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Review

ORGANOMETALLIC COMPOUNDS AND LIVING ORGANISMS

JOHN S. THAYER
Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221 (U.S.A.)
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Contents

I. General considerations

A. Scope and nature

Carbon will form bonds to almost every other element in the Periodic Table. Many of these compounds are important, even necessary, to vital processes in living organisms. The vast research in the area of biological chemistry has focused on compounds of carbon to hydrogen, oxygen, nitrogen, or sulfur. Yet the compounds involving metals (or metalloids) and carbon, collectively termed organometallic compounds, also show biological effects. Such effects have been known ever since organometals themselves began to be reported. Table 1 gives a chronological summary. Gilman discussed some of these back in 1941 [1]. More detailed coverage appears in an article by Thayer [2]. A substantial literature exists in this area, and has been growing rapidly in recent years, but its wide dispersion has made comparison and correlation difficult.

This article hopes to remedy that situation, at least in part. It will discuss the biological aspects and effects displayed by organic compounds of metals and metalloids, and point out areas where further research may be desirable. Most of the major literature through the end of 1973 has been included.

B. Comparative studies

For most organometals, the study of their biological properties is the study of their toxicology. From the steadily increasing amount of available research data, one can make the following generalizations about organometal toxicity:

1. Metal. If the metal is toxic (e.g. mercury, lead), its organic derivatives will be toxic. Frequently, the toxicity becomes enhanced. Metals and metalloids that are harmless by themselves or as inorganic derivatives often become deadly when combined with organic groups. Tin and phosphorus are prime examples.

2. Organic group(s). For most σ-bonded organometals, the alkyl derivatives tend to be more toxic than the aryls, and both show greater toxicity than purely inorganic derivatives. Substituents on the organic groups tend to effect toxicity, especially in the aryl derivatives. This trend is quite marked in metalloids and has been most studied for arsenic.

3. Inorganic group(s). Most inorganic groups have little effect on toxicity. Exceptions occur in the organometalloids when such groups may be hydrolyzed off as acids.

4. Physical state. This may occasionally make a compound more (or less) deadly than intrinsic toxicity might indicate. Volatile compounds are especially dangerous to handle. The peralkylmetals tend to be gases or easily vaporizable liquids; hence they may be more hazardous than the compounds with one alkyl replaced by an inorganic group (usually solids), even though the latter have higher intrinsic toxicity.

TABLE 1

CHRONOLOGICAL DEVELOPMENT

1837	Bunsen's first report on cacodyl. About this time "arsenic rooms" began receiving the attention of Gmelin and others.
1849	Frankland prepares $(CH_3)_2Zn$ and $(C_2H_5)_2Zn$, and observes that inhalation causes zinc poisoning.
1858	Buckton notes irritating effects of alkyltin compounds on nasal passages.
1866	First reported fatality from dimethylmercury poisoning.
1890	Mond prepares $Ni(CO)_4$, leading industrial uses of metal carbonyls and concomitant health problems.
1891	Gosio determines that the arsenic of "arsenic rooms" exists in the form of an alkylarsenic compound.
1894	Hofmeister suggests that "bismuth breath" is actually $(CH_3)_2Te$.
1908—1912	Ehrlich lays the foundation of chemotherapy and greatly extends the known chemistry of organic compounds of arsenic, antimony, and bismuth.
1914—1918	World War I. This conflict involves Lewisite and other organoarsenicals as poison gases.
1923	Development of tetraethyllead as gasoline additive. Its toxicity causes special handling measures to be developed.
1933	Challenger reports generation of $(CH_3)_3As$ and $(CH_3)_2Te$ by molds. Subsequent work over next two decades leads to formulation of "biological methylation".
1954	"Stalinon" disaster in France (organotins). About the same time the first cases of "Minimata Disease" (methylmercury poisoning) appear.
1961	Coenzyme form of B_{12} containing Co—C bond is reported.
1967	Discovery that methylmercury compounds can be generated by microorganisms from inorganic mercury by biological methylation.

5. Method of ingestion. Very often the toxicity of an organometal depends on how it is ingested. These compounds may be breathed in, absorbed through the skin, eaten or drunk with food or beverage, or directly injected into bloodstream or tissue. Usually direct injection has the strongest effect per dose.

6. Nature of organism. Biocidal effects vary from species to species. The variation may be small, or it may be substantial. Even for a given species, the effect may vary from individual to individual. If sublethal doses are given repeatedly, tolerance may build up, and the sensitivity of one individual becomes far less than that of another individual of the same species.

7. Concentration. For any given compound and species, there is usually some minimum dosage required for fatal effect. Since, as already noted, individual susceptibility may vary, dosages are frequently given in terms of effect on a percentage of the total population. For interspecific comparisons, a common measurement standard becomes desirable. One frequently used is LD_{50}, the minimum quantity required to kill 50% of the organisms over some arbitrary time span. The quantity is often measured in units of milligram compound per kilogram of body weight. Another measure frequently used is parts per million, especially in solutions.

Biocidal organometals, of course, may show sublethal effects. In fact, certain ones owe their importance to these effects. Some organometals have biological effects totally unrelated to toxicity.

Very few comparative studies have been made. Organometallic toxicology has been reviewed by Barnes and Magos [3]. Sijpesteijn and coworkers have studied relative effects of Group IV metals [4]; their detailed results are given in Section IIID. Thayer has studied the effects of various organometals in aqueous solution [5] on the sprouting of cucumber seeds. Table 2 lists the concentrations for these compounds at which teratological effects first become significant. These organometallic cations apparently work by suppressing chlorophyll formation at lower concentrations and damaging cell membrane walls at higher concentrations. The metals of the Sixth Period seem to be the most effective.

TABLE 2

COMPARATIVE TERATOLOGICAL EFFECTS OF ORGANOMETALS IN SOLUTION [5]

Metal	Ion	Concentration (mg/l water)	Metalloids	Ion	Concentration (mg/l water)
Platinum	$(CH_3)_3Pt^+$	1.0	Silicon	$(CH_3)_3SiCH_2$-$CH_2CH_2SO_3^-$	350
Gold	$(CH_3)_2Au^+$	0.85	Phosphorus	$(C_4H_9)_4P^+$	0.23
Mercury	CH_3Hg^+	0.98	Arsenic	$(CH_3)_2AsO_2^-$	1.1
	$C_2H_5Hg^+$	5.7		$CH_3AsO_3^{2-}$	3.2
	$C_3H_7Hg^+$	2.4	Tellurium	$(CH_3)_3Te^+$	210
Thallium	$(CH_3)_2Tl^+$	2.3		$(CH_3)_2Te(OH)_3^-$	240
Tin	$(CH_3)_3Sn^+$	4.8			
	$(C_2H_5)_3Sn^+$	0.34			
	$(C_3H_7)_3Sn^+$	0.78			
	$(C_4H_9)_3Sn^+$	0.20			
Lead	$(CH_3)_3Pb^+$	2.8			
	$(C_2H_5)_3Pb^+$	0.13			
	$(C_3H_7)_3Pb^+$	0.98			
	$(C_4H_9)_3Pb^+$	0.68			
	$(i\text{-}C_4H_9)_3Pb^+$	0.18			

II. Metalloids

A. General considerations

Organic derivatives of metalloids show a wider diversity of biochemical properties than those of the metals. Except for arsenic, these elements and most of their inorganic compounds are not toxic. Boron, silicon and phosphorus are necessary trace elements (in the case of boron, primarily for plants). The low toxicity of many organometalloids enables them to be used in living organisms for nonbiocidal purposes.

The metalloids all have a strong affinity for oxygen, which affects their chemical properties. The simple alkyls of boron and phosphorus inflame in air. For these two elements, therefore, the aryl compounds have been the most studied. Alkyl compounds of silicon, arsenic and tellurium are more stable and have therefore received considerable attention. Arylarsenics, however, had much use as antibiotics, and have a substantial literature. Phosphorus and arsenic form organic derivatives in two different oxidation states, and this also affects their biological properties.

Electronegative groups, particularly halogens, bonded directly to the metalloid, can be hydrolyzed by water. This releases heat, often in large amounts concentrated in a small volume, which can cause havoc in a delicately balanced biochemical system. The acid HX itself may react further. Organometalloidal cyanides, for example, are extremely dangerous because they can generate toxic HCN in a living system. These two properties, along with the intrinsic toxicity of arsenic itself, combined to make organochloroarsines such effective war gases. Arylmetalloid compounds will also hydrolyze but considerably more slowly in most cases. The hydroxides and oxides will not react with water at all; it is these species that are most frequently encountered in boron and, to a lesser extent, in silicon biochemistry.

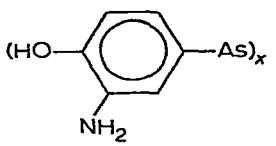
Except for tellurium, all the organometalloids have been used for medicinal purposes. Organoboron compounds show special promise for use in cancer therapy. Organosilicon and organophosphorus compounds likewise show great promise for

medicinal and therapeutic applications, and are currently the center of considerable research. Actual usage, however, has been comparatively limited so far. No doubt this will change as more becomes known about the bonding and chemical properties of these materials, and better ways of preparing and storing them become available.

