

Naturally Occurring Organohalogen Compounds†

GORDON W. GRIBBLE*

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

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Introduction

Once considered to be rare chemical freaks of nature or artifacts formed during isolation, naturally occurring organohalogen compounds in recent years have assumed an important role both in the field of natural products per se and in the drama of global halogen burdens vis-à-vis their anthropogenic counterparts.^{1–3} The number of natural organohalogen compounds has multiplied about 250 times in the past 40 years—from a dozen in 1954⁴ to more than 2900 as of December 1997.^{1,5} This explosion of information parallels the general resurgence of natural products discovery that is due to improved collection and isolation methods, the development of 2D NMR spectroscopy, advances in mass spectrometry, new and more sensitive bioassays, and the perpetual need to find new medicinal leads.

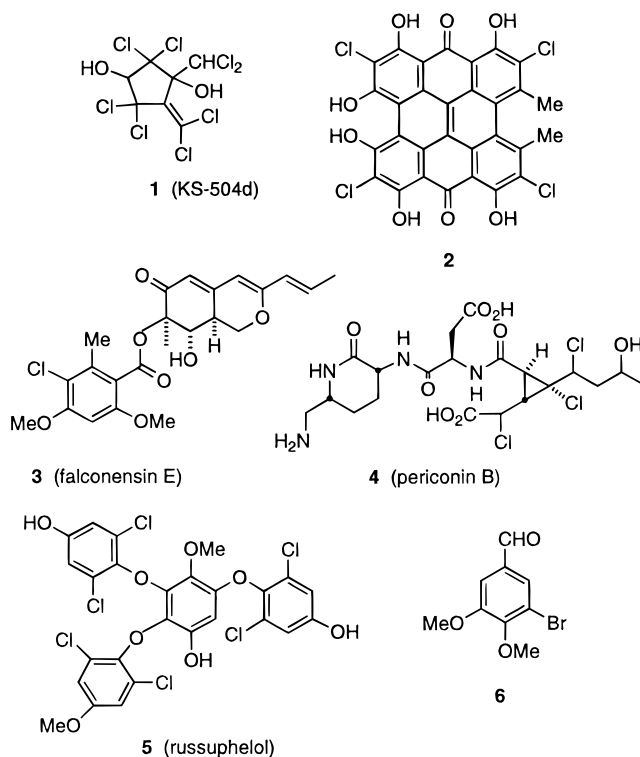
Since it is obviously impractical to describe all natural organohalogens in this Account, only the most interesting and biologically important compounds will be presented, with emphasis on recent examples. Most of the compounds chosen herein have not appeared in our comprehensive review,¹ and the few exceptions can be found in ref 1. Halogen-containing examples from nearly every organic chemical class are known; equally diverse are the organisms that biosynthesize these structurally and biologically extraordinary chemicals.

Sources and Structures

Fungi and Lichen. Fungi and lichen, the latter of which are symbionts consisting of a fungus and an alga living together in a united structure, are a bountiful source of novel organochlorine metabolites, and the earliest examples of natural chlorine-containing metabolites include fungal metabolites such as griseofulvin, chloramphenicol,

aureomycin, caldariomycin, sporidesmin, ochratoxin A, and others.

The fungus *Mollisia ventosa* produces several organochlorine calmodulin inhibitors such as KS-504d (**1**), which contains 70% chlorine by weight! The lichen *Nephroma laevigatum* has yielded **2**,⁶ and falconensin E (**3**) from the Venezuelan soil fungus *Emericella falconensis* is one of several chlorinated azaphilones that have potent inhibitory activity against diacylglycerol acyltransferase and acyl-CoA: cholesterol acyltransferase.⁷ The fungal pathogen *Periconia circinata*, which causes “milo disease” of grain, produces periconin B (**4**) as one of four chlorinated metabolites.⁸ The mushroom *Russula subnigricans* contains a number of chlorohydroquinones (e.g., russuphelol (**5**)),⁹ and the wood-rotting forest fungus *Lepista nuda* produces 14 organohalogens including several brominated phenols (e.g., **6**).¹⁰



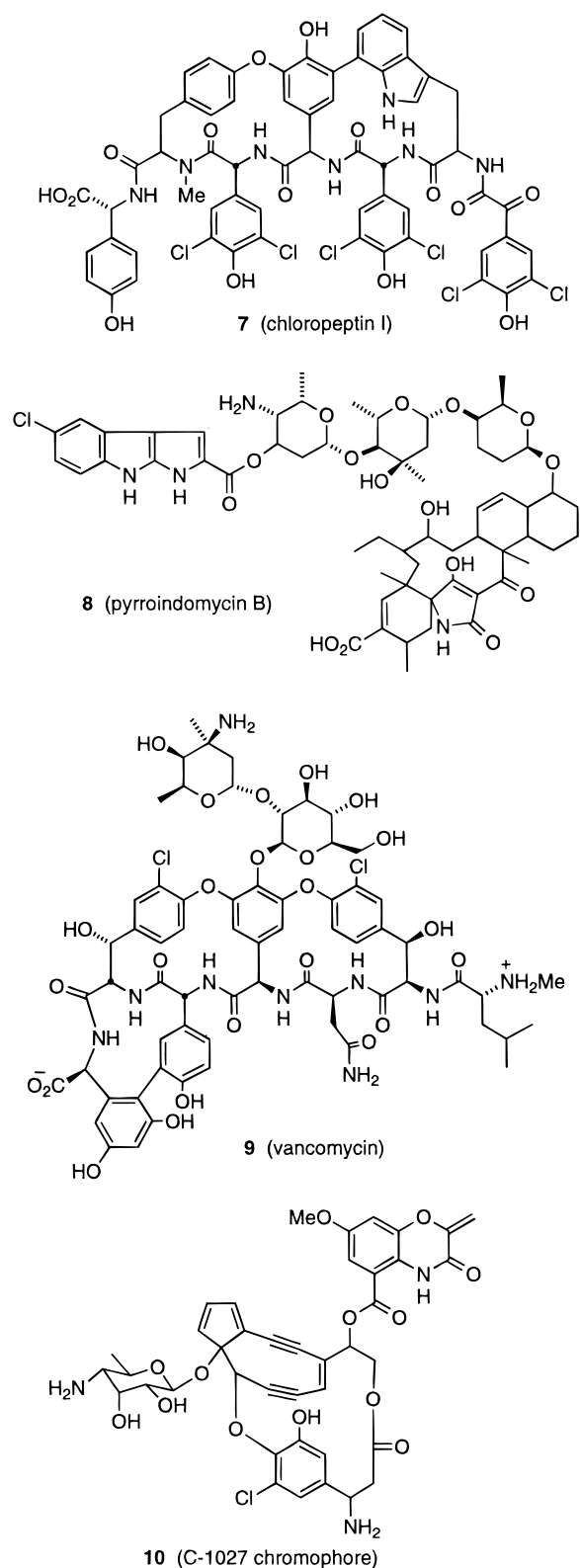
Bacteria. *Streptomyces* sp. bacteria produce an incredible array of complex metabolites, many of which contain halogens. Chloropeptin I (**7**), which inhibits HIV replication, is produced by *Streptomyces* sp. WK-349,¹¹ and *Streptomyces rugosporus* has furnished the antibiotic pyrroindomycin B (**8**), which is active against both penicillin-resistant *Staphylococcus aureus* and vancomycin-resistant Enterococci.¹² The glycopeptide antibiotic vancomycin (**9**), which is produced by *Amycolatopsis orientalis*, has been used for 40 years to treat life-threatening infections. More than 40 *Streptomyces* species have

† Offered in memory of Professor Karen E. Wetterhahn, 1948–1997, revered colleague, respected teacher and administrator, and eminent researcher, who left us too soon.

