Chemistry of Phosphorous Acid: New Routes to Phosphonic Acids and Phosphate Esters

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Imines derived from aryl aldehydes, when heated with phosphorous acid in the absence of solvent, yield α-amino phosphonic acids (**6**). Imines from aliphatic aldehydes give only moderate yields of phosphonic acids together with amines from reduction of the imines. Phosphorous acid can give exclusively phosphonic acids, by addition of strong acid, or exclusively reduction, by addition of base (Et_3N) when reacted with imines. Enamines are readily reduced with phosphorous acid and, in the presence of an alcohol phosphoric acid monoesters are produced. Aqueous formaldehyde and phosphorous acid methylate amines in a procedure analogous to the Eshweiler–Clark method.

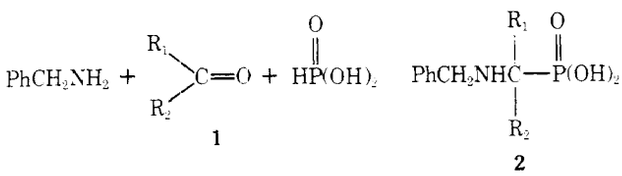
Although many phosphorus compounds are recognized as important reagents in organic chemistry, phosphorous acid itself has been almost neglected. Probably the most significant use is in the preparation of phosphonic acid chelating agents.[1,2] Acylation of phosphorous acid[3] to hydroxyethylidenediphosphonic acid and the Mannich-type reaction involving phosphorous acid, amine, and formaldehyde[2] are examples. The Mannich-type procedure is applicable to a wide range of primary and secondary aliphatic amines.

$$>NH + HCHO + HP(=O)(OH)_2 \xrightarrow{HCl} >NCH_2P(=O)(OH)_2 \quad (1)$$

This reaction only proceeds efficiently when performed under strongly acidic conditions which, in practice, is provided by an excess of hydrochloric acid. Another drawback to this procedure, in addition to the requirement for low pH, is that only formaldehyde can be used as the carbonyl reactant.[4] The present study was undertaken in an attempt to find conditions which would allow the use of a variety of carbonyl compounds. As discussed below, conditions were discovered which extended the scope of the α-amino phosphonic acid synthesis and which also uncovered high-yield reduction processes.

Results

Phosphonic Acids. As indicated above, the Mannich-type procedure of Moedritzer and Irani[2] is only applicable to the synthesis of aminomethylenephosphonic acids. A recent report[5] that the *N*-benzyl-α-aminophosphonic acids **2b–d** could be prepared by this procedure appears to be in error. A careful examination of the reaction mixture failed to reveal even trace amounts of these phosphonic acids.[4b] Furthermore, authentic samples of the acids **2b–d** exhibited properties (^1H and ^{13}C

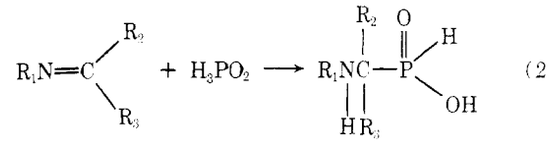


1 **2**

a, $R_1 = R_2 = H$
b, $R_1 = R_2 = CH_3$
c, $R_1 = H$; $R_2 = CH_2CH_3$
d, $R_1 = CH_3$; $R_2 = CH_2CH_3$

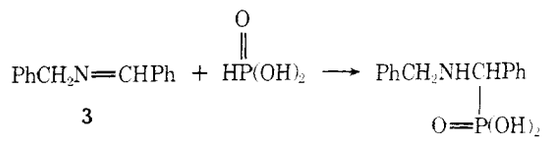
NMR spectra, dissociation constants) consistent with expectation but significantly different from those reported by Szczepaniak and Siepak.[5]

The addition of hypophosphorous acid (H_3PO_2) to a variety of amines in solvents such as ethanol (eq 2) has been known for a number of years.[6] Attempts to carry out the addition of phosphorous acid to imines under similar conditions were



(2)

unsuccessful, but nevertheless it seemed reasonable to assume that conditions could be found which would allow such an addition. In fact, this was realized by simply heating equimolar amounts of imine and phosphorous acid in the absence of solvent. For example, *N*-benzylidenebenzylamine (**3**) when heated with phosphorous acid gave an almost quantitative yield of *N*-benzyl-α-aminobenzylphosphonic acid (**4**). Solid phosphorous acid was added to the imine and as the temperature was raised to 70–80 °C a homogeneous liquid was obtained. Further heating to 100–115 °C induced a vigorous exothermic reaction which was complete in a few minutes. Table I lists a number of phosphonic acids obtained by this procedure. Previous preparations of structures such as **4** had



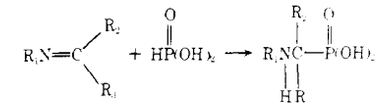
3 **4**

been effected by adding dialkyl phosphonates to imines, such as **3**, followed by hydrolysis.[7] The addition of phosphorous acid to 3,4-dihydroisoquinoline (**7**) to yield 1,2,3,4-tetrahydroisoquinoline-1-phosphonic acid (**8**) is a further example.

