Chem. Pharm. Bull. 28(7)2045—2051(1980)

Therapy for Urolithiasis with Hydroxamic Acids. I. Synthesis of New N-(Aroyl)glycinohydroxamic Acid Derivatives and Related Compounds

Kei-ichi Munakata, Satoru Tanaka, and Shoji Toyoshima

Research Laboratories, Eisai Co., Ltd.[1]

(Received January 18, 1980)

With the aim of finding a therapeutic agent for urolithiasis, forty-three new N-(aroyl)-glycinohydroxamic acid derivatives and related compounds were synthesized and examined for urease inhibitory activity. Their urinary excretion in rats was also determined.

Keywords——urolithiasis; N-(aroyl)glycinohydroxamic acid; urease; phosphate stone; *Proteus mirabilis*

Urolithiasis is at present considered to be incurable. The phosphate stone is generally formed according to the following mechanism.[2] Urea in the urine is hydrolyzed to yield ammonia by urea-splitting bacteria such as *Proteus mirabilis* infecting the urinary tract; this causes alkalinization of the urine, resulting in a decrease of solubility of phosphates and leading to the formation of struvite and apatite stones.

Therefore, hydroxamic acid, a potent and specific inhibitor of urease,[3] might be expected to act as a therapeutic agent for the treatment of phosphate stones. In fact, Griffith *et al.*[4] have reported that acetohydroxamic acid was effective for the prevention of urinary stone formation in rats, but this compound was demonstrated to be teratogenic in rats.[5] On the other hand, Kobashi *et al.*[6] have reported that the urinary excretion of known hydroxamic acids, in general, is rather low, owing to their rapid metabolic degradation. This observation suggests that hydroxamic acids at present known may offer poor bioavailability as therapeutic agents for urolithiasis.

Thus, it seems desirable to seek new hydroxamic acid derivatives having good bioavailability and also reduced toxicity compared with acetohydroxamic acid. We have been able to obtain several compounds having improved properties, and we describe the synthesis of these new hydroxamic acid derivatives in the present paper.

It is well known that hippuric acid and pyridone-1-acetic acid are mostly excreted unchanged in the urine,[7] so we planned to synthesize hydroxamic acid derivatives bearing these compounds as the pharmacokinetic moiety and to examine their urease inhibitory activity and urinary excretion in rats. Based on this drug design, we synthesized various N-(aroyl)-glycinohydroxamic acid derivatives and related compounds, and their α-methylated derivatives with one or two methyl group (s) at the α-position of the hydroxamic acid moiety, in the hope

1) Location: *4 Koishikawa, Bunkyo-ku, Tokyo.*
2) H. Takeuchi, O. Yoshida, S. Takebe, K. Kobashi, and J. Hase, *Acta Urol. Jap.*, **23**, 647 (1977).
3) *a*) K. Kobashi, J. Hase, and K. Uehara, *Biochim. Biophys. Acta*, **65**, 380 (1962); *b*) K. Kobashi, J. Hase, and T. Komai, *Biochim. Biophys. Res. Commun.*, **23**, 34 (1965); *c*) J. Hase and K. Kobashi, *J. Biochem.* (Tokyo), **62**, 293 (1965); *d*) K. Kobashi, K. Kumaki, and J. Hase, *Biochim. Biophys. Acta*, **227**, 429 (1971).
4) D.P. Griffith and D.M. Musher, *Invest. Urol.*, **11**, 228 (1973).
5) T. Kreybig, R. Preussmann, and W. Schmidt, *Arzneim.-Forsch.*, **18**, 645 (1968).
6) K. Kobashi, S. Takebe, and J. Hase, *Yakugaku Zasshi*, **93**, 1564 (1973).
7) S. Kato, "Iyakuhin-Kaihatsu-Kisokoza," (in Japanese), Vol. 7, ed. by K. Tsuda and H. Nogami, Chigin Shokan, Tokyo, 1972, pp. 315—339.

of obtaining reduced metabolic degradation.[8]

Hydroxamic acids were synthesized by the routes shown in Charts 1, 2 and 3, and are listed in Tables I and II.

Four kinds of synthetic methods were used to obtain lower alkyl esters of N-(substituted benzoyl)glycinate or alkyl esters of N-(heteroaromatic carbonyl)glycinate (III).

Method A: Compounds (III) were obtained by condensing ethyl glycinate with an aromatic carbonyl chloride (II), prepared by reacting an aromatic carboxylic acid (I) with thionyl chloride in the presence of dimethyl formamide (DMF) (III, $R_1=R_2=H$). In the cases of (III) ($R_1=H$, $R_2=CH_3$ and $R_1=R_2=CH_3$), methyl DL-alaninate or methyl α-amino-isobutyrate was used, respectively, instead of ethyl glycinate.

