Polycyclic *N*-Hetero Compounds. XXXV. Syntheses and Anti-platelet Aggregation Activity of 5,6-Dihydro-4*H*-benzo[3,4]cyclohept[1,2-*e*]imidazo[1,2-*c*]pyrimidines with an Oxygen Function at the 1-Position

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Various 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines bearing amino acid group at the 4-position of the skeleton were synthesized by the reaction of 4-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]-pyrimidine with some amino acid, which were cyclized to 5,6-dihydro-4*H*-benzo[3,4]cyclohept[1,2-*e*]imidazo-[1,2-*c*]pyrimidines, corresponding to B-homo-11,13,15-triazasteroids. Their inhibitory activities against platelet aggregation induced by collagen were also investigated.

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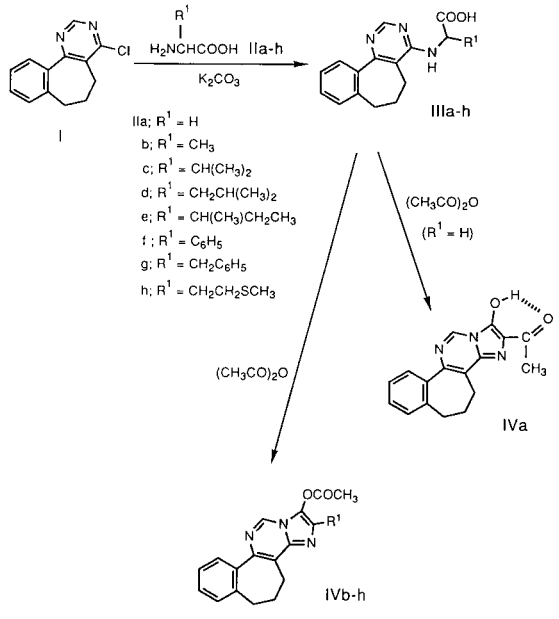
We have previously reported that some 4-alkylamino-5,6-dihydrobenzo[*h*]quinazolines [1] and 4-alkylamino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines [2] indicated inhibitory activity against rabbit platelet aggregation, especially, 4-ethylamino-5,6-dihydrobenzo[*h*]quinazoline has about 10 times more potent activity than that of aspirin which was familiar as an anti-platelet agent.

As a development of such work, this paper deals with the syntheses of the compounds having amino acid group at the 4-position of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta-[1,2-*d*]pyrimidine, and its ring closure compounds, which are corresponding to the B-homo analogues of 11,13,15-triazasteroid, and furthermore the evaluation of their inhibitory activity against rabbit platelet aggregation induced by collagen.

As shown in Scheme 1, the reaction of 4-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**I**) [3] with glycine (**IIa**) in the presence of potassium carbonate in dioxane and water gave *N*-(6,7-dihydro-5*H*-benzo[6,7]-cyclohepta[1,2-*d*]pyrimidin-4-yl)glycine (**IIIa**) [4,5]. Furthermore, the reaction of compound **I** with several other amino acids in a similar manner gave the corresponding *N*-heteryl amino acids **IIIb-h** in good yield. Next, the cyclization of these *N*-heteryl amino acid **IIIa-h** to the corresponding tetracyclic compounds was planned. We have already obtained the ring closure compounds of *N*-(5,6-dihydrobenzo[*h*]quinazolin-4-yl)glycine with phosphoryl chloride, dimethylformamide-phosphoryl chloride, or acetic anhydride, and the cyclization with acetic anhydride has progressed in the best yield among them to afford 2-acetyl-1-hydroxy-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline [5]. Therefore, the cyclizations of *N*-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)amino acid derivatives **III** were carried out using acetic anhydride to afford the corresponding tetracyclic compounds. In these products, the enol acetate was formed. The presence of a carbonyl stretching band around 1780 cm^{-1} in their ir spectra and other instrumental analyses well supported this fact. However, compound **IVa** was not acetylated under similar conditions. We have already presumed that the reason was the presence of strong hydrogen bonding between the hydroxyl group at the 1-position and the acetyl group at the 2-position, thus the hydroxyl group at the 1-position of 2-acetyl-1-hydroxy-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazoline could not be acetylated in the cyclization reaction of *N*-(5,6-dihydrobenzo[*h*]quinazolin-4-yl)glycine in excess acetic anhydride [5]. Grounds for this suggestion were the findings that the carbonyl and hydroxyl bands appeared at 1640 cm^{-1} and 2660 (broad) cm^{-1} in the ir spectrum and the signal of the pyrimidine ring proton at the 11-position was shifted downfield (δ 10.24 ppm, in DMSO-d_6) in the pmr spectrum. In the case of compound **IVa**, the stretching bands

