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Preparation of trimethyl -2-hydroxyethylarsonium (arsenocholine) compounds

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Trimethyl-2-X-ethylarsonium salts (X = OH, Cl, Br, CH_3COO; anion = Br) and trimethyl-2-diethoxyethylarsonium bromide were prepared from trimethylarsine and the appropriate organic bromides in sealed tubes at elevated temperatures or by refluxing the neat reagents. The yields ranged from 33 to 85%. Anion exchange reactions produced the arsonium iodides, nitrates, acetates, tosylates, tetraphenylborates, picrates, hydroxides, and carbonates. Arsenocholine bromide (X = OH) was phosphorylated with concentrated phosphoric acid. The product was isolated as the barium salt. Treatment of the barium salt with sulfuric acid yielded trimethyl-2-(dihydrogen phosphato)ethylarsonium bromide. These substances were synthesized to serve as precursors for arsenic-containing phospholipids and as standards for the chromatographic identification of arsenocholines. The synthesized compounds were characterized by elemental analyses and ^1H and ^{13}C NMR spectroscopy. The shifts of the arsenic compounds were compared with those of the corresponding nitrogen compounds and found to be sufficiently different to be used for the identification of these compounds in their mixtures.

Keywords: Trimethyl-2-hydroxyethylarsonium salts, arsenocholine, trimethyl-2-haloethylarsonium bromide, trimethyl-2-acetoxyethylarsonium bromide, acetylarsenocholine, trimethyl-2-(dihydrogen phosphato)ethylarsonium bromide, ^1H and ^{13}C NMR spectra.

INTRODUCTION

The identification of arsenocholine and arsenobetaine in marine organisms added organic arsenic compounds more complex than simple methylated arsenic derivatives to the natural arsenic cycle (Scheme 1)[1]. Arsenocholine, the trimethyl-2-hydroxyethylarsonium cation, is isologous to choline, the trimethyl-2-hydroxyethylammonium cation. Choline is an important constituent of lecithins (phosphatidyl cholines). Experiments with marine unicellular algae growing in a medium containing arsenate provided evidence that arsenic-containing phospholipids are formed by these organisms.[2] These findings suggest that arsenocholine is incorporated into phospholipids.[3]

Hardly anything is known of how arsenocholine is synthesized by organisms, how arsenolecithins are formed, and how arsenocholine is catabolized. For the chromatographic identification of arsenocholine and related arsenic compounds,[4] standards were needed. The preparation of arsenolecithins begins with arsenocholine or one of its derivatives. For these reasons, several arsenocholine salts and arsenocholine derivatives were synthesized and characterized.

EXPERIMENTAL

Materials and instrumentation

Trimethylarsine was prepared from arsenic trichloride and methylmagnesium iodide in dibutyl ether.[5] The organic halides were purchased from Aldrich, Eastman Chemicals, or Fisher Scientific

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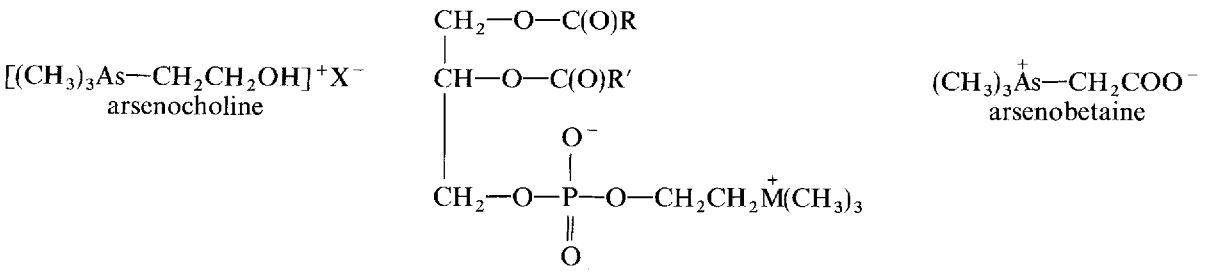


$[(CH_3)_3As{-}CH_2CH_2OH]^+X^-$ arsenocholine

$(CH_3)_3\overset{+}{As}{-}CH_2COO^-$ arsenobetaine

M = N: phosphatidyl choline
M = As: phosphatidyl arsenocholine

Scheme 1

and purified by distillation. The ^1H NMR spectra were obtained on a Varian HA-100 spectrometer and the ^{13}C spectra on a JEOL-PFT 100 spectrometer equipped with a Nicolet 1080 computer.

Precautions

All work with arsenic compounds must be carried out in a well-ventilated hood. Gloves should be worn when handling trimethylarsine and arsenic chlorides to avoid contact of the skin with these compounds. Trimethylarsine is rather volatile (b.p. 53°C). Special precautions must be taken to avoid contact of trimethylarsine vapors with the air passages. Trimethylarsine is easily oxidized on contact with air and might ignite and it also has a penetrating, disagreeable odor. The arsonium salts are solid and can be handled much more easily than liquid arsenic compounds. Arsonium salts should, nevertheless, be handled with care, because little is known about their toxicity.

