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Cyclic Guanidines. I. Synthesis of Hypoglycemic 1-Substituted 2-Imino-1,3-diazacycloalkanes[1]

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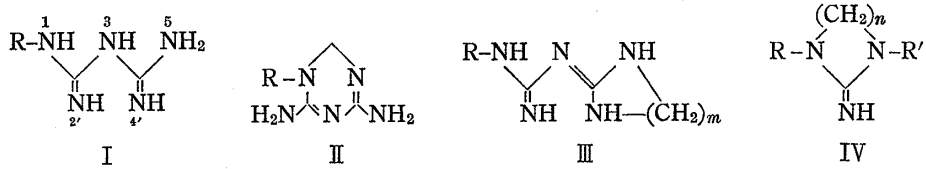
Reaction of 2-benzylaminoethylamine (**1a**) with cyanogen bromide was investigated under various conditions to obtain desired 1-benzyl-2-iminoimidazolidine (**2a**) in quantitative yield. In addition, in the presence of base this reaction gave 3-carbamoyl derivative (**3a**) or 3-methoxyformimidoyl derivative (**6**) of **2a**. The 3-carbamoyl group of **3a** was rearranged to the 2-imino group on heating to give 2-carbamoylimino derivative (**5a**). On the other hand, **6** was derived to **3a** or 3-methoxycarbonyl derivative (**7**) by heating under strong or mild acidic medium, respectively. 3-Amidino-1-benzyl-2-iminoimidazolidine (**9**) was prepared through 2-benzylaminoethylguanidine (**8**) from **1a**. 1-Benzyl- or 1-benzhydryl-2-cyanoimino-1,3-diazacycloalkanes (**10**) having five-, six- and seven-membered ring size were obtained on heating of **1** with dimethyl cyanoimidodithiocarbonate and then the cyano group of **10** was selectively removed to yield 1-benzyl- or 1-benzhydryl-2-imino-1,3-diazacycloalkanes (**2**).

Some of 1-substituted 2-imino-1,3-diazacycloalkane derivatives showed hypoglycemic activity.

Keywords——cyclic guanidine; 1-benzhydryl-2-imino-1,3-diazacycloalkane; cyclization; elimination; rearrangement; hypoglycemic activity

Many compounds possessing a guanidine group as a biological active substituent have been known. Alkyl or aralkyl biguanides (I) have been used as hypoglycemic drugs abreast with sulfonyl urea derivatives. The interest in guanidino group led us to synthesize some cyclic guanidine derivatives in an attempt to exploit novel hypoglycemics.

As hypoglycemic cyclic guanidines, 1-substituted 2,4-diamino-1,6-dihydro-*s*-triazine (II)[3] linked between N_1 and N_5 of biguanide with methylene and 2-substituted guanidino-1,3-diazacycloalkanes (III)[4] linked between $N_{4'}$ and N_5 with an alkylene chain have been reported. This report deals with the synthesis of 1-substituted 2-imino-1,3-diazacycloalkanes (IV)[5] linked between N_1 and N_3 of aralkyl substituted biguanide with an alkylene chain and the related cyclic guanidine derivatives.



