NATURAL DIARYL ETHERS

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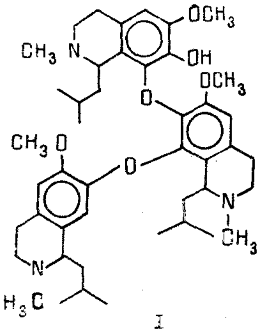
In this review, on the basis of an analysis of voluminous literature material on natural phenolic compounds belonging to various structural types, the interrelationship between the dimeric molecules formed as the result of the oxidative coupling of the corresponding monomeric compounds is considered.

Compounds containing a diphenyl ether bond are found both in plant and in animal sources. They include alkaloids, tanning substances, the phenolic components of wood, metabolites of lichens, flavonoids, coumarins, the hormones of the thyroid gland, etc. In spite of the diversity of their structures and different functions in the organisms, the biosynthesis of these substances takes place by a general plan — by the oxidative coupling of phenolic units. This genetic principle has been made the basis of the present review.

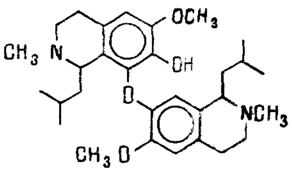
ISOQUINOLINE ALKALOIDS

Alkaloids of the Cacti. The alkaloids of the majority of the cacti are simple derivatives of 2-phenylethylamine (mescaline) or of tetrahydroisoquinoline (carnegine, anhalinine, pellotine).

A special group is formed by the alkaloid pilocereine, which has been detected in a number of species of cacti. The natural alkaloid is known in the optically inactive form. Originally, a dimeric isoquinoline formula with a 8-7' diphenyl ether bond was established for it by chemical methods (the potassium permanganate oxidation of its methyl ether, cleavage with sodium and liquid ammonia of the alkaloid and its methyl and ethyl ethers). However, on the basis of a determination of the molecular weight of its methyl ether by mass spectrometry (M^+ 757), a study of PMR spectra, and also a repeat study of the products of the cleavage of O-ethylpilocereine by sodium and liquid ammonia the formula of the alkaloid has been corrected to trimeric [1]. Pilocereine (I), together with the corresponding dimer isopilocereine (II) is formed by the oxidative phenolic coupling of lophocereine with the aid of potassium ferricyanide [2, 3]. Isopilocereine dimethiodide has been obtained by the analogous oxidation of lophocereine methiodide [4], and also by enzymatic oxidation in the presence of hydrogen peroxide [5].



I



II

Isopilocereine has also been synthesized by the condensation of the corresponding isoquinoline fragments by Ullmann's method [6], or from a bisamine containing a diphenyl ether bond and isovaleroyl chloride followed by Bischler—Napieralski cyclization, reduction, and methylation of the resulting mixture of diastereoisomers [7].

Pilocereine is toxic for *Drosophila* [8] and exhibits hypertensive properties and antimalarial activity.

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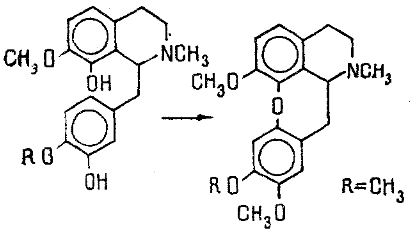
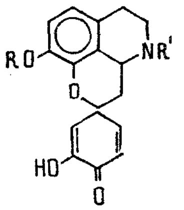
Cularine Alkaloids. This group of alkaloids consists of derivatives of 1-benzylisoquinoline with an intramolecular 8-10 ether bond. It consists of, in addition to cularine, several of its O- and N-demethyl derivatives. The structure of cularine (III) and other alkaloids of this group has been established by the Hofmann cleavage of the alkaloid, by its decomposition with ethyl chloroformate and with sodium and liquid ammonia. by oxidation of the cleavage products, etc.

Numerous unsuccessful attempts to synthesize cularine or other alkaloids of the cularine group have been described, and only recently have these attempts been crowned with success. The chemistry of the cularine alkaloids has been generalized in the literature [9, 10].



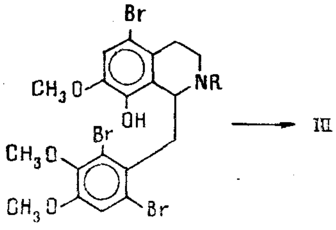
IV III



V

Interest is presented by a biomimetic method of synthesizing cularine by the cyclocondensation of a dihydroxyisoquinoline base of structure (IV) with potassium ferricyanide followed by methylation of the phenolic hydroxyl [11]. The starting compound was obtained by the Pomeranz–Fritsch method. Oxidation was performed through the intermediate spiro compound (V) [12]. However, British authors did not succeed in isomerizing the intermediate spirodienone (V) into cularine [13].

It was possible successfully to perform a intramolecular Ullmann ether reaction for compound (VI) (yield 49%) followed by hydrodebromination to d*l*-cularimine and d*l*-cularine (71%) [14]. The synthesis of cularicine has been described by Noguchi and MacLean [15].



VI

Cularine, like papaverine causes anesthesia of the rabbit eye cornea. On intravenous injection it causes a temporary fall of blood pressure in rabbits [16].

The Bisbenzylisoquinoline Alkaloids. The bisbenzylisoquinoline alkaloids unite a large group of structurally related natural bases including more than 160 representatives which are found in the plants of ten families: *Lauraceae, Menispermaceae, Magnoliaceae, Berberidaceae, Ranunuculaceae, Annonaceae, Hernandiaceae, Nymphaceae, Monimiaceae,* and *Rhamnaceae*. Since alkaloids of this type have been considered in detail in reviews [17-24], we shall dwell on them very briefly. A characteristic feature of the bisbenzylisoquinoline alkaloids is the presence in them of two substituted benzylisoquinoline units linked by one, two, or three ether bonds. The position and number of the ether bonds serve as suitable criteria for the classification of these alkaloids. The difference between the individual members of each subgroup consists mainly in the degree of methylation and optical isomerism. The majority of the alkaloids contain two centers of asymmetry. The biogenetic formation of alkaloids of this type consists in the oxidative coupling of two molecules of coclaurine or its derivatives with the subsequent methylation of the dimeric molecule. It has been possible in the laboratory by the oxidative coupling of N-methylcoclaurine or its methiodide to obtain dimeric molecules of the subgroup of dauricine and liensinine. However, it was impossible to perform double cyclic condensation in compounds of the oxyacanthine-berbamine type. The majority of the alkaloids of this group have also been obtained by complete multistage syntheses [18, 19]. For the case of cycleanine it has been shown that O-demethylation with electrophilic reagents takes place selectively with the formation of 7-norcycleanine and isochondodendrine, the reaction taking place stepwise under controlled conditions [25, 26].

