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PREPARATION OF OPTICALLY ACTIVE 1-AMINOALKYLPHOSPHONIC ACIDS BY STEREOSELECTIVE ENZYMATIC HYDROLYSIS OF RACEMIC N-ACYLATED 1-AMINOALKYLPHOSPHONIC ACIDS

V.A.Solodenko[a], T.N.Kasheva[a], V.P.Kukhar[a], E.V.Kozlova[b], D.A.Mironenko[b] and V.K.Švedas[b]*

[a]Institute of Bioorganic Chemistry of the Ukrainian Academy of Sciences, Kiev 252660, USSR

[b]A.N.Belozersky Laboratory of Molecular Biology and Bioorganic Chemistry, Moscow State University, Moscow 119899, USSR

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Abstract. N-Phenylacetylated derivatives of 1-aminoalkylphosphonic acids were synthesized and high enantioselectivity of their hydrolysis by penicillin acylase (EC 3.5.1.11) was demonstrated. Stereoselective enzymatic hydrolysis of racemic 1-(N-phenylacetylamino)alkylphosphonic acids was used for preparation of enantiomeric 1-aminoalkylphosphonic acids. The kinetic regularities of penicillin acylase catalyzed hydrolysis were established and the biocatalytic process was optimized to increase the optical purity and the yield of the optically active product.

Aminoalkylphosphonic acids have been attracting a good deal of attention ever since the first compounds with a phosphorus-to carbon bond were detected among natural products[1]. As mimetics of the natural amino acids, they seem to be strong potential bioregulators. These compounds are found to be the substrates and inhibitors of enzymes, as well as plant growth regulators and herbicides. They also display antibacterial and neuronal activities[2,3]. Aminoalkylphosphonic acids, now readily available thanks to a large number of methods for their synthesis[4], are widely used in biochemical studies. Evidently, the bioactivity of these compounds essentially depends on the stereochemistry of the asymmetric carbon which must correspond to L-configuration of the natural amino acids[5,6]. There are two general approaches in preparing the optically active 1-aminoalkylphosphonic acids - (i) asymmetric synthesis of enantiomers[7-11] and (ii) resolution of racemates using diastereomeric compounds[12-14]. These methods are not devoid of certain drawbacks: unsatisfactory optical purity in the former, and low yields of the products in the latter. Both these approaches need additional, optically active reagents.

By contrast the enzymatic separation of racemates is free from the above constraints.

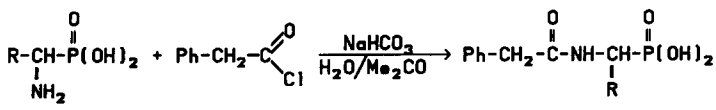
As reported previously[15], penicillin acylase from E.coli (EC 3.5.1.11)

hydrolyzes stereoselectively N-phenylacetylated derivatives of 1-aminoalkylphosphonic acids and their esters. Penicillin acylase is widely used for modification of β-lactam antibiotics. The enzyme exhibits high affinity for the phenylacetyl moiety and hydrolyzes different phenylacetic acid derivatives and, among other compounds, N-phenylacetylated amino acids and peptides[16,17].

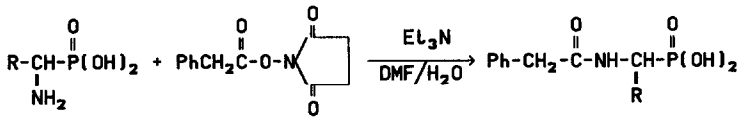
In this paper we describe optimization of the enzymatic resolution of racemates and a procedure for preparing the L- and D-enantiomers of 1-aminoalkylphosphonic acids.