Imines derived from aliphatic aldehydes or dialkyl ketones give much lower yields of phosphonic acids than those derived from aryl aldehydes. In these cases it was found that reduction of the imine to the corresponding amine was a competing reaction.

Reduction Reactions of Phosphorous Acid. The reducing properties of phosphorous acid are quite well known, for

Table I. α-Aminophosphonic Acids



5 **6**

Compd	R_1	R_2	R_3	Yield, %
a	$PhCH_2$	Ph	H	98
b	CH_3	Ph	H	61
c	CH_3CH_2	Ph	H	68
d	t-C_4H_9	Ph	H	40
e	$PhCH_2$	p-ClC_6H_4	H	87
f	$PhCH_2$	$-CH(CH_3)_2$	H	40
g	$PhCH_2$	o-HOC_6H_4	H	10

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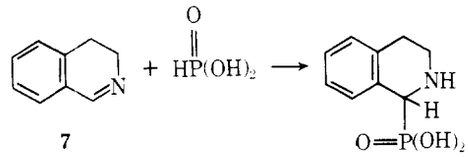
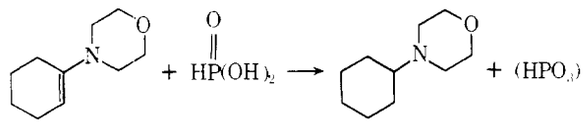


7 8

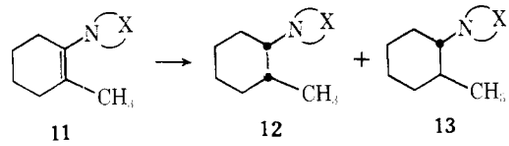
example, in the reduction of halogens to halide ions.[8] However, as far as can be ascertained, there are no reports in the literature of the use of phosphorous acid as a reducing reagent in organic chemistry. The reaction of the imine **5f** with phosphorous acid, in which the competing pathways of addition and reduction were observed, suggested that under appropriate conditions reduction could become predominant. In fact, when equimolar amounts of 1-morpholinocyclohexene (**9**) and phosphorous acid were heated to 100 °C a vigorous reaction ensued which gave the reduction product **10** in 91%



9 10

yield. Similar results were obtained with morpholinocyclopentene. Enamines derived from aldehydes such as isobutyraldehyde were also reduced, although in lower yield. An examination of the ^{31}P NMR spectra of the reaction mixtures from the enamine reductions provides convincing evidence for the fate of the phosphorous acid. The major absorption occurs at +22 ppm (relative to 85% H_3PO_4) assigned to trimetaphosphate (minor absorption at 0 ppm). By carrying out the reduction in the presence of an alcohol, such as butanol, butyl phosphate is obtained, but no ^{31}P NMR absorption is observed at +22 ppm. On the basis of these results, it can be claimed that the combination of enamine and phosphorous acid is a new phosphorylating reagent. Phosphorylation of alcohols using phosphorous acid and an oxidizing agent, e.g., iodine[9] or mercuric ion,[10] has been reported by other workers.

In light of the similarity in reducing properties of phosphorous acid and formic acid noted by Van Wazer,[8] it was of interest to compare these reagents in the reduction of the enamines **11a** and **11b**, derived from 2-methylcyclohexanone.



11 12 13

a, X = $-(CH_2)_4-$
b, X = $-(CH_2)_2O(CH_2)_2-$

Madsen and Iversen have recently reported that formic acid reduces these or related enamines with a high degree of stereoselectivity.[11] The results in Table II show that phosphorous acid is slightly less stereoselective than formic acid, a somewhat surprising result in view of the apparent larger size of the phosphorous acid.

In an investigation of the effect of reaction conditions on the reduction process, it was found that heating imine **3** with phosphorous acid in the presence of triethylamine dramatically altered the course of the reaction. Under these conditions no phosphonic acid **4** was formed, but instead an efficient reduction reaction yielding dibenzylamine (>95%) took place. The course of the reaction of imine **5f** with phosphorous acid was similarly influenced by added acid or amine as summarized in Table III.

