in Table II.

Acknowledgment. We thank the Robert A. Welch Foundation of Houston TX, and the University of Texas at Arlington Organized Research Fund for partial support. We also thank Professor Daniel Blake for providing several of the phosphines.

Registry No. 1, 123-77-3; **2a**, 603-35-0; **2b**, 1486-28-8; **2c**, 607-01-2; **2d**, 672-66-2; **2e**, 1605-53-4; **2f**, 554-70-1; **2g**, 1663-45-2; **3a**, 79731-18-3; **3b**, 79731-19-4; **3c**, 79731-20-7; **3d**, 79731-21-8; **3e**, 79731-22-9; **3f**, 79731-23-0; **3g**, 79731-24-1.

Synthesis with α-Heterosubstituted Phosphonate Carbanions. 12.[1] X-ray Structure Determination of (*R*,*S*)-Diphenyl 1-(4-Bromoanilino)-1-(4,5-methylenedioxy-2-nitrophenyl)methanephosphonate

Michael D. Crenshaw, S. J. Schmolka, Hans Zimmer,* Robert Whittle, and R. C. Elder*

Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221

Received June 15, 1981

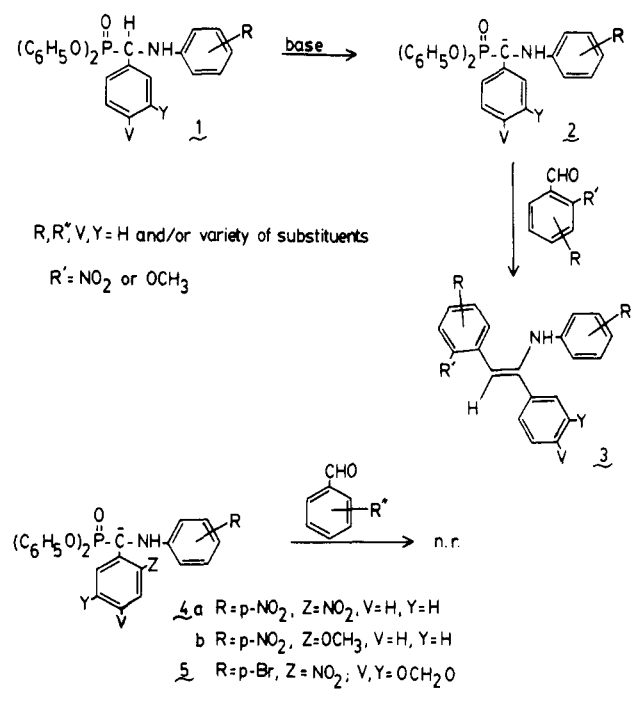
The reaction of (*R*,*S*)-diphenyl 1-(4-nitroanilino)-1-(2-methoxyphenyl)methanephosphonate with KOH in methanol followed by addition of an aldehyde is expected to yield rapidly in an aldol-type condensation the corresponding enamine. However, transesterification of the phosphonate occurs instead to yield (*R*,*S*)-dimethyl 1-(4-nitroanilino)-1-(2-methoxyphenyl)methanephosphonate at a somewhat slower rate. If the ortho substituent is either NO_2 or OCH_3, the desired enamine is not produced under a variety of conditions. An X-ray structure determination of an analogous, unreactive phosphonate, (*R*,*S*)-diphenyl 1-(4-bromoanilino)-1-(4,5-methylenedioxy-2-nitrophenyl)methanephosphonate, $P2_1/n$, a = 10.779 (4) Å, b = 20.694 (7) Å, c = 13.336 (3) Å, β = 109.470 (1)°, U = 2803.4 Å^3, Z = 4 (with two solvent molecules per unit cell when recrystallized from benzene), d_{measd} = 1.48 (2), d_{calcd} = 1.467 g cm^{-3}, R_1 = 0.054, R_2 = 0.033, indicates that steric hindrance may explain the failure of the resulting carbanion to react with the aldehyde. The structure results are compared to those for the reactive compound, diethyl 1-anilino-1-phenylmethanephosphonate.

