Amino Acids. 7.[1a] A Novel Synthetic Route to L-Proline

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Reaction of L-5-oxoproline esters L-2 with phosgene at 0 °C gives L-5,5-dichloro-1-(chlorocarbonyl)proline esters L-6, which readily lose hydrogen chloride to form L-5-chloro-1-(chlorocarbonyl)-4,5-dehydroproline esters L-7. Catalytic hydrogenation (Pd/C, 180 bar) of L-7 yields L-1-(chlorocarbonyl)proline esters L-15 and thence, upon hydrolysis, L-proline (L-17). A "one-pot reaction" for the whole sequence is described, starting from easily accessible L-5-oxoproline esters and yielding L-proline in 78% overall yield and 99.7% optical purity.

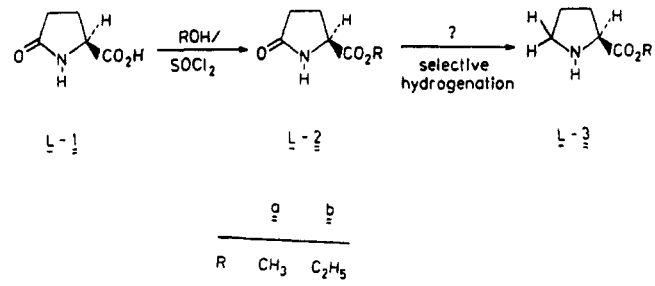
L-Proline is gaining increasing importance as the central component in pharmaceutical products and agricultural chemicals; several of its derivatives are valuable chiral auxiliary reagents. Some highly active ACE inhibitors, for instance, are derived from L-proline, e.g., Captopril[2a] and its cyclic analogue[2b] and Merck's Enalapril.[2c] Bicyclic hydantoins derived from L-proline are employed as fungicides.[3] Chiral diamines that can be prepared from either L-proline or L-hydroxyproline in high optical purity have been employed as chiral auxiliary reagents in asymmetric syntheses[4] (e.g., (*S*)-2-(anilinomethyl)pyrrolidine, (2*S*,2′*S*)-2-(hydroxymethyl)-1-[(1-methylpyrrolidin-2′-yl)-methyl]pyrrolidine, (2*S*,4*S*)-2-(anilinomethyl)-1-ethyl-4-hydroxypyrrolidine,[5] and (*S*)-1-amino-2-(methoxymethyl)pyrrolidine).[6]

Until today, L-proline is obtained almost exclusively from protein hydrolysates by ion-exchange chromatography. The broad spectrum of applications for L-proline and its derivatives, listed above, makes it doubtful whether the amounts obtained from protein hydrolysates will suffice to meet the demand for this amino acid in the near future. Many efforts are directed, toward making L-proline accessible by either straightforward chemical synthesis or fermentation processes.

In this paper, we report a high-yield preparation of optically pure L-proline, starting from easily accessible and low-priced L-glutamic acid.

Several procedures have been reported for the synthesis of racemic D,L-proline,[8a] starting from, e.g., 2-pyrrolidinone[8b] or pyrrolidine.[8c] A technically interesting variation is the preparation of D,L-proline from acrolein with HCN and ammonia.[8d] The disadvantage of all these processes lies in the necessity for a resolution of the racemate.

Scheme I



The obvious chiral precursors for a direct, enantioselective synthesis of L-proline are L-5-oxoproline (L-1) or its easily accessible esters L-2 (see Scheme I)[9] whence, by selective hydrogenation of the carboxamido function, the corresponding L-proline derivatives L-3 might be obtained directly. Many efforts have been directed therefore toward selective hydrogenation L-2 to L-3.

All attempts at selective catalytic hydrogenation of L-5-oxoproline (L-1) have failed completely, however.[10a] Reaction of L-5-oxoproline ethyl ester with sodium/ethanol gave L-proline in only 3.7% yield.[10b] Hydrogenation of L-2 with diborane[9b] or $LiAlH_4$[11] affords almost exclusively L-prolinol. From γ-methyl L-glutamate and $NaBH_4$, L-proline is obtained in 34.5% yield. High-pressure hydrogenation of 5-thioxopyrrolidine-2-carboxylic acid with Raney nickel also affords less than 20% of L-proline.[13] Reaction of the *O*-alkyl derivative, obtained from L-2 with Meerwein's salt, with excess $NaBH_4$ has been reported to yield 76% of L-3,[14a] but this result could not be reproduced

