Synthesis and Antiallergy Activity of [1,3,4]Thiadiazolo[3,2-*a*]-1,2,3-triazolo[4,5-*d*]pyrimidin-9(3*H*)-one Derivatives. II.[1,2] 6-Alkyl- and 6-Cycloalkylalkyl Derivatives

Shuichi YOKOHAMA, Tamotsu MIWA, Shunzo AIBARA, Hiroyuki FUJIWARA, Hiroo MATSUMOTO, Kiyoshi NAKAYAMA, Teiji IWAMOTO, Mikio MORI, Reimei MOROI, Wataru TSUKADA, and Sumiro ISODA*

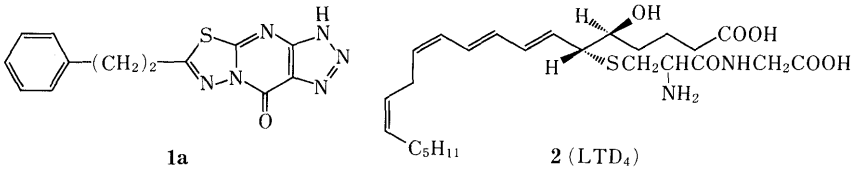
Exploratory Research Laboratories III, Daiichi Pharmaceutical Co., Ltd., 16–13, Kitakasai 1-chome, Edogawa-ku, Tokyo 134, Japan.
Received January 16, 1992

A series of 6-alkyl- or 6-(cycloalkylalkyl)-[1,3,4]thiadiazolo[3,2-*a*]-1,2,3-triazolo[4,5-*d*]pyrimidin-9(3*H*)-ones 1b—o was synthesized from the corresponding 1,3,4-thiadiazol-5-amines 3b—o and the antiallergic activities of the products were evaluated. Among the compounds 6-(2-cyclohexylethyl)-[1,3,4]thiadiazolo[3,2-*a*]-1,2,3-triazolo[4,5-*d*]pyrimidin-9(3*H*)-one 1h, whose X-ray crystallographic stereostructure is shown, was found to be a promising new antiallergic agent, which has low toxicity and dual activity as a leukotriene D_4 receptor antagonist and as an orally active mast cell stabilizer.

Keywords [1,3,4]thiadiazolo[3,2-*a*]-1,2,3-triazolo[4,5-*d*]pyrimidin-9(3*H*)-one; X-ray analysis; stereostructure; leukotriene D_4; passive cutaneous anaphylaxis; antiallergy; antagonist

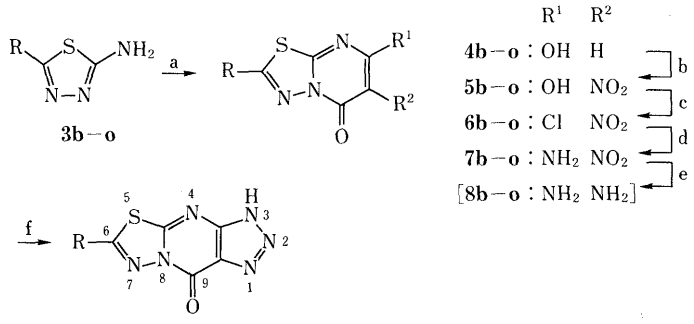
In a previous paper,[1] we reported the method of synthesis of 6-substituted [1,3,4]thiadiazolo[3,2-*a*]-1,2,3-triazolo[4,5-*d*]pyrimidin-9(3*H*)-ones **1** and identified the characteristic orally available antiallergy activities of 6-[2-(substituted or unsubstituted phenyl)ethyl] derivatives, their antagonistic actions against the slow reacting substance of anaphylaxis (SRS-A) and their activities against passive cutaneous anaphylaxis (PCA). Subsequent investigations revealed that the SRS-A antagonistic activity of 6-(2-phenylethyl) derivative **1a** was mainly attributable to its competitive inhibitory effect against leukotriene D_4 (LTD_4) **2**.

We postulated that the following structural and/or functional resemblance might exist between **1a** and **2** (Chart 1): 1) The phenethyl moiety of **1a** functions as the lipophilic part of **2**, the long aliphatic chain derived from arachidonic acid; 2) the sulfur atom in the tricyclic ring of **1a** corresponds to that of the cysteine part of **2**; and 3) the acidic triazole ring of **1a** acts in a similar manner to the carboxyl group of the arachidonic acid or the glycine part of **2**, although it is uncertain which carboxyl group acts more effectively. Concerning the relationship between the structure of **1a** and its anti-PCA activity, both the acidic tetrazole ring and the carbonyl group of the 9-position are



1a **2** (LTD_4)

Chart 1



3b—o **1b—o**

	R^1	R^2	
4b—o	OH	H	b
5b—o	OH	NO_2	c
6b—o	Cl	NO_2	d
7b—o	NH_2	NO_2	e
[**8b—o**]	NH_2	NH_2	

	R
b:	$C_6H_{13}(CH_2)_2$–
c:	*tert*-$Bu(CH_2)_2$–
d:	$(Et)_2CH(CH_2)_2$–
e:	cyclo$C_5H_9(CH_2)_2$–
f:	cyclo$C_5H_9(CH_2)_3$–
g:	cyclo$C_6H_{11}CH_2$–
h:	cyclo$C_6H_{11}(CH_2)_2$–
i:	cyclo$C_6H_{11}(CH_2)_3$–
j:	(*E*)-cyclo$C_6H_{11}CH$=CH–
k:	*cis*-4-Me-cyclo$C_6H_{10}(CH_2)_2$–
l:	*trans*-4-Me-cyclo$C_6H_{10}(CH_2)_2$–
m:	cyclo$C_7H_{13}(CH_2)_2$–
n:	cyclo$C_8H_{15}(CH_2)_2$–
o:	cyclo$C_{12}H_{23}(CH_2)_2$–

reagents

a) CH_2(COO-2,4,6-$Cl_3C_6H_2)_2$–xylene; b) fuming HNO_3–AcOH; c) $POCl_3$–Pr_3N; d) conc. NH_4OH–EtOH; e) tin powder–conc. HCl–dioxane; f) aqueous $NaNO_2$–6 N HCl

