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Natural Products Chemistry in the Marine Environment

William Fenical

Summary. Significant differences and numerous similarities exist in the biosynthetic activities of marine and terrestrial plants and animals. While the more primitive marine biota are recognized to possess the common biosynthetic pathways to produce terpenes, acetogenins, aromatic compounds, and alkaloids, in many cases these pathways have been modified in unusual ways. The halogens in seawater, for example, appear to be fundamentally involved in terpene biosynthesis and in the production of bromine-containing acetogenins and phenolic compounds. Marine metabolites have high physiological activities, and these molecules are conceived to function, in part at least, as defensive adaptations in the marine environment.

Since antiquity extracts of plants and animals have been recognized to possess biologically important properties. Later, discrete organic compounds were discovered to be responsible for these properties, and these components are now referred to as primary or secondary metabolites, depending upon their direct involvement in the essential metabolic processes of the producing species. Since functions for the secondary metabolites could not be found in cellular processes, these compounds were conceived as by-products of detoxification. These unique and often exceptionally complex compounds were widely exploited for their biological activities, ultimately producing the foundations for the modern pharmaceutical and agricultural chemical industries. A more recent explanation is that secondary metabolite synthesis represents an evolutionary event yielding the production of a biologically active compound that ultimately results in enhanced survival of the species. The subtle biological functions of many of these compounds in intra- and interspecies communication have been recognized, and the discipline of chemical ecology has become firmly established (*1*).

Studies of the secondary metabolites of terrestrial plants and animals were begun in the 1800's. However, comparable studies of the marine environment were not started until the last two decades of this century. With the invention of the self-contained underwater breathing apparatus (scuba) during World War II, came the first opportunity for scientists to observe, firsthand, the biologically diverse and ecologically complex marine environment. Subsequent chemical investigations, and particularly those over the last decade, have produced a fundamental knowledge of marine secondary metabolism, and more recent studies have been directed toward defining the biological functions of these metabolites. Commonly accepted biosynthetic pathways to produce terpenoids (compounds derived from isopentenyl pyrophosphate), acetogenins (compounds produced from acetate), aromatic compounds (products from shikimic acid), and with lesser frequency, alkaloids (nitrogen-containing bases), do exist in marine organisms. However, alterations of these fundamental pathways that yield unusual structure modifications have been observed. These findings have expanded our overall concept of secondary metabolite biosynthesis and produced a greater understanding of the chemical nature of the sea.

It is beyond the scope of this article to effectively review the field of marine natural products chemistry, nor is it necessary considering the many fine specialist reports that have appeared (*2–16*). In this article I present several examples of unique marine metabolism that compare and contrast the marine and terrestrial environments.

Primary Metabolism

Before proceeding to unusual examples of secondary metabolism, it is appropriate to point out several contrasting features between marine and terrestrial organisms in primary metabolic processes. The carotenoid pigments, which are involved as accessory pigments in photosynthesis, provide one such example. Marine plants produce carotenoids via terpenoid pathways, in complete analogy to terrestrial plants. However, in the latter stages of biosynthesis, modifications that yield carotenoids of exceptional structure types occur. The carotenoid pigment β,β-carotene (**1**) is the major and most common accessory pigment found in terrestrial plants, and it usually occurs with related oxygenated derivatives in reasonably predictable mixtures. In the sea, the algae are the major plants, and these more primitive photosynthetic organisms produce a wider variety of structurally unique carotenoids. The major carotenoid pigment of the abundant marine dinoflagellate group (of the phylum Pyrrophyta), for example, is the highly unusual tris-norcarotenoid, peridinin (**2**) (*17*) (Fig. 1). Peridinin has several unusual features, including the lactone and allene functional groups; but,

