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CHLORINE-CONTAINING NATURAL COMPOUNDS IN HIGHER PLANTS

KJELD C. ENGVILD

Agricultural Research Department, Risø National Laboratory, DK-4000 Roskilde, Denmark

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Key Word Index—Asteraceae; chlorine-containing compounds; halogenated compounds; acetylenes; terpenoids; sesquiterpenoids; alkaloids; maytansinoids; phenolics.

Abstract—More than 130 chlorine-containing compounds have been isolated from higher plants and ferns; about half are polyacetylenes, thiophenes and sesquiterpene lactones from the Asteraceae. A chlorinated chlorophyll may be an important part of photosystem 1. High biological activity is found in 4-chloroindoleacetic acid from pea and in the cancerostatic maytansinoids. Many compounds are chlorohydrins isolated along with the related epoxides. Some compounds, like gibberellin A_6 hydrochloride from bean, are perhaps artefacts.

INTRODUCTION

Natural chlorine-containing compounds of higher plants were last reviewed in 1973 [1–3]. They are not very common, although halogen compounds are frequently found in certain marine algae and in fungi [4, 5]. However, they may be more important than the low frequency of their isolation suggests. Chlorine-containing compounds often show strong biological activity. Many antibiotics, fungicides, herbicides and pesticides contain chlorine or other halogens. Man and higher animals contain the iodinated hormone thyroxine and the bromine-containing sleep-related substance **1** [6, 7].

Some of the natural chlorine-containing compounds of plants also have strong biological activity, either within the plant itself as plant hormones or against other organisms as antifeedants or toxins. Chlorine-containing compounds are probably more common in plants than realized today since at least 11 out of 15 crop species incorporated $^{36}Cl^-$ into lipid-soluble compounds migrating on TLC [8].

The presence of covalently bound chlorine in a plant compound was probably first established in 1951 in sceleratinic acid lactone from the highly toxic *Senecio sceleratus* [9]. However a detailed chemical structure was first published in 1958 on an acetylenic chlorohydrin by Bohlmann's group [10].

POLYACETYLENES AND THIOPHENES

The chlorine-containing acetylenes and thiophenes are found in secretory canals in the Asteraceae. Some of the straight chain acetylenic chlorohydrins (**2–8**) are found in gram quantities in *Centaurea ruthenica* [10–13], and *C. scabiosa* [14] and **6** in *Carthamus tinctorius* [15]. The structures **4** and **5** have been confirmed by synthesis [16]. Polyacetylenes with one thiophene ring (**9–16**) are found in several genera: **10, 16** and **19** in *Eclipta erecta* [18], **11** and **12** in *Echinops sphaerocephalus* [17], **12** and **13** in *Pluchea dioscoridis* [19], and **14, 15** and **17** in *Pterocaulon virgatum* [20]. Dithiophenes (**17–20**) have been found in *Tagetes minuta* [21], *Berkheya adlamii* [22] and in *Epaltes brasiliensis* [23].

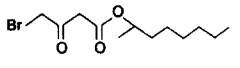
A number of cyclic compounds (**21–28**) probably derived from chlorohydrins have been isolated from species of *Anaphalis* [24, 25], *Gnaphalium* [25] and *Dicoma* [26]. The structures of some of these compounds have been confirmed by synthesis [27, 28]. Very interesting chlorophenols (**29–32**) were isolated from *Helichrysum* species [29, 30]. Further information about the distribution of chlorine-containing polyacetylenes can be found in ref. [31].

IRIDOIDS

The known chlorine-containing monoterpenoids are iridoids: linarioside (**33**) from *Linaria japonica* [32] and *Cymbalaria muralis* [33], both Scrophulariaceae; 7-chlorodeutziol (**34**) of *Mentzelia decapetala* (Loasaceae) [34], valechlorine (**35**) and valeridine (**36**) of *Valeriana officinalis* [35]; eustoside (**37**) of *Eustoma russellianum* (Gentianaceae) [36]; and cistachlorin (**38**) of *Cistanche salsa*, Orobanchaceae [37].

