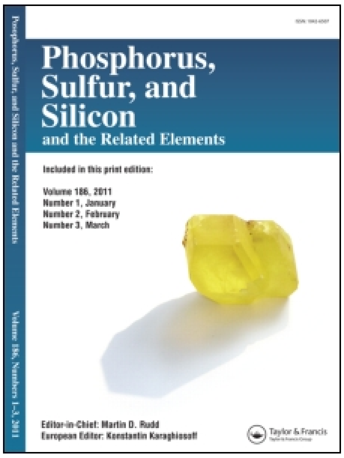


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

On C--As Bond Formation: Preparation of Aliphatic Arsonic Acids

Panayiotis V. Ioannou[a]
[a] Department of Chemistry, University of Patras, Patras, Greece

To cite this Article Ioannou, Panayiotis V.(2002) 'On C--As Bond Formation: Preparation of Aliphatic Arsonic Acids', Phosphorus, Sulfur, and Silicon and the Related Elements, 177: 1, 1 — 14
To link to this Article: DOI: 10.1080/10426500210237
URL: http://dx.doi.org/10.1080/10426500210237

Phosphorus, Sulfur and Silicon, 2002, 177:1–14
Copyright © 2002 Taylor & Francis
1042-6507/02 $12.00 + .00

ON C–As BOND FORMATION: PREPARATION OF ALIPHATIC ARSONIC ACIDS

Panayiotis V. Ioannou
Department of Chemistry, University of Patras, Patras, Greece

(Received June 12 2001.)

A review of the attempts to create a C—As bond in aliphatic arsonic acids using a variety of As(III) nucleophiles and carbon electrophiles is presented together with our additional efforts on this subject. The results suggest that the Meyer reaction cannot be realized by bulky As(III) nucleophiles or substrate electrophiles most likely from inability to attain the S_N2 transition state. The reaction cannot be run in organic solvents but works in aqueous or aqueous/alcoholic alkaline arsenite solutions, and the main challenge is to render a lipophilic substrate water soluble. Such a substrate is the α-halocarboxylic acid due to its hydrophilic —$CHXCOO^-$ part which after conversion to —$CH(AsO_3H_2)COOH$ and decarboxylation, yields the aliphatic arsonic acid. The mechanisms for these two reactions have been studied and the conditions for optimal yields have been found. Thus a new, and most likely a widely applicable, strategy for the preparation of aliphatic arsonic acids is now available.

Keywords: 2-arsonocarboxylic acids; α-halocarboxylic acids; arsenites; arsonic acids; decarboxylation; Meyer reaction

INTRODUCTION

For the preparation of aliphatic arsonic acids there exists two methodologically general methods:[1]

1. A carbanion displaces a good leaving group attached to a suitable As(III) compound. The other two groups must also be labile when the new As(III) is transformed to As(V) in arsonic acid. This is the case with Grignard reagents as shown in Eq. 1:[2]

$$(Et_2N)_2\ddot{A}s\text{—}Cl + RMgX \rightarrow R\text{—}\ddot{A}s(NEt_2)_2 \xrightarrow{H_2O_2, H_2O} RAsO_3H_2 \quad (1)$$

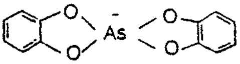
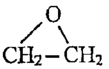
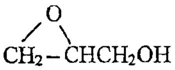
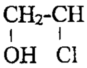
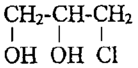
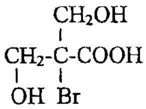
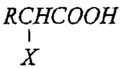
Address correspondence to Panayiotis V. Ioannou, Department of Chemistry, University of Patras, Patras, Greece.

However, aliphatic Grignard reagents cannot be prepared when the R contains —OH, —NH_2, >C=O, —COOR′ etc. groups.[3]

2. Using the lone electron pair on the arsenic in the As(III) compounds to attack an electrophilic carbon as shown in Eq. 2:

$$\rightarrow As\!: + R\text{—}Y \xrightarrow{\text{solvent}} \rightarrow As^{+}\text{—}R \xrightarrow{\text{work-up}} RAsO_3H_2 \tag{2}$$

TABLE I Arsenic Nucleophiles and Carbon Electrophiles Tested for Creation of a C—As Bond in Aliphatic Arsonic Acids Under Various Conditions (Those in Italics are Reported Herein)

Nucleophile	Electrophile	Solvent	Catalyst
$(RO)_3As$:	**1** RX	**7** H_2O	$BuAsO_3H_2$
$(RS)_3$ As:	**2** RO-SO_2-Me	**8** H_2O/MeOH	*neutral*
Na_3AsO_3[α]	**3** 	**9** *MeOH*	*anionic*
	(amsylate)	*EtOH*	*cationic*
		DMSO	
	4 $RO\text{-}SO_2\text{–}[CH_2]_3\text{-}\overset{+}{N}Me_3$	**10** *H_2O/monoglyme*	
Ag_3AsO_3	**5** ([3]betylate)	*H_2O/diglyme*	
$(Me_4N)_3AsO_3$[b]	**6** 	*H_2O/triglyme*	
		11 *H_2O/THF*	
		H_2O/$HOCH_2CH_2OH$	
		**12**	
	 $\underset{OH}{CH_2}\text{-}\underset{Cl}{CH}$	**13**	
	 $\underset{OH}{CH_2}\text{-}\underset{OH}{CH}\text{-}\underset{Cl}{CH_2}$	**14**	
	 $\underset{OH}{CH_2}\text{-}\overset{CH_2OH}{\underset{Br}{C}}\text{-}COOH$	**15**	
	 *$R\underset{X}{CH}COOH$*	**16**	

[α] Na_3AsO_3 means an aqueous alkaline arsenite solution prepared using the stoichiometry: $1/2As_2O_3 + 3NaOH \rightarrow Na_3AsO_3 + 3/2\ H_2O$. Actually the Na_3AsO_3 is in trace amounts in such solutions.[14]

[b] *$(Me_4N)_3AsO_3$* means a methanolic solution prepared using the stoichiometry: $1/2As_2O_3 + 3Me_4NOH \rightarrow (Me_4N)_3AsO_3 + 3/2H_2O$. The solution should also contain $(Me_4N)_2HAsO_3$, $(Me_4N)H_2AsO_3$, and Me_4NOH due to hydrolysis of $(Me_4N)_3AsO_3$.

