Methylated and thiolated arsenic species for environmental and health research — A review on synthesis and characterization☆

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A R T I C L E   I N F O

A B S T R A C T

Hundreds of millions of people around the world are exposed to elevated concentrations of inorganic and organic arsenic compounds, increasing the risk of a wide range of health effects. Studies of the environmental fate and human health effects of arsenic require authentic arsenic compounds. We summarize here the synthesis and characterization of more than a dozen methylated and thiolated arsenic compounds that are not commercially available. We discuss the methods of synthesis for the following 14 trivalent (III) and pentavalent (V) arsenic compounds: monomethylarsonous acid (MMA^{III}), dicysteinylmethyldithioarsenite (MMA^{III}(Cys)$_2$), monomethylarsonic acid (MMA^V), monomethylmonothioarsonic acid (MMMTA^V) or monothio-MMA^V, monomethyldithioarsonic acid (MMDTA^V) or dithio-MMA^V, monomethyltrithioarsonate (MMTTA^V) or trithio-MMA^V, dimethylarsinous acid (DMA^{III}), dimethylarsino-glutathione (DMA^{III}(SG)), dimethylarsinic acid (DMA^V), dimethylmonothioarsinic acid (DMMTA^V) or monothio-DMA^V, dimethyldithioarsinic acid (DMDTA^V) or dithio-DMA^V, trimethylarsine oxide (TMAO^V), arsenobetaine (AsB), and an arsenicin-A model compound. We have reviewed and compared the available methods, synthesized the arsenic compounds in our laboratories, and provided characterization information. On the basis of reaction yield, ease of synthesis and purification of product, safety considerations, and our experience, we recommend a method for the synthesis of each of these arsenic compounds.

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Contents

Introduction

The Agency for Toxic Substances and Disease Registry (ATSDR, 2015) has, for many years, consistently ranked arsenic at the top of its Priority List of Hazardous Substances, on the basis of its occurrence, toxicity, and potential for human exposure. Arsenic is commonly associated with oxygen, sulphur, carbon, and hydrogen, forming a variety of arsenic compounds (species). A variety of arsenic compounds have been made in the laboratory primarily for medical research (Cullen, 2008; Chen et al., 2015). Nearly one hundred arsenic species have been detected in the environment (Cullen and Reimer, 1989; Edmonds and Francesconi, 1977; Foster and Maher, 2016; Francesconi and Edmonds, 1997; Francesconi, 2010; Goessler et al., 1997; Jackson et al., 2012; Mandal and Suzuki, 2002; Nearing et al., 2016; Oremland and Stolz, 2003; Popowich et al., 2016; Reimer et al., 2010; Wallschläger and Stadey, 2007; Zhao et al., 2010) and as human metabolites (Abedin et al., 2002; Leffers et al., 2013; Rubin et al., 2014; Thomas et al., 2001, 2007; Vahter, 2002; Wang et al., 2015). These arsenic species have very different toxicities, ranging by several orders of magnitude in median lethal dose (LD_{50}) and median lethal concentration (LC_{50}) values (Charoensuk et al., 2009; Ebert et al., 2014; Kaise and Fukui, 1992; Moe et al., 2016; Molin et al., 2015; Naranmandura et al., 2011; Petrick et al., 2000; Styblo et al., 2000). Therefore, it is crucial to characterize all arsenic species encountered in studies of arsenic biotransformations, human exposure, and health effects (Carlin et al., 2016; Feldmann and Krupp, 2011; Le et al., 2004; Liu et al., 2016). The identification and quantification of arsenic species are greatly facilitated by the availability of appropriate arsenic standards.

Synthetic arsenic chemistry has a long history dating back to the late 1700s. The French chemist Louis Claude Cadet de Gassicourt prepared a noxious inflammable mixture of two liquids; one became known as cacodyl, $As_2(CH_3)_4$ and the other as cacodyl oxide, $[As_2(CH_3)_4]O$. Bunsen was a major contributor to these early studies, and subsequent extensive research by others has provided an understanding of the chemistry of these organoarsenicals. However, some newly discovered arsenic metabolites have presented synthetic challenges. There is no review on the preparation and characterization of some important newly discovered arsenic metabolites, such as some methyl arsenicals and their sulphur-containing analogues: monomethylarsonous acid (MMA^{III}), dimethylarsinous acid (DMA^{III}), monomethylmonothioarsonic acid (MMMTA^V), monomethyldithioarsonic acid (MMDTA^V), dimethylmonothioarsinic acid (DMMTA^V), and dimethyldithioarsinic acid (DMDTA^V) (Chen et al., 2013, 2016; Kubachka et al., 2009; Le et al., 2000a, 2000b; Naranmandura et al., 2007; Thomas et al., 2007; Ochi et al., 2008; Rubin et al., 2014; Sun et al., 2016; Suzuki et al., 2004; Wallschläger and Stadey, 2007; Wang et al., 2015; Yoshida et al., 2003). The separation, identification, and detection of these arsenic species often rely on high performance liquid chromatography (HPLC), inductively coupled plasma mass spectrometry (ICP-MS), and electrospray ionization mass spectrometry (ESI-MS) (Beauchemin et al., 1989; Heitkemper et al., 1989; Gong et al., 2002; Larsen et al., 1993; McSheehy et al., 2002; Hansen et al., 2003; Nischwitz and Pergantis, 2006; Peng et al., 2014; Yang et al., 2016). The use of respective arsenic standards in speciation analysis is vital to confirm the identity of the suspected arsenic species.

A lack of authentic arsenic standards or the use of improperly characterized synthetic products can lead to incorrect identification of arsenic species. For example, a dimethylthioarsenical has been mistaken for DMA^{III}, because of the use of an uncharacterized synthetic product serving as arsenic standard (Hansen et al., 2004; Suzuki et al., 2004). In this case the method used for synthesizing DMA^{III} was based on the method that Reay and Asher (1977) used to reduce the pentavalent inorganic arsenate to the trivalent arsenite. However, when this method is used to reduce the pentavalent dimethylarsenical, the product is not the trivalent dimethylarsenical as assumed but the thiolated dimethylarsenicals, dimethylmonothioarsinate ($Me_2As(S)OH$) and dimethyldithioarsinate ($Me_2As(S)SH$) (Hansen et al., 2004; Fricke et al., 2005). Thus, relying on this uncharacterized product led to the incorrect identification of arsenic species (Hansen et al., 2004; Suzuki et al., 2004; Naranmandura et al., 2007).

The primary objectives of this paper are (1) to review and compare the methods of synthesis reported in the literature, and (2) to recommend detailed procedures for the synthesis and characterization of the methylated and thiolated arsenicals. These new arsenicals are not commercially available but are in high demand for research purposes. This review of the various methods of synthesis provides perspectives on the diverse chemistry of arsenic. The detailed procedures for the synthesis of specific arsenic species will help guide other researchers to synthesize arsenic compounds for use in studies of the transformations/metabolism, environmental fate and behaviour, human exposure, and toxicological effects of arsenicals.

1. Monomethylarsonic acid or monomethylarsonate [$(CH_3As(O)(OH)_2)$] (MMA^V)

MMA^V is a common metabolite of inorganic arsenic formed intracellularly in the majority of organisms: animals, plants, and microorganisms. MMA^V, *e.g.*, the commercially available monosodium methanearsonate, has been used as an active ingredient in human medicines and in pesticides and herbicides for weed control (Moore and Ehman, 1977). MMA^V can be prepared on an industrial scale.

1.1. Methods for the synthesis of MMA^V

MMA^V is usually prepared as sodium methylarsonate (NaCH$_3$AsO$_3$H·6 H$_2$O) or disodium methylarsonate (Na$_2$CH$_3$AsO$_3$·6H$_2$O). Several methods are available to synthesize MMA^V. The Meyer reaction (Meyer, 1883) produces sodium

methylarsonate by reacting sodium arsenite with an alkyl halide, such as methyl iodide (CH_3I). Quick and Adams (1922) investigated the synthesis of arsonic ($RAsO_3H_2$) and arsinic (R_2AsO_2H) acids by using different alkyl halides. Miller and Seaton (1948) developed and patented a method for the industrial manufacturing of sodium methylarsonate. This method employs a closed system, high temperature (60°C), high pressure (60 psi), and the less expensive methyl chloride as the methylating agent.

1.2. Comparison of the methods for the synthesis of MMA^V

The Meyer reaction is an effective method for preparing sodium methylarsonate. When methyl iodide is used in the Meyer reaction, practically pure sodium methylarsonate can be obtained with mere cooling of the reaction mixture (Miller and Seaton, 1948). The patented Miller reaction uses conditions under which the less costly methyl chloride is able to act as the methylating agent (Miller and Seaton, 1948; Morgan, 1918). Furthermore, the addition of ammonia and calcium chloride to the reaction mixture allows for the precipitation of the arsenic compound as a calcium salt, which is easily isolated. Because the Miller reaction requires a closed system, high pressure, and elevated temperature, it is not always practical for use in a research laboratory. It is an efficient method for larger scale manufacturing of sodium methylarsonate.

1.3. Our procedures for the synthesis of MMA^V

According to the method of Quick and Adams (1922), As_2O_3 (9.9 g or 50 mmol) was added to a 10 mol/L NaOH solution, forming tri-sodium arsenite (Na_3AsO_3). CH_3I (15 g, 106 mmol) was added to the solution. The mixture was heated to 50°C for 3 hr, forming a white solid. Ethanol (30 mL) was then added, and the mixture was allowed to stand overnight. A white crystalline solid was isolated by filtration and air dried, producing 25 g of MMA^V, corresponding to a yield of 86%.

1.4. Characterization of MMA^V

Previous reports have shown that MMA^V has a melting point of 161°C (Morgan, 1918). Proton nuclear magnetic resonance (^1H NMR) of MMA^V dissolved in D_2O plus D_2SO_4 detected the methyl protons at 1.99 ppm (Naranmandura et al., 2007). ESI-MS analysis of $Na_2CH_3AsO_3$ in negative ionization mode detected signals at 139 m/z, corresponding to the $[M – H]^-$ ion. Tandem mass spectrometry (MS/MS) showed fragment ions at m/z 91 ($[AsO]^-$), 107 ($[AsO_2]^-$), 121 ($[CH_2AsO_2]^-$), and 124 ($[AsO_2OH]^-$).

