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Syntheses of *N*-Substituted Carbamimidoylformic Acids

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A few synthetic methods of *N*-substituted-carbamimidoylformic acid (**6**) were examined. Among them, condensation of ethyl 1-carbethoxyformimidate or ethyl thiooxamidate with amines and followed by partial hydrolysis gave unsuccessful results, except of the case of benzylamine in the latter reaction. Direct substitution of potassium thiooxamidate (**9**) with alkylamines in water gave **6**, potassium and/or alkylammonium *N*-substituted-thiooxamidate in fairly good yield, depending on conditions used. The presence of heavy metal ions in the reaction system caused an extensive decomposition of **9**, however, the substitution proceeded smoothly by treatment of alkyl- and aryl-ammonium *N*-unsubstituted- or *N*-substituted-thiooxamidate in methanol with mercuric oxide or lead oxide to give in a good yield **6** or *N,N*-disubstituted-carbamimidoylformic acid, respectively.

N-Substituted-carbamimidoylformic acid which is known only as a partial structure of kasugamycin[1-3] is unique as regards a carboxyl group attaches directly to the carbon atom of formamidine, and kasugamycin has been synthesized in *ca.* 10% yield by condensation of kasuganobiosamine with diethyl ester of oxalimidic acid and followed by partial hydrolysis.[4] However, such a partial hydrolysis was considered to proceed non-selectively, and consequently, to be not profitable for a synthesis of *N*-substituted- or *N,N'*-disubstituted-carbamimidoylformic acid.

In this paper, the authors examined the condensation of ethyl 1-carbethoxyformimidate or ethyl thiooxamidate with amines and successive partial hydrolysis, and direct substitution of potassium thiooxamidate or its free acid with amines.

Results and Discussion

Reaction of Ethyl 1-Carbethoxyformimidate or Ethyl Thiooxamidate with Amines. Although the formation of 1-carbethoxyformamidine hydrobromide from ethyl 1-carbethoxyformimidate (**1**) and ammonium bromide is

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1) H. Umezawa, Y. Okami, T. Hashimoto, Y. Suhara, M. Hamada, and T. Takeuchi, *J. Antibiotics*, **18A**, 101 (1965).

2) Y. Suhara, K. Maeda, H. Umesawa, and M. Ohno, *Tetrahedron Lett.*, **1966**, 1239.

3) T. Ikekawa, H. Umezawa, and Y. Iitaka, *J. Antibiotics*, **19A**, 49 (1966).

4) Y. Suhara, F. Sasaki, K. Maeda, H. Umezawa, and M. Ohno, *J. Amer. Chem. Soc.*, **90**, 6559 (1968).

known,[5] condensation of **1** with amine hydrochlorides at room temperature was unsuccessful, excepting that the reaction of **1** and 2-amino-2-deoxy-D-glucose (**8**) hydrochloride in methanol at elevated temperature gave 2-carbomethoxy-4-(D-*arabino*-1′,2′,3′,4′-tetrahydroxybutyl)-imidazole (**2**) in 10% yield, together with 3,6-diethoxy-2,5-dihydro-2,5-dioxo-pyrazine (**3**) as a by-product. Condensation of **1** and free amines (*p*-toluidine and **8**) gave complicated products, however, the presence of *N*-substituted-1-carbethoxyformamidine (**4**) was proved by different ways. In the case of **8**, the reaction mixture in methanol was refluxed in the presence of catalytic amount of hydrogen chloride to give **2**, and moreover, decomposition of it with water yielded 2-deoxy-2-oxalylamino-D-glucose methyl ester (**5a**: RNH_2=**8**) which was converted to the corresponding amide by treatment with methanolic ammonia. However, direct partial hydrolysis of the reaction mixture in 0.1 *N*-hydrochloric acid at room temperature gave only a intractable sirup. In the case of *p*-toluidine, direct partial hydrolysis of reaction mixture gave unknown white crystals in 39% yield, $C_{10}H_{10}O_3N_2$, and an attempted ester-exchange reaction with acetic or formic acid gave methyl *N*-*p*-tolyl-oxamidate (**5b**: R=*p*-tolyl) and *N*,*N*′-di-*p*-tolyl-carbamimidoylform-*p*-toluidide.

