common organic solvents and in dilute HCl. Significant amounts will dissolve in concentrated HCl and in dilute base, producing solutions that foam copiously. Data on the various amino acids are found in Table III.

$$RR'C(CH_2)_xPO(OH)_2$$
$$|$$
$$NH_2$$

A special case was the Curtius reaction of triethyl 1-phenyl-1-phosphonoacetate (**2i**). When this ester and hydrazine were condensed in a 1:2 molar ratio, the solution deposited crystals of the hydrazide after 2 days. The solid hydrazide (106.0 g) was slurried with ether and treated with HCl and $NaNO_2$ by the usual procedure. However, the two-phase mixture contained 10.0 g of a solid, which was removed and found to be slightly soluble in hot water (slightly acidic solution) but essentially insoluble in the common organic solvents. However, if this solid was suspended in boiling ethyl alcohol and a few drops of acetone were added, the solid dissolved completely. Cooling caused the separation of white needles, mp 187.5–189.5° dec. All of the properties of this compound were consistent with structure **4**.

Anal. Calcd for $C_{10}H_{17}N_2O_5P$: C, 43.48; H, 6.20; N, 10.14; P, 11.21. Found: C, 43.61, 43,83; H, 6.16, 6.06; N, 10.02, 9.95; P, 11.49, 11.52.

When the ether–alcohol solution of the acyl azide from **2i** was allowed to decompose overnight, a solid product (9.5 g) separated from solution. This solid had mp 248° dec, was soluble in cold water (neutral solution), and was insoluble in all common organic solvents. Hydrolysis of 1.0 g of this solid with 20% HCl allowed the recovery of 0.83 g of 1-amino-1-phenylmethylphosphonic acid (**3i**). Since no satisfactory recrystallization solvent was found, the unknown solid was washed thoroughly with ethyl alcohol, dried in a vacuum desiccator, and analyzed. All of the properties of the solid (mp 248°) were consistent with structure **5**.

Anal. Calcd for $C_9H_{14}NO_3P$: C, 50.23; H, 6.56; N, 6.51; P, 14.39. Found: C, 50.40, 50.47; H, 6.44, 6.57; N, 6.55, 6.68; P, 14.44, 14.48.

Approximate pK Values and Neutralization Equivalents.—Weighed quantities of the amino acids were dissolved in standardized HCl in a volumetric flask, and aliquots were taken and titrated with standardized NaOH with a Sargent Model D recording titrator. From at least three such plots, the approximate pK values and neutralization equivalents were read.

Preparation of Benzoyl Derivatives.—The amino acid (6–7 g) was dissolved in 25 ml of water and enough 3 M NaOH to give pH 10. The solution was cooled to 5° and 100% excess benzoyl chloride was added. While a temperature of 5° was maintained and while 3 M NaOH was added at a rate to maintain pH 10, the mixture was stirred with a high-speed stirrer. When there was no further reaction, concentrated HCl was added to pH 2 and the product was recovered as described earlier.[4] The derivatives were recrystallized usually from acetonitrile; see Table IV.

$$RR'C(CH_2)_xPO(OH)_2$$
$$|$$
$$NHCOC_6H_5$$

Highly purified samples of amino acids were obtained by the hydrolysis of the purified benzoyl derivatives and recovery of the amino acid by ion exchange chromatography.

Registry No.—**2b**, 35051-49-1; **2c**, 35051-50-4; **4**, 35045-80-8; **5**, 35045-81-9.

Amino Phosphonic Acids. III. The Synthesis and Properties of 2-Aminoethylphosphonic and 3-Aminopropylphosphonic Acids[1]

A. F. ISBELL,* JAMES P. BERRY,[2a] AND L. WAYNE TANSEY[2b]

Department of Chemistry, Texas A & M University, College Station, Texas 77843

Received July 6, 1970

2-Aminoethylphosphonic acid (2-AEP, **2**) is the first compound having a C–P bond to be isolated from biological materials. Because of its wide distribution in the animal kingdom, 2-AEP appears to be an important new biological compound. This paper reports our findings concerning the polymorphism of **2**, some of its other physical and chemical properties, and two new syntheses. The behavior of 3-aminopropylphosphonic acid is compared with that of **2**.

