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Synthetic and Mechanistic Aspects of 4-Substituted-3,5-bis(methoxycarbonyl)isoxazoline N-Oxides and the Corresponding 3,5-Bis-(butylcarbamoyl)isoxazoles derived therefrom¹⁾

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An improved method for the synthesis of 4-substituted-3,5-bis(methoxycarbonyl)-isoxazoline N-oxides (**3**) was developed by one-step cyclization of aldehydes with methyl nitroacetate in N,N-dimethylacetamide. The reaction mechanism was found to involve intramolecular nitrite ion displacement by the nitronate anion (**9**); this was confirmed by the formation of 3,5-bis(methoxycarbonyl)-4-phenylisoxazoline N-oxide-4-*d* (**11**), starting from benzaldehyde-1-*d* and methyl nitroacetate. Conversion of isoxazoline N-oxides (**3**) to the corresponding 3,5-bis(butylcarbamoyl)isoxazoles (**7**) is also discussed.

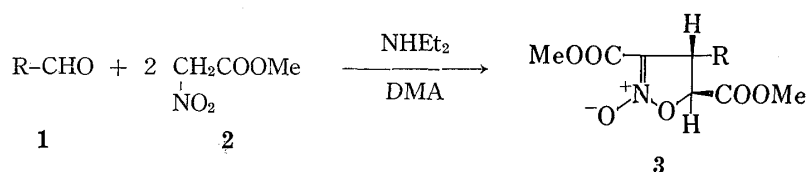
Keywords—methyl nitroacetate; isoxazoline N-oxide; isoxazole; dipolar aprotic solvent; condensation; transformation; nitrite ion displacement mechanism

In a previous communication³⁾ we have described the synthesis of 4-substituted-3,5-bis(methoxycarbonyl)isoxazoline N-oxides (**3**) by means of O-alkylation of methyl nitroacetate (**2**) with *n*-alkyl iodides in N,N-dimethylacetamide (DMA). The yields of **3** are relatively low (30—40%) inasmuch as the reaction is accompanied by the formation of α -nitro ester resulting from the C-alkylation of **2** with alkyl iodide. However, such a method might be suitable for the synthesis of 4-alkyl analogs of **3**, since they cannot be obtained by Dornow's method⁴⁾ for the synthesis of 4-aryl isoxazoline-3,5-dicarboxylate N-oxides. In an effort to improve the yield of **3** and to clarify the reaction mechanism, we describe here an alternative route to **3**, with subsequent conversion into the corresponding 3,5-bis(butylcarbamoyl)isoxazoles (**7**).

Synthesis of 4-Substituted-3,5-bis(methoxycarbonyl)isoxazoline N-Oxides

The technique adopted was a modification of the previous procedure³⁾ in which a dipolar aprotic solvent (DMA) played an important role in the synthesis of **3**. We attempted a direct condensation of aldehyde (**1**) rather than alkyl iodide with nitroacetate (**2**) in such a solvent. Several aliphatic aldehydes (**1a—1h**) and benzaldehyde were condensed with a 2-fold molar excess of **2** in DMA in the presence of one equivalent of diethylamine at room temperature, affording 4-substituted-3,5-bis(methoxycarbonyl)isoxazoline N-oxides (**3a—3i**) in good yields without any by-product except in the case of **3i**.⁵⁾ The results are shown in Chart 1 and Table I. It was necessary to use a dipolar aprotic solvent such as DMA, since the use of other non-polar or protic solvents resulted in little or no formation of **3** except in the case of **3i**.⁵⁾ An organic base such as diethylamine is preferred and room temperature is usually adequate. Compounds **3** gave satisfactory spectral data and elemental analysis, as shown in Tables I and V. The relative configuration of substituents at C-4 and C-5 in

- 1) The Synthetic Reactions of Aliphatic Nitro Compounds. Part XVI; Part XV of this series: E. Kaji, H. Ichikawa, and S. Zen, *Bull. Chem. Soc. Jpn.*, **52**, 2928 (1979).
- 2) Location: 5-9-1, Shirokane, Minato-ku, Tokyo 108, Japan.
- 3) S. Zen and E. Kaji, *Chem. Pharm. Bull.*, **22**, 477 (1974).
- 4) A. Dornow and G. Wiehler, *Ann. Chem.*, **578**, 113 (1952); A. Dornow and A. Frese, *Ann. Chem.*, **581**, 122 and 211 (1953).
- 5) S. Zen and M. Koyama, *Bull. Chem. Soc. Jpn.*, **44**, 2882 (1971).