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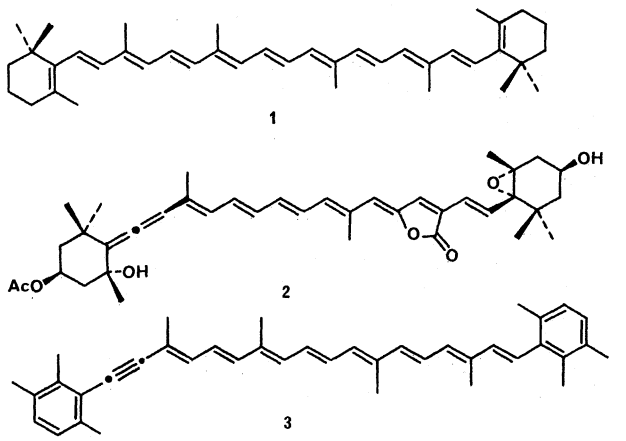

1

2

3

Fig. 1. Examples of common terrestrial and marine-derived carotenoid pigments.

more interestingly, peridinin has been modified by the loss of a three-carbon unit in unknown and unprecedented metabolic steps. This form of "irregular" carotenoid biosynthesis is more common in marine organisms, and the existence of the rare allene and acetylene linkages, while found in the trace components of terrestrial plants, are consistent features of the major marine carotenoids (*18*).

Given the diversity of carotenoids produced by marine plants, it is not surprising that marine invertebrates contain an even greater array of carotenoids produced by modification of these dietary pigments (*18*). An interesting example of this process is found in the pigments of sponges of the genus *Reniera*. Several related carotenoids have been reported, among them the aryl carotenoid **3**, which possesses an acetylenic bond as well as aromatic terminal groups (*19*). Carotenoid **3** would appear to be derived from a simple carotenoid precursor such as β,β-carotene itself. The distribution of methyl groups on the aromatic rings is typical of compounds produced by methyl group migrations from a terpenoid precursor.

The production of sterols in the marine environment is also worthy of mention. On land, plant-produced sterols are usually closely related to β-sitosterol (**4**), which is a simple modification of cholesterol through the addition of a two-carbon unit on the side chain at C-24 (Fig. 2). In contrast, marine plants and animals contain a much wider diversity of sterols, many of which are highly akylated at various positions of the side chain. Gorgosterol (**5**), for example, is an unusual cyclopropane-containing sterol found in filter-feeding soft corals and several other marine invertebrates (*20*, *21*). Alkylation at C-22 and C-23, as illustrated in gorgosterol, is a common feature of marine sterols, whereas alkylation at these positions is a rare or unknown phenomenon in terrestrial organisms. Since sterols are recognized to be important in membrane composition and permeability, these structural variations could indicate functional differences (*22*).

Secondary Metabolism

Elemental composition. The composition of marine secondary metabolites, while in part identical to those from land plants and animals, is also significantly modified by virtue of the composition of available elements in the sea. The halide-rich seawater environment, consisting of Cl$^-$, 19,000 mg/liter; Br$^-$, 65 mg/liter; and I$^-$/IO$^-_3$, 5×10^{-4} mg/liter, has readily allowed marine organisms to incorporate bromine, chlorine, and iodine, in that order, into covalent organic structures. Furthermore, these elements are not only incorporated into diverse structure types, but they appear to play essential roles in terpene biosynthesis. The utilization of halogens in terrestrial secondary metabolism is, by comparison, a rare process observed in only a few microorganisms (*23*). The halogenation process attains a major significance in the sea.

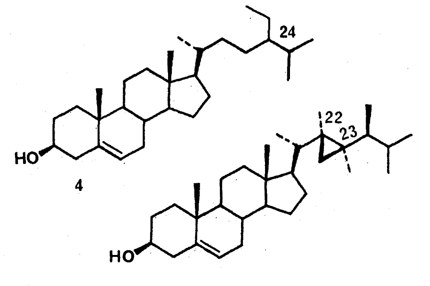

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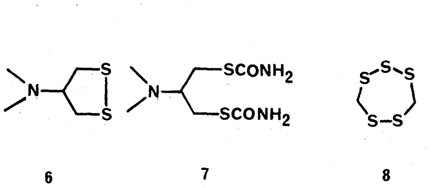
Fig. 2. Examples of common terrestrial and marine-derived sterols.



