A Novel Heterocyclic Compound. Synthesis and Reactivities of an Oxazolo[3,2-*a*]thieno[3,2-*d*]-pyrimidine Derivative

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A practical preparation of 2,3-dihydro-5*H*-oxazolo[3,2-*a*]thieno[3,2-*d*]pyrimidin-5-one (2) from methyl 3-aminothiophene-2-carboxylate in two steps was developed. The addition reactions of various nucleophiles to 2 were investigated and oxazole-ring-opened compounds were produced (5, 6, 12, 13 and 14). Desulfurization reaction of 2 with Raney Ni gave an oxazolo[3,2-*a*]pyrimidine derivative (15). It was found that 2 showed potent anti-gastric secretion activity.

Keywords oxazolothienopyrimidine; 2-chloroethyl isocyanate; oxazole-ring opening; oxazolopyrimidine; anti-gastric secretion activity

A number of compounds possessing a quinazoline ring as a biologically active skeleton are in clinical use, *e.g.* methaqualone as a hypnotic, prazosin as an antihypertensive and others.[1] Certain tricyclic quinazoline derivatives of type **1**, which have a five-membered heterocyclic ring fused to the 2,3-positions of the quinazoline, were reported to exhibit significant hypoglycemic (**1a**)[2a] and antihypotensive (**1b**) activities.[2b,c] The isosteric properties of benzene and thiophene are, in general, of interest to medicinal chemists. As an extension of our continuing interest in thienopyrimedine medicinal chemistry,[3] we wish to describe the synthesis of 2,3-dihydro-5*H*-oxazolo[3,2-*a*]-thieno[3,2-*d*]pyrimidin-5-one (**2**), a hitherto-unknown heterocyclic ring system, and its reactivities with various nucleophilic reagents.

1a : X=Ph,H, Y=NH
1b : X=Y=O

Chart 1

The synthesis of **2** is shown in Chart 2. Reaction of methyl 3-aminothiophene-2-carboxylate (**3**) with ethyl chloroformate ($ClCO_2Et$) followed by pyrimidine ring formation with ethanolamine gave 3-(2-hydroxyethyl)-thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**5**) in excellent yield. The treatment of **5** with thionyl chloride ($SOCl_2$) afforded 3-(2-chloroethyl)thieno[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**6**), which cyclized to yield the desired tricyclic compound **2** on treatment with triethylamine (Et_3N). The structure of **2** was proposed to be 2,3-dihydro-5*H*-oxazolo[3,2-*a*]thieno[3,2-*d*]pyrimidin-5-one on the basis of its proton nuclear magnetic resonance (NMR) spectrum, which shows the signals of the C-3 protons at δ 4.15—4.33 ppm and the C-2 protons at δ 4.67—4.87 ppm, both as triplet-like multiplets (A_2B_2-type). Nevertheless, cyclization of **6** could, in principle, proceed differently to form an isomer of **2**, such as **10**. The structure of **2** was, therefore, determined by comparison with that of the sample prepared through the following reactions (Chart 2). Methyl 3-isothiocyanatothiophene-2-carboxylate (**7**)[4] was treated with ethanolamine at room temperature in tetrahydrofuran (THF) to give 3-(2-hydroxyethyl)-2-mercaptothieno[3,2-*d*]pyrimidin-4(3*H*)-one (**8**) in 83% yield. Reaction of **8** with methyl iodide (MeI) in *N*,*N*-dimethylformamide (DMF) gave the 2-methylthio analogue **9**, and cyclization reaction by oxidative elimination of the methylthio group on **9** with *m*-chloroperbenzoic acid (MCPBA) afforded the corresponding tricyclic compound, which was identical with a compound obtained from **6**. This result excluded the pos-