Method B: Compounds (III) were obtained by condensing ethyl glycinate with a mixed acid anhydride, prepared by reacting compounds (I) with ethyl chloroformate in the presence of triethylamine.

Method C: Compounds (III) were obtained by condensing compounds (I) with ethyl glycinate in the presence of dicyclohexylcarbodiimide (DCC).

Method D: Ethyl N-(acylaminobenzoyl)glycinate (IIIb) was obtained by condensing ethyl N-(aminobenzoyl)glycinate (IIIa), prepared by hydrogenation of the corresponding ethyl N-(nitrobenzoyl)glycinate, with acyl chloride or acid anhydride.

Hydroxamic acids (IV), (V) and (VI) were obtained by reacting the corresponding compounds (III) with hydroxylamine in alkaline methanol solution.

On the other hand, pyridone derivatives (VIII) were obtained by reacting ethyl ester of 5-halogeno-α-pyridone-1-acetic acid (VII), synthesized according to the method of Kahlbaum,[9] with hydroxylamine in the manner described above.

In most case, hydroxamic acid derivatives could be isolated by adjusting the pH of the aqueous reaction mixture to 5 with acetic acid, and could be purified by recrystallization as described in Tables I and II. When the hydroxamic acid was difficult to isolate from the aqueous reaction mixture due to its high hydrophilicity, it was necessary to form an insoluble chelate of the hydroxamic acid with cupric chloride, followed by decomposition of the chelate with H_2S to isolate the hydroxamic acid.

By adding a trace of DMF, chlorination of aromatic carboxylic acids could be completed within 15 to 30 min, and the reaction product gave a single spot on thin-layer chromatography [Kieselgel 60 F_{254} (Merck), $CHCl_3$–acetones (4: 1, v/v)], whereas in the absence of DMF, the reaction took 1 to 3 hr to complete and the product was less pure.[10]

In most cases, compounds (III) were obtained in high yields by Method A, but Methods B and D were employed when the substituents on the benzene nuclei were unstable in an acidic medium, *e. g.* in the case of acylamino groups. The ethyl ester of 3,4-methylenedioxybenzoylglycinate was prepared by Method C, since resin formation and complete recovery of the starting material were obtained by Methods A and B, respectively.

The forty-three new hydroxamic acids listed in Tables I and II were tested for inhibitory potency against the activity of urease of both plant and bacterial origins, and their urinary excretion rates in rats were also measured. The apparent I_{50} value, which represents the molar concentration of the compound causing 50% inhibition of the urease activity, was determined according to the method of Kobashi *et al.*,[11] and the urinary content of unchanged hydroxamic acid was determined enzymatically by the method reported previously.[12] Apparent I_{50}

8) *a*) S.J. Fu, S.M. Birnbaum, and J.P. Greenstein, *J. Am. Chem. Soc.*, **76**, 6054 (1954); *b*) R.M. Levine and B.B. Clark, *J. Pharmacol. Expt. Ther.*, **113**, 272 (1955); *c*) M.C. Kloetzel, S.J. Davis, U. Pandit, C.R. Smith, and H. Nishihara, *J. Med. Chem.*, **1**, 197 (1959); *d*) L.E. Leafe, *Nature* (London), **193**, 485 (1962).

9) A.G. Kahlbaum, Brit. Patent 339436 (1929) [*C.A.*, **25**, 1036 (1931)].

10) Y. Egawa, M. Suzuki, and T. Okuda, *Chem. Pharm. Bull.*, **11**, 589 (1963).

11) K. Kobashi, K. Kumaki, and J. Hase, *Biochim. Biophys. Acta*, **227**, 492 (1971).

12) K. Kobashi, N. Terashima, S. Takebe, and J. Hase, *J. Biochem.* (Tokyo), **83**, 287 (1978).

values of N-(substituted benzoyl)glycinohydroxamic acids (IV) against sword bean urease activity were mostly about 0.5 to 2.0 μM, almost the same as that of caprylohydroxamic acid, the most potent urease inhibitor reported hitherto (0.87 μM).[11] However, IV-10 showed markedly less inhibitory activity, with a value of 180 μM. Compounds (V) and (VI), the α-monomethylated and the α, α-dimethylated derivatives of the hydroxamic acids (IV), respectively, were very much less inhibitory than the corresponding parent compounds (IV) (VI-1, I_{50}=1200 μM). Furthermore, the inhibitory potencies of hydroxamic acids (IV) against the ureolytic activity of intact *Proteus mirabilis* were half to one-tenth of those against the sword bean urease activity. On the other hand, IV-2, IV-3, IV-21, IV-22, IV-23 and IV-24 showed high urinary excretion rates of 14 to 16% of the dose administered orally, while most of the others had excretion rates of 3 to 5%. These recoveries are high, compared with those

