action series constants ρ^* listed in Table II. Others[1-3,8] have postulated that hydration is proportional to the number of hydrated $\overset{+}{N}$–H groups in the ammonium ion. That hydration is directly proportional to the number of $\overset{+}{N}$–H groups (condition d) is supported by the fact that a single hydration constant, H, is applicable to all classes of amines; the use of a single constant H for both the aliphatic and aromatic amines also implies that the hydration of a single $\overset{+}{N}$–H group is little affected by the electron density on the amino nitrogen.

The effect of steric hindrance on base strength of aliphatic amines has been discussed by Hall.[1,9] For aromatic amines, steric hindrance to solvation (base weakening) may occur as in the aliphatic series; in addition, steric inhibition of resonance (base strengthening) may take place. Benzoquinuclidine appears to be a clear example of this latter effect.[10] In fact, if this compound is considered an "aliphatic" tertiary amine ($n = 0$), the correlation with eq. 1 is good (pK_a 7.79; pK_a 7.60, calcd. from eq. 1).

(8) R. W. Taft, Jr., *J. Am. Chem. Soc.*, **82**, 2965 (1960).
(9) H. K. Hall, Jr., *ibid.*, **79**, 5444 (1957).
(10) B. M. Wepster, *Rec. trav. chim.*, **71**, 1171 (1952).

The deviation of the *t*-butylanilines (compounds 13 and 26) can be abscribed to steric inhibition of resonance, however, neither pK_a value was determined at 25°. In view of the deviation of N-*t*-amylaniline (compound 12) it would seem that steric factors alone cannot explain the deviation of the N-*t*-butylanilines.

In order to obtain the correlation of the data by eq. 1 using a single adjustable parameter, H, the value of ρ^* (3.23 ± 0.05) for the 3° aliphatic amines was used. It was then assumed that the correlation line for the aliphatic amines would pass through the trimethylamine point. This method permits the evaluation of H by eq. 2 and gives the value of −1.12 ± 0.14.

$$H = \frac{\Sigma[\log K/K_0 - 3.23(\Sigma\sigma^*)]}{\Sigma(n)} \qquad (2)$$

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A New Synthesis of Amino Phosphonic Acids[1]

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A new synthesis of amino phosphonic acids has been developed, involving the Curtius degradation of substituted diethyl phosphonoacetylhydrazides. This appears to be a general synthesis for 1-aminoalkylphosphonic acids since aminomethylphosphonic (glycine analog), 1-aminoethylphosphonic (alanine analog), and 1-amino-2-phenylethylphosphonic (phenylalanine analog) acids were synthesized in this manner successfully. Two additional phosphonic acid analogs of the naturally occurring amino carboxylic acids also were synthesized by special methods. These were 2-amino-4-phosphonobutyric acid (a glutamic acid analog) and 2-amino-3-phosphonopropionic acid (an aspartic acid analog). An improved isolation procedure for amino phosphonic acids is described and the over-all yields of the three amino acids produced by the Curtius degradation were 56–80%, based on the parent phosphonoacetic esters.

Kabachnik and Medved[3] have described what appears to be a general method for producing 1-aminoalkylphosphonic acids. They condensed both aldehydes and ketones with ammonia and a dialkyl phosphonate to give dialkyl esters of 1-aminoalkylphosphonic acids. Hydrolysis of the esters produced the free amino acids. Kabachnik and Medved did not prepare any phosphonic acid analog of a naturally occurring amino acid and their method gave over-all yields of 40% or less. Chalmers and Kosolapoff[4] used the same method for preparing 1-amino-2-phenylethylphosphonic acid (phenylalanine analog) and 1-aminoethylphosphonic acid (α-alanine analog) as well as a number of additional similar products. Their over-all yields were never greater than 41.5%. Aminomethylphosphonic acid (glycine analog) has been prepared by the ammonolysis of halomethylphosphonic acid esters[5] and by condensing N-(bromomethyl)phthalimide with dibutyl sodiophosphonate, followed by the hydrolysis of the resulting product.[4,6]

Since so few phosphonic acid analogs of the naturally occurring amino carboxylic acids have been prepared, it seemed desirable to consider the synthesis of additional ones. However, Kabachnik and Medved's method suffers from serious deficiencies—many of the aldehydes necessary for the synthesis of additional 1-aminoalkylphosphonic acids are not available readily and the yields of the phosphonic acids prepared by this method have been relatively poor. We report the first use of the Curtuis reaction[7] for the preparation of 1-amino-

