HETEROCYCLIC COMPOUNDS OF MARINE ORGANISMS (REVIEW)

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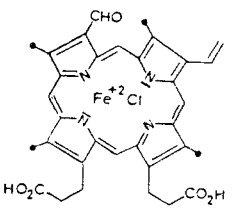
The literature data on heterocyclic compounds of marine organisms are systematized. Chief attention is directed to physiologically active substances.

The last several decades have been characterized by a sharp acceleration in the mastery of the biological and mineral resources of the sea and oceans by mankind. A new trend in bioorganic chemistry, the chemistry of marine organisms, has developed within the framework of this process. Heterocyclic compounds constitute a significant and most important, in a practical respect, part of the physiologically active substances of "marine" origin. However, the literature does not contain review papers specially devoted to these substances. The authors hope that the present review will in some measure fill this gap and be of assistance in attracting the attention of Soviet chemists to the study of the structures of and the synthesis and biogenesis of heterocyclic compounds of marine organisms.

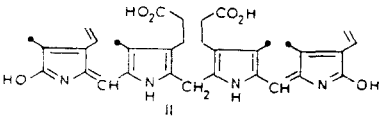
Nitrogen Heterocycles

Pyrrole and Pyrrolidine Derivatives. Of the natural pyrrole compounds, porphine derivatives play the most important role. The blood of all vertebrates contains the same hemin, which is also found in more primitive organisms. One of the few exceptions is chlorocruorin, the green respiratory pigment of marine worms of the genus Spirografis. Like hemoglobin, it consists of a protein and protoporphine with covalently bonded ionic iron; the molecular weight of chlorocruorin is 2,750,000 [1]. However, the hemin of this pigment (I) differs from the hemin of hemoglobin in that it has a formyl group in the 2 position [2].

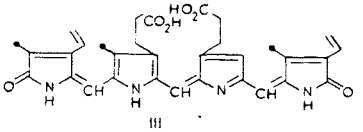
It is known that the oxidative decomposition of hemin in the liver of vertebrates gives bilirubin (II), a yellow pigment of the liver in which two oxidopyrrylmethane fragments are bonded to the central methylene group. Biliverdine (III), a compound in which all four pyrrole rings are conjugated, can be obtained by oxidation of bilirubin with ferrocyanide [3]. The same pigment has been isolated from extracts of the calcium skeleton of the blue coral Heliopora coerules [4].



I



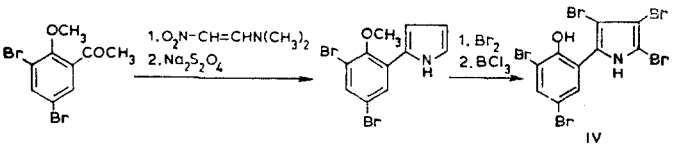
II



III

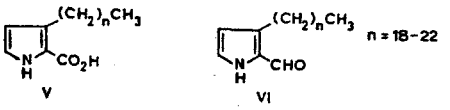
An unusual pyrrole compound (IV), which has antibiotic properties, has been detected in extracts of the marine bacterium Pseudomonas bromoutilis [5]; its structure has been established by x-ray diffraction analysis [6] and confirmed by synthesis [7]:

Pacific Institute of Bioorganic Chemistry, Far-Eastern Scientific Center, Academy of Sciences of the USSR, Vladivostok 690022. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 435-452, April, 1977. Original article submitted August 16, 1976.



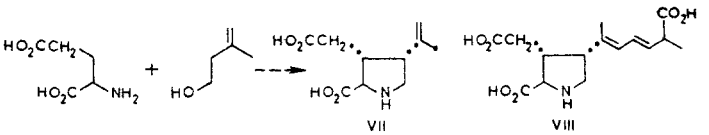
IV

Long-chain pyrrole-2-carboxylic acid (V) and 2-formylpyrrole (VI) derivatives were recently isolated from extracts of the sponge Oscarella lobularis [8]; their biogenesis is unclear.



V VI

Of the pyrrolidine derivatives of marine organisms, two algae metabolites, kainic acid (VII) and domoic acid (VIII) [9, 10], are the most interesting with respect to their physiological activity. Their synthesis is evidently based on condensation of glutamic acid with one (for VII) or two (for VIII) isoprene units:

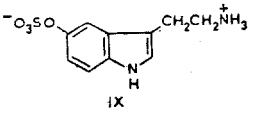


VII VIII

The discovery of kainic acid was initiated by the utilization in eastern medicine of extracts of the red alga Digenea simplex for the treatment of helminthiases. The chemical study of the components of these extracts led to the isolation of acid VII. A related compound (VIII) was later isolated from another form of algae, Chondria armata. Kainic and domoic acids are toxic to worms, and kainic acid has found application in Japan together with santonin and piperazine adipate for ascariasis therapy.

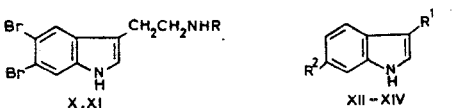
Indoles. 5-Hydroxytryptamine has been identified in the extracts of many forms of marine invertebrates [11]; the nerve tissues of these organisms contained more of this compound than the corresponding tissues of higher animals [12]. This circumstance is in agreement with the assumption that 5-hydroxytryptamine is one of the principal mediators of excitation in several marine invertebrates [12, 13]. 5-Hydroxytryptamine has been detected in various forms of plants and animals, from the simplest animals to mammals and humans. However, the physiological role of this compound still remains unknown. The assumption that 5-hydroxytryptamine also has mediator functions for higher animals was stated in [14] in 1957.

