Polycyclic *N*-Heterocyclic Compounds. XLV. Synthesis of 4-Substituted 5,6-Dihydrobenzo[*h*]quinazolines and 6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines and their Inhibitory Activity on Platelet Aggregation

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The synthesis of 4-substituted 5,6-dihydrobenzo[*h*]quinazolines and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta-[1,2-*d*]pyrimidines with substituents which are an electron-attracting group such as a nitrile, an amide, a thione, or a carboxyl group is described. Their inhibitory activity against collagen-induced platelet aggregation was also investigated.

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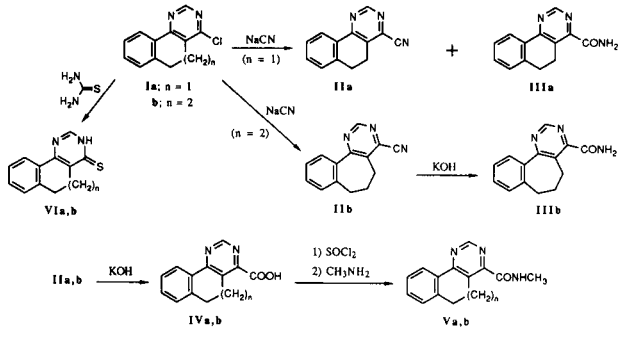
In previous papers [2], we reported that some 5,6-dihydrobenzo[*h*]quinazolines and 6,7-dihydro-5*H*-benzo[6,7]-cyclohepta[1,2-*d*]pyrimidines which have monoalkylamino, dialkylamino, or an amino acid group on their 4-position showed more potent inhibitory activity against collagen-induced platelet aggregation than that of aspirin. In these compounds, the nitrogen atom of the amino acid or the alkylamino group is attached to the carbon atom at the 4-position of their nucleus.

As a part of the investigation of the structure-activity relationship of the above compounds, this paper deals with the synthesis of 4-substituted 5,6-dihydrobenzo[*h*]quinazolines and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines which have a substituent at 4-position and is linked to the nucleus with a C-C or a C-S bond and decreases the electron density of the carbon atom at the 4-position. Evaluation of these compounds for inhibitory activity against collagen-induced platelet aggregation is also described.

As shown in the Scheme, 4-chloro-5,6-dihydrobenzo[*h*]-quinazoline **Ia** [3] was used as the starting material. 4-(5,6-Dihydrobenzo[*h*]quinazoline)carbonitrile **IIa** was prepared by the reaction of **Ia** with sodium cyanide in dimethyl sulfoxide (DMSO) by heating at 80°. 4-(5,6-Dihydrobenzo[*h*]quinazoline)carboxamide **IIIa** was simultaneously produced in the same reaction. 4-(5,6-Dihydrobenzo-[*h*]quinazoline)carboxylic acid **IVa** was obtained by the alkaline hydrolysis of **IIa** under refluxing in methyl cellosolve as the solvent. After reaction of **IVa** with thionyl chloride followed by treatment with methylamine, 4-(5,6-dihydrobenzo[*h*]quinazoline)-*N*-methylcarboxamide **Va** could be obtained. In the same manner, 4-substituted 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines were prepared; that is, 4-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta-[1,2-*d*]pyrimidine)carbonitrile **IIb** was prepared by the reaction of 4-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta-[1,2-*d*]pyrimidine **Ib** [4] with sodium cyanide in DMSO with heating at 75°. Compound **IIb** was hydrolyzed with potassium hydroxide with heating at 40° for 4.5 hours to afford 4-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine)carboxamide **IIIb** in 59% yield. On the other hand, hydrolysis of **IIb** under reflux in methyl cellosolve as the solvent, for 4 hours gave 4-(6,7-dihydro-5*H*-benzo[6,7]-cyclohepta[1,2-*d*]pyrimidine)carboxylic acid **IVb** in 61% yield. 4-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine)-*N*-methylcarboxamide **Vb** was prepared by the reaction of **IVb** with thionyl chloride followed by treatment with methylamine. Previously, we reported the synthesis of 3,4,5,6-tetrahydrobenzo[*h*]quinazoline-4-thione **VIa** [5] and now 3,4,6,7-tetrahydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine-4-thione **VIb** was obtained by the reaction of **Ib** with thiourea under similar conditions.

