Polycyclic *N*-Hetero Compounds. XXXIII. Syntheses of 4-Substituted 6,7-Dihydro-5*H*-benzo[6,7]-cyclohepta[1,2-*d*]pyrimidines and Their Inhibitory Activities on Platelet Aggregation and on Reserpine-Induced Hypothermia

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Various 4-substituted 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines were synthesized by the reaction of 4-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine with amines. Their inhibitory activities against collagen-induced platelet aggregation and also against reserpine-induced hypothermia in mice were investigated.

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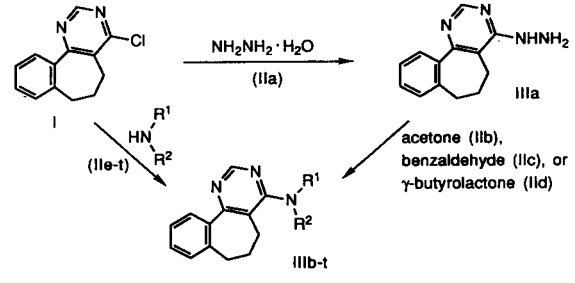
In the previous paper [1], we reported that 4-amino-, 4-hydrazino-, and some 4-alkylamino-5,6-dihydrobenzo[*h*]-quinazolines showed more potent inhibitory activity against collagen-induced platelet aggregation than that of aspirin, and especially 4-ethylamino-5,6-dihydrobenzo[*h*]-quinazoline exhibited the most potent activity among them. On the other hand, we have reported that some similar 4-substituted 5,6-dihydrobenzo[*h*]quinazolines exhibited anti-reserpine activity in mice [2-4]. That is, it has been found that one of the similar compounds, which had the same benzo[*h*]quinazoline ring system and only different substituent at 4-position of their nuclei, exhibited an inhibitory activity against platelet aggregation, but another one showed an anti-reserpine activity. From a pharmacological point of view, it is not desirable that platelet aggregation inhibitor has an activity on the central nervous system, and it is also disagreeable that antidepressant has an inhibitory activity against platelet aggregation. Fortunately, in our case, many compounds synthesized by us had only one inhibitory activity either against platelet aggregation or against reserpine-induced hypothermia, and few compounds exhibited these both activities [5]. These results encouraged us to performed the chemical modification of 4-substituted 5,6-dihydrobenzo-[*h*]quinazolines with the view to developing a more effective and new platelet aggregation inhibitor or antidepressant.

As a part of the investigation of the chemical modification, this paper deals with the syntheses of 4-substituted 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines corresponding to the homologue of 4-substituted 5,6-dihydrobenzo[*h*]quinazoline and evaluation of them on inhibitory activities against collagen-induced platelet aggregation and against reserpine-induced hypothermia in mice.

As shown in Scheme 1, 4-chloro-6,7-dihydro-5*H*-benzo-[6,7]cyclohepta[1,2-*d*]pyrimidine (**I**) [6] was used as a starting material. 4-Hydrazino derivative **IIIa** was prepared by the reaction of **I** with hydrazine hydrate in ethanol at room temperature. The reaction of **IIIa** with ketones gave the corresponding hydrazones, that is, 4-isopropylidenehydrazino and 4-benzylidenehydrazino derivatives **IIIb,c**.

Scheme 1



IIIb; R^1 = H, R^2 = N=C(CH$_3$)$_2$

IIIc; R^1 = H, R^2 = N=C(Ph)(H)

IIId; R^1 = H, R^2 = N(CH$_2$CH$_2$CO)

IIIe; R^1 = R^2 = CH$_3$

IIIf; R^1 = H, R^2 = CH$_2$CH$_3$

IIIg; R^1 = H, R^2 = (CH$_2$)$_2$N(CH$_2$CH$_3$)$_2$

IIIh; R^1 = H, R^2 = (CH$_2$)$_2$N(pyrrolidine)

