MODERN STATE OF THE CHEMICAL STUDY OF SPECIES OF THE GENUS *Hypericum*

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UDC 582.824.547

This review gives complete information on the chemical study of 66 species of the genus *Hypericum L.* In individual sections the study of various groups of substances is discussed in a historical framework. The compounds isolated are given — hypericins, flavanols and tanning substances, flavones, flavonols, xanthones, coumarins, phenolcarboxylic acids, antibiotic substances, essential-oil compositions, nonvolatile saturated hydrocarbons, and other compounds. The value of these groups of substances in the connection with the pharmacological action and the therapeutic use of *Hypericum* species is shown. The structural formulas of 85 isolated compounds and their distribution in the species studied are given. The chemosystematic value of individual substances for the genus *Hypericum* and the family Guttiferae is discussed.

The genus *Hypericum* L. belongs to the tribe Hypericeae Choisy, subfamily Hypericoideae Engl. and is the largest genus of the family Guttiferae Juss. [1]. It numbers about 400 species belonging to 30 sections [2, 3].

Representatives of the *Hypericum* genus are widely used in folk and scientific medicine for various diseases. In all modern handbooks on medicinal plants voluminous information is given on the use of common St. John's wort (*H. perforatum*). The antiinflammatory, astringent, capillary-strengthening, wound-healing, psychotropic and antibiotic action of preparations of it is widely known. According to folk medicine, a number of other species of this genus also have medicinal properties. Even Dioscorides referred to the use of four species of *Hypericum*: Upericon, Askuron, Androsaimon, and Koris [2]. It has recently been established that the diuretic action of preparations of *H. elongatum* Lebed. and *H. scabrum* L. several times exceed the action of *H. perforatum* L. [4]. Information on pharmacological investigations, the use in folk and scientific medicine and the economic value of plants of the genus *Hypericum* has been given in a review [5].

Interest in the chemical study of representatives of the genus *Hypericum* is due not only to their economic value and their use in medicine but also to the development of chemosystematic investigations [6, 7]. The greatest number of investigations has been devoted to a phytochemical study of *H. perforatum*, but information is also found in the literature on the chemical composition of 66 species. The majority of them have been investigated for the presence of phenolic compounds and essential oil. Results on the chemistry of the *Hypericum* genus obtained up to 1976 has been summarized in several publications [6, 8-11]. The majority of authors give information on common St. John's wort, but in a review by Bandyukova and Khalmatov [10] the information relates to the presence of flavonoids and hypericin in plants of the *Hypericum* genus. Hegnauer [6] mentions some of the investigations more important for the chemosystematics of the genus up to 1965. At the present time, a considerable amount of material on the chemistry of the genus has accumulated, and is therefore appeared desirable to generalize the results of the investigation of all *Hypericum* species.*

DIANTHRONE DERIVATIVES. HYPERICINS

One of the most interesting biologically active substances of St. John's wort is hypericin (I). This red pigment, which is specific for the *Hypericum* genus causes a peculiar

*Publications relating to the properties, accumulation, concentration, and localization in the plants of the groups of substances considered are not included in this review.

Pharmaceutical Faculty, Sofia Medical Scademy. Leningrad Institute of Pharmaceutical Chemistry. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 185-203, March-April, 1987. Original article submitted June 11, 1986; revision submitted November 27, 1986.

0009-3130/87/2302-0151$12.50

TABLE 1. Distribution of Phenolic Compounds in Species of the Genus *Hypericum* L.

Sections and species*	Hypericin	Flavanols	Flavanones and flavanols	Xanthones	Coumarins and phenolic acids	Literature
Campylosporus (Spach) R. Keller (10)	+					3, 41
Psorophytum (Spach) Nyman (1)	—					3, 41
H. balearicum L.			XIV	XXXVII, XXXIX, XLIV		69
Ascyreia Choisy (36)	—					3, 41
H. calycinum L.		VII	XIV, XV, XXI	LVIII		48, 51, 80, 94
H. chinense L. (=H. monogynum L.)		VII	XI, XIV, XVI, XVII			51, 70
H. hookeranum Wight et Arn.		VII, VIII	XI, XIV, XV, XVII, XXI		LXIII, LXIV	50, 51, 77
H. mysorense Wight et Arn.				XXXVII, XXXVIII, XXXIX, XLI, XLII, XLV XLVII		96, 97, 141
H. patulum Thunb. ex Murray		VII, VIII	XI, XIV, XV, XXI			48, 51
Takasagoya (Y. Kimura) N. Robson (4)	—					3, 41
Androsaemum (Duhamel) Godron (4)	—					3, 41
H. androsaemum L.		VII, VIII	XI?, XIV, XV	XLIII, XLIV, XLVIII, L LI, LII, LIV, LVI, LVIII	LXIII, LXV	6, 51, 76, 94, 95, 103
H. elatum Ait. (=H. inodorum Miller)			XIV, XV, XXI			48, 80
H. hircinum L.		VII	XIV, XV, XVII		LXIII, LXIV	6, 50, 77
Inodora Stef. (1)	—					3, 41
H. inodorum Willd. (=H. xylosteifolium (Spach) N. Robson)		VII	XI, XIV, XV, XVI			51, 85
Roscyna (Spach) R. Keller (3—4)	—					3, 41
H. ascyron L.		VII	XI, XIV, XV, XVI, XVII, XXI		LXIII, LXIV	50, 51, 77, 78
H. przewalskii Maxim.		VII	XI, XIV			51
Bupluroides Stef. (1)	+					3, 41
Hypericum (48)	+					3, 41
H. attenuatum Choisy			XIV, XV		LXIV	67
H. elegans Stephan ex Willd.			XVII			65

