(5) 2-Arylimidazol-4-ones analogous to **6** have been shown to be reactive intermediates in the following reports: (a) A. Kjaer, *Acta Chem. Scand.*, **7**, 1030 (1953); (b) T. Wieland and H. Biener, *Tetrahedron*, **15**, 1 (1961); (c) W. Ried and W. von der Emden, *Justus Liebigs Ann. Chem.*, **661**, 76 (1963); (d) I. Kh. Fel'dman, Yu. Ya. Usaevich, and E. I. Boksiner, *Zh. Obshch. Khim.*, **37**, 1246 (1967); (e) T. Wang, *J. Org. Chem.*, **39**, 3591 (1974).

(6) A related cyclization of *N*-acetylglycyl peptides to give oxazoles has recently been reported: R. G. Harrison, M. R. J. Jolley, and J. C. Saunders, *Tetrahedron Lett.*, 293 (1976).

(7) The synthesis of compounds analogous to **2** via an alternate route has recently been reported: G. M. Devasia, *Tetrahedron Lett.*, 571 (1976). The stereochemistry of the compounds obtained was, however, not reported.

(8) The calculated[9] values are: *Z* stereoisomer = δ 6.83; *E* stereoisomer = δ 6.17. Experimentally determined values are: **2a** = δ 6.96; **2b** = δ 7.11. See also A. Maquestiau, Y. Van Haverbeke, and R. N. Muller, *Bull. Soc. Chim. Belg.*, **83**, 259 (1974); *Chem. Abstr.*, **82**, 42895u (1975).

(9) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon, New York, 1969, p 184.

(10) For an earlier mass spectral study of imidazolones, see J. A. Ballantine and R. G. Fenwick, *Org. Mass. Spectrom.*, **5**, 615 (1971).

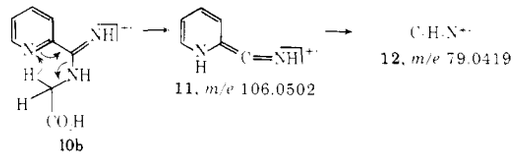
(11) For an analogous participation by carboxyl group, see J. H. Smith, *J. Am. Chem. Soc.*, **98**, 3598 (1976); M. K. Priebat and L. Chauffe, *J. Org. Chem.*, **41**, 3914 (1976).

(12) For details regarding instrumentation used, see S. K. Gupta, *J. Org. Chem.*, **41**, 2642 (1976).

(13) Glycyl-R-2-phenylglycine was obtained by reacting chloroacetyl chloride with R-2-phenylglycine in water (pH 11.5–12.5) followed by acidification to first give *N*-(2-chloroacetyl)-R-2-phenylglycine (85%), mp 99–101 °C, $[\alpha]^{25}_D$ −178 (CH_3OH, *c* 1). The aminolysis of the latter with NH_4OH gave the desired compound (80%), mp 235–237 °C $[\alpha]^{25}_D$ −189 (1 N HCl, *c* 1).

(14) S. R. Sandler and W. Karo, "Organic Functional Group Preparations", Vol. III, Academic Press, New York, 1972, p 268. The base-catalyzed addition of methanol to 2- and 4-cyanopyridines was effected in the present study with an anion-exchange resin (Rexyn-201, HO-form, 2–10% w/w). The filtration of the catalyst followed by displacement of excess methanol with hexane gave the desired imidates in 90–95% yield.

(15) The ionization of **10b** to give ions **11** and **12** was indeed observed.[16]



Although **10c** and **1** did not give ion **11**, the formation of *m/e* 106.0503 ($C_6H_6N_2$) ion in the case of **10a** and *m/e* 106.0547 ($C_6H_6N_2$, **11**) ion in the case of **2d** was unexpected.[16]

(16) P. H. Chen, *J. Org. Chem.*, **41**, 2973 (1976).

New Synthesis of Azaserine

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There has been a recent resurgence of interest in the antibiotic azaserine [*O*-(diazoacetyl)-L-serine, **4**]. Rats receiving repeated doses of this cytotoxic amino acid develop a high incidence of tumors of the exocrine pancreas, thus providing one of the first useful animal models of pancreatic cancer.[1,2] Moreover, interest in azaserine as an antitumor agent has been continuous since the late 1950's,[3] and two phase I clinical trials of this drug have been recently completed.[4,5] When studies in our laboratory of the mechanism of azaserine carcinogenesis required radiochemically labeled compound, we were prompted to reexamine the synthesis of azaserine, with the results reported in this note.

