

Bismuth Compounds and Preparations with Biological or Medicinal Relevance

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I. Introduction and Scope

The chemistry of bismuth is diverse but is perhaps the least well established of the heavier stable elements in terms of a coherent or comprehensive database. Complexes of bismuth typically have low solubilities in most solvents, so that definitive formula assignments are usually based on X-ray diffraction studies of crystalline samples that have been isolated in small or indefinite quantities. Comprehensive characterization of the compounds is rare, and most isolated compounds are unique, rather than members of series of related compounds which illustrate fundamental chemical trends.

The bioutilty of bismuth and its compounds has a 250 year history, which is described in a number of key review articles,^{1–5} but the appearance of bismuth compounds in the British Pharmaceutical Codex,^{6–10} the French Pharmacopeia,¹¹ the German Pharmacopeia,¹² and the new Czechoslovakian Pharmacopeia¹³ is more recent. Some compounds have been approved for human use under the Federal Food, Drug, and Cosmetic Act¹⁴ for more than 30 years. After extensive use in the treatments of syphilis as well as other bacterial infections, the heavy metal label effected a decline in usage with the advent of antibiotics and incidents of reversible bismuth encephalopathy in France and Australia in the 1960s and early 1970s. Nevertheless, bismuth compounds remain important components of stomach remedies, such as Pepto-Bismol (bismuth subsalicylate, BSS) and De-Nol (colloidal bismuth subcitrate, CBS), and derivatives of CBS, such as ranitidine bismuth citrate (RBC), are currently under development.



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Neil Burford is a native of Liverpool, England. He obtained his B.Sc. Honors degree in 1979 from the University of Wales, College Cardiff, and his Ph.D. research was supervised by Professor T. Chivers at the University of Calgary. After a postdoctoral fellowship at the University of Alberta with Professor R. Cavell and a Research Associateship at the University of New Brunswick with Professor J. Passmore, he was appointed Assistant Professor at Dalhousie University in 1987. He became Full Professor in 1995, was awarded an Alexander von Humboldt Fellowship in 1996, and was appointed Killam Professor of Chemistry in 1998. His research is generally classified as synthetic chemistry involving the elements of group 15, with a focus on new structure and bonding.

This review provides an overview of the data available for bismuth compounds which have been discovered, developed, or designed to have biological

activity or medicinal utility, while botanical utility is outside the scope of this review. A number of compounds have been sufficiently well characterized to assign formulas accurately; however, a wide variety of materials, mixtures, or preparations containing bismuth have been examined and documented, many of which have ill-defined formulas or vague name designations. In section II, we catalog the use of bismuth and bismuth compounds in the treatment of various medical disorders and sections III–VII discuss and compare the chemical aspects of compounds for which definitive formulas or characterization data are available. Tables 7 and 8 are lists of compounds with literature references to each item of characterization data, and a more detailed and general overview of the structural features for bismuth complexes involving pnictogen and chalcogen donors is available.¹⁵

Illustrations of bismuth compounds are used to define connectivity and coordination number and are not intended to describe electronic structure or bonding; for example, Lewis drawings of these compounds are not meaningful or are misleading. In an attempt to provide a comprehensive chemical literature review, we have included reference to *Chemical Abstracts* for articles written in a language other than English or literature which was not available (e.g., patents and journals with low accessibility).

II. Bismuth Compounds in Medicine, Microbiology, and Pharmacology

The vast array of biological or medicinal activity that has been suggested or evaluated for compounds containing bismuth are presented in Tables 1–5 and include the preparation or compound name and formula where available. Many preparations are not definitively characterized so that the designations are sometimes vague, e.g., “bismuth” referring to a compound, “bismuth preparations”, or “bismuth compounds”. Other components of the preparations are given as well as the method of administration. The tables are intended as an introduction to give the reader an appreciation of the magnitude and diversity of the bioutilility of bismuth compounds and preparations.

Bismuth compounds are most commonly used for treating gastrointestinal disorders. The roles of CBS/TDB and BSS in gastric and duodenal ulcer therapy^{1,3,5,16–33} and the eradication of *Helicobacter pylori* (a bacterium associated with the pathogenesis of gastroduodenal ulcers)^{22,30,32,34–37} have been studied extensively. In addition to antimicrobial action, pharmacological studies suggest that the treatment and prevention of ulcers by CBS involves the fortification of gastric mucus and the stimulation of cytoprotective processes, such as the synthesis of endogenous prostaglandins and the secretion of mucosal bicarbonate.^{38,39} Clinical trials have been extensive, employing CBS or BSS alone or concurrently with H₂ antagonists and/or antibiotics. The treatment of travellers' diarrhea (BSS)^{17,22,32,40,41} nonulcer dyspepsia,^{20,28} nonsteroidal antiinflammatory drug damage,²⁰ and various other digestive disorders⁴² with bismuth-containing compounds has also been examined. The diversity

of bismuth compounds in medicine extends to the treatment of syphilis^{43–47} and tumors,^{48,49} in radioisotope therapies,^{50,51} in the reduction of the renal toxicity of cisplatin,⁵² and in pharmacy and other areas.^{33,53–57} Elemental bismuth has also been found in natural medicinal plants⁵⁸ and Chinese mineral drugs.⁵⁹

Tables 1, 2, and 3 catalog the application of bismuth compounds for the treatment of gastrointestinal, syphilitic, and other medical disorders, respectively. Inorganic salts and polycarboxylates of bismuth are most common, of which CBS and BSS have been most extensively used. The contents of Tables 4 and 5 overview the assessment of antimicrobial activity for bismuth preparations and compounds according to in vitro and in vivo investigations, respectively.

Table 6 is a list of reviews describing pharmacological studies, pharmacokinetic studies, and the toxicity of bismuth compounds. The absorption, distribution, and excretion of bismuth in animals and in the human body is usually assessed by determination of elemental bismuth concentrations in urine and blood by atomic absorption spectroscopy. The biochemical forms of bismuth have not been assessed, but it is clear that the highest concentrations of bismuth are in the kidneys and the liver, with trace amounts in the skeleton and other organs. As a heavy metal, the toxicity assumed for bismuth is not definitively confirmed, although there is association with neoparthy, osteoarthy, gingivitis, stomatitis, colitis, and hepatitis and cases of encephalopathy in France and Australia.

III. Inorganic Salts of Bismuth

Inorganic bismuth salts were the first compounds to be recognized for therapeutic utility; for example, bismuth subnitrate (BSN) was known as “magisterium bismuti”⁴³⁰ as early as the 17th century. A listing of compounds with medicinal relevance including assigned formulas and references to characterization data are given in Table 7. Some named compounds (e.g., subcarbonate and subnitrate) have a variety of formulas, which arise from the variable preparative procedures. Their designation as “sub” salts has likely been justified on the basis of high oxygen content and the assignment of Bi–O moieties. Some formula assignments are based on elemental analysis data and maybe overinterpreted. For example, bismuth hydroxides are sometimes written as BiO(OH) but could be bismuth oxide (Bi₂O₃) with variable water content.

Bismuth is mined as bismuth oxide (Bi₂O₃, “bismite”, also mined as bismuth sulfide Bi₂S₃, “bismuthinite”), which is also readily accessible from other inorganic bismuth salts (nitrate, subnitrate, subchloride, sulfate) by reaction with carbonates or alkali hydroxides,^{434,442,443,447,448,451,453,640} by hydrolysis,⁴⁴⁴ or by thermal decomposition.^{435,436,441} α -, β -, γ - and δ -Bismuth sesquioxide form at higher temperatures and have been studied extensively by DTA and X-ray and neutron powder diffraction. The crystal structure of the α -oxide⁴³¹ shows parallel layers of oxygen atoms in a pattern of three- and five-sided polygons,

with the corners bridged by bismuth atoms. The hydrated forms [e.g., $\text{Bi}(\text{OH})_3$ bismuth hydroxide, $\text{BiO}(\text{OH})$] have been studied at various pH values spectrophotometrically⁴⁵⁸ and polarographically⁴⁹⁸ and through electromigration of radionuclides.⁶⁴¹ Bismuth carbonate is formed from Bi_2O_3 with excess CO_2 or from $\text{Bi}(\text{NO}_3)_3$ with excess Na_2CO_3 or K_2CO_3 , and its composition is sensitive to reaction conditions, accounting for "light" and "heavy" terminology for bismuth subcarbonate and bismuth subnitrate in the pharmaceutical and medical literature.^{540,642} "Bismuth aluminate" has variable composition of Bi_2O_3 , Al_2O_3 , and H_2O , containing CO_2 in one instance. It is employed to combine the antacid properties of the basic bismuth and aluminum oxides.

Of the inorganic salts employed in medicine, only bismuth chloride, oxychloride, and nitrate pentahydrate have definitive compositions. Bismuth chloride (BiCl_3) and nitrate [$\text{Bi}(\text{NO}_3)_3$] are prepared from bismuth oxide by reaction with the corresponding mineral acids. The crystal structure of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ ⁵¹⁷ confirms the ionicity in the solid state, with one unique bismuth atom chelated symmetrically by two nitrate ions and asymmetrically by the third. Four-coordinated water molecules give a coordination number of 10 for bismuth. BiCl_3 ⁵⁶⁷ is molecular in the solid state, in which bismuth has three closely bound chlorine atoms ($\text{Bi}-\text{Cl}$ 2.468, 2.513, 2.518 Å) in a near pyramidal arrangement and five long chlorine contacts ($\text{Bi}-\text{Cl}$ 3.216–3.450 Å) for a trigonal prismatic eight-coordinate environment.

In weakly acidic to basic conditions, inorganic bismuth salts are hydrolyzed to the corresponding oxide products, commonly referred to as "basic," "oxy-," or "sub-" salts, with formation of the bismuthyl ion (BiO^+), which has a low aqueous solubility. In the case of bismuth oxychloride (BiOCl), solubility increases with acidity possibly due to the liberation of Bi^{3+} from BiO^+ by the hydronium ion,⁶⁴³ but the formation of anionic [BiCl_4]⁻ is also postulated on the basis that BiOCl is more soluble in hydrochloric acid than in nitric acid.⁶⁴⁴ Moreover, the solubility of BiCl_3 in nitric acid increases with addition of NaCl .

Complexation of bismuth(III) with the chloride ion has been studied by potentiometry,^{645–647,647,648} and hydrolysis of bismuth chloride^{649–652} reveals the formation of a variety of solid phases, $\text{BiOCl} \cdot 2\text{H}_2\text{O}$, BiOCl , and $\text{BiCl}_3 \cdot \text{H}_2\text{O}$,⁶⁵³ but only BiOCl has been comprehensively characterized (hydrolysis of bismuth subiodide has also been studied).⁶⁵⁴ The crystal structure of BiOCl ⁶¹⁴ shows one unique bismuth center surrounded by four oxygen atoms and four chlorine atoms in an asymmetric decahedral geometry.

Hydrolysis of bismuth nitrate seems to be more complicated, and the products are sensitive to precipitation conditions.^{539,541,558,655–657} Electrical conductivity⁵³⁷ experiments have prompted the speculation of various species in solution. A wide range of compounds have been isolated, and chemical analysis has been used to assign most formulas, which are written to illustrate proposed component units of the structures: $(\text{BiO})\text{NO}_3$, $(\text{BiO})\text{NO}_3 \cdot \frac{1}{2}\text{H}_2\text{O}$,⁴⁵⁴ $5(\text{BiONO}_3) \cdot \text{BiOOH} \cdot 4\text{H}_2\text{O}$,⁵²⁸ $\text{Bi}_2\text{O}(\text{NO}_3)_4$, $\text{Bi}_4\text{O}_5(\text{NO}_3)_2$,⁵³⁰ Bi_5O_7 -

(NO_3) ,^{531,532} $\text{Bi}_2\text{O}_3 \cdot \text{N}_2\text{O}_5 \cdot 2\text{H}_2\text{O}$, $10\text{Bi}_2\text{O}_3 \cdot 9\text{N}_2\text{O}_5 \cdot 7\text{H}_2\text{O}$,⁵³⁴ $[\text{Bi}_6\text{O}_6(\text{OH})_3](\text{NO}_3)_3 \cdot 2\text{H}_2\text{O}$, $[\text{Bi}_6\text{O}_7(\text{OH})_2](\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$,⁵³³ $\text{BiONO}_3 \cdot 2\text{H}_2\text{O}$, $2\text{BiONO}_3 \cdot \text{H}_2\text{O}$, $6\text{Bi}_2\text{O}_3 \cdot 5\text{N}_2\text{O}_5 \cdot 9\text{H}_2\text{O}$,⁵³⁵ $[\text{Bi}_6\text{O}_6(\text{OH})_3](\text{NO}_3)_3 \cdot 2\text{H}_2\text{O}$, $[\text{Bi}_6\text{O}_7(\text{OH})_2](\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$,⁵³⁶ $[\text{Bi}_6\text{O}_4(\text{OH})_4](\text{NO}_3)_6 \cdot 4\text{H}_2\text{O}$, $[\text{Bi}_4\text{O}_4(\text{OH})_4](\text{NO}_3)_6 \cdot \text{H}_2\text{O}$, $[\text{Bi}_6(\text{H}_2\text{O})(\text{NO}_3)_4(\text{OH})_4](\text{NO}_3)_5 \cdot \text{H}_2\text{O}$, $[\text{Bi}_6\text{O}_5(\text{OH})_3](\text{NO}_3)_5 \cdot 5\text{H}_2\text{O}$, $[\text{Bi}_6\text{O}_6(\text{OH})_3](\text{NO}_3)_3 \cdot 2\text{H}_2\text{O}$, $[\text{Bi}_6\text{O}_7(\text{OH})_2](\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$,⁵³⁸ $\text{Bi}(\text{OH})_2\text{NO}_3$,⁵³⁷ $\text{BiO}(\text{NO}_3) \cdot 0.5\text{H}_2\text{O}$, $\text{Bi}(\text{OH})_{3-x}(\text{NO}_3)_x$ ($x = 9-10$).⁵⁴¹ Solid-state structures have been determined crystallographically for $[\text{Bi}_6\text{O}_5(\text{OH})_3](\text{NO}_3)_5 \cdot 3\text{H}_2\text{O}$ ^{543,557} {empirical formula: $\text{Bi}_6\text{N}_5\text{O}_{26}\text{H}_9$; modified formula: $\text{BiONO}_3 \cdot 0.1\text{Bi}_2\text{O}_3 \cdot 0.9\text{H}_2\text{O}$ }, $\text{Bi}_6\text{O}_4(\text{OH})_4(\text{NO}_3)_6 \cdot \text{H}_2\text{O}$ ⁵⁴⁵ {empirical formula $\text{Bi}_6\text{N}_6\text{O}_{27}\text{H}_6$; modified formula: $\text{BiONO}_3 \cdot 0.5\text{H}_2\text{O}$; also independently determined as $[\text{Bi}_6(\text{H}_2\text{O})(\text{NO}_3)_4(\text{OH})_4](\text{NO}_3)_5$,⁵⁴⁴ and $[\text{Bi}_6\text{O}_4(\text{OH})_4](\text{NO}_3)_6 \cdot 4\text{H}_2\text{O}$ ⁴³⁰ {empirical formula $\text{Bi}_6\text{N}_6\text{O}_{30}\text{H}_{12}$; modified formula: $\text{BiONO}_3 \cdot \text{H}_2\text{O}$ }, whose empirical formulas are primarily distinguished by the degree of hydrolysis of the subnitrate, as indicated by the modified formulas. The structures are all composed of Bi_6O_8 polyhedral clusters involving an octahedron of bismuth atoms with oxygen atoms capping the octahedral faces, as illustrated in Figure 1. Therefore, the structural formulas indicate the

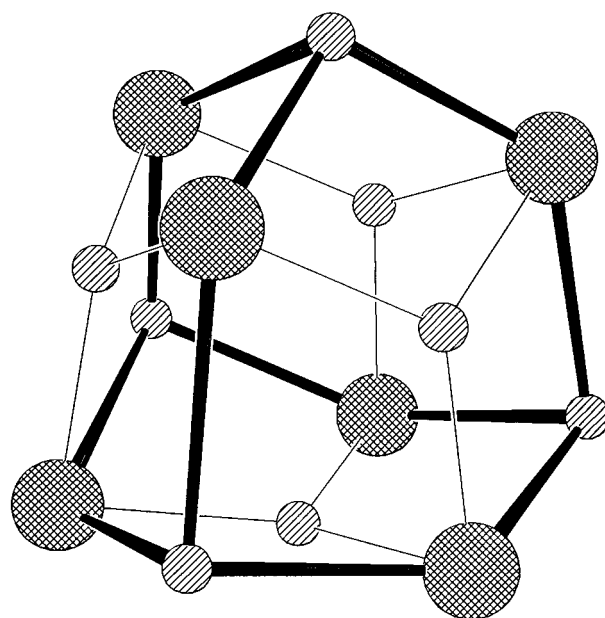


Figure 1. Bi_6O_8 cluster observed in the solid state for some bismuth nitrates (Bi -dark, O -grey).

degree of protonation of this cluster to give the cations $[\text{Bi}_6\text{O}_5(\text{OH})_3]^{5+}$ and $[\text{Bi}_6\text{O}_4(\text{OH})_4]^{6+}$. The former exists as water hydrogen-bonded dimers, while the more acidified compound is monomeric in the solid state. The same cationic unit is formed in the hydrolysis of bismuth perchlorate^{658,659} to give $[\text{Bi}_6\text{O}_4(\text{OH})_4](\text{ClO}_4)_6 \cdot 7\text{H}_2\text{O}$.⁶⁶⁰

