Polycyclic *N*-Heterocyclic Compounds. XLIV. Synthesis of the Novel B,D-Dihomo-11,13,15-triazasteroidal Skeleton and their Effect on Reserpine-Induced Hypothermia and Inhibitory Activity on Platelet Aggregation

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Synthesis of benzo[3,4]cyclohepta[1,2-*e*]pyrimido[1,2-*c*]pyrimidines, corresponding to the B,D-dihomo-11,13,15-triazasteroidal skeleton as a novel ring system is described. Their effects on reserpine-induced hypothermia in mice and inhibitory activity against collagen-induced platelet aggregation were also investigated.

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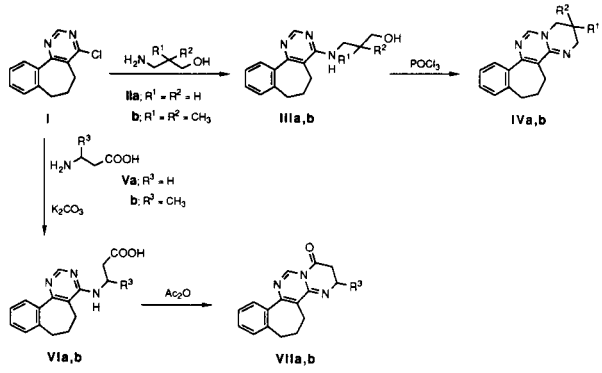
In previous papers [2], we reported that some derivatives of benzo[*h*]imidazo[1,2-*c*]quinazoline (corresponding to 11,13,15-triazasteroids), benzo[*h*]pyrimido[1,2-*c*]quinazoline (corresponding to a D-homo-11,13,15-triazasteroid), and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4(3*H*)-one (corresponding to the precursor of a B-homo-11,13,15-triazasteroid) exhibited inhibitory activity on reserpine-induced hypothermia in mice. With regard to the tricyclic 4-oxo derivative as a precursor of a triazasteroid, it was also found that some cycloheptadiene derivatives which have a seven-membered ring system as the B-ring had a superiority over the cyclohexadiene one [2c]. On the other hand, it has been reported that some benzo[*h*]quinazoline and benzo[6,7]cyclohepta[1,2-*d*]pyrimidine derivatives which have alkylamino or other groups on the 4-position of their nuclei and their cyclized products, benzo[*h*]imidazo[1,2-*c*]quinazoline and benzo[3,4]cyclohepta[1,2-*e*]imidazo[1,2-*c*]pyrimidine derivatives, had inhibitory activity on collagen-induced platelet aggregation [3].

In this paper, as a series on the research of the structure-activity relationship between anti-reserpine or antiplatelet aggregation activity and azasteroids, we describe the synthesis of benzo[3,4]cyclohepta[1,2-*e*]pyrimido[1,2-*c*]pyrimidine derivatives, corresponding to the B,D-dihomo-11,13,15-triazasteroids. The effect on reserpine-induced hypothermia and antiplatelet aggregation activity of them and their precursors are also described.

As shown in Scheme 1, 4-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine **I** [2c] was used as the starting material. The reaction of 3-amino-1-propanol derivatives **IIa,b** with **I** gave the corresponding 4-(3-hydroxypropylamino)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]-pyrimidines **IIIa,b**. These products were respectively cyclized to the corresponding tetracyclic compounds, 2,3,6,7-tetrahydro-1*H*,5*H*-benzo[3,4]cyclohepta[1,2-*e*]pyrimido[1,2-*c*]pyrimidines **IVa,b**, by using phosphoryl chloride in the similar manner previously reported [3b]. For the purpose of introducing the oxygen function on the pyrimidine ring corresponding to D-ring, the following reactions were performed. That is, 4-chloro derivative **I** was allowed to react with β-alanine derivatives **Va,b** in the presence of potassium carbonate to give *N*-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-β-alanines **VIa,b**. These compounds **VIa,b** were cyclized to afford the expected 1-oxo-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[3,4]-cyclohepta[1,2-*e*]pyrimido[1,2-*c*]pyrimidines **VIIa,b** by stirring with acetic anhydride. On the other hand, as shown in Scheme 2, heating of 4-amino-6,7-dihydro-5*H*-