N-Phenylacetylated 1-aminoalkylphosphonic acids were prepared as shown in Scheme 1:

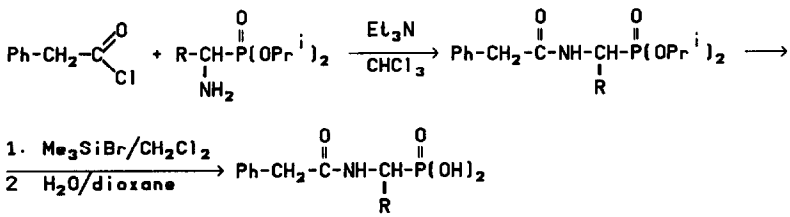
Scheme 1



(A)



(B)



(C)

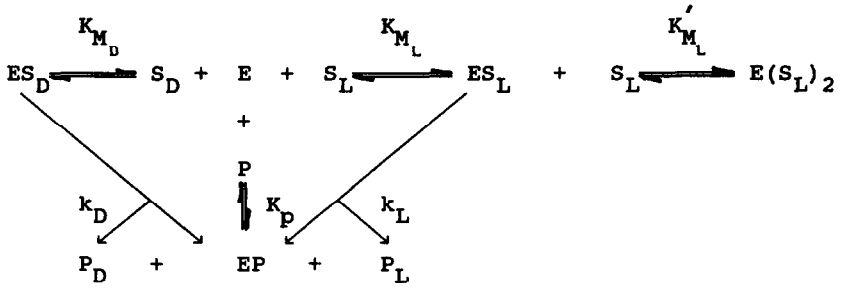
1-Aminophosphonic acids were N-acylated with phenylacetyl chloride according to a modified procedure of Schotten and Baumann (method A), or with N-hydroxysuccinimide ester of phenylacetic acid in aqueous DMF in the presence of a tertiary amine (method B). According to method C, the 1-aminoalkylphosphonic acid diisopropyl esters were N-acylated with phenylacetyl chloride followed by P-deprotection with trimethylsilyl bromide. This procedure yields both N-phenylacetylated 1-aminoalkylphosphonic acids and corresponding esters.

The enzymatic hydrolysis of racemic N-phenylacetylated 1-aminoalkylphosphonic acids was found to proceed according to Scheme 2 (see next page).

Computer simulation of the enzymatic hydrolysis of 1-(N-phenylacetylamino)ethylphosphonic acid, using the kinetic parameters obtained previous-

ly[15], was attempted in order to find the conditions of the maximum conversion of L-1-(N-phenylacetylamino)ethylphosphonic acid to L-1-aminoethylphosphonic acid and optical purity of the product. This simulation visualizes the conversion of L-form of the substrate and the content of L-isomer in a total 1-aminoethylphosphonic acid as a function of initial concentra-

Scheme 2



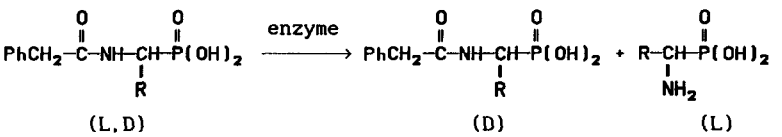
Here E is penicillin acylase, S_D and S_L - L- and D-enantiomers of the N-phenylacetylated derivative of 1-aminoalkylphosphonic acid, P_D and P_L - L- and D-enantiomers of 1-aminoalkylphosphonic acid, and P - phenylacetic acid[15].

tions of the enzyme and racemic 1-(N-phenylacetylamino)ethylphosphonic acid (Fig.1). It is seen that the both parameters vary with the change in the concentration in a different way. In particular, the conversion increases up to 100% with the increase in the enzyme and the decrease in the racemic substrate concentrations, while the content of L-isomer decreases from 100% (the optically pure product) to 50% (racemic aminophosphonic acid).

Optimal enzyme and substrate concentration intervals can be selected on the basis of the results presented in Fig.1. The cross-hatched area indicates concentration intervals where the conversion is more than 90% and the content of L-isomer in a total 1-aminoethylphosphonic acid exceeds 98%. It is to be noted that these requirements hold even for the concentrated solutions of racemic substrate.

Under the optimal conditions, the enzymatic hydrolysis of racemic N-phenylacetylated 1-aminoalkylphosphonic acids can be carried out according to Scheme 3.

