

## Natural Chlorine Updates – No. 4

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## I. Introduction

This literature review is the fourth in a series of periodic updates to the natural halogen literature, with a particular focus on organochlorine compounds.

The coverage is approximately from April 1996 through December 1996, with inclusions of earlier material as appropriate. Due to the relatively large time span between the last *Updates #3* and the present, and the large amount of new material, *Updates #5* will appear in the near future.

The International Union of Pure and Applied Chemistry (IUPAC) has published a special issue, "IUPAC White Book on Chlorine", in their official journal (1). This book consists of a series of invited contributions "to the debate on the effect of chlorine and chlorine-containing compounds on the environment." In addition to a paper on the diversity of natural organochlorines in living organisms by this author (2), there are fourteen other chapters on virtually all aspects of the chlorine issue including the chlorine industry, water disinfection, pulp bleaching, stratospheric chemistry, environmental dioxins, and waste management.

A special Colloquium on Biohalogenation was held in the Netherlands and was attended by 50 scientists from around the world (3). Topics included sources and function of organohalogens, biohalogenation, biodegradation of organohalogens, and applications of haloperoxidase enzymes.

The Department of Water and Environmental Studies at Linköping University in Sweden continues to produce important studies in the area of natural occurring organochlorine compounds, particularly the occurrence and formation of these compounds by fungi in the soil and during the decay of plant material. Two such Ph.D. theses were published in 1996, "Organohalogens in Coniferous Forest Soil" (4) and "Halogenated Structures in Natural Organic Matter" (5). The results from these two theses will be discussed in later sections as appropriate and also in *Updates #5*.

The monograph "Naturally Occurring Organohalogen Compounds — A Comprehensive Survey" has been published (6), and the subject of natural chlorine and chlorine in general has been presented on the Internet (7). A paper on naturally occurring bromine compounds was delivered at the 1997 Orga' Bromine Conference in New Orleans (8). An essay "Chlorine and Organochlorines in the Environment: A Perspective" has appeared in the *Canadian Chemical News* (9). This author concludes that "judgements about chlorine and organochlorines must be made on a chemical-by-

chemical and case-by-case basis if scientific logic and judgement are to prevail."

Other reviews will be cited in the following sections as appropriate.

## II. New Natural Organohalogens

The discovery of novel natural organochlorine and organobromine compounds continues inexorably, particularly as natural products chemists search for new medicinal leads from terrestrial and marine life. This *Updates* describes 103 new natural organohalogens, bringing the total to 2787. Thus, the current breakdown of natural organohalogen compounds reported to date is as follows:

Organochlorine:	1650
Organobromine:	1436
Organoiodine:	87
Organofluorine:	21

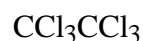
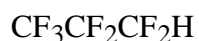
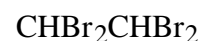
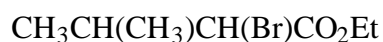
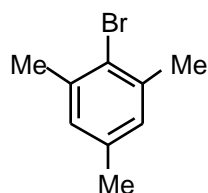
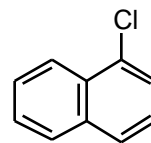
As in previous *Updates*, only newly discovered organohalogens are given compound numbers (in bold), so as to making counting them easier.

A new and surprising source of chloroform has been reported in a study of Australian termites in the wild (10). Six termite species produce chloroform within their mounds, and in the mound of one species, *Coptotermes lacteus*, the chloroform concentration is 1000 times higher than the ambient concentration. The authors conclude that chloroform produced from termites accounts for less than 15% ( $<10^{11}$  grams/year) of the global emissions. Another study reiterates the observation reported in *Updates #3* that the simple chloroethenes, trichloroethylene and perchloroethylene, as well as chloroform, bromoform, diiodomethane, dibromomethane, chloriodomethane, and 1-iodobutane have biogenic (presumably algal) sources (11). Several other studies confirm the fact that marine phytoplankton are an important natural source of these volatile organohalogens, including methyl chloride in addition to those mentioned above (12-14). An earlier study identified in the atmosphere  $\text{CH}_3\text{Br}$ ,  $\text{CH}_2\text{Br}_2$ ,  $\text{CHBr}_3$ ,  $\text{CH}_2\text{BrCl}$ ,  $\text{CF}_3\text{Br}$ ,  $\text{CF}_2\text{BrCl}$ ,  $\text{CH}_3\text{CH}_2\text{Br}$ ,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$ , and  $\text{CHBr}_2\text{Cl}$ , with the latter three compounds also being found in coastal seawater (15). The origin of the two fluorinated compounds is unknown at this time. The atmospheric estimated lifetime of  $\text{CH}_3\text{Br}$  has been revised to approximately 0.7 years, with oceanic

emissions estimated to be 56 Gg/year, larger than anthropogenic sources (46 Gg) or biomass burning (20 Gg/year) (16).

The most exciting discovery in the area of volatile natural organohalogens is the simultaneous report by two groups of the natural occurrence for the first time of 1,2-dibromoethane (**1**) in several meltwater ponds on the McMurdo Ice Shelf (17) and in Antarctic macroalgae (18). The latter report, which is the first study on the release of organohalogens by Antarctic macroalgae, also identified the other commonly found volatile organohalogens ( $\text{CHBr}_3$ ,  $\text{CH}_2\text{Br}_2$ ,  $\text{CHBr}_2\text{Cl}$ ,  $\text{CHBrCl}_2$ ,  $\text{CH}_2\text{I}_2$ ,  $\text{CH}_2\text{ClI}$ ).

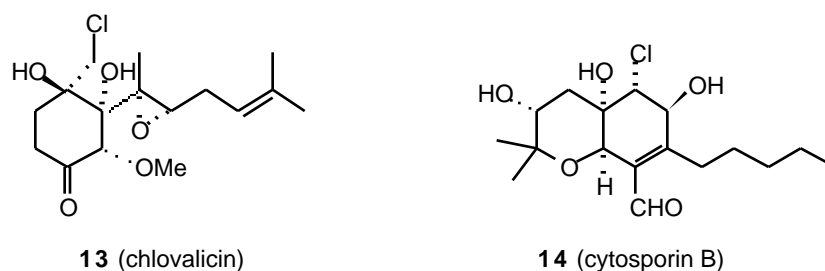
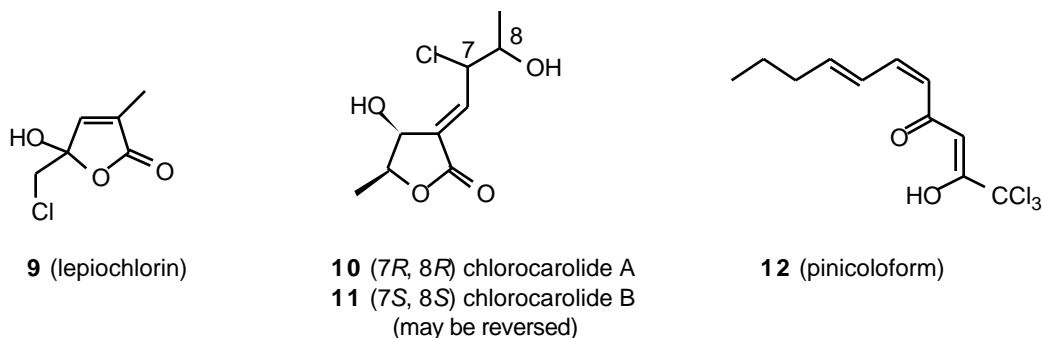
A study of carbonaceous black shales and related minerals from Central Asia has revealed the presence of several new organohalogen compounds **2-8**, in addition to  $\text{CCl}_4$ . The author proposes that these compounds could have formed from the interaction of organic compounds with halogens (hydrogen halide) present in the rocks, since such reactions can occur at the temperatures and pressures characteristic for geological processes (19). This intriguing study should be confirmed.

