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# Synthesis of arsonium salts and betaines based on triphenylarsine and ω-bromoalkanoic acids

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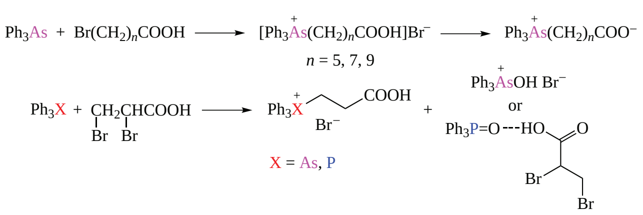
**The reactions between $Ph_3As$ and ω-bromoalkanoic acids with the length of polymethylene fragment *n* = 5, 7, 9 afford quaternary arsonium salts. Their treatment with alkali gives biologically active arsenobetaines. Solvent-free reactions of $Ph_3P$ or $Ph_3As$ with 2,3-dibromopropionic acid lead to the corresponding arsonium and phosphonium salts bearing $(CH_2)_2COOH$ substituent.**

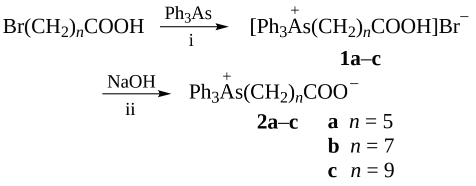


*Keywords*: arsonium salts, arsenobetaines, carboxylic acids, biological activity, antitumor agents, phosphonium salts, phosphobetaine, organoarsenic compounds.

Arsenic compounds exist in nature in both inorganic (arsenates and arsenites) and oil- and water-soluble organic (betaine) forms. Inorganic arsenic compounds are usually strongly toxic while some organoarsenic compounds are absolutely non-toxic, *e.g.*, $Me_3As^+CH_2COO^-$ ($LD_{50} > 10$ g kg$^{-1}$).[1,2] The first works presenting arseno- and phosphabetaine synthesis were published in the beginning of the 20th century. A lot of them described separation of trimethylarsonium carboxylate from a variety of biological sources:[3–8] algae, invertebrates, marine[4] and freshwater fish[5,6] and even from some species of fungi[7] and lichens.[8] Synthetic articles started to appear only in 1960s when the prepared arsenobetaines had characteristics identical to those separated from natural objects, as confirmed by IR or $^1$H NMR spectroscopy and mass spectrometry.[9]

The main method for the preparation of arsenobetaines involves the corresponding arsonium salts, similarly to the phosphorus-containing analogue synthesis based on reaction of tertiary phosphine and halo carboxylic acid.[10] Arsonium salts and arsenobetaines formed from halo carboxylic acid described in Gamaurova's work[11] contained short alkylene fragment $(CH_2)_n$ ($n = 1, 2$) between As and CO moieties. To expand these data, our group synthesized analogous phosphonium salts and the corresponding betaines with longer polymethylene fragments $(CH_2)_n$ ($n = 1$–$4$).[12]

Here, we describe the synthesis of arsonium salts and arsenobetaines with longer polymethylene fragments $(CH_2)_n$ between As atom and carbonyl group. The method is based on the reaction of $Ph_3As$ with ω-haloalkanoic acids[13] comprising the melting of the reactants at 100 °C for 25–55 h (Scheme 1).



$$Br(CH_2)_nCOOH \xrightarrow[\text{i}]{Ph_3As} [Ph_3\overset{+}{As}(CH_2)_nCOOH]Br^- \;\; \mathbf{1a{-}c} \xrightarrow[\text{ii}]{NaOH} Ph_3\overset{+}{As}(CH_2)_nCOO^- \;\; \mathbf{2a{-}c}$$

**a** $n = 5$
**b** $n = 7$
**c** $n = 9$

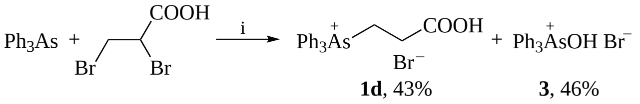
**Scheme 1** *Reagents and conditions*: i, melting, ~100 °C (water bath), 25–55 h; ii, NaOH (aq., 1 equiv.), MeCN, room temperature.

Bromide anion was eliminated from arsonium salts **1a–c** with sodium hydroxide solution by analogy to phosphonium salts. As a result, arsenobetaines **2a–c** were formed (see Scheme 1). The dehydrohalogenation was performed in a titration mode controlled with phenolphthalein. The obtained arsonium salts **1a–c** as well as arsenobetaines **2a–c** were characterized by IR, $^1$H and $^{13}$C NMR spectroscopy (see Table 1 and Online Supplementary Materials). The IR spectra of substances **2a–c** contain two absorption bands corresponding to symmetric (~1400 cm$^{-1}$) and antisymmetric (~1560 cm$^{-1}$) vibrations of the carboxylate anion, which proves the formation of arsenobetaines from the arsonium salt.