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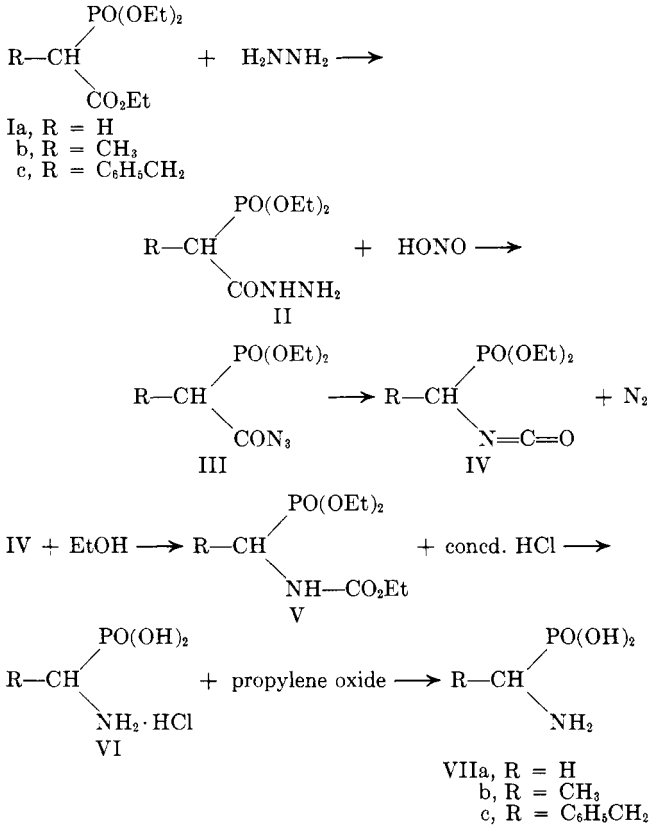
(2) Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the A. and M. College of Texas, Aug., 1958; Department of Chemistry, Walla Walla College, College Place, Wash.
(3)(a) M. I. Kabachnik and T. Ya. Medved, *Dokl. Akad. Nauk SSSR*, **83**, 689 (1952); (b) M. I. Kabachnik and T. Ya. Medved, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, 868 (1953); (c) T. Ya. Medved and M. I. Kabachnik, *ibid.*, 314 (1954).
(4) M. E. Chalmers and G. M. Kosolapoff, *J. Am. Chem. Soc.*, **75**, 5278 (1953).
(5) (a) M. I. Kabachnik and T. Ya. Medved, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 635 (1950); (b) M. I. Kabachnik and T. Ya. Medved, *ibid.*, 95 (1951).
(6) V. Chavane, *Bull. soc. chim. France*, 774 (1948).
(7) P. A. S. Smith, "Organic Reactions," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 337.



alkylphosphonic acids, thus avoiding some of the limitations of the earlier syntheses.

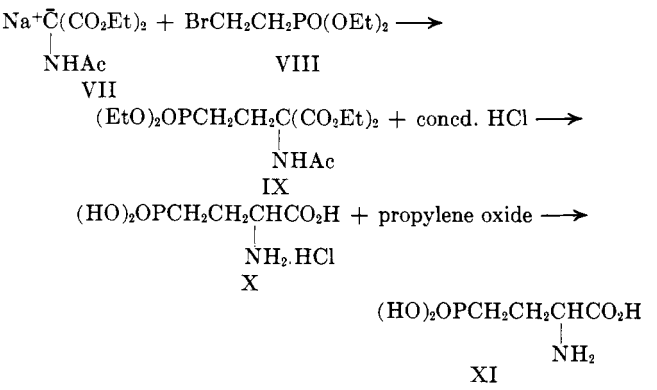
Apparently the key step in this synthesis was the condensation of hydrazine with the phosphonoacetic esters (I). This reaction usually was mildly exothermic, but for the less reactive esters it appeared desirable to heat the mixture at 40–50°. For reasons not yet determined, heating the mixture to 100° usually resulted in the isolation of none of the desired product. No attempt was made to isolate intermediates II–VI. Hydrolysis of crude V gave a viscous residue believed to be VI. It was noted that continued heating of this viscous residue *in vacuo* resulted in the liberation of hydrogen chloride and the production of the free amino acid (VII). This is not surprising since the phosphonic acid group is a relatively strong acid. However, the preferred method of isolating the amino acid (VII) was to leave sufficient hydrochloric acid in the crude residue so that the residue dissolved completely in 95% ethanol. To this ethanolic solution was added propylene oxide or butylene oxide slowly until no chloride ion remained. The amino acid (VII) separated from solution occasionally as an oil which quickly solidified, and the solid was of sufficient purity that it often required only one recrystallization to produce an analytically pure product.

