[Chem. Pharm. Bull. 35(1) 90—96 (1987)]

Synthesis and Reactions of 2,3-Dihydrothiazolo[3,2-*a*]pyrimidine Derivatives

TOSHIO KINOSHITA,* YASUJI UESHIMA, KOUJI SAITOH, YASUFUMI YOSHIDA, and SUNAO FURUKAWA

Faculty of Pharmaceutical Sciences, Nagasaki University, 1–14 Bunkyo-machi, Nagasaki 852, Japan

(Received June 9, 1986)

The reaction of 2-amino-2-thiazoline (**1**) with acetylene carboxylates (**2**) afforded 5-substituted 2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-ones (**3**). 7-Bromomethyl-2,3-dihydro-5*H*-thiazolo-[3,2-*a*]pyrimidin-5-one (**10**) was obtained by the reaction of **1** with γ-bromoacetoacetyl bromide. Treatment of **10** with *N*-bromosuccinimide provided the 6-bromo compound (**12**). The 7-bromomethyl compounds (**10** and **12**) were converted to 7-morpholinomethyl derivatives by treatment with morpholine. When **3a** (unsubstituted-), **3b** (5-ethoxycarbonyl-), and **3c** (5-hydroxymethyl-) were treated with 5% hydrochloric acid, covalent hydration occurred across the 5,6-carbon–carbon bond, giving 5-hydroxy-2,3,5,6-tetrahydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one derivatives (**16a**, **16b**, and **16c**). On the other hand, in the case of **11** (7-methyl-) and **17** (5-phenyl-), the dihydrothiazole ring was cleaved to give 3(and 1)-(2-mercaptoethyl)-6-methyl(and phenyl)-2,4(1*H*,3*H*)-pyrimidinedione (**19** and **18**).

Keywords——dihydrothiazolo[3,2-*a*]pyrimidine; γ-bromoacetoacetyl bromide; 2-amino-2-thiazoline; covalent hydration; ring cleavage; bromination; cyclization; acetylene carboxylate

Various syntheses have been reported of 2,3-dihydrothiazolo[3,2-*a*]pyrimidine derivatives, some of which have analgesic, antithrombic and antiinflammatory activities. The compounds have been synthesized in two ways, when classified in terms of the starting materials. One involves cyclization of 2-thiouracil with 1,2-dibromoethane,[1] ethyl γ-chloroacetoacetate,[2] or ethyl chloroacetate,[3] or intramolecular cyclization of 1-(2-hydroxyethyl)-thiouracil with methanesulfonyl chloride[4] or of 1-allylthiouracil with iodine.[5] The other consists of the reaction of 2-amino-2-thiazoline (**1**) with diketene,[6] acetoacetic esters,[7] ethoxymethylenemalonic esters,[1b] ethoxymethylenecyanoacetamide,[8] acetylene carboxylic ester,[9] ethyl malonyl chloride[10] or diethyl malonate.[11] In this paper we describe the synthesis of 2,3-dihydrothiazolo[3,2-*a*]pyrimidine derivatives from 2-amino-2-thiazoline (**1**) as a starting material, and some reactions of the thiazolopyrimidines.

The reaction of 2-amino-2-thiazoline (**1**) with ethyl propiolate (**2a**, R=H) and diethyl acetylenedicarboxylate (**2b**, R=COOEt) gave unsubstituted 2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**3a**) and 2,3-dihydro-5-ethoxycarbonyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**3b**). Similarly, the 5-hydroxymethyl compound (**3c**) was obtained in 62.0% yield by treatment with ethyl γ-hydroxytetrolate (**2c**)[12] in ethanol. The structures of the above products (**3a**, **3b**, and **3c**) are supported by the infrared (IR) and ultraviolet (UV) spectral data.[1b]

Compound **3b** was converted to the carboxamide (**4**) by reaction with ethanolic ammonia in a flask sealed by a stopcock at room temperature. The reaction of **3c** with acetic anhydride afforded the corresponding acetoxy compound (**5**). For the preparation of the 5-halomethyl compounds (**8** and **10′**), **3c** was treated with thionyl chloride, phosphorus oxychloride or phosphorus tribromide under various conditions; however, no reaction occurred and the starting material was recovered.

6-Hydroxymethyl-2-thioxo-1,3-thiazin-4-one (**6**)[12] was converted to 2,3-dihydro-1-(2-