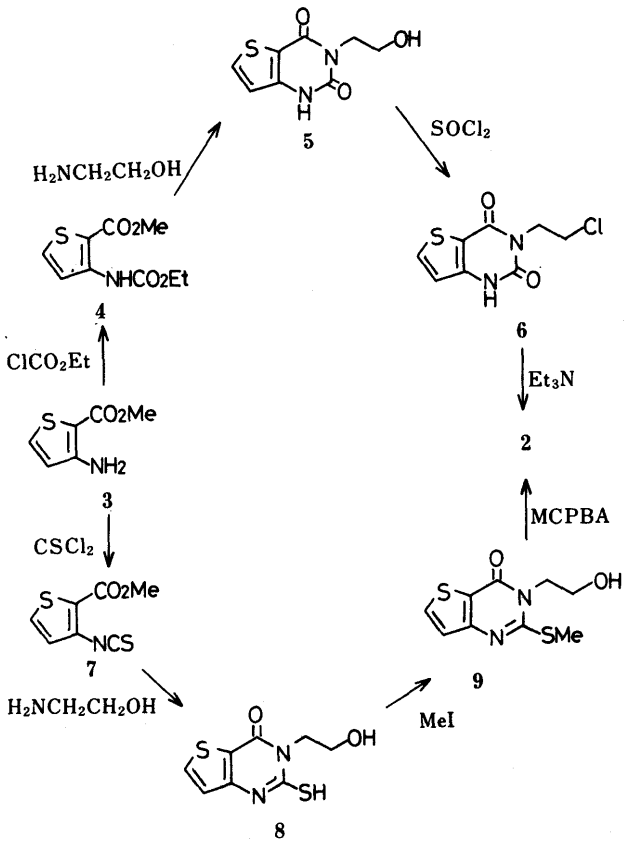
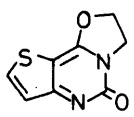


Chart 2



10

Chart 3

sibility of formation of the isomer **10**.

A convenient alternative synthetic method for **2** was examined. Refluxing of **3** with 2-chloroethyl isocyanate in ethyl acetate (AcOEt) gave methyl 3-[*N'*-(2-chloroethyl)-ureido]thiophene-2-carboxylate (**11**) in 87% yield, as shown in Chart 4. Cyclization of **11** with an equimolar amount of sodium hydroxide (NaOH) in water–dioxane was readily achieved in one pot to give **2** in 75% yield. This procedure may provide a simple and practical method for the synthesis of 2,3-dihydro-5*H*-oxazolo[3,2-*a*]thieno[3,2-*d*]pyrimidin-5-one (**2**).

The ready availability of **2** prompted us to investigate its reactivities. It was found to be readily susceptible to oxazole-ring opening by nucleophilic attack at the C-2 position, when **2** was reacted with acids, bases or amines. The oxidation of **2** with MCPBA gave only resinous material; no oxidized product was isolated. An attempted desulfurization reaction of **2** with Raney Ni W-2 in dioxane–methanol (MeOH) gave 2,3-dihydro-7-ethyl-5*H*-oxazolo[3,2-*a*]pyrimidin-5-one (**15**), whose structure was confirmed by the NMR spectrum to contain an ethyl group (δ 1.20 ppm, 3H, and δ 2.48 ppm, 2H). Lithiation of **2** with *n*-butyl lithium (*n*-BuLi) followed by methylation (or protonation) afforded **16a** (**16b**) (Chart 5). The structure of **16a** is based on the following data; its NMR spectrum revealed the presence of a vinyl group (H_a: δ 5.21 ppm, d, J=9.6 Hz,

