[Chem. Pharm. Bull. 26(12)3666—3674(1978)]

UDC 547.495.9.04.09 : 615.272.3.011.5.076.9

Cyclic Guanidines. II.[1] Synthesis of Hypoglycemic Acyl or Alkyl Derivatives of 1-Substituted 2-Imino-1,3-diazacycloalkane[2]

Fumiyoshi Ishikawa, Akira Kosasayama, and Tsuneo Konno

Research Institute, Daiichi Seiyaku Co., Ltd.[3]

(Received April 28, 1978)

Synthesis of acyl and alkyl derivatives of 1-benzyl or 1-benzhydryl-2-imino-1,3-diazacycloalkanes (**1**) was attempted.

Acetylation of **1a, c** having five-membered ring with ethyl acetate gave 2-acetyl derivatives. However, reactions of **1a, c** with dialkylcarbonate, acyl chloride and alkyl or aryl isocyanate afforded a mixture of 2- and 3-substituted compounds and reactions of **1a, c** with isothiocyanate derivatives gave predominantly 3-substituted compounds. On the other hand, **1b, d** having six-membered ring gave predominantly 2-substituted compounds by the similar reactions.

Direct alkylation of **1a, c** with alkyl iodide in the presence of sodium hydride yielded 3-alkyl derivatives (**5**). In the similar alkylations, 2-alkoxycarbonylimino and 2-cyanoimino derivatives, **2** and **9**, gave 3-alkyl compounds **7** and **8**, in which 2-alkaxycarbonyl and 2-cyano groups were removed on heating in *t*-butanol containing a small amount of hydrochloric acid to give **5** in good yields.

Heating **7** and **8** having 1-benzhydryl group with sodium hydride gave 2-oxo- or 2-imino-3,3-diphenylimidazo[1,2-*a*][1,3]diazacycloalkane derivatives (**10, 11** and **12**).

Some of 1-substituted 3-acyl and 3-alkyl-2-imino-1,3-diazacycloalkanes showed hypoglycemic activity.

Keywords——cyclic guanidine; 1-substituted 2-imino-1,3-diazacycloalkane; acylation; alkylation; intramolecular cyclization; hypoglycemic activity

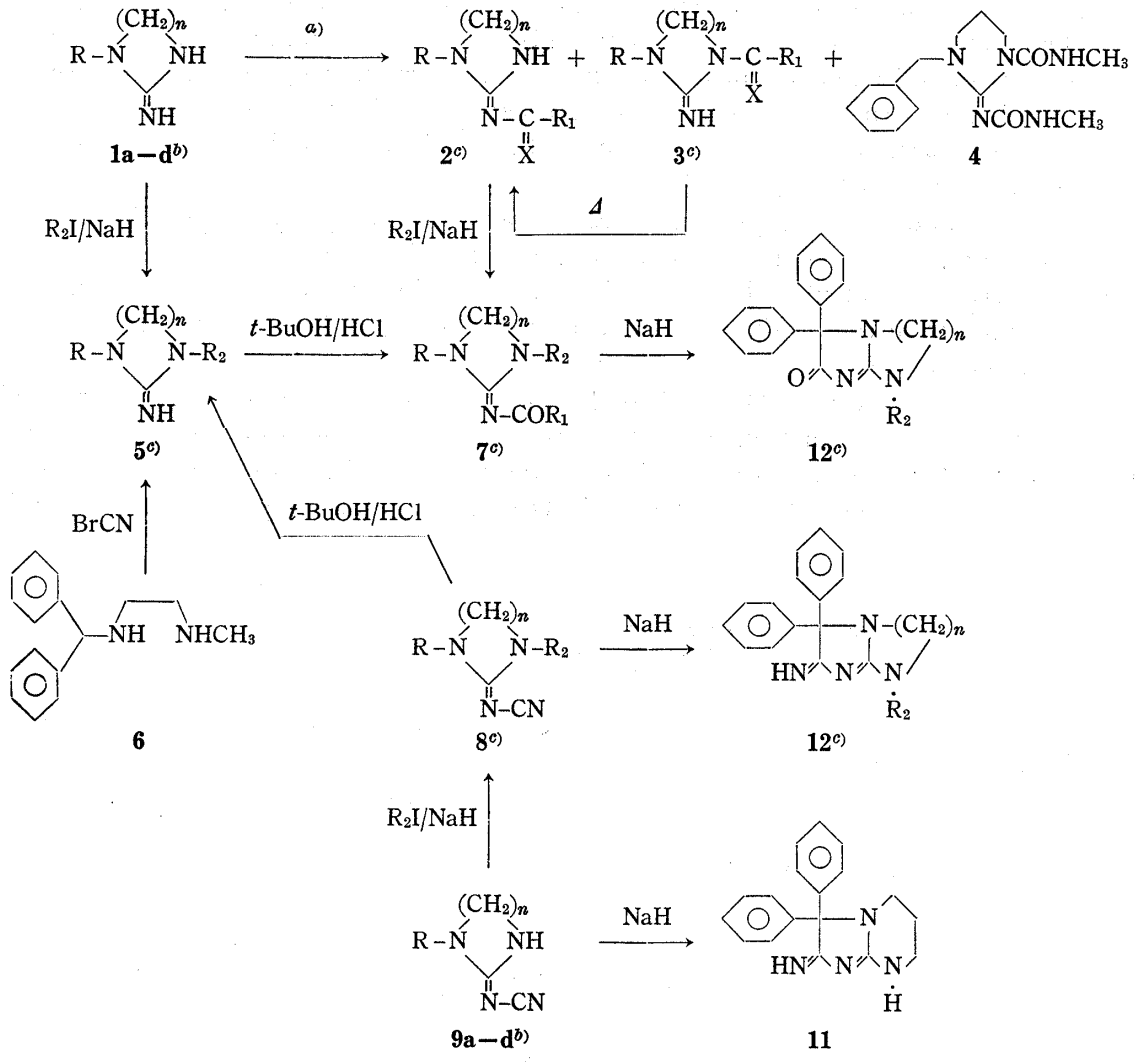
In the preceding paper,[1] it was reported that 2-imino-1,3-diazacycloalkanes (**1**)[4] substituted with a bulky group at the 1 position showed hypoglycemic activity. Acylation or alkylation of cyclic guanidine derivatives has not been investigated in detail. This report deals with reactions of 1-substituted 2-imino-1,3-diazacycloalkanes (**1**) with acylating or alkylating reagents and biological activity of the reaction products. And we report on a novel cyclization reaction of 1-benzhydryl-2-alkoxycarbonylimino- or 2-cyanoimino-1,3-diazacycloalkanes to bicyclic guanidine derivatives.

