balances with 96% of the carbamation product, 8, along with 3% of the elimination product, 7. On the other hand, another method to prevent the α-hydrogen abstraction was the use of gaseous ammonia during the ammonolysis. The corresponding ammonolysis after addition of 4 to phosgene (in a ratio of 1:6) at -30 °C proceeded cleanly, giving not only the single product, 8 (93%), at 0 °C, but also a single product, 6 (96%), at -70 °C. To confirm the pathway for the preparation of 8 from 6, a separate experiment was carried out by addition of ammonia gas to 6 at 0 °C.[13] The sole product was found to be 8 in a quantitative yield without any other products.

In summary, the carbamation reaction mechanism (phosgenation and ammonolysis) of representative substrate, 2-(2-pyridyl)-1,3-propanediol (4), has been systematically investigated. The relatively stable cyclic intermediates involving the pyridine moiety, 5 and 6, have been synthesized and characterized. It appears that the monocarbamation (8) occurs via either the intermediate 5 or the intermediate 6. From the intermediate 5, undesired products, 6 and 7, are formed by α-hydrogen abstraction. The data indicate that not only the use of low temperatures, -30 °C for phosgenation and -70 °C for ammonolysis but also the use of gaseous ammonia at 0 °C, prevents α-hydrogen abstraction.

Experimental Section

^{1}H-FT-NMR spectra were recorded on a JEOL FX-90Q FT NMR spectrometer. All ^{1}H chemical shifts are relative to tetramethylsilane (δ 0). FT-IR spectra were recorded on a FX-6160 FT-IR spectrometer. Mass spectra were recorded on a Finnigan TSQ-70 instrument operating in the chemical ionization (isobutane) mode. All glassware were dried thoroughly in a drying oven and cooled under a stream of dry nitrogen. All experiments were carried out under a dry nitrogen atmosphere. Hypodermic syringes were used to transfer the solutions. Melting points were taken on a Thomas-Hoover melting point apparatus and were uncorrected.

All reagents were commercially available (Aldrich Chemical Co.) except for 2-(2-pyridyl)-1,3-propanediol (4) which is prepared from 2-picoline by the published procedure.[14] Tetrahydrofuran (THF) was dried with excess lithium aluminum hydride and distilled under nitrogen prior to use.

Reaction of 2-(2-Pyridyl)-1,3-propanediol (4) with Phosgene in THF in the Presence of Triethylamine (TEA). To a 50-mL round-bottom flask with a side arm was added 0.77 g (5 mmol) of 4 followed by 12.8 mL of THF and 1.74 mL (12.5 mmol) of TEA. To 0.45 mL (6.5 mmol) of phosgene in 5 mL of THF was slowly added the solution at -30 °C. After the mixture was stirred at -30 °C for 0.25 h, a reaction aliquot was monitored by TLC showing the disappearance of 4. The reaction mixture was then concentrated under water aspirator vacuum, collecting 1.82 g (103%) of the mixture of 3,4-dihydro-4-(hydroxymethyl)-1-oxo-1*H*-pyrido[1,2-*c*][1,3]oxazinium chloride (5) and TEA·HCl as a white powder under nitrogen: ^{1}H NMR (DMSO-d_6) δ 3.1 (q, 1 H, ArCH), 3.75 (d, 2 H, CH_2O), 4.75 (d, 2 H, CH_2OCO), and 7.4-8.9 (m, 4 H, ArH); FT-IR (KBr, neat) 1761 (s), 2930 (s), 3411 (br, s), 1460 (sh, s), 1160 (sh, s), 1030 cm^{-1} (sh, s); MS (isobutane-CI) m/z (relative intensity) 136 (40), 180 (100), 181 (59), and 218 (18, M + 1).