IV. Bismuth Complexes of Hydroxycarboxylic Acids and Aminocarboxylic Acids

Despite the widespread medicinal use and biological assessment of bismuth subsalicylate evident in Tables 1–5, there is little documented chemical

Table 1. Treatment of Gastrointestinal Disorders Using Bismuth Preparations

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
General gastrointestinal	BSS	Veegun N, Keltral F, flavorants, sodium saccharin, KOH, colorants, water			60
General gastrointestinal	BSS	cimetidine, microcrystalline cellulose, sodium starch glycolate, magnesium stearate	clinical trial	tablet	61
General gastrointestinal	BSS	penicillin, Mg stearate,	most effective for bacterial induced disorders, e.g. Campylobacter-like organisms; clinical trial	tablet	62
General gastrointestinal	BSS		C. pylori-based; clinical trial		63
General gastrointestinal	bismuth compounds	ranitidine hydrochloride-form 1, nitazoxanide			64
General gastrointestinal	CBS	tetracycline-HCl, metronidazole	C. pylori associated infections; clinical trials		65
infections	BSS	amoxicillin	treatment of patients at risk of C. difficile infection; clinical trial	oral	66
infectious gastrointestinal disorders	BSS		H. pylori or similar organisms; clinical trial		67
gastrointestinal conditions e.g. duodenal ulcers, colitis, diarrhea	carbonate or BSN	3-hydroxy-N-(diethylaminoethyl)naphthyl-2-amide benzyl chloride, gum arabic, sirup, orange flavor, water			68
digestive diseases	BSN, silicate, polysilicate, aluminate, carbonate, alumino carbonate, BSG or salicylate	sorbitol	other drugs may be added	oral	69
nonulcer dyspepsia	TDB (De-Nol)	amoxicillin, cornstarch, magnesium stearate	disorder associated with C. pyloridis; clinical studies	tablet	70
digestive troubles	BSN	C(CH ₂ OH) ₄			71
gastric disease treatment	BSN	protein secretion from Helix family gastropod, mineral salt or an organic compound (e.g. sorbitol or tartaric or citric acids)			72
regulation of gastrointestinal digestion	BSN	BSN-CaCO ₃ -MgO ₂ -Ca lactate-5H ₂ O	BSN is Bi ₂ O ₃ · 4BiNO ₃ (OH) ₂ · Bi(OH)O	in water	73
antiulcer drug	citrate	potassium citrate, KOH	prep	oral; powder dissolved in water	74

Table 1 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
ulcers and gastritis	gallate	sodium dihydrogen citrate, PVP		oral; tablet	75
diarrhea in pigs and cattle	bismuth 8-hydroxy-quinoline salt	sodium 8-hydroxy-7-iodoquinolinesulfonate, basic aluminum salicylate, magnesium fumarate, sodium glutamate, excipient and flavor	clinical study		76
inflammatory bowel disease	bismuth carbopol complex	lactose, povidone, Na starch glycolate, magnesium stearate, talc, Eudragit L, antifoam emulsion SE-2		oral and rectal; capsules	77
H. pylori infection in non-ulcer dyspepsia	BSN	amoxicillin, metronizazole	mixture removed from stomach after 1hr to avoid side effects	nasogastric tube	78
age-related gastric lesions	CBS		rat studies		79
cinchophen induced gastric ulcers	carbonate		dog studies		80
gastrointestinal disturbances	BSN	kaolin			81
antidiarrhetic	Bi(OH) ₃	simple syrup, EtOH, oil of cinnamon			82
gastric ulcers	BSN (colloidal and ordinary)		rat studies		83
gastric mucosal lesion prevention	BSS		prevention of gastric mucosal lesions resulting from noxious stimuli; rat studies	slurry	84
gastric ulcer prevention	BSS		rat studies; prevention of aspirin induced ulcers		85
peptic ulcer disease	bismuth compounds				86
paradigestive circulatory troubles of nervous origin	BSN				87
H. pylori eradication from its various niches	subcitrate	other antibacterial compounds and/or antibiotics	e.g. from dental plaque, gastric mucosa, ocular and dermal wounds	topical, oral and peroral; chewing gum	88
H. hepaticus eradication	bismuth	amoxicillin-metronidazole or tetracycline-metronidazole	mice studies	oral	89
dyspepsias	BSN		clinical data		90
gastroprotective effect	carbonate	magnesium carbonate, calcium carbonate, silica gel	rat studies		91

Table 1 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
diarrhea	BSS	veegum, Me cellulose, loperamide · HCl, FD&C Red No. 3, FD&C Red No. 40, sodium saccharin, sodium salicylate, saicylic acid, Me salicylate, peppermint oil, water		oral liquid	92
diarrhea	"Bismustut" (nitrate)	aqueous protein derivative of serpent root (<i>Polygonum bistorta</i>)			93
diarrhea	BSS		mouse and rat studies		94
diarrhea	BSS	flavoring, coloring, magnesium aluminum silicate, methylcellulose	clinical trials		95
chronic diarrhea	BSS		clinical trials, infants and children	oral	96
chronic diarrhea	BSS		clinical trials, infants and children		97
acute diarrhea	BSS		clinical trials, children		98
acute diarrhea	BSS		clinical trials; comparison with loperamide hydrochloride	oral	99
acute diarrhea	BSS	salicylic acid, sodium salicylate	clinical trials, children		100
travelers' diarrhea	BSS		clinical trails		101,102
travelers' diarrhea	BSS		clinical trials	tablet	103,104
E. coli induced diarrhea	BSS		clinical trials		105
enteritis	BSN	semisynthetic glycerol fatty acid esters, vitamin C, rifampin		capsules	106
diarrhea, heartburn, nausea	BSS	magnesium aluminum silicate, Me cellulose, FD & C red no.4, FD & C red no.40, sodium saccharin, sodium salicylate, salicylic acid, Me salicylate, peppermint oil, benzoic acid, sorbic acid,	clinical trials	oral, tablet	107
upper gastrointestinal tract distress	bismuth containing drug	3-l-menthoxypropane-1,2-diol (MPD)		injection	108
upper gastrointestinal tract stress	BSS	microcryst. cellulose, croscarmellose Na, PVP, Mg stearate, polysorbate		oral	109
upper gastrointestinal tract disease	subcitrate	tetracycline antibiotics		oral	110

Table 1 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
gastrointestinal disturbances	BSS	Veegum, Me cellulose, red dye, sodium saccharin, sodium salicylate, salicylic acid, Me salicylate, peppermint oil, water		oral	111
disorders associated with gastric mucosal damage, ulcers, Campylobacter-associated gastrointestinal disorders (type B gastritis)	bismuth hydroxide sucrose octasulfate				112
gastrointestinal disease by pathogenic infection	subcitrate	Lactobacillus and/ or Bifidobacterium	clinical trials on Helicobacter patients	capsule	113
ulcer related H. pylori	colloidal citrate, subcitrate, CBS, salicylate, BSS, BSN, BSC, tartrate, BSG, aluminate		contains unspecified chewing gum components, bismuth salt as active ingredient	oral (e.g. chewing gums)	114
H. pylori	humic acid bismuth salt, BSC, subcitrate, BSS	metronidazole, and/or furaxone		dentifrice	115
Campylobacter-induced gastrointestinal disease	subcitrate	KOH-NH ₄ OH soln, tripotassium citrate-citric acid soln	single dose contains 120mg Bi ₂ O ₃		116
Hp induced gastritis	citrate	amoxicillin, PVP, microcrist. Cellulose, Na-CMC, Mg stearate, colloidal SiO ₂		tablet	117
ulcers/ Hp related infections	BSS, citrate	nitazoxanide, ranitidine			118
duodenal ulcers	citrate	K citrate, carmine, pepsin, sucrose, poly(vinylpyrrolidone)			119
ulcers, esp. visceral ulcers	bismuth ammonium citrate	pepsin, carmine, sugar cane	starting material had no appreciable activity against ulcers in animals, good activity in preparation		120

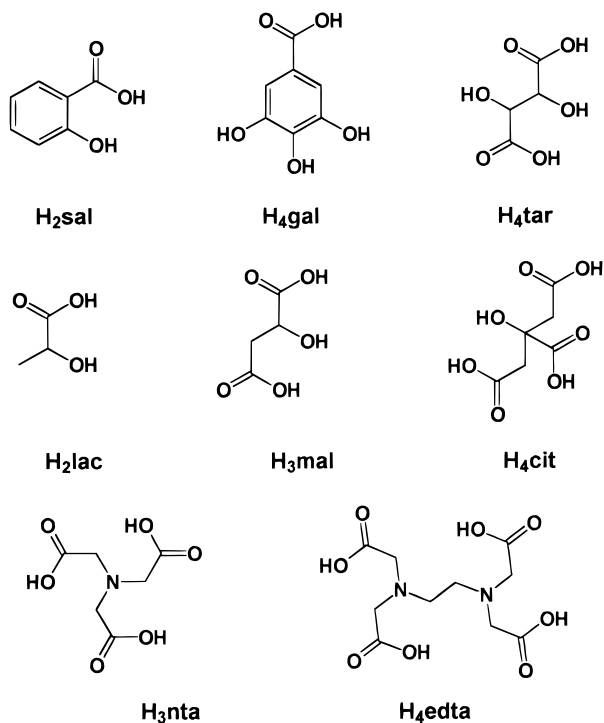
Table 1 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
gastric ulcers (pepsin), duodenal ulcers (trypsin or chymotrypsin)	bismuth pepsin/ trypsin/ chymotrypsin complex	bismuth citrate, pepsin/ trypsin/ chymotrypsin, water, aq. Chloroform BP, liq. Azorubri BPC or carminic acid, potassium citrate, simple syrup, NH ₄ OH	gastric ulcer patient clinical trials with pepsin prepn.	tablets, capsules	121
stomach ulcers	bismuth citrate	NH ₄ OH, proteins (pepsin, ovalbumin, α-casein, trypsin, chymotrypsin), Carmine dye in CHCl ₃ , potassium citrate, simple syrup, H ₂ O	>3 mg Bi/mL, 4x5mL doses daily		122
gastric and duodenal ulcers, gastritis	BSS "Magnesio-Bismuthin"	magnesium oxide, papaverine hydrochloride	DTA studies, Polish product	tablet	123
gastric and duodenal ulcers, gastritis	BSN "Gastrin"	magnesium subcarbonate, sodium hydrogen carbonate, plant components	DTA studies, Polish product	tablet	123
gastric and duodenal ulcers, gastritis	BSN "Gastro"	magnesium subcarbonate, plant components	DTA studies, Polish product	tablet	123
dyspepsia, digestive disorders, gastroduodenal ulcers, colopathies, enteropathies, diarrhea, constipation, hepatobiliary and nutritional conditions	BSN	sorbitol or pentaerythritol			69
gastritis, gastric and duodenal ulcers, hypostenic dyspepsia, fermentaion cholites, secondary diseases of gastrectomy	BSN	metoclopramide, dried starch gum, sodium bicarbonate, sodium lauryl sulfate, ethylvanillin, Mg stearate, Na alginate,		tablets	124
gastrointestinal ulcers, gastritis, diarrhea	phytate, BSN	guar gum		cream	125
digestive tract diseases	BSN	sorbitol, KOH, pectin	reactants form "bismuth pectin gels"	tablet, other forms	126
medicament (stomach)	BSC (BiO) ₂ CO ₃	sucralfate, HCl(aq), water			127
soluble medicament, release delaying agent					
gastrointestinal disease, wound healing, hemostatic agents	base nitrate	alginic acid	clinical studies on ulcer patient		128

Table 1 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
gastrointestinal diseases	BSN	guar gum, pectin or sorbitol			129
cicatrizacion promotor, disinfection of sores, gastric ulcers	neutral bismuth phosphate (BiPO ₄)	ointment - H ₂ O, glycerol, or propylene glycol; gum arabic, gum tragacanth, gum acacia, carob flour, carboxymethyl cellulose, a polysaccharide, or a polysiloxane; dusting powder - ZnO and tannin; gastroenterology - antispasmodics, barbituate sedatives, antipeptic substances, antibiotics, fermentation inhibitors	toxicity is slight; gastric ulcers tests with rats and humans	ointment; dusting powder	130
gastritis, duodenitis, ulcer	phosphate gel	Bi subnitrate, HNO ₃ , H ₃ PO ₄ , water	no clinical data		131
gastroenterology	oxynitrate	sorbitol, NaHCO ₃		suspension, tablet, capsule, emulsion	132

characterization data for compounds formed between bismuth and salicylic acid, H₂sal. Although assess-



ments of bioactivity for preparations involving mixtures of bismuth with other hydroxycarboxylic acids or aminocarboxylic acids are less common, complexes of the conjugate bases of gallic acid (H₄gal), tartaric

acid (H₄tar), lactic acid (H₂lac), malic acid (H₃mal), citric acid (H₄cit), nitriloacetic acid (H₃nta), and ethylenediaminetetracetic acid (H₄edta) have been characterized in some detail as listed in Table 8. The polyprotic nature of these ligands and the lability of the carboxylate–bismuth interaction are responsible for a wide variety of compounds, some of which have been extensively characterized and others that have been speculated as components of mixtures. Complexes are readily obtained from reactions of inorganic bismuth salts (usually nitrate) with the acid or an alkali salt of the acid. The products are usually sensitive to the reaction conditions, and in some cases a wide range of formulas have been isolated from a given system. For example, a variety of formulas have been isolated or proposed to exist in the bismuth tartrate system,^{661–670} including mixed cation systems, involving an alkali metal or ammonium cation in addition to bismuth.^{671–685}

Solutions containing bismuth tartrate complexes and bismuth malate complexes have been examined by a variety of techniques (solubility,⁷⁴⁷ spectrographic,⁷⁴⁸ optical rotation,⁶⁸¹ visual,⁷⁴⁹ ¹H NMR,⁶⁸³ polarimetric,^{681,748,750} potentiometric,^{751–754} polarographic,^{751,755–757} electrometric,^{750,758} and oscillography⁷⁵⁷) to determine compositions^{747,751} and stability constants.^{759,760} More numerous solution studies are reported for aminocarboxylate complexes, which have been prompted by their higher stability (stability constants > 10²⁰)⁷⁵⁴ imposed by the greater denticity of the ligands (spectrophotometric,^{761–766} IR,⁷⁶⁷ NMR,⁷⁶⁷ Raman,⁷⁶⁸ UV–vis,^{738,769} electrometric

Table 2. Treatment of Syphilis Using Bismuth Preparations

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
gonorrhea, other therapeutic purposes	oxide-iodide	bismuth and potassium double iodide, lactic acid, H ₂ O	solution may be used with ointment bases		133
syphilis and yaws	bismuth sodium potassium tartrate		comparison with neokharsivan		134
neurosyphilis	bismuth sodium tartrate	tryparsamide			135
neurosyphilis	bismuth			intraspinal	136
endemic syphilis	bismuth				137
acute syphilitic orchitis	sobisminol solution, potassium bismuth tartrate		rabbit studies	oral, intramuscular injection	138
late syphilis	salicylate	oil; arsphenamine, neoarsphenamine or mapharsen			139
syphilis	bismuth sodium tartrate "Bismocillin"	benzathine, penicillin	synergistic effects	injection	140
syphilis	bismuth salts	bicillin-3	clinical data		141
syphilis	sodium and potassium tartrobismuthate		rabbit and guinea pig studies		142
syphilis	ammonical bismuth citrate, sol. Bismuth lactate, BSG, oxyiodogallate		rabbit studies		143
syphilis	tartratobismuthate of potassium and sodium				144
syphilis	basic α -carbethoxy- β -methylnonanoic acid bismuth salt "bivatoI"		mouse studies		145
syphilis	bismuth quinine iodide	CHCl ₃ , eucalyptus oil, lecithin	pharmacology	injection	146
syphilis	metallic bismuth		cream containing metallic bismuth	injection in buttock	147
syphilis	basic tartro-bismuthate, metallic bismuth, potassium and sodium tartro-bismuthate, proteo-bismuth compound, 3,4-AcNH(HO)C ₆ H ₃ AsO ₃ H-Bi(OH) ₂		pharmacology	intravenous	148
syphilis	bismuth metal		rabbit studies		149
syphilis	bismuth hydrate "Casbis"	oil suspension			150
syphilis	iodobismitol Na ₂ BiI ₅		rabbit studies; clinical trials		151
syphilis	chloride (bismutate)		rabbit studies	oral	152