Scheme 3



(L,D) (D) (L)

This enzymatic reaction was used for the preparation of optically active 1-aminoalkylphosphonic acids. The method includes a biocatalytic step (Scheme 3) followed by chromatographic separation of the L-aminophosphonic

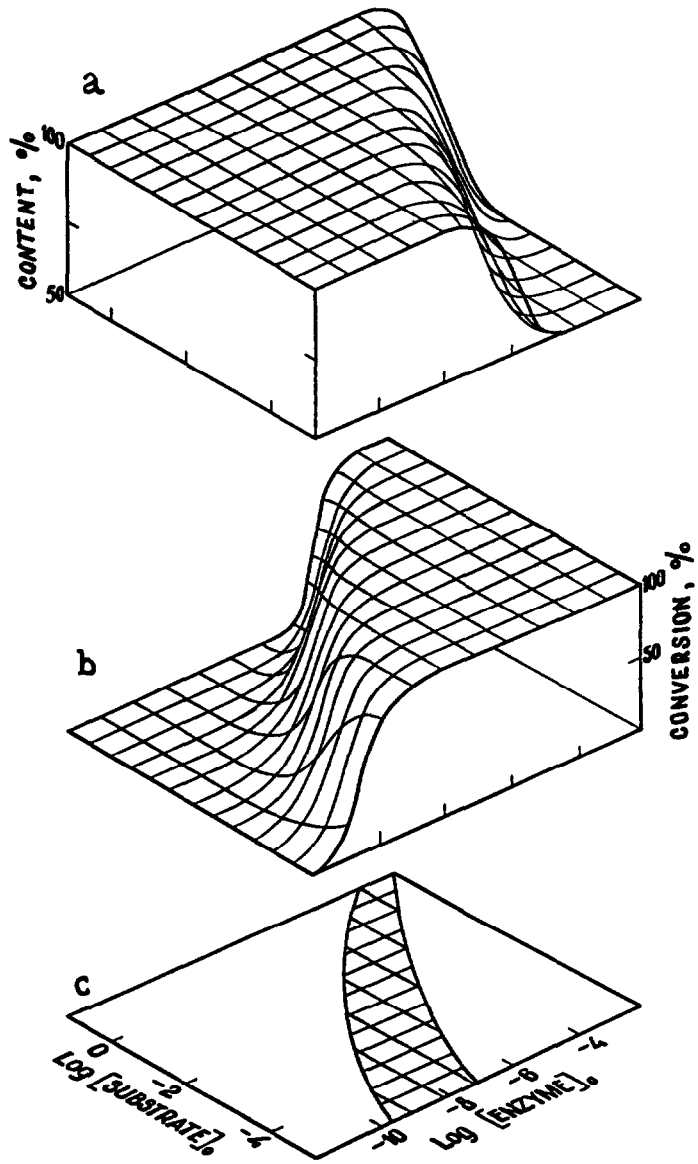


Fig.1. The dependence of the conversion of L-1-(N-phenylacetylamino)ethylphosphonic acid to L-1-aminoethylphosphonic acid (b) and the content of the later in the total 1-aminoethylphosphonic acid after enzymatic hydrolysis of racemic substrate (a) on the initial concentrations of penicillin acylase and racemic substrate. Cross-hatched area (c) shows the concentration range where conversion and content exceed 90% and 98%, respectively. For the other substrates the similar dependences are observed.

acid from the unreacted D-1-(N-phenylacetylamino)alkylphosphonic acid. Acid hydrolysis of the latter is enabled by D-aminophosphonic acid. Yields and some physico-chemical characteristics of 1-aminoalkylphosphonic acids are shown in Table 1.

