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Cyclic Guanidines. VI.[1] Synthesis of Hypoglycemic Tricyclic Guanidines[2]

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Synthesis of linear and angular tricyclic guanidine derivatives, imidazo- or pyrimido-[2,1-*b*]- or [1,2-*a*]quinazoline derivatives, is described.

Cyclization of 2-(ω-chloroalkyl)-4-phenyl-3,4-dihydroquinazolines (**9**) gave two isomers and their isolation was troublesome. 2-Aminobenzhydrylaminoalkanols (**10**) obtained from 2-aminobenzophenone (**5**) were converted to linear tricyclic guanidine derivatives (**3**, **12**, **13**, **14**, **15**), and other tricyclic compounds (**22** and **24**) containing an oxygen or a sulfur atom. Reaction of 2-benzoylaminoalkanols (**26**) obtained from (**5**) also gave angular products.

Most of the tricyclic guanidine derivatives showed a hypoglycemic activity.

Keywords——tricyclic guanidine; imidazo- or pyrimido[2,1-*b*]quinazoline; imidazo- or pyrimido[1,2-*a*]quinazoline; oxazolo- or [1,3]oxazino[2,3-*b*]quinazoline; oxazolo- or [1,3]oxazino[3,2-*a*]quinazoline; cyclization; alkylation; acylation; hypoglycemic activity

Our previous papers[1,4] reported that cyclic guanidines having a bulky group show hypoglycemic activity. This paper deals with the synthesis and hypoglycemic activity of linear tricyclic guanidines and their alkyl and acyl derivatives, such as 5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinoline (**3a**), which are cyclic derivatives of hypoglycemic 1-benzhydryl-2-imino-1,3-diazacycloalkanes[4a] (**1**) having a linkage between its 2-imino-nitrogen and ortho position of the benzene ring. Angular tricyclic guanidine derivatives (**4**) obtained from hypoglycemic 2-benzhydrylimino-1,3-diazacycloalkanes[4c] (**2**), were also synthesized and their hypoglycemic activities were investigated.

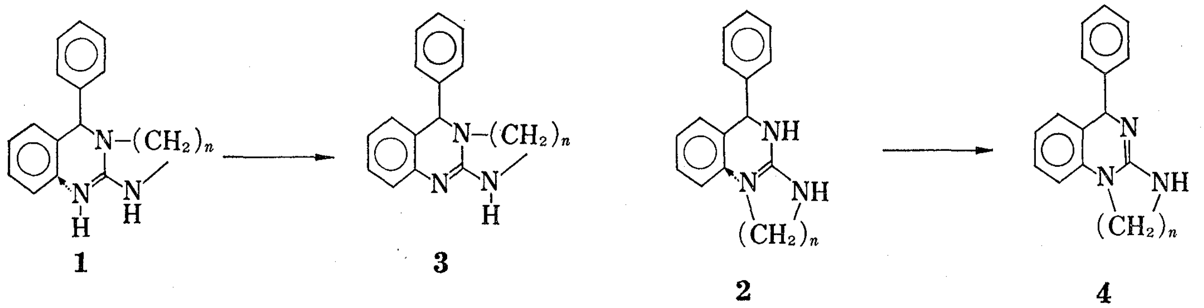

Chart 1

4-Phenyl-1,2,3,4-tetrahydroquinazoline-2-thione[5] (**7**) was methylated with methyl iodide to give 2-methylthio derivatives (**8**). Reaction of **8** with aminoalcohols yielded 2-(ω-hydroxy-

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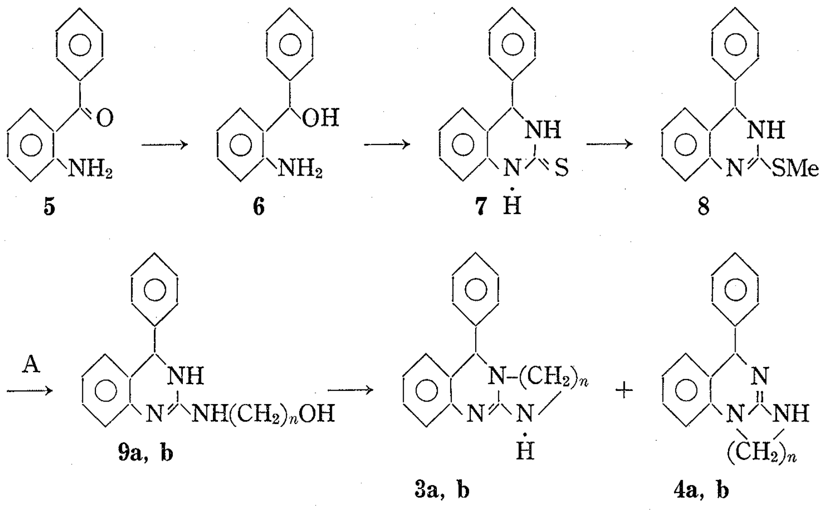
[1] Part V: A. Kosasayama, T. Konno, K. Higashi, and F. Ishikawa, *Chem. Pharm. Bull.* (Tokyo), **27**, 848 (1979).

[2] This work was 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] *a*) F. Ishikawa, A. Kosasayama, S. Nakamura, and T. Konno, *Chem. Pharm. Bull.* (Tokyo), **26**, 3658 (1978); *b*) F. Ishikawa, A. Kosasayama, and T. Konno, *ibid.*, **26**, 3666 (1978); *c*) A. Kosasayama, Y. Watanabe, K. Higashi, and F. Ishikawa, *ibid.*, **27**, 831 (1979); *d*) A. Kosasayama, T. Konno, K. Higashi, and F. Ishikawa, *ibid.*, **27**, 841 (1979).

[5] S. Gabriel and R. Stelzner, *Chem. Ber.*, **29**, 1300 (1896).



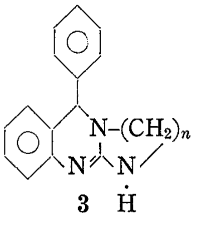
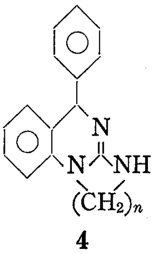
a: n=2, b: n=3, A=$H_2N(CH_2)_nOH$

Chart 2

alkylamino) derivatives (**9**). A mixture of the desired linear and angular tricyclic guanidines (**3** and **4**) was obtained by treatment of **9** with phosphoryl chloride and subsequently with sodium hydroxide in aqueous methanol. Separation of **3** and **4** from the reaction mixture was performed by silica gel chromatography. The formation of **4** predominated over that of **3**. The results are similar to that of cyclization reaction of 4-phenyl-2-(ω-chloroalkylamino)-quinoazolines reported by Kwon *et al.*[6]

Although the structures of **3** and **4** obtained here were finally determined by identification with the samples prepared by alternative routes described below, they were presumed from their spectral data. Since in the linear tricyclic guanidines (**3**), C=N double bond in quinazoline ring is able to conjugate with the benzene ring while that of the angular deriva-

Table I. UV, IR, and NMR Spectra of Imidazo- or Pyrimido[2,1-*b*]-quinazolines (3) and Imidazo- or Pyrimido-[1,2-*a*]quinazolines (4)

Compound	n	UV (nm) ($\lambda_{max}^{CHCl_3}$)	IR (cm^{-1}) (ν_{max}^{KBr})	NMR (δ)[a] 5- or 6-methine
 **3**	2	283	1640	5.70(s)
	3	256 292	1620	5.56(s)
 **4**	2	262	1675	5.90(s)
	3	256	1650	5.70(s)

a) Solvent=CF_3COOH.

