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Cyclic Guanidines. XIII.[1] Synthesis of 2-Amino-4-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine Derivatives[2]

Fumiyoshi Ishikawa and Hitoshi Yamaguchi

Research Institute, Daiichi Seiyaku Co., Ltd.[3]

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A method for the synthesis of 2-amino-4-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine derivatives (**12** and **13b**) is described. Reduction of the 3-substituted 2,3-dihydrothieno-[2,3-*d*]pyrimidin-2-one (**4c**) and -2-thione (**9b, c**) with sodium borohydride gave the 1,2,3,4-tetrahydro derivatives (**6c** and **10b, c**), whereas the 3-unsubstituted compound **4a** could be reduced only with lithium aluminum hydride to afford the 1,2,3,4-tetrahydro derivative **6a**. The 2-chloro derivative (**7**) was reduced with sodium borohydride to give the 2-chloro-3,4-dihydro derivative **8a**, which was reacted with ethyl bromoacetate to yield predominantly the 3-substituted derivative (**8c**). Amination of **8c** gave compound **12**. Methylation of **10b** and **10c**, followed by amination similarly yielded **13b** and **12**, respectively. In this amination some oxidative products (**14**) were also obtained. Compounds **12** and **13b** had lower inhibitory effects against blood platelet aggregation than the quinazoline analogs (**1**) and (**2**).

Keywords——partial reduction of thieno[2,3-*d*]pyrimidine; 2-amino-4-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine; 5-phenyl-1,2,3,5-tetrahydroimidazo[1,2-*a*]thieno[2,3-*d*]-pyrimidin-2-one; oxidative rearrangement; blood platelet aggregation inhibitor

We have found that 2-amino-3-benzyl-4-phenyl-3,4-dihydroquinazoline (**1**) shows blood platelet aggregation inhibitory action.[4] It was also reported that 6-methyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one (**2**) is a potent inhibitor.[5] This paper deals with the synthesis of the thieno analogs of **1** and **2**, *i.e.*, 2-amino-4-phenyl-3,4-dihydrothieno[2,3-*d*]-pyrimidine derivatives (**13b** and **12**).

Although the 2-amino-3-aminomethylthiophene derivative may be a suitable intermediate for the preparation of 3,4-dihydrothieno[2,3-*d*]pyrimidine derivatives, its preparation is difficult because of the instability of 2-aminothiphene derivatives.[6] Only 4-alkyl-3,4-dihydrothieno[2,3-*d*]pyrimidines were obtained by the reaction of thieno [2,3-*d*]pyrimidine with alkyl lithiums.[7] However, we were able to reduce various 4-phenylthieno[2,3-*d*]pyrimidines selectively to obtain the dihydro derivatives.

2-Amino-3-benzoyl-4,5-dimethylthiophene[8] (**3**) was heated with urea at 200° to give the corresponding 2,3-dihydrothieno[2,3-*d*]pyrimidin-2-one (**4a**). Reaction of **3** with ethyl isocyanatoacetate in toluene under reflux gave the 3-substituted compound **4c**, whereas at room temperature the product was a noncyclized intermediate (**5c**) which was converted into **4c** on

