118.2, 118.3, 128.2, 128.3, 128.4, 129.7 (s), 136.1 (s), 136.3 (s), 136.4, 149.3 (s), 152.7 (s), 189.9; mass spectrum (relative intensity) 282 (M^+, 5), 91 (100). Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.42; H, 6.31.

Ethyl 1-(4-Methoxyphenyl)-6-(benzyloxy)-2-methyl-5-methoxy-2,3-dihydro-1*H*-1,9-diazaphenalene-8-carboxylate (18f). The reaction of iminophosphorane **28** with 4-methoxyphenyl isocyanate under the same conditions described for the preparation of **18** led to **18f**: yield 51%; mp 176–177 °C, white prisms; IR (Nujol) 1732, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (d, 3 H, J = 6.5 Hz, 2-CH_3), 1.32 (t, 3 H, J = 7.0 Hz, CH_3CH_2), 2.91 (dd, 1 H, J = 15.7, 3.7 Hz, 3-H_a), 3.51 (dd, 1 H, J = 15.7, 5.1 Hz, 3-H_b), 3.81 (s, 3 H, CH_3O), 3.97 (s, 3 H, CH_3O), 4.23 (qdd, 1 H, J = 6.5, 5.1, 3.7 Hz, 2-H), 4.28 (q, 2 H, J = 7.0 Hz, CH_3CH_2), 5.13 (s, 2 H, $PhCH_2O$), 6.94 (d, 2 H, J = 9.0 Hz, 2 H_0), 7.02 (s, 1 H, 4-H), 7.24–7.41 (m, 5 H), 7.52–7.57 (m, 2 H), 8.04 (s, 1 H, 7-H); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3CH_2), 18.3 (2-CH_3), 35.9 (C_3), 54.8 (C_2), 55.4 (CH_3O), 56.3 (CH_3O), 60.8 (CH_3CH_2), 75.9 ($PhCH_2O$), 108.6 (C_7), 112.8 (s), 113.1, 113.8, 128.0, 128.2, 128.3, 128.4, 129.9 (s), 132.7 (s), 136.8 (s), 137.4 (s), 140.2 (s), 141.6 (s), 152.2 (s), 153.6 (s), 157.1 (s), 166.4 (CO); mass spectrum (relative intensity) 498 (M^+, 10), 407 (100). Anal. Calcd for $C_{30}H_{30}N_2O_5$: C, 77.27; H, 6.06; N, 5.62. Found: C, 77.38; H, 5.84; N, 5.79.

Acknowledgment. We are indebted to Dirección General de Investigación Científica y Técnica for financial support, Project number PB86-0039.

Registry No. 1, 28752-82-1; 2, 92832-21-8; 3, 129732-98-5; 5a, 129708-13-0; 5b, 129708-14-1; 5c, 129708-15-2; 5d, 129708-16-3; 6a, 129733-03-5; 6b, 129708-17-4; 6c, 129708-18-5; 6d, 129708-19-6; 7, 129708-12-9; 8, 129732-99-6; 9, 129733-00-2; 10, 129708-05-0; 11, 148-53-8; 12, 23343-06-8; 13, 127983-47-5; 14, 127983-48-6; 18a, 127983-53-3; 18b, 127983-54-4; 18c, 127983-55-5; 18d, 127983-56-6; 18e, 127983-57-7; 18f, 129708-20-9; 19a, 129708-06-1; 19b, 129708-21-0; 19c, 129708-22-1; 19d, 129708-23-2; 19e, 129708-24-3; 20, 129708-07-2; 21, 129733-01-3; 22, 129708-08-3; 23, 129708-09-4; 24, 129708-10-7; 25, 22934-51-6; 26, 129708-04-9; 27, 129708-11-8; 28, 129733-02-4; $EtO_2CCH_2N_3$, 637-81-0; PhNCO, 103-71-9; p-MeC_6H_4NCO, 622-58-2; p-$MeOC_6H_4NCO$, 5416-93-3; H_2C=CH-CH_2Br, 106-95-6; $PhCH_2Br$, 100-39-0; p-FC_6H_4NCO, 1195-45-5; 2-(benzyloxy)-3-methoxybenzaldehyde, 2011-06-5; 5-allyl-2-(benzyloxy)-3-methoxybenzaldehyde, 129708-04-9; 6-allyl-2-methoxyphenyl, 579-60-2.

Novel Amino Acid Derivatives. Preparation and Properties of Aminoacylphosphonates and Amino Hydroxyimino Phosphonates

Eli Breuer,* Muhammad Safadi, Michael Chorev, and Dan Gibson

Department of Pharmaceutical Chemistry, The Hebrew University School of Pharmacy, Jerusalem 91120, Israel

Received April 16, 1990

Reaction of *N*-(benzyloxycarbonyl)prolyl chloride with $(MeO)_3P$ followed by treatment of the resulting acylphosphonate **5** with LiBr in MeCN gave lithium methyl Cbz-prolylphosphonate (**6a**). Didemethylation of **5** by treatment with Me_3SiBr led to sodium Cbz-prolylphosphonate (**6b**). Fmoc-alanyl chloride and Fmoc-phenylalanyl chloride were converted similarly to the corresponding dimethyl Fmoc-aminoacylphosphonates **7**, which were monodemethylated to methyl ester lithium salts **8**. Phthalimidoacyl **9** derived from β-Ala, γ-aminobutyric acid, and DL-Ala gave dimethyl phthalimidoacylphosphonates **10**, which were converted to oximes **11** by NH_2OH, to methyl phthalimidoacylphosphonate lithium salts **12** and methyl phthalimido α-hydroxyimino phosphonate lithium salts **13** by LiBr demethylation of compounds **10** and **11**, respectively. Diisopropyl phthalimidoacylphosphonates **14** derived from Gly, β-Ala, γ-aminobutyric acid, DL-Ala, and L-Phe were prepared by the Arbuzov reaction of their *N*-phthaloyl chlorides with $(2\text{-}PrO)_3P$, which in turn yielded oximes **16**. These were deblocked by hydrazine to yield diisopropyl amino-α-(hydroxyimino)alkylphosphonates **17**. Similarly oxime derivatives **18** of diethyl phthalimidoacylphosphonates **15** derived from amino acids Ala and Phe could be hydrazinolyzed to diethyl amino hydroxyimino phosphonates **19**.

Introduction

There is considerable economic and biological interest in phosphorus derivatives of amino acids since phosphonate and phosphinate analogues of amino acids (both natural and synthetic) have been proven to possess activities in a variety of fields. Among the phospha amino acids there are compounds active as pesticides,[1,2] insecticides,[1] herbicides,[3] bactericides,[4] enzyme inhibitors,[3] and receptor antagonists.[5] These observations stimulated extensive synthetic activity, which yielded phospha analogues of all natural amino acids.[6] In addition to phospha amino acids, there is considerable interest in other types

(1) Kafarski, P.; Mastalerz, P. In *Beitrage zur Wirkstofforschung*; Oehme, P., Loewe, H., Gores, E., Axt, J., Eds.; 1984; Vol. 21. Part of a series published by Akademie-Industrie-Komplex, Arzneimittelforschung. Institut fur Wirkstofforschung, Berlin, DDR.

(2) Fest, C.; Schmidt, K. *The Chemistry of Organophosphorus Pesticides*; Springer Verlag: New York, 1982; p 166, 175.

