Notes

[Chem. Pharm. Bull. 30(1) 326—332 (1982)]

3,4-Dihydrothienopyrimidines. II.[1] Synthesis and Sodium Borohydride Reduction of 2-Substituted 4-Chloro- and 4-Unsubstituted-thieno[2,3-*d*]pyrimidines

HITOSHI YAMAGUCHI and FUMIYOSHI ISHIKAWA*

Research Institute, Daiichi Seiyaku Co., Ltd., 1-16-13 Kitakasai, Edogawa-ku, Tokyo 134, Japan

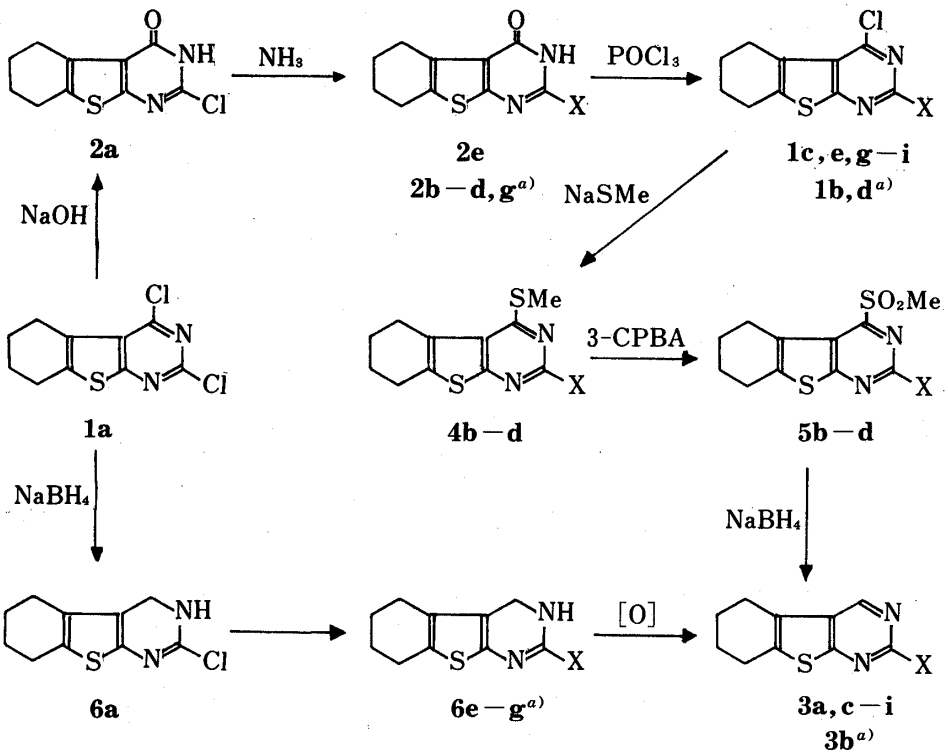
(Received December 3, 1980)

The synthesis and sodium borohydride reduction of 4-chloro- (**1**) and 4-unsubstituted- (**3**) 5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidines, substituted with various groups, such as chloro, hydrogen, methyl, phenyl, amino, ethoxy, methylthio, methylsulfinyl and mesyl, at position 2, are described. In the reduction of **1**, the 2-chloro and 2-methylsulfinyl derivatives only gave the corresponding 3,4-dihydro derivatives. The compounds **3**, except for the 2-phenyl, 2-amino and 2-ethoxy derivatives, were reduced to give the corresponding 3,4-dihydro derivatives. The reduction was promoted by the presence of an electron withdrawing group at position 2. A 2- or 4-mesyl group was eliminated in the course of the 3,4-dihydrogenation.

Keywords——2-substituted 4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine; 2-substituted 5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine; 2-substituted 3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine; sodium borohydride reduction; dechlorination; demesylation; 3,4-dihydrogenation of thienopyrimidine