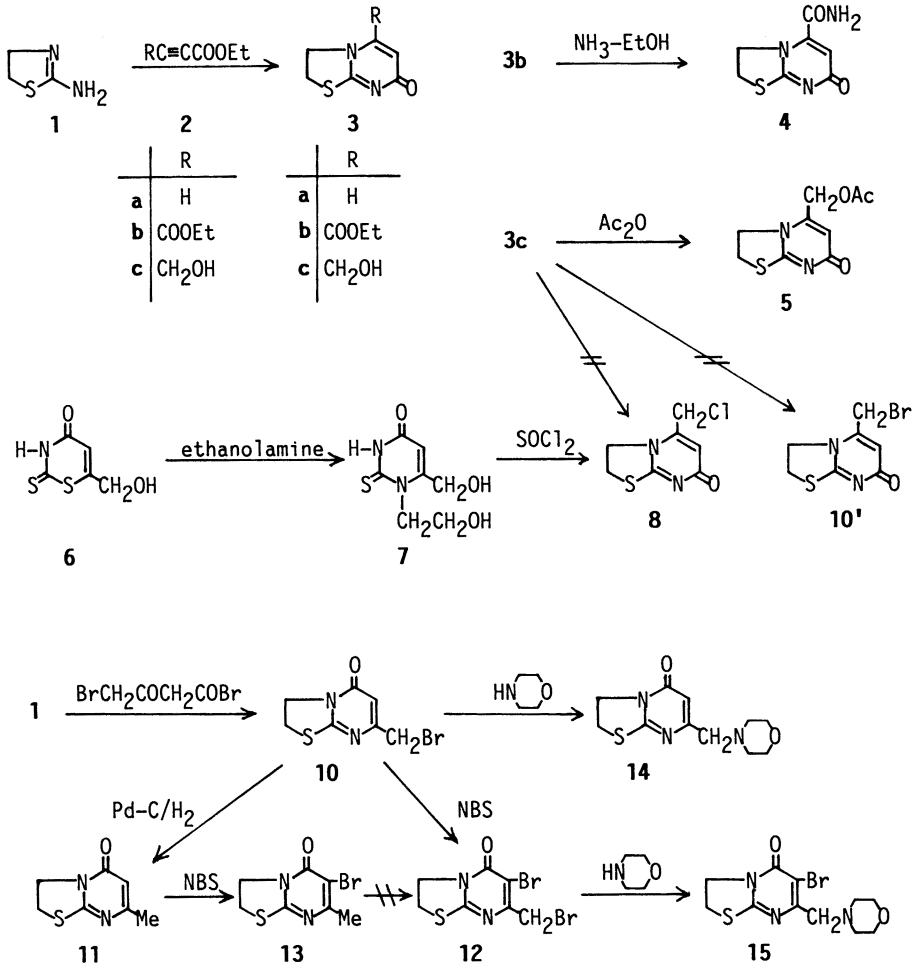

Chart 1

hydroxyethyl)-6-hydroxymethyl-2-thioxo-4(1*H*)-pyrimidinone (**7**) by reaction with 2-aminoethanol. In order to prepare 1-(2-chloroethyl)-6-chloromethyl-2-thioxo-4(3*H*)-pyrimidinone, **7** was treated with thionyl chloride, but the cyclized product **8** was obtained.

It has been reported that the reaction of acid chlorides with 2-aminoethiazole or 2-amino-2-thiazoline (**1**) gives 2-acylaminothiazole[13] or 2-acylamino-2-thiazoline.[12] Therefore we expected that the reaction of γ-bromoacetoacetyl bromide (**9**)[14] with **1** would afford 2-(γ-bromoacetoacetylamino)-2-thiazoline, followed by ring closure to yield 5-bromomethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**10'**). However, we found that the product is 7-bromomethyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**10**). The structure of **10** was confirmed by IR and UV spectral data and chemical evidence. Compound **10** was converted to 7-methyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**11**)[1b,6] by catalytic hydrogenolysis over palladium–carbon catalyst.

With *N*-bromosuccinimide in ethanol, **10** was converted to the corresponding 6-bromo compound **12**. Similarly, **11** was converted to the 6-bromo compound **13** by treatment with *N*-bromosuccinimide or bromine in acetic acid.[1b] The position of the bromine substituent was determined from the proton nuclear magnetic resonance (^{1}H-NMR) spectra of **12** and **13**, in which no olefinic protons were not observed. It is well known that 5-bromo-1,3-disubstituted-

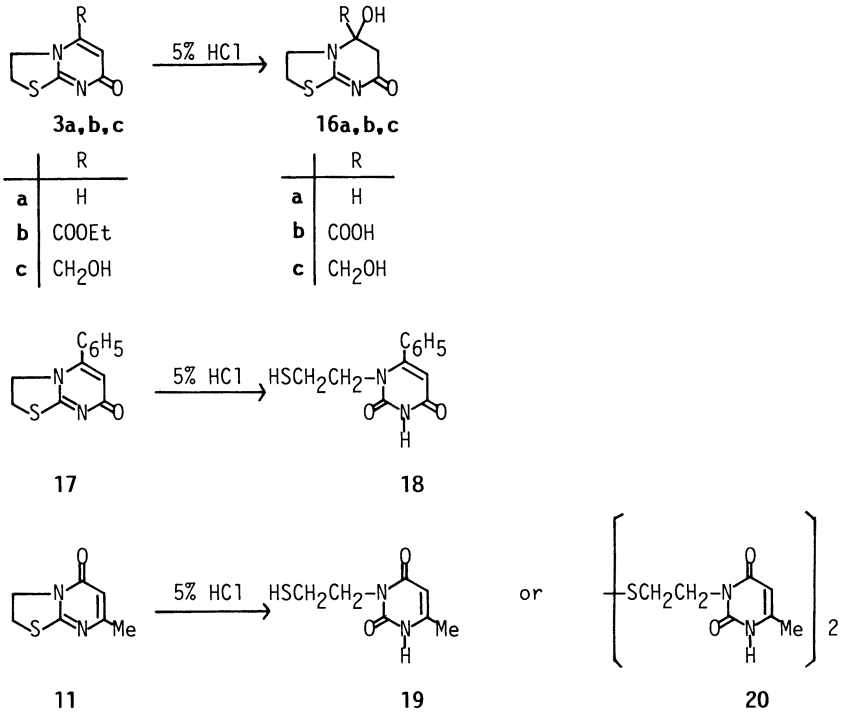

Chart 2

6-methyl-2,4(1*H*,3*H*)-pyrimidinediones are converted to the 6-bromomethyl derivatives by reaction with bromine in acetic acid.[15] However, in the case of **13**, no reaction occurred under these conditions. The reaction of the 7-bromomethyl compound (**10** and **12**) with morpholine yielded the corresponding 7-morpholinomethyl derivatives (**14** and **15**).

