

***N*-Benzyl- α -ethoxycarbonylnitrone (1).** To an ice-cooled mixture of 5.3 g of *N*-benzylhydroxylamine and 1.5 g of calcium chloride in 40 ml of ether,⁴⁾ 4.5 g of ethyl glyoxylate was added dropwise, after which the whole was stirred at 0 °C for 1 h. The solids were removed by filtration through an anhydrous sodium sulfate layer, and the filtrate was evaporated to give crystalline **1** (7.8 g, 88%). Two recrystallizations from benzene afforded an analytical sample of **1**: mp 84.0–86.5 °C; ν (KBr): 1720, 1560, 1200 br, 1045, 965, 825, and 700 cm⁻¹; δ (CDCl₃): 7.4 (m, 5H), 7.17 (**1b**)

and 7.09 (**1a**) (s, 1H), 5.69 (**1b**) and 4.96 (**1a**) (s, 2H), 4.25 (**1b**) and 4.22 (**1a**) (q, 2H, $J=7$ Hz), and 1.30 (**1b**) and 1.27 (**1a**) (t, 3H, $J=7$ Hz). Found: C, 63.93; H, 6.31; N, 6.82%. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76%. The ratio of **Z**(**1a**) and **E**(**1b**) was calculated as 1:2 from the peak areas of the benzylic methylene signals. The ratio changed between 1:2 and 1:3.5 according to the difference in preparation and/or recrystallization, but attempts at the separation of each isomer were unsuccessful, and so the mixture of a known ratio was used in the subsequent reactions.

2-Benzyl-5,5-dimethyl-3-ethoxycarbonylisoxazolidine (2). A mixture of 535 mg of **1** (**Z**:**E**=1:2), 3.1 g of isobutylene, and 12 ml of benzene in a sealed tube was heated at 80 °C for 3 d. The subsequent evaporation of the solvent gave **2** (630 mg). An analytical sample was obtained by Kugelrohr distillation (bath temp: 144–145 °C/2 mmHg). ν (CHCl₃): 1730, 1600, 1375, and 1365 cm⁻¹; δ (CDCl₃): 7.3 (m, 5H), 4.07 (s, 2H), 4.07 (q, 2H, $J=7$ Hz), 3.52 (dd, 1H, $J=7.5$ and 9.5 Hz, C part of ABC), 2.3 (m, 2H, AB part of ABC), 1.38 (s, 3H), 1.30 (s, 3H), and 1.21 (t, 3H, $J=7$ Hz). Found: C, 68.39; H, 7.97; N, 5.40%. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.03; N, 5.31%.

γ -Hydroxyleucine Lactone Hydrochloride (3). A mixture of 188 mg of **2**, 90 mg of Pd(OH)₂,⁶ and 40 ml of methanol was shaken under a hydrogen atmosphere (3 atm) for 3 d. After the removal of catalysts by filtration, the filtrate was concentrated to give an oily solid (118 mg); ν (CHCl₃): 1760 cm⁻¹. A part of the oily solid was dissolved in ethanol, and 1.1 eq of hydrochloric acid was added. The whole was left in a desiccator *in vacuo* to give **3**: mp 206–207 °C (from ethanol); the IR spectrum (KBr disk: 3500–2400 br, 1765, 1575, and 1490 cm⁻¹) of **3** was coincident with that of the authentic γ -hydroxyleucine lactone hydrochloride (mp 208–209 °C).⁵

trans-2-Benzyl-3-ethoxycarbonyl-5-methoxycarbonylisoxazolidine (4) and cis-2-Benzyl-3-ethoxycarbonyl-5-methoxycarbonylisoxazolidine (5). A solution of 200 mg of the nitron **1** (**Z**:**E**=1:2) and 175 mg of methyl acrylate in 3 ml of benzene was stirred at room temperature for 36 h. The subsequent evaporation of the solvent gave an oil (285 mg), which showed three spots on TLC (Merk silica gel 60, 0.25 mm; hexane–ethyl acetate = 3:1). The oil was chromatographed on silica gel (30 g) with benzene–ethyl acetate (100:2) to give an unidentified compound ($R_f=0.30$, 6 mg), 158 mg of **4** ($R_f=0.22$), 55 mg of a mixture of **4** and **5** (2:1), and 27 mg of **5** ($R_f=0.17$). Analytical samples were prepared by a flash chromatography¹⁰ (hexane–ethyl acetate=3:1), followed by Kugelrohr distillation.

4: Bath temp 131–134 °C/0.08 mmHg; ν (CCl₄): 1755 sh, 1735, and 1190 cm⁻¹; δ (CDCl₃, 100 MHz): Δ values show the pseudocontact shifts upon the addition of 0.8 eq of Eu(fod)₃: 7.3 (m, 5H), 4.68 (dd, 1H, $J=6$ and 8 Hz, Δ 0.18), 4.16 (AB center, 2H, $J=13$ Hz, Δ 0.52), 4.14 (q, 2H, $J=7$ Hz, Δ 0.02), 3.78 (dd, 1H, $J=6$ and 8 Hz, Δ 0.66), 3.76 (s, 3H, Δ 0.06), 2.92 (ddd, 1H, $J=8$, 6 and 14 Hz, Δ 0.38), 2.68 (ddd, 1H, $J=6$, 8, and 14 Hz, Δ 0.48), and 1.24 (t, 3H, $J=7$ Hz, Δ 0.00). Found: C, 61.29; H, 6.47; N, 4.92%. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.52; N, 4.77%.