a: R=methyl, b: R=ethyl, c: R=propyl, d: R=isopropyl, e: R=butyl,
f: R=isobutyl, g: R=pentyl, h: R=2,6-dimethyl-5-heptenyl, i: R=phenyl

Chart 1

TABLE I. 4-Substituted-3,5-bis(methoxycarbonyl)isoxazoline N-Oxides (3)

Compd. 3	R	Yield (%)	mp (°C)	Recryst. ^{d)} solvent	Formula	Analysis (%)		
						Calcd (Found)		
						C	H	N
a	CH ₃	69	63—64	A	C ₈ H ₁₁ NO ₆	44.24 (44.22)	5.11 5.13	6.45 6.44
b	C ₂ H ₅	78	83—84	B	C ₉ H ₁₃ NO ₆	46.75 (46.85)	5.67 5.62	6.06 6.05
c	n-C ₃ H ₇	82	50—51	A	C ₁₀ H ₁₅ NO ₆	48.98 (48.91)	6.17 6.31	5.71 5.63
d	iso-C ₃ H ₇	95	84.5—85	C	C ₁₀ H ₁₅ NO ₆	48.98 (48.75)	6.17 6.20	5.71 5.60
e	n-C ₄ H ₉	74	Syrup	—	C ₁₁ H ₁₇ NO ₆	50.96 (50.67)	6.61 6.49	5.40 5.35
f	iso-C ₄ H ₉	67	59—60	D	C ₁₁ H ₁₇ NO ₆	50.96 (51.25)	6.61 6.81	5.40 5.36
g	n-C ₅ H ₁₁	78	Syrup	—	C ₁₂ H ₁₉ NO ₆	52.74 (53.02)	7.01 7.03	5.13 5.12
h	C ₉ H ₁₇ ^{a)}	72	Syrup ^{b)}	—	—	—	—	—
i	C ₆ H ₅	57	94—95 ^{c)}	A	—	—	—	—

a) 2,6-Dimethyl-5-heptenyl.

b) A diastereomeric mixture; MS *m/e*: 327 (M⁺).

c) Reported⁹⁾ mp 94.5—96°.

d) A: methanol-water, B: methanol, C: ethyl acetate-hexane, D: hexane.

3 was established as *trans* on the basis of the $J_{4,5}$ value (2.0—3.0 Hz) as suggested in a previous communication.³⁾

As an application of this method to an optically active aldehyde, the reaction of 2 with (+)-citronellal⁶⁾ was carried out to give 3h in 72% yield. The NMR spectrum of 3h indicated the presence of two diastereomers in a *ca.* 3:1 ratio, but we could not separate them and could not assign specific stereochemistry to the isomers. On the other hand, the 4-phenyl analog (3i) was obtained together with by-products and was isolated by column chromatography on silica gel. The by-products were shown by IR, NMR and mass spectroscopy to be a mixture of two diastereomers, 5 and 6 (Chart 2), in a *ca.* 2:1 ratio. The major isomer was characterized as 5, in which the 4-phenyl and 5-methoxycarbonyl groups are *trans*, while the minor isomer (6) was *cis*. These assignments were based upon the large diamagnetic shielding of the eclipsed 5-ester Me (δ 3.25) by the 4-phenyl group in the *cis*-isomer (6), whereas the 5-ester Me signal appeared at δ 3.80 in the *trans*-isomer (5), and are supported by other examples⁷⁾ of shielding of ester groups by a vicinal *cis*-phenyl group. The $\Delta\delta$ (0.55) of the

6) (R)-(+)-Citronellal purchased from Wako Pure Chemical Co., Ltd. was distilled *in vacuo* before use; bp 59—60° (3 mmHg), $[\alpha]_D^{25} + 8.4^\circ$ (neat). The optical purity was 50% based on $[\alpha]_D^{25} + 16.8^\circ$ (neat) for an optically pure (R)-(+)-citronellal: S. Hashimoto, S. Yamada, and K. Koga, *Chem. Pharm. Bull.*, 27, 771 (1979).