* E-mail: grib@dartmouth.edu. Fax: (603) 646-3946.

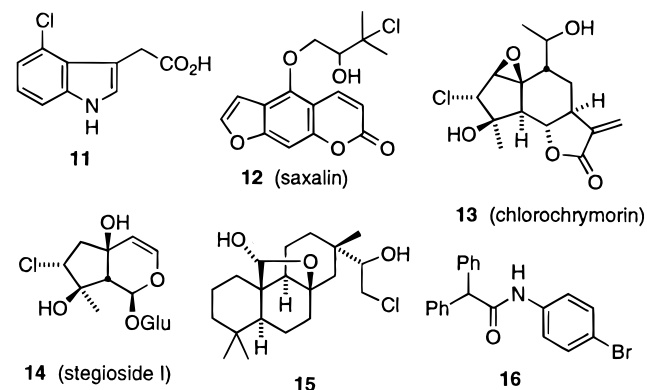
Gordon W. Gribble was born in San Francisco, CA, and attended San Francisco City College and the University of California, Berkeley, for his undergraduate training. Early exposure to organic chemistry from John E. Booher and Andrew Streitwieser, Jr., continued at the University of Oregon with Lloyd J. Dolby, under whose guidance he received a Ph.D. in indole alkaloid chemistry in 1967. He was a National Cancer Institute postdoctoral fellow at UCLA with Frank A. L. Anet and has been at Dartmouth since 1968. Apart from his scholarly interest in naturally occurring organohalogen compounds, his research program focuses on heterocyclic chemistry and the synthesis of biologically active natural products, and he has published more than 150 papers in these areas. As an amateur winemaker, he also has a strong interest in the chemistry of wine and winemaking.

yielded organohalogen metabolites, and one of the more interesting is the enediynes C-1027, the chromophore of which is shown in **10**.



Plants. Relatively few plant metabolites contain halogens. A notable exception is the plant growth hormone 4-chloroindole-3-acetic acid (**11**) and its methyl ester which are produced by green peas, lentil, vetch, sweet pea,

grass pea, and fava bean. Parsley and other plants contain the psoralen saxalin (**12**).¹³ Chlorochrymorin (**13**) is found in *Chrysanthemum morifolium*,¹⁴ and stegioside I (**14**), from *Physostegia virginiana* ssp. *virginiana*, is one of 15 chlorine-containing iridoids.¹⁵ Chlorohydrins such as **13** and **14** are usually not artifacts of the isolation process, as shown either by direct sampling of the plant material or by subjecting the corresponding epoxide to the isolation protocol. For example, the epoxide corresponding to **15**, both of which were isolated from the Brazilian plant *Vellozia bicolor*, is not converted to **15** under the isolation conditions.¹⁶ Although organobromines are rare in terrestrial life, the Thai plant *Arundo donax* produces **16**, which repels weevils,¹⁷ and, joining nicotine, cocaine, and the pyrethrins, **16** appears to be another natural plant-produced insecticide.

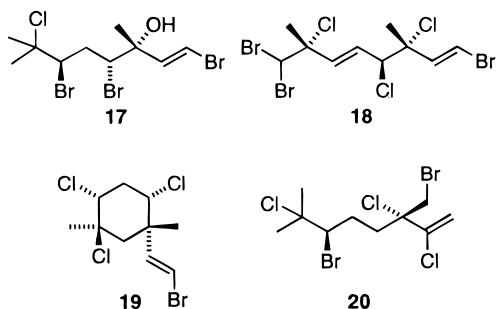


Remarkably, chloromethane is produced by evergreen trees, potato tubers, mushrooms, the ice plant, marine algae and giant kelp, a bryozoan, and wood-rotting fungi.¹ In the latter instance, chloromethane appears to play a key role in the degradation of wood lignin by acting as a methyl donor in the biosynthesis of anisoles.

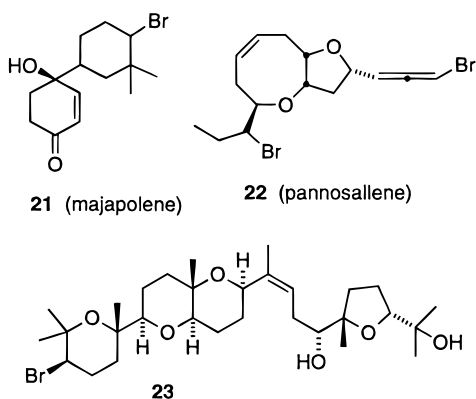
Marine Plants. The array and diversity of organohalogen compounds that are produced by marine algae, both macro and micro, are truly astounding. Such compounds probably number more than 1000.

The favorite edible seaweed of native Hawaiians is "limu koku" (*Asparagopsis taxiformis*). This red alga has yielded nearly 100 organohalogen compounds, including many lachrymatory haloacetones and related metabolites.¹ Bromoform (CHBr_3) is the major (80%) constituent. A myriad of simple haloalkanes have been isolated from marine algae: CH_2Cl_2 , CHCl_3 , CCl_4 , CH_3Br , CH_3I , CH_2Br_2 , CHBr_3 , CBr_4 , CH_2ClBr , CH_2ClI , CH_2BrI , CH_2I_2 , CHI_3 , CHCl_2Br , CHClBr_2 , CHBr_2I , CHBrI_2 , CHClBrI , $\text{CH}_3\text{CH}_2\text{Br}$, $\text{CH}_3\text{CH}_2\text{I}$, $\text{BrCH}_2\text{CH}_2\text{I}$, $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$, and others.¹ The commercial fumigant $\text{BrCH}_2\text{CH}_2\text{Br}$ is made by antarctic macroalgae,^{18,19} and the dry-cleaning solvents trichloroethylene and tetrachloroethylene are produced by at least 27 species of marine algae.²⁰ The authors of this latter study conclude that "the measured rates suggest that emission of trichloroethylene and perchloroethylene from the oceans to the atmosphere may be of such a magnitude that it cannot be neglected in the global atmospheric chlorine budget." It seems likely that the "smell of the ocean" is due to this potpourri of volatile halocarbons.