**2****3****4****5****6****7****8**

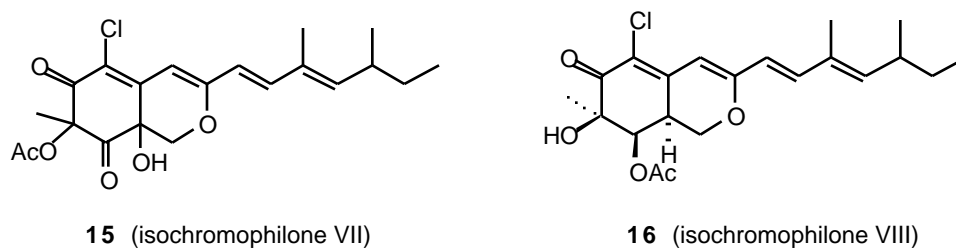
Several North American biomass fires were found to contain high amounts of the CFC,  $\text{CF}_2\text{Cl}_2$ , and the authors conclude that this compound results from the burning of pollutants already present in the fuel since " $\text{CF}_2\text{Cl}_2$  cannot be produced by fires" (20). They estimate that ~0.06 Tg/year (15% of total flux) of  $\text{CF}_2\text{Cl}_2$  originates from biomass global burning. This compound has been previously identified in volcanic gases, drill wells, and mine air (6), so natural production in biomass fires cannot be ruled out.

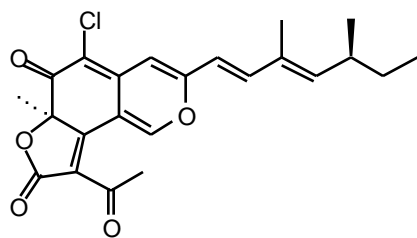
The simple lactone lepiochlorin (**9**) is produced by the ant-cultivated fungus *Lepiota* sp. (21), and chlorocarolides A and B (**10**, **11**) are produced by an *Aspergillus ochraceus* fungus associated with the sponge *Jaspis* cf. *coriacea* (22). The fungus *Resinicium pinicola* has afforded

the antibiotic and cytotoxic pinicoloform (**12**), a novel trichloromethyl  $\beta$ -diketone (**23**). Chlovalicin (**13**) from *Sporothrix* sp. inhibits interleukin 6 (**24**), and a *Cytospora* sp. produces cytosporin B (**14**) an antagonist of angiotensin II (**25**).

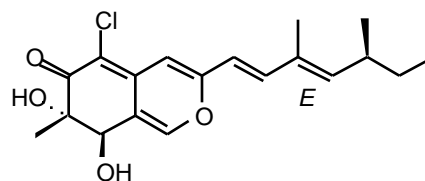


Several new examples of azaphilones, which were cited in *Updates #3*, have recently been extracted from fungi. Thus, a *Penicillium* sp. has furnished isochromophilones VII (**15**) and VIII (**16**) (**26**). Like the other isochromophilones, these compounds inhibit diacylglycerol acyltransferase and acyl-CoA: cholesterol acyltransferase. Isochromophilone III (cf. *Updates #3*) has been found in *P. sclerotiorum* along with the new 5-chloroisorotiorin (**17**) (**27**). Five new azaphilones have been found in *Talaromyces luteus*, luteusins A-E (**18-22**), compounds with monoamine oxidase activity (**28, 29**). Luteusins A and B were previously named TL-1 and TL-2 (**28**).

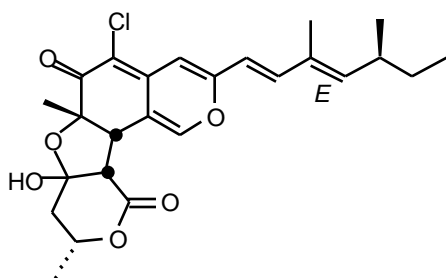




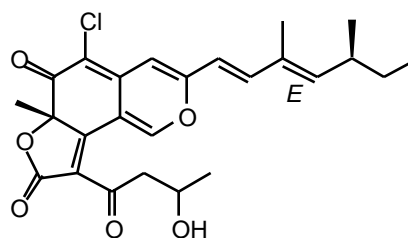
**17** (5-chloroisorotirin)



**18** (luteusin A)  
**19** (luteusin B) (Z)

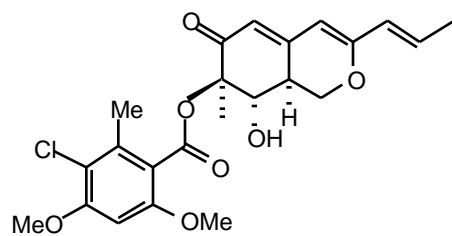


**20** (luteusin C)  
**21** (luteusin D) (Z)

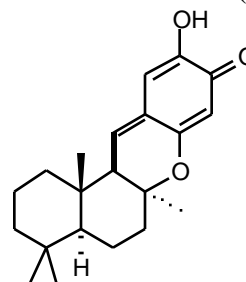


**22** (luteusin E)

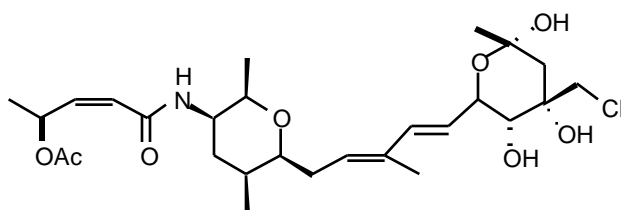
A new falconensin (E, **23**) has been isolated from the Venezuelan soil fungus *Emericella falconensis*, and this study established the absolute configuration for all the falconensins (30). A structure for the novel antitumor *Pseudomonas* sp. metabolite FR 901463 (**24**) has finally been advanced (31), following its isolation a year earlier (32, 33). Although two related epoxides (FR 901464 and FR 901465) are also produced by this organism, the chlorohydrin **24** is not an artifact and was shown by the authors to be present in the culture broth prior to extraction and isolation. The absolute configuration of puupehenone has been determined (34) and this may establish the absolute configuration of the previously known chlorine and bromine derivatives (6).