We have reported that 2-chloro-5,6-dimethyl-4-phenylthieno[2,3-*d*]pyrimidine reacted with sodium borohydride to give 2-chloro-5,6-dimethyl-4-phenyl-3,4-dihydrothieno[2,3-*d*]-pyrimidine, but the corresponding 2-hydroxy derivative did not react with the same reagent.[2] Also, reaction of 2,4-dichloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**1a**) with sodium borohydride readily gave the corresponding 2-chloro-3,4-dihydro derivative (**6a**).[1] This elimination of the 4-chloro atom with concomitant selective reduction at position 3 and 4 may be due to the substituent at position 2. In the present study we have synthesized various 2-substituted 4-chloro- (**1**) and 4-unsubstituted- (**3**) 5,6,7,8-tetrahydro[1]benzothieno-[2,3-*d*]pyrimidine derivatives and examined the reaction of these compounds with sodium borohydride to elucidate the influence of the 2-substituent. Synthetic routes to compounds **1** and **3** are shown in Chart 1. 2-Unsubstituted, 2-methyl, 2-phenyl and 2-methylthio derivatives (**1b**—**d**, **g**) were obtained from the known corresponding 4 (3*H*)-one derivatives.[3] According to Robba's method,[4] the 2,4-dichloro derivative (**1a**) was partially hydrolyzed to the 2-chloro-4(3*H*)-one (**2a**).

Reported syntheses of 4-unsubstituted thieno[2,3-*d*]pyrimidines having a 2-alkyl or 2-aryl group consist of catalytic reduction of the corresponding 4-chloro derivatives,[5] or of treatment of 4-hydrazino derivatives with mercuric oxide[5a,6] or oxygen.[6b,7] In this study, several new methods had been investigated in order to prepare the desired 2-substituted compounds (**3**). Reaction of 2-substituted 4-chloro derivatives (**1b**—**d**) with sodium methylthiolate in the presence of a phase transfer catalyst gave the corresponding 4-methylthio derivatives (**4b**—**d**). Oxidation of **4b**—**d** with an excess of 3-chloroperbenzoic acid yielded the corresponding 4-mesyl derivatives (**5b**—**d**), which were reduced with sodium borohydride to give 4-unsubstituted derivatives (**3b**—**d**). In the case of **5b**, **c**, further reduced products, *i.e.*, the 3,4-dihydro derivatives (**6b**, **c**) ,were obtained as by-products.



a: X=Cl; **b**: X=H; **c**: X=Me; **d**: X=Ph; **e**: X=NH_2; **f**: X=OEt; **g**: X=SMe; **h**: X=SOMe; **i**: X=SO_2Me

a) Known compounds.

Chart 1

3,4-Dihydrothieno[2,3-*d*]pyrimidines (compounds **6a**, **e**—**g**[1]) substituted with a group containing a hetero atom at position 2 and compound **6b** were oxidized with chloranil or air (oxygen) to give the desired compounds **3a**, **b**, **e**—**g**, respectively. Compound **3g** was treated with an equimolar amount of hydrogen peroxide to give readily the 2-methylsulfinyl derivative (**3h**), and with excess of the reagent to give the 2-mesyl derivative (**3i**).

The results of the reaction of **1** and **3** with sodium borohydride are shown in Table I. Although the reaction of the 2,4-dichloro derivative (**1a**) readily gave the 2-chloro-3,4-dihydro

Table I. Reduction of 2-Substituted 4-Chloro- (**1**) and 4-Unsubstituted- (**3**) thieno[2,3-*d*]pyrimidine Derivatives with $NaBH_4$ *a*)

Starting material (S.M.)	X	Reaction time (h)	Ratio *b*) in reaction mixture S.M.: prod.	Isolated compounds	(%)
1a	Cl	20		**6a**	(70)
1h	SOMe	4		**1g**	(2)
				6h	(30)
1i	SO_2Me	1.5		**1b**, **4b** *c*)	
				1b *c*)	(49)
				3b	(22)
3a	Cl	8	0 : 10	**6a**	(81)
3b	H	15	2 : 8	**6b**·HCl	(21)
3c	Me	15	6 : 4	**6c**·HCl	(20)
3g	SMe	15	6 : 4	**6g**	(8)
3h	SOMe	2	0 : 10	**6h**	(52)
3i	SO_2Me	2	0 : 10	**6b**·HCl	(21)

a) The starting materials were recovered intact in the cases of **1b**—**e**, **1g** and **3d**—**f**.
b) The ratio was determined by the NMR spectroscopy.
c) See experimental section.

derivative (**6a**),[1] similar treatments of the 2-hydrogen (**1b**), 2-methyl (**1c**), 2-phenyl (**1d**), 2-amino (**1e**) and 2-methylthio (**1g**) derivatives resulted in recovery of the starting materials.