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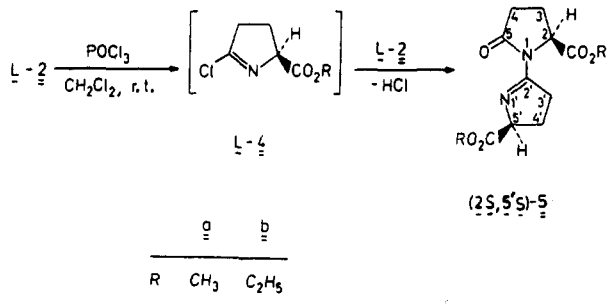
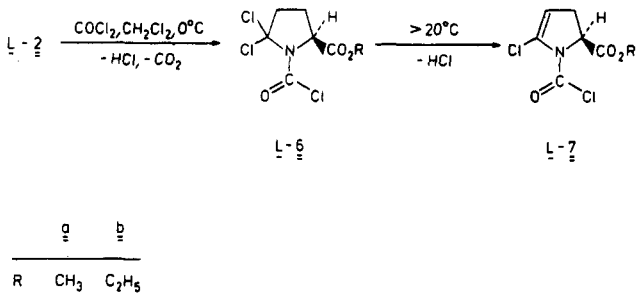
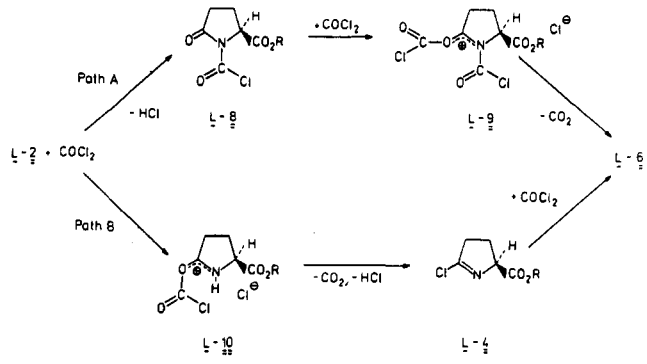
Scheme II



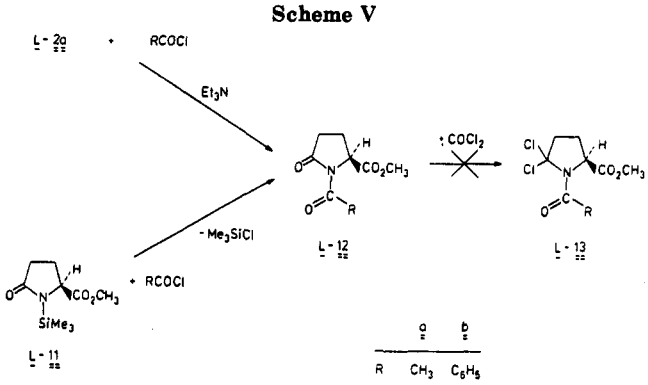
Scheme III



Scheme IV



Scheme V



by other authors.[14b] In a very recent publication, Cbz-protected methyl L-glutamate was reduced with diborane to give L-proline in 16% total yield with respect to L-glutamic acid.[14c]

A synthesis of L-proline from L-norvaline has recently been reported;[15] considering the poor accessibility of L-norvaline, this is of little practical importance. From electrochemical reductions of L-**2**, L-proline likewise is obtained only in moderate yields and with partial racemization.[16]

One may state, thus, in summing up, that all methods employed so far for selective hydrogenation of L-**2** to L-**3** have given at best only poor to moderate yields of L-proline derivatives, due to simultaneous or even preferred hydrogenation of the ester group. In view of the higher carbonyl reactivity of an alkoxycarbonyl relative to a carboxamido function, this is to be expected.

It is necessary, therefore, if the 5-oxo group in L-**2** is to be hydrogenated while still preserving the 1-carboxylate function, either to mask this function (by acetalization), or to activate the 5-oxo function, e.g., by sulfuration[13] or alkylation,[14a] as detailed above. One well-established method for selective reduction of carboxylic acid derivatives in the presence of other carbonyl functions is hydrogenation of the respective imide chlorides with any of a variety of hydrogenating agents.[17]

Chlorination of L-5-Oxoproline Esters. Imide or amide chlorides generally are prepared from the respective carboxamides with PCl_5, $POCl_3$, $SOCl_2$, $COCl_2$, or $(COCl)_2$ as halogenating agents.[18] We have treated the L-5-oxoproline esters L-**2** with $POCl_3$ in dichloromethane at room temperature and obtained the *N*-pyrrolidino-L-5-oxoproline esters (*S*)-**5** in good yield (Scheme II).

Apparently, under the reaction conditions employed, the imide chlorides L-**4**, once formed, are immediately scavenged by still present educt L-**2**. The same result has been reported for the reaction of 2-pyrrolidone with PCl_5.[19] With phosgene, on the other hand, the L-5-oxoproline esters L-**2** are indeed converted into the surprisingly stable, readily handled amide chlorides L-**6**. At slightly higher temperature, the compounds L-**6b** lose hydrogen chloride to form the α-chloro enamines L-**7b** (Scheme III). From the reaction of ϵ-caprolactam with phosgene, likewise only an elimination product, comparable to L-**7**, has been isolated.[20]

There are two possible mechansms for formation of L-**6**. (i) The NH group of L-**2** is initially attacked by phosgene to give intermediate L-**8**, the 5-oxo function of which is then halogentaed via L-**9** (path A, Scheme IV). (ii) After primary reaction of the carbonyl group, via L-**10**, L-**4** then adds phosgene to give L-**6** (path B).

