[Chem. Pharm. Bull. 27(7)1596—1603(1979)]

UDC 547.873.04.09 : 615.272.4.011.5.015.11.076.9

Cyclic Guanidines. VII.[1] Structure-Activity Relationships of Hypoglycemic Cyclic Guanidines[2]

Akira Kosasayama and Fumiyoshi Ishikawa

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

(Received January 5, 1979)

The hypoglycemic activity and physico-chemical properties (pK_a, log P) of cyclic guanidines were measured. Qualitative structure-activity relationships were investigated in various mono-, bi-, and tricyclic guanidines and it became apparent that compounds which have a bulky group and a pK_a value between 8—11 showed potent activity. It was possible to correlate hypoglycemic activity with the pK_a values and partition coefficients of cyclic guanidines.

Keywords——cyclic guanidines; hypoglycemic activity; qualitative structure-activity relationships; quantitative structure-activity relationships; pK_a value; partition coefficient

It has been reported that cyclic 1-substituted biguanides,[4] such as imidazolines,[5] triazines,[6] and triazoles,[7] have various potent biological activities. Recently, Grisar *et al.*[8] reported that lactamimides with bulky substituents at the N^2 position have high hypoglycemic activity. In our synthetic investigation of cyclic guanidines which are modifications of phenformin (**1**), 1-benzhydryl-2-imino-1,3-diazacycloalkanes (**2**) and 2-benzhydrylimino-1,3-diazacycloalkanes (**12**) were found to be effective in lowering the blood glucose of normal fasted rats.[9,10] To search for more active compounds, many cyclic guanidines were prepared by structural modification of **2** and **12**. This paper deals with the structure-activity relationships of these cyclic guanidines synthesized in this Institute.

In the previous papers,[1,9–13] various synthetic routes to cyclic guanidines have been reported. The compounds synthesized were as follows. First, alkyl and acyl derivatives (**3**—**6**) of **2** were prepared. Next, bicyclic guanidines (**7**) linked between $N^{2'}$ and the benzhydryl methine carbon with one carbon unit were synthesized. Tricyclic guanidines (**10** and **11**) linked between $N^{2'}$ and the ortho position of benzene were also prepared. These compounds showed potent activity. Using the procedures described for **2**, alkyl- and acyl derivatives (**13**—**16**) of mono- (**12**), bi- and tricyclic guanidines (**17**—**19**) were also prepared by modification of **12**.

Method

Measurement of Hypoglycemic Activity——The blood glucose level was determined in comparison to that of control fasted rats at 1, 2, 3, 5 hours after *i.p.* (10 mg/kg) or *p.o.* (25

1) Part VI: A. Kosasayama, K. Higashi, and F. Ishikawa, *Chem. Pharm. Bull.* (Tokyo), **27**, 880 (1979).
2) Presented at a Meeting of the Society of Synthetic Organic Chemistry, Japan, June, 1978.
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo 132, Japan.*
4) G. Ungar, L. Freedman, and S.L. Shapiro, *Proc. Soc. Exper. Biol. Med.*, **95**, 190 (1957).
5) S. Hayashi, M. Furukawa, J. Yamamoto, and Y. Nishizima, *Chem. Pharm. Bull.* (Tokyo), **16**, 471 (1968).
6) T.L. Loo, *J. Am. Chem. Soc.*, **76**, 5096 (1954).
7) B. Blank, D.M. Nicholas, and P.D. Vaidya, *J. Med. Chem.*, **15**, 794 (1972).
8) J.M. Grisar, G.P. Claxton, A.A. Carr, and N.L. Wiech, *J. Med. Chem.*, **16**, 679 (1973).
9) F. Ishikawa, A. Kosasayama, S. Nakamura, and T. Konno, *Chem. Pharm. Bull.* (Tokyo), **26**, 3658 (1978).
10) A. Kosasayama, Y. Watanabe, K. Higashi, and F. Ishikawa, *Chem. Pharm. Bull.* (Tokyo), **27**, 831 (1979).
11) F. Ishikawa, A. Kosasayama, and T. Konno, *Chem. Pharm. Bull.* (Tokyo), **26**, 3666 (1978).
12) A. Kosasayama, T. Konno, K. Higashi, and F. Ishikawa, *Chem. Pharm. Bull.* (Tokyo), **27**, 841 (1979).
13) A. Kosasayama, T. Konno, K. Higashi, and F. Ishikawa, *Chem. Pharm. Bull.* (Tokyo), **27**, 848 (1979).

