deacylated analogs. The key question in the structural analysis of acylglycosides is the determination of the position of attachment of the acyl residue. The contribution of PMR and ^{13}C NMR spectroscopy to the solution of this question is considerable.

The establishment of the structures of acylglycosides in fact reduces to identifying the signals of the gem-acyl protons in the PMR spectrum which, as the result of a paramagnetic shift, appear in a weaker field than in the analogous compounds having no acyl residue. In some cases (as, for example, in the case of glycosides (41) and (63)) this can be done directly from the spectrum taken under the usual conditions. In more complex cases, recourse is had to special methods of PMR (INDOR and double resonance). These methods have been used to prove the structures of the acylglycosides (26), (47), and (48).

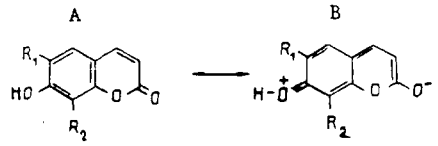
Many questions relating to the structures of the coumarin glycosides can be solved successfully with the aid of ^{13}C NMR spectroscopy [38, 40, 52, 78, 81, 82-84]. A comparative study of the ^{13}C NMR spectra of a glycoside and its aglycon permits the position of attachment of the carbohydrate moiety, the size of the oxide ring of the sugar residue, and the configuration of the glycosidic bond, and also, in the case of biosides, the order and position of attachment of the sugar residues to be determined. It has been established that the carbon atom of the coumarin nucleus to which the sugar residue is attached experiences a glycosylation effect which is calculated as the difference between the chemical shifts of the corresponding carbon atoms in the spectra of the free coumarin and of the glycoside corresponding to it. The glycosylation of a phenolic hydroxy group in a coumarin nucleus leads to a diamagnetic shift of the signal of the α-carbon atom by 0.3-1.8 ppm, while the signals of the β-carbon atoms undergo downfield shifts of the order of 0.5-3.4 ppm. In the spectra of fraxetin glycosides the value of the shift of the signals of the β-carbon atoms is about 5 ppm [85].

A comparison of the ^{13}C NMR spectra of 7-O-α- and 7-O-β-D-glucopyranosides [82] and also of the 7-O-β-D-glucofuranoside of 4-methylumbelliferone [86] shows that these isomers differ substantially with respect to the chemical shifts of the signals of the carbohydrate moiety. Consequently, from the ^{13}C NMR spectrum it is possible to distinguish different isomeric forms of one and the same monosaccharide residue. The signals of the anomeric carbon atom of O-glycosides appears in a weaker field than the analogous signals in the spectra of C-glycosides [18, 19, 82].

The sequence of monosaccharide units in biosides can be determined in the light of fine differences in the glycosylation effects in the ^{13}C NMR spectra, which depend on the structure of the glycosylating and glycosylated residues and the type of substitution in the latter [42, 46, 47, 55, 65].

The acylation of a hydroxy group of a carbohydrate leads to a paramagnetic shift of the signal of the carbon atom to which it is attached, while the signals of the vicinal carbon atoms undergo diamagnetic shifts. A comparative study of the ^{13}C NMR spectra of an acylated glycoside and the product of its deacylation permits the site of attachment of the acyl residue to be determined unambiguously. This method has been used successfully to establish the structures of the acylated coumarin glycosides (36), (40), (43), and (48) [46, 50, 55].

The crystalline and molecular structures of esculin (9) [87], cichoriin (8) [87], daphnin (11) [88], and daphnetin 8-O-β-D-glucoside (10) [89] have been studied by the method of x-ray structural analysis. It has been shown that the glycosylation of the hydroxy groups in positions 8 of daphnetin (69) and 6 of esculetin (70) has only a slight influence on the coumarin structure, and the carbohydrate moiety adopts a conformation which decreases the intramolecular repulsion. Conversely, in the molecules of glucosides (8) and (11), each of which contains the carbohydrate residue in position 7, the coumarin nucleus is almost planar, and the torsion angle around the glycosidic C–O bond is considerably greater than the corresponding values in glycosides (9) and (10), as a result of which an intramolecular repulsion arises between the coumarin nucleus and the glycosyl moiety. This is due to the fact that the glycosylation of the hydroxy group in position 7 of esculetin and daphnetin decreases the contribution of resonance structure B.



(68) R_1=H, R_2=OH
(70) R_1=OH, R_2=H

For the reason given above, glycosides (9) and (10) are more stable than glycosides (8) and (11). In plants, under the action of the enzyme transglycosidase, the latter are readily converted into glycosides (9) and (10), respectively [90, 91], while the reverse transformation is not observed.

Table 1 gives the structures of 63 coumarin glycosides. Adicardin has been assigned the structure of umbelliferone β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside (31) [41]. The same structure has been put forward for a glycoside isolated from Phlojodicarpus villosus [38]. although these substances have different physicochemical constants. It is possible that they differ by the configuration of the glycosidic bond of the D-apiose residue.

