Polycyclic *N*-Heterocyclic Compounds. Part 59[1]: Rearrangement Reactions of Fused Tricyclic 3-(2-Bromoethyl)pyrimidin-4(3*H*)-ones with Primary Amines *via* a Dimroth-Type Rearrangement

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Reaction of some fused tricyclic 3-(2-bromoethyl)pyrimidin-4(3*H*)-ones with primary alkyl amines gave abnormal fused 3-alkyl-4-alkyliminopyrimidines *via* a Dimroth-type rearrangement, as well as normal substituted 3-(2-alkylaminoethyl) derivatives in methanol. This abnormal rearrangement reaction depended on reaction solvent.

Key words Dimroth rearrangement; 3-alkyl-4-alkyliminopyrimidine; pyrimidin-4(3*H*)-one; heterocycle; tandem reaction

Synthetic heterocycles are a rich source of pharmaceutical compounds. Among them, ring-fused pyrimidines and their corresponding pyrimidin-4(3*H*)-ones are unique due to their bioactivity. We have already showed that these heterocyclic compounds had antidepressant activity and anti-platelet aggregation activity.[2,3] Therefore, we decided to search for more potent derivatives by chemical modification.

Fused 3-alkyl-4-alkyliminopyrimidines have been reported to be accessible from either 1) 3-alkyl-4-acyliminopyrimidines by nucleophilic attack of alkylamines at the C4-position[4] or 2) N3 alkylation of 4-alkylaminopyrimidines.[5] In our previous paper,[1] we described that fused 3-(2-bromoethyl)pyrimidin-4(3*H*)-ones (**1**) with primary amines afforded abnormal rearranged products, such as fused 3-alkyl-4-alkyliminopyrimidines (**2**), as well as the normally substituted 3-(2-alkylaminoethyl) derivatives (Fig. 1). This rearranged reaction seemed to be a new type of Dimroth rearrangement reaction.[6] We also showed that one of the rearranged products had considerable antidepressant activity comparable with imipramine.[1] This reaction chart should be applicable to other ring systems with fused aliphatic rings for the synthesis of potential pharmaceutics. Here we report the detailed reaction of 3-(2-bromoethyl)-5,6-dihydro[1]benzoxepino (or benzothiepino)[5,4-*d*]pyrimidin-4(3*H*)-one (**3**, **4**) with primary amines.

5,6-Dihydro[1]benzoxepino (or benzothiepino)[5,4-*d*]pyrimidin-4(3*H*)-one (**5**, **6**)[2,3] were converted to **3** and **4**, respectively by a similar manner described in the literature (Chart 1).[1,7] When **3** was treated with methylamine in methanol, the expected abnormal product, 3-methyl-4-methylimino-3,4,5,6-tetrahydro[1]benzoxepino[5,4-*d*]pyrimidine (**9a**) was obtained as well as standard substituted 3-(2-methylaminoethyl)-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4(3*H*)-one (**11a**) in 33% and 31% yield, respectively, both as the hydrobromide salts. In the ^{1}H-NMR spectrum of **9a**, two methyl groups appeared at 3.45 and 3.75 ppm while the two methylene signals of the 3-substituted bromoethyl moiety of **3** have disappeared. One pyrimidine ring proton was observed at 8.06 ppm as a singlet. In the IR spectrum of **9a**, the lactam carbonyl band disappeared. These results suggested that a Dimroth-type rearrangement had occurred when **3** reacted with methylamine.[1] Similar rearrangement reactions were also carried out with ethyl- and *n*-propylamine. As expected, the rearranged compounds (**9b**, **c**) were isolated as the major products with the normal substituted 3-(2-alkylaminoethyl) derivatives (**11b**, **c**) as either the hydrobromide salts or the free bases. Reaction of **4** with primary amines in methanol also gave the rearranged compounds (**10a**—**c**) as the major products with the normal substituted 3-(2-alkylaminoethyl) derivatives (**12a**—**c**) as either the hydrobromide salts or the free bases. Therefore, it seemed that this type of rearrangement reaction is common among tricyclic aliphatic ring fused pyrimidin-4(3*H*)-ones.

