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(14) The effectiveness of chloroacetic acid as a catalyst for this reaction was serendipitously uncovered when it was observed that crude samples of **3** reacted with aqueous lithium nitrite much more rapidly than did recrystallized samples. Investigation by TLC pointed to *N*-trifluoroacetylserine as a likely catalytic impurity and chloroacetic acid was selected as an acid of similar strength. Neither acetic nor hydrochloric acids were as effective.
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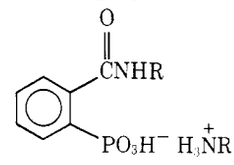
**Table I**



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| compd | R | mp, °C |
|---|---|---|
| **4a** | Ph | 194–196 |
| **b** | 4-Me-Ph | 201–205 |
| **c** | 3-$CF_3$-Ph | 155–158 |
| **d** | 4-Cl-2-$CF_3$-Ph | 195–205 (hydrate) |
| **e** | 2,6-di-Me-Ph | 116–123 (hydrate) |
| **f** | 2-COOEt-Ph | 198–200[a] |
| **g** | 2-F-Ph | 160–162 |
| **h** | 3-COOEt-Ph | 160–162 |
| **i** | 4-Cl-Ph | 208–222 |
| **j** | 3,4-di-Cl-Ph | 211–215 |
| **k** | 1-naphthyl | 169–171[b] |
| **l** | 2-Cl-5-$CF_3$-Ph | 142–144[b] |
| **m** | $H_2C$=$CHCH_2$ | 153–155 (hydrate) |

[a] Isolated as the free phosphonic acid. [b] Isolated as the crystalline half-phosphonate.

## Synthesis and Reactions of 1-Ethoxy-2,1-benzoxaphosphol-3-one 1-Oxide, a Phosphorus Counterpart of Phthalic Anhydride

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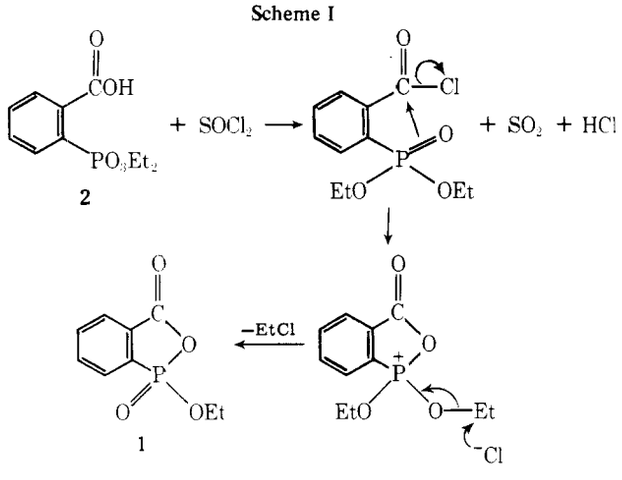
*Received July 11, 1978*

The intermediacy of the anhydride 1-ethoxy-2,1-benzoxaphosphol-3-one 1-oxide (**1**) has been postulated in the study of the hydrolysis of diethyl 2-carboxyphenylphosphonate (**2**).[1,2] We wish to report an improved synthesis of **1** and to discuss some of its properties. Blackburn and Brown reported,[1] without experimental detail, that **1** was produced upon gentle thermolysis of **2**. Indeed, we found that **1** was formed upon heating **2** at 120–135 °C at 1.0 mm pressure for 14 h. However, under these conditions, the product readily sublimed and the conversion was poor. On the other hand, treatment of **2** in refluxing thionyl chloride for 1 h afforded anhydride **1** in quantitative yield. The product, a white crystalline solid, mp 104–107 °C, was recovered by evaporation of the excess thionyl chloride in vacuo. A possible mechanism for this reaction is depicted in Scheme I.