Numerous halogenated monoterpenes are produced by marine algae, and the first such compounds were **17** and **18**, which were actually isolated in 1973 from a sea hare, *Aplysia californica*, which feeds on the algae containing these monoterpenes.²¹ Such a "procured" chemical defense is apparently common in marine life.²² Telfairine (**19**), which was identified in *Plocamium telfairiae*, is a potent insecticide resembling the commercial pesticide lindane in toxicity and structure. Monoterpene **20** from *Portieria hornemannii* has very pronounced anticancer activity against human cancer cell lines and was started in preclinical development.²³

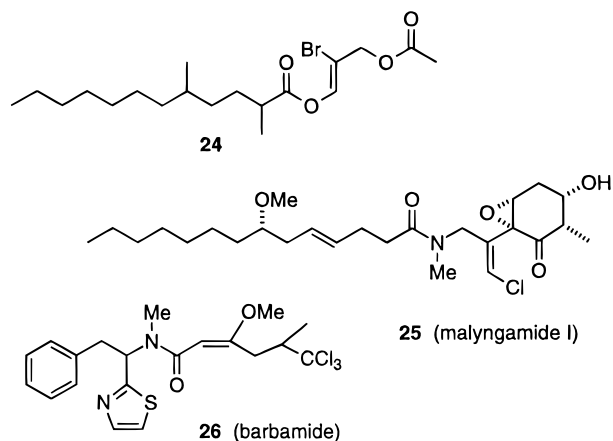


More than 40 species of red algae of genus *Laurencia* have yielded hundreds of halogenated terpenes. The Philippine *Laurencia majuscula* contains 13 novel halogenated sesquiterpenes, e.g. majapolene (**21**),²⁴ and the Vietnamese *Laurencia pannosa* has yielded pannosallene (**22**),²⁵ one of a large number of nonterpene-C₁₅ acetogenins found in *Laurencia* red algae. These prolific and versatile algae are the source of several squalene-derived organohalogen metabolites, and *Laurencia viridis* from the Canary Islands has yielded five such brominated triterpenoids such as 15,16-dehydrovenustatriol (**23**).²⁶

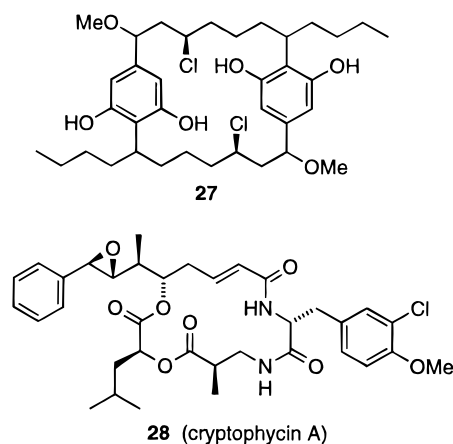


Blue-green algae (cyanobacteria) yield organohalogen compounds, which frequently have potent biological activity. Several such metabolites are produced by *Lyngbya majuscula*, one of which is the highly toxic bromine-containing aplysiatoxin believed to be the cause of "swimmer's itch" in Hawaii. An Australian *Lyngbya* sp. contains **24**, and malyngamide I (**25**) was isolated from *L. majuscula*,²⁷ as was barbamide (**26**)²⁸ from the Curacao species.

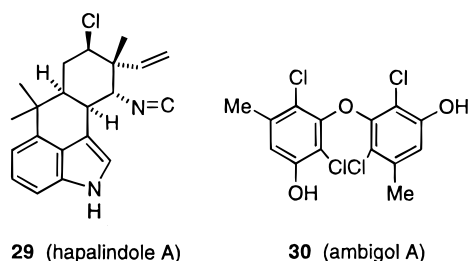
A series of nostocyclophanes, e.g. **27**, are produced by the blue-green alga *Nostoc linckia*, and at least 18 chlorine-



containing cryptophycins, e.g. **28**, are found in cultures of a *Nostoc* sp.²⁹ Some of these latter compounds have unprecedented anticancer activity against solid tumors, and a drug candidate seems highly probable.



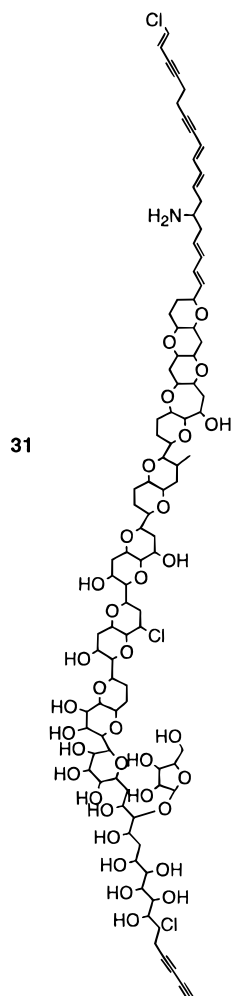
The terrestrial blue-green alga *Fischerella muscicola* and other cyanobacteria produce more than 20 indole isonitriles, such as hapalindole A (**29**), and *Fischerella ambigua* contains the HIV reverse transcriptase inhibitor ambigol A (**30**).³⁰



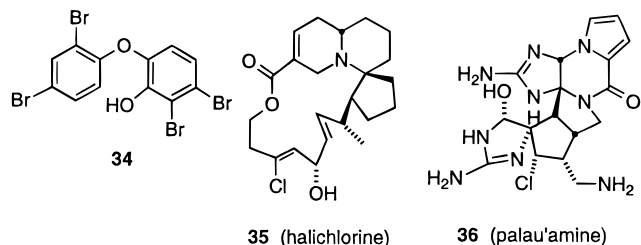
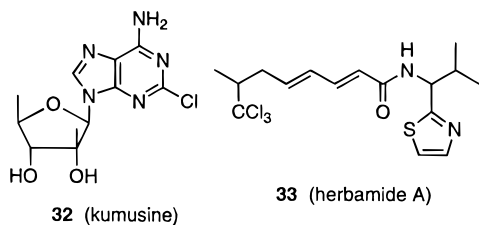
The red tide alga *Prymnesium parvum* produces the incredibly complex prymnesin-2 (**31**), which is a potent fish toxin.³¹

Marine Sponges. The phylum Porifera contains those animals commonly called sponges, and a mind-boggling collection of diverse halogen-containing sponge metabolites is known.¹

The nucleoside kumusine (**32**) is found in both *Theonella* sp.³² and *Trachycladus laevispirulifer*.³³ The unusual trichloromethyl herbamide A (**33**) is found in