SESQUITERPENE LACTONES

Chlorine-containing sesquiterpenoids are found in the Asteraceae. The first, eupachlorin (**39**), eupachlorin acetate (**40**) and eupachloroxin (**42**), were isolated from *Eupatorium rotundifolium* by Kupchan's group [38, 39] with extensive controls showing that the compounds were not artefacts. Eupachloroxin and eupachifolin-D (**41**) were isolated from other species of *Eupatorium* [40, 41].

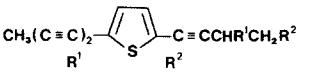
1 

$CH_3(C\equiv C)_4CH=CHCHR^1CH_2R^2$

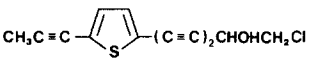
	R^1	R^2
2	OH	Cl
3	OAc	Cl
4	Cl	OH
5	Cl	OAc

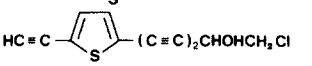
$CH_3CH=CH(C\equiv C)_3CH=CHCHR^1CH_2R^2$

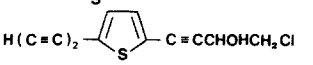
	R^1	R^2
6	OH	Cl
7	Cl	OAc
8	Cl	OH

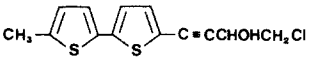


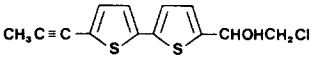
	R^1	R^2
9	OH	Cl
10	OAc	Cl
11	Cl	OH
12	Cl	OAc
13	Cl	OiVal

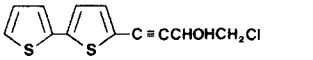
14 

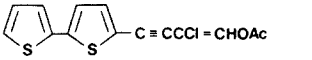
15 

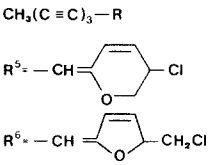
16 

17 

18 

19 

20 

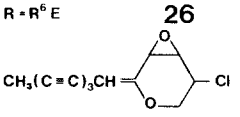


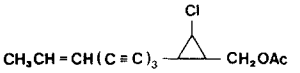
21 R = R^5 E 22 R = R^5 Z

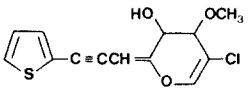
23 R = R^6 E 24 R = R^6 Z

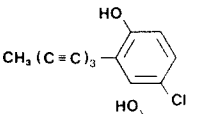
$CH_3CH=CH(C\equiv C)_2-R$

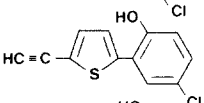
25 R = R^6 E 26 R = R^6 Z

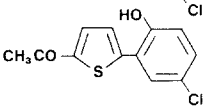
27 

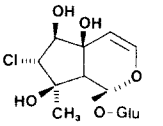
28 

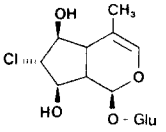
29 

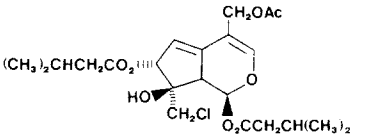
30 

31 

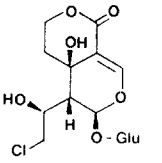
32 

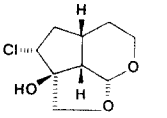
33 

34 

35 

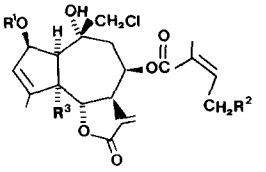
36 R—35

37 

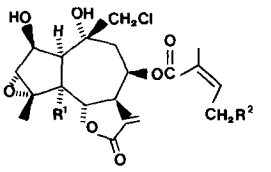
38 

Graminichlorin (**43**), spicatin hydrochloride (**44**) and desacetylspicatin hydrochloride (**45**) were isolated from *Liatris graminifolia* [42], *L. pychnostachya* [43] and *L. squarrosa* [44].

