α-Aminoarylmethylphosphonic Acids and Diethyl α-Aminoarylmethylphosphonate Hydrochlorides. Aluminum–Amalgam Reduction of Oximes of Diethyl Aroylphosphonates[1]

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A new general procedure has been developed for the synthesis of α-aminoarylmethylphosphonate hydrochlorides and the corresponding acids. Dialkyl aroylphosphonates form oximes (65–100%) when treated with hydroxylamine hydrochloride. Reduction of the oximes in water–ethanol by Al–Hg gave excellent yields (up to 85%) of α-aminoarylmethylphosphonates which were converted into hydrochlorides for purification. Acid hydrolysis of the hydrochlorides gave the corresponding α-aminoarylmethylphosphonic acids (73–88%). Spectral assignments (nmr and infrared) are recorded for the first time for the oximes, α-aminoarylmethylphosphonates, and the α-aminoarylmethylphosphonic acids. Analysis of the data indicates intramolecular hydrogen bonding between the P→O group and the proton on the OH group and NH_2 group in the oximes and α-aminoarylmethylphosphonates, respectively.

Certain α-aminoalkylphosphonic acids may be considered to be phosphorus analogs of aminocarboxylic acids. Although none of the α-aminoalkylphosphonic acids has yet been found in living organisms, they have been found to possess biological activity.[3] Quin[4,5] has found 2-aminoethylphosphonic acid in protozoa, in certain coelenterata, in some fresh-water mollusks, in bovine brain, and in caprine liver.

Present general methods for the preparation of α-aminoarylmethylphosphonic acids and dialkyl α-aminoarylmethylphosphonate hydrochlorides have certain intrinsic limitations. The most recent synthetic route[6] utilizes the Curtius degradation of substituted diethyl phosphonoacetylhydrazides; it is long and depends upon the availability of suitable phosphonoacetic esters. Chambers and Isbell prepared three α-aminoalkylphosphonic acids *via* this route and reported over-all yields from the α-halocarboxylate of 21% for aminomethylphosphonic acids, 66% for 2-aminoethylphosphonic acid, and less than 56% for 1-amino-2-phenylethylphosphonic acid.

This method apparently cannot be used to prepare esters of α-aminoalkylphosphonic acids inasmuch as the reaction sequence calls for boiling the urethan derivative of the dialkyl α-aminoalkylphosphonates in concentrated hydrochloric acid for 2 days which would remove the alkyl groups of the phosphorus esters.

Kabachnik and Medved[7–9] have obtained α-aminoalkylphosphonic acids from both aldehydes and ketones, ammonia, and dialkyl hydrogenphosphonates. Yields were low (8–43%) and the dialkyl α-aminoalkylphosphonates could not be easily separated from the dialkyl α-hydroxyalkylphosphonates which occurred as by-products. Kosolapoff[10] reduced the *p*-nitrophenylhydrazone of diethyl benzoylphosphonate with 2% palladium–charcoal catalyst but was unable to separate the α-aminobenzylphosphonic acid from traces of the aniline salt. Dialkyl α-aminoalkylphosphonates remain difficult substances to prepare to date and α-aminoalkylphosphonic acids have not been realized in high yields.

Results and Discussion

This paper reports the synthesis of a new family of compounds, the oximes **3** of dialkyl aroylphosphonates **2**. Also new methods are given for the syntheses of α-aminoarylmethylphosphonic acids **7** and diethyl α-aminoarylmethylphosphonate hydrochlorides **5** in good yields by aluminum–amalgam reduction of oximes **3** of dialkyl aroylphosphonates **2**. The infrared and nmr spectra of diethyl aroylphosphonate oximes **3**, diethyl α-aminoarylmethylphosphonate hydrochlorides **5**, and α-aminoarylmethylphosphonic acids **7** are reported for the first time. Unique intramolecularly hydrogen-bonded structures, as indicated by the infrared spectra, were found to exist in the oximes **3** of diethyl aroylphosphonates **2** and the diethyl α-aminoarylmethylphosphonate hydrochlorides **5**. The nmr analysis of diethyl α-aminoarylmethylphosphonate hydrochlorides **5** indicated the existence of magnetically nonequivalent alkoxy groups as expected from the presence of an asymmetric center. See Scheme I.

This present synthetic route begins with readily available acid halides and leads to diethyl aroylphosphonates **2**, diethyl aroylphosphonate oximes **3**, diethyl α-aminoarylmethylphosphonates **4**, diethyl α-aminoarylmethylphosphonate hydrochlorides **5**, α-aminoarylmethylphosphonic acid hydrochlorides **6**, and α-aminoarylmethylphosphonic acids **7**. Several members of families **2**, **3**, **5**, and **7** were isolated and characterized. Starting from the diethyl aroylphosphonates **2**, the free α-aminoarylmethylphosphonic acids can be prepared in reasonable yields [29, 45, and 71% (Table I) of pure material was obtained for **7b**, **7d**, and **7h**, respectively] when one isolates the inter-

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(2) Predoctoral candidate 1964–1967; National Science Foundation Trainee, Summer, 1966. This work is abstracted from the thesis (R. T. C.) submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy to the Oklahoma State University.

(3) V. L. Ryzhkov, M. I. Kabachnik, L. M. Tarasevich, T. Ya. Medved, N. A. Zeitlenok, N. K. Marchenko, V. A. Vagzhanova, E. F. Vlanova, and N. V. Chebarkina, *Dokl. Akad. Nauk. SSSR*, **98**, 849 (1954); *Chem. Abstr.*, **49**, 3403 (1955).

(4) L. D. Quin, "Topics in Phosphorus Chemistry," Vol. 4, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, New York, N. Y., 1967, pp 23–48.

