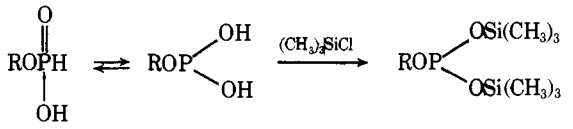
Silyl Phosphites. I. The Reaction of Silyl Phosphites with Diphenyl Disulfide. Synthesis of *S*-Phenyl Nucleoside Phosphorothioates

Sir:

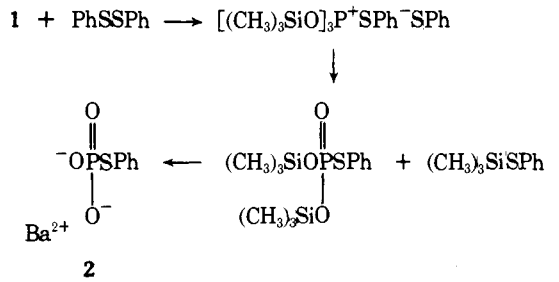
It is well recognized that trialkyl phosphites are highly reactive compounds toward electrophiles and oxidizing agents and that the reactivity is due to the lone pair electrons on the trivalent phosphorus atom. On the contrary, dialkyl and monoalkyl phosphites and phosphorous acid are less reactive and do not behave as trivalent phosphorus compounds because they exist substantially in the phosphonate form. Recently, we have found that monoalkyl phosphites can be converted easily with trimethylsilyl chloride to the corresponding trivalent phosphorus silyl esters, namely, silyl phosphites, which may be valuable intermediates in organophosphorus chemistry, especially in the field of nucleotide chemistry.



R = nucleoside residue

In this communication, we wish to report the synthesis of *S*-phenylphosphorothioates by the reaction of phosphorous acid or nucleoside phosphites with diphenyl disulfide *via* trimethylsilyl phosphite intermediates.

When 1 equiv of phosphorous acid was treated with 3.3 equiv of trimethylsilyl chloride in the presence of 3.3 equiv of triethylamine in dry pyridine, tris(trimethylsilyl) phosphite (**1**), $[(CH_3)_3SiO]_3P$, bp 86.5° (18 mm),[1] was obtained in 72% yield. In this reaction, when **1**, without isolation, was further treated with 1.2 equiv of diphenyl disulfide at room temperature for 4 hr, *S*-phenylphosphorothioate (**2**) [$\lambda_{max}^{H_2O}$ 247 nm (ϵ = 6560), $\lambda_{min}^{H_2O}$ 237 nm] was obtained in almost quantitative yield.[2] It was isolated as a barium salt after treatment with aqueous barium acetate.