Published syntheses of azaserine converge on the same penultimate intermediate, *O*-(glycyl)-L-serine, which is converted by nitrous acid to the final product.[6–8] The yield in the nitrosation step is low, and azaserine must be isolated from the reaction mixture by carbon column chromatography. Attempts by Buchanan and co-workers to prepare ^{14}C-labeled azaserine by these procedures led to a 6% yield of material with only 50% radiochemical purity.[9] Neither the overall yield nor purity of this product was judged satisfactory for the synthesis of the large amount of pure radiochemical necessary for our work. Our attempts to improve the yield in the nitrosation step by varying reaction time, stoichiometry, pH, and temperature were without issue. In all cases yields of azaserine, as determined by TLC and by NMR spectroscopy, were uniformly low. Reasoning that the low yields in this step might arise from competing reaction of the serine amino group with nitrous acid, a new synthesis was sought in which a suitable blocking group would prevent the offending amino nitrogen from reacting. The sensitivity of azaserine toward light, heat, and extremes of pH[10,11] placed rather stringent requirements on the blocking group. It would have to be stable enough to survive several synthetic operations, yet be removable under very mild conditions. These requirements suggested the use of a group removable by enzymatic means, with trifluoroacetyl as a promising candidate. Trifluoroacetylamides are stable to a number of different reaction conditions, while those derived from α-amino acids undergo very rapid hydrolysis catalyzed by acylase I at neutral pH.[12] From these considerations a new synthesis of azaserine, shown in Scheme I, was developed.

Scheme I

$$\underset{\mathbf{1}}{HOCH_2CH(NHCOCF_3)CO_2CH_2Ph} \xrightarrow[4\text{-DMAP}]{ZNHCH_2CO_2COCMe_3} \underset{\mathbf{2}}{ZNHCH_2CO_2CH_2CH(NHCOCF_3)CO_2CH_2Ph}$$

$$\xrightarrow[\text{aq MeOAc}]{H_2\text{-Pd/C}} \underset{\mathbf{3}}{H_3N^+CH_2CO_2CH_2CH(NHCOCF_3)CO_2^-}$$

$$\xrightarrow[2.\ \text{acylase I}]{1.\ LiNO_2,\ ClCH_2CO_2H} \underset{\mathbf{4}}{N_2CHCO_2CH_2CH(NH_3^+)CO_2^-}$$

The serine component for the synthesis, *N*-(trifluoroacetyl)-L-serine benzyl ester (**1**), was prepared from *N*-(trifluoroacetyl)-L-serine, triethylamine, and benzyl bromide in DMF. Esterification of **1** by benzyloxycarbonylglycine was best accomplished by allowing the protected serine derivative to react in the presence of 4-dimethylaminopyridine[13] with the mixed anhydride formed from benzyloxycarbonylglycine, pivaloyl chloride, and *N*-methylmorpholine. Other coupling procedures such as the use of *N,N'*-dicyclohexylcarbodiimide with various additives, benzenesulfonyl chloride in the presence of pyridine, and carbonate mixed anhydrides proved less effective. Although previous workers have synthesized azaserine from serine components with free carboxyl groups,[6–8] we found it advantageous to block this group as the benzyl ester, hence our choice of **1** as a starting material. The yield in the coupling step appeared to improve, and the ester **2**, as the only neutral product, was more readily isolated from the reaction mixture. Hydrogenolysis of **2** to form the amino acid **3** was best conducted over a palladium on charcoal catalyst using aqueous methyl acetate as solvent. This unconventional choice of solvent was made to facilitate isolation of the hydrolytically labile product **3**. After filtration of the hydrogenation reaction mixture to remove catalyst, methyl acetate was removed in vacuo at room temperature, and the resulting aqueous solution lyophilized to give **3**.