1) Part XII: F. Ishikawa, *Chem. Pharm. Bull.*, **28**, 2587 (1980).
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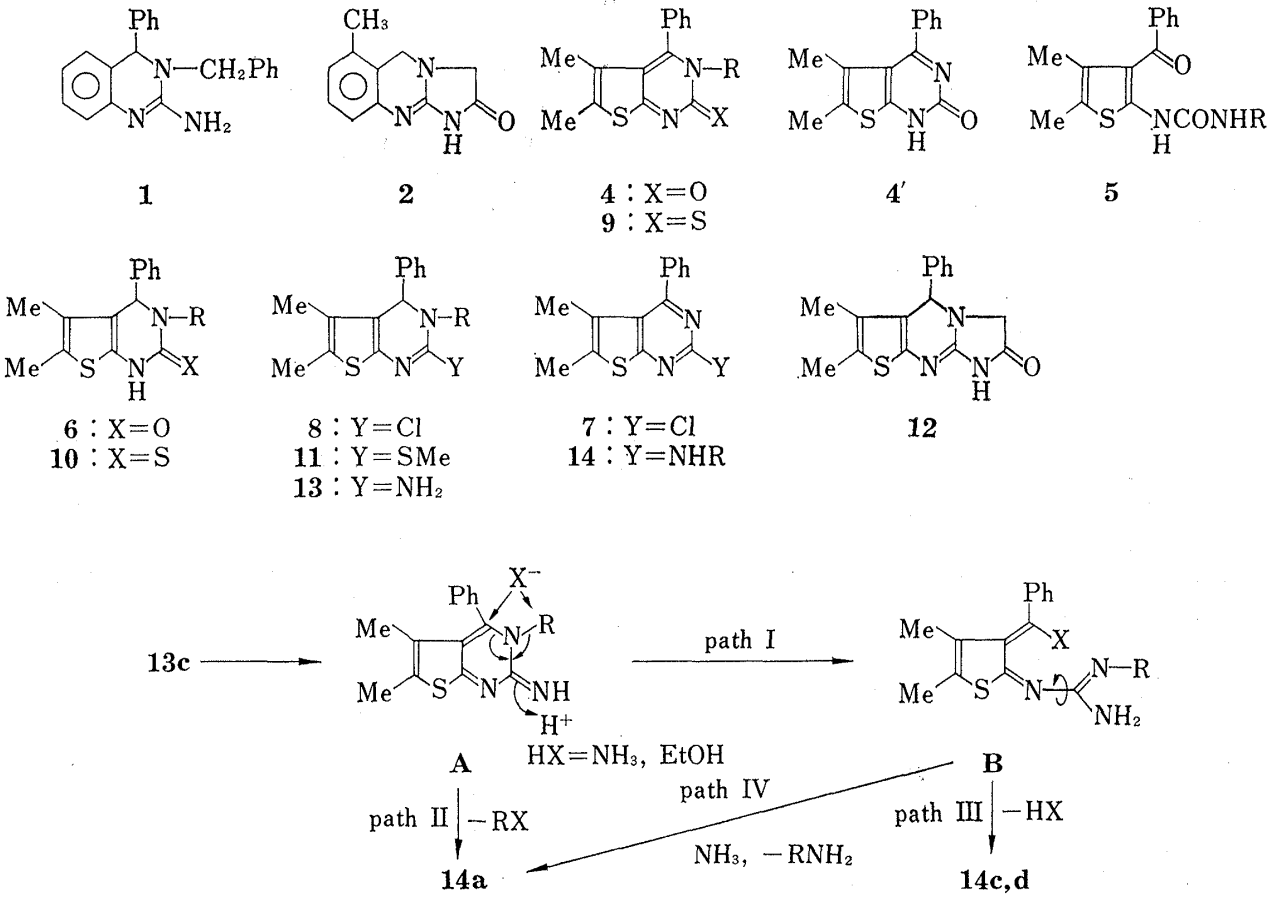

R: **a**=H, **b**=CH_2Ph, **c**=CH_2CO_2Et, **d**=CH_2CONH_2

Chart 1

heating. The structure of **5c** was confirmed by nuclear magnetic resonance (NMR) spectroscopy: the proton on the nitrogen adjacent to the methylene group was observed at δ 6.24 as a triplet coupled with the methylene protons.

According to the reported procedure for the reduction of 3-substituted 2,3-dihydroquinazolin-2-ones,[9] **4c** was treated with sodium borohydride to give the 3,4-dihydro-2(1H)-one derivative (**6c**). Compound **4a** was not reduced by this reagent, but reduction with lithium aluminum hydride gave the corresponding compound (**6a**). Compound **4a** may exist as the tautomeric structure **4'a**, while **4c** takes a fixed *ortho* quinoid form. The reduction of **4c**, therefore, proceeded easily.

An attempt to chlorinate **6c** with phosphoryl chloride to provide the 2-chloro-3-ethoxycarbonylmethyl derivative (**8c**) was unsuccessful, whereas treatment of **4a** with phosphoryl chloride gave the 2-chloro derivative (**7**). By adaptation of the method used for the reduction of 2-chloro-4-phenylquinazoline,[10] **7** was treated with sodium borohydride to give the corresponding 2-chloro-3,4-dihydrothieno[2,3-*d*]pyrimidine derivative (**8a**). Heating **8a** with ethyl bromoacetate in the presence of finely powdered potassium carbonate in methyl ethyl ketone gave predominantly the 3-substituted product (**8c**), as in the alkylation of 3,4-dihydroquinazoline.[11] Reaction of **8c** with ammonia in a sealed tube under a nitrogen atmosphere

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yielded the desired compound **12**, which was identical with a sample prepared by the reaction of **11c** with ammonia as described below.