Scheme 1



of carbonyl and hydroxyl groups were similarly observed at 1650 cm^{-1} and 2930 (broad) cm^{-1} in its ir spectrum, and the pyrimidine ring proton also was shifted downfield (δ 10.59 ppm, in deuteriochloroform) in the pmr spectrum. Thus, it was also supposed that the presence of strong hydrogen bonding between the hydroxyl group at the 1-position and the acetyl group at the 2-position prevented the acetylation of the hydroxyl group at the 1-position in compound **IVa**. Other instrumental analyses of this compound also supported this assumption.

The inhibitory activity against platelet aggregation of the products obtained was screened by a turbidimetric method developed by Born and Cross [6] using an aggregometer. Preparation of the platelets and measurement of platelet aggregation were performed as stated in the previous paper [1] except for the final concentration of the test compound and aspirin. In this paper, the final concentration was 25 μmol/l, however, in the previous paper [1] the concentration was 50 μmol/l. The maximum aggregation rate (MAR) was calculated from an aggregation response curve obtained by equation 1, and then the inhibition rate of the test compound at each concentration was calculated by equation 2, where **X** is maximum optical transmission on the aggregation response curve, PRP is platelet rich plasma, and PPP is platelet poor plasma.

Equation 1:

$$MAR = \frac{X - \text{optical transmission of PRP}}{\text{optical transmission of PPP} - \text{optical transmission of PRP}} \times 100$$

Equation 2:

$$\text{Inhibition rate} = \left(1 - \frac{\text{MAR of test compound-treated PRP}}{\text{MAR of vehicle-treated PRP}}\right) \times 100$$

The inhibitory activity of aspirin against rabbit platelet aggregation was simultaneously determined as a positive control. When the inhibition rate of the test compound was significantly different from that of aspirin at $p < 0.05$ on statistical analysis using Student's *t*-test, the amount of the test compound, which was required to produce a 50% inhibition against rabbit platelet aggregation induced by collagen, was calculated by a probit method (IC_{50}). Inhibition rates, IC_{50} values, and 95% confidence limits of the test compounds and aspirin are listed in Table I.

Many compounds produced a potent and dose-dependent inhibition against rabbit platelet aggregation induced by collagen. As shown in Table I, only compound **IIIh** exhibited obviously higher potency than that of aspirin among all *N*-heteryl amino acids **III**, and many of them had weaker potency. Comparing with the introduction of alkylamines at the 4-position of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine, that of amino acid at the same position seems to have a tendency to be less active. Among tetracyclic compounds, compounds **IVb,g** showed about 2 times greater activity than aspirin in terms of IC_{50}, and compound **IVh** was a little less active than the other compounds. Compounds **IVa,b,f,g**, obviously showed more potent activity than those of their pre-ring closure compounds **IIIa,b,f,g**, respectively. Therefore, it seems that the tetracyclic compounds **IV** have a tendency to be more favorable for the exhibition of activity than the tricyclic compounds **III**.