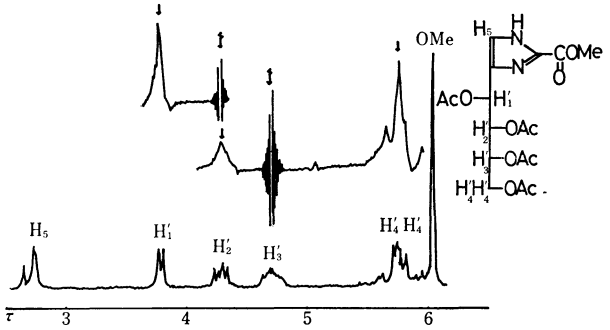
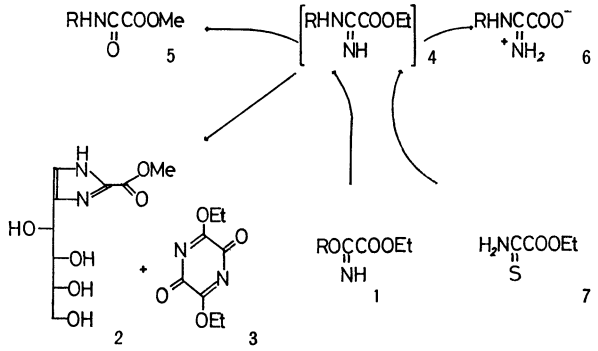


Fig. 1. NMR spectrum of 2-carbomethoxy-4-(D-*arabino*-1′,2′,3′,4′-tetraacetoxybutyl)-imidazole (100 MHz, $CDCl_3$).

The structure of **2** was determined from the following facts: it shows λ_{max}^{MeOH} 267 nm (ε 1.25×10^4), consumes 3.08 equimolar amount of sodium periodate, and gave the corresponding tetraacetate by a usual acetylation, whose NMR spectrum was shown in Fig. 1. In the NMR spectrum, signals at τ 2.74 (*s*, 1H), 3.78 (*d*, 1H), 4.28 (*q*, 1H), 4.71 (*m*, 1H), and 5.6—6.0 (*m*, 2H) were assigned by the double-resonance technique to H_5, H_1', H_2', H_3', and H_4', respectively. The lower chemical shift of H_5 than usual ring protons in sugar moiety indicates the presence of imidazole ring, and the change of chemical shifts of H_5 and H_1' to τ 2.54 and 3.67 by addition of trifluoroacetic acid supports this deduction. Recently, Fischer and Lewis[6] reported that the reaction of **8** and ethyl iminoacetate hydrochloride in dimethylformamide gave D-glucopyrano[1′,2′:4,5]-2-methylimidazoline which had a lactol ring in the sugar portion. The reason for the difference between these facts is now under studying.



Scheme 1

On the other hand, it has been known that the reaction of thioamides and amines give amidines[7] and the presence of metal salts such as mercuric chloride assists in driving the reaction to completion, owing to the formation of insoluble metal sulfides.[8] Direct substitution of equimolar amount of ethyl thiooxamidate (**7**) and benzylamine in ethanol at room temperature for an hour gave only *N*,*N*′-dibenzyl-thiooxamidic acid amide as precipitates, however, a solution of equimolar amount of **7** and mercuric chloride in methanol showed a strong acidity, indicating a chelate formation, and further addition of two mol of amine induced the precipitation of the sulfide. Thus, the partial hydrolysis of the product in *N*-hydrochloric acid liberated *N*-benzylcarbamimidoylformic acid (**6j**: R=benzyl) in 32% yield. Similar treatment of the chelate solution with **8** gave again **2** in 8% yield, but, other usual amines could not be condensed successfully. From these results presented in Scheme 1, it is concluded that the two methods mentioned above are not recommendable, because the formation of **4** is accompanied with side reaction and is not realized in the case of usual amines.

Substitution of Potassium Thiooxamidate or Its Free Acid with Amines. Thiooxamidic acid is stable in a salt state, but potassium salt decomposes by refluxing in dioxane with liberation of hydrogen sulfide, and the free acid decomposes gradually in acidic solution to carbon dioxide, hydrogen sulfide and hydrogen cyanide. Moreover, it was found that potassium thiooxamidate (**9**)[9] decomposed extensively by addition of Ag^+, Hg^{2+}, or Pb^{2+} ion with liberation of the corresponding metal sulfide, and formed corresponding chelate compounds by addition of Cu^{2+}, Fe^{3+}, or Zn^{2+} ion. Consequently, the substitutions were examined in the absence or presence of metal ion, and metal oxides such as mercuric oxide and lead oxide were found to be the best accelerator on the substitutions.