From Ia, VIIa has been recovered in an over-all yield of 54%, VIIb has been produced from Ib in an over-all yield of 80%, and VIIc has been produced from Ic in an over-all yield of 56%. It is believed that further studies of these reactions may result in additional increases in yields.

The phosphonoacetic esters (I) can be produced readily by two routes. One involves the Arbuzov reaction between triethyl phosphite and ethyl chloroacetate to give Ia,[8] followed by the alkylation of Ia by the method of Kosolapoff and Powell.[9] This method gave approximately a 40% yield of the monoalkylated product, plus a small amount of what appeared to be the dialkylated product when benzyl chloride was employed as the alkylating agent.

The second and preferred synthesis of Ib was that of Ackerman and co-workers.[10] Ib was obtained in 83% yield from ethyl 2-bromopropionate and triethyl phosphite. Ib cannot be produced satisfactorily by the alkylation method of Kosolapoff and Powell[9] because a mixture of the unalkylated, the monoalkylated, and the dialkylated phosphonoacetic esters results, and all three of these compounds have virtually identical boiling points.

The synthesis of 2-amino-4-phosphonobutyric acid was accomplished by first condensing diethyl 2-bromoethylphosphonate with the sodium derivative of diethyl acetamidomalonate to give what was undoubtedly the desired substituted malonate (IX). Without attempting to isolate IX, the crude product from the first step was hydrolyzed by heating with concentrated hydrochloridic acid, and, after removal of the excess acid, the crude X, dissolved in 95% alcohol, was treated with an excess of propylene oxide. XI was recovered in an over-all yield of 46% from diethyl acetamidomalonate.



At times, recrystallization of XI from alcohol–water and other purification procedures failed to give pure XI. Finally an excellent chromatographic method was devised, involving the use of an ion-exchange resin. This method also worked well for purifying 2-amino-3-phosphonopropionic acid (XV).

Kamai and Kukhtin[11] described the esterification of carboxylic acids with trialkyl phosphites; with acrylic acid, simultaneous esterification and addition of the resulting dialkyl phosphonate to the C to C double bond occurred, forming trialkyl 3-phosphonopropionate. Thus, it appeared that a trialkyl phosphite might react with 2-acetamidoacrylic acid[12] (XII) to give a derivative of a phosphonic acid analog of aspartic acid. Such a reaction occurred when XII was heated with a mixture of trimethyl phosphite and dimethyl phosphonate. It is believed that the first reaction produced methyl 2-acetamidoacrylate (XIII) and this compound in turn condensed with dimethyl phosphonate to produce trimethyl 2-acetamido-3-phosphonopropionate (XIV). The hydrolysis of crude XIV gave 2-amino-3-

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(9) G. M. Kosolapoff and J. S. Powell, *J. Am. Chem. Soc.*, **72**, 4198 (1950).

(10) B. Ackerman, R. M. Chladek, and D. Swern, *ibid.*, **79**, 6524 (1957).

(11) G. Kamai and V. A. Kukhtin, *Khim. i Primenenie Fosfororgan. Soedin. Akad. Nauk SSSR Kazansk. Filial Tr. 1-Konf.*, 91 (1955).

(12) T. Wieland, G. Ohnancker, and W. Ziegler, *Ber.*, **90**, 194 (1957).

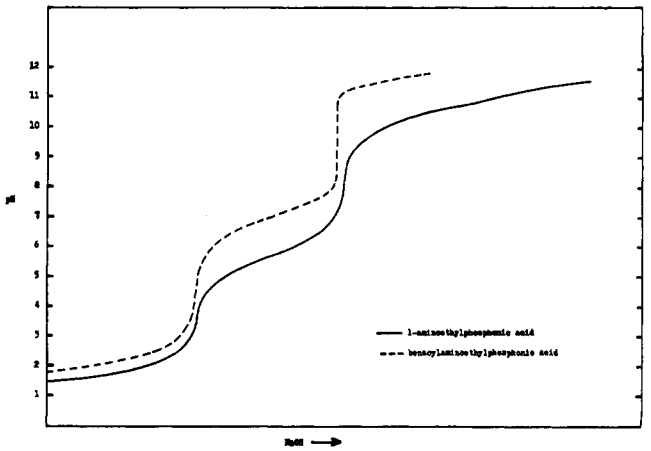

Fig. 1.—Titration curves for amino phosphonic acids and derivatives.