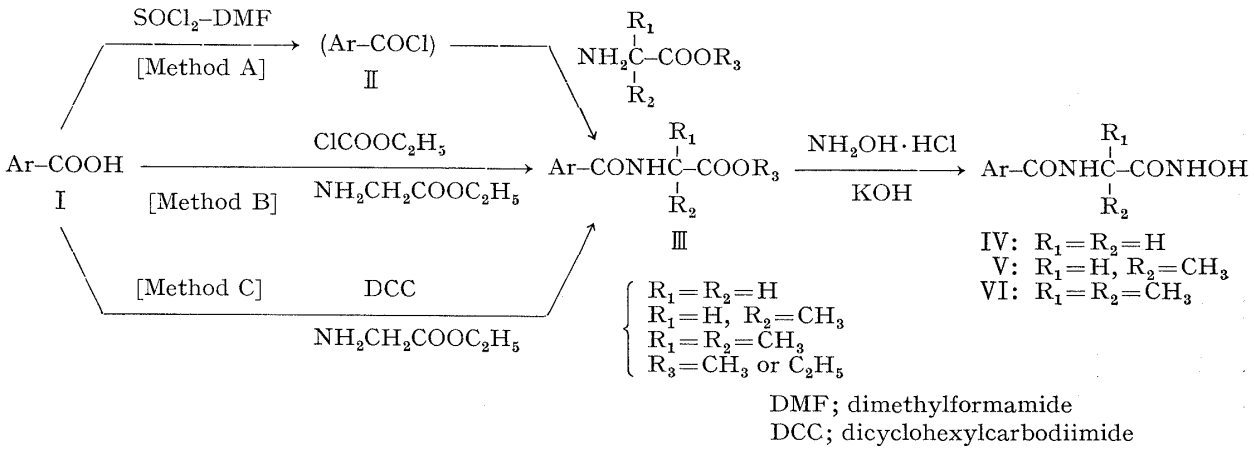


Chart 1. The Synthetic Routes to N-(Aroyl)glycinohydroxamic Acids

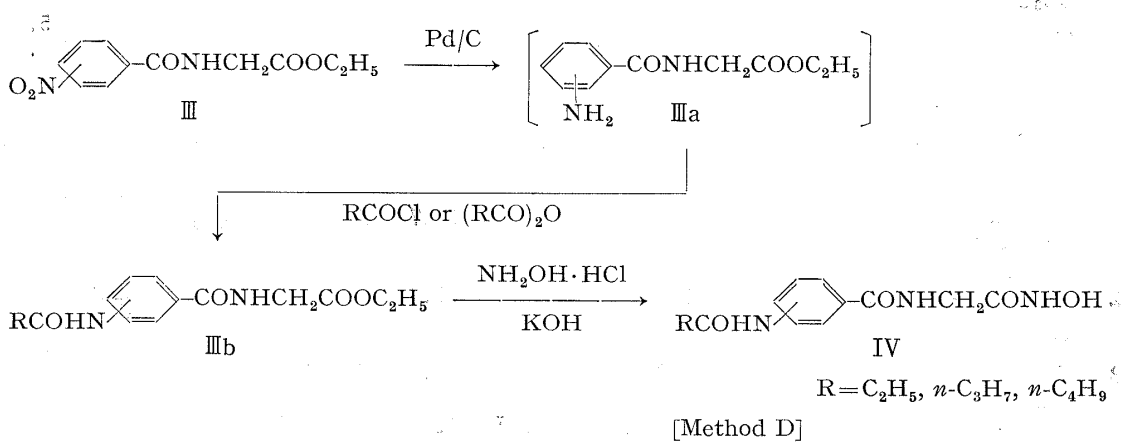


Chart 2. The Synthetic Routes to N-(Acylaminobenzoyl)glycinohydroxamic Acids

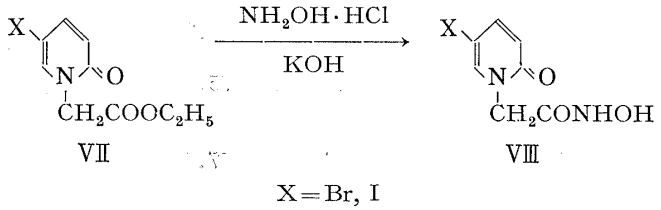
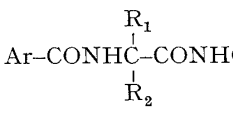