Reaction of 4 with Phosgene at -30 °C Followed by Addition of Gaseous Ammonia at -70 °C. To a 50-mL round-bottom flask with a side arm was added 0.77 g (5 mmol) of 4 followed by 12.8 mL of THF and 1.74 mL (12.5 mmol) of TEA. To 0.45 mL (6.5 mmol) of phosgene in 5 mL of THF was added dropwise this solution at -30 °C. After the mixture was stirred at -30 °C for 0.25 h, a reaction aliquot was monitored by TLC showing the disappearance of 4. Ammonolysis with gaseous ammonia was carried out at -70 °C for 0.25 h. The reaction mixture was concentrated, and then the residue was extracted three times with 50 mL of hot acetone each. The combined extracts were concentrated to 1.12 g of oily material. The crude product was purified by column chromatography using an acetone-hexane (8:1) mixture with silica gel. The final yield was 0.86 g (96%) of 4-(hydroxymethyl)-1*H*,3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one (6), an oily material: TLC (silica, acetone-hexane, 8:1) a single spot with an R_f of 0.58; ^{1}H NMR (acetone-d_6) δ 3.78 (m, 1 H, OH), 4.68 (s, 2 H, CH_2OCO), 4.73 (d, 2 H, CH_2OH), 7.29-7.9 (m, 3 H, ArH), and 8.55 (m, 1 H, ArH); FT-IR (KBr, neat) 3482 (br, s), 2978 (br, s), 1748 (sh, s), 1592 (sh, s), 1473 (sh, s), 1146 (sh, s), and 1049 cm^{-1} (sh, s); MS (isobutane-CI) m/z 179.9 (M + 1).

Reaction of 4 with Phosgene at -30 °C Followed by Addition of Liquid Ammonia at -70 °C. To a 50-mL round-bottom flask with a side arm were added 0.77 g (5 mmol) of 4, 12.8 mL of THF, and 1.74 mL (12.5 mmol) of TEA at rt under a nitrogen atmosphere. To 0.45 mL (6.5 mmol) of phosgene in 5 mL of THF in a 50-mL round-bottom flask with a side arm at -30 °C was slowly added the mixed solution by double-ended needle technique. After the mixture was stirred at -30 °C for 0.25 h, a reaction aliquot was monitored by TLC showing the disappearance of 4. At -70 °C, 6.25 mL (250 mmol) of liquid ammonia was then added dropwise using an additional funnel. The reaction mixture was stirred at 0.25 h at -70 °C and then warmed to rt. The reaction mixture was concentrated and extracted three times with 50 mL of hot acetone each. The combined extracts were concentrated to an oily material, 1.24 g (126%). The crude product was purified by a column chromatography with silica gel and acetone-hexane, 8:1. The products purified are distributed to 0.07 g (8%) of 6, 0.03 g (4%) of 2-(2-pyridyl)-3-hydroxypropene (7), and 0.76 g (77%) of 2-(2-pyridyl)-1,3-propanediol monocarbamate (8). 7: TLC (silica, acetone-hexane, 8:1) a single spot with an R_f of 0.70; ^{1}H NMR (acetone-d_6) δ 4.78 (s, 2 H, CH_2O), 5.71 (s, 1 H, =CH), 6.08 (s, 1 H, =CH), 7.32 (m, 1 H, ArH), 7.56, (m, 2 H, ArH), 8.58 (m, 1 H, ArH); MS (isobutane CI) m/z 136.1 (M + 1). 8: mp 114-115 °C; TLC (silica, acetone-hexane-ammonium hydroxide, 8:1:1) a single spot with a R_f of 0.35; ^{1}H NMR (acetone-d_6): δ 3.23 (m, 1 H, ArCH), 3.87 (d, 2 H, CH_2OH), 4.38 (d, 2 H, CH_2OCO), 5.82 (br, 2 H, NH), 7.25 (m, 2 H, ArH), 7.70 (m, 1 H, ArH), and 8.52 (d, 1 H, ArH); MS (isobutane-CI) m/z 197 (M + 1). Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.91; H, 6.17; N, 14.05.

(13) Additional potential intermediate suggested, 5-(2-pyridyl)-1,3-dioxanone is not involved in the formation of 8 by a model experiment by the reaction of 6 with triethylamine.

