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# A Novel Synthesis of δ-Amino Acid Derivatives

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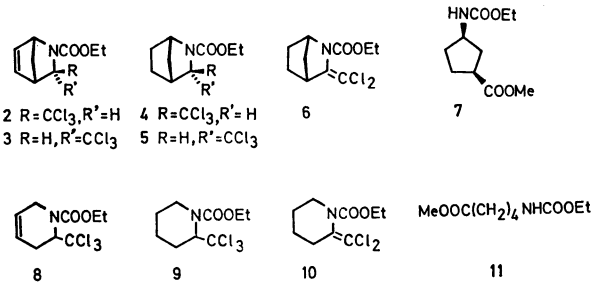
**Synopsis.** The Diels-Alder adducts of "anhydrochloral-urethane" with some 1,3-dienes were successfully utilized for the synthesis of some δ-amino acid derivatives by the sequence of the reactions, *viz.*, hydrogenation, dehydrochlorination, and ozonolysis.

Polar cycloaddition reactions are ingeniously utilized for the introduction of a substituent at the specific position.[1] We describe here a method of synthesis of δ-amino acid derivatives making use of the Diels-Alder adducts between "anhydrochloral-urethane" *N*-(2,2,2-trichloroethylidene)carbamates (**1**) and 1,3-dienes reported by us previously.[2]

The *exo*- and *endo*-adducts (**2** and **3**) of **1** with cyclopentadiene[2] were hydrogenated over Pd–C to afford in about 90% yields ethyl *exo*- and *endo*-3-trichloromethyl-2-azabicyclo[2.2.1]heptane-2-carboxylates (**4** and **5**), respectively. Upon treatment of **4** and **5** with sodium methoxide in refluxing benzene, ethyl 3-dichloromethylene-2-azabicyclo[2.2.1]heptane-2-carboxylate (**6**) in 60—75% yields. When **6** was oxidized with ozone in methanol, followed by treatment with dimethyl sulfide, methyl *cis*-3-ethoxycarbonylamino-1-cyclopentanecarboxylate (**7**) was obtained in 76% yield. The *cis*-configuration of **7** is evident from the consideration of the reaction course. This product (**7**) is a potential intermediate for the synthesis of an antibiotics "amidinomycin."[3]

In a similar manner, 1-ethoxycarbonyl-2-trichloromethyl-1,2,3,6-tetrahydropyridine (**8**) obtained from **1** and butadiene was converted into methyl 5-(ethoxycarbonylamino)pentanoate (**11**) by the sequence of the reactions, *viz.*, hydrogenation, dehydrochlorination, and ozonolysis.

Consequently, the present procedure has merged into a powerful synthetic route to δ-amino acid derivatives.




## Experimental

*Ethyl* exo-*3-Trichloromethyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (4).* A solution of 1.956 g of **2**[2] in 50 ml of ethanol was hydrogenated over 500 mg of Pd–C until 154 ml (1.0 equiv.) of hydrogen-uptake (5 min). Removal of the catalyst and the solvent, followed by distillation, gave 1.793 g (91%) of **6**: bp 132.5—135 °C/3 Torr; IR (neat): 1725 $cm^{-1}$; MS: *m/e* 242 (small), 240 (small), 168 (100), 140 (38), 68 (31%); NMR ($CCl_4$): δ 4.31 (m, $H_1$), 4.16 (s, $H_3$), 2.98 (m, $H_4$), 1.62 (4H, m, $2\times H_5$ and $2\times H_6$), 2.68 (bd, 10 Hz, syn-$H_7$), 1.23 (bd, 10 Hz, anti-$H_7$), 4.18 (q, 7 Hz, $COO\underline{H}_2CH_3$), 1.31 (t, 7 Hz, $COOCH_2\underline{H}_3$). Found: C, 42.14; H, 4.93; N, 4.71%. Calcd for $C_{10}H_{14}NO_2Cl_3$: C, 41.91; H, 4.92; N, 4.89%.

*Ethyl* endo-*3-Trichloromethyl-2-azabicyclo[2.2.1]heptane-2-carboxylate (5).* A solution of 1.0 g of **3**[2] in 30 ml of ethanol was hydrogenated over 500 mg of 5% Pd–C until 1.14 equiv. of hydrogen-uptake. Removal of the catalyst and the solvent, followed by recrystallization from ether–petroleum ether 894 mg (89%) of **5**, mp 63.5—65.0 °C; IR ($CCl_4$): 1722 $cm^{-1}$; MS: *m/e* 242 (small), 240 (small), 168 (100), 140 (34), 96 (21), 68 (36), 67 (28%); NMR ($CCl_4$): δ 4.61 (m, $H_1$), 4.67 (d, 4.0 Hz, $H_3$), 3.09 (m, $H_4$), 1.2—2.3 (6H, m, $2\times H_5$, $2\times H_6$, and $2\times H_7$), 4.12 (q, 7.3 Hz, $COOH_2$–), 1.27 (t, 7.3 Hz, $COOCH_2$-$C\underline{H}_3$). Found: C, 42.08; H, 4.92; N, 4.66%. Calcd for $C_{10}H_{14}NO_2Cl_3$: C, 41.91; H, 4.92; N, 4.89%.