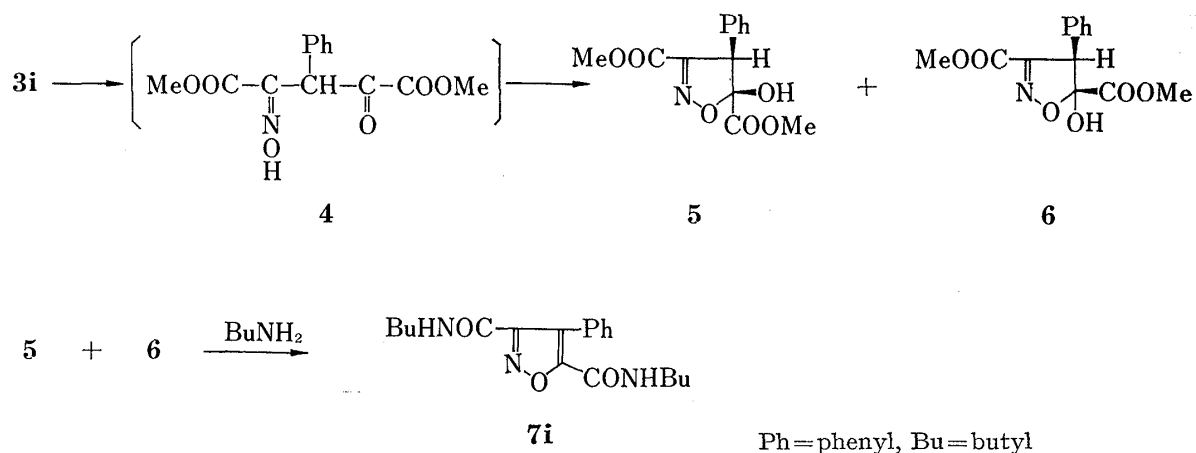


Chart 2

5-ester Me between **5** and **6** was in accord with that ($\Delta\delta=0.54-0.62$) of the ester methylene group in *cis*- and *trans*-ethyl 2-nitro-3-(*p*-nitrophenyl)bicyclo[2,2,1]-5-heptene-2-carboxylate.⁷⁾

The formation of **5** and **6** may occur as shown in Chart 2, in which an initially formed β -oximino ketone (**4**)⁸⁾ cyclizes to **5** and **6**. The stereoselectivity of cyclization may be thermodynamically controlled. Treatment of a mixture of **5** and **6** with excess butylamine readily gave the corresponding 3,5-bis(butylcarbamoyl)-4-phenylisoxazole (**7i**) in 80% yield.

Mechanism of Formation of Isoxazoline N-Oxide

The formation of isoxazoline N-oxide (**3**) is believed to involve 1,3-dinitroglutarate (**8**)³⁻⁵⁾ as an intermediate. However, the elimination of nitrous acid from **8** may occur *via* a nitro olefin intermediate (**10**) or by direct intramolecular displacement of nitrite by the nitronate anion (**9**) (Chart 3). Nielsen *et al.*⁹⁾ showed that the nitrite ion displacement mechanism is predominant in the formation of 3,4,5-triphenylisoxazoline N-oxide from 1,3-dinitro-1,2,3-triphenylpropane. We have examined the mechanism of formation of **3i** employing benzaldehyde-1-*d*.¹⁰⁾ The reaction of **2** with benzaldehyde-1-*d* under the reaction conditions used

