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BIOLOGY OF METALS

Mini review

Biological activity of organometallic bismuth compounds

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Summary. The chemical aspects of organometallic bismuth(III) compounds are discussed with respect to the stability of the metal-carbon σ bond, their low dipole moments, and the limited solubility of these complexes in hydrophilic solvents. A new Bi heterocycle, which is of potential interest in terms of stability and solution behaviour, was shown to exist as an intermediate under the conditions in the mass spectrometer.

Although generally bismuth organic compounds are extremely toxic, in the 1970s they became important as biocides and this is still being investigated. They have also been discussed as irritation causing chemical warfare agents. While their application in chemotherapy never became very widespread because antibiotics were discovered, in the last few years the antitumor activity of some derivatives has been reported.

Key words: Antitumor activity — Biological activity — Chemical aspects — Organometallic bismuth compounds — Toxicity

Introduction

Organometallic chemistry is the chemistry of compounds which contain at least one carbon atom directly bonded to the metal centre (e.g. bismuth acetate is not an organometallic compound whereas triethylbismuth is).

In 1760 Cadet prepared, in a military chemist's shop in Paris, cacodyl derivatives (cacodyl = Me_2As), the first of all organometallic compounds. These were identified by Bunsen in 1848 as being a mixture of Me_2As-$AsMe_2$ (dimer cacodyl) and Me_2As-O-$AsMe_2$ (cacodyl oxide) (Smith 1973; Strube et al. 1986). Since then, many thousands of organometallic derivatives have been made. Between 1850 and 1950 mainly σ-bonded (η') main-group organometallic compounds were synthesized. Even at a very early stage Schweizer and Loewig in 1850 succeeded in preparing $BiEt_3$, the first organobismuth compound, which they called *'Wismuthaethyl'* (Elschenbroich and Salzer 1986). At that time nobody could know how important the biological aspects of organometallic compounds would become, although Paracelsus, 'the true father of modern metallo-therapy', had already administered mixtures of diverse heavy metals, including arsenic and bismuth, against various diseases (Dyson 1928). In 1909 Paul Ehrlich's Salvarsan (**A**) became the most famous example of an arsenic compound in clinical application and indicates the beginning of modern chemotherapy (Elschenbroich and Salzer 1986). It showed pronounced bacteriostasis and was approved as a drug against syphilis, caused by *Treponema pallidum,* before the era of antibiotics (Ehrlich 1910). Some other organoarsenic compounds are still applied today against advanced stages of the African sleeping disease, caused by the protozoa trypanosomes (Gross and Schoelmerich 1973).

Arsenic is definitely biologically essential (cf. isolation of **B** from the tail muscle of Western rock lobster; Haiduc and Zuckerman 1985) and is probably essential in human life also. In contrast

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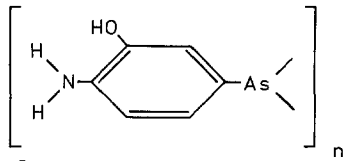
Abbreviations: BE, bond energy; *IC,* inhibition concentration; *MIC,* minimal inhibition concentration; χ, electronegativity (Allred and Rochow); *X,* halogen, pseudohalogen = F, Cl, Br, CN; Me, CH_3; Et, C_2H_5; Bu, C_4H_9; Ph, C_6H_5; Ac, CH_3COO; *MS,* mass spectrometry



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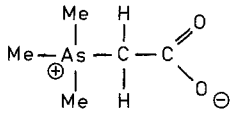


B

to arsenic, as far as we are aware, no naturally existing organobismuth compound has been identified or isolated and bismuth is not known to be essential.