2. MMA^{III} [$CH_3As(OH)_2$]

MMA^{III} is a trivalent methylarsenical metabolite of inorganic arsenic. It is formed during arsenic biomethylation that involves the stepwise reduction of the pentavalent arsenicals to the trivalent arsenicals followed by the oxidative addition of a methyl group (Challenger, 1945; Cullen et al., 1989; Cullen, 2014; Le et al., 2004; Thomas et al., 2001, 2004, 2007; Vahter, 2002). MMA^{III} is more toxic than its pentavalent counterpart MMA^V (Charoensuk et al., 2009; Naranmandura et al., 2011;

Petrick et al., 2000; Styblo et al., 1997, 2000; Vega et al., 2001). MMA^{III} has been detected in biological and environmental samples (Aposhian et al., 2000; Currier et al., 2016; Del Razo et al., 2001; Le et al., 2000a, 2000b; McKnight-Whitford et al., 2010; Naranmandura et al., 2013).

2.1. Methods for the synthesis of MMA^{III}

Both diiodomethylarsine (CH_3AsI_2) and methylarsine oxide (CH_3AsO) have been synthesized. The main process for the synthesis of diiodomethylarsine (CH_3AsI_2) involves the treatment of sodium methylarsonate solution with iodide, hydrochloric acid, and sulphur dioxide (Auger, 1906) (Scheme 1).

Two methods are available for the synthesis of methylarsine oxide. The first method, developed by Cullen et al. (1989), uses the commercially available sodium methylarsonate as the starting material, and SO_2 gas for the reduction of MMA^V to MMA^{III}, as shown in Scheme 2.

The second method, which is depicted in Scheme 3, is that of Auger (1903, 1906). The starting material, diiodomethylarsine, is dissolved in benzene and then treated with an excess of sodium carbonate and cooled until the solution becomes discoloured. After the benzene is decanted, the remaining solvent is evaporated and methylarsine oxide crystallizes.

It was previously thought that the Reay and Asher (1977) method produced methylarsine oxide through the reduction of MMA^V using a reducing solution containing sodium metabisulphite, sodium thiosulphate, and sulphuric acid. Hansen et al. (2004) and Naranmandura et al. (2007) demonstrated that the Reay and Asher method produced mostly thioarsenicals instead of methylarsine oxide.

2.2. Comparison of the methods for the synthesis of MMA^{III}

Diiodomethylarsine (CH_3AsI_2) is more stable than methylarsine oxide (CH_3AsO) during storage, although the trivalent methylarsenicals are prone to oxidation in general. Both methylarsine oxide and diiodomethylarsine dissolved in dilute aqueous solutions act as MMA^{III}. Both methods for the synthesis of CH_3AsO are simple and produce (CH_3AsO)$_n$ in high yields. Cullen's method (Cullen et al., 1989) uses a commercially available starting material, whereas Auger's method requires CH_3AsI_2 which is not commercially available and must be synthesized prior to the production of CH_3AsO.

2.3. Our procedures for the synthesis of MMA^{III}

We used the following procedures (Auger, 1906; Millar et al., 1960; Zingaro, 1996a) for the synthesis of CH_3AsI_2. $Na_2CH_3AsO_3$ (25.1 g, 86 mmol) and KI (31.3 g, 188 mmol) were dissolved in a mixture of 16 mL of concentrated hydrochloric acid and 40 mL of water. SO_2 gas was bubbled into the solution for 20–30 min. A yellow solid, with an oily liquid at the bottom, formed. The solid was collected by filtration and recrystallized in diethyl ether, affording 20 g of CH_3AsI_2 (68% yield and 98.1% purity).

We synthesized methylarsine oxide using two methods. Method A followed the report of Cullen et al. (1989). $Na_2CH_3AsO_3$ (10 g, 34 mmol) was dissolved in 20 mL of warm water. $SO_{2(g)}$ was bubbled into the solution for 20 min. The solution was heated to boiling for 10 min and then allowed to cool. The solution was
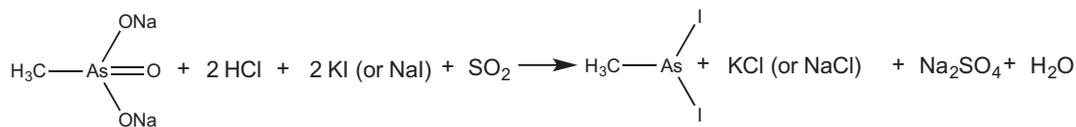
Scheme 1 – Synthesis of diiodomethylarsine (CH$_3$AsI$_2$) from monomethylarsonate (MMA^V).

neutralized with Na$_2$CO$_3$ and evaporated to dryness. The resulting powder was extracted with hot benzene and the extracts were evaporated to dryness, giving an oily substance that solidified later. After crystallization in ether, white crystals were obtained, giving 3.5 g (75% yield) of methylarsine oxide.

Method B for the synthesis of CH$_3$AsO was adopted from Auger (1903, 1906). CH$_3$AsI$_2$ (20 g, 58 mmol) was dissolved in benzene. Na$_2$CO$_3$ (6 g) and 10 mL of H$_2$O were added. The solution was refluxed for 2 hr and the benzene layer was then removed. The aqueous layer was dried over anhydrous Na$_2$SO$_4$ and evaporated to dryness. The resulting white powder was recrystallized from ether, giving 5.1 g (84% yield) of methylarsine oxide (98.2% purity).

2.4. Characterization of MMA^{III}

Analysis of our synthesized CH$_3$AsI$_2$ showed a melting point of 30°C, which is consistent with that reported by Millar et al. (1960). ^{1}H NMR gave signals at 3.11 ppm in CDCl$_3$ and 1.37 ppm in D$_2$O (DHO residual at 4.72 ppm). CH$_3$AsI$_2$ undergoes slow decomposition and darkening even when stored under an inert atmosphere. For this reason, CH$_3$AsI$_2$ should be stored in the dark, but does not need to be stored under nitrogen (Matuska et al., 2010).

Analysis of our methylarsine oxide showed a melting point of 95°C and ^{1}H NMR signals in CDCl$_3$ at 1.406 ppm, 1.451 ppm (Major), 1.476 ppm and 1.484 ppm. ESI-MS analysis of MMA^{III} is difficult because MMA^{III} is not easily ionizable by electrospray. We introduced on-line derivatization with dimercaptosuccinic acid (DMSA), by mixing the chromatographic effluent with DMSA, to form a DMSA–MMA^{III} complex. DMSA introduces negative charges, making the DMSA–MMA^{III} complex amenable for ESI-MS analysis (McKnight-Whitford et al., 2010; McKnight-Whitford and Le, 2011).

When dissolved and diluted in aqueous solutions, both methylarsine oxide and diiodomethylarsine are present as CH$_3$As(OH)$_2$ (MMA^{III}). In dilution aqueous solutions, MMA^{III} is easily oxidized to the pentavalent MMA^V (Gong et al., 2001),
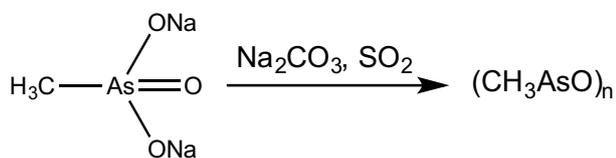
and therefore MMA^{III} solutions need to be prepared/diluted fresh before use.

3. Dimethylarsinic acid [(CH$_3$)$_2$As(O)OH] (DMA^V)

DMA^V is a major metabolite of inorganic arsenic in many organisms including humans (Vahter, 2002). DMA^V has been produced in large quantities for industry (agricultural) uses, and it is also known as cacodylic acid.

3.1. Methods for the synthesis of DMA^V

The first reported method of industrial preparation of DMA^V dates back to 1923 (Inverni, 1923). The methylation of As$_2$O$_3$ was achieved by heating a mixture of As$_2$O$_3$ and crude fused potassium acetate. Cacodyl oxide ((CH$_2$As)$_2$O), which was produced and distilled during the heating, was further air-oxidized and converted to cacodylic acid. The general reaction is described in Scheme 4. The use of this method was continued into the 1940s (Treffler, 1944). The air oxidation of cacodyl oxide was further optimized (Fioretti and Portelli, 1963).

Another method, using alkyl halides and dimethyl sulphate as alkylating agents, is more efficient and applicable to research laboratory settings. The synthesis reaction is described in Scheme 5, as summarized by Moore and Ehman (1977).

3.2. Comparison of different methods for the synthesis of DMA^V

Cost and efficiency are two major considerations in choosing the preferred method for the industrial preparation of cacodylic acid. The method described in Scheme 4 predominated in the early 20th century because crude fused potassium acetate is much cheaper than methyl iodide (CH$_3$I). However, the method using crude fused potassium acetate has a very limited yield. Only 5 kg of cacodylic acid was obtained from 60 kg of the mixed As$_2$O$_3$ and potassium acetate (Inverni, 1923).

Scheme 2 – Synthesis of methylarsine oxide (CH$_3$AsO) from monomethylarsonate (MMA^V). The synthetic product is a polymer, with an empirical formula CH$_3$AsO shown in the scheme.
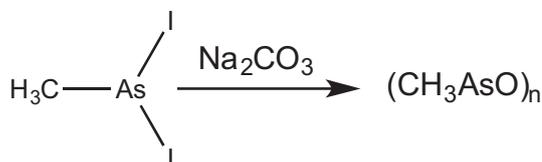
Scheme 3 – An alternative method for the synthesis of methylarsine oxide from diiodomethylarsine. The synthetic product is a polymer, with an empirical formula CH$_3$AsO shown in the scheme.
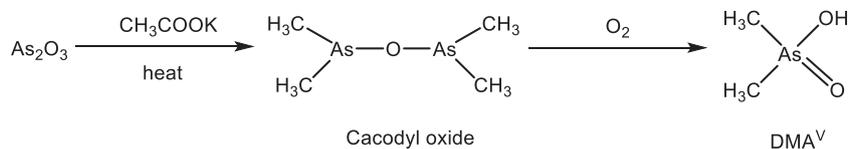
Scheme 4 – Synthesis of dimethylarsinic acid (DMA^V) from arsenic trioxide.

The second method uses an alkyl halide as the methylating agent. CH_3I has a higher reactivity but is more expensive than methyl chloride (CH_3Cl). In 1965, a patent on the synthesis of DMA^V using methylarsine oxide and CH_3Cl was approved (Moyerman and Ehman, 1965). The cost of manufacturing DMA^V was reduced using CH_3Cl as the methylating agent in Scheme 5.

3.3. Characterization of DMA^V

DMA^V is commercially available from most chemical reagent distributors. The melting point of the commercially available DMA^V is 192–198°C. ESI-MS analysis in negative ionization showed parent ion [M – H]$^-$ at an m/z of 137. MS/MS analyses detected characteristic fragment ions at m/z of 107 ([AsO$_2$]$^-$) and 122 ([CH$_3$AsO$_2$]$^-$).