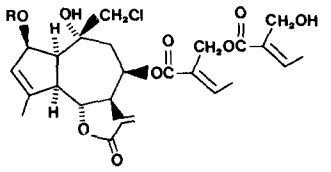
Centaurepensin (**47**; = chlorohyssopifolin A) was isolated from *Centaurea repens* [45–47], chlorohyssopifolin B (**46**) from *C. hyssopifolia* [45], as were chlorohyssopifolins D (**48**) and E (**49**) [47, 48]. Acroptilin (**54**; = chlorohyssopifolin C) was isolated from *Acroptilon repens* [49, 50]. Linichlorins A (**51**), B (**55**) and C (**56**) were isolated from *Centaurea linifolia* [51, 52], chlorojanerin (**57**) from *C. janeri* and *Jurinea derderioides* [53, 54], and elegin (**52**) and salegin (**50**) from *Saussurea elegans* [55–57]. Compound **53** was isolated from *Centaurea imperialis* [58]. There is confusion about the correct structure of some of these compounds [47, 48, 50] and it is not clear if linichlorin A (**51**) and elegin (**52**) are identical [51, 56].



	R^1	R^2	R^3
39	H	H	OH
40	Ac	H	OH
41	Ac	OH	H

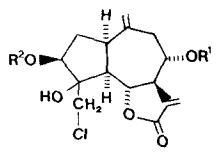


	R^1	R^2
42	OH	H
43	H	OAc

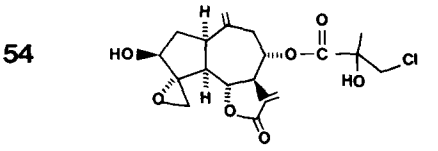


44	R = Ac
45	R = H

Chlorodihydroatripliciolide derivatives (**58–61**) were isolated from *Calea pilosa*, *C. morii* [59] and *C. villosa* [60], and 3-chlorodihydroleucodins (**62–64**) from *Lasiolaena santosii* [61]. Compound **65** was isolated from *Lasiolaena morii* [62] and **66** from *Trichogonia gardneri* [63]; however, **65** may be deacetylated **66** [63]. The chlorodihydroleucodins are not chlorohydrins, but contain chlorine in vinylic linkage. Chlorfastin (**67**) occurs in *Ajania fastigiata* [64] and bibsanin (**68**) in *Achillea biebersteinii* and *A. santolina* [65]. Chlorochrymorin (**69**) was isolated from *Chrysanthemum morifolium* [66], while a chlorinated guaianolide lactone (**70**) was obtained from the artichoke, *Cynara scolymus* [67], and a chlorinated heliangolide (**71**) from *Liatris acidota* [68]. Some of the



	R^1	R^2
46	H	H
47	—COC(CH$_3$)OHCH$_2$Cl	H
48	—COC(CH$_3$)OEtCH$_2$OH	H
49	—COCCH$_3$OHCH$_2$OH	H
50	—COC(CH$_3$)OHCH$_2$Cl	Ac
51	—COC(CH$_3$)=CH$_2$	H
52	—COC(CH$_3$)=CH$_2$	H
53	—COC(CH$_3$)=CHCH$_2$OH	H



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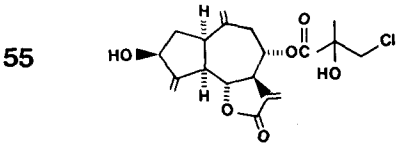

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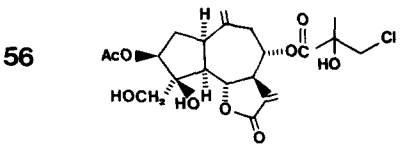

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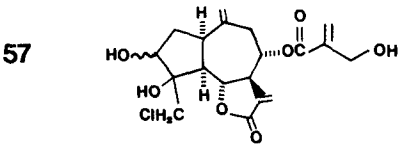

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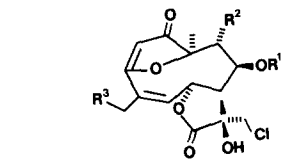
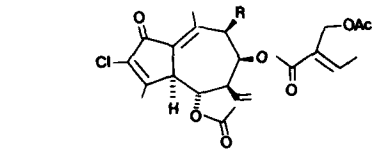
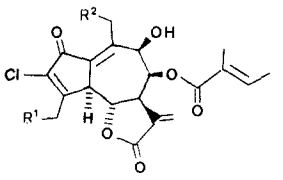