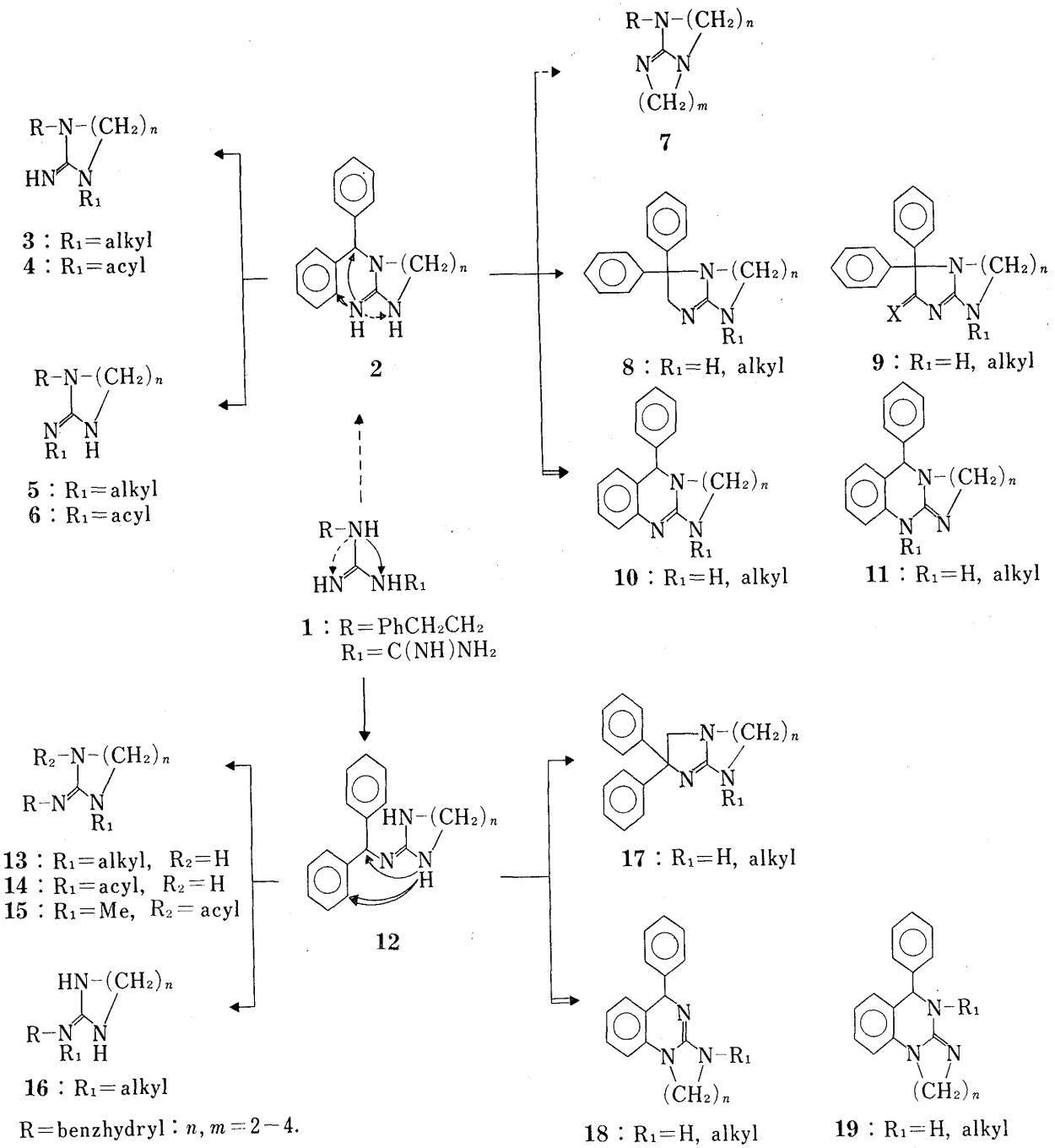


Chart 1

mg/kg) administration, using the glucose oxidase method.[14] At this dose, no hypoglycemic symptoms were observed even with the most potent compound, **7c**. The hypoglycemic activity was qualitatively evaluated as a percentage of maximum blood glucose decrease. On the other hand, for quantitative determination, the sum of the blood glucose decreases (%) at selected times was taken as the hypoglycemic potency (log C) of the compounds. The results are summarized in Tables I—IV together with pK_a values and partition coefficients (log p).

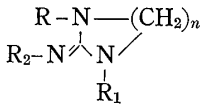
Acid Dissociation Constants (pK_a)——The pK_a values of cyclic guanidine were determined with a potentiometer (Potentiograph E 366, Metrohm Ltd., Herisau, Switzerland)

14) W. Werner, H.G. Rey, and H. Wielinger, *Z. Analyt. Chem.*, **252**, 224 (1970).

following Albert's method.[15] A sample (0.25 mmol) was dissolved in 50 ml of methylcellosolve: water=5: 1. In the case of weakly basic compounds, the hydrochloride was titrated with 1 N KOH at 27°. On the other hand, in compounds having strong basicity the free base was titrated with 1 N HCl. The results are summarized in Tables I—IV.