Heating **3** with isothiocyanates gave 3-substituted 2,3-dihydrothieno[2,3-*d*]pyrimidine-2-thiones (**9b, c**), which were easily reduced by treatment with sodium borohydride to 3,4-dihydro-2(1H)-thiones (**10b, c**). Methylation of **10b, c** with methyl iodide, followed by reaction with ammonia under a nitrogen atmosphere also gave the desired compounds **13b** and **12**, respectively. The reaction of **11c** with ammonia in the presence of air afforded compounds **12**, **14a**, **14c** and **14d** in 37, 9, 1 and 16% yields, respectively. In the NMR spectra of **14c, d**, the methylene protons of the carbonylmethylamino group were observed as a doublet. UV spectra of **14** were similar to those of **4** rather than to those of the 3,4-dihydro derivatives (**6**) or (**13**). Compounds **14a, d** were identical with the samples prepared by the reaction of **8a** with ammonia and glycinamide, respectively.

The formation of **14a, c, d** from **13c** can be explained by in terms of the routes shown in Chart 1. 2-Amino-3,4-dihydrothieno[2,3-*d*]pyrimidine (**13c**) is unstable under oxidative conditions in faver of the dehydro imino derivative (**A**), which yields **14c, d** through Path I and Path III by a reaction similar to Dimroth's rearrangement in the case of 3-alkyl-2-imino-quinazoline.[12] Compound **14a** is formed through Path II or Paths I and IV. This mechanism is supported by the fact that **13b** itself is stable but is readily oxidized with chloranil to give the rearrangement product (**14b**).

The blood platelet aggregation inhibitory activities of the 2-amino-3,4-dihydrothieno[2,3-*d*]pyrimidine derivatives (**12** and **13b**) are less potent than those of the corrsponding benzene analogs, **1** and **2**, respectively.

Experimental

Melting points are uncorrected. IR spectra were recorded with a Hitachi 285 spectrometer. UV spectra were taken with a Hitachi 124 spectrometer. Mass spectra (MS) were determined on a JEOL OISG-2 mass spectrometer. NMR spectra were taken with a Hitachi Perkin-Elmer R-20B (60 MHz) or a Hitachi R-40 (90 MHz) spectrometer with tetramethylsilane as an internal standard. The abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. For column chromatography on silica gel and preparative thin-layer chromatography, we used Merck Kieselgel (70—230 mesh) and Merck Kieselgel 60 GF_{254}, respectively.

5,6-Dimethyl-4-phenyl-2,3-dihydrothieno[2,3-*d*]pyrimidin-2-one (**4a**)——A mixture of 3.46 g (15 mmol) of **3** and 1.0 g (18 mmol) of urea was heated at 170—200° for 2 hr. The reaction mixture was cooled, then a small amount of MeOH was added to give 1.44 g of an insoluble material, which was filtered off. The MeOH solution was concentrated *in vacuo* and benzene was added to the residue to give 1.56 g of insoluble material. The insoluble materials were combined and recrystallized from AcOH–AcOEt to give 1.90 g (50%) of **4a**, mp 253—259°. IR ν_{max}^{KBr} cm^{-1}: 3240—3100, 1620. NMR ($CDCl_3$) δ: 1.57 (3H, s, 5-CH_3), 2.24 (3H, s, 6-CH_3), 7.41 (5H, s, Ph). *Anal.* Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.50; H, 4.82; N, 10.93.

Ethyl 5,6-Dimethyl-4-phenyl-2-oxo-2,3-dihydrothieno[2,3-*d*]pyrimidine-3-acetate (**4c**)——A mixture of 3.48 g (15 mmol) of **3**, 3 drops of Et_3N and 7.00 g of ethyl isocyanatoacetate[13] in 40 ml of dry toluene was stirred at room temperature for 20 hr and heated under reflux for 4 hr. Insoluble material was filtered off and the filtrate was diluted with benzene. The solution was washed with H_2O, dried, and concentrated. The residue was recrystallized from benzene–petr. ether to give 3.42 g (67%) of **4c**, mp 173—177°. IR ν_{max}^{KBr} cm^{-1}: 1750, 1655. UV λ_{max}^{EtOH} nm: 231, 256, 282, 293 (s), 377. NMR ($CDCl_3$) δ: 1.16 (3H, t, CH_3), 1.25 (3H, s, 5-CH_3), 2.22 (3H, s, 6-CH_3), 4.13 (2H, q, CH_2), 7.2—7.65 (5H, m, Ph). *Anal.* Calcd for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18. Found: C, 62.78; H, 5.28; N, 8.18.

