Tetrahedron Letters, Vol. 33, No. 15, pp. 2067-2068, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

BECKMANN REARRANGEMENT OF N-(α-HYDROXYIMINOALKYLPHOSPHONYL)AMINO ACIDS. A CONVENIENT SYNTHETIC APPROACH TO NOVEL PEPTIDE-TRANSITION-STATE ANALOGS.

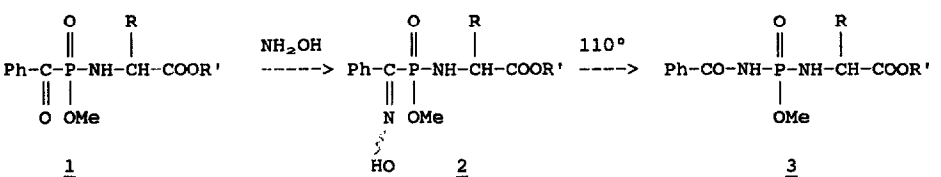
Eli Breuer,* Hisham Zaher and Zeev Tashma

Department of Pharmaceutical Chemistry, The School of Pharmacy, The Hebrew University of Jerusalem, P. O. Box 12065, Jerusalem, 91120 Israel

Abstract: Thermal Beckmann rearrangment of N-(α-hydroxyiminoalkylphosphonyl)amino acid derivatives (2) yields acylphosphordiamidates (3), which represent a new type of peptide analogs.

"Transition-state (TS) analogs"[1] are designed on the assumption that structures mimicking intermediates in enzymatic reactions bind better than the substrates to the enzyme, and they represent an important approach to enzyme inhibitors. For example, several phosphonamidate peptide analogs, which resemble the tetrahedral intermediate in the hydrolysis of the amide bond, show powerful inhibitory activity towards some peptidases.[2]

Recently we found that in analogy to α-hydroxyiminophosphonates and phosphinates,[3] α-hydroxyiminobenzylphosphonamidates undergo a facile Beckmann rearrangement to acylphosphordiamidates.[4] In the course of our continuing quest for new types of potentially biologically active compounds derived from acylphosphonates and hydroxyiminophosphonates,[5,6,7] we considered that application of the Beckmann rearrangement to N-(α-hydroxyiminoalkylphosphonyl)amino acids (2), would lead to acylphosphordiamidates of type 3. Such products can be viewed as a novel types of TS analogs.[8] This communication reports the realization of this plan.



a, R = H, R' = Et; b, R = R' = Me

Methyl benzoylphosphonochloridate[10] was reacted with Gly-OEt in CH_2Cl_2 in the presence of pyridine to yield methyl N-(ethoxycarbonylmethyl)benzoylphosphonamidate (1a),[11] which was converted *in situ* by treatment with $NH_2OH.HCl$, to α-hydroxyiminobenzylphosphonamidate 2a.[12] Similarly L-Ala-OMe gave 1b[13] and subsequently 2b[14] as mixtures of diastereoisomers. Heating (E)-2a or (E)-2b in refluxing toluene for 4 or 6 h,

respectively, caused them to rearrange cleanly to phosphordiamidates 3a[15] and 3b.[16] These compounds may be viewed as tripeptide analogs with a missing α-carbon and the tetrahedral phosphoryl substituting for the carbonyl of the middle amino acid. We believe that reaction of acylphosphonochloridates with the free amino groups of peptides should proceed equally well, leading eventually to more complex acylphosphordiamidates with potential biological activity. Toward this goal, we shall combine, in the next phase of our work, this strategy with the methodology developed for the synthesis of aminohydroxyiminophosphonates we described recently.[5,6]

Acknowledgement This work was supported in part by the Fund for Basic Research administered by the Israel Academy of Sciences and Humanities.

References and Notes

1. R. Wolfenden, Ann. Rev. Biophys. Bioeng. 1976, 5, 271. R. Wolfenden and L. Frick, in "Enzyme Mechanisms, M. I. Page, A. Williams, Eds. 1987, Royal Society of Chemistry, London, p. 97. A. Tramontano, A. A. Amman, R. A. Lerner J. Am. Chem. Soc. 1988, 110, 2282. J. Jacobs, P. G. Schultz, R. Sugasawara, M. Powell, J. Am. Chem. Soc. 1987, 109, 2174.
2. A. P. Kaplan, P. A. Bartlett, Biochemistry, 1991, 30, 8165.
3. E. Breuer, A. Schlossman, M. Safadi, D. Gibson, M. Chorev, H. Leader, J. Chem. Soc. Perkin 1, 1990, 3263.
4. E. Breuer, H. Zaher, Z. Tashma, in preparation.
5. E. Breuer, M. Safadi, M. Chorev, D. Gibson, J. Org. Chem. 1990, 55, 6147.
6. E. Breuer, M. Safadi, M. Chorev, A. Vincze, P. Bel, Tetrahedron 1991, 47, 1257.
7. G. Golomb, A. Schlossman, H. Saadeh, J. M. Van Gelder, M. Levi and E. Breuer, Pharm. Res., 1992, in press.
8. Statin, an unusual ß-hydroxy-τ-amino acid, a constituent of pepstatine,[9] a naturally occurring inhibitor of aspartic proteinases, is also considered a TS analog of a shortened dipeptide, lacking the nitrogen of the C-terminal acid.
9. G. R. Marshall, Fed. Proc., Fed. Am. Soc. Exp. Biol. 1976, 35, 2494. M. P. Marciniszyn, J. A. Hartsuck, J. J. N. Tang, J. Biol. Chem. 1976, 251, 7088.
10. E. Breuer, M. Mahajna, L. D. Quin, G. S. Quin, J. Org. Chem. 1991, 56, 4791.
11. ^{31}P NMR: δ = 7.9 ppm (septet, J = 11 Hz).
12. (E):(Z) = 3:1, NMR, ($CDCl_3$) ^{31}P: δ (ppm) 17.27 (septet, J = 11 Hz, E-2a), 10.85 (septet, J = 11 Hz, Z-2a). ^1H: 7.76 (2H, m), 7.42 (1H, m), 7.36 (2H, m) 3.6 (3H, d, J = 12 Hz), 4.04 (2H, q), 3.95 (2H, m), 1.15 (3H, t).
13. NMR (CH_2Cl_2) ^{31}P: δ (ppm) = 7.25 and 6.84 (two sextets, J = 11 Hz each).
14. (E):(Z) = 4:1, NMR ($CDCl_3$) ^{31}P: δ (ppm) 15.86, 15.5 (two sextets, E-2b), 10.85, 10.46 (two sextets, Z-2b); ^1H: (E-2b): 7.46 (2H), 7.26 (3H) 4.05 (2H) 3.54-3.6 (6H) 1.24 (3H).
15. NMR ($CDCl_3$) ^{31}P: 6.59 ppm (appears as sextet); ^1H, 7.95, (2H, m), 7.39 (3H, m); 4.07 (2H, q), 3.82, (2H, m), 3.97 (3H, d, J = 12 Hz), 1.13 ppm (3H). IR (neat): 3300-3100, 1735, 1710, 1650, 1240, 1040 cm^{-1}.
16. NMR ($CDCl_3$) ^{31}P: 5,8 and 4,8 ppm (appear as two septets); ^1H: 7.95 (2H, m), 7.78 (3H, m), 4.2 (1H, m), 3.68 (3H, dd) 3.5 (3H, s) 1.34 (3H, dd). IR (neat: 3300-3100, 1730, 1710, 1655, 1595, 1220, 1035 cm^{-1}.

(Received in UK 6 January 1992)