Table 2 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
syphilis	bismuth chloride, bismuth sodium iron citrate, potassium bismuth tartrate		rabbit studies; all were ineffective	oral	153
syphilis	$C_6H_3(OH)(NHCOCH_3)A$ $sO_3Bi(OH)_2$ "bistoval", bismuth arsanilate, bismuth tryparsamide	oil		intramuscular injection, oral	154
syphilis	bismuth				155
syphilis	bismuth sodium tartrate, bismuth ethyl camphorate, iodobismitol, bismuth sodium citrate, thiobismol		comparison of several bismuth compounds in rabbits	intravenous and intramuscular injection	47
syphilis	bismuth	terramycin	rat studies; less effective than bismuth-penicillin treatment		156
syphilis	bismuth compounds		mice studies		157
syphilis	sobisminol solution			oral	158
syphilis	salicylate	terramycin hydrochloride, mapharsen	synergistic effects	intramuscular	159
syphilis	bismuth preparations	arsenical drugs			160
syphilis	sodium bismuthate "Sobisminol"	tri-isopropanolamine, propylene glycol	clinical trials; pharmacology	oral, capsule	161
syphilis	organic hydroxy acid Bi salt "Pentabismol"		rabbit studies; clinical trials; physical data on "pentabismol"		162
syphilis	bismuth	penicillin	no interference or synergism		163
syphilis	iodobismuthite "Iodobismitol"	NaI, propylene glycol, saligenin	clinical trials		164
syphilis	bismuth preparations	penicillin, K orotate, methylandrostenediol, hydrolysine, aminopeptide			165
syphilis	basic bismuth acetoxaminophenyl- arsenate				166
syphilis	bismuth				167
syphilis	bismuth		mode of application studies; comparison with As and Hg		168
syphilis	bismuth acetoxaminophenyl- arsenate		rabbit studies; synergistic effects with As	injection	169

Table 2 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
syphilis	bismuth acetoxyaminophenyl- arsenate		clinical trials		170
syphilis	bismuth compounds				171
syphilis	bismuth				172
syphilis	basic bismuth α - methylhydrocinnamate				173
syphilis	bismuth-protein preparations		clinical trials		174
syphilis	basic bismuth camphocarboxylate "bismo-cymol"	olive oil			175
syphilis	metallic bismuth "neo- trepol"		colloidal solution of bismuth metal	intravenous	176
syphilis	potassium bismuth tartrate		comparison to Hg compounds; pharmacology in rats and rabbits	oral	177
syphilis	bismuth		therapy in infants		178
syphilis	bismuth sodium p- aminophenylarsonate		compound is combination of bismuth subgallate and p- aminophenylarsonate; rabbit studies, pharmacology	intramuscular injection	179
syphilis	"bismuthoidal", "bismudol", iodobismuthate		rabbit studies; total of 12 commercial bismuth preparations studied	intramuscular injection	180
syphilis	Bi-Hg electrocolloid				181
syphilis	bismuth dihydroxybenzoate monomethyl ether "mesurol"				182
syphilis	bismuth ethyl octylmalonate "bivatol"	penicillin methyl ester	studies in rabbit mouse, man		183
syphilis	bismuth		clinical trials		184,185
syphilis	sodium potassium tartratobismuthate	liver extract	clinical trials		186,187
syphilis	bismuth				188
syphilis	bismuth		effect of arsenic compounds		189,190
syphilis	bismuth		clinical trials, summary		191
syphilis	sodium iodobismuthite	NaI, ethylene or propylene glycol		intramuscular injection	192

Table 2 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
syphilis	citrate, lactate, subgallate, oxyiodogallate, sodium tartrobismuthate, potassium tartrobismuthate				193
syphilis	complex amino acid-bismuth salt of oxytricarballic acid "Bismutate"	sacch. alb., talcum, stearic acid, oleum anisi, succus glycyrr.	clinical trials	lozenges, oral	194
syphilis	BSN	Na and K tartrate, nitric acid, sodium bicarbonate	rabbit studies; clinical trials	injection	195
syphilis	salicylate "Agoran"	rape oil, camphor, phenol			196
syphilis	Bi oxide hydrate, sulfamide salt, p-glycoloylaminobenzene-arsenate	hydrophilic colloids - pectin, alginates, cellulose ethers, polyvinyl compounds, salts of (polyacrylic acid) [e.g. Bi oxide hydrate, Na cellulose glycolate, urea, water (dispersed by colloid mill or supersonic)]	studies of syphilis in rabbits, specific viscosities given		197
syphilis	sodium bismuthate "Sobisminol"	triisopropylamine, propylene glycol (solution contains water)	review of pharmacological and clinical data on animals and humans	injection (solution), oral (solid)	198

titration,⁷²⁹ pHmetric,⁷⁷⁰ metric,⁷⁷⁰ polarographic,^{756,761,771-775} potentiometric,^{754,776-779} and isotope exchange⁷⁸⁰. Complexes of thioglycolic acid,^{781-784,784,784} which have been assessed for absorption and toxicity in rats,⁷⁸⁴ have been characterized by UV-vis spectroscopy.⁷⁸⁵

Solid-state structures determined by single-crystal X-ray diffraction studies confirm the formulas in specific cases and reveal important features of structure and bonding at the bismuth center and regarding the molecular, oligomeric, or polymeric nature of the compound. The citrate complexes have been most extensively examined and are discussed in detail in section V. Isolated examples involving other ligands have been reported.

The tartrate complexes $\text{NH}_4[\text{Bi}(\text{H}_2\text{tar})_2(\text{H}_2\text{O})]\cdot\text{H}_2\text{O}$ ⁷⁰⁴ and $\text{Bi}(\text{H}_3\text{tar})(\text{H}_2\text{tar})\cdot 3\text{H}_2\text{O}$ ⁷⁰³ have distinctly different formulas, the former mixed cation salt representing a replacement of one proton of the triprotic tartrate ligand of the latter by an ammonium ion. Nevertheless, these structures contain a similar asymmetric unit in which two tartrate ligands chelate bismuth by means of a carboxylate and a hydroxy donor, as illustrated in Figure 2. Bismuth adopts a coordination number of nine by engaging two additional chelate tartrate ligands from neighboring asymmetric units and the oxygen atom

of a water molecule, imposing a trigonal prismatic geometry. Lattice water molecule(s) (and the ammonium ion) are responsible for intermolecular hydrogen bonding to give one-dimensional coordination polymers.

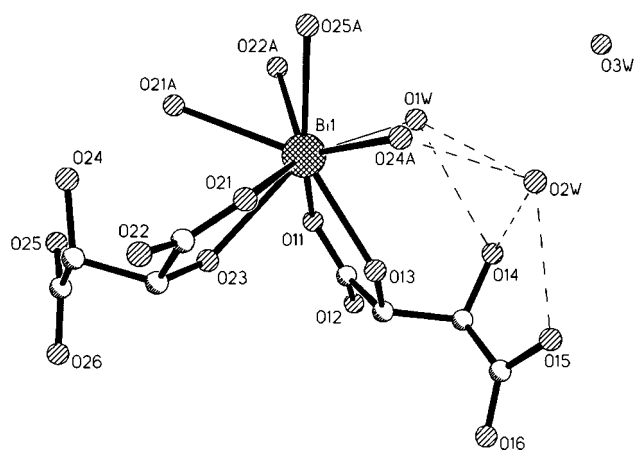


Figure 2. Asymmetric unit for $\text{Bi}(\text{H}_3\text{tar})(\text{H}_2\text{tar})\cdot 3\text{H}_2\text{O}$.

A three-dimensional polymeric structure is observed for the only crystallographically characterized bismuth lactate complex $\text{Bi}(\text{Hlac})_3$.⁷⁰⁸ Bismuth is bound by three carboxylate/hydroxy chelates (five-

Table 3. Treatment of Other Medical Disorders Using Bismuth Preparations

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
exanthema, vehicle for arspenamine/neoarphenamine	complex galactoglucuronic acid basic bismuth sodium salt "bismuth-diasporal"	glucose solution		intragluteal, subcutaneous or intravenous injection	199,200
hemorrhoids, anal fissures	BSN	PhOH, menthol, starch, dibucaine or benzocaine, lanolin- and petrolatum base	provides protective coating for treated tissues, relax spasm and improve blood circulation and healing	paste	201
mastitis in cattle	BSN	acriflavine, distilled water, white beeswax, white soft paraffin, procaine penicillin G	injection into teat canal		202
medicinal	hydrolysed bismuth chloride	glucose, CH ₂ O, suitable alkali		intramuscular injection	203
medicinal	camphanilanic acid bismuth salt	olive oil, salicylic acid			204
medicinal	bismuth carbonate	CaCO ₃ , basic MgCO ₃ , water, NaHCO ₃ , 95% alc.			205
medicinal	BSG	oil		enemata	206
medicinal	alkali metal bismuth tartrate	aqueous hypertonic sugar solution	compatible with blood, sufficiently stable to allow absorption and distribution in body before decomposition		207
medicinal	lactate	alkali lactate, alkali solution, glycerol			208
microbicidal	Bi ³⁺	aluminosilicate (zeolite or amorphous), resins			209
antibacterial	Bi ₂ (CO ₃)O ₂	sulfaethoxypridazine, ethyl cellulose	pharmacological studies in cattle	oral	210
germicides in skin diseases, wounds, abrasions, burns; therapeutic agents; preparation of potable and sterile water; production of selfsterilizing surfaces on various materials	Bi ₂ O ₃	Ag ₂ O, Ag ₂ CO ₃ , or other basic silver compounds	complexes are more active than simple silver compounds; do not substantially denature proteins; not true compounds in a chemical sense		211
ophthalmic	tetrabromopyrocatechol	unguentum alcoholium lanae, Eucerinum anhydricum, or lanolin		ointment	212
pharmaceutical prepn	sodium bismuthyl polygalacturone	gelatin or gum arabic, maize starch, Mg trisilicate, Al(OH) ₃ or MgCO ₃		tablet	213

Table 3 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
pharmaceutical	subcitrate	micronized guar gum, lactose, Et cellulose, hydroxypropyl cellulose, talc		tablet	214
pharmaceutical	basic bismuth inositol hexaphosphate	guar gum		cream	215
therapeutic	oleate, tartrate, linolate	olive/almond oil		injection	216
therapeutic	metallic Bi, water insoluble Bi compounds	higher alcohols, plant oils		injection	217
therapeutic	iodide	thiamin		injection	218
therapeutic	hydroxy polybasic acid organic base bismuth double salt	tartaric, citric, or malic acid; bismuth compound, diethylamine, diethylaminoethanol, (CH ₂) ₆ N ₄ or piperazine; alcohol; glucose solution			219
therapeutic	Bi salts [other than Bi(OAc) ₃]	mineral acid, lactates, alkali			220
antiluetic	subiodide	sunflower-seed oil	prep (see table 7)	injection	221
counteraction of toxic effects of ingested ethyl alcohol	BSN	calcium acetate, sorbose	in vivo (rats)	powder, granules, or drinkable suspension	222
antismoking aid	basic bismuth nitrate	organic Ag salt, quinine-HCl, MgO, Na benzoate, pseudonicotine, vitamin B ₁ , NaHCO ₃ , poly(vinyl acetate) chewing gum base		chewing gum	223
anti-inflammatory	hydroxide, sulfate, carbonate, bicarbonate, or BSC	nonsteroidal systemic anti-inflammatory	cytoprotective action in rats		224
anti-inflammatory	BSN "Bismutannal"	albumin tannate, plant component	DTA studies	tablet	123
chronic amebic infection of the bowel	Kurchi bismuthous iodide		case histories		225
preventative antiamebic treatment	glycolylarsanilate "Milibis"				226
antiamebic	glycolylarsanilate "Milibis"		clinical trials; action against Entamoeba histolytica		227
angina	bismuth				228
angina (streptococcic)	Bi(OH) ₃	oil	oil suspension of Bi(OH) ₃ is referred to as "Casbis"		229

Table 3 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
agranulocytosis	bismuth compounds	arsphenamine			230
arthritis	bismuth		experimental arthritis in rats		231
biomaterial powders	carbonate	auto-hardening tricalcium phosphate containing insoluble fluorides, magnesium compounds	bismuth carbonate as x-ray contrast agent		232
biological stain	$\text{Bi}(\text{NO}_3)_3$	HNO_3 , Me_2CO	staining of bovine nasal septal cartilage; $\text{Bi}(\text{NO}_3)_3$ in acidic solution		233
biological stain	BSN	uranyl acetate			234
biological stain	bismuth solution		staining of paraformaldehyde-fixed Calpodes tissues		235
biological stain	bismuth salts		staining of aldehyde-fixed tissues		236
bone substitute material	bismuth compound	polymer	bismuth compound as filler particles		237
carcinoma	bismuth		in combination with x-ray therapy causes temporary improvement		238
colitis	BSN		activity in cats		239,240
distal ulcerative colitis	bismuth citrate and polyacrylate complex		clinical trials	enema	241
<i>Clostridium difficile</i> colitis	BSS		hamster study	orogastric intubation	242
catabolic disorders (AIDS related)	oleate	sesame oil	clinical trials		243
colds	bismuth	nose drops, argyrol, aspirin			244
diaper rash (diaper dermatitis)	BSN		not recommended by US FDA		245
control of antibiotic side effects	hyponitrite	corn starch, lactose, Mg stearate,		tablet	246
treating withdrawal from drug addictions	BSN	atropine, borneol, <i>Zanthoxylum nitidum</i> , <i>Datura stramonium</i> flower, <i>Aconitum carmichaeli</i> , cystine, <i>Bungarus multicinctus</i> , <i>Scolopendra subspinipes multillans</i> , <i>Buthus martensii</i> , <i>Officinale</i> , Realgar, glycyrrhizic acid, <i>Angelica sinensis</i> , deoxycholic acid, muskone, bufotoxin, honey		tablet	247
diuretic	bismuth metal, potassium bismuth tartrate, bismuth salicylate	dextrose, oil	clinical trials	injection; oral	248

Table 3 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
fistulous tracts, tuberculous sinuses, abscess cavities	BSN	vaselin, white wax, soft paraffin	clinical trials	paste, injection	249
simple or sporadic goiter	bismuth salts				250
hepatitis and typhlitis	bismuth drugs	amoxycillin-metronidazole or tetracycline-metronidazole	activity in mice; diseases associated with <i>Helicobacter hepaticus</i> infection		251
hyperhidrosis of the feet	salicylate	spirits of camphor, talc, zinc	can prevent secondary symptoms	rub	252
hemorrhagic icterus	bismuth		prevents <i>Spirochaeta icterohemorrhagiae</i> in guinea pig; activity against disease		253
quartan malaria	sodium bismuth thioglycolate		human clinical trials	injection	254
malaria	thiobismol		effective against <i>P. vivax</i> , ineffective against <i>P. malariae</i> and <i>P. falciparum</i> infections		255
mouthwash	(BiO) ₂ CO ₃	Na ₂ HPO ₄ , citric acid monohydrate, tartaric acid, NaHCO ₃ , KHCO ₃ , saccharin, aluminum dihydroxy allantoinate, synthesized cinnamon, allantoin proteinate, flavoring agent	effervescent	mouthwash; loose powder or tablet added to water	256
rabies	bismuth thioglycolate		activity in rabbits	intravenous injection	257
upper respiratory spirochete infection	bismuth sodium tartrate			injection	258
treponemicial	bismuth metal	arsenic	pharmacological data for guinea pig; human clinical trials	injection	259
trypanosomiasis	bismuthoidol		ineffective against <i>Trypanosoma cazalboui</i> and <i>T. congolense</i> , effective against <i>T. brucei</i> in vivo in animals		260
suppurative tonsillitis	bismuth salt of heptadienic acid "medobis" Chinoïn		"medobis" is stabilized oily solution of bismuth salt	intramuscular injection	261
adeno-tonsillectomy	BSG	adrenaline, saline	clinical trials		262
tonsillectomy	BSG	adrenaline, saline	clinical trials		263,264
verrucae	bismuth sodium thioglycolate	procaine solution		injection	265
Weil's disease	bismuth-yatren		treatment in guinea pigs		266
	bismuto-yatren, "Bismogenol", French tryparsol preparations		treatment in guinea pigs		267

Table 3 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
wound dressing	BSN	merbromin, imidotetraethyldiaminodiphenylmethane-HCl, Hg(II) amide chloride, ZnO, HgO, panthenol, bolus alba	clinical trials	impregnated sponge	268
wounds	BSN "Bipp"	iodoform, paraffin liquid	clinical trials	topical	269
whipworms in dogs	bismuthyl-N-glycolylarsanitate (glycobiarsol), Milibis-V			tablet	270
warts	sodium bismuth triglycollamate "Bistrimate"		clinical trials	tablets, oral	271
leukemia	6-mercaptopurine salt		activity in mice		272
cancer	BSN	lentinan, interleukin-2, indomethacin, 5'-DFUR	activity in mice		273
cancer	bismuth compounds		activity in mice	injection	274
cancer	bismuth ammonium tartrate		activity in rats	injection	275
cancer	colloidal bismuth		activity in rabbits in combination with x-ray therapy	intravenous, intramuscular or intratumoral injection	276
cancer	bismuth-yatren-A		activity in animals and humans		277
cancer	bismuth ammonium citrate cum pepsino	syrupe simplex, cochineal dye, potassium citrate, NH ₄ OH			278
cancer	colloidal bismuth		activity in rabbits	intravenous, intramuscular or intratumoral injections	279
leukemia	bismuth 6-mercaptopurine complex		rat studies	intraperitoneal injection	280
dental alloys	bismuth	In, Sn, and possibly Ba, Cd, Mg, Sb, Ca, Li or Pb	substitution for Hg amalgams		281
dental filling materials	Bi ₂ O ₃	MgO, quartz sand, ammonium molybdate, zinc oxide			282
dental cements	Bi ₂ O ₃	poly(vinylphosphonic acid)			283
dental cements	Bi ₂ O ₃	substituted oxaloacetic acid diethylates (di-ethyl oxosuccinates), β-keto esters, guaiacols, salicylaldehydes or 8-quinolinols (eg. 7-propyl-8-quinolinol)	determination of cement-forming properties of resulting chelates		284