When we conducted this reaction of **3** and **4** with primary amines in dioxane instead of methanol, we only got the normal substituted products in fairly high yields (**11a**—**c** and **12a**—**c**, 52—89%) as either the hydrobromide salts or the free bases. Usually an aprotic solvent accelerates a *SN*2 reac-

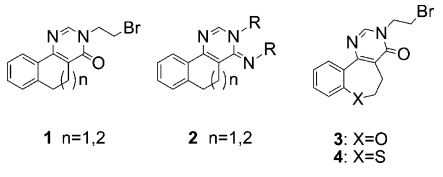

Fig. 1

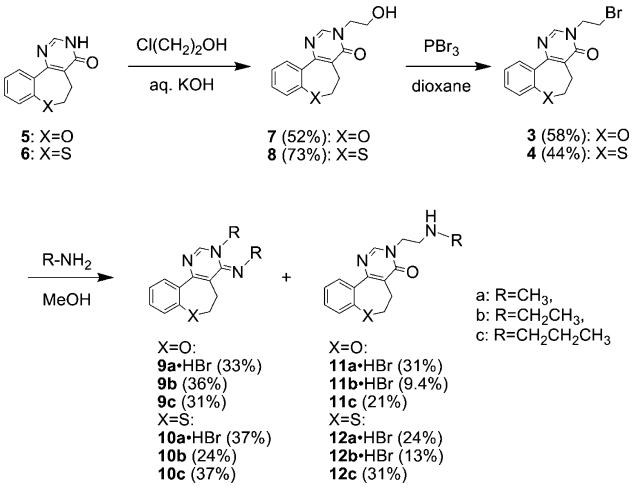

Chart 1

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tion; therefore it is reasonable that the normal substitution reaction proceeded only in dioxane.

The proposed formation mechanism of **9** and **10** is shown in Chart 2. No reaction occurred when 3-(2-methylaminoethyl)pyrimidin-4(3*H*)-one hydrobromide derivatives were reacted with methylamine, unlike successful reactions with 3-(2-bromoethyl)pyrimidin-4(3*H*)-one derivatives.[1)] This result suggests that 3-(2-methylaminoethyl)pyrimidin-4(3*H*)-one hydrobromide derivatives are not the intermediates of this Dimroth-type rearrangement reaction.

The primary amine must attack the stable lactam carbonyl moieties of **3** and **4** to facilitate the rearrangement reaction. Therefore, we postulate that the rearrangement reaction would proceed through a charge separated transition state (i) to facilitate such a nucleophilic attack that results in an intermediate (ii). After pyrimidine N1 protonation, the second amine attacks the 2-position of the pyrimidine ring[8)] promoting the Dimroth-type rearrangement to afford **9** and **10**. Gondela *et al.* has also reported such reaction pathway differences between protic and aprotic solvents in Dimroth rearrangement.[9)]

In summary, reaction of aliphatic ring fused 3-(2-bromoethyl)pyrimidin-4(3*H*)-ones (**3**, **4**) with primary alkyl amines gave abnormal 3-alkyl-4-alkyliminopyrimidines *via* a Dimroth-type rearrangement as major products, as well as normal substituted 3-(2-alkylaminoethyl) derivatives. This rearrangement reaction required protic solvent. We are currently exploring their structure–activity relationships for further elucidation of potential pharmaceutics.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The FAB-mass spectra were obtained on a VG 70 mass spectrometer and *m*-nitrobenzyl alcohol was used as the matrix. The IR spectra were recorded on a Japan Spectroscopic FT/IR-200 spectrophotometer with nujol and frequencies are expressed in cm^{-1}. The ^{1}H-NMR spectra were recorded on a Varian VXR-200 instrument operating at 200 MHz with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ) and *J* values in Hz, and the signals are designated as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; tt, triple triplet; q, quartet; br, broad; m, multiplet. Solvent systems are as follows: methylamine as a 40% methanol solution, ethylamine as a 70% aqueous solution, and *n*-propylamine was neat. Column chromatography was performed on silica gel (IR-60-63-210-W, Daiso). TLC was carried out on Kieselgel 60F254 (Merck).

3-(2-Hydroxyethyl)-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4(3*H*)-one (7) To a solution of compound **5**[2)] (5.00 g, 23.3 mmol) in aq. 1 N-KOH (100 ml) was added 2-chloroethanol (5.60 g, 70.0 mmol) and the solution was stirred at room temperature for 4 h. The precipitate was filtered and the solid was recrystallized from ethyl acetate to give 3.13 g (52%) of **7** as colorless needles. mp 142—143 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.96 (2H, t, *J*=5.9 Hz, H-5), 3.97 (2H, t, *J*=4.7 Hz, C$\underline{H}_2$OH), 4.16 (2H, t, *J*=4.7 Hz, NCH_2), 4.56 (2H, t, *J*=5.9 Hz, H-6), 7.10 (1H, d, *J*=8.3 Hz, H-8), 7.22 (1H, dd, *J*=7.8, 7.5 Hz, H-10), 7.35—7.46 (1H, m, H-9), 8.00 (1H, dd, *J*=7.8, 1.7 Hz, H-11), 8.28 (1H, s, H-2). IR (nujol) cm^{-1}: 3355 (OH), 1630 (CO). FAB-MS *m*/*z*: 259 (MH^+). *Anal.* Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N; 10.85. Found: C, 64.92; H, 5.49; N, 10.80.