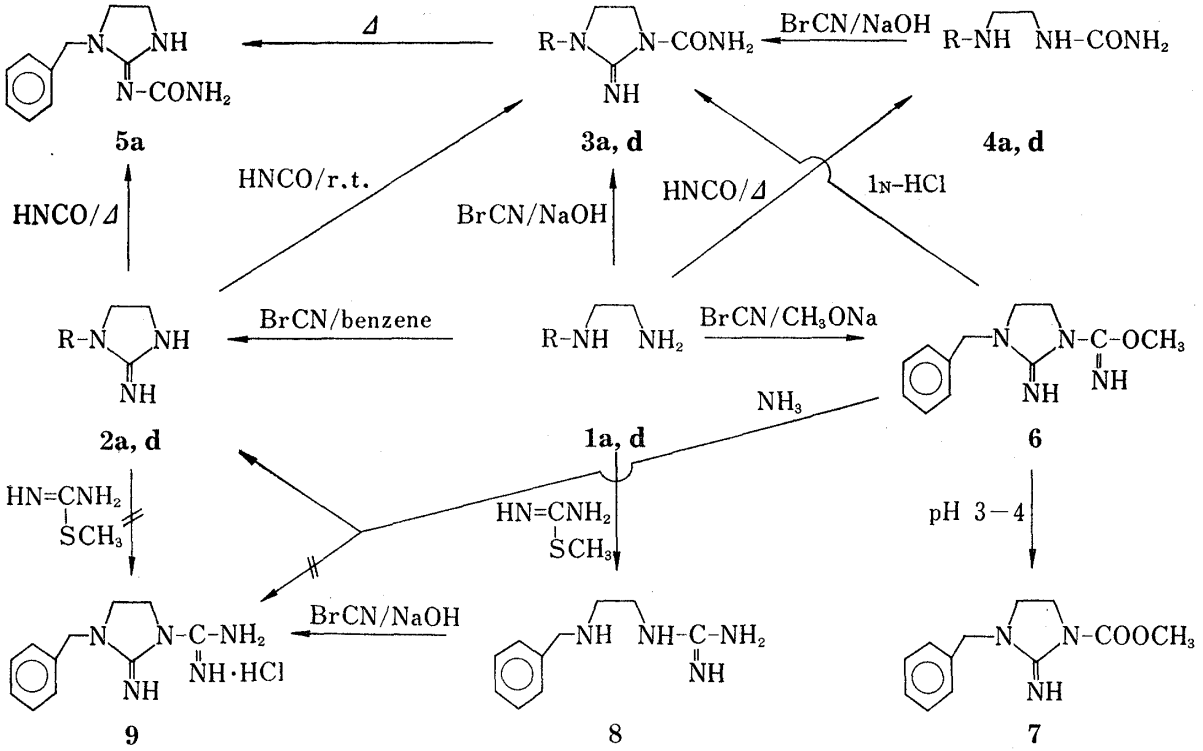
I II III IV

R=alkyl, aralkyl; R′=amidino, alkyl, acyl; m=2, 3; n=2—4

Chart 1

1) Presented at the 97th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1977.
2) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo 132, Japan.*
3) J.G. Lombardino, *J. Med. Chem.*, **6**, 213 (1963).
4) R. Sauter and G. Gris, Ger. Offen, 2205744 (1973) [*Chem. Abstr.*, **79**, 126522*w* (1973)].
5) For the sake of convenience, all cyclic guanidines are shown and named here in 2-imino form, one of two possible tautomeric forms, and the 1 position of their compounds was always fixed upon the nitrogen substituted with benzyl or benzhydryl group.

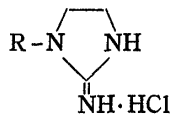
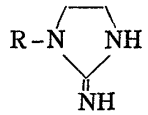
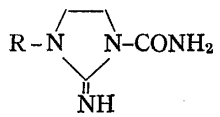
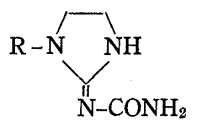
A synthesis of 3-amidino-1-benzyl-2-iminoimidazolidine (**9**) was first undertaken. In order to prepare 1-benzyl-2-iminoimidazolidine (**2a**) as a key intermediate for this purpose, reaction of 2-benzylaminoethylamine (**1a**) with cyanogen bromide was widely investigated.



a: R=benzyl, d: R=benzhydryl

Chart 2

TABLE I. NMR Spectra of 1-Benzyl-2-iminoimidazolidine and Its 2- or 3-Carbamoyl Derivatives (**2a**, **3a** and **5a**)

Compound		Chem. shift of methylene group (δ from TMS)		
		Benzyl	C-4	C-5
	**2a**	4.53(s)	3.63(s)	
	**2a**	4.42(s)	3.30(s)	
	**3a**	4.36(s)	3.62(m)	3.24(m)
	**5a**	4.44(s)	3.39(m)	3.21(m)

Solvent=d_6-DMSO; R=benzyl-.

According to Wollwerber's procedure[6] a solution of cyanogen bromide in benzene was added to a benzene solution of **1a** however the isolation of **2a** from the reaction mixture, which contained the hydrobromide of **1a** formed in initial stage of the reaction, was very difficult. When the addition order of the reagents was reversed in order to avoid excess of **1a**, **2a** was obtained in quantitative yield.

On the other hand, the reaction of **1a** with cyanogen bromide in aqueous sodium hydroxide gave 1-benzyl-3-carbamoyl-2-iminoimidazolidine (**3a**) as a colorless crystal, mp 140—141°, in 14% yield. The analytical values were in good agreement with the molecular formula, $C_{11}H_{14}N_4O$, and its infrared (IR) spectrum showed strong absorption at 1670 cm^{-1} (C=O). Its structure was determined to be 3-carbamoyl derivative by nuclear magnetic resonance (NMR) spectrum, in which the C-4 methylene signal of **3a** shifted to lower field than that of 2-carbamoyl derivative (**5a**), prepared as described below, as shown in Table I.