IIIi; R^1 = H, R^2 = (CH$_2$)$_2$N(morpholine)

IIIj; R^1 = H, R^2 = (CH$_2$)$_2$OH

IIIk; R^1 = H, R^2 = (CH$_2$)$_2$OCH$_3$

IIIl; R^1 = H, R^2 = CH(CH$_3$)CH$_2$OH

IIIm; R^1 = H, R^2 = CH$_2$CH(CH$_3$)OH

IIIn; R^1 = H, R^2 = CH$_2$CH(CH$_2$CH$_3$)OH

IIIo; R^1 = H, R^2 = (CH$_2$)$_3$N(CH$_3$)$_2$

IIIp; R^1 = H, R^2 = (CH$_2$)$_3$N(morpholine)

IIIq; R^1 = H, R^2 = (CH$_2$)$_3$OH

IIIr; R^1 = H, R^2 = (CH$_2$)$_3$OCH$_2$CH$_3$

IIIs; R^1 = H, R^2 = CH$_2$C(CH$_3$)$_2$CH$_2$OH

IIIt; R^1 = H, R^2 = CH$_2$CH(OH)CH$_2$OH

Lancelot *et al.* [7] reported that the treatment of hydrochloride of 2-hydrazinopyrimidines with excess acetone afforded 3,3-dimethyl[1,2,4]triazolopyrimidines. However, in our case, the formation of such triazolo derivatives could not be confirmed on the reaction of **IIIa** with acetone. The reaction of **IIIa** with γ-butyrolactone gave the lactam **IIId** in 10% yield [8], which was probably formed *via* ring-opening of lactone and the further recyclization. The ir spectrum of this compound showed the absorption band at 1690 cm^{-1} attributed to carbonyl stretching vibration of

Equation 1:

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

Equation 2:

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

5-membered lactam ring and the ms spectrum showed the parent peak at m/z 294 and the base peak at m/z 210 (M^+ - lactam ring). These instrumental data and its pmr spectrum supported the proposal structure.

Some 4-alkylamino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines **IIIe-t** were obtained by the reaction of **I** with various alkylamines **IIe-t**. Among these compounds **IIIe-t**, syntheses of several compounds **IIIj,l-n** were already reported [6,9].

The inhibitory activity against platelet aggregation of the products **III** was screened by a turbidimetric method developed by Born and Cross [10] using an aggregometer. Preparation of platelet and measurement of platelet aggregation were performd the same as that stated in the previous paper [1] except for the final concentration of the test compound and aspirin. In this paper, the final concentration is 25 μmol/l, however in that paper [1] it was 50 μmol/l. The maximum aggregation rate (MAR) was calculated from an aggregation response curve obtained by equation 1, and then 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.

The inhibitory activity of aspirin against rabbit platelet aggregation was also screened as a positive control. Only 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. A comparison of the inhibition rate at the final concentration of 25 μmol/l of our compounds with

Table I 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]
IIIa	46.4±3.5		IIIl	44.0±2.7	
IIIb	33.2±5.1		IIIm	37.0±1.0	
IIIc	51.0±2.4[c]	15.5 (8.8 - 24.1)	IIIn	42.6±3.7	
IIId	73.9±2.6[c]	11.0 (8.5 - 13.5)	IIIo	24.5±0.6	
IIIe	66.0±3.7[c]	12.8 (8.7 - 16.9)	IIIp	18.9±3.5	
IIIf	50.1±5.6[d]	19.8 (13.0 - 29.5)	IIIq	23.4±5.4	
IIIg	57.9±6.6[c]	13.3 (7.9 - 19.2)	IIIr	26.0±2.9	
IIIh	18.1±1.2		IIIs	38.9±7.4	
IIIi	31.5±6.7		IIIt	42.0±7.6	
IIIj	26.5±2.0		aspirin	35.5±2.2	44.6 (37.6 - 55.0)
IIIk	28.6±2.5				

