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Cyclic Guanidines. III.[1] Synthesis of Hypoglycemic 2-Benzhydrylimino-1,3-diazacycloalkanes[2]

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2-Benzhydryliminoimidazolidine derivatives were prepared by the reactions of benzhydrylamines with 2-methylthio- or 2-chloro-2-imidazoline. The reaction of 1-benzhydryl-2-methylisothiourea or benzhydrylisocyanidedichloride with alkylenediamines gave the many 2-benzhydrylimino-1,3-diazacycloalkanes (**14**—**21**). Compound **14**, **15**, and **17** were alkylated or acylated to give the ring nitrogen substituted derivatives.

The alkyl or acyl derivatives of 2-benzhydryliminoimidazolidine obtained here have two tautomeric form, 2-amino and 2-imino form, which were discussed by use of the NMR spectral data.

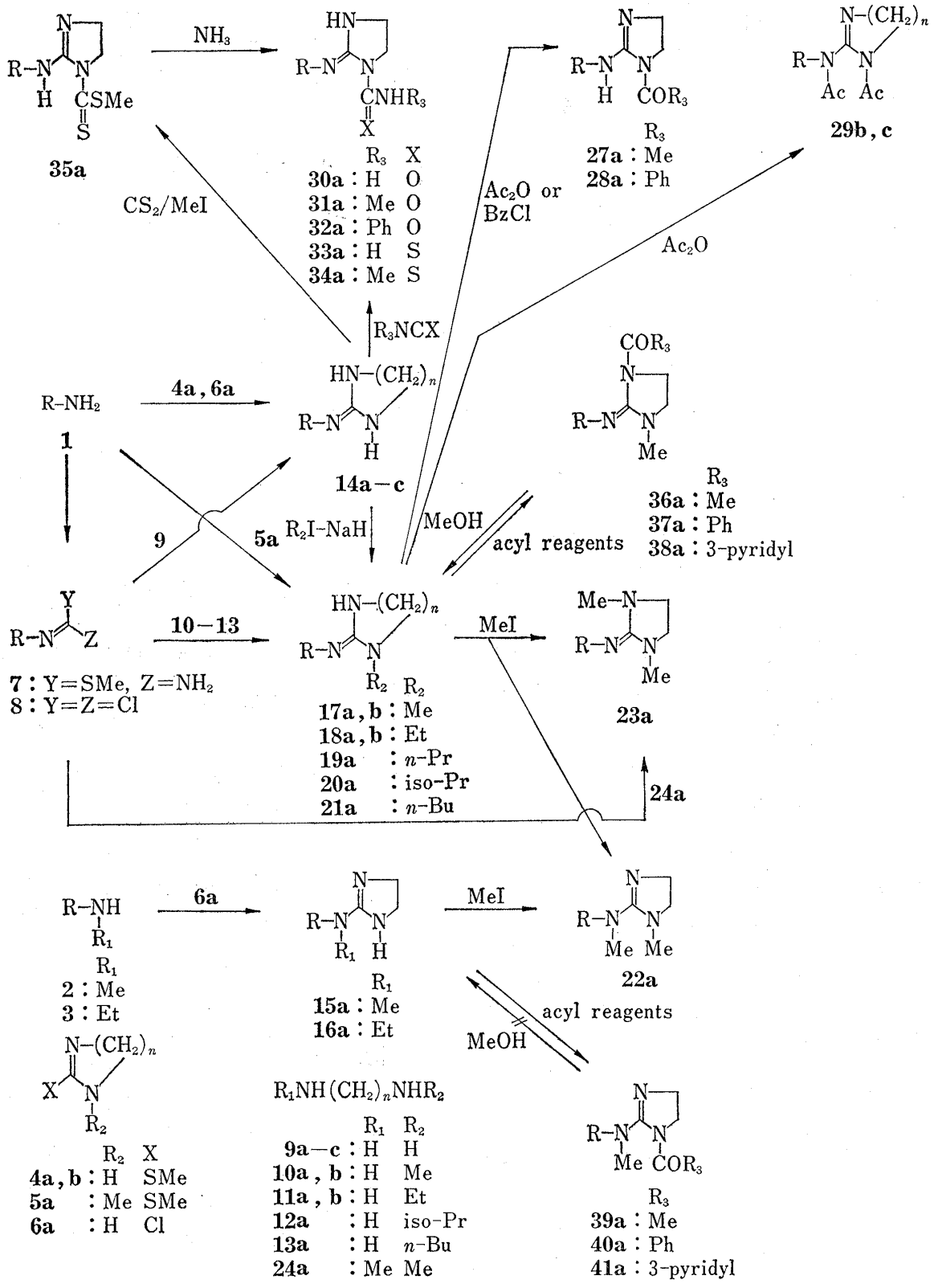
Some of 2-benzhydrylimino-1,3-diazacycloalkanes showed hypoglycemic activity.

