

## POLYCYCLIC N-HETERO COMPOUNDS. XXX.

## SYNTHESIS AND ANTIDEPRESSIVE EVALUATION OF 3-SUBSTITUTED

## 3,4,5,6-TETRAHYDROBENZO[h]QUINAZOLIN-4-ONES

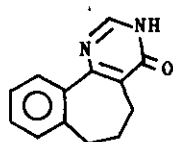
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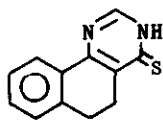
Tsushima, Okayama 700, Japan

**Abstract** - Synthesis of 3-substituted 3,4,5,6-tetrahydrobenzo[h]-quinazolin-4-ones is described. Antidepressive evaluation of these compounds was performed by antireserpine action and compounds IX and X exhibited the positive action.

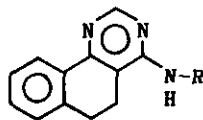
In the previous papers concerning the structure-activity relationship between antidepressive activity and azasteroidal analogs, we have reported that 3,4,6,7-tetrahydro-5H-benzo[6,7]cyclohepta[1,2-d]pyrimidin-4-one (I)<sup>1</sup> and 3,4,5,6-tetrahydrobenzo[h]quinazolin-4-thione (II)<sup>2</sup> exhibit the antireserpine action in mice. Furthermore, some 4-substituted 5,6-dihydrobenzo[h]quinazolines (III)<sup>3</sup> and 4-substituted 6,7-dihydro-5H-pyrimido[5,4-d]benzazepine (IV)<sup>4,5</sup> also showed the same action. Compounds I and II usually exist as lactam- and thiolactam-forms. These results prompted us to synthesize 3-substituted analogs of 5,6-dihydrobenzo[h]quinazolin-4-one<sup>6</sup> (V) with methyl (or ethyl) bromoacetate in the presence of triethylamine afforded 3-substituted esters (VIa,b). Ir spectra of VI showed two carbonyl



