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

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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; nitron; (*Z*)-2-furaldehyde oxime

N-Hydroxyamino acids are useful intermediates for the synthesis of several naturally occurring pyrazine *N*-oxides¹⁾ and have also been identified as component(s) of various peptidyl antibiotics²⁾ 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 reported⁵⁾ 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 one⁶⁾ using the nitron 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 isomerization⁷⁾ 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⁾

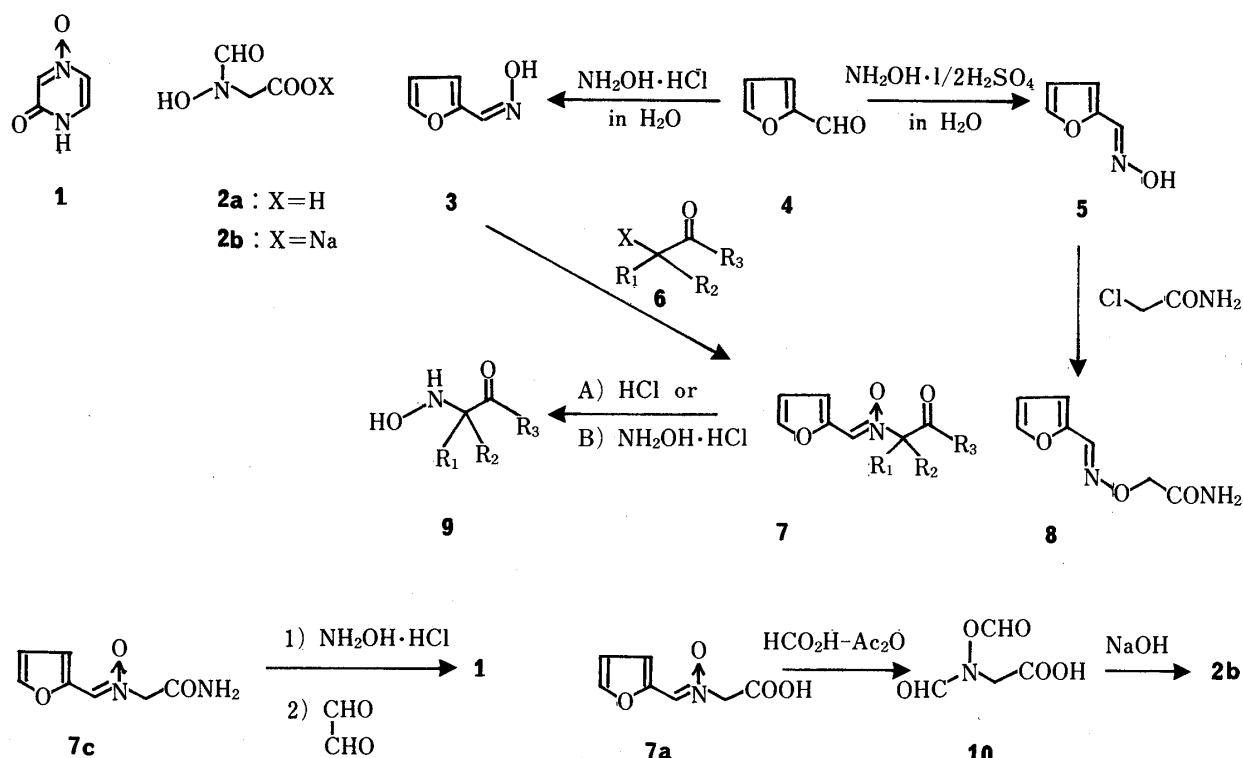


Chart 1

TABLE I. Melting Points and Elemental Analyses of *N*-Furfurylidenealkoxy- (and hydroxy)carbonylalkylamine *N*-Oxides (7a, b, d—g) and *N*-Furfurylidene carbamoylmethylamine *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 ₇ H ₇ NO ₄	49.71 (49.93)	4.17 4.29	8.28 8.04
b	H	H	OMe	77	81	C ₈ H ₉ NO ₄	52.46 (52.55)	4.95 4.76	7.65 7.71
c	H	H	NH ₂	82	175—176	C ₇ H ₈ N ₂ O 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 ₆ H 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*-furfurylidene carbamoylmethylamine *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*-Furfurylidenebamoylmethylamine *N*-Oxide (**7c**)

