[Chem. Pharm. Bull. 33(2) 497—502 (1985)]

Cyclization of (2-Hydroxyethyl)urea Derivatives to Give 3-Nitroso-2-oxazolidinones under Usual Nitrosation Conditions

MAKOTO MIYAHARA,* MASAHIRO NAKADATE, and SHOZO KAMIYA

National Institute of Hygienic Sciences, 1–18–1, Kamiyoga, Setagaya-ku, Tokyo 158, Japan

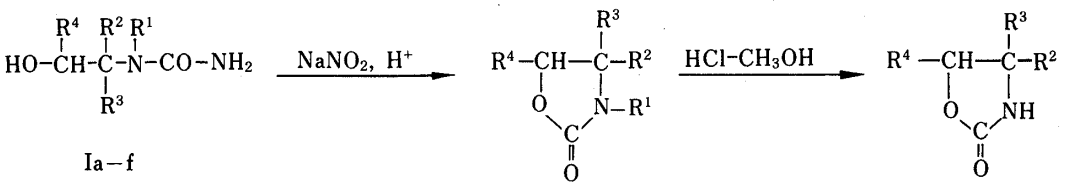
(Received May 17, 1984)

Treatment of (2-hydroxyethyl)urea derivatives (Ia—e) with sodium nitrite in the presence of acids or with nitrosyl chloride in chloroform gave 3-nitroso-2-oxazolidinones (IIa—e) in 10—77% yields. These 3-nitroso-2-oxazolidinones were denitrosated with hydrogen chloride in methanol to give the corresponding 2-oxazolidinones (IIIa—e) in 35—60% yields. An N,N-disubstituted urea, 1-(2-hydroxyethyl)-1-methylurea (If) also cyclized to give 3-methyl-2-oxazolidinone (IIf) under the same conditions.

The mechanism of this type of cyclization is discussed.

Keywords——nitrosation; cyclization; (2-hydroxyethyl)urea; 3-nitroso-2-oxazolidinone; sodium nitrite; nitrosyl chloride

In the course of our studies[1] on the synthesis of antitumor-active N-nitrosoureas, we have already found that some 3-nitroso-2-oxazolidinones are active against rat ascites hepatoma AH-13 and mouse lymphoid leukemia L-1210.[2] This paper describes the nitrosation of (2-hydroxyethyl)urea derivatives to give 3-nitroso-2-oxazolidinones and discusses the mechanism of this type of cyclization.

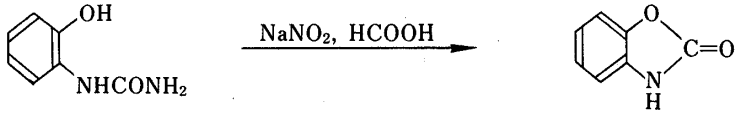


Ia–f

a : $R^1=R^2=R^3=R^4=H$
b : $R^1=R^2=R^3=H$, $R^4=CH_3$
c : $R^1=R^2=R^3=H$, $R^4=C_6H_5$
d : $R^1=H$, $R^2=C_6H_5$, $R^3=R^4=H$
e : $R^1=H$, $R^2=R^3=CH_3$, $R^4=H$
f : $R^1=CH_3$, $R^2=R^3=R^4=H$

IIa–f
IIa–e : $R^1=NO$

IIIa–e



Ig

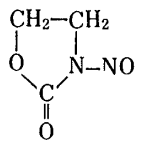
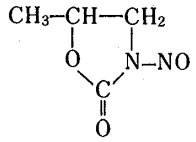
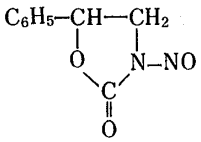
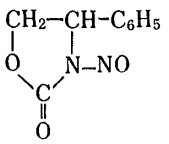
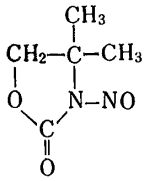
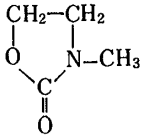
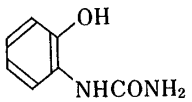
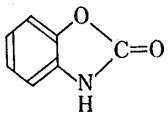
IIg

