9. Acid esters

Although the microbicides described in this section all belong to the same substance class, namely to the acid esters, their antimicrobial activity is based on different mechanisms of action. The halogen containing esters (9.2.–9.6.) and dimethyl dicarbonate (9.7.) are substances with electrophilic character, a character which enables them to react with nucleophilic groups of the microbial cell and which equips the substances with a wide spectrum of antimicrobial effectiveness. The electrophilic character of the halogenated esters mentioned here is reduced due to the fact that the substances are bearing an activated halogen group in the α-position to an electronegative group (see 17.). Bromo compounds are preferred, because due to the average electronegativity of the bromo atom in comparison to other halogen atoms (for scale of electonegativity values of halogen atoms see Table 83) these compounds are not too stable (not persistent) but also not too reactive (unstable), so that they are preferably used as slimicides not causing waste problems.

Table 83 Relative electronegativity values of halogen atoms according to müller (1951).

Fluoro (F)	4.0
Chloro (Cl)	3.0
Bromo (Br)	2.8
Iodo (I)	2.4

Using these microbicides one has to bear in mind that in accordance with their reactivity these chemicals have skin and mucous membrane irritating properties.

The dicarbonate configuration in dimethyl dicarbonate (DMDC, 9.7.) is responsible not only for the electrophilic character of the chemical but also for its distinguished reactivity (instability), which does not allow use of DMDC as a preservative, but as a powerful cold sterilizing agent.

The phenyl esters of long chain fatty acids (Sections 9.8 and 9.9) are membrane active microbicides; they release phenolic compounds as the active ingredients. The advantage of these esters is that they are easier to handle and to apply than the phenolic compounds they are based on.

Finally it has to be pointed out that the antimicrobial esters of *p*-hydroxy-benzoic acid (*p*-hydroxy-benzoates) are not described in this chapter, because of their high acidity they are listed under 8. Acids.

Microbicide group (substance class)	9. ACID ESTERS
Chemical name	9.1. Ethyl formate
Chemical formula	$C_3H_6O_2$
Structural formula	$H\text{-}COOC_2H_5$
Molecular mass	74.08
CAS-No.	109-94-4
EC-No.	203-721-0
EPA TSCATS	Data base, Jan. 2001
Synonym/common name	formic acid ethylester, ethyl formic ester
Supplier	FLUKA
Chemical and physical properties	
Appearance	colourless, volatile fluid with an odour similar to arrack
Content (%)	~98
Boiling point/range °C (101 kPa)	52–55
Solidification point °C	– 80
Density g/ml (20°C)	0.921
Vapour pressure hPa (20°C)	261
Refractive index nD (20°C)	1.360
Flash point °C	– 19.44
Upper flammability limit %v/v i.air	28
Lower flammability limit %v/v i.air	16
Stability	sensitive to hydrolysis especially in solutions with a pH > 6

Solubility	hardly soluble in H_2O; soluble in organic solvents
Toxicity data	
LD_{50} oral	1850 mg/kg rat 2075 mg/kg rabbit 1110 mg/kg guinea pig
LD_{50} dermal	>20 mg/kg rabbit

Mildly irritant on the skin; vapours irritate eyes and respiratory tract.

Occupational exposure limit	300 (100) mg/m^3 (ppm)

Antimicrobial effectiveness/applications

Ethyl formate has to be regarded as a formic acid releasing compound and corresponds in its activity to the quantity of acid set free (see 8.1.1.)

