was centrifuged and the solution was decanted. The residue was washed with 25% aqueous NH_3 and the combined solutions were evaporated *in vacuo*. The residue was then allowed to stand overnight in 3 ml of pyridine:25% aqueous NH_3 (1:2, v/v). The solution was then evaporated *in vacuo* and the free nucleotide or oligonucleotide was isolated *via* chromatography (Tables II, III). In all cases where a lower yield than 30% was obtained, zinc in 5% acetic acid in pyridine or in 80% aqueous acetic acid was used instead of the above procedure to cleave the β,β,β-trichloroethyl function.

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Activated Phosphate Triesters. The Synthesis and Reactivity of *N*-Hydroxysuccinimide and *N*-Mercaptosuccinimide Esters

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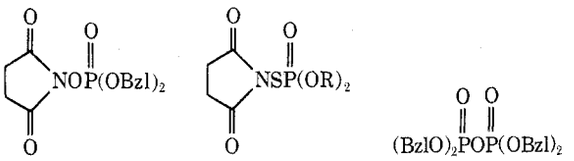
Phosphate esters based upon *N*-hydroxysuccinimide and *N*-mercaptosuccinimide have been prepared. It is shown that the reaction of *N*-hydroxysuccinimide with dibenzyl phosphate through the agency of diisopropylcarbodiimide can give a variety of products. Low temperatures in nonpolar solvents give the desired esters exclusively. Higher temperatures and polar solvents give mainly tetrabenzyl pyrophosphate. *O,O*-Dibenzyl *O*-(*N*-succinimidyl) phosphate phosphorylates benzyl alcohol in high yield: it does not react, however, with 3′-acetylthymidine. The thio esters phosphorylate benzyl alcohol in low yield, giving a large number of side products.

Although there have been remarkable achievements in the field of nucleotide synthesis,[1] it is clear that current methods for the synthesis of the internucleotide phosphate linkage are not satisfactory. The most successful procedures involve the use of condensing agents that remove a molecule of water between a nucleotide and a nucleoside. The most popular of these agents, dicyclohexylcarbodiimide[2] and triisopropylbenzenesulfonyl chloride,[3] are known to produce undesirable side reactions which become more serious when oligonucleotides are condensed; the starting materials are degraded[4-6] and larger and larger excesses of the phosphate-containing unit are required as the oligonucleotides grow in size. Just as the use of active esters[7,8] in peptide synthesis constituted an important advantage, the isolation of an activated phosphate species followed by coupling with a nucleoside hydroxyl group would be expected to result in much cleaner reactions. The possible utility of this scheme in phosphorylation reactions has been demonstrated with various reactive phosphates, *e.g.*, phosphorochloridates,[9] the adduct of phosphorochloridates with dimethylformamide,[10] phosphoromorpholidates,[11] imidazoyl phosphates,[12] oxidized or alkylated thio esters,[13] and activated phosphate esters with 2,4-dinitrophenol,[14] *p*-nitrophenol,[15] 2-hydroxypyridine,[16] and 2-mercaptopyridine.[17]

As a model for possible nucleotide synthesis we have prepared and studied phosphate *N*-hydroxysuccinimide and *N*-mercaptosuccinimide esters. These are *O,O*-dibenzyl *O*-(*N*-succinimidyl) phosphate (**1**), *O,O*-diethyl *S*-(*N*-succinimidyl) phosphorothioate (**2**), and *O,O*-di-*tert*-butyl *S*-(*N*-succinimidyl) phosphorothioate (**3**).



1 **2**, R = Et; **3**, R = *t*-Bu **4**

It was our purpose to study phospho triesters because of advantages in maintaining phospho triester linkages during oligonucleotide synthesis[18] and their high susceptibility to attack by hydroxide ion.[19] *N*-Hydroxysuccinimide active esters have proven their value in peptide synthesis.[20]

The synthesis of **1** was accomplished by the reaction of dibenzyl phosphate (DBP) and *N*-hydroxysuccinimide (NHS) with diisopropylcarbodiimide in acetonitrile or anisole at low temperature. It was seen that solvent polarity or basicity[21,22] and temperature play an important role in determining the course of the reaction which can proceed to give **1**, tetrabenzyl

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pyrophosphate (**4**),[23] or a mixture of the two (Table I). The reaction could be readily followed, since the