Formation of **3a** in this reaction was explained as follows. The reaction of **1a** with cyanogen bromide gave 2-benzylaminoethylcyanamide and then the cyanamide derivative was partially hydrolyzed with alkali to 2-benzylaminoethylurea (**4a**), which further reacted with excess cyanogen bromide to yield **3a**. Thus, in order to prepare **3a** in better yield, the hydrochloride of **1a** was heated with potassium cyanate in dimethylsulfoxide (DMSO) to afford **4a** and then treatment of **4a** with cyanogen bromide gave **3a** in a moderate yield as was expected.

The 3-carbamoyl group of **3a** showed interesting behavior. It was observed in the NMR spectrum that **3a** in d_6-DMSO came to an equilibrium between **2a**, **3a** and **5a**, in which the 3-carbamoyl group was rearranged to 2-imino group, on standing at room temperature overnight. When the solution was heated at 100°, **2a** and **3a** almost changed to **5a**. So, **3a** was heated in DMSO at 100° or refluxed in ethanol to afford 1-benzyl-2-carbamoyliminoimidazolidine (**5a**) in a good yield. However, the hydrochloride of **3a** did not changed under the same conditions. Furthermore, reaction of the hydrochloride of **2a** with potassium cyanate in DMSO at room temperature for several hours gave **3a** in 26% yield, after acidic treatment of the reaction mixture to avoid the rearrangement of **3a** to **5a**. The above reaction was carried out at 100° to yield directly **5a** in a good yield.

Reaction of **1a** with cyanogen bromide and sodium methoxide in methanol gave 1-benzyl-2-imino-3-methoxyformimidoylimidazolidine (**6**) in 10% yield. When an aqueous solution of **6** was heated at 50—60°, maintaining pH 3—4 with diluted hydrochloric acid, 1-benzyl-2-imino-3-methoxycarbonylimidazolidine (**7**) was obtained, whereas heating of **6** in 1 N hydrochloric acid gave **3a**.

An attempt of reaction of **2a** with methylisothiourea to yield 3-amidino-1-benzyl-2-iminoimidazolidine (**9**) was unsuccessful. Elimination of methyl mercaptan from methylisothiourea occurred because of very strong basicity of **2a** and dicyandiamide was isolated from the reaction mixture. Also, the preparation of **9** from **6** and ammonia was tried, but 3-methoxyformimidoyl group was eliminated to yield only **2a**. By a method similar to that producing **3a** through **4a** from **1a**, **9** could be successfully obtained. Reaction of **1a** with methylisothiourea gave 2-benzylaminoethylguanidine (**8**), which was treated with cyanogen bromide in aqueous alkali to give **9** in 27% yield.

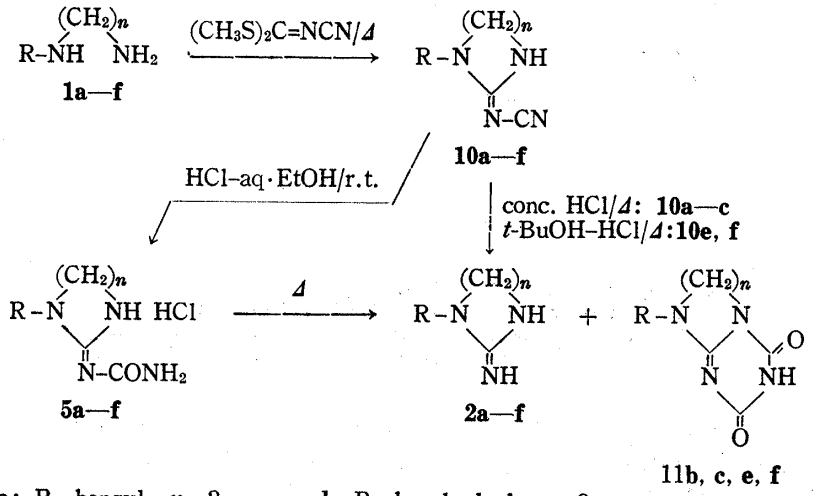
Grisar and co-workers[7] reported that the lactamimides having bulky group such as benzhydryl group showed hypoglycemic activity. On the analogy of the cyclic guanidine and lactamimide in structure, we designed synthesis of the cyclic guanidines having benzhydryl and benzyl groups as bulky groups, and having various ring size.

