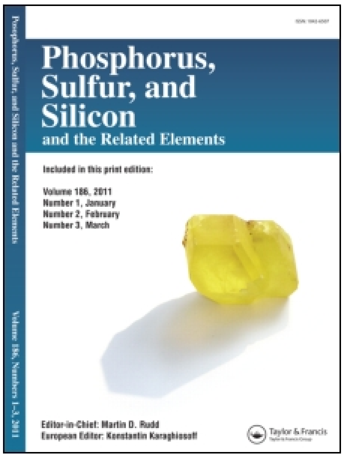

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ONE POT SYNTHESIS OF ARSONOLIPIDS *VIA* THIOARSENITE PRECURSORS

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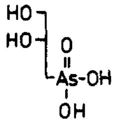
Reduction of the racemic and optically active 1,2-dihydroxypropyl-3-arsonic acids by thiophenol gives the chloroform soluble phenyl esters of rac-, (*R*)-, and (*S*)-1,2-dihydroxypropyl thioarsonous acids which are acylated by fatty acid chlorides/pyridine to give the racemic and optically active arsonolipids (1,2-diacyloxypropyl-3-arsonic acids). The yields of long chain arsonolipids are significantly higher than those reported from the acylation of salts of 1,2-dihydroxypropyl-3-arsonic acid. The yield of short chain arsonolipids are lower, partly because of difficulties in removing traces of coprecipitated fatty acids. The esters of alkylthioarsonous acids are decomposed by carboxylic acids and on silica gel and a mechanism for their acylation is proposed. The melting points of arsonolipids [(*R*) = (*S*) > *rac*] increase smoothly with the fatty chain length while the enthalpies of fussion [(*R*) > (*S*) > *rac*] show a maximum at 1,2-dimyristoyloxypropyl-3-arsonic acid. The thermal behaviour of the aqueous dispersions of short chain arsonolipids, suggests that their head groups are not easily hydrated because of strong intermolecular hydrogen bonding of the head groups.

Key words: Optically active arsonic acids; optically active esters of alkylthioarsonous acids; acylation; decomposition; optically active arsonolipids; thermotropic phase transitions; conglomerates.

INTRODUCTION

We have recently synthesized a novel class of compounds, racemic[1] and optically active[2] long chain arsonolipids **4** by acylating the hygroscopic salts, DPAH(Bu_4N) and DPA(Bu_4N)$_2$, of 1,2-dihydroxypropyl-3-arsonic acid,[3,4] DPAH$_2$, **1**, with fatty acid anhydrides. The yields, although better than those reported for the corresponding phosphotidic acids,[5] were low (20–42%). This was partly due to the C—As bond fission by acylating agents.[6]

A synthetic alternative could involve the acylation of an As(III) instead of an As(V) compound. From the possible candidates, the dihaloarsines **2a** would require isolation[7,8] and oxidative hydrolysis (under neutral[7] or alkaline[9,10a] conditions) of the product **3a** to give the arsonolipids **1** but such treatment could also hydrolyse the acid- and base-labile ester bonds. Amides of alkylarsonous acid are difficult to prepare from dihaloarsines[10b] and deprotection of the hydroxyl group protected **2b** could also hydrolyse the As—N bond[10c,11] thus rendering the preparation of **2b** problematic. Thioarsenites (esters of alkylthioarsonous acids) are easily and quantitatively prepared under very mild conditions from arsonic acids[12–14] and revert



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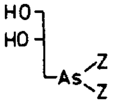

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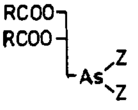

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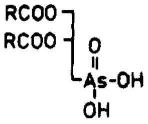
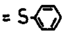
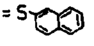


4

a $Z = Cl, I$

b $Z = NMe_2$

c $Z =$ 

d $Z =$ 

back to arsonic acids also under mild conditions.[12,13,15] However, they possess a reactive As—S bond, the rupture of which requires somewhat severe conditions[16] not likely to be encountered in acylations.

Herein we report that by using the thioarsenites **2c** or **2d** the yields of long chain arsonolipids can be doubled compared to published yields.[1,2] We also report the synthesis and thermotropic properties, as dry powders and in aqueous dispersions, of racemic and enantiomeric short chain arsonolipids, **4**, namely *rac*-, (*R*)- and (*S*)-1,2-didodecanoyloxy-, 1,2-didecanoyloxy-, and 1,2-dioctanoyloxypropyl-3-arsonic acids *via* their corresponding thioarsenites **2c** and **3c**.