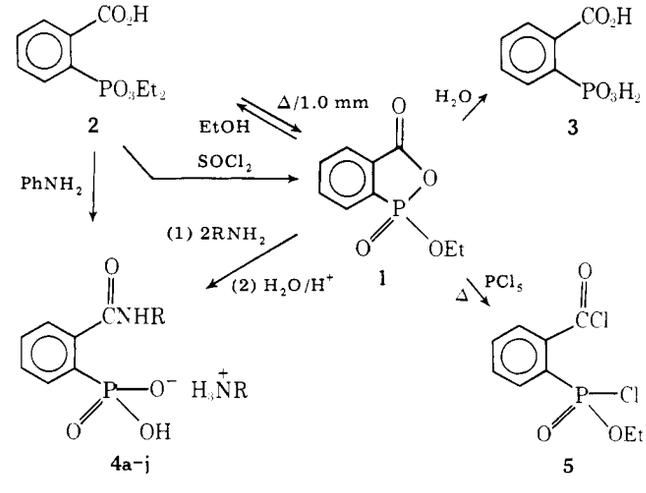
Scheme I



The anhydride exhibited carbonyl absorptions at 5.6 and 5.82 μm.[3] The mass spectrum indicated a molecular ion at *m/e* 212.2 (8.2) and major fragment ions as follows: *m/e* 185.1 (100, $C_7H_6PO_4^{+}\cdot$), 184.1 (10.2, $C_7H_5PO_4^{+}\cdot$), 167.2 (37.8, $C_7H_4PO_3^{+}\cdot$), 104.1 (62.8, $C_7H_4O^{+}\cdot$), and 76.1 (57.2, $C_6H_4^{+}\cdot$).

The reaction of this novel anhydride with a variety of reagents (Scheme II) was examined. It was found that **1** was hydrolyzed rapidly to 2-carboxyphenylphosphonic acid (**3**) when exposed to moist air.[4] Treatment of **1** with various amines afforded carboxamide derivatives (**4**) (Table I), whereas treatment of **1** with ethanol afforded diester **2**. This apparent selectivity of attack at carbonyl by amine nucleophiles and at phosphorus by alcohol has been previously noted by others.[1,5–8] The carboxamide (**4**) products were often foams or glasses due to the presence of a phosphonate half-ester function. Crystalline products were obtained after hydrolysis of the half-ester in dilute hydrochloric acid for 0.5 h on a steam bath. According to published reports, this hydrolysis is greatly assisted by the neighboring amide group.[4,5] Yields of the

Scheme II



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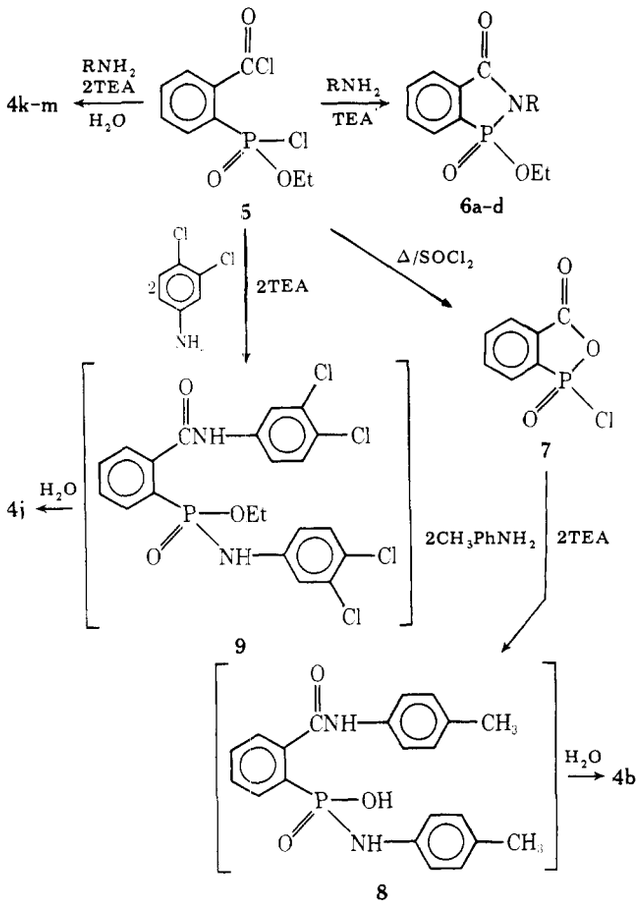
**Scheme III**



crystallized product were not optimized, but were generally in the range of 25 to 65%.