Carboxamides, as ambident nucleophiles, are known to be attacked by electrophiles preferentially at the oxygen center. Path B, which represents the mechanistic analogue for the reaction of L-**2** with phosgene, receives further confirmation from the nature of the byproducts, isolated from these preparations. (*S*)-**5**, which is the main product from the reaction of L-**2** with $POCl_3$, can also be detected in small amounts in the crude product mixture from the phosgene reactions but not the substituted urea expected from reaction of L-**8** with L-**2** in the case of path A.

To further establish path B, we have investigated the reaction of *N*-acyl-5-oxoproline esters L-**12** with phosgene in the temperature range −10 to +45 °C. The acyl compounds L-**12** can be obtained by acyldesilylation of 5-

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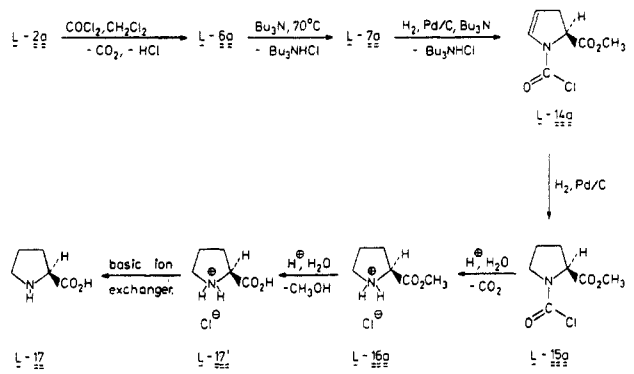
Scheme VI



oxo-1-(trimethylsilyl)proline methyl ester (L-**11**) as well as by direct acylation of L-**2** (see Scheme V). No chlorination products L-**13** were formed, however, even after an extended reaction period (9 h at 45 °C). This is clear evidence for the reaction of L-**2** with phosgene to proceed via path B (see Scheme IV). Carbonyl fluoride (COF_2), on the other hand, reacts with N-monosubstituted amides via initial N-carboxylation and subsequent fluorination of the ring carbonyl function. This mechanism which has been definitely established for the reaction of ε-caprolactam with COF_2 corresponds to path A in Scheme IV.

Catalytic Hydrogenation of α-Chloro Enamines L-7. Catalytic hydrogenation was expected to work best for the hydrodehalogenation of the chlorinated L-proline derivatives L-**6** and L-**7**, respectively, while still preserving the carboxylate function. Catalytic hydrogenation of the L-5,5-dichloro-1-(chlorocarbonyl)proline esters L-**6**, however, gave a multitude of products, with only a minor percentage of the desired L-proline derivatives. We have therefore concentrated on hydrogenation of the α-chloro enamines L-**7**. By systematic optimization of catalyst, solvent, HCl acceptor, temperature, and hydrogen pressure, excellent yields for the conversion of L-**7** into the L-1-(chlorocarbonyl)proline esters L-**15** were obtained (Scheme VI). α-Chloro enamines L-**7** are easily accessible from L-**6** either upon warming up (L-**6b**→L-**7b** >20 °C, L-**6a**→L-**7a** >100 °C) or by treatment with a tertiary amine.

Of all catalysts investigated, palladium on activated charcoal support was found to work best, with the highest yield obtained with the E 10 R type (Degussa, Pd content 10%). Platinum catalysts, on the other hand, proved completely unsuitable.

Hydrogenations were carried out in dioxane, with an tertiary amine added as HCl acceptor. If triethyl- or tripropylamine were used, the respective trialkylammonium chlorides precipitated onto the catalyst surface in the course of the reaction. The catalyst thus was rapidly deactivated, and yields consequently were only 37% and 52%, respectively. Tributylammonium chloride, on the other hand, formed with tributylamine as HCl acceptor, remains in solution, and the catalyst retains its full activity. At the end of the reaction, the catalyst is simply filtered off, washed with alcohol, and, without further treatment, reemployed without significant loss of activity. Excellent yields of L-**15** are likewise obtained from hydrogenations carried out in neat excess tributylamine.

The temperature optimum for hydrogenation lies between 50 and 80 °C. Below 50 °C, the reaction becomes too slow; above 80 °C, decomposition reactions become increasingly important. Within the optimum temperature range, 150–180 bar of H_2 pressure is required for good yields.

As a rule, 1-(chlorocarbonyl)proline esters L-**15** are obtained as final hydrogenation products from L-**7**. Hydrogenation (in dioxane with E 10 R catalyst) of isolated L-1-(chlorocarbonyl)-4,5-dihydroproline methyl ester (L-**14a**), on the other hand, gave high yields (>99%) of L-1-(chlorocarbonyl)proline methyl ester (L-**15a**) at 40 °C and 100 bar of H_2 pressure. Hydrodehalogenation (L-**7** → L-**14**) consequently must be far slower than hydrogenation (L-**14** → L-**15**).

