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Synthesis and Hypoglycemic Activity of 7,8-Dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine Derivatives and Related Compounds[1)]

SACHIO OHNO,* KIYOSHI MIZUKOSHI, OSAMU KOMATSU, YASUO KUNOH, YOSHIKI NAKAMURA, EIICHI KATOH, and MITSUAKI NAGASAKA

Research Laboratories, Maruko Seiyaku Co., Ltd., 1212 Teramae, Gejo-cho, Kasugai 486, Japan

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A series of 2-amino-7,8-dihydro-4-piperazinyl- and 4-amino-7,8-dihydro-2-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines and related compounds were synthesized and evaluated for hypoglycemic activity. Several compounds exhibited excellent activity, and 7,8-dihydro-2-(4-methylpiperazinyl)-4-(1-pyrrolidinyl)- (**8c**, dimaleate: MTP-1307) and 2-amino-7,8-dihydro-4-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidine (**18a**, dimaleate: MTP-1403) were selected for further investigation. Oral administration of **8c** and **18a** at 50 mg/kg markedly improved oral glucose tolerance in ob/ob mice. In this test, buformin also showed activity, whereas tolbutamide produced no significant improvement.

Keywords——6*H*-thiopyrano[3,2-*d*]pyrimidine; hypoglycemic activity; ob/ob mice; antidiabetic; tolbutamide; buformin; ciglitazone

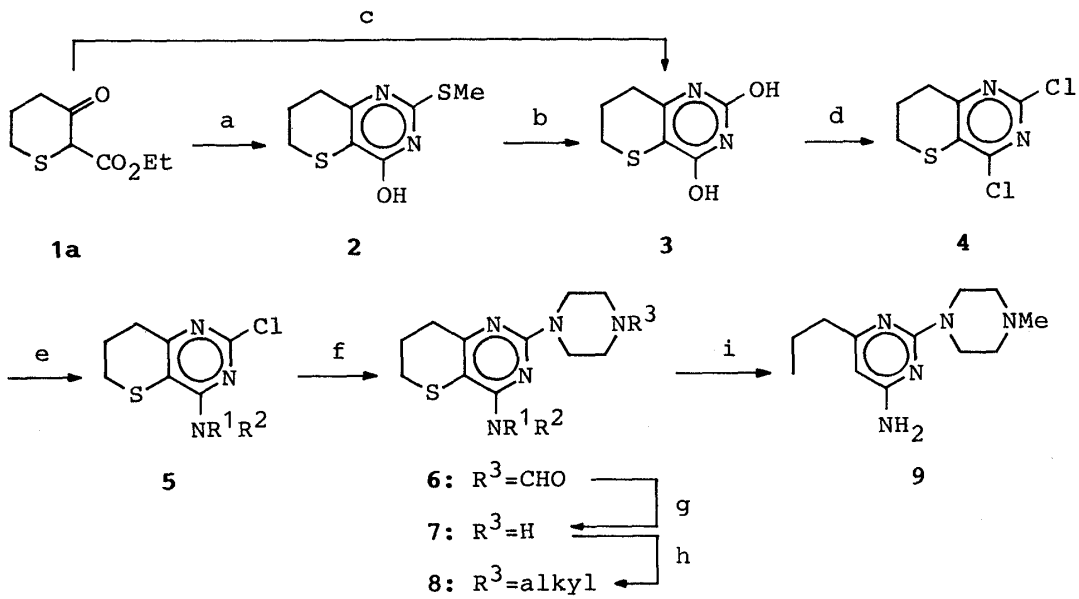
Oral hypoglycemic drugs for the therapy of non-insulin-dependent diabetes mellitus can be mainly classified into sulfonylureas, such as tolbutamide, and biguanides, such as buformin, from a structural point of view. The sulfonylureas and the biguanides have the risk of causing serious hypoglycemia[2)] and lactic acidosis,[3)] respectively. At present, these drugs are usually used only for treatment of patients whose blood glucose levels cannot be controlled by dietotherapy and kinesitherapy. Therefore, much effort has been made to find new antidiabetic drugs.[4)]

The thiopyrano[3,2-*d*]pyrimidine skeleton was reported in 1970, and it was claimed that some derivatives[5)] possess vasodilating activity.[6)] Since then no report on compounds with this skeleton has appeared.

We synthesized 2-amino-7,8-dihydro-4-piperazinyl- and 4-amino-7,8-dihydro-2-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidine derivatives, and found that some of them have excellent hypoglycemic activity. These derivatives differ structurally from the conventional antidiabetics. In this paper we describe the synthesis and the hypoglycemic activity of the 7,8-dihydrothiopyrano[3,2-*d*]pyrimidines and related compounds.

Chemistry

Cyclization of ethyl 3-oxotetrahydrothiopyran-2-carboxylate (**1a**)[7)] with *S*-methylisothiourea in methanol yielded 7,8-dihydro-4-hydroxy-2-methylthio-6*H*-thiopyrano[3,2-*d*]-pyrimidine (**2**), which was heated with aqueous acetic acid under reflux to afford the dihydroxypyrimidine (**3**) in high yield. The pyrimidine **3** was also directly obtained from **1a** and urea in low yield. Reaction of **3** with phosphorus oxychloride gave 2,4-dichloro-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine (**4**), which selectively reacted at the 4-position with amines, yielding the 4-amino-2-chloropyrimidines (**5**).[8)] Heating of **5** with piperazines afforded 4-amino-7,8-dihydro-2-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines (**6**, **7b—i**, **8a—h**). The formylpyrimidine **6** was hydrolyzed with hydrochloric acid to **7a**. The pyrimidines **8i—q** were prepared by reaction of **7** with alkyl halides or styrene oxide. Desulfurization of **8a** with



a) $H_2NC(=NH)SMe$, KOH/MeOH; b) AcOH-H_2O; c) $(H_2N)_2C=O$, NaOEt/EtOH; d) $POCl_3$, $PhNMe_2$; e) HNR^1R^2; f) HN⟨⟩NR^3; g) HCl/EtOH; h) R^3X, K_2CO_3/DMF or PhCH(O)CH_2; i) Raney-Ni/EtOH

Chart 1

TABLE I. 4-Amino-2-chloro-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidines (**5**)

No.	NR^1R^2	Yield (%)	mp (°C)	Recryst. solvent
5a	NH_2	90	196—197	EtOH
5b	NHMe	77	171—172	CH_2Cl_2–Et_2O
5c	NHPr	71	67—68	CH_2Cl_2–petr. ether
5d	NMe_2	82	55—57	Et_2O–petr. ether
5e	NEt_2	81	115—116	Et_2O–petr. ether
5f	NEtPr	69	Oil	
5g	N⟨⟩	73	75—76	AcOEt
5h	N⟨⟩	75	77—78	CH_2Cl_2–Et_2O
5i	N⟨⟩O	82	88—89	CH_2Cl_2–Et_2O
5j	$NHCH_2CH_2OH$	90	150—151	CH_2Cl_2–Et_2O

W-7 Raney nickel in ethanol afforded **9**.

The dichloropyrimidine **4** reacted with piperazines to give the 4-piperazinyl-2-chloropyrimidines (**10**),[8] which were treated with amines to yield 2-amino-7,8-dihydro-4-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines (**11**, **12b—d**, **f**, **g**, **13a—c**, **e—j**). Compounds **11a—e** were hydrolyzed with hydrochloric acid to **12a**, **e**, and **h—j**, respectively. Reaction of **12** with alkyl halides gave **13m—o**. Eschweiler–Clarke reaction of the 2-amino-4-piperazinylpyrimidines (**18a**, **19b**) gave **13d** and **k**, respectively. Reduction of **23c** with lithium aluminium hydride in tetrahydrofuran afforded **13l**.

Ethyl 4-chloropentanoate (**14a**)[10] and 4-chloro-2-methylbutanoate (**14b**)[10b,11] reacted with ethyl 2-mercaptoacetate to give the thioethers (**15**). Dieckmann reaction of **15a** and **b** afforded **1b** and **c**, respectively. The keto-carboxylates (**1**) were treated with guanidine in

TABLE II. 4-Amino-7,8-dihydro-2-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines (**6**—**8**)

