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Cyclofunctionalization of Olefinic Urethanes and Ureas with Halogens. Synthesis of 1-Substituted Spiro[piperidine-4,4′(3′*H*)-quinazolin]-2′(1′*H*)-one Derivatives

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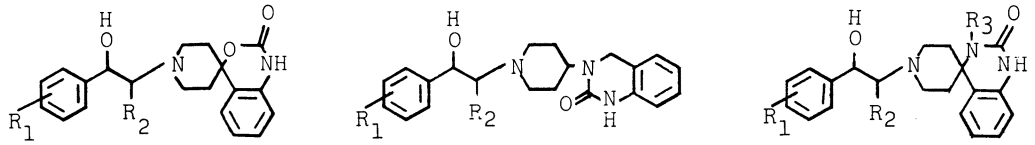
The cyclization reaction of 4-(2-carbamoylaminophenyl)-1,2,5,6-tetrahydropyridine derivatives (**9**) and a 4-(2-methoxycarbonylaminophenyl)-1,2,5,6-tetrahydropyridine derivative (**4**) with halogen was investigated. Treatment of the former (**9**) with bromine or *N*-chlorosuccinimide (NCS) under acidic conditions gave the corresponding 3′-halogeno-2-amino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] derivatives (**11**) and with iodine under basic conditions gave 5,6-dihydro-3-iodo-spiro[pyridine-4(1*H*),4′(3′*H*)-quinazolin]-2′(1′*H*)-one derivatives (**14**), which were converted to spiro[piperidine-4,4′(3′*H*)-quinazolin]-2′(1′*H*)-one derivatives (**15** and **17**). Treatment of the latter (**4**) with bromine under acidic conditions gave 3′-bromo-spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one derivatives (**5** and **6**).

Keywords——spiro compound; piperidine; quinazoline; benzoxazine; olefin; urea; urethane; halogenocyclization

Previous reports[1] on piperidine derivatives with a spirooxazinone ring (**1**) or a quinazolinone ring (**2**) at the 4 position led us to consider the possibility of developing a useful antihypertensive agent through further modification of this series. During this investigation, we were interested in the effect of the stereochemical relationship between the piperidine ring and quinazolinone ring on the antihypertensive activity. Accordingly, we selected the spiroquinazolinone derivatives **3** (Chart 1) for further modification. In this report, we wish to describe the synthesis of spirooxazinone and spiroquinazolinone skeletons by the cyclization of the olefinic urethane **4** and the olefinic ureas **9** with halogens.

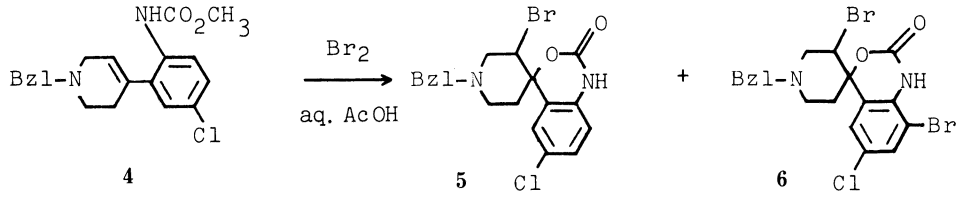
Iodolactonization is a well-known reaction that has been applied to the preparation of various compounds.[2] Recently, the application of this reaction to carbamate was developed for the preparation of aminosugar derivatives.[3] We were interested in the application of this



1 **2** **3**

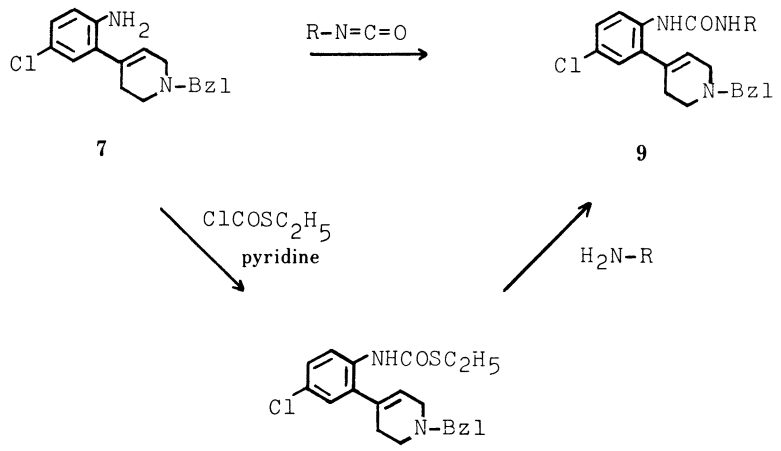
4 **9**

Chart 1



4 5 6

Chart 2



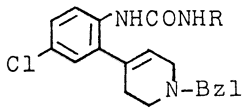
7 9 8

Chart 3

reaction to the preparation of spiro compounds. Firstly, we treated the olefinic urethane **4**[4] with bromine in aqueous acetic acid (AcOH) at room temperature. The expected cyclization reaction occurred to give **5** and **6** in 10.9% and 36.4% yields, respectively. Next, we tried to apply this reaction to the cyclization of the olefinic ureas **9** in expectation of the formation of the spiroquinazolinone skeleton. The starting materials **9** were prepared from **7**, which was previously reported by us,[4] as shown in Chart 3. Compound **9a** was obtained by treatment of **7** with sodium cyanate in aqueous AcOH in 92.6% yield and compounds **9b**—**g**, **k** were obtained by treatment of **7** with the appropriate isocyanate in ethyl acetate (AcOEt) in moderate yields. The analytical data are summarized in Table I. Compounds **9h**—**j** were also obtained by treatment of **7** with ethyl chlorothioformate in pyridine in 38.2% yield, followed by treatment with the appropriate amine, and used *in situ* for the next reaction. The treatment of **9** with bromine in aqueous AcOH at room temperature, contrary to our expectation, resulted in the formation of the aminooxazines (**11A**) with no production of the quinazolines (**10**). Treatment with *N*-chlorosuccinimide (NCS) instead of bromine also afforded **11B** (Chart 4). The results are summarized in Table II and the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectral data of **11** are given in Table III.

Recently, several methods for iodocyclization of an amide or carbamate nitrogen onto an intramolecular carbon–carbon double bond have been reported.[5] Accordingly, compound **9b** was treated with an aqueous solution of I_2 and NaI in CH_2Cl_2 and aqueous 10% $NaHCO_3$ at room temperature to give the spiro compound **14b**. In order to complete this reaction, 2 eq of iodine was needed. A proposed mechanism for the formation of **14b** is shown in Chart 5. The reaction seems to proceed by initial cyclization of the urea **9b** to the intermediate **12b** and then to the enamine **13b** by the elimination of HI. The enamine **13b** may be iodized to give the iodoenamine **14b**. The same reaction of the other ureas (**9c**, **d**, **f**, **h**, and **i**) also gave the spiro

TABLE I. Analytical Data for the Ureas (**9**)