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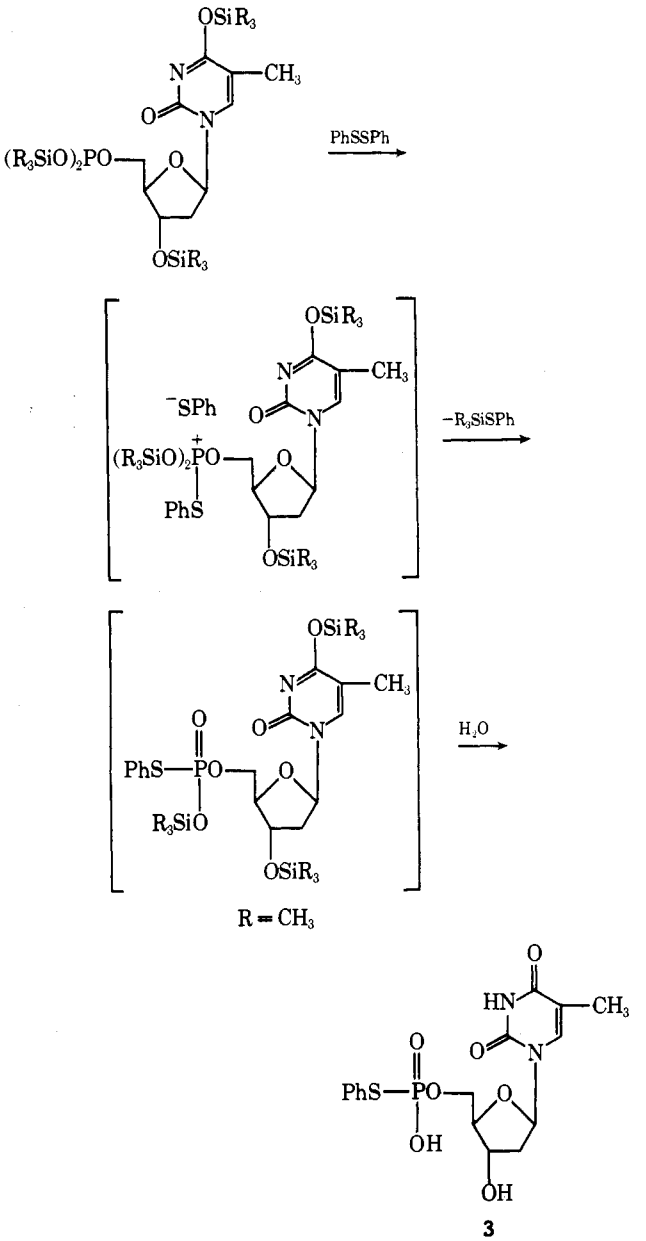
An interest in the ethylthio group for the protection of nucleotides developed by Nussbaum[3] led us to examine a useful synthetic route for the synthesis of *S*-phenyl nucleoside phosphorothioates which were previously difficult to obtain. As the starting material, nucleoside phosphite was prepared by a modification of the procedure of Todd.[4]

When thymidine 5′-phosphite (0.1 mmol) was allowed to react with trimethylsilyl chloride (0.072 ml, 0.5 mmol) in the presence of triethylamine (0.063 ml, 0.5 mmol) in dry pyridine and then with diphenyl disulfide (26.2 mg, 0.12 mmol) at room temperature for 24 hr, *S*-phenylthymidine 5′-phosphorothioate (**3**) [$\lambda_{max}^{H_2O}$ 267 (ϵ = 10,100), 243 nm (ϵ = 8800); $\lambda_{min}^{H_2O}$ 250, 236 nm. *Anal.* Calcd for $C_{33}H_{50}N_5O_8PS\cdot H_2O$: C, 54.61; H, 7.22; N, 9.65; S, 4.42. Found: C, 54.98; H, 7.20; N, 9.86; S, 4.38.] was obtained in 97% yield after removal of trimethylsilyl group on bihydrolysis.[5]



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According to this method, *S*-phenyl 5′-*O*-tritylthymidine 3′-phosphorothioate [$\lambda_{max}^{H_2O}$ 266 nm (ϵ = 10,100); $\lambda_{min}^{H_2O}$ 234 nm], *S*-phenyl 2′,3′-*O*-isopropylideneuridine 5′-phosphorothioate [$\lambda_{max}^{H_2O}$ 263 (ϵ 10,700), 243 nm (ϵ 9800); $\lambda_{min}^{H_2O}$ 251, 236 nm], and *S*-phenyl 2′,3′-*O*-isopropylideneadenosine 5′-phosphorothioate [$\lambda_{max}^{H_2O}$ 259 nm (ϵ 19,100); $\lambda_{min}^{H_2O}$ 230 nm] were obtained in quantitative

Table I. Chromatographic Properties of the Reported Compounds

Compound	Pc[a]	Pe[b]
S-Phenylphosphorothioate	0.25	1.10
S-Phenyl thymidine 5′-phosphorothioate	0.67	0.51
S-Phenyl tritylthymidine 3′-phosphorothioate	0.88	0.25[c]
S-Phenyl 2′,3′-*O*-isopropylideneuridine 5′-phosphorothioate	0.80	0.50
S-Phenyl 2′,3′-*O*-isopropylideneadenosine 5′-phosphorothioate	0.83	0.48

[a] Pc = paper chromatography. Paper chromatography was carried out by the descending technique using Toyo-Roshi No. 51 paper. Solvent system used was: isopropyl alcohol–concentrated ammonium hydroxide–water (7:1:2 v/v). [b] Pe = paper electrophoretic mobility relative to thymidine 5′-phosphate. The buffer used was phosphate (0.2 *M*), pH 8. [c] Tailing was observed in this buffer.

yields. Their structures were confirmed by paper electrophoresis, paper chromatograms (see Table I), and ultraviolet spectra and by identification of the corresponding nucleotides on hydrolysis.