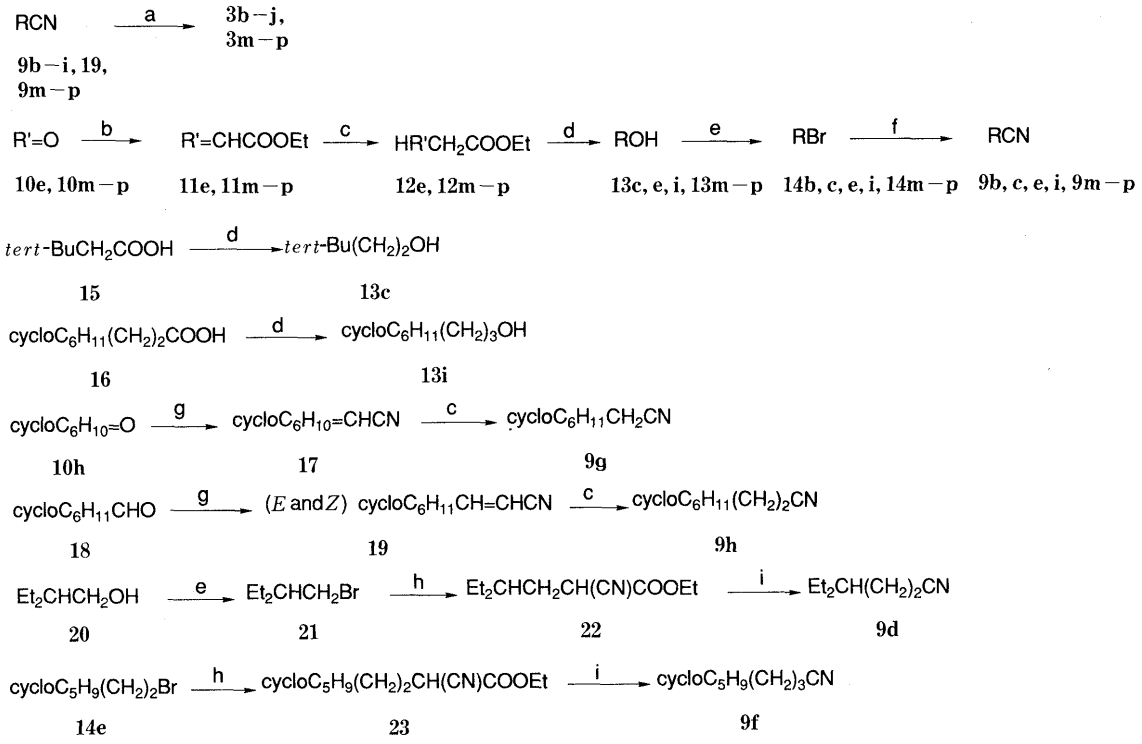
Chart 2

presumed to function more than the other part of **1a**, which make it possible for **1a** to be absorbed orally. These hypotheses suggested the possibility of obtaining a compound more competitively antagonistic to LTD_4, while retaining the oral anti-PCA activity, by further chemical modification of **1a** through replacement of the lipophilic phenethyl residues with an alkyl or a cycloalkylalkyl group, which seems to function more as the arachidonic lipophilic aliphatic chain. Accordingly, we synthesized a series of 6-alkyl- or 6-(cycloalkylalkyl)-[1,3,4]thiadiazolo[3,2-*a*]-1,2,3-triazolo[4,5-*d*]pyrimidin-9(3*H*)-ones, **1b**—**o**, and the LTD_4-antagonistic and anti-PCA activities were evaluated.

Chemistry

The designed compounds **1b**—**o** were synthesized from the corresponding 5-alkyl- or 5-(cycloalkylalkyl)-1,3,4-thiadiazol-2-amines **3b**—**o** according to the stepwise method described in the previous paper[1] (Chart 2). The *E*-form of the 2-cyclohexylethenyl derivative **1j**, the *cis*-configuration of 2-(4-methylcyclohexyl)ethyl derivative **1k**, and the *trans* one of **1l** were maintained during these reactions, which were confirmed by proton nuclear magnetic resonance (^{1}H-NMR) spectra of these compounds: 1) The signals due to ethenyl protons of **1j** were observed at 6.28 and 6.49 ppm with coupling constant 15.9 Hz in NaOD solution; 2) the methyl signal for the *cis*-derivative **1k** appeared at 0.92 ppm as doublet with coupling constant 6.5 Hz, and that for *trans* ones **1l** at 0.88 ppm with coupling constant 5.7 Hz in $CDCl_3$-trifluoroacetic acid; 3) the width of cyclohexyl methylene signals of **1l** was broader than that of **1k**.

The amines **3b**—**i**, **3j**, and **3m**—**p** were obtained from cyano derivatives **9b**—**i**, **19**, and **9m**—**p**, respectively, by the known method,[1,3] and the starting cyano derivatives **9b**—**i**, **19**, and **9m**—**p** were prepared by a series of reactions (Chart 3). A mixture (*E*/*Z* = *ca.* 2/1) of 3-cyclohexyl-2-propenenitrile **19**, which was prepared from cyclohexanecarbaldehyde **18** and diethyl cyanomethylphosphonate, gave only (*E*)-5-(2-cyclohexylethenyl)-1,3,4-thiadiazol-2-amine **3j** under the conditions of thiadiazole ring closure: ^{1}H-NMR spectra revealed the signals for ethenyl protons at 6.07 and 6.45 ppm with coupling constant 16 Hz in dimethyl-d_6-sulfoxide (DMSO-d_6). 5-[2-(*cis*-4-Methylcyclohexyl)ethyl] amine **3k** and its *trans* isomer **3l** were separated by repeated fractional crystallization of the mixture **3p** and their configurations were determined by comparison of their carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra with those of reported methylcyclohexyl derivatives[4]: The signals due to the methyl carbons of **3k** and **3l** in DMSO-d_6–$CDCl_3$ were observed at 20.10 and 22.58 ppm, respectively.



3, 9, 13, 14 R
b—**j** and **m**—**o**: see Chart 2
p: *cis*- and *trans*-4-Me-cyclo$C_6H_{10}(CH_2)_2$–

10—**12** HR′
e: cycloC_5H_9– **m**: cycloC_7H_{13}– **o**: cyclo$C_{12}H_{23}$–
h: cycloC_6H_{11}– **n**: cycloC_8H_{15}– **p**: *cis*- and *trans*-4-Me-cycloC_6H_{10}–

reagents
a) $NH_2NHCSNH_2$–CF_3COOH, NH_4OH; b) $(EtO)_2POCH_2COOEt$–NaH–benzene; c) H_2/Pd–carbon–EtOH; d) $LiAlH_4$–THF; e) PBr_3–Et_2O; f) NaCN–DMSO; g) $(EtO)_2POCH_2CN$–40% NaOH–CH_2Cl_2; h) $NCCH_2COOEt$–NaOEt–EtOH; i) NaCl–DMSO

Chart 3

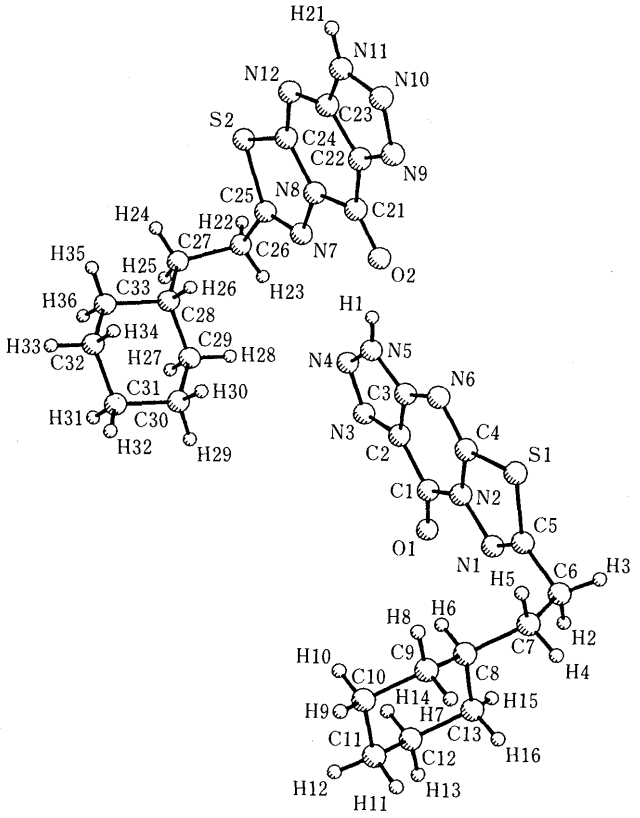


Fig. 1. Perspective View of the Crystal Structure of **1h**

The X-ray crystal analysis of 6-(2-cyclohexylethyl) derivative **1h** indicated that it crystallized with two molecules in an asymmetric unit, and that the hydrogen of the triazole ring is located at position 3. Intermolecular hydrogen bonding was observed between O(2) and H(1) with the oxygen–hydrogen distance of 2.03(4) Å, the O(2)–N(5) distance of 2.811(4) Å, and the N(5)–H(1)–O(2) angle of 155(3)°. The thermal parameters of the cyclohexane carbon atoms are significantly larger than those of the remaining non-hydrogen atoms. This may be due to the thermal motion of the cyclohexane rings. Figure 1 shows a stereoscopic view of **1h**.