Determination of Partition Coefficients——Partition coefficients were determined by the method of Hansch and Fujita[16] in chloroform-water (10 ml—25 ml). The $CHCl_3$ phase was saturated with carbon dioxide-free water and the water phase was saturated with $CHCl_3$ before partitioning was performed. A mixture containing about 20 mg of sample was shaken mechanicaly for 1 hr and centrifuged at 3000 rpm for 30 min. The concentrations of both layers were measured by ultraviolet (UV) spectrophotometry. The results, which are corrected for ionization fraction, are summarized in Tables I—IV.

TABLE I. Hypoglycemic Activities of 1-Substituted Monocyclic Guanidines



Compd. No.	R	R_1	R_2	n	Activity[a]		pK_a	log P	log C	
					i.p.[b]	*p.o.*[c]			Obsvd.[d]	Calcd.[e]
2a	*n*-Bu	H	H	2	+1					
2b	$PhCH_2$	H	H	2	—					
2c	$Ph(CH_2)_2$	H	H	2	+2	+1				
2d	Ph_2CH	H	H	2	+2	+3	10.98	2.09	1.75	1.90
2e	Ph_2CH	H	H	3	+2	+2	12.30	2.41	1.77	1.72
2f	Ph_2CH	H	H	4	+2	+2				
3a	Ph_2CH	Me	H	2	+5	+5				
3b	Ph_2CH	Et	H	2	+4	+5				
3c	Ph_2CH	Et	H	3	+3	+1				
4a	Ph_2CH	$CONH_2$	H	2	+5	+3	7.82	1.77	1.75	1.75
4b	Ph_2CH	CONHMe	H	2	+2	+2				
4c	Ph_2CH	COOMe	H	2	+3	+4				
4d	Ph_2CH	COMe	H	2	+3	+4				
5a	Ph_2CH	H	Me	2	+4	+4				
6a	Ph_2CH	H	$CONH_2$	2	+1		4.93			
6b	Ph_2CH	H	$CONH_2$	4	—					

a) Activity: +1 represents a blood glucose decrease of 10—20%.
b) Dose: 10 mg/kg.
c) Dose: 25 mg/kg.
d) The logarithm of the sum of blood glucose decreases (%) at 1, 2, 3, and 5 hr after *p.o.* administration.
e) Calculated using equation 1.