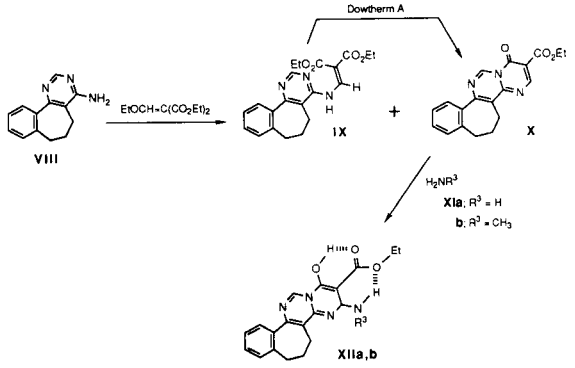
Scheme 1



benzo[6,7]cyclohepta[1,2-*d*]pyrimidine **VIII** [2c] with diethyl ethoxymethylenemalonate gave a mixture of diethyl *N*-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)aminomethylenemalonate **IX** and ethyl 1-oxo-6,7-dihydro-1*H*,5*H*-benzo[3,4]cyclohepta[1,2-*e*]pyrimido[1,2-*c*]-pyrimidine-2-carboxylate **X**. Compound **I4** was also able to be converted to compound **X** by heating in Dowtherm A. In our previous study [3], some of tricyclic compounds which has an alkylamino or an amino group on the pyrimidine-ring had antiplatelet aggregation activity. This result

prompted us to prepare the tetracyclic compounds which have an amino or an alkylamino group on the pyrimidine-ring. As shown in Scheme 2, the reaction of compound **X** with concentrated ammonia water gave ethyl 3-amino-1-hydroxy-6,7-dihydro-3*H*,5*H*-benzo[3,4]cyclohepta[1,2-*e*]-pyrimido[1,2-*c*]pyrimidine-2-carboxylate **XIIa** in 48% yield. On the other hand, compound **X** was allowed to react with methylamine to afford ethyl 1-hydroxy-3-methylamino-6,7-dihydro-3*H*,5*H*-benzo[3,4]cyclohepta[1,2-*e*]-pyrimido[1,2-*c*]pyrimidine-2-carboxylate **XIIb** in 61% yield.

Scheme 2



Evaluation of the activity of the newly synthesized tetracyclic compounds and their precursors was screened by the effect against reserpine-induced hypothermia in mice [4] and compared with that of the 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 statistical analysis using the Student's *t*-test, the test compound was estimated as the potential one. Interestingly, compounds **VIb**, **VIIa**, and **XIIa** obviously decreased the body temperature of mice. That is, it seemed that they have co-reserpine activity. On the other hand, there was no compound which obviously increased the body temperature.

The inhibitory activity against platelet aggregation of the tetracyclic compound and their precursors was screened by a turbidimetric method developed by Born and Cross [5] using an aggregometer. Preparation of platelet, measurement of platelet aggregation and the calculation of the inhibition rate were performed in the same manner described previously [3b]. Only when the inhibition rate of the test compound was significantly different from that of aspirin at $p < 0.05$ on statistical analysis using the Student's *t*-test, the test compound was estimated as being potential. Many compounds in this paper produced a dose-dependent inhibition against rabbit platelet aggregation induced by collagen, however, the inhibition rate of all compounds was not significantly different from that of aspirin as a potential compound.

Finally, it seemed that the ring-expansion of the B,D-rings at the same time reduced both inhibitory activities on reserpine-induced hypothermia and on collagen-induced 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 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 as potassium bromide pellets and frequencies are expressed in cm^{-1}. The pmr 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 and chemical shifts are reported in ppm (δ) and J values in Hz, and the signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br, broad.