Table 3 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
dental cements	Bi ₂ O ₃	ZnO, MgO, CaF ₂ or NaF, H ₃ PO ₄ , aluminum phosphate, water			285
dental material	Bi ₂ O ₃	SiO ₂ , Ca(OH) ₂ , Al ₂ O ₃ , MgO, MoO ₃ , Na ₃ AlF ₆ , ZnO, NaF, acrylic acid copolymer			286
dental cavity liners	BSN or (BiO)CO ₃	Ca(OH) ₂			287
radiopaque material for dental plastics	BSC	acrylic resin denture bases	effect of bismuth subnitrate on color change, compatability and radiopacity of dental plastic		288
dental paste	BSN	collagen, methyluracil, eugenol, ZnO			289
dental alloy	bismuth metal	In, Sn; Pt, Pd, Rh, Ir, Os, Ru, Ta, Ti, Zr, Re, W, Mo, Fe, Ni, Co, Cr, Hf, V, and/or Y; Ag, Al, Zn, Au, Ba, Cd, Si, Sb, Mg, Ca, Li, and/or Pb; Ga	amalgam substitute		290
prosthetics and dental materials	bismuth	calcium phosphates (eg. tetracalcium phosphate, tricalcium phosphate, hydroxyapatite); possibly Ba, Zr, Sr, and/or Si			291
erythemetic lupus	bismuth			injection	292
lupus erythematosus	bismuth metal		clinical trials	intramuscular injections	293,294
lupus erythematosus	bismuth "Bivatol"		clinical trial		295,296
hypertensive arterial disease	BSN		liberation of nitrate ions dilates arteries		297
arterial hypertension	BSN		intensity and duration of effect directly related to dose	oral	298
arterial hypertension	BSN		clinical trials	oral	299,300
arterial hypertension	BSN		clinical trials	oral, capsule	301
hypertension	BSN		modes of action are reduction of Cl in blood by NO ₃ induced diuresis and release of NO ₂		302
arteriolar hypertension	BSN		clinical trials	pill	303
veterinary skin diseases	BSG	white petrolatum, AcOH, peppermint, sesame seed oil, ZnO, p-H ₂ NC ₆ H ₄ CO ₂ Et, CHI ₃ , acrinol		ointment	304

Table 3 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
tuberculosis	2-mercaptobenzothiazole bismuth salt	and/ or 2-mercaptobenzothiazole Mn salt	in vivo in mice	injection	305
antacid	(BiO) ₂ CO ₃	beef tallow, glyceryl monostearate, glyceryl monooleate, propylene glycol monostearate, or vegetable oils, C ₈ aliphatic hydrocarbons with reacting or neutral amino groups		oral	306
antacid	oxynitrate	Al phosphate, liquorice juice	may be used to treat gastrointestinal disorders without side-effects, e.g. diarrhoea		307
antacid	bismuth salts		discussion of use and abuse of antacids		308
antacid	bismuth salt	Al ₂ (OH) ₃ Cl, Na ₂ CO ₃	prep is a cogel	wet or dry	309
antacid	salt	powdered carbonate or bicarbonate, organic acid			310
antacid	phosphosilicates	mean composition BiMg ₈ Al ₁₄ Na _n (SiO ₄) ₁₆ (PO ₄) ₆	adsorbant for gas toxins, cholesterol		311
antacid, demulcent	citrate	NH ₃ , H ₂ O, phenol, glycerol		internal	312
MRI and x-ray imaging	6-carboxymethyl-3,9-bis(2-fluoroethyl-carbamoylmethyl)-3,6,9-triazaundecadicarbonic acid bismuth complex				313
x-ray contrasting medical tubes	white Bi compound (83-88% Bi)	ethylene-tetrafluoroethylene copolymer			314
radiopaque acrylic resins	bismuth compounds	methyl methacrylate-based systems (e.g PMMA)	materials suitable for dental devices		315
MRI, x-ray and radiation diagnosis imaging agents	bismuth metal	cyclodextrin, monosugar oxidative degradation products			316
x-ray contrast media	BSN	PbSO ₄	for examination of precapillaries and capillaries of bone tissue		317
contrast media	di-sodium bismuth diethylenetriaminepenta-acetate (Bi DTPA)		pharmacology and effectiveness in dog bronchograms and cardiograms		318
radiopaque dental and medical materials	BiBr ₃	poly(vinyl acetate)	useful as resins, in fabricating appliances, prosthetic and radiation shielding devices, radiopaque polyester clothing fabrics		319

Table 3 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
scintigraphy	bismuth metal	$^{203}\text{Tl}^m$, ascorbic acid	Bi gives increased concentration of activity in kidney		320
radioscopic exam of stomach	carbonate	gum arabic, gum tragacanth, simple syrup, water, orange flowers water			321
biol. inert, atraumatic, highly elastic and x-ray contrasting intrauterine contraceptive devices	oxide	high-mol. Plasticizer, polyisobutylene, polyethylene, internal lubricant			322
Other	magistery of bismuth (BSN)	neutral glycerol, water	substitute for iodoform gauze	gauze	323
	BSN "resorcinol"	$\text{C}_6\text{H}_4(\text{OH})_2$, ZnO	composition analysis	ointment	324
	BSN	sucrose, EtOH		oral	325
	basic bismuth nitrate	NaHCO_3 ; concd. sugar solution; alcohol, water, starch paste or gelatin solution		tablet	326
	BSS	olive oil, water		intramuscular injection	327
	colloidal bismuth	ascorbic acid	ascorbic acid is an antioxidant and inhibits foaming	injection	328
	soluble Bismuth compounds	α -campholenic acid, alkali, sorbitol, oil		injection	329
	BSS	microcryst. Cellulose, CaCO_3 , mannitol, sodium starch glycolate, PVP, magnesium stearate, Polysorbate-80, silica, dye		tablets, capsules, chewable tablets	330
	BSS	microcryst. Cellulose, CaCO_3 , CaCl, sodium starch glycolate, magnesium stearate, povidone, dyes	unit dose form	caplet	331
	BSS	Plasdone XL		tablets	332
	bismuth oxyiodogallate		method of prep described	suppository	333
	oxychloride			injection	334

Table 3 (Continued)

Medical disorder	Compound/preparation designation or formula	Other components/reactants	Comments/data	Method of administration	Ref.
	bismuth tartrate (mist. Bismuthi comp. cum pepsino)	stronger glycerin of pepsin, soln of styrcnine, tincture of cudbear, dil. HCN, CHCl ₃ -H ₂ O (several variations, include carmine, tincture of nux vomica)	in the British Pharm. Codex		7-10,335
	tartrate	Bi(OH) ₃ , NaOH, H ₂ O, tartaric acid, phenol, glycerol		local injection	336

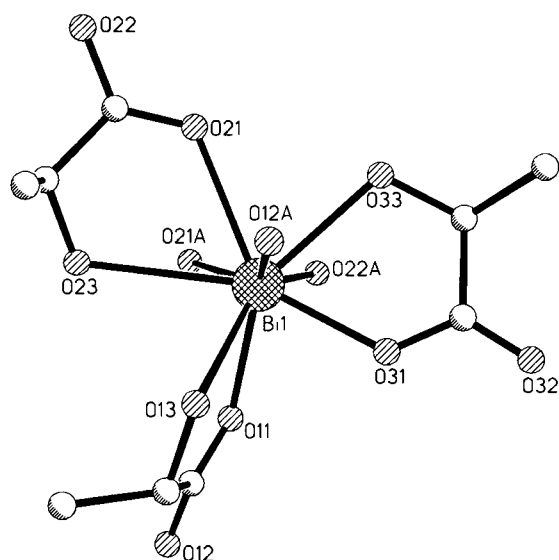


Figure 3. Coordination sphere of bismuth in the solid-state structure of Bi(Hlac)₃.

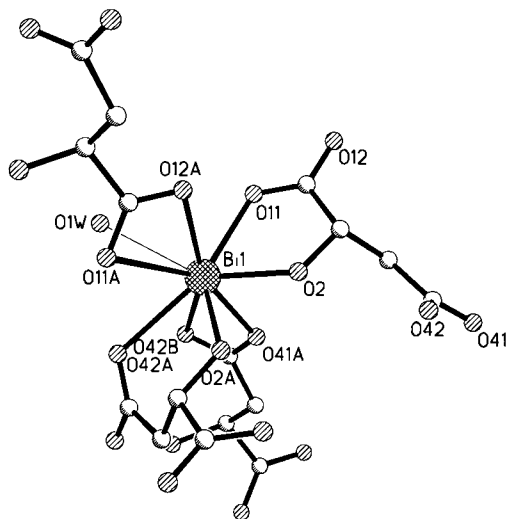


Figure 4. Ligand distribution around one bismuth center in the solid-state structure of Bi(mal)·H₂O.

membered rings), two of which are bound more strongly than the third. As illustrated in Figure 3, the carboxylate of the weakly bound ligand of a neighboring complex forms a four-membered chelate, and monodentate interaction with a carbonyl (car-

boxylate) of another neighbor imposes a total of nine coordination on bismuth. The multifunctional nature of the trianionic malate ligand in Bi(mal)·H₂O (bismuth malate)⁷⁰³ is responsible for an interesting coordination environment for bismuth, involving two four-membered carboxylate chelates, one five-membered carboxylate/alkoxide chelate, and one six-membered carboxylate/alkoxide chelate, which together with water gives a familiar coordination number of nine, illustrated in Figure 4.

The high denticity of the aminocarboxylates, nta and edta, simplify the solid-state structure of the complex. Nevertheless, intermolecular interactions are made possible by the high coordination numbers accessible to bismuth. Figure 5 shows the tetraden-

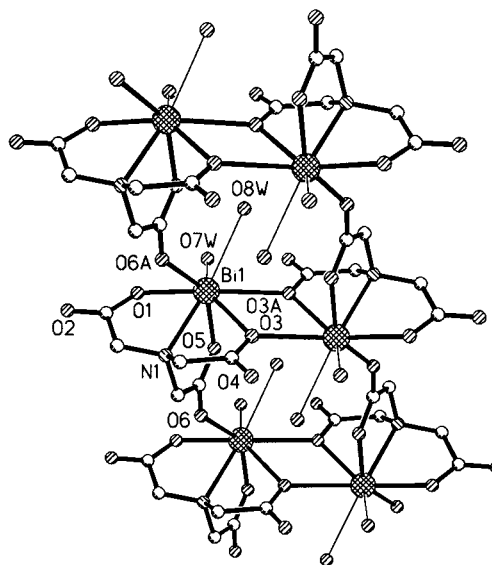


Figure 5. Polymeric association observed in the solid-state structure of Bi(NTA)·2H₂O.

tate interaction in Bi(NTA)·2H₂O⁷²² and illustrates two types of secondary intermolecular carboxylate–bismuth coordination imposing a coordination number of eight and a ribbonlike polymeric structure. Excess ligand circumvents the polymeric arrangement, and the ammonium salt [NH₄]₃[Bi(NTA)₂]^{726,727} contains the novel 3-fold symmetric anion involving eight-coordinate bismuth. Bismuth–edta complexes have been extensively studied by X-ray crystal-

Table 4. In Vitro Antimicrobial Studies Involving Bismuth Compounds

Bacteria	Compound/preparation designation or formula	Other components	Comments	Ref.
<i>Helicobacter pylori</i>	BSS		unsuccessful attempts to select resistant organisms	337
<i>Helicobacter pylori</i>	RBC, bismuth citrate	ranitidine	activity comparison	338
<i>Helicobacter pylori</i>	BSS, CBS	nitecapone	effect on acetaldehyde production	339
<i>Helicobacter pylori</i>	BSS		comparison to lansoprazole	340
<i>Helicobacter pylori</i>	BSS		by urease activity	341
<i>Helicobacter pylori</i>	bismuth subcitrate, BSS		used to transform helical forms of <i>H. pylori</i> to coccoid-like forms	342
<i>Helicobacter pylori</i>	bismuth gallate, BSS, carbonate, nitrate, citrate		Bi gallate and BSS reduced respiratory chain-dependent phosphorylation; respiratory chain inhibition suggested as mechanism of action	343
<i>Helicobacter pylori</i>	CBS		effect on phospholipase activity	344
<i>Helicobacter pylori</i>	BSS, BSG and carbonate, CBS, TDB		inhibited <i>H. pylori</i> adhesion to lipid species phosphatidylethanolamine and gangliotetraosylceramide	345
<i>Helicobacter pylori</i>	CBS			346
<i>Campylobacter pylori</i>	CBS		cultured specimens from duodenal ulcer patients before and after oral treatment with CBS	347
<i>Campylobacter pylori</i>	bismuth subcitrate, BSG, BSN, BSN, TDB			348
<i>Campylobacter pylori</i>	BSC	citric acid, potassium citrate	comparison of activity of bismuth subcarbonate alone, combined with citric acid, and combined with potassium citrate	349
<i>Campylobacter pyloridis</i>	bismuth subcitrate	various antibiotics (ampicillin, cefaclor, difloxacin, erythromycin, metronidazole, minocycline, nifuroxazide, nitrofurantoin, norfloxacin, ofloxacin, oxolinic acid, polymyxin B, rifampin, tobramycin)	test for synergism with various antibiotics	350
<i>Campylobacter pyloridis</i>	TDB, bismuth sodium tartrate			351
<i>Campylobacter pyloridis</i>	TDB		accumulation of bismuth complex under cell wall	352
<i>Eb. Typhi, Es. Coli</i>	bismuth salts			353
<i>B. coli</i> , typhoid-paratyphoid groups	liq. Bismuthi et ammonii cit.	Sodium sulfite		354
<i>Candida tropicalis</i> , <i>C. pseudotropicalis</i> , <i>C. guilliermondii</i>	$\text{Bi}(\text{NO}_3)_3$	sodium sulfite	Na_2SO_3 reduced to Na_2S , Bi_2S_3 decomposed to Bi and S	355

Table 4 (Continued)

Bacteria	Compound/preparation designation or formula	Other components	Comments	Ref.
<i>B. coli communis</i> , <i>B. brassicae</i> , <i>Sarcina agilis</i> , <i>B. gossypii</i> , <i>Penicillium glaucum</i>	bismuth metal		very weak toxic action	356
<i>Spirochaeta pallida</i>	water soluble bismuth compounds			357
<i>Treponema pallidum</i>	bismuth compounds			358
<i>Treponema pallidum</i>	bismuth compounds			359
<i>Treponema pallidum</i>	bismuth complexes of disodium pyrocatecholdisulfonate, gallic acid, tartaric acid		a combination of Sb and Bi pyrocatecholdisulfonate and other tartrate and gallate salts were less effective	360
<i>Treponema pallidum</i>	bismuth sodium tartrate, bismuth ethylenediaminetetraacetate, bismuth sodium triglycollamate, bismuth sodium pyrocatecholdisulfonate		activity depends on ability to liberate "bismuthyl radical"	361
<i>tubercle bacillus</i>	bismuth citrate			362
<i>tubercle bacillus</i>	bismuth nitrate	glycerol		362
<i>Staphylococcus aureus</i> , <i>Aerobacter aerogenes</i> , <i>Pseudomonas aeruginosa</i>	butylbismuth dichloride, phenylbismuth dichloride		other examples include phenylbismuth disalicylate, diphenylbismuth acetate, triphenylbismuth dihydroxide, propylbismuth diacetate, octylbismuth diphenoxide, dibutylbismuth acetate, triphenylbismuth dichloride, phenylbismuth dilaurylmercaptide, butylbismuth diacetate, octylbismuth dilaurylmercaptide; as aerosols, liquids, emulsions, solids	363
<i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , enterococci, <i>Candida albicans</i>	BSS		in simulated gastric fluid, varying pH	364
<i>treponema</i>	water soluble bismuth complex			365
<i>Entamoeba histolytica</i>	"Glycobiarsol"			366

Table 4 (Continued)

Bacteria	Compound/preparation designation or formula	Other components	Comments	Ref.
<i>B. subtilis</i> , <i>Enterobacteriaceae</i> , <i>Legionellaceae</i> , <i>Micrococcaceae</i> , <i>P. aeruginosa</i>	bismuth metal		oligodynamic action study	367
atypical <i>mycobacteria</i> (<i>Mycobacterium kansasii</i> , <i>M. fortuitum</i>)	bismuth salts			368
<i>Escherichia coli</i>	BSS		BSS binds bacteria; intra-/extracellular ATP measurements; loss of membrane integrity or cessation of ATP synthesis suggested as possible mechanism	369
<i>Escherichia coli</i>	bismuth salts		effect on expression of fimbriae; mechanism may be mediation of outer membrane proteins	370
<i>Escherichia coli</i>	bismuth 1,3-propanedithiol, dimercaptrol (BAL), dithiothreitol, 3-mercapto-2-butanol, β -mercaptoethanol, 1-monothioglycerol and mercaptoethylamine complexes		several other bismuth thiol, dithiol and nonthiol complexes were also tested but were less active; the activity of Bi-BAL was tested against a variety of other Gram-positive and Gram-negative using a variety of methods	371
<i>Veillonella alcalescens</i>	bismuth compound		reduction of Bi(III) to Bi metal	372
spirocheticidal and trypanocidal	"Bismarsen"		mechanism of action discussed	373
<i>Neisseria pharyngis perflava</i>	sodium bismuth tartrate		more effective than penicillin/ sulfonamides	374
<i>Staphylococcus aureus</i>	bismuth dimethyl-, diethyl-, 1-piperidyl- and ethylphenyldithiocarbamate			375
<i>Staphylococcus aureus</i>	BSC	benzalkonium chloride	effect of bismuth salt of activity of benzalkonium chloride	376
<i>Micrococcus pyogenes var. aureus</i> , vegetative forms and spores of <i>Bacillus anthracis</i>	$\text{NaCO}_2\text{CHOBiOHCCO}_2\text{K}$		addition of proteins or glucose inhibited antimicrobial effect	377
trichomonocidal, amebicidal	bismuthoxyquinoline and alky-, bromo- and chloro-substituted bismuthoxyquinolines		substitutions include 2-methyl-, 6-methyl-, 6-isopropyl-, 5,7-dibromo-, 5-chloro-	378