On the other hand, despite its relatively low toxicity, 5-hydroxytryptamine is found in the venom organs and secretions of coelenterates and mollusks. [13]. It is assumed that its contribution to the action of the poison is only indirect and consists in facilitation of resorption and transport of the highly toxic components of the poison [15]. 5-Hydroxytryptamine sulfate (IX) has been identified in the extracts of the zoantharia Palythoa mamilosa and Palythoa carribbiorum [16]; nothing has been reported regarding its physiological activity.



IX

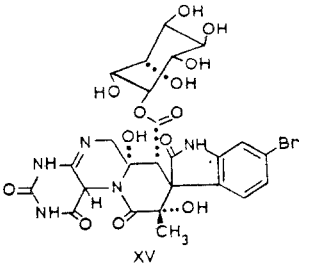
Bromoindoles X and XI, which have structures similar to that of 5-hydroxytryptophan and were isolated from extracts of the sponge Polyfibrospongia maynardii, displayed antibiotic properties and protected mice from affliction with bacterial infections (they inhibited the development of both Gram-negative and Gram-positive bacteria) [17]. Halogenated indoles XII-XIV have also been identified in the strong-smelling mucus secreted by the vermiform animals Ptychodera flava (of the hemichordata type) [18].



X, XI XII – XIV

X R = H; XI R = CH_3; XII R^1 = Cl, R^2 = H; XIII R^1 = Br, R^2 = H; XIV R^1 = Cl, R^2 = Br

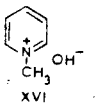
In 1970 a group of Japanese scientists [19] isolated a new toxin of unestablished structure from Babylonia japonica mollusks. The physiological action of this substance was characterized by a strong mydriatic effect. A subcutaneous dose of 20 μg/kg induced dilation of the pupil. Later another Japanese group began a study of venomous mollusks collected in the bay of Suruga. They were able not only to isolate the active component, the properties of which are identical to those of the toxin from Babylonia japonica, but also were able to establish its structure by x-ray diffraction analysis [20]. Surugatoxin (XV) was found to be a complex heterocyclic compound that contains a 6-bromoindole ring; it is a representative of a new structural type of substances that induce mydriasis. It does not have the structural elekents from which atropine molecules and alkaloids related to them are constructed.



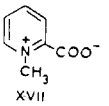
XV

Hydroxy derivatives of indole, including 4,6- and 6,7-dihydroxyindoles, which display antimicrobial, activity, have been identified in extracts of the sponge Agelas sp. [21].

Pyridine Derivatives. Few pyridine and piperidine derivatives have been found in marine organisms. At the same time, pyridinium salts have been identified along with noncyclic ammonium compounds in the toxins of many forms of coelenterata. N-Methylpyridinium oxide (XVI)



XVI

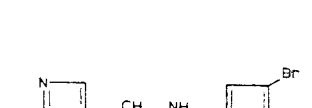


XVII

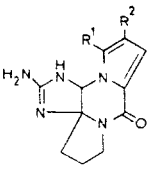
and homarine (XVII) are examples of coelenterata metabolites of this kind [22].

Homarine and similar compounds have also been detected in extracts of sponges [23].

Imidazole Derivatives. Among the series of brominated compounds that display antibiotic properties that have been identified in recent years in extracts of sponges one should mention the imidazole antibiotics oroidine (XVIII) from Agelas oroides and phakellin (XIX) and debromophakellin (XX) from Phakellia flabellata.



XVIII

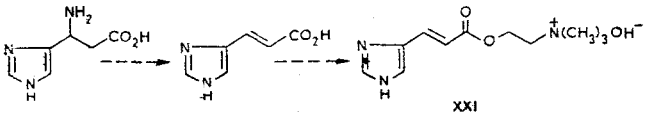


XIX, XX

XIX $R^1 = R^2 = Br$; XX $R^1 = H, R^2 = Br$

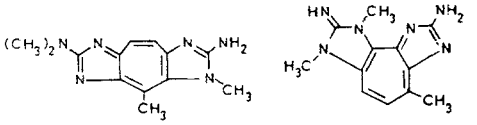
The structures of oroidin [24] and the phakellin [25] have been definitively established by means of x-ray diffraction analysis. Since oroidin and phakellin are structurally similar, the detection in the same biological specimen of antibiotics with an open chain of the oroidin and phakellin type would confirm the assumption of the existence of a relationship between them.

Murexine (XXI), an effective nerve-blocking agent, has been isolated along with 5-hydroxytryptamine from the hypobranchial gland of the mollusk Murex trunculus [26, 27]. Cholinic acid ester XXI, like many other structural analogs of acetylchline, interrupts transmission of an impulse to the muscle; it also causes depolarization of a membrane. Murexine is similar to decamethonium ion with respect to its depolarizing action [28]. According to Giretti [13], the biosynthesis of murexine is realized from histidine, which, by the action of histidine deaminase, is converted initially to uraconic acid, the reaction of which with choline leads to XXI.