Ethyl [3-[2-(3-Benzoyl-4,5-dimethyl)thienyl]ureido]acetate (**5c**)——By a procedure similar to that described above, 1.16 g (5 mmol) of **3** was treated with ethyl isocyanatoacetate at room temperature to give 0.22 g (11%) of **5c**, mp 144—146° (from $CHCl_3$–petr. ether). IR ν_{max}^{KBr} cm^{-1}: 3300, 1640, 1595, 1540, 1505, UV λ_{max}^{EtOH} nm: 253, 268 (s), 373. NMR ($CDCl_3$) δ: 1.20 (3H, t, CH_3), 1.50 (3H, s, 4-CH_3), 2.65 (3H, s, 5-CH_3), 3.85 (2H, d, N–CH_2), 4.15 (2H, q, O–CH_2), 6.24 (1H, br t, N–H), 7.44 (5H, s, Ph), 10.92 (1H, br s, N–H). *Anal.* Calcd for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77. Found: C, 59.98; H, 5.60; N, 7.63.

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13) W. Siefken, *Ann.*, **562**, 75 (1945).

5,6-Dimethyl-4-phenyl-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-2-one (6a)——Compound **4a** (1.28 g, 5 mmol) was added portionwise to a suspension of 0.57 g (15 mmol) of $LiAlH_4$ in 50 ml of THF at 15—25° during 0.5 hr with stirring. The mixture was heated at 50—55° for 2 hr then under reflux for 1 hr. It was cooled, then 1 ml of H_2O was added dropwise below 20°. The mixture was concentrated *in vacuo* and 20 ml of 10% HCl was added to the residue. The precipitate was collected, washed with 10% HCl, and recrystallized from DMF to give 0.75 g (58%) of **6a**, mp 279—283° (dec.). IR ν_{max}^{KBr} cm^{-1}: 3180, 3060, 2900, 1680. UV λ_{max}^{EtOH} nm: 235 (s), 283. NMR (DMSO-d_6) δ: 1.63 (3H, s, 5-CH_3), 2.11 (3H, s, 6-CH_3), 5.30 (1H, d, J= 3 Hz, CH), 7.28 (5H, s, Ph), 9.40 (1H, br, N–H). *Anal.* Calcd for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.35; N, 10.36. Found: C, 64.62; H, 5.46; N, 10.84.

Ethyl 5,6-Dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-3-acetate (6c)——$NaBH_4$ (0.38 g, 10 mmol) was added to a solution of 3.40 g (10 mmol) of **4c** in 20 ml of $CHCl_3$–EtOH (1: 1). The mixture was stirred at room temperature for 0.5 hr and concentrated *in vacuo*. After addition of H_2O to the residue, the mixture was neutralized with 1 N HCl and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residue was recrystallized from $CHCl_3$–EtOH to give 2.89 g (85%) of **6c**, mp 208—211°. IR ν_{max}^{KBr} cm^{-1}: 3290, 3170, 2900, 1740, 1650, 1610. NMR ($CDCl_3$) δ: 1.22 (3H, t, CH_3), 1.61 (3H, s, 5-CH_3), 2.13 (3H, s, 6-CH_3), 3.47, 4.52 (1H×2, d×d, J=18 Hz, N–CH_2), 4.16 (2H, q, CH_2), 5.39 (1H, s, CH), 7.30 (5H, s, Ph), 8.78 (1H, br s, N–H). *Anal.* Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13. Found: C, 62.72; H, 5.86; N, 8.19.

Corresponding 2-thione derivatives **10b, c** were similarly prepared.

10b: Yield 100%, mp 205—206° (from $CHCl_3$–hexane). IR ν_{max}^{KBr} cm^{-1}: 3150, 2970, 1610, 1520, 1480, 1280. NMR ($CDCl_3$) δ: 1.61 (3H, s, 5-CH_3), 2.13 (3H, s, 6-CH_3), 3.98, 6.43 (1H×2, d×d, J=15 Hz, N–CH_2), 5.35 (1H, s, CH), 7.3—7.5 (10H, m, Ph), 10.65 (1H, br, N–H). *Anal.* Calcd for $C_{21}H_{20}N_2S_2$: C, 69.19; H, 5.53; N, 7.68. Found: C, 69.39; H, 5.57; N, 7.74.