Table II. Reduction of Enamines 11a and 11b

Enamine	Reducing agent	Yield, %	Ratio of cis/trans[12] (12/13)
11a	Phosphorous acid	85	75:25
11a	Formic acid	87	85:15[11]
11b	Phosphorous acid	64	81:19
11b	Formic acid	50	87:13

Table III. Effect of Added Amine or Acid on Imine/$HP(O)(OH)_2$ Reactions

Imine (equiv)	H_3PO_3, equiv	Additive (equiv)	Products (equiv)
3 (1)	1	None	Phosphonic acid **4** (0.95)
3 (1)	1	Et_3N (1)	Dibenzylamine (0.95)
5f (1)	1	None	Phosphonic acid (0.41), amine (0.5)
5f (1)	1	Et_3N (1)	Amine (0.72)
5f (1)	1	TsOH (1)	Phosphonic acid (0.9)

Table IV. *N*-Methylated Amines via Reductive Methylation

Amine	Yield, % $HP(O)(OH)_2$/formaldehyde	Yield, % Eshweiler–Clark[13]
Piperidine	40	80
Morpholine	54	
Cyclohexylamine	55	
Benzylamine	72	80

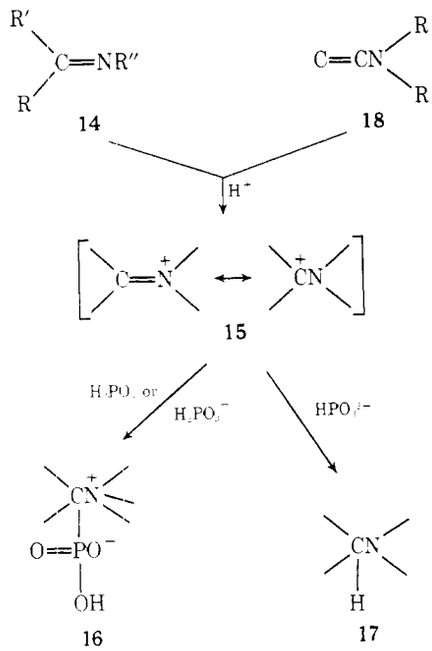
Attempts to carry out reductions with phosphorous acid in the presence of water were moderately successful. A number of amines were readily methylated in good yield upon heating with aqueous formaldehyde and phosphorous acid. Examples are presented in Table IV which also provide a comparison with the familiar Eshweiler–Clark method. A somewhat less efficient reductive alkylation was achieved by heating morpholine with benzaldehyde and aqueous phosphorous acid from which benzylmorpholine (18%) was obtained.

Discussion

On the basis of the results described in the preceding sections, it does not seem possible to provide a detailed mechanism for the phosphorous acid reactions. The addition of diesters of phosphorous acid (dialkyl phosphonates) to imines is generally considered to involve the phosphorus specie acting as a nucleophile.[14] Phosphorous acid may therefore be acting in a similar manner.

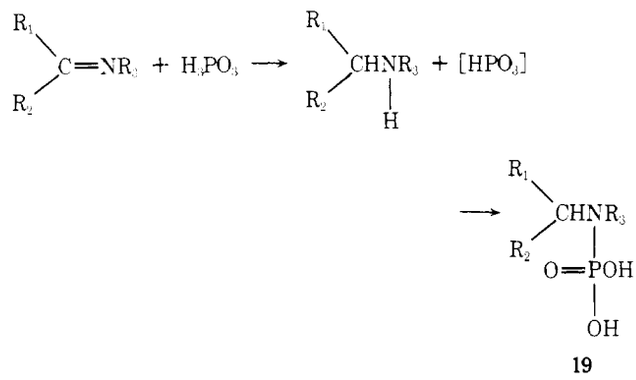
The initial step in the interaction between imines and phosphorous acid is postulated to be protonation of the imine[15] by the acid to yield **15** (Scheme I). In imines from aryl aldehydes (**14**, R = Ar), efficient addition of the phosphite monoanion to iminium cation **15** occurs to produce α-aminophosphonic acid **16**. When these same imines **14** (R = Ar) are heated with phosphorous acid and an equivalent of basic amine, the product is amine **17**. The phosphorous acid must be present as the dianion in this case. Reduction is not surprising in view of the oxidation potential of HPO_3^{2-}, 1.12 V,[8] comparable to that of formate ion, 1.01 V. An imine from an aliphatic aldehyde **14** (R^1 = alkyl) or an enamine **18** is considerably more basic than **14** (R = Ar),[16] so that some phosphite dianion could be formed from **14** (R = alkyl) and phosphorous acid. Although the concentration of dianion should be quite low, the results (see Table III) indicate that reduction is faster than addition. The formation of phosphonic acids **16** by reaction of imines and phosphorous acid in the presence

Scheme I



of strong acid (TsOH), which presumably protonates the imine, suggests that neutral phosphorous acid is sufficiently nucleophilic to add to **15**. This conclusion is supported by the results of Moedritzer and Irani,[2] which show that very low pH is *required* for the formaldehyde/amine/H_3PO_3 reaction (eq 1) to be efficient.