(5) L. D. Quin, *Science*, **144**, 1133 (1964). The general subject has been reviewed recently: D. G. Simonsen, M. Horiguchi, and J. S. Kittredge, *ibid.*, **159**, 886 (1968).

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

(7) M. I. Kabachnik and T. Ya. Medved, *Dokl. Akad. Nauk SSSR*, **83**, 689 (1952).

(8) M. I. Kabachnik and T. Ya. Medved, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 868 (1953); *Chem. Abstr.*, **49**, 840 (1955).

(9) M. I. Kabachnik and T. Ya. Medved, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 314 (1954); *Chem. Abstr.*, **48**, 10541 (1954).

(10) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **69**, 2112 (1947).

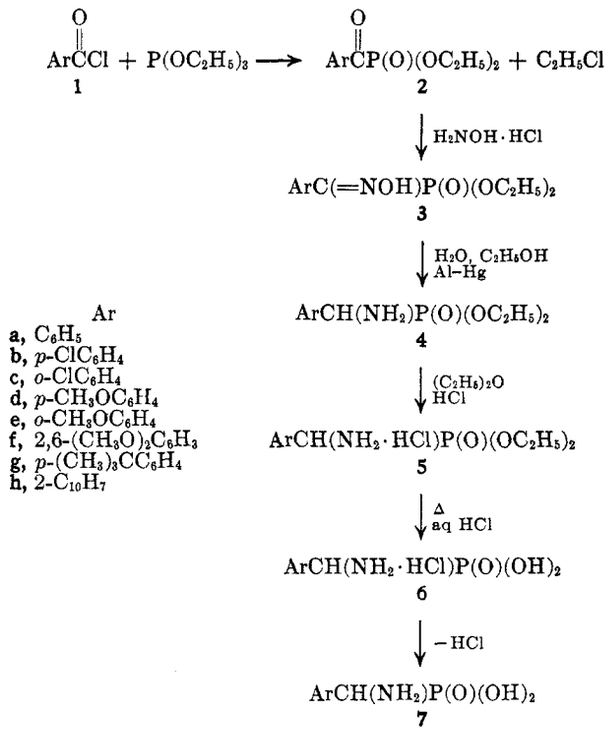
TABLE I

α-AMINOARYLMETHYLPHOSPHONIC ACIDS, $ArCH(NH_2)P(O)(OH)_2$

Acid[a]	Moles of 5 × 10^3	Mp, °C of acid	Yield % of acid	Anal, % N Calcd	N Found	P Calcd	P Found
7b	5.79 (5b)	291.3–292.5	72.7	6.32	6.39	13.98	14.16
7d	5.92 (5d)	277.8–278.3	87.5	5.98[b]	5.91	...	...
7h	3.06 (5h)	307.3–308.4	75.9	5.90	5.01	13.06	13.28

[a] Recrystallized from water. [b] The analysis is for the monohydrate.

SCHEME I

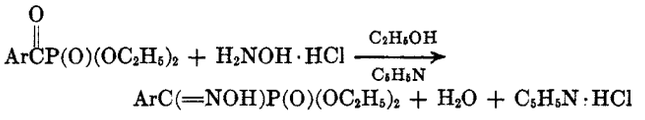


mediates. However, in one case if one does not isolate the intermediate materials, the yield improved. For example, in a study beginning with **2b**, an over-all yield of 66.5% **7b** was achieved.

Yields of 66% (quantitative) were realized in the preparation of the oximes of diethyl aroylphosphonates. The reduction of the oximes to diethyl α-aminoarylmethylphosphonates **4** and subsequent formation of the hydrochlorides **5** were accomplished with yields ranging from 38 to 85%. The hydrolysis of the diethyl α-aminoarylmethylphosphonate hydrochlorides **5** to the free acids gave 73–88% yields of products.

Diethyl Aroylphosphonates 2.—The diethyl aroylphosphonates **2** were prepared from triethyl phosphite and aroyl chlorides **1** utilizing the classical Michaelis–Arbuzov rearrangement as described previously.[11–13] The Experimental Section contains a list of the diethyl aroylphosphonates **2** along with some of their physical properties. The nmr and infrared spectra for some members of **2** have been adequately discussed elsewhere[11–13] and further elaboration will not be included herein.

Diethyl Aroylphosphonate Oximes 3.—White, crystalline oximes **3** can generally be formed from the diethyl aroylphosphonates **2** through reaction with hydroxylamine hydrochloride in pyridine and ethanol (if dialkyl esters other than those from ethanol are desired, the alcohol containing the same alkyl group as the dialkyl



aroylphosphonate employed must be used to prevent transesterification). Yields for the crude oximes **3** are generally near quantitative, and the crude oximes can be used directly in the aluminum–amalgam reduction. The Experimental Section contains a list of the oximes along with some of their physical properties. The proton of the oxime moiety of the diethyl aroylphosphonate oximes is probably slightly acidic.[14]

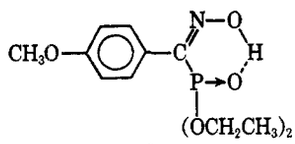
Infrared and nmr spectral data were recorded for the oximes **3**. Inasmuch as **3** is a new family of compounds, no infrared or nmr data have been previously reported. The infrared spectra showed phosphoryl absorptions of 1214–1252 cm^{-1} for **3**. It is widely believed that phosphoryl absorptions between 1200 and 1250 cm^{-1} indicate hydrogen-bonded phosphoryl groups, whereas P→O frequencies from 1250 to 1300 cm^{-1} represent free phosphoryl functions.[11,15–19] In all cases the phosphoryl absorptions in the oximes **3** occurred at longer wavelengths than did the phosphoryl absorptions in the corresponding diethyl aroylphosphonates **2**. The differences for cognomers of the two families varied from 11 to 40 cm^{-1}. No correlation of the shifts of the phosphoryl absorptions with the structures of the compounds was obvious.