XXI

Pigments of a new structural type containing imidazole rings have been found in Mediterranean zoantharia [29, 31]. These fluorescing pigments are N-methyl-substituted tetraazapentazulenes. Two series of pigments of this sort have been discovered. Zoanthoxanthin (XXII) is a representative of one of them, and pseudozoanthoxanthin (XXIII) is a representative of the other.



XXII XXIII

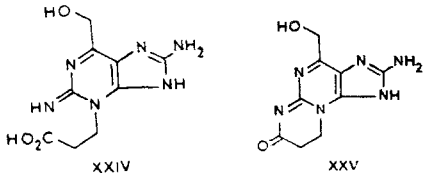
Saxitoxin. Saxitoxin is one of the most toxic natural compounds; it is ~ 50 times more toxic than strychnine and 1000 times more toxic than sodium cyanide. Its LD_{50} in the case of intravenous injection in mice is 3.4 μg/kg, as compared with 8 μg/kg in the case of intraperitoneal injection. Saxitoxin is produced by one-cell marine organisms – flagellates (order Dynoflagellata), which are one of the components of plankton. The toxin gets into the organism of mollusks and subsequently into humans through the nutritive chain [33]. Poisoning by food mollusks that are "contaminated" with saxitoxin (paralytic poisoning by mollusks) commonly occurs during the so-called "red tides," which are phenomena associated with coloring of sea water as a result of outbreaks of the development of flagellates. During this period 1 ml of sea water may contain up to 20,000 of these minute toxic organisms. Mollusks become poisonons even when there are only several hundred flagellates per milliliter of water. Approximately 1 mg of saxitoxin may produce fatal poisoning of humans when orally administered. [34]. Cases of poisoning by toxic mollusks are noted particularly frequently on the Pacific coast of the United States, where for prophylactic purposes the catching of clams and mussels is even discontinued from May to October, during which period the outbreak of propagation of flagellates is heightened.

The pure toxin has been obtained from several sources: from a culture of the flagellates Gonyaulax catanella [35] and G. tamarensis [36], from the tissues of the mollusks Saxidomus giganteus and Mytilus californianus [37], and from extracts of the crab Zosimus aeneus [38].

Saxitoxin is a colorless amorphous hygroscopic compound that does not crystallize in the form of chloride, acetate, or sulfate salts. It is a strong base (pK_a 8.1-8.3 and 11.5), and it is stable in acidic media but decomposes rapidly in alkaline media.

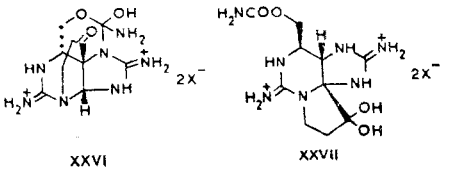
From the time that the optimum conditions for the cultivation of the saxitoxin producer G. catanella were selected, this toxin became a relatively accessible compound [39]. However, more than 10 yr after this were required for the establishment of its structure.

A study of the products of acid and alkaline cleavage of saxitoxin did not lead to any serious conclusions regarding its structure. An investigation of the products of oxidative dehydration proved to be a more promising route. Rapoport and co-workers [40,41] obtained 8-amino-6-hydroxymethyl-2-iminopurine-3(2H)-propionic acid (XXIV), which was rapidly converted to cyclization product XXV during isolation, by the action of hydrogen peroxide in an alkaline medium on saxitoxin.



XXIV XXV

Thus a substituted purine ring lies at the foundation of the structure of saxitoxin. An analysis of the spectral characteristics of the starting toxin and its oxidation products led Rapoport and co-workers to formula XXVI for saxitoxin. However,



XXVI XXVII

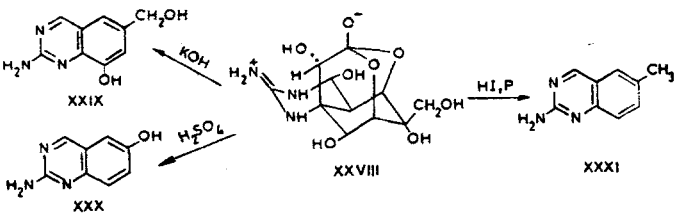
x-ray diffraction analysis of saxitoxin p-bromobenzenesulfonate showed [42] that structure XXVII, which is characterized by the presence of a unique structural element – the hydrated form of a keto group – corresponds to this compound.

Saxitoxin is one of the powerful neurotoxic agents. It causes muscle paralysis as a result of blocking of the activity potentials in the motor axons [43]. The mechanism of the action of saxitoxin [44] is similar to the mechanism of the action of other guanidine derivatives. The toxin inhibits sodium conductance, during which it acts both presynaptically (blocking of the conductance of the nerve endings) and postsynaptically (blocking of the conductance of the muscle membrane). The ability of saxitoxin to stop the flow of ions through the membranes of a nerve fiber and its specific effect on the transport of sodium ions have been used by Hille [45] to calculate the distances between the "sodium channels" in the nerves of frogs, squids, and lobsters. It was found that these channels are rather "far" from one another. For example, they are separated by a distance of 600 Å in the nerve fibers of frogs.

