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Cyclic Guanidines. IV.[1] Synthesis of Hypoglycemic N-Benzhydryl Bicyclic Guanidines[2]

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Synthesis of N-benzhydryl bicyclic guanidines (**12**) was attempted. The key intermediates, 1-benzhydryl-2-N- or 3-(ω-hydroxyalkyl)-2-imino-1,3-diazacycloalkanes (**4**) and (**9**) were prepared. The intramolecular cyclization of **4** to **12** was not advantageous because of the low yield. On the other hand, the intramolecular cyclization of **9** to **12** resulted in good success. In our synthetic course, imidazo[1,2-*a*][1,3,5]oxadiazocine derivative (**11**), a new ring system, and N^1-benzhydryl-N^1-[2-(1-pyrrolidinyl)ethyl]urea (**13**) were isolated as by-products.

The N-benzhydryl bicyclic guanidines (**12**) showed potent hypoglycemic activity.

Keywords——N-benzhydryl bicyclic guanidine; imidazo[2,1-*d*][1,3,5]oxadiazocine; alkylation; intramolecular cyclization; hypoglycemic activity

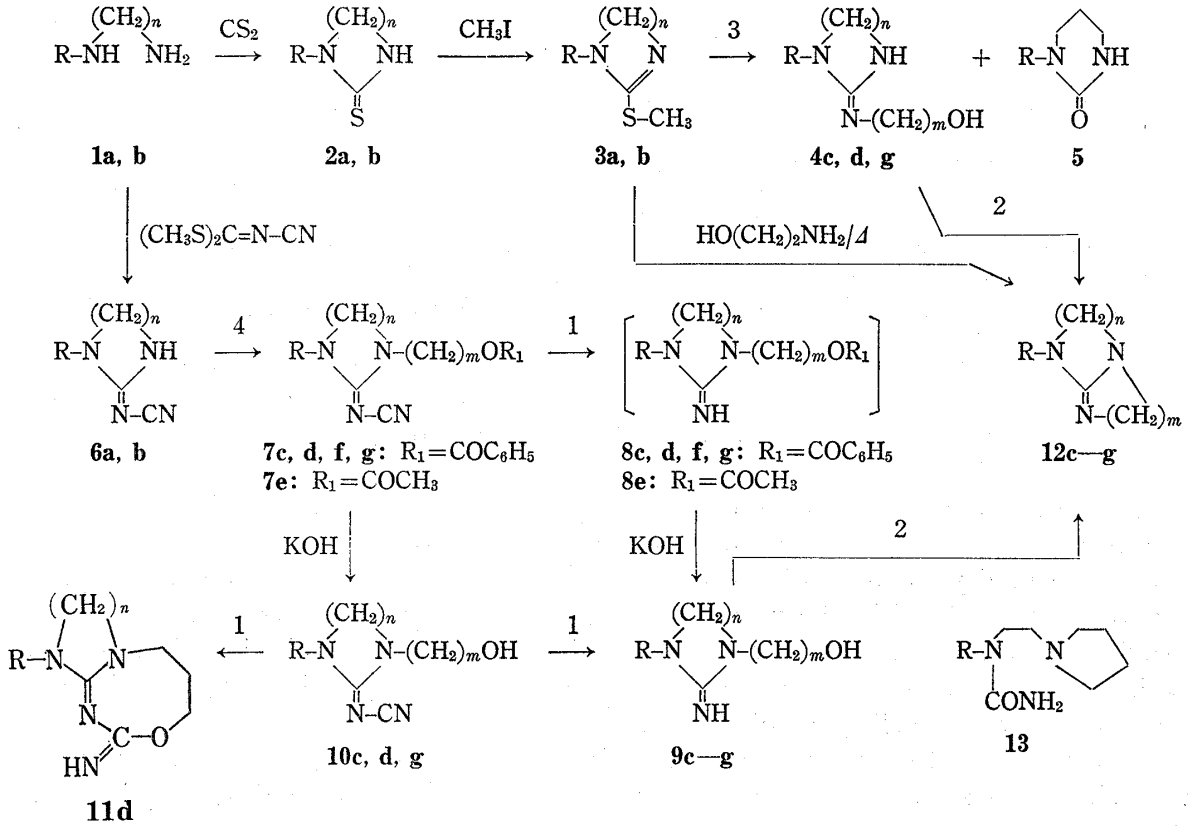
Our previous papers[1,4,5] have described that the cyclic guanidines with a bulky group at position N_1 and N_2, such as 3-alkyl-1-benzhydryl-2-imino-1,3-diazacycloalkanes[5] and 1-alkyl-2-benzhydrylimino-1,3-diazacycloalkanes[1] have potent hypoglycemic activity. Synthesis of N-benzhydryl bicyclic guanidines (**12**) which are cyclic analog of above compounds is particularly interesting from the viewpoint of structure–activity relationships. This paper describes new observations containing the synthesis and hypoglycemic activity of the N-benzhydryl substituted bicyclic guanidines (**12**).

