Base-Catalyzed Epimerization Behavior and Unusual Reactivity of N-Substituted Derivatives of 2,5-Dicarbalkoxypyrrolidine. Preparation of a Novel Mixed Carbamic Carbonic Anhydride by a 4-(Dimethylamino)pyridine-Catalyzed Acylation

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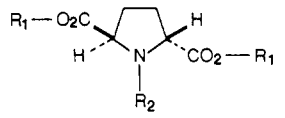
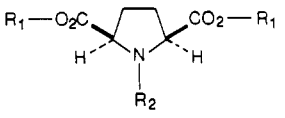
The equilibration of cis–trans isomers of 1-substituted 2,5-dicarbalkoxypyrrolidine derivatives (1 = CH_2Ph, H, CN, CO_2R) results in nearly 1:1 mixtures, contrary to a literature report for 1-benzyl-2,5-dicarbalkoxypyrrolidine. Apparent conversion to the trans isomer in ethanol solution is shown to result from more rapid hydrolysis of the cis ester function. The acylation of 2,5-dicarbethoxypyrrolidine with di-*tert*-butyl dicarbonate and DMAP results in the expected 1-Boc urethane in the case of the cis isomer; the trans isomer is shown to form an unstable, novel carbamic carbonic anhydride.

In the course of syntheses of rigid analogues of amino acids that can serve as templates for peptide and protein secondary structure, we required *N*-urethane blocked derivatives of *trans*-2,5-dicarbethoxypyrrolidine (**3a**). The preparation of these species proved unexpectedly difficult, and several unusual reactions have been discovered during the development of practical syntheses. Recent interest[1] in the 2,5-dicarbalkoxypyrrolidines as intermediates in the preparation of C_2-symmetric chiral agents prompts us to report our findings.



a R_1 = Et
1 R_2 = CH_2Ph
3 R_2 = H
5 R_2 = CO_2-t-Bu
7 R_2 = CN
9 R_2 = CO_2CO_2-t-Bu



b R_1 = Me
2 R_2 = CH_2Ph
4 R_2 = H
6 R_2 = CO_2-t-Bu
8 R_2 = CN

A natural precursor of **3a** is the *N*-benzyl analogue **1a**, which has been reported by Lowe and Ridley[2] to be readily prepared in 45% yield by epimerization (0.5 M sodium ethoxide in ethanol, 25 °C, 4 days) of the cis isomer **2a** or a cis–trans mixture which is in turn available by reaction of benzylamine with diethyl *meso*-2,5-dibromoadipate.[3] Initially, in our hands this procedure resulted only in a nearly quantitative recovery of a 1:1 mixture of the epimers 1a and 2a. More careful study revealed that this outcome is observed only if anhydrous ethanol is used as solvent and precautions are taken to exclude moisture. Use of 95% ethanol gives the outcome reported by Lowe and Ridley (recovered diester is less than 2% cis), owing evidently to the selective hydrolysis of the cis isomer **2a** under the reaction conditions.[4]

Table I. Equilibrium Ratios of Cis–Trans Isomers of 1-Substituted 2,5-Dicarbethoxypyrrolidines

isomers	1-substituent	equilibration conditions[a]	cis/trans ratio[a]
1a, 2a	CH_2Ph	NaOEt–EtOH; 5×10^{-2} M; 12 h, 23 °C	52:48
3a, 4a	H	NaOEt–EtOH; 9×10^{-2} M; 12 h, 23 °C	55:45
5a, 6a	CO_2tBu	NaOEt–EtOH; 6×10^{-2} M; 12 h, 23 °C	55:45
7a, 8a	CN	DBU–toluene;[b] 6×10^{-2} M; 2 h, 90 °C	45:55[b]

[a] Equimolar base and urethane were used. All equilibra were studied from both directions by starting with pure cis and pure trans isomers; identical final equilibrium ratios were observed in each of the four cases studied. Equilibra were determined by ^1H NMR measurements of the mixture resulting from solvent removal and extractive workup; the overall recovery of material was <90° in each case. The estimated error in the ratio is ±2%. [b] The rapid decomposition of the cyanamides under protic conditions dictated use of a nonpolar solvent and a nonnucleophilic base.