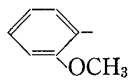
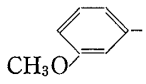
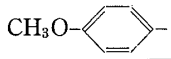
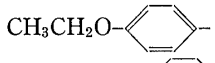
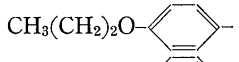
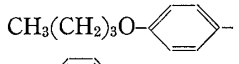
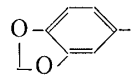
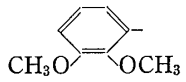
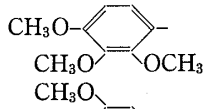
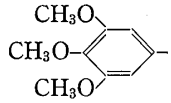
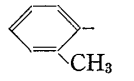
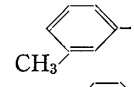
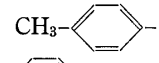
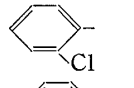
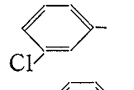
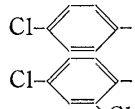
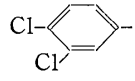
Chart 3. The Synthetic Route to 5-Halogeno-α-pyridone-1-acetohydroxamic Acids

of caprylohydroxamic acid and nicotinohydroxamic acid.[6] The results of these examinations and structure-activity correlations in these compounds will be reported in detail elsewhere.[13]

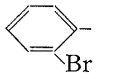
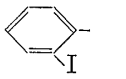
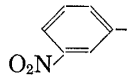
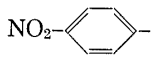
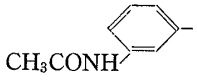
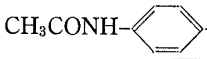
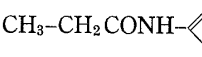
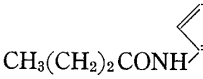
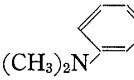
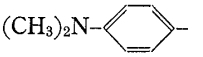
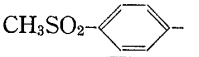
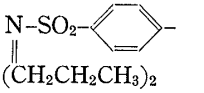
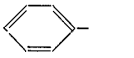
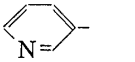
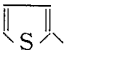
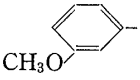
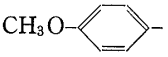
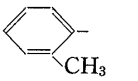
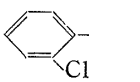
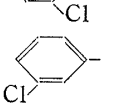
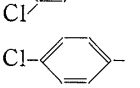
Table I. N-(Aroyl)glycinohydroxamic Acid Derivatives

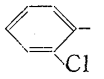
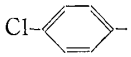


Ar–CONHC(R$_1$)(R$_2$)–CONHOH (IV, V and VI)

