(1972); (b) R. Lett and A. Marquet, *Tetrahedron*, **30**, 3379 (1974); (c) I. Sataty, *Org. Magn. Reson.*, **6**, 8 (1974).
(19) The formation of sulfone may be minimized by careful exclusion of moisture.
(20) M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Chem. Soc., Perkin Trans. 1*, 1886 (1972).
(21) In Schemes II and III partially labeled products are indicated as single products rather than mixtures, as they actually are. Formulas representing such mixtures are indicated by capital letters. The percent deuterium or protium at a given position (as obtained from NMR) is indicated by a figure at the upper right of the symbol. Thus the 60:40 mixture of **1b** and **1c** obtained by reductive debromination of **2a** is indicated by structure **A** in Scheme III.
(22) C. R. Johnson, *J. Am. Chem. Soc.*, **85**, 1020 (1963); C. R. Johnson and D. McCants, *ibid.*, **87**, 5404 (1965).
(23) M. Cinquini, S. Colonna, and D. Landini, *J. Chem. Soc., Perkin Trans. 2*, 296 (1972).
(24) G. Barbarella, A. Garbesi, A. Boicelli, and A. Fava, *J. Am. Chem. Soc.*, **95**, 8051 (1973).
(25) Previously, the halogenation of conformationally biased sulfoxides, *trans*-4-R-thiane 1-oxides (R = Ph, *t*-Bu), had also been found to give results incompatible with the concerted mechanism.[8-11]
(26) N. L. Wendler, D. Taub, and N. Kuo, *J. Am. Chem. Soc.*, **82**, 5701 (1960).
(27) C. H. De Puy, C. G. Naylor, and J. A. Beckman, *J. Org. Chem.*, **35**, 2750 (1970).
(28) A small percentage (<5) of the isomeric bromosulfoxide formed by collapse from the opposite side could have escaped detection, however.

Syntheses of and Structural Assignments for Some N-Phosphono-2-iminoimidazolidines (Cyclic Guanidines)[1]

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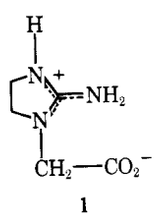
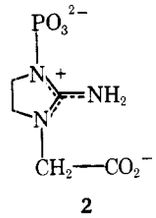
Received June 20, 1977

Phosphorylated derivatives of 1-carboxymethyl-2-iminoimidazolidine (1) with phosphorus attached to the primary and secondary nitrogen positions, respectively, were prepared. Dilithium 1-carboxymethyl-3-phosphono-2-iminoimidazolidine (2) was obtained by treatment of 1 with $POCl_3$ in aqueous LiOH solution. Compound 2 was shown to be identical with the product of phosphorylation of 1 by adenosine 5′-triphosphate, catalyzed by creatine kinase. Thus, the previous structural assignment for this compound [G. L. Rowley, A. L. Greenleaf, and G. L. Kenyon, *J. Am. Chem. Soc.*, **93**, 5542 (1971)] is incorrect. 1-Carboxymethyl-2-(diphenoxyphosphinylimino)imidazolidine sodium salt (**13**), the diphenyl ester of the isomeric substance, was obtained by coupling of *N*-(2-aminoethyl)-glycine sodium salt with *S,S*-dimethyl-*N*-(diphenoxyphosphinylimino) dithiocarbonimidate. Structural assignments for both 2 and 13 were made using NMR spectroscopy; especially valuable were measurements of $J_{^{31}P-^{15}N}$ values of appropriate selectively ^{15}N-enriched compounds. Some model 2-iminoimidazolidines, unequivocally phosphorylated on either the primary or secondary nitrogen, were synthesized for use in spectral comparisons. The measured apparent first-order rate constant for the hydrolysis of the P–N bond of 2 at pH 2.96 was found to be consistent with the structural assignment given here.

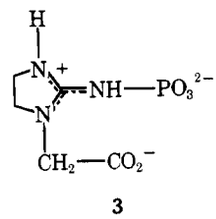
The synthetic creatine analogue 1-carboxymethyl-2-iminoimidazolidine (1)[5] is an excellent substrate for the enzyme creatine kinase, having a maximal velocity of 90% of that of creatine itself.[6] The two possible products of this enzymatic phosphorylation are salts of 1-carboxymethyl-3-phosphono-2-iminoimidazolidine (2) and 1-carboxymethyl-2-(phosphonoimino)imidazolidine (3). After an exhaustive analysis of the products of this enzymatic process, only one of these was detected, and it was tentatively identified as 3.[5] This identification was based upon examination of the proton NMR spectrum of the isolated product and its observed minimal $^{31}P-N-C-^{1}H$ coupling of phosphorus to the protons of one of the ring methylene groups. Such coupling had been anticipated to be relatively pronounced in structure 2, but not in 3.[7] The present work includes the chemical syntheses and structural assignments for 2, the diphenyl ester of 3, and several other *N*-phosphono-2-iminoimidazolidines. As a result of this work, the structural assignment given previously[5] for the product of the creatine kinase catalyzed phosphorylation of 1 has been shown to be incorrect; that is, this product has structure 2, not 3.



1



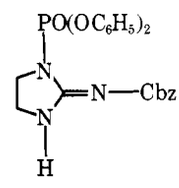
2



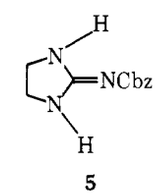
3

Results and Discussion

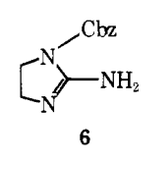
In the course of this work, synthetic routes to both 2 and 3 were sought so that the chemical and biochemical behaviors of each could be examined. One of the compounds synthesized as a potential precursor to 2 was 1-diphenoxyphosphinyl-2-(benzyloxycarbonylimino)imidazolidine (4). The precursor to 4, 2-(benzyloxycarbonylimino)imidazolidine (5), and the isomeric 6 had both been prepared and characterized by Matsumoto and Rapoport.[8] Using proton NMR spectroscopy, the distinction between 5 and 6 is straightforward, since 5 is symmetrically substituted and 6 is not.