**23** (falconensin E)

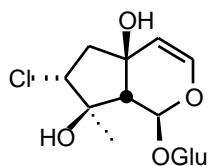


puupehenone

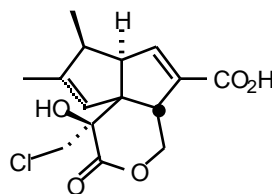


**24** (FR 901463)

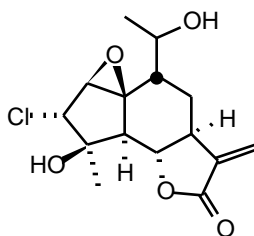
A number of new halogenated terpenes and related metabolites have been isolated from both terrestrial and marine sources. Stegioside I (**25**) is a new iridoid from *Physostegia virginiana* ssp. *virginiana* that is a dehydroxylinarioside derivative (35). The pentalenolactone-related AA-57 (**26**) is produced by a *Streptomyces* sp. (36), and *Chrysanthemum morifolium* has yielded chlorochrymorin (**27**) (37). The latter two papers were inadvertently missed in earlier reviews and previous *Updates*. The absolute configuration of the newly isolated chlorolissoclimide (**28**) from the New Caledonian ascidian *Lissoclinum voeltzkowi* (38, 39) and the earlier isolated dichlorolissoclimide (**28**, R=Cl) from the same organism have been determined and the stereochemistry at C-7 has been revised to that shown (39).



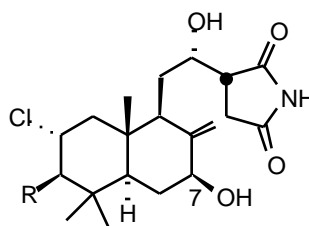
**25** (stegioside I)



**26** (AA-57)



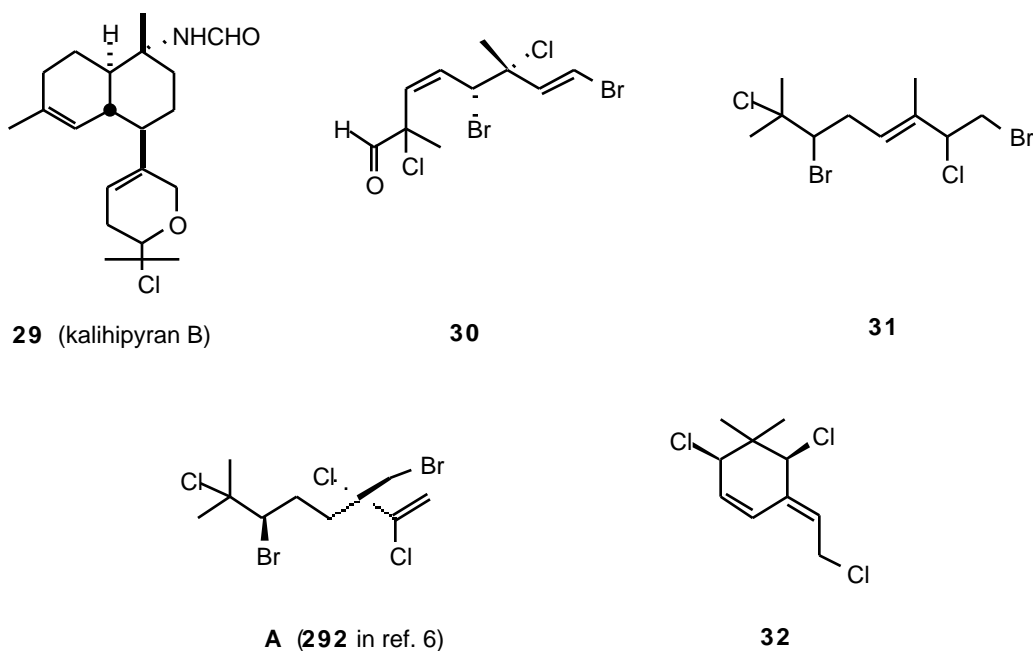
**27** (chlorochrymorin)



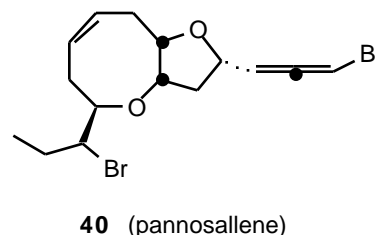
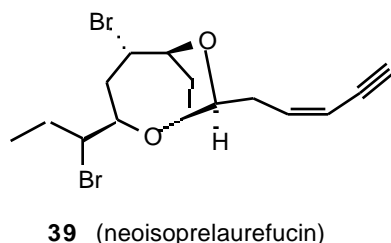
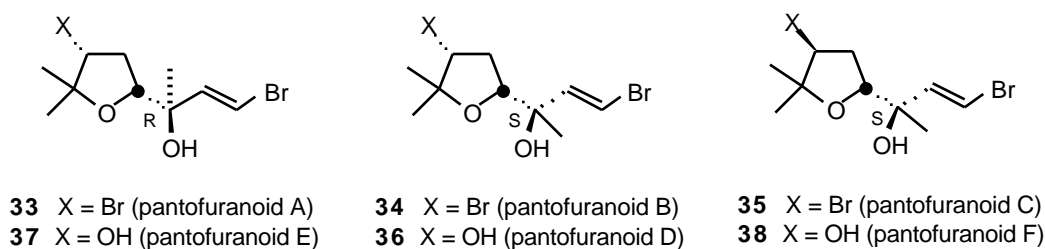
**28** R=H (chlorolissoclimide)

A new antifouling metabolite, kalihipyran B (**29**), has been found in the sponge *Acanthella cavernosa* (40). The Portuguese red alga *Plocamium cartilagineum* has yielded two new monoterpenes, **30** and **31**, along with five known halogenated monoterpenes (41). Compound **30** is the first natural halogenated 2,6-dimethyloctadiene with a *cis*-alkene. The structure of a previously reported monoterpene has now been established as A (**292** in ref. 6), a compound that has broad

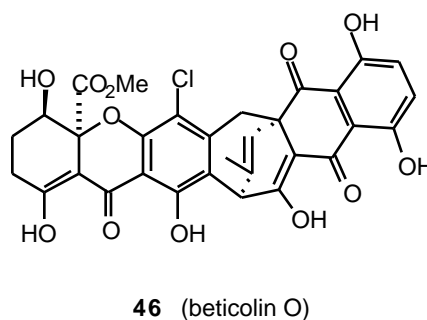
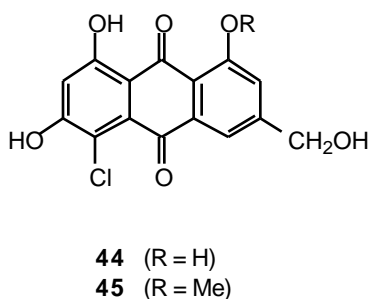
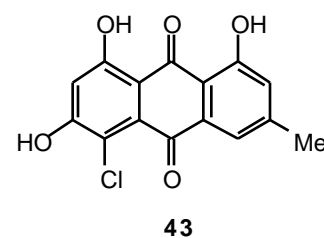
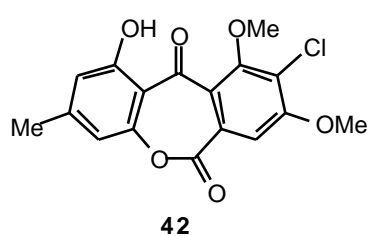
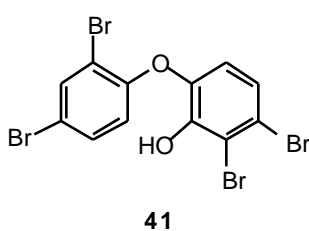
range activity against human cancer cell lines and is now in preclinical drug development (42). Also isolated in this study from *Portieria hornemannii* is the new monoterpene **32** (42). A study of the sea hare *Aplysia punctata* has revealed for the first time seven known halogenated cyclic monoterpenes (43). These compounds are derived from the animals' diet of *Plocamium coccineum* and are apparently used in chemical defense. They are especially toxic to larvae of the crustacean *Artemia salina*.



