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### The Autoxidation of Triaryl Trithioarsenites, (ArS)<sub>3</sub>As: Evidence for Binding and Activation of Triplet Dioxygen by Arsenic(III)

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## The Autoxidation of Triaryl Trithioarsenites, $(\text{ArS})_3\text{As}$ : Evidence for Binding and Activation of Triplet Dioxygen by Arsenic(III)

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*Triaryl trithioarsenites,  $(\text{ArS})_3\text{As}$ , are oxidized by air to  $\text{As}_2\text{O}_3$  and  $\text{ArSSAr}$ . In two cases the parent "thiol" (pyrid-2-thione and 1-hydroxypyrid-2-thione) is coproduced. The oxidation, in nonprotic solvents, is favored by electron-withdrawing groups at the para position of the phenyl group. The products obtained in nonprotic solvents were rationalized by assuming that the binding of the triplet dioxygen to arsenic(III) gives a triplet diradical,  $(\text{ArS})_3\text{As}-\text{O}-\dot{\text{O}}$ , or an arsenadioxirane,  $(\text{ArS})_3\text{As}(\text{O}_2)$ , intermediate, which decomposes after nucleophilic attack by another  $(\text{ArS})_3\text{As}$  molecule. In protic solvents a zwitterion,  $(\text{ArS})_3\text{As}^+-\text{O}-\text{O}^-$ , and in the presence of moisture a hydroperoxy arsenic(V) compound,  $(\text{ArS})_3\text{As}(\text{OH})-\text{O}-\text{OH}$ , may be intermediates in the air oxidation of some aromatic trithioarsenites. These data tend to indicate that arsenic(III) bound to suitable groups can directly bind dioxygen, a property which may have implications in chemotherapy and carcinogenesis.*

**Keywords** Activation; binding; dioxygen; triaryl trithioarsenites

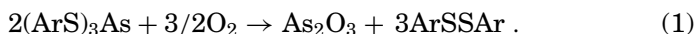
## INTRODUCTION

Evidence begins to accumulate indicating that arsenic(III) coordinated to suitable organic groups can directly combine with dioxygen to give unstable adducts that decompose to various products depending on the nature of the organic groups. Thus, ascorbic acid complexed with arsenous acid,  $\text{H}_3\text{AsO}_3$ , in a ratio of 1:2 As(III)/ascorbic acid is oxidized by air to dehydroascorbic acid much faster than in the absence of As(III).<sup>1</sup> The reaction of allyl and benzylarsonic acids with thiophenol gave not only the expected diphenyl alkylidithioarsonites,  $\text{R}-\text{As}(\text{SPh})_2$ , and diphenyl disulfide,  $\text{PhSSPh}$ , but also various other products, some of which ( $\text{As}_2\text{O}_3$ ,  $(\text{PhS})_3\text{As}$ ,  $\text{PhCH}_2\text{OH}$ ,  $\text{PhCH}=\text{O}$ ) arose from the reaction

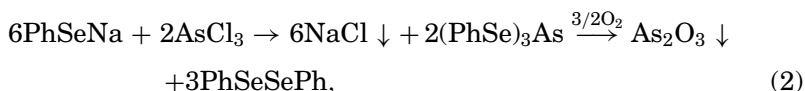
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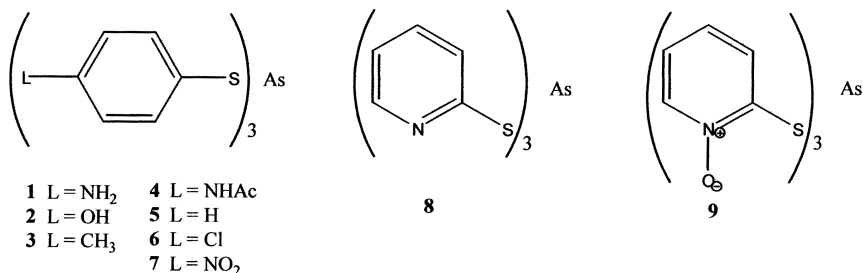
of these alkylthioarsonites with the dissolved dioxygen.<sup>2</sup> Attempted oxidation<sup>3</sup> of the esters **1–3**, **5**, **7**, and **8** (without exclusion of air) by octasulfur in refluxing solvent, as melts, or in solution in the presence of triethylamine, as an activator of octasulfur, did not give the expected arsenic(V) esters,  $(\text{ArS})_3\text{As}=\text{S}$ , but various amounts of  $\text{As}_2\text{O}_3$  and disulfides,  $\text{ArSSAr}$ , (in the case of **8**, the parent thiol, 2-mercaptopyridine, in its thioketo form was also coproduced) were obtained according to Eq. (1):



Brill and Campbell,<sup>4</sup> after 4 h of refluxing a benzene/methanol solution of  $\text{PhSeNa}$  and  $\text{AsCl}_3$ , isolated the diselenide  $\text{PhSeSePh}$  instead of the ester  $(\text{PhSe})_3\text{As}$ . This result can be rationalized by Eq. (2):



To the best of our knowledge, there are no reports in the literature on the air oxidation of aromatic trithioarsonites except for the observation previously mentioned.<sup>3</sup> In order to understand the effect of the trithioarsonite structure on its air oxidation, compounds **1–7** were prepared having electron-donating and electron-withdrawing *para* substituents. The esters **8** and **9** contain an electron-withdrawing pyridine group and seem to be interesting ligands containing As, S, and N and As, S, and O donor atoms.