Trimethyl-2-hydroxyethylarsonium chloride (arsenocholine chloride)

Trimethylarsine (25.9 g, 0.21 mol) was transferred under an atmosphere of nitrogen into a 100 cm^3, thick-walled, nitrogen-flushed glass tube chilled in a dry ice/acetone bath. Deoxygenated 2-chloroethanol (19.2 g, 0.24 mol) was then added. The chilled tube was evacuated with an oil vacuum pump and then flame-sealed. The tube was allowed to warm to room temperature and was then heated in a bomb furnace at 120–140°C for 24 h. The contents of the tube solidified when cooled to room temperature.

The tube was placed in a dry ice/acetone bath and carefully opened. The solid material was washed from the tube with absolute ethanol (35 cm^3). The ethanolic solution was mixed with activated charcoal, stirred, and filtered. The treatment with charcoal was repeated until the filtrate had become colorless. Careful addition of acetone to the filtrate precipitated white crystals. The mixture was filtered and the crystals dissolved in amyl alcohol. Addition of anhydrous diethyl ether precipitated white hygroscopic crystals of arsenocholine chloride. Yield: 14.7 g (35%); m.p. 230°C (lit. 220°C[6]).

[Found (cal.) for $C_5H_{14}AsClO$ (200.54): C, 29.77 (29.95); H, 6.99 (7.04)%.]

Trimethyl-2-chloroethylarsonium bromide

Trimethylarsine (6.0 cm^3, 6.7 g, 56 mmol) and 1-bromo-2-chloroethane (8.6 g, 60 mmol) were heated at 75–80°C for 84 h in a sealed tube as described above. The tube was then opened and kept evacuated at 0.01 Torr at room temperature for several hours to remove unreacted starting materials. The arsonium bromide was left as a white, crystalline, analytically pure material. Recrystallization was not necessary. Yield: 4.3 g (33%); m.p. 225–257°C (dec).

[Found (cal.) for $C_5H_{13}AsBrCl$ (263.43): C, 22.90 (22.79); H, 4.99 (4.97)%.]

Trimethyl-2-bromoethylarsonium bromide

Trimethylarsine (6.0 cm^3, 6.7 g, 56 mmol) and 1,2-dibromoethane (13.1 g, 60 mmol) were heated at 75–80°C for 84 h in a sealed tube. The product was isolated as described above. Yield: 9.1 g (59%), m.p. 239°C (lit. 239°C).

[Found (cal.) for $C_5H_{13}AsBr_2$ (307.88): C, 19.64 (19.50); H, 4.40 (4.26)%.]

Trimethyl-2-hydroxyethylarsonium bromide (arsenocholine bromide)

Trimethylarsine (34.5 g, 0.28 mmol) was transferred by means of a nitrogen-flushed syringe into a dry, nitrogen-filled, 250 cm^3, three-necked, round-bottomed flask equipped with a reflux condenser through which chilled water was circulated, a nitrogen-inlet tube, and a magnetic stirring bar. A slight excess of deoxygenated 2-bromoethanol (36.5 g, 0.29 mmol) was poured onto the arsine. The stirred mixture was refluxed for 24 h. When the mixture was cooled to room temperature, a solid formed. The solid was recrystalized from dry acetonitrile. The acetonitrile solution was cooled in a freezer. The white, hygroscopic crystals were isolated in a dry-box and stored in a vacuum desiccator over phosphorus pentoxide. Yield: 58.3 g (85%); m.p. 227°C (lit. 238–241°C^7, 219°C^{6,8}).

Found (cal.) for $C_5H_{14}AsBrO$ (244.99): C, 24.47 (24.51); H, 5.85 (5.71)%.]

Trimethyl-2-hydroxyethylarsonium iodide (arsenocholine iodide)

Arsenocholine bromide (5.75 g, 23 mmol) was dissolved in 75 cm^3 dry acetonitrile and sodium iodide (3.52 g, 23 mmol) in 125 cm^3 dry acetonitrile. The two solutions were mixed in a 500 cm^3 Erlenmeyer flask. A white precipitate of sodium bromide formed immediately. The mixture was stirred for 1 h at room temperature, then filtered. The filtrate was concentrated at room temperature under reduced pressure to approximately 75 cm^3. The concentrated filtrate was kept in a freezer to allow the product to crystallize. The white nonhygroscopic crystals were collected by filtration and air-dried. Yield: 6.2 g (83%); m.p. 213–215°C.

[Found (cal.) for $C_5H_{14}AsIO$ (291.99): C, 20.34 (20.56); H, 4.74 (4.83)%.]

Trimethyl-2-hydroxyethylarsonium hydroxide (arsenocholine hydroxide)

Arsenocholine bromide (12.2 g, 50 mmol) and freshly prepared silver oxide in a medium of aqueous acetone were stirred at room temperature overnight in the dark. The mixture was filtered. Attempts to remove the solvent at room temperature under reduced pressure led to decomposition. The arsenocholine hydroxide is stable only in solution.