10c: Yield 75%, mp 251—254° (from $CHCl_3$–petr. ether). IR ν_{max}^{KBr} cm^{-1}: 3150, 2980, 1740, 1200. NMR ($CDCl_3$) δ: 1.27 (3H, t, CH_3), 1.67 (3H, s, 5-CH_3), 2.18 (3H, s, 6-CH_3), 3.85, 5.30 (1H×2, d×d, N–CH_2), 4.22 (2H, q, CH_2), 5.54 (1H, s, CH), 7.33 (5H, s, Ph), 9.35 (1H, br s, N–H). *Anal.* Calcd for $C_{18}H_{20}N_2O_2S_2$: C, 59.97; N, 5.59; N, 7.77. Found: C, 59.99; H, 5.69; N, 7.76.

2-Chloro-5,6-dimethyl-4-phenylthieno[2,3-*d*]pyrimidine (7)——DMF (6.2 ml, 80 mmol) was added dropwise to 15 ml of $POCl_3$ below 30° with stirring. After addition of 5.16 g (20 mmol) of **4a** to the mixture, it was heated at 75—90° for 3 hr with stirring, poured into ice-water and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column with benzene to give 3.79 g (69%) of **7**, mp 126—128° (from benzene–petr. ether). IR ν_{max}^{KBr} cm^{-1}: 1480, 1210. UV λ_{max}^{EtOH} nm: 249, 295, 322 (s). NMR ($CDCl_3$) δ: 1.82 (3H, s, 5-CH_2), 2.47 (3H, s, 6-CH_3), 7.40 (5H, s, Ph). *Anal.* Calcd for $C_{14}H_{11}ClN_2S$: C, 61.20; H, 4.04; N, 10.20. Found: C, 61.15; H, 3.99; N, 10.19.

2-Chloro-5,6-dimethyl-4-phenyl-3,4-dihydrothieno[2,3-d]pyrimidine (8a)——By a procedure similar to that described for the preparation of **6c**, 3.05 g (11 mmol) of **7** was treated with 2.09 g (55 mmol) of $NaBH_4$ in $CHCl_3$–EtOH to give 1.75 g (63%) of **8a**, mp 215—218° (from $CHCl_3$–hexane). IR ν_{max}^{KBr} cm^{-1}: 3180, 1590, 1280. NMR ($CDCl_3$) δ: 1.60 (3H, s, 5-CH_3), 2.21 (3H, s, 6-CH_3), 5.30 (1H, br, N–H), 5.71 (1H, d, CH), 7.30—7.45 (5H, m, Ph). *Anal.* Calcd for $C_{14}H_{13}ClN_2S$: C, 60.75; H, 4.73; N, 10.12. Found: C, 60.75; H, 4.69; N, 10.19.

Ethyl 2-Chloro-5,6-dimethyl-4-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine-3-acetate (8c)——A mixture of 0.83 g (3 mmol) of **8a**, 0.55 g (3.3 mmol) of ethyl bromoacetate and 0.83 g (6 mmol) of finely powdered K_2CO_3 in 50 ml of MeCOEt was heated under reflux for 4 hr with stirring under a nitrogen atmosphere. Insoluble material was filtered off and washed with MeCOEt. The combined filtrate and washings were concentrated. The oily residue was crystallized from EtOH to give 0.475 g (44%) of **8c**, mp 119—120° (from $CHCl_3$–EtOH). IR ν_{max}^{KBr} cm^{-1}: 1760, 1560, 1190, 1170. UV λ_{max}^{EtOH} nm: 230 (s), 248 (s), 265 (s), 333, 346 (s). NMR ($CDCl_3$) δ: 1.23 (3H, t, CH_3), 1.60 (3H, s, 5-CH_3), 2.22 (3H, s, 6-CH_3), 3.92, 4.27 (1H×2, d×d, J=18 Hz, N–CH_2), 4.17 (2H, q, CH_2), 5.64 (1H, s, CH), 7.40 (5H, s, Ph). *Anal.* Calcd for $C_{18}H_{18}ClN_2O_2S$: C, 59.58; H, 5.28; N, 7.72. Found: C, 59.52; H, 5.32; N, 7.91.

