BROMINE, ORGANIC COMPOUNDS

1. Introduction

Organic bromine compounds, which are organic compounds in which the bromine is covalently bonded to carbon or (rarely) to nitrogen and oxygen, are a very important group of organic halogen compounds. Even naturally occurring bromine containing organic compounds produced by marine and terrestrial plants, bacteria, fungi, insects, marine animals, and some higher animals, number nearly 1500 compounds (1). Historically, the organic bromine compound, Tyrian, or Royal Purple, (dibromoindigo [19201-53-7],) extracted from a Mediterranean Sea mollusk, was one of the first used dyes (2). However, far more important are synthetic organic bromine compounds. Organic bromine compounds are the predominant industrial bromine compounds and in terms of bromine consumption, account for ~80% of bromine production. The industrially produced organic bromine compounds can be divided into two main groups.

(*1*) Organic bromine compounds in which the bromine atom is retained in the final molecular structure, and where its presence contributes to the properties of the desired products, are the largest segment in terms of consumed volumes. This segment includes mainly flame retardants, biocides, gasoline additives, halons, bromobutyl rubber, pharmaceuticals, agrochemicals, and dyes. Some of the products in this category, such as methyl bromide, ethylene dibromide, and halons are being subjected to environmental restrictions that will lower their consumption, although the overall market of this segment is still forecast to use because of the increasing demand of other products, especially flame retardants and biocides.

(*2*) Organic bromine compounds have traditionally played an important role as intermediates in the production of agrochemicals, pharmaceuticals and dyes, while new process developments that result in new applications in ultraviolet (uv) sunscreens, high performance polymers, and others, are forecast to increase their market share. The world consumption of bromine for intermediates is dwarfed by the corresponding consumption of chlorine. On the simple grounds of raw material halogen cost, organic chlorine intermediates have dominated in the manufacture of low value, high volume commodity products. Bromine, however, has tended to compete more favorably with chlorine for application as an intermediate in the above mentioned, more specialized, higher value areas (3). The diverse applications of organic bromine intermediates in commercial manufacture provide ample illustrations of the many virtues of bromine chemistry serving to outweigh the penalty of high halogen cost. These virtues are reflected in process benefits for both the production and application of intermediates, summarized below.

(a) Improved selectivity in the production of bromine intermediates.

(b) Improved reactivity of the intermediates in bromine displacement, resulting in (c).

(c) Cleaner processes, reduction of waste, and reduced environmental impact. While (a) and (b) provide obvious improvements in manufacturing economics, the rapidly increasing demand for environmentally clean chemical processes makes (c) a major, and often dominant factor, in the choice of the intermediate and process route for a new production.

Of course, the above division is relative. Several compounds can be used both as final products and as intermediates for the production of other products.

The scope of this article is limited to those organic bromine compounds having industrial application. A short description of the chemical properties and routes for the synthesis of the organic bromine compounds as a specific group, including references to the corresponding monographs and reviews, is given.

2. Chemical Properties

Substitution of bromine by other groups proceeds as a nucleophilic, electrophilic, or radical process (4). Nucleophilic displacement of bromine, both in aliphatic and aromatic molecules, by neutral or anionic nucleophiles, is the leading process in the application of brominated intermediates. As a rule, the reactivity of bromine compounds in the nucleophilic substitution is greater than the corresponding chlorine derivatives, owing to the difference in the bond energies (C−Br 276 kJ/mol vs. C−Cl 328 kJ/mol). This reactivity is the main advantage of using bromine compounds as intermediates. The reaction of aliphatic bromides, either with water or with dilute aqueous solutions of bases, gives alcohols (5), the reaction with alcoholates gives ethers, the reaction with salts of carbonic acids gives esters, and the reaction with sodium cyanide gives nitriles. Interaction with ammonia, both in solution and in the gaseous phase, gives primary, secondary, or tertiary amines and quaternary ammonium salts, depending on the reaction conditions. Aldehydes and ketones are formed by the hydrolysis of dibromides, $RCHBr_2$ or $RCBr_2R'$, respectively, and the hydrolysis of tribromides, $RCBr_3$, gives carbonic acids.

The nucleophilic substitution in the aliphatic series may be accompanied by elimination, and the yield of the target compound depends on a number of factors (structure of the initial compound, presence and nature of solvent and catalyst, etc). Thus, alkyl bromides eliminate HBr under the action of concentrated solutions of bases, forming alkenes:

$$CH_3CH_2Br \rightarrow CH_2{=}CH_2 + HBr \qquad (1)$$

Vicinal dibromoalkanes are debrominated by zinc, forming unsaturated compounds.

$$RCHBrCH_2Br + Zn \rightarrow RCH{=}CH_2 + ZnBr_2 \qquad (2)$$

When the bromine atoms are located at more remote carbons, a cyclic compound can be formed

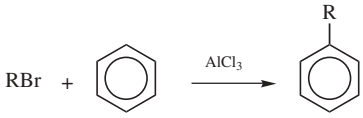
$$CH_2BrCH_2CH_2Br + Zn \longrightarrow \begin{array}{l} H_2C\!-\!CH_2 \\ \quad\backslash\ /\ \\ \quad CH_2 \end{array} + ZnBr_2 \qquad (3)$$

The action of Mg or Li on the organic bromides leads to the formation of alkyl magnesium bromides (Grignard reagents) or alkyl lithium reagents, widely used both in laboratory and industrial organic synthesis.

The bromine atoms in organic bromine compounds can be replaced by hydrogen forming hydrocarbons

$$BrCH_2CH_2Br + H_2 \rightarrow CH_3CH_3 \tag{4}$$

Aliphatic bromides are used for the alkylation of aromatic hydrocarbons in the presence of Lewis acids (6)



(5)

Under the same conditions, these alkyl bromides add to unsaturated hydrocarbons and take part in telomerization reactions (7)

$$CBr_4 + n\,CH_2{=}CH_2 \rightarrow CBr_3(CH_2 - CH_2)_nBr \tag{6}$$

Figure 1 illustrates the various reactivities of organic bromine compounds.

The reactions with Mg, Li, and NaR are also typical for aromatic bromine compounds; the reactions in the above scheme proceed in the aromatic series either under drastic conditions or with aromatic compounds containing activated bromine. Substitution of an aromatic bromine with ammonia, amines, phenols, and other nucleophiles is accelerated by the addition of a copper catalyst (8). The Ullmann ether condensation is a more widely used industrial process, carried out in the presence of copper (9).

The modern metal-catalyzed coupling reactions of aryl and alkenyl bromides are very efficient and reliable methods for the formation of a new carbon–carbon bond. The Heck stereospecific palladium-catalyzed coupling of alkenes with organic bromides lacking an sp^3 hybridized β-hydrogen is one of the most valuable strategies in modern organic synthesis, including industrial

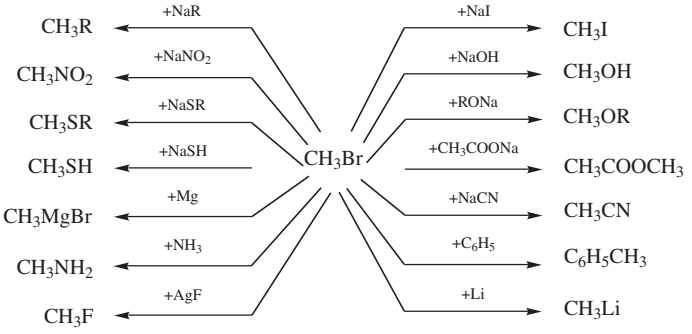


Fig. 1. The reactivity of alkyl bromides.

processes (10–12). Palladium-catalyzed Suzuki cross-couplings of organic bromides with organoboron derivatives are also powerful methods for C–C bond formation (12,13).

3. Preparation and Production

Organic bromine compounds can be produced by a great number of different chemical reactions (14–23); however, substitution and addition reactions (substitutive and additive bromination) are the most common methods employed in industrial processes.

3.1. Substitutive Bromination. The process of bromination of saturated hydrocarbons (alkanes and alkylarenes) both in the gas and liquid phase, proceeds by a free-radical chain mechanism and requires photolytic or thermal initiation

$$\begin{aligned} &Br_2 \xrightarrow{h\nu} 2\,Br^{\cdot} \\ &RH + Br^{\cdot} \rightarrow R^{\cdot} + HBr \\ &R^{\cdot} + Br_2 \rightarrow RBr + Br^{\cdot} \\ &R = \text{alkyl or aralkyl} \end{aligned} \tag{7}$$

This substitution reaction is selective in the case of alkylarenes and branched alkanes, giving correspondingly, 1-bromo-1-arylalkanes and tertiary alkyl bromides. In the presence of Lewis acids, the bromination of branched alkanes occurs by an electrophilic mechanism.