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

Table I

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

Compound	Max. inhibit. rate [a]	IC_{50}[b]	Compound	Max. inhibit. rate [a]	IC_{50}[b]
IIIa	13.7 ± 2.2		**IVa**	26.4 ± 3.6	
IIIb	25.2 ± 2.1		**IVb**	49.9 ± 6.0 [d]	25.7 (16.8-45.2)
IIIc	26.1 ±8.8		**IVc**	25.5 ±10.1	
IIId	34.2 ±5.5		**IVd**	24.6 ±3.3	
IIIe	28.7 ±4.9		**IVe**	32.1 ±4.4	
IIIf	15.9 ±3.1		**IVf**	35.5 ±0.9	
IIIg	10.2 ±4.6		**IVg**	50.2 ±5.4 [c]	19.1 (11.8-28.2)
IIIh	49.3 ±2.6 [d]	25.9 (18.2-41.0)	**IVh**	68.1 ±6.5 [c]	30.9 (14.4-86.0)
aspirin	35.5 ±2.2	44.6 (37.6-55.0)			

[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 $p < 0.01$. [d] Significantly different from aspirin at $p < 0.05$.

elemental analyzer. The ir spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer. The pmr spectra were recorded on a Hitachi R-22 FTS FT-NMR spectrometer (90-MHz) or Varian VXR-200 Instrument (200-MHz). The chemical shifts (δ) in ppm are measured relative to tetramethylsilane as an internal standard, and the signals are designated as follows; s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; dd, doublet doublet. The EI-ms spectra were taken on a Shimadzu LKB-9000 Instrument and FAB-ms spectra on a VG-70SE Instrument.

N-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-glycine (**IIIa**).

A mixture of 4-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta-[1,2-*d*]pyrimidine (**I**, 231 mg, 1 mmole), glycine (**IIa**, 300 mg, 4 mmoles), and potassium carbonate (276 mg, 2 mmoles) in 6 ml of 2-methoxyethanol and water (1:1, v/v) was refluxed for 2 hours. After evaporation of the solvent, a small amount of water was added to dissolve the residue. The resulting solution was acidified with acetic acid, and the precipitated crystalline solid was collected on a filter and recrystallized from ethanol to give 179 mg (67%) of **IIIa** as colorless needles, mp 240-241°; EI-ms: molecular ion peak was not observed, m/z 251 (M^+-H_2O); ir (potassium bromide): cm^{-1} 3370 (N-H), 3050 (O-H), 1710 (C=O); pmr (DMSO-d_6): 2.14, 2.32 and 2.49 (each 2H, m, t (J = 6.5 Hz), and m, 5-, 6-, and 7-H), 3.99 (2H, d, J = 5.8 Hz, changed to singlet after addition of deuterium oxide, CH_2N), 7.34 (3H, m, 8-, 9-, and 10-H), 7.57 (2H, m, changed to 1 proton multiplet after addition of deuterium oxide, 11-H and NH), 8.42 (1H, s, 2-H).

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.68; H, 5.42; N, 15.41.

Unless otherwise stated, this procedure was carried out as a usual work-up for the preparation of *N*-(6,7-Dihydro-5*H*-benzo-[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)amino Acid.

N-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-DL-alanine (**IIIb**).

A mixture of compound **I** (231 mg, 1 mmole), DL-alanine (**IIb**, 356 mg, 4 mmoles), and potassium carbonate (276 mg, 2 mmoles) in 6 ml of dioxane and water (1:1, v/v) was refluxed for 30 hours. After the usual work-up, recrystallization of the solid from ethanol afforded 212 mg (75%) of **IIIb** as colorless needles, mp 240-241°; EI-ms: molecular ion peak was not observed, m/z 265 (M^+-H_2O); ir (potassium bromide): cm^{-1} 3350 (broad, N-H, O-H), 1690 (C=O); pmr (DMSO-d_6): 1.42 (3H, d, J = 7.4 Hz, $CHCH_3$), 2.16, 2.34 and 2.49 (each 2H, each m, 5-, 6-, and 7-H), 4.47 (1H, m, NCHCO), 7.18 (1H, d, J = 6.8 Hz, exchangeable with deuterium oxide, NH), 7.36 (3H, m, 8-, 9-, and 10-H), 7.56 (1H, m, 11-H), 8.41 (1H, s, 2-H).