5: Bath temp 140–145 °C/0.1 mmHg; ν (CCl₄): 1769 sh, 1730, and 1190 cm⁻¹; δ (CDCl₃, 100 MHz): 7.4 (m, 5H), 4.65 (dd, 1H, $J=5.5$ and 8.5 Hz), 4.15 (q, 2H, $J=7$ Hz), 4.15 (s, 2H), 3.77 (s, 3H), 3.61 (dd, 1H, $J=6$ and 8 Hz), 2.6–3.1 (m, 2H), and 1.24 (t, 3H, $J=7$ Hz). Found: C, 61.55; H, 6.50; N, 5.08%. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.52; N, 4.77%.

*Amino Acid Analysis.*⁷⁾

A solution of 364 mg of **4** in

50 ml of methanol was hydrogenolyzed over 100 mg of Pd(OH)₂ under a hydrogen atmosphere (3 atm) for 2 d. After the catalysts had then been removed, the filtrate was concentrated to give an oil. The oil was refluxed for 4 h with 20 ml of 6 M hydrochloric acid. After decolorizing with activated carbon, the solution was concentrated to give crystals (234 mg). The amino acid chromatogram of the crystals showed the presence²⁾ of *threo*- γ -hydroxyglutamic acid (0.270 mmol), *erythro*- γ -hydroxyglutamic acid (0.023 mmol), and *threo*- γ -hydroxyglutamic acid lactone (0.113 mmol).

2-Benzyl-r-3-ethoxycarbonyl-c-4-methoxycarbonyl-t-5-methylisoxazolidine (6) and 2-Benzyl-r-3-ethoxycarbonyl-t-4-methoxycarbonyl-c-5-methylisoxazolidine (7). A mixture of 205 mg of the nitron **1** (**Z**:**E**=1:3.5), 198 mg of methyl crotonate, and 5 ml of benzene was stirred at room temperature for 3 d. The subsequent removal of the solvent gave an oil containing some crystals. VPC analysis (5% OV-1, 1.7 m, 180 °C) showed that two components of $R_t=6$ min and $R_t=7$ min were present in the product. They were separated by column chromatography on silica gel (33 g). Elution with benzene–ethyl acetate (98:2) afforded 47 mg of **7** ($R_t=6$ min) and 206 mg of **6** ($R_t=7$ min).

6: Mp 41.5–42.5 °C (from pentane); ν (CHCl₃): 1735 cm⁻¹; δ (CDCl₃, 100 MHz): 7.3 (m, 5H), 4.40 (dq, 1H, $J=8$ and 6 Hz), 4.14 (q, 2H, $J=6$ Hz), 4.10 (AB center, 2H, $J=14$ Hz), 3.78 (d, 1H, $J=8$ Hz), 3.66 (s, 3H), 3.12 (t, 1H, $J=8$ Hz), 1.36 (d, 3H, $J=6$ Hz), and 1.22 (t, 3H, $J=6$ Hz). Found: C, 62.43; H, 6.72; N, 4.50%. Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.88; N, 4.55%.

7: Liquid, bath temp 105–109 °C/0.09 mmHg; ν (CHCl₃): 1735 cm⁻¹; δ (CDCl₃, 100 MHz): 7.4 (m, 5H), 4.56 (quint, 1H, $J=6$ Hz), 4.18 (q, 2H, $J=7$ Hz), 4.14 (s, 2H), 4.13 (d, 1H, $J=8$ Hz), 3.79 (s, 3H), 3.52 (dd, 1H, $J=6$ and 8 Hz), 1.44 (d, 3H, $J=6$ Hz), and 1.24 (t, 3H, $J=7$ Hz). Found: C, 62.92; H, 6.94; N, 4.56%. Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.88; N, 4.55%.

We are deeply indebted to Dr. Minoru Tamura, The University of Tsukuba, for his measurements of the amino acid chromatograms.

References

- 1) H. Sato, T. Kusumi, K. Imae, and H. Kakisawa, *Bull. Chem. Soc. Jpn.*, **49**, 2815 (1976).
- 2) T. Kusumi, H. Kakisawa, S. Suzuki, K. Harada, and C. Kashima, *Bull. Chem. Soc. Jpn.*, **51**, 1261 (1978).
- 3) For a recent review, see D. St. C. Black, R. F. Crozier, and V. C. Davis, *Synthesis*, **1975**, 205, and the references cited therein.
- 4) G. E. Utzinger and F. A. Regenass, *Helv. Chim. Acta*, **37**, 1892 (1954).
- 5) J. Fillman and N. Albertson, *J. Am. Chem. Soc.*, **70**, 171 (1948).
- 6) R. G. Hiskey and R. C. Northrop, *J. Am. Chem. Soc.*, **83**, 4798 (1961).
- 7) The amino acid chromatograms were taken on a Yanagimoto amino acid analyzer LC-5S. For the conditions, see Ref. 2.
- 8) a) B. G. Murray and A. F. Turner, *J. Chem. Soc., C*, **1966**, 1338; b) R. Huisgen, H. Hauk, R. Grashey, and H. Seidl, *Chem. Ber.*, **101**, 2568 (1968).
- 9) R. Huisgen, *J. Org. Chem.*, **41**, 403 (1976).
- 10) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).