Table 1. Optically active 1-aminoalkylphosphonic acids $R-CH(NH_2)-P(O)(OH)_2$

R	Time of enzymatic reaction, h	Stereochemical configuration	Yield[a], %	m.p., °C(dec)	Specific optical rotation, deg $[\alpha]_D^{20}$ ($[\alpha]_{578}^{20}$)	^{31}P NMR[d], δ, ppm
CH_3	2	L	82	274-277	-17.0 (-17.8)	22 3
	24	L	80	274-277	-17.0[b]	22 3
	-	D	80	276-278	+16.5 (+17.0)[b]	22.3
C_6H_5	24	L	73	281-283	+24 0[b]	18.2
	-	D	71	280-282	-23 0[b]	18.2
CH_3 \ CH_3 / $CH-CH_2$	24	L	76	275-278	-34 5 (-36 5)[c]	22 7
$C_6H_5CH_2$	50	L	77	275-277	-50 0 (-52.0)[c]	20.0

[a] Overall yield, whereas the degree of enzymatic conversion is almost quantitative.

[b] C = 0.5%, 1 N NaOH

[c] C = 0.25%, 1 N NaOH

[d] in $NaOH/H_2O$

A comparison of the values of optical rotation obtained here with those reported in the literature[12,14,18] indicates that the proposed method makes it possible to achieve the highest yield and excellent optical purity. This approach can be applied successfully either in distilled water or in a buffered solution (pH 5.5 - 10.5) at substrate concentrations 0.04 - 0.13 M, the substrate/enzyme molar ratios varying from $2 \cdot 10^5$ to $1.5 \cdot 10^6$. Both the native and the immobilized penicillin acylases were used at temperatures allowing the enzyme stability.

It is noteworthy that changing the time of the enzymatic step from 2 to 24 hours does not affect the yield and optical purity of L-1-aminoethylphosphonic acid. This indicates high stereoselectivity of the penicillin acylase catalysed hydrolysis.

Considering the excellent technological exploitation characteristics

of penicillin acylase, first of all its high stability and activity, and the broad substrate specificity of this enzyme among N-acylated derivatives of 1-aminoalkylphosphonic acids we hope that the proposed biocatalytic method will be suitable for obtaining optically active 1-aminoalkylphosphonic acids on a preparative scale.

EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. NMR spectra were recorded on Varian VXR-300 and Bruker WP-200 spectrometers and chemical shifts were presented in ppm from TMS (^1H) and 85% H_3PO_4 (^{31}P) as standards. Optical rotations were measured on Polamat A and Spectropol polarimeters. TLC analysis was performed on Silufol plates, the spots being visualized by iodine vapor, ninhydrin, and chlorine-tolidine. A cation-exchange resin was Dowex W50x8 freshly regenerated in the acid cycle.

Diisopropyl esters of 1-aminoalkylphosphonic acids were synthesized according to the procedure of Kowalik et al.[19]. Additionally, diisopropyl ester of 1-aminoethylphosphonic acid was obtained by catalytic hydrogenation of diisopropyl 1-hydroxyiminoethylphosphonate[20] using Reney nickel under atmospheric pressure at room temperature (isolated as oxalate salt, yield 75%). 1-Aminoalkylphosphonic acids were obtained as previously described[21].

Penicillin acylase (EC 3.5.1.11) from E.coli ATCC 9637 was used in soluble and immobilized forms. The enzyme concentration was determined as described[22]. The specific activity of the immobilized enzyme was determined with benzylpenicillin as a substrate[23].

1-(N-Phenylacetylamino)alkylphosphonic acids and their esters. Method A. Phenylacetyl chloride (4.0 g, 26 mmol) in 15 ml acetone was added at -5°C for 0.5 h to a solution of 1-amino-3-methylbutylphosphonic acid (3.34 g, 20 mmol) and sodium hydrogen carbonate (4.03 g, 48 mmol) in 90 ml acetone and 30 ml water. The mixture was stirred at -5°C for 2 h and then for 1 h at room temperature. Acetone was removed *in vacuo*, the residual aqueous solution was washed with ether, acidified with 10% HCl to pH 2 and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was passed through a cation-exchange resin (eluent methanol/water = 3:2). The acidic eluate was evaporated, the residue was dried over P_2O_5 to give **1-(N-phenylacetylamino)-3-methylbutylphosphonic acid** as a waxy material (4.6 g). Yield 75.7%. ^1H NMR (D_2O/CD_3OD), δ: 0.70 and 0.80 (2d, J = 6 Hz, 6H, $(C\underline{H}_3)_2CH$), 1.46 (m, 3H, $Me_2C\underline{H}C\underline{H}_2$), 3.45 (s, 2H, $PhC\underline{H}_2$), 4.09 (m, 1H, $C\underline{H}P$), 7.22 (s, 5H, $C_6\underline{H}_5$).