The last two steps of the synthesis were carried out without isolating the intermediate diazoacetyl compound. Exposure of **3** to aqueous lithium nitrite in the presence of a catalytic amount of chloroacetic acid smoothly coverted the *O*-glycyl residue to diazoacetyl.[14] After adjusting the pH to 7.3 with Tris buffer, acylase I was added to catalyze hydrolysis of the intermediate trifluoroacetylamide. Azaserine was isolated from the lyophilized reaction mixture by trituration with alcohol and recrystallization of the insoluble fraction from aqueous alcohol. No chromatography was necessary. Although intermediates **2** and **3** are solids which may be recrystallized, if desired, the whole synthetic sequence may advantageously be conducted with only minimal purification of intermediates.

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Operating in this manner, 0.5 mmol of glycine-*U*-^{14}C was converted in 49% overall yield to azaserine, whose chemical and radiochemical purity exceeded 99%. While to date this synthesis has been conducted only on a millimole scale, there appears to be no obstacle to scale up, and preparation of gram quantities of azaserine should be entirely feasible.[15]

Experimental Section

Melting points, measured in capillary tubes using a Hershberg apparatus with short-range thermometers, are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. The ultraviolet absorption spectra were measured with a Gilford Model 2400-2 spectrophotometer using 1-cm matched cells. Proton magnetic resonance spectra were determined at 60 mHz using a Hitachi Perkin-Elmer R-24 spectrometer. Reagent grade ethyl acetate was redistilled and dried over 4A molecular sieves. Other solvents were reagent grade, redistilled, and dried, where indicated, over 3A sieves. Vacuum evaporations were performed on a Buchi rotary evaporator.

***N*-(Trifluoroacetyl)-L-serine Benzyl Ester (1).** In a three-neck flask equipped with mechanical stirrer and Drierite drying tube were placed finely ground L-serine (10.5 g, 0.1 mol), dry methanol (50 mL), triethylamine (14 mL, 0.1 mol), and methyl trifluoroacetate (16 g, 0.125 mol). The mixture was stirred 15 h at room temperature, during which time the amino acid dissolved completely. Removal of methanol *in vacuo* left the triethylammonium salt of *N*-trifluoroacetylserine (30.8 g) as a crystalline mass.[16] This was dissolved in dry DMF (50 mL) containing triethylamine (14 mL, 0.1 mol), and with mechanical stirring under dry nitrogen benzyl bromide (35.1 g, 0.205 mol) was added rapidly. Ice cooling was applied, as necessary, to maintain the flask contents below 40 °C. After the exotherm had subsided, the reaction mixture was stirred at room temperature for 2 days. To the resulting dark mixture was added ethyl acetate (250 mL) and water (250 mL). The organic phase was washed with 0.2 M hydrochloric acid, water, saturated sodium bicarbonate solution, water, and saturated salt solution. The extract was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The resulting oily residue was triturated with hexane to initiate crystallization, filtered, and the crude solid recrystallized twice from carbon tetrachloride (Darco) to give *N*-(trifluoroacetyl)-L-serine benzyl ester (1, 21.5 g, 74%) as pale yellow needles: mp 74–75 °C; NMR ($CDCl_3$) δ 2.75 (broad s, 1 H), 3.95 (m, 2 H), 4.6 (m, 1 H), 5.17 (s, 2 H), 7.31 (s, 5 H), 7.5 (broad s, 1 H).

Anal. Calcd for $C_{12}H_{12}NO_4F_3$: C, 49.49; H, 4.15; N, 4.81. Found: C, 49.26; H, 4.25; N, 4.74.