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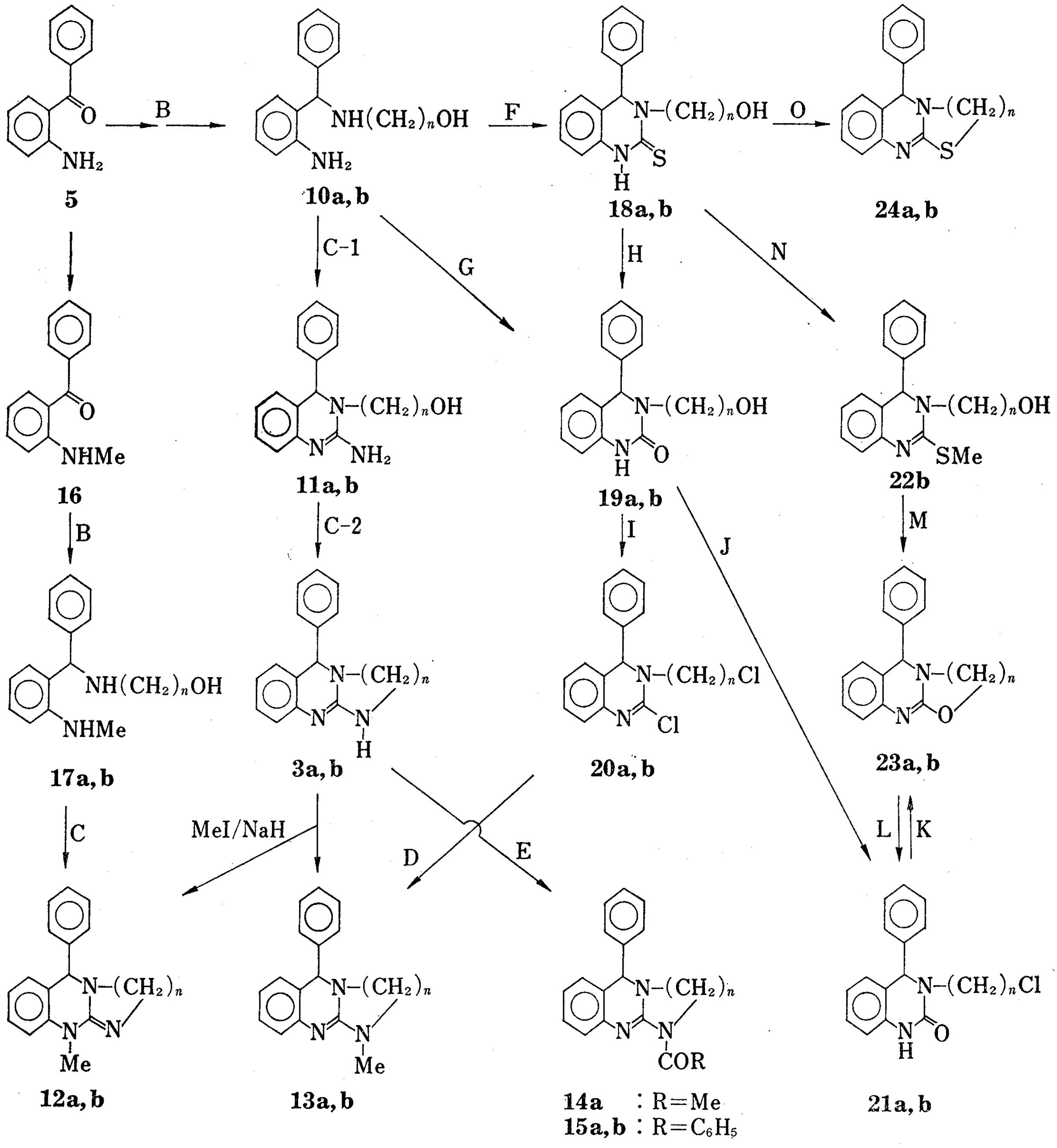
6) S. Kwon, F. Ikeda, and K. Isagawa, *Nippon Kagaku Zasshi*, **1973**, 1944.

tives (**4**) is not, the C=N stretching frequency of **3** in its infrared (IR) spectrum is present in a lower wave number region than that of **4**, the maximum absorption of **3** appears at higher wavelength than that of **4** in ultraviolet (UV) spectrum, and a signal of the methine proton adjacent to the phenyl group in **3** is shifted to a higher field than that of **4** in nuclear magnetic resonance (NMR) spectrum, as shown in Table I.

The preparation of **3** and **4** by the method described above was not practical because the separation of the isomers was troublesome. Possible alternative methods for synthesizing linear and angular tricyclic guanidines were examined.



a: n=2, b: n=3.
B=1. $H_2N(CH_2)_nOH$, 2. $NaBH_4$; C=1. BrCN, 2. $SOCl_2$, 3. KOH; D=$MeNH_2$; E=Ac_2O or BzCl; F=CS_2; G=EtOCOCl; H=H_2O_2–NaOH; I=$POCl_3$–PCl_5; J=$SOCl_2$; K=K_2CO_3; L=HCl–MeOH; M=Heating in EtOH; N=MeI; O=Heating in $MeSO_3H$.

Chart 3

The synthesis of linear type compounds, [1,3]diazacyclo[2,1-*b*]quinazoline derivatives, was investigated. 2-Aminobenzophenone (**5**) was heated with aminoalcohols at 150—160° to give the Shiff bases which were reduced to 2-aminobenzhydrylaminoalkanols (**10**) with sodium borohydride in methanol. Reaction of **10** with cyanogen bromide gave 3-(ω-hydroxyalkyl)quinazoline derivatives (**11**), and subsequent treatment of **11** with thionyl chloride afforded 3-(ω-chloroalkyl) derivatives which cyclized to give the corresponding linear compounds (**3**) by treatment with potassium hydroxide in aqueous methanol. The overall yield from **10** was satisfactory. These compounds (**3**) obtained here were identical with the samples prepared from **9**.

Preparation of alkylated derivatives of **3** was then undertaken. Jen *et al.*⁷⁾ reported that the methylation of 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline gave 1- and 10-methyl derivatives and that its product ratio changed according to reaction conditions. Reaction of **3a** with methyl iodide in the presence of sodium hydride yielded two isomers in which 1-methyl derivative (**13a**) was predominant, similarly to the results described by Jen.⁷⁾ Alkylation of **3b** having a six-membered ring has not been reported. Since **3b** is more basic than **3a**, the result of alkylation would be interesting. Under the same conditions, methylation of **3b** also gave two isomers but formation ratio of the isomers inclined to 11-methyl derivative (**12b**). Total yield of **12b** and **13b** was not good compared with that of the methylation of **3a**.

The methyl derivatives (**12** and **13**) were identified with the samples prepared by the alternative methods described below. 2-Methylaminobenzophenone (**16**) obtained by the method described by the Upjohn group⁸⁾ was treated successively with aminoalcohols, sodium borohydride, cyanogen bromide, thionyl chloride, and finally potassium hydroxide to give the desired derivatives (**12**) in a satisfactory yield. Reaction of **10** with ethyl chloroformate yielded 3-(ω-hydroxyalkyl)quinoline derivatives (**19**). Treatment of 2-thione derivatives (**18**) obtained by reaction of **10** with carbon disulfide and hydrogen peroxide in a basic medium also gave **19**. Compounds **19** were refluxed in a mixture of phosphoryl chloride and phosphorus pentachloride to yield 2-chloro-3-(ω-chloroalkyl) derivatives (**20**), whose treatment with methylamine gave the desired 1-methyl derivatives (**13**).

Jen *et al.*⁷⁾ also reported that acetylation of 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline occurred at N^1-position under heating with acetic anhydride. Heating of **3a** with acetic anhydride also gave 1-acetyl derivative (**14a**), predominantly. However, 1-acetyl derivative could not be isolated from **3b** due to its unstable nature. Reaction of **3** with benzoyl chloride in pyridine at room temperature yielded predominantly 1-benzoyl derivatives (**15**). The acylated positions of **14a** and **15** were confirmed by NMR spectral data. The C-2 methylene proton signal is shifted 0.8 ppm to a lower field compared to that of C-3 methylene.

Synthesis of the tricyclic compounds with an oxygen or a sulfur atom in place of the nitrogen at position 1 in imidazo- or pyrimido[2,1-*b*]quinazoline derivatives (**3**) was undertaken for the search of hypoglycemic activity.

Only oxazolo[2,3-*b*]quinazoline ring system has been reported by Grout and Partridge⁹⁾; 2,3-dihydro-5H-oxazolo[2,3-*b*]quinazolin-5-one obtained by treatment of 1,2,3,4-tetrahydroquinazoline-2,4-dione with ethylene bromide. However, 2,3-dihydro-5H-oxazolo- or 3,4-dihydro-2H,5H-[1,3]oxazino[2,3-*b*]quinazoline has not been reported.