The main advances in establishing the structures and stereoconfigurations of the bisbenzylisoquinoline alkaloids have been achieved by the use of the method of cleaving the nonphenolic alkaloids or the corresponding methyl or ethyl ethers of phenolic bases with sodium in liquid ammonia, which has permitted the simultaneous determination of the position of the phenolic hydroxyl, the diphenyl ether bond, and the configuration at the center of asymmetry. In recent years, this method has been improved by the use of deuteroammonia for cleavage or by the preliminary deuteration of the alkaloid before cleavage, which has permitted the labeling of a definite position in the aromatic nuclei of the alkaloid and thus the exclusion of errors in doubtful cases. Although the methods of NMR spectroscopy and mass spectrometry have been developed fairly well for the bisbenzylisoquinoline alkaloids at the present time, they are used to determine the structures of alkaloids of this group only as supplementary material to the results of cleavage by sodium in liquid ammonia.

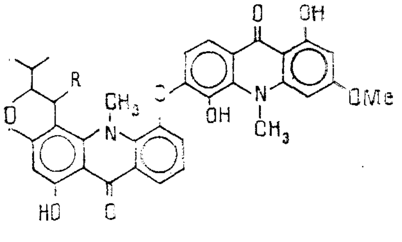
It has been shown that a definite chemotaxonomic interconnection exists between taxons on the one hand, and the structural type of the bisbenzylisoquinoline alkaloids, the set of alkaloids, and their absolute configuration, on the other hand, which undoubtedly is connected with features of the biosynthesis of these alkaloids [27].

The biological activities of these alkaloids are fairly diverse. The quaternary ammonium derivatives exhibit a curare activity (tubocurarine chloride) the tertiary alkaloids tetrandrine, cycleanine, thalsimine, dihydrothalsimine, hernandezine, and thalmine exhibit anti-inflammatory activity; tetrandrine, isotetrandrine, trilobine, and cepharanthine exhibit antitubercular activity, and thalamine, O-methyldauricine, cocsulinine, and tetrandrine exhibit antitumoral activity [17].

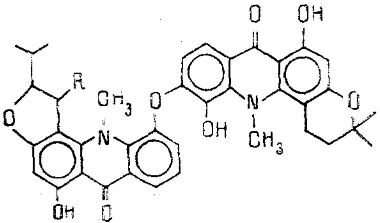
Compounds of this type are found in close generic relationship with the benzylisoquinoline-aporphine, benzylisoquinoline-proaporphine, benzylisoquinoline-pavine, and bishomogenzylisoquinoline and other bases, which are also discussed in the reviews mentioned above [17-24].

BISACRIDONE ALKALOIDS

The bisacridone alkaloids atalantines 1-3 and staline (VII-X) have been found in *Atalantia ceylanica* Enol. [28].



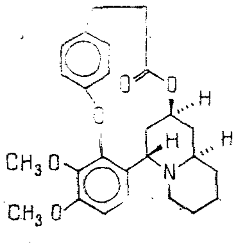
VII.R=H . VIII.R=OH



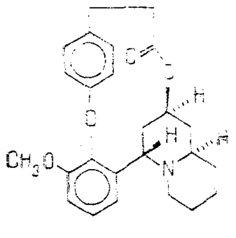
IX.R=H, X.R=OH

QUINOLIZIDINE ALKALOIDS FROM PLANTS OF THE FAMILY LYNTHRACEAE

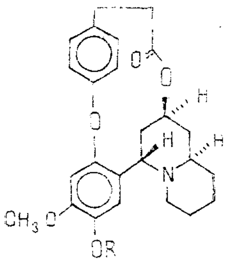
The alkaloids of this group consist of macrocyclic lactones with a diphenyl ether bond. More than 20 alkaloids of this type are known at the present time. As in the case of the bisbenzylisoquinoline alkaloids, in addition to the ether alkaloids, compounds with a diphenyl bond have been found. Methyllagerine (XI) [29], lagerine (XII) [30], and decaline (XIII) [29] have been isolated from *Lagerstroemia indica* L.



XI

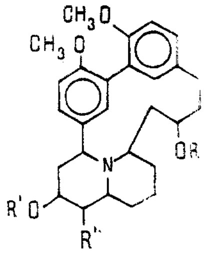


XII

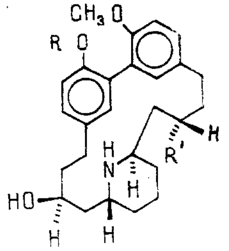


XIII

Alkaloids of the second group are represented by compounds (XIV) and (XV) [31].



XIV	R = R' = H, R'' = OH	Lythrancine-I
XIV	R = Ac, R' = H, R'' = OH	Lythrancine-II
XIV	R = R' = Ac, R'' = OH	Lythrancine-III
XIV	R = R' = Ac, R'' = OAc	Lythrancine-IV
XIV	R = R' = R'' = H	Lythranepine-I
XIV	R = Ac, R' = R'' = H	Lythranepine-II
XIV	R = R' = Ac, R'' = H	Lythranepine-III

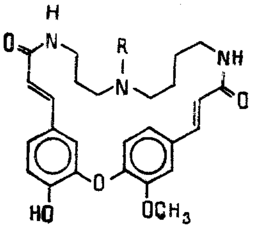


XV	R = H, R' = Ac	Lythranine
XV	R = R' = H	Lythranidine
XV	R = CH_3, R' = H	O-Methylthranidine

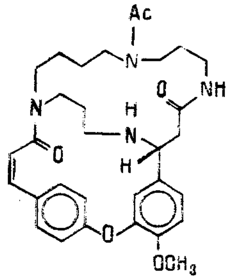
The structure of this type of alkaloid has been confirmed by the synthesis of lagerine [30], methyllagarine [29], *dl*-demethyldecaline [32], *dl*-vertaline [33], *dl*-decaline [32, 33, 35], methyldecaline [34], carpaine [34, 36], etc., and *dl*-methyldecamine [37], etc. In all cases a substituted diphenyl ether was first obtained and then a quinolizidine nucleus was added; and the final stage of the synthesis was the formation of the ester group.