Although several synthetic methods of the bicyclic guanidines have been reported, the preferable methods are intramolecular dehydration of 1- or 2-N-(ω-hydroxyalkyl)-2-imino-1,3-diazacycloalkanes[6] or intramolecular dehydrochlorination of 1- or 2-N-(ω-chloroalkyl)-2-imino-1,3-diazacycloalkanes. McKay and co-worker prepared 1-substituted 2,3,5,6-tetrahydro-1H-imidazo[1,2-*a*]imidazoles by treatment of 1-chloroethyl-2-substituted iminoimidazolidines with potassium hydroxide in aqueous methanol.[7] They also obtained similar 1H-bicyclic guanidines from 2-(ω-chloroalkylimino)-1,3-diazacycloalkanes under the same conditions.[8]

The reactions of 2-substituted iminoimidazolidines with alkylenedihalides[9] or 1-(2-chloroethyl)-2-nitroiminoimidazolidine with amines[10] to give 1-substituted bicyclic guanidines have been also reported but the yield of the desired products were very low.

1) Part III: A. Kosasayama, Y. Watanabe, K. Higashi, and F. Ishikawa, *Chem. Pharm. Bull.* (Tokyo), **26**, 831 (1979).
2) This work was presented at 98th Annual Meeting of Pharmaceutical Society of Japan, Okayama, April 1978.
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo 132, Japan.*
4) F. Ishikawa, A. Kosasayama, S. Nakamura, and T. Konno, *Chem. Pharm. Bull.* (Tokyo), **26**, 3658 (1978).
5) F. Ishikawa, A. Kosasayama, and T. Konno, *Chem. Pharm. Bull.* (Tokyo), **26**, 3666 (1978).
6) J.L.H. Van Gelder, A.H.M.B. Raeymaekers, L.F.C.R. Rovens, and W.J. Van Laerhover, Ger. Offen., 2361188 (1974) [*Chem. Abstr.*, **81**, 77962 (1974)].
7) A.F. McKay and D.L. Garmaise, *Can. J. Chem.*, **35**, 8 (1957).
8) A.F. McKay and M.B. Kreling, *Can. J. Chem.*, **35**, 1438 (1957).
9) H. Staehle, H. Koeppe, W. Kummer, and H.W. Samtleben, Ger. Offen., 2118261 (1972) [*Chem. Abstr.*, **78**, 29773*a* (1973)].
10) A.F. McKay and J.R. Gilpin, *J. Am. Chem. Soc.*, **78**, 486 (1956).