Treatment of **19** with thionyl chloride gave 3-(ω-chloroalkyl) derivatives (**21**) which yielded the desired compounds (**23**) by reaction with potassium carbonate in acetone or sodium hydride in dimethylformamide (DMF). On the other hand, reaction of **18b** with methyl iodide in acetone at room temperature gave 2-methylthio derivative (**22b**) and refluxing of **22b** in ethanol also yielded **23b** in a good yield. However, reaction of **18a** with methyl iodide gave

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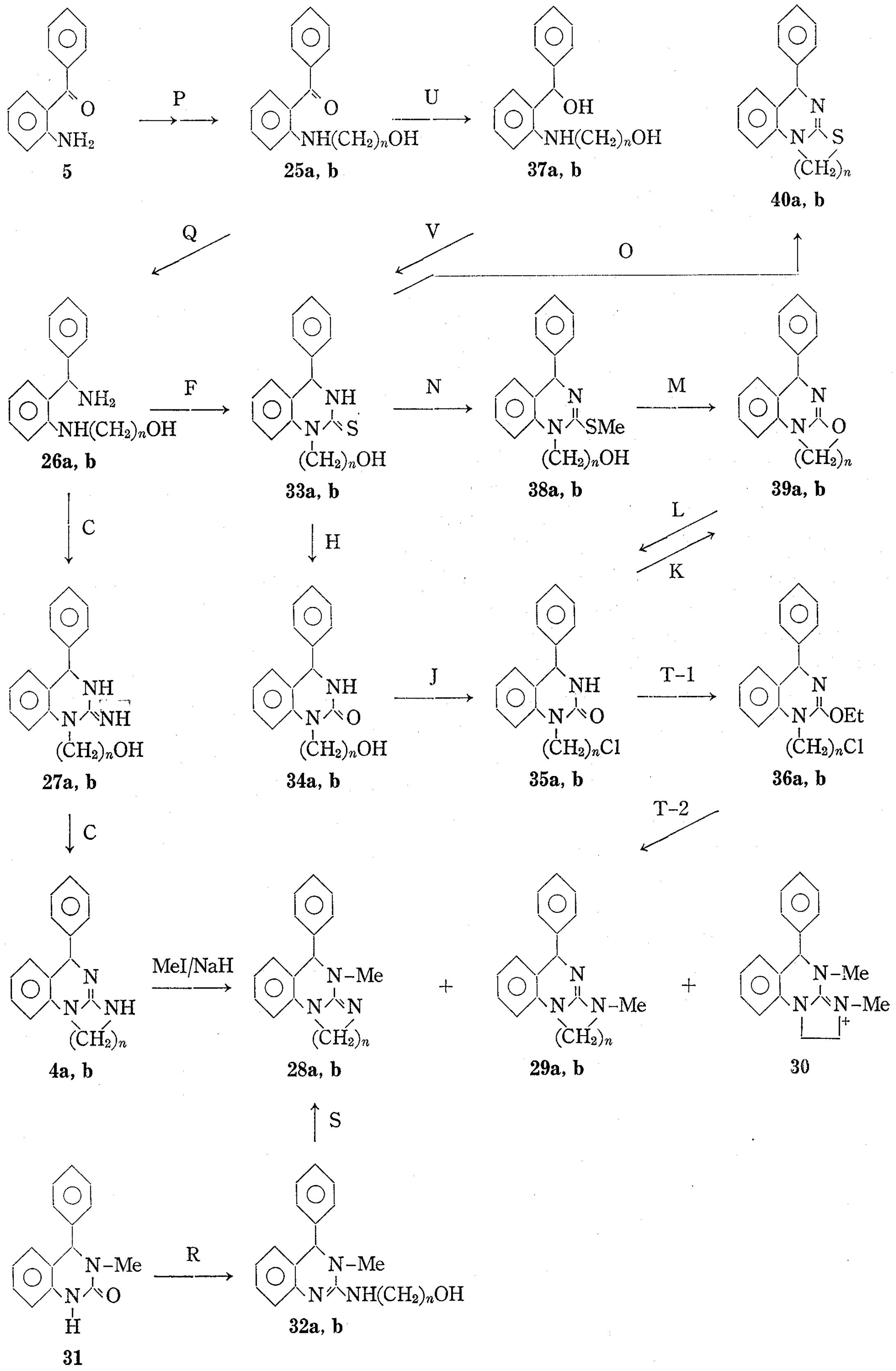
7) B. Loev, T. Jen, and R.A. Mclean, *J. Med. Chem.*, **15**, 727 (1972).
8) Upjohn Co., Netherland Patent. Appl. No. 6603034 (1966) [*Chem. Abstr.*, **66**, 46441 (1967)].
9) R. Grout and M.W. Partridge, *J. Chem. Soc.*, **1960**, 3551.



a: n=2, b: n=3

C—O=See Chart 3; P=1. $ClCO_2(CH_2)_nCl$, 2. NaOH; Q=1. NH_2OH, 2. Raney Ni alloy–NaOH; R=1. $POCl_3$, 2. $H_2N(CH_2)_nOH$; S=1. $SOCl_2$, 2. KOH; T=1. Et_3OBF_4, 2. $MeNH_2$; U=$NaBH_4$; V=HSCN.

Chart 4

a resinous product. Compounds **23** are relatively unstable. For example, treatment of **23** with methanolic hydrogen chloride at room temperature resulted in ring cleavage to **21**.

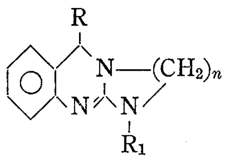
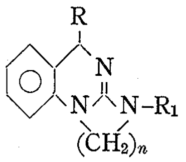
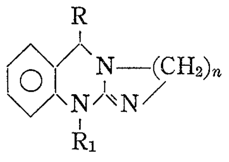
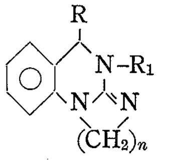
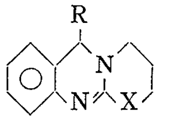
According to Jen's method,[10] **18** were heated in methanesulfonic acid to give 2,3-dihydro-5H-thiazolo- or 3,4-dihydro-2H,5H-[1,3]thiazino[2,3-*b*]quinazoline derivatives (**24**).

Syntheses of angular tricyclic compounds were attempted in a similar manner to that for linear compounds. Since direct ω-hydroxyalkylation of 2-amino group in 2-aminobenzophenone (**5**) is difficult, **5** was treated successively with chloroalkyl chloroformate and sodium hydroxide according to Adams' method[11] and 2-(ω-hydroxyalkylamino)benzophenone (**25**) was obtained in a good yield. Compounds **25** gave their oximes with hydroxylamine and their treatment with Raney nickel alloy and sodium hydroxide in aqueous ethanol yielded 2-(ω-hydroxyalkylamino)benzhydrylamines (**26**) which gave angular tricyclic guanidines (**4**) in a satisfactory yield by successive reactions with cyanogen bromide, thionyl chloride, and finally potassium hydroxide.

Methylation of **4a** with methyl iodide in the presence of sodium hydride gave 3-methyl derivative (**28a**) (25%), 4-methyl derivative (**29a**) (trace), and further methylated quaternary salt (**30**) (36%). On the other hand, methylated compounds of **4b** could not be isolated from the reaction mixture.

An alternative procedure for the synthesis of **28** was attempted following the method described by Kwon.[6] 3-Methyl-1,2,3,4-tetrahydro-2-qinazolinone[12] (**31**), obtained by successive treatment of **5** with methyl isocyanate and sodium borohydride, was reacted with phosphoryl chloride. Subsequent treatment of 2-chloro intermediate with aminoalcohols gave 2-(ω-hydroxyalkylamino) derivative (**32**). Treatment of **32** with thionyl chloride afforded 2-(ω-chloroalkylamino) intermediate, which was converted to **28** with potassium hydroxide in a satisfactory yield. On the other hand, **29** was obtained from **25** *via* **37**, **33**, **34**, **35**, and **36** by a method similar to that for the preparation of **13** from **10**. Intermediate 2-quin-

Table II. Hypoglycemic Activity of Tricyclic Guanidine Derivatives

Compound	Plasma glucose[a]		Compound	Plasma glucose[a]	
	Dose (mg/kg, *p.o.*)	Reduction (%)		Dose (mg/kg, *p.o.*)	Reduction (%)
	25	20—50		25	30—40
	25	30—40		25	20—30
	25	30—50			

$R=C_6H_5$; $R_1=H$, Me, Ac, Bz; X=O, S; $n=2,3$.

[a] The test compound was orally administered to rats which had been fasted overnight. Plasma glucose was determined by the glucose oxidase method at 2—5 hr after the administration.

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10) T. Jen, B. Dienel, F. Dowalo, H. van Hoeven, P. Bender, and B. Loev, *J. Med. Chem.*, **16**, 633 (1973).

11) *a*) R. Adams and J.B. Segur, *J. Am. Chem. Soc.*, **45**, 785 (1923); *b*) *Idem*, *ibid.*, **45**, 790 (1923); *c*) J.M. Rudesill, R.F. Severson, and J.G. Pomonis, *J. Org. Chem.*, **36**, 3071 (1971).