3-(2-Bromoethyl)-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4(3*H*)-one (3) To a solution of **7** (3.00 g, 11.6 mmol) in dry dioxane (100 ml) was added PBr_3 (9.44 g, 34.9 mmol) and the solution was stirred at 80 °C for 1 h. After evaporation of dioxane (about 50 ml), the residual solution was added to ice water (100 ml) and the resulting solution was basified with $NaHCO_3$. The solution was extracted with ethyl acetate (100 ml×3) and the combined organic layer was washed with saturated brine, dried over anhydrous Na_2SO_4, and then evaporated *in vacuo*. The residue was recrystallized from cyclohexane to give 2.16 g (58%) of **3** as colorless needles. mp 96—97 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.98 (2H, t, *J*=5.8 Hz, H-5), 3.78 (2H, t, *J*=5.7 Hz, C$\underline{H}_2$Br), 4.34 (2H, t, *J*=5.7 Hz, NCH_2), 4.56 (2H, t, *J*=5.8 Hz, H-6), 7.10 (1H, dd, *J*=8.0, 1.3 Hz, H-8), 7.16—7.27 (1H, m, H-10), 7.34—7.46 (1H, m, H-9), 8.07 (1H, dd, *J*=7.8, 1.7 Hz, H-11), 8.17 (1H, s, H-2). IR (nujol) cm^{-1}: 1655 (CO). FAB-MS *m*/*z*: 321 (MH^+), 323 (MH^++2). *Anal.* Calcd for $C_{14}H_{13}BrN_2O_2$: C, 52.36; H, 4.08; N, 8.72. Found: C, 52.46; H, 4.23; N, 8.73.

General Procedure for the Reaction of 3 with Primary Amines To a solution of **3** (300 mg, 0.934 mmol) in methanol or dioxane (50 ml) was added primary amine (9.34 mmol) and the solution was stirred at room temperature for the appropriate time. After evaporation of solvent *in vacuo*, the residue was purified by column chromatography and/or recrystallization.

3-Methyl-4-methylimino-3,4,5,6-tetrahydro[1]benzoxepino[5,4-*d*]pyrimidine (9a) and 3-(2-Methylaminoethyl)-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4(3*H*)-one (11a) 1) Reaction time was 5 d in methanol. The residue was recrystallized from ethanol–diethyl ether to give **9a**·HBr (99.0 mg, 33%) as a white powder. The mother liquid was evaporated and the residue was chromatographed on silica gel. Eluate of ethyl acetate–methanol (7 : 3, v/v) was evaporated and the residue was recrystallized from ethyl acetate to give **11a**·HBr (102 mg, 31%) as colorless needles. **9a**·HBr: mp 212—214 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.92 (2H, t, *J*=6.1 Hz, H-5), 3.45 (3H, s, NCH_3), 3.75 (3H, s, NCH_3), 4.70 (2H, t, *J*=6.1 Hz, H-6), 7.15 (1H, d, *J*=7.4 Hz, H-8), 7.23—7.34 (1H, m, H-10), 7.41—7.52 (1H, m, H-9), 7.83 (1H, dd, *J*=7.8, 1.8 Hz, H-11), 8.06 (1H, s, H-2). FAB-MS *m*/*z*: 242 (MH^+−HBr). *Anal.* Calcd for $C_{14}H_{15}N_3O\cdot HBr\cdot 0.5H_2O$: C, 50.77; H,