Simple oximes in general absorb broadly at 3150–3300 cm^{-1} owing to bonded O–H stretching and near 930 cm^{-1} owing to the stretching of the N–O linkage.[15] The diethyl aroylphosphonate oximes **3** exhibited O–H stretching frequencies of 3104–3208 cm^{-1}, N–O stretching frequencies of 927–933 cm^{-1}, and P–O–CH_2–CH_3 absorptions (CH_3 rocking)[15] at 1163–1171 cm^{-1}.

The infrared spectrum of diethyl *p*-methoxybenzoylphosphonate oxime (**3d**) was obtained both in a KBr pellet and in chloroform solution in order to determine whether the oxime was inter- or intramolecularly hydrogen bonded. By the aid of dilution studies of **3d** in chloroform it was found that the hydroxyl group was

(11) K. D. Berlin and H. A. Taylor, *J. Amer. Chem. Soc.*, **86**, 3862 (1964).
(12) K. D. Berlin, D. M. Hellwege, and M. Nagabhsushanam, *J. Org. Chem.*, **30**, 1265 (1965).
(13) K. D. Berlin and D. H. Burpo, *ibid.*, **31**, 1304 (1966).
(14) Sodium hydroxide titrations (aqueous solutions) of diethyl acetylphosphonate oxime (prepared in the same manner as were the diethyl aroylphosphonate oximes) gave data from which a pK_a of 9.33 was calculated.
(15) N. B. Colthrup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964.
(16) E. M. Popov, M. I. Kabachnik, and L. S. Mayants, *Usp. Khim.*, **30**, 846 (1961); *Russ. Chem. Rev.* (Eng. Transl.), **30**, 362 (1961).
(17) J. P. Phillips, "Spectra-Structure Correlation," Academic Press, New York, N. Y., 1964, p 134 ff.
(18) L. W. Daasch and D. C. Smith, *Anal. Chem.*, **23**, 853 (1951).
(19) D. E. C. Corbridge, *J. Appl. Chem.*, **6**, 456 (1956).

shifted only slightly in position although the intensity was reduced. This suggests the hydrogen bonding is intramolecular as shown by **8**. The variations are



8

within the limits (± 199 cm^{-1}) found for various other related examples of phosphorus compounds in the literature.[20] Miller and coworkers have studied the infrared spectra of dialkyl α-hydroxyalkylphosphonates both in crystalline (mineral oil mull) and in carbon disulfide solution and reported shifts as high as 64 cm^{-1} for P→O and shifts up to 45 cm^{-1} for O–H.[20] These workers concluded that the dialkyl α-hydroxyalkylphosphonates were intramolecularly hydrogen-bonded structures.

The nmr spectra for the oximes **3** are quite similar to those for the diethyl aroylphosphonates **2**. In addition to the aromatic proton absorptions the ethyl groups exhibit a triplet at δ 1.17–1.30 (J = 7 cps, CH_3) and an imperfect quintet (due to H–H and P–H splitting patterns which overlap) at δ 8–4.6 (J = *ca.* 7 cps, CH_2). A broad multiplet (integration showed that this peak represented one proton) is observed in the region of δ 10.1–14.6 for the proton of the oxime moiety.

The chemical shifts of the hydroxyl proton of oximes have recently been studied.[21] This reference[21] lists signals of δ 8.6–13.3 for the hydroxyl proton in various oximes. Two peaks were observed in the spectra of those oximes possessing nonequivalent or *syn* and *anti* oxime groupings. Our observation of a single, broad absorption for the hydroxyl proton in diethyl aroylphosphonate oximes **3** correlates well with the nmr data just mentioned[21] and lends support to the presence of a single intramolecularly hydrogen-bonded structure, **8**, and precludes *syn*- and *anti*-oxime formation.

Aluminum–Amalgam Reduction of Diethyl Aroylphosphonate Oximes 3 to Diethyl α-Aminoarylmethylphosphonates 4. Subsequent Formation of the Hydrochloride Salts 5.—An aluminum–amalgam–ethanol–water mixture easily reduces the oximes **3** of diethyl aroylphosponates under very mild conditions without hydrolyzing the ester function to any noticeable extent. The diethyl α-aminoarylmethylphosphonates **4** can be isolated as the hydrochlorides **5** in yields of 38–85% based on the oximes.

$$\mathrm{ArC(=NOH)P(O)(OC_2H_5)_2 + Al(Hg) + H_2O \xrightarrow{C_2H_5OH} ArCH(NH_2)P(O)(OC_2H_5)_2}$$

Although a few dialkyl α-aminoalkylphosphonates and their salts have been reported previously, no infrared or nmr data have been given. The infrared spectra exhibited a phosphoryl absorption between 1221 and 1258 cm^{-1} which indicated hydrogen bonding. In all cases the phosphoryl absorptions from **5** were lower than that of the corresponding diethyl aroylphosphonate cognomers. Inasmuch as the phosphoryl frequency is influenced both by hydrogen bonding and by the total electronegativity of the substituents on the phosphorus atom, the lowering of the phosphoryl absorption cannot easily be correlated with hydrogen-bonding effects alone.

