# Natural Halogenated Alkanes, Cycloalkanes and Their Derivatives

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## Abstract

Simple halogenated alkanes and their derivatives comprise relatively large group of natural compounds which were discovered in cyanobacteria, algae, phytoplankton, fungi and plants. The structures of more than 100 compounds are considered.

## Contents

### INTRODUCTION

Halogen-containing ($F^-$, $Cl^-$, $Br^-$ and $I^-$) compounds are widespread in nature. They are synthesized by marine and land plants, bacteria, fungi, insects, marine organisms, even by mammals. Along with halogen-containing compounds generated by living organisms, a large number of halogenated compounds was found to be the products of abiotic origin. These compounds include the majority of halogenated hydrocarbons and their derivatives formed as a result of various geothermal processes, such as eruptions (both on land and under water) [1–12], karst phenomena [13–15], and some meteorological processes (lightning). It should be mentioned that many halogen-containing compounds are the products of human vital activity and are detected in various animal species [16–19].

Marine organisms, first of all algae, invertebrates, cyanobacteria and microorganisms, generate mainly brominated metabolites, chlorinated ones are more rare, and iodine-containing ones are the rarest [20–24]; fluorinated metabolites were not detected in marine organisms. Such a ratio between the brominated and chlorinated compounds is not quite clear since the content of $Cl^-$ ions is several orders of magnitude higher than that of $Br^-$ ions. The concentration of chloride ions in the ocean is 19.000 mg/l, while that of bromide ions is only 65 mg/l [25, 26]. Iodine and bromine in the free state were discovered in some species of algae and invertebrates. For instance, such algae as *Asparagopsis armata*, *Falkenbergia doubleti* and *Bonnemaisonia asparagoides* contain free iodine [27]. Fifty species of cyanobacteria (Cyanophyta), green (Chlorophyta), brown (Phaeophyta) and red (Rhodophyta)

contain free iodine [28], while free bromine was detected in 46 species of sea sponges [29]. Total content of halogens (per dry mass) in algae can be 0.64 % in *Laurencia pacifica* and 0.29 % in *Plocamium pacificum* [30]. Though the concentration of $F^-$ ions in sea water is not high and makes only 1.3 mg/l [25], sea sponge *Halichondria moori* contains potassium fluorosilicate ($K_2SiF_6$) in the amount of 10 % of the dry mass [31]. Though this sponge contains much fluorine, no organic metabolites containing fluorine were detected in this sponge. Fluorine was not detected also in the sponges belonging to this family.

## ALKANES OF ABIOTIC ORIGIN

As we have already mentioned above, halogenated alkanes of abiotic origin include compounds discovered in volcanic gases or in sea water. For example, simple halogenated hydrocarbons, such as $CH_3Br$ [32−34], $CH_3I$ [32, 33], $Cl_2C=CHCl$ [35], $Cl_2C=CCl_2$ [36, 37], $CFCl_3$, $CF_2Cl_2$, $CHFCl_2$ [35−37], $CHF_2Cl$, $F_2C=CF_2$, $FClC=CF_2$, $CCl_2FCClF_2$, $CF_3CF=CF_2$, [35], $CF_4$ [38, 39], $(CH_3)_2SiF_2$ [36, 37], were discovered in gases evolving during eruptions.

Some halogenated alkanes − $CH_3Br$ [40], $CH_3I$ [41−43], $CH_2Br_2$ [42, 44−46], $CHBr_3$ [46−50], $CH_2ClBr$ [45, 49], $CH_2ClI$ [45, 49, 51], $CH_2I_2$ [44, 45, 51, 52], $CHCl_2Br$, $CHClBr_2$ [42, 44−46], $CH_3CH_2CH_2I$, $CH_3CH_2CH_2CH_2I$ [51−53], $CH_3CH_2CH_2CH_2CH_2I$, $CH_3CH_2CH_2CH_2CH_2Br$ [53], $CH_3CH_2CH(CH_3)I$ [51] и $CH_3CCl_3$ [50] − were found in the sea water of the Atlantic, Indian and Pacific oceans, as well as in the water of Arctic and Antarctic, where there is no direct effect of anthropogenic action. The majority of authors of the cited works believe that the above-mentioned halogenated alkanes are of abiotic origin; however, some authors think that these compounds are the products of vital activity of marine microorganisms and/or algae [17, 18, 21]. Many bromine- and iodine-containing simple alkanes were also found in algae.