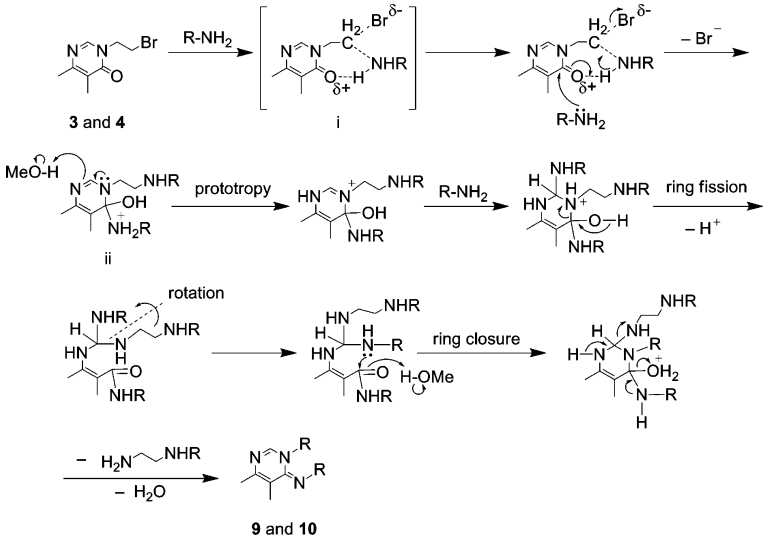

Chart 2

5.17; N, 12.69. Found: C, 50.98; H, 5.06; N, 12.48. **11a**·HBr: mp 243—245 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.29 (3H, s, NCH_3), 2.75 (2H, t, J=5.9 Hz, $NC\underline{H}_2CH_2N$), 2.83 (2H, t, J=5.8 Hz, H-5), 3.97 (2H, t, J=5.9 Hz, $NCH_2C\underline{H}_2N$), 4.43 (2H, t, J=5.8 Hz, H-6), 7.08 (1H, d, J=7.7 Hz, H-8), 7.21 (1H, dd, J=7.8, 6.5 Hz, H-10), 7.35—7.48 (1H, m, H-9), 8.05 (1H, dd, J=7.8, 1.7 Hz, H-11), 8.38 (1H, s, H-2). IR (nujol) cm^{-1}: 1640 (CO). FAB-MS m/z: 272 (MH^+−HBr). *Anal.* Calcd for $C_{15}H_{17}N_3O_2$·HBr: C, 51.15; H, 5.15; N, 11.93. Found: C, 51.14; H, 5.19; N, 11.91.

2) Reaction time was 6 d in dioxane. The residue was chromatographed on silica gel. Eluate of ethyl acetate–ethanol (6 : 4, v/v) was evaporated. The residue was recrystallized from ethyl acetate to give **11a**·HBr (211 mg, 64%) as colorless needles. The spectroscopic properties were coincident with the ones for **11a**·HBr in the methanolic reaction.

3-Ethyl-4-ethylimino-3,4,5,6-tetrahydro[1]benzoxepino[5,4-*d*]pyrimidine (9b) and 3-(2-Ethylaminoethyl)-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4(3*H*)-one (11b) 1) Reaction time was 6 d in methanol. The residue was chromatographed on silica gel. Eluate of *n*-hexane–ethyl acetate–triethylamine (2 : 18 : 1, v/v) was evaporated to give **9b** (91.0 mg, 36%) as a yellow oil. Eluate of ethyl acetate–methanol (1 : 1, v/v) was evaporated and the residue was recrystallized from methanol–diethyl ether to give **11b**·HBr (32.0 mg, 9.4%) as a white powder. **9b**: ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.2 Hz, CH_3), 1.36 (3H, t, J=7.1 Hz, CH_3), 2.76 (2H, t, J=6.1 Hz, H-5), 3.61 (2H, q, J=7.1 Hz, $=NC\underline{H}_2CH_3$), 3.80—4.15 (2H, br m, $NC\underline{H}_2CH_3$), 4.65 (2H, t, J=6.1 Hz, H-6), 7.10 (1H, dd, J=8.0, 1.3 Hz, H-8), 7.16—7.32 (1H, m, H-10), 7.30—7.46 (1H, m, H-9), 7.77 (1H, dd, J=7.7, 1.7 Hz, H-11), 7.83 (1H, s, H-2). FAB-MS m/z: 270 (MH^+). FAB-HR-MS m/z: 270.1559 (Calcd for $C_{16}H_{20}N_3O$: 270.1606). **11b**·HBr: mp 265—267 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.98 (3H, t, J=7.2 Hz, CH_3), 2.54 (2H, q, J=7.2 Hz, $NC\underline{H}_2CH_3$), 2.80 (2H, t, J=5.7 Hz, H-5), 2.83 (2H, t, J=5.9 Hz, $NC\underline{H}_2CH_2N$), 3.96 (2H, t, J=5.9 Hz, $NCH_2C\underline{H}_2N$), 4.43 (2H, t, J=5.7 Hz, H-6), 7.08 (1H, d, J=7.9 Hz, H-8), 7.21 (1H, dd, J=7.8, 7.5 Hz, H-10), 7.35—7.50 (1H, m, H-9), 8.05 (1H, dd, J=7.8, 1.8 Hz, H-11), 8.39 (1H, s, H-2). IR (nujol) cm^{-1}: 3345 (NH), 1640 (CO). FAB-MS m/z: 286 (MH^+−HBr). *Anal.* Calcd for $C_{16}H_{19}N_3O_2$·HBr: C, 52.47; H, 5.50; N, 11.47. Found: C, 52.69; H, 5.69; N, 11.35.