Microbicide group (substance class)	9. ACID ESTERS
Chemical name	9.2. Ethyl bromoacetate
Chemical formula	$C_4H_7BrO_2$
Structural formula	Br-CH_2-$COOC_2H_5$
Molecular mass	167.01
CAS-No.	105-36-2
EC-No.	203-290-2
EPA genotox program 1988	tumorigenic
Synonym/common name	bromoacetic acid ethyl ester, ethoxycarbonylmethyl bromide
Supplier	SIGMA-ALDRICH
Chemical and physical properties	
Appearance	colourless, irritant fluid having an unpleasant smell
Content (%)	~100
Boiling point/range °C (101 kPa)	168–169
Density g/ml (20°C)	1.499
Vapour pressure hPa (20°C)	3.57
Refractive index nD (20°C)	1.4510
Flash point °C	48
Stability	hydrolysis in aqueous solutions (increasingly with increasing pH values) to hydroxyacetic acid under nucleophilic substitution of the bromo atom
Solubility	sparingly soluble in water, highly soluble in organic solvents, miscible with ethanol
Toxicity data	
LD_{50} oral	50 mg/kg rat 100 mg/kg mouse

Highly toxic by inhalation and skin absorption. Severely irritant to skin, mucous membranes and eyes. Tumorigenic.

Antimicrobial effectiveness/applications

2-Bromo-ethylacetate is especially effective against yeasts, but at higher concentrations also against bacteria, fungi, slime forming micro-organisms and algae. The active ingredient has been used as a non-persistent preservative in drinks, e.g. wine and fruit juices. However, these applications are no longer permitted because of the toxicity and the irritant properties of the compound.

Microbicide group (substance class)	9. ACID ESTERS
Chemical name	9.3. Benzyl bromoacetate
Chemical formula	$C_9H_9BrO_2$
Structural formula	$Br\text{-}CH_2\text{-}COOCH_2\text{-}C_6H_5$
Molecular mass	229.08
CAS-No.	5437-45-6
EC-No.	226-611-4
EPA FIFRA 1988	Pesticide subject to registration or re-registration
Synonym/common name	bromoacetic acid benzyl ester, bromoacetic acid phenylmethyl ester
Supplier	MERCK, SIGMA-ALDRICH

Chemical and physical properties

Appearance	colourless irritant fluid
Content (%)	~100
Boiling point/range °C (2.9 kPa)	166 – 170
Density g/ml (20°C)	1.46
Refractive index nD (20°C)	1.5436
Flash point °C	> 110
Stability	sensitive to hydrolysis in aqueous alkaline solutions
Solubility	sparingly soluble in water, highly soluble in organic solvents

Toxicity data:

Irritant to skin, mucous membranes, eyes, respiratory tract. May be toxic by inhalation and skin absorption.

Antimicrobial effectiveness/applications

Benzyl bromoacetate acts as an electrophilic active compound; due to its electron attracting power (electronegativity) the bromo atom may be substituted nucleophilically, i.e. by nucleophilic active components of the microbe cell.

On hydrolytic cleavage of the ester group benzyl alcohol (1.4.) is liberated, an membrane active microbicide. These properties equip benzyl bromoacetate with a broad spectrum of activity which covers bacteria, yeasts and fungi. It may be used as a preservative for the in-can protection of water based functional fluids, e.g. paints. However, due to its properties- irritant, moderate stability-the microbicide has been applied to a limited extent only.

Microbicide group (substance class)	9. ACID ESTERS
Chemical name	9.4. 1,2-Bis(bromoacetoxy) ethane
Chemical formula	$C_6H_8Br_2O_4$
Structural formula	$Br\text{-}CH_2\text{-}COO\text{-}CH_2\text{-}CH_2\text{-}OOC\text{-}CH_2\text{-}Br$
Molecular mass	303.94
CAS-No.	3785-34-0
EC-No.	223-250-4
Synonym/common name	ethylene bromoacetate, bromoacetic acid ethenediyl ester
Supplier	DEAD SEA BROMINE GROUP

Chemical and physical properties

Appearance	almost colourless, irritant fluid
Content (%)	~100
Boiling point/range °C (1,85 kPa)	176.5–177.5
Stability	hydrolysis in water based solutions (increasingly with increase in pH and temperature) to glycol, bromoacetic acid and further to hydroxyacetic acid
Solubility	sparingly soluble in water, highly soluble in alcohols, ether and benzene

Toxicity data

LD_{50} oral	>400 mg/kg rat
LD_{50} intraperitoneal	39 mg/kg mouse
LD_{50}intravenous	56 mg/kg mouse

Severely irritant to skin, mucosa and eyes.