However, it is known that some organometallic compounds of bismuth, a heavier homologue of arsenic and the heaviest stable metal, are also characterized by antimicrobial activity. Even in Ehrlich's time, bismuth-containing Salvarsan derivatives ('Arsalyt' and 'Chlorarsalyt') were used and were reported to be as active as Salvarsan itself but without such strong side-effects (Giemsa 1924). $BiPh_3$ was also shown to be active against syphilis and diseases caused by trypanosomes (Giemsa 1924). Inorganic as well as organic bismuth compounds, however, have severe toxic side-effects which limit their medical use (Kuschinsky and Luellmann 1974; Raiziss et al. 1934 and references therein); indeed, $BiPh_2X$ are chemical warfare agents more powerful than $AsPh_2Cl$, used as *'Blaukreuz'* during World War II (McCombie and Saunders 1947). Moreover the pharmacists did not actually succeed in preparing homogeneous products (without toxic solvents); due to these problems the application of bismuth-containing medicaments could not be expanded (Giemsa 1924). It seems possible that the difficulties were based on the limited solubility of organobismuth compounds, which is still a problem today (Klapötke 1987c, d).

Although various compounds of the so-called pnicogen group (15th group) elements have an old tradition as germicides and therapeutic agents, the general interest seemed not to be centered on those particular problems and no review summarizing their use exists. However, during the last few years several attempts have been made to test the biocide activity of new organobismuth compounds; new toxicological data are available and the solution to some important problems has been suggested, e.g. increasing the solubility of organobismuth derivatives in hydrophilic solvents by suitable changes of their molecular structures (Klapötke 1987a; Köpf et al. 1986). This paper is intended to review the information and to collect together all the new efforts and facts, not least the antiproliferative activity of sulfur-containing bismuth organic compounds, first detected in 1987 (Köpf-Maier and Klapötke 1988).

It has been necessary to select from numerous publications and it is impossible to give a complete summary of all published results on the biological activity of organometallic bismuth compounds, some of which are reviewed elsewhere (Coates et al. 1967; Wieber 1977; see also Bagramyan et al. 1975; Delmas-Marsalet and Arné 1949; Dyson 1928; Pyman 1935; Raiziss et al. 1934 and references therein; Sollmann and Seifter 1939). Some connections between biology and chemistry are highlighted, especially the latest results of research, in order to encourage scientists to continue working in this field.

Chemical aspects of organometallic bismuth compounds

The organic chemistry of elements of the 15th group, the heaviest one being bismuth, shows various connections between non-metallic phosphorus, the semimetals of arsenic and antimony, and metallic bismuth; however, these special problems will not be discussed here (see Wieber 1977 and references therein). The large variety of compounds is based on two degrees of oxidation, E(III) and E(V), which distinguishes this group from groups 13 and 14. There is an energy decrease of both the homonuclear (E-E) and the heteronuclear (E-C) bond in the order P > As > Sb > Bi. On the other hand, the polarity of the E-C bond shows an increase from P to Bi (Elschenbroich and Salzer 1986). In terms of chemical thermodynamics a significant difference between the formation enthalpies (ΔH_f^0) of the group 15 trimethyls (EMe_3) is noted. While PMe_3 is slightly exothermic ($\Delta H_f^0 = -101$ kJ/mol), $AsMe_3$ shows a weak positive formation enthalpy ($\Delta H_f^0 = +13$ kJ/mol), whereas the corresponding $BiMe_3$ is endothermic ($\Delta H_f^0 = +194$ kJ/mol) and therefore unstable (Elschenbroich and Salzer 1986). The latter is due to the extremely weak Bi-C bond (BE = 141 kJ/mol, the weakest main-group metal-carbon bond) which is caused by the high bond energies of the constituting elements (Bi, C, H) in their standard states. So BiR_3 can decompose photolytically or upon heating and, like the lead or mercury compounds PbR_4 and HgR_2, shows radicals $R^{\cdot}$ (e.g. $Me^{\cdot}$) as intermediates. This affects the instability, toxicity, and

methylation of the compounds (see Biological aspects below).

Trends in bond energies are also shown in mass spectra. Thus the most abundant peaks in the 70-eV mass spectra (MS) of AsR_3 and SbR_3 compounds are $AsMe_2^+$, $SbMe_2^+$, $AsPh^+$, and $SbPh^+$, but in the spectra of both $BiMe_3$ and $BiPh_3$ the ion Bi^+ ($m/z = 209$) dominates (Smith 1973) and is also seen predominantly in the spectra of most of the S-coordinated biologically active compounds of the type $BiR(SR')_2$ (Klapötke 1988). For $MeBi(SMe)_2$ the preferential fragmentation of the Bi-C bond instead of the S-C bond could be proved by MS under test conditions using an isotopically labelled derivative $Me^*Bi(SMe)_2$. This kind of fragmentation may be explained by the bond energies (S-C: BE = 289 kJ/mol) as well as by the resonance stabilization of the cation formed, $Bi(SMe)_2^+$ (see Klapötke 1988).