Keywords——cyclic guanidine; cyclization; alkylation; acylation; amino-imino tautomerism; NMR; hypoglycemic activity

Recently, Grisar and co-workers[4] reported that hypoglycemic activity of 2-substituted lactamimide derivatives largely depend upon the presence of a bulky group such as benzhydryl group at position 2. In the previous papers,[1,5] we described that the 2-imino-1,3-diazacycloalkanes[6] substituted by a bulky group at the position 1 also revealed hypoglycemic activity. On the basis of previous observations, we attempted to prepare 2-imino-1,3-diazacycloalkanes, which possess a benzhydryl group on the 2-imino function, in order to examine the hypoglycemic activity. In this paper, we wish to describe some chemical and pharmacological results obtained in the synthesis and hypoglycemic assay of 2-benzhydrylimino-1,3-diazacycloalkane derivatives.

Aspinal and co-workers[7] prepared many 2-alkyl- or aralkyl-iminoimidazolidine derivatives by the reaction of amines such as ethylamine or benzylamine with 2-methylthio-2-imidazoline (**4a**). According to the method, benzhydrylamine (**1**) was allowed to react with **4a** or its 1-methyl derivative (**5a**) at 150—160° to give 2-benzhydryliminoimidazolidine (**14a**) and its

1) Part II: F. Ishikawa, A. Kosasayama, and T. Konno, *Chem. Pharm. Bull.* (Tokyo), **26**, 3666 (1978).
2) Presented at the 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, April 1978.
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo 132, Japan.*
4) J.M. Grisar, G.P. Claxton, A.A. Carr, and N.L. Wiech, *J. Med. Chem.*, **16**, 679 (1973).
5) F. Ishikawa, A. Kosasayama, S. Nakamura, and T. Konno, *Chem. Pharm. Bull.*, (Tokyo), **26**, 3658 (1978).
6) For the sake of convenience, all cyclic guanidines are shown in 2-imino form except for clear 2-amino compounds.
7) S.R. Aspinal and E.J. Bianco, *J. Am. Chem. Soc.*, **73**, 602 (1951).



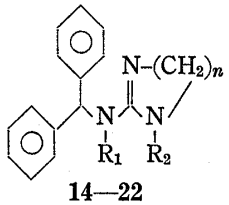
R=benzhydryl, **a**: n=2, **b**: n=3, **c**: n=4

Chart 1

1-methyl derivative (**17a**), respectively. However, reaction of N-methyl- or N-ethyl-benzhydrylamine (**2** or **3**) with **4a** did not give the desired 2-(N-alkylbenzhydrylamino)-2-imidazoline (**15a, 16a**). Accordingly, **2** was treated with more active 2-chloro-2-imidazoline (**6a**)[8] to obtain 2-(N-methylbenzhydrylamino)-2-imidazoline (**15a**). Analogous reaction of **3** with **6a**, however, gave only trace amount of the corresponding N-ethyl derivative (**16a**).

In order to prepare 2-benzhydryliminoperhydropyrimidine (**14b**), a six-membered cyclic guanidine analog, the reaction of 2-methylthio-1,4,5,6-tetrahydropyrimidine (**4b**)[9] with **1** was attempted. In place of the expected **14b**, however, perhydro-2-pyrimidinone (**25**) was obtained in quantitative yield. Bloom[10] reported preparation of 2-phenylimino-1,3-diazacycloalkanes

Table I. 2-Benzhydrylimino-1,3-diazacycloalkanes and Their Alkyl Derivatives



14—22

No.	R_1	R_2	n	Method	Yield (%)	mp[a] (°C)	Formula	Analysis Calcd. (Found) C	H	N
14a	H	H	2	A B C D	62 98 74 34	207—209 (HCl)	$C_{16}H_{18}ClN_3$	66.77 (66.81	6.30 6.31	14.60 14.63)
14b	H	H	3	C	84	240—242 (HCl)	$C_{17}H_{20}ClN_3$	67.65 (67.77	6.68 6.67	13.92 13.70)
14c	H	H	4	C	46	227—229 (HCl)	$C_{18}H_{22}ClN_3$	68.45 (68.38	7.02 7.07	13.31 13.24)
15a	Me	H	2	B	100	161—162	$C_{17}H_{19}N_3$	76.94 (76.96	7.22 7.23	15.92 15.89)
16a	Et	H	2	B	5	141—142	$C_{18}H_{21}N_3$	77.38 (77.63	7.58 7.43	15.04 14.97)
17a	H	Me	2	A C D E	30 81 50 60	154—156 (HCl)	$C_{17}H_{20}ClN_3$	67.65 (67.75	6.68 6.61	13.92 14.04)
17b	H	Me	3	C E	69 43	219—221 (HCl)	$C_{18}H_{22}ClN_3$	68.45 (68.74	7.02 6.92	13.30 13.19)
18a	H	Et	2	C E	66 44	274—276 (HCl)	$C_{18}H_{22}ClN_3$	68.45 (68.29	7.02 6.88	13.30 13.29)
18b	H	Et	3	E	52	247—249 (HCl)	$C_{19}H_{24}ClN_3$	69.18 (68.95	7.33 7.43	12.74 12.58)
19a	H	*n*-Pr	2	E	40	261—263 (HCl)	$C_{19}H_{24}ClN_3$	69.18 (69.31	7.33 7.11	12.74 12.71)
20a	H	iso-Pr	2	C E	13 0	200—202 (HI)	$C_{19}H_{24}IN_3$	54.16 (54.19	5.74 5.94	9.97 10.00)
21a	H	*n*-Bu	2	C E	61 55	240—242 (HCl)	$C_{20}H_{26}ClN_3$	69.85 (69.63	7.62 7.53	12.22 12.36)
22a	Me	Me	2	E	67	Oil	$C_{18}H_{21}N_3 \cdot 2/1H_2O$	74.97 (74.89	7.69 7.63	14.57 14.27)
23a	2-Benzhydrylimino-1,3-dimethyl-imidazolidine			C	43	68— 70	$C_{18}H_{21}N_3$	77.39 (77.45	7.58 7.43	15.04 15.06)