Ecotoxicity:
Due to its distinct reactivity the microbicide is unstable in the environment (see: Stability) and easily degraded.

Antimicrobial effectiveness/applications

The electrophilic active compound impresses by its activity against slime forming microorganisms. Hence it has been an active ingredient in non-presistant slimicides for use preponderantly in the paper industry.

Microbicide group (substance class)	9. ACID ESTERS
Chemical name	9.5. 1,4-Bis(bromoacetoxy)-2-butene, (BBAB)
Chemical formula	$C_8H_{10}Br_2O_4$
Structural formula	Br-CH_2-C(=O)-O-CH_2-CH=CH-CH_2-O-C(=O)-CH_2-Br
Molecular mass	329.97
CAS-No.	20679-58-7
EC-No.	243-962-9
Synonym/common name	2,3-butylene bromoacetate, bromoacetic acid 2,3-butene-1, 4-diyl ester
Supplier	DEAD SEA BROMINE GROUP, BUCKMANN

Chemical and physical properties

Appearance	dark brown, oily liquid with an irritant odour
Content (%)	>95
Boiling point/range °C (6.7×10^{-4} kPa)	135–136
Solidification point °C	<-20
Stability	sensitive to hydrolysis, especially in aqueous systems at pH values >7 (release of bromoacetic acid and finally butenyl alcohol, hydroxyacetic acid and bromide); half-lives: 8.25 days at pH 5; 6.89 h at pH 7; 4.15 min at pH 9 (Cohen, 1997)
Solubility	practically insoluble in water; soluble in organic solvents, such as acetone, toluene, methylene chloride

Toxicity data (source: DEAD SEA BROMINE GROUP)

LD_{50} oral	191 mg/kg rat
	125 mg/kg mouse
LD_{50} dermal	983 mg/kg rat

Corrosive to skin, eyes, upper respiratory tract and mucous membranes. – Not mutagenic (Ames test). Not included in NTP 9th Report on carcinogens.

Ecotoxicity:

LC_{50} for Zebra fish	0.32 mg/l (48 h)
EC_{50} for Daphnia magna	0.024 mg/l (24 h)
EC_{50} for fresh water algae	0.29 mg/l (96 h)

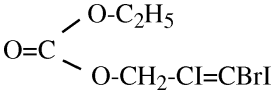
BBAB is classified as biodegradable.

Antimicrobial effectiveness/applications

The minimum inhibition concentrations of bis-1,4-(bromoacetoxy)-2-butene for fungi and some species of bacteria are in the range of 20 mg/litre only (see Table 84). The a.i. therefore was successfully introduced as a substitute for the persistent and highly toxic organomercurials (19.) and penta-chlorophenol (7.5.4.) in slimicides for the treatment of industrial water circuits, mainly in the paper industry.

Table 84 Minimum inhibition concentrations (MIC) of bis-1,4-(bromoacetoxy)-2-butene in nutrient agar

Test organism	MIC (mg/litre)
Aspergillus niger	<20
Botrytis cinerea	20
Chaetomium globosum	<20
Penicillium glaucum	35
Bacillus subtilis	20
Escherichia coli	200
Staphylococcus aureus	200

Microbicide group (substance class)	9. ACID ESTERS
Chemical name	9.6. 1-Bromo-3-ethoxycarbonyloxy-1,2-diiodo-1-propene
Chemical formula	$C_6H_7BrI_2O_3$
Structural formula	
Molecular mass	460.84
CAS-No.	77352-88-6
EC-No.	unknown
Synonym/common name	(3-bromo-2,3-diiodopropenyl)-ethyl carbonate, (3-bromo-2,3-diiodoally)-ethyl carbonate
Supplier	SANKYO CO.

