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Polycyclic *N*-heterocyclic compounds. Part 58: Rearrangement reactions of fused 3-(2-bromoethyl)pyrimidin-4(3*H*)-ones with primary amines and antidepressive evaluation of the products☆

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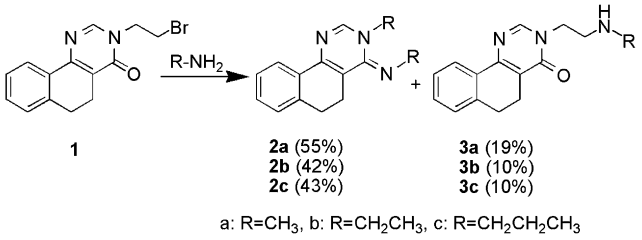
Abstract—Reaction of fused 3-(2-bromoethyl)pyrimidin-4(3*H*)-ones with primary alkylamines gave abnormal fused 3-alkyl-4-alkylimino-pyrimidines via a new rearrangement, as well as normal substituted 3-(2-alkylaminoethyl) derivatives. Antidepressive evaluation of these compounds was performed by antireserpine action and one compound exhibited the positive activity comparable to imipramine.

1. Introduction

5,6-Dihydrobenzo[*h*]quinazolines and their quinazolin-4(3*H*)-ones[2] are important heterocyclic compounds in the light of their bioactivity. We have already reported their preparation as intermediates of the triazasteroidal-skeleton compounds,[3] and showed that some of them had antidepressant activity and anti-platelet aggregation activity.[4–6] In addition, their carbon homologous compounds, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidines, turned out to be bioactive compounds as well.[7,8] Therefore we decided to search for more potent compounds by their chemical modification.

In our previous paper,[5] we selected 3-(2-bromoethyl)-5,6-dihydrobenzo[*h*]quinazoline (**1**, Scheme 1) as an intermediate for more effective antidepressant and the bromine moiety of **1** was transformed to dialkylamino groups such as dimethylamino or morpholino. We next selected to modify the substitution reaction of **1** with primary amines for further investigation. Here we report the detailed reaction, which accompanied the new type of Dimroth rearrangement and the antidepressive activity of the products.



Scheme 1.

2. Results and discussion

Initially, methylamine was used for this reaction. However, the expected product, 3-(2-methylaminoethyl)-5,6-dihydrobenzo[*h*]quinazoline (**3a**), was obtained in only 19% yield and the abnormal product, 3-methyl-4-methylimino-3,4,5,6-tetrahydrobenzo[*h*]quinazoline (**2a**), was obtained in 55% yield, both as hydrobromide crystals despite excess coexistent amine (Scheme 1). In ^{1}H NMR spectrum of **2a**, two methyl groups appeared at 3.33 and 3.83 ppm and two methylene signals of 3-substituted alkyl moiety of **1** have disappeared. One pyrimidine ring proton was observed at 8.80 ppm as singlet. In the IR spectrum of **2a**, disappearance of the lactam carbonyl band and appearance of NH^+ ammonium band (broad ambiguous, 2700 cm^{-1}) was observed. These results suggested that a Dimroth-type rearrangement had occurred in this reaction of **1** with methylamine,[9–12] in which the pyrimidine ring-opening and -closure had been involved to lead *exo*- and *endo*-cyclic translocated heteroatoms. For the purpose of the confirmation of this rearrangement reaction, ethyl- and *n*-propylamine were allowed to react with **1**. As expected, the rearranged compounds (**2b**,**c**) were isolated as the major products with the normal substituted 3-(2-alkylaminoethyl) derivatives (**3b**,**c**) as either the hydrobromide salts or the free bases.[13] It is the new type of Dimroth reaction in that leaving of the 3-bromoethyl group and introduction of 3-alkyl and 4-alkylimino groups

☆ See Ref. 1.

Keywords: Pyrimidin-4(3*H*)-one; Rearrangement; 3-Alkyl-4-alkylimino-pyrimidine; Antidepressant.