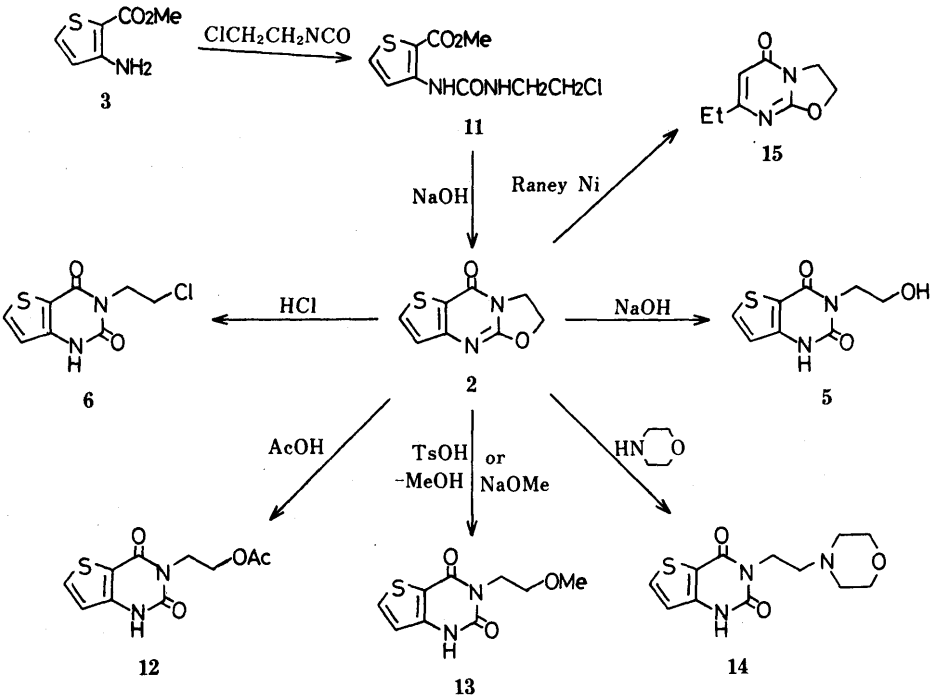


Chart 4

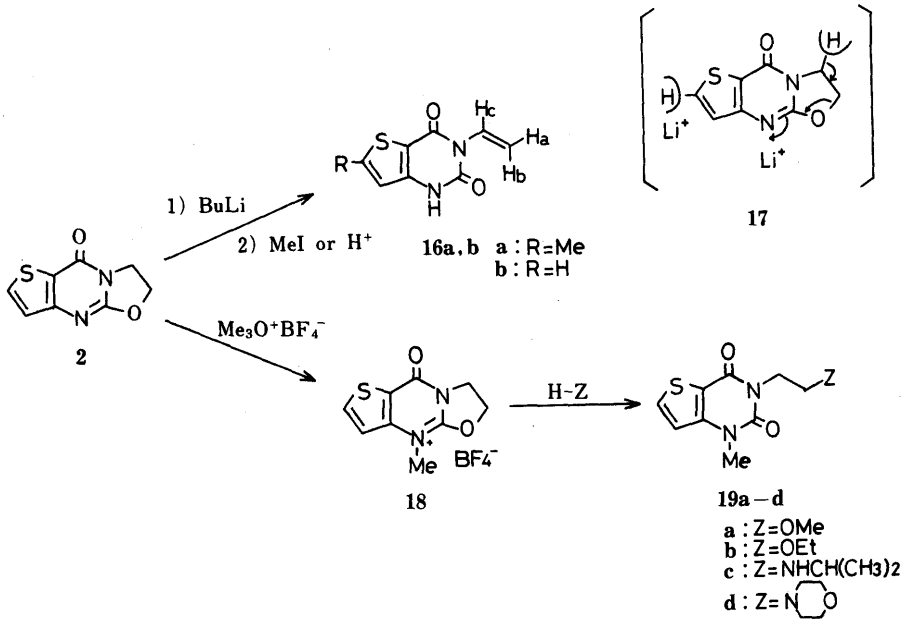


Chart 5

H_b: δ 5.92 ppm, d, J = 16.2 Hz, and H_c: δ 6.95 ppm, dd, J = 16.2, 9.6 Hz). It seemed that the reaction might proceed *via* **17**. Further, the treatment of **2** with trimethyloxonium tetrafluoroborate ($Me_3O^+BF_4^-$) in methylene chloride (CH_2Cl_2) produced the desired quaternary salt **18** in quantitative yield. Reactions of **18** with alcohols or amines proceeded smoothly, and the corresponding ring-opened products **19a—d** were obtained in satisfactory yield.

The oxazolothienopyrimidine derivative **2** did not exhibit antihypotensive activity, in contrast to that of **1b**. On the other hand, **2** possessed significant anti-gastric secretion activity. Further studies of the synthesis and structure–activity relationships of various oxazolothienopyrimidines will be reported elsewhere.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured on a JASCO A-102 spectrometer. NMR spectra were recorded with a Varian T-60A (60 MHz) or EM-390 (90 MHz) spectrometer and the chemical shifts are expressed in ppm from tetramethylsilane as internal standard; s, singlet; d, doublet; t, triplet; q, quartet; sep, septet; dd, doublet of doublets; m, multiplet; br, broad. Mass spectra (MS) were obtained with a JEOL JMS-01SG or JMS-G300 mass spectrometer. Merck silica gel (Kieselgel 60 Art. 7734) was employed for column chromatography.

Methyl 3-Ethoxycarbonylaminothiophene-2-carboxylate (4) A solution of methyl 3-aminothiophene-2-carboxylate (**3**) (40.0 g) and ethyl chloroformate (34.8 ml) in toluene (200 ml) was refluxed for 2 h. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel with AcOEt–hexane (1 : 1) as an eluent to give **4** (53.7 g 92%), which was recrystallized from AcOEt–hexane to give an analytical sample as colorless needles. mp 63—66 °C. *Anal.* Calcd for $C_9H_{11}NO_4S$: C, 47.15; H, 4.84; N, 6.11; S, 13.98. Found: C, 47.23; H, 4.88; N, 5.96; S, 14.28. IR (KBr): 1730, 1675 cm^{-1}. NMR ($CDCl_3$) δ: 1.30 (3H, t, J = 7.0 Hz, OCH_2CH_3), 3.86 (3H, s, OCH_3), 4.22 (2H, q, J = 7.0 Hz, OCH_2CH_3), 7.44 and 7.90 (each 1H, d, J = 5.4 Hz, ArH), 9.2—9.8 (1H, br, NH). MS *m/z*: 229 (M^+), 125.