Under basic conditions where reduction of enamine or imine takes place it is postulated that metaphosphate (HPO_3) is formed. As mentioned above ^{31}P NMR evidence for the formation of trimetaphosphate and the phosphorylation of alcohols lead to this conclusion. When an imine is reduced, a secondary amine and metaphosphate are formed as primary products which can then interact to form the phosphoramidate **19**. Although isolation and characterization of **19** have



not been achieved, indirect evidence for its formation has been obtained. First a significant improvement in the isolated yield of secondary amines is obtained if the reaction mixture from reduction is heated with aqueous acid prior to basification and extraction and, secondly, ^{31}P NMR spectra suggest the presence of **19**.

Scheme I summarizes the chemistry involved in the reactions between phosphorous acid and imines or enamines. From a synthetic standpoint the important results are: (a) α-aminophosphonic acids are formed in high yield from imines and phosphorous acid under anhydrous acidic conditions; (b) imines and enamines are reduced by phosphorous acid under anhydrous basic conditions; and (c) phosphorous acid can also be used for phosphorylation or reductive methylation.

Experimental Section

Melting points are uncorrected. The elemental analyses were performed by Clark Microanalytical Laboratories and Petrolite Corporation, Analytical Section. ^1H NMR spectra were obtained with a Varian A-60 spectrometer, and ^{31}P and ^{13}C spectra with a Jeol FX-60 spectrometer operating at 24.15 and 15.04 MHz, respectively.

General Procedure for the Preparation of Phosphonic Acids. A mixture of imine (0.2 mol) and phosphorous acid (0.2 mol) was stirred with a mechanical stirrer and slowly heated to 75–80 °C, whereupon the reactants gave a homogeneous liquid. Further heating to 100–120 °C brought about a vigorous reaction resulting in a significant viscosity increase and an internal temperature of 140–160 °C. The source of heat was removed and water (100 mL) was added as the temperature reached 95–100 °C. The crude α-aminophosphonic acid is purified by crystallization or by ion exchange chromatography.

***N*-Benzyl-α-aminobenzylphosphonic Acid (6a).** The crude acid separated from water, mp 230–234 °C, in 98% yield. Recrystallization from acetic acid/water gave pure **6a:** mp 233–234 °C (lit.[7b] 233–236 °C); NMR (D_2O + NaOH) δ 3.67 (s, 2, CH_3N), 3.8 (d, 1, J = 16 Hz, CHP), 7.33 (s, 5, PhH), 7.45 (s, 5, PhH).

***N*-Methyl-α-aminobenzylphosphonic Acid (6b).** Upon cooling the aqueous solution of the crude reaction mixture the acid was obtained in 61% yield. Recrystallization from water gave pure acid **6b:** mp 242–245 °C (lit.[17] 255 °C dec); NMR (D_2O) δ 2.63 (s, 3, NCH_3), 4.05 (d, 1, J = 14 Hz, CHP), 7.50 (s, 5, PhH); ^{13}C NMR (D_2O) δ 33.7 (NCH_3), 65.1 (d, J = 125 Hz, CP).

Anal. Calcd for $C_8H_{12}NO_3P$: N, 6.97; P, 15.42. Found: N, 6.90; P, 15.52.

***N*-Ethyl-α-aminobenzylphosphonic Acid (6c).** The crude acid, mp 223–226 °C, was obtained in 68% yield. Recrystallization from water/ethanol gave pure phosphonic acid: mp 225–226 °C; NMR (D_2O) δ 1.25 (t, 3, J = 7 Hz, CH_3CH_2), 3.06 (q, 2, J = 7 Hz, CH_2CH_3), 4.35 (d, 1, J = 16 Hz, CHP), 7.50 (s, 5, PhH).

Anal. Calcd for $C_9H_{14}NO_3P$: C, 50.23; H, 6.51; N, 6.51; P, 14.42. Found: C, 50.68; H, 6.84; N, 6.60; P, 14.47.

***N*-*tert*-Butyl-α-aminobenzylphosphonic Acid (6d).** The crude acid was obtained in 80% yield. Recrystallization from aqueous ethanol gave pure acid **6d** (40%): mp 228–230 °C dec; NMR (D_2O) δ 1.33 (s, 9, CH_3), 4.63 (d, 1, J = 18 Hz, CHP), 7.60 (s, 5, PhH); ^{31}P NMR δ −10.1.

Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76; P, 12.76. Found: C, 54.84; H, 7.68; N, 6.06; P, 12.60.

***N*-Benzyl-α-amino-(4-chlorobenzyl)phosphonic Acid (6e).** The crude acid, mp 226–230 °C, was obtained in 87% yield. Recrystallization from acetic acid/water gave pure acid **6e,** mp 227–230 °C.

Anal. Calcd for $C_{14}H_{15}ClNO_3PH_2O$: C, 50.98; H, 5.16; N, 4.35; P, 9.41. Found: C, 51.46; H, 5.39; N, 4.50; P, 9.53.