Table 4 (Continued)

Bacteria	Compound/preparation designation or formula	Other components	Comments	Ref.
<i>Saccharomyces cerevisiae</i>	NaBiO ₃		study of effects on recombination and production of disomic and/ or diploid spores during meiosis	379
<i>Klebsiella pneumoniae</i> , <i>Salmonella typhimurium</i> , <i>Enterobacter cloacae</i> , <i>Serratia marcescens</i> , other Gram.-neg. bacteria	BSS, Bi(NO ₃) ₃		effects of bismuth compounds with aminoglycoside antibiotics on capsular polysaccharide, potentiation of aminoglycoside inhibition, and bacterial growth inhibition	380
enteric pathogens	BSS	rifampicin, gentamicin, imipenem, other antibiotics	BSS had synergistic, antagonistic or no effects on the activity of various antibiotics	381
<i>Pseudomonas aeruginosa</i>	diphenyl bismuth acetate	zinc 1-hydroxy-2-pyridinethione	synergistic effects	382
<i>Escherichia coli</i> , <i>Saccharomyces cerevisiae</i> , <i>Staphylococcus aureus</i> , <i>Candida albicans</i> , <i>Cryptococcus laurentii</i> , Trichophyton mentagrophytes, <i>Bacillus subtilis</i>	bismuth carbonate, BSN			383
Enterotoxigenic <i>E. coli</i> , Enterics, <i>Salmonella</i> , <i>Shigella</i> , <i>Pseudomonas</i> , <i>Staphylococcus</i> , <i>B. fragilis</i> group, Clostridium species, <i>C. difficile</i>	BSS			384
<i>Escherichia coli</i> , <i>Salmonellai</i> , <i>Shigella</i> , <i>Yersinia</i> , <i>Vibrio</i> , <i>Campylobacter</i>	BSS, bismuth sodium tartrate, bismuth citrate, bismuth sulfate, bismuth oxychloride		BSS hydrolysis products were also tested	385
colonic bacteria	TDB (in DeNol), BSS (in Pepto-Bismol), BSN		effect on fermentation by colonic bacteria in stool samples with added fermentable substrate	386

Table 4 (Continued)

Bacteria	Compound/preparation designation or formula	Other components	Comments	Ref.
<i>Yersinia enterocolitica</i>	BSS		scanning electron microscopy (SEM), energy dispersive spectroscopy (EDS), transmission electron microscopy (TEM) and scanning transmission electron microscopy (STEM) studies of bismuth inclusions; BSS is deposited on bacteria, reduced to metallic bismuth and taken up by bacteria	387
<i>Yersinia enterocolitica</i> , <i>Escherichia coli</i> , <i>Listeria monocytogenes</i> , <i>Listeria ivanovii</i> , <i>Salmonella typhimurium</i>	BSS, Pepto-Bismol, BiOCl, BiS		effect of invasion of mammalian epithelial	388
<i>B. coli</i> , <i>B. typhosus</i> , <i>B. lactis aerogenes</i> , <i>B. welchii</i> , <i>B. proteus</i> , etc.	liquor bismuthi et ammonii citratis	glucose, sulfite, ferrous sulfate	medium is selective for growth of <i>B. typhosus</i> and <i>B. proteus</i>	389

lography and are best represented by $\text{Bi}(\text{Hedta}) \cdot 2\text{H}_2\text{O}^{722}$ (Figure 6), showing the hexadentate chela-

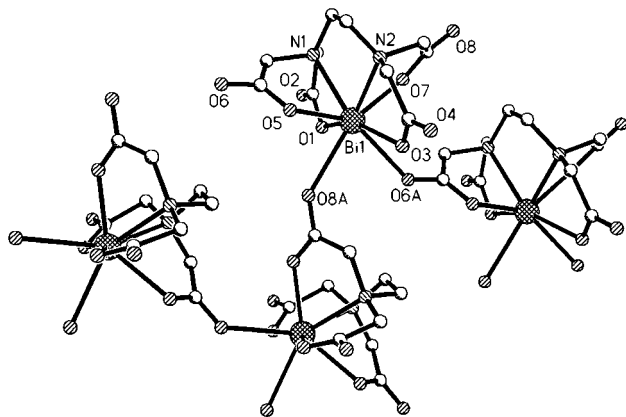


Figure 6. Polymeric association observed in the solid-state structure of $\text{Bi}(\text{Hedta}) \cdot 2\text{H}_2\text{O}$.

tion of bismuth. Two exocyclic carboxylate oxygen atoms are responsible for intermolecular coordination to neighboring bismuth centers, so that each bismuth is eight coordinate in a polymeric array.

V. Colloidal Bismuth Subcitrate (CBS)

Citrate salts of bismuth represent the most extensively studied series of bismuth compounds by virtue of their widespread medicinal use. Bismuth citrate is essentially insoluble in water, but a dramatic increase in solubility with increasing pH has been exploited as a bioready source of soluble bismuth, a material referred to as "colloidal bismuth subcitrate"

(CBS). Formulation of these solutions is complicated by the variability of the bismuth:anion stoichiometry, the presence of potassium and/or ammonium cations, the susceptibility of bismuth to oxygenation (to $\text{Bi}=\text{O}$), and the incorporation of water in isolated solids. Consequently, a variety of formulas are classified in the literature as CBS.^{661,665,680,697,709–711,713,714,786} The composition of solutions and stability constants have been determined (visual studies,⁷⁴⁹ solubilities,⁶⁸⁵ bismuth ion-selective electrodes,⁷⁶⁰ potentiometry,^{754,755,787} polarography,^{755,756} and oscillography⁷⁸⁸) as well as other physicochemical properties.^{716,789} ^1H and ^{13}C NMR spectroscopy studies^{790–792} indicate rapid exchange of citrate moieties at low concentration and the existence of oligomeric or polymeric units at higher concentrations.⁷⁹³

Solids isolated from various, often ill-defined combinations of bismuth citrate, citric acid, potassium hydroxide, and/or ammonium hydroxide have been assigned formulas $\text{K}_{2.7}(\text{NH}_4)_{0.3}[\text{Bi}(\text{cit})]_3(\text{H}_2\text{O})_4$, $\text{K}_{1.4}(\text{NH}_4)_{1.6}[\text{Bi}(\text{cit})]_3(\text{H}_2\text{O})_6$, $\text{KBi}(\text{cit})\text{H}_2\text{O}$, $(\text{NH}_4)_3(\text{BiO})_2\text{Bi}(\text{cit})_2(\text{H}_2\text{O})_6$, $(\text{NH}_4)_3(\text{BiO})_2\text{Bi}(\text{cit})_2(\text{H}_2\text{O})_3$, $\text{K}_{1.4}(\text{NH}_4)_{1.6}(\text{BiO})_2[\text{Bi}(\text{cit})_2(\text{H}_2\text{O})_5]$,⁷⁹³ $\text{K}_{0.8}(\text{NH}_4)_{0.2}\text{Bi}(\text{cit})\text{H}_2\text{O}$, and $\text{K}_{0.6}(\text{NH}_4)_{0.4}\text{Bi}(\text{cit})(\text{H}_2\text{O})_2$ ⁷⁹⁴ on the basis of elemental analysis data or by determination of water and ammonia content and are described as different forms of CBS. Additional speculation is made for their presentation as modified formulas ($\text{cit} = \text{C}_6\text{H}_4\text{O}_7^{4-}$; $\text{Hcit} = [\text{CO}_2\text{CH}_2\text{C}(\text{OH})(\text{CO}_2)\text{CH}_2\text{CO}_2]^{3-}$); however, assignments for such complex systems are of low significance in the absence of complementary data other than thermal analysis,⁷⁹⁴ infrared spectroscopy,⁷⁹⁴ or NMR spectroscopy.⁷⁹⁵ In this context, Merck Index lists the chemical formula of CBS as

Table 5. In Vivo Antimicrobial Studies Involving Bismuth Compounds

Bacteria	Compound/preparation designation or formula	Animal	Method of administration	Comments	Ref.
<i>T. gambiense</i>	quinine iodobismuthate	guinea pig	intramuscular/ subcutaneous injection		390
spirocheticidal and trypanocidal	"Bismarsen"			mechanism of action discussed	373
<i>Neisseria pharyngis perflava</i>	sodium bismuth tartrate	mice, rabbits, humans			374
<i>pneumococcus</i> type I	bismuth dimethyldithiocarbamate	mice			375
<i>streptococci</i>	BSS	mice		Bi increases effectiveness of penicillin therapy	391
<i>Streptococcus pyogenes, Brucella melitensis</i>	bismuth salicylate	guinea pigs, rabbits			377
<i>Hymenolepis nan, Syphacia obvelata</i>	5,7-dibromo- and 5-chloro-8-bismuthoxyquinoline	mouse		total of ten 8-bismuthoxyquinolines tested	378
trypanosomes, (<i>Tr. congolense</i>)	sodium 2,6-dimercaptoisonicotinate [Bi ₂ (S ₂ C ₃ H ₂ NCO ₂ Na) ₃]	white mice			392
spirochetes of Sodoku	sodium tartratobismuthate	guinea pig			393
colonic bacteria	TDB (in DeNol), BSS (in Pepto-Bismol), BSN	human	oral	effect on fermentation of ingested raffinose by colonic bacteria	386
<i>B. duttonii</i>	sodium bismuth ethylenediaminetetraacetate	mice	oral, subcutaneous		394
	bismuth sodium pyrocatecholdisulfonate complex, bismuth sodium tartrate, bismuth EDTA	mice	oral, subcutaneous		395
<i>Trypanosoma equiperdum</i>	sodium bismuth pyrocatecholsulfonates, sodium bismuth tartrate, bismuth EDTA	mice	subcutaneous		396
fecal microflora (e.g. <i>Pseudomonas, Staphylococcus, Enterococcus, Clostridium difficile</i>)	BSS	human	oral	with/without a standard oral intestinal lavage preparation	397

Table 6. Review Articles Describing Pharmacological Studies, Pharmacokinetic Studies, and Toxicity Involving Bismuth Compounds

Topics	Compound designation	Ref.
Pharmacology (gastric), toxicity	TDB	398
analytical methodology, pharmacology (pharmacokinetics, drug interactions), toxicity (animal and human toxicology, overdose, encephalopathy)	TDB, BSS, various others	399
pharmacology (gastric related), pharmacokinetics	CBS	400
analytical methodology, pharmacokinetics, toxicity (human - nephropathy, hepatitis, oteoarthropathy; neurotoxicity/encephalopathy)	various	401
pharmacology (gastric), pharmacokinetics, toxicity	CBS, BSS	402
analytical methodology, environmental levels, pharmacokinetics, toxicity (animal, human; treatment)	various	403,404
pharmacology (gastric)	CBS	405
toxicity (melanosis, erythema, oral manifestations, skeletal, nephrotoxicity, hepatotoxicity, methaemoglobinaemia, central nervous system)	BSS, diallylacetate, sodium bismuth thioglycollate (thiobismol), BSN, sodium bismuth tartrate, basic bismuth campho-carboxylate (bismocymol)	406
pharmacokinetics (correlation to toxicity)	CBS	407
toxicology (intracellular inclusions)		408,409
toxicity (domestic and farm animals)	bismuth	410
environmental (natural occurrence, pollution), pharmacology, pharmacokinetics, toxicity (liver, kidney, nervous system, other organs)	various	411
analytical methodology, environmental (natural occurrence), pharmacology, toxicity (occupational health hazards)	bismuth	412
pharmacology, toxicity	bismuth	413
toxicity	BSN, BSC	414
environmental (workplace air pollution in processing), toxicity	Bi, sulfides, oxides, nitrates, chlorides	415
pharmacokinetics, toxicity	subcitrate, various others	416
pharmacology, toxicity	organic bismuth compounds	417
toxicity	insoluble bismuth salts	418
toxicity (encephalopathy)	various	419
pharmacology (absorption), toxicity	various	420
pharmacology, pharmacokinetics, toxicity	various	421
pharmacology (absorption), toxicity	TDB, BSS, RBC	422
pharmacokinetics (animals), toxicity (brain, in animals)	various	423
environmental (sewage and waste water), pharmacology	various	424
analytical methodology, environmental (waste products, recycling, distribution), pharmacology (humans, animals)	various	425
environmental (health hazards, safety, pollution), toxicity	organo	426
environmental (natural distribution, pollution), pharmacology, toxicity	various	411
environmental (natural distribution), pharmacology and toxicity (animals, humans)	various	427

Table 6 (Continued)

Topics	Compound designation	Ref.
toxicity	various	428
pharmacology (histochemical; distribution in animals and humans), toxicity	CBS/TDB, others	16
pharmacology, toxicity (encephalopathy)	CBS, BSS, others	17
pharmacology (gastric)	CBS	38,39
pharmacology, toxicity	BSS, others	40
pharmacology, toxicity (human)	BSS, CBS, BSG, BSN, BSC	22
pharmacology (gastric), pharmacokinetics, toxicity	CBS	28
pharmacology	salts	37
pharmacology, toxicity	various	32
pharmacology (absorption), toxicity (neurotoxicity, humans and animals)	BSS	429
pharmacology (gastric, animal), pharmacokinetics (human), toxicity (various animals)	sodium bismuth triglycollamate (bistrimate)	44
pharmacology (animals, human), pharmacokinetics (animals, human)	various	50
toxicity	organo	49

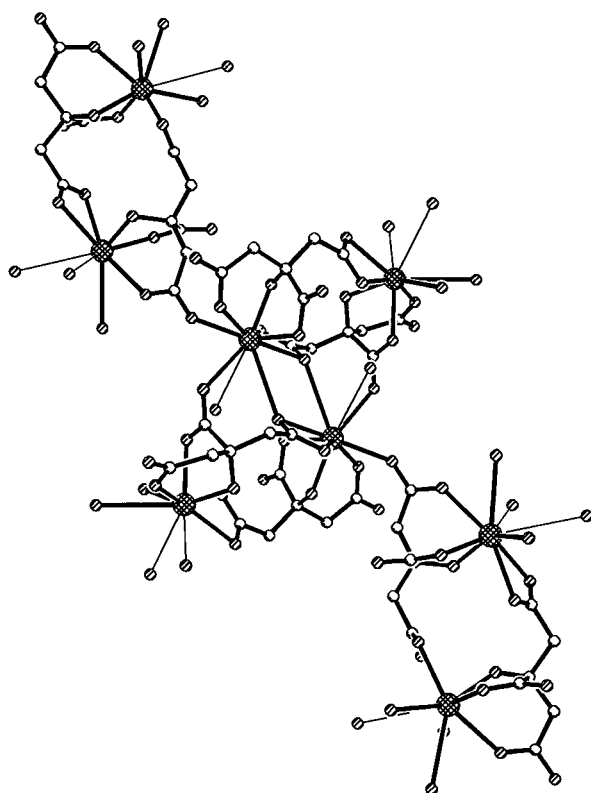


Figure 7. Zigzag polymeric array of dimers observed in the solid state for formulas A and B of CBS (Bi-dark, O-grey, C-white).

