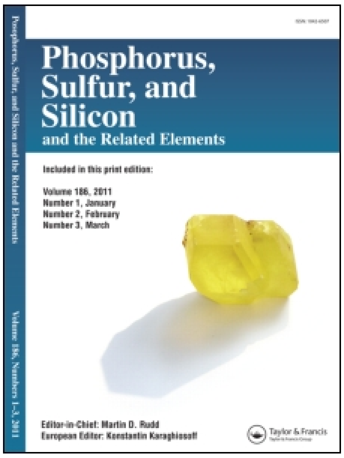

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SYNTHESIS OF ISOSTERIC ARSONOLIPIDS: *rac*-3,4-DIACYLOXYBUTYLARSONIC ACIDS

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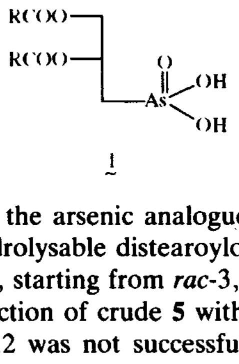
Acylation of diphenyl *rac*-3,4-dihydroxybutyldithioarsonite with acyl chlorides and oxidation by hydrogen peroxide gave in low yields (7–14%) a new class of isosteric arsonolipids, *rac*-3,4-diacyloxybutylarsonic acids. The low yields are partially due to carbon-arsenic bond cleavage.

Key words: Arsonic acids, esters of alkyldithioarsonous acid, acylation, isosteric arsonolipids.

We have synthesized[1–3] a novel class of lipids, **1**, called arsonolipids,[4] which are the arsenic analogues of phosphonolipids, **2**. The arsonolipids **1** although being non-isosteric[5] analogues of phospholipids **3** are substrates of phospholipase A_2 (J. Rogers *et al.*, manuscript in preparation).



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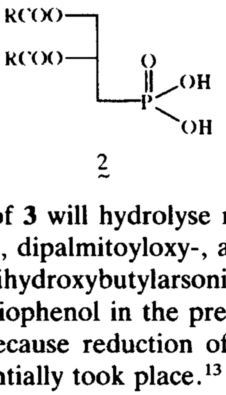

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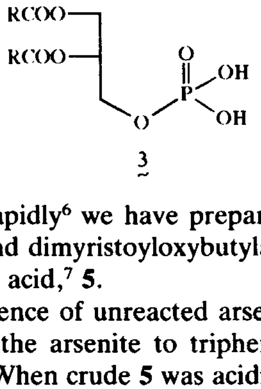

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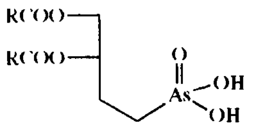
Since the arsenic analogues of **3** will hydrolyse rapidly[6] we have prepared the non-hydrolysable distearoyloxy-, dipalmitoyloxy-, and dimyristoyloxybutylarsonic acids, **4**, starting from *rac*-3,4-dihydroxybutylarsonic acid,[7] **5**.

Reduction of crude **5** with thiophenol in the presence of unreacted arsenite at pH 7–12 was not successful because reduction of the arsenite to triphenyl trithioarsonite, $(PhS)_3As$, preferentially took place.[13] When crude **5** was acidified to pH 0.5–1.0 (instead of pH 1.8) in order to completely remove the unreacted arsenite as As_2O_3 and then adding thiophenol we did not obtain any **6** but only $(PhS)_3As$. Presumably protonation of **6** facilitated C—As bond fission. An analogous C—As bond fission was observed by Zingaro's group[8] where phenylbis(benzenethio)arsine was isolated on reacting phenylcarboxymethylarsinic acid with thiophenol.



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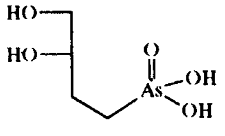

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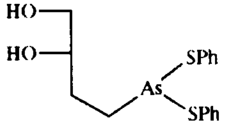

6

The reduction,[7] therefore of slightly impure **5** gives **6**, diphenyl disulfide and 5–10% $(PhS)_3As$. Since the disulfide is unreactive towards acyl chlorides[3] while the $(PhS)_3As$ reacts only slowly in the presence of pyridine (TLC analysis), we acylated **6** with excess acyl chloride in the presence of pyridine.[3] The acylations stopped after ca 6 days at room temperature.

Oxidation of the acylated **6** and of $(PhS)_3As$ gave the product, **4**, diphenyl disulfide and arsenate. The arsonolipids **4** could not be purified by fractional crystallizations as was done[3] with the arsonolipids **1** but they could be purified by column chromatography.