In 1959, Horiguchi and Kandatsu[3] first described the isolation of **2** from ciliate protozoa. Since then, **2** has been found in numerous other organisms and a new area of biochemistry has grown up around this compound. A review covering developments through March 1964 is available.[4] Although man has modest quantities of **2** available in his food, it has not been determined whether or not he makes any use of this compound.

2-Aminoethylphosphonic acid (**2**) was first synthesized by Finkelstein[5] by the use of the Hofmann reaction.

$$\underset{\mathbf{1}}{EtO_2CCH_2CH_2PO(OEt)_2} \xrightarrow{NH_3} H_2NOCCH_2CH_2PO(OEt)_2 \xrightarrow[\text{conc HBr}]{NaOBr} \underset{\mathbf{2}}{H_2NCH_2CH_2PO(OH)_2}$$

Finkelstein added that "the corresponding hydrazide was also prepared from the ester but would not undergo the Curtius rearrangement." In 1947 both Kosolapoff[6] and Chavane[7] reported an alternate synthesis of **2**.

In contrast to Finkelstein's findings, we have been able to synthesize **2** by the Curtius synthesis in yields as high as 83%. 2-Aminoethylphosphonic acid may also be prepared by the catalytic reduction of readily available diethyl cyanomethylphosphonate.

2-Aminoethylphosphonic acid (**2**) gives the characteristic color with ninhydrin reagent but the color yield is only about 3% of the color produced by 1-aminoethylphosphonic acid and the color yield varies with the nature of the ninhydrin reagent.

Horiguchi and Kandatsu[8] first found that samples of **2** from different sources occasionally give different ir spectra when the spectra are run on Nujol mulls or on KBr disks. They correctly interpreted this as the result of polymorphism. We have also studied this be-

(1) Supported in part by a research grant from the National Institutes of Health, GM 09014, which is gratefully acknowledged.

(2) (a) Taken in part from the Ph.D. dissertation submitted by J. P. B. to Texas A & M University, May 1963. (b) Taken in part from the M.S. thesis submitted by L. W. T. to Texas A & M University, Jan 1965.

(3) M. Horiguchi and M. Kandatsu, *Nature (London)*, **184**, 901 (1959); *Bull. Agr. Chem. Soc. Jap.*, **24**, 565 (1960).

(4) L. D. Quin, "Topics in Phosphorus Chemistry," Vol. 4, M. Grayson and E. J. Griffith, Ed., Interscience, New York, N. Y., 1966, p 23.

(5) J. Finkelstein, *J. Amer. Chem. Soc.*, **68**, 2397 (1946).

(6) G. M. Kosolapoff, *ibid.*, **69**, 2112 (1947).

(7) V. Chavane, *C. R. Acad. Sci.*, **224**, 406 (1947); *Ann. Chim. (Paris)*, **4**, 352 (1949).

(8) M. Horiguchi and M. Kandatsu, *Agr. Biol. Chem. (Tokyo)*, **28**, 408 (1964).

havior of **2** and, although we agree with the main conclusions of Horiguchi and Kandatsu, some of our results differ significantly.

Whereas there is evidence that **2** forms a hydrochloride salt in solution, we were unable to prepare a dry salt with a satisfactory amine:HCl ratio; prolonged drying under vacuum produced a hygroscopic solid with an amine:HCl ratio of 1:0.9.

3-Aminopropylphosphonic acid behaved like **2** on cation and anion exchange resins, gave a weak color with ninhydrin reagent, but failed to give a dark blue, water-soluble cupric chelate. When added to a suspension of basic cupric carbonate, **2** produced a deep blue solution but with about half the color intensity produced by 1-aminoethylphosphonic acid.

Experimental Section[9]

Triethyl 3-Phosphonopropionate (**1**).—Sodium (2 g) was dissolved in 304 g (2.2 mol) of freshly distilled diethyl phosphonate, and an equal volume of dry benzene was added, followed by 200 g (2.0 mol) of ethyl acrylate, added dropwise to maintain a temperature of 60°. After the solution cooled to room temperature, a slight excess of acetic acid was added, the mixture was filtered, and the filtrate was distilled, giving 400.8 g (84%) of **1**, bp 109–110° (0.6 mm), n^{25}D 1.4308 [lit.[10] bp 156–158° (12 mm), n^{20}D 1.4338].

