[Chem. Pharm. Bull. 34(8)3202—3207(1986)]

An Improved Synthesis of *N*-Hydroxyamino Acids and Their Esters Using (*Z*)-2-Furaldehyde Oxime

GIICHI GOTO,*[,a] KENJI KAWAKITA,[a] TETSUYA OKUTANI,[a] and TAKUICHI MIKI[b]

Central Research Division, Takeda Chemical Industries, Ltd.,[a] Jusohonmachi, Yodogawa-ku, Osaka 532, Japan and Faculty of Pharmaceutical Sciences, Setsunan University,[b] Nagaotoge-cho, Hirakata, Osaka 573-01, Japan

(Received January 31, 1986)

A series of *N*-hydroxyamino acids and their esters (**9a**, **b**, **d**—**k**) coupled with *N*-hydroxyglycinamide (**9c**) were synthesized through facile preparations of *N*-furfurylidenealkoxy (and hydroxy) carbonylalkylamine *N*-oxides (**7a**, **b**, **d**—**g**) and *N*-furfurylidenecarbamoylmethylamine *N*-oxide (**7c**) followed by hydrolysis. The method was applied to the syntheses of emimycin (**1**) and hadacidin monosodium salt (**2b**).

Keywords——*N*-hydroxyamino acid; *N*-hydroxyamino acid ester; *N*-hydroxyglycinamide; emimycin; hadacidin; nitrone; (*Z*)-2-furaldehyde oxime

N-Hydroxyamino acids are useful intermediates for the synthesis of several naturally occurring pyrazine *N*-oxides[1] and have also been identified as component(s) of various peptidyl antibiotics[2] isolated from microbial cultures. Emimycin (**1**)[1a,3] and hadacidin (**2a**)[4] are simple examples of the biologically active pyrazine *N*-oxides and *N*-hydroxyamino acids, respectively. Most of the methods so far reported[5] for the synthesis of *N*-hydroxyamino acids and their esters suffer from defects such as low yield or limited applicability. In this paper, we wish to describe an improved method for the synthesis of *N*-hydroxyamino acids, their esters (**9a**, **b**, **d**—**k**) and *N*-hydroxyglycinamide (**9c**), together with an application to the syntheses of emimycin (**1**) and hadacidin monosodium salt (**2b**).

Of the numerous methods employed in the synthesis of *N*-hydroxyamino acids, the one[6] using the nitrone of (*Z*)-benzaldehyde oxime seemed to be most convenient and useful. An important feature of the method was selective *N*-alkylation of (*Z*)-benzaldehyde oxime. However, since (*Z*)-benzaldehyde oxime readily isomerizes to the thermodynamically more stable (*E*)-isomer,[7] the formation of considerable amounts of *O*-alkylated product was unavoidable.[8] In addition, a troublesome isomerization[7] of (*E*)-benzaldehyde oxime to the (*Z*)-isomer was required. These problems appeared to us to be soluble by the use of (*Z*)-2-furaldehyde oxime (**3**),[9] which is thermodynamically more stable than the (*E*)-isomer (**5**) (*vide infra*).

Reaction of 2-furaldehyde (**4**) and hydroxylamine hydrochloride in the presence of sodium hydroxide in water gave selectively (*Z*)-2-furaldehyde oxime (**3**) in 91% yield. When this reaction was carried out in methanol, the product was a mixture of the (*Z*)- and (*E*)-isomers of 2-furaldehyde oxime in a ratio of 8 : 2. On the other hand, treatment of **4** with hydroxylamine hydrogen sulfate in water afforded selectively (*E*)-2-furaldehyde oxime (**5**)[9c] in 88% yield. Each of the pure isomers (**3** and **5**) was equilibrated with hydrochloric acid in methanol to yield a mixture of (*Z*)- and (*E*)-2-furaldehyde oxime in almost the same ratio (75 : 25). The result shows that (*Z*)-2-furaldehyde oxime (**3**) is thermodynamically more stable than the (*E*)-isomer (**5**).[10]