Chemical and physical properties

Appearance	white crystals with a faint characteristic odour
Content (%)	~100
Melting point °C	40
Vapour pressure hPa (20°C)	2.4×10^{-5}
Stability	limited thermostability at temperatures >40°C; stable to UV light; hydrolyses in alkaline solutions
Solubility g/l (25°C)	0.119 in H_20, soluble in organic solvents

Toxicity data

LD_{50} oral	641–529 mg/kg rat
dermal	2858-2849 mg/kg rat
LC_{50} on inhalation (4 h)	820–1480 mg/m^3 for rats

Moderately irritant to skin and mucosa. Several mutagenicity tests conducted in different biological systems demonstrated lack of genetic effects.

Antimicrobial effectiveness/applications

In view of the minimum inhibition concentrations listed in Table 85 it has to be stated that the electrophilic active microbicide's antimicrobial activity is above all directed against fungi. On cleavage the carbonic acid ester liberates ethanol and 3-bromo-2,3-diiodoallyl alcohol; the latter represents a highly reactive and effective agent as well. The efficacy of (3-bromo-2,3-diiodoallyl)-ethyl carbonate is not influenced by anionic, cationic or non-ionic components. Because of its effectiveness against wood-rotting fungi it has been recommended for use in wood preservatives, and for the protection of plywood incorporating the fungicide into the glue for the production of plywood.

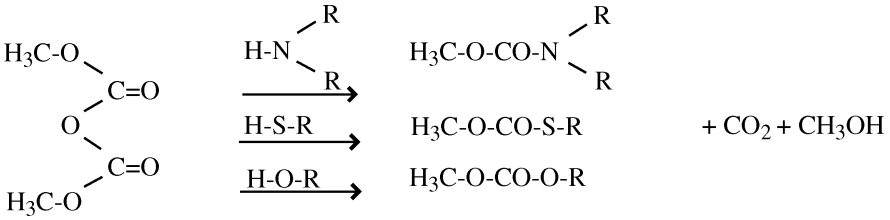
Table 85 Minimum inhibition concentrations (MIC) of (3-bromo-2,3-diiodoallyl)-ethyl carbonate in nutrient agar

Test organisms	MIC (mg/l)
Alternaria alternata	50
Aspergillus niger	20
Aureobasidium pullulans	50
Chaetomium globosum	20
Cladosporium cladosporioides	10
Lentinus tigrinus	20
Penicillium glaucum	15
Sclerophoma pityophila	50
Trichoderma viride	100
Escherichia coli	350
Staphylococcus aureus	150

Microbicide group (substance class)	9. ACID ESTERS
Chemical name	9.7. Dimethyl dicarbonate (DMDC)
Chemical formula	$C_4H_6O_5$
Structural formula	$H_3C–O–CO–O–CO–O–CH_3$
Molecular mass	134.09
CAS-No.	4525-33-1
EC-No.	224-859-8
Registration	as food additive permitted for direct addition to food for human consumption–FDA Register 21 CFR Part 172. 133. E 242.
Supplier	BAYER

Chemical and physical properties

Appearance	colourless liquid with a slightly pungent odour
Content (%)	>99.5
Boiling point/range °C (101 kPa)	approx. 172 (decomposition)
Solidification point °C	17
Density g/ml (20°C)	1.25
Vapour pressure hPa (20°C)	0.7
Viscosity mPas (20°C)	2.1
Refractive index nD (20°C)	1.3915–1.3925
Flash point °C	approx. 85
Ignition temperature °C	approx. 465
Upper flammability limit %v/v i.air	29.9
Lower flammability limit %v/v i.air	3
Stability	highly reactive carbmethoxylation agent, which means hydrolysis in water to methanol and carbon dioxide, reaction with N–H, S–H and O–H groups according to the following reaction scheme:



Half-life in water	At pH 2.8/10°C: 40 min pH 2.8/20°C: 15 min pH 2.8/30°C: 8 min
Solubility	approx. 35 in H_2O; miscible in organic solvents, e.g. ethanol, toluene

Toxicity data

LD_{50} oral	497 mg/kg male rat
	335 mg/kg female rat
LD_{50} dermal	>1250 mg/kg rat
LC_{50} on inhalation (4 h)	711 mg/m^3 air for rats

DMDC causes severe irritation to skin, eyes, mucous membranes and the respiratory tract.