Anal. Calcd. for $C_{16}H_{17}N_3O_2 \cdot \frac{1}{2}H_2O$: C, 65.73; H, 6.20; N, 14.37. Found: C, 66.02; H, 6.26; N, 14.13.

N-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-DL-valine (**IIIc**).

A mixture of compound **I** (231 mg, 1 mmole), DL-valine (**IIc**, 469 mg, 4 mmoles), and potassium carbonate (276 mg, 2 mmoles) in 6 ml of 2-methoxyethanol and water (1:1, v/v) was refluxed for 2 hours. After the usual work-up, recrystallization of the solid from ethanol afforded 205 mg (70%) of **IIIc** as colorless needles, mp 208-210°; EI-ms: molecular ion peak was not observed, m/z 250 [M^+-H_2O-$CH(CH_3)_2$]; ir (potassium bromide): cm^{-1} 3360 (broad, N-H, O-H), 1700 (C=O); pmr (DMSO-d_6): 0.97 and 1.00 (each 3H, each d, J = 6.7 Hz, 2 x CH_3), 2.17, 2.38 and 2.49 (each 2H, each m, 5-, 6-, and 7-H), 2.20 [1H, m, overlapped with the absorption of 6-H, $CH(CH_3)_2$], 4.37 (1H, t, J = 7.5 Hz, changed to doublet (J = 7.4 Hz) after addition of deuterium oxide, NCHCO), 7.05 (1H, m, exchangeable with deuterium oxide, NH), 7.34 (3H, m, 8-, 9-, and 10-H), 7.59 (1H, m, 11-H), 8.41 (1H, s, 2-H).

Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.50. Found: C, 69.30; H, 6.80; N, 13.31.

N-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-DL-leucine (**IIId**).

A mixture of compound **I** (231 mg, 1 mmoles), DL-leucine (**IId**, 527 mg, 4 mmoles), and potassium carbonate (276 mg, 2 mmoles) in 6 ml of dioxane and water (1:1, v/v) was refluxed for 18 hours. After evaporation of the solvent, a small amount of water was added to the residue and the mixture was acidified with acetic acid. The precipitated crystalline solid was collected on a filter, washed with 50 ml of hot water, and recrystallized from ethanol. Thus the first crop obtained was unchanged **IId**. The mother liquor was further evaporated and the residue was recrystallized from ethanol-diethyl ether to give 288 mg (89%) of **IIId** as colorless needles, mp 229-231°; EI-ms: molecular ion peak was not observed, m/z 264 (M^+-CH_3-HCOOH); ir (potassium bromide): cm^{-1} 3300 (broad, N-H, O-H), 1660 (C=O); pmr (DMSO-d_6): 0.84 and 0.87 (each 3H, each d, J = 5.9 Hz, 2 x CH_3), 1.67 (3H, m, $CH_2CH(CH_3)_2$), 2.14, 2.21 and 2.49 (each 2H, each m, 5-, 6-, and 7-H), 4.08 (1H, m, NCHCO), 6.83 (1H, br d, J = 5.5 Hz, exchangeable with deuterium oxide, NH), 7.32 (3H, m, 8-, 9-, and 10-H), 7.59 (1H, m, 11-H), 8.34 (1H, s, 2-H).

Anal. Calcd. for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 69.91; H, 7.15; N, 12.73.

N-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-DL-isoleucine (**IIIe**).