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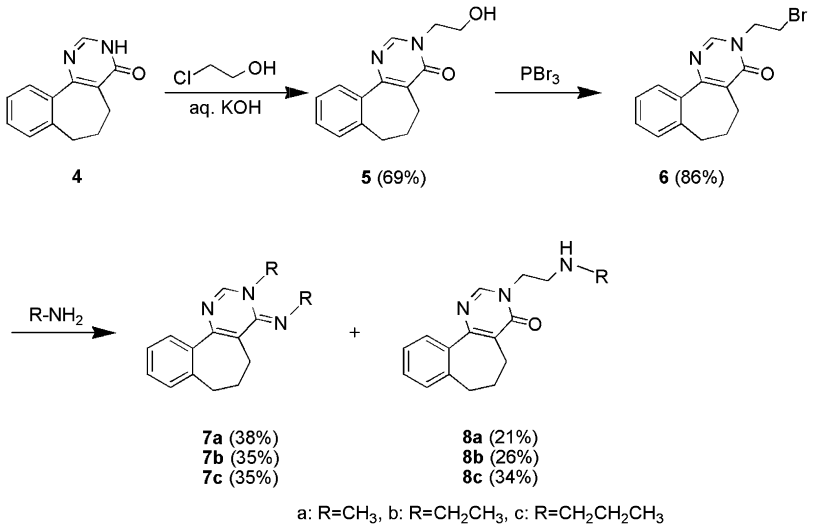
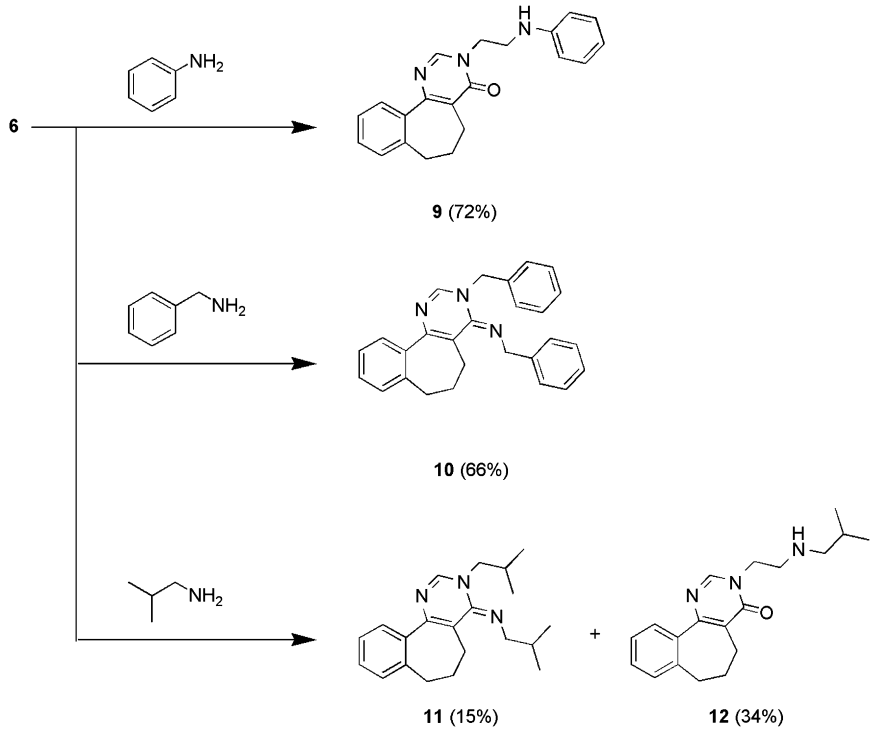


Scheme 2.

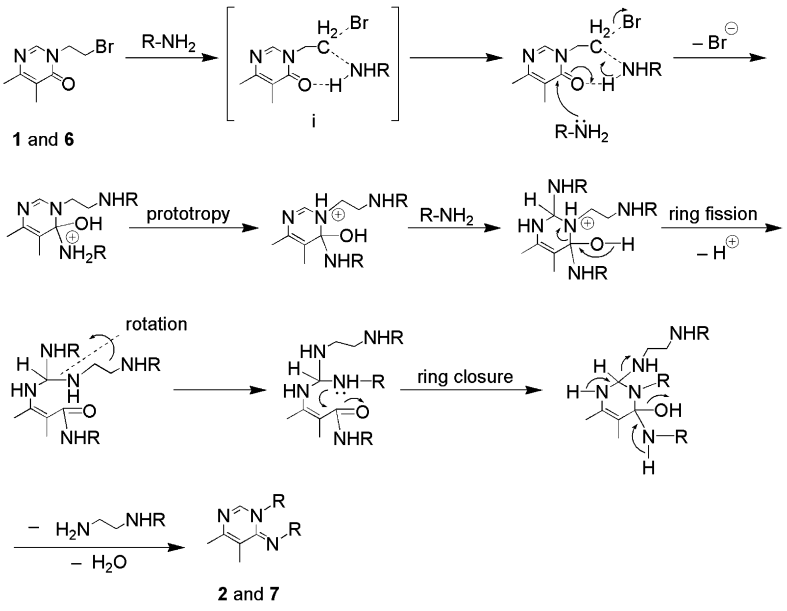
occur at the same time. The reaction of secondary amines with **1** gave only normal substituted products such as **3** in high yield,[5] so the rearrangement reaction of this type occurs only for primary amines.