The direct bromination of carboxylic acids in the α-position is carried out by an acid -catalyzed process. Various reagents are available for the introduction of a bromine atom into a fatty acid but in the conventional Hell–Volhard–Zelinsky reaction, bromine and red phosphorus are used and α-bromination normally results (24). A number of modified procedures are available, including the use of bromine in the presence of a catalytic amount of phosphorus trichloride or phosphorus tribromide. The substitution of α-hydrogen atoms in aliphatic carbonyl compounds occurs via the addition of bromine to the enol form of the carbonyl compound (25)

$$CH_3COR \rightleftharpoons CH_2{=}\overset{\overset{OH}{|}}{C}R \xrightarrow{Br_2} \overset{Br}{\underset{|}{CH_2}}-\overset{\overset{OH}{|}}{\underset{|}{C}}RBr \longrightarrow CH_2BrCOR + HBr \tag{8}$$

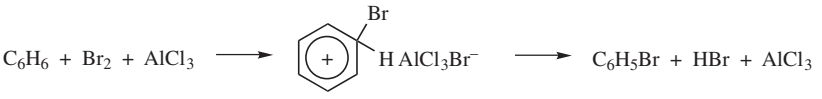
Other substitution reactions that are often used in industrial chemical processes for the production of brominated aliphatic compounds include

(*1*) Substitution of the hydroxyl group of alcohols by bromine using HBr, PBr_3, or $P + Br_2$.

(*2*) Replacement of the chlorine atoms of chlorinated hydrocarbons by bromine using various Lewis acids and a phase-transfer catalyst (26).

(*3*) Replacement of a carboxyl group by the action of bromine on the salts of carboxylic acids (27,28).

The substitutive nuclear bromination of aromatic and heteroaromatic compounds proceeds by an electrophilic mechanism. No catalyst is required for the bromination of activated aromatics, such as polyalkylbenzenes, naphthalene, and polycyclic aromatic compounds (29). Phenols and anilines readily undergo mono-, di-, or tribromination (30). The bromination of nonactivated and deactivated aromatics is usually carried out in the presence of a Lewis acid catalyst ($AlCl_3$, $FeBr_3$, I_2, etc) (31)



(9)

Very strongly deactivated aromatic compounds containing two or more electron-withdrawing groups, eg, dinitrobenzene or di(trifluoromethyl)benzene, undergo bromination in the presence of sulfuric acid in combination with nitric acid (32).

The amount and orientation of the bromine substitution of aromatic compounds depends on the effect of other substituents in the aromatic ring, the activity of the catalyst used, the reaction conditions, and other factors. In general, bromine is a less strong and more selective electrophile than chlorine; therefore its application enables the obtaining of more valuable haloaromatic intermediates than with the application of chlorine. For example, it is known that aluminum trihalides and other Lewis acids cause the isomerization of haloaromatics. The migration of chlorine is generally most likely to be intermolecular. In contrast, the migration of bromine may be both intra- and intermolecular. The intramolecular migration of bromine is used as a practical route for the preparation of some meta-substituted and meta-disubstituted bromobenzenes (33,34). The isomerization of a mixture of brominated anilines gives the para-brominated isomer in high yield (35).

The catalytic decomposition of aromatic diazocompounds in the presence of Cu (Gattermann reaction) or of Cu_2Br_2 (Sandmeyer reaction) is often used for the production of bromoaromatic compounds (36).

Since the use of bromine as a brominating agent is not always easy because of its volatile and toxic character, several bromine derivatives, especially *N*-bromo derivatives, are used as brominating agents. The more often used reagents are *N*-bromosuccinimide (NBS) [128-08-5], (37), 1,3-dibromo-5,5-dimethylhydantoin [77-48-5], (38), and stable crystalline organic ammonium tribromides, such as benzyltrimethylammonium tribromide [111865-47-5] (39), pyridinium tribromide [39416-48-3] (40), and phenyltrimethylammonium tribromide [4207-56-1], (41). These compounds are used for the Wohl–Ziegler radical bromination of the methyl or methylene groups of alkenes, alkylarenes, and heteroaromatic compounds (42); electrophilic bromination of activated aromatic compounds—phenols, anilines; bromination of carbonyl compounds, and several other brominations. Bromination using these solid reagents usually proceeds under milder conditions and is more selective than using bromine itself. The application of polymer-supported *N*-brominating compounds is a recent achievement of the bromination technology (43).

3.2. Additive Bromination. The addition of bromine to aromatic and heteroaromatic compounds proceeds by a radical mechanism under the action of light or heat. The uncatalyzed addition of bromine to a C=C bond is rapid and quantitative. In the case of asymmetrical reagents such as hydrogen bromide (hydrobromination), BrCl, or hypobromite, the reaction proceeds by a radical or electrophilic mechanism (44,45). In the absence of peroxides, the reaction with hydrogen bromide proceeds by an electrophilic mechanism. The obtained product is formed from the most stable intermediate carbocation, generated by the addition of a proton to the double bond (Markovnikov addition) (46). The carbocation stability follows the order tertiary > secondary > primary, and therefore hydrogen adds to the most hydrogenated carbon atom

$$CH_3CH{=}CH_2 + HBr \rightarrow CH_3CHBrCH_3 \tag{10}$$

Under free-radical conditions, the direction of the addition of hydrogen bromide takes place in a reverse order (anti-Markovnikov addition)

$$CH_3CH{=}CH_2 + HBr \rightarrow CH_3CH_2CH_2Br \tag{11}$$

The addition of hydrogen bromide to the C=C, conjugated with electron-withdrawing groups, proceeds more slowly than addition to an isolated double bond. The bromine atom adds in the β-position to the electron-withdrawing group

$$CH_2{=}CHR + HBr \rightarrow BrCH_2CH_2R \quad \begin{matrix} R = COR', COOR', CN \\ R' = H, alkyl, Ar \end{matrix} \tag{12}$$

In nucleophilic solvents like water, dimethylsulfoxide (DMSO), dimethylformamide (DMF), carboxylic acids, alcohols, nitriles, and even ethers, the solvent can compete with the bromide ion, leading to incorporation of the latter. These cobromination (mixed bromination) processes have great synthetic potential (47,48).

4. Aliphatic Bromine Compounds

4.1. Methyl Bromide. Methyl bromide, CH_3Br, (bromomethane) [74-83-9], is a colorless liquid or gas with practically no odor. Its physical properties are mp −93.7°C; bp 3.56°C; $d^{20}{}_4$ 1.6755 kg/m^3; 3.974 kg/m^3; $n_D{}^{20}$ 1.4218; vapor pressure at 20°C, 189.3 kPa (1420 mmHg); viscosity at −20, 0, and 25°C: 0.475, 0.397, and 0.324 mPa·s, respectively. Heat capacity of the liquid at −13°C and of the vapor at 25°C, 824 (197) and 448 (107) J/kg · K, (cal/kg · K), respectively; heat of vaporization at 3.6°C, 252 J/g (60.2 cal/g); critical temperature (calculated) 194°C; expansion coefficient −15 to 3°C, 0.00163/K; dielectric constant at 0°C and 0.001–0.01 MHz, 9.77; dipole moment gas, 1.81D. Methyl bromide is miscible with most organic solvents and forms a bulky, crystalline hydrate below 4°C. Its solubility in water varies with pressure: at normal pressure, methyl bromide plus water vapor, the solubility is 1.75 g/100-g solution (20°C).

Methyl bromide reacts with several nucleophiles and is a useful methylation agent for the preparation of ethers, sulfides, amines, etc. Tertiary amines are methylated by methyl bromide to form quaternary ammonium bromides. The reactivity of methyl bromide is summarized in Figure 1.

Methyl bromide, when dry (<100 ppm water), is inert toward most materials of construction. Carbon steel is recommended for storage vessels, piping, pumps, valves, and fittings. Copper, brass, nickel, and their alloys are sometimes used. Aluminum, magnesium, zinc, and alloys of these metals should not be used, because under some conditions dangerous pyrophoric Grignard-type compounds may be formed. A severe explosion due to the ignition of a methyl bromide–air mixture by pyrophoric methylaluminum bromides produced by the corrosion of an aluminum fitting has been reported. Nylon and poly(vinyl chloride) (PVC) should also be avoided for handling methyl bromide.

Methyl bromide is nonflammable over a wide range of concentration in air at atmospheric pressure, and offers practically no fire hazards. With an intense source of ignition its explosive limits are from 13.5 to 14.5% by volume.

The commercial manufacture of methyl bromide is based on the reaction of hydrogen bromide with methanol. The hydrogen bromide used could be generated in situ from bromine and a reducing agent. The uses of sulfur (49) or hydrogen sulfide (50) as reducing agents are described, the latter process having the advantage. A new continuous process for the production of methyl bromide from methanol and aqueous HBr in the presence of a silica supported heteropolyacid catalyst has recently been described (51). Methyl bromide can also be coproduced with other organic bromine compounds by the reaction of the methanol solvent with hydrogen bromide formed as a by-product. The processes include coproduction of methyl bromide with bromostyrenes (52), tribromophenol (53), potassium and sodium bromide (54), and especially tetrabromo bisphenol A (55,56).