Diethyl 2-Cyanoethylphosphonate.—This preparation was similar to the method used to prepare **1**, using 159 g (3 mol) of acrylonitrile, 455.4 g (3.3 mol) of diethyl phosphonate, 6.9 g of Na, and 200 ml of benzene at a reaction temperature of 40–45°. The product weighed 444.7 g (77.5%), bp 111–112° (0.4 mm), n^{25}D 1.4386 [lit.[11] bp 127–128° (2 mm), n^{20}D 1.4380].

Diethyl Cyanomethylphosphonate.—A mixture of 365.2 g (2 mol) of triethyl phosphite and 151.0 g (2 mol) of chloroacetonitrile was heated to boiling under reflux. The boiling temperature slowly increased from 138° to 175° (EtCl evolution). More triethyl phosphite (33.2 g) was added and the heating was continued again to 175°. Distillation produced 323.5 g (91.5%) of liquid, bp 95° (0.3 mm), n^{25}D 1.4315 [lit.[12] bp 126–127° (2.0 mm), n^{20}D 1.4310].

2-Aminoethylphosphonic Acid (**2**) *via* **the Curtius Reaction.**—Triethyl 3-phosphonopropionate (0.1 mol) was added to hydrazine (0.2 mol) or to hydrazine hydrate at a rate to maintain a temperature of 30° and the clear solution was allowed to stand for an additional 1 hr to complete the hydrazide formation. The remainder of the reaction was run as has been described[13] with 16.5 ml of concentrated HCl, 0.2 mol of $NaNO_2$ in 20 ml of water, a total of 200 ml of ether, and 100 ml of absolute ethanol; the crude urethane was hydrolyzed for 48 hr with 50 ml of water and 100 ml of concentrated HCl.

After excess HCl was removed and the solution was decolorized (Norit A), **2** was recovered by absorbing it on Dowex 50 (H^+), washing with water to remove acidic impurities, and eluting **2** with 0.1–0.5 *M* NH_4OH. After this eluate was evaporated to dryness, the residue was dissolved in a small volume of water and passed through Dowex 21K (OH^-) to remove the NH_4^+. Then **2** was eluted with 0.1–0.5 *M* acetic acid, the eluate was evaporated to dryness, and the solid residue was dissolved in a minimum of hot water. Ethyl alcohol (95%) was added until solid began to separate and the mixture was chilled. The recovered **2** had mp 289–290° dec. Potentiometric titration gave neut equiv 127 (calcd 125), and the following pK values were obtained from the titration curve: pK_1 = 2.13, pK_2 = 6.45, pK_3 = 11.05. (Literature melting points have varied from 250°[7] to 296–299°;[3] lit.[7] pK_1 = 2.45, pK_2 = 7.00, pK_3 = 10.8.)

The *N*-benzoyl derivative of **2** was prepared,[14] mp 191–192°.

Anal. Calcd for $C_9H_{12}NO_4P$: C, 47.17; H, 5.28; P, 13.52; neut equiv, 229. Found: C, 47.22, 47.23; H, 5.20, 5.30; P, 13.52, 13.38; neut equiv, 230.

2-Aminoethylphosphonic Acid (**2**) *via* **Diethyl Cyanomethylphosphonate.**—Approximately 37 ml of wet Raney Ni was washed by pressure filtration with glacial acetic acid and then with acetic anhydride. This catalyst was quickly placed in a Parr hydrogenator bottle (250 ml) with 70.8 g (0.4 mol) of diethyl cyanomethylphosphonate, 12.0 g of anhydrous sodium acetate, and 120 ml of acetic anhydride. This mixture was shaken under hydrogen (60 psi) until absorption ceased (70% of the H_2 was absorbed in 1 hr but reaction was continued overnight). The mixture was filtered, the catalyst was washed with ethanol (95%), and the combined filtrates were evaporated to dryness under vacuum, leaving 127.8 g of crude yellow oil. This oil was heated under reflux with 100 ml of water, and three successive 100-ml portions of concentrated HCl were added during the 40-hr heating. From here on **2** was recovered by ion exchange chromatography as described above, except that as much as 1.2 equiv capacity of Dowex 50 resin was required to hold the Na^+ and to allow good separation of the fractions. When **2** was eluted from Dowex 21K (OH^-) with 0.5 *M* acetic acid, care was taken to avoid excessive heating of the resin by too rapid flow of the acid. The yield of **2** was 43.0 g (86.1%).