Tetrodotoxin. Tetrodotoxin (XXVIII) is a highly polar nonvolatile compound, the toxicity of which is equivalent to that of saxitoxin; it is concentrated in the roe of globe (puffer) fish. The roe of the fish Fugu rubripes, which is common to the shores of Japan, has become the principal source for the isolation of the toxin. A total of 1-2 g of tetrodotoxin has been obtained from 100 kg of the roe of this fish. Poisoning by the venomous fish from the tetrodonotoid suborder to which the puffer fish belong has become one of the chief health problems in Japan, where this fish is considered to be a delicacy.

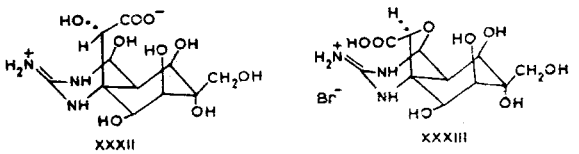
The pure toxin was obtained in 1950. From this point on, this unique compound was subjected to structural studies, which culminated in 1964 in the determination of its structure. Three groups of investigators – two in Japan (the Tsuda and Goto groups) and one in the United States (Woodward and co-workers) – participated in these studies [46-50].

The most important steps on the road to the establishment of the structure of the toxin were the exposure of the fact that the toxin contains a 2-aminoperhydroquinazoline fragment and the collection of data on the structure of tetrodonic acid. The first fact became clear after 2-aminoquinazoline derivatives XXIX-XXXI were obtained under conditions of acid and alkaline hydrolysis.



XXIX XXVIII XXXI XXX

The key compound, tetrodonic acid (XXXII), which is the product of addition of a molecule of water to the starting compound, was formed after heating an aqueous solution of tetrodotoxin [51, 52]. Treatment of XXXII with hydrobromic acid gave crystalline hydrobromide XXXIII, the structure of which was determined by x-ray diffraction analysis [53].



XXXII XXXIII

After this, the problem of the establishment of the structure of tetrodotoxin reduced to the selection of a structure that could be converted to acid XXXII under mild conditions and would correspond to all of the properties of the toxin, primarily its low basicity (pK_a 8.3) and the absence in its IR spectrum of absorption bands at 1700-1800 cm^{-1}. Of all of the possible variants, structure XXVIII was in better agreement with all of the

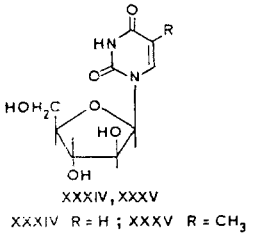
properties of the toxin and its derivatives than the others.

In 1963-1964 Brown and Mosher [54, 55] studied the toxin from the roe of fresh-water California tritons, animals that are quite different, in a systematic respect, from puffer fish. The active compound that they isolated (tarichatoxin) was found to be identical to tetrodotoxin. This discovery is of great interest for clearing up the as yet completely unclear problems associated with the biogenesis of tetrodotoxin. The more widespread occurrence of tetrodotoxin than was previously supposed is also confirmed by the research of Hashmoto and co-workers [56, 57], who showed that the skin and milt of the tropical fish Gobius criniger from the family Gobidae also contain tetrodotoxin.

The approximately three-step total synthesis of toxin XXVIII by Goto and co-workers [58-61] in 1970-1972 should be regarded as a remarkable achievement of modern organic chemistry.

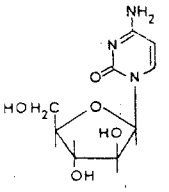
Saxitoxin and tetrodotoxin display some features of structural similarity – the functional groups in both molecules are rigidly fixed and are in direct proximity to one another, both toxins have guanidine fragments as parts of the cyclic system, and all of the carbon atoms in both compounds bear functional groups. These toxins are also similar with respect to their physiological activity, and they are powerful nerve blocking agents, the basis of the inhibiting effect of which is their ability to block the active transport of sodium ions, during which potassium transport remains unaffected [62]. As a result of the high specificity of the inhibition of the sodium conductance of the nerves, tetrodotoxin has found application as the instrument in physiological investigations. Tetrodotoxin is much more effective than local anesthetics; for example, it induces blocking of the axon in concentrations 160,000 times lower than cocaine. Tetrodotoxin is used clinically in small doses to eliminate muscular spasms and as an anesthetic [23].

Nucleosides of Sponges. In 1950 Bergmann and co-workers [63, 64] isolated two unusual nucleosides, spongouridine (XXXIV) and spongothymidine (XXXV), which contain D-xylose residues instead of ribose components, from the extracts of the sponge Cryptotethia crypta. Shortly thereafter, other investigators also turned their attention to these unique compounds and reported their antivirus and antitumorigenic properties [65]. Spongouridine and spongothymidine have served as models for the synthesis of a number of cytotoxic compounds, one of which was D-arabinocytotoxin (XXXVI), which has found application in the chemotherapy of malignant tumors [66].

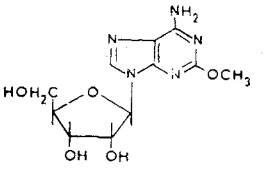


XXXIV, XXXV

XXXIV R = H ; XXXV R = CH_3



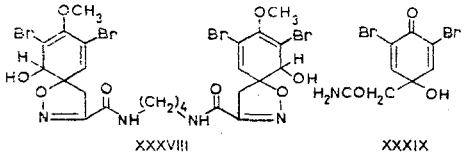
XXXVI



XXXVII

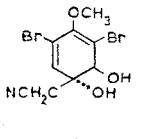
Another nucleoside from the extracts of the same sponge, the so-called spongosine (XXXVII), was the first methoxylated purine derivative of those found in nature [64]. In contrast to XXXIV and XXXV, it had a ribose residue.