2) Reaction time was 5 d in dioxane. The residue was chromatographed on silica gel. Eluate of ethyl acetate–ethanol (8 : 2, v/v) was evaporated. The residue was recrystallized from methanol–diethyl ether to give **11b**·HBr (178 mg, 52%) as a white powder. The spectroscopic properties were coincident with the ones for **11b**·HBr in the methanolic reaction.

3-(*n*-Propyl)-4-(*n*-propylimino)-3,4,5,6-tetrahydro[1]benzoxepino[5,4-*d*]pyrimidine (9c) and 3-(2-*n*-Propylaminoethyl)-5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4(3*H*)-one (11c) 1) Reaction time was 5 d in methanol. The residue was chromatographed on silica gel. Eluate of *n*-hexane–ethyl acetate–triethylamine (5 : 5 : 1, v/v) was evaporated and the residue was recrystallized from *n*-hexane to give **9c** (86.0 mg, 31%) as yellow needles. Eluate of ethyl acetate was evaporated and the residue was recrystallized from ethyl acetate to give **11c** (59.0 mg, 21%) as colorless needles. **9c**: mp 58—59 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.4 Hz, CH_3), 0.99 (3H, t, J=7.3 Hz, CH_3), 1.54—1.94 (4H, m, $2\times CH_2C\underline{H}_2CH_3$), 2.78 (2H, t, J=6.1 Hz, H-5), 3.52 (2H, t, J=6.6 Hz, $=NC\underline{H}_2CH_2CH_3$), 3.70—4.05 (2H, br m, $NC\underline{H}_2CH_2CH_3$), 4.65 (2H, t, J=6.1 Hz, H-6), 7.09 (1H, dd, J=7.8, 1.3 Hz, H-8), 7.17—7.34 (1H, m, H-10), 7.30—7.46 (1H, m, H-9), 7.78 (1H, dd, J=7.7, 1.7 Hz, H-11), 7.80 (1H, s, H-2). FAB-MS m/z: 298 (MH^+). *Anal.* Calcd for $C_{18}H_{23}N_3O$: C, 72.70; H, 7.80; N, 14.13. Found: C, 72.40; H, 7.69; N, 14.11. **11c**: mp 83—84 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.84 (3H, t, J=7.2 Hz, CH_3), 1.27—1.51 (2H, m, $NCH_2C\underline{H}_2CH_3$), 2.49 (2H, t, J=7.2 Hz, $NC\underline{H}_2CH_2CH_3$), 2.80 (2H, t, J=5.6 Hz, H-5), 2.83 (2H, t, J=5.7 Hz, $NC\underline{H}_2CH_2N$), 3.97 (2H, t, J=5.7 Hz, $NCH_2C\underline{H}_2N$), 4.43 (2H, t, J=5.6 Hz, H-6), 7.08 (1H, d, J=7.8 Hz, H-8), 7.20 (1H, dd, J=7.8, 7.4 Hz H-10), 7.34—7.50 (1H, m, H-9), 8.05 (1H, dd, J=7.8, 1.7 Hz, H-11), 8.39 (1H, s, H-2). IR (nujol) cm^{-1}: 3335 (NH), 1640 (CO). FAB-MS m/z: 300 (MH^+). *Anal.* Calcd for $C_{17}H_{21}N_3O_2\cdot 0.2H_2O$: C, 67.39; H, 7.12; N, 13.87. Found: C, 67.73; H, 7.02; N, 13.64.

2) Reaction time was 7 d in dioxane. The residue was chromatographed on silica gel. Eluate of ethyl acetate was evaporated. The residue was recrystallized from ethyl acetate to give **11c** (248 mg, 89%) as colorless needles. The spectroscopic properties were coincident with the ones for **11c** in the methanolic reaction.