Trimethyl-2-hydroxyethylarsonium nitrate (arsenocholine nitrate)

A suspension of silver nitrate (2.09 g, 12.3 mmol) in 50 cm^3 dry acetonitrile was added to a solution of arsenocholine bromide (3.02 g, 12.4 mmol) in 50 cm^3 dry acetonitrile. The mixture was stirred for 1 h at room temperature and then filtered. The filtrate was concentrated to approximately 50 cm^3 at 40°C under reduced pressure. Acetone (200 cm^3) was carefully layered on the concentrate. The mixture was cooled in a freezer, until grayish crystals had formed. The liquid was decanted. The crystals were dissolved in 20 cm^3 hot acetonitrile. Activated charcoal was added to the solution. The mixture was filtered, and the filtrate chilled in a freezer. The white, hygroscopic crystals were separated from the solution by filtration in a dry-box. Yield: 1.2 g (41%); m.p. 119–121°C.

[Found (cal.) for $C_5H_{14}AsNO_4$ (227.09): C, 26.17 (26.45); H, 6.20 (6.21)%.]

Bis(trimethyl-2-hydroxyethylarsonium) carbonate (arsenocholine carbonate)

Arsenocholine bromide (12.2 g, 50 mmol) dissolved in water was stirred with silver carbonate (6.9 g, 25 mmol) overnight. The mixture was filtered to remove the precipitated silver bromide. The precipitate was washed with water. The filtrate combined with the washings was evaporated under reduced pressure. The residue was dried in a vacuum desiccator over phosphorus pentoxide. The yellowish solid is very hygroscopic.

Trimethyl-2-hydroxyethylarsonium hydrogen carbonate (arsenocholine hydrogen carbonate)

Arsenocholine bromide (12.2 g, 50 mmol) and freshly prepared silver oxide (12.5 g, 54 mmol) in water were stirred at room temperature overnight. The precipitated silver bromide was removed by filtration. Carbon dioxide was bubbled through the filtrate for 4 h. The colorless solution was evaporated at room temperature. When the solution became concentrated, a brownish color appeared, indicating that the compound had begun to decompose. Yellowish-brown crystals were isolated.

Trimethyl-2-hydroxyethylarsonium tetraphenylborate (arsenocholine tetraphenylborate)

Arsenocholine chloride (1.05 g, 5 mmol) was dissolved in 15 cm^3 water. An aqueous solution of sodium tetraphenylborate (2.08 g, 6 mmol, in 60 cm^3 water) was added. The arsenocholine tetraphenylborate precipitated immediately. The mixture was stirred at room temperature overnight, then filtered and the solid recrystallized from a water/acetone mixture (1:9, v/v). The white crystals were dried in a vacuum desiccator over phorphorus pentoxide. Yield: 1.9 g (80%); m.p. 262°C.

[Found (cal.) for $C_{29}H_{34}AsBO$ (484.32): C, 71.84 (71.92); H, 7.29 (7.08)%.]

Trimethyl-2-hydroxyethylarsonium acetate (arsenocholine acetate)

Arsenocholine hydrogen carbonate dissolved in water was treated with an equivalent amount of acetic acid. The resulting solution was evaporated at room temperature under reduced pressure. The resulting yellow oil did not crystallize. The compound was characterized by ^{1}H NMR spectroscopy.

Trimethyl-2-hydroxyethylarsonium 4-methylbenzenesulfonate (arsenocholine tosylate)

Arsenocholine bromide (6.63 g, 27 mmol) was dissolved in 50 cm^3 water. An excess of silver oxide (5.0 g, 22 mmol) was added to the solution. The mixture was stirred for 1 h at room temperature. After the precipitated silver bromide and the excess silver oxide had settled, the supernatant was decanted and filtered. The solid in the flask was washed with three 50 cm^3 portions of water. The washings were decanted, filtered, and combined with the main filtrate. 4-Methylbenzenesulfonic acid (5.15 g, 27 mmol) was added to the combined filtrates. The slightly acidic mixture (pH 5–6) was concentrated at 40–50°C under an aspirator vacuum to a thick syrup. Toluene (100 cm^3) was added to the syrup. The mixture was distilled. This procedure was repeated three more times to remove all water. The resulting white powder was recrystallized from acetone (125 cm^3). The arsenocholine tosylate, a white, nonhygroscopic crystalline material, was stored in a vacuum desiccator over phosphorus pentoxide. Yield: 8.3 g (91%); m.p. 104°C.

[Found (cal.) for $C_{12}H_{21}AsO_4S$ (336.28): C, 42.88 (42.86); H, 6.54 (6.29)%.]

