(β-Chloro-α-aminoethyl)phosphonic Acids as Inhibitors of Alanine Racemase and D-Alanine:D-Alanine Ligase

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The (β-chloro-, (β,β-dichloro-, and (β,β,β-trichloro-α-aminoethyl)phosphonic acids have been synthesized and their inhibitory properties on the alanine racemases [EC 5.1.1.1] and the D-Ala:D-Ala ligases [EC 6.3.2.4] from *Pseudomonas aeruginosa* and *Streptococcus faecalis* have been evaluated. The monochloro and the dichloro derivatives of Ala-P exhibit a strong inhibition on the racemases of the two species tested but do not behave as suicide substrates. Only the D-Ala:D-Ala ligase of *S. faecalis* is inhibited by these compounds. The poor antibacterial activity observed with β-chloro- and β,β-dichloro-Ala-P might be enhanced by the peptide-transport strategy.

Enzymes involved in the synthesis of uridine diphosphate–*N*-acetylmuramyl pentapeptide are targets of choice for the rational design of antibiotic agents. Alanine metabolism in murein synthesis is particularly interesting since the pentapeptide possesses three alanyl residues, two of these being of the D configuration. Alanine racemase and D-Ala:D-Ala ligase are initial enzymes involved in the elaboration of this precursor of peptidoglycan. A number of components that interfere with the alanine metabolism have long been studied.[2a] Among them, the phosphonic analogue of alanine, (1-aminoethyl)phosphonic acid, has been found to be a potent inhibitor of the alanine racemase[2b-6] and of the D-Ala:D-Ala ligase[5,7] of several Gram-positive and Gram-negative bacteria.[2-5] This molecule became an effective antibiotic agent when the problem of its transport was elegantly resolved by its incorporation in a peptide linkage.[5]

On the other hand, β-haloalanines were demonstrated to be reversible or irreversible mechanism-based inactivators of bacterial PLP-dependent enzymes: β-chloroalanine is a potent competitive inhibitor of D-amino acid transaminase of *Bacillus sphaericus*[8] and irreversibly inactivates L-aspartate β-decarboxylase of *Alcaligenes faecalis*[9] as well as transaminase B of *Salmonella typhimurium*.[10] It was also found to interact with the alanine racemase of *Escherichia coli*[11] and to be bacteriostatic against both Gram-positive and Gram-negative organisms.[12] Monofluoro- and trifluoroalanines are suicide substrates that yield stable adducts with *E. coli* alanine racemase whereas the difluoro derivative is an exceedingly inefficient inactivator of this enzyme.[13]

Given these findings one would expect that inactivation of alanine racemase by (1-aminoethyl)phosphonate could be enhanced by its chloro derivatives which may behave as suicide substrates.[14] Hence the synthesis of (β-chloro-, (β,β-dichloro-, and (β,β,β-trichloro-α-aminoethyl)-phosphonic acids was undertaken in order to study the mode of inactivation they may exert on the alanine racemases [EC 5.1.1.1] and on the D-Ala:D-Ala ligases [EC 6.3.2.4] from *P. aeruginosa* and *S. faecalis*.

Results and Discussion

Chemistry. The selective tri-*n*-butyl hydride reduction on alkyl (1-acylamino-2,2,2-trichloroethyl)phosphonates provides a readily available access to monochloro- and dichloro-substituted (1-aminoethyl)phosphonate derivatives.[15] We used this method to prepare dimethyl [1-[(benzyloxycarbonyl)amino]-2,2-dichloroethyl]phosphonate (**2**) and dimethyl [1-[(benzyloxycarbonyl)amino]-2-chloroethyl]phosphonate (**3**) from dimethyl [1-[(benzyloxycarbonyl)amino]-2,2,2-trichloroethyl]phosphonate (**1**). An Arbusov–Michaelis reaction of 1,2,2,2-tetrachloro-*N*-