(3) (a) Bayel, E.; Gugel, K. H.; Haegele, K.; Hagenmaier, H.; Jessipow, S.; Koenich, W. A.; Zaehner, H. *Helv. Chim. Acta* **1972**, *55*, 224. (b) Weissermel, K.; Kleiner, H. J.; Finke, M.; Felcht, U. H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 223. (c) Seto, H.; Imai, S.; Tsuruoka, T.; Ogawa, H., Satoh, A.; Sasaki, T.; Otake, N. *Biochem. Biophys. Res. Commun.* **1983**, *111*, 1008. (d) Maier, L.; Rist, G. *Phosphorus Sulfur* **1983**, *17*, 21. (e) Steinruchen, H. C.; Amrhein, N. *Eur. J. Biochem.* **1984**, *143*, 351.

(4) (a) Mine, Y.; Kamimura, T.; Nonoyama, S.; Nishida, M.; Goto, S.; Kuwahara, S. *J. Antibiot.* **1980**, *33*, 36. (b) Park, B.; Hirota, A.; Sakai, H. *Agric. Biol. Chem.* **1976**, *40*, 1905.

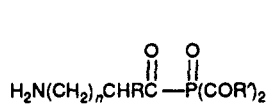
(5) (a) Cates, L. A.; Li, V.-S.; Hu, Z.-S.; Lehman, J.; Coyle, J. T.; Ferkany, J. W. *J. Pharm. Sci.* **1984**, *73*, 1550. (b) Perkins, M. N.; Stone, T. W.; Collins, J. F.; Curry, K. *Neurosci. Lett.* **1981**, *23*, 333. (c) Davies, J.; Francis, A.; Kones, A.; Watkins, J. *Neurosci. Lett.* **1981**, *21*, 77.

(6) (a) Merret, J. H.; Spurden, W. C.; Thomas, W. A.; Tong, B. P.; Whitcombe, I. W. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 61. (b) Bayliss, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845. (c) Maier, L. *Phosphorus Sulfur* **1983**, *14*, 295. (d) Soroka, M.; Mastalerz, P. *Rocz. Cem.* **1976**, *50*, 661. (d) Cates, L. A.; Li, V.-S.; Yakshe, C. C.; Fadeyi, M. O.; Andree, T. H.; Enna, S. J. *J. Med. Chem.* **1984**, *27*, 654. (e) Crappel, S. F.; Giovanella, A. J.; Nisbet, L. *J. Antimicrob. Agents Chemother.* **1985**, *27*, 961. (f) Chen, S. F.; Kumar, S. D.; Tishler, M. *Tetrahedron Lett.* **1983**, *24*, 5461. (g) Natchev, I. A. *Synthesis* **1987**, 1079. (h) Schrader, T.; Steglich, W. *Synthesis* **1989**, 97. (i) Dhawan, B.; Redmore, D. *Phosphorus Sulfur* **1987**, *32*, 119–144. (j) Togni, A.; Pastor, S. D. *Tetrahedron Lett.* **1989**, *30*, 1071. (k) Hoppe, I.; Schoellkopf, U.; Nieger, M.; Egert, E. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1067. (l) Schollkopf, U.; Hoppe, I.; Thiele, A. *Liebigs Ann. Chem.* **1985**, 555. (m) Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1953. (n) Huber, R.; Knierzinger, A.; Obrecht, J.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 1730. (o) Minowa, N.; Hirayama, M.; Fulatsu, S. *Tetrahedron Lett.* **1984**, *25*, 1147.

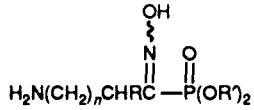
0022-3263/90/1955-6147$02.50/0

of phosphorylated amino acids and their corresponding peptide derivatives. This interest stems from the recent recognition that enzymatic protein phosphorylations are essential regulatory processes,[7] inhibition of which could provide novel therapeutic leads, e.g., inhibitors of protein kinases may be valuable antiproliferative drugs.

In recent years we have been involved in the study of the chemistry of acylphosphonic acids[8] and of oximes derived from them.[9] One of the aspects in the chemistry of acylphosphonic acids that seemed worthy of exploring was the possibility of synthesizing aminoacylphosphonates and amino oxyimino phosphonates, represented by the general formulas **1** and **2**, and subsequently to use them as components in modified peptides. There is only one unconfirmed report on aminoacylphosphonates and none on their oxime derivatives in the literature.[10]



1

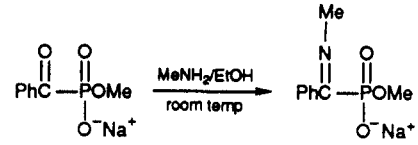


2

Prior to our work, several acylphosphonate derivatives have been shown to possess biological activity in various fields.[11] Our interest in the acylphosphonic functionality is stimulated on the one hand by its structural analogy to acyl phosphates that have important roles in several types of biochemical processes[12] and on the other hand by recent results that link enzyme inhibitory activity to the presence of electron-deficient carbonyl groups in the molecule.[13] We have shown previously that even in ionized acylphosphonates, the carbonyl groups are electrophilic.[8d,14] In addition, the acylphosphonic functionality has the capability of interacting with calcium ions in vivo and thus affecting metabolic processes that involve this cation, such as bone resorption and tissue calcification.[15]

Compounds containing the oxyimino phosphonic moiety can be used as precursors to monomeric metaphosphate anion[9a] or metaphosphate monoesters[9c] and thus to act as phosphorylating agents. α-(Hydroxyimino)benzylphosphonic acid (as an example) undergoes facile fragmentation, releasing metaphosphate anion at physiological pH.[9a] Consequently we postulated that this functional group offers the potential for the design of in situ, site specific biological phosphorylating agents, if by structural modifications the transport and binding properties of the molecule can be suitably adjusted to achieve affinity to specific sites. One of the goals of our ongoing research program is to design reagents that would be able to phosphorylate proteins under physiological conditions. In addition, oxyimino phosphonic groups have been shown to possess interesting metal binding properties[16] and thus might yield new inhibitors of metalloenzymes, which may become of medicinal importance.

The syntheses of multifunctional molecules of type **1** and **2** pose problems regarding the selection of appropriate protecting groups. Acylphosphonates are most commonly made by the Arbuzov reaction of acyl halides with trialkyl phosphites,[17] and therefore the amine protecting group should be compatible with the conditions necessary to prepare protected aminoacyl halide and the subsequent Arbuzov reaction. The second problem arises from the inherent reactivity of the carbonyl groups of acylphosphonates toward nucleophiles such as amines that break the C–P bond and result in the fomation of carboxamides.[18] The acylphosphonic function can be stabilized by monodealkylation to the corresponding monoester monoanion (e.g., **3**), in which the C–P bond is resistant to cleavage of nucleophiles,[8d] but its carbonyl group is still reactive toward nucleophiles, such as primary amines that condense to form α-imino phosphonates **4**.[8d]



3 **4**

On the other hand, dialkyl α-hydroxyimino phosphonates (that can exist as two geometrical isomers[9b]) are quite stable. In contrast, monoesters derived from these are stable as salts only. The corresponding acids, namely, alkyl hydrogen hydroxyimino phosphonates undergo fragmentation to the corresponding nitriles and to monomeric metaphosphate esters.[9c,d]

Consequently, the heart of the problem at hand is the selection of protecting groups compatible with reaction conditions and the properties of intermediates and products. In this paper we describe results of our initial experiments regarding the use of various protecting groups

(7) (a) Krebs, E. G. In *The Enzymes*, 3rd ed.; Boyer, P. D., Krebs, E. G., Eds.; Academic: New York, 1986; Vol. 17, p 3. Krebs, E. G.; Beavo, J. A. *Annu. Rev. Biochem.* **1979**, *48*, 923. (b) Cohen, P. *Nature* **1982**, *296*, 613. Cohen, P. *Eur. J. Biochem.* **1985**, *151*, 439. (c) De Bont, H. B. A.; Liskamp, R. M. J.; O'Brian, C. A.; Erkelens, C.; Veeneman, G. H.; Van Boom, J. H. *Int. J. Pept. Protein Res.* **1989**, *33*, 115. (d) Van Oijen, A. H.; Erkelens, C.; Van Boom, J. H.; Liskamp, R. M. J. *J. Am. Chem. Soc.* **1989**, *111*, 9103.