The major world producers of methyl bromide are as follows (1996): the Dead Sea Bromine Group (DSBG–Israel) supplies ~41% of the world market, two U.S. producers–Great Lakes Chemical Corporation (31%) and Albermarle Corporation (12%), supply ~43% of the world market; Elf Atochem, the dominant producer in Western Europe, had a world market share of ~6%; and five producers in Japan have a collective share of ~10%.

The world consumption of methyl bromide in 1996 was 68.4 thousand metric tons. The United States accounted for nearly 31% of total world consumption, Western Europe accounted for ~23% and Japan accounted for 13%.

Worldwide, methyl bromide is used principally as a space fumigant used for killing soil parasites (nematodes, fungi, weeds, insects, and rodents) in agriculture and for the sanitation of cereal and other crops under storage and before shipment (57,58). Methyl bromide is also used as an intermediate for the manufacture of pharmaceuticals (clidinium bromide [3485-62-9], clobazam [22316-47-8], glycopyrrolate [596-51-0], mepenzolate bromide [25990-43-6], mepivacaine hydrochloride [1722-62-9], methscopolamine bromide [155-41-9], pancuronium bromide [15500-66-0], propantheline bromide [50-34-0], pyridostigmine bromide [101-26-8]),biocides (CTAB [57-09-0]), insecticides (pirimicarb [23103-98-2]), and chemical reagents (methylmagnesium bromide [75-16-1] and tetramethylammonium bromide [64-20-0]). The current world consumption of methyl bromide as an intermediate is ~1000 t/a (~1.5% of total world consumption).

Due to its role in the depletion of the ozone layer, an international agreement has been reached calling for its reduced consumption and complete phasing out in the developed countries. In September 1997 at the Ninth Meeting of the Parties of Montreal Protocol, members agreed to a schedule for a reduction in the use of the fumigant. The final agreements include

(*1*) For industrial nations, a 25% reduction in use in 1999 followed by a 50% reduction in 2001 and a complete phaseout in 2005 with an allowance for critical exemptions.

(*2*) For developing nations, a 20% reduction in consumption in 2005 at a level based upon average consumption across 1995–1998 followed by a complete phaseout in 2015.

The nonagricultural uses of methyl bromide (its use in organic synthesis) are not restricted, provided that the compound is destroyed during the reaction.

Methyl bromide is a toxic compound (59–61). Repeated splashes on the skin result in severe skin lesions. In cases of lesser exposure, a severe itching dermatitis can develop. Overexposure to methyl bromide may cause dizziness, nausea, vomiting, headache, drowsiness, dimming of vision, and convulsions in the short term. Repeated and prolonged exposure to lower concentrations (30–100 ppm) causes severe nervous system effects. The time-weighted average limit for daily 8-h exposure to the vapor in air is 5 ppm by volume, or 19 mg/m^3; the short-time exposure limit is 15 ppm (62).

Bromochloromethane, CH_2BrCl, (methylene chlorobromide) [74-97-5], is a colorless liquid with a characteristic sweet odor. Its physical properties are bp 68.1°C; mp − 86.5°C; $d^{25}{}_4$ 1.9229 kg/m^3; $n^{25}{}_D$ 1.4808; vapor pressure at 20°C 117 mmHg; heat of vaporization at bp 232 kJ/kg (55.4 kcal/kg). The liquid is completely miscible with common organic solvents. Its solubility in water is 0.9%. For the solubility data, bromochloromethane–water system, see (63).

Common routes for its production involve the partial replacement of chlorine in dichloromethane [75-09-2] by a halogen-exchange reaction using either bromine (64) or hydrogen bromide (65). Both processes are carried out in the presence of aluminum or aluminum trihalide. Other patented processes to produce bromochlorometane include the gas-phase bromination of methyl chloride with a mixture of chlorine and HBr (66) or bromine and chlorine (67), and the liquid-phase displacement reaction of dichloromethane with inorganic bromides (68,69). A mixture of bromochloromethane and dibromomethane is formed in all the above reactions. The compounds are separated by fractional distillation.

The major use of bromochloromethane is as a fire-extinguishing fluid (70); its effectiveness per unit weight makes it suitable for use in aircraft and portable systems. It is also used as an explosion suppression agent, as a solvent, and as an intermediate in the manufacture of some insecticides (chlormephos [24934-91-6]).

The TWA limit or daily 8-h exposure to the vapor of bromochloromethane in air is 200 ppm by volume, or 1050 mg/m^3; the short-time exposure limit is 250 ppm.

Dibromomethane, CH_2Br_2, (methylene bromide) [74-95-3], is a similar liquid, mp −52.7°C; bp 96.9°C; $d^{20}{}_4$ 2.4956 kg/L; $n^{25}{}_D$ 1.5419; vapor pressure 34.9 mmHg (20°C). Its solubility in water is 1.17 g/100 g at 15°C. For the solubility data, dibromomethane–water system, see (71). The compound is produced by the same methods as bromochloromethane. The compound is used as high-density solvent (mineral separation, gauge fluid) and as an intermediate (piperonal [120-57-0], methylene bisthiocyanate [6317-18-6]). Dibromomethane is more toxic than bromochloromethane.

Both dibromomethane and bromochloromethane (or mixtures of these two compounds) are used as solvents for bromination reactions, especially for the production of polybrominated aromatic compounds and polymers (72–74).

Tribromomethane, $CHBr_3$, (bromoform), [75-25-2]. The pure liquid has a mp 8.3°C, bp 149.5°C, $d^{20}{}_4$, 2.8912 kg/L, $n^{19}{}_D$ 1.5419, vapor pressure 5 mmHg (20°C). Its water solubility is ∼0.3 g/100 g at 25°C. For the solubility data, tribromomethane–water system, see (75). Bromoform is prepared by reaction of bromine with acetone or ethanol in the presence of sodium hydroxide (76). Uses have been found as high-density solvent for mineral separation, in gauge fluids and as an intermediate (deltametrin [52918-63-5]). Bromoform is a toxic and irritant compound, TLV 0.5 ppm (skin).

Tetrabromomethane, CBr_4, (carbon tetrabromide), [558-13-4] crystallized in two forms, α-form mp 48.4°C, β-form mp 92.5°C, bp 189.5°C; $d^{20}{}_4$ 3.240 kg/m^3, $d^{99.5}$ 2.9609, $n^{99.5}{}_D$ 1.600. It is prepared by the replacement of chlorine in carbon tetrachloride using hydrogen bromide and an aluminum halide catalyst (65) or by action of sodium hypobromite on bromoform by an extension of the haloform reaction (77). Tetrabromomethane is used as intermediate both in ionic (78) and in homolytic reactions and telomerisation processes (7).

Bromotrifluoromethane, $CBrF_3$, [75-63-8], bromochlorodifluoro methane, $CBrClF_2$ [353-59-3], and 1,2-dibromotetrafluoroethane, $CBrF_2\,CBrF_2$, [124-73-2], are volatile bromine-containing halogenofluorocarbons, known under the technical name "halons". Their physical properties are presented in Table 1.

Halons are fire-extinguishing agents, which replace the more toxic methyl bromide and carbon tetrachloride.

4.2. Ethylene Dibromide. Ethylene dibromide CH_2BrCH_2Br (ethylene bromide, 1,2-dibromoethane), [106-93-4] (commonly abbreviated as EDB) is a clear, colorless liquid with a characteristic sweet odor. Its properties include: mp 9.9°C; bp 131.4°C; $d^{20}{}_4$ 2.1792 kg/L, $n^{20}{}_D$ 1.5380, vapor pressure 1.13 (8.5),

Table 1. **Physical Properties of Halons**

Halon	Formula	bp °C (1 atm)	mp °C	*d* Liquid (25°C)	Critical temperature (°C)	Toxicity[a] (% in air)
1301	$CBrF_3$	−57.8	−168	1.539	67	TWA1000
1211	$CBrClF_2$	−3.9	−161	1.83	154	32
2402	$CBrF_2CBrF_2$	47.3	−110	2.16	214	12.6

[a] Approximately lethal concentration for 15-min exposure.