3-(2-Hydroxyethyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (5) A mixture of **4** (30.0 g) and ethanolamine (50 ml) was stirred at 145—155 °C for 1 h and cooled. iso-PrOH (*ca.* 100 ml) was added to the mixture and the resulting crystalline solid was collected by filtration. Recrystallization from DMF–MeOH afforded **5** (25.5 g, 94%) as colorless needles. mp 261—262 °C (dec.). *Anal.* Calcd for $C_8H_8N_2O_3S$: C, 45.28; H, 3.80; N, 13.20; S, 15.11. Found: C, 44.98; H, 3.90; N, 13.19; S, 15.00. IR (KBr): 1675, 1640 (sh), 1630 cm^{-1}. NMR (DMSO-d_6) δ: 3.55 (2H, t, J = 6.9 Hz, NCH_2CH_2O), 3.98 (2H, t, J = 6.9 Hz, NCH_2CH_2O), 6.93 and 8.05 (each 1H, d, J = 5.1 Hz, ArH). MS *m/z*: 213 (M^+), 152.

3-(2-Chloroethyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (6) A suspension of **5** (485 mg) in $CHCl_3$ (5 ml) was treated with $SOCl_2$ (0.5 ml) and the whole was refluxed for 2 h. After cooling, the precipitate was collected and washed with water and $CHCl_3$. Recrystallization from AcOEt gave **6** in 88% yield (462 mg) as colorless needles. mp 214—217 °C (dec.). *Anal.* Calcd for $C_8H_7ClN_2O_2S$: C, 41.66; H, 3.06; Cl, 15.37; N, 12.14; S, 13.90. Found: C, 41.75; H, 3.19; Cl, 15.33; N, 12.42; S, 13.90. IR (KBr): 1710, 1655 cm^{-1}. NMR (DMSO-d_6) δ: 3.79 (2H, t, J = 6.9 Hz, NCH_2CH_2Cl), 4.21 (2H, t, J = 6.9 Hz, NCH_2CH_2Cl), 6.95 and 8.04 (each 1H, d, J = 5.4 Hz, ArH), 11.00 (1H, br s, NH). MS *m/z*: 230 (M^+), 152.

2,3-Dihydro-5*H*-oxazolo[3,2-*a*]thieno[3,2-*d*]pyrimidin-5-one (2) (a) Et_3N (6 ml) was added to a stirred suspension of **6** (3.00 g) in EtOH (30 ml) and the whole was refluxed for 1.5 h. After evaporation of the solvent, water was added to the residue and the resulting mixture was extracted with $CHCl_3$. The residue obtained from the $CHCl_3$ extracts was recrystallized from $CHCl_3$–AcOEt to afford **2** (1.81 g, 72%) as colorless prisms. mp 183—185 °C (dec.). *Anal.* Calcd for $C_8H_6N_2O_2S$: C, 49.48; H, 3.11; N, 14.42; S, 16.51. Found: C, 49.69; H, 3.11; N, 14.27; S, 16.12. IR (KBr): 1690, 1610, 1605 cm^{-1}. NMR (DMSO-d_6) δ: 4.15—4.33 (2H, m, NCH_2CH_2O), 4.67—4.87 (2H, m, NCH_2CH_2O), 7.20 and 8.11 (each 1H, d, J = 5.4 Hz, ArH). MS *m/z*: 194 (M^+), 152.

(b) MCPBA (85% pure) (280 mg) was added to a solution of **9** (311 mg) in $CHCl_3$ (10 ml) and the reaction mixture was stirred at room temperature for 4 h, then poured into water. The precipitate was filtered off and the filtrate was extracted with $CHCl_3$. The residue obtained from the $CHCl_3$ extracts was chromatographed on silica gel and eluted with AcOEt to give **2** (72 mg, 30%). mp 184—185 °C (dec.). This sample was identical with the specimen prepared by method (a).

(c) An NaOH solution [prepared from NaOH (584 mg) in water (20 ml)] was added dropwise to a stirred mixture of **11** (3.58 g), dioxane (12 ml) and water (40 ml) under reflux. Then the whole was stirred for 20 min at the same temperature. After cooling, the precipitate was collected and washed with water and $CHCl_3$. The filtrate was extracted with $CHCl_3$. The residue obtained from the $CHCl_3$ extracts was combined with the crude crystals and recrystallized from $CHCl_3$–AcOEt to give **2** (2.00 g, 75%).