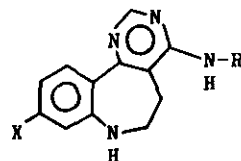
I



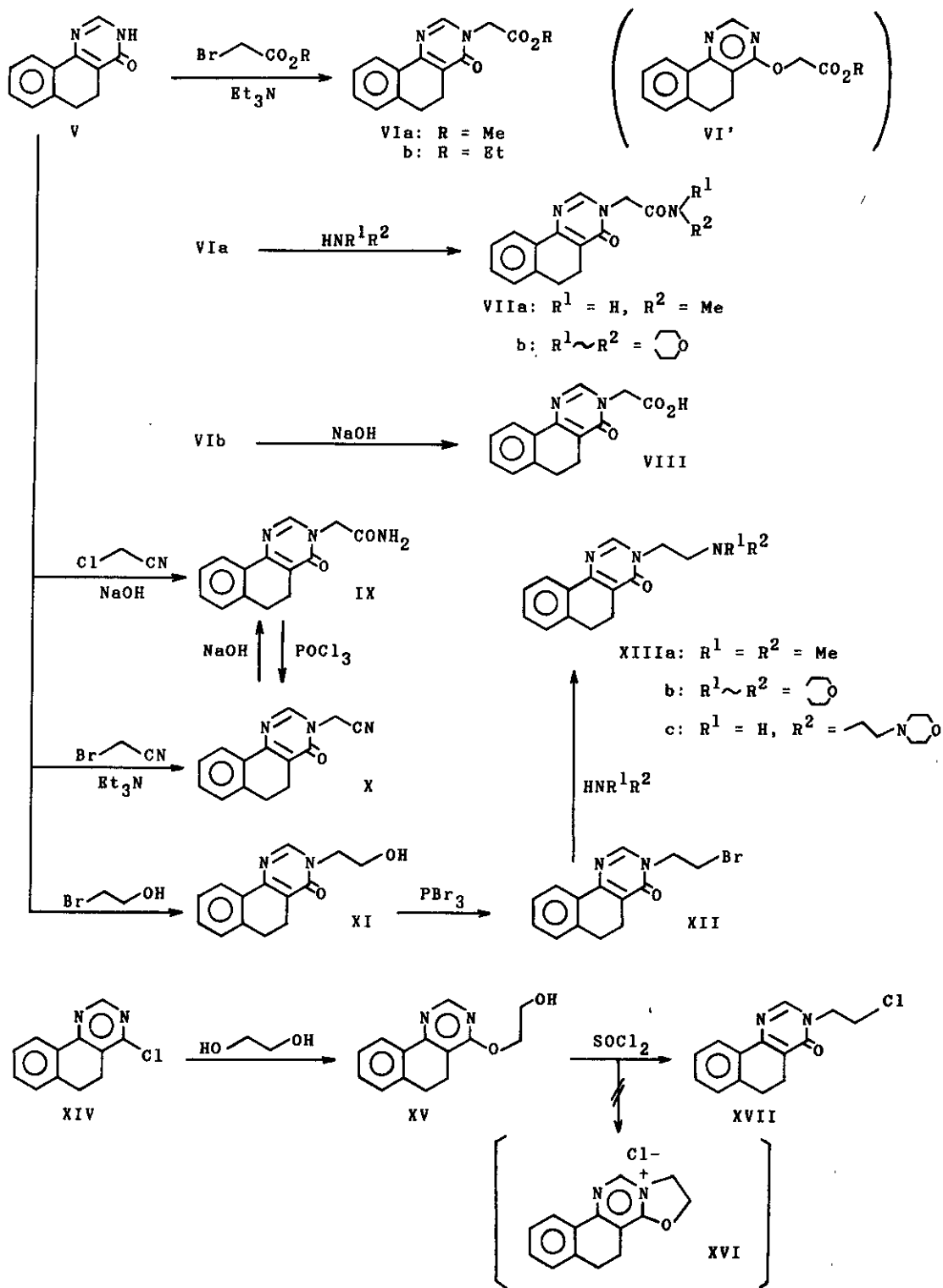
II



III



IV: X = H or Cl



Scheme 1

bands attributable to lactam ( $1638\text{ cm}^{-1}$  in VIa and  $1630\text{ cm}^{-1}$  in VIb) and ester ( $1744\text{ cm}^{-1}$  in VIa and  $1730\text{ cm}^{-1}$  in VIb) (Table I). Furthermore, nmr spectra of these esters in  $\text{CDCl}_3$  indicated pyrimidine protons at  $\delta$  8.05 ppm (VIa) and  $\delta$  8.08 ppm (VIb), individually, which also supported the lactam-form excluding the possibility of ether-form (VI'). Usually, pyrimidine proton of type III in

Table I Elemental Analyses and Ms and Ir Spectral Data of Products

Compd.	Formula	Analysis (%); Calcd. (Found)			Ms (m/z) M <sup>+</sup>	Ir <sup>a)</sup> ( $\text{cm}^{-1}$ )
		C	H	N		
VIa	$\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$	66.65 (66.72)	5.22 (5.18)	10.36 (10.26)	270	1744, 1638, 1659(sh)
VIb	$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$	67.59 (67.32)	5.67 (5.62)	9.85 (9.75)	284	1730, 1630, 1660(sh)
VIIa	$\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$	66.90 (66.76)	5.61 (5.56)	15.60 (15.51)	269	3300, 1654
VIIb	$\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_3$	66.44 (66.53)	5.88 (5.83)	12.91 (13.08)	325	1648, 1680(sh)
VIII	$\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_3$	65.61 (65.38)	4.71 (4.66)	10.93 (10.74)	256	3000-2400 1710, 1648
IX	$\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2$	65.87 (65.94)	5.13 (5.10)	16.46 (16.40)	255	3410, 3285, 1678, 1648
X	$\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}$	70.87 (70.92)	4.67 (4.55)	17.71 (17.50)	237	1640, 1660(sh)
XI	$\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2$	69.40 (69.55)	5.82 (5.83)	11.56 (11.52)	242	3220, 1660
XII	$\text{C}_{14}\text{H}_{13}\text{BrN}_2\text{O}$	55.10 (55.19)	4.29 (4.24)	9.17 (9.16)	304 <sup>b)</sup>	1646
XIIIa	$\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}$	71.34 (71.23)	7.11 (7.15)	15.60 (15.56)	269	1650
XIIIb	$\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_2 \cdot \text{HCl}$	62.15 (61.89)	6.37 (6.45)	12.08 (12.17)	311 <sup>c)</sup>	1650
XIIIC	$\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_2$	67.77 (67.91)	7.39 (7.48)	15.80 (15.79)	354	3330, 1643
XV	$\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2$	69.40 (69.53)	5.82 (5.82)	11.56 (11.60)	242	3350
XVII	$\text{C}_{14}\text{H}_{13}\text{ClN}_2\text{O}$	64.49 (64.59)	5.02 (5.01)	10.74 (10.71)	260 <sup>d)</sup>	1655

a) Absorption bands due to N-H, O-H, and/or C=O; measured in KBr disk except for XIIIa ( $\text{CHCl}_3$ ). b) Intensity ratio; m/z 304 : m/z 306 = 1 : 1. c) M<sup>+</sup> - HCl. d) Intensity ratio; m/z 260 : m/z 262 = 3 : 1.