Next we turned our attention to 6,7-dihydro-5*H*-benzo[6,7]-cyclohepta[1,2-*d*]pyrimidine. It is of interest whether the reaction of 3-(2-bromoethyl) derivatives (**6**, Scheme 2) with primary amines undergoes the same rearrangement. Therefore cycloheptapyrimidone **4** was converted into **6** by a similar manner described in the literature (Scheme 2).[5] The reaction of **6** with methylamine afforded, as expected, 3-methyl-4-methylimino-3,4,6,7-tetrahydro-5*H*-benzo[6,7]-cyclohepta[1,2-*d*]pyrimidine (**7a**) as a major product along with the normal substituted 3-(2-methylaminoethyl) derivative (**8a**), both as hydrobromide salts. Examination of IR and ^{1}H NMR spectra of **7a** resembled those of **2a**. Similarly reaction of **6** with ethyl- and *n*-propylamine gave same results as with **1**.[13]

Next, we investigated whether a similar rearrangement reaction would occur in the case of using an arylamine such as aniline instead of a primary alkylamine. However, no rearrangement reaction occurred and only normal 3-(2-anilinoethyl) derivative (**9**) was obtained (Scheme 3). It appears that the weaker basicity and the steric hindrance of aniline, which should attack lactam carbonyl carbon, caused this result (see Scheme 4). On the other hand benzylamine



Scheme 3.



Scheme 4.

and isobutylamine, which are relatively hindered primary amines and have sufficient basicity, gave the corresponding rearranged products by the reaction with **6**.[13]

To investigate the reaction mechanism, **3a** and **8a** were allowed to react with methylamine but no reaction occurred, suggesting that this type of rearrangement reaction does not proceed via intermediate **3** and **8**. Investigation of the abnormal reaction is now under progress.

The proposed formation mechanism of **2** and **7** is shown in Scheme 4. At the predictable transition state (i), the lone pair of amine nitrogen attacks active methylene carbon and the hydrogen bond is formed between the carbonyl oxygen and the amine hydrogen at the same time. In this state, the second attack of amine occurs at the carbonyl carbon and the S_N2 reaction proceeds at methylene carbon adjacent to bromine. Then, prototropy and third attack of amine occur at 2-position of pyrimidine ring. Subsequently, the Dimroth-type rearrangement occurs to afford **2** and **7**.

Finally, evaluation of the antidepressive activity of the above compounds was screened by the inhibition against reserpine-induced hypothermia in mice[14] and compared with that of control (saline). As shown in Table 1, only compound **2a** exhibited an antireserpine action comparable with imipramine. We are currently exploring their structure–activity relationships for further elucidation of antidepressive compounds.

3. Experimental

3.1. General

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 glycerol or *m*-nitrobenzyl alcohol was used as a matrix. The IR spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer with Nujol and frequencies are expressed in cm^{-1}. The ^1H 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 parts per million (δ) and J values in hertz, and the signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; quint, quintet; br, broad; m, multiplet. Methylamine as 40% methanol solution, ethylamine as 70% aqueous solution, and other amines were used as neat. Column chromatography was performed on silica gel (IR-60-63-210-W, Daiso). TLC was carried out on Kieselgel 60F254 (Merck).

3.1.1. General procedure for the reaction of 1 with primary amines. To a solution of **1**[5] (0.50 g, 1.64 mmol) in methanol (50 mL) was added primary amine (16.4 mmol)

Table 1. Effect of **2a** on reserpine-induced hypothermia in mice

Compounds	Body temperature (°C, mean value±SE)				
	Before administration	Time for administration			
		30 min	1 h	2 h	4 h
2a	23.4±0.1	26.0±0.2**	28.5±0.5**	31.2±0.7**	30.9±0.5*
Saline	23.2±0.6	23.9±0.2	24.2±0.2	24.9±0.6	25.8±1.5
Imipramine	23.9±0.5	25.5±0.3*	28.6±0.4**	31.1±1.0**	32.0±0.4*

Significantly different from the control (saline) at $p<0.05$ (*) and $p<0.01$ (**).

and the solution was stirred at room temperature for the appropriate time. After evaporation of methanol in vacuo, the residue was purified by crystallization or column chromatography.