Chart 1

(2-Hydroxyethyl)ureas (Ia—d) dissolved in 10% hydrochloric acid or formic acid were mixed with a solution of sodium nitrite at 0 °C, and the mixtures were stirred for 1— 2 h (Chart

NII-Electronic Library Service

TABLE I. Products and Yields Obtained in the Nitrosation of (2-Hydroxyethyl)urea Derivatives (Ia—g)

	Compounds (Ia—g)	Products (IIa—g)	Yield (%)	mp (°C)	IR νcm^{-1} (C=O)
a	$HOCH_2CH_2NHCONH_2$		23	41	1800
b	$HOCHCH_2NHCONH_2$ CH_3		19	30—32	1805
c	$HOCHCH_2NHCONH_2$ C_6H_5		77	76—79	1790
d	$HOCH_2CHNHCONH_2$ C_6H_5		50	105—107	1740
e	$HOCH_2\overset{CH_3}{\underset{CH_3}{C}}NHCONH_2$		—[a]	—	1800
f	$HOCH_2CH_2\underset{CH_3}{N}CONH_2$		65	Oil	1710
g			18	137—139	1680

a) A mixture of IIe and IIIe (1 : 1).

1). The resulting 3-nitroso-2-oxazolidinone derivatives (IIa—d) were extracted with ether and purified by recrystallization. The yields of these 3-nitroso-2-oxazolidinones (IIa—d) and related 2-oxazolidinone derivatives (IIe—g) are summarized in Table I. The yields of 3-nitroso-2-oxazolidinone derivatives (IIc, d) bearing a phenyl ring were higher than those of the alkyl derivatives of 3-nitroso-2-oxazolidinones (IIa, b). The structures of these 2-oxazolidinones were confirmed by comparing their infrared (IR) and proton nuclear magnetic resonance (^{1}H-NMR) spectra with those of authentic samples prepared by direct nitrosation of the corresponding oxazolidinone derivatives.

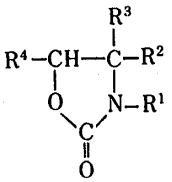
The nitrosation of (1-hydroxy-2-methyl-2-propyl)urea (Ie) gave a mixture of 4,4-dimethyl-3-nitroso-2-oxazolidinone (IIe) and the denitrosated compound, 4,4-dimethyl-2-oxazolidinone (IIIe) in a ratio of 1 : 1, as determined by ^{1}H-NMR spectroscopy. However, because of its instability, compound IIe was completely denitrosated to afford 4,4-dimethyl-2-oxazolidinone (IIIe) during its purification.

NII-Electronic Library Service

TABLE II. Nitrosating Reagents and Yields of 3-Nitroso-2-oxazolidinone (IIa)

Reagent	Yield (%)
10% $HCl/NaNO_2$	17
5% $H_2SO_4/NaNO_2$	23
25% $H_2SO_4/NaNO_2$	6
99% $HCOOH/NaNO_2$	20
NOCl in $CHCl_3$	42

TABLE III. 2-Oxazolidinones (IIIa—d) Obtained by Denitrosation



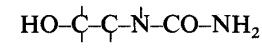
Compounds (IIIa—d)	R^1	R^2	R^3	R^4	mp (°C)	Yield (%)	IR cm^{-1} C=O	IR cm^{-1} NH	^{1}H-NMR NH
	H	H	H	H	86—89	35	1710	3240	7.35
	H	H	H	CH_3	15—17	38	1740	3240	6.26
	H	H	H	C_6H_5	89—90	57	1735	3250	6.52
	H	C_6H_5	H	H	127—128	60	1735	3210	6.30

A 1,1-disubstituted urea, 1-(2-hydroxyethyl)-1-methylurea (If) also cyclized to afford 3-methyl-2-oxazolidinone (IIf) under the same conditions.