B. Organoarsenic compounds

1. Early work

Organoarsenicals were among the first organometals to be used in medicine. Much of this early work is reviewed in Raiziss and Gavron [6] and in articles by Thayer [2, 7]. The work by Ehrlich on Salvarsan and related compounds laid the groundwork, both theoretical and practical, for the development of chemotherapy [8, 9]. From this sprang a tremendous amount of work on organoarsenic compounds, along with lesser amounts on antimony and bismuth. Salvarsan (I) and related compounds remained in widespread use until about 1940, when they were largely replaced by penicillin. Today they retain certain specialized therapeutic applications.



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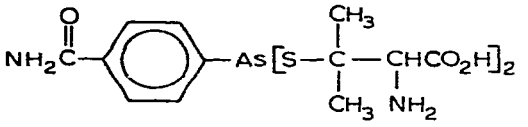
During World War I, a number of organoarsenicals were developed as poison gases. Best known of these was Lewisite (β-chlorovinyldichloroarsine) [10, 11]. The compound British Anti-Lewisite (BAL) emerged from studies for an antidote to Lewisite poisoning [12, 13].

In 1891, Gosio claimed that $(C_2H_5)_2AsH$, generated by mold action on wallpaper, was the cause of poisoning in "arsenic rooms" [7, 14]. Challenger identified this compound ("Gosio-gas") as trimethylarsine, and studied the conditions under which it formed [15—17]. He found that various arsenic compounds, plus those of selenium and tellurium, would be converted to the methyl derivatives. He termed this process "Biological methylation"; it is also called "transmethylation" and in recent years has become extremely important in connection with Vitamin B_{12} and methylmercury poisoning (vide infra).

2. Medicinal and metabolic studies

Salvarsan and related compounds show their greatest effect on spirochetes and trypanosomes rather than bacteria. Hence most of their applications have been directed against illnesses arising from these organisms. Considerable research has been reported [18—23]. Aromatic arsenicals show a marked substituent effect, and much early work consisted of attempts to find the right combination for maximum potency with minimum danger. Most therapeutic organoarsenicals are derivatives of Atoxyl (arsanilic acid; p-$NH_2C_6H_4AsO_3H_2$). It is noteworthy that phosphorus and antimony analogs of Atoxyl also show therapeutic activity, while the sulfur analog (as the amide), p-$NH_2C_6H_4SO_2NH_2$ (sulfanilamide) was one of the first "sulfa" drugs to receive widespread use. All are structurally analogous to p-aminobenzoic acid, which serves as a precursor to the biologically important

folic acid. Replacement of the carboxyl group by the S, As, etc. equivalent interferes with this crucial synthesis. Recently the related compound (II) has been



(II)

reported as a trypanocide and filaricide [24]. Organoarsenicals have been used in treatment of heartworm infections in dogs [25].

Much work has been done on the metabolism of organoarsenicals, usually in relation to their medicinal potentialities. While both tri- and pentavalent As derivatives are used, the former tend to be more potent. The metabolism of organoarsenicals depends on their valency [26]: aromatic As^{V} compounds are eliminated in urine, whereas aromatic As^{III} species are eliminated in bile, with the rate decreasing as hydrophobic character increases. Arsanilic acid derivatives are occasionally used in antibody studies [27, 28].

The earlier work by Challenger on methylation of arsenic by molds [17, 29] continues to be extended. McBride and Wolfe found that *Methanobacterium* species will convert arsenate to dimethylarsine [30]. Da Costa reports that phosphate ion overcomes arsenite and arsenate toxicity to fungi [31]. Cox and Alexander have made a detailed study on the formation of trimethylarsine by *Candida humicola* [32]. They find that arsenite, arsenate, methylarsonate, and cacodylate all yield this compound, with arsenate giving the highest conversion. The optimal pH was 5.0. Addition of KH_2PO_4 tended to suppress trimethylarsine formation, except from cacodylate. Since salts of cacodylic acid and methylarsonic acid are widely used as herbicides, Cox and Alexander point out that soil microorganisms may be able to convert these salts to volatile trimethylarsine, leading to human intoxication [32]. Both occur naturally in nanogram quantities [33].

3. Other biological applications

Some work has been done on non-medicinal applications of organoarsenicals to animals. Atoxyl administered to mice tends to lower resistance to infection by various viruses [34]. Sodium methylarsonate is fatal to cattle at doses of 80—100 mg/kg [35]. A number of investigators have reported on the efficacy of organoarsenicals for promoting growth in turkey or chickens [36—39]. The most effective dosage seems to be about 0.02—0.03%.

Organoarsenicals have also been used as herbicides, most notably methylarsonic acid and cacodylic acid. Some comparative phytotoxicities are discussed by Sachs and Michael [40]. In the majority of cases reported, these compounds are simply used to destroy weeds [41—44]. However, there has been at least one reported instance in which these compounds have been used as an aid in cultivation [45]. Salts of aromatic arsonic acids cause chromosomal aberration and mitotic inhibition in maize root tips [46]. Methylarsonate and cacodylate ions both have effects on cucumber seed development similar to those for alkylmetals [5]; cacodylate is appreciably more effective.

Some work has been done with organoarsenicals as fungicides or insecticides. Phenarsazines have been studies [47, 48]. Methylarsenic sulfide can overcome

leaf spot or seedling blight strains that are resistant to mercury-containing preparations [49]. Cacodylic acid has some effect in suppressing southern pine beetle (*Dendroctonus frontalis*) in pines [50, 51].

C. Organoboron compounds

Boron and borates play an important role in plant growth and development. Consequently, they have been extensively studied, and some of this research has included organoboron compounds. The boron atom in R_3B has a strong tendency to accept additional electrons from any available source. This tendency may be satisfied by formation of a fourth σ bond to boron, as in $(C_6H_5)_3BNH_3$ or $(C_6H_5)_4B^-$, or by electron delocalization through π-bonding with electron donors, such as oxygen or nitrogen. Most biologically active organoboranes fall into these two categories. Arylboronic acids are perhaps the most commonly studied.

Numerous organoboron compounds have been investigated with respect to their possible use in cancer therapy [52]. Boron-10 (19.6% natural abundance) has an unusually large cross-sectional capture area. Capture of a slow-moving neutron (ca. 0.025 eV energy) causes a fission, releasing a fair quantity of energy. This energy would be lethal to cells, but confined to a rather small area. If boron atoms can be concentrated in tumor tissue, this fission might provide a way for its destruction. Work has concentrated on the boronic acid series, which combines the highest percentage of boron with the greatest resistance to oxidative degradation in a biological system. Some aliphatic boronic acids have been tested, and they appear to have some promise; however, they also have fairly high toxicities. Hence the aromatic series has received more emphasis. Their stability varies considerably depending on substituents on the aromatic ring. Electron-donating groups tend to facilitate boron—carbon bond cleavage, whereas electron-withdrawing groups will stabilize this bond towards both hydrolysis and oxidation. A series of organoboron compounds was investigated to see if there was any correlation between a tendency to concentrate in tumor tissue and aromatic substituent. Results for some of these compounds are shown in Table 3. Those aromatic boronic acids with fairly high lipid solubility more readily penetrate the brain, cause central nervous system toxicity, and give lower tumor/brain ratios than those having higher solubility in water. The lethal dose varied along the same line: 4-chlorobenzeneboronic acid caused death in mice at a dosage of 35 mg/kg, whereas 4-carboxybenzeneboronic acid showed little toxic effect at dosages of 140—200 mg/kg.

TABLE 3

SUBSTITUENT EFFECT ON TUMOR/BRAIN RATIO IN 4-$XC_6H_4B(OH)_2$ [52]

X	Tumor/brain ratio
$(CH_3)_3Si$	0.1
CH_3S	0.2
F	0.3
Cl	0.4
CH_3O	0.7
H	0.7
$(CH_3)_2N$	1.4
HO	1.6
$(HO)_2B$	2.3
HO_2C	4.8
$HO_2CCH(NH_2)CH_2$	8.5

In closely related work, a carborane derivative, 1,2-$B_{10}H_{10}CHC(C_6H_4N_2$-$p^+)$ has been reported which can be incorporated into anti-bovine serum albumen with little effect on its activity and specificity [53].

A variety of organoboron compounds has been investigated for bactericidal and other medicinal uses [54—58]. Alkylboronic acids act as reversible enzyme inhibitors, with the extent of inhibition depending on alkyl chain length [58]. Organoborate esters of chloramphenicols retain the antibiotic properties of chloramphenicol but show a reduction in undesirable side effects [59].