Table II Nmr Spectral Data of Products

Compd. <sup>a)</sup>	Chemical shifts, $\delta$ (J in Hz)				
	Side chain proton	Ring proton			
		2-H <sup>b)</sup>	5,6-H	7,8,9-H <sup>c)</sup>	10-H <sup>c)</sup>
VIa	3.82(3H, s, OMe), 4.68(2H, s, CH <sub>2</sub> )	8.05	2.91(br s)	7.31	8.15
VIb	1.32 and 4.28(3H and 2H, t and q, J = 7, OEt), 4.67(2H, s, CH <sub>2</sub> )	8.08	2.92(br s)	7.30	8.14
VIIa	2.65(3H, d, J = 5, changed to singlet after addition of D <sub>2</sub> O, N-Me), 4.58(2H, s, CH <sub>2</sub> ), 8.15(1H, br, exchangeable with D <sub>2</sub> O, NH)	8.36	2.78(m)	7.34	8.09
VIIb	3.70(8H, br s, morpholine-H), 4.75(2H, s, NCH <sub>2</sub> CO)	8.12	2.90(br s)	7.29	8.17
VIII	4.77(2H, s, CH <sub>2</sub> )	8.32	2.85(m)	7.34	8.11
IX	4.59(2H, s, CH <sub>2</sub> ), 7.25 and 7.72 (each 1H, each br, exchangeable with D <sub>2</sub> O, NH <sub>2</sub> )	8.37	2.79(m)	7.33	8.06
X	4.85(2H, s, CH <sub>2</sub> )	8.20	2.92(br s)	7.33	8.15
XI	3.66(2H, q, J = 5.5, changed to triplet after addition of D <sub>2</sub> O, OCH <sub>2</sub> ), 4.00(2H, t, J = 5.5, NCH <sub>2</sub> )	8.35	2.82(m)	7.34	8.10
XII	3.76 and 4.33(each 2H, each t, J = 6, CH <sub>2</sub> CH <sub>2</sub> Br)	8.12	2.91(br s)	7.32	8.11
XIIIa	2.29(6H, s, 2 x Me), 2.63 and 4.01 (each 2H, each t, J = 6, CH <sub>2</sub> CH <sub>2</sub> N)	8.10	2.88(br s)	7.26	8.07
XIIIb <sup>d)</sup>	3.40 and 3.52(4H and 2H, each m, N(CH <sub>2</sub> ) <sub>3</sub> ), 3.92(4H, m, CH <sub>2</sub> OCH <sub>2</sub> ), 4.40(2H, t, J = 7, C=NCH <sub>2</sub> )	8.56	2.83(m)	7.37	8.06
XIIIc	2.45(6H, m, N(CH <sub>2</sub> ) <sub>3</sub> ), 2.76 and 3.08(each 2H, each t, J = 6, CH <sub>2</sub> NHCH <sub>2</sub> ), 3.67(4H, m, CH <sub>2</sub> OCH <sub>2</sub> ), 4.05(2H, t, J = 6, NCH <sub>2</sub> CH <sub>2</sub> NH)	8.16	2.91(br s)	7.32	8.13
XV	4.05 (2H, m, changed to triplet after addition of D <sub>2</sub> O, J = 5, CH <sub>2</sub> OH), 4.63(2H, t, J = 5, CH <sub>2</sub> CH <sub>2</sub> OH)	8.72	2.95(br s)	7.35	8.28
XVII	3.95 and 4.26 (each 2H, each t, J = 5, NCH <sub>2</sub> CH <sub>2</sub> Cl)	8.15	2.91(br s)	7.32	8.16

a) Measured in CDCl<sub>3</sub> except for VIIa, IX, XI and XIIIb (DMSO-d<sub>6</sub>) and VIII (MeOH-d<sub>4</sub>). b) All signals were singlet. c) All signals were multiplet. d) Measured as HCl salt.