3-Benzyl-5,6-dimethyl-4-phenyl-2,3-dihydrothieno[2,3-*d*]pyrimidine-2-thione (9b)——A mixture of 11.6 g (50 mmol) of **3** and 8.20 g (55 mmol) of benzyl isothiocyanate in 200 ml of EtOH was heated under reflux for 16 hr. The precipitate was collected and washed with cold EtOH to give 7.15 g of **9b**. The filtrate and the washings were combined and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel. Elution with benzene–$CHCl_3$ (7: 1) resulted in the recovery of 3.30 g (28%) of **3**, then eluate with $CHCl_3$ gave 1.37 g of **9b**. Total yield of **9b**, mp 206—207° (from benzene–petr. ether), was 8.88 g (49%). IR ν_{max}^{KBr} cm^{-1}: 1560, 1380. NMR ($CDCl_3$) δ: 1.25 (3H, s, 5-CH_3), 2.32 (3H, s, 6-CH_3), 6.04 (2H, br s, N–H), 6.75—7.60 (10H, m, Ph). *Anal.* Calcd for $C_{21}H_{18}N_2S_2$: C, 69.58; H, 5.00; N, 7.73. Found: C, 69.37; H, 5.16; N, 7.69.

Ethyl 5,6-Dimethyl-4-phenyl-2-thioxo-2,3-dihydrothieno[2,3-*d*]pyrimidine-3-acetate (9c)——A mixture of 1.16 g (10 mmol) of **3** and 0.73 g (10 mmol) of ethyl isothiocyanatoacetate[14] in 16 ml of benzene was heated

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under reflux for 20 hr under a nitrogen atmosphere. After removal of the benzene, the residue was chromatographed on a column of silica gel. The eluate with $CHCl_3$ gave 0.914 g (51%) of **9c**, mp 201—204° (from $CHCl_3$–petr. ether). IR ν_{max}^{KBr} cm^{-1}: 1735, 1230. NMR ($CDCl_3$) δ: 1.21 (3H, t, CH_3), 1.30 (3H, s, 5-CH_2), 2.31 (3H, s, 6-CH_3), 4.21 (2H, q, CH_2), 5.13 (2H, br s, N–CH_2), 7.3—7.7 (5H, m, Ph). *Anal.* Calcd for $C_{18}H_{18}N_2O_2S_2$: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.65; H, 5.18; N, 7.88.

3-Benzyl-5,6-dimethyl-2-methylthio-4-phenyl-3,4-dihydrothieno[2,3-d]pyrimidine Hydroiodide (11b)——A suspension of 3.65 g (10 mmol) of **9b** and 1.70 g (12 mmol) of CH_3I in 60 ml of EtOH was heated under reflux for 3 hr. After concentration of the mixture to about 10 ml, Et_2O was added to the residue. The precipitate was collected, washed with EtOH–Et_2O (1: 1) and dried to give 3.99 g (79%) of **11b**, mp 166—168° (from EtOH–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 3030, 2890, 1600, 1530, 1500. NMR ($CDCl_3$) δ: 1.61 (3H, s, 5-CH_3), 2.21 (3H, s, 6-CH_3), 3.34 (3H, s, S–CH_3), 4.43, 5.24 (1H×2, d×d, J=16 Hz, N–CH_2), 5.56 (1H, s, CH), 7.2—7.65 (10H, m, Ph). *Anal.* Calcd for $C_{22}H_{22}IN_2S_2$: C, 52.17; H, 4.58; N, 5.53. Found: C, 52.26; H, 4.72; N, 5.47. The free base of **11b**: mp 155—157° (from benzene–petr. ether).

Compound **11c** was similarly prepared. Yield was 83%, mp 235—243° (from EtOH–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 3200—2600, 1750, 1540. NMR ($CDCl_3$) δ: 1.14 (3H, t, CH_3), 1.66 (3H, s, 5-CH_3), 2.19 (3H, s, 6-CH_3), 3.19 (3H, s, S–CH_3), 4.03 (2H, q, CH_2), 4.52 (1H, br s, N–H), 6.01 (1H, s, CH), 7.40 (5H, s, Ph). *Anal.* Calcd for $C_{19}H_{23}IN_2O_2S_2$: C, 45.42; H, 4.61; N, 5.58. Found: C, 45.88; H, 4.63; N, 5.79. The free base of **11c**: mp 114—116° (from benzene–petr. ether).