Acknowledgment. The authors heartily thank Professor Teruaki Mukaiyama for his encouragement and discussion throughout the investigation.

References and Notes

(1) Tris(trimethylsilyl) phosphite was reported by M. G. Voronkov and Yu. I. Skorik, *Zh. Obshch. Khim.*, **35**, 106 (1965); *Chem. Abstr.*, **62**, 13173*d* (1965); N. F. Orlov and E. V. Sudakova, *ibid.*, **39**, 222 (1969); *Chem. Abstr.*, **70**, 87881 (1969).

(2) *S*-Phenylphosphorothioate has not previously been described. This compound may be used for the synthesis of phosphomonoesters of alcohols in a way similar to that described by A. L. Nussbaum and R. Tiberi, *J. Amer. Chem. Soc.*, **87**, 2513 (1965), using *S*-ethyl phosphorothioate because the phenylthio group can be easily removed by iodine or by silver acetate in aqueous pyridine at room temperature.

(3) A. F. Cook, M. J. Holman, and A. L. Nussbaum, *J. Amer. Chem. Soc.*, **91**, 1522, 6479 (1969); A. F. Cook, *ibid.*, **92**, 190 (1970); A. F. Cook, E. P. Meimer, M. J. Holman, D. T. Maichuk, and A. L. Nussbaum, *ibid.*, **94**, 1334 (1972); E. P. Heimer, M. Ahmad, S. Roy, A. Ramel, and A. L. Nussbaum, *ibid.*, **94**, 1707 (1972); E. P. Heimer, M. Ahmad, and A. L. Nussbaum, *Biochem. Biophys. Res. Commun.*, **48**, 348 (1972); A. F. Cook, A. DeCzekala, T. F. Gabriel, C. L. Harvey, M. Holman, J. E. Michalewsky, and A. L. Nussbaum, *Biochim. Biophys. Acta*, **324**, 433 (1973).

(4) J. A. Schofield and A. R. Todd, *J. Chem. Soc.*, 2316 (1961). In this experiment, 2,4,6-triisopropylbenzenesulfonyl chloride was used as a condensing agent.

(5) The trimethylsilyl groups can be removed from nucleotides by a simple treatment of the reaction mixture with water at room temperature for 30 min.

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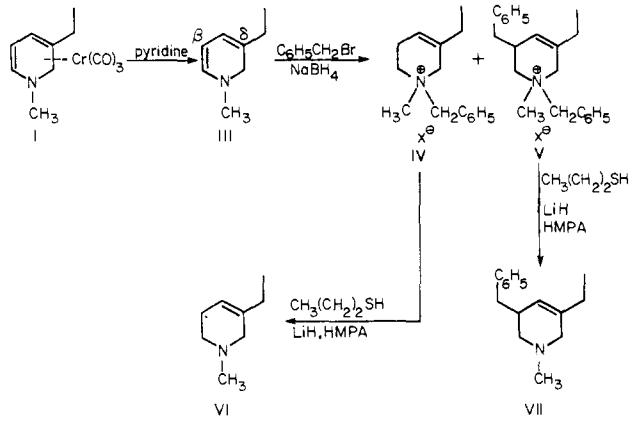
Studies in the Dihydropyridine Series. II.[1] Unstable Dihydropyridines Generated from Their Chromium Complexes and Their C-Alkylation

Sir:

In a previous study[1] we have described the preparation and characterization of two novel and stable complexes of *N*-methyl-3-ethyl-1,2-dihydropyridine (I) and *N*-methyl-3-ethyl-1,6-dihydropyridine (II). It was noted that such complexes might provide a convenient and stable system for the generation of unstable dihydropyridines, many of which are important in synthetic as well as biosynthetic considerations. We wish to describe some results which reveal that such metal carbonyl complexes are indeed useful synthetic intermediates and will undoubtedly serve to investigate much of the unknown chemistry of these interesting systems.