The 3,4-dihydro derivative (**6h**) and the 4-chloro-2-methylthio derivative (**1g**) were separated from the reaction mixture of **1h** with sodium borohydride. Furthermore, an inseparable mixture of almost equimolar amounts of the 2-unsubstituted 4-chloro derivative (**1b**) and the 4-methylthio derivative (**4b**) was obtained. The structure of **4b** was confirmed by comparison with a sample prepared by reaction of **1b** with methanethiol. When **1h** is reacted with sodium borohydride, sulfur-oxygen bond fission in the 2-methylsulfinyl group and 2-pyrimidine carbon-sulfur bond fission might occur. The former reaction may give **1g**, while the latter would give **1b** and methanesulfenic acid. Subsequent reaction of **1b** with methanesulfenic acid followed by reaction, or reaction of **1b** with methanethiol formed by reduction of methanesulfenic acid with sodium borohydride would give **4b**.

The 2-mesyl derivative (**1i**) reacted with sodium borohydride to give the corresponding 2-demesylated derivatives (**1b**) and (**3b**). Since the reaction of **1b** with sodium borohydride did not give the 3,4-dihydro derivative (**6b**), **1b** might react with methanesulfinic acid formed

Table II. 2-Substituted 5,6,7,8-Tetrahydro[1]benzothieno[2,3-*d*]pyrimidine Derivatives (**3**)

Compd.	X	Method	Yield (%)	mp (recryst. solv.) (°C)	IR (cm^{-1})	Formula	Analysis Calcd (Found) C	H	N	NMR[d] (δ)
3a	Cl	A B	80 91	101—103 (C_6H_6–hexane)	1400 1330 1150	$C_{10}H_9ClN_2S$	53.45 (53.53	4.04 4.16	12.47 12.30)	1.85—2.1 (4H, m) 2.7—3.0 (4H, m) 8.73 (1H, s, 4-H)
3b[g]	H	D[a]	63	63—64.5 (Et_2O–pet. ether)						1.85—2.1 (4H, m) 2.7—3.05 (4H, m) 8.92 (1H, s, 4-H)[e] 9.06 (1H, s, 2-H)
3c	Me	D[a]	49	46—49 (Et_2O–pet. ether)	1580 1420 1370	$C_{11}H_{12}N_2S$	64.67 (64.29	5.92 6.04	13.71 13.67)	1.85—2.05 (4H, m) 2.6—2.95 (4H, m) 2.82 (3H s) 8.78 (1H, s, 4-H)
3d	Ph	D	55	123—124 (Et_2O–hexane)	1420 1370 750 690	$C_{16}H_{15}N_2S$	71.87 (71.94	5.65 5.74	10.48 10.56)	1.7—2.1 (4H, m) 2.6—2.95 (4H, m) 7.4—7.6 (3H, m) 8.45—8.6 (2H, m) 8.88 (1H, s, 4-H)
3e	NH_2	A C	13 57	254—258 ($CHCl_3$–MeOH)	3300 3130 1660 1580	$C_{10}H_{11}N_3S$	58.51 (58.70	5.40 5.30	20.47 20.03)	1.7—2.0 (4H, m) 2.5—2.9 (4H, m) 8.58 (1H, s, 4-H)
3f	OEt	A C	73 33	97—99 (C_6H_6–hexane)	1580 1520 1440 1380 1340 1310	$C_{12}H_{14}N_2OS$	61.51 (61.68	6.02 6.02	11.96 12.12)	1.47 (3H, t) 1.8—2.1 (4H, m) 2.65—2.95 (4H, m) 4.50 (2H, q) 8.61 (1H, s, 4-H)
3g	SMe	A C	72 41	93—94.5 (pet. benzine)	1570 1540 1500 1400	$C_{11}H_{12}N_2S_2$	55.90 (56.19	5.12 5.14	11.85 11.92)	1.9—2.1 (4H, m) 2.65 (3H, s) 2.7—2.0 (4H, m) 8.63 (1H, s, 4-H)
3h	SOMe	E[b]	52	145—147 (C_6H_6–pet. ether)	1060	$C_{11}H_{12}N_2OS_2$	52.35 (51.92	4.79 4.78	11.10 10.99)	1.9—2.1 (4H, m) 2.75—3.0 (4H, m) 3.02 (3H, s) 8.96 (1H, s, 4-H)
3i	SO_2Me	E[c]	69	194—196 ($CHCl_3$–pet. ether)	1310 1120	$C_{11}H_{12}N_2O_2S_2$	49.23 (49.26	4.51 4.40	10.44 10.59)	1.9—2.1 (4H, m) 2.8—3.1 (4H, m) 3.43 (3H, s) 9.01 (1H, s, 4-H)

a) These methods also gave **6b** (31%) and **6c** (25%) respectively, as by-products. *b*) H_2O_2 used amounted to 1 mol eq *c*) H_2O_2 used amounted to 3 mol. eq. *d*) The solvent was $CDCl_3$, except that DMSO-d_6 was used in the case of **3e**. *e*) When **5b** was treated with $NaBD_4$, the signal at δ 8.92 in the product disappeared.

by elimination of the 2-mesyl group to give **5b**, which is demesylated again with sodium borohydride.