On the other hand, an only example of intramolecular cyclization of 1-substituted 2-N- or 3-(ω-hydroxyalkyl)-2-imino-1,3-diazacycloalkanes has been reported, *i. e.*, the cyclization of 3-(2-hydroxy-2-phenylethyl)-2-imino-1-methylimidazolidine has been achieved upon treatment with thionyl chloride.[11] Taking previous results[1,4,5] into consideration, our efforts were directed toward to accomplish the cyclization of 1-benzhydryl-2-N- or 3-(ω-hydroxyalkyl)-2-imino-1, 3-diazacycloalkanes (**4**) or (**9**) to N-benzhydryl bicyclic guanidines (**12**).



R=benzhydryl; a: $n=2$; b: $n=3$; c: $n=2$, $m=2$; d: $n=2$, $m=3$; e: $n=2$, $m=4$; f: $n=3$, $m=2$; g: $n=3$, $m=3$.
1=*tert*-BuOH/HCl. 2=$SOCl_2$, KOH. 3=$OH(CH_2)_mNH_2$. 4=$X(CH_2)_mOR_1$.

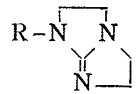
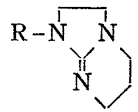
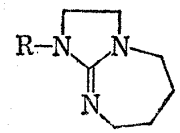
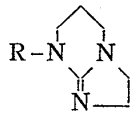
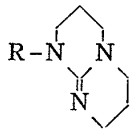
Chart 1

Reaction of 2-benzhydrylaminoethylamine (**1a**) or 3-benzhydrylaminopropylamine (**1b**) with carbon disulfide gave 1-benzhydrylethylene- or propylene thiourea (**2a**, **b**), which were treated with methyl iodide to give 2-methylthio derivatives (**3a**, **b**) in good yields. Heating **3a** with aminoalcohols such as 2-aminoethanol or 3-aminopropanol in ethanol afforded 1-benzhydryl-2-(ω-hydroxyalkylimino)-imidazolidines (**4c**, **d**) in 70% yield. However, under the same conditions, **3b** gave only 1-benzhydrylpropyleneurea (**5**). Heating **3b** with 2-aminoethanol at 180—200° without solvent also did not give satisfactory result, although the desired product, 8-benzhydryl-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrimidine (**12f**), was obtained in low yield. On the other hand, heating **3b** with 3-aminopropanol gave the corresponding 2-substituted compound **4g** in 31% yield. Chlorination of **4c**, **d**, **g** with thionyl chloride, followed by treatment with hot methanolic potassium hydroxide gave the desired N-benzhydryl bicyclic guanidines (**12c**, **d**, **g**).

The synthesis of **12** from **3** as described above was not advantageous because of the low overall yield and nongenerality. Consequently, the following useful method was exploited.

11) L.F. Miller and R.F. Bamburg, *J. Med. Chem.*, **15**, 415 (1972).

