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3,4-Dihydrothienopyrimidines. III.[1] Alkylation of 2-Chloro-3,4,5,6,7,8-hexahydro-[1]benzothieno[2,3-*d*]pyrimidines and Related New Heterocycles

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Methylation of 2-chloro-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine (**1**) gave the 3-methyl derivative as a major product, but benzylation predominantly afforded the 1-substituted product. On the other hand, alkylation of **1** with an α-carbonylalkyl halide predominantly occurred at position 3. The 2-chloro-1- or-3-alkylated compounds were easily hydrolyzed to give the corresponding 1-alkyl-2(1*H*)- or 3-alkyl-2(1*H*)-one derivatives, which were readily oxidized to the corresponding 3,4- or 1,4-dehydrogenated compounds, respectively.

The 2-chloro-3-substituted compounds were used for the synthesis of new heterocycles, imidazo[1,2-*a*]thieno[2,3-*d*]pyrimidine and 2,3-dihydro-5*H*-oxazolo[3,2-*a*]thieno[2,3-*d*]-pyrimidine.

Keywords——1-substituted 1,4-dihydrothienopyrimidines; 3-substituted 3,4-dihydrothienopyrimidines; imidazo[1,2-*a*]thieno[2,3-*d*]pyrimidine; 2,3-dihydro-5*H*-oxazolo[3,2-*a*]-thieno[2,3-*d*]pyrimidine; alkylation; oxidation; sodium borohydride reduction; phase transfer catalyst

It has been reported that thieno[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-diones were predominantly alkylated at position 3,[2] and alkylation of 4-arylthieno[2,3-*d*]pyrimidin-2(1*H*)-ones occurred on the nitrogen atom at position 1 or 3 and on the carbonyl-oxygen at position 2.[3] We were interested in the possibility of alkylation of 2-chloro-3,4-dihydrothieno[2,3-*d*]pyrimidines[4] without affecting the active chlorine atom at position 2 and in the sites of such alkylation, since the resulting N-alkylated 2-chloro derivatives would give a new heterocycle upon substitution of the active chlorine atom with a nucleophile. This paper deals with the alkylation of 2-chloro-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine (**1**), as a procedure for the synthesis of new heterocycles.

Heating 2-chloro-3,4-dihydrothienopyrimidines with ethyl bromoacetate gave 3-substituted compounds.[5] However, **1** did not react with alkyl halide under similar conditions. Alkylations were attempted under various conditions, and the best result was obtained in the presence of tetrabutylammonium iodide (TBAI) as a phase transfer catalyst in a mixture of methylene dichloride and sodium hydroxide solution. Table I shows the results of alkylation of **1**.

Reaction of **1** with methyl or ethyl iodide gave a mixture of 1-substituted (**2a, b**) and 3-substituted derivatives (**3a, b**), and the dehydrogenated compound **4**. The formation ratios of **2** and **3** in the mixture were determined by nuclear magnetic resonance (NMR) spectroscopy. The signals of the 4-methylene protons in **2a, b** were observed at lower fields, δ 4.75 and 4.70, than those in **3a, b**, δ 4.67 and 4.63, respectively, due to the influence of the adjacent C=N double bond. The spectra showed that methylation predominantly gave the 3-substituted derivative (**3a**), while ethylation proceeded more readily at position 1. The 3-methyl compound (**3a**) was successfully isolated from the reaction mixtures but the 3-ethylated product (**3b**) and the unstable 1-substituted products (**2a, b**) could not be separated. However, on treatment of the reaction mixture with silica gel, **2a, b** were dehalogenated to provide the 1-substituted 3,4-dihydro-2(1*H*)-one derivatives (**5a, b**). Heating **3a** in acetic acid also afforded 3-methyl-3,4-dihydro-2(1*H*)-one (**6a**), while heating crude **3b** yielded 3-ethylthieno-