Then, a range of As(III) compounds, electrophiles and solvents can be used, as shown in Table I.

Trialkyl arsenites, (**1**) do not react with alkyl halides.[4] In fact, the arsonic acid ester on heating reverts back to the trialkyl arsenite[5] (retro-Arbuzov reaction[6]), as seen in Eq. 3:

$$(RO)_3\,As + R'{-}X \overset{\not\rightharpoonup}{\leftharpoondown} R'{-}As(O)(OR)_2 + RX \tag{3}$$

The trialkyl[4] and triphenyl[7] trithioarsenites (**2**) did not give the Arbuzov type reaction (3) with alkyl halides. Likewise, we found that the $(PhS)_3As$ with the amsylate **9** in dichloromethane gave As_2O_3 and PhSSPh without consuming the substrate.[8] These experiments demonstrated that the lone electron pair on arsenic in **1** and **2** was chemically inactive.

Aqueous alkaline arsenite, symbolized Na_3AsO_3, **3** (Table I), reacts with alkyl halides to give the arsonic acid, the Meyer reaction.[9] It works with a variety of short chain alkyl halides,[10–12] but with lipophilic ones, such as butyl bromide, shows an induction period[13] of ~100 h the cause of which still remains unknown. Addition of a cosolvent, usually methanol, accelerates the reaction presumably by increasing the solubility of the alkyl halide.[13] The mechanism of the Meyer reaction was found[14] to be S_N2 and the nucleophile is the bulky trianion, ${AsO_3}^{3-}$, the dianion $HAsO_3^{2-}$ not having an appreciable activity. The concentration of ${AsO_3}^{3-}$ increases in concentrated aqueous arsenite solutions or in the presence of excess sodium hydroxide.[15] In practice a little excess of base is preferable.[16]

The complex **4** although in the solid state has a stereochemically active lone electron pair[17] it was chemically unreactive against 1-bromooctane in benzene solution, probably for steric reasons, while with **9** or **10** gave the monooctyl ether of catechol.[8]

Therefore, if one wishes to prepare an aliphatic arsonic acid one has to use the ${AsO_3}^{3-}$ nucleophile and modify the electrophilic substrate and the reaction solvent.

A lipophilic substrate like an alkyl halide can be made somewhat hydrophilic, at least near the electrophilic carbon, by converting it to mesylate, **8**, amsylate, **9**, or [3]betylate, **10**. However, these substrates under the Meyer conditions gave the parent alcohol, ROH, implying attack of HO^- and not of ${AsO_3}^{3-}$ most likely for steric reasons.[8]

The Meyer reaction of Na_3AsO_3 is not restricted to alkyl halides but other substrates, like ethylene oxide, **11**,[18,19] and *rac, R* or *S* glycidols, **12**,[20,21] can be used to prepare specific arsonic acids.

When vicinal to a halide leaving group there is a hydrophilic group, then the Meyer reaction with Na_3AsO_3 will be facilitated. Moreover, if this group can be removed under mild conditions, then a valuable strategy for the preparation of arsonic acids will be available.

A hydrophilic, nonremovable, group is the —OH one. Thus, the substrates **13**, **14**, and **15** give 2-hydroxyethylarsonic,[22–24] 2,3-dihydroxypropylarsonic,[16, 25] and 3-arsono-2-hydroxy-2-(hydroxymethyl)propionic[26] acids, respectively. Mechanistically, these substrates react mainly by first being converted to their epoxides,[16,23,26] and to a lesser degree by direct displacement of the halide.[14]

The substrate **16** contains the very hydrophilic $—COO^-$ group, which will either render the whole molecule soluble or bring the halide into contact with the aqueous alkaline arsenite phase and will also facilitate the displacement of the halide. Once the geminal arsonocarboxylic acid has been prepared it can be decarboxylated,[27] because the $—AsO_3H_2$ group is somewhat electron withdrawing, thus giving the aliphatic arsonic acid. This represents a method of wider scope for the preparation of aliphatic arsonic acids and it was first described for the preparation of the arsonomethyl analogue of AMP.[28]

In this article we report on the mainly disappointing results in achieving the Meyer reaction with the lipophilic 1-bromopentane, 1-bromooctane and 1-bromododecane by the nucleophiles **3**, **5**, and **6** in various solvents, in the presence of various catalysts and by using sonication. Because of the low yields obtained during the synthesis of the arsonomethyl analogue of the AMP[28] we prepared 2-arsonohexanoic acid and decarboxylated it to pentylarsonic acid in order to optimize the reaction conditions.

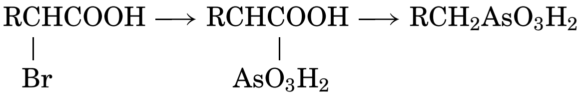
RESULTS AND DISCUSSION

Silver orthoarsenite suspended in DMSO in the presence of 1-bromooctane did not give any octylarsonic acid. Similarly, $(Me_4N)_3AsO_3$ in methanol and various alkyl bromides at RT did not give alkylarsonic acids probably because it was in the nonnucleophilic[14] $HAsO_3{}^{2-}$ form.