Direct substitution of **9** with four equivalent of ammonia in absolute methanol under vigorous stirring at room temperature gave carbamimidoylformic acid (**6a**: R=H) in 90% yield, whose structure was supported by characteristic IR absorptions of amidine (3350, 3310, and 3020 cm^{-1}) and intramolecular carboxylate (1640 cm^{-1}), and by its hydrolysis to oxalic acid in alkaline conditions. However, other amines

5) F.C. Schaefer, *J. Org. Chem.*, **27**, 3608 (1962).
6) M.H. Fischer and B.A. Lewis, *Chem. Ind.* (London), **1967**, 192 (1967).
7) A. Bernthsen, *Ann.*, **184**, 321 (1876).
8) A. Bernthsen, *ibid.*, **192**, 1 (1878).
9) A. Weddige, *J. Prakt. Chem.*, **9**, 132 (1874).

Table 1. *N*-Substituted-carbamimidoylformic acid (**6**)

No.	Compound R	Formula	Method	Time (hr)	Yield (%)	Mp. (°C, dec.)	Found (%) C	Found (%) H	Found (%) N	Calcd (%) C	Calcd (%) H	Calcd (%) N
a	hydrogen	$C_2H_4N_2O_2$	A	1	90	230	27.05	4.78	31.87	27.27	4.58	31.81
b	ethyl	$C_4H_8N_2O_2$	B	7	63	177—178	41.28	6.93	24.33	41.37	6.94	24.13
c	hydroxyethyl	$C_4H_8N_2O_3$	B	7	53	186—187	36.62	6.38	20.98	36.36	6.10	21.20
d	*i*-propyl	$C_5H_{10}N_2O_2$	B	7	65	182—183	45.94	7.80	21.84	46.14	7.75	21.53
e	*n*-butyl	$C_6H_{12}N_2O_2$	A	1	48	192	50.61	8.32	19.63	49.98	8.39	19.43
f	*i*-butyl	$C_6H_{12}N_2O_2$	A	1	45	191—192	50.18	8.15	19.20	49.98	8.39	19.43
g	*sec*-butyl	$C_6H_{12}N_2O_2$	B	5	67	180—182	49.58	8.39	19.58	49.98	8.39	19.43
h	*n*-hexyl	$C_8H_{16}N_2O_2$	A	1	46	164—165	55.57	9.22	16.26	55.79	9.36	16.27
i	cyclohexyl	$C_8H_{14}N_2O_2$	B	5	75[d]	173	56.28	8.31	16.28	56.45	8.29	16.46
j	benzyl	$C_9H_{10}N_2O_2$	A	1	64	172—173	60.66	5.97	15.43	60.66	5.66	15.72
k	*p*-tolyl	$C_9H_{10}N_2O_2$	B	3	51	210—213	61.56	5.68	15.93	60.66	5.66	15.72
l	*o*-tolyl	$C_9H_{10}N_2O_2$	B	3	55	162—163	60.57	5.88	15.77	60.66	5.66	15.72
m	a)	$C_{14}H_{24}N_2O_7$	B	3	66	203—204	50.51	7.37	8.42	50.59	7.28	8.43
n	b)	$C_{15}H_{20}N_2O_7$[c]	B	3	53	180—181	51.32	6.13	8.09	51.57	6.06	8.02

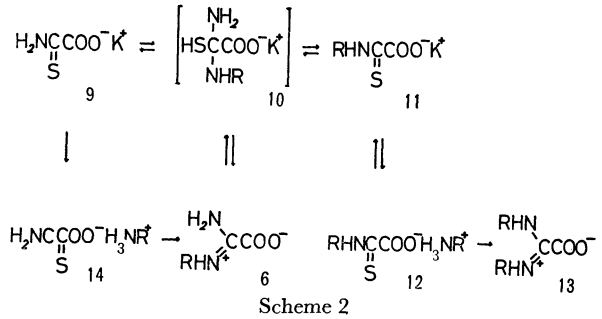
a) **6m**: RNH_2=cyclohexyl 2-amino-2-deoxy-α-D-glucopyranoside; $[\alpha]_D^{23}$ +114° (*c* 0.1, water).
b) **6n**: RNH_2=benzyl 2-amino-2-deoxy-α-D-glucopyranoside; $[\alpha]_D^{23}$ +164° (*c* 0.1, water).
c) Compound **6n** was analyzed as 1/2 hydrate.
d) The yield was 35% in the case of Method A.