4. DMA^{III} [(CH$_3$)$_2$AsOH]

Similar to MMA^{III}, DMA^{III} is another trivalent methylarsenical metabolite of inorganic arsenic in animals including humans (Cohen et al., 2016; Currier et al., 2016; Del Razo et al., 2001; Le et al., 2000b; Wang et al., 2004). DMA^{III} ((CH$_3$)$_2$AsOH) is more toxic than DMA^V, and DMA^{III} is reactive with available cysteine groups in proteins (Lu et al., 2004). DMA^{III} in dilute aqueous solutions is unstable, and can easily be oxidized to the pentavalent DMA^V (Gong et al., 2001). Therefore, its iodide form, dimethyliodoarsine ((CH$_3$)$_2$AsI), is usually prepared and stored. (CH$_3$)$_2$AsI can be dissolved in dimethyl sulphoxide (DMSO) and further diluted in water, forming (CH$_3$)$_2$AsOH.

4.1. Methods for the synthesis of DMA^{III}

Cacodyl oxide is first converted into cacodyl chloride in the presence of mercuric chloride, and further converted into cacodyl bromide or cacodyl iodide using KBr or KI. The reaction is described in Scheme 6.

Another method to synthesize (CH$_3$)$_2$AsI involves the reduction of cacodylic acid using sulphur dioxide (Burrows and Turner, 1920; Millar, 1960). Burrows and Turner (1920) developed this method, borrowing Auger's method (Auger, 1906) for the reduction of methylarsinic acid to diiodomethylarsine. The main reaction is shown in Scheme 7.
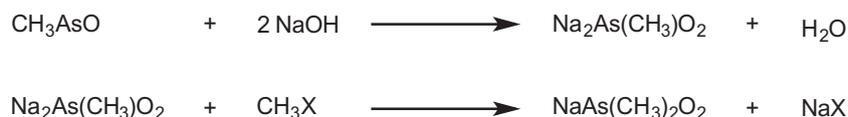
4.2. Comparison of different methods for the synthesis of DMA^{III}

The method that uses cacodyl oxide as the starting material is a two-step reaction (Scheme 6). The second conversion is nearly quantitative. The conditions for the reduction of cacodylic acid using SO$_2$ are mild (Scheme 7). Burrows and Turner (1920) obtained a yield of 90%.

Because cacodylic acid could not be cost-effectively synthesized from MMA^{III} and CH_3Cl until the late 1960s, cacodyl oxide was produced in a large quantity as a starting material for the syntheses of other organoarsine compounds in the early 1920s. This is probably the main reason why cacodyl oxide was directly used to prepare (CH$_3$)$_2$AsI at that time. Now that cacodylic acid can be cost-effectively synthesized, the method shown in Scheme 7 is widely used.

After cacodylic acid is reduced to (CH$_3$)$_2$AsI, an oily yellow product is formed, which can be easily separated. The oil solution is dried over calcium chloride and distilled. A yellow liquid that boils at 154–157°C is collected. Millar et al. (1960) synthesized (CH$_3$)$_2$AsI from CH$_3$AsI$_2$, which involved methylation to form cacodylic acid and reduction to produce (CH$_3$)$_2$AsI. Improvements were made to the purification procedures. The oil solution separated from the reaction system was first extracted with ether, and then the ether solution was dried and distilled under nitrogen. Fractional distillation was used to collect the fraction boiling at 154–166°C. The material collected was re-distilled and the fraction boiling at 154–157°C was collected. The overall yield of (CH$_3$)$_2$AsI starting from CH$_3$AsI$_2$ was 50%.

4.3. Our procedures for the synthesis of DMA^{III}

Potassium iodide (56 g, 0.34 mol) and cacodylic acid (28 g, 0.20 mol) were dissolved in 230 mL water mixed with 18 mL H$_2$SO$_4$. SO$_2$ gas was bubbled into the solution for 30 min. The colour of the solution changed from orange to colourless, then to yellow. The yellow oil was separated and dried over anhydrous Na$_2$SO$_4$. After distillation under a nitrogen atmosphere and collecting the fraction at 155–157°C, 40 g (85% yield) of (CH$_3$)$_2$AsI (pure yellow liquid) was obtained.

4.4. Characterization of DMA^{III}

Dimethylarsine hydroxide [(CH$_3$)$_2$AsOH] was obtained after dissolving a small amount of (CH$_3$)$_2$AsI in DMSO and further

Scheme 5 – Synthesis of dimethylarsinic acid (DMA^V) from methylarsine oxide (CH$_3$AsO) X denotes halide (Cl, Br, I).
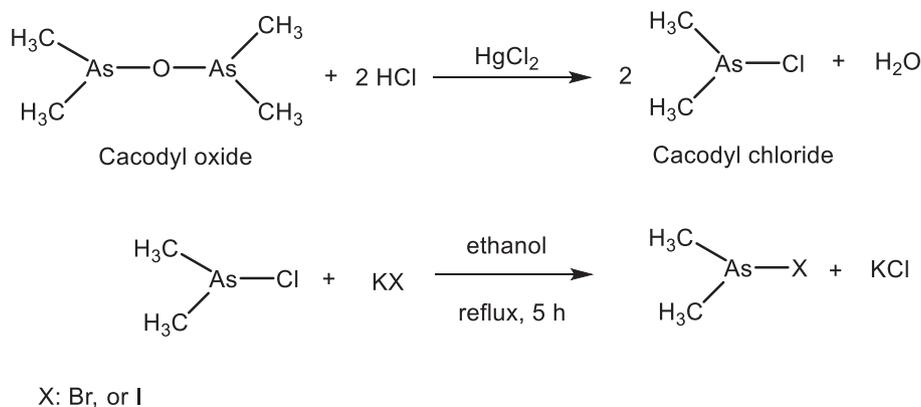
Scheme 6 – Synthesis of (CH$_3$)$_2$AsI and (CH$_3$)$_2$AsBr from cacodyl oxide.

diluting it in water. The purity of (CH$_3$)$_2$AsI was determined using HPLC separation followed by ICP-MS detection. We found that the freshly prepared dilute DMA^{III} solution contained 88% ± 1% DMA^{III} and 12% ± 1% DMA^V. The presence of DMA^V is likely due to oxidation of DMA^{III} during sample preparation and HPLC analysis. ^{1}H NMR spectra showed signals at δ 2.02 ppm in CDCl$_3$ and 1.3 ppm in D$_2$O. The boiling point of (CH$_3$)$_2$AsI was 154–160°C and the melting point was *ca.* −35°C.

Because DMA^{III} can be easily oxidized to DMA^V in solution under normal laboratory atmosphere, and DMA^{III} is poorly ionized by electrospray, it is difficult to obtain a mass spectrum of DMA^{III}. We used post-column derivatization with DMSA to form the DMSA–DMA^{III} complex (McKnight-Whitford et al., 2010; McKnight-Whitford and Le, 2011). The presence of DMSA contributed to the ionization of the complex. HPLC separation of DMA^{III}, followed by DMSA derivatization and ESI-MS detection of the DMSA–DMA^{III} complex gave a molecular ion (M$^-$) at *m/z* 285. MS/MS analysis of this molecular ion detected characteristic fragment peaks at *m/z* 103 ([C$_3$H$_3$O$_2$S]$^-$), 122 ([CH$_3$AsS]$^-$), and 137 ([(CH$_3$)$_2$AsS]$^-$).

5. Trimethylarsine oxide [(CH$_3$)$_3$AsO] (TMAO^V)

TMAO^V has been detected in marine microorganisms (Cullen et al., 1979; Kaise et al., 1987). As a metabolite of inorganic arsenic, it has also been shown to be produced in rodents (Chen et al., 2011, 2013; Lu et al., 2003; Yamauchi et al., 1990; Yoshida et al., 2001).

5.1. Methods for the synthesis of TMAO^V

Two methods have been reported to synthesize TMAO^V from trimethylarsine [(CH$_3$)$_3$As]. The main difference between these methods lies in the choice of oxidizing agent.

Razuvaev et al. (1935) used iodine to oxidize (CH$_3$)$_3$As in an aqueous solution. The di-hydroxyl derivative, (CH$_3$)$_3$As(OH)$_2$, was obtained instead of (CH$_3$)$_3$AsO. The product was then dried over P$_2$O$_5$ under vacuum, giving the oxide form. The overall reaction is described in Scheme 8. Razuvaev et al. also mentioned the use of bromine to oxidize (CH$_3$)$_3$As in diethyl ether, producing (CH$_3$)$_3$AsO. The yield varied from 70% to 80%.

Another method is to use hydrogen peroxide (H$_2$O$_2$) to oxidize (CH$_3$)$_3$As (Merijani and Zingaro, 1966; Zingaro, 1996). The reaction is described in Scheme 9. However, because of safety concerns over using hydrogen peroxide to oxidize (CH$_3$)$_3$As, we recommend that this method be avoided.

5.2. Comparison of different methods for the synthesis of TMAO^V

Both methods described above use (CH$_3$)$_3$As as the starting material. (CH$_3$)$_3$As was synthesized by methylating dimethylarsine halide using Grignard reagents. Other reagents, such as I$_2$ and Br$_2$, can be used to oxidize (CH$_3$)$_3$As. The solvent can affect the chemical form of the product. Generally, the di-hydroxyl form is obtained in an aqueous solution, and the oxide form is obtained in ether.

When H$_2$O$_2$ is used to oxidize (CH$_3$)$_3$As in ether, extreme precautions should be taken. This reaction is exothermic and (CH$_3$)$_3$As is volatile and flammable. Peroxides could be formed. An efficient fume hood and effective personal protective equipment should be used. Secondly, exposure of (CH$_3$)$_3$As to normal laboratory atmosphere or to an excessive amount of H$_2$O$_2$ solution will result in the formation of cacodylic acid instead of (CH$_3$)$_3$AsO. Therefore, the reaction should take place in an atmosphere of nitrogen and only equivalent molar amounts of H$_2$O$_2$ (30%, aq.), not excessive amounts, should be added dropwise into the ether solution of (CH$_3$)$_3$As.