Pharmacological Evaluation and Discussion

The compounds were first tested for their ability to inhibit the PCA reaction in rats and to antagonize LTD_4 using guinea pig ileum, and for acute toxicity. The results are shown in Table I. The following findings concerning the relationship between LTD_4 antagonistic activity and the substituent of the 6-position of **1** were obtained. (a) Compounds having a branched chain have more potent activity than those bearing a straight chain (**1c**, **1d** and **1b**). (b) Cycloalkylalkyl groups contribute generally to potentiation of the activity. (c) The activity attained a maximum when the number of methylenes between the cycloalkyl and the tricyclic ring was 2 (**1e** and **1f**; **1g**, **1h** and **1i**). (d) The activity is increased according to the ring size of the cycloalkyl group and the cycloheptyl derivative shows maximum activity (**1e**, **1h**, **1m**, **1n** and **1o**). (e) The *trans* 4-methyl group on the cyclohexane ring (**1l**) slightly weakened the activity of the nonsubstituted compound **1h** but the *cis*-4-methyl group (**1k**) affected it little. (f) The

TABLE I. Biological Data for **1**

Compd. No.	R	Antiallergy activity		Toxicity[c]
		Anti LTD_4[a]	Anti PCA[b]	
1a	$Ph(CH_2)_2$–	1.0	58.0±12.8[d]	
1b	$C_6H_{13}(CH_2)_2$–	0.15 (3.7×10^{-5})	ND	ND
1c	*tert*-$Bu(CH_2)_2$–	0.62 (3.0×10^{-6})	37.5±16.0	3/3
1d	$Et_2CH(CH_2)_2$–	0.83 (7.1×10^{-6})	56.7± 9.1[d]	ND
1e	$cycloC_5H_9(CH_2)_2$–	8.2 (6.3×10^{-7})	61.6±17.2[d]	0/3
1f	$cycloC_5H_9(CH_2)_3$–	4.4 (1.1×10^{-6})	90.6± 4.5[e]	0/3
1g	$cycloC_6H_{11}CH_2$–	0.53 (1.3×10^{-5})	77.0± 9.6[e]	ND
1h	$cycloC_6H_{11}(CH_2)_2$–	14.8 (1.7×10^{-7})	81.0±10.4[e]	0/3
1i	$cycloC_6H_{11}(CH_2)_3$–	6.9 (1.2×10^{-6})	27.3± 8.4	0/4
1j	(*E*)-$cycloC_6H_{11}CH$=CH–	12.3 (5.4×10^{-7})	58.8± 8.8[d]	0/3
1k	*cis*-4-Me-$cycloC_6H_{10}$–$(CH_2)_2$–	9.0 (1.0×10^{-6})	55.8±15.7[d]	ND
1l	*trans*-4-Me-$cycloC_6H_{10}(CH_2)_2$–	1.8 (2.0×10^{-6})	88.1± 7.3[e]	0/3
1m	$cycloC_7H_{13}(CH_2)_2$–	46.4 (8.0×10^{-8})	87.8± 9.0[e]	0/5
1n	$cycloC_8H_{15}(CH_2)_2$–	7.2 (1.2×10^{-6})	29.9±17.2	ND
1o	$cycloC_{12}H_{23}(CH_2)_2$–	0.54 (1.9×10^{-5})	—	ND

a) Relative activity to **1a** and IC_{50}(M) in parenthesis. IC_{50}(M) of **1a** is 1.0×10^{-5}—9.2×10^{-6}. *b*) Percent inhibition, mean±S.E. ($n=5$). ND: not done, —: inactive. *c*) Number of dead mice/number of tested mice, ND: not done. *d*) $p<0.05$, *e*) $p<0.01$, significantly different from the vehicle control.

TABLE II. Biological Data for **1h**, DSCG, and FPL-55712

	Anti PCA ID_{50} (mg/kg)[a]		Anti LTD_4[d] K_i value (μM)
	p.o.	i.v.	
1h	2.8 (1.26—5.68)	0.55 (0.22—0.90)	0.72
DSCG	—[b]	0.92 (0.67—1.25)	—[e]
FPL-55712	—[c]		0.72

a) ID_{50} values and 95% confidence limits in parentheses. *b*) Inactive at the dose of 100 mg/kg. *c*) Inactive at the dose of 20 mg/kg. *d*) Inhibition of [^{3}H]LTD_4 specific binding to guinea pig lung membranes. *e*) Inactive at the concentration of 10^{-4} M.

activity of the cyclohexylethyl derivative **1h** is 14 times that of phenethyl derivative **1a**. Thus, the cycloalkylalkyl groups were found to be appropriate substituents of **1**, and the steric shape of the cycloalkylalkyl group thus plays an important role in the development of high LTD_4 antagonistic activity more than their lipophilicity. Every compound except **1o** has marked anti-PCA activity.

A great many compounds having single antiallergy activity: leukotriene antagonist, anti PCA, anti platelet activating factor activity, *etc.*, have been reported aimed at finding new antiallergic agents,[5] and some of them are under clinical investigation. The compounds described in

this paper proved to be orally available antiallergy agents of a new type, characteristically having dual antiallergy, anti chemical mediator release and anti leukotriene activities. Table II shows detailed comparison data of anti-PCA activities and of effects on specific binding of LTD_4 to guinea pig lung membrane of **1h** with those of cromolyn sodium (DSCG) or FPL-55712,[6] the prototypical compound having anti-PCA activity or antagonist against leukotriene, respectively. After further preclinical toxicological and pharmacological studies, some of which are shown in separate papers,[7] compound **1h**, DS-4574, was chosen and is now under clinical investigation.

Experimental

All melting points were determined on a Yanagimoto MP-1 melting point apparatus and are uncorrected. Infrared spectra (IR) were obtained with a Hitachi 270-30 spectrophotometer. ^{1}H-NMR spectra were measured on a Hitachi R-40 or JEOL GSX-500 spectrometer and ^{13}C-NMR spectra on a Varian XL-200 spectrometer using Me_4Si or $Me_3Si(CD_2)_2COONa$ as an internal standard.

Ethyl Cycloheptylideneacetate (11m) Triethyl phosphonoacetate (100.0 g, 0.45 mol), NaH (60% in oil) (17.2 g, 0.43 mol) and cycloheptanone **10m** (48.0 g, 0.43 mol) were reacted in dry benzene (250 ml) and worked up in a similar manner as in the case of cyclohexanone[8] to give **11m** (54.7 g, 70.1%), bp 65—76 °C (0.5—1 mmHg).[9] ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, CH_2CH_3), 1.40—1.80 (8H, m, 4×CH_2), 2.25—2.56 (2H, m, CH_2), 2.74—2.96 (2H, m, CH_2), 4.13 (2H, q, J=7 Hz, CH_2CH_3), 5.60—5.72 (1H, m, =CHCOO).

Compounds **11e** and **11n—p** were prepared by an analogous procedure. **11p**: 78.0% yield, bp 86 °C (3 mmHg).

Ethyl Cycloheptylacetate (12m) Catalytic hydrogenation of **11m** (54.0 g) in EtOH (700 ml) in the presence of 5% Pd–carbon (5.00 g) at atmospheric pressure gave **12m** (45.7 g, 83.7%), bp 80—85 °C (3 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, CH_2CH_3), 1.05—2.30 (15H, m, 7×CH_2 and CH), 4.12 (2H, q, J=7 Hz, CH_2CH_3).

Compounds **9g**, **9h**, **12e**, and **12n—p** were prepared by an analogous procedure. **9g**[10]: 98.0% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.80—2.00 (11H, m, 5×CH_2 and CH), 2.26 (2H, d, J=7 Hz, CH_2CN). **9h**[11]: 94.1% yield, bp 81—85 °C (4 mmHg). **12e**: 81.4% yield, from **10e**, bp 93—95 °C (25 mmHg). **12p**: 97.0% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.88 and 0.95 (total 3H, d, CH_3), 0.99—2.30 (15H, m, CH_2CH_3, 5×CH_2 and 2×CH), 4.15 (2H, q, CH_2CH_3). **12n**: 80.7% yield from **10n**, bp 103—104 °C (2 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.17—1.80 (18H, m, CH_3, 7×CH_2 and CH), 2.17 (2H, br s, CH_2COO), 4.12 (2H, q, J=7 Hz, CH_2CH_3).