TABLE 1 (Continued)

Sections and species*	Hypericin	Flavanols	Flavones and flavonols	Xanthones	Coumarins and phenolic acids	Literature
H. erectum Thunb. ex Murray			XIV, XV, XXI		LXI, LXII	63, 143
H. maculatum Crantz (=H. quadrangulum L.)		VII, VIII	XI, XIV, XV, XVII, XXI	LV, LVII, LVIII	LXIII, LXIV	50, 51, 62, 65, 77, 83, 85, 87, 93, 94, 99
H. perforatum L.		VII, IX, X	XIV, XV, XVI? XVII, XXI	LVIII	LIX, LX LXIII, LXIV	4, 47, 50, 52 57, 58, 61, 62, 66, 77, 83, 87, 89, 94, 105, 106
H. tetrapterum Fries (=H. acutum Moench)		VII, VIII	XI, XIV, XV, XVI, XVII, XXI		LXIII, LXIV	50, 51, 58, 70, 77, 83, 87
H. undulatum Schousb. ex Willd.		VII	XIV, XV, XVII, XXI		LXIII, LXIV	50, 77
Olympia (Spach) Nyman (2)	+					3, 41
H. olympicum L.		VII, VIII	XIV, XV, XXI, XXIV		LXIV	51, 62, 88
H. polyphyllum Boiss. et Bal.		VII, VIII	XI, XIV, XV XVII, XXIV		LXIII LXIV	50, 51, 77
Campylopus Boiss. (1)	+					3, 41
Origanifolia Stef. (4)	+					3, 41
Drosocarpium Spach. (12)	+					3, 41
H. rumeliacum Boiss.		VII, VIII	XI, XIV, XXIV	LV		51, 90, 99
H. richerii Vill.			XV, XVII, XXI			62
H. barbatum Jack.				LV		99
Olygostema (Boiss.) Stef. (7)	+					3, 41
H. aucheri Jaub. et Spach.			XI, XIV, XVI, XXIV, XXXVI	LI, LV		75, 79, 99, 100
H. humifusum L.		VII, VIII	XI, XIV, XV, XXI, XXIV	LV		51, 70, 83,
Thasia Boiss. (1)	+					3, 41
Crossophyllum Spach. (2)	±					3, 41
H. ptarmicifolium Spach (H. orientale L.)			XIV, XV, XVII			60, 80
Hyrtella Stef. (24)	+					3, 41
H. elongatum Ledeb.			XIV, XV, XVII, XXI		LIX, LX	4, 59, 66, 80

TABLE 1 (Continued)

Sections and species*	Hyper-icin	Flavanols	Flavones and flavonols	Xanthones	Coumarins and phenolic acids	Literature
H. helianthemoides (Spach) Boiss.			XIV, XV, XXI		LIX, LX	66
H. scabrum L.			XIV, XV, XVI, XVII, XVIII, XXI, XXII? XXIII, XXIV, XXV		LIX, LX	4, 59, 63, 71, 80, 91
Taeniocarpium Jaub. et Spach. (23)	+					3, 41
H. hirsutum L.		VII, VIII, IX, X	XIV, XV, XVI, XVII, XXI, XXIV, XXVI, XXVIII, XXXI, XXXII		LXIII, LXIV, LXVI, LXVII, LXVIII	50, 51, 54, 58, 61, 62, 73, 74, 77, 83, 84, 104
H. nummularioides Trautv.			XIV, XV			60, 80
H. nummularium L.		VII, VIII	XI, XIV, XXI, XXVI?		LXIV	51, 56, 70
H. pulchrum L.		VII, VIII	XIV, XVI, XVIII			51, 70
Coridium Spach (5)	+					3, 41
H. empetrifolium Willd.		VII, VIII	XI?, XIV			51
H. ericoides L.			XIV, XV, XXXIII	XXXVII, XXXIX, XLIX LIII, LVIII		68, 98
Myriandra (Spach) R. Keller (30)	−					3, 41
H. crux—andreae (L.) Crantz			XIX, XXIX, XXX			140
H. densiflorum Pursh			XIV, XV, XXI			48, 80
H. edisonianum (Small) Adams et Robson			XX			140
H. galioides Lam.			XIV, XV, XXI			48
H. hypericoides (L.) Crantz			XX			140
H. microsepalum (T. et G.) A. Gray ex S. Watson			XII, XIII, XX			140
H. prolificum L.		VII	XI, XIV			51
H. suffruticosum Adams et Robson			XVII			140
H. stragalum Adams et Robson			XV, XVII, XIX			140
H. tetrapetalum Lam.			XIII, XIV, XVII, XXVII, XXIX, XXXIV, XXXV			140

TABLE 1 (Continued)