The antarctic red alga *Pantoneura plocamioides* produces the novel pantofuranoids A-F (**33-38**) (44), which are the first monoterpenes with a tetrahydrofuran ring. The incredibly prolific *Laurencia* red algae continues to be a rich source of novel C-15 nonterpenes. Thus, *L. nipponica* has yielded neoisoprelaufucin (**39**), a stereoisomer of 3*Z*-isoprelaufucin (45), and the Vietnamese *L. pannosa* contains pannosallene (**40**), in addition to the known chloro- and bromofucin (46). An antitumor study of three previously known brominated chamigrane sesquiterpenes has revealed a novel pattern of activity (47).

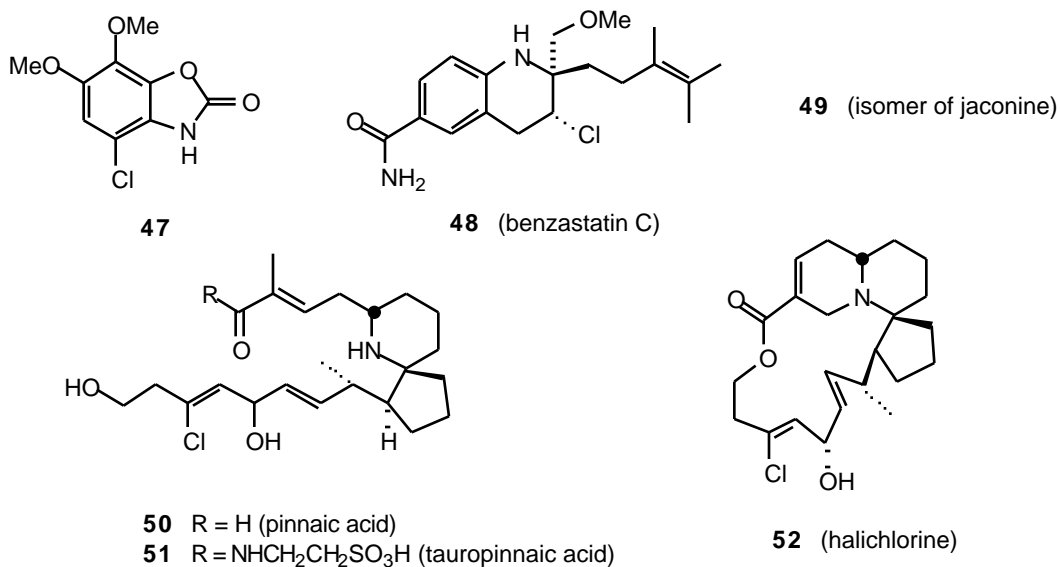


A new diphenyl ether **41** (a "pre-dioxin") has been identified in the sponge *Dysidea* sp. (48), and a new fungal metabolite CT-1 (**42**) is found in *Coniochaeta tetraspora* (49). The lichen *Nephroma laevigatum* has yielded the new 5-chloroemodin anthraquinones **43-45** (50). This study established via radioactive chloride feeding that this lichen can chlorinate the preformed anthraquinone ring system, and that these metabolites arise by the polyketide pathway ( $^{13}\text{C}$ -acetate). A new beticolin O (**46**) has been found in *Cercospora Beticola* (51).

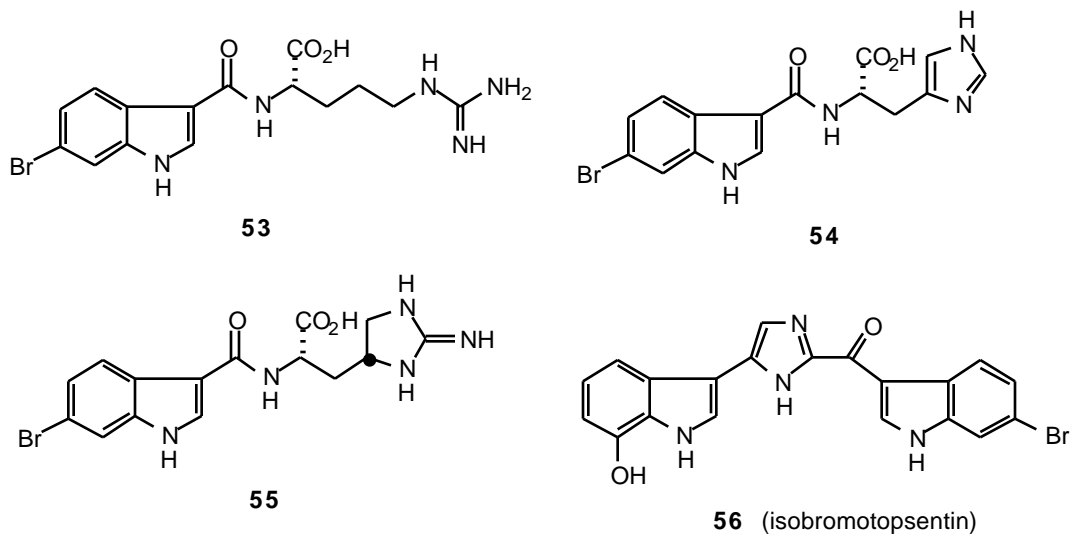


The simple heterocyclic auxin-inhibitor **47** has been isolated from maize (52), and the amide of virantmycin, benzastatin C (**48**), is produced by *Streptomyces nitrosporeus* (53, 54). This compound is a potent free radical scavenger. The previously known acridone alkaloid

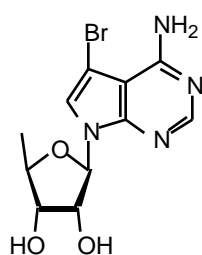
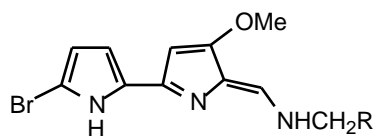
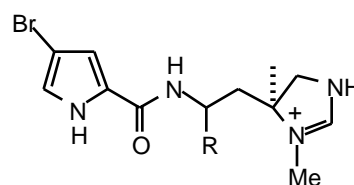
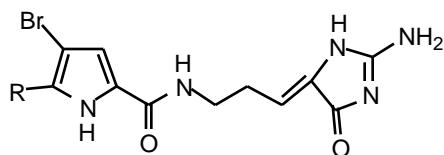
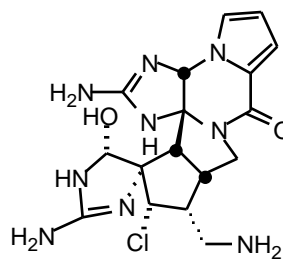
isogravacridonchlorine is produced by cell suspension cultures of *Thamnosma montana* (55). A new chlorine-containing isomer **49** of the pyrrolizidine alkaloid jaconine from *Senecio jacobea* (Tansy Ragwort) has been found (56). The structure remains unknown. The novel fatty acid alkaloids pinnaic acid (**50**) and taupinnaic acid (**51**) have been isolated from the Okinawan bivalve *Pinna muricata* (57). These two compounds have phospholipase A<sub>2</sub> activity. The related halichlorine (**52**) from the sponge *Halichondria okadai* inhibits the induction of VCAM-1 (58).