On treatment of 2-substituted 5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidines (**3**) with sodium borohydride, the 2-phenyl (**3d**), 2-amino (**3e**) and 2-ethoxy (**3f**) derivatives did not react but the 2-methyl (**3c**) and 2-methylthio (**3g**) derivatives gave, in very slow reactions, the corresponding 3,4-dihydro derivatives (**6c, g**). Reduction of the 2-chloro (**3a**), 2-hydrogen (**3b**) and 2-methylsulfinyl (**3h**) derivatives readily gave the corresponding 3,4-dihydro derivatives (**6a, b, h**). In the case of the 2-mesyl derivative (**3i**), demesylation easily occurred to yield finally the 2-unsubstituted 3,4-dihydro derivative (**6b**).

The reactivity of **1** and **3** was influenced by the functional group at position 2 and the order of the promoting effect was $MeSO_2 \simeq MeSO > Cl > H > Me \simeq SMe \gg Ph \simeq OEt \simeq NH_2$. This order seems to reflect the electron-withdrawing potency of the substituents. Presumably the negatively charged transition state formed by addition of hydride ion to the thienopyrimidine ring would be more effectively stabilized due to the influence of the electron-withdrawing substituent at position 2. In order to examine the influence of the 2-substituent on the electron density, the chemical shifts of the protons at position 4 in the nuclear magnetic resonance (NMR) spectra were measured and are shown in Table II. The presence of electron-withdrawing groups at position 2 shifted the 4-proton signal to lower field. Compounds **3e, f**, in which the chemical shift was higher than δ 8.61, did not react with sodium borohydride and the derivatives **3a—c, g, h** with lower field shifts than that were reduced to the 3,4-dihydro derivatives (**6a—c, g, h**), except for the 2-phenyl derivative (**3d**).

The reduction of the thieno[2,3-*d*]pyrimidine ring to the 3,4-dihydro system is dependent on the magnitude of electron density in the ring. Substituents that decrease the electron density promote the reaction.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 285 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 (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.

General Procedure for the Synthesis of 1b—d,g——A mixture of **2**[3] (10—80 mmol) and $POCl_3$ (30—100 ml) was heated under reflux for 3 h. After removal of excess $POCl_3$ *in vacuo*, the residue was poured into ice-water. The resulting precipitate was dissolved in $CHCl_3$. The extract was washed with H_2O, dried and concentrated *in vacuo*. The resulting crystalline powder was purified by recrystallization or by silica gel chromatography. The physical data and yields of **1b—d,g** are given below.

4-Chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine[8] (**1b**)——Yield 87%, mp 113—114°C (from C_6H_6–petr. ether).

4-Chloro-2-methyl Derivative (**1c**)——Yield 91%, mp 93—94.5°C (from hexane). IR ν_{max}^{KBr} cm^{-1}: 1480, 1410, 1190. NMR ($CDCl_3$) δ: 1.8—2.1 (4H, m), 2.78 (3H, s, 2-CH_3), 2.8—3.2 (4H, m). *Anal.* Calcd for $C_{11}H_{11}ClN_2S$: C, 55.34; H, 4.64; N, 11.73. Found: C, 55.56; H, 4.45; N, 11.73.

4-Chloro-2-phenyl Derivative[9] (**1d**)——Yield 88%, mp 174—176°C (from CH_2Cl_2–hexane) (lit. mp 171—172°C).

4-Chloro-2-methylthio Derivative (**1g**)——Yield 88%, mp 111—112.5°C (from $CHCl_3$–EtOH). IR ν_{max}^{KBr} cm^{-1}: 1470, 1390, 1190. NMR ($CDCl_3$) δ: 1.7—2.0 (4H, m), 2.64 (3H, s, S-CH_3), 2.7—3.1 (4H, m). *Anal.* Calcd for $C_{11}H_{11}ClN_2S_2$: C, 48.79; H, 4.09; N, 10.34. Found: C, 48.79; H, 4.07; N, 10.45.

