

## Synthesis of 11,13,15-Triazasteroid with an Alkyl Group in the D-Ring and an Investigation of Its Antidepressive Activity

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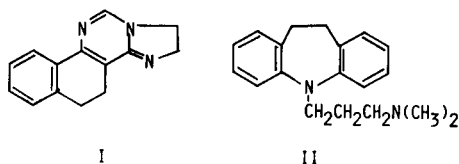
Received September 23, 1985

11,13,15-Triazasteroidal skeleton with an alkyl group in the D-ring was synthesized and it was screened for antidepressive activity. Compounds VIII<sub>d</sub> and XIII<sub>a</sub> exhibited antireserpine action.

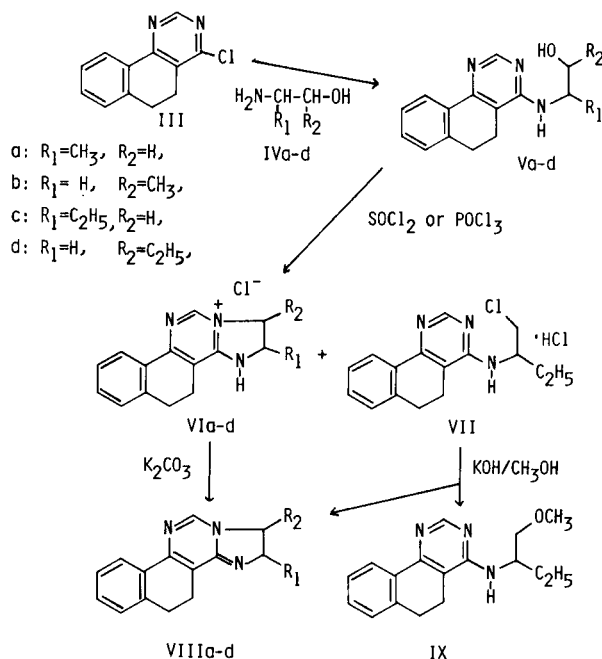
*J. Heterocyclic Chem.*, **23**, 685 (1986).

1,2,4,5-Tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (I), corresponding to 11,13,15-triazasteroidal skeleton, was originally synthesized by us [1]. Although Petridou-Fischer and Papadopoulos [2] recently synthesized the derivatives with this ring system, they did not describe about their pharmacological activities. Since the authors were interested in the pharmacological activities of compound I, random screening tests of the compound were performed in mice.

As one of the results of the tests, it was found that compound I exhibited an inhibitory action against reserpine-induced ptosis, which was used in one of the screening protocols for antidepressive activity. In further tests, it was found that compound I had an inhibitory action against reserpine-induced hypothermia and an increasing action of serotonin. These results seemed to indicate that compound I had an antidepressive activity. From the results of the above screening tests, the potency of compound I was as strong as imipramine (II), but compound I exhibited moderate toxicity in mice. The results prompted us to synthesize more effective but non-toxic derivatives with this ring system.



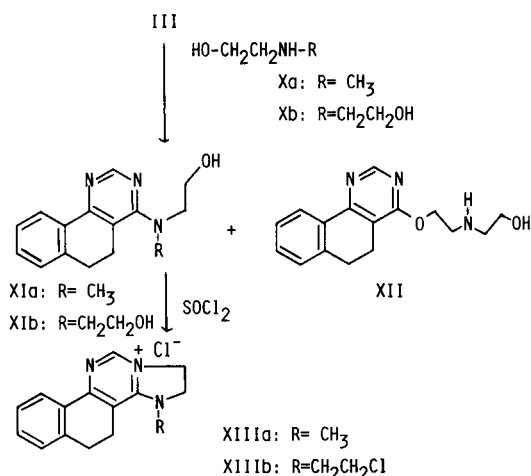
This paper deals with modification of the D-ring of the 11,13,15-triazasteroidal skeleton with alkyl group and screening of their antireserpine activities. As shown in Scheme 1, 4-chloro-5,6-dihydrobenzo[*h*]quinazoline (III) [1b] was used as a starting material. Reaction of III with excess 2-hydroxyethylamine derivatives IV<sub>a-d</sub> afforded 4-(2-hydroxyethylamino)-5,6-dihydrobenzo[*h*]quinazolines V<sub>a-d</sub> in good yield. Cyclization of V with thionyl chloride or phosphoryl chloride gave 1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazolinium chlorides (VI<sub>a-d</sub>). In the case of



Scheme 1

V<sub>c</sub> to VI<sub>c</sub>, cyclized product VI<sub>c</sub> and its intermediate, 4-(1-chloromethylpropylamino)-5,6-dihydrobenzo[*h*]quinazoline hydrochloride (VII), were obtained. A similar observation was reported by Osbond [3] who obtained 2,4-bis-(2-chloroethylamino)quinoline hydrochloride by treating 2,4-bis(2-hydroxyethylamino)quinoline with phosphoryl chloride. Compound VII could be converted to 2-ethyl-1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (VIII<sub>c</sub>) and 4-(1-methoxymethylpropylamino)-5,6-dihydrobenzo[*h*]quinazoline (IX) by heating with methanolic potassium hydroxide. Treatment of VI with potassium carbonate afforded the corresponding 1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazolines VIII<sub>a-d</sub>.