As noted in Table I, a limiting value of 52% **1a**, and 48% **2a** in ethanol at 25 °C was observed starting with either isomer, which corresponds to a $\Delta G°$ of isomerization of +0.05 kcal/mol. Similarly, small energy differences have been reported for cis–trans isomers of 1,3-dicarbethoxycyclopentanes.[5] In the pyrrolidine series, the further data of Table I show that the electron-withdrawing character and steric bulk of the 1-substituent (**3a** and **4a**, R = H; **5a** and **6a**, R = CO_2tBu; **7a** and **8a**, R = CN) have essentially no effect on this energy difference. As with the 1-benzyl derivatives **1a** and **2a**, the urethanes **5a** and **6a** hydrolyze at different rates, and the equilibration must be carried out under strictly anhydrous conditions with assays of absolute concentrations to yield interpretable data.

Since the equilibration results imply that the cis and trans isomers are nearly isoenergetic and therefore lack significant destabilizing interactions in the ground state between the carbalkoxy groups, it is surprising that they hydrolyze at different rates. Results of a preliminary rate comparison of hydrolysis of the urethanes **5b** and **6b** suggest some interesting mechanistic differences. Thus the cis isomer **6b** reacts with LiOH in water nearly two times faster than the trans isomer **5b**, a small but significant difference that must be attributed entirely to a transition-state effect and may be the result of structural differences in the solvation shell of the pertinent tetra-

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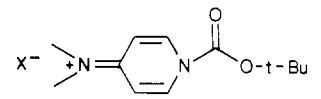
hedral intermediate. When allowed to react with an equivalent of hydroxide, **5b** generates monoester carboxylate and diacid dianion in a 5:1 ratio, roughly what is expected on inductive grounds. By contrast, the cis isomer **6b** is converted under identical conditions to a nearly 1:1 mixture of the corresponding monoester carboxylate and dianion, implying an unusually rapid rate of saponification for the cis monoester anion, probably the result of intramolecular general base catalysis of nucleophilic attack by a water molecule.[6]

Attempts to generate the urethanes **5a** and **6a** from **3a** and **4a** reveal striking reactivity differences for this cis–trans pair of secondary amines. The cis pyrrolidine **4a** reacts normally with a slight excess of di-*tert*-butyl dicarbonate in water under buffered conditions (pH 8.5) to give 80% of **6a** in 2 h. Under comparable conditions, the trans pyrrolidine **3a** generates only traces of urethane, and prolonged reaction times with repeated addition of excess Boc_2O and buffer result in only slow and partial reaction, forming the urethane **5a** in a maximum yield of 30%. With one notable exception, change to anhydrous conditions, variation of solvent, or addition of acylation catalysts failed to improve the efficiency of this acylation. Among the common dipolar aprotic solvents acetonitrile alone in our hands has permitted a slow but exceptionally clean reaction between hindered or inductively deactivated secondary amines and the relatively unstable acylating agent Boc_2O. Although only a few percent of product can be detected after 2 h at 23 °C when **3a** is combined with a 30% excess of Boc_2O in acetonitrile, after 2 days **5a** can be isolated reproducibly in 85% yield. Under comparable conditions, **4a** gives nearly a quantitative yield of **6a** (80% isolated yield, after chromatography) in 2 h.

An attempt to accelerate the reaction of **5a** by addition of a trace (ca. 0.1 equiv) of the potent acylation catalyst 4-(dimethylamino)pyridine (DMAP)[8] resulted in the formation in high yield of the novel, unstable carbamic carbonic anhydride **9a**, which to our knowledge is the second example of this structural class.[9] The structure of **9a** rests on the following observations. On heating, treatment with bases, in a mass spectrometer inlet or simply on standing at 23 °C for a few weeks, **9a** is cleanly converted to **5a**, presumably by a four-center rearrangement with loss of carbon dioxide.[10] The IR spectrum of **9a** contains distinctive carbonyl peaks at 1802 and 1740 cm^{-1}, and the ^{13}C NMR spectrum shows resonances at 146 and 148 ppm, attributable to the carbamate–carbonate structure. A sample of **9a** that is burned within hours of its chromatographic purification gives a correct elemental analysis.