3-(2-Hydroxyethyl)-5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4(3*H*)-one (8) To a solution of compound **6**[3] (5.00 g, 21.7 mmol) in aq. 1 N-KOH (100 ml) was added 2-chloroethanol (5.30 g, 65.8 mmol) and the solution was stirred at room temperature for 4 h. The precipitate was filtered and the solid was recrystallized from methanol to give 4.35 g (73%) of **8** as yellow plates. mp 149—151 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.62 (2H, t, J=6.5 Hz, H-5), 3.43 (2H, t, J=6.5 Hz, H-6), 3.68 (2H, dt, changed to t after addition of D_2O, J=5.2, 5.2 Hz, $C\underline{H}_2OH$), 4.02 (2H, t, J=5.2 Hz, NCH_2), 5.03 (1H, t, D_2O exchangeable, J=5.2 Hz, $CH_2O\underline{H}$), 7.37—7.74 (4H, m, H-8, 9, 10, 11), 8.37 (1H, s, H-2). IR (nujol) cm^{-1}: 3320 (OH), 1650 (CO). FAB-MS m/z: 275 (MH^+). *Anal.* Calcd for $C_{14}H_{14}N_2O_2S\cdot 0.2H_2O$: C, 60.50; H, 5.22; N; 10.08. Found: C, 60.88; H, 5.32; N, 10.07.

3-(2-Bromoethyl)-5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4(3*H*)-one (4) To a solution of **8** (3.00 g, 10.9 mmol) in dry dioxane (100 ml) was added PBr_3 (8.85 g, 32.7 mmol) and the solution was stirred at 80 °C for 1 h. After evaporation of dioxane (about 50 ml), the residual solution was added to ice water (100 ml) and the resulting solution was neutralized with $NaHCO_3$. The solution was extracted with ethyl acetate (100 ml×3) and the combined organic layer was washed with saturated brine, dried over anhydrous Na_2SO_4, and then evaporated *in vacuo*. The residue was recrystallized from ethyl acetate to give 1.62 g (44%) of **4** as colorless plates. mp 136—138 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.79 (2H, t, J=6.7 Hz, H-5), 3.53 (2H, t, J=6.7 Hz, H-6), 3.80 (2H, t, J=5.8 Hz, $C\underline{H}_2Br$), 4.39 (2H, t, J=5.8 Hz, NCH_2), 7.32—7.46 (1H, m, H-10), 7.45—7.57 (1H, m, H-9), 7.66 (1H, dd, J=7.5, 1.5 Hz, H-8), 7.75 (1H, dd, J=7.6, 1.7 Hz, H-11), 8.29 (1H, s, H-2). IR (nujol) cm^{-1}: 1655 (CO). FAB-MS m/z: 337 (MH^+), 339 (MH^++2). *Anal.* Calcd for $C_{14}H_{13}BrN_2OS\cdot 0.5H_2O$: C, 48.56; H, 4.08; N, 8.09. Found: C, 48.79; H, 3.87; N, 7.95.

General Procedure for the Reaction of 4 with Primary Amines To a solution of **4** (300 mg, 0.890 mmol) in methanol or dioxane (50 ml) was added primary amine (8.90 mmol) and the solution was stirred at room temperature for the appropriate time. After evaporation of solvent *in vacuo*, the residue was purified by column chromatography and/or recrystallization.

3-Methyl-4-methylimino-3,4,5,6-tetrahydro[1]benzothiepino[5,4-*d*]pyrimidine (10a) and 3-(2-Methylaminoethyl)-5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4(3*H*)-one (12a) 1) Reaction time was 3 d in methanol. The residue was recrystallized from ethanol–diethyl ether to give **10a**·HBr (112 mg, 37%) as a white powder. The mother liquid was evaporated and the residue was chromatographed on silica gel. Eluate of *n*-hexane–ethyl acetate (3 : 7, v/v) was evaporated and the residue was recrystallized from methanol to give **12a**·HBr (77 mg, 24%) as a white powder. **10a**·HBr: mp 213—214 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.86 (2H, t, J=6.5 Hz, H-5), 3.37 (3H, s, NCH_3), 3.58 (2H, t, J=6.5 Hz, H-6), 3.88 (3H, s, NCH_3), 7.54—7.82 (4H, m, H-8, 9, 10, 11), 8.48 (br s, 1H, D_2O exchangeable, $N^+\underline{H}CH_3$), 8.88 (1H, s, H-2). FAB-MS m/z: 258 (MH^+−HBr). *Anal.* Calcd for $C_{14}H_{15}N_3S\cdot HBr\cdot 0.5H_2O$: C, 48.42; H, 4.93; N, 12.10. Found: C, 48.80; H, 4.84; N, 12.20. **12a**·HBr: mp 236—238 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.38 (3H, s, NCH_3), 2.62 (2H, t, J=6.6 Hz, H-5), 2.92 (2H, t, J=5.9 Hz, $NC\underline{H}_2CH_2N$), 3.43 (2H, t, J=6.6 Hz, H-6), 4.07 (2H, t, J=5.9 Hz, $NCH_2C\underline{H}_2N$), 7.36—7.74 (4H, m, H-8, 9, 10, 11), 8.41 (1H, s, H-2). IR (nujol) cm^{-1}: 1655 (CO). FAB-MS m/z: 288 (MH^+−HBr). *Anal.* Calcd for $C_{15}H_{17}N_3OS\cdot HBr\cdot 0.25H_2O$: C, 48.33; H, 5.00; N, 11.27. Found: C, 48.25; H, 5.04; N, 10.90.