Some work has also been done on the use of organoboranes as insecticides, fungicides or as plant-growth agents. Benzeneboronic acid and its substituted derivatives stimulate root growth in tickbeans [60]. The substituted derivatives usually showed the greater potency. Like silicon analogs, 2-haloethyleneboron alkoxides can regulate plant growth through the release of ethylene [61]. Benzeneboronic acids have had some attention as chemosterilants [62—64]. The carborane $K^+[B_9H_9C_2H_2]^-$ shows toxicity to insects and fungi without being toxic towards oats or wheat [65]. Various boroxarophenanthrenes act as fungicides [66].

Unique among organoborons is the tetraphenylborate anion, $(C_6H_5)_4B^-$. It is one of the few organometallic anions containing only metal—carbon bonds, and is the only one that has been used in biological research. Tetraphenylborate ion will form precipitates with large cations, and is often used in analytical chemistry for just that purpose. Potassium is one of these cations, and much of the biologica work done with $(C_6H_5)_4B^-$ takes advantage of its affinity for K^+. It can be used to test potassium content in soils [67, 68] and in fertilizers [69]. Tetraphenylborate ion will affect the permeability of membranes, both in corn roots [70] and in brains [71]. It can stimulate the incorporation of labeled phosphorus into phospholipids [72], and induces a transient acceleration of activity in bull heart mitochondria [73]. This ion also resembles acetylcholine in its effect on rat hemidiaphragm, interacting with electrophilic sites and relieving the curare block [74].

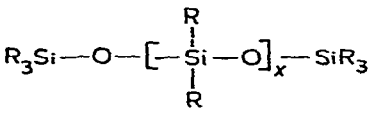
D. Organosilicon compounds

1. Medicinal applications of silicones

In recent years there has been intesne activity on the biological and therapeutic applications of organosilicon compounds. Much of this is covered in the monograph by Voronkov [75] and in 3 reviews [76, 77, 77a]. Structures III—IX represent some organosilicon compounds used for these purposes.

Most widely known and used among organosilicon compounds for biological purposes are the silicones. The name "silicone" was originally coined because these compounds, with general formula $(R_2SiO)_x$, are formally analogous to ketones. However, the similarity is strictly formal; there are no chemical or structural resemblances.

The properties that make these compounds useful biologically come from the Si—O skeletal framework. Depending on the value of x and the particular method of preparation, silicones may be fluids (IIIa) varying in viscosity, rubbery solids, greases, or hard, rigid materials (IIIb). In the great majority of cases, the methyl silicones are used, but once in a while another organic group will be attached to silicon, usually because it endows the molecule with some especially desired property.



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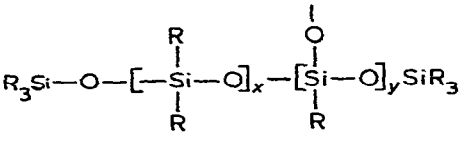

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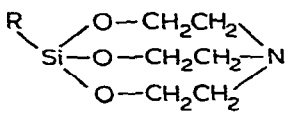

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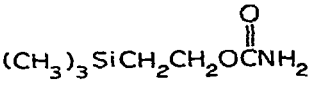

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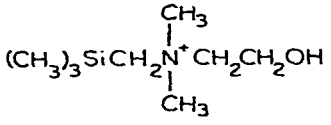

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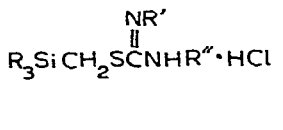

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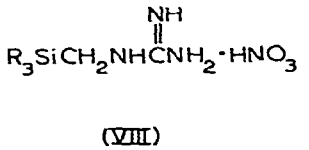

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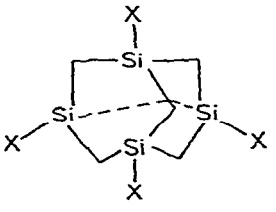


(IX)

The silicones have three properties that make them outstanding, almost unique, for biochemical research: (1) inertness to biochemical processes; (2) imperviousness to water; (3) very low surface tension. Silicones are virtually unique among organometals in being almost totally unaffected by the myriad chemical reactions occurring within living organisms. Silicones have been employed for a variety of therapeutic applications, some of which are listed below:

Ointments, especially for burns. Silicone ointments eliminate the tendency for a dressing to stick to the skin, making subsequent removal easier.

Prosthetic materials, replacement of worn-out blood vessels. Their durability exceeds that of other materials.

Plastic surgery, augmentation of soft tissue or loose skin. This is their most widely known use!

Antifoaming additives

Skin protection

For a more detailed description of the various uses, readers should consult the reviews by Noll [78] or Levin [79].

This inertness is not total. Silicones have been shown to interfere with mammalian reproduction [80], and to cause an irritation to the retina of the eye [77, 81, 82]. These effects seem to arise from physical (rather than chemical)

causes, but will have to be taken more fully into account as the medicinal-therapeutic uses of silicones increase. These compounds have been tested as preservatives for skin grafts [83], aerosols for dogs [84], and as bacteriostats [85].

2. Medicinal nitrogen-containing organosilicon compounds

One group of organosilicon compounds shows exceptionally high toxicity. These all have nitrogen bonded to an organic group which in turn is linked to the silicon atom. The toxicity varies over an enormous range; for example, LD_{50} for $(C_2H_5)_3SiOCH_2CH_2N(C_4H_9)_2$ is 1650 mg/kg, but for $(C_2H_5O)_2CH_3SiCH_2CH_2$-$CH_2NH_2$ it is 0.045 mg/kg! Greatest toxicity seems to occur in those compounds having the nitrogen atom attached to the γ position on the organic chain. Evidence indicates that this nitrogen can form a dative bond to the silicon, forming a pentacoordinated species. Just why such a species should show enhanced toxicity remains to be determined. Numerous series have been studied and reported [77]. Best known are the organosilicon derivatives of triethanolamine; these compounds are commonly called silatranes (IV). The entire molecule exists as a compact cage. Toxicities for various silatranes are shown in Table 4, with the well known poisons strychnine and prussic acid (hydrogen cyanide) also listed for comparison. The substituted arylsilatranes are the most dangerous. Furthermore, this toxicity affects mammals to the greatest extent. Silatranes show little or no effect on frogs, bacteria or fungi [86]. *p*-Chlorophenylsilatrane is being tried out as a commercial rodenticide. Silatranes must be introduced into the body for effect; they have no effect when applied to human skin. Voronkov, who has done most of the research on these compounds, suggests that they act on the central nervous system, activate the cortex unduly, and react with enzymes. They are inactivated by the body fairly rapidly. Numerous other metallatranes have been tested, but all show much lower effects than the silicon species [87].

3. Other medicinal organosilicon compounds

Numerous organosilicon compounds have been investigated with respect to their biological effects. Some of these are deliberately-chosen analogs of organic biochemicals, with a silicon atom replacing one of the carbons. By and large, such compounds are none too easy to synthesize, which is one reason that more work has not been done with them. Most of those that have been investigated show little or no change in properties because of the substitution. The compound

TABLE 4

SILATRANE ($RSi(OCH_2CH_2)_3N$) TOXICITIES [77] (PERITONEAL INJECTIONS INTO WHITE MICE. DOSAGES IN mg/kg

R	LD_{50}
p-$CH_3C_6H_4$	0.20
C_6H_5	0.43
3-ClC_6H_4	4.4
3,5-$(CH_3)_2C_6H_3$	14.7
H	100
C_6H_5O	200
$C_6H_5CH_2$	1115
CH_3CH_2	5000
CH_3	5000
Strychnine [a]	0.5—1.25
Prussic acid [a]	3 —10

[a] LD_{100}.

2-trimethylsilyl-1-ethanol carbamate (V) has a lethal dose ten times that of the carbon analog, and behaves antithetically: it is a muscle relaxant, whereas the carbon analog is a muscle convulsant!

Silyl derivatives of choline (VI) reduce hypertension, while trialkylsilyl derivatives of thiopseudourea (VII) and guanidine (VIII) show anti-inflammatory action [88]. A cyclic tetrasiloxane shows hormonal activity in female rats [89]. A silicon-containing analog of stilbestrol shows very little estrogenic activity [90]. The compound $(CH_3)_2N^+(C_{18}H_{37})CH_2CH_2CH_2Si(OCH_3)_3Cl^-$ shows activity both against bacteria such as *Streptococcus faecalis* [91] and against algae [92].

Very little work has been done on the actual metabolism of organosilicon compounds. Phenyldimethylsilyl derivatives have been studied by Fessenden and Hartman [93]. They found that, with phenyltrimethylsilane, an atom of oxygen inserts into a carbon—hydrogen bond, giving *para*-hydroxyphenyltrimethylsilane, phenyldimethylsilylmethanol, and an unidentified conjugate of $C_6H_5(CH_3)_2SiCH_2O$. Phenyldimethylsilane, by contrast, gives exclusively the siloxane as product. This was explained as arising from insertion of oxygen into the silicon—hydrogen bond to form the silanol, which then rapidly condensed to form the siloxane. On the basis of their experiments, the authors concluded that the Si—H bond would not be stable in biological systems.