Barium salt of trimethyl-2-phosphatoethylarsonium bromide dihydrate

Arsenocholine bromide (7.0 g, 28 mmol) and concentrated phosphoric acid (85%, 6.6 g, 54 mmol) were mixed in a 100 cm^3, round-bottom flask equipped with a magnetic stirrer. The flask was kept evacuated at 0.2 Torr and heated for 20 h in an oil bath kept at 165°C. The mixture was cooled to room temperature. The glassy material was dissolved in 25 cm^3 hot water. Hydrobromic acid (48%, 5 cm^3, 42 mmol) was added. The solution was evaporated to dryness at 70°C on a rotary evaporator. The residue was dissolved in 200 cm^3 water. A large excess of barium carbonate (20 g, 100 mmol) was added to the solution. The barium phosphate precipitate was removed by filtration. The solid was washed with 20 cm water. The washings and the filtrate were combined and concentrated under reduced pressure. Traces of solid material were removed by centrifugation. The solution (pH 6.5) was then further concentrated, until crystals began to form. Ice-cold methanol (50 cm^3) was added. The mixture was kept in a refrigerator at +5°C for 1 h, then filtered and the crystals washed with cold methanol and dried in air. Yield: 2.7 g (19%); does not melt below 300°C.

[Found (cal.) for $C_5H_{13}AsBaBrO_4P \cdot 2H_2O$ (406.30): C, 12.14 (12.09); H, 3.57 (3.42)%.]

Trimethyl-2-(dihydrogen phosphato)ethylarsonium bromide

Aqueous sulfuric acid (0.1 mol dm^{-3}) was dropped onto a solution of the barium salt of trimethyl-2-phosphatoethylarsonium bromide dihydrate (1.5 g, 3 mmol) in 50 cm^3 water, until no more barium sulfate precipitated. The mixture was filtered. The filtrate was evaporated to dryness at 60°C under reduced pressure. The yellow, oily residue was kept at 0.1 Torr at room temperature for two days. During this time the oil crystallized partly but never completely. A mixture of oily and crystalline product gave satisfactory elemental analyses. Yield: 0.97 g (100%).

[Found (cal.) for $C_5H_{15}AsBrO_4P$ (324.98): C, 18.98 (18.48); H, 4.85 (4.65)%.]

Trimethyl-2-acetoxyethylarsonium bromide (acetylarsenocholine bromide)

Trimethylarsine (10.21 g, 85 mmol) was transferred by means of a nitrogen-flushed syringe into a 250 cm^3, three-necked, nitrogen-filled, round-bottom flask equipped with a reflux condenser through which chilled water was circulated, a nitrogen-inlet tube, and a magnetic stirring bar. Bromoethyl acetate (15 cm^3, 22.7 g, 136 mmol) was added. The mixture was stirred and refluxed under an atmosphere of nitrogen for 24 h. Upon cooling the mixture formed a white solid, which was dissolved in 50 cm^3 dry acetonitrile. The solution was cooled in a freezer. Ethyl acetate was added to the cool solution, until it became turbid. The solution was kept in a freezer to allow crystals to form. The mixture was filtered in a dry-box to isolate the white, hygroscopic product. Yield: 12.5 g (51%); m.p. 107°C (lit. 107°C[7]).

[Found (cal.) for $C_7H_{16}AsBrO_2$ (287.04): C, 28.93 (29.29); H, 5.55 (5.62)%.]

Trimethyl-2-acetoxyethylarsonium iodide (acetylarsenocholine iodide)

Crude acetylarsenocholine bromide (7.02 g, 24.5 mmol) and sodium iodide (3.67 g, 24.5 mmol) were each dissolved in 40 cm^3 dry acetonitrile. The two solutions were mixed. A precipitate of sodium bromide formed immediately. The mixture was stirred for 2 h and then filtered. The filtrate was evaporated to dryness at 60°C under an aspirator vacuum. The residue was dissolved in 25 cm^3 acetonitrile. The solution was kept in a freezer, until a precipitate had formed. The mixture was filtered. The filtrate was carefully mixed with ethyl acetate, until the solution (total volume 110 cm^3) had become turbid. The turbid solution was stored in a freezer to allow crystals to form. The mixture was filtered in a dry-box to collect the white, hygroscopic crystalline product. Yield: 5.3 g (61%); m.p. 103°C.

[Found (cal.) for $C_7H_{16}AsIO_2$ (334.03): C, 25.17 (25.17); H, 4.63 (4.83)%.]

