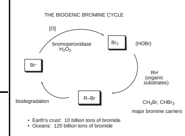
The diversity of naturally occurring organobromine compounds



Gordon W. Gribble

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, USA

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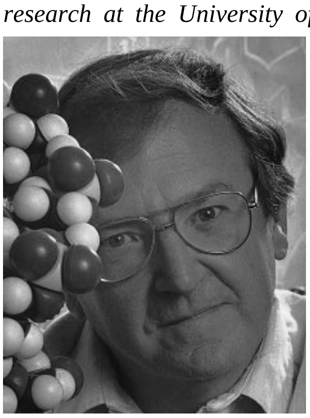
Of the nearly 3200 known naturally occurring organohalogen compounds, more than 1600 contain bromine. These organobromines, which range in structural intricacy from the simple but enormously abundant bromoform ($CHBr_3$) and bromomethane to the highly complex bryozoan bromine-containing indole alkaloids, are produced by marine and terrestrial plants, marine animals (sponges, tunicates, bryozoans, gorgonians, sea hares, nudibranchs), bacteria, fungi, some higher animals, and a few mammals including humans.

1 Introduction

Once considered to be even more bizarre than naturally occurring organochlorine compounds were natural organobromine compounds, and the few early examples were deemed artifacts of the isolation process. However, in recent years it has become clear that all types of organohalogen compounds are widely dispersed in nature and in many cases these natural organohalogens are more abundant than their anthropogenic counterparts.

Known natural organobromine compounds numbered about 60 in 1973, but in the intervening 25 years this number has grown to more than 1600. Whereas previous reviews have focused on natural organochlorine compounds or natural organohalogen compounds of all types,[1–3] the present article summarizes the most interesting and biologically important natural organobromine compounds, with an emphasis on recent examples. Most of the compounds discussed herein have not appeared in our comprehensive review,[1] and the exceptions can be found in references 1 or 3. Organobromine compounds from nearly every organic chemical class are known, and equally diverse are the organisms that produce these extraordinary chemicals.

Gordon W. Gribble was born in San Francisco, California, and received his undergraduate training at the University of California, Berkeley. He obtained his PhD at the University of Oregon with Lloyd J. Dolby in 1967, and did postdoctoral research at the University of California, Los Angeles, with Frank A. L. Anet. Professor Gribble has been at Dartmouth since 1968. In addition to his research program on heterocyclic chemistry and natural product synthesis, he has a fascination with naturally occurring organohalogen compounds, and he has published more than 170 papers in these areas. As an amateur winemaker, he also has a strong interest in the chemistry of wine and winemaking.

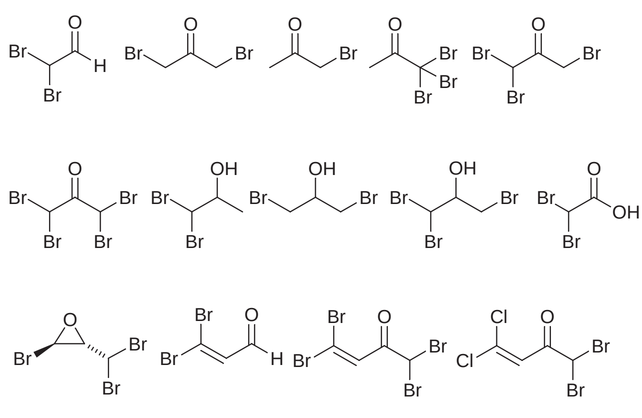


2 Sources and structures

2.1 Marine plants

Although the ocean contains much more chloride than bromide (19 000 *vs*. 65 mg L^{-1}), marine plants and animals apparently make use of the facile oxidation of bromide to bromine (or hypobromite) or biobromination processes. The result is an astounding array of organobromine metabolites in marine organisms.

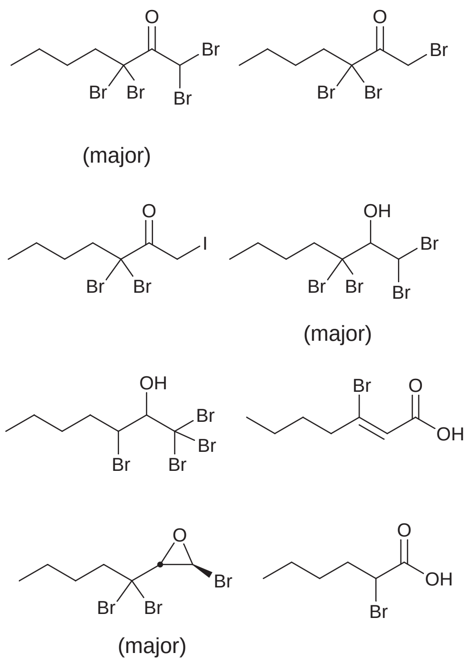
Numerous simple bromoalkanes have been isolated from marine algae: CH_3Br, CH_2Br_2, $CHBr_3$, CBr_4, CH_2ClBr, CH_2BrI, $CHCl_2Br$, $CHClBr_2$, $CHBr_2I$, $CHBrI_2$, CHBrClI, CH_3CH_2Br, $BrCH_2CH_2Br$, $BrCH_2CH_2I$, $CH_3CH_2CH_2Br$, $CH_3CH_2CH_2CH_2CH_2Br$, $Br_2C{=}CHCHCl_2$, $Br_2C{=}CHCHClBr$, $Br_2C{=}CHCHBr_2$, and $BrIC{=}CHCHBr_2$. Bromoform ($CHBr_3$) is particularly abundant in the marine environment and it comprises 80% by weight of 'limu kohu' (*Asparagopsis taxiformis*), the favorite edible seaweed of native Hawaiians prized for its flavor and aroma. Indeed, this one alga contains more than 50 organobromine compounds, many of which are anticipated to be powerful S_N2 alkylating agents and potential lachrymators (Scheme 1).



Scheme 1

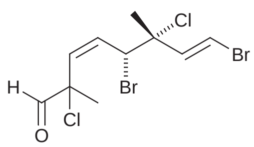
The red alga *Bonnemaisonia hamifera* contains more than 20 organobromine compounds, including several polybrominated ketones that are lachrymatory and account for the persistent sweet aroma of this seaweed (Scheme 2). It seems likely that these compounds may be a source of bromoform *via* a haloform cleavage reaction.

A myriad of brominated terpenes is known from marine plants, including bromine-containing monoterpenes, sesquiterpenes, diterpenes, and triterpenes. Nearly 50 *Laurencia* species of red algae have furnished hundreds of brominated

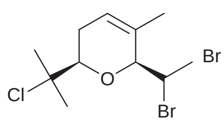


Scheme 2

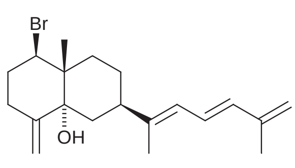
terpenes. Some recent examples of algae metabolites include **1** from the Portuguese red alga *Plocamium cartilagineum*,[4] pantoneurine A (**2**) from *Plocamium plocamioides*,[5] and anhydroaplysiadiol (**3**) from *Laurencia japonensis*.[6]



1



2 (pantoneurine A)

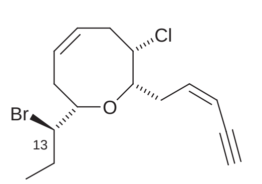


3 (anhydroaplysiadiol)

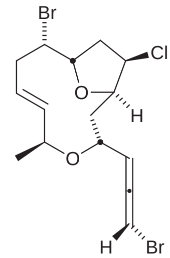
A large number of bromine-containing C_{15} acetogenins are also found in marine plants and in sea hares of genus *Aplysia* that feed on these seaweeds. For example, (3*Z*)-13-epipinnatifidenyne (**4**) has been isolated from *Laurencia claviformis* from Easter Island[7] and both *Laurencia obtusa* and the sea hare *Aplysia dactylomela* have yielded dactylallene (**5**).[8] The sea hare *Dolabella auricularia* contains the cytotoxic bromotriterpene aurilol (**6**),[9] and the Japanese sea hare *Aplysia parvula* contains aplyparvunin (**7**), a potent ichthyotoxin.