4



5

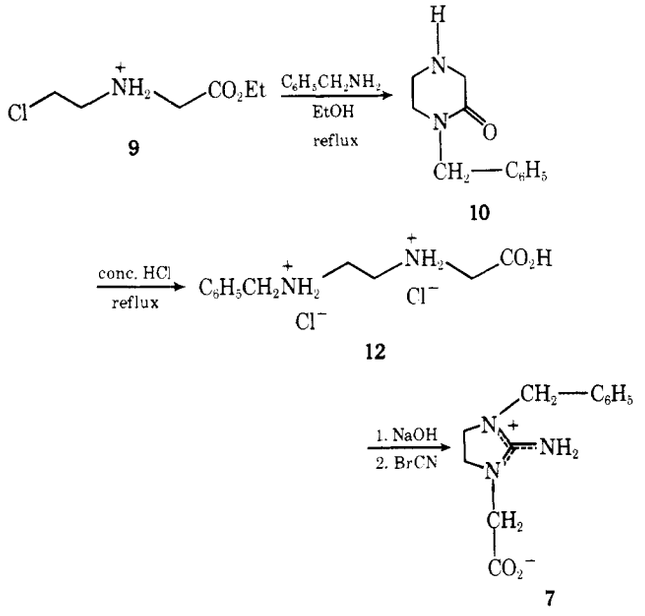


6

Where Cbz = $-CO_2CH_2C_6H_5$

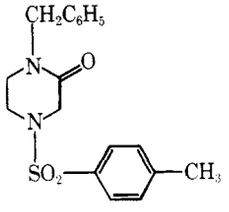
When 5 was treated with diphenyl chlorophosphate and triethylamine in tetrahydrofuran solution, product 4 was generated. Consistent with the structural assignment, the proton NMR spectrum clearly indicated asymmetric substitution, since the two ring methylene groups were now in different magnetic environments. Attempts to carboxymethylate 4 at the N-3 position were unsuccessful,[9] precluding its use as a precursor to 2. The proton NMR spectrum was valuable, however, since 4 *unequivocally* possesses the structure with

Scheme I



phosphorus attached to the *secondary* nitrogen in the ring. At 220 MHz the $-CH_2CH_2-$ proton region (for spectrum, see ref 9) was remarkably similar to the AA'BB' spectrum previously seen for the product of the creatine kinase catalyzed phosphorylation of **1**.[5] Thus, determination of the J_{PNCH} value for coupling of phosphorus to one of the ring methylene groups is not a reliable method of determining structure for this type of compound.

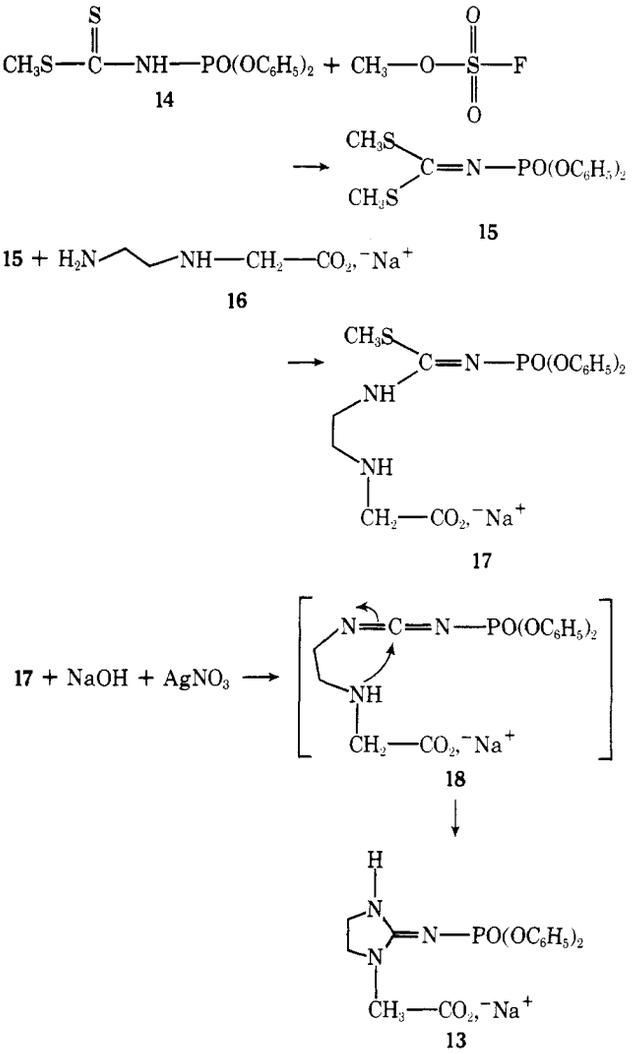
A potential route to the unequivocal synthesis of **3**, centered on the preparation of **7**, is outlined in Scheme I. The use of Na/liquid NH_3, a successful procedure employed in similar syntheses,[10] was proposed for the ultimate removal of the *N*-benzyl blocking group. For the synthesis of **7**, 2-hydroxyethylaminoacetonitrile (**8**) was converted to ethyl-*N*-(2-chloroethyl)glycine hydrochloride (**9**), by modification of the methods of Jones and Wilson.[11] In our hands, the conditions reported by Jones and Wilson were too severe and resulted in intractable tars. When **9** was treated with benzylamine in refluxing ethanol, spontaneous cyclization to 1-benzyl-2-ketopiperazine (**10**) occurred. Isolated as a viscous oil, **10** was characterized as its crystalline *N*-tosyl derivative **11**. When



either **10** or **11** were hydrolyzed, *N*-(2-benzylaminoethyl)-glycine dihydrochloride (**12**) was produced. In analogy to the synthesis of **1**,[5] intermediate **12** was then converted to **7** by treatment with cyanogen bromide in aqueous solution. A variety of conditions, described elsewhere,[9] were used in unsuccessful attempts to phosphorylate **7**.