4. Nonmedicinal applications

A variety of nonmedicinal uses have been found for organosilicon compounds other than silicones. Tetrasilaadamantanes (IX) have been tested as mosquito repellants [94, 95]. Compounds containing 2-chloroethyl groups bonded to silicon can regulate the growth of plants, apparently through the release of ethylene [96, 97]. Polydimethylsiloxane fluids, when coated upon eggs, help to preserve the quality of the albumen and retard spoilage [98]. Silicones coated on leaf surfaces cut down on loss of water by evaporation [99]. Organosilyl imidazoles serves as fungicides [100].

In recent years, trimethylsilyl compounds have become useful analytical tools in biochemical research. Reactive species, such as trimethylchlorosilane or hexamethyldisilazane, will combine with carbohydrates, amino acids, and other compounds containing OH or NH_2 groups. One of the hydrogens is replaced by a trimethylsilyl group [101]. Such replacement destroys intramolecular and intermolecular hydrogen bonding enabling easier separation and characterization, especially those compounds present in small quantities. These derivatives are usually liquids which can be readily separated and/or purified by chromatography. Once isolated, they may readily be reconverted back to the starting material if desired. A number of papers along these lines have appeared [102—106]. So far, these silylated compounds have been used solely as convenient analytical intermediates. No investigations on their possible biochemical effects have been reported. Such derivatives may hold promise for generation of an otherwise unstable active compound in situ.

E. Organophosphorus compounds

1. Medicinal and metabolic applications

Phosphorus is one of the six elements most vital to living organisms. Most commonly it occurs in the form of phosphates. Because phosphates are so important in many processes, structurally related compounds are frequently used

as insecticides. Since these often contain organic groups, they usually are termed "organophosphorus" compounds. Actually, they are esters of phosphoric or thiophosphoric acids. Typical of such esters is tetraethylpyrophosphate, $(C_2H_5O)_2P(=O)OP(=O)(OC_2H_5)_2$. Many compounds so used can be quite deadly; the LD_{50} for mice of the cage compound $P(OCH_2)_3CC_2H_5$ is 0.18 mg/kg [107]. Note its similarity in structure to the silatranes.

Considerable research has been done on "true" organophosphorus compound (those with C—P bonds), some of which are extremely toxic. One such species is "Sarin", $CH_3P(F)(=O)OCH_2CH_3$. These compounds act as cholinesterase inhibitors. Neural synapses involve enzyme-controlled hydrolysis of acetylcholine (X); the enzyme involved is termed acetylcholinesterase. Sarin and certain other organ

$$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2N^+(CH_3)_3$$

(X)

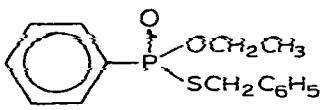
phosphorus compounds combine with this enzyme, preventing its action and causing disruption of the nervous system [108—110a]. This inhibitory action has been used for beneficial purposes, however. Certain "nerve disorders" arise from excessive cholinesterase activity. Careful control over selection and application of selected organophosphorus compounds will provide relief in such conditions. Also, measurement of cholinesterase levels provides a means of determining possible poisoning by organophosphorus compounds, difficult to detect by other methods.

Numerous medicinal applications have been found for organophosphorus compounds, and no doubt others will subsequently appear. Phosphonomycin [(—)-(1*R*, 2*S*)-2-methyl-1,2-epoxypropylphosphonic acid] acts against both Gram-positive and Gram-negative bacteria by inhibiting the biosynthesis of murein, an important component of cell walls [111]. Arylphosphonic and -phosphonous acids often show analgesic and anti-inflammatory activity [112]. Some have been used for the treatment of tumors [113]. A phosphonic acid pyrimidine derivative shows antimetabolite activity [114]. Several aralkylphosphonium compounds show promise as antiulcerogenic agents because they inhibit gastric secretions [115]. Trialkylphosphine complexes of Au^I species have been used in the treatment of rheumatoid arthritis [116]; the triethyl species were most effective. The compound $[AuSCH_2CH_2P(C_2H_5)_2]_2$ also showed activity [117]. A number of mono- and di-arylphosphorus analogs of methadone have been prepared and tested [118]. They show analgetic activity that is apparently related to the degree of lipophilicity; the diaryls are appreciably more active.

Metabolic activity of some organophosphorus compounds has been looked at. Ribose-5-phosphate-1-methylenediphosphonate did not show the same activity as the 1-diphosphate analog [109]. Phosphonic acid isosteres of various phosphoglyceric acids likewise showed no appreciable activity [110]. The role of organophosphorus metabolism in insecticide metabolism has also been studied [120—122]. Salts of triphenylmethylphosphonium ion induce accelerated activity in bull heart mitochondria [73].

Sea organisms have been found to contain 2-aminoethylphosphonic acid and some derivatives, apparently through natural metabolism [123]. Considerable

research has gone into this area [109, 124, 125], and ^{31}P labeling used to study the metabolic paths. The compound tris(1-aziridinyl)phosphine oxide induces mutagenesis in mice at a level of 1 mg/kg [126]. Metabolism of Inezin (XI)



(XI)

gives a variety of products, including phenylphosphonic acid, benzylsulfonic acid, benzoic acid, and sulfuric acid [122].

2. Nonmedicinal biological studies

A number of workers have investigated the effects of organophosphorus compounds on plants. Certain phosphonium salts serve as inhibitors of plant growth [127]. Best known of these is 2,4-dichlorobenzyltributylphosphonium chloride (Phosphon D). Three butyl groups bonded to phosphorus seem to be needed for such inhibitory action to occur. Tetrabutylphosphonium bromide has an effect on cucumber seed sprouting comparable to alkylmetal salts [5]. Some 2-aminoethylphosphonates will stimulate peanut germination and accelerate the ripening of bananas [128], while ammonium phosphonates show a strong stimulant effect on corn and barley [129]. Like boron and silicon analogs, 2-chloroethylphosphonic acid can be used in controlling plant growth [130, 131]. It is phytotoxic to sugar beets at 200 ppm and induces pollen sterility at lower levels [132].

Considering their similarity to the widely used organophosphate insecticides, it is not surprising that some biocidal uses have been found for organophosphorus compounds. Various compounds of the formula $XC_6H_4P(=S)(OR)(SR')$ act against red spider mites [133]. Certain P-containing heterocycles have been proposed as fungicides [134]. The unusual salt $Cu[\{OP(=O)(OH)\}_2C(OH)CH_3]$ can serve as an algacide [135]. Interestingly enough, *Escherichia coli* can grow on a medium containing arylphosphonic acids [136]. No inorganic phosphate forms, and only the quantity required for growth is taken up. Research on biocidal organophosphorus compounds has recently been reviewed by Mel'nikov [137]

$(C_6H_5)_2P(=S)X$ (X = halogen, isothiocyanate) can be used to label immunoglobulins with ^{32}P [138]. Triphenylphosphine will extract sulfur from the iron—sulfur protein adrenodoxin [139].

F. Organotellurium compounds

Much less work has been done on the biological effects of organotellurium compounds than for the lighter congenors, sulfur and selenium, or for the other metalloids. The element itself is known to show some toxic effects [140—142]. Tellurium can be methylated by a variety of organisms [15—17], including man, to give the volatile, malodorous dimethyltelluride. A strain of *Penicillium* will methylate a variety of tellurium compounds, but only when some selenium is present [143]. Aqueous solutions of $(CH_3)_2Te(OH)_2$ and $(CH_3)_3Te^+$ had less effect on seed sprouting than virtually any other alkylmetal [5]. The former, but not the latter, was reduced to $(CH_3)_2Te$ and Te by the germinating seedling.

III. Metals

A. General considerations

The majority of metals form organic derivatives that are reactive towards water. Not unsurprisingly, they have been little studied as to their biological effects. The numerous π-complexes of transition metals likewise have not been studied. Metal carbonyls are known to be toxic [144], and extensive research has been done on carboxyhemoglobin and its properties. However, most biological work on organometals has concentrated on the derivatives of the heavy metals. There is a voluminous literature on mercury and only slightly less extensive studies on lead, tin, antimony and bismuth.

Many thousands of organic derivatives of these metals have been isolated. Usually, the alkyl derivatives show higher toxicity than the aryls, though too little is known about antimony or bismuth compounds to be certain as to whether this generalization applies to them. In the alkyl series, the effect is greatest when the number of alkyls is one less than the Group number. Inorganic groups have comparatively little effect, unless they markedly change the solubility in water. Apparently the active species is the ion $R_{n-1}M^+$. Activity increases going from methyl to ethyl (mercury is an exception), passes through a maximum, and falls off sharply for alkyls of six or more carbon atoms.