Scheme



The inhibitory activity against platelet aggregation of compounds **II-VI** was screened by a turbidimetric method developed by Born and Cross [6] using an aggregometer. Preparation of the platelets, measurement of platelet aggregation, the calculation of the inhibition rate, and estimation of the test compound were performed in the same manner described previously [2c]. Many compounds in this paper produced a dose-dependent inhibition against

rabbit platelet aggregation induced by collagen. As shown in the Table, comparison of the inhibition rate at the final concentration of 25 μmole/l of our compounds with that of aspirin showed that **IVb**, **Vb**, and **VIa,b** respectively, were more potent compounds than aspirin at $p < 0.01$ on

Table Maximum Inhibition Rate and IC_{50} on Platelet Aggregation Induced by Collagen

Compd.	Max. inhibit. rate[a]	IC_{50}[b]	Compd.	Max. inhibit. rate[a]	IC_{50}[b]
IIa	42.7±2.8		**Va**	34.6±5.6	
IIb	30.0±6.4		**Vb**	51.8±4.0[c]	16.9 (11.8-23.2)
IIIa	20.1±1.9		**VIa**	89.1±2.1[c]	12.0 (9.9-14.9)
IIIb	38.3±3.7		**VIb**	51.7±7.4[c]	23.9 (19.8-29.4)
IVa	48.1±9.2		aspirin	35.5±2.2	44.6 (37.6-55.0)
IVb	71.5±2.8[c]	13.0 (9.8-16.5)			

[a] Value is expressed as % and the mean ± S.E. of at least 3 experiments at final concentration of 25 μmol/l. [b] Figures in upper lines and lower lines for each compound represent the IC_{50} value (μmol/l) and 95% confidence limits (μmol/l-μmol/l), respectively. Experiments were repeated at least each 3 times at final concentrations of 5, 25, 50 μmol/l (in the case of aspirin, final concentrations were 10, 25, 100 μmol/l). [c] Significantly different from aspirin at $p<0.01$.

statistical analysis. Compared with 4-alkylamino, dialkylamino, or amino acid derivatives previously described [2], the potency rate of the compounds described here was not much different. It is interesting that carboxylic acid derivative **IV** was the most potent and that the carboxamide derivative **III** was the weakest between compounds **III**, **IV**, and **V** in both ring systems, namely, 5,6-dihydrobenzo[*h*]-quinazoline and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine.

EXPERIMENTAL

All melting points 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 EI-ms spectra were measured on a Shimadzu LKB-9000 instrument. The FAB-ms were recorded on a VG 70-SE mass spectrometer, using glycerol as the matrix agent. The ir spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer. Unless otherwise stated, it was measured as potassium bromide pellets and frequencies are expressed in cm^{-1}. The ^1H nmr spectra were recorded on a Hitachi R-22 FTS FT-NMR spectrometer (90-MHz) or Varian VXR-200 instrument (200-MHz) in the solvent indicated with tetramethylsilane as the internal standard. Chemical shifts are reported in ppm (δ) and J values in Hz, and the signals are designated as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad.

4-(5,6-Dihydrobenzo[*h*]quinazoline)carbonitrile (**IIa**) and 4-(5,6-Dihydrobenzo[*h*]quinazoline)carboxamide (**IIIa**).

To a solution of 1.00 g (20.4 mmoles) of sodium cyanide in 20 ml of dimethyl sulfoxide (DMSO) was added 3.00 g (13.9 mmoles) of 4-chloro-5,6-dihydrobenzo[*h*]quinazoline **Ia** [3] and the resulting solution was heated at 80° for 7.5 hours. After cooling of the reaction mixture, 200 ml of water was added to the mixture. The precipitated brown solid was collected by filtration, washed with water, and chromatographed on silica gel. The eluate from benzene-chloroform (1:1, v/v) was recrystallized from benzene to give 0.57 g (20%) of **IIa** as pale orange needles, mp 115-117°; ir: 2225 (C≡N stretching); EI-ms: m/z 207 (M^+); ^1H nmr (deuteriochloroform): 3.16 (m, 4H, 5,6-H), 7.43 (m, 3H, 7,8,9-H), 8.49 (dd, $J_{10,9}$ = 6.5, $J_{10,8}$ = 2.5, 1H, 10-H), 9.30 (s, 1H, 2-H).

Anal. Calcd. for $C_{13}H_9N_3$: C, 75.34; H, 4.37; N, 20.27. Found: C, 75.18; H, 4.45; N, 20.02.