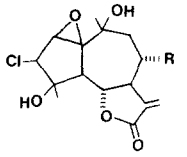
	R^1	R^2	R^3
58	Ang.	H	H
59	Ang.	OH	H
60	Tigl.	H	H
61	Ang.	H	OH



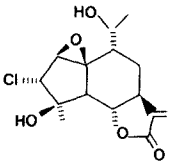
	R
62	OAc
63	H
64	OH



	R^1	R^2
65	OH	H
66	H	OAc



67 R=H
68 R=OH



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chlorinated sesquiterpene lactones show anticancer activity [38, 39, 69], but are probably not as active as the maytansinoids.

PTEROSINOIDS

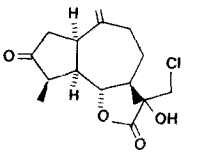
The pterosinoids are sesquiterpenoids containing one benzene ring which occur in ferns. The chlorine is bound to the aliphatic part of the molecule. Although most of the pterosinoids were isolated during a search for the toxic and carcinogenic compounds of Bracken fern [70, 71], they are not themselves toxic [72]. Pterosins F (**72**), J (**73**) and K (**75**) were isolated from *Pteridium aquilinum* [70, 71, 73, 74] and hypolepin A (**74**) from *Hypolepis punctata* [75].

DITERPENOIDS

Gutierolide (**76**) was isolated from *Gutierrezia dracunculoides* (Asteraceae) [76], ajugamarin chlorohydrin (**77**) from *Ajuga nipponensis* (Lamiaceae) [77] and tafricanins A (**78**) and B (**79**) from *Teucrium africanum* (Lamiaceae) in gram quantities [78].

STEROIDS AND GIBBERELLINS

Some Solanaceae contain gram quantities of steroidal lactone chlorohydrins. Jaborosalactones C (**80**) and E (**81**) were isolated from *Jaborosa integrifolia* [79], 6-chloro-5-hydroxywithaferin (**82**) from *Withania frutescens* [80], 6-chloro-5-hydroxywithanolide (**83**) from *Withania somnifera* [81], deoxyphysalolactone (**84**), physalolactone (**85**) and physalolactone C (**86**) from *Physalis peruviana* [82–84]. Bourjotinolone C (**87**) (a possible artefact) was isolated from *Flindersia bourjotiana* (Rutaceae) [85].



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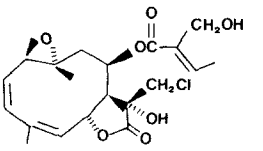

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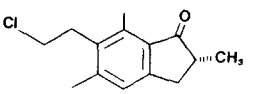

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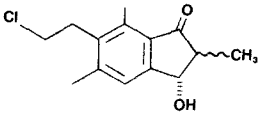

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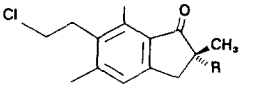
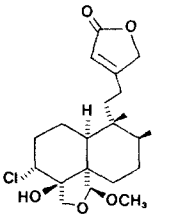


74 R = CH_3 75 R = CH_2OH



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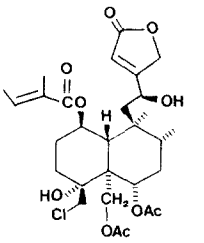

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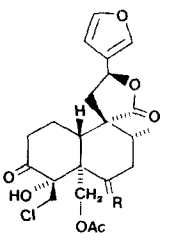
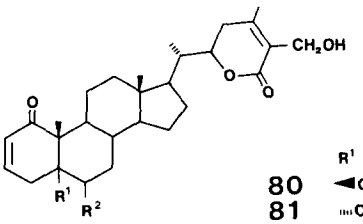
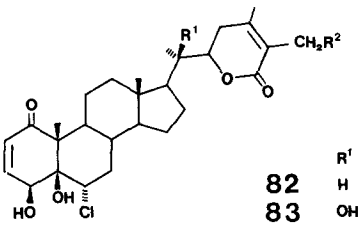