Table II shows the yields of 3-nitroso-2-oxazolidinone (IIa) obtained by the use of sodium nitrite and various acids at several concentrations or of nitrosyl chloride in chloroform, as nitrosating reagents. This cyclization proceeded in all nitrosating conditions tested.

Nitrosation of *o*-hydroxyphenylurea (Ig) gave benzoxazolidinone (IIg) in 20% yield and the corresponding *N*-nitroso-2-oxazolidinone was not obtained (Chart 1). (3-Hydroxy-1-propyl)urea [$HOCH_2CH_2CH_2NHCONH_2$] (Ih), which has three carbons between the hydroxy group and the ureido N^1 nitrogen, did not cyclize, giving the corresponding N-nitrosourea. (2-Methoxyethyl)urea [$CH_3OCH_2CH_2NHCONH_2$] (Ii) and 1-(2-hydroxyethyl)-3-methylurea [$HOCH_2CH_2NHCONHCH_3$] (Ij) also did not give the expected cyclized compounds.

From these results, it was concluded that the following structure is required for this type of cyclization.



When the carbons adjacent to the ureido N^1 nitrogen are sterically hindered as in the case of Ie, the resulting 3-nitroso-2-oxazolidinones become unstable. If the terminal N^3 amino group or the hydroxy group of the starting urea is methylated, this cyclization did not occur.

When methanolic solutions of 3-nitroso-2-oxazolidinones (IIa—d) were treated with dry hydrogen chloride at 0 °C, the denitrosated compounds, 2-oxazolidinones (IIIa—d) were obtained in 35—60% yields (Chart 1, Table III). Thus, the denitrosation of these 3-nitroso-2-oxazolidinones proceeds smoothly as compared with that of the corresponding open-chain N-

NII-Electronic Library Service

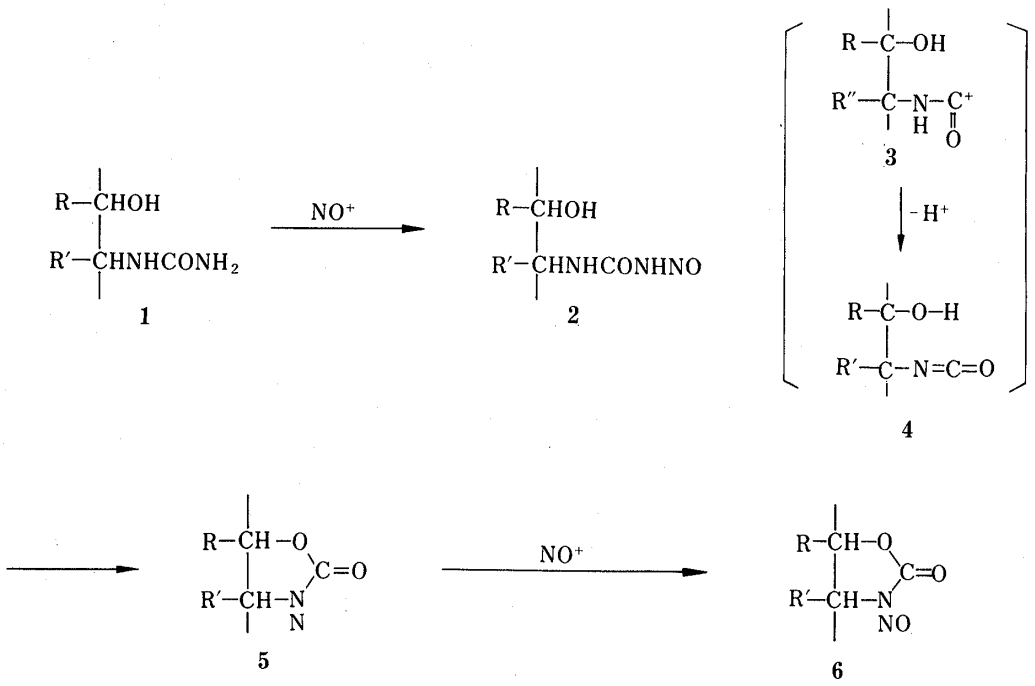


Chart 2

alkyl-N-nitrosocarbamates.