RESULTS AND DISCUSSION

Racemic and enantiomeric $DPAH_2$, **1**, prepared from racemic and optically active glycidols,[2] were purified from water to ~4% As_2O_3. Ethanol-water crystallization solvent gave **1** with ~7% As_2O_3 impurity.[2] Arsenic trioxide did not react with a solution of palmitoyl chloride/pyridine in dry chloroform for 8 days at room temperature. Therefore, further purification of **1** using an ion-exchange resin[4] was not necessary.

Thiophenol and β-naphthalenethiol reacted with **1** giving quantitatively the phenyl and β-naphthyl esters of 1,2-dihydroxypropylthioarsenous acids **2c** and **2d** as gums. The mechanism of the reaction has been discussed.[14] Their IR spectra showed mainly the aromatic ring vibrations. The products, **2c** and **2d** on TLC gave one spot when run in various non-acidic solvents but in chloroform/acetic acid 10:1 v/v they partially decomposed giving 3 or 4 additional slower running spots. Since thioarsenites are stated[13] to be hydrolytically stable in an acidic environment, it seems that silica gel catalyses their decomposition to arsonous acid (or arsenoso compound) and either PhSH[13] or AcSPh.[16] Because these by-products have $R_f \simeq 1.0$, the decomposition route could not be established. Glycerol (R_f 0.05), arising from C—As bond fission, could not be positively identified while oxidation of the As(III) species[14] to **1** (R_f 0.00) probably did not take place during the TLC run in $CHCl_3/AcOH$ 10:1 v/v.

Thioarsenites react with alkyl halides, acyl halides and acid anhydrides.[16] We found that *rac*-**2c** reacts slowly (43 days stirring at room temperature) in chloroform with decanoic and benzoic acids but the products could not be positively identified.

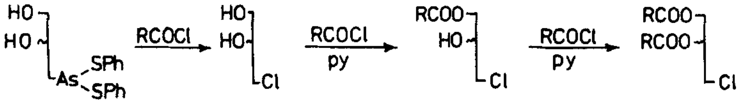
Because the disulfide, Ar—SS—Ar, which is formed during the reduction of **1** by thiols, does not interfere with the acylation that follows we do not remove it, so the synthesis can be called "one pot synthesis."

Acylations of 1 mmol *rac*-**2c** with 4 mmol palmitic anhydride in the presence of 2 mmol pyridine in refluxing dry chloroform for 4–14 days gave at best 31% of isolated arsonolipid, **4**. Best yields of **4** (60–65%) were obtained when 1 mmol *rac*-**2c** was acylated by 3 mmol palmitoyl chloride and 2 mmol pyridine in dry chloroform for 6–9 days at room temperature. The progress of the acylation was followed up by TLC in chloroform/acetic acid 10:1 v/v which at $1.00 \geq R_f \geq 0.80$ concentrates PhSSPh, RCOCl, RCOSPh and RCOOH and at $0.15 > R_f > 0.00$ a hydrolysis product of the lyso-thioarsenite runs. At R_f 0.40 a hydrolysis product of **3c** or **3d** (due to catalytic effect of silica gel) run and at R_f 0.34 and 0.42 two by-products appeared.

Oxidation of thioarsenite **3c** and probably of **3** (Z = Cl, SPh) to arsonolipid **4** can be effected by iodine or hydrogen peroxide in moist solvents, e.g. ether, chloroform/methanol or chloroform/ethanol, but best results were obtained with ether/water/hydrogen peroxide. Long chain arsonolipids, e.g. **4**, $R = C_{15}H_{31}$, precipitated out and they were obtained pure after one recrystallization from absolute ethanol; yield 60–65%.

The two by-products (R_f 0.34 and 0.42) did not react when the ether phase was again treated with excess of hydrogen peroxide for 24 h. When pooled ether phases from various experiments were chromatographed on silica gel column the two by-products could not be isolated in pure form. All fractions eluted with $CHCl_3$/CH_3OH 20:1 v/v contained arsenic (by wet digestion[17]). The fractions with R_f 0.42 (30 mg) were contaminated by palmitic acid and PhSSPh, melted at 147–150°C and had 14.5% As. The spectra did not allow positive identification and TLC ($CHCl_3$/MeOH 20:1 v/v) showed a spot at R_f 0.40 which was neither 1,3-diglyceride (R_f 0.85) nor 1,2-diglyceride (R_f 0.73) nor monoglyceride (R_f 0.32). The fractions with R_f 0.34 (66 mg) were also contaminated by palmitic acid and PhSSPh, melted at 66–70°C and had 3.6% As. The spectra indicated that it probably was a monoglyceride, which was confirmed by TLC.