One disquieting result uncovered by research on these organometals is that they tend to be considerably more toxic than the free metals or most inorganic derivatives. Mercury and lead are poisonous in any form, but the deadliest compounds are the organic derivatives, especially the alkyls. Tin, a necessary trace element, becomes extremely toxic in its organic compounds. Germanium seems to be totally harmless to living organisms, except in certain alkyl compounds The reasons for this change have not yet been completely determined. In general, the organometals tend to have longer retention times in the body relative to inorganic derivatives and also are frequently more soluble in lipids. Consequently, they become accessible to portions of the body previously unaffected. Furthermore, for mercury, tin, and lead the organic derivatives act in quite a different manner than the inorganic compounds on bodily processes.

Most research done on microorganisms (in most cases, bacteria) tends to focus on their growth and reproduction as a function of organometal nature and concentration. Bacteria have long been empirically divided into two broad categories. If a bacterial strain, upon treatment with methyl violet, retained the color after washing with alcohol and addition of a counterstaining dye, it was termed *Gram-positive.* If instead it lost the methyl violet stain and picked up the counterstain, it was termed *Gram-negative.* This dichotomy actually turns out to be more than a simple experimental laboratory classification. Gram-positive bacteria usually have rather simple cell walls. Their food-synthesizing capabilities are poorly developed, and they tend to be rather exacting about their nutritional requirements. By contrast, Gram-negative bacteria have more complex cell walls, better developed food-synthetic capabilities, and greater tolerance for variations in nutritional supplies. It is not surprising, therefore, that Gram-positive bacteria generally show greater sensitivity towards organometals.

Most of these metals, and especially mercury, have an affinity for sulfur. Their toxicity arises in part from their ready combination with sulfhydryl groups of crucial enzymes. The compound $HSCH_2CH(SH)CH_2OH$, (BAL), has often been used in treatment for poisoning arising from heavy metals [12, 13]. Thiol resins have been used to treat methylmercury poisoning [145].

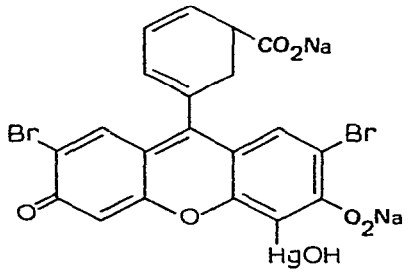
These organometals apparently act at two levels: molecular and cellular. At the molecular level, they tie up some crucial enzyme and disrupt an important biochemical cycle. Cellular-level effects occur when these compounds bond to sites on cell walls. In addition to preventing such sites from being used in other reactions, these bonds change the physical properties of the cell walls, especially the permeability. As a result, necessary molecules may be unable to pass, or undesirable molecules, usually excluded, do enter. In either case, the result is deleterious.

B. Organomercury compounds

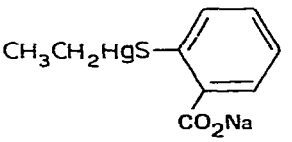
1. Medicinal uses

Organomercurials have long been used in medicine. They were originally applied to the treatment of syphilis. Although partially replaced by Salvarsan in this area, organomercurials continued to be prepared and investigated for use against venereal disease. Many of these compounds subsequently found other applications. In his 1920 monograph on organomercury compounds, Whitmore [146] listed 27 proprietary mercury compounds. Ten of these were organomercurials, ten inorganic, and the remainder rather indefinite in nature. At present, medicinal organomercurials serve primarily as antiseptics and diuretics.

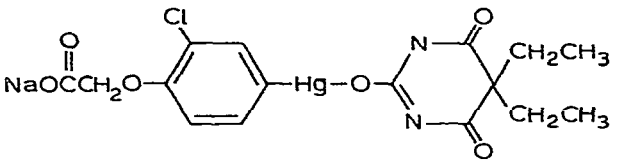
Antiseptic organomercurials include such familiar names as mercurochrome (2,7-dibromo-4-hydroxymercurifluorescein) (XII) and merthiolate (sodium ethylmercuric thiosalicylate) (XIII). Mercurichrome was originally developed to treat gonorrhea and did have some use against other internal infections. These compounds also serve as disinfectants for medicinal instruments. Merbaphen (XIV)



(XII)



(XIII)



(XIV)

was the first of various organomercurials developed for the treatment of edema (accumulation of excess water in bodily tissues). These compounds are believed to act on thiol groups of enzymes in the kidneys, stimulating their activity. The great affinity between mercury and thiols led to the name "mercaptan", a contraction of mercurium captans (mercury catcher).

Recent work indicates that phenylmercuric borate can be used in treatment of fungal skin afflictions [147—149]. Traces studies with ^{203}Hg found that this compound penetrated human skin infected with *Tricophyton rubrum* faster than normal skin [150].

2. Arylmercurials

Arylmercurials generally show less biological activity than alkyls [151], and have frequently been used as fungicides. These uses have been reviewed by Ulfvarson [152], and by Lukens [153]. One common application is to use these compounds as seed coatings. This may have some limitations: Greenaway has reported [151, 154, 155] that certain mercury-resistant strains of mold will develop on oat seeds treated with phenylmercuric acetate. This compound also had a slight stimulatory effect on the development of sugar beet seedlings [156], in contrast to the inhibiting effect of alkylmercurials. Wheat seeds showed a lowered rate of emergence when coated with phenylmercuric acetate [157].

para-Chloromercuribenzoic acid and its derivatives are frequently used for biological studies. Its salt will stimulate the production of carotenoids by the mold *Fusarium aquaeductuum* [158]. The *p*-hydroxy compound will sterilize houseflies as a 1% solution [159]. A comparative study of the effect of various arylmercurials on the growth of cells from root ganglia showed that phenylmercuric *p*-toluenesulfonamide had a very toxic effect, while phenylmercuric iodide was much less toxic [160]; in this study, the hydrophobic nature of the inorganic group was a major factor. The antibacterial action of phenylmercuric nitrate was antagonized by $Na_2S_2O_5$ and prevented by ethylenediaminetetraacetic acid (EDTA) [161]. A variety of arylmercury compounds were found to interact with human hemoglobin, causing it to dissociate into α- and β-chains [162].

The carbon—mercury bond shows surprising lability. This may be used for exchange reactions in aqueous solutions:

$$^{*}Hg^{++} + RHg^{+} \rightarrow Hg^{++} + R^{*}Hg^{+}$$

Since ^{203}Hg is a radioactive isotope, the exchange enables preparation of labeled organomercurials, which in turn can be used in metabolic investigation. In a labeling study on the metabolism of phenylmercuric acetate by rats, the mercury ended up as mercuric ion and the phenyl group as phenol [163]. Labeled phenylmercuric borate served as a tracer in the study of absorption through wounded rabbit skin [164].

3. Alkylmercurials

In recent years, the toxic effects of alkylmercury compounds, especially methylmercuric, have become known worldwide. However, poisoning by organomercury compounds was first reported over a century ago [165]:

> "It can be said that the history of the alkyl compounds [of mercury] began with a tragedy. In 1865 two young chemists, while working on the preparation of diethylmercury, inhaled the vapours and were poisoned by the very

volatile product. One of them died in 11 days, and the other died after a year during which he had been blind, deaf and almost completely demented".

The use of organomercurials for coating seeds began early in the twentieth century. Most of these were arylmercurials, but some used alkylmercurials. One such was "Panogen", whose active ingredient was methylmercuric dicyanadiamide. Careless handling of this preparation led to poisoning [166]. During the decade of the 1950's, numerous cases of birds poisoned by eating treated seeds were reported from Sweden. In April 1953 the first reports of a strange ailment came from a Japanese village on Minimata Bay. Over a period of years, some 121 cases were reported, with 46 deaths. Similar reports came later from Niigata and Ariake. Workers from Kumamoto University traced the causative agent of "Minimata Disease" to CH_3HgSCH_3 found in the shellfish *Hormomya mutabilis* [167—170], which in turn came from the effluent of a nearby factory [171]. Methylmercuric compounds built up in the tissues of fish and shellfish to concentrations far in excess of the level of the surrounding water. Then, when these were eaten by humans or other predators, rapid poisoning ensued. Similar poisoning happened when Panogen-coated seed was eaten in Iraq [172].

The use of organomercurials as seed coatings was banned in Sweden in 1964. This ban gradually caused a lowering in the levels of mercury found in most fishes and fowls. Populations of seed-eating birds recovered fairly rapidly, and those of predators somewhat more slowly. Yet raptorial birds failed to share in this recovery, and mercury levels in fishes remained high. Many lakes received mercury runoffs from pulp mills or chlorine-alkali factories. In most cases this was metallic mercury or inorganic mercurials. Yet in 1966 Westöö found that mercury from fish, birds eggs or mammalian tissue existed almost exclusively as methylmercury compounds [173].

The cause of this became revealed in two now-classic papers. Jensen and Jernelöv [174] showed that inorganic mercury compounds could be converted to CH_3Hg^+ or $(CH_3)_2Hg$ by microorganisms living in the sludge found on lake bottoms. They also showed that fishes exposed to these compounds would absorb them and build up tissue concentrations considerably in excess of those found in the surrounding water. Wood et al. [175] reported that this process could occur with cell-free extracts from methanogenic bacteria and that the methylated mercurials could form through both enzymatic and non-enzymatic pathways. Actually, such a process, termed "biological methylation" or "transmethylation" had been known to occur with arsenic and tellurium compounds for many years (see Section IIB).

