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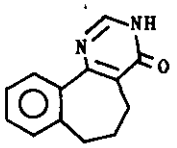
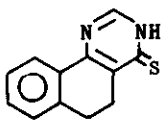
Abstract - Synthesis of 3-substituted 3,4,5,6-tetrahydrobenzo[h]-quinazolin-4-ones is described. Antidepressive evaluation of these compounds was performed by antireserpine action and compounds IX and X exhibited the positive action.

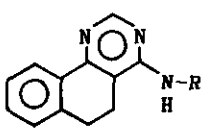
In the previous papers concerning the structure-activity relationship between antidepressive activity and azasteroidal analogs, we have reported that 3,4,6,7-tetrahydro-5H-benzo[6,7]cyclohepta[1,2-d]pyrimidin-4-one (I)[1] and 3,4,5,6-tetrahydrobenzo[h]quinazoline-4-thione (II)[2] exhibit the antireserpine action in mice. Furthermore, some 4-substituted 5,6-dihydrobenzo[h]quinazolines (III)[3] and 4-substituted 6,7-dihydro-5H-pyrimido[5,4-d]benzazepine (IV)[4,5] 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]quinazoline and to examine the antidepressive activity.
As shown in Scheme 1, reaction of 3,4,5,6-tetrahydrobenzo[h]quinazolin-4-one[6] (V) with methyl (or ethyl) bromoacetate in the presence of triethylamine afforded 3-substituted esters (VIa,b). *Ir spectra of VI showed two carbonyl*