Sections and species*	Hypericin	Flavanols	Flavones flavanols	Xanthones	Coumarins and phenolic acids	Literature
Webbia (Spach) R. Keller (1)	—					3, 41
H. canariense L.		VII, VIII	XI, XIV	XXXVII, XXXIX, XL XLIII	LXIII	6, 142
Arthrophyllum Jaub. et Spach (1)	—					3, 41
Triadenoides Jaub. et Spach (5)	+					3, 41
Heterophylla N. Robson (1)	—					3, 41
Adenotrias (Jaub. et Spach) R. Keller (3)	—					3, 41
Humifusoideum R. Keller (10)	+					3, 41
Adenosepalum Spach (33)	+					3, 41
H. degenii Bornm. (=H. annulatum Moris)		VII, IX, X	XI, XIV, XV, XVII, XXI, XXIV	XLVI	LXIII LXIV	50, 53, 62, 77, 81, 82
H. montanum L.		VII, VIII	XI, XIV, XV, XVII, XXI, XXIV			51, 65, 70, 83
H. tomentosum L.		VII	XIV, XV, XVII		LXIII, LXIV	50, 77, 92
Elodes (Adans.) W. Koch. (1)	—					3, 41
Brathys (Mutis ex L. f.) Choisy (48)	—					3, 41
Spachium (R. Keller) N. Robson (54)	—					3, 41
H. japonicum Thumb. ex Murray			XIV, XXII			64, 72
Species not given in N. K. Robson's classification						
H. caucasicum (Woron.) Gorschk.			XIV, XV			60, 80
H. grandifl rum Salisb.		VII, VIII	XIV		LXIII	6
H. polygonifolium Rupr.			XIV, XVII			60, 80
H. prolisfirum L.			XVI, XVII, XXI			61
H. pyramidatum Ait.		VII	XI, XIV			51

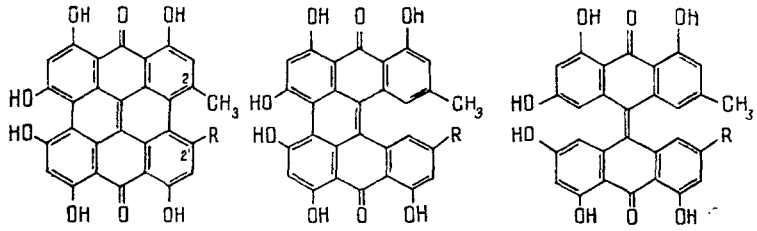
*The names of the sections and species are given in accordance with N. K. Robson's classification [2, 3]. The number of species in a section is shown in parentheses.

light-sensitivity and disease in animals with light-colored wool (photodynamic effect). Hypericin was first reported by Buchner in 1830 and was isolated by Dietrich in 1891. It was given the name "hypericin" by S. Czerny in 1911 [9, 11].

The greatest contribution to its all-sided study was made by Hans Brockmann and his school. The investigations were begun in 1939 [12]; in 1942 the basic skeleton was established, and in 1950-1951 its definitive structure [13-15]; and later the complete synthesis of hypericin was performed [16-19]. It was established that (I) is 4,4',5,5',7,7'-hexahydroxy-2,2'-dimethyl-meso-naphthodianthrone.

It was also found that the herbage of St. John's wort contains not only hypericin but also photodynamic pigments. In 1941, N. Pace and G. Mackinney reported the isolation from St. John's wort of other photodynamic fractions in addition to hypericin [20]. R. C. Betty and V. M. Trikojus, working in the absence of light, isolated from the herbage of St. John's wort a nonfluorescing pigment as a precursor which, after irradiation, was rapidly converted into hypericin [21, 22]. Later, H. Brockman et al., detected in a number of species and isolated a new red pigment — pseudohypericin (II) [23-25]. Its definitive structure was established in 1975 and it was synthesized [26-28].

A more detailed study of these experiments led to the detection and isolation from plants of precursors of hypericin and pseudohypericin. *H. montanum* L. yielded protohypericin (III)) and hypericodehydrodianthrone (V), and *H. perforatum* yielded frangula emodin athranol a mixture of (III) and protopseudohypericin (IV), and also a mixture of (V) and pseudohypericodehydrodianthrone (VI) [19]. H. J. Banks et al., however, have shown the absence of emodin anthrone and of hypericodehydrodianthrone from fresh flowers of *H. perforatum* [30]. The synthesis of protohypericin has been carried out from penicilliopsin, emodin anthrone and emodin [31-35].



I. R = CH_3 III. R = CH_3 V. R = CH_3

II. R = CH_2OH IV. R = CH_2OH VI. R = CH_2OH

On the basis of these investigations, it is assumed that the biosynthesis of hypericin in plants takes place from frangula emodin via emodin anthrone, dianthrone (penicilliopsin), hypericodehydrodianthrone (V), and protohypericin (III) [29].

A number of authors have studied the distribution of (I) in species of the genus *Hypericum* [25, 34-40], but the fullest information on their presence in about 222 species has been given by C. Mathis and G. Ourisson [41]. The distribution of hypericin in representatives of sections of the genus *Hypericum* is given in Table 1. The fact that (I) is not present in all species of St. John's wort but only in representatives of certain taxons has served as a basis for its use for the purposes of chemosystematics and it has great value for the classification of these species of the genus *Hypericum* [3, 41, 42]. Its presence explains the antidepressant action of St. John's wort and its use in some skin diseases [8, 43-46].

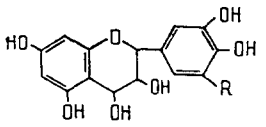
TANNING SUBSTANCES. FLAVANOLS

Tanning substances are widely distributed in the species of the genus *Hypericum*. They belong to the catechin type and are condensed products of flavan-3-ol (catechin) and of flavan-3,4-diol (leucoanthocyanidin).

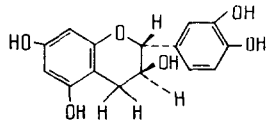
Tanning substances have been detected in 29 species of *Hypericum* [4, 40, 47-49], but their chemical composition has been little studied. The presence of precursors of condensed tannides — leucoanthocyanidins — in the leaves, stems, buds, and flowers of *H. perforatum* has been studied by A. Michaluk. Leucocyanidin (VII) was identified by chromatographic and spectrographic methods and its distribution in ten other species was studied. Poly-

leucocyanidin was detected in a methanolic extract of the leaves of *H. perforatum*. Lebreton and Buchez investigated the distribution of leucoanthocyanidins in 21 species of *Hypericum* and found that all species contained (VII). Only in certain species was leucodelphinidin (VIII) and one unknown leucoanthocyanin detected [51].