A somewhat different procedure involved combining 50 ml of absolue ethanol, saturated with NH_3, 17.7 g (0.1 mol) of diethyl cyanomethylphosphonate, and 1 ml of W-4 Raney Ni[15] in a hydrogenation bottle and shaking the mixture with an initial pressure of 60 psi of H_2. When the calculated amount of H_2 had been absorbed, the mixture was filtered, the filtrate was evaporated to dryness under vacuum, and the residue was dissolved in 50 ml of 50% ethanol. This solution was saturated with H_2S, the precipitated NiS was removed by filtration, the filtrate was heated under reflux for 48 hr with 25 ml of concentrated HCl, and **2** was recovered as above. There resulted 5.8 g (47%) of **2**. The Ni may also be removed after the hydrolysis when the crude **2** is chromatographed on Dowex 50 resin; when **2** is eluted with 0.5 *M* NH_4OH, the Ni remains on the resin.

A further modification involved reducing 17.7 g (0.1 mol) of diethyl cyanomethylphosphonate in 70 ml of 95% ethanol and 40 ml of 10% HCl over 1 g of 10% Pd/C at 60 psi H_2 for 26 hr (calculated amount of H_2 absorbed). After removal of the catalyst, the filtrate was neutralized with $NaHCO_3$, the solution was evaporated to dryness under vacuum, the residue was extracted with two 50-ml portions of absolute ethanol, and the clear extract was distilled. There was recovered 11.4 g (63%) of diethyl 2-aminoethylphosphonate, a colorless liquid, bp 54–56° (0.025 mm), n^{25}D 1.4426 [lit.[16] bp 93–95° (4.0 mm), n^{20}D 1.4270].

Reaction of 2 with Ninhydrin.—Ninhydrin reagent prepared in various ways, as reported in the literature, gave varying color productions with **2**; in some instances, no color at all resulted. The ninhydrin solution recommended in an earlier paper[14] was not suitable for **2**; instead, a freshly prepared solution of 100 mg of ninhydrin in 100 ml of pH 7.0 buffer gave reliable results.

Polymorphism of 2.—In numerous ways, we have attempted to prepare samples of the metastable α form[3] of **2**, without success. The α form has been described as heavy rhombic plates and the more stable β form as needles.[3] In one instance, a drop of a hot, saturated, aqueous solution of **2** was placed in the depression of a microscope slide, covered with a cover glass, and watched through a microscope as crystals formed. Perfect, heavy rhombic plates separated. To be certain that these were the desired α form, their ir spectrum (Nujol mull) was determined. These

(9) All melting points were determined with a Hershberg apparatus and with a thermometer which had been calibrated with a set of thermometers having Bureau of Standards calibrations; boiling points were uncorrected. Triethyl phosphite was kindly supplied by the Hooker Chemical Corp. and was redistilled before being used. Anhydrous hydrazine (95+%) was obtained from Matheson Coleman and Bell. Raney Ni, grade #28, was obtained from the Grace Co. Dowex 50W-X8 and Dowex 21K resins were kindly supplied by the Dow Chemical Co. All other reagents were the best grade available and were used without further purification. Infrared spectra were produced with a Beckman IR-8 spectrometer and titrations were carried out with a Sargent Model D recording titrator. A Nestor-Faust refractive index monitor was used to detect changes of composition of the ion exchange column eluates. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(10) N. Kreutzkamp and W. Mengel, *Chem. Ber.*, **100**, 709 (1967).

(11) B. A. Arbuzov and B. P. Lugovkin, *Zh. Obshch. Khim.*, **21**, 99 (1951).

(12) A. N. Pudovik and N. M. Lebedeva, *ibid.*, **25**, 2235 (1955).