A possible mechanism for this type of cyclization is shown in Chart 2. The N^3 primary amino group in the ureido group is first nitrosated to give compound (**2**), followed by deamination to form a carbonium ion (**3**) as an active intermediate. Subsequently, the carbonium ion (**3**) readily forms an isocyanate (**4**) through deprotonation. The isocyanato group reacts intramolecularly with the hydroxy group to give the 2-oxazolidinone derivative (**5**), which is finally nitrosated with nitrous acid to produce 3-nitroso-2-oxazolidinone (**6**). In the case of the N,N-disubstituted urea, 1-(2-hydroxyethyl)-1-methylurea (If), the carbonium ion (**3**) directly reacts with the hydroxy group to produce compound (**5**) (IIf).

The following mechanism is also conceivable.

$$RN(NO)CONH_2 \xrightarrow{OH^-} R\text{-}NHNO + NH_2COOH$$

However, the N^1-methylurea derivative (If) cyclized to give the corresponding cyclic carbamate, but the N^3-methylurea derivative (Ij) did not. Consequently, in this stage, the main pathway for the cyclization is considered to be that shown in Chart 2.

Experimental[3]

(2-Hydroxyalkyl)ureido Derivatives (Ia—j)——Typical experiments are described for the cases of Ia, Ig and Ij. (2-Hydroxyethyl)urea (Ia): A mixture of ethanolamine hydrochloride (2.0 g) and potassium cyanide in water (50 ml) was heated at 85—90 °C for 1 h, then cooled. The precipitated colorless prisms were filtered off, and recrystallized from water–ethanol several times, then from dioxane. Colorless cubes, mp 95 °C (lit.,[4] 94—95 °C). Yield, 1.7 g (68%). IR ν_{max}^{Nujol} cm^{-1}: 3280 (NH), 3420 (OH), 1630 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 6.07 (NH), 5.56 (NH_2), 4.76 (OH). ^{13}C-NMR (DMSO-d_6) δ: 159.16 (C=O), 60.88 (CH_2), 42.10 (CH_2).

(2-Hydroxy-1-propyl)urea (Ib): Colorless prisms, mp 110—112 °C. Yield, 6.0 g (54%). IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 3290 (NH_2), 3200 (NH), 1639 (C=O), 1560. ^{1}H-NMR (DMSO-d_6) δ: 6.06 (NH), 5.53 (NH_2), 3.65 (CH), 2.89 (CH_2), 1.04 (CH_3). ^{13}C-NMR (DMSO-d_6) δ: 159.50 (C=O), 66.14 (CH), 47.16 (CH_2), 21.11 (CH_3). *Anal.* Calcd for $C_4H_{10}N_2O_2 \cdot 1/5\ H_2O$: C, 39.43; H, 8.54; N, 23.00. Found: C, 39.65; H, 8.55; N, 22.83.

(2-Hydroxy-2-phenylethyl)urea (Ic): Colorless needles (from ethanol–water), mp 79—82 °C (lit.,[5] 95 °C). Yield, 3.6 g (98%). IR ν_{max}^{Nujol} cm^{-1}: 3420 (OH), 3300, 3200 (NH, NH_2), 1620 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 6.01 (NH),

NII-Electronic Library Service

5.56 (NH_2), 4.4 (OH). ^{13}C-NMR (DMSO-d_6) δ: 159.16 (C=O), 143.88, 128.00, 126.93, 126.03 (phenyl ring), 72.34 (CH), 47.53 (CH_2). *Anal.* Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.15; H, 6.70: N, 15.35.