The causative agents of a red alga (*Gracilaria coronopifolia*) poisoning episode in Hawaii have been characterized as three manauealides, such as **8**.[10] These compounds may in fact be derived from an associated blue–green alga.

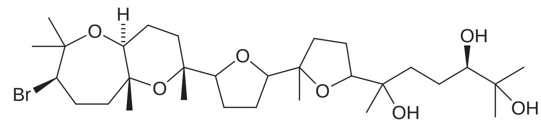
Blue–green algae (cyanobacteria) are a rich source of organobromine compounds. Recent examples include lyngbyaloside (**9**) from *Lyngbya bouillonii*,[11] grenadadiene (**10**) from *Lyngbya majuscula*,[12] and **11** from an Australian *Lyngbya* sp. Oscillariolide (**12**) is produced by the blue–green alga *Oscillatoria* sp., and the highly toxic aplysiatoxin (**13**), which is responsible for 'swimmer's itch' in Hawaii, is produced by *Lyngbya majuscula*, *Oscillatoria nigroviridis*, and *Schizothrix calcicola*. It is noted that **13** is the *para*-isomer of manauealide B (**8**).



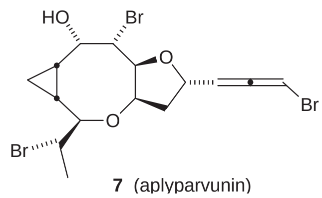
4 ((3*Z*)-13-epipinnatifidenyne)



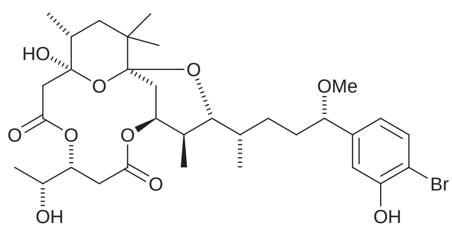
5 (dactylallene)



6 (aurilol)



7 (aplyparvunin)



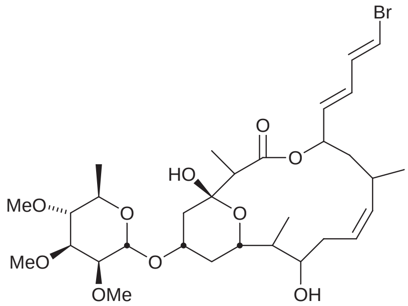
8 (manauealide B)

Both blue–green and red alga have yielded a wide range of bromoindoles. Thus, the blue–green alga *Rivularia firma* contains an array of bis-indoles, such as **14**, most of which are optically active, and the New Zealand red alga *Rhodophyllis membranacea* has yielded 2,3,7-tribromoindole and 2,3,4,7-tetrabromoindole. Other novel brominated heterocycles from red algae include the pyrone **15** from *Ptilonia australasica* and **16** from the Tasmanian *Phacelocarpus labillardieri*. At least 32 brominated furanones are produced by *Delisea* sp. red algae, some of which contain six bromines (*e.g.*, **17**).

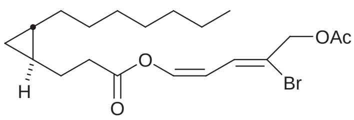
Bromophenols are widespread in the environment, which is not surprising given the alacrity with which phenols undergo electrophilic bromination. Lanosol (**18**) is found in many red and blue–green algae, and **19** has been isolated from the red alga *Rytiphlea tinctoria*. The related vidalols A and B (**20**) are found in the red alga *Vidalia obtusaloba*. The potent feeding deterrent avrainvilleol (**21**) is found in the tropical green alga *Avrainvillea longicaulis*, and *Avrainvillea rawsoni* has yielded the HMG-CoA reductase inhibitor rawsonol (**22**). Several bromine-containing phlorethols, *e.g.*, **23**, are produced by the brown alga *Cystophora congesta*.

2.2 Marine animals

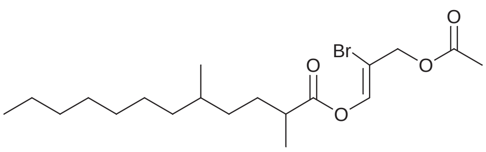
2.2.1 Sponges. Sponges, which are in the phylum Porifera, produce an astonishing array of organobromine metabolites, and only a few examples can be presented here. It should be noted that recent work has indicated that many sponge metabolites may actually be biosynthesized by bacteria or microalgae associated with the sponge.



9 (lyngbyaloside)



10 (grenadadiene)



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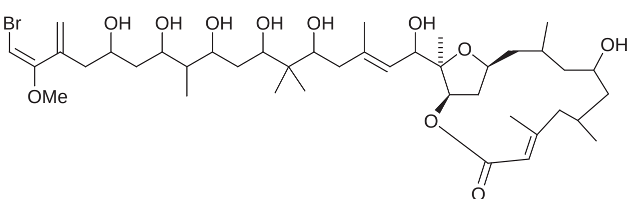
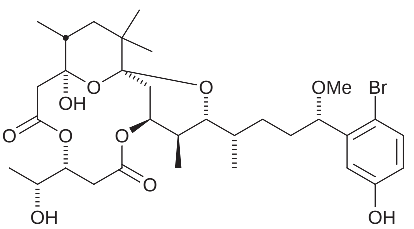
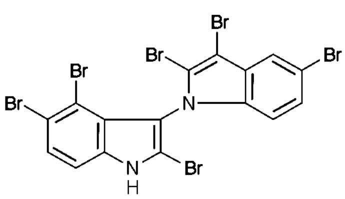


12 (oscillariolide)



13 (aplysiatoxin)



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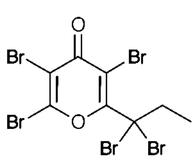

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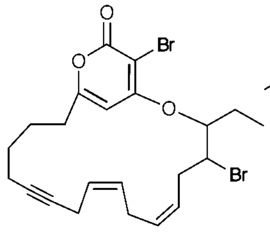

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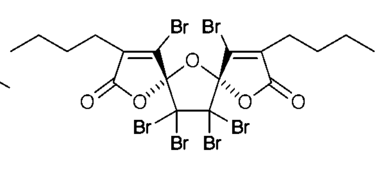

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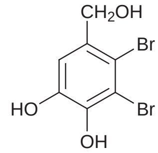
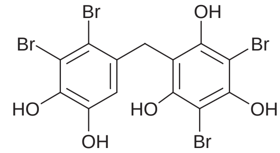
Several dozen brominated fatty acids are found in sponges. An Okinawan sponge *Xestospongia* sp. contains 14 bromine-containing fatty acids (*e.g.*, **24**),[13] and *Oceanapia* sp. has



18 (lanosol)



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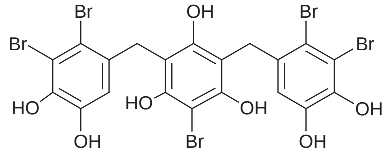
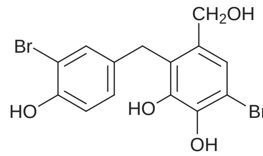
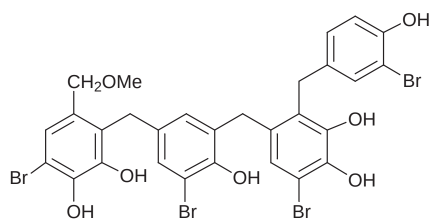


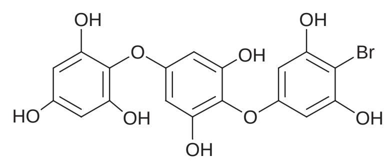
20 (vidalol B)