The great concern over the tragic poisonings by methylmercury compounds has caused a voluminous quantity of research on all aspects of alkylmercurials. Developments in this area have been extensively reviewed [165, 176—185]. Research reported generally falls into one of several overlapping categories: toxicology and mechanism of action; the mechanism and conditions of metabolism; methods of analysis; model systems. Perhaps the greatest amount of work is on the toxicology and physiology of methylmercuric compounds. It is known to be neurotoxic [186—188], and numerous studies, some using ^{203}Hg labels, have been made on its metabolism and mode of action [189—195]. Possibly the most tragic effect of mercury poisoning has been the effect on fetuses in utero. Research on prenatal effects [196—201] indicates that these are often severe. Even at

extremely low concentrations, where no significant changes are physically apparen there are marked effects on development and learning [202, 203]. Methylmercuri chloride can induce a nonconditioned taste aversion in rats [204].

Methylmercuric compounds have also been studied from an ecological point of view, usually in connection with aquatic species. These compounds tend to reduce photosynthesis in plankton [205], will accumulate in *Myriophyllum* [206] and otherwise adversely affect the metabolism of aquatic plants [207, 208]. Fish are likewise affected, and a recent study indicates that methylmercury can be found in old specimens but has increased in recent years [209]. Numerous analytical studies on mercury in fish tissue have appeared [210—214].

Considerable research has been reported on the extent and conditions for biological methylation of mercury. Methylcobalamin has been shown to methylate mercuric salts in aqueous solutions [215, 216]; this will even occur with variou trimethylsilyl compounds [217]! The fungus *Neurospora crassa* [218] and the bacterium *Clostridium cochlearium* [219] will both methylate inorganic mercury compounds. Recently Vonk and Kaars Sijpesteijn reported a detailed study on methylation of mercury by various fungi and bacteria [220]. Among these was *Scopulariopsis brevicaulis*, which had been earlier studied by Challenger (see Section IIB). The amount of methylation was comparable to that reported by Jensen and Jernelöv [174], and occurred under aerobic conditions. Less methylmercury was produced by *Escherichia coli* and *Aerobacter aerogenes* under anaerobic conditions than under aerobic. While some organisms used methylcobalamin as methylating agents, others did not. Phenylmercuric acetate is not converted to a methylmercury compound under these conditions [221]. Certain bacterial strains have also been found that will demethylate methylmercuric compounds to methane and metallic mercury [222, 223].

Ethylmercuric chloride and related compounds have received some study. Generally speaking, they are similar to the methyl analogs. In a comparative study, Thrasher and Adams [224] found that mercury compounds increased the time required for cell generation by *Tetrahymena pyriformis*. For the compounds $HgCl_2$, CH_3HgCl, C_2H_5HgCl, and C_6H_5HgOAc, the amounts required to double the cell generation time were 16.0, 0.56, 0.74, and 1.3 micromoles/liter. Work by Ulfvarson [152] and Thayer [5] indicate that the biological effect of alkylmercurials remains constant or decreases as the alkyl chain length increases. Span et al. report that ethylmercuric chloride has a lethal effect on pheasant reproduction [225]. The compound 1-(methylsulfonyl)-2-acetoxymercuri-3-methoxypropane has been proposed as an industrial biocide [226]. Methanol, ethanol, or acetic acid will yield methylmercury compounds upon photolysis, while propionic acid gives a mixture of methyl- and ethyl-mercury compounds [227]. The molecule p-$IC_6H_4NHCNHCH_2CH(OCH_3)CH_2HgCl$ has proven a useful tool, when ^{125}I or ^{131}I labels are used, for renal studies in rats or rabbits [228]. Various plants, especially beans and tomatoes, strongly absorbed Panogen and phenylmercuric acetate [229].

C. Organo-gallium, indium, and -thalium compounds

Very little work has been done on the biological effects of the organic derivatives of these metals. The little that has been reported indicates that there is considerable potential for further research. Radioactive isotopes of gallium

and indium have been used for tracer studies. Lilien et al. [230] found that ^{111}In strongly resembles ^{59}Fe in its transport properties and recommended it for bone marrow studies. Tl^{III}-coproporphyrin isomers have been studied by NMR [231].

Srivastava et al. [232] report that $(C_6H_5)_2MX$ compounds are effective against a variety of fungi and bacteria. Fungitoxicity varies in the order Ga > In > Tl. The methyl derivatives show antimicrobial activity. Thayer [5] found that aqueous solutions of dimethylindium and dimethylthallium show biological effectiveness comparable to that for methylmercuric and trimethyllead compounds.

The similarity of the organic chemistry of thallium to that for mercury and lead, plus the known toxicity of thallous salts, suggests that organothallium compounds should be quite toxic and that, since these compounds are Tl^{III} derivatives, their mechanism of action should be markedly different than that of Tl^+.

DeSimone reported that $TlNO_3$ was not methylated by trimethylsilyl compounds [217]. Agnes et al. [233] find that methylcobalamin will methylate Tl^{III} but not Tl^I; however, the resulting methylthallium species could not be isolated. Thayer [234] has pointed out that monomethylthallium and monomethyllead compounds are quite unstable. The ability of thallium to undergo biological methylation may well depend on conditions used, especially as to whether chelating groups may be present.

D. Organogermanium compounds

Metallic germanium and its inorganic compounds generally have no biological effects. In fact, about the only organogermanium compounds that do interact with biochemical processes seem to be the di- and tri-alkyl systems. These are markedly less toxic than their tin or lead analogs, but do show antibacterial activity. Gram-positive bacteria are the most sensitive. Interestingly enough, if a small amount of fresh blood is added, this bactericidal activity vanished. Apparently hemin, and to a lesser extent erythrocyte catalase, remove the growth-inhibitory effect [235]. Tributylgermanium oxide has been found to inhibit lactic acid bacteria lacking a cytochrome system [236], but this inhibition is reduced by the incorporation of hemin. Triethylgermanium acetate was much less toxic to rats than the corresponding tin or lead compounds [237], while the tributylgermanium compound was ineffective. The mechanism of interaction seems to be the same as for trialkyl-tin and -lead: inhibition of glucose oxidation and oxidative phosphorylation by rat liver mitochondria. Arylgermanium compounds show little or no effect. 1-Phenylgermatrane is about 1% as toxic as its silicon analog (see Section IID).

Various other biological uses for organogermanium compounds have been reported. $[HO_2CCH_2CH_2GeO_{1.5}]_n$ and the corresponding amide affected the rate of growth of tumors in rats by changing the electrochemical potential of the abnormal cells [238]. Iminodiacetates of diphenylgermanium have been used as insecticides [239]. Dimethylgermanium oxide induces teratogenic effects in chick embryos [240]. Carboxyethylgermanium sesquioxide will promote the growth of rice [241], and can be used in the treatment of hypertonia [242].

Most research on organogermanium compounds have stressed its resemblance to tin, in which there is enormous current interest. However, there is likewise similarity to organosilicon compounds, and the growth in that area should have a stimulating and directing effect as well.

E. Organotin compounds

With the possible exception of mercurials, organotin compounds have received more attention for their biological effects than organic compounds of any other metal. Several reviews have appeared [4, 243—245]. In 1954, "Stalinon", a medical preparation of diethyltin diiodide and isolinoleic acid esters, was marketed in France as a treatment for staphylococcal infections [246]. 102 persons died and about the same number were permanently affected. While some uncertainty existed about the exact nature of the toxic species, there was no doubt that it was an organotin compound. Tributyltin oxide, in conjunction with formaldehyde, has been used in hospitals as a protection against *Staphylococcus aureus* [245].

While all organotin compounds are toxic, the effect varies according to the number and type of organic group present. Alkyls tend to be more toxic than aryls, and triorganotins are more toxic than di- or tetra-organotins. Tin tends to be intermediate in its activity between germanium and lead. Table 5 shows some typical comparative results. Dialkyltin compounds behave differently than trialkyltins. The former behave similarly to organomercurials and arsenicals by reacting with sulfhydryl groups and inhibiting enzyme-catalyzed metabolism. Khana and Sijpesteijn [247] found that, when *E. coli* strains were treated with diethyltin dichloride, pyruvic acid tended to accumulate. They explained this by postulating that the requisite pyruvate-metabolizing enzyme was tied up in a complex with the diethyltin group. In contrast, trialkyltin compounds are known to interfere with oxidative phosphorylation. Considerable research has been reported on this interaction [248—254]. Rat-liver mitochondria underwent swelling in the presence of trialkyltins, and their inhibitory activity showed a very marked dependence on pH [249]. As the medium became more acidic, the effect dropped sharply. $(C_4H_9)_3SnCl$ inhibits photophosphorylation in isolated chloroplasts [250]. The amount required is small, 1 mole per 60—120 moles chlorophyll, and the inhibition is believed to occur by tight binding at the site of coupling. Similar effects of various organotin compounds on O_2 evolution from pea chloroplasts have been reported [251]. Effectiveness varied in the order $Bu_3Sn > Ph_3Sn > Pr_3Sn > Me_3Sn > Et_3Sn$. Tri-n-butyltin acted at a level of 0.3 μM, while triethyltin required 800 μM. Ammonium chloride or carbonyl cyanide *m*-chlorophenylhydrazone strongly reduced this inhibiting effect. In a study of various triethyltin compounds, Rose and Aldridge [252] report some variation

TABLE 5

COMPARATIVE BACTERICIDAL EFFECTS OF GROUP IVA ORGANOMETALS [4, p. 339, 346]

Figures represent the minimum concentration in μg/ml needed to inhibit all growth on *Streptococcus lactis*.