did not react in the same conditions, probably due to the greater insolubility of **9** than products in methanol. The same substitution with alkylamines in water proceed much faster than in methanol, and gave **6**, potassium *N*-substituted-thiooxamidate (**11**) and/or the corresponding alkylamine salt (**12**) in fairly good yield, respectively, depending on conditions used (Method A). The formation of each product could be controlled by adjustment of the amount of water and amine, reaction period, and pH of the reaction mixture. And the mixture of the products was sometimes separated by crystallization.

In general, **6** is formed at first, the use of large amount of water accumulate **11**, and deposition of **12** is accelerated by use of large amount of amine and by neutralization of potassium ion. For example, the reaction of each 50 mmol of **9** and benzylamine in minimum amount of water (25 m*l*) for 15 min at room temperature deposited **6j** in 61% yield, then standing the filtrate overnight gave **11a** (R=benzyl) in 9% yield, and further neutralization of the filtrate caused the deposition of **12a** (R=benzyl) in 10% yield. A similar phenomenon was also observed in the case of cyclohexylamine.

The existence of an equilibrium in this reaction[10] was ascertained by the following experiment; *i. e.*, reaction of **11a** with seven equivalents of ammonia gave **6a**, **6j**, and **12a** in 22, 37, and 11% yield, respectively. From this result, it is obvious that α-alkylamino-α-amino-α-mercaptoacetic acid (**10**) should be exist as an intermediate in the equilibrium between **6**, **9**, and **11**, as shown in Scheme 2. Such a tetrahedral intermediate was deduced in the hydrolysis of thioimidate esters,[11] and also in the hydrolysis of amidines to amides from a kinetic study.[12]

As an attempted acceleration with a metal ion, Zn^{2+} was examined. Addition of zinc chloride to a suspended solution of **9** in methanol made a homogeneous brown solution. However, addition of amines to this brown solution caused the precipitation of a white chelate composed of **9** and zinc (1:1), which did not show the tendency of reaction with large excess amount of amines under stirring for a week at room temperature. A homogeneous mixture of equimolar amount of **9**, cylcohexylamine or benzylamine, and zinc cyanide or equimolar mixture of zinc chloride and sodium methoxide gave **6i** (R=cyclohexyl) or **6j** in 18 and 17% yield, respectively, under stirring for ten days. These facts indicate that the affinity of zinc to sulfur is very weak in the systems used.



Scheme 2

On the other hand, the structure of **12** was at first deduced to be α,α-bisalkylamino-α-mercaptoacetic acid, from the facts that **12b** (R=cyclohexyl) showed a intense peak *m/e* 187 ($C_8H_{13}NO_2S$) in the mass spectrum which indicates the presence of C–S bond, and the treatment of **12b** with mercuric oxide in methanol gave *N*,*N'*-dicyclohexyl-carbamimidoylformic acid (**13b**: R=cyclohexyl) in 85% yield. However, the deduction was discarded by the facts that it showed $\lambda_{max}^{H_2O}$ 270 nm (ε 8.04×10^3) instead of an end-absorption in usual amidine, and electrophoresis of **12a** at pH 8 showed two ninhydrin-positive spots, where benzylamine moved to the direction of the cathode and **11a** to the

10) R. L. Shriner and F. W. Neumann, *Chem. Rev.*, **35**, 351 (1944).
11) R. K. Chaturvedi and G. L. Schmir, *J. Amer. Chem. Soc.*, **91**, 737 (1969).
12) D. R. Robinson, *ibid.*, **92**, 3138 (1970).

anode. Successful conversion of **12** to **13** indicated the possibility of a synthesis of **6** by treatment of alkylammonium thiooxamidate (**14**) with metal oxides in methanol. In fact, **14** obtained from **9** and amine hydrochlorides or free thiooxamidic acid[13] and amines were smoothly converted to **6** by stirring at room temperature with mercuric oxide or lead oxide in methanol. This method (Method B) was successfully applied to alkyl- and arylamines, and also amino-sugars, as was summarized in Table 1. Among them, benzyl and cyclohexyl 2-amino-2-deoxy-α-D-glucopyranoside were newly prepared from the corresponding 2-acetamido derivatives by an improved method of Gross and Jeanloz.[14]