Further elution with chloroform-acetone (9:1, v/v) of the above chromatograph provided a product which was recrystallized from benzene to give 1.10 g (35%) of **IIIa** as pale yellow granules, mp 209-211° (sublimed at 180°); ir: 3420, 3140 (N-H stretching), 1690 (C=O stretching); EI-ms: m/z 225 (M^+); ^1H nmr (DMSO-d_6): 2.90, 3.21 (each dd, J = 8.8, 6.7, each 2H, 5,6-H), 7.41 (m, 3H, 7,8,9-H), 7.86, 8.20 (each br s, each 1H, exchangeable with deuterium oxide, NH_2), 8.24 (dd, $J_{10,9}$ = 7.4, $J_{10,8}$ = 1.7, 1H, 10-H), 9.10 (s, 1H, 2-H).

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.31; H, 4.92; N, 18.65. Found: C, 69.53; H, 5.05; N, 18.44.

4-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine)carbonitrile (**IIb**).

To a solution of 1.18 g (24.1 mmoles) of sodium cyanide in 30 ml of DMSO was added 3.69 g (16.0 mmoles) of 4-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine **Ib** [4], and the resulting mixture was heated at 75° for 7 hours. After cooling of the reaction mixture, 350 ml of water was added to the mixture. The precipitated pale yellow solid was collected by filtration, washed with water, and recrystallized from cyclohexane to give 3.12 g (88%) of **IIb** as pale yellow prisms, mp 131-132.5°; ir: 2230 (C≡N stretching); EI-ms: m/z 221 (M^+); ^1H nmr (deuteriochloroform): 2.56 (m, 6H, 5,6,7-H), 7.30 (m, 3H, 8,9,10-H), 7.50 (m, 1H, 11-H), 9.32 (s, 1H, 2-H).

Anal. Calcd. for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 76.24; H, 5.00; N, 19.33.

4-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine)carboxamide (**IIIb**).

To a solution of 1.11 g (5.02 mmoles) of **IIb** in 30 ml of methyl cellosolve was added 5.5 ml (5.5 mmoles) of 1*N* potassium hydroxide, and the resulting solution was heated at 40° for 4.5 hours. After cooling of the reaction mixture, 300 ml of water was added to the mixture and the mixture was extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The thus obtained residue was recrystallized from benzene to give 0.71 g (59%) of **IIIb** as pale yellow scales, mp 170-172°; ir: 3420 (N-H stretching), 1690 (C=O stretching); EI-ms: m/z 239 (M^+); ^1H nmr (deuteriochloroform): 2.49 and 3.62 (m and t, J = 6, 4H and 2H, 5,6,7-H), 5.87 and 7.12 (each br s, each 1H, exchangeable with deuterium oxide, NH_2), 7.40 (m, 3H, 8,9,10-H), 7.85 (m, 1H, 11-H), 9.22 (s, 1H, 2-H).

Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.47; N, 17.56. Found: C, 70.21; H, 5.44; N, 17.81.

4-(5,6-Dihydrobenzo[*h*]quinazoline)carboxylic Acid (**IVa**).

To a solution of 145 mg (0.70 mmole) of **IIa** in 4 ml of methyl cellosolve was added 1.0 ml (1.0 mmole) of 1*N* potassium hydroxide, and the resulting solution was refluxed for 4.5 hours. After cooling of the reaction mixture, 40 ml of water was added to the mixture. The mixture was acidified once with diluted hydrochloric acid and again made alkaline with sodium hydrogen carbonate. The mixture was washed with chloroform, and acidified with diluted hydrochloric acid. The thus obtained mixture was extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized from benzene to give 103 mg (65%) of **IVa** as pale yellow needles, mp 168-171°; ir: 2900 (O-H stretching), 1705 (C=O stretching); EI-ms: m/z 226 (M^+); ^1H nmr (DMSO-d_6): 2.94 and 3.08 (each dd, J = 7.5, 4.8, each 2H, 5,6-H), 7.44 (m, 3H, 7,8,9-H), 8.25 (dd, $J_{10,9}$ = 7.4, $J_{10,8}$ = 1.5, 1H, 10-H), 9.12 (s, 1H, 2-H).

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.45; N, 12.38. Found: C, 68.91; H, 4.53; N, 12.50.

4-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine)carboxylic Acid (**IVb**).

To a solution of 1.11 g (5.02 mmoles) of **IIb** in 10 ml of methyl cellosolve was added 7.0 ml (7.0 mmoles) of 1*N* potassium hydroxide, and the resulting solution was refluxed for 4 hours. After cooling of the reaction mixture, 150 ml of water was added to the mixture. The mixture was once acidified with diluted hydrochloric acid and again made alkaline with sodium hydrogen carbonate. The thus obtained mixture was washed with chloroform, and acidified with diluted hydrochloric acid. This acidic mixture was extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized from benzene to give 0.74 g (61%) of **IVb** as colorless prisms, mp 175-177°; ir: 2900 (O-H stretching), 1700 (C=O stretching); EI-ms: m/z 240 (M^+); ^1H nmr (deuteriochloroform): 2.47 and 3.13 (m and t, J = 6, 4H and 2H, 5,6,7-H), 7.39 (m, 3H, 8,9,10-H), 7.79 (m, 1H, 11-H), 9.27 (s, 1H, 2-H).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.98; H, 5.03; N, 11.65. Found: C, 70.13; H, 4.98; N, 11.73.

