uated at δ 3.0, H-3e. Although the proton H-3e is not observed, its coupling constants can be measured on the difference spectrum. From the apparent asymmetry of the H-3e doublet of doublets and from difference spectrum 2, it appears that H-3e is coupled either with the doublet at δ 3.3 or with the triplet at δ 3.5. This ambiguity is removed by monitoring the triplet giving a response within the assembly of peaks around δ 3.0, but at a frequency lower than that of H-3e (plot 7). H-3e is thus coupled with the doublet at δ 3.3 due to H-3a which is linked to the same carbon as shown by their large coupling constant (J = 16 Hz).

The last olefinic proton is coupled with a small coupling constant to the doublet at δ 1.9, which in turn gives difference responses at δ 1.6 and 2.5 (H-17a and H-18a). Finally, H-17e is coupled with H-18e, H-18a, and H-17a (plot 5). The results, in addition to the measure of coupling constants enable us to place the five protons on a unit such as $=CHCH_2CH_2$.

The four remaining protons, δ 3.5, 2.9 (two protons), and 2.6 can be attributed to the tryptamine moiety certainly present here. Coupling between them can be seen in plots 2, 6, and 7. Definitive assignments of protons on tryptamine carbons 5 and 6 could only be made after displacement of the triplet at δ 3.5 to higher frequencies by protonation of the nitrogen with trifluoroacetic acid.[6] As this proton is not coupled with the doublet of doublets at δ 2.6, it is one of the H-5 protons and the other one is one of the H-6.

Using the above-mentioned elements to reconstitute the "puzzle", we propose the pentacyclic structure **2** for andranginine. The X-ray crystal structure[7] has confirmed this hypothesis and has established the stereochemistry of the C, D, and E ring junctures as trans-trans.

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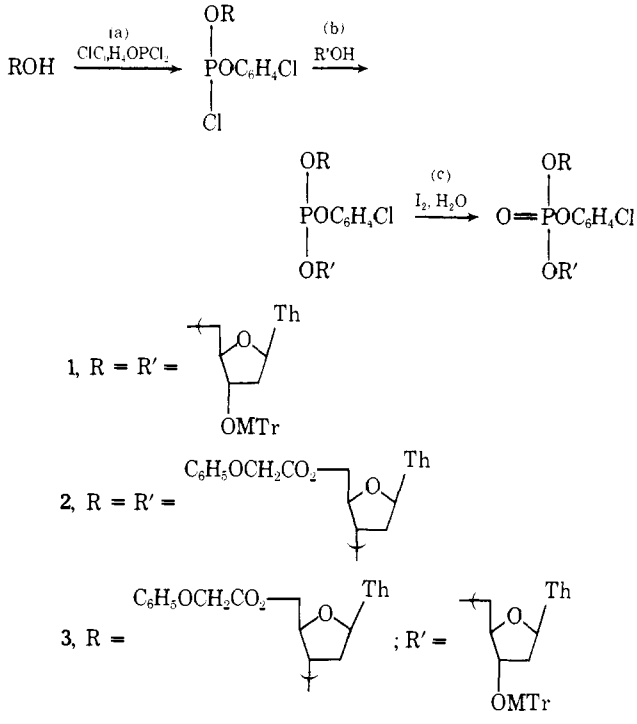
Phosphite Coupling Procedure for Generating Internucleotide Links[1]

Sir:

The phosphotriester procedure utilizing activation of a nucleoside phosphodiester and condensation of the active phosphoryl compound with a nucleoside has proven useful in synthesizing short oligonucleotide chains in quantity.[2] For routine synthesis of long polynucleotides, however, more efficient and rapid coupling methods are needed. Attempts to prepare phosphotriester derivatives of oligonucleotides by stepwise condensation of nucleosides with alkyl or aryl phosphorodichloridates [$(RO)P(O)Cl_2$] have been only partially successful;[2f-h] the reactions are slow and the yields are low.

We report in this communication a new procedure for generating nucleotide phosphotriesters that shows considerable promise in polynucleotide synthesis. The sequence is based on the remarkable reactivity of phosphorochloridites [$ROPCl_2$ and $ROP(OR')Cl$] toward alcohols in tetrahydrofuran at low temperatures and on the facile oxidation of phosphites to phosphates by iodine and water.[3]



A typical example is provided by the synthesis of the *o*-chlorophenyl ester of bis(mono-*p*-methoxytrityl)thymidylyl[5′-5′]thymidine (**1**). 3′-*O*-Mono-*p*-methoxytritylthymidine[4] was stirred at −78° with 0.55 equiv of *o*-chlorophenyl phosphorodichloridite[5] and 1.1 equiv of pyridine in tetrahydrofuran for 30 min. The mixture was warmed to ca. −10° in <1 min and treated with an equivalent of iodine in tetrahydrofuran–water (2:1). Oxidation proceeded about as rapidly as the iodine was added, as indicated by loss of the iodine color. Isolation of the solid product and purification by chromatography on silica plates afforded **1** (76%); mp[6] 140–143°; R_f (EtOAc–THF, 2:1) 0.38; λ_{max} (MeOH) 265 nm (ε 20,100); λ_{min} 251 nm (ε 17,200). Anal. Calcd for $C_{66}H_{62}ClN_4O_{14}P$: C, 65.97; H, 5.20; N, 4.66. Found: C, 65.82; H, 5.19; N, 4.57.