## ACYCLIC ALKANES AND THEIR DERIVATIVES

Chloromethane ($CH_3Cl$) is generated by some species of parasitic fungi causing wood putre-faction: *Fomes conchatus, F. occidentalis, F. pomaceus, F. ribis, F. rimosus* and *F. robiniae* [54], and also by the fungi belonging to the *Phllinus* genus: *P. ignarius, P. lundelli, P. pomaceus, P. ribis, P. occidentalis, P. pachyploes, P. pini, P. populicola* and *P. trivialis* [55−58]. Fungi *Inonotus andersoni* and *Inonotus hispidus* [57] generate chloromethane which accounts for 75−90 % of all the volatile components. Among 63 species of parasitic fungi causing wood putrefaction and belonging to *Phellinus, Hymeno-chaete, Fomitoporia, Omnia, Inonotus* and *Phaeolus*, only 34 generate chloromethane [57]. Among 27 fungi species of Ganodermataceae and Polyporaceae orders, only one species, namely, *Fomitopsis cytisina*, was able to include chloromethane in other metabolites [57]. These results indicate that wood putrefaction is due to the evolution of chloromethane by fungi, especially by those of *Phellinus* and *Inonotus* geni, which are widespread in tropical and subtropical forests [55, 57, 58].

Chloromethane was also detected in *Agaricus bisporus* fungi [59], in sea phytoplankton [53], in tubers of *Solanum tuberosum* plant [60], in *Endocladia muricata* alga [61], in giant kelp *Macrocystis pyrifera* [62], in pearlworts *Biflustra perfragilis* living near the island of Tasmania (Australia) [63], in cedar and cypress wood [64], and in *Mesembryanthemum crystallium* plant [61].

Dichloromethane ($CH_2Cl_2$) was discovered in in pearlworts *Biflustra perfragilis* living near the island of Tasmania (Australia) [63], in sea kelp macrophytes *Ascophyllum nodosum, Fucus vesiculosis*, green algae *Enteromorpha linza* and *Ulva lacta*, and in red algae *Gigartina stellata* [53].