Results and Discussion

1. Structure-Activity Relationships (SAR)

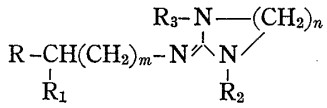
SAR was investigated qualitatively in three groups of mono-, bi-, and tricyclic guanidines.

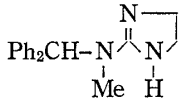
1-1: Hypoglycemic Activity in Monocyclic Guanidines——a) 1-Benzhydryl-2-imino-1,3-diazacycloalkane Series (Table I):

The compounds **2a**—**c**, which have relatively small substituents (*n*-butyl, benzyl, phenethyl), were ineffective. However, **2d** which contains a benzhydryl group, showed potent activity. Thus, it appears that bulky substituents are required for activity in this series as

15) S. Matuura "Ionization Constants of Acids and Bases," ed A. Albert, E.P. Serjeant, Maruzen, Japan, 1962.
16) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).

Table II. Hypoglycemic Activities of 2-(N-Substituted) Monocyclic Guanidines



Compd. No.	R	R_1	m	R_2	R_3	n	Activity		pK_a	log P	log C	
							i.p.	*p.o.*			Obsvd.	Calcd.
12a	2-Cl-Ph	H	0	H	H	2	+1					
12b	Ph	Ph	0	H	H	2	+1	+2	11.09	2.04	1.85	1.86
12c	Ph	Ph	0	H	H	3	+1	—	12.31	1.76	1.42	1.41
12d	Ph	Ph	0	H	H	4	+2	—				
12e	2-Cl-Ph	Ph	0	H	H	2	+3	+2				
12f	4-Cl-Ph	Ph	0	H	H	2	+3	+3				
13a	Ph	Ph	0	Me	H	2	+3	+4	10.64	2.62	2.17	2.09
13b	Ph	Ph	0	Et	H	2	+2	+4				
13c	Ph	Ph	0	*n*-Pr	H	2	+1	+2				
13d	Ph	Ph	0	*n*-Bu	H	2	+2	+3				
13e	Ph	Ph	0	$PhCH_2$	H	2	+1					
13f	2-Pyridyl	Ph	0	Me	H	2	+3	+3				
13g	C_6H_{11}	Ph	0	Me	H	2	+3	+2				
13h	Ph	Ph	0	Me	H	3	+3	+1	12.14	2.55	1.68	1.79
13i	Ph	Ph	1	Me	H	2	+1		11.38			
14a	Ph	Ph	0	$CONH_2$	H	2	+2	+2				
14b	Ph	Ph	0	CONHMe	H	2	—		7.16			
14c	Ph	Ph	0	CONHPh	H	2	—		5.03			
14d	Ph	Ph	0	$CSNH_2$	H	2	—					
14e	Ph	Ph	0	CSNHMe	H	2	—		5.56			
14f	Ph	Ph	0	COMe	H	2	—					
15a	Ph	Ph	0	Me	COMe	2		+3				
15b	Ph	Ph	0	Me	COPh	2		+3				
15c	Ph	Ph	0	Me	Nicotinoyl	2		+5				
15d	Ph	Ph	0	Me	2-Thienoyl	2		+4				
16								+4				

well as in lactamimides.[8] The activity of alkyl derivatives of **2d** generally increased regardless of the alkylation positions. Acyl derivatives (**4a—d**) showed appreciable activity, whereas **6a**, **b** did not. As **6a**, **b** are chemically more stable than **4a—c** (*e.g.*, to heating), it is assumed that this difference in activity is related to the stability of the acyl groups[11] and **4a—d** may be deacylated to give active forms *in vivo*.

b) 2-Benzhydrylimino-1,3-diazacycloalkane Series (Table II):