	R_3MX			R_2MX_2		
	Ge	Sn	Pb	Ge	Sn	Pb
CH_3	>500	>500	200		200	1
C_2H_5	50	100	50	>500	50	5
n-C_3H_7	5	5	2		20	0.5
n-C_4H_9	1	5	1	>500	20	0.2
n-C_5H_{11}	2	10	5		50	0.2
n-C_6H_{13}	20	50	10		>500	1
C_6H_5	>500	5	1	>500	50	1

with the inorganic group; for example, triethyltin nitrate has a less inhibiting effect than the chloride, possibly because of lower lipid solubility. The change of anions does not seem to affect the binding of the triethyltin group, but it does affect anion—hydroxide exchange across mitochondrial membranes. Rose [253] has suggested that the toxicological activity of trialkyltin compounds may be due to a specific affinity for bonding sites in proteins containing two histidine residues. He notes a correlation between the decreasing tendency towards five-coordination (Pb > Sn > Ge) and a decreasing inhibition of mitochondrial oxidative phosphorylation. In mammals, trialkyltin compounds are known to cause an edema in the white matter of the brain and spinal cord [245]; a mechanism for this action has been proposed [255]. Interperitoneal doses of triethyltin sulfate increase the permeability of the blood—brain barrier [256], even at concentrations of 0.01 mg/kg. It is worth noting here that one reason for the great toxicity of methylmercuric compounds is their ability to pass this barrier and enter the brain. Triethyltin sulfate also inhibits oxygen uptake by rat brain cortex [257].

The major interest and application of organotin compounds has been for their biocidal activity [245]. Table 6 lists some representative applications. One preparation receiving widespread use is Plictran, whose active ingredient is tricyclohexyltin hydroxide. In tests against mites on roses [257], it was effective at concentrations as low as 0.004%. In a comparative test with triphenyltin hydroxide against cotton leafworms and bollworms, Plictran was the most effective [258]. It combines an inherent toxicity with an antifeedant effect, and is believed to act on the sulfhydryl group of dehydrogenase. Similar tests were carried out on potato beetles using a variety of trialkyltin compounds [259]. Interestingly, tributyltin tetrahydrofurylacetate had the highest antifeeding index for males, but trioctyltin acetate had the highest one for females! Most work has been done on compounds containing the same alkyl groups. However, mixed compounds of the type $R_2R'SnCl$ have also been found to be effective as insecticides, herbicides, and fungicides [260].

One major use of organotin compounds, as well as other organometal bio-

TABLE 6

REPRESENTATIVE BIOCIDAL APPLICATIONS OF ORGANOTIN COMPOUNDS

Fungicidal	
	Control of fungi on potatoes and sugar beets
	Control of scab on pecans and peanuts
	Control of rice blast and pine needle blight
	Preservation of wood (from fungi and insects)
	Paint additive to prevent mold growth in humid climates
Bacteriostatic	
	Control of slime in paper and wood pulp production
	Fabric disinfectant
	Antimicrobial activity in synthetic fibers
Insecticidal	
	Antifeedant against insect larvae
	Chemosterilant (preventing reproduction)
	Arachnidicide against rust mites and scorpions
Other	
	Tapeworm and helminthes eradication in poultry
	Protection of surfaces (ships, piers, etc.) exposed to seawater from attack by marine organisms
	Plankton control in reservoirs

cides, has been in the control of schistosomiasis (Bilharzia). This debilitating affliction is found in many tropical areas of the world. It arises from water-dwelling blood flukes or schistosomes. These parasites can penetrate human skin and multiply within the body. While not necessarily fatal in itself, Bilharzia weakens resistance to other infections and causes a continuous state of bad health. The life-cycle of the schistosomes has one phase in which they dwell within certain species of snails. Since water serves both as a habitation of the snail and the medium of infection, Bilharzia has spread considerably as waterways have been extended for purposes of irrigation or flood control. It is also enhanced by frequently poor local sanitary conditions. The readiest mode of attack is the intermediate host snails. These are vulnerable to triphenyltin compounds [261]. They even act at concentrations of 0.015—0.030 ppm, which is too low to affect fish. Triphenyltin acetate and various tributyltin compounds under these conditions show no toxicity to warm-blooded species, but do affect small fish, snails and zooplankton [262]. Various alkyltin and alkyllead compounds were recently tested as fungicides against *Poria monticola*, *Coniophora olivacea*, and *Fomes lividus*, all of which attack wood [263]. In general, the lead compounds were more effective. In the tin series, the greatest effects were found in the propyl, butyl and pentyl compounds. Interestingly, the effectiveness of $(CH_3)_3SnCl$ and $(C_2H_5)_3SnCl$ was reduced after weathering. Triisobutyltin acetate proved somewhat less effective than tri-n-butyltin acetate. In tests run on soil microorganisms, tributyltin oxide showed no effect at concentrations up to 100 ppm [264]; however, there was reduction in the mold count and the nitrite N content.

Organotin compounds have a major advantage over organomercurials and organolead compounds as biocides: the final degradation product, SnO_2 or an inorganic tin compound, will have little or no toxicity, whereas mercury and lead compounds are all toxic. With the growing concern over immediate and long-range effects of heavy metal poisoning arising from environmental pollution, this factor may well override the lower effectiveness of organotins on a weight basis. If organomercurials and organoleads are forced out of pesticidal applications, organotins are the logical replacements. The enormous variety of uses ensures that the present research activity on these compounds should become even greater in future years.

F. Organolead compounds

Because of the importance of tetraethyllead as a gasoline additive, the toxicity of this and related compounds has received considerable study. This work has been reviewed [265, 266]. Tetraethyllead has even appeared as a poison in a murder mystery (Ellery Queen, The Roman Hat Mystery)!

Like the tin analogs, tetraalkyllead compounds owe their toxicity to the cleavage in vivo of one lead—carbon bond to form R_3Pb^+. Since such cleavage occurs more readily, and since lead has a higher intrinsic toxicity, the alkylleads are considerably more poisonous than the alkyltins. This is true for all compounds on which comparative studies have been made. Also, the variation in toxicity as a function of organic group seems to be appreciably less for organoleads than for organotins.

Inorganic lead compounds, Pb^{II} species in all cases, interfere with the formation of heme in the blood by inhibiting an enzyme that causes δ-amino-

levulinic acid to form porphobilinogen, a heme precursor. By contrast, organolead compounds (which are Pb^{IV} derivatives) act in a manner analogously to organotins. The trialkylleads interfere with oxidative phosphorylation, while the dialkylleads tie up the sulfhydryl groups of enzymes. It is noteworthy that BAL, either by itself or in conjunction with EDTA, can be used to treat poisoning by inorganic lead and dialkyllead compounds, but trialkyllead compounds are not amenable to such treatment.

Some work on the mode of action of tetramethyl- and tetraethyl-lead has been reported. In rats, tetraethyllead is converted to $(C_2H_5)_3Pb^+$, but in rabbits it is degraded to inorganic lead [267]. In a comparative study using mice and rats, Hayakawa found that $(CH_3)_4Pb$ was more toxic to mice, but $(C_2H_5)_4Pb$ was more toxic to rats [268]. In mice, half the tetramethyllead was converted to trimethyllead ion within two days, but only 40% of tetraethyllead was similarly converted after three days. Tetraethyllead inhibits spermatogenesis in men upon long contact [269]. When these compounds were administered in sublethal doses to maternal rats, the embryos showed retarded growth and delayed ossification [270].