Hydrolysis of the 1-(chlorocarbonyl)proline esters L-**15** gives the respective N-substituted carbamic acids, which spontaneously decarboxylate to form L-proline ester hydrochlorides L-**16**. With sufficiently long reaction times, these are further hydrolyzed to L-proline hydrochloride (L-**17**′), which can be converted into free L-proline (L-**17**) either via basic ion exchange or by treatment with propylene oxide (see Scheme IV). If hydrolysis of **15** is carried out in the usual manner with aqueous HCl at 25 °C, roughly 5% of the urea derivative are isolated, formed by reaction of L-**15** with L-**16**. Formation of this urea derivative which can be hydrolyzed only under drastic conditions, may be suppressed completely, though, if L-**15** is added to 15% hydrochloric acid warmed to 70 °C.

No intermediates have to be isolated in the L-proline synthesis outlined above if the individual steps are each carried out under optimized conditions. An overall yield of 75–80% of L-proline (L-**17**), relative to starting material L-**2a**, can thus be attained.

The crude L-proline, obtained from such a "one-pot reaction" after workup of the hydrolysate with ion exchangers, exhibits a specific rotation $[\alpha]^{20}_D$ of −72° to −75°. Chiral phase HPLC shows a D-proline content for this crude product between 1% and 6%. GC analysis of the starting material revealed that the L-**2a** employed contained 0.7–6% D-**2a**, depending upon the distillation conditions for the educt. Thence, one may safely conclude that all stages of this preparation of L-proline from L-5-oxoproline esters are virtually free from racemization.

The crude L-proline can easily be purified by recrystallization from water/isopropyl alcohol. The recrystallized product exhibits a specific rotation $[\alpha]^{20}_D$ of −83°. Chiral phase HPLC establishes the optical purity of the L-proline from this new synthetic route to be 99.7%.

Experimental Section

Melting points were determined in a silicon bath (Büchi SMP 20) and are uncorrected. ^1H NMR spectra were recorded on Varian A 60, T 60, EM 360, and Bruker HX 90 instruments. Chemical shifts are given in δ (ppm) relative to Me_4Si as internal standard.

The L-proline/glutamic acid ratio in the products was determined with amino acid analyzer Biotronic LC 2000. HPLC analyses were performed on a chiral column (4.6 i.d. × 250 mm, packed with L-*N*-(2-hydroxydodecyl)-4-hydroxyproline) and with 10% CH_3OH/90% 1×10^{-4} M $Cu(OCOCH_3)_2$ aqueous solution as eluent. Hydrogenations were carried out with Pd catalyst on an activated charcoal support, Pd/C E 10 R (Degussa).

L-5-Oxoproline Esters L-2. (a) First, 275.0 g (165.0 mL, 2.3 mol) of thionyl chloride and then 2.0 mL of dimethylformamide and L-5-oxoproline (L-**1**) were slowly added at −10 to −15 °C under stirring to 505 mL of methanol (400.0 g, 12.5 mol). The mixture was stirred 26 h at room temperature, the solvent removed in vacuo (bath 40 °C), and the residue distilled (10^{-2} torr) to yield 151.1 g (91%) of **L-5-oxoproline methyl ester (L-2a)**: bp 130–135 °C (10^{-2} torr) [lit.[22] (bp 107–113 °C (0.06–0.12 torr)]; $[\alpha]^{20}_D$ −6.947° (*c* 1, CH_2Cl_2) [lit.[23] $[\alpha]_D$ −5.6° (*c* 2.8, H_2O)].

(b) **L-5-Oxoproline ethyl ester (L-2b)** was prepared in analogy to the procedure in ref 9a,b to give a product with mp 44–48 °C (lit.[9b] mp 50 °C) and $[\alpha]^{20}_D$ −7.97° (*c* 1, ethyl acetate).

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Table I

amine (mol %)	catalyst Pd/C E 10 R, wt % rel to L-7a	H_2, bar	time, h	temp, °C	yield, %[a] L-17	yield, %[a] glutamic acid
tributyl (120)	58	180	30	50	76.3	<0.2
tributyl (120)	58[b]	150	30	50	75.8	1.2
tributyl (120)	58[c]	150	30	50	74.9	1.4
triethyl (120)	50	100	30	60	36.8	6.1
tripropyl (120)	50	150	30	50	52.3	1.2
tributyl (excess, neat)	50	150	30	50	81.3	1.3

[a] After hydrolysis and workup as described above. [b] Catalyst recovered and reemployed for the second time. [c] Catalyst recovered and reemployed for the fourth time.