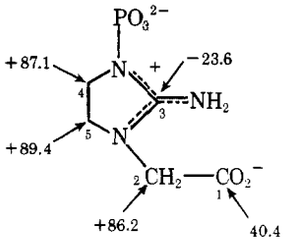
Scheme II shows a successful route to the unequivocal synthesis of 1-carboxymethyl-2-(diphenoxyphosphinylimino) imidazolidine (**13**), the diphenyl ester of **3**. The scheme was patterned after syntheses of other cyclic guanidines by Bosin *et al.*[12] The use of the powerful methylating agent, methyl fluorosulfonate,[13] was found to be necessary for the conversion of **14** to **15**. Intermediate **17** was purified by the unusual procedure of chromatography over silica gel of its sodium salt, using methanol as eluent. The final ring-closure presumably

Scheme II



proceeds *via* the hypothetical carbodiimide **18**. Despite several attempts,[9] including catalytic hydrogenation under a variety of non-acidic conditions, efforts to remove the phenyl groups from **13** to generate **3** have so far been fruitless.

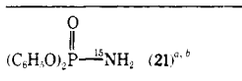
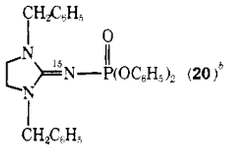
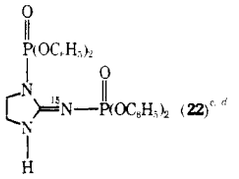
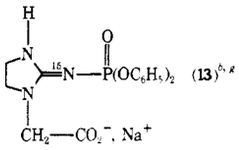
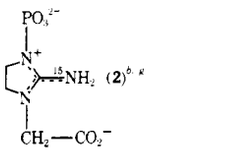
Compound **1** was phosphorylated in aqueous base with $POCl_3$, using a slight modification of the procedure which Ennor and Stocken[14] used for the conversion of creatine to phosphocreatine. Surprisingly, only one phosphorylated product could be detected and isolated, and it was identical to the sole product of the creatine kinase-catalyzed phosphorylation of **1**.[5] The natural abundance, proton-decoupled carbon-13 NMR spectrum of this product was examined. The chemical shift assignments are shown below (relative to dioxane):



^{13}C NMR of **2**

The spectrum was consistent with the structure of **2**, not **3**. The carbons furthest removed from phosphorus (C-1, C-2, and C-5) appeared as singlets. Both C-3 and C-4, however, appeared as doublets with *J* values of 4 ± 1 Hz, consistent with

Table I. ^{31}P NMR Data for Some ^{15}N-Enriched Phosphoramidates

Structure	Registry no.	$J_{^{15}N-^{31}P}$ (Hz)
 (21)[a,b]	63784-03-2	45
 (20)[b]	63784-04-3	35
 (22)[c,d]	63784-05-4	~50[e], 0[f]
 (13)[b,g]	63784-06-5	11
 (2)[b,g]	63784-07-6	0[h]

[a] Solvent = acetone-d_6. [b] 99% ^{15}N enriched. [c] Solvent = $CDCl_3$. [d] 96% ^{15}N enriched. [e] Since this measurement was made using only 96% ^{15}N-enriched material, the resolution of the doublet was not complete. The value given is an estimate based on the width at half-height. [f] As expected, a second ^{31}P peak was observed as a sharp singlet. [g] Solvent = D_2O. [h] This ^{31}P peak appeared 5.33 ppm downfield from trimethyl phosphate which was included in the sample at a concentration of 0.10 M.

$J_{^{31}P^{N13}C}$ coupling. Nevertheless, since very few similar coupling constants have ever been determined, this evidence was considered insufficient for a definitive structural assignment.

More convincing evidence for the structural assignments given to **2** and **13** came from measurement of $J_{^{31}P-^{15}N}$ values for some selectively ^{15}N-enriched phosphoramidates using phosphorus-31 NMR. The data are shown in Table I. Compound **20,** owing to appropriate substitution, unequivocally has phosphorus attached to the 2-imino nitrogen. As expected,[15] the ^{31}P NMR spectra of both **20** and **21** showed large $J_{^{31}P-^{15}N}$ values. Because its ring methylene groups are in different magnetic environments as determined by proton NMR,[9] compound **22** must have one phosphorus attached to a secondary nitrogen and one phosphorus attached to the 2-imino nitrogen. This latter example provides direct evidence that J_{NCNP} values must be relatively small in systems of this type.

Within experimental error, selectively ^{15}N-enriched **2** shows no evidence of coupling to phosphorus, whereas selectively enriched **13** does. This lack of observed coupling of ^{15}N to phosphorus provides evidence that the product of creatine kinase catalyzed phosphorylation of **1** is **2,** not **3** as previously proposed.[5]

Further evidence for the structure of **2** is provided by a comparison of the rate of removal of phosphorus from **2** by hydrolysis to the rate of removal of phosphorus from a phosphoguanidine where the bond is between phosphorus and a primary nitrogen. The apparent first-order rate constant for appearance of inorganic phosphate when **2** undergoes hydrolysis in acetate buffer (30.5 °C, pH 2.96, μ 0.2) was found to be 1.39 (±0.08) × 10^{-3} min^{-1}. Assuming that the apparent pK_a' values for **2** are similar to those for phosphocreatine,[16] then the species here would be monoprotonated on the phosphate moiety and electronically comparable to the phosphocreatine species present in solution at pH 1–3.5.[17] Under the conditions described above, the apparent first-order rate constant for the hydrolysis of this species of phosphocreatine[16] is 1.5–1.65 × 10^{-2} min^{-1}. This 11- to 12-fold difference in rates could be due to a pK_a' difference in the guanidines of about 1 unit (if the phosphorus were joined to a primary nitrogen in both cases).[18] However, such a difference in pK_a' is unlikely and a more plausible explanation of the difference in rate constants is that the compounds are of different types. Benkovic and Sampson[18] found that various phosphorylpyridinium ions have a rate of hydrolysis 50-fold lower than phosphoramidates formed from primary alkyl amines. A similar situation could be present here where the difference in rate constants may be due to the fact that phosphorus is bound to a primary nitrogen in one case and a secondary in the other.