The presence of chloroform $CHCl_3$ was detected in wood moss, northern white cedar [64], in barley, lemons and oranges [36], in *Cantharellus cibarium* fungi 65], in land plants *Farsetia aegyptia* and *F. ramosissima* [66], in fruit of plants: *Achras sapota* [67], *Sergia lecens* [68] and *Basella rubra* [69]. Sea algae *Asparagopsis taxiformis, A. armata* [69] and *Meristiella gelidium* [70] generate chloroform and other chlorine-containing metabolites. Tetrachloromethane $CCl_4$ was discovered in some land plants [66].
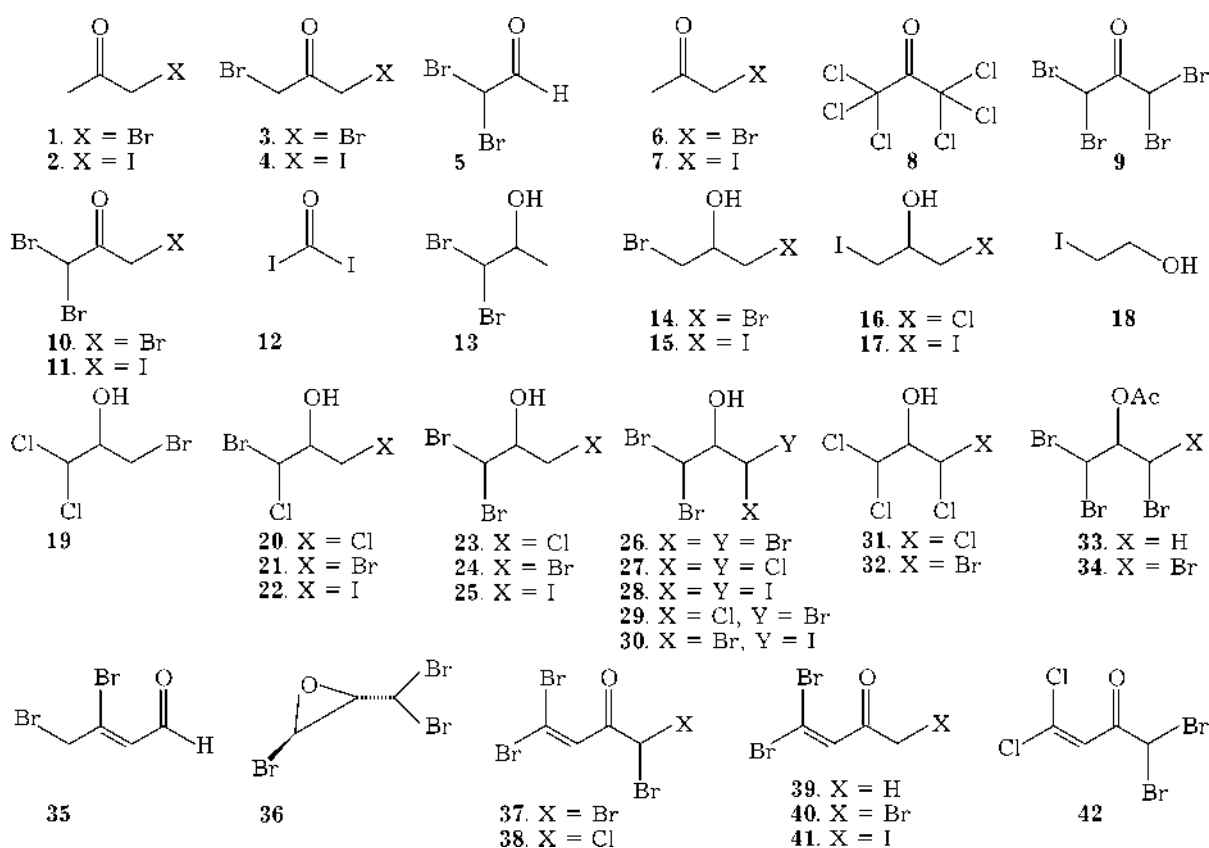
Many algae generate halogenated metabolites and can accumulate them in rather large amounts from seawater. For example, the content of methyl iodide $CH_3I$ in *Laminaria* sp. alga is 1000 times higher than in the oceanic water [71]. Many other sea species of red, green and brown macrophyte algae growing near the coast of South California generate methyl iodide [72]. It is interesting that a number of parasitic fungi of *Fomes* [54] and *Phellinus* [58] geni transform bromide and iodide ions into methyl bromide and methyl iodide, respectively. Bromoform $CHBr_3$ was detected in seawater; however, its main producers are algae and phytoplankton. For instance, about 80 % of all the halogenated metabolites generated by *Asparagopsis taxiformis* alga growing near the Hawaiian Isls is bromoform [73, 74].
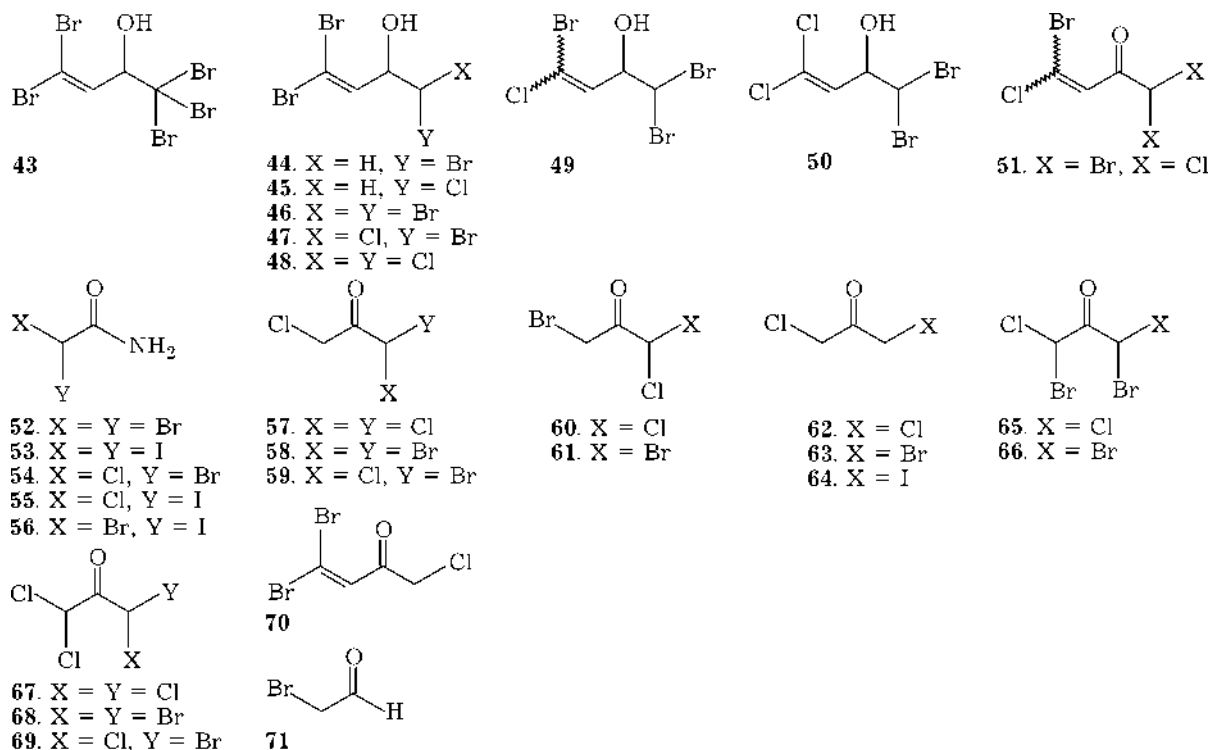
Halogenated alkanes, such as $CH_3Cl$, $CH_3Br$, $CH_3I$, $CH_2Br_2$ and $CHBr_3$, are generated by the brown alga *Macrocycstis pyrifeara* [62, 72, 75]. Brown algae *Eisenia arborea, Egregia menziesii, Custoseria osmundacea* and *Laminaria farlowii* generate $CH_3I$, $CHBr_3$ and $CH_2Br_2$ [72, 75], while *Prerygophora californica* and *Dictyota bingha-*