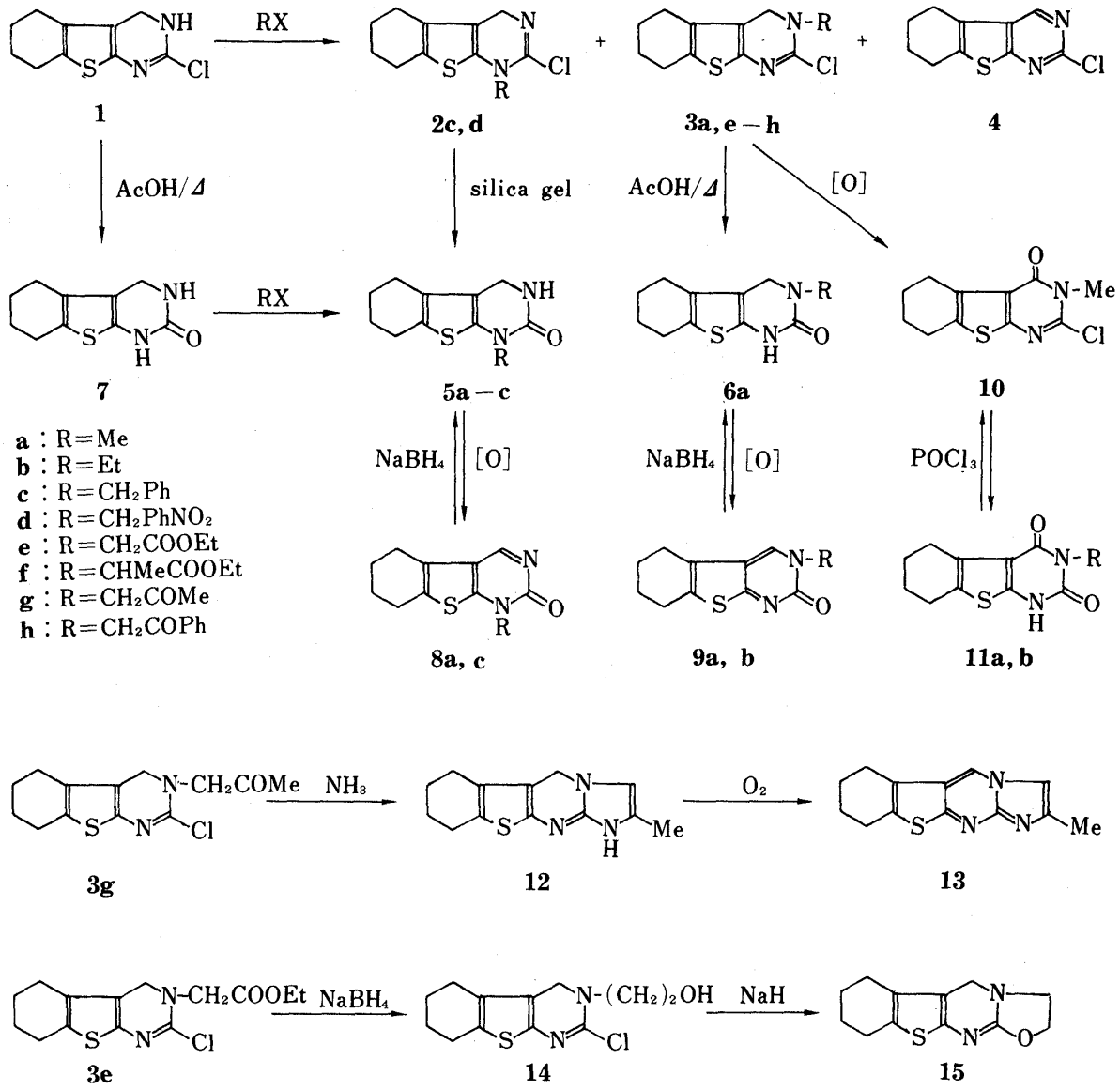

Chart 1

TABLE I. Alkylation of 2-Chloro-3,4-dihydro[1]benzothieno[2,3-*d*]pyrimidines in the Presence of a Phase Transfer Catalyst

Alkylating agent	Product ratio in reaction mixture 2 : 3	Products (yield, %) 1-Substitution	3-Substitution
MeI	1 : 3	**5a** (9)	**3a** (37) **4** (9)
EtI	4 : 3	**5b** (5)	**9b** (3) **11b** (2) **4** (25)
$PhCH_2I$	1 : 0	**2c**[b] (71)	
p-NO_2-$PhCH_2Br$	1 : 0	**2d**[b] (53)	
$EtOOCCH_2Br$	0 : 1		**3e** (65)
EtOOCCHMeBr[a]	0 : 1		**3f**[b] (53)
$MeCOCH_2Br$	1 : 8		**3g** (74)
$PhCOCH_2Br$	1 : 5		**3h** (46)

a) This reaction was carried out in the presence of potassium carbonate.
b) Isolated as the hydrochloride salt.

pyrimidin-2(3*H*)-one (**9b**) and -2,4(1*H*, 3*H*)-dione (**11b**).

Reactions with benzyl iodide or 4-nitrobenzyl bromide gave only the 1-substituted derivatives (**2c, d**), isolated as their hydrochlorides. Compound **2c** was also converted into 1-benzyl-3,4-dihydro-2(1*H*)-one (**5c**) by treatment with silica gel.

Compound **1** was allowed to react with ethyl bromoacetate, bromoacetone or phenacyl bromide to give mainly the 3-substituted derivatives (**3e, g, h**). Reaction of **1** with ethyl 2-bromopropionate in the presence of a phase transfer catalyst at room temperature did not give any substituted products. When the reaction was carried out by heating in the presence of potassium carbonate in ethyl methyl ketone, the 3-substituent (**3f**) was obtained as the hydrochloride.

Reaction of the 3,4-dihydro-2(1*H*)-one (**7**), which was obtained by heating of **1** in acetic acid,[4] with methyl iodide or benzyl bromide gave only the 1-substituted compounds (**5a, c**).