Compd. No.	R	Yield (%)	Recrystn. solvent	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
9a	H	92.6	EtOH	185—187	$C_{19}H_{20}ClN_3O$	66.76	5.90	12.29
						(66.79	5.88	12.35)
9b[a]	CH_3							
9c	C_2H_5	60.4	AcOEt	152—155	$C_{21}H_{24}ClN_3O$	68.19	6.54	11.36
						(68.39	6.66	11.32)
9d	$(CH_2)_2CH_3$	54.4	AcOEt–hexane	67—69	$C_{22}H_{26}ClN_3O \cdot H_2O$	65.74	7.02	10.45
						(65.92	6.94	10.44)
9e	$CH(CH_3)_2$	47.7	AcOEt	150—152	$C_{22}H_{26}ClN_3O \cdot 0.25H_2O$	68.03	6.88	10.82
						(68.31	6.94	10.97)
9f	$(CH_2)_3CH_3$	50.3	AcOEt–hexane	61—63	$C_{23}H_{28}ClN_3O \cdot H_2O$	66.41	7.27	10.10
						(66.88	7.38	10.07)
9g	$CH(CH_3)C_6H_5$	42.8	Amorphous powder		$C_{27}H_{28}ClN_3O$	MS *m/z* Calcd: 445.1923 (M^+) Found: 445.1922		
9k	Cyclo-hexyl	68.4	AcOEt	167—169	$C_{25}H_{30}ClN_3O$	70.82	7.13	9.91
						(70.78	6.97	10.15)

a) This compound was previously reported by us.[3]

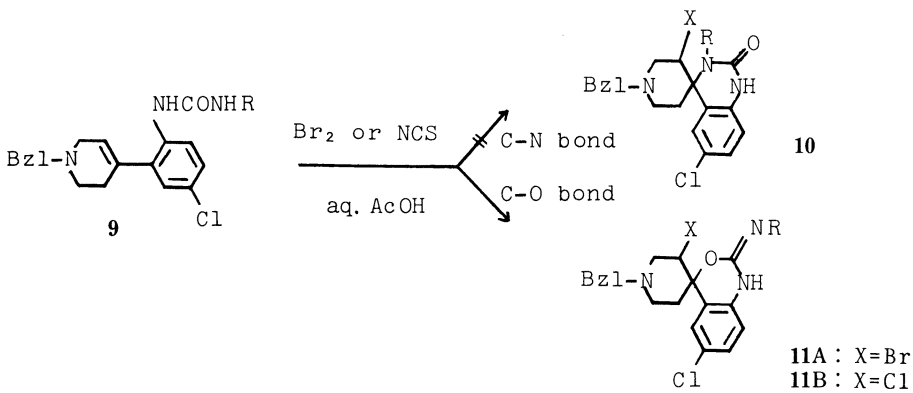
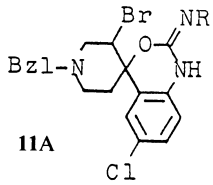


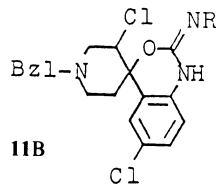
Chart 4

compounds (**14c**, **d**, **f**, **h**, and **i**, respectively) (Tables IV and V), but compounds **9e** and **k** with bulky substituents, such as an isopropyl or a cyclohexyl group at the nitrogen atom, gave only an unknown crude product in low yield under the same conditions. The catalytic hydrogenation of **14b** at 40 °C in aqueous EtOH was examined, to ascertain the structure. The reaction without additives gave **15** in 13.0% yield. The reaction in the presence of 1 eq of HCl gave **16** as the main product in 22.2% yield. The reaction in the presence of 10 eq of triethylamine (TEA) gave **17** in 98.8% yield. These results are shown in Chart 6. The structure of **14b** was established by confirming the structure of **15** on the basis of its spectral similarity to the oxazine **18**, the structure of which was already determined by us.[6] The physical properties of **15** and **18** are summarized in Table VI. Compound **15** had the molecular

TABLE II. Analytical Data for the Aminooxazines (**11**)



11A



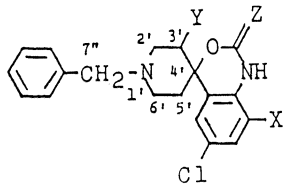
11B

Compd.[a] No.	R	Yield (%)	Method[b]	Recrystn. solvent	mp (°C)	Formula	Analysis (%) Calcd (Found) C H N
11Aa	H	50.8	B	$CHCl_3$–EtOH	176—180	$C_{19}H_{19}BrClN_3O$	54.24 4.55 9.99 (53.97 4.75 9.71)
11Ab	CH_3	75.5	B	$CHCl_3$–EtOH	173—174	$C_{20}H_{21}BrClN_3O$	55.25 4.87 9.67 (55.06 4.85 9.58)
11Ac	C_2H_5	56.1	B	EtOH	138—139	$C_{21}H_{23}BrClN_3O$	56.20 5.17 9.36 (56.30 5.22 9.33)
11Ad	$(CH_2)_2CH_3$	58.7	B	EtOH	111—113	$C_{22}H_{25}BrClN_3O$	57.09 5.44 9.08 (57.13 5.47 8.99)
11Ae	$CH(CH_3)_2$	61.7	B	Oil		$C_{22}H_{25}BrClN_3O$	MS *m/z* Calcd: 461.0872 (M^+) Found: 461.0863
11Af	$(CH_2)_3CH_3$	55.0	B	EtOH	123—124	$C_{23}H_{27}BrClN_3O$	57.93 5.70 8.81 (58.21 5.93 8.71)
11Ag	$CH(CH_3)Ph$	25.0	B	Oil		$C_{27}H_{27}BrClN_3O$	MS *m/z* Calcd: 523.1028 (M^+) Found: 523.1022
11Ah	$(CH_2)_4CH_3$	31.8	C	AcOEt–hexane	117—120	$C_{24}H_{29}BrClN_3O$	58.73 5.95 8.56 (58.56 6.02 8.33)
11Ai	$(CH_2)_2CH(CH_3)_2$	55.3	D	EtOH	137—138	$C_{24}H_{29}BrClN_3O$	58.72 5.96 8.56 (58.97 5.80 8.38)
11Aj	$(CH_2)_5CH_3$	24.2	C	Hexane	131—133	$C_{25}H_{31}BrClN_3O$	59.47 6.19 8.32 (59.19 6.08 8.05)
11Ak	Cyclo-hexyl	67.4	B	Oil		$C_{25}H_{29}BrClN_3O$	MS *m/z* Calcd: 501.1185 (M^+) Found: 501.1165
11Al	$(CH_2)_6CH_3$	21.6	D	Hexane	102—104	$C_{26}H_{33}BrClN_3O$	60.18 6.41 8.10 (60.01 6.45 8.04)
11Be	$CH(CH_3)_2$	46.6	E	Oil		$C_{22}H_{25}Cl_2N_3O$	MS *m/z* Calcd: 417.1378 (M^+) Found: 417.1350
11Bf	$(CH_2)_3CH_3$	27.5	E	MeOH	126—128	$C_{23}H_{27}Cl_2N_3O$	63.89 6.29 9.72 (63.66 6.30 9.63)
11Bi	$(CH_2)_2CH(CH_3)_2$	11.9	F	MeOH	138—139	$C_{24}H_{29}Cl_2N_3O$	64.57 6.55 9.41 (64.42 6.54 9.19)
11Bk	Cyclo-hexyl	34.7	E	Oil		$C_{25}H_{29}Cl_2N_3O$	MS *m/z* Calcd: 457.1691 (M^+) Found: 457.1679

a) Each product except for **11Ag** (1—1.5 : 1 diastereomixture) was a single isomer, the configuration of which could not be determined. *b*) See Experimental.

formula $C_{20}H_{22}N_3O$ on the basis of its elemental analysis data and mass spectrum (MS) (M; *m/z*: 355 for ^{35}Cl). Its proton and carbon-13 nuclear magnetic resonance (^1H-NMR and ^{13}C-NMR) spectra indicated the presence of a benzyl group, a piperidine ring and a 1-chloro-3,4-disubstituted benzene ring by comparison with those of **18**. The remaining group ($C_2H_4N_2O$), which was not determined, was a partial structure corresponding to the isourea group of **18**. The infrared (IR) absorption indicated the presence of a carbonyl group or an imino group (1667 cm^{-1}).