3.1.1.1. 3-Methyl-4-methylimino-3,4,5,6-tetrahydrobenzo[*h*]quinazoline hydrobromide (2a) and 3-(2-methylaminoethyl)-5,6-dihydrobenzo[*h*]quinazolin-4(3*H*)-one hydrobromide (3a). Reaction time was 1 day. The residue was recrystallized from methanol to give **2a** (55%) as colorless needles. The mother liquid was evaporated and the residue was recrystallized from acetonitrile–methanol to give **3a** (19%) as colorless needles. Compound **2a**: mp 233–234 °C; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 2.92, 3.16 (each 2H, each t, J=8.2 Hz, H-5,6), 3.33, 3.83 (each 3H, each s, 2×NCH_3), 7.37–7.55 (3H, m, H-7,8,9), 8.11 (1H, br d, J=7.3 Hz, H-10), 8.32 (1H, br s, deuterium oxide exchangeable, N^+H), 8.80 (1H, s, H-2); FABMS: m/z 226 (MH^+-HBr). Anal. Calcd for $C_{14}H_{15}N_3\cdot HBr$: C, 54.91; H, 5.27; N, 13.72. Found: C, 54.79; H, 5.23; N, 13.52. Compound **3a**: mp 231–233 °C; IR 1650 (CO); ^{1}H NMR (dimethyl sulfoxide-d_6): δ 2.60 (3H, s, NCH_3), 2.73, 2.89 (each 2H, each t, J=7.0 Hz, H-5,6), 3.31, 4.23 (each 2H, each t, J=5.5 Hz, NCH_2CH_2N), 7.29–7.42 (3H, m, H-7,8,9), 8.07 (1H, dd, J=6.3 Hz, 2.6 Hz, H-10), 8.44 (1H, s, H-2), 8.49 (2H, br s, deuterium oxide exchangeable, NH_2^+); FABMS: m/z 256 (MH^+-HBr). Anal. Calcd for $C_{15}H_{17}N_3O\cdot HBr\cdot 1/2CH_3CN$: C, 53.87; H, 5.51; N, 13.74. Found: C, 53.96; H, 5.46; N, 13.41.

3.1.1.2. 3-Ethyl-4-ethylimino-3,4,5,6-tetrahydrobenzo[*h*]quinazoline hydrobromide (2b) and 3-(2-ethylaminoethyl)-5,6-dihydrobenzo[*h*]quinazolin-4(3*H*)-one (3b). Reaction time was 2 days. The residue was recrystallized from ethyl acetate to give **2b** (42%) as colorless needles. The mother liquid was evaporated and the residue was chromatographed on silica gel. Eluate of ethyl acetate–ethanol (3:1, v/v) was evaporated in vacuo to give **3b** (10%) as pale yellow viscous oil. Compound **2b**: mp 204–206 °C; ^{1}H NMR (deuteriochloroform): δ 1.50, 1.61 (each 3H, each t, J=7.2 Hz, 2×CH_3), 2.98, 3.13 (each 2H, each t, J=7.3 Hz, H-5,6), 3.93 (2H, quint, J=7.2 Hz, changed to quartet after addition of deuterium oxide, $=N^+HCH_2CH_3$), 4.94 (2H, q, J=7.2 Hz, NCH_2CH_3), 7.27–7.54 (3H, m, H-7,8,9), 8.18 (1H, dd, J=7.6 Hz, 1.5 Hz, H-10), 8.45 (1H, s, H-2), 9.36 (1H, br t, J=5.4 Hz, deuterium oxide exchangeable, N^+H); FABMS: m/z 254 (MH^+-HBr). Anal. Calcd for $C_{16}H_{19}N_3\cdot HBr$: C, 57.49; H, 6.03; N, 12.57. Found: C, 57.32; H, 6.24; N, 12.47. Compound **3b**: IR 1655 (CO); ^{1}H NMR (deuteriochloroform): δ 1.10 (3H, t, J=7.2 Hz, CH_3), 2.68 (2H, q, J=7.2 Hz, CH_2CH_3), 2.86–2.91 (4H, m, H-5,6), 3.01, 4.06 (each 2H, each t, J=6.0 Hz, NCH_2CH_2N), 7.20–7.36 (3H, m, H-7,8,9), 8.14 (1H, m, H-10), 8.16 (1H, s, H-2). FABHRMS m/z Calcd for $C_{16}H_{20}N_3O$ (MH^+): 270.1606. Found: 270.1637.