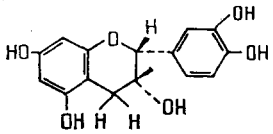
Shakirova and Khazanovich [48] have reported on the presence of monomeric catechins, finding by means of their R_f values six compounds of the catechin group in certain shrubby species. Four catechins were detected in the herbage of other species. Two of them, the predominating components in the mixture of catechins, were isolated in the crystalline form and were identified as (+)-catechin (IX) and (−)-epicatechin (X) [52-54]. Their absolute configurations were established [55].



VII. R = H
VIII. R = OH



IX



X

It has been reported in the literature that *H. perforatum* contains not only tanning substances of the catechin type but also gallotannins [11]. The distribution of flavanols in the species of the genus *Hypericum* is given in Table 1.

Condensed tanning substances are responsible for the internal and external use of the herbage of St. John's wort as astringent, antiinflammatory, and styptic agents, and monomeric flavonols possess a high capillary-strengthening activity.

FLAVONOLS AND FLAVONES

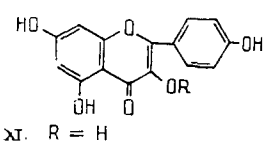
Flavonoid compounds have ubiquitous distribution in representatives of the genus *Hypericum*. The presence of flavonoids in *H. perforatum* was first reported in 1915, and in 1918 O'Neill detected quercetin [9]. The first glycoside isolated in the crystalline form was hyperin or hyperoside [57]. Systematic investigations of *Hypericum* flavonoids were begun in 1956 [47]. So far, flavonoids have been detected in 61 species [6, 47-49, 51, 58-69, 140]. Individual compounds have been detected in 54 species. The majority of them have been investigated comparatively by chromatographic methods.

All the species investigated contain quercitin (XIV) and some of its glycosides. In the majority of species, kaempferol is presence in trace amounts, while myricetin (XXIV) has a limited distribution. It has been detected in only nine species.

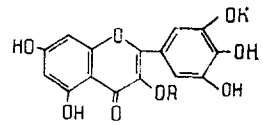
The main component among the flavonol glycosides is hyperoside (XV). A number of authors has reported that the isolation and study of isoquercitrin (XVI) is difficult because its properties are very similar to those of hyperoside. Avicularin (XVIII) has been found in two species, and compounds (XXII) and (XXIII) in only one [70-72].* Biosides in representatives of the genus *Hypericum* are kaempferol 3-O-glucogalactoside (XIII), quercetin 3-O-glucogalactoside (XX) quercetin 3-O-rutinoside (rutin) (XXI), and myricetin 3-O-rutinoside (XXV). Compound (XIII) has been detected in two, and bioside (XX) in three, species [140]. The myricetin bioside (XXV) has been isolated from the herbage of *H. scabrum* [71]. Rutin is the most widely distributed of these compounds. Information on its presence in several species is contradictory, while in others it is definitely absent. N. Nikolov et al. have reported the isolation of an isomorphous mixture of two biosides (rutin and quercitin 3-O-galactorhamnoside) from *H. perforatum* [62].

It was considered for a long time that only flavonols accumulate in species of the *Hypericum* genus. The presence of favones was first reported by Lebreton and

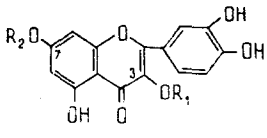
*Zaichikova and Barabanov report that quercetin 7-rhamnoside (XXII) has been detected chromatographically in *H. scabrum* but they give it the trivial name quercitrin, which corresponds to structure (VII) (quercetin 3-O-rhamnoside) [71].



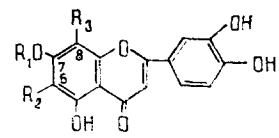
XI. R = H
XII. R = sugar*
XIII. R = glucogalactosyl



XXIV. R = H
XXV. R = rhamnoglucosyl

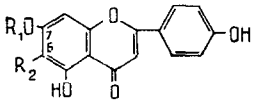


XIV. $R_1=R_2=H$
XV. R_1 = galactosyl, $R_2=H$
XVI. R_1 = glucosyl, R_2 = H
XVII. R_1 = rhamnosyl, R_2 = H
XVIII. R_1 = arabinosyl, R_2 = H
XIX. R_1 = sugar* $R_2=H$
XX. R_1 = glucogalactosyl $R_2=H$
XXI. R_1 = rhamnoglucosyl $R_2=H$
XXII. R_1 = H, R_2 = rhamnosyl

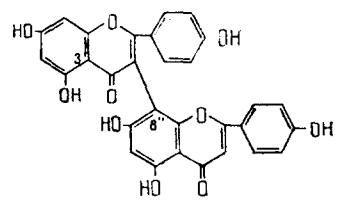


XXIII. $R_1=H$, R_2 = arabinosyl
XXVI. $R_1=R_2=R_3=H$
XXVII. R_1 = glucosyl, $R_2=R_3=H$
XXVIII. $R_1=R_3=H$, R_2 = glucosyl
XXIX. $R_1=R_3=H$, R_2 = sugar*
XXX. $R_1=R_3=H$, R_2 = sugar*
XXXI. $R_1=R_2=H$, R_3 = glucosyl
XXXII. $R_1=R_2=H$, R_3 = 2-O-acetylglucosyl