***N*-Benzyl-α-amino(2-hydroxybenzyl)phosphonic Acid (6g).**[18] The crude acid was purified by the procedure of Zon and Mastalerz[18] to yield the pure phosphonic acid in 10% yield, mp 277–280 °C. The identity of the acid was verified by comparison with an authentic sample prepared as described by Zon and Mastalerz:[18] NMR (D_2O + NaOH) δ 3.70 (s, 2, CH_2N), 4.30 (d, 1, J = 17 Hz, CHP), 6.7–7.5 (m, 9, ArH); ^{13}C NMR δ 52.9, 59.7 (d, J = 135 Hz), 117.6, 119.1, 128.4, 128.8, 129.0, 129.9, 131.2, 131.6; ^{31}P NMR δ −16.9.

1,2,3,4-Tetrahydroisoquinolyl-1-phosphonic Acid (8). The crude acid separated as pale yellow needles from water (60%). Recrystallization gave analytically pure acid: mp 256–258 °C; NMR (D_2O) δ 1.5–3.2 (m, 4, CH_2), 4.11 (d, 1, J = 17 Hz CHP), 7.2–7.3 (m, 4, ArH); ^{31}P NMR δ −15.9 (J_{PCH} = 17 Hz); ^{13}C NMR (D_2O) δ 28.8 (C_4), 40.7 (C_3), 57.0 (d, J = 126 Hz, C_1) 126.6–130.0.

Anal. Calcd for $C_9H_{12}NO_3P$: C, 50.70; H, 5.63; N, 6.57; P, 14.55. Found: C, 51.05; H, 5.99; N, 6.30; P, 14.74.

***N*-Benzyl-1-amino-2-methylpropylphosphonic Acid.** The imine (18.9 g, 0.12 mol) derived from isobutyraldehyde and benzylamine was reacted with phosphorous acid (9.6 g, 0.12 mol) by the general method described above, but a modified workup procedure was applied as follows. The reaction mass was cooled to 85 °C and dissolved in water (40 mL). Concentrated HCl (20 mL) was added and the solution heated at reflux for 30 min. After cooling, the solution was basified and extracted with ether to yield benzyl isobutylamine: 10.3 g (54%); NMR ($CDCl_3$) δ 0.89 (d, 6, J = 6 Hz, CH_3), 1.4–2.2 (m, 1, CH), 2.43 (d, 2, J = 7 Hz, CH_2CH), 3.75 (s, 2, CH_2Ph), 7.28 (s, 5, ArH); ^{13}C NMR ($CDCl_3$) δ 20.7, 28.4, 54.2, 57.6, 126.7, 128.0, 128.2, 140.9. The hydrochloride from ethanol had mp 183–184 °C (lit.[19] 175–176 °C).

The basic aqueous solution was reacidified, evaporated to dryness, and extracted with anhydrous ethanol. The ethanol extract yielded

N-benzyl-1-amino-2-methylpropylphosphonic acid: 13.4 g (41%); mp 100–103 °C; NMR (D_2O) δ 1.05 (d, 6, J = 6 Hz, CH_3), 2.0–2.5 (m, 1, $CH(CH_3)_2$), 2.48 (d of d, 1, J = 15, 5 Hz, PCH), 3.97 (s, 2, CH_2Ph), 7.50 (s, 5, ArH); ^{31}P NMR (D_2O) δ −10.7; ^{13}C NMR (D_2O) δ 22.1, 23.0, 30.6, 53.8, 65.5 (d, J = 132 Hz, CP), 132.7, 133.1, 133.5, 134.5.

Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76; P, 12.76. Found: C, 54.54; H, 7.86; N, 5.42; P, 12.71.

Modification of the General Phosphonic Acid Procedure. (a) Effect of Added Acid. A mixture of the imine (**5f**) from isobutyraldehyde and benzylamine (0.1 mol), phosphorous acid (0.1 mol), and *p*-toluenesulfonic acid (0.1 mol) was heated with gentle stirring at 120–130 °C for 45 min. After cooling to 85 °C, water (35 mL) was added. ^{31}P NMR analysis of this solution showed one major peak at −12.9 ppm (phosphonic acid) and a minor peak at −4.7 ppm (phosphorous acid), but no evidence of phosphate. Ion exchange on Dowex 50-W and elution with water yielded *p*-toluenesulfonic acid. Elution with 5 N HCl yielded *N*-benzyl-1-amino-2-methylpropylphosphonic acid (**6f**) (90%), identical with that from the previous experiment.

(b) Effect of Added Base. A mixture of imine **5f** (0.13 mol), triethylamine (0.13 mol), and phosphorous acid (0.13 mol) was heated at 115–120 °C for 6 h. After cooling to 75 °C, water (45 mL) and HCl (40 mL) were added and the solution was heated at reflux before extraction of neutral and acidic components. Basification and extraction yielded *N*-benzylisobutylamine (15.9 g, 72%), bp 205–208 °C, identical with the sample above.