A preliminary report[19] of the x-ray crystal structure of the product from the creatine kinase catalyzed phosphorylation of **1** confirms the structural assignment made here. Moreover, there is evidence[10,20] which indicates that **2** can substitute for phosphocreatine in the creatine kinase catalyzed reaction in the direction of adenosine 5′-triphosphate formation. Further studies on the biochemical properties of **2** will be reported at a later date.

Experimental Section[21]

Dilithium 1-Carboxymethyl-3-phosphono-2-iminoimidazolidine Dihydrate (2). A solution of 0.5 g (3.5 mmol) of 1-carboxymethyl-2-iminoimidazolidine (**1**)[5] in 0.5 mL of 3.7 N LiOH and 5 mL of H_2O was cooled in an ice–salt bath. While using vigorous mechanical stirring, 1.6 mL (17.5 mmol) of freshly distilled $POCl_3$ and 32 mL of 3.7 N LiOH were added in 16 portions at appropriate time intervals over a period of 2 h. At the end of the 2-h addition period, the pH of the solution was carefully adjusted to 7.2 with 6 N HCl. Solids in the reaction mixture were removed by either centrifugation or filtration and washed with 30% methanol–water (v/v). The filtrate (or supernatant) and washings were combined, and an aliquot was analyzed by polyethylenimine (PEI) cellulose thin-layer chromatography, as previously described.[22] Only one phosphorus-containing spot was in evidence, and its R_f value corresponded favorably to that of other phosphocreatine analogues.[22] To complete the purification of the product, the solution was reduced in vacuo at room temperature to a volume of 5 mL. The resulting solution, slightly turbid due to a small amount of insoluble material, was filtered through a fine-grade sintered-glass funnel to give a clear filtrate. Absolute ethanol was added to this filtrate until it became slightly turbid. After standing overnight, crystals had formed. They were collected by filtration and recrystallized once more from H_2O–EtOH. This resulted in 400 mg of colorless crystals. Addition of more EtOH to the mother liquor until it turned turbid gave an additional 168 mg of product. The combined yield amounted to 568 mg (57%). Both the IR and 220-MHz NMR spectra were identical with those of the product obtained from the creatine kinase catalyzed phosphorylation of 1.[5] PEI-cellulose thin-layer chromatography and NMR analyses of the mother liquors at various stages of purification of **2** gave no evidence for the presence of a second isomer.

Anal. Calcd for $C_5H_8N_3O_5PLi_2 \cdot 2H_2O$: N, 15.50; P, 11.43. Found: N, 15.36; P, 11.56.

The hydrolysis of compound **2** in acetate buffer was followed by measuring inorganic phosphate using the method of Jencks and Gilchrist[23] (developed for use with labile phosphoramidates). A 10 mM solution of **2** in sufficient acetate buffer to give an ionic strength of 0.2 and a pH of 2.96 was heated at 30.5 °C (±0.2 °C) until no further hydrolysis occurred. The pH changed no more than ±0.02 unit. With the sample of **2** used here the initial concentration of inorganic phosphate was 0.3 mM and the final concentration (>6 half-lives) was 7.4 mM. Duplicate sets of data were plotted on graphs of ln ($P_\infty - P_t$) vs. time, and the slope and standard deviation were derived by the method of least squares.

1-Diphenoxyphosphinyl-2-(benzyloxycarbonylimino)imidazolidine (4). To a stirred solution of 1.00 g (4.56 mmol) of 2-(benzyloxycarbonylimino)imidazolidine (**5**)[8] and 1.20 mL (8.72 mmol) of triethylamine in 80 mL of tetrahydrofuran (THF) under an atmosphere of N_2 was added a solution of 2.32 g (8.72 mmol) of diphenylchlorophosphate (Aldrich) in 80 mL of THF. Addition was carried out over a period of 10 min. Following completion of addition, the mixture was evaporated to dryness. The resulting material was dissolved in a minimal amount of 5% Et_3N–$CHCl_3$ (v/v) and applied to a silica gel column. The column was eluted with 5% Et_3N–$CHCl_3$ (v/v), and the fractions containing the component with an R_f value of 0.6 on silica gel thin-layer plates were pooled and the solvent was removed. The white solid thus obtained was recrystallized from $CHCl_3$–ether. A total of 1.54 g of product was obtained (75% yield): mp 141–142 °C; IR (Nujol) 6.02, 6.26, 6.78, 7.78 μm; NMR ($CDCl_3$) δ 3.63 (m, 1), 5.22 (s, 2), 7.18 (s, 5), 8.40 (br s, 1).

Anal. Calcd for $C_{23}H_{22}N_3O_5P$: C, 61.23; H, 4.93; N, 9.33; P, 6.88. Found: C, 60.93; H, 4.80; N, 9.29; P, 6.72.