No.	NR^1R^2	R^3	Salt[a]	Yield (%) SM[b]	mp (°C) (Recryst. solvent[c])	Formula	Analysis (%) Calcd (Found) C	H	N
6	NH_2	CHO	B	86	178—180	$C_{12}H_{17}N_5OS$	51.59	6.13	25.07
				5a	(D–I)		(51.83	6.24	25.14)
7a	NH_2	H	M	55	163—165	$C_{11}H_{17}N_5S\cdot$	45.50	5.43	13.96
				6	(M–I)	$2C_4H_4O_4\cdot H_2O$	(45.17	5.47	13.94)
7b	NHMe	H	M	61	172—174	$C_{12}H_{19}N_5S\cdot$	48.28	5.47	14.08
				5b	(E)	$2C_4H_4O_4$	(48.20	5.60	14.11)
7c	NHPr	H	F	65	182—184[d]	$C_{14}H_{23}N_5S\cdot$	50.27	5.95	13.33
				5c	(E–W)	$2C_4H_4O_4$	(50.30	6.02	13.26)
7d	NEt_2	H	H	63	210—219	$C_{15}H_{25}N_5S\cdot$	47.36	7.15	18.41
				5e	(M–R)	2HCl	(47.10	7.26	18.25)
7e	NEtPr	H	F	67	163—164	$C_{16}H_{27}N_5S\cdot$	53.79	7.22	15.68
				5f	(E–W)	$C_4H_4O_4\cdot 1/2\,H_2O$	(54.01	7.09	15.41)
7f		H	M	87	180—183	$C_{15}H_{23}N_5S\cdot$	51.39	5.81	13.03
				5g	(E–R)	$2C_4H_4O_4$	(51.30	5.45	13.22)
7g		H	H	85	228—230	$C_{16}H_{25}N_5S\cdot$	47.88	7.03	17.45
				5h	(E)	$2HCl\cdot 1/2\,H_2O$	(48.09	7.14	17.64)
7h		H	M	88	177—179	$C_{15}H_{23}N_5OS\cdot$	51.63	6.27	15.84
				5i	(E–W)	$C_4H_4O_4\cdot 1/4\,H_2O$	(51.86	6.48	15.57)
7i	$NHCH_2CH_2OH$	H	M	73	169—171	$C_{13}H_{21}N_5OS\cdot$	47.81	5.54	13.28
				5j	(M–R)	$2C_4H_4O_4$	(47.66	5.67	13.25)
8a	NH_2	Me	M	82	168—170	$C_{12}H_{19}N_5S\cdot$	48.28	5.47	14.08
				5a	(E)	$2C_4H_4O_4$	(48.19	5.47	13.98)
8b	NHMe	Me	M	80	176—178	$C_{13}H_{21}N_5S\cdot$	49.31	5.71	13.69
				5b	(M–A)	$2C_4H_4O_4$	(49.10	5.60	13.67)
8c		Me	M	68	189—191	$C_{16}H_{25}N_5S\cdot$	52.26	6.03	12.70
				5g	(E–R)	$2C_4H_4O_4$	(52.19	6.08	12.68)
8d		Me	M	68	165—168	$C_{17}H_{27}N_5S\cdot$	53.09	6.24	12.38
				5h	(E)	$2C_4H_4O_4$	(52.98	6.17	12.32)
8e		Me	M	70	164—169	$C_{16}H_{25}N_5OS\cdot$	50.78	5.86	12.34
				5i	(E–R)	$2C_4H_4O_4$	(51.04	5.97	12.41)
8f	$NHCH_2CH_2OH$	Me	M	67	168—170	$C_{14}H_{23}N_5OS\cdot$	48.79	5.77	12.93
				5j	(E–R)	$2C_4H_4O_4$	(48.78	5.77	12.78)
8g		CH_2CH_2OH	M	63	153—155	$C_{17}H_{27}N_5O_2S\cdot$	48.80	5.51	9.81
				5i	(M–R)	$3C_4H_4O_4$	(49.01	5.57	9.85)
8h	$NHCH_2CH_2OH$	Ph	M	65	172—174	$C_{19}H_{25}N_5OS\cdot$	56.66	6.00	14.36
				5j	(E–R)	$C_4H_4O_4$	(56.54	6.08	14.29)
8i	NMe_2	Pr	F	68	159—161	$C_{16}H_{27}N_5S\cdot$	54.90	7.14	16.01
				5d	(E–R)	$C_4H_4O_4$	(54.63	7.20	15.65)
8j	NMe_2	iso-Pr	F	55	198—201	$C_{16}H_{27}N_5S\cdot$	54.90	7.14	16.01
				5d	(E)	$C_4H_4O_4$	(54.66	7.39	15.76)
8k		CH_2Ph	H	82	240—243[d]	$C_{23}H_{31}N_5S\cdot$	56.20	6.97	14.25
				7g	(M–A)	$2HCl\cdot 1/2\,H_2O$	(56.30	7.12	14.10)
8l		CH_2Ph	M	80	195—197	$C_{22}H_{29}N_5OS\cdot$	59.19	6.30	13.27
				7h	(E–R)	$C_4H_4O_4$	(59.07	6.30	13.23)
8m	NHMe	$CH_2C_6H_4$-2-Cl	H	70	195—198	$C_{19}H_{24}ClN_5S\cdot$	46.58	5.97	14.30
				7b	(M–A)	$2HCl\cdot 3/2\,H_2O$	(46.45	6.03	14.34)
8n	NH_2	CH_2CH_2Ph	H	77	243—246[d]	$C_{19}H_{25}N_5S\cdot$	49.09	6.07	15.06
				7a	(M–L)	3HCl	(49.30	6.29	15.17)
8o	NH_2	$CH_2CH_2C_6H_4$-4-OMe	H	75	235—265[d]	$C_{20}H_{27}N_5OS\cdot$	51.39	6.47	14.98
				7a	(M–E)	$2HCl\cdot 1/2\,H_2O$	(51.15	6.36	14.94)
8p	NEt_2	$CH_2CH(OH)Ph$	B	60	91—93	$C_{23}H_{33}N_5OS$	64.60	7.78	16.38
				7d	(D–R)		(64.73	8.02	16.01)
8q		$CH_2CH(OH)Ph$	M	54	148—150	$C_{23}H_{31}N_5O_2S\cdot$	57.53	6.38	12.42
				7h	(M–R)	$C_4H_4O_4\cdot 1/3\,H_2O$	(57.60	6.30	12.50)

a) B, base; F, fumarate; H, hydrochloride; M, maleate. *b*) Starting material. *c*) A, Me_2CO; C, $CHCl_3$; D, CH_2Cl_2; E, EtOH; H, hexane; I, iso-PrOH; L, AcOEt; M, MeOH; P, petroleum ether; R, Et_2O; W, H_2O. *d*) Decomposition.

TABLE III. 2-Amino-7,8-dihydro-4-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines (**11**—**13**)

No.	NR^1R^2	R^3	Salt[a]	Yield (%) SM[b]	mp (°C) (Recryst. solvent[c])	Formula	Analysis (%) Calcd (Found) C	H	N
11a	NHMe	CHO	B	44	149—151	$C_{13}H_{19}N_5OS$	53.22	6.53	23.87
				10a	(L–H)		(53.09	6.57	23.99)
11b	NMe_2	CHO	B	53	132—133	$C_{14}H_{21}N_5OS$	54.70	6.89	22.78
				10a	(C–R)		(54.75	7.01	22.67)
11c		CHO	B	50	135—137	$C_{16}H_{23}N_5OS$	57.63	6.95	21.00
				10a	(L–H)		(57.78	7.15	20.56)
11d		CHO	B	52	103—105	$C_{17}H_{25}N_5OS$	58.76	7.25	20.15
				10a	(D–P)		(58.78	7.46	20.47)
11e		CHO	B	55	131—134	$C_{16}H_{23}N_5O_2S$	54.99	6.63	20.04
				10a	(D–P)		(54.61	6.71	19.86)
11f	NMe_2	COOEt	B	76	65—69	$C_{16}H_{25}N_5O_2S$	54.68	7.17	19.93
				10b	(H)		(54.97	7.30	19.99)
11g		COOEt	B	82	91—92	$C_{18}H_{27}N_5O_2S$	57.27	7.21	18.55
				10b	(D–P)		(56.98	7.35	18.27)
12a	NHMe	H	M	70	163—165	$C_{12}H_{19}N_5S \cdot$	47.42	5.57	13.83
				11a	(M–I)	$2C_4H_4O_4 \cdot 1/2\,H_2O$	(47.38	5.58	13.53)
12b	NHEt	H	F	67	148—150	$C_{13}H_{21}N_5S \cdot$	46.30	5.74	11.74
				10a	(W–E)	$5/2\,C_4H_4O_4 \cdot 3/2\,H_2O$	(46.44	6.02	12.06)
12c	NHPr	H	F	70	150—152	$C_{14}H_{23}N_5S \cdot$	48.61	6.12	12.88
				10a	(W–E)	$2C_4H_4O_4 \cdot H_2O$	(48.66	6.26	12.52)
12d	NH–iso-Pr	H	F	68	183—186	$C_{14}H_{23}N_5S \cdot$	49.47	6.44	14.42
				10a	(E–W)	$3/2\,C_4H_4O_4 \cdot H_2O$	(49.77	6.35	14.09)
12e	NMe_2	H	F	65	193—196	$C_{13}H_{21}N_5S \cdot$	51.63	6.37	17.71
				11b	(E–W)	$C_4H_4O_4$	(51.44	6.41	17.52)
12f	NEt_2	H	F	70	190—191	$C_{15}H_{25}N_5S \cdot$	53.31	6.95	16.36
				10a	(E)	$C_4H_4O_4 \cdot 1/4\,H_2O$	(53.13	6.96	16.07)
12g	NEtPr	H	F	68	173—175	$C_{16}H_{27}N_5S \cdot$	54.90	7.14	16.01
				10a	(M–R)	$C_4H_4O_4$	(54.69	7.32	15.70)
12h		H	F	82	166—169	$C_{15}H_{23}N_5S \cdot$	49.72	5.99	12.61
				11c	(E–W)	$2C_4H_4O_4 \cdot H_2O$	(49.81	5.93	12.52)
12i		H	M	80	198—200	$C_{16}H_{25}N_5S \cdot$	55.15	6.71	16.08
				11d	(M–W–I)	$C_4H_4O_4$	(54.80	6.75	16.29)
12j		H	M	86	202—204	$C_{15}H_{23}N_5OS \cdot$	52.16	6.22	16.01
				11e	(M–W)	$C_4H_4O_4$	(51.99	6.29	16.26)
13a	NHMe	Me	F	78	202—207[d]	$C_{13}H_{21}N_5S \cdot$	49.31	5.71	13.69
				10c	(M–E)	$2C_4H_4O_4$	(49.51	5.74	13.65)
13b	NHEt	Me	F	71	231—236[d]	$C_{14}H_{23}N_5S \cdot$	50.73	6.31	14.79
				10c	(W–E)	$3/2\,C_4H_4O_4 \cdot 1/3\,H_2O$	(50.82	6.21	14.81)
13c	NH–iso-Pr	Me	M	73	194—206[d]	$C_{15}H_{25}N_5S \cdot$	51.20	6.16	12.98
				10c	(W–E)	$2C_4H_4O_4$	(51.33	6.19	13.07)
13d	NMe_2	Me	M	78	143—144	$C_{14}H_{23}N_5S \cdot$	49.43	6.03	13.10
				18a	(E–I)	$2C_4H_4O_4 \cdot 1/2\,H_2O$	(49.21	6.11	13.03)
13e	NEt_2	Me	F	76	161—163	$C_{16}H_{27}N_5S \cdot$	51.65	6.41	12.55
				10c	(W–E)	$2C_4H_4O_4 \cdot 1/4\,H_2O$	(51.79	6.42	12.21)
13f	NEtPr	Me	F	79	148—152	$C_{17}H_{29}N_5S \cdot$	52.07	6.64	12.14
				10c	(W–E)	$2C_4H_4O_4 \cdot 1/2\,H_2O$	(52.39	6.49	12.40)
13g		Me	F	83	143—146	$C_{16}H_{25}N_5S \cdot$	50.43	5.84	10.14
				10c	(E)	$3C_4H_4O_4 \cdot 1/2\,C_2H_6O$	(50.37	5.86	10.14)
13h		Me	H	78	226—232[d]	$C_{17}H_{27}N_5S \cdot$	49.51	7.25	16.98
				10c	(M–A–R)	$2HCl \cdot 1/3\,H_2O$	(49.79	7.48	16.77)

TABLE III. (continued)

No.	NR^1R^2	R^3	Salt[a]	Yield (%) SM[b]	mp (°C) (Recryst. solvent[c])	Formula	Analysis (%) Calcd (Found) C	H	N
13i		Me	M	67	150—151	$C_{16}H_{25}N_5OS\cdot$	49.99	5.94	12.15
				10c	(M–I)	$2C_4H_4O_4\cdot 1/2\,H_2O$	(49.97	6.04	12.10)
13j	$NHCH_2CH_2OH$	Me	M	68	179—182	$C_{14}H_{23}N_5OS\cdot$	49.68	6.05	14.48
				10c	(M–I)	$3/2\,C_4H_4O_4\cdot H_2O$	(49.84	6.22	14.17)
13k	NMe_2	Et	F	90	175—176	$C_{15}H_{25}N_5S\cdot$	53.88	6.90	16.54
				19b	(E–R)	$C_4H_4O_4$	(53.81	6.99	16.41)
13l	NHPr	Pr	F	32	171—181[d]	$C_{17}H_{29}N_5S\cdot$	52.07	6.64	12.14
				23c	(E–W)	$2C_4H_4O_4\cdot 1/2\,H_2O$	(51.87	6.41	12.19)
13m	NEtPr	iso-Pr	F	66	156—159	$C_{19}H_{33}N_5S\cdot$	55.85	7.31	13.03
				12g	(M–R)	$3/2\,C_4H_4O_4$	(56.19	7.51	12.91)
13n	NMe_2	CH_2Ph	H	85	199—205	$C_{20}H_{27}N_5S\cdot$	50.20	6.95	14.64
				12e	(A–M)	$2HCl\cdot 2H_2O$	(50.33	6.93	14.70)
13o		CH_2Ph	H	84	193—195	$C_{22}H_{29}N_5S\cdot$	54.31	6.84	14.40
				12h	(A–M)	$2HCl\cdot H_2O$	(53.99	6.93	14.23)

a—d) See footnotes *a—d* in Table II.