15.98 (119.8), and 38.03 kPa · s (285.2 mmHg) at 20, 75, and 100°C, respectively; viscosity 1.727 mPa · s (20°C); heat capacity of the solid at 15.3°C, 519 J/kg · K (124 cal/kg · K) and of the liquid at 21.3°C, 724 J/kg · K (173 cal/kg · K); heat of fusion at 9.9°C, 53.4 J/g (12.76 cal/g); heat of vaporization at bp 191 J/g (45.7 cal/g); heat of transition at −23.6°C, 10.34 J/g (2.47 cal/g); critical temperature, 309.8°C; critical pressure 7154 kPa (70.6 atm); expansion coefficient at 15–30°C, 0.000958/K; dielectric constant at 20.5°C (0.1 MHz), 4.77. The liquid is completely miscible with carbon tetrachloride, benzene, gasoline, and anhydrous alcohols at 25°C and its solubility in water at 20°C is 0.404 g/100-g solution.

EDB is nonflammable and quite stable under ordinary conditions. Ethylene glycol is produced by its high temperature hydrolysis under pressure. Reaction with metals (zinc, magnesium) yields ethylene, reaction with ammonia proceeds with explosion, yielding ethylenediamine and higher polymers.

EDB is manufactured via uncatalyzed, liquid-phase bromination of ethylene. Gaseous ethylene is brought into contact with bromine by various methods, allowing for dissipation of the heat of the reaction (79–81).

The largest single application of EDB has traditionally been its use as a lead scavenger in leaded gasoline. Since the U.S. Environmental Protection Agency (EPA) mandated a reduction in the lead content in gasoline beginning in 1974, U.S. consumption of EDB in antiknock mixes has declined dramatically, from 60 thousand metric tons in 1978 to <1000 metric tons in 1997.

The second-largest traditional use of EDB was as an insect fumigant and soil nematocide. In 1983, however, the EPA banned the use of EDB in most agricultural applications because of concerns about the chemical's toxicity. As a result, EDB consumption in this market has also dropped. Currently, most EDB in the USA is produced for export.

Other uses of EDB are believed to consume ∼1000 metric tons annually (USA, 1999). Major uses in this category are as an intermediate for pharmaceuticals (tetramisole [5036-02-2], theodrenaline [13460-98-5]), herbicides (diquat dibromide [85-00-7]), and dyes, (vat Blue 16), where it provides an "ethylene bridge" in the molecular structure. EDB is used as a nonflammable solvent for resins, gums, and waxes. Additionally, EDB can be used as a raw material in the synthesis of chemicals such as vinyl bromide (a precursor of flame-retardants) and styrenic block copolymers.

EDB is an acutely toxic, severely irritating to skin, mutagenic, and carcinogenic compound. Its current time-weighted average limit is 20 ppm. The toxicology of EDB has been reviewed (82).

5. Industrial Chemical Intermediates

Tables 2–4 list some organic bromine compounds used as intermediates and reagents on the industrial scale, their physical properties, and main applications.

6. Industrial Chemical Products

6.1. Flame Retardants. Brominated flame retardants are the more significant and voluminous part of all bromine derivatives. Bromine consumption in

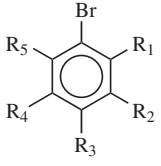
Table 2. **Industrial Aliphatic Bromine Compounds**

Compound	CAS Registry Number	Molecular formula	mp, °C	bp, °C[a]	d_4^{20}	n_D^{20}	Derivatives, uses and miscellaneous properties
allyl bromide	[106-95-6]	$CH_2{=}CHCH_2Br$	−119	71.3	1.398	1.4654	methohexital, nalorhine
n-amyl bromide	[110-53-2]	$CH_3(CH_2)_3CH_2Br$	−95	130	1.218	1.4436	photographic coupling agent intermediate
benzyl bromoacetate	[5437-45-6]	$BrCH_2COOCH_2Ph$		$166^{2.9}$	1.446	1.5440	Merbac-35 (preservative for water-based paints)
bromoacetic acid	[79-08-3]	$BrCH_2COOH$	50	208	1.93		methoprene
bromoacetyl bromide	[598-21-0]	$BrCH_2COBr$		148	2.317		cefotetan, labetalol, sotalol
2-bromobutyric acid	[80-58-0]	$CH_3CH_2CHBrCOOH$	−4	$181^{4.5}$	1.567	1.4720	commercial product is racemate
3-bromo-3-butene-1-ol	[76334-36-6]	$CH_2{=}CBrCH_2CH_2OH$		$64^{1.2}$	1.522	1.4990	building block for sesquiterpenes
1-bromo-3-chloropropane	[109-70-6]	$BrCH_2CH_2CH_2Cl$		142-5	1.46		fluphenazine, perphenazine, prochlorperazine, trazodone, verapamil
2-bromopropionic acid	[598-72-1]	$CH_3CHBrCOOH$	25	204	1.700	1.4750	naproxene, prilocaine
3-bromopropionic acid	[590-92-1]	$BrCH_2CH_2COOH$	62.5	140^{6}	1.480		quaternization reagent for biosensors
5-bromovaleric acid	[2067-33-6]	$Br(CH_2)_4COOH$	38–40				allethrolone
trans-bromostyrene	[103-64-0]	$PhCH{=}CHBr$	7	$110^{2.7}$	1.427	1.6070	fragrance ingredient
n-butyl bromide	[109-65-9]	$CH_3(CH_2)_3Br$	−112	101	1.276	1.4390	bupivacaine, tetracaine, tetra-*n*-butylammonium bromide
cetyl bromide	[112-82-3]	$CH_3(CH_2)_{15}Br$	17.3	$190^{1.5}$	1.99	CTAB	
cetylpyridinium bromide	[140-72-7]	$CH_3(CH_2)_{15}Py^+\ Br^-$					topical disinfectant
cyclopropyl bromide	[4333-56-6]	*cyclo*-C_3H_5Br		68–70	1.510	1.4600	biotin, nortriptiline
cyclopropylmethyl bromide	[7051-34-5]	*cyclo*-$C_3H_5CH_2Br$		105–107	1.392	1.4570	buprenorphine, naltrexone, prazepam
1,4-dibromobutane	[110-52-1]	$BrCH_2CH_2CH_2CH_2Br$		194–196	1.81	1.5186	pentoxyverine
1,3-dibromopropane	[109-64-8]	$BrCH_2CH_2CH_2Br$	−34.2	166.7	1.9822	1.5232	building block

2,3-dibromopropan-1-ol	[96-13-9]	$BrCH_2CHBrCH_2OH$		95[1.3]		1.5590	building block for fire retardant
ethyl bromide	[74-96-4]	C_2H_5Br	−119	38	1.45		pentobarbital, phenobarbital, thiopental
ethyl bromoacetate	[105-36-2]	$BrCH_2COOC_2H_5$	−14	159	1.50	1.451	building block for pharmaceuticals
n-hexyl bromide	[111-25-1]	$CH_3(CH_2)_5Br$	−85	154	1.18		building block for fragrances
isobutyl bromide	[78-77-3]	$(CH_3)_2CHCH_2Br$	−119	91.5	1.260	1.4350	building block for fragrances and dyes
isopropyl bromide	[75-26-3]	$(CH_3)_2CHBr$	−89	59	1.310	1.4251	ipratropium bromide, verapamil
octyl bromide	[111-83-1]	$CH_3(CH_2)_7Br$	−55	201	1.118	1.4518	building block for fragrances
n-propyl bromide	[106-94-5]	$CH_3CH_2CH_2Br$	−110	71	1.353	1.4341	penconazole, valproic acid
tetrabromoethane	[79-27-6]	$Br_2CHCHBr_2$	0	246	2.96		high density solvent for mineral separation
vinyl bromide	[593-60-2]	$CH_2{=}CHBr$	−138	16	1.51		fire retardant comonomer

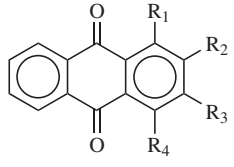
[a] At 101 kPa, unless otherwise indicated in parentheses; pressure in kilo pascals (kPa). To convert kPa to mmHg, multiply by 7.5.