3-(2-Hydroxyethyl)-2-mercaptothieno[3,2-*d*]pyrimidin-4(3*H*)-one (8) A solution of methyl 3-isothiocyanatothiophene-2-carboxylate (**7**)[4] (9.00 g) in THF (20 ml) was added to a stirred solution of ethanolamine (4 ml) in THF (150 ml) at room temperature. The mixture was stirred for 1.5 h, then the resulting precipitate was collected, washed with THF, and recrystallized from DMF–acetone to give **8** (8.57 g, 83%) as colorless prisms. mp 255—257 °C. *Anal.* Calcd for $C_8H_8N_2O_2S_2$: C, 42.09; H, 3.53; N, 12.27; S, 28.09. Found: C, 42.31; H, 3.70; N, 12.38; S, 28.29. IR (KBr): 1650 cm^{-1}. NMR (DMSO-d_6) δ: 3.67 (2H, t, J = 6.8 Hz, NCH_2CH_2O), 4.53 (2H, t, J = 6.8 Hz, NCH_2CH_2O), 7.04 and 8.15 (each 1H, d, J = 5.3 Hz, ArH). MS *m/z*: 228 (M^+), 185.

3-(2-Hydroxyethyl)-2-methylthiothieno[3,2-*d*]pyrimidine-4(3*H*)-one (9) A mixture of **8** (3.00 g) and MeI (9.82 g) in DMF (45 ml) was stirred at room temperature for 23 h. The crystalline residue obtained by evaporation of the solvent was collected, washed with water, and recrystallized from MeOH to afford **9** (2.19 g, 69%) as colorless needles. mp 166—167 °C. *Anal.* Calcd for $C_9H_{10}N_2O_2S_2$: C, 44.61; H, 4.16; N, 11.56; S, 26.46. Found: C, 44.54; H, 4.26; N, 11.65; S, 26.29. IR (KBr): 1655 cm^{-1}. NMR (DMSO-d_6) δ: 2.60 (3H, s, SCH_3), 3.67 (2H, q, J = 6.0 Hz, NCH_2CH_2O), 4.17 (2H, t, J = 6.6 Hz, NCH_2CH_2O), 4.98 (1H, t, J = 6.0 Hz, OH), 7.29 and 8.12 (each 1H, d, J = 5.5 Hz, ArH). MS *m/z*: 242 (M^+), 198.

Methyl 3-[*N'*-(2-Chloroethyl)ureido]thiophene-2-carboxylate (11) A mixture of **3** (10.00 g) and 2-chloroethyl isocyanate (6.55 ml) in AcOEt (70 ml) was refluxed for 7 h, and then cooled. The crystalline residue obtained by evaporation of the solvent was recrystallized from AcOEt to give **11** (14.57 g, 87%) as colorless needles. mp 147—150 °C. *Anal.* Calcd for $C_9H_{11}ClN_2O_3S$: C, 41.15; H, 4.22; Cl, 13.50; N, 10.66; S, 12.20. Found: C, 41.04; H, 4.05; Cl, 13.52; N, 10.53; S, 12.47. IR (KBr): 1685, 1645 cm^{-1}. NMR (DMSO-d_6) δ: 3.44—3.70 (4H, m, NCH_2CH_2Cl), 3.85 (3H, s, OCH_3), 7.46 and 8.04 (each 1H, d, J = 5.6 Hz, ArH), 7.6—8.1 and 9.4—9.6 (each 1H, br, NH × 2). MS *m/z*: 262 (M^+), 157.

Reaction of 2 with Hydrochloric Acid A mixture of **2** (307 mg) and concentrated HCl (3 ml) was stirred at 100 °C for 15 min, and cooled. The precipitate was collected by filtration, washed with water, and dried. Compound **6** was obtained in 95% yield (347 mg). mp 217—219 °C (dec.). The sample was identical with an authentic specimen.

Reaction of 2 with AcOH A mixture of **2** (408 mg) and AcOH (8 ml) was refluxed for 4 h, and concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The crystalline residue obtained from the $CHCl_3$ extracts was recrystallized from MeOH–AcOEt to give 3-(2-acetoxyethyl)thieno[3,2-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (**12**) (397 mg, 74%) as colorless prisms. mp 173—175 °C. *Anal.* Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.96; N, 11.02; S, 12.61. Found: C, 47.16; H, 3.83; N, 10.95; S, 12.70. IR (KBr): 1730, 1720, 1640, 1630 cm^{-1}. NMR (DMSO-d_6) δ: 1.96 (3H, s, $COCH_3$), 4.03—4.42 (4H, m, NCH_2CH_2O), 6.95 and 8.08 (each 1H, d, J = 4.8 Hz, ArH), 10.5—13.2 (1H, br, NH). MS *m/z*: 254 (M^+), 169.