6,7-Dimethyl-5-phenyl-1,2,3,5-tetrahydroimidazo[1,2-*a*]thieno[2,3-*d*]pyrimidin-2-one (12)——a) A mixture of 0.37 g (1 mmol) of **8c** in 5 ml of 5% NH_3–EtOH solution was heated at 120° for 16 hr in a sealed tube under a nitrogen atmosphere. The mixture was cooled, then the precipitate was collected and washed with EtOH and H_2O successively to give 0.042 g (14%) of **12**, mp 287—290° (from $CHCl_3$–EtOH). IR ν_{max}^{KBr} cm^{-1}: 3100—2300, 1730, 1460. UV λ_{max}^{EtOH} nm: 230 (s), 249, 319. NMR (CF_3CO_2H) δ: 1.68 (3H, s, 6-CH_3), 2.31 (3H, s, 7-CH_3), 3.97, 4.48 (1H×2, d×d, J=20 Hz, CH_2), 5.90 (1H, s, CH), 7.2—7.6 (5H, m, Ph). MS *m/e*: 297 (M^+), 220 ($M-C_6H_5$). *Anal.* Calcd for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.93; H, 5.04; N, 14.32.

b) A mixture of 2.00 g (4 mmol) of **11c** and 1 ml of AcOH in 45 ml of 10% NH_3–EtOH solution was heated at 100—110° for 60 hr in a sealed tube. The mixture was cooled, then the precipitate was collected by filtration and washed with EtOH to give 0.21 g of **12**. The combined filtrate and washings were concentrated *in vacuo*. Addition of EtOH to the residue gave a further 0.19 g of **12**. The EtOH-soluble fraction was concentrated *in vacuo*. The residue was mixed with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated *in vacuo*. The residue was chromatographed on silica gel. The first eluate with benzene–$CHCl_3$ (2: 1) gave 0.30 g of the free base of **11c**. The second eluate with benzene–$CHCl_3$ (2: 1) gave 0.18 g of a mixture of **14a** and **14c**, which was separated by preparative thin-layer chromatography with benzene–acetone (10: 1) to give 87 mg (9%) of **14a** and 16 mg (1%) of **14c**. Compound **14c**: mp 163—165°. IR ν_{max}^{KBr} cm^{-1}: 3250, 1745, 1550. UV λ_{max}^{EtOH} nm: 229 (s), 258, 276 (s), 286 (s), 346. NMR ($CDCl_3$) δ: 1.24 (3H, t, CH_3), 1.66 (3H, s, 5-CH_3), 2.32 (3H, s, 6-CH_3), 3.9—4.4 (4H, m, N–CH_2 and O–CH_2), 5.75 (1H, br, N–H), 7.43 (5H, s, Ph). MS *m/e*: 341 (M^+), 268. The third eluate with $CHCl_3$–EtOH (30: 1) gave a further 43 mg of **12**. The total yield of **12** was 0.44 g (37%). The fourth eluate with $CHCl_3$–EtOH (30: 1) gave 0.20 g (16%) of **14d**. Compounds **12**, **14a**, and **14d** were identical with samples obtained by the methods described above and below, respectively.

2-Amino-3-benzyl-5,6-dimethyl-4-phenyl-3,4-dihydrothieno[2,3-*d*]pyrimidine Hydrochloride Hemihydrate (13b)——A mixture of 4.93 g (13 mmol) of the free base of **11b** and 1.5 ml of AcOH in 50 ml of 10% NH_3–EtOH solution was heated at 130° for 134 hr in a sealed tube under a nitrogen atmosphere. The mixture was cooled and the precipitate was collected by filtration to recover 2.56 g (53%) of the free base of **11b**. The filtrate was concentrated *in vacuo*. The residue was mixed with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated *in vacuo*. The residue was chromatographed on silica gel. The eluate with $CHCl_3$–MeOH (20: 1) was collected and treated with 10% HCl–MeOH solution to give 1.44 g (29%) of **13b**, mp 148—151° (from EtOH–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 3400—2700, 1640, 1540. UV λ_{max}^{EtOH} nm: 240, 296; $\lambda_{max}^{EtOH-2N\ NaOH}$ nm: 326. NMR (DMSO-d_6) δ: 1.70 (3H, s, 5-CH_3), 2.19 (3H, s, 6-CH_3), 4.35, 5.12 (1H×2, d×d, J=18 Hz, N–CH_2), 5.71 (1H, s, CH), 7.40, 7.45 (5H×2, s, Ph), 8.43 (3H, br s, N–H). *Anal.* Calcd for $C_{21}H_{22}ClN_3S\cdot 0.5H_2O$: C, 64.68; H, 6.38; N, 11.01. Found: C, 64.19; H, 5.90; N, 10.69.