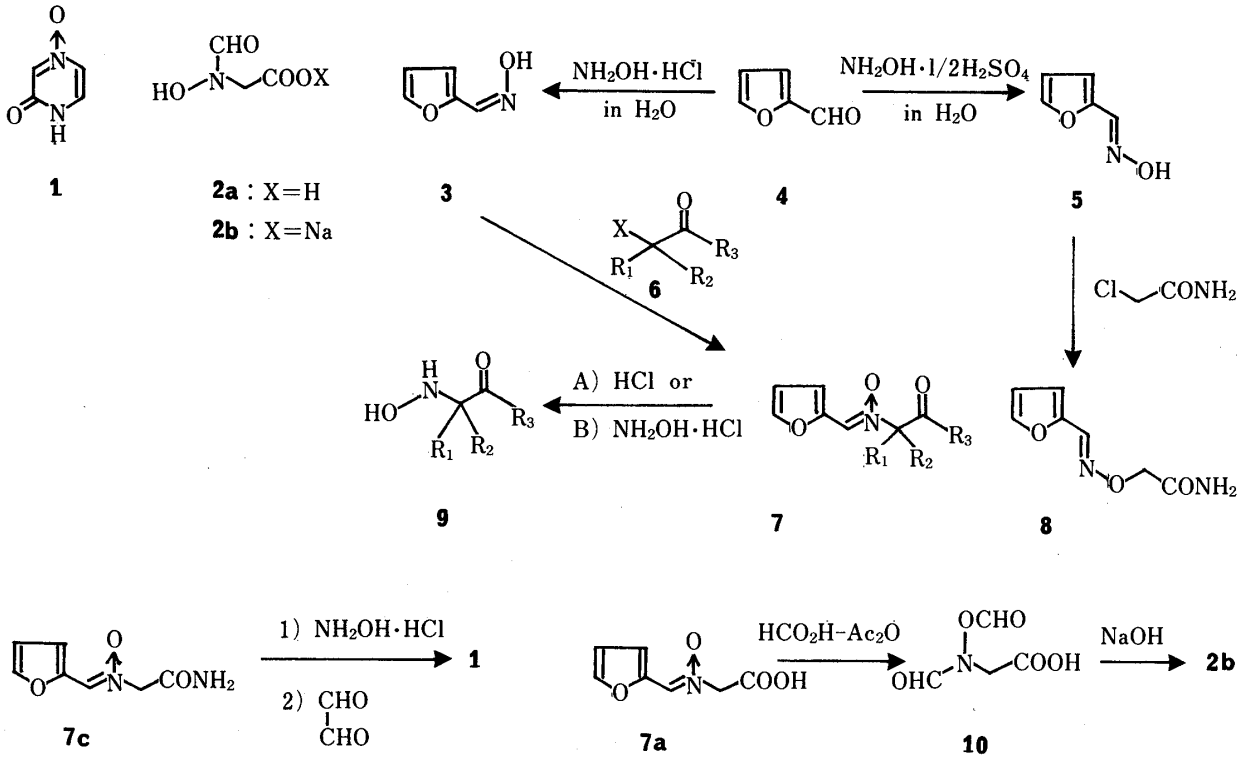


Chart 1

TABLE I. Melting Points and Elemental Analyses of *N*-Furfurylidenealkoxy-(and hydroxy)carbonylalkylamine *N*-Oxides (**7a**, **b**, **d**—**g**) and *N*-Furfurylidenecarbamoylmethylamine *N*-Oxide (**7c**)