In this article we present our results on the air oxidation of the aromatic trithioarsonites **1–9** in solution and compared the relative rates of the air oxidation of **1–9** *vis-a-vis* the air oxidation of their corresponding thiols. The results are best interpreted by assuming  $\text{O}_2$  binding to  $\text{As(III)}$ .

## RESULTS AND DISCUSSION

### On the Preparation of Aromatic Trithioarsenites

We have developed a simple method for the preparation of aliphatic,  $(\text{RS})_3\text{As}$ , and aromatic,  $(\text{ArS})_3\text{As}$ , trithioarsenites by reacting  $\text{As}_2\text{O}_3$  with equivalent amounts of thiol in methanol, ethanol, or water,<sup>3,5</sup> thus avoiding the use of the liquid  $\text{AsCl}_3$  and the preparation of a salt (usually sodium) of the thiol.<sup>6</sup> However, compounds with pronounced thioketo rather than thiol character, e.g., the antithyroid agent 2-mercapto-1-methylimidazole, do not react with  $\text{As}_2\text{O}_3$ .<sup>5</sup> Moreover, the sodium salt of 2-mercapto-1-methylimidazole does not react with  $\text{AsCl}_3$  (T. D. Sideris, unpublished results). 4-Mercaptopyridine, which exists predominantly as pyrid-4-thione,<sup>7</sup> reacts with  $\text{As}_2\text{O}_3$  in methanol. The colored solid obtained is not the expected tris(4-pyridyl) trithioarsenite but probably a mixture of  $\text{As}_2\text{O}_3$  and *cyclo*- $\text{As}_4\text{S}_4$  containing 4-pyridyl group(s). Such mixtures have been obtained previously by reacting  $(\text{ArS})_3\text{As}$  with  $\text{S}_8$  in the presence of triethylamine as a catalyst without exclusion of air.<sup>3</sup> These sulfur-containing molecules probably arise from the reaction of  $\text{As}_2\text{O}_3$  with  $\text{HS}^-/\text{H}_2\text{S}$ . The latter most likely comes from the attack of another 4-mercaptopyridine molecule.<sup>8</sup>

The thiols 2-mercaptopyridine and 2-mercaptopyridine *N*-oxide also exist predominantly as the tautomeric pyrid-2-thione and 1-hydroxypyrid-2-thione.<sup>7,9</sup> The products obtained upon their reaction with  $\text{As}_2\text{O}_3$  are the aromatic trithioarsenites **8** and **9** as evidenced by their solid state IR spectra. Thus, the spectrum of **8** resembles the spectrum of bis(2-pyridyl) disulfide,<sup>10</sup> except that the two peaks at 1149 (mw) and 1114 (s) of the latter are found as a somewhat broad peak centered at  $1130\text{ cm}^{-1}$  (m) in **8**. The solid state IR spectrum of **9** is similar to that 2,2'-dithiobis(pyridine *N*-oxide).<sup>10</sup> In the spectrum of 2,2'-dithiobis(pyridine *N*-oxide) two peaks appeared at 1250 (vs) and 1226 (s), which fall in the region  $1300\text{--}1200\text{ cm}^{-1}$  for the  $\text{N}^+\text{--O}^-$  stretching vibration. In the spectrum of **9**, which should be approximately the same as that of the disulfide, these peaks changed intensity and shifted to 1260 (w) and  $1206\text{ cm}^{-1}$  (vs), probably indicating coordination of the  $\text{--O}^-$  to As(III) to give an As(III) complex, based on the observation that the  $\text{N}^+\text{--O}^-$  stretching vibration in pyridine *N*-oxide appears at  $1242\text{ cm}^{-1}$  and on coordination to Pt(II) is shifted to  $1235\text{ cm}^{-1}$ .<sup>11</sup>

Because the esterification gives a solid trithioarsenite from the solid  $\text{As}_2\text{O}_3$ , a 24–48 h stirring was used. In view of the facile autoxidation of some trithioarsenites in solution, especially **2**, **8**, and **9**, deaerated solvent should be used for their preparation. However, **2**, **8**, and **9** were found to be stable as solids at  $-20^\circ\text{C}$  without special precautions for at least 5 months.

## Air Oxidation of the Trithioarsenites 1–9 Versus the Air Oxidation of Their Parent Thiols

The oxidation of thiols to disulfides by dioxygen is faster in alkaline solutions, is fast in aprotic (e.g., *N,N*-dimethylformamide) but slow in protic (e.g., MeOH) anhydrous solvents; the rates (in methanol) depend on the nature of the thiol (e.g., *n*-BuSH > *p*-H<sub>2</sub>N-Ph-SH > Ph-SH  $\gg$  *p*-O<sub>2</sub>N-Ph-SH). It is a free radical process involving RS $\dot{\text{S}}$ , O<sub>2</sub><sup>1-·</sup>, and O<sub>2</sub><sup>2-·</sup> species generated by the reaction of RS<sup>-</sup> with O<sub>2</sub> in a rate determining step.<sup>12</sup> The autoxidation of thiols in neutral media at r.t. does not take place in the absence of radical initiators, e.g., trace metals, UV, and peroxides.<sup>13</sup>

The data in Table I show that 4-chloro and 4-nitrothiophenol are not autoxidized, while the other *para* substituted thiophenols as well as 2-mercaptopyridine and 2-mercaptopyridine *N*-oxide (the latter two existing predominantly in their thioketo forms<sup>7,9</sup>) dissolved in nondried solvents are oxidized by air to a very small extent to their disulfides, which is consistent with the proposal<sup>12</sup> that it is the anion, ArS<sup>-</sup>, that reacts with O<sub>2</sub>. The addition of methanol to a chloroform solution of thiophenol does not seem to increase its autoxidation to diphenyl disulfide.