Scheme 7 – Synthesis of (CH$_3$)$_2$AsI from dimethylarsinic acid (DMA^V).
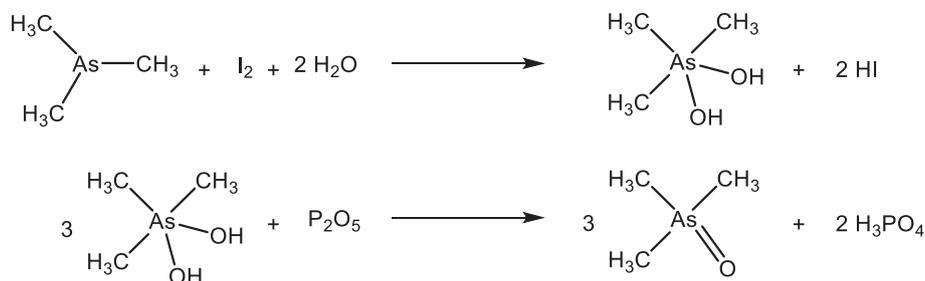
Scheme 8 – Synthesis of trimethylarsine oxide (TMAO^V) from trimethylarsine.

The oxidation of $(CH_3)_3As$ using H_2O_2 described by Zingaro and coauthors (Merijani and Zingaro, 1966; Zingaro, 1996) has been the primary synthetic route for preparing $(CH_3)_3AsO$ for 40 years. The procedures can be scaled up to 25 g. However, note that in one case a damaging explosion occurred during this reaction, causing personal injury. This accident prompted the re-evaluation of the method (Fricke, 2004).

5.3. Our procedures for the synthesis of TMAO^V

Because of the challenges associated with handling $(CH_3)_3As$ and the danger of the H_2O_2 oxidization, we developed a new method to synthesize $(CH_3)_3AsO$. The synthesis starts from $(CH_3)_2AsI$ instead of $(CH_3)_3As$. $(CH_3)_2AsI$ is methylated using dimethyl sulphate (method A) or methyl iodide (method B). During the methylation, the trivalent arsenic is oxidized to the pentavalent species, thus producing $(CH_3)_3AsO$. This process mimics the biotransformation of DMA^{III} to TMAO^V in microorganisms (Cullen et al., 1979). The general reaction is described in Scheme 10.

Method A: $(CH_3)_2AsI$ (1.15 g, 5 mmol) was dissolved in 5 mL of water containing NaOH (0.8 g, 20 mmol). $(CH_3)_2SO_4$ (0.75 g, 6 mmol) was added slowly. The reaction mixture was stirred overnight and then heated to 80°C for 1 hr. The solution was neutralized with concentrated H_2SO_4. Ten grams of pre-treated Amberlite IRA-402 resin (Sigma, St. Louis, MO, USA) was added and the mixture was shaken for 10 min. The purpose of using this anion exchange resin was to remove the excess iodine ion; otherwise, TMAO^V could not be isolated and only hydroxytrimethylarsonium iodide could be obtained (Patrick et al., 2005). The resin was filtered out and washed with water and the washings were combined with the filtrate. The combined filtrate and washings were evaporated to dryness, leaving a solid which was sublimed to give 0.6 g of $(CH_3)_3AsO$. The yield was 88%.

Method B: $(CH_3)_2AsI$ (2.0 g, 8.6 mmol) was dissolved in 10 mL of water containing NaOH (1.38 g, 34.5 mmol) in a Carius tube.

CH_3I (1.2 g, 8.6 mmol) was added slowly into the reaction solution. The tube was sealed and left in an oven at 60°C overnight. The cleanup procedure of Method A was used to obtain $(CH_3)_3AsO$ in a similar yield.

5.4. Characterization of TMAO^V

As reported by Kaise et al. (1987), the signal of ^1H NMR spectrum was at δ 1.778 ppm (singlet) and the signal of ^{13}C NMR spectrum was at δ 17.27 ppm (CH_3). Infrared analysis of $(CH_3)_3AsO$ showed 921 cm^{-1} (As=O stretch), 590 cm^{-1} (As–C stretch), 275 cm^{-1} (As=O bend), and 215 cm^{-1} (C–As–C bend) (Jensen and Jensen, 2004).

Our ESI-MS analysis in the positive mode showed a characteristic $[M + H]^+$ peak at m/z 137. Fragments of the parent ion $[M + H]^+$ obtained from MS/MS analysis included peaks at m/z 89 ($[AsCH_2]^+$), 91 ($[AsOH]^+$), 107 ($[CH_3AsOH]^+$), and 122 ($[(CH_3)_2AsOH]^+$). We also observe a peak at m/z 117, as did by McSheehy et al. (2002); however, we could not assign the identity of this fragment. Similar results have also been reported in previous studies (McSheehy et al., 2002; Nischwitz and Pergantis, 2005, 2006; Schaeffer et al., 2006).

6. Arsenobetaine

In 1925, Cox (1925) found elevated levels of arsenic in human urine from those who consumed shellfish as part of their diet. One year later, Chapman (1926) showed that crustaceans contained particularly high concentrations of arsenic. Arsenic was eliminated rapidly in the urine of people who had eaten shellfish (Crecelius, 1977; Freeman et al., 1979; Le et al., 1994a, 2004; Popowich et al., 2016).

Arsenobetaine was referred to as "hidden arsenic" because it could not be detected using the then available hydride generation methods (Cullen and Reimer, 1989; Le et al., 1993). The identification of arsenobetaine was reported in 1977 by
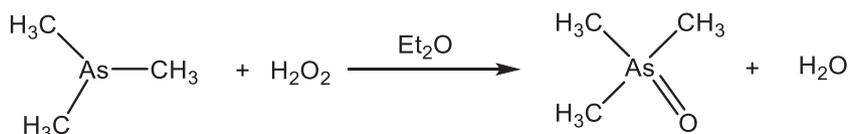
Scheme 9 – An alternate method for the synthesis of trimethylarsine oxide (TMAO^V) from trimethylarsine. Extreme caution should be taken when using hydrogen peroxide to oxidize trimethylarsine.
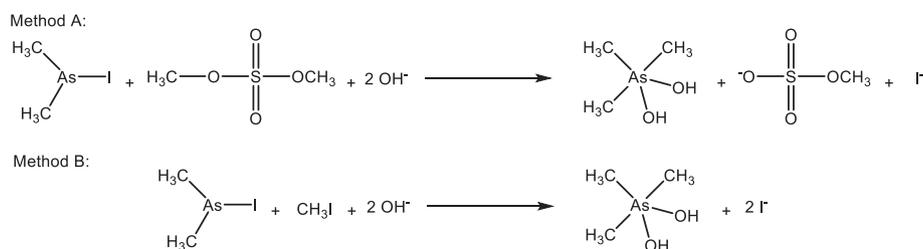
Scheme 10 – Two methods for the synthesis of hydroxytrimethylarsonium, precursor of trimethylarsine oxide (TMAO^V), from dimethyliodoarsine [(CH$_3$)$_2$AsI].

Edmonds et al. (1977). The structure was confirmed by using X-ray crystallography (Cannon et al., 1981).

Before the structure of arsenobetaine became known, it had been isolated from commercially important seafood, such as the liver of cod, the tail muscle of the western rock lobster, and from the flesh of the dusky shark (Cannon et al., 1981; Lunde, 1975). Methanol was used for extraction. After evaporation of the organic solvent, the residue was dissolved in water. The aqueous solution was then mixed and shaken with phenol. The impurities remained in the aqueous layer. The phenol layer was diluted with ether and shaken with water, and the aqueous solution passed through an ionic exchange column to remove acids and bases. The final product was purified by using chromatography and crystallized.

6.1. Methods for the synthesis of arsenobetaine

Edmonds et al. (1977) synthesized arsenobetaine from DMA^V (Scheme 11). Cacodylic acid was converted to dimethyliodoarsine, based on the method of Burrows and Turner (1920). The resulting dimethyliodoarsine was treated with methylmagnesium iodide, as recommended by Challenger and Ellis (1935), to generate trimethylarsine, which was then condensed with ethyl bromoacetate to afford the quaternary arsonium bromide. According to the method of Kosower and Patton (1961), hydrolysis of this substance produced arsenobetaine. The total yield from dimethyliodoarsine was 10.8%.

Goetz and Norin (1983) used the reaction depicted in Scheme 12 to synthesize ^{73}As-labelled trimethylarsine. The synthesis of trimethylarsine is a key step in the preparation of ^{73}As-labelled arsenobetaine. ^{73}As(OH)$_3$ was added to a solution of HCl, forming AsCl$_3$ which was then extracted by

n-pentane. LiCH$_3$ in di-n-butylether was used as a methyl donor in the preparation of trimethylarsine. After bathing at 190°C, 95% ^{73}As was distilled out as ^{73}As(CH$_3$)$_3$. The rest procedure of using ^{73}As(CH$_3$)$_3$ to synthesize arsenobetaine followed the method of Edmonds et al. (Scheme 11). The total yield of this method was 72%.

To improve the yield of arsenobetaine from trimethylarsine, Ismail and Toia (1988) used bromoacetic acid to react with trimethylarsine; their procedures are illustrated in Scheme 13 (bottom). A yield of 81% was obtained in this reaction. The reaction of trimethylarsine with bromoacetic acid leads to the formation of the hydrobromide of arsenobetaine, which crystallizes directly from the reaction mixtures.

Minhas et al. (1998) modified Ismail and Toia's method to synthesize arsenobetaine bromide. (CH$_3$)$_3$As was reacted with bromoacetic acid, and the final product was collected and gave a yield of 96%.

Although the yields for the synthesis of arsenobetaine gradually improved, trimethylarsine remained difficult to isolate due to its low boiling point (52°C) and flammability. Fricke (2004) developed a synthesis method for arsenobetaine that avoided the use of volatile trimethylarsine (Scheme 14). Sodium dimethylarsenide, instead of trimethylarsine, was condensed with ethyl bromocarboxylate. The product was then converted to quaternary arsonium salts by the addition of methyl iodide, and the quaternary arsonium ion could be hydrolyzed to the arsenobetaine.