Ethyl-*N*-(2-chloroethyl)glycine Hydrochloride (9). This compound was prepared by the method of Jones and Wilson,[11] modified as follows. While stirring in a water bath at room temperature, 51.1 g (0.9 mol) of cyanohydrin[24] was added dropwise to 54.7 g (0.90 mol) of ethanolamine over a period of 2 h. The mixture was stirred overnight. A distillation head was fitted to the flask, and the reaction system was evacuated to a pressure of ca. 8 mm while stirring and cooling. After 5–10 min of pumping, the material in the flask turned into a wet, white, crystalline mass. Pumping was continued for an additional 30–45 min. This intermediate, 2-hydroxyethylaminoacetonitrile (**8**), was not purified further and was stored at 4 °C until used. A flask containing 200 g of absolute ethanol containing 65 g of HCl was stirred on an ice bath. To this was added cautiously 30.8 g (0.308 mol) of **8**. Stirring was continued for 30 min while still cooling in an ice bath. The mixture was then heated at reflux for ca. 2 h. Following filtration of the reaction mixture, the filtrate was evaporated to remove all of the ethanol. The remaining residue was taken up in 45 mL of $CHCl_3$. This solution was cooled in ice while 100 g (0.84 mol) of $SOCl_2$ was added dropwise. Stirring at room temperature was continued for 14 h. The solvent was then removed. A large amount of ether was poured over the residue, and the crude product was collected by filtration. The product melted between 150 and 156 °C (lit.[11] 152 °C).[25] The material failed to recrystallize under the conditions reported by the original authors.[11] No straightforward method of further purification could be found, but the material was used successfully in its somewhat impure form in subsequent reactions.

1-Benzyl-2-ketopiperazine (10). To a solution of 21 g (0.10 mol) of ethyl-*N*-(2-chloroethyl)glycine hydrochloride (**9**) in 1400 mL of refluxing 95% ethanol was added dropwise a solution of 39.2 g (0.366 mol) of benzylamine (Aldrich, 99%) in 350 mL of 95% ethanol. Heating at reflux was continued overnight. The ethanol was removed, and the residue which remained was triturated with $CHCl_3$. Filtration removed the insoluble benzylammonium chloride. The excess benzylamine was removed by vacuum distillation. Once again $CHCl_3$ was added to the residue, and a small amount of benzylammonium chloride which remained was removed by filtration. Removal of solvent yielded a red, viscous oil which was further purified by one of the following two procedures:

(a) Purification by tosylation. The crude oil was dissolved in 60 mL of 3 N NaOH. While cooling in a water bath, 22.8 g (0.122 mol) of *p*-toluenesulfonyl chloride, dissolved in acetone, was added with stirring. After standing overnight, the crude, crystalline tosyl derivative, 1-benzyl-4-*p*-toluenesulfonyl-2-ketopiperazine (**11**), was collected by filtration. After recrystallization from 95% ethanol, 7.3 g (21%) of the pure derivative was obtained: mp 153–155 °C; IR (Nujol) 6.03, 8.61 μm.

Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.70; H, 5.86; N, 8.13. Found: C, 62.58; H, 5.76; N, 8.36.

(b) Purification by silica gel chromatography. The crude oil was chromatographed on silica gel by eluting with either 50% MeOH–EtOAc (v/v) or MeOH–$CHCl_3$ (2:3, v/v). The pure, hygroscopic oil was obtained in a yield of 30–40%, and it had an R_f value of 0.4 on silica gel thin-layer plates when chromatographed with 50% MeOH–$CHCl_3$ (v/v). Due to its extremely hygroscopic nature, a satisfactory elemental analysis was not obtained for this product. Conversion of the chromatographically pure oil to the tosyl derivative gave a crystalline material identical to the one described above.

***N*-(2-Benzylaminoethyl)glycine Dihydrochloride (12).** This compound was obtained by hydrolysis of either 1-benzyl-2-ketopiperazine (**10**) itself (method 1) or its *N*-tosyl derivative **11** (method 2).

Method 1. A solution of 0.6 g of (**10**) was heated at reflux in 14 mL of 6 N HCl for 30 h. After cooling to room temperature, a mass of colorless crystals had formed. They were collected by filtration and washed with 3 mL of cold water. A total of 0.60 g of product was obtained (72% yield): mp 215–216.5 °C; IR (Nujol) 3.55, 5.74 μm; NMR (D_2O) δ 3.50 (s, 4), 4.00 (s, 2), 4.25 (s, 2), 7.45 (s, 5).

Anal. Calcd for $C_{11}H_{18}Cl_2N_2O_2$: C, 46.98; H, 6.47; N, 9.97; Cl, 25.22. Found: C, 47.14; H, 6.38; N, 10.16, Cl, 25.14.

Method 2. A solution of 5.9 g of (**11**) was heated at reflux for 72 h in 80 mL of 6 N HCl. The hydrolyzed product crystallized upon cooling of the solution. Collection of the product by filtration, followed by further workup of the mother liquors, resulted in 3.3 g (69% yield) of product, identical to the material obtained by method 1.

1-Carboxymethyl-3-benzyl-2-iminoimidazolidine (7). To a solution of 2.3 g (8.2 mmol) of *N*-(2-benzylaminoethyl)glycine dihydrochloride (**12**) in 2.8 mL of 8.7 N NaOH was added dropwise with stirring a solution of 0.87 g (8.2 mmol) of BrCN in 1.2 mL of methanol. After 4.75 h of stirring at room temperature, the solvent was removed. The residue was triturated with warm absolute ethanol and filtered to remove the insoluble material. The ethanolic filtrate was reduced in volume and applied to a column of silica gel. It was washed onto the column with a small amount of $CHCl_3$, followed by 50% MeOH–$CHCl_3$ (v/v). Elution was completed using absolute methanol. The product had an R_f value on silica gel thin-layer plates of 0.5 when eluted with methanol. The white product began to discolor at 180 °C and melted with decomposition between 262 and 265 °C; IR (Nujol) 6.2 μm; NMR (D_2O) δ 3.25 (s, 4), 3.75 (s, 2), 4.40 (s, 2), 7.3 (s, 5).

Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.72; H, 6.53; N, 18.05. Found: C, 61.68; H, 6.49; N, 17.89.