The structures of the 1- or 3-substituted 3,4-dihydro-2-chloro (**2** or **3**) and 2-oxo derivatives (**5** or **6**) were deduced from their spectral data (shown in Table II).

Table II. NMR and UV Spectral Data for 1-and 3-Substituted 3,4-Dihydrothienopyrimidine Derivatives (**2**, **3**, **5** and **6**)

Compound	NMR (δ)		UV λ_{max} nm (ε)		
	4-CH_2	N-CH_2 or CH_3	EtOH	EtOH–HCl	EtOH–NaOH
2a	4.75	3.45			
2b	4.70	3.72			
2c	4.75	4.90			
2c·HCl	4.92	5.17	320 (4900)	334 (5700)	310 (5160)
2d	4.77	5.00			
2d·HCl	5.00	5.34	320[a] (4860)	330 (5360)	315[a] (5360)
2g	4.73	4.30			
2h	4.80	5.10			
3a	4.67	3.07	330 (7430)	335 (5890)	
3b	4.63	3.49			
3e	4.67	4.14	332 (6590)	336 (6000)	
3f	4.48, 4.69				
3f·HCl	4.69, 5.03		333 (7840)	337 (6970)	332 (8100)
3g	4.60	4.21	334 (7720)	337 (6870)	
3h	4.68	4.86	332 (9840)	337 (8850)	
5a	4.40	3.23	286 (8520)		287 (8500)
5b	4.37	3.69	287 (8600)		290 (8470)
5c	4.40	4.89	285 (6750)		287 (6360)
6a	4.30	3.01	282 (8570)		308 (7260)

a) Shoulder.

The NMR spectrum of the benzyl derivative (**2c**) showed signals due to the methylene protons of the benzyl group at δ 4.90 and due to the 4-methylene protons at δ 4.75 (a pair of singlets) which accorded with the 4-methylene proton signals of the 1-substituted derivatives (**2a, b**), indicating substitution of the benzyl group at position 1. Similarly, the spectrum of the 4-nitrobenzyl derivative (**2d**) indicated a 1-substituted structure. The 4-methylene signals of 3-substituted derivatives (**3e, g, h**) were observed at δ 4.60—4.68 (singlet) except for **3f**, which gave signals at δ 4.48 and 4.69 as a pair of doublets due to the nonequivalence of the methylene protons at position 4 resulting from the asymmetric carbon of the substituent at position 3.

In the ultraviolet (UV) spectra taken in ethanol solution, the absorption maxima of **3a, e—h** appeared at longer wavelength (330—334 nm) than that (310 nm) of **2c** because of the presence of C=N double bond conjugated with the thiophene ring. Upon addition of hydrochloric acid to a solution of the free base (**2c**) in ethanol, the absorption shifted 24 nm

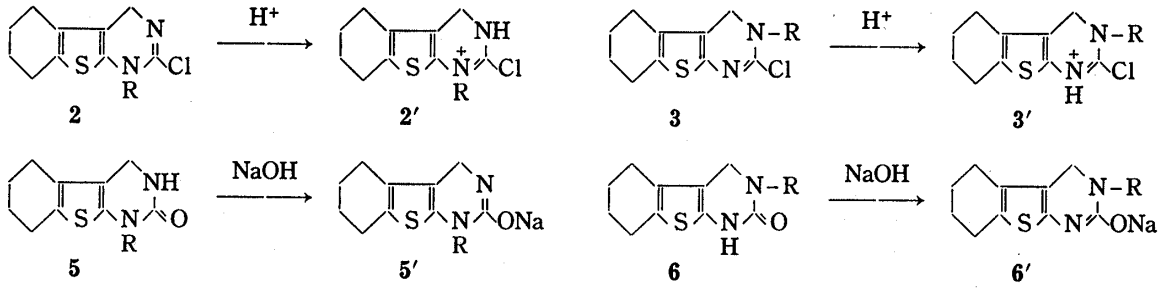

Chart 2

to longer wavelength. On the other hand, the bathochromic shift of **3** was very slight, which suggests that the chromophores of **2** and **3** become similar (**2′** and **3′**) as shown in Chart 2.

The absorption maxima of **5a—c** and **6a** appeared at 282—286 nm in the UV spectra in ethanol solution. The absorption of **6a** was, however, shifted 26 nm to longer wavelength by addition of sodium hydroxide solution. This is the absorption of a changed chromophore (**6′**) having a C=N double bond conjugated with the thiophene ring.

The structure of the 3-methyl derivative (**3a**) was confirmed as follows: air oxidation of **3a** gave the 2-chloro-3-methyl-4(3*H*)-one (**10**), which was identical with a sample prepared from the 3-methyl-2,4(1*H*, 3*H*)-dione (**11a**) by Arya's method.[2)]

It was anticipated that alkylation of 2-chloro-3,4-dihydrothieno[2,3-*d*]pyrimidine would preferentially occur at position 3 as in the case of 3,4-dihydroquinazoline derivatives.[6)] The alkylation of **1** with α-carbonylalkyl halides predominantly gave 3-substituted compounds. However, in the alkylation of **1** with typical alkyl halides such as methyl, ethyl and benzyl iodide, considerable amounts of 1-substituted products were formed.