Contrary to common amidines, exchange-reaction of *N*-substituent in **6** or **13** was generally unsuccessful. For example, reaction of *N*-(*n*-butyl)-carbamimidoylformic acid (**6e**: R=*n*-butyl) and benzylamine at 200°C gave a decarboxylated product: *N,N'*-dibenzylformamidine in 64% yield, and reaction of **6j** and benzylamine in ethanol by refluxing for 5 hr gave *N*-benzylformamide in 37% yield. Direct condensation of **6a** and large excess amount of benzylamine at room temperature for 2 days gave **6j** in 2.8% yield.

Application of the new method mentioned here to the preparation of unsymmetric *N,N'*-disubstituted-carbamimidoylformic acid is now undertaking.

Experimental

All the melting points are uncorrected. The solutions were evaporated under diminished pressure at a bath temperarure not exceeding 45°C. Optical rotations were measured in a 0.5-dm tube at 578 and 546 nm with Carl-Zeiss Polarimeter. The infrared spectra were measured in KBr discs, and the NMR spectra were determined at 100 MHz with a JNM-100H spectrometer, using TMS as an internal reference. The mass spectra were obtained on a Hitachi RMU6E mass spectrometer, using a direct inlet and an ionization energy of 70 eV.

Reaction of Ethyl 1-Carbethoxyformimidate (1) and 2-Amino-2-deoxy-D-glucose (8) Hydrochloride. A suspended solution of 2-amino-2-deoxy-D-glucose hydrochloride (7 g, 33 mmol) and ethyl 1-carbethoxyformimidate (5 g, 34 mmol) in methanol (200 m*l*) was refluxed for 5 hr, and the hydrochloride unchanged was filtered off. Addition of two-fold of ether to the filtrate gave a white crystals, 2-carbomethoxy-4-(D-*arabino*-1',2',3',4'-tetrahydroxybutyl)-imidazole (**2**) which was recrystallized from methanol, in 10% yield (0.8 g). Mp 177.5—176°C; $[\alpha]_D^{23}$ −32° (*c* 1.0, water); UV (nm): λ_{max}^{MeOH} 267 (ε 1.25×10^4); IR (cm^{-1}): 1725 (C=O).

Found: C, 43.46; H, 5.58; N, 11.64%. Calcd for $C_9H_{14}N_2O_6$: C, 43.90; H, 5.73; N, 11.38%.

Concentration of the mother liquor gave a small amount of 3,6-diethoxy-2,5-dihydro-2,5-dioxo-pyrazine (**3**) which was recrystallized from methanol. Mp 167.5—168.2°C; NMR (τ): 5.37 (*q*, 2H, *J*=7.4 Hz), 8.50 (*t*, 3H); IR (cm^{-1}): 1725 (C=O).

Found: C, 49.18; H, 5.13; N, 14.32%. Calcd for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14%.

The compound **2** showed negative Fehling test, and the structure was determined as described before. Among them, the periodate oxidation was performed by the method of Fleury and Lange[15], using methyl α-D-glucopyranoside as a reference. The compound **2** consumed 3.23 mol of periodate at room temperature for 15 hr and 3.08 mol at 2.5°C for 18 hr, and the reference 2.30 and 1.94 mol, respectively.

2-Carbomethoxy-4-(D-arabino-1',2',3',4'-tetraacetoxybutyl)-imidazole. To a solution of acetic anhydride (1.74 g, 17 mmol) and pyridine (30 m*l*) was added **2** (0.7 g, 2.8 mmol) with shaking at room temperature, and the reaction mixture was concentrated, after standing for 3 hr. Crystallization of the residual precipitate from methanol gave 0.7 g (60.5%) of white crystals. Mp 171°C; $[\alpha]_D^{23}$ −9° (*c* 1.0, methanol); UV (nm): λ_{max}^{MeOH} 260 (ε 1.05×10^4); IR (cm^{-1}): 3250 (NH), 1745, and 1715 (C=O).

Found: C, 49.20; H, 5.33; N, 6.86%. Calcd for $C_{17}H_{22}N_2O_{10}$: C, 49.27; H, 5.36; N, 6.76%.

