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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 therefrom[1]

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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.

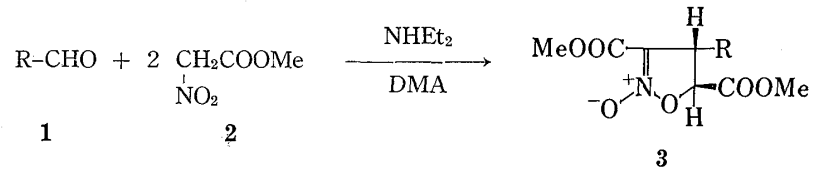
Keywords——methyl nitroacetate; isoxazoline N-oxide; isoxazole; dipolar aprotic solvent; condensation; transformation; nitrite ion displacement mechanism

In a previous communication[3] 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 method[4] for the synthesis of 4-arylisoxazoline-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 procedure[3] 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)

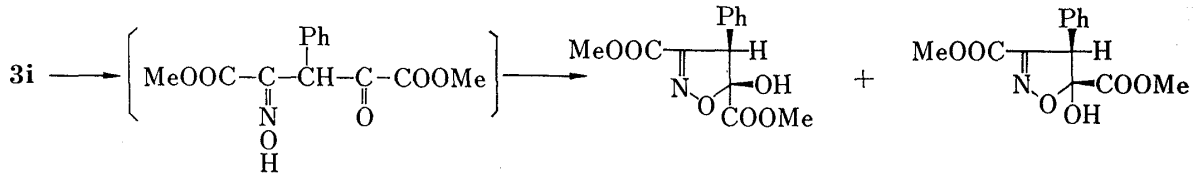
Compd. 3	R	Yield (%)	mp (°C)	Recryst.[d] solvent	Formula	Analysis (%) Calcd (Found) C	H	N
a	CH_3	69	63—64	A	$C_8H_{11}NO_6$	44.24 (44.22	5.11 5.13	6.45 6.44)
b	C_2H_5	78	83—84	B	$C_9H_{13}NO_6$	46.75 (46.85	5.67 5.62	6.06 6.05)
c	n-C_3H_7	82	50—51	A	$C_{10}H_{15}NO_6$	48.98 (48.91	6.17 6.31	5.71 5.63)
d	iso-C_3H_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_4H_9	74	Syrup	—	$C_{11}H_{17}NO_6$	50.96 (50.67	6.61 6.49	5.40 5.35)
f	iso-C_4H_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_5H_{11}	78	Syrup	—	$C_{12}H_{19}NO_6$	52.74 (53.02	7.01 7.03	5.13 5.12)
h	C_9H_{17}[a]	72	Syrup[b]	—	—	—	—	—
i	C_6H_5	57	94—95[c]	A	—	—	—	—

a) 2,6-Dimethyl-5-heptenyl.
b) A diastereomeric mixture; MS *m/e*: 327 (M^+).
c) Reported[5] 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 (+)-citronellal[6] 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 examples[7] 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° (neat). The optical purity was 50% based on $[\alpha]_D^{25}$ +16.8° (neat) for an optically pure (*R*)-(+)-citronellal: S. Hashimoto, S. Yamada, and K. Koga, *Chem. Pharm. Bull.*, **27**, 771 (1979).



4 5 6

7i

Ph=phenyl, Bu=butyl

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

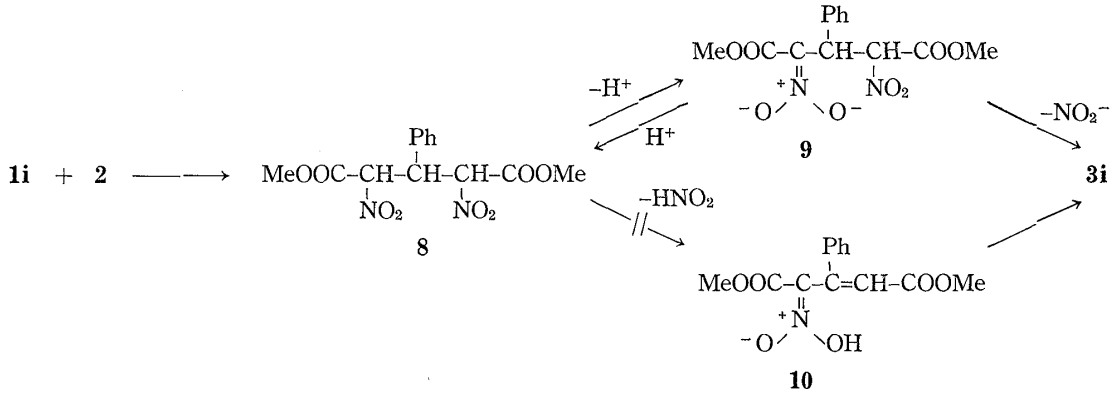


Chart 3

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).