2-Amino-4-chloro Derivative (**1e**)——A mixture of **2e** (2.46 g, 11 mmol) and $POCl_3$ (30 ml) was treated as in the general procedure. A suspension of the residue in 15% aq. HCO_2H (20 ml) was heated at 90—100°C for 1 h, then cooled. Insoluble material was collected, washed with H_2O, dried and chromatographed on silica gel (10 g) with $CHCl_3$ to give pale yellow prisms (1.34 g, 51%), mp 219—221°C (from $CHCl_3$–hexane). IR ν_{max}^{KBr} cm^{-1}: 3300, 3180, 1630, 1560, 1490. NMR ($CDCl_3$) δ: 1.7—2.0 (4H, m), 2.65—3.1 (4H, m), 5.22 (2H, br, NH_2). *Anal.* Calcd for $C_{10}H_{10}ClN_3S$: C, 50.10; H, 4.30; N, 17.53. Found: C, 50.12; H, 4.17; N, 17.36.

4-Chloro-2-methylsulfinyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**1h**)——A suspension of **1g** (10 g, 37 mmol) in AcOH (150 ml) was treated with 35% aq. H_2O_2 (4.0 g, 41 mmol). The mixture was stirred at room temperature for 19 h and then heated at 40—50°C for 1.5 h. The solution was concentrated

to one-fourth of the initial volume *in vacuo*, and the residue was 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 silica gel (90 g). After elution of the starting material with C_6H_6, the eluate with $CHCl_3$ was collected and the product was recrystallized from C_6H_6–hexane to give **1h** (7.78 g, 73%), mp 120.5—122.5°C. IR ν_{max}^{KBr} cm^{-1}: 1080. NMR ($CDCl_3$) δ: 1.8—2.1 (4H, m), 3.00 (3H, s, SO–CH_3). 2.8—3.25 (4H, m). *Anal.* Calcd for $C_{11}H_{11}ClN_2OS_2$: C, 46.07; H, 3.87; N, 9.77. Found: C, 46.23; H, 3.84; N, 9.71.

4-Chloro-2-mesyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (1i)——To a suspension of **1g** (5.42 g, 20 mmol) in Me_2CO (200 ml) was added portionwise 70% 3-chloroperbenzoic acid (10.85 g, 44 mmol) below 20°C. The mixture was stirred at room temperature for 17 h then concentrated *in vacuo*. The residue was dissolved in $CHCl_3$. The solution was washed with 5% $NaHCO_3$ solution, dried and concentrated *in vacuo*. The residue was triturated in hexane to give **1i** (5.29 g, 87%), which, on recrystallization from C_6H_6–hexane, afforded colorless plates, mp 150—152°C. IR ν_{max}^{KBr} cm^{-1}: 1310, 1140. NMR ($CDCl_3$) δ: 1.8—2.1 (4H, m), 2.8—3.3 (4H, m), 3.44 (3H, s, SO_2–CH_3). *Anal.* Calcd for $C_{11}H_{11}ClN_2O_2S_2$: C, 43.90; H, 3.93; N, 9.64. Found: C, 43.63; H, 3.66; N, 9.25.

2-Chloro-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-4-one (2a)——A mixture of **1a**[1] (23.3 g, 0.1 mol), tetrahydrofuran (THF) (400 ml) and 1.2 N NaOH (450 ml) was stirred vigorously at room temperature for 75 h. The solution was concentrated to half the initial volume below 35°C *in vacuo*, and H_2O (300 ml) was added to the residue. Insoluble material was filtered off and the filtrate was acidified with 10% HCl solution. The resulting precipitate was collected, washed with H_2O and dried to give **2a** (13.5 g, 54%), which, on recrystallization from $CHCl_3$–EtOH, afforded colorless fine needles, mp 269—272°C. IR ν_{max}^{KBr} cm^{-1}: 3150—2650, 1650. NMR (DMSO-d_6) δ: 1.65—1.95 (4H, m), 2.65—2.95 (4H, m). *Anal.* Calcd for $C_{10}H_9ClN_2OS$: C, 49.90; H, 3.77; N, 11.64. Found: C, 49.64; H, 3.57; N, 11.49.