2-Cycloheptylethanol (13m) A solution of **12m** (45.5 g, 0.25 mol) in tetrahydrofuran (THF, 300 ml) was added to an ice cooled suspension of $LiAlH_4$ (7.03 g, 0.185 mol) in THF (500 ml), and the mixture was treated by the usual method[12] to give **13m** (31.1 g, 88.6%), bp 83—85 °C (3 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.00—1.88 (15H, m, 7×CH_2 and CH), 3.65 (2H, t, J=6 Hz, CH_2OH).

Compounds **13c**, **13e**, **13i** and **13n—p** were prepared by an analogous procedure. **13c**: 72.1% yield from **15**, bp 140 °C. **13e**: bp 95—97 °C (27 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.70—2.00 (11H, m, 5×CH_2 and CH), 3.64 (2H, d, J=7 Hz, CH_2OH). **13n**[13]: 94.5% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.53 (17H, br s, 8×CH_2 and CH), 2.12 (1H, s, OH), 3.45 (2H, t, J=6.5 Hz, CH_2OH). **13o**: ^{1}H-NMR ($CDCl_3$) δ: 1.34 (25H, br s, 12×CH_2 and CH), 3.71 (2H, m, CH_2OH).

1-Bromo-2-cycloheptylethane (14m)[14] A solution of PBr_3 (11 ml, 0.12 mol) in ether (100 ml) was added to a solution of **13m** (31.0 g, 0.22 mol) in Et_2O (500 ml) cooled with ice, and the mixture was stirred for 16 h at room temperature, and poured into ice water. The organic layer was separated, washed successively with water, dilute $NaHCO_3$, water and brine, and dried. After removal of the solvent, the residue was distilled to give **14m** (23.1 g, 51.6%), bp 80—81 °C (3 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.00—1.96 (15H, m, 7×CH_2 and CH), 3.42 (2H, t, J=7 Hz, CH_2Br).

Compounds **14c**, **14e**, **14i**, **14n—p**, and **21** were prepared by an analogous procedure. **14c**: 37.4% yield, bp 130—135 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (9H, s, 3×CH_3), 1.72—1.94 (2H, m, CH_2), 3.28—3.48 (2H, m, CH_2Br). **14e**[15]: 71.0% yield from **12e**, bp 85—87 °C (30 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.9—2.0 (11H, m, 5×CH_2 and CH), 3.41 (2H, t, J=7 Hz, CH_2Br). **14i**: 71.0% yield from **16**, bp 85—87 °C (5 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.65—2.05 (15H, m, 7×CH_2 and CH), 3.40 (2H, t, J=7 Hz, CH_2Br). **14n**: 64.2% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.20 (17H, m, 8×CH_2 and CH), 3.43 (2H, t, J=7.2 Hz, CH_2Br). **14o**: 57.9% yield from **10o**, bp 120—133 °C (1 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.00—1.91 (25H, m, 12×CH_2 and CH), 3.44 (2H, m, CH_2Br). **14p**[16]: 51.6% yield from **12p**, bp 93 °C (5 mmHg). **21**: 44.2% yield, bp 140—145 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.76—1.00 (6H, m, 2×CH_2CH_3), 1.24—1.60 (5H, m, 2×CH_2 and CH), 3.45 (2H, d, J=4.4 Hz, CH_2Br).

3-Cycloheptylpropionitrile (9m)[17] A mixture of **14m** (22.0 g, 0.11 mol) and NaCN (6.80 g, 0.14 mol) in DMSO (100 ml) was treated and worked up by the usual procedure[18] to give **9m** (91.7%) as an oil which was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.00—1.96 (15H, m, 7×CH_2 and CH), 2.34 (2H, t, J=7 Hz, CH_2CN).

Compounds **9b**, **9c**, **9e**, **9i** and **9n—p** were prepared by an analogous procedure. **9b**: 91.0% yield from **14b**. ^{1}H-NMR ($CDCl_3$) δ: 0.80—1.85 (15H, m, CH_3 and 6×CH_2), 2.33 (2H, t, J=6.5 Hz, CH_2CN). **9c**[19]: 90.0% yield, bp 78—80 °C (38—43 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (9H, s, 3×CH_3), 1.48—1.76 (2H, m, CH_2), 2.12—2.44 (2H, m, CH_2CN). **9e**: 94.7% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.90—2.00 (11H, m, 5×CH_2 and CH), 2.34 (2H, t, J=7 Hz, CH_2CN). **9i**[20]: 96.2% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.60—2.00 (15H, m, 7×CH_2 and CH), 2.32 (2H, t, J=7 Hz, CH_2CN). **9n**: ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.70 (17H, m, 8×CH_2 and CH), 2.34 (2H, t, J=7.2 Hz, CH_2CN). **9o**[21]: ^{1}H-NMR ($CDCl_3$) δ: 1.00—1.80 (25H, m, 12×CH_2 and CH), 2.33 (2H, m, CH_2CN). **9p**: 95.0% yield, ^{1}H-NMR ($CDCl_3$) δ: 0.87 and 0.90 (total 3H, d, CH_3), 0.95—1.85 (12H, m, 5×CH_2 and 2×CH), 2.34 (2H, t, J=7.6 Hz, CH_2CN).

***(E)*- and *(Z)*-3-Cyclohexyl-2-propenenitrile (19)**[22] A solution of cyclohexanecarbaldehyde **18** (22.4 g, 0.2 mol) and diethyl cyanomethylphosphonate (39.0 g, 0.22 mol) in dichloromethane (80 ml) was added dropwise to a cold 40% NaOH over a 1 h period, while the temperature was maintained at 5—15 °C. The mixture was stirred for 2 h at room temperature, poured into ice water and extracted with dichloromethane. The extract was washed with water and brine, dried and concentrated *in vacuo*. The residual oil was distilled to afford **19** (25.4 g, 94.1%), bp 75—81 °C (5 mmHg).

The compound **17** was prepared from cyclohexanone **10h** by an analogous procedure in 87.2% yield, bp 68—78 °C (6 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.80—2.60 (10H, m, 5×CH_2), 5.04 (1H, br s, =CHCN).

Ethyl 2-Cyano-4-ethylhexanoate (22) A solution of **21** (43.7 g, 0.265 mol) and ethyl cyanoacetate (30.0 g, 0.265 mol) in EtOH (100 ml) was added dropwise to an ice cooled solution of NaOEt (19.0 g, 0.265 mol) in EtOH (400 ml) under stirring. The resultant mixture was heated to reflux for 3 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried, and concentrated. The residue was distilled to give **22** (23.4 g, 44.8%), bp 100—110 °C (3 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, t, J=6 Hz, 2×CH_2CH_3), 1.10—1.60 (6H, m, 2×CH_2CH_3 and CH_2), 1.25 (3H, t, J=7 Hz, OCH_2CH_3), 1.68—2.00 (1H, m, $CH(C_2H_5)_2$), 3.30—3.60 (1H, m, CH(CN)COO), 4.26 (2H, q, J=7 Hz, OCH_2CH_3).

The compound **23** was prepared by an analogous procedure.

4-Ethylhexanenitrile (9d)[23] A solution of **22** (23.4 g), NaCl (0.92 g), and water (4.7 ml) in DMSO (70 ml) was heated at 170—180 °C for 8 h. The reaction mixture was partitioned between Et_2O and water, and the organic layer was washed with water and brine, and dried. The solvent was removed under reduced pressure to give **9d** as a colorless oil (14.7 g, 99.3%). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, t, J=7 Hz, 2×CH_2CH_3), 1.00—1.70 (7H, m, 3×CH_2 and CH), 2.34 (2H, t, J=7 Hz, CH_2CN).