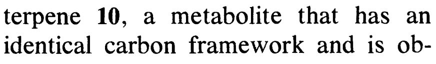
6 7 8

Fig. 3. Various sulfur-containing compounds from terrestrial and marine sources, and Padan, an insecticide developed from the sulfide **6**.

Although sulfur is in high concentrations in seawater, mainly as sulfate ($\sim$ 2700 mg/liter), and in reducing sediments as sulfide, the element in the reduced organic form is encountered only infrequently in marine secondary metabolism. A few interesting examples exist, however, and, in one case, the isolation of the disulfide **6** (nereistoxin) from the marine worm *Lumbriconereis heteropoda* (*24*), was the foundation for the development of the structurally related insecticide Padan (**7**), in common use in Japan (Fig. 3). Perhaps illustrating the similarity between marine and terrestrial sulfur biosynthesis is the isolation of the polysulfide, lenthionine (**8**), from the red seaweed *Chondria californica* (*25*). Lenthionine had earlier been isolated as an antibacterial component of the mushroom, *Lentinus edodes* (*26*).

Terpene biosynthesis. The most significant modifications of secondary metabolism in the marine environment lie in terpene biosynthesis. Terpenes are common metabolites in marine plants and animals, and their formation via the condensation of isopentenyl pyrophosphate units is, in this regard, comparable to terrestrial metabolism. On land, monoterpene (C$_{10}$) synthesis is a prominent feature to produce the odorous essential oils characteristic of many common plants. The emphasis in the marine environment lies largely in the production of higher molecular weight terpenes, especially the diterpenes (C$_{20}$).

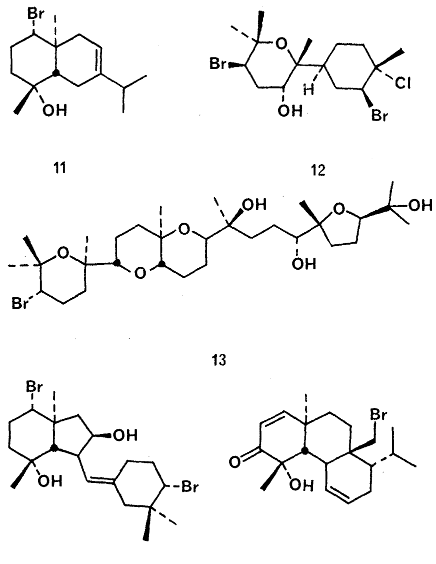
A more important modification of marine terpene biosynthesis is found in the involvement of the halogens, particularly bromine, in the primary production of terpenes through cyclization reactions. In the terrestrial environment the production of cyclized terpenoids is a process that can be exemplified by the apparent biosynthesis of the cyclic monoterpene aldehyde **9**, one of the sex pheromones of the male boll weevil *Anthonomus grandis* (*27*). On the basis of structural features, this process would appear to involve preliminary modifications of the linear monoterpene precursor geraniol, followed by a hydrogen ion–induced cyclization to produce the carbocyclic ring (Fig. 4). In many marine organisms, but particularly in marine plants, the hydrogen ion mechanism of cyclization is replaced by a bromine-induced cyclization, presumably involving an electron-deficient bromonium ion species (*15*). The marine equivalent of the process to produce **9** is found in the biosynthesis of the highly halogenated monoterpene **10**, a metabolite that has an identical carbon framework and is obtained from tropical red seaweeds of the family Rhizophyllidaceae (*28*). Bromine-induced cyclization of a slightly modified monoterpene precursor yields a bromoterpene that can then be further halogenated to yield **10**. This process, which appears to emphasize bromine, is common in marine organisms and a wide variety of haloterpenoids (approximately 400 are known) are produced. The molecules shown as **11** to **15** were all isolated from red seaweeds (*29–33*) and have been selected as examples of this process since, as a consequence of the strategic locations of bromine, each illustrates the very probable involvement of the element in cyclization reactions. The brominated terpenoids **11** to **14** are but a few examples of the many structurally diverse secondary metabolites produced by the prolific red seaweeds of the genus *Laurencia* (*2*) (Fig. 5). Although *Laurencia* species were first recognized for their involvement in brominated terpene synthesis, this genus must now be considered among the most prolific of terpene producers. Over the past decade more than 400 terpenoids representing 26 structure classes have been isolated from members of this genus. Of the 26 classes, 16 were novel structure groups found only in the marine environment.