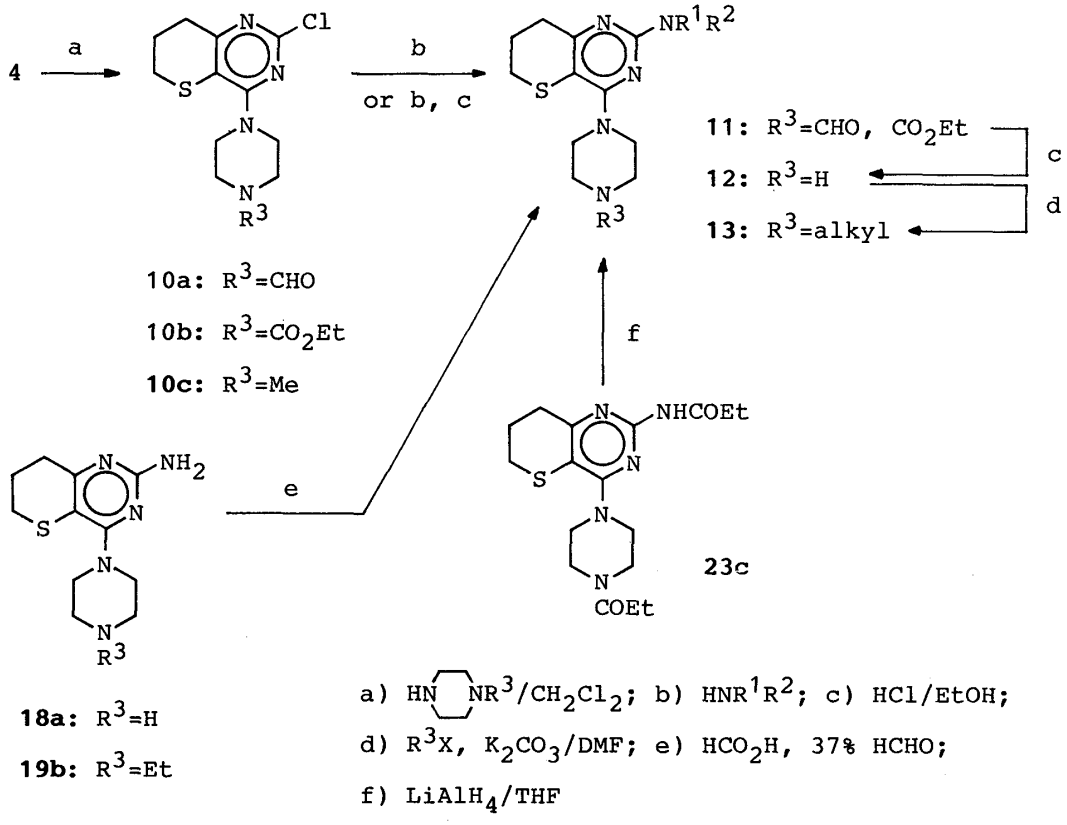
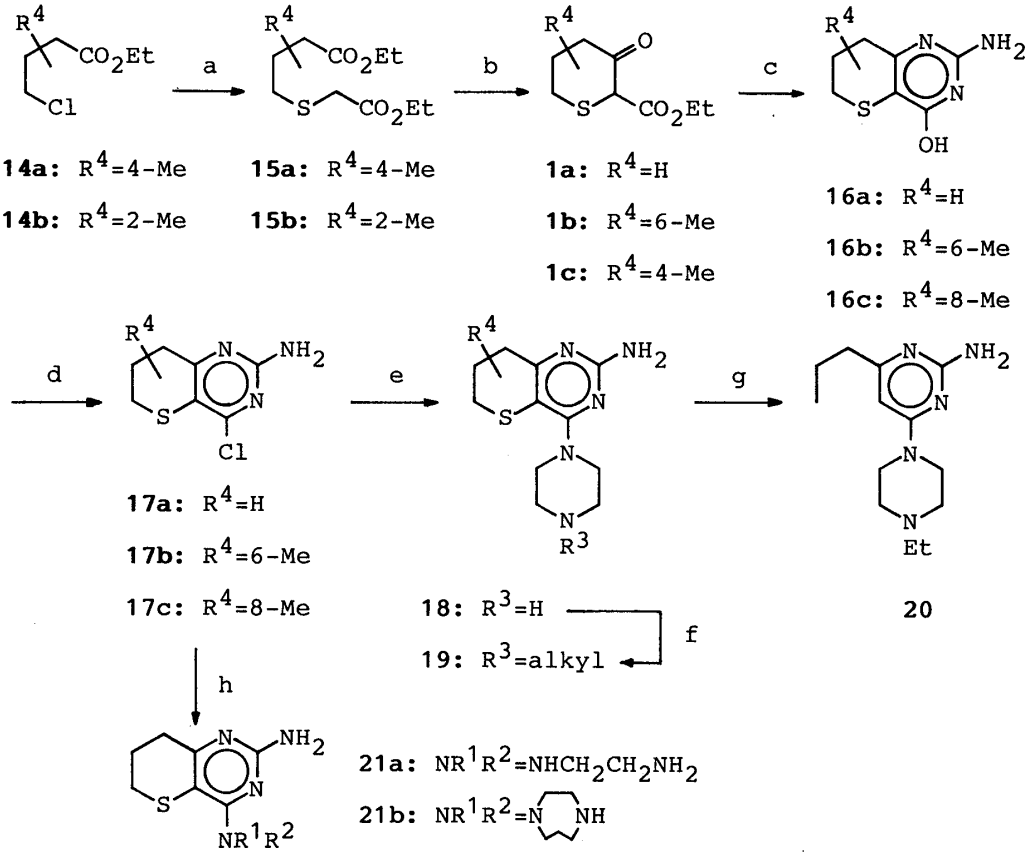


Chart 2

ethanol to afford the 2-amino-4-hydroxypyrimidines (**16**), which were heated with phosphorus oxychloride to give **17**. Treatment of **17** with the piperazines gave **18** and **19a**. Alkylation of **18a** with alkyl halides afforded compounds **19b—e**. Desulfurization of **18a** with W-7 Raney nickel in ethanol unexpectedly gave the 4-ethylpiperazinylpyrimidine (**20**). The pyrimidines **21**



a) $HSCH_2CO_2Et$, NaOEt/EtOH; b) NaOEt/C_6H_6; c) $(H_2N)_2C{=}NH$, NaOEt/EtOH; d) $POCl_3$, $PhNMe_2$; e) HN NR3; f) R^3X, K_2CO_3/DMF; g) Raney-Ni/EtOH; h) HNR^1R^2

Chart 3

were obtained by reaction of **17a** with ethylenediamine or homopiperazine.

Some derivatives of **18a** were synthesized as follows. Treatment of **18a** with acid anhydrides gave **22**. Heating of **18a** with acid anhydrides yielded **23**. The triacetylpyrimidine (**24**), prepared from **18a** or **23b** by refluxing in acetic anhydride, was oxidized with 3-chloroperbenzoic acid to give **25** and subsequent alkaline hydrolysis afforded the 5-oxide (**26a**) and the 5,5-dioxide (**26b**).

The thiopyrano[3,2-*d*]pyrimidines (**28**, **31**) with other groups instead of the amino group were prepared in the following manner. Treatment of **4** with sodium methoxide in methanol and dichloromethane gave **27**, which was heated with piperazines to afford **28a**—**c**. Reaction of **28a** with benzyl bromide in dimethylformamide gave **28d**. Cyclization of **1a** with formamidine in methanol gave **29**. The hydroxypyrimidines (**2**, **29**) were treated with phosphorus oxychloride to afford the chlorides (**30**), which reacted with piperazine, giving **31b** and **c**. Reaction of **10a** with sodium acetate in acetic acid gave the acetoxypyrimidine (**31a**), which was treated with hydrochloric acid to afford **31d**. The methoxy derivative (**31e**) was also obtained by reaction of **10a** with sodium methoxide followed by hydrolysis.

The pyrimidines **35** with other condensed rings instead of the condensed thiopyran ring were prepared as follows. Reaction of the keto-carboxylates (**32**) with guanidine in ethanol gave **33a**, **b**, and **d**. The hydroxypyrimidines (**33**)[12] were treated with phosphorus oxychloride to afford the chloropyrimidines (**34**),[13] which reacted with piperazines to give **35a** and **c**—**e**. Treatment of **35a** with hydrochloric acid afforded **35b**.

TABLE IV. 2-Amino-7,8-dihydro-4-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines (**18**, **19**)

No.	R^3	R^4	Salt[a]	Yield (%) SM[b]	mp (°C) (Recryst. solvent[c])	Formula	Analysis (%) Calcd (Found) C	H	N
18a	H	H	M	79	191—192[d]	$C_{11}H_{17}N_5S \cdot 2C_4H_4O_4$	47.20	5.21	14.49
				17a	(E–R)		(47.24	5.28	14.25)
18b	H	6-Me	F	82	192—195	$C_{12}H_{19}N_5S \cdot 2C_4H_4O_4 \cdot 1/2\,H_2O$	47.42	5.57	13.83
				17b	(M)		(47.42	5.27	13.51)
18c	H	8-Me	F	85	188—191	$C_{12}H_{19}N_5S \cdot 2C_4H_4O_4 \cdot H_2O$	46.60	5.67	13.58
				17c	(E–W)		(46.33	5.91	13.43)
19a	Me	H	M	75	183—185	$C_{12}H_{19}N_5S \cdot 2C_4H_4O_4 \cdot 3/2\,H_2O$	45.80	5.76	13.35
				17a	(W–M)		(45.93	5.63	13.29)
19b	Et	H	F	75	210—217[d]	$C_{13}H_{21}N_5S \cdot 3/2\,C_4H_4O_4 \cdot H_2O$	48.40	6.20	14.85
				18a	(W–E)		(48.65	6.14	14.98)
19c	Pr	H	F	78	205—208	$C_{14}H_{23}N_5S \cdot 2C_4H_4O_4$	50.28	5.95	13.33
				18a	(M)		(50.18	6.08	13.63)
19d	iso-Pr	H	F	60	211—215	$C_{14}H_{23}N_5S \cdot 3/2\,C_4H_4O_4 \cdot 2H_2O$	47.70	6.61	13.91
				18a	(E–W)		(47.90	6.36	13.56)
19e	CH_2Ph	H	B	83	156—157	$C_{18}H_{23}N_5S$	63.31	6.79	20.51
				18a	(D–R)		(63.69	6.85	20.55)

a—*d*) See footnotes *a*—*d* in Table II.