a) Hydrochoride (HCl) was recrystallized from iso-PrOH. Free base was recrystallized from AcOEt or AcOEt–ether.

8) A. Trani and E. Bellasio, *J. Heterocycl. Chem.*, **11**, 257 (1974).
9) A.F. McKay and M.B. Kreling, *Can. J. Chem.*, **35**, 1438 (1957).
10) B.M. Bloom, US Patent 2899426 (1959) [*C.A.*, **54**, 588 (1960)].

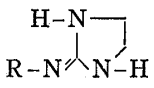
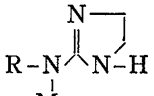
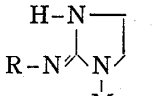
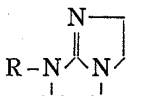
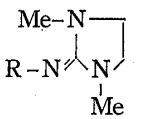
by the reaction of 1-phenyl-2-methylisothiourea with alkylenediamines. According to the modified Bloom's procedure, the reaction of 1-benzhydryl-2-methylisothiourea (**7**)[11] with alkylenediamine derivatives (**9**—**13**) under reflux in methanol yielded many 2-benzhydrylimino-1,3-diazacycloalkane derivatives (**14**, **17**—**21**) including six-membered compounds. However, in the same conditions, the reaction of **7** with 1,4-butanediamine (**9c**) allowed isolation of an intermediate, 1-benzhydryl-3-(4-aminobutyl)-guanidine (**26**), which was converted to the corresponding 1,3-diazepine derivative (**14c**) on heating at 180—200°. Similarly, 2-benzhydrylimino-1,3-diazacycloalkane derivatives (**14a**, **17a**) were also obtained by the reaction of benzhydrylisocyanidedichloride (**8**)[12] with **9a** or **10a**.

Another synthetic method of 1-alkyl-2-benzhydrylimino-1,3-diazacycloalkanes (**17**—**21**), the alkylation of **14a**, **b** with alkyl iodide in the presence of sodium hydride in dimethylformamide (DMF) gave 1-alkylated compounds (**17**—**21**) in 39—69% yields. However, seven-membered cyclic compound **14c** did not give the alkylated derivatives.

Similarly, compound **15a** was allowed to react with methyl iodide and sodium hydride in DMF to give 1,2-exo-N-dimethyl derivative (**22a**) in 67% yield. On the other hand, methylation of **17a** under the same conditions gave a mixture of 1,2-exo-N- and 1,3-dimethyl derivatives (**22a** and **23a**) (1 : 5), which were detected with nuclear magnetic resonance (NMR) spectrum. The compound **23a** was also obtained by the reaction of **7** with 1,2-bismethylaminoethane (**24a**).

NMR spectra of 2-benzhydryliminoimidazolidine (**14a**) and its methyl derivatives (**15a**, **17a**, **22a** and **23a**) are shown in Table II.

Table II. NMR Spectra of 2-Benzhydryliminoimidazolidine and Its N-Methyl Derivatives

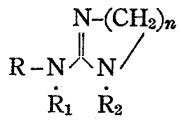
Compound[a]		Solvent[b]	Chemical shift (δ)			
			Methine	Methylene C_4	Methylene C_5	Methyl
14a		C	5.77(s)	3.23(s)		
15a		C	6.41(s)	3.57(s)		2.75(s)
17a		C	5.40(s)	3.18(s)		2.80(s)
22a		C	6.12(s)	3.71(m)	3.39(m)	2.50(s) 2.70(s)
23a		C	5.97(s)	3.07(s)		2.77(s)

a) R=benzhydryl group.
b) C=$CDCl_3$.

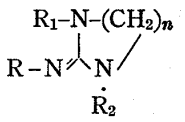
The chemical shifts of the methylene protons at C_4 and C_5 in **15a** existing in the amino form appear at δ 3.57 as a singlet. The methylene proton signals at C_4 and C_5 in **22a** are

11) S.O. Winthrop, S. Sybulsky, G. Gavin, and G.A. Grant, *J. Am. Chem. Soc.*, **79**, 3496 (1957).
12) E. Kuhle, B. Anders, and G. Zumach, *Angew. Chem. Int. Ed. Engl.*, **6**, 649 (1967).