^{31}P NMR δ_P 23.80 (CH_3OH). Anal. Found: C 51.14, H 7.35, N 4.74, P 10.61. Calcd for $C_{13}H_{20}NO_4P \cdot H_2O$: C 51.47, H 7.31, N 4.61, P 10.21%.

1-(N-Phenylacetylamino)-1-phenylmethylphosphonic acid was synthesized in a similar way, yield 72.6%, mp 101-102°C (H_2O). ^{1}H NMR (acetone-d_6),δ: 3.58 (s, 2H, PhC$\underline{H}_2$), 5.44 (m, 1H, C$\underline{H}$P), 6.9-7.6 (m, 10H, 2xC$_6\underline{H}_5$), 8.34 (broad, 1H, N$\underline{H}$). ^{31}P NMR δ_P 18.23 (NaOH). Anal. Found: C 55.72, H 5.61, N 4.33, P 9.58. Calcd for $C_{15}H_{16}NO_4P \cdot H_2O$: C 56.07, H 5.58, N 4.36, P 9.79%.

Method B. A slurry of 1-amino-3-methylbutylphosphonic acid (0.75 g, 4.5 mmol) in a mixture of water (3 ml), DMF (11 ml) and triethylamine (0.91 g, 9 mmol) was cooled to 0°C and N-hydroxysuccinimide ester of phenylacetic acid (1.16 g, 5 mmol) was added. The resulting slurry was stirred at 0°C for 0.5 h and then at room temperature overnight. The almost clear solution was filtered, the filtrate was evaporated *in vacuo* to give a gummy material which was dissolved in a minimal volume of a mixture methanol:water (3:2); the solution was passed through a cation-exchange resin and eluted by the same solvent. Acidic fractions were evaporated *in vacuo* to give 0.94 g of **1-(N-phenylacetylamino)-3-methylbutylphosphonic acid** (yield 73.5%) fully identical with the substance prepared according to method A.

Method C. 1) **Diesters of 1-(N-phenylacetylamino)alkylphosphonic acids.** Phenylacetyl chloride (3.08 g, 20 mmol) was added to a stirred solution of hydrogen oxalate of diisopropyl ester of 1-aminoethylphosphonic acid (5.98 g, 20 mmol) and triethylamine (4.1 g, 40 mmol) in chloroform (40 ml). The mixture was stirred for 1 h and allowed to stand overnight. Then it was diluted with 50 ml chloroform and washed successively with water (3x20 ml), a saturated solution of sodium hydrogen carbonate (2x20 ml), 10% potassium hydrogen sulfate (2x20 ml), water (20 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo*, and the residue was crystallized from benzene-hexane to give 4.3 g (66%) of **1-(N-phenylacetyl-amino)ethylphosphonic acid diisopropyl ester**, mp 114-115°C. ^{1}H NMR ($CDCl_3$),δ: 1.04-1.43 {m, 15H, C$\underline{H}_3$CHP and 2xOCH(C$\underline{H}_3$)$_2$}, 3.52 (s, 2H, PhC$\underline{H}_2$), 4.27-4.75 (m, 3H, CH_3C$\underline{H}$P and 2xOC$\underline{H}$Me$_2$), 7.26 (s, 5H, C$_6\underline{H}_5$). ^{31}P NMR δ_P 21.2 ($CDCl_3$). Anal. Found: C 58.21, H 7.91, N 4.46, P 9.41. Calcd for $C_{16}H_{26}NO_4P$: C 58.70, H 8.00, N 4.27, P 9.46%.