Table 3. **Industrial Aromatic Bromine Compounds (Benzene Series)**



Compound	CAS Registry Number	Molecular formula	mp, °C	bp, °C	$d^{20}{}_4$	$n_D{}^{20}$	Derivatives, uses and miscellaneous properties
2-amino-3-bromo-5-nitrobenzonitrile	[17601-94-4]	$R_1 = NH_2$, $R_2 = CN$, $R_4 = NO_2$, $R_3 = R_5 = H$	186				disperse Blue 183
4-bromoaniline	[106-40-1]	$R_3 = NH_2$, $R_1 = R_2 = R_4 = R_5 = H$	64				metobromuron, resorantel
bromobenzene	[108-86-1]	$R_1 = R_2 = R_3 = R_4 = R_5 = H$	−30.6	156.1	1.4951	1.5604	bromopropylate, clobazam, fenoprofen, flubiprofen, phenylmagnesium bromide
4-bromobenzyl cyanide	[16532-79-9]	$R_3 = CH_2CN$, $R_1 = R_2 = R_4 = R_5 = H$	48				brompheramine
2-bromo-4,6-dinitroaniline	[1817-73-8]	$R_1 = NH_2$, $R_2 = R_4 = NO_2$, $R_3 = R_5 = H$	152				disperce Blue 79, dyestuffs intermediate
bromo-2,4-difluorobenzene	[348-57-2]	$R_1 = R_3 = F$, $R_2 = R_4 = R_5 = H$		145–146	1.708	1.5050	fluconazole, saperconazole, trovafloxacin
4-bromofluorobenzene	[460-00-4]	$R_3 = F$, $R_1 = R_2 = R_4 = R_5 = H$	−17	155	1.593	1.5270	flustiazole, flutriafol
tetrabromo-*o*-cresol	[576-55-6]	$R_1 = R_2 = R_3 = Br$, $R_4 = OH$, $R_5 = CH_3$	206				disinfectant
2,4,6-tribromoaniline	[147-82-0]	$R_1 = NH_2$, $R_2 = R_4 = Br$	120	300			building block for fire-retardants
2,4,6-tribromophenol	[118-79-6]	$R_1 = OH$, $R_2 = R_4 = Br$	95	290			wood preservative

Table 4. **Industrial Organic Bromine Compounds—Derivatives of Anthraquinone**



Compound	CAS Registry Number	Molecular formula	mp °C	Derivatives
2-amino-3-bromo-anthraquinone	[6337-00-4]	$R_1 = R_4 = H$, $R_3 = Br$, $R_2 = NH_2$	235–303	vat Blue 30, vat Red 10
1-amino-2-bromo-4-hydroanthraquinone	[116-82-5]	$R_1 = NH_2$, $R_2 = Br$, $R_3 = H$, $R_4 = OH$		disperse Red 60
1-amino-2-bromo-4-(4′-methylphenylsulfamido)-anthraquinone	[26868-32-6]	$R_1 = NH_2$, $R_2 = Br$, $R_3 = H$, $R_4 = NHSO_2C_6H_4CH_3$		acid Blue 45
1-amino-2,4-dibromoanthraquinone	[81-49-2]	$R_1 = NH_2$, $R_2 = R_4 = Br$, $R_3 = H$	226	acid Blue 96
bromamine acid, 1-amino-4-bromoanthraquinone-2-sulfonic acid	[116-81-4]	$R_1 = Br$, $R_2 = H$, $R_3 = SO_3H$, $R_4 = NH_2$		acid Blue 25, 40, 41, 53, 62, 111, 124, 127, 129, 138, 145, 230, direct Green 28, pigment Red 177, reactive Blue 2, 4, 19, 94
1-bromo-4-methylaminoanthraquinone	[128-93-8]	$R_1 = Br$, $R_2 = H$, $R_3 = SO_3H$, $R_4 = NHCH_3$	194	acid Blue 27, acid Violet 80, basic Blue 22

flame retardants has risen substantially from the early 1990s and at present forms, on average, one-half of organic bromine compounds consumption and ~40% of the total bromine consumption.

Brominated flame retardants can be divided into two groups according to their chemical structure: brominated aliphatic compounds and brominated aromatic compounds. The latter are much more stable and may be used in thermoplastics at fairly high temperatures without the use of stabilizers and at very high temperature with stabilizers.

Brominated flame retardants can also be divided into two general classes according to their relation to polymers—additive flame retardants and reactive flame retardants. Additives are mixed into the polymer in common polymer processing equipment. Reactive flame retardants literally become part of the polymer by either reacting into the polymer backbone or grafting onto it. The characteristics of commercial brominated flame retardants are given in Tables 5–7. The world consumption of brominated flame retardants is presented in Table 8.

The average annual growth rate for brominated compounds is forecast through 2003 at 2.5–3% per year for additive compounds and 4% for reactive compounds. These products will benefit from more exacting fire safety standards in consumer products, building products, automobile and aircraft components. The proliferation of computers and other consumer electronics is boosting demand for plastics that have enhanced flame retardancy characteristics. Because of the effectiveness and performance advantages of brominated flame retardants, smaller amounts can be used, which enhances the cost effectiveness of these products while maintaining the functional characteristics of the host material.

6.2. Pesticides. A list of bromine-containing pesticides is presented in Table 9.

A more significant and expanding group of brominated biocides is for water treatment (83). While chlorine controls the majority of the water treatment market, brominated compounds are becoming increasingly popular. In general, both industrial and consumer segments of the water treatment industry are increasingly replacing chlorine and chlorinated compounds as sanitizers and biocides with bromine-based products. Chlorine is now subject to a wide range of EPA limitations, and although bromine is itself a halogen, no restrictions have yet been placed on brominated biocides. In addition, the greater strength of bromine-based biocides allows treatment of a given amount of water with considerably less biocide. This not only reduces the amount of halogen released into the environment, but can also reduce costs for municipal and industrial water treatment plants. Benefits accrue through reduced chemical costs, avoidance of the dechlorination step common in chlorine water treatment, and reduced corrosion to condensers, tubing and other equipment.

Brominated biocides also perform better than chlorinated biocides in a number of industrial applications because of their higher tolerance to a wide range of pH levels, a concern in cooling towers and process waters. A trend in recent years has been to run cooling water towers at a higher pH to minimize corrosion, but this often leads to a larger formation of algae. Brominated

Table 5. **Brominated Additive Flame Retardants**

Compound	CAS Registry Number	Molecular formula	mp, °C	Bromine content, %	Producers[a]
bis(2-ethylhexyltetrabromophthalate)	[26040-51-7]	$C_{24}H_{34}Br_4O_4$		45	EA, GL
bis(methyl)tetrabromophthalate	[55481-60-2]	$C_{10}H_6Br_4O_4$		63	EA
bis(tribromophenoxy)ethane	[37853-59-1]	$C_{14}H_8Br_6O_2$	224	68	GL
brominated trimethylphenylindane	[155613-93-7]	$C_{18}H_{12}Br_8$	240–255	73	DS
decabromobiphenyl	[13654-09-6]	$C_{12}Br_{10}$		84.5	EA
decabromodiphenyl ether	[1163-19-5]	$C_{12}Br_{10}O$	303–307	83	AL, ASC, DS, GL, ISC, MI, MT, NC, TS, WI
decabromodiphenylethane	[137563-36-1] [84852-53-9]	$C_{14}H_4Br_{10}$	350–356	82.3	AL
dibromoethyldibromocyclohexane	[3322-93-8]	$C_8H_{12}Br_4$	175–185	73	AL, DS, GL, ISC
ethylenebisdibromonorbornanedicarboximide	[52907-07-0] [41291-34-3]	$C_{20}H_{20}Br_4N_2O_4$	294	45	AL, GL
ethylenebis(tetrabromophthalimide)	[32588-76-4]	$C_{18}H_4Br_8N_2O_4$	456	67.2	AL
hexabromocyclododecane	[3194-55-6]	$C_{12}H_8Br_6$	180	74.7	AL, DS, GL, ISC
octabromodiphenyl ether	[32536-52-0]	$C_{12}H_2Br_8O$	70–150	78	AL, DS, GL, ISC, MI
pentabromotoluene	[87-83-2]	$C_7H_3Br_5$		82	DS
tetrabromobisphenol A bis(2,3-dibromopropyl ether)	[21850-44-2]	$C_{23}H_{20}Br_8O_2$	95	67.7	Al, DS, GL
tetrabromobisphenol A	[79-94-7] [6386-73-8]	$C_{15}H_{12}Br_4O_2$	180	58.4	AL, ASC, DS, GL, T, TS
tetradecabromodiphenoxybenzene	[58956-66-5]	$C_{18}Br_{14}O_2$	370	82	AL
tris-dibromopropylisocyanurate	[52434-90-9]	$C_{12}H_{15}Br_6N_3O_3$	106–108	65.8	AC, ASC, T

[a] Company and country are as follows: AC = Akzo Chemicals BV, Netherlands; AL = Albemarle, USA; ASC = Asahi Chemical, Japan; DS = DSBG, Israel; EA = Elf Atochem, France; GL = Great Lakes, USA; ISC = ISC Chemicals, Ltd, UK; MI = Manac Inc., Japan; M = Marubishi, Japan; MT = Mitsui Toatsu Fine Chemicals, Japan; NC = Nippon Chemicals Corp., Japan; T = Teijin, Japan; TS = Tosoh, Japan; WI = Warwick Int., UK; CECA = CECA, SA, France.