TABLE I. N-Benzhydryl Bicyclic Guanidines and Their Hypoglycemic Activities

No.	Structure[a]	Starting material	Yield (%)	mp (°C) (Recryst. solv.)	IR (cm^{-1})	NMR ($CDCl_3$)[b] (δ)	Formula	Analysis Calcd. (Found) C	H	N	Plasma glucose[c] Dosage (*p.o.*) (mg/kg)	Reduction (%)
12c		**4c** **9c**	28 84	113—115 (Ether–petr. ether)	1650 (C=N)	6.27(1H, s, Ar–CH) 3.99(2H, t, C_6–CH_2) 3.51(2H, t, C_5–CH_2) 3.10(4H, m, $C_{3,5}$–CH_2)	$C_{18}H_{19}N_3$	77.95 (77.78	6.90 7.09	15.15 15.32)	25	50
12d		**4d** **9d**	89 92	215—219[d] (Acetone)	1645 (C=N)	6.53(1H, s, Ar–CH) 3.40(2H, t, C_7–CH_2) 3.10(6H, m, $C_{2,3,5}$–CH_2) 1.80(2H, m, C_6–CH_2)	$C_{19}H_{22}ClN_3$	69.61 (69.57	6.76 6.42	12.82 12.90)	25	57
12e		**9e**	30	200—203[d] (Acetone)	1625 (C=N)	6.70(1H, s, Ar–CH) 3.40(2H, t, C_8–CH_2) 3.10(6H, m, $C_{2,3,5}$–CH_2) 1.75(4H, m, $C_{6,7}$–CH_2)	$C_{20}H_{24}ClN_3$	70.26 (69.99	7.08 6.96	12.29 12.19)	25	61
12f		**9f**	37	89— 90 (Ether)	1590 (C=N)	6.95(1H, s, Ar–CH) 3.52(2H, t, C_2–CH_2) 3.32(2H, t, C_3–CH_2) 2.90(4H, t, $C_{5,7}$–CH_2) 1.94(2H, m, C_6–CH_2)	$C_{19}H_{21}N_3$	78.32 (77.92	7.26 7.29	14.42 14.26)	25	42
12g		**4g** **9g**	24 63	104—105 (Ether)	1590 (C=N)	7.30(1H, s, Ar–CH) 3.45(2H, t, C_8–CH_2) 3.10(6H, m, $C_{2,4,6}$–CH_2) 1.95(4H, m, $C_{3,7}$–CH_2)	$C_{20}H_{23}N_3$	78.65 (78.60	7.59 7.64	13.76 13.78)	25	14

a) R=benzhydryl group.
b) In free base.
c) The test compound was orally administrated to rats which had been fasted overnight. Plasma glucose was determined by the glucose oxidase method at 2—3 hr after the administration.
d) Hydrochloride.

1-Benzhydryl-2-cyanoimino-1,3-diazacycloalkanes (**6a**, **b**)[4] obtained by the reaction of **1a**, **b** with dimethylcyanoimidodithiocarbonate were treated with ω-haloalkyl acylate, such as 2-iodoethyl benzoate, 3-chloropropyl benzoate and 4-chlorobutyl acetate, in the presence of sodium hydride to yield 3-acyloxyalkyl derivatives (**7c**—**g**) in moderate yield. When the compounds **7** were heated in *t*-butyl alcohol with 3—4 molar equivalent amounts of hydrochloric acid for several hours, the selective removal of the cyano group[4] occurred to give 2-imino derivatives (**8c**—**g**) in good yields. The compounds **8** were treated with potassium hydroxide in aqueous methanol to give 3-hydroxyalkyl derivatives (**9c**—**g**) quantitatively.

After chlorination of **9** with thionyl chloride at room temperature for several hours, the crude products were heated with potassium hydroxide in hot methanol to yield the desired bicyclic guanidines (**12c**—**g**). However, the cyclization of 3-(4-chlorobutyl) derivative (**9e**) gave an interesting by-product (**13**). This reaction may be explained as follows: the alkylation of 3-(4-chlorobutyl) group could occur at the N_3 nitrogen rather than the imino nitrogen to give quarternary salt because of difficulty in the formation of seven-membered ring. The quarternary salt could cause hydrolytic ring-cleavage of the imidazoline ring to give (**13**). The infrared (IR) spectrum of **13** showed an absorption at 1660 cm^{-1}, which can be assigned to the ureid carbonyl group. The nuclear magnetic resonance (NMR) spectrum of **13** showed the signals of four methylene hydrogen adjacent to nitrogen at δ 3.40 (t, corresponding to methylene protons adjacent to urea nitrogen), 2.35 (t, C_2 and C_5 methylene protons in pyrrolidine ring) and 2.00 (t, corresponding to methylene protons adjacent to pyrrolidine nitrogen). Thus, the structure of **13** was confirmed.