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

A mixture of 346 mg (1.50 mmoles) of 4-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine **I** and 563 mg (7.51 mmoles) of 3-amino-1-propanol **IIa** was heated at 90-100° for 1 hour. To the reaction mixture was added 10 ml of water and the precipitated solid was recrystallized from cyclohexane to afford 333 mg (83%) of **IIIa** as colorless needles, mp 135-136°; ir: 3280, 3130 (N-H and O-H stretching); EI-ms: m/z 269 (M^+); ^1H nmr (deuteriochloroform): 1.83 (quin, J = 6.0, 2H, 2'-H), 2.26 and 2.57 (each m, 4H and 2H, 5,6,7-H), 3.72 (m, 4H, 1',3'-H), 5.44 (br, 2H, exchangeable with deuterium oxide, OH and NH), 7.37 (m, 3H, 8,9,10-H), 7.75 (m, 1H, 11-H), 8.60 (s, 1H, 2-H).

Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 71.34; H, 7.11; N, 15.60. Found: C, 71.49; H, 7.18; N, 15.30.

2,3,6,7-Tetrahydro-1*H*,5*H*-benzo[3,4]cyclohepta[1,2-*e*]pyrimido-[1,2-*c*]pyrimidine (**IVa**).

A mixture of 204 mg (0.76 mmole) of compound **IIIa** and 0.4 ml of phosphoryl chloride in 1.6 ml of dry chloroform was refluxed for 1 hour. After cooling, the mixture was evaporated and 10 ml of water was added to the residue. The resulting mixture was made alkaline with sodium hydrogen carbonate and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The resulting residue was crystallized from benzene and recrystallized from acetone to give 80 mg (42%) of **IVa** as colorless needles, mp 269-270°; EI-ms: m/z 251 (M^+); ^1H nmr (deuteriochloroform): 2.30 and 2.65 (each m, 2H and 6H, 2,5,6,7-H), 3.30 and 4.33 (each m, each 2H, 1,3-H), 7.38 (m, 3H, 8,9,10-H), 7.65 (m, 1H, 11-H), 8.17 (s, 1H, 13-H).

Anal. Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.81; N, 16.71. Found: C, 76.34; H, 6.86; N, 16.60.

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

A mixture of 346 mg (1.50 mmoles) of **I** and 782 mg (7.59 mmoles) of 3-amino-2,2-dimethyl-1-propanol **IIb** was heated at 90-100° for 1 hour. After cooling, a small amount of water was

added to the mixture. The precipitated solid was collected by filtration and recrystallized from cyclohexane to afford 324 mg (73%) of **IIIb** as colorless needles, mp 142-143°; ir: 3360, 3270 (N-H and O-H stretching); EI-ms: m/z 297 (M^+); ^1H nmr (deuteriochloroform): 0.97 (s, 6H, 2 x CH_3), 2.30 and 2.57 (m and br t, J = 6.0, 4H and 2H, 5,6,7-H), 3.22 and 3.38 (br s and d, J = 6.5, each signal changed to singlet respectively after addition of deuterium oxide, each 2H, 1',3'-H), 5.10 and 5.30 (each br, each 1H, exchangeable with deuterium oxide, NH and OH), 7.32 (m, 3H, 8,9,10-H), 7.73 (m, 1H, 11-H), 8.57 (s, 1H, 2-H).

Anal. Calcd. for $C_{18}H_{23}N_3O$: C, 72.69; H, 7.79; N, 14.12. Found: C, 72.75; H, 7.92; N, 14.08.

2,2-Dimethyl-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[3,4]cyclohepta-[1,2-*e*]pyrimido[1,2-*c*]pyrimidine (**IVb**).

A mixture of 195 mg (0.66 mmole) of **IIIb** and 0.3 ml of phosphoryl chloride in 1.6 ml of dry chloroform was refluxed for 22 hours. After cooling, the mixture was evaporated, and a small amount of water was added to the residue. The resulting mixture was made alkaline with sodium hydrogen carbonate and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized from cyclohexane to afford 78 mg (42%) of **IVb** as colorless needles, mp 114-116°; EI-ms: m/z 279 (M^+); ^1H nmr (deuteriochloroform): 1.07 (s, 6H, 2 x CH_3), 2.20-2.70 (m, 6H, 5,6,7-H), 3.31 and 3.46 (each s, each 2H, 1,3-H), 7.25 (m, 3H, 8,9,10-H), 7.47 (s, 1H, 13-H), 7.62 (m, 1H, 11-H).