[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, and 50 μmol/l (in the case of aspirin, final concentrations were 10, 25, and 100 μmol/l). [c] Significantry different from aspirin at $p<0.01$. [d] Significantry different from aspirin at $p<0.05$.

that of aspirin shows that the inhibition rates of five compounds **IIIc,d,e,f,g** were respectively significantly different from that of aspirin at $p < 0.05$ on statistical analysis. That is, it was found that these five compounds had more potent activities than aspirin at that concentration. There are no significant differences from each other in their IC_{50} values in these five compounds. Compounds which showed similar activity to that of aspirin at the final concentration of 25 μmol/l, were **IIIa,b,i-n,r-t**. Compounds **IIIh,o-q** indicated significantly less activities. Hydrazine derivatives have a tendency to show higher activity. Comparison of

Table II Effect of Compounds IIIc, IIId, and IIIt on Reserpine-Induced Hypothermia in Mice

Compound	Body temperature (°C), mean value ± SE				
	Before administration	Time after administration			
		30 minutes1	1 hour	2 hours	4 hours
saline	24.5 ± 0.4	25.7 ± 0.3	27.1 ± 1.0	28.4 ± 0.6	30.3 ± 0.6
imipramine	24.5 ± 0.4	27.9 ± 1.0	30.8 ± 1.2[b]	33.0 ± 0.2[a]	32.0 ± 0.9
IIIc	24.6 ± 0.2	27.1 ± 0.4[b]	29.2 ± 0.5[b]	29.9 ± 0.7	30.4 ± 0.9
IIId	24.4 ± 0.3	26.1 ± 0.3	28.3 ± 0.6	30.4 ± 0.5[b]	31.0 ± 1.4
IIIt	24.5 ± 0.5	27.9 ± 1.5	29.0 ± 1.2	30.1 ± 0.3[b]	31.6 ± 0.9

Five male ICR-JCL mice weighing 20 to 32 g were used in all experiments and test compounds (10 mg/kg, *i.p.*) were injected at 18 hours after reserpine (2 mg/kg, *i.p.*) was administered to mice. [a] Significantly different from the control (saline) at $p<0.01$. [b] Significantly different from the control (saline) at $p<0.05$.

the number of carbon atoms between the nitrogen atom attached to the 4-position of the nucleus and another nitrogen or oxygen atom in the side chain showed that two is in preference to three. Compounds having free hydroxyl group at the terminal site of the side chain were less active than those having ether at the same site, and compounds having linear side chain were less active than those having branched one.

When the nucleus is took into account, it seems that we can have some presumptions as follows; dialkylaminoethylamino derivatives of benzo[*h*]quinazoline had poor inhibitory activity against platelet aggregation [1], but, similar derivatives of benzocycloheptapyrimidine **IIIg,i** showed higher potency except for **IIIh**. On the other hand, dialkylaminopropylamino derivatives of benzo[*h*]quinazoline had higher potency [1], and similar those of benzocycloheptapyrimidine **IIIo,p** were much less active. These facts seem to indicate that there are somewhat relationships between the shape of the middle ring of nucleus, cyclohexadiene or cycloheptadiene, and the length between two nitrogen atoms in the side chain. Furthermore, in the cases of dimethylamino derivatives and ethylamino derivatives, there were no significant differences in IC_{50} values between two nuclei. In the case of hydrazine derivatives, compound **IIIa** which is the derivative of benzocycloheptapyrimidine was less active than the similar derivative of benzo[*h*]quinazoline [1].