1- Or 3-substituted 3,4-dihydro-2(1*H*)-ones (**5a, c** and **6a**) were readily oxidized with potassium permanganate or even with air to give the corresponding dehydrogenated products (**8a, c** and **9a**). This is of interest in comparison with the case of oxidation of 3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one with potassium permanganate, which gives the 4-oxo derivative.[7)] Compounds **8c** and **9a** were readily converted to the parent 3,4-dihydro products (**5c** and **6a**, respectively) by reduction with sodium borohydride.

We have reported that the reaction of ethyl 2-chloro-3,4-dihydrothienopyrimidine-3-acetate with ammonia gave cyclized compounds, 1,2,3,5-tetrahydroimidazo[1,2-*a*]thienopyrimidin-2-ones, which were potent platelet aggregation inhibitors.[5b)] Similar reaction of the 3-acetonyl derivative (**3g**) with ammonia gave 2-methyl-1,5-dihydroimidazo[1,2-*a*]thieno-[2,3-*d*]pyrimidine (**12**), which was easily oxidized with air to yield 2-methylimidazo[1,2-*a*]-thieno[2,3-*d*]pyrimidine (**13**). Furthermore, the ethyl 2-chloro-3,4-dihydro-3-acetate derivative (**3e**) was reduced with sodium borohydride to give the 3-hydroxyethyl derivative (**14**), which was cyclized on treatment with base to afford a new heterocycle, 2,3,-dihydro-5*H*-oxazolo[3,2-*a*]thieno[2,3-*d*]pyrimidine (**15**).

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 285 spectrometer. UV spectra were taken with a Hitachi 323 spectrometer. NMR spectra were taken with a Hitachi R-40 (90 MHz) or a Varian EM-360 (60 MHz) spectrometer with tetramethylsilane as an internal standard (δ value). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; *q*, quartet; m, multiplet;br,broad. For column chromatography, silica gel (Merck, 0.05—0.2 mm) was used.

Methylation of 2-Chloro-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine (1)——Methyl iodide (2.35 g, 16.5 mmol) was added to a suspension of **1** (3.40 g, 15 mmol), TBAI (0.25 g) and 10 N NaOH (7.5 ml) in CH_2Cl_2 (75 ml) at room temperature. The mixture was stirred at the same temperature for 4.5 h under a nitrogen atmosphere. The CH_2Cl_2 layer was separated, washed with H_2O and dried over Na_2SO_4. After removal of the solvent, the oily residue was triturated with CH_2Cl_2–Et_2O. The resulting precipitate was collected to give **3a** (1.32 g, 37%), which was recrystallized from CH_2Cl_2–Et_2O to give colorless plates, mp

107—112°C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1580. NMR ($CDCl_3$) δ: 1.7—2.0 (4H, m), 2.25—2.45 (2H, m), 2.5—2.75 (2H, m), 3.07 (3H, s), 4.67 (2H, s). *Anal.* Calcd for $C_{11}H_{13}ClN_2S$: C, 54.88; H, 5.44; N, 11.64. Found: C, 54.91; H, 5.32; N, 11.67.

After **3a** had been removed as described above, the mother liquor was concentrated and the residue was chromatographed on a column of silica gel (30 g). The first eluate with benzene gave **4** (0.316 g, 9%), mp 101—103°C (lit.[1] 101—103°C). The second eluate with benzene gave a mixture (0.51 g) of **3a** and **4**. The third eluate with benzene–$CHCl_3$ (1: 1, v/v) gave crude **5a**, which was recrystallized from CH_2Cl_2–MeOH to give pale yellow fine needles (0.29 g, 9%), mp 213—215°C. IR ν_{max}^{KBr} cm^{-1}: 3240, 3100, 1670. NMR ($CDCl_3$) δ: 1.7—2.0 (4H, m), 2.3—2.5 (2H, m), 2.6—2.85 (2H, m), 3.23 (3H, s), 4.40 (2H, s), 5.20 (1H, br). *Anal.* Calcd for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.35; N, 12.60. Found: C, 59.08; H, 6.12; N, 12.65.

Ethylation of 1——A mixture of **1** (1.13 g, 5 mmol), EtI (0.858 g, 5.5 mmol), TBAI (0.08 g) and 10 N NaOH (2.5 ml) in CH_2Cl_2 (25 ml) was stirred at room temperature for 24 h under a nitrogen atmosphere. The CH_2Cl_2 layer was separated, washed and dried. After removal of the solvent, the residue was chromatographed on a column of silica gel (10 g). The eluate with benzene gave a mixture (fraction A, 0.62 g) of **3b** and **4**. The eluate with $CHCl_3$ gave crude **5b**, which was recrystallized from CH_2Cl_2 to give yellow crystals (0.062 g, 5%), mp 190—192°C. IR ν_{max}^{KBr} cm^{-1}: 3330, 3220, 3070, 1680. NMR ($CDCl_3$) δ: 1.26 (3H, t), 1.7—1.9 (4H, m), 2.25—2.5 (2H, m), 2.55—2.75 (2H, m), 3.69 (2H, q), 4.37 (2H, s), 5.40 (1H, br). *Anal.* Calcd for $C_{12}H_{16}N_2OS$: C, 60.98; H, 6.82; N, 11.85. Found: C, 60.95; H, 7.07; N, 12.16.