$\text{CDCl}_3$  appears around  $\delta$  8.60 ppm<sup>3</sup> and indeed, that of compound XV appears at  $\delta$  8.72 ppm (Table II). Aminolysis of VIa with methylamine or morpholine afforded the corresponding amide (VIIa,b). Hydrolysis of VIb with sodium hydroxide gave carboxylic acid (VIII).

Reaction of V with chloroacetonitrile in the presence of sodium hydroxide in diluted 2-methoxyethanol gave 3-substituted amide (IX), which was dehydrated with phosphoryl chloride to obtain nitrile (X). The nmr spectra of IX and X showed pyrimidine protons at  $\delta$  8.37 ppm (IX, in DMSO- $d_6$ ) and  $\delta$  8.20 ppm (X) similar to those of esters (VI). While nmr and ms spectra and elemental analysis of X supported the structure in Scheme 1, apparent C $\equiv$ N band was not observed in ir spectrum. Why C $\equiv$ N absorption can not be detected is not understandable at present. However, the existence of the nitrile group was settled by the following experiments; 1) the nitrile (X) was also synthesized by treating V with bromoacetonitrile in the presence of triethylamine; 2) formation of IX was confirmed on TLC by the hydrolysis of X with sodium hydroxide (1.2 equiv.) in 2-methoxyethanol-water (4 : 1, v/v).

Next, compound V was allowed to react with 2-bromoethanol to yield hydroxyethyl derivative (XI). Treatment of XI with phosphorus tribromide gave bromoethyl derivative (XII). Instrumental data of XI and XII also indicated that they existed as lactam-form. Aminolysis of XII with dimethylamine, morpholine, or morpholinoethylamine afforded the corresponding aminoethyl derivatives

Table III Effects of IX and X on Reserpine-Induced Hypothermia in Mice

Compd.	Body temperature ( $^{\circ}\text{C}$ ) mean value $\pm$ SD				
	Before administration	Time after administration			
		30 min	1 h	2 h	4 h
saline	23.8 $\pm$ 0.4	25.4 $\pm$ 1.0	26.0 $\pm$ 1.2	27.0 $\pm$ 1.5	29.7 $\pm$ 2.4
imipramine	23.9 $\pm$ 1.1	28.1 $\pm$ 1.6*	31.5 $\pm$ 1.9**	33.7 $\pm$ 1.3**	33.2 $\pm$ 0.5*
IX	24.2 $\pm$ 0.7	27.0 $\pm$ 1.2	29.1 $\pm$ 1.1**	30.4 $\pm$ 1.7*	32.3 $\pm$ 1.9
X	24.1 $\pm$ 0.6	26.0 $\pm$ 1.2	26.8 $\pm$ 1.4	29.3 $\pm$ 0.9*	30.8 $\pm$ 2.7

Five male ICR-JCL mice weighing 20 to 29 g were used in all experiments and test compounds (10 mg/kg, *i.p.*) were injected at 18 h after reserpine (2 mg/kg, *i.p.*) was administered to mice.

Significantly different from the control (saline) at  $p < 0.05$ (\*) and  $p < 0.01$ (\*\*).

(XIIIa,b,c).

Finally, reaction of 4-chloro-5,6-dihydrobenzo[h]quinazoline<sup>6</sup> (XIV) with ethylene glycol afforded hydroxyethoxy derivative (XV), which was considered as a convenient intermediate of 15-oxa-11,13-diazasteroidal skeleton (XVI). However, cyclization of XV with thionyl chloride gave 3-(2-chloroethyl)-3,4,5,6-tetrahydrobenzo[h]quinazolin-4-one (XVII). Formation of XVII suggested that ring closure initially occurred and then ring opening resulted. Physical data of these compounds (VI - XIII, XV, and XVII) are listed in Tables I, II and IV.

Evaluation of the antidepressive activity of the above 3-substituted compounds was screened by the inhibition against reserpine-induced hypothermia in mice<sup>7</sup> and compared with that of control (saline). As shown in Table III, compounds IX and X exhibited an antireserpine action; however, these activities were weaker than that of imipramine.

#### EXPERIMENTAL

Mps were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The ir spectra were obtained with a Japan Spectroscopic A-102 diffraction grating infrared spectrophotometer. The nmr spectra were measured on a Hitachi R-22FTS FT-NMR spectrometer (90 MHz). The chemical shifts ( $\delta$ ) in ppm are measured relative to tetramethylsilane as an internal standard. The ms spectra were taken with a Shimadzu LKB-9000 instrument at 70 eV.