Trimethyl-2-acetoxyethylarsonium picrate (acetylarsenocholine picrate)

Sodium carbonate (7.0 g, 66 mmol) was added to a solution of silver nitrate (10 g, 53 mmol) in 400 cm^3 water. The mixture was filtered. The moist, solid silver carbonate (~10 g) was added to a solution of picric acid (14 g, 50 mmol) in ethanol. The mixture was stirred for 1 h. The slurry of silver picrate was decanted through a Buchner filter funnel, leaving unreacted silver carbonate as lumps at the bottom of the flask. The silver picrate was quickly dissolved in 400 cm^3 water. The solution was extracted with three 50 cm^3 portions of diethyl ether to remove excess picric acid. The silver picrate solution was added slowly to a solution of crude acetylarsenocholine bromide (6.74 g, 23 mmol) in 125 cm^3 water, until no more silver bromide precipitated. The mixture was stirred at room temperature for 10 h, then filtered and the silver bromide washed with water. The filtrate combined with the washings was evaporated at 40–50°C under reduced pressure. The residue was extracted with three 75 cm^3 portions of diethyl ether. The residue was mixed with 100 cm^3 ethanol. The mixture was boiled and filtered while hot. The filtrate was concentrated and refrigerated. Bright yellow crystals of the product precipitated. Yield: 94 g (94%); m.p. 123°C.

[Found (cal.) for $C_{13}H_{18}AsN_3O_9$ (435.23): C, 35.57 (35.88); H, 3.90 (4.17)%.]

Trimethyl-2,2-diethoxyethylarsonium bromide

Trimethylarsine (12.2 g, 0.102 mmol) was placed into a 100 cm^3, nitrogen-filled, round-bottom flask equipped with a chilled-water condenser and a magnetic stirring bar. 2,2-Diethoxy-1-bromoethane (20.1 g, 0.102 mol) was added. The mixture was stirred at room temperature for 18 h and then gently heated at 40°C for 24 h. The resulting solid was triturated with 50 cm^3 diethyl ether. The suspension was stirred overnight. The mixture was filtered. The tan solid was dissolved in acetonitrile and treated with activated charcoal. The mixture was filtered. The filtrate was evaporated to dryness. The residue was recrystallized from acetone. Yield: 14.4 g (45%); m.p. 137°C.

[Found (cal.) for $C_9H_{22}AsBrO_2$ (317.10): C, 34.55 (34.09); H, 7.49 (6.99)%.]

RESULTS AND DISCUSSION

Preparation of arsenocholine salts

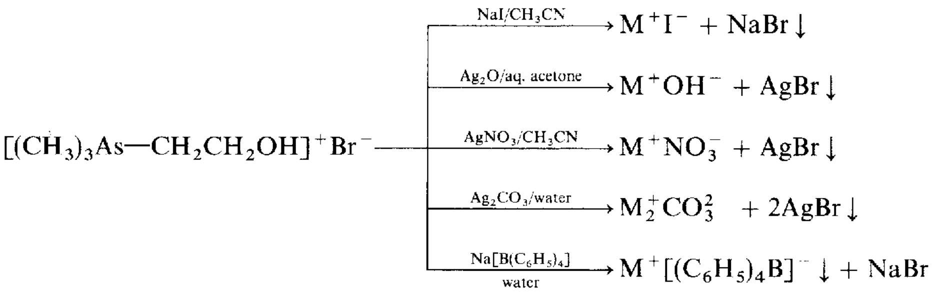
Arsenocholine salts were prepared by quaternization of trimethylarsine with 2-haloethanols (Eqn [1]). The reaction with chloroethanol is sluggish and must be promoted by heating the neat reactants in a sealed tube at 140°C for 24 h. The yield of arsenocholine chloride did not exceed 35%.

$$(CH_3)_3As + X{-}CH_2CH_2OH \xrightarrow{\text{heat}} [(CH_3)_3As{-}CH_2CH_2OH]^+X^- \quad X = Cl, Br \qquad [1]$$

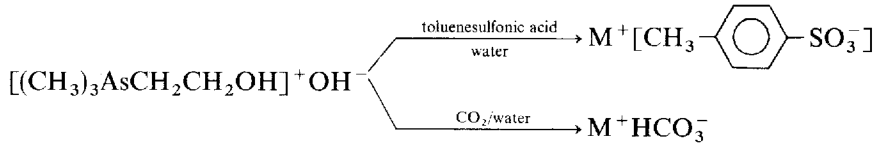
Bromoethanol reacted easily with trimethylarsine when heated in a flask. After 24 h heating, the arsonium bromide was isolated in 85% yield. This reaction was used previously to prepare arsenocholine bromide. However, the yield was only 52% and the reported melting point 10°C too high.[7] Arsenocholine bromide was also obtained by hydrolysis of trimethyl-2-bromoethylarsonium bromide with water at 180°C.[8]

Arsenocholine chloride and bromide are very hygroscopic and must be stored under anhydrous conditions. In search of nonhygroscopic and halide-free derivatives, anion exchange reactions were carried out. These reactions were driven by the insolubility of silver bromide, by the solubility difference between sodium iodide and sodium bromide in acetonitrile, and by the insolubility of arsenocholine tetraphenylborate (Scheme 2).