12) W. Metesics, G. Silverman, V. Toome, and L.H. Sternback, *J. Org. Chem.*, **31**, 1007 (1966).

TABLE III. Tricyclic Guanidines and Their Related Compounds

Compd.	Start. Mater.	Method	Yield (%)	mp (°C) (Recryst. Solv.)	IR (cm^{-1})	Formula	Analysis		NMR	
							Calcd. C H N	Found C H N	Solv.[a]	Chemical shift (δ)
3a	**10a**	C	55	250—253 (dec.) (EtOH)	1640 1575 1570	$C_{16}H_{16}ClN_3$	67.24 5.68 14.71	67.13 5.75 14.81	T	5.70 (1H, s, C_5–H), 3.5—4.1 (4H, m, C_2–, C_3–H_2)
3b	**10b**	C	82	187—189 (dec.) (EtOH)	1620 1580 1530	$C_{17}H_{18}ClN_3$	68.10 6.05 14.02	67.80 6.09 13.92	T	5.57 (1H, s, C_6–H), 3.3—3.7 (4H, m, C_2–, C_4–H_2)
4a	**27a**	C	60	>275 (EtOH)	1680 1600 1565	$C_{16}H_{16}ClN_3$	67.24 5.68 14.71	67.25 5.50 14.66	T	5.90 (1H, s, C_5–H), 4.0—4.4 (4H, m, C_2–, C_3–H_2)
4b	**27b**	C	85	252—255 (dec.) (EtOH)	1655 1600 1580	$C_{17}H_{18}ClN_3$	68.10 6.05 14.02	67.94 6.26 14.09	T	5.70 (1H, s, C_6–H), 4.03 (2H, t, J=7 Hz, C_2–H_2), 3.60 (2H, t, J=7 Hz, C_4–H_2)
9a	**8**	A	77	148—152 (dec.)	1580	$C_{16}H_{18}ClN_3O$	63.26 5.97 13.83	63.08 6.20 13.53	D	5.93 (1H, s, C_4–H)
9b	**8**	A	89	155—157 (dec.)	1580	$C_{17}H_{20}ClN_3O$	64.24 6.34 13.22	64.04 6.27 13.03	D	5.91 (1H, s, C_4–H)
10a	**5**	B	Quant.	168—170 (dec.) (iso-PrOH)	3320 1600 1490	$C_{15}H_{20}Cl_2N_2O$	57.14 6.40 8.89	57.28 6.59 8.60	C	4.84 (1H, s, Ph_2–CH), 3.62 (2H, t, J=6 Hz, $C_{2'}$–H_2), 2.70 (2H, m, $C_{1'}$–H_2)
10b	**5**	B	Quant.	144—146 (dec.) (iso-PrOH)	3320 1600 1490	$C_{16}H_{22}Cl_2N_2O$	58.36 6.73 8.51	58.50 6.75 8.11	C	4.80 (1H, s, Ph_2–CH), 3.71 (2H, t, J=6 Hz, $C_{3'}$–H_2), 2.73 (2H, m, J=6 Hz, $C_{1'}$–H_2)
11b	**10b**	C	Quant.	152—154 (iso-PrOH)	3480 1530 1480	$C_{18}H_{19}N_3O$	72.57 6.81 14.94	72.10 6.68 14.55	C	5.31 (1H, s, C_4–H), 3.2—3.6 (4H, m, $C_{1'}$–, $C_{2'}$–H_2)
12a	**16**	C	30	267—271 (dec.) (EtOH– ether)	1635 1580	$C_{17}H_{18}ClN_3$	68.10 6.05 14.02	67.76 5.95 13.98	T	5.64 (1H, s, C_5–H), 3.86, 3.72 (2H × 2, m, C_2–, C_3– H_2)
12b	**16**	C	35	270 (EtOH– ether)	1615 1590 1560	$C_{18}H_{20}ClN_3$	68.89 6.42 13.39	68.61 6.39 13.01	C	4.93 (1H, s, C_6–H), 3.43 (2H, t, C_2–H_2), 3.17 (2H, t, C_4–H_2)
13a	**20a**	D	85	244—249 (EtOH– ether)	1655 1610	$C_{17}H_{18}ClN_3$	68.10 6.05 14.02	68.16 6.09 14.30	T	5.62 (1H, s, C_5–H), 3.76, 3.60 (2H × 2, m, C_2–, C_3– H_2)
13b	**20b**	D	87	178—180 (MeOH)	1535 1505	$C_{18}H_{19}N_3$	77.94 6.91 15.15	77.78 6.70 15.02	C	5.17 (1H, C_6–H), 3.31 (2H, t, C_2– or C_4–H_2), 3.10 (2H, t, C_4– or C_2–H_2)
14a	**3a**	E1	62	148—150 (ether)	1660 1630	$C_{18}H_{17}N_3O$	74.20 5.88 14.41	74.06 5.51 14.29	C	5.42 (1H, s, C_5–H), 3.75 (2H, m, C_2–H_2), 2.96 (2H, m, C_2–H_2)
15a	**3a**	E2	53	115—118 (benzene– ether)	1680 1630	$C_{23}H_{19}N_3O$	78.16 5.42 11.89	77.90 5.30 11.70	C	5.49 (1H, s, C_5–H), 3.1—3.9 (4H, m, C_2–, C_3–H_2)
15b	**3b**	E2	77	190—192 (benzene– ether)	1655 1610	$C_{24}H_{21}N_3O$	78.75 5.67 11.44	78.65 5.86 11.35	C	5.42 (1H, s, C_5–H), 3.5—4.3 (2H, m, C_2–H_2), 3.32 (2H, t, C_4–H_2)
18a	**10a**	F	88	157—159 (MeOH)	1525 1480	$C_{16}H_{16}N_2OS$	67.58 5.67 9.85	67.70 5.68 9.91	C	5.72 (1H, s, C_4–H), 2.0—3.0, 4.3—4.9 (2H, t, $C_{1'}$–H_2), 3.65 (2H, t, $C_{2'}$–H_2)
18b	**10b**	F	66	Amorph.	1525 1485	$C_{17}H_{18}N_2OS$	68.42 6.08 9.39	68.15 6.04 9.39	C	5.49 (1H, s, C_4–H), 4.4—5.0 (2H, m, $C_{1'}$–H_2), 3.60 (2H, t, $C_{3'}$–H_2)
19a	**10a** **18a**	G H	62 85	153—154 (MeOH– acetone)	1650	$C_{16}H_{16}N_2O_2$	71.62 6.01 10.44	71.49 5.89 10.68	C	5.55 (1H, s, C_4–H), 3.1—3.9 (2H, m, $C_{1'}$–H_2), 3.65 (2H, m, $C_{2'}$–H_2)

Table III. (Continued)

