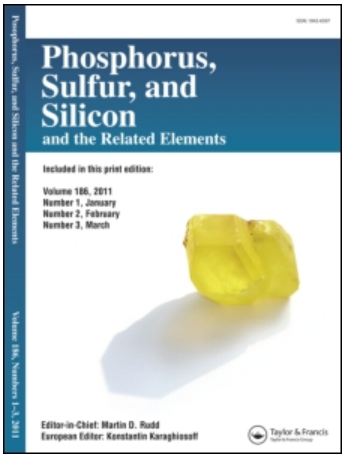

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1,2-DIHYDROXYPROPYL-3-ARSONIC ACID: A KEY INTERMEDIATE FOR ARSONOLIPIDS

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1,2-DIHYDROXYPROPYL-3-ARSONIC ACID: A KEY INTERMEDIATE FOR ARSONOLIPIDS

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The synthesis and properties of a key intermediate for arsonolipids, *rac*-1,2-dihydroxypropyl-3-arsonic acid and its salts, are described. The mechanism of the Meyer reaction with β-hydroxy alkyl halides is discussed.

Key words: Arsonic acids; the Meyer reaction; salts of arsonic acids; arsonolipids.

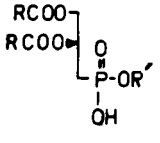
INTRODUCTION

Arsenic containing lipids have been isolated from certain marine organisms.[1] They all contain C—As(V) bond because compounds with the grouping C—O—As(V) are hydrolytically unstable.[2]

Phosphonolipids (**1**) are known to exist in nature[3] and many of them, have been synthesized in order to verify their structure and to determine their biochemical and biophysical properties.[4,5]

Arsonolipids* (**2**) have not yet been detected in nature nor have they been synthesized. They are expected to have interesting properties because As can be interconverted, As(V) ⇌ As(III), easily, a property not exhibited by P(V) compounds, such as phospholipids or phosphonolipids.

Two of the key intermediates for the synthesis of arsonolipids are the *rac*-1,2-dihydroxypropyl-3-arsonic acid, *rac*-$DPAH_2$, (**3**) and its optically active analogue (**4**). Herein we report on the synthesis and the properties of the free acid **3** and its salts.



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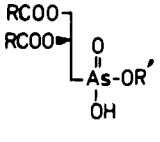

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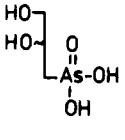

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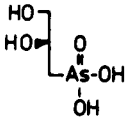

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RESULTS AND DISCUSSION

We found that ethylene oxide is formed during the synthesis of 2-hydroxyethylarsonic acid[6,7] from 2-chloroethanol and sodium arsenite (the Meyer reaction) which

*We propose the term arsonolipids to be restricted, by analogy with phosphonolipids, to compounds having the structure (**2**) and to their analogues.

we used as a model for the synthesis of **3**. The yield of the Meyer reaction with β-hydroxy alkyl halides were found to depend on the following factors.

The reaction temperature should be less than the boiling point of the epoxide, and best results were obtained in the narrow range of 10–20°C for 2-chloroethanol (but see References 6 and 7) and 15–45°C for 3-chloro-1,2-propanediol. Lower temperatures (<10°C) decreased the yield of **3**.

The nucleophile in the Meyer reaction is the anion AsO_3^{3-},[8] which functions at high pH values and concentrated solutions of sodium hydroxide.[9] Under our experimental conditions the consumption of As(III) was ~80% 10 min after the addition of the alkyl halide and **3** was isolated in acceptable yields (40–45%) contaminated with 0.8–1.5% As_2O_3, 3–4% ethanol (by ^{1}H-NMR) and traces of glycerol (overspotted TLC).

The product **3** keeps tenaciously ethanol; its removal at higher temperatures was not attempted because arsonic acids easily dehydrate to anhydrides.[2,10,11] The product **3** is stable in alkaline environment, but a 0.33 M solution in 6 M hydrochloric acid after 24 h at 70°C revealed 2.0% decomposition to As(III). Neat **3** gave 6.2% decomposition to As(III) after 3 days at 120°C.