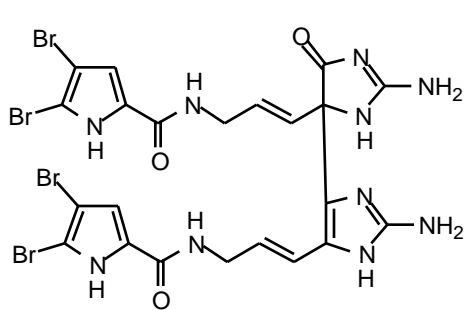
Several newly discovered halogenated indoles from marine sources have been reported since the last *Updates*. The ascidian *Leptoclinides dubuis* has yielded three new brominated indoles **53-55** (59). Metabolite **55** contains the rare amino acid enduracididine. The deep water Australian sponge *Spongosorites* sp. contains the new isobromotopsentin (**56**) (60).



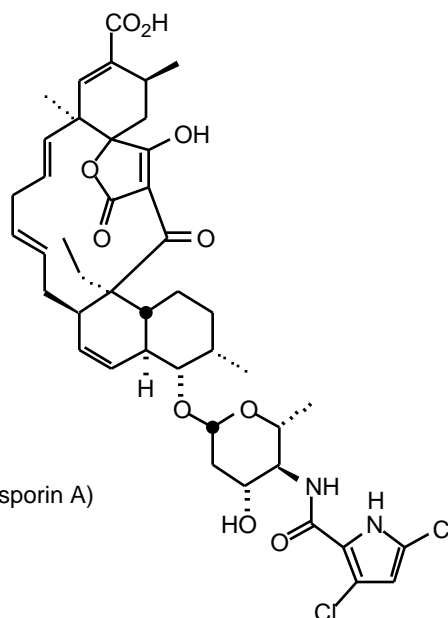
The ascidian *Didemnum voeltzkowi* contains the novel nucleoside **57** along with the previously known iodo analog (**61**). The latter compound is a potent inhibitor of adenosine kinase and of adenosine uptake as is an earlier isolated marine bromopyrrolopyrimidine (**1549** in ref. 6) (**62**, **63**). Several new tambjamines G-J (**58-61**) have been found in the bryozoan *Bugula dentata* (**64**). The sponge *Agelas clathrodes* has yielded clathramides A (**62**) and B (**63**) (**65**), and several Caribbean *Agelas* sponges produce dispacamide **64** and **65** (**66**). The sponge *Stylotella agminata* produces the cytotoxic and immunosuppressive palau'amine (**66**), an alkaloid of great complexity (**67**).

**57****58** R = CH<sub>3</sub> (tambjamine G)**59** R = CH<sub>2</sub>CH<sub>3</sub> (tambjamine H)**60** R = CH(CH<sub>3</sub>)<sub>2</sub> (tambjamine I)**61** R = CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub> (tambjamine J)**62** R = -CO<sub>2</sub><sup>-</sup> (clathramide A)**63** R = -CO<sub>2</sub><sup>-</sup> (clathramide B)**64** R = Br (dispacamide)**65** R = H**66** (palau'amine)

The antifouling metabolite mauritiamine (**67**), which inhibits the growth of the barnacle *Balanus amphitrite*, is produced by the sponge *Agelas mauritiana* (**68**). Pyrrolosporin A (**68**) is a novel chloropyrrole-containing metabolite found in *Micromonospora* sp. (**69**, **70**).

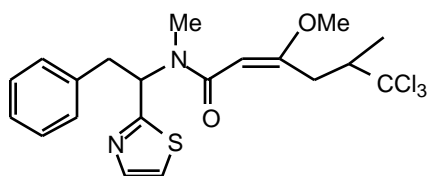


67 (mauritiamine)

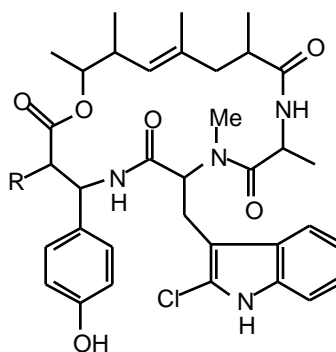


68 (pyrrolosporin A)

The blue-green alga *Lyngbya majuscula* has been a rich source of chlorine-containing metabolites, and the Curacao species has furnished barbamide (**69**) (71). This interesting alga produces four compounds, each of which is toxic to a different predator. The myxobacteria *Chondromyces crocatus* produces the novel chondramides A-D, two of which (**70, 71**) contain chlorine (72). Studies on derivatives of the dichloroproline-containing cyclic peptides astin A and C reveal that the chlorinated ring plays a crucial role in the antitumor activity exhibited by these compounds (74, 75).



69 (barbamide)

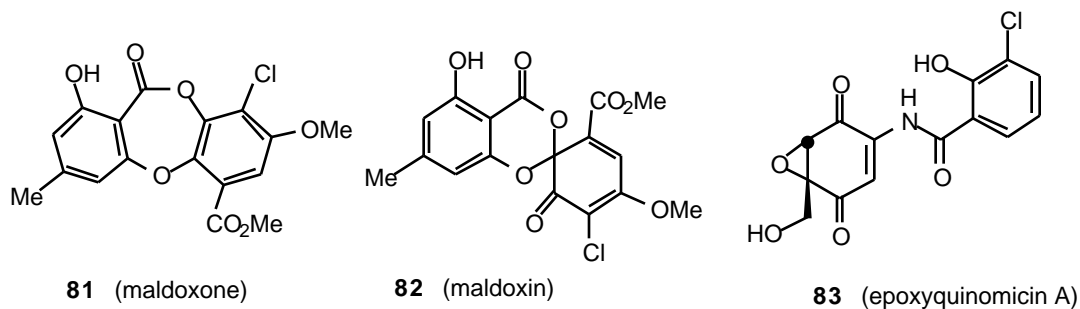
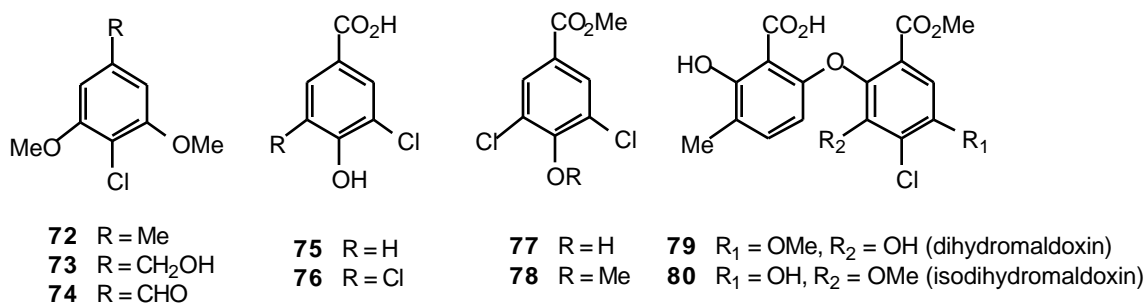