Ecotoxicity:

LC_0 for fish (Leuciscus idus)	50 mg/l (48 h)

Remark: In contact with water DMDC decomposes completely to methanol and carbon dioxide (see: half life).

Antimicrobial effectiveness/applications

The strong reactivity of DMDC is responsible for the antimicrobial action. When checking the microbicidal effectiveness of DMDC one has to bear in mind the short-half life of the chemical in water based media depending on temperature and pH. DMDC kills normal yeasts, mycoderma and fermentive bacteria at relatively low concentrations. At higher concentrations it also destroys other bacteria, wild yeasts and mould producing fungi. Minimal lethal concentrations of DMDC for a great number of individual microbe species are listed in Table 86.

The killing effect of DMDC bases on its irreversible reaction with nucleophilic components of microbe cells. In consequence DMDC destroys high cell numbers only at higher concentrations. The lethal concentrations in Table 86 were determined as follows: the microbe species concerned was introduced into an uncarbonated acidic

Table 86 Minimum lethal concentrations (MIC) of DMDC (mg/litre)

Yeasts	
Saccharomyces carlsbergensis (non-flocculating yeast)	100
Saccharomyces carlsbergensis (flocculating yeast)	60
Saccharomyces diastaticus	200
Saccharomyces oviformis	100
Saccharomyces bailii	120
Saccharomyces cerevisiae	40
Saccharomyces uvarum	30
Saccharomyces pastorianus	100
Saccharomyces apiculatus	60
Saccharomyces globosum	40
Zygosaccharomyces priorianus	75
Rhodotorula mucilaginosa	50
Rhodotorula glutinosa	40
Rhodotorula rubra	200
Candida krusei	200
Pichia membranefaciens	40
Pichia farinosa	100
Torulopsis candida	100
Torulopsis versatilis	100
Torulopsis stellata	65
Torula utilis	240
Endomyces lactis	60
Kloeckera apiculata	40
Hansenula anomala	50
Bacteria	
Acetobacter pastorianum	80
Acetobacter xylinum	300
Escherichia coli	400
Staphylococcus aureus	100
Pseudomonas aeruginosa	100
Lactobacterium buchneri	40
Lactobacillus pastorianus	300
Lactobacillus brevis	200
Pediococcus cerevisiae	300
Moulds	
Penicillium glaucum	200
Byssochlamys fulva	100
Botrytis cinerea	100
Mucor racemosus	500
Fusarium oxysporum	100

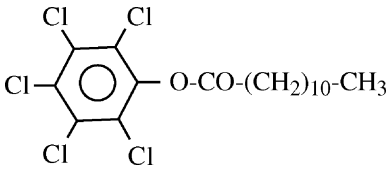
drink (approx. pH 3) to give a viable cell count of 500 per ml; the effect of the treatment with DMDC was determined after the drink had been stored for 3 weeks at 28°C.

Although DMDC is highly effective, it cannot, because of its short half-life, be used as a preservative in water based media, when there is a risk of recontamination after the addition of DMDC. However, DMDC has found application for the cold sterilization of soft drinks and wine, and for the degermination of water, which is used for the production of drinks, cosmetics and pharmaceuticals. Once DMDC has decomposed there is no further sterilizing effect. It should therefore not be added until shortly before the drink is put into bottles or other containers and tightly closed. It has to be regarded as an important advantage that DMDC is not a persistent preservative and that its application does not influence either taste or quality of drinks. Addition rates range between 10 and 20 ml DMDC per 100 litre drink. But before DMDC is added the number of viable cells in the drink has to be reduced to approx. 500 per ml by filtration of flash pasteurization; the latter also inactivates enzymes which may decompose pectin. It is also recommendable to cool the drink before the addition of DMDC, preferably to 10–15°C; otherwise DMDC decomposes too fast not leaving time for sufficient antimicrobial action.