Table 6. **Polymeric and Oligomeric Additive Flame Retardants**

Compound	CAS Registry Number	Molecular Formula[a]	mp, °C	Bromine content, %	Producers[b]
brominated polystyrene low molecular weight	[88497-56-7]	$(C_8H_{5.3}Br_{2.7})_n$	130–140	66	KC
brominated polystyrene	[88497-56-7]	$(C_8H_{5.3}Br_{2.7})_n$	195	66	KC
poly(dibromophenylene oxide)	[26023-27-8]	$(C_6H_2Br_2O)_n$	225	62	GL
poly(pentabromobenzylacrylate)	[59447-55-1]	$(C_{10}H_5Br_5O_2)n$	210	71	DS
poly(dibromostyrene)	[62354-98-7]	$(C_6H_6Br_2)_n$	155–165	59	GL
tetrabromobisphenol A carbonate oligomer, phenoxy end capped	[94334-64-2]	$(C_{16}H_{12}Br_4O_3)_n$	210–230	52	GL, MG, T
tetrabromobisphenol A carbonate oligomer, tribromophenoxy end capped	[71342-77-3]	$(C_{16}H_{12}Br_4O_3)_n$	230–260	58	GL
tetrabromobisphenol A epoxy oligomers	[68928-70-1]	$(C_{16}H_{12}Br_4O_3)_n$		52–54	DS, DI, DC, H, MI, SY, TK
tetrabromobisphenol A epoxy oligomers, tribromophenoxy end capped	[400039-93-8]	$(C_{16}H_{12}Br_4O_3)_n$		55–58	DI, H, TK

[a] Formulas for polymeric compounds are for the repeat unit only and ignore the end groups.

[b] Company and country are as follows: DS = DSBG, Israel; DI = Dainippon Ink and Chemical, Japan; DC = Dow Chemical, USA; GL = Great Lakes, USA; H = Hitachi, Japan; KC = Keil Chemical Div., Ferro Corp., USA; MI = Manac Inc., Japan; MG = Mitsubishi Gas Chemical Co, Japan; SY = Sakamoto Yukuhin Co., Japan; T = Teijin, Japan; TK = Tohto Kasei, Japan.

Table 7. **Brominated Reactive Flame Retardants**

Compound	CAS Registry Number	Molecular formula	mp, °C	Bromine content,%	Producers[a]
dibromoneopentyl glycol	[3296-90-0]	$C_5H_{10}Br_2O_2$	109.5	60	AL, DS
pentabromobenzylacrylate	[59447-55-1]	$C_{10}H_5Br_5O_2$		71.0	DS
pentabromobenzyl bromide	[38521-51-6]	$C_7H_2Br_6$		84.8	DS
tetrabromobisphenol A	[79-94-7]	$C_{15}H_{12}Br_4O_2$	181	58.5	AL, ASC, CECA, DS, GL, T, TS
tetrabromobisphenol A bis(allyl ether)	[25327-89-3]	$C_{21}H_{20}Br_4O_2$	119	51.2	DS, GL
tetrabromobisphenol A bis(2-hydroxyethyl ether)	[4162-45-2]	$C_{19}H_{20}Br_4O_4$	116	51.6	DS, GL
tetrabromophthalic anhydride	[632-79-1]	$C_8Br_4O_3$	270	68	AL, CECA, GL
tetrabromophthalic anhydride/diol	[7709807-8]	$C_{15}H_{16}Br_4O_7$	liquid	46	AL, GL
tribromophenylmaleinimide	[59789-51-4]	$C_{10}H_8Br_3NO_2$		57.9	DS
tribromoneopentyl alcohol	[1522-92-5]	$C_5H_9Br_3O$	62–67	73.6	AL, DS
2,4,6-tribromophenol	[118-79-6]	$C_6H_3Br_3O$	93	72.3	DS, GL, MI
vinyl bromide	[593-60-2]	C_2H_3Br	liquid	74.5	AL

[a] Company and country are as follows: AL = Albemarle, USA; ASC = Asahi Chemical, Japan; CECA = CECA, SA, France; DS = DSBG, Israel; GL = Great Lakes, USA; MI = Manac Inc., Japan; TS = Tosoh, Japan.

Table 8. **Consumption of Brominated Flame Retardants 1998, $\times 10^3$ t**

USA	Western Europe	Japan	Other Asia	Total	Total value (millians of dollars)
68.3	51.5	47.8	97	264.5	790

Table 9. **Organic Bromine Compounds Used as Pesticides**

Compound	CAS Registry Number	Toxicity LD_{50} mg/kg rats
Acaricide		
bromopropylate	[18181-80-1]	1700
Fungicides		
(2-bromo-1,2-diiodoacryl)ethylcarbonate	[77352-88-6]	500–600
BMPCA, *N*-(4-bromo-2-methylphenyl)-2-chloracetamide	[96686-51-0]	4044
Herbicides		
bromacil	[314-40-9]	
bromobutide	[74712-19-9]	
bromofenoxim	[13181-17-4]	1200
bromoxynil	[1089-84-5]	
bromoxynil octanoate	[1689-99-2]	
chlorbromuron	[13360-45-7]	
diquat dibromide	[85-00-7]	300
metobromuron	[3060-89-7]	
Insecticides		
bromofos (and acaricide)	[2104-96-3]	2800
deltametrin	[52918-63-5]	
leptophos	[21609-90-5]	
naled (and acaricide)	[300-76-5]	430
profenofos	[41198-08-7]	358
Microbicides (water treatment biocides)		
benzyl bromoacetate[a]	[5437-45-6]	
bis-1,2-(bromoacetoxy)ethane[b]	[3785-34-0]	
bis-1,4-(bromoacetoxy)-2-butene[b]	[20679-58-7]	
bromochlorophen[c]	[15435-29-7]	3700–8000
BNP (2-bromo-2-nitropropanol)	[24403-04-1]	~300
BNS (2-bromo-2-nitrostyrene)[b]	[7166-19-0]	
bronidox	[30007-47-7]	590
bronopol	[52-51-7]	325
cetrimonium bromide CTAB	[57-09-0] [77-48-5]	
DBDMH (1,3-dibromo-5,5-dimethylhydantoine)	[77-48-5]	
DBNPA (2,2-dibromo-2-cyanoacetamide)	[10222-01-2]	126
1,2-dibromo-2, 4-dicyanobutane[a]	[35691-67-7]	
dibromohexamidine isethionate	[93856-82-7]	541
disanyl	[87-12-7]	>4000
halobrom (BCDMH, bromochlorodimethylhydantoin)	[126-06-7], [32718-18-6], [107846-11-7]	1700
2-hydroxyethyl 2,3-dibromo-propionate[a]	[68479-77-6]	
trisanyl	[87-12-7]	570

Table 9 (*Continued*)

Compound	CAS Registry Number	Toxicity LD_{50} mg/kg rats
Nematocides		
1,2-dibromo-3-chloropropane	[96-12-8]	173
1,2,3-tribromopropane	[96-11-7]	
Rodenticides		
brodifacum	[56073-10-0]	
bromadiolone	[28772-56-7]	
bromethalin	[63333-35-7]	

[a] Used as preservative for in-can protection of water based paints, adhesives and polishes.
[b] Used as ingredient in nonpersistent slimicides in the paper industry.
[c] Used as a preservative for cosmetics.

Table 10. **Bromine Demand in Water Treatment Biocides in USA, $\times 10^3$ t**

Year	1985	1989	1995	2000	2005
Water treatment biocides	12.7	22.7	36.3	47.2	61.3

Table 11. **Bromine Containing Pharmaceuticals**

Compound	CAS Registry Number	Compound	CAS Registry Number
Adrenergic		*Anticoagulant*	
hydroxyamphetamine hydrobromide[a]	[306-21-8]	bromindione	[1146-98-1]
Analgesic		*Anticonvulsant*	
		cinromide	[58473-74-8]
bromadoline	[67579-24-2]		
bromfenac	[91714-94-2]	*Antidepressant*	
phenazocine	[1239-04-9]		
		zimeldine	[56775-88-3]
Anesthetic (inhalation)		*Antihistaminic*	
halothane[a]	[151-67-7]	bromodiphenhydramine[a]	[118-23-0]
roflurane	[679-90-3]	brompheniramine[a]	[86-22-6]
teflurane	[124-72-1]	dexbrompheniramine[a]	[132-21-8]
		temelastine	[86181-42-2]
Antiadrenergic		*Antihypertensive*	
bretylium tosylate	[61-75-6]		
		guanisonium	[154-73-4]
Anticholinergic		quinuclium bromide	[35425-83-3]
anisotropine methylbromide	[80-50-2]	*Antiinfective*	
benzilonium bromide	[1050-48-2]		
clidinium bromide[a]	[3485-62-9]	domiphen bromide	[538-71-6]
glycopyrrolate[a]	[596-51-0]		
heteronium bromide	[7247-57-6]	*Antiinflamatory*	
hyoscyamine hydrobromide[a]	[306-03-6]		
mepenzolate bromide	[76-90-4]	broperamole	[33144-79-5]
methantheline bromide	[53-46-3]	halopredone acetate	[57781-14-3]
methscopolanine bromide	[155-41-9]		