2-Oxalylamino-2-deoxy-D-glucose Methylester (5a). To a cooled solution of **1** (3.4 g, 23 mmol) in methanol (20 m*l*) was added dropwise a solution of **8** (5 g, 28 mmol) in methanol (200 m*l*), and the mixture was allowed to stand at room temperature for one day. To the resulted pale yellow solution was added half a volume of ether to give a yellow sirup which could not be crystallized. After a treatment of the sirup once with water, a part of it was crystallized from methanol-ether. Yield, 0.9 g (15%). Mp 188.5—189°C (dec.); $[\alpha]_D^{23}$ +49°→+22° (*c* 1.0, water, 24 hr).

Found: C, 40.99; H, 5.91; N, 5.86%. Calcd for $C_9H_{15}NO_8$: C, 40.75; H, 5.70; N, 5.28%.

2-Oxamidoylamino-2-deoxy-D-glucose. To a cooled solution of **5a** (0.1 g, 3.8 mmol) in methanol (50 m*l*) was passed an excess amount of ammonia, and the solution was evaporated to give a white powder which was crystallized from water-ethanol. Yield, 0.08 g (84%). Mp 190°C (dec.); $[\alpha]_D^{25}$ +24°→+21° (*c* 1.0, water, 45 hr).

Found: C, 38.51; H, 5.50; N, 10.96%. Calcd for $C_8H_{14}N_2O_7$: C, 38.40; H, 5.64; N, 11.20%.

Reaction of p-*Toluidine and 2.* A solution of *p*-toluidine (2.14 g, 20 mmol) and **1** (2.9 g, 20 mmol) in methanol (40 m*l*) was stood at room temperature for one hr, and then concentrated. The sirup obtained could not be crystallized. A solution of the sirup in N-hydrochloric acid was heated for 1.5 hr at 65°C, neutralized to pH 4.6, and concentrated to about half volume to give a white powder which was crystallized from water. The product melts at 158°C (dec.), and the structure could not be characterized. Yield, 1.6 g (39%). IR (cm^{-1}): 3270, 3160, 1655.

Found: C, 58.46; G, 5.35; N, 13.97%. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.58%.

On the other hand, treatment of the sirup with acetic or formic acid and evaporation were repeated twice to give a small amount of *N,N'*-di-(*p*-tolyl)-carbamimidoyl-*p*-toluidide. Mp 178—178.5°C (lit.[16] mp 182°C).

Found: C, 76.82; H, 6.46; N, 10.84%. Calcd for $C_{23}H_{23}N_3O$: C, 77.28; H, 6.49; N, 11.76%. From the mother liquor, a small amount of methyl *N*-(*p*-tolyl)-oxamidate (**5b**), mp 144.5—145.5°C (lit.[17], mp 145°C) was obtained.

Found: C, 62.34; H, 5.62; N, 7.38%. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25%.

When the above ester-exchange was performed in the presence of hydrochloride, a small amount of *N,N'*-di-*p*-tolyloxamide was obtained. Mp 264°C (lit.[18]), mp 269°C).

Found: C, 71.69; H, 5.89; N, 9.75%. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.10; N, 10.44%.

13) R. Rätz and H. Schroeder, *J. Org. Chem.*, **23**, 1931 (1958).
14) P. H. Gross and R. W. Jeanloz, *ibid.*, **32**, 2759 (1967).
15) P.F. Fleury and J. Lange, *J. Pharm. Chim.*, **107**, 196 (1933).
16) R. Anschütz and T. Charke, *Ann.*, **306**, 21 (1899).
17) R. Anschütz and T. Charke, *ibid.*, **306**, 14 (1899).
18) E. Willm and C. Cirard, *Ber.*, **8**, 1196 (1875).

N-Benzylcarbamimidoylformic Acid from Ethyl Thiooxamidate and Benzylamine. To an ice-cooled solution of mercuric chloride (13.5 g, 50 mmol) in ethanol (100 m*l*) was added ethyl thiooxamidate[9] (6.7 g, 50 mmol) to give white precipitates, and then further addition of benzylamine (10.7 g, 0.1 mol) in ethanol (10 m*l*) caused the precipitation of mercuric sulfide. The reaction mixture was filtered, and the filtrate was concentrated after addition of concentrated hydrochloric acid (5 m*l*) and water (100 m*l*), to give a sirup. After standing this sirup at room temperature for one day, it was dissolved in water and the solution was neutralized to pH 7.0 with N-sodium hydroxide to give white crystals. Yield, 3.0 g (32%), mp 170—171°C (dec.).