$K_3(NH_4)_2Bi_6O_3(OH)_5(C_6H_5O_7)_4$ in the 11th edition⁷⁹⁶ but in the most recent edition provides a less precise name "tripotassium dicitrate bismuthate".⁷⁹⁷

More definitive formulas have been determined by X-ray crystallography, and data are listed for

comparison in Table 9. The conditions for isolation of these crystalline materials from solutions similar to those defined above are provided in some cases but are sometimes incomplete and often involve time periods of months. Isolation of the sodium salt E was somewhat unusual in that it was unexpectedly obtained from a reaction mixture of ranitidine bismuth citrate, glutathione, D_2O , and $NaOD$.⁷⁹⁵

The structures in Table 9 are all closely related and are generally composed of a citrate anion ($cit = C_6H_4O_7^{4-}$) intimately bound to a bismuth center, an appropriate number of potassium or ammonium cations (to balance the charge), and solvated or coordinated water molecules. Three of the structures contain an additional citrate trianion ($Hcit$), and one structure is constructed around a hexanuclear bismuth oxygen cluster (Bi_6O_4). Potassium and ammonium cations are essentially interchangeable, in that the compositions are not dependent on the presence of the ions in the reaction mixture; for example, $KBi(cit)(H_2O)_3$ A was obtained from an aminated solution. Moreover, three structures (B, D, F) contain both potassium and ammonium cations in a fractional stoichiometry, and the ammonium salt C is isostructural with compound D, which contains a equimolar combination of potassium and ammonium, but is otherwise identical. In this context, the variety of reported structures is somewhat misleading when one recognizes that of the eight structures listed in Table 9, only compounds F, G, and H can be considered unique. Structures A–E are constructed from the monoanionic complex of Bi^{3+} with a tridentate (dicarboxylate/alkoxide) tetra-anionic citrate ligand. This unit is also evident in F, G, and H, but these structures involve additional chemically different units. $[Bi(cit)]^-$ together with a cation and

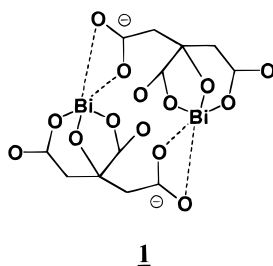
Table 7. Inorganic Salts of Bismuth with Medicinal Relevance and Literature References to Characterization Data (see abbreviations section I)

compound name	formula	p r e p	s o l	M S	I R	R a m	U V	M i c	P E S	E A	N Q R	X r a y	N D	D T A	E D	E C	S E M	B S	P o l
oxide (bismite)	Bi_2O_3	431 432 - 456	457, 458		459 - 463	459, 462 465			466, 467		468 - 473	431, 433, 437, 474 - 484	432, 480, 485 478, 491	433, 436, 437, 479, 481, 486 - 489	455, 456, 490, 492	481, 486, 492			493
hydroxide		494 - 496	497																498
hydroxide	$\text{Bi}(\text{OH})_3$	336, 499			500														
hydroxide	$\text{BiO}(\text{OH})$				500														
carbonate		496, 501			502														
basic carbonate		503, 504																	
subcarbonate					505														
subcarbonate (bismutite)	$(\text{BiO})_2\text{CO}_3$	432, 453, 506, 507			506, 508	506				507		506	506						
subcarbonate	$(\text{BiO})_4(\text{OH})_2\text{CO}_3$	506			506	506						506	506						
subcarbonate	$\text{Bi}_2(\text{OH})_4\text{CO}_3$	499																	
subcarbonate	BiOHCO_3	454																	
subcarbonate	$5\text{Bi}_2\text{O}_3 \cdot \text{Bi}_2(\text{CO}_3)_3$	507								507									
subcarbonate	$\text{BiO}(\text{HCO}_2)$				508														
nitrate/ trinitrate		509 - 511			512	512, 513													
nitrate/ trinitrate	$\text{Bi}(\text{NO}_3)_3$	454			514						515		514						
nitrate/ trinitrate	$\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$	516 - 518			518	519, 520	521					517, 518, 522, 523	518						
basic bismuth nitrate	various, see text	524 - 527								525									
subnitrate	various, see text	430, 454, 504, 528 - 546	529, 547, 548		538, 549, 550					534, 539, 540, 543, 551 - 555		430, 523, 539, 541 - 546, 556 - 558	538, 541, 546				539		
subnitrate	$\text{BiONO}_3 \cdot \text{H}_2\text{O}$				559														
subnitrate	$\text{BiONO}_3 \cdot 0.5\text{H}_2\text{O}$											556							
subnitrate	$\text{Bi}_6\text{O}_4(\text{OH})_4(\text{NO}_3)_6 \cdot \text{H}_2\text{O}$	545										545							

Table 7 (Continued)

compound name	formula	p r e p	s o l	M S	I R	R a m	U V	M i c	P E S	E A	N Q R	X r a y	N D	D T A	E D C	E M	S E	B S	P o l
subnitrate	[Bi ₆ (H ₂ O)(NO ₃) ₄ (OH) ₄] (NO ₃) ₅	544										544							
subnitrate	[Bi ₆ O ₂ (OH) ₃] (NO ₃) ₅ • 3H ₂ O	543							543			543, 557							
subnitrate	[Bi ₆ O ₄ (OH) ₄] (NO ₃) ₆ • 4H ₂ O	430										430							
chloride/ trichloride	BiCl ₃	560 -	569	570	571	574	587	588	589		590	567, 568, 601	603	604	572, 605				
oxychloride/ subchloride	BiOCl	606, 607, 607 -	547		612, 617 -	609, 618, 622			467		598, 600, 613	614 -		610, 616, 627	628 -	630			
subiodide		607, 611 -	547		612, 618, 620, 622, 631	618, 622					613	624 -		627, 631				633	
oxyiodide	BiOI	221																	
aluminate		634, 635																	
aluminate	Bi ₂ (Al ₂ O ₄) ₃ • 10H ₂ O	636, 637																	
aluminate	Bi ₂ O ₃ • 10Al ₂ O ₃ • 20H ₂ O	638																	
aluminate	Bi ₂ O ₃ • 3Al ₂ O ₃ • CO ₂ • 5H ₂ O	639																	

two water molecules defines the asymmetric unit of compounds C–E but adopts a well-defined dimeric arrangement imposed by chelate coordination of the pendant carboxylate moiety to a neighboring bismuth center **1**. The same dimer unit exists in A and B, and differences in the macrostructures result from distinctions in the interactions between the dimers. The ubiquitous tridentate chelation apparently arises from deprotonation of the hydroxy moiety of insoluble bismuth citrate [Bi(Hcit)] and implies a special stability enforcing a pendant carboxylate, which may be responsible for the unique water solubility with avoidance of hydrolysis to bismuthyl (BiO⁺). The coincident chelate coordination of this third (pendant)



carboxylate is precluded by the required tetrahedral geometry of the central carbon center of the citrate anion.

For compounds A and B, the bismuth centers interact with an additional two carboxylate oxygen centers of a neighboring dimer to effect a face-to-face tetramer (dimer of the asymmetric unit **1**), shown in the center of Figure 7. Interaction with a single carboxylate oxygen center of a third citrate moiety is responsible for a polymeric array of the tetramers (Figure 7). The structures of compounds C–E contain an identical tetramer but are associated in a side-by-side interaction (also single carboxylate oxygen donor to bismuth) giving a parallel array of dimers (Figure 8) and contrasting the zigzag structure of compounds A and B (Figure 7). The two types of polymeric structures are distinguished by the degree of hydration.

Compounds F, G, and H also contain the tridentate coordinated citrate tetranion (cit); however, the presence of an additional citrate trianion (Hcit) complicates and opens the structures, enabling the incorporation of additional water for compound F. Nevertheless, the familiar pendant carboxylate bound dimer is

Table 8 (Continued)

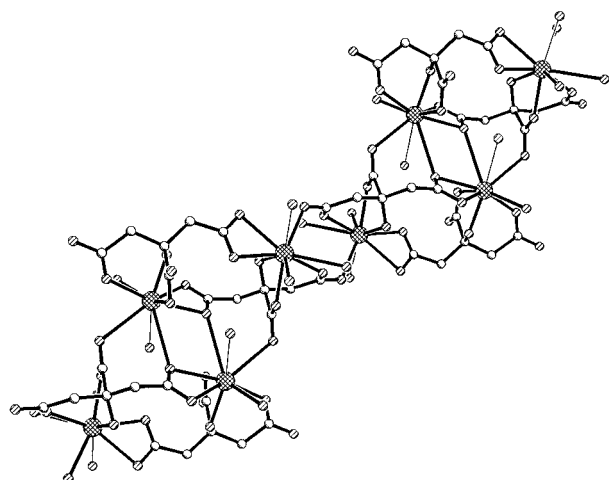
Compound designation	Formula	Prep	EA	mp	Pol	IR	Xray	Raman	sol	DTA	NMR
	$\text{Bi}(\text{Hcit}) \cdot \text{H}_2\text{O}$	712				712				712	
	$\text{Bi}(\text{Hcit})_2(\text{OH})_3$	710	710								
"pentabismol"	$16\text{NH}_4\text{OH} \cdot 11\text{Bi}(\text{Hcit}) \cdot \text{Bi}(\text{OH})_3 \cdot 6\text{H}_2\text{O}$	713,714									
bismuthocitric acid		665									
sodium bismuth citrate		715									
dibismuthyl monosodium citrate									716		
oxalate						717				688	
	$\text{Bi}_2(\text{ox})_3$	707				707					
	$\text{Bi}_2(\text{ox})_3 \cdot 7\text{H}_2\text{O}$									707	
	$\text{NaBi}(\text{ox})_2 \cdot 2.5\text{H}_2\text{O}$							718,719			
	$(\text{CN}_3\text{H}_6)_3\text{Bi}_2(\text{ox})_3\text{Cl}_3$						720				
suboxalate	$(\text{BiO})_2(\text{ox})$									547	
nitrilotriacetate											
	$\text{Bi}(\text{nta}) \cdot 2\text{H}_2\text{O}$	721,722	722			721	722,723				
	$\text{Bi}(\text{nta}) \cdot 3\text{H}_2\text{O}$	724	724			724					
	$\text{M}_3\text{Bi}(\text{nta})_2 \cdot n\text{H}_2\text{O}$ (M = Li, Na, K, Cs, NH_4^+ , CN_3H_6^+)	721				721					
	$\text{M}_3\text{Bi}_2(\text{nta})_4$ (M = Ca, Ba)	725				725					
	$(\text{NH}_4)_3\text{Bi}(\text{nta})_2$	726,727					726,727				
	$(\text{NH}_4)_2[\text{Bi}(\text{nta})(\text{SCN})_2] \cdot 2\text{H}_2\text{O}$	721				721					
	$(\text{NH}_4)_4[\text{Bi}(\text{nta})_2(\text{NCS})] \cdot \text{H}_2\text{O}$						723				
sodium bismuth triglycollamate	$\text{Bi}(\text{Na}_2\text{nta})_3$	728									
sodium bismuth triglycollamate	$\text{BiOH}(\text{Hnta}) \cdot \text{H}_2\text{O}$	729		729							
sodium bismuth triglycollamate	$\text{BiOH}(\text{Hnta}) \cdot (\text{Na}_2\text{Hnta}) \cdot n\text{H}_2\text{O}$ (n = 0-5)	730									
sodium bismuth triglycollamate	$\text{BiO}(\text{NaHnta})(\text{Na}_2\text{Hnta}) \cdot 4\text{H}_2\text{O}$	729									
ethylenediaminetetraacetic acid						731				732	
	$\text{Bi}(\text{Hectd}) \cdot 2\text{H}_2\text{O}$	722	722				722,733				734
	α - and β - $\text{Bi}(\text{Hedta}) \cdot 2\text{H}_2\text{O}$	735					735				
	$\text{Bi}(\text{Naedta}) \cdot 2\text{H}_2\text{O}$	736,737	736,			736,					
			737			737					
	$\text{Bi}(\text{Hedta}) \cdot \text{H}_2\text{O}$	738	738			736	738				
	$\text{Bi}(\text{Hedta})$	735,739, 740	739	740			735,741				734
	$(\text{CN}_3\text{H}_6)\text{Bi}(\text{edta}) \cdot \text{H}_2\text{O}$	742,743	742, 743				742,743				
	$(\text{NH}_4)[\text{Bi}(\text{edta})] \cdot \text{H}_2\text{O}$						741				
	$\text{M}[\text{Bi}(\text{edta})]_2 \cdot n\text{H}_2\text{O}$ (M = Mg, Ca, Sr, Ba, Ni, Co, Zn, Cd)	725				725					
	$[\text{Co}(\text{H}_2\text{O})_6][\text{Bi}(\text{edta})]_2 \cdot 3\text{H}_2\text{O}$						744				
	$\text{Mo}(\text{H}_2\text{O})_6[\text{Bi}(\text{edta})]_2 \cdot 3\text{H}_2\text{O}$						744				

Table 8 (Continued)

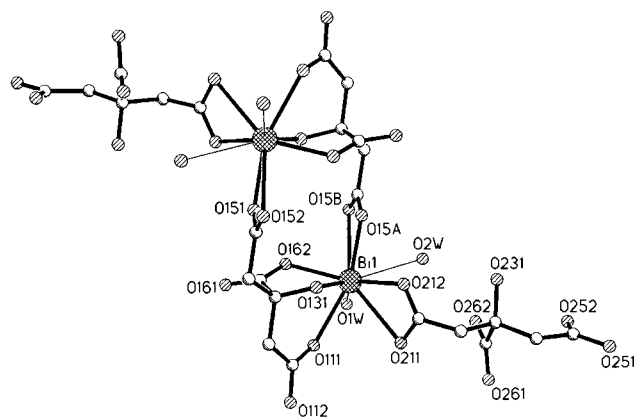
Compound designation	Formula	Prep	EA	mp	Pol	IR	Xray	Raman	sol	DTA	NMR
	Cu[Bi(edta)] ₂ ·9H ₂ O	745					745			745	
	[Ca(H ₂ O) ₇][Bi(edta)] ₂ ·2H ₂ O						746				
	M[Bi(edta)]·H ₂ O (M = K, NH ₄)										734
	M ₂ [Bi(OH)(edta)]·nH ₂ O (M = K, NH ₄ ; n = 1, 3)										734
	K ₂ [BiF(edta)]·3H ₂ O										734

Table 9. X-ray Crystallographic Data for Solids Described as Colloidal Bismuth Subcitrate. Modified Formulas Units: Cit = C₆H₄O₇⁴⁻ and Hcit = [CO₂CH₂C(OH)(CO₂)CH₂CO₂]³⁻

Formula	#	Bi:cit ratio	Space Group	Cell parameters: a, b, c, β	Coordination # at Bi	Ref.
KBi(cit)(H ₂ O) ₃	A	1:1	P2 ₁ /n	10.924, 15.280, 14.967, 105.48	9	798
K _{0.5} (NH ₄) _{0.5} Bi(cit)(H ₂ O) ₃	B	1:1	P2 ₁ /n	10.923, 15.424, 15.037, 105.67	9	790
NH ₄ Bi(cit)(H ₂ O) ₂	C	1:1	C2/c	16.805, 12.544, 10.401, 91.27	8	799
K _{0.5} (NH ₄) _{0.5} Bi(cit)(H ₂ O) ₂	D	1:1	C2/c	16.860, 12.395, 10.328, 91.79	8	790
Na ₂ [Bi(cit)] ₂ (H ₂ O) ₇	E	1:1	C2/c	15.723, 13.899, 10.423, 94.39	8	795
K _{4.75} (NH ₄) _{0.25} [Bi(cit)] ₂ (Hcit)(H ₂ O) ₁₃	F	2:3	P-1	11.801, 12.973, 15.856, 98.15, 108.39, 100.91	9	793
(NH ₄) ₄ Bi(cit)(Hcit)(H ₂ O) ₃	G	1:2	P2 ₁ /c	8.998, 9.492, 27.021, 99.42	8	793
(NH ₄) ₆ (Bi ₆ O ₄)cit ₄ (H ₂ O) ₅ initially assigned as (NH ₄) ₆ (Bi ₆ O ₄ OH)(cit) ₃ (H ₂ O) ₅ Hcit	H	3:2	R-3	17.807, 17.807, 31.596		791 800

**Figure 8.** Parallel array of dimers observed in the solid state for formulas C, D, and E of CBS (Bi-dark, O-grey, C-white).

evident as one of two moieties responsible for associating the dibismuth asymmetric units and is the only interbismuth association in compound G (Figure 9). Although the dimer unit is not obvious in compound H, the tridentate chelation of one of the two unique bismuth centers is clear as well as association

**Figure 9.** Nonpolymeric dimer unit observed in the solid-state structure for formula G of CBS.

of the second bismuth center via a chelate involving a single oxygen of the pendant carboxylate and a bifurcated alkoxide oxygen center, as illustrated in Figure 10.

Ranitidine bismuth citrate (RBC) is a new water-soluble therapy for peptic ulcer disease, which is obtained from the reaction of ranitidine hydrochloride (*N,N*-dimethyl-5-(3-nitromethylene-7-thia-2,4-diazaoctyl)furan-2-methanamine) with bismuth citrate.

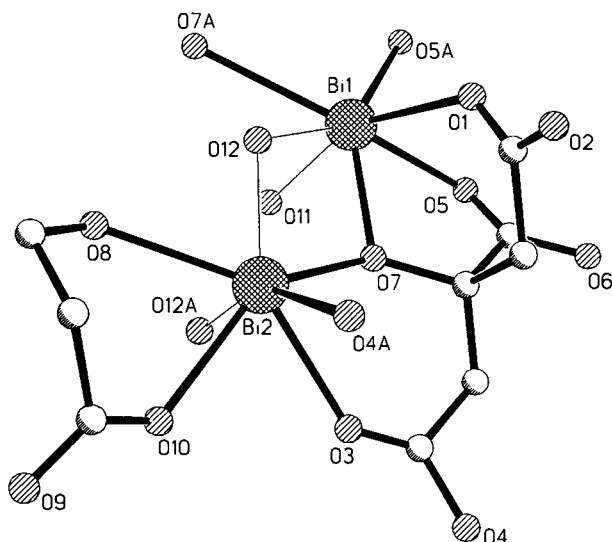


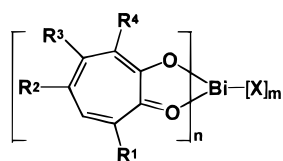
Figure 10. Unique asymmetric unit observed in the solid state for formula H of CBS.