21 (avrainvilleol)

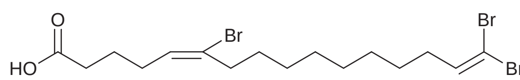


22 (rawsonol)



23

yielded **25** and **26**. The Pohnpei sponge *Dysidea fragilis* produces the novel antazirines, *e.g.*, **27**.[14]



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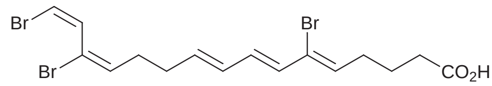

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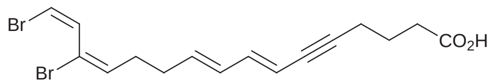

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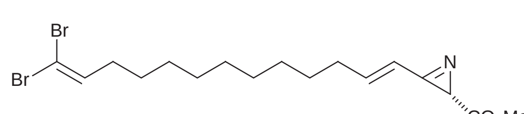
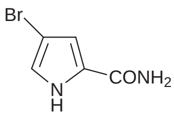


27 ((4*E*)-*S*-antazirine)

Like phenols, pyrroles and indoles readily undergo electrophilic bromination reactions and it is not surprising that dozens of such brominated metabolites are produced by sponges or their associated organisms. An *Agelas* sp. sponge contains

2,3-dibromopyrrole and the simple pyrroles **28** and **29** are found in the Red Sea sponge *Acanthella carteri*.[15] The Papua New Guinea sponge *Agelas nakamurai* has furnished **30** and **31**,[16] and longamide B (**32**) and clathramides C (**33**) and D (**34**) were isolated from the Bahamaian sponge *Agelas dispar*.[17] Spongiacidin A (**35**) is the latest in a series of related bromopyrrole alkaloids to be identified in a *Hymeniacidon* sp. sponge.[18]



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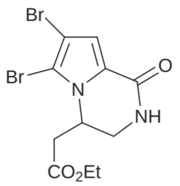
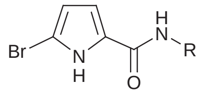
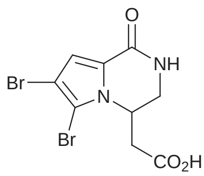


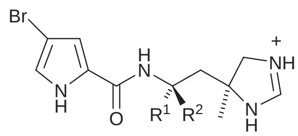
29 (hanishin)



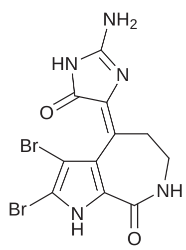
30 R = H
31 R = CH_2OCH_3



32 (longamide B)



33 R^1 = H, R^2 = CO_2^- (clathramide C)
34 R^1 = CO_2^-, R^2 = H (clathramide D)



35 (spongiacidin A)

Bromoindoles are also common metabolites of sponges. These vary from the relatively simple psammopemmins A–C (**36–38**) from the antarctic *Psammopemma* sp. to the complex dragmacidin E (**39**), from the Southern Australian deep water *Spongosorites* sp.,[19] and the New Caledonian *Orina* sp. metabolite **40**.

An *Echinodictyum* sp. sponge contains the brominated pyrrolopyrimidine **41**, and the incredibly complex palau'amines **42** and **43** are found in the Belau sponge *Stylotella aurantium*,[20] and calyculin J (**44**) has been characterized from the sponge *Discodermia calyx*.[21]

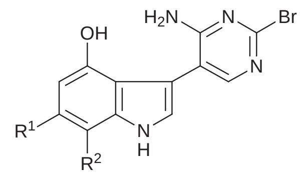
Bromophenols and related metabolites are also found in sponges and some examples are dibromoanisic acid **45** from *Psammaplysilla purpurea*, several polybrominated diphenyl ethers, *e.g*., **46–48**, from the Indonesian *Dysidea herbacea*, and the novel disulfate aplysillin A (**49**) from the deep water Grand Bahama Island *Aplysina fistularis fulva*.

Interestingly, two brominated dioxins, **50** and **51**, have been tentatively characterized from the sponge *Tedania ignis*, along with the diphenyl ether **52**, a possible biogenetic precursor.

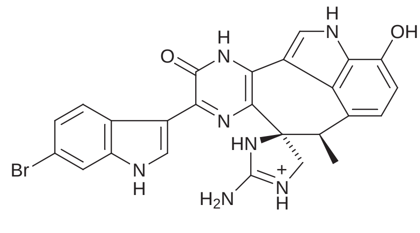
Being phenolic, the amino acid tyrosine is readily biobrominated and numerous such metabolites are found in sponges. Examples include the simple brominated tyrosines **53–56** and the 'transformed' tyrosines **57–59**. Metabolite **57** has been found in at least ten sponges. A recent example is **60** found in *Psammaplysilla purpurea*.[22]

More complex brominated tyrosine derivatives include lipopurealin A (**61**) from *Psammaplysilla purea*, pseudoceratininine C (**62**) from *Pseudoceratina verrucosa*, and bastadin-1 (**63**) from the Queensland sponge *Ianthella basta*. Some 20 bastadins, most of which are cyclic, have been identified.

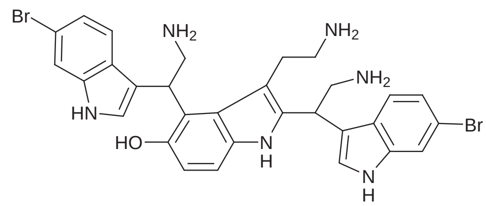
Several bromine-containing amino acids and peptides have been discovered in sponges. In particular 6-bromotryptophan



36 R^1 = R^2 = H (psammopemmin A)
37 R^1 = H, R^2 = Br (psammopemmin B)
38 R^1 = Br, R^2 = H (psammopemmin C)



39 (dragmacidin E)



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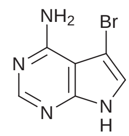

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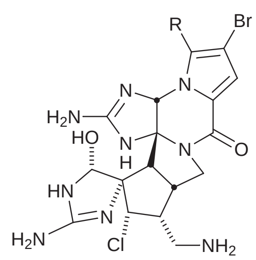
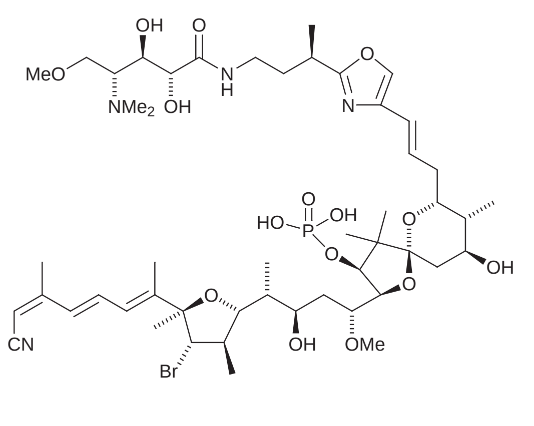


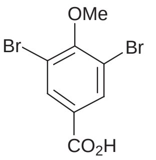
42 R = H
43 R = Br



44 (calyculin J)

units appear in several sponge metabolites, such as celenamide E (**64**) from the Patagonian sponge *Cliona chilensis*,[23] and cyclocinamide A (**65**) from *Psammocinia* sp. Some 2-bromotryptophan metabolites, such as jaspamide (**66**) isolated from several sponges, are also known.