The IR spectra of alkyl arsonic acids have been discussed.[2,10,12] The IR spectra (KBr pellets) of 2-hydroxyethylarsonic acid and of **3** are qualitatively similar, all bands being broad. The very strong band at 3600–3200 cm^{-1}, centered at 3400 cm^{-1}, is due to hydrogen bonded C—OH groups and is indicative of inter- and intramolecular polymeric association. The band at 2800–2400 cm^{-1}, due to stretching vibration of As—OH group in alkylarsonic acids,[12] is absent in the spectrum of **3**, while the deformation vibration of the As—OH group, which occurs at 2345 cm^{-1} in simple alkylarsonic acids,[12] is split into two broad, medium bands at 2370 and 2280 cm^{-1} indicative of complex hydrogen bonding of the As—OH group. The combination vibrations of the AsO_2H group, which in simple alkylarsonic acids occur at 1690 cm^{-1},[2,12] is found at 1620 cm^{-1} in the case of **3** which again indicates that the AsO_2H group is involved in strong hydrogen bonding. The stretching vibration of the hydrogen bonded As=O group (As=O · · · H—O—As) is found at 940 cm^{-1},[12] while for **3** is found at 900 cm^{-1} with a shoulder at 880 cm^{-1} probably as a result of inter- and intramolecular[13] hydrogen bonding. Finally, the symmetric and asymmetric stretching of the As—O group is found at 760 cm^{-1}, some 20 cm^{-1} lower than in simple alkylarsonic acids.[12] In summary, the solid state structure of **3** is polymeric and complex, involving inter- and intramolecular hydrogen bonds between the C—OH, As—OH and As=O groups, which explains its relatively high melting point and solubility behaviour.

The preparation of salts of **3** with inorganic cations was uneventful. However with cyclohexylamine and dicyclohexylamine only the mono salts were obtained due to the slow volatilization of the second equivalent of the amine. The same results have been obtained by precipitating the salts of various other arsonic acids with organic amines.[13,14] With triethylamine and tributylamine the mono salt continued losing the amine on drying.

The hygroscopicity of the salts varied, the most hygroscopic being those of potassium. In general, the neutral salts were less hygroscopic than the mono salts. The salts were soluble in H_2O (except DPABa · $2H_2O$ and DPACd · $2H_2O$), slightly

TABLE

Analytical, physical and infra red data of *rac*-1,2-dihydroxypropyl-3-arsonic acid and

Compound	M.p.,°C *	% As		Hygroscopic	IR absorptions of th	
		Calcd	Found		δ(As-OH)	combination band of AsO_2H
$DPAH_2$	202	37.5	37.5	yes	2370 m, 2280 m	1620 m
$DPAHLi.H_2O$	235	33.5	32.4	yes	2350 w	1660 m
$DPALi_2.2H_2O$	240	30.3	29.8	no	-	1650 mw, 1580 mw
$DPAHNa.2H_2O$	215	29.1	29.3	yes	2350 w	1660 mw
$DPANa_2.2H_2O$	193	26.8	26.1	yes	2220 w≠	1660 m
$DPAHK.2H_2O$	199	27.4	26.3	very	2400 w	1660 m
$DPAK_2.4H_2O$	200	21.6	21.3	extremely	2270 w≠	1650 m,1620 sh
$DPAHMg_{\frac{1}{2}}.2H_2O$	255	30.4	31.3	no	2400 w	1650 m
$DPAMg.4H_2O$	260	25.5	25.6	no	2400 w	1640 sh,1595 m
$DPAHBa_{\frac{1}{2}}.2H_2O$	235	24.7	25.8	very	2350 w	1640 m
$DPABa.2H_2O$	200	20.2	20.1	no	-	1660 m, 1580 sh
$DPAHCd_{\frac{1}{2}}.2H_2O$	215	25.8	26.8	no	2350 w	1640 m
$DPACd.2H_2O$	250	21.7	21.8	no	-	1640 sh,1590 m
$DPAHC_6H_{11}NH_3.C_2H_5OH$	148	21.7	22.8	very	2350 w	1680 m
$DPAH(C_6H_{11})_2NH_2$	180	19.7	18.9	yes	2350 w	1680 m

* All compounds decomposed at the melting point

+ s = strong, m = medium, mw = medium weak, sh = shoulder, w = weak

≠ the absorption is due to water of crystallization (ref.15)

to moderately soluble in methanol and in dimethylsulfoxide, and insoluble in non polar solvents such as ether and dichloromethane.