From Table I it can be seen that the esters **1–9** are air oxidized to As<sub>2</sub>O<sub>3</sub> (and disulfides) to various degrees depending on the nature of the aryl group and the solvent. This is a clear indication that the As(III) in the esters **1–9** can bind and, thus, activate the dioxygen towards oxidation of the bound ArS- ligands.

## The Effect of the Aryl Group on the Air Oxidation of the Trithioarsenites 1–9

The ease of the oxidative decomposition of **1–7** does not seem to follow a linear trend when the Hammett *para* substituent constants  $\sigma$ <sup>14,15</sup> are considered. In fact, the trend seems to parallel the development of a positive charge on sulfur in diaryl disulfides, i.e., electron-donating groups result in a low, constant positive charge, while this charge increases with the electron-withdrawing power of the *para* substituents of the phenyl groups.<sup>16</sup> The data of Table I indicate that, in CHCl<sub>3</sub> or CHCl<sub>3</sub>-rich solvents, electron-donating groups tend to disfavor while electron-withdrawing groups tend to favor the oxidative decomposition of **1–7**. The esters **8** and **9**, also having electron-withdrawing aryl groups, decomposed by air, much faster than **1–7**, to As<sub>2</sub>O<sub>3</sub> and a mixture of their disulfide and free “thiol” instead of only the disulfide.

From the literature it is known that the sensitized photooxygenation (i.e., with singlet dioxygen, <sup>1</sup>O<sub>2</sub>) of aliphatic sulfides (the aromatic ones

**TABLE I** Percent of Oxidative Decomposition, Based on the Isolated  $\text{As}_2\text{O}_3$ , of the Triaryl Trithioarsenites 1–9 Dissolved in a Solvent ( $\sim 20$  mM) and Stirred in Air at r.t. and Percent of the Parent Thiol Oxidized by Air to Its Disulfide Under the Same Conditions. Duplicate (in Most Cases) Experiments

Ester	Solvent	Time (hours)	Decomposition (%)	Hammett $\sigma$ -value <sup>15</sup>	Disulfide from thiol (%)
<b>1</b>	$\text{Me}_2\text{CO}/\text{CHCl}_3$ 1 : 9	72	8–14	–0.660	5–10 <sup>a</sup>
	$\text{Me}_2\text{CO}/\text{MeOH}$ 1 : 2	72	6–12		—
<b>2</b>	$\text{CHCl}_3^b$	72	10 <sup>a</sup>	–0.370	—
	MeOH	24	100 <sup>a</sup>		5–10 <sup>a</sup>
	$\text{MeOH}^c$	72	100 <sup>a</sup>		—
<b>3</b>	$\text{CHCl}_3$	72	13–19	–0.151	D <sup>d</sup>
<b>4</b>	$\text{Me}_2\text{CO}/\text{CHCl}_3$ 1 : 4	72	11–14	0.00	<5 <sup>a</sup>
	$\text{Me}_2\text{CO}/\text{MeOH}$ 1 : 1	72	37–41		—
<b>5</b>	$\text{CHCl}_3$	72	8–16	0.00	D <sup>d</sup>
	$\text{CHCl}_3/\text{MeOH}$ 3 : 1	72	64–66		D <sup>d</sup>
	$\text{CHCl}_3/\text{MeOH}$ 3 : 2	72	85–89		D <sup>d</sup>
<b>6</b>	$\text{CHCl}_3$	72	30–36	+0.227	ND <sup>d</sup>
<b>7</b>	$\text{CHCl}_3$	72	69–73	+0.778	ND <sup>d</sup>
<b>8</b>	$\text{CHCl}_3$	8	100 <sup>e</sup>	—	<5 <sup>a</sup>
	$\text{CH}_2\text{Cl}_2^c$	48	94 <sup>e</sup>		—
<b>9</b>	$\text{MeOH}/\text{CHCl}_3$ 1 : 3	7	100 <sup>e</sup>	—	<5 <sup>a</sup>
	MeOH	7	100 <sup>e</sup>	—	
	$\text{MeOH}/\text{CH}_2\text{Cl}_2^c$ 1 : 3	48	70 <sup>f</sup>	—	

<sup>a</sup> Visual estimation of TLC spots.

<sup>b</sup> Suspension, 4 mM.

<sup>c</sup> Dry solvent/pure dioxygen.

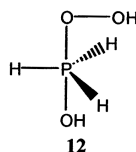
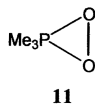
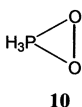
<sup>d</sup> The thiol and its disulfide have the same  $R_f$  values on TLC. D = disulfide was detected and ND = disulfide was not detected after capturing the thiol with mercury(II).

<sup>e</sup> Thiol and disulfide were produced (see Experimental section).