The following compounds were synthesized in a similar way:

a) **1-(N-phenylacetylamino)-3-methylbutylphosphonic acid diisopropyl ester**, yield 72.7%, mp 146-148°C (benzene-hexane). ^{1}H NMR ($CDCl_3$), δ: 0.87 and 0.91 {2d, J = 6Hz, 6H, $CH_2CH(C\underline{H}_3)_2$}, 1.24 {m, 12H, 2xOCH(C$\underline{H}_3$)$_2$}, 1.54 (m, 3H, C$\underline{H}_2C\underline{H}$), 3.59 (s, 2H, PhC$\underline{H}_2$), 4.61 {m, 3H, P(OC$\underline{H}$<)$_2$and NC$\underline{H}$P}, 5.55 (s, 1H, N$\underline{H}$), 7.29 (s, 5H, C$_6\underline{H}_5$). ^{31}P NMR δ_P 23.05 ($CHCl_3$). Anal. Found:

C 61.66, H 8.68, N 3.94, P 8.16. Calcd for $C_{19}H_{32}NO_4P$: C 61.76, H 8.73, N 3.79, P 8.38%;

b) **1-(N-phenylacetylamino)-2-phenylethylphosphonic acid diisopropyl ester,** yield 81%, mp 122-124°C (benzene-hexane). ^1H NMR ($CDCl_3$), δ: 1.14 (m, 12H, 4xCH_3), 2.60-3.20 (m, 2H, CH_2CHP), 3.37 (s, 2H, $PhCH_2CO$), 4.42-4.78 (m, 3H, CHPand $P(OCH<)_2$), 6.16 (s, 1H, NH), 7.07 and 7.17 (2m, 2x5H, 2xC_6H_5). ^{31}P NMR δ_P 21.54 ($CHCl_3$). Anal. Found: C 65.65, H 7.67, N 3.48, P 7.28. Calcd for $C_{22}H_{30}NO_4P$: C 65.49, H 7.49, N 3.47, P 7.67%.

2) **1-(N-Phenylacetylamino)alkylphosphonic acids.** Trimethylsilylbromide (1.68 g, 11 mmol) was added to a solution of 1-(N-phenylacetylamino)ethylphosphonic acid diisopropyl ester (1.63 g, 5 mmol) in 25 ml methylene chloride under argon. The mixture was stirred for 5 h at room temperature and then refluxed for 2 h. Methylene chloride was removed *in vacuo*, the oilish residue dissolved in 5 ml dioxane, and water (0.25 ml, 11 mmol) added. The mixture was heated for 1 h and cooled. The precipitated **1-(N-phenylacetylamino)ethylphosphonic acid** was filtered off and recrystallized from dioxane. Yield 1.0 g (83%), mp 145-147°C (dioxane). ^1H NMR (D_2O), δ: 1.63 (dd, J_{HH} = 7.0 Hz, J_{PH}= 16.0 Hz, 3H, CH_3CHP), 3.93 (s, 2H, $PhCH_2$), 4.20-4.75 (m, 1H, CHP), 7.64 (s, 5H, C_6H_5). ^{31}P NMR δ_P 20.2 (CD_3OD). Anal. Found: C 49.65, H 6.00, N 5.55, P 12.44. Calcd for $C_{10}H_{14}NO_4P$: C 49.38, H 5.80, N 5.76, P 12.73%.

The following compounds were synthesized in a similar way:

a) **1-(N-phenylacetylamino)-3-methylbutylphosphonic acid,** yield 69%, a glassy material after purification by cation-exchange chromatography as described in method A;

b) **1-(N-phenylacetylamino)-2-phenylethylphosphonic acid,** yield 68%, mp 145-146°C (methanol-water). ^1H NMR (acetone-d_6), δ: 2.78-3.32 (m, 2H, $PhCH_2CHP$), 3.41 (s, 2H, $PhCH_2CO$), 4.55 (m, 1H, CHP), 6.95-7.23 (m, 10H, 2xC_6H_5). ^{31}P NMR δ_P 22.15 (CH_3OH). Anal. Found: C 58.26, H 5.45, N 4.32, P 9.40. Calcd for $C_{16}H_{18}NO_4P \cdot 0.5\ H_2O$: C 58.50, H 5.83, N 4.26, P 9.43%.