The Meyer reaction has also been run in mixed solvents: H_2O/MeOH,[13] H_2O/EtOH[9,11,12,29] and H_2O/glycerol[30,31] to assist the dissolution of the alkyl halide in the aqueous alkaline arsenite phase, but still the reactions were slow, for example, 356 h refluxing for the preparation of 2-methylpropylarsonic acid in 42% yield.[12] We tried as cosolvents THF, ethylene glycol, and mono-, di-, and triglyme in such proportions as to give a one phase solution with the aqueous alkaline arsenite. From these systems only the H_2O/monoglyme showed some promise but the reaction was still quite slow with the 1-bromooctane : $\sim$50% reaction after 6 days at 60°C.

It was reported[32,33] that upon addition of butylarsonate to the system butyl bromide and Na_3AsO_3, the rate of the reaction, at 91°C, increased giving 60% of the product after an unspecified period of time. We used neutral, anionic and cationic compounds as catalysts for the Meyer reaction with 1-bromooctane but without any success. Therefore, the origin of the induction period noted by Pietsch[13] is still an open question. Sonication as a means of bringing the aqueous alkaline arsenite and lipophilic alkyl halide into close contact was also tried but without success.

In order to optimize the reaction conditions for the transformation[28]

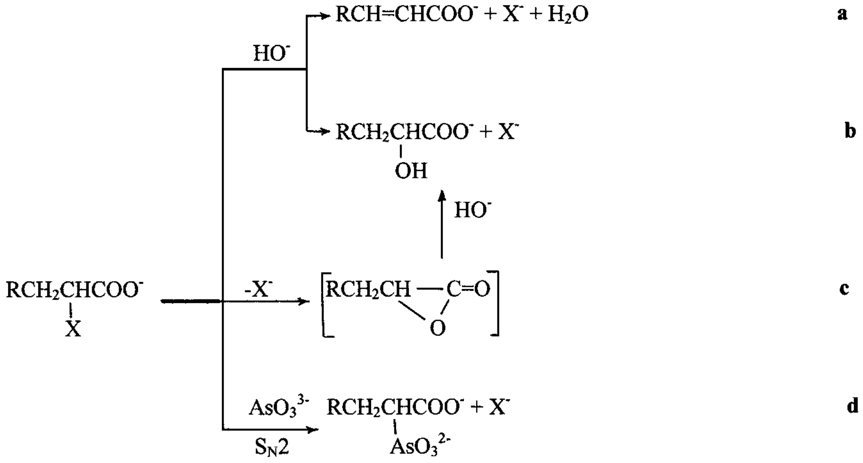


$$\underset{\underset{\mathrm{Br}}{|}}{\mathrm{RCHCOOH}} \longrightarrow \underset{\underset{\mathrm{AsO_3H_2}}{|}}{\mathrm{RCHCOOH}} \longrightarrow \mathrm{RCH_2AsO_3H_2} \qquad (4)$$

we prepared 2-bromohexanoic acid by the Hell-Volhard-Zelinskii method.[34] This procedure gives impure product[35] and the fatty acid contaminant can only be removed by repeated distillations.[36] Moreover, the aggressive reagents and conditions used in this method may not be tolerated by many substances if one wishes to prepare their arsonic acids. However, there are milder ways to create the $-CHBrCOOH$ functionality such as from an alcohol via its aldehyde using $Ph_3P{=}CBrCOOCMe_3$[28] or an alkyl halide using $(EtO_2C)_2CHNHAc$.[37]

A classical example of conversion of a 2-halocarboxylic acid into a 2-arsonocarboxylic acid is in the preparation of arsonoacetic acid.[38] This preparation is unique for its rapidity and high yields, which imply that side reactions, for example path b in Scheme 1, did not take place. In the case of a secondary halide, which is known to react only slightly in the Meyer reaction,[11] the possible routes leading to product and by-products are shown in Scheme 1. Therefore, the yield of the conversion into 2-arsonocarboxylic acid will depend on the relative quantities of substrate/Na_3AsO_3/NaOH, their concentrations and reaction temperature.

Adams et al.[28] using excess of Na_3AsO_3 and even larger excess NaOH at 2.5 M concentration obtained 20% of their 2-arsonocarboxylic acid after 24 h at 40°C. At RT sodium 2-bromohexanoate with stoichiometric amount of Na_3AsO_3 or with 100% excess of both Na_3AsO_3 and NaOH at 13 M concentration gave traces of 2-hexanoic acid, the main by-product being 2-hydroxyhexanoic acid. This acid is produced in greater amounts when the system becomes warm during the addition