On the other hand, heating III with *N*-methyl-2-hydroxyethylamine (X<sub>a</sub>) or 2,2'-iminodiethanol (X<sub>b</sub>) gave 4-(*N*-alkyl-2-hydroxyethylamino)-5,6-dihydrobenzo[*h*]quinazolines XI<sub>a,b</sub>. In the case of the reaction of III with X<sub>b</sub>, an



Scheme 2

isomer of XIb, 4-[2-(2-hydroxyethylamino)ethoxy]-5,6-dihydrobenzo[*h*]quinazoline (XII), was simultaneously isolated as a by-product. Cyclization of XI with thionyl chloride afforded *N*-alkyl-1,2,4,5-tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazolinium chlorides XIIIa,b.

The antidepressive activity of these azasteroids was screened by the inhibition against reserpine-induced hypothermia in mice [4] and compared with that of imipramine (II).

Although compound VIII d and XIII a exhibited somewhat weaker activity than imipramine, other compounds did not. Recently, we reported two manuscripts entitled "Synthesis of the 11,13,15-Triazasteroidal Skeleton with an Oxygen Function at C-17" [5] and "Synthesis of Novel Meso-ionic Benz[*h*]imidazo[1,2-*c*]quinazoline and Benzo[*h*]pyrrolo[1',2':3,4]imidazo[1,2-*c*]quinazoline Derivatives" [6]. The compounds in these papers were screened with the same method. Meso-ionic compounds in the latter manuscript did not exhibit an inhibitory action against reserpine-induced hypothermia. While 1-acetoxy-2-benzyl-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline (No. VIII e in lit [5]) indicated antireserpine action, 2-acetyl-1-hydroxy-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline (No. VI in lit [5]) exhibited coreserpine action. Further works of this series are in progress.

## EXPERIMENTAL

Melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. Analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The ir spectra were obtained with a Nihon Bunko A-102 spectrometer and the frequencies are expressed in cm<sup>-1</sup>. The nmr spectra were measured with a Hitachi R-22FTS instrument (90 MHz for pmr and 22.6 MHz for cmr) with tetramethylsilane as an internal standard ( $\delta$  value), and the signals are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. The mass spectra (70 eV) were taken with a Shimadzu LKB-9000 spec-

trometer. The uv spectra were recorded on a Hitachi ESP-2 spectrophotometer, using spectrograde ethanol, and the results are expressed as  $\lambda$  max in nanometers (nm). IUPAC numbering is used for all compounds in the experimental section (not steroidal numbering).

### 4-(2-Hydroxy-1-methylethylamino)-5,6-dihydrobenzo[*h*]quinazoline (Va).

A mixture of 648 mg (3 mmoles) of III, 528 mg (7.2 mmoles) of DL-3-hydroxy-2-propylamine (IVa), and 3 ml of triethylamine in 5 ml of dry dioxane was refluxed for 2 days. The reaction mixture was evaporated to dryness. The resulting residue was suspended with water and extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate, and evaporated. Crystallization of the resulted pale yellow oil was unsuccessful. The oily residue was subjected to preparative tlc with silica gel (Wako-gel B5-FM, 20 cm  $\times$  20 cm  $\times$  1 mm; chloroform:ethyl acetate:methanol:acetic acid = 10:5:2:1). The pale yellow zone having Rf value ca. 0.3-0.4 gave 534 mg (70%) of Va as a pale yellow viscous oil; ir (chloroform): 3450, 3350 (br); pmr (deuteriochloroform): 1.27 (3H, d, J = 7 Hz, CH<sub>3</sub>), 2.75 (4H, m, H-5 and 6), 3.63 (2H, m, O-CH<sub>2</sub>), 4.30 (1H, m, N-CH), 4.75 and 5.3 (each 1H, m and br, NH and OH, exchanged with deuterium oxide), 7.22 (3H, m, H-7,8, and 9), 8.21 (1H, m, H-10), 8.53 (1H, s, H-2); ms: m/z 255 (M<sup>+</sup>, 73), 225 (M<sup>+</sup> - 30, 47), 224 (M<sup>+</sup> - CH<sub>2</sub>OH, 100).

Anal. Calcd. for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.85; H, 6.94; N, 16.41.