TABLE I

THE INFLUENCE OF SOLVENT AND TEMPERATURE ON THE FORMATION OF PHOSPHATE ACTIVE ESTER 1

Solvent	[NHS]:[DBP]	Temp, °C	% Yield of ester 1	% Yield of pyrophosphate 4
Acetonitrile	3:1	−18 to −15	45[a]	0
	4:1	0–4°	70	30
	7:1	Ambient	10	90
Anisole	3:1	−18 to −15	45	0
	3:1	Ambient	18	82
Dimethylformamide	3:1	−78	5	95
	7:1	−18 to −15	5	95
	3:1	Ambient	5	95
Dioxane	3.5:1	0–4	45	55
	3.5:1	10	30	70
	3:1	Ambient	5	95
	4:1	50–60	0	100
Hexamethylphosphoramide	5:1	0–4	0	90
Tetrahydrofuran	1:1	−18 to −15	40	9
	1:1	0–4	24	28
	1:1	Ambient	5	95

[a] The reaction stops after 50 hr; addition of more NHS or carbodiimide effects no further change. Reaction proceeds, however, upon warming.

chemical shifts and coupling constants of the benzyl protons differ. At all temperatures studied DMF gives a 95% yield of pyrophosphate; similar results are obtained in acetonitrile and anisole at ambient temperature, but at −18° *no pyrophosphate forms.* These results may be generally applicable to reactions of phosphates with acidic alcohols. All attempts to treat dibenzyl phosphate with copoly(ethylene-*N*-hydroxymaleimide)[24] yielded only **4**, probably owing to the insolubility of the polymer in any but dipolar solvents.

Compounds **2** and **3** were prepared by the reaction of the corresponding sodium dialkyl phosphorothioates[25] (**7a,b**) with *N*-chlorosuccinimide.[26] Di-*tert*-butyl phosphonate (**6a**)[27] was obtained by heating tri-*tert*-butyl phosphite (**5a**)[28] with a trace of sulfuric

$$(RO)_3P \longrightarrow (RO)_2P(O)H \longrightarrow (RO)_2P(O)S^-Na^+ \longrightarrow \mathbf{2, 3}$$

5a, R = *t*-Bu; **6a**, R = *t*-Bu; **7a**, R = *t*-Bu
b, R = Et; **b**, R = Et

acid. The dialkyl phosphorothioates **7a,b** were prepared by refluxing phosphonates **6a,b** with sodium and sulfur in dioxane. Compound **3** was a crystalline product but decomposed with the release of isobutylene, even at −18°. Tri-*tert*-butyl phosphate *has* been reported to undergo autocatalytic decomposition.[29]

Phosphorylation reactions were attempted by mixing the esters **1**, **2**, and **3** with alcohols in an excess of tertiary amine. The *N*-hydroxysuccinimide ester **1** reacts with simple alcohols to give phosphoryl product. The reaction with a twofold excess of benzyl alcohol in 2,6-lutidine proceeded to give a solution which showed a single product by nmr. Tribenzyl phosphate (**8**) was isolated in 80% yield; *N*-hydroxysuccinimide was recovered quantitatively. Other bases tried did not give substantial yields of phosphorylated products, these bases being triethylamine, pyridine, *N*-methylmorpholine, quinuclidine, and 1,8-bis(dimethylamine)naphthalene. A twofold excess of benzyl alcohol with **2** in 2,6-lutidine gave complete reaction; however, only a 13% yield of *O,O*-diethyl *O*-benzyl phosphate (**9**) could be isolated along with consider-

$$1 + PhCH_2OH \xrightarrow[2,6\text{-lutidine}]{} \underset{\mathbf{8}}{(PhCH_2O)_3P{=}O} + NHS$$

able amounts of *O,O*-diethyl phosphorothioate and *O,O,O,O*-tetraethyl thiopyrophosphate (**10**). Under similar conditions **3** phosphorylated benzyl alcohol to an extent of only 2%.

$$\underset{\mathbf{9}}{(EtO)_2P(O)OBzl} \qquad \underset{\mathbf{10}}{(EtO)_2P(O)SP(O)(OEt)_2}$$

An attempt was made to phosphorylate a deoxy ribonucleoside by treating **1** in lutidine with 3′-acetylthymidine. After 20 days there was no phosphorylation. The apparent lack of reactivity of nucleoside-hydroxyl groups compared to simple alcohols has been observed by others.[16,17,30]

Experimental Section

General.—All solvents were distilled from appropriate drying agents and stored over molecular sieves. Dibenzyl phosphate, *N*-chlorosuccinimide, and diisopropylcarbodiimide were purchased from Aldrich Chemical Co. and used without further purification; *N*-hydroxysuccinimide, also purchased from Aldrich, was recrystallized from ethyl acetate. *O,O*-Diethylphosphonic acid was distilled before using. Known compounds prepared in this work gave the expected nmr and ir spectra.