The compound **9f** was prepared from **23** by an analogous procedure in 86.0% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.95—2.00 (13H, m, 6×CH_2 and CH), 2.30 (2H, t, J=7 Hz, CH_2CN).

5-(2-Cyclohexylethyl)-1,3,4-thiadiazol-2-amine (3h) A mixture of **9h** (10.3 g, 75 mmol), thiosemicarbazide (6.81 g, 75 mmol) and CF_3COOH (23 ml) was treated according to the previously reported method for 2-amino-5-phenyl-1,3,4-thiadiazole[1] to obtain **3h** (13.2 g, 83.0%), mp 253—255 °C. IR (KBr): 3100, 2920, 2848, 1641, 1527 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.70—2.90 (13H, m, 6×CH_2 and CH), 2.79 (2H, t, J=8 Hz, CH_2Ar), 6.97 (2H, br s, NH_2).

Compounds **3b—g** and **3i—o** were prepared by an analogous procedure, and data are listed in Table III.

3j: ^{1}H-NMR (DMSO-d_6) δ: 1.0—2.0 (10H, m, 5×CH_2), 2.0—2.4 (1H, m, ring-CH), 6.09 (1H, dd, J=6, 16 Hz, C_2-H), 6.42 (1H, dd, J=1.5, 16 Hz, CH-Ar), 7.18 (2H, s, NH_2). **3k**: ^{13}C-NMR (DMSO-d_6–$CDCl_3$) δ:

TABLE III. 5-Substituted 1,3,4-Thiadiazol-2-amines **3** and 2-Substituted 7-Hydroxy-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-ones **4**

Compd. No.	Recrystn. solvent[a] (Yield, %)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Compd. No.	Recrystn. solvent[a] (Yield, %)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
3b	— (62.4)	186—187	$C_{10}H_{19}N_3S$	56.30 (56.44	8.98 8.77	19.70 19.78)	**4b**	— (73.1)	211—218 (dec.)	$C_{13}H_{19}N_3O_2S$	55.49 (55.44	6.81 6.70	14.93 15.03)
3c	— (71.5)	240—242	$C_8H_{15}N_3S$	51.85 (51.82	8.16 8.25	22.68 22.64)	**4c**	— (60.7)	209—212	$C_{11}H_{15}N_3O_2S$	52.15 (52.47	5.97 5.90	16.59 16.61)
3d	A (48.9)	202—203	$C_9H_{17}N_3S$	54.23 (53.86	8.60 8.54	21.08 21.07)	**4d**	— (75.3)	203—209	$C_{12}H_{17}N_3O_2S$	53.91 (53.89	6.41 6.13	15.72 15.76)
3e	B (78.0)	245—246[b]	$C_9H_{15}N_3S$	54.78 (54.60	7.67 7.70	21.30 21.11)	**4e**	— (70.8)	215—218	$C_{12}H_{15}N_3O_2S$	54.32 (54.30	5.70 5.69	15.84 15.91)
3f	B (81.0)	210—212	$C_{10}H_{17}N_3S$	56.83 (56.88	8.10 7.97	19.88 19.99)	**4f**	— (64.0)	205—208	$C_{13}H_{17}N_3O_2S$	55.90 (55.78	6.14 6.11	15.05 15.14)
3g	— (56.3)	250—267	$C_9H_{15}N_3S$	54.79 (54.59	7.66 7.73	21.30 21.24)	**4g**	— (45.7)	203—205	$C_{12}H_{15}N_3O_2S$	54.32 (54.18	5.70 5.60	15.84 15.68)
3h	— (83.0)	253—255	$C_{10}H_{17}N_3S$	56.83 (56.77	8.11 8.04	19.88 19.71)	**4h**	— (85.7)	216—220	$C_{13}H_{17}N_3O_2S$	55.89 (56.04	6.13 6.17	15.04 15.22)
3i	— (73.0)	227—228	$C_{11}H_{19}N_3S$	58.62 (58.61	8.50 8.45	18.65 18.69)	**4i**	D (59.6)	164—167	$C_{14}H_{19}N_3O_2S$	57.31 (57.13	6.53 6.41	14.32 14.33)
3j	B (34.8)	247—249 (dec.)	$C_{10}H_{15}N_3S$	57.38 (57.34	7.22 7.32	20.08 19.99)	**4j**	B (73.4)	244—248 (dec.)	$C_{13}H_{15}N_3O_2S$	56.30 (56.18	5.45 5.36	15.15 14.98)
3k	B (16.7)	210—215	$C_{11}H_{19}N_3S$	58.62 (58.86	8.50 8.50	18.65 18.65)	**4k**	— (35.0)	195—198	$C_{14}H_{19}N_3O_2S \cdot 1/4H_2O$	56.44 (56.76	6.60 6.45	14.11 14.17)
3l	C (16.4)	269—271	$C_{11}H_{19}N_3S$	58.62 (58.40	8.50 9.04	18.65 18.78)	**4l**	— (82.0)	218—220	$C_{14}H_{19}N_3O_2S$	57.31 (57.38	6.53 6.63	14.32 14.39)
3m	— (74.6)	250—266	$C_{11}H_{19}N_3S$	58.62 (58.38	8.50 8.24	18.65 18.68)	**4m**	— (79.5)	222—225	$C_{14}H_{19}N_3O_2S$	57.31 (57.26	6.53 6.33	14.32 14.33)
3n	— (98.0)	248—250	$C_{12}H_{21}N_3S$	60.21 (60.20	8.84 8.76	17.55 17.58)	**4n**	— (77.5)	226—230 (dec.)	$C_{15}H_{21}N_3O_2S$	58.45 (58.60	6.87 6.85	13.63 13.68)
3o	— (80.8)	226 (unclear)	$C_{16}H_{29}N_3S$	65.04 (65.39	9.89 9.87	14.22 14.38)	**4o**	— (91.9)	224—227 (dec.)	$C_{19}H_{29}N_3O_2S$	62.78 (62.67	8.04 7.96	11.56 11.73)

a) A: EtOH–H_2O, B: EtOH, C: MeOH, D: EtOH–Et_2O, —: not recrystallized. *b*) Reported[28] mp 234—236 °C.

TABLE IV. 2-Substituted 7-Hydroxy-6-nitro-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-ones **5** and 2-Substituted 7-Chloro-6-nitro-5*H*-1,3,4-thiadiazolo-[3,2-*a*]pyrimidin-5-ones **6**