### 4-(2-Hydroxypropylamino)-5,6-dihydrobenzo[*h*]quinazoline (Vb).

A mixture of 648 mg (3 mmoles) of III and 0.62 ml (8 mmoles) of DL-2-hydroxy-1-propylamine (IVb) was heated at 100° for 3 hours. After addition of water to the reaction mixture, the deposited crystals were collected on filter and recrystallized from diluted ethanol to give 657 mg (86%) of Vb as pale yellow fine needles, mp 160-161°; ir (potassium bromide): 3350, 3150 (br); pmr (DMSO-d<sub>6</sub>): 1.10 (3H, d, J = 6 Hz, CH<sub>3</sub>), 2.80 (4H, m, H-5 and 6), 3.38 (2H, dd, J = 6 Hz and 9 Hz, N-CH<sub>2</sub>), 3.92 (1H, m, O-CH), 4.78 (1H, br, OH, exchanged with deuterium oxide), 6.83 (1H, br t, J = 6 Hz, NH, exchanged with deuterium oxide), 7.31 (3H, m, H-7,8, and 9), 8.15 (1H, m, H-10), 8.45 (1H, s, H-2); ms: m/z 255 (M<sup>+</sup>, 6), 211 (M<sup>+</sup> - 44, 60), 210 (M<sup>+</sup> - CH<sub>2</sub>-CH-OH, 100).

Anal. Calcd. for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.86; H, 6.84; N, 16.47.

### 4-(1-Hydroxymethylpropylamino)-5,6-dihydrobenzo[*h*]quinazoline (Vc).

A mixture of 1 g (4.6 mmoles) of III and 2.5 ml (26 mmoles) of DL-1-hydroxy-2-butylamine (IVc) was heated at 100° for 3.5 hours. After addition of water to the reaction mixture, the precipitated crystals were collected, washed with cold water, and recrystallized from diluted ethanol to give 1.06 g (85%) of Vc as colorless scales, mp 125-127°; ir (potassium bromide): 3350, 3150 (br); pmr (DMSO-d<sub>6</sub>): 0.90 (3H, t, J = 6 Hz, CH<sub>3</sub>), 1.45 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 2.82 (4H, m, H-5 and 6), 3.35 (3H, m, N-CH-CH<sub>2</sub>-O), 4.76 and 6.81 (each 1H, m, OH and NH, exchanged with deuterium oxide), 7.32 (3H, m, H-7,8, and 9), 8.16 (1H, m, H-10), 8.43 (1H, s, H-2); ms: m/z 269 (M<sup>+</sup>, 5), 239 (M<sup>+</sup> - 30, 49), 238 (M<sup>+</sup> - CH<sub>2</sub>OH, 100).

Anal. Calcd. for C<sub>16</sub>H<sub>19</sub>N<sub>3</sub>O: C, 71.34; H, 7.11; N, 15.60. Found: C, 71.24; H, 7.16; N, 15.67.

### 4-(2-Hydroxybutylamino)-5,6-dihydrobenzo[*h*]quinazoline (Vd).

A mixture of 1 g (4.6 mmoles) of III and 2.5 g (28 mmoles) of DL-2-hydroxybutylamine (IVd) was heated at 100° for 8 hours. After addition of water to the reaction mixture, the precipitated crystals were collected, washed with cold water, and recrystallized from diluted ethanol to give 888 mg (71%) of Vd as colorless fine needles, mp 120-122°; ir (potassium bromide): 3350, 3150 (br); pmr (DMSO-d<sub>6</sub>): 0.87 (3H, d, J = 6 Hz, CH<sub>3</sub>), 1.62 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 2.80 (4H, m, H-5 and 6), 3.47 (2H, m, N-CH<sub>2</sub>), 4.13 (1H, m, O-CH), 4.65 and 6.34 (each 1H, m, OH and NH, exchanged with deuterium oxide), 7.31 (3H, m, H-7,8, and 9), 8.13 (1H, m, H-10), 8.41 (1H, s, H-2); ms: m/z 269 (M<sup>+</sup>, 5), 240 (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>, 12), 222 (240 - H<sub>2</sub>O, 17), 211 (M<sup>+</sup> - 58, 72), 210 (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>-CH-OH, 100).

Anal. Calcd. for C<sub>16</sub>H<sub>19</sub>N<sub>3</sub>O: C, 71.34; H, 7.11; N, 15.60. Found: C, 71.46; H, 7.14; N, 15.64.