Compd.	Start. Mater.	Method	Yield (%)	mp (°C) (Recryst. Solv.)	IR (cm^{-1})	Formula	Analysis		NMR	
							Calcd. C H N	Found C H N	Solv.$^{a)}$	Chemical shift (δ)
19b	**10b** **18b**	G H	66 85	112—114 (MeOH–acetone)	1660	$C_{17}H_{18}N_2O_2$	72.32 6.43 9.92	72.01 6.21 9.78	C	5.44 (1H, s, C_4–H), 3.0—4.3 (2H, m, $C_{1'}$–H_2), 3.60 (2H, m, $C_{3'}$–H_2)
20a	**19a**	I	62	108—110 (ether)	1610 1580 1560	$C_{16}H_{14}Cl_2N_2$	62.96 4.62 9.18	63.20 4.66 9.15	C	5.69 (1H, s, C_4–H), 3.3—4.1 (4H, m, $C_{1'}$–, $C_{2'}$–H_2)
20b	**19b**	I	73	Oil	1650 1580 1550				C	5.60 (1H, s, C_4–H), 2.8—4.1 (4H, m, $C_{1'}$–, $C_{3'}$–H_2)
21a	**19a** **23a**	J L	41 61	130—132 (ether)	1660	$C_{16}H_{15}ClN_2O$	67.01 5.27 9.77	66.85 5.38 9.92	C	5.61 (1H, s, C_4–H), 3.1—4.3 (4H, m, $C_{1'}$–, $C_{2'}$–H_2)
21b	**19b** **23b**	J L	61 68	156—157 (MeOH–ether)	1650	$C_{17}H_{17}ClN_2O$	67.88 5.70 9.31	67.44 5.73 9.34	C	5.47 (1H, s, C_4–H), 2.8—4.1 (4H, m, $C_{1'}$–, $C_{3'}$–H_2)
22b	**18b**	N	84	142—143 (MeOH–ether)	1515 1480	$C_{18}H_{20}N_2OS$	69.20 6.45 8.97	68.81 6.37 8.91	C	5.44 (1H, s, C_4–H), 3.0—4.0 (2H, m, $C_{3'}$–H_2), 3.57 (2H, t, $C_{1'}$–H_2)
23a	**21a**	K1	84	130—131 (MeOH–ether)	1630 1590	$C_{16}H_{14}N_2O$	76.78 5.64 11.19	76.55 5.70 11.06	C	5.50 (1H, s, C_5–H), 4.25 (2H, m, C_2–H_2), 3.17 (2H, m, C_3–H_2)
23b	**21b** **22b**	K2 M	70 89	191—192 (EtOH)	1605 1580 1560	$C_{17}H_{16}N_2O$	77.25 6.10 10.60	77.26 6.12 10.41	C	5.26 (1H, s, C_6–H), 4.10 (2H, m, C_2–H_2), 3.07 (2H, m, C_4–H_2)
24a	**18a**	O	94	171—173 (MeOH)	1600 1575 1545	$C_{16}H_{14}N_2S$	72.82 5.30 10.52	72.60 5.35 10.57	C	5.38 (1H, s, C_5–H), 3.2—3.5 (2H, m, C_2–H_2), 2.8—3.1 (2H, m, C_3–H_2)
24b	**18b**	O	94	206—208 (EtOH)	1520 1460	$C_{17}H_{16}N_2S$	72.82 5.30 10.52	72.60 5.35 10.57	C	5.25 (1H, s, C_6–H), 3.15 (2H, m, C_2–H_2), 2.89 (2H, t, C_4–H_2)
25a	**5**	P	84	Oil	1615				D	3.65 (2H, m, C_1–H_2), 3.34 (2H, m, C_2–H_2)
25b	**5**	P	78	63— 64 (benzene–petr. ether)	1610	$C_{16}H_{17}NO_2$	75.27 6.71 5.49	74.88 6.79 5.48	D	3.62 (2H, m, C_1–H_2), 3.28 (2H, m, C_3–H_2)
26a	**25a**	Q	72	76— 78 (ether)	1600 1575	$C_{15}H_{18}N_2O$	74.35 7.49 11.56	74.14 7.40 11.32	D	5.09 (1H, s, Ph_2–CH), 3.58 (2H, t, $C_{2'}$–H_2), 3.16 (2H, t, $C_{1'}$–H_2)
26b	**25b**	Q	79	62— 64 (ether)	1650 1580	$C_{16}H_{20}N_2O$	74.96 7.86 10.93	74.85 7.93 10.85	D	5.10 (1H, s, Ph_2–CH), 3.50 (2H, t, $C_{3'}$–H_2), 3.08 (2H, t, $C_{1'}$–H_2)
27a	**26a**	C	67	230—232 (EtOH–ether)	1660 1610	$C_{16}H_{19}BrN_3O$	55.18 5.21 12.07	55.45 5.25 12.05	D	5.89 (1H, d, $J=4$ Hz, C_4–H), 4.15 (2H, t, $C_{2'}$–H_2), 3.80 (2H, m, $C_{1'}$–H_2)
27b	**26b**	C	58	189—190 (EtOH–ether)	1650	$C_{17}H_{20}BrN_3O$	56.36 5.56 11.60	56.33 5.61 11.63	D	5.89 (1H, d, $J=4$ Hz, C_4–H), 4.05 (2H, t, $C_{3'}$–H_2), 3.45 (2H, t, $C_{1'}$–H_2)
28a	**32a**	S	75	81— 84 (EtOH–ether)	1670 1540	$C_{17}H_{18}Cl_2N_3 \cdot 1/2H_2O$	66.11 6.20 13.61	66.20 6.15 13.56	T	5.68 (1H, s, C_5–H), 3.9—4.6 (4H, m, C_1–, C_2–H_2)
28b	**32b**	S	82	233—236 (dec.) (EtOH–ether)	1620 1600 1550	$C_{18}H_{20}ClN_3$	68.89 6.42 13.39	68.59 6.25 13.25	C	5.17 (1H, s, C_6–H), 3.3—3.8 (4H, m, C_1–, C_3–H_2)
29a	**35a**	T	41	240—244 (dec.) (EtOH–ether)	1660 1590	$C_{17}H_{18}ClN_3$	68.19 6.05 14.02	67.89 6.00 14.00	T	5.92 (1H, s, C_5–H), 4.0—4.4 (4H, m, C_1–, C_2–H_2)

Table III. (Continued)

Compd.	Start. Mater.	Method	Yield (%)	mp (°C) (Recryst. Solv.)	IR (cm^{-1})	Formula	Analysis Calcd. C H N	Analysis Found C H N	NMR Solv.[a]	NMR Chemical shift (δ)
29b	**35b**	T	59	224—226 (dec.) (EtOH–ether)	1610 1600	$C_{18}H_{20}ClN_3$	68.89 6.42 13.39	68.63 6.21 13.49	C	5.58 (1H, s, C_6–H), 3.56 (2H, t, C_1–H_2), 3.23 (2H, t, C_3–H_2)
32a	**31**	R	22	169—170 (acetone)	1580 1520	$C_{17}H_{19}N_3O$	72.57 6.81 14.93	72.36 6.77 14.83	C	5.21 (1H, s, C_4–H), 3.4—3.8 (4H, m, $C_{1'}$–, $C_{2'}$–H_2)
32b	**31**	R	35	135—136 (acetone–ether)	1580 1520	$C_{18}H_{21}N_3O$	73.19 7.17 14.23	73.55 7.18 14.19	C	5.21 (1H, s, C_4–H), 3.4—3.8 (4H, m, C_1,–, $C_{3'}$–H_2)
33a	**26a** **37a**	F V	35 73	129—131 (MeOH)	1600 1540	$C_{16}H_{16}N_2OS$	67.57 5.67 9.85	67.30 5.66 9.89	D	5.52 (1H, d, $J=4$ Hz, C_4–H), 4.57 (2H, m, $C_{1'}$–H_2), 3.77 (2H, m, $C_{2'}$–H_2)
33b	**37b**	V	96	101—103 (EtOH)	1595	$C_{17}H_{18}N_2OS$	68.43 6.08 9.39	68.91 6.15 9.39	C	5.52 (1H, d, $J=4$ Hz, C_4–H), 4.67 (2H, m, $C_{1'}$–H_2), 3.62 (2H, t, $C_{3'}$–H_2)
34a	**33a**	H	76	133—135 (AcOEt)	1660 1595	$C_{16}H_{16}N_2O_2$	71.62 6.01 10.44	71.84 6.00 10.28	D	5.50 (1H, d, $J=4$ Hz, C_4–H), 3.95 (2H, t, $C_{2'}$–H_2), 3.64 (2H, t, $C_{1'}$–H_2)
34b	**33b**	H	77	100—101 (AcOEt)	1650	$C_{17}H_{18}N_2O_2$	72.32 6.43 9.92	72.42 6.41 9.81	D	5.53 (1H, d, $J=4$ Hz, C_4–H), 4.44 (2H, t, $C_{3'}$–H_2), 3.54 (2H, t, $C_{1'}$–H_2)
35a	**34a**	J	91	134—136 (acetone)	1670 1590	$C_{16}H_{15}ClN_2O$	67.01 5.27 9.77	66.99 5.29 9.94	D	5.50 (1H, d, $J=4$ Hz, C_4–H), 4.20 (2H, m, $C_{1'}$–H_2), 3.76 (2H, t, $C_{2'}$–H_2)
35b	**34b** **39b**	J L	94 50	138—149 (acetone)	1680	$C_{17}H_{17}ClN_2O$	67.88 5.70 9.31	67.51 5.67 9.31	D	5.47 (1H, d, $J=4$ Hz, C_4–H), 4.00 (2H, t, $C_{1'}$–H_2), 3.50 (2H, t, $C_{3'}$–H_2)
37a	**25a**	U	71	113—115 (AcOEt)	1600 1580	$C_{15}H_{17}NO_2$	74.05 7.04 5.76	74.55 7.09 5.82	D	5.71 (1H, d, $J=6$ Hz, Ph_2–CH), 3.60 (2H, m, $C_{2'}$–H_2), 3.09 (2H, m, $C_{1'}$–H_2)
37b	**25b**	U	96	75— 76 (benzene–petr. ether)	1600 1580	$C_{16}H_{19}NO_2$	74.68 7.44 5.44	74.61 7.41 5.49	D	5.75 (1H, d, $J=6$ Hz, Ph_2–CH), 3.42 (2H, t, $C_{3'}$–H_2), 3.05 (2H, m, $C_{1'}$–H_2)
38a	**33a**	N	75	150—153 (acetone)	1600 1560	$C_{17}H_{19}IN_2OS$	47.89 4.49 6.57	47.50 4.25 6.40	D	6.11 (1H, s, C_4–H), 4.2—4.6 (2H, m, $C_{2'}$–H_2), 3.5—4.0 (2H, m, $C_{1'}$–H_2)
38b	**33b**	N	64	147—153 (dec.) (MeOH–ether)	1595 1545	$C_{18}H_{21}IN_2OS$	49.10 4.81 6.36	49.33 4.87 6.43	D	6.17 (1H, s, C_4–H), 4.34 (2H, t, $C_{3'}$–H_2), 3.49 (2H, t, $C_{1'}$–H_2)
39a	**35a** **38a**	K2 M	75 50	184—186 (EtOH)	1680 1600 1585	$C_{16}H_{15}IN_2O$	50.81 3.99 7.41	50.72 4.02 7.21	D	5.69 (1H, s, C_5–H), 4.49 (2H, m, C_2–H_2), 3.85 (2H, m, C_1–H_2)
39b	**35b**	K2	86	110—112 (benzene–ether)	1640 1475	$C_{17}H_{16}N_2O$	77.25 6.10 10.60	76.92 6.04 10.43	D	5.63 (1H, s, C_6–H), 4.15 (2H, t, C_3–H_2), 3.68 (2H, t, C_1–H_2)
40a	**33a**	O	75	240—245 (dec.) (MeOH)	1615 1600 1580	$C_{16}H_{15}ClN_2S$	63.46 4.99 9.27	63.49 5.05 9.20	D	6.16 (1H, s, C_5–H), 3.6—4.3 (2H, m, C_2–H_2), 3.41 (2H, t, C_1–H_2)
40b	**33b**	O	79	244—246 (dec.) (MeOH)	1595	$C_{17}H_{17}ClN_2S$	64.44 5.41 8.84	64.16 5.47 8.70	C	5.99 (1H, s, C_6–H), 3.77 (2H, t, C_3–H_2), 3.05 (2H, t, C_1–H_2)