Reaction of *N*-methyl-3-ethyl-1,2-dihydropyridinetricarbonylchromium(I) with pyridine at room temperature provides essentially pure *N*-methyl-3-ethyl-1,2-dihydropyridine (III) which, without further isolation, can be used directly for various studies. Independent isolation and complete characterization of this unstable dihydropyridine was performed in another series of reactions to be described below.

Reaction of III with an excess of benzyl bromide and sodium borohydride in a two-phase system (ethyl ether, aqueous methanol containing sodium hydroxide) provided the mono- and dialkylated products IV and V. Direct debenzylation of IV and V employing *n*-propyl mercaptan, lithium hydride, and hexamethylphosphoramide[2] provided *N*-methyl-3-ethyl-1,2,5,6-tetrahydropyridine (VI) and *N*-methyl-3-ethyl-5-benzyl-1,2,5,6-tetrahydropyridine (VII). Characterization of these products is presented below.



In a complementary series of investigations designed to isolate the above dihydropyridine (III) from a direct reductive process, *N*-methyl-3-ethylpyridinium iodide was allowed to react in a two-phase system (ethyl ether, aqueous methanol containing sodium hydroxide) with sodium borohydride, under a nitrogen atmosphere, for 5 min. Careful evaporation of the ether solution provided III as a nearly colorless oil in 86% yield. Nmr analysis of this product revealed it to be the 1,2-dihydropyridine III of high purity with virtually no contamination by the 1,6-isomer. The nmr spectrum of III (100 MHz in deuteriobenzene) revealed the signals δ 1.0 (CH_3CH_2, t), 1.88 (CH_3CH_2, q), 2.27 (N-CH_3, s), 3.58 (N-CH_2, s), 4.84 (1 H, dd, J = 7 Hz, olefinic), and 5.73 (2 H, m, olefinic) while the uv spectrum (in methanol) showed a maximum at 327 nm. This product proved identical with that obtained when the metal carbonyl ligand had been removed from I. In this instance, the reductive process provided a more desirable route to III.

During the various alkylation studies with the dihydropyridine system it was found that optimum conditions for the desired C-alkylated product VII (or its salt V) could be obtained when various reagents were allowed to transfer between the layers in a two-phase system. This method provides a convenient isolation of the desired product with little or no complication from side reactions. Interestingly it was found that the ratio of products IV, V, and VII was markedly dependent on the molar ratios of alkylating agent employed.

When *N*-methyl-3-ethylpyridinium iodide was allowed to react in a vigorously stirred mixture of sodium borohydride, benzyl bromide (1.05 equiv) in ether, and aqueous methanol containing sodium hydroxide, the product mixture, after purification, consisted of the C-alkylated base VII (6%) and the quaternary salts IV (X = I), mp 178.5–179.5° (46%), and V (X = I, 17%), mp 204.5–205.5°.[3]

The base VII exhibited the following signals in the nmr spectrum (100 MHz, C_6D_6), δ 0.91 (CH_3CH_2, t), 1.83 (CH_3CH_2, q), 2.10 (N-CH_3, s), 5.34 (olefinic, s), 7.09 (aromatic, s), and 1.95–2.70 (7H, methylene and methine, m), while the mass spectrum revealed fragments at *m/e* 215 (M^+), 200, 143 (base peak), 129, 128, 124, 94, 91 (high resolution measurement, 215.67; calcd for $C_{15}H_{21}N$, 215.167).

On the other hand when *N*-methyl-3-ethylpyridinium iodide was allowed to react in the above manner except that 10 equiv of benzyl bromide were employed, the reaction mixture, as monitored by tlc, consisted almost entirely of salt V which upon direct debenzylation, under conditions described above, provided VII in an overall yield of 48%.