The solid state (KBr pellets) IR spectra of the mono and neutral salts show the expected shifts. Thus, the very strong and broad band at 3600–3200 cm^{-1} perists in the salts. The bands at 2370 and 2280 cm^{-1} are obscured by the broad and weak band due to the water of crystallization which is found[15] at 2300 ± 100 cm^{-1} and are hardly visible in the amine salts. The combination band of **3** at 1620 cm^{-1} is moved 20–60 cm^{-1} to higher frequencies for the mono salts indicating relaxation of the hydrogen bonding. This band in neutral salts of **3** shows a complex behaviour probably reflecting variations in the coordination of the cations; it is a doublet for the lithium salt, singlet for the sodium salt, and singlet with shoulder for the other salts (see Table). Neutral salts of simple alkylarsonic acids showed only a single peak at 1680 cm^{-1}.[15] The 900 cm^{-1} band in the mono salts is moved to 880–860 cm^{-1} due to the $—As(OH)O_2^-$ group, while in the neutral salts is moved further lower (see Table) as a result of the formation of the $—As(O)O_2^{2-}$ group. The band at 760 cm^{-1} is moved to 750–730 cm^{-1} and is of lower intensity for the mono salts which is probably due to the grouping $—As(OH)O_2^- \cdots H—O—As—$. This band is absent in the neutral salts indicative of complete deprotonation of the $—AsO(OH)_2$ group.

EXPERIMENTAL

The reagents were purified according to the literature.[16] The techniques used were the same as previously described.[17] The As in the organoarsenic compounds was determined after wet digestion with conc. sulfuric acid and hydrogen peroxide.[18]

rac-1,2-Dihydroxypropyl-3-arsonic acid (**3**). To a stirred solution of arsenic trioxide (1.9800 g; 10 mmol) in 13.3 M NaOH (6 ml; 80 mmol) was added dropwise (1 drop/min) 3-chloro-1,2-propanediol (2.25 g; 20.4 mmol). The heterogeneous pale yellow-green system was then stirred at room temperature for an additional one hour. Titration revealed ~80% consumption of As(III) and TLC (CH_3OH/conc. NH_3 4:1 v/v) showed the ammonium salt of $DPAH_2$ (R_f 0.14), glycerol (R_f 0.70) and no 3-chloro-1,2-propanediol (R_f 0.74). The pH was adusted to 6.5–7.0 with conc. hydrochloric acid and evaporated (Rotary, ≤40°C) to give a semi-solid mass which was dried in vacuo for 1 h and extracted with boiling absolute ethanol (4 × 10 ml). The residue was dissolved in warm water (12 ml), cooled to room temperature, the pH was adjusted with conc. hydrochloric acid to 1.8–2.0, evaporated (Rotary, ≤40°C) and dried in vacuo over phosphorus pentoxide overnight. The white solid (~7.5 g) was extracted with boiling absolute ethanol (4 × 20 ml). The extracts were combined by pouring them in cold (10°C), stirred absolute ethanol (10 ml) so as the precipitate, which was formed at once, did not adhere on the walls of the flask. After cooling at −20°C for 3 h the precipitate was filtered, washed with absolute ethanol/acetone (1:3 v/v, 2 × 5 ml) and acetone (3 × 7 ml), and dried in vacuo over phosphorus pentoxide overnight to give the product (**3**) (1.8170 g, 45%) as white amorphous solid, pure by TLC (CH_3OH/conc. NH_3 4:1 v/v, R_f = 0.26) but containing ~1% arsenic trioxide and 3–4% ethanol.

The combined filtrate and washings, after evaporation, gave more product (~1 g) contaminated with glycerol and ~10% arsenic trioxide, which can be purified to ~2% arsenic trioxide and traces of glycerol by recrystallization from absolute ethanol (~60% recovery).