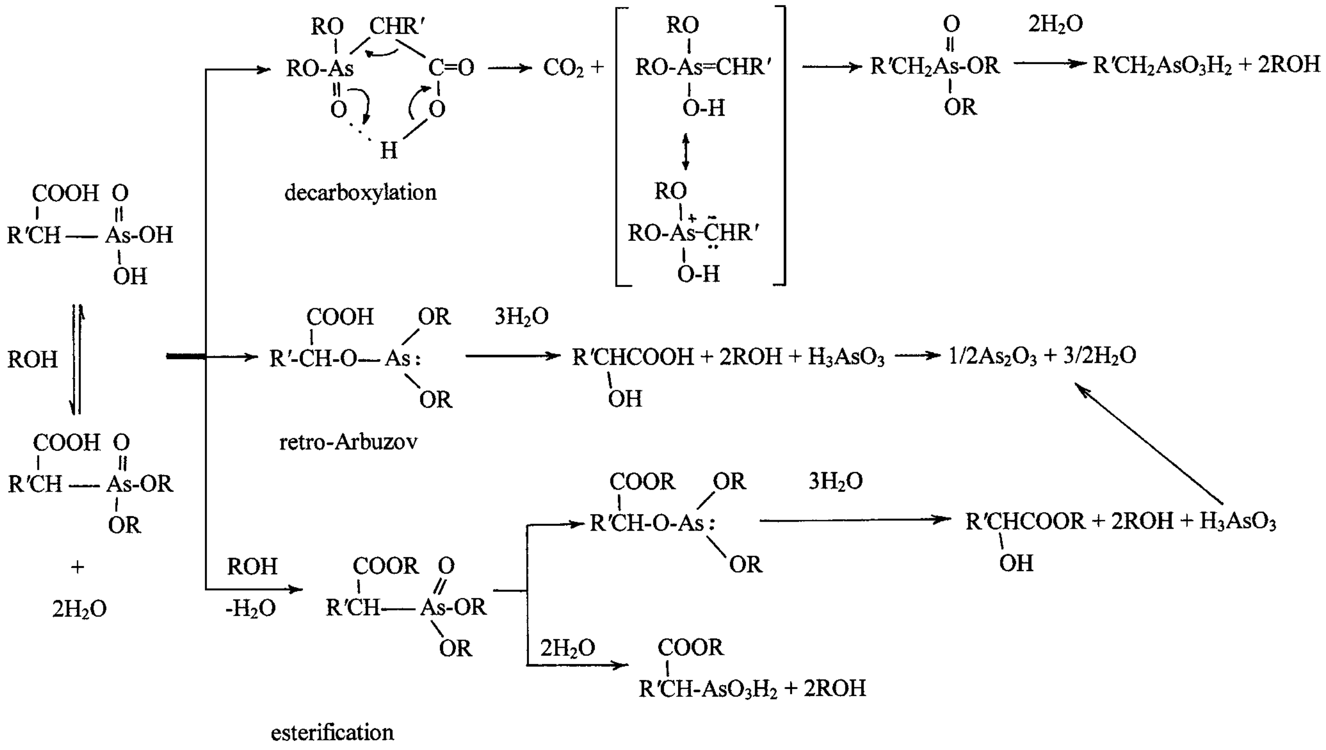


SCHEME 1

of the substrate to the alkaline arsenite. We have observed faster attack by HO^- than by $AsO_3{}^{3-}$ at higher reaction temperatures in other Meyer reactions.[39] Best yields of 2-arsonohexanoic acid are obtained with excess Na_3AsO_3, in the presence of NaOH and in concentrated solutions all these factors leading to increased concentration of the active nucleophile,[14] $AsO_3{}^{3-}$.

There are only three reports in the literature on the decarboxylation (under different conditions) of arsenic containing molecules. By heating arsonoacetic acid and ethylene glycol (1:2 molar ratio) at 140°C for 10 min, Englund[40] isolated the lead methylarsonate in 70% yield. Adams et al.[28] also decarboxylated this acid in 1-propanol by azeotropic removal of the water of esterification of the $—As(O)(OH)_2$ group. The arsenic acid, [hydroxy(phenyl)arsinyl]acetic acid, Ph—As(O)(OH)—CH_2COOH, was decarboxylated in 85% yield in benzene/1-butanol by azeotropic removal of the water of esterification of the >As(O)OH group.[41] Finally, Adams et al.[28] decarboxylated in 50% yield the precursor of the arsonomethyl analogue of AMP in DMSO/1-propanol by azeotropic distillation of the water produced. Since the decarboxylation will be the last reaction in this novel preparation of arsonic acids and in view of the not quantitative yields reported, we studied the conditions of decarboxylation of 2-arsonohexanoic acid. A suggestion as to what happens during the decarboxylation is shown in Scheme 2.

Since salts of phenylmalonic acid[42] and arsonic acids[28] do not decarboxylate, a free —COOH must be present for intramolecular hydrogen transfer to one of the arsenic oxygens to take place.[28] An esterified, $—AsO(OR')_2$, group must also be present. If the reaction is run in water


COOH
R'CH — As-OH
O
OH
ROH
COOH
R'CH — As-OR
O
OR
+
2H₂O
RO
RO-As
CHR'
C=O
O
O
H
decarboxylation
CO₂ +
RO
RO-As=CHR'
O-H
RO
RO-As-CHR'
O-H
O
R'CH₂As-OR
OR
2H₂O
R'CH₂AsO₃H₂ + 2ROH
COOH
R'-CH-O— As :
OR
OR
3H₂O
retro-Arbuzov
R'CHCOOH + 2ROH + H₃AsO₃
OH
1/2As₂O₃ + 3/2H₂O
ROH
-H₂O
COOR
R'CH— As-OR
O
OR
COOR
R'CH-O-As :
OR
OR
3H₂O
R'CHCOOR + 2ROH + H₃AsO₃
OH
2H₂O
COOR
R'CH-AsO₃H₂ + 2ROH
esterification

SCHEME 2

either no reaction takes place after 3 h at 100°C (this work) or slow C—As bond cleavage takes place.[28]

Decarboxylation of 2-arsonohexanoic acid in the presence of ethylene glycol in 1:1, 1:2 or 1:2.5 molar ratios by thermal removal of the water of esterification at 130–140°C (oil bath temperature) could not be effected. Partial esterification of the —COOH group was observed and As_2O_3 was produced via the retro-Arbuzov reaction[5,6] shown in Scheme 2.