A solution of fraction A in AcOH (5 ml) was refluxed for 2 h. After removal of the solvent *in vacuo*, the residue was chromatographed on a column of silica gel (5 g). The first eluate with benzene gave **4** (0.284 g, 25%). The second eluate with benzene–$CHCl_3$ (1: 1) gave a crude product, which was further purified by preparative thin layer chromatography with benzene–acetone (7: 1) to give **11b** (0.022 g, 2%), mp 263—265°C (from CH_2Cl_2–MeOH). IR ν_{max}^{KBr} cm^{-1}: 2700—3100, 1700, 1640. UV λ_{max}^{EtOH} nm (ε): 233 (29100), 262 (6160) (sh.), 297 (3770). NMR ($CDCl_3$) δ: 1.27 (3H, t), 1.75—1.95 (4H, m), 2.6—2.8 (2H, m), 2.85—3.05 (2H, m), 4.10 (2H, q), 11.10 (1H, br). *Anal.* Calcd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.08; H, 5.57; N, 10.98. The third eluate with $CHCl_3$–MeOH (100: 1) gave **9b**, which was recrystallized from MeOH to give yellow prisms (0.030 g, 3%), mp 242—244°C. IR ν_{max}^{KBr} cm^{-1}: 1640. NMR ($CDCl_3$) δ: 1.40 (3H, t), 1.8—2.0 (2H, m), 2.4—2.8 (4H, m), 4.14 (2H, q), 7.86 (1H, s). *Anal.* Calcd for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.11; H, 5.97; N, 11.77.

1-Benzyl-2-chloro-1,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine (2c)——A mixture of **1** (0.68 g, 3 mmol), benzyl iodide (0.88 g, 4 mmol), TBAI (0.05 g) and 10 N NaOH (1.5 ml) in CH_2Cl_2 (15 ml) was stirred at room temperature for 1 h under a nitrogen atmosphere. The CH_2Cl_2 layer was separated, washed and dried. After removal of the solvent, 5% HCl–MeOH was added to the residue. The solution was concentrated *in vacuo*, and the residue was triturated with CH_2Cl_2–Et_2O to give the hydrochloride of **2c** (0.75 g, 71%), which was recrystallized from EtOH–Et_2O to give colorless feathers, mp 158—160°C. IR ν_{max}^{KBr} cm^{-1}: 2300—2700, 1640. NMR ($CDCl_3$) δ: 1.7—1.9 (4H, m), 2.3—2.5 (2H, m), 2.55—2.75 (2H, m), 4.92 (2H, s), 5.17 (2H, s), 7.3—7.5 (5H, m). *Anal.* Calcd for $C_{17}H_{18}Cl_2N_2S$: C, 57.79; H, 5.14; N, 7.93. Found: C, 57.42; H, 5.03; N, 7.89.

2-Chloro-1-(4-nitrobenzyl)-1,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine (2d)——By a procedure similar to that used for the preparation of the hydrochloride of **2c**, the hydrochloride of **2d** was obtained in 53% yield, mp 170—172°C (from EtOH–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 2300—2700, 1640, 1520, 1340. NMR ($CDCl_3$) δ: 1.7—2.0 (4H, m), 2.3—2.8 (4H, m), 5.00 (2H, s), 5.34 (2H, s), 7.60 (2H, d), 8.34 (2H, d). *Anal.* Calcd for $C_{17}H_{17}Cl_2N_3O_2S$: C, 51.26; H, 4.30; N, 10.55. Found: C, 50.82; H, 4.12; N, 10.40.

Ethyl 2-Chloro-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine-3-acetate (3e)——A mixture of **1** (2.26 g, 10 mmol), ethyl bromoacetate (1.84 g, 11 mmol), TBAI (0.185 g) and 10 N NaOH (5 ml) in CH_2Cl_2 (50 ml) was stirred at room temperature for 0.5 h under a nitrogen atmosphere. The CH_2Cl_2 layer was separated, washed and dried. After removal of the solvent, the oily residue was triturated with EtOH to give **3e** (2.04 g, 65%), which was recrystallized from $CHCl_3$–EtOH to afford pale yellow prisms, mp 105—110°C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1740, 1580. NMR ($CDCl_3$) δ: 1.33 (3H, t), 1.7—1.95 (4H, m), 2.25—2.5 (2H, m), 2.6—2.8 (2H, m), 4.14 (2H, s), 4.30 (2H, q), 4.67 (2H, s). *Anal.* Calcd for $C_{14}H_{17}ClN_2O_2S$: C, 53.75; H, 5.48; N, 8.95. Found: C, 53.48; H, 5.42; N, 8.70.