(2-Hydroxy-1-phenylethyl)urea (Id): Colorless prisms (from ethanol–water), mp 188 °C (lit.,[6] 167.5 °C). Yield, 2.4 g (66%). IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 3260 (NH_2, NH), 1620 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 6.45 (NH_2), 5.51 (NH). ^{13}C-NMR (DMSO-d_6) δ: 158.58 (C=O), 142.54, 128.00, 126.83, 126.54 (phenyl ring), 65.31 (CH_2), 55.26 (CH_2). *Anal.* Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.90; H, 6.75; N, 15.60.

(1-Hydroxy-2-methyl-2-propyl)urea (Ie): Recrystallized from ethanol–ether–water several times. Colorless prisms, mp 100—105 °C. Yield, 4.0 g (61%). IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 3300 (NH_2), 3150 (NH), 1640 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 5.88 (NH), 5.45 (NH_2), 3.32 (CH_2), 1.15 (CH_3). ^{13}C-NMR (DMSO-d_6) δ: 159.21 (C=O), 69.32 (CH_2), 53.12 (C(CH_3)), 24.40 (CH_3). *Anal.* Calcd for $C_5H_{12}N_2O_2$: C, 45.44; H, 9.15; N, 21.20. Found: C, 44.48; H, 9.06; N, 21.30.

1-(2-Hydroxyethyl)-1-methylurea (If): Recrystallized from ethanol–ether twice, then from a large volume of dioxane. Colorless needles, mp 66—68 °C. Yield, 1.8 g (57%). IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 3350, 3200 (NH, NH_2), 1650 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 5.79 (NH_2), 4.60 (NH), 3.47 (CH_2), 3.21 (CH_2), 2.81 (CH_3). ^{13}C-NMR (DMSO-d_6) δ: 159.33 (C=O), 59.57 (CH_2), 50.84 (CH_2), 35.17 (CH_3). *Anal.* Calcd for $C_4H_{10}N_2O_2$: C, 40.66; H, 8.53; N, 23.71. Found: C, 40.39; H, 8.64; N, 23.56.

o-Hydroxyphenylurea (Ig): Potassium cyanide (2.0 g) was added to a solution of *o*-hydroxyaniline hydrochloride (3.0 g) in water (50 ml) in small portions. The resulting precipitates were filtered, and recrystallized from water. Colorless needles, mp 168 °C (lit.,[7] 154 °C). Yield, 0.6 g (20%). IR ν_{max}^{Nujol} cm^{-1}: 3440 (OH), 3300 (NH), 1630 (C=O), 1540, 1200, 1100, 1040, 870, 650. ^{1}H-NMR (DMSO-d_6) δ: 9.91 (NH), 7.99 (OH), 6.15 (NH_2), 7.85, 6.5—6.8 (ring protons). ^{13}C-NMR (DMSO-d_6) δ: 156.77 (C=O), 146.00, 128.31, 121.87, 119.31, 119.17, 115.25. *Anal.* Calcd for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.55; H, 5.32; N, 18.13.

(3-Hydroxy-1-propyl)urea (Ih): Colorless prisms, mp 118 °C (lit.,[4] 119 °C). Yield, 84%. IR ν_{max}^{Nujol} cm^{-1}: 3410 (OH), 3280 (NH), 1640 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 6.04 (NH), 5.50 (NH_2), 4.57 (OH), 3.41, 3.00, 1.51. ^{13}C-NMR (DMSO-d_6) δ: 159.43 (C=O), 58.62, 36.49, 33.30.

(2-Methoxyethyl)urea (Ii): Colorless needles (from ether), mp 64—65 °C (lit.,[8] 63 °C). Yield, 6.2 g (94%). IR ν_{max}^{Nujol} cm^{-1}: 3350 (NH_2), 3210 (NH), 1640 (C=O), 1110 (–O–). ^{1}H-NMR (DMSO-d_6) δ: 6.01 (NH), 5.46 (NH_2), 3.30 (CH_2), 3.25 (CH_2), 3.13 (CH_2). ^{13}C-NMR (DMSO-d_6) δ: 158.70 (C=O), 71.66, 57.82, 38.99.