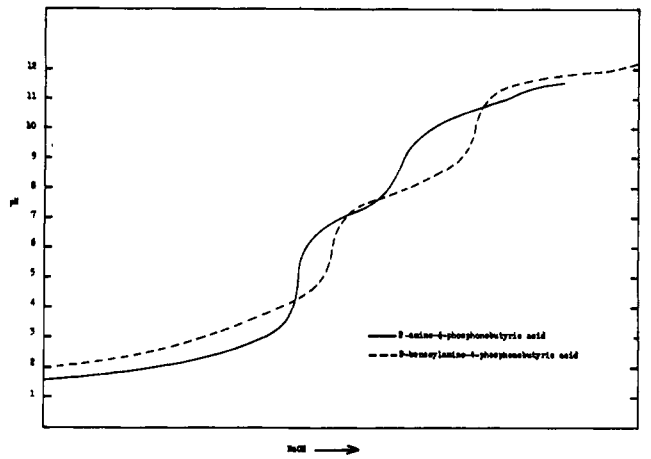

Fig. 2.—Titration curves for amino carboxy phosphonic acids and derivatives.

$$CH_2{=}CCO_2H + P(OMe)_3 \longrightarrow \underset{\underset{XII}{NHAc}}{\phantom{CH_2{=}CCO_2H}}$$

$$CH_2{=}\underset{\underset{XIII}{NHAc}}{CCO_2Me} + HPO(OMe)_2 \longrightarrow (MeO)_2OPCH_2\underset{\underset{XIV}{NHAc}}{CHCO_2Me}$$

$$XIV + \text{concd. HCl} + \text{propylene oxide} \longrightarrow$$

$$(HO)_2OPCH_2\underset{\underset{XV}{NH_2}}{CHCO_2H}$$

phosphonopropionic acid (XV) in a 50% over-all yield from XII.

Since our melting points for 1-aminoethylphosphonic acid and 1-amino-2-phenylethylphosphonic acid were in serious disagreement with values reported earlier,[4] all five of the amino acids were converted into the N-benzoyl derivatives. The benzoyl derivative of XV was an amorphous solid for which no suitable solvent could be found for recrystallization. The remaining derivatives were thoroughly purified and then hydrolyzed back to the parent amino acids.

Potentiometric titrations were carried out with the amino phosphonic acids and the N-benzoyl derivatives. All five amino acids gave two sharp breaks in the titration curves and one very weak break, as illustrated by the curves for 1-aminoethylphosphonic acid and 2-amino-4-phosphonobutyric acid in Fig. 1 and 2. The N-benzoyl derivatives of VIIa, b, c, and XI gave two sharp breaks in the titration curve (Fig. 1 and 2). It should be noted that in the titration curve of the N-benzoyl derivative of XI, the first break corresponded to the neutralization of two acid groups.

Since XI and XV are 2-amino carboxylic acids, it was not surprising that they gave positive ninhydrin tests. However, the ninhydrin tests on the remaining three amino acids were also positive. The intense characteristic violet color was produced only after adding a small amount of sodium bicarbonate to neutralize the excess acidity. Since the formation of free ammonia is believed to be one step in the production of the color in the ninhydrin test, the requirement of a slightly basic solution to produce an intense color seems reasonable. That a more or less normal ninhydrin reaction was taking place with VIIc was indicated by the fact that the characteristic odor of phenylacetaldehyde was noted soon after the reaction started. This surprising cleavage of the C to P bond was further confirmed by the positive identification of phosphate ion in the solution following the ninhydrin test on VIIa.

Experimental

All melting points were determined with a Hershberg apparatus and are corrected. Boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. All reagents were the best grade available and were used generally without further purification.

Determination of Neutralization Equivalents.—Potentiometric titrations of the amino phosphonic acids and their N-benzoyl derivatives were carried out with a Beckman Zeromatic pH meter and with a Model D Sargent automatic titrator.

The amino acid, dissolved in water containing 1 mole of hydrochloric acid per mole of amino acid, was titrated with 0.1 *N* sodium hydroxide. The N-benzoyl derivatives were dissolved in water or 50% alcohol and titrated with 0.1 *N* sodium hydroxide. Curves similar to those shown in Fig. 1 and 2 resulted.