Ethyl 2-(2-Chloro-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-3-yl)propionate (3f)——A suspension of **1** (2.26 g, 10 mmol), ethyl 2-bromopropionate (2.26 g, 13 mmol) and finely powdered K_2CO_3 (4.15 g, 30 mmol) in ethyl methyl ketone (75 ml) was refluxed with vigorous stirring for 14 h under a nitrogen atmosphere, then concentrated *in vacuo*. The residue was mixed with CH_2Cl_2 and H_2O. The organic layer was separated, washed and dried. The residue was dissolved in 10% HCl–EtOH. The solution was concentrated to a small volume *in vacuo* and the residue was triturated with CH_2Cl_2–Et_2O to give the hydrochloride of **3f** (1.91 g, 53%), which was recrystallized from MeOH–Et_2O to afford pale yellow prisms, mp 109—111°C. IR ν_{max}^{KBr} cm^{-1}: 3530, 3450, 2400—2700, 1740, 1590. NMR ($CDCl_3$) δ: 1.31 (3H, t), 1.76 (3H, d), 1.6—2.0 (4H, m), 2.3—2.75 (4H, m), 4.29 (2H, q), 4.69, 5.03 (2H, each of d, J=14 Hz), 5.16 (1H, q), 10.50 (1H, br). *Anal.* Calcd for $C_{15}H_{20}Cl_2N_2O_2S$: C, 49.59; H, 5.55; N, 7.71. Found: C, 49.22; H, 5.46; N, 7.60.

3-Acetonyl-2-chloro-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine (3g)——Compound **3g** was obtained in 46% yield by a method similar to that used for the synthesis of **3e**, mp 123—125°C (from CH_2Cl_2–

Et_2O). IR ν_{max}^{KBr} cm^{-1}: 1720, 1585, 1575. NMR ($CDCl_3$) δ: 1.7—1.9 (4H, m), 2.23 (3H, s), 2.2—2.4 (2H, m), 2.55—2.75 (2H, m), 4.21 (2H, s), 4.60 (2H, s). *Anal.* Calcd for $C_{13}H_{15}ClN_2OS$: C, 55.22; H, 5.35; N, 9.91. Found: C, 55.21; H, 5.34; N, 9.88.

2-Chloro-3-phenacyl-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine (**3h**)——Compound **3h** was obtained in 74% yield by a method similar to that used for the synthesis of **3e**, mp 152—154°C (dec.) (from CH_2Cl_2–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 1690, 1580. NMR ($CDCl_3$) δ: 1.65—1.9 (4H, m), 2.2—2.4 (2H, m), 2.55—2.75 (2H, m), 4.68 (2H, s), 4.86 (2H, s), 7.4—7.7 (3H, m), 7.9—8.1 (2H, m). *Anal.* Calcd for $C_{18}H_{17}ClN_2OS$: C, 62.69; H, 4.97; N, 8.12. Found: C, 62.77; H, 5.06; N, 8.20.

1-Methyl-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-2(1*H*)-one (**5a**)——A mixture of **7**[4] (0.208 g, 1 mmol), K_2CO_3 (0.138 g, 1 mmol) and methyl iodide (0.150 g, 1.1 mmol) in dimethyl sulfoxide (DMSO) (50 ml) was heated with stirring at 40°C for 5 h under a nitrogen atmosphere. Further methyl iodide (0.150 g, 1.1 mmol) was added, and the mixture was stirred at the same temperature for 13 h. The mixture was poured into H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated to dryness *in vacuo*. The residue was chromatographed on a column of silica gel (5 g). The first eluate with $CHCl_3$ gave **5a** (0.077 g, 35%) as pale yellow crystals, which were identical with a sample obtained by methylation of **1**. The second eluate with $CHCl_3$–MeOH (10: 1) yielded unreacted **7** (0.095 g, 47%).

1-Benzyl-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-2(1*H*)-one (**5c**)——Compound **2c** (0.95 g, 3 mmol) was chromatographed on a column of silica gel (7 g). The eluate with $CHCl_3$ gave **5c** (0.264 g, 30%), which was recrystallized from EtOH to afford pale yellow prisms, mp 186—187.5°C. IR ν_{max}^{KBr} cm^{-1}: 3340, 3220, 3090, 1680. NMR ($CDCl_3$) δ: 1.65—1.9 (4H, m), 2.2—2.7 (4H, m), 4.40 (2H, s), 4.89 (2H, s), 5.50 (1H, br), 7.2—7.5 (5H, m). *Anal.* Calcd for $C_{17}H_{18}N_2OS$: C, 68.43; H, 6.08; N, 9.39. Found: C, 68.49; H, 6.09; N, 9.40.