[a] Solvent: C=$CDCl_3$, D=d_6-DMSO, T=CF_3CO_2H.

azolinethiones (**33**) were also given by treatment of **26** with carbon disulfide but the yield was not good.

Following a procedure similar to the synthesis of linear tricyclic compounds (**23**), angular tricyclic derivatives (**39**) with a replaced oxygen at 2-position in the quinazoline ring were obtained from **35** with sodium hydride in DMF. Refluxing of methyl derivative (**38a**) in ethanol gave **39a**, but **39b** could not be isolated under the same conditions because of its unstability. Reaction of **39** with methanolic hydrogen chloride at room temperature gave ring opened products **35**.

Similarly, the tricyclic compounds **40** containing sulfur were obtained by treatment of **33** with hot methanesulfonic acid. These tricyclic compounds **39** and **40** have new ring system.

Hypoglycemic activity was determined in normal fasted rats. Most of the tricyclic guanidines had this activity as shown in Table II. Methyl or acyl derivatives showed a high activity. In the tricyclic compounds with a replaced oxygen or sulfur, only oxazino- and thiazino[2,3-*b*]quinazoline derivatives (**39b** and **40b**) had the activity. The structure–acticity relationship in a series of the cyclic guanidines will be reported in a subsequent paper in detail.

Experimental

All melting points are uncorrected. IR spectra were recorded with a Hitachi 285 spectrometer, mass spectra determined on a JEOL 01SG-2 MS spectrometer, and 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. For column chromatography, silica gel (Merck, 0.05—0.2 mm) were used.

2-Methylthio-4-phenyl-3,4-dihydroquinazoline Hydroiodide (**8**)——A solution of 18.1 g (75 mmol) of **7** and 13.5 g (95 mmol) of MeI in 700 ml of MeOH was refluxed for 2 hr. After cooling, about 600 ml of MeOH was removed *in vacuo* and 600 ml of ether was added to the residual solution. The pale yellow precipitate formed was collected to yield 28.0 g (quantitative) of **8**, mp 212—215° (dec.). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2900, 1611, 1570, 1540. NMR (d_6-DMSO) δ: 6.19 (1H, s, 4-H), 2.80 (3H, s, CH_3). *Anal.* Calcd. for $C_{15}H_{15}IN_2S$: C, 47.13; H, 3.98; N, 7.33. Found: C, 47.51; H, 4.11; N, 7.53.

Cyclization of 2-(2-Hydroxyethylamino)-4-phenyl-3,4-dihydroquinazoline (**9a**)——A mixture of 2.90 g (11 mmol) of **9a** in 30 ml of $POCl_3$ was refluxed for 2 hr and excess of $POCl_3$ was removed *in vacuo*. To the residue was added ice-water, the mixture was stirred for 1 hr. An insoluble solid collected was dissolved in MeOH and the solution was made alkaline with conc. NaOH solution. MeOH was removed *in vacuo* and the residual mixture was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g) with mixture of iso-PrOH, MeOH, and conc. NH_4OH.

The fraction with iso-PrOH–MeOH–conc. NH_4OH (100: 100: 1) was collected to give 0.20 g (7.4%) of **3a**, mp 277—280°. The next fraction with iso-PrOH–MeOH–conc. NH_4OH (10: 10: 1) was collected to give 1.40 g (51.5%) of **4a**, mp 187—190°.

Cyclization of 2-(3-Hydropropylamino)-4-phenyl-3,4-dihydroquinazoline (**9b**)——Following the method of the cyclization reaction of **9a**, 3.00 g (10.7 mmol) of **9b** was treated with 30 ml of $POCl_3$ and then with NaOH to give mixture of **3b** and **4b**. The mixture was chromatographed on silica gel (100 g) with iso-PrOH–MeOH–conc. NH_4OH (10: 10: 1) to give 0.42 g (15%) of **3b**, mp 197—200° (dec.). Silica gel remained in column was taken out and treated with MeOH–$CHCl_3$–conc. NH_4OH (2: 2: 1) to give 1.10 g (39%) of **4b**, mp 259—262°.

Methylation of 3a with MeI and NaH——A mixture of 1.90 g (7.8 mmol) of **3a** and 0.40 g (8 mmol) of NaH (50% oil suspension) in 30 ml of DMF was stirred at room temperature for 1 hr and then 1.68 g (12 mmol) of MeI was added to the mixture. The mixture was stirred for 2 hr and poured into ice-water. 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 chromatographed on silica gel (100 g). Eluate with iso-PrOH–MeOH–conc. NH_4OH (100: 100: 1) was collected. As first fraction, 1.01 g (48%) of **13a** was obtained, mp 145—146°. As second fraction, 0.51 g (25%) of **12a** was obtained as oil, which was converted to the hydrochloride in usual way, mp 267—271°.

Methylation of 3b with MeI and NaH——Following the procedure for methylation of **3a**, 2.55 g (10 mmol) of **3b** was treated with 2.13 g (15 mmol) of MeI and 0.60 g (12 mmol) of NaH (50% oil suspension) to give mixture of **12b** and **13b**, which was separated by silica gel chromatogiving, as to first fraction, 0.40 g (15%) of **13b** and as the second fraction, 0.63 g (20%) of **12b** as an oil which was converted to the hydrochloride salt in usual way.

Methylation of 4a with MeI and NaH——A mixture of 1.90 g (7.6 mmol) of **4a** and 0.40 g (9 mmol) of NaH (50% oil suspension) in 30 ml of DMF was stirred for 1 hr. To the mixture was added 1.65 g (11 mmol) of MeI and the mixture was stirred for 5 hr. The mixture was concentrated to dryness *in vacuo*. The residue was extracted with $CHCl_3$ and the extract was evaporated *in vacuo*. A yellow crystal from the residue was collected to yield 1.10 g (36%) of **30**, mp 235—240° (dec.) (from EtOH). IR ν_{max}^{KBr} cm^{-1}: 1635, 1590, 1530. NMR (TFA) δ: 5.65 (1H, s, 5-H), 4.0—4.3 (4H, m, C_1 and C_2–H_2), 3.35, 3.51 (3H, 2, s, N–CH_3). *Anal.* Calcd. for $C_{18}H_{20}IN_3$: C, 53.34; H, 4.97; N, 10.37. Found: C, 53.18; H, 5.03; N, 10.71.