Found: C, 57.52; H, 6.03; N, 14.88%. Calcd for $C_9H_{10}N_2O_2 \cdot 1/2H_2O$: C, 57.74; H, 5.92; N, 14.97%.

When a solution of **7** (6.7 g, 50 mmol) and benzylamine (5.4 g, 50 mmol) in ethanol (100 m*l*) was stood at room temperature in the absence of metal oxide, a small amount of yellow crystals (*N,N'*-dibenzyl-thiooxamic acid amide) were precipitated, which was recrystallized from ethanol. Yield, 0.9 g (12%), mp 118—121°C. IR (cm^{-1}): 3260 (N-H), 1665 (C=O).

Found: C, 67.70; H, 5.55; N, 9.95%. Calcd for $C_{16}H_{16}N_2OS$: C, 67.59; H, 5.67; N, 9.85%.

General Preparation of N-*Substituted-carbamimidoylformic Acid (6) by Substitution of Potassium Thiooxamidate (9) with Amines in Water (Method A).* Addition of equimolar amount of amines to **9** in the minimum amount of water caused the deposition of **6** within 15 min–1 hr. If the product is soluble in water, **Method B** must be used, because the enforcement of deposition of **6** by neutralization of the reaction mixture yielded sometimes **12**, which was isolated in the case of benzylamine and cyclohexylamine. Results obtained were summarized in Table 1.

Potassium N-*Benzyl-thiooxamidate (11a).* To a solution of **9** (7.2 g, 50 mmol) in water (200 m*l*) was added benzylamine (5.4 g, 50 mmol) in water (100 m*l*), and then concentrated after standing for half an hour to give yellow crystals which was recrystallized in ethanol-water. (2:1 v/v). Yield, 10.0 g (86%), mp 235—238°C.

Found: C, 46.61; H, 3.60; N, 6.04%. Calcd for $C_9H_8KNO_2S$: C, 46.33; H, 3.46; N, 6.02%.

Alkylammonium N-*Substituted-thiooxamidate (12).* *a) Benzylammonium* N-*Benzylthiooxamidate (12a)*: A solution of **9** (4.3 g, 30 mmol) and benzylamine (4.3 g, 40 mmol) in water (50 m*l*) was stood for one day to deposit yellow crystals. Yield, 2.7 g (30%), mp 166—167°C (dec.).

Found: C, 63.32; H, 5.76; N, 9.56; S, 10.68%. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.56; H, 6.00; N, 9.27; S, 10.59%.

b) Cyclohexylammonium N-*Cyclohexylthiooxamidate (12b)*: A solution of **9** (14.3 g, 0.1 mol) and cyclohexylamine (25 g, 0.25 mol) in water (100 m*l*) was stood at room temperature for 15 hr, and neutralized to pH 5.0 with N-hydrochloric acid. The pale yellow crystal separated was purified from ethanol. Yield, 9.2 g (32.2%), mp 181—182°C (dec.). MS (*m/e*): 187 ($C_8H_{13}NO_2S$), 141 ($C_7H_{11}NS$), 112, 106, 99 ($C_6H_{13}N$; cyclohexylamine).

Found: C, 59.04; H, 9.05; N, 9.69; S, 11.25%. Calcd for $C_{14}H_{26}N_2O_2S$: C, 58.72; H, 9.15; N, 9.78; S, 11.18%.

The structure of **12** was determined as described before. Among which, electrophoresis was carried out on Toyo Filterpaper No. 51 at pH 8 and 20 Volt/cm for 2 hr with phosphate buffer. In the case of **12a**, *N*-benzylthiooxamidic acid moved 9.7 cm to anode and benzylamine 4.6 cm to cathode, whereas reference substances moved as the same distance.

N,N'-*Disubstituted-carbamimidoylformic Acid (13).* *a) Benzyl Derivative (13a)*: A suspended solution of **12a** (6 g, 20 mmol) and mercuric oxide (4.8 g, 22 mmol) was stirred for 15 hr at room temperature, and filtered. Concentration of the filtrate gave white crystals which was purified from water-methanol (1:1). Yield, 3.2 g (60%), mp 143—144°C.