This compound was also obtained in 25% yield by a procedure similar to that used for the preparation of **5a**.

3-Methyl-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-2(1*H*)-one (**6a**)——A solution of **3a** (0.722 g, 3 mmol) in AcOH (10 ml) was refluxed for 2 h under a nitrogen atmosphere. The resulting precipitate was washed with MeOH to give **6a** (0.258 g, 39%), which was recrystallized from $CHCl_3$–EtOH to afford colorless plates, mp 231—234°C. IR ν_{max}^{KBr} cm^{-1}: 3200, 3150, 1650. NMR ($CDCl_3$) δ: 1.7—2.0 (4H, m), 2.25—2.75 (4H, m), 3.01 (3H, s), 4.30 (2H, s), 7.63 (1H, br). *Anal.* Calcd for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.35; N, 12.60. Found: C, 59.24; H, 6.15; N, 12.87.

1-Methyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-2(1*H*)-one (**8a**)——Potassium permanganate (0.300 g, 1.9 mmol) was added to a solution of **5a** (0.213 g, 0.96 mmol) in Me_2CO (100 ml) at 40°C. The mixture was stirred at the same temperature for 1.5 h, then EtOH (4 ml) was added. The whole was stirred for 2 h, then insoluble material was filtered off. The filtrate was concentrated *in vacuo* and the residue was mixed with $CHCl_3$ and H_2O. The organic layer was separated, washed with H_2O and dried. After removal of the solvent, the residue was recrystallized from benzene–hexane to give **8a** (0.096 g, 45%) as yellow prisms, mp 149—151°C. IR ν_{max}^{KBr} cm^{-1}: 1660. UV λ_{max}^{EtOH} nm (ε): 252 (19300), 270s (5570), 285s (2720), 355 (3610). NMR ($CDCl_3$) δ: 1.8—2.0 (4H, m), 2.6—2.85 (4H, m), 3.68 (3H, s), 8.69 (1H, s). *Anal.* Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 59.74; H, 5.48; N, 12.72.

1-Benzyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-2(1*H*)-one (**8c**)——Compound **8c** was similarly prepared using 1 mol eq instead of 2 mol eq of $KMnO_4$. Yield 82%, mp 169—171°C (from benzene–hexane). IR ν_{max}^{KBr} cm^{-1}: 1660. UV λ_{max}^{EtOH} nm (ε): 254 (15400), 270s (5460), 285s (2140), 353 (2470). NMR ($CDCl_3$) δ: 1.7—2.0 (4H, m), 2.5—2.8 (4H, m), 5.32 (2H, s), 7.2—7.6 (5H, m), 8.71 (1H, s). *Anal.* Calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.72; H, 5.45; N, 9.30.

3-Methyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-2(3*H*)-one (**9a**)——a) A solution of $KMnO_4$ (0.053 g, 0.33 mmol) in H_2O (3 ml) was added dropwise to a suspension of **6a** (0.074 g, 0.33 mmol) in 5% $NaHCO_3$ solution (20 ml) at 80—100°C. The mixture was stirred at the same temperature for 15 min. Insoluble material was filtered off and washed with 5% $NaHCO_3$ solution. The filtrate and washings were combined and acidified with 10% HCl. The mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated to dryness *in vacuo* to give **9a** (0.022 g, 30%), which was recrystallized from CH_2Cl_2–hexane to afford yellow prisms, mp 239—242°C. IR ν_{max}^{KBr} cm^{-1}: 1650. UV λ_{max}^{EtOH} nm (ε): 224 (20600), 232 (21500), 252 (30000), 278 (6240), 370 (3300). NMR ($CDCl_3$) δ: 1.8—2.0 (4H, m), 2.4—2.7 (4H, m), 3.69 (3H, s), 7.84 (1H, s). *Anal.* Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 59.97; H, 5.31; N, 12.75.

b) A solution of **6a** (0.050 g, 0.23 mmol) in $CHCl_3$ (30 ml) was stirred at room temperature for 60 h. After removal of the solvent, the residue was washed with Et_2O to give **9a** (0.042 g, 83%) as yellow crystals, which were identical with a sample prepared by method a).

Sodium borohydride Reduction of 8c and 9a——Sodium borohydride (0.050 g, 1.3 mmol) was added to a solution of **8c** (0.090 g, 0.3 mmol) in $CHCl_3$–EtOH (4 ml, 1: 1). The mixture was stirred at room temperature for 0.5 h, then concentrated to dryness *in vacuo*. The residue was mixed with $CHCl_3$ and H_2O. The organic layer was separated, washed with H_2O and dried. After removal of the solvent, the powdered residue was washed with Et_2O to give **5c** (0.080 g, 90%) as pale yellow prisms, which were identical with

a sample obtained from **2c**.

Compound **6a** was obtained from **9a** in quantitative yield by a similar method involving the reduction of **8c**.