6) H. Wollwerber, R. Hiltmann, K. Stopel, and G. Kronber, Belg. Patent 613662 (1962) [*Chem. Abstr.*, **57**, 15121*e* (1962)].
7) J.M. Grisar, G.P. Claxton, N.L. Wiech, P.N. Lucas, R.D. Mackenzie, and S. Goldstein, *J. Med. Chem.*, **16**, 885 (1973).

In the same manner as with 1-benzyl derivatives, 1-benzhydryl-2-iminoimidazolidine derivatives (**2d** and **3d**) were obtained from 2-benzhydrylaminoethylamine (**1d**) in good yield. However, preparation of six- and seven-membered 1-substituted cyclic guanidines was unsuccessful in a method similar to that described above, because of the low reactivity of cyanogen bromide. In order to synthesize the benzhydryl substituted compounds more active reagent was required.

As active reagents for preparing six- or seven-membered cyclic guanidines from alkylenediamines, cyanamide,[8] guanidine,[9] nitroguanidine,[10] and methylisothiourea[10] have been known. Furthermore, N-substituted imidodithiocarbonate, for example, dimethyl cyanoimidodithiocarbonate,[11] dimethyl *p*-toluenesulfonylimidodithiocarbonate,[12] and N-alkoxy(methylthio)methylene carbamates[13] have been reported recently.

A mixture of equimolar amounts of ω-benzyl or ω-benzhydrylaminoalkylamine (**1a—f**) and dimethyl cyanoimidodithiocarbonate was heated at 100—200° to give 1-substituted 2-cyanoimino-1,3-diazacycloalkanes (**10a—f**). Although Bultzer and co-worker[11a] and Sauter and co-worker[11b] did not report the preparation of seven membered ring compound, 1-benzhydryl-2-cyanoiminoperhydro-1,3-diazepine (**10f**) could be obtained on heating at 220°.



a: R=benzyl, n=2 **d**: R=benzhydryl, n=2
b: R=benzyl, n=3 **e**: R=benzhydryl, n=3
c: R=benzyl, n=4 **f**: R=benzhydryl, n=4

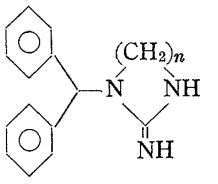
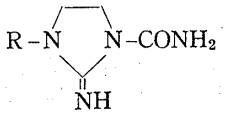
Chart 3

Next, removal of the cyano group of **10** was required to prepare the cyclic guanidines (**2**). 1-Benzyl derivatives (**10a—c**) were heated in concentrated hydrochloric acid to give 1-benzyl-2-imino-1,3-diazacycloalkanes (**2a—c**). However, heating of 1-benzhydryl derivatives (**10d—f**) in diluted hydrochloric acid caused elimination of the benzhydryl group at the same time. Under mild conditions in acidic medium **10a—f** gave only 2-carbamoylimino derivatives (**5a—f**). It was found that heating of the hydrochloride of **5** at 200° gave **2** along with by-product, *s*-triazine derivatives (**11**). However, the yield of **2** was only about 30—40%. Heating of six- or seven-membered ring compounds (**10e, f**) in *t*-butanol containing hydro-

8) B. Ascock, A. Lawson, and D.H. Miles, *J. Chem. Soc.*, **1961**, 5120.
9) D.J. Brown and R.F. Evans, *J. Chem. Soc.*, **1962**, 4039.
10) L.S. Hafner and R.F. Evans, *J. Org. Chem.*, **24**, 1157 (1957); A.F. Mckay and G.F. Wright, *J. Am. Chem. Soc.*, **70**, 430 (1948).
11) *a*) C.M. Baltzer and C.G. McCarty, *J. Org. Chem.*, **38**, 155 (1973); *b*) R. Sauter and W. Reuter, Ger. Offen. 2205745 (1973) [*Chem. Abstr.*, **79**, 146548*n* (1973)].
12) P.R. Atkins, S.E.J. Glue, and I.T. Kay, *J. Chem. Soc., Perkin I*, **1973**, 2644.
13) J.V. Rodrick and H. Rapoport, *J. Org. Chem.*, **36**, 46 (1971).

chloric acid of 3—4 molar equivalents for several hours gave **2e, f** in good yields. On the other hand, five-membered ring compound (**10d**) gave only 2-carbamoylimino derivative (**5d**) under the same conditions. This reaction was presumed to proceed as follows. On heating of **10d—f** in *t*-butanol containing hydrochloric acid, *t*-butanol added to the cyanamide group of **10** to yield O-*t*-butylisourea, which decomposed to 2-*t*-butoxycarbonylimino derivative in the case of **10e, f** while to 2-carbamoyilmino derivative in the case of **10d**, because of the difference in the basicity between adducts of *t*-butanol to **10e, f** and that of **10d**.[14] Then, 2-*t*-butoxycarbonylimino derivative decomposed easily to cyclic guanidines (**2e, f**).