***O*-(Benzyloxycarbonylglycyl)-*N*-(trifluoroacetyl)-L-serine Benzyl Ester (2).** A solution of benzyloxycarbonylglycine (1.05 g, 5 mmol) and *N*-methylmorpholine (0.55 mL, 5 mmol) in dry ethyl acetate (5 mL) was stirred in a dry nitrogen atmosphere at −15 °C (bath temperature) while pivaloyl chloride (0.62 mL, 5 mmol) was added dropwise over a 5-min period. After stirring an additional 20 min at −15 °C, the bath temperature was lowered to −78 °C and a solution of serine ester 1 (1.46 g, 5 mmol) and 4-dimethylaminopyridine (61 mg, 0.5 mmol) in dry ethyl acetate (5 mL) was added over a 5-min period. The mixture was allowed to warm to room temperature and stirred an additional 15 h. The mixture was diluted with ethyl acetate (25 mL) and washed with 2 M hydrochloric acid, water, saturated sodium bicarbonate solution, water, and saturated salt solution. The extract was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to give 2 (2.25 g, 93%) as a white solid. Thin-layer chromatography showed a single spot with minor impurities. Recrystallization from isopropyl ether–isopropyl alcohol gave 2 as fine cottony needles (1.55 g, 64%): mp 101–102 °C; NMR ($CDCl_3$) δ 3.78 (d, 2 H, J = 6 Hz), 4.5 (m, 2 H), 4.9 (m, 1 H), 5.12 (s, 2 H), 5.2 (broad s, 1 H), 5.25 (s, 2 H), 7.37 (s, 10 H), 7.6 (broad s, 1 H). When the signal at δ 5.2 was irradiated with an external field, the doublet at δ 3.78 collapsed to a singlet. Similarly, irradiation at δ 7.6 collapsed the multiplet at δ 4.9 to a triplet.

Anal. Calcd for $C_{22}H_{21}N_2O_7F_3$: C, 54.77; H, 4.39; N, 5.81. Found: C, 54.77; H, 4.38; N, 5.75.

***O*-(Glycyl)-*N*-(trifluoroacetyl)-L-serine (3).** A mixture of 10% palladium on charcoal (0.5 g), water (30 mL), methyl acetate (140 mL), and ester 2 (4.82 g, 10 mmol) was shaken on a Parr apparatus until uptake of hydrogen ceased (30 min). Water (40 mL) was added to dissolve the precipitate of 3, the mixture filtered through Supercel, and methyl acetate removed from the filtrate in vacuo at room temperature. The residue was shell frozen and lyophilized to give crude 3 (2.66 g) as a glass which crystallized upon trituration with methanol. Recrystallization from aqueous methanol gave 3 as small white plates (2.03 g, 76%): NMR (D_2O, external Me_4Si) δ 4.40 (s, 2 H), 5.08 (s, 3 H). This substance melted with decomposition in the range 150–160 °C, but the exact melting point depended closely on the initial bath temperature and rate of heating. A sample dried over P_2O_5 for 3 h at 80 °C in vacuo gave analytical figures in agreement with those for a hemihydrate.

Anal. Calcd for $C_7H_9N_2O_5F_3 \cdot \frac{1}{2}H_2O$: C, 31.47; H, 3.77; N, 10.49. Found: C, 31.26; H, 3.91; N, 10.39.

***O*-(Diazoacetyl)-L-serine (4).** Amino acid 3 (77.4 mg, 0.3 mmol) was dissolved in water (0.55 mL) contained in a 12 × 100 mm test tube equipped with Teflon stirring bar and pH microelectrode. Aqueous 4 M chloroacetic acid (6 μL, 0.024 mmol) was added, followed by 5.82 M lithium nitrite solution (103 μL, 0.6 mmol). After being stirred for 10 min, a solution of acylase I (1.5 mg, Sigma No. A-3010, 2740 units) in 0.2 M Tris–0.1 M acetic acid buffer (1.5 mL) was added and the pH adjusted to 7.3 with 2 M Tris. The course of the hydrolysis was followed by TLC on silica gel GF-coated microscope slides developed in 5:1 acetonitrile–0.1 M ammonium acetate. The pH of the reaction mixture was maintained in the range 7.0 to 7.3 by periodic additions of 2 M Tris. After 90 min the spot due to 3 could no longer be detected. Two hours after addition of enzyme, the mixture was shell frozen and lyophilized. The resulting light tan foam was treated with alcohol (2 mL), scratched well, and allowed to stand for 2 h. Filtration and drying gave crude azaserine (4, 40.5 mg, 78%). Solution in water, filtration through Supercel to remove protein, and precipitation by alcohol gave 27 mg (52%) of pale yellow crystals whose NMR, UV, and thin-layer properties were identical to that of an authentic sample.