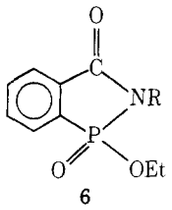
The direct reaction of **2** with aniline was examined briefly. Refluxing **2** in chlorobenzene for 20 h afforded the carboxamide **4a** in poor yield, but no effort to optimize the conditions was made.

Due to the expected difficulties in cyclization of carboxamides (**4**) to the corresponding heterocycles (**6**),[9] another more flexible approach was sought. Treatment of **1** with 1 equiv of phosphorus pentachloride in refluxing benzene for 1 h provided the highly reactive 2-(chloroethoxyphosphinyl)-benzoyl chloride (**5**) (Scheme II). This product, a dark amber oil, was isolated in excellent purity and in 96–99% yield after solvent removal on a rotary evaporator and then finally at 0.5 mm and 25 °C for 1 h. This crude **5** was used successfully to prepare a variety of 2-azaphosphindolin-3-one 1-oxides (**6**) by treatment of **5** with the appropriate amines or hydrazines (Scheme III).

These compounds, Table II, exhibited characteristic carbonyl absorptions at 5.82–5.85 μm, whereas the carboxamide derivatives (**4**) had carbonyl absorptions at 6.05–6.1 μm. The P–N bond of **6** is extremely susceptible to nucleophilic attack, and isolation of the imides was difficult without rigorous exclusion of hydroxylic reagents (water, alcohol). For example, dissolution of **6a** in aqueous ethanol afforded a mixture of ring-opened products (eq 1). This instability was further noted in the attempt to prepare certain imides, which were not isolated, but instead apparently hydrolyzed in the workup to **4k–m.**

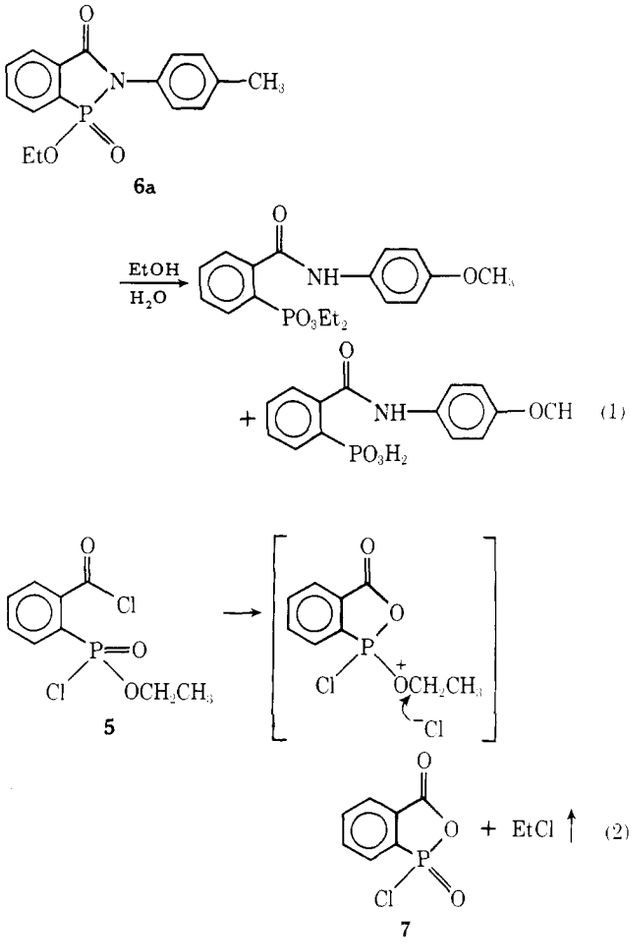
During the course of this work it was observed that **5** decomposed slowly over a period of several days while stirred under vacuum at room temperature. Bubbles were slowly evolved, apparently indicative of gas evolution. Presumably a type of internal Arbusov reaction was occurring, as depicted in eq 2. To test this hypothesis and prepare a usable quantity