Scheme I

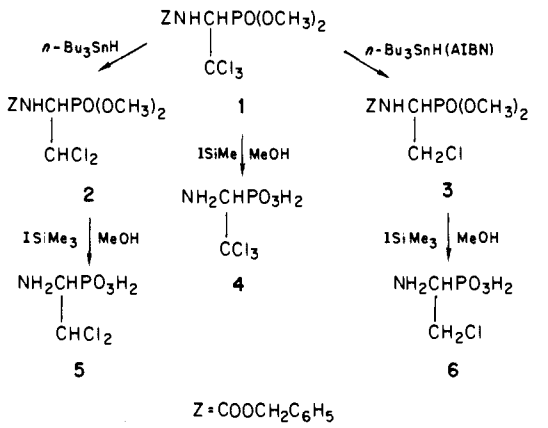

Table I. Properties of **4–6**

product	mp, °C	mol formula	anal.	^{13}C NMR, $\delta(^1J_{^{13}C-P}$, Hz) C_α	C_β
4	220–230	$C_2H_5Cl_3NO_3P$	C, H, N, O, Cl, P	66.93 (146.6)	94.07
5	205–210	$C_2H_6Cl_2NO_3P$	C, H, N, O, Cl, P	58.90 (142.8)	67.53
6	202 (21)				

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(1) The abbreviations used are as follows: Ala-P, (1-aminoethyl)phosphonic acid; PLP, pyridoxal 5′-phosphate; PL, pyridoxal; D-Ala:D-Ala ligase, D-alanine:D-alanine ligase.

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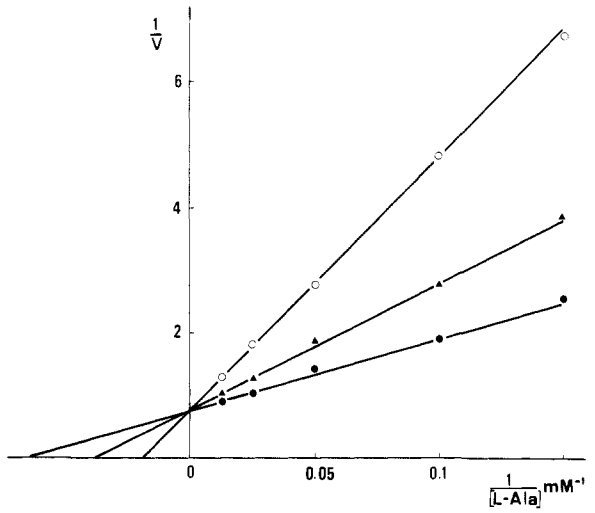

Figure 1. Competitive inhibition of alanine racemase from *Pseudomonas aeruginosa* by 5 mM of (β-chloro-α-aminoethyl)-phosphonic acid (▲) and by 10 mM of (β,β-dichloro-α-aminoethyl)phosphonic acid (○). Control curve (●). The points shown in the figure are the mean of three experiments.

(benzyloxycarbonyl)ethylamine with trimethyl phosphite easily affords the trichloro compound **1**, which can be selectively reduced with 1 equiv of tri-*n*-butyltin hydride in toluene into the dichloro derivative **2** or with 2 equiv of tri-*n*-butyltin hydride and a catalyst, azobis(isobutyronitrile) (AIBN), into the chloro derivative **3** in almost quantitative yield[15] (Scheme I).

Protected aminophosphonates **1–3** were converted into their respective (aminoethyl)phosphonic acids **4–6** by using the silylation procedure.[16] Iodotrimethylsilane[17] was found to be an extremely efficient reagent for the dealkylation of phosphonic esters[18] and the removal of the carbamate protecting group[19,20] under mild and neutral conditions. Physical data for the (β-chloro- (β,β-dichloro-, and (β,β,-β-trichloro-α-aminoethyl)phosphonic acids (Cl-Ala-P, Cl_2-Ala-P, and Cl_3-Ala-P, respectively) obtained are summarized in Table I.

Enzymatic Assays. Alanine racemase from *P. aeruginosa* was competitively inhibited by compounds **4–6**, the extent of inhibition decreasing from mono- to di- to trichloro derivative. A K_m value of 14.2 mM for L-Ala and K_i values of 2.2 mM for Cl-Ala-P and 15 mM for Cl_2-Ala-P were obtained as shown in Figure 1. Cl_3-Ala-P is a poor inhibitor: the enzymatic activity was reduced to 10% when a ratio of [inhibitor]/[substrate] = 4 was used in the reaction mixture.