For the preparation of 1-(2-mercaptoethyl)-6-hydroxymethyl-2,4(1*H*,3*H*)-pyrimidinedione, **3c** was treated with 5% hydrochloric acid according to Falch and Natvig.[16] The product (**16**) was found to have the molecular formula $C_7H_{10}N_2O_3$ by elemental microanalysis, but the UV spectrum showed no absorption maximum and was different from those of 2,4-(1*H*,3*H*)-pyrimidinedione derivatives.[17]

The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **16b** indicated the presence of three methylene groups at δ 48.93, 40.80, and 28.77. The former two signals are assignable to the carbons of the dihydrothiazole ring by comparison with those of the starting material (**3b**). Further structural assignment was possible from the ^{1}H-NMR (270 MHz) spectrum, which exhibited signals due to one isolated methylene moiety at δ 3.70 and 3.18 as doublets, complicated ethylene signals at δ 4.32, 4.13, and 3.5—3.3 and a characteristic broad singlet signal at δ 9.48 due to a hydroxyl group.

The structure of **16b**, based on the above spectral data, was assumed to 5-carboxy-5-hydroxy-2,3,5,6-tetrahydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one, which corresponded to covalent hydration across the 5,6-carbon–carbon double bond of **3b**. Similarly, **3a** and **3c** were converted to the covalent hydration products **16a** and **16c**. However, under the same reaction conditions, no covalent hydration was observed in the case of compounds **17** and **11**; instead, the dihydrothiazole ring was cleaved to afford **18** and **19**, as described by Falch and Natvig.[16] The UV spectra of the reaction products (**18** and **19**) showed absorption maxima at 275 and 264 nm, and the IR spectra showed SH stretching absorptions at 2530 and 2555 cm^{-1}. The

^{1}H-NMR spectrum of **18** showed signals at δ 1.48, 2.80, and 4.14 due to NCH_2CH_2SH and δ 5.91 due to ring proton. Similarly, **19** exhibited signals at δ 1.19, 2.64, and 3.83 due to NCH_2CH_2SH and δ 5.63 due to a ring proton in the ^{1}H-NMR spectrum. On the basis of the above data, the structures of **18** and **19** were concluded to be 1-(2-mercaptoethyl)-6-phenyl-2,4-(1*H*,3*H*)-pyrimidinedione and 3-(2-mercaptoethyl)-6-methyl-2,4-(1*H*,3*H*)-pyrimidinedione, respectively. When **11** was treated with 5% hydrochloric acid for 7 h, an alternative product **20** was obtained which showed an absorption maximum at 263 nm in the UV spectrum (similar to that of **19**). The ^{1}H-NMR spectrum exhibited two double-doublet signals due to an ethylene group (δ 4.33 and 2.97) and no peak due to an SH group. Furthermore, fast atom bombardment mass spectrometry (FAB-MS) showed the hydrogenated molecular ion peak $[(M+1)^+]$ at *m/z* 371. Therefore, **20** was concluded to be 3,3′-bis[6-methyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidinyl]diethyldisulfide. When **19** was treated with iodine in ethanol, **20** was obtained in good yield.

Experimental

Melting points reported here are uncorrected. IR spectra were recorded on JASCO IRA-2 and IR-810 spectrophotometer. UV spectra were recorded in ethanol on a Hitachi 323 spectrophotometer. The NMR spectra were obtained on Hitachi R-600 (60 MHz, for ^{1}H), JEOL JNM FX-90Q (90 MHz for ^{1}H and 22.5 MHz for ^{13}C) and JEOL JNM GX-270 (270 MHz, for ^{1}H) spectrometers. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL JMS-DX-303 spectrometer by the electron impact (EI) or fast atom bombardment (FAB) ionization method.

2,3-Dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (3a)——A solution of 2-amino-2-thiazoline (**1**) (0.51 g, 5.0 mmol) and ethyl propiolate (**2a**) (0.5 g, 5.0 mmol) in EtOH (20 ml) was refluxed for 9 h. The reaction mixture was concentrated to dryness *in vacuo* and the residue was washed with ether. The insoluble material was crystallized from MeOH, giving 0.53 g (68.8%) of colorless needles, mp 225 °C (lit.[1b] mp 227—228 °C). ^{1}H-NMR ($CDCl_3$) δ: 7.27 (1H, d, J=7.8 Hz, C(5)-H), 6.02 (1H, d, J=7.8 Hz, C(6)-H), 4.34 (2H, t, J=6.8 Hz, N–CH_2), 3.50 (2H, t, J=6.8 Hz, S–CH_2). MS *m/z*: 154 (M^+).