2-Chloro-3-methyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (10)——A solution of **3a** (0.070 g, 0.29 mmol) in benzene (20 ml) was vigorously stirred at room temperature for 7 d. Triethylamine (1 ml) was added to the solution and the mixture was further stirred for 1 d. After removal of the solvent, the residue was chromatographed on a column of silica gel (3 g). The eluate with benzene gave **10** (0.008 g, 11%), which was recrystallized from EtOH to afford colorless crystals, mp 173°C (lit.[2] 172—174°C).

2-Methyl-1,5,6,7,8,9-hexahydro[1]benzothieno[2,3-*d*]imidazo[1,2-*a*]pyrimidine (12) and 2-Methyl-6,7,8,9-tetrahydro[1]benzothieno[2,3-*d*]imidazo[1,2-*a*]pyrimidine (13)——A mixture of **3g** (0.25 g, 0.88 mmol) and 10% NH_3–EtOH solution (5 ml) was heated at 120—140°C for 11 h under a nitrogen atmosphere in a sealed tube, then cooled. The resulting precipitate was collected and washed successively with EtOH, H_2O and EtOH to give **12** (0.145 g, 67%), mp 236—240°C (dec.). The hydrochloride of **12** was obtained in 58% yield by treatment of the free base of **12** with HCl–MeOH solution, mp 236—239°C (dec.) (from MeOH). IR ν_{max}^{KBr} cm^{-1}: 2550—2950, 1640, 1590. UV λ_{max}^{EtOH} nm: 298. NMR (CF_3CO_2H) δ: 1.5—3.2 (8H, m), 2.43 (3H, s), 4.85 (1H, br), 5.40 (2H, s), 7.02 (1H, s). *Anal.* Calcd for $C_{13}H_{16}ClN_3S$: C, 55.41; H, 5.72; N, 14.91. Found: C, 55.05; H, 5.57; N, 14.90.

After **12** had been removed from the reaction mixture as described above, the mother liquor concentrated *in vacuo*. The residue was mixed with $CHCl_3$ and H_2O. The organic layer was separated, washed with H_2O, dried and concentrated *in vacuo*. The residue was recrystallized from $CHCl_3$–hexane to give **13** (0.020 g, 9%) as pale yellow crystals, mp 253—257°C. IR ν_{max}^{KBr} cm^{-1}: 3100, 3050, 1620, 1330. UV λ_{max}^{EtOH} nm: 250s, 256, 270, 278, 326s, 340, 374; $\lambda_{max}^{EtOH\text{-}HCl}$ nm; 250, 267, 277, 328, 354. NMR ($CDCl_3$) δ: 1.8—2.2 (4H, m), 2.53 (3H, s), 2.5—3.0 (4H, m), 7.38 (1H, s), 8.46 (1H, s). *Anal.* Calcd for $C_{13}H_{13}N_3S$: C, 64.17; H, 5.38; N, 17.27. Found: C, 63.88; H, 5.24; N, 16.98.

2-(2-Chloro-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-3-yl)ethanol (14)——Sodium borohydride (1.14 g, 30 mmol) was added portionwise to a solution of **3e** (1.88 g, 6 mmol) in $CHCl_3$–EtOH (20 ml, 1: 1). The mixture was stirred at room temperature for 16 h. After removal of the solvent, the residue was mixed with $CHCl_3$ and H_2O. The organic layer was separated, washed with H_2O, dried and concentrated to dryness *in vacuo*. The residue was recrystallized from $CHCl_3$–hexane to give **14** (0.78 g, 48%), mp 117—118°C. IR ν_{max}^{KBr} cm^{-1}: 3230, 1570. NMR ($CDCl_3$) δ: 1.7—1.9 (4H, m), 2.2—2.4 (2H, m), 2.55—2.75 (2H, m), 3.25 (1H, br), 3.57 (2H, t), 3.93 (2H, t), 4.73 (2H, s). *Anal.* Calcd for $C_{12}H_{15}ClN_2OS$: C, 53.23; H, 5.58; N, 10.35. Found: C, 53.47; H, 5.35; N, 9.92.

2,3,6,7,8,9-Hexahydro[1]benzothieno[2,3-*d*]oxazolo[3,2-*a*]pyrimidine (15)——A mixture of 50% NaH in oil (0.050 g, 1 mmol; washed with Et_2O), **14** (0.271 g, 1 mmol) and dimethylformamide (DMF) (2 ml) was stirred at room temperature for 4 h. The mixture was poured into ice-cold H_2O and extracted with $CHCl_3$. The extract was washed with a saturated NaCl solution, dried and concentrated to dryness *in vacuo*. The powdered residue was recrystallized from CH_2Cl_2–Et_2O to give **15** (0.095 g, 41%) as pale yellow prisms, mp unclear. IR ν_{max}^{KBr} cm^{-1}: 1620. NMR ($CDCl_3$) δ: 1.7—2.0 (4H, m), 2.25—2.75 (4H, m), 3.50 (2H, t), 4.47 (4H, s and t). *Anal.* Calcd for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.30; H, 5.94; N, 11.93.

References and Notes

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