*mie* contain only $CH_3I$ [72, 75]. Brown alga *Fucus Vesiculosis* generates $CH_2Br_2$, $CHBr_3$, $CHBr_2Cl$, $CH_2Cl_2$, $CHBrCl_2$, $CH_2I_2$, $CH_3I$ and $CH_2ICl$ [52,] 53]; *Ascophyllum nodosum* generates $CHBr_3$, $CHBr_2Cl$, $CH_2Cl_2$, $CHBrCl_2$, $CH_2I_2$, $CH_3I$ [53]. Halogenated alkanes $CH_2I_2$, $CH_3I$, $CHBr_3$, $CHBr_2Cl$, $CH_2Br_2$ and $CHBrCl_2$ were detected in *Fucales sargassum* [44, 45].

Red algae *Corallina officinales,Pterocladia capillacea* and *Rhodymenia californica* synthesize three halogenated alkanes: $CH_3I$, $CHBr_3$ and $CH_2Br_2$ [72]; *Bonnemaisonia hamifera* synthesizes only $CHBr_3$ [76]. *Meristiella gelidium* contains $CH_3I$ and $CH_2ClI$ [70], while *Gigartina stellata* − the same alkanes except $CH_2ClI$ [53].

Two species of the *Asparagopsis* genus (*A. armata* and *A. taxiformis*) generate approximately the same set of halogenated alkanes: $CH_3I$, $CH_2Br_2$. In addition to the indicated halomethanes, *A. taxiformis* alga contains also $CCl_4$, $CHBrClI$, $CH_2BrI$ and $CHI_3$ [69, 73, 74]. Red alga *Asparagopsis taxiformis*, which is spread near the Hawaiian Isls (USA), generates a unique set of halogenated organics (**1**)−(**61**) [73, 74, 77, 78]. The Mediterranean red alga



