

A Synthetic Phosphinate-Phosphonate Liponucleotide Analogue

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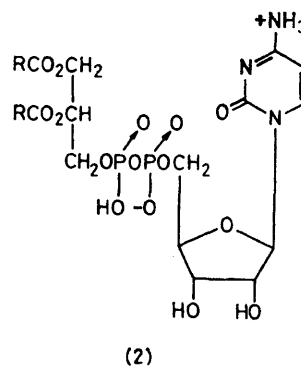
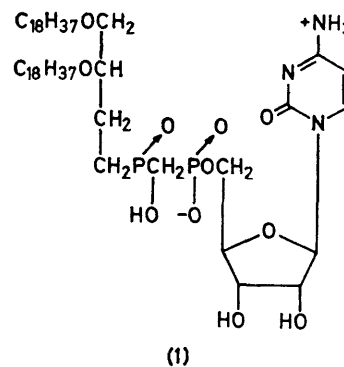
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Summary A nine-step synthesis of the nucleotide coenzyme analogue (1) is reported, providing the first example of a nucleotide coenzyme analogue containing three isosteric C-P bonds, and of a phosphinate-phosphonate nucleotide of any type.

We report herein the first synthesis of an isosteric analogue of a nucleoside diphosphate coenzyme containing three carbon-phosphorus bonds. The compound prepared, (1), is an analogue of cytidine diphosphate 1,2-diacyl-*sn*-glycerol (2). In addition to the replacement of three of the four -P-O-C(P) bonds by methylene linkages, the analogue also has long-chain ether moieties substituting the more common fatty acyl groups. Thus, the only points of hydrolytic lability remaining in (1) are the metabolically fairly resistant ribose-phosphorus ester and glycosidic bonds.

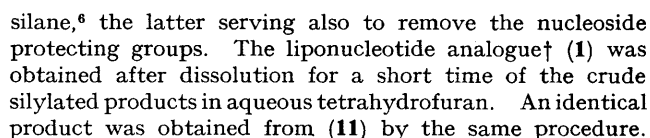
Liponucleotide coenzymes (2) are obligatory intermediates in the biosynthesis of several important phospholipids, such as phosphatidylserine, phosphatidylglycerol, and phosphatidylinositol. In these reactions the coenzyme serves as a phosphatidyl group donor for the appropriate alcohol. Thus, the absence of the central P-O-P group makes such reactions impossible for (1), making such analogues potential inhibitors of phospholipid biosynthesis.

Heating of phenyl bis(chloromethyl)phosphinate¹ with triphenylphosphine in xylene precipitated the monophosphonium salt† (3), from which the ylide (4) was readily prepared by treatment with aqueous potassium carbonate. Reaction of (4) with the diether aldehyde² (5) produced the chloromethylphosphinate† (6), which reacted



† These compounds gave correct analyses for C, H, P, and N and Cl if present.

Good results were finally achieved by treatment of **(10)** sequentially with caesium fluoride in methanol⁵ and then by brief reaction of the crude methyl ester with bromotrimethyl-



‡ Prepared from (6) and excess of tris(trimethylsilyl) phosphite,⁷ followed by hydrolysis, hydrogenation and condensation with the protected cytidine as above. Arbuzov reaction with the silyl phosphite is accompanied by loss of phenyl ester, as shown by the presence of aryl protons in the distillate of volatile material from the reaction.



The overall yield of (1) for the seven steps[¶] (isolated intermediates) from (5) was 9.6%, but fortunately most of the loss was in the first and third steps.

It is suggested that the methodology developed above is of potential value for the synthesis of C-P-containing nucleotide coenzyme analogues of diverse types.

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¶ Actual number of separate chemical transformations from (5) to (1) is ten.

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