Nuclear magnetic resonance spectra were recorded using a Varian T-60 and a Varian A-60D spectrometer and are reported in parts per million downfield from internal tetramethylsilane. Mass spectra were obtained from an LKB 9000 mass spectrograph and ir spectra from a Beckman IR4 and Perkin-Elmer 247 ir spectrophotometer. Analyses were obtained by Galbraith Laboratories, Knoxville, Tenn., and Scandinavian Microanalytical Laboratories, Herlev, Denmark. Melting points are uncorrected.

***O,O*-Dibenzyl *O*-(*N*-Succinimidyl) Phosphate (1).**—*O,O*-Dibenzyl phosphate, 1.36 g (4.9 mmol), was dissolved in dry acetonitrile, 30 ml, with *N*-hydroxysuccinimide, 0.615 g (5.3 mmol). After the mixture was cooled to −15°, 0.6 ml (5 mmol) diisopropylcarbodiimide was added over a 30-min period. The reaction vessel was kept at −15° over a 5-day period with periodic monitoring for product formation using the nmr. The reaction mixture was then poured into cold (3°) 5% sodium bicarbonate and extracted twice with chloroform. The chloroform was dried over anhydrous sodium sulfate, evaporated to 5 ml, and filtered through a Millipore filter to remove diisopropylurea. Evaporation of the chloroform left an oil which crystallized upon addition of a seed crystal. Recrystallization from chloroform–petroleum ether (bp 30–60°) gave 0.69 g (51%). It was possible to recover 0.47 g of DBP from the basic aqueous solution. The yield of ester is 78% based upon unrecovered starting materials: mp 77–78°; mass spectrum parent *m/e* 284 (loss of benzyl); ir (KBr) 2900, 1782 (shoulder), 1730, 1210, 1010–1040, 850, 730, 690 cm^{-1}; nmr ($CDCl_3$) δ 7.4 (d, 10, PhH), 5.3 (d, 4, J_{PH} = 8 Hz, $POCH_2$), 2.7 (d, 4, J_{HP} = 1 Hz, O=CCH_2).

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Anal. Calcd for $C_{18}H_{18}O_6NO$: C, 57.5; H, 4.8; N, 3.7; P, 8.4. Found: C, 57.8; H, 5.03, N, 4.01; P, 8.09.

Sodium *O,O*-Diethyl Phosphorothioate (7b).—Sodium wire (1.9 g, 0.082 g-atom) and *O,O*-diethylphosphonic acid (**6b**) (12.0 g, 0.085 mol) were refluxed in 100 ml of anhydrous ether until all the sodium had reacted. Sulfur flowers (2.87 g, 0.089 mol) suspended in benzene were added over a 15-min period. This was refluxed for 35 min and then allowed to stand overnight. Evaporation gave a white precipitate which was recrystallized from benzene–ether, giving 11 g (80%) of product, mp 205–206° (lit.[25,31] mp 196°).

***O,O*-Diethyl *S*-(*N*-Succinimidyl) Phosphorothioate (2).**—*N*-Chlorosuccinimide (1.2 g, 10 mmol) and sodium *O,O*-diethyl phosphorothioate (1.6 g, 9 mmol) were stirred in 20 ml of dry benzene for 10 min, then left to stand for 2 hr. Filtration and evaporation gave a crude oil, 2.14 g (97%). Alternatively, a sample was dissolved in chloroform and extracted with dilute citric acid, and the chloroform was dried over anhydrous sodium sulfate and evaporated to an oil which crystallized on standing: yield 72%; mp 61–63°; mass spectrum parent *m/e* 267 (corresponds to molecular ion); ir (KBr) 2950, 1780 (shoulder), 1720, 1300, 1250, 1140, 990–1000, 780 cm^{-1}; nmr ($CDCl_3$) δ 4.35 (dq, 4, J_{HH} = 7 Hz, J_{HP} = 8 Hz, $POCH_2$), 2.85 (d, 4, J_{HP} = 1 Hz, $CH_2C{=}O$), 1.3 (dt, 6, J_{HH} = 7 Hz, J_{HP} = 1 Hz, $POCH_2CH_3$).