Evaluation of the antidepressive activity of the newly synthesized 4-substituted compounds was screened by the inhibition against reserpine-induced hypothermia in mice [11] and compared with that of control (saline). Only when the body temperature of mice administered with a test compound was significantly different from those of mice administered with saline at $p < 0.05$ on the statistical analysis using Student's *t*-test, the test compound was estimated as the potential one. It has been already reported that compounds **IIIl-n** had potent activity [9] and compound **IIIj** did not [6]. Among compounds **IIIa-i,k,o-t**, as shown in Table II, compounds **IIIc,d,t** exhibited the anti-reserpine activity, however, these activities were weaker than that of imipramine. Among 4-alkylamino derivatives **IIIe-t**, it was found that only some compounds showed potent activity, and interestingly all of them contained two carbon atoms between the nitrogen atom attached to the 4-position of nucleus and oxygen atom in the side chain, and also had a branched substituent. Furthermore, it was found that dimethylamino derivative **IIIe** and diethylaminoethylamino derivative **IIIg** which had much higher inhibitory activity against platelet aggregation were non-active against reserpine-induced hypothermia, however, all compounds which had anti-reserpine activity showed similar potency to that of aspirin or more than that against platelet aggregation.

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 ir spectra were obtained with a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer. The pmr spectra were measured with a Hitachi R-22 FTS FT-NMR spectrometer (90 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; q, quartet, quin, quintet; m, multiplet; br, broad. The EI ms spectra were taken with a Shimadzu LKB-9000 instrument at 70 eV. Amines used as reagents are commercially available. IUPAC numbering were used in the experimental.

General Procedure of the Reaction of 4-Chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**I**) with Various Amines **II**.

A mixture of 1 mmole of **I** and 5-8 mmoles of **II** was reacted at room temperature-80° for 1-4 hours. After evaporation of excess amine, 10-15 ml of water was added to the oily residue. The precipitated crystalline solid was collected by suction and recrystallization from an appropriate solvent. When the residue did not solidify on addition of water, it was extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The resulting residue was recrystallized from an appropriate solvent. When the residue thus obtained could not be recrystallized, it was treated with hydrochloric acid and crystallized as hydrochloride.

Preparation of 4-Hydrazino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIa**).

To a solution of 15.0 g (65.4 mmoles) of **I** in 50 ml of ethanol was added 32 ml of 80% hydrazine hydrate, and the resulting mixture was stirred for 4 hours at room temperature. The precipitated crystalline solid was collected by suction, washed with water, and recrystallized from benzene to give 13.7 g (93%) of the titled product as colorless prisms, mp 209-211°; ir (potassium bromide): 3370, 3300 (N-H) cm^{-1}; pmr (deuteriochloroform): 2.29 and 2.56 (4H and 2H, each m, 5,6,7-H), 4.60 (3H, br, exchangeable with deuterium oxide, $NHNH_2$), 7.34 (3H, m, 8,9,10-H), 7.77 (1H, m, 11-H), 8.72 (1H, s, 2-H); ms: m/z 226 (M^+).

Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.00; H, 6.23; N, 24.75. Found: C, 68.94; H, 6.28; N, 24.63.

Preparation of 4-Isopropylidenehydrazino-6,7-dihydro-5*H*-benzo-[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIb**).

A mixture of 453 mg (2.0 mmoles) of **IIIa** and 20 ml of acetone was relfuxed for 30 minutes. The mixture was evaporated to dryness and the resulting residue was recrystallized from benzene-cyclohexane to give 498 mg (94%) of the titled product as pale yellow needles, mp 184-186°; ir (potassium bromide): 3190 (N-H) cm^{-1}; pmr (DMSO-d_6): 2.01 and 2.04 (each 3H, each s, 2 × CH_3), 2.56 (6H, m, 5,6,7-H), 7.36 (3H, m, 8,9,10-H), 7.67 (1H, m, 11-H), 8.50 (1H, s, 2-H), 9.18 (1H, br, exchangeable with deuterium oxide, NH); ms: m/z 266 (M^+).

Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 72.08; H, 6.88; N, 20.76.

Preparation of 4-Benzylidenehydrazino-6,7-dihydro-5*H*-benzo-[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIc**).