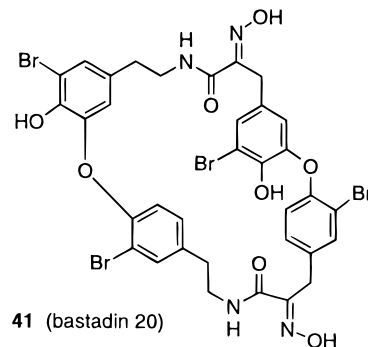
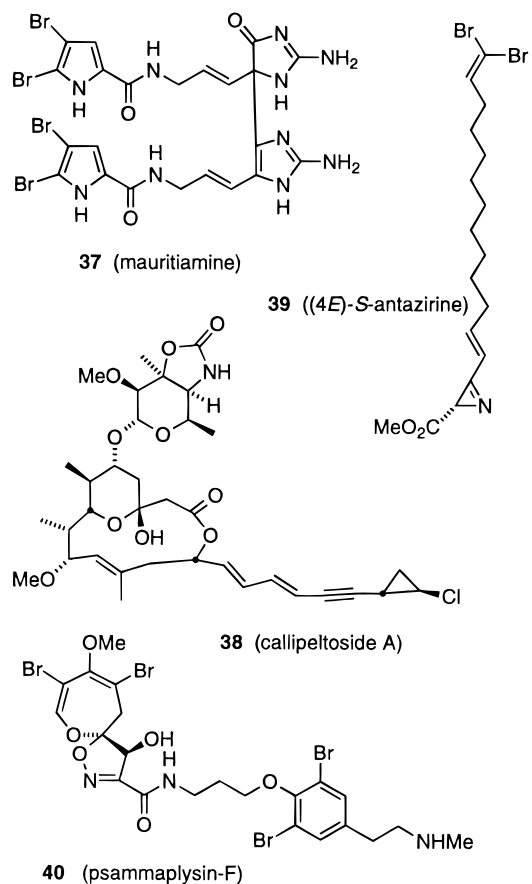


Dysidea herbacea,³⁴ a sponge genus known to produce both trichloromethyl metabolites and polybrominated diphenyl ethers such as **34**.³⁵ The latter compound might be viewed as a "pre-dioxin" since such in vitro enzymatic transformations are known (vide infra). The quinolizidine halichlorine (**35**) has been characterized from *Halichondria okadai*,³⁶ and the highly congested palau'amine (**36**), which is cytotoxic and immunosuppressive, is found in *Stylotella agminata*.³⁷



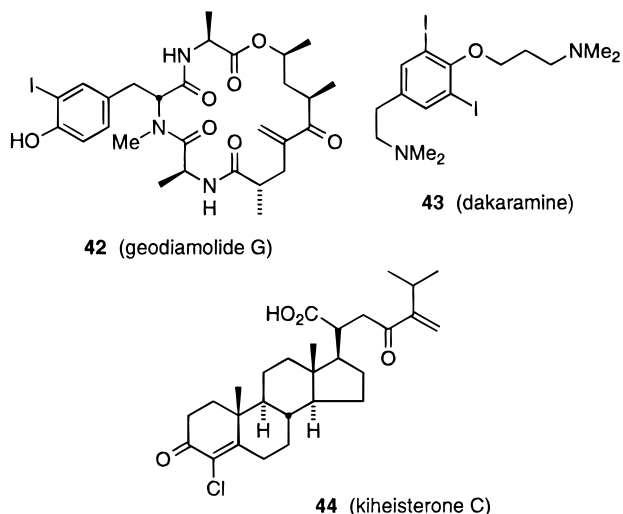
Brominated pyrroles are plentiful in sponges, and

mauritiamine (**37**) is an antifouling compound produced by *Agelas mauritiana* that prevents the overgrowth of the barnacle *Balanus amphitrite*.³⁸ The cytotoxic macrolide callipeltoside A (**38**), which contains a chlorocyclopropane, is one of three such metabolites produced by the lithistid sponge *Callipelta* sp.^{39,40} Another unusual metabolite is **39**, one of two bromine-containing antazirines from the Pohnpei sponge *Dysidea fragilis*,⁴¹ and psammaplysin F (**40**) from *Aplysinella* sp. is one of many transformed brominated tyrosines found in sponges.⁴² Another group are the bastadins, such as bastadin 20 (**41**), recently isolated from *Ianthella basta*.⁴³

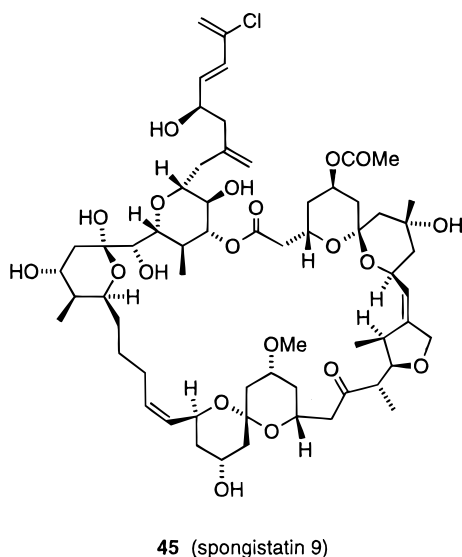


Apart from the iodine-containing thyroid hormones, organoiodine is rarely found in nature and fewer than 100 examples are known.^{1,5} The sponge *Cymbastela* sp. has afforded geodiamolide G (**42**),⁴⁴ and the Senegalese sponge *Ptilocaulis spiculifer* contains dakaramine (**43**).⁴⁵ The

Maui sponge *Strongylacidon* sp. has yielded three chlorosteroids, e.g. kiheisterone C (**44**).⁴⁶



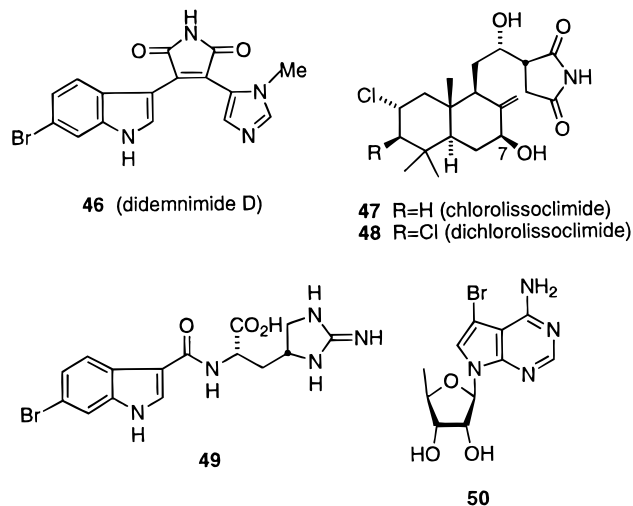
The macrolide spongistatins, five of which contain a chlorovinyl moiety, e.g. spongistatin 9 (**45**), are among the most potent substances screened in the National Cancer Institute panel of 60 human cell lines. These macrolides are found in the Indian Ocean sponge *Spongia* sp. and the African sponge *Spirastrella spinispirulifera*.⁴⁷ The chlorine atom seems to be important for activity. Ironically, vinyl chloride itself is a well-known human liver carcinogen.



Ascidians. These marine animals, often called tunicates or sea squirts, belong to the subphylum Urochordata (or Tunicata) of the phylum Chordata and, thus, are closer evolutionary to humans. These filter feeders may be solitary or colonial but, like sponges, apparently rely heavily on chemical defense for survival.