TABLE III. ^{13}C-NMR Spectral Data for **5**, **6**, **11A** and **11B**



Compd. No.	Z	X	Y	Chemical shifts (ppm)					Solvent
				Position					
				C-2′,6′	C-3′	C-4′	C-5′	C-7′′	
5	O	H	Br	47.40 53.58	49.89	79.93	28.78	60.71	DMSO-d_6
6	O	Br	Br	47.76 54.16	49.04	81.97	29.73	61.83	$CDCl_3$
11Aa	NH	H	Br	47.55 53.34	49.89	78.13	28.75	60.83	DMSO-d_6
11Ab	NCH_3	H	Br	47.58 53.40	49.71	77.64	28.69	60.80	DMSO-d_6
11Ac	NC_2H_5	H	Br	48.19 54.74	49.31	78.77	29.88	62.14	$CDCl_3$
11Ag[a]	$NCH(CH_3)Ph$	H	Br	48.10 (47.79) 53.88	49.13	79.74 (80.26)	29.45 (29.85)	61.74 (61.93)	$CDCl_3$
11Be	$NCH(CH_3)_2$	H	Cl	47.83 54.28	55.98	79.76	29.62	62.08	$CDCl_3$
11Bf	$N(CH_2)_3CH_3$	H	Cl	47.35 53.05	56.27	77.28	28.57	61.03	DMSO-d_6
11Bi	$N(CH_2)_2CH(CH_3)_2$	H	Cl	47.37 53.07	56.27	77.43	28.60	61.06	DMSO-d_6
11Bk	N-Cyclo-hexyl	H	Cl	47.91	55.96	—	29.72	62.18	$CDCl_3$

a) Compound **11Ag** was obtained as a diastereomixture and the chemical shifts of the other diastereoisomer are noted in parentheses.

In the ^{13}C-NMR spectra of **18** and **11**, a singlet due to C-4 of piperidine was observed in the vicinity of 80 ppm, but in the case of **15**, the signal appeared at higher field (57.08 ppm). On the basis of the above results, the presence of the C–N bond at the 4′-position of the piperidine ring of **15** was determined. Compound **17** was converted into aminoketones **20a—c** by reaction with the appropriate bromoketone **19a—c** in ethanol using TEA as a base. The aminoketones **20a** thus obtained were reduced to the alcohol **3a** by treatment with sodium borohydride. The selective reduction of **20b** and **20c** with L-Selectride gave **3b** and **3c**, respectively. Analysis of the proton nuclear magnetic resonance (^{1}H-NMR) spectra of **3a** and **3b** permitted assignment of the configurations. The coupling constants of the benzylic proton were 10 Hz for **3b** and 9 Hz for **3c**. These are comparable with the values of 8.3 and 4.0 Hz for pseudoephedrine (*threo*) and ephedrine (*erythro*),[8] as described previously for compounds **1** and **2**.[1] The virtual identity of the coupling constants of these compounds supported the assignment of *threo* configuration to **3b** and **3c**.

Experimental

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. IR

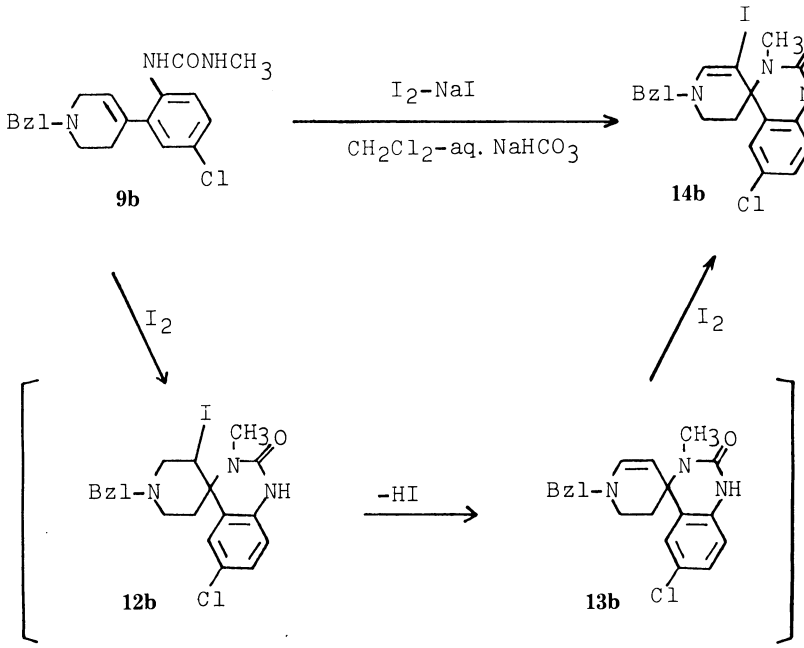
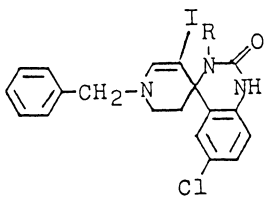


Chart 5

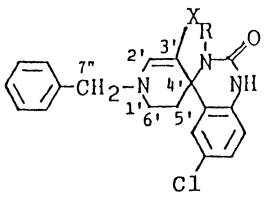
TABLE IV. Analytical Data for the Quinazolinones (**14**)



Compd. No.	R	Yield (%)	Method[a]	Recrystn. solvent	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
14b	CH_3	83.4	G	EtOH	197—198	$C_{20}H_{19}ClIN_3O$	50.07 (50.15)	3.99 (3.82)	8.76 (8.53)
14c	C_2H_5	75.1	G	MeOH	196—197	$C_{21}H_{21}ClIN_3O$	51.08 (50.80)	4.29 (4.14)	8.51 (8.46)
14d	$(CH_2)_2CH_3$	44.5	G	MeOH	199—200	$C_{22}H_{23}ClIN_3O$	52.03 (52.25)	4.57 (4.60)	8.28 (8.08)
14f	$(CH_2)_3CH_3$	62.3	G	$CHCl_3$–MeOH	216—217	$C_{23}H_{25}ClIN_3O$	52.93 (53.16)	4.83 (4.78)	8.05 (8.33)
14h	$(CH_2)_4CH_3$	40.5	H	AcOEt	167—170	$C_{24}H_{27}ClIN_3O$	53.79 (53.89)	5.08 (5.15)	7.84 (7.64)
14i	$(CH_2)_2CH(CH_3)_2$	32.5	H	AcOEt	184—186	$C_{24}H_{27}ClIN_3O$	53.79 (53.87)	5.08 (4.96)	7.84 (8.05)

a) See Experimental.