Alanine racemase from *S. faecalis* was noncompetitively inhibited by **4–6** (K_m and V_m modified). This may be explained by the loose binding of the cofactor to the protein. Excess PLP added in the reaction mixture to reactivate the racemase is able to combine with Cl-Ala-P much more rapidly than with L-Ala (as shown in Figure 2 by use of PL instead of PLP), giving a new inhibitory species, the aldimine PLP-Cl-Ala-P. Similar to the reduced cofactor–L-Ala adduct we have recently tested,[22] this Schiff base should behave as a competitive inhibitor toward the cofactor and as a noncompetitive one toward L-Ala whereas Cl-Ala-P is only a competitor of the substrate. In our experimental conditions, with an excess of PLP and varying concentrations of L-Ala, the overall reaction can be formally analyzed according to a mixed inhibition type:

$$V = \frac{Vs}{K_m\,[1 + (i/K_i)] + s\,[1 + (i/K'_i)]}$$

The apparent K_i and K'_i dissociation constant values are given in Figure 3 as demonstrated by Cornish-Bowden[23] K_m = 8 mM; K_i = 0.38 mM and K'_i = 0.82 mM for Cl-Ala-P; K_i = 1.3 mM and K'_i = 2 mM for Cl_2-Ala-P.

Since β-chloro-,[11] β-fluoro-, and β,β,β-trifluoroalanines[13] were found to irreversibly inactivate alanine racemase, we have researched whether compounds **4–6** would exhibit a time-dependent inactivation. For that purpose alanine racemase and inhibitor were incubated in the buffer at 20 °C and 50-μL aliquots were removed at 0, 5, 10, and 15 min for dilution into a standard assay. The activity of the enzyme of *P. aeruginosa* was not modified whereas that of *S. faecalis* was reduced to about 30%. But this is not an irreversible process since regeneration of catalytic activity can be achieved by dialysis against phosphate buffer, pH 8, containing 0.5 mM PLP.

The D-Ala:D-Ala ligase from *S. faecalis* (K_m = 7.2 mM) was competitively inhibited by the mono- and dichloro derivatives with apparent K_i values of 15 and 24 mM, respectively, established from Lineweaver–Burk and Dixon plots. The enzyme of *P. aeruginosa* was insensitive to these compounds, showing a different profile of the two ligases.

All the compounds used in this note were of DL configuration. Considering that only the D form is recognized by D-Ala:D-Ala ligase, the true K_i values are likely to be half of the observed values, thus closely related to the K_m of the enzyme for Cl-Ala-P. The bulky Cl_3-Ala-P did not interact with the ligase.

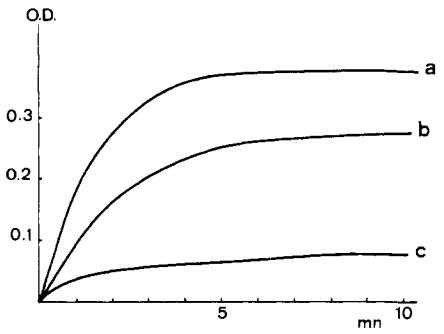

Figure 2. Time course formation of Schiff bases between pyridoxal and phosphonic analogues of alanine. The velocity of the reactions, performed in 10^{-1} M phosphate buffer, pH 7.5, containing 2.10^{-4} M of PL and 5.10^{-2} M of β-Cl-Ala-P (a), Ala-P (b), or L-Ala (c), was recorded on a Varian spectrophotometer at λ 410 nm.