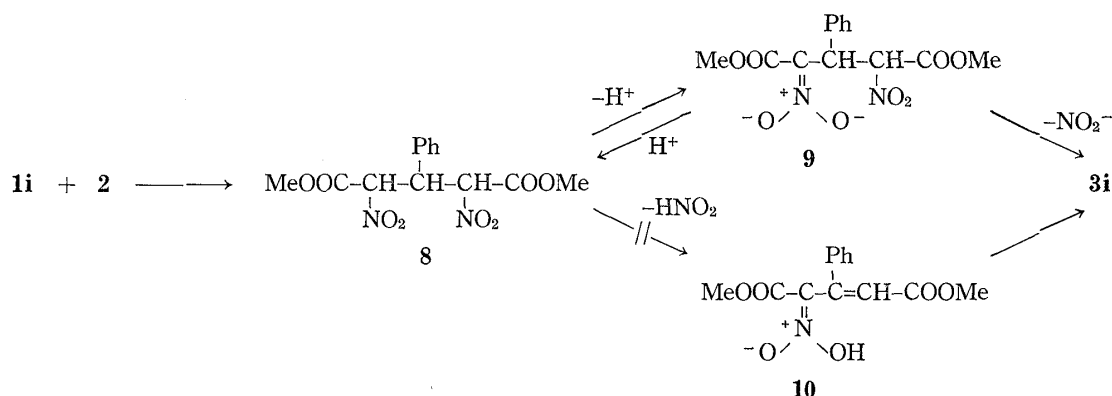


Chart 3

- 7) M. Kinoshita, H. Yanagisawa, S. Doi, E. Kaji, and S. Umezawa, *Bull. Chem. Soc. Jpn.*, **42**, 194 (1969), and references cited therein.
- 8) a) A. Quilico, "The Chemistry of Heterocyclic Compounds," Vol. 17, ed. by R.H. Wiley, Interscience Publishers, Inc., New York, 1962, pp. 113-114; b) R.A. Barnes, "Heterocyclic Compounds," Vol. 5, ed. by R.C. Elderfield, John Wiley and Sons, Inc., New York, 1957, p. 482; c) T. Sakakibara and R. Sudoh, *Bull. Chem. Soc. Jpn.*, **51**, 3401 (1978).
- 9) A.T. Nielsen and T.G. Archibald, *Tetrahedron Lett.*, **1968**, 3375; *J. Org. Chem.*, **34**, 984 (1969).
- 10) D. Seebach, B.W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966).

for **3i** resulted in quantitative deuterium incorporation at C-4 on isoxazoline N-oxide (**11**), as confirmed by NMR and mass spectroscopy. This assignment was corroborated by the observation that a singlet peak for H-5 in the NMR spectrum of **11** was changed to a multiplet in the corresponding 5-hydroxymethyl derivative (**12**) prepared by selective reduction of **11** with lithium aluminum hydride (LAH) (see Table IV). Accordingly, the mechanism of formation of **3i** involves nitrite ion displacement and not the nitro olefin intermediate which we proposed in our previous paper.³⁾ The effect of DMA on this reaction is consonant with a nitrite ion displacement mechanism inasmuch as this mechanism is generally facilitated in dipolar aprotic solvents.¹¹⁾

Conversion of Isoxazoline N-Oxides into Isoxazoles

Base-catalyzed transformation of isoxazoline N-oxides into isoxazoles is a well-known reaction.^{8a)} For example, 4-aryl-3,5-bis(butylcarbamoyl)isoxazoles were prepared by the action of excess butylamine on 4-aryl-3,5-bis(methoxycarbonyl)isoxazoline N-oxides.⁵⁾ When this method was applied to the isoxazoline N-oxides (**3**), the corresponding 3,5-bis(butylcarbamoyl)isoxazoles (**7**) were obtained together with 3,5-bis(butylcarbamoyl)isoxazoline N-oxides (**13**) (Chart 4). The yields of **7** and **13** were found to show a remarkable dependence on the duration of refluxing. In the case of **3e**, refluxing for 2 hr resulted in 10% and 55% yields of **7e** and **13e**, respectively, while refluxing for 10 hr resulted in 53% and 11% yields. The results are shown in Tables II and III.

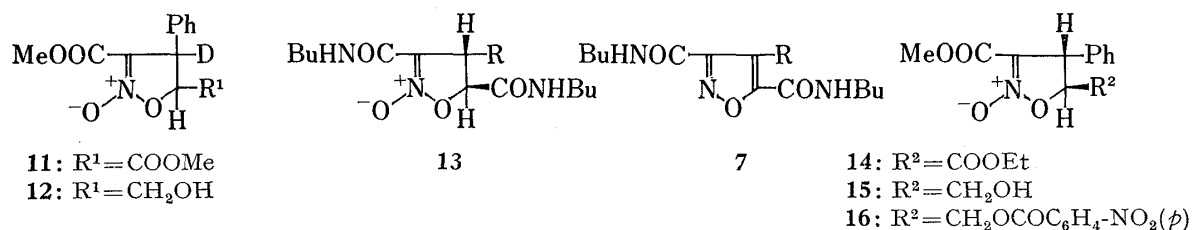


Chart 4

TABLE II. 4-Substituted-3,5-bis(butylcarbamoyl)isoxazoline N-Oxides (**13**)

Compd. 13	R	Reflux time (hr)	Yield (%)	mp (°C)	Recryst. ^{a)} solvent	Formula	Analysis (%)		
							Calcd (Found)	C	H N
a	CH ₃	10	7	122.5—123.5	A	C ₁₄ H ₂₅ N ₃ O ₄	56.17 (56.23)	8.42 8.51	14.04 14.14
b	C ₂ H ₅	10	14	89—90	A	C ₁₅ H ₂₇ N ₃ O ₄	57.49 (57.58)	8.68 8.76	13.41 13.39
c	<i>n</i> -C ₃ H ₇	10	19	103—104	A	C ₁₆ H ₂₉ N ₃ O ₄	58.69 (59.02)	8.93 9.20	12.83 13.00
d	iso-C ₃ H ₇	2	44	102.5—104.5	A	C ₁₆ H ₂₉ N ₃ O ₄	58.69 (58.35)	8.93 8.73	12.83 12.77
e	<i>n</i> -C ₄ H ₉	2	55	104—105	B	C ₁₇ H ₃₁ N ₃ O ₄	59.80 (59.75)	9.15 9.11	12.31 12.27
f	iso-C ₄ H ₉	2	49	104.5—105.5	A	C ₁₇ H ₃₁ N ₃ O ₄	59.80 (60.22)	9.15 9.06	12.31 12.12
g	<i>n</i> -C ₅ H ₁₁	2	54	102.5—103.5	C	C ₁₈ H ₃₃ N ₃ O ₄	60.82 (60.64)	9.36 9.32	11.82 11.98
i	C ₆ H ₅	0.5	32	94.5—96	C	C ₁₉ H ₂₇ N ₃ O ₄	63.14 (63.21)	7.53 7.42	11.63 11.49