The product (**3**) was soluble in water, formic acid, and dimethylsulfoxide, moderately soluble in methanol, 95% ethanol, slightly soluble in acetic acid, dimethylformamide, ethyl acetate and pyridine and insoluble in acetone, acetonitrile and acetic anhydride. Absolute ethanol (100 ml) dissolved 0.55 g, at 25°C, and 5.0 g of **3**, at boiling.

200 MHz ^{1}H-NMR (D_2O): δ 2.64 (m, $\underline{CH_2}As$), 3.50 (m, $\underline{CH_2}OH$), 4.10 (m, $\underline{CH}OH$); 50 MHz ^{13}C – NMR (D_2O) δ: 40.35 ($\underline{C}H_2As$), 67.63 ($\underline{C}H_2OH$), 68.53 ($\underline{C}HOH$).

Preparation of salts of $DPAH_2$. General Procedure. To a solution of $DPAH_2$ (**3**) (1 mmol) in warm absolute ethanol, the desired equivalent amount (1 or 2 mmol) of the salt (lithium acetate dihydrate, magnesium acetate tetrahydrate, cadmium acetate dihydrate) or base (sodium hydroxide, potassium

hydroxide, cyclohexylamine and dicyclohexylamine) dissolved in absolute ethanol or in water (in the case of barium hydroxide octahydrate) was added and, after stirring at room temperature for 15 min., the solvent was evaporated and the residue dried in vacuo over phosphorus pentoxide till constant weight.

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REFERENCES

1. W. R. Cullen and K. J. Reimer, *Chem. Rev.*, **89,** 713 (1989).
2. G. O. Doak and L. D. Freedman, "*Organometallic Compounds of Arsenic, Antimony, and Bismuth*", (Wiley, New York, 1970), Chap. 2, pp. 17–62.
3. J. S. Kittredge and E. Roberts, *Science*, **164,** 37 (1969).
4. R. Engel, *Chem. Rev.*, **77,** 349 (1977).
5. E. Baer and H. Basu, *Can. J. Biochem.*, **47,** 955 (1969).
6. a) C. A. McAuliffe, K. Minten and D. G. Watson, *Inorg. Chim. Acta*, **39,** 249 (1980); b) D. G. Watson, Ph.D. Thesis, University of Manchester Institute of Science and Technology, (1973).
7. R. H. Edee, *J. Am. Chem. Soc.*, **50**, 1394 (1928).
8. G. V. Chelintsev and V. K. Kuskov, *J. Gen. Chem. (U.S.S.R.)*, **16,** 1481 (1946); *Chem. Abs.*, **41,** 5441a (1947).
9. T. M. Loehr and R. A. Plane, *Inorg. Chem.*, **7,** 1708 (1968).
10. C. F. McBrearty Jr., K. Irgolic and R. A. Zingaro, *J. Organometal. Chem.*, **12**, 377 (1968).
11. M. R. Smith, K. J. Irgolic and R. A. Zingaro, *Thermochim. Acta*, **4,** 1 (1972).
12. U. Dietze, *J. lorakt. Chem.*, **313,** 889 (1971).
13. V. S. Gamayurova, M.A. Krylova, F. G. Khalitov and R. R. Shagidullin, *J. Gen. Chem. (U.S.S.R.)*, **51**, 726 (1981).
14. A. S. Selivanova, Zh. V. Molodykh, V. S. Gamayurova, B. D. Chernokal'skii and S. V. Il'ina, *Proc. Acad. Sci. (U.S.S.R.)*, **218,** 433 (1974).
15. A. von Simon and H.-D. Schumann, *Z. anorg. allg. Chem.*, **393,** 23 (1972).
16. D. D. Perrin, W. L. F. Armarego and D. R. Perrin, "*Purification of Laboratory Chemicals,*" (Pergamon Press, Oxford, 1980) 2nd ed.
17. G. M. Tsivgoulis, D. N. Sotiropoulos and P. V. Ioannou, *Phosphorus, Sulfur and Silicon*, **00,** 000 (1990).
18. W. W. Scott and N. H. Furman "*Standard Methods of Chemical Analysis*" (van Nostrand, London, 1939) 5th ed., p. 67, 115.