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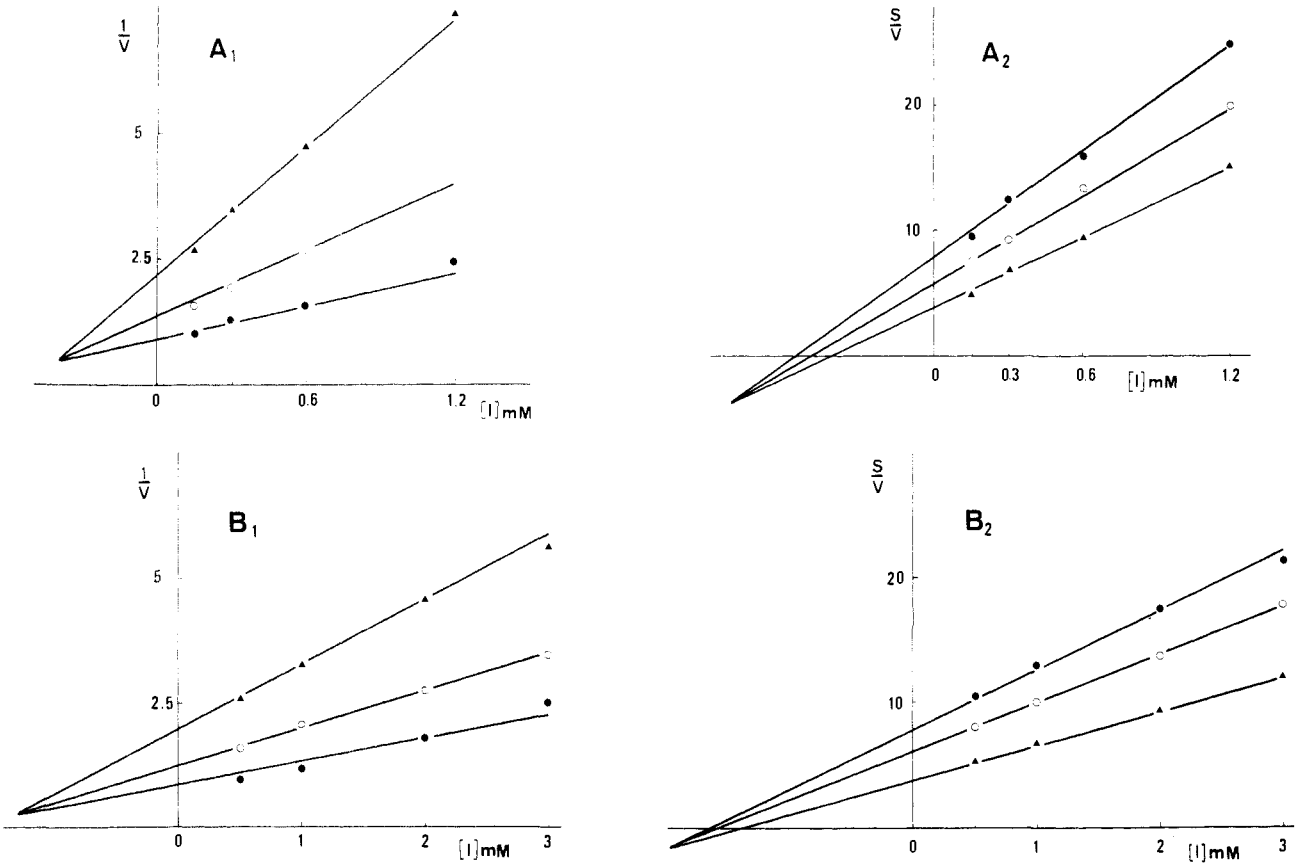

Figure 3. Determination of the inhibition constants of the alanine racemase from *Streptococcus faecalis* for (β-chloro- and (β,β-dichloro-α-aminoethyl)phosphonic acids (A_1, A_2, and B_1, B_2, respectively) following the Cornish-Bowden graphical method. The concentrations of L-Ala were 2 mM (▲), 5 mM (○), and 10 mM (●).

Antimicrobial Activity. Compounds **4–6** were tested for antimicrobial activity against a variety of organisms on both complete and minimal media with use of penicillin G and amphothericin as standards for comparison. The only activity observed for **6** was very poor against *Staphylococcus* 209 P. This difference in inhibitory activity between the whole bacteria and the cell-free systems we have studied (K_i for **5** and **6** < K_m of alanine racemase) appears to be attributed to cell impermeability such as in the examples of other analogues of alanine, L-Ala-P[5] and β-chloro-L-Ala.[24]

Conclusion

Our findings show that the β-chloro derivatives of Ala-P are not suicide substrates of the alanine racemase.