2-Amino-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-4-one (2e)——A mixture of **2a** (4.80 g, 20 mmol) and 10% NH_3–EtOH solution (50 ml) was heated at 120°C for 23 h in a sealed tube, then cooled. The resulting precipitate was collected, washed with H_2O and EtOH, and dried to give **2e** (3.41 g, 77%), which, on recrystallization from AcOH, afforded colorless fine needles, mp>300°C. IR ν_{max}^{KBr} cm^{-1}: 3450, 3150, 3000—2700, 1660, 1640, 1600. NMR (DMSO-d_6) δ: 1.6—1.9 (4H, m), 2.5—2.9 (4H, m), 6.41 (2H, s, NH_2), 10.70 (1H, br, NH). *Anal.* Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.03; H, 5.09; N, 18.65.

General Procedure for the Synthesis of 2-Substituted 5,6,7,8-Tetrahydro[1]benzothieno[2,3-*d*]pyrimidine Derivatives (3)——Compounds **3** were prepared by the general methods described below. The results are shown in Table II.

Method A: A mixture of **6**[1] (2—3 mmol) and an equimolar amount of chloranil in C_6H_6 (20—30 ml) was heated under reflux for 0.5 h. The mixture was cooled and diluted with C_6H_6. The solution was washed with 0.5 N NaOH and H_2O, and then dried. After removal of the solvent, the residue was purified by silica gel chromatography using C_6H_6 as an eluent.

Method B: A solution of **6** (0.5 mmol) in EtOH (100 ml) was stirred at room temperature for 160 h. After removal of the solvent, the residue was purified by silica gel chromatography using $CHCl_3$ as an eluent.

Method C: A solution of **6** (0.2—1 mmol) in EtOH (20—200 ml) was treated with 2 N NaOH (5 mol eq.) and the mixture was stirred at room temperature for 70—170 h. After removal of the solvent, the residue was mixed with H_2O and $CHCl_3$. The organic layer was separated, washed with H_2O, dried and concentrated *in vacuo*. The residue was recrystallized.

Method D: $NaBH_4$ (5 mmol) was added portionwise to a solution of **5** (1 mmol) in $CHCl_3$–EtOH (1: 1, 10—15 ml) at room temperature. The mixture was stirred at the same temperature for 2—20 h, then worked up as in Method C. The residue was purfied by silica gel chromatography or recrystallization.

Method E: A solution of **3g** (1.0—2.6 mmol) in AcOH (10—20 ml) was treated with 35% H_2O_2 (1 or 3 mol eq.) at room temperature. The mixture was stirred at the same temperature for 14—16 h then concentrated to a small volume below 50°C *in vacuo*, and worked up as in method D.

4-Methylthio-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine[7] **(4b)**——A mixture of **1b** (11.2 g, 50 mmol), tetrabutylammonium iodide (1.9 g, 2.7 mmol) and 15% aq. MeSNa solution in C_6H_6 (200 ml) was heated under reflux for 2 h with stirring under an N_2 atmosphere. The organic layer was separated, washed with H_2O, dried and concentrated *in vacuo*. The residue was crystallized from Et_2O–hexane to give **4b** (9.95 g, 84%), mp 107—108°C (lit. mp 102°C).

2-Methyl-4-methylthio-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (4c)——This compound was obtained by a method similar to that used for the synthesis of **4b**. Yield 76%, mp 127—129°C (from C_6H_6–hexane). IR ν_{max}^{KBr} cm^{-1}: 2930, 1480, 1410. NMR ($CDCl_3$) δ: 1.8—2.0 (4H, m), 2.63 (3H, s, 2-CH_3), 2.72 (3H, s, S-CH_3), 2.7—3.15 (4H, m). *Anal.* Calcd for $C_{12}H_{14}N_2S_2$: C, 57.56; H, 5.64; N, 11.19. Found: C, 57.50; H, 5.63; N, 11.23.

4-Methylthio-2-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine[10] **(4d)**——This compound was obtained by a method similar to that used for the synthesis of **4b**. Yield 84%, mp 164—166°C (from C_6H_6–hexane) (lit. not given). IR ν_{max}^{KBr} cm^{-1}: 1490, 1410. NMR ($CDCl_3$) δ: 1.75—2.0 (4H, m), 2.73 (3H, s, S-CH_3), 2.7—3.15 (4H, m), 7.45—7.6 (3H, m, arom. protons), 8.45—8.65 (2H, m, arom. protons). *Anal.* Calcd for $C_{17}H_{16}N_2S_2$: C, 65.35; H, 5.16; N, 8.97. Found: C, 65.17; H, 5.04; N, 8.66.