a) A: acetone-water, B: ethyl acetate-hexane, C: benzene-hexane.

- 11) N. Kornblum, *Angew. Chem. Int. Ed. Engl.*, **14**, 734 (1975); N. Kornblum, L. Cheng, R.C. Kerber, M.M. Kestner, B.N. Newton, H.W. Pinnick, R.G. Smith, and P.A. Wade, *J. Org. Chem.*, **41**, 1560 (1976).

TABLE III. 4-Substituted-3,5-bis(butylcarbamoyl)isoxazoles (7)^{a)}

Compd. 7	R	Yield ^{c)} (%)	mp (°C)	Recryst. ^{f)} solvent	Formula	Analysis (%)		
						Calcd (Found)	C	H N
a	CH ₃	56	92—93 ^{d)}	A	—	—	—	—
b	C ₂ H ₅	51	81—82	A	C ₁₅ H ₂₅ N ₃ O ₃	60.99 (61.06)	8.53 8.68	14.23 14.37
c	<i>n</i> -C ₃ H ₇	60	114.5—115.5 ^{e)}	A	—	—	—	—
e	<i>n</i> -C ₄ H ₉	53	91.5—92.5	A	C ₁₇ H ₂₉ N ₃ O ₃	63.13 (63.05)	9.04 9.06	12.99 12.93
f	iso-C ₄ H ₉	65	97.5—98.5	A	C ₁₇ H ₂₉ N ₃ O ₃	63.13 (63.41)	9.04 8.94	12.99 12.60
g	<i>n</i> -C ₅ H ₁₁	49	83—85	A	C ₁₈ H ₃₁ N ₃ O ₃	64.06 (64.16)	9.26 9.29	12.45 12.67
h	C ₉ H ₁₇ ^{b)}	46	85—87.5	A	C ₂₂ H ₃₇ N ₃ O ₃	67.48 (67.16)	9.53 9.47	10.72 10.62

a) Conversion of **3i** into **7i** was described in the previous paper.⁹⁾

b) 2,6-Dimethyl-5-heptenyl.

c) After refluxing for 10 hr.

d) Reported¹²⁾ mp 84—86°.e) Reported¹²⁾ mp 111.5—113°.

f) A: hexane.

It should be noted that this dehydration might be affected sterically by the C-4 substituent. Thus 4-isopropylisoxazoline N-oxide (**3d**) gave only the corresponding diamide (**13d**) in 44% yield, and no isoxazole derivative was obtained even after refluxing for 10 hr. When **3i** was treated with butylamine for 0.5 hr, the 5-butylcarbamoyl derivative (**17**) and 3,5-bis(butylcarbamoyl)isoxazoline N-oxide (**13i**) were obtained. On the other hand, the 5-ethoxycarbonyl derivative (**14**) was isolated from an ethanolic solution of **3i** after standing at room temperature for a week. The difference of chemical reactivity of the methoxycarbonyl groups at C-3 and C-5 might be due to π -conjugation of the 3-carbonyl with the isoxazoline C=N bond. The assignments of ester groups of C-3 and C-5 were confirmed on the basis of their NMR spectra, compared with those of the 5-hydroxymethyl derivative (**15**) and its *p*-nitrobenzoate (**16**). Table IV summarizes these results. Based on these observations, the sequence of conversion of **3i** into **7i** is postulated to be as shown in Chart 5.