Several bromotyrosine and bromophenylalanine cyclic peptides are known from sponge sources. Geodiamolide I (**67**) is found in the sponge *Geodia* sp. and theopalauamide (**68**) is



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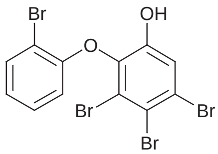

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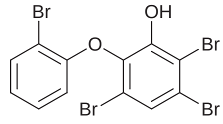

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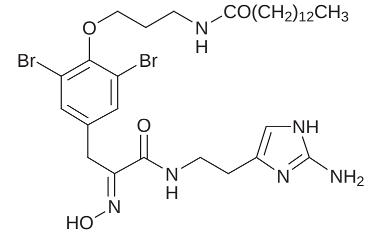
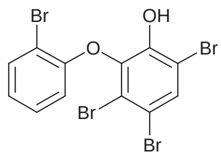


61 (lipopurealin A)



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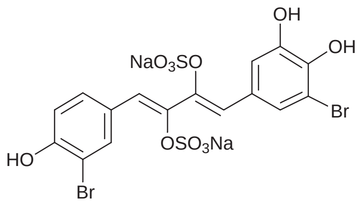
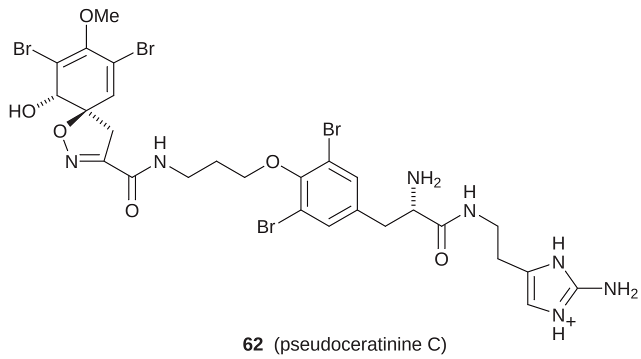
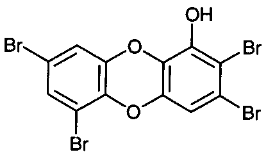


49 (asplysillin A)



62 (pseudoceratinine C)



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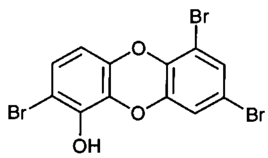

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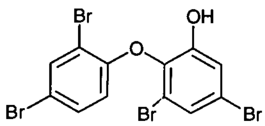

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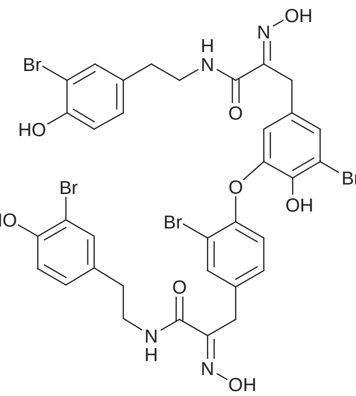
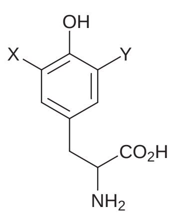


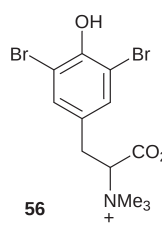
63 (bastadin-1)

produced by filamentous bacteria associated with the lithistid sponge *Theonella swinhoei*.[24]

2.2.2 Ascidians. Ascidians, also known as tunicates or sea squirts, belong to the subphylum Urochordata (or Tunicata) of the phylum Chordata. They are filter feeders like sponges and may be solitary or colonial. Since ascidians are immobile they rely heavily on chemical defense for survival. The Caribbean tunicate *Eudistoma olivaceum* produces at least 15 brominated carbolines, *e.g.*, eudistomin A (**69**), and the New Caledonian tunicate *Pseudodistoma arborescens* has yielded several related compounds, e.g., arborescidine B (**70**). The novel quinazolinedione **71** is found in *Pyura sacciformis* and the nucleoside **72** was extracted from *Didemnum voeltzkowi*. Meridianins B–E (**73**–**76**) were recently found in *Aplidium meridianum*,[25] as was the simple phenethylamine **77** from the New Zealand ascidian *Cnemidocarpa bicornuta*.[26]



53 X = Br, Y = H
54 X = Y = Br
55 X = Br, Y = Cl



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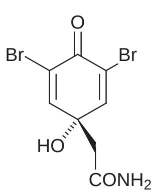

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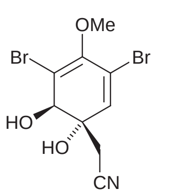
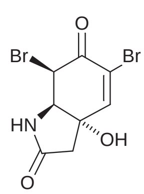


58
((+)-aeroplysinin 1)



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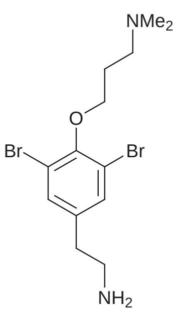
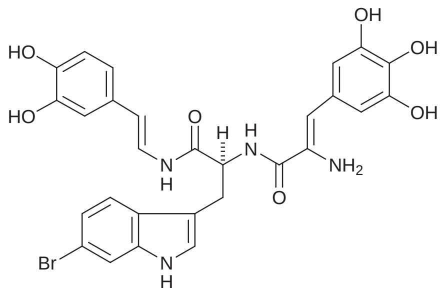


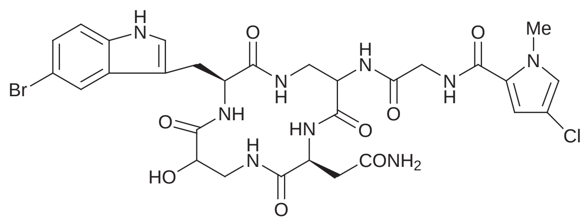
60

The novel bis-indole alkaloids, rhopaladins A (**78**) and C (**79**) are found in the tunicate *Rhopalaea* sp., and the colonial *Ritterella rubra* has yielded several brominated rubrolides, e.g., **80**. The related cadiolides A (**81**) and B (**82**) are produced by an Indonesian *Botryllus* ascidian.[27] The Western Australian *Aplidiopsis* sp. contains the unusual adenine aplidiamine (**83**).[28]

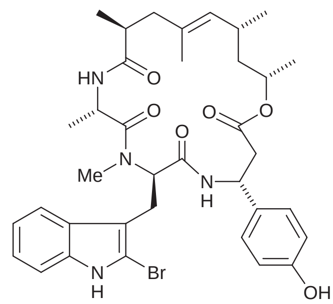
2.2.3 Nudibranchs and other molluscs. Nudibranchs—'sea slugs'—are brightly colored animals in the phylum Mollusca (class Gastropoda), and, like sea hares (*vide supra*), they can apparently 'steal' their chemical weapons by feeding on sponges and, in some cases, on smaller nudibranchs. This gives new meaning to the term 'lazy slug'! For example, the predatory *Tambje eliora* and *Tambje abdere* prey upon and confiscate from the bryozoan *Sessibugula translucens* the chemical defensive and fish antifeedant tambjamine B (**84**) and related compounds.



64 (celenamide E)



65 (cyclocinamide A)



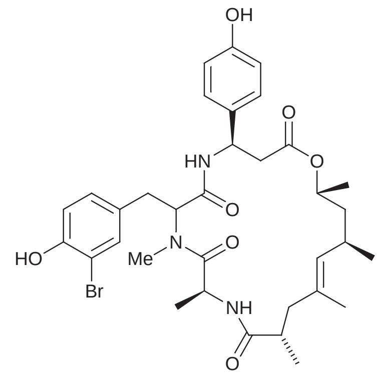
66 (jaspamide)

One of the first naturally occurring organobromine compounds to be characterized was the ancient Egyptian dye Tyrian Purple (**85**) which is found in several Mediterranean molluscs. The muricid gastropod *Drupella fragum*, which preys on corals, contains the brominated indoles **86–88**, which are potent antioxidants. The venomous cone snails *Conus imperialis* and *Conus radiatus* produce three peptides which contain 6-bromotryptophan.