4-(5,6-Dihydrobenzo[*h*]quinazoline)-*N*-methylcarboxyamide (**Va**).

A mixture of 80 mg (0.35 mmole) of **IVa** and 0.3 ml of thionyl chloride was stirred at room temperature for 20 hours. After evaporation of the thionyl chloride, 0.6 ml of methylamine was added to the residue. The thus obtained solution was stirred at room temperature for 1.5 hours. To the reaction mixture was added 10 ml of water and the mixture was extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated. The resulting oily residue was chromatographed on silica gel. The eluate from benzene-acetone (9:1, v/v) gave 25 mg (30%) of **Va** as a pale yellow viscous oil which behaved as a single spot on tlc; ir (chloroform): 3350 (N-H stretching), 1650 (C=O stretching); EI-ms: m/z 239 (M^+); ^1H nmr (deuteriochloroform): 2.94 and 3.67 (each br t, J = 7.0, each 2H, 5,6-H), 3.02 (d, J = 5.1, changed to singlet after addition of deuterium oxide, 3H, CH_3), 7.38 (m, 3H, 7,8,9-H), 8.14 (br, 1H, exchangeable with deuterium oxide, NH), 8.33 (dd, $J_{10,9}$ = 6.9, $J_{10,8}$ = 2.4, 1H, 10-H), 9.04 (s, 1H, 2-H).

Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.47; N, 17.56. Found: C, 70.02; H, 5.56; N, 17.91.

4-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine)-*N*-methylcarboxamide (**Vb**).

A mixture of 300 mg (1.25 mmoles) of **IVb** and 0.5 ml of thionyl chloride was stirred at room temperature for 24 hours. After evaporation of the thionyl chloride, 0.9 ml of methylamine was added to the residue. The resulting solution was stirred at room temperature for 1 hour. The precipitated crystalline solid was collected by filtration, and thoroughly washed with water. The filtrate and washings were combined and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The resulting residue was combined with the crystalline solid described above, and recrystallized from benzene-diethyl ether to give 131 mg (41%) of **Vb** as pale yellow prisms, mp 111-112°; ir: 3400 (N-H stretching), 1650 (C=O stretching); EI-ms: m/z 253 (M^+); ^1H nmr (deuteriochloroform): 2.49 and 3.12 (each m, 4H and 2H, 5,6,7-H), 3.07 (d, J = 6.7, changed to singlet after addition of deuterium oxide, 3H, CH_3), 7.44 (m, 3H, 8,9,10-H), 7.94 (m, 1H, 11-H), 8.20 (br, 1H, exchangeable with deuterium oxide, NH), 9.27 (s, 1H, 2-H).

Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.12; H, 5.96; N, 16.58. Found: C, 71.16; H, 6.00; N, 16.80.

3,4,6,7-Tetrahydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine-4-thione (**VIb**).

A suspension of 231 mg (1.00 mmole) of **IIb** and 380 mg (5.00 mmoles) of thiourea in 5 ml of dioxane was refluxed with stirring for 7 hours. After cooling of the reaction mixture, the solvent was evaporated to dryness and 10 ml of 1*N* sodium hydroxide was added to the yellow powdered residue. The alkaline mixture was filtered and the filtrate was made acidic with acetic acid. The precipitated crystalline solid was collected by filtration, washed with water, and recrystallized from methanol to give 172 mg (75%) of **VIb** as pale yellow plates, mp 232-235°; ir: 3150 (N-H stretching); FAB-ms: m/z 229 (MH^+); ^1H nmr (deuteriochloroform): 2.43 and 2.91 (m and t, J = 6, 4H and 2H, 5,6,7-H), 7.38 (m, 3H, 8,9,10-H), 7.77 (dd, $J_{11,10}$ = 6, $J_{11,9}$ = 2, 1H, 11-H), 8.23 (s, 1H, 2-H), 13.18 (br s, 1H, exchangeable with deuterium oxide, NH).

Anal. Calcd. for $C_{13}H_{12}N_2S$: C, 68.38; H, 5.29; N, 12.26. Found: C, 68.25; H, 5.31; N, 12.17.

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