(C=N); mass spectrum m/z (relative intensity) no M^+, 238/40 (Me^{*+} - Et; 1), 223/5 (1), 188 (-Br; 3), 133 (31), 91 (100), 86 (6), 84 (8), 82 (6), 81 (4), 80 (6), 79 (4), 69 (17), 65 (21), 55 (6), 49 (15), 44 (81), 43 (11), 41 (21). Anal. Calcd for $C_{13}H_{18}BrN$: N, 5.22; Br, 29.79. Found: N, 5.13; Br, 29.56.

Dehydrobromination of α-Bromo Aldimine 4 ($R^1 = R^2$ = Et; R^3 = H). α-Bromo aldimine 4 was dehydrobrominated with potassium *tert*-butoxide (1.4 equiv) in dry ether under reflux for 1 h. Workup was performed as described above in the general synthesis of 2-aza-1,3-dienes 5 from α-chloro aldimines 3. *N*-Benzylidene-2-ethyl-1-butenylamine (5a) was obtained in 94% yield: bp 72-80 °C (0.1 mmHg). See spectroscopic data above.

Unique Carbamation of 2-(2-Pyridyl)-1,3-propanediol by Phosgenation Followed by Ammonolysis†

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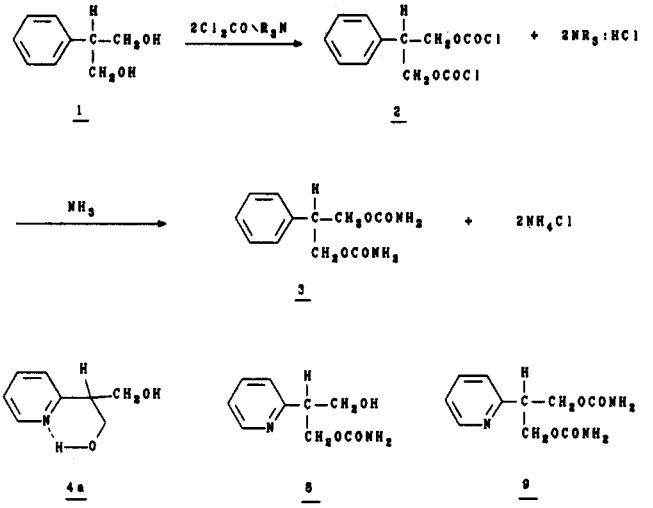
2-Phenyl-1,3-propanediol dicarbamate (3, felbamate) has been developed as a new antiepileptic drug in our laboratories.[1,2] 2-Phenyl-1,3-propanediol (1) has been used as an important intermediate in the synthesis of 3 by a two-step procedure, phosgenation followed by ammonolysis as shown in Scheme I.[3] The administration of 3 in solution to animals or human subjects has been difficult due to the poor solubility of 3 in water.[4] To synthesize not only water-soluble but also more active felbamate backups or analogs, the first series of analogs selected was 2-(2-pyridyl)-substituted dicarbamates. During synthesis of the 2-(2-pyridyl)-1,3-propanediol dicarbamate, we observed that the two-step carbamation of 2-(2-pyridyl)-1,3-propanediol (4) even with an excess of phosgene provides only formation of 2-(2-pyridyl)-1,3-propanediol monocarbamate (8), not the dicarbamate (9).

Accordingly, we undertook a detailed study of the carbamation reaction mechanism of the representative substrate, 2-(2-pyridyl)-1,3-propanediol (4), compared to that with 2-phenyl-1,3-propanediol (1) under mild, controlled reaction conditions. The results of these investigations are reported.

The phosgenation reaction mixture was 0.65 M in phosgene and 0.5 M in the functional group (FG) in substrate 4 in tetrahydrofuran (THF) unless otherwise indicated. The ammonolysis reaction mixture was 10 M in ammonia and 0.2 M in FG in substrate in THF. The addition of substrate to phosgene was carried out at both 0 and -30 °C for 0.25 h. The ammonolysis was carried out at both 0 and -70 °C for 0.25 h unless otherwise indicated. The phosgenation aliquots removed at 0.25 h were monitored by thin-layer chromatography (TLC) analysis before and after the ammonolysis for the reaction progress including disappearance of starting material.