The DMAP catalyst must play a highly unusual role to generate **9a**. We have examined the DMAP-catalyzed acylation of structurally related secondary amines including proline methyl ester and the cis isomer **4a** and find that normal urethanes are formed in high yield. Evidently the unusual inertness of **3a** toward acylation permits a reaction sequence to dominate that is not observed during normal DMAP-catalyzed urethane synthesis, which is expected to involve species **10**, previously characterized as a halide salt,[11] as the acylating agent.

The formation of **9a** is best rationalized as proceeding from **11**, which could be formed along with *tert*-butyl alcohol in a minor equilibrium from Boc_2O and a salt of DMAP and a weak acid. The hindered, deactivated **3a** could selectively react with the trace amount of **11** rather than with the more abundant, more hindered **10**. Attempts to generate **10** or **11** directly by combination of DMAP and Boc_2O in acetonitrile result in immediate decomposition to isobutylene and carbon dioxide. The trace of weak acid required to form **11** could be generated by reaction of Boc_2O to generate 1 equiv each of carbon dioxide, isobutylene, and the *tert*-butyl bicarbonate salt of DMAP. Alternatives that involve the *tert*-butoxide anion as a leaving group are much less attractive.



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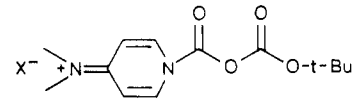

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Experimental Section

NMR spectra were obtained on Bruker WM 250-MHz or Varian XL-300 spectrometers using tetramethylsilane as the internal standard. IR spectra were obtained on an IBM IR/32 FTIR spectrometer. Mass spectra were obtained on a Varian MATT 8000 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, and by MultiChem Laboratories, Lowell, MA. Merck silica gel 60 (0.40–0.063 mm) was employed for column chromatography. TLC was performed on Merck precoated silica gel 60 plates. HPLC was performed on a Waters 501 instrument using a Waters 441 detector set at λ = 214 nm and using a C_{18} Vydac column.

Synthesis and Chromatographic Separation of 1a and 2a: *cis*- and *trans*-1-Benzyl-2,5-dicarbethoxypyrrolidines. The title compounds were separated by flash chromatography (3:2 hexane/ether) after synthesis as a mixture from diethyl 2,5-dibromoadipate following the procedure of Cignarella and Nathansohn[7] (toluene was substituted for benzene). **2a**: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.38–7.20 (5 H, m), 4.06 (4 H, q, J = 7.6 Hz), 3.96 (2 H, s), 3.50–3.36 (2 H, m), 2.14–2.02 (4 H, m), 1.20 (6 H, t, J = 7.6 Hz); TLC R_f 0.45 (1.1 ether/hexane). A similar procedure was used to prepare the methyl esters **1b** and **2b**.

Preparation of *cis*-1-Benzyl-2,5-dicarbethoxypyrrolidine (1a) from a Cis–Trans Mixture of 1a and 2a by Selective Hydrolysis of the Trans Isomer. To a solution prepared by dissolving 6.5 g (0.28 mol, 1.0 equiv) of sodium in 500 mL of absolute ethanol was added a solution of 86.3 g (0.283 mol, 1.0 equiv) of a 48:52 mixture of **1a** and **2a** in 100 mL of ethanol, followed by 3.1 mL (0.17 mol, 0.6 equiv) of water. After 3 h at 23 °C the solvent was evaporated, and the residue was dissolved in 250 mL water and extracted with 4 × 100 mL ether. The pooled organics were dried ($MgSO_4$), filtered, and evaporated to yield 34.8 g (42% based on total ester) of **1a** (>98:2 trans–cis by HPLC) as a clear oil. TLC: R_f 0.25 (1:1 ether/hexane); other physical data identical with the prior report.[2] A similar procedure was used to separate **1b** from **2b**.

***trans*-1-(*tert*-Butoxycarbonyl)-2,5-dicarbethoxypyrrolidine (5a).** A solution of 15.6 g (72.4 mmol, 1.0 equiv) of **3a**, prepared from **1a** by hydrogenolysis,[7] in 15 mL of dry MeCN was treated with 20.6 g (94.5 mmol, 1.3 equiv) of Boc_2O in 25 mL of dry MeCN. The solvent was evaporated after 2 days at 23 °C to yield an oil that crystallized on standing. Trituration with 75 mL of cold petroleum ether followed by filtration yielded 19.3 g (85%) of **5a**: mp 73–75 °C after recrystallization from hexane; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.52 (1 H, d, J = 9.2 Hz), 4.44 (1 H, d, J = 9.2 Hz), 4.20–4.14 (4 H, m), 2.40–2.22 (2 H, m), 2.04–1.94 (2 H, m), 1.41 (9 H, s), 1.34–1.24 (6 H, m); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 172.9, 172.6, 153.7, 80.7, 61.2, 61.1, 59.8, 59.6, 29.1, 28.4, 27.3, 14.4, 14.3; IR ($CHCl_3$) 1746 cm^{-1}; TLC R_f 0.57 (7:3) ether/hexane).