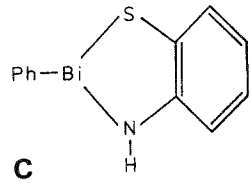
Although Bi is distinctly more electropositive ($\chi_{Bi} = 1.7$) than As ($\chi_{As} = 2.2$), one of its less heavy homologues, and therefore the Bi-C bond is distinctly more polar than the As-C bond ($\chi_C = 2.5$), nevertheless most of the biologically active organometallic Bi derivatives of the type $R_nBi(SR')_{3-n}$ ($n = 1, 2, 3$) are unfortunately very hydrophobic. Thus it is very difficult to dissolve them in physiologically and ecologically harmless solvents.

Inorganic derivatives such as $Bi^{3+}(X^-)_3$ do not suffer from these problems, but they are generally less biocidal, as are Bi(V) compounds. They also lack any lipophilic group (R) which could be attached to some carrier function, e.g. for transportation through hydrophobic membranes. The weak dipole moment of the organobismuth mercaptides, such as $MeBi(SMe)_2$, is due to the trigonal pyramidal structure (showing a distorted pseudo-tetrahedral coordination at Bi caused by stereochemical activity of the lone-pair electrons), as determined for analogous compounds in crystals as well as in the gas phase. This structure results, to a first approximation, in a dipole moment ($\chi_S \approx \chi_C$; $\chi_S = 2.4$) with its vector directed from Bi to the CSS plane and perpendicular to the plane. The presence of the antiparallel aligned dipole vector, conditioned by the lone-pair electrons (sp^3 hybrid), results (by vector addition) in a total dipole moment $\mu \approx 0$.

Therefore attention has been directed to more soluble derivatives, especially to those with substituents —OH, $—NH_2$, $—NR_2$, and $—SO_3H$, where R may be aromatic or aliphatic (Dub 1968; Klapötke 1987a; Köpf et al. 1986; Smith 1973) (cf. Salvarsan, Ehrlich 1910). Amino derivatives should have some solubility, especially in acidic aqueous media, due to partial protonation of N.

On the other hand, these prerequisites can not always be realized (pH of human blood = 7.41, Pschyrembel 1982). Thus the formation of salt-like mercaptoanilinium derivatives is of special interest in the synthesis of organobismuth compounds (Eq. 1); a promising way may be the alkylation of the amino group by means of methyl iodide (Klapötke 1987a).

$$>Bi—(SC_6H_4NH_2\text{-}p) + MeI \rightleftarrows [>Bi—(SC_6H_4NH_2\{Me\}\text{-}p)]^+ I^- \quad (1)$$



C

Heterocyclic organometallic complexes are often marked by increased stability (chelate effect) compared with their non-cyclic analogues and have therefore been included in discussions on metallocene antitumor agents (Köpf et al. 1986). The S,N-coordinated *o*-aminothiophenoldiates avoid the hydrophobicity of the S,S-coordinated derivatives; in addition, the secondary amino group can act as a Lewis base, thus increasing the solubility of these compounds. Although several attempts have been made, as far as we are aware no heterocyclic *o*-aminothiophenol derivative has been synthesized (Klapötke 1987b).