TABLE III. Acyl Derivatives of 2-Benzhydrylimino-1,3-diazacycloalkanes



2-Amino form



2-Imino form

No.	Form	R_1	R_2	n	Yield (%)	mp (°C) (Recryst. solv.)[c]	NMR chemical shift (δ)[a] Solvent[b]	Methine	Methylene C_4	Methylene C_5	Formula	Analysis Calcd. (Found) C	H	N
27a	Amino	H	COMe	2	71	234—236[d] (C)	C	6.08(d)	3.77(m)		$C_{18}H_{20}ClN_3O$	65.55 (65.55	6.11 6.31	12.74 12.64)
28a	Amino	H	COPh	2	78	172—175 (B)	C	6.15(d)	3.71(m)		$C_{23}H_{21}N_3O$	77.72 (78.10	5.96 6.10	11.82 11.99)
29b	Amino	COMe	COMe	3	69	86— 88 (D)					$C_{21}H_{23}N_3O_2$	72.18 (71.92	6.63 6.68	12.03 12.08)
29c	Amino	COMe	COMe	4	47	118—120 (E)					$C_{22}H_{25}N_3O_2$	72.70 (72.65	6.93 6.88	11.56 11.71)
30a	Imino	H	$CONH_2$	2	50	176—179[d] (B)	D	5.50(s)	3.25(m)	3.70(m)	$C_{17}H_{19}ClN_4O$	61.72 (61.69	5.79 5.73	16.94 16.85)
31a	Imino	H	CONHMe	2	99	215—217[d] (B)	C	5.30(s)	3.20(m)	3.80(m)	$C_{18}H_{21}ClN_4O$	62.69 (62.81	6.14 6.23	16.25 16.36)
32a	Imino	H	CONHPh	2	83	165—167[d] (A)	C	5.38(s)	3.30(m)	3.99(m)	$C_{23}H_{23}ClN_4O\cdot H_2O$	65.01 (65.49	5.93 5.99	13.19 13.41)
33a	Imino	H	$CSNH_2$	2	44	160—162 (B)	D	5.30(s)	3.40(m)	4.10(m)	$C_{17}H_{19}ClN_4S$	58.86 (59.04	5.52 5.48	16.15 16.49)
34a	Imino	H	CSNHMe	2	94	213—215[d] (B)	C	5.32(s)	3.30(m)	4.32(m)	$C_{18}H_{21}ClN_4S$	59.90 (59.78	5.59 5.78	15.52 15.52)
35a	Amino	H	CSSMe	2	72	133—135 (B)	C	6.10(d)	3.69(m)	4.11(m)	$C_{18}H_{19}N_3S_2$	63.31 (63.64	5.61 5.60	12.30 12.51)

a) Chemical shift (δ) of free base.
b) C=$CDCl_3$, D=d_6-DMSO.
c) A=EtOH, B=IPA, C=EtOH–ether, D=benzene–IPE, E=acetone–IPE.
d) Hydrochloride.

observed at δ 3.71 and 3.39 as multiplet, respectively. The methylene proton signal of **23a** (δ 3.07) is more shielded than that of C_5 methylene protons in **22a**. On the other hand, the chemical shifts of the methylene protons at C_4 and C_5 in **14a** and **17a** appear at δ 3.23 and 3.18 as singlet, respectively. If these compounds **14a** and **17a** have the amino form, the methylene proton signals at C_4 must be observed in the lower field (δ 3.6—3.7) and the methine proton of the benzhydryl group must be also coupled with the 2-amino hydrogen as well as 1-acetyl-2-benzhydrylamino-2-imidazoline (**27a**) as described below. Thus, it was presumed that the imino form in these compounds predominates over the amino form. Some research groups[13–15] also reported the similar results in the tautomerism of 2-(2,6-dichlorophenylimino)-imidazolidine on the basis of the NMR spectral analysis.

There have been some reports[16] in regard to acylation of 2-imino-1,3-diazacycloalkane and its derivatives. A variety of acylation products are obtained, and their distribution varies with the substituents and the reaction conditions. In the previous paper,[1] we have also studied on the reactions of 1-substituted 2-imino-1,3-diazacycloalanes with acylating reagents under the various conditions.

Acylation of **14a** with excess of acetic anhydride or benzoyl chloride in the presence of sodium hydride in DMF gave 1-acetyl or 1-benzoyl derivatives (**27a** and **28a**), respectively. On the other hand, the reaction of **14b** and **14c** having six- or seven-membered ring with excess of acetic anhydride yielded only 1,2-exo-N-diacetylated derivatives (**29a** and **29c**), respectively. The structures were confirmed on the basis of the NMR spectra in which two kinds of methyl signals of acetyl groups were observed at δ 1.9 and 2.4 in **29b** and δ 1.8 and 2.2 in **29c**, respectively.