TABLE V. ^{13}C-NMR Spectral Data for **14** and **16** in $CDCl_3$



Compd. No.	R	X	Chemical shifts (ppm)			
			Position			
			C-3′,4′	C-5′	C-6′	C-7″
14b	CH_3	I	63.82 64.62	32.65	42.53	59.24
14c	C_2H_5	I	63.75 65.99	34.76	42.61	59.21
14d	$(CH_2)_2CH_3$	I	63.70 65.76	34.89	42.59	59.24
14f	$(CH_2)_3CH_3$	I	63.75 65.78	34.96	42.61	59.24
14h	$(CH_2)_4CH_3$	I	63.72 65.80	34.98	42.63	59.26
14i	$(CH_2)_2CH(CH_3)_2$	I	63.66 65.82	35.06	42.64	59.24
16	CH_3	H	95.08 (3′) 58.98 (4′)	32.19	42.85	59.37

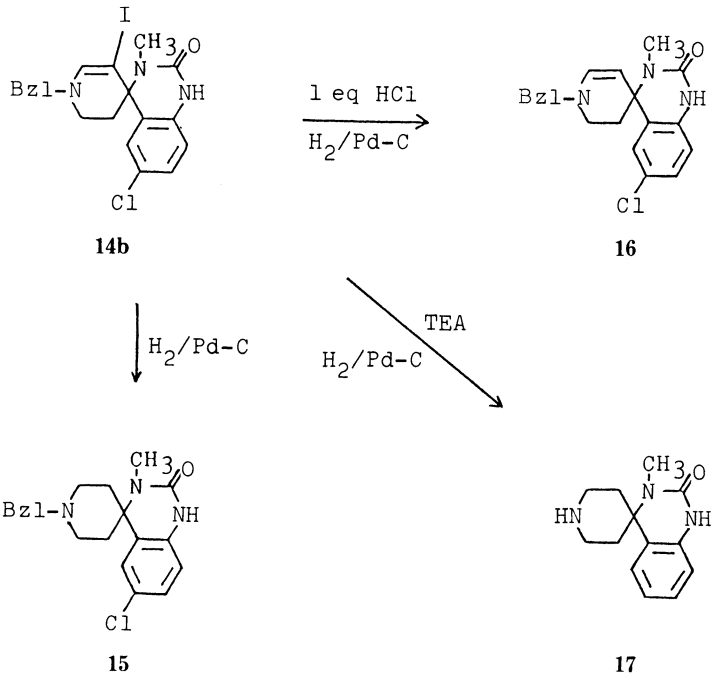
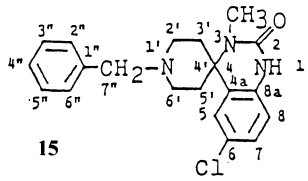
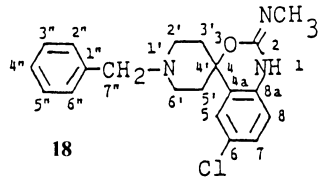


Chart 6

TABLE VI. IR, MS, ^{1}H-NMR (270 MHz), and ^{13}C-NMR (25.1 MHz) Spectral Data for **15** and **18**



15



18

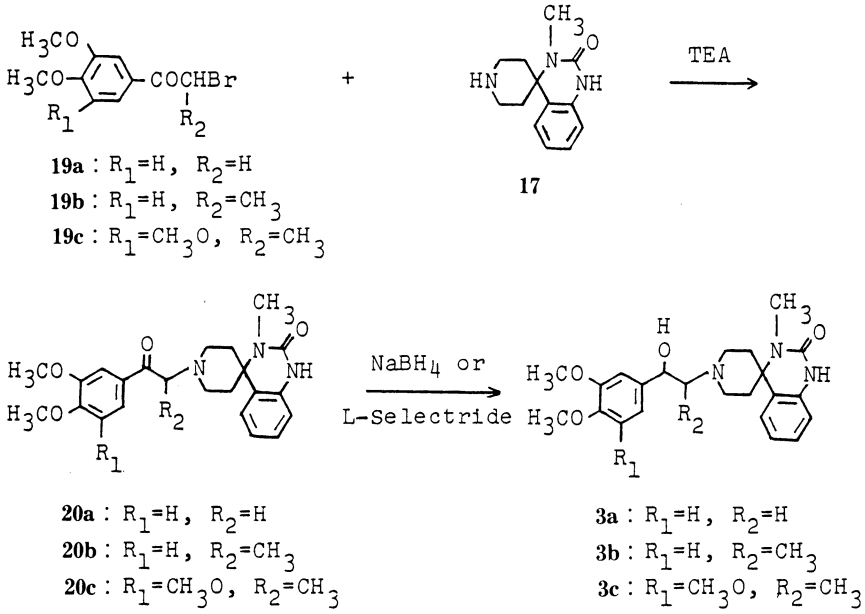
IR	1667 cm^{-1} (C=O) (KBr)	1665 cm^{-1} (C=N) (KBr)
MS	355 (M^+)	355 (M^+)
^{1}H-NMR ($CDCl_3$)	2.1—2.5 (6H, m, piperidine H), 2.7—2.9 (2H, m, piperidine H), 3.11 (3H, s, N-CH$_3$), 3.56 (2H, s, NCH$_2$Ph), 6.80 (1H, d, J=8.3 Hz, aromatic H), 7.14—7.39 (7H, m, aromatic H), 8.87 (1H, brs, NH)	1.95—2.1 (4H, m, piperidine H), 2.3—2.5 (2H, m, piperidine H), 2.75—2.85 (2H, m, piperidine H), 2.93 (3H, s, N-CH$_3$), 3.56 (2H, s, NCH$_2$Ph), 4.8 (1H, brs, NH), 6.85—7.4 (8H, m, aromatic H)

^{13}C-NMR[a] ($CDCl_3$)	Carbons	Chemical shifts (ppm)	Carbons	Chemical shifts (ppm)
	2	156.53 (s)	2	154.41 (s)
	4 (4′)	57.08 (s)	4 (4′)	78.12 (s)
	5	115.69 (d)	5	122.32 (d) or 123.36 (d)
	7	127.24 (d)	7	127.14 (d)
	8	127.83 (d)	8	128.48 (d)
	4a	126.63 (s)	4a	127.08 (s)
	6	128.38 (s)	6	129.87 (s)
	8a	135.65 (s)	8a	140.81 (s)
	9	29.40 (q)	9	28.14 (q)
	3′ 5′	31.93 (t)	3′ 5′	34.87 (t)
	2′ 6′	50.89 (t)	2′ 6′	48.55 (t)
	1″	138.02 (s)	1″	138.26 (s)
	2″ 6″	129.06 (d)	2″ 6″	129.10 (d)
	3″ 5″	128.33 (d)	3″ 5″	128.28 (d)
	4″	124.80 (d)	4″	122.32 (d) or 123.36 (d)
	7″	62.92 (t)	7″	63.20 (t)

a) Benzyl group signals were assigned on the basis of the data in reference 7.

spectra were measured on a Shimadzu IR-27G spectrometer, ^{1}H-NMR spectra on a Varian EM 390 spectrometer, a JEOL JNM-PS-100 spectrometer, or a JEOL JNM-GX 270 spectrometer with tetramethylsilane as an internal standard, and ^{13}C-NMR spectra on a JEOL JNM-FX-100 spectrometer at 25.1 MHz, operating in the Fourier-transform mode with tetramethylsilane as an internal standard. MS were measured on a JEOL JMS-OISG-2 spectrometer.