(13) J. R. Chambers and A. F. Isbell, *J. Org. Chem.*, **29**, 832 (1964).

(14) J. P. Berry, A. F. Isbell, and G. E. Hunt, *ibid.*, **37**, 4396 (1972).

(15) A. A. Pavlic and H. Adkins, *J. Amer. Chem. Soc.*, **68**, 1471 (1946).

(16) A. M. Pudovik and G. M. Denisova, *Zh. Obshch. Khim.*, **23**, 263 (1953).

rhombic crystals gave the spectrum normally given by needles—in other words, by the β form! From 30 samples of **2** prepared at different times, three samples gave the spectrum corresponding to the α form. All attempts to recrystallize these samples of the α form have invariably given the β form. We have normally been unable to determine which form we have either by observation of the solid with the unaided eye or with a microscope.

Registry No.—**2**, 2041-14-7; **2** (*N*-benzoyl), 35045-99-9.

The Stereochemistry of Aziridine Ring Expansion Reactions with Sulfur Nucleophiles to Give Thiazolidines and 2-Amino-2-thiazolines

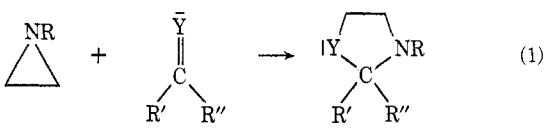
RONALD A. WOHL* AND DAVID F. HEADLEY

School of Chemistry, Rutgers University, New Brunswick, New Jersey 08903

Received May 11, 1972

The ring enlargement reactions of aziridines with thiocyanic acid and acetone plus hydrogen sulfide to 2-amino-2-thiazolines **2** and 2,2-dimethylthiazolidines **9** proceed 100% stereospecifically with Walden inversion; for example *cis*- and *trans*-2,3-dimethylaziridine, **11** and **12**, with thiocyanic acid gave exclusively *trans*- and *cis*-2-amino-4,5-dimethyl-2-thiazoline, **13** and **14**, respectively. For the 2-amino-2-thiazolines **2** it was shown by means of ir and nmr spectra, that the tautomeric equilibrium between the forms with exocyclic and endocyclic double bond (eq 5) lies completely toward the 2-amino form **19a** with endocyclic double bond.

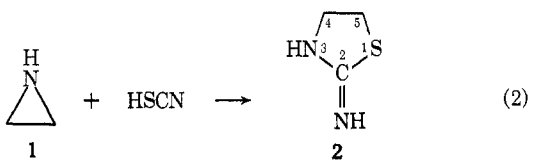
Aziridines can be ring expanded with suitable reagents according to the following general scheme (eq 1).[1]



(1)

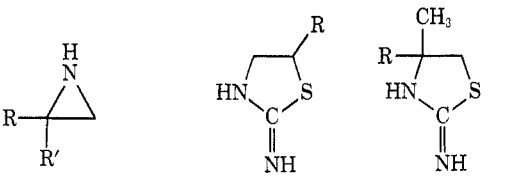
The reagent attacking the aziridine must have a multiple bond attached to an atom Y possessing a free electron pair. Only reactions in which the aziridine reacts under carbon–nitrogen cleavage (rather than carbon–carbon cleavage) are considered here. The ring expansion of aziridines with aldehydes,[2] aldehydes and ketones in the presence of H_2S,[2b,3-6] carbon disulfide,[1,7-10] xanthates,[1] isocyanates,[1] alkali thiocyanate or thiocyanic acid,[8,10,11] organic isothiocyanates,[1] thioacetamide,[1] and nitriles[1] have been reported. Many of these reactions proceed under acid catalysis which facilitates the opening of the aziridine ring.