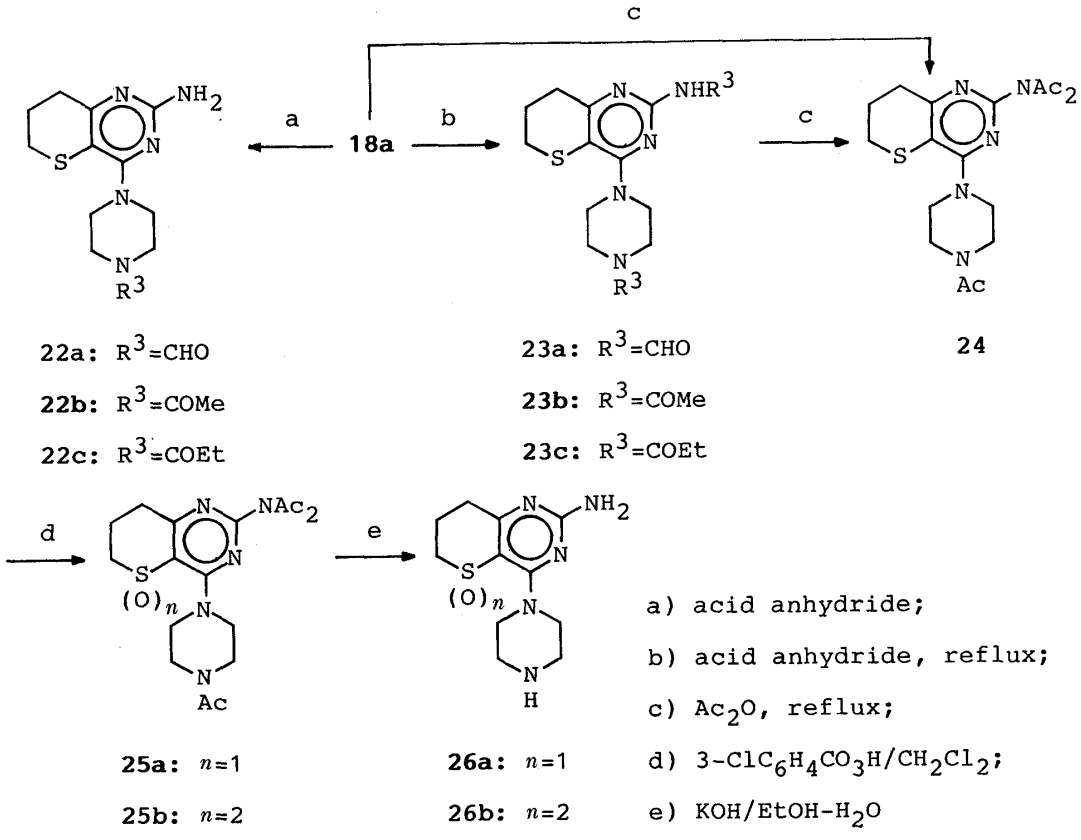
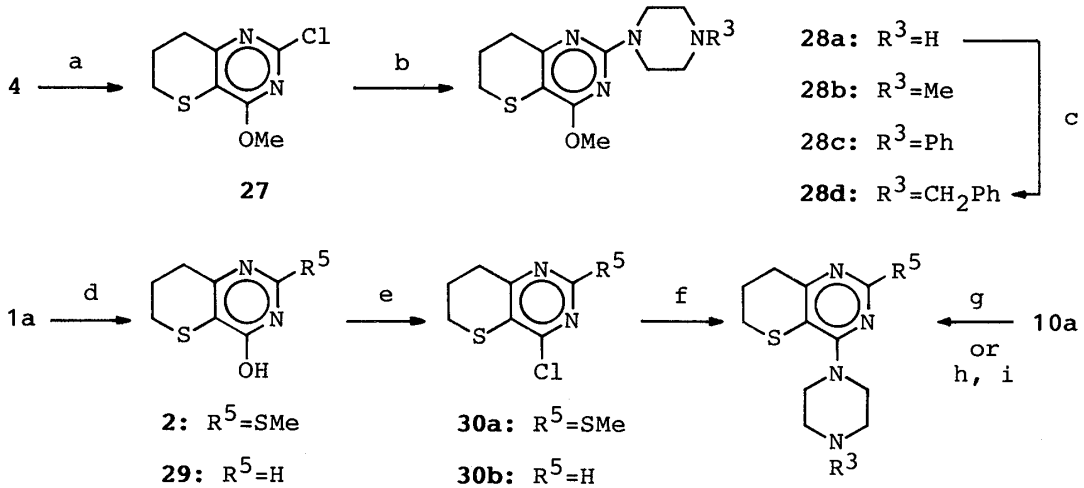


Chart 4

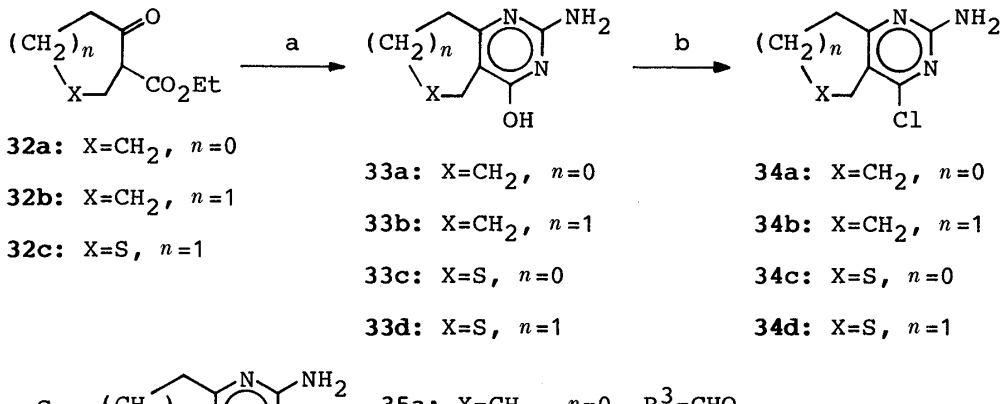
Pharmacology

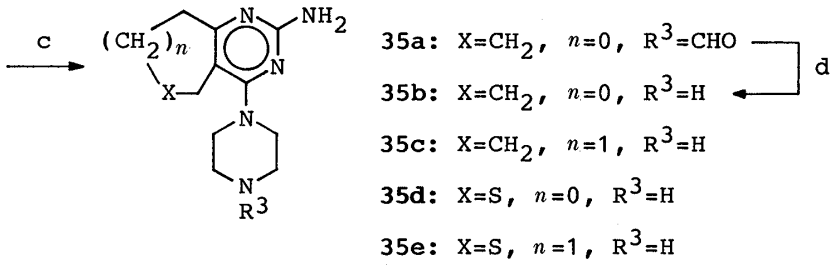
Screening for hypoglycemic activity was carried out by using the oral glucose tolerance test in ob/ob mice (C57BL/6J-ob/ob). The test drugs were administered orally at 50 mg/kg



a) $NaOMe/MeOH\text{-}CH_2Cl_2$; b) HN NR3/$C_6H_6$; c) $PhCH_2Br$, K_2CO_3/DMF; d) $H_2NC(=NH)R^5$, KOH/MeOH; e) $POCl_3$, $PhNMe_2$; f) HN NH/C_6H_6; g) NaOAc/AcOH; h) NaOMe/MeOH; i) HCl/MeOH

Chart 5





a) 1) $(H_2N)_2C{=}NH$, HCl/EtOH, 2) 5% NaOH, 3) AcOH; b) $POCl_3$, $PhNMe_2$; c) HN NR3; d) HCl/EtOH

Chart 6

0.5 h prior to oral loading of glucose. The results are summarized in Table VI.

In the series of 4-amino-7,8-dihydro-2-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines, **7a** and **8c** exhibited potent hypoglycemic activity, and **7b**, **c**, **f**, **h**, **8n**, **o**, and **q** showed moderate

TABLE V. 7,8-Dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidines (**21**, **28**, **31**) and Related Compounds (**35**)

No.	Salt[a]	Yield (%) SM[b]	mp (°C) (Recryst. solvent[c])	Formula	Analysis (%) Calcd (Found)		
					C	H	N
21a	M	58	187—190	$C_9H_{15}N_5S \cdot 2C_4H_4O_4$	44.63	5.07	15.31
		17a	(E)		(44.80	5.19	15.10)
21b	M	65	175—177	$C_{12}H_{19}N_5S \cdot 2C_4H_4O_4 \cdot H_2O$	46.60	5.67	13.58
		17a	(M–W)		(46.50	5.62	13.55)
28a	M	77	183—187	$C_{12}H_{18}N_4OS \cdot C_4H_4O_4$	50.25	5.80	14.65
		27	(E–R)		(50.38	5.86	14.32)
28b	M	81	169—171	$C_{13}H_{20}N_4OS \cdot C_4H_4O_4$	51.50	6.10	14.13
		27	(M–R)		(51.35	6.15	13.83)
28c	B	73	99—101	$C_{18}H_{22}N_4OS$	63.13	6.48	16.36
		27	(D–H)		(63.25	6.84	16.11)
28d	H	83	235—240[d]	$C_{19}H_{24}N_4OS \cdot HCl$	58.08	6.41	14.26
		28a	(M–A)		(57.94	6.56	14.05)
31a	B	68	131—135	$C_{14}H_{18}N_4O_3S$	52.16	5.63	17.38
		10a	(D–R)		(52.45	5.58	17.20)
31b	M	72	196—198	$C_{12}H_{18}N_4S_2 \cdot C_4H_4O_4$	48.22	5.56	14.06
		30a	(M–W)		(48.29	5.64	13.86)
31c	F	73	180—182[d]	$C_{11}H_{16}N_4S \cdot 2C_4H_4O_4 \cdot 1/2H_2O$	47.79	5.28	11.73
		30b	(M)		(48.06	5.52	12.10)
31d	F	61	175—180[d]	$C_{11}H_{16}N_4OS \cdot 3/2C_4H_4O_4 \cdot H_2O$	45.94	5.44	12.61
		31a	(E)		(46.14	5.07	12.35)
31e	F	43	150—156[d]	$C_{12}H_{18}N_4OS \cdot 3/2C_4H_4O_4 \cdot 1/3H_2O$	48.43	5.57	12.55
		10a	(W–M)		(48.61	5.84	12.02)
35a	B	84	210—216[d]	$C_{12}H_{17}N_5O$	58.28	6.93	28.32
		34a	(C–R)		(57.97	6.99	28.55)
35b	F	75	240—255[d]	$C_{11}H_{17}N_5 \cdot C_4H_4O_4 \cdot 1/2H_2O$	52.32	6.44	20.34
		35a	(E–W)		(52.17	6.40	20.28)
35c	M	87	242—244[d]	$C_{12}H_{19}N_5 \cdot 2C_4H_4O_4 \cdot H_2O$	49.69	6.05	14.49
		34b	(M–W)		(49.47	5.92	14.54)
35d	M	75	158—162[d]	$C_{10}H_{15}N_5S \cdot 2C_4H_4O_4$	46.05	4.94	14.92
		34c	(E)		(45.87	5.01	14.80)
35e	M	60	178—180	$C_{11}H_{17}N_5S \cdot 2C_4H_4O_4$	47.20	5.21	14.49
		34d	(E–W)		(47.03	5.31	14.40)

a—*d*) See footnotes *a*—*d* in Table II.

activity. Compared with the activity of **7a**, the methylated compound **8a** was unexpectedly weakly active. The pyrimidines **28a**, **b**, and **d** having a methoxy group instead of the 4-amino group were highly toxic, and **28c** exhibited no activity.