The hydrochlorides **5** exhibit a peak in the region of 1947–2062 cm^{-1} which is assigned to the $-{}^+NH_3$ moiety. Amino carboxylic acids show an absorption[15] between 2000 and 2200 cm^{-1} which is assigned as a combination band of $-{}^+NH_3$ asymmetric deformation and $-{}^+NH_3$ hindered rotation. Primary amine salts also exhibit a band near 2000 cm^{-1} which is believed to be a combination band of $-{}^+NH_3$ torsional oscillation and asymmetric deformation.[15] The $-{}^+NH_3$ frequency near 2000 cm^{-1} in **5** is believed to be a combination band for this group.

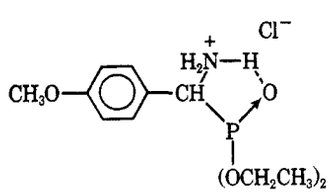
That the diethyl α-aminoarylmethylphosphonate hydrochlorides **5** are intramolecularly hydrogen-bonded structures can be shown by comparison of infrared spectral data of a KBr pellet of the compounds with that of a solution of the same. This study of infrared spectra was done with diethyl α-amino-*p*-methoxybenzylphosphonate (**5d**) and showed only insignificant changes in the $-{}^+NH_3$ and P→O absorptions. Table II gives the infrared spectral data for chloroform solutions of **5d**.

TABLE II

INFRARED ANALYSIS OF CHLOROFORM SOLUTIONS OF **3d** AND **5d** (cm^{-1})

Compd	Concn. of solution, %	N–H	O–H	P→O
3d	5.4	...	3236	1260
3d	1.8	...	3236	1260
3d	0.48	...	3234	1260
5d	1.3	2950	...	1250
5d	0.93	2965	...	1244

The shift of 15 cm^{-1} by the N–H band and the shift of 6 cm^{-1} by P→O are within the variation ± 199 cm^{-1} mentioned previously.[20] The structure for **5d** showing intramolecular hydrogen bonding is illustrated.

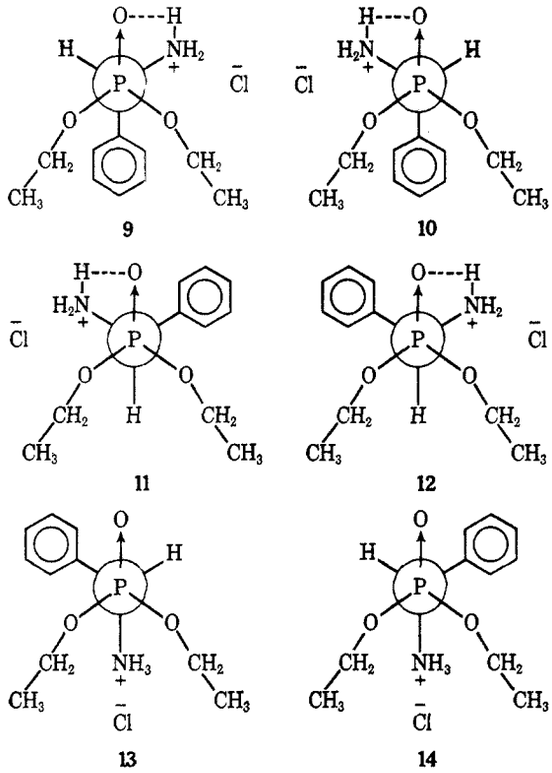


5d

The diethyl α-aminoarylmethylphosphonate hydrochlorides **5** are, consequently, believed to exist as the intramolecularly hydrogen-bonded structures represented by Newman projections **11** [(*R*)-diethyl α-aminobenzylphosphonate hydrochloride (**5a**)] and **12** [(*S*)-diethyl α-aminobenzylphosphonate hydrochloride (**5a**)]. Conformations **9**, **10**, **13**, and **14** are probably higher energy forms which may not be present in high population. In **11** and **12** the aromatic ring lies between the oxygen of the phosphoryl group and an ethoxy group (the least hindered position for the bulkier aromatic function) and the ammonium group lies between an ethoxy group and the oxygen of the phosphoryl group to which it is intramolecularly hydrogen

(20) C. D. Miller, R. C. Miller, and W. R. Rogers, *J. Amer. Chem. Soc.*, **80**, 1562 (1958).

(21) G. C. Kleinspehn, J. A. Jung, and S. A. Studniarz, *J. Org. Chem.*, **32**, 460 (1967).



9 10

11 12

13 14

bonded. Although structures **9** and **10** allow for intramolecular hydrogen bonding, they force the aromatic moiety to a position between two ethoxy groups, and these are expected to be high energy conformations. In structures **13** and **14**, although the aromatic ring lies between the phosphoryl oxygen and an ethoxy group, intramolecular hydrogen bonding between the P→O and $-{}^{+}NH_3$ groups is not possible.

The nmr spectra for **5** are not so simple as those for families **2** and **3** and exhibit several interesting features. The benzyl proton in **5** occurs as a doublet and is seen at δ 4.7–5.6. The P–C–H splitting pattern generally results in a doublet with a coupling constant of 18 cps [a value of 17 cps is observed for diethyl α-amino-*p*-methoxyphosphonate hydrochloride (**5d**)]. The nmr spectra of dialkyl α-hydroxybenzylphosphonates exhibit a coupling constant of J_{P-C-H} = 13.5 cps for diethyl and dimethyl α-hydroxybenzylphosphonates[22] which are known also to exist as intramolecularly hydrogen-bonded structures.[20] Geminal P–C–H coupling reportedly is related to the electron densities in both the P–C and C–H bonds (and thus dependent upon the substituents on both phosphorus and carbon)[23] and the P–C–H angle.[24] Unfortunately, very little bond-angle data are available for compounds similar to those being studied. It also seems reasonable that the P–C–H coupling constant may vary with the strength of the hydrogen bond that forms in both **5** and the corresponding dialkyl α-hydroxybenzylphosphonates.