(2*S*,5′*S*)-1-[(Alkoxycarbonyl)-1′-pyrrolin-2′-yl]-5-oxoproline Esters (*S*)-5. Phosphorus oxychloride (5.25 g, 34.5 mmol) was added at 0 °C to a solution of 35 mmol of L-2 (5.0 g of L-2a and 5.5 g of L-2b, respectively) in 20 mL of dichloromethane. The mixture was stirred for 16 h at 25 °C, washed with aqueous solution of potassium carbonate, and dried over $MgSO_4$ and the solvent distilled off. The oily residue was chromatographed on a silica gel column with ethyl acetate as eluent to give 3.0 g (64%) of **(2*S*,5′*S*)-1-[(methoxycarbonyl)-1′-pyrrolin-2′-yl]-5-oxoproline methyl ester [(*S*)-5a]** and 3.5 g (67%) of **(2*S*,5′*S*)-1-[(ethoxycarbonyl)-1′-pyrrolin-2′-yl]-5-oxoproline ethyl ester [(*S*)-5b]**, respectively.

(*S*)-**5a**: ^1H NMR ($CDCl_3$) δ 5.1–4.8 and 4.8–4.4 (2 m, 1 H, 2-H and 5′-H, respectively), 3.80 and 3.76 (2 s, 3 H, OCH_3), 3.26 (t, 2 H, 3-H), 2.8–1.9 (m, 6 H, 4-H, 3′-H, 4′-H). Anal. Calcd for $C_{12}H_{16}N_2O_5$ (M_r 268.3): C, 53.73; H, 6.01; N, 10.44. Found: C, 52.06; H, 5.76; N, 10.62.

(*S*)-**5b**: ^1H NMR ($CDCl_3$) δ 5.1–4.8 and 4.7–4.4 (2 m, H, 2-H and 5′-H, respectively), 4.23 and 4.20 (2 q, 2 H, J = 7 Hz, OCH_2CH_3), 3.20 (t, 2 H, 4-H), 2.7–1.9 (m, 6 H, 3-H, 3′-H, 4′-H), 1.3 (t, 6 H, J = 7 Hz, 2 OCH_2CH_3). Anal. Calcd for $C_{14}H_{20}N_2O_5$ (M_r 296.3): C, 56.75; H, 6.80; N, 9.45. Found: C, 56.40; H, 7.03; N, 9.20.

L-5,5-Dichloro-1-(chlorocarbonyl)proline Methyl Ester (L-6a) and Ethyl Ester (L-6b). (a) Phosgene (103.8 g, 74 mL, 1.05 mol) was condensed into a cooled dropping funnel and added at once to a solution of 50.0 g (0.35 mol) of L-2a, also cooled to −10 °C. The mixture was stirred for 1 h at −10 °C and warmed to room temperature overnight. After evaporation in vacuo, 90.4 g (98.2%) crude crystalline L-6a was isolated. After recrystallization from diisopropyl ether colorless needles of L-6a, mp 76–78 °C, $[\alpha]^{20}_D$ −49.74° (*c* 3.384, CH_2Cl_2) were obtained: ^1H NMR ($CDCl_3$) δ 4.97–4.73 (m, 1 H, 2-H), 3.90 (s, 3 H, CH_3), 3.0 (mc, 2 H, 3-H), 2.30 (mc, 2 H, 4-H). Anal. Calcd for $C_7H_8Cl_3NO_3$ (M_r 260.5): C, 32.27; H, 3.10; Cl, 40.83; N, 5.38. Found: C, 32.48; H, 3.17; Cl, 40.56; N, 5.55.

(b) A solution of 31.4 mg (0.2 mol) of L-2b in 300 mL of dichloromethane and phosgene (43 mL, 0.6 mol) were treated as described above (a). The oily crude product was purified by extraction in portions one after another with *n*-pentane by stirring for 30 min at 25 °C. The combined extracts were evaporated to yield 54.9 g of L-6b: colorless oil; $[\alpha]^{20}_D$ −48.26° (*c* 7.364, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 4.95–4.75 (m, 1 H, 2-H), 4.30 (q, 2 H, J = 7 Hz, CH_2CH_3), 3.08 (mc, 2 H, 3-H), 2.38 (mc, 2 H, 4-H), 1.30 (t, 3 H, J = 7 Hz, CH_2CH_3). Anal. Calcd for $C_8H_{10}Cl_3NO_3$ (M_r 274.5): C, 35.00; H, 3.67; Cl, 38.74; N, 5.10. Found: C, 35.24; H, 3.60; Cl, 38.72; N, 5.07.

L-(Methoxycarbonyl)- and L-(Ethoxycarbonyl)-2-chloro-1-(chlorocarbonyl)-2-pyrroline (L-7a and L-7b, Respectively). (a) L-6a (71.6 g, 0.275 mol) was distilled (0.05 torr) to give 35.7 g (58%) of L-7a: bp 120–124 °C; $[\alpha]^{20}_D$ −112° (*c* 2, ethyl acetate); ^1H NMR δ 5.43 (t, 1 H, J = 3 Hz, 3-H), 5.10 (2 d, 1 H, J = 4 Hz, 5-H), 3.90 (s, 3 H, CH_3), 3.47–2.33 (m, 2 H, 4-H). Anal. Calcd for $C_7H_7Cl_2NO_3$ (M_r 224.0): C, 37.53; H, 3.15; Cl, 31.65; N, 6.25. Found: C, 37.75; H, 3.01; Cl, 31.78; N, 6.34.