Buchez, who detected luteolin (XXVI) in *H. hirsutum* L. chromatographically [51]. From the same species, Kitanov et al. isolated (XXVI) and its C-glycosides homoorientin (XXVIII) and orientin (XXXI) and an acylated C-glucoside for which structure (XXXII) (2"-acetylorientin) was established [73-74]. Two new flavones, apigenin derivatives, were isolated later: 6-C-methyl-7-O-methylapigenin (XXXIII) from *H. erichoides* L. [68] and 3,8"-bisapigenin (XXXVI) from *H. aucheri* Jaub. et Spach [75]. Compounds (XXXII), (XXXIII), and (XXXIV) have so far been found only in representatives of the genus *Hypericum*. The structures of flavonoids (XII, XIX, XXIX, XXX, XXXIV, and XXXV) has not yet been completely established [140]. The distribution of flavonoid compounds in representatives of the *Hypericum* genus is given in Table 1.



XXXIII. $R_1 = R_2 = CH_3$
XXXIV. R_1 = sugar* $R_2 = H$
XXXV. $R_1 = H$ R_2 = sugar*



XXXVI

The high level of flavonoids in species of the *Hypericum* genus is also reponsible for some aspects of their use in folk and scientific medicine — capillary-strengthening, antiinflammatory, diuretic, and cholagogic effects. Hyperoside expands the coronary vessels and the use of St. John's wort as a cardiototonic agent may be connected with this fact.

XANTHONES

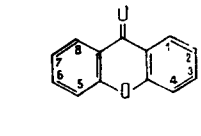
Considerable interest from the chemosystematic and medical points of view has been aroused by the detection of xanthones in species of the *Hypericum* genus and their isolation. Since some botanists assign the genus *Hypericum* to the broader family *Guttiferae*, in representatives of which a large number of xanthone compounds have been found, while others separated it as an independent family Hypericaceae, the study of the presence and distribution of xanthones in species of the *Hypericum* genus will permit an elucidation of the systematic position of this genus and also the validity of the existence of this genus of the Hypericaceae family as an independent one [7]. This fact was the starting point for the investigation of representatives of the *Hypericum* genus for the presence of xanthones.

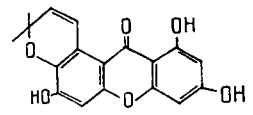
Up to 1978, only the xanthone C-glycoside mangiferin (LV) has been isolated from *H. humifusum* L. and maculatoxanthone (LVII) from the roots of *H. maculatum* Crantz [70, 93]. Recently, work has been done on the isolation of xanthones from other *Hypericum* species.

*Sugar not identified.

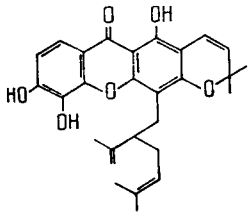
They have been found in 23 species [49, 69, 70, 94, 96, 98, 142], but seven species have been studied in more detail (Table 1).

Up to the present time, 17 simple xanthones (XXXVII-LIII), the pyranoxanthones toxiloxanthone B (LVI) and maculatoxanthone (LVII), the prenylxanthone (LIV), and the xanthonolignoid kielcorin (LVIII) have been isolated. Xanthones with two substituents are found more frequently. Xanthone glycosides are represented by mangiferin (LV), which has been detected in 5 species. The xanthonolignoid (LVIII) has been isolated from the roots of four species [94] and from the epigeal part of *H. ericoides* [68]. The largest number of xanthones has been found in the roots of *H. androsaemum* L. [95].

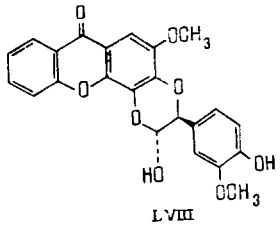




LVI



LVII



LVIII

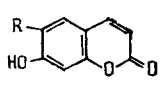
XXXVII. 2-Hydroxyxanthone
XXXVIII. 2-Methoxyxanthone
XXXIX. 1,7-Dihydroxyzanthone
XL. 2,5-Dihydroxyxanthone
XLI. 1-Hydroxy-7-methoxyxanthone
XLII. 2-Hydroxy-3-methoxyxanthone
XLIII. 2-Hydroxy-5-methoxyxanthone
XLIV. 3-Hydroxy-2-methoxyxanthone
XLV. 2,3-Dimethoxyxanthone
XLVI. 1,3,7-Trihydroxyxanthone

XLVII. 1-Hydroxy-6,7-dimethoxyxanthone
XLVIII. 3-Hydroxy-2,5-dimethoxyxanthone
XLIX. 2,3,4-Trimethoxyxanthone
L. 1,3,5,6-Tetrahydroxyxanthone
LI. 1,3,6,7-Tetrahydroxyxanthone
LII. 1,5,6-Trihydroxy-3-methoxyxanthone
LIII. 2-Hydroxy-5,6,7-trimethoxyxanthone
LIV. 1,3,6,7-Tetrahydroxy-8-prenylxanthone
LV. 2-C-glucosyl-1,3,6,7-tetrahydroxyxanthone (= mangiferin)

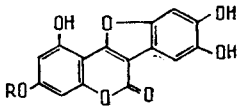
The study of these compounds is interesting not only for the taxonomy of the genus but also from the pharmacological point of view. Xanthones possess an antidepressant action and an antitubercular activity, while xanthone glycosides have a depressant action. A choleretic, diuretic, antimicrobial, antiviral, and cardiotonic action of some xanthones has also been established [46, 101, 102].