(8) (a) Breuer, E.; Karaman, R.; Leader, H.; Goldblum, A.; Moshe, R. *Phosphorus Sulfur* **1987**, *30*, 113. (b) Breuer, E.; Karaman, R.; Leader, H.; Goldblum, A. *Phosphorus Sulfur* **1987**, *33*, 61. (c) Breuer, E.; Karaman, R.; Goldblum, A.; Leader, H. *J. Chem. Soc., Perkin Trans. 2* **1988**, 2029–34. (d) Karaman, R.; Goldblum, A.; Breuer, E.; Leader, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 765–774.

(9) (a) Breuer, E.; Karaman, R.; Gibson, D.; Leader, H.; Goldblum, A. *J. Chem. Soc., Chem. Commun.* **1988**, 504. (b) Breuer, E.; Karaman, R.; Goldblum, A.; Gibson, D.; Leader, H.; Potter, B. V. L.; Cummins, J. H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3047; **1989**, 1367. (c) Breuer, E.; Karaman, R.; Leader, H.; Goldblum, A. *J. Chem. Soc., Chem. Commun.* **1987**, 671. (d) Katzhendler, J.; Karaman, R.; Gibson, D.; Leader, H.; Breuer, E. *J. Chem. Soc., Perkin Trans. 2* **1989**, 589.

(10) Arbuzov, B. A.; Zolotova, M. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1964**, 1793; *Chem. Abstr.* **1965**, 1793; *62*, 3921h. ^{31}P NMR spectral investigation of the reaction mixture obtained when the preparation of diethyl glycylphosphonate hydrochloride according to the procedure reported in this paper was attempted showed a complex mixture. The procedure claimed in this paper to lead to diethyl β-alanylphosphonate via the addition of ammonia to the diethyl acryloylphosphonate is unlikely to be correct, in view of the pronounced sensitivity of dialkyl acylphosphonates to basic C–P bond fission reactions.[18]

(11) (a) Kluger, R.; Pike, D. C. *J. Am. Chem. Soc.* **1977**, *99*, 4504. (b) Kluger, R.; Pike, D. C. *J. Am. Chem. Soc.* **1979**, *101*, 6425. (c) O'Brian, T. A.; Kluger, R.; Pike, D. C.; Gennis, R. B. *Biochem. Biophys. Acta* **1980**, *613*, 10. (d) Gulyaev, N. N.; Sharkova, E. V.; Dedyukina, M. M.; Severin, E. S.; Khomutov, R. M. *Biokhimiya* **1971**, *36*, 1267; *Engl. Transl.* **1971**, 1060. (e) Mirsalikhova, N. M.; Baranova, L. A.; Tunitskaya, V. C.; Gulyaev, N. M. *Biokhimiya* **1981**, *46*, 314; *Engl. Transl.* **1981**, 258. (f) Angelides, K. J.; Hammes, G. G. *Biochemistry* **1979**, *18*, 5531.

(12) (a) Tang, K.-C.; Coward, J. K. *J. Org. Chem.* **1983**, *48*, 5001. (b) Goring, G.; Cramer, F. *Chem. Ber.* **1973**, *106*, 2460. (c) Southgate, C. C.; Dixon, H. B. F. *Biochem. J.* **1978**, *175*, 461. (d) Chakravarty, P. K.; Combs, P.; Roth, A.; Greenlee, W. J.; *Tetrahedron Lett.* **1987**, *28*, 611. (e) Farrington, G. K.; Kumar, A.; Wedler, F. C. *J. Med. Chem.* **1985**, *28*, 1668.

(13) (a) Angelastro, M. R.; Mehdi, S.; Burkhart, J. P.; Peet, N. P.; Bey, P. *J. Med. Chem.* **1990**, *33*, 13. (b) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* **1990**, *33*, 394.

(14) The formation of hemiacetals was observed by ^{31}P NMR upon the examination of alcoholic solutions of acylphosphonate anions. Breuer, E.; Katzhendler, J. Unpublished results.

(15) Breuer, E.; Golomb, G. Unpublished results.

(16) Gibson, D.; Karaman, R. *Inorg. Chem.* **1989**, *28*, 1928; *J. Chem. Soc., Dalton Trans.* **1989**, 1911.

(17) Zhdanov, Yu. A.; Uzlova, L. A.; Glebova, Z. I. *Russ. Chem. Rev.* **1980**, *49*, 843.

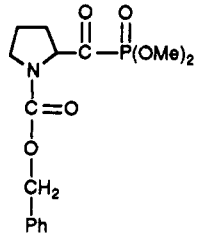
(18) Sekine, M.; Satoh, M.; Yamagata, H.; Hata, T. *J. Org. Chem.* **1980**, *45*, 4162.

for the preparation of some N-protected aminoacylphosphonates and amino hydroxyimino phosphonates derived from them. The protecting groups that have been examined are benzyloxycarbonyl (Cbz), [(9-fluorenylmethyl)oxy]carbonyl (Fmoc), and phthaloyl (Pht).[19]

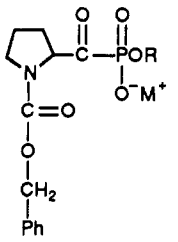
In subsequent papers we shall describe results from additional deblocking experiments and the modified peptides[20] derived from the N-deprotection of the incorporated amino hydroxyimino phosphonate residues.

Results and Discussion

Benzyloxycarbonyl amino acids are sensitive to certain acidic reagents and can be quite easily converted to *N*-carboxy anhydrides.[21a] In spite of this it was possible to convert proline to dimethyl Cbz-prolylphosphonate (**5**) by reacting Cbz-prolyl chloride with trimethyl phosphite. This product could not be isolated due to its apparent lack of stability. Its identification is based on the infrared spectrum of the crude product, which showed disappearance of the absorption band attributed to the carbonyl of the acyl halide (1790 cm^{-1}) and the appearance of a new broad band at 1700 cm^{-1}, which presumably encompasses both the carbonyl absorption of the keto phosphonate and that of the carbamate function. In the same manner as other acylphosphonates,[8d] **5** could be monodealkylated by reaction with lithium bromide in acetonitrile to yield the analytically pure lithium salt **6a**. ^1H and ^{31}P NMR of this compound taken at room temperature showed that it exists as a mixture of cis and trans conformers arising from hindered rotation of the benzyloxycarbonyl group around the CO–N bond. Coalescence of the cis and trans signals was observed when the ^{31}P NMR spectrum of **6a** was measured at 90 °C in DMSO-d_6. Attempts to convert **6a** to the N-unprotected prolylphosphonate by hydrogenolytic cleavage of the (benzyloxy)carbonyl group resulted in decomposition.