9

10

Fig. 4. A biosynthetic sequence illustrating the contrast between hydrogen ion and bromonium ion-induced cyclizations of a geraniol-derived precursor in the terrestrial and marine environments.



11

12

13

14

15

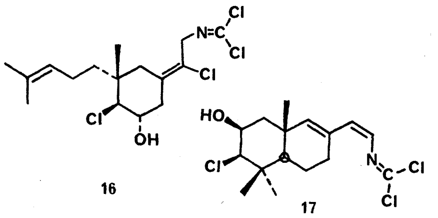
Fig. 5. Examples of the numerous haloterpenes isolated from marine red seaweeds (phylum Rhodophyta).

It is very important to qualify the above biosynthetic proposals as hypotheses since encompassing labeling studies have not been completed with marine organisms that are difficult to culture. The structural evidence to support these conclusions is strong, however, and progress has been made to thoroughly define the marine halogenation process (*34*). A brominating enzyme, bromoperoxidase, has been isolated from red seaweeds and its bromination of selected substrates has been well documented (*35*).

Interesting examples of halogen-containing compounds that extend the concepts of naturally occurring functional groups have also been isolated from marine organisms. The haloterpenes **16** and **17**, isolated from the sponge *Pseudaxinyssa pitys* (Fig. 6), are exceptional metabolites, the cyclic structures of which may be produced by chlorine-induced cyclization (*36, 37*). The carbonimidic dichloride functional groups of **16** and **17** had, until this discovery, only been produced in the laboratory. These rare functionalities appear to be produced by biological chlorination of an isonitrile precursor (R−N≡C), which although rare itself in terrestrial sources (*38*), exists in numerous terpenoids isolated from marine sponges (*12, 39*).

A curious feature of many nonhalogenated marine terpenoids is their deviation from the "regular" head-to-tail arrangement of isoprene (C_5) units. In many cases, these deviations appear to be the direct result of the instability of bromine in bromoterpenoid precursors (*40*). The biosynthesis of the rearranged sesquiterpene **19**, for example, is conceived to involve bromine solvolysis and methyl migration from an appropriate "regular" terpene such as α-synderol (**18**) (Fig. 7).

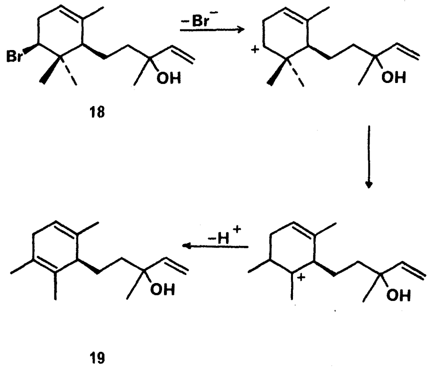
Marine alkaloids. Basic, nitrogen-containing compounds historically termed alkaloids are common components of terrestrial plants, and numerous alkaloids, such as morphine, vincristine, and quinine, are extensively utilized clinically for their biomedicinal properties. While a few examples of true marine alkaloids have been discovered, the alkaloids as a structural class are rare in the marine environment. Examples of two marine alkaloids are illustrated in Fig. 8.