Reaction of **14a** with other acylating reagents such as isocyanates and isothiocyanates gave also 1-substituted compounds **31a**, **32a**, and **34a**. Similarly, in the reaction of the hydrochloride of **14a** with potassium isocyanate in dimethylsulfoxide (DMSO) at room temperature 1-carbamoyl derivative (**30a**) was obtained. Furthermore, **14a** was allowed to react with carbon disulfide in the presence of sodium hydride and then methyl iodide to give 1-methyldithiocarbonyl derivative (**35a**), which was converted to 1-thiocarbamoyl derivative (**33a**) by use of ammonia.

The structures of these monoacylated compounds obtained here were confirmed on the basis of the NMR data. Compounds **27a**, **28a**, and **35a** have 2-amino form because a coupling (J=6 Hz) between the benzhydryl methine proton and the 2-amino hydrogen (N–H) is observed. Hence, the acyl group of these compounds is not substituted at 2-exo-N position. In the compounds **30a**—**34a**, two kinds of multiplet signals of C_4 and C_5 methylene protons are observed. If these compounds are 2-exo-N-acyl derivatives, the methylene protons must be shown as singlet signal.[16d] Thus, the acyl group of these compounds is substituted at N_1 position. Furthermore, these compounds probably have 2-imino form because the benzhydryl methine proton does not coupled with 2-amino hydrogen (N–H).

When 2-benzhydrylimino-1-methylimidazolidine (**17a**) was allowed to react with various acyl chlorides in the presence of triethylamine in chloroform at room temperature, only 3-acylated compounds **36a**—**38a** were obtained in 66—86% yields. Some of these compounds were easily deacylated with methanol at room temperature. For example, acetyl or nicotinoyl derivatives were completely methanolyzed within 30 minutes.

13) L.M. Jackman and T. Jen, *J. Am. Chem. Soc.*, **97**, 2811 (1975).
14) K-H. Pook, H. Staehle, and H. Daniel, *Chem. Ber.*, **107**, 2644 (1974).
15) *a*) C.G. Wermuth, J. Schwartz, G. Leclerc, J. Garnier, and B. Rouot, *Chim. Ther.*, **8**, 115 (1973); *b*) B. Rouot, G. Leclerc, and C.G. Wermuth, *ibid.*, **8**, 545 (1973).
16) *a*) R.A. Lucas and H.M. Blatter, S. Afr. Patent 7003276 (1970) [*Chem. Abstr.*, **75**, 40127*j* (1971)]; *b*) C.H. Boehringer Sohn, Belg. Patent 741947 (1969); *c*) T. Jen, H. Van Hoeven, W. Groves, R.A. McLean, and B. Loev, *J. Med. Chem.*, **18**, 90 (1975); *d*) R. Franzmair, Ger. Offen. 25211709 (1976) [*Chem. Abstr.*, **84**, 180214 (1976)].

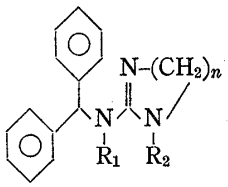
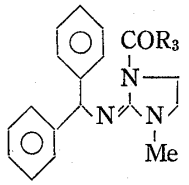
TABLE IV. 3-Acyl-2-benzhydrylimino-1-methylimidazolidines (**36**—**38**) and 1-Acyl-2-(N-methylbenzhydrylamino)-2-imidazolines (**39**—**41**)

36—**38** **39**—**41**

No.	R_3	Yield (%)	mp (°C) (Recryst. solv.)[b]	NMR (δ)[a] Methine	Methylene C_4	Methylene C_5	Formula	Analysis Calcd. (Found) C	H	N
36a	Me	85	164—165 (A)	6.04 (s)	3.77 (m)	3.20 (m)	$C_{19}H_{21}N_3O$	74.24 (74.54	6.89 6.93	13.67 13.58)
37a	Ph	77	157—158 (A)	5.76 (s)	3.52 (m)	3.19 (m)	$C_{24}H_{23}N_3O$	78.02 (78.07	6.27 6.29	11.37 11.31)
38a	3-Pyridyl	66	168—170 (A)	5.73 (s)	3.71 (m)	3.25 (m)	$C_{22}H_{22}N_4O$	74.54 (74.36	5.99 5.96	15.12 15.17)
39a	Me	69	99—101 (B)	6.18 (s)	3.50 (m)	3.90 (m)	$C_{19}H_{21}N_3O$	74.24 (74.08	6.89 6.90	13.67 13.57)
40a	Ph	47	161—163[c] (C)	6.52 (s)	3.54 (m)	3.81 (m)	$C_{23}H_{23}ClN_4O$	71.01 (71.11	5.96 6.33	10.35 10.31)
41a	3-Pyridyl	18	188—190[c] (C)	6.47 (s)	3.59 (m)	3.86 (m)	$C_{23}H_{23}ClN_4O$	67.89 (68.26	5.70 5.73	13.77 13.29)

R=benzhydryl.
a) Chemical shift (δ) of free base in $CDCl_3$.
b) A=AcOEt, B=ether, C=IPE–ether.
c) Hydrochloride.