MACROCYCLIC SPERMINE ALKALOIDS

The alkaloids codonocarpine (XVI, R = H) and N-methylcodonocarpine (XVI, R = CH_3) have been isolated from *Codonocarpus australis* A. Cunn., family Phytolaccaceae [38, 39]. Close to them is the alkaloid chenorrhine (XVII) from *Chaenorrhinum organitolium* (Scrophulariaceae) [40-42].



XVI



XVII

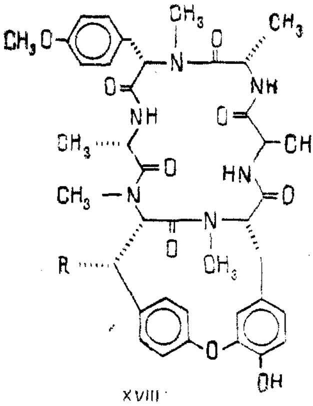
CYCLOPEPTIDE DERIVATIVES

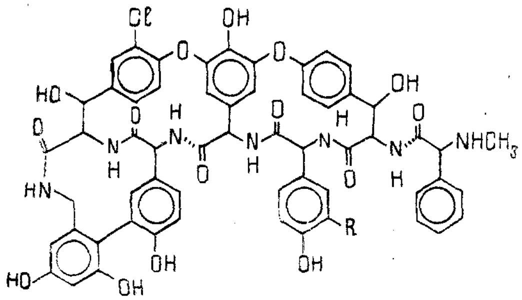
The antitumoral cyclic heptapeptides bouvardine (XVIII, R = OH) and deoxybouvardine (XVIII, R = H) have been isolated from *Bouvardia ternifolia* (Rubiaceae), which is used by the Mexican Indians in the treatment of dysentery, hydrophobia, and other diseases [43].

The antibiotic vancomycin (XIX) is also a heptapeptide in which three amino acids are bound to one another by a diphenyl ether bond [44, 45]. Avoparcine (XX) is similar to it in structure [46].

Hydrolysates of the glycopeptide antibiotic ristomycin A and ristocetin A have been found to contain ristomycinic acid (XXI), which is a bis(amino acid) with a diphenyl ether bond, and also actinoidinic acid (XXII) with a diphenyl bond [47].

Structure (XXIII) has been proposed for the aglycone of the antibiotic ristolicin A [48].


XVIII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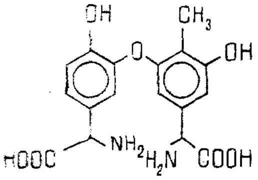
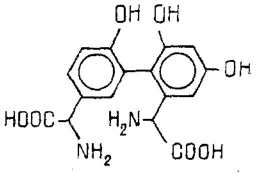
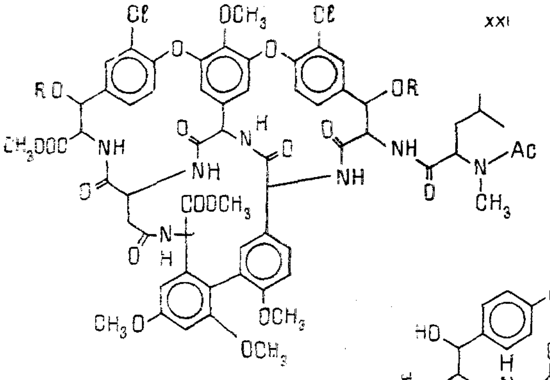
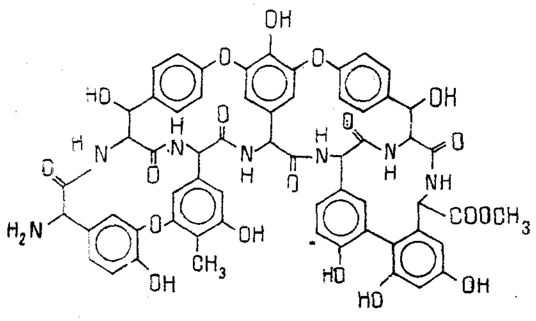

XXI

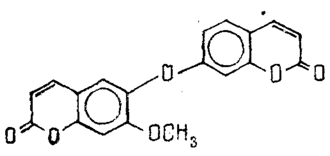

XXII

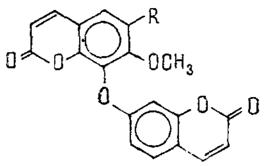

XIX


XXIII

DICOUMARINS

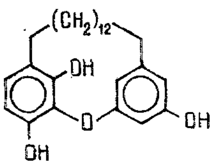
At the present time three dicoumarins with diphenyl ether bonds are known: lasiocephalin (XXIV) [49, 50], isolated from *Lasiosiphon eriocephalus*, and oreojasmin and fatagarin (XXV, R = OCH_3, H) from *Ruta oreojasme* [51, 52]. The structure of lasiocephalin has been confirmed by independent synthesis using the Ullmann condensation of umbellifreone with 6-bromo-7-methoxycoumarin.


XXIV

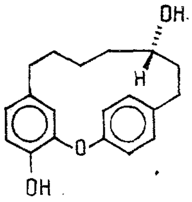

XXV

MACROCYCLIC NITROGEN-FREE COMPOUNDS FORMING DERIVATIVES OF DIPHENYL ETHERS

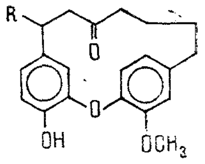
The macrocyclic 21-membered phenol robustin (XXVI) has been isolated from *Crevilla robusta* [52], and the 15-membered phenolic alcohol acrogenin A (XXVII) from *Acer nikense* Maxim. (Aceraceae) [53]. The 15-membered macrocyclic ketone (XXVIII, R = H) and the hydroxy ketone hydroxygaleon (XXVIII R = OH) have been found in *Myrica nagi* [54].