2,3-Dihydro-5-ethoxycarbonyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (3b)——A solution of **1** (0.5 g, 5.0 mmol) and diethyl acetylenedicarboxylate (**2b**) (0.85 g, 5.0 mmol) in EtOH (20 ml) was refluxed for 3 h. The reaction mixture was concentrated to dryness *in vacuo*, and the residue was recrystallized from AcOEt, giving 0.61 g (61.0%) of colorless needles, mp 121—122 °C. *Anal.* Calcd for $C_9H_{10}N_2O_3S$: C, 47.79; H, 4.42; N, 12.39; S, 14.16. Found: C, 47.53; H, 4.43; N, 12.43; S, 14.27. IR (KBr): 1724, 1625 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 239 (4.34), 290 (3.68). ^{1}H-NMR ($CDCl_3$) δ: 6.70 (1H, s, C(6)-H), 4.80 (2H, t, J=7.5 Hz, N–CH_2), 4.38 (2H, q, J=7.2 Hz, $C\underline{H}_2CH_3$), 3.48 (2H, t, J=7.5 Hz, S–CH_2), 1.39 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$). FAB-MS *m/z*: 227 $[(M+1)^+]$.

2,3-Dihydro-5-hydroxymethyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (3c)——A solution of **1** (0.25 g, 2.5 mmol) and ethyl γ-hydroxytetrolate (**2c**) (0.32 g, 2.5 mmol) in MeOH (10 ml) was refluxed for 3 h. The reaction mixture was concentrated to dryness *in vacuo*, and the residue was crystallized from MeOH, giving 0.28 g (62.0%) of colorless needles, mp 267—269 °C. *Anal.* Calcd for $C_7H_8N_2O_2S$: C, 45.65; H, 4.38; N, 15.21; S, 17.40. Found: C, 45.79; H, 4.50; N, 15.14; S, 17.32. IR (KBr): 3210 (OH), 1632 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 232.5 (4.45), *ca.* 268 (sh, 4.00). ^{1}H-NMR (DMSO-d_6–CF_3COOH=1:1): 6.27 (1H, s, C(6)-H), 5.48 (1H, s, OH), 4.78 (2H, dd, J=7.6, 8.3 Hz, N–CH_2), 4.74 (2H, s, O–CH_2), 3.85 (2H, dd, J=7.6, 8.3 Hz, S–CH_2). FAB-MS *m/z*: 185 $[(M+1)^+]$.

5-Carbamoyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (4)——A solution of **3b** (0.1 g, 0.44 mmol) in NH_3–EtOH (saturated, 20 ml) was sealed in a flask with a stopcock and allowed to stand at room temperature overnight. The separated crystalline mass was collected and recrystallized from MeOH, giving 70 mg (61.0%) of colorless needles, mp 289—290 °C. *Anal.* Calcd for $C_7H_7N_3O_2S$: C, 42.63; H, 3.58; N, 21.30; S, 16.26. Found: C, 42.33; H, 3.64; N, 21.08; S, 16.04. IR (KBr): 3440, 3320 (NH_2), 1695 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 236 (4.42), 286 (sh, 3.88). ^{1}H-NMR (DMSO-d_6–CF_3COOH=1:1) δ: 8.41 (1H, br s, NH), 8.00 (1H, br s, NH), 6.77 (1H, s, C(6)-H), 4.87 (2H, t, J=7.9 Hz, N–CH_2), 3.74 (2H, t, J=7.9 Hz, S–CH_2). FAB-MS *m/z*: 198 $[(M+1)^+]$.

5-Acetoxymethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (5)——A mixture of **3c** (1.8 g, 9.8 mmol) and acetic anhydride (30 ml) was refluxed for 3 h. The reaction mixture was concentrated to dryness *in vacuo*, and the residue was crystallized from acetone, giving 2.0 g (90.3%) of colorless needles, mp 137—138 °C. *Anal.* Calcd for $C_9H_{10}N_2O_3S$: C, 47.77; H, 4.46; N, 12.38; S, 14.17. Found: C, 47.84; H, 4.44; N, 12.49; S, 13.88. IR (KBr): 1740, 1630 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 233 (4.38), *ca.* 268 (sh, 3.82). ^{1}H-NMR ($CDCl_3$) δ: 6.00 (1H, s, C(6)-H), 4.58 (2H, s, O–CH_2), 4.38 (2H, dd, J=6.8, 7.9 Hz, N–CH_2), 3.49 (2H, dd, J=6.8, 7.9 Hz, S–CH_2), 2.17 (3H, s, CO–CH_3). FAB-MS *m/z*: 227 $[(M+1)^+]$.

2,3-Dihydro-1-(2-hydroxyethyl)-6-hydroxymethyl-2-thioxo-4(1*H*)-pyrimidinone (7)——A solution of **6**[12] (2.4 g,

13.7 mmol) and ethanolamine (1.6 g, 26.5 mmol) in EtOH (10 ml) was refluxed for 1 h. After cooling, the mixture was acidified with 10% HCl, and left to stand in a refrigerator overnight. After concentration, the separated crystalline mass was collected and recrystallized from EtOH, giving 1.05 g (37.9%) of colorless prisms, mp 199—200 °C. *Anal.* Calcd for $C_7H_{10}N_2O_3S$: C, 41.58; H, 4.98; N, 13.85; S, 15.85. Found: C, 41.45; H, 4.99; N, 13.71; S, 15.78. IR (KBr): 1650 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 221 (4.25), 278 (4.21). ^{1}H-NMR ($CDCl_3$) δ: 12.44 (1H, br s, NH), 5.98 (1H, s, ring), 4.51 (2H, br s, C(6)-CH_2), 4.29 (2H, t, J=5.5 Hz, N–CH_2), 3.74 (2H, q, J=5.5 Hz, S–CH_2).