The residual oil was chromatographed on silica gel (50 g) with iso-PrOH–MeOH–conc. NH_4OH (100: 100: 1—50: 50: 1). As the first fraction, 0.51 g (25%) of **29a** was obtained, mp 137—139° (from acetone). As the second fraction, trace of **28a** was obtained as an oil which was converted to the hydrochloride, mp 222—224° (dec.).

Reaction A 2-(2-Hydroxyethylamino)-4-phenyl-3,4-dihydroquinazoline (9a)——A solution of 7.60 g (20 mmol) of **8** and 2.50 g (40 mmol) of 2-aminoethanol in 150 ml of MeOH was refluxed for 2 hr. After cooling, the solution was concentrated to dryness *in vacuo* and the residual solid was collected with $(iso\text{-}PrO)_2O$ to give 6.10 g (77%) of the hydroiodide of **9a**, mp 165—168°. The hydroiodide salt was converted to the hydrochloride salt.

Reaction B 2-(2-Aminobenzhydryl)aminoethanol (10a)——A mixture of 9.90 g (50 mmol) of **5**, 30.5 g (0.5 mol) of 2-aminoethanol and 0.3 g of 4-methylbenzenesulfonic acid was heated with stirring at 150—160° for 1.5 hr. After cooling, to the mixture were added 150 ml of H_2O and 150 ml of AcOEt and the mixture was stirred. The organic layer was separated and the water layer was extracted with AcOEt. The AcOEt layers were combined, washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to give 13.5 g of yellow oil. To a solution of the oil in 250 ml of MeOH was added portionwise 4.0 g of $NaBH_4$ with stirring and the mixture was stirred for 1 hr. The solvent was removed *in vacuo*. The residue was mixed with water and extracted with $CHCl_3$. The extract was washed with water, and evaporated *in vacuo* to yield 12.6 g (93%) of **10a** as an oil. This oil could be used for subsequent reaction without further purification. A part of the oil was converted to the hydrochloride salt.

Reaction C 5-Phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (3a)——To a solution of 1.90 g (8 mmol) of **10a** in 30 ml of EtOH was added 1.00 g (9.6 mmol) of BrCN. The mixture was allowed to stand at room temperature for 30 min. The reaction mixture was refluxed for 2 hr. After cooling, the solution was made basic with conc. NaOH and concentrated to dryness *in vacuo*. The residue was extracted with $CHCl_3$. The extract was evaporated *in vacuo* and to the residue was added 10 ml of $SOCl_2$. The mixture was allowed to stand at room temperature for 1 hr and concentrated to dryness *in vacuo*. The residue was dissolved in 40 ml of MeOH and to the solution was added a solution of 8.0 g of KOH in 8 ml of H_2O. The mixture was refluxed for 30 min and then MeOH was removed *in vacuo*. A crystalline solid was collected and recrystallized from acetone to give 1.09 g (55% from **10a**) of **3a**, which was converted to the hydrochloride.

10-Methyl-5-phenyl-2,3,5,10-tetrahydroimidazo[2,1-*b*]qunazoline (12a)——A mixture of 1.47 g (7.5 mmol) of **16**,[8] 4.70 g (70 mmol) of 2-aminoethanol and 0.1 g of 4-methylbenzenesulfonic acid was heated at 150—160° for 1.5 hr. After cooling, to the mixture were added 30 ml of AcOEt and 30 ml of water. The mixture was shakened and the organic layer was separated. The solvent was removed *in vacuo*. The residue was dissolved in 20 ml of MeOH and to the solution was added 0.80 g of $NaBH_4$. The mixture was stirred for 1.5 hr and concentrated to dryness *in vacuo*. The residue was extracted with $CHCl_3$ and the extract was evaporated *in vacuo*. The residue was dissolved in 20 ml of EtOH and to the solution was added 1.20 g of BrCN. The mixture was refluxed for 1.5 hr. After cooling, the mixture was made basic with conc. NaOH solution and evaporated to dryness *in vacuo*. The residue was extracted with $CHCl_3$ and the extract was evaporated *in vacuo*. To the residue was added 10 ml of $SOCl_2$ and the mixture was allowed to stand at room temperature for 1 hr. The mixture was concentrated to dryness *in vacuo*. The residue was dissolved in 30 ml of MeOH and to the solution was added a solution of 5.0 g of KOH in 7 ml of H_2O. The mixture was refluxed for 30 min and concentrated to dryness *in vacuo*. The residue was extracted with $CHCl_3$. The extract was evaporated *in vacuo*. The residual red oil (2.0 g) was purified with silica gel (30 g) chromatography to give 0.62 g (30% from **16**) of **12a** as pure oil, which was converted to the hydrochloride.

Reaction D 1-Methyl-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (13a)——A mixture of 1.00 g (3.3 mmol) of **20a** and 5 ml of 40% aqueous $MeNH_2$ solution in 5 ml of EtOH was refluxed for 6 hr. After cooling, the mixture was basified with conc. NaOH solution and concentrated to dryness *in vacuo*. The residue was extracted with $CHCl_3$. The extract was evaporated *in vacuo* and the residue was recrystallized from EtOH–ether to give 0.74 g (83%) of **13a**.

Reaction E1 1-Acetyl-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (14a)——A solution of 1.09 g (4.4 mmol) of **3a** in 20 ml of Ac_2O was heated at 100° for 1 hr and concentrated to dryness *in vacuo*. The residue was extracted with benzene. The extract was washed with 5% $NaHCO_3$ solution and water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was treated with alumina (10 g) chromatography with benzene to give 0.78 g (62%) of **14a**.

Reaction E2 1-Benzoyl-6-phenyl-1,2,3,4-tetrahydro-6H-pyrimido[2,1-*b*]quinazoline (15b)——To a solution of 0.35 g (1.34 mmol) of **3b** in 5 ml of pyridine was added 0.21 g (1.5 mmol) of BzCl. The mixture was stirred at room temperature for 2 hr and then concentrated to dryness *in vacuo*. The residue was mixed with 5% $NaHCO_3$ solution and extracted with benzene. The extract was washed with water, dried over

Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized form benzene–ether to give 0.38 g (77%) of **15b**.

Reaction F **3-(2-Hydroxyethyl)-4-phenyl-3,4-dihydro-2(1H)-quinazolinthione (18a)**——A solution of 9.60 g (40 mmol) of **10a** and 9.00 g of CS_2 in 100 ml of EtOH was refluxed for 5 hr and concentrated to dryness *in vacuo*. The residue was recrystallized from iso-PrOH to give 7.50 g (66%) of **18a**.

Reaction G **3-(2-Hydroxyethyl)-4-phenyl-3,4-dihydro-2(1H)-quinazolinone (19a)**——To a mixture of 2.70 g (11.2 mmol) of **10a** in solution of 10 ml of pyridine and 10 ml of benzene was added 1.64 g (15 mmol) of EtOCOCl at 0—5° with stirring. The mixture was allowed to stand at room temperature and concentrated to dryness *in vacuo*. The residue was mixed with 2 N NaOH solution and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was heated at 190—200° for 1 hr and chromatographed on silica gel (25 g) with $CHCl_3$–MeOH to give 1.87 g (62%) of **19a**.

Reaction H **3-(2-Hydroxyethyl)-4-phenyl-3,4-dihydro-2(1H)-quinazolinone (19a)**——To a mixture of 16.6 g (56 mmol) of **18a**, 7.00 g (170 mmol) of NaOH, 200 ml of H_2O of dioxane was added 25.0 g of 30% H_2O_2 solution at 0—5° with stirring. After stirring 2 hr, dioxane was removed *in vacuo*. The residual mixture was extracted with $CHCl_3$. The extract was evaporated *in vacuo*. The residue was recrystallized from acetone to give 13.3 g (85%) of **19a**.

Reaction I **2-Chloro-3-(2-chloroethyl)-4-phenyl-3,4-dihydroquinazoline (20a)**——A mixture of 1.02 g (3.8 mmol) of **19a**, 1.5 g of PCl_5 and 15 ml of $POCl_3$ was refluxed for 4 hr and concentrated to dryness *in vacuo*. The residue was poured into ice-water. The mixture was neutrallized with conc. NH_4OH and extracted with benzene. The extract was evaporated *in vacuo*. The residue was recrystallized from ether to give 0.73 g (62%) of **20a**.