Found: C, 71.89; H, 5.94; N, 10.31%. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44%.

b) Cyclohexylamine Derivative (13b): A similar treatment of **12b** with mercuric oxide gave **13b** in 85% yield, which was purified from ethanol. Mp 139°C.

Found: C, 66.40; H, 9.77; N, 10.93%. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10%.

General Preparation of 6 by Treatment of 14 with Lead Oxide (Method B). A mixture of **14**, which was prepared from equimolar amount of **9** and amine hydrochlorides or free thiooxamidic acid[13] and amines, and about four equimolar amount of lead oxide in suitable amount of methanol was shaked at room temperature for 3 to 7 hr, and lead sulfide was filtered off. Concentration of the filtrate gave *N*-monosubstituted-carbamimidoylformic acids usually in 50—80% yield, as shown in Table 1.

Benzyl 2-Amino-2-deoxy-α-D-glucopyranoside Hydrochloride. A solution of benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside (31 g, 0.1 mol) and potassium hydroxide (60 g, 1.1 mol) in ethanol (150 m*l*) was refluxed in an oil-bath for 5 hr at 120—125°C, neutralized with concentrated hydrochloric acid (95 m*l*) under cooling, and potassium chloride precipitated was then filtered off. Evaporation of the filtrate gave crystals in 85% yield, which was recrystallized from methanol. Mp 235—236°C (dec.); $[\alpha]_D^{23}$ +122° (*c* 1.0, water).

Found: C, 50.84; H, 6.43; N, 4.97%. Calcd for $C_{13}H_{19}NO_6HCl$: C, 51.06; H, 6.59; N, 4.58%.

Cyclohexyl 2-Amino-2-deoxy-α-D-glucopyranoside Hydrochloride. A similar treatment of cyclohexyl 2-acetamido-2-deoxy-α-D-glucopyranoside, which was prepared from 2-acetamido-2-deoxy-D-glucose by the method of the authors[19] in 60% yield (Mp 184—186°C; $[\alpha]_D^{23}$ +126° (*c* 1.0, water); Found: C, 55.39; H, 8.03; N, 4.78%. Calcd for $C_{14}H_{25}NO_6$: C, 55.43; H, 8.31; N, 4.62%), with potassium hydroxide gave crystals in 35% yield, which was recrystallized from methanol. Mp 250°C (dec.); $[\alpha]_D^{23}$ +120° (*c* 1.0, water).

Found: C, 48.28; H, 8.34; N, 4.62%. Calcd for $C_{12}H_{23}NO_5HCl$: C, 48.39; H, 8.13; N, 4.70%.

Attempted Substitutions of 6 with Amines. a) A suspended solution of **6a** (0.88 g, 10 mmol) in benzylamine (30 m*l*) was stirred for two days to give pale yellow homogeneous solution. This solution was neutralized with acetic acid, and mixed with a small amount of water. Filtration of the insoluble material gave **6j** in 2.8% yield. Mp 170°C.

b) A mixture of **6e** (1.4 g, 10 mmol) and benzylamine (2.1 g, 20 mmol) was heated at 200°C for 1 hour, and crystals appeared after cooling was filtered and recrystallized from ligroin. This crystals was determined to be *N,N'*-dibenzylformamidine from elemental analysis and mp. Yield, 1.4 g, (63.5%). Mp 76—77°C (lit.[20] mp 79°C) (Found: C, 80.59; H, 7.10; N, 12.51%. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49%).

c) A solution of **6j** (1.8 g, 10 mmol) and benzylamine (1.1 g, 10 mmol) in the ethanol was refluxed for 5 hr, and concentrated. The residue was dissolved in ether, and insoluble materials (**6j**, 0.8 g) was filtered off. Concentration of the filtrate gave *N*-benzylformamide, which was recrystallized from ligroin - ether. Yield, 0.5 g (37%). Mp 61—62°C

19) J. Yoshimura, H. Ando, Y. Takahashi, H. Ono, and T. Sato, *Nippon Kagaku Zasshi*, **85**, 142 (1964).

20) O. Mathieson, Brit. 807767 (1959).

(Lit.[21]), mp 61°C) (Found: C, 71.33; H, 6.47; N, 10.40%. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36%).

21) Houben-weyl, "Methoden der Organischen Chemie," Vol. XI-12, ed. by Eugen Müller, Georg Thieme Verlag, Stuttgart, Germany (1958), p. 29.

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