Compd. No.	Ar	R_1	R_2	mp °C (dec.)	Recryst. solvent	Yield[f] %	Method	Formula	Analysis % Calcd (Found) C	H	N
IV-1		H	H	177—178	MeOH	42.0	A	$C_{10}H_{12}N_2O_4$	53.57 (53.45)	5.39 (5.37)	12.50 (12.61)
IV-2		H	H	132—133	*sec*-PrOH	66.0	A	$C_{10}H_{12}N_2O_4$	53.57 (53.53)	5.39 (5.42)	12.50 (12.70)
IV-3		H	H	(160—161)	EtOH	76.5	A	$C_{10}H_{12}N_2O_4$	53.57 (53.56)	5.39 (5.39)	12.50 (12.61)
IV-4		H	H	138—139	EtOH	48.2	A	$C_{11}H_{14}N_2O_4$	55.45 (55.43)	5.92 (5.97)	11.76 (11.67)
IV-5		H	H	150—151	MeOH	40.5	A	$C_{12}H_{16}N_2O_4$	57.13 (57.23)	6.39 (6.48)	11.11 (11.21)
IV-6		H	H	126—127	EtOH	50.0	A	$C_{13}H_{18}N_2O_4$	58.63 (58.59)	6.81 (6.61)	10.52 (9.80)
IV-7		H	H	156—157	EtOH	32.1	C	$C_{10}H_{10}N_2O_5$	50.42 (50.26)	4.23 (4.22)	11.76 (11.85)
IV-8		H	H	139—140	EtOH	35.0	A	$C_{11}H_{14}N_2O_5$	51.96 (51.84)	5.55 (5.61)	11.02 (11.13)
IV-9		H	H	155—156	EtOH	62.4	A	$C_{11}H_{16}N_2O_6$	50.70 (50.67)	5.67 (5.70)	9.86 (9.99)
IV-10		H	H	134—135	EtOH	52.4	A	$C_{12}H_{16}N_2O_6$	50.70 (50.37)	5.67 (5.92)	9.86 (9.46)
IV-11		H	H	145—146	EtOH	26.7	A	$C_{10}H_{12}N_2O_3$	57.68 (57.46)	5.81 (5.84)	13.46 (13.50)
IV-12		H	H	149—150	EtOH	29.9	A	$C_{10}H_{12}N_2O_3$	57.68 (57.69)	5.81 (5.84)	13.46 (13.39)
IV-13		H	H	158—159	EtOH	29.6	A	$C_{10}H_{12}N_2O_3$	57.68 (57.62)	5.81 (5.84)	13.46 (13.42)
IV-14		H	H	168—169	MeOH	16.8	A	$C_9H_9ClN_2O_3$	47.28 (46.96)	3.97 (4.01)	12.25 (12.45)
IV-15		H	H	163—164	MeOH	65.5	A	$C_9H_9ClN_2O_3$	47.28 (47.09)	3.97 (3.92)	12.25 (12.52)
IV-16		H	H	179—180[a]	MeOH	83.2	A	$C_9H_9ClN_2O_3$	47.28 (46.95)	3.97 (3.98)	12.25 (12.44)
IV-17		H	H	142—143	EtOH	75.3	A	$C_9H_8Cl_2N_2O_3$	41.09 (40.79)	3.07 (3.13)	10.64 (10.73)
IV-18		H	H	161—162	MeOH	77.6	A	$C_9H_8Cl_2N_2O_3$	41.09 (41.04)	3.07 (3.07)	10.64 (10.71)

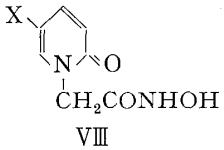
13) K. Kobashi, K. Munakata, S. Takebe, and J. Hase, *J. Pharm. Dyn.*, accepted.

Compd. No.	Ar	R_1	R_2	mp °C (dec.)	Recryst. solvent	Yield[f] %	Method	Formula	Analysis % Calcd (Found) C	H	N
IV-19		H	H	161—162	MeOH	83.5	A	$C_9H_9BrN_2O_3$	39.58 (39.41)	3.32 (3.37)	10.25 (10.24)
IV-20		H	H	145—146	EtOH	83.1	A	$C_9H_9IN_2O_3$	33.77 (33.75)	2.83 (2.83)	8.75 (9.10)
IV-21		H	H	162—163	EtOH	67.8	A	$C_9H_9N_3O_5$	45.10 (45.40)	3.79 (4.03)	17.57 (17.55)
IV-22		H	H	173—174[b]	MeOH	81.4	A	$C_9H_9N_3O_5$	45.19 (45.01)	3.79 (3.82)	17.57 (17.52)
IV-23		H	H	178—179	MeOH	66.3	B	$C_{11}H_{13}N_3O_4$	52.58 (52.21)	5.22 (5.41)	16.73 (16.72)
IV-24		H	H	(>205)	MeOH	30.2	B	$C_{11}H_{13}N_3O_4$	52.58 (52.37)	5.22 (5.27)	16.73 (16.75)
IV-25		H	H	159—160	EtOH	44.4	D	$C_{12}H_{15}N_3O_4$	54.33 (54.14)	5.70 (5.72)	15.84 (15.80)
IV-26		H	H	(>205)	MeOH	65.2	D	$C_{12}H_{15}N_3O_4$	54.33 (54.07)	5.70 (5.74)	15.84 (15.88)
IV-27		H	H	158—159	EtOH	24.6	D	$C_{13}H_{17}N_3O_4$	55.90 (55.71)	6.14 (6.13)	15.05 (15.01)
IV-28		H	H	144—145	EtOH	63.3	A	$C_{11}H_{15}N_3O_3$	55.68 (55.36)	6.37 (6.36)	17.71 (17.64)
IV-29		H	H	167—168	MeOH	84.4	A	$C_{11}H_{15}N_3O_3$	55.68 (55.63)	6.37 (6.37)	17.71 (17.84)
IV-30		H	H	(>183)	MeOH	67.3	A	$C_{10}H_{12}N_2O_5S$	44.11 (44.07)	4.44 (4.45)	10.28 (10.35)
IV-31		H	H	153—154	MeOH	48.0	A	$C_{15}H_{23}N_3O_5S$	50.41 (50.33)	6.49 (6.55)	11.75 (11.69)
IV-32		H	H	148—149[c]	EtOH	67.0	A	$C_9H_{10}N_2O_3$	55.66 (55.52)	5.19 (5.20)	14.43 (14.58)
IV-33[d]		H	H	249—251	MeOH	25.7	A	$C_8H_9N_3O_3$	49.23 (49.00)	4.65 (4.68)	21.53 (21.71)
IV-34[d]		H	H	150—151	EtOH	34.6	B	$C_7H_8N_2O_4$	45.65 (45.85)	4.38 (4.46)	15.21 (15.01)
IV-35		H	H	153—154	EtOH	33.3	A	$C_7H_8N_2O_3S$	41.99 (41.89)	4.03 (4.02)	13.99 (14.25)
V-1[e]		H	CH_3	(152—153)	EtOH	82.0	A	$C_{11}H_{14}N_2O_4$	55.45 (55.39)	5.92 (6.03)	11.76 (11.92)
V-2[e]		H	CH_3	(151—152)	EtOH	75.6	A	$C_{11}H_{14}N_2O_4$	55.45 (55.42)	5.92 (6.00)	11.76 (12.00)
V-3[e]		H	CH_3	(153—154)	EtOH	70.3	A	$C_{11}H_{14}N_2O_3$	59.45 (59.31)	6.35 (6.43)	12.60 (12.55)
V-4[e]		H	CH_3	(185—186)	MeOH	53.5	A	$C_{10}H_{11}ClN_2O_3$	49.50 (49.51)	4.57 (4.53)	11.54 (11.85)
V-5[e]		H	CH_3	(179—180)	MeOH	42.8	A	$C_{10}H_{11}ClN_2O_3$	49.50 (49.37)	4.57 (4.58)	11.54 (11.78)
V-6[e]		H	CH_3	(182—183)	MeOH	77.4	A	$C_{10}H_{11}ClN_2O_3$	49.50 (49.51)	4.57 (4.59)	11.54 (11.75)
V-7[e]		H	CH_3	159—160	EtOH	34.7	A	$C_3H_{10}N_2O_3S$	44.85 (44.99)	4.71 (5.06)	13.07 (12.67)