The synthesis of 2-alkyl-1,3-propanediol dicarbamate starting with 2-alkyl-1,3-propanediol has been reported by various methods.[5-7] One simple carbamation method is to perform a two-step procedure combining the phosgenation and then the ammonolysis. For example, addition of phosgene to 1 in a 4:1 molar ratio results in the expected

Scheme I



formation of 2-phenyl-1,3-propanediyl bis(chloroformic acid ester) (2) as indicated in Scheme I.[3,8] The phosgenation reaction required room temperature (rt) for 16 h in toluene with antipyrine as a hydrogen chloride trapping agent and 1 h in THF.[3] The intermediate, 2, readily reacts with ammonia to yield 2-phenyl-1,3-propanediol dicarbamate (3).

In a similar manner, the preliminary phosgenation between 2-(2-pyridyl)-1,3-propanediol (4) and phosgene in a 4:1 molar ratio in THF with triethylamine (TEA) was performed at 0 °C but formed immediate precipitates along with disappearance of 4 as monitored by TLC analysis. This is probably due to formation of a coordinating bond of the electrophilic phosgene to the 2-pyridyl moiety in the substrate 4. With pyridine, the corresponding phosgenation with a phosgene to 4 ratio of 12:1 resulted in the expected precipitates with no starting material, 4. To the precipitates were introduced additional amounts of pyridine, making a homogenous solution. The solution was stirred at 0 °C for 18 h. Indeed, as shown in Table I, ammonolysis of this solution in pyridine with gaseous ammonia at 0 °C resulted in quantitative formation of only one product corresponding to 2-(2-pyridyl)-1,3-propanediol monocarbamate (8) without formation of the dicarbamate (9) as expected. Therefore, a systematic mechanistic study including optimal preparation of 8 was performed under various reaction conditions (solvents, temperatures, molar ratios of reactants, and trapping agents). The results are summarized in Table I.

It has been previously reported that the reactions of pyridine with acyl chloride form salt complexes of *N*-acylpyridinium.[9] These salts can be isolated although they are highly reactive, being rapidly hydrolyzed even by atmospheric moisture.[10,11] Addition of 4 with TEA, trapping

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† This paper is dedicated to Professor Herbert C. Brown on the occasion of his 80th birthday.

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Table I. Reaction of 2-(2-Pyridyl)-1,3-propanediol (4) with Phosgene in THF[a] Followed by Addition of Liquid Ammonia[b] in the Presence of Triethylamine (TEA)

phosgene, 4	phosgenation temp (°C)	TEA, 4	ammonolysis temp (°C)	isolated yield (%) 6	7	8
1.3	0	2.5	-70	5	14	65
1.3	0	2.5	0	42	10	33
1.3	-30	2.5	-70	8	4	77
1.3	-30	2.5	-70[c]	0	3	96
6	-30	2.5	-70[d]	96	0	0
6	-30	2.5	0[d]	0	6	93
12	0	2.5	-70	68	11	19
12	0	300[e]	0[d]	0	0	100
12	0	300[e]	-70	71	0	15
12	0	2.5[f]	-70	27	39	27

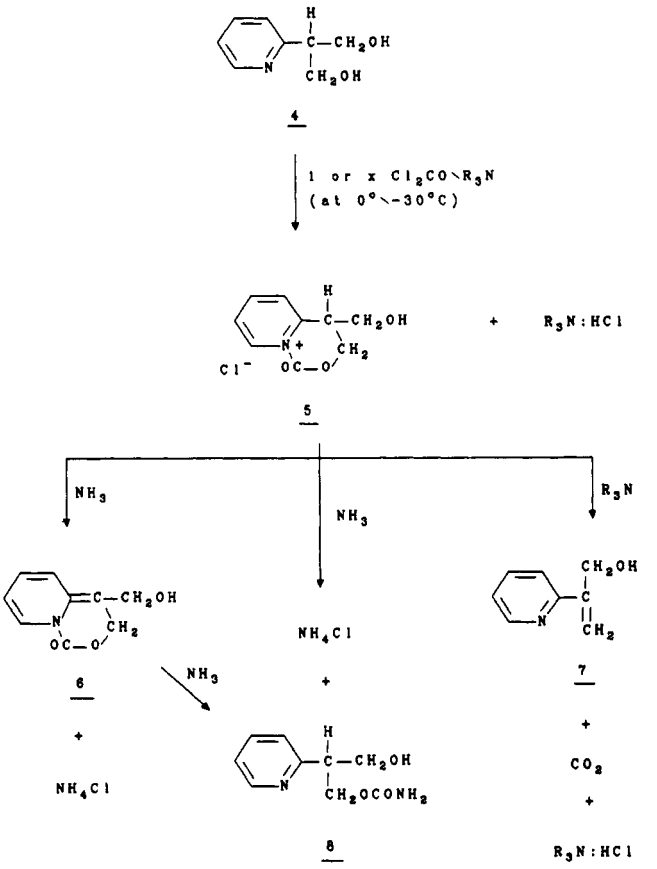
[a] 0.50 M in FG in 4, 0.65 M in phosgene, and 0.62 M in TEA, 10 M in ammonia unless otherwise indicated. [b] 0.20 M in FG in 4 and 10 M in ammonia unless otherwise indicated. [c] 25 M in ammonia used for ammonolysis. [d] Ammonia gas used for ammonolysis. [e] Pyridine used as solvent and hydrogen chloride trapping agent. [f] Acetonitrile used as solvent.