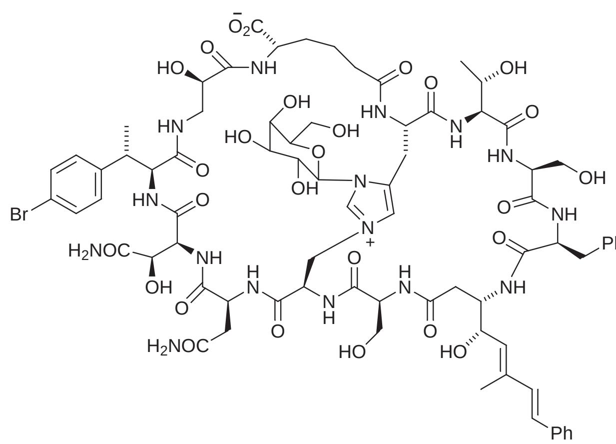
2.2.4 Bryozoans. Probably the least attractive animals in the ocean are the bryozoans (phylum Bryozoa = Ectoprocta). But these 'moss animals' are unsurpassed in their ability to construct complex organobromine compounds. Their synthetic virtuosity is quite fantastic (*cf*. **96** and **97**). The bryozoan *Bugula dentata* produces several brominated tambjamines similar to **84**, *Amathia convoluta* has yielded several compounds of the types **89** and **90**, and the Atlantic *Amathia alternata* contains several bromotryptamine amides, *e.g.*, **91**. The simple 7-bromoquinoline **92** is produced by *Flustra foliacea*. The novel euthyroideones A–C (**93–95**) were recently identified as metabolites of *Euthyroides episcopalis*.[29]

The bryozoan *Chartella papyracea* produces an array of stunningly complex metabolites, exemplified by chartellamide B (**96**), and *Securiflustra securifrons* contains at least seven intricate securamines, *e.g.*, **97**. Since only a handful of the 4000 species of bryozoans have been examined for their chemical content, it is certain that a treasure trove of novel complex brominated natural products is awaiting discovery from these moss animals.

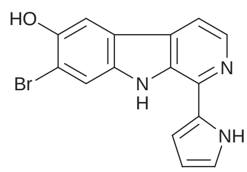
2.2.5 Acorn worms. Although rarely seen by the diver or snorkeler, marine acorn worms (phylum Hemichordata) produce a tremendous quantity of bromine-containing compounds, usually simple phenols and indoles. The Floridian *Ptychodera bahamensis* produces ten different brominated phenols, *Balanoglossus biminiensis* produces up to 15 mg per animal of 2,6-dibromophenol, and *Phoronopsis viridis* contains 2,4,6-tribromophenol. *Thelepus setosus* has furnished thelephenol (**98**),



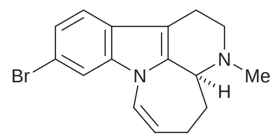
67 (geodiamolide I)



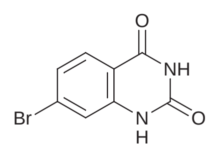
68 (theopalauamide)



69 (eudistomin A)



70 (arborescidine B)



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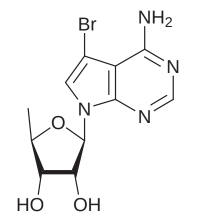

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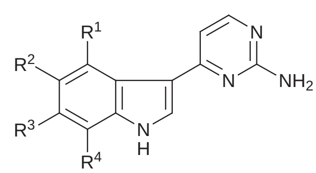
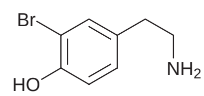
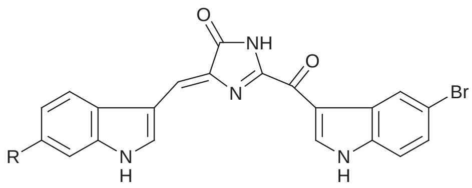


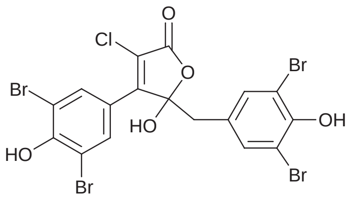


77

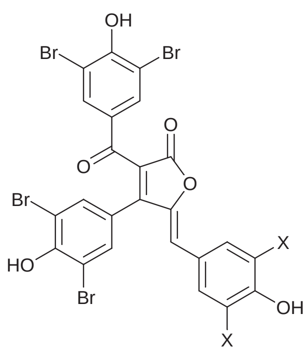
73 R^1 = OH, R^2 = R^4 = H, R^3 = Br (meridianin B)
74 R^1 = R^3 = R^4 = H, R^2 = Br (meridianin C)
75 R^1 = R^2 = R^4 = H, R^3 = Br (meridianin D)
76 R^1 = OH, R^2 = R^3 = H, R^4 = Br (meridianin E)



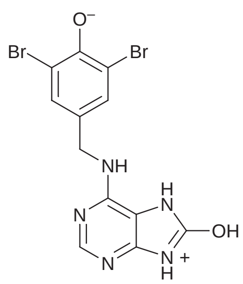
78 R = OH (rhopaladin A)
79 R = H (rhopaladin C)



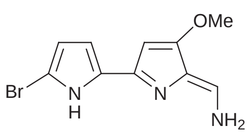
80 (rubrolide H)



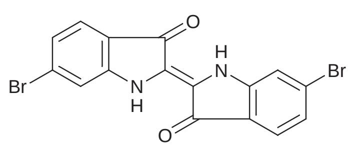
81 X = H (cadiolide A)
82 X = Br (cadiolide B)



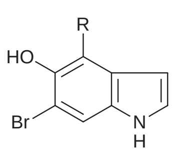
83 (aplidiamine)



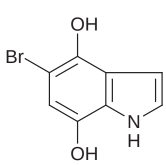
84 (tambjamine B)



85 (Tyrian Purple)



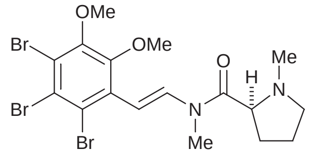
86 R = H
87 R = OH



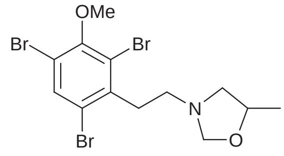
88

99 and thelepin (**100**). The latter compound has antifungal activity comparable to the drug griseofulvin, which is a naturally occurring organochlorine compound. The octabromo metabolite **101** is the major compound found in *Ptychodera flava*, and 4-bromophenol is the major metabolite in *Notomastus lobatus*. Epoxide **102**, which was isolated from a Maui *Ptychodera* sp., is highly cytotoxic. *Polyphysia crassa* contains 2,3,4-tribromopyrrole (**103**). *Ptychodera* and *Glossobalanus* spp. also contain 3-bromoindole, 3,6-dibromoindole, 4,6-dibromoindole, 3,5,7-tribromoindole, and 3,4,6-tribromoindole.