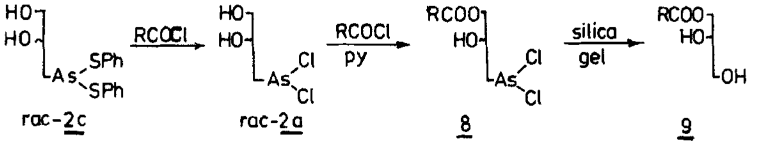
We hypothesize that the by-product with R_f 0.42 is **6** which arises via Equation (i):



rac-**2c** **5** **6** **7**

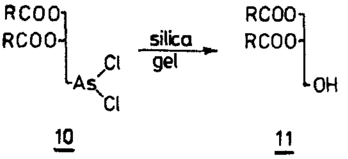
(i)

Compound **7** cannot be differentiated on the TLCs ($CHCl_3$/AcOH 10:1 v/v and $CHCl_3$/MeOH 20:1 v/v). It was observed that **6** was formed during the initial 10–20 min after the immediate addition of the palmitoyl chloride at room temperature. When the addition was carried out slowly and at 0°C only traces of it were seen on the TLC. The by-product with R_f 0.34 (monoglyceride, **9**) probably arises from the dichloroarsine **8** which is formed during the acylation[16] of **2c**, survives the hydrolysis/oxidation step[10a] but decomposes[10d] on silica gel giving the monoglyceride, Equation (ii):



(ii)

and an As(III) compound which is converted to As_2O_3. Arsenic trioxide can be eluted from silica gel [spotting H_3AsO_3 in water, development with $CHCl_3/CH_3OH$ 20:1 v/v, visualization with I_2 gives a white spot R_f 0.05, while with 5:1 v/v trails with R_f 0.2]. Diglyceride, **11**, probably arising *via* Equation (iii) could not be positively identified on the TLC.



(iii)

The acylation of **2c** with short chain acyl chlorides under the optimum conditions established for palmitoyl chloride gave the arsonolipids **4** in lower than 65% yields partially because more recrystallizations from acetone were needed to free **4** from traces of fatty acids. The (*S*)-**4** crystallized from acetone faster and purer while two of the (*R*)-**4** tenaciously kept their free fatty acids (by IR). However, recrystallization from absolute ethanol gave pure (*R*)-**4** in good yields (Table I). Column chromatography of the supernatants gave good material balance, thus indirectly indicating that greater losses due to decompositions *via* Equations (i–iii) incurred during the acylations with short chain acyl chlorides.

The new, short chain, arsonolipids **4** are white amorphous powders and their IR (KBr pellets) and 60 MHz ^1H-NMR ($CDCl_3$) spectra are similar to their higher homologues.[1]

The method of preparation of arsonolipids *via* the thioarsenites is better than that using the $DPAH_2$ salts and fatty acid anhydrides.[1,2] Although in both methods the isolation of long chain arsonolipids, being insoluble in ether, possess no problems, the isolation of short chain arsonolipids, especially the (*R*)-isomers, would be problematic in the presence of large amounts of fatty acid and its salts produced in the acylations with fatty acid anhydrides.

The melting points of *rac* and (*R*)-didodecanoyl arsonolipids are ~40°C higher than the corresponding phosphatidic acids[18] implying stronger intermolecular hydrogen bonding of the head groups in arsonolipids. The melting points of arsonolipids are considerably lower (20–90°C) than the di-*n*-alkylarsinic[19,20] or *n*-alkylarsonic[11] acids with the same number of carbon atoms per chain implying weaker intermolecular bonding in arsonolipids. Since the melting points of *n*-alkylarsonic acids are higher than the corresponding di-*n*-alkylarsinic acids[11] it seems that replacement of an —OH by an alkyl chain on the As seriously disrupts the hydrogen bonding system of the As(O)OH group. The fact that the melting points of arsonolipids increase smoothly with the chain length (Figure 1) while those of *n*-alkylarsonic and di-*n*-alkylarsinic acids decrease[11] can be explained by

TABLE I

Physical constants and elemental analyses of esters of 1,2-dihydroxypropylthioarsonous acids and 1,2-diacyloxypropyl-3-arsonic acids