## 2-Methyl-1,2,4,5-tetrahydrobenz[h]imidazo[1,2-c]quinazolinium Chloride (VIa).

A solution of 617 mg (2.4 mmoles) of Va and 1.9 ml (26 mmoles) of thionyl chloride in 10 ml of dry, alcohol-free chloroform was stirred at room temperature for 1 hour. The reaction mixture was evaporated to dryness and the residue was treated with about 10 ml of water. After evaporation of the mixture, the resulting crystals were recrystallized from ethanol-acetone to give 394 mg (58%) of VIa as colorless granules, mp 280-284° dec; ir (potassium bromide): 2685 (br), 1640; pmr (DMSO-d<sub>6</sub>): 1.42 (3H, d, J = 7 Hz, CH<sub>3</sub>), 2.95 (4H, s, H-4 and 5), 4.33-4.95 (3H, m, H-1 and 2), 7.45 (3H, m, H-6,7, and 8), 8.16 (1H, m, H-9), 8.83 (1H, s, H-11); uv: 259 (log ε 3.95), 273 (3.79), 290 (3.69), 310 (shoulder), 326 (3.49), 338 (3.52), 345 (shoulder); ms: m/z 237 (M - HCl, 88), 223 (237 - 14, 50), 222 (237 - CH<sub>3</sub>, 100).

Anal. Calcd. for C<sub>15</sub>H<sub>16</sub>ClN<sub>3</sub>: C, 65.81; H, 5.85; N, 15.36. Found: C, 65.58; H, 5.95; N, 15.31.

## 1-Methyl-1,2,4,5-tetrahydrobenz[h]imidazo[1,2-c]quinazolinium Chloride (VIb).

A solution of 365 mg (1.6 mmoles) of Vb and 0.93 ml (10 mmoles) of phosphoryl chloride in 10 ml of dry, alcohol-free chloroform was refluxed for 3 hours. After cooling, the reaction mixture was evaporated to dryness and the resulting residue was treated with water. After evaporation of water, the crystals thus obtained were recrystallized from ethanol to give 283 mg (73%) of VIb as colorless granules, mp 189-190°; ir (potassium bromide): 2695 (br), 1650; pmr (DMSO-d<sub>6</sub>): 1.62 (3H, d, J = 7 Hz, CH<sub>3</sub>), 2.92 (4H, m, H-4 and 5), 3.67 and 4.20 (each 1H, m, H-2), 5.0 (1H, br, H-1), 7.43 (3H, m, H-6,7, and 8), 8.10 (1H, br s, NH, exchanged with deuterium oxide), 8.16 (1H, m, H-9), 8.83 (1H, s, H-11); uv: 258 (log ε, 3.98), 285 (3.76), 310 (shoulder), 328 (3.55), 340 (3.56); ms: m/z 237 (M - HCl, 95), 236 (237 - H, 100), 222 (237 - CH<sub>3</sub>, 26).

Anal. Calcd. for C<sub>15</sub>H<sub>16</sub>ClN<sub>3</sub>: C, 65.81; H, 5.85; N, 15.36. Found: C, 65.48; H, 5.94; N, 15.30.

## Reaction of Vc with Thionyl Chloride.

A solution of 800 mg (2.97 mmoles) of Vc and 0.27 ml (3.3 mmoles) of thionyl chloride in 15 ml of dry, alcohol-free chloroform was stirred at room temperature for 7 hours. After evaporation of the reaction mixture, the crystalline residue was recrystallized from ethanol to afford 427 mg (45%) of 2-ethyl-1,2,4,5-tetrahydrobenz[h]imidazo[1,2-c]quinazolinium chloride (VIc) as colorless granules, mp 267-270° dec; ir (potassium bromide): 2700 (br), 1640; pmr (DMSO-d<sub>6</sub>): 0.95 (3H, t, J = 7 Hz, CH<sub>3</sub>), 2.04 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 2.95 (4H, br s, H-4 and 5), 3.79 (1H, dd, J = 7 Hz and 10 Hz, H-1), 4.17 (1H, t, J = 10 Hz, H-1), 5.03 (1H, m, H-2), 7.47 (3H, m, H-6,7, and 8), 8.16 (1H, m, H-9), 8.99 (1H, s, H-11), 10.95 (1H, br, NH, exchanged with deuterium oxide); uv: 256 (log ε 4.13), 270 (4.04), 290 (3.80), 323 (3.55), 340 (3.60); ms: m/z 251 (M - HCl, 15), 222 (251 - C<sub>2</sub>H<sub>5</sub>, 100).

Anal. Calcd. for C<sub>16</sub>H<sub>18</sub>ClN<sub>3</sub>: C, 66.77; H, 6.30; N, 14.60. Found: C, 66.70; H, 6.34; N, 14.70.

After evaporation of the mother liquor of VIc, the residue was repeatedly recrystallized from diluted ethanol to give 239 mg (25%) of 4-(1-chloromethylpropylamino)-5,6-dihydrobenzo[h]quinazoline hydrochloride (VII) as pale yellow fine needles, mp 171-173°; ir (potassium bromide): 3220, 1635; pmr (DMSO-d<sub>6</sub>): 1.05 (3H, t, J = 6 Hz, CH<sub>3</sub>), 1.81 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 3.01 (4H, s, H-5 and 6), 4.05 (2H, br d, J = 6 Hz, CH<sub>2</sub>Cl), 4.40 (1H, m, N-CH), 7.35 (3H, m, H-7,8, and 9), 8.50 (1H, m, 10-H), 8.70 (1H, s, H-2), 8.80 (1H, m, NH, exchanged with deuterium oxide); uv: 249 (log ε 4.01), 298 (3.71), 312 (3.77), 322 (3.77), 339 (shoulder); ms: m/z 289 (M - HCl + 2, 13), 287 (M - HCl, 37), 252 (287 - Cl, 47), 251 (287 - HCl, 53), 222 (251 - C<sub>2</sub>H<sub>5</sub>); Beilstein test and silver nitrate test: positive.