TABLE V. Hypoglycemic Activity of 2-Benzhydrylimino-1,3-diazacycloalkanes

Compound	Plasma glucose[a] Dose (mg/kg, *p.o.*)	% reduction
	25	20—40
	25	30—60

R_1, R_2=H or lower alkyl group; R_3=Me, Ph, 3-pyridyl; n=2,3.
a) The test compound was orally administrated to rats which had been fasted overnight. Plasma glucose was determined by the glucose oxidase method at 2—5 hr after the administration.

The structure of **36a**—**38a** were confirmed on the basis of the NMR spectral data, in which two sets of multiplet signals were observed at δ 3.5—3.8 and 3.2—3.3. The former signals can be assignable to the C_4 methylene protons adjacent to the acyl nitrogen and the later signals can be ascribed to the C_5 methylene protons adjacent to the unsubstituted or alkyl nitrogen in the 2-iminoimidazolidine. If the acyl group is located on the 2-amino

group, the methylene signals at C_4 and C_5 must be appeared in the analogous field to that of **22a** (δ 3.4—3.8).

On the other hand, reaction of **15a** with acyl chloride under the same conditions gave 1-acyl derivatives **39a—41a**, which are stable in methanol. In the NMR spectra of these compounds, methylene proton signals of C_4 and C_5 were observed at δ 3.5—3.6 and 3.8—3.9 as multiplet, respectively.

Hypoglycemic activity was determined in normal fasted rats. The bulky group as 2-N-substituents in 2-imino-1,3-diazacycloalkanes was necessary for hypoglycemic activity. The order of the activity in the 1,3-diazacycloalkane ring size was five, six and seven. The compounds 1-loweralkyl-2-benzhydryliminoimidazolidines (**17a, 18a**) and 2-(N-loweralkyl-benzhydrylamino)-2-imidazolines (**15a, 16a**) showed potent activity. Furthermore, the unstable 3-acyl-1-methyl derivatives (**36a—38a**) in methanol were the most effective compounds. The activity of some derivatives obtained here is shown in Table V. The structure–activity relationships in a series of the cyclic guanidines will be reported elsewhere in detail.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 285 spectrometer. Mass spectra (MS) were determined on a JEOL 01SG-2 Mass 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). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

2-Benzhydrylimino- or amino-1,3-diazacycloalkane and Its N-Alkylated Derivatives (14—23)

Method A. [**Reaction of Benzhydrylamine (1) with 2-Methylthiocyclic Isothiourea (4, 5)**]——2-Benzhydryliminoimidazolidine (**14a**): A mixture of **4a** (8.0 g, 30 mmol) and **1** (5.5 g, 30 mmol) was heated at 150—160° for 20 min. After cooling, the reaction mixture was recrystallized from AcOEt to give the hydroiodide of **14a** (7.0 g, 62%). It was dissolved in 40 ml of MeOH and treated with 20 ml of 2 N NaOH solution to give the free base of **14a** (4.4 g, 96%), mp 189—190°.

The free base of **14a** was dissolved in HCl–EtOH and the solution was evaporated *in vacuo* to yield the hydrochloride of **14a**, mp 207—209° (from iso-PrOH (IPA)).

Method B. [**Reaction of Benzhydrylamine (1) with 2-Chloro-2-imidazoline (6a)**]——2-(N-Methylbenzhydrylamino)-2-imidazoline (**15a**): To an ice-cooled solution of NaOH (1.2 g, 30 mmol) in 20 ml of water was added the sulfate of **6a**[8] (6.0 g, 30 mmol) and then the solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and a small amount of $CHCl_3$ was evaporated *in vacuo*. To the solution was added **1** (3.0 g, 15 mmol) and the reaction mixture was allowed to stand at room temperature for 2 days. The mixture was evaporated to dryness *in vacuo* and the residue was treated with 20 ml of 2 N NaOH. The mixture was extracted with $CHCl_3$ and the extract was washed with water, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was recrystallized from AcOEt to give **15a** (4.0 g, 98%).

Method C. [**Reaction of 1-Benzhydryl-2-methylisothiorea (7) with Alkylenediamines (9—13 and 24a)**]——2-Benzhydrylimino-1-methylimidazolidine (**17a**): A mixture of the hydroiodide of **7** (3.84 g, 10 mmol) and 2-methylaminoethylamine (**10a**) in 30 ml of MeOH was refluxed for 15 hr with stirring. The mixture was evaporated *in vacuo* and the residue was mixed with 20 ml of 2 N NaOH. The mixture was extracted with $CHCl_3$ and the extract was worked up in the usual way to give **17a** (2.14 g, 81%).