Table II. Hypoglycemic Activity of 1-Substituted Cyclic Guanidines

Compound	Plasma glucose[a] Dose (mg/kg, *p.o.*)	% Reduction
 **2d—f**	25	20—30
 **3a, d**	5—25	30—60

R=benzyl and benzhydryl; n=2—4.
a) The test compound was orally administered to a rat which had been fasted overnight. Plasma glucose was determined by the glucose oxidase method at 2, 3, and 5 hour after the administration.

Hypoglycemic activity of 1-substituted 2-imino-1,3-diazacycloalkane derivatives obtained above was determined in normal fasted rats and is shown in Table II. 1-Benzhydryl-2-imino-1,3-diazacycloalkanes (**2d—f**) and 1-substituted 3-carbamoyl-2-iminoimidazolidines (**3a, d**) exhibited hypoglycemic activity but 3-amidino-1-benzyl-2-iminoimidazolidine (**9**) fixed between N_1 and N_3 of biguanide with an ethylene chain had no activity. It was suggested that the presence of bulky group is also preferable to show hypoglycemic activity in the cyclic guanidines. The structure–activity relationships in a series of cyclic guanidines will be reported elsewhere in detail.

Experimental

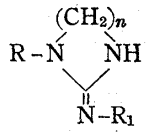
All melting points are uncorrected. IR spectra were recorded with a Hitachi 285 spectrometer. NMR spectra were taken with a Hitachi Perkin-Elmer R-20B (60 MHz) or a Varian EM-360 (60 MHz) spectrometer with tetramethylsilane as an internal standard (δ value), s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

1-Substituted 2-Imino-1,3-diazacycloalkanes (2a—f)——Compounds **2a—f** were prepared by following methods and are shown in Table III.

Method A——To a solution of cyanogen bromide (4.5 g, 40 mmol) in 150 ml of benzene was added dropwise a solution of **1a** (6.0 g, 40 mmol) in 50 ml of benzene with stirring at room temperature. The mixture was stirred at room temperature over a period of 2—3 hr. A solid separated out was collected by filtration to give 9.8 g (98%) of the hydrobromide of **2a**.

14) 1-Benzhydryl-2-cyanoimino-3-alkylimidazolidine gave easily 1-benzhydryl-2-imino-3-alkylimidazolidine under the same conditions, because the basicity of the intermediate, O-*t*-butylisourea, increased on alkylation of **10d** at 3 position, as will be described in a following paper.

TABLE III. 1-Substituted 2-Imino-1,3-diazacycloalkane Derivatives (**2**, **5** and **10**)