			Thermal analysis					Elemental analyses							
								C		H		As			
Compound	Yield %	Capillary m.p., °C	m.p., °C	ΔH, kcal/mol	Optical purity, %	$[a]_D^{25}$	Molecular formula	Calcd	Found	Calcd	Found	Calcd	Found	T_m,[f] °C	ΔH, kcal/mol
rac-**2d**[a]	93	—	—	—	—	—	$C_{23}H_{21}O_2S_2As$	—	—	—	—	15.99	15.63	—	—
rac-**2c**[b]	89	—	—	—	—	—	$C_{15}H_{17}O_2S_2As$	—	—	—	—	20.34	20.06	—	—
(*R*)-**2c**[c]	86	—	—	—	—	−67.7[e]	$C_{15}H_{17}O_2S_2As$	—	—	—	—	20.34	19.94	—	—
(*S*)-**2c**[d]	89	—	—	—	—	+66.7[f]	$C_{15}H_{17}O_2S_2As$	—	—	—	—	20.34	20.04	—	—
rac-**4**, *R* = C_7H_{15}	34	66–68	64.7	6.45	—	—	$C_{19}H_{37}O_7As$	50.44	50.20	8.24	8.07	—	—	54.5	—
(*R*)-**4**, *R* = C_7H_{15}	17	73–75	74.5	11.50	>95	+2.0[g]	$C_{19}H_{37}O_7As$	50.44	50.90	8.24	8.05	—	—	56.0	7.5
(*S*)-**4**, *R* = C_7H_{15}	21	73–75	73.5	9.00	>95	−2.0[g]	$C_{19}H_{37}O_7As$	50.44	50.31	8.24	8.39	—	—	58.5	7.6
rac-**4**, *R* = C_9H_{19}	51	76–78	75.0	10.20	—	—	$C_{23}H_{45}O_7As$	54.32	54.50	8.92	8.92	—	—	72.3	12.7
(*R*)-**4**, *R* = C_9H_{19}	35	84–85	85.1	16.30	>95	+2.0[g]	$C_{23}H_{45}O_7As$	54.32	54.30	8.92	9.06	—	—	72.6	11.6
(*S*)-**4**, *R* = C_9H_{19}	44	83–85	85.3	13.00	>95	−2.0[g]	$C_{23}H_{45}O_7As$	54.32	54.28	8.92	8.90	—	—	74.5	14.5
rac-**4**, *R* = $C_{11}H_{23}$	51	84–86	83.1	14.00	—	—	$C_{27}H_{53}O_7As$	57.43	56.76	9.46	9.48	—	—	72.8	13.0
(*R*)-**4**, *R* = $C_{11}H_{23}$	44	90–92	91.7	18.40	>95	+2.0[g]	$C_{27}H_{53}O_7As$	57.43	56.91	9.46	9.39	13.27	13.22	79.2	8.0
(*S*)-**4**, *R* = $C_{11}H_{23}$	48	91–92	90.1	15.70	>95	−2.0[g]	$C_{27}H_{53}O_7As$	57.43	56.97	9.46	9.61	—	—	78.5	13.8

[a]contains 1.8% As_2O_3; [b]contains 2.0% As_2O_3; [c]contains 5.2% As_2O_3; [d]contains 4.1% As_2O_3; [e](c, 1.98; $CHCl_3$/MeOH 7:2 v/v); [f](c, 2.37; $CHCl_3$/MeOH 7:2 v/v); [g](c, 2.0; $CHCl_3$/MeOH 7:2 v/v).

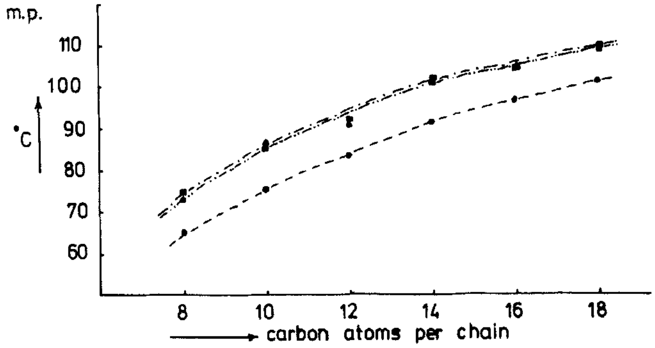


FIGURE 1 Melting points of dry racemic (- - -), (*R*) (–·–) and (*S*) (–··–) arsonolipids as a function of carbon atoms per chain.

assuming constant hydrogen bonding strength and increased van der Waals interactions of the fatty acyl chains in arsonolipids while in the arsonic and arsinic acids the increased van der Waals interactions do not offset the diminution of the strength of the hydrogen bonding.