2-Cyanoimino-3-(ω-acyloxyalkyl) derivatives (**7**) were treated with alkali to yield deacylated compounds **10** in good yields. Although treatment of **10** with *t*-butyl alcohol and hydrochloric acid gave **9**, the yield of the products **9** were not satisfactory because of occurrence of undesired side reaction. The compound **10d** gave 10-benzhydryl-2-imino-2,5,6,8,9,10-hexahydro-4H-imidazo[2,1-*d*][1,3,5]oxadiazocine (**11d**) in 70% yield. The IR spectrum of **11d** did not show an absorption resulted from nitrile streching. The triplet at δ 4.08 in the NMR spectrum is assignable to methylene signal adjacent to oxygen. The mass (MS) spectrum of **11d** presented a molecular ion peak at *m/e* 334. These spectral data and the molecular formula $C_{20}H_{22}N_4O$ by micro analysis supported the structure (**11d**).

The formation of **11** from **10** is explained as follows: the ω-benzoyloxy or acetoxy compounds **7** could undergo addition of *t*-butyl alcohol to the cyano group, deamination from the adduct, further hydrolysis of the ester, followed by decarboxylation of the acid to give **9**. However, the compound **10** having an alcoholic hydroxy group in the molecule could cause intramolecular addition of the hydroxy group to the cyano group to afford bicyclic compound **11**. To our best knowledge, this type of bicyclic ring system has not been reported.

Hypoglycemic activity was determined in normal fasted rats and is shown in Table I. 1-Benzhydryl-2,3,5,6,7,8-hexahydro-1H-imidazo[1,2-*a*][1,3]diazepine (**12e**) is the most effective compound in a series of the cyclic guanidine derivatives. On the other hand, 1-benzhydryl-1,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-*a*]pyrimidine (**12g**) having the same formula as **12e** is ineffective. The difference in the both compounds is only the ring system. Since the compound **12g** condenced two six-membered rings has more strong basicity than others, **12g** may be ineffective. The structure–activity relationships in a series of the cyclic guanidines will be reported elsewhere in detail.

Experimental

All melting points are uncorrected. IR spectra were recorded with a Hitachi 285 spectrometer. MS spectra were determined on a JEOL 01SG-2 MS 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.

1-Benzhydrylimidazolidin-2-thione (**2a**)——To a solution of 22.6 g (0.1 mol) of 2-benzhydrylaminoethylamine (**1a**) in 100 ml of 80% aqueous EtOH was added 8 g (0.105 mol) of CS_2. The mixture was heated for 1 hr. After cooling 1 ml of conc. HCl was added to the reaction mixture and the mixture was refluxed for 3 hr. After cooling, a crystal was collected to give 23.0 g (88%) of **2a**, mp 198—204° (from iso-PrOH (IPA)). *Anal.* Calcd. for $C_{16}H_{16}N_2S$: C, 71.61; H, 6.01; N, 10.44. Found: C, 71.49; H, 6.02; N, 10.33.

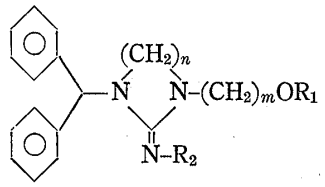
1-Benzhydrylperhydropyrimidin-2-thione (**2b**)——3-Benzhydrylaminopropylamine (**1b**) (4.80 g, 20 mmol) was treated with CS_2 as described in the preparation of **2a** to give 4.30 g (77%) of **2b**, mp 195—196° (from IPA). *Anal.* Calcd. for $C_{17}H_{18}N_2S$: C, 72.30; H, 6.42; N, 9.92. Found: C, 72.49; H, 6.32; N, 9.85.

1-Benzhydryl-2-methylthio-2-imidazoline Hydroiodide (**3a**)——A mixture of 2.68 g (10 mmol) of **2a** and 1.56 g (11 mmol) of MeI in 20 ml of EtOH was refluxed for 2 hr and concentrated to dryness *in vacuo*. The residue was mixed with excess of ether and colorless crystal was collected to give 3.80 g (93%) of **3a**, mp 148—150° (from EtOH–ether). *Anal.* Calcd. for $C_{17}H_{19}IN_2S$: C, 49.76; H, 4.67; N, 6.83. Found: C, 49.89; H, 4.73; N, 6.64.