No.	R_1	Method or reaction condition (°C, min)	Yield (%)	mp (°C)	IR (cm^{-1})	Formula	Analysis Calcd. (Found) C	H	N
2a	H	A	98	219—221	1660(C=N)	$C_{10}H_{14}ClN_3$	56.73	6.67	19.85
		C	82	(HCl)	1570(C=N)		(56.49	6.75	19.94)
2b	H	B	43	160—164	1620(C=N)	$C_{11}H_{16}ClN_3$	58.58	7.15	18.62
				(HCl)	1590(C=N)		(58.26	7.15	18.42)
2c	H	B	40	163—165	1660(C=N)	$C_{12}H_{18}ClN_3$	60.15	7.56	17.52
				(HCl)	1620(C=N)		(60.04	7.52	17.21)
					1570(C=N)				
2d	H	A	93	269—270	1660(C=N)	$C_{16}H_{18}ClN_3$	66.77	6.30	14.60
				(HCl)	1590(C=N)		(66.66	6.34	14.84)
					1565(C=N)				
2e	H	B	38	218—220	1660(C=N)	$C_{17}H_{20}ClN_3$	67.65	6.68	13.92
		D	58	(HCl)	1630(C=N)		(67.77	6.73	13.92)
					1600(C=N)				
2f	H	B	40	225—227	1640(C=N)	$C_{18}H_{22}ClN_3 \cdot$	67.16	7.13	12.93
		D	62	(HCl)	1600(C=N)	$1/2H_2O$	(67.33	6.87	13.25)
5a	$CONH_2$	H	88	203—205	1710(C=O)	$C_{11}H_{15}ClN_4O$	51.87	5.94	22.00
		I	54	(HCl)	1620(C=N)		(51.62	5.89	21.89)
		J	93						
		K	73						
5b	$CONH_2$	J	54	210—214	1700(C=O)	$C_{12}H_{17}ClN_4O$	53.63	6.38	20.85
		K	76	(HCl)	1640(C=N)		(53.93	6.41	20.98)
5c	$CONH_2$	K	77	173—175	1700(C=O)	$C_{13}H_{19}ClN_4O$	55.21	6.76	19.81
				(HCl)	1620(C=N)		(55.16	6.46	19.48)
5d	$CONH_2$	K	92	180—182	1720(C=O)	$C_{17}H_{19}ClN_4O$	61.71	5.79	16.94
				(HCl)	1595(C=N)		(61.53	5.92	16.81)
5e	$CONH_2$	K	83	200—202	1710(C=O)	$C_{18}H_{21}ClN_4O$	62.69	6.14	16.25
				(HCl)	1630(C=N)		(62.54	6.15	16.24)
5f	$CONH_2$	K	75	178—180	1720(C=O)	$C_{19}H_{23}ClN_4O$	63.58	6.46	15.61
				(HCl)	1610(C=N)		(63.69	6.53	15.67)
10a	CN	100—120 15	82	134—136	2170(C≡N)	$C_{11}H_{12}N_4$	65.98	6.04	27.98
					1600(C=N)		(65.77	6.06	27.76)
10b	CN	100—120 15	78	170—172	2150(C≡N)	$C_{12}H_{14}N_4$	67.27	6.59	26.15
					1580(C=N)		(67.13	6.61	26.14)
10c	CN	180—200 10	27	145—146	2150(C≡N)	$C_{13}H_{16}N_4$	68.39	7.06	24.59
					1580(C=N)		(68.63	7.07	24.53)
10d	CN	180—200 15	77	180—182	2170(C≡N)	$C_{17}H_{16}N_4$	73.89	5.84	20.28
					1610(C=N)		(73.55	5.94	20.15)
10e	CN	200—220 15	72	234—236	2160(C≡N)	$C_{18}H_{18}N_4$	74.45	6.25	19.30
					1580(C=N)		(74.30	6.28	19.02)
10f	CN	200—220 20	8	157—158	2160(C≡N)	$C_{19}H_{20}N_4$	74.98	6.62	18.41
					1580(C=N)		(75.30	6.62	18.41)

HCl=hydrochloride.

Method B——The hydrochloride of **5e** (2.74 g, 8 mmol) was heated at 200—220° for 30 min. The reaction mixture was mixed with water and an insoluble solid was collected to give 0.67 g (25%) of **11e**, mp 243—245°. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O). *Anal.* Calcd. for $C_{19}H_{18}N_4O_2$: C, 68.24; H, 5.42; N, 16.76. Found: C, 68.37; H, 5.49; N, 16.83.

The aqueous filtrate was treated with 2 N NaOH and extracted with $CHCl_3$. The extract was washed with a saturated aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was treated with HCl–EtOH and the solution was evaporated *in vacuo* to give 0.92 g (38%) of the hydrochloride of **2e**.

By the same procedure as described above, following compounds were isolated from the reaction mixture.

11b, Yield 29%, mp 220—222°. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O). *Anal.* Calcd. for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.42; H, 5.50; N, 21.55.

11c, Yield 39%, mp 185—188°. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). *Anal.* Calcd. for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.83; H, 5.89; N, 20.77.

11f, Yield 23%, mp 245—247°. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). *Anal.* Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.89; H, 5.91; N, 15.96.

Method C——A mixture of **10a** (1.00 g, 5 mmol) in 5 ml of conc. HCl was heated for 10 hr and evaporated to dryness *in vacuo*. The residue was mixed with 10 ml of 2 N NaOH and extracted with $CHCl_3$. The extract was worked up as method B to give 0.86 g (82%) of **2a**.

Method D——A mixture of **10e** (0.58 g, 2 mmol) and 0.60 ml of conc. HCl in 10 ml of *t*-BuOH was heated for 6 hr. The mixture was worked up as Method C to give 0.34 g (58%) of **2e**.

1-Benzyl-3-carbamoyl-2-iminoimidazolidine (**3a**)

Method E——To a solution of **1a** (3.0 g, 20 mmol) in 30 ml of 2 N NaOH was added portionwise cyanogen bromide (3.2 g, 30 mmol) at room temperature. The mixture was stirred for 30 min. A solid separated from the reaction mixture was collected to give 0.61 g (14%) of **3a**, mp 140—141° (from MeOH). IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O). *Anal.* Calcd. for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.30; H, 6.55; N, 26.01.