Introduction

Phosphonates of the general form, diphenyl 1-(4-nitroanilino)-1-arylmethanephosphonate (**1**) are useful in the syntheses of ketones, indoles,[2a] benzo[*b*]furans,[2b] and quinolines.[2c] They are readily deprotonated by base to give the carbanions (**2**) which subsequently react with a wide variety of aldehydes to yield the corresponding enamines (**3**; Scheme I). If an ortho substituent (as in **4**) is present on the phenyl ring bound to the carbanion carbon atom, enamines are not obtained. However, the color change asociated with the carbanion formation is observed. For example, with the ortho substituents NO_2 or OCH_3 and the reactant aldehydes *trans*-cinnamaldehyde or benzaldehyde, no aldol-type condensation product is formed. Carbanions of 1-anilino-1-phenylmethanephosphonates which lack an ortho substituent[2a,b] do react with ortho-substituted benzaldehydes.

Since it apeared likely that carbanion formation takes place for all of these compounds but that the carbanion formed in nonreactive cases might be too sterically hindered for subsequent, successful nucleophilic attack on the aldehyde,[3] we have determined the single-crystal structure of one of the nonreactive phosphonate starting materials by X-ray methods and report it here.

Scheme I



Results and Discussion

The structure of the title compound, **5**, is shown in Figure 1. The structure of another phosphonate, (*R*,*S*)-diethyl 1-anilino-1-phenylmethane phosphonate, **6** (Figure 2), which will react under similar conditions to yield an enamine, has been published.[4] Pertinent bond lengths and angles from the structures of the two phosphonates are included in Table I for comparison. The O–C bond lengths of the esters differ as expected due to the difference in hybridization between phenyl carbon (sp^2)

(1) Koenigkramer, R. E.; Zimmer, H. *J. Org. Chem.* **1980**, *45*, 3994.
(2) (a) Zimmer, H.; Nene, D. M. *Chimia* **1977**, *31*, 330. (b) Zimmer, H.; Seemuth, P. D. *J. Org. Chem.* **1978**, *43*, 3063. (c) Zimmer, H.; Nene, D. M. *J. Heterocycl. Chem.* **1978**, *15*, 1237.
(3) Petrova, J.; Coutrot, P.; Dreux, M.; Savignac, P. (*Synthesis* **1975**, 658) report what they believe to be steric hindrance with diethyl (2-chlorophenyl)methanephosphonate.
(4) Ruzic-Toros, Živa; Kojic-Prodic, Biserka; Sljukic, M. *Acta Crystallogr., Sect. B.* **1978**, *34*, 3110. Structure **6** is published under the equivalent name: D,L-Diethyl α-anilinobenzylphosphonate.

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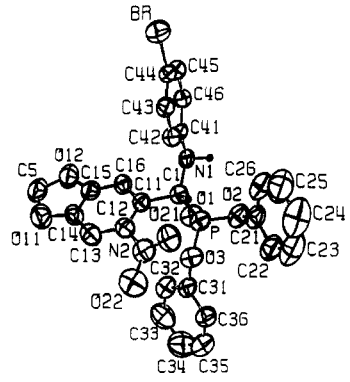


Figure 1. ORTEP drawing of (*R*)-diphenyl 1-(4-bromoanilino)-1-(4,5-methylenedioxy-2-nitrophenyl)methanephosphonate (**5**). Both enantiomers exist in the unit cell.

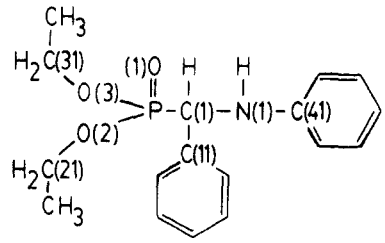


Figure 2. Diethyl 1-anilino-1-phenylmethanephosphonate (**6**).

and alkyl carbon (sp^3). All other comparable bond lengths agree within the expected error.[5] The most significant differences in bond angles appear to be those around the phosphorus atom. Specifically the O,P,O angle between the two ester oxygen atoms is 106.7 (2)° for the diphenyl compound and only 99.1 (2)° for the diethyl compound. It appears that this difference results from the greater bulk of the phenyl moieties compared to the ethyl groups. However, comparison of the central portions of these two molecules gives no indication why they differ so completely in reactivity.