The melting points of the (*R*) and (*S*) arsonolipids with the same acyl groups are identical but they are ~10°C higher than the melting points of the corresponding racemic arsonolipids. The same phenomenon was observed with the longer fatty acyl chains, arsonolipids[2] (Figure 1). Summarizing the available data, the melting points vary as in the series: phosphatidic acids < phophotidic acids < arsonolipids, **4** < di-*n*-alkylarsinic acids < *n*-alkylarsonic acids.

The dry arsonolipids did not show an endothermic transition prior to melting as most di-*n*-alkylarsinic acids do,[20] due to reorientation of the chains.[21] The dry short chain arsonolipids showed significant hystereses on re-run. We did not get the same profile even after several days. The reason for this behaviour is not as yet known.

The enthalpies of fusion of the dry arsonolipids (Figure 2), are, in general, greater than the enthalpies of fusion and the total enthalpies (transition plus fusion) of di-*n*-alkylarsinic acids with the same number of carbon atoms per chain.[20] The very small enthalpies of fusion of the short chain dry arsonolipids compared to the long chain arsonolipids may be due to different polymorphic forms, i.e. different crystalline forms.

The enthalpies of fusion of the dry arsonolipids are of the order *rac* < (*S*) < (*R*) (Figure 2). The stereoconfiguration seems to have little effect on the enthalpies for the short chain arsonolipids, but becomes important for the dimyristoyl one. It seems that in the optically active dimyristoyl arsonolipid there are very strong intermolecular interactions due to favorable packing of the chains and head group, which drastically diminish in the racemic one.

The racemic short chain arsonolipids, *rac*-**4**, form racemic mixtures (conglomerates) by mixed melting point determinations, and since in the samples of (*R*)- and (*S*)-**4** we did not detect any endotherm due to their respective conglomerates we conclude that they are >95% optically pure.

The short chain arsonolipids were not easily dispersed in buffer solutions of pH = 8.00. The dispersions were studied by D.S.C. The peaks were broad and in the

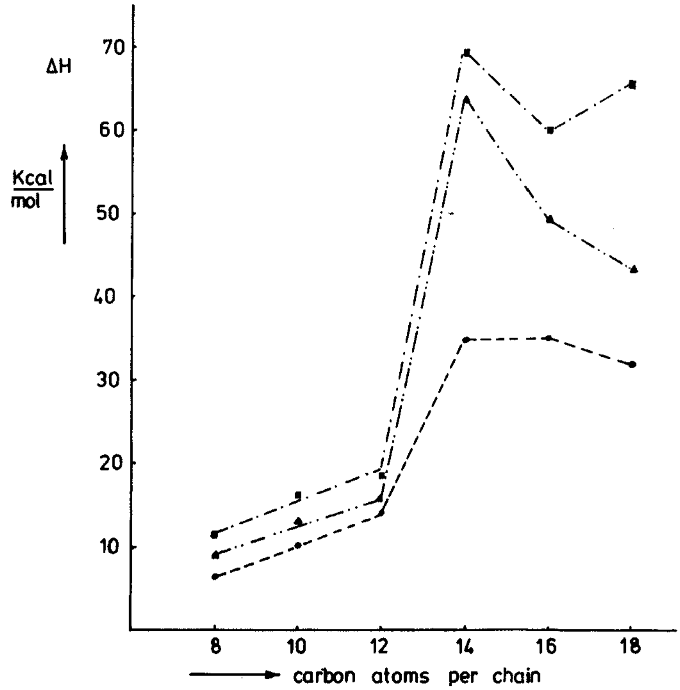


FIGURE 2 Enthalpies of fusion of dry racemic (– – –), (*R*) (–·–) and (*S*) (–··–) arsonolipids as a function of carbon atoms per chain.