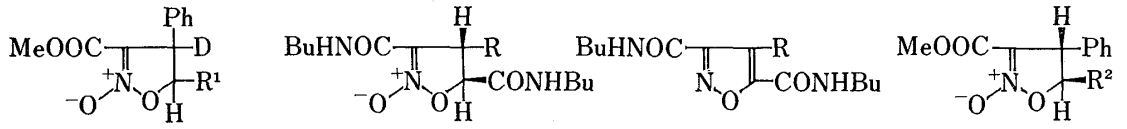
9) A.T. Nielsen and T.G. Archibald, *Tetrahedron Lett.*, **1968**, 3375; *J. Org. Chem.*, **34**, 984 (1969).

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.



11: R^1=COOMe
12: R^1=CH_2OH

13

7

14: R^2=COOEt
15: R^2=CH_2OH
16: R^2=$CH_2OCOC_6H_4$-NO_2(*p*)

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	$C_{14}H_{25}N_3O_4$	56.17 (56.23	8.42 8.51	14.04 14.14)
b	C_2H_5	10	14	89—90	A	$C_{15}H_{27}N_3O_4$	57.49 (57.58	8.68 8.76	13.41 13.39)
c	*n*-C_3H_7	10	19	103—104	A	$C_{16}H_{29}N_3O_4$	58.69 (59.02	8.93 9.20	12.83 13.00)
d	iso-C_3H_7	2	44	102.5—104.5	A	$C_{16}H_{29}N_3O_4$	58.69 (58.35	8.93 8.73	12.83 12.77)
e	*n*-C_4H_9	2	55	104—105	B	$C_{17}H_{31}N_3O_4$	59.80 (59.75	9.15 9.11	12.31 12.27)
f	iso-C_4H_9	2	49	104.5—105.5	A	$C_{17}H_{31}N_3O_4$	59.80 (60.22	9.15 9.06	12.31 12.12)
g	*n*-C_5H_{11}	2	54	102.5—103.5	C	$C_{18}H_{33}N_3O_4$	60.82 (60.64	9.36 9.32	11.82 11.98)
i	C_6H_5	0.5	32	94.5—96	C	$C_{19}H_{27}N_3O_4$	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_2H_5	51	81—82	A	$C_{15}H_{25}N_3O_3$	60.99 (61.06	8.53 8.68	14.23 14.37)
c	n-C_3H_7	60	114.5—115.5[e]	A	—	—	—	—
e	n-C_4H_9	53	91.5—92.5	A	$C_{17}H_{29}N_3O_3$	63.13 (63.05	9.04 9.06	12.99 12.93)
f	iso-C_4H_9	65	97.5—98.5	A	$C_{17}H_{29}N_3O_3$	63.13 (63.41	9.04 8.94	12.99 12.60)
g	n-C_5H_{11}	49	83—85	A	$C_{18}H_{31}N_3O_3$	64.06 (64.16	9.26 9.29	12.45 12.67)
h	C_9H_{17}[b]	46	85—87.5	A	$C_{22}H_{37}N_3O_3$	67.48 (67.16	9.53 9.47	10.72 10.62)

a) Conversion of **3i** into **7i** was described in the previous paper.[5]
b) 2,6-Dimethyl-5-heptenyl.
c) After refluxing for 10 hr.
d) Reported[12] mp 84—86°.
e) Reported[12] mp 111.5—113°.
f) A: hexane.

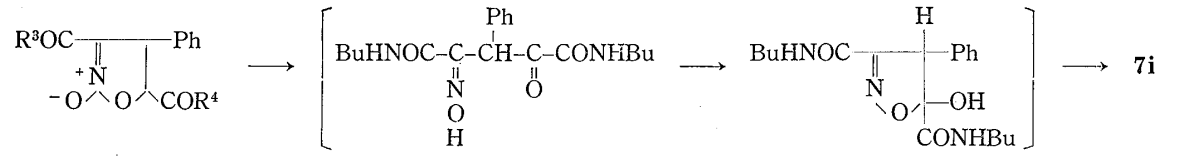
It should be noted that this dehydration might be affected sterically by the C-4 substituent. Thus 4-isopropylisoxazoline N-oxide (**3d**) gave only the corresponding diamide (**13d**) in 44% yield, and no isoxazole derivative was obtained even after refluxing for 10 hr. When **3i** was treated with 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 $CDCl_3$ H-4	H-5	Ester Me-3	Ester Me-5	Amide NH-3	Amide NH-5	$J_{4,5}$ (Hz)
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

12) S. Zen and S. Umezawa, *Bull. Chem. Soc. Jpn.*, **36**, 1146 (1963).