In this series too, **12b** (having a benzhydryl group) was more potent than **12a**, **c**, **d** which contain an *o*-chlorobenzyl group or six- or seven-membered diazacycloalkane. To increase the solubility in organic solvents, many alkyl derivatives of **12b** were prepared. Among these derivatives, **13a**, **b**, **16**, which have small alkyl groups, showed more potent activity than the parent compound (**12b**). **13a** showed hypoglycemic activity in rats, guinea pigs, and dogs, and was the best hypoglycemic agent among our cyclic guanidines. However, this compound, which was considered to be effective through insulin release[17] was ineffective in alloxan- and or streptozotocin-treated rats. To decrease the strong basicity of **12** and **13**, their acyl derivatives (**14**, **15**) were prepared and tested. Although **15** showed potent

17) K. Kameda, S. Ono, and Y. Abiko, The 98th Meeting of the Pharmaceutical Society of Japan 5B 10-3 (4, 1978, Okayama).

Table III. Hypoglycemic Activities of Bicyclic Guanidines

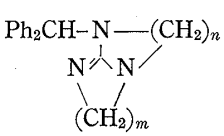
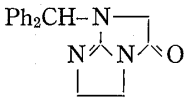
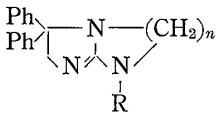
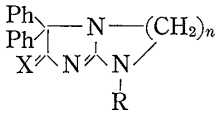
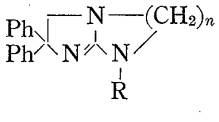
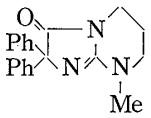
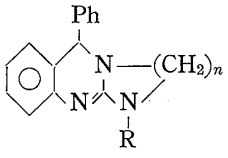
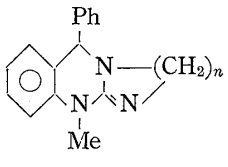
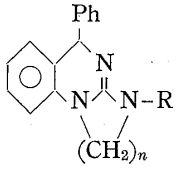
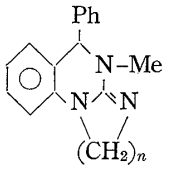
Compd. No.	Structure	n	m	R	X	Activity *i.p.*	Activity *p.o.*	pK_a	log P	log C Obsvd.	log C Calcd.
7a		2	2			+4					
7b		2	3			+5	+5	11.17	2.96	2.20	1.99
7c		2	4				+6				
7d		3	2			+4	+4	10.98	3.16	1.98	1.96
7e		3	3				+1	12.36			
7f							—	5.01			
8a		2		H			+3	8.95	2.26	2.11	2.09
8b		3		H			+4	10.75	2.68	2.09	2.08
9a		2		Me	NH	+3	+5	8.59	2.07	2.06	2.00
9b		2		Et	O	—					
17a		2		H			+2	8.64	2.28	1.89	2.09
17b		3		H			+4	10.86	2.76	2.09	2.06
17c		4		H			+3				
17d		2		Me			+4				
17e		3		Me			+5				
17f							—				

Table IV. Hypoglycemic Activities of Tricyclic Guanidines

Compd. No.		n	R	Activity *i.p.*	Activity *p.o.*	pK_a	log P	log C Obsvd.	log C Calcd.
10a		2	H	+3	+3	7.92	2.25	2.12	2.01
10b		3	H	+4	+4	9.30	3.16	2.14	2.10
10c		2	Me	—		7.15			
10d		3	Me	+4	+5	8.80	2.39	2.24	2.13
10e		3	$(CH_2)_2OH$		+5	8.44	2.32	2.25	2.09
11a		2		+2	+3	8.14	2.79	1.91	2.11
11b		3		+3	+4	10.24			
18a		2	H	+2	+4	9.08	2.47	2.04	2.15
18b		3	H	+2	+3	10.79	3.10	1.86	2.01
18c		2	Me		+2				
18d		3	Me		+4				
19a		2			+3				
19b		3			+2				

activity, like **13a**, **14** was ineffective. Chemical stability studies showed that **15** was very easily deacylated to give **13a**, but **14** was stable.[10] Therefore it is concluded that **15** was deacylated to show activity *in vivo*, like **4a—d**. Moreover, the compound **13i** in which one methylene group was introduced between the 2-imino group and benzhydryl group of **12b** was less active than the parent compound. This may be due to increased basicity.