The nmr spectra of diethyl α-aminoarylmethylphosphonate hydrochlorides **5** exhibit magnetically nonequivalent ethyl groups. The methylene group (of the alcoholic portion of the molecule) exhibits a multiplet in the region δ 3.5–4.6 in **5** in contrast to the better defined "imperfect" quintet patterns observed for **2** and **3**. The methyl groups of the ethoxy functions give rise to two triplets. These two triplets may give the appearance of a quartet (as in the cases of **5a**, **5e**, and **5f**) when their centers are separated by 7 cps, a sextet (as in the case of **5h**) when their centers are separated by 3.5 cps, or as a multiplet when separations other than 3.5 or 7 cps are realized. These methyl signals show chemical shifts of δ 0.8–1.4.

The intramolecularly hydrogen-bonded structures shown by the Newman projections for (*RS*)-diethyl α-aminobenzylphosphonate hydrochloride (**5a**) conformations (shown previously by **11** and **12**) are the least hindered conformations which also allow for hydrogen bonding. In conformers **11** and **12** one of the ethoxy groups lies nearer the magnetically anisotropic benzene ring than the second ethoxy group. Thus the two ethoxy moieties in **5** experience different magnetic environments and consequently exhibit two triplets. This magnetic nonequivalence found in **5** is likely not a result of "long-range" P–O–C–C–H splitting since this type of splitting generally does not exceed 1.1 cps. Also "long-range" P–O–C–C–H splitting is not observed in the nmr spectra of the similar **2** and **3**.

Magnetically nonequivalent alkoxy groups in phosphorus esters have been reported previously.[25,26] Magnetically nonequivalent alkoxy groups have also been observed in the nmr spectra of racemic dialkyl α-hydroxybenzylphosphonates.[22]

α-Aminoarylmethylphosphonic Acids 7.—The acid salts **6** were obtained through acid hydrolysis of the diethyl α-aminoarylmethoxyphosphonate hydrochlorides **5**. The solution was evaporated to dryness, and the resulting solid was dissolved in a minimum of cold water and boiled until the free white acid began to

$$\mathrm{RCH(NH_2\cdot HCl)P(O)(OC_2H_5)_2} + \mathrm{H_2O} \xrightarrow[\Delta]{\mathrm{HCl}} \mathrm{RCH(NH_2\cdot HCl)P(O)(OH)_2} \downarrow -\mathrm{HCl} \rightarrow \mathrm{RCH(NH_2)P(O)(OH)_2}$$

crystallize. High yields (73–88%) of the free acids were realized (based on **5**). The new α-aminoarylmethylphosphonic acids along with some of their physical properties are listed in Table I.

Infrared spectral data for three acids **7b**, **7d**, and **7h** are characterized by broad diffuse bands from 1800 to 3650 cm^{-1} making it difficult to make definitive assignments in this region. These broad diffuse bands are anticipated in light of data reported for similar compounds.[15–19] Inasmuch as aminomethylphosphonic acid has been shown to exist as a zwitterion,[27] other α-aminoalkylphosphonic acids are expected to exist also as zwitterions. Whether or not this is the case, α-aminoarylmethylphosphonic acids **7** would be expected to show extensive hydrogen bonding which would contribute heavily to the broadness of the absorptions of **7** in the 1800–3650-cm^{-1} region.

Bands in the areas of 1077–1085 and 1193–1270 cm^{-1} also occur in the spectra of **7**. Phosphonic and phosphinic acids generally show a strong absorption at 910–

(22) D. M. Hellwege, Ph.D. Thesis, Oklahoma State University, 1966.
(23) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, Chapter 8.
(24) M. Gordon, Ph.D. Thesis, University of Pittsburgh, 1965.
(25) T. H. Siddall, III, *J. Phys. Chem.*, **70**, 2249 (1966).
(26) K. D. Berlin, D. H. Burpo, R. U. Pagilagan, and D. Bude, *Chem. Commun.*, **20**, 1060 (1967).
(27) V. Chavane, *Bull. Soc. Chim. Fr.*, **27**, 774 (1948).

1040 cm^{-1} which probably involves the stretching of the P–O bond of the P–O–H linkage.[15] Salts of $R_2P(O)(O^-)$ and $R(H)P(O^-)$ display two strong bands at 1100–1190 and 1000–1075 cm^{-1} which are reported to be a result of symmetric and asymmetric stretch of O←P–O⁻.[15] The phosphoryl group in **7** also gives rise to an absorption in the 1200–1300-cm^{-1} region but cannot be definitely assigned since other vibrations occur in the same area. The hydrogen-bonding capabilities of **7** could cause the peaks in the 970–1300-cm^{-1} region to be diffuse creating even greater difficulty in assigning frequencies.

The nmr spectra of the free acids **7** exhibit a multiplet in the region δ 7.2 and 8.4 and is assigned to the ammonium group. Suitable solvents for **7** are lacking and trifluoroacetic acid was used to obtain these nmr spectra. This solvent would protonate a free NH_2 group if $Ar–CH(NH_2)–P(O)(OH)_2$ is the prevailing structure for **7** or would protonate the oxide ion if $Ar–CH(^+NH_3)–P–(O)(O^-)(OH)$ is the actual form. In any case, a signal for the ammonium group would result in the nmr spectra of **7** and would integrate for three protons. Thus the multiplet at δ 7.2 to 8.4 in the nmr spectra cannot be taken as evidence for the existence of **7** as zwitterions even though integration shows three protons for this band. The benzyl proton in **7** occurs as a broad doublet near δ 5.0, and the coupling constant is estimated to be about 16 ± 2 cps.