Microbicide group (substance class)	9. ACID ESTERS
Chemical name	9.8. Glyceryl monolaurate (α- and β-form)
Chemical formula	$C_{15}H_{30}O_4$
Structural formula	$H_3C–(CH_2)_{10}–COO–CH_2–CH(OH)–CH_2OH$ (α-form)
Molecular mass	274.41
CAS-No.	27215-38-9
EC-No.	unknown
FDA Approval	for food use as an emulsifier (21 CFR GRAS 182.4505)
Synonym/common name	Lauricidin, 1- and 2-lauroylglycerol, n-dodecanoic acid monoglyceride
Supplier	SIGMA-ALDRICH
Chemical and physical properties	
Appearance	powder or pastelike, off-white solid
Content (%)	>90
Melting point °C	55–56
Stability	very stable under normal conditions; with increasing storage time the more stable α-form reaches values of 90–95%; unaffected in the pH range 3.5–8; on hydrolyses glycerine and Lauric acid (8.1.13.) are liberated
Solubility g/l (25°C)	<1 in H_2O, 2500 in methanol, 800 in ethanol, 600 in isopropanol, 45 in propylene glycol, 2 in glycerine and mineral oil
Toxicity data (source: Kabara, 1984)	
LD_{50} oral	>25 g/kg mouse
Only moderately irritant to skin and eyes.	Classified as a mild sensitizer (grade II; guinea pig test according to Magnusson-Kligman).

Antimicrobial effectiveness/application (Kabara, 1984)

Lauricidin can be characterized as a nonionic emulsifier with antimicrobial properties. There is no difference in the antimicrobial activity of both isomeric monoglycerides. Lauricidin's antibacterial activity is restricted to gram-positive bacteria (MIC ~5000 mg/l); MIC's for Gram-negative bacteria are beyond 10000 mg/l. However the activity against molds and yeasts and also against lipid-coated viruses is remarkable. It is recommended to applicate Lauricidin in combination with other microbicides (Parabens, etc.) to achieve a sufficiently broad spectrum of effectiveness, e.g. for the in-can protection of cosmetic and pharmaceutical products. Addition rates 0.5–1%; optimum pH 6–7.5.

Microbicide group (substance class)	9. ACID ESTERS
Chemical name	9.9. Dodecanoic acid pentachlorophenyl ester
Chemical formula	$C_{18}H_{23}Cl_5O_2$
Structural formula	
Molecular mass	448.65
CAS-No.	3772-94-9
EC-No.	308-706-3
Synonym/common name	pentachlorophenyl laurate

Chemical and physical properties

Appearance	oily, brown, odourless liquid
Content (%)	approx. 100
Density g/ml (20°C)	1.25
Stability	non-volatile, unaffected by dilute acids or alkalis, hydrolysis by high concentrations of alkali or by enzymatic action, sensitive to photochemical breakdown
Solubility	practically insoluble in water and alcohols, soluble in all portions of acetone, methyl ethyl ketone, trichloroethylene, toluene, white spirit, oils, fats and waxes

Toxicity data:
Pentachlorophenyl laurate (PCPL) is, as long as pentachlorophenol (7.5.4. = PCP) is not liberated, of low toxicity and good skin compatibility, however the ester may release approx. 57% pentachlorophenol the toxicity data of which are listed under 7.5.4.