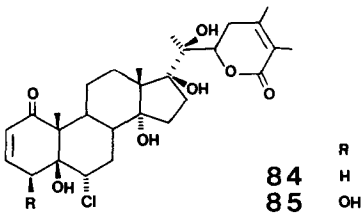
78 R=O
79 R=OAc, H



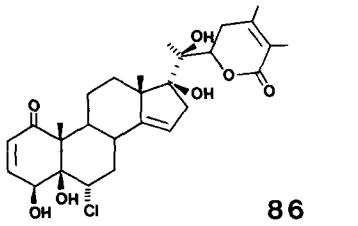
	R^1	R^2
80	◀OH	⁞⁞Cl
81	⁞⁞Cl	◀OH



	R^1	R^2
82	H	OH
83	OH	H



	R
84	H
85	OH



86

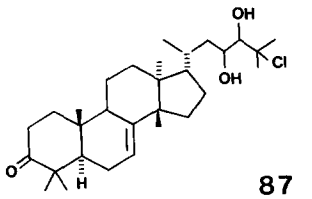
A gibberellin from bean, compound b [86, 87], believed to be GA_6 chlorohydrin (**88**), is almost as active a hormone as GA_3 [86]. However, later work indicated that compound b is probably an artefact [88].

MAYTANSINOIDS

The maytansinoids are interesting macrolides with considerable anti-tumour activity. The chlorine is attached to a benzene ring *ortho* to a methoxy group and an amino group. The benzene ring and the nitrogen are part of the macrocyclic structure. Maytansinoids are found in several plant families, typically in very low concentrations. The scarcity and high cost have limited the clinical evaluation of these compounds [89], but the isolation of maytansinoids from the microorganism *Nocardia* may change this [90].

The first maytansinoids maytansine (**89**), maytanprine (**90**) and maytanbutine (**91**) were isolated by Kupchan's group [91, 92] from *Maytenus serrata* (syn. *M. ovatus*) and *Maytenus buchanii*, Celastraceae, in their search for anti-tumour agents. Maytanvaline (**92**), maytanbutacine (**103**) and maytanacine (**97**) were isolated from *Maytenus* sp. or *Putterlickia verrucosa*, Celastraceae [93, 94], as were the maytansides normaysine (**93**), maysine (**94**), maysenine (**95**) and maytansinol (**96**) which have much less biological activity.

Colubrinol (**101**) and colubrinol acetate (**102**) were found in *Colubrina texensis*, Rhamnaceae [95] while normaytansine (**98**) and normantancyprine (**99**) occur in *P. verrucosa* [96, 97]. Many maytansinoids have recently been isolated from *Trewia nudiflora*, Euphorbiaceae [98–100], namely trewiasine (**104**), dehydrotrewiasine (**105**), demethyltrewiasine (**106**), 10-epitrewiasine (**107**), nortrewiasine (**100**), treflorine (**108**), trenudine (**110**) and *N*-methyltrenudone (**109**).



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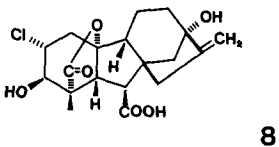
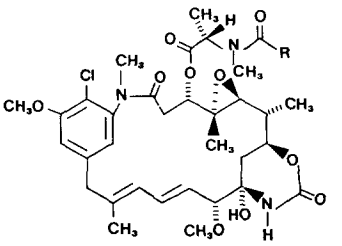


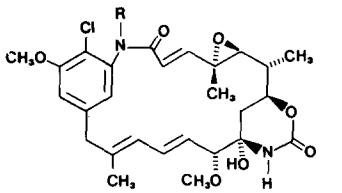
88

ALKALOIDS

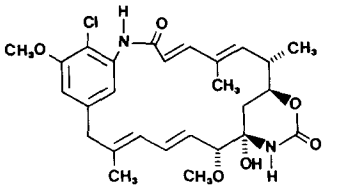
Four types of chlorinated alkaloids are known. The pyrrolizidine alkaloidal chlorohydrins of *Senecio* species