Reaction J **3-(2-Chloroethyl)-4-phenyl-3,4-dihydro-2-(1H)-quinazolinone (21a)**——A mixture of 5.40 g (20 mmol) of **19a** in 30 ml of $SOCl_2$ was allowed to stand at room temperature for 3 hr and concentrated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$. The solution was washed with 5% $NaHCO_3$ solution and water, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from MeOH–ether to yield 2.40 g (41%) of **21a**.

Reaction K1 **5-Phenyl-2,3-dihydro-5H-oxazolo[2,3-*b*]quinazoline (23a)**——A mixture of 3.00 g (10.5 mmol) of **21a** and 10.0 g of K_2CO_3 in 100 ml of acetone was refluxed with stirring for 5 hr and concentrated *in vacuo*. The residue was mixed with water and extracted with $CHCl_3$. The extract was mixed with water and extracted with $CHCl_3$. The extract was evaporated *in vacuo*. The residue was recrystallized from MeOH–ether to give 2.20 g (84%) of **23a**.

Reaction K2 **6-Phenyl-3,4-dihydro-2H,6H-[1,3]oxazino[2,3-*b*]quinazoline (23b)**——A mixture of 1.32 g (4.3 mmol) of **21b** and 0.23 g (4.8 mmol) of NaH (50% oil suspension) was stirred at room temperature for 3 hr and concentrated to dryness *in vacuo*. The residue was mixed with water and extracted with $CHCl_3$. The extract was evaporated *in vacuo* and the residue was recrystallized from EtOH to give 0.80 g (70%) of **23b**.

Reaction L **3-(2-Chloroethyl)-4-phenyl-3,4-dihydro-2(1H)-quinazolinone (21a)**——To a solution of 0.36 g (1.43 mmol) of **23a** in 5 ml of MeOH was added 0.5 ml of conc. HCl until the pH of the solution become to 1—2. The solution was allowed to stand at room temperature for 2 hr and concentrated to dryness *in vacuo*. The residue was mixed with 5% $NaHCO_3$ solution and a precipitate was collected to yield 0.25 g (61%) of **21a**.

Reaction M **6-Phenyl-3,4-dihydro-2H,6H-[1,3]oxazino[2,3-*b*]quinazoline (23b)**——A solution of 0.60 g (1.9 mmol) of **22b** in 6 ml of EtOH was refluxed for 6 hr and concentrated to dryness *in vacuo*. The residue was recrystallized from EtOH to give 0.45 g (89%) of **23b**.

Reaction N **3-(3-Hydroxypropyl)-2-methylthio-4-phenyl-3,4-dihydroquinazoline (22b)**——A solution of 1.50 g (5 mmol) of **17b** and 2.20 g (15 mmol) of MeI in 15 ml of acetone was allowed to stand at room temperature overnight. A solid was collected to give 1.91 g (84%) of the hydroiodide of **22b**, mp 164—166°. The salt was converted to the free base, mp 142—143°, in the usual way.

Reaction O **5-Phenyl-2,3-dihydro-5H-thiazolo[2,3-*b*]quinazoline (24a)**——A mixture of 1.13 g (4 mmol) of **18a** and 10 ml of methanesulfonic acid was heated at 120—130° for 20 min and poured into ice-water. The mixture was basified with conc. NaOH solution. A solid was collected and recrystallized from MeOH to yield 1.00 g (94%) of **24a**.

Reaction P **2-(2-Benzoylanilino)ethanol (25a)**——To a solution of 3.02 g (20 mmol) of **5** and 2.0 g of pyridine in 50 ml of $CHCl_3$ was added 2.85 g (20 mmol) of 2-chloroethylchloroformate in small portions at room temperature with stirring. After stirring for 2 hr, $CHCl_3$ was removed *in vacuo*. The mixture was treated with H_2O and a solid was collected to give crude 2-(2-chloroethoxycarbonyl)benzophenone in almost quantitative yield. The solid was dissolved in a solution of 4.50 g of KOH in 50 ml of EtOH and the mixture was refluxed for 4 hr. After cooling, EtOH was removed *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* to give 4.80 g (84%) of **25a** as a pale yellow oil. This oil was used for subsequent reaction without further purification.

Reaction Q **2-(2-Hydroxyethylamino)benzhydrylamine (26a)**——A mixture of 22.5 g (95 mmol) of **25a**, 13.2 g (0.19 mol) of $H_2NOH\cdot HCl$ and 16 ml of pyridine in 140 ml of EtOH was refluxed for 30 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* to yield crude 2-(2-hydroxyethylamino)-

benzophenone oxime as an oil in quantitative yield. The crude oil was dissolved in a solution of 40 g of NaOH in 1 l of H_2O–EOH (1 : 1). To the solution was added portionwise 37.0 g of Raney Ni alloy with stirring under refluxing. After addition, the mixture was stirred at room temperature for 5 hr. An insoluble material was filtered off and the filtrate was concentrated to dryness *in vacuo*. The residue was extracted with $CHCl_3$ and the extract was evaporated *in vacuo*. The residue was recrystallized from *n*-hexane–ether to give 18.1 g (92%) of **26a**.

Reaction R 2-(2-Hydroxyethylamino)-3-methyl-4-phenyl-3,4-dihydroquinazoline (32a)——A mixture of 6.00 g (25 mmol) of 31 in 180 ml of $POCl_3$ was refluxed for 50 hr. Excess of $POCl_3$ was removed *in vacuo*. To the residue was added dry benzene and the mixture was evaporated to dryness *in vacuo*. To the residue was added 12.0 g of 2-aminoethanol and the mixture was heated at 140—150° for 1.5 hr. The mixture was concentrated to dryness *in vacuo*. The residue was mixed with 10% NaOH solution and extracted with $CHCl_3$. The extract was evaporated *in vacuo*. The residue was recrystallized from acetone to yield 2.70 g (39% from 31) of 32a.

Reaction S 4-Methyl-5-phenyl-1,2,4,5-tetrahydroimidazo[1,2-*a*]quinazoline (28a)——A mixture of 0.34 g (1.2 mmol) of 32 in 8 ml of $POCl_3$ was refluxed for 4 hr. Excess of $POCl_3$ was removed *in vacuo* and the residue was dissolved in a solution of 2.0 g of KOH in 10 ml of H_2O–EtOH (1 : 1) solution. EtOH was removed *in vacuo* and the residue was extracted with $CHCl_3$. The extract was evaporated *in vacuo* and the residue was recrystallized from ether to yield 0.24 g of **28a**. It was converted to the hydrochloride in usual way.

Reaction T 3-Methyl-5-phenyl-1,2,3,5-tetrahydroimidazo[1,2-*a*]quinazoline (29a)——A solution of 4.00 g (14 mmol) of **35a** and 12.0 g of Et_3OBF_4 (Meerwein reagent) in 50 ml of CH_2Cl_2 was allowed to stand at room temperature overnight. The mixture was added to 5% $NaHCO_3$ solution. The organic layer was separated and the water layer was extracted with $CHCl_3$. The organic layer was combined and evaporated *in vacuo* to yield 3.25 g (74%) of 2-ethoxyderivative (36a). The crude oil was dissolved in a solution of 20 ml of 40% $MeNH_2$ and 20 ml of EtOH. The solution was refluxed for 6 hr. To the solution was added 10 ml of 10% NaOH solution and the mixture was concentrated to remove EtOH *in vacuo*. The residual mixture was extracted with $CHCl_3$. The extract was evaporated *in vacuo* and the residue was dissolved in HCl–MeOH. The solution was concentrated to dryness *in vacuo* to yield 1.62 g (41% from **35a**) of the hydrochloride of **29a**.

Reaction U 2-(2-Hydroxyethylamino)benzhydrol (37a)——To a solution of 7.00 g (29 mmol) of **25a** in 100 ml of MeOH was added 2.40 g (64 mmol) of $NaBH_4$ with stirring. The mixture was stirred for 2 hr and concentrated to dryness *in vacuo*. The residue was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to yield 5.01 g (71%) of **37a**.

Reaction V 1-(2-Hydroxyethyl)-4-phenyl-1,2,3,4-tetrahydroquinazoline-2-thione (33a)——To a mixture of 1.00 g (4.1 mmol) of **37a** in 5 ml of 1 N HCl was added a solution of 0.41 g (5.05 mmol) of NaSCN in 5 ml of H_2O with stirring and then the mixture was heated at 80—90° for 30 min with stirring. After cooling, the mixture was extracted with $CHCl_3$. The extract was evaporated to dryness *in vacuo*. The residue was recrystallized from benzene to yield 0.85 g (73%) of **33a**.

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