On acylation of cyclic guanidine, Rapoport and co-worker[5] reported that the reaction of 2-iminoimidazolidine with carbobenzoxy chloride gave the 1- or 2-substituted derivatives. Lucas and co-worker[6] obtained the 2-acyl derivatives on benzoylation of 1-substituted 2-imino-1,3-diazacycloalkanes. Furthermore, it was reported by Boehringer group[7] that the acylation products of 2-phenyliminoimidazolidines were 2-(N-acylphenylamino)-2-imidazolines. On the other hand, it was reported by Jen and co-workers[8] that 1-acetyl-2-phenyliminoimidazoli-

1) Part I: F. Ishikawa, A. Kosasayama, S. Nakamura, and T. Konno, *Chem. Pharm. Bull.* (Tokyo), **26**, 3656 (1978).
2) Presented at the 97th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1977.
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo 132, Japan.*
4) 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.
5) K. Matsumoto and H. Rapoport, *J. Org. Chem.*, 33, 552 (1968).
6) R.A. Lucas and H.M. Blater, Ger. Offen. 2031920 (1970) [*Chem. Abstr.*, **74**, 88028*b* (1971)].
7) C.H. Boehringer Sohn, Belg. Patent 741947 (1969).
8) T. Jen, H.V. Hoeven, W. Groves, R.A. Mclean, and B. Loev, *J. Med. Chem.*, **18**, 90 (1975).

dine was obtained by acetylation of 2-phenyliminoimidazolidine with acetic anhydride at room temperature.

Heating 1-benzyl-2-iminoimidazolidine (**1a**) with ethyl acetate gave 2-acetylimino derivative (**2a**) in a yield of about 50% together with the acetic acid salt of **1a**. Reaction of 1-benzhydryl-2-iminoimidazolidine (**1c**) or 1-benzyl-2-iminoperhydropyrimidine (**1b**) with ethyl acetate gave the same result. The occurrence of the acetic acid salt of **1** is rationalized by the initial formation of 3-acetyl derivative in the reaction of **1** with ethyl acetate, followed by hydrolysis to **1** and acetic acid with adventitious water in the reaction medium, because the 3-acetyl derivative is unstable in protic solvent as described below. On the other hand, heating **1a, c** with alkyl carbonate afforded mixtures of 2-alkoxycarbonylimino derivatives (**2d,e,g,h**) and 3-alkoxycarbonyl derivatives (**3d,e,g,h**). However, **1b,d** having six-membered ring gave predominantly 2-alkoxycarbonyl derivatives (**2f,i**).



R=$C_6H_5CH_2$–, $(C_6H_5)_2CH$–; R_1=CH_3–, CH_3O–, C_2H_5O–, H_2N–, CH_3NH–, C_6H_5NH–; R_2=CH_3–, C_2H_5–; X=O, S; n=2, 3.
a) Acylating reagents: $CH_3CO_2C_2H_5$, CH_3COCl, CH_3OCOCl, C_2H_5OCOCl, $(C_2H_5O)_2CO$, CH_3NCO, C_6H_5NCO, CH_3NCS, and $Si(NCS)_4$.
b) a: R=$C_6H_5CH_2$–, n=2; b: R=$C_6H_5CH_2$–, n=3; c: R=$(C_6H_5)_2CH$–, n=2; d: R=$(C_4H_5)_2CH$–, n=3.
c) R, R_1, R_2, X and n of **2**, **3**, **5**, **7**, **8**, **10**, and **12** are shown in Table III—VII, respectively.