In the series of 2-amino-7,8-dihydro-4-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines, **12a**, **b**, **e**, **13a**, **b**, **d**, and **18a** showed excellent activity, but **12a**, **b**, **e**, and **13b** were relatively toxic. The pyrimidine **12i** was moderately active. The pyrimidines **18b** and **c** with a methyl group on the thiopyran ring of **18a** were weakly active. Substitution of the 2-amino group of **18a** with alkyl groups (**12a**—**g**, **i**) and conversion of the methyl groups of **13a** and **d** into larger alkyl groups (**13b**, **c**, **e**, **f**, **k**—**m**) tended to increase the toxicity. Introduction of acyl groups (**11f**, **22a**—**c**, **23a**, **c**) and oxidation of the sulfur atom (**26a**, **b**) caused disappearance of the activity. The activities of **21a** and **b** were low. The pyrimidines **31b**—**e** with other groups instead of the 2-amino group of **18a** showed weak activity. The activities of **35b**—**e** with other condensed rings instead of the thiopyran ring were low.

In this screening test, buformin hydrochloride[14] and tolbutamide were weakly active and

TABLE VI. Hypoglycemic Activity of 7,8-Dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidines and Related Compounds in Glucose-Loaded ob/ob Mice

No.	Salt[a]	Reduction in blood glucose (%)[b]	LD_{50} or mortality (mice, mg/kg, *p.o.*)	No.	Salt[a]	Reduction in blood glucose (%)[b]	LD_{50} or mortality (mice, mg/kg, *p.o.*)
7a	M	75	820	**13h**	H		500 (2/2)
7b	M	60	580	**13i**	M	29	1470
7c	F	60	500 (0/2), 1000 (2/2)	**13j**	M	12	1000 (0/2)
7d	H		280	**13k**	F		500 (1/3), 1000 (2/2)
7e	F		500 (1/2), 1000 (2/2)	**13l**	F		250 (2/2)
7f	M	68	1170	**13m**	F		500 (1/2), 1000 (2/2)
7g	H	31	500 (1/2), 1000 (2/2)	**13n**	H	23	
7h	M	58	960	**13o**	H	27	
7i	M	50	1200	**18a**	M	71	1400
8a	M	31	1450	**18b**	F	45	500 (2/2), 1000 (2/2)
8b	M	49	1000 (0/2)	**18c**	F	41	500 (0/2), 1000 (1/2)
8c	M	76	1250	**19a**	M	38	1730
8d	M	34	1000 (1/2)	**19b**	F	26	500 (0/2), 1000 (1/2)
8e	M	8	1580	**19c**	F		500 (2/2)
8f	M	15	2000	**19d**	F	16	500 (0/2), 1000 (2/2)
8g	M	34	1100	**19e**	B	35	500 (2/2)
8h	M	0	1820	**20**	M		500 (1/2), 1000 (2/2)
8i	F		500 (2/2)	**21a**	M	8	1000 (0/2), 2000 (1/2)
8j	F		500 (2/2)	**21b**	M	32	500 (0/2), 1000 (1/2)
8l	M	30	1850	**22a**	B	0	500 (0/2), 1000 (2/2)
8m	H	51	1000 (0/2)	**22b**	B	2	1000 (0/2)
8n	H	61	1500 (2/2)	**22c**	B	0	1000 (0/2)
8o	H	57	500 (0/2), 1000 (2/2)	**23a**	B	12	500 (0/2), 1000 (1/2)
8q	M	62	580	**23b**	B		500 (1/2), 1000 (1/2)
9	B		200 (2/2)	**23c**	B	0	500 (0/2), 1000 (2/2)
11f	B	18	500 (0/2), 1000 (2/2)	**26a**	B	0	100 (0/2)
12a	M	84	500 (0/2), 750 (2/2)	**26b**	B	0	1000 (0/2)
12b	F	77	500 (0/2), 750 (2/2)	**28a**	M		200
12c	F		500 (2/2)	**28b**	M		320
12d	F		500 (2/2)	**28c**	B	13	1470
12e	F	88	500 (4/4)	**28d**	H		450
12f	F		500 (2/2)	**31b**	M	34	88
12g	F		500 (2/2)	**31c**	F	46	500 (2/2)
12h	F	15		**31d**	F	12	500 (2/2)
12i	M	66	500 (2/2), 1000 (2/2)	**31e**	F	37	500 (1/2), 1000 (2/2)
12j	M	31		**35b**	F	30	1000 (0/2)
13a	F	77	1000 (1/2), 1500 (2/2)	**35c**	M	41	500 (0/2), 1000 (2/2)
13b	F	88	500 (0/2), 750 (2/2)	**35d**	M	54	500 (0/3), 1000 (1/2)
13c	M	26	500 (1/2), 1000 (2/2)	**35e**	M	32	1000 (0/2)
13d	M	82	1000 (0/2), 1500 (1/2)	Buformin[c]		39	380
13e	F		500 (2/2)	Tolbutamide		10	>3000
13f	F	44	500 (0/2), 1000 (2/2)	Ciglitazone		20[d]	
13g	F	17	1000 (0/2)				

a) See footnote *a* in Table II. *b*) The reduction in blood glucose was calculated by means of the formula reduction (%) = $100(A-B)/A$. The symbols A and B represent the differences between maximum blood glucose levels and the initial levels in control mice and in treated mice, respectively. Test samples were administered orally at 50 mg/kg 30 min before oral loading of glucose at 4 g/kg. *c*) Hydrochloride. *d*) 100 mg/kg, *p.o.*

inactive, respectively. Ciglitazone[4d] showed no activity even at 100 mg/kg.

The effects of **8c**, **18a**, tolbutamide, and buformin on glucose tolerance in ob/ob mice are shown in Table VII. Oral administration of **8c** and **18a** at 50 mg/kg markedly improved glucose tolerance. Buformin also showed activity, whereas tolbutamide produced no signi-

TABLE VII. Effects of **8c**, **18a**, Tolbutamide, and Buformin Administered Orally at 50 mg/kg on Oral Glucose Tolerance in ob/ob Mice[a]

Compound	n[b]	Blood glucose concentration (mg/dl)				
		Pretreatment values		Post-treatment values		
		−30	0	30	60	120 (min)
Control	5	244.9±25.4	270.5±27.2	571.9±23.8	500.8±45.9	288.0±43.8
8c	5	262.8±28.2	220.8±44.8	305.0±35.4[c]	246.0±57.8[d]	158.6±16.9[e]
Control	6	170.8±11.3	256.9±15.6	555.5±53.6	467.5±72.0	262.2±57.0
18a	6	161.8±19.7	129.4± 9.9[c]	243.1±44.9[d]	213.0±36.2[e]	109.7± 9.0[e]
Control	6	172.4±10.5	251.1±15.1	510.6±49.5	465.8±61.2	264.9±55.3
Tolbutamide	6	195.0±13.7	181.7±16.9[e]	406.6±36.2	298.6±51.2	165.3±62.9
Control	3	231.5±48.9	248.3±48.0	546.1±56.0	475.5±92.0	329.9±73.9
Buformin	3	189.0±34.8	179.4±35.3	310.9±58.6[e]	275.2±23.3	194.0±30.2

a) The values are the means±standard error. Statistical analysis was performed by using Student's *t*-test to evaluate the significance of differences from the control values. *b*) Number of animals. *c*) $p<0.001$. *d*) $p<0.01$. *e*) $p<0.05$.

ficant improvement.

The thiopyrano[3,2-*d*]pyrimidines (**8c**, **18a**) are structurally unrelated to the conventional antidiabetics and exhibit excellent antidiabetic activities.[15,16] For example,[15] **8c** (dimaleate) lowered blood glucose levels in fasted ob/ob mice and mild alloxan-diabetic rats at 25 and 100 mg/kg, respectively, but tolbutamide did not at 50 mg/kg. Furthermore, **8c** significantly improved glucose tolerance in normal rats, genetically diabetic KK mice, and ob/ob mice even at 10, 15, and 12.5 mg/kg, respectively. On the other hand, tolbutamide improved glucose tolerance in normal rats at 10 mg/kg, but did not in KK mice and ob/ob mice at 150 and 50 mg/kg, respectively. In addition, tolbutamide reduced blood glucose in normal rats and mice at 10 and 50 mg/kg, respectively, but **8c** did not even at 100 mg/kg, in spite of its potent hypoglycemic activities in other animal models. Successive treatment with **8c** at 300 mg/kg did not increase blood lactate levels in rats and mice, in contrast with buformin at 100 mg/kg.

We have selected **8c** (dimaleate: MTP-1307) and **18a** (dimaleate: MTP-1403) for further investigation, which is in progress.

Experimental

All melting points were determined on a Yanagimoto MP-S3 apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a Hitachi R-90H or JEOL PMX-60 spectrometer with tetramethylsilane as an internal standard. Column chromatography was carried out on Wakogel C-200 or activated alumina (about 300 mesh). All acid salts were prepared in the usual way.

7,8-Dihydro-4-hydroxy-2-methylthio-6*H*-thiopyrano[3,2-*d*]pyrimidine (2)——Ethyl 3-oxotetrahydrothiopyran-2-carboxylate (**1a**,[7] 20 g) and then *S*-methylisothiourea hydrobromide (20 g) were added to a solution of KOH (9 g) in MeOH (120 ml) with stirring. After being stirred for 2 h, the reaction mixture was poured into ice water, followed by acidification with AcOH. The resulting precipitate was filtered off, washed with H_2O, and recrystallized from AcOH to give colorless needles (20.5 g), mp 243—248 °C. ^{1}H-NMR [dimethyl sulfoxide-d_6 (DMSO-d_6)] δ: 1.85—2.18 (2H, m), 2.32—2.71 [5H, m, 2.45 (3H, s)], 2.76—3.00 (2H, m). *Anal.* Calcd for $C_8H_{10}N_2OS_2$: C, 44.84; H, 4.70; N, 13.07. Found: C, 44.80; H, 4.78; N, 12.88.