*Ethyl 3-Dichloromethylene-2-azabicyclo[2.2.1]heptane-2-carboxylate (6).* *From 4*: To a solution of 1.356 g of **4** in 50 ml of benzene, was added 505 mg (2 equiv.) of methanol-free sodium methoxide, and heated under reflux for 40 h. The reaction mixture was washed twice with water, dried ($Na_2SO_4$), and distilled to give 888 mg (75%) of **6**, bp 128—130 °C/3 Torr; IR (neat): 1740 (broad), 1646 $cm^{-1}$; MS: *m/e* 249 ($M^+$, 43), 251 (M+2, 27), 254 (M+4, 5), 214 (87), 177 (24), 151 (33), 150 (68), 149 (51), 148 (100), 144 (27), 142 (53), 114 (37), 67 (34%); NMR ($CCl_4$): δ 4.52 (m, $H_1$), 3.47 (m, $H_4$), 1.74 (6H, m, $2\times H_5$, $2\times H_6$, and $2\times H_7$), 4.18 (q, 7 Hz, $COOC\underline{H}_2CH_3$), 1.34 (t, $COOCH_2C\underline{H}_3$). Found: C, 47.86; H, 5.12; N, 5.32%. Calcd for $C_{10}H_{13}NO_2Cl_3$: C, 48.02; H, 5.24; N, 5.60%. *From 5*: To a solution of 582 mg of **5** in 20 ml of benzene, was added 220 mg (2 equiv.) of sodium methoxide, and heated under reflux for 9 h. The reaction mixture was worked up as described above, giving 324 mg (64%) of **6**.

*Methyl* cis-*3-Ethoxycarbonylamino-1-cyclopentanecarboxylate (7).* A slow stream of ozonized oxygen was bubbled into a solution of 888 mg of **6** in 40 ml of dichloromethane and 10 ml of methanol cooled to −50 °C until the blue color persisted. The solution was flushed with oxygen for 10 min, removed from the cooling bath, and added with 2 ml of dimethyl sulfide. The mixture was allowed to warm to room temp for 4 h. After evaporation of the solvent, distillation gave 715 mg (76%) of **7**, bp 137—141 °C/3 Torr; MS: *m/e* 215 ($M^+$, 16), 156 (20), 142 (100), 138 (25), 129 (55), 128 (30), 84 (20), 83 (21), 67 (52), 57 (23), 56 (55), 55 (23%); NMR ($CDCl_3$): δ 1.5—2.5 (8H, m), 1.26 (3H, t), 3.73 (3H, s), 4.15 (2H, q); IR (neat): 3325, 1730 (broad) $cm^{-1}$. Found: C, 55.58; H, 7.86; N, 6.41%. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51%.

*2-Trichloromethyl-1-(ethoxycarbonyl)piperidine (9).* A solution of 6.156 g of **8** in 50 ml of ethanol was hydrogenated over 3.0 g of 5% Pd–C until 538 ml (1.07 equiv.) of hydrogen-uptake. After removal of the catalyst and the solvent, distillation gave 5.578 g (90.4%) of **10**, bp 121—122 °C/4 Torr; $n_D^{25.6}$ 1.5020; IR (neat): 1720, 1735 (shoulder) $cm^{-1}$; MS: *m/e* 163 (100), 154 (33), 128 (30), 84 (50%). Found: C, 39.37; H, 5.15; N, 4.95%. Calcd for $C_9H_{14}NO_2Cl_3$: C, 39.37; H, 5.14; N, 5.10%.

*2-Dichloromethylene-1-(ethoxycarbonyl)piperidine (**10**).* To 1.026 g of **9** in 30 ml of benzene, was added 400 mg (2 equiv.) of sodium methoxide, and refluxed for 23 h. The reaction mixture was poured into water, and extracted with dichloromethane. The organic layer was washed with water, dried ($Na_2SO_4$), and distilled to give 672 mg (75%) of **10**, which solidified on standing; mp 54.0—54.7 °C; IR (Nujol): 1740 (broad), 1635 $cm^{-1}$; NMR ($CCl_4$): $\delta$ 2.82 (2H, m, $-N-CH_2-$), 1.2—2.5 (6H, complex m, $3\times CH_2$), 4.12 (bq, $COOCH_2CH_3$), 1.28 (t, $COOCH_2CH_3$); MS: *m/e* 237 ($M^+$, small), 239 (M+2, small), 204 (23), 202 (75), 176 (31), 174 (100%). Found: C, 45.53; H, 5.54; N, 5.61%. Calcd for $C_9H_{13}NO_2Cl_2$: C, 45.39; H, 5.52; N, 5.88%.

*Methyl 5-(Ethoxycarbonylamino)pentanoate (**11**).* A slow stream of ozonized oxygen was bubbled into a solution of 1.427 g of **10** in 30 ml of methanol at room temp for 2 h. After the solution was flushed with oxygen for 20 min, 3 ml of dimethyl sulfide was added to the reaction mixture, and allowed to stand overnight. After evaporation of the solvent, fractional distillation gave 889 mg of crude **11**, bp 125—128 °C/3 Torr. Pure sample of **11** was obtained by preparative GLC; MS: *m/e* 203 ($M^+$, 14), 172 (20), 171 (22), 130 (22), 126 (27), 115 (47), 102 (100), 100 (67), 98 (54), 82 (22), 74 (37), 70 (22), 59 (37), 58 (26), 56 (61), 55 (60), 44 (23), 43 (45), 42 (30), 41 (36). Found: C, 53.35; H, 8.56; N, 6.60%. Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89%.

## References

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4) Mass spectra were obtained with an ionization potential of 70 eV.