Bernardo et al. (2004) also developed a "one-pot" synthesis method to produce ^{14}C-labelled arsenobetaine, as shown in Scheme 15. Dimethylarsinylacetic acid was the reduction product of the pentavalent 2-(dimethylarsinyl)acetic acid. The trivalent arsinylacetic acid was methylated by [^{14}C]methyl
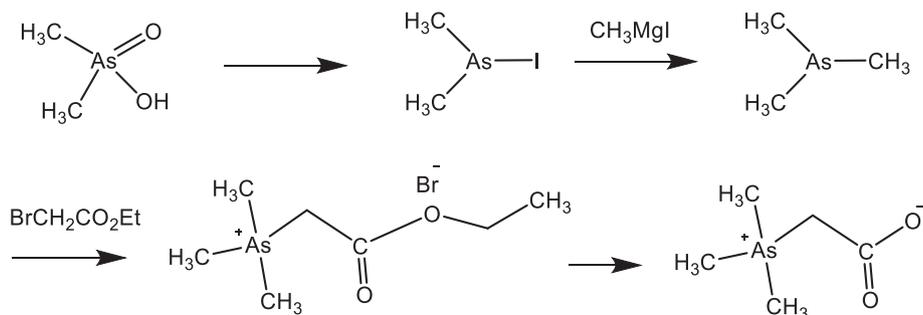
Scheme 11 – Synthesis of arsenobetaine from dimethylarsinic acid (DMA^V).
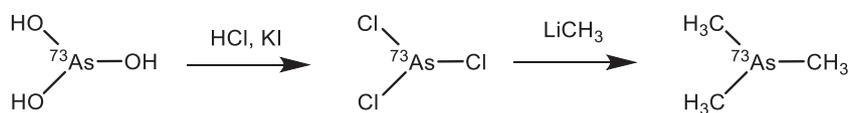
Scheme 12 – Synthesis of [73]As-labelled trimethylarsine from [73]As-labelled arsenite.

iodide, which resulted in ^{14}C-labelled arsenobetaine. The chemical yield of ^{14}C-labelled arsenobetaine was only 19%. Starting from trimethylarsine, Lischka et al. (2011) followed the methods of Irgolic et al. (1987) and Lagarde et al. (1999) to synthesize a ^{13}C-labelled arsenobetaine by using ethyl bromoacetate-[13]C_2. The yield of ^{13}C-labelled product was 88%.

6.2. Our procedures for the synthesis of arsenobetaine

DMA^V (50 g, 362 mmol) was dissolved in 200 mL of water. Potassium iodide (165 g, 994 mmol) and sodium bisulphite (5 g, 48 mmol) were added, followed by rapid addition (2 min) of 250 mL of concentrated hydrochloric acid. This mixture was stirred for 24 hr at room temperature with occasional addition of sodium bisulphite (total of 23 g, 221 mmol). The resulting yellow oil was separated and dried over calcium chloride. Distillation gave 75 g of dimethyliodoarsine as yellow oil.

Sodium (9.0 g, 390 mmol) in 150 mL of tetrahydrofuran (THF) was prepared and the flask was cooled in a dry ice/ acetone bath. Dimethyliodoarsine (26.8 g, 116 mmol) dissolved in 65 mL of THF was added with stirring in 1 hr. The reaction was observed to produce a dark brownish-green mixture. The solution of sodium dimethylarsenide was separated from excess sodium and the sodium iodide byproduct under a positive argon pressure.

Ethyl bromoacetate (19.3 g, 115 mmol) was slowly added (30 min) to the above green product, as the reaction was stirred and cooled in an ice bath. This reaction was allowed to stir for two days, under argon, at room temperature. This arsine (9.8 g, 51 mmol) was purified as a clear oil by vacuum distillation and dissolved in 20 mL of toluene. An excess of methyl iodide (9.1 g, 64 mmol) was slowly added with stirring

under argon. Immediately, a white precipitate began to form. After 24 hr, 20 mL of pentane was added and the precipitate was collected by filtration and washed with pentane. The resulting white solid was dried and recrystallized from methanol to yield 15.5 g of ethoxycarbonylmethyl(trimethyl)arsonium iodide as a white microcrystalline precipitate.

The ethoxycarbonylmethyl(trimethyl)arsonium iodide (15 g, 50 mmol) in water was applied to 250 g of Dowex 2 (OH^-) resin. Upon elution with 400 mL of water, evaporation, and drying, the resulting white crystals were dissolved in a minimum of hot ethanol (15 mL), and 200 mL of acetone was added to initiate recrystallization. Argon was bubbled into the solution and the container sealed. After 48 hr, the white crystals were removed by filtration and dried under vacuum to afford 5.58 g (64% yield) of arsenobetaine (Scheme 14).

6.3. Characterization of arsenobetaine

The synthetic arsenobetaine melted at 204–210°C, consistent with the report of Edmonds et al. (1977). Lischka et al. (2011) reported the melting point of the synthesized ^{13}C-labelled arsenobetaine as 203°C.

In the ^{1}H NMR spectra of arsenobetaine bromide (Minhas et al., 1998), the singlet at δ 1.997 ppm was attributed to nine equivalent protons of the $(CH_3)_3As$ group. The second singlet at 3.577 ppm was assigned to the two protons of the $AsCH_2$ group. The proton ratio as calculated from the integration of peaks was 8.98:2 (9:2). The signal at 4.726 ppm was from the DHO impurity in the D_2O solvent. The singlets at 33.28 and 172.46 ppm corresponded to $AsCH_2$ and COOH groups, respectively. These results are similar to those reported by Fricke (2004) and Cannon et al. (1981). In the ^{13}C NMR spectra of arsenobetaine (Fricke, 2004), the three singlets at δ 9.87, 32.81,
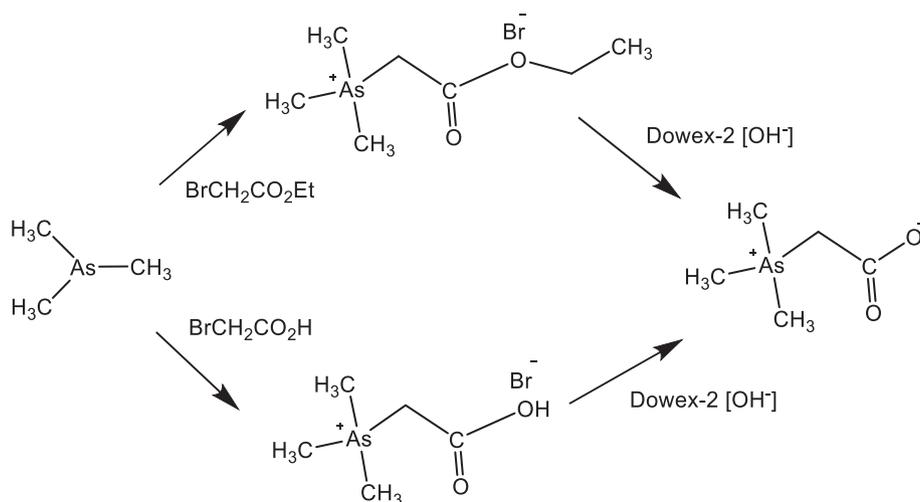
Scheme 13 – Methods for the synthesis of arsenobetaine from trimethylarsine.
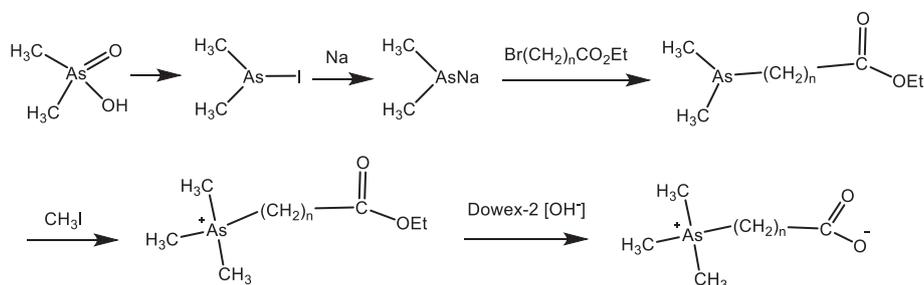
Scheme 14 – Synthesis of arsenobetaine from dimethylarsinic acid (DMA^V). The final product is arsenobetaine where n = 1.

and 172.17 ppm corresponded to the carbon(s) of the (CH$_3$)$_3$As group, the AsCH$_2$ group, and the COOH group, respectively.

Mass spectrometry analysis of arsenobetaine, a zwitterion, is usually carried out in positive ionization mode. The major product ions from the mass spectrum (200°C/70 eV) of Edmonds et al. (1977) were: m/z 134 (37% — intensity normalized against m/z 91), 120 (20%), 117 (18%), 105 (28%), 103 (50%), 101 (20%), 91 (100%), 90 (18%), and 89 (55%). The accurate precursor ion and product ions were also obtained by high resolution MS (Fricke, 2004). The detected molecular ion [M + H]$^+$ at m/z 179.0040 was consistent with the theoretical value (179.0053) for arsenobetaine (C$_5$H$_{12}$As$^+$O$_2$). The major product ions were similar to the results of Edmonds et al. (1977).

7. Arsenicin-A model compound

Arsenicin-A, the only naturally occurring polyarsenic compound, has been isolated from extracts of the poecilosclerid sponge *Echinochalina bargibanti*, collected in New Caledonia (Mancini et al., 2006). NMR, MS, and Fourier transform infrared spectroscopy (FT-IR) analyses were used to characterize arsenicin-A. Crystals of the arsenical suitable for X-ray studies were not available but an initial quantum chemical calculation of the IR spectral data suggested that the structure was an adamantane-type (Scheme 16) with C$_2$ symmetry. A model as a structural analogue of arsenicin-A was synthesized and characterized (Marx et al., 1996; Mancini et al., 2006). Lu et al. (2010, 2012) subsequently synthesized arsenicin-A and

confirmed its adamantane-type structure with NMR and crystallography.

7.1. Methods for the synthesis of the arsenicin-A model compound

Marx et al. (1996) and Mancini et al. (2006) synthesized the arsenicin-A model compound according to Scheme 17. It involved heating a mixture of arsenic trioxide, propionic acid, propionic anhydride, and potassium carbonate at 165°C for 2 hr, followed by separation and purification.

7.2. Our procedures for the synthesis of the arsenicin-A model compound

The method of Marx et al. (1996) and Mancini et al. (2006), with minor modifications (Chen, 2013), was used for the synthesis of the arsenicin-A model compound. As$_2$O$_3$ (0.40 g, 2.02 mmol), K$_2$CO$_3$ (0.29 g, 2.10 mmol), propionic acid (0.5 ml, 6.68 mmol), and propionic anhydride (2.0 mL, 17.16 mmol) were mixed together in a 50 mL round-bottom flask, and refluxed at 165°C for 2 hr. After the mixture was cooled to room temperature, 0.8 mL of water was added, followed by heating to 88°C for 1 hr. Additional water (20 mL) was added to quench the reaction. The reaction product was extracted with CH$_2$Cl$_2$ (3 × 30 mL). The combined organic extracts were treated with Na$_2$SO$_4$, filtered, and the liquid phase evaporated from the filtrate. The resultant oily solid was dissolved in CH$_2$Cl$_2$ (20 mL) and fractionated by silica gel chromatography. CH$_2$Cl$_2$ was used as the eluent. The solvent was evaporated

Scheme 15 – Synthesis of ^{14}C-labelled arsenobetaine.