2-Amino-5,6-dimethyl-4-phenylthieno[2,3-*d*]pyrimidine (14a)——A mixture of 0.275 g (1 mmol) of **7** in 10% NH_3–EtOH solution in a sealed tube was heated at 110° for 13 hr. After removal of the solvent, the residue was dissolved in $CHCl_3$. The solution was washed with H_2O, dried and concentrated *in vacuo*. The residue was chromatographed on silica gel. The eluate with benzene gave 0.125 g of recovered **7**. The eluate with $CHCl_3$ gave 0.031 g (12%) of **14a**, mp 172—174° (from benzene–petr. ether). IR ν_{max}^{KBr} cm^{-1}: 3470, 3300, 3160, 1610, 1520. UV λ_{max}^{EtOH} nm: 254, 284 (s), 345. NMR ($CDCl_3$) δ: 1.66 (3H, s, 5-CH_3), 2.33 (3H, s, 6-CH_3), 5.18 (2H, br s, N–H), 7.42 (5H, s, Ph). *Anal.* Calcd for $C_{14}H_{13}N_3S$: C, 65.86; H, 5.13; N, 16.46. Found: C, 66.13; H, 5.17; N, 16.39.

2-Benzylamino-5,6-dimethyl-4-phenylthieno[2,3-*d*]pyrimidine (14b)——a) A mixture of 0.275 g (1 mmol) of **7** and 0.235 g (2.2 mmol) of benzylamine in 10 ml of EtOH was heated under reflux for 92 hr. After removal of the solvent, the residue was mixed with H_2O and extracted with $CHCl_3$. The extract was

washed with H_2O, dried and concentrated *in vacuo*. The residue was chromatographed on a silica gel column with benzene to give 0.199 g (58%) of **14b**, mp 133—136° (from benzene–hexane). IR ν_{max}^{KBr} cm^{-1}: 3260, 1580, 1550. UV λ_{max}^{EtOH} nm: 230 (s), 261, 289, 351. NMR ($CDCl_3$) δ: 1.67 (3H, s, 5-CH_3), 2.31 (3H, s, 6-CH_3), 4.67 (2H, d, N–CH_2), 4.78 (1H, br t, N–H), 7.2—7.4 (5H, m, Ph), 7.45 (5H, s, Ph). *Anal.* Calcd for $C_{21}H_{19}N_3S$: C, 73.01; H, 5.54; N, 12.16. Found: C, 73.02; H, 6.07; N, 12.29.

b) Chloranil (0.16 g, 0.65 mmol) was added to a solution of 0.25 g (0.72 mmol) of the free base of **13b** in 15 ml of CCl_4. The mixture was stirred at room temperature for 0.5 hr and then heated under reflux for 0.5 hr. The mixture was cooled, then diluted with $CHCl_3$. The solution was washed with 2 N NaOH and H_2O successively, dried and concentrated *in vacuo*. The residue was chromatographed on silica gel with benzene to give 0.057 g (23%) of **14b**, which was identical with a specimen obtained by method a).

(5,6-Dimethyl-4-phenylthieno[2,3-*d*]pyrimidin-2-ylamino)acetamide (14d)——A mixture of 0.275 g (1 mmol) of **7**, 0.121 g (1.1 mmol) of glycinamide hydrochloride and 0.222 g (1 mmol) of Et_3N in 10 ml of EtOH was heated under reflux for 8 hr. After removal of the solvent, the residue was mixed with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated *in vacuo*. The residue was triturated with benzene. The precipitate was collected and recrystallized from EtOH to give 0.035 g (11%) of **14d**, mp 215—217°. IR ν_{max}^{KBr} cm^{-1}: 3400—2800, 1660, 1540. UV λ_{max}^{EtOH} nm: 229 (s), 258, 285 (s), 355. NMR ($CDCl_3$) δ: 1.62 (3H, s, 5-CH_3), 2.31 (3H, s, 6-CH_3), 3.86 (2H, d, J=6 Hz, N–CH_2), 6.9—7.35 (3H, m, N–H), 7.46 (5H, s, Ph). *Anal.* Calcd for $C_{16}H_{16}N_4OS$: C, 61.52; H, 5.16; N, 17.93. Found: C, 61.01; H, 5.28; N, 17.75.

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