Examination of the stereoscopic drawing of **5**, presented in Figure 3, shows that the nitro group in the ortho poition lies above the protocarbanionic carbon atom, effectively completing a cage about this atom. From the color change which is observed when base is added to a solution of either the nitro or methoxy ortho substituted phosphonate, it appears that this site is not so tightly enclosed that carbanion formation is prevented, but only that the carbanion once formed is too hindered for subsequent nucleophilic attack on the aldehyde. Similar behavior for both nitro and methoxy substituents rules out some more esoteric ring-forming interaction between an oxygen atom of the nitro group and the phosphorus atom.[6] The positioning of the nitro group found in the crystal seems likely to be maintained in solution for both the starting phosphonate and the subsequent carbanion, since in this position the principal contact of the nitro group oxygen, O(21), is with the hydrogen atom, H(1), on C(1) or with the electron pair of the carbanion, and these are clearly the least sterically demanding groups on C(1). As it is, the nitro moiety is twisted 34.5° from the plane of the phenyl ring, thus increasing the contact distance between O(21) and H(1) to 2.15 Å. Although that hydrogen atom is clearly acidic, it is unlikely that the O···H interaction is attractive (hydrogen bond): the distance is too great[7] (O···H distances of 1.7 Å occur in strong hydrogen bonds) and hydrogen bonds tend toward linearity at hydrogen, whereas the angle O(21),H(1),C(1) is 128°.

Table I. Comparison of Bond Lengths (Å) and Angles (deg) of Diphenyl 1-(4-Bromoanilino)-1-(4,5-methylenedioxy-2-nitrophenyl)methanephosphonate (**5**) vs. Diethyl 1-Anilino-1-phenylmethanephosphonate (**6**)

bond	5	6
P-C(1)	1.803 (3)	1.821 (6)
C(1)-C(11)	1.532 (5)	1.523 (7)
C(1)-N(1)	1.464 (5)	1.446 (7)
N(1)-C(41)	1.408 (5)	1.413 (8)
P-O(1)	1.453 (3)	1.465 (4)
P-O(2)	1.579 (3)	1.564 (4)
P-O(3)	1.588 (3)	1.567 (4)
O(2)-C(21)	1.386 (7)	1.459 (8)
O(3)-C(31)	1.396 (5)	1.451 (9)
angle	**5**	**6**
P-C(1)-C(11)	110.9 (2)	114.0 (4)
P-C(1)-N(1)	108.6 (2)	105.5 (4)
C(11)-C(1)-N(1)	113.5 (3)	115.1 (4)
C(41)-N(1)-C(1)	119.3 (3)	121.3 (5)
O(1)-P-C(1)	116.4 (2)	113.0 (2)
O(2)-P-C(1)	108.3 (2)	106.5 (2)
O(3)-P-C(1)	99.0 (2)	104.6 (2)
O(1)-P-O(2)	109.4 (2)	115.7 (2)
O(1)-P-O(3)	116.3 (2)	116.3 (2)
O(2)-P-O(3)	106.7 (2)	99.1 (2)
C(21)-O(2)-P	123.9 (2)	120.9 (4)
C(31)-O(3)-P	126.0 (2)	124.1 (4)

Since the carbanion, once formed, is prevented from attacking the aldehyde, this system is quite stable. However, a much slower reaction, that of transesterification to yield the dimethyl phosphonate, probably occurs after the reaction mixture is allowed to warm to room temperature.[8] As a test, compound **4b** was reacted with methanolic KOH at room temperature and shown to produce the corresponding dimethyl phosphonate. Transesterification, monitored by TLC, is quite slow, with none of the dimethyl phosphonate product being observed during the first 6 h. However, the eventual yield (71%) under nonoptimized conditions is relatively high.

In conclusion, the ortho substituent effectively completes the "cage" about the carbanion site so as to render the generated carbanion unreactive toward aldehydes without imposing any noticeable distortions on the rest of the molecule, particularly around C(1). When KOH in methanol is used, this lack of carbanion reactivity allows the slower competing transesterification reaction to occur, a phenomenon which is not observed with these compounds under normal experimental conditions.