Scheme 16 – Structures of arsenicin-A and arsenicin-A model compound.

Scheme 18 – Synthesis of dicysteinylmethyldithioarsenite (MMA^{III}(Cys)$_2$) from monomethylarsonic acid (MMA^V).

MMA^{III}(Cys)$_2$ dissolved in D$_2$O plus D$_2$SO$_4$ showed expected signals corresponding to the methyl protons at 1.34 ppm (Naranmandura et al., 2007).

9. Dimethylarsino-glutathione (DMA^{III}(SG))

DMA^{III}(SG) has been suggested as an intermediate in the metabolism of inorganic arsenic (Hirano and Kobayashi, 2006), although it has not been consistently detected in urine or bile samples of test animals exposed to inorganic arsenic. DMA^{III}(SG), under the trade names of Darinaparsin, ZIO-101, and SGLU-1, has been shown to have antitumor activity on an As$_2$O$_3$-resistant myeloma cell line (Matulis et al., 2009) and on an MRP1/ABCC1-overexpressed cell line (Diaz et al., 2008).

9.1. Methods for the synthesis of DMA^{III}(SG)

Two methods for the synthesis of DMA^{III}(SG) have been reported. In the method reported by Cullen et al. (1984a, 1984b), cacodylic acid and glutathione (GSH) were mixed in a 1:3 molar ratio in water under nitrogen atmosphere. GSH reduced the pentavalent arsenic to trivalent arsenic, which formed the complex with GSH (Scheme 19).

The second method (Scheme 20) uses cacodyl chloride as the starting material (Amedio and Waligora, 2009). GSH reacts with cacodyl chloride in the presence of trimethylamine at temperatures no higher than 5°C, under nitrogen atmosphere.

9.2. Comparison of the methods for the synthesis of DMA^{III}(SG)

GSH acts as both the reducing agent and the coordinating agent in the method developed by Cullen et al. (1984a, 1984b). Cacodylic acid is stable in a normal laboratory atmosphere making handling the starting material and the reaction simple to execute. However the reaction is slow. Cullen et al. (1984a, 1984b) kept the incubation for 12 hr and obtained a yield of 38%.
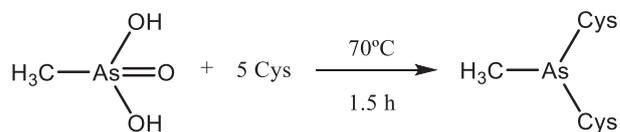
from the fractions of interest, yielding the arsenicin-A model compound (0.11 g, 0.26 mmol, 26% yield). Our yield was lower than those reported by Marx et al. (1996) (87%) and Mancini et al. (2006) (80%). The use of too much water for quenching the reaction is likely the cause of our lower yield (we used 20 mL water for one tenth of the starting materials compared to Marx et al. who used 25 mL water with a starting material of 4.0 g As$_2$O$_3$).

7.3. Characterization of the arsenicin-A model compound

The melting point of the compound is 132°C (Marx et al., 1996). Infrared spectra showed strong signals at 726 and 794 cm^{-1} (As–O stretching) and a weaker signal at 1112 cm^{-1} (CH bending) (Mancini et al., 2006). Mass spectrometry analyses in positive ionization mode showed the parent ion at m/z 421 [M + H]$^+$ and the fragments at m/z 377 [M + H–CH$_3$CHO]$^+$, 333 [M + H–2CH$_3$CHO]$^+$ and 225 [As$_3$]$^+$ (Mancini et al., 2006). ^{1}H and ^{13}C NMR results of the compound have also been reported (Mancini et al., 2006; Marx et al., 1996; Tähtinen et al., 2008).

8. Dicysteinylmethyldithioarsenite (MMA^{III}(Cys)$_2$)

Styblo et al. (1997) prepared MMA^{III}(Cys)$_2$ based on the reduction of TMAO^V by thiols (Cullen et al., 1984a, 1984b). Suzuki et al. (2004) synthesized MMA^{III}(Cys)$_2$ by reducing MMA^V with cysteine (Scheme 18). While MMA^{III} is readily oxidized, MMA^{III}(Cys)$_2$ could be more stable than MeAsI$_2$ as a trivalent MMA^{III} species. A higher stability of MMA^{III}(Cys)$_2$ was achieved probably because of the excess unreacted cysteine present in the solution, minimizing the oxidation of the trivalent methyl arsenical back to MMA^V. ^{1}H NMR analysis of

Scheme 17 – Synthesis of arsenicin-A model compound from arsenic trioxide.
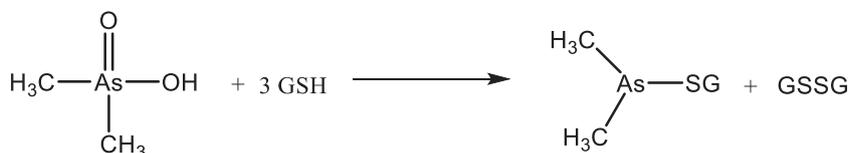
Scheme 19 – Synthesis of dimethylarsino-glutathione [DMA^{III}(SG)] from dimethylarsinic acid (DMA^V). Glutathione (GSH) is oxidized to glutathione disulphide (GSSG).

Cacodyl chloride oxidizes easily under a normal atmosphere, but it is more reactive and can bind with GSH quickly. The reaction duration was 4 hr. Amedio and Waligora (2009) reported a yield of 75% and product purity of 99.5%. The reaction can be scaled up at least to 100 g of the product DMA^{III}(SG).

9.3. Our procedures for the synthesis

We followed the method of Cullen et al. (1984a, 1984b) for the synthesis of DMA^{III}(SG). DMA^V (0.899 g, 6.5 mmol) and GSH (6 g, 19.5 mmol) were dissolved in 50 mL of water and the solution was stirred for 24 hr under a nitrogen atmosphere. After drying with a vacuum rotary evaporator at room temperature, the residue was extracted three times with 100 mL of cold methanol. The methanol solution was evaporated to dryness and a white solid was recrystallized from water/methanol (50:50).

9.4. Characterization of DMA^{III}(SG)

As reported by Cullen et al. (1984a, 1984b), the ^{1}H NMR spectrum of DMA^{III}(SG) in D$_2$O showed signals at δ 1.73 (doublet, 6H), 2.53 (quartet, 2H), 2.92 (triplet, 1H), 3.38 (doublet, 1H), 3.54 (doublet of doublets 1H), 4.14 (triplet, 1H), 4.18 (doublet, 2H), and 4.94 (triplet, 1H). The ^{13}C NMR spectrum in D$_2$O/HCl showed signals at δ 15.19 (CH$_3$), 27.22 (CH$_2$), 32.67 (CH$_2$), 33.79 (CH$_2$), 42.85 (CH$_2$), 54.28 (CH), and 56.68 (CH).

ESI-MS analysis of DMA^{III}(SG) observed parent ions at m/z 412 ([(CH$_3$)$_2$As(SG) + H]$^+$) (Park and Butcher, 2010). Product ions at m/z 394 ([412 – H$_2$O]$^+$), 337 ([412 – Gly]$^+$), 283 ([412 – Glu]$^+$), 266 ([283 – H$_2$O]$^+$), 155 ([(CH$_3$)$_2$AsSOH + H]$^+$), 266 ([283 – NH$_3$]$^+$), 155 ([(CH$_3$)$_2$AsSOH$_2$]$^+$), 122 ([(CH$_3$)$_2$AsNH$_3$]$^+$), 155 ([(CH$_3$)$_2$AsSOH$_2$]$^+$), 144 ([266 – (CH$_3$)$_2$AsOH]$^+$), 137 ([(CH$_3$)$_2$AsS]+), 112 ([266 – (CH$_3$)$_2$AsSOH]$^+$) were also observed under various conditions of collision energy. Kala et al. (2000) reported a negative parent ion at m/z 410 ([(CH$_3$)$_2$As(SG) – H]$^-$) and a product ion at m/z 306 (GS$^-$).

10. DMMTA^V [Me$_2$As(S)(OH)], or monothio-DMA^V

Yoshida et al. (2001) found several unidentified metabolites of DMA^V in the liver of rats administered DMA^V. Kuroda et al. (2004) and Yoshida et al. (2003) later identified these metabolites as monothio-DMA^V and dithio-DMA^V, also known as DMMTA^V and DMDTA^V. DMMTA^V was also found as a common metabolite in the urine of Bangladesh women who were chronically exposed to inorganic arsenic (Raml et al., 2007). DMMTA^V has also been detected in rice samples (Ackerman et al., 2005). DMMTA^V is more toxic than DMA^V (Moe et al., 2016; Naranmandura et al., 2009, 2011).

10.1. Methods for the synthesis of DMMTA^V (monothio-DMA^V)

Three methods have been reported for the synthesis of DMMTA^V. The first method was developed by Reay and Asher (1977). The main reaction is shown in Scheme 21.

Suzuki et al. (2004) modified the method of Reay and Asher (1977), attempting to obtain DMA^{III}, but the reaction actually produced DMMTA^V (Scheme 22). The identity of the DMMTA^V product was determined by Hansen et al. (2004), Fricke et al. (2005), and Naranmandura et al. (2006).

The third method for the synthesis of DMMTA^V is to bubble H$_2$S directly into a DMA^V solution (Scheme 23). This reaction is successful under either acidic (HCl solution) (Wallschläger and London, 2008) or alkaline (NaOH solution) conditions (Fricke et al., 2007).

10.2. Comparison of the methods for the synthesis of DMMTA^V

All three methods involve the replacement of an oxygen on DMA^V with a sulphur to form DMMTA^V. The difference between them lies in how the sulphur-containing reducing reagents are supplied. Although the method of Reay and Asher (1977) produced some DMMTA^V (no yield was reported), a portion of the starting DMA^V remained, resulting in a mixture of arsenic compounds. Suzuki et al. (2004) stated that it was difficult to scale up this reaction to produce concentrated DMMTA^V solution for use in *in vivo* experiments. The method of Suzuki et al. (2004) uses Na$_2$S and stepwise addition of H$_2$SO$_4$ to form H$_2$S, and thus the stoichiometry ratio of the reducing reagent H$_2$S and DMA^V can be controlled. When the ratio of Na$_2$S:H$_2$SO$_4$:DMA^V was 1.6:1.6:1, the predominant species in the product mixture was DMMTA^V. During this process, the H$_2$SO$_4$ solution was added stepwise under a nitrogen atmosphere, and the reaction solution was allowed to stand for

Scheme 20 – An alternative method for the synthesis of dimethylarsino-glutathione [DMA^{III}(SG)] from cacodyl chloride [(CH$_3$)$_2$AsCl].
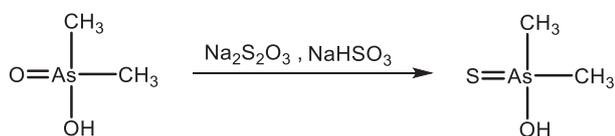
Scheme 21 – An earlier method for the synthesis of dimethylmonothioarsinic acid (DMMTA^V) from dimethylarsinic acid (DMA^V).