#### General Procedure for Preparation of VIa, VIb, X, and XI

A solution of 3 mM of V, 6 mM of Et<sub>3</sub>N, and 5 mM of halogeno compound dissolved in 30 ml of dry acetone was refluxed for an appropriate period. The precipitated crystals (Et<sub>3</sub>N·HBr) were filtered off and the filtrate was evaporated to dryness. The residue was washed with H<sub>2</sub>O to remove Et<sub>3</sub>N·HBr and recrystallized (Table IV).

#### 2-(4-Oxo-3,4,5,6-tetrahydrobenzo[h]quinazolin-3-yl)-N-methylacetamide (VIIa)

A mixture of 270 mg (1.0 mM) of VIa and 10 ml of 40% methanolic MeNH<sub>2</sub> was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was recrystallized from 50% aqueous EtOH to give 245 mg (91%) of VIIa

Table IV Reaction Times, Appearances, Melting Points, and Yields of VIa, VIb, X, and XI

Compd.	React. time (h)	Appearance (Recryst. solv.)	Mp (°C)	Yield (%)
VIa	27	colorless rhombi (benzene-cyclohexane)	196 - 198	87
VIb	34	colorless needles (benzene-CHCl <sub>3</sub> )	217 - 219	65
X	25	colorless needles (benzene-CHCl <sub>3</sub> )	214 - 216	84
XI <sup>a)</sup>	16	colorless prisms (CHCl <sub>3</sub> -EtOH)	204 - 206	85

a) Three millimoles of V and 12 mM of Et<sub>3</sub>N were dissolved in 30 mM of 2-bromoethanol.

as colorless needles, mp 259 - 261 °C (closed capillary).

2-(4-Oxo-3,4,5,6-tetrahydrobenzo[h]quinazolin-3-yl)-N,N-(3-oxapentamethylene)-acetamide (VIIb)

A mixture of 135 mg (0.5 mM) of VIa and 2 ml of morpholine was heated at 70 - 75 °C for 8 h. After evaporation of morpholine *in vacuo*, the residue was recrystallized from diluted EtOH to give 109 mg (67%) of VIIb as colorless fine needles, mp 216 - 217 °C.

2-(4-Oxo-3,4,5,6-tetrahydrobenzo[h]quinazolin-3-yl)acetic Acid (VIII)

(Hydrolysis of VIb)

To a solution of 142 mg (0.5 mM) of VIb in 5 ml of EtOH (dissolved at 60 °C and then returned to room temperature), was added 1.2 ml of 0.5 N NaOH (0.6 mM) and the solution was allowed to stand at room temperature for 1 h. After addition of 10 ml of H<sub>2</sub>O to the reaction mixture, the solution was acidified with AcOH. The mixture was condensed up to about half volume and extracted with AcOEt after salting-out. The organic layer was washed with a small amount of brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The residue was recrystallized from acetonitrile-benzene-cyclohexane to give 87 mg (67%) of VIII as colorless rhombi, mp 204 - 207 °C.

2-(4-Oxo-3,4,5,6-tetrahydrobenzo[h]quinazolin-3-yl)acetamide (IX)

A mixture of 1.98 g (10 mM) of V, 0.40 g (10 mM) of NaOH, and 1.13 g (15 mM) of

chloroacetonitrile in 40 ml of  $\text{MeOCH}_2\text{CH}_2\text{OH}-\text{H}_2\text{O}$  (1 : 1, v/v) was heated at 70 - 75 °C for 3 h. The reaction mixture was allowed to stand overnight and the precipitated crystals were collected on a filter. Subsequently, the same amounts of NaOH and chloroacetonitrile were added to the filtrate, because the starting material V remained in the filtrate (on TLC). The solution was heated at 70 - 75 °C for 4 h. After cooling of the reaction mixture, 10 ml of  $\text{H}_2\text{O}$  was added and the deposited crystals were filtered. The combined crystals were recrystallized from 70% aqueous EtOH to give 1.99 g (78%) of IX as colorless feathers, which sublimed at 260 - 280 °C, mp 291.5 - 293 °C (closed capillary).  
2-(4-Oxo-3,4,5,6-tetrahydrobenzo[h]quinazolin-3-yl)acetonitrile (X)

(Dehydration of IX)

A mixture of 255 mg (1 mM) of IX, 306 mg (2 mM) of  $\text{POCl}_3$ , and 0.5 ml of pyridine was heated at 110 - 115 °C for 3 h. After evaporation of the solvent in vacuo, the residue was basified with diluted  $\text{NaHCO}_3$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with  $\text{H}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$ , and evaporated. The residue was recrystallized from benzene-cyclohexane to give 147 mg (62%) of X as colorless needles, which was identified with the product obtained by the reaction of V with bromoacetonitrile (Table IV).