Anal. Calcd. for $C_{18}H_{21}N_3$: C, 77.38; H, 7.57; N, 15.04. Found: C, 77.02; H, 7.69; N, 14.76.

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

A mixture of 461 mg (2.00 mmoles) of **I**, 356 mg (4.00 mmoles) of β-alanine **Va**, 345 mg (2.50 mmoles) of potassium carbonate in 20 ml of a mixture of dioxane and water (1:1, v/v) was heated at 90-95° for 25 hours. After evaporation of the reaction mixture, a small amount of water was added to the residue and the resulting solution was adjusted to *p*H 4-5 by addition of acetic acid. The precipitated crystalline solid was collected by filtration and recrystallized from ethanol to afford 489 mg (87%) of **VIa** as colorless needles, mp 227-228°; ir: 3360, 2920 (N-H and O-H stretching), 1700 (C=O stretching); EI-ms: m/z 283 (M^+); ^1H nmr (DMSO-d_6): 2.23 and 2.60 (each m, 4H and 2H, 5,6,7-H), 2.56 (t, J = 7.0, 2H, $COCH_2$), 3.61 (q, J = 7.0, changed to triplet after addition of deuterium oxide, J = 7.0, 2H, NCH_2), 7.33 (m, 4H, changed to 3H after addition of deuterium oxide, 8,9,10-H and NH), 7.57 (m, 1H, 11-H), 8.44 (s, 1H, 2-H), 12.10 (br, 1H, exchangeable with deuterium oxide, COOH).

Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.04; N, 14.83. Found: C, 67.65; H, 6.13; N, 14.86.

1-Oxo-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[3,4]cyclohepta[1,2-*e*]pyrimido[1,2-*c*]pyrimidine (**VIIa**).

A solution of 198 mg (0.70 mmole) of **VIa** in a mixture of 2 ml of acetic anhydride and 3 ml of pyridine was stirred at room temperature for 73 hours. After evaporation of the reaction mixture, the hot benzene soluble fraction of the residue was chromatographed on silica gel. The eluate from chloroform-acetone (2:1, v/v) was recrystallized from cyclohexane-benzene to afford 45 mg (24%) of **VIIa** as colorless needles, mp 282-284°; ir: 1640 (C=O stretching); EI-ms: m/z 265 (M^+); ^1H nmr (DMSO-d_6): 2.27 and 2.57 (each m, 2H and 4H, 5,6,7-H), 2.64 (t, J = 7.5, 2H, 2-H), 4.42 (t, J = 7.5, 2H, 3-H), 7.36 (m, 3H, 8,9,10-H), 7.61 (m, 1H, 11-H), 8.48 (s, 1H, 13-H).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.69; N, 15.83. Found: C, 72.61; H, 5.72; N, 16.02.

N-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-3-amino-*n*-butyric Acid (**VIb**).

A mixture of 346 mg (1.50 mmoles) of **I**, 309 mg (3.00 mmoles) of 3-amino-*n*-butyric acid **Vb**, and 260 mg (1.88 mmoles) of potassium carbonate in 15 ml of a mixture of dioxane and water (1:1, v/v) was heated at 90° for 4 days. After evaporation of the solvent, 5 ml of water was added to the residue. The resulting solution was adjusted to *p*H 4 by addition of acetic acid and extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated. The resulting oily residue was crystallized and recrystallized from diluted ethanol to afford 203 mg (45%) of **VIb** as colorless needles, mp 195-196°; ir: 3400 (N-H and O-H stretching), 1680 (C=O stretching); FAB-ms: m/z 298 (MH^+); ^1H nmr (DMSO-d_6): 1.20 (d, J = 6.4, 3H, CH_3), 2.12 (br quin, J = 6.2, 2H, 6-H), 2.28 (br d, J = 6.0, 2H, $COCH_2$), 2.32-2.70 (m, 4H, 5,7-H), 4.59 (br septet, J = 6.9, changed to broad sextet after addition of deuterium oxide, J = 6.7, 1H, C*H*CH_3), 6.86 (d, J = 7.9, 1H, exchangeable with deuterium oxide, NH), 7.35 (m, 3H, 8,9,10-H), 7.56 (dd, $J_{11,10}$ = 6.3, $J_{11,9}$ = 3.3, 1H, 11-H), 8.43 (s, 1H, 2-H).