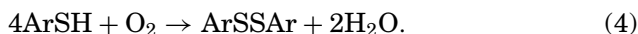
<sup>f</sup> Calculated from the isolated thiol plus disulfide.

being unreactive because they do not have an  $\alpha$ -H) to their sulfoxides is favored in protic solvents (e.g., methanol) and the first intermediate that is formed, the persulfoxide  $\text{R}_2\text{S}(\text{O}_2)$ , has a zwitterionic character,  $\text{R}_2\text{S}^+-\text{O}-\text{O}^-$ .<sup>17–19</sup> Trialkylphosphines,  $\text{R}_3\text{P}$ , react with dioxygen in air giving a variety of products that were explained by assuming that  $^3\text{O}_2$  (triplet dioxygen) reacted with the R group rather than with P(III),<sup>20</sup> while in the gas phase reaction of  $\text{Me}_3\text{P}$  with  $^3\text{O}_2$ , the formation of the diradical,  $\text{Me}_3\text{P}^\cdot-\text{O}-\text{O}^\cdot$ , was suggested as the first intermediate.<sup>21</sup> An analogous diradical,  $\text{R}_2\text{HP}^\cdot-\text{O}-\text{O}^\cdot$ , has also been suggested as an intermediate in the air oxidation of dialkylphosphines,  $\text{R}_2\text{HP}$ , to dialkylphosphine oxides,  $\text{R}_2\text{HP}=\text{O}$ , in isopropyl alcohol<sup>22</sup> and it is different from that obtained by dioxygen oxidation of dimethylarsine,  $\text{Me}_2\text{HAS}$ , i.e.,

$\text{Me}_2\ddot{\text{As}}-\text{O}-\text{O}\cdot$ ,<sup>23,24</sup> *en route* to cacodyl oxide,  $\text{Me}_2\text{As}-\text{O}-\text{AsMe}_2$ , and cacodylic acid,  $\text{Me}_2\text{AsO}_2\text{H}$ .<sup>25</sup> Theoretical calculations<sup>26</sup> on the interaction of  $\text{PH}_3$  and  $\text{Me}_3\text{P}$  with  $^1\text{O}_2$  show that the species  $\text{R}_3\text{P}-\text{O}-\text{O}\cdot$  or  $\text{R}_3\text{R}^+-\text{O}-\text{O}^-$  are not stable as intermediates. The energy minima correspond to the phosphadioxiranes **10** and **11** and the addition of water to **10** exothermally gives **12**.



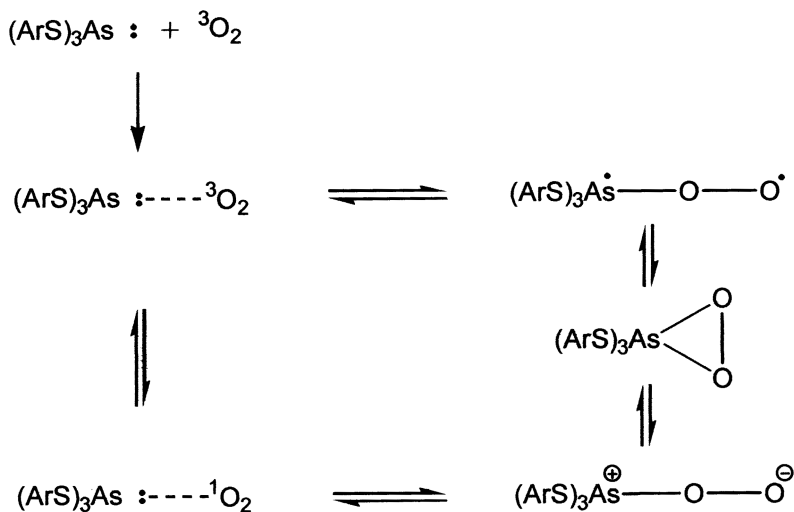
The oxidative decomposition of the esters **1–9** in nondried solvents can be interpreted by two routes. The first, “hydrolysis-oxidation,” involves hydrolysis of the trithioarsenite and then oxidation of the thiol by dioxygen, (Eqs. (3) and (4)):



This route, if followed, should be a minor one because trithioarsenites are stable in a neutral environment and unstable in alkaline or acidic solutions,<sup>5,27</sup> and because while the esters **6** and **7** decompose to  $\text{As}_2\text{O}_3$  and disulfide, their parent thiols, 4-chlorothiophenol and 4-nitrothiophenol, are not oxidized by air (Table I). 4-nitrothiophenol is not oxidized even in alkaline solutions.<sup>12</sup>

The second route requires the formation of an  $(\text{ArS})_3\text{As}/\text{O}_2$  adduct and the ability of  $^3\text{O}_2$  in air to combine with the  $\text{As}(\text{III})$  in certain compounds has been inferred in previous reports.<sup>1–4,23</sup> The adduct can most likely be a loosely bound complex,  $(\text{ArS})_3\text{As}:\dots^3\text{O}_2$ , rather than an exciplex,  $(\text{ArS})_3\text{As}:\dots^1\text{O}_2$ . These species can give a diradical or a zwitterion, respectively, Scheme 1.<sup>28,29</sup>

For a diradical to be formed, a transfer of a  $\pi^*$  electron from  $^3\text{O}_2$  into a contracted<sup>30,31</sup> empty 4d orbital of  $\text{As}(\text{III})$  is envisioned.<sup>32</sup> Electron-withdrawing groups on  $(\text{ArS})_3\text{As}$  (i.e., the development of positive charge on the sulfur atoms bound to  $\text{As}(\text{III})$ ) will contract the d orbitals to a point favorable for electron transfer to form the diradical, and this may explain the facile air oxidation of the esters **6** and **7** (Table I). Electron-donating groups will not contract the d orbitals, making the electron transfer less favorable. The diradical  $(\text{ArS})_3\text{As}-\text{O}-\text{O}\cdot$  can react with another  $(\text{ArS})_3\text{As}$  molecule to give the new diradical  $(\text{ArS})_3\text{As}-\text{O}-\text{O}-\text{As}(\text{SAr})_3$  which, by homolytic fission



