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Aldol-Type Cyclization of Bisacylphosphonates. A Unique Concerted Catalytic Effect of Diamines

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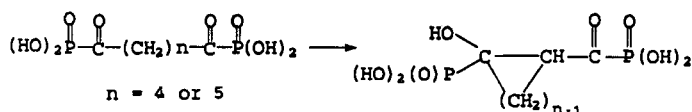
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ALDOL-TYPE CYCLIZATION OF BISACYLPHOSPHONATES. A UNIQUE CONCERTED CATALYTIC EFFECT OF DIAMINES

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Some bisacylphosphonates are biologically active in calcium related disorders, such as bone resorption and ectopic calcification.¹ In the course of our studies directed towards the preparation of stable, pharmaceutically acceptable salts of bisacylphosphonates, we found that in the presence of N,N'-dibenzylethylenedi-



amine (benzathine), adipoylbisphosphonate (AdBP) underwent cyclization to 2-hydroxy-2-phosphonocyclopentanecarbonylphosphonic acid. Similarly, pimeloylbisphosphonate (PiBP) cyclized to 2-hydroxy-2-phosphonocyclohexanecarbonylphosphonic acid, although at a rate about 30 times slower than AdBP. Study of the catalytic effect of amines on the cyclization of PiBP revealed a striking dependence on the pH, the chain length of the diamine, and the amine used. Thus the following relative efficacy was observed for the different amines at pH 5: Me₂N(CH₂)₂NH₂ (120), H₂N(CH₂)₂NH₂ (100), H₂N(CH₂)₃NH₂ (4), H₂N(CH₂)₄NH₂ (1), PhCH₂NHCH₂CH₂NHCH₂Ph (0.1), Me₂NCH₂CH₂NMe₂ (0.02), MeNH₂ (0.02). These data show that depending on the chain length, 1,2-diamines are far more efficient catalysts than longer chain diamines and monoamines in these cyclizations. The mechanism which accommodates these results involves attack of a primary amine group on one of the keto groups, followed by removal of an alpha proton by the second amine group and the formation of an enamine. The latter then cyclizes by attacking the second keto group.

1. J. M. van Gelder, E. Breuer, A. Ornoy, A. Schlossman, N. Patlas, and G. Golomb, *Bone*, 1995, **16**, 511-520.

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