(b) L-6a (65.1 g, 0.26 mol) and tributylamine (51.0 g, 0.275 mol) in 300 mL of dioxane were stirred under nitrogen for 4 h at 70 °C. The reaction mixture was then evaporated in vacuo to dryness to yield 58.2 g (100%) of L-7a.

(c) L-6b (14.0 g, 51.0 mmol) was distilled (0.01 torr) to give 7.7 g (64%) L-7b: bp 110–118 °C; $[\alpha]^{20}_D$ −132.9° (*c* 2.83, ethyl acetate); ^1H NMR ($CDCl_3$) δ 5.40 (t, 1 H, J = 3 Hz, 3-H), 5.05 (2 d, 1 H, J = 4 Hz, 5-H), 4.31 (q, 2 H, J = 7 Hz, CH_2CH_3), 3.43–2.30 (m, 2 H, CH_2), 1.35 (t, 3 H, J = 7 Hz, CH_2CH_3). Anal. Calcd for $C_8H_9Cl_2NO_3$ (M_r 238.1): C, 40.36; H, 3.81; Cl, 29.78; N, 5.88. Found: C, 40.56; H, 3.89; Cl, 29.50; N, 5.91.

L-1-Acetyl- and L-1-Benzoyl-5-oxoproline Methyl Ester (L-12a and L-12b, Respectively). (a) Triethylamine (50.60 g, 0.50 mol) was added dropwise (4.5 h) to a stirred solution of L-2a (70.60 g, 0.49 mol) and acetyl chloride (48.0 g, 0.61 mol) in 800 mL of toluene at room temperature. The mixture was kept overnight at room temperature, the precipitate filtered off, and the filtrate concentrated. The oily residue was fractionated (10^{-3} torr) to yield 72.0 g (79%) of L-12a: bp 90 °C; ^1H NMR ($CDCl_3$) δ 2.00–2.90 (m, 4 H, $(CH_2)_2$), 2.53 (s, 3 H, $COCH_3$), 3.80 (s, 3 H, OCH_3), 4.70–4.90 (m, 1 H, 2-H). Anal. Calcd for $C_8H_{11}NO_4$ (M_r 185.2): C, 51.89; H, 5.99; N, 7.56. Found: C, 51.80; H, 5.99; N, 7.64.

(b) Triethylamine (51.61 g, 0.51 mol) was added dropwise (1 h) to the stirred solution of L-2a (71.57 g, 0.5 mol) and benzoyl chloride (71.69 g, 0.51 mol) in 500 mL of toluene at 80 °C. The mixture was kept 1 h at 80 °C, the precipitated solid triturated with 200 mL of ether, and the cooled mixture filtered by suction. The crystals were washed twice with hot water and twice with ether. The mother liquor was worked up likewise. The total yield was 110.4 g (89%) of L-12b: mp 154 °C; $[\alpha]^{20}_D$ +30.67° (*c* 0.68, CH_2Cl_2). Anal. Calcd for $C_{13}H_{13}NO_4$ (M_r 247.3): C, 63.15; H, 5.29; N, 5.66. Found: C, 63.00; H, 5.58; N, 5.68.

L-5-Oxo-1-(trimethylsilyl)proline Methyl Ester (L-11). In analogy to a related procedure[24] triethylamine (40.4 g, 0.40 mol) was added to a stirred mixture of L-2a (57.3 g, 0.40 mol) and chlorotrimethylsilane (43.3 g, 0.40 mol) in dichloromethane (500 mL)/ligroin (600 mL) at room temperature. The mixture was stirred for 14 h at 70 °C, the orange-brown solution evaporated in vacuo, and the residue fractionated (10^{-3} torr) to yield 57.2 g (66%) of L-11: bp 75–79 °C; $[\alpha]^{20}_D$ −51.3415° (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 4.38–4.2 (m, 1 H, 2-H), 3.8 (s, 3 H, OCH_3), 2.57–2.2 (m, 4 H, 3-H, 4-H), 0.3 (s, 9 H, 3 Si $(CH_3)_3$). Anal. Calcd for $C_9H_{17}NO_3Si$ (M_r 215.2): C, 50.20; H, 7.96; N, 6.51. Found: C, 50.27; H, 7.97; N, 6.74.

(c) In analogy to ref 24, the stirred mixture of L-11 (50.0 g, 0.23 mol) and benzoyl chloride (32.64 g, 23.2 mmol) was slowly heated to 60 °C, in a distillation apparatus. At the onset of the reaction, the mixture abruptly turned turbid, and chlorotrimethylsilane rapidly distilled off. The colorless, extremely hard, crystalline residue was powdered and dried in vacuo (50 °C, 1 h) to give 57.31 g (99%) of L-12b, mp 149–150 °C, $[\alpha]^{20}_D$ +26.81° (*c* 0.83, CH_2Cl_2).