Characterization has included elemental analysis, ^1H and ^{13}C NMR and IR spectroscopies, polarography, and X-ray powder diffraction; however, definitive structural assignment has been complicated by the extensive hydrogen bonding.^{338,801,802}

VI. Discovery and Design of Bioactive Bismuth Compounds

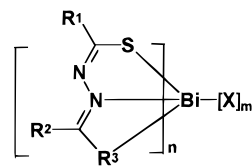
The apparent chemical complexity of the commercial bismuth-containing pharmaceutical agents has prompted the discovery and development of new bioactive compounds and model compounds. As catalogued in Table 10, therapeutic or antibacterial activity has been speculated or suggested for many bismuth compounds, and some have been assessed in vivo and or in vitro. Most compounds are superficially characterized and the molecular structures or the formulas have not been defined, with some examples exhibiting varying composition depending on specific reaction conditions.^{803,804}

Recent systematic synthetic studies coupled with bioactivity assessments confirm the biosignificance of bismuth, provide comprehensive characterization data for the compounds, and reveal important trends. Tropolone complexes of bismuth(III)^{914–917} have been



2

X = Cl, NO₃, Ph
n = 2; m = 1
n = 3; m = 0
n = 4; m = 0; X = Na
R = H, Me, Ph, CH₂OH,
COMe, NO₂

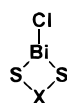


3

X = Cl, NO₃, Ph, OAc
n = 1; m = 2
n = 2; m = 1
n = 3; m = 0
R1 = amine, pyridine or
thioether substituents
R2 = H, Me
R3 = pyridine or cyclic
ether/thioether

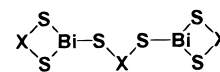
extensively derivatized^{918,919} (general structure **2**) as well as less common examples of bismuth(V) complexes,^{919,920} and derivatives of bismuth(III) thiosemicarbazones and dithiocarbazonic acid methylester^{921–924} (general structure **3**) are now numerous, allowing for comparison of relationships between specific structural features and bioactivity. Assessment of the anti-*H. pylori* activity of these series of compounds reveals substantially lower minimum inhibitory concentrations for the thiosemicarbazone derivatives.^{919,921}

Thiosemicarbazone complexes are representatives of a wide range of thiobismuth compounds, made possible by the thermodynamically favorable bismuth–sulfur interaction. The high thiophilicity of bismuth routinely imposes multithiolation, but substitution can be controlled by manipulating stoichiometric conditions for the reactions of BiCl₃ or Bi(NO₃)₃ or by the use of pendant donors which mediate the thiophilicity of the bismuth center. In this way, the systematic series of thiobismuth compounds, **4**,^{925–927} **5**,⁹²⁷ **6**,^{928–930} and **7**,^{931,932} have been isolated and comprehensively characterized.⁹³² Assessment of

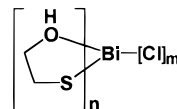


4

X = CH₂CH₂,
CH₂CH₂CH₂,
CH₂CH₂CH₂CH₂,
CH₂CH₂OCH₂CH₂,
CH₂CH₂SCH₂CH₂



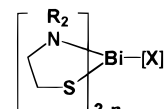
5



6

X = Cl, NO₃, CH₃COO;
n = 2, m = 1

X = NO₃, SCH₂CH₂O;
n = 2, m = 1; n = 3, m = 0



7

X = Cl, NO₃;
n = 1, 2, 3

antimicrobial bioactivity against *Clostridium difficile*, *H. pylori*,⁹³⁰ *Escherichia coli*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*⁹³³ reveals significant differences within a series, suggesting a structure/activity relationship for the bismuth environment. In addition, a rat model gastric ulceration study for derivatives of **4** and **5** indicates distinct differences in the ulcer healing efficacy.⁹³⁴ More general biological activity, including antibacterial (*Bacillus subtilis*, *E. coli*, *Candida tropicalis*, *Penicillium camembertii*),⁹³⁵ fungicidal (yeast and moulds),^{935,936} and antitumor,⁹³⁷ is reported for a series of spectroscopically characterized bis(thiolato)bismuth compounds.

VII. Interactions of Bismuth Compounds with Biomolecules and Pharmaceutical Agents

The binding of bismuth with proteins of exposed ulcer tissue and the formation of a protective coating is proposed as a mode of action for the antilucer behavior of some bismuth compounds. In this context, the chemistry of bismuth complexes involving bio-

Table 10. Other Bioactive Bismuth Compounds

Compound designation	ligand	Chemical Data	Suggested or evaluated medicinal application (Mode of Administration)	Ref.
Sulfanilamide $X_3 \cdot BiY_3$	(X = 3-sulfanilamido-6-methoxy-pyridazine, 2-sulfanilamidothiazole, 2-sulfanilamidopyridine, 4-sulfanilamido-2,6-methoxy-pyrimidine, 3-sulfanilamino-2-phenylpyrazole, 5-sulfanilamido-3,4-dimethylisoxazole, sulfanylguanidine)(Y = halide)	prep	pharmaceutical (suppository)	805
aluminum-bismuth carbohydrate sulfates	carbohydrate = sucrose, chondroitin, lactose starch, mannitol	prep	ulcers	806
phenylbismuthbis(2-pyridinethiol 1-oxide)	$PhBi(C_5H_4NOS)_2$	prep (in vitro - gram positive, gram negative)	detergents, soaps, shampoos	807,808
organobis(thio-phenylato) bismuth(III)	$C_6H_5Bi(SC_6H_4Cl-p)_2$, $CH_3Bi(SC_6H_4NH_2-p)_2$, $[CH_3Bi(SC_6H_4NH_2CH_3-p)_2]_2$, $[CH_3Bi(SC_6H_4NH_2CH_3-p)_2][NO_3]_2$	prep, spectroscopy (bacterial)	bactericide	809
Methylbis(2,6-dichlorothiophenolato) bismuth(III)	$MeBi(SC_6H_3Cl_2-2,6)_2$	prep, EA, NMR, IR, MS (bacteria, yeasts, molds)		810
triphenyliodobismuth hexafluoroarsenate	$[Ph_3BiI][AsF_6]$	prep, NMR, IR, Raman (bacterial)		811
antibiotic chelates	e.g. azithromycin; Bi^{3+} and other metal ions	(in vivo, rats)	ulcers	812
phenylbismuth derivatives	$[AC_6H_4]_nBiQ_t$ (A = H, Cl, Me, MeO, etc; s = 1-3; t = 0-2; s = 1, t = 1 or 2, when t = 1, Q = $Br_2(pyr)_2$, $Br_2(dipy)$, when t = 2, Q = PhS, Me_2NCS_2 ; s = 2, t = 1, Q = cyano, azido, Br(phenyltrimethylammonium halide), etc; s = 3, t = 0-2, when t = 1, Q = Cl(OH), when t = 2, Q = Cl, OAc, etc.; s = 3, t = 0, A = m- CF_3)	prep (in vivo, Eimeria tenella in chickens)	anticoccidial drugs	813
organic bismuth salts	$XBi(OH)_2$ (X = $C_{10}H_4O_3SR^1R^2R^3$, residue of carnosine, sucrose, octasulfate, (N-acetyl)glutamine, glycylglutamine, or alanylglutamine; R1 = alkyl; R2, R3 = H, lower alkyl) e.g. 3-ethyl-7-isopropylazulenesulfonic acid basic salt	prep (in vivo, rats)	ulcers	814
3-phenylthio- and phenylsulfonylacrylic acid bismuth salt	Bi salts of $RC_6H_4S(O)_nCH=CHCO_2H$ (R = H; halo, C_{1-4} alkyl or alkoxy, NO_2 ; n = 0, 2)	prep (cytoprotective and gastric acid secretion-inhibitory)	ulcers	815
tropolone thiosemicarbazone, thiocarbamic acid complexes	$[Bi_{1-3}]X_{0-2}$ (HL = derivatives of tropolone, thiosemicarbazone, dithiocarbamic acid; X = arbitrary ion)	prep (anti-Hp)		816
aryl bismuth compounds	e.g. tris(4-hydroxymethylphenyl)bismuthine, chelate complexes, Bi clusters	prep	diagnostic imaging for x-ray, MRI, scintillography, ultrasound; antimicrobial; antiulcer	817
3,6,9-triaza-3,9-bis(carboxymethyl)-6-{2-[4-(1,4,7-trioxaoctyl)phenyl]-1-carboxyethyl}4,8-bis[4-(1,4,7-trioxaoctyl)benzyl]-undecanedioic acid bismuth complex	(multisubstituent DTPA derivative)		contrast media for xray, NMR, radio diagnostics of liver, gall.bile duct, liver; antidote	818
organobismuth derivatives	$Bi[C_6H_2X^1X^2X^3]_3$ (X^1 = (substituted) carboxamido, sulfonamido; X^2, X^3 = H, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylsulfonyl, C_{1-4} alkylcarbonyl, NO_2 , cyano, X^1) $Bi[(C_6H_4)_o-(SO_2NHCH_2(C_3H_5O_2)Me_2)$	prep	contrast media for xray (tablet, capsule, injection)	819

Table 10 (Continued)

Compound designation	Ligand	Chemical Data	Suggested or evaluated medicinal application (Mode of Administration)	Ref.
organobismuth compounds	phenylbismuth bis(p-vinylbenzoate), diphenylbismuth methacrylate, triphenylbismuth bis(p-vinylbenzoate), triphenylbismuth bis(methacrylate), polymers and copolymers	prep, mp (Staphylococcus aureus)	additives and coatings, prepn of foamed material for hospitals	820
methylbis(thiomethanolato) bismuth(III)	MeBi(SMe) ₂	prep, NMR, MS (bacterial)		821
bismuth 3-hydroxy-2-naphthoate		prep	intestinal bactericide	822
Bi humates		prep	gastroenterology	823
3,4-dihydroxybenzenarsonic acid bismuth salt		prep	therapeutic	824
hydroxyflavone bismuth salts	e.g. quercetin, robenitin, fisetin, quercetagin	prep (astringent, capillary tightening properties)	therapeutic	825
tri-(thiocarbamoylamino) guanidine derivative bismuth chelate	derivative is (RNHCSNHNH) ₂ C=NNHCSNHR (R = H ₂ C=CHCH ₂)	prep	coccidiostatics	826
bismuth		prep	antiparasitic agent,	827
hydroxyquinoline salicylate			antiseptic	
pamoic acid bismuth salt		prep	intestinal infections	805
p-chlorophenoxyisobutyric acid bismuth salt	mono- and bis-p-Cl(C ₆ H ₄)OC(Me) ₂ CO ₂ H salts	prep	depressant for blood cholesterol	828
bismuth carboxylates	BiR ₃ , BiOR R = camphenilante, the endomethylenebenzoate obtained by oxidation of β-pinene, endomethyleneterahydro-methyl- or ethyl-benzoate, monoiodoendomethylenhexahydromethylenebenzoate	prep, sol	therapeutic	829
organodithiocarbamic and organothiocarbamoylsulfonic acid bismuth salts	(MeMeNCS ₂) ₂ Bi(SO ₂ CSNMeMe), (MeMeNCS ₂)Bi(SO ₂ CSNMeMe) ₂	prep, yield, mp (Aspergillus niger, Bacillus subtilis, Staphylococcus aureus, Salmonella typhosa)	biocides, agricultural fungicides, antioxidants, vulcanization accelerators	830
bismuth o-mercaptobenzamide	Bi(SC ₆ H ₄ CONH ₂) ₃	prep, sol (fungicidal, bactericidal activity)	(ointments, talc)	831
basic bismuth p-aminobenzoate		prep	rheumatic fever, acute rheumatoid arthritis, acute streptococcal infections, acute staphylococcal infections (injection)	832
hydroxyquinoline bismuth iodides	8-hydroxyquinoline, 5-bromo-, 5-methyl-8-hydroxyquinoline	prep (antiseptic)		833
dipropylacetic acid bismuth salt	Bi[(C ₃ H ₇) ₂ CHCO ₂] ₃	prep, mp, sol	throat infections (rectal suppository with cocoa butter)	834

Table 10 (Continued)

Compound designation	ligand	Chemical Data	Suggested or evaluated medicinal application (Mode of Administration)	Ref.
Bi isopropyl camphorate		prep, EA, mp, soln preparation (spirocheticidal)	syphilis	
bismuth salts of ether acids	ether acid = $\text{ROC}_n\text{H}_{2n}\text{CO}_2\text{H}$ R = alkyl radical C4-10, monocyclic hydroaromatic hydrocarbonradical e.g. capryloxyacetic acid	(spirocheticidal)		835
polyhydric alcohol bismuth salts	dihydroxypropyl, trihydroxybutyl, pentahydroxyhexyl, pentahydroxycyclohexyl bismuthates	prep	therapeutic	836
3-pyridinethiol bismuth salt		prep (fungicidal, bactericidal)		837
fatty acid bismuth salt	laurate, myristate, palmitate, stearate, behenate	prep, yield, mp	bismuth therapy	838
<i>p</i> -amino- and <i>p</i> -benzamidosalicylic acid bismuth salts	$[\text{Bi}(\text{C}_7\text{H}_5\text{NO}_3)_2]\text{I}$, $[\text{Bi}(\text{C}_{14}\text{H}_{10}\text{NO}_4)]_2$	prep	tuberculostatic	839
5-pyrrolidinone-2-carboxylic acid bismuth salt			therapeutic	840
6-methyl-8-hydroxyquinoline bismuth salt	$\text{Me}(\text{C}_9\text{H}_5\text{NO})\text{Bi}(\text{OH})_2$	prep (diarrhea and intestinal flora)		841
malonic acid ester bismuth salts	e.g. dipropylcarbonyl octylmalonic ester	prep	therapeutic agents	842
methylarsonate of bismuth	$(\text{MeAsO}_3)_3\text{Bi}_2$	prep, sol (active in the body)		843
bismuth 1-thioglucose		prep	therapeutic	844
mixed bismuth carboxylates	camphenilanic and salicylic acid, camphenilanic and acetylsalicylic acid, campholytic and salicylic acid, oleic acid, stearic acid, phenylacetic acid bismuth salts	prep, sol	therapeutic (injection, in oil)	845
bismuth thiolates	mercaptocyclopentyltridecane acid, mercaptocyclopentane, mercaptocyclohexane bismuth salts	prep (therapeutic properties)		846
bismuth nicotinate		prep	therapeutic	847
bismuth subcompounds	<i>o</i> - $\text{AcOC}_6\text{H}_4\text{CO}_2\text{BiO}$	prep (stable in stomach - no data)	intestinal (oral, rectal)	848
pyridinic ligand bismuth salts	$[\text{BiL}_4][\text{HL}]$ L = pyridine, γ -picoline	prep, spectrophotometric, conductometric, potentiometric (Ehrlich ascites tumor in mice - solid and soln)		849
bismuth allantoinate	$\text{C}_4\text{H}_5\text{N}_4\text{O}_3 \cdot \text{Bi}(\text{OH})_2$	prep	external and internal ulcers, wounds, etc.	850
phenylbismuth bis(2-pyridinethiol 1-oxide)	$(\text{C}_5\text{H}_4\text{NO})\text{S}\text{Bi}(\text{Ph})\text{S}(\text{C}_5\text{H}_4\text{NO})$	prep	bacterial/ fungicidal agent in soaps, shampoos, oral products	851

Table 10 (Continued)

Compound designation	ligand	Chemical Data	Suggested or evaluated medicinal application (Mode of Administration)	Ref.
mucilage-bismuth complex	undisclosed mucilage	prep, EA, IR, carbohydrate composition of mucilage (antipeptic activity)		852
2-(<i>p</i> -aminobenzenesulfonamido)-5-ethylthio-1,3,4-thiadiazole bismuth complex		prep, IR, EA (therapeutic applicability)		853
mono- or polyhydroxyflavone bismuth salts	flavonol, quercetin, robinetin, fisetin, quercetagenin bismuth salts	prep, yield (astringent, vasoconstrictor properties as external powder, cream, lotion and as internal stomach powders)		854
hydroxyflavone-sulfonic acid basic bismuth salts	quercetin-6'-sulfonic acid	prep, sol	astringents (local application)	855
"bioquinol" variation	$C_{20}H_{24}N_2O_2 \cdot 2BiI_4H$	EA - 18% quinine (Spirochaeta pallida, clinical treatment of syphilis, comparison to usual bioquinol)		856
sulfanilamide bismuth salt		prep	ringworm, fungal infections	857
camphorcarboxylic acid bismuth salt	$(C_{10}H_{15}OCO_2)_2BiOBi(OH)(O_2COC_{10}H_{15})$	EA, sol in oil (therapeutic activity in rabbits; syphilitic patients)		858
γ,γ -diethylthiovaleric acid bismuth salt	$(C_9H_{17}O_2S_2)_3Bi, (C_9H_{17}O_2S_2)BiO$	prep, sol in oil	chemotherapeutic	859
dihydroxypropyl bismuthate		prep, mp, soln studies (stable soln in blood serum; toxicity and pharmacological studies in rats)		860
dihydroxypropyl bismuthate	$C_3H_5(OH)_2BiO_3$	prep, EA, sol (stability in dog gastric juice; toxicity and pharmacological studies in rats)		861
bismuth d-ascorbate		prep	(intramuscular injection)	862
mixed lecithin bismuth compounds	e.g. bismuth quinine iodide, cholate, 2-phenylquinoline-4-carboxylate	prep	late forms of syphilis	863
bismuth thioglycolylsulfanilamide		prep (readily absorbed, minimal local toxicity)	therapeutic agents	864

Table 10 (Continued)

