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SYNTHESIS AND PROPERTIES OF 1-AMINO-2-ARYLETHYLPHOS- PHONIC AND -PHOSPHINIC ACIDS AS WELL AS -PHOSPHINE OXIDES¹

by Ludwig MAIER

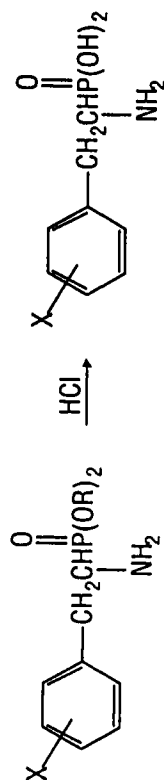
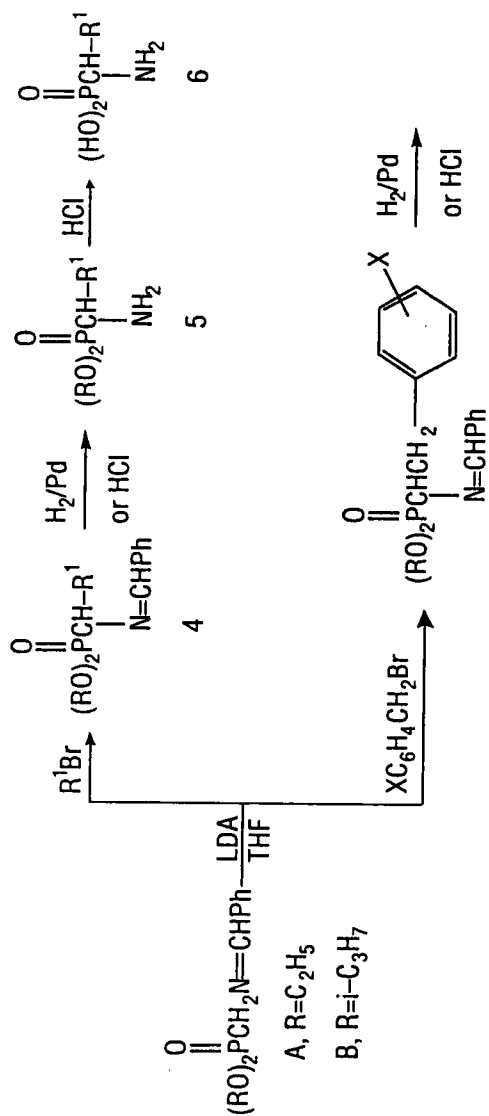
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Abstract: The preparation, physical, spectroscopic and biological properties of 1-amino-2-arylethylphosphonic, and -phosphinic acids as well as -phosphine oxides, the phosphorus analogues of phenylalanine are described.

Results and Discussion

The study of phosphorus analogues of the natural α -amino acids has accelerated in the past ten years, not least due to the finding of molecules with useful biological activity. In a recent review article we have summarized our knowledge in this area². Furthermore they find increasing use as a tool in investigating the metabolism of natural amino acids³.

The family of 1-aminoalkylphosphonic acids has been most studied and to date analogues of all the common protein amino acids have been described. Several procedures are known of the preparation of the phosphonic acid analog of phenylalanine but for the synthesis of differently substituted 1-amino-2-arylethylphosphonic acid derivatives the modified procedure of Ratcliffe and Christensen⁴ is best suited. Furthermore we observed that this procedure can be extended to the preparation of the corresponding phosphinic acid and phosphine oxide derivatives. In addition this method has the advantage that a large number of aryl- and alkyl substituted 1-aminophosphonic- and -phosphinic acids and derivatives can be prepared from the same starting materials. α -Methylsubstituted derivatives were obtained either by double alkylation of N-benzylidenaminomethylphospho-



nate or by the interaction of the corresponding Schiff' base with secondary phosphites.

Reactions of 1-amino-2-aryl-ethylphosphonates

The 1-amino-2-aryl-ethylphosphonates give all the reactions typical for a primary amine. Thus the interaction of **2** ($X = 4\text{-F}$) and dimethylformamid-dimethylacetal gives a formamidine, with isocyanates a urea derivative is obtained, and acylation with formate, oxalate or chloroacetic anhydride produces the acylated derivatives. Arylation with trifluoromethyl-dinitro-chlorobenzene proceeds well and gives the N-arylated compound in 63% yield. A dipeptide is obtained when **2** is treated with Z-L-alanine in the presence of dicyclohexylcarbodiimide and a diphenylether derivative is formed when **2** is caused to react with 3,4-dinitro-2'-chloro-4'-trifluoromethyl-diphenylether. Other 1-amino-2-aryl-ethylphosphonates react similarly.

Biological activity

Several of the 1-amino-2-substituted arylethyl-phosphonic acids inhibit one of the key enzymes of plant metabolism the phenylalanine ammonia lyase (PAL)⁵. The results so far obtained indicate that the PAL-inhibition is associated with the phosphonic group, since the corresponding phosphonous and phosphinic acid derivatives are much less active. The phosphine oxide 1-amino-2-phenylethyl-dimethylphosphine oxide shows no inhibition of PAL. The inhibition of the anthocyanynthesis in buckwheat-hypocotyledons is comparable with the PAL inhibition, the same order of activity seems to exist. A comparison of the activity of racemic 1-amino-2-(4-fluorophenyl)ethylphosphonic acid **3f** and racemic 4-fluorophenylalanine shows that **3f** is a better inhibitor (by two orders of magnitude) of anthocyanynthesis than 4-fluorophenylalanine. This indicates that the inhibition is mainly due to the introduction of the phosphonic acid group.

We observed that many of the 1-amino-2-arylethylphosphonic acids are quite active botryticides, the order of activity being comparable to the inhibition constants of PAL.

The fluoro-derivative 3f is also highly effective as a seeddressing agent showing a 100% protection against the fungus *Fusarium nivale* at 600 ppm⁶.

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