1-Benzhydryl-2-methylthio-1,4,5,6-tetrahydropyrimidine (**3b**)——Compound **2b** (2.82 g, 10 mmol) was treated with MeI as described in the preparation of **3a** to give 3.90 g (92%) of **3b**, mp 176—178° (from EtOH–ether). *Anal.* Calcd. for $C_{18}H_{21}IN_2S$: C, 51.20; H, 4.99; N, 6.60. Found: C, 51.20; H, 5.08; N, 6.70.

1-Benzhydryl-2-(2-hydroxyethylimino)imidazolidine (**4c**)——A solution of 8.20 g (20 mmol) of **3a** and 2.40 g (40 mmol) of 2-aminoethanol in 80 ml of EtOH was refluxed for 10 hr and evaporated *in vacuo*. The residue was mixed with 50 ml of 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 recrystallized from AcOEt to give 4.10 g (70%) of **4c**, mp 168—169°. *Anal.* Calcd. for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.18; H, 7.27; N, 14.11.

Table II. 3-Substituted 1-Benzhydryl-2-cyanoimino- or 2-Imino-1,3-diazacycloalkanes (**7**), (**9**) and (**10**)



No.	R_1	R_2	n	m	Yield (%)	mp[d] (°C)	Formula	Analysis Calcd. (Found) C	H	N
7c	COC_6H_5	CN	2	2	85[a]	136—138	$C_{26}H_{24}N_4O_2$	73.57 (73.50	5.70 5.85	13.30 13.25)
7d	COC_6H_5	CN	2	3	38[b]	117—118	$C_{27}H_{26}N_4O_2$	73.95 (73.67	5.98 6.02	12.78 12.68)
7e	$COCH_3$	CN	2	4	61[c]	Oil				
7f	COC_6H_5	CN	3	2	28[a]	Oil				
7g	COC_6H_5	CN	3	3	54[b]	146—147	$C_{28}H_{28}N_4O_2$	74.31 (74.51	6.24 6.35	12.38 12.48)
9c	H	H	2	2	74	152—153	$C_{18}H_{21}N_3O$	73.19 (73.01	7.17 7.09	14.23 14.93)
9d	H	H	2	3	80	126—127	$C_{19}H_{23}N_3O$	73.75 (73.51	7.49 7.57	13.58 13.58)
9e	H	H	2	4	87	Oil				
9f	H	H	3	2	87	Oil				
9g	H	H	3	3	76	133—135	$C_{20}H_{25}N_3O$	74.27 (73.95	7.79 7.74	12.99 13.06)
10c	H	CN	2	2	96	127—129	$C_{19}H_{20}N_4O$	71.22 (71.23	6.29 6.33	17.49 17.62)
10d	H	CN	2	3	79	99—100	$C_{20}H_{22}N_4O$	71.83 (71.89	6.63 6.62	16.76 16.91)
10g	H	CN	3	3	88	130—132	$C_{21}H_{24}N_4O$	72.38 (72.10	6.94 6.85	16.08 16.24)

a) Alkylating reagent= $I(CH_2)_2OCOC_6H_5$, reaction condition= 25°, 2 hr.
b) Alkylating reagent=$Cl(CH_2)_2OCOC_6H_5$, reaction condition=100°, 2 hr.
c) Alkylating reagent=$Cl(CH_2)_4OCOCH_3$, reaction condition=120°, 2 hr.
d) Recrystallization solvent=acetone or acetone–ether.

1-Benzhydryl-2-(3-hydroxypropylimino)imidazolidine (4d)——Compound **3a** (16.3 g, 40 mmol) was treated with 3-aminopropanol as described in the preparation of **4c** to give 8.60 g, (70%) of **4d**, mp 100—102° (from AcOEt). *Anal.* Calcd. for $C_{19}H_{23}N_3O$: C, 73.76; H, 7.49; N, 13.58. Found: C, 73.68; H, 7.37; N, 13.41.