To a solution of 453 mg (2.0 mmoles) of **IIIa** in 10 ml of benzene was added 0.20 ml (2.0 mmoles) of benzaldehyde, and the mixture was refluxed for 30 minutes. After evaporation of the mixture to dryness, the resulting residue was recrystallized from benzene-cyclohexane to give 605 mg (97%) of the titled product as pale yellow prisms, mp 195-197°; ir (potassium bromide): 3200 (N-H) cm^{-1}; pmr (deuteriochloroform): 2.30-3.00 (6H, m, 5,6,7-H), 7.36 (6H, m, 8,9,10- and 3',4',5'-H), 7.63 (3H, m, 11- and 2',6'-H), 8.60 (1H, br, exchangeable with deuterium oxide, NH), 8.73 (1H, s, 2-H); ms: m/z 314 (M^+).

Anal. Calcd. for $C_{20}H_{18}N_4$: C, 76.40; H, 5.77; N, 17.82. Found: C, 76.43; H, 5.83; N, 17.71.

Preparation of 4-[*N*-(2-Oxo-1-pyrrolidinyl)amino]-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIId**).

A mixture of 453 mg (2.0 mmoles) of **IIIa** and 10 ml of γ-butyrolactone was refluxed for 20 hours. After evaporation of excess γ-butyrolactone, the ethanol soluble fraction of the residue was recrystallized from benzene-*n*-hexane to give 59 mg (10%) of the titled product as colorless prisms, mp 232-234°; ir (potassium bromide): 3210 (N-H), 1690 (C=O) cm^{-1}; pmr (deuteriochloroform): 2.00-2.70 (10H, m, 5,6,7- and 3',4'-H), 3.81 (2H, t, J = 7 Hz, 5'-H), 7.33 (3H, m, 8,9,10-H), 7.63 (1H, m, 11-H), 7.82 (1H, br, exchangeable with deuterium oxide, NH), 8.70 (1H, s, 2-H); ms: m/z 294 (M^+).

Anal. Calcd. for $C_{17}H_{18}N_4O$: C, 69.36; H, 6.16; N, 19.03. Found: C, 69.34; H, 6.36; N, 18.79.

Preparation of 4-Dimethylamino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIe**).

To a solution of 1.2 g (5.0 mmoles) of **I** in 5 ml of dioxane was added 9.0 g (200 mmoles) of 50% dimethylamine aqueous solution, and the resulting solution was stirred at room temperature for a few minutes. The reaction mixture was evaporated to dryness and the residue was recrystallized from ethanol to give 1.2 g (99%) of the titled product as colorless needles, mp 131-132°; pmr (deuteriochloroform): 2.46 (6H, m, 5,6,7-H), 3.15 (6H, s, 2 × CH_3), 7.30 (3H, m, 8,9,10-H), 7.82 (1H, m, 11-H), 8.67 (1H, s, 2-H); ms: m/z 239 (M^+).

Anal. Calcd. for $C_{15}H_{17}N_3$: C, 75.28; H, 7.15; N, 17.55. Found: C, 75.19; H, 7.25; N, 17.47.

Preparation of 4-Ethylamino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIf**).

To a solution of 230 mg (1.0 mmole) of **I** in 5 ml of dioxane was added 0.77 g (12 mmoles) of 70% ethylamine aqueous solution, and the resulting mixture was stirred at room temperature for 48 hours. After evaporation of the reaction mixture, a small amount of water was added to the residue and the mixture was extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The obtained residue was recrystallized from cyclohexane to give 237 mg (99%) of the titled product as colorless needles, mp 151-152°; ir (potassium bromide): 3310 (N-H) cm^{-1}; pmr (deuteriochloroform): 1.30 (3H, t, J = 7 Hz, 2'-H), 2.27 and 2.58 (4H and 2H, m and t, J = 5.5 Hz, 5,6,7-H), 3.60 (2H, quin, J = 7 Hz, changed to quartet after addition to deuterium oxide, J = 7 Hz, 1'-H), 4.83 (1H, br, exchangeable with deuterium oxide, NH), 7.37 (3H, m, 8,9,10-H), 7.77 (1H, m, 11-H), 8.70 (1H, s, 2-H); ms: m/z 239 (M^+).