General Procedure for Reductive Methylations Using Formaldehyde/Phosphorous Acid. A solution of phosphorous acid (1 equiv) in 40% aqueous formaldehyde (1 equiv) was added dropwise to the amine (1 NH equiv) during 20–30 min with vigorous stirring and ice bath cooling to maintain a temperature of 15–25 °C. Following the addition, the reaction mixture was heated at reflux for 2 h. After cooling, the reaction mixture was basified and the amine recovered by ether extraction in the normal manner.

Benzyldimethylamine. Benzylamine was converted into benzyldimethylamine in 72% yield: bp 179–180 °C (lit.[20] 181 °C); picrate mp 88–89 °C (lit.[20] 93 °C); NMR ($CDCl_3$) δ 1.92 (s, 6, NCH_3), 3.12 (s, 2, CH_2Ph), 7.03 (s, 5, ArH).

Cyclohexyldimethylamine. Cyclohexyldimethylamine was obtained from cyclohexylamine in 55% yield: bp 156 °C (lit.[21] 159 °C); picrate mp 178–180 °C (lit.[21] 176–177 °C).

***N*-Methylmorpholine.** *N*-Methylmorpholine was obtained in 54% yield: bp 116 °C (lit.[20] 116–117 °C); picrate mp 224–226 °C (lit.[20] 225 °C); NMR ($CDCl_3$) δ 1.77 (s, 3, NCH_3), 2.07 (m, 4, NCH_2), 3.35 (m, 4, OCH_2).

***N*-Methylpiperidine.** Piperidine was converted into *N*-methylpiperidine in 40% yield: bp 106 °C (lit.[20] 107 °C); picrate mp 225–227 °C (lit.[20] 223–224 °C); NMR ($CDCl_3$) δ 1.52 (m, 6, CH_2), 2.26 (s, 3, NCH_3), 2.38 (m, 4, NCH_2).

Enamine Reductions. Preparation of *N*-Cyclohexylmorpholine (10). A mixture of morpholinocyclohexene (32.3 g, 0.19 mol) and phosphorous acid (15.9 g, 0.19 mol) was stirred and heated. As the temperature reached 90–100 °C, an exothermic reaction took place. The reaction mass was maintained at 95–100 °C for 30 min, cooled, diluted with water, basified, and extracted with ether. Evaporation of the ether extract yielded *N*-cyclohexylmorpholine (29.7 g, 91%): picrate mp 177–178 °C (lit.[22] 176–177 °C); NMR ($CDCl_3$) δ 1.0–2.2 (m, 11, CH_2, CH), 2.50 (m, 2, NCH_2), 3.66 (m, 2, OCH_2); ^{13}C NMR ($CDCl_3$) δ 25.7, 26.4, 29.0, 49.8, 63.6, 67.4.

***N*-Cyclopentylmorpholine.** A mixture of cyclopentenylmorpholine (30 g, 0.2 mol) and phosphorous acid (16.4 g, 0.2 mol) was stirred and heated. As the mixture reached 70–75 °C, an exothermic reaction ensued with a resulting viscosity increase. After heating at 100–105 °C for 30 min, the reaction mixture was dissolved in water, basified, and extracted with ether. Evaporation yielded *N*-cyclopentylmorpholine: 24 g (80%); picrate mp 163–164 °C (lit.[22] 159–162 °C); ^{13}C NMR ($CDCl_3$) δ 24.6, 30.0, 53.9, 68.0, 68.6.

1-Methyl-2-morpholinocyclohexane (12b and 13b). By the procedure described above the morpholine enamine of 2-methylcyclohexanone was reduced in 65% yield to a mixture of *cis*- and *trans*-1-methyl-2-morpholinocyclohexane (**12b** and **13b**): bp 105–106 °C (5.2 mm). GLC gives a cis/trans ratio of 81:19. Utilizing formic acid, a ratio of cis/trans of 87:13 was obtained.

1-Methyl-2-pyrrolidinocyclohexane (12a and 13a). The pyrolidine enamine of 2-methylcyclohexanone was reduced with phosphorous acid as above to a cis/trans mixture of 1-methyl-1-pyrrolidinocyclohexane (**12a** and **13a**) in 85% yield: bp 85–87 °C (5.1 mm). GLC gave a cis/trans ratio of 75:25.

1-Isobutylpiperidine. The enamine from isobutyraldehyde and piperidine was reduced by the above method to yield 1-isobutylpiperidine (68%): bp 159–160 °C (lit.[23] 160–162 °C); NMR ($CDCl_3$) δ 1.07 (d, 6, J = 6 Hz, CH_3), 1.4–1.8 (m, 7, CH_2, CH), 2.0–2.5 (m, 6, NCH_2). The amine yielded a picrate, mp 145–146 °C (lit.[23] 144–145 °C).