(A) Conversion of 4 to 5 and 6. Synthesis of 1′-Benzyl-3′-bromo-6-chloro-spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (5) and 1′-Benzyl-6-chloro-3′,8-dibromo-spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (6)——A solution of bromine (2.00 g, 12.5 mmol) and sodium bromide (NaBr) (1.29 g, 12.5 mmol) in H_2O (15 ml) was added dropwise over 30 min to a stirred solution of 1-benzyl-4-(2-methoxycarbonyl-5-chlorophenyl)-1,2,5,6-tetrahydropyridine (**4**) (1.81 g, 5.08 mmol) in acetic acid (60 ml) and H_2O (15 ml) at room temperature. Then, the reaction mixture was stirred for 30 min and concentrated *in vacuo*. The residue thus obtained was mixed with ice-water, made basic with concentrated aqueous NaOH, and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated to give an oily residue, which was chromatographed on silica gel (AcOEt : hexane = 3 : 7, v/v) to afford **5** (233 mg, 10.9%) and **6** (927 mg, 36.4%). Recrystallization of **5** from $CHCl_3$–EtOH gave an analytical sample, mp 185—187 °C. *Anal.* Calcd MS *m/z*: 420 (M^+) for ^{79}Br and ^{35}Cl. IR (KBr): 1741 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.1 (1H, m, piperidine H), 2.7—3.1 (5H, m, piperidine H), 3.55 (1H, d, J=13.5 Hz, $C_6H_5CH_2$), 3.76 (1H, d, J=13.5 Hz, $C_6H_5CH_2$), 4.33—4.50 (1H, m, >CHBr), 6.82 (1H, d, J=9 Hz, aromatic H), 7.2—7.6 (7H, m, aromatic H), 9.23 (1H, s, NH). Recrystallization of **6** from $CHCl_3$–EtOH gave an analytical sample, mp 194—195 °C. *Anal.* Calcd MS *m/z*: 498 (M^+) for ^{79}Br and ^{35}Cl. IR (KBr): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.1 (1H, m, piperidine H), 2.7—3.1 (5H, m, piperidine H), 3.55 (1H, d, J=13.5 Hz, $C_6H_5CH_2$), 3.76 (1H, d, J=13.5 Hz, $C_6H_5CH_2$), 4.30—4.46 (1H, m,



19a : R_1=H, R_2=H
19b : R_1=H, R_2=CH_3
19c : R_1=CH_3O, R_2=CH_3

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20a : R_1=H, R_2=H
20b : R_1=H, R_2=CH_3
20c : R_1=CH_3O, R_2=CH_3

3a : R_1=H, R_2=H
3b : R_1=H, R_2=CH_3
3c : R_1=CH_3O, R_2=CH_3

Chart 7

>CHBr), 7.2—7.6 [8H, m, NH and aromatic H (d, J=2 Hz at 7.52 ppm)].

(B) Conversion of 9 to 11. Typical Procedure. Synthesis of 1′-Benzyl-3′-bromo-6-chloro-2-methylamino-spiro-[4*H*-3,1-benzoxazine-4,4′-piperidine] (11Ab)——A solution of bromine (800 mg, 5.00 mmol) and NaBr (515 mg, 5.00 mmol) in H_2O (5 ml) was added dropwise over 1 h to a stirred solution of 1-benzyl-4-[2-(*N*-methylcarbamoyl)-amino-5-chlorophenyl]-1,2,5,6-tetrahydropyridine (**9b**) (1.42 g, 3.99 mmol) in acetic acid (40 ml) and H_2O (10 ml) at room temperature. Then, the reaction mixture was stirred for 30 min and concentrated *in vacuo*. The residue was mixed with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residue was crystallized from MeOH to give **11**Ab (1.31 g, 75.5%). Recrystallization of **11**Ab from $CHCl_3$–EtOH gave an analytical sample, mp 173—174 °C. IR (KBr): 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.0 (2H, m, piperidine H), 2.6—3.2 [7H, m, piperidine H and CH_3 (s at 2.93 ppm)], 3.55 (1H, d, J=13.5 Hz, $C_6H_5CH_2$), 3.76 (1H, d, J=13.5 Hz, $C_6H_5CH_2$), 4.26—4.40 (1H, m, >CHBr), 6.93 (1H, d, J=9 Hz, aromatic H).

(C) Conversion of 7 to 11. Typical Procedure. Synthesis of 1′-Benzyl-3′-bromo-6-chloro-2-*n*-pentylamino-spiro-[4*H*-3,1-benzoxazine-4,4′-piperidine] (11Ah)——Ethyl chlorothioformate (0.200 ml, 1.92 mmol) was added dropwise over 30 min to a solution of 4-(2-amino-5-chlorophenyl)-1-benzyl-1,2,5,6-tetrahydropyridine (**7**) (299 mg, 1.00 mmol) in pyridine (5 ml) at 0 °C. Then, the mixture was stirred at room temperature for 30 min and concentrated *in vacuo*. The residue was heated at 80 °C for 45 min in pentylamine (5 ml) and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ and the solution was washed with H_2O, dried, and concentrated *in vacuo* to give an oily residue. The crude product (urea) was dissolved in AcOH (10 ml) and H_2O (4.5 ml). To this stirred solution, a solution of bromine (0.105 ml, 2.04 mmol) in AcOH (1 ml) was added dropwise over 30 min at room temperature. Then, the reaction mixture was stirred for 2 h, mixed with H_2O (80 ml), made basic with concentrated aqueous NaOH, and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo* to give an oily product, which was chromatographed on silica gel (AcOEt : hexane = 2 : 8, v/v) to afford **11**Ah (156 mg, 31.8%). Recrystallization from AcOEt–hexane gave an analytical sample, mp 117—120 °C. IR (KBr): 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=6 Hz, CH_3), 1.2—1.65 (6H, m, $-CH_2CH_2CH_2CH_3$), 1.75—2.0 (1H, m, piperidine H), 2.5—3.2 (5H, m, piperidine H), 3.31 (2H, t, J=6 Hz, $=NCH_2-$), 3.55 (1H, d, J=13.5 Hz, $C_6H_5CH_2$), 3.76 (1H, d, J=13.5 Hz, $C_6H_5CH_2$), 4.26—4.40 (1H, m, >CHBr), 6.90 (1H, d, J=9 Hz, aromatic H), 7.1—7.5 (7H, m, aromatic H).