It seemed interesting to study alternative methods for obtaining these compounds. Earlier Khachikyan's group presented results[14] on the reactions between P- and N-nucleophiles and 2,3-dihalopropionic acids in solvents (acetonitrile, methanol or benzene). The reaction between triphenylphosphine and 2,3-dibromopropionic acid afforded (2-carboxyethyl)triphenylphosphonium bromide, while the corresponding phosphabetaine was formed as the intermediate. We herein extended these findings onto solvent-free reaction of triphenylarsine with 2,3-dibromopropionic acid, whose mixture

**Table 1** Characteristics of arsonium salts **1a–c** and the corresponding arsenobetaines **2a–c**.

| Compound | *n* | mp/°C | IR spectra, *ν*/cm$^{-1}$ | Yield (%) |
|---|---|---|---|---|
| **1a** | 5 | 172–177 | 1705 ν(C=O), 1162 ν(C–O), 1251 ν(COH) | 24 |
| **1b** | 7 | 107–112 | 1694 ν(C=O), 1163 ν(C–O), 1249 ν(COH) | 47 |
| **1c** | 9 | 70 | 1687 ν(C=O), 1156 ν(C–O), 1258 ν(COH) | 45 |
| **2a** | 5 | 54 | 1563 $\nu_{as}$(C=O), 1393 $\nu_s$(COO$^-$) | 81 |
| **2b** | 7 | 79–90 | 1564 $\nu_{as}$(C=O), 1409 $\nu_s$(COO$^-$) | 75 |
| **2c** | 9 | oil | 1562 $\nu_{as}$(C=O), 1405 $\nu_s$(COO$^-$) | 76 |



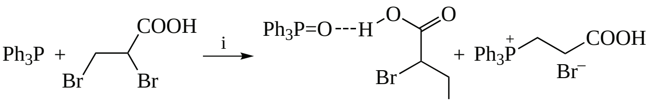
**1d**, 43%  **3**, 46%

**Scheme 2** *Reagents and conditions*: i, melting, ~80 °C (water bath), 10 h.

was melted in a water bath for 10 h. In fact, $^1$H NMR spectrum of the reaction mixture indicated formation of arsonium salt **1d** (Scheme 2). After some time, single crystals were deposited from the reaction mixture and their XRD analysis established the formation of another arsonium salt **3**.

Compound **3** can be in principle formed upon hydrolysis of triphenylarsine dibromide [dibromo(triphenyl)arsorane]. Arsonium salt **3** was previously[15] prepared by such a hydrolysis and its crystal was studied by XRD (CCDC number 1228478).[15] Our XRD analysis of **3** fully coincided with those data,[15] which confirms its structure.

It also looked interesting to study the possibility of conducting similar reactions to synthesize analogous phosphonium salts from 2,3-dibromopropionic acid (Scheme 3). The reactants were fused upon heating with a water bath for 30 min. The $^{31}$P NMR spectra showed the formation of two products (47 : 53) resonating at 24.78 and 36.63 ppm. The signal at 36.63 ppm was referred to hydrogen-bonded adduct **4** of triphenylphosphine oxide and initial dibromo acid, and the signal at 24.78 ppm to phosphonium salt **5** (see Scheme 3).



**4**, 45%  **5**, 40%

**Scheme 3** *Reagents and conditions*: i, melting, ~80 °C (water bath), 30 min.

A mechanism for formation of compounds **1d** and **5** may be the same as in the Khachikyan's work.[14] The reaction is carried out on contact with air and without solvent, so traces of water may be taken from the environment. Supposedly, these conditions can also affect formation of compound **3** (see Scheme 2).

The structure of compound **4** was established by single crystal XRD study (Figure 1).[†] This compound is truly an adduct of triphenylphosphine oxide and 2,3-dibromopropionic acid coordinated by hydrogen bonding (O···O bond length 2.52 Å). Carboxy group C–O bonds are unequal [1.193(5) and 1.301(5) Å]. In addition, modified bond lengths indicate adduct formation: O–P bond [1.497(3) Å] is shorter than that in triphenylphosphine oxide while P–C bond length is the same.[16] The 2,3-dibromopropionic acid molecule is presented in two isomeric forms in a 50 : 50 ratio with different dihedral angles.

Some works describe similar adducts of triphenylphosphine oxide. Hydrogen bond lengths in these compounds are close but slightly longer, which can be explained by the fact that the different compounds form adducts. The O···O bond length is 2.73 Å in adduct of benzotrifuroxan and phosphine oxide[17] and 2.63 Å between the phenol OH and the phosphine oxide P=O groups.[18]

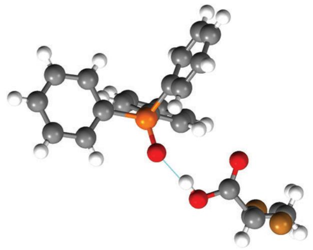
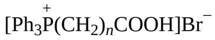


**Figure 1** The structure of hydrogen-bonded adduct **4**.

Organoelement betaines and their derivatives are widely used in medicine as antidiabetic, hypolipidemic, hepatoprotective and cardioprotective drugs.[19–21] Thus, antimycotic and bactericidal activity of synthesized arsenobetaines **2a–c** and arsonium salts **1a–c** was examined (Table 2). This study revealed the dependence of the compound activity towards *B. cereus, S. aureus, Candida albicans* on the length of the polymethylene fragment of the initial bromo carboxylic acid. All the compounds exhibited high biological activity comparable to that of many commercial drugs. Based on data in Table 2, it can be concluded that arsonium salts **1** showed higher activity, which might be attributed to their better solubility.