Chart 1

Acylation of **1a,c** with acetyl chloride or alkyl chloroformate in chloroform yielded mixtures of 2- and 3-substituted derivatives. The 2- and 3-alkoxycarbonyl derivatives could be separated by means of silica gel chromatography, respectively. However, 3-acetyl deriva-

tive (**3c**) in the mixture was decomposed to **1c** on the silica gel. Finally, in this procedure only 2-acetyl derivative (**2c**) was isolated. Acetylation of **1c** with acetyl chloride in dimethylformamide (DMF) in the presence of sodium hydride at low temperature gave predominantly the 3-acetyl derivative (**3c**) in 35% yield.

It was observed that the 3-acetyl group of **3c** was rearranged to 2-imino group on heating in absolute ethanol or dimethylsulfoxide (DMSO) at 80—100°, in the same way as the rearrangement of 3-carbamoyl group of 1-benzyl-3-carbamoyl-2-iminoimidazolidine to the 2-imino group.[1] Rapoport[5] also reported that the formation of the 2-acetyl derivative from 1,3-diacetyl-2-iminoimidazolidine under various conditions might be attributable to a rearrangement reaction. The 3-methoxycarbonyl group of **3g** did not migrate on heating in DMSO and **3g** decomposed on heating in absolute methanol to **1c**.

1-Substituted 2-imino-1,3-diazacycloalkanes (**1a—c**) reacted easily with alkyl or aryl isocyanate in benzene to give mixtures of 2- and 3-substituted carbamoyl derivatives in good yields. Their mixtures could be separated by silica gel chromatography and the formation ratio of 2- and 3-isomers inclined to the 2-isomer. Particularly, the reaction of **1b** having six-membered ring with methyl isocyanate afforded predominantly the 2-methylcarbamoylimino derivative (**21**), which further reacted with remained methyl isocyanate to give the 2,3-disubstituted derivative (**4**).

Reaction of **1a,c** with methyl isothiocyanate gave predominantly 3-methylthiocarbamoyl derivatives (**3n,o**). Treatment of **1a,c** with silicon tetraisothiocyanate yielded also 3-thiocarbamoyl derivatives (**3p,q**) and a trace of 1-benzyl-2-thiocarbamoyliminoimidazolidine (**2p**) could be isolated from the residual mixture, from which **3p** had been separated, by means of silica gel chromatography.

The structure of the 2- or 3-substituted derivatives obtained above was determined by the chemical shifts of C-4 methylene protons in nuclear magnetic resonance (NMR) spectra. The signals of C-4 methylene protons of 3-acyl derivatives shifted to lower field than those of the 2-acyl derivatives. These chemical shifts of the 2- and 3-acyl compounds are listed in Table I.

Table I. NMR Spectra of 1-Substituted 2- or 3-Acyl-2-iminoimidazolidine Derivatives

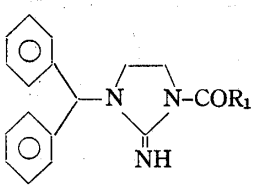
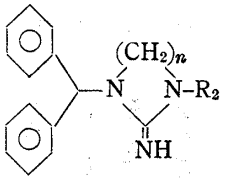
R	R_1	X	Solvent	Chemical shift of methylene or methine group: (2) N-1 (s)	(2) C-4 (m)	(2) C-5 (m)	(3) N-1 (s)	(3) C-4 (m)	(3) C-5 (m)
$C_6H_5CH_2$	CH_3	O	$CDCl_3$	4.55	3.56	3.27			
$C_6H_5CH_2$	OC_2H_5	O	$CDCl_3$	4.55	3.55	3.30	4.48	3.72	3.13
$C_6H_5CH_2$	$NHCH_3$	O	$CDCl_3$	4.49	3.44	3.24	4.43	3.69	3.29
$C_6H_5CH_2$	NH_2	S	d_6-DMSO	4.49	3.51	3.27	4.41	4.01	3.18
$C_6H_5CH_2$	$NHCH_3$	S	d_6-DMSO				4.46	4.07	3.22
$(C_6H_5)_2CH$	CH_3	O	$CDCl_3$	6.90	3.58	3.22	6.55	3.81	3.10
$(C_6H_5)_2CH$	OCH_3	O	$CDCl_3$	6.83	3.50	3.28	6.71	3.78	3.08
$(C_6H_5)_2CH$	$NHCH_3$	O	$CDCl_3$	6.72	3.51	3.16	5.75	3.85	3.07
$(C_6H_5)_2CH$	NH_2	S	$CDCl_3$				5.72	4.20	3.08
$(C_6H_5)_2CH$	$NHCH_3$	S	$CDCl_3$				6.34	4.10	3.18

It has been reported that the reaction of 1-alkyl-2-iminoimidazolidine with alkyl halide gave predominantly the 3-alkyl derivative.[9] Alkylation of **1c** with methyl iodide in DMF in the presence of sodium hydride also gave 1-benzhydryl-2-imino-3-methylimidazolidine (**5e**), which was identical with a specimen prepared from 1-benzhydrylamino-2-methylaminoethane (**6**) and cyanogen bromide in benzene. In this case, alkylation of **1c** also occurred at 3 position but this direct alkylation was not practical for preparation of 3-alkyl derivatives because of their low yield.