1-(2-Hydroxyethyl)-3-methylurea (Ij): Ethanolamine (2.0 g) was dissolved in ether (200 ml) with vigorous stirring. A solution of methyl isocyanate (1.9 g) in benzene (30 ml) was added dropwise to the solution at 10 °C with stirring. After 30 min, the solution was concentrated to give a viscous liquid under reduced pressure, and the resulting liquid was treated with ether and dioxane. Colorless prisms,[9] 27—30 °C. Yield, 2.9 g (73%). IR ν_{max}^{neat} cm^{-1}: 3400 (OH), 3350 (NH), 1620 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 6.1 (NH), 4.48 (OH), 2.53 (CH_3), 3.04, 3.35. ^{13}C-NMR (DMSO-d_6) δ: 158.917 (C=O), 60.88, 42.18, 26.22. *Anal.* Calcd for $C_4H_{10}N_2O_2 \cdot 1/4H_2O$: C, 39.14; H, 8.56; N, 22.84. Found: C, 39.23; H, 8,50; N, 22.72.

Nitrosation of (2-Hydroxyethyl)urea Derivatives (IIa—g)——A typical experiment is described for the case of IIa.

3-Nitroso-2-oxazolidinone (IIa): Urea (Ia) (1.0 g) was dissolved in 10% hydrochloric acid (5 ml) at 0 °C with stirring, and a solution of sodium nitrite (1.0 g) in water (1 ml) was added dropwise at 0—2 °C. The reaction mixture was stirred further for 1 h at 0 °C, then extracted with ether. The combined extracts were dried over anhyd. sodium sulfate, and evaporated under reduced pressure. The residue was recrystallized from ether–*n*-hexane. Pale yellow prisms, mp 41 °C (lit.,[8] 51 °C). Yield, 270 mg (23%). IR ν_{max}^{Nujol} cm^{-1}: 1800 (C=O), 1160 (–O–), 1480 (NO), 1380, 1340, 1020, 970, 840, 750. Mass spectrum (MS) (*m/e*): 116.013 (M^+). *Anal.* Calcd for $C_3H_4N_2O_3$: C, 31.04; H, 3.47; N, 24.14. Found: C, 30.85; H, 3.72; N, 24.26.

5-Methyl-3-nitroso-2-oxazolidinone (IIb): Pale yellow needles (from *n*-hexane–ether), mp 30—32 °C. Yield, 251 mg (19%). IR ν_{max}^{Nujol} cm^{-1}: 1815 (C=O), 1495, 1345, 1160. ^{1}H-NMR ($CDCl_3$) δ: 4.87 (–CH), 4.08 (1H, dd, CH_2), 3.42 (1H, dd, CH_2), 1.52 (3H, d, CH_2). MS (*m/e*): 130.032 (M^+). *Anal.* Calcd for $C_4H_6N_2O_3$: C, 36.93; H, 4.65; N, 21.53. Found: C, 36.85; H, 4.71; N, 21.78.

3-Nitroso-5-phenyl-2-oxazolidinone (IIc): Pale yellow needles (from ether–hexane), mp 76—79 °C (lit.,[10] 76.5—77.5 °C). Yield, 0.75 g (77%). IR ν_{max}^{Nujol} cm^{-1}: 1800 (C=O), 1480, 1340, 1150 (–O–), 900, 730. ^{1}H-NMR ($CDCl_3$) δ: 5.72 (1H, dd, CH), 4.37 (1H, dd, CH_2), 3.75 (1H, dd, CH_2).

3-Nitroso-4-phenyl-2-oxazolidinone (IId): Yellow crystalline powder, mp 105—107 °C. Yield, 55 mg (10%). IR ν_{max}^{KBr} cm^{-1}: 1790 (C=O), 1510, 1380, 1300, 1130, 1010, 880, 770, 700. *Anal.* Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 55.98; H, 4.46; N, 14.78.