16

17

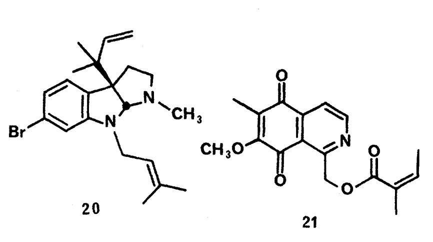
Fig. 6. Examples of two sponge-derived haloterpenes which possess the unique carbonimidic dichloride functional groups.



18

19

Fig. 7. A biosynthetic proposal involving the solvolysis of haloterpenoids which explains the production of the "rearranged terpenoids" found in marine organisms.



20

21

Fig. 8. Examples of "true" marine alkaloids, compounds rarely found in marine organisms.

Flustramine A (**20**), an alkaloid recently isolated from the marine bryozoan *Flustra foliacea*, is an interesting brominated derivative of the well-known physostigmine type (*41*). The isoquinoline alkaloid **21**, also isolated from a marine sponge, is atypical of the isoquinoline class of alkaloids from terrestrial sources (*42*).

Marine acetogenins. Acetogenins are linear, nonbranched compounds generally produced from the condensation of C_2 acetate units via the precursor, acetyl-coenzyme A. This major primary metabolic pathway is responsible for the production of the basic plant lipids, as fatty acids, and this process is ubiquitous in nature. Frequently, in both terrestrial and marine organisms, modifications of this process which yield secondary metabolites of unusual structure and biological significance are observed. It is within the acetate biosynthetic framework that marine species produce widely diverse types of unusual and unprecedented molecules.

One such example is the tropical red seaweed *Asparagopsis taxiformis*, which must be credited with the most simple and yet unprecedented synthesis of biologically important acetogenins. This highly odorous plant produces large amounts (about 3 to 5 percent dry weight) of the halomethane derivatives **22** to **26**, with bromoform (**22**) found as the major volatile metabolite (*43, 44*) (Fig. 9). Halogenated methanes are regarded as potent biocides, and their natural synthesis would certainly not have been predicted. Inspection of the minor metabolites of *Asparagopsis* species revealed a large number of small molecules such as tetrabromoacetone (**27**), and dibromoacetic acid (**28**), indicative of their origin in acetate biosynthesis. *Asparagopsis* produces minor quantities of chloroform (**25**) and carbon tetrachloride (**26**), which are recognized as environmental pollutants but considered totally manmade (*45*). While biosynthesis experiments must be completed to totally define the origins of the halomethanes in *Asparagopsis*, based upon known chemistry, these compounds are conceived as cleavage products of halogenated C_3 or C_4 ketones such as **27**. The simultaneous isolation of halogenated acetic acids, such as **28**, supports this latter contention. Studies of the reactivity of a brominating enzyme, bromoperoxidase, from the related seaweed *Bonnemaisonia hamifera*, with several substrates generated the same conclusion (*46*).