1. X = Br
2. X = I

3. X = Br
4. X = I

5

6. X = Br
7. X = I

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10. X = Br
11. X = I

12

13

14. X = Br
15. X = I

16. X = Cl
17. X = I

18

19

20. X = Cl
21. X = Br
22. X = I

23. X = Cl
24. X = Br
25. X = I

26. X = Y = Br
27. X = Y = Cl
28. X = Y = I
29. X = Cl, Y = Br
30. X = Br, Y = I

31. X = Cl
32. X = Br

33. X = H
34. X = Br

35

36

37. X = Br
38. X = Cl

39. X = H
40. X = Br
41. X = I

42

**43**

**44.** X = H, Y = Br
**45.** X = H, Y = Cl
**46.** X = Y = Br
**47.** X = Cl, Y = Br
**48.** X = Y = Cl

**49**

**50**

**51.** X = Br, X = Cl

**52.** X = Y = Br
**53.** X = Y = I
**54.** X = Cl, Y = Br
**55.** X = Cl, Y = I
**56.** X = Br, Y = I

**57.** X = Y = Cl
**58.** X = Y = Br
**59.** X = Cl, Y = Br

**60.** X = Cl
**61.** X = Br

**62.** X = Cl
**63.** X = Br
**64.** X = I

**65.** X = Cl
**66.** X = Br

**67.** X = Y = Cl
**68.** X = Y = Br
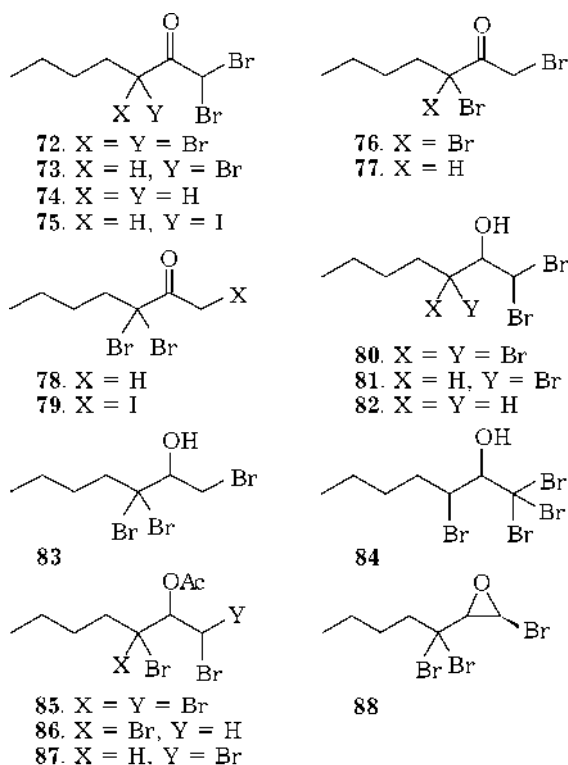**69.** X = Cl, Y = Br

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*Asparagopsis armata* and *Asparagopsis taxiformis* from the Californian Bay (USA) generate halogenated metabolites (**62**)–(**71**) [69, 79].
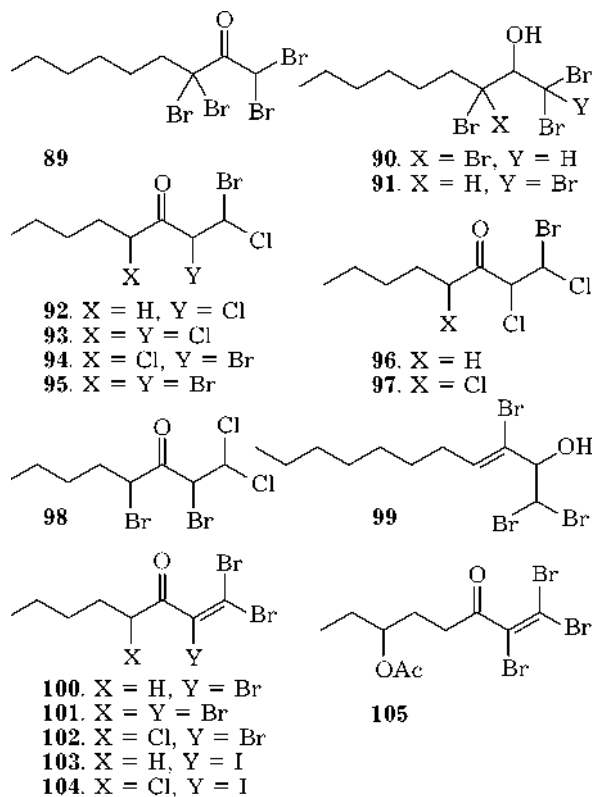
Halogenated metabolites (**72**)–(**88**) were isolated from the red alga *Bonnemaisonia hamifera* [80–82]. Two other species of the same genus, *B. nootkana* and *B. asparagoides* [82, 84] generate metabolites (**89**)–(**91**) and (**92**)–(**98**), respectively [82, 83]. Red algae *Delisea fimbriata* [85] and *D. pulchra* [86] contain compounds (**99**)–(**105**).

Three bromine-containing ketones (**106**)–(**108**) were isolated from red alga *Ptilonia australasica*, dichloroacetoamide (**109**) was discovered in the extract of red alga *Marginisporium aberrans* [87]. Halogenated metabolites (**110**)–(**114**) are generated by the Australian red alga *Falkenbergia rufolanosa* [88].