XXVI



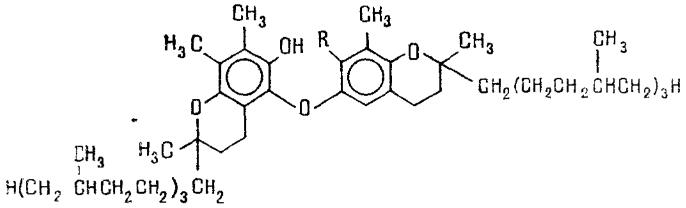
XXVII



XXVIII

TOCOPHEROL DERIVATIVES

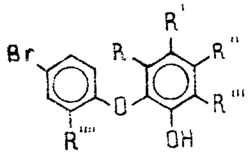
Tocopherol dimers of the general formula (XXIX, R = H, CH_3, etc.) have been found in fresh maize oil, and they have also been obtained by the oxidative dimerization of the corresponding tocopherols [55].



XXIX

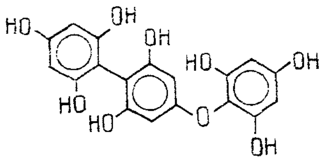
DIPHENYL ETHERS FROM MARINE ORGANISMS

Diphenyl ethers are fairly widely distributed in marine animals and algae. For example, in the sponges *Dysidea herbacea* a whole group of bromine-substituted diphenyl ethers with a structure (XXX) has been found [56-58].

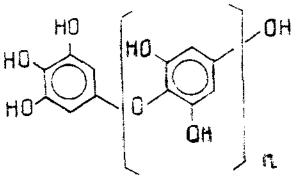


XXX

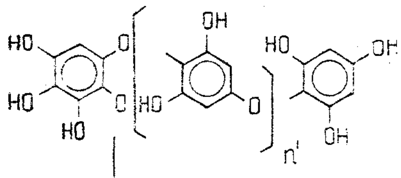
R	R'	R''	R'''	R''''
Br	Br	Br	H	Br
Br	H	H	H	H
H	Br	Br	Br	Br
H	Br	H	Br	Br
Br	H	Br	H	H



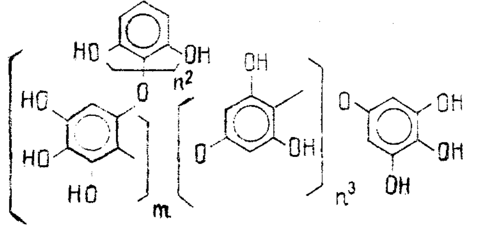
XXXI



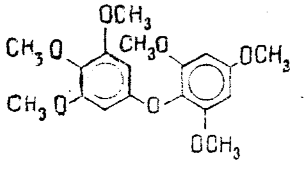
n = 1 – 2



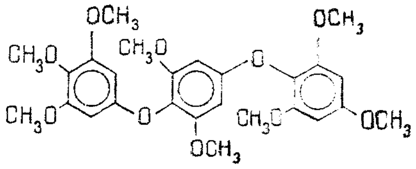
XXXII



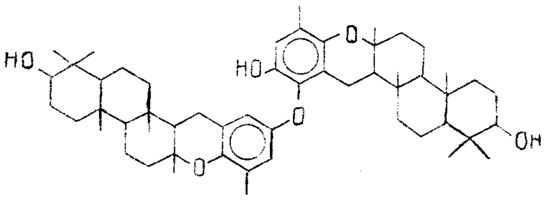
XXXIII



XXXIV



XXXV



XXXVI

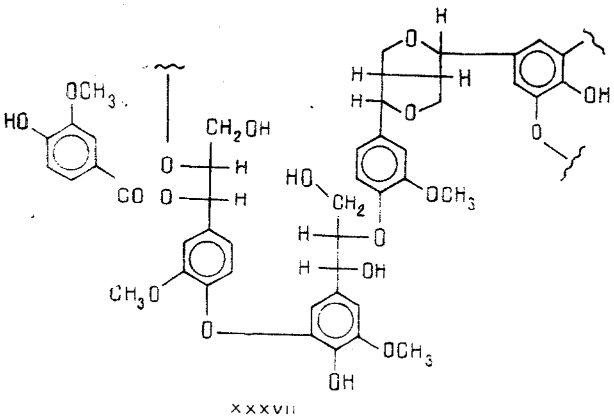
In the brown algae *Fucus vesiculosus* (L.) and *Halidrys siliquosa* (L.) of the Phaeophyceae there are the phloroglucinol oligomers the physodes (XXXI-XXXIII) [59-62], which possess antibiotic properties.

Ethers of bifuhalol (XXXIV), trifuhalol (XXXV) and some of their analogs have been synthesized by Ullmann condensation [63, 64].

The dimer taondiol (XXXVI), which is a sesquiterpine derivative has also been isolated from the marine algae *Taonia atomaria* with a yield of 0.005% [65].

LIGNIN

Lignin, one of the basic components of wood, consists of a complex polymer of coniferyl alcohol in which fragments with a diphenyl ether bond have been determined (XXXVII) [66].

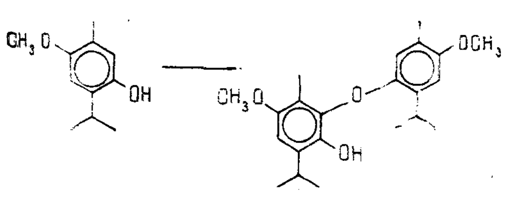


XXXVII

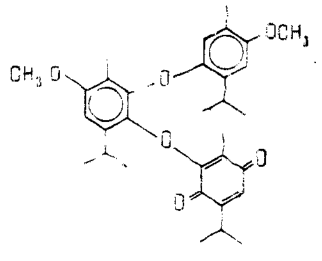
PHENOLIC COMPONENTS OF THE CALIFORNIA INCENSE CEDAR

From the wood of the California incense cedar *Libocedrus decurrens* Torrey has been isolated the cryptophenolic compound libocedrol (XXXVIII), which is p-methoxythymyl-p-methoxythymol [67], and the corresponding trimer, libocedrol-thymoquinone (XXXIX) [68, 69].

The structure of libocedrol has been confirmed by biomimetic synthesis: the oxidation of an alkaline solution of p-methoxythymol with potassium ferricyanide at room temperature [70].