**Table II**



| compd | R | mp, °C |
|---|---|---|
| **6a** | 4-MeO-Ph | 117–119 |
| **b** | 2-MeO-Ph | 98–100 |
| **c** | $N(CH_3)_2$ | 80–82 |
| **d** | 3,4-di-Cl-Ph | 115–116 |
| **e** | $CH_2COOEt$ | glass[a] |

[a] Decomposed upon recrystallization.



of the presumed chloroanhydride **7**, **5** was thermolyzed in boiling thionyl chloride. The reaction was monitored periodically by NMR via disappearance of the ethyl group in **5**. A plot of the log of the ethyl group concentration vs. time gave excellent first-order kinetics extrapolated to complete reaction at 10.5 h. After a total reaction time of 11 h, the solution was concentrated to a brown oil which crystallized to a low melting solid. The NMR spectrum of this solid showed no ethyl group. Its infrared spectrum showed carbonyl absorptions at 5.6 (strong) and 5.9 (weak) μm. The crude yield was 96%, with a chloride analysis of 17.0% (theoretical 17.6%). Further support for the structure of **7** was demonstrated by treatment of the crude product with 3 equiv of anhydrous ethanol and 1 equiv of triethylamine in benzene. The exothermic reaction which

resulted gave the known phosphonate **2** and 1 equiv of triethylamine hydrochloride.

Several attempts to prepare a diamide such as **8** were unsuccessful. Treatment of **5** with 2 equiv of 3,4-dichloroaniline afforded only the carboxamide derivative **4j** upon workup. Similarly, treatment of **7** with 2 equiv of *p*-toluidine gave only carboxamide **4** after workup.

## Experimental Section[10]

Infrared spectra were obtained on a Perkin-Elmer 727B spectrophotometer. $^1$H NMR spectra were obtained in $CDCl_3$ or $Me_2SO$-$d_6$ solutions with a Varian T-60 or EM-360 spectrometer; chemical shifts are reported in parts per million downfield from $Me_4Si$. Combustion analyses were performed by Atlantic Microlabs, Atlanta, Ga.

**1-Ethoxy-2,1-benzoxaphosphol-3-one 1-Oxide (1).** A solution of 17.8 g (0.069 mol) of 2-(diethoxyphosphinyl)benzoic acid (**2**) in 27 mL of purified thionyl chloride[11] was refluxed under a nitrogen blanket for 0.75–1.0 h. The pale straw-colored solution was cooled and concentrated to dryness in vacuo. A few milliliters of benzene was added to the residue, and the solution was concentrated again to remove residual thionyl chloride. Purification was completed by holding the product under vacuum (0.55 mm) at room temperature for 1 h. A white crystalline product (14.1 g, 97%), mp 104–107 °C, was obtained: NMR ($CDCl_3$) $\delta$ 1.4 (t, 3, $J$ = 7 Hz), 4.1–4.7 (q, 2), and 7.8–8.3 (m, 4). The product was stored in a stoppered flask under vacuum until used.

**General Procedure for 2-Phosphonobenzamide Derivatives.**[4] A solution of 3.5 g (0.0165 mol) of 1-ethoxy-2,1-benzoxaphosphol-3-one 1-oxide (**1**) and 0.033 mol of amine in 25 mL of chloroform was refluxed for 1 h. The solution was cooled and concentrated to a glass-like residue on a rotary evaporator. This material, the monoethyl phosphonate ester, was hydrolyzed in 10 mL of ethanol containing 3 mL of 0.5 M hydrochloric acid and about 10 mL of water. The hydrolysis was complete after heating for 0.5 h on a steam bath. The product (**4**) crystallized from the solution; or if not, it was concentrated to dryness and crystallized from aqueous ethanol or ethylacetate–cyclohexane.