A mixture of compound **I** (231 mg, 1 mmole), DL-isoleucine (**IIe**, 262 mg, 4 mmoles), and potassium carbonate (166 mg, 1.2 mmoles) in 6 ml of dioxane and water (1:1, v/v) was refluxed for 30 hours. After the usual work-up, recrystallization of the solid from ethanol afforded 270 mg (83%) of **IIIe** as colorless needles, mp 198-200°; EI-ms: molecular ion peak was not observed, m/z 278 (M^+ -H_2O -CH_2CH_3); ir (potassium bromide): cm^{-1} 3370 (broad, N-H, O-H), 1710 (C=O); pmr (DMSO-d_6): 0.87 (3H, t, J = 7.3 Hz, CH_2CH_3), 0.94 (3H, d, J = 6.8 Hz, $CHCH_3$), 1.40 (2H, m, CH_2CH_3), 2.00 [1H, m, $CH(CH_3)C_2H_5$], 2.15 and 2.42 (2H and 4H, each m, 5-, 6-, and 7-H), 4.44 (1H, t, J = 7.4 Hz, changed to doublet (J = 7.4 Hz) after addition of deuterium oxide, $NHCH$), 7.36 (4H, m, changed to three protons multiplet after addition of deuterium oxide, 8-, 9-, and 10-H and NH), 7.58 (1H, m, 11-H), 8.41 (1H, s, 2-H).

Anal. Calcd. for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 69.88; H, 7.13; N, 12.69.

N-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-DL-phenylglycine (**IIIf**).

A mixture of compound **I** (231 mg, 1 mmole), DL-phenylglycine (**IIf**, 302 mg, 2 mmoles), and potassium carbonate (166 mg, 1.2 mmoles) in 6 ml of dioxane and water (1:1, v/v) was refluxed for 30 hours. After evaporation of the solvent, a small amount of water

was added to the residue and undissolved solid was filtered off. The filtrate was acidified with acetic acid and the precipitated solid was collected. The hot ethanol soluble fraction of the solid was recrystallized from ethanol-water to give 305 mg (90%) of **IIIf** as colorless needles, mp 188-190°; EI-ms: molecular ion peak was not observed, m/z 327 ($M^+ - H_2O$); ir (potassium bromide): cm^{-1} 3350 (broad, N-H, O-H), 1720 (C=O); pmr (DMSO-d_6): 2.18 and 2.45 (2H and 4H, each m, 5-, 6-, and 7-H), 5.68 (1H, d, J = 6.6 Hz, changed to singlet after addition of deuterium oxide, NHC*H*CO), 7.26-7.62 (10H, m, changed to nine protons multiplet after addition of deuterium oxide, 8-, 9-, 10-, and 11-H, phenyl-H, and NH), 8.46 (1H, s, 2-H).

Anal. Calcd. for $C_{21}H_{19}N_3O_2 \cdot \frac{1}{2}H_2O$: C, 71.16; H, 5.68; N, 11.85. Found: C, 71.25; ;H, 5.49; N, 11.68.

N-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-DL-phenylalanine (**IIIg**).

A mixture of compound **I** (231 mg, 1 mmole), DL-phenylalanine (**IIg**, 330 mg, 2 mmoles), and potassium carbonate (166 mg, 1.2 mmoles) in 6 ml of dioxane and water (1:1, v/v) was refluxed for 30 hours. After the usual work-up, the first crop of the recrystallization of the solid from ethanol-water was unchanged **IIg**, so that, the mother liquor was evaporated and the residue was further recrystallized from methanol-ethyl acetate to give 327 mg (91%) of **IIIg** as colorless needles, mp 187-190°; EI-ms: molecular ion peak was not observed, m/z 341 ($M^+ - H_2O$); ir (potassium bromide): cm^{-1} 3200 (broad, N-H, O-H), 1720 (C=O); pmr (DMSO-d_6): 2.18, 2.36 and 2.49 (each 2H, each m, 5-, 6-, and 7-H), 3.24 (2H, d, J = 6.5 Hz, CHCH_2), 4.95 (1H, m, NHC*H*CO), 7.15-7.59 (10H, m, changed to nine protons multiplet after addition of deuterium oxide, 8-, 9-, 10-, and 11-H, phenyl-H, and NH), 8.62 (1H, s, 2-H).

Anal. Calcd. for $C_{22}H_{21}N_3O_2$: C, 73.51; H, 5.89; N, 11.69. Found: C, 73.63; H, 5.66; N, 11.90.