SCHEME 1

of the peroxy bond, will give two molecules of the arsenic(V) ester,  $(\text{ArS})_3\text{As}=\text{O}$ , which decompose to  $\text{As}_2\text{O}_3$  and disulfide (see next section). The ester  $(\text{ArS})_3\text{As}=\text{O}$  can also be produced by attack of an  $(\text{ArS})_3\text{As}$  molecule at the apical oxygen of an arsenadioxirane,  $(\text{ArS})_3\text{As}(\text{O}_2)$ , (see ref. 26). These two possibilities can explain the air oxidation of **1–7** in nonprotic solvents.

### The Effect of the Solvent on the Air Oxidation of the Trithioarsenites 1–9

In nonprotic and nondried solvents, **1–5** were air oxidized to an extent of 10–15% while **6** and **7**, having electron-withdrawing groups, were 35% and 70% air oxidized, respectively. Ester **8** was completely consumed during the air oxidation in ~8 h giving  $\text{As}_2\text{O}_3$ , disulfide, and 80–90% free “thiol.” Part of the latter arose from the hydrolysis of **8** because in dry dichloromethane under dioxygen the decomposition was incomplete after 48 h and the “thiol” was only ~30%.

In dry methanol under dioxygen, ester **2** was slowly oxidized to  $\text{As}_2\text{O}_3$  and disulfide, but in nondried methanol in air the oxidation was faster (Table I), indicating involvement of water in the process. In dry  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  under dioxygen the consumption of **9** was incomplete after 48 h, giving  $\text{As}_2\text{O}_3$ , disulfide (~50%), and free “thiol” (~50%), but in  $\text{MeOH}$  or in  $\text{MeOH}/\text{CHCl}_3$  the consumption of **9** during its air oxidation was fast, giving  $\text{As}_2\text{O}_3$ , disulfide (~60%), and free “thiol” (~40%).



In the presence of methanol, the air oxidation of **1** was unaffected, while that of **4** and **5** increased.

In protic solvents the diradical or the arsenadioxirane, Scheme 1, can be converted to the zwitterion  $(\text{ArS})_3\text{As}^+-\text{O}-\text{O}^-$ . Methanol can affect a zwitterion in several ways: It can stabilize it by solvation; it can (by hydrogen bonding to the  $-\text{O}^-$  terminal) decrease the negative charge on the oxygen thus facilitating the nucleophilic attack<sup>17</sup> of another  $(\text{ArS})_3\text{As}$  to give two molecules of  $(\text{ArS})_3\text{As}=\text{O}$ ; and, finally, can convert it to a hydroperoxy compound  $(\text{ArS})_3(\text{MeO})\text{As}-\text{OOH}$  (see ref. 19), which will be more easily attacked by an  $(\text{ArS})_3\text{As}$  nucleophile. By one of these possibilities, the increased decomposition of **4** and **5**, assuming no water participation, can be rationalized.

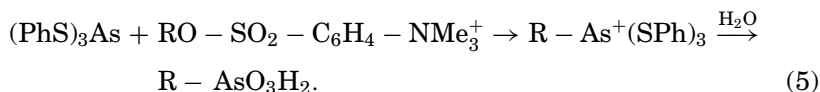
Air oxidation of solutions of **1-9** introduces another variable, that of moisture, especially when methanol is used as solvent or co-solvent. Entry of a water molecule to the tetracoordinated  $\text{As(V)}$ ,  $(\text{ArS})_3\text{As}^+-\text{O}-\text{O}^-$ , to give the pentacoordinated  $\text{As(V)}$  hydroperoxide analogous to **12** should be favorable due to the bigger size of arsenic compared to phosphorus.<sup>33</sup> The effect of water is most profoundly seen in the case of **2**, **8**, and **9**. From **8** and **9**,  $\text{As}_2\text{O}_3$ , disulfide, and free "thiol" are produced, the latter arising from both oxidative decomposition and hydrolysis of the esters.

The mono esters of arsenic acid,  $\text{RO}-\text{AsO}_3\text{H}_2$ , are hydrolytically very unstable,<sup>34</sup> probably because the size of arsenic permits the easy entry of a water molecule.<sup>33</sup> Thioesters of arsenic acid of the type  $\text{ArS}-\text{AsO}_3\text{H}_2$ , if formed, are also hydrolytically unstable,<sup>3</sup> while those of the type  $(\text{ArS})_2\text{AsO}_2\text{H}$  and  $(\text{ArS})_3\text{As}=\text{O}$ , postulated in this work, once formed have two options: either to hydrolyse to arsenic acid,  $(\text{HO})_3\text{As}=\text{O}$ , and thiol,  $\text{ArSH}$ , or to suffer a redox reaction giving  $[\text{HO}-\text{As}=\text{O}]$  and  $[\text{ArS}-\text{As}=\text{O}]$  by expulsion of a disulfide,  $\text{ArSSAr}$ . The hydrolysis route does not take place because  $\text{As}_4\text{O}_6$ , and not  $\text{H}_3\text{AsO}_4$ , is produced. We propose that the  $\text{As}_4\text{O}_6$  arises from the tetramer  $(\text{HO}-\text{As}=\text{O})_4$  by dehydration and from the tetrameric  $(\text{ArS}-\text{As}=\text{O})_4$  via oxidative hydrolysis. Compounds of the type  $\text{RS}-\text{As}=\text{O}$ , e.g., (arsenate reductase)-cys-S- $\text{As}=\text{O}$ , was postulated to hydrolytically give  $\text{As}_2\text{O}_3$  and (arsenate reductase)-cys-SH.<sup>35</sup> The enzyme prevents the oxidation of cysteine to cystine, while in our case such an inhibition is not possible and a disulfide,  $\text{ArSSAr}$ , is produced.