When the decarboxylation was done in DMSO/1-propanol at 110°C without removal of the water of esterification, only 20% of pentylarsonic acid was obtained. Esterification of the —COOH group took place and As_2O_3 was also produced. Decarboxylation in 1-propanol with removal of the water of esterification at oil bath temperature of 160°C was accompanied by 37% C—As bond fission. At the same time some esterification of the —COOH group took place. The yield of the pentylarsonic acid was 38%.

In an attempt to avoid the ester, —COOR′, formation we tried the decarboxylation in *t*-butanol. Since *t*-butanol does not form an easily separable azeotrope with water, we slowly distilled the solvent at 130°C. A 20% C—As bond fission and some esterification were observed, the decarboxylation was incomplete, and the pentylarsonic acid could not be isolated.

Because of the esterification, —COOR′ could not be avoided, we therefore focused on the problem of C—As bond fission which occurs via the retro-Arbuzov reaction. The temperature at which an ester of an aliphatic arsonic acid starts isomerizing depends on both alkyl groups: R′ and R of Eq. 3, ranging from 115° to 282°C.[5] Evidently, the 1-propyl and *t*-butyl esters of 2-arsonohexanoic acid start isomerizing in the region of 110°C. The water of esterification then, before being removed as an azeotrope, reacted with the ester of the arsenious acid giving the observed opalescence due to As_2O_3 produced (Scheme 2). Therefore, the decarboxylation has to be done at as low a temperature as possible. The benzene/water azeotrope contains 8.9% water and boils at 69°C.[43] The esterification of an arsonic acid is best done with 100% excess alcohol[44] and for our purpose the best candidate[41] is 1-butanol (b.p. 118°C) for it will remain in the benzene phase during the azeotropic removal of the water. Using these conditions we noticed that very small amounts of As_2O_3 were produced at 75°C oil bath temperature. Keeping the temperature at 115°C during the azeotropic removal of water the yield of the product was >66% and the As_2O_3 could not be isolated. Since some esterification to —COOBu was observed and C—As bond cleavage was minute, then the major by-product should be the $RCH(AsO_3H_2)COOBu$.

Summarizing the results on the series of reactions (Eq. 4), for the preparation of arsonic acids, the first reaction must be run at low temperature and with excess NaOH and Na_3AsO_3. Most of the latter is recovered as As_2O_3. The second reaction must be run at as low temperatures as possible to minimize the C—As bond cleavage via the retro-Arbuzov reaction. It seems that ester, —COOR, formation cannot be avoided. Under our conditions the overall yield of Eq. 4 is 30–50%.

The IR spectrum of pentylarsonic acid resembles the published[2,45] spectra and has the ν(As=O) at 938 cm^{-1} and the ν(As—OH) at 776 cm^{-1} flanked by two much smaller peaks at 882 and 730 cm^{-1}. However, in the spectrum of 2-arsonohexanoic acid these peaks are moved to 890 and 784 cm^{-1}. Since the ν(C=O) is at 1712 cm^{-1} implying dimeric, —COOH HOOC—, association, then the $-AsO_3H_2$ group should be involved in much stronger hydrogen bonding with an $-AsO_3H_2$ group of another molecule. While in the anhydrous dilithium methylarsonate the $-AsO_3{}^{2-}$ group absorbs[46] at 862 and 845 cm^{-1}, in the trilithium salt of 2-arsonhexanoic acid the $-AsO_3{}^{2-}$ group absorbs at 898 and 820 cm^{-1}, probably because it is affected by the geminal $-COO^-$ group.

EXPERIMENTAL

1-Bromopentane was from Aldrich (Athens, Greece). 1-Bromooctane (b.p. 106°C, 15 mm Hg) and 1-bromododecane (b.p. 104–6°C, 0.8 mm Hg) were prepared form 1-octanol and 1-dodecanol by the HBr + H_2SO_4 and red P/Br_2 methods, respectively.[47] 2-Bromohexanoic acid (b.p. 98°C, 1.5 mm Hg) contaminated by ~9% hexanoic acid was prepared according to the literature.[34] The yellow silver orthoarsenite, Ag_3AsO_3, was prepared by adding a dilute solution of Na_3AsO_3 *into* an aqueous solution of silver nitrate in 1:3 molar ratio (m.p. 150°C dec; lit.[43] 150°C dec). It is soluble in acetic acid and it gives a yellow suspension in DMSO and in DMF. Tetramethylammonium hydroxide 25% by weight in methanol from Aldrich was used to prepare methanolic solutions of $(Me_4N)_3AsO_3$ (Table I). Aliquat 336 (methyltrioctylammonium chloride) was a generous gift of Henkel (Kankakee, IL). Ethylene glycol, ethylene glycol dimethyl ether (monoglyme), di- and triethylene glycol dimethyl ether (diglyme and triglyme), and sodium silicate solution (extra pure) were from Merck. Silica gel Si60 (Serva; Heidelberg, Germany) was used for column chromatography and silica gel H (Merck) for thin layer chromatography. Methanol, absolute ethanol, 1-propanol, 1-butanol, *t*-butanol, benzene, and DMSO were stored over A_4 molecular sieves. Thin layer chromatography (TLC) was run on microslides, always using appropriate standards. Visualization was effected first by iodine vapours (for hexanoic acid, 2-bromohexanoic acid, and $AsO_3{}^{3-}$,[8]) followed by spraying with 35% H_2SO_4 and charring. Arsenic(III) oxide was detected by IR (sharp peak at 802 cm^{-1}).[48] Arsenic(III) was determined titrimetrically in buffered, with $NaHCO_3$, solution with standard iodine solution.[49] A Soniprep 150 sonicator (MSE) was used. IR spectra were obtained on a Perkin-Elmer model 16PC FT-IR spectrometer. ^1H NMR spectra were run on a Brucker DPX Avance (400 MHz) spectrometer. Elemental analyses were done by CNRS, Vernaison, France.