BIOLOGICAL ACTIVITY

The role of the coumarins and their glycosides in the vital activity of plants has not yet been definitively elucidated, although certain interesting results have been obtained in this field. In J. B. Harborne's opinion the glycosylation reaction taking place in plants is one of the methods for the detoxication of phenols [92]. Scopolin is one of the preinfection protective substances of plants, and its amount rises after infection with pathogenic microorganisms. Thus, the infection of potato tubers with the fungus Phytophthora infestans leads to a 10- to 20-fold rise in the concentration of scopolin. An increase in the amount of scopoletin and scopolin is also characteristic for tobacco, sunflowers, and other plants on infection and under the influence of stress factors. Scopolin possesses a considerable toxicity in relation to a number of microorganisms in vitro. Scopolin and scopoletin have been described as growth inhibitors in oat roots. According to Schreiner and Reed [93], esculin very powerfully suppresses the growth of wheat shoots.

Coumarins and their glycosides have been detected in a number of plants used in scientific and folk medicine. From the seeds of Aesculus hippocastanum L. is prepared the aqueous alcoholic extract eskuzan, which is used for the prophylaxis of thromboses and in venous congestion and hemorrhoids [94]. The action of this substance is due to the presence of esculin and fraxin, which possess the properties of a dicoumarin. Abroad, the preparations flavazid and esflazid are obtained from this plant [95]. Esculin is a component of sun-protecting creams [96].

The dried bark of Fraxinus japonica is used in folk medicine as a diuretic, analgesic, and antirheumatic agent [81]. Diuretic and antiphlogistic properties are also shown by the glycoside of esculin and fraxin that have been isolated from the above-mentioned plant. The plant Exostema caribaeum, containing glycosides of 4-phenylcoumarin, is used in Mexico as an antimalarial agent [64].

Esculin and fraxin possess vitamin P activity [4]. Fraxin promotes an enhanced elimination of uric acid from the organism [7]. A comparison of the spasmolytic activities of esculin and fraxetin, and their aglycons has shown that the glycosylation of fraxetin leads to enhancement of pharmacological activity [97].

Umbelliferone α-glucoside exhibits pronounced antiarrhythmic activity in various models of arrhythmia [21]. Obtusoside, dauroside D, scopolin, and haploperoside A possess spasmolytic and hypotensive actions [98, 99]. The activity of obtusoside exceeds that of the other compounds but the deviation of its action is less. An antiarrhythmic activity is also characteristic for haploperoside A [98].

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METHODS OF ISOLATING ALKALOIDS OF THE COLCHICINE SERIES

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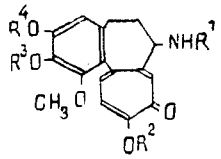
This review considers methods for the isolation of colchicine, colchamine, and colchicoside. The literature for the period from 1884 to 1997 has been used.

Colchicine, a long-known alkaloid of the autumn crocus, has appeared in the pharmacopeias of many countries [1]. Colchamine (synonyms: demecolcine, colcemide), which was discovered later [2, 3], is used in some cases of malignant neoplasms [4]. Colchicine is used for treating gout [1], amyloidosis [5], periodic disease [1, 6], and disseminated sclerosis. Some generalizations concerning the medical use of colchicine have been given in [8]. Colchicine has recently been used in the derivation of new varieties of plants [9].

Some artificial derivatives of colchicine have acquired medicinal value. Abroad, the drug Thiocolceran (deacetylthiocolchicine) is used [10]. Thiocolchicoside (Coltramyl) is employed in rheumatic and nonperiodic diseases [10]. For its pharmacology, see [11]. This drug is synthesized [12] from colchicoside, which is 3-glucosyl-3-demethylcolchicine [13]. Recent patents witness the unabating interest in the practical use of the biological properties of colchicine and its derivatives. In an American patent application antiphlogistic agents based on 2,3-didemethylcolchicine are described [14]. There are patents on medicinal forms of colchicine [15]. A solution of colchamine has been patented for lowering intraocular pressure [16].



	R^1	R^2	R^3	R^4
Colchicine	$COCH_3$	OCH_3	CH_3	CH_3
Colchamine	CH_3	OCH_3	CH_3	CH_3
Deacetylthiocolchicine	H	SCH_3	CH_3	CH_3
Thiocolchicoside	$COCH_3$	SCH_3	CH_3	$C_6H_{11}O_5$
Colchicoside	$COCH_3$	OCH_3	CH_3	$C_6H_{11}O_5$
2-Demethylcolchicine	$COCH_3$	OCH_3	H	CH_3
3-Demethylcolchicine	$COCH_3$	OCH_3	CH_3	H
2,3-Didemethylcolchicine	$COCH_3$	OCH_3	H	H
2-Demethylcolchamine	CH_3	OCH_3	H	CH_3
N-formyldeacetylcolchicine	HCO	OCH_3	CH_3	CH_3
17-Oxocolchicine	$COCH_2OH$	OCH_3	CH_3	CH_3
Colchiceine	$COCH_3$	OH	CH_3	CH_3

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