Experimental Section

General Methods. Melting points, determined with a Mel-Temp melting point apparatus, are uncorrected. Infrared (IR) spectra were recorded with a Perkin-Elmer Model 599 or 700 spectrometer calibrated against the 1601-cm^{-1} band of styrene. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Varian T-60 spectrometer. Chemical shifts are expressed in δ units relative to 1% tetramethylsilane as an internal standard; coupling constants (J values) are given in hertz. Mass spectral data were obtained on a Perkin-Elmer RMU-7 mass spectrometer. Elemental analyses were preformed at Integral Microanalytical Laboratories of Raleigh, NC, or M-H-W Laboratories, Phoenix, AZ.

(5) The error in the difference between A and B, computed as $\sigma(A-B) = \{[\sigma(A)]^2 + [\sigma(B)]^2\}^{1/2}$ and $\Delta(AB) < 3\sigma(A-B)$, is considered insignificant.

(6) (a) Ramirez, F. *Acc. Chem. Res.* **1968**, *1*, 168. (b) Hudson, R. F.; Brown, C. *Acc. Chem. Res.* **1972**, *5*, 204.

(7) Joesten, M. D.; Schaad, L. J. "Hydrogen Bonding"; Marcel Dekker; New York, **1974**; pp 35–40.

(8) Kozlov, N. S.; Pak, V. D.; Elin, E. S. *Vestsn. Akad. Nauk Belarus, SSR, Ser. Khim. Nauk* **1970**, *2*, 102; *Chem. Abstr.* **1970**, *73*, 25586r.

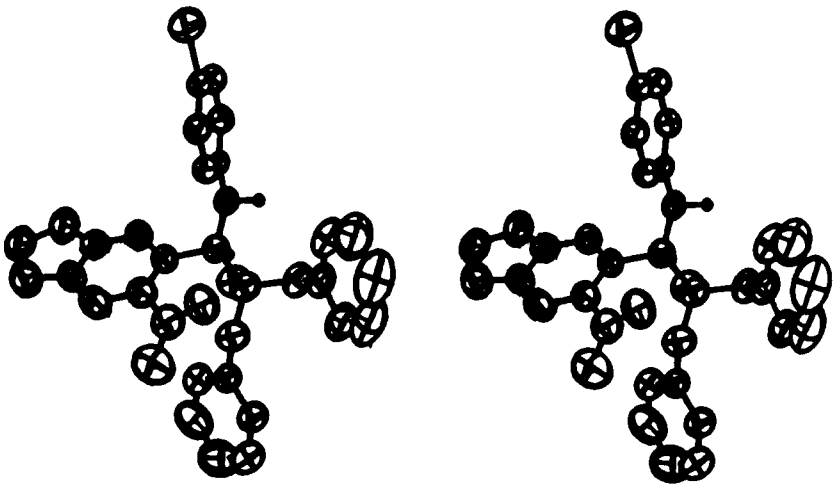


Figure 3. Stereoview of (*R*)-diphenyl 1-(4-bromoanilino)-1-(4,5-methylenedioxy-2-nitrophenyl)methanephosphonate (**5**).

Tetrahydrofuran (THF) was purified by continuous distillation under argon from sodium metal and benzophenone. Diisopropylamine and dimethyl sulfoxide (reduced pressure) were distilled from CaH_2 and stored under nitrogen. Standardized solutions of *n*-butyllithium in hexane were a gift from Lithium Corp. of America. Sodium hydride, obtained as a 57% oil dispersion from Alfa Inorganics, was washed with hexane prior to use. Other reagents were commercially available from Aldrich Chemical Co. Aldehydes were distilled, and *p*-nitroaniline was recrystallized prior to use.

Preparation of Phosphonates. The phosphonates were obtained as previously reported.[2a] Yields were not optimized.

Diphenyl 1-(4-nitroanilino)-1-(2-nitrophenyl)methanephosphonate (4a): yellow needles, mp 144–145 °C (absolute EtOH), yield 52%; NMR ($CDCl_3$) δ 6.4–8.2 (m); mass spectrum, *m/e* 505 (M^+). Anal. Calcd for $C_{25}H_{20}N_3O_7P$: C, 59.41; H, 3.99; N, 8.31. Found: C, 59.62; H, 4.22; N, 8.35.