Anal. Calcd. for C<sub>16</sub>H<sub>18</sub>ClN<sub>3</sub>·HCl: C, 59.25; H, 5.86; N, 12.96. Found: C, 59.27; H, 5.97; N, 12.98.

## 1-Ethyl-1,2,4,5-tetrahydrobenz[h]imidazo[1,2-c]quinazolinium Chloride (VIId).

A solution of 800 mg (2.97 mmoles) of Vd and 0.24 ml (3.2 mmoles) of thionyl chloride in 15 ml of dry, alcohol-free chloroform was stirred at

room temperature for 12 hours. The reaction mixture was evaporated and a small amount of water was added to the oily residue. After removal of water, the resulting crystalline residue was recrystallized from ethanol to give 441 mg (52%) of VIId as colorless granules, mp 257-260°; ir (potassium bromide): 2700 (br), 1645; pmr (DMSO-d<sub>6</sub>): 0.98 (3H, d, J = 7 Hz, CH<sub>3</sub>), 1.76 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 2.96 (4H, s, H-4 and 5), 4.40 (2H, m, H-2), 4.73 (1H, m, H-1), 7.45 (3H, m, H-6,7, and 8), 8.15 (1H, m, H-9), 8.85 (1H, s, H-11); uv: 260 (log ε 4.19), 272 (4.10), 290 (shoulder), 325 (3.61), 340 (3.60), 355 (3.64); ms: m/z 251 (M - HCl, 17), 222 (251 - C<sub>2</sub>H<sub>5</sub>, 100).

Anal. Calcd. for C<sub>16</sub>H<sub>18</sub>ClN<sub>3</sub>: C, 66.77; H, 6.30; N, 14.60. Found: C, 66.66; H, 6.32; N, 14.58.

## General Procedure for the Conversion of VI to VIII.

A solution of VI in a small amount of water was basified with 10% aqueous potassium carbonate and extracted with chloroform. The extract was washed with brine, dried over sodium sulfate, and evaporated to give crude VIII.

## 2-Methyl-1,2,4,5-tetrahydrobenz[h]imidazo[1,2-c]quinazoline (VIIIa).

This compound was purified by preparative tlc on silica gel (Wako-gel B5-FM, 20 cm × 20 cm × 1 mm; chloroform:acetone:methanol = 10:5:1). The zone with Rf value ca. 0.05-0.15 gave pure VIIIa (68%) as a yellow viscous oil; pmr (deuteriochloroform): 1.39 (3H, d, J = 7 Hz, CH<sub>3</sub>), 2.82 (2H, m, H-4 and 5), 3.63 (1H, m, H-2), 4.25 (2H, m, H-1), 7.26 (3H, m, H-6,7, and 8), 7.83 (1H, s, H-11), 8.05 (1H, m, H-9); uv: 235 (log ε 3.68), 242 (3.84), 262 (4.13), 271 (4.11), 292 (shoulder), 302 (shoulder), 325 (4.28), 340 (3.37), 355 (shoulder); ms: m/z 237 (M<sup>+</sup>, 38), 236 (M<sup>+</sup> - H, 14), 222 (M<sup>+</sup> - CH<sub>3</sub>, 100).

Anal. Calcd. for C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.71; H, 6.41; N, 17.75.

## 1-Methyl-1,2,4,5-tetrahydrobenz[h]imidazo[1,2-c]quinazoline (VIIIb).

This compound was purified by formation of picrate, which was recrystallized from acetone, yellow needles (89%), mp 224-226° dec.

The picrate of VIIIb was treated with aqueous ammonia and the resulting suspension was extracted with chloroform. The extract was successively washed with aqueous ammonia, water, and brine. The chloroform layer was dried over sodium sulfate and evaporated to afford pure VIIIb (87%) as a yellow oil; pmr (deuteriochloroform): 1.50 (3H, d, J = 6 Hz, CH<sub>3</sub>), 2.83 (4H, m, H-4 and 5), 3.63 (1H, m, H-2), 4.30 (2H, m, H-1 and 2), 7.29 (3H, m, H-6,7, and 8), 7.84 (1H, s, H-11), 8.05 (1H, m, H-9); uv: 262 (log ε 4.14), 271 (4.11), 290 (shoulder), 328 (3.36), 340 (3.37), 355 (shoulder); ms: m/z 237 (M<sup>+</sup>, 99), 236 (M<sup>+</sup> - H, 100), 222 (M<sup>+</sup> - CH<sub>3</sub>, 28).