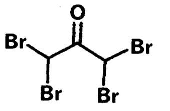
$CHBr_3$ 22

$CHBr_2I$ 23

$CHBr_2Cl$ 24

$CHCl_3$ 25

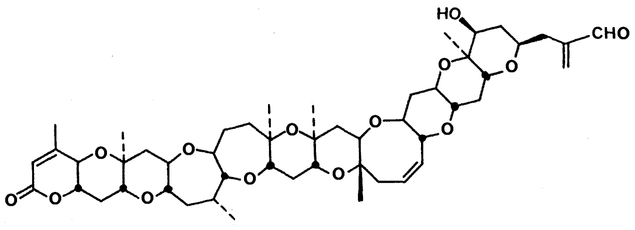
CCl_4 26



27

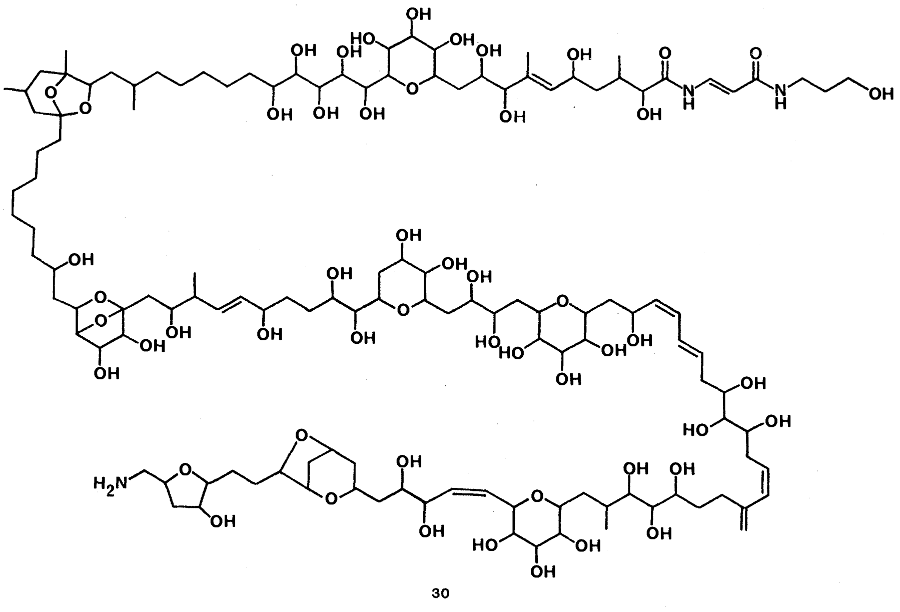
$Br_2CHCOOH$ 28

Fig. 9. Halomethanes and two other brominated metabolites produced by the red seaweed *Asparagopsis taxiformis*.



29

Fig. 10. Molecular structure of brevetoxin B, a toxic component of the "red tide"-producing dinoflagellate *Gymnodinium breve*.



30

Fig. 11. Molecular structure of palytoxin, a potent neuromuscular toxin from marine zoanthids of the genus *Palythoa*.

The last two examples of marine acetogenins are the recently reported structures of two complex marine toxins, brevetoxin B (BTX-B) and palytoxin, each of which has been the subject of investigation for more than a decade.

Outbreaks, in the southeastern United States, of the toxic marine dinoflagellate *Gymnodinium breve* (a "red-tide"-producing photosynthetic organism) are well documented to result in massive fish and bird mortalities, as well as considerable human discomfort through ingestion of subsequently toxic oysters and clams. Other *Gymnodinium* species occur worldwide, and the effects of "red tides," especially in Japan, have been particularly devastating. The toxins of *G. breve* have been established, for many years, as a series of readily extractable lipid-soluble substances, but because of the difficulty in obtaining modest amounts of these toxins in purified form, descriptions of the structural chemistry of these important molecules have not been possible. Recently, however, the first of the *G. breve* toxins, BTX-B, has been described (*47*) (Fig. 10). The toxin was isolated from laboratory cultures of *G. breve*, and one of the toxins crystallized upon successful purification. X-ray crystallographic techniques were then used to fully define BTX-B as structure **29**. Brevetoxin B, an exceptional C_{50} polyether, is unlike the polyether antibiotics produced by some terrestrial microorganisms. It possesses eight randomly placed methyl groups and is devoid of ketal functionalities. Pharmacological investigations of BTX-B are, no doubt, in progress. Polyethers are regarded in general as ion chelators (ionophores), and this mechanism could account for the potent biological activity of the *G. breve* toxins.

"Limu-make-o-Hana," the deadly seaweed of Hana, is the Hawaiian name of a highly toxic marine organism found in shallow waters in Hawaii. The early Hawaiians, recognizing the potent toxicity of this organism, used it to poison the tips of their spears. Although the Hawaiians called this organism a seaweed (limu), Limu-make-o-Hana is properly classified as a zoanthid coral of the genus *Palythoa*. *Palythoa* species are found in abundance in most tropical waters, and numerous *Palythoa* species have been subsequently reported to be moderately toxic. The toxin isolated from *P. toxica*, palytoxin, is the most poisonous nonproteinaceous substance known (*48*).