Antimicrobial effectiveness/applications

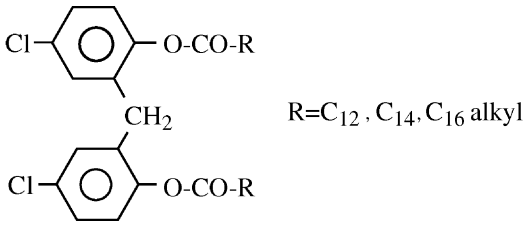
As can be seen from Table 87 the intact PCPL does not exhibit significant antimicrobial activity, especially not in comparison to PCP. Nevertheless PCPL has had considerable use as a microbicide for rot- and mold-proofing of various types of materials, mainly textiles, ropes and cordage (addition rates approx. 2% calculated on the weight of material to be protected), as in fact the active ingredient is PCP which is set free by enzymatic ester cleavage. In consequence PCPL is under pressure for substitution as is PCP and the application of PCPL is indeed in decline.

Table 87 Minimum inhibition concentrations (MIC) of PCPL and PCP in nutrient agar

Test organism	MIC (mg/litre)	
	PCPL	PCP
Aspergillus niger	> 1000	50
Chaetomium globosum	> 1000	20
Penicillium glaucum	> 1000	50
Escherichia coli	> 2500	500
Staphylococcus aureus	750	10

Microbicide group (substance class)	9. ACID ESTERS
Chemical name	9.10. Fatty acid esters (mix.) of 5,5′-dichloro-2,2′-dihydroxydiphenylmethane (Deiner, 1983)

Structural formula



Supplier PFERSEE CHEM.

Chemical and physical properties

Appearance oily, brown liquid of high viscosity
Content (%) 70 Lauric acid ester, 20 Myristic acid ester, 10 Palmitic acid ester
Stability non-volatile, heat resistant ($>200^{\circ}C$), hydrolyses in alkaline solutions
Solubility insoluble in water, highly soluble in organic solvents, preferably in non-polar solvents

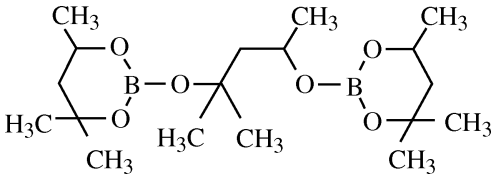
Toxicity data

As the active ingredient of the mixture of esters is Dichlorophen (7.7.3., CAS-no. 97-23-4, EC-no. 292-567-1) which is liberated through enzymatic ester cleavage for antimicrobial action, one has to note the toxicity data of Dichlorophen.

Antimicrobial effectiveness/applications

The mixture of Dichlorophen fatty acid esters develops antimicrobial activity by the reconstitution of Dichlorophen (7.7.3.) through hydrolysis. The most important advantage of the ester mixture is the possibility of transferring it easily into stable emulsions which can be used for the impregnation of textile material together with water repellents without disturbing the effect of the water repellents. The application of Dichlorophen itself is fraught with difficulties. Stable emulsions of Dichlorophen for dilution with water are not available. Alkaline solutions of Dichlorophen are easy to apply on textile material by impregnation, but the alkali salts of Dichlorophen are not compatible with most of the water repellents. The application of Dichlorophen in solutions in organic solvents is not the solution to the problem, as the use of organic solvents is disliked in the textile industry.

Microbicide group (substance class) 9. ACID ESTERS
Chemical name 9.11. 2,2′-[(1,1,3-trimethyl-1,3-propanediyl)bis(oxy)] bis[4,4,6-trimethyl-1,2,3-dioxyborinane]
Chemical formula $C_{18}H_{36}B_2O_6$
Structural formula



Molecular mass 370.11
CAS-No. 100-89-0
EC-No. 200-899-0
Synonym/common name 2,2′-(2-methylpentane-2,5-dioxy)bis(4,4,6-timethyl-1,2,3-dioxyborinane), trihexylene glycol biborate
Supplier RHONE-POULENC