Compd. No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Compd. No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
5b	70.4	118—119	$C_{13}H_{18}N_4O_4S$	47.84 (47.84	5.56 5.49	17.17 17.28)	**6b**	96.4	70—72	$C_{13}H_{17}ClN_4O_3S$	45.28 (45.29	4.97 4.94	16.25 16.42)
5c	60.3	189—194	$C_{11}H_{14}N_4O_4S$	44.29 (44.68	4.73 4.66	18.78 19.00)	**6c**	99.5	145—157	$C_{11}H_{13}ClN_4O_3S$	41.71 (41.46	4.14 4.13	17.69 17.61)
5d	74.9	157—159	$C_{12}H_{16}N_4O_4S$	46.14 (45.80	5.16 4.85	17.94 17.86)	**6d**	94.8	77—78	$C_{12}H_{15}ClN_4O_3S$	43.57 (43.40	4.57 4.60	16.94 16.89)
5e	72.0	164—165	$C_{12}H_{14}N_4O_4S$	46.44 (46.22	4.55 4.54	18.05 18.31)	**6e**	92.5	146—147	$C_{12}H_{13}ClN_4O_3S$	43.84 (43.50	3.99 4.02	17.04 17.02)
5f	71.0	118—120	$C_{13}H_{16}N_4O_4S$	48.15 (48.16	4.97 4.73	17.28 17.51)	**6f**	90.0	120—124	$C_{13}H_{15}ClN_4O_3S$	45.54 (45.25	4.40 4.34	16.34 16.49)
5g	81.0	159—162	$C_{12}H_{14}N_4O_4S$	46.44 (46.34	4.55 4.41	18.05 18.14)	**6g**	96.7	152—153	$C_{12}H_{13}ClN_4O_3S$	43.84 (43.46	3.99 3.91	17.04 16.90)
5h	91.2	170—171	$C_{13}H_{16}N_4O_4S$	48.14 (47.87	4.97 4.69	17.27 17.41)	**6h**	96.3	136—137	$C_{13}H_{15}ClN_4O_3S \cdot 1/4H_2O$	44.95 (44.92	4.50 4.38	16.13 16.24)
5i	78.1	121—122	$C_{14}H_{18}N_4O_4S$	49.69 (49.68	5.36 5.26	16.56 16.72)	**6i**	99.0	136—138	$C_{14}H_{17}ClN_4O_3S \cdot 1/2H_2O$	45.96 (46.24	4.96 4.60	15.32 15.64)
5j	81.6	206—208 (dec.)	$C_{13}H_{14}N_4O_4S$	48.44 (48.51	4.38 4.31	17.38 17.24)	**6j**	—	200—203	$C_{13}H_{13}ClN_4O_3S$	45.82 (45.77	3.85 3.78	16.44 16.40)
5k	90.0	125—131	$C_{14}H_{18}N_4O_4S$	49.69 (49.66	5.36 5.39	16.56 16.53)	**6k**	100	108—115	$C_{14}H_{17}ClN_4O_3S \cdot 3/2H_2O$	43.81 (43.49	5.25 5.09	14.60 14.27)
5l	93.0	170—173	$C_{14}H_{18}N_4O_4S$	49.69 (49.73	5.36 5.30	16.56 16.70)	**6l**	95.0	152—153	$C_{14}H_{17}ClN_4O_3S \cdot 1/4H_2O$	46.53 (46.56	4.88 4.75	15.51 15.61)
5m	76.8	149—151	$C_{14}H_{18}N_4O_4S$	49.69 (49.41	5.36 5.20	16.56 16.61)	**6m**	95.5	91—94	$C_{14}H_{17}ClN_4O_3S$	47.12 (46.94	4.80 4.64	15.70 15.76)
5n	94.7	148—150	$C_{15}H_{20}N_4O_4S$	51.12 (51.01	5.72 5.98	15.90 15.85)	**6n**	66.5	62—73	$C_{15}H_{19}ClN_4O_3S$	48.58 (48.72	5.16 5.32	15.11 15.07)
5o	96.8	212—216 (dec.)	$C_{19}H_{28}N_4O_4S$	55.86 (56.50	6.91 6.98	13.71 13.58)	**6o**	—	147—153	$C_{19}H_{27}ClN_4O_3S \cdot 1/2H_2O$	52.34 (52.27	6.47 6.63	12.85 12.51)

20.10 (CH$_3$), 27.99 (2-C), 28.23 (2'- and 6'-C), 29.79 (4'-C), 30.46 (3'- and 5'-C), 33.82 (1-C), 34.28 (1'-C), 159.78 (Ar-C), 168.41 (Ar-C). **31**: ^{13}C-NMR (DMSO-d_6–CDCl$_3$) δ: 22.58 (CH$_3$), 27.66 (2-C), 32.50 (4'-C), 32.74 (2'-and 6'-C), 34.92 (3'- and 5'-C), 36.51 (1-C), 36.91 (1'-C), 159.87 (Ar-C), 168.36 (Ar-C).

2-(2-Cyclohexylethyl)-7-hydroxy-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (4h) A mixture of **3h** (9.50 g, 45 mmol) and bis(2,4,6-trichlorophenyl) malonate (21.8 g, 47 mmol) in xylene (70 ml) was heated at 140—150 °C for 2 h. After the mixture had been cooled to room temperature, the precipitate was collected and washed thoroughly with EtOH and Et$_2$O to give **4h** (10.30 g, 81.7%), mp 215—219 °C. IR (KBr): 1690, 1514 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.80—1.90 (13H, m, 6×CH$_2$ and CH), 3.05 (2H, t, J=7 Hz, CH$_2$Ar), 5.77 (1H, s, C$_6$-H).

Compounds **4b—g** and **4i—o** were prepared by an analogous procedure, and data are listed in Table III.

2-(2-Cyclohexylethyl)-7-hydroxy-6-nitro-5*H*-1,3,4-thiadiazolo[3,2-*a*]-pyrimidin-5-one (5h) Fuming HNO$_3$ (3.5 ml, 79 mmol) was added dropwise to a stirred suspension of **4h** (9.77 g, 35.0 mmol) in AcOH (125 ml) at room temperature within 20 min, and the stirring was continued for a further 2.5 h at room temperature. The precipitate was collected and washed successively with ice-water, EtOH and Et$_2$O to give **5h** (10.30 g, 91.2%), mp 170—171 °C. IR (KBr): 1725, 1566, 1494, 1443 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.70—1.90 (13H, m, 6×CH$_2$ and CH), 3.08 (2H, t, J=7 Hz, CH$_2$Ar).

Compounds **5b—g** and **5i—o** were prepared by an analogous procedure, and data are listed in Table IV.

7-Chloro-2-(2-cyclohexylethyl)-6-nitro-5*H*-1,3,4-thiadiazolo[3,2-*a*]-pyrimidin-5-one (6h) Tripropylamine (4 ml, 21 mmol) was added to a suspension of **5h** (10.20 g, 31.5 mmol) in POCl$_3$ (30 ml, 322 mmol), and the mixture was heated at 80—85 °C for 3 h. After the mixture had been cooled to room temperature the reaction mixture was poured into ice water and stirred for 30 min. The resulting precipitate was collected and washed with water to give **6h** (10.40 g, 96.3%), mp 136—137 °C. IR (KBr): 1710, 1545, 1521, 1491 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.80—1.90 (13H, m, 6×CH$_2$ and CH), 3.13 (2H, t, J=7 Hz, CH$_2$Ar).

Compounds **6b—g** and **6i—o** were prepared by an analogous procedure and data are listed in Table IV.

7-Amino-2-(2-cyclohexylethyl)-6-nitro-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (7h) Concentrated NH$_4$OH (7 ml, 56 mmol) was added to a suspension of **6h** (9.59 g, 28 mmol) in EtOH (100 ml) at room temperature. The mixture was further stirred for 5.5 h at the same temperature and cooled. The precipitate formed was collected to obtain **7h** (7.05 g, 78.0%). A small amount was recrystallized from EtOH, mp 249—251 °C. IR (KBr): 3448, 3280, 1710, 1593 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 0.80—1.90 (13H, m, 6×CH$_2$ and CH), 3.01 (2H, t, J=7 Hz, CH$_2$Ar).

Compounds **7b—g** and **7i—o** were prepared by an analogous procedure and data are listed in Table V.

6-(2-Cyclohexylethyl)-[1,3,4]thiadiazolo[3,2-*a*]-1,2,3-triazolo[4,5-*d*]-pyrimidin-9(3*H*)-one (1h) A suspension of **7h** (6.46 g, 20.0 mmol) and tin powder (11.90 g, 0.10 g atom) in dioxane (100 ml) was treated according to the procedure reported for 2-(2-phenylethyl) derivative.[1] Recrystallization from 95% EtOH gave **1h** (2.0 g, 32.9%), mp 265—270 °C (dec.). IR (KBr): 2926, 2848, 1713, 1578, 1536 cm^{-1}. ^{1}H-NMR (CDCl$_3$–TFA) δ: 0.80—1.90 (13H, m, 6×CH$_2$ and CH), 3.10 (2H, t like, J=7 Hz, CH$_2$Ar).