70 R = OMe (chondramide B)  
71 R = H (chondramide D)

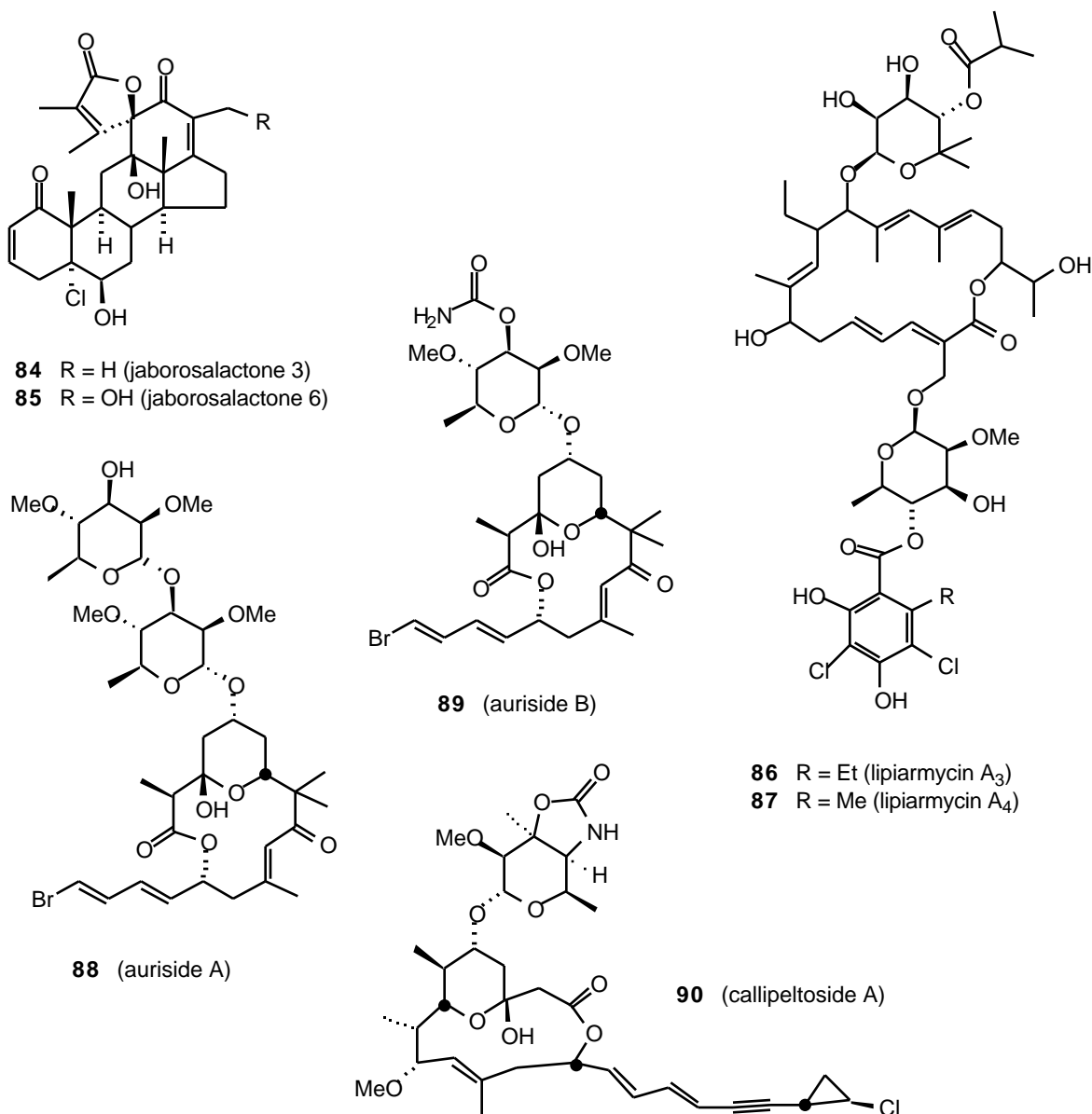
The fungus *Hericium erinaceum* produces three novel orcinols **72-74** (76), *Bjerkandera* sp. has furnished four novel chlorinated benzoic acid derivatives **75-78**, and *B. adusta* produces **75**

(77). The fungus *Xylaria* sp. has yielded the novel diphenyl ethers dihydromaldoxin (**79**) and isodihydromaldoxin (**80**), the depsidone maldoxone (**81**), and maldoxin (**82**) (78).

Epoxyquinomicin A (**83**) is an interesting antibiotic found in *Amycolatopsis* sp. (79). A review of marine bromophenols has appeared (80), a paper which focuses on natural occurrence, mechanisms of formation, toxicology, and significance in foods.



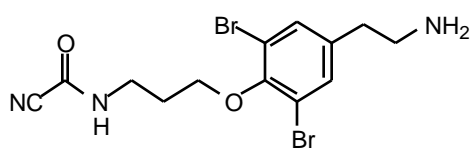
The plant *Jaborosa runcinata* has yielded the new withanolides jaborosalactones 3 (**84**) and 6 (**85**) (81). The previously unknown components of *Actinoplanes deccanensis* (**82**, **83**) have now been identified as lipiarmycin A<sub>3</sub> (**86**) and A<sub>4</sub> (**87**) (84). The Japanese sea hare *Dolabella auricularia* produces the cytotoxic macrolides aurisides A (**88**) and B (**89**) (85). The marine lithistid sponge *Callipelta* sp. has yielded the novel cytotoxic macrolide callipeltoside A (**90**) (86).