N-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-DL-methionine (**IIIh**).

A mixture of compound **I** (231 mg, 1 mmole), DL-methionine (**IIh**, 597 mg, 4 mmoles), and potassium carbonate (276 mg, 2 mmoles) in 6 ml of dioxane and water (1:1, v/v) was refluxed for 40 hours. After evaporation of the solvent, a small amount of water was added to the residue and the resulting mixture was filtered. The filtrate was acidified with acetic acid and the mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated. The resulting residue was recrystallized from chloroform-*n*-hexane to give 292 mg (89%) of **IIIh** as colorless needles, mp 156-157°; EI-ms: molecular ion peak was not observed, m/z 325 ($M^+ - H_2O$); ir (potassium bromide): cm^{-1} 2350 (broad, N-H, O-H), 1700 (C=O); pmr (DMSO-d_6): 2.05 (3H, s, CH_3), 2.13 and 2.44 (4H and 2H, each m, 5-, 6-, and 7-H), 2.35 (2H, m, CH_2CH$_2$SCH$_3$), 2.54 (2H, m, CH$_2$CH_2SCH$_3$), 4.64 (1H, m, changed to doublet doublet (J_1 = 5.3 Hz, J_2 = 8.7 Hz) after addition of deuterium oxide, NHC*H*CO), 7.17 (1H, d, J = 7.6 Hz, exchangeable with deuterium oxide, NH), 7.35 (3H, m, 8-, 9-, and 10-H), 7.59 (1H, m, 11-H), 8.41 (1H, s, 2-H).

Anal. Calcd. for $C_{18}H_{21}N_3O_2S$: C, 62.94; H, 6.16; N, 12.23. Found: C, 62.82; H, 6.26; N, 12.01.

2-Acetyl-1-hydroxy-5,6-dihydro-4*H*-benzo[3,4]cyclohept[1,2-*e*]imidazo[1,2-*c*]pyrimidine (**IVa**).

A solution of **IIIa** (135 mg, 0.5 mmole) in acetic anhydride (0.5 ml, 5 mmoles) was heated at 90° for 30 minutes. After evaporation of the solvent, a small amount of xylene was added to the residue and the mixture was evaporated to dryness again. The resulting residue was recrystallized from pyridine to give 64 mg (44%) of **IVa** as dark green needles, mp >300°; EI-ms: m/z 293 (M^+); ir (potassium bromide): cm^{-1} 2930 (broad, O-H), 1650 (C=O); pmr (deuteriochloroform): 2.63 (3H, s, CH_3), 2.50 and 2.85 (4H and 2H, m and t (J = 7.0 Hz), 4-, 5-, and 6-H), 7.40 (3H, m, 7-, 8-, and 9-H), 7.80 (1H, m, 10-H), 10.59 (1H, s, 12-H).

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.44; H, 5.10; N, 14.06.

Unless otherwise stated, this procedure was carried out as a usual work-up for the cyclization of *N*-(6,7-dihydro-5*H*-benzo-[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)amino acid.

1-Acetoxy-2-methyl-5,6-dihydro-4*H*-benzo[3,4]cyclohept[1,2-*e*]-imidazo[1,2-*c*]pyrimidine (**IVb**).

After the usual work-up of a solution of **IIIb** (71 mg, 0.25 mmole) in acetic anhydride (0.2 ml, 2.5 mmoles), recrystallization of the residue from chloroform-*n*-hexane afforded 73 mg (92%) of **IVb** as colorless feathers, mp 168-169°; FAB-ms: m/z 308 (MH^+); ir (potassium bromide): cm^{-1} 1770 (C=O); pmr (deuteriochloroform): 2.38 (3H, s, CH_3), 2.50 (3H, s, $COCH_3$), 2.43, 2.61 and 2.90 (each 2H, m, t (J = 6.3 Hz) and t (J = 7.0 Hz), 4-, 5-, and 6-H), 7.38 (3H, m, 7-, 8-, and 9-H), 7.73 (1H, m, 10-H), 8.57 (1H, s, 12-H).