L-1-(Chlorocarbonyl)-4,5-dihydroproline Methyl Ester (L-14a). Into a solution of L-2a (65.0 g, 0.454 mol) in 650 mL of dichloromethane, phosgene was passed for 3 h at 15–25 °C. After removal of solvent and excess phosgene, the crystalline residue was dissolved in 450 mL of ethyl acetate and the solution hydrogenated in an agitator autoclave with 9 g of Pd/C E 10 R (10 wt. % relative to L-2a) and 200 bar of H_2 pressure for 72 h at 60 °C and then with 100 bar of H_2 pressure for 24 h at 60 °C. The catalyst was filtered off, HCl stripped off in a nitrogen stream, the solvent distilled off, and the residue distilled in vacuo (10^{-3} torr) to yield 19.5 g (23%) of L-14a, yellow oil: bp 95–99 °C; ^1H NMR ($CDCl_3$) δ 6.75 and 5.35 (2 mc, 1 H, 2-H and 3-H, respectively), 5.1–4.70 (m, 1 H, 5-H), 3.85 (s, 3 H, CH_3), 3.50–2.0 (m, 2 H, 4-H). Anal. Calcd for $C_7H_8ClNO_2$ (M_r 189.6): C, 44.34; H, 4.25; Cl, 18.70; N, 7.39. Found: C, 44.16; H, 4.42; Cl, 18.46; N, 7.67.

(24) Kricheldorf, H. R. *Chem. Ber.* **1970**, *103*, 3353.

L-1-(Chlorocarbonyl)proline Methyl Ester (L-15a) and Ethyl Ester (L-15b). (a) L-**14a** (1.0 g, 5.3 mmol) in 20 mL of dioxane was hydrogenated with 1.0 g of Pd/C E 10 R (10 wt.% relative to L-**14a**) and 100 bar of H_2 pressure for 30 h at 40 °C as described above. LGC analysis of the reaction mixture gave ≥99% L-**15a**/≤1% L-**14a**.

(b) A solution of L-proline methyl ester hydrochloride (828.1 g, 5.0 mol) in 2 L of chloroform was saturated with gaseous NH_3 at 0 °C, the precipitated ammonium chloride filtered off, and the filtrate concentrated in vacuo. The crude L-**2a** residue was added (45 min) to a stirred solution of 1 L of phosgene in 2 L of chloroform at 0 °C. The mixture was stirred for 12 h at 25 °C, chloroform and excess phosgene were removed, and the residue was fractionated in vacuo (0.01 torr) to yield 896.1 g (93%) of L-**15a**; bp 90–95 °C; $[\alpha]^{20}_D$ −50.3° (*c* 2.262, ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 4.53 (mc, 1 H, 2-H), 3.97–3.53 (m, 2 H, 5-H), 3.83 (s, 3 H, CH_3), 2.19 (mc, 4 H, 3-H and 4-H). Anal. Calcd for $C_7H_{10}ClNO_3$ (M_r 191.6): C, 43.88; H, 5.26; Cl, 18.50; N, 7.31. Found: C, 44.16; H, 5.46; Cl, 17.93; N, 7.38.

(c) A solution of L-proline ethyl ester hydrochloride (179.6 g, 1.0 mol) in 500 mL of chloroform was saturated with gaseous NH_3 at 0 °C and worked up as described above. The crude L-**2b** was added (45 min) to the stirred solution of 200 mL of phosgene in 500 mL of chloroform at 0 °C. Stirring was continued for 12 h at 5 °C, for 5 h at 25 °C, and for 12 h at 40 °C. Workup as in b yielded (10^{-3} torr) 196.4 g (95%) of L-**15b**: bp 90 °C; $[\alpha]^{20}_D$ −54.03° (*c* 2.362, ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 4.47 (mc, 1 H, 2-H), 4.27, 4.23 (q, 2 H, J = 7 Hz, CH_2CH_3), 3.75 (mc, 2 H, 5-H), 2.13 (mc, 4 H, 3-H and 4-H), 1.33 (t, 3 H, J = 7 Hz, CH_3). Anal. Calcd for $C_8H_{12}ClNO_3$ (M_r 205.6): C, 46.73; H, 5.88; Cl, 17.24; N, 6.81. Found: C, 46.80; H, 6.03; Cl, 17.20; N, 7.21.

Hydrolysis of L-15. Aqueous HCl (200 mL, 10%) was vigorously stirred at 73 °C and 0.10 mol of L-**15** (19.2 g of L-**15a** and 20.6 g of L-**15b**, respectively) added within 45 min. Stirring was continued at 73 °C until CO_2 evolution subsided and then for 5 h at 25 °C. Excess HCl was evaporated in vacuo and the residue dehydrohalogenated with a weak basic ion exchanger (MP 62). Evaporation of the eluate yielded L-proline (L-**17**). From L-**15a**: 11.2 g (97%); mp 222–229 °C dec; $[\alpha]^{20}_D$ −83.6° (*c* 1, H_2O). From L-**15b**: 11.3 g (98%); mp 224–230 °C dec; $[\alpha]^{20}_D$ −83.7° (*c* 1, H_2O) (lit.[15] mp 224–226 °C, $[\alpha]^{20}_D$ −84 ±2° (*c* 0.1, H_2O).