7	R_1	R_2	R_3	Yield[a] (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
a	H	H	OH	64	177—180	$C_7H_7NO_4$	49.71 (49.93)	4.17 4.29	8.28 8.04)
b	H	H	OMe	77	81	$C_8H_9NO_4$	52.46 (52.55)	4.95 4.76	7.65 7.71)
c	H	H	NH_2	82	175—176	$C_7H_8N_2O_3$	50.00 (49.86)	4.80 4.76	16.66 16.64)
d	Me	H	OEt	87	111—112	$C_{10}H_{14}NO_4$	56.86 (56.84)	6.20 6.14	6.63 6.60)
e	Me	Me	OEt	89	59	$C_{11}H_{15}NO_4$	58.65 (58.74)	6.71 6.75	6.22 6.37)
f	Et	H	OEt	77	72	$C_{11}H_{15}NO_4$	58.65 (58.77)	6.71 6.79	6.22 6.28)
g	C_6H_5	H	OEt	74	95—96	$C_{15}H_{15}NO_4$	65.92 (65.92)	5.53 5.45	5.13 5.18)

a) Isolated yield after recrystallization from ether.

Treatment of **3** with the appropriate α-halogenocarboxylic acid derivatives (**6**) in the presence of sodium alkoxide afforded *N*-furfurylidenealkoxy(and hydroxy)carbonylalkylamine *N*-oxides (**7a**, **b**, **d**—**g**) in good yields. When 2-chloroacetamide was used as the halide, *N*-furfurylidenecarbamoylmethylamine *N*-oxide (**7c**) was obtained in high yield (Tables I and II).[11] On the other hand, the reaction of **5** with 2-chloroacetamide gave mainly the iminoether

TABLE II. Spectral Data for *N*-Furfurylidenealkoxy(and hydroxy)carbonylalkylamine *N*-Oxides (**7a**, **b**, **d**—**g**) and *N*-Furfurylidenecarbamoylmethylamine *N*-Oxide (**7c**)

7	UV λ_{max}^{EtOH} nm (ε)	IR ν_{max}^{KBr} cm^{-1}		N=CH (1H, s)	N–CH–CO	^{1}H-NMR ($CDCl_3$) δ Furan			Others
		C=O	C=N			H_3 (d, J=5 Hz)	H_4 (dd, J=5, 2 Hz)	H_5 (d, J=2 Hz)	
a[a]	308 (18200)	1715	1603	8.05	4.73 (2H, s)	7.58	6.63	7.78	10.7 (1H, br s, COOH)
b	310 (18400)	1740	1605	7.60	4.67 (2H, s)	7.77	6.52	7.47	3.79 (3H, s, OMe)
c	309 (18200)	1695[b] 1705	1620	8.00	4.57 (2H, s)	7.57	6.60	7.78	7.32 (2H, br s, NH_2)
d	310 (18000)	1740	1595	7.63	4.70 (1H, q, J=7 Hz)	7.77	6.52	7.47	1.25 (3H, t, J=7 Hz, Me), 1.71 (3H, d, J=7 Hz, Me), 4.23 (2H, q, J=7 Hz, OCH_2)
e	310 (18000)	1735	1590	7.67	—	7.75	6.52	7.47	1.78 (6H, s, Me_2), 1.26 (3H, t, J=7 Hz, Me), 4.23 (2H, q, J=7 Hz, OCH_2)
f	310 (18100)	1735	1595	7.67	4.45 (1H, dd, J_1=8 Hz, J_2=6 Hz)	7.82	6.54	7.50	1.00 (3H, t, J=7 Hz, Me), 1.27 (3H, t, J=7 Hz, Me), 1.9—2.6 (2H, m, CH_2), 4.24 (2H, q, J=7 Hz, OCH_2)
g	313 (18500)	1740	1595	7.32	5.74 (1H, s)	7.78	6.50	7.42	1.27 (3H, t, J=7 Hz, Me), 4.28 (2H, q, J=7 Hz, OCH_2), 7.47 (5H, s, Ar)

a) ^{1}H-NMR was taken in DMSO-d_6. *b*) Two different bands of C=O were observed.