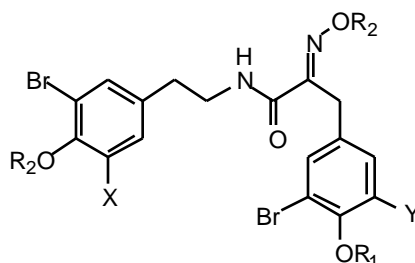
The absolute configuration of the previously described cytotoxic bromine-containing macrolides phorboxazoles A and B has been reported (87, 88). The glycopeptide antibiotics continue to receive a great deal of attention in view of their powerful clinical activity in treating penicillin-resistant bacteria (89). For example, the teicoplanin aglycone has been employed in combinatorial chemistry (90), and dimers of vancomycin — the prototype of this group of glycopeptides — show activity against vancomycin-resistant bacteria (91). The mode of action of these glycopeptides, many of which contain chlorine, continues to be actively studied (92-95). Similarly, the halogen-containing enediyne antitumor antibiotics continue to be intensely examined. For example, a number of hybrid calicheamicin analogs have been designed and synthesized (96-98), and the role of the aromatic iodide unit in the sequence-selective cleavage of DNA by

calicheamicin has been probed (99). The absolute configuration of the enediyne C-1027 chromophore has been determined (100), and the interaction of it with a self-complementary nucleotide hexamer has been examined (101).

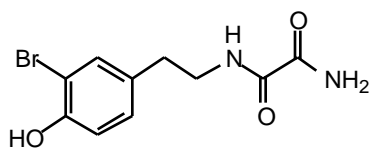
A number of new bromotyrosines were discovered last year. The sponge *Pseudoceratina purpurea* produces ceratinamine (91), which is active against cyrids of the barnacle *Balanus amphitrite* and which is the first example of the cyanoformamide functional group found naturally (102). The sponge *Ianthella basta* has yielded nine new metabolites 92-100 (103), as well as three new bastadins 101-103 (104). Bastadin 102 is the first bastadin disulfate.



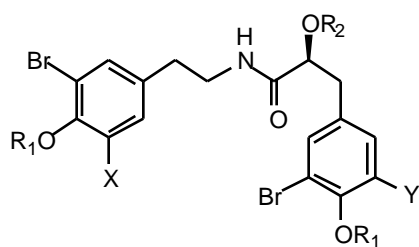
91 (ceratinamine)



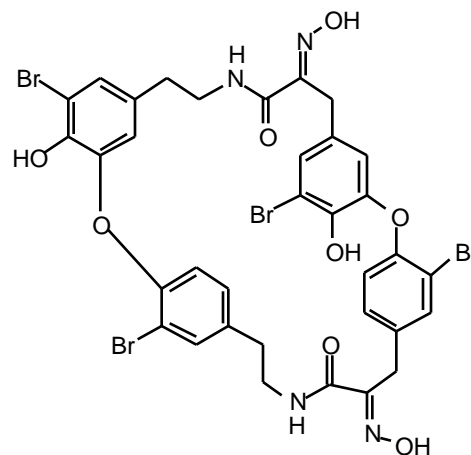
- 92 X = Y = R<sub>1</sub> = R<sub>2</sub> = H (hemibastadin 1)  
 93 X = R<sub>1</sub> = R<sub>2</sub> = H, Y = Br (hemibastadin 2)  
 94 Y = R<sub>1</sub> = R<sub>2</sub> = H, X = Br (hemibastadin 3)  
 95 X = Y = R<sub>2</sub> = H, R<sub>1</sub> = Me  
 96 X = R<sub>2</sub> = H, R<sub>1</sub> = Me, Y = Br



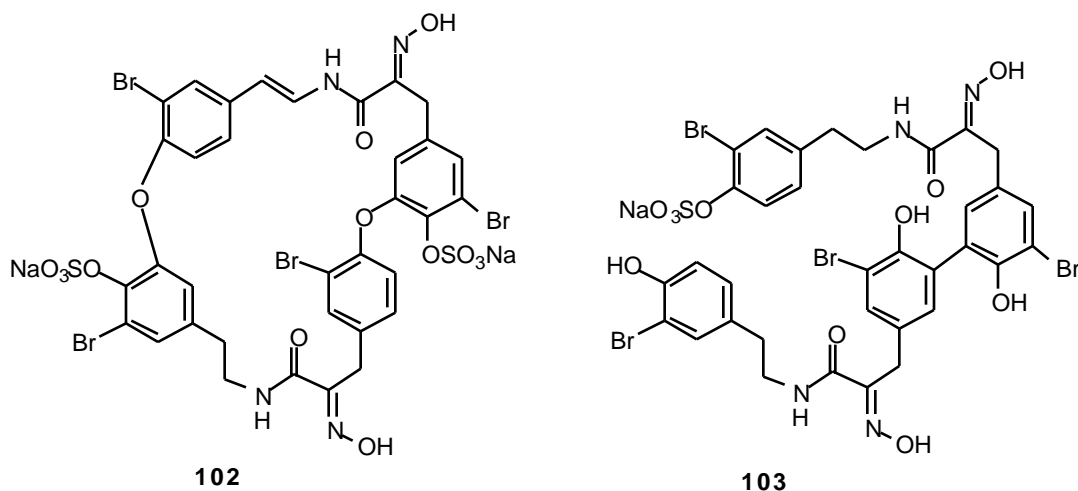
97



- 98 X = Y = R<sub>1</sub> = R<sub>2</sub> = H (hemibastadinol 1)  
 99 X = R<sub>1</sub> = R<sub>2</sub> = H, Y = Br (hemibastadinol 2)  
 100 Y = R<sub>1</sub> = R<sub>2</sub> = H, X = Br (hemibastadinol 3)



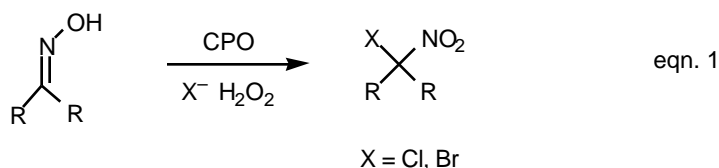
101 (bastadin 20)



### III. Biohalogenation

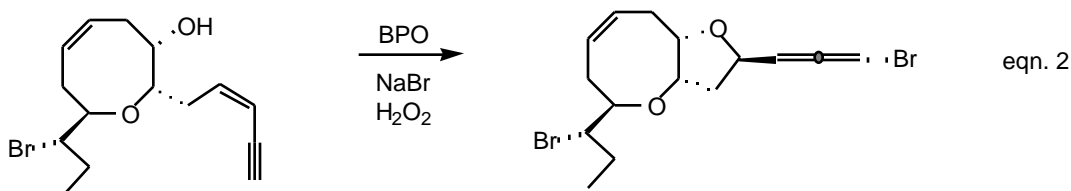
The ever-growing number of natural organohalogens has spawned more studies on the biological formation of these metabolites. As mentioned earlier, an entire symposium was devoted to this topic last year in Amsterdam (3).

The bromoperoxidase (BPO) enzyme presumed to be responsible for the production of volatile organohalogens ( $\text{CHBr}_3$ ,  $\text{CH}_2\text{Br}_2$ ,  $\text{CH}_2\text{I}_2$ ,  $\text{CH}_2\text{ClI}$ ,  $\text{CH}_2\text{BrI}$ ) by marine phytoplankton was isolated for the first time from such organisms (105). An iodoperoxidase was also found in one alga. Indeed, bromoperoxidase activity was detected in 94 species of red (76%), green (71%), and brown (10%) algae surveyed (106). The percentages refer to those species in each phylum that had BPO activity. An X-ray crystal structure of the vanadium-containing chloroperoxidase from the fungus *Curvularia inaequalis* has been determined (107), and the mechanism of the chlorination reaction performed by this enzyme continues to be studied (108). The authors propose an  $\text{Fe(III)-OCl}$  species as the chlorinating agent. Functional models for vanadium haloperoxidase enzymes have been prepared and studied (109). Synthetic applications of chloroperoxidase (CPO) continue to be pursued and an example is shown in eqn. 1 (110).