89	R=CH_3
90	R=C_2H_5
91	R=$-CH(CH_3)_2$
92	R=$-CH_2CH(CH_3)_2$



93	R=H
94	R=CH_3



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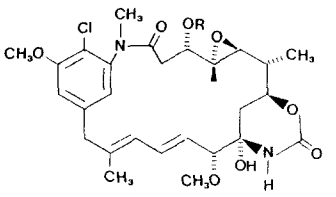
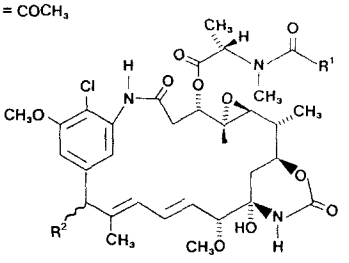
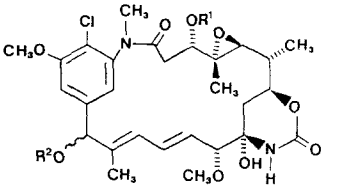


96 R = H
97 R = $COCH_3$



	R¹	R²
98	CH_3	H
99		H
100	$-CH(CH_3)_2$	OCH_3



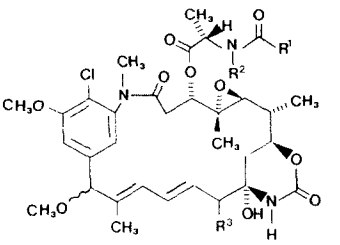
	R¹	R²
101	$-COCH(CH_3)N(CH_3)COCH(CH_3)_2$	H
102	$-COCH(CH_3)N(CH_3)COCH(CH_3)_2$	$COCH_3$
103	$-COCH(CH_3)_2$	$COCH_3$

(Asteraceae) are very toxic. Sceleratinic acid lactone, a degradation product of chlorodeoxysceleratine, was isolated in 1951 and found to contain chlorine [9], but its structure (**111**) was only clarified later [101, 105]. The structure of jaconine (**112**) from *Senecio jacobaea* was solved in 1959 [102]. A dehydro derivative of jaconine (**113**) also probably occurs naturally [103, 104]. Chlorodeoxysceleratine (**114**) was isolated from *Senecio sceleratus* [105] while doronine (**115**) was obtained from *Doronicum macrophyllum* (Asteraceae) [106].

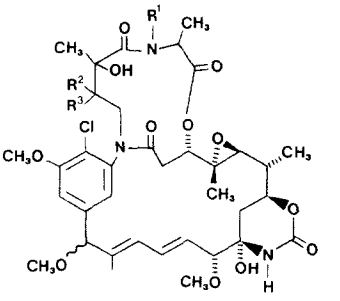
A pyrrolizidine alkaloid (lolidine, **116**) with chlorine attached to the ring has been isolated from *Lolium cuneatum* (Poaceae) [107]. Acutumidine (**117**) and acutumine (**118**) were found in *Sinomenium acutum*, *Menispermum dauricum* and *M. canadense* (all Menispermaceae). Acutuminine (**119**) was found in *M. dauricum* leaves [108–111]. From the roots of *Ruta graveolens* (Rutaceae) gravacridonchlorin (**120**), gravacridonolchlorin (**121**) and isogravacridonchlorin (**122**) were isolated [112, 113].

CHLORINATED CHLOROPHYLL

A chlorinated chlorophyll (**123**), also known as chlorophyll-RCI, has been isolated from algae in microgram quantities, but it is also present in spinach, *Spinacia oleracea* [114–116]. It seems to be closely related to P-700,

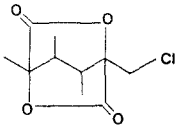


	R¹	R²	R³
104	$-CH(CH_3)_2$	CH_3	OCH_3
105	$-C(CH_3)=CH_2$	CH_3	OCH_3
106	$-CH(CH_3)_2$	H	OCH_3
107	$-CH(CH_3)_2$	CH_3	OCH_3

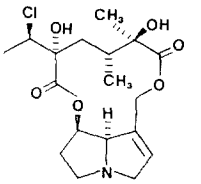


	R¹	R²	R³
108	H	H	H
109	CH_3	=O	
110	H	OH	H

111

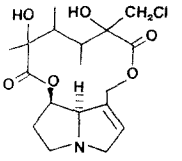


112



113 112 - 2H

114



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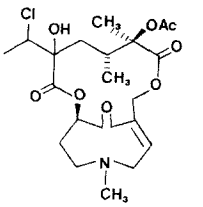