Compound designation	ligand	Chemical Data	Suggested or evaluated medicinal application (Mode of Administration)	Ref.
bismuth ascorbate		prep	therapeutic	865
hexamethylenetetra amine N bismuth iodide		prep, sol	therapeutic, syphilis (oral)	866
organic carboxylic acid bismuth salt	dimethylacetic, methylallylacetic, diallylacetic, crotylpropylacetic, ethylisoamylacetic, isopropylphenylacetic, methyloctylacetic, ethylbenzylacetic, isobutyltolylacetic, ethylanisylacetic, dicyclopentylacetic, heptylcyclohexenylacetic acid	prep, sol	therapeutic	867
bismuth sodium gluconate		prep	syphilis (intramuscular injection)	868
organic aromatic compound of bismuth	NH ₂ CONHC ₆ H ₄ BiO(OH)ONO	EA (toxicity in white mice)	frambesia (intravenous injection)	869
thiosalicylic acid butyl ester bismuth salt		prep, sol	therapeutic	870
1-bismuth thioglucose		prep	pharmaceutical purposes	871
bismuth salt	Bi(C ₇ H ₁₃ O ₂) ₃	prep, sol (spirilli)		872
aminoarylseno-bismuth compounds		prep, sol	therapeutic	873
bismuth compound of pyrogallolsulfonic acid		prep	therapeutic	874
bismuth mercapto acid esters	butyl ester of thiosalicylic acid, isoamyl ester of thiosalicylic acid, isoamyl ester of thioacetic acid	prep	therapeutic (injection)	875
bismuth methyl-, ethyl-, and n-butyl camphorate		prep, mp, sol (toxicity in albino rats, intramuscular injection)		876
monosodiumdi-bismuthyl gluconate, monosodiumtri-bismuthyl gluconate		prep, EA (toxicity in rats, intravenous injection)		877
bismuth aristol compound	aristol = thymol iodide Bi[[C ₆ (O)(I)(CH ₃)(C ₃ H ₇)C ₆ (O)(I)(CH ₃)(C ₃ H ₇)] ₂ BiI	prep, EA, sol (antiseptic properties)	dermatology	878
octyloxyacetic acid bismuth salt		prep, EA, sol	therapeutic, syphilis (injection)	879
pyrocatecholsulfonic acid bismuth compound		prep	therapeutic	880
aliphatic and aromatic mercaptocarboxylic ester bismuth compounds	2-mercapto-1-carboxylic acid butyl ester bismuth compound	prep, EA	therapeutic	881
phenylethylacetic, phenylbutylacetic, diethylacetic, and cyclohexenylethylacetic acid bismuth salts		prep, sol	therapeutic	882
hydroxymercuri organic acid bismuth salts		prep	syphilis	883

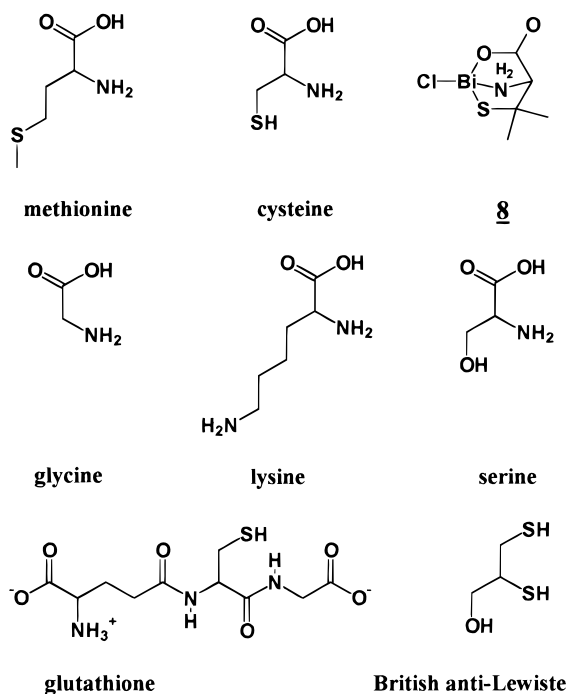
Table 10 (Continued)

Compound designation	ligand	Chemical Data	Suggested or evaluated medicinal application (Mode of Administration)	Ref.
organic bismuth acid mercury salts	bismuthyl sodium tartrate, bismuth sodium gallate or bismuthyl sodium nucleate mercury salts	(toxicity)	syphilis	884
alkali bismuthyl mannonate	alkali = Na or K	prep	therapeutic	885
bismuth camphocarboxylate		prep, EA	spirochetic infections	886
basic bismuth guaiacolcarboxylate	$C_6H_3(OH)(OCH_3)COOBiO$	prep, sol	syphilis (ointment, subcutaneous)	887
bismuth hydroxyquinolate	$Bi(OH)_2OC_9H_6N$	prep, sol	(antiseptic on wounds)	888
double iodide of emetine and bismuth	emetine · 2HI · 1.5BiI ₃	prep, EA	(gelatin capsules)	889
basic bismuth gycyrrhizate		prep, yield, mp, sol (active against gastritis, stomach and duodenal ulcers)		890
2-ethylhexylethylmalonate bismuth salt		prep	spirocheticide	891
compound of bismuth with triphenylmethane dye	e.g. hexamethyl-p-rosaniline	prep	germicide	892
inorganic phosphate	$Bi_aA_bM_c(PO_4)_d \cdot nH_2O$ (A = alkali metal, alk.-earth metal, NH ₄ ; M = tetravalent metal; $0 \leq n \leq 6$; $a, b > 0$; when $la + mb = 1$ then $c = 2$ and $d = 3$; when $la + mb = 2$ then $c = 1$ and $d = 2$; l = valence of Bi; m = valence of A)	prep	microbicides, algicides	893,894
Bi 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionate	$Bi[C_9H_6NO]CH_2CH(CO_2)NHCO(C_6H_4)Cl$	prep, mp (MIC against Hp)	Hp-induced peptic ulcers and peptic inflammatory disease	895
hydrated complex salt of bismuth hydroxide sucrose octasulfate		prep	pharmaceuticals, treatment of disorders associated with gastric mucosal damage	896
bismuth cevitamate		prep	(intramuscular injection)	897
basic bismuth inositol hexaphosphate	$C_6H_6(OPO_3)_6 \cdot Bi_6(OH)_6$	prep, yield, EA	intestinal and stomach disorders	215
pectin aluminum bismuth double salt		prep, optical rotation	gastric or duodenal ulcers or inflammations, dyspepsia, spastic colitis, postamebic colitis, diarrhea	898
o-thymolcarboxylic acid bismuth salt		mp	analgesics, antirheumatics, antipyretics, sedatives	899
4,4'-sulfonyldianiline derivative di-Bi(OH) ₂ salt	$\{4-[2,4,5-Me(HO)(iso-Pr)C_6H_2N=N]C_6H_4\}_2SO_2[Bi(OH)_2]_2$	prep	leprosy, tuberculosis	900
bismuth tribromophenol		prep	drug	901

Table 10 (Continued)

Compound designation	ligand	Chemical Data	Suggested or evaluated medicinal application (Mode of Administration)	Ref.
bicyclononanedione tetracarboxylic tetramethyl ester bismuth salt	$\text{Bi}_2[\text{C}_9\text{H}_6(\text{CO}_2\text{Me})_4\text{O}_2]_3$		algicides, fungicides, bactericides	902
bismuth bitannate		prep	pharmaceutical, phytochemical	903
bismuth iodotannate		prep	pharmaceutical, phytochemical	904
bismuth glutathione compound		prep	syphilis (injection)	905
dialkylcysteine bismuth compound	Bi salt of $\text{RR}^1\text{C}(\text{SH})\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$	prep	paraciticides	906
D-penicillamine bismuth complex			syphilis, pinta, yaws, Vincent's angina	907
quinine iodobismuthate		prep, EA	medicinal, therapeutic	803
bismuth phenate	$\text{C}_6\text{H}_5\text{OBi}(\text{OH})_2$	prep, EA	intestinal antiseptic	804
2,6-dimercaptopyridine-4-carboxylic acid Bi-NH ₄ salt/ Bi-methylaniline salt		prep	drug	908
Bi pyrochatecholdisulfonate Na salt		prep, EA, sol - water/oil partition, pH studies (sol in blood and blood serum, egg albumin, MLD and trypanosomiasis in mice and guinea pigs)		909
organobismuth monomers, copolymers and polymers	phenylbismuth bis(p-hydroxybenzoate), triphenylbismuth bis(p-aminobenzoate), dioctylbismuth triricinoleate, phenylbismuth bis(2-hydroxyethylmercaptide), phenylbismuth bis(hydroxyacetate)	prep, mp (bactericidal studies against <i>Staphylococcus aureus</i> , <i>Aerobacter aerogenes</i> , <i>Pseudomonas aeruginosa</i> , <i>Candida albicans</i> , <i>Aspergillus flavus</i>)	additives and coatings; preparation of foamed material useful in hospitals	910
triphenylphosphinimine bismuth derivative	$\text{Ph}_3\text{Bi}(\text{N}:\text{PPh}_3)_2$	prep, stability (activity toward cockroaches, <i>Staphylococcus aureus</i> , <i>Sorsenaelutea</i>)		911
tris(thiocarbamoylamino) guanidine bismuth chelate	$(\text{RNHCSNHNH})_2\text{C}:\text{NNHCSNHR}$ bismuth chelate (R = allyl, Bu, cyclohexyl, etc.)	prep (coccidiostatic activity)	coccidiostatics for poultry	912
	$\text{Na}_2[\text{Bi}(\text{O}(\text{mp})_3] \cdot 3\text{H}_2\text{O}$, $[\text{Bi}(\text{tgn})_3(\text{H}_2\text{O})] \cdot 3.5\text{H}_2\text{O}$ (mp = 6-mercaptapurine, tgn = thioguanine)	prep, EA (activity against various cancers)		913

molecules as ligands represents an important component in understanding aspects of the bioactivity. However, complexes of amino acids and proteins are rare, characterization is generally incomplete, and their formation is predictably pH dependent.^{938,939} The sulfur-based ligands are speculated to achieve tris-substitution in Bi(methionine)₃ (mp, EA, IR solubility)⁹⁴⁰ and Bi(cysteine)₃·H₂O (IR, spectrometric),^{941,942} while D-(−)-penicillamine (a dimethyl derivative of cysteine) is shown by X-ray crystallography to behave as a dianionic ligand on bismuth **8**.⁹⁴³ This tridentate chelate complex and other dialkylcysteine complexes have been suggested for medicinal use.^{906,907} Also of note are amperometric studies of glycine complexes,⁹⁴⁴ pH-metric studies of L-lysine complexes,⁹⁴⁵ and polarographic studies of serine complexes.⁹⁴⁶



More extensive data is available for the RBC–glutathione complex, which is suggested for treatment of syphilis and other diseases.⁹⁰⁵ NMR spectroscopic studies in aqueous media and in red blood cells⁹⁴⁷ indicate that the ligand is sulfur bound to bismuth.⁹⁴⁸ Stability constant determinations reveal that binding is competitive with EDTA and is pH dependent. Conclusive comparative spectroscopic data is also available for complexes involving human serum transferrin (hTF) with Bi(NTA) and Bi(Hcit);^{949,950} for complexes with red blood cells, human serum albumin, bovine serum albumin, and human serum;⁹⁵¹ for CBS with erythrocytes and erythrocyte lysate;⁹⁵² and for complexes of tripotassium dicitrate bismuthate with bile acids cholate, glycocholate, taurocholate, and glycochonoxycholeate.⁹⁵³ Complexes of renal metal binding proteins⁹⁵⁴ and other proteins have also been studied.^{955–957}

Other important bioresponse observations for bismuth compounds include Pepto-Bismol and its components bismuth subsalicylate and montmorillonite sequester bile acids from aqueous solutions in vit-

ro,⁹⁵⁸ bismuth compounds retard the action of enzymes,⁹⁵⁹ bismuth hydroxide catalyzes the hydrolysis of ribonucleic acids to dinucleoside phosphates,^{960–963} and bismuth influences the production of prostaglandins,⁹⁶⁴ the level of metallothionein-like proteins in rat kidneys,⁹⁶⁵ and the formation of metallothionein in cell cultures.^{966–969}

The solubility of bismuth compounds is enhanced by a number of biological molecules (phenothiazine derivatives, citric acid, citrus juices, and wines⁹⁷⁰ polyols, ascorbic acid, aspirin, tetracyclines, vinegars,⁹⁷¹ tetracycline, oxytetracycline, chlorotetracycline streptomycin, penicillin-G,⁹⁷² mucate, saccharate⁹⁷³ chlorophyll, pheophytin⁹⁷⁴ uracil, thiouracil,⁹⁷⁵ D-mannitol,⁹⁷⁶ L-ascorbic acid,⁹⁷⁷ and ascorbic acid⁹⁷⁸), which are considered to effectively chelate the bismuth center. Enhanced solubility or therapeutic responses indicate that some bismuth compounds modify the effect of co-ingested materials (food or drugs). For example, the adsorptive capacity of bismuth subcarbonate has been determined as high for antirheumatics such as salicylates, mefenamic acid, flufenamic acid, metiazinic acid, indomethacin,⁹⁷⁹ and corticosteroids⁹⁸⁰ and low for antibiotics such as tetracyclines.^{981–984} In comparison, bismuth nitrate has an adsorptive capacity for antihistamines such as diphenhydramine, orphenadrine and bromazine,⁹⁸⁵ indicating a selectivity in these interactions, which is confirmed by the fact that adsorption does not occur between all bismuth salt–drug combinations, as revealed in studies of aureomycin hydrochloride/terramycin hydrochloride with BSS.⁹⁸⁶ Evidence of adsorption on inorganic and organic bismuth salts has been obtained for diazepam,⁹⁸⁷ anticoagulants,⁹⁸⁸ preservatives,⁹⁸⁹ warfarin Na,⁹⁹⁰ tetracycline hydrochloride,⁹⁹¹ propranolol,^{992,993} norfloxacin,⁹⁹⁴ and penicillin.⁹⁹⁵ However, some of the observed effects are variable.^{381,996} Strong chelating ligands such as British anti-Lewisite (BAL) (2,3-dimercaptopropanol),^{997–999} *p*-aminobenzoic acid,¹⁰⁰⁰ cysteine,¹⁰⁰¹ mucin,¹⁰⁰² and dithiol ethers¹⁰⁰³ are recognized as a detoxification approach for heavy metals including bismuth. The high stability of the bismuth complexes such as Bi–BAL³⁷¹ have identified them for antimicrobial assessment in vitro and in vivo.^{394–396}

Bismuth compounds trigger the effect of penicillin against *Trypanosoma equiperdum* in rats, which is independently inactive.¹⁰⁰⁴ Conversely, biologically active molecules, especially thiols, are observed to decrease the therapeutic action of bismuth salts.¹⁰⁰⁵ Penicillin and bismuth salt suppositories are both effective in treating fusospirillary infections separately, however, coadministration is ineffective,¹⁰⁰⁶ perhaps due to reaction.¹⁰⁰⁷

VIII. Conclusions

The vast array of medicinal or antimicrobial uses for bismuth compounds indicates a diverse biorelevance for the element, which is likely valid but has not yet been unequivocally demonstrated. A wide selection of compounds and complexes of bismuth have been investigated for potential bioactivity without justification other than bismuth content. Some therapeutic utility is best described as suggested, and

most experimental studies are impeded by the chemical complexity of the bismuth compound or the superficial chemical knowledge base that is currently available for bismuth. Most importantly, few definitive identifications of bio-bismuth interactions have been reported. Nevertheless, the unquestionable antimicrobial activity of some bismuth compounds at low concentrations, the relatively low elemental human cell cytotoxicity, and the ill-defined gastric cytoprotective properties of certain bismuth salts highlights the chemistry of bismuth as an important focus for the development or discovery of new pharmaceutical agents. The efficiency of such developments will depend on the systematic assessment of bismuth chemistry as a foundation for understanding biochemical interactions. The pioneering work of Asato, Herrmann, Keppler, and Sadler represent key directions which should be exploited in the future.

IX. Abbreviations

BAL	British anti-Lewisite
BS	band spectrum, optical transitions
BSC	bismuth subcarbonate
BSG	bismuth subgallate
BSN	bismuth subnitrate
BSS	bismuth subsalicylate
CBS	colloidal bismuth subcitrate
DTA	thermal analysis, differential thermal analysis, thermogravimetry (thermogravimetric analysis), differential thermogravimetry, differential scanning calorimetry, thermobalance, thermal conductivity
EA	elemental analysis/chemical analysis
EC	electrical conductivity
ED	electron diffraction
<i>Hp</i>	<i>Helicobacter pylori</i>
H ₄ cit	citric acid
H ₄ edta	ethylenediaminetetraacetic acid
H ₄ gal	gallic acid
H ₂ lac	lactic acid
H ₃ mal	malic acid
H ₃ nta	nitrilotriacetic acid
H ₂ ox	oxalic acid
H ₂ sal	salicylic acid
H ₄ tar	tartaric acid
IR	infrared spectroscopy
Mic	microwave spectroscopy
MIC	minimum inhibitory concentration
MLD	minimal lethal dose
mp	melting point
MS	mass spectrometry
ND	neutron diffraction
NQR	²⁰⁹ Bi NQR; ¹⁷ O, ³⁵ Cl, and ³⁷ Cl NMR
PES	photoelectron spectroscopy
Pol	polarography
prep	preparation or synthesis
Ram	Raman spectroscopy
RBC	ranitidine bismuth citrate
SEM	scanning electron microscopy
sol	solubility
soln	solution
TDB	tripotassium dicitrato bismuthate
UV	solid and liquid vis, UV, and VUV spectroscopy
X-ray	X-ray diffraction data on crystal or powder

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