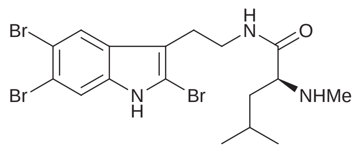
2.2.6 Corals. Although a few bromine-containing compounds have been isolated from hard corals, most of these metabolites are found in octocorals (gorgonians and soft corals). The stony coral *Tubastraea micrantha* has yielded 3-bromobenzoic acid (**104**), bromoanthraquinone **105**, and tubastraine



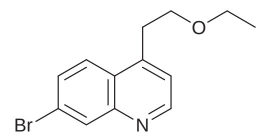
89 (amathamide G)



90 (convolutamine D)



91 (alternatamide B)



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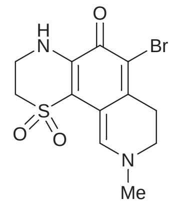
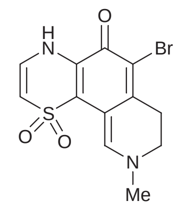
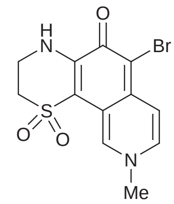


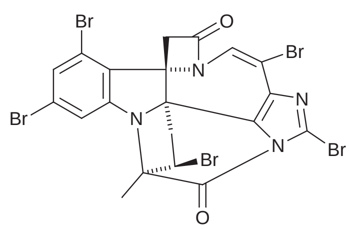
93 (euthyroideone A)



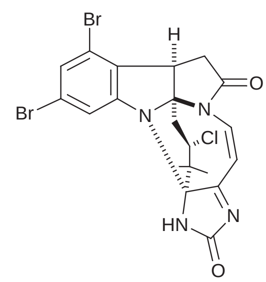
94 (euthyroideone B)



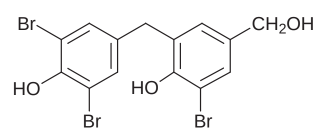
95 (euthyroideone C)



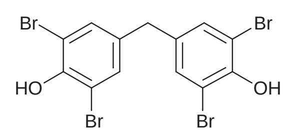
96 (chartellamide B)



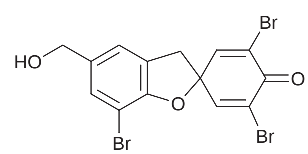
97 (securamine E)



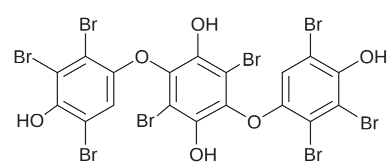
98 (thelephenol)



99



100 (thelepin)



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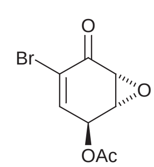

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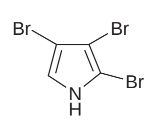
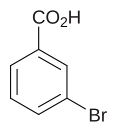
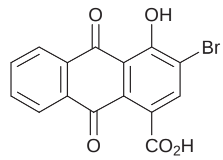


103

(**106**). Interestingly, this coral is avoided by the coral-destroyer Crown-of-Thorns seastar (*Acanthaster planci*). Bromoazulenes **107** and **108** are found in a deep-sea gorgonian. Both the anemone *Condylactis gigantea* and the zoanthid *Palythoa caribaeorum* have yielded fatty acid **109**, and the stolonifer *Clavularia viridis* produces the bromoprostaglandin bromovulone I (**110**).



104



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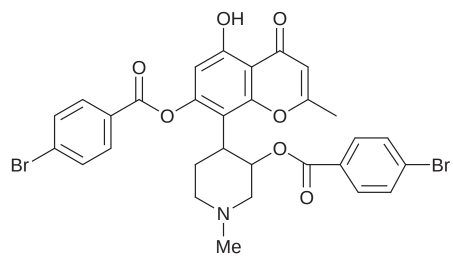
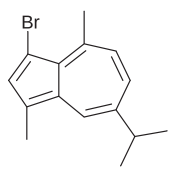


106 (tubastraine)



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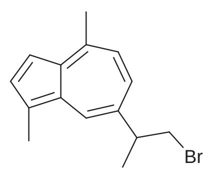
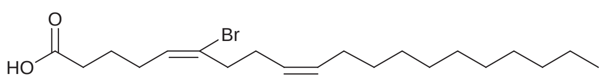


108 (ehuazulene)



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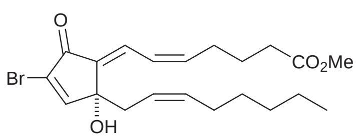
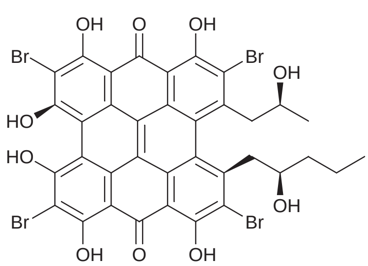


110 (bromovulone I)

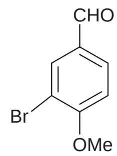
The deep-water (520 m) crinoid *Gymnocrinus richeri* contains five novel gymnochromes, e.g., **111**.



111 (gymnochrome A)

2.3 Fungi and lichen

Although fungi produce many more organochlorine compounds than organobromine compounds, several interesting examples of the latter are known. The wood-rotting fungus *Lepista nuda* (common wood blewitt) produces the bromophenols **112–114**.[30] These compounds represent the first time natural brominated low-molecular weight compounds have been found in the soil. A *Fusarium* sp. marine fungus, which may be *Fusarium heterosporum*, from the Bahamas has yielded the novel sesterterpene neomangicol B (**115**).[31] The corresponding chloro compound was also isolated. The fresh water lichen *Acorospora gobiensis* contains the novel fatty acids **116** and **117**.[32]



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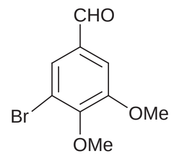

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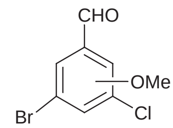

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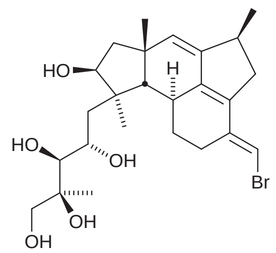
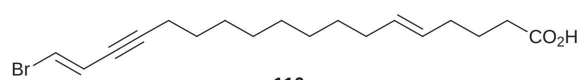


115 (neomangicol B)



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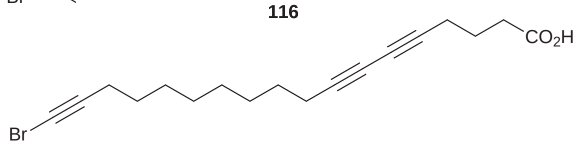


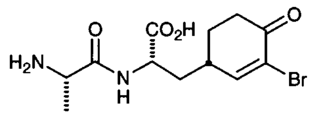
117

2.4 Bacteria

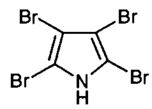
As with fungi, most of the bacterial-derived organohalogen metabolites contain chlorine rather than bromine. The common *Bacillus subtilis* has furnished the novel dipeptide bromotetaine (**118**), and the marine bacterium *Chromobacterium* sp. contains 2,3,4,5-tetrabromopyrrole (**119**), bipyrrole **120**, and **121**. Marinone (**122**) and napyradiomycin B3 (**123**) are both produced by bacteria, the latter from *Chainia rubra*. The walnut pathogen *Xanthomonas juglandis* produces several novel brominated aryl polyene esters, a cleavage product of which, xanthomonadin I (**124**), has been characterized.

2.5 Plants

Hundreds of chlorine-containing compounds have been isolated from terrestrial plants, but only a few bromine-containing examples are known. One very surprising example is bromomethane, which is produced in significant quantities by several terrestrial plants (rapeseed, mustard, cabbage, Chinese cabbage, broccoli, pak-choi, alyssum, wild mustard, turnip, radish) from natural bromide in the soil. The amounts of bromomethane range from 18–36 ng g^{-1} plant material per day.[33] The authors conclude that this source of natural bromomethane contributes



118 (bromotetaine)



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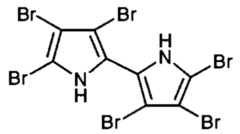

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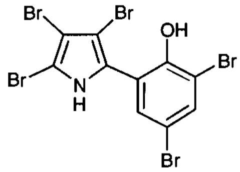

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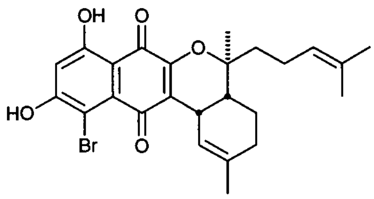
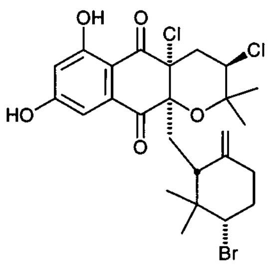
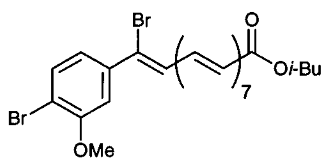


122 (marinone)





124 (xanthomonadin I)

123 (napyradiomycin B3)

significantly to the overall atmospheric concentration of bromomethane.