Compounds **1b—g** and **1i—o** were prepared by an analogous procedure, and data are listed in Table V.

X-Ray Crystallography of 1h Light yellow prism crystals (0.250×0.200×0.200 mm^3) obtained by crystallization from a mixture of THF and dimethylformamide (DMF) were used. Crystal data: C$_{13}$H$_{16}$N$_6$OS, M_r=304.67, triclinic with space group $P\bar{1}$(#2), a=12.320(2), b=14.084(3), c=8.738(1) Å, α=90.44(2), β=103.34(1), γ=90.63(2)°, V=1475.2(5) Å^3, Z=4, D_{calcd}=1.370 g/cm^3, $F(000)$=640, μ for CuK_α=19.85 cm^{-1}. Intensities were collected on a Rigaku AFC5R diffractometer using the ω-2θ scan mode with graphite monochromated CuK_α (λ=1.54178 Å) radiation up to 2θ=120.1°; 3430 unique reflections with $I>3.00\sigma$ (I) were used for refinement. The structure was solved by direct methods and refined by full-matrix least-squares and different Fourier method. All non-hydrogen atoms were refined anisotropically and the hydrogen atoms of the triazole groups were located from difference Fourier maps and

TABLE V. 2-Substituted 7-Amino-6-nitro-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-ones **7** and 6-Substituted [1,3,4]Thiadiazolo[3,2-*a*]-1,2,3-triazolo-[4,5-*d*]pyrimidin-9(3*H*)-ones **1**

Compd. No.	Recrystn. solvent[a] (Yield, %)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Compd. No.	Recrystn. solvent[a] (Yield, %)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
7b	— (81.6)	175—182	$C_{13}H_{19}N_5O_3S$	47.98 (47.72	5.89 5.88	21.52 21.21)	**1b**	D (45.9)	231—232	$C_{13}H_{18}N_6OS$	50.96 (50.78	5.92 5.96	27.43 27.32)
7c	— (67.9)	264—268	$C_{11}H_{15}N_5O_3S$	44.43 (44.62	5.09 5.12	23.55 23.58)	**1c**	D (17.4)	275—279 (dec.)	$C_{11}H_{14}N_6OS$	47.47 (47.09	5.07 4.98	30.20 30.29)
7d	— (80.5)	243—246	$C_{12}H_{17}N_5O_3S$	46.29 (46.53	5.50 5.50	22.49 22.61)	**1d**	D (34.8)	255—260	$C_{12}H_{16}N_6OS$	49.30 (49.11	5.52 5.48	28.75 28.63)
7e	— (81.5)	238—239	$C_{12}H_{15}N_5O_3S$	46.58 (46.46	4.89 5.00	22.63 22.36)	**1e**	D (50.5)	271—275 (dec.)	$C_{12}H_{14}N_6OS$	49.64 (49.74	4.86 4.90	28.95 29.31)
7f	— (81.0)	225—227	$C_{13}H_{17}N_5O_3S$	48.29 (48.31	5.30 5.28	21.66 21.66)	**1f**	A (66.0)	269—271	$C_{13}H_{16}N_6OS$	51.31 (51.53	5.30 5.26	27.62 27.77)
7g	— (86.7)	274—280	$C_{12}H_{15}N_5O_3S$	46.59 (46.63	4.89 4.91	22.64 22.50)	**1g**	D (50.2)	285—290 (dec.)	$C_{12}H_{14}N_6OS$	49.64 (49.40	4.86 4.92	28.95 28.72)
7h	A (78.0)	249—251	$C_{13}H_{17}N_5O_3S$	48.28 (48.31	5.30 5.32	21.66 21.66)	**1h**	A (55.9)	266—270 (dec.)	$C_{13}H_{16}N_6OS$	51.30 (51.01	5.30 5.41	27.61 27.54)
7i	— (84.8)	238—242	$C_{14}H_{19}N_5O_3S$	49.84 (49.70	5.68 5.57	20.76 20.79)	**1i**	D (37.0)	268—271	$C_{14}H_{18}N_6OS$	52.81 (52.76	5.70 5.77	26.40 26.30)
7j	B (80.1)[b]	275—277 (dec.)	$C_{13}H_{15}N_5O_3S$	48.59 (48.17	4.71 5.08	21.80 20.88)	**1j**	A (21.0)	256—260	$C_{13}H_{14}N_6OS$	51.64 (51.45	4.67 4.85	27.80 27.23)
7k	— (69.0)	140—141	$C_{14}H_{19}N_5O_3S$	49.84 (49.89	5.68 5.81	20.76 20.58)	**1k**	A (42.0)	251—254	$C_{14}H_{18}N_6OS$	52.81 (52.58	5.70 5.81	26.40 26.22)
7l	— (70.0)	241—245	$C_{14}H_{19}N_5O_3S$	49.84 (50.11	5.68 5.71	20.76 20.92)	**1l**	A (63.0)	274—276	$C_{14}H_{18}N_6OS$	52.81 (52.54	5.70 5.65	26.40 26.28)
7m	— (84.7)	252—255	$C_{14}H_{19}N_5O_3S$	49.84 (49.40	5.68 5.64	20.76 20.62)	**1m**	D (62.1)	257—270 (dec.)	$C_{14}H_{18}N_6OS$	52.81 (52.98	5.70 5.82	26.40 26.48)
7n	B (77.8)	260—267	$C_{15}H_{21}N_5O_3S$	51.26 (51.10	6.02 6.19	19.93 19.81)	**1n**	E (37.3)	269—273	$C_{15}H_{20}N_6OS$	54.20 (54.21	6.06 6.30	25.28 25.19)
7o	C (58.3)[c]	209—210	$C_{19}H_{29}N_5O_3S$	56.00 (56.16	7.17 7.20	17.18 17.08)	**1o**	E (33.3)	282—290 (dec.)	$C_{19}H_{28}N_6OS$	58.74 (58.58	7.26 7.10	21.63 21.69)

a) A: EtOH, B: CHCl$_3$–EtOH, C: AcOH, D: 95% EtOH, E: EtOH–CHCl$_3$. *b*) Yield from **5j**. *c*) Yield from **5o**.

TABLE VI. Positional Parameters and Equivalent Isotropic Temperature Factors of Non-hydrogen and Triazole–Hydrogen Atoms with Standard Deviations in Parentheses for **1h**