During the preparation of **4** 40–60% decomposition of C—As bond took place. Such decompositions, but to a lower degree, were observed previously when arsonic acids,[9] salts of arsonic acids[1,2] and diphenyl 2,3-dihydroxypropyldithioarsonite[3] were acylated. The mechanism of the decomposition has not been established; it may be analogous to that described[3] for the preparation of **1**. The yields of **4** were in the 10% range. The analogous phosphonolipids have been obtained in 50–65% yields.[10–11]

The new, long chain isosteric arsonolipids, **4**, ($R = C_{17}H_{35}$, $C_{15}H_{31}$ and $C_{13}H_{27}$) are white amorphous solids, soluble in $CHCl_3$, CCl_4 and petroleum ether. Their melting points are quite similar to those of homologous non-isosteric arsonolipids,[2] **1**, and higher than the homologous isosteric phosphonolipids.[10,11] The same phenomenon, i.e. higher melting points, was observed previously[2] comparing the melting points of arsonolipids **1** with the homologous phosphonolipids. It seems therefore that in arsonolipids, **1** and **4**, there are stronger intermolecular hydrogen bonding of the head groups, $—AsO(OH)_2$, compared to the $—PO(OH)_2$.

The 60 MHz ^1H-NMR spectra of **4** are not informative. Their IR (KBr pellets) spectra are qualitatively similar to the non-isosteric arsonolipids,[1] **1**, except that the band at 2250 and the shoulder at 2600 cm^{-1} were weaker. The stretching vibration of the hydrogen bonded As═O was found in the 870–912 cm^{-1} region while in simple arsonic acids was found[12] at 940 cm^{-1}, implying that in **4** there is stronger hydrogen bonding as a result of the side-by-side packing of the arsonolipid molecules.

EXPERIMENTAL

The *rac*-3,4-dihydroxybutylarsonic acid, **5**, and diphenyl *rac*-3,4-dihydroxybutyldithioarsonite, **6**, (containing diphenyl disulfide and triphenyl trithioarsonite) were prepared as described.[7] The techniques used were described previously.[3]

Preparation of arsonolipids **4** *($R = C_{17}H_{35}$, $C_{15}H_{31}$ and $C_{13}H_{27}$): General procedure.* 0.673 g of a mixture of 0.377 g (0.99 mmol) of *rac*-3,4-dihydroxybutyldithioarsonite, **6**, 0.215 g (0.99 mmol) of diphenyldisulfide and 0.081 g of triphenyl trithioarsonite were dissolved in 10 ml of dry chloroform and 0.16 ml (1.98 mmol) of pyridine was added. The solution was cooled at 0°C and a solution of 0.816 g (2.97 mmol) palmitoyl chloride in 5 ml of dry chloroform was added dropwise during 90 min. The solution was stirred at 0°C for 1 h and at 25°C for 8 days. TLC ($CHCl_3$/AcOH 10:1 v/v) showed that the spot at R_f 0.42 (argonolipid **4**) did not increase after 6 days. The chloroform was removed (rotary), the solid dissolved in 8 ml of ether and 8 ml of water, and treated with 0.20 ml of 50% hydrogen peroxide (2 mmol H_2O_2) for 90 min. Centrifugation gave an aqueous phase [which contained (by magnesia mixture precipitation) 0.78 mmol of arsenate], an ether phase and a semi-solid at the interface. The organics were evaporated, taken up in chloroform and applied onto a column of silica gel (90 g) in chloroform. Elution was done by chloroform (200 ml), chloroform/methanol 15:1 (200 ml), 5:1 (100 ml) and 1:1 (600 ml), collecting 50 ml fractions. The product (0.082 g) appeared in fractions 13–15 while in fractions 16–19 some product and, presumably, lysoarsonolipid (0.095 g) were eluted. Yield 12% of a white solid, m.p. 95–97°C. Calcd for $C_{36}H_{71}AsO_7$ 10.84 %As; found 10.70%. IR(KBr): 2916 vs, 2850 vs, 1732 s, 1472 m, 1176 m, 912 m.

Similarly prepared: *rac*-3,4-Distearoyloxybutylarsonic acid: Yield 14% of a white solid, m.p. 108–110°C. Calcd for $C_{40}H_{79}AsO_7$ 10.03% As; found 9.98%. IR (KBr): 2918 vs, 2850 vs, 1736 s, 1468 m, 1178 m, 897 w.

rac-3,4-Dimyristoyloxybutylarsonic acid: Yield 7% of a white solid, m.p. 83–5°C. Calcd for $C_{32}H_{63}AsO_7$ 11.80% As; found 11.73%. IR (KBr): 2924 vs, 2854 vs, 1740 s, 1466 m, 1170 m, 870 w.

ACKNOWLEDGEMENTS

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