[*glycyl*-U-^{14}C]-Benzyloxycarbonylglycine. We have found the procedure of Guibe-Jampel et al.[17] to be very useful for the preparation of small amounts of benzyloxycarbonyl amino acids: An oven-dried 5-mL round-bottomed flask with a Teflon stirring bar was fitted with a serum cap and flushed with dry nitrogen. Dry ethyl acetate (2.5 mL) was introduced, the flask cooled in an ice-bath, and *N*-methylimidazole (44 μL, 0.55 mmol) added, followed by benzyl chloroformate (79 μL, 0.55 mmol). The resulting thick white slurry was transferred with the aid of ethyl acetate washes (3 × 0.5 mL) to a magnetically stirred solution of glycine-*U*-^{14}C (37.5 mg, 0.50 mmol, 15 mCi) in 1 M lithium hydroxide (0.50 mL). After stirring for 3 h, 1 M hydrochloric acid (0.65 mL) was added, the aqueous phase was extracted twice with ethyl acetate, and the combined organic phases were washed with saturated salt solution and dried over anhydrous $MgSO_4$. Evaporation of the filtered extract in vacuo left the crude benzyloxycarbonyl derivative (107 mg, 102%) as a white solid, which was utilized without further purification.

[*diazoacetyl*-U-^{14}C]-*O*-(Diazoacetyl)-L-serine. The ^{14}C-labeled benzyloxycarbonylglycine was converted to ester 2 by the procedure described above. The crude 2 obtained by evaporation of the ethyl acetate extract weighed 231 mg and, without further purification, was converted to 3 by catalytic hydrogenation in a 35-mL Fisher-Porter tube connected to the Parr apparatus. The reaction mixture was stirred magnetically rather than shaken. The crude lyophilized 3 was triturated with methanol (5 mL) and the mixture stored at −20 °C for 15 h. Filtration gave 3 as a white solid (104 mg). This was nitrosated and unblocked as described above to give, after recrystallization from aqueous alcohol, fine pale yellow needles of azaserine (42.3 mg, 49% overall, based on glycine): UV (water) 250 nm (ϵ 21 000 ± 700) (lit.[10] 250.5 nm, ϵ 19 700). The specific activity of this material was 29.9 ± 0.9 mCi/mmol. Aliquots chromatographed on 5 × 20 cm silica gel GF plates in three-solvent systems (4:1 acetonitrile–0.1 M ammonium acetate, 9:3:2:2:4 *n*-butyl alcohol–acetone–acetic acid–3 M ammonia-water, 3:1 phenol–water) showed less the 0.3% labeled impurity upon scanning with a Packard Radiochromatogram scanner.

Acknowledgment. We wish to thank the National Cancer Institute, NO1 CP55708 and CA-17843, for support of this work.

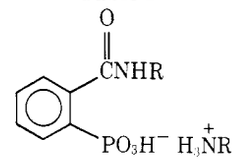
Registry No.—1, 67815-09-2; 2, 67815-10-5; [*glycyl*-U-^{14}C]-2, 67844-77-3; 3, 67815-11-6; [*glycyl*-U-^{14}C]-3, 67815-12-7; 4, 115-02-6; [*gyycyl*-U-^{14}C]-4, 67815-13-8; *N*-trifluoroacetylserinetriethylamine salt, 67815-14-9; [*glycyl*-U-^{14}C]benzyloxycarbonylglycine, 67815-15-0; L-serine, 56-45-1; methyl trifluoroacetate, 431-47-0; benzyl bromide, 100-39-0; benzyloxycarbonylglycine, 1138-80-3; benzyl chloroformate, 501-53-1; glycine-*U*-^{14}C, 18875-39-3.

References and Notes

(1) D. S. Longnecker and B. G. Crawford, *J. Natl. Cancer Inst.*, **53**, 573 (1974).
(2) D. S. Longnecker and T. J. Curphey, Cancer Res., **35**, 2249 (1975).
(3) L. R. Duvall, *Cancer Chemother. Rep.*, **7**, 65 (1960); R. B. Livingston, J.