Atom	*x*	*y*	*z*	*B*(eq)	Atom	*x*	*y*	*z*	*B*(eq)
S(1)	0.13589 (8)	0.13657 (6)	0.2093 (1)	4.50 (4)	S(2)	0.13837 (8)	0.63986 (6)	1.0777 (1)	4.64 (4)
O(1)	0.1241 (2)	−0.0342 (1)	0.6794 (3)	4.2 (1)	O(2)	0.1256 (2)	0.4663 (1)	0.5978 (3)	4.6 (1)
N(1)	0.1376 (2)	−0.0146 (2)	0.3743 (3)	3.6 (1)	N(7)	0.1367 (2)	0.4875 (2)	0.9116 (3)	3.7 (1)
N(2)	0.1323 (2)	0.0628 (2)	0.4718 (3)	3.2 (1)	N(8)	0.1313 (2)	0.5640 (2)	0.8109 (3)	3.4 (1)
N(3)	0.1201 (2)	0.1545 (2)	0.8578 (3)	4.2 (1)	N(9)	0.1330 (2)	0.6540 (2)	0.4223 (3)	4.2 (1)
N(4)	0.1213 (2)	0.2468 (2)	0.8755 (3)	4.6 (1)	N(10)	0.1376 (2)	0.7462 (2)	0.4080 (3)	4.5 (1)
N(5)	0.1269 (2)	0.2868 (2)	0.7366 (3)	4.1 (1)	N(11)	0.1383 (2)	0.7869 (2)	0.5486 (3)	3.9 (1)
N(6)	0.1308 (2)	0.2329 (2)	0.4752 (3)	3.8 (1)	N(12)	0.1341 (2)	0.7344 (2)	0.8095 (3)	3.9 (1)
C(1)	0.1264 (2)	0.0469 (2)	0.6292 (4)	3.4 (1)	C(21)	0.1280 (3)	0.5466 (2)	0.6496 (4)	3.4 (1)
C(2)	0.1245 (2)	0.1355 (2)	0.7063 (4)	3.3 (1)	C(22)	0.1304 (3)	0.6358 (2)	0.5745 (4)	3.4 (1)
C(3)	0.1277 (2)	0.2201 (2)	0.6276 (3)	3.2 (1)	C(23)	0.1337 (2)	0.7200 (2)	0.6559 (4)	3.4 (1)
C(4)	0.1325 (2)	0.1511 (2)	0.4039 (4)	3.4 (1)	C(24)	0.1333 (3)	0.6533 (2)	0.8798 (4)	3.6 (1)
C(5)	0.1408 (3)	0.0138 (2)	0.2367 (4)	3.8 (1)	C(25)	0.1419 (3)	0.5174 (2)	1.0527 (4)	3.6 (1)
C(6)	0.1539 (3)	−0.0520 (3)	0.1084 (4)	4.7 (2)	C(26)	0.1575 (3)	0.4524 (2)	1.1896 (4)	4.5 (2)
C(7)	0.2704 (3)	−0.0456 (3)	0.0754 (4)	5.3 (2)	C(27)	0.2772 (3)	0.4570 (3)	1.2906 (4)	5.3 (2)
C(8)	0.3643 (3)	−0.0758 (3)	0.2123 (4)	5.2 (2)	C(28)	0.3654 (3)	0.4230 (3)	1.2070 (5)	5.6 (2)
C(9)	0.4769 (4)	−0.0453 (4)	0.1919 (7)	9.7 (3)	C(29)	0.3631 (4)	0.3178 (4)	1.1836 (7)	8.9 (3)
C(10)	0.5705 (5)	−0.0753 (7)	0.327 (1)	13.5 (5)	C(30)	0.4537 (6)	0.2836 (6)	1.105 (1)	15.7 (6)
C(11)	0.5686 (6)	−0.1787 (7)	0.3472 (9)	12.8 (5)	C(31)	0.5653 (6)	0.3148 (8)	1.189 (1)	14.2 (6)
C(12)	0.4600 (6)	−0.2094 (6)	0.3727 (9)	14.4 (5)	C(32)	0.5692 (5)	0.4219 (7)	1.209 (1)	14.0 (6)
C(13)	0.3643 (4)	−0.1799 (4)	0.2387 (6)	8.7 (3)	C(33)	0.4811 (4)	0.4535 (4)	1.2905 (7)	10.2 (3)
H(1)	0.116 (3)	0.344 (3)	0.717 (4)	6 (1)	H(21)	0.135 (3)	0.851 (2)	0.555 (4)	5.3 (9)

refined isotropically. The final R value was 0.048. The final positional parameters with the estimated standard deviations and the equivalent isotropic temperature factors for the non-hydrogen atoms and two triazole–hydrogen atoms are given in Table VI.

Preparation of Rat Anti-ovalbumin Antiserum[24] Female Sprague-Dawley rats (Charles River Japan, Inc.) weighing 170—250 g were immunized intramuscularly with 5.0 mg/kg of egg albumin dissolved in saline (1.0 mg/ml), and intraperitoneally with 2×10^{10} *Bordetella pertussis* organisms in 1.0 ml of saline. Ten days later, *Nippostrongylus brasiliensis* (3×10^3 larvae) were administered subcutaneously to the rats. The rats were bled on the 24th day and the serum containing immuno globulin E (IgE) was pooled. The 48-h PCA titer of this serum was found to be 1: 128—512.

PCA[24] Male Sprague rats (160—230 g) were used in groups of 5—6 animals. The antiserum was diluted with saline so as to form a blue spot having a diameter of about 10 mm in the following control group. The diluted antiserum (0.05 ml) was injected into the shaved dorsal skin. After a 48-h sensitization period, the animals were challenged with 1 ml of saline containing 5 mg of ovalbumin and 5 mg of Evans blue dye *via* a tail vein. After 30 min, the animals were sacrificed, the dorsal skin was removed and the amount of dye in each blue wheal that resulted was measured. The extraction and measurement of the dye from the wheal site were carried out by the procedure described by Katayama *et al.*[25] In the case of screening, the test compound (10 mg/kg suspended in 5.0 ml of 0.05% carboxymethyl cellulose (CMC) was administered orally 30 min prior to the antigen challenge. To determine the activity of **1h** and DSCG, they were administered orally 30 min before or intravenously just before challenge of the animal with ovalbumin. The effect of the drug was expressed as percent inhibition of the control. The ID_{50} values were calculated as the dose required to inhibit 50% of the control. Statistical significance of the data was calculated using Dunnett's multiple comparison technique.

LTD_4 Antagonistic Activity The antagonistic activity against LTD_4 was measured by the LTD_4-induced guinea pig ileum contraction *in vitro*. Strips of the isolated ileum from male Hartley guinea pigs (weighing 300—600 g) were suspended in an organ bath filled with 5 ml of Tyrode's solution at 37±1 °C and bubbled with a 95% O_2–5% CO_2 mixture. Ileal tissue responses induced by LTD_4 (3 ng/ml) were measured isotonically with a load of 0.6 g using isotonic transducers (Nihon Kohden, TS-112S) and recorded on a recorder (Rikadenki, R54GP-1B). The duration of pretreatment with the test compound was 1 min. The percent inhibition was calculated by comparing the responses before and after addition of the test compound. Thereafter, the concentration required to produce a 50% inhibition of control (IC_{50}) was calculated to compare the activities of test compounds. The values in Table I are the mean of duplicate experiments. The compound **1a** was used as the postive control, and the relative activity to **1a** was also calculated.

Binding of [^{3}H]LTD_4 to Guinea Pig Lung Membranes The procedure was adopted from that described by Pong and Dehaven.[26] Male Hartley guinea pigs were sacrificed by decapitation and the lungs were isolated and homogenized for 45—90 s in 5 volumes (w/v) of 50 mM Tris–HCl buffer (pH 7.4) with a polytron homogenizer. The homogenate was centrifuged at $1000 \times g$ for 10 min at 0 °C. The supernatant was recentrifuged at $45000 \times g$ for 10 min at 0 °C to yield pellets which were referred to as crude membrane fractions. The mixture of 50 μl guinea pig lung membranes (100 μg of protein), 0.95 ml of Tris–HCl buffer (pH 7.4) containing 20 mM $CaCl_2$, the test compound and 0.37 nM [^{3}H]LTD_4 (38.4 Ci/mM) was incubated at 20 °C for 40 min. At the end of the incubation, samples were filtered immediately through Whatman GF/B glass filters to separate free and bound radioligand. The filters were washed rapidly 3 times with 5 ml of ice-cold buffer, placed in scintillation vials. Specific binding was calculated as the difference between total binding and non-specific binding in the presence of 100 nM of LTD_4. Assay was carried out in triplicate. To determine the activities of test compounds, apparent K_i values were calculated following the equation[27]: $K_i = IC_{50}/(1+[L]/K_d)$. [L] is the concentration of [^{3}H]LTD_4 in the assay. The IC_{50} values were calculated as the concentration required to inhibit 50% of the control. The K_d were determined from the slopes of Scatchard plots of specific binding data.

Acute Toxicity Male Std:ddY mice weighing 15—25 g were used. The test compounds were suspended in 0.5% CMC and administered orally at a dose of 2.0 g/kg, and the mortality was evaluated after 14 d.

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