1-Benzhydryl-2-(3-hydroxypropylimino)perhydropyrimidine (4 g)——A mixture of 4.24 g (10 mmol) of **3b** and 15 ml of 3-aminopropanol was heated at 180—200° for 2 hr. After cooling, the reaction mixture was poured into water and basified with 2 N NaOH. The mixture was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was dissolved in 50 ml of 2 N HCl and the mixture was washed with benzene to remove **5**. The water layer was again basified with conc. NaOH solution and extracted with benzene. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to yield 1.00 g (31%) of **4g** as oil. NMR δ (d_6-DMSO): 3.55 (2H, t, $C_{3'}$–CH_2), 3.25 (4H, t, C_4– and $C_{1'}$–CH_2), 2.90 (2H, t, C_6–CH_2), 1.60 (4H, m, C_5– and $C_{2'}$–CH_2).

1-Benzhydylperhydropyrimidin-2-one (5)——A solution of 8.48 g (20 mmol) of **3b** and 2.40 g (40 mmol) of 2-aminoethanol in 80 ml of EtOH was refluxed for 10 hr. The reaction mixture was worked up by a method similar to that described in the preparation of **4c**. The residue was mixed with 2 N NaOH and a crystal separated out was recrystallized from MeOH to give 4.20 g (79%) of **5**, mp 226—228°. IR ν_{max}^{KBr} cm^{-1}: 1640 (C=O). *Anal.* Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.45; H, 6.87; N, 10.39.

1-Benzhydryl-3-(2-benzoyloxyethyl)-2-cyanoimonoimidazolidine (7c)——A mixture of 2.76 g (10 mmol) of 1-benzhydryl-2-cyanoiminoimidazolidine (**6a**)[4] and 0.48 g (10 mmol) of NaH in 50% mineral oil in 30 ml of dimethylformamide (DMF) was stirred at room temperature for 1 hr. To the mixture was added portionwise 2.76 g (10 mmol) of 2-iodoethylbenzoate with stirring. The mixture was continued to stir at room temperature for another 2 hr and concentrated *in vacuo*. The residue was washed 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 treated with ether to yield 3.60 g (85%) of **7c**.

Other 3-(ω-acyloxyalkyl)-1-benzhydryl-2-cyanoimino-1,3-diazacycloalkane (**7d—g**) listed in Table II were prepared as described above. The oily compounds were used to subsequent reaction without further purification.

1-Benzhydryl-3-(3-hydroxypropyl)-2-iminoimidazolidine (9d)——A mixture of 3.50 g (8 mmol) of **7d** and 3.2 ml of conc. HCl in 50 ml of *tert*-BuOH was refluxed for 6 hr. and concentrated *in vacuo*. To the residue was added a solution of 5.60 g of KOH in 50 ml of 20% aqueous MeOH and the mixture was allowed to stand at room temperature for 30 min. The mixture was concentrated *in vacuo*. The residual oil was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from acetone–ether to give 1.98 g (80%) of **9d**.

Other 1-benzhydryl-3-(ω-hydroxyalkyl)-2-imino-1,3-diazacycloalkanes (**9c, e—g**) listed in Table II were prepared by a method similar to that described above. The oily compounds were used to subsequent reaction without further purification.

1-Benzhydryl-2-cyanoimino-3-(2-hydroxyethyl)imidazolidine (10c)——A mixture of 2.97 g (7 mmol) of **7c** and 4.5 g of KOH in 60 ml of 30% aqueous MeOH was stirred at room temperature for 30 min and MeOH was removed *in vacuo*. The residual oil was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from acetone–ether to give 2.15 g (96%) of **10c**.

Other 1-benzhydryl-2-cyanoimino-3-(ω-hydroxyalkyl)-1,3-diazacycloalkanes (**10d,g**) listed in Table II were prepared similarly as described above.