(14) Lipp, A.; Richard, J. *Chem. Ber.* **1904**, *37*, 737. (b) Koenigs, W.; Happe, G. *Chem. Ber.* **1902**, *35*, 1343. (c) Lipp, A.; Zirngibl, E. *Chem. Ber.* **1906**, *39*, 1045. (d) Profft, V. E.; Busse, G. *Z. Chem.* **1961**, *1*, 19.

Isolation and Characterization of a Unique Hydrated γ-Lactam[1]

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During the course of our research efforts we desired the synthesis of the γ-lactam 1. We envisaged a possible synthetic route that involved the alkylation-acylation with methyl 4-bromo-4-phenylbutyrate (2)[2] of 2,4,6-trimethoxyaniline (3), Scheme I.

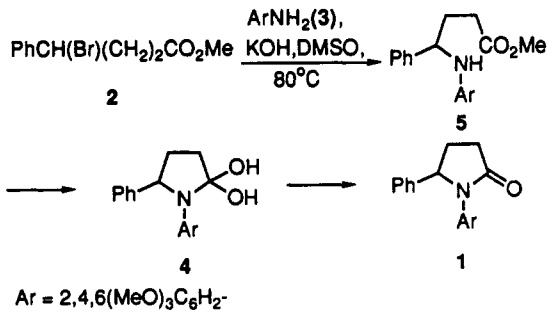
The initial product of this reaction was not the desired γ-lactam but a stable intermediate 4 which was a close structural analog of 1 as indicated by its ^{1}H-NMR spectrum. However, 4 converted *quantitatively* to the desired

(1) Presented at the 203rd National Meeting of the American Chemical Society, San Francisco, CA, April 5-10, 1992.

(2) 4-Bromo-4-phenylbutyrate was prepared by treatment of 5-phenylbutyrolactone with boron tribromide in methylene chloride followed by methanol quench. For a detailed experimental procedure, see: Olah, G. A.; Karpeles, R.; Narang, S. *Synthesis* **1982**, 963.

0022-3263/92/1957-5766$03.00/0

Scheme I



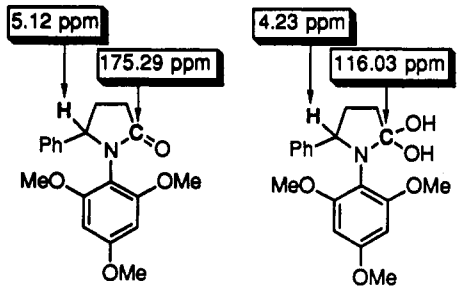


Figure 1. Diagnostic ^{1}H- and ^{13}C-NMR chemical shifts of 1 and 4.

γ-lactam 1 on standing as a solution in $CDCl_3$ over 5 days at ambient temperature or on heating overnight in a drying pistol. The identity of 1 as the γ-lactam was consistent with its IR, NMR, and mass spectra as well as elemental composition.

The ^{1}H-NMR spectrum of 4 and its transformation to 1 suggested that 4 was structurally related to 1. TLC analysis of the product indicated that 4 was a very polar compound, R_f = 0.05 in ethyl acetate–hexane (1:1), when compared to 1 which had an R_f = 0.5 in the same solvent system. The ^{13}C-NMR spectrum of 4 exhibited a signal at 116.03 ppm which was absent in the spectrum of the lactam 1. Moreover, a resonance for the lactam carbonyl moiety at 175.29 ppm was absent from the ^{13}C-NMR spectrum of 4. This observation suggested that the essential difference between 1 and 4 might be in the nature of the carbonyl moiety. Based on these observations, the structure of 4 was tentatively assigned as the hydrate shown in Scheme I. This is similar to the tetrahedral intermediate in peptide hydrolysis where the chemical shift of the tetrahedral carbon in the ^{13}C-NMR spectrum is estimated to be ≈118 ppm.[3,4] Further evidence for our proposed structure came from the IR spectrum of intermediate 4, which had a strong hydroxyl absorption at 2985 cm^{-1}, a strong C–O absorption at 1120 cm^{-1}, and a weak absorption in the carbonyl region (1735 cm^{-1}).[5] The IR spectrum of the lactam 1 indicated a strong carbonyl absorption at 1735 cm^{-1} and no hydroxyl or C–O stretching absorption. The two important ^{1}H- and ^{13}C-NMR assignments for the hydrate 4 and the lactam 1 are shown in Figure 1. The changes in the chemical shifts of these signals are those that would be expected from the proposed change in the structure. We also determined the change in the chemical shift of the orthoamide carbon in the ^{13}C-NMR spectrum due to secondary deuterium isotope