***S,S*-Dimethyl-*N*-(diphenoxyphosphinylimino) Dithiocarbonimidate (15).** Methyl-*N*-(diphenoxyphosphinyl) dithiocarbamate (**14**)[27] was dissolved in the minimal amount of CH_2Cl_2 necessary to bring it into solution at room temperature. While stirring the solution at room temperature, a fivefold molar excess of methyl fluorosulfonate (Aldrich, 97%) was added. Stirring at room temperature was continued for ca. 6 h. At the end of this period the initial yellow tint had disappeared, and the solution was colorless. The solvent was removed, and the oil which remained was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with a portion of 5% $NaHCO_3$ solution followed by two portions of water. After drying the $CHCl_3$ layer over $MgSO_4$, it was filtered and the solvent was removed. The remaining oil was pure product. The oil was dried with mild heating over P_2O_5 before submitting for elemental analysis, and the product was analyzed as a monohydrate. The yield from this reaction was consistently in the range of 80–90%: IR (neat) 3.2, 6.29, 6.50, 6.84 μm.

Anal. Calcd for $C_{15}H_{16}NO_3PS_2 \cdot H_2O$: C, 48.49; H, 4.89; N, 3.78; P, 8.34; S, 17.27. Found: C, 48.34; H, 4.55; N, 4.02; P, 8.32; S, 17.06.

On one occasion a portion of the oil crystallized spontaneously. Ether was poured over the mixture of oil and crystals, and the crystals were collected by filtration, mp 75–77 °C. The crystals were dried over P_2O_5 and submitted for analysis; this time anhydrous product was obtained: NMR ($CDCl_3$) δ 2.4 (s, 6), 7.1 (s, 10).

Anal. Calcd for $C_{15}H_{16}NO_3PS_2$: C, 50.97; H, 4.57; N, 3.97; P, 8.76; S, 18.18. Found: C, 51.28; H, 4.41; N, 4.19; P, 8.63; S, 18.40.

***N*-[2-*N*-(Methylmercapto-*N*-diphenoxyphosphinylcarbonimidoyl)aminoethyl]glycine Sodium Salt Dihydrate (17).** A flask containing 0.45 g (3.2 mmol) of *N*-(2-aminoethyl)glycine (**16**), sodium salt, and 1.20 g (3.4 mmol) of *S,S*-dimethyl-*N*-(diphenoxyphosphinylimino) dithiocarbonimidate (**15**) in a total of 10 mL of absolute ethanol was stirred for 24 h at room temperature, and then the solvent was removed. The yellow oil which remained was dissolved in water, and the basic aqueous solution was carefully adjusted to pH 7.1 by the addition of 1 N HCl. The aqueous solution was then extracted with several portions of $CHCl_3$. The combined $CHCl_3$ extracts were dried over $MgSO_4$, the solution was filtered, and the solvent was removed. The crude oil which remained consisted of two components as could be observed on a silica gel thin-layer plate eluted with methanol. The two components had R_f values of 0.9 and 0.5, respectively. The crude oil was dissolved in $CHCl_3$ and applied to a column (2 × 80 cm) containing 70 g of silica gel. Elution of the column was carried out using methanol. The fractions containing the component of R_f 0.5 were pooled and the solvent was removed. Carbon tetrachloride was repeatedly poured over the oily material and removed. Following this treatment, 0.4 g (29% yield) of a white, glassy solid was obtained. After drying for several hours over P_2O_5, the product was submitted for analysis: IR (Nujol) broad peak at 6.3 μm; NMR ($CDCl_3$) δ 2.1–3.4 (br m, 9), 7.15 (s, 10).

Anal. Calcd for $C_{18}H_{21}N_3O_5PSNa \cdot 2H_2O$: C, 44.81; H, 5.24; N, 8.73; S, 6.65; P, 6.43. Found: C, 44.91; H, 4.88; N, 8.56; S, 6.42; P, 6.38.

1-Carboxymethyl-2-(diphenoxyphosphinylimino)imidazolidine Sodium Salt Hemihydrate (13). A solution of 0.39 g (0.81

mmol) of N-[2-N-(methylmercapto-N-diphenoxyphosphinylcarbonimidoyl)aminoethyl]glycine sodium salt dihydrate (17) in 13 mL of CH_3CN was cooled in an ice bath. While stirring, 0.43 mL (0.81 mmol) of 1.88 N NaOH was added, followed by a solution of 0.137 g (0.81 mmol) of $AgNO_3$ in 1.1 mL of CH_3CN. A precipitate of yellow silver mercaptide formed immediately upon addition of the $AgNO_3$ solution. Stirring of the reaction mixture was continued for an additional 2 h in an ice bath and for 1 h more at room temperature. The reaction mixture was then centrifuged. After spinning down the solid material, the supernatants were decanted and saved. A small amount of CH_3CN was added to each tube, the solid was resuspended, and the tubes were once again centrifuged. The supernatants were decanted from the tubes. All the decanted supernatants were combined and the solvents were removed. The residue was dissolved in $CHCl_3$ and filtered. The filtrate was evaporated. A glassy solid remained. A total of 0.26 g (79% yield) of product was obtained. After drying over P_2O_5 it was submitted for analysis: IR (Nujol) 6.15, 6.50, 7.28 μm; NMR (D_2O) δ 3.5 (s, 4) 3.7 (s, 2), 7.3 (s, 10).

Anal. Calcd for $C_{17}H_{17}N_3O_5PNa \cdot 0.5H_2O$: C, 50.21; H, 4.47; N, 10.35; P, 7.63. Found: C, 50.18; H, 4.82; N, 10.20; P, 7.62.

1,3-Dibenzyl-2-iminoimidazolidine Hydrobromide (19). To a solution of 11.0 g (46 mmol) of N,N'-dibenzylethylenediamine (99%, Aldrich) in 9.0 mL of methanol was added dropwise a solution of 5 g (46 mmol) of BrCN (97%, Aldrich) in 7 mL of methanol while cooling in an ice bath. About halfway through the addition a white mass precipitated from solution. The reaction flask was removed from the ice bath and placed in a water bath at room temperature while addition of the BrCN solution was completed. After stirring 1 h, the white crystalline material was collected by filtration, and the product was washed well with ether. A total of 15.1 g (94% yield) of crystalline hydrobromide was obtained. The analytically pure product melted between 253 and 258 °C: NMR [$(CD_3)_2SO$] δ 3.4 (s, 4), 4.6 (s, 4), 7.4 (s, 10), 8.6 (br s, 1).