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Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.10; H, 7.91; N, 4.42.

In a similar manner **3b** was converted into **5b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.53 (1 H, d, J = 9 Hz), 4.43 (1 H, d), 3.73 (6 H, s), 2.40–2.20 (2 H, m), 2.04–1.92 (2 H, m), 1.41 (9 H, s).

***cis*-1-(*tert*-Butoxycarbonyl)-2,5-dicarbethoxypyrrolidine (6a).** A solution of 35.4 mg (0.165 mmol, 1.0 equiv) of **4a** and 39.7 mg (0.174 mmol, 1.05 equiv) of Boc_2O in 1.0 mL of MeCN was stirred for 2 h at 23 °C and then evaporated. The residue was dissolved in 10 mL of ether, and the solution was washed with 3 × 2 mL 0.1 M HCl and 1 × 2 mL of brine, dried ($MgSO_4$), and evaporated. The resulting oil was flash chromatographed (1:1 ether/hexane) to yield **6a** as a clear oil, 41.8 mg, 80%: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.40 (1 H, t, J = 4.3 Hz), 4.31–4.16 (5 H, m), 2.25–2.09 (4 H, m), 1.42 (9 H, s), 1.30 (3 H, t, J = 6.8 Hz), 1.27 (3 H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 172.2, 171.9, 153.8, 80.9, 61.1, 60.4, 60.2, 29.8, 29.0, 28.5, 14.5, 14.4; TLC R_f 0.51 (7:3 ether/hexane); MS, m/e 315 (M^+), 242 ($M^+ - CO_2Et$), 214 ($M^+ - CO_2tBu$); HRMS; calcd for $C_{15}H_{25}NO_6$ 315.16818, found 315.16795.

In a similar manner **4b** was converted into **6b**: ^{1}H NMR ($CDCl$, 300 MHz) δ 4.43 (1 H, br s), 4.30 (1 H, br s), 3.76 (6 H, s), 2.28–2.10 (4 H, m), 1.43 (9 H, s).

Hydrolysis Experiments with 5b and 6b. Preliminary hydrolysis kinetics were followed at 23 °C in 4:1 methanol–water containing lithium hydroxide and a trace of (benzyloxycarbonyl)glycine as an internal HPLC standard. Disappearance of starting material was followed for 60–70% of the reaction by acid quench, followed by HPLC analysis. In a typical experiment, 94.0 mg (0.33 mmol) of **5b** and 2.1 mg of Z-Gly-OH in 9.8 mL of 4:1 methanol–water was treated with 15.6 mg (0.371 mmol) of $LiOH·H_2O$. Data were taken at 30–40-min intervals, and half-times of 160 and 90 min were observed for **5b** and **6b**, respectively. Treatment of 0.18 mmol each of **5b** and **6b** in 1.2 mL of 4:1 methanol–water with 0.18 mmol of LiOH for 4 h gave after extractive workup an 11% recovery of a 77:23 mixture of 5b:6b. Products of hydrolysis were determined by HPLC, using the known retention times of the monoesters and assigning the diacid structures corresponding to **5b** and **6b** to peaks formed after prolonged reaction time.

***cis*- and *trans*-1-Cyano-2,5-dicarbethoxypyrrolidines (7a and 8a).** The same general procedure[12] was followed for both isomers. To a 1.0 M solution of 2 equiv of **3** or **4** in dry MeCN was added 1 equiv of 5 M BrCN in MeCN; after 24 h the product was isolated by evaporation, solution in CH_2Cl_2, washing with 3 × 8 mL of 0.1 M HCl and 1 × 8 mL of brine, drying, and evaporation.