3i: $R^3=R^4=OMe$
17: $R^3=OMe$, $R^4=NHBu$
13i: $R^3=R^4=NHBu$

Chart 5

Experimental

Melting points are uncorrected. NMR spectra were recorded with Varian T-60 60 MHz and JEOL PS-100 100 MHz spectrometers using tetramethylsilane as an internal standard in chloroform-*d*. IR, UV, and mass spectra were measured with Jasco IRA-1, Hitachi 340, and JMS D-100 spectrometers, respectively. Specific rotations were obtained with a Jasco DIP-180 digital polarimeter. TLC was carried out on Kiesel gel G (Merck), spots being detected with iodine vapor or 10% sulfuric acid on a hot plate. Silica gel (Kanto Kagaku, up to 100 mesh) was used for column chromatography. Benzaldehyde-1-*d* was prepared by Seebach's method[10] and was found to have a deuterium incorporation of more than 99% by NMR and mass spectroscopy.

3,5-Bis(methoxycarbonyl)-4-methylisoxazoline N-Oxide (3a): A General Procedure——A solution of freshly distilled acetaldehyde (0.31 ml, 5.5 mmol) and methyl nitroacetate[13] (1.19 g, 10 mmol) in anhydrous DMA (15 ml) was treated with diethylamine (0.52 ml, 5 mmol) with external ice-cooling. The mixture was stirred at room temperature overnight (16 hr). The resulting yellow solution was partitioned between ice-water (60 ml) and benzene (30 ml). The aqueous phase was extracted with benzene (2×30 ml). The combined extracts were washed with water (3×60 ml), dried (Na_2SO_4) and concentrated to furnish a yellow syrup (920 mg) which was chromatographed on silica gel, eluting with ethyl acetate–hexane (1:2), to give 740 mg of **3a** as a yellowish syrup. On standing at room temperature this solidified, and it was recrystallized from acetone–water. Yield, mp, and elemental analysis data are shown in Table I, and spectral data are summarized in Table V.

Table V. Spectral Data for 4-Substituted-3,5-bis(methoxycarbonyl)isoxazoline N-Oxides (3)

Compd. 3	R	IR ν_{max}^{KBr} cm^{-1} Ester C=O	C=N	UV λ_{max}^{MeOH} nm (log ε)	NMR ($CDCl_3$) δ Ester Me[d]	H-4[e]	H-5[f]	$J_{4,5}$ (Hz)
a	CH_3	1760—1735	1615	267(3.94)	3.83, 3.87	3.67	4.68	3.0
b	C_2H_5	1780—1730	1620	268(3.97)	3.87, 3.90	3.68	4.80	3.0
c	n-C_3H_7	1770—1730	1620	268(3.96)	3.80, 3.85	3.70	4.77	2.5
d	iso-C_3H_7	1755, 1735	1630	269(3.95)	3.87, 3.91	3.68	4.86	2.5
e	n-C_4H_9	1760—1730[c]	1630[c]	268(3.95)	3.83, 3.88	3.67	4.77	2.5
f	iso-C_4H_9	1765—1740	1630	268(3.89)	3.82, 3.85	3.67	4.75	2.5
g	n-C_5H_{11}	1770—1720[c]	1630[c]	266(3.39)	3.84, 3.88	3.67	4.78	2.5
h[a]	C_9H_{17}[b]	1760—1740[c]	1630[c]	268(3.73)	3.80, 3.84	3.70	4.72	2.0[h]
					(3.76, 3.81	[g]	4.74	2.0)[i]
i	C_6H_5	1730	1610	267(3.99)	[j]	[j]	[j]	[j]

a) A diastereomeric mixture: $[\alpha]_D^{20}$ −2° (*c*=0.5, $CHCl_3$).
b) 2,6-Dimethyl-5-heptenyl.
c) Measured as a liquid film.
d) Each 3H, singlet.
e) 1H, multiplet except in the case of **3d** (double doublet).
f) 1H, doublet.
g) Could not be observed because of overlap with other signals.
h) For the major isomer.
i) For the minor isomer.
j) Summarized in Table IV.

Reaction of Benzaldehyde with Methyl Nitroacetate: Compounds 3i, 5, and 6——Benzaldehyde (2.12 g, 20 mmol), methyl nitroacetate (4.76 g, 40 mmol), diethylamine (1.46 g, 20 mmol), and 60 ml of DMA were

13) S. Zen, M. Koyama, and S. Koto, "Organic Syntheses," Vol. 55, ed. by S. Masamune, John Wiley and Sons, Inc., New York, 1976, p. 77.