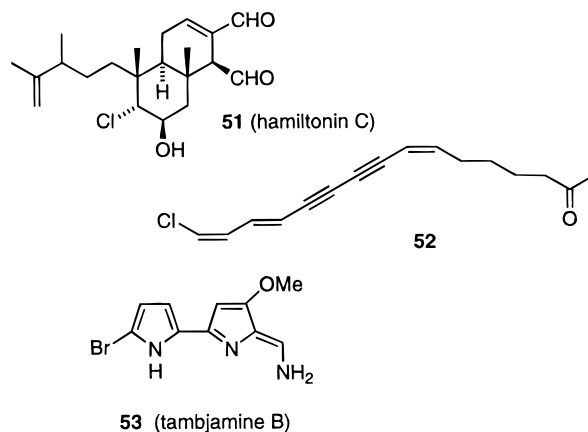
The Caribbean mangrove ascidian *Didemnum conchyliatum* produces four didemnimides, two of which contain bromine, e.g. D (**46**), which is a potent feeding deterrent.⁴⁸ The novel chlorine-containing lissoclimides (**47** and **48**) are produced by the New Caledonian ascidian

Lissoclinum voeltzkowi.⁴⁹ These compounds, which are the first organochlorines to be isolated from Urochordata, are active at the nanograms per milliliter level against both P388 and KB cancer cells.⁵⁰ The ascidian *Leptoclinides dubuis* has afforded three novel brominated indoles, one of which (**49**) contains the rare amino acid enduracidine,⁵¹ and the novel nucleoside **50** is produced by *Didemnum voeltzkowi*.⁵²



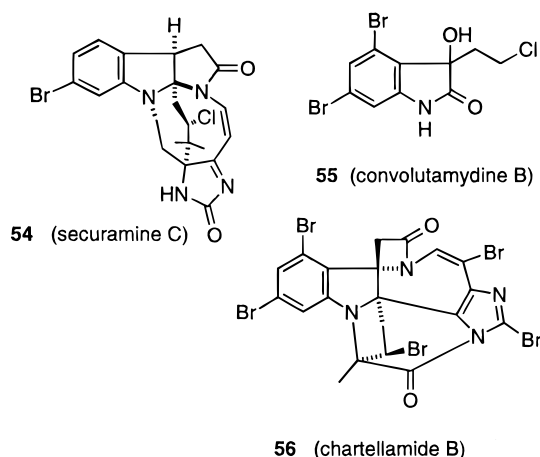
Nudibranchs. These brightly colored marine animals, often called sea slugs, are in the phylum Mollusca (class Gastropoda) and, like sea hares, can apparently “steal” their chemical arsenal by feeding on sponges. This gives new meaning to the phrase “lazy slug”!

The African nudibranch *Chromodoris hamiltoni* contains four chlorinated homo-diterpenes such as hamiltonin C (**51**),⁵³ and *Diaulula sandiegensis* secretes nine chloroacetylenes as chemical defensive agents, of which the most abundant is **52**.⁵⁴ The venomous cone snail *Conus imperialis* produces two toxic peptides which contain a 6-bromotryptophan amino acid.⁵⁵ The grazing predatory nudibranchs *Tambje eliora* and *Tambje abdere* prey upon and confiscate from the bryozoan *Sessibugula translucens* the chemical defensive and fish antifeedant tambjamine B (**53**) (and others).⁵⁶



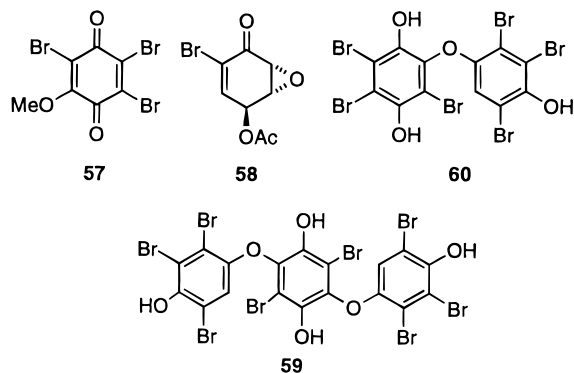
Bryozoans. These “moss animals” (phylum Bryozoa = Ectoprocta) have produced some of the most novel and elaborate organohalogen metabolites from any source.

Several bromine-containing tambjamines similar to **53** have been isolated from the bryozoan *Bugula dentata*,⁵⁷ and *Securiflustra securifrons* produces seven chlorinated and brominated securamines of great complexity (e.g., **54**).^{58,59} Four halogenated convolutamydines (e.g., **55**), which display differentiation of HL-60 cells, are found in *Amathia convoluta*.⁶⁰ The maestro of organic synthesis in the Bryozoa is clearly *Chartella papyracea*, which synthesizes a stunning array of halogen metabolites, one of which is chartellamide B (**56**).⁶¹ The Atlantic *Amathia convoluta* has yielded five brominated volutamides, which have antifeedant properties.⁶²



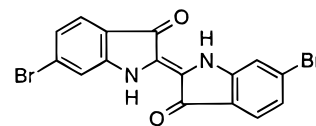
Acorn Worms. These marine worms in phylum Hemichordata are a rich and prolific source of novel halogenated phenols and indoles.¹

The acorn worm *Balanoglossus biminiensis* produces up to 15 mg of 2,6-dibromophenol per animal, and this phenol and 2,4,6-tribromophenol are secreted by *Phoronopsis viridis*. The Florida *Ptychodera bahamensis* has furnished 12 different halogenated phenols and hydroquinones, such as 2,6-dibromo-4-chlorophenol and 2-bromo-6-chlorohydroquinone. Several bromine-containing benzoquinones are found in *Ptychodera flava laysanica*, such as **57**, and epoxide **58** is found in a Maui *Ptychodera* sp. and is highly cytotoxic against P-388 cells in vitro (IC₅₀ = 10 ng/mL). The major metabolite of *P. flava* is the octabrominated ether **59**, and this animal has also yielded two other brominated diphenyl ethers (e.g., **60**).



Halogenated indoles are also manufactured (or acquired) by acorn worms. Thus, *P. flava laysanica* pro-

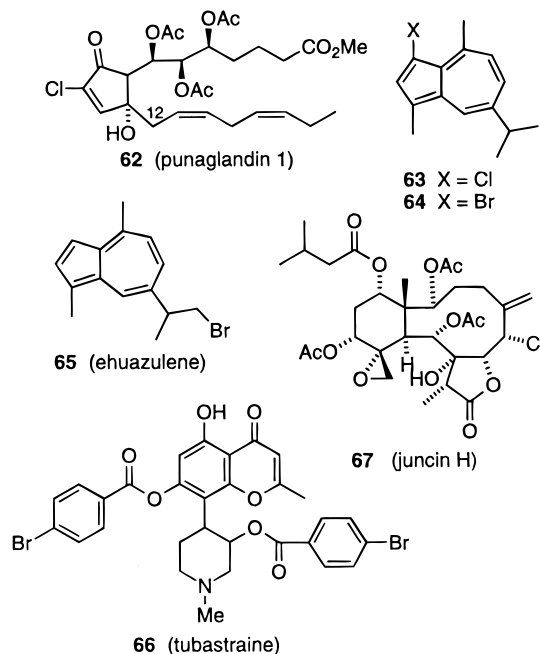
duces not only seven chlorinated/brominated indoles (e.g., 3-chloro-, 3-bromo-, 6-bromo-3-chloro-, 3,6-dibromo-, and 3,5,7-tribromoindole) but also Tyrian Purple (**61**) and two other 6,6'-dibromoindigotins.