Arsenocholine iodide and tetraphenylborate were found to be nonhygroscopic, whereas the nitrate and carbonate easily absorbed water from the air. Upon evaporation of the solution containing the arsenocholine carbonate, a yellowish-brown solid was obtained. The ^1H NMR spectrum of this solid indicated that some decomposition had occurred. Arsenocholine hydroxide, prepared previously from arsenocholine chloride[6] and from trimethylarsine and ethylene oxide,[9] reacts strongly alkaline in aqueous solution. When solutions in water or water/acetone were evaporated, arsenocholine hydroxide decomposed leaving a black semi-solid residue. However, solutions of arsenocholine hydroxide can be used to prepare other arsenocholine salts (Scheme 3). Addition of an equivalent amount of 4-methylbenzenesulfonic acid and evaporation of the resulting solution produced the nonhygroscopic arsenocholine tosylate. Passing a stream of carbon dioxide through a freshly prepared aqueous solution of arsenocholine hydroxide formed the water-soluble arsenocholine hydrogen carbonate. Concentration of the resulting solution at room temperature led to partial decomposition of the compound. When the bottle in which the brownish arsenocholine hydrogen carbonate had been



Scheme 2



Scheme 3

$$[(CH_3)_3As\text{—}CH_2CH_2OH]^+Br^- \xrightarrow[\text{(ii) HBr}\ \text{(iii) BaCO}_3]{\text{(i) H}_3\text{PO}_4} [(CH_3)_3As\text{—}CH_2CH_2OPO_3Ba]^+Br^- \cdot 2H_2O$$

Scheme 4

stored was opened, the distinct odor of trimethylarsine was detected. The same results were obtained when a solution of arsenocholine carbonate was saturated with carbon dioxide.

Trimethylarsonio-2-ethyl phosphate is a potential starting material for the preparation of arsenic-containing phospholipids. When arsenocholine bromide and concentrated phosphoric acid were heated at 165°C/0.2 Torr for 20 h, the reagents condensed. The trimethylarsonio-2-ethyl phosphate was isolated as its barium salt. The yield was never higher than 20% (Scheme 4).

The mother liquor had proton resonances that indicated the presence of arsenocholine moieties with an esterified hydroxyl group. Several ^{31}P resonances were present. The products of the reaction between arsenocholine and phosphoric acid that did not crystallize were probably polyphosphates.

When an aqueous solution of the barium salt was mixed with the amount of sulfuric acid required to precipitate all barium as barium sulfate, a solution of trimethyl-2-(dihydrogen phosphato)ethylarsonium bromide was obtained. Evaporation of the solvent, and drying of the oily residue under reduced pressure, caused the oil to crystallize partially. Elemental analyses and NMR data agreed with the expected composition of the product.

Preparation of arsenocholine derivatives with functional groups other than hydroxyl

Arsenocholine derivatives, in which functional groups other than the hydroxy group are bonded to the 2-ethyl carbon atom, were prepared by heating trimethylarsine with the pertinent bromoethyl compounds (Eqn [2]). The yields of purified products were in the vicinity of 50%. Care must be taken in controlling the temperature of the reaction mixture in the preparation of trimethyl-2,2-diethoxyethylarsonium bromide. To prevent decomposition the temperature must not exceed 60°C.

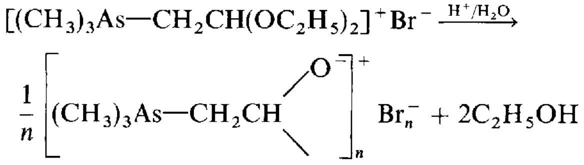
Anion exchange reactions were used to prepare trimethyl-2-acetoxyethylarsonium iodide and picrate from the bromide. Trimethyl-2-acetoxyethylarsonium chloride was previously prepared by acetylation of arsenocholine chloride with acetyl chloride/acetic anhydride,[10] and the corresponding bromide from arsenocholine and isopropenyl acetate.[7]

$$(CH_3)_3As + X\text{—}CH_2\text{—}Br \xrightarrow{\text{heat}} [(CH_3)_3As\text{—}CH_2\text{—}X]^+Br$$

$$X = CH_2Cl,\ CH_2Br, CH_2OC(O)CH_3, CH(OC_2H_5)_2 \qquad [2]$$

Hydrolysis of trimethyl-2,2-diethoxyethylarsonium bromide

An aqueous solution of trimethyl-2,2-diethoxyethylarsonium bromide was treated with a drop of concentrated hydrochloric acid. After two weeks at room temperature the reaction mixture was evaporated to dryness. The oily residue was dissolved in D_2O. The proton-decoupled ^{13}C spectrum consisted of three peaks at 9.2, 34.4 and 87.5 ppm, unequivocally assignable on the basis of the ^1H coupled ^{13}C spectrum to methyl, methylene and methine carbons. Signals for the ethyl groups present in the starting material at 16.1 (CH_3) and 65.3 ppm (CH_2) were not present in the spectrum of the hydrolysis product. In contrast to the methine-carbon signal, which shifted from 100.2 ppm in the parent compound to 87.5 ppm in the hydrolysis product, the methyl shift (10.1 to 9.2) and methylene shift (31.9 to 34.4) changed only a few ppm. The methine-carbon resonance in the hydrolysis product at 87.5 ppm is not sufficiently far downfield to represent an aldehyde-carbon. The carbonyl-carbon in a monomeric aldehyde resonates in the range 195 to 205 ppm.[11] However, the observed shift falls into the range 90 to 100 observed for acetals.[11-13] The hydrolysis of trimethyl-2,2-diethoxyethylarsonium bromide produces, therefore, a polymeric trimethyl-2-oxoethylarsonium bromide (Eqn [3]). Whether this aldehyde is