Anal. Calcd. for C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.62; H, 6.11; N, 17.54.

## 2-Ethyl-1,2,4,5-tetrahydrobenz[h]imidazo[1,2-c]quinazoline (VIIIc).

This compound was purified by recrystallization from n-hexane to give pure VIIIc as pale yellow granules, mp 81-82°; pmr (deuteriochloroform): 1.00 (3H, t, J = 7 Hz, CH<sub>3</sub>), 1.81 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 2.83 (4H, m, H-4 and 5), 3.82 (1H, m, H-1), 4.21 (2H, m, H-1 and 2), 7.26 (3H, m, H-6,7, and 8), 7.82 (1H, s, H-11), 8.03 (1H, m, H-9); uv: 263 (log ε 4.26), 270 (4.26), 291 (shoulder), 303 (shoulder), 340 (3.27), 355 (shoulder); ms: m/z 251 (M<sup>+</sup>, 63), 250 (M<sup>+</sup> - H, 41), 222 (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>, 100).

Anal. Calcd. for C<sub>16</sub>H<sub>17</sub>N<sub>3</sub>·H<sub>2</sub>O: C, 71.34; H, 7.11; N, 15.60. Found: C, 70.97; H, 6.80; N, 15.44.

## 1-Ethyl-1,2,4,5-tetrahydrobenz[h]imidazo[1,2-c]quinazoline (VIIId).

This compound was purified by preparative tlc on silica gel (Wako-gel B5-FM, 20 cm × 20 cm × 1 mm; chloroform:acetone:methanol = 10:5:1). The zone with Rf value ca. 0.05-0.15 afforded pure VIIIId (69%) as a yellow oil; pmr (deuteriochloroform): 1.00 (3H, t, J = 7 Hz, CH<sub>3</sub>), 1.82 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 2.82 (4H, m, H-4 and 5), 3.77 (1H, m, H-2), 4.21 (2H, m, H-1 and 2), 7.23 (3H, m, H-6,7, and 8), 7.82 (1H, s, H-11), 8.03 (1H, m, H-9); uv: 235 (log ε 3.70), 262 (4.15), 271 (4.14), 292 (shoulder), 302 (shoulder), 325 (3.17), 340 (3.26), 355 (shoulder); ms: m/z 251 (M<sup>+</sup>, 62), 250 (M<sup>+</sup> - H, 42), 222 (M<sup>+</sup> - C<sub>2</sub>H<sub>5</sub>, 100).

*Anal. Calcd.* for  $C_{16}H_{17}N_3 \cdot \frac{1}{2}H_2O$ : C, 73.81; H, 6.97; N, 16.14. *Found:* C, 74.14; H, 6.97; N, 16.28.

#### Treatment of VII with Methanolic Potassium Hydroxide.

To a solution of 112 mg (2 mmoles) of potassium hydroxide in 20 ml of methanol, was added 145 mg (0.45 mmole) of VII and the solution was refluxed for 1.5 days. The reaction mixture was concentrated to about 5 ml under reduced pressure and poured into ice-cold water. The resultant suspension was extracted with chloroform. The chloroform layer was washed with brine, dried over sodium sulfate, and evaporated to dryness to give a yellow oil. Since the oil showed two spots on tlc, separation was carried out by preparative tlc on silica gel (Wako-gel B5-FM, 20 cm  $\times$  20 cm  $\times$  1 mm; chloroform:acetone:methanol = 10:5:1). The more polar fraction with Rf value ca. 0.08-0.18 was collected and recrystallized from *n*-hexane to give 51 mg (41%) of VIIIc as pale yellow granules, mp 81-82°; identical with the above product VIIIc (mixed mp, tlc, and instrumental data).

The less polar fraction with Rf value ca. 0.55-0.65 gave 56 mg (44%) of 4-(1-methoxymethylpropylamino)-5,6-dihydrobenzo[h]quinazoline (IX) as colorless fine needles, mp 75-77°; ir (potassium bromide): 3275; pmr (deuterioacetone): 0.95 (3H, t, J = 7 Hz, CH<sub>3</sub>), 1.66 (2H, m, CH<sub>2</sub>CH<sub>3</sub>), 2.96 (4H, m, H-5 and 6), 3.33 (3H, s, OCH<sub>3</sub>), 3.56 (2H, d, J = 5 Hz, CH<sub>2</sub>-O), 4.54 (1H, br, N-CH), 5.75 (1H, br, NH, exchanged with deuterium oxide), 7.40 (3H, m, H-7,8, and 9), 8.27 (1H, m, H-10), 8.46 (1H, s, H-2); uv: 250 (log  $\epsilon$  4.44), 292 (3.76), 315 (3.91), 330 (shoulder); ms: m/z 283 (M<sup>+</sup>, 4), 251 (M<sup>+</sup> - CH<sub>3</sub>OH, 36), 250 (M<sup>+</sup> - 33, 41), 238 (M<sup>+</sup> - CH<sub>2</sub>OCH<sub>3</sub>, 55), 236 (M<sup>+</sup> - 49, 77), 222 (251 - C<sub>2</sub>H<sub>5</sub>, 100).