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.22; H, 5.46; N, 13.47.

1-Acetoxy-2-isopropyl-5,6-dihydro-4*H*-benzo[3,4]cyclohept[1,2-*e*]-imidazo[1,2-*c*]pyrimidine (**IVc**).

After the usual work-up of a solution of **IIIc** (156 mg, 0.5 mmole) in acetic anhydride (0.5 ml, 5 mmoles), crystallization of the residue from *n*-hexane followed by recrystallization from dioxane afforded 104 mg (62%) of **IVc** as colorless prisms, mp 171.5-172°; FAB-ms: m/z 336 (MH^+); ir (potassium bromide): cm^{-1} 1785 (C=O); pmr (deuteriochloroform): 1.35 and 1.38 (each 3H, each d, J = 7.0 Hz, 2 x CH_3), 2.49 (3H, s, $COCH_3$), 2.46, 2.63 and 2.93 (each 2H, m, t (J = 6.3 Hz) and t (J = 7.0 Hz), 4-, 5-, and 6-H), 3.12 (1H, m, C*H*(CH$_3$)$_2$), 7.35 (3H, m, 7-, 8-, and 9-H), 7.70 (1H, dd, J_1 = 2.0 Hz, J_2 = 7.0 Hz, 10-H), 8.53 (1H, s, 12-H).

Anal. Calcd. for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.23; H, 6.09; N, 12.38.

1-Acetoxy-2-isobutyl-5,6-dihydro-4*H*-benzo[3,4]cyclohept[1,2-*e*]imidazo[1,2-*c*]pyrimidine (**IVd**).

After the usual work-up of a solution of **IIId** (163 mg, 0.5 mmole) in acetic anhydride (0.5 ml, 5 mmoles), 5 ml of water was added to the resulting residue. The mixture was basified with sodium hydrogen carbonate and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. Recrystallization of the residue from benzene-petroleum ether afforded 87 mg (47%) of **IVd** as colorless needles, mp 112-113°; FAB-ms: m/z 350 (MH^+); ir (potassium bromide): cm^{-1} 1780 (C=O); pmr (deuteriochloroform): 0.96 (6H, d, J = 6.0 Hz, 2 x CH_3), 2.24 (1H, m, C*H*(CH$_3$)$_2$), 2.50 (3H, s, $COCH_3$), 2.60 (2H, d, J = 7 Hz, CH_2CH), 2.40, 2.65 and 2.90 (each 2H, each m, 4-, 5-, and 6-H), 7.38 (3H, m, 7-, 8-, and 9-H), 7.76 (1H, m, 10-H), 8.71 (1H, s, 12-H).

Anal. Calcd. for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03.

Found: C, 72.16; H, 6.79; N, 12.00.

1-Acetoxy-2-*sec*-butyl-5,6-dihydro-4*H*-benzo[3,4]cyclohept[1,2-*e*]-imidazo[1,2-*c*]pyrimidine (**IVe**).

After the usual work-up of a solution of **IIIe** (163 mg, 0.5 mmole) in acetic anhydride (0.5 ml, 5 mmoles), crystallization of the residue from petroleum ether followed by recrystallization from ethyl acetate afforded 131 mg (75%) of **IVe** as colorless prisms, mp 153-154°; FAB-ms: m/z 350 (MH^+); ir (potassium bromide): cm^{-1} 1785 (C=O); pmr (deuteriochloroform): 0.90 (3H, t, J = 7.4 Hz, CH_2CH_3), 1.34 (3H, d, J = 7.0 Hz, $CHCH_3$), 1.80 (2H, m, CH_2CH_3), 2.49 (3H, s, $COCH_3$), 2.43, 2.63 and 2.91 (each 2H, m, t (J = 6.6 Hz) and t (J = 7.3 Hz), 4-, 5-, and 6-H), 2.80 (1H, m, $CHCH_3$), 7.33 (3H, m, 7-, 8-, and 9-H), 7.70 (1H, dd, J_1 = 2.0 Hz, J_2 = 7.0 Hz, 10-H), 8.52 (1H, s, 12-H).