Aerothionine. Aerothionine (XXXVIII) [67] is a heterocyclic antibiotic from extracts of sponges of the genus Verogia that has a structure similar to the structures of some other antimicrobial metabolites of sponges (for example, cyclohexadiene derivatives XXXIX and XL) [68, 69]:



XXXVIII

XXXIX



XL

These compounds are probably formed in the sponges as a result of biotransformation of bromo derivatives of tyrosine, which were previously identified in marine organisms [70, 71].

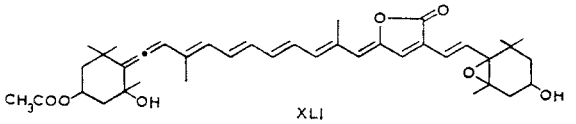
Oxygen-Containing Heterocycles

Under this heading, in addition to "true" heterocycles we also examine their acyclic and cyclic analogs that do not contain a heteroatom, as well as products of mixed biogenesis. This is due to the fact that the

biosynthesis of these compounds is presently not completely clear.

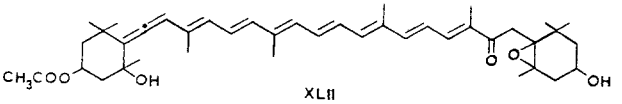
α-Oxides. Terpenoid and carotenoid metabolites of marine organisms that contain an α-oxide ring are in some cases intermediates and in other cases the final products of a chain of biosynthetic reactions. They are frequently found in the producer organisms together with the corresponding ethylene analogs. A number of the α-oxides of marine "origin" are previously unknown structures that are not present in land plants and animals.

One of the most astonishing examples of secondary metabolites with α-oxide rings is peridine (XLI), a unique 37-carbon three-ring carotenoid, the terminal rings of which are bonded to a carbon chain that differs from the usual chain of carotenoids with respect to the absence of two carbon atoms and two methyl branches. One methyl group in peridine is replaced by a carboxyl group that participates in the formation of a butenolide structural unit. There is also an allene fragment in the carbon chain of peridinine.

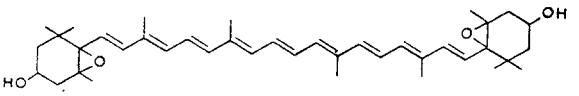


XLI

The pigment is produced by microalgae zooxanthella – symbionts of many forms of marine invertebrates – and it was therefore, isolated not only from a culture of Amphidinium operculatum but also from extracts of invertebrates (actinia and mollusks) [72-76].



XLII



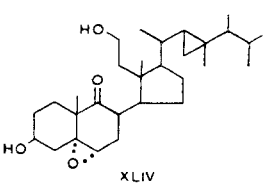
XLIII

Peridinine is similar to the carotenoids of brown algae – fucoxanthin (XLII) and violaxanthin (XLIII) and is found together with the latter [77-80].

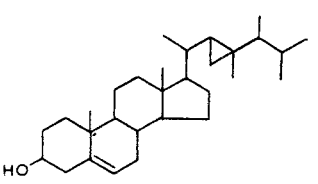
Before the discovery of peridinine and fucoxanthin, only one natural allene – mycomycin – was known [81]. The origin of the allene grouping in XLI and XLII is not clear: it has been assumed that this fragment is formed through photooxidation of carotenoids of the usual type (for example, zooxanthin [82,83]), but according to other data, fucoxanthin (XLII) is the product of biotransformation of violaxanthin (XLIII) [84]. The detection of alloxanthin and the related acetylenic carotenoid pigments in algae makes it possible to also assume another pathway for the formation of the allene structure – from an acetylenic precursor. The finding of fucoxanthin together with an acetylenic carotenoid – diatoxanthin – in diatomaceous algae constitutes evidence in favor of the latter hypothesis [75]. There is evidently a relationship between acetylenic and allenic pigments, but it is not known whether the allenic carotenoids are formed from the acetylenic carotenoids or vice versa.

Of the α-oxide derivatives of steroids, one should mention the unusual secosterine (XLIV) from the gorgonaria Pseudopterogorgia americana [85], which is related to gorgosterine (XLV). Both of these compounds have a side chain that bears a cyclopropane ring (see scheme below).

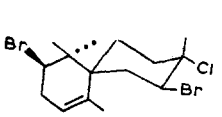
α-Oxide derivatives are frequently encountered in extracts of marine organisms together with their nonoxidized analogs. Sesquiterpenes XLVI and XLVII and diterpenes XLVIII and XLIX from extracts of the algae Laurencia are examples of such pairs [86,87] (see scheme on page 352).