For **7a**, 354 mg (1.65 mmol) of **3a** yielded a solid that was subjected to flash chromatography (3:2 ether/hexane) to yield 154 mg, 80%, of **7a**: mp 75–77 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.40 (2 H, d, J = 6.6 Hz), 4.26 (4 H, q, J = 7.2 Hz), 2.28–2.10 (4 H, m), 1.32 (6 H, t, J = 7.2 Hz); IR ($CHCl_3$) 2226, 1774 cm^{-1}; TLC R_f 0.76 (ether).

Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.91; H, 6.75; N, 11.62.

For **8a**, 326 mg (152 mmol) of **4a** yielded 152 mg, 86%, of an oil after flash chromatography (7:3 ether/hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.30–4.24 (6 H, m), 2.26–2.22 (4 H, m), 1.32 (6 H, t, J = 7.2 Hz); IR ($CHCl_3$) 2224, 1740 cm^{-1}; TLC R_f 0.62 (ether).

Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.86; H, 6.88; N, 11.83.

***trans*-1-[[(*tert*-Butoxycarbonyl)oxy]carbonyl]-2,5-dicarbethoxypyrrolidine (9a).** A mixture of 37.3 mg (0.175 mmol, 1.05 equiv) of **3a** and 0.5 mg (0.02 equiv) of DMAP was added to a stirred solution of 36.5 mg (0.167 mmol, 1.0 equiv) Boc_2O in 1 mL dry MeCN. After 30 min at 23 °C, the solvent was evaporated, and the residue was dissolved in 10 mL of ether. The solution was washed with 3 × 2 mL of pH 3.5 citrate buffer and 1 × 2 mL of brine, dried ($MgSO_4$), filtered, and evaporated to give 50.2 mg of crude product, 95%. Immediate flash chromatography (3:2 ether/hexane) yielded 33.7 mg (64%) of **9a** as a clear oil that decomposes relatively rapidly at 23 °C: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.57 (2 H, t, J = 8.2 Hz), 4.28–4.14 (4 H, m), 2.44–2.24 (2 H, m), 2.14–2.00 (2 H, m), 1.51 (9 H, s), 1.32–1.24 (6 H, m); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 171.7, 171.5, 148.5, 146.7, 85.4, 62.0, 61.9, 60.5, 60.4, 29.5, 28.5, 27.8, 14.5; IR ($CHCl_3$) 1802, 1740 cm^{-1}; TLC R_f 0.49 (7:3 ether/hexane).

Anal. Calcd for $C_{16}H_{25}NO_8$: C, 53.47; H, 6.96; N, 3.90. Found: C, 53.37; H, 6.75; N, 4.05.

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Registry No. **1a**, 50990-24-4; **1b**, 116836-61-4; **2a**, 52321-06-9; **2b**, 102508-03-2; **3a**, 50990-25-5; **3b**, 116836-62-5; **4a**, 90514-00-4; **4b**, 116836-63-6; **5a**, 116724-75-5; **5b**, 116724-76-6; **5b** (diacid), 116724-77-7; **6a**, 116724-78-8; **6b**, 116724-79-9; **6b** (diacid), 116724-80-2; **7a**, 116724-81-3; **8a**, 116724-82-4; **9a**, 116724-83-5.

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Palladium(2+)-Catalyzed Intramolecular Aminocarbonylation of 3-Hydroxy-4-pentenylamines and 4-Hydroxy-5-hexenylamines

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Palladium(2+) salt, in the presence of $CuCl_2$ as an oxidant, catalyzes an intramolecular aminocarbonylation of N-protected 3-hydroxy-4-pentenylamines under 1 atm of carbon monoxide and selectively provides *cis*-3-hydroxypyrrolidine-2-acetic acid lactones. N-Protected 4-hydroxy-5-hexenylamines undergo a similar cyclization; however, in these cases, *cis*- and *trans*-3-hydroxypiperidine-2-acetic acids are formed nonstereoselectively. As an N-protecting group, urea serves as the most reactive and versatile nitrogen nucleophile. Carbamate is more reactive than sulfonamide. The dependence of diastereoselectivity for the cyclization is discussed in terms of the kinds of N-protecting groups, solvents, and electrophiles (Pd^{2+} vs Hg^{2+}, halogens, etc.).

Development of new methodologies for the stereoselective synthesis of multifunctionalized nitrogen heterocycles is a current strong concern of organic chemists because of increasing demands for the syntheses of physio-

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