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A Synthetic Phosphinate-Phosphonate Liponucleotide Analogue

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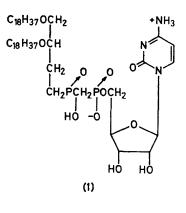
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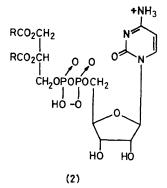
Summary A nine-step synthesis of the nucleotide coenzyme analogue (1) is reported, providing the first example of a nucleotide coenzyme analogue containing three isosteric C-P bonds, and of a phosphinate-phosphonate nucleotide of any type.

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

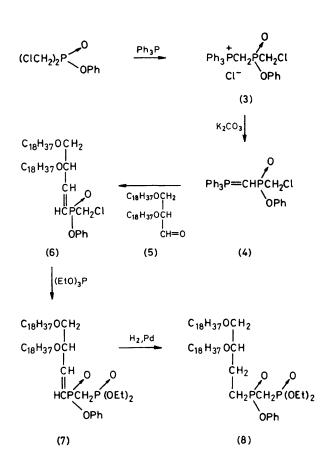


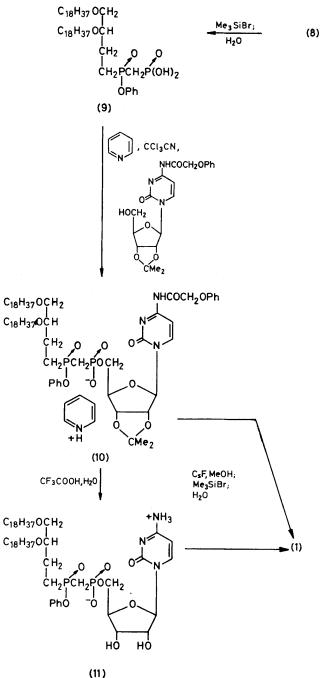


† These compounds gave correct analyses for C, H, P, and N and Cl if present.

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normally with triethyl phosphite to give the phosphinatephosphonate (7). Hydrogenation of (7) gave (8),† from which the ethyl groups could be removed by mild treatment with bromotrimethylsilane while leaving the phenyl ester intact. Alternatively (6) could be hydrogenated over palladium directly, but some loss of chlorine could not always be avoided in this process. Condensation of the phosphonic acid (9) with N⁴-phenoxyacetyl-2',3'-isopropylidenecytidine³ by use of trichloroacetonitrile in pyridine solution gave the protected liponucleotide (10).





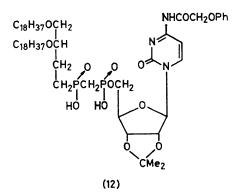
Complete deprotection of (10) proved unexpectedly difficult. Aqueous trifluoroacetic acid removed the phenoxyacetyl and isopropylidene protecting groups fairly readily to give $(11)^{\dagger}$, but removal of the phenyl ester could not be achieved by hydrogenation over palladium or iridium. Treatment of (10) with tetrabutylammonium fluoride⁴ led to extensive degradation of the molecule, as did similar treatment of (11). Moreover, the dephenylated derivative[†][‡] (12) suffered considerable degradation on treatment with trifluoroacetic acid as well.

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-

silane,⁶ the latter serving also to remove the nucleoside protecting groups. The liponucleotide analogue \dagger (1) was obtained after dissolution for a short time of the crude silylated products in aqueous tetrahydrofuran. An identical product was obtained from (11) by the same procedure.

[‡] 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.

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The purified (1) showed no aryl-H n.m.r. resonances. Its i.r. spectrum showed the expected absorptions at 1660 and 1710 (cytidine), § 1100 (ether), and 1270 and 1200 cm^{-1} (PO); $\lambda_{\rm max}$ 280 nm; (ϵ 3.6 \times 10³).

The overall yield of (1) for the seven steps \P (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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 $The absorption at 1700-1710 \text{ cm}^{-1}$ appears to be characteristic of the ionised amino-group of cytosine, since it is given by cytidine hydrochloride but not by cytidine.

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

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