Anal. Calcd for $C_8H_{14}NO_5PS$: C, 35.93; H, 5.24; N, 5.24; S, 12.00. Found: C, 35.28; H, 5.29; N, 4.73; S, 14.30.

Di-*tert*-butylphosphonic Acid (6a).—Tri-*tert*-butyl phosphite (**5a**) was prepared by the method of Mark and Van Wazer.[32] Conversion to **6a** required heating **5a** (13.07 g) with a catalytic amount of concentrated H_2SO_4 to 80° at aspirator pressure for 30 min. Vigorous bubbling occurred. The product (8 g, 80%) was obtained by distillation, bp 64° (5 mm), $n^{25}D$ 1.4186 (lit.[27,32] $n^{25}D$ 1.4168).

Sodium *O,O*-Di-*tert*-butyl Phosphorothioate (7a).—Sulfur flowers (1.32 g, 0.04 mol) and sodium wire (0.82 g, 0.04 mol) were stirred into a dioxane solution (80 ml) of di-*tert*-butylphosphonic acid (**6a**) (8.24 g, 0.04 mol). An exothermic reaction took place. After refluxing for 1 hr and stirring overnight at 60–70°, the solution was flash evaporated to 50 ml. The product was precipitated by addition of petroleum ether, collected by centrifugation, twice washed with petroleum ether, and crystallized from 2-propanol–petroleum ether, giving 7.72 g (77% yield): mp 156° dec; nmr (D_2O) δ 1.35 (s), 4.57 (s, HOD); ir (KBr) 3000, 1400, 1370, 1250, 1170, 1110, 970, 920, 820, 720 cm^{-1}. Comparison by ir of the free acid prepared by treatment of the sodium salt with Dowex 50WX8 ion exchange resin (H^+ form) with the same acid prepared in an alternative procedure[32] showed the identity of the two.

***O,O*-Di-*tert*-butyl *S*-(*N*-Succinimidyl) Phosphorothioate (3).**—Sodium *O,O*-di-*tert*-butyl phosphorothioate (1.32 g, 0.530 mol) was suspended in 30 ml of dimethoxyethane. To this *N*-chlorosuccinimide (0.715 g, 0.530 mol) was added with stirring. A mildly exothermic reaction took place dissolving the sodium salt as well as the *N*-chlorosuccinimide. Finely divided sodium chloride formed after 10 min. The reaction was conveniently monitored by nmr as the succinimide protons are split by phosphorous–hydrogen coupling (1 Hz). This resonance is partially obscured by the solvent protons until a few drops of benzene are added to the nmr tube. This caused the succinimide protons to shift (δ 2.85 in dimethoxyethane, δ 1.85 in pure benzene.) After 2 hr the solution was centrifuged and the supernatant was evaporated to an oil. The oil was taken up in chloroform, extracted twice with dilute citric acid and twice with water, and then dried over anhydrous sodium sulfate. The solvent was evaporated, giving an oil which crystallized on standing (1.45 g, 85% yield): nmr ($CDCl_3$) δ 2.85 (d, 4, J_{HP} = 1 Hz, $CH_2C{=}O$), 1.57 (s, 18).

Tribenzyl Phosphate[33] (8).—Benzyl alcohol (0.097 g, 0.9 mmol) and *O,O*-dibenzyl *O*-(*N*-succinimidyl) phosphate (0.152 g, 0.4 mmol) were dissolved in 0.38 g of 2,6-lutidine. This was allowed to stand at room temperature in a desiccator for 8 days. The reaction was monitored by nmr. The benzyl protons of the product are separated from those of the starting material by 0.3 ppm. The nmr showed quantitative transesterification to the tribenzyl ester. The reaction mixture was evaporated to an oil and then evacuated at 0.1 mm for 4 hr to remove the 2,6-lutidine and most of the excess benzyl alcohol. The oil was then placed on a 10-g silica gel column and eluted with hexane (200 ml), carbon tetrachloride (100 ml), chloroform (100 ml), ethyl acetate (100 ml), and finally methanol (100 ml). From the chloroform eluate 0.115 g of pure tribenzyl phosphate was obtained, 80% yield, nmr ($CDCl_3$) δ 7.3 (s, 15 H), 5.0 (d, 6, J_{HP} = 8.5 Hz). Comparison of the ir spectrum obtained for the above with that of tribenzyl phosphate, Stadler index 9209, showed them to be identical. *N*-Hydroxysuccinimide was quantitatively recovered from the methanol fraction.