From the results of Brill and Campbell,<sup>4</sup> mentioned in the introduction, and the data of Table I, it follows that the ester  $(\text{PhSe})_3\text{As}$  is oxidized by air much faster than the  $(\text{PhS})_3\text{As}$ , **5**. Since the Pauling electronegativities of sulfur (2.58) and of selenium (2.55) do not differ appreciably, it seems that the size (covalent radii: S 102, Se 114 pm)

plays a role in the binding of dioxygen to the  $(\text{ArE})_3\text{As}$  ( $\text{E}=\text{S}$  or  $\text{Se}$ ). The structure of the  $(\text{ArE})_3\text{As}$  may also be a factor because the conformation of **5** in solution<sup>36a</sup> (but not in the solid state<sup>36b</sup>) has been shown to have a “picket-fence” arrangement of the three phenyl groups, which probably prevents the approach of  $\text{O}_2$  to  $\text{As(III)}$ , while such a conformation of  $(\text{PhSe})_3\text{As}$ , due to the bigger size of  $\text{Se}$ , will not prevent such a binding.

Some years ago we<sup>37</sup> tried the reaction between **5** and *n*-octyl amsylate in dry dichloromethane in an effort to prepare arsonic acids according to Eq. (5):



However, after 3 days of stirring at r.t. we obtained  $\text{As}_2\text{O}_3$  and  $\text{PhSSPh}$  (100% oxidative decomposition). This result, which differs from that shown in Table I, implies that the oxidation of **5** by dioxygen is catalyzed by the amsylate. The mechanism of the catalysis is not yet known. Another interesting case is the following<sup>38</sup>: sodium arsenite is nearly unaffected by dioxygen (a 0.12%-per-24-h rate of oxidation to sodium arsenate has been published<sup>39</sup>) and sodium sulfite is slowly oxidized by air. However, in the presence of both salts, air oxidized both salts to arsenate and sulfate, and under proper conditions one molecule of arsenate was produced for every molecule of sulfate formed.

Summarizing, the results of the air oxidation of the triaryl trithioarsenites **1–9** reported herein, of triphenyl triselenoarsenite,<sup>4</sup> trialkyl trithioarsenites,<sup>4,6</sup> diphenyl allyldithioarsonite and diphenyl benzyldithioarsonite,<sup>2</sup> and of  $\text{As(III)}$ /ascorbic acid 1:2 complex<sup>1</sup> tend to indicate that the  $\text{As(III)}$  in these compounds can bind dioxygen, giving a diradical  $\text{L}_3\text{As}^+-\text{O}-\text{O}^\cdot$ , or an arsenadioxirane  $[\text{L}_3\text{As}(\text{O}_2)]$ , or a zwitterion  $\text{L}_3\text{As}^+-\text{O}-\text{O}^-$  intermediate, depending on the reaction conditions. This intermediate in the previously mentioned compounds reacts further to give the various observed products. From the limited literature data<sup>37,38</sup> it seems that the binding and/or the reaction of the bound dioxygen can be “catalyzed” by other nonarsenic-containing molecules, which themselves can remain unaffected (e.g., amsylate) or be oxidized (e.g., sulfite).

The ability of  $\text{As(III)}$  to bind and activate dioxygen may have implications in chemotherapy or induction of carcinogenesis<sup>40</sup> because both may involve reactive oxygen species.<sup>41,42</sup>

## EXPERIMENTAL

The source and purification of the aromatic thiols used to prepare the esters **1–3**, **5**, **7**, and **8** have been described.<sup>3</sup> 4-chlorothiophenol and 2-mercaptopyridine *N*-oxide (Aldrich) were used as received. 4-acetamidothiophenol (Aldrich, 90%) was purified by fractional crystallization (60% recovery) from acetone-petroleum ether, m.p. 155–156°C (lit.<sup>16</sup> 155–158°C). 4-mercaptopyridine (Aldrich) was purified by recrystallization from methanol<sup>8</sup>, m.p. 173–177°C sinters, 184–189°C melts to a red oil with evolution of hydrogen sulfide (lit.<sup>8</sup> 186°C). The disulfides of thiophenol, 4-mercaptophenol, 4-nitrothiophenol, 4-methylthiophenol, 4-aminothiophenol, and 2-mercaptopyridine were isolated as byproducts of the attempted oxidation of the esters **1–3** and **5–7** by octasulfur.<sup>3</sup> 4-acetamidophenyl disulfide was prepared by hydrogen peroxide oxidation of a methanolic solution of 4-acetamidothiophenol, m.p. 213–215°C (lit.<sup>16</sup> 150–153°C, lit.<sup>43</sup> 218–220°C). 2,2'-dithiobis(pyridine *N*-oxide) was prepared by hydrogen peroxide oxidation of a methanolic solution of 4-mercaptopyridine *N*-oxide, m.p. 174°C starts darkening, 203°C dec. (lit.<sup>44</sup> 235–237°C, lit.<sup>45</sup> 205°C dec., lit.<sup>46</sup> 200–203°C dec.). Its IR (KBr) spectrum was the same as reported.<sup>10</sup> Bis(4-chlorophenyl) disulfide was prepared by hydrogen peroxide oxidation of a methanolic solution of 4-chlorothiophenol, m.p. 73–74°C (lit.<sup>47</sup> 72°C). The esters **1–3**, **5–7**, and **8** have been prepared as described.<sup>3</sup> Nondried AR grade solvents and solutions were deaerated by boiling, flushing with nitrogen, stoppering, and cooling to r.t. Dichloromethane and methanol, used in some experiments, were dried over A<sub>4</sub> molecular sieves.