Reaction of 2 with *p*-Toluenesulfonic Acid (TsOH) A mixture of **2** (299 mg) and TsOH (32 mg) in MeOH (5 ml) was refluxed for 1.5 h, and the solvent was evaporated off *in vacuo*. The residue was dissolved in $CHCl_3$, washed with water, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel and eluted with CH_2Cl_2–AcOEt (1 : 2). Recrystallization from MeOH–AcOEt gave 3-(2-methoxyethyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**13**) (242 mg, 70%) as colorless needles. mp 167—169 °C. *Anal.* Calcd for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.46; N, 12.38; S, 14.17. Found: C, 47.52; H, 4.55; N, 12.14; S, 13.99. IR (KBr): 1705, 1650 cm^{-1}. NMR ($CDCl_3$) δ: 3.37 (3H, s, OCH_3), 3.71 (2H, t, J = 6.0 Hz, NCH_2CH_2O), 4.30 (2H, t, J = 6.0 Hz, NCH_2CH_2O), 6.93 and 7.69 (each 1H, d, J = 5.7 Hz, ArH), 10.8—11.7 (1H, br, NH). MS *m/z*: 226 (M^+), 152.

Reaction of 2 with NaOMe Compound **2** (304 mg) was added to a solution of NaOMe (257 mg) in MeOH (6 ml) at room temperature, and the whole was refluxed for 1.5 h. The residue obtained by evaporation of the solvent was dissolved in water. The solution was washed with $CHCl_3$, then the aqueous layer was acidified with 10% HCl solution and extracted with $CHCl_3$. The extracts were dried over $MgSO_4$ and concentrated, and

the residue was recrystallized from CH_2Cl_2–AcOEt to give **13** (247 mg, 70%).

Reaction of 2 with NaOH A mixture of **2** (502 mg) and aqueous 10% NaOH solution (3 ml) in EtOH (10 ml) was refluxed for 1 h. The residue obtained by evaporation of the solvent was dissolved in water. This solution was washed with $CHCl_3$, and the aqueous layer was acidified with 10% HCl solution. The precipitate was collected, washed with water, and dried to give **5** in 86% yield (470 mg). The sample was identical with an authentic specimen.

Reaction of 2 with Morpholine A solution of **2** (303 mg) and morpholine (0.67 ml) in EtOH (10 ml) was refluxed for 14 h, and then the solvent was evaporated off. The residue was chromatographed on silica gel with CH_2Cl_2–MeOH (19 : 1) as an eluent. Recrystallization from CH_2Cl_2–hexane gave 3-(2-morpholinoethyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**14**) (329 mg, 75%) as colorless needles. mp 212—214 °C (dec.). *Anal.* Calcd for $C_{12}H_{15}N_3O_3S \cdot 1/5H_2O$: C, 50.58; H, 5.38; N, 14.75; S, 11.25. Found: C, 50.84; H, 5.39; N, 14.82; S, 11.23. IR (KBr): 1610 (sh), 1580 cm^{-1}. NMR ($CDCl_3$) δ: 2.40—2.91 (6H, m, $NCH_2CH_2N(CH_2CH_2)_2O$), 3.53—3.84 (4H, m, $N(CH_2CH_2)_2O$), 4.32 (2H, t, J=6.9 Hz, NCH_2CH_2N), 6.85 and 7.68 (each 1H, d, J=5.4 Hz, ArH), 10.7—12.0 (1H, br, NH). MS *m/z*: 281 (M^+), 152.

Desulfurization Reaction of 2 with Raney Ni Raney Ni W-2 (*ca.* 10 g) was added to a solution of **2** (1.016 g) in MeOH (7 ml)–dioxane (63 ml), and the whole was stirred at 100 °C for 10 h under a nitrogen atmosphere. The catalyst was filtered off, the filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel with AcOEt as an eluent. Recrystallization from AcOEt–hexane gave 2,3-dihydro-7-ethyl-5*H*-oxazolo[3,2-*d*]pyrimidin-5-one (**15**) (300 mg, 35%) as colorless prisms. mp 57—60 °C. *Anal.* Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.78; H, 6.11; N, 16.56. IR (KBr): 1685, 1600 cm^{-1}. NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.5 Hz, CH_2CH_3), 2.48 (2H, q, J=7.5 Hz, CH_2CH_3), 4.17—4.37 (2H, m, NCH_2CH_2O), 4.64—4.84 (2H, m, NCH_2CH_2O), 5.91 (1H, s, ArH). MS *m/z*: 166 (M^+).