$$[(CH_3)_3As{-}CH_2CH(OC_2H_5)_2]^+Br^- \xrightarrow{H^+/H_2O} \frac{1}{n}\left[(CH_3)_3As{-}CH_2CH\langle O \rangle\right]^+_n Br_n^- + 2C_2H_5OH$$

[3]

trimeric cannot be decided on the basis of the experimental data available at this time.

Comparison of ^{1}H and ^{13}C resonances of arsenocholine and choline

The proton NMR spectra of arsenocholine and its derivatives in D_2O solution are characterized by a methyl singlet in the range 2.15 to 2.53 ppm, a well-separated triplet with a coupling constant of 6 Hz in the range 3.13 to 3.38 ppm for the methylene group bonded to the arsenic, and a signal in the range 3.98 to 5.52 ppm for the methylene group in the β-position to the arsenic atom. The signals for the arsenocholine tetraphenylborate that were recorded with a DMSO-d solution are all upfield of the stated ranges (Table 1).

The signal generated by the CH_2—O protons in trimethyl-2-hydroxyethylarsonium salts are broad without much structure in neutral D_2O and in D_2O/DCl solutions. Only in strongly alkaline NaOD/D_2O solutions is the triplet observed (Fig. 1). Arsenocholine derivatives, in which the proton of the hydroxyl group is replaced by an acetyl or phosphate group or the hydroxyl group by chlorine or bromine, have methylene resonances that show the expected multiplicities. The shape of this methylene resonance is a good indicator whether or not reactions affecting the hydroxyl group in arsenocholine have occurred.

The protons on the methyl and methylene groups bonded to nitrogen in choline, acetylcholine, and phosphorylcholine resonate 0.3 to 1.2 ppm downfield from the signals generated by the corresponding protons in the arsenic analogs. However, the CH_2—O resonances of the nitrogen compounds are 0.5 ppm upfield from those of the arsenic compounds (Table 2). These shift dif-

Table 1 Proton and ^{13}C NMR shifts[a] for arsenocholine and arsenocholine derivatives, $[(CH_3)_3AsCH_2R]^+X^-$, in D_2O solution with external TMS as standard

R	X	^{1}H			^{13}C		
		CH_3As(s)	CH_2As(t)[b]	CH_2/CH	CH_3As	CH_2As	CH_2 or CH[i]
CH_2OH	Cl	2.44	3.13	4.47(b)	—	—	—
	Br	2.46	3.21	4.54(b)	8.3[h]	29.1[h]	56.4 (145)
	I	2.44	3.19	4.51(b)			
	OH	2.42	3.15	4.49(b)			
	NO_3	2.39	3.20	4.42(b)			
	HCO_3	2.44	3.19	4.53(b)			
	$CO_3/2$	2.44	3.19	4.53(b)			
	CH_3COO	2.49	3.13	4.47(b)			
	Tosylate[c]	2.27	3.00	4.36(b)	8.4	30.9	56.2
	$(C_6H_5)_4B$[d]	1.76	2.00	3.74(b)			
CH_2Cl	Br	2.15	3.15	4.21(t)			
CH_2Br	Br	2.18	3.28	3.98(t)			
$CH_2OC(O)CH_3$	Br[e]	2.50	3.32	5.00(t)	9.3	25.9	60.5
	I[e]	2.53	3.38	5.06(t)			
	picrate	—	—	—	7.7[h]	24.5[h]	58.6 (152)
$CH(OC_2H_5)_2$	Br[f]	2.44	3.32(d)	5.52(t)	10.1[h]	31.9	100.2 (165)
CH_2OPO_3Ba[k]	Br	2.45	3.30	4.85[g]	8.6	28.0[j]	59.1[j]
$CH_2OPO_3H_2$[l]	Br	2.45	3.30	4.85[g]	10.2	28.7[j]	63.2[j]

[a] s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. [b] $J_{HCCH} = 6$ Hz unless otherwise stated. [c] Tosylate = 4—$CH_3C_6H_4SO_3$; anion signals 2.78(s), 7.74(m), 8.13(m). [d] In DMSO-d_6 relative to internal TMS; anion signals 6.82(m), 7.14(m). [e] CH_3CO at 2.65 (Br) and 2.72 (I) (s). [f] CH_3CH_2O signals 4.23(m), 1.71(t); J_{H_2CCH} 4.6 Hz. [g] Doublet of triplets due to H–^{31}P coupling. [h] $^1J_{CH} = 138$ Hz. [i] J_{CH} given in parentheses. [j] Doublet due to C–P coupling. [k] P-31 resonance at −6.8 ppm relative to H_3PO_4. [l] P-31 resonance at +1.4 ppm.