TABLE IV. NMR Data for 4-Phenylisoxazoline N-Oxide and Isoxazole Derivatives

Compd. No.	Chemical shift (δ) in CDCl ₃						<i>J</i> _{4,5} (Hz)
	H-4	H-5	Ester Me-3	Ester Me-5	Amide NH-3	Amide NH-5	
3i	4.82(d)	4.92(d)	3.73(s)	3.87(s)	—	—	3.0
11	—	4.92(s)	3.73(s)	3.88(s)	—	—	—
12	—	4.57(t)	3.68(s)	—	—	—	—
15	4.68(d)	4.6(m)	3.70(s)	—	—	—	4.0
16	4.57(d)	4.87(m)	3.73(s)	—	—	—	4.0
17	4.80(d)	5.07(d)	3.73(s)	—	—	6.83(b)	3.0
13i	4.82(d)	5.16(d)	—	—	7.88(b)	6.73(b)	3.0
7i	—	—	—	—	6.80(b)	6.33(b)	—

s: singlet, d: doublet, t: triplet, m: multiplet, b: broad signal

employed. After work-up as described above, 5.5 g of crude product was obtained. Two recrystallizations from methanol-water gave 3.2 g (57% yield) of **3i** which was identical (mixed melting point, NMR, IR, and TLC) with an authentic sample.⁵⁾ The mother liquor was concentrated and further purified through a silica gel column with ethyl acetate-hexane (1:1) as an eluant, affording 1.28 g (23% yield) of a mixture of **5** and **6** in a *ca.* 2:1 ratio as determined by NMR integration. Recrystallization from benzene-hexane gave colorless needles: mp 102.5–103.5°, UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 224 shoulder (3.83), 324 (3.41). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3400 (OH), 1730 (ester C=O), 1600 (C=N). NMR (CDCl₃) δ : 3.25 (3/2H, s, ester Me-5 of **6**), 3.80 (3H, s, ester Me-5 of **5**), 3.83 (3/2H, s, ester Me-3 of **6**), 3.95 (3H, s, ester Me-3 of **5**), 4.0–4.3 (3/2H, broad, OH of **5** and **6**), 4.75 (1/2H, s, H-4 of **6**), 5.15 (1H, s, H-4 of **5**), 7.0–7.5 (15/2H, m, C₆H₅ of **5** and **6**). MS *m/e*: 279 (M⁺). Anal. Calcd for C₁₃H₁₃NO₆: C, 55.91; H, 4.66; N, 5.01. Found: C, 55.62; H, 4.55; N, 4.80.

Reaction of a Mixture of 5 and 6 with Butylamine—A solution of a mixture of **5** and **6** (0.30 g, 1.1 mmol) in methanol (10 ml) was refluxed for 5 hr in the presence of excess butylamine (0.79 g, 11 mmol). After concentration, the crude product was recrystallized from ethanol, affording 0.30 g (80% yield) of **7i** as colorless needles: mp 159.5–160.5° (reported¹²⁾ mp 161–162°). The melting point was undepressed on admixture with authentic material, and the NMR and IR spectra were identical with those of the authentic sample.¹²⁾

3,5-Bis(methoxycarbonyl)-4-phenylisoxazoline N-Oxide-4-d (11)—Benzaldehyde-1-*d*¹⁰⁾ (1.07 g, 10 mmol), methyl nitroacetate (2.38 g, 20 mmol), diethylamine (1.03 ml, 10 mmol), and 30 ml of DMA were employed. Work-up gave 2.15 g of crude product, which was recrystallized from methanol-water to furnish 1.02 g of **11**: mp 92.5–93.5°. The mother liquor, after column chromatography on silica gel, gave a further 0.10 g of **11** and 0.63 g of a mixture of methyl nitroacetate and benzaldehyde-1-*d*. The combined yield of **11** was 40%. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 267 (4.02). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1745 and 1730 (ester C=O), 1610 (C=N). The NMR data are listed in Table IV; the signal for H-4 had completely disappeared. MS *m/e*: 280 (M⁺). Anal. Calcd for C₁₃H₁₂DNO₆: C, 55.71; H+D, 5.04; N, 5.00. Found: C, 55.82; H+D, 4.72; N, 4.82.