Alkylation of 1-substituted 2-acetyl- or 2-alkoxycarbonylimino-1,3-diazacycloalkanes (**2**) with alkyl iodide in DMF in the presence of sodium hydride gave 3-alkyl derivatives (**7a—g**) in good yields. The alkylated products (**7a—d**) substituted with 1-benzyl group could be readily derived to 3-alkyl-1-benzyl-2-imino-1,3-diazacycloalkanes (**5a—c**) on heating in 10% hydrochloric acid. However, 1-benzhydryl derivatives (**7e—g**) did not give the desired compounds under the same conditions because of the elimination of the benzhydryl group as described in the preceding paper.[1] Then the 3-alkylated compounds (**7**) were heated with 3—4 equimolar amounts of hydrochloric acid in *t*-butanol (*t*-BuOH) to give the desired products (**5**) in good yields. 1-Substituted 2-cyanoimino-1,3-diazacycloalkanes (**9a—d**) were similarly treated with alkyl iodide and sodium hydride to give 3-alkyl derivatives (**8a—e**), which were heated in *t*-butanol containing hydrochloric acid to give **5** in good yields. These results, the formation of **5** from **2**, were also used to elucidate the structures of **3**, in which the acyl groups were situated at the 3 position.

Alkylation of 2-alkoxycarbonylimino-1-benzhydryl-1,3-diazacycloalkanes (**2e—i**) with excess sodium hydride in DMF under heating did not afford the 3-alkylated derivatives (**7**) but gave interesting compounds, 1-alkyl-6-oxo-5,5-diphenyl-2,3,5,6-tetrahydro-1H-imidazo-[1,2-*a*]imdazoles or 8-alkyl-2-oxo-3,3-diphenyl-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrimidines (**10a—c**), which were formed by attack of the active benzhydryl methine group to the 2-alkoxycarbonyl group of **7**. When 3-nonalkylated derivatives (**2g—i**) were heated in the presence of excess of sodium hydride in DMF, the corresponding bicyclic guanidines could not be obtained.

Table II. Hypoglycemic Activity of 3-Acyl or Alkyl Derivatives of 1-Benzhydryl-2-imino-1,3-diazacycloalkane

Compound	Plasma glucose[a]	
	Dosage (mg/kg, *p.o.*)	% reduction
	5—25	30—60
	25	30—60

R_1=CH_3, CH_3O, C_2H_5O; R_2=CH_3, C_2H_5; n=2, 3.

a) The test compound was orally administered to a rat which had been fasted over 24 hr. Plasma glucose was determined at 2, 3, and 5 hr by the glucose oxidase method.

9) *a*) J. Bindler, E. Model, and R. Zinkernagel, Ger. Patent 1069634 (1959) [*Chem. Abstr.*, **55**, 21147*d* (1961)]; *b*) L.F. Miller and R.M. Bambug, *J. Med. Chem.*, **15**, 415 (1972).

TABLE III. 1-Substituted 2-Acylimino-1,3-diazacycloalkanes (2) and 1-Substituted 3-Acyl-2-imino-1,3-cycloalkanes (3)