Since the amino phosphonic acids gave only two sharp breaks after the addition of excess hydrochloric acid, the neutralization equivalents were calculated from the amount of base required to go from the first to the second break. The first break corresponded to the isoelectric points for Ia, Ib, and Ic but not for XI and XV. Thus, these neutralization equivalents are actually molecular weights.

The neutralization equivalents of the N-benzoyl derivatives were determined from the amount of base required to go to the second sharp break. Since this corresponded to 2 equiv. of base for the Ia, Ib, and Ic derivatives and 3 equiv. of base for the derivative of XI, these were conventional neutralization equivalents.

Aminomethylphosphonic Acid (VIIa).—A mixture of 22.4 g. (0.1 mole) of triethyl phosphonoacetate,[8] b.p. 121–123° (4 mm.), $n^{30}D$ 1.4280, and 3.7 g. (0.11 mole) of 95+% hydrazine was stirred vigorously in a flask protected from moisture. The temperature of the mixture rose spontaneously to 48°. The homogeneous solution was heated to 75° and then allowed to cool to room temperature over a 24-hr. period. The suspension which resulted when 100 ml. of anhydrous ether was added with vigorous stirring was cooled to 0° and 20.5 ml. of 6 *N* hydrochloric acid was added dropwise at 0°. A white solid separated. The temperature was decreased to −10° and a solution of 8.3 g. (0.12 mole) of sodium nitrite in 15 ml. of water was added dropwise. After stirring for 10 min. longer at −10°, the resulting two layers were separated rapidly and the water layer was extracted with four 50-ml. portions of ether. To the combined ether extracts was added 50 ml. of absolute ethanol. This solution slowly evolved gas as it warmed to room temperature. Standing over night usually resulted in the separation of a small amount of white solid which was removed by filtration. The ether and excess alcohol were removed by distillation, leaving a somewhat viscous residue. To this residue was added 100 ml. of concentrated

hydrochloric acid and the resulting solution was heated under reflux for 2 days. The hydrolysate was treated with carbon to remove a small amount of dark-colored oil and was evaporated nearly to dryness on a steam bath under vacuum. A small excess of hydrochloric acid should remain in this viscous residue as this point in order for it to be completely soluble in 95% ethanol. If the residue were heated at reduced pressure for a prolonged period of time, increasing quantities of the residue failed to dissolve in alcohol. Aminomethylphosphonic acid and the other related amino phosphonic acids appeared to give hydrochloride salts in solution, but all attempts to isolate dry hydrochloride salts have given only the free amino acid.

The hydrolysate residue, containing excess hydrochloric acid, was dissolved in 100 ml. of 95% ethanol, and to this solution was added propylene oxide[13] or butylene oxide[13] dropwise with good stirring until there was no further precipitation of the amino acid. At times the precipitate was at first gummy but became granular on standing. This solid was collected on a filter, washed with ethyl alcohol, and dried in a vacuum oven. It was purified further by dissolution in a small quantity of hot water, filtration to remove any insoluble solid, followed by the addition of ethyl alcohol to the hot filtrate with good stirring until the separation of crystalline solid ceased. After chilling, the mixture was filtered and the solid was washed with ethyl alcohol and dried; it weighed 6.0 g. (54% over-all yield from triethyl phosphonoacetate). The titration curve showed two sharp breaks, the first at pH 3.45 (isoelectric point) and the second at pH 7.85. The neutralization equivalent found was 114 (calcd. 111) and this compound melted at 286.5° dec., lit.[5a] m.p. 310°.

A 3-g. portion of the amino acid was converted into the N-benzoyl derivative by the method of Staiger[14] utilizing 4.2 g. of benzoyl chloride and 29 ml. of 2 *N* sodium hydroxide. The resulting solution was brought to pH 2 with dilute hydrochloric acid and was extracted with ether, and the water layer was evaporated to dryness on a steam bath under vacuum. The product was extracted from the residue with 100 ml. of hot ethyl alcohol, but it was found that the extract contained sodium ions which could not be removed by recrystallizations. Therefore, the alcohol solution was evaporated to dryness, the residue was dissolved in 20 ml. of water, and this solution was passed through Dowex 50 resin in the H^+ form. The eluate was evaporated to dryness *in vacuo*, and the residue was recrystallized several times from glacial acetic acid and finally from ethyl alcohol. The white crystals melted at 179–180°, lit.[15] m.p. 182°; the neutralization equivalent found was 109 (calcd. 107.5).