Nmr spectral investigations of α-aminoalkylphosphonic acids have not been previously reported. The nmr of 2-aminoethylphosphonic acid has been determined in D_2O but exchange with the ammonium protons and POH protons prevented information for these protons.[28] Berlin and Nagabhushanam have investigated the nmr of several organophosphorus acids (no α-aminoalkylphosphonic acids were included).[29] These workers observed a geminal P–C–H coupling constant of 17 cps for the CH_2 group in phenylbenzylphosphinic acid (P–O–H exhibited a peak at δ 10.28). Ferraro and Peppard have also studied the nmr spectra of acidic organophosphorous compounds.[30]

Some preliminary studies on inhibition of growth of certain microorganisms by esters **5a, 5b,** and **5d** appear in Table III. In all cases where inhibition was observed a fivefold lower concentration of the compound failed to inhibit growth. The concentrations listed are the highest tested. Growth after prolonged incubation was probably due to mutation to resistance rather than to inactivation of the inhibition compound since this varied with the organism for any specific compound.

TABLE III
RESULTS OF GROWTH STUDIES

	Compound					
	5a		**5b**		**5d**	
Organism	μg/ml	% I	μg/ml	% I	μg/ml	% I
Micrococcus roseus	850	79	850	100	850	100
Pseudomonas aeruginosa					850	0
Escherichia coli					850	9
Bacillus megaterium					850	19[a]
Alcaligenes species	850	0	850	100[a]	850	14
Arthrobacter species	850	100[a]	850	100[a]	850	77[a]
Sarcina hansenii	850	100	850	86	850	92
Staphylococcus aureus	850	0	850	29	850	18

[a] Inhibition was overcome after prolonged incubation.

Experimental Section

Procedures.—All melting points were corrected and determined with a Thomas–Hoover capillary melting point apparatus. Boiling points were uncorrected. Elemental analyses were performed by the Galbraith Laboratories, Inc., Knoxville, Tenn. Nuclear magnetic resonance spectra were obtained from a Varian Associates Model A-60 spectrophotometer using tetramethylsilane (TMS) as an internal reference.

The infrared spectra were obtained using a Beckman IR-5A recording spectrometer (as films on sodium chloride cells for liquid samples or as potassium bromide pellets where the compounds were solids). Infrared spectra of chloroform solutions of diethyl *p*-methoxybenzoylphosphonate oxime (**3d**) and diethyl α-amino-*p*-methoxybenzylphosphonate hydrochloride (**5d**) were obtained using a rock salt cell having a film thickness of 0.01 mm. The chloroform peaks were eliminated in the spectra by adjustment of a variable wedge rock salt cell until a flat response was obtained. Copies of infrared and nmr data can be obtained from the senior author.

Preparation of Diethyl Aroylphosphonates 2.—The general procedure employed is described. A slight excess of triethyl phosphite [bp 62–64° (24 mm)] was added dropwise to an aroyl chloride (commercially available materials or synthesized from commercially available acids using standard methods) under deoxygenated, anhydrous nitrogen[31] and at such a rate so that the temperature of the reaction mixture did not exceed 40°. When necessary, an ice–water bath was provided to control the temperature of the exothermic reaction. The solutions became yellow while being stirred for 4 hr. Chloroethane was evolved during the course of the reaction. The products were purified by vacuum distillation. Elemental analyses and spectral data were used to confirm the structure of new diethyl aroylphosphonates **2**. In examples where the diethyl aroylphosphonates were known, the comparison of spectral and physical properties with those of authentic samples established identity.

Deviations from the above general procedure were employed with 2-naphthoyl chloride (**1h**) and 2,6-dimethoxybenzoyl chloride (**1f**), both of which were solids. These aroyl chlorides were heated (48° for 2-naphthoyl chloride and 66° for 2,6-dimethoxybenzoyl chloride, *i.e.*, to temperatures just above their melting points) prior to the addition of triethyl phosphite.

Preparation of Diethyl Aroylphosphonate Oximes 3.—A diethyl aroylphosphonate **2** (0.100 mol)[32] was slowly added (dropwise at such a rate so as to maintain the temperature of the slightly exothermic reaction below 30°) to a mixture of 200 ml[32] of absolute ethanol, 9.25 g (0.133 mol[32]—33% excess) of hydroxylamine hydrochloride and 11.85 g (0.150 mol[32]—50% excess) of pyridine. The yellow color of the diethyl aroylphosphonates **2** slowly disappeared [except in the case of diethyl 2,6-dimethoxybenzoylphosphonate (**2f**)] in the course of oxime formation. The mixtures were stirred at room temperature for 72 hr. Evaporation of the ethanol *in vacuo* gave a syrup which was mixed with 75 ml of distilled water. This aqueous mixture was extracted with three 75-ml portions of methylene chloride. The organic layers were combined and dried ($MgSO_4$). The solvent was removed, and the syrup was vacuum dried (1–5 mm, room temperature) for 1–3 hr. Infrared spectra and nmr spectra were also recorded.

Deviations from the above general procedure are as follows. Efforts to purify crude diethyl benzolphosphonate oxime (**3a**) through crystallization from a variety of solvents and mixtures of solvents failed. Attempted distillation of **3a** resulted in a violent decomposition as the temperature at the head of the distillation column approached 60° (0.7 mm). The vacuum-dried diethyl benzoylphosphonate oxime (**3a**) was, therefore, used

(28) J. S. Kittredge and R. R. Hughes, *Biochemistry*, **3**, 991 (1964). See also, M. Horiguchi and M. Kandatsu, *Nature*, **184**, 901 (1959), and *Bull. Agr. Chem. Soc. Jap.*, **24**, 565 (1960); and J. S. Kittredge, E. Roberts, and D. G. Simonsen, *Biochemistry*, **1**, 624 (1962).