Bromobenzene (**125**) has been detected in the volatiles of oakmoss, the Thai plant *Arundo donax* produces **126**, which is an antifeedant against weevils, and the lignan **127** is found in *Gmelina arborea*. The seed oil of *Eremostachys molucelloides* contains the brominated stearic acids **128** and **129**.

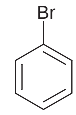
2.6 Insects

A few chlorinated insect pheromones are known but the only brominated insect compounds appear to be proteins in the cuticle of locusts that contain mono- and dibromotyrosine (**53** and **54**).

2.7 Mammals

The only reported bromine-containing compound in mammals is the bromo ester **130** found in the cerebrospinal fluid of normal humans and the cat and rat. This compound is reported to be a very effective inducer of REM (rapid-eye-movement) sleep and may play an important role in inducing the sleep phenomenon. Obviously, such a startling discovery needs to be corroborated.

Since our white blood cells use bromide in combination with myeloperoxidase to fight infection as part of the immune system, it is only a matter of time until the products of this biobromination reaction are identified. Such biodisinfection byproducts have been isolated that contain chlorine (*e.g.*, chlorotyrosine).



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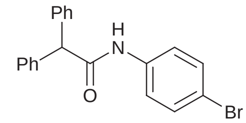

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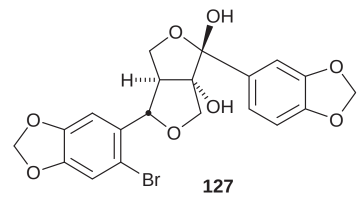
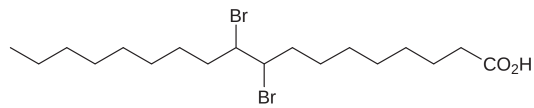
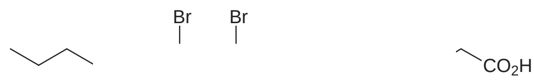
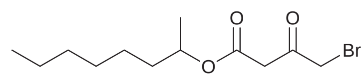


127



128

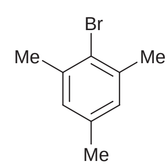




130

2.8 Abiogenic sources

Combustion and geochemical events are known to produce a wide range of organohalogen compounds and a few of these contain bromine. For example, bromomesitylene (**131**) and 1,1,2,2-tetrabromoethane (**132**) have been found in carbonaceous black shales, perhaps as the result of the decay of ancient plant material at the high temperatures and pressures characteristic of geological processes. In fact, benzene is the major organic component of the Kamchatka volcanoes in this same area of Asia.



131

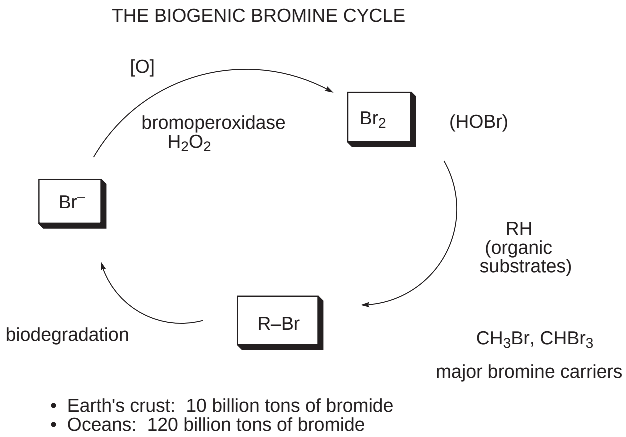
$Br_2CHCHBr_2$

132

Bromomethane, along with chloromethane and iodomethane, were reported to be present in the gases from the 1980 eruption of Mt. St. Helens. Biomass burning is estimated to yield bromomethane to the extent of 20 000–50 000 tons year^{-1}, or about 30% of the stratospheric bromine budget.[3] Marine sediments from the Baltic Sea reveal the presence of high molecular weight brominated materials, and bromine-containing units of 4-ethoxybenzoic acid have been isolated.

3 Biobromination

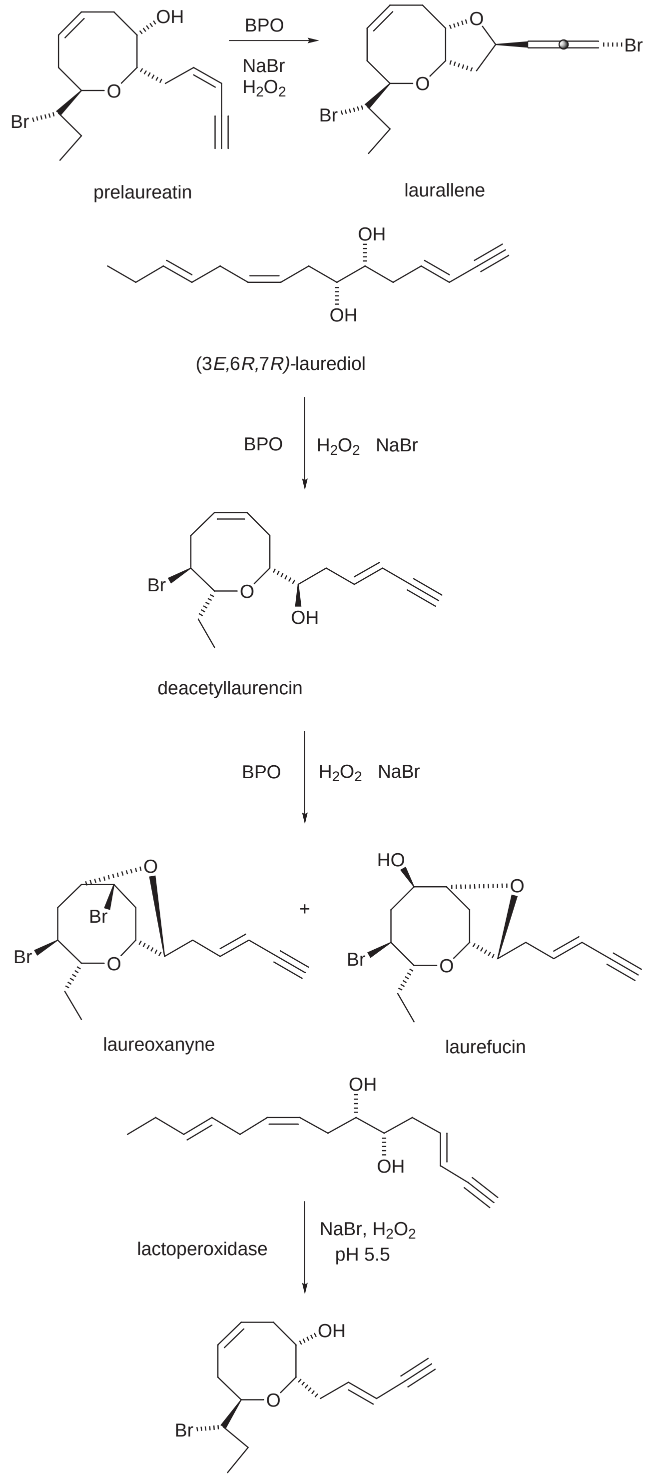
The sequence of events leading from natural bromide to organobromine compounds is on a firm footing and the bromine cycle is illustrated in Scheme 3.



