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The Preparation of *N*-Benzyl-α-ethoxycarbonylnitrone and Its Reactions with Some Olefins

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Synopsis. *N*-Benzyl-α-ethoxycarbonylnitrone (**1**) was prepared from ethyl glyoxylate and *N*-benzylhydroxylamine. The reactions of **1** with isobutylene, methyl acrylate, and methyl crotonate are described.

In the course of our synthetic studies of the hydroxy amino acid moiety *via* 1,3-dipolar cycloaddition,[1,2] *N*-benzyl-α-alkoxycarbonylnitrone (*e.g.*, **1**) was expected to be a suitable 1,3-dipole, especially for the preparation of the γ-hydroxy α-amino acid.

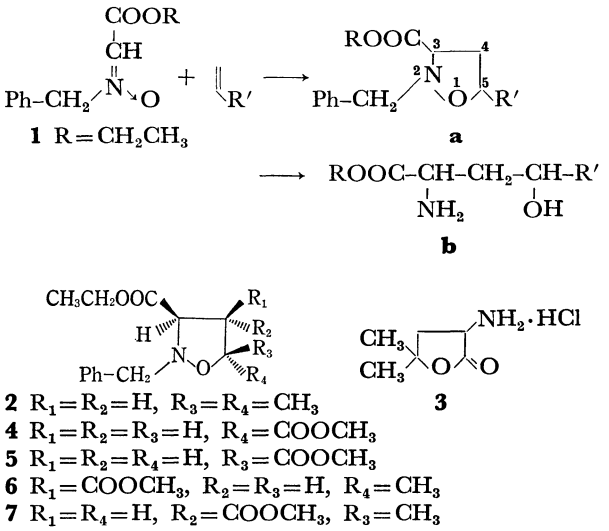
The removal of the benzyl group and the fission of the N–O bond in the adduct, **a**, would be attained simultaneously under such conditions of catalytic hydrogenolysis, and the stereochemistry of the product, **b**, would directly reflect the regio- and stereospecificities in the 1,3-dipolar cycloaddition of the nitrone.[3]

A hitherto unknown nitrone, **1**, was prepared by the condensation of ethyl glyoxylate and *N*-benzylhydroxylamine in the presence of calcium chloride.[4] **1** crystallized easily, but it was found to be a mixture of *Z*(**1a**) and *E*(**1b**) isomers (*Z*: *E*=1: 2), as is shown in its NMR spectrum. The two singlets at 5.69 and 4.96 are assignable to the methylene protons at the benzylic position in **1b** and **1a** respectively. The difference in chemical shift can be explained by the effect of the neighboring ester group. The ratio depends slightly on the reaction and/or recrystallization conditions.

When the nitrone **1**(*Z*: *E*=1: 2) and isobutylene in benzene were heated at 80 °C for 3 d, only a single adduct was isolated by distillation. The structure of the adduct was characterized as 2-benzyl-5,5-dimethyl-3-ethoxycarbonylisoxazolidine (**2**) from its spectroscopic properties and its conversion to the known[5] γ-hydroxyleucine lactone hydrochloride (**3**) by hydrogenolysis over $Pd(OH)_2$.[6]

The reaction of the nitrone **1** (*Z*: *E*=1: 2) with methyl acrylate proceeded at room temperature, and two adducts, **4** and **5** (**4**: **5**=4: 1), were isolated in 84% yield. Two pairs of doublets, at 4.68 and 3.78, in the NMR spectrum of **4**, and similar pairs at 4.65 and 3.61 in **5**, reveal the substitution pattern on the isoxazolidine ring in both **4** and **5** to be a 2,3,5-trisubstituted one. The stereochemistry of **4**, assumed to be *trans* from the pseudocontact shift with $Eu(fod)_3$ (see Experimental), was confirmed by subjecting **4** to catalytic hydrogenolysis over $Pd(OH)_2$, followed by hydrolysis with 6 M (1 M=1 mol dm^{-3}) hydrochloric acid. In the amino acid chromatogram[7] of the products, almost all (>94%) of the γ-hydroxyglutamic acids and their lactones were recognized as having the *threo*-configuration.

Among the various dipolarophiles reported, the cycloadducts from the crotonic ester have been shown to have a "reverse" regioselectivity.[8] This was observed also in the present case. The mixture of **1** (*Z*: *E*=1: 3.5) and methyl crotonate was allowed to stand at room temperature to give **6** and **7** (4.4: 1) in 83% yield. The arrangement of substituents and the stereochemistry of **6** and **7** were assumed from the analyses of the NMR spectra. Of the three protons on the isoxazolidine ring, H^5 is the most downfield in both **6** (δ at 4.40) and **7** (δ at 4.56) and is assignable to the partial structure –O–C**H**^{5}(CH_3)–CH– on the basis of the chemical shifts and multiplicities. The differences in the chemical shifts of H^3 (Δ 0.35) and H^4 (Δ 0.40) of **7** as compared with those of **6** are attributable to a deshielding effect of the neighboring ester group, which is *cis* to the protons in question in the case of **7**. The two ester groups, thus, can be arranged *cis* to each other in **6** and *trans* in **7**. The *trans* relationship between C_4 and C_5 was assumed from the reaction mechanism.[9]



2 $R_1=R_2=H$, $R_3=R_4=CH_3$ **3**
4 $R_1=R_2=R_3=H$, $R_4=COOCH_3$
5 $R_1=R_2=R_4=H$, $R_3=COOCH_3$
6 $R_1=COOCH_3$, $R_2=R_3=H$, $R_4=CH_3$
7 $R_1=R_4=H$, $R_2=COOCH_3$, $R_3=CH_3$

Experimental

All the melting points are uncorrected. The IR spectra were recorded on a Hitachi 215 grating spectrophotometer, and the NMR spectra were obtained on a Hitachi H-60 and a JEOL MH-100 spectrophotometers, using TMS as an internal standard.

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 ($CDCl_3$): 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($CHCl_3$): 1730, 1600, 1375, and 1365 cm^{-1}; δ ($CDCl_3$): 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($CHCl_3$): 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 nitrone **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 chromatography[10] (hexane–ethyl acetate=3:1), followed by Kugelrohr distillation.

4: Bath temp 131—134 °C/0.08 mmHg; ν (CCl_4): 1755 sh, 1735, and 1190 cm^{-1}; δ ($CDCl_3$, 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 (CCl_4): 1769 sh, 1730, and 1190 cm^{-1}; δ ($CDCl_3$, 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 presence[2] 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 nitrone **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 ($CHCl_3$): 1735 cm^{-1}; δ ($CDCl_2$, 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($CHCl_3$): 1735 cm^{-1}; δ ($CDCl_3$, 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%.

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