(29) K. D. Berlin and M. Nagabhushanam, *Proc. Okla. Acad. Sci.*, **45**, 111 (1965).

(30) J. R. Ferraro and P. F. Peppard, *J. Phys. Chem.*, **67**, 2639 (1963).

(31) P. Arthur, *Anal. Chem.*, **36**, 701 (1964).

(32) In all cases 200 ml of ethanol was used. The quantity of aroylphosphonate varied from 0.05 to 0.2 mol, and the quantities of hydroxylamine hydrochloride and pyridine varied so as to maintain the 0.100:0.133:0.150 molar ratio of reagents.

without further purification. In addition to stirring at room temperature (70 hr), the reaction mixture in the preparation of diethyl 2,6-dimethoxybenzoylphosphonate oxime (**3f**) was boiled an additional 2 hr at the end of the stirring period.

Preparation of Aluminum–Amalgam.—This procedure is a modification of that used by Hartman and Phillips.[33] Approximately 100 ml of aqueous 5% mercuric chloride solution was added to 10.0 g (3.70 g-atoms) of aluminum foil (6 × 6 × 0.001 in.) which had been cut into approximately 2-cm squares. The foil remained in contact with the mercuric chloride solution for 5–10 min to effect amalgamation. Three 1-l. portions of distilled water were used to wash the coated aluminum which was used immediately since it rapidly reacts with moisture.

Aluminum–Amalgam Reduction of Diethyl Aroylphosphonate Oximes 3 and Subsequent Salt Formation.—Reduction of either the pure or crude oximes of diethyl aroylphosphonates could be effected by aluminum–amalgam in ethanol–water.

To a fresh aluminum–amalgam prepared in a 2-l. flask was added 500 ml of ethanol (absolute). The oxime (0.01–0.05 mol) dissolved in 200 ml of ethanol (absolute) was added to the aluminum–amalgam mixture. Distilled water (200 ml) was added, and the mixture was stirred for 24 hr. The solids obtained were filtered and thoroughly washed with two 100-ml portions of ethanol (absolute). All washings were combined with the mother liquor. The solvents were stripped from the crude diethyl α-aminoarylmethylphosphonates **4** which was then dissolved in approximately 100 ml of anhydrous ether. Dry hydrogen chloride was slowly bubbled through the ether solution for 5 min. The insoluble hydrochloride salts **5** separated either as oils or white, crystalline solids. The oily materials were crystallized using various solvents. Infrared and nmr spectra data were recorded.

Hydrolysis of the Hydrochloride Salts 5 of Diethyl α-Aminoarylmethylphosphonates 4 to α-Aminoarylmethylphosphonic Acids 7.—The free α-aminoarylmethylphosphonic acids **7** were obtained by boiling the hydrochloride salts **5** in 9 *M* hydrochloric acid for 4 hr. Water was removed by evaporation to give the hydrochloride salts **6** of the α-aminoarylmethylphosphonic acids. These salts were dissolved in a minimum of cold water and heated to boiling. The less soluble free acids **7** precipitated as white crystalline solids and were collected after cooling. A listing of acids **7** along with some of their physical properties are found in Table I. Nmr spectral data for **7** were also recorded.

The Direct Preparation of α-Amino-*p*-chlorobenzylphosphonic Acid (7b) from Diethyl *p*-Chlorobenzoylphosphonate (2b).—A total of 23.12 g (0.0761 mol) [bp 164–166° (0.4–0.6 mm)] of diethyl *p*-chlorobenzoylphosphonate (**2b**) was added dropwise to a mixture of 7.05 g (0.101 mol) of hydroxylamine hydrochloride, 13.11 g (0.166 mol) of pyridine, and 100 ml of ethanol (absolute) at such a rate that the temperature of the mixture did not exceed 30°. The mixture was stirred for 72 hr. The solvent was removed *in vacuo* and 100 ml of water was added to the syrup. Four 100-ml portions of CH_2Cl_2 were used to extract the aqueous mixture. The CH_2Cl_2 layers were dried ($MgSO_4$); the solvent was removed *in vacuo*. The crude diethyl *p*-chlorobenzylphosphonate oxime (**3b**) was dissolved in 100 ml of ethanol and the resulting solution added to a mixture of aluminum–amalgam (prepared as described previously from 20 g of aluminum foil, 1 l. of absolute ethanol, and 400 ml of water). These materials were stirred for 40 hr. The solids were filtered off and washed with ethanol. The washings and filtrate were combined and the solvents were removed *in vacuo*. The resultant syrup was boiled in a solution of 130 ml of concentrated HCl and 100 ml of water for 14 hr. Removal of the volatile components *in vacuo* left an amber syrup. This syrup was mixed with a solution of 30 ml of water and 40 ml of concentrated HCl and decolorized. After the solution was filtered, the solvent was removed *in vacuo*. A syrup resulted which was mixed with 30 ml of water; crystals formed upon standing. The solid was filtered off and dissolved in a minimum of cold water and boiled. The less soluble free acid **7b** precipitated as a white crystalline solid which was collected after cooling. The yield of α-amino-*p*-chlorobenzylphosphonic acid (**7b**) was 11.16 g [66.5% based on diethyl *p*-chlorobenzoylphosphonate (**2b**)]. The infrared and nmr spectra of the free acid were identical with those for a sample prepared and characterized as described previously. A melting point of 288.5–289.2° (mmp 290.4–291.8) was observed.