Diphenyl 1-(4-nitroanilino)-1-(2-methoxyphenyl)-methanephosphonate (4b): yellow plates, mp 168–170 °C (absolute EtOH), yield 76%; NMR ($CDCl_3$) δ 3.9 (s, 3 H), 5.9 (dd, 1 H, J = 7 Hz, J' = 24 Hz, collapses to doublet upon addition of D_2O), 6.5–8.1 (m, 19 H); mass spectrum, *m/e* 490 (M^+). Anal. Calcd for $C_{26}H_{23}N_2O_6P$: C, 63.67; H, 4.73; N, 5.71. Found: C, 63.95; H, 4.84; N, 5.77.

Diphenyl 1-(4-bromoanilino)-1-(4,5-methylenedioxy-2-nitrophenyl)methanephosphonate (5): yellow crystals, mp 167–168.5 °C (benzene/ether), yield 55%; NMR ($CDCl_3$) δ 6.0 (s, 2 H), 6.5 (d, 2 H, J = 8 Hz), 6.8–7.5 (m, 16 H). Anal. Calcd for $C_{26}H_{20}BrN_2O_7P$: C, 53.53; H, 3.46; N, 4.80. Found: C, 53.30; H, 3.48; N, 4.82.

Reaction of Phosphonates with Base and Aldehyde. To a stirred solution of 5×10^{-3} mol of phosphonate in 50 mL of anhydrous THF at −78 °C was added 1 equiv of base[9,10] dropwise (Scheme I). Thirty minutes after addition of base, 1.1 equiv of aldehyde in 25 mL of anhydrous THF was added dropwise to the deep red solution. The reaction mixture was maintained at −78 °C for an additional 2–4 h and then left to warm to room temperature, usually overnight. The THF was flash evaporated, and water was added to the residual dark oil, which was extracted three times with $CHCl_3$. The organic layers were combined and dried over $MgSO_4$. Removal of the $CHCl_3$ yielded no enamine. The tarry material contained unreacted aldehyde and/or starting phosphonate. Aldehydes used were *trans*-cinnamaldehyde and benzaldehyde.

Preparation of Dimethyl 1-(4-Nitroanilino)-1-(2-methoxyphenyl)methanephosphonate (7) via Transesterification of 4b. Method A. As above with benzaldehyde and 10% KOH in methanol, most of the benzaldehyde was recovered. After the removal of $CHCl_3$, 95% ethanol was added and the resulting precipitate was collected: yellow needles, mp 198.5–200 °C (absolute EtOH), yield 59%; NMR ($CDCl_3$) δ 3.4 (d, 3 H, J = 10 Hz), 3.8 (d, 3 H, J = 10 Hz), 4.0 (s, 3 H), 5.6 (m, 2 H, collapses to doublet upon addition of D_2O, 1 H, J = 24 Hz), 6.5–8.2 (m, 8 H); mass spectrum, *m/e* 366 (M^+). Anal. Calcd for $C_{16}H_{19}N_2O_6P$: C, 52.46; H, 5.23; N, 7.65. Found: C, 52.42; H, 5.54; N, 7.62.

Method B. To a stirred solution of 5×10^{-3} mol of diphenyl phosphonate **4b** in 50 mL of anhydrous THF and 25 mL of methanol at room temperature under a nitrogen atmosphere was added 1 equiv of 10% KOH in methanol. The reaction was followed by TLC. No dimethyl phosphonate **7** appeared before 6 h. Starting phosphonate was consumed after 24 h. The reaction was continued for 24 more h, then the solvents were removed, and the resulting yellow oily solid was passed through a short silica column eluting with chloroform: 71% yield of **7**, mp 197.5–200 °C (95% EtOH), mixed mp with actual sample showed no depression.