The free base of **3a** was treated with HCl–EtOH to give the hydrochloride of **3a**, mp 182—183°. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). *Anal.* Calcd. for $C_{11}H_{15}ClN_4O$: C, 51.87; H, 5.94; N, 22.00. Found: C, 51.64; H, 5.96; N, 21.71.

Method F——A mixture of the hydrochloride of **1a** (1.86 g, 10 mmol) and potassium cyanate (0.88 g, 11 mmol) in 8 ml of DMSO was heated at 100—110° for 1 hr. The mixture was concentrated to dryness *in vacuo*. The residue was dissolved in 15 ml of 2 N NaOH. To the solution was added portionwise cyanogen bromide (1.5 g, 15 mmol) under stirring and the mixture was continued to stir at room temperature for further 30 min. A solid separated from the reaction mixture was collected to give 0.75 g (34%) of **3a**.

Method G——A mixture of the hydrochloride of **2a** (0.84 g, 4 mmol) and potassium cyanate (0.32 g, 4 mmol) in 4 ml of DMSO was stirred at room temperature for 2—3 hr. After addition of 0.5 ml of conc. HCl, the mixture was concentrated to dryness *in vacuo*. The residue was mixed with 2 N NaOH and extracted with $CHCl_3$. The extract was worked up as usual to give 0.22 g (26%) of **3a**.

1-Benzhydryl-3-carbamoyl-2-iminoimidazolidine (**3d**)——By method F, **3d** was prepared from the hydrochloride of **1d** (1.3 g, 5 mmol) in yield of 0.73 g (51%), mp 115—116°. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). NMR (d_6-DMSO) δ: 6.68 (1H, s, ArCH), 3.45 (2H, m, C_4–CH_2), 3.06 (2H, m, C_5–CH_2). *Anal.* Calcd. for $C_{17}H_{18}N_4O$: C, 69.36; H, 6.16; N, 19.04. Found: C, 69.12; H, 6.03; N, 19.28.

The free base of **3d** was converted to the hydrochloride, mp 197—198°. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O). *Anal.* Calcd. for $C_{17}H_{19}ClN_4O$: C, 61.72; H, 5.79; N, 16.94. Found: C, 61.69; H, 5.80; N, 17.04.

1-Substituted 2-Carbamoyliminoimidazolidines (**5a—f**)——Compounds **5a—f** were prepared by following methods and are shown in Table III.

Method H——A mixture of **3a** (1.0 g, 4.6 mmol) in 5 ml of DMSO was heated at 100° for 15 min. After cooling, the mixture was poured into water. A solid was collected to yield 0.88 g (88%) of **5a**.

Method I——A mixture of **3a** (1.0 g, 4.6 mmol) in 20 ml of EtOH was refluxed for 2 hr and concentrated to dryness *in vacuo*. The residue was recrystallized from EtOH to give 0.54 g (54%) of **5a**.

Method J——A mixture of the hydrochloride of **2a** (2.56 g, 10 mmol) and potassium cyanate (0.81 g, 10 mmol) in 30 ml of DMSO was heated at 100° for 3 hr. The mixture was concentrated to dryness *in vacuo* and the residue was mixed with water. A solid was collected to give 2.02 g (93%) of **5a**.

Method K——A mixture of **10a** (0.80 g, 4 mmol) in 4 ml of 10% HCl in aqueous EtOH was stirred overnight. The mixture was concentrated *in vacuo* to give 0.74 g (73%) of the hydrochloride of **5a**.

1-Benzyl-2-imino-3-methoxyformimidoylimidazolidine Hydrochloride (**6**)——To a mixture of **1a** (6.0 g, 40 mmol) and sodium methoxide (6.4 g, 120 mmol) in 120 ml of MeOH was added portionwise cyanogen bromide (8.1 g, 80 mmol) under stirring at 50—60°. The mixture was stirred at room temperature for 20 min and then evaporated to dryness *in vacuo*. The residue was mixed with water and extracted with $CHCl_3$. The extract was evaporated *in vacuo* to give 2.4 g of an oily residue, which was dissolved in 20 ml of absolute MeOH. The solution was acidified with HCl–MeOH to pH 3—4 and evaporated to dryness *in vacuo* to give 1.1 g (10%) of **6**, mp 138—139°. IR ν_{max}^{KBr} cm^{-1}: 1685 (C=N). NMR (d_6-DMSO) δ: 4.88 (2H, s, $ArCH_2$), 3.83 (3H, s, OCH_3), 3.95 (2H, m, C_4–CH_2), 3.55 (2H, m, C_5–CH_2). *Anal.* Calcd. for $C_{12}H_{17}ClN_4O$: C, 53.63; H, 6.83; N, 20.85. Found: C, 53.34; H, 6.36; N, 21.23.

