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Synthesis of Imidazo[4,5-*c*][1,2,6]thiadiazine 2-Oxides from Hydrolytes of Xanthines and Determination of Their Vasodilating Activity

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Novel 1,3,6,7-tetrahydro-7-oxoimidazo[4,5-*c*][1,2,6]thiadiazine 2-oxide derivatives (**2a**—**q**) were synthesized by the reaction of imidazole derivatives (**1**), obtained by alkaline hydrolysis of 1,3,7-trisubstituted xanthines (**3**), with $SOCl_2$ in 42—93% yields. Chlorination of **2** with SO_2Cl_2 gave the 5-chloro derivatives (**10a**, **d**, **i**—**q**), though in low yields. The reaction of **2** with benzoyl chloride derivatives (**14**) gave 3,7-dihydro-6*H*-purin-6-one derivatives (**15a**—**d**).

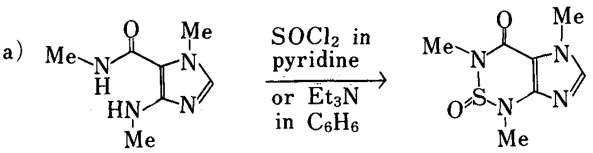
Among **2** and **10**, compounds having the phenoxyalkyl group at the 1-position exhibited potent vasodilating activity on the mesenteric artery of spontaneously hypertensive rats. In particular, ED_{50} values of the order of 10^{-7} M were obtained with those having a 1-[6-(4-chlorophenoxy)hexyl]-6-propyl (**2o**), 6-hexyl-1-[6-(4-methoxyphenoxy)hexyl] (**2p**), 1-[6-(4-chlorophenoxy)hexyl]-6-hexyl (**2q**), 5-chloro-1-[6-(4-chlorophenoxy)hexyl]-6-methyl (**10l**), 5-chloro-1-[4-(4-methoxyphenoxy)-butyl]-6-propyl (**10m**), 5-chloro-1-[6-(4-methoxyphenoxy)hexyl]-6-propyl (**10n**), or 5-chloro-1-[6-(4-chlorophenoxy)hexyl]-6-propyl (**10o**) substituent.

Keywords——xanthine hydrolyte; imidazo[4,5-*c*][1,2,6]thiadiazine 2-oxide; thionyl chloride; sulfuryl chloride; 3,7-dihydro-6*H*-purin-6-one; vascular relaxation

The xanthine skeleton is a basic structure of natural alkaloids such as caffeine and theophylline and of synthetic medicines such as oxyetophylline,[1a)] proxiphylline,[1b)] and pentoxifylline.[1c)] In a series of studies on the synthesis of novel compounds having the xanthine skeleton, we have studied the structural conversion of xanthine derivatives and examined the physiological activities of the newly synthesized compounds.[2—4)] It has been found that 1,2,3,7-tetrahydro-6*H*-purine-6-one derivatives show vasodilating activity. Thus, in the hope of synthesizing compounds having more potent vasodilating activity, we attempted to introduce a sulfoxide group into the xanthine skeleton in place of the carbonyl group at the 2-position, based on the fact that a sulfur atom participates in the active centers of many enzymes that control biological phenomena as well as materials such as acyl carrier protein, coenzyme A and insulin that are essential for the maintenance of life. The present paper deals with the synthesis of imidazo[4,5-*c*][1,2,6]thiadiazine 2-oxides (**2**) from the hydrolytes of 1,3,7-trisubstituted xanthines (**3**) and $SOCl_2$, and also with the reactivities of **2**. The pharmacological activity of **2** and the 5-chloro derivatives (**10**) is also discussed.

Barluenga *et al.* synthesized 1,2,6-thiadiazine 1-oxide derivatives having an SO group between two amino groups by cyclization of 3-iminoprop-1-enamine derivatives with $SOCl_2$.[5)] On the other hand, Deyrup *et al.* carried out the reaction of 2-aminoamide derivatives with $SOCl_2$ to obtain 5-imino-2-oxo-1,2,3-oxathiazolidine derivatives containing an SO group between the nitrogen atom of the amino group and the oxygen atom of the amido group.[6] However, the cyclization of 3-aminoamide-type compounds such as caffeidine (**1a**) with $SOCl_2$ has not been investigated, to our knowledge. Thus, we examined the reaction of **1a** with $SOCl_2$.

The reaction of **1a** with $SOCl_2$ in dry pyridine or in dry benzene in the presence of Et_3N gave colorless needles (**2a**) (mp 106—107 °C) in 86% or 40% yield, respectively (Chart 1a). The elemental analysis and mass spectrum (M^+ *m/z*: 214) of **2a** suggested the molecular formula, $C_7H_{10}N_4O_2S$, which corresponds to the molecular formula of **1a** plus SO minus 2H. The infrared (IR) spectrum of **2a** showed very strong absorptions at 1665 and 1110 cm^{-1} but no absorption band corresponding to ν_{NH} of **1a**. In the proton nuclear magnetic resonance (^1H-NMR) spectrum of **2a**, singlet signals were observed at δ 3.34 (3H), 3.45 (3H), 3.96 (3H) and 7.42 (1H) (Tables I and II). These data suggested that the SO group was taken into **1a**. In order to clarify whether the SO group combined with the nitrogen or oxygen atom of the amido group, the IR data of **2a** were compared with those of *N*-[3-(1,1-dimethylethyl)-1,2,3-oxathiazolidin-5-ylidene]-2-propanamine S-oxide (**16**) synthesized by Deyrup *et al.*[6] There was as large a difference as 50 cm^{-1} between the absorption band due to $\nu_{C=N}$ of **