A portion of the benzoylaminomethylphosphonic acid was hydrolyzed by heating with concentrated hydrochloric acid for 48 hr. After removing the benzoic acid by extraction with ether, the water layer was evaporated almost to dryness and the free amino acid was recovered by solution in ethyl alcohol, followed by treatment with propylene oxide. The melting point of this recovered amino acid was 286.5° dec.

1-Amino-2-phenylethylphosphonic Acid (VIIc).—This compound was synthesized by essentially the same method as compound VIIa When 31.4 g. of triethyl β-phenyl-α-phosphonopropionate[9] was mixed with 3.7 g. of hydrazine, there was only about a 3° rise in temperature, and the mixture did not become completely homogeneous for a number of hours. Since VIIb was only slightly soluble in water, the crude amino acid was dissolved in approximately 1 l. of boiling water, the solution was filtered, and the filtrate was diluted with alcohol until crystallization started and then was chilled. There was recovered 11.3 g. of white crystals (56% yield from Ic), m.p. 281° dec., lit.[4] m.p. 225–227°. The titration curve produced two sharp breaks, one at pH 3.8 (isoelectric point) and the second at pH 7.5; the neutralization equivalent found was 192 (calcd. 201).

The N-benzoyl derivative, prepared as described for compound VIIa, was only slightly soluble in water. In order to remove sodium ions completely, an alcoholic solution was passed through the Dowex 50 resin. The product was purified further by recrystallization from water, producing a white solid, m.p. 207–208°. When this derivative was titrated in a 50% alcohol solution, there was a sharp break at pH 5 and a less distinct one at approximately pH 10.

Anal. Calcd. for $C_{15}H_{16}NO_4P$: C, 59.01; H, 5.28; P, 10.15; neut. equiv., 152.5. Found: C, 58.99, 59.15; H, 5.44, 5.45; P, 10.27, 10.36; neut. equiv., 156.5.

When this benzoyl derivative was hydrolyzed, the parent amino acid was recovered, m.p. 281° dec.

Anal. Calcd. for $C_8H_{12}NO_3P$: C, 47.76; H, 6.01; P, 15.40. Found: C, 47.83, 47.65; H, 6.02, 6.24; P, 15.48, 15.42.

1-Aminoethylphosphonic Acid (VIIb).—A study was made of the conditions required to produce the best yield of this compound. The following is the procedure which gave consistently good results. To 32 g. (1 mole) of 95+% hydrazine, contained in a 250-ml. three-necked flask fitted with a good stirrer, dropping funnel, and drying tube, was added 119 g. (0.5 mole) of triethyl α-phosphonopropionate[8a,10] dropwise. The reaction temperature increased rapidly to 40° and was controlled at this point by the rate of addition of the ester After standing overnight, a 1-mm. vacuum was applied, while the mixture was heated to 50°. The clear, viscous residue was dissolved in 56 ml. of water, 500 ml. of absolute ether was added, and the mixture was cooled to −10°. At this temperature, 56 ml. of concentrated hydrochloric acid was added, followed by a solution of 46.7 g. of sodium nitrite dissolved in 88 ml. of water. After stirring for 5 min. longer, the layers were separated and the cold water was extracted twice with 100-ml. portions of ether. The ether extracts were added to 250 ml. of absolute ethanol and this solution was allowed to stand overnight. After filtration, the filtrate was concentrated to dryness under vacuum. There remained 106.1 g. of viscous residue. To this residue was added 100 ml. of water and 300 ml. of concentrated hydrochloric acid, and the solution was heated under reflux for 36 hr. After treating the hydrolysate with carbon, the filtrate was evaporated almost to dryness at reduced pressure and the residue was dissolved in 95% ethanol. The amino acid was recovered by treatment with propylene oxide, yielding 50 g. of solid (80% from Ib) which was in a high state of purity without additional recrystallization. A quantity of this product was purified further by dissolution in a small quantity of water, followed by the addition of alcohol. The pure compound had a melting point of 283–285° dec. and has been reported[4] to melt above 340°. A potentiometric titration produced two sharp breaks at pH 3.6 (isoelectric point) and pH 8.2 (Fig. 1).