1-(4-Aminobutyl)-3-benzhydrylguanidine Hydroiodide (**26**): A mixture of the hydroiodide of **7** (5.0 g, 13 mmol) and **9c** (5.8 g, 6.5 mmol) in 40 ml of MeOH was refluxed for 20 hr. The mixture was evaporated *in vacuo* and the residue was triturated with water. An insoluble solid was collected and recrystallized from EtOH to yield **26** (5.1 g, 93%), mp 175—177°. IR ν_{max}^{KBr} cm^{-1}: 3250, 3150, 1620, 1480. *Anal.* Calcd. for $C_{18}H_{25}IN_4$: C, 50.94; H, 5.94; N, 13.92. Found: C, 51.22; H, 6.33; N, 13.99.

2-Benzhydryliminoperhydro-1,3-diazepine (**14c**): Compound **26** (3.4 g, 8.0 mmol) was heated at 185—190° for 15 min. After cooling, the solid was recrystallized from EtOH to yield the hydroiodide of **14c** (1.8 g, 55%), mp 217—219°. It was worked up in the usual way to yield the hydrochloride of **14c**. IR ν_{max}^{KBr} cm^{-1}: 3180, 3030, 1620. NMR (d_6-DMSO) δ: 6.14 (1H, s, ArCH), 3.0—3.3 (4H, m, C_4– and C_7–CH_2), 1.4—1.7 (4H, m, C_5– and C_6–CH_2).

Method D. [**Reaction of Benzhydrylisocyanidedichloride (8) with Alkylenediamines (9 and 10)**]——2-Benzhydryliminoimdazolidine (**14a**): To a solution of ethylenediamine (**9**) (4.2 g, 70 mmol) in 40 ml of ether was added an ether solution of **8** prepared from benzhydrylisothiocyanate (3.2 g, 14 mmol) and Cl_2 gas at 5—10° with stirring. The mixture was allowed to stand at room temperature overnight and mixed with 100 ml of 2 N NaOH. An insoluble solid was collected to give **14a** (1.4 g, 34%).

Method E. [Reaction of 2-Benzhydrylimino-1,3-diazacycloalkanes (14, 15 and 17) with Alkyl Iodide in the Presence of Sodium Hydride (NaH)]——2-Benzhydrylimino-1-ethylimidazolidine (**18a**): A mixture of **14a** (1.52 g, 5 mmol) and NaH (0.16 g, 6.7 mmol) in 7 ml of DMF was stirred at room temperature for 1.5 hr. To the mixture was added ethyl iodide (1.10 g, 7 mmol) and the mixture was stirred at room temperature overnight. The mixture was concentrated to dryness *in vacuo*. The residue was mixed with water and extracted with $CHCl_3$. The extract was worked up in the usual way to yield the hydrochloride of **18a** (0.69 g, 44%).

1-Acetyl-2-benzhydrylamino-2-imidazoline (**27a**): After stirring a mixture of **14a** (2.51 g, 10 mmol) and NaH (0.60 g, 25 mmol) in 100 ml of DMF at room temperature for 30 min, Ac_2O (2.55 g, 25 mmol) was added to the mixture. The mixture was further stirred for 3 hr and 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 IPA to yield **27a** (2.10 g, 71%), mp 155—157°. It was converted to the hydrochloride of **27a** in the usual way, mp 234—236° (from EtOH–ether). IR ν_{max}^{KBr} cm^{-1}: 1705, 1570.

1-Acetyl-2-(N-acetylbenzhydrylamino)-1,4,5,6-tetrahydropyrimidine (**29b**): To a mixture of NaH (0.60 g, 25 mmol) and **14b** (1.65 g, 10 mmol) in 100 ml of DMF was added Ac_2O (2.55 g, 25 mmol) with stirring. The mixture was further stirred for 30 min and concentrated to dryness *in vacuo*. The residue was mixed with water and extracted with $CHCl_3$. The extract was worked up in the usual way and the oily residue was chromatographed over silica gel (50 g) with $CHCl_3$. The eluate was evaporated *in vacuo* and the residue was recrystallized from benzene–isopropylether (IPE) to yield **29b** (2.40 g, 69%). NMR ($CDCl_3$) δ: 7.30 (10H, s, aromatic protons), 5.68 (1H, s, Ar–CH), 4.26 (2H, m, C_6–CH_2), 3.05 (2H, m, C_4–CH_2), 2.50 (3H, s, N_1– or N_2'–$COCH_3$), 1.92 (3H, s, N_2'– or N_1–$COCH_3$). IR ν_{max}^{KBr} cm^{-1}: 1670, 1655. MS *m/e*: 349 (M^+).

1-Acetyl-2-(N-acetylbenzhydrylamino)-4,5,6,7-tetrahydro-1H-1,3-diazepine (**29c**): Following a similar procedure for the synthesis of **29b**, **14c** (2.79 g, 10 mmol) was treated with NaH (0.60 g, 25 mmol) and Ac_2O (2.55 g, 25 mmol) in 100 ml of DMF to give **29c** (1.71 g, 47%). IR ν_{max}^{KBr} cm^{-1}: 1670, 1650. MS *m/e*: 363 (M^+). NMR ($CDCl_3$) δ: 7.35 (10H, m, aromatic protons), 5.70 (1H, s, Ar–CH), 4.62 (2H, m, C_7–CH_2), 2.70 (2H, m, C_4–CH_2), 2.17 (3H, s, N_1– or N_2'–$COCH_3$), 1.85 (3H, s, N_2'– or N_1–$COCH_3$).