Phosphorylation Using Phosphorous Acid. Phosphorylation of 1-Butanol. Phosphorous acid (8.2, 0.1 mol) was added to morpholinocyclohexene (16.6 g, 0.1 mol) in butanol (16 g, 0.216 mol), and the mixture was heated at 110 °C for 30 min. After the reaction, the mixture was dissolved in ethanol (30 mL) and ether (100 mL) was added. The ether phase was discarded and the ether-insoluble portion dissolved in water (50 mL). Passage of the aqueous solution through Dowex 50-W ion-exchange resin and elution with water yielded butyl phosphate (13.3 g, 86%). The monoanilinium salt from ethanol gave mp 133–135 °C (lit.[10a] 138–140 °C); NMR (D_2O) δ 0.93 (t, 3, J = 7 Hz, CH_3), 1.1–1.7 (m, 4, CH_2), 3.82 (q, 2, OCH_2), 7.47 (m, 5, PhH); ^{31}P NMR (D_2O) δ 0.5; ^{13}C NMR (D_2O) δ 14.2, 19.5, 33.2 (d, J = 7 Hz), 67.0 (d, J = 5, 5 Hz), 124.0, 130.2, 131.3. Elution with 4 N HCl yielded *N*-cyclohexylmorpholine as its hydrochloride (11 g, 66%).

Phosphorylation of Benzyl Alcohol. Following the above procedure, benzyl phosphate was obtained in 90% yield (based on phosphorous acid) upon elution from Dowex 50-W ion-exchange resin. The phosphate was characterized as its anilinium salt: mp 150–153 °C (from ethanol) (lit.[10a] mp 150–153 °C); ^{31}P NMR (D_2O) δ 0.3; ^{13}C NMR (D_2O) δ 68.3, 122.3, 127.6, 128.8, 129.3, 129.9, 131.2, 132.0.

***N*-Benzylmorpholine.** A mixture of benzaldehyde (24 g, 0.22 mol), morpholine (19.1 g, 0.22 mol), phosphorous acid (18.0 g, 0.22 mol), and water (75 mL) was heated under reflux for 8 h. The basic fraction was separated to yield *N*-benzylmorpholine (7.2 g, 18%): hydrochloride, from ethanol, mp 245–246 °C (lit.[20] 243 °C).

Anal. Calcd for $C_{11}H_{15}NOHCl$: N, 6.56; Cl^-, 16.63. Found: N, 6.30; Cl^-, 16.16.

***N*-Benzylcyclohexylamine.** Under the general conditions for phosphonic acid formation, the imine from cyclohexanone and benzylamine underwent mainly reduction. Distillation of the basic extract gave benzylamine (15%) and *N*-benzylcyclohexylamine (65%): bp 120–125 °C (3 mm); NMR ($CDCl_3$) δ 1.0–1.6 (m, 10, CH_2), 2.4 (m, 1, CHN), 3.67 (s, 2, CH_2Ph), 7.03 (s, 5, PhH); hydrochloride mp 252–254 °C (lit.[24] 252–253 °C).

Registry No.—**5a,** 780-25-6; **5b,** 622-29-7; **5c,** 6852-54-6; **5c,** 6852-58-0; **5e,** 13540-93-7; **5f,** 22483-21-2; **5g,** 886-08-8; **6a,** 25881-35-0; **6b,** 36032-68-5; **6c,** 64760-70-9; **6d,** 64760-69-6; **6e,** 64760-71-0; **6f,** 64760-72-1; **6g,** 61146-25-6; **7,** 3230-65-7; **8,** 64760-73-2; **9,** 670-80-4; **10,** 6425-41-8; **11a,** 5049-40-1; **11b,** 6127-98-6; **12a,** 36949-94-7; **12b,** 64760-74-3; **13a,** 36949-95-8; **13b,** 64760-75-4; isobutyraldehyde, 78-84-2; benzylamine, 100-46-9; benzylisobutylamine, 42882-36-0; cyclopentenylmorpholine, 936-52-7; benzyldimethylamine, 103-83-3; *N*-methylmorpholine, 109-02-4; morpholine, 110-91-8; piperidine, 110-89-4; *N*-methylpiperidine, 626-67-5; *N*-cyclopentylmorpholine, 39198-78-2; 1-piperido-2-methyl-prop-1-ene, 673-33-6; 1-isobutylpiperidine, 10315-89-6; butanol, 71-36-3; butylphosphonate aniline salt, 64760-76-5; benzyl alcohol, 100-51-6; benzylphosphonate aniline salt, 64760-77-6; benzaldehyde, 100-52-7; *N*-benzylmorpholine HCl, 64760-78-7; cyclohexanone, 108-94-1; *N*-benzylcyclohexylamine, 4383-25-9; phosphorous acid, 13598-36-2; cyclohexyldimethylamine, 98-94-2; cyclohexylamine, 108-91-8; butyl phosphonate, 16456-56-7; benzyl phosphonate, 10542-07-1.