Syntheses of Compounds

2-Arsonohexanoic Acid, $CH_3[CH_2]_3CH(AsO_3H_2)COOH$

To arsenic(III) oxide (990 mg, 5 mmol As_2O_3) dissolved in 13 M NaOH (3.1 ml, 40 mmol NaOH) was added at RT, dropwise (during 1 h) 2-bromohexanoic acid (975 mg, 5 mmol). During the addition, the temperature did not rise and a gel was formed. After stirring at RT for 2 days a clear viscous solution was formed and on further stirring for 2 days a semigel was formed. TLC (MeOH/conc. NH_3 4:1) showed traces of the starting acid (R_f 0.80), Na_3AsO_3 (R_f 0.53), the product (R_f 0.32) and an unknown impurity at R_f 0.05. The system was neutralized with 6 M HCl (calculated for 35 mmol HO^-:5.8 ml) and centrifugation gave As_2O_3 (255 mg). The solution was extracted with ether (3 × 20 ml), separating the phases by centrifugation. The aqueous phase contained As_2O_3 and 2-hydroxyhexanoic acid. The ether phase gave an oil (1.23 g) which was chromatographed (silica gel, 12 g, in ether). Elution with Et_2O (100 ml) gave 2-hexenoic acid (traces), hexanoic acid (~80 mg), 2-bromohexanoic acid (~20 mg), and 2-hydroxyhexanoic acid (~250 mg). These impurities on TLC (Et_2O/petroleum ether 1:1) had R_f : 0.88, 0.76, 0.76, and 0.38 respectively, and their quantities were calculated from the ^1H NMR spectrum of the mixture. Then, elution with methanol (75 ml) gave the methanol-contaminated product (834 mg, 70%) as a very viscous-to-glassy oil, purity >90%, soluble in water, methanol and DMSO and insoluble in chloroform. IR (neat): 3318 broad s, 2960 vs, 2872 s, 1714 vs, 1642 shoulder m, 1460 m, 1382 w, 1330 m, 1298 s, 1266 s, 1246 s, 1190 s, 1112 m, 1016 m, 890 vs, 784 vs, 675 w. ^1H NMR (D_2O), δ : 0.76 (t, J 6.8 Hz, 3 H, CH_3), 1.23 (multiplet, 2 H, CH_3CH_2), 1.31 (multiplet, 2 H, $CH_3CH_2CH_2$), 1.92 (multiplet, 2 H, CH_2CH), 3.21 (s, MeOH), 3.60 (double doublet, $J_{AX} + J_{BX}$ 14 Hz, 1 H, CH), 3.69 (s, 0.26 H, impurity). For elemental analyses a sample was converted into its trilithium salt.

Trilithium Salt of 2-Arsonohexanoic Acid, $CH_3[CH_2]_3CH(AsO_3Li_2)$ COOLi

To a saturated solution of lithium hydroxide in methanol (~3 ml), a solution of 2-arsonohexanoic acid (95 mg, 0.4 mmol) in methanol was added. The voluminous precipitate was centrifuged, washed with methanol (2 × 2 ml), and dried in vacuo over phosphorus pentoxide to give the product (90 mg, 86%) as a white, hard solid. At ~275°C the product turns light brown and does not melt until up to 300°C. Found: C 26.23, H 4.33%; calculated for $C_6H_{10}O_5AsLi_3$; $0.2CH_3OH$: C 26.34, H 4.55%. IR (KBr): 3420 m, 2958 s, 2930 m, 2864 m, 1582 vs, 1467 m, 1462 m, 1398 vs, 1164 w, 1100 w, 898 vs, 820 vs, 728 w. ^1H NMR (D_2O), δ : 0.76 (t, J 6.0 Hz, 3 H, CH_3), 1.19 (m, 4 H, $CH_2CH_2CH_3$), 1.68 and 1.80 (multiplets, 2 H, CH_2CH), 2.69 (double doublet, $J_{AX} + J_{BX}$ 15.2 Hz, 1 H, CH), 3.23 (s, ~2% MeOH).

The MeOH could not be completely removed after 10 h drying at 100°C, 2 mm Hg.

Decarboxylation of 2-Arsonohexanoic Acid to Pentylarsonic Acid

In DMSO/1-Propanol

2-Arsonohexanoic acid (360 mg, 1.5 mmol) dissolved in DMSO (2 ml) and 1-propanol (2 ml) was refluxed for 2 h (oil bath temperature 110°C) at which point the solution became opalescent due to As_2O_3. TLC (MeOH/conc. NH_3 4:1) showed traces of 2-arsonohexanoic acid (R_f 0.35), the product (R_f 0.61), and by-products (see Scheme 2), (R_f 0.95). Water (0.5 ml) was added, the propanol and water evaporated (rotary, 50°C), and most of the DMSO removed in vacuo (oil bath at 90°C, 4 mm Hg). To the oil, water (4 ml) was added, boiled, and, on cooling to RT 48 mg of a solid (As_2O_3 and product, by IR), precipitated. The supernatant on cooling at 4°C overnight gave the product (55 mg, 19%), m.p. 162°C (lit.[2] 163–165°C), insoluble in chloroform and water at RT, soluble in DMSO and warm water. IR (KBr): 4132 broad w, 3420, broad w, 2965 s, 2870 ms, 2740 broad m, 1460 w, 1198 m, 938 s, 776 vs. ^1H NMR (DMSO$-d_6$), δ: 0.86 (t, J 7.2 Hz, 3 H, CH_3), 1.30 and 1.37 (multiplets, 4 H, $CH_2CH_2CH_3$), 1.63 (quintet, J 7.6 Hz, 2 H, CH_2CH_2As), 2.15 (t, J 7.6 Hz, 2 H, CH_2As), 3.81 (broad s, 2 H, AsO_3H_2). The final supernatant after evaporation and drying gave an oil which had by IR: DMSO and molecules with −COOR (1734 cm^{-1}) and $-AsO_3H_2$ (952, 910 and 776 cm^{-1}) groups.