Anal. Calcd. for $C_{15}H_{17}N_3$: C, 75.28; H, 7.15; N, 17.55. Found: C, 75.37; H, 7.04; N, 17.42.

Preparation of 4-(2-Diethylaminoethylamino)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIg**).

The reaction was continued for 1 hour at 80°. The titled product was obtained (52%) as colorless needles (diethyl ether), mp 86-87°; ir (potassium bromide): 3260 (N-H) cm^{-1}; pmr (deuteriochloroform): 1.05 (6H, t, J = 6 Hz, 2 × CH_3), 2.10 and 2.27 (2H and 4H, each m, 5,6,7-H), 2.55 (2H, t, J = 6 Hz, 2'-H), 2.67 (4H, q,

J = 6 Hz, 2 × CH_2CH$_3$), 3.53 [2H, q, J = 6 Hz, changed to triplet (J = 6 Hz) after addition of deuterium oxide, 1'-H], 5.87 (1H, br, exchangeable with deuterium oxide, NH), 7.36 (3H, m, 8,9,10-H), 7.77 (1H, m, 11-H), 8.67 (1H, s, 2-H); ms: m/z 310 (M$^+$).

Anal. Calcd. for $C_{19}H_{26}N_4$: C, 73.51; H, 8.44; N, 18.04. Found: C, 73.45; H, 8.40; N, 17.92.

Preparation of 4-(2-Pyrrolidinoethylamino)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIh**) as the Dihydrochloride.

The reaction was continued for 2 hours at 80°. The titled product was obtained (74%) as colorless plates (ethanol-acetone), mp 119-123°; ir (potassium bromide): 3330 (N-H) cm^{-1}; pmr (DMSO-d_6): 2.00 (4H, m, pyrrolidine-3,4-H), 2.36 and 2.65 (2H and 4H, each m, 5,6,7-H), 3.50 (8H, m, 1',2'- and pyrrolidine-2,5-H), 7.40, 9.42 and 11.28 (each 1H, each br, exchangeable with deuterium oxide, 3 × NH), 7.60 (4H, m, 8,9,10,11-H), 8.87 (1H, s, 2-H); ms: (parent peak was not observed) m/z 308 (M − 72).

Anal. Calcd. for $C_{19}H_{26}Cl_2N_4$: C, 59.84; H, 6.87; N, 14.67. Found: C, 59.97; H, 6.81; N, 14.53.

Preparation of 4-(2-Morpholinoethylamino)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIi**).

The reaction was continued for 2 hours at 90°. The titled product was obtained (87%) as pale yellow prisms (cyclohexane), mp 114-115°; ir (potassium bromide): 3227 (N-H) cm^{-1}; pmr (deuteriochloroform): 2.12 and 2.32 (2H and 4H, each m, 5,6,7-H), 2.56 (4H, m, morpholine-3,5-H), 2.68 (2H, t, J = 6 Hz, 2'-H), 3.57 (2H, m, 1'-H), 3.73 (4H, m, morpholine-2,6-H), 5.67 (1H, br, exchangeable with deuterium oxide, NH), 7.38 (3H, m, 8,9,10-H), 7.80 (1H, m, 11-H), 8.69 (1H, s, 2-H); ms: (parent peak was not observed) m/z 113 (M$^+$ - 211, base peak).

Anal. Calcd. for $C_{19}H_{24}N_4O$: C, 70.34; H, 7.45; N, 17.26. Found: C, 70.48; H, 7.43; N, 17.11.

Preparation of 4-(2-Methoxyethylamino)-6,7-dihydro-5*H*-benzo-[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIk**).