*Anal. Calcd.* for  $C_{17}H_{21}N_3O$ : C, 72.05; H, 7.47; N, 14.83. *Found:* 71.74; H, 7.39; N, 14.64.

#### 4-(N-Methyl-2-hydroxyethylamino)-5,6-dihydrobenzo[h]quinazoline (XIa).

A mixture of 648 mg (3 mmoles) of III and 0.63 ml (8 mmoles) of 2-hydroxy-*N*-methyl ethylamine (Xa) was heated at 100° for 3 hours. After addition of water to the reaction mixture, the suspension was extracted with chloroform. The chloroform layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography on silica gel (Wako-gel C-200). After elution of benzene-dichloromethane gradient, the eluate of chloroform-acetone (9:1) was recrystallized from benzene-cyclohexane to give 500 mg (65%) of XIa as pale yellow granules, mp 64-65°; ir (potassium bromide): 3300; pmr (deuteriochloroform): 2.89 (4H, s, H-5 and 6), 3.10 (3H, s, N-CH<sub>3</sub>), 3.67 and 3.92 (each 2H, t, J = 5 Hz, N-CH<sub>2</sub>-CH<sub>2</sub>-O), 5.25 (1H, br, s, OH, exchanged with deuterium oxide), 7.35 (3H, m, H-7,8, and 9), 8.20 (1H, m, H-10), 8.61 (1H, s, H-2); ms: m/z 255 (M<sup>+</sup>, 9), 225 (M<sup>+</sup> - 31, 71), 224 (M<sup>+</sup> - CH<sub>2</sub>OH, 100).

*Anal. Calcd.* for  $C_{15}H_{17}N_3O$ : C, 70.56; H, 6.71; N, 16.46. *Found:* C, 70.80; H, 6.80; N, 16.36.

#### Reaction of III with 2,2'-Iminodiethanol (Xb).

A solution of 2.16 g (10 mmoles) of III and 5.26 g (50 mmoles) of 2,2'-iminodiethanol (Xb) in 2 ml of dry dioxane was heated at 90° for 4 hours. After addition of water to the reaction mixture, the resulting suspension was extracted with chloroform. The organic layer was washed with brine, dried over sodium sulfate, and evaporated. The brown oily residue was separated by column chromatography on silica gel (Wako-gel C-200). After elutions with ethyl acetate, the eluate of ethyl acetate-methanol (9:1) was recrystallized from cyclohexane-methyl acetate to give 1.37 g (48%) of 4-[bis(2-hydroxyethyl)amino]-5,6-dihydrobenzo[h]quinazoline (XIb) as colorless prisms, mp 93-94°; ir (potassium bromide): 3350; pmr (deuteriochloroform): 2.84 (4H, s, H-4 and 5), 3.73 (8H, m, N(CH<sub>2</sub>CH<sub>2</sub>O)<sub>2</sub>), 4.3 and 5.4 (each 1H, br, s, br, OH  $\times$  2, exchanged with deuterium oxide), 7.30 (3H, m, H-7,8, and 9), 8.18 (1H, m, H-10), 8.61 (1H, s, H-2); cmr (deuteriochloroform): 24.44 and 27.78 (each t, C-5 and 6), 52.5 (t, N-CH<sub>2</sub>  $\times$  2), 60.42 (t, O-CH<sub>2</sub>  $\times$  2), 115.86 (s, C-4a), 125.58, 127.25, and 130.31 (each d, C-7,8,9, and 10, a signal at 127.25 ppm exhibited two carbons), 133.36 and 138.08 (each s, C-6a and C-10a), 154.75 (s, C-2), 159.19 (d, C-10b), 163.78 (s, C-4); ms: m/z 285 (M<sup>+</sup>, 1), 284 (M<sup>+</sup> - H, 2), 267

(M<sup>+</sup> - H<sub>2</sub>O, 4), 266 (284 - H<sub>2</sub>O, 4), 254 (M<sup>+</sup> - CH<sub>2</sub>OH, 83), 236 (254 - H<sub>2</sub>O, 72), 222 (236 - CH<sub>2</sub>, 100).

*Anal. Calcd.* for  $C_{16}H_{19}N_3O_2$ : C, 67.34; H, 6.71; N, 14.73. *Found:* C, 66.98; H, 6.70; N, 14.71.