61 (Tyrian Purple)

Corals. Although some hard corals have afforded halogen-containing metabolites, octocorals (gorgonians and soft corals) have furnished most of these chemicals.

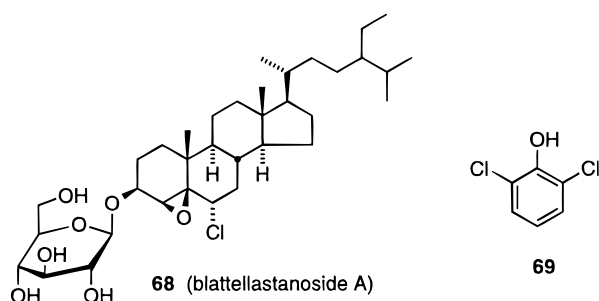
The beautiful octocoral *Telesto riisei*, which was featured on the cover of a journal in 1994,⁶³ is the source of 19 chlorine-containing punaglandins (e.g., **62**), some of which have promising anticancer activity. Related chlorine-, bromine-, and iodine-containing vulones are produced by *Clavularia viridis*. Azulenes **63–65** are found in a deep-sea gorgonian, and both 3-bromobenzoic acid and tubastraine (**66**) are produced by the stony coral *Tubastraea micrantha*. This coral is avoided by the coral-destroying Crown-of-Thorns seastar (*Acanthaster planci*). Many chlorine-containing briarane diterpenes have been isolated from gorgonians such as juncin H (**67**) from the Indian Ocean *Junceella juncea*.⁶⁴



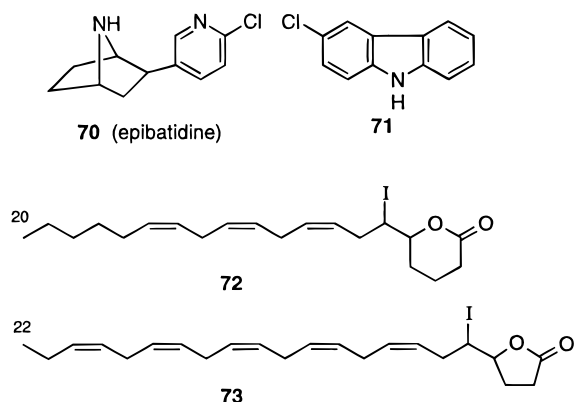
Insects. Although insect pheromones have long provided a fertile and active arena for natural products research, only a few of these compounds contain halogens.

The German cockroach (*Blattella germanica*) employs the chlorinated stigmastane steroids blattellastanoside A (**68**) and B as aggregation pheromones. Several different insects contain 2-(or 4)-iodohistidine and mono- and dibromotyrosines, and 3-chlorotyrosine occurs in the cuticle of locusts. These halogenated tyrosine residues

are believed to improve adhesion between protein fibers and sheets. Remarkably, 2,6-dichlorophenol (**69**) is the sex pheromone of a dozen species of ticks. Radiolabeled chloride feeding studies prove that **69** is biosynthesized within the female tick. The isomeric 2,5-dichlorophenol has been isolated from the common grasshopper and is an ant repellent, and 2,4-dichlorophenol, the precursor to the common herbicide "2,4-D", is produced by a *Penicillium* sp. soil fungus. A surprising source of chloroform are Australian termites in the outback.⁶⁵ Six termite species produce chloroform within their mounds, and in the mound of one species, *Coptotermes lacteus*, the chloroform concentration was 1000 times higher within the mound than the ambient concentration. The authors conclude that chloroform produced from termites accounts for up to 15% (100 000 tons/year) of the global emissions.

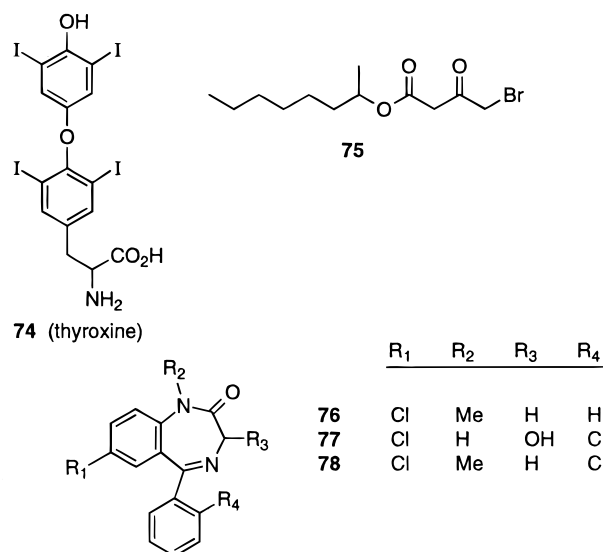


Higher Animals. The Ecuadorian tree frog *Epipedobates tricolor* secretes epibatidine (**70**), a compound which is a potent analgesic. 3-Chlorocarbazole (**71**), which is a potent monoamine oxidase inhibitor, is found in bovine urine and is believed to have a natural origin. Iodolactones **72** and **73** have been identified in the thyroid gland of dogs. The transformation of arachidonic acid and docosahexaenoic acid with lactoperoxidase, iodide, and hydrogen peroxide into **72** and **73** in vitro suggests that this pathway may operate in vivo with thyroid peroxidase.



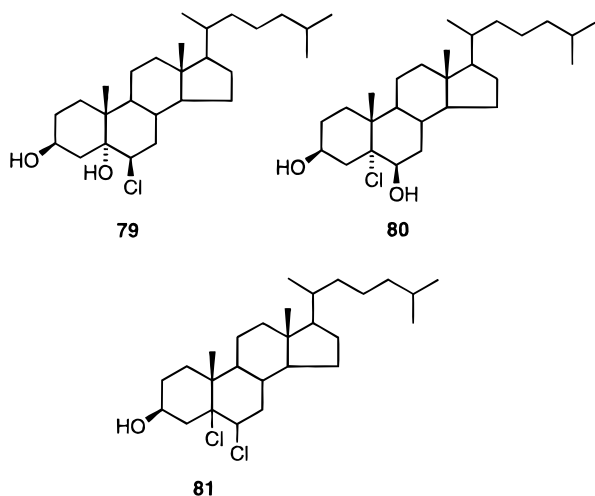
Humans. Until recently, and with the exception of the thyroid hormones, such as thyroxine (**74**), the only organohalogen to be found in humans was bromoester **75**, which had been isolated from the cerebrospinal fluid of normal humans. This remarkable compound, which is also present in cats and rodents, is a very effective inducer of REM (rapid-eye-movement) sleep and may play an

important role in inducing the sleep phenomenon. The concentration of **75** is 100–200 times higher in the retina, hypophysis, and cerebral cortex than in the blood.¹ Seven chlorine-containing benzodiazepines (e.g., **76–78**), including diazepam (**76**) (valium) have been isolated from the brains of humans and other animals,¹ including three human brains that were preserved years before diazepam was synthesized in the laboratory!⁶⁵ These naturally occurring chlorine-containing benzodiazepines are synthesized in plants (corn, potatoes, lentils, rice, wheat, mushrooms, soybeans) and thus enter the food chain in this manner.⁶⁶ Levels in plants are 0.005–0.05 ppb. Benzodiazepine biosynthesis in *Penicillium cyclopium* is well-known,⁶⁷ as it is in bovine rumen.⁶⁸ Some of these benzodiazepines may be synthesized by neural cells, and they may have a biological role.⁶⁹