2) Reaction time was 2 d in dioxane. The residue was chromatographed on silica gel. Eluate of *n*-hexane–ethyl acetate (3 : 7, v/v) was evaporated. The residue was recrystallized from methanol to give **12a**·HBr (207 mg, 63%) as colorless needles. The spectroscopic properties were coincident with the ones for **12a**·HBr in the methanolic reaction.

3-Ethyl-4-ethylimino-3,4,5,6-tetrahydro[1]benzothiepino[5,4-*d*]pyrimidine (10b) and 3-(2-Ethylaminoethyl)-5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4(3*H*)-one (12b) 1) Reaction time was 4 d in methanol. The residue was chromatographed on silica gel. Eluate of ethyl acetate–triethylamine (9 : 1, v/v) was evaporated to give **10b** (61.0 mg, 24%) as a yellow powder. Eluate of ethyl acetate–methanol (9 : 1, v/v) was evaporated and the residue was recrystallized from diethyl ether to give **12b**·HBr (45.0 mg, 13%) as a white powder. **10b**: mp 97—98 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.28—1.52 (6H, m, $2\times CH_3$), 2.73 (2H, t, J=6.6 Hz, H-5), 3.52 (2H, t, J=6.6 Hz, H-6), 3.74 (2H, q, J=7.1 Hz, $=NC\underline{H}_2CH_3$), 4.10—4.38 (2H , br m, $NC\underline{H}_2CH_3$), 7.32—7.45 (1H, m, H-10), 7.42—7.55 (1H, m, H-9), 7.64 (1H, dd, J=7.5, 1.5 Hz, H-8), 7.72 (1H, dd, J=7.6, 1.7 Hz, H-11), 7.99 (1H, s, H-2). FAB-MS m/z: 286 (MH^+). *Anal.* Calcd for $C_{16}H_{19}N_3S$: C, 67.33; H, 6.71; N, 14.72. Found: C, 67.12; H, 6.67; N, 14.51. **12b**·HBr: mp 285—286 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.20 (3H, t, J=7.2 Hz, CH_3), 2.64 (2H, t, J=6.5 Hz, H-5), 3.02 (2H, q, J=7.2 Hz, $NC\underline{H}_2CH_3$), 3.37 (2H, t, J=5.9 Hz, $NC\underline{H}_2CH_2N$), 3.46 (2H, t, J=6.5 Hz, H-6), 4.26 (2H, t, J=5.9 Hz, $NCH_2C\underline{H}_2N$), 7.39—7.74 (4H, m, H-8, 9, 10, 11), 8.49 (1H, s, H-2), 8.54 (1H, br s, D_2O exchangeable, $N^+\underline{H}CH_2CH_3$). IR (nujol) cm^{-1}: 1650 (CO). FAB-MS m/z: 302

($MH^+ - HBr$). *Anal.* Calcd for $C_{16}H_{19}N_3OS \cdot HBr$: C, 50.26; H, 5.27; N, 10.99. Found: C, 50.07; H, 5.22; N, 10.89.

2) Reaction time was 3 d in dioxane. The residue was chromatographed on silica gel. Eluate of ethyl acetate–ethanol (7 : 3, v/v) was evaporated. The residue was recrystallized from diethyl ether to give **12b**·HBr (184 mg, 54%) as a white powder. The spectroscopic properties were coincident with the ones for **12b**·HBr in the methanolic reaction.