Thin Layer Chromatography, TLC, using silica gel H (Merck), was run on microslides, always using the appropriate standards. The following developing solvents were used and the *R<sub>f</sub>* values for the triaryl trithioarsenite, disulfide, and thiol, respectively, were for **1**: Et<sub>2</sub>O, *R<sub>f</sub>* 0.13, 0.54, 0.77; for **2**: Et<sub>2</sub>O/petroleum ether 1:1, *R<sub>f</sub>* 0.12, 0.38, 0.58; for **3**: petroleum ether, *R<sub>f</sub>* 0.22, 0.46, 0.46; for **4**: Et<sub>2</sub>O, *R<sub>f</sub>* 0.07, 0.47, 0.37; for **5**: petroleum ether, *R<sub>f</sub>* 0.14, 0.46, 0.46; for **6**: petroleum ether, 0.18, 0.57, 0.57; for **7**: Et<sub>2</sub>O/petroleum ether 1:3, *R<sub>f</sub>* 0.0, 0.45, 0.45; for **8**: Et<sub>2</sub>O, *R<sub>f</sub>* 0.31, 0.77, 0.31; and for **9**: Et<sub>2</sub>O, *R<sub>f</sub>* 0.64, 0.0, 0.73. Spots were made visible first with iodine vapors followed by spraying with 35% sulfuric acid and charring. Compounds containing an ArS- group gave colored spots before being charred. The pairs thiol/disulfide having the same *R<sub>f</sub>* values could not be separated using a variety of other developing solvents.

Isolated arsenic(III) oxide was measured by weighing and its purity was checked by IR<sup>48</sup> (sharp peak at 802 cm<sup>-1</sup>). IR spectra were obtained on a Perking-Elmer model 16PC FT-IR spectrometer.

Elemental analyses were obtained through the Centre of Instrumental Analyses, University of Patras, Greece.

## Preparation of the Trithioarsenites 4, 6, and 9

### ***Tris(4-acetamidophenyl) trithioarsenite, 4***

To a deaerated colorless solution of the orange 4-acetamidothiophenol (524 mg, 3.13 mmol) in methanol (5 mL), arsenic(III) oxide (103 mg, 0.52 mmol  $\text{As}_2\text{O}_3$ ) was added, and the suspension was stirred at r.t. for 24 h. The suspension cleared and the clear pale yellow-green solution was evaporated and dried to give a yellow-green foam (619 mg), which was recrystallized from boiling ethyl acetate (15 mL) to give the product (486 mg, 80%) as a white powder. It is soluble in MeOH and  $\text{Me}_2\text{CO}$ , insoluble (at r.t.) in AcOEt and  $\text{CHCl}_3$ , moderately soluble in boiling AcOEt, and soluble in boiling chloroform, M.p.  $\sim 135^\circ\text{C}$  sinters,  $171\text{--}174^\circ\text{C}$  melts. Calculated for  $\text{C}_{24}\text{H}_{24}\text{N}_3\text{O}_3\text{S}_3\text{As}$  ( $M_r$  573.56): C, 50.25; H, 4.22; N, 7.33; S, 16.77%; found: C, 50.12; H, 4.39; N, 7.07; S, 16.03%. IR (KBr): 3300 m, 3246 mw, 3176 mw, 3102 mw, 3048 mw, 1660 s, 1592 vs, 1534 vs, 1490 s, 1394 m, 1370 mw, 1318 s, 1258 mw, 1178 mw, 1041 w, 1014 w, 820 m, 734 w, 702 w, 604 w, 585 w, 516 mw.

### ***Tris(4-chlorophenyl) trithioarsenite, 6***

A suspension of arsenic(III) oxide (198 mg, 1 mmol  $\text{As}_2\text{O}_3$ ) and 4-chlorothiophenol (867 mg, 6 mmol) in deaerated methanol (7 mL) was stirred at r.t. for 24 h. Centrifugation and washing with methanol ( $2 \times 2$  mL) gave the product **6** (861 mg, 85%) as a white powder soluble in petroleum ether and ether and sparingly soluble in methanol. M.p.  $\sim 70^\circ\text{C}$  shrinks,  $77\text{--}78^\circ\text{C}$  melts. Calculated for  $\text{C}_{18}\text{H}_{12}\text{Cl}_3\text{S}_3\text{As}$  ( $M_r$  505.76): C, 42.74; H, 2.39; S, 19.02%; found: C, 42.53; H, 2.42; S, 19.55%. IR (KBr): 1892 vw, 1636 vw, 1568 w, 1472 vs, 1386 m, 1090 vs, 1012 s, 818 vs, 742 w, 542 w, 496 m.