No.	R	R_1	X	n	Reaction	Compouud 2 Yield (%)	mp (°C)	IR (cm^{-1})	Formula	Analysis Calcd. (Found) C	H	N	Compound 3 Yield (%)	mp (°C)	IR (cm^{-1})	Formula	Analysis Calcd (Found) C	H	N
a	$C_6H_5CH_2$	CH_3	O	2	A	51	137—139	1600(C=O) 1555(C=N)	$C_{12}H_{15}N_3O$	66.33 (66.53	6.96 7.20	19.34 19.73)							
b	$C_6H_5CH_2$	CH_3	O	3	A	42	99—102	1580(C=O)	$C_{13}H_{17}N_3O$	67.50 (67.52	7.41 7.52	18.17 18.05)							
c	$(C_6H_5)_2CH$	CH_3	O	2	A C D	47 35	149—151	1605(C=O)	$C_{18}H_{19}N_3O$	73.69 (73.58	6.53 6.42	14.33 14.31	34	134—136	1700(C=O)	$C_{18}H_{19}N_3O$	73.69 (73.35	6.53 6.47	14.33 14.24)
d	$C_6H_5CH_2$	CH_3O	O	2	B C	25 26	159—160	1640(C=O) 1600(C=N)	$C_{12}H_{15}N_3O_2$	61.78 (61.80	6.48 6.42	18.02 18.34)	48 51	125—127	1730(C=O)	$C_{12}H_{16}ClN_3O_2$	53.43 (53.30	5.98 5.82	15.58 15.31)
e	$C_6H_5CH_2$	C_2H_5O	O	2	B C	31 12	119—120	1630(C=O) 1590(C=N)	$C_{13}H_{17}N_3O_2$	63.14 (62.92	6.93 6.92	16.99 17.11)	24 70	150—152	1720(C=O)	$C_{13}H_{17}ClN_3O_2$	55.02 (55.25	6.39 6.54	14.81 15.08)
f	$C_6H_5CH_2$	C_2H_5O	O	3	B	80	66— 67	1620(C=O) 1580(C=N)	$C_{14}H_{19}N_3O_2$	64.34 (64.34	7.33 7.39	16.08 16.14)							
g	$(C_6H_5)_2CH$	CH_3O	O	2	B C	36 49	169—170	1635(C=O) 1585(C=N)	$C_{18}H_{19}N_3O_2$	69.88 (69.97	6.19 5.91	13.58 13.53)	29 45	144—145	1725(C=O)	$C_{18}H_{20}ClN_3O_2$	62.51 (62.41	5.83 5.51	12.15 12.07)
h	$(C_6H_5)_2CH$	C_2H_5O	O	2	B	28	131—132	1640(C=O) 1590(C=N)	$C_{19}H_{21}N_3O_2$	70.56 (70.52	6.55 6.67	13.00 13.15)	25	164—166	1730(C=O)	$C_{19}H_{22}ClN_3O_2$	63.41 (63.42	6.16 6.10	11.68 11.65)
i	$(C_6H_5)_2CH$	CH_3O	O	3	B	76	158—159	1620(C=O)	$C_{19}H_{21}N_3O_2$	70.56 (70.46	6.55 6.62	13.00 13.12)							
j	$C_6H_5CH_2$	CH_2NH	O	2	E	31	152—153	1600(C=O)	$C_{12}H_{16}N_4O$	62.05 (62.33	6.94 6.89	24.12 24.49)	24	146—147	1660(C=O)	$C_{12}H_{16}N_4O$	62.05 (62.08	6.94 6.89	24.12 23.97)
k	$C_6H_5CH_2$	C_6H_5NH	O	2	E	63	119—120	1640(C=O) 1580(C=N)	$C_{17}H_{18}N_4O$	69.36 (69.15	6.16 6.12	19.04 18.96)	29	122—123	1675(C=O)	$C_{17}H_{18}N_4O$	69.36 (69.28	6.16 6.15	19.04 18.85)
l	$C_6H_5CH_2$	CH_3NH	O	3	E	35	144—146 (HCl)	1640(C=O) 1600(C=N)	$C_{13}H_{19}ClN_4O$	55.21 (55.07	6.77 6.89	19.82 20.06)							
m	$(C_6H_5)_2CH$	CH_3NH	O	2	E	42	163—164	1600(C=N)	$C_{18}H_{20}N_4$	70.10 (70.32	6.54 6.55	18.17 18.23)	19	128—129	1670(C=O)	$C_{18}H_{20}N_4O$	70.10 (70.16	6.54 6.49	18.17 18.30)
n	$C_6H_5CH_2$	CH_3NH	S	2	F								65	131—132	1630(C=N)	$C_{12}H_{16}N_4S$	58.03 (58.31	6.49 6.75	22.56 22.78)
o	$(C_6H_5)_2CH$	CH_3NH	S	2	F								74	130—132	1625(C=N)	$C_{18}H_{20}N_4S$	66.63 (66.80	6.21 6.33	17.27 17.06)
p	$C_6H_5CH_2$	NH_2	S	2	G	1	148—150	1570(C=N)	$C_{11}H_{14}N_4S$	56.38 (56.73	6.02 5.84	23.91 23.95)	17	147—148	1630(C=N)	$C_{11}H_{14}N_4S$	56.38 (56.45	6.02 6.09	23.91 23.78)
q	$(C_6H_5)_2CH$	NH_2	S	2	G								34	149—151	1635(C=N)	$C_{17}H_{18}N_4S$	65.78 (65.66	5.85 5.90	18.05 17.75)

Similarly, reaction of 2-cyanoimino derivatives (**9c,d**) with alkyl iodide in the presence of excess sodium hydride in DMF at moderate temperature gave 2-imino bicyclic guanidines (**12a—d**). Although heating **9c** with sodium hydride did not give bicyclic guanidine, **9d** having six-membered ring gave the desired compound **11** on heating with sodium hydride in DMF at 100°. In order to proceed with this cyclization, it may be necessary to have active 2-carbonyl or 2-cyano group such as those of **7e—g** or **8b—e** and not to have large strain on the cyclization reactions.

The hypoglycemic activity of 1-substituted acyl or alkyl cyclic guanidine derivatives obtained above was determined in normal fasted rats. As shown in Table II, some series of the compounds **3** and **5** substituted with bulky benzhydryl group showed hypoglycemic activity. 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 R20B (60 MHz) or a Varian EM-360 (60 MHz) spectrometer with tetramethylsilane as an internal standard (δ value). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Reactions of 1-Substituted 2-Imino-1,3-diazacycloalkanes (1a—d) with Acylating Reagents——2-Acylimino derivatives (**2**) and 3-acyl derivatives (**3**) were prepared by the following reactions and are shown in Table III.

A. Reaction of 1 with AcOEt: A solution of **1a** (1.78 g, 10 mmol) in 15 ml of AcOEt was refluxed for 15—20 hr and evaporated to dryness *in vacuo*. The residue was triturated with benzene and an insoluble solid (the acetic acid salt of **1a**) was filtered off. The filtrate was evaporated *in vacuo* and the residue was recrystallized from ether to give 1.04 g (51%) of **2a**.

B. Reaction of 1with Dialkylcarbonate: A solution of **1a** (0.88 g, 5 mmol) in 5 ml of dimethylcarbonate was refluxed for 2—3 hr and evaporated *in vacuo*. The residue was chromatographed on silica gel and the fractions eluted with $CHCl_3$ were collected to give 0.35 g (31%) of **2e** and 0.31 g (24%) of **3e**.