The conversion of prelaureatin into laurallene, both of which are metabolites in the red alga *Laurencia nipponica*, has been accomplished both chemically and enzymatically with

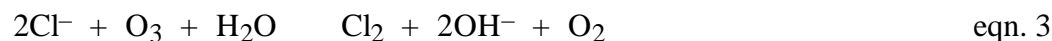
bromoperoxidase (BPO) (eqn. 2) (111).



#### IV. Other Natural Sources of Organohalogens

Researchers at Linköping University in Sweden continue to provide compelling evidence for the natural production of organohalogen compounds in the soil. Organochlorines of high molecular weight were found in the soil collected from a coniferous forest (112). After chemical degradation, lignin-derived chlorinated aromatic compounds were found in all samples. The formation of these organically bound halogens is a function of soil pH (113). Thus, organohalogen material is omnipresent in the soil and is stored in large amounts, and both the *in situ* production and the biodegradation of these compounds occurs in the soil (114, 115). One of the end products of this natural chlorination process is trichloroacetic acid, which is found in bog water, 100-year old glacier ice, snow, rain, and in soil samples (116). Several of these results clearly indicate a natural origin for trichloroacetic acid. Enzymatic studies with CPO, H<sub>2</sub>O<sub>2</sub>, NaCl and the well known soil carboxylic acids (acetic, malic, lactic, fumaric, malonic, citric, acetonedicarboxylic) show that each is converted to trichloroacetic acid under these conditions.

Additional research has corroborated the production of free Cl<sub>2</sub> and HOCl over marine air from sea-salt aerosol (117-119). One possible reaction is shown in eqn. 3.

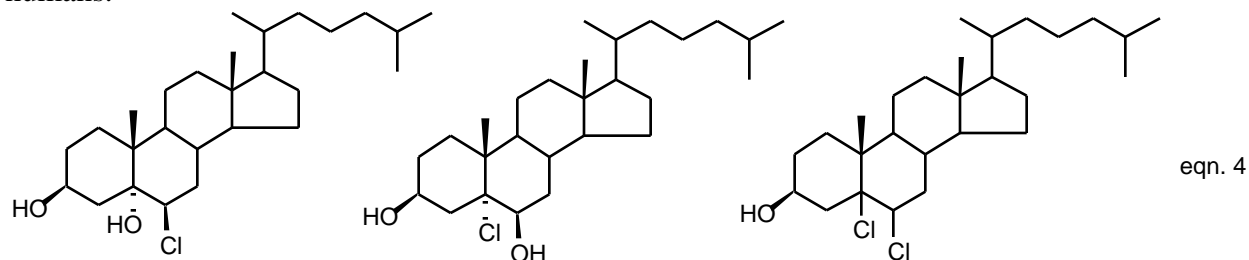


#### V. Human Production of Chlorine and Organochlorines

Unarguably, the most exciting recent development in natural chlorine science is the observation of the production of free chlorine and organochlorine compounds in humans! A recent review of this topic has appeared (120).

Although it has been known for many years that halide is oxidized to free halogen (or hypohalite) in neutrophils as part of the immune system, only recently has free chlorine been

demonstrated to be involved in this process (121). Moreover, free chlorine is involved in the *in vitro* conversion of low density lipoprotein (LDL) cholesterol by myeloperoxidase (MPO) into several chlorinated sterols eqn. 4 (122). These organochlorines have not yet been detected in humans.



In addition, 3-chlorotyrosine has been detected in human atherosclerotic lesions (123), and also as the product of the reaction of human serum albumin with neutrophils with MPO, H<sub>2</sub>O<sub>2</sub>, and chloride (124). In the former study the highest concentration of 3-chlorotyrosine was observed in two patients with known coronary artery disease, and this compound was generally undetectable in the LDL isolated from young, healthy donors. Thus, 3-chlorotyrosine may now be counted as a bonafide human organochlorine compound, although it was previously found in the cuticle of locusts and in *Limulus polyphemus* (6).

A quantitative study determined that 28% of the oxygen consumed by stimulated human neutrophils is used to oxidize chloride ion to chlorinating agents (chlorine) (125). Another group has proposed that the active oxidants produced by human neutrophils are long-lived *N*-chloramines (126). It will perhaps be ironic if a recent study of the aqueous chlorination of purines and pyrimidines, with regard to environmental concerns (127), proves to be relevant to the aqueous chlorination of pathogens by human neutrophils.

## VI. Biodegradation

The metabolism and biodegradation of organohalogen compounds continues to be pursued. The degradation of 2,4,5-trichlorophenol by the white rot fungus *Phanerochaete chrysosporium* has been studied in depth and a detailed mechanism has been advanced (128). The microbial transformation of trichloroethylene to trichloro- and dichloroacetic acid has been found to occur in rodent gut (129). The entire field of the biodegradation of organochlorine compounds has been reviewed (130).

## VII. Function

A recent study seems to reveal that the peroxidase-induced bromination reactions in some marine algae are a means of scavenging excess hydrogen peroxide during oxidative stress (131). The release rates for a number of volatile organobromine and organoiodine compounds from polar macroalgae have been measured and discussed in terms of their importance to the global halogen budget (132). The role of chloromethane as a methyl donor in the biosynthesis of methyl esters and anisoles in wood-rotting fungi has been reviewed (133), and this same author has also summarized the contribution of natural halogenation processes to the formation of other halomethanes and their environmental significance (134). The distinct physiological role of natural chlorinated anisyl metabolites produced by wood-rotting fungi has been demonstrated (135). Thus, these natural chloroaromatics, which are present at concentrations of approximately 75 ppm in wood or environmental litter, are substrates for extracellular aryl alcohol oxidases and generate hydrogen peroxide for ligninolytic enzymes.

The erythrolide metabolites of the gorgonian coral *Erythropodium caribaeorum* have pronounced antifeedant activity against reef fishes at the natural concentrations of these metabolites found in the gorgonian (136). Several synthetic analogs of the brominated aeropylsinin sponge metabolites are more active than the natural products themselves on sodium-potassium ATPase *in vitro* in rat brain microsomes (137). A mechanistic study of the chlorine-containing ochratoxin A has indicated that the toxicity of this compound is likely to involve superoxide radicals and hydrogen peroxide (138). Moreover, the combination of superoxide dismutase and catalase almost completely prevents the nephrotoxicity induced by ochratoxin A in rats.

The possible role of natural methyl chloride in evolution has been discussed, along with a brief summary of other simple organohalogens as produced naturally. Thus, it is estimated that we inhale with each breath  $10^{12}$ - $10^{13}$  molecules of naturally produced methyl chloride! (139).

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