However, the strong affinity of Cl-Ala-P and Cl_2-Ala-P for the alanine racemase encourages us to improve the transport efficiency of such compounds by their incorporation into peptidyl structures as it was demonstrated for other bacterial cytotoxic moieties.[24-26] The intracellular cleavage of some of these peptides may lead to interesting antibacterial agents.

Experimental Section

Chemistry. Elemental analyses were performed in the Laboratory of Microanalyses (CNRS–Gif sur Yvette). Melting points were obtained on a Mettler FP-61 apparatus. ^{13}C and ^{31}P NMR spectra were recorded in CF_3CO_2D on a 80 WP SY Brucker spectrometer equipped with an heterospin decoupler at 20.150 MHz for ^{13}C (Me_4Si as an external standard) and 32.435 MHz for ^{31}P (85% H_3PO_3 as an external standard) in the CNRS–SNPE Laboratory–Thiais.

The dimethyl (β-chloro-α-aminoethyl)phosphonates **1–3** were prepared by using the method previously described.[15] Hydrolysis was accomplished upon treatment with $ISiMe_3$ according to the following general procedure.

To a solution of 10 mmol of dimethyl (β-chloro-α-aminoethyl)phosphonates **1–3**, in 10 mL of anhydrous acetonitrile, was added dropwise 32 mmol of $ISiMe_3$, while the temperature was maintained under 50 °C, and with stirring under argon. The colorless mixture becomes dark red and after stirring for 3 h at room temperature is evaporated under reduced pressure. To the oily residue is added slowly 10 mL of methanol at room temperature with stirring. After 15–20 min, the (β-chloro-α-aminoethyl)phosphonic acid precipitates. The precipitate is filtered off and recrystallized from ethanol/water. The purity was checked by microanalysis and by means of ^{31}P NMR spectrometry (single line). ^{13}C NMR spectra provided additional proof of structure.[27] Yield (not optimized) in analytically pure product: 25–30%.

Enzymology. (A) Preparation of the alanine racemases[22] and D-Ala:D-Ala ligases[7] from *P. aeruginosa* A 237 and *S. faecalis* ATTC 8043 has been previously described.

(B) Alanine Racemase Assays. The enzymatic activity was measured in the direction L-Ala → D-Ala by monitoring pyruvate → lactate formation by coupling D-amino acid oxidase (Boehringer, hog kidney) and LDH and following the oxidation of NADH at 340 nm on a Varian spectrometer. We had previously verified that compounds **4–6** were not substrate of D-amino acid oxidase, which is able to convert β-chloro-D-Ala into β-chloropyruvate.[28] The assays were carried out as described recently[22] for the

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evaluation of the inhibitory properties of coenzyme–substrate adduct analogues of these PLP enzymes. The reaction mixture contained L-Ala (2–40 mM), PLP (150 μM), inhibitor (0–20 mM), enzyme solution (50 μL) in a final volume of 1 mL of buffer (0.1 M Tris-HCl, pH 8.9, for the enzyme of *P. aeruginosa*, 0.1 M phosphate, pH 8, for the enzyme of *S. faecalis*). Unlike the crude preparation of *P. aeruginosa*, the crude extract of *S. faecalis* required PLP for activity.

(C) D-Ala:D-Ala Ligase Assays. The formation of radioactive D-Ala-D-Ala from D-[U-^{14}C]Ala (specific activity, 43 mci/mmol, Radiochemical Center, Amersham, England) was evaluated by autoradiochromatography.[7] The assays were performed in a final volume of 50 μL containing 50 mM Tris-HCl, pH 7.8, 1 mM KCl, 5 mM ATP, 5 mM $MnCl_2$, 5–40 mM D-[^{14}C]Ala, 0–20 mM inhibitor, and enzyme solution in appropriate amount. The reaction was stopped after an incubation of 30 min at 37 °C by adding 20 μL of 0.1 M formate containing 10 mM of D-Ala-D-Ala as carrier. A 30-μL aliquot of the supernatant was chromatographied on Schleicher & Schull 2043 B paper in pyridine/acetic acid/H_2O (10:7:3) as the solvent phase; the amino acid (R_f 0.47) and the dipeptide (R_f 0.66) were located by autoradiography and counted with an Intertechnique SL 36 liquid scintillation spectrometer.