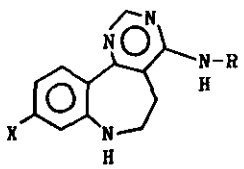
I



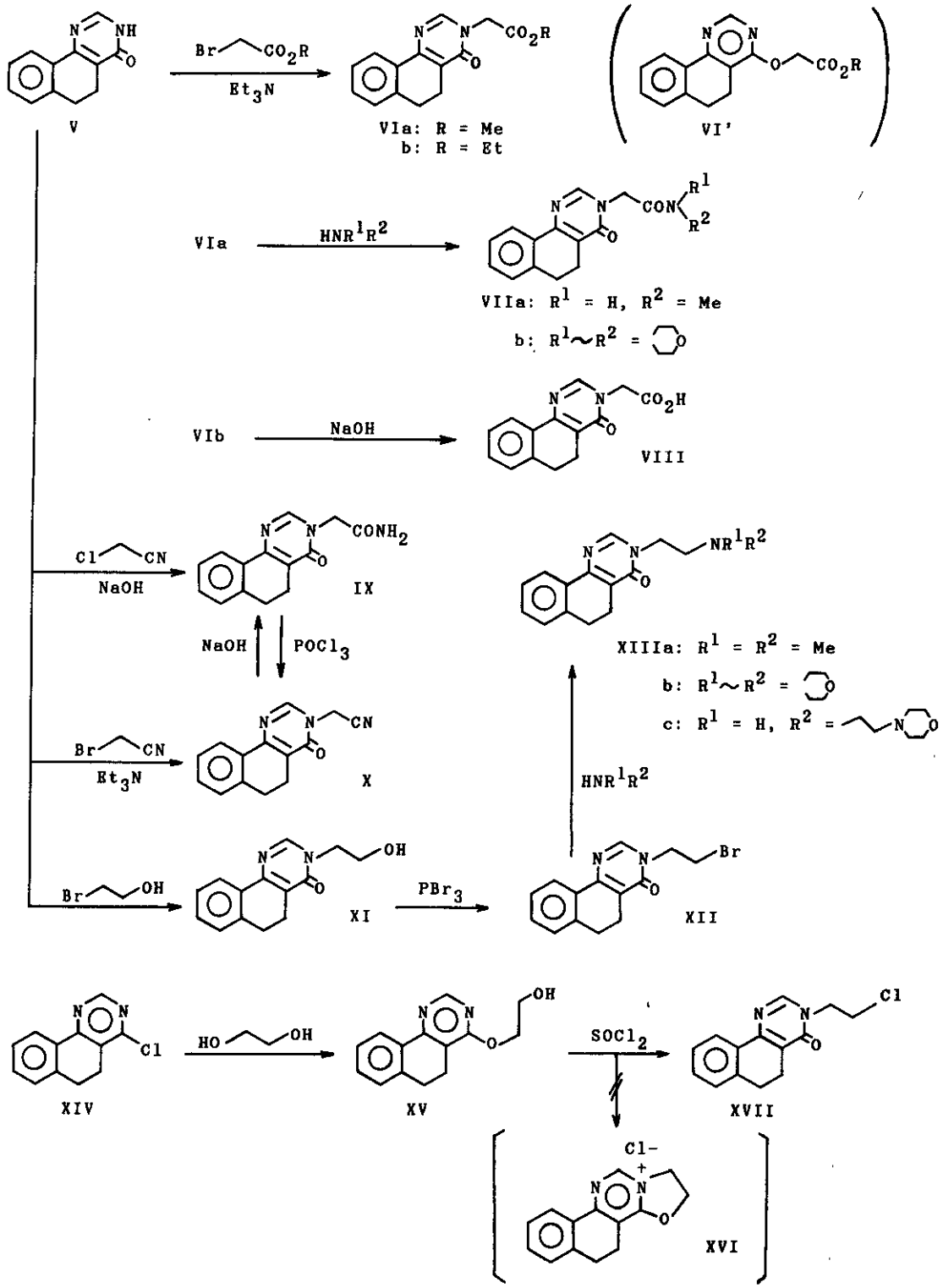
II



III



IV: X = H or Cl


V
VIa: R = Me
b: R = Et
VI'
VIa
VIIa: R1 = H, R2 = Me
b: R1~R2 =
VIb
VIII
IX
NaOH
POCl3
X
XI
PBr3
XII
XIIIa: R1 = R2 = Me
b: R1~R2 =
c: R1 = H, R2 =
HNR1R2
XIV
XV
SOCl2
XVII
XVI
Cl-

Scheme 1

bands attributable to lactam (1638 cm^{-1} in VIa and 1630 cm^{-1} in VIb) and ester (1744 cm^{-1} in VIa and 1730 cm^{-1} in VIb) (Table I). Furthermore, nmr spectra of these esters in $CDCl_3$ indicated pyrimidine protons at δ 8.05 ppm (VIa) and δ 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)	Ir[a]
		C	H	N	M^+	(cm^{-1})
VIa	$C_{15}H_{14}N_2O_3$	66.65	5.22	10.36	270	1744, 1638,
		(66.72	5.18	10.26)		1659(sh)
VIb	$C_{16}H_{16}N_2O_3$	67.59	5.67	9.85	284	1730, 1630,
		(67.32	5.62	9.75)		1660(sh)
VIIa	$C_{15}H_{15}N_3O_2$	66.90	5.61	15.60	269	3300, 1654
		(66.76	5.56	15.51)		
VIIb	$C_{18}H_{19}N_3O_3$	66.44	5.88	12.91	325	1648,
		(66.53	5.83	13.08)		1680(sh)
VIII	$C_{14}H_{12}N_2O_3$	65.61	4.71	10.93	256	3000-2400
		(65.38	4.66	10.74)		1710, 1648
IX	$C_{14}H_{13}N_3O_2$	65.87	5.13	16.46	255	3410, 3285,
		(65.94	5.10	16.40)		1678, 1648
X	$C_{14}H_{11}N_3O$	70.87	4.67	17.71	237	1640,
		(70.92	4.55	17.50)		1660(sh)
XI	$C_{14}H_{14}N_2O_2$	69.40	5.82	11.56	242	3220, 1660
		(69.55	5.83	11.52)		
XII	$C_{14}H_{13}BrN_2O$	55.10	4.29	9.17	304[b]	1646
		(55.19	4.24	9.16)		
XIIIa	$C_{16}H_{19}N_3O$	71.34	7.11	15.60	269	1650
		(71.23	7.15	15.56)		
XIIIb	$C_{18}H_{21}N_3O_2 \cdot HCl$	62.15	6.37	12.08	311[c]	1650
		(61.89	6.45	12.17)		
XIIIC	$C_{20}H_{26}N_4O_2$	67.77	7.39	15.80	354	3330, 1643
		(67.91	7.48	15.79)		
XV	$C_{14}H_{14}N_2O_2$	69.40	5.82	11.56	242	3350
		(69.53	5.82	11.60)		
XVII	$C_{14}H_{13}ClN_2O$	64.49	5.02	10.74	260[d]	1655
		(64.59	5.01	10.71)		

a) Absorption bands due to N-H, O-H, and/or C=O; measured in KBr disk except for XIIIa ($CHCl_3$). b) Intensity ratio; m/z 304 : m/z 306 = 1 : 1. c) M^+ - HCl. d) Intensity ratio; m/z 260 : m/z 262 = 3 : 1.