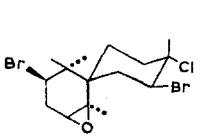


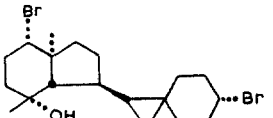
XLIV

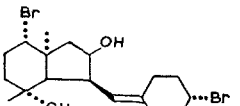


XLV

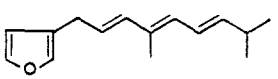

XLVI

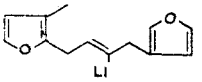

XLVII


XLIII

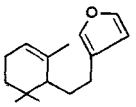

XLIX

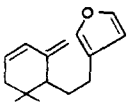
Furanoterpenoids. The formation of heterocyclic metabolites containing a furan ring is a characteristic of the biosynthesis of terpenoid compounds in some groups of marine invertebrates. Compounds of this type are widely represented in sponges. The investigated (almost exclusively by Italian chemists) forms of the family Spongidae from the suborder Dictioceratida contained C_{15}-, C_{25}-, C_{30}-, and C_{35}-furanoterpenes with a linear skeletal system and, in addition, C_{21}- and C_{31}-furanoterpenes. Sponges of the family Aplysillidae from the same suborder produce primarily furan sesquiterpenes (C_{15}) [88-94]. Of the sesquiterpenes of sponges, the most simply constructed are the linear derivatives, which are found in Pleraplysilla spinifera [94], for example, L and LI. They can be considered to be derivatives of sequiterpenes with an open chain in which the terminal link or links are oxidized and form a furan ring.

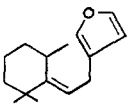

L

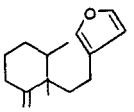

LI

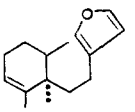
Another group of furanosesquiterpenes from the sponges Disidea pallescens [89] and Microciona toxystila [92] have a monocyclofarnesan skeleton:

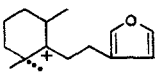

LII


LIII


LIV

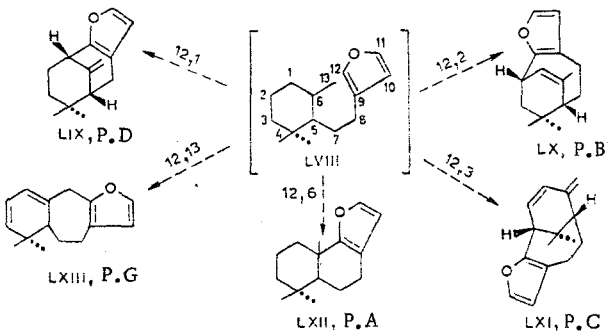

LV


LVI


LVII

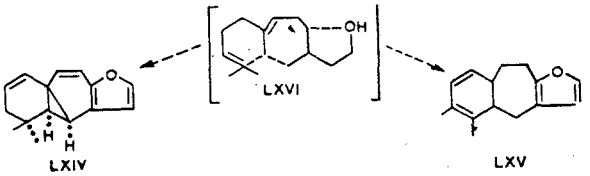
It might be assumed that these metabolites originated from a common precursor (for example, ion LVII).

Similar monocyclofarnesan precursors (LVIII) evidently are the basis of the biosynthesis of a group of three-ring derivatives (LIX-LXIII), that were recently found in various forms of sponges:

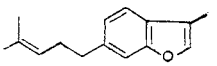


→ bond formation P = pallescensin

The only furanosesquiterpene found in coelenterate – furoventalene (LXVII) – is most likely the product of dehydration of higher-molecular-weight compounds formed during isolation by steam distillation [95].

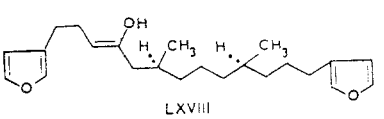


Several furanoterpenoids (LXIV, LXV) from Pleraplysilla spinifera are apparently formed from a cis-farnesyl precursor (LXVI) rather than from a cyclic precursor:

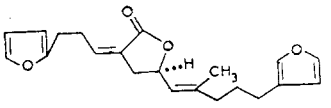


LXVII

The unusual C_{21}-furanoterpenes of sponges [96,97] [for example, furospongin-I (LXVIII) and nitenin (LXIX)] may originate biosynthetically from higher terpenoids constructed from isoprene compounds in accordance with the "head-to-tail" principle. Another possible pathway for the biosynthesis of C_{21} derivatives consists in joining of two C_{10} and one C_1 unit.

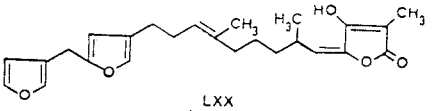


LXVIII



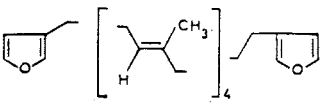
LXIX

The discovery in sponges of linear sesterterpenes (C_{25} derivatives) containing a furan ring [98-100] confirmed the hypothesis that the C_{21} derivatives are formed by dehydration of the higher-molecular-weight compounds. Ircynine-I (LXX) is an example of such furanosesterterpenes.

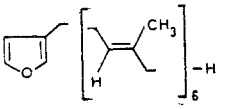


LXX

C_{31}-Furan metabolite LXXI and C_{35}-furano derivative LXXII have been found in the sponge Ircinia spinosula [101]. Their joint presence in a single organism substantiates the hypothesis that the C_{31} compounds, like the C_{21} furanoterpenes, are also formed from higher-molecular-weight precursors, in this case from C_{35} compounds as a result of splitting out of four carbon atoms and closing of a terminal furan ring.