3.1.1.3. 3-Propyl-4-*n*-propylimino-3,4,5,6-tetrahydrobenzo[*h*]quinazoline (2c) and 3-(2-*n*-propylaminoethyl)-5,6-dihydrobenzo[*h*]quinazolin-4(3*H*)-one (3c). Reaction time was 2 days. The residue was chromatographed on silica gel. Eluate of ethyl acetate–ethanol (9:1, v/v) was evaporated in vacuo to give **2c** (43%) as pale yellow viscous oil. Eluate of ethyl acetate–ethanol (3:1, v/v) was evaporated to give **3c** (10%) as pale yellow viscous oil. Compound **2c**: ^{1}H NMR (deuteriochloroform): δ 0.95 (6H, t, J=7.2 Hz, 2×CH_3), 1.50–1.67, 1.67–1.86 (each 2H, each m, 2×$CH_2CH_2CH_3$), 2.78, 3.00 (each 2H, each t, J=7.3 Hz, H-5,6), 3.63 (2H, t, J=6.7 Hz, NCH_2), 3.79 (2H, t, J=7.2 Hz, NCH_2), 7.13–7.34 (3H, m, H-7,8,9), 7.75 (1H, s, H-2), 7.95–8.00 (1H, m, H-10). FABHRMS m/z Calcd for $C_{18}H_{24}N_3$ (MH^+): 282.1970. Found: 282.1982. Compound **3c**: IR 1655 (CO); ^{1}H NMR (deuteriochloroform): δ 0.91 (3H, t, J=7.4 Hz, CH_3), 1.41–1.59 (2H, m, $CH_2CH_2CH_3$), 2.52 (1H, br s, deuterium oxide exchangeable, NH), 2.61 (2H, t, J=7.2 Hz, $NCH_2CH_2CH_3$), 2.82–2.94 (4H, m, H-5,6), 3.02, 4.06 (each 2H, each t, J=5.9 Hz, NCH_2CH_2N), 7.20–7.36 (3H, m, H-7,8,9), 8.08–8.19 (1H, m, H-10), 8.16 (1H, s, H-2). FABHRMS m/z Calcd for $C_{17}H_{22}N_3O$ (MH^+): 284.1763. Found: 284.1714.

3.1.2. 3-(2-Hydroxyethyl)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4(3*H*)-one (5). To a solution of compound **4**[7] (5.0 g, 0.024 mol) in 1 N-KOH (100 mL) was added 2-chloroethanol (5.79 g, 0.072 mol) and the solution was stirred at room temperature for 4 h. The precipitated powder was filtered and the solid was recrystallized from ethyl acetate–methanol to give 4.17 g (69%) of **5** as colorless needles. Mp 196–198 °C; IR 3230 (OH), 1650 (CO); ^{1}H NMR (dimethyl sulfoxide-d_6): δ 2.15 (2H, quint, J=6.8 Hz, H-6), 2.32 (2H, t, J=6.4 Hz, H-7), 2.52 (2H, t, J=7.4 Hz, H-5), 3.66 (2H, q, J=5.3 Hz, changed to triplet after addition of deuterium oxide, CH_2O), 3.99 (2H, t, J=5.3 Hz, NCH_2), 4.99 (1H, t, J=5.3 Hz, deuterium oxide exchangeable, OH), 7.30–7.43 (3H, m, H-8,9,10), 7.57–7.64 (1H, m, H-11), 8.32 (1H, s, H-2); FABMS: m/z 257 (MH^+). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 69.96; H, 6.25; N, 10.82.

3.1.3. 3-(2-Bromoethyl)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4(3*H*)-one (6). To a solution of **5** (3.0 g, 11.7 mmol) in dry dioxane (100 mL) was added phosphorus tribromide (9.52 g, 35.2 mmol) and the solution was stirred at 80 °C for 1 h. After evaporation of dioxane (about 70 mL), the residual solution was added to ice water (100 mL) and the resulting solution was basified with sodium bicarbonate. The solution was extracted with ethyl acetate (100 mL×3) and combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and then evaporated in vacuo. The residue was recrystallized from methanol to give 3.21 g (86%) of **6** as colorless needles. Mp 138–140 °C; IR 1650 (CO); ^{1}H NMR (dimethyl sulfoxide-d_6): δ 2.16 (2H, quint, J=6.4 Hz, H-6), 2.33 (2H, t, J=6.6 Hz, H-7), 2.52 (2H, t, J=6.3 Hz, H-5), 3.85 (2H, t, J=6.2 Hz, CH_2Br), 4.35 (2H, t, J=6.2 Hz, NCH_2), 7.31–7.45 (3H, m, H-8,9,10), 7.58–7.66 (1H, m, H-11), 8.51(1H, s, H-2); FABMS: m/z 319 (MH^+), 321 (MH^++2). Anal. Calcd for $C_{15}H_{15}BrN_2O$: C, 56.44; H, 4.74; N, 8.78. Found: C, 56.17; H, 4.93; N, 8.73.

