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A SIMPLE SYNTHESIS OF PHOSPHONATE — CONTAINING LIPIDS. INTRODUCTION OF THE PHOSPHONIC ACID MOIETY INTO HYDROLYTICALLY-LABILE COMPOUNDS

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In recent years a good deal of effort has been devoted to the synthesis of phosphonic acid analogs of various phosphoric ester metabolites, including nucleoside monophosphates,[1] cyclic phosphates,[2] oligophosphates,[3] and carbohydrate metabolites.[4] Such analogs often show interesting biological properties.[5] In the lipid field the literature describing synthetic phosphonate-containing analogs of phospholipids is by now fairly extensive;[6] without exception, these syntheses utilize a classic Arbuzov or Becker reaction at a stage in which no hydrolytically labile group is present in the alkyl halide moiety in order to allow subsequent hydrolysis of the intermediate dialkyl alkylphosphonate under the vigorous conditions required. The long-chain ester groups are then introduced at a later step; e.g., by diacylation of 2,3-dihydroxypropylphosphonic acid.[7] In our experience, however, this type of reaction is erratic, often (depending on the nature of the acyl groups) giving impure products in low yields.

A possible means of avoiding this synthetic limitation is the selective removal of phosphonate ester groups in the presence of previously introduced carboxylic esters by means of trimethylsilylation;[8] however, in our experience this type of exchange reaction is rarely successful with lipids, although it often yields good results with short-chain compounds.

Another possible approach to the synthesis of labile phosphonic acids is the use of a phosphite triester which (a) forms a volatile halide byproduct that is itself poorly reactive to

the phosphite, and (b) produces a phosphonate ester which is convertible to the free acid when labile groups such as saturated or unsaturated carboxylic esters are present in the same molecule. Until recently this represented virtually an unsolved classical problem in organophosphorus chemistry. Tris(trimethylsilyl) phosphite, however, recently described by Orlov and co-workers,[9] offers a remarkably simple solution. Although these authors showed that this compound undergoes normal reaction with halides, its potential utility as an Arbuzov reagent appears to have been little exploited to the present time.

The reagent itself is very readily prepared by reaction of trimethylchlorosilane with phosphorous acid in the presence of sufficient excess triethylamine to tautomerize the intermediate bis(trimethylsilyl) phosphite.[9a] Tris(trimethylsilyl) phosphite appears to be of nucleophilic reactivity comparable to that of the trialkyl phosphites usually employed in the Arbuzov reaction, but the resulting bis(trimethylsilyl) phosphonate esters are, as is usual with silyl esters, hydrolyzed with extreme ease in the presence of other labile groups. Thus, the synthesis of the previously unknown lecithin analog $C_{17}H_{35}COOCH_2CH(OCOC_{17}H_{35})CH_2P(O)(O^-)(OCH_2CH_2\overset{+}{N}Me_3)$ is accomplished in good yield with unusual facility: DL-3-iododistearin[10] in a 7.5-fold excess of $(Me_3SiO)_3P$ at 120° under N_2 for 16 hr, followed by stirring of the acetonitrile-insoluble reaction products with aqueous tetrahydrofuran at 23° overnight, gave almost pure DL-2,3-distearoylpropylphosphonic acid, mp 73-76°, in 89% yield. Monoesterification by choline toluenesulfonate (salt) using CCl_3CN in pyridine and decolorization of the product by Amberlite MB-3[6e] gave the lecithin analog in 79% yield (from phosphonic acid), mp 204-206° (dec.), after reprecipitation from chloroform with hexane. The product was homogeneous on TLC and gave the expected IR bands (P⟶O, 1210 cm^{-1}, typical H-bonded pattern; P-O-C, 970 cm^{-1}).[11]

This successful synthetic route suggests the use of analogous syntheses of other classes of phosphonic acid analogs of labile phosphoric ester metabolites, which should similarly avoid the limitation that a hydrolytically-stable halide reactant must be used.[12]

References

1. (a) D.H. Rammler, L. Yengoyan, A.V. Paul, and P.C. Bax, Biochemistry, 6, 1828 (1967); (b) G.H. Jones and J.G. Moffatt, J. Am. Chem. Soc., 90, 5337 (1968); (c) H.P. Albrecht, G.H. Jones, and J.G. Moffatt, J. Am. Chem. Soc., 92, 5511 (1970).