Reaction of 2 with *n*-BuLi a) Methylation: A 1.6 N *n*-BuLi solution in hexane (1.8 ml) was added dropwise to a stirred suspension of **2** (435 mg) in dry THF (20 ml) at −60 °C during 5 min under a nitrogen atmosphere, and the whole was stirred for 20 min at the same temperature. A solution of MeI (670 mg) in dry THF (5 ml) was added and the resulting reaction mixture was stirred at −60 °C for 1 h. The mixture was quenched with AcOH, poured into brine, and extracted with AcOEt. The residue obtained from the AcOEt extracts was chromatographed on silica gel and eluted with AcOEt–hexane (1 : 1). Recrystallization from MeOH–AcOEt gave 6-methyl-3-vinylthieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**16a**) (95 mg, 20%) as colorless needles. mp 229—232 °C. *Anal.* Calcd for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45; S, 15.40. Found: C, 51.62; H, 3.74; N, 13.38; S, 15.52. IR (KBr): 1721, 1646, 1631 cm^{-1}. NMR (DMSO-d_6) δ: 2.53 (3H, d, J=1.5 Hz, $ArCH_3$), 5.21 (1H, d, J=9.6 Hz, NC=CH), 5.92 (1H, d, J=16.2 Hz, NC=CH), 6.70 (1H, d, J=1.5 Hz, ArH), 6.95 (1H, dd, J=16.2, 9.6 Hz, $NCH=CH_2$), 10.9 (1H, br s, NH). MS *m/z*: 208 (M^+), 139.

b) Protonation: A 1.6 N *n*-BuLi solution in hexane (2.0 ml) was added dropwise to a stirred suspension of **2** (518 mg) in dry THF (20 ml) at −60 °C during 5 min under a nitrogen atmosphere, and the whole was stirred for 1 h at the same temperature. The mixture was quenched with AcOH, poured into brine, and extracted with AcOEt. The residue obtained from the AcOEt extracts was chromatographed on silica gel and eluted with AcOEt–hexane (1 : 1). Recrystallization from MeOH–AcOEt gave 3-vinylthieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**16b**) (122 mg, 24%) as colorless needles. mp 208—211 °C (dec.). *Anal.* Calcd for $C_8H_6N_2O_2S \cdot 1/10H_2O$: C, 49.02; H, 3.19; N, 14.29; S, 16.36. Found: C, 49.22; H, 3.31; N, 14.04; S, 16.07. IR (KBr): 1723, 1660, 1635 cm^{-1}. NMR (DMSO-d_6) δ: 5.24 (1H, d, J=9.3 Hz, NC=CH), 5.91 (1H, d, J=16.2 Hz, NC=CH), 6.77—7.12 (2H, m, ArH, $NCH=CH_2$), 8.10 (1H, d, J=5.4 Hz, ArH), 12.00 (1H, br s, NH). MS *m/z*: 194 (M^+).

2,3-Dihydro-9-methyl-5-oxoxazolo[3,2-*a*]thieno[3,2-*d*]pyrimidinium Tetrafluoroborate (18) Compound **2** (1.06 g) was added portionwise to a suspension of trimethyloxonium tetrafluoroborate (0.94 g) in dry CH_2Cl_2 (40 ml) at 0 °C under a nitrogen atmosphere and the whole was stirred for 3 h at the same temperature. The precipitate was collected by filtration, washed with CH_2Cl_2, and dried to give **18** in quantitative yield (1.60 g). mp 167—170 °C. IR (KBr): 1692, 1652 cm^{-1}. NMR (DMSO-d_6) δ: 3.53 (3H, s, NCH_3), 4.15—4.70 (4H, m, NCH_2CH_2O), 7.35 and 8.22 (each 1H, d, J=5.6 Hz, ArH). The crude material was used for the subsequent step without further purification.

Reaction of 18 with MeOH A suspension of **18** (128 mg) in MeOH (6 ml) was refluxed for 1 min, and the solution was then filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel with AcOEt–hexane (2 : 1) as an eluent. Recrystallization from MeOH gave 3-(2-methoxyethyl)-1-methylthieno[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**19a**) (60 mg, 58%) as colorless leaflets. mp 127—128 °C. *Anal.* Calcd for $C_{10}H_{12}N_2O_3S$: C, 49.99; H, 5.03; N, 11.66; S, 13.34. Found: C, 50.03; H, 4.96; N, 11.47; S, 13.20. IR (KBr): 1695, 1657 cm^{-1}. NMR ($CDCl_3$) δ: 3.36 (3H, s, OCH_3), 3.58 (3H, s, NCH_3), 3.67 (2H, t, J=6.0 Hz, NCH_2CH_2O), 4.31 (2H, t, J=6.0 Hz, NCH_2CH_2O), 6.98 and 7.76 (each 1H, d, J=5.4 Hz, ArH). MS *m/z*: 240 (M^+), 182.