Anal. Calcd. for $C_2H_8NO_3P$: C, 19.20; H, 6.44, P, 24.77; neut. equiv., 125. Found: C, 19.28; 19.08; H, 6.57, 6.31; P, 24.65, 24.83; neut. equiv., 123.

The N-benzoyl derivative was prepared as described for compound VIIa. The deionized product was recrystallized from ethyl acetate containing a trace of acetic acid. The derivative melted at 183° dec.

Anal. Calcd. for $C_9H_{12}NO_4P$: C, 47.16; H, 5.28; P, 13.52; neut. equiv., 114.5. Found: C, 47.15, 47.35; H, 5.33, 5.19; P, 13.70, 13.59; neut. equiv., 115.5.

Hydrolysis of this benzoyl derivative produced 1-aminoethylphosphonic acid, m.p. 283–285° dec.

2-Amino-4-phosphonobutyric Acid (XI).—The sodium derivative of diethyl acetamidomalonate was prepared from 120 ml. of absolute ethanol, 6.9 g. of sodium metal, and 65.1 g. of diethyl acetamidomalonate. About 115 ml. of ethanol was distilled from this solution, 150 ml. of dry toluene was added, and the distillation was continued. When the last of the ethanol was removed, a tan solid separated and broke into small particles by the action of the Hershberg stirrer. An additional 100 ml. of dry toluene was added and the distillation was continued until approximately 150 ml. of toluene had distilled. To the suspension, 125 ml. of diethyl carbonate was added, causing the tan solid to form a well-dispersed suspension. To this finely divided suspension was added 80 g. of diethyl β-bromoethylphosphonate[16] and the stirring was continued for 2 hr. at 115°. The reaction temperature was lowered to 85° and the suspension was held at this temperature for an additional 11 hr. The mixture was filtered hot to remove sodium bromide, the solvent was removed from the filtrate at 30-mm. pressure, and distillation was then continued at 1 mm. until the temperature of the distilling vapors reached 145°. Since the viscous distillation residue showed no tendency to distil or to crystallize, it was heated under reflux with 200 ml. of 6 *N* hydrochloric acid for 22 hr. After concentrating this solution nearly to dryness under vacuum, 150 ml. of water was added, and the dark color was removed by treating the solution

(13) Supplied through the courtesy of The Dow Chemical Co.

(14) R. E. Staiger, *J. Org. Chem.*, **9**, 396 (1944).

(15) M. Engelmann and J. Pikl, U. S. Patent 2,304,156 (1942).

(16) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **70**, 1971 (1948).

with activated charcoal.[17] The decolorized solution was evaporated almost to dryness and the residue was dissolved in 200 ml. of 80% ethanol. If necessary, a few drops of hydrochloric acid was added to make the residue completely soluble in the alcohol solution. Addition of propylene oxide precipitated 28 g. (46% from diethyl acetamidomalonate) of product, which at times could not be purified completely by recrystallization from water. Preferably the crude solid was dissolved in a minimum of water, and the solution was passed through 400 ml. of Dowex 50W-X8 resin (H^+ form). A strongly acidic impurity passed through rapidly, washing with distilled water caused the eluate to become neutral, and more water caused XI to be eluated as a mildly acidic eluate. Finally, washing the column with 3 *N* hydrochloric acid removed a small amount of an amino acid impurity that was not identified. Evaporation of the XI eluate to a small volume, adding alcohol until the hot solution began to cloud, followed by chilling produced highly purified XI as a white solid, m.p. 226° dec. Titration of this compound gave no break at the isoelectric point, pH 2.1, but gave moderately strong breaks at pH 4.8 and 8.7 and a weak break at pH 11 (Fig. 2).

Anal. Calcd. for $C_4H_{10}NO_5P$: C, 26.24; H, 5.50; P, 16.92; neut. equiv., 183. Found: C, 26.30, 26.23; H, 5.63, 5.58; P, 16.78, 16.82; neut. equiv., 185.

For some reason, the first preparation of the N-benzoyl derivative gave a solid, m.p. 205.5°, from water, but subsequent preparations, after alternate recrystallizations from water and from dioxane, melted at 197°. A potentiometric titration of this compound produced the first sharp break at pH 6.0, the amount of base consumed being twice that required for attaining the second break in the titration curve at pH 10.2. Thus, the first end point included the neutralization of two acidic hydrogens (Fig. 2).