$BiPh_3$ reacts with thiols with formation of Bi-S bonds and elimination of benzene but the acidity of an aromatically substituted amino group is too low for Bi-N bond formation. Treating $BiPh_3$ with equimolar amounts of *o*-aminothiophenol yielded the monosubstituted complex $Ph_2Bi(SC_6H_4NH_2\text{-}o)$ instead of the desired S,N-coordinated derivative (no reaction was observed when $H_2N—C_6H_4—NH_2$-*o* was refluxed). However, the formation of $PhBi(SC_6H_4NH\text{-}o)$ (**C**) could be observed in the gas phase under the conditions in the mass spectrometer, proved by metastable transition (Eq. 2), (for MS see Klapötke 1987b).

$$Ph_2Bi(SC_6H_4NH_2\text{-}o)^+ \xrightarrow[(MS)]{*} C^+ + PhH \quad (2)$$

Even though with elements of the 15th group coordinated five-membered Bi(III) metallacyclic compounds are still unknown under "normal" conditions, their existence should be noted and

Table 1. Microbiological activity of organometallic bismuth compounds

Species	MIC (μg/g) of $BiPh_3$, $BiPh_3Cl_2$[a]	$BiPh_3$ + neomycin[b]	$BiBuCl_2$, $BiPhCl_2$[c]	$BiPh_3Cl_2$, $BiPh_2Ac$[d]	I[e]	II[f]	III[g]	IV[g]	V[g]
Pseudomonas aeruginosa			2000	1000					
Aerobacter aerogenes			2000	1000					
Staphylococcus aureus	1000	200	2000	1000					
Streptococcus faecalis							10	5.0	5.0
Bacillus subtilis					0.5	1.0	10	5.0	5.0
Escherichia coli		200			1.0	1.0	10	5.0	5.0
Candida tropicalis					1000	1000			
Penicillium camembertii					100	10			
Lactobacillus plantarum							10	0.5	1.0

Compounds: I = $MeBi(SMe)_2$ II = $MeBi(SC_6H_3Cl_2\text{-}2,6)_2$ III = $PhBi(SC_6H_4Cl\text{-}p)_2$
IV = $MeBi(SC_6H_4NH_2\text{-}p)_2$ V = $[MeBi(SC_6H_4NH_2Me)_2]^{2+}$ $(I^-)_2$

[a] American Cyanamid Co. (1965)
[b] Gross (1964; 1968)
[c] Leebrick (1962; 1966)
[d] Leebrick (1962; 1965)
[e] Klapötke (1988)
[f] Klapötke and Gowik (1987)
[g] Klapötke (1987a)

their synthesis attempted in the future since these compounds are of interest both chemically and biologically.

Biological aspects of organometallic bismuth compounds

Antimicrobial activity

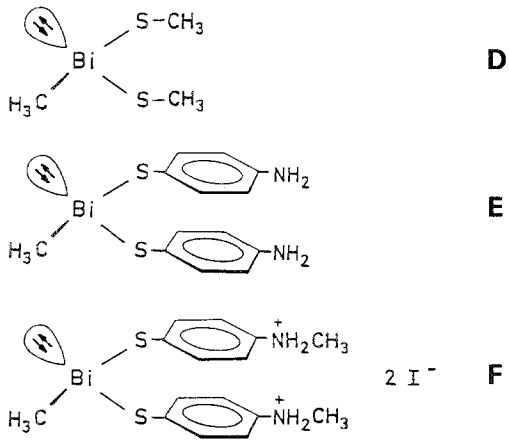
Up to now, all investigations on organometallic bismuth compounds have proved they have strong biological activity. Generally, the organic Bi(III) derivatives, like the analogous As(III) derivatives, are more poisonous than the corresponding Bi(V) and As(V) compounds. On the other hand, derivatives with aromatic ligands are more toxic than those with aliphatic ligands (Meyer and Pietsch 1952).

During the last 20 years various organobismuth compounds have been tested for their biocidal properties against fungi, gram-positive and gram-negative bacteria, and yeasts (Table 1; American Cyanamid Co. 1965; Klapötke and Gowik 1987; Klapötke 1988; Kooistra 1970/74; Leebrick 1962/65 and 1962/66; M&T Chemicals 1964a) and compared to some corresponding As derivatives (Klapötke 1987a).

Several compounds mentioned in Table 1 can be used for bactericidal or fungicidal applications to textile fibers such as cotton, wool or synthetics (Leebrick 1962/65 and 1962/66) or to paints (American Cyanamid Co. 1965) and to marine antifouling compositions (Gross 1962/65). Some bismuth derivatives are also useful as additions and coatings for the preparation of foam materials like pillows, pads, and mattresses, which are preferred in hospitals (M&T Chemicals 1964a, b). A combination of $BiPh_3$ and neomycin is used as an antibacterial finish to cellulose materials and is effective after many washes even when chlorine bleach is used (Gross 1964/68).