X-ray Analysis. A crystal of **5** of approximate dimensions (0.16 × 0.19 × 0.35 mm) was mounted on a glass fiber and examined by precession photographs (*h0l*, *hk0*, *hk1*, *h1l*). The crystal exhibited 2/*m* Laue symmetry and absences of *h0l* for $h + l$ odd and *0k0* for *k* odd consistent with the nonstandard monoclinic space group $P2_1/n$ which could be converted to $P2_1/c$ (No. 14), the standard space group.[11] Unit cell dimensions were as follows: a = 10.779 (4) Å, b = 20.694 (7) Å, c = 13.336 (3) Å, β = 109.470 (1)°, Z = 4 (one-half C_6H_6 of crystallization per formula unit), d_{measd} = 1.48 (2), d_{calcd} = 1.47 g cm^{-3}. Intensity data were measured for 5095 reflections ($2.5 < 2\theta < 47.5°$), using Mo Kα radiation (λ = 0.710 69 Å) on a Syntex P$\bar{1}$ diffractometer equipped with a graphite single-crystal monochromator. From these, 4481 unique reflections were obtained by averaging (mean discrepancy for multiply measured reflections, 0.011). Of the unique reflections, 2968 had $I > 2\sigma(I)$, where ρ, the ignorance factor used to calculate[12] $\sigma(I)$, was set equal to 0.03. Other conditions of data collection were as follows: scan range 1.4° in 2θ; scan rate 2.0–4.0° min^{-1}; four standard reflections measured after every 56 reflections; drift correction (from standards) 1.032 to 1.000. Empirical absorption corrections were applied[13] (μ = 14.84 cm^{-1}).

Structure Solution and Refinement. All nonhydrogen atoms were located by heavy atom methods and the hydrogen atoms subsequently located via difference electron density syn-

(9) Bases used were as follows: 10% KOH in methanol, dimsylsodium, *n*-butyllithium, LDA (lithium diisopropylamide), and DBN (1,5-diazabicyclo[4.3.0]non-5-ene).

(10) Reverse addition was used for dimsyl anion and LDA. Prepared by methods in Fieser and Fieser "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol 1, pp 310, 611.

(11) "International Tables for X-Ray Crystallography", 3rd ed; Kynoch Press: Birmingham, England, 1968; Vol.1. Space group $P\,2_1/n$, equivalent positions: x, y, z; $^1/_2 + x, ^1/_2 - y, ^1/_2 + z$; $-x, -y, -z$; $^1/_2 - x, ^1/_2 + y, ^1/_2 - z$.

(12) Corfield, P. W. R.; Doedens, R. J.; Ibers, J. A. *Inorg. Chem.* **1967**, *6*, 197.

(13) PSICOR: A Fortran program to calculate empirical data corrections was extensively modified by J. C. Barrick from a program by D. Tipton of the University of Southern California. Corrections are based on repetitive scans of a reflection as it stepped around the diffraction vector. Several reflections at various values of 2θ are scanned. The program is used to preprocess the data tape written by the diffractometer, producing a corrected tape in the same format as the original.

thesis. In the final cycles of weighted least-squares refinement, 361 parameters were refined including the overall scale factor, position parameters, and anisotropic thermal parameters for all nonhydrogen atoms. The hydrogen atoms were placed at ideal positions and distances[14] and given arbitrary isotropic temperature parameters[15] (B = 4.0 Å^2). Convergence was achieved with R_1 = 0.054 and R_2 = 0.33.[16] In the last cycle of refinement, the maximum shift per error was 0.246 and the average shift per error was 0.055. The highest peak on a final difference electron density map represented less than 0.39 e Å^{-3}. Neutral atom scattering factors were used for Br, P, O, N, C,[17] and H[18] and corrected for anomalous dispersion.[19]

Registry No. 4a, 79839-11-5; **4b**, 79839-12-6; (±)-**5**, 79839-13-7; **6**, 68374-69-6; **7**, 79839-14-8; *trans*-cinnamaldehyde, 14371-10-9; benzaldehyde, 100-52-7.

Supplementary Material Available: Tables B-F, nonhydrogen atomic positional parameters, hydrogen atomic positional parameters, anisotropic thermal parameters, bond lengths, and bond angles (5 pages). Ordering information is given on any current masthead page.

(14) Hydrogen atoms were placed at 0.97 Å from the atoms to which they bond with the expected geometry.
(15) Isotropic thermal parameters were of the form: $\exp(-B \sin^2\theta/\lambda^2)$.
(16) $R_1 = \sum||F| - |F_c||/\sum|F_o|$; $R_2 = [\sum w(|F_o| - |F_c|)^2/w(F_o)^2]^{1/2}$.
(17) Cromer, D. T.; Mann, J. B. *Acta Crystallogr., Sect. A* **1968**, *24*, 321.
(18) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.
(19) "International Tables for X-Ray Crystallography", 3rd ed.; Kynoch Press: Birmingham, England, 1968; Vol. 3, p 215.