A comparison of biological activities of compounds **1a–c** synthesized herein and earlier prepared phosphonium salts **6a–c**[22] revealed that the phosphonium cation slightly reduces the biological activity. For example, arsonium salt **1c** with nine methylene fragments demonstrated activity against


$[Ph_3\overset{+}{P}(CH_2)_nCOOH]Br^-$

**6a–c**

**a** $n = 5$
**b** $n = 7$
**c** $n = 9$

**Table 2** Antimicrobial activity of compounds **1a**–**c** and **2a**–**c** in EtOH ($C$ = 10 mg ml$^{-1}$).

| Sample | Diameter of inhibition zone, *d*/mm | | | | |
|---|---|---|---|---|---|
| | *Kl. pneumoniae* | *B. cereus* | *Ps. aeruginosa* | *S. aureus* | *Candida albicans* |
| **1a** | 9 | 7 | 9 | 8 | 9 |
| **1b** | 10 | 16 | 11 | 20 | 13 |
| **1c** | 10 | 29 | 9 | 33 | 25 |
| **2a** | 7 | – | 7 | 8 | 7 |
| **2b** | 7 | 15 | 7 | 18 | 10 |
| **2c** | 7 | 25 | 7 | 30 | 21 |
| Penicillin | 12 | 6 | 13 | 23 | – |
| Fluconazole | – | – | – | – | 17 |

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[†] *Crystal data for* **4**. $C_{21}H_{19}Br_2O_3P$ ($M$ = 510.15), monoclinic, space group $P21/n$ (no. 14), $Z$ = 4, $a$ = 13.5085(3), $b$ = 9.73571(17) and $c$ = 17.0492(4) Å, $\alpha$ = 90°, $\beta$ = 110.342(3)°, $\gamma$ = 90°, $V$ = 2102.37(8) Å$^3$, $\rho_{\text{calc}}$ = 1.612 g cm$^{-3}$, $\mu$ = 5.763 mm$^{-1}$, 24710 reflections collected ($-17 \leqslant h \leqslant 17$, $-12 \leqslant k \leqslant 12$, $-21 \leqslant l \leqslant 21$), $2\theta$ range is 7.242 to 154.222, 4352 independent ($R_{\text{int}}$ = 0.0483) and 4018 observed reflections [$I \geqslant 2\sigma(I)$], 263 refined parameters, $R_1$ = 0.0521, $wR_2$ = 0.1323, goodness of fit $S$ = 1.095, $R_{\text{sigma}}$ = 0.0304.

X-ray diffraction data were collected on a Rigaku XtaLab Synergy S instrument with a HyPix detector and a PhotonJet microfocus X-ray tube using CuKα ($\lambda$ = 1.54184 Å) radiation at low temperature. Images were indexed and integrated using the CrysAlisPro data reduction package. Data were corrected for systematic errors and absorption using the ABSPACK module: numerical absorption correction based on Gaussian integration over a multifaceted crystal model and empirical absorption correction based on spherical harmonics according to the point group symmetry using equivalent reflections. The GRAL module was used for analysis of systematic absences and space group determination. The structure was solved by direct methods using SHELXT[28] and refined by the full-matrix least-squares on $F^2$[29] using SHELXL.[29] Non-hydrogen atoms were refined anisotropically. The hydrogen atoms were inserted at the calculated positions and refined as riding atoms. The figures were generated using Mercury 4.1 program.[30] Crystals were obtained by slow evaporation method.

CCDC 182307 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

*Ps. aeruginosa* while phosphonium salt **6a** had no effect on this bacterium.

Quaternary phosphonium salts show antibacterial[23,24] and antitumor activity as well as the capability of delivering targeted substance to mitochondria.[25] Recent works present that quaternary phosphonium salts based on salicylic and acetylsalicylic acids,[26] some (3-halo-2-hydroxypropyl)-triphenylphosphonium triflates[27] and phosphonium salts obtained from unsaturated amides[23] exhibit increased antitumor activity *in vitro* against some cancer lines.

In summary, we have described the Menshutkin synthesis of novel arsonium salts and arsenobetaines with the polymethylene fragments $(CH_2)_n$ ($n$ = 5, 7, 9). The activity of compounds with respect to the bacterium lines was found to be dependent on the length of these fragments.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.02.032.

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