Chemical and physical properties

Appearance clear, colourless to pale yellow easy pourable liquid
Content (%) ~100 (boron content 5.6–5.8; equivalent to 32.0–33.2% boric acid)
Boiling point/range °C (101 kPa) 314–326 (143–149 at 0.267 kPa)

Density g/ml (20°C)	0.98
Refractive index nD (18.5)	1.4408
Flash point °C	175 (closed cup)
Stability	hydrolyzes in contact with water, even when exposed to atmospheric moisture
Solubility	soluble in all proportions in white spirit, kerosene, carbon tetrachloride, benzene, toluene, xylene, petroleum ether

Toxicity data (source: PHONE-POULENC)

LD_{50} oral	>4000 mg/kg rat
dermal	>2000 mg/kg rat

Moderate irritant to skin and mucosa; not a skin sensitizer.

Antimicrobial effectiveness/applications

Trihexylene glycol biborate can be regarded as a boric acid (8.2.1.) releasing compound. It has been developed for the remedial (preservative) treatment of timber. After penetration in situ the hydrolysis to boric acid occurs providing fungicidal and insecticidal properties. For boric acid on Pinus sylvestris sapwood the following toxic limits have been established:

for Coniophora puteana	0.43–0.65 kg/m^3
For Poria xantha	0.08–0.20 kg/m^3

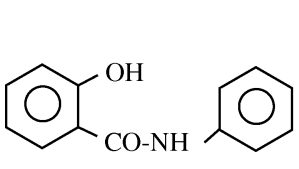
(Forest Products Research Laboratory, Princes Risborough, 1968).

The biborate is used in solvent based wood preservatives. It is also effective on white rots such as Polystictus versicolor. Minimum recommended concentration for in-situ applications: 3.2%.

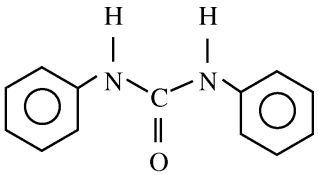
10 Amides

Carboxylic acid amides do not generally belong to the substances with antimicrobial effect. Toxophoric groups or toxophoric structural elements have to be introduced to obtain antimicrobially active aliphatic carboxylic acid amides. This possibility is exemplified by amides which in 2-position to the electronegative carboxylamide grouping possess a halogen atom, thus ranking among the electrophilic active microbicides which are described under '17. Compounds with Activated Halogen Atoms'. The addition of formaldehyde (2.1.) to such halogenated amides leads to antimicrobially effective N-hydroxymethyl amides, whose special feature is the presence of two toxophoric groups: an activated halogen atom and an activated hydroxymethyl group. Being formaldehyde releasing compounds, they are treated under '3.4. Amide-Formaldehyde-Reaction-Products', as well as N-hydroxymethyl diamides of carbonic acid = N-hydroxymethyl ureas (3.4.3.).

Salicylanilides (2-hydroxybenzanilides), long chain N-alkyl-salicylamides and carbanilides (urea derivatives) belong to the amides with antimicrobial efficacy, too. They are membrane-active substances, i.e. very small concentrations suffice to achieve microbistatic effects whereas microbicidal effects call for much higher addition rates.



Salicylanilide



Carbanilide

As in the case of the membrane-active phenol derivatives (7.) the halogenation of salicylanilides or carbanilides increases the antimicrobial efficacy. The best results are obtained by means of di- to penta-chlorination or bromination, the halogen atoms being more or less evenly distributed on the two phenyl rings. On the other hand halogenated salicyl anilides have photosensitizing properties, which has reduced their practical importance.

Also haloalkylthio amides are well-known microbicides; they are electrophilic active agents disposing of an activated N-S bond. Their role as an important class of microbicides is described separately under 16.

For sake of completeness it should be mentioned a carboxylic acid hydrazide, namely pyridine-4-carboxylic acid hydrazide (isonicotinic acid hydrazide, Isoniazide), a pyridine derivative which is appropriately described under 13. 'Pyridine Derivatives and Related Compounds' (see 13.2.).