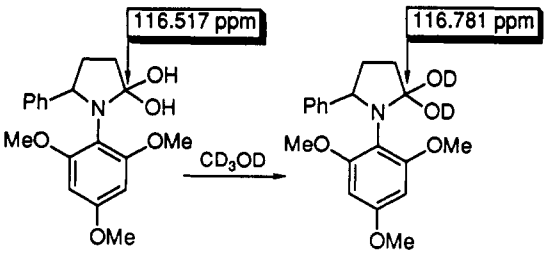


Figure 2. Change in the chemical shift of the orthoamide carbon in the ^{13}C-NMR spectrum of 4 due to the secondary deuterium isotope effect.

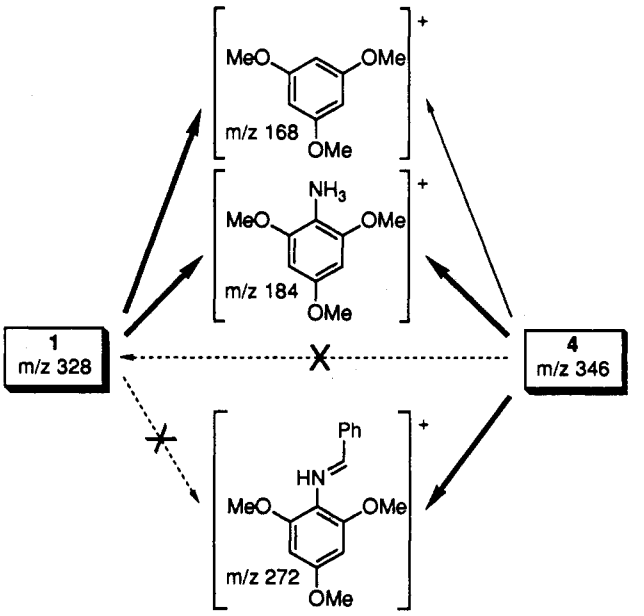


Figure 3. Mass spectral fragmentation of 1 and 4.

effect.[6] As shown in Figure 2, there is a 0.264 ppm downfield shift due to this exchange; however, in our case the observed chemical shift is in the opposite direction to that reported in literature.[7]

Analyses of the IR and NMR spectral data are consistent with the proposed structure of 4. Additional supporting data came from mass spectral studies. The collisionally activated dissociation (CAD) mass-analyzed ion kinetic energy (MIKE) spectrum using Cs^+ liquid secondary ion mass spectrometry (SIMS) of 4 [m/z 346 $(4 + H)^+$] displayed two major daughter ions at m/z 272 and 184 and a weak ion at m/z 168, Figure 3. In contrast, the CAD MIKE spectrum of 1 [m/z 328 $(1 + H)^+$] exhibited two major daughter ions at m/z 184 and 168 and no daughter ion at m/z 272. Significantly absent from the spectrum for 4 was a daughter ion at m/z 328 corresponding to loss of water. This observation supports the hypothesis that 4 is a separate stable entity which dissociates via a pathway different from the lactam 1 without producing 1 as a daughter ion.

High-resolution mass spectral (HRMS) analysis confirms the identity of the ions involved. Elemental composition of the lactam 1 was established as $C_{19}H_{22}NO_4$ $(M + H)^+$ (calcd 328.1549, obsd 328.1554), the ion at m/z 184 as $C_9H_{14}NO_3$ $(M + H)^+$ (calcd 184.0974, obsd 184.0975), and the ion at m/z 168 as $C_9H_{12}O_3$ $(M + H)^+$ (calcd 168.0786, obsd 168.0789). The elemental compositions of 4 and the

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(4) Hänni, R.; Tamm, C.; Gullo, V.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1975**, 563.