COUMARINS AND PHENOLIC CARBOXYLIC ACIDS

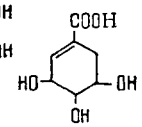
Very few species of the *Hypericum* genus have been studied for the presence of coumarins. So far, only umbelliferone (LIX) and scopoletin (LX) have been isolated from four species of St. John's wort [66]. Two coumarinocoumarones, demethylwedelolactone (LXI) and wedelolactone (LXII), which possess an antihemorrhagic action have recently been isolated from the epigeal part of *H. erectum* Th. [143]. This is stimulating a further study of representatives of the *Hypericum* genus for the presence of coumarin compounds.



LIX. R = H
LX. R = OCH_3



LXI. R = H
LXII. R = CH_3



LXV

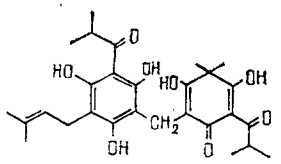
Phenolic carboxylic acids are represented among the St. John's worts mainly by caffeic acid (LXIII) and chlorogenic acid (LXIV). Both acids were detected in *H. perforatum* for the first time in 1960 [87, 105]. Their presence has been determined in 17 species. Caffeic acid has been isolated from *H. perforatum* in an amount of 0.1% [1-5] and chlorogenic acid from *H. nummularium* L. in an amount of 2% [56]. Shikimic acid (LXV) has been obtained from the fruit of *H. androsaemum* [103]. The presence of ellagic acid in *H. olympicum* L. [51] and of gentisic acid in *H. perforatum* [107] has been mentioned, but they have not been iso-

lated in the pure form. p-Hydroxybenzoic acid (LXVI), protocatechuic acid (LXVII), and gallic acid (LXVIII) have been isolated from *H. hirsutum* [104]. The distribution of phenolic carboxylic acids and coumarins in species of the *Hypericum* genus is given in Table 1.

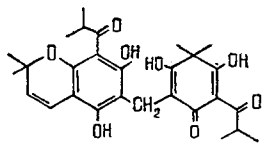
PHLOROGLUCINOL DERIVATIVES AND HYPERFORIN

Great interest has been caused by the detection and isolation of plant antibiotic substances from several species of the genus *Hypericum*. The antimicrobial properties of common St. John's wort were described by Osborn in 1943 [108]. The presence of antibacterial substances has also been detected in other species of the *Hypericum* genus [11, 109]. The antimicrobial preparations "Imanin" and "Novoimanin" have been created on the basis of extracts from *H. perforatum* and have recently been introduced into medical practice [11].

Two antibiotic compounds have been isolated from *H. uliginosum* H.B.K. and have been called uliginoside A (LXIX) and uliginoside B (LXX) [110]. Their structures have been established by Parker and Johnston [111]. Both uliginosides are derivatives of phloroglucinol and are very similar in structure to the components of ferns such as aspidin and flavaspidinic acid. Compounds with a similar structure — japonicin A (LXXI) and sarothralin (LXXII) — have recently been isolated from *H. japonicum* Thumb. [112, 114], the first of them having an antimalarial action and the second an antibiotic action. A sub-

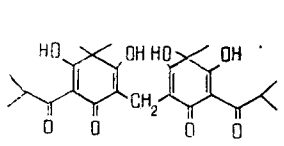


LXIX

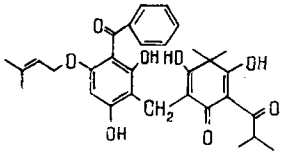


LXX

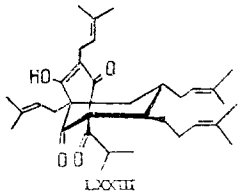
stance with a high antibiotic activity has been isolated from *H. perforatum* and has been called hyperforin [113]. As a results of detailed investigation, structure (LXXIII) has been established for hyperforin [114] and its stereochemistry has been determined [115]. Under the action of light and atmospheric oxygen, (LXXIII) is converted into a complex mixture of substances possessing a considerably lower antimicrobial activity.



LXXI



LXXII



LXXIII

COMPONENTS OF THE ESSENTIAL OIL AND ALKANES

The presence of essential oil is a characteristic feature of species of the genus *Hypericum*. It is localized in the secretory channels of the fruit and stems and in numerous endogenous formations of the leaves and flowers.

In 1905, H. Hensel studied some physical constants of the essential oil of *H. perforatum* for the first time [9]. In 1925, Zellner and Porodko studied its composition and detected α-pinene, myrcene, cinneole, sesquiterpenes, and esters of isovaleric acid in it [116]. Then Miller also showed the presence of α-pinene, sesquiterpenes, and olefinic hydrocarbons [117]. In 1961, n-decanal was found in the same species and limonene and benzyl alcohol in the essential oil of *H. androsaemum* [39]. Later, Chialva et al. in a study of the composition of the essential oil of *H. perforatum* identified 29 compounds (10 monoterpenes, 6 sesquiterpenes, and 13 aliphatic hydrocarbons) [145].

At the present time, an essential oil has been found and determined quantitatively in 41 *Hypericum* species, while the composition of the essential oil has been studied for 37 species [4, 48, 118-121, 124, 125, 146]. The broadest investigations have been performed by Mathis and Ourisson. From the essential oils of *H. perforatum*, *H. hirsutum*, and

H. calycinum L. they have isolated and identified 13 compounds represented by monoterpenes, monoterpene alcohols, saturated hydrocarbons, saturated aldehydes, and sesquiterpenes. They studied their distribution in 35 species [121-123]. The compositions of the essential oils of another two species — *H. ericoides* [125] and *H. elodeoides* Choisy [146] — have been studied in detail.