When the urea (Id) (0.45 g) was nitrosated in formic acid (1 ml) or acetic acid (7 ml), the yields improved to 52 and 50%, respectively.

4,4-Dimethyl-2-oxazolidinone (IIIe): Recrystallized from *n*-hexane–ether, then from ether–ethanol. When the crude product was left at room temperature, the intensity of the peak at 1740 cm^{-1} increased at the expense of that at 1800 cm^{-1}. The ratio of 4,4-dimethyl-3-nitroso-2-oxazolidinone (IIe) and 4,4-dimethyl-2-oxazolidinone (IIIe) in the crude mixture was determined from the intensities of the signals due to the methyl groups (1.53 ppm for IIe, 1.41 ppm for IIIe) in the ^{1}H-NMR spectra. The peak at 1.41 ppm disappeared in 2—3 h.

NII-Electronic Library Service

Colorless needles, mp 54 °C (lit.,[11] 55—56 °C). IR ν_{max}^{Nujol} cm^{-1}: 1740, 1480, (DMSO-d_6) δ: 4.20 (2H, s, NH_2), 3.93 (1H, br, OH), 1.52 (3H, s, CH_3).

3-Methyl-2-oxazolidinone (IIf): Oil. fp 16—18 °C (lit.,[12] fp 15 °C). Yield, 0.34 g (65%). IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O), 1280, 1130, 1040 (–O–), 950, 830, 760. ^{1}H-NMR ($CDCl_3$) δ: 4.43 (2H, dd, $-CH_2-$), 3.67 (2H, dd, $-CH_2-$), 2.90 (3H, s, CH_3). ^{13}C-NMR ($CDCl_3$) δ: 159.47 (C=O), 61.92 (CH_2), 46.50 (CH_2), 30.54 (CH_3).

2-Benzoxazolidinone (IIg): Dark brown crystalline powder, mp 138 °C. (lit.,[13] 138—139 °C). Yield, 0.25 g (18%). IR ν_{max}^{Nujol} cm^{-1}: 3200 (NH), 1760, 1720, 1470, 1300, 1250, 1140, 934, 740. ^{1}H-NMR (DMSO-d_6) δ: 11.67 (1H, s, NH), 7.12 (4H, m, ring protons).

Denitrosation of 3-Nitroso-2-oxazolidinones (IIa—d)——A typical experiment is described for the case of IIIa.

2-Oxazolidinone (IIIa): 3-Nitroso-2-oxazolidinone (IIa) (0.60 g) was dissolved in dry methanol (50 ml), and dry hydrogen chloride was bubbled into the solution at 0 °C, until the solution turned red. The reaction mixture was stirred for 15 min at 0 °C, then at room temperature for 15 min. After the color of the reaction mixture had faded, the solution was evaporated to dryness under reduced pressure at below 30 °C and the residue was recrystallized from methanol. Colorless needles, mp 86—89 °C (lit.,[14] 89 °C). Yield, 0.16 g(35%). IR ν_{max}^{Nujol} cm^{-1}: 3230 (NH), 1710 (C=O), 1245 (–O–), 1080, 1020, 960, 910, 800. ^{1}H-NMR (DMSO-d_6) δ: 7.40 (1H, br, NH), 4.29 (2H, t, CH_2), 3.47 (2H, t, CH_2). ^{13}C-NMR (DMSO-d_6) δ: 157.67 (C=O), 40.38, 39.96.

5-Methyl-2-oxazolidinone (IIIb): Colorless prisms, mp 15—17 °C (lit.,[15] bp 136—137 °C/5 mm). Yield, 38%. IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1740 (C=O), 1220 (–O–), 1060, 960, 760. ^{1}H-NMR (DMSO-d_6) δ: 5.66 (1H, br, NH), 4.82 (1H, m, CH).