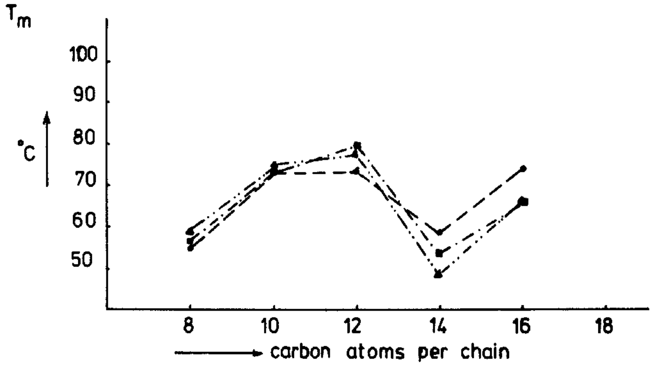


FIGURE 3 Endothermic phase transition temperatures, T_m, of racemic (– – –), (*R*) (–·–) and (*S*) (–··–) arsonolipid dispersions at pH 8.00, as a function of carbon atoms per chain.

case of *rac*-1,2-dioctanoyloxypropyl-3-arsonic acid was very broad. There were also significant hystereses on repeated runs and the results which we report were taken from the first run. From these profiles the endothermic phase transition, T_m, and the enthalpy of the transition, ΔH, were obtained[2,22] (see Table I).

The T_m and ΔH values for the short chain arsonolipids are higher than expected from the extrapolation of the values for the longer chain-arsonolipids (Figures 3 and 4), and they are quite close to the melting points and enthalpies of fusion of

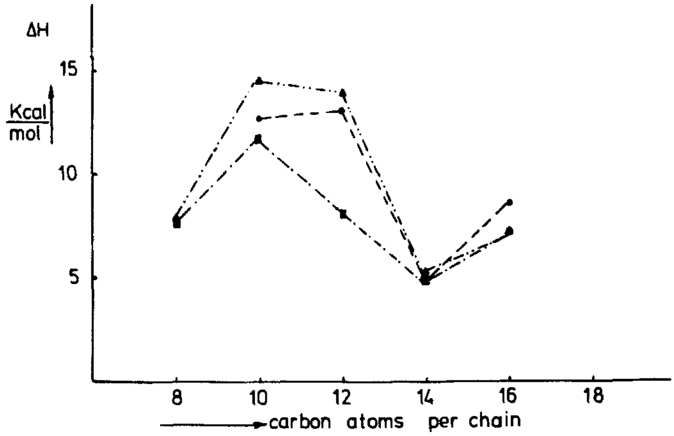


FIGURE 4 Enthalpies of the gel-to-fluid phase transitions of racemic (---), (*R*) (-·-) and (*S*) (-··-) arsonolipid dispersions at pH 8.00, as a function of carbon atoms per chain.

the *dry* samples (Table I and Figures 1–4). It seems therefore that the aqueous behaviour of arsonolipids fall into two groups. The long chain arsonolipids (C_{14}, C_{16} and C_{18}) behave as normal swelling amphipathic molecules giving a liquid crystalline phase (probably lamellar) at temperatures well below the melting point of the dry samples. The short chain arsonolipids (C_8, C_{10} and C_{12}) probably behave as soluble amphipathic molecules which at high concentrations give indefinitely long cylindrical aggregates.[23] This difference may be due to the strong intermolecular hydrogen bonding of the head groups giving rise to unusually high Krafft point (the temperature at which there is a simultaneous dissociation of the ionic lattice by the penetration of water molecules and melting of the hydrocarbon chain region). Disruption of the intermolecular hydrogen bonding may be effected by increasing the pH whereby the equilibrium $—AsO_3H_2 \rightleftharpoons —AsO_3H^-$ is shifted to the right. Indeed at pH 9.00 the short chain arsonolipids give dispersions that look like multilamellar vesicles. The ester bond may not be stable if sonicated at higher pH.

EXPERIMENTAL

Racemic, (*R*)- and (*S*)-1,2-dihydroxypropyl-3-arsonic acids, DPAH$_2$, **1**, contaminated with 10–15% As_2O_3 were prepared[2] from racemic, (*R*)-, and (*S*)-glycidol respectively and purified as described below. Octanoyl chloride (b.p. 66° C/2 mm Hg), decanoyl chloride (b.p. 72°C/1 mm Hg) and dodecanoyl chloride (b.p. 100°C/2 mm Hg) were prepared from the corresponding fatty acids (dodecanoic, Serva, 98% purity; decanoic, Sigma, 99%; octanoic acid, Merck, 96%) and redistilled thionyl chloride. Palmitoyl chloride, palmitic anhydride, ethanol-free chloroform and dry pyridine were as described.[1,2] TLCs were run on microslides coated with silica gel type 60H (Merck); visualization was effected by spraying with 35% H_2SO_4 and charring. Silica gel Si 60 (Serva) was used for column chromatography. The IR, ^{1}H-NMR, polarimeter and differential scanning calorimeter instruments used were as described.[2,6] Carbon and hydrogen elemental analyses were done by the Centre National de la Recherche Scientifique, Vernaison, France while the arsenic in the organoarsenic compounds was determined after wet digestion with conc. sulfuric acid and hydrogen peroxide.[17] The As_2O_3 present in *rac*, (*R*)- and (*S*)-**1c** and *rac*-**1d** was substracted in calculating the %As in these compounds.