7,8-Dihydro-2,4-dihydroxy-6*H*-thiopyrano[3,2-*d*]pyrimidine (3)——a) A mixture of **2** (24 g), AcOH (120 ml), and H_2O (70 ml) was refluxed for 50 h. After cooling, the precipitate was filtered off and recrystallized from *N*,*N*-dimethylformamide (DMF) to give colorless plates (19 g), mp >300 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.80—2.23 (2H, m), 2.30—2.67 (2H, m), 2.70—3.00 (2H, m), 10.84 (1H, br), 11.50 (1H, br). *Anal.* Calcd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.38; N, 15.21. Found: C, 45.62; H, 4.46; N, 15.02.

b) Compound **1a** (3.8 g) and then urea (2.5 g) were added to a solution of NaOEt, prepared from Na (0.5 g) and EtOH (50 ml), with stirring. After being stirred for 2 h, the whole was heated at 70—80 °C for 1 h. The reaction

mixture was poured into ice water, followed by acidification with AcOH. The resulting precipitate was filtered off and recrystallized from DMF to give colorless plates (0.1 g), mp >300 °C.

2,4-Dichloro-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine (4)——A mixture of **3** (6.0 g), $POCl_3$ (15 ml), and *N*,*N*-dimethylaniline (1 ml) was refluxed for 3 h. After cooling, the reaction mixture was poured onto ice, followed by extraction with CH_2Cl_2. The extract was washed with H_2O and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from CH_2Cl_2–hexane to give colorless prisms (6.2 g), mp 108—110 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.07—2.60 (2H, m), 2.78—3.37 (4H, m).

4-Amino-2-chloro-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidines (5)——a) 4-Amino-2-chloro-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine (**5a**): A mixture of **4** (22 g), conc. NH_4OH (70 ml), and EtOH (50 ml) was heated at about 90 °C for 6 h in a sealed tube. The reaction mixture was concentrated *in vacuo*. The residue was recrystallized from EtOH to give colorless prisms (18 g). ^{1}H-NMR ($CDCl_3$) δ: 2.06—2.40 (2H, m), 2.68—3.18 (4H, m), 5.59 (2H, br).

b) 2-Chloro-7,8-dihydro-4-methylamino-6*H*-thiopyrano[3,2-*d*]pyrimidine (**5b**): Aqueous 40% methylamine (17 ml) was added to a solution of **4** (20 g) in tetrahydrofuran (THF) (100 ml) with stirring. After being stirred for 5 h, the reaction mixture was poured into H_2O, followed by extraction with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from CH_2Cl_2–Et_2O to give colorless prisms (15 g). ^{1}H-NMR ($CDCl_3$) δ: 1.93—2.47 (2H, m), 2.53—3.20 (7H, m), 4.67—5.07 (1H, m).

c) 2-Chloro-7,8-dihydro-4-(1-pyrrolidinyl)-6*H*-thiopyrano[3,2-*d*]pyrimidine (**5g**): Pyrrolidine (20 ml) was added dropwise to a solution of **4** (20 g) in CH_2Cl_2 (80 ml) with stirring at 0—10 °C. After being stirred for 3 h, the reaction mixture was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was recrystallized from AcOEt to give colorless prisms (17 g). ^{1}H-NMR ($CDCl_3$) δ: 1.50—2.43 (6H, m), 2.50—3.10 (4H, m), 3.53—4.03 (4H, m).

The chlorides (**5c**—**f**, **h**—**j**) were prepared in the same manner as described for **5g**.

4-Amino-7,8-dihydro-2-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines (6, 7, 8)——a) 4-Amino-7,8-dihydro-2-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidine (**7a**): A mixture of **6** (10 g), conc. HCl (50 ml), and EtOH (20 ml) was heated at about 80 °C for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in H_2O. The solution was made alkaline with K_2CO_3 and extracted with CH_2Cl_2. The extract was washed with H_2O, and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from AcOEt–hexane to give colorless needles (5.4 g), mp 115—117 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.98—2.32 (2H, m), 2.32—2.53 (8H, m), 3.53—3.83 (4H, m), 4.72 (2H, br).

b) 7,8-Dihydro-4-(1-morpholinyl)-2-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidine (**7h**): A mixture of **5i** (10 g), piperazine (30 g), and EtOH (100 ml) was heated at 70—80 °C for 5 h. The reaction mixture was concentrated and the residue was dissolved in CH_2Cl_2. The solution was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was washed with Et_2O to give colorless needles (11 g), mp 103—107 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.93—2.33 (2H, m), 2.53—3.02 (8H, m), 3.17—3.50 (4H, m), 3.52—3.87 (8H, m).

c) 2-[4-(2-Chlorobenzyl)piperazinyl]-7,8-dihydro-4-methylamino-6*H*-thiopyrano[3,2-*d*]pyrimidine (**8m**): 2-Chlorobenzyl chloride (4.0 g) was added dropwise to a mixture of **7b** (2.0 g), K_2CO_3, and DMF (50 ml) with stirring. The mixture was heated at about 40 °C for 1 h. After addition of AcOEt and H_2O, the reaction mixture was made acidic with 10% HCl. The aqueous layer was separated, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was recrystallized from CH_2Cl_2–Et_2O to give colorless needles (2.2 g), mp 82—85 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.36 (2H, m), 2.42—3.08 (8H, m), 2.93 (3H, d, J=4.8 Hz), 3.60—3.95 (4H, m), 3.64 (2H, s), 4.60 (1H, br), 7.07—7.65 (4H, m).

d) 7,8-Dihydro-2-[4-(2-hydroxy-2-phenylethyl)piperazinyl]-4-(1-morpholinyl)-6*H*-thiopyrano[3,2-*d*]pyrimidine (**8q**): A mixture of **7h** (5.0 g), styrene oxide (8.0 g), and benzene (50 ml) was refluxed for 5 h. The reaction mixture was concentrated *in vacuo*. The residual oil was crystallized with hexane to give colorless crystals (4.1 g), mp 155—157 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.94—2.99 (12H, m), 3.24—3.47 (4H, m), 3.55—3.90 (8H, m), 4.74 (1H, t, J=7.1 Hz), 7.14—7.42 (5H, m).

The pyrimidines **6**, **7b**—**g**, **i**, and **8a**—**h** were prepared in the same manner as described for **7h**, while **8i**—**l**, **n**, and **o** were prepared as described for **8m**, and **8p** was prepared as described for **8q**.

4-Amino-2-(4-methylpiperazinyl)-6-propylpyrimidine (9)——A mixture of **8a** (7.6 g), W-7 Raney nickel [prepared from Raney nickel alloy (85 g)], and EtOH (230 ml) was refluxed for 3.5 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed on a silica gel column with EtOH–hexane (3 : 1). The product was recrystallized from hexane to give colorless prisms (1.4 g), mp 76—80 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, t, J=6.9 Hz), 1.61 (2H, m), 2.18—2.52 [9H, m, 2.31 (3H, s)], 3.68—3.88 (4H, m), 4.51 (2H, br), 5.61 (1H, s). *Anal.* Calcd for $C_{12}H_{21}N_5$: C, 61.25; H, 8.99; N, 29.76. Found: C, 61.22; H, 8.98; N, 29.47.

2-Chloro-7,8-dihydro-4-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines (10)——These compounds were prepared from **4** in the same manner as described for **5g**.

10a: 74% yield, colorless needles (CH_2Cl_2–petroleum ether), mp 138—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.05—2.53 (2H, m), 2.76—3.20 (4H, m), 3.36—3.86 (8H, m), 8.12 (1H, s).

10b: 81% yield, colorless prisms (CH_2Cl_2–Et_2O), mp 86—88 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.0 Hz), 2.00—2.49 (2H, m), 2.74—3.23 (4H, m), 3.33—3.83 (8H, m), 4.18 (2H, q, J=7.0 Hz).

10c: 80% yield, colorless prisms (CH_2Cl_2–Et_2O), mp 88—90 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.94—2.37 [5H, m, 2.32 (3H, s)], 2.40—2.64 (4H, m), 2.71—3.04 (4H, m), 3.37—3.67 (4H, m).

2-Amino-7,8-dihydro-4-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines (11, 12, 13)——a) 4-(4-Formylpiperazinyl)-7,8-dihydro-2-methylamino-6*H*-thiopyrano[3,2-*d*]pyrimidine (**11a**): Aqueous 40% methylamine (50 ml) was added dropwise to a solution of **10a** (7 g) in EtOH (100 ml) with stirring. After being stirred at 50—60 °C for 7 h, the reaction mixture was diluted with H_2O and the whole was extracted with $CHCl_3$. The extract was washed with H_2O and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on a silica gel column with AcOEt–hexane (1 : 1) to give colorless prisms (3.0 g). ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.43 (2H, m), 2.63—3.08 (4H, m), 2.96 (3H, m), 3.25—3.85 (8H, m), 4.97 (1H, br), 8.10 (1H, s).

b) 7,8-Dihydro-2-dimethylamino-4-(4-methylpiperazinyl)-6*H*-thiopyrano[3,2-*d*]pyrimidine (**13d**): A mixture of **18a** (2.5 g), HCO_2H (9.3 g), and 37% aqueous HCHO (10 g) was refluxed for 6 h. The reaction mixture was concentrated *in vacuo*, and then aqueous K_2CO_3 and CH_2Cl_2 were added to the residue. The organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated *in vacuo* to give a pale yellow oil (2.5 g). ^{1}H-NMR ($CDCl_3$) δ: 1.95—3.05 [13H, m, 2.32 (3H, s)], 3.12 (6H, s), 3.30—3.70 (4H, m).

c) 7,8-Dihydro-2-propylamino-4-(4-propylpiperazinyl)-6*H*-thiopyrano[3,2-*d*]pyrimidine (**13l**): Compound **23c** (1.5 g) was added to a suspension of $LiAlH_4$ (0.4 g) in THF (60 ml) in portions with stirring. Stirring was continued for 1 h, and AcOEt and then H_2O were added to the reaction mixture. The whole was filtered, and the organic layer was separated, washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column with AcOEt. The product was recrystallized from hexane to give colorless prisms (0.5 g), mp 66—69 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.1 Hz), 0.94 (3H, t, J=7.4 Hz), 1.36—1.75 (4H, m), 1.86—2.95 (12H, m), 3.10—3.58 (6H, m), 4.68 (1H, br).