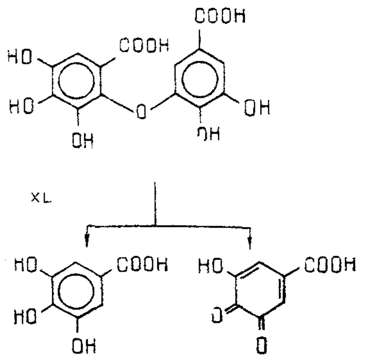
XXXVIII



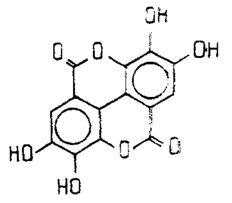
XXXIX

TANNING SUBSTANCES

Derivatives of Dehydrodigallic Acid. Dehydrogallic acid (XL), which is 2,5'-dicarboxy-2',3',4,5,6-pentahydroxy(diphenyl ether), has been detected in young leaves and shoots of the sweet chestnut *Castanea versea* [71] and on the leaves of the nut tree. It is extremely stable in an acid medium, but in a dilute solution of caustic soda it readily undergoes cleavage with the formation of gallic acid and a quinone (dehydrogallic acid) [72, 73]. This process is the reverse of the biosynthesis of dehydrogallic acid by the oxidative coupling of two molecules of gallic acid. The sweet chestnut also contains, together with dehydrogallic acid, the dilactone ellagic acid (XLI), in which the aromatic rings are connected by a carbon–carbon bond. This compound has been detected in the leaves of many dicotyledonous plants.

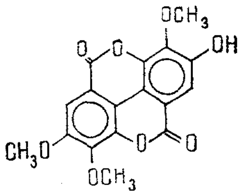


XL

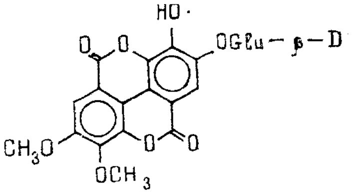


XLI

The trimethyl ether of ellagic acid (XLII) has been found in *Euphorbia tirucalli* [74], and the glycoside lagertannin (XLIII) in *Lagerstroemia speciosa* [75].

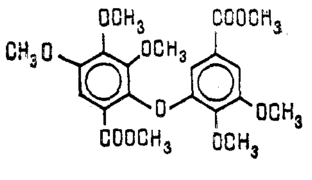


XLII

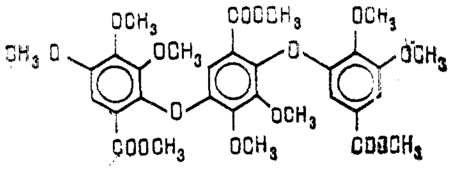


XLIII

The heptamethyl derivative of dehydrodigallic acid (XLIV) and the decamethyl derivative of dehydrotrigallic acid (XLV) are found in *Myricaria alopecuroides* [76].



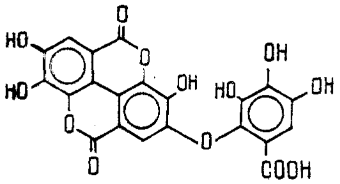
XLIV



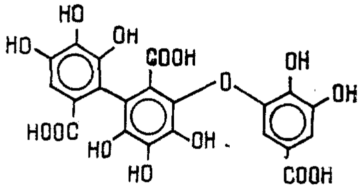
XLV

Ellagic acid is readily formed when air is passed through an ammoniacal solution of ethyl gallate at room temperature [77]. Dehydrodigallic acid has been synthesized with the aid of the Ullmann reaction [78, 72].

Valoneaic acid (XLVI) and its lactone, consisting of the product of the condensation of ellagic and gallic acids [79, 80], the structures of which have been confirmed by synthesis [81], have been isolated from the tissues of oak and from valonia. Isovaloneaic acid (XLVII) has been obtained from hairy willow weed (*Epilobium hirsutum*) by the acid hydrolysis of its ellagotannins [82].

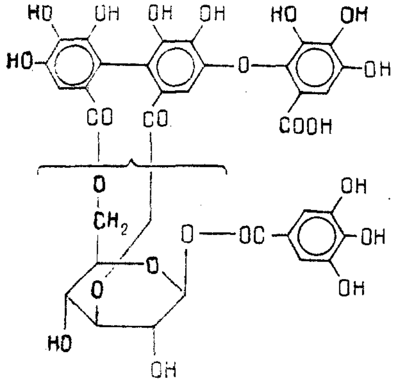


XLVI

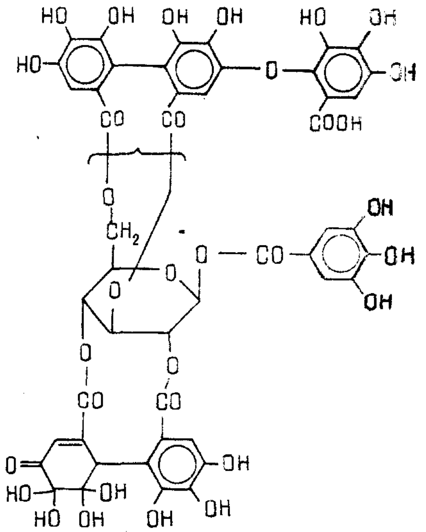


XLVII

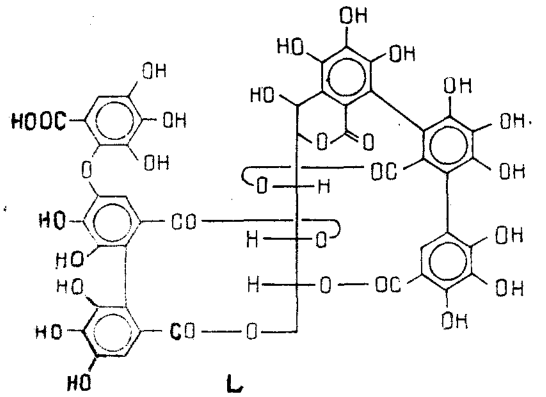
Its glycosides mallotinic and mallotusinic acids (XLVIII and IL) have been isolated from *Mallotus japonicus* [83], and castavalonic acid (L) from *Quercus valonea* [84]. The chemistry of tannin compounds has been generalized in a review [85].