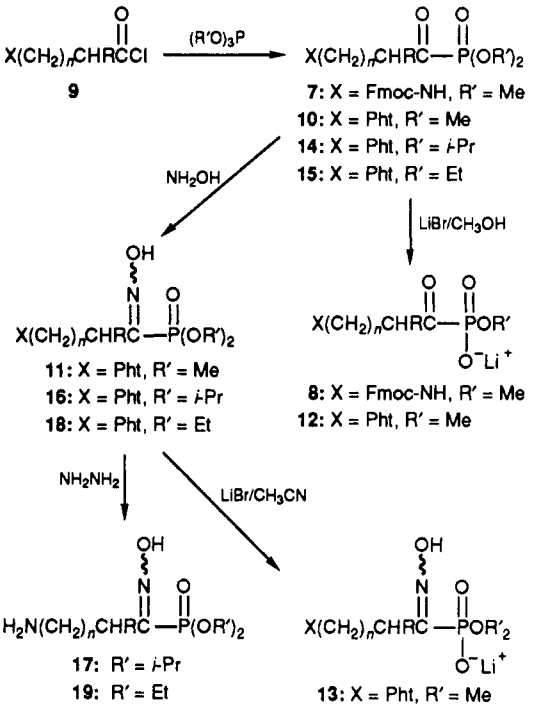
5



6a: R = Me, M = Li
6b: R = H, M = Na

Dimethyl ester **5** was also didemethylated by treatment with bromotrimethylsilane. The diacid obtained could be isolated as the monosodium salt **6b**. This salt was characterized by ^1H NMR, which showed the disappearance of the characteristic doublet corresponding to the P–OMe

Scheme I[a]



[a] **a**: n = 0, R = Me. **b**: n = 0, R = Bn. **c**: n = 1, R = H. **d**: n = 2, R = H. **e**: n = 0, R = H. **f**: n = 4, R = H. Fmoc = (9-fluorenylmethoxy)carbonyl. Pht = Phthalimido.

groups. In this case too, as in **6a**, ^{31}P NMR showed the presence of two conformers around the amide bond.

Another carbamate-type protecting group, known for its acid stability, is [(9-fluorenylmethyl)oxy]carbonyl (Fmoc). Fmoc amino acids are stable enough to withstand conversion to acid chlorides.[22] This protecting group can be deblocked by using mildly basic conditions.[20] The reagents that can be used for the deblocking include various (even weakly basic) amines.[23] Fmoc-alanyl chloride and Fmoc-phenylalanyl chloride reacted with trimethyl phosphite to yield the corresponding dimethyl *N*-Fmoc-aminoacylphosphonates **7** (Scheme I). Due to the hydrolytic susceptibility of the resulting products, diesters **7** were not isolated. They were characterized in the crude product mixture by infrared spectroscopy, showing absorptions at 1710–20 cm^{-1}, which contained both the carbonyl absorptions of the carbamate carbonyl and that of the keto phosphonate. In addition, bands at 1250–60 cm^{-1} (P=O) and 1020 cm^{-1} (P–O–C) could be seen. Diesters **7** were subsequently monodemethylated by lithium bromide in acetonitrile to the analytically pure monomethyl ester lithium salts **8**. These were identified through their ^1H NMR spectra, which showed the required ratio of the methoxy protons to the rest of the molecule, and by the shape of the phosphorus signal (quartet) in the ^{31}P NMR spectrum. There were several attempts to remove the Fmoc group from these compounds. These included the use of various amines (such as piperidine, triethyl- or trimethylamine in methanol, methylamine in ethanol) and lithium hydroxide in water. In all these attempts we obtained 9-methylenefluorene; however, no aminoacylphosphonate could be isolated. The removal of the Fmoc

(19) Another amino protecting group compatible with acyl halide formation is the trifluoroacetyl group, which was used successfully in Friedel–Crafts acylations by *N*-(trifluoroacetyl)aminoacyl chlorides (Nordlander, J. E.; Payne, M. J.; Njoroge, F. G.; Balk, M. A.; Laikos, G. D.; Vishwanath, V. M. *J. Org. Chem.* **1984**, *49*, 4107). On attempted reaction of *N*-trifluoroacetylglycyl chloride with trimethyl phosphite we observed formation of a complex mixture of products. ^{31}P NMR of this mixture showed absorptions at 33, 18.8, 13.2, 10.8, 7.5, 1.5, 1, −2.5 ppm. This behavior probably results in part from the strong electron-withdrawing properties of the trifluoroacetyl group. It was previously observed that Arbuzov reaction of aroyl halides substituted by strongly electron-withdrawing groups is followed by the addition of a second molecule of phosphite to the acylphosphonate and leads to compounds containing two phosphorus atoms and showing resonances at 13.9 and −2.29 ppm: Griffiths, D. V.; Jamali, H. A. R.; Tebby, J. C. *Phosphorus Sulfur* **1981**, *11*, 95.

(20) Breuer, E.; Safadi, M.; Chorev, M.; Vincze, A.; Bel, P. Submitted.

(21) Schroeder, E.; Luebke, K. *The Peptides*, Vol. I; Academic Press: New York and London, 1965, (a) p 25, (b) p 12.

(22) Carpino, L. A.; Cohen, B. J.; Stephens, K. E., Jr.; Sadat-Aalaee, S. Y.; Tien, J.-H.; Langridg, D. C. *J. Org. Chem.* **1986**, *51*, 3734.

(23) (a) Chang, C.-D.; Michinori, W.; Mushtaq, A.; Meienhofer, J.; Lundell, E. O.; Haug, J. D. *Int. J. Pept. Protein Res.* **1980**, 15, 59. (b) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404.

group from **8b**, using 1,8-diazabicyclo[5.4.0]undec-7-ene in methanol at room temperature, was monitored by high performance liquid chromatography (HPLC) and ^{31}P NMR. In this experiment the deblocking was complete in 20 min (based on the yield of 9-methylenefluorene determined by HPLC). This was accompanied by the disappearance, in the ^{31}P NMR, of the signal at 0.01 ppm (q) characteristic of the starting material **8b** and the appearance of two new signals, the major at 0.27 ppm (q), and the minor at 6.4 ppm (q). Upon standing at room temperature, the major peak disappeared and new signals appeared at 4.6 ppm (q), 7.8 ppm (dq), 9.1 ppm (dq), and 17.9 ppm (m), in addition to the previously mentioned signal at 6.4 ppm. the chemical shifts observed are consistent with imine-type products resulting from intermolecular self condensation of aminoacylphosphonates formed.[8b] Attempts to isolate products from such solutions were unsuccessful.

An additional common amino protecting group known to be suitable for the preparation of an aminoacyl halides is the phthaloyl moiety. Phthalimido acid chlorides **9** were prepared from β-alanine, τ-aminobutyric acid, and DL-alanine and subjected to the Arbuzov reaction with trimethyl phosphite, which gave the expected dimethyl phthalimidoacylphosphonates **10**. However, since phthalimido groups are usually removed by treatment with hydrazine,[21b] to which the keto groups of acylphosphonates are quite reactive,[24] it was necessary to protect the keto group during the hydrazinolysis of the phthaloyl group. Consequently acylphosphonates **10** were converted to the corresponding oximes **11** in order to protect the keto groups.[25] Reactions of dimethyl phthalimido α-hydroxyimino phosphonates **11** with hydrazine resulted in a mixture of products due to partial loss of one of the phosphonate methyl groups through nucleophilic demethylation as shown by NMR examination (^1H and ^{31}P) of the reaction mixture.

Methyl phthalimidoacylphosphonate monolithium salts **12** and methyl phthalimido α-hydroxyimino phosphonate monolithium salt **13** were prepared by lithium bromide demethylation according to the procedure for the corresponding Fmoc derivatives **8** described above. These compounds were characterized by ^1H NMR spectroscopy, which showed the anticipated ratios of the various hydrogens in the molecules.

As a consequence of the results described above, it became clear that in order to succeed in the hydrazine-mediated deprotection of phthalimido α-hydroxyimino phosphonates the phosphonic acid needs to be esterified with a hindered alkyl group, which would not be a good substrate in an S_N2 reaction. To achieve this, phthalimidoacyl chlorides **9** derived from the amino acids glycine, β-alanine, τ-aminobutyric acid, DL-alanine, and L-phenylalanine were subjected to the Arbuzov reaction with triisopropyl phosphite to give diisopropyl phthalimidoacylphosphonates **14**.