Anal. Calcd. for $C_{11}H_{14}NO_8P$: C, 46.00; H, 4.91; P, 10.79; neut. equiv., 95.7. Found: C, 45.77, 45.83; H, 4.45, 4.98; P, 10.73, 10.65; neut. equiv., 95.7.

Hydrolysis of the benzoyl derivative produced XI, m.p. 226° dec.

2-Amino-3-phosphonopropionic Acid (XV).—A mixture of 12.9 g. (0.10 mole) of N-acetyl-α-aminoacrylic acid[12] (XII), 12.4 g. (0.10 mole) of trimethyl phosphite, and 14 ml. of dimethyl phosphonate was heated on a steam bath until XII had dissolved. This required 10–15 min. The solution was heated for an additional 60 min. on the steam bath and then was allowed to stand at room temperature for 36 hr. Volatile materials were removed by heating the mixture to 130° in a dibutyl phthalate bath at a pressure of 0.7 mm. The residue was hydrolyzed by refluxing with 130 ml. of concentrated hydrochloric acid for 55 hr. The hydrolysate was filtered to remove a small amount of dark, insoluble material and the filtrate was evaporated almost to dryness *in vacuo*. The residue was dissolved in 200 ml. of water and the hot solution was treated with carbon and filtered, producing a colorless filtrate. This filtrate was concentrated to about 20 ml., 100 ml. of ethyl alcohol was added, followed by butylene oxide dropwise until no more solid separated from solution. This compound also was purified best by the Dowex 50 treatment described for XI. The yield of XV was 8.45 g. (50% from XII), m.p. 228° dec. The titration curve was very similar to that of XI, giving no break at the isoelectric point (pH 2.2), moderate breaks at pH 4.5 and 8.8, and a very weak break at pH 11.

Anal. Calcd. for $C_2H_8NO_5P$: C, 21.32; H, 4.77; P, 18.33; neut. equiv., 169. Found: C, 21.09, 21.17; H, 4.59, 4.88; P, 18.26, 18.26; neut. equiv., 172.

An attempt was made to prepare the N-benzoyl derivative of XV, but this was not entirely satisfactory, since no good method was found to purify the product.

General Properties and Reactions with Ninhydrin.—Compounds VIIa, VIIb, and XV were soluble in cold water, but VIIc and XI were appreciably soluble only in hot water. They were all insoluble in the usual organic solvents.

Dilute solutions of VIIa, VIIb, VIIc, XI, and XV were mixed with a 0.1% aqueous solution of ninhydrin and were heated to boiling. All produced pale blue to red colors. When the same tests were carried out after the acidic solutions of the amino acids had been neutralized with sodium bicarbonate, intense violet solutions resulted.[18] It was further noted that the characteristic odor of phenylacetaldehyde was produced during the ninhydrin reaction with VIIc.

To the lavender solution from the ninhydrin reaction with VIIa, excess 6 *N* nitric acid was added, followed by a solution of ammonium molybdate. There resulted the characteristic positive test for the phosphate ion. When the same procedure was employed with VIIa with the exception that no ninhydrin was added, the resulting phosphate test was negative.

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(17) If much hydrochloric acid were left in this solution, the charcoal would not remove the color. However, if all the hydrochloric acid were removed, the solid residue had a low solubility in water.

(18) D. A. MacFadyen [*J. Biol. Chem.*, **158**, 507 (1944)] has shown that α-amino carboxylic acids react with ninhydrin at pH 5–7 to give the characteristic purple-colored solution, whereas at pH 2.5 or less no colored product results.

Synthesis of 3-Phospholenes by Reduction of Diene–Phosphonous Dichloride Adducts[1]

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Seven 3-phospholenes were prepared in moderate yield by reduction with magnesium of the cyclic chlorophosphoranes resulting from addition of phosphonous dichlorides to 1,3-dienes. This class of compounds has not been characterized previously. They react rapidly with air but readily form stable quaternary salts. Infrared and n.m.r. spectra confirm the 3-phospholene structure.

Cyclic chlorophosphoranes (I) are formed by a Diels–Alder reaction between 1,3-dienes and phosphonous dichlorides.[3] The reaction generally is conducted at room temperature without a solvent, in the presence of a polymerization inhibitor. The adducts, which are probably ionic as are other trialkyldichlorophosphoranes,[4] are hydrolyzed readily to 3-phospholene oxides; and over-all yields of 60–70% are, in fact, common. The reaction constitutes one of the simplest methods of constructing a phosphorus-containing ring system. It has the additional valuable feature of providing a system

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