Recently some sulfur-containing organobismuth(III) compounds, in particular a novel group of organomercaptoaniliniumbismuth(III) complexes (**D, E, F;** Klapötke 1987a) have been tested for bacteriostatic properties.

They showed very low MIC values, thus being



more effective than many organotin derivatives or inorganic copper and zinc compounds. Two of them (**E, F**) are highly antibacterial against both gram-positive *(Streptococcus faecalis)* and gram-negative *(Escherichia coli)* bacteria, both being used as indicator strains of bacilli. They are even more effective than some organomercury thiolates which are already in use as disinfectants (Wallhäuser 1984). In comparison with only C-coordinated Bi(III) containing compounds they show by 10^{-3} decreased MIC values (American Cyanamid Co. 1965 and 1964/68; Klapötke 1987a). There is also an interesting highly chlorinated compound (Klapötke and Gowik 1987), its strong activity against *Bacillus subtilis* being illustrated by the dose/response curve shown in Fig. 1.

Toxicity

The earliest references to the curative properties of elements towards human diseases include arsenic, antimony, and bismuth. In 1768 Odier used a bismuth compound in the treatment of intestinal disorders, while the first attempts to study the spirillicidal and trypanocidal properties of some bismuth tartrates date back to the end of the 19th century; the toxic effects of bismuth, however, stopped these early experiments (Raiziss et al. 1934 and references therein). Nevertheless, in comparison with arsenic, bismuth generally exhibits advantages because it is less severely toxic. The pattern of toxicity induced by bismuth and its compounds is similar to that of mercury, being characterized by typical symptoms of heavy-metal toxicity like nephrotoxicity and gastrointestinal irritation, but lacking phenomena due to lesions of capillaries and other blood vessels which are characteristic for acute arsenic poisoning (Kuschinsky and Lüllmann 1974).

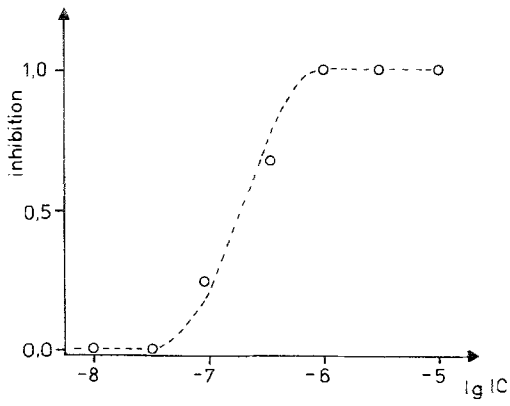


Fig. 1. Dose/response curve of $MeBi(SC_6H_3Cl_2\text{-}2,6)_2$ against *Bacillus subtilis*. Incubation temperature 37° C, incubation period 72 h, culture medium APT agar

The first detailed toxicity report on an organometallic bismuth compound, $Bi(Me)_3$, noted that it produced marked effects which share the characteristics of antimony, arsenic, and lead (Sollmann and Seifter 1939). This study further confirms trimethyl bismuth as definitely anti-syphilitic, the same effect being noted for triphenyl bismuth (Giemsa 1924). This derivative also shows an anthelmetic activity in curing rats, experimentally infected with *Fasciola hepatica* (Saggers 1970), while the toxicity of an iminodiacetate organobismuth chelate is useful in insecticides (Langer 1964/69).

The diphenyl bismuth halides (X = Cl or Br) and the pseudo-halide CN exhibit severe toxicity and have proved to be very strong sternutators. They are probably more powerful than diphenyl chloroarsine which was used as *'Blaukreuz'*, a chemical warfare agent, in World War II (Ammedick 1980; McCombie and Saunders 1947; Stöhr 1985).

Some studies have been made on the toxicity of organometallic bismuth compounds (Köpf-Maier and Klapötke 1988; Lecoq 1937; Sollmann and Seifter 1939; see Table 2), but it is important that this research work be extended by more bacteriological, physiological, and clinical methods in order to be able to select derivatives which should be relatively more toxic to pathogenic organisms than to their human or animal hosts. Moreover no research has yet been published about biochemical reactions in the toxicity of bismuth compounds.