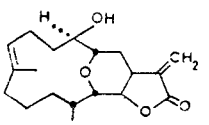
LXXI



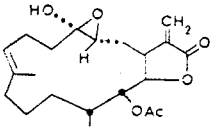
LXXII

Heterocyclic Derivatives of Cembranolides. Derivatives of C_{20} acids – prostaglandins – that have a broad spectrum of physiological activity have been detected in the gorgonaria homomalla [102]. Studies of the chemical compositions of representatives of other groups of the subclass of octocarallia corals, to which the gorgonaria belong, showed that other cembranolide metabolites are widely represented in coelenterata. Heterocyclic derivatives of cembranolides (diterpenes with a 14-membered ring) are examined in this section.

Eunicin (LXXIII), a heterocyclic lactone of the cembrane series, was obtained in the form of well-formed crystals from a pentane extract of the gorgonaria Eunicea mammosa [103]. The structure of lactone LXXIII has been studied by chemical degradation methods [104] and has been established definitively by x-ray diffraction analysis [105]. Eunalmerin acetate (LXXIV), which is similar to eunicin, is evidently a precursor in the biosynthesis of LXXIII.



LXXIII

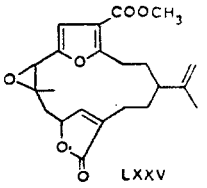


LXXIV

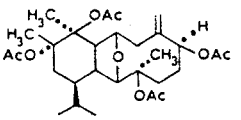
It is interesting that E. mammosa from various collection regions contains nonidentical sets of cembranolides related to eunicin. It is assumed that the biosynthesis of these compounds in gorgonaria is realized with the participation of zooxanthella, symbionts of gorgonaria. Whereas different samples of the same form differ with respect to their zooxanthella, the differences in the compositions of the cembranolides are easily explainable [16]. The eunicin and its analogs, which have antibiotic action and are concentrated on the surface of the bodies of the coelenterata, protect the gorgonaria from infestation by various swimming organisms.

It has recently been proven that homocyclic and heterocyclic cembranolides are typical not only for gorgonaria but also for other groups of the Cnidaria type [106-109]. Scheuer and co-workers [110], for example,

isolated furanocembranolide LXXV with a unique (for natural compounds) β-carbomethoxy group in the furan ring from an extract of Sinularia abrupta:



LXXV



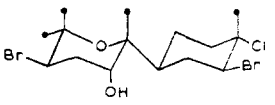
LXXVI

Eunicellin (LXXVI) from the gorgonaria Eunicella strieta, the structure of which has been determined by x-ray diffraction analysis [111], is a C_{20} heterocyclic compound that is similar to cembranolides.

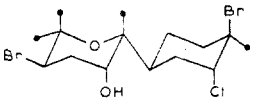
Halogenated Heterocycles Related to Terpenes. A large diversity of cyclic and acyclic halogen-containing compounds is extremely characteristic for marine organisms. These compounds are particularly widely represented in algae and mollusks and sponges. Acyclic monoterpenes with covalently bonded bromine or chlorine [112,113] undergo biological oxidation and subsequent cyclization to give heterocycles of the chondrocol A type (LXXVII) containing a dihydrofuran ring from the red algae Chondrococcus hornemanni [114].

LXXVII

Another group of heterocycles of this sort is represented by derivatives of sesquiterpenes that have a tetrahydropyranone ring. Caespitol (LXXVIII) [115, 116] and isocaespitol (LXXIX) [117] from the algae Laurencia are examples of compounds of this type.

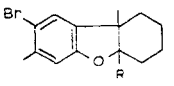


LXXVIII



LXXIX

Another group of C_{15} oxygen-containing heterocycles is represented by aplisin (LXXX), aplisinol (LXXXI), and some similar compounds from the algae Laurencia [118, 119] and extracts of the sea hare Aplysia kurodai [120], which lives on these algae.

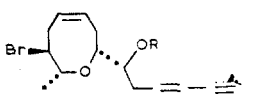


LXXX, LXXXI

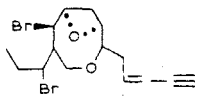
LXXX $R = CH_3$; LXXXI $R = CH_2OH$

Aplisin is strongly toxic to mice when it is administered orally; it stops the heartbeat of frogs and causes muscle contracture and a drop in the blood pressure.

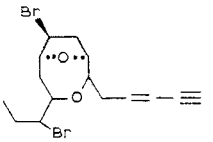
Halogenated Heterocycles with a Vinylacetylene Group. A group of cyclic halogen-containing ethers that originate biogenetically from hexadeca-4,7,10,13-tetraenic acid and related compounds is found in marine organisms [122]. The red algae Laurencia are the chief producers of these heterocycles. Laurencin (LXXXII) and deacetyllaurencin (LXXXIII), laurentin and T-laurentin (LXXXIV, LXXXV), isolauretin and T-isolauretin (LXXXVI, LXXXVII), and laurefucin and acetyllaurefucin (LXXXVIII, LXXXIX) [123-128] serve as examples of cyclic ethers of this sort.



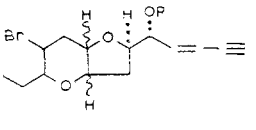
LXXXII, LXXXIII



LXXXIV, LXXXV



LXXXVI, LXXXVII

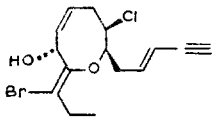


LXXXVIII, LXXXIX

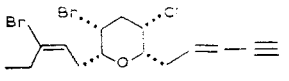
LXXXII, LXXXIX R=$COCH_3$; LXXXIII, LXXXVIII R=H ; LXXXIV, LXXXVI Δ^3-cis ; LXXXV, LXXXVII Δ^3- trans

In contrast to the previously examined representatives of this group, the antivirus metabolite chondriol (XC) from the algae Chondria oppositiclada [129] contains a chlorine atom.