Purification of crude rac-, (R)- *or* (S)-*DPAH$_2$*, **1**. Crude *rac*-DPAH$_2$ (2.68 g containing 0.40 g As_2O_3) obtained from the Meyer reaction of 13.2 mmol *rac*-glycidol, was dissolved in 3 ml water at room temperature and cooled at -20°C for 2 days. Centrifugation and washing the solid with 3 ml cold water gave an aqueous solution of *rac*-DPAH$_2$. Evaporation and drying over phosphorus pentoxide gave 2.188 g of product contaminated with 3.9% As_2O_3 and traces of glycerol. The recovery was 92% and the overall yield of *rac*-DPAH$_2$ was 80%.

Phenyl ester of rac-, (R)- *or* (S)-*1,2-dihydroxypropylthioarsonous acid*, **2c**. 0.1303 g containing 0.63 mmol *rac*-DPAH$_2$ and 0.02 mmol As_2O_3 (i.e. 3.3% by weight) as impurity, was dissolved in 15 ml absolute ethanol by warming to 70°C and 0.26 ml (2.52 mmol) thiophenol was added. The clear colorless solution was stirred at RT for 1 h. TLC ($CHCl_3$/MeOH 20:1 v/v) revealed that the reaction was over in ~10 min. Evaporation of solvent and drying in vacuo over P_2O_5 gave 0.371 g white solid which was extracted (3 × 4 ml) with pentane. The pentane phase upon evaporation afforded quantitatively the impure diphenyldisulfide (m.p. 58–9°C; lit[24] 61–2°C). The product remained in the flask as a gum (0.211 g, 91%). TLC: $CHCl_3/CH_3OH$ 20:1 v/v R_f 0.48; $CHCl_3/CH_3COOH$ 10:1 v/v R_f 0.68, 0.32, 0.12, 0.07 and 0.00. The product was insoluble in pentane and soluble in chloroform and absolute ethanol. IR (film, main bands): 3400 broad, s, 1576 m, 1470 s, 1435 s, 1058 s, 1017 s, 988 s, 953 s, 729 vs, 682 s. ^{1}H-NMR ($CDCl_3$): δ 2.4 (m, $\underline{CH_2}As$), 3.6 (m, $\underline{CH_2}OH$), 4.2 (m, $\underline{CH}OH$), 7.5 (m, $C_6\underline{H_5}$).

From (*R*)-DPAH$_2$ and (*S*)-DPAH$_2$ the corresponding phenyl esters of (*R*)-, and (*S*)-1,2-dihydroxypropylthioarsonous acids, (*R*)-**2c** and (*S*)-**2c**, were prepared. Data are shown in Table I.

β-Naphthyl ester of rac-*1,2-dihydroxypropylthioarsonous acid*, **2d**. 46 mg containing 0.22 mmol *rac*-DPAH$_2$ and 0.01 mmol As_2O_3 (i.e. 4% As_2O_3) was dissolved by warming in 8 ml absolute ethanol and 141 mg (0.88 mmol) β-naphthalenethiol was added. After 3 h stirring at room temperature the precipitated β,β'-dinaphthyl disulfide was removed by centrifugation. Evaporation of the ethanol and drying in vacuo afforded the product (97 mg, 95%) as a gum. TLC: $CHCl_3/CH_3OH$ 20:1 v/v R_f 0.50; $CHCl_3/CH_3COOH$ 10:1 v/v R_f 0.57, 0.19, 0.03 and 0.00. The product was soluble in chloroform and absolute ethanol. IR (KBr, main bands): 3400 broad, s, 1058 broad, s, 817 vs, 741 vs. ^{1}H-NMR ($CDCl_3$): δ 2.6 (m, $\underline{CH_2}As$), 3.7 (m, $\underline{CH_2}OH$), 4.3 (m, $\underline{CH}OH$), 7.7 (m, $C_{10}\underline{H_7}$).