Numerous biocidal applications for organolead compounds have been proposed. Dibutyllead diacetate acts strongly against tapeworms and has comparatively low toxicity [271]. This compound, when administered to monkeys or rats, could successfully be treated by BAL, provided treatment was early [272]. With a view towards its use in controlling schistosomiasis, Hira and Webbe studied the effect of triphenyllead acetate on the snail *Biomphalaria glabrata* and the parasite *Schistosoma mansoni* [273]. When *Drosophilia melanogaster* (fruit flies) were fed 4 mg/l triethyllead chloride during their larval development, they showed significant increase in loss of sex chromosomes [274]. Organolead compounds also affect plants and their development. Di- and tri-alkyllead compounds affected the spindle fiber mechanism on onion (*Allium cepa*) root tips in a manner similar to that of alkylmercurials [274]. These compounds showed activity at concentrations of 10^{-6} or 10^{-7} *M*, whereas $Pb(NO_3)_2$ acted only at concentrations above 10^{-4} *M*. Thayer found that trialkyllead compounds, like other alkylmetals in aqueous solution, inhibited seed development [5]. Several workers have found that, like tin, the trimethyllead ion is somewhat less toxic than higher alkyls (see Tables 2 and 6). Triphenylplumbylacetic anhydride has been used as a tree defoliant [275]. Di- and tri-phenyllead compounds, when used to treat seeds, seedlings, or burlap, effectively repelled rodents [276]. Triphenyllead compounds in conjunction with Cu_2O proved useful additives to antifouling paints, retaining their efficacy even after 27 months [277].

The enormous interest in organotin chemistry has stimulated increasing attention to lead analogs, and applications of these latter will doubtlessly increase. However, the enhanced toxicity of organolead, along with the concern over environmental lead pollution, will doubtlessly have a restraining influence on their potential uses.

G. Organoantimony and organobismuth compounds

A substantial literature exists on the biological effects of organoantimony compounds, and, to a lesser extent, of organobismuth compounds. Much of this is older research generated by the search for analogs of Salvarsan. The therapeu-

tical uses of antimony have been reviewed by Christiansen [278]; those of bismuth by Gilman and Yale [279]. Some recent work has been included in the review by Sijpesteijn et al. [4]. Two features distinguish these compounds from those of other heavy metals, as far as biological activity is concerned: both can exist in two different oxidation states, but only the trivalent state compounds show important effects; the aromatic compounds are the most potent. The less stable aliphatic derivatives of antimony and bismuth have received little attention. Apparently the organobismuth compounds are less toxic towards mammals than those of antimony, just the reverse of the tin—lead pair [4].

Early work on organoantimony compounds concentrated on their similarity to Salvarsan and related arsenicals. These species did prove useful against infections by trypanosomal and leishmanial organisms, especially where those organisms resisted arsenicals. Organobismuth compounds were likewise effective, but apparently much of their efficacy depended on the ability of organic compounds to generate metallic bismuth in situ [279].

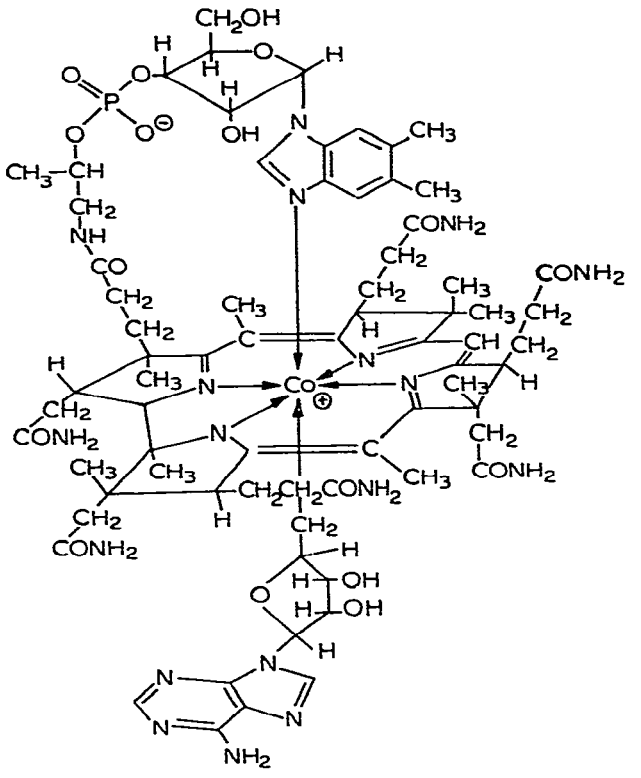
Some recent research has been reported. Organoantimony iminodiacetates can be used as insecticides [239]. Captostibone (*O*-carboxymethylthiobenzenestibonic acid) acts effectively against *Trypanosoma evansi* in rodents and has a chemotherapeutic index of 3.4 [280]. A *p*-aminobenzenestibonic acid derivative gave full protection to ponies for ninety days against *T. evansi* at a level of 50 mg/kg [281]. Phenylantimony and phenylbismuth pyrimidine derivatives show antifungal activity [282]. Phenylbismuth bis(2-thiopyridine-*N*-oxide) has been proposed as a bactericidal and fungicidal additive to soaps [283].

H. Transition metals

The great advances in the chemistry of organotransition metal compounds over the last twenty years has not seen a corresponding activity in their biological effects. To be sure, metal carbonyls have long been known for their toxicity [144], and nickel carbonyl has recently been identified as a component of smoke [284, 285]. The combination of carbon monoxide with the iron of hemoglobin to form carboxyhemoglobin has been extensively studied and reviewed [286—288], particularly in conjunction with air pollution.

As σ-bonded organic derivatives of transition metals have become better known, their biological effects have begun to be investigated. Certain arylcopper compounds can be used as pesticides [289]. The suggestion has been made that dimethylplatinum(IV) compounds might serve as anti-tumor agents [290]. Thayer has found that trimethylplatinum(IV) and dimethylgold(III) compounds resemble methyl-mercury, -tin, and -lead compounds in their effects on sprouting seeds [5]. Most important in this area, however, has been the research growing out of the discovery that derivatives of Vitamin B_{12} contain Co—C bonds.

The history of the discovery and determination of the structure of Vitamin B_{12} (cobalamin) has been amply reviewed [291—293]. A coenzyme form (5,6-dimethylbenzimidazolylcobamide) (XV), containing the Co—C linkage, had its structure determined by X-ray crystallography [294]. Perhaps most studied of B_{12} derivatives has been methylcobalamin, in which a methyl group is bonded to cobalt. This compound acts as a methyl transfer agent and has been shown to be intermediate in the microbial methylation of mercury [179, 215, 216, 218—220, 293] and arsenic [295]. Numerous studies on the mechanism of transfer



(XV)

have been reported [293, 296—299]. Most evidence seems to indicate that the methyl group is transferred as an anion, though radical exchange may also occur [293].

A number of B_{12} model compounds have been prepared, of which the most studied is bis(dimethylglyoximato)cobalt(III) derivatives, generally termed cobaloximes [300, 301]. These model compounds have provided much useful information. An epimer of B_{12} has also been studied and found to show much lower activity [302]. Other Co—C compounds have been proposed as intermediates in B_{12}-catalyzed reactions [297, 303]. Some of these compounds are discussed in connection with the chemistry of organocobalt(III) compounds generally [291, 304, 305].

Almost no work has been done on π-complexes in biological systems. Hydroxymethylferrocene will bind to horse liver alcohol dehydrogenase and is useful as a marker [306]. The compound *o*-carboxyethylbenzoylferrocene has been claimed to be useful in the treatment of anemia [307].

IV. Conclusions

The role of organometallic compounds in all aspects of biological studies has been substantial, both historically and currently. While a vast literature has appeared and, like other areas of chemistry proliferated in recent years, it has

been widely scattered and dispersed. Likewise, research activity has been erratic. Some compounds receive very intense attention, others considerably less, and most none at all. Attempts to correlate, compare, and predict have been equally irregular. Certainly the research reported, substantial and worthwhile as it is, is little more than an opening wedge.

The advances in synthetic technique, structural investigation, and mechanistic knowledge certainly indicate that many organic derivatives of boron, silicon, phosphorus, arsenic, and even germanium or tin may have medicinal uses not yet realized. Earlier in this century Salvarsan was often used in conjunction with compounds of antimony or bismuth because such combinations enhanced its effectiveness. Other combinations may be found.

Organometals provide valuable approaches to metabolic studies. Already they have provided useful information about oxidative phosphorylation, transmethylation, and the principles of chemotherapy. They can aid with other processes also. Compounds of silicon, phosphorus, and boron would seem to be most promising here, and perhaps also tellurium, this last especially as there is a growing interest in the role of selenium. The use of certain organometals as biocides adds a further dimension here.

Arsenic and mercury compounds have featured prominently in the concern about man's environment, and lead to only a slightly lesser degree. Almost certainly this will continue. The need for continuing biocides, balanced against the need to avoid contamination by long-lived, toxic materials, will enhance the development of organotin compounds and probably those of certain other metals

The vast development in the chemistry of π-complexes since 1950 has not seen any corresponding growth in biological uses. Almost certainly such will be found, especially as bioinorganic chemsitry continues to develop. One likely role is as metabolic intermediates in reactions involving carbon—carbon unsaturated bonds.

Certainly a tremendous amount remains to be done. Biological applications have already greatly abetted the growth of organometallic chemistry, but the best seems yet to come.

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