(D) Conversion of 8 to 11. Typical Procedure. Synthesis of 1′-Benzyl-3′-bromo-6-chloro-2-isopentylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (11Ai)——A mixture of 1-benzyl-4-(5-chloro-2-ethylthiocarbonylamino-phenyl)-1,2,5,6-tetrahydropyridine (**8**) (1.77 g, 4.57 mmol) and isopentylamine (5 ml) was stirred at 90 °C for 30 min. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in AcOH (50 ml) and H_2O (22.5 ml). To this stirred solution, a solution of bromine (0.37 ml, 7.18 mmol) in AcOH (3.5 ml) was added dropwise over 30 min at room temperature. The reaction mixture was stirred for a further 1 h and concentrated *in vacuo*. The residue was mixed with H_2O (100 ml), made basic with conc. aqueous NaOH, extracted with $CHCl_3$, and concentrated *in vacuo*. The residue was crystallized from EtOH to give **11**Ai (1.24 g, 55.3%). Recrystallization from EtOH gave an analytical

sample, mp 137—138 °C. IR (KBr): 1661 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 [6H, d, J=6 Hz, $-CH(CH_3)_2$], 1.2—2.0 [4H, m, $-CH_2CH(CH_3)_2$ and piperidine H], 2.4—3.15 (5H, m, piperidine H), 3.30 (2H, t, J=7 Hz, $=NCH_2CH_2-$), 3.51 (1H, d, J=13.5 Hz, $C_6H_5CH_2-$), 3.72 (1H, d, J=13.5 Hz, $C_6H_5CH_2-$), 4.23—4.40 (1H, m, $>CHBr$), 5.5 (1H, br s, NH), 6.90 (1H, d, J=9 Hz, aromatic H), 7.0—7.5 (7H, m, aromatic H).

(E) Conversion of 9 to 11B. Typical Procedure. Synthesis of 1′-Benzyl-2-*n*-butylamino-3′,6-dichloro-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (11Bf)——NCS (534 mg, 4.00 mmol) was added to a stirred solution of 1-benzyl-4-(2-*n*-butylcarbamoylamino-5-chlorophenyl)-1,2,5,6-tetrahydropyridine (**9f**) (398 mg, 1.00 mmol) in AcOH (10 ml) and H_2O (2.5 ml). Then, the reaction mixture was stirred at room temperature overnight, mixed with ice-water (100 ml), made basic with aqueous NaOH, and extracted with ether. The extract was washed with H_2O, concentrated *in vacuo*, and chromatographed on silica gel (AcOEt–hexane=2:8, v/v) to afford **11Bf** (119 mg, 27.5%) (crystallized from MeOH), mp 126—128 °C. IR (KBr): 1656 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.89 (3H, t, J=7 Hz, $-CH_2CH_3$), 1.2—1.6 (4H, m, $-CH_2CH_2CH_3$), 1.7—1.85 (1H, m, piperidine H), 2.6—3.2 (7H, m, piperidine H and $=NCH_2CH_2-$), 3.53 (1H, d, J=13.4 Hz, $C_6H_5CH_2$), 3.69 (1H, d, J=13.4 Hz, $C_6H_5CH_2$), 4.13—4.20 (1H, m, $>CHCl$), 6.82 (1H, d, J=8.1 Hz, aromatic H), 7.15—7.4 (7H, m, aromatic H).

(F) Conversion of 8 to 11B. Typical Procedure. Synthesis of 1′-Benzyl-3′,6-dichloro-2-isopentylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (11Bi)——A mixture of **8** (355 mg, 0.917 mmol) and isopentylamine (1 ml) was stirred at 90 °C for 30 min. The reaction mixture was concentrated *in vacuo* and dissolved in AcOH (10 ml) and H_2O (2.5 ml). To this stirred solution, NCS (534 mg, 4.00 mmol) was added at room temperature. Then, the reaction mixture was stirred at room temperature overnight, mixed with ice-water (100 ml), made basic with aqueous NaOH, and extracted with ether. The extract was washed with H_2O, dried, concentrated *in vacuo*, and chromatographed on silica gel (AcOEt–hexane=2:8, v/v) to afford **11Bi** (49 mg, 11.9%) (recrystallized from MeOH), mp 138—139 °C. IR (KBr): 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.89 [6H, d, J=6.6 Hz, $-CH(CH_3)_2$], 1.35—1.45 [2H, m, $-CH_2CH(CH_3)_2$], 1.52—1.68 [1H, m, $-CH_2CH(CH_3)_2$], 1.71—1.82 (1H, m, piperidine H), 2.6—3.2 (7H, m, piperidine H and $=NCH_2CH_2-$), 3.53 (1H, d, J=13.6 Hz, $C_6H_5CH_2$), 3.69 (1H, d, J=13.6 Hz, $C_6H_5CH_2-$), 4.13—4.20 (1H, m, $>CHCl$), 6.82 (1H, d, J=8.2 Hz, aromatic H), 7.15—7.4 (7H, m, aromatic H).

(G) Conversion of 9 to 14. Typical Procedure. Synthesis of 1-Benzyl-6′-chloro-5,6-dihydro-3-iodo-3′-methyl-spiro[pyridine-4(1*H*),4′(3′*H*)-quinazolin]-2′(1′*H*)-one (14b)——A solution of I_2 (5.08 g, 20.0 mmol) and NaI (9.00 g, 60.0 mmol) in H_2O (50 ml) was added dropwise over 30 min to a stirred solution of 1-benzyl-4-(2-methylcarbamoyl-amino-5-chlorophenyl)-1,2,5,6-tetrahydropyridine (**9b**) (3.56 g, 10.0 mmol) in CH_2Cl_2 (150 ml) and 10% aqueous $NaHCO_3$ (100 ml) at room temperature. After a further 1.5 h, the reaction mixture was treated with a small amount of $Na_2S_2O_3$ and this CH_2Cl_2 layer was washed with 5% aqueous $NaHCO_3$, and H_2O, dried, and concentrated *in vacuo*. The residue thus obtained was crystallized from MeOH and collected by filtration to give **14b** (4.00 g, 83.4%). Recrystallization from EtOH gave an analytical sample, mp 197—198 °C. MS *m/z*: 479 (M^+). IR (KBr): 1668 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.6 (2H, m, piperidine H), 2.8—3.2 [5H, s at 3.06 ($N-CH_3$) and m, piperidine H), 4.16 (2H, s, $C_6H_5CH_2$), 6.7—7.6 (9H, m, $N-CH=C-I$ and aromatic H), 9.2 (1H, br s, NH).

(H) Conversion of 8 to 14. Typical Procedure. Synthesis of 1-Benzyl-6′-chloro-5,6-dihydro-3-iodo-3′-*n*-pentyl-spiro[pyridine-4(1*H*),4′(3′*H*)-quinazolin]-2′(1′*H*)-one (14h)——A mixture of **8** (1.77 g, 4.57 mmol) and pentylamine (1.2 ml, 10 mmol) was stirred for 30 min at 80 °C. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (75 ml) and 10% aqueous $NaHCO_3$ (50 ml). To this stirred solution, a solution of I_2 (2.54 g, 10.0 mmol) and NaI (4.50 g, 30.0 mmol) in H_2O (25 ml) was added dropwise over 30 min at room temperature. After a further 1.5 h, the reaction mixture was treated with a small amount of $Na_2S_2O_3$ and diluted with $CHCl_3$ (200 ml). Then, the organic layer was washed successively with 5% aqueous $NaHCO_3$ and H_2O, dried, and concentrated *in vacuo*. The oily residue thus obtained was crystallized from MeOH and the precipitated crystals were collected by filtration to give **14h** (993 mg, 40.5%). Recrystallization from AcOEt afforded an analytical sample, mp 167—170 °C. IR (KBr): 1661 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=6 Hz, CH_3), 1.15—1.6 (4H, m, $-CH_2CH_2CH_2CH_3$), 1.7—2.6 (4H, m, $=NCH_2CH_2-$ and piperidine H), 2.8—3.05 (2H, m, piperidine H), 3.30 (2H, t, J=7 Hz, $=NCH_2CH_2-$), 4.16 (2H, s, $C_6H_5CH_2$), 6.68 (1H, d, J=9 Hz, aromatic H), 7.0—7.5 (7H, m, aromatic H), 9.20 (1H, s, NH).