Continuous elution of column chromatography with ethyl acetate-methanol (9:1) gave 4-[2-(2-hydroxyethylamino)ethoxy]-5,6-dihydrobenzo[h]quinazoline (XII), which was recrystallized from methyl acetate-cyclohexane to give as colorless prisms, mp 58-60°; ir (potassium bromide): 3350 (br); pmr (deuteriochloroform): 2.78 and 3.09 (each 2H, t, J = 6 Hz, N-CH<sub>2</sub>  $\times$  2), 2.90 (4H, s, H-5 and 6), 3.25 (2H, br s, NH and OH, exchanged with deuterium oxide), 3.69 and 4.55 (each 2H, t, J = 6 Hz, O-CH<sub>2</sub>  $\times$  2), 7.30 (3H, m, H-7,8, and 9), 8.24 (1H, m, H-10), 8.65 (1H, s, H-2); cmr (deuteriochloroform): 19.72 and 27.22 (each t, C-5 and 6), 47.92 and 50.97 (each t, CH<sub>2</sub>NHCH<sub>2</sub>), 59.72 (t, CH<sub>2</sub>-OH), 64.86 (t, O-CH<sub>2</sub>), 114.89 (s, C-4a), 125.58, 127.25, 128.22, and 130.72 (each d, C-7,8,9, and 10), 132.39 and 138.78 (each s, C-6a and 10a), 155.72 (d, C-2), 159.19 (s, C-10b), 166.14 (s, C-4); ms: m/z 267 (M<sup>+</sup> - H<sub>2</sub>O, 2), 254 (M<sup>+</sup> - CH<sub>2</sub>OH, 14), 225 (254 - CH<sub>2</sub>NH, 29), 211 (225 - CH<sub>2</sub>, 40), 199 (M<sup>+</sup> - 86, 100), 197 (211 - CH<sub>2</sub>, 46).

*Anal. Calcd.* for  $C_{16}H_{19}N_3O_2$ : C, 67.34; H, 6.71; N, 14.73. *Found:* C, 67.08; H, 6.64; N, 14.99.

#### 3-Methyl-1,2,4,5-tetrahydrobenz[h]imidazo[1,2-c]quinazolinium Chloride (XIIIa).

A solution of 460 mg (1.8 mmoles) of XIa and 1.2 ml (13.9 mmoles) of thionyl chloride in 20 ml of dry, alcohol-free chloroform was stirred at room temperature for 1 hour. The precipitated crystals were collected by filtration and recrystallized from ethanol-acetone to afford 187 mg (38%) of XIIIa as colorless granules, mp 235-238°; pmr (DMSO-d<sub>6</sub>): 3.06 (4H, m, H-4 and 5), 3.42 (3H, s, N-CH<sub>3</sub>), 4.07 and 4.67 (each 2H, br t, J = 10 Hz, H-1 and 2), 7.48 (3H, m, H-6,7, and 8), 8.17 (1H, m, H-9), 8.93 (1H, s, H-11); uv: 255 (log  $\epsilon$  3.54), 258 (4.06), 264 (4.09), 288 (3.89), 342 (3.68); ms: m/z 238 (M - Cl, 29), 210 (238 - CH<sub>2</sub>CH<sub>2</sub>, 100).

*Anal. Calcd.* for  $C_{15}H_{16}ClN_3 \cdot H_2O$ : C, 61.85; H, 6.18; N, 14.43. *Found:* C, 62.18; H, 6.19; N, 14.44.

#### 3-(2-Chloroethyl)-1,2,4,5-tetrahydrobenz[h]imidazo[1,2-c]quinazolinium Chloride (XIIIb).

A mixture of 1.02 g (3.58 mmoles) of XIb and 10 ml (138 mmoles) of thionyl chloride was gently boiled for 4 hours. After evaporation of thionyl chloride, the resulting oily residue was triturated with ether and the crystalline product was recrystallized from water to yield 419 mg (65%) of XIIIb as colorless granules, mp 213-215°; pmr (deuterioethanol): 3.11 (4H, H-4 and 5), 4.0-4.3 (6H, m, N-CH<sub>2</sub>  $\times$  2, CH<sub>2</sub>Cl), 4.75 (2H, m, N-CH<sub>2</sub>), 7.39 (3H, m, H-6,7, and 8), 8.24 (1H, m, H-9), 8.72 (1H, s, H-11); uv: 262 (log  $\epsilon$  4.01), 285 (3.86), 347 (3.53); ms: m/z 285 (M - HCl, 2), 222 (285 - CH<sub>2</sub>CH<sub>2</sub>Cl, 100).

*Anal. Calcd.* for  $C_{16}H_{17}Cl_2N_3$ : C, 53.78; H, 5.90; N, 11.76. *Found:* C, 54.03; H, 5.64; N, 11.49.

#### Acknowledgement.

We wish to thank Mrs. M. Aiki for micro analyses.

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