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.13. Found: C, 68.83; H, 6.59; N, 13.84.

3-Methyl-1-oxo-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[3,4]cyclohepta-[1,2-*e*]pyrimido[1,2-*c*]pyrimidine (**VIIb**).

A solution of 387 mg (1.30 mmoles) of **VIb** in a mixture of 1 ml of acetic anhydride and 1 ml of pyridine was heated at 90° for 30 minutes. After cooling of the reaction mixture, the precipitated crystalline solid was collected by filtration and recrystallized from acetone-methanol to afford 105 mg (29%) of **VIIb** as colorless needles, mp 274-275°; ir: 1635 (C=O stretching); FAB-ms: m/z 280 (MH^+); ^1H nmr (deuteriochloroform): 1.55 (d, J = 6.9, 3H, CH_3), 2.32 (br quin, J = 6.6, 2H, 6-H), 2.58 (d, J = 7.0, 2H, 2-H), 2.61-3.00 (m, 4H, 5,7-H), 4.59 (m, 1H, 3-H), 7.35 (m, 3H, 8,9,10-H), 7.68 (dd, $J_{11,10}$ = 6.5, $J_{11,9}$ = 2.9, 1H, 11-H), 8.13 (s, 1H, 13-H).

Anal. Calcd. for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04. Found: C, 72.95; H, 6.18; N, 14.94.

Diethyl *N*-(6,7-Dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)aminomethylenemalonate (**IX**) and Ethyl 1-Oxo-6,7-dihydro-1*H*,5*H*-benzo[3,4]cyclohepta[1,2-*e*]pyrimido[1,2-*c*]pyrimidine-2-carboxylate (**X**).

A mixture of 2.11 g (10.0 mmoles) of **VIII** and 4.28 g (19.8 mmoles) of diethyl ethoxymethylenemalonate in 200 ml of xylene was refluxed for 2 days. After evaporation of the reaction mixture, *n*-hexane was added to the residue, and concentration of the hot *n*-hexane soluble fraction followed by recrystallization from ethanol gave 1.93 g of a mixture of **IX** and **X** (approximately 1:1). For instrumental data, an aliquot of this mixture was crystallized from petroleum ether and recrystallized from *n*-hexane to afford **XI** as colorless needles, mp 95-97°; ir: 3240 (N-H stretching), 1690 (C=O stretching); EI-ms: m/z 381 (M^+); ^1H nmr (deuteriochloroform): 1.36 and 1.39 (each t, J = 7.0, each 3H, 2 x CH_3),

2.53 (m, 6H, 5,6,7-H), 4.31 and 4.36 (each q, J = 7.0, each 2H, 2 x CH_2CH_3), 7.40 (m, 3H, 8,9,10-H), 7.77 (dd, $J_{11,10}$ = 7.0, $J_{11,9}$ = 3.0, 1H, 11-H), 8.89 (s, 1H, 13-H), 9.30 (d, J = 11.5, changed to singlet after addition of deuterium oxide, 1H, C*H*NH), 11.59 (br d, J = 11.5, 1H, exchangeable with deuterium oxide, NH).

Anal. Calcd. for $C_{21}H_{23}N_3O_4$: C, 66.12; H, 6.07; N, 11.01. Found: C, 66.45; H, 5.84; N, 11.30.

The mixture of **IX** and **X** described above was heated with 7.4 g of Dowtherm A at 250-260° for 1 hour. After cooling of the reaction mixture, petroleum ether was added to the mixture. The precipitated crystalline solid was collected by filtration, washed with petroleum ether, and recrystallized from ethanol to give 1.52 g (overall yield from **VIII** was 45%) of **X** as pale yellow needles, mp 159-161°; ir: 1720, 1695 (C=O stretching); EI-ms: m/z 335 (M^+); ^{1}H nmr (deuteriochloroform): 1.43 (t, J = 7.5, 3H, CH_3), 2.57 and 3.03 (m and t, J = 6.5, 4H and 2H, 5,6,7-H), 4.46 (q, J = 7.5, 2H, CH_2CH_3), 7.46 (m, 3H, 8,9,10-H), 7.85 (dd, $J_{11,10}$ = 6.5, $J_{11,9}$ = 3.5, 1H, 11-H), 9.10 (s, 1H, 3-H), 9.92 (s, 1H, 13-H).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.04; H, 5.10; N, 12.52. Found: C, 68.24; H, 5.03; N, 12.71.