TABLE III. Physicochemical Data for *N*-Hydroxyamino Acids (**9a**, **d**, **f**, **h**, **j**), Their Esters (**9b**, **e**, **g**, **i**, **k**) and *N*-Hydroxyglycinamide (**9c**)

9	R_1	R_2	R_3	Method[a]	Yield[b] (%)	mp (°C)	State	Formula	Analysis (%) Calcd (Found)		
									C	H	N
a	H	H	OH	A	72	138—139	Free	$C_2H_5NO_3$	26.38	5.53	15.38
									(26.41	5.49	15.27)
b	H	H	OMe	B	95	90—91	HCl salt	$C_3H_8ClNO_3$	25.45	5.70	9.90
									(25.46	5.90	9.93)
c	H	H	NH_2	B	98	138—140	HCl salt	$C_2H_7ClN_2O_2$	18.98	5.58	22.14
									(18.99	5.47	22.11)
d[c]	Me	H	OH	A	56	147	Free	$C_3H_7NO_3$	34.28	6.71	13.33
									(34.47	6.67	13.28)
e[d]	Me	H	OEt	B	93	Oil	HCl salt	$C_5H_{12}ClNO_3$	35.41	7.13	8.26
									(35.49	7.21	8.13)
f	Me	Me	OH	A	66	136—138	Free	$C_4H_9NO_3$	40.33	7.62	11.76
									(40.27	7.71	11.79)
g	Me	Me	OEt	B	89	88—89	HCl salt	$C_6H_{14}ClNO_3$	39.24	7.69	7.63
									(39.15	7.79	7.70)
h	Et	H	OH	A	52	126—129	Free	$C_4H_9NO_3$	40.33	7.62	11.76
									(40.50	7.81	11.77)
i[e]	Et	H	OEt	B	88	61—62	HCl salt	$C_6H_{14}ClNO_3$	39.24	7.69	7.63
									(39.29	7.73	7.86)
j[c]	C_6H_5	H	OH	A	39	131—132	Free	$C_8H_9NO_3$	57.48	5.43	8.38
									(57.49	5.52	8.22)
k	C_6H_5	H	OEt	B	94	135—137	HCl salt	$C_{10}H_{14}ClNO_3$	51.84	6.09	6.05
									(51.76	6.11	6.21)

a) Method A: Hydrolysis with 35% HCl. Method B: Cleavage with $NH_2OH \cdot HCl$. *b*) Isolated yield. *c*) Ref. 6*a*. *d*) Ref. 6*b*. *e*) Ref. 5*k*.

(**8**) along with a small amount of **7c**. The formation of **7c** from **5** suggests that the isomerization[12] occurred before the *N*-alkylation. The nitrones (**7**) were converted to *N*-hydroxyamino acids (**9a**, **d**, **f**, **h**, **j**) by hydrolysis with hydrochloric acid (A) or to *N*-hydroxyamino acid esters (**9b**, **e**, **g**, **i**, **k**) and *N*-hydroxyglycinamide (**9c**) by cleavage with hydroxylamine hydrochloride (B) in good yields (Table III). In addition, it was found that the 2-furaldehyde oxime recovered in method B was exclusively the (*Z*)-isomer (**3**). It is an advantage of this method that the recycling of **3** is feasible.

By utilizing the present method, emimycin (**1**) and hadacidin monosodium salt (**2b**) were conveniently synthesized as follows. Reaction of **7c** with *N*-hydroxylamine hydrochloride in water gave **9c** in an almost quantitative yield. Without purification, the resulting solution was treated with glyoxal in the presence of sodium hydroxide at 5 °C to afford **1** in 91% yeild after purification by column chromatography on activated charcoal. On the other hand, the nitrone (**7a**) was cleaved with concomitant formylation by treatment with a mixture of formic acid and acetic anhydride (2 : 1) at room temperature and the intermediate (**10**) was hydrolyzed with sodium hydroxide to give hadacidin monosodium salt (**2b**) in 87% yield. The physicochemical data of the synthetic products (**1** and **2b**) were in good agreement with the reported values.[3,4,7c]

Experimental

All melting points were determined on a micro hot stage apparatus and are uncorrected. Infrared (IR) spectra and ultraviolet (UV) spectra were taken with a Hitachi 215 spectrophotometer and a Hitachi EPS-3T spectrophoto-

meter, respectively. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM-390 (90 MHz) with tetramethylsilane (TMS) as an internal standard. Chemical shifts were given as δ values (ppm): s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad.