Scheme 3

The bromoperoxidase (BPO) enzyme(s) responsible for the oxidation of bromide to bromine (hypobromite) or to an enzyme-bound bromine complex have been isolated from nearly 100 species of marine algae and phytoplankton, terrestrial lichen, bacteria, an acorn worm, and a marine annelid. Chloroperoxidase and other peroxidases also have the ability to oxidize bromide. For example, chloroperoxidase is the principal enzyme involved in the production of bromophenols in the acorn worm *Notomastus lobatus*. Two BPO genes from *Streptomyces aureofaciens* have been cloned and sequenced, and one of these BPO enzymes has been characterized by X-ray crystallography.

The production of $CHBr_3$, $CHBr_2Cl$, $CHBrCl_2$, and CH_2Br_2 has been observed both in batch culture and directly from the red alga *Meristiella gelidium* and from unialgal cultures of marine phytoplankton. The release of these bromomethanes by 11 species of macroalgae both in the laboratory and from rock pools under natural conditions has been observed. A recent study of several phytoplankton cultures (*Chaetoceros calcitrans*, *Isochrysis* sp., *Porphyridium* sp., *Synechococcus* sp., *Phaeodactylum tricornutum*, *Tetraselmis* sp., *Prorocentrum* sp., *Emiliania huxleyi*, and *Phaeocystis* sp.) in the laboratory found that bromomethane is produced by all but two of these cultures.[34] Several biomimetic syntheses of *Laurencia* sp. red algae metabolites using BPO are shown in Scheme 4.



Scheme 4

4 Quantities

The current best estimate of the atmospheric budget of bromomethane puts the marine emissions at 56 000 tons year^{-1}, and biomass burning, as shown by direct measurement, may produce 20 000–50 000 tons year^{-1}.[35] The marine production of bromoform is much larger than that of bromomethane, and is estimated at 1–2 million tons year^{-1}. Macroalgae may contribute an estimated 200 000 tons year^{-1}, and Arctic ice microalgae may contribute an estimated maximum of 70 000 tons year^{-1}.

Another major source of organobromine compounds—yet to be explored in detail—is the high molecular weight matter in marine sediments as mentioned earlier. These studies indicate that there is large-scale bromination of high molecular weight organic matter in the marine environment.

A detailed study of the acorn worm *Ptychodera flava* has established that the annual fecal secretion of the 64 million worms living in a one-square kilometer habitat on Okinawa contains four tons of organic matter (primarily bromophenols and bromoindoles, *vide supra*). If one extrapolates this quantity to the world's acorn worm population, then an enormous quantity of organobromine compounds is biosynthesized and excreted by these acorn worms. A similar study of the Floridian *Ptychodera bahamensis* acorn worm estimated an annual output of 0.5–1.3 tons per kilometer of coastline. A study of the brown alga *Ascophyllum nodosum* has determined that two tons of HOBr is produced annually by this seaweed along a 30-kilometer stretch of dike in the Netherlands.

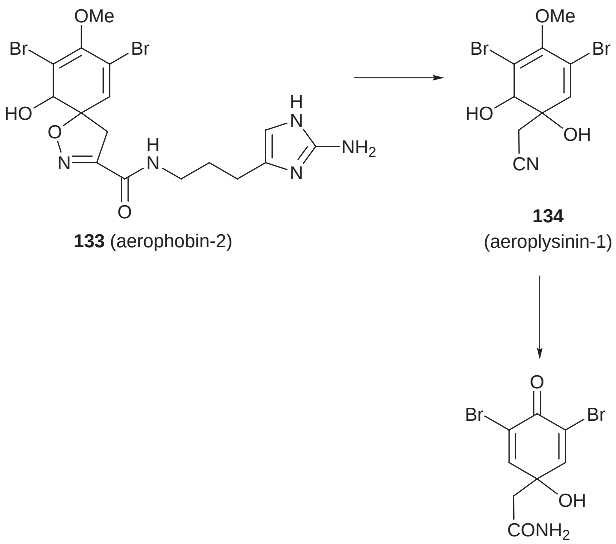
5 Biodegradation

An essential component of the natural bromine cycle (Scheme 3) is the recycling of organobromine compounds when an organism dies. Many studies have shown that microbial systems can biodegrade bromoalkanes, bromophenols, and other organobromine compounds.[1,36] The acorn worm *Amphitrite ornata* possesses a dehaloperoxidase capable of catalyzing peroxidedependent dehalogenation reactions of bromophenols.[37] Bromomethane and the mixed bromochloromethanes are degraded by *Methylosinus trichosporium* to carbon dioxide and bromide, and bromomethane is degraded anaerobically in salt marsh sediments to form methanethiol. Bromomethane is rapidly and irreversibly removed from the atmosphere by soil bacteria, representing a large and previously unrecognized natural sink for bromomethane.

6 Function

Although it is commonly assumed that many organobromine metabolites serve in a chemical protection role for the organism (antibacterial, antifungal, antifeedant, antifouling agent, etc.), this function has only been established in a few cases.

The brominated compounds in the sponge *Verongia aerophoba* seem to prevent overgrowth by fouling organisms such as barnacles. Thus, when the cells of the sponge are perturbed, the inactive **133** is enzymatically transformed into the active repellent compounds **134** and **135**.



133 (aerophobin-2)

134 (aeroplysinin-1)

135

Another possible role for peroxide-induced bromination reactions (*e.g.*, Scheme 4) in marine algae may be to scavenge excess hydrogen peroxide during oxidative stress. The green seaweed metabolite avrainvilleol (**21**), which is a potent feeding deterrent to reef fish, is sequestered by the ascoglossan gastropod *Costasiella ocellifera* and used as a defense against predatory fish.

The role of the simple bromoalkanes, such as bromomethane, may be to recycle bromide/bromine between the ocean, atmosphere, and land.

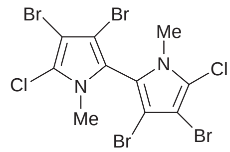
It seems clear that the investment in genetic energy required to code for the enzymes necessary to synthesize some of the incredibly complex organobromine compounds that we have seen must have a specific purpose for the survival of the organism.

7 Future outlook

Most of the more than 1600 known naturally occurring organobromine compounds are found in marine organisms. Thus, the fact that relatively few of the extant 500 000 species of marine plants, animals, and bacteria have been studied for their chemical content portends that fantastic chemical riches await the natural products chemist! And, many of these yet to be discovered compounds will contain bromine.

The exploration of marine bacteria and fungi is only beginning and the role of bromide in the mammalian immune system is a fascinating area of research.

The recent discovery of four novel polybrominated bipyrroles, possibly **136**, in seabirds and their eggs, which is certainly of marine origin,[38] may mean that the claim of alleged anthropogenic organobromine compounds in whales, dolphins, seals, and other large marine animals is in reality indicative of new naturally occurring organobromine compounds.



136 (possible)

8 Concluding remarks

Although the field of naturally occurring organochlorine compounds is more mature than that of organobromine compounds, the latter area of natural products is rapidly evolving and the number of such compounds may surpass the 1800 mark by the turn of the century. Moreover, as our understanding of the function and toxicity of natural organobromines continues to unfold, we will be able to make more informed decisions regarding the use of anthropogenic organobromine compounds in society, several of which (bromomethane, brominated phenols, 1,2-dibromoethane, bromoform, and a few others) are the identical chemicals that nature has used for probably millions of years.

As novel natural organobromine compounds are discovered and evaluated for their biological activity, it seems certain that new antibiotics, anticancer and antifungal agents, and other important medicinal drugs will be discovered.

9 Acknowledgements

The author wishes to thank the environment activist organization Greenpeace for their role in this research. Were it not for their crusade against chlorine and bromine and their accusation that organobromine (and organochlorine) compounds are inherently unnatural (‘The Product is the Poison—The Case for a Chlorine Phase-Out’, A Greenpeace Report by J. Thornton, 1991), the research in the present article and in references 1–3 would not have been pursued.

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