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 λ_{max}^{MeOH} nm (log ε): 224 shoulder (3.83), 324 (3.41). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1730 (ester C=O), 1600 (C=N). NMR ($CDCl_3$) 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, C_6H_5 of **5** and **6**). MS *m/e*: 279 (M^+). *Anal.* Calcd for $C_{13}H_{13}NO_6$: 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° (reported[12] 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 λ_{max}^{MeOH} nm (log ε): 267 (4.02). IR ν_{max}^{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 $C_{13}H_{12}DNO_6$: 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 (Na_2SO_4) 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 $\nu_{max}^{liq.\ film}$ cm^{-1}: 3450 (OH), 1730 (ester C=O), 1615 (C=N), 1500 (phenyl). NMR ($CDCl_3$) δ: 2.4—3.0 (1H, broad, OH), 3.68 (3H, s, ester Me), 3.83 (2H, m, CH_2), 4.57 (1H, t, J=4 Hz, H-5), 7.33 (5H, s, C_6H_5). 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 *Rf* 0.7 (silica gel, ethyl acetate–hexane (1: 2)). This product was identical with an authentic sample[12] (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 *Rf* 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 ν_{max}^{KBr} cm^{-1} Amide C=O	C=N	UV λ_{max}^{MeOH} nm (log ε)	NMR ($CDCl_3$) δ Amide NH[a]	H-4[b]	H-5[c]	$J_{4,5}$ (Hz)
a	CH_3	1680—1640, 1540	1615	256(3.95)	6.5, 7.9	3.98	4.51	3.0
b	C_2H_5	1665, 1620, 1535	1610	258(3.94)	6.6, 7.9	3.92	4.60	3.0
c	*n*-C_3H_7	1655, 1635, 1530	1610	257(3.90)	6.6, 8.0	3.97	4.63	3.0
d	iso-C_3H_7	1670, 1650, 1535	1615	258(3.91)	6.7, 8.0	3.97	4.72	3.0
e	*n*-C_4H_9	1660, 1640, 1535	1615	258(3.93)	6.6, 8.0	3.97	4.63	2.5
f	iso-C_4H_9	1655—1645, 1530	1615	258(3.95)	6.7, 8.0	4.07	4.65	2.5
g	*n*-C_5H_{11}	1660, 1640, 1540	1610	257(3.90)	6.6, 8.0	3.95	4.62	3.0
i	C_6H_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 ν_{max}^{KBr} cm^{-1} Amide C=O	Ring[c]	UV λ_{max}^{MeOH} nm (log ε)	NMR ($CDCl_3$) δ 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_2H_5	1660, 1550	1615	244(4.02)	6.3—7.0	3.08(q)	3.43
c	n-C_3H_7	1660, 1530	1605	246(4.03)	6.3—7.0	3.02(dd)	3.43
e	n-C_4H_9	1660, 1550	1620	246(3.99)	6.2—7.0	3.07(m)	3.45
f	iso-C_4H_9	1660, 1545	1615	245(4.01)	6.2—6.9	2.98(d)	3.44
g	n-C_5H_{11}	1660, 1545	1615	245(4.00)	6.3—7.0	3.05(m)	3.45
h[a]	C_9H_{17}[b]	1665, 1550	1615	246(4.00)	6.3—6.9	3.02(d)	3.45

a) $[\alpha]_D^{20}$ +6.7° (c=0.7, $CHCl_3$).
b) 2,6-Dimethyl-5-heptenyl.
c) Isoxazole ring stretching.
d) Each 2H, broad signal.
e) Each 2H except **7a** (3H for CH_3-4).
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 *Rf* 0.4 (silica gel, ethyl acetate–benzene (1: 5)). IR $\nu_{max}^{liq.\ film}$ 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 λ_{max}^{MeOH} nm (log ε): 267 (4.01). IR ν_{max}^{KBr} cm^{-1}: 1760 and 1740 (ester C=O), 1630 (C=N), 1500 (phenyl). NMR ($CDCl_3$) δ: 1.35 (3H, t, $COOCH_2C\underline{H}_3$), 3.74 (3H, s, $COOCH_3$), 4.33 (2H, q, $COOC\underline{H}_2CH_3$), 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, C_6H_5). *Anal.* Calcd for $C_{14}H_{15}NO_6$: 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 $\nu_{max}^{liq.\ film}$ 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, $C\underline{H}_2OH$), and 7.33 (5H, s, C_6H_5).

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 ν_{max}^{KBr} cm^{-1}: 1720 (ester C=O), 1610 (C=N), 1520 and 1350 (aromatic NO_2). NMR data are listed in Table IV except for δ: 4.63 (2H, d, J=4 Hz, CH_2), 7.37 (5H, s, C_6H_5), 8.22 (4H, d, *p*-NO_2-C_6H_4). *Anal.* Calcd for $C_{19}H_{16}N_2O_8$: C, 57.00; H, 4.03; N, 7.00. Found: C, 57.32; H, 3.91; N, 7.02.

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