An unimaginable discovery is the finding of free chlorine and organochlorine compounds in humans! A review of this topic has appeared.⁷⁰ Although it has long been known that halides are oxidized to free halogens (or hypohalites) in neutrophils (white blood cells) as part of the immune system, only recently has free chlorine been demonstrated to be involved in this process.⁷¹ Chlorine is also involved in the in vitro conversion of low-density lipoprotein (LDL) cholesterol by myeloperoxidase (MPO) into several chlorinated sterols **79–81**.⁷²

3-Chlorotyrosine has been detected in human atherosclerotic lesions⁷³ and also in the reaction of human serum albumin with MPO, H₂O₂, and chloride in neutrophils.⁷⁴ In the former study the highest concentration of 3-chlorotyrosine was observed in two patients with coronary artery disease, and this compound was generally undetectable in the LDL isolated from young, healthy donors. Thus, 3-chlorotyrosine is a bona fide human organochlorine compound, although it was previously found in the cuticle protein of locusts and in *Limulus polyphemus*.¹ Twenty eight percent of the oxygen consumed by stimulated human neutrophils is used to oxidize chloride ion to chlorine or hypochlorite,⁷⁵ and the active oxidants produced by human neutrophils might be long-lived



N-chloramines.⁷⁶ The aqueous chlorination of purines and pyrimidines, studied with regard to environmental concerns,⁷⁷ may be relevant to the aqueous chlorination of pathogens by human neutrophils.

Volcanoes and Other Geophysical Phenomena. Although volcanoes emit large quantities of HCl and HF,⁷⁸ the emissions of organohalogen compounds is less well known. The gases from a fumarole on the Santiaguito volcano in Guatemala contain CF₂=CF₂, CF₃CF=CF₂, CHF₂Cl, CHFCl₂, CClF=CF₂, CH₃Cl, CFCl₃, CCl₂=CHCl, and CCl₂FCClF₂ among other organic compounds.⁷⁹ Other organohalogens were unidentified because of the complexity of the mass spectra. The Siberian Kamchatka volcanoes produce CF₂Cl₂, CHFCl₂, CFCl₃, CHCl₃, CCl₄, CCl₂=CCl₂, and (CH₃)₂SiF₂.^{80,81} Likewise, the 1980 eruption of Mt. St. Helens released CH₃Cl, CH₃Br, CH₃I, and other (unidentified) organohalogens.⁸² Their formation probably originates from the high-temperature and -pressure reactions of organic-rich sediments or fossil soils and HCl and HF during the eruption event. From one solfataric vent of a Kamchatka volcano, the concentration of a CFC was 400 times that of the background. CFCs are also found in the gases from hydrothermal vents and thermal springs in the Kamchatka, Ashkhabad, and Tskhaltubo regions of the former Soviet Union.^{83–85}

Minerals and Meteorites. When certain rocks, shales, and minerals are crushed in mining operations, the gases released contain CH₃Cl, CH₂Cl₂, CHCl₃, CCl₄, CH₃CH₂Br, CHF₃, CFCl₃, CF₂Cl₂, CCl₃CHCl₂, CCl₃CCl₃, CH₃CHCl₂, CH₂-ClCH₂Cl, CF₃CF₂CF₂H, CHBr₂CHBr₂, 1-chloronaphthalene, and 2-bromomesitylene.^{81,86,87} Following the identification of chlorobenzene, dichlorobenzene, and several chloroalkanes in carbonaceous chondrites (meteorites),^{88,89} another examination of four meteorites discovered adsorbable organic halogens in levels up to 200 ppm.⁹⁰ For example, 2-chloro-, 2,4-, and 2,6-dichlorobenzoic acids could be detected in the Cold Bokkeveld meteorite.

Both hydrogen chloride and hydrogen fluoride have been detected in interstellar space,⁹¹ and the possibility that organochlorine and organofluorine compounds will be counted among the more than 100 organic chemicals found in deep space is quite real. An examination of

ancient sediments reveals the presence of unidentified organohalogens in peat, lignite, bituminous coal, and anthracite, which reflect different stages of coalification.⁹²

Forest Fires. Natural biomass burning, such as lightning-triggered forest and brush fires, of which some 200 000 occur annually worldwide, produce large quantities of CH₃Cl.¹ Since all biomass contains carbon and chloride, the formation of CH₃Cl and other organochlorines is not surprising. Natural fires have occurred on earth since terrestrial vegetation evolved 350–400 million years ago, and it must be true that CH₃Cl has been a natural component of our atmosphere for eons. The total global annual production of CH₃Cl is (5–6) × 10⁶ tons from all natural sources, dwarfing the 26 000 tons per year from anthropogenic sources.¹ Methyl bromide is also formed in biomass burning to the extent of 10 000–50 000 tons/year, or about 30% of the stratospheric bromine budget.^{93,94} Several North American biomass fires were found to contain high amounts of CF₂Cl₂ (60 000 tons/year), and the authors conclude that this compound results from the burning of pollutants already present in the biomass since “CF₂Cl₂ cannot be produced by fires.”⁹⁵

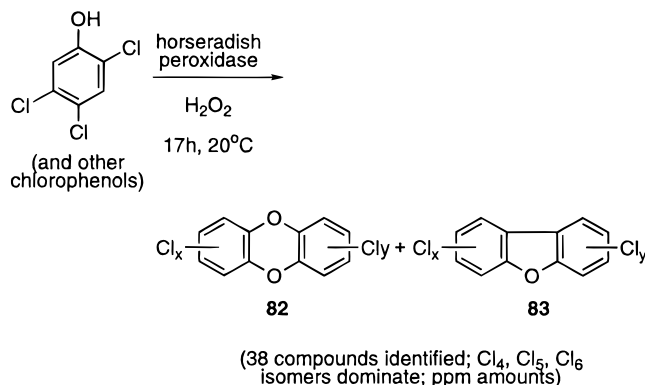
Dioxins are produced in forest fires,^{1,96,97} but the amounts are difficult to quantify, and they are found in 8000-year-old deep sediments in Japan.⁹⁸ Dioxins and the related polychlorinated dibenzofurans are present “in small but significant levels during the period 1882–1962” in sediment samples from 1882, 1906, 1922, 1938, and later.⁹⁹