In 1-Propanol

2-Arsonohexanoic acid (1.376 g, 5.73 mmol) was dissolved in dry 1-propanol (25 ml) in a two-neck 100 ml round bottom flask connected to an insulated 15 cm Dufton condenser having on top an insulated sloping Claisen stillhead, and immersed into a silicone oil bath. After 15 min the oil temperature reached 145°C and the solution became opalescent due to As_2O_3. After 90 min the azeotrope had distilled (88°C) the oil temperature being 160°C. After 4 h refluxing TLC showed no starting diacid present, and the solution cooled to RT. Water (1 ml) was added, the propanol/water evaporated (rotary, 50°C) and the residue dried in vacuo. The solid (1.383 g) was extracted with warm methanol (3 × 3 ml) leaving As_2O_3 (by IR) (190 mg, corresponding to 34% C—As bond cleavage). The methanol extracts gave a solid which recrystallized from boiling acetone (4 ml), filtering traces of As_2O_3 through a cotton plugged Pasteur pipette. The crystallized product (407 mg) was impure (by TLC). From the supernatant 92 mg impure product was obtained after evaporation and trituration with ether (5 ml). The ether gave 416 mg of an oil which by TLC contained some product. Its IR spectrum showed a —COOR (1730 cm^{-1}) and a —COOH (1720 cm^{-1}) group. The presence of the ester —COOR group was verified in the complex ^{1}H NMR (triplet at 4.14 ppm, J 6.3 Hz, —$COOCH_2CH_2CH_3$). The impure products were combined and triturated with acetone (10 ml) and ether (5 ml) to give pure product (420 g, 38%), m.p. 162–164°C. Data: as in case DMSO/1-propanol.

In 1-Butanol/Benzene

2-Arsonohexanoic acid (1.668 g, 6.95 mmol), dry 1-butanol (2.6 ml, 27.8 mmol), and dry benzene (25 ml) were placed in a two-neck 100 ml round bottom flask connected to an insulated Dean-Stark trap and immersed in an oil bath. When the oil temperature (after 5 min heating) reached 75°C, the solution became very slightly opalescent and when the temperature reached 105°C, it became slightly opalescent and remained so until the end of the heating (5 h). Water production seems to have ended after ~2 h of distillation. The progress of the decarboxylation was followed by TLC (as in DMSO/1-propanol) and at the end traces of starting material and by-products could be seen. After cooling to RT the slightly opalescent solution could not be clarified by filtration through a cotton plugged Pasteur pipette. To the filtrate, water (1 ml) was added, evaporated, and briefly dried in vacuo to give a butanol smelling semisolid (3.07 g, expected 1.362 g). Ether (10 ml) was added and warmed to extract the impurities. The still impure solid product was triturated with boiling acetone (3 ml) and, after cooling to RT, centrifugation gave the product (775 mg, 57%), m.p. 161–164°C. Spectra as in DMSO/1-propanol. The ether and acetone extracts were combined and evaporated. Trituration of the residue with boiling ether (5 ml) gave more product (121 mg, 9%), m.p. 161–163°C. The ether phase gave a butanol smelling oil (420 mg) which by IR had an ester group at 1730 cm^{-1} and by TLC it contained nearly equal amounts of product and by-products.

ACKNOWLEDGMENTS

It is our pleasure to thank Dr. H. B. F. Dixon (University of Cambridge) for his valuable comments on an early draft of this paper and for very constructive discussions on the reactions of Eq. 4 which he and his group conceived as a novel method of wider scope for the preparation of aliphatic arsonic acids.

REFERENCES

[1] G. O. Doak and L. D. Freedman, *Organometallic Compounds of Arsenic, Antimony, and Bismuth* (Wiley, New York, 1970), pp. 17–26.

[2] C. F. McBrearty Jr., K. Irgolic, and R. A. Zingaro, *J. Organometal. Chem.*, **12,** 377 (1968).

[3] R. T. Morrison and R. N. Boyd, *Organic Chemistry* (Allyn and Bacon, Boston, 1966), 2nd ed, pp. 519–521.

[4] B. E. Abalonin, *Russian Chem. Rev.*, **60,** 1346 (1991).

[5] B. D. Chernokal'skii, V. S. Gamayurova, and G. Kh. Kamai, *J. Gen. Chem. USSR*, **36,** 1670 (1966).

[6] V. S. Gamayurova, V. I. Savdur, and B.D. Chernokal'skii, *J. Gen. Chem. USSR*, **50,** 437 (1980).

[7] N. A. Chadaeva, G. Kh. Kamai, K. A. Mamako, and M. P. Osipova, *J. Gen. Chem. USSR*, **42,** 120 (1972).

[8] G. M. Tsivgoulis, D. N. Sotiropoulos, and P. V. Ioannou, *Phosphorus, Sulfur, and Silicon*, **141,** 97 (1998).

[9] G. Meyer, *Ber. Dtsch. Chem. Ges.*, **16,** 1439 (1883).