7	UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ)	IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹		N=CH (1H, s)	N-CH-CO	¹ H-NMR (CDCl ₃) δ			Others
		C=O	C=N			H ₃ (d, $J=5$ Hz)	Furan H ₄ (dd, $J=5, 2$ Hz)	H ₅ (d, $J=2$ Hz)	
a ^{d)}	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) 1.78 (6H, s, Me ₂), 1.26 (3H, t, $J=7$ Hz, Me), 4.23 (2H, q, $J=7$ Hz, OCH ₂) 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) 1.27 (3H, t, $J=7$ Hz, Me), 4.28 (2H, q, $J=7$ Hz, OCH ₂), 7.47 (5H, s, Ar)
e	310 (18000)	1735	1590	7.67	—	7.75	6.52	7.47	
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	
g	313 (18500)	1740	1595	7.32	5.74 (1H, s)	7.78	6.50	7.42	

a) ¹H-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 ₂ H ₅ NO ₃	26.38 (26.41)	5.53 5.49	15.38 15.27
b	H	H	OMe	B	95	90—91	HCl salt	C ₃ H ₈ ClNO ₃	25.45 (25.46)	5.70 5.90	9.90 9.93
c	H	H	NH ₂	B	98	138—140	HCl salt	C ₂ H ₇ ClN ₂ O ₂	18.98 (18.99)	5.58 5.47	22.14 22.11
d^{c)}	Me	H	OH	A	56	147	Free	C ₃ H ₇ NO ₃	34.28 (34.47)	6.71 6.67	13.33 13.28
e^{d)}	Me	H	OEt	B	93	Oil	HCl salt	C ₅ H ₁₂ ClNO ₃	35.41 (35.49)	7.13 7.21	8.26 8.13
f	Me	Me	OH	A	66	136—138	Free	C ₄ H ₉ NO ₃	40.33 (40.27)	7.62 7.71	11.76 11.79
g	Me	Me	OEt	B	89	88—89	HCl salt	C ₆ H ₁₄ ClNO ₃	39.24 (39.15)	7.69 7.79	7.63 7.70
h	Et	H	OH	A	52	126—129	Free	C ₄ H ₉ NO ₃	40.33 (40.50)	7.62 7.81	11.76 11.77
i^{e)}	Et	H	OEt	B	88	61—62	HCl salt	C ₆ H ₁₄ ClNO ₃	39.24 (39.29)	7.69 7.73	7.63 7.86
j^{c)}	C ₆ H ₅	H	OH	A	39	131—132	Free	C ₈ H ₉ NO ₃	57.48 (57.49)	5.43 5.52	8.38 8.22
k	C ₆ H ₅	H	OEt	B	94	135—137	HCl salt	C ₁₀ H ₁₄ ClNO ₃	51.84 (51.76)	6.09 6.11	6.05 6.21

a) Method A: Hydrolysis with 35% HCl. Method B: Cleavage with NH₂OH·HCl. b) Isolated yield. c) Ref. 6a. d) Ref. 6b. e) Ref. 5k.