XLVIII



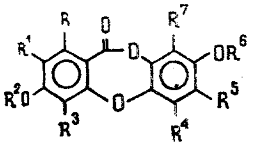
XLIX



L

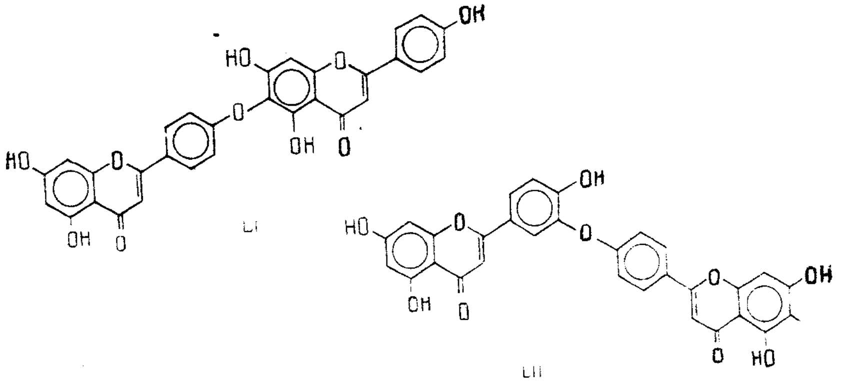
Biflavonoids. Bimolecular flavonoids are represented by several types of compounds with diphenyl ether and carbon–carbon bonds. Nine types of biflavonoids are distinguished, among which only two contain the diphenyl ether bond [86-92]. The latter include hinokiflavone (LI) [93-97] and ochnaflavone (LII) [98]. Other compounds consist of biflavones with 8-8', 6-8', 6-5', and 8-5' carbon–carbon bonds.

It has been established that the catechins of the tea leaf are readily oxidized by atmospheric oxygen in an alkaline medium with the formation of oligomers having diphenyl ether bonds together with C–C oligomers [99, 100]. Such compounds are, for example, the 6'-8 dimer (LIII) and the trimer (LIV) detected in the bark of *Quercus robur* [101-103].

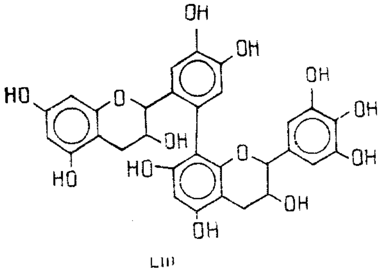


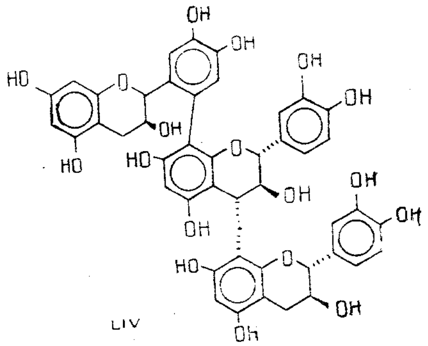
LICHEN METABOLITES

Depsidones. Depsidones consist of a large group of phenolic antibiotics, ether lactones, isolated together with the corresponding esters, depsides (presumed biogenetic precursors of the depsidones) from various lichens. The aromatic rings of the depsidones may be substituted by alkyl (methyl, amyl, hydroxyamyl, valeroyl, etc.) groups, chlorine atoms, etc. Table 1 gives examples of depsidones isolated in recent years.

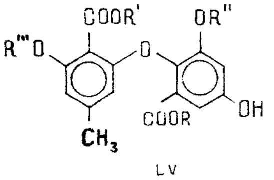

LI

LII


LIII


LIV

On methylation with an excess of diazomethane, the ester group of a depsidone is readily opened with the formation of the corresponding o-methoxycarbonyl(diphenyl ether). Compounds of this type (LV) have been detected in *Oospora sulphurea-ochacea* Beyma [129], *Scylalidium* sp. strain PZ [130], *Aspergillus terreus* [131], etc.

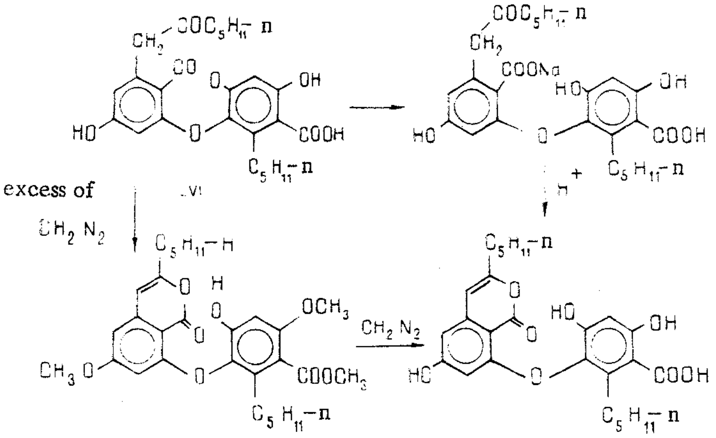

LV

$R = R'' = CH_3$, $R' = R''' = H$
$R = R'' = CH_3$, $R' = H$, $R''' = Ac$
$R = R'' = R' = CH_3$, $R''' = H$
$R'' = CH_3$, $R = R' = R''' = H$
$R = R' = R'' = R''' = H$

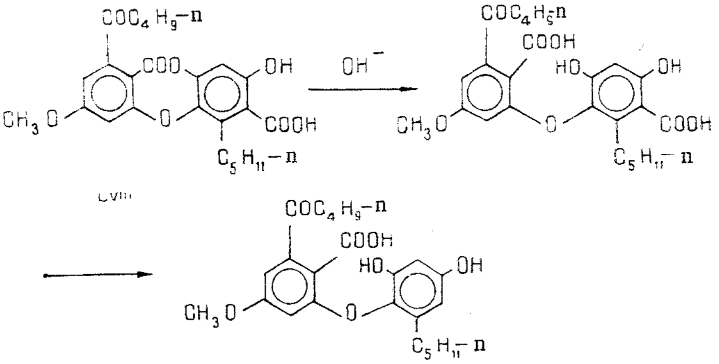
TABLE 1. Main Representatives of Depsidones Found in Lichens