Dilution Studies by Infrared Analysis of Diethyl *p*-Methoxybenzoylphosphonate Oxime (3d) and Diethyl α-Amino-*p*-methoxybenzylphosphonate Hydrochloride (5d).—The infrared spectra of **3d** and **5d** in chloroform solution were determined using the cells previously described. After balancing the cells until a flat base line was obtained for the chloroform, solutions of **3d** and **5d** at several concentrations were analyzed. See Table II.

Growth Studies. Materials and Methods.—The compounds were tested at concentrations ranging from 20 to 2500 μg/ml. The medium used for testing was nutrient broth (Difco) and incubation was in 18-mm tubes on a reciprocal shaker at 30°. Compounds were dissolved in nutrient broth, filter sterilized, and diluted with broth to the desired final concentration before inoculation. Growth was measured as optical density at 540 mμ using a Coleman Model 6-D spectrophotometer. The bacteria were grown overnight on nutrient agar, and a small amount of growth was transferred with a sterile loop to control tubes (broth only) and those containing the compound to be tested. Initial optical density at 540 mμ was approximately 0.1. Measurements of optical density were made at frequent intervals and the per cent inhibition was calculated at the point of maximum growth in the control cultures. Incubation was continued for an additional 24–48 hr for cultures showing significant inhibition. The results are found in Table III.

Data on Compounds.—**Diethyl aroylphosphonates ArC(O)P(O)$(OC_2H_5)_2$** obtained yielded the following data: **2a**, bp 136–137° (1.4–1.5 mm),[34] yield 84.0%; **2b**, bp 192–197° (0.4–0.6 mm), 33.6% [Calcd (found): C, 47.76 (47.81), H, 5.10 (5.17); P, 11.20 (11.10)]; **2c**, bp 158–160 (2.3 mm), 80.4% [Calcd (found): C, 47.76 (47.71); H, 5.10 (5.25)]; **2d**, bp 175–179° (1.5 mm),[35] 75.9%; **2e**, bp 170–171 (2.2 mm), 89.7% [Calcd (found): C, 52.94 (52.16); H, 6.29 (6.31)]; **2f**, bp 186–189° (0.6–0.8 mm), 69.6% [Calcd (found): C, 51.66 (52.22); H, 6.34 (6.48)]; **2g**, bp 153–155° (3.0 mm), 88.4% [Calcd (found): C, 60.39 (60.20); H, 7.77 (7.83); P, 10.38 (10.52)]; **2h**, bp 188–191° (1.2 mm), 70.2% [Calcd (found): C, 61.64 (61.88); H, 5.86 (5.87); P, 10.60 (10.00)].

Oximes obtained yielded the following data: **3a**;[36] **3b**, bp 93–95°, 82.6% [Calcd (found): N, 4.80 (5.01); P, 10.62 (10.75)]; **3c**, mp 123.3–123.8°, 66.7% [Calcd (found): N, 4.80 (4.82); P, 10.62 (10.77)]; **3d**, mp 83.6–84.9°, 99.0% [Calcd (found): N, 4.88 (5.08); P, 10.78 (11.00)]; **3e**, mp 113.4–114.6°, 89.5% [Calcd (found): N, 4.88 (5.12); P, 10.78 (10.82)]; **3f**, mp 137.5–138.7°, 64.8%;[37] **3g**, mp 117.9–119.1°, 76.3% [Calcd (found): N, 4.47 (4.61); P, 9.88 (9.77)]; **3h**.[37]

Diethyl α-aminoarylmethylphosphonates, ArCH(NH_2·HCl)P(O)$(OC_2H_5)_2$, obtained yielded the following data: **5a**, mp 162.2–163.4°, 74.5% [Calcd (found): P, 11.07 (11.30)]; **5b**, mp 173.3–173.8°, 48.5% [Calcd (found): P, 9.86 (9.83)]; **5d**, mp 169.3–169.7°, 82% [Calcd (found): P, 10.00 (9.79)]; **5e**, mp 126.7–127.1°, 37.9% [Calcd (found): P, 10.00 (10.45)]; **5f**, mp 143.7–144.2°, 85.2% [Calcd (found): P, 9.12 (9.39)]; **5g**, mp 168.5–169.7°, 77.9% [Calcd (found): C, 53.65 (53.78)], H, 8.10 (8.13); **5h**, mp 181.3–183.1°, 58.7% [Calcd (found): P, 8.96 (9.17)].

Registry No.—**2a**, 3277-27-8; **2b**, 10570-46-4; **2c**, 16656-42-1; **2d**, 16703-95-0; **2e**, 16656-43-2; **2f**, 16656-44-3; **2g**, 10570-47-5; **2h**, 16656-46-5; **3b**, 16656-47-6; **3c**, 16656-48-7; **3d**, 16703-96-1; **3e**, 16703-97-2; **3f**, 16703-98-3; **3g**, 16656-49-8; **5a**, 16656-50-1; **5b**, 16656-51-2; **5d**, 16656-52-3; **5e**, 16656-53-4; **5f**, 16656-54-5; **5g**, 16656-56-7; **5h**, 16656-58-9; **7b**, 16656-60-3; **7d**, 16656-61-4; **7h**, 16703-99-4.

(33) W. W. Hartman and R. Phillips, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p 232.

(34) M. I. Kabachnik and P. A. Rossiiskaya [*Bull. Acad. Sci. SSSR, Classe Sci. Chim.*, 364 (1945); *Chem. Abstr.*, **40**, 4688 (1948)] found bp 141° (2.5 mm).

(35) K. D. Berlin and H. A. Taylor, *J. Amer. Chem. Soc.*, **86**, 3862 (1964): bp 158 (0.4 mm).

(36) Liquid sample; **3a** could not be crystallized using a variety of solvents and violently decomposed upon attempted distillation.

(37) This material was reduced directly since it also tended to decompose on heating.