The most intense works of the recent years dealing with investigation of the occurrence of halogenated alkanes in sea macrophyte algae which are widespread in the Antarctic and Arctic water were carried out by the author of [89–92]. These investigations, which have made a substantial contribution into our notions concerning the ability of sea algae to synthesize halogenated alkanes were summarized in the review [89]. On the basis of investigation of more than 50 species of alga species, the

author concluded that the main generators of halogenated alkanes in polar regions are brown algae. For example, the Antarctic brown algae *Adenocyctis utricularis, Ascoseira mirabilis, Cystosphaera jacquinotii, Desmarestia antarctica, D. anceps, D. menziesii, Halopteris obovata,*

**72.** X = Y = Br
**73.** X = H, Y = Br
**74.** X = Y = H
**75.** X = H, Y = I

**76.** X = Br
**77.** X = H

**78.** X = H
**79.** X = I

**80.** X = Y = Br
**81.** X = H, Y = Br
**82.** X = Y = H

**83**

**84**

**85.** X = Y = Br
**86.** X = Br, Y = H
**87.** X = H, Y = Br

**88**

**89**

**90.** X = Br, Y = H
**91.** X = H, Y = Br

**92.** X = H, Y = Cl
**93.** X = Y = Cl
**94.** X = Cl, Y = Br
**95.** X = Y = Br

**96.** X = H
**97.** X = Cl

**98**

**99**

**100.** X = H, Y = Br
**101.** X = Y = Br
**102.** X = Cl, Y = Br
**103.** X = H, Y = I
**104.** X = Cl, Y = I

**105**

*Himantothalus gradifolius* and *Phaeurus antarcticus* generate $CH_2ClI$, $CH_2I_2$, $CHBrCl_2$, $CHBr_2Cl$, $CH_2Br_2$, $CHBr_3$ and 1,2-$C_2H_4Br_2$ [92]. The concentration of halogenated alkanes is 3.9 mg/g (calculated with respect to the dry mass of the alga) in *Desmarestia anceps*, 1.3 mg/g in *D. menziesii* alga, 0.84 mg/g in *Cystosphaera jacquinotii* and 0.3 mg/g in *Himantothalus gradifolius* alga [92]. High content of $CH_2ClI$ and $CHBrCl_2$ was discovered for the first time in the goldish alga *Antarctosaccion applanatum* (Chrysophyta section). Red and green algae generate the same alkanes but in substantially smaller amount.

High content of halogenated alkanes is also characteristic of the brown algae growing in the Arctic seas. For example, alkanes $CH_2ClI$, $CH_2I_2$, $CHBrCl_2$, $CHBr_2Cl$, $CH_2Br_2$, $CHBr_3$ and 1,2-$C_2H_4Br_2$ were detected in the following species of brown algae: *Alaria* sp., *Chorda filum*, *Ch. tomentosa*, *Chordaria flagelliformis*, *Fucus distichus*, *Dictyosiphon foeniculaceus*, *Pilayella littoralis*, *Laminaria digitata*, *L. saccharina*, *L. Solidungula*. The concentration of halogenated alkanes was lower than that in the Antarctic species of brown algae, varying within 0.15−0.30 mg/g of the dry mass [91].

Red algae contained a small amount of halogenated alkanes, while high level of alkanes $CH_2ClI$, $CHBrCl_2$, $CHBr_2Cl$, $CH_2Br_2$, $CHBr_3$ and 1,2-$C_2H_4Br_2$ was discovered the green algae *Urospora penicilliformis*, *Blidingia minima*, *Acrosiphonia sonderi*, *Monostroma arcticum*, *Enteromorpha compressa* and *Chaetomorpha melagonium* [91].

A number of green algae from the tropic seas also generate halogenated alkanes. For instance, *Ulva sp.* and *Enteromorpha intestinales* [72] generate $CH_3I$, $CHBr_3$ and $CH_2Br_2$; *Penicillus capitalus* generate only one alkane $CHBr_3$. The *Entoromorpha linza* and *Ulva lacta* algae generate the same compounds: $CHBrCl_2$, $CHBr_2Cl$, $CH_2Br_2$, $CHBr_3$, $CH_2Cl_2$, $CH_2I_2$ and $CH_3I$ [53].