Scheme 23 – A third method for the synthesis of dimethylmonothioarsinic acid (DMMTA^V) from dimethylarsinic acid (DMA^V).

1 hr. The DMMTA^V was extracted using an organic solvent, such as chloroform or ethyl ether, while DMA^V remained in the aqueous solution. DMMTA^V was recrystallized from ethyl ether/methanol under nitrogen atmosphere. In the third method, H$_2$S was bubbled directly into an organic solution containing DMA^V and NaOH. The use of ethanol facilitated the direct extraction of DMMTA^V. Raml et al. (2007) used HCl instead of NaOH, preventing the formation of undesired products.

10.3. Our procedures for the synthesis of DMMTA^V

Our procedures for the synthesis of DMMTA^V were slightly modified from those of Suzuki et al. (2004). DMA^V (2.76 g, 20 mmol) and sodium sulphide nonahydrate (7.6 g, 32 mmol) were dissolved in 30 mL of water. Concentrated H$_2$SO$_4$ (1.7 mL, 32 mmol) was added dropwise to the solution. The reaction mixture was extracted with ether and dried over anhydrous Na$_2$SO$_4$. The ether was evaporated under N$_2$ and colourless crystals were formed. We obtained 2.7 g of DMMTA^V corresponding to a yield of 88%.

### 10.4. Characterization of DMMTA^V

The melting point of our synthesized DMMTA^V was 68.5°C and the ^{1}H NMR signals in CDCl$_3$ were at 1.54 (s, 3H) and 2.15 (s, 3H). Further characterization of DMMTA^V has been carried out using HPLC separation with mass spectrometry detection, including ICP-MS, high resolution quadrupole time-of-flight (qTOF) MS, and triple quadrupole MS/MS. The arsenic compounds were separated using ion pairing chromatography on an ODS-3 column (Prodigy 3 μm) with a mobile phase containing 3 mmol/L malonic acid, 5% methanol, and 0.15% tetrabutylammonium hydroxide (pH 5.7). Negative ionization ESI with high resolution MS analysis gave molecular ion of DMMTA^V at m/z 153.9357 and characteristic fragment ions at m/z 122.8885 and 137.9114.

Suzuki et al. (2004) and Naranmandura et al. (2006) used similar gel filtration and anion exchange chromatography for separation and both ICP-MS and ESI-MS for detection of
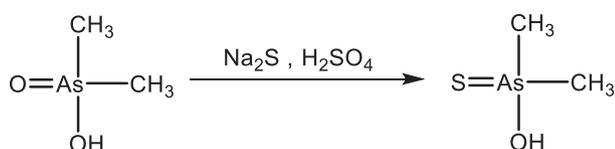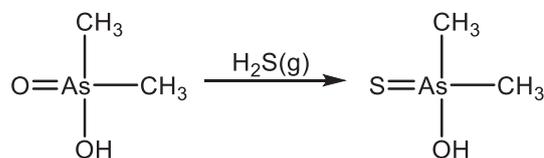
arsenic compounds. The anion exchange chromatography (column ES-502 7N) could not resolve DMMTA^V from DMDTA^V, although it separated the two sulphur-containing compounds from other arsenicals. The gel filtration chromatography (column GS-220 HQ) successfully separated DMMTA^V from DMDTA^V and other arsenicals including MMA^V, DMA^V, and inorganic arsenicals.

Hansen et al. (2004) used anion exchange chromatography and slightly different conditions. The effluent from HPLC was split between ICP-MS and ESI-MS for simultaneous detection. The simultaneous detection of m/z 34(^{34}S), m/z 48 (^{32}S^{16}O) and m/z 75 (^{75}As) by ICP-MS, and the molecular ion at m/z 155 ([(CH3)$_2$AsSOH$_2$]$^+$) together with the fragment ions at m/z 137 ([(CH$_3$)$_2$AsS]$^+$) and m/z 107 ([AsS]$^+$) by ESI-MS indicated that the detected arsenic compound contained sulphur. ESI-qTOF-MS analysis showed a species at m/z 153.941, consistent with the theoretical value (153.950) of DMMTA^V. To determine whether the structure of DMMTA^V is Me$_2$As(=S)OH or Me$_2$As(=O)SH, the authors used tautomeric energies' models to calculate the energy difference and Boltzmann population ratio at 300 K. Their results suggest that Me$_2$As(=S)OH is more favoured.

In the work by Fricke et al. (2005), the reaction of DMA^V and H$_2$S was monitored using reversed phase chromatography with ICP-MS and ESI-MS detection. Positive ionization ESI-MS analysis produced a main peak at m/z 155 ([C$_2$H$_8$AsSO]$^+$), corresponding to DMMTA^V. DMMTA^V became the predominant species in the reaction mixture after 1 hr of reaction.

Wallschläger and London (2008) used anion exchange chromatography and ICP-MS with the dynamic reaction cell (DRC) function to monitor simultaneously arsenic (m/z 91, AsO) and sulphur (m/z 48, ^{32}SO and m/z 50, ^{34}SO). ESI-MS/MS in negative mode detected ions at m/z 152.9, 137.8, and 122.8, corresponding to DMMTA^V.

11. DMDTA^V [Me$_2$As(S)SH], or dithio-DMA^V

DMDTA^V, also known as dithio-DMA^V, was observed by Yoshida et al. (2001) and identified by Yoshida et al. (2003) and Kuroda et al. (2004). It was detected in the urine of rats after chronic oral administration of DMA^V, MMA^V, As^{III}, or TMAO^V (Yoshida et al., 2001). Yoshida et al. (2003) isolated *Escherichia coli* A3-6 from the intestinal tract of rats orally administered DMA^V and detected DMDTA^V as one of the microbial metabolites of DMA^V. DMDTA^V has also been detected in a groundwater aquifer that was severely impacted by methylated arsenic pesticides

Scheme 22 – A second method for the synthesis of dimethylmonothioarsinic acid (DMMTA^V) from dimethylarsinic acid (DMA^V).

(Wallschläger and London, 2008) and in sulphidic water sources (Wallschläger and Stadey, 2007).

11.1. Methods for the synthesis of DMDTA^V (dithio-DMA^V)

Two methods have been reported for the synthesis of DMDTA^V. One method is similar to that of Suzuki et al. (2004) for the synthesis of DMMTA^V, except that the molar ratio of Na$_2$S and H$_2$SO$_4$ to DMA^V was increased (Na$_2$S:H$_2$SO$_4$:DMA^V ratio 7.5:7.5:1), and the reaction time was extended (to 1 day). The increased amount of H$_2$S formation resulted in replacement of oxygen by sulphur, forming DMDTA^V (Scheme 24).

Fricke et al. (2005) provided an alternative method for the synthesis of DMDTA^V. H$_2$S was directly bubbled into an alkaline solution containing DMA^V and NaOH (Scheme 25). A H$_2$S gas cylinder was used to supply H$_2$S. The reaction vessel was sealed to allow residual H$_2$S to react. The reaction rate could be enhanced if ethanol or a mixture of ethanol and water was used as the solvent, instead of water. The increased reaction rate is likely due to the enhanced solubilisation of H$_2$S in ethanol.

11.2. Comparison of the methods for the synthesis of DMDTA^V

The two methods differ by how H$_2$S is supplied to the reaction mixture. Suzuki et al. (2004) used Na$_2$S and H$_2$SO$_4$ to produce H$_2$S in the reaction, while Fricke et al. (2005) introduced H$_2$S from a gas cylinder. Wallschläger and Stadey (2007) stated that the method of Fricke et al. (2005) gave a higher purity (>95%). In both methods, DMDTA^V can be further self-conjugated to form Me$_2$As(S)SAsMe$_2$ (Fricke et al., 2005).

11.3. Our procedures for the synthesis of DMDTA^V

We synthesized sodium dimethyldithioarsinate [Me$_2$As(S)SNa] using the method of Fricke et al. (2005, 2007). Cacodylic acid (2.02 g, 14.6 mmol) and NaOH (0.58 g, 14.5 mmol) were dissolved in 25 mL of boiling ethanol. Hydrogen sulphide was bubbled into the boiling solution for 30 min, and a white solid precipitated. After cooling, colourless crystals were isolated by filtration and air dried, giving a yield of 2.61 g (93%).

11.4. Characterization of DMDTA^V

DMDTA^V cannot be purified as the free acid, and can only be isolated as a salt, which requires the presence of appropriate metal ions. Förster et al. (1970) listed several metals as appropriate counter ions, including Na(I), Cr(II), Ni(II), Co(II), Zn(II), and Cd(II).

The sodium salt of DMDTA^V is a stable colourless crystal with a melting point of 181–182°C. The melting point may vary
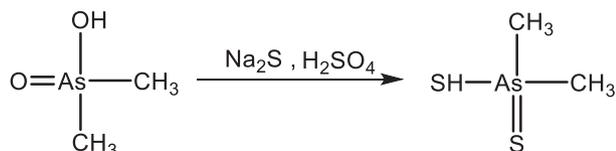
Scheme 24 – Synthesis of dimethyldithioarsinic acid (DMDTA^V) from dimethylarsinic acid (DMA^V).
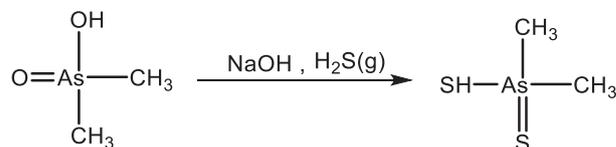
Scheme 25 – A second method for the synthesis of dimethyldithioarsinic acid (DMDTA^V) from dimethylarsinic acid (DMA^V).

according to the degree of hydration and purity. Other salts of DMDTA^V have different colours and varying melting points. ^{1}H NMR signals were found at 1.53 ppm in CDCl$_3$ and 1.90 ppm in D$_2$O (DHO residual at 4.63 ppm). Slow evaporation of the ethanol solution afforded a quality single crystal for X-ray crystal structure determination.