C. Reaction of 1 with Acyl Chloride: To a mixture of **1a** (1.0 g, 5.7 mmol) and Et_3N (1.0 g) in 12 ml of $CHCl_3$ was added dropwise methyl chloroformate (0.59 g, 6.3 mmol) with stirring at 0°. The mixture was continued to stir at room temperature for 1 hr. The mixture was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on silica gel to give 0.35 g (26%) of **2d** and 0.67 g (51%) of **3d**.

D. Reaction of 1 with Acetyl Chloride in DMF: A mixture of **1c** (2.0 g, 8 mmol) and 0.44 g (8.8 mmol) of NaH (50% oil suspension) in 30 ml of DMF was stirred at room temperature for 30 min. To the mixture was added dropwise acetyl chloride (0.77 g, 8.8 mmol) with stirring at 0°. After stirring at the same temperature for 30 min, the mixture was concentrated to dryness *in vacuo*. The residue was mixed with water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from ether to give 0.82 g (34%) of **3c**.

E. Reaction of 1 with Methyl Isocyanate or Phenyl Isocyanate: To a solution of **1a** (2.6 g, 15 mmol) in 20 ml of benzene was added methyl isocyanate (1.0 g, 15 mmol) at 0—5°. The mixture was allowed to stand at the same temperature for 30 min and evaporated *in vacuo*. The residue was chromatographed on silica gel and the fractions eluted with $CHCl_3$ were collected to give 1.1 g (31%) of **2j** and 0.82 g (24%) of **3j**.

F. Reaction of 1 with Methyl Isothiocyanate: A mixture of **1a** (0.88 g, 5 mmol) and methyl isothiocyanate (0.37 g, 5 mmol) in 10 ml of EtOH was stirred at room temperature for 1 hr. A solid separated was collected to give 0.80 g (65%) of **3n**.

G. Reaction of 1 with Silicon Tetraisothiocyanate: A mixture of **1a** (2.1 g, 12 mmol) and fresh silicon tetraisothiocyanate (1.04 g, 4 mmol) in 30 ml of benzene was heated for 45 min. The mixture was evaporated *in vacuo*. After addition of 20 ml of 10% aqueous iso-PrOH (IPA), the mixture was heated for 15 min and evaporated *in vacuo*. The residue was treated with $CHCl_3$ and the $CHCl_3$ extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from IPA to give 0.47 g (17%) of **3p**. The filtrate was evaporated to dryness *in vacuo* and the residue was chromatographed on silica gel. The fractions eluted with $CHCl_3$ and MeOH–$CHCl_3$ were collected to give trace of **2p**.

1-Benzyl-2-methylcarbamoylimino-3-methylcarbamoylperhydropyrimidine (**4**)——To a solution of **1b** (2.8 g, 15 mmol) in 15 ml of benzene was added methyl isocyanate (0.90 g, 15 mmol) at 0—5°. The mixture was allowed to stand at the same temperature for 30 min and evaporated *in vacuo*. The residue was chromatographed on silica gel and the fractions eluted with $CHCl_3$ and MeOH–$CHCl_3$ were collected. As first fraction, 0.70 g (15%) of **4** was obtained, mp 126—127°; IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O), 1610, 1580 (C=N); NMR ($CDCl_3$) δ:

4.45 (2H, s, Ar–CH_2), 3.90 (2H, m, C_4–CH_2), 3.20 (2H, m, C_6–CH_2), 2.88, 2.82 (2H s, d, J=5 Hz, N–CH_3), 1.95 (2H, m, C_5–CH_2). *Anal.* Calcd. for $C_{15}H_{21}N_5O_2$: C, 59.38; H, 6.96; N, 23.09. Found: C, 59.47; H, 7.03; N, 23.03.

Pure oil of **21** obtained as second fraction was treated with HCl–EtOH to give 1.5 g (35%) of the hydrochloride of **21**.

1-Substituted 3-Alkyl-2-imino-1,3-diazacycloalkanes (5a—h)——Compounds **5a—h** were prepared by the following methods and listed in Table IV.

Table IV. 1-Substituted 3-Alkyl-2-imino-1,3-diazacycloalkanes (5)

No.	R	R_2	n	Method	Yield (%)	mp (°C)	IR (cm^{-1})	Formula	Analysis Calcd. (Found) C	H	N
a	$C_6H_5CH_2$	CH_3	2	J	81.5	200—202	1650(C=N)	$C_{11}H_{16}ClN_3$	58.52 (58.64	7.14 7.27	18.62 19.01)
b	$C_6H_5CH_2$	C_2H_5	2	K	74	197—198	1650(C=N)	$C_{12}H_{18}ClN_3$	60.11 (60.11	7.57 7.59	17.53 17.47)
c	$C_6H_5CH_2$	CH_3	3	K	70	178—180	1640(C=N)	$C_{12}H_{18}ClN_3$	60.11 (60.01	7.57 7.73	17.53 17.86)
d	$C_6H_5CH_2$	C_2H_5	3	H	19	157—158	1640(C=N)	$C_{13}H_{20}ClN_3$	61.52 (61.67	7.94 7.98	16.56 16.56)
e	$(C_6H_5)_2CH$	CH_3	2	H I J	28.6 46 81	243—245	1650(C=N)	$C_{17}H_{20}ClN_3$	58.96 (59.06	5.82 5.98	12.14 12.46)
f	$(C_6H_5)_2CH$	C_2H_5	2	J	77	236—237	1660(C=N)	$C_{18}H_{22}ClN_3$	68.45 (68.34	7.02 7.07	13.31 13.40)
g	$(C_6H_5)_2CH$	CH_3	3	J	59	278—280	1650(C=N)	$C_{18}H_{22}ClN_3$	68.45 (68.33	7.02 6.96	13.31 13.26)
h	$(C_6H_5)_2CH$	C_2H_5	3	J	65	218—221	1640(C=N)	$C_{19}H_{24}ClN_3$	69.18 (68.93	7.33 7.14	12.74 12.67)