(I) Synthesis of the Other Compounds. 1-Benzyl-4-[5-chloro-2-ethylthiocarbonylaminophenyl)-1,2,5,6-tetrahydropyridine (8)——Ethyl chlorothioformate (18.5 ml, 177 mmol) was added dropwise at 0 °C over 30 min to a solution of 1-benzyl-4-(2-amino-5-chlorophenyl)-1,2,5,6-tetrahydropyridine (**7**) (26.5 g, 88.7 mmol) in pyridine (200 ml). Then, the mixture was stirred at room temperature for 2 h and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and the solution was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated *in vacuo* to give an oily residue, which was chromatographed on silica gel (AcOEt : hexane = 1 : 10, v/v) to afford **8** (13.1 g, 38.2%) as an oily product. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.5 Hz, OCH_2CH_3), 2.2—2.5 (2H, m, $>NCH_2CH_2-$), 2.71 (2H, t, J=6 Hz, $>NCH_2CH_2-$), 2.96 (2H, q, J=7.5 Hz, OCH_2CH_3), 3.05—3.25 (2H, m, $NCH_2CH=C<$), 3.66 (2H, s, $C_6H_5CH_2$), 5.65—5.8 (1H, m, $-CH=C<$), 7.05—7.5 (7H, m, aromatic H), 7.98 (1H, d, J=9 Hz, aromatic H).

1-Benzyl-4-[2-carbamoylamino-5-chlorophenyl]-1,2,5,6-tetrahydropyridine (9a)——Sodium cyanate (325 mg, 5.00 mmol) was added to a solution of **7** (745 mg, 2.49 mmol) in acetic acid (8 ml) and H_2O (2 ml), and the mixture was stirred at room temperature for 1 h, mixed with H_2O (50 ml), and made basic with concentrated aqueous NaOH.

Precipitated crystals were collected by filtration, washed with H_2O, and dried to give **9a** (788 mg, 92.6%). Recrystallization from EtOH afforded an analytical sample, mp 185—187 °C. IR (KBr): 1670 cm^{-1}.

1-Benzyl-4-[5-chloro-2-(*N*-butylcarbamoylamino)phenyl]-1,2,5,6-tetrahydropyridine (9f)——*n*-Butyl isocyanate (1.98 g, 20.0 mmol) was added to a solution of **7** (2.98 g, 10.0 mmol) in AcOEt (20 ml), and the mixture was stirred at 50 °C for 9 h, then allowed to stand at room temperature overnight. The solution was concentrated *in vacuo* and the oily residue was chromatographed on silica gel (AcOEt : hexane = 2 : 8, v/v) to afford **9f** (2.00 g, 50.3%) as crystals. Recrystallization from AcOEt–hexane gave an analytical sample, mp 61—63 °C. IR (KBr): 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J = 6 Hz, CH_3), 1.10—1.70 (4H, m, $-CH_2CH_2CH_3$), 2.2—2.5 (2H, m, $>NCH_2CH_2-$), 2.73 (2H, t, J = 6 Hz, $>NCH_2CH_2-$), 3.0—3.5 (4H, m, $>NCH_2CH=C<$, and $NHCH_2-$), 3.62 (2H, s, $C_6H_5CH_2$), 5.55—5.8 (2H, m, $-CH=C<$ and $-NHCH_2-$), 6.95—7.4 (8H, m, $-NHCO-$ and aromatic H), 8.08 (1H, d, J = 9 Hz, aromatic H).

1-Benzyl-4-[2-(*N*-substituted carbamoylamino)-5-chlorophenyl]-1,2,5,6-tetrahydropyridine (9c—e, 9g, and 9k)——These compounds were prepared in the same manner as described for **9f** from **7** except for the use of the appropriate isocyanate in the place of *n*-butyl isocyanate.

1-Benzyl-6′-chloro-3′-methyl-spiro[piperidine-4,4′(3′*H*)-quinazolin]-2′(1′*H*)-one (15)——A mixture of 1-benzyl-6′-chloro-5,6-dihydro-3-iodo-3′-methyl-spiro[pyridine-4(1*H*),4′(3′*H*)-quinazolin]-2′(1′*H*)-one (**14b**) (480 mg, 1.00 mmol) and 10% Pd–C (480 mg) in H_2O (20 ml) and MeOH (30 ml) was stirred at 40 °C under a hydrogen atmosphere for 4 h 40 min. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was mixed with H_2O, made basic with aqueous NaOH, and extracted with $CHCl_3$. The extract was concentrated *in vacuo* to give an oily residue, which was crystallized from MeOH to afford **15** (46.0 mg, 13.0%). Recrystallization from EtOH gave an analytical sample, mp 197—198 °C. *Anal.* Calcd for $C_{20}H_{22}ClN_3O$: C, 67.50; H, 6.23; N, 11.81. Found: C, 67.47; H, 6.20; N, 11.97.

1-Benzyl-6′-chloro-5,6-dihydro-3′-methyl-spiro[pyridine-4(1*H*),4′(3′*H*)-quinazolin]-2′(1′*H*)-one (16)——A mixture of 1-benzyl-6′-chloro-5,6-dihydro-3-iodo-3′-methyl-spiro[pyridine-4(1*H*),4′(3′*H*)-quinazolin]-2′(1′*H*)-one (**14b**) (240 mg, 0.500 mmol), 10% Pd–C (240 mg), and 1 N HCl (0.5 ml) in H_2O (9.5 ml) and MeOH (15 ml) was stirred at 40 °C under a hydrogen atmosphere for 17.5 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was mixed with H_2O, made basic with aqueous NaOH, and extracted with $CHCl_3$. The extract was concentrated *in vacuo* to give an oily residue, which was chromatographed on silica gel with AcOEt and crystallized from EtOH to afford **16** (39.2 mg, 22.2%), mp 167—168 °C. *Anal.* Calcd for $C_{20}H_{20}ClN_3O$: C, 67.88; H, 5.70; N, 11.88. Found: C, 67.84; H, 5.73; N, 11.83. MS *m/z*: 353 (M^+). IR (KBr): 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.7—1.8 (2H, m, piperidine H), 2.7—2.85 (2H, m, piperidine H), 3.03 (3H, s, $N-CH_3$), 4.14 (2H, s, $C_6H_5CH_2$), 4.29 (1H, q, J = 8.1 Hz, J' = 1.2 Hz, $N-CH=CH-$), 6.54 (1H, d, J = 8.1 Hz, $N-CH=CH-$), 6.70 (1H, d, J = 8.3 Hz, aromatic H), 7.08—7.41 (7H, m, aromatic H), 8.65 (1H, br s, NH).

3′-Methyl-spiro[piperidine-4,4′(3′*H*)-quinazolin]-2′(1′*H*)-one (17)——A mixture of **14b** (9.60 g, 20.0 mmol), 10% Pd–C (9.6 g) and triethylamine (27.9 ml, 200 mmol) in H_2O (400 ml) and MeOH (600 ml) was stirred at 40 °C under a hydrogen atmosphere for 16 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was mixed with H_2O, made basic with aqueous NaOH, and extracted with $CHCl_3$. The extract was concentrated *in vacuo* to give **17** (4.57 g, 98.8%) as an amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 2.0—3.2 [11H, m, piperidine H and s at δ 3.1 (NCH_3)], 6.8—7.5 (4H, m, aromatic H), 9.25 (1H, br s, NH).