Studies of the complex structure of palytoxin have spanned the last decade, and while progress has been made, it was not until early this year that Moore and his associates in Hawaii announced the successful structure assignment of this complex compound (*48, 49*) (Fig. 11). Palytoxin (**30**), as isolated from a Hawaiian *Palythoa* species, is composed of a linear arrangement of 115 carbon atoms with 8 methyl groups and 40 hydroxyl functionalities. Unusual features of palytoxin are two cyclic ketal constellations which are part of 11 ether linkages.

Since palytoxin was not a crystalline substance, x-ray crystallographic techniques could not be applied to solving this complex structure. Instead, the Moore group used classical degradation chemistry to cleave palytoxin into smaller fragments more easily analyzed by instrumental methods. Even then, smaller fragments were complex and high-resolution techniques such as 600-megahertz proton nuclear magnetic resonance spectroscopy were absolutely necessary. Once all carbon fragments were accounted for, the structure of palytoxin was reconstructed on the basis of its reactivity and spectral properties. The successful elucidation of this highly complex structure should be considered a major achievement in natural products chemistry (Fig. 11).

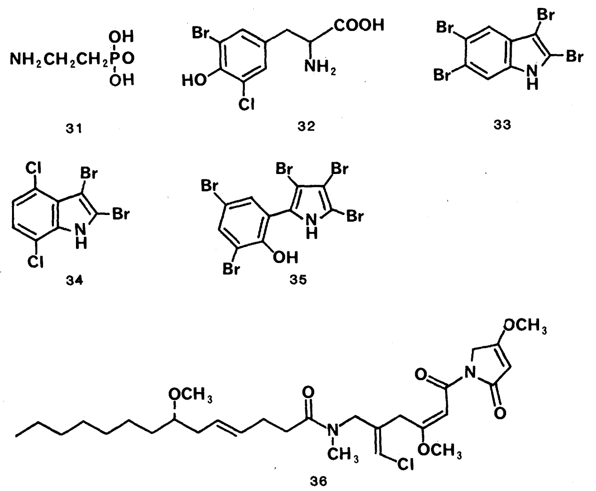


Fig. 12. Miscellaneous nitrogen-containing metabolites found in numerous marine organisms.

Nitrogen-containing metabolites. Nitrogen-containing compounds, which are not basic and not, therefore, classified as true alkaloids, are common substances in both the marine and terrestrial environments. In marine organisms a great degree of specificity has been found to exist in the production of unusual nitrogen-containing metabolites (Fig. 12). Many amino acids, for example, are considered as only occurring in the marine environment, and an interesting example is the aminophosphonic acid **31**, which contains an uncommon carbon-phosphorus bond (Fig. 12).This compound was isolated from the sea anemone *Anthopleura elegantissima* (*50*), and several closely related phosphonic acids have subsequently been isolated from other marine coelenterates (*3*). The widespread marine halogenation process is also represented in marine amino acid biosynthesis. The halogenated tyrosine derivative **32**, for example, was isolated from the marine mollusk *Buccinum undatum* (*51*). Numerous brominated tyrosine derivatives have also been found in various marine plants and animals (*3*).

Metabolism of the amino acid tryptophan is a process well known to generate the aromatic degradation product indole, and this metabolic pathway is useful in the taxonomic assignments of bacteria. This process seems to also occur in marine organisms, but indole residues are frequently found to have undergone further transformations via halogenation. Extreme examples of this are the isolations of polyhaloindoles, such as **33** and **34**, from the red seaweeds *Laurencia brongniartii* and *Rhodophyllis membranaceae* (*52, 53*).