Compd. No.	Ar	R_1	R_2	mp °C (dec.)	Recryst. solvent	Yield[f] %	Method	Formula	Analysis % Calcd (Found) C	H	N
VI-1		CH_3	CH_3	(164—165)	EtOH	32.7	A	$C_{11}H_{13}ClN_2O_3$	51.47 (51.23	5.11 5.14	10.91 10.87)
VI-2		CH_3	CH_3	(179—180)	MeOH	74.7	A	$C_{11}H_{13}ClN_2O_3$	51.47 (51.28	5.11 5.06	10.91 11.13)

a) R.N. Johnson and J.A. Andersen; Ger. Patent 2223857 (1973) [*C.A.*, **78**, 71707 (1973)], mp 171—172°.
b) R.N. Johnson and J.A. Andersen; Ger. Patent 2223857 (1973) [*C.A.*, **78**, 71707 (1973)], mp 160—161°.
c) S.A. Bernhard, W.C. Coles, and J.F. Nowell; *J. Am. Chem. Soc.*, **82**, 3043 (1960), mp 140—141°.
d) These compounds were separated from the reaction solutions as insoluble chelate compounds with cupric ions.
e) DL-isomer.
f) Calculated from aromatic carboxylic acids (I).

TABLE II. 5-Halogeno-α-pyridone-1-acetohydroxamic Acids



VIII

Compd. No.	X	mp °C	Recryst. solvent	Yield %	Formula	Analysis % Calcd (Found) C	H	N
VIII-1	Br	176—177	MeOH	25.3	$C_7H_7BrN_2O_3$	34.03 (34.00	2.86 2.86	11.33 11.59)
VIII-2	I	179—180	MeOH	34.0	$C_7H_7IN_2O_3$	28.59 (28.92	2.40 2.64	9.52 9.42)

Experimental

All melting points are uncorrected. IR spectra (cm^{-1}) were determined with a Hitachi 215 spectrometer, PMR spectra (δ, 60 MHz, 100 MHz) were measured using tetramethylsilane as an internal standard with Hitachi-Perkin Elmer R24 and JEOL JNM-PS100 spectrometers, and mass spectra were recorded with a JEOL JMS-01SG spectrometer.