***O,O*-Diethyl *O*-Benzyl Phosphate (9).**—*O,O*-Diethyl *S*-(*N*-succinimidyl) phosphorothioate (0.177 g, 0.45 mmol), **2**, benzyl alcohol (0.193 g, 1.8 mmol), and 2,6-lutidine (1.65 g) were allowed to stand for 12 hr at room temperature in a desiccator. Nmr showed succinimidyl protons, split 1 Hz by the phosphorus, to gradually give way to succinimide protons (singlet). The reaction mixture became dark brown and some succinimide (mp 126–127°) crystallized. The solution was evaporated to an oil (1 mm room temperature) to remove the 2,6-lutidine and most of the benzyl alcohol. The oil was then placed on a 10-g silica gel column, and eluted with methylene chloride (100 ml), chloroform (100 ml), ethyl acetate–chloroform (1:3, 100 ml), ethyl acetate–chloroform (1:1, 100 ml), and ethyl acetate–chloroform (3:1, 100 ml). From the chloroform–ethyl acetate fractions was isolated *O,O,O,O*-tetraethyl pyrophosphorothioate (**10**) (0.0105 g), 7% yield (calcd for $C_8H_{20}O_6P_2S$: 306 g/mol; parent *m/e* 306); nmr ($CDCl_3$) δ 4.6 (dq, 8, J_{HH} = 8, J_{HP} = 9 Hz, $POCH_2$), 1.3 (dt, 12, J_{HH} = 8, J_{HP} = 1 Hz, $POCH_2CH_3$). This was followed by the desired product **9** (0.032 g, 13% yield).

***O,O*-Di-*tert*-butyl *O*-Benzyl Phosphate.**—*O,O*-Di-*tert*-butyl *S* (*N*-succinimidyl) phosphorothioate (**3**) (0.122 g) was dissolved in pyridine (5 ml). The pyridine slows the decomposition observed for the compound as a solid. To this an excess of benzyl alcohol (0.5 ml) was added. The reaction mixture was allowed to stand at room temperature with periodic monitoring by nmr. The succinimidyl protons of the triester **3** were no longer visible after 12 hr. The dark brown solution was decanted from precipitated succinimide and sulfur. The nmr spectrum of the benzyl protons of the solution gave the yield of product to be approximately 2%. No further characterization was possible; nmr ($CDCl_3$) δ 7.3 (s, 5), 5.0 (d, 2, J_{HP} = 8 Hz, PhC_2H-), 1.55 (s, 18, *tert*-butyl).

Attempted Preparation of 5′-Dibenzylphosphoryl-3′-acetylthymidine.[34]—*O,O*-Dibenzyl *O*-(*N*-succinimidyl) phosphate (1) (0.120 g, 0.32 mmol) and 3′-acetylthymidine (0.089 g, 0.31 mmol) were dissolved in 1.67 g of 2,6-lutidine, then allowed to stand at room temperature in a desiccator for 20 days. Column chromatography of the products gave none of the desired material; however, recovery was made of 3′-acetylthymidine (0.073, g, 82%), *N*-hydroxysuccinimide (100%), and a mixture of dibenzyl phosphate and tetrabenzyl pyrophosphate. These compounds were identified by nmr, mass spectra, and/or melting point. No compound having the paper chromatographic properties reported for the desired product were found. Thioester **2** also failed to give phosphorylated nucleoside.

Registry No.—**1**, 37173-10-7; **2**, 37173-11-8; **3**, 37173-12-9; **4**, 990-91-0; **6a**, 13086-84-5; **7a**, 37173-14-1; **8**, 1707-92-2; **9**, 884-90-2; **10**, 7342-94-1; di-*tert*-butyl benzyl phosphate, 37173-17-4.

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