5-Phenyl-2-oxazolidinone (IIIc): Colorless needles, mp 89—90 °C, (lit.,[2] 87—88 °C). Yield, 57%. IR ν_{max}^{Nujol} cm^{-1}: 3250 (NH), 1700 (C=O), 1235 (–O–), 1070, 965, 755, 690. ^{1}H-NMR (DMSO-d_6) δ: 6.52 (1H, br, NH), 5.6 (1H, dd, CH), 4.05 (1H, dd, CH_2), 3.55 (1H, dd, CH_2).

4-Phenyl-2-oxazolidinone (IIId): Colorless prisms, mp 127—128 °C (lit.,[2] 127.8 °C). Yield, 60%. IR ν_{max}^{Nujol} cm^{-1}: 3200 (NH), 1735 (C=O), 1230 (–O–), 910. ^{1}H-NMR (DMSO-d_6) δ: 6.3 (1H, br, NH), 4.95 (1H, dd, CH), 4.71 (1H, dd, CH_2).

Nitrosation of (2-Hydroxyethyl)urea (Ia) with Nitrosyl Chloride——Finely powdered urea (Ia) (0.50 g) was suspended in dry chloroform (300 ml) at 0 °C with stirring, and nitrosyl chloride (0.50 g) in chloroform (50 ml) was added. The reaction mixture was stirred until the crystals disappeared keeping the temperature at 0 °C. The solution was concentrated under reduced pressure, and the residue was recrystallized from *n*-hexane–ether. Yield, 0.28 g (42%).

Acknowledgment The authors are indebted to Dr. N. Miyata for useful discussions.

References and Notes

1) *a*) M. Miyahara, M. Nakadate, M. Miyahara and I. Suzuki, *Chem. Pharm. Bull.*, **26**, 2635 (1978); *b*) Mi. Miyahara, S. Kamiya, M. Nakadate, S. Sueyoshi, M. Tanno and M. Miyahara, *Eisei Shikensho Hokoku*, **100**, 163 (1982).
2) Mi. Miyahara, M. Miyahara, S. Kamiya and A. Maekawa, *Chem. Pharm. Bull.*, **29**, 2366 (1981).
3) The following instruments were used to obtain physical data. IR spectra: a JASCO model IR 102 spectrophotometer; NMR spectra: a Varian model EM 360A spectrometer and a JEOL model FX 200 spectrometer (^{13}C, 50.1 MHz, digital resolution 0.012 ppm; ^{1}H, 199.5 MHz, digital resolution 0.001 ppm). Melting points are uncorrected. The melting points of some compounds obtained in this work were significantly different from those reported in the literature, and these compounds were subjected to elemental analysis.
4) P. W. Charlton and A. R. Day, *J. Org. Chem.*, **1**, 552 (1937).
5) C. Mannich and Thiele, *Archiv der Pharmazie*, **253**, 188 (1915); *idem, Beil.*, **13**, I 242 (1933).
6) A. Kötz and Schneider, *J. Prakt. Chem.* (*2*), **90**, 139 (1914); *idem, Beil.*, **13**, I 243 (1933).
7) F. Kalckhoff, *Ber.*, **16**, 374 (1883).
8) W. Traube and E. Peiser, *Ber.*, **53**, 1508 (1920).
9) Y. Yoshizaki, Y. Kondo, and T. Takemoto, *Heterocycles*, **3**, 827 (1975).
10) M. S. Newman and A. Kutner, *J. Am. Chem. Soc.*, **73**, 4199 (1951).
11) A. H. Homeyer, U. S. Patent 2399118 (1946) [*Chem. Abstr.*, **40**, 4084 (1946)].
12) J. B. Bell, Jr. and J. D. Malkemus, U. S. Patent 2755286 (1956) [*Chem. Abstr.*, **51**, 2871 (1957)].
13) C. Graebe and A. Rostovzeff, *Ber.*, **35**, 2747 (1902).
14) C. Scholtissek, *Chem. Ber.*, **89**, 5262 (1956).
15) E. Katchalski and D. B. Ishai, *J. Org. Chem.*, **15**, 1067 (1950).

NII-Electronic Library Service