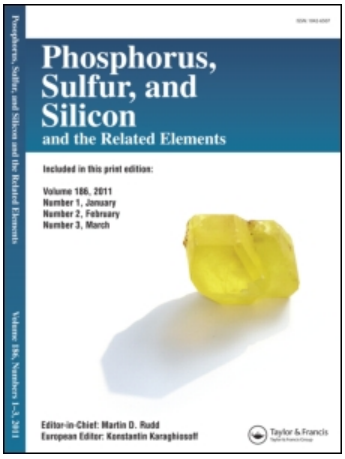

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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

Ivan S. Alferiev[a]; Eli Breuer[a]
[a] Department of Pharmaceutical Chemistry, The Hebrew University of Jerusalem, Jerusalem, Israel

To cite this Article Alferiev, Ivan S. and Breuer, Eli(1996) 'Aldol-Type Cyclization of Bisacylphosphonates. A Unique Concerted Catalytic Effect of Diamines', Phosphorus, Sulfur, and Silicon and the Related Elements, 111: 1, 164
To link to this Article: DOI: 10.1080/10426509608054793
URL: http://dx.doi.org/10.1080/10426509608054793

Phosphorus, Sulfur, and Silicon, 1996, Vol. 111, p. 164
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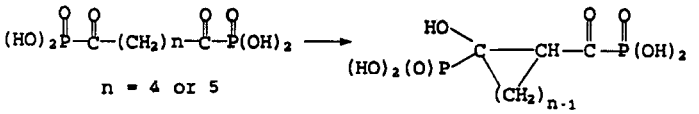
ALDOL-TYPE CYCLIZATION OF BISACYLPHOSPHONATES. A UNIQUE CONCERTED CATALYTIC EFFECT OF DIAMINES

Ivan S. Alferiev and Eli Breuer
Department of Pharmaceutical Chemistry, The Hebrew University of Jerusalem, Jerusalem, Israel

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: $Me_2N(CH_2)_2NH_2$ (120), $H_2N(CH_2)_2NH_2$ (100), $H_2N(CH_2)_3NH_2$ (4), $H_2N(CH_2)_4NH_2$ (1), $PhCH_2NHCH_2CH_2NHCH_2Ph$ (0.1), $Me_2NCH_2CH_2NMe_2$ (0.02), $MeNH_2$ (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 be 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.

Acknowledgement This research was supported by a grant from the G.I.F., The German Israeli Foundation for Scientific Research and Development.