Although the heavy-metal toxicity of bismuth is somewhat less than that of mercury (Klapötke 1987a; Raiziss et al. 1934 and references therein), the strong biological activity of the bismuth or-

Table 2. Toxicity of organobismuth(III) compounds

Compound	Application	LD_{100}		LD_{50}		Ref.
		[mg/kg]	[mmol/kg]	[mg/kg]	[mmol/kg]	
$BiMe_3$	i.v.	182	0.05	—	—	a
$BiMe_3$	s.c.	2736	0.72	—	—	a
$PhBiCl_2$	s.c.	200	0.56	—	—	b
$MeBi(SMe)_2$	i.p.	80	0.25	32	0.10	c
$MeBi(SC_6H_4NH_2\text{-}p)_2$	i.p.	140	0.30	85	0.18	c
$[MeBi(SC_6H_4NH_2Me)_2]^{2+}$ $(I^-)_2$	i.p.	160	0.21	100	0.13	c

i.v. = intravenous, *s.c.* = subcutaneous, *i.p.* = intraperitoneal

[a] Sollmann and Seifter (1939)
[b] Lecoq (1937)
[c] Köpf-Maier and Klapötke (1988)

ganic compounds will have to be considered with respect to the total amount of the heavy-metal toxicity of mercury in addition to the biological activity of the organomercury compounds. Further work and developments are required before the practical use of organometallic bismuth compounds can be judged.

Antitumor activity

As reported above, a previous study on the biological activity of organobismuth(III) thiolates revealed antimicrobial properties of those compounds (Klapötke 1987a; Klapötke and Gowik 1987; Klapötke 1988). Some derivatives were able to inhibit the growth of *E. coli*, for example, at concentrations as low as 1 μg/g. After careful study it was noticed that under this treatment the bacteria became elongated and filamentous (Köpf-Maier and Klapötke 1988). A similar finding of elongation of *E. coli* was the first hint to the biological activity of inorganic platinum complexes (*cis*platin) (Rosenberg et al. 1965, 1967a, b) which led to the detection of pronounced antitumor effectivity against animal and human tumors (Rosenberg et al. 1969; Rosenberg 1985).

Thus when two neutral organobismuth(III) bis(thiolates) and one MeI adduct (**D, E, F**) were tested for antiproliferative properties against Ehrlich ascites tumor, growing as fluid tumor in the peritoneal cavity of mice, they were all 100% effective (Köpf-Maier and Klapötke 1988; see Figs. 2–4).

The therapeutic index TI, determined by calculation of the ratio LD_{50}/ED_{75} (Köpf-Maier and Klapötke 1988), increases from **D** (3.2) to **E** (4.3)

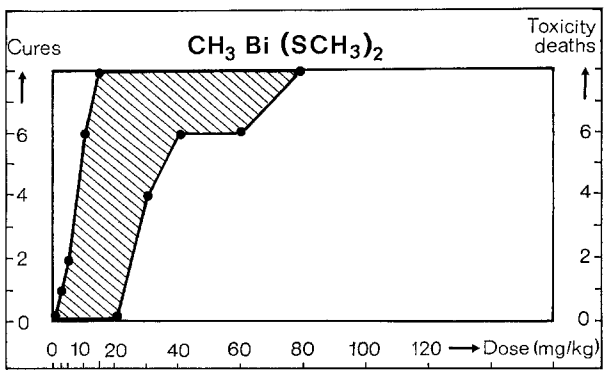


Fig. 2. Dose/response *(left)* and dose/lethality *(right)* curves obtained by treatment of mice bearing fluid Ehrlich ascites tumor with $MeBi(SMe)_2$ (**D**). The *shaded area* indicates the range of surviving animals. Deaths within 7 days after application of the Bi compound were defined as 'toxicity deaths', those occurring later as 'tumor deaths'. On day 60 after tumor transplantation, the key date for determining the survival rate, no animals still alive had recognizable signs of tumor and were thus considered cured