Reactions of ketones **14** with hydroxylamine yielded oximes **16**. It is interesting to point out that under the reaction conditions the optically active diisopropyl phthaloylphenylalanylphosphonate[26] (**14b**) gave the racemic (*E*)-oxime **16b**. This was apparent both from the lack of optical activity and from the X-ray crystallographic structure determination of **16b**. We were able to obtain single crystals of compounds **16b** (Figure 1) and **16c** (Figure 2) and determined their structure by single-crystal X-ray crystallography. Both compounds crystallized in the monoclinic system and both possess the *E* stereochemistry. Compound **16b** belongs to the space group $P2_1/n$ with four molecules in the unit cell. $P2_1/n$ is a uniquely defined nonchiral centrosymmetric space group, which necessarily contains a racemic mixture in the unit cell. All crystallographic details of both compounds are given in the supplementary material.

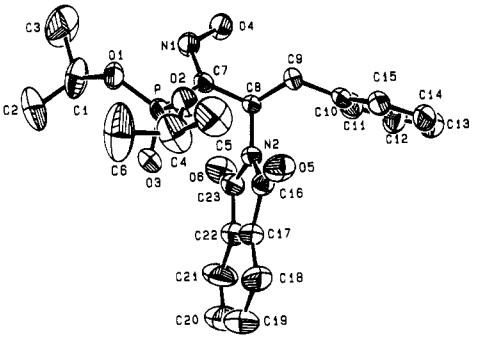


Figure 1. ORTEP view of compound **16b** displaying 50% probability density ellipsoids.

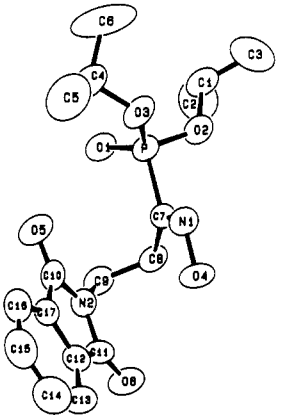


Figure 2. ORTEP view of compound **16c** depicting the geometry and labeling scheme.

Oximes **16** could be deblocked by hydrazine to yield diisopropyl amino-α-(hydroxyimino)alkylphosphonates **17** in which the amino groups were unprotected. Following the successful preparation of compounds **17**, it was of interest to test whether the same procedure could be carried out with diethyl phosphonates **15**. The use of the less hindered ethyl groups is desirable in view of the difficulties we experienced in attempts to monodealkylate diisopropyl phosphonates **17**. Indeed we found that the ethyl groups withstood the conditions employed in the hydrazine-mediated deprotection of oximes **18** and yielded diethyl amino hydroxyimino phosphonates **19**, derived from amino acids alanine and phenylalanine.

Compounds **17c**, **17d**, and **17e**, being structural analogues of GABA, were evaluated for their anticonvulsant activity. Compounds **17c** and **17d** were not active in the maximal electroshock test (MES) and the subcutaneous MET (Sc MET) tests[27] (for details see Experimental Section) at doses of 30 and 100 mg/kg and were found to

(24) In a separate paper we report the results for our study on the comparative reactivity of the acylphosphonic and the phthalimide functions toward hydrazine: Breuer, E.; Safadi, M.; Chorev, M. Submitted.
(25) Greene, T. W. *Protective Group in Organic Synthesis*; Wiley: New York, 1981; pp 144–6.
(26) Although **14b** was not isolated and examined, it is assumed to be optically active similarly to **12b**, which was sufficiently stable to have its optical rotation determined (see Table I).
(27) Porter, R. J.; Cereghino, J. J.; Gladding, G. D.; Hessie, B. J.; Kupferberg, H. J.; Scoville, B.; White, B. G. *Cliv. Clin. Q.* **1984**, *51*, 293.
(28) It is possible, as well, to prepare the corresponding Na salts by using NaI in acetone.

Table I. Physical Data on N-Protected Aminoacylphosphonates

product[a]	yield (%)	elemental anal. found (calcd) C	H	N	NMR
6a	87	50.21 (50.45)	5.15 (5.10)	4.20 (4.20)	^{1}H: (DMSO-d_6) 7.36 (5 H, m), 5.10 (1 H, s), 5.20 (1 H, s), 4.91 (1 H, t), 3.43 ($^3/_2$ H, d, J = 11 Hz), 3.34 (2 H, m), 3.30 ($^3/_2$ H, d, J = 11 Hz), 2.2–2.05 (2 H, bm), 1.78 (1 H, m), 1.56 (1 H, m)
					^{31}P: (DMSO-d_6) at 20 °C −3.62 (dq), H-decoupled −3.60 and −3.64 (2 s); at 90 °C −3.29
6b	94	44.77 (46.56)	4.55 (4.47)	4.23 (4.18)	^{1}H: (D_2O) 7.39 (5 H, m), 5.11 (1 H, s), 5.07 (1 H, s), 3.48 (3 H, m), 2.34–1.89 (4 H, m)
					^{31}P: −6.48 (bd), −6.64 (bd) 40:60
8a	65	55.94 (55.21)	4.80 (5.08)	3.54 (3.39)	^{1}H: (D_2O) 7.27–7.01 (8 H, m), 4.55 (1 H, m), 4.05 (3 H, m), 3.59 (3 H, d, J = 11 Hz), 1.30 (3 H, d, J = 7 Hz)
8b	48	63.15 (62.88)	5.06 (4.80)	2.99 (3.05)	^{1}H: (CD_3OD) 7.67–7.18 (13 H, m), 4.89 (1 H, m), 4.07 (3 H, m), 3.6 (3 H, d, J = 10 Hz), 2.67 (2 H, m)
					^{31}P: 0.02 (q)
12a	60				^{1}H: (D_2O) 7.85 (4 H, m), 5.21 (1 H, m), 3.59 (3 H, d, J = 11 Hz), 1.78 (3 H, d, J = 7 Hz)
12b	88	55.51 (56.99)	4.42 (3.95)	3.45 (3.69)	^{1}H: (CD_3OD) 7.72 (4 H, m), 7.13 (5 H, m), 5.47 (1 H, m), 3.93 (2 H, m), 3.64 (3 H, d, J = 11 Hz)
12d	70	48.21 (49.21)	4.20 (4.10)	4.46 (4.41)	^{1}H: (D_2O) 7.74 (2 H, m), 7.69 (2 H, m), 3.63 (3 H, d, J = 11 Hz), 3.60 (2 H, t), 2.69 (2 H, m), 1.92 (2 H, m)
12f	47	52.74 (52.17)	4.91 (4.93)	3.12 (4.06)	^{1}H: (D_2O) 7.81 (4 H, m), 3.65 (2 H, t), 3.63 (3 H, d, J = 11 Hz), 2.80 (2 H, t), 1.63 (2 H, m), 1.31 (4 H, m)

[a] Specific rotations: **6a** $[\alpha]^{25}_D$ = −53.60° (c = 0.58, MeOH); **6b** $[\alpha]^{25}_D$ = +2.90° (c = 1.0, MeOH): **8b** $[\alpha]$ = +35.80° (c = 0.55, MeOH): **12b** $[\alpha]^{25}_D$ = −83.80° (c = 4.0, MeOH).

be toxic, using a dose of 300 mg/kg. Compound **17e** demonstrated some anticonvulsant activity in the MES test at doses of 100 mg/kg and 300 mg/kg. However this compound was also toxic at a dose of 300 mg/kg.