[10] A. J. Quick and R. Adams, *J. Am. Chem. Soc.*, **44,** 805 (1922).

[11] C. K. Banks, J. F. Morgan, R. L. Clark, E. B. Hatlelid, F. H. Kahler, H. W. Paxton, E. J. Cragoe, R. J. Andres, B. Elpern, R. F. Coles, J. Lawhead and C. S. Hamilton, *J. Am. Chem. Soc.*, **69,** 927 (1947).

[12] J. G. du Preez and N. M. Sumter, *Solv. Extr. Ion Exchange*, **14,** 417 (1996).

[13] R. Pietsch, *Monatsch. Chem.*, **96,** 138 (1965).

[14] S. V. Serves, D. N. Sotiropoulos, P. V. Ioannou, and H. B. F. Dixon, *Phosphorus, Sulfur, and Silicon*, **90,** 103 (1994).

[15] J. M. Loehr and R. A. Plane, *Inorg. Chem.*, **7,** 1708 (1968).

[16] G. M. Tsivgoulis, D. N. Sotiropoulos, and P. V. Ioannou, *Phosphorus, Sulfur, and Silicon*, **57,** 189 (1991).

[17] A. C. Skapski, *J. Chem. Soc. Chem. Commun.*, 10 (1966).

[18] G. V. Chelintsev and V. K. Kushkov, *J. Gen. Chem. USSR*, **16,** 1481 (1946).

[19] G. V. Chelintsev and V. K. Kushkov, *Chem. Abs.*, **41,** 5441a (1947).

[20] S. V. Serves, G. M. Tsivgoulis, D. N. Sotiropoulos, P. V. Ioannou, and M. K. Jain, *Phosphorus, Sulfur, and Silicon*, **71,** 99 (1992).

[21] S. V. Serves, D. N. Sotiropoulos, P. V. Ioannou, and M. K. Jain, *Phosphorus, Sulfur, and Silicon*, **81,** 181 (1993).

[22] R. H. Edee, *J. Am. Chem. Soc.*, **50,** 1394 (1928).

[23] G. A. C. Gough and H. King, *J. Chem. Soc.*, 2426 (1928).

[24] C. A. McAuliffe, K. Minten and D. G. Watson, *Inorg. Chim. Acta*, **39,** 249 (1980).

[25] A.-M. Lacoste, C. Dumora, B. R. S. Ali, E. Neuzil, and H. B. F. Dixon, *J. Gen. Microbiol.*, **138,** 1283 (1992).

[26] S. Chawla, E. K. Mutenda, H. B. F. Dixon, S. Freeman, and A. W. Smith, *Biochem. J.*, **308,** 931 (1995).

[27] J. March, *Advanced Organic Chemistry* (Wiley-Interscience, New York, 1985), 3rd ed., pp. 562–565.

[28] S. R. Adams, M. J. Sparkes, and H. B. F. Dixon, *Biochem. J.*, **221,** 829 (1984).

[29] W. M. Dehn and S. J. McGrath, *J. Am. Chem. Soc.*, **28,** 347 (1906).

[30] L. M. Facchinetti and E. M. G. de Casal, *An. Asoc. Quim. Argent.*, **60,** 525 (1972);

[31] L. M. Fachinetti and E. M. G. de Casal, *Chem. Abs.*, **78,** 97772z (1973).

[32] E. M. G. de Casal and L. M. Facchinetti, *An. Asoc. Quim. Argent.*, **63,** 79 (1975);

[33] E. M. G. de Casal and L. M. Fachinetti, *Chem. Abs.*, **83,** 192121y (1975).

[34] H. T. Clarke and E. R. Taylor, *Organic Syntheses*, **1,** 115 (1941).

[35] J. Cason, N. L. Allinger, and G. Sumrell, *J. Org. Chem.*, **18,** 850 (1953).

[36] C. S. M. Birnbaum, S.-C. J. Fu, and J. P. Greenstein, *J. Biol. Chem.*, **203,** 333 (1953).

[37] S. R. Adams, M. J. Sparkes, and H. B. F. Dixon, *Biochem. J.*, **213,** 211 (1983).

[38] C. S. Palmer, *Organic Syntheses*, **1,** 73 (1941).

[39] S. V. Serves, D. N. Sotiropoulos, P. V. Ioannou, E. K. Mutenda, M. J. Sparkes, and H. B. F. Dixon, *Phosphorus, Sulfur, and Silicon*, **101,** 75 (1995).

[40] B. Englund, *J. Prakt. Chem.*, **120,** 179 (1928).

[41] G. S. Levskaya and A. F. Kolomiets, *J. Gen. Chem. USSR*, **36,** 2016 (1966).

[42] B. C. Challis, S. H. Kerr, and I. R. McDermott, *J. Chem. Soc. Perkin II*, 1829 (1974).

[43] R. C. Weast, *Handbook of Chemistry and Physics* (CRC Press, Boca Raton, Florida, 1985), 65th ed.

[44] G. S. Levskaya and A. F. Kolomiets, *J. Gen. Chem. USSR*, **37,** 855 (1967).

[45] U. Dietze, *J. Prakt. Chem.*, **313,** 889 (1971).

[46] A. von Simon and H.-D. Schumann, *Z. Anorg. Allg. Chem.*, **393,** 23 (1972).

[47] A. I. Vogel, *Practical Organic Chemistry* (Longmans, London, 1964), 3rd ed., pp. 277, 282.

[48] F. A. Miller and C. H. Wilkins, *Anal. Chem.*, **24,** 1253 (1952).

[49] A. I. Vogel, *Textbook of Quantitative Inorganic Analysis* (Longman, London, 1979), p. 378.