3-(2-Bromoethyl)-3,4,5,6-tetrahydrobenzo[h]quinazolin-4-one (XII)

A mixture of 1.98 g (8.2 mM) of XI, 2.65 g (9.8 mM) of  $\text{PBr}_3$ , 30 ml of dry benzene, and 20 ml of dry dioxane was refluxed for 30 h. To the reaction mixture, was added 500 ml of  $\text{H}_2\text{O}$ , and the mixture was basified with diluted  $\text{NaHCO}_3$  and extracted with  $\text{CHCl}_3$ . The organic layer was washed with  $\text{H}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$ , and evaporated to dryness. The crystalline residue was recrystallized from diluted EtOH to give 2.26 g (91%) of XII as colorless needles, mp 146 - 147 °C.

3-(2-Dimethylaminoethyl)-3,4,5,6-tetrahydrobenzo[h]quinazolin-4-one (XIIIa)

To a solution of 305 mg (1 mM) of XII dissolved in 4 ml of dioxane-MeOH (3 : 1, v/v), was added 0.5 ml (5.6 mM) of 50 % aqueous  $\text{Me}_2\text{NH}$ . The solution was allowed to stand at room temperature for 2.5 days in a sealed flask. The reaction mixture was evaporated to dryness and a small amount of  $\text{H}_2\text{O}$  was added to the residue. The solution was basified with diluted NaOH and extracted with  $\text{CHCl}_3$ . The organic layer was washed with  $\text{H}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$ , and evaporated to give 240 mg (89%) of XIIIa as brownish viscous oil.

3-(2-Morpholinoethyl)-3,4,5,6-tetrahydrobenzo[h]quinazolin-4-one (XIIIb)



A solution of 153 mg (0.5 mM) of XII and 218 mg (2.5 mM) of morpholine dissolved in 1 ml of dioxane was heated at 85 - 90 °C for 1 h. The reaction mixture was evaporated to dryness and ca. 20 ml of H<sub>2</sub>O was added to the residue. The mixture was basified with diluted NaOH and extracted with CHCl<sub>3</sub>. The organic layer was washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. Since crystallization of the oily residue was unsuccessful, it was converted to HCl salt, which was recrystallized from diluted EtOH to give 125 mg (72%) of XIIIb·HCl as colorless prisms, mp 246 - 249 °C.

3-[2-(2-Morpholinoethylamino)ethyl]-3,4,5,6-tetrahydrobenzo[h]quinazolin-4-one (XIIIc)

A mixture of 305 mg (1 mM) of XII and 780 mg (6 mM) of 4-(2-aminoethyl)-morpholine was heated at 95 °C for 2.5 h. To the reaction mixture, was added 10 ml of H<sub>2</sub>O and the mixture was extracted with CHCl<sub>3</sub>. The organic layer was washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated to dryness. The residue was chromatographed on silica gel using AcOEt-MeOH (3 : 2, v/v) as the eluent to give 246 mg (70%) of XIIIc as colorless needles from benzene-n-hexane, mp 93 - 94.5 °C.

4-(2-Hydroxyethoxy)-5,6-dihydrobenzo[h]quinazoline (XV)

A mixture of 216 mg (1 mM) of XIV, 5 ml of ethylene glycol, and 1 ml of Et<sub>3</sub>N was heated at 75 - 80 °C for 15 h. After excess of Et<sub>3</sub>N was evaporated, ca. 30 ml of H<sub>2</sub>O was added to the residue and the resulting mixture was extracted with CHCl<sub>3</sub>. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated to dryness. The residue was recrystallized from diluted EtOH to give 174 mg (72%) of XV as colorless needles, mp 77 - 78 °C.

3-(2-Chloroethyl)-5,6-dihydrobenzo[h]quinazolin-4-one (XVII)

A solution of 197 mg (0.81 mM) of XV, 0.065 ml (0.89 mM) of SOCl<sub>2</sub>, and 0.51 ml (1.1 mM) of Et<sub>3</sub>N dissolved in 10 ml of alcohol-free dry CHCl<sub>3</sub> was stirred at room temperature for 20 h. After evaporation of the solvent, the residue was recrystallized from diluted EtOH to give 107 mg (51%) of XVII as colorless feathers, mp 149 - 150 °C.

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