3.1.4. General procedure for the reaction of 6 with primary amines. To a solution of **6** (0.30 g, 0.94 mmol) in methanol (50 mL) was added primary amine (9.4 mmol) and the solution was stirred at room temperature for the appropriate time. After evaporation of methanol in vacuo, the residue was purified by crystallization or column chromatography.

3.1.4.1. 3-Methyl-4-methylimino-3,4,6,7-tetrahydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine hydrobromide (7a) and 3-(2-methylaminoethyl)-6,7-dihydro-5*H*-benzo-[6,7]cyclohepta[1,2-*d*]pyrimidin-4(3*H*)-one hydrobromide (8a). Reaction time was 2 days. The residue was recrystallized from ethanol–diethyl ether to give **7a** (38%) as colorless fine crystals. The mother liquid was evaporated in vacuo and the residue was chromatographed on silica gel. Eluate of ethyl acetate–methanol (3:1, v/v) was evaporated and the residue was recrystallized from ethyl acetate to give **8a** (21%) as colorless needles. Compound **7a**: mp 215–217 °C; ^{1}H NMR (deuteriochloroform): δ 2.44 (2H, quint, J=6.4 Hz, H-6), 2.63 (2H, t, J=6.8 Hz, H-7), 2.70 (2H, t, J=6.8 Hz, H-5), 3.59 (3H, d, J=5.1 Hz, changed to singlet after addition of deuterium oxide, $=N^+HCH_3$), 4.28 (3H, s, 3-NCH_3), 7.30–7.58 (3H, m, H-8,9,10), 7.84 (1H, dd, J=7.1 Hz, 2.1 Hz, H-11), 8.38 (1H, s, H-2), 9.51 (1H, br s, deuterium oxide exchangeable, N^+H); FABMS: m/z 240 (MH^+-HBr). Anal. Calcd for $C_{15}H_{17}N_3\cdot HBr\cdot 1/2H_2O$: C, 54.72; H, 5.82; N, 12.76. Found: C, 54.84; H, 5.80; N, 12.90. Compound **8a**: mp 173–175 °C; IR 1650 (CO); ^{1}H NMR (deuteriochloroform): δ 2.27 (2H, q, J=6.5 Hz, H-6), 2.46 (2H, t, J=6.6 Hz, H-7), 2.62 (2H, t, J=6.8 Hz, H-5), 2.62 (3H, s, NCH_3), 3.32, 4.32 (each 2H, each t, J=5.6 Hz, NCH_2CH_2N), 7.22–7.40 (3H, m, H-8,9,10), 7.60–7.68 (1H, m, H-11), 8.40 (1H, s, H-2); FABMS: m/z 270 (MH^+-HBr). Anal. Calcd for $C_{16}H_{19}N_3O\cdot HBr\cdot 1/2H_2O$: C, 53.49; H, 5.89; N, 11.70. Found: C, 53.78; H, 5.81; N, 11.74.