Table II Nmr Spectral Data of Products

Compd.[a]	Chemical shifts, δ (J in Hz)				
	Side chain proton	Ring proton			
		2-H[b]	5,6-H	7,8,9-H[c]	10-H[c]
VIa	3.82(3H, s, OMe), 4.68(2H, s, CH_2)	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_2)	8.08	2.92(br s)	7.30	8.14
VIIa	2.65(3H, d, J = 5, changed to singlet after addition of D_2O, N-Me), 4.58(2H, s, CH_2), 8.15(1H, br, exchangeable with D_2O, NH)	8.36	2.78(m)	7.34	8.09
VIIb	3.70(8H, br s, morpholine-H), 4.75(2H, s, NCH_2CO)	8.12	2.90(br s)	7.29	8.17
VIII	4.77(2H, s, CH_2)	8.32	2.85(m)	7.34	8.11
IX	4.59(2H, s, CH_2), 7.25 and 7.72 (each 1H, each br, exchangeable with D_2O, NH_2)	8.37	2.79(m)	7.33	8.06
X	4.85(2H, s, CH_2)	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_2O, OCH_2), 4.00(2H, t, J = 5.5, NCH_2)	8.35	2.82(m)	7.34	8.10
XII	3.76 and 4.33(each 2H, each t, J = 6, CH_2CH_2Br)	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_2CH_2N)	8.10	2.88(br s)	7.26	8.07
XIIIb[d]	3.40 and 3.52(4H and 2H, each m, $N(CH_2)_3$), 3.92(4H, m, CH_2OCH_2), 4.40(2H, t, J = 7, $C{=}NCH_2$)	8.56	2.83(m)	7.37	8.06
XIIIc	2.45(6H, m, $N(CH_2)_3$), 2.76 and 3.08(each 2H, each t, J = 6, $C\underline{H}_2NHC\underline{H}_2$), 3.67(4H, m, CH_2OCH_2), 4.05(2H, t, J = 6, $NC\underline{H}_2CH_2NH$)	8.16	2.91(br s)	7.32	8.13
XV	4.05 (2H, m, changed to triplet after addition of D_2O, J = 5, $C\underline{H}_2OH$), 4.63(2H, t, J = 5, $C\underline{H}_2CH_2OH$)	8.72	2.95(br s)	7.35	8.28
XVII	3.95 and 4.26 (each 2H, each t, J = 5, NCH_2CH_2Cl)	8.15	2.91(br s)	7.32	8.16

a) Measured in $CDCl_3$ except for VIIa, IX, XI and XIIIb (DMSO-d_6) and VIII (MeOH-d_4). b) All signals were singlet. c) All signals were multiplet. d) Measured as HCl salt.

$CDCl_3$ appears around δ 8.60 ppm[3] and indeed, that of compound XV appears at δ 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 δ 8.37 ppm (IX, in DMSO-d_6) and δ 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≡N band was not observed in ir spectrum. Why C≡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 (°C) mean value ± SD				
	Before administration	Time after administration			
		30 min	1 h	2 h	4 h
saline	23.8 ± 0.4	25.4 ± 1.0	26.0 ± 1.2	27.0 ± 1.5	29.7 ± 2.4
imipramine	23.9 ± 1.1	28.1 ± 1.6*	31.5 ± 1.9**	33.7 ± 1.3**	33.2 ± 0.5*
IX	24.2 ± 0.7	27.0 ± 1.2	29.1 ± 1.1**	30.4 ± 1.7*	32.3 ± 1.9
X	24.1 ± 0.6	26.0 ± 1.2	26.8 ± 1.4	29.3 ± 0.9*	30.8 ± 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[6] (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[7] and compared with that of control (saline). As shown in Table III, compounds IX and X exhibited a 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 (δ) 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_3N, and 5 mM of halogeno compound dissolved in 30 ml of dry acetone was refluxed for an appropriate period. The precipitated crystals ($Et_3N \cdot HBr$) were filtered off and the filtrate was evaporated to dryness. The residue was washed with H_2O to remove $Et_3N \cdot HBr$ 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 $MeNH_2$ 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-$CHCl_3$)	217 - 219	65
X	25	colorless needles (benzene-$CHCl_3$)	214 - 216	84
XI[a)]	16	colorless prisms ($CHCl_3$-EtOH)	204 - 206	85

a) Three millimoles of V and 12 mM of Et_3N 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_2O 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_2SO_4, 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 $MeOCH_2CH_2OH$-H_2O (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 H_2O 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 $POCl_3$, 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 $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_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 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 H_2O, and the mixture was basified with diluted $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_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 Me_2NH. 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 H_2O was added to the residue. The solution was basified with diluted NaOH and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_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_2O was added to the residue. The mixture was basified with diluted NaOH and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, 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_2O and the mixture was extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, 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_3N was heated at 75 - 80 °C for 15 h. After excess of Et_3N was evaporated, ca. 30 ml of H_2O was added to the residue and the resulting mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, 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 $SOCl_2$, and 0.51 ml (1.1 mM) of Et_3N dissolved in 10 ml of alcohol-free dry $CHCl_3$ 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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