Anal. Calcd for $C_{17}H_{20}N_3Br$: C, 58.91; H, 5.89; N, 12.12; Br, 23.05. Found: C, 58.71; H, 5.56; N, 12.28; Br, 22.84.

1,3-Dibenzyl-2-(diphenoxyphosphinylimino)imidazolidine (20). The free base of 1,3-dibenzyl-2-iminoimidazolidine was obtained by dissolving 1.5 g (4.4 mmol) of its hydrobromide salt (19) in 7.7 mL of 0.97 N NaOH and extracting with several portions of ether. The combined ether extracts were dried over Na_2SO_4, the solution was filtered, and the solvent was removed. The resultant clear oil was dissolved in 3.5 mL of dry THF. To the THF solution was added a solution of 0.56 g (2.0 mmol) of diphenyl chlorophosphate in 3.5 mL of dry THF. The mixture was stirred 12 h at room temperature. It was then filtered to remove precipitated salt, and the salt was washed with 3 mL of THF. The filtrate was evaporated, and the resultant oil was further purified by silica gel chromatography. The oil was applied to a column of 25 g of silica gel packed in 1% Et_3N–$CHCl_3$ (v/v), and the elution was carried out using Et_3N–MeOH–$CHCl_3$ (1:5:94, v/v). The fractions containing the component with R_f 0.9 on a silica gel thin-layer plate eluted with 5% MeOH–$CHCl_3$ (v/v) were pooled and the solvent was removed. This resulted in 0.44 g (44% yield) of a yellow oil. The oil was dried in vacuo over P_2O_5 and required no further purification: NMR ($CDCl_3$) δ 3.2 (s, 4), 4.5 (s, 4), 7.2 (s, 20); IR (neat) 6.15, 6.29, 6.74 μm.

Anal. Calcd for $C_{29}H_{28}N_3O_3P$: C, 70.02; H, 5.68; N, 8.45; P, 6.22. Found: C, 70.07; H, 5.76; N, 8.49; P, 6.35.

1-Diphenoxyphosphinyl-2-(diphenoxyphosphinylimino)imidazolidine (22). In a 100-mL three-neck flask, 2.4 g (14.5 mmol) of 2-iminoimidazolidine hydrobromide[28] was dissolved in a mixture of 15 mL of 0.97 N NaOH and 15 mL of THF. The flask was fitted with two dropping funnels, one of which contained 15 mL of 0.97 N NaOH and the other of which contained 3.9 g (14.5 mmol) of diphenyl chlorophosphate diluted to 15 mL with THF. The contents of the two funnels were added simultaneously over a period of 15 min while cooling the flask in an ice bath. The mixture was transferred to a 250-mL flask, and the THF was removed. The resulting aqueous solution was extracted with $CHCl_3$. After drying the combined extracts over $MgSO_4$, they were filtered and the solvent was removed. The resulting oil was applied to a column of 75 g of silica gel, and the column was eluted with a mixture of $CHCl_3$–CH_3OH–Et_3N (94:5:1, v/v). The product had an R_f value of 0.6 on silica gel thin-layer plates using the same solvent system. The fractions containing this component were pooled and the solvent was removed. Ether was poured over the resulting oil, and after several hours of standing at room temperature crystals began to form. A total of 1.3 g of crystals was collected (16% yield): mp 83–86 °C; IR (Nujol) 2.95, 6.07, 6.26 μm; NMR ($CDCl_3$) δ 3.5 (m, 4), 7.2 (s, 20).

Anal. Calcd for $C_{27}H_{25}N_3O_6P_2$: C, 58.97; H, 4.60; N, 7.65; P, 11.27. Found: C, 58.97; H, 5.02; N, 7.61; P, 11.07.

^{15}N-Diphenyl Phosphoramidate (21). The synthesis was based on the method of Chambers and Khorana.[29] A test tube containing 1 equiv of diphenyl chlorophosphate and an ampule containing 2.2 equiv of 99% enriched ^{15}N-NH_3 (Bio-Rad) were seated firmly against rubber seals on two closed stopcocks of a vacuum manifold. Both vessels were cooled in liquid N_2. After evacuation of the manifold, the system was closed. The stopcock to the ampule of ammonia was opened, and the liquid N_2 coolant was removed. The stopcock to the test tube containing the diphenyl chlorophosphate was opened, and the ammonia was allowed to distill into it. Gentle heating of the manifold was used to force all of the ammonia into the cooled test tube. The stopcock to the test tube was closed, and the liquid N_2 coolant was replaced with a dry ice–acetone bath. The test tube was removed from its rubber seal, and it was filled with water while still cooled. The product precipitated as a white crystalline material and was collected immediately by filtration. It was dried in vacuo over P_2O_5. The melting point of the product was in agreement with the value reported by Chambers and Khorana (148–149 °C).[29]

^{15}N-Cyanogen Bromide. The synthesis of enriched BrCN used 99% enriched ^{15}N-KCN (Bio-Rad) as starting material. The procedure of Hartman and Dreger[30] was modified for this preparation. In a 25-mL flask in a room-temperature water bath was placed 1.3 g (8.1 mmol) of Br_2 and one drop of water. A small dropping funnel containing a solution of 0.50 g (7.6 mmol) of 99% enriched ^{15}N-KCN dissolved in 2.5 mL of water was connected to the flask. The KCN solution was added slowly to the stirred Br_2 over a period of 10 min. Stirring was continued an additional 50 min. A short-path distillation head with a 10-mL receiving flask containing 1 mL of methanol was attached to the reaction flask in place of the dropping funnel, and the BrCN was distilled with heating on a steam bath. After distillation appeared complete, an additional 0.5 mL of methanol was added to the distillation pot, and the added methanol was distilled to chase the last traces of product into the receiving flask. The methanolic solution of ^{15}N-BrCN was used immediately in reaction with the appropriate diamine to obtain the desired labeled guanidine. All reactions were carried out assuming the presence of 7.6 mmol of BrCN.