A typical procedure for the preparation of optically active 1-aminoalkylphosphonic acids. (L,D)-1-(N-phenylacetylamino)ethylphosphonic acid (9.72 g, 40 mmol) was dissolved in 300 ml of 0.01 M phosphate buffer and pH was adjusted to 6.85 with 1 N KOH. The enzyme solution (3 ml of $2 \cdot 10^{-5}$ M) was added,* and the mixture was stirred at room temperature. The pH was kept at 6.8-7.0 by addition of 1 N KOH. The reaction progress was controlled by determination of aminophosphonic acid released (i) by automatic titration with 10 mM KOH or (ii) spectrophotometrically, using o-

*or 5-7 g of immobilized penicillin acylase with specific activity $2 \cdot 10^3$ U/g.

phthalaldehyde. After stirring for 2 h, the reaction completed and 1 N HCl was added to make pH 5. The solution was heated with activated carbon (65-70°C, 10 min) and filtered.* The clear cold solution was washed with ether (3x100 ml). The aqueous layer was concentrated *in vacuo* to 75 ml, the bath temperature being 50-55°C, and the pH was adjusted to 2 by the addition of concentrated HCl. This solution was passed through a cation-exchange resin (4x45 cm column) using distilled water as an eluent. Weakly acidic ninhydrin-positive fractions were evaporated to dryness, and the solid residue was crystallized from water-ethanol to give 2.05 g of **L-1-aminoethylphosphonic acid.** Yield 82%, mp 274-277°C dec, $[\alpha]_{578}^{20}$ -17.8°, $[\alpha]_{589}^{20}$ -17.0°(c=0.5%, 1 N NaOH), $[\alpha]_{589}^{20}$ -5.5°(c=0.5%, H_2O). ^{31}P NMR δ_P 22.3 (NaOH). Lit.[18] $[\alpha]_{589}^{20}$ -16.9° (c=2%, 1 N NaOH).

More acidic ninhydrin-negative and chlorine-tolidine-positive fractions were evaporated, the solid residue was crystallized from water to give 3.79 g (78%) of **D-1-(N-phenylacetylamino)ethylphosphonic acid,** mp 149-152°C. $[\alpha]_{589}^{20}$ +11.4° (c=0.5%, 1 N NaOH), $[\alpha]_{589}^{20}$ +38.0 (c=0.5%, H_2O). ^1H NMR (D_2O) was as for the racemate. Anal. Found: N 5.66, P 12.75. Calcd for $C_{10}H_{14}NO_4P$: N 5.76, P 12.73%. 2.43 g (10 mmol) of D-1-(N-phenylacetylamino)ethylphosphonic acid was dissolved in 20 ml concentrated HCl and 5 ml acetic acid, and then refluxed for 8 h. The solution was evaporated. The solid residue was partitioned between water and ether. The aqueous extract was evaporated to dryness, the residue dissolved in 15 ml absolute ethanol and 2 ml propylene oxide was added. The solid precipitate was filtered off and recrystallized from water-ethanol to give 1.0 g (80%) of **D-1-aminoethylphosphonic acid,** mp 276-278°C dec, $[\alpha]_{578}^{20}$ +17.0°, $[\alpha]_{589}^{20}$ +16.5° (c=0.5%, 1 N NaOH). ^{31}P NMR δ_P 22,3 (NaOH).

The characteristics of optically active 1-aminoalkylphosphonic acids prepared by this method are summarized in Table 1.

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*this stage was omitted, when the immobilized enzyme was used: upon completion of the reaction the enzyme was filtered off and the filtrate was washed with ether.

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