3.1.4.2. 3-Ethyl-4-ethylimino-3,4,6,7-tetrahydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (7b) and 3-(2-ethylaminoethyl)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta-[1,2-*d*]pyrimidin-4(3*H*)-one hydrobromide (8b). Reaction time was 3 days. The residue was chromatographed on silica gel. Eluate of ethyl acetate–methanol (9:1) was evaporated to dryness and the residue was recrystallized from ethanol–diethyl ether to give **8b** (26%) as colorless fine crystals. Eluate of methanol–acetic acid (20:1, v/v) was evaporated to give **7b** (35%) as pale yellow viscous oil. Compound **7b**: ^{1}H NMR (deuteriochloroform): δ 1.31, 1.38 (each 3H, each t, J=7.1 Hz, 2×CH_3), 2.23–2.39 (4H, m, H-6,7), 2.64 (2H, t, J=6.3 Hz, H-5), 3.65 (2H, q, J=7.0 Hz, $=NCH_2CH_3$), 3.99 (2H, br s, NCH_2CH_3), 7.14–7.42 (3H, m, H-8,9,10), 7.65–7.74 (1H, m, H-11), 7.84 (1H, s, H-2). FABHRMS m/z Calcd for $C_{17}H_{22}N_3$: 268.1814. Found: 268.1795. Compound **8b**: mp 216–218 °C; IR 1650 (CO); ^{1}H NMR (dimethyl sulfoxide-d_6): δ 1.19 (3H, t, J=7.2 Hz, CH_3), 2.17 (2H, quint, J=6.8 Hz, H-6), 2.34 (2H, t, J=6.8 Hz, H-7), 2.54 (2H, t, J=7.3 Hz, H-5), 3.01 (2H, q, J=7.2 Hz, CH_2CH_3), 3.35, 4.22 (each 2H, each t, J=5.9 Hz, NCH_2CH_2N), 7.31–7.48 (3H, m, H-8,9,10), 7.58–7.66 (1H, m, H-11), 8.44 (1H, s, H-2); FABMS: m/z 284 (MH^+-HBr). Anal. Calcd for $C_{17}H_{21}N_3O\cdot HBr\cdot H_2O$: C, 53.41; H, 6.33; N, 10.99. Found: C, 53.51; H, 6.18; N, 10.93.

3.1.4.3. 3-Propyl-4-*n*-propylimino-3,4,6,7-tetrahydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (7c) and 3-(2-*n*-propylaminoethyl)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4(3*H*)-one hydrobromide (8c). Reaction time was 3 days. The residue was chromatographed on silica gel. Eluate of ethyl acetate–methanol (1:1, v/v) was evaporated and the residue was recrystallized from ethyl acetate to give **8c** (34%) as colorless fine crystals. Eluate of methanol–acetic acid (20:1) was evaporated to give **7c** (35%) as pale yellow viscous oil. Compound **7c**: ^{1}H NMR (deuteriochloroform): δ 1.00 (6H, t, J=7.3 Hz, 2×CH_3), 1.52–1.92 (4H, m, 2×$CH_2CH_2CH_3$), 2.32 (4H, br s, H-6,7), 2.64 (2H, t, J=6.3 Hz, H-5), 3.55, 3.81 (each 2H, each br s, $=NCH_2$, NCH_2), 7.14–7.42 (3H, m, H-8,9,10), 7.62–7.82 (1H, m, H-11), 7.77 (1H, s, H-2). FABHRMS m/z Calcd for $C_{19}H_{26}N_3$: 296.2127. Found: 296.2108. Compound **8c**: mp 198–200 °C; IR 1660 (CO); ^{1}H NMR (dimethyl sulfoxide-d_6): δ 0.93 (3H, t, J=7.4 Hz, CH_3), 1.52–1.71 (2H, m, CH_2CH_3), 2.10–2.26 (2H, m, H-6), 2.35 (2H, t, J=7.1 Hz, H-7), 2.54 (2H, t, J=7.3 Hz, H-5), 2.93 (2H, t, J=7.8 Hz, $CH_2CH_2CH_3$), 3.35, 4.24 (each 2H, each t, J=5.9 Hz, NCH_2CH_2N), 7.32–7.45 (3H, m, H-8,9,10), 7.58–7.67 (1H, m, H-11), 8.45 (2H, s, deuterium oxide exchangeable, NH_2^+), 8.45 (1H, s, H-2); FABMS: m/z 298 (MH^+-HBr). Anal. Calcd for $C_{18}H_{23}N_3O\cdot HBr$: C, 57.15; H, 6.39; N, 11.11. Found: C, 57.21; H, 6.44; N, 11.15.

3.1.4.4. 3-(2-Anilinoethyl)-6,7-dihydro-5*H*-benzo[6,7]-cyclohepta[1,2-*d*]pyrimidin-4(3*H*)-one (9). Reaction time was 3 days. The residue was chromatographed on silica gel. Eluate of ethyl acetate was evaporated to give **9** (72%) as pale yellow viscous oil. IR 1650 (CO); ^{1}H NMR (deuteriochloroform): δ 2.31 (2H, quint, J=6.9 Hz, H-6), 2.51 (2H, t, J=7.2 Hz, H-7), 2.58 (2H, t, J=6.9 Hz, H-5), 3.63, 4.19 (each 2H, each t, J=5.7 Hz, NCH_2CH_2N), 6.62–6.77 (3H, m, H-Ar), 7.12–7.41 (5H, m, H-Ar-8,9,10), 7.60–7.69 (1H, m, H-11), 7.99 (1H, s, H-2); FABHRMS m/z Calcd for $C_{21}H_{22}N_3O$: 332.1763. Found: 332.1736.