(**8**) along with a small amount of **7c**. The formation of **7c** from **5** suggests that the isomerization¹²⁾ 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% yield 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 ($^1\text{H-NMR}$) 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 $\text{NH}_2\text{OH} \cdot \text{HCl}$ (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 $\text{C}_5\text{H}_5\text{NO}_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.06; H, 4.39; N, 12.41. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3150, 3050 (OH), 1640 (C=N). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 264 (8000). $^1\text{H-NMR}$ (CDCl_3) δ : 6.45 (1H, dd, $J_1 = 5 \text{ Hz}$, $J_2 = 2 \text{ Hz}$, furan- H_4), 7.30 (1H, d, $J = 5 \text{ Hz}$, furan- H_3), 7.42 (1H, d, $J = 2 \text{ Hz}$, 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 $\text{NH}_2\text{OH} \cdot 1/2\text{H}_2\text{SO}_4$ (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 $\text{C}_5\text{H}_5\text{NO}_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.02; H, 4.41; N, 12.08. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3154 (OH), 1635 (C=N). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 269 (7800). $^1\text{H-NMR}$ (CDCl_3) δ : 6.38 (1H, dd, $J_1 = 5 \text{ Hz}$, $J_2 = 2 \text{ Hz}$, furan- H_4), 6.60 (1H, d, $J = 5 \text{ Hz}$, furan- H_3), 7.43 (1H, d, $J = 2 \text{ Hz}$, furan- H_5), 8.00 (1H, s, N=CH), 9.91 (1H, br s, OH).

N-Furfurylidene-methoxycarbonylmethylamine 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**; $\text{R}_1 = \text{R}_2 = \text{H}$, $\text{R}_3 = \text{OCH}_3$, $\text{X} = \text{Br}$; 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 $\text{C}_7\text{H}_8\text{N}_2\text{O}_5$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.89; H, 4.93; N, 16.68. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3400, 3200, 1660, 1620. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 275 (8300). $^1\text{H-NMR}$ (CDCl_3) δ : 4.60 (2H, s, OCH_2), 6.1–6.7 (2H, br, NH_2), 6.42 (1H, dd, $J_1 = 5 \text{ Hz}$, $J_2 = 2 \text{ Hz}$, furan- H_4), 6.67 (1H, d, $J = 5 \text{ Hz}$, furan- H_3), 7.45 (1H, d, $J = 2 \text{ Hz}$, 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; $\text{R}_3 = \text{OH}$)—Method A: A mixture of **7** ($\text{R}_3 = \text{OH}$ 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** ($\text{R}_3 = \text{OH}$) as colorless needles (Table III).

N-Hydroxyamino Acid Esters and Amide (9; $\text{R}_3 = \text{O-Alkyl}$ and NH_2)—Method B: A mixture of **7** ($\text{R}_3 = \text{O-alkyl}$ and NH_2 ; 10 mmol) and $\text{NH}_2\text{OH} \cdot \text{HCl}$ (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 ($\text{R}_3 = \text{O-alkyl}$ and NH_2) as colorless needles (Table III).

2(1H)-Pyrazinone 4-Oxide (Emimycin) (1)—A mixture of **7c** (8.4 g) and $\text{NH}_2\text{OH} \cdot \text{HCl}$ (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 $\text{C}_4\text{H}_4\text{N}_2\text{O}_2 \cdot 1/4\text{H}_2\text{O}$: C, 41.20; H, 3.89; N, 24.03. Found: C, 41.49; H, 3.62; N, 24.27. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3400, 1640. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm (ϵ): 332 (4040). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 7.13 (1H, dd, $J_1 = 6 \text{ Hz}$, $J_2 = 2 \text{ Hz}$, H_5), 7.48 (1H, d, $J = 2 \text{ Hz}$, H_3), 7.53 (1H, d, $J = 6 \text{ Hz}$, H_6).

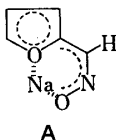
N-Formyl-N-hydroxyglycine (Hadacidin) Monosodium Salt (2b)—A mixture of **7a** (3.38 g) in HCOOH – Ac_2O

(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.^{7c)} at a temperature below 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 CaCl₂ to give **2b** (3.1 g; 87%), mp 190—192 °C (lit.^{4,7c)} mp 191—193 °C). *Anal.* Calcd for C₃H₄NNaO₄·2H₂O: C, 20.34; H, 4.55; N, 7.91. Found: C, 20.43; H, 4.62; N, 7.69. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3550—3100, 2900—2600, 1670.

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- 10) The X-ray crystal and ¹H-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.



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