5-Chloromethyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (8)——A mixture of **7** (0.3 g, 14.9 mmol) and thionyl chloride (4.9 g, 41.2 mmol) with 2 drops of pyridine as a catalyst was stirred at room temperature for 5 h. The reaction mixture was poured onto ice, then neutralized with 5% $NaHCO_3$. The mixture was extracted with $CHCl_3$, and the extract was dried over Na_2SO_4. After evaporation of the solvent, the residue was crystallized from acetone, giving 50 mg (16.7%) of colorless needles, mp 174—175 °C. *Anal.* Calcd for $C_7H_7ClN_2OS$: C, 41.49; H, 3.48; N, 13.82; S, 15.82. Found: C, 41.74; H, 3.68; N, 13.57; S, 15.74. UV $\lambda_{max}^{ethanol}$ nm (log ε): 234 (4.40), *ca.* 270 (sh, 3.85). ^{1}H-NMR ($CDCl_3$) δ: 6.30 (1H, s, C(6)-H), 4.59 (2H, t, J=7.5 Hz, N–CH_2), 3.55 (2H, t, J=7.5 Hz, S–CH_2), 3.06 (2H, s, CH_2–Cl).

7-Bromomethyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (10)——A solution of bromine (6.4 g, 40 mmol) in CCl_4 (15 ml) was added to a solution of diketene (3.36 g, 40 mmol) in CCl_4 (30 ml) under ice cooling with stirring, and the temperature was maintained for 2 h. The reaction mixture was added to a solution of **1** (2.04 g, 20 mmol) in $CHCl_3$ (30 ml) under ice cooling with stirring, and the whole was maintained at the same temperature for 2 h, then at room temperature for 3 h. The separated crystalline mass was collected and recrystallized from MeOH, giving 2.4 g (36.5%) of brown prisms, mp 299—300 °C (HBr salt). These crystals were dissolved in 5% $NaHCO_3$, and the solution was extracted with $CHCl_3$. The extract was dried over $MgSO_4$. After evaporation of the solvent, the residue was crystallized from MeOH, giving 0.9 g (18.2%) of colorless needles, mp 98—99 °C. *Anal.* Calcd for $C_7H_7BrN_2OS$: C, 34.02; H, 2.85; Br, 32.34; N, 11.34; S, 12.97. Found: C, 34.18; H, 2.87; Br, 31.87; N, 11.32; S, 12.97. IR (KBr): 1660 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 233 (3.94), 298 (3.81). ^{1}H-NMR ($CDCl_3$) δ: 6.25 (1H, s, C(6)-H), 4.47 (2H, t, J=7.5 Hz, N–CH_2), 4.14 (2H, s, CH_2–Br), 3.47 (2H, t, J=7.5 Hz, S–CH_2). MS *m/z*: 248 and 246 (M^+).

Hydrogenolysis of 10——A mixture of **10** (60 mg, 0.24 mmol) and 5% Pd–C (50 mg) in EtOH (20 ml) was stirred under a hydrogen atmosphere at room temperature for 8 h. The reaction mixture was filtered, and the filtrate was concentrated to dryness *in vacuo*. The residue was treated with 5% $NaHCO_3$, then extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and filtered. The filtrate was evaporated to dryness and the residue was crystallized from AcOEt, giving **11**, 40 mg (99.2%) of colorless needles, mp 126—127 °C (lit.[1b] mp 127—128 °C).

6-Bromo-7-bromomethyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-5-one (12)——A solution of **10** (247 mg, 1.00 mmol) and *N*-bromosuccinimide (200 mg, 1.12 mmol) in EtOH (20 ml) was refluxed for 9 h. The reaction mixture was concentrated to dryness *in vacuo*, and the residue was crystallized from MeOH, giving 200 mg (61.3%) as colorless needles, mp 166—167 °C. *Anal.* Calcd for $C_7H_6Br_2N_2OS$: C, 25.79; H, 1.86; N, 8.59; Br, 49.02. Found: C, 25.96; H, 2.00; N, 8.57; Br, 48.57. IR (KBr): 1661 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 245 (3.94), 317 (3.94). ^{1}H-NMR ($CDCl_3$) δ: 4.52 (2H, t, J=7.9 Hz, N–CH_2), 4.39 (2H, s, CH_2–Br), 3.52 (2H, t, J=7.9 Hz, S–CH_2). MS *m/z*: 328, 326, and 324 (M^+).