Name	R	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Source of isolation, literature
Vicanicin	CH_3	Cl	H	Cl	CH_3	H	CH_3	CH_3	[104]
Nidulin	CH_3	Cl	H	Cl	Cl	$C(CH_3){=}CH$ CH_3	CH_3	CH_3	Aspergillus nidulans [105]
Pasoromic acid	CH_3	H	H	CHO	COOH	H	CH_3	CH_3	Usnea sp. [106]
2'-O-Demethylpsoromic acid	CH_3	H	H	CHO	COOH	H	H	CH_3	Usnea sp. [106]
Lodoxin	COC_4H_9	H	H	H	C_5H_{11}-n	$COOCH_3$	H	H	Parmelia Havescenti reagens Gjel. [107]
Colensoic acid	C_5H_{11}-n	H	CH_3	H	C_5H_{11}-n	COOH	H	H	Stereocaulon colensoi [108]
Physidol	COC_5H_{11}-n	H	H	OH	C_5H_{11}-n	COOH	H	H	[109]
Oxyphysodic acid	$CH_2COC_5H_{11}$	H	H	OH	C_5H_{11}-n	COOH	H	H	Hypogymnia enteromorpha (Ach.) Nyl. [110]
Vitatolic acid	$CH_2\overset{OH}{\underset{H}{C}}C_3H_5$	H	H	H	C_5H_{11}-n	COOH	H	H	Hypogymnia vittata [111]
Menegazziaic acid	CH_3	H	CH_3	H	CH(OH)OCO—		H	CH_3	Menegazzia asahinae [112]
Salazinic acid	CH_3	H	H	CHO	CH(OH)OCO—		H	CH_2OH	Parmelia saxatilis [113]
Dechlorodiploicin	CH_3	Cl	H	H	CH_3	Cl	CH_3	Cl	Buellia canescens (Dicks.) De Not [114—115]
Dechloro-O-methyldiploicin	CH_3	Cl	CH_3	H	CH_3	Cl	CH_3	Cl	Buellia canescens (Dicks.) De Not [114—115]
Lividic acid	$CH_2COC_5H_{11}$-n	H	CH_3	OH	C_5H_{11}-n	COOH	OH	H	Parmelia formosana [116]
2'-O-Methylphysodic acid	$CH_2COC_5H_{11}$-n	H	H	H	C_5H_{11}-n	COOH	CH_3	H	Hypogymnia vitata [111] H. billardieri [117—119]
Oxyphysodic acid	$CH_2COC_5H_{11}$-n	H	H	OH	C_5H_{11}-n	COOH	H	H	H. vittata [111], H. billardieri [117—119]
Norstictic acid	CH_3	H	H	CHO	CH(OH)—O—CO		H	CH_3	Diploschistes ocellatus [119]
1'-Chloropannarin (argopsin)	CH_3	Cl	H	CHO	CH_3	Cl	CH_3	CH_3	Argopsis friesiana [120]
Variolaric acid	CH_3	H	H	H	CH_2—O—CO—		H	H	Ochrolechia ssp. [121]
Pannarin	CH_3	Cl	CH_3	CH_3	OH	CH_3	CH_3	H	[122—124]
Alectoronic acid	$CH_2COC_5H_{11}$-n	H	H	H	$CH_2COC_5H_{11}$	COOH	H	H	Palmeria rigida Lynge [125]
Palnarin	CH_3	Cl	H	CHO	CH_3	H	CH_3	H	[123]
Argopsin	CH_3	Cl	H	CHO	CH_3	Cl	CH_3	CH_3	Argopsis megalospora [126]
Gangaleoidin	CH_3	Cl	H	Cl	H	$COOCH_3$	CH_3	H	[127—128]

For compounds containing the CH_2COOR group in the ortho position to the carbonyl of a depsidone, this reaction of the opening of the depsidone ring is accompanied by the formation of a new isocoumarine ring, for example, in hydroxyphysodic acid (LVI) [132], lividic acid [116], etc. Lobaric acid (LVIII), which contains a valeroyl substituent, has no tendency to undergo lactonization. When it is heated it readily decarboxylates [132].

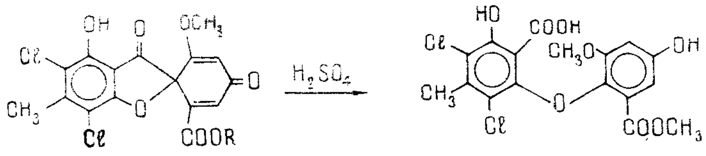


The lactonization of 2-carboxy-2'-hydroxy(diphenyl ether)s with the formation of depsidones takes place with great difficulty, and in view of this it is suggested that the true biogenetic precursors of the latter are depsides, esters of aromatic acids, and phenols, which are converted into depsidones by enzymatic oxidation. The chemistry of the depsidones and other lichen metabolites has been generalized in reviews [132,133].



The synthesis of the depsidones gangaleoidin, diploicin [134], caloploicin [135], grayanic acid [136], colensoic acid [137], and others [138, 139] have been effected through the corresponding diphenyl ethers.

Antibiotics with a Spirodienone Structure. Compounds of this type are genetically related to the depsidones including erdin and geodin (LIX, R = H, CH_3) [140]. Under the action of strong mineral acids they are converted into o-carboxy(diphenyl ether)s (LX).

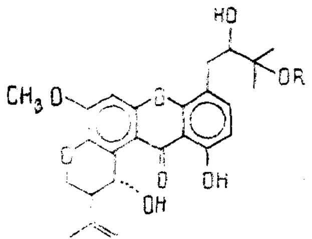


LIX LX

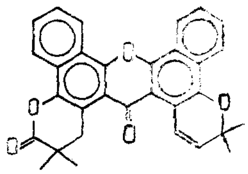
Xanthones. Xanthones can be obtained by the dehydration of o-carboxy(diphenyl ether)s. Compounds of this type are found together with depsidones in the products of the metabolism of lower organisms, and also in the roots, wood, leaves, and bark of some tropical plants. Some of them are used as dyestuffs.

For example, tajixanthone hydrate and methanolate (LXI, R = H, CH_3) has been isolated from *Aspergillus varicolor* [141], guayin (LXII) and guayaconin (LXIII) from *Tabebuia guayacan* [142], and the glycosides dillanoside (LXIV) from *Anethum graveolens* [143] and xanthone-2 (LXV) from *Canscora decussata* [144].

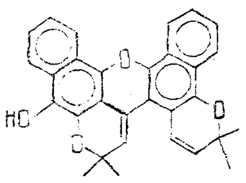
The synthesis of some natural compounds of this type such as the methyl ether of selebixanthone (LXVI) [145] and bikaverine (LXVII) [146] has been described in the literature.