2. G.H. Jones, H.P. Albrecht, N.P. Damodaran, and J.G. Moffatt, J. Am. Chem. Soc., 92, 5510 (1970).
3. (a) D.B. Trowbridge and G.L. Kenyon, J. Am. Chem. Soc., 92, 2181 (1970); (b) D.B. Trowbridge, D.M. Yamamoto, and G.L. Kenyon, J. Am. Chem. Soc., 94, 3816 (1972).
4. (a) H. Paulsen, J. Thiem, and M. Moner, Tetrahedron Letters, 1971, 2105; (b) E. Baer and R. Robinson, Can. J. Chem., 51, 104 (1973); (c) S.L. Goldstein, D. Braksmayer, B.E. Tropp, and R. Engel, J. Med. Chem., 17, 364 (1974); (d) H. B.F. Dixon and M.J. Sparkes, Biochem. J., 141, 715 (1974).
5. (a) E.D. Duee and P.V. Vignais, Biochem. Biophys. Res. Comm., 30, 546 (1968); (b) D.H. Rammler, A. Bagdasarian, and F. Morris, Biochemistry, 11, 9 (1972); (c) A. Hampton, F. Perini, and P.J. Harper, Biochemistry, 12, 1730 (1973); (d) P.J. Cheng, R. Hickey, R. Engel, and B.E. Tropp, Biochim. Biophys. Acta, 341, 85 (1974); (e) C.S. Shopsis, R. Engel, and B.E. Tropp, J. Bacteriol., 112, 408 (1972); (f) G.A. Orr and J.R. Knowles, Biochem. J., 141, 721 (1974).
6. (a) E. Baer and N.Z. Stanacev, J. Biol. Chem., 239, 3209 (1964); (b) A.F. Rosenthal and M. Pousada, Rec. Trav. Chim., 84, 833 (1965); (c) A.F. Rosenthal, G.M. Kosolapoff and R.P. Geyer, Rec. Trav. Chim., 83, 1273 (1964); (d) A.F. Rosenthal, J. Chem. Soc., 1965, 7345; (e) A.F. Rosenthal, J. Lipid Research, 7, 779 (1966); (f) E. Baer and N.Z. Stanacev, J. Biol. Chem., 240, 3754 (1965); (g) D.L. Turner, M.J. Silver, R.R. Holburn, E. Baczynski, and A.B. Brown, Lipids, 3, 234 (1968); (h) E. Baer and K.V.J. Rao, Can. J. Biochem., 48, 184 (1970); (i) P.P. M. Bonsen, G.J. Burbach-Westerhuis, G.H. deHaas, and L.L.M. vanDeenen, Chem. Phys. Lipids, 8, 199 (1972); (j) E. Baer and G.R. Sarma, Can. J. Biochem., 47, 609 (1969). For a more complete review and bibliography, see (k) A.J. Slotboom and P.P.M. Bonsen, Chem. Phys. Lipids, 5, 301 (1970). For biochemical effects of these analogs see, e.g., (l) A.F. Rosenthal and S.C.H. Han, Biochim. Biophys. Acta, 152, 96 (1968); (m) A.F. Rosenthal and M. Pousada, Biochim Biophys. Acta, 164, 226 (1968); (n) A.F. Rosenthal and S.C.H. Han, Biochim. Biophys. Acta, 218, 213 (1970).
7. E. Baer and H. Basu, Can. J. Biochem., 48, 1010 (1970).
8. R. Rabinowitz, J. Org. Chem., 28, 2975 (1963).

9. (a) N.F. Orlov, B.L. Kaufman, L. Sukhi, L.N. Slesar, and E.V. Sudakova, Khim. Prakt. Prim. Kremniiorg. Soldin., Tr. Sovesch., 111 (1966); Chem. Abstr., 72, 21738y (1970); (b) M.A. Belokrinitskii and N.F. Orlov, Kremniiorg. Mater., 1971, 145; Chem. Abstr., 78, 29929f (1973).

10. G.H. deHaas and L.L.M. vanDeenen, Rec. Trav. Chim., 80, 951 (1961).

11. TLC on silica gel G showed no low-polar impurities in hexane-ether-acetic acid 85:15:1, and a homogeneous spot (Rf 0.58) in $CHCl_3$-MeOH-H_2O, 65:25:4. Good analyses for C, H, N, and P were obtained for a hemihydrate structure. The nmr spectrum accorded with the expected structure, e.g., $Me_3\overset{+}{N}$ (singlet, 3.4 ppm). The CH_2-P could not be identified in the presence of the very large $-CH_2-$ centered at $1 \cdot \overline{30}$ ppm.

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