(*Z*)-2-Furaldehyde Oxime (3)——An aqueous solution of NaOH (40 g in 150 ml of H_2O) was added dropwise to a solution of 2-furaldehyde (96.1 g) and $NH_2OH \cdot HCl$ (69 g) in H_2O (250 ml) with stirring under cooling in an ice bath over a period of 2 h. Stirring was continued for an additional 1 h and the resulting crystals were washed with cold H_2O (300 ml), followed by drying over P_2O_5. Recrystallization from ether–hexane (1 : 1) gave colorless needles (101 g, 91%), mp 89—91 °C. *Anal.* Calcd for $C_5H_5NO_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.06; H, 4.39; N, 12.41. IR ν_{max}^{KBr} cm^{-1}: 3150, 3050 (OH). 1640 (C=N). UV λ_{max}^{EtOH} nm (ε): 264 (8000). ^{1}H-NMR ($CDCl_3$) δ: 6.45 (1H, dd, J_1=5 Hz, J_2=2 Hz, furan-H$_4$), 7.30 (1H, d, J=5 Hz, furan-H$_3$), 7.42 (1H, d, J=2 Hz, furan-H$_5$), 7.47 (1H, s, N=CH), 10.04 (1H, br s, OH).

(*E*)-2-Furaldehyde Oxime (5)——An aqueous solution of NaOH (82 g in 300 ml of H_2O) was added dropwise to a solution of 2-furaldehyde (192 g) and $NH_2OH \cdot 1/2H_2SO_4$ (164 g) in H_2O (700 ml) with stirring under cooling in an ice bath over a period of 3 h. Stirring was continued for an additional 1 h and the resulting crystals were washed with cold H_2O (600 ml), followed by drying over P_2O_5. Recrystallization from ether–hexane (1 : 1) gave colorless needles (196 g, 88%), mp 70—75 °C. *Anal.* Calcd for $C_5H_5NO_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.02; H, 4.41; N, 12.08. IR ν_{max}^{KBr} cm^{-1}: 3154 (OH), 1635 (C=N). UV λ_{max}^{EtOH} nm (ε): 269 (7800). ^{1}H-NMR ($CDCl_3$) δ: 6.38 (1H, dd, J_1=5 Hz, J_2=2 Hz, furan-H$_4$), 6.60 (1H, d, J=5 Hz, furan-H$_3$), 7.43 (1H, d, J=2 Hz, furan-H$_5$), 8.00 (1H, s, N=CH), 9.91 (1H, br s, OH).

***N*-Furfurylidenemethoxycarbonylmethylamine *N*-Oxide (7b)**——Na (0.7 g) was dissolved in EtOH (20 ml) under an N_2 atmosphere, and the resulting solution was added to a solution of **3** (3.4 g) and methyl bromoacetate (**6**: R_1=R_2=H, R_3=OCH_3, X=Br; 4.7 g) in EtOH (15 ml).[13] The mixture was stirred at 40 °C for 2 h and then the excess solvent was removed. H_2O (100 ml) was added to the residue and the product was extracted with ether, followed by drying over Na_2SO_4. The solvent was evaporated to give crystals. Recrystallization from ether yielded **7b** (4.3 g) as colorless needles.

The other compounds (**7a, c—g**) were prepared by the same method as described above, and the physicochemical data are listed in Tables I and II.