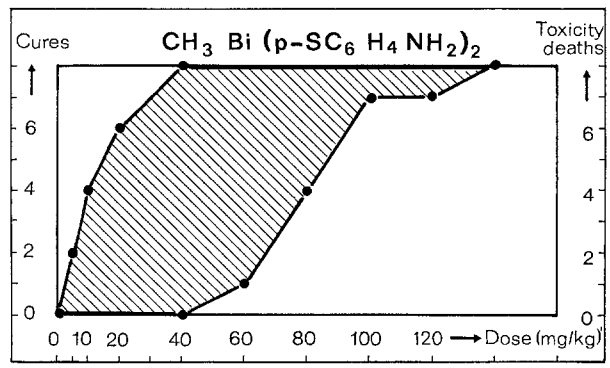


Fig. 3. Dose/response and dose/lethality curves after treatment with $MeBi(SC_6H_4NH_2\text{-}p)_2$ (**E**). For further details, see legend to Fig. 2

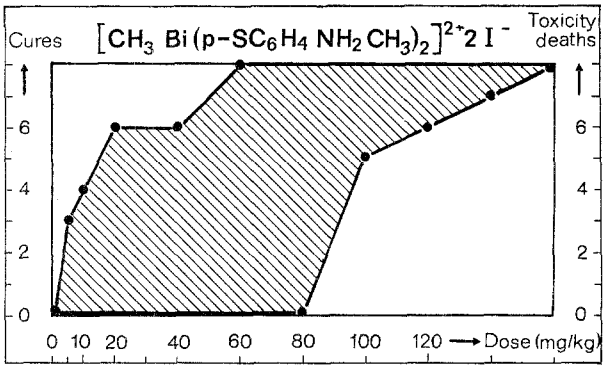


Fig. 4. Dose/response and dose/lethality curves after treatment with $[MeBi(SC_6H_4NH_2Me)_2]^{2+}$ $(I^-)_2$ (**F**). For further details, see legend to Fig. 2

and **F** (5.0). Whereas **D** shows only a narrow therapeutic range (see Fig. 2), for both **D** and **E**, deaths due to toxicity occur with the 100% cure rate. Compound **F**, which has the highest TI and the largest therapeutic range, shows the best antitumor activity. Though its optimum dose is higher than that of **D** and **E**, the LD_{50} and LD_{100} values are higher, too, and so **F** seems to be the most promising complex for further investigations.

These studies enlarge the spectrum of non-platinum-group metal antitumor agents which have been detected and developed during the past ten years (Köpf-Maier 1987 and references therein). The toxic properties of most non-platinum-group metal antitumor agents differ fundamentally from those of platinum compounds, and it is known that the toxic effects induced by certain elements can be modified or masked by suitable changes of the molecular structures. Toxicological studies will be essential for evaluating the actual pattern of organ toxicity induced by organobismuth(III) compounds. Further investigations are also necessary to compare their antitumor activity, especially against solid tumor models.

Moreover the solubility in polar solvents is an important parameter for the biological application of chemicals. In this respect, the polar bismuth compound is better than the neutral derivatives because of its salt-like character; although it is not sufficiently water-soluble to be administered in pure saline without addition of a solubilizer, it is worth further investigation.

Conclusions

This paper indicates, against the historical background, the importance of biologically active organometallic bismuth compounds. Within the last few years it has been possible to synthesize some new organobismuth derivatives having similar germicidal activity to the well known organomercury compounds. Moreover, it is only in the last year that the antitumor activity of some organobismuth thiolates has been detected. Further investigations are essential to confirm the antiproliferative properties, especially against solid tumor models. Organobismuth complexes could increase the number of non-platinum-group metal antitumor agents and, as these compounds exhibit different patterns of antiproliferative behaviour and toxicity, it may be possible to combine platinum and non-platinum-group metal compounds without increasing their toxic side effects. Some combinations of these agents may open up new perspectives ultimately for clinical cancer therapy.

Although organometallic As and Bi compounds were the earliest and brightest stars of chemotherapy, they lost their importance and faded. Will the end of our century, due to the work that should be done now, see their old glamour return again?

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