According to the data obtained by the researchers from the Stockholm University [93], tropical algae *Hypnea spinoides*, *Grateloupia doryphora* and *Falkenbergia hillebrandii* (the Canary Isls, Spain) more actively generate halogenated alkanes ($CH_3I$, $CHCl_3$, $CH_3CCl_3$, $CCl_4$, $CHBrCl_2$, $CH_2Br_2$, $CHCl=CCl_2$, $CH_3CHICH_3$, $CH_2ClI$, $CHBr_3$, $CH_2CH_2CHICH_2CH_3$, $Cl_2C=CCl_2$, $CHBr_2Cl$, $CH_3CH_2CH_2CH_2I$ and $CH_2I_2$) in daytime from 10 A.M. till 14 and at the temperature of 28 °C. At night and at lower temperature, the biosynthesis of alkanes decreases by a factor of 2−3.

Some sea microalgae isolated from phytoplankton are also the source of halogenated alkanes. For example, *Nitzschia* sp. and *Porosira glacialis* contain the same set of halogen-sub-

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**107**

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**109**

**110**

**111**

**112.** X = Br, R = Me
**113.** X = Br, R = Et
**114.** X = I, R = Et
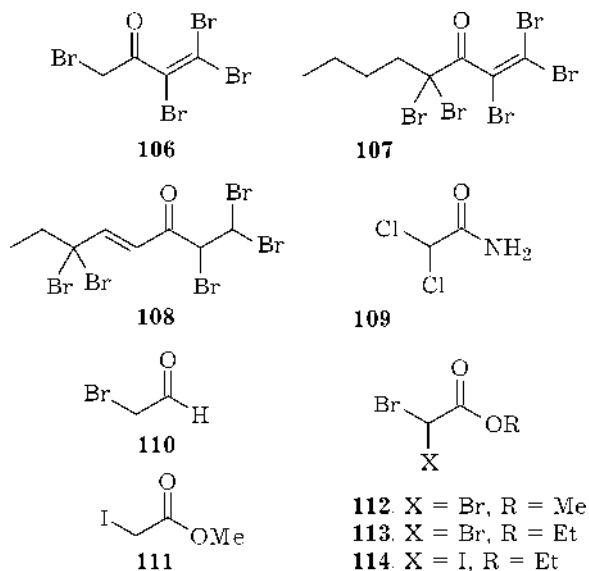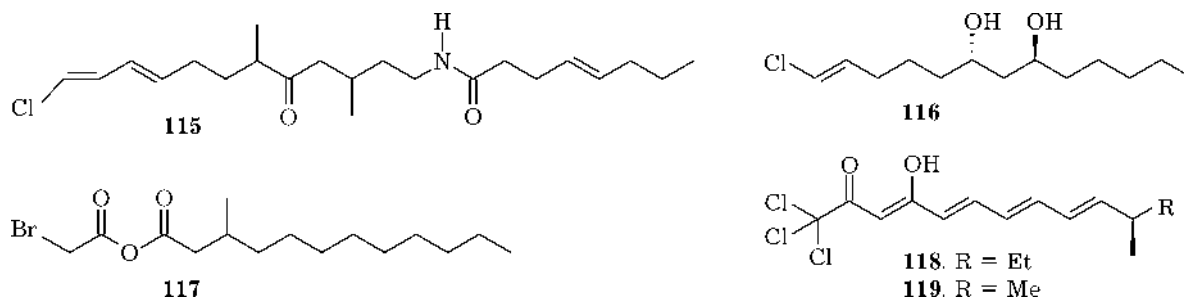
stituted alkanes: $CH_2ClI$, $CHBr_2Cl$, $CHBr_3$ and $CH_2Br_2$ [94]. The compounds $CH_3Br$, $CH_2BrCl$, $CHBrCl_2$, $CHBr_2Cl$, $CHBr_3$ and $CH_2Br_2$ are the products of the vital functions of *Nitzschia stellata* and *Porosira pseudodenticulata* [95].

A new chlorine-containing amide pitiamide A (115) was isolated from a symbiotic mixture of cyanobacteria *Lyngbya majuscula* and *Microcoleus* sp., which naturally inhabit *Porites cylindrical* coral near the Guam Is. (USA) [96]. Another metabolite, 1-chlorotridec-1(E)-en-6(R)-diol (116), is generated by cyanobacteria *Lyngbya majiscula* and a mixture of cyanobacteria *Schzothrix calciola* and *Oscillatoria nigroviridis* [97]. This metabolite exhibited high activity against pathogenic microorganism *Mycobacterium smagmatis*.

Bromine-containing metabolite (117) was the first halogen-containing compound isolated from normal human cerebrospinal fluid [98]. It has physiological functions of hormones.