Conclusion

The work described above opens possibilities for the introduction of acylphosphonic and oxyimino phosphonic moieties as building blocks in the design of novel potential bioactive agents such as inhibitors of proteolytic enzymes, in situ phosphorylating agents, in vivo calcium chelators, and metal sequestering agents. The synthetic methodologies addressed in this work provide the ground work for the synthesis of model drugs as demonstrated by the anticonvulsant activity of the diisopropyl 1-(hydroxyimino)-2-aminoethylphosphonate (**17e**). Our current efforts are directed to incorporate these moieties in peptidic and pseudopeptidic constructs designed to inhibit specific metalloendopeptidases.

Experimental Section

General. Melting points were determined by a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the Hebrew University of Jerusalem. Infrared spectra were determined on an Analect FTIR spectrometer. Nuclear magnetic resonance spectra were obtained on a Bruker WH-300 or on a Varian VXR-300S instrument. Chemical shifts are reported in ppm. downfield from TMS or TSP as internal standards in ^{1}H spectra and from 85% H_3PO_4 as external standard in ^{31}P spectra. Positive chemical shifts are at low field with respect to the standard. Mass spectra were obtained on LKB 2091 gas chromatograph–mass spectrometer. High performance liquid chromatography was carried out on a Merck Hitachi Model L-6200 intelligent pump. Specific rotations were measured on a Perkin-Elmer 141 polarimeter, using 10-cm cell.

Synthesis. All solvents and commercial reagents were dried prior to use with the appropriate drying agents.

Typical Procedure for the Preparation of N-Protected Lithium Methyl Acylphosphonates (Compounds 6, 8, and 12; see Table I). Lithium Methyl *N*-(Benzyloxycarbonyl)prolylphosphonate (6a).[29] To a solution of Cbz-Pro-OH[28] (1 g, 4 mmol) in dry benzene (50 mL) was added PCl_5 (0.92 g, 4.4 mmol), and the mixture was heated for 1 h under nitrogen at 55 °C. The solvent was evaporated and the residue was treated with dry toluene and evaporated again to give the acid chloride as an oil (ν_{max} (C=O) at 1790 cm^{-1}). This crude compound was reacted in the next step without further purification by adding to it trimethyl phosphite (0.5 g, 4 mmol) and stirring for 10 min and then evaporating the solution in vacuo at room temperature to yield dimethyl *N*-Cbz-prolylphosphonate (**5**), 1.2 g 87%. IR ν_{max} (neat): 1700, 1410, 1340, 1260, 1020 cm^{-1}. The crude **5** was dissolved in dry acetonitrile (20 mL), lithium bromide (0.34 g, 3.9 mmol) was added, and the reaction mixture was stirred at room temperature overnight. The lithium salt was isolated by filtration to yield **6a** (1.13 g, 85%).

Sodium Hydrogen *N*-(Benzyloxycarbonyl)prolylphosphonate (6b). To a solution of dimethyl *N*-(benzyloxycarbonyl)prolylphosphonate (**5**, 3.50 g, 8.95 mmol) in dry acetonitrile (20 mL), which was cooled to 0 °C, was added bromotrimethylsilane (2.6 mL, 19.5 mmol) dropwise, the solution was stirred for 1.5 h and evaporated, and the residue was treated with a solution of sodium hydroxide (0.36 g, 8.95 mmol) in methanol (20 mL). After stirring for 30 min, the solvent was evaporated to dryness. The residue was taken up in ether and filtered to give (3.25 g, 94%) of product as a white solid.

Typical Procedure for the Preparation of Dialkyl 1-(Hydroxyimino)phthalimidoalkylphosphonates (Compounds 11, 16, 18; see Table II). Diisopropyl 1-(Hydroxyimino)-4-phthalimidobutyrylphosphonate (16d). Triisopropyl phosphite (0.1 mol) was added to 4-phthalimidobutyryl chloride (**9d**)[30] (0.1 mol) in dry benzene (20 mL). The solution was left to stir overnight and evaporated in vacuo to yield **14d**, which was characterized by IR [ν_{max} (neat) 1772, 1713, 1396, 1259, and 1105 cm^{-1}] and ^{1}H NMR [($CDCl_3$) 7.77 (4 H, m), 4.71 (2 H, m), 3.77 (2 H, m), 2.87 (2 H, m), 2.08 (2 H, m), 1.36 (12 H, m)].

To the crude **14d** obtained in the previous step was added a solution of hydroxylamine hydrochloride (0.12 mol) and pyridine (0.16 mol) in absolute ethanol (30 mL). The resulting solution was stirred at ambient temperature for 2 days and the ethanol was evaporated. The residue was dissolved in dichloromethane (100 mL) and washed successively with 1 N HCl (2 × 20 mL), brine (2 × 20 mL), saturated sodium bicarbonate (2 × 20 mL), and again with brine (2 × 20 mL). After drying over $MgSO_4$ the dichloromethane was evaporated, and the residue was crystallized from ethyl acetate. The product was obtained in the overall yield of 76% for the two steps. Mp: 131 °C. IR ν_{max} (KBr): 3150,

(29) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer Verlag: Berlin, 1984; p 24, 185.

(30) *N*-Phthaloyl amino acids were synthesized from *N*-carbethoxy phthalimide and the corresponding amino acid salts, according to Nephkens, G. H. L.; Tesser, G. I.; Nivard, R. J. F. *Recl. Trav. Chim.* **1960**, *79*, 688. *N*-Phthaloyl amino acid chlorides were prepared from the corresponding acids with a large excess of thionyl chloride in benzene or without solvent: Losse, G.; Muller, G. *Chem. Ber.* **1961**, *94*, 2768.