The pyrimidines **11b—g**, **13a—c**, and **13e—j** were prepared in the same manner as described for **11a**, while **12a**, **e**, and **h—j** were prepared as described for **7a**, **13k** was prepared as described for **13d**, and **13m—o** were prepared as described for **8m**. The pyrimidines **12b—d**, **f**, and **g** were prepared by amination in the same manner as described for **7h**, followed by hydrolysis in the same manner as described for **7a**.

Ethyl 4-Ethoxycarbonylmethylthioalkanoates (15)——Ethyl 4-ethoxycarbonylmethylthiopentanoate (**15a**): Ethyl 2-mercaptoacetate (10.5 g) was added dropwise to a solution of NaOEt, prepared from Na (2.0 g) and EtOH (100 ml), with stirring. After 0.5 h, ethyl 4-chloropentanoate (**14a**,[10] 14 g) was added and the whole was heated at 80 °C for 3 h, then concentrated *in vacuo*. After addition of H_2O, the residue was extracted with Et_2O. The extract was washed with H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. The oily residue was distilled under reduced pressure to give a colorless oil (18 g), bp 140—145 °C (8 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7.2 Hz), 1.21 (3H, t, J=7.0 Hz), 1.24 (3H, d, J=6.9 Hz), 1.62—1.92 (2H, m), 2.36 (1H, t, J=7.4 Hz), 2.37 (1H, t, J=7.5 Hz), 2.66—3.07 (1H, m), 3.15 (2H, s), 4.03 (2H, q, J=7.2 Hz), 4.09 (2H, q, J=7.0 Hz).

The butanoate (**15b**) was prepared from **14b**[10b,11] in the same manner as above. Yield 85%, colorelss oil, bp 148—153 °C (8 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, d, J=6.9 Hz), 1.21 (3H, t, J=7.2 Hz), 1.23 (3H, t, J=6.9 Hz), 1.48—2.15 (2H, m), 2.31—2.73 [3H, m, 2.59 (2H, t, J=7.4 Hz)], 3.14 (2H, s), 4.05 (2H, q, J=7.2 Hz), 4.12 (2H, q, J=6.9 Hz).

Ethyl 3-Oxotetrahydrothiopyran-2-carboxylates (1)——Ethyl 6-methyl-3-oxotetrahydrothiopyran-2-carboxylate (**1b**): Compound **15a** (85 g) was added dropwise to a solution of NaOEt (58 g) in dry benzene (500 ml) in an ice bath with stirring. Subsequently, the mixture was stirred at room temperature for 1 h. After addition of H_2O, the reaction mixture was made acidic with AcOH and extracted with benzene. The extract was washed with H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. The oily residue was distilled under reduced pressure to give a colorless oil (45 g), bp 126—128 °C (7 mmHg).

The carboxylate (**1c**) was prepared from **15b** in the same manner as above. Yield 46%, bp 125—126 °C (7 mmHg).

2-Amino-7,8-dihydro-4-hydroxy-6*H*-thiopyrano[3,2-*d*]pyrimidines (16)——2-Amino-7,8-dihydro-4-hydroxy-6*H*-thiopyrano[3,2-*d*]pyrimidine (**16a**): Compound **1a** (56.4 g) and then guanidine carbonate (33 g) were added to a solution of NaOEt, prepared from Na (6.9 g) and EtOH (300 ml), in portions with stirring. After being stirred overnight, the reaction mixture was poured into H_2O, followed by acidification with AcOH. The precipitate was filtered off and washed with H_2O to give a crude product (45 g). Recrystallization from MeOH afforded colorless needles, mp >300 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.70—2.25 (2H, m), 2.30—2.66 (2H, m), 2.69—3.03 (2H, m), 6.48 (2H, br). *Anal.* Calcd for $C_7H_9N_3OS$: C, 45.89; H, 4.95; N, 22.93. Found: C, 45.80; H, 4.98; N, 22.99.

The pyrimidines **16b** and **c** were prepared in the same manner as above.

16b: 82% yield, colorless needles (DMF), mp >300 °C. *Anal.* Calcd for $C_8H_{11}N_3OS$: C, 48.71; H, 5.62; N, 21.30. Found: C, 48.68; H, 5.66; N, 21.38.

16c: 75% yield, colorless needles (DMF), mp >300 °C. *Anal.* Calcd for $C_8H_{11}N_3OS$: C, 48.71; H, 5.62; N, 21.30. Found: C, 48.65; H, 5.68; N, 21.33.

2-Amino-4-chloro-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidines (17)——2-Amino-4-chloro-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine (**17a**): A mixture of **16a** (14 g), $POCl_3$, and *N*,*N*-dimethylaniline (10 ml) was heated at 135—140 °C for 1 h. After cooling, the reaction mixture was poured onto ice. The mixture was adjusted to pH about 4

with conc. NH_4OH. The resulting precipitate was filtered off and washed with H_2O and then a small amount of Et_2O to give pale yellow prisms (14 g). Recrystallization from $CHCl_3$–Et_2O afforded colorless prisms, mp 196—198 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.50 (2H, m), 2.60—3.30 (4H, m), 5.32 (2H, br).

The pyrimidines **17b** and **c** were prepared in the same manner as above.

17b: 71% yield, colorless prisms (CH_2Cl_2–Et_2O), mp 185—186 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, d, J=6.9 Hz), 1.82—2.38 (2H, m), 2.65—2.91 (2H, m), 3.13—3.54 (1H, m), 5.00 (2H, br).

17c: 64% yield, colorless needles (CH_2Cl_2–Et_2O), mp 133—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=7.2 Hz), 1.77—2.43 (2H, m), 2.65—3.27 (3H, m), 4.94 (2H, br).

2-Amino-7,8-dihydro-4-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines (18, 19)——The pyrimidines **18a**—**c** and **19a** were prepared in the same manner as described for **7h**, and **19b**—**e** were prepared as described for **8m**.

2-Amino-4-(4-ethylpiperazinyl)-6-propylpyrimidine (20)——In the same manner as described for **9**, **20** was prepared from **18a**. Yield 24%, a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=6.0 Hz), 1.11 (3H, t, J=6.8 Hz), 1.66 (2H, m), 2.27—2.59 (8H, m), 3.47—3.72 (4H, m), 4.80 (2H, br), 5.80 (1H, s). Dimaleate: colorless prisms (EtOH–Et_2O), mp 168—171 °C. *Anal.* Calcd for $C_{13}H_{23}N_5 \cdot 2C_4H_4O_4 \cdot 1/2H_2O$: C, 51.42; H, 6.58; N, 14.28. Found: C, 51.17; H, 6.64; N, 14.31.

2-Amino-6*H*-thiopyrano[3,2-*d*]pyrimidines (21)——In the same manner as described for **7h**, compounds **21** were prepared from **17a**.

4-(4-Acylpiperazinyl)-2-amino-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine (22)——a) 2-Amino-4-(4-formylpiperazinyl)-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine (**22a**): The pyrimidine **18a** (20 g) was added in portions to a mixed anhydride prepared from Ac_2O (30 ml) and HCO_2H (30 ml). The mixture was refluxed for 7 h and then concentrated *in vacuo*. The residual oil was chromatographed on a silica gel column with AcOEt and then CH_2Cl_2–MeOH (5 : 1). The first fraction afforded **23a**, which was recrystallized from CH_2Cl_2–isopropyl ether to give colorless needles (9.3 g), mp 215—218 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.99—2.37 (2H, m), 2.69—3.06 (4H, m), 3.30—3.76 (8H, m), 7.96 (1H, br), 8.07 (1H, s), 9.32 (1H, d, J=10.8 Hz). *Anal.* Calcd for $C_{13}H_{17}N_5O_2S$: C, 50.80; H, 5.57; N, 22.78. Found: C, 50.91; H, 5.39; N, 22.81.

The second fraction afforded **22a**, which was recrystallized from CH_2Cl_2–AcOEt to give colorless scales (7.1 g), mp 216—220 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.99—2.34 (2H, m), 2.57—3.01 (4H, m), 3.24—3.77 (8H, m), 4.72 (2H, br), 8.05 (1H, s). *Anal.* Calcd for $C_{12}H_{17}N_5OS$: C, 51.59; H, 6.13; N, 25.07. Found: C, 51.78; H, 6.32; N, 24.70.

b) 4-(4-Acetylpiperazinyl)-2-amino-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine (**22b**): A mixture of **18a** (5.0 g) and Ac_2O (30 ml) was stirred for 2 h. The reaction mixture was diluted with Et_2O. The resulting precipitate was filtered off, and dissolved in MeOH. The solution was concentrated to a small volume and allowed to stand, giving colorless needles (2.4 g), mp 214—218 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.31 [5H, m, 2.12 (3H, s)], 2.55—2.98 (4H, m), 3.18—3.79 (8H, m), 4.81 (2H, br). *Anal.* Calcd for $C_{13}H_{19}N_5OS$: C, 53.22; H, 6.53; N, 23.87. Found: C, 53.53; H, 6.74; N, 24.08.

The pyrimidine **22c** was prepared in the same manner as above.

22c: 46% yield, colorless prisms (MeOH), mp 181—184 °C. *Anal.* Calcd for $C_{14}H_{21}N_5OS$: C, 54.70; H, 6.89; N, 22.78. Found: C, 54.54; H, 7.14; N, 22.42.

2-Acylamino-4-(4-acylpiperazinyl)-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine (23)——7,8-Dihydro-2-propionylamino-4-(4-propionylpiperazinyl)-6*H*-thiopyrano[3,2-*d*]pyrimidine (**23c**): A mixture of **18a** (3.0 g) and $(EtCO)_2O$ (10 ml) was refluxed for 5 h. The reaction mixture was made alkaline with aqueous K_2CO_3 and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was recrystallized from CH_2Cl_2–Et_2O to give colorless needles (3.4 g), mp 129—131 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7.4 Hz), 1.20 (3H, t, J=7.4 Hz), 2.02—2.53 (4H, m), 2.60—3.07 (6H, m), 3.31—3.84 (8H, m), 8.28 (1H, br). *Anal.* Calcd for $C_{17}H_{25}N_5O_2S$: C, 56.18; H, 6.93; N, 19.27. Found: C, 56.45; H, 6.94; N, 18.97.

The pyrimidines **23a** and **b** were prepared from **18a** in the same manner as above, and **23a** was also obtained with **22a** from **18a**.

23b: 57% yield, colorless prisms (CH_2Cl_2–Et_2O), mp 129—133 °C. *Anal.* Calcd for $C_{15}H_{21}N_5O_2S \cdot 1/3H_2O$: C, 52.77; H, 6.40; N, 20.51. Found: C, 52.64; H, 6.18; N, 20.47.