Reaction of 18 with EtOH The same procedure as described for **19a** was applied to **18** (97 mg) and EtOH (5 ml). Recrystallization from MeOH afforded 3-(2-ethoxyethyl)-1-methylthieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**19b**) (54 mg, 65%) as colorless needles. mp 62—63 °C. *Anal.* Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.55; N, 11.02; S, 12.61. Found: C, 51.92; H, 5.54; N, 11.14; S, 12.53. IR (KBr): 1692, 1648 cm^{-1}. NMR ($CDCl_3$) δ: 1.13 (3H, t, J=6.9 Hz, OCH_2CH_3), 3.58 (3H, s, NCH_3), 3.43—3.82 (4H, m, $NCH_2CH_2OCH_2CH_3$), 4.31 (2H, t, J=6.2 Hz, NCH_2CH_2O), 6.95 and 7.73 (each 1H, d, J=5.4 Hz, ArH). MS *m/z*: 254 (M^+), 182.

Reaction of 18 with iso-$PrNH_2$ The same procedure as described for **19a** was applied to **18** (106 mg), iso-$PrNH_2$ (77 mg) and CH_2Cl_2 (5 ml). Recrystallization from AcOEt–hexane gave 1-methyl-3-(2-isopropylaminoethyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**19c**) (72 mg, 75%) as colorless needles. mp 76—78 °C. *Anal.* Calcd for $C_{12}H_{17}N_3O_2S \cdot 1/4H_2O$: C, 53.02; H, 6.48; N, 15.46; S, 11.89. Found: C, 53.02; H, 6.13; N, 15.28; S, 12.20. IR (KBr): 1686, 1645 cm^{-1}. NMR ($CDCl_3$) δ: 1.07 (6H, d, J=6.0 Hz, $NCH(CH_3)_2$), 1.83 (1H, s, NH), 2.90 (1H, sep, J=6.0 Hz, $NHCHMe_2$), 2.95 (2H, t, J=6.9 Hz, NCH_2CH_2NHPr), 3.58 (3H, s, NCH_3), 4.25 (2H, t, J=6.9 Hz, NCH_2CH_2NHPr), 6.95 and 7.72 (each 1H, d, J=5.1 Hz, ArH). MS *m/z*: 267 (M^+), 209.

Reaction of 18 with Morpholine The same procedure as described for **19a** was applied to **18** (202 mg), morpholine (174 mg) and CH_2Cl_2 (10 ml). Recrystallization from AcOEt–hexane gave 1-methyl-3-(2-morpholinoethyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**19d**) (130 mg, 65%) as colorless prisms. mp 146—149 °C. *Anal.* Calcd for $C_{13}H_{17}N_3O_3S \cdot 1/2H_2O$: C, 51.30; H, 5.96; N, 13.81; S, 10.53. Found: C, 51.59; H, 5.67; N, 13.53; S, 10.47. IR (KBr): 1692, 1649 cm^{-1}. NMR (DMSO-d_6) δ: 2.30—2.63 (6H, m, $NCH_2CH_2N(CH_2CH_2)_2O$), 3.33—3.67 (7H, m, NCH_3, $N(CH_2CH_2)_2O$), 4.04 (2H, t, J=6.9 Hz, NCH_2CH_2N), 7.33 and 8.16 (each 1H, d, J=5.4 Hz, ArH). MS *m/z*: 295 (M^+), 100.

References

1) S. Johne, "Progress in Drug Research Vol. 26," ed. by E. Jucker, Birkhäuser Verlag, Basel, 1982, pp. 259—341.
2) *a*) A. Kosasayama, K. Higashi and F. Ishikawa, *Chem. Pharm. Bull.*, **27**, 880 (1979); *b*) R. J. Grout and M. W. Partridge, *J. Chem. Soc.*, **1960**, 3551; *c*) K. D. Kampe, Ger. Patent 2252122 (1974) [*Chem. Abstr.*, **81**, 13543*b* (1974)].
3) T. Fujiwara, Y. Sakamoto, I. Fukazawa, H. Horikoshi, M. Sugiyama and H. Fukumi, *Arzneim.-Forsch.*, **36**, 1770 (1986).
4) F. Kienzle, A. Kaizer and R. E. Minder, *Helv. Chim. Acta*, **66**, 148 (1983).