10-Benzhydryl-2-imino-2,5,6,8,9,10-hexahydro-4H-imidazo[2,1-*d*][1,3,5]oxadiazocine (11d)——A mixture of 0.84 g (2.5 mmol) of **10d** and 1.0 ml of conc. HCl in 15 ml of *tert*-BuOH was refluxed with stirring for 10 hr and concentrated *in vacuo*. To the residue was added 10 ml of water and a crystal separated out was collected to yield 0.54 g (59%) of the hydrochloride salt of **11d**, mp 120—123° (from water). The hydrochloride salt of **11d** was stirred with a mixture of $CHCl_3$ and 2 N NaOH. The organic layer was isolated and evaporated *in vacuo*. The residue was recrystallized from ether to give the free base of **11d**, mp 134—135°. IR ν_{max}^{KBr} cm^{-1}: 3430 (N–H), 1625 (C=N). MS *m/e* (relative intensity): 334 (M^+, 24), 191 (63), 290 (100), 167 (27). NMR δ ($CDCl_3$): 7.34 (10H, s, C_6H_5), 6.70 (1H, s, Ar–CH), 5.75 (1H, s, NH), 4.03 (2H, t, C_4–CH_2), 3.0—3.7 (6H, m, C_6–, C_8– and C_9–CH_2), 1.90 (2H, m, C_5–CH_2). *Anal.* Calcd. for $C_{20}H_{22}N_4O$: C, 73.75; H, 7.49; N, 13.58. Found: C, 73.51; H, 7.57; N, 13.58.

1-Benzhydryl-2,3,5,6-tetrahydroimidazo[1,2-a]imidazole (12c)——To a mixture of 6 ml of $SOCl_2$ and 6 ml of benzene was added portionwise 1.00 g (3.4 mmol) of **9c** at 0—5°. The solution was allowed to stand at room temperature for 2—3 hr and concentrated *in vacuo*. The residue was mixed with 10 ml of benzene and the mixture was concentrated. To the residue was added a solution of 2.0 g of KOH in 30% aqueous MeOH and the mixture was heated for 2 hr. The mixture was concentrated *in vacuo* and the oily residue was 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–petr. ether to yield 0.77 g (84%) of **12c**.

Other 1-benzhydryl bicyclic guanidines (**12d—g**) listed in Table I were prepared by a procedure like that described above.

8-Benzhydryl-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyrimidine (12f)——A mixture of 8.48 g (20 mmol) of **3b** and 30 ml of 2-aminoethanol was heated at 180—200° for 2 hr. After cooling, the mixture was poured into 2 N HCl and extracted with benzene to remove **5**. The water layer was basified with 2 N NaOH and extracted with benzene. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on aluminum oxide (60 g) and eluted with benzene to give 0.80 g (14%) of **12f**.

N^1-Benzhydryl-N^1-[2-(1-pyrrolidinyl)ethyl]urea (13)——Compound **9e** (2.80 g, 8.7 mmol) was worked up by the same method in the preparation of **12c** from **9c**. The residue extracted with $CHCl_3$ was chromatographed on aluminum oxide (30 g). Eluate with benzene gave 0.20 g of **13**, mp 153—155° (from acetone). IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O). NMR δ (d_6-DMSO): 7.28 (10H, s, C_6H_5), 6.85 (1H, s, Ar–CH), 3.40 (2H, t, C_1–CH_2), 2.35 (4H, m, C_2 and C_5–CH_2 in pyrrolidine), 2.00 (2H, t, C_2–CH_2), 1.62 (4H, m, C_3– and C_4–CH_2 in pyrrolidine). *Anal.* Calcd. for $C_{20}H_{25}N_3O \cdot 1/2H_2O$: C, 72.26; H, 7.88; N, 12.64. Found: C, 72.37; H, 7.61; N, 12.49.

Eluate with $CHCl_3$–benzene gave 0.80 g (30%) of **12c**.

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