Protected Lactam-Bridged Dipeptides for Use as Conformational Constraints in Peptides

Roger M. Freidinger,* Debra Schwenk Perlow, and Daniel F. Veber

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

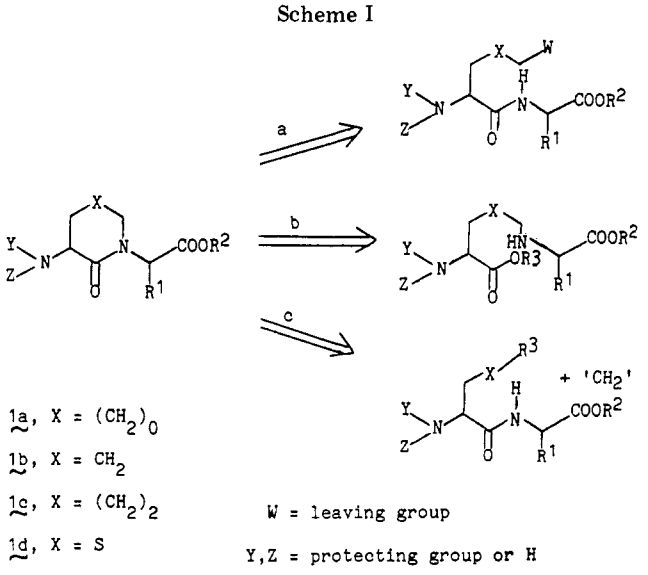
Received September 4, 1981

General methods have been devised for the synthesis of lactam-constrained dipeptide analogues having five-, six-, and seven-membered rings. Three different paths from protected chiral α-amino acids to lactams involving intramolecular alkylation, intramolecular acylation, and insertion of a one carbon unit by condensation with formaldehyde have been utilized. The first two methods produce chiral products stereospecifically, but considerable racemization occurs in the third route which leads to a 4-oxo-5-amino-1,3-thiazine (**13**). The products are prepared in good yield and have protecting groups making them suitable for incorporation into higher peptides by methods commonly used.

Lactams have been shown to be a useful new type of conformational constraint in peptides. Information may be obtained about the bioactive conformation of a peptide, and biological potency may be increased by incorporation of a lactam.[1] Not only does this restriction fix the trans peptide bond but it also introduces constraints which limit conformation by noncovalent interactions. Ring size of the lactam has been shown to have an important effect on conformation and also on biological potency of an analogue. In a comparison of rumen methane inhibiting analogues differing only in lactam ring size (five, six, or seven membered), only the six-membered ring showed high activity.[2] The lactam constraint can also be useful synthetically by allowing construction of cyclic hexapeptide analogues through cyclotrimerization.[3] We report here the synthesis of γ-, δ-, and ε-lactam-bridged dipeptides **1**, including 4-oxo-1,3-thiazines **1d** which have been used as peptide conformational constraints.

Several criteria had to be met in order for the use of compounds **1** in peptide synthesis to be practical. These structures should be obtainable in a small number of steps and in a protected form. Protecting groups should be of a type that allows incorporation of the lactams into peptides by using standard procedures. The lactams preferably should be obtained optically pure from chiral starting materials.

Scheme I



We have utilized three different synthetic routes from α-amino acids to the target lactam structures (illustrated retrosynthetically in Scheme I). These approaches involve

(1) (a) Freidinger, R. M.; Veber, D. F.; Perlow, D. S.; Brooks, J. R.; Saperstein, R. *Science* **1980**, *210*, 656. (b) Freidinger, R. M. In "Peptides: Proceedings of the 7th American Peptide Symposium"; Rich D., Ed.; Pierce Chemical Co.: Rockford, IL, in press.
(2) Freidinger, R. M.; Veber, D. F.; Hirschmann, R.; Paege, L. M. *Int. J. Pept. Protein Res.* **1980**, *16*, 464.
(3) Freidinger, R. M.; Schwenk, D. A.; Veber, D. F. In "Peptides: Proceedings of the 6th American Peptide Symposium"; Gross, E., Meienhofer, J., Eds.; Pierce Chemical Co.: Rockford, IL, 1979; p 703.

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