Compound **2**, a 3′-3′ dinucleoside phosphate derivative, was similarly prepared from 5′-*O*-phenoxyacetylthymidine;[7] yield of isolated **2**: 66%; mp[6] 91–94°; (R_f EtOAc–THF, 2:1) 0.31; λ_{max} (MeOH) 265 nm (ε 21,500); λ_{min} 234 nm (ε 5030).

For synthesis of a triester with a natural 3′-5′ internucleotide link (compound **3**), 5′-*O*-phenoxyacetylthymidine was treated (10 min) with *o*-chlorophenyl phosphorodichloridite (0.9 mol equiv) and 2,6-lutidene (3.6 equiv) in tetrahydrofuran at −78°. 3′-*O*-Mono-*p*-methoxytritylthymidine (0.5 equiv) was added; then the mixture was stirred

(20 min) at −78°, warmed rapidly to ca. −10°, and treated with iodine as in the previous cases to oxidize the phosphite. It was found that the 3′-5′ phosphotriester was more readily separated from the 3′-3′-phosphotriester (formed in small amount by reaction of excess phenoxyacetylthymine with the dichloridite) after removal of the phenoxyacetyl protecting groups. Accordingly the reaction products were treated (20 min) with 4.5 *M* ammonium hydroxide in 1:1 dioxane–water, conditions which led to complete cleavage of the phenoxyacetic esters without disturbing the *o*-chlorophenyl protecting group. Thin layer chromatography on silica (with perchloric acid spray to indicate the position of methoxytrityl ethers) showed that all the methoxytritylthymidine had reacted and that none of the 5′-5′ phosphotriester (**1**) had formed.[8] The *o*-chlorophenyl ester of thymidylyl[3′-5′]-3′-*O*-mono-*p*-methoxytritylthymidine (**4**) was isolated by preparative chromatography on silica plates using tetrahydrofuran–1,2-dichloroethane (1:3): 65% yield; mp[6] 130–133°; R_f (EtOAc–THF 2:1) 0.15; λ_{max} 232 nm (shoulder, ϵ 18,600); 265 nm (ϵ 20,800); λ_{min} 246 (ϵ 14,600).[9]

These phosphotriesters were converted by successive hydrolysis with 80% aqueous acetic acid (10 min at 100°; to hydrolyze the *p*-methoxytrityl ether) and 0.1 *M* sodium hydroxide (3 hr at 25°; to remove the phenoxyacetyl and *o*-chlorophenyl protecting groups) to the corresponding dinucleoside phosphates, which were characterized by their reactivity toward snake venom and spleen phosphodiesterase. For example, the 3′-5′ isomer, dTpT, was completely degraded to thymidine and thymidine phosphate (1:1 ratio) by both enzymes.

Control tests with 3′,5′-O-protected nucleosides showed that the thymine ring and the *N*-benzoyl derivatives of the purine nucleosides and deoxycytidine are stable to phosphorochloridites in the reaction medium, even at room temperature. In addition to phenoxyacetyl and methoxytrityl, the benzoyl and β-benzoylpropionyl protecting groups were found to be compatible with the phosphorylating reagent.

Experiments are in progress to optimize the yields and to extend the phosphite coupling method to the synthesis of oligonucleotides containing all four common nucleotides.

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(9) Compound **3** was separated in 52% yield from products of a comparable reaction before treatment with ammonia by multiple development on silica plates with ether–ethyl acetate (3:1), mp 110–115°, R_f (EtOAc–THF, 2:1) 0.34.

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Book Reviews

Introduction to Modern Inorganic Chemistry. Second Edition. By K. M. MacKay and R. Ann MacKay (University of Waikato, Hamilton, New Zealand). Intext Educational Publishers, New York, N.Y. 1974. xiv + 305 pp. $11.50.

The second edition, which was originally published in Great Britain in 1972, is not substantially changed from the first edition. The first portion is concerned with the electronic structure of atoms and molecules, the solid state, solutions, and experimental methods. The larger, second portion follows with a discussion of periodicity and the descriptive chemistry of various groups of elements.

A total of twenty-nine additional pages have been distributed throughout the new edition, with sections discussing spectroscopic methods and inorganic reaction mechanisms particularly expanded. A new, brief (7 pp) appendix entitled "Molecular Symmetry and Point Groups" has been provided, and the appendix entitled "Further Reading" now contains specific references for topics appearing in all sections of the text. SI units are used throughout, with minor exceptions. No problems have been included.

The title of this text is not supported by the light treatment afforded some of the more recent developments in inorganic chemistry. Thus, the chemistry of the transition metals is presented with heavy emphasis on oxides and halides whereas topics in bioinorganic or organometallic chemistry receive relatively little attention (the latter is covered in three pages). In general, an effort to cover the widespread areas which loosely constitute inorganic chemistry has resulted in too many topics which are only briefly discussed. As such, their presentation is often too condensed to educate the neophyte and too superficial to be useful to those more experienced.

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Polyvinyl Alcohol. Edited by C. A. Finch. Wiley-Interscience, New York, N.Y. 1973. 622 pp. $35.00.

Because it cannot be prepared from its own monomer, poly(vinyl alcohol) stands out as a unique polymer of industrial importance. All attempts to synthesize the monomer vinyl alcohol have resulted in its rearrangement tautomer, acetaldehyde. Instead, poly(vinyl acetate) is synthesized, followed by the hydrolysis or ester inter-