Preparation of ether soluble arsonolipids: rac-, (R)- *and* (S)-**4** (R = C_7H_{15}) *and* rac- *and* (R)-**4** (R = C_9H_{19}). 0.1525 g containing 0.73 mmol *rac*-DPAH$_2$ and 0.03 mmol As_2O_3 was dissolved in warm (70°C) absolute ethanol and 0.30 ml (2.93 mmol) thiophenol was added. After stirring for 1 h at room temperature the solvent was removed (rotary, 30°C) and the solid was dried in vacuo over phosphorus pentoxide for 3 days. The solid (0.453 g, 104%) was dissolved in 8 ml dry chloroform, 0.12 ml (1.46 mmol) pyridine was added and the solution cooled to 0°C (ice-water-sodium chloride). Octanoyl chloride (0.38 ml; 2.2 mmol) in 4 ml dry chloroform was added dropwise (2 h), the solution was stirred at 0°C for further 2 h, and then at room temperature (in the dark) for 8 days. The reaction was followed by TLC (see Results and Discussion). The chloroform was evaporated and to the residue were added ether (6 ml), water (4 ml), and 40% hydrogen peroxide (0.21 ml; 2.35 mmol). After 2 h stirring at room temperature the ether phase was evaporated. The residue was dissolved in warm acetone (3 ml), transferred to a centrifuge tube, and cooled at -20°C for 3 days. Centrifugation without delay and drying in vacuo afforded contaminated product (63%, m.p. 56°C). The acetone supernatant was kept for chromatography. The impure product was dissolved in warm acetone (2 ml) and cooled at -20°C overnight. Centrifugation washing with cold acetone (1 ml), and drying afforded the pure, by TLC and IR, product *rac*-**4** ($R = C_7H_{15}$) (113 mg, 34%) as a white amorphous solid.

The acetone phases were concentrated, applied onto a silica gel (50 g in $CHCl_3$) column and eluted with $CHCl_3$ (50 ml), $CHCl_3/CH_3OH$ 20:1 v/v (250 ml), $CHCl_3/CH_3OH$ 1:1 v/v 40 ml, and CH_3OH (50 ml). The pooled fractions were: R_f 0.80–1.00 (in $CHCl_3$/AcOH 10:1 v/v) (470 mg), R_f 0.45 (4 mg), R_f 0.32 (15 mg) and R_f 0.10 (27 mg; presumed to be lyso-arsonolipid).

The other ether soluble arsonolipids were similarly prepared and recrystallized as follows: (*R*)-**4** ($R = C_7H_{15}$); warm acetone to -20°C (3×), yield 17%; (*S*)-**4** ($R = C_7H_{15}$): warm acetone to -20°C (2×), yield 21%; *rac*-**4** ($R = C_9H_{19}$): warm acetone to +4°C (1×), yield 51%; (*R*)-**4** ($R = C_9H_{19}$): warm absolute ethanol to +4°C (1×), yield 35%.

Preparation of ether insoluble arsonolipids: rac-**4** (R = $C_{15}H_{31}$), rac-, (R)- *and* (S)-**4** (R = $C_{11}H_{23}$), (S)-**4** (R = C_9H_{19}). The preparation of thioarsenites, their acylations and their oxidations in ether-water system by 40% hydrogen peroxide were carried out as described above. Now, the precipitated arsonolids were separated by centrifugation, washed with ether (2 × 2 ml) and dried. Yields of slightly impure products were 35–70%. They were twice recrystallized from warm acetone [except the *rac*-**4** ($R = C_{15}H_{31}$) and (*R*)-**4** ($R = C_{11}H_{23}$) which were once recrystallized from absolute ethanol by leaving at room temperature overnight, centrifuging, washing with cold acetone and drying in vacuo]. Yields and data are shown in Table I. From the ether phase additional small amounts of short chain of arsonolipids can be obtained after evaporation of the ether and 2–3 recrystallizations from acetone.

Differential scanning calorimetric studies of short chain arsonolipids. A known amount (1–4 mg) of dry short chain arsonolipid or of a dispersion in 30 μl of 50 mM Tris buffer pH = 8.00 were scanned as described.[2] In both cases only the results of the first scan were considered because there was a significant hysteresis on repeated runs. The peaks were unusually broad (5–10°C) and consequently the enthalpy values have a percentage error of ±15%.

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