(*E*)-2-Furaldehyde Oxime *O*-Carbamoylmethyl Ether (8)——Na (2.3 g) was dissolved in EtOH (100 ml) under an N_2 atmosphere, and the resulting solution was added to a solution of **5** (11.1 g) and 2-chloroacetamide (7.0 g) in EtOH (30 ml). The mixture was stirred at 50 °C for 2 h. The excess solvent was removed and the residue was extracted with ether. The extracts were washed with H_2O, followed by drying over Na_2SO_4. Evaporation of the solvent gave crystals, which were recrystallized from ether to give **8** (10.9 g, 65%) as colorless needles, mp 95 °C. *Anal.* Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.89; H, 4.93; N, 16.68. IR ν_{max}^{KBr} cm^{-1}: 3400, 3200, 1660, 1620. UV λ_{max}^{EtOH} nm (ε): 275 (8300). ^{1}H-NMR ($CDCl_3$) δ: 4.60 (2H, s, OCH_2), 6.1—6.7 (2H, br, NH_2), 6.42 (1H, dd, J_1=5 Hz, J_2=2 Hz, furan-H$_4$), 6.67 (1H, d, J=5 Hz, furan-H$_3$), 7.45 (1H, d, J=2 Hz, furan-H$_5$), 8.05 (1H, s, N=CH).

Concentration of the mother liquors yielded an oil (2.1 g), which was chromatographed on silica gel (200 g) with CH_2Cl_2–CH_3OH (10 : 1) as an eluent. The eluates (about 200 ml) were concentrated to afford crystals. Recrystallization from ether gave colorless needles (1.3 g, 7.7%), mp 175—176 °C. The physicochemical data of the product were fully consistent with those of **7c**.

***N*-Hydroxyamino Acids (9: R_3=OH)**——Method A: A mixture of **7** (R_3=OH and *O*-alkyl; 10 mmol) in 35% HCl (7 ml) was heated to 80 °C for 5 min. The solution was evaporated to dryness under reduced pressure and the residue was dissolved in H_2O (1 ml). Conc. NH_4OH was added to adjust the pH to 5.5. After the addition of EtOH (2 ml), the resulting crystals were recrystallized from EtOH to give **9** (R_3=OH) as colorless needles (Table III).

***N*-Hydroxyamino Acid Esters and Amide (9: R_3 = *O*-Alkyl and NH_2)**——Method B: A mixture of **7** (R_3=*O*-alkyl and NH_2: 10 mmol) and $NH_2OH \cdot HCl$ (10 mmol in CH_3OH–H_2O (1 : 1) (20 ml) was stirred at room temperature for 4 h. After the removal of the excess CH_3OH, the crystals (**3**) were filtered off and the filtrates were evaporated to dryness, giving crude crystals. Recrystallization from ether containing 1% CH_3OH gave **9**·HCl (R_3=*O*-alkyl and NH_2) as colorless needles (Table III).

2(1*H*)-Pyrazinone 4-Oxide (Emimycin) (1)——A mixture of **7c** (8.4 g) and $NH_2OH \cdot HCl$ (3.5 g) in H_2O (20 ml) was stirred for 1 h at room temperature, then cooled to 5 °C. The resulting crystals (**3**) were filtered off and the filtrates were added to a solution of 20% glyoxal (20 ml, 1.4 eq) in H_2O (20 ml) at 5 °C under an N_2 atmosphere. A solution of 5.5 N NaOH (20 ml, 2.5 eq) was added and the mixture was stirred at 5 °C for 15 min. After the addition of 1 N HCl solution (50 ml), the whole was passed through a column of activated charcoal to adsorb the product. The column was washed with distilled water (90 ml) and then eluted with CH_3OH–H_2O–28% NH_4OH (25 : 24 : 1). The eluates (about 300 ml) were concentrated under reduced pressure to one-third of the original volume. The remaining solution was lyophilized and the residue (pale yellow powder) was recrystallized from EtOH–ether (1 : 1) to give **1** (5.1 g 91%) as pale yellow needles, mp 245—252 °C (dec.) [lit.[1a,3] mp 250 °C (dec.)]. *Anal.* Calcd for $C_4H_4N_2O_2 \cdot 1/4H_2O$: C, 41.20; H, 3.89; N, 24.03. Found: C, 41.49; H, 3.62; N, 24.27. IR ν_{max}^{KBr} cm^{-1}: 3400, 1640. UV $\lambda_{max}^{H_2O}$ nm (ε) 332 (4040). ^{1}H-NMR (DMSO-d_6) δ: 7.13 (1H, dd, J_1=6 Hz, J_2=2 Hz, H$_5$), 7.48 (1H, d, J=2 Hz, H$_3$), 7.53 (1H, d, J=6 Hz, H$_6$).