1-2: Hypoglycemic Activity in Bicyclic Guanidines (Table III)——Very high activity was observed with bicyclic guanidines (**7a—d**) which have at least one five-membered ring. The most potent compound, **7c**, gave a decrease of 60—70 percent of blood glucose. Compounds **7e**, **f** which have a 6–6 ring system or a carbonyl group were ineffective, presumably because of their strong and weak basicities, respectively. Similar results were obtained with other bicyclic guanidines. That is, **9b** and **17f**, having a carbonyl group, were ineffective whereas **8a**, **b**, **9b**, and **17a—c** showed potent activity.

1-3: Hypoglycemic Activity in Tricyclic Guanidines (Table IV)——Modification of monocyclic guanidines (**2**, **12**) to the corresponding tricyclic guanidines (**10—11**, **18—19**) generally gave more potent compounds. It is assumed that the basicity of these compounds was reduced by this modification. The alkyl derivatives (**10d**, **e**, **11a**, **b**) of linear type compounds (except for **10c**) showed potent activity. When the ring nitrogen at N^1 of (**10a**, **b**) is alkylated, the pK_a values decrease by more than about 0.5 from those of the parent compounds. From the relationship between pK_a and hypoglycemic activity described later (Fig. 1), the pK_a values of compounds which show high activity were found to be close to 9.3. Therefore the weak activity of **10c** is attributable to a decrease of pK_a on alkylation. In addition, moderate activity was observed in angular type compounds. It is interesting that **18b** showed potent activity whereas **12c** was only slightly active because of its high pK_a value.

2. Quantitative Structure-Activity Relationship (QSAR)

QSARs for hypoglycemic activity of sulfonylureas and isoxazoles were reported by Ahrens *et al.*,[18] and Kubota *et al.*,[19] respectively. To determine hypoglycemic potency, in the former case ED_{50} (dose for 50% decrease of blood glucose), and in the latter case the sum

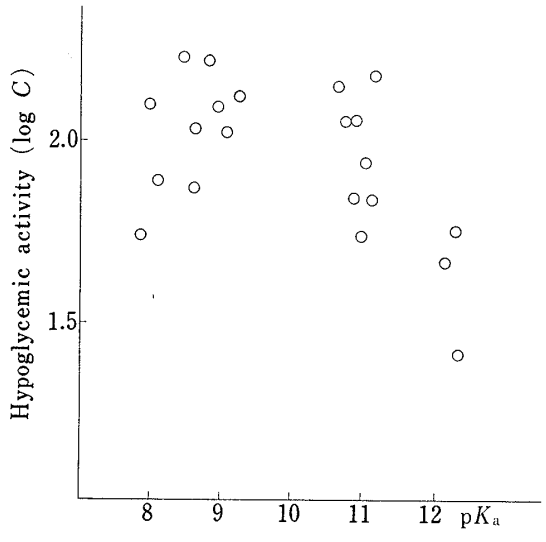


Fig. 1. Relationship between Hypoglycemic Activity (log C) and pK_a

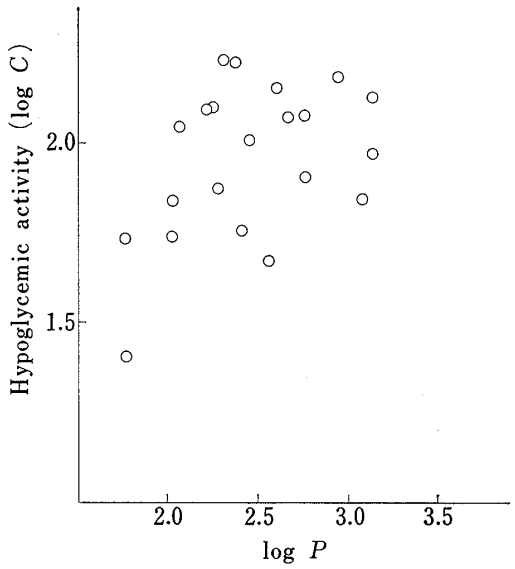


Fig. 2. Relationship between Hypoglycemic Activity (log C) and Partition Coefficient