Anal. Calcd. for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 71.93; H, 6.56; N, 11.81.

1-Acetoxy-2-phenyl-5,6-dihydro-4*H*-benzo[3,4]cyclohept[1,2-*e*]imidazo[1,2-*c*]pyrimidine (**IVf**).

After the usual work-up of a solution of **IIIf** (173 mg, 0.5 mmole) in acetic anhydride (0.5 ml, 5 mmoles), recrystallization of the residue from benzene afforded 156 mg (84%) of **IVf** as colorless feathers, mp 213-215°; FAB-ms: m/z 370 (MH^+); ir (potassium bromide): cm^{-1} 1780 (C=O); pmr (deuteriochloroform): 2.50, 2.63 and 3.00 (each 2H, m, t (J = 6.6 Hz) and t (J = 7.3 Hz), 4-, 5-, and 6-H), 2.56 (3H, s, $COCH_3$), 7.40 and 7.90 (6H and 2H, each m, 7-, 8-, and 9-H and phenyl-H), 7.74 (1H, dd, J_1 = 2.0 Hz, J_2 = 7.0 Hz, 10-H), 8.61 (1H, s, 12-H).

Anal. Calcd. for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.38. Found: C, 74.71; H, 5.10; N, 11.27.

1-Acetoxy-2-benzyl-5,6-dihydro-4*H*-benzo[3,4]cyclohept[1,2-*e*]-imidazo[1,2-*c*]pyrimidine (**IVg**).

After the usual work-up of a solution of **IIIg** (72 mg, 0.2 mmole) in acetic anhydride (0.2 ml, 2 mmoles), recrystallization of the residue from benzene-*n*-hexane afforded 68 mg (88%) of **IVg** as pale yellow needles, mp 112-114.5°; FAB-ms: m/z 384 (MH^+); ir (potassium bromide): cm^{-1} 1780 (C=O); pmr (deuteriochloroform): 2.31 (3H, s, $COCH_3$), 2.56 and 2.92 (4H and 2H, m and t (J = 6.3 Hz), 4-, 5-, and 6-H), 4.17 (1H, s, CH_2), 7.33 (8H, m, 7-, 8-, and 9-H and phenyl-H), 7.73 (1H, m, 10-H), 8.57 (1H, s, 12-H).

Anal. Calcd. for $C_{24}H_{21}N_3O_2$: C, 75.17; H, 5.52; H, 10.96. Found: C, 75.25; H, 5.23; N, 10.96.

1-Acetoxy-2-(2-methylthioethyl)-5,6-dihydro-4*H*-benzo[3,4]cyclohept[1,2-*e*]imidazo[1,2-*c*]pyrimidine (**IVh**).

After the usual work-up of a solution of **IIIh** (172 mg, 0.5 mmole) in acetic anhydride (0.5 ml, 5 mmoles), the resulting brown oily residue was chromatographed on silica gel, and *n*-hexane-ethyl acetate (2:1, v/v) eluate afforded 101 mg (55%) of **IVh** as pale yellowish-brown oil; EI-ms: m/z 367 (M^+); ir (potassium bromide): cm^{-1} 1790 (C=O); pmr (deuteriochloroform): 2.15 (3H, s, SCH_3), 2.21-2.68 (6H, m, 4-, 5-, and 6-H), 2.48 (3H, s, $COCH_3$), 2.91 (4H, m, $CH_2CH_2SCH_3$), 7.37 (3H, m, 7-, 8-, and 9-H), 7.75 (1H, m, 10-H), 8.62 (1H, s, 12-H).

Anal. Calcd. for $C_{20}H_{21}N_3O_2S$: C, 65.37; H, 5.76; N, 11.43. Found: C, 65.08; H, 5.71; N, 11.19.

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