6-Bromo-2,3-dihydro-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (13)——a) A solution of **11** (168 mg, 1.00 mmol) and *N*-bromosuccinimide (200 mg, 1.12 mmol) in EtOH (20 ml) was refluxed for 4.5 h. The reaction mixture was ice-cooled and the separated crystalline mass was collected, then crystallized from MeOH, giving 100 mg (40.0%) of colorless prisms, mp 209—210 °C. *Anal.* Calcd for $C_7H_7BrN_2OS$: C, 34.02; H, 2.86; Br, 32.34; N, 11.34; S, 12.97. Found: C, 33.90; H, 2.93; Br, 32.34; N, 11.26; S, 13.06. IR (KBr): 1662 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 250 (3.78), 304 (3.99). ^{1}H-NMR ($CDCl_3$) δ: 4.51 (2H, t, J=7.5 Hz, N–CH_2), 3.50 (2H, t, J=7.5 Hz, S–CH_2), 2.43 (3H, s, CH_3). MS *m/z*: 248 and 246 (M^+).

b) A solution of bromine (0.3 ml) in acetic acid (1 ml) was added to a solution of **11** (340 mg, 2.02 mmol) in acetic acid (7 ml) with stirring; a reddish brown crystalline mass immediately separated. The mixture was heated at 90—95 °C for 2 h. After cooling, the separated crystalline mass was collected and recrystallized from MeOH, giving 340 mg (68.1%) of colorless prisms, mp 209—210 °C.

2,3-Dihydro-7-morpholinomethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (14)——A solution of **10** (1.0 g, 4.0 mmol) and morpholine (0.7 g, 8.0 mmol) in EtOH (80 ml) was refluxed for 6 h. The reaction mixture was concentrated to dryness *in vacuo*. The residue was crystallized from MeOH, giving 0.9 g (87.9%) of colorless plates, mp 163—164 °C. *Anal.* Calcd for $C_{11}H_{15}N_3O_2S$: C, 52.15; H, 5.97; N, 16.59; S, 12.66. Found: C, 51.94; H, 6.00; N, 16.55; S, 12.72. IR (KBr): 1675, 1653 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 230 (3.89), 292 (3.85). ^{1}H-NMR ($CDCl_3$) δ: 6.29 (1H, s, C(6)-H), 4.47 (2H, t, J=7.9 Hz, N–CH_2), 3.74 (4H, m, 2×O–CH_2), 3.46 (2H, t, J=7.9 Hz, S–CH_2), 3.33 (2H, s, C(7)-CH_2), 2.52 (4H, m, 2×N–CH_2). MS *m/z*: 253 (M^+).

6-Bromo-2,3-dihydro-7-morpholinomethyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (15)——A solution of **12** (652 mg, 2.0 mmol) and morpholine (348 mg, 4.0 mmol) in EtOH (60 ml) was refluxed for 3 h. The reaction mixture was concentrated, and the separated crystalline mass was collected and recrystallized from MeOH–AcOEt, giving 300 mg (45.2%) of colorless needles, mp 141—142 °C. *Anal.* Calcd for $C_{11}H_{14}BrN_3O_2S$: C, 39.77; H, 4.25; N, 12.65. Found: C, 39.85; H, 4.07; N, 12.53. IR (KBr): 1661 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 242 (3.84), 308 (3.94). ^{1}H-NMR

($CDCl_3$) δ: 4.52 (2H, t, J=7.8 Hz, N–CH_2), 3.74 (4H, m, 2×O–CH_2), 3.61 (2H, s, C(7)-CH_2), 3.49 (2H, t, J=7.8 Hz, S–CH_2), 2.60 (4H, m, 2×N–CH_2). MS m/z: 333 and 331 (M^+).

5-Hydroxy-2,3,5,6-tetrahydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (16a)——A solution of **3a** (1.0 g, 6.49 mmol) in 5% HCl (20 ml) was heated at 95—100 °C for 9 h. The reaction mixture was concentrated to dryness *in vacuo*. Water was added to the residue, and the mixture was evaporated to dryness *in vacuo*. The crystalline residue was recrystallized from H_2O, giving 720 mg (64.5%) of colorless prisms, mp 211—213 °C. *Anal.* Calcd for $C_6H_8N_2O_2S$: C, 41.85; H, 4.68; N, 16.27; S, 18.62. Found: C, 41.86; H, 4.48; N, 16.16; S, 18.81. IR (KBr): 3400, 3170 (OH), 1700 (br) (C=O) cm^{-1}. UV: no absorption maximum. ^{1}H-NMR (270 MHz: $CDCl_3$ and 3 drops of CF_3COOH) δ: 9.23 (1H, s, OH), 5.02 (1H, dd, J=4.4, 12.6 Hz, C(5)-H), 4.16 (1H, dt, J=6.6, 6.6, 11.5 Hz, N–CH), 3.85 (1H, quintet, J=5.5, 5.5, 11.5 Hz, N–CH), 3.3—3.15 (2H, m, S–CH_2), 3.14 (1H, dd, J=4.4, 17.0 Hz, C(6)-H), 2.92 (1H, dd, J=12.6, 17.0 Hz, C(6)-H). ^{13}C-NMR (pyridine-d_5) δ: 169.29 (s, C(7 or 1a)), 151.33 (s, C(1a or 7)), 57.43 (d, C(5)), 48.82 (t, C(3)), 38.44 (t, C(2)), 29.28 (t, C(6)). FAB-MS m/z: 173 [$(M+1)^+$].