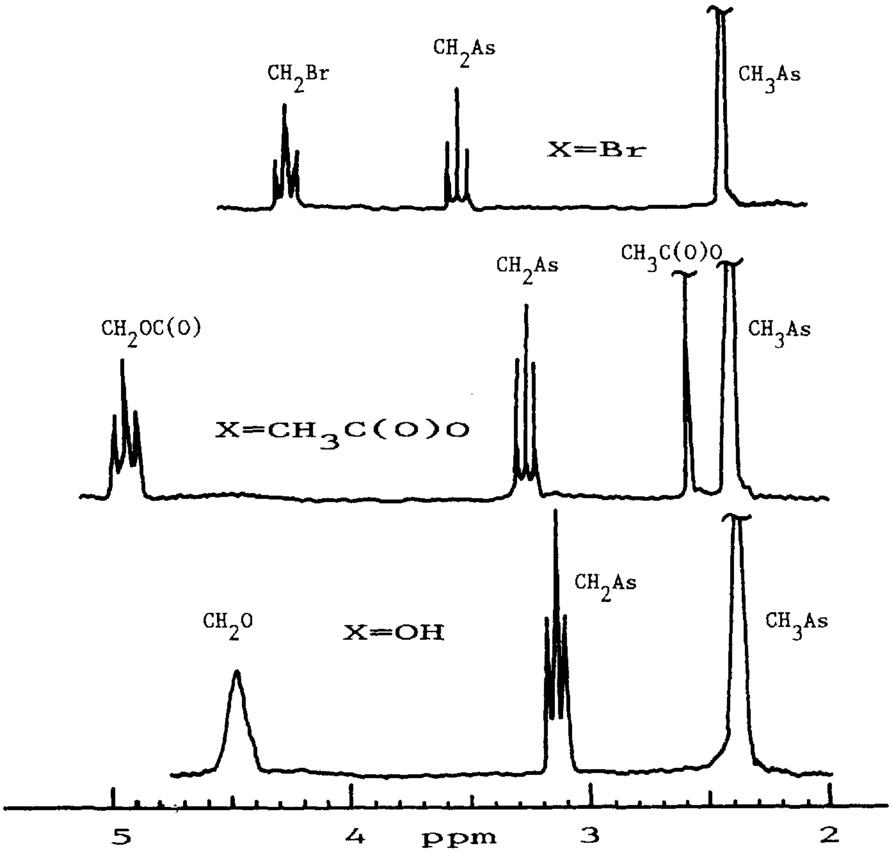


Figure 1 The proton NMR spectra of trimethyl-2-X-ethylarsonium bromides, $[(CH_3)_3AsCH_2CH_2X]^+Br^-$, in D_2O solution.

Table 2 Proton and ^{13}C NMR shifts for arsenocholine, acetylarsenocholine, trimethyl-2-(dihydrogen phosphato)ethylarsonium bromide and the corresponding nitrogen compounds

X		Chemical shift (ppm) (TMS ext) for $[(CH_3)_3ECH_2CH{-}X]Br$					
		CH_3		$CH_2{-}E$		$CH_2{-}X$	
		As	N	As	N	As	N
OH	^1H	2.46	3.61[a]	3.13	3.99[a]	4.47	4.05[a]
	^{13}C	8.3	54.9[a]	29.1	68.3[a]	56.4	66.5[a]
$CH_3C(CO)$	^1H	2.50	3.23[b]	3.32	3.74[b]	5.00	4.55[b]
	^{13}C	9.3		25.9		60.5	
OPO_3H_2	^1H	2.45	3.21[a,c]	3.30	3.65[a]	4.85	4.30[a]
	^{13}C	8.6[d]	55.2[a,c]	28.0	67.2[a]	59.1	60.3[a]

[a] Ref. 14. [b] Ref. 15. [c] As the *sn*-clycero-3-phosphorylcholine. [d] As the dihydrate of the barium salt.

ferences are sufficient to identify unequivocally these compounds in their mixtures.

The ^{13}C resonances of arsenocholine, acetylarsenocholine, and phosphorylated arsenocholine were located in the range 8.3 to 8.6 ppm for the methyl groups, 28 to 31 ppm for the methylene group bonded to arsenic, and 56.2 to 60.5 ppm for the methylene group bonded to oxygen (Table 1). In the analogous nitrogen compounds the CH_3—N and CH_2—N protons, influenced by the high electronegativity of the nitrogen atom, resonate approximately 40 ppm downfield from the signals generated by the arsenic compounds (Table 2). These differences in chemical shifts can be used to distinguish between choline and arsenocholine.

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