Primary Antimicrobial Screening of 4–6. Antimicrobial screening was carried out by an agar well diffusion method using both complete and minimal media. Penicillin G was used as a standard for bacteria and amphothericin B for fungi. Cultures employed for screening were *Escherichia coli* EK 12, UB 105, DC 2, MRE 600. The others were obtained either from the American Type Culture Collection, Rockeville, MD [*Candida albicans* (ATCC 26278), *Saccharomyces cerevisiae* (ATCC 7754)], from the Food and Drug Administration, Washington, DC (*Staphylococcus aureus* FDA 209P), or from the Pasteur Institut, Paris (*Candida albicans* 886, *Candida tropicalis* 204, *Torulopsis* 811).

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Registry No. GAR synthetase, 9032-01-3; GAR transformylase, 9032-02-4; AIR synthetase, 9023-53-4; **1**, 98779-23-8; **2**, 98779-24-9; **3**, 98779-25-0; **4**, 98779-26-1; **5**, 98779-27-2; **6**, 98855-93-7; L-Ala, 56-41-7; D-Ala, 338-69-2; 1,2,2,2-tetrachloro-*N*-(benzyloxycarbonyl)ethylamine, 98779-28-3; alanine racemase, 9024-06-0; D-Ala:D-Ala ligase, 9023-63-6.

Nucleosides. 136. Synthesis and Antiviral Effects of Several 1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-alkyluracils. Some Structure–Activity Relationships

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In order to study structure–activity relationships between antiherpetic activity and the size of the C-5 alkyl substituents of 2′-fluoro-ara-U derivatives, six new nucleosides (**1c–h**) were synthesized. The 5-allyl analogue **1c** was prepared by a Pd(II)-catalyzed reaction of 5-(chloromercuri)-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil with allyl chloride. Partial hydrogenation of **1c** afforded the 5-*n*-propyl derivative **1d** (FPAU). Nucleosides **1e–h** were obtained by condensation of 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinosyl bromide with the corresponding 5-substituted uracils. Preliminary in vitro data show that, as the alkyl side chain is increased by one carbon unit, the antiherpetic potency is decreased by approximately 1 log order. The cytotoxicity also diminishes as the size of the 5-substituent is increased. FPAU exerts good activity against HSV-1 and HSV-2. FiPAU still shows good therapeutic indices, whereas the higher alkyl analogues are essentially inactive.

In 1979, we reported[1] the syntheses and anti herpes virus activity of several 5-substituted (2-fluoro-2-deoxyarabinofuranosyl)cytosines and -uracils. Among these, 2′-fluoro-5-iodo-ara-C (FIAC) was found to be a potent inhibitor of the replication of herpes simplex virus (HSV) 1 and 2, varicella zoster virus (HZV), cytomegalovirus (CMV), and Epstein–Barr virus (EBV) in cell culture.[1-4] FIAC has demonstrated clinical efficacy against herpes virus infections in both phase 1[5] and phase 2[6] clinical trials in host compromised patients. Subsequently, the corresponding thymine analogue, 2′-fluoro-5-methyl-ara-U (FMAU) (**1a**), was found to be more potent than FIAC in mice infected with HSV-1[7] or with HSV-2[8] without toxicity at effective dose levels. FMAU was also found to be active in vitro and in vivo against P-815 and L-1210 cell lines resistant to arabinosylcytosine (ara-C).[9,10] A phase I clinical trial of FMAU in patients with advanced cancer showed that drug-induced central nervous system toxicity was dose-limiting. In view of the potent and selective antiviral activity of FMAU, future trials using low doses

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