***N*-Formyl-*N*-hydroxyglycine (Hadacidin) Monosodium Salt (2b)**——A mixture of **7a** (3.38 g) in HCOOH–Ac_2O

(2 : 1) (15 ml) was stirred at 5 °C for 4 h. The solution was cooled to 0 °C, and the excess acids were neutralized to pH 3.7[7c] at a temperature bellow 5 °C by careful addition of 4 N NaOH solution (about 24 ml). The aqueous solution was washed twice with ether to remove 2-furaldehyde formed. The solution was concentrated to half of its original volume at a temperature below 10 °C, and then EtOH (70 ml) was added slowly with stirring. The solution was kept at 0 °C for 12 h and the precipitates were collected by filtration, washed with EtOH and dried over $CaCl_2$ to give **2b** (3.1 g; 87%), mp 190—192 °C (lit.[4,7c] mp 191—193 °C). *Anal.* Calcd for $C_3H_4NNaO_4 \cdot 2H_2O$: C, 20.34; H, 4.55; N, 7.91. Found: C, 20.43; H, 4.62; N, 7.69. IR ν_{max}^{KBr} cm^{-1}: 3550—3100, 2900—2600, 1670.

Acknowledgement We are grateful to Dr. K. Hiraga for his encouragement throughout this work, and to Mr. H. Yamamoto for his technical assistance. We are also indebted to the staff members in charge of elemental analyses and measurement of spectral data.

References and Notes

1) *a*) M. Terao, K. Karasawa, N. Tanaka, H. Yonehara, and H. Umezawa, *J. Antibiot. Ser. A*, **13**, 401 (1960); *b*) M. Terao, *ibid., Ser. A*, **16**, 182 (1963); *c*) A. H. Cook and C. A. Slater, *J. Chem. Soc.*, **1956**, 4133; *d*) A. J. Birch, R. A. Massy-Westropp, and R. W. Rickards, *ibid.*, **1956**, 3717; *e*) J. D. Dutcher, *J. Biol. Chem.*, **171**, 321 (1947); *f*) *Idem, ibid.*, **171**, 341 (1947); *g*) Y. Maebayashi, M. Sumita, K. Fukushima, and M. Yamazaki, *Chem. Pharm. Bull.*, **26**, 1320 (1978).

2) For example, *a*) *δ-N*-hydroxyornithine in ferrichromes: J. Turkova, O. Mikes, and F. Sorm, *Collect. Czech. Chem. Commun.*, **27**, 591 (1962); *b*) *ε-N*-hydroxylysine in mysobactin: G. A. Snow, *J. Chem. Soc.*, **1954**, 2588.

3) M. Mano, T. Seo, and K. Imai, *Chem. Pharm. Bull.*, **28**, 2720 (1980); M. Bobek and A. Bloch, *J. Med. Chem.*, **15**, 164 (1972).

4) E. A. Kaczka, C. O. Gitterman, E. L. Dulaney, and K. Folkers, *Biochemistry*, **1**, 340 (1962).