Table II. Physical Data on Dialkyl 1-(Hydroxyimino)phthalimidoalkylphosphonates

product	yield (%)	mp (°C)	elemental anal. found (calcd) C	H	N	P	NMR
11a	44	142	47.84 (47.74)	4.60 (4.59)	8.58 (8.54)		^{1}H: ($CDCl_3$) 7.84 (2 H, m), 7.78 (2 H, m), 3.75 (7 H, d, J = 11, Hz), 1.73 (3 H, d, J = 6 Hz)
11c	47	160	47.84 (47.70)	4.60 (4.58)	8.58 (8.56)		^{1}H: ($CDCl_3$) 7.81 (2 H, m), 7.67 (2 H, m); 3.99 (2 H, t), 3.70 (6 H, d, J = 11 Hz), 2.89 (2 H, m)
11d	50	138	49.10 (49.41)	5.04 (5.00)	8.40 (8.24)	9.11 (9.11)	^{1}H: ($CDCl_3$) 7.71 (2 H, m), 7.62 (2 H, m), 3.70 (d, J = 11 Hz) + 3.65 (d, J = 11 Hz) together 6 H, 3.59 (2 H, t), 2.50 (2 H, m), 1.91 (2 H, m) ^{31}P: 9.10 (septet) 80%, 6.20 (septet) 20%
16a	75	127–9	53.06 (53.40)	5.87 (6.06)	6.97 (7.33)	8.51 (8.10)	^{1}H: ($CDCl_3$) 7.74 (2 H, m), 7.63 (2 H, m), 5.5 and 5.0 (total 1 H, two m's, CH at position 2), 4.66 (2 H, m), 1.76 and 1.58, (total 3 H, two d's, J = 7.5 Hz, CH_3's at position 3), 1.13 (12 H, m) ^{31}P: 2.88 (dt, 60%), 0.36 (dt, 40%)
16b	70	149	60.45 (60.26)	5.82 (5.94)	6.27 (6.11)		^{1}H: ($CDCl_3$) 7.72 (2 H, m), 7.69 (2 H, m), 7.17 (5 H, m), 5.45 (1 H, m), 4.74 (2 H, m), 3.50 (2 H, m), 1.26 (12 H, m) ^{31}P: 3.67 (m, 20%), −0.13 (m, 80%)
16c	70	113–5	53.42 (53.40)	6.00 (6.06)	6.98 (7.33)	8.21 (8.10)	^{1}H: ($CDCl_3$) 7.84 (2 H, m), 7.70 (2 H, m), 4.75 (2 H, m), 4.0 (2 H, t), 2.85 (2 H, m), 1.30 (12 H, dd, J = 6 Hz) ^{31}P: 3.78 (septet, J = 7 Hz)
16d	76	131	54.84 (54.54)	6.23 (6.36)	6.71 (7.07)	7.80 (7.81)	^{1}H: ($CDCl_3$) 7.84 (2 H, m), 7.71 (2 H, m), 4.75 (2 H, m); 3.74 (2 H, t), 2.1 (2 H, m); 2.01 (2 H, m), 1.3 (12 H, m) ^{31}P: 3.47 (t)
16e	78	153–5	51.95 (52.17)	5.76 (5.70)	7.57 (7.60)	8.42 (8.42)	(Z) ($CDCl_3$) ^{1}H: 7.87 (2 H, m), 7.73 (2 H, m), 4.76 (2 H, d, J = 9.3 Hz), 4.61 (2 H, m), 1.36 (12 H, d, J = 6.3 Hz) ^{31}P: −0.65 (quintet, J = 21 Hz) (E) ($CDCl_3$) ^{1}H: 7.87 (2 H, m), 7.72 (2 H, m), 4.76 (2 H, d, J = 9.3 Hz), 4.66 (2 H, octet, J = 6.3 Hz), 1.24 (6 H, d, J = 6.3 Hz), 1.15 (6 H, d, J = 6.3) ^{31}P: 4.07 (quintet)
18a	45	120	50.68 (50.80)	5.36 (5.36)	7.98 (7.90)	8.68 (8.75)	^{1}H: ($CDCl_3$) 7.82 (2 H, m), 7.74 (2 H, m), 5.30 (1 H, m), 4.10 (4 H, m), 1.65 (3 H, d, J = 6 Hz), 1.25 (3 H, t), 1.19 (3 H t) ^{31}P: 2.68 (quintet)
18b	50	136	58.34 (58.60)	5.43 (5.35)	6.68 (6.68)	7.18 (7.20)	^{1}H: ($CDCl_3$) 7.72 (2 H, m), 7.64 (2 H, m), 7.14 (5 H, m), 5.43 (1 H, m), 4.16 (4 H, m), 3.53 (2 H, m), 1.26 (3 H, t), 1.21 (3 H, t) ^{31}P: 2.33 (m)

Table III. Physical Data on Dialkyl 1-(Hydroxyimino)aminoalkylphosphonates

product	yield (%)	mp (°C)	elemental anal. found (calcd) C	H	N	P	NMR
17a	44	146	37.39 (37.40)	7.31 (7.62)	9.81 (9.70)		^{1}H: (D_2O) at 17 °C 4.47 (1 H, m), 1.60 (3 H, dd, J = 7 Hz), 1.38 (12 H, dt) at 35 °C 4.85 (2 H, m), 4.47 (1 H, m), 1.61 (3 H, d, J = 7 Hz), 1.38 (12 H, t) ^{31}P: 4.21 (m)
17b	50	172	49.11 (49.38)	6.88 (7.13)	8.17 (7.68)	8.65 (8.50)	^{1}H: (D_2O) 7.38 (5 H, m), 4.67 (1 H, m), 4.53 (2 H, m), 3.46 (1 H, m), 3.30 (1 H, m), 1.28 (12 H, m) ^{31}P: 6.56 (q)
17c	85	155	37.49 (37.40)	7.47 (7.62)	9.65 (9.70)		^{1}H: (D_2O) 4.52 (2 H, m), 3.35 (2 H, t), 2.96 (2 H, t), 1.31 (12 H, m) ^{31}P: 0.0 (mjor peak) 5.3 (minor peak)
17d	52	149	40.45 (39.67)	7.74 (7.93)	9.02 (9.25)		^{1}H: 3.0 (2 H, t), 2.61 (2 H, m), 1.94 (2 H, m), 1.34 (12 H, m) ^{31}P: 5.70 (m)
17e	42	165	32.93 (34.92)	6.99 (7.28)	10.08 (10.20)		^{1}H: (D_2O) 4.83 (2 H, m), 3.96 (2 H, d, J = 9 Hz), 1.36 (12 H, t) ^{31}P: 6.50 (m)
19a	93						^{1}H: (D_2O) 4.30 + 3.97 (4 H, m), 1.71 (1 H, d, J = 6 Hz), 1.62 (2 H, d, J = 6 Hz), 1.36 (3 H, t): 1.27 (3 H, t)
19b	60						^{1}H: (D_2O) 7.44 (5 H, m), 4.21 (1 H, m), 4.00 (4 H, m), 3.35 (2 H, m), 1.29 (2 H, m) ^{31}P: 3.01 (m, 40%), 0.91 (m, 60%)

1770, 1710, 1610, 1245, 1020 cm^{-1}.

Lithium Methyl 1-(Hydroxyimino)-3-phthalimidopropylphosphonate (13c).[28] This compound was obtained by monodealkylation of **11a** with lithium bromide in acetonitrile at room temperature. IR ν_{max} (Nujol mull): 1780, 1720, 1250, 1100, 1050 cm^{-1}. ^{1}H NMR (D_2O): 7.81 (4 H, m), 3.95 (2 H, t), 3.47 (3 H, d, J = 10.6 Hz), 2.79 (2 H, m). Anal. Calcd for $C_{12}H_{12}N_2O_6PLi$: C, 45.28; H, 3.77; N, 8.80. Found: C, 44.92; H, 3.81; N, 8.66.

Lithium Methyl 1-(Hydroxyimino)-4-phthalimidobutylphosphonate (13d).[28] This compound was obtained in 75% yield by monodealkylation of **11d** with lithium bromide in acetonitrile at room temperature. Anal. Calcd for $C_{13}H_{14}N_2O_6PLi$: C, 46.98; H, 4.21; N, 8.43. Found: C, 46.85; H, 4.00; N, 8.65. ^{1}H NMR (D_2O): 7.79 (4 H, m), 3.68 (2 H, m), 3.53 (3 H, d, J = 11 Hz), 2.50 (2 H, m), 1.92 (2 H, m).

Typical Procedure for the Preparation of Dialkyl 1-(Hydroxyimino)aminoalkylphosphonates (Table III). Diisopropyl 1-(Hydroxyimino)-4-aminobutylphosphonate Hydrochloride (17d). Diisopropyl 1-(Hydroxyimino)-4-phthalimidobutyrylphosphonate (**16d**) (3.96 g, 10 mmol) was added to a 1 M solution of hydrazine hydrate in absolute ethanol (10 mL). The mixture was diluted with ethanol (30 mL) and was stirred at 25 °C overnight. The alcohol was removed in vacuo, and the residue was treated with 2 N HCl (25 mL) and kept at room temperature for 1 h. The insoluble phthalohydrazide was removed by filtration and the filtrate was lyophylized, the residue was triturated with acetone to give 1.57 g of **17d** as the hydrochloride salt (yield 52%).

Diisopropyl Phthalylglycylphosphonate (14e). This compound was synthesized by the Arbuzov reaction of *N*-

phthaloylglycyl chloride[29] (**9e**) with triisopropyl phosphite in quantitative yield. Anal. Calcd for $C_{16}H_{20}NO_6P$: C, 54.40; H, 5.66; N, 3.97. Found: C, 54.52; H, 5.45; N, 3.77. ^1H NMR ($CDCl_3$): 7.88 (2 H, m), 7.74 (2 H, m), 4.71 (2 H, d, J = 9 Hz), 4.76 (2 H, m), 1.40 (12 H, m).