2-Diacetylamino-4-(4-acetylpiperazinyl)-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine (24)——a) A mixture of **18a** (31 g) and Ac_2O (150 ml) was refluxed for 12 h. The reaction mixture was concentrated *in vacuo*, and H_2O and then CH_2Cl_2 were added to the residue. The organic layer was washed with aqueous K_2CO_3, dried over $MgSO_4$, and evaporated *in vacuo*. The resulting oil was chromatographed on a silica gel column with AcOEt. The product was recrystallized from CH_2Cl_2–Et_2O to give colorless needles (10.7 g), mp 146—148 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, s), 2.13—2.39 [8H, m, 2.28 (6H, s)], 2.81—3.09 (4H, m), 3.31—3.79 (8H, m). *Anal.* Calcd for $C_{17}H_{23}N_5O_3S \cdot 1/3H_2O$: C, 53.25; H, 6.22; N, 18.26. Found: C, 53.32; H, 6.28; N, 17.97.

b) A mixture of **23b** (0.5 g) and Ac_2O (10 ml) was refluxed for 48 h. Work-up as described above gave colorless needles (0.3 g), mp 146—148 °C.

2-Diacetylamino-4-(4-acetylpiperazinyl)-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine 5-Oxide (25a)——A solution of 85% 3-$ClC_6H_4CO_3H$ (6.0 g) in CH_2Cl_2 (30 ml) was added dropwise to a solution of **24** (10 g) in CH_2Cl_2 (100 ml) in an ice-salt bath with stirring. Stirring was continued for 4 h. The reaction mixture was washed with

aqueous K_2CO_3 and then H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column with AcOEt, AcOEt–EtOH (20 : 1), and then EtOH to give a colorless oil (5.8 g), which was used for the next reaction without further purification.

2-Diacetylamino-4-(4-acetylpiperazinyl)-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine 5,5-Dioxide (25b)——A solution of 85% 3-$ClC_6H_4CO_3H$ (6.2 g) in CH_2Cl_2 (30 ml) was added dropwise to a solution of **24** (7.7 g) in CH_2Cl_2 (300 ml) with stirring in an ice bath. After 48 h, further 3-$ClC_6H_4CO_3H$ (5.7 g) was added and stirring was continued for 24 h. The reaction mixture was washed with aqueous K_2CO_3 and then H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residual oil was chromatographed on a silica gel column with AcOEt. The product was recrystallized from isopropyl alcohol to give colorless needles (6.1 g), mp 151—153 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, s), 2.33 (6H, s), 2.40—2.67 (2H, m), 2.99—3.37 (4H, m), 3.52—4.01 (8H, m). *Anal.* Calcd for $C_{17}H_{23}N_5O_5S$: C, 49.87; H, 5.66; N, 17.10. Found: C, 50.15; H, 5.75; N, 16.81.

2-Amino-7,8-dihydro-4-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidine 5-Oxide (26a)——The pyrimidine **25a** (1.8 g) was added to a solution of KOH (1.7 g) in EtOH (20 ml) and H_2O (4 ml). The mixture was refluxed for 7 h, and then concentrated *in vacuo*. The residue was chromatographed on an alumina column with AcOEt and then AcOEt–EtOH (20 : 1→20 : 12). The product was recrystallized from CH_2Cl_2–Et_2O to give colorless needles (0.6 g), mp 188—192 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.97—2.23 (2H, m), 2.33—3.30 (8H, m), 3.41—3.95 (4H, m), 5.07 (2H, br). *Anal.* Calcd for $C_{11}H_{17}N_5OS$: C, 49.42; H, 6.41; N, 26.20. Found: C, 49.05; H, 6.50; N, 25.97.

2-Amino-7,8-dihydro-4-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidine 5,5-Dioxide (26b)——The pyrimidine **25b** (7.1 g) was added to a solution of KOH (13.3 g) in EtOH (150 ml) and H_2O (40 ml). The mixture was refluxed for 17 h and then concentrated to a small volume *in vacuo*. The whole was allowed to cool in an ice-salt bath. The precipitate was filtered off, washed with a small amount of H_2O, and recrystallized from EtOH to give colorless prisms (2.2 g), mp 220—226 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.22—2.55 (2H, m), 2.72—3.22 (8H, m), 3.62—3.86 (4H, m), 4.93 (2H, br). *Anal.* Calcd for $C_{11}H_{17}N_5O_2S$: C, 46.63; H, 6.05; N, 24.72. Found: C, 46.76; H, 5.97; N, 24.36.

2-Chloro-7,8-dihydro-4-methoxy-6*H*-thiopyrano[3,2-*d*]pyrimidine (27)——A solution of **4** (22 g) in CH_2Cl_2 (50 ml) was added dropwise to a solution of NaOMe, prepared from Na (2.6 g) and MeOH (60 ml), with stirring in an ice bath. The mixture was stirred for 1.5 h at room temperature. After addition of H_2O, the organic layer was separated, washed with H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was recrystallized from CH_2Cl_2–Et_2O to give colorless plates (12.5 g), mp 92—93 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.41 (2H, m), 2.67—3.13 (4H, m), 4.07 (3H, s).

7,8-Dihydro-4-methoxy-2-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines (28)——The pyrimidines **28a—c** were prepared in the same manner as described for **7h**, and **28d** was obtained from **28a** in the same manner as described for **8m**.

7,8-Dihydro-4-hydroxy-6*H*-thiopyrano[3,2-*d*]pyrimidine (29)——In the same manner as described for **2**, **29** was prepared from **1a** and formamidine hydrochloride. Yield 65%, colorless needles ($CHCl_3$), mp 188—190 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.37 (2H, m), 2.63—3.10 (4H, m), 7.92 (1H, s), 12.98 (1H, br). *Anal.* Calcd for $C_7H_8N_2OS$: C, 49.98; H, 4.79; N, 16.65. Found: C, 49.95; H, 4.83; N, 16.70.

4-Chloro-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidines (30)——In the same manner as described for **4**, **30a** and **b** were prepared from **2** and **29** in 83 and 81% yields, respectively. The crude chlorides were used for the next reaction without further purification.

7,8-Dihydro-4-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidines (31)——a) 2-Acetoxy-4-(4-formylpiperazinyl)-7,8-dihydro-6*H*-thiopyrano[3,2-*d*]pyrimidine (**31a**): A mixture of **10a** (3.0 g), NaOAc (5.7 g), and AcOH (50 ml) was heated at about 80 °C for 3 h with stirring. After addition of H_2O, the mixture was extracted with CH_2Cl_2. The extract was washed with H_2O and dried over $MgSO_4$. The solvent was evaporated off to give the product (2.2 g), mp 131—135 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.05—2.39 (2H, m), 2.78—3.12 (4H, m), 3.36—3.76 [11H, m, 3.51 (3H, s)], 8.06 (1H, s).

b) 7,8-Dihydro-2-hydroxy-4-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidine (**31d**): The pyrimidine **31a** (1.5 g) was added in portions to a mixture of conc. HCl (7 ml) and MeOH (10 ml). The whole was refluxed for 2 h and allowed to cool. The reaction mixture was made alkaline with aqueous K_2CO_3 and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over $MgSO_4$, and evaporated *in vacuo* to give a colorless oil (0.9 g). ^{1}H-NMR ($CDCl_3$) δ: 1.98—2.37 (2H, m), 2.68—3.08 (8H, m), 3.32—3.62 (4H, m).

c) 7,8-Dihydro-2-methoxy-4-piperazinyl-6*H*-thiopyrano[3,2-*d*]pyrimidine (**31e**): The pyrimidine **10a** (3.0 g) was added to a solution of NaOMe, prepared from Na (0.7 g) and MeOH (50 ml), with stirring, and the whole was refluxed for 2 h. The reaction mixture was concentrated *in vacuo*, and H_2O and then CH_2Cl_2 were added to the residue. The organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated to give an oil (2.5 g). A mixture of the oil (2.0 g), conc. HCl (7 ml), and MeOH (10 ml) was heated at about 80 °C for 0.5 h. After cooling, the residue was made alkaline with aqueous K_2CO_3 and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over K_2CO_3, and evaporated *in vacuo* to give pale yellow needles (1.1 g), mp 230—240 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.98—2.37 (2H, m), 2.67—3.94 [15H, m, 3.87 (3H, s)].

The pyrimidines **31b** and **c** were prepared from **30a** and **b**, respectively, in the same manner as described for **18a**.

2-Amino-4-hydroxypyrimidines (33)[12]——2-Amino-4-hydroxy-5,6-tetramethylenepyrimidine (**33b**): A mixture of **32b** (8.5 g) and guanidine carbonate (6.8 g) was refluxed in EtOH (80 ml) containing conc. HCl (0.5 ml) for 1.5 h.

After cooling, the precipitate was filtered off and washed with EtOH to give crystals, which were refluxed in 5% aqueous NaOH (80 ml) for 1 h. Acidification of the reaction mixture with AcOH afforded a precipitate, which was filtered off and washed with EtOH to give colorless prisms (7.2 g). Recrystallization from DMF–MeOH gave colorless prisms, mp >300 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.49—1.71 (4H, m), 2.03—2.40 (4H, m), 6.18 (2H, br).

The pyrimidines **33a** and **d** were prepared in the same manner as above.

33a: 60% yield, colorless needles (MeOH), mp 285—296 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 1.65—2.07 (2H, m), 2.30—2.67 (4H, m), 6.28 (2H, br).

33d: 72% yield, colorless needles (MeOH), mp > 300 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.43—2.91 (6H, m), 6.33 (2H, br).

2-Amino-4-chloropyrimidines (34)[13]——In the same manner as described for **17**, **34a**—**c** were prepared from **33**.

34a: 75% yield, colorless needles ($CHCl_3$–Et_2O), mp 196—198 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.89—2.28 (2H, m), 2.69—3.01 (4H, m), 4.99 (2H, br).

34b: 70% yield, colorless needles ($CHCl_3$–Et_2O), mp 208—214 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.63—1.99 (4H, m), 2.43—2.82 (4H, m), 5.18 (2H, br).

34c: The crude product was obtained in 82% yield. ^{1}H-NMR ($CDCl_3$) δ: 4.17 (2H, s), 4.19 (2H, s), 5.15 (2H, br).

2-Amino-4-piperazinylpyrimidines (35)——The pyrimidines **35a** and **c**—**e** were prepared in the same manner as described for **7h**, and **35b** was prepared as described for **7a**.

Hypoglycemic Activity——Male ob/ob mice, 3—4 months of age, were used after fasting for 18 h. Glucose was administered orally at 4 g/kg 30 min after administration of test compounds. Blood (50 μl) was collected from the tail vein. Blood glucose was measured by the *o*-toluidine–borate method. Compounds were administered orally as a solution or suspension.

In screening tests, the reduction in blood glucose was calculated by means of the formula reduction (%) = $100(A-B)/A$. The symbols A and B represent the differences between maximum blood glucose levels after glucose loading and the blood glucose levels before glucose loading in control mice and in treated mice, respectively.

Acute Toxicity——Male ddy mice, weighing 22—28 g, were used, and compounds were administered orally. LD_{50} values were assessed by Behrens–Kärber method, based on the number of dead animals during 7 d.

References and Notes

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