Marine bacteria and blue-green algae (Cyanophyta) also appear to be engaged in biosynthetic activities that separate them from their terrestrial counterparts. Several species of marine bacteria, for example, are known to produce the highly brominated pyrrole derivative **35** (*54*), and while these bacteria appear to belong to the common genera *Pseudomonas* and *Chromobacter*, their terrestrial relatives do not appear to produce these or related compounds. The closely related marine blue-green algae have more recently been recognized to be prolific in their production of nitrogenous metabolites. Various strains of the very abundant marine cyanophyte *Lyngbya majuscula*, for example, have been found to produce complex compounds such as the unique chlorinated amide, malyngamide A (**36**) (*55*).

Conclusions

It can clearly be concluded that, while similarities exist, marine organisms have evolved secondary metabolic pathways quite distinct from their terrestrial counterparts. Marine and terrestrial plants and animals are not easily compared, however, as they generally represent different taxonomic groups. Many of the chemically distinctive marine plants—for example, the red and brown seaweeds—represent almost exclusively marine phyla. Similarly, chemically prolific marine invertebrates, such as sponges and corals, have limited numbers of freshwater relatives. Hence, the diversity recognized may reflect the differences in the abundant taxa within the marine environment.

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The Ice Lover: Biology of the Harp Seal (*Phoca groenlandica*)

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The exploitation of other animals by man has often proceeded undeterred by any knowledge of the exploited species' biology and ecology. Biological investigations now provide us with a more rational base for the exploitative and nonexploitative use of some species. In the case of certain marine species, it is now recognized that modification of certain environmental conditions affecting their habitat may also have a direct effect on ourselves. In this article we review the biology of one such species, the harp seal (*Phoca groenlandica*).

Migration of the Harp Seal

In the late summer, a slow gathering together and movement of harp seals begins in the high Arctic. The summering grounds are abandoned to the slowly encroaching Arctic ice, as the seals move south toward winter or spring breeding grounds. Estimates provided by the scientific community during the last decade suggest a world population of some 2.25 million to 3 million harp seals, divided among three separate breeding stocks (Fig. 1). In the Northeast Atlantic, 500,000 (*1*) to 800,000 (*2*) harp seals arrive each year in the White Sea (the East Ice) to breed and an estimated 100,000 to 150,000 (*3*) gather annually at breeding grounds in the Greenland Sea (the West Ice) between Jan Mayen and Svalbard. The harp seals in the Northwest Atlantic combine to form the largest stock, estimated variously to include fewer than 1 million (*4*) to 1.57 million (*3*) seals aged 1 year and older, producing some 250,000 (*5*) (1977 estimate) to 400,000 pups annually. Recent information suggests that these estimates may be somewhat low.

The differences between the estimates are associated with the lack of a solid data base. Critical to the attainment of a data base are accurate values for natural mortality rates and reproductive potential. Because estimates of natural mortality have varied (for animals 1 year and older, from 8 to 14 percent per year) a compromise figure of 10 percent now is being used (*6*). This will require further substantiation either by tagging and recapturing methods or by aerial censusing techniques. Attempts are currently being made to evaluate reproductive rates by studying seals killed by hunters and calculating percentages of successful fertilizations and subsequent implantations. Other variables are also integral in accurate population determination, such as density-dependent changes in maturation rates. As the scientific activity supporting the management strategies for the seal herds continues to increase, so presumably will the availability of more precise data on which to base population estimates.

Most of the Northwest Atlantic harp seals congregate to breed on the ice off the east coast of Newfoundland-Labrador (the Front). The remainder, the Gulf herd, gather to whelp near the Magdalen Islands in the Gulf of St. Lawrence. The genetic similarity between the harp seals at the Front and at the Gulf suggests that interbreeding occurs between these groups (*7*), and management in the Northwest Atlantic is currently based on the existence of one interbreeding stock. There is some suggestion, however, based on analyses of biocide residues in seal carcasses, that two units may exist, separated at least with regard to feeding habits (*8*, *9*). Certainty as to whether

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