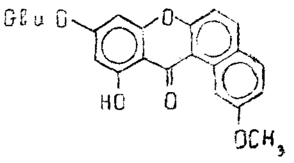
LXI



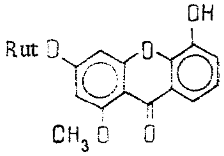
LX



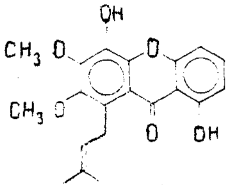
LXIII



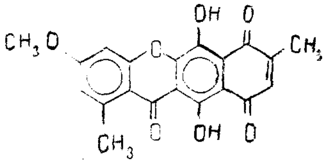
LXIV



LXV



LXVI

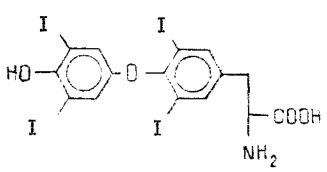


LXVII

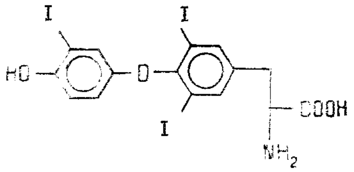
The lichens are very similar in their external characteristics but differ with respect to the depsides, depsidones, and other substances which they contain, and this has been proposed for use in their chemosystematics [147].

THYROID HORMONES

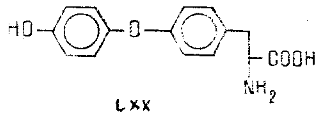
The thyroid glands of vertebrates elaborate the protein thyreoglobulin, which contains about 0.6% of iodine. The biologically active iodine-containing part of the thyreoglobulin molecule consists of the amino acids L-thyroxine (LXVIII) and 3,3'-5-triiodothyronine (LXIX), which are converted on reduction into thyronine (LXX). The activity of triiodothyronine is six times greater than that of L-thyroxine. The elimination of more iodine atoms or their replacement by other groupings leads to a decrease in the activity or to complete inactivation. In view of this, an exceptional importance of the iodine atoms in the mechanism of the action of the thyroid hormones has been deduced. However, it has recently been shown that 3-isopropyl-3,5-dimethylthyronine[sic], containing no iodine atoms, also possesses hormonal activity, although it is weaker (18% of the activity of L-thyroxine) [148]. The chemistry and biological function of the thyroid gland and its hormones and the biosynthesis, interrelationship of structure and thyroid activity of compounds of the thyroxine series and their analogs, "antihormones," and their synthesis and transport in the organism and other questions have been discussed in a series of reviews [149-152].



LXVIII



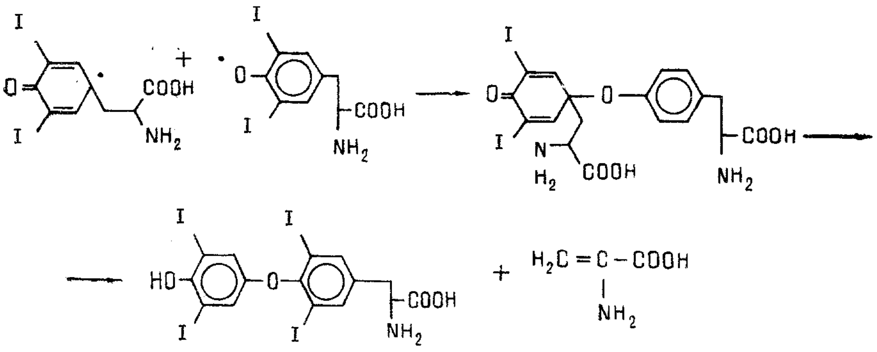
LXIX



LXX

It has been shown that the thyroxine molecule has a rigid structure in which one aromatic ring is perpendicular to the other and the angle on the linking O atom is about 120°. There is information that the outer ring undergoes oxidation. If it is oxidized (with difficulty), the compound is free from thyroid activity [153, 154]. Thus, the hormone acts as a structurally specific matrix of definite conformation, which has been shown on the basis of an analysis of a number of thyroxine analogs [155].

Several methods for the synthesis of thyroxine have been realized, and a large number of its analogs have also been synthesized. The greatest interest is presented by the biomimetic synthesis of thyroxine from diiodotyrosine under physiological conditions, the oxidative coupling of the latter being accompanied by the splitting out of the side chain in the form of pyruvic acid or alanine [156-162]:

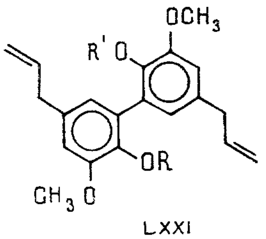


HUMIC ACIDS

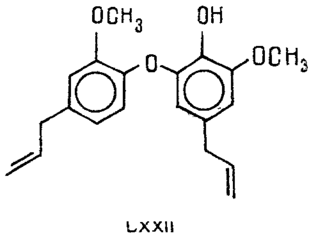
It is assumed that humic acids consist of complex compounds of iron with very complicated compositions which contain diphenyl ether bonds [163].

DEHYDRODIEUGENOLS

Dimers of euginol have been found in *Ocotea cymbarum*: dehydrodieugenol (LXXI, R = R' = H), its monomethyl ether (LXXI, R = H, R' = CH_3), in which the aromatic rings are connected with one another by a carbon—carbon bond and dehydrodieugenol-B (LXXII), which is the corresponding diaryl ether [164].



LXXI



LXXII

The detection of similar compounds in plants of the genus *Ocotea* is of great interest from the chemotaxonomic point of view. From another species, *O. rodiaei*, have been isolated the bisbenzylisoquinoline alkaloids curine, norrodiasine, ocotosine, demerarine, and sepeerine (see the review [17]), in which the benzylisoquinoline nuclei are linked similarly.

In this review we did not set ourselves the task of giving exhaustive information on the chemistry of the above-mentioned classes of compounds, since this would complicate the assimilation of the material. As the result of the analysis of literature information on natural phenolic compounds belonging to various structural types, an interconnection has been revealed between dimeric molecules formed as the result of the oxidative coupling of the corresponding monomeric compounds.

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