Sediments and Soil Production. Halogenated fulvic acids have been isolated from groundwater samples that date back 1300, 4600, and 5200 years. Preindustrial glacial ice from Antarctica and northern Sweden contains organohalogen levels of 1–3 ppb, including trichloroacetic acid. The latter and chloroform are found to be ubiquitous in soil, the biogenesis of which was confirmed by ³⁷Cl⁻ labeling experiments. Trichloroacetic acid is present in bog water, snow, rain, and soil samples from pristine locations.¹⁰⁰ The analysis of 35 000-year-old organic matter (¹⁴C-dating) reveals the presence of organochlorine, organobromine, and organoiodine compounds. Organochlorines have also been found in 1000-year-old peat, in 4000-year-old marine clay, in two lignite samples that date from the Tertiary era, 15 million years ago, and in a 300 million year old bituminous coal sample from the Upper Carboniferous period. These natural organochlorines in sediments either result from the deposition of biogenic materials from plants already containing organochlorines or arise by the formation of organochlorines within the sediments. Microfossils in billion-year-old Precambrian rocks are identical with the blue-green alga *Nostoc*, and other microfossils are morphologically indistinguishable from *Oscillatoria*, two present-day species rich in organohalogen compounds. All of these data demonstrate that organochlorine compounds predate the arrival of man on earth!

The organochlorines found in pristine forests and lakes appear to form from the in situ chlorination of humic acid by the ubiquitous soil enzyme chloroperoxidase, chloride

ion, and hydrogen peroxide, which is part of the natural decay and recycling of organic matter in the forest soil.¹⁰¹ High molecular weight organochlorines have been identified in the soil collected from a coniferous forest.^{102–105}

Dioxins (**82**) and polychlorodibenzofurans (**83**) are produced from chlorophenols in the presence of horseradish peroxidase and hydrogen peroxide.⁹⁷ This reaction occurs under true in vivo conditions in fresh garden compost piles and sewage sludge.^{106,107}



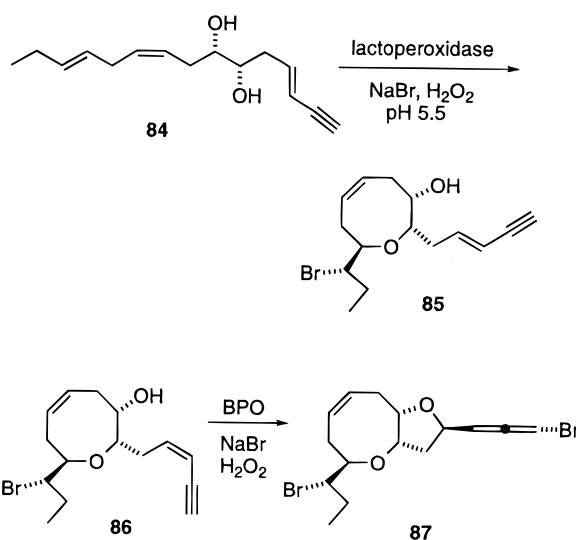
For a recent review of the natural production of organohalogens in water and sediments, see ref 108.

Biohalogenation

The formation of natural organohalogens in living organisms is well established.¹ For many of these compounds, the mechanism for their formation initially involves the oxidation of halide by a peroxidase enzyme and hydrogen peroxide. Chloroperoxidase (CPO), bromoperoxidase (BPO), and one iodoperoxidase enzyme have been characterized. Other peroxidases such as myeloperoxidase generate halogens in white blood cells to fight infection. Moreover, these enzymes are becoming valuable catalysts in organic synthesis.¹⁰⁹

The BPO responsible for the production of CHBr₃, CH₂Br₂, CH₂I₂, CH₂ClI, and CH₂BrI by marine phytoplankton has been isolated.¹¹⁰ BPO activity has been detected in 94 species of red, green, and brown algae.¹¹¹ An X-ray crystal structure has been reported for a vanadium-containing CPO from the fungus *Curvularia inaequalis*.¹¹² The BPO from *Streptomyces aureofaciens*, which produces 7-chlorotetracycline, has been characterized by X-ray crystallography,¹¹³ and the gene for this enzyme has been cloned and sequenced.¹¹⁴ The CPO gene from the fungus *Caldariomyces fumago*, which produces the dichloro caldariomycin, has been isolated and sequenced.¹¹⁵

Several in vitro reactions with peroxidases support the proposed biosynthetic pathways for some organohalogens. Laurediol **84** cyclizes to the *Laurencia* metabolite (*E*)-prelaureatin (**85**),¹¹⁶ and the biosynthetic conversion of (*Z*)-prelaureatin (**86**) to laurallene (**87**) has been demonstrated.¹¹⁷



Function

Many organisms use organohalogens (and nonhalogenated compounds) in chemical defense, in food gathering, or as regulatory hormones. Telfairine (**19**) is 100% lethal to mosquito larvae at 10 ppm, and the related plocamene B is three times more effective than lindane against mosquito larvae. But not all organohalogen compounds have a defensive role. The German cockroach (*Blattella germanica*) utilizes blattellastanosides A (**68**) and B as aggregation pheromones. Chloromethane serves a key role in the degradation of lignin by wood-rotting fungi, such as *Phellinus pomaceus* and *Phanerochaete chrysosporium*. 4-Chloroindole-3-acetic acid (**11**) is a natural plant growth hormone, and 3,5-dichlorohexanophenone, which is produced by *Dictyostelium discoideum*, is a signal molecule that triggers the transformation of undifferentiated cells of this slime mold into fruiting bodies. The chlorine atoms in the clinical antibiotic vancomycin (**9**) are crucial in enforcing the requisite conformation for receptor binding. The extraordinary bromo ester **75** found in human cerebrospinal fluid may play an important role in inducing the sleep phenomenon. The role of simple halomethanes may be to recycle halogens/halides between oceans, the atmosphere, and land.

Future Outlook

Not counting terrestrial organisms, the 500 000 species of marine animals, plants, and bacteria guarantees that thousands of new organohalogen compounds are awaiting discovery. Of the 4000 species of bryozoans fewer than 20 have been examined for their chemical content. The 3000 species of opisthobranchs, 9000 sponges, 4000 segmented worms, and 80 000 molluscs each represent a fantastically rich and largely untapped source of new chemical structures, many of which are certain to contain halogens. The exploration of marine bacteria and fungi is only beginning, and this will be an important area for future research.

The exploitation of chlorine by white blood cells in the immune process may account for the higher concentra-

tion of organochlorines in human urine than in drinking water. Organochlorine byproducts, such as 3-chlorotyrosine, produced during this "biodisinfection" will soon be isolated and identified, and this research should provide insight into the human immune process.

Chlorine—once called the "devil's element"—and the other halogens play an important role in natural processes, both biogenic and abiogenic, and any attempt to regulate chlorine and organohalogens must take these natural sources and functions into consideration. With an improved understanding of biohalogenation processes, we will be able to quantify more accurately natural versus anthropogenic sources of halogenated chemicals. As organohalogen natural products research unfolds, new antibiotics, anticancer and antifungal agents, pesticides, herbicides, and other important medicinal drugs will be discovered.

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