### ***Tris(2-pyridyl N-oxide) trithioarsenite, 9***

To a yellowish solution of 2-mercaptopyridine N-oxide (994 mg, 7.8 mmol) in deaerated methanol (10 mL), arsenic(III) oxide (258 mg, 1.3 mmol  $\text{As}_2\text{O}_3$ ) was added, and the suspension was stirred at r.t. for 48 h. The precipitated product **9** (574 mg, 49%), as a faint yellowish powder, was obtained by centrifugation and washing with methanol ( $1 \times 2$  mL). It is moderately soluble in methanol and insoluble in  $\text{Et}_2\text{O}$ ,  $\text{Me}_2\text{CO}$ , AcOEt, and  $\text{CHCl}_3$ . M.p.  $155\text{--}157^\circ\text{C}$ . Calculated for  $\text{C}_{15}\text{H}_{12}\text{N}_3\text{O}_3\text{S}_3\text{As}$  ( $M_r$  453.38): C, 39.73; H, 2.67; N, 9.27; S, 21.21%; found: C, 39.41; H, 2.55; N, 9.20; S, 21.45%. IR (KBr): 3442 w, 3062

w, 1586 w, 1542 m, 1460 vs, 1406 s, 1260 m, 1206 vs, 1138 s, 1084 s, 1034 mw, 834 s, 762 s, 694 s, 578 s, 546 m.

### ***Attempted Preparation of Tris(4-pyridyl) trithioarsenite***

The reaction of arsenic(III) oxide and 4-mercaptopyridine (1:6 mol/mol) in deaerated methanol gave yellow, orange, or orange-brown solids insoluble in all common organic solvents and decomposed by 2 M sodium hydroxide. Their IR (KBr) spectra were very weak, indicating low content of the 4-pyridyl group in the solid. The percent analyses showed very low C, H, and N and very high S contents. The supernatants contained at least two compounds (by TLC [acetone]) and were not studied further.

## **Air Oxidation of Triaryl Trithioarsenites**

### ***Triaryl Trithioarsenites 1–7***

The ester (0.1 mmol) dissolved in a solvent (Table I) (4–6 mL) in a centrifuge tube was stirred at r.t. in air, replenishing from time to time the solvent that evaporated. All solutions (except those containing the ester **2** in methanol) became opalescent and TLC showed that only the esters and disulfides (when separated from their thiols) were present. Centrifugation and washing (1 × 1 mL solvent) gave pure (by IR) As<sub>2</sub>O<sub>3</sub> from which the percent decomposition was calculated. The percent decomposition of **2** in chloroform and in methanol was estimated by TLC.

### ***Tris(2-pyridyl) trithioarsenite, 8***

The ester **8** (0.1 mmol) dissolved in chloroform (6 mL) was stirred in air at r.t. for 8 h. Centrifugation and washing with chloroform gave pure, by IR, As<sub>2</sub>O<sub>3</sub> (11 mg) corresponding to 100% decomposition. The supernatant contained (TLC estimation) bis(2-pyridyl) disulfide (~15%) and 2-mercaptopyridine (~85%) and gave a solid, which melted at 118–121°C. Pure disulfide melts at 52–53°C<sup>49</sup> and pure thiol melts at 128–130°C.<sup>50</sup>

To the ester **8** (0.25 mmol) dissolved in dry dichloromethane (18 mL) oxygen was added, stoppered, and stirred at r.t. for 48 h. Centrifugation and washing with chloroform gave pure, by IR, As<sub>2</sub>O<sub>3</sub> (23 mg), corresponding to 94% decomposition. The supernatant contained (by TLC) the disulfide (~70%) and thiol plus **8** (~30%) and gave a solid, which melted at 45–47°C.

### ***Tris(2-pyridyl N-oxide) trithioarsenite, 9***

The ester **9** (0.1 mmol) dissolved in methanol (or methanol/chloroform 1:3) (6 mL) was stirred in air at r.t. for 7 h. Evaporation, drying in vacuum, and the addition of acetone (3 mL) precipitated pure, by IR,

As<sub>2</sub>O<sub>3</sub> (11 mg) corresponding to 100% decomposition of **9**. The supernatant contained, by TLC, 2,2'-dithiobis(pyridine *N*-oxide) (~60%) and 2-mercaptopyridine *N*-oxide (~40%).

To a solution of **9** (0.23 mmol) in dry methanol (3 mL) and dry dichloromethane (9 mL) oxygen was added, stoppered, and stirred at r.t. for 48 h. Evaporation, drying in vacuum, and the addition of acetone (7 mL) precipitated As<sub>2</sub>O<sub>3</sub> and the insoluble **9**, which did not react. The supernatant contained, by TLC, disulfide (~50%) and thiol (~50%) and gave 61 mg of a semisolid from which a 70% decomposition of **9** was calculated.

### Air Oxidation of Thiols Used to Prepare the Esters 1–9

The parent thiols for the esters **1**, **2**, **4**, **8**, and **9** dissolved in a solvent were stirred in air at r.t. and the disulfide produced was visually estimated from the TLCs.

In order to detect the disulfides produced by air oxidation of 4-methylthiophenol, thiophenol, 4-chlorothiophenol, and 4-nitrothiophenol, the free thiol was captured by mercuric acetate in methanol. Centrifugation and washing with methanol gave the mercuric mercaptide, ArSHgSAr, and a supernatant. The latter was evaporated, dried in vacuum, and analyzed by TLC. Thiophenol and 4-methylthiophenol produced disulfides but 4-chlorothiophenol and 4-nitrothiophenol did not (Table I).

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