(5) The weak absorption in the carbonyl region of the IR spectrum of 4 is probably due to residual ethyl acetate and partial conversion of 4 to 1.

(6) CD_3OD (30 μL) was added to a $CDCl_3$ solution of 4. A simultaneous ^{13}C-NMR spectrum was recorded using the same stock solution of 4 with 30 μL of CD_3OH.

(7) (a) Gorin, P. A. J. *Can. J. Chem.* **1974**, *52*, 458. (b) Everett, J. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1878 and references cited therein.

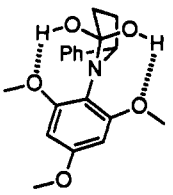

Figure 4. Stabilization of 4 by hydrogen bonding.

ion at m/z 272 were determined to be $C_{19}H_{24}NO_5$ (M + H)$^+$ (calcd 346.1654, obsd 346.1657) and $C_{16}H_{18}NO_3$ (M + H)$^+$ (calcd 272.1287, obsd 272.1299), respectively. The data from these observations clearly indicates that the intermediate is the unprecedented hydrated γ-lactam 4. Hydrate 4 represents a unique and stable hydrated amide bond, commonly postulated in enzymatic hydrolysis of peptides, which to our knowledge has not been reported as a stable isolable entity in a nonenzymatic environment.[8]

The unusual stability of this hydrate appears to be due to the presence of the 2,6-dimethoxy substitution in the *N*-aryl moiety. When 2,6-diethylaniline was substituted for 2,4,6-trimethoxyaniline, the corresponding hydrate was not isolated. This suggests that the methoxy groups are very important for the formation and the stabilization of the hydrate via intramolecular hydrogen bonding as shown in Figure 4. Also, as indicated by following the conversion of 4 to 1 by ^{1}H-NMR, 4 converts exclusively to 1. The corresponding amino acid that would result from the ring opening of the orthoamide was not detected. We were unable to convert 1 to 4 by subjecting 1 to the standard reaction conditions indicating that there is no equilibrium process involved between 1 and 4. We are not certain of the mechanism for the formation of 4, but we believe that the presence of water and/or hydroxide is important,[9] for when the cyclization of the amino ester 5 was affected in anhydrous DMF using NaH as the base, a 64% isolated yield of lactam 1 was obtained, but the presence of hydrate 4 was not detected.

In conclusion, we were able to isolate and assign the structure of the tetrahedral intermediate 4. To our knowledge 4 represents the first isolated stable hydrate reported in a nonenzymatic environment.[8]

Experimental Section

Both ^{1}H- and ^{13}C-NMR spectra were obtained in $CDCl_3$ using TMS as the internal standard. Signals are given in parts per million. All reactions were carried out under a nitrogen atmosphere. For flash column chromatography, silica gel 40-μm (Universal Scientific Inc.) and, for TLC analysis, silica gel GF 250-μm plates (Analtech Inc.) were used.

Procedure for the Alkylation–Acylation of 2,4,6-Trimethoxyaniline with Methyl 4-Bromo-4-phenylbutyrate. A mixture of potassium hydroxide (1.56 mmol) and DMSO (2.5 mL) was stirred for 10 min at ambient temperature. 2,4,6-Trimethoxyaniline (0.39 mmol) was then added, and the reaction mixture was stirred for an additional 1 h at ambient temperature. Methyl 4-bromo-4-phenylbutyrate (0.39 mmols) was then added, and the reaction mixture was heated at 80 °C for 6 h. The reaction mixture was diluted with water (10 mL) and extracted with ether (2 × 10 mL). The ether layer was washed with water (30 mL), and the combined aqueous layers were treated with saturated ammonium chloride solution (30 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed consecutively with water and brine and concentrated to give the crude hydrate 4 (57 mg, 42% yield): ^{1}H NMR ($CDCl_3$) δ 1.95–2.08 (m, 1 H), 2.24–2.40 (m, 1 H), 2.61–2.88 (m, 2 H), 3.64 (s, 6 H), 3.74 (s, 3 H), 4.25 (dd, J = 4, 10 Hz, 1 H), 6.05 (s, 2 H), 7.07–7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 31.1, 33.3, 55.3, 55.7, 62.6, 91.3, 116.0, 126.9, 127.5, 128.0, 128.3, 142.4, 152.9, 156.8; liquid SIMS m/z 346 (M + H)$^+$, 272, 184, 168; HRMS (SIMS) exact mass calcd for $C_{19}H_{24}NO_5$ (M + H)$^+$ MW 346.1654, found 346.1657.