4-Mesyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (5b)——3-Chloroperbenzoic acid (3.80 g, 22 mmol) was added portionwise to a solution of **4b** (2.36 g, 10 mmol) in Me_2CO (50 ml) below 10°C. The whole was stirred at room temperature for 13 h, then the resulting precipitate was collected, washed with cold Me_2CO and dried to give **5b** (0.73 g). The filtrate and washings were combined and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$. The solution was washed with $NaHCO_3$ solution and dried. Removal of the solvent gave further **5b** (0.69 g). Yield 1.42 g (53%), mp 178—180°C (from C_6H_6–hexane). IR ν_{max}^{KBr} cm^{-1}: 1300, 1120. NMR ($CDCl_3$) δ: 1.85—2.05 (4H, m), 2.9—3.3 (4H, m), 3.51 (3H, s, SO_2–CH_3), 8.97 (1H, s, 2-CH). *Anal.* Calcd for $C_{11}H_{12}N_2O_2S_2$: C, 49.23; H, 4.40; N, 10.59. Found: C, 49.55; H, 4.53; N, 10.43.

4-Mesyl-2-methyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (5c)——This compound was obtained by a method similar to that used for the synthesis of **5b**. Yield 90%, mp 117—119°C (Me_2CO–hexane). IR ν_{max}^{KBr} cm^{-1}: 1310, 1120. NMR ($CDCl_3$) δ: 1.85—2.05 (4H, m), 2.83 (3H, s, 2-CH_3), 2.9—3.3 (4H, m), 3.50 (3H, s, SO_2–CH_3). *Anal.* Calcd for $C_{12}H_{14}N_2O_2S_2$: C, 51.04; H, 5.00; N, 9.92. Found: C, 51.53; H, 5.02; N, 9.93.

4-Mesyl-2-phenyl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (5d)——This compound was obtained by a method similar to that used for the synthesis of **5b**, but using $CHCl_3$ instead of Me_2CO as the solvent. Yield 84%, mp 228—229°C (from C_6H_6). IR ν_{max}^{KBr} cm^{-1}: 1410, 1300, 1150. NMR ($CDCl_3$) δ: 1.85—2.05 (4H, m), 2.85—3.35 (4H, m), 3.60 (3H, s, SO_2–CH_3), 7.45—7.6 (3H, m, arom. protons), 8.4—8.55 (2H, m, arom. protons). *Anal.* Calcd for $C_{17}H_{16}N_2O_2S_2$: C, 59.28; H, 4.68; N, 8.13. Found: C, 59.28; H, 4.62; N, 8.18.

General Procedure for the Reduction of 2-Substituted 4-Chloro- (1) and 4-Unsubstituted- (3) 5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine——$NaBH_4$ (5 mol eq.) was added portionwise to a solution of 1 or 3 (1—2 mmol) in a mixed solvent of $CHCl_3$–EtOH (2—30 ml). The mixture was stirred at room temperature for the reaction time shown in Table I, then concentrated *in vacuo*. Water was added to the residue and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated *in vacuo*. The residue was purified by silica gel chromatography or recrystallization. The molar ratio of products in the reaction mixture and the yields of the products are shown in Table I. The melting points and spectral data are listed below.

2-Chloro-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine[1] (6a)——mp 141—143°C (dec.) (from $CHCl_3$–hexane) (lit. mp 141—143°C (dec.)).

3,4,5,6,7,8-Hexahydro[1]benzothieno[2,3-*d*]pyrimidine Hydrochloride (6b)——mp 286—288°C (dec.) (from EtOH–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 3100, 3020, 2940, 2600. NMR (DMSO-d_6) δ: 1.55—1.9 (4H, m), 2.3—2.5 (4H, m), 4.67 (2H, s, 4-CH_2), 8.30 (1H, d, J=6 Hz, 2-CH), 10.60, 12.75 (1H×2, br). *Anal.* Calcd for $C_{10}H_{13}ClN_2S$: C, 52.51; H, 5.73; N, 12.25. Found: C, 52.68; H, 5.73; N, 12.30.