M. Venditti, D. A. Cooney, and S. K. Carter, *Adv. Pharmacol. Chemother.*, **8**, 57 (1970).
(4) D. M. Hayes, R. R. Ellison, O. Glidewell, J. F. Holland, and R. T. Silver, *Cancer Chemother. Rep.*, **4**, 233 (1974).
(5) William L. Wilson et al., Central Oncology Group Study, UCLA Medical School, manuscript in preparation (private communication from Dr. Wilson).
(6) J. A. Moore, J. R. Dice, E. D. Nicolaides, R. D. Westland, and E. L. Wittle, *J. Am. Chem. Soc.*, **76**, 2884 (1954).
(7) E. D. Nicolaides, R. D. Westland, and E. L. Wittle, *J. Am. Chem. Soc.*, **76**, 2887 (1954).
(8) A. R. Ronzio and T. J. DeCino, *Microchem J.*, **4**, 531 (1960).
(9) T. C. French, I. B. David, R. A. Day, and J. M. Buchanan, *J. Biol. Chem.*, **238**, 2171 (1963).
(10) S. A. Fusari, R. P. Frohardt, A. Ryder, T. H. Haskell, D. W. Johannessen, C. C. Elder, and Q. R. Bartz, *J. Am. Chem. Soc.*, **76**, 2878 (1954).
(11) S. A. Fusari, T. H. Haskell, R. P. Frohardt, and Q. R. Bartz, *J. Am. Chem. Soc.*, **76**, 2881 (1954).
(12) W. S. Fones and M. Lee, *J. Biol. Chem.*, **201**, 847 (1953).
(13) W. Steglich and G. Höfle, *Angew. Chem., Int. Ed. Engl.*, **8**, 981 (1969); G. Höfle and W. Steglich, *Synthesis*, 619 (1972). Yields were lower when pyridine was used as catalyst.
(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.
(15) Azaserine is commercially available from Calbiochem.
(16) Application of this highly convenient procedure to preparation of other trifluoroacetyl amino acids is under investigation.
(17) E. Guibe-Jampel, G. Bram, and M. Vilkas, *Bull. Soc. Chim. Fr.*, 1021 (1973).

Table I



4

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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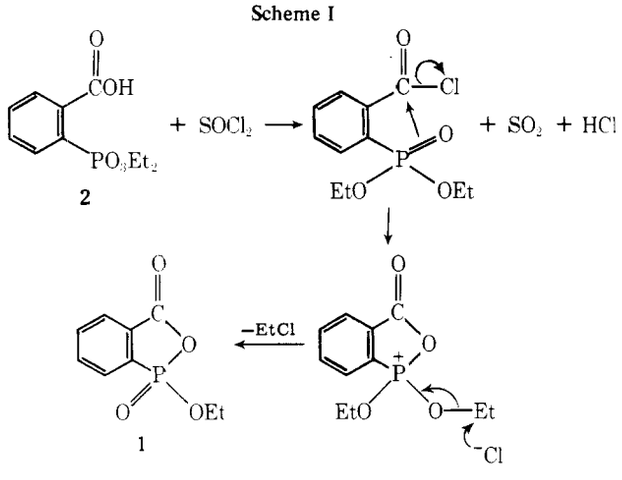
The intermediacy of the anhydride 1-ethoxy-2,1-benzoxaphosphol-3-one 1-oxide (**1**) has been postulated in the study of the hydrolysis of diethyl 2-carboxyphenylphosphonate (**2**).[1,2] We wish to report an improved synthesis of **1** and to discuss some of its properties. Blackburn and Brown reported,[1] 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.

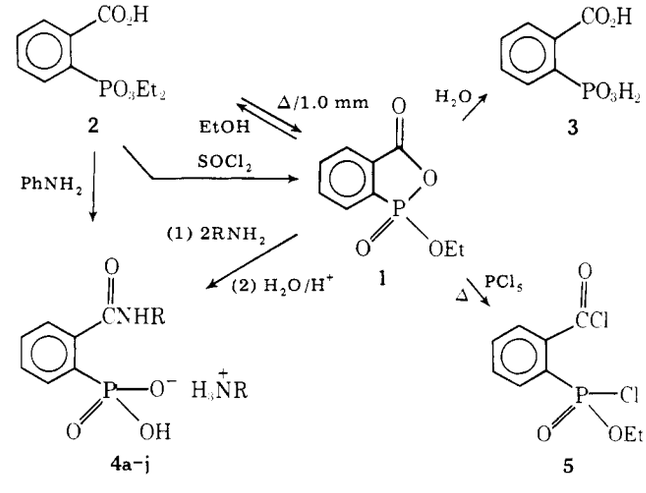
Scheme I



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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