Method H: A mixture of **1c** (1.0 g, 4 mmol), 0.22 g (4.4 mmol) of NaH (50% oil suspension) and methyl iodide (0.63 g, 4.4 mmol) in 15 ml of DMF was stirred at room temperature for 4 hr. The mixture was poured into a large amount of water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was dissolved in HCl–EtOH and evaporated *in vacuo*. The residue was dissolved in a small amount of acetone and the solution was allowed to stand in refrigerator for 2—3 days. Crystals separated were collected by filtration and recrystallized several times from acetone to give pure hydrochloride of **5e**, which was identical with a specimen prepared by following Method I.

Method I: To a solution of cyanogen bromide (3.4 g, 33 mmol) in 100 ml of benzene was added dropwise solution of **6** (7.3 g, 30 mmol) in 15 ml of benzene. After the addition, the mixture was stirred at room temperature for 30 min. A solid separated was collected and recrystallized from IPA to give 4.8 g (46%)

Table V. 1-Substituted 2-Acylimino-3-alkyl-1,3-diazacycloalkanes (7)

No.	R	R_1	R_2	n	Yield (%)	mp (°C)	IR (cm^{-1})	Formula	Analysis Calcd. (Found) C	H	N
a	$C_6H_5CH_2$	CH_3	C_2H_5	2	63	157—159 (HCl)	1720(C=O) 1620(C=N)	$C_{14}H_{20}ClN_3O$	59.67 (59.48	7.15 7.34	14.91 15.22)
b	$C_6H_5CH_2$	C_2H_5O	C_2H_5	2	50	Oil					
c	$C_6H_5CH_2$	C_2H_5O	CH_3	3	87	Oil					
d	$C_6H_5CH_2$	C_2H_5O	C_2H_5	3	76	Oil					
e	$(C_6H_5)_2CH$	CH_3	C_2H_5	2	50	Oil					
f	$(C_6H_5)_2CH$	C_2H_5O	C_2H_5	2	83	83— 85	1650(C=O) 1570(C=N)	$C_{21}H_{25}N_3O_2$	71.77 (71.63	7.17 7.23	11.96 11.98)
g	$(C_6H_5)_2CH$	CH_3O	C_2H_5	3	65	84— 86	1610(C=O) 1535(C=N)	$C_{21}H_{25}N_3O_2 \cdot 1/2H_2O$	69.97 (69.84	7.27 7.37	11.66 11.42)

of the hydrobromide of **5e**, mp 233—235°. *Anal.* Calcd. for $C_{17}H_{20}BrN_3$: C, 58.96; H, 5.82; N, 12.14. Found: C, 59.06; H, 5.98; N, 12.46.

The hydrobromide was mixed with 2 N NaOH and extracted with $CHCl_3$. The extract was worked up as usual to give the hydrochloride of **5e**.

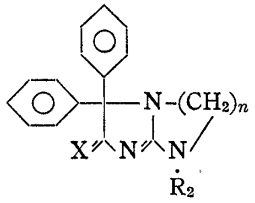
Method J: A mixture of **8c** (1.82 g, 6 mmol) and conc. HCl (2 ml, 20 mmol) in 50 ml of *t*-BuOH was heated for 10 hr. The mixture was concentrated to dryness *in vacuo*. The residue was mixed with 2 N NaOH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was treated with HCl–EtOH to give 1.46 g (77%) of **5f**.

Method K: A mixture of **7a** (1.0 g, 3.6 mmol) in 20 ml of 10% HCl was heated for 5 hr. After cooling, the mixture was poured into ice-cold 2 N NaOH and the mixture was extracted with $CHCl_3$. The extract was worked up as Method J to give 0.74 g (74%) of **5b**.