Supplementary Material Available. Calculated ^{13}C spectra of 1-methyl-2-morpholinocyclohexane are presented in Table V (1 page). Ordering information is given on any current masthead page.

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Notes

N-Benzyl-α-amino Phosphonic Acids

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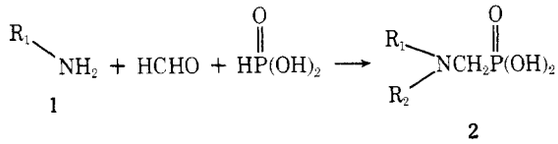
The Mannich-type reaction of amines with formaldehyde and phosphorous acid is a very useful procedure for the preparation of aminomethylenephosphonic acids.[1] One of the limitations of this procedure is that primary amines (**1**) treated with 1 equiv of formaldehyde and phosphorous acid yield a mixture of mono- and bis(methylenephosphonic) acids (**2a** and **2b**).[2] A further limitation appears to be in the choice of

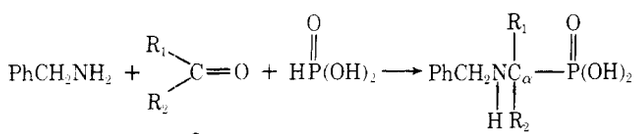


1 **2**

a, $R_2 = H$
b, $R_2 = CH_2P(=O)(OH)_2$

carbonyl component; all examples reported use formaldehyde with one exception in a patent.[3]

In light of the above, the recent report[4] that benzylamine reacts with a series of carbonyl compounds (**3a–d**) to yield



3 **4**

a, $R_1 = R_2 = H$
b, $R_1 = R_2 = CH_3$
c, $R_1 = CH_2CH_3$; $R_2 = H$
d, $R_1 = CH_2CH_3$; $R_2 = CH_3$

monophosphonic acids **4a–d** and, in particular, that best yields are obtained upon reacting 2 equiv of **3** and phosphorous acid for each equivalent of benzylamine is unexpected. Furthermore, the dissociation constants reported for these phosphonic acids are significantly different from those of other α-amino phosphonic acids.[2b] The present work was, therefore, undertaken in an attempt to resolve these discrepancies.

In our hands benzylamine heated with acetone, propionaldehyde or methyl ethyl ketone, and phosphorous acid by the procedure of Szczepaniak[4] yielded white crystalline products. The ^1H NMR spectra of these products showed only two peaks, at δ 4.2 and 7.5, in the ratio 2:5. Basification of these solids liberated benzylamine, showing that the solids were benzylamine salts. Careful examination of the mother liquors from the crystallization by ^{31}P NMR yielded no evidence for the presence of even traces of phosphonic acids. In the case of formaldehyde the only product isolated was the bis(methylenephosphonic) acid **2b** (R_1 = $PhCH_2$–).

Authentic samples of the phosphonic acids **4a–d** were obtained by hydrolysis of the corresponding ethyl or isopropyl esters **5a–d** prepared by the method of Fields.[5] In the hydrolysis of the esters **5b** and **5d**, some degradation was observed resulting in the recovery of benzylamine. The ^{13}C and ^{31}P NMR spectra of the acids **4a–d**, as shown in Table I, provided proof of structure together with other analytical data.

The dissociation constants of the acids **4a–d** were measured by potentiometric titration. Table II summarizes the results of our measurements and includes for comparison the results of Szczepaniak[4] and some other data from the literature for α-amino phosphonic acids.[6] It can be seen that the results from the present study are consonant with results from other workers.[6]

We conclude that the phosphonic acids **4a–d** cannot be prepared by the direct route from phosphorous acid and that the acids, when obtained by an authentic process, yield the expected acid dissociation constants.

Experimental Section

Melting points are uncorrected. The elemental analyses were performed by Clark Microanalytical Laboratories and Petrolite Corpo-

Table I. ^{31}P and ^{13}C NMR Data for α-Amino Phosphonic Acids

Registry no.	Compd	R_1	R_2	δ ^{31}P[a]	δ ^{13}C[b] (J_{C-P}, Hz)		
					C_α	R_1	R_2
49622-09-5	**4a**	H	H	−16.6	53.1 (138)		
49622-10-8	**4b**	CH_3	CH_3	−15.4	59.8 (136)	25.1	25.1
26067-66-3	**4c**	CH_2CH_3	H	−17.3	65.2 (135)	29.9, 18.5	
49622-12-0	**4d**	CH_2CH_3	CH_3	−14.8	62.9 (143)	26.9, 8.4 (6)	19.7

[a] Relative to 85% H_3PO_4 internal reference. [b] Relative to Me_4Si internal reference.

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