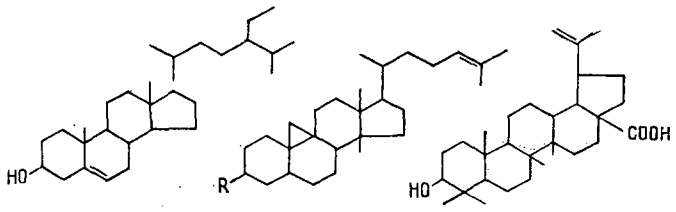
The essential oil of St. John's wort has not found independent use in medicine, but its complex action in ethanolic and oil extracts used in medical practice is not excluded.

The presence of nonvolatile saturated hydrocarbons (alkanes and alkanols) in *H. perforatum* has been studied by a number of authors [116, 127, 128], but the most profound and critical study was performed by Brondz et al. They discovered normal alkanes with hydrocarbon chains from C_{16} to C_{29}. The main component was nonacosane ($C_{29}H_{60}$) [129]. Alkanols were represented by tetracosan-1-ol, hexacosan-1-ol, octacosan-1-ol, and triacontan-1-1-ol [130]. In addition to common St. John's wort (*H. perforatum*) another six species have been studied for the presence of hydrocarbons. The main components in *H. ericoides* are octacosanol and octacosanal [125], in the roots of *H. laxiusculum* A St. Hil they are octacosane ($C_{28}H_{58}$), and in *H. connatum* Lam. octatriacontane ($C_{38}H_{78}$) [39]. Nonacosane and a mixture of unbranched hydrocarbons ($C_{19}H_{40}$, $C_{21}H_{44}$, and $C_{23}H_{48}$) have been obtained from the seeds of *H. androsaemum*, and a mixture with $C_{27}H_{56}$ as the main component from the seeds of *H. elatum* Ait. [76, 126]. Octacosanol has also been isolated from *H. mysorense* [139]. High-molecular-weight alcohols have been found in *H. japonicaum* [64].

OTHER COMPOUNDS

Comparatively few investigations have been devoted to the study of other compounds in the *Hypericum* genus. There is information on a study of the composition of the fatty acids of some species [8, 131]. Choline [48, 132, 133], carotenes [48, 134], ascorbic acid [48, 134, 135], and amino acids [66] have been detected in some species. Costes found that in the leaves of common St. John's wort almost 95% of the carotenoids were represented by epoxyxanthophylls and considered that the use of St. John's wort flowers on burns can be explained by the great activity of the oxygen in the epoxide groups of the xanthophylls (violaxanthin, luteoxanthin, etc.) [136].

It is as yet impossible to speak with complete reliability about the presence of alkaloids and saponins. Information is found in the literature on the presence of saponins [134, 138] and of alkaloids [134], but other authors indicate their absence in representatives of the *Hypericum* genus [48]. β-Sitosterol (LXXIV) has been isolated in the crystalline form from *H. perforatum* [127] and has also been found in *H. japonicum* [64]. Cycloartenone (LXXV) and cycloartenone 3-acetate (LXXVI) [139] has been isolated from *H. mysorense*, and betulinic acid (LXXVII) has been detected and identified in the roots of *H. androsaemum* and *H. elatum* [137].



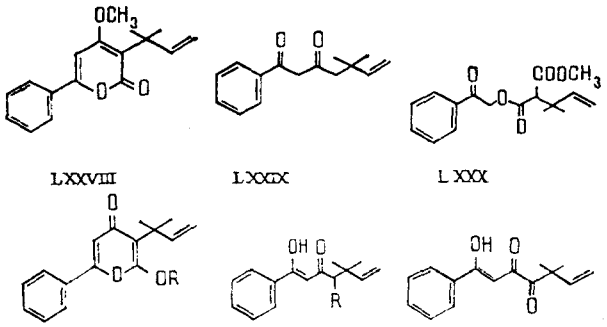
LXXIV LXXV R = O LXXVII

LXXVI. R = $OCOCH_3$

Recently, eight new natural substances containing phenyl radicals in the molecule have been isolated from *H. mysorense*: compounds (LXXVIII), (LXXIX), (LXXX), hyperenone A (LXXXI), hyperenone B (LXXXII), mysorenone A (LXXXIII), mysorenone B (LXXXIV), and mysorenone C (LXXXV) [139, 141, 147].

CHEMOSYSTEMATIC STUDY

The systematic position of the subfamily Hypericoideae is not yet completely clear. Some authors regard it as part of the family Guttiferae [1] while others isolate it as an independent family [148, 149]. Robson, however, considers that the morphological and anatomical differences are insufficient for the separation of the two families [2].



LXXVIII LXXIX LXXX

LXXXI. R = CH_3 LXXXIII. R = $COOCH_3$ LXXXV

LXXXII. R = H LXXXIV. R = H

Recently, Takhtadzhyan has also regarded the subfamily Hypericoideae as part of the family Guttiferae for which he gives the name Clusiaceae Lindl. (sensu lato) [150].