agent to phosgene, in a ratio of 1:2.5:1 at -30 °C resulted in the expected formation of an intramolecular cyclic 3,4-dihydro-4-(hydroxymethyl)-1-oxo-1*H*-pyrido[1,2-*c*]-[1,3]oxazinium chloride (**5**), as indicated in Scheme II, without the appearance of any side products. As described in the Experimental Section, the structure of **5** was confirmed by ^{1}H-FT-NMR, FT-IR, and CI-MS analysis. This compound is remarkably stable when stored in the solid state at room temperature under nitrogen atmosphere, as indicated by ^{1}H-NMR and mass spectral data.

The initial phosgenation by addition of **4** to phosgene in a 1:1.3 ratio was carried out in THF at 0 °C, providing immediate precipitates. TLC analysis of the clear aliquots qualitatively showed disappearance of starting material, **4**, along with no formation of other than salt-like products. By the addition of liquid ammonia at -70 °C the distribution of the products was found to be 51% of **4**, 4% of 4-(hydroxymethyl)-1*H*,3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one (**6**) corresponding to a deprotonated second intermediate (called a "conjugated product"), and 42% of **8**. The compound **6** was also confirmed by ^{1}H-FT-NMR, FT-IR, and CI-MS analysis. The stoichiometric 1 equiv of phosgene reacts with the pyridyl moiety or a potential internal hydrogen bonded alcohol group in **4a**[12] to generate 0.5 equiv of the expected intramolecular cyclic pyridinium ion intermediate (**5**). This intermediate leads to a potential monocarbamation process upon addition of liquid ammonia. The generated 0.5 equiv of hydrogen chloride precipitated 0.5 equiv of **4** as the hydrochloride salt.

A similar reaction mechanism is confirmed by the combined two-step reactions in the presence of the hydrogen chloride trapping agent, TEA. The corresponding phosgenation with 2.5 equiv of TEA proceeded at 0 °C, providing the intermediate **5** and 2-(2-pyridyl)-3-hydroxypropene (**7**) as an elimination product detected by TLC analysis. At -70 °C, addition of liquid ammonia to the reaction mixture resulted in 5% of **6** and 65% of **8**, along with 14% of **7** (Table I). These experiments clearly indicate that the elimination reaction giving **7** and the conjugation reaction forming **6** proceeded through the α-hydrogen abstraction in **5** by TEA and ammonia, respectively, during the course of the carbamation (Scheme II). However, when the ammonolysis was conducted at a higher temperature of 0° C, under similar conditions, the yield of **6** was remarkably enhanced to 42%. On the other hand, the effect of the solvents (THF, pyridine, and acetonitrile)

Scheme II



on the carbamation process at 0 °C for phosgenation and -70 °C for ammonolysis was examined by the use of a ratio of 12:1, phosgene to **4**. As shown in Table I, the results clearly indicate that (1) the conjugation significantly predominated over both the carbamation and the elimination except when acetonitrile was used and (2) the use of pyridine selectively prevented the formation of **7** during the entire course of the reactions.

To avoid the α-hydrogen abstraction resulting in the formation of **6** and **7** from **5**, it was then decided to carry out both the phosgenation and the ammonolysis at lower temperatures (-30 and -70 °C, respectively). Addition of **4** to phosgene in a ratio of 1:1.3 at -30 °C resulted in the pyridinium salt, **5**, only with no other products present. Subsequently, treatment of ammonia to **5** in a ratio of 50:1 at -70 °C yielded a more selective product distribution of 77% of **8**, 8% of **6**, and 4% of **7**. Indeed, after addition of more liquid ammonia to **5** at -70 °C, the ammonolysis was found to be extremely clean, giving excellent mass

(12) March, J. *Advanced Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1977; pp 225-243. Internal hydrogen bonding results in an increased acidity due to a resonance stabilization in **4a**; as with IR spectra, intramolecular hydrogen bonding (3348 cm^{-1} in **4a**) can be distinguished from intermolecular by its consistency when the concentration is varied.

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.

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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.

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