Reaction of 6 with Ammonia in Aqueous MeOH——A mixture of **6** (0.54 g, 2 mmol) and 6 ml of conc. ammonium hydroxide in 3 ml of MeOH was allowed to stand at room temperature over a period in 3—4 days. After concentration of the mixture, the residue was mixed with 2 N NaOH and extracted with $CHCl_3$. The extract was washed with a saturated aqueous NaCl solution, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was treated with HCl–EtOH to give 0.32 g (76%) of the hydrochloride of **2a**, which was identical with a sample prepared by method A.

Reaction of 6 in 1 N HCl——A solution of **6** (1.34 g, 2 mmol) in 50 ml of 1 N HCl was heated at 80—90° for 15 min. After concentration of the mixture, the residue was recrystallized from iso-PrOH to give 1.08 g (85%) of the hydrochloride of **3a**, which was identical with a sample prepared by method E.

Reaction of 6 in Acidic Medium of pH 3—4——To a solution of **6** (0.54 g, 2 mmol) in 20 ml of water was added portionwise 18 ml of 0.1 N HCl at 50—55° maintaining pH 3—4. The solution was kept at the same temperature for 1 hr. The solution was evaporated *in vacuo*. The residue was treated with HCl–EtOH to give 0.34 g (69%) of 1-benzyl-2-imino-3-methoxycarbonylimidazolidine hydrochloride (**7**), mp 125—127° (from MeOH–acetone). IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O). NMR (d_6-DMSO) δ: 4.51 (2H, s, $ArCH_2$), 3.62 (2H, m, C_4–CH_2), 3.28 (2H, m, C_5–CH_2), (free base). *Anal.* Calcd. for $C_{12}H_{10}ClN_3O_2$: C, 53.42; H, 5.98; N, 15.58. Found: C, 53.30; H, 5.85; N, 15.31.

2-Benzylaminoethylguanidine Sulfate (**8**)——A mixture of **1a** (6.0 g, 40 mmol) and methylisothiourea (5.6 g, 40 mmol) in 32 ml of water was allowed to stand overnight. The reaction mixture was evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH to give 8.2 g (87%) of **8**, mp 168—171°. IR ν_{max}^{KBr} cm^{-1}: 2800—3500 (N=H), 1660 (C=N). *Anal.* Calcd. for $C_{20}H_{24}N_8O_4S$: C, 49.71; H, 7.10; N, 23.22. Found: C, 49.88; H, 6.94; N, 23.53.

3-Amidino-1-benzyl-2-iminoimidazolidine (**9**)——To a solution of **8** (4.8 g, 20 mmol) in 6 ml of 2 N NaOH was added cyanogen bromide (2.3 g, 22 mmol). The mixture was stirred at room temperature for 1 hr. A solid separated out was collected and dissolved in hot water. After filtration of an insoluble solid, the filtrate was concentrated to dryness *in vacuo* to give crude **9**. The crude product was dissolved in HCl–EtOH and the solution was evaporated *in vacuo*. The residue was recrystallized from iso-PrOH to give 1.4 g (27%) of **9**, mp 178—179°. IR ν_{max}^{KBr} cm^{-1}: 3250 (N–H), 1680 (C=N). NMR (d_6-DMSO) δ: 4.51 (2H, s, $ArCH_2$), 3.90 (2H, m, C_4–CH_2), 3.35 (2H, m, C_5-CH_2). *Anal.* Calcd. for $C_{11}H_{16}ClN_5$: C, 52.07; H, 6.36; N, 27.60. Found: C, 51.86; H, 6.22; N, 27.59.

1-Benzyl-2-cyanoiminoimidazolidine (**10a**)——A mixture of **1a** (4.5 g, 30 mmol) and dimethyl N-cyanoimidodithiocarbonate (4.5 g, 30 mmol) was heated at 100—120° for 15 min. After cooling, the mixture was recrystallized from EtOH to give 4.9 g (82%) of **10a**.

By the same method, other compounds **10b—f** were obtained and are shown in Table III.

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