18) H. Ahrens and W. Losert, *J. Med. Chem.*, **18**, 234 (1975).
19) M. Yamakawa, T. Kubota, Y. Tochino, and H. Takase, 26th International Congress of Pure and Applied Chemistry 7C-201 (9, 1977, Tokyo).

of blood glucose decreases (log C) at various times were employed. On the basis of qualitative considerations, it is assumed that pK_a values and partition coefficients (log P) correlate with hypoglycemic activity in cyclic guanidines. Therefore pK_a values and log P were mesured by the usual methods and the relationships between log C and these parameters were investigated. The compounds treated in this section were selected from those which showed activity in *p.o.* administration. Figures 1 and 2 show the relationships between log C and pK_a or log P, respectively.

It appears from Fig. 1 that a parabolic relationship exists between log C and pK_a. On the other hand, although the relationship between log C and log P is not well-defined, an increase of log P tends to increase log C. Regression analysis was performed using these parameters and equations 1—5 were obtained. The best correlation coefficient was obtained in equation 1.

$$\log C = -0.046\mathrm{p}K_a^2 + 0.859\mathrm{p}K_a - 0.377p^2 + 2.044p - 4.577 \quad (1)$$
$$(2.368) \quad (2.178) \quad (2.411) \quad (2.592)$$
$$n=21;\ r=0.845;\ s=0.128;\ F=9.957$$

$$\log C = -0.052\mathrm{p}K_a^2 + 0.965\mathrm{p}K_a + 0,153p - 2.768 \quad (2)$$
$$(2.357) \quad (2.175) \quad (0.167)$$
$$n=21;\ r=0.781;\ s=0.145;\ F=8.837$$

$$\log C = -0.421p^2 + 2.361p - 0.074\mathrm{p}K_a - 0.489 \quad (3)$$
$$(2.402) \quad (2.695) \quad (3.335)$$
$$n=21;\ r=0.783;\ s=0.145;\ F=8.957$$

$$\log C = -0.071\mathrm{p}K_a^2 + 1.351\mathrm{p}K_a - 4.319 \quad (4)$$
$$(3.588) \quad (3.412)$$
$$n=21;\ r=0.739;\ s=0.152;\ F=10.832$$

$$\log C = -0.489p^2 + 2.655p - 1.526 \quad (5)$$
$$(2.246) \quad (2.437)$$
$$n=21;\ r=0.600;\ s=0.181;\ F=5.058$$

n: compound number; r: correlation coefficient; s: standard deviation; F: F-value; ( ) t-value.

Tables I—IV summarize the calculated values using equation 1. The observed values for long-acting compounds, such as **7b**, were generally larger than the calculated values. If the durations of action were similar, the relationships in equations 1—5 would be improved.

Conclusion

Our investigations of structure-activity relationships for hypoglycemic activity gave the following results. 1) Bulky substituents, such as a benzhydryl group, are required for potent activity. 2) In monocyclic guanidines five-membered compounds are more potent than six- or seven-membered compounds. 3) The introduction of one methylene group between the 2-imino group and benzhydryl group of **12b** reduces the activity. 4) Among our cyclic guanidines the most potent activity was observed in bicyclic guanidines, but even in this series, **7e** with its 6–6 ring system showed poor activity. 5) Modification of monocyclic guanidines to tricyclic guanidines caused potent activity. 6) In various ring systems stable acyl derivatives always show poor activity.