The reaction was continued for 4 hours at 90°. The titled product was obtained (66%) as colorless plates (cyclohexane), mp 139-140°; ir (potassium bromide): 3253 (N-H) cm^{-1}; pmr (deuteriochloroform): 2.20 and 2.58 (4H and 2H, m and t, J = 6 Hz, 5,6,7-H), 3.45 (3H, s, CH$_3$), 3.67 (4H, m, 1',2'-H), 5.26 (1H, br, exchangeable with deuterium oxide, NH), 7.36 (3H, m, 8,9,10-H), 7.78 (1H, m, 11-H), 8.68 (1H, s, 2-H); ms: m/z 269 (M$^+$).

Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 71.34; H, 7.11; N, 15.60. Found: C, 71.55; H, 6.97; N, 15.46.

Preparation of 4-(3-Dimethylaminopropylamino)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIo**).

The reaction was continued for 2 hours at room temperature. The titled product was obtaind (66%) as pale yellow prisms (cyclohexane), mp 80-82°; ir (potassium bromide): 3240 (N-H) cm^{-1}; pmr (deuteriochloroform): 1.84 [2H, m, changed to quintet (J = 6 Hz) after addition of deuterium oxide, 2'-H], 2.08, 2.27, and 2.55 (each 2H, each m, 5,6,7-H), 2.32 (6H, s, 2 × CH$_3$), 2.55 (2H, m, superimposed on 5- or 7-H, 3'-H), 3.62 [2H, q, J = 6 Hz, changed to triplet (J = 6 Hz) after addition of deuterium oxide, 1'-H], 6.90 (1H, br, exchangeable with deuterium oxide, NH), 7.36 (3H, m, 8,9,10-H), 7.77 (1H, m, 11-H), 8.67 (1H, s, 2-H); ms: m/z 296 (M$^+$).

Anal. Calcd. for $C_{18}H_{24}N_4$: C, 72.93; H, 8.16; N, 18.90. Found: C, 72.70; H, 8.23; N, 18.79.

Preparation of 4-(3-Morpholinopropylamino)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIp**).

The reaction was continued for 1 hour at 90°. The titled product was obtained (88%) as colorless prisms (cyclohexane), mp 145-146°; ir (potassium bromide): 3260 (N-H) cm^{-1}; pmr (deuteriochloroform): 1.87 (2H, quin, J = 6 Hz, 2'-H), 2.12 and 2.34 (2H and 4H, each m, 5,6,7-H), 2.53 (6H, m, 3 × NCH$_2$), 3.63 [2H, m, changed to triplet (J = 7 Hz) after addition of deuterium oxide, 1'-H], 3.73 (4H, m, 2 × OCH$_2$), 6.72 (1H, br, exchangeable with deuterium oxide, NH), 7.34 (3H, m, 8,9,10-H), 7.77 (1H, m, 11-H), 8.69 (1H, s, 2-H); ms: (parent peak was not observed) m/z 252 (M$^+$ - 87, base peak).

Anal. Calcd. for $C_{20}H_{26}N_4O$: C, 70.97; H, 7.74; N, 16.55. Found: C, 70.80; H, 7.85; N, 16.37.

Preparation of 4-(3-Hydroxypropylamino)-6,7-dihydro-5*H*-benzo-[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIq**).

The reaction was continued for 1 hour at 90°. The titled product was obtained (83%) as colorless needles (cyclohexane), mp 135-136°; ir (potassium bromide): 3280, 3130 (O-H and N-H) cm^{-1}; pmr (deuteriochloroform): 1.84 (2H, quin, J = 6 Hz, 2'-H), 2.40 (6H, m, 5,6,7-H), 3.72 (4H, m, 1',3'-H), 5.44 (2H, br, exchangeable with deuterium oxide, NH and OH), 7.33 (3H, m, 8,9,10-H), 7.75 (1H, m, 11-H), 8.60 (1H, s, 2-H); ms: m/z 269 (M$^+$).

Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 71.34; H, 7.11; N, 15.60. Found: C, 71.15; H, 7.06; N, 15.41.

Preparation of 4-(3-Ethoxypropylamino)-6,7-dihydro-5*H*-benzo-[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIr**).

The reaction was continued for 1 hour at 80°. The titled product was obtained (82%) as colorless needles (cyclohexane), mp 77-78°; ir (potassium bromide): 3270 (N-H) cm^{-1}; pmr (deuteriochloroform): 1.14 (3H, t, J = 8 Hz, CH$_3$), 1.85 (2H, br quin, J = 6 Hz, 2'-H), 2.19 and 2.48 (4H and 2H, each m, 5,6,7-H), 3.55 (6H, m, 1',3'-H and CH_2CH$_3$), 5.88 (1H, br, exchangeable with deuterium oxide, NH), 7.29 (3H, m, 8,9,10-H), 7.68 (1H, m, 11-H), 8.58 (1H, s, 2-H); ms: m/z 297 (M$^+$).

Anal. Calcd. for $C_{18}H_{23}N_3O$: C, 72.69; H, 7.79; N, 14.12. Found: C, 72.51; H, 7.92; N, 14.28.

Preparation of 4-(2,2-Dimethyl-3-hydroxypropylamino)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIs**).

The reaction was continued for 1.5 hours at 80°. The titled prodcut was obtained (84%) as colorless needles (cyclohexane), mp 142-143°; ir (potassium bromide): 3360, 3270 (O-H and N-H) cm^{-1}; pmr (deuteriochloroform): 1.00 (6H, s, 2 × CH$_3$), 2.43 (6H, m, 5,6,7-H), 3.21 (2H, br s, 1'- or 3'-H), 3.42 (2H, d, J = 6 Hz, 3'- or 1'-H), 5.20 (2H, br, exchangeable with deuterium oxide, NH and OH), 7.33 (3H, m, 8,9,10-H), 7.72 (1H, m, 11-H), 8.60 (1H, s, 2-H); ms: m/z 297 (M$^+$).

Anal. Calcd. for $C_{18}H_{23}N_3O$: C, 72.69; H, 7.79; N, 14.12. Found: C, 72.81; H, 7.74; N, 14.35.

Preparation of 4-(2,3-Dihydroxypropylamino)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (**IIIt**).

A mixture of 461 mg (2.0 mmoles) of **I**, 455 mg (5.0 mmoles) of 3-amino-1,2-propanediol (**IIt**), 3 ml of dioxane, and 3 ml of monoglyme was refluxed for 4 days. After addition of 20 ml of water to the reaction mixture, the precipitated crystalline solid was collected by suction and recrystallized from acetone-methanol to give 500 mg (88%) of the titled product as colorless needles, mp 175-177°; ir (potassium bromide): 3387, 3297 (O-H and N-H) cm^{-1};

pmr (DMSO-d_6): 2.26 and 2.50 (4H and 2H, m and t, J = 7 Hz, 5,6,7-H), 3.42 (4H, m, 1'- and 3'-H), 3.68 (1H, m, 2'-H), 4.61 (1H, t, J = 5.5 Hz, exchangeable with deuterium oxide, CH_2OH or NH), 4.86 (1H, d, J = 5 Hz, exchangeable with deuterium oxide, CHO*H*), 7.05 (1H, m, exchangeable with deuterium oxide, NH or CH_2OH), 7.38 (3H, m, 8,9,10-H), 7.65 (1H, m, 11-H), 8.48 (1H, s, 2-H); ms: m/z 285 (M^+).

Anal. Calcd. for $C_{16}H_{19}N_3O_2$: C, 67.34; H, 6.71; N, 14.72. Found: C, 67.36; H, 6.60; N, 14.56.

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