2-Benzhydrylimino-1-carbamoylimidazolidine (**30a**): A mixture of the hydrochloride of **14a** (5.0 g, 17.5 mmol) and potassium isocyanate (1.42 g, 17.5 mmol) in 50 ml of DMSO was stirred at room temperature for 9 hr. After acidifying the mixture with conc. HCl to pH 3—4, the mixture was concentrated to dryness *in vacuo*. The residue was mixed with 10% Na_2CO_3 solution 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 IPA to give **30a** (2.3 g, 50%), mp 163—165°. It was converted to the hydrochloride of **30a** in the usual way. IR ν_{max}^{KBr} cm^{-1}: 1660, 1710.

2-Benzhydrylimino-1-methylcarbamoylimdazolidine (**31a**): A mixture of **14a** (1.26 g, 5 mmol) and methyl isocyanate (0.34 g, 6 mmol) in 15 ml of benzene was stirred at room temperature for 40 min. A solid was collected and recrystallized from IPA to yield **31a** (1.46 g, 95%), mp 116—118°. It was converted to the hydrochloride of **31a** in the usual way. IR ν_{max}^{KBr} cm^{-1}: 1700.

2-Benzhydrylimino-1-phenylcarbamoylimidazolidine (**31a**): Following a similar procedure for the synthesis of **31a**, **14a** (2.51 g, 10 mmol) was treated with phenyl isocyanate (0.88 g, 12 mmol) in 30 ml of benzene to give **32a** (3.00 g, 94%), mp 154—156°. It was converted to the hydrochloride of **32a** in the usual way. IR ν_{max}^{KBr} cm^{-1}: 1705.

2-Benzhydrylimino-1-thiocarbamoylimidazolidine (**33a**): A solution of **35a** (5.4 g, 16 mmol) in 400 ml of 15% ethanolic ammonia solution was allowed to stand at room temperature for 10 days. The solution was concentrated to dryness *in vacuo* and the residue was recrystallized from IPA to give **33a** (2.3 g, 44%), mp 160—162°. It was converted to the hydrochloride of **33a** in the usual way. IR ν_{max}^{KBr} cm^{-1}: 1670.

2-Benzhydrylimino-1-methylthiocarbamoylimidazolidine (**34a**): Following a similar procedure for the synthesis of **31a**, **14a** (2.51 g, 10 mmol) was treated with methyl isothiocyanate (0.88 g, 12 mmol) in 30 ml of benzene to give **34a** (3.03 g, 94%), mp 154—156°. It was converted to the hydrochloride of **34a** in the usual way. IR ν_{max}^{KBr} cm^{-1}: 1660, 1570.

2-Benzhydrylamino-1-methyldithiocarbonyl-2-imidazoline (**35a**): After stirring a mixture of **14a** (6.2 g, 25 mmol) and NaH (0.8 g, 33.3 mmol) in 100 ml of DMF at room temperature for 1 hr, 3 ml of carbon disulfide was added to the mixture. The mixture was further stirred at room temperature for 15 hr and to the mixture was added methyl iodide (2 ml, 32 mmol). The mixture was stirred for 1 hr and concentrated to dryness *in vacuo*. The residue was mixed with water and extracted with $CHCl_3$. The extract was evaporated *in vacuo*. The residue was recrystallized from IPA to yield **35a** (6.1 g, 71%).

3-Acetyl-2-benzhydrylimino-1-methylimidazolidine (**36a**): To a solution of **17a** (1.00 g, 3.8 mmol) and triethylamine (0.42 g, 4.1 mmol) in 5 ml of $CHCl_3$ was added acetyl chloride (0.33 g, 3.8 mmol) at 0—5° with stirring. The mixture was stirred at room temperature for 2 hr and then washed with water. The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from AcOEt to give **36a** (0.98 g, 85%).

Following a similar procedure for the synthesis of **36a**, other compounds **37a** and **38a** were obtained from **17a** and acyl chlorides. These results are shown in Table IV.

1-Acetyl-2-(N-methylbenzhydrylamino)-2-imidazoline (**39a**): To a solution of **15a** (1.00 g, 3.8 mmol) and triethylamine (0.42 g, 4.1 mmol) in 5 ml of $CHCl_3$ was added acetyl chloride (0.33 g, 3.8 mmol) at 0—5° with stirring. The mixture was worked up the same procedure for the synthesis of **36a** to yield **39a** (0.80 g, 69%).

Following a similar procedure for the synthesis of **39a**, other compounds **40a** and **41a** were obtained from **15a** and acyl chlorides. These results are shown in Table IV.

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