Ethyl N-(*p*-Methoxybenzoyl)glycinate (III, Ar=*p*-Methoxy-Ph, $R_1=R_2=H$, $R_3=C_2H_5$)——As a typical example of Method A, a mixture of 15.2 g (0.1 mol) of *p*-methoxybenzoic acid (I, Ar=*p*-CH_3O-Ph), 12 ml of $SOCl_2$ and 0.5 ml of DMF in 70 ml of toluene was heated at 60 to 70° for 30 min. The reaction mixture was concentrated *in vacuo* to give *p*-methoxybenzoyl chloride (II, Ar=*p*-CH_3O-Ph), which was used in the following reaction without purification. A solution of 16.8 g (0.12 mol) of ethyl glycinate hydrochloride and 34.5 g (0.25 mol) of K_2CO_3 in 100 ml of H_2O was mixed with 50 ml of toluene, then compound (II) in 20 ml of toluene was added dropwise at −5 to 5°. Crystalline masses formed were collected by filtration to yield 21.5 g (90.5% from I) of III (Ar=*p*-CH_3O-Ph, $R_1=R_2=H$), mp 98—99° (from benzene), MS *m/e*: 237 (M^+). IR ν_{max}^{Nujol}: 3250 (NH), 1760 ($COOC_2H_5$), 1640 (CONH), 1600 (aromatic). *Anal.* Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90, Found: C, 60.69; H, 6.31; N, 5.87.

Ethyl N-(2-Furoyl)glycinate (III: Ar=2-Furyl, $R_1=R_2=H$, $R_3=C_2H_5$)——As a typical example of Method B, a solution of 6.1 g (0.054 mol) of 2-furoic acid (I, Ar=2-furyl) and 5.5 g (0.054 mol) of triethylamine in 70 ml of DMF was treated dropwise with 5.9 g (0.054 mol) of ethyl chloroformate in 30 ml of $CHCl_3$ at −5 to 0° to yield the corresponding mixed acid anhydride. A solution of 8.4 g (0.06 mol) of ethyl glycinate hydrochloride and 6.1 g (0.06 mol) of triethylamine in 50 ml of DMF was then added at 0 to 5°, and the mixture was kept at this temperature with stirring for 1 hr, then allowed to stand overnight at room temperature. The solvent was removed *in vacuo*, and the residue was dissolved in 100 ml of $CHCl_3$, followed by washing three times with 100 ml of H_2O. The organic layer was dried with anhyd. $MgSO_4$ and $CHCl_3$ was removed *in vacuo* to yield 6.8 g (63.4%) of III (Ar=2-furyl, $R_1=R_2=H$, $R_3=C_2H_5$), mp 79—80° (from *n*-hexane–benzene), IR ν_{max}^{Nujol}: 3300 (NH), 1740 ($COOC_2H_5$), 1640 (CONH), 1580 (furan). *Anal.* Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.76; H, 5.75; N, 7.19.

Ethyl N-(3,4-Methylenedioxybenzoyl)glycinate (III; Ar=Piperonyl, $R_1=R_2=H$, $R_3=C_2H_5$)——As an example of Method C, 16.6 g (0.1 mol) of 3,4-methylenedioxybenzoic acid (I; Ar=piperonyl), 16.8 g (0.12 mol) of ethyl glycinate hydrochloride, 12.1 g (0.12 mol) of triethylamine and 24.7 g (0.12 mol) of DCC were dissolved in 150 ml of DMF at −5 to 0°. The reaction mixture was stirred at this temperature for 1 hr and allowed to stand overnight at 5°. The dicyclohexylurea formed was filtered off and the solvent was removed *in vacuo*. The residue was dissolved in 100 ml of $CHCl_3$, and the solution was washed three times with 100 ml of H_2O. The organic layer was dried with anhyd. $MgSO_4$, and the solvent was removed *in vacuo* to give 12.7 g (50.5%) of III (Ar=piperonyl, $R_1=R_2=H$, $R_3=C_2H_5$) as a pale yellow liquid. Mass *m/e*: 251 (M^+), IR ν_{max}^{Nujol}: 3325 (NH), 1750 ($COOC_2H_5$), 1630 (CONH), 1600 (aromatic).