Table 11 (*Continued*)

Compound	CAS Registry Number
penthienate bromide	[60-44-6]
pipenzolate bromide	[125-51-9]
propantheline bromide[a]	[50-34-0]
scopolanine hydrobromide[a]	[114-49-8]
thihexinol methylbromide	[7219-91-2]
valethamate bromide	[90-22-2]
Anticholinergic (ophthalmic)	
homatropine hydrobromide[a]	[51-56-9]
homatropine methylbromide[a]	[80-49-9]
Antitussive	
dextromethorphan hydrobromide[a]	[125-69-9]
Antiviral	
sorivudine	[77181-69-2]
Bronchodilator	
ipratropium bromide	[22254-24-6]
rimiterol hydrobromide	[32953-89-2]
Cholinergic	
neostigmine bromide[a]	[114-80-7]
pyridostigmine bromide[a]	[101-26-8]
Cholinergic ophtalmic	
demecarium bromide[a]	[56-94-0]
Detergent	
thonzonium bromide	[553-08-2]
Diagnostic aid (hepatic function)	
sulfobromophthalein sodium	[71-67-0]
Diagnostic aid (hepatobiliary function)	
mebrofenina	[78266-06-5]
Diuretic	
brocrinate	[72481-99-3]
pamabrom	[606-04-2]
Enzyme inhibitor (prolactin)	
bromocriptine	[25614-03-3]
bromocriptine mesylate[a]	[22260-51-1]
Antineoplastic	
bropirimine	[56741-95-8]
pipobroman[a]	[54-91-1]
Antipsychotic	
brofoxine	[21440-97-1]
bromperidol	[10457-90-6]
Expectorant	
bromohexine	[3572-43-8]
Inhibitor aldose reductase	
ponalrestat	[72702-95-5]
Neuromuscular blocker	
pancuronium bromide	[15500-66-0]
pipecuronium bromide	[52212-02-9]
rocuronium bromide	[119302-91-9]
vecuronium bromide	[50700-72-6]
Progestin	
haloprogesteron	[3538-57-6]
Sceletal muscle relaxant	
azumolene	[64748-79-4]
hexafluorenium bromidea	[317-52-2]
Sedative and hypnotic	
brotizolam	[57801-81-7]
Tranquilizer minor	
bromazepam	[1812-30-2]
Vasodilator	
brovincamine	[57475-17-9]
nicergoline	[27848-84-6]
Veterinary medicine	
halofuginone	[55837-20-2]

[a] Listed in the *U.S. Pharmacopeia* 24 (2000).

Table 12. **Bromine-Containing Dyes**

Dye	CAS Registry Number	CI Number	Dye used for
acid orange 11, 4′,5′-dibromofluorescein	[596-03-2]	45370	wool, silk, paper
alizarin pure Blue B	[6424-75-5]	1088	wool
Ciba Bordeaux B, 5,5′-dibromothioindigo	[6371-14-8]	1208	cotton
5,5′-dibromoindigo	[19201-53-7]	1183	cotton
disperse Blue 20	[26846-51-5]		polyester, acetate
disperse Blue 56	[12217-79-7]	63285	polyester, acrylic, acetate
disperse Yellow 64 4-bromo-3-hydroxy-quinophthalone	[10319-14-9]	47023	acetate, polyamide, 4-polyester
eosine B, acid Red 91, 4′,5′-dibromo-2′,7′-dinitrofluorescein	[548-24-3]	45400	wool, cotton, paper differential staining
eosine Y, Acid Red 87, 2′,4′,5′,7′-tetrabromofluorescein	[17372-87-1]	45380	cosmetics, paper and inks, biological stain
pigment Green 36 brominated phthalocyanine	[14302-13-7]	74265	paints, printing inks, plastics
pigment Red 216, tribromopyranthrone	[1324-33-0]	59710	paints, plastics
vat Blue 5, 5,5′,7,7′-tetrabromoindigo	[2475-31-2]	73065	cotton, viscose, silk
vat Blue 19, dibromodibenzanthrone	[1328-18-3]	59805	cotton, viscose
vat Orange 1, dibromodibenzopyrenequinone	[1324-11-4]	59105	cotton
vat Orange 2, 4,12-dibromopyranthrone	[1324-35-2]	59705	cotton, viscose, silk
vat Orange 3, dibromoanthantrone	[4378-61-4]	59300	cotton, plastics

Table 13. **Bromine-Containing Indicators**

Indicator	CAS Registry Number	Transition range, pH	Color change
bromophenol blue	[115-39-9]	3.0–4.5	yellow–blue violet
bromochlorophenol blue	[2553-71-1]	3.2–4.6	yellow–blue violet
bromocresol green	[76-60-8]	3.8–5.4	blue–green
bromophenol red	[2800-80-8]	5.2–6.8	yellow–purple
bromocresol purple	[115-40-2]	5.2–6.8	yellow–purple
bromoxylenol blue	[40070-59-5]	5.7–7.5	yellow–blue
bromothymol blue	[76-59-5]	6.0–7.6	yellow–blue

products (especially DBDMH and Halobrom) are both more effective at higher pH ranges than chlorine, and are estimated to be three times more effective than chlorine at controlling algae blooms.

Apart from their increasing use in industrial and municipal water treatment, bromine derivatives are also registering gains in the consumer water conditioning market as biocides for spas and hot tubs. In these applications, DBDMH and Halobrom are displacing chlorinated biocides for the same reasons as in large-scale water treatment.

In addition, brominated biocides are more stable than chlorine in higher temperature waters, do not readily decompose on exposure to sunlight and are less irritating to the eyes and mucous membranes. This is particularly important in the recreational segment of the water treatment market. As a result, brominated biocides for water treatment will continue to expand their market share (Table 10).

6.3. Pharmaceuticals. Organic pharmaceuticals containing bromine can be divided into two groups. The main group includes actual organic bromine compounds, in which bromine is bonded with the carbon atom. The second group includes salts of hydrobromic acid and ammonium organic compounds. Both these groups are presented in Table 11.

6.4. Dyes and Indicators. The effect of bromine in dye (Table 12) or indicator molecules in place of hydrogen includes a shift of light absorption to longer wavelengths, increased dissociation of phenolic hydroxyl groups, and lower solubility. The first two effects probably result from increased polarization caused by bromine's electronegativity compared to that of hydrogen.

Bromine containing indicators are listed in Table 13.

BIBLIOGRAPHY

"Bromine Compounds" in *ECT* 1st ed., Vol. 2, pp. 645–660, by V. A. Stenger and G. J. Atchison, The Dow Chemical Company; in *ECT* 2nd ed., Vol. 3, pp. 766–786, by V. A. Stenger and G. J. Atchison, The Dow Chemical Company; in *ECT* 3rd ed., Vol. 4, pp. 243–263, by N. A. Stenger, Dow Chemical U.S.A.; in *ECT* 4th ed., Vol. 4, pp. 560–589 by Philip F. Jackisch, Ethyl Corporation; "Bromine Compounds" in *ECT* (online), posting date: April 12, 2000, by Philip F. Jackisch, Ethyl Corporation.