5-Carboxy-2,3,5,6-tetrahydro-5-hydroxy-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (16b)——A solution of **3b** (0.56 g, 2.48 mmol) in 5% HCl (6 ml) was heated at 90—95 °C for 8 h. The reaction mixture was worked up as described above, giving 0.4 g (74.7%, H_2O), of colorless powder, mp 236 °C (bub.). *Anal.* Calcd for $C_7H_8N_2O_4S$: C, 38.88; H, 3.73; N, 12.96; S, 14.83. Found: C, 38.18; H, 3.66; N, 12.98; S, 14.88. IR (KBr): 3245 (OH), 1738, 1720 (sh), 1659 (C=O) cm^{-1}. UV: no absorption maximum. ^{1}H-NMR (270 MHz: $CDCl_3$ and 3 drops of CF_3COOH) δ: 9.48 (1H, s, OH), 4.32 (1H, dt, J=6.9, 6.9, 11.5 Hz, N–CH), 4.13 (1H, ddd, J=5.0, 6.9, 11.5 Hz, N–CH), 3.70 (1H, d, J=17.0 Hz, C(6)-H), 3.5—3.3 (2H, m, S–CH_2), 3.18 (1H, d, J=17.0 Hz, C(6)-H). ^{13}C-NMR (DMSO-d_6) δ: 171.43 (s, COOH), 167.47 (s, C(7 or 1a)), 149.43 (s, C(1a or 7)), 67.08 (s, C(5)), 48.93 (t, C(3)), 40.80 (t, C(2)), 28.77 (t, C(6)). FAB-MS m/z: 217 [$(M+1)^+$].

5-Hydroxy-5-hydroxymethyl-2,3,5,6-tetrahydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (16c)——A solution of **3c** (300 mg, 1.63 mmol) in 5% HCl (8 ml) was heated at 95—100 °C for 6 h. The reaction mixture was worked up as described above, giving 190 mg (57.7%, H_2O) of colorless prisms, mp 210—212 °C. *Anal.* Calcd for $C_7H_{10}N_2O_3S$: C, 41.58; H, 4.98; N, 13.85. Found: C, 41.50; H, 4.85; N, 13.71. IR (KBr): 3395, 3190 (OH), 1710 (sh), 1695 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 262 (sh, 3.45). ^{1}H-NMR (270 MHz: $CDCl_3$ and 3 drops of CF_3COOH) δ: 9.32 (1H, s, OH), 4.44 (1H, ddd, J=5.0, 7.0, 12.1 Hz, N–CH), 3.96 (1H, d, J=12.6 Hz, C(6)-H), 3.80 (1H, dt, J=6.6, 7.0, 12.1 Hz, N–CH), 3.78 (1H, d, J=12.6 Hz, C(6)-H), 3.3—3.15 (2H, m, S–CH_2), 3.23 (2H, s, O–CH_2). ^{13}C-NMR (pyridine-d_5) δ: 169.4 (s, C(7)), 151.5 (s, C(1a)), 71.5 (s, C(5)), 69.0 (t, CH_2OH), 48.4 (t, C(3)), 41.8 (t, C(2)). FAB-MS m/z: 203 [$(M+1)^+$].

1-(2-Mercaptoethyl)-6-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (18)——A solution of **17** (0.5 g, 2.17 mmol) in 5% HCl (10 ml) was refluxed for 4 h. The reaction mixture was worked up as described above, giving 0.30 g (55.8%, AcOEt) of colorless needles, mp 164—165 °C. *Anal.* Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.35; H, 4.97; N, 11.06. IR (KBr): 2530 (SH), 1702 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 275 (4.05). ^{1}H-NMR ($CDCl_3$) δ: 9.4 (1H, br s, NH), 7.6—7.2 (5H, m, C_6H_5), 5.63 (1H, s, ring), 3.83 (2H, dd, J=7.25, 5.27 Hz, N–CH_2), 2.63 (2H, m, S–CH_2), 1.19 (1H, t, J=8.8 Hz, SH).

3-(2-Mercaptoethyl)-6-methyl-2,4(1*H*,3*H*)-pyrimidinedione (19)——A solution of **11** (1.0 g, 5.95 mmol) in 5% HCl (20 ml) was refluxed for 2 h. The reaction mixture was worked up as described above, giving 0.65 g (58.1%, H_2O) of colorless prisms, mp 203 °C. *Anal.* Calcd for $C_7H_{10}N_2O_2S \cdot 1/10H_2O$: C, 44.71; H, 5.47; N, 14.90. Found: C, 44.76; H, 5.30; N, 14.67. IR (KBr): 2555 (SH), 1725, 1705, 1642 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 264 (4.08). FAB-MS m/z: 187 [$(M+1)^+$]. ^{1}H-NMR ($CDCl_3$ and 5 drops of CF_3COOH) δ: 10.37 (1H, br s, NH), 5.91 (1H, q, J=0.88 Hz, ring), 4.14 (2H, dd, J=7.03, 5.71 Hz, N–CH_2), 2.80 (2H, m, S–CH_2), 2.26 (3H, d, J=0.88 Hz, CCH_3), 1.41 (1H, t, J=8.7 Hz, CH_2S<u>H</u>). ^{13}C-NMR (DMSO-d_6) δ: 162.43 (C(4)), 151.27 (C(2 or 6)), 151.16 (C(6 or 2)), 98.18 (C(5)), 41.77 (CH_2N), 21.02 (CH_2SH), 17.93 (CH_3).