TABLE VI. 1-Substituted 3-Alkyl-2-cyanoimino-1,3-diazacycloalkanes (**8**)

No.	R	R_2	*n*	Yield (%)	mp (°C)	IR (cm^{-1})	Formula	Analysis Calcd. (Found) C	H	N
a	$C_6H_5CH_2$	CH_3	2	82	Oil	2160(C≡N) 1600(C=N)				
b	$(C_6H_5)_2CH$	CH_3	2	97	134—135	2150(C≡N) 1595(C=N)	$C_{18}H_{18}N_4$	74.45 (74.28	6.25 6.29	19.30 19.24)
c	$(C_6H_5)_2CH$	C_2H_5	2	97	142—243	2160(C≡N) 1595(C=N)	$C_{19}H_{20}N_4$	74.97 (75.17	6.62 6.52	18.41 18.68)
d	$(C_6H_5)_2CH$	CH_3	3	93	161—163	2150(C≡N) 1550(C=N)	$C_{19}H_{20}N_4$	74.97 (75.15	6.62 6.57	18.41 18.19)
e	$(C_6H_5)_2CH$	C_2H_5	3	96	171—173	2150(C≡N) 1550(C=N)	$C_{20}H_{22}N_4$	75.44 (75.46	6.96 7.12	17.60 17.55)

TABLE VII. 2-Oxo- or 2-Imino-3,3-diphenyl Bicyclic Guanidines (**10**), (**11**) and (**12**)



No.	X	R_2	*n*	Yield (%)	mp (°C)	IR (cm^{-1})	Formula	Analysis Calcd. (Found) C	H	N
10a	O	CH_3	2	89	220—221	1720(C=O) 1600(C=N)	$C_{18}H_{17}N_3O$	74.20 (73.87	5.88 5.91	14.42 14.72)
10b	O	C_2H_5	2	76	148—149	1720(C=O) 1600(C=N)	$C_{19}H_{19}N_3O$	74.73 (74.59	6.27 6.12	13.76 13.68)
10c	O	C_2H_5	3	68	175—177	1790(C=O) 1590(C=N)	$C_{20}H_{21}N_3O$	75.21 (75.03	6.63 6.72	13.16 13.02)
11	NH	H	3	52	248—251 (HCl)	1580(C=N)	$C_{18}H_{19}ClN_4 \cdot 1/2H_2O$	64.37 (64.59	6.00 5.88	16.68 16.77)
12a	NH	CH_3	2	81	197—198	1580(C=N)	$C_{18}H_{18}N_4$	74.45 (74.72	6.25 6.43	19.30 19.03)
12b	NH	C_2H_5	2	69	281—283 (HCl)	1635(C=N)	$C_{19}H_{21}ClN_4$	66.95 (66.80	6.21 6.27	16.44 16.29)
12c	NH	CH_3	3	76	191—193	1590(C=N)	$C_{19}H_{20}N_4$	74.97 (74.89	6.62 6.66	18.41 18.14)
12d	NH	C_2H_5	3	66	184—186	1590(C=N)	$C_{20}H_{22}N_4$	75.44 (75.25	6.96 6.96	17.60 17.83)

1-Substituted 2-Acylimino-3-alkyl-1,3-diazacycloalkanes (7a—g)——Compounds **7a—g** were prepared by the following procedure and are listed in Table V. The oily compounds in Table V were used to the next reaction without further purification.

A mixture of **2a** (0.88 g, 4 mmol) and 0.22 g (4.4 mmol) of NaH (50% oil suspension) in 15 ml of DMF was stirred at room temperature for 1 hr. To the mixture was added ethyl iodide (0.67 g, 4.4 mol) and the mixture was stirred at room temperature for 2 hr. The mixture was concentrated to dryness *in vacuo*. The residue was mixed with water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified on silica gel chromatography to give 0.61 g (63%) of **7a**.

1-Substituted 3-Alkyl-2-cyanoimino-1,3-diazacycloalkanes (8a—e)——Compounds **8a—e** were prepared by the following procedure and are listed in Table VI.

A mixture of **9c** (2.76 g, 10 mmol) and 0.45 g (9 mmol) of NaH (50% oil suspension) in 15 ml of DMF was stirred at room temperature for 1 hr. To the mixture was added methyl iodide (1.7 g, 12 mmol) and the mixture was continued to stir at room temperature for 2 hr. The mixture was worked up as the procedure for the synthesis of **7** to give 2.8 g (97%) of **8c**.

1-Methyl-6-oxo-5,5-diphenyl-2,3,5,6-tetrahydro-1H-imidazo[1,2-*a*]imidazole (10a)——A mixture of **7g** (3.1 g, 10 mmol) and 1.0 g (20 mmol) of NaH (50% oil suspension) in 30 ml of DMF was stirred at room temperature for 1 hr. To the mixture was added methyl iodide (1.4 g, 10 mmol) and the mixture was heated at 100° for 1—2 hr. After cooling, the mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from EtOH–ether to give 2.7 g (89%) of **10a**.

By the same procedure, other compounds **10b, c** were obtained and are shown in Table VII.

6-Imino-1-methyl-5,5-diphenyl-2,3,5,6-tetrahydro-1H-imidazo[1,2-*a*]imidazole (12a)——A mixture of **8b** (0.58 g, 2 mmol) and 0.10 g of NaH (50% oil suspension) in 3 ml of DMF was heated at 50—70° for 2 hr. The mixture was worked up as a similar procedure for the synthesis of **10a**. The product was recrystallized from AcOEt to give 0.44 g (81%) of **12a**.

Acknowledgement The authors are grateful to Dr. G. Ohta, Director of this Institute, for encouragement throughout the course of this work. The authors also thank Dr. Y. Abiko, Messrs. K. Kameda and S. Ono for biological assay. Acknowledgement is also to the members of this Institute for the analysis.