Chromatography and mass spectrometry methods for the characterization of DMDTA^V were similar to those for DMMTA^V. Our results from HPLC–ICP-MS analyses showed that the product contained 98.5% ± 0.3% DMDTA^V, 1.2% ± 0.1% DMMTA^V, and 0.22% ± 0.03% DMA^V. ESI-MS analysis in negative mode revealed a characteristic molecular ion of DMDTA^V at m/z 168.9184 and characteristic fragment ions at m/z 153.8894 and 138.8663.

Fricke et al. (2005) reported a main mass spectral peak at m/z 171 ([C$_2$H$_8$AsS$_2$]$^+$) and fragment ion at m/z 137 ([C$_2$H$_6$AsS]$^+$) (positive mode). Suzuki et al. (2004) observed an m/z of 169 (in negative mode) ([(CH$_3$)$_2$As($=$S)S]$^-$). Wallschläger and London (2008) detected m/z 166.8, 153.8 and 138.8 by ESI-MS/MS (in negative mode).

Wallschläger and London (2008) suggested that an oxidation half-life of all methylated As–S species in unpreserved samples at 4°C was on the order of one month. During storage, the thiolated arsenic compounds converted slowly into their oxy-analogues following: DMDTA^V → DMMTA^V → DMA^V. Cryofreezing or acidification did not improve stability.

12. MMMTA^V[CH$_3$As($=$S)(OH)$_2$], or monothio-MMA^V

MMMTA^V, also known as monothio-MMA^V, was detected in the urine (Naranmandura et al., 2007; Chen et al., 2016) and blood plasma (Chen et al., 2013) of experimental animals. The mechanism underlying the biotransformation of MMMTA^V is not yet well understood. Emerging evidence suggests that gastrointestinal microbiota with the ability to produce H$_2$S are responsible for the thiolation of MMA^V, leading to the formation of MMMTA^V (Van de Wiele et al., 2010; Bu et al., 2011; Alava et al., 2012; Rubin et al., 2014).

12.1. Methods for the synthesis of MMMTA^V

Methods for the synthesis of MMMTA^V are similar to those for the synthesis of DMMTA^V, such as the method of Naranmandura et al. (2007) (Scheme 26). MMMTA^V was prepared by the dropwise addition of H$_2$SO$_4$ to an aqueous solution of MMA^V and Na$_2$S to give a final molar ratio of MMA^V:Na$_2$S:H$_2$SO$_4$ = 1:3:4. The reaction solution was allowed to stand for 1 hr. MMMTA^V in the reaction solution was purified
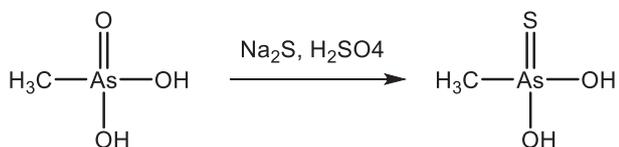
Scheme 26 – Synthesis of monomethylmonothioarsonic acid (MMMTA^V) from monomethylarsonic acid (MMA^V).

by chromatography (on a Wako Gel 100 C18 column by elution with 10 mmol/L ammonium acetate buffer, pH 6.5, 25°C).

Alava et al. (2012) used a mixture of MMA^V and H$_2$S solutions to prepare MMMTA^V (Scheme 27). They mixed 900 µL MMA^V solution (equivalent 40 µg As/mL) with 100 µL saturated H$_2$S solution in a 1-mL glass vial, and placed the mixture on a mechanical shaker overnight. The 40 µg As/mL MMA^V solution was prepared in 10% V/V formic acid. The saturated H$_2$S solution was prepared using a reaction between iron(II) sulphide and hydrochloric acid, which generated H$_2$S.

### 12.2. Comparison of the methods for the synthesis of MMMTA^V

Although the two methods used different reaction conditions, the principle of the reaction is the same. However, neither yield nor purity information was provided for either method. The method described by Naranmandura et al. (2007) is more convenient, since it is easier to use solid Na$_2$S than to prepare a saturated H$_2$S solution as described by Alava et al. (2012).

12.3. Our procedures for the synthesis of MMMTA^V

We prepared MMMTA^V according to the method of Naranmandura et al. (2007) with slight modifications. First, sodium methylarsonate (2.9 g, 10 mmol) and sodium sulphide nonahydrate (7.2 g, 30 mmol) were dissolved in 100 mL of water and kept under nitrogen atmosphere. Then, H$_2$SO$_4$ (60 mmol) diluted in 20 mL of water was added dropwise to the solution. The reaction mixture was stirred at room temperature for 3 hr. The molar ratio of MMA^V/Na$_2$S/H$_2$SO$_4$ was 1:3:6.

12.4. Characterization

A molecular ion detected with HPLC–ESI-MS in negative mode was at m/z 155 [M – H]$^-$, corresponding to the theoretical value for MMMTA^V. The ratio of sulphur to arsenic (S:As) was determined to be 1:1 by HPLC–ICP-MS. The chemical shift of methyl protons measured by ^{1}H NMR was 1.235 ppm in D$_2$O plus D$_2$SO$_4$, which is similar to that of pentavalent
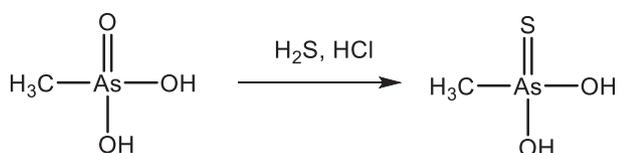
MMA^V (1.317 ppm) and different from that of trivalent MMA^{III} (0.731 ppm). The results of characterization were consistent with those reported by Naranmandura et al. (2007) for MMMTA^V.

MMMTA^V is air sensitive and rapidly converts to MMA^V when exposed to an air atmosphere. MMMTA^V in solution is stable for a few days in a sealed flask at room temperature.

13. Sodium monomethyltrithioarsonate (MMTTA^V), MeAs(=S)(SNa)$_2$)

There has been no report on the occurrence of MMTTA^V in the natural environment or in biological systems. It is possible that MMTTA^V is not stable or that its environmental concentration is very low.

13.1. A method for the synthesis of MMTTA^V

There has been no report on a method for the synthesis of MMTTA^V. We synthesized MMTTA^V (Scheme 28) using a method similar to that for the synthesis of DMDTA^V. H$_2$S gas was bubbled into the solution containing MMA^V and NaOH. A H$_2$S gas cylinder provided a stable source of H$_2$S to enable the thiolation of MMA^V to MMTTA^V.

13.2. Characterization

Ion pairing and weak anion exchange HPLC separation with ICP-MS detection indicated several arsenic species in the reaction products, including: 22% ± 1% MMTTA^V, 55% ± 2% MMDTA^V, 8% ± 2% MMMTA^V, 9.1% ± 0.3% MMA^V, 4.2% ± 0.2% MMA^{III}, and 0.17% ± 0.06% As^V. HPLC–ESI-TOF-MS analysis (negative mode) showed a molecular ion [M^{-1}] at m/z 186.8698 and a fragment ion at m/z 152.8817, consistent with the theoretical value of MMTTA^V. Additional fragment ions at m/z 138.8662 and m/z 106.8942, corresponding to AsS$_2^-$ and AsS$^-$, were also observed. Likewise, MMDTA^V and its fragment ions were also detected using HPLC–ESI-TOF-MS. A molecular ion at m/z 170.8916 and fragment ions at m/z 155.9695, 136.9044, 122.8890, 106.8940, and 90.9167 are consistent with the expected spectrum of MMDTA^V.

^{1}H NMR analysis showed a peak located at 1.99 ppm (D$_2$O, 4.744 ppm). An attempt to crystallize the compound from the crude white solid failed due to the decomposition of the products in the air. Consequently, X-ray crystallographic analysis could not be performed. No other physical and chemical information has been reported.

Scheme 27 – A second method for the synthesis of monomethylmonothioarsonic acid (MMMTA^V) from monomethylarsonic acid (MMA^V).
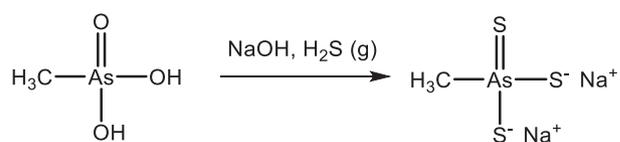
Scheme 28 – Synthesis of disodium monomethyltrithioarsonate (MMTTA^V) from monomethylarsonic acid (MMA^V).

14. Concluding remarks

We have focused this review on 14 trivalent (III) and pentavalent (V) organic arsenic compounds, MMA^{III}, $MMA^{III}(Cys)_2$, MMA^V, $MMMTA^V$, $MMDTA^V$, $MMTTA^V$, DMA^{III}, $DMA^{III}(SG)$, DMA^V, $DMMTA^V$, $DMDTA^V$, $TMAO^V$, arsenobetaine, and an arsenicin-A model compound. Although these 14 arsenic compounds are very important because of their frequent occurrence and diverse toxicities, they represent only a small fraction of arsenic compounds reported.

Other major groups of naturally occurring organic arsenic compounds, such as arsenosugars (Feldmann and Krupp, 2011; Francesconi, 2010; Le et al., 1994b), arsenolipids (Khan and Francesconi, 2016), and arsenoproteins/peptides, are worthy of similar review. Arsenosugars in particular occur widely in marine algae at much higher concentrations than other arsenic species. Arsenosugars are also present in marine bivalves and some terrestrial organisms. The potential health effects of arsenosugars have not been elucidated (Carlin et al., 2016), although DMA^V is one of the major metabolites excreted into the urine following human ingestion of arsenosugars in food (Le et al., 1994a; Ma and Le, 1998; Thomas and Bradham, 2016).

Another class of arsenic-containing compounds deserving future attention were synthesized for the purposes of analytical detection, biosensing, and cellular imaging (Adams et al., 2002; Griffin et al., 1998; Shen et al., 2013; Yan et al., 2016). Most of these arsenic compounds were designed to alter the fluorescence properties of test molecules, enabling fluorescence detection/imaging. FlAsH is a good example (Adams et al., 2002); it is widely used for imaging cellular production of specific target proteins.

This review provides a summary of the methods available for the synthesis of key arsenic compounds encountered during environmental, biological, and health research. The availability of these arsenic compounds should facilitate further studies of the role of arsenic in these human endeavours.

Acknowledgments

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