3-(*n*-Propyl)-4-(*n*-propylimino)-3,4,5,6-tetrahydro[1]benzothiepino[5,4-*d*]pyrimidine (10c) and 3-(2-*n*-Propylaminoethyl)-5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4(3*H*)-one (12c) 1) Reaction time was 6 d in methanol. The residue was chromatographed on silica gel. Eluate of *n*-hexane–ethyl acetate–triethylamine (14 : 6 : 1, v/v) was evaporated to give **10c** (103.0 mg, 37%) as a yellow oil. Eluate of ethyl acetate–ethanol (9 : 1, v/v) was evaporated to give **12c** (86.0 mg, 31%) as a yellow oil. **10c**: ^{1}H-NMR ($CDCl_3$) δ: 1.00 (6H, t, J=7.3 Hz, 2×CH_3), 1.42—2.06 (4H, br m, 2×$CH_2\underline{CH_2}CH_3$), 2.69 (2H, br s, H-5), 3.50 (2H, t, J=6.5 Hz, H-6), 3.58 (2H, br t, J=5.7 Hz, =$NC\underline{H_2}CH_2CH_3$), 3.66—4.02 (2H, br m, $NC\underline{H_2}CH_2CH_3$), 7.20—7.54 (2H, m, H-9, 10), 7.61 (1H, d, J = 7.3 Hz, H-8), 7.70 (1H, d, J = 7.4 Hz, H-11), 7.81 (1H, br s, H-2). FAB-MS m/z: 314 (MH^+). FAB-HR-MS m/z: 314.1679 (Calcd for $C_{18}H_{24}N_3S$: 314.1691). **12c**: ^{1}H-NMR (DMSO-d_6) δ: 0.85 (3H, t, J=7.4 Hz, CH_3), 1.29—1.50 (2H, m, $NCH_2C\underline{H_2}CH_3$), 2.49 (2H, t, J=7.2 Hz, $NC\underline{H_2}CH_2CH_3$), 2.62 (2H, t, J=6.6 Hz, H-5), 2.82 (2H, t, J=5.9 Hz, $NC\underline{H_2}CH_2N$), 3.43 (2H, t, J=6.6 Hz, H-6), 4.00 (2H, t, J=5.9 Hz, $NCH_2C\underline{H_2}N$), 7.37—7.49 (1H, m, H-10), 7.48—7.62 (1H, m, H-9), 7.63 (1H, dd, J=7.4, 1.4 Hz, H-8), 7.68 (1H, dd, J=7.6, 1.7 Hz, H-11), 8.41 (1H, s, H-2). IR (nujol) cm^{-1}: 1655 (CO). FAB-MS m/z: 316 (MH^+). FAB-HR-MS m/z: 316.1472 (Calcd for $C_{17}H_{22}N_3OS$: 316.1484).

2) Reaction time was 3 d in dioxane. The residue was chromatographed on silica gel. Eluate of ethyl acetate–ethanol (9 : 1, v/v) was evaporated to give **12c** (199 mg, 71%) as a yellow oil. The spectroscopic properties were coincident with the ones for **12c** in the methanolic reaction.

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References and Notes

1) Part 58: Ohtomo H., Tagata T., Sasaki K., Hirota T., Okuda K., *Tetrahedron*, **63**, 12541—12546 (2007).
2) Nagamatsu T., Tsurubayashi S., Sasaki K., Hirota T., *Synthesis*, **1991**, 303—306 (1991).
3) Nagamatsu T., Kinoshita K., Sasaki K., Nakayama T., Hirota T., *J. Heterocycl. Chem.*, **28**, 513—515 (1991).
4) Mikhailov S. N., Rozenski J., Efimtseva E. V., Busson R., Van Aerschot A., Herdewijn P., *Nucleic Acids Res.*, **30**, 1124—1131 (2002).
5) Fujii T., Saito T., Mori S., Chikazawa J., *Tetrahedron Lett.*, **32**, 97—100 (1991).
6) El Ashry E. S. H., El Kilany Y., Rashed N., Assafir H., "Advances in Heterocyclic Chemistry," Vol. 75, ed. by Katritzky A. R., Academic Press, San Diego, 2000, pp. 79—165.
7) Hirota T., Sasaki K., Yamamoto H., Katsu T., *Heterocycles*, **26**, 3211—3220 (1987).
8) An attack of the intramolecular amine is not probable due to a 5-*endo*-trig cyclization.
9) Gondela A., Gabański R., Walczak K., *Tetrahedron Lett.*, **45**, 8007—8009 (2004).