Hegnauer considers that the chemical differences are also insufficient for the separation as independent families the Guttiferae (sensu stricto) and Hypericoideae Juss. [6]. A review of literature on the chemical composition shows that the family Guttiferae. (sensu stricto) is characterized by the presence of xanthones, biflavonoids, neoflavonoids (4-phenylcoumarins), and triterpenes of the friedelin and β-amyrin groups. A distinguishing feature of the family Hypericaceae is the presence of anthrones. However, the isolation of xanthones from representatives of the *Hypericum* genus confirms the close relationships between the species of the subfamily Hypericoideae and other representatives of the Guttiferae family. Consequently, this class of compounds cannot be regarded as a chemotaxonomic index for the separation of the two families [49, 96, 97, 100]. The isolation of the biflavone 3,8"-bisapigenin from *H. aucheri* also shows the existence of certain chemosystematic links between the species of the two families [75]. For the purpose of chemosystematics, interest is presented by the search for other biflavonoids and neoflavonoids in representatives of the subfamily Hypericoideae and for anthrones in the other subfamilies of the family Guttiferae.

The distribution of anthrones in the subfamily Hypericoideae has been used for the intragenus specification of *Hypericum*. Even before the structure of the hypericins had been established the presence of black receptacles served as a characteristic for the classification of the species of this genus [42]. Mathis and Ourisson have made a classification of about 220 species of St. John's wort on the basis of the distribution and localization of hypericin and botanical characteristics [41]. Their results have, in the main, been adopted in Robson's new intergenus classification, one of the main taxonomic characteristics in which is the distribution of the hypericins [2, 3].

The chemosystematic value of the components of the essential oil has been studied for 35 species [122, 123]. All the species investigated were subdivided by the authors concerned into two groups: containing up to 5% of limonene in the essential oil and containing more than 10% of it. They came to the conclusion that from the chemotaxonomic point of view, hypericin is of greater value since the amount and composition of the oil depends greatly on the phase of growth and the origin of the plant material. The components of the essential oil are of great importance in the study of hybrid forms and species that are close in the morphological respect.

Lebreton and Buchez have studied the distribution of flavonoid aglycons and leucocyanidins in 21 species of St. John's wort assigned to six sections according to Keller's scheme [51]. They found that all the species contained leucocyanidin and quercetin. Although kaempferol is found in many species, its amount is more considerable only in representatives of the section *Roscyna*. Myricetin has been found in only nine species, and of them five also contain small amounts of leucodelphinidin. The latter, which were previously placed in the large section *Euhypericum* in Keller's system [86], were separated by Robson into independent sections. As can be seen from Table 1, all nine species in which myricetin has been detected belong to sections included in the "*Olympia*" group (sections 10-19) and the section *Adenosepalum* [2].

Some authors have reported the chemosystematic value of the flavonoid glycosides. Grims studied six species of St. John's wort and divided them into two groups: species containing hypericin have identical flavonoid compositions but differ in composition from species not containing hypericin [58]. Michaluk, however, on the basis of a study of eleven species, questions this conclusion of Grims [77]. Leifertova, in a comparison of the flavonoid glycosides of six species, divided them into three chemotaxonomic groups [83]. Alyukina [61] also detected some regularities in the flavonoid composition of the eight species investigated. Calie et al., in a study of seven species from the section *Myriandra* found that the majority of these species had different sets of flavonoids [140]. As can be seen from Table 1, hyperoside, quercitrin and rutin are found most frequently in representatives of the genus *Hypericum*, and at this stage of study it is difficult to make any chemosystematic conclusions whatever on the basis of the flavonoid glycosides.

The xanthones, and also other compounds found in representatives of the *Hypericum* genus, do not yet have any systematic value for intragenus classification because of the low level at which they have been studied. A systematic and more profound study of the chemical composition of St. John's wort species will permit the revelation of more generalizing laws in the chemosystematics of this genus.

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SYNTHESIS OF METHYL ETHERS OF METHYL (METHYL α-D-MANNOPYRANOSID)-URONATE

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UDC 547.917+543.544.45

Methyl (methyl α-D-mannopyranosid)uronate (I) has been obtained by the catalytic oxidation of methyl α-D-mannopyranoside with oxygen in the presence of platinum carbon with a yield of 20%. The partial methylation of (I) and preparative column chromatography on silica gel has provided a convenient method of obtaining all the methyl ethers of (I) in the individual state.

The methyl ethers of D-mannuronic acid are necessary in structural investigations of polysaccharides containing D-mannuronic acid residues. Directed syntheses of the methyl ethers of methyl (methyl α-D-mannopyranosid)uronate (I) described previously [1, 2] are fairly laborious with many stages.

In the present work we have used an approach that we have suggested previously [3] for obtaining methyl ethers of methyl (methyl α-D-glucopyranosid)uronate. The initial (I) was obtained with a yield of 20% by the catalytic oxidation of methyl α-mannopyranoside with oxygen in the presence of platinum on carbon followed by treatment with methanol. The mixture of methyl ethers of (I) obtained after the partial methylation of (I) was separated by liquid column chromatography into fractions with the same degree of substitution and, partly,

Position of the methyl groups	R_J	R_T, NPGS	R^*_T, NPGS	R^*_T, QF-1
—	0,08	—	2,40	2,37
2	0,16	2,00	1,96	1,70
3	0,16	1,74	1,36	1,00 (8,7 min)
4	0,23	2,29	1,36	1,30
2,3	0,31	1,00 (8,4 min)	1,00 (9,3 min)	0,74
2,4	0,38	0,74	0,85	0,67
3,4	1,36	0,64	0,50	0,33
2,3,4	0,51	0,32	0,36	0,22

Pacific Ocean Institute of Bioorganic Chemistry, Far Eastern Scientific Center, Academy of Sciences of the USSR, Vladivostok. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 203-205, March-April, 1987. Original article submitted November 13, 1986.

 0009-3130/87/2302-0166$12.50