Ethyl 3-Amino-1-hydroxy-6,7-dihydro-3*H*,5*H*-benzo[3,4]cyclohepta[1,2-*e*]pyrimido[1,2-*c*]pyrimidine-2-carboxylate (**XIIa**).

A solution of 224 mg (0.67 mmole) of **X** in a mixture of 4 ml of concentrated ammonia water **XIa** and 20 ml of dioxane was stirred at room temperature for 6 days. After evaporation of the reaction mixture, the hot *n*-hexane soluble fraction of the oily residue was crystallized from petroleum ether and recrystallized from cyclohexane-benzene to afford 113 mg (48%) of **XIIa** as pale yellow granules, mp 182-183°; ir: 3300, 3180, 3100 (O-H and N-H stretching), 1660 (C=O stretching); EI-ms: m/z 352 (M^+); ^{1}H nmr (deuteriochloroform): 1.33 (t, J = 7.0, 3H, CH_3), 2.45 (m, 6H, 5,6,7-H), 4.27 (q, J = 7.0, 2H, CH_2CH_3), 6.30 (br, 1H, exchangeable with deuterium oxide, NH), 7.30 (m, 3H, 8,9,10-H), 7.77 (dd, $J_{11,10}$ = 6.0, $J_{11,9}$ = 3.5, 1H, 11-H), 8.27 (dd, J = 16.0 and 8.0, changed to singlet after addition of deuterium oxide, 1H, 3-H), 9.02 (s, 1H, 13-H), 9.87 (br, 1H, exchangeable with deuterium oxide, NH), 11.65 (br s, 1H, exchangeable with deuterium oxide, OH).

Anal. Calcd. for $C_{19}H_{20}N_4O_3$: C, 64.75; H, 5.72; N, 15.89. Found: C, 65.03; H, 5.79; N, 15.64.

Ethyl 1-Hydroxy-3-methylamino-6,7-dihydro-3*H*,5*H*-benzo[3,4]-cyclohepta[1,2-*e*]pyrimido[1,2-*c*]pyrimidine-2-carboxylate (**XIIb**).

A solution of 168 mg (0.50 mmole) of **X** and 388 mg of 40% methylamine (containing 5.00 mmoles of methylamine) **XIb** in 5 ml of dioxane was stirred for 25 hours. After evaporation of the reaction mixture, the chloroform-ethanol (1:1, v/v) soluble fraction of the residue was crystallized from acetone-petroleum ether and recrystallized from ethanol to afford 111 mg (60%) of **XIIb** as pale yellow granules, mp 170-173°; ir: 3400, 3180 (O-H and N-H stretching), 1665 (C=O stretching); FAB-ms: m/z 367 (MH^+); ^{1}H nmr (deuteriochloroform): 1.33 (t, J = 7.0, 3H, CH_2CH_3), 2.55 (m, 6H, 5,6,7-H), 3.18 (d, J = 5.0, 3H, NCH_3), 4.26 (q, J = 7.0, 2H, CH_2CH_3), 7.30 (m, 3H, 8,9,10-H), 7.76 (dd, $J_{11,10}$ = 7.0, $J_{11,9}$ = 3.0, 1H, 11-H), 8.08 (d, J = 14.0, changed to a singlet after addition of deuterium oxide, 1H, 3-H), 9.02 (s, 1H, 13-H), 10.36 (br, 1H, exchangeable wiht deuterium oxide, NH), 11.67 (br s, 1H, exchangeable with deuterium oxide, OH).

Anal. Calcd. for $C_{20}H_{22}N_4O_3$: C, 65.55; H, 6.05; N, 15.29. Found: C, 65.70; H, 6.10; N, 15.45.

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