Ethyl (N-*m*-Propioaminobenzoyl)glycinate (IIIb, $R=C_2H_5$)——As a typical example of Method D, a mixture of 12.6 g (0.05 mol) of ethyl (*m*-nitrobenzoyl)glycinate (III) and 0.5 g of 5% Pd-C (50% water suspension) in 200 ml of MeOH was shaken at normal pressure under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give 11.0 g (in quantitative yield) of ethyl (*m*-aminobenzoyl)glycinate (IIIa) as a pale yellow liquid, MS *m/e*: 222 (M^+), IR ν_{max}^{neat}: 3350 (NH), 1740 ($COOC_2H_5$), 1640 (CONH), 1600, 1580 (aromatic), which was used in the following reaction without purification. A solution of 8.9 g (0.04 mol) of IIIa in 100 ml of $CHCl_3$ was treated with a solution of 5.5 g (0.04 mol) of K_2CO_3 in 100 ml of H_2O, followed by dropwise addition of 3.7 g (0.04 mol) of propionyl chloride in 20 ml of $CHCl_3$ at 0 to 10°. The organic layer was separated and washed three times with 50 ml of H_2O. After drying, the solvent was removed to give 10 g (89.5%) of IIIb ($R=C_2H_5$), MS *m/e*: 278 (M^+), IR ν_{max}^{Nujol}: 3275 (NH), 1740 ($COOC_2H_5$); 1640 (CONH), 1580 (aromatic).

N-(*p*-Methoxybenzoyl)glycinohydroxamic Acid (IV-3)——A solution of 6.95 g (0.1 mol) of $NH_2OH\cdot HCl$ in 50 ml of MeOH was added to a solution of 11.2 g (0.2 mol) of KOH in 50 ml of MeOH, and inorganic salts formed were filtered off. Next, 14.2 g (0.06 mol) of III (Ar=*p*-CH_3O-Ph, $R_1=R_2=H$, $R_3=C_2H_5$) was added to the filtrate and the mixture was stirred for 1 hr at room temperature, then allowed to stand overnight. The reaction solution was concentrated at 60° *in vacuo* and the residue was dissolved in 50 ml of H_2O, adjusting the pH of the solution to 5.0 with AcOH. Crystalline masses formed were collected by filtration to yield 11.4 g (84.6%) of IV-3, mp 160—161° (from EtOH). IR ν_{max}^{Nujol}: 3330 (NH), 3120 (OH), 1660, 1630, 1620 (CONH, CONHOH), 1600 (aromatic). PMR (100 MHz, CD_3OD): 3.80 (3H, OCH_3, s), 3.95 (2H, CH_2, s), 6.95 (2H, arom H, d, $J=8.0$ Hz), 7.80 (2H, arom H, d, $J=8.0$ Hz). *Anal.* Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.50. Found: C, 53.56; H, 5.39; N, 12.61.

N-(2-Furoyl)glycinohydroxamic Acid (IV-34)——A solution of 9.7 g (0.14 mol) of $NH_2OH\cdot HCl$ in 60 ml of MeOH was added to a solution of 16.4 g (0.25 mol) of KOH (85.5%) in 60 ml of MeOH, and inorganic salts formed were filtered off. Next, 19.7 g (0.1 mol) of III (Ar=2-furyl, $R_1=R_2=H$, $R_3=C_2H_5$) was added to the filtrate and the reaction mixture was stirred for 1 hr at room temperature, then allowed to stand overnight. The reaction solution was concentrated at 60° *in vacuo* and the residue was dissolved in 100 ml of H_2O, adjusting the pH of the solution to 5.0 with AcOH. To this solution, 8.5 g (0.05 mol) of $CuCl_2\cdot 2H_2O$ was added to obtain an insoluble copper salt of IV-33. This complex was suspended in 100 ml of MeOH and H_2S was passed through the suspension. The precipitate of CuS was filtered off and the solvent was removed *in vacuo* from the filtrate to yield 10.7 g (54.5%) of IV-34, mp 150—151° (from EtOH). IR ν_{max}^{Nujol}: 3350 (OH), 3200 (NH), 1700, 1660, 1620 (CONH, CONHOH), 1600, 1530 (furan ring). PMR (60 MHz, DMSO-d_6): 3.8 (2H, CH_2, d, $J=6.0$ Hz), 6.6 (1H, furan H, d×d), 7.15 (1H, furan H, d×d), 7.8 (1H, furan H, d×d), 8.4, 8.8, 10.7 (each 1H, $N\underline{H}CH_2CON\underline{H}O\underline{H}$, b.s., disappeared on addition of D_2O). *Anal.* Calcd for $C_7H_8N_2O_4$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.85; H, 4.46; N, 15.01.

Acknowledgement We wish to thank Drs. J. Hase and K. Kobashi, Faculty of Pharmaceutical Science, Toyama Medical and Pharmaceutical University, for valuable discussions, and Dr. M. Tomoeda, Eisai Co., Ltd., for his encouragement throughout this work.