Two new polyenes, neocarziline A (118) and B (119), are generated by *Stroptomyces carzinostaticus* fungus [99]. Neocarziline B (119) exhibited high activity against the leukemia cells K562.

## ALICYCLIC ALKANES

Halogenated alicyclic alkanes comprise a small group of natural metablites. Caldariomycine (120) was isolated for the first time in 1940 from *Caldariomyces fumago* fungus [100]. Its bromide-containing analog (121) is generated by the same fungus when bromide ion is present in the incubation mixture [101]. The structure of (120) was confirmed by synthesis [102]. Brominated dihydrofulvene (122) was discovered in the Australian alga *Vidalia spiralis* [103]. The *Mollisia* fungus generates inhibitors of phosphodiesterases. For instance, compounds (123), (127)−(129) inhibit phosphodiesterases KS-
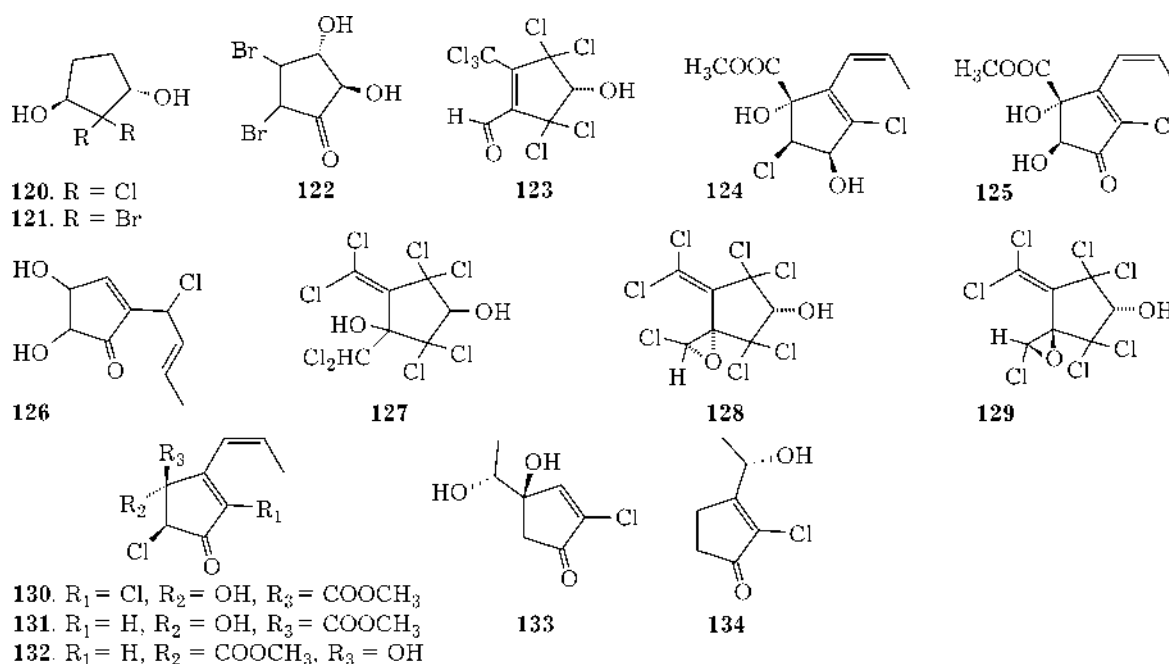
504E, KS-504D, KS-504B and KS-504A, respectively [104, 105].

The derivatives of cyclopentanone (**124**), (**125**), (**130**)−(**132**) are generated by several different fungi. The *Cryptosporiopsis* sp. contains metabolite (**124**) [106], and *Periconia macrospinosa* fungus contains chlorocyclopentadiol (**125**) ]107]. Cryptosporiopsine (**130**) and compounds (**131**), (**132**) were detected in *Sporormia affinis* fungus [108]. The same metabolites (**130**)−(**132**) are generated by *Periconia macrospinosa* [107], *Cryptosporiopsis* sp. and *Phialophra asteris* f. sp. *helianthi* fungus [110]. Cryptosporiopsine (**130**) inhibits the growth of pathogenic sunflower fungus *Sclerotina sclerotiorum* [110]. A new biologically active cyclopenthenone (**126**) inhibiting the development of carcinoma was isolated from the fungus related to *Ascomycota* [111]. Trichodenones B (**133**) and C (**134**) are generated by microorganism *Trichoderma harzianum* (OUPS-N115 strain), which is a symbiont of the sea sponge *Halichondria okadai* [112].

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