2-Methyl-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine Hydrochloride (6c)——mp 291—300°C (dec.) (from EtOH). IR ν_{max}^{KBr} cm^{-1}: 2900, 2700, 1640, 1610. NMR (DMSO-d_6) δ: 1.6—1.9 (4H, m), 2.27 (3H, s, 2-CH_3), 2.3—2.75 (4H, m), 4.63 (2H, s, 4-CH_2), 10.47, 12.61 (1H×2, br). *Anal.* Calcd for $C_{11}H_{14}ClN_2S$: C, 54.42; H, 6.23; N, 11.54. Found: C, 54.36; H, 6.41; N, 11.56.

2-Methylthio-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine[1] (6g)——mp 125—127 (dec.) (from C_6H_6–hexane) (lit. mp 125—127°C).

2-Methylsulfinyl-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidine (6h)——mp 130—132°C (dec.) (from C_6H_6–hexane). IR ν_{max}^{KBr} cm^{-1}: 3270, 1600, 1050. NMR ($CDCl_3$) δ: 1.7—2.0 (4H, m), 2.25—2.5 (4H, m), 2.83 (3H, s, SO–CH_3), 4.79 (2H, s, 4-CH_2), 6.33 (1H, br). *Anal.* Calcd for $C_{11}H_{14}N_2OS_2$: C, 51.94; H, 5.55; N, 11.01. Found: C, 51.95; H, 5.58; N, 10.93.

Reduction of 1h with $NaBH_4$——$NaBH_4$ (0.19 g, 5 mmol) was added portionwise to a suspension of **1h** (0.27 g, 1 mmol) in $CHCl_3$–EtOH (1: 1, 14 ml). The mixture was stirred at room temperature for 4 h and 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 (5 g). The first eluate with C_6H_6 gave **1g** (9 mg, 2%). The second eluate with $CHCl_3$ gave a mixture of **1b** and **4b** (about 1: 1, 0.1 g) as a crystalline powder which could not be separated by preparative thin-layer chromatography or by recrystallization. The structures of **1b** and **4b** were confirmed by comparison with authentic sample by NMR spectroscopy. The third eluate with $CHCl_3$ gave **6g** (76 mg, 30%).

Reduction of 1i with $NaBH_4$——$NaBH_4$ (0.19 g, 5 mmol) was added portionwise to a suspension of **1i** (0.303 g, 1 mmol) in $CHCl_3$–EtOH (1: 1, 8 ml). The mixture was stirred at room temperature for 1.5 h and worked up as above. The residue was chromatographed on silica gel (5 g). The first eluate with $CHCl_3$ gave **1b** (0.109 g, 49%) and the second eluate with $CHCl_3$–EtOH (20: 1) gave **3b** (40 mg, 22%).

References and Notes

1) Part I: H. Yamaguchi and F. Ishikawa, *J. Heterocycl. Chem.*, **18**, 67 (1981).
2) F. Ishikawa and H. Yamaguchi, *Chem. Pharm. Bull.*, **28**, 3172 (1980).
3) *a*) F. Sauter, *Monatsh. Chem.*, **99**, 1507 (1968); *b*) M.S. Manhas, V.V. Rao, P.A. Seetharaman, D. Succardi, and J. Pazdera, *J. Chem. Soc.*, (*C*) **1969**, 1937; *c*) F. Sauter and W. Deinhammer, *Monatsh. Chem.*, **104**, 1593 (1973).

4) M. Robba, J.M. Lecomte, and M. Cugnon de Sevricourt, *Bull. Soc. Chim. Fr.*, **1975**, 592.
5) *a*) M. Robba and M. Cugnon de Sevricourt, *Bull. Soc. Chim. Fr.*, **1976**, 761; *b*) J. Bourguignon, M. Moreau, G. Queguiner, and P. Pastour, *Bull. Soc. Chim. Fr.*, **1977**, 676.
6) *a*) M. Robba, P. Touzot, and R.M. Riquelme, *Tetrahedron Lett.*, **1972**, 4549; *b*) J. Bourguignon, M. Moreau, G. Queguiner, and P. Pastour, *Bull. Soc. Chim. Fr.*, **1975**, 2483.
7) J. Bourguignon, E. Gougeon, G. Queguiner, and P. Pastour, *Bull. Soc. Chim. Fr.*, **1975**, 815.
8) M. Robba, P. Touzot, and R.M. Riquelme, *C.R. Acad. Sci.*, Paris, Ser. C, **276**, 93 (1973).
9) M.S. Manhas and S.D. Sharma, *J. Heterocycl. Chem.*, **8**, 1051 (1971).
10) M.S. Manhas, S.G. Amin, and B. Dayal, *J. Heterocycl. Chem.*, **13**, 633 (1976).