In order to determine the yield of BrCN obtained from this procedure, several trial runs were made using unlabeled KCN as starting material. An excess of standard NaOH was added to the methanolic distillate, and the basic solution was back-titrated with standard HCl. The results of these determinations indicated a reliable yield of 99–100%.

^{15}N-Potassium Thiocyanate. Using 99% enriched ^{15}N-KCN (Bio-Rad) as starting material, the procedure was exactly the same as that used by Greenberg and Rothstein[31] for the synthesis of the analogous ^{14}C-labeled compound. The only change made in the procedure was the use of a potassium instead of a sodium salt.

Acknowledgments. Financial support for this work by Grant AM 17323, National Institute of Arthritis, Metabolism, and Digestive Diseases, is gratefully acknowledged. We thank Dr. I. D. Kuntz, Jr., for suggesting the use of ^{31}P–^{15}N coupling constants for some of the structural determinations in this paper. We also thank Dr. R. N. Hanson for valuable synthetic advice, and Dr. D. M. Wilson and Dr. S. J. Kohler for NMR measurements.

Registry No.—1, 35404-50-3; 2, 63784-08-7; 4, 63784-09-8; 5, 15230-93-0; 7, 63784-10-1; 8, 54961-35-2; 9, 63784-11-2; 10, 59702-21-5; 11, 63784-12-3; 12, 63784-13-4; 13, 63784-14-5; 14, 63784-15-6; 15, 63784-16-7; 16, 35404-68-3; 17, 63784-17-8; 19, 63784-18-9; 20, 63784-19-0; 22, 63784-20-3; LiOH, 1310-65-2; $POCl_3$, 10025-87-3; diphenyl chlorophosphate, 2524-64-3; benzylamine, 100-46-9; methyl fluorosulfonate, 421-20-5; N,N'-dibenzylethylenediamine, 140-28-3; 2-iminoimidazolidine hydrobromide, 33325-25-6.

References and Notes

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(2) United States Public Health Service Predoctoral Fellow, 1970–1974, Fellowship No. 5 F01 GM 41809.
(3) Recipient of a Career Development Award, 1 KO4AM00014, from the National Institute of Arthritis, Metabolism, and Digestive Diseases.
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Synthesis and Properties of Carbamate Derivatives of Tetrakis(hydroxymethyl)phosphonium Chloride

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Received December 28, 1976

Tetrakis(hydroxymethyl)phosphonium chloride (**1**) condenses with primary or secondary alkyl carbamates, forming stable quaternary phosphonium salts having the structure $(RO_2CNHCH_2)_4PCl$ (**3**) or $[EtO_2CN(R)CH_2]_4PCl$ (**6**). The alkyl carbamates are too feebly basic to cause the displacement of formaldehyde and HCl that characterizes the reaction of **1** with primary or secondary amines. The quaternary phosphonium salt **3a** (R = Me) undergoes halogen exchange, either by metathesis or by passage over an ion-exchange column, giving the corresponding iodide **9a** or bromide **11a**. Acid hydrolysis of **3a** unexpectedly regenerates **1**—a rare case of alkyl–nitrogen fission in a carbamate. The reaction of **3a** with sodium hydroxide is complicated by interaction of the product $(RO_2CNHCH_2)_3P$ (**13**) with the by-product $RO_2CN{=}CH_2$ (**16**), resulting in a different tertiary phosphine **15**, but this can be avoided by replacing the base by a reagent capable of reacting with the by-product, such as ammonium hydroxide, morpholine, or sodium sulfite. Oxide and sulfide derivatives of **13** are described.

The development of durable flame-retardant finishes for cotton based on the reaction of tetrakis(hydroxymethyl)phosphonium chloride (**1**) with trimethylolmelamine and urea[2] has led to the investigation of many other nitrogen compounds as resin-forming substrates.[3] The alkyl carbamates are particularly appealing in this respect, for they are the substrates of another important set of cotton finishes, the durable-press finishes.[4] Some attempts have been made to combine these properties in a single finish, without notable success.[5–7] In this paper, we report our investigation of the reaction of **1** with alkyl carbamates, leading to a series of novel nitrogen-containing quaternary phosphonium salts and their tertiary phosphine, phosphine oxide, and phosphine sulfide derivatives.

Quaternary Phosphonium Salts. Condensation of the phosphonium salt **1** with the alkyl carbamates **2a–e** took place in refluxing toluene (bp 110 °C) with azeotropic removal of the water, giving tetrakis(*N*-carbalkoxylaminomethyl)phosphonium chlorides (**3a–e**) in moderate to good yield (eq 1).[8,9]

$$\underset{\mathbf{1}}{(HOCH_2)_4PCl} + 4\underset{\mathbf{2}}{RO_2CNH_2} \rightarrow \underset{\mathbf{3}}{(RO_2CNHCH_2)_4PCl} + 4H_2O \quad (1)$$

a, R = Me; b, R = Et; c, R = *i*-Pr; d, R = *n*-Bu; e, R = $MeOCH_2CH_2$–

The methyl (**3a**), ethyl (**3b**), and isopropyl (**3c**) esters crystallized and were purified by recrystallization, giving yields of 86, 60, and 45%, respectively. The others were purified by adsorption on a cation-exchange resin, followed by displacement with hydrogen chloride, adopting a procedure developed for the analysis of tetramethylphosphonium chloride.[10,11] The 2-methoxyethyl ester **3e**, which is water soluble, was isolated in 53% yield as a viscous colorless oil. The *n*-butyl ester **3d**, which is not water soluble, was isolated in 38% yield as a viscous colorless oil, together with 21% of unreacted carbamate (**2d**) and 14% of di-*n*-butyl *N,N'*-methylenedicarbamate (**4d**).[12]