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3′-methyl-spiro[piperidine-4,4′(3′*H*)-quinazolin]-2′(1′*H*)-one (3a)——A mixture of α-bromo-3,4-dimethoxyacetophenone (**19a**) (518 mg, 2.00 mmol), 3′-methyl-spiro[piperidine-4,4′(3′*H*)-quinazolin]-2′(1′*H*)-one (**17**) (462 mg, 2.00 mmol), and TEA (0.28 ml, 2.0 mmol) in EtOH (15 ml) was stirred at room temperature for 34 h. Then, $NaBH_4$ (500 mg, 13.2 mmol) was added in one portion to the stirred solution and the reaction mixture was further stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*, mixed with H_2O, and extracted with $CHCl_3$. The extract was concentrated *in vacuo* and the residue was chromatographed on silica gel (CH_2Cl_2 : MeOH = 30 : 1) to give **3a** (379 mg, 46.1%) as an amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 2.1—3.5 [13H, m, piperidine H, d at δ 2.53, J = 7 Hz, $-CH_2CH(OH)-$ and s at δ 3.13, $>NCH_3$], 3.86 and 3.88 (6H, each s, $2 \times CH_3O$), 4.71 [1H, t, J = 7 Hz, $-CH(OH)-$], 6.8—7.5 (7H, m, aromatic H), 8.6 (1H, s, NH).

1-[2-(3,4-Dimethoxyphenyl)-1-methyl-2-oxoethyl]-3′-methyl-spiro[piperidine-4,4′(3′*H*)-quinazolin]-2′(1′*H*)-one (20b)——A mixture of α-bromo-3,4-dimethoxypropiophenone (**19b**) (1.09 g, 3.99 mmol), **17** (924 mg, 3.99 mmol), NaI (600 mg, 4.00 mmol), and TEA (0.56 ml, 4.0 mmol) in EtOH (20 ml) was stirred at room temperature for 34 h. The reaction mixture was concentrated *in vacuo* and chromatographed on silica gel (CH_2Cl_2 : MeOH = 30 : 1) to give **20b** (648 mg, 38.3%) as an amorphous powder. IR (KBr): 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J = 7 Hz, $>CHCH_3$), 1.9—3.0 (9H, m, piperidine H and $>CHCH_3$), 3.10 (3H, s, NCH_3), 3.95 (6H, s, $2 \times CH_3O$), 6.7—7.9 (7H, m, aromatic H), 8.7 (1H, s, NH).

3′-Methyl-1-[2-oxo-2-(3,4,5-trimethoxyphenyl)-1-methylethyl]-spiro[piperidine-4,4′(3′*H*)-quinazolin]-2′(1′*H*)-one (20c)——A mixture of α-bromo-3,4,5-trimethoxypropiophenone (**19c**) (1.21 g, 3.99 mmol), **17** (924 mg, 3.99 mmol), NaI (600 mg, 4.00 mmol), and TEA (0.56 ml, 4.0 mmol) in EtOH (20 ml) was stirred at room temperature for 34 h. Precipitated crystals were collected by filtration, washed successively with MeOH and H_2O, and dried to give **20c** (1.06 g, 58.5%). Recrystallization from EtOH afforded an analytical sample, mp 181—186 °C. *Anal.* Calcd for

$C_{25}H_{31}N_3O_5$: C, 66.21; H, 6.89; N, 9.27. Found: C, 66.17; H, 6.97; N, 8.99. IR (KBr): 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=6 Hz, >CHC$\underline{H}_3$), 1.8—3.0 (9H, m, piperidine $\underline{H}$ and >C$\underline{H}$CH$_3$), 3.10 (3H, s, >NC$\underline{H}_3$), 3.93 and 3.90 (9H, each s, 3 × C$\underline{H}_3$O), 6.75—7.5 (6H, m, aromatic $\underline{H}$), 8.55 (1H, s, N$\underline{H}$).

***threo*-1-[2-Hydroxy-1-methyl-2-(3,4-dimethoxyphenyl)ethyl]-3′-methyl-spiro[piperidine-4,4′(3′*H*)-quinazolin]-2′(1′*H*)-one (3b)**——A stirred solution of 3′-methyl-1-[2-oxo-2-(3,4-dimethoxyphenyl)-1-methylethyl]-spiro[piperidine-4,4′(3′*H*)-quinazolin]-2′(1′*H*)-one (**20b**) (423 mg, 0.999 mmol) in dry THF (20 ml) was treated with 1 M L-Selectride/THF (3 ml) and the mixture was stirred for 1 h at room temperature. The reaction mixture, after addition of H_2O, was extracted with CH_2Cl_2. The extract was concentrated *in vacuo* and the residue was crystallized from MeOH–AcOEt to afford **3b** (205 mg, 48.2%). Recrystallization from EtOH gave an analytical sample, mp 212—214 °C. *Anal.* Calcd for $C_{24}H_{31}N_3O_4$: C, 67.73; H, 7.34; N, 9.88. Found: C, 67.63; H, 7.60; N, 9.60. IR (KBr): 1666 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 0.82 (3H, d, J=7 Hz, >CHC$\underline{H}_3$), 2.0—3.2 (12H, m, piperidine $\underline{H}$, >C$\underline{H}$CH$_3$, and s at δ 3.13, NC$\underline{H}_3$), 3.88 and 3.90 (6H, each s, 2 × C$\underline{H}_3$O), 4.25 [1H, d, J = 10 Hz, –C$\underline{H}$(OH)–], 6.8—7.5 (7H, m, aromatic $\underline{H}$), 9.0 (1H, s, N$\underline{H}$).

***threo*-1-[2-(Hydroxy-1-methyl-2-(3,4,5-trimethoxyphenyl)ethyl]-3′-methyl-spiro[piperidine-4,4′(3′*H*)-quinazolin]-2′(1′*H*)-one (3c)**——This compound (218 mg, 47.9%) was prepared from 3′-methyl-1-[2-oxo-2-(3,4,5-trimethoxyphenyl)-1-methylethyl]-spiro[piperidine-4,4′(3′*H*)-quinazolin]-2′(1′*H*)-one (**20c**) (453 mg, 0.999 mmol) as described for **3b**. mp 205—208 °C. *Anal.* Calcd for $C_{25}H_{33}N_3O_5$: C, 65.91; H, 7.30; N, 9.23. Found: C, 65.72; H, 7.55; N, 9.16. IR (KBr): 1667 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 0.90 (3H, d, J=7 Hz, >CHC$\underline{H}_3$), 2.1—3.5 (12H, m, piperidine $\underline{H}$ and s at δ 3.10, >NC$\underline{H}_3$), 3.76 and 3.85 (9H, each s, 3 × C$\underline{H}_3$O), 4.33 [1H, d, J=9 Hz, –C$\underline{H}$(OH)–], 6.62 (2H, s, aromatic $\underline{H}$), 6.85—7.5 (4H, m, aromatic $\underline{H}$), 9.30 (1H, s, N$\underline{H}$).

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