5) *a*) C. W. Young, G. Schochetman, S. Hodas, and M. E. Balis, *Cancer Res.*, **27**, 535 (1967); *b*) E. Falco and G. B. Brown, *J. Med. Chem.*, **11**, 142 (1968); *c*) L. Neelakantan and W. H. Hartung, *J. Org. Chem.*, **23**, 964 (1958); *d*) L. W. Kissinger and H. E. Ungnade, *ibid.*, **25**, 1471 (1960); *e*) E. F. J. Duynstee, J. L. J. P. Hennenkens, and M. E. A. H. Mevis, *Recl. Trav. Chim. Pays-Bas*, **84**, 1442 (1965); *f*) T. Posner, *Justus Liebigs Ann. Chem.*, **389**, 1 (1912); *g*) N. Grosswicz and Y. Lichtenstein, *Nature* (London), **191**, 412 (1961); *h*) T. F. Emery, *Biochemistry*, **2**, 1041 (1963); *i*) A. H. Cook and C. A. Slater, *J. Chem. Soc.*, **1956**, 4130; *j*) G. C. Lancini, A. Diena, and E. Lazzari, *Tetrahedron Lett.*, **1966**, 1769; *k*) C. Shin, K. Nanjo, E. Ando, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **47**, 3109 (1974); *l*) J. B. Neilands and P. Azari, *Acta Chem. Scand.*, **17**, S 190 (1963); *m*) S. Rogers and J. B. Neilands, *Biochemistry*, **2**, 6 (1963); *n*) J. D. M. Herscheid and H. C. J. Ottenheijm, *Tetrahedron Lett.*, **1978**, 5143.

6) *a*) E. Buehler and G. B. Brown, *J. Org. Chem.*, **32**, 265 (1967); *b*) T. Polonski and A. Chimiak, *ibid.*, **41**, 2092 (1976); *c*) B. Liberek and Z. Palacz, *Roczniki Chemii*, **45**, 1173 (1971).

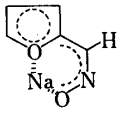
7) *a*) E. Beckmann, *Chem. Ber.*, **23**, 1680 (1890); *b*) O. L. Brady and F. P. Dunn, *J. Chem. Soc.*, **1923**, 1783; *c*) E. F. Schoenewaldt, R. B. Kinnel, and P. Davis, *J. Org. Chem.*, **33**, 4270 (1968).

8) E. Buehler, *J. Org. Chem.*, **32**, 261 (1967).

9) *a*) A. Pinner, *Chem. Ber.*, **23**, 2336 (1890); *b*) H. Goldschmidt and B. Zanoli, *ibid.*, **25**, 2573 (1892); *c*) O. L. Brady and R. F. Goldstein, *J. Chem. Soc.*, **1927**, 1959.

10) The X-ray crystal and ^{1}H-NMR spectral analyses of (*Z*)-2-furaldehyde oxime (**3**) and the (*E*)-isomer (**5**) revealed that **3** and **5** exist exclusively in *s-cis* and *s-trans* forms, respectively, although in the (*Z*)-isomer the intramolecular hydrogen-bonded form is 5.5 kcal/mol more stable than the *s-cis* form: B. Jensen and B. Jerslev, *Acta Chem. Scand.*, **21**, 730 (1967); R. Wasylishen and T. Schaefer, *Can. J. Chem.*, **50**, 274 (1972).

11) The selective *N*-alkylation of **3** could be attributable to steric hindrance at the oxygen atom. In addition, a plausible explanation of the selectivity is the participation of a chelated intermediate such as A, although **3** exists *s-cis* form in the crystalline state.



A

12) Isomerization of **5** to **3** under the reaction conditions was estimated to be about 10—15% by ^{1}H-NMR spectral analysis.

13) Isomerization of **3** under the reaction conditions may be minimized by the addition of sodium ethoxide to the mixture of **3** and **6**.