**General Procedure for 2-Aryl-1-ethoxy-2-azaphosphinolin-3-one 1-Oxide Derivatives (6).** A solution of 0.012 mol of amine or hydrazine and 0.025 mol of triethylamine in 50 mL of benzene was added dropwise with stirring to a solution of 0.012 mol of 2-(chloroethoxyphosphinyl)benzoyl chloride (**5**) in 50 mL of benzene. A slight exotherm occurred during the addition period. The mixture was then heated to reflux for 1.5–2 h. The mixture was cooled to room temperature, and triethylamine hydrochloride was filtered off. The benzene filtrate was washed with 50 mL water, dried over sodium sulfate, filtered, and concentrated to dryness. The residue was crystallized from ethyl acetate–cyclohexane.

**Registry No.**—**1**, 67873-07-8; **2**, 22537-93-5; **4a**, 67872-84-8; **4b**, 67872-86-0; **4c**, 67872-88-2; **4d**, 67872-90-6; **4e**, 67872-92-8; **4f**, 67872-93-9; **4g**, 67872-95-1; **4h**, 67872-97-3; **4i**, 67904-76-1; **4j**, 67872-99-5; **4k**, 67873-00-1; **4l**, 67873-01-2; **4m**, 67873-03-4; **5**, 67873-08-9; **6a**, 67904-77-2; **6b**, 67904-78-3; **6c**, 67873-04-5; **6d**, 67873-05-6; **6e**, 67873-06-7.

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# Restricted Rotation of the Amino Group Bonded to Thiamin and to 2-(1-Hydroxyethyl)thiamin and the Question of Intramolecular Amino Group Catalysis


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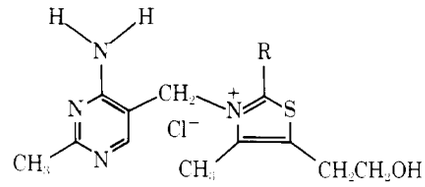
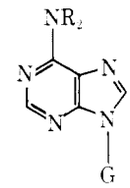
A controversy of long standing concerns the role of the amino group of thiamin or vitamin $B_1$ (**1**) and its biochemically important derivative 2-(1-hydroxyethyl)thiamin (**2**).[1] The



1. R = H
2. R = CH(OH)CH$_3$



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dispute deals with whether or not this substituent serves as a base in intramolecular deprotonation reactions[2-4] involving both enzymic and nonenzymic systems. It is said that the amino group of **1** may deprotonate the thiazolium ion ring at position 2 to produce an ylide and that the amino group of **2** may remove a proton from the carbinol carbon of the 1-hydroxyethyl substituent to form an "enamine" intermediate.

We report results of the first low temperature NMR investigation of **1** and **2**. Our observations reveal that rotation of the amino groups in these molecules is markedly restricted. Moreover, with a knowledge of the barrier to rotation and with information on related molecules already in the literature, we are able to estimate for the first time the p$K_a$ of the amino substituents. These estimates allow us to make clear statements about intramolecular general base catalysis in enzyme-free systems.

## Results and Discussion

Hydrochlorides of both salts are sparingly soluble in dry methanol but readily yield 0.3 M solutions when neutralized and buffered by 0.4 M 1,4-diazabicyclo[2.2.2]octane (Dabco).[5,6] At ambient temperatures, the signals of the amino protons are broad, owing to rapid exchange with the solvent.[2] But as the temperature is lowered and the rates of proton exchange decrease, these signals sharpen considerably, having, for example, a width at half-height of 8 Hz at −20 °C. Additional cooling leads to a separation of the singlet into two separate signals; integration with respect to the carbon-bonded proton of the pyrimidine ring shows that each signal is associated with one proton. As temperatures are reduced well below that for coalescence, differences in chemical shifts increase; the signal at lower field undergoes a larger shift. Relevant data for the reversible changes are given in Table I.

Variations in chemical shifts below coalescence largely reflect hydrogen bonding. In order to determine whether Dabco influences the chemical shifts of the amino protons, a sample

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