5-Hydroxymethyl-3-methoxycarbonyl-4-phenylisoxazoline N-Oxide-4-d (12)—A stirred solution of **11** (0.50 g, 1.79 mmol) in 20 ml of dry tetrahydrofuran-diethyl ether (1:5) mixture was treated with lithium aluminum hydride (LAH, 90 mg, 2.38 mmol) in one portion under nitrogen. The mixture was refluxed for 1 hr with vigorous stirring until most of **11** had been consumed. The excess LAH was decomposed by adding 10 ml of 1 M hydrochloric acid. Diethyl ether (20 ml) was added to the mixture, which was partitioned. The aqueous layer was extracted with diethyl ether (2 × 20 ml), and the combined extracts were washed with water (3 × 40 ml), dried (Na₂SO₄) and concentrated to furnish 253 mg of a yellow syrup. This was purified through a column of silica gel, eluting with ethyl acetate-hexane (1:1), to give 70 mg (16% yield) of the mono-alcohol (**12**) as a yellowish syrup. IR $\nu_{\text{max}}^{\text{LiAlH}_4 \text{ film}}$ cm⁻¹: 3450 (OH), 1730 (ester C=O), 1615 (C=N), 1500 (phenyl). NMR (CDCl₃) δ : 2.4–3.0 (1H, broad, OH), 3.68 (3H, s, ester Me), 3.83 (2H, m, CH₂), 4.57 (1H, t, *J* = 4 Hz, H-5), 7.33 (5H, s, C₆H₅). MS *m/e*: 252 (M⁺).

3,5-Bis(butylcarbamoyl)-4-methylisoxazoline N-Oxide (13a) and 3,5-Bis(butylcarbamoyl)-4-methylisoxazole (7a): A General Procedure—A solution of **3a** (0.37 g, 1.57 mmol) and butylamine (0.93 ml, 9.42 mmol) in methanol (8 ml) was refluxed for 10 hr. The resulting orange-yellow solution was concentrated to furnish 0.62 g of a viscous syrup, which solidified on standing at room temperature. Purification through a silica gel column, eluting with ethyl acetate-hexane (1:2), gave 0.22 g of **7a** as colorless crystals: TLC *R_f* 0.7 (silica gel, ethyl acetate-hexane (1:2)). This product was identical with an authentic sample¹²⁾ (NMR, IR and mixed melting point). Yields, mp, and analytical data for **7** are shown in Table III, and spectral data for **7** are summarized in Table VII.

Further elution of the column with the same solvent gave 0.03 g of **13a** as colorless crystals: TLC *R_f* 0.3 (the same system as for **7a**). Yields, mp, and analytical data for **13** are listed in Table II, and spectral data are summarized in Table VI.

TABLE VI. Spectral Data for 4-Substituted-3,5-bis(butylcarbamoyl)isoxazoline N-Oxides (**13**)

Compd. 13	R	IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹		UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ)	NMR (CDCl ₃) δ				<i>J</i> _{4,5} (Hz)
		Amide C=O	C=N		Amide NH ^{a)}	H-4 ^{b)}	H-5 ^{c)}		
a	CH ₃	1680–1640, 1540	1615	256(3.95)	6.5, 7.9	3.98	4.51		3.0
b	C ₂ H ₅	1665, 1620, 1535	1610	258(3.94)	6.6, 7.9	3.92	4.60		3.0
c	<i>n</i> -C ₃ H ₇	1655, 1635, 1530	1610	257(3.90)	6.6, 8.0	3.97	4.63		3.0
d	iso-C ₃ H ₇	1670, 1650, 1535	1615	258(3.91)	6.7, 8.0	3.97	4.72		3.0
e	<i>n</i> -C ₄ H ₉	1660, 1640, 1535	1615	258(3.93)	6.6, 8.0	3.97	4.63		2.5
f	iso-C ₄ H ₉	1655–1645, 1530	1615	258(3.95)	6.7, 8.0	4.07	4.65		2.5
g	<i>n</i> -C ₅ H ₁₁	1660, 1640, 1540	1610	257(3.90)	6.6, 8.0	3.95	4.62		3.0
i	C ₆ H ₅	1670, 1650, 1530	1615	252(4.00)	^{d)}	^{d)}	^{d)}	^{d)}	

a) Each 1H, broad signal.

b) Each 1H, multiplet except in the case of **13d** (double doublet).

c) Each 1H, doublet.

d) Summarized in Table IV.

TABLE VII. Spectral Data for 4-Substituted -3,5-bis(butylcarbamoyl)isoxazoles (7)

Compd. 7	R	IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹		UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ)	NMR (CDCl ₃) δ		
		Amide C=O	Ring ^{c)}		Amide NH ^{d)}	CH ₂ -4 ^{e)}	NHCH ₂
a	CH ₃	1660, 1550	1620	245(4.03)	6.3—7.1	2.60(s)	3.45
b	C ₂ H ₅	1660, 1550	1615	244(4.02)	6.3—7.0	3.08(q)	3.43
c	<i>n</i> -C ₃ H ₇	1660, 1530	1605	246(4.03)	6.3—7.0	3.02(dd)	3.43
e	<i>n</i> -C ₄ H ₉	1660, 1550	1620	246(3.99)	6.2—7.0	3.07(m)	3.45
f	iso-C ₄ H ₉	1660, 1545	1615	245(4.01)	6.2—6.9	2.98(d)	3.44
g	<i>n</i> -C ₅ H ₁₁	1660, 1545	1615	245(4.00)	6.3—7.0	3.05(m)	3.45
h ^{a)}	C ₉ H ₁₇ ^{b)}	1665, 1550	1615	246(4.00)	6.3—6.9	3.02(d)	3.45

a) $[\alpha]_D^{20} + 6.7^\circ$ ($c=0.7$, CHCl₃).