Although dactylene (XCI) from extracts of the sea hare Aplysia dactylomella is similar to XC, it differs with respect to the configuration at 6-C and 7-C [130].



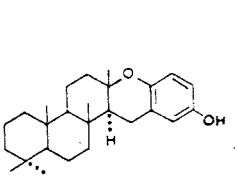
XC



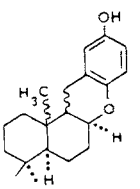
XCI

Vinylacetyleneyl-substituted heterocycles of marine organisms have a C_{15} skeleton but are not derivatives of sesquiterpenes. Their detection in marine organisms expands earlier concepts regarding the limits of distribution of acetylenic compounds in nature.

Four- and Five-Ring Derivatives with Pyran and Furan Rings. Similar biosynthetic pathways leading to products of mixed biogenesis formed partially through mevalonate and partially from a benzenoid precursor are observed in algae and sponges [131-133]. Taondiol (XCII) from Taonia atomaria [134-135], stereoisomeric chromazonarol (XCIII) and ent-chromazonarol (XCIV) from Dictyopteris undulata and Disidea pallescens [136, 137] are examples of products of this type.

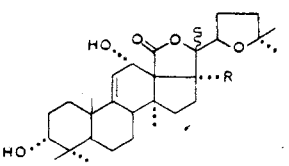


XCII



XCIII, XCIV

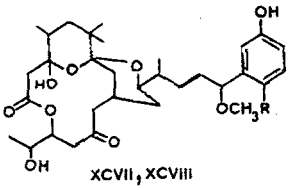
Triterpene derivatives XCV and XCVI, which contain a tetrahydrofuran ring, are aglycones of glucosides identified in several dozen forms of Holothurioidea [138-141].



XCV, XCVI

XCV R=OH ; XCVI R=H

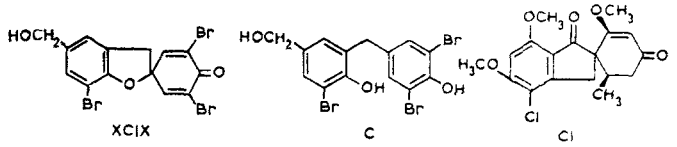
Aplisiotoxin. Sea hares are a group of mollusks that are frequently encountered in the tropical parts of the Indian and Pacific oceans. Although their toxicity has been known for quite some time, the study of the toxins of these animals was begun only recently [142]. Scheuer and co-workers were able to isolate the active compounds aplisiotoxin and its debromo derivative (XCVII, XCVIII) from an extract of Stylocheilus longicauda [143]. Aplisiotoxin had LD_{100} (in the case of intraperitoneal injection in mice) of ~200 μg/kg. The toxin contains two spiro-fused tetrahydropyran rings and hemiketal and ketal fragments, which are rare for natural compounds. During purification, XCVII readily loses a molecule of water, and this hinders its isolation in the individual state. The pharmacological properties of a mixture of XCVII and XCVIII were examined in [142].



XCVII, XCVIII

XCVII R = Br ; XCVIII R = H

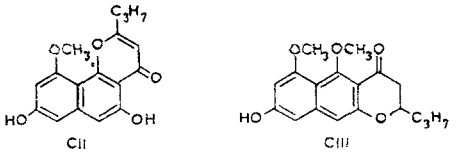
Thelepin. An effective antifungus agent – thelepin (XCIX) – which was identified together with its noncyclic analog and possible precursor thelepinol (C), was recently found in extracts of the marine worm Thelepus setosus [144].



XCIX C CI

Spiran XCIX is structurally similar to the antibiotic griseofulvin (CI) [145] used to combat dermatophytes.

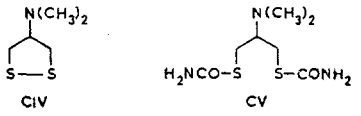
Naphthopyrone Pigments of Echinoderms. Sea lilies are representatives of one of the classes of echinoderms and contain primarily anthraquinone derivatives as pigments. It was recently shown that the extracts of sea lilies also contain pigments of different structural types – comaparvin (CII) [146] and neocomantherin (CIII), which contain a naphthopyrone ring [147].



CII CIII

Heterocycles Containing Sulfur

An interesting neurotoxic substance has been isolated by Japanese scientists from extracts of the marine worm Lambriconereis heteropoda. The investigation of this form was stimulated by the observation that insects that fed on the dead worms died. Research on the isolation of the neurotoxin (CIV) was begun in 1934 [148]. Later Hashimoto and co-workers established the structure of this ganglion-blocking compound [149-151] as 4-dimethylamino-1,2-dithiolane (CIV) and confirmed it by synthesis [152].



CIV CV

The neurotoxin has strong insecticidal action but is also quite toxic to vertebrates. The synthesis of a number of related compounds led to the less toxic 1,3-bis(carbamoylthio)-2-dimethylaminopropane (CV), which under the commercial name "Padan" is used in Japan as an insecticide.

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