X-ray Crystallography. Data collection was performed on a Philips PW 1100 automated diffractometer using a θ–2θ scan mode. The data were corrected for Lorentz polarization but no absorption correction was applied due to the low absorption coefficients. All non-hydrogen atoms were located by the direct methods of SHELX-86 and by subsequent difference maps. The refinement was carried out with SHELX-76.[31] Other pertinent information can be found in Tables S1 and S8 in the supplementary material.

Anticonvulsant Activity. Compounds **17c**, **17d**, and **17e** were screened in mice for their anticonvulsant activity at the Epilepsy Branch of the U.S. National Institute of Health, Bethesda, MD.[26] The screening procedure involved the following: (i) the maximal electroshock (MES) test, which measures seizure spread; (ii) the subcutaneous pentylenetetrazol test (Sc MET test), which measures seizure threshold; and (iii) the rotorod ataxia test, which assesses neurotoxicity.

Acknowledgment. This research was supported, in part, by The Fund for Basic Research, Administered by The Israel Academy of Sciences and Humanities (to E.B.). We thank Mr. James Stables of the NIH Epilepsy Branch for screening our compounds in the anticonvulsant screening project.

Registry No. **5**, 129034-39-5; **6a**, 129034-40-8; **6b**, 129034-41-9; **8a**, 129034-42-0; **8b**, 129034-43-1; **9d**, 10314-06-4; **9e**, 6780-38-7; **11a**, 129034-44-2; **11c**, 129034-45-3; **11d**, 129034-46-4; **12a**, 129034-47-5; **12b**, 129034-48-6; **12d**, 129034-49-7; **12f**, 129034-50-0; **13c**, 129034-51-1; **13d**, 129034-52-2; **14d**, 129034-53-3; **14e**, 129034-54-4; **16a**, 129034-55-5; **16b**, 129034-56-6; **16c**, 129034-57-7; **16d**, 129034-58-8; **16e**, 129034-59-9; **17a**, 129034-60-2; **17b**, 129034-61-3; **17c**, 129034-62-4; **17d**, 129034-63-5; **17d**·HCl, 129034-69-1; **17e**, 129034-64-6; **18a**, 129034-65-7; **18b**, 129034-66-8; **19a**, 129034-67-9; **19b**, 129034-68-0; Cbz-Pro-OH, 1148-11-4; Cbz-Pro-Cl, 61350-60-5; $P(OMe)_3$, 121-45-9; $P(OPr\text{-}i)_3$, 116-17-6.

Supplementary Material Available: Experimental details of the X-ray diffraction studies of **16b** and **16c** (12 pages); observed and calculated structure factors for **16b** and **16c** (27 pages). Ordering information is given on any current masthead page.

(31) Sheldrick, G. M. "SHELX-76" in *Computing in Crystallography*; Schenck, H., Olthof-Hazekamp, R., van Koningsveld, H., Bassi, G. C., Eds.; Delft University Press: Delft, The Netherlands, 1978; pp 34–42.

Ozonolysis of Vinyl Ethers in Solution and on Polyethylene

Karl Griesbaum,*[1a] Woo-Sun Kim,[1a] Norinaga Nakamura,[1b] Mitsuyuki Mori,[1b] Masatomo Nojima,*[1b] and Shigekazu Kusabayashi[1b]

Engler-Bunte-Institut, Bereich Petrochemie, Universität Karlsruhe (TH), D-7500 Karlsruhe, Germany, and Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan

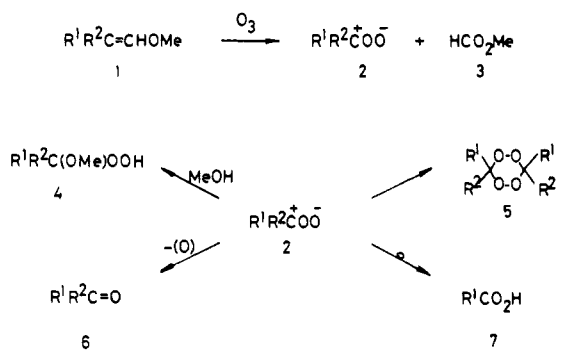
Received February 27, 1990

Ozonolyses of the vinyl ethers **1a–f** in methanol afforded almost exclusively the corresponding α-methoxy hydroperoxides **4**, suggesting the preferred formation of the carbonyl oxides **2**. In aprotic solvents including methyl formate, the predominant modes of decay of the carbonyl oxides **2** were cyclodimerization, reduction, and rearrangement, yet no ozonide formation. By contrast, ozonolyses of **1a–f** on polyethylene gave the α-methoxy-substituted ozonides **14** in fair yields. Ozonolyses of **1a–f** in the presence of added carbonyl compounds **6** in methylene chloride or ether yielded the corresponding cross ozonides. Judged from the ozonide yields, the reactivities of the carbonyl compounds follow the sequence: $(ClCH_2)_2C{=}O > ClCH_2COCH_3 > (CH_3)_2C{=}O$ and $2\text{-}CF_3C_6H_4CHO > PhCHO$.

Introduction

Vinyl ethers, as electron-rich alkenes, exhibit high reactivity toward electrophilic ozone. The ozonolysis of trisubstituted vinyl ethers is well known to yield mainly epoxides and other "partial cleavage" products derived by oxygen atom transfer from ozone.[2] Recently, Kuczkowski discovered that the reaction of unsubstituted vinyl ethers resulted in the exclusive formation of formaldehyde *O*-oxide, which in aprotic solvents cycloadds to the substrate to afford the corresponding 1,2-dioxolanes.[3] When the reaction was carried out in methyl formate, however, α-methoxy-substituted ozonides were obtained in good yields.[4,5] It was, therefore, of interest to investigate the reaction pathways of mono- and disubstituted vinyl ethers. Another interest is the ozonolysis on polyethylene, since we have discovered that this method may be suitable for preparing ozonides which could not be obtained by conventional methods.[6] Hence, if the ozonolysis of mono- and

Scheme I



(1) (a) Universität Karlsruhe. (b) Osaka University.

(2) (a) Hoffmann, R. W.; Schneider, J. *Chem. Ber.* **1967**, *100*, 3698. (b) Borowitz, I. J.; Rapp, R. D. *J. Org. Chem.* **1969**, *34*, 1370. (c) Gassman, P.; Creary, X. *Tetrahedron Lett.* **1972**, 4407, 4411. (d) Clark, R. O.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396.

(3) Keul, H.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1984**, *106*, 5370.

(4) (a) Keul, H.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1984**, *106*, 3383. (b) Wojciechowski, B. J.; Pearson, W. H.; Kuczkowski, R. L. *J. Org. Chem.* **1989**, *54*, 115.

(5) Examples are also known for intramolecular cycloaddition of a carbonyl oxide moiety to an ester group. (a) Bunnelle, W. H.; Meyer, L. A.; Schlemper, E. O. *J. Am. Chem. Soc.* **1989**, *111*, 7612. (b) Bunnelle, W. H. *Ibid.* **1989**, *111*, 7613.

(6) (a) Griesbaum, K.; Volpp, W.; Greinert, R. *J. Am. Chem. Soc.* **1985**, *107*, 5309. (b) Griesbaum, K.; Volpp, W. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 81. (c) Griesbaum, K.; Volpp, W.; Greinert, R.; Greunig, H.; Schmid, J.; Henke, H. *J. Org. Chem.* **1989**, *54*, 383.

0022-3263/90/1955-6153$02.50/0