3,3′-Bis[6-methyl-1,2,3,4-tetrahydro-2,4-dioxopyrimidinyl]diethyldisulfide (20)——A solution of **11** (336 mg, 2.00 mmol) in 5% HCl (30 ml) was heated at 95—100 °C for 7 h. The reaction mixture was concentrated to dryness *in vacuo*. Water was added to the residue, and the mixture was evaporated to dryness *in vacuo*. The residue was treated with 5% $NaHCO_3$, and the insoluble crystalline mass was collected and recrystallized from MeOH, giving 100 mg (26.6%) of colorless powder, mp 283—285 °C. *Anal.* Calcd for $C_{14}H_{18}N_4O_4S_2 \cdot 0.3H_2O$: C, 44.74; H, 4.99; N, 14.91. Found: C, 44.69; H, 4.95; N, 14.50. IR (KBr): 3550, 3430 (NH), 1730, 1707 (sh), 1645 (C=O) cm^{-1}. UV $\lambda_{max}^{ethanol}$ nm (log ε): 263 (4.36). FAB-MS m/z: 371 [$(M+1)^+$]. ^{1}H-NMR ($CDCl_3$ and 3 drops of CF_3COOH) δ: 5.92 (2H, s, 2× ring), 4.33 (4H, dd, J=7.91, 6.59 Hz, 2×N–CH_2), 2.97 (4H, dd, J=7.91, 6.59 Hz, 2×S–CH_2), 2.28 (6H, s, 2×CH_3).

Acknowledgement The authors are grateful to Mr. Y. Kinoshita, Kissei Pharmaceutical Industry, for measuring the ^{1}H-NMR (270 MHz) spectra. Thanks are also due to Mrs. H. Mazume, Mr. M. Ohwatari, Mr. K. Inada, and Mr. N. Yamaguchi for elemental analysis, IR, UV, NMR, and mass spectra.

References

1) *a*) N. G. Pashkurov and V. S. Reznik, *Khim. Geterotsikl. Soedin*, **1968**, 918 [*Chem. Abstr.*, **71**, 13088 (1969)]; *b*)

G. R. Brown and W. R. Dyson, *J. Chem. Soc. C*, **1971**, 1527.
2) *a*) E. Campaigne, J. C. Huffman, and T. P. Selby, *J. Heterocycl. Chem.*, **16**, 725 (1979); *b*) E. Campaigne, K. Folting, J. C. Huffman, and T. P. Selby, *ibid.*, **18**, 575 (1981).
3) M. Szajda and E. Wyrzykiewicz, *Pol. J. Chem.*, **57**, 1027 (1983).
4) G. Shaw and R. N. Warrener, *J. Chem. Soc.*, **1959**, 50.
5) *a*) S. Giambrone, *Bull. Sci. Fac. Chim. Ind. Bologna*, **11**, 86 (1953) [*Chem. Abstr.*, **49**, 4662 (1955)]; *b*) V. Škarić, D. Škarić, and A. Čižmek, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 2221; *c*) M. Mizutani, Y. Sanemitsu, Y. Tamura, and Z. Yoshida, *J. Org. Chem.*, **50**, 764 (1985).
6) T. Kato, N. Katagiri, U. Izumi, Y. Miura, T. Yamazaki, and Y. Hirai, *Heterocycles*, **15**, 399 (1981).
7) *a*) M. Seperic, Ger Offen. 2140601 [*Chem. Abstr.*, **77**, 5516 (1972)]; *b*) J. Baetz, Brit. Patent 1334628 [*Chem. Abstr.*, **80**, 48028 (1974)]; *c*) SEPERIC, Fr. Demande, 2173668 [*Chem. Abstr.*, **80**, 96015 (1974)]; *d*) SEPERIC, Neth. Appl. 7600885 [*Chem. Abstr.*, **87**, 85046 (1977)]; *e*) SEPERIC, Bel. 778911 [*Chem. Abstr.*, **80**, 48028 (1974)].
8) K. D. Kampe, *Angew. Chem.*, **94**, 543 (1982).
9) H. N. Al-Jallo and M. A. Muniem, *J. Heterocycl. Chem.*, **15**, 849 (1978).
10) R. A. Glennon, R. G. Bass, and E. Schubert, *J. Heterocycl. Chem.*, **16**, 903 (1979).
11) *a*) N. Okamura, T. Toru, T. Tanaka, K. Watanabe, K. Bannai, S. Kurozumi, T. Naruchi, and K. Kamoriya, Eur. Pat. Appl., EP 49902 [*Chem. Abstr.*, **97**, 92311 (1982)]; *b*) Teijin Ltd., Jpn. Kokai Tokkyo Koho JP 83 24590 [*Chem. Abstr.*, **98**, 215611 (1983)]; *c*) Teijin Ltd., Jpn. Kokai Tokkyo Koho JP 84 88491 [*Chem. Abstr.*, **101**, 230562 (1984)].
12) R. N. Warrener and E. N. Cain, *Aust. J. Chem.*, **24**, 785 (1971).
13) D. W. Dunwell and D. Evans, *J. Chem. Soc. C*, **1971**, 2094.
14) K. Tabei, E. Kawashima, T. Takeda, and T. Kato, *Chem. Pharm. Bull.*, **30**, 3987 (1982).
15) K. Hirota, Y. Yamada, Y. Kitade, and S. Senda, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2943.
16) E. Falch and T. Natvig, *Acta Chem. Scand.*, **24**, 1423 (1970).
17) T. Kinoshita, H. Tanaka, and S. Furukawa, *Chem. Pharm. Bull.*, **34**, 1809 (1986).