***N*-(2,4,6-Trimethoxyphenyl)-4-phenyl-4-butanelactam.** The hydrate 4 (57 mg) was either placed in a drying pistol (refluxing 2-propanol) overnight or heated neat at 80 °C under nitrogen overnight to give *N*-(2,4,6-trimethoxyphenyl)-4-phenyl-4-butanelactam as the only product. The crude was purified by silica gel chromatography eluting with ethyl acetate yielding the γ-lactam 1 (38 mg, 70% yield): ^{1}H NMR ($CDCl_3$) δ 2.06–2.23 (m, 1 H), 2.50–2.81 (m, 3 H), 3.64 (s, 3 H), 3.70 (s, 3 H), 3.79 (s, 3 H), 5.12 (t, J = 8 Hz, 1 H), 5.98 (d, J = 2 Hz, 1 H), 6.02 (d, J = 2 Hz, 1 H), 7.14–7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 29.1, 30.6, 55.0, 55.5, 63.9, 90.8, 91.0, 107.8, 127.4, 127.6, 127.9, 141.3, 156.9, 157.5, 160.5, 175.3; liquid SIMS m/z 328 (M + H)$^+$ 184, 168; HRMS (SIMS) exact mass calcd for $C_{19}H_{22}NO_4$ (M + H)$^+$ MW 328.1549, found 328.1554.

Mass Spectrometry. The samples were analyzed by Cs^+ ion liquid secondary ion mass spectrometry (SIMS) obtained on a VG-ZAB-SE double-focusing reverse geometry mass spectrometer operating at an accelerating voltage of 8 kV, using a VG 11-250J data system. The samples were dissolved in DMSO, and glycerol/thioglycerol (1/1) was used as the matrix. The collisionally activated dissociation (CAD) spectra were obtained in the mass-analyzed ion kinetic energy (MIKE) mode. This was done by colliding the precursor ion with helium in the MIKES gas cell to reduce the intensity of the precursor ion beam by approximately 50% and scanning the electrostatic analyzer (ESA) to pass the daughter ions. The CAD MIKE spectrum for each ion was obtained by summing over 30 scans at 5 s/scan. All operations were conducted at room temperature.

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Supplementary Material Available: 300-MHz ^{1}H- and ^{13}C-NMR spectra of 1 and 4 (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) Cipiciani et al. have reported the formation of a tetrahedral intermediate in the acid hydrolysis of *N*-(trifluoroacetyl)pyrrole. Cipiciani, A.; Linda, P.; Savelli, G. *J. Chem. Soc., Chem. Commun.* **1977**, 857.

(9) In all reactions that yielded the orthoamide 4, commercial reagent-grade potassium hydroxide was used which normally contains ~ 10–15% water.

In Situ Formation of Vinylboranes for Use in Diels–Alder Reactions. An Easy One-Pot Diels–Alder Synthesis of Cyclohexenols

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Recent reports from this laboratory have detailed the high reactivity and selectivity of vinylboranes as Diels–Alder dienophiles and have described the exceptional physical organic aspects of these reactions.[1] The major limitation on the utility and synthetic appeal of vinylboranes is the difficulty associated with manipulating these highly pyrophoric materials. This is particularly true of the highly volatile vinyldimethylborane, with which standard syringe and septa techniques provide insufficient safeguards. We now report a simple methodology that

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