L-Proline (L-17). (a) L-**6a**, prepared from L-**2a** (0.25 mol) and phosgene as described above, was dehydrogenated as in b. The L-**7a** thus obtained was dehydrogenated and hydrogenated catalytically in 300 mL of dioxane (Table I). The catalyst and triethyl-, tripropyl- or tributylammonium chloride, respectively, were filtered off, the filtrate was concentrated under reduced pressure. The resulting L-**15a** was hydrolyzed in 500 mL of 10% aqueous HCl as described above. The percentage of L-**17** and of glutamic acid in the reaction product was determined with an amino analyzer.

(b) Liquid phosgene (52.0 g, 0.525 mol) was added to the stirred solution of 35.8 g (0.25 mol) of L-**2a** in 250 mL of dichloromethane at −10 °C. Stirring was continued at 25 °C for 3 h, phosgene evaporated, and the residue stirred with 350 mL of tributylamine (under nitrogen, 70 °C, 4 h). The solution was hydrogenated for 30 h at 50 °C in a hastelloy autoclav with 32.6 g of Pd/C E 10 R catalyst/180 bar of H_2 pressure. The catalyst was filtered off, excess tributylamine evaporated in vacuo, and the solution added dropwise at 75 °C to 400 mL of vigorously stirred 10% aqueous HCl. Stirring was continued for 5 h at 25 °C, until CO_2 evolution had subsided, excess HCl removed in vacuo, and the remaining solution neutralized with aqueous NaOH. Tributylamine was separated and the filtrate acidified with 10% aqueous HCl, treated with activated charcoal, and concentrated. The residue was worked up by column chromatography (basic ion exchanger MP62). The eluate was concentrated and the residue recrystallized from H_2O/isopropyl alcohol to yield 22.6 g (78%) of L-**17**: mp 227–229 °C; $[\alpha]^{20}_D$ 83° (*c* 1, H_2O), optical purity 99.7% (HPLC).

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Registry No. L-**1**, 98-79-3; L-**2a**, 4931-66-2; L-**2b**, 7149-65-7; (*S*)-**5a**, 103322-10-7; (*S*)-**5b**, 103322-11-8; L-**6a**, 86050-91-1; L-**6b**, 86042-46-8; L-**7a**, 86042-45-7; L-**7b**, 86042-47-9; L-**11**, 96105-69-0; L-**12a**, 75857-93-1; L-**12b**, 103322-12-9; L-**14a**, 103322-13-0; L-**15a**, 85665-59-4; L-**15b**, 86050-92-2; L-**17**, 147-85-3; AcCl, 75-36-5; BaCl, 98-88-4; Me_3SiCl, 75-77-4; L-proline methyl ester hydrochloride, 2133-40-6; L-proline ethyl ester hydrochloride, 33305-75-8.

Kinetics and Mechanism of Aminolysis of Carbamates

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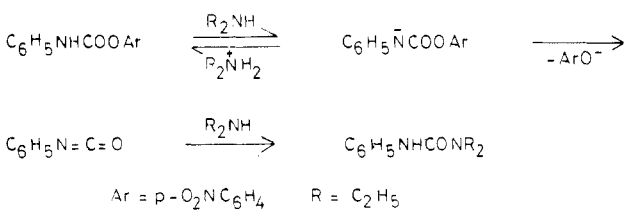
The kinetics of the *n*-butylaminolysis of three series of mono- and disubstituted phenyl *N*-phenylcarbamates **1–3** have been studied spectrophotometrically under pseudo-first-order conditions in dioxane. The relation $k_{obsd} = k_2[n\text{-BuNH}_2] + k_3[n\text{-BuNH}_2]^2$ was found applicable for all esters. The rate constants k_2 and k_3 were correlated by the Hammett equation, and the corresponding activation parameters were determined. The reaction was found to be much more sensitive to a substituent on the leaving group (OAr) than to a substitutent on the amine portion (NHAr) of the esters. Results from crossover experiments revealed the absence of isocyanate intermediate. The mechanism of the aminolysis of carbamates is discussed in terms of these facts.

A fairly large amount of information exists about the kinetics and mechanism of hydrolysis of aryl carbamates.[1-4] However, not too much is known about the aminolysis of such esters. At present, there are two conflicting reports concerning the mechanism of aminolysis of carbamates. Menger and Glass[5] proposed an E1cB mechanism (Scheme I) for the reaction of *p*-nitrophenyl *N*-phenylcarbamate

Scheme I



with diethylamine in toluene, while Stohandl and Vecera[6] assigned a $B_{Ac}2$ path (Scheme II) for the aminolysis of

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