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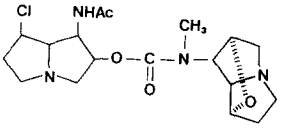
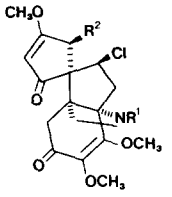
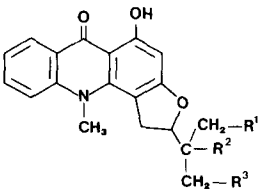


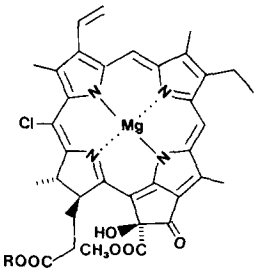


	R^1	R^2
117	H	OH
118	CH_3	OH
119	CH_3	H

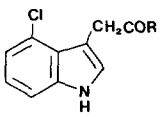


	R^1	R^2	R^3
120	OH	Cl	H
121	OH	Cl	OH
122	Cl	OH	H

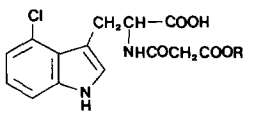
123



R = Phytyl ?



124	R=OH
125	$R=OCH_3$
126	$R=-NH(CHCH_2COO-)H.CH_3$ (COO−)



127	$R=CH_3$
128	$R=C_2H_5$

the reaction centre of photosystem 1. However, chlorinated chlorophyll is a well known artefact [117], and much more work is needed before chlorochlorophyll can be finally accepted as a genuine natural compound with a well defined function in photosynthesis.

CHLOROINDOLES AND AMINO ACIDS

From immature seeds of pea, *Pisum sativum*, 4-chloroindoleacetic acid (**124**) and its methyl ester (**125**) [118–120], an aspartate conjugate (**126**) [121], and two derivatives of 4-chlorotryptophan (**127, 128**) [122] were isolated. 4-Chloroindoleacetic acid is the strongest natural auxin known, being about 10 times more active than IAA [123], but with interesting differences in sensitivity between species [124]. Compound **125** is present in tens of mg per kg in pea and *Vicia faba* [125, 126], and is present in *Lens culinaris* and *Lathyrus* and *Vicia* species [127], but it has not been found outside the tribe Vicieae [128; Engvild, unpublished].

PHENOLICS

One chlorinated flavonoid, 6-chloroapigeninin (**129**) has been isolated from *Equisetum arvense* (Equisetaceae) in small amounts [129]. The Apiaceae contain several chlorinated coumarins; peuchlorin (**130**), peuchloridin (**131**) and peuchloronin (**132**) in *Peucedanum arenarium* [130]; saxalin (**133**) in *Angelica saxatilis* [131–133]; (**134**) in *Prangos pabularia* and *Heracleum granatense* [134, 135]; and **135** in *Heracleum pyrenaicum* [136].

Two isocoumarins (**136, 137**) were isolated from *Swartzia laevicarpa* (Caesalpiniaceae) [137] and the antileukemic xanthone psorospermin chlorohydrin (**138**) was obtained from *Psorospermum febrifugum* (Clusiaceae) [138]. The naphthoquinone 3-chloroplumbagin (**139**) was isolated from species of *Drosera* (Droseraceae) [139] and *Plumbago zeylanica* (Plumbaginaceae) [140] and pipoxide chlorohydrin (**140**) was isolated from *Piper hookerii* (Piperaceae) [141]. The cyclic hydroxamic acid derivative (**141**) was isolated from young *Zea mays* (Poaceae) roots [142].

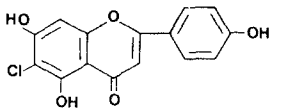
FATTY ACIDS

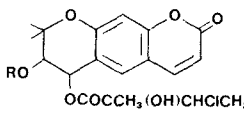
Seed oil of *Eremostachys moluccelloides* (Lamiaceae) [143] contains dibromo- and tetrabromostearic acids (**142, 143**). As some of the seed oil fractions also contain 0.1 % chlorine [144], one might suspect that chlorinated fatty acids also occur in the same plant.