Additions of Thiocyanic Acid to Give 2-Iminothiazolidines.—Gabriel and Colman discovered the reaction of aziridines (**1**) with thiocyanic acid to give 2-iminothiazolidines[8] according to eq 2. From phenylaziridine (**3a**)



(2)

in the presence of HCl they obtained 2-imino-5-phenylthiazolidine (**4a**). Earley, *et al.*, investigated in detail

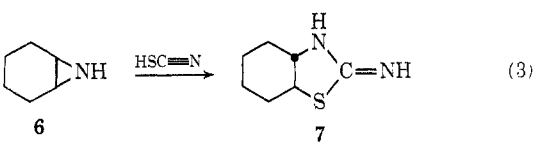


3a, R = C_6H_5; R′ = H
b, R = C_2H_5; R′ = H
c, R = CH_3; R′ = CH_3
d, R = CH_3; R′ = H

4a, R = C_6H_5
b, R = CH_3

5a, R = H
b, R = CH_3

the mechanism and kinetics of the addition of potassium thiocyanate to four aziridines, aziridine (**1**) itself, 2-ethylaziridine (**3b**), 2,2-dimethylaziridine (**3c**), and *N*-(*n*-butyl)aziridine and obtained in all cases the corresponding 2-iminothiazolidines.[11] From 2,2-dimethylaziridine (**3c**) they obtained 2-imino-4,4-dimethylthiazolidine (**5b**) by attack of the thiocyanate ion at the primary carbon atom of the aziridine ring. Finally, Mousseron, *et al.*, reported the addition of thiocyanic acid to *cis*-cyclohexenimine (**6**) to give the trans-fused thiazolidine **7** (eq 3).[10] The latter is



(3)

the only example where the stereochemistry of the reaction has been mentioned at all.

Additions of Aldehydes and Ketones in the Presence of Hydrogen Sulfide to Give 2-Alkyl- and 2,2-Dialkylthiazolidines.—Bestian[3] has shown that aziridine (**1**) treated with hydrogen sulfide in the presence of an aldehyde or ketone **8** gives a thiazolidine **9** according to eq 4; for example, the addition of hydrogen sulfide to

(1) P. E. Fanta in "Heterocyclic Compounds with Three- and Four-Membered Rings," Part 1, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, pp 524–575. H. Bestian in "Methoden der Organischen Chemie," Vol. 11/2, Houben-Weyl, George Thieme Verlag, Stuttgart, 1958, p 223 ff; O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines," Academic Press, New York, N. Y., 1969, Chapter 3; J. McCormick, R. I. Kaplan, and B. J. Stormer, *Can. J. Chem.*, **49**, 699 (1971).

(2) (a) J. B. Doughty, C. L. Lazzell, and A. R. Collett, *J. Amer. Chem. Soc.*, **72**, 2866 (1950). (b) See, however, R. Tondeur, R. Sion, and E. Doray, *Bull. Soc. Chim. Fr.*, 2493 (1964).

(3) (a) H. Bestian, *Justus Liebigs Ann. Chem.*, **566**, 210 (1950); (b) H. Bestian (I. G. Farbenindusttie A.-G.), German Patent 747,733 (1939) [*Chem. Zentralbl.*, **I**, 952 (1945)].

(4) G. Drehfahl and M. Huebner, *J. Prakt. Chem.*, (4) **23**, 149 (1964); R. G. Kostyanovskii, *Dokl. Akad. Nauk SSSR*, **135**, 853 (1960) [*Chem. Abstr.*, **55**, 12380 (1961)]; F. Asinger, *Monatsh. Chem.*, **99**, 2090 (1968).

(5) J. Metzger and J.-L. Larice, *Bull. Soc. Chim. Fr.*, 575 (1965).

(6) J.-L. Larice, J. Roggero, and J. Metzger, *ibid.*, 3637 (1967).

(7) S. Gabriel and H. Ohle, *Chem. Ber.*, **50**, 804 (1917).

(8) S. Gabriel and J. Colman, *ibid.*, **47**, 1866 (1914).

(9) T. A. Foglia, L. M. Gregory, G. Maerker, and S. F. Osman, *J. Org. Chem.*, **36**, 1068 (1971), and references cited therein.

(10) M. Mousseron, F. Winternitz, and R. Dennilauer, *C. R. Acad. Sci.*, **239**, 278 (1954); F. Winternitz, M. Mousseron, and R. Dennilauer, *Bull. Soc. Chim. Fr.*, **382**, 1228 (1956).

(11) J. E. Earley, O. E. O'Rourke, L. B. Clapp, J. O. Edwards, and B. C. Lawes, *J. Amer. Chem. Soc.*, **80**, 3458 (1958).