b) 2,6-Dimethyl-5-heptenyl.

c) Isoxazole ring stretching.

d) Each 2H, broad signal.

e) Each 2H except 7a (3H for CH₃-4).

f) Each 4H, multiplet.

5-Butylcarbamoyl-3-methoxycarbonyl-4-phenylisoxazoline N-Oxide (17) and 3,5-Bis(butylcarbamoyl)-4-phenylisoxazoline N-Oxide (13i)—The reaction of 3i (0.20 g, 0.72 mmol) and butylamine (0.42 ml, 4.3 mmol) was conducted under conditions similar to those described above, except that the reaction was carried out at 25° for 0.5 hr. On work-up 72 mg (32% yield) of 17 was obtained as a yellowish syrup: TLC *R_f* 0.4 (silica gel, ethyl acetate–benzene (1:5)). IR $\nu_{\text{max}}^{\text{liq. film}}$ cm⁻¹: 3300 (NH), 1730 (ester C=O), 1700—1600 (amide I), 1620 (C=N), 1535 (amide II). MS *m/e*: 320 (M⁺). NMR data are summarized in Table IV. This was followed by 84 mg (32% yield) of 13i as colorless needles; mp and analytical data are listed in Table II. Spectral data are summarized in Tables IV and VI.

5-Ethoxycarbonyl-3-methoxycarbonyl-4-phenylisoxazoline N-Oxide (14)—An ethanolic solution of 3i (0.90 g, 3.2 mmol) was stored for 1 week at room temperature. Trituration with ligroin resulted in the precipitation of cubic crystals which were collected and recrystallized from methanol, affording 330 mg (43% yield) of 14 as colorless prisms: mp 125.5—127°. UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 267 (4.01). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1760 and 1740 (ester C=O), 1630 (C=N), 1500 (phenyl). NMR (CDCl₃) δ : 1.35 (3H, t, COOCH₂CH₃), 3.74 (3H, s, COOCH₃), 4.33 (2H, q, COOCH₂CH₃), 4.84 (1H, d, $J_{4,5}=3.0$ Hz, H-4), 4.93 (1H, d, $J_{4,5}=3.0$ Hz, H-5), 7.37 (5H, s, C₆H₅). Anal. Calcd for C₁₄H₁₅NO₆: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.13; H, 5.10; N, 4.74.

5-Hydroxymethyl-3-methoxycarbonyl-4-phenylisoxazoline N-Oxide (15) and Its *p*-Nitrobenzoate (16)—Reduction of 3i (1.0 g, 3.58 mmol) with LAH (160 mg, 4.3 mmol) was conducted under the conditions described for 12. Work-up gave 340 mg of crude product, which was chromatographed on silica gel, eluting with ethyl acetate–hexane (1:1), to afford 170 mg (20% yield) of 15 as a yellow syrup. IR $\nu_{\text{max}}^{\text{liq. film}}$ cm⁻¹: 3460 (OH), 1730 (ester C=O), 1610 (C=N), 1500 (phenyl). NMR data are listed in Table IV except for δ : 2.4—3.0 (1H, broad, OH), 3.85 (2H, m, CH₂OH), and 7.33 (5H, s, C₆H₅).

p-Nitrobenzoylation of 15 (114 mg, 0.45 mmol) with *p*-nitrobenzoyl chloride (125 mg, 0.68 mmol) in pyridine (3 ml) gave 124 mg (69% yield) of 16 as yellowish prisms: mp 162—163° (ethyl acetate–hexane). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1720 (ester C=O), 1610 (C=N), 1520 and 1350 (aromatic NO₂). NMR data are listed in Table IV except for δ : 4.63 (2H, d, $J=4$ Hz, CH₂), 7.37 (5H, s, C₆H₅), 8.22 (4H, d, *p*-NO₂-C₆H₄). Anal. Calcd for C₁₉H₁₆N₂O₈: C, 57.00; H, 4.03; N, 7.00. Found: C, 57.32; H, 3.91; N, 7.02.

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