BIOSYNTHESIS

Feeding experiments with a ^{14}C-labelled polyacetylene show that a terminal double bond is converted into a chlorohydrin probably via epoxidation and introduction of chlorine as the chloride anion [145, 146]. Reasonable hypotheses have been proposed for the biosynthesis of most of the chlorine-containing heterocyclic polyacetylenes (**21–29**) by cyclizing chlorohydrins; but more experimental work is needed in this area. It is not known if all chlorine-containing compounds are formed from chloride ion, or if some are formed by chloroperoxidase [147, 148]-generated Cl_2.

129

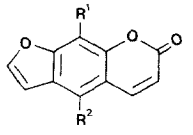




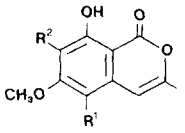
130 R=$CH_3CH=CCH_3CO-$

131 R=$CH_3CHClC(OH)CH_3CO-$

132 R=$CH_3CH(O)CCH_3CO-$

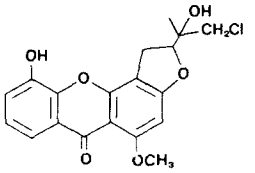


	R^1	R^2
133	H	$(CH_3)_2CClCHOHCH_2O-$
134	$(CH_3)_2CClCHOHCH_2O-$	H
135	$(CH_3)_2CClCHOHCH_2O-$	OCH_3



	R^1	R^2
136	Cl	H
137	H	Cl

138



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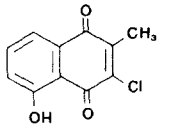

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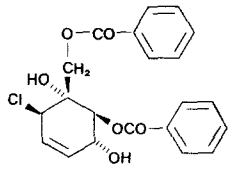
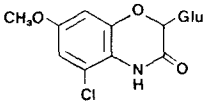


141



142 $CH_3(CH_2)_7CHBrCHBr(CH_2)_7COOH$

143 $CH_3(CH_2)_4CHBrCHBrCH_2CHBrCHBr(CH_2)_7COOH$

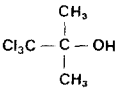
*The author would appreciate references or reprints on new chlorine-containing natural compounds in higher plants, as well as comments on omissions or errors.

ARTEFACTS

Most of the compounds described in this paper are chlorohydrins and they are often isolated together with the corresponding epoxides. Some of them may be artefacts of isolation; some epoxides are very sensitive to acids and incorporate Cl^- from the plant, the silica gel [81] or the solvent, e.g. chloroform [138]. However, the chlorohydrins are sometimes also very labile and may be converted to the epoxides with traces of alkali or by chromatography [38, 39, 42] or silica gel [42]. In some cases it is not at all clear which is the artefact, the chlorohydrin or the epoxide. Controls for artefact formation have involved isolation without chlorine containing solvents [39] or presence of the chlorine-containing compound in crude extracts has been proven by specific tests [128, 134], or by the incorporation of radioactive $^{36}Cl^-$ [8, 116].

Some compounds are without doubt artefacts. Compound **144** found in *Ilex aquifolium* was only found in nursery plants [149]; its formation is not understood. The dichlorocyclopropyl compound (**145**) is probably an artefact formed from chloroform [150]. Chlorodehydroabietic acids (**146**) are formed in paper manufacture during the Kraft liquor cooking [151]; they are important fish poisons. Chlorine-containing compounds derived from fats (**147**, **148**) are formed in the hydrolysis of proteins [152]. Senegenin (**149**) was isolated from *Polygala senega* [153] but later shown to be an artefact [154].*

144



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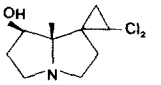
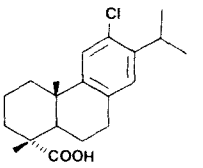


146

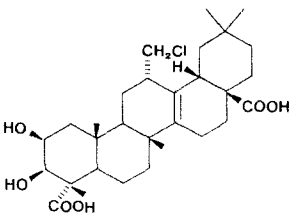


147 $CH_2Cl-CHO-R-CH_2Cl$

148 $CH_2O-R-CHO-R-CH_2Cl$ (R=H)

R=fatty acids

149



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