3.1.4.5. 3-Benzyl-4-benzylimino-3,4,6,7-tetrahydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (10). Reaction time was 3 days. The residue was chromatographed on silica gel. Eluate of *n*-hexane–ethyl acetate–triethylamine (8:2:1) was evaporated and the residue was recrystallized from *n*-hexane to give **10** (66%) as pale yellow fine crystals. Mp 61–62 °C; ^{1}H NMR (deuteriochloroform): δ 2.32 (4H, br s, H-6,7), 2.65 (2H, t, J=6.2 Hz, H-5), 4.85, 5.18 (each 2H, each br s, $=NCH_2$, NCH_2), 7.14–7.42 (13H, m, H-8,9,10, 2×Ph), 7.69–7.78 (1H, m, H-11), 7.95 (1H, s, H-2); FABMS: m/z 392 (MH^+). Anal. Calcd for $C_{27}H_{25}N_3$: C, 82.83; H, 6.44; N, 10.73. Found: C, 82.64; H, 6.58; N, 10.82.

3.1.4.6. 3-Isobutyl-4-isobutylimino-3,4,6,7-tetrahydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine (11) and 3-(2-isobutylaminoethyl)-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4(3*H*)-one (12). Reaction time was 5 days. The residue was chromatographed on silica gel. Eluate of ethyl acetate–methanol (8:2) was evaporated to give **11** (15%) as pale yellow viscous oil. Eluate of *n*-hexane–ethyl acetate–triethylamine (10:10:1) was evaporated to give **12** (34%) as pale yellow viscous oil. Compound **11**: ^{1}H NMR (deuteriochloroform): δ 0.96 (6H, d, J=7.3 Hz, 2×CH_3), 0.99 (6H, d, J=6.7 Hz, 2×CH_3), 1.64–1.76 (2H, m, 2×$CH_2CH(CH_3)_2$), 2.20–2.41 (4H, m, H-6,7), 2.63 (2H, t, J=6.4 Hz, H-5), 3.37 (2H, d, J=5.8 Hz, $=NCH_2CH(CH_3)_2$), 3.62 (2H, d, J=6.8 Hz, 3-$CH_2CH(CH_3)_2$), 7.16–7.41 (3H, m, H-8,9,10), 7.65–7.74 (1H, m, H-11), 7.72 (1H, s, H-2); FABHRMS m/z Calcd for $C_{21}H_{30}N_3$: 324.2440. Found: 324.2410. Compound **12**: IR 1660 (CO); ^{1}H NMR (deuteriochloroform): δ 0.91 (6H, d, J=6.5 Hz, 2×CH_3),

1.62–1.83 (1H, m, $CH_2CH(CH_3)_2$), 2.20–2.38 (4H, m, H-6,7), 2.48 (2H, d, J=6.8 Hz, $CH_2CH(CH_3)_2$), 2.59 (2H, t, J=7.0 Hz, H-5), 3.05, 4.08 (each 2H, each t, J=5.8 Hz, NCH_2CH_2N), 7.24–7.43 (3H, m, H-8,9,10), 7.64–7.72 (1H, m, H-11), 8.19 (1H, s, H-2); FABHRMS *m/z* Calcd for $C_{19}H_{26}N_3O$: 312.2076. Found: 312.2086.

3.2. Evaluation of chemicals on reserpine-induced hypothermia in mice

The evaluation was performed according to the literature procedure.[14] Five male ICR-JCL mice weighing 20–30 g were used in all experiments. Reserpine (2 mg/kg, ip) was administered to the mice. Test compounds (10 mg/kg, ip) were injected 18 h after the administration. Their body temperature was measured up to a maximum of 4 h following the injection.

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13. These reactions with amines gave products as crystals or viscous oil (see Section 3). All crystalline products turned out to be the hydrobromide salts based on their elemental analysis data. On the contrary, viscous oily products did not give satisfactory elemental analytical data due to their slight instability and/or familiarity with air moisture. We tentatively assign that these oily products were all the free bases, not the hydrobromide salts, because their H-2 pyrimidine proton resonance in ^{1}H NMR is in quite high field region (7.7–8.2 ppm) compared to those of the hydrobromide salts (8.4–8.8 ppm).
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