These results can be quantitatively correlated with the physico-chemical properties of cyclic guanidines. That is, stable acyl derivatives with low pK_a values, and mono- and bicyclic guanidines with high pK_a values show poor activity. It can be concluded that pK_a and log p are correlated with hypoglycemic activity in cyclic guanidines. However, as log C was evaluated under conditions of *p.o.* administration *in vivo*, the duration factor should be considered in order to develop a better treatment.

Experimental

2-Benzhydrylmethylimino-1-methylimidazolidine (13i)——A mixture of 2,2-diphenylethylamine (1.97 g, 0.01 mol) and 1-methyl-2-methylthioimidazoline hydroiodide (2.58 g, 0.011 mol) was heated at 150—160° for 20 min. After cooling, the reaction mixture was washed with iso-PrOH (30 ml) to give the hydroiodide of **13i** (3.4 g, 84%). mp 218—220°. It was dissolved in 20 ml of MeOH and treated with 20 ml of 2 N NaOH solution to give the free base of **13i**. mp 104—107° (*n*-hexane–ether). The free base of **13i** was dissolved in HCl–EtOH and the solution was evaporated down *in vacuo* to yield the hydrochloride of **13i**. mp 235—237° (iso-PrOH). IR ν_{max}^{KBr} cm^{-1}: 1650, 1485, 1295. NMR (DMSO-d_6) δ: 7.33 (10H, multiplet, phenyl protons), 4.52 (1H, triplet, methine proton), 4.00 (2H, broad, >CH–C$\underline{H}_2$), 3.43 (4H, singlet, ring methylene protons), 2.81 (3H, singlet, methyl proton). *Anal.* Calcd. for $C_{18}H_{22}ClN_3$: C, 68.48; H, 7.02; N, 13.30; Cl, 11.22. Found: C, 68.39; H, 6.86; N, 13.38; Cl, 10.90.

1-Benzhydryl-3-oxo-2,3,5,6-tetrahydroimidazo[1,2-*a*]imidazole (7f)——Chloroacetylchloride (3.6 g, 0.03 mol) was added gradually to a mixture of 2-benzhydryliminoimidazolidine (**12b**) (7.53 g, 0.03 mol), DMF (45 ml), and 50% NaH (3.16 g, 0.066 mol) with stirring at room temperature. The solution was allowed to stand at room temperature for 2 hr. After acidifying with conc. HCl the mixture was evaporated down *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 down *in vacuo*. The residue was chromatographed on silica gel (210 g). 1-Benzhydryl-2-oxo-2,3,5,6-tetrahydroimidazo[1,2-*a*]imidazole (130 mg) was obtained from the first fraction eluted with $CHCl_3$. mp 125—127°. IR ν_{max}^{KBr} cm^{-1}: 1745, 1660, 1440, 1420. NMR (DMSO-d_6) δ: 7.38 (10H, multiplet, phenyl protons), 6.42 (1H, singlet, methine proton), 3.85 (2H, singlet, C_3–CH_2), 3.3 (2H, multiplet, C_5–CH_2), 3.7 (2H, multiplet, C_6–CH_2). *Anal.* Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.03; H, 5.92; N, 14.08. 1-Benzhydryl-3-oxo-2,3,5,6-tetrahydroimidazo[1,2-*a*]imidazole (**7f**) (1.0 g) was obtained from the second fraction eluted with $CHCl_3$. mp 128—130° (AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1740, 1675, 1460, 1440, 1250. NMR (DMSO-d_6) δ: 7.0—7.6 (10H, multiplet, phenyl protons), 6.15 (1H, singlet, methine proton), 4.0 (2H, singlet, C_2–CH_2), 4.0 (2H, multiplet, C_5–CH_2), 3.6 (2H, multiplet, C_6–CH_2). *Anal.* Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.15; H, 5.71; N, 14.19.

Acknowledgement The authors are grateful to Dr. G. Ohta, Director of this Institute, for encouragement throughout the course of this work. Thanks are also due to Dr. Y. Abiko and Messrs. K. Kameda and S. Ono for biological assays.