CITED PUBLICATIONS

1. G. W. Gribble, *Verh.- K. Ned. Akad. Wet., Afd Natuurkd., Tweede Reeks* **98**, 1 (1997) (in English); *Chem. Abstr.* **128**, 267–273 (1998).
2. P. Friedlender, *Chem. Ber.* **55**, 1655 (1922).
3. P. Ashworth and J. Chetland, *Ind. Chem. Libr.*, **3** (*Adv. Organobromine Chem.* **1**), 263 (1991).
4. P. B. D. de la Mere and B. E. Swedlund in S. Patai, ed., *The Chemistry of Carbon–Halogen Bond*, Part 1, John Wiley & Sons, Inc., New York, 1973, pp. 407–548.
5. C. Hill, *Activation and Functionalization of Alkanes*, John Wiley and Sons, Inc., New York, 1989.
6. F. A. Drahowzal in G. Olah, ed., *Friedel–Crafts and Related Reactions*, Interscience Publishers, New York, Vol. 2, 1964, pp. 417–475.
7. A. B. Terent'ev and T. T. Vasil'eva, *Russ. Chem. Rev.* **63**, 269 (1994).
8. J. Lindley, *Tetrahedron* **40**, 1433 (1984).
9. A. M. Moroz and M. S. Shvartsberg, *Russ. Chem. Rev.* **43**, 679 (1974).
10. R. F. Heck, *Org. Reactions* **27**, 345 (1982).
11. S. Brase and A. De Meijere in F. Diderich and P. Stang, eds., *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, 1998, pp. 99–166.
12. R. Franzen, *Can. J. Chem.* **78**, 957 (2000).
13. A. Suzuki, *J. Organomet. Chem.* **576**, 147 (1999).
14. A. Roedig in Houben-Weyl, *Methoden der Organische Chemie*, 4th ed., Thieme Verlag, Stuttgart, V/4, 1960, pp. 13–516.
15. R. C. Larock, *Comprehensive organic transformations*, VCH, New York, 1989, pp. 307–383.
16. P. L. Spargo in A. R. Katritzky, O. Meth-Cohn, and C. W. Rees, eds., *Comprehensive Organic Functional Group Transformations*, Pergamon, Oxford, 1995, Vol. 2, pp. 1–37.
17. C. J. Urch in Ref. 16, pp. 605–635.
18. P. L. Spargo, *Contemp. Org. Synth.* **1**, 113 (1993).
19. P. L. Spargo, *Contemp. Org. Synth.* **2**, 85 (1994).
20. S. P. Marsden, *Contemp. Org. Synth.* **3**, 133 (1995).
21. S. P. Marsden, *Contemp. Org. Synth.* **4**, 118 (1996).
22. S. D. Christie, *J. Chem. Soc. Perkin Trans.* **1**, 1577 (1998).
23. S. D. Christie, *J. Chem. Soc. Perkin Trans.* **1**, 737 (1999).
24. H. J. Harwood, *Chem. Rev.* **62**, 99 (1962).
25. N. De Kimpe and R. Verhe in S. Patai and Z. Rappoport, eds., *The Chemistry of Functional Groups*, Update Vol., John Wiley and Sons, Inc., New York, 1988.
26. Y. Sasson, M. Weiss, and G. Barak in D. Price, B. Iddon, and B. J. Wakefield, eds., *Bromine Compounds Chemistry and Applications*, Elsevier, 1988, pp. 252–271.
27. R. A. Sheldon and J. K. Kochi, *Org. Reactions* **19**, 279 (1972).
28. D. Crich, *Comp. Org. Synth.* **7**, 723 (1991).
29. S. M. Kelley and H. Schad, *Helv. Chim. Acta* **68**, 813 (1985).
30. O. S. Tee, *Ind. Chem. Libr.* **3** (*Adv. Organobromine Chem.* **1**), 99 (1991).
31. H. P. Braendlin and E. T. McBee in G. Olah (ed.), *Friedel–Crafts and Related Reactions*, Interscience Publishers, New York, Vol. 3, (1964), p. 1517.
32. A. M. Andrievskii, M. V. Gorelik, S. V. Avidon and E. S. Altman, *Russ. J. Org. Chem.* **29**, 1519 (1993).
33. G. A. Olah, W. C. Tolguesi, and R. E. Dear, *J. Org. Chem.* **31**, 1262 (1962).
34. U.S. Pat. 4,347,390 (1982), R. Nishiyama and co-workers (to Ishihara Sangyo Kaisha Ltd).
35. D. Ioffe, *Mendeleev Comm.* 16 (1993).

36. H. Zollinger, *Diazo Chemistry I*, VCH, Weinheim, 1994, pp. 230–235.
37. J. S. Pizey, *Synthetic Reagents* **2**, John Wiley and Sons, Inc., New York, 1974, pp. 1–63.
38. M. Zviely, J. Hermolin, and A. Kampf, *Ind. Chem. Libr.* **3** (*Adv. Organobromine Chem.* **1**), 171 (1991); GB 2,175,895 (Apr 01 1985, to Bromine Compounds Ltd.).
39. S. Kajigaeshi and T. Kakinami, *Ind. Chem. Libr.* **7** (*Adv. Organobromine Chem.* **2**, 29 (1995).
40. M. K. Chaudhuri and co-workers, *Tetrahedron Lett.* **39**, 8163 (1998).
41. J. Jacques and A. Marquet, *Org. Synth.* **VI**, 175 (1988).
42. A. Nechvatal, *Adv. Free-Radical Chem.* **4**, 175 (1972).
43. M. Zupan and N. Segatin, *Synthetic Comm.* **24**, 2617 (1994).
44. M. F. Ruasse, *Ind. Chem. Libr.* **7** (*Adv. Organobromine Chem.* **2**), 100 (1995).
45. G. Belluchi, C. Chiappe, and R. Bianchini, *Ind. Chem. Libr.* **7** (*Adv. Organobromine Chem.* **2**), 128 (1995).
46. F. W. Stacey and J. F. Harri, *Org. Reactions* **13**, 150 (1963).
47. L. S. Boguslavskaya, *Russ. Chem. Rev.* **41**, 740 (1972).
48. J. Rodriguez and J. P. Dulcere, *Synthesis* 1177 (1993).
49. GB Pat. 768,893 (Feb. 20, 1957, to Degussa).
50. U.S. Pat. 2,717,911 (1955), L. Hunter, and H. Veith (to Degussa).
51. N. A. Alekar and co-workers, *Indian J. Chem. Technol.* **7**, 79 (2000).
52. Ger. Offen 2,339,612 (Aug 08, 1973), D. Vofsi, M. Levy, S. Daren, and E. Cohen.
53. H. M. Bhavnagary and S. K. Maiumder, *Res. Ind.* **29**, 5 (1984).
54. JP-Kokai 74,108,003 (1974), K. Matsuda, M. Sigino, and S. Kaji (to Nippon Kayaku Co).
55. U.S. Pat. 3,182,088 (1965), H. E. Hennis (to Dow Chemical).
56. U.S. Pat. 5,0177,728 (May 21 1991), B. G. McKinnie and D. A. Wood (to Ethyl Corp).
57. C. Bell, N. Price, and B. Chakrabarti, eds., *The Methyl Bromide Issue. Vol. 1: Agrochemical and Plant Protection*, UK 1996.
58. J. Katan, *J. Plant. Pathol.* **81**, 153 (1999).
59. G. V. Alexeev and W. W. Kilgore, *Residue Rev.* **88**, 101 (1983).
60. R. Yang and co-workers, *Rev. Environ. Contam. Toxicol.* **142**, 65 (1995).
61. D. J. Guth and co-workers, *Inhalation Toxicol.* **6**, 327 (1994).
62. "Threshold Limit Values and Biological Exposure Indices for 1989-1990", American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, 1989.
63. A. L. Horvath, *Solubility Data, Ser.* **60**, 143 (1995).
64. Ger. Offen 727,690 (Oct. 8, 1942), O. Scherer, F. Dostal, and K. Dachlauer (to I. G. Farbenindustrie A.- G); U.S. Pat. 2,347,000 (Apr. 18, 1944, to Alien Property Custodian).
65. U.S. Pat. 2,553,518 (May 15, 1951), D. E. Lake and A. A. Asadorian (to Dow Chemical).
66. GB 874,062 (May 31, 1959) (to Soc. Chimica Dell'Aniene SpA).
67. DE 1,283,214 (1968), U. Giacopelli and M. Manca (to Solvay et Cie).
68. Fr. 1,441,233 (June 03, 1966), (to Shell International Research).
69. U.S. Pat. 3,923,914 (1975), P. Kobetz and K. L. Lindsay (to Ethyl Corp.).
70. U.S. Pat. 5,207,953 (Nov. 27, 1991), D. Thorssen and D. Loree, (to Trisol Inc).
71. Ref. 63, p. 146.
72. Eur. Pat. Appl. EP 995,733 (Apr. 26, 2000), N. Kornberg, T. Fishler, and S. Antebi, (to Bromine Compounds Ltd).
73. PCT Int. Appl. WO 9,813,396 (Apr. 02, 1998), M. Ao and co-workers (to Albermarle Corp.).
74. PCT Int. Appl. WO 9,504,409 (Nov. 12, 1998), B. Dalgar and co-workers (to Albermarle Corp.).

75. Ref. 63, p. 82.
76. A. Kergomard, *Bull. Soc. Chim.* 2360 (1961).
77. W. H. Hunter and D. E. Edgar, *J. Am. Chem. Soc.* **54**, 2025 (1932).
78. E. Abele and E. Lukevics, *Org. Prep. Proced. Int.* **31**, 359 (1999).
79. U.S. Pat. 2,746,999 (May 22, 1956), A. A. Gunkler, D. E. Lake, and B. C. Potts (to Dow Chemical Company).
80. Brit. Pats. 804,995 and 804,996 (Nov. 26, 1958), W. J. Read and co-workers (to Associated Ethyl Co.).
81. U.S. Pat. 2,921,967 (Jan. 19, 1960), F. Yaron (to Dead Sea Bromine Co.).
82. S. D. Humphreys, H. G. Huw, and P. A. Routledge, *Adverse Drug React. Toxicol. Rev.* **18**, 125 (1999).
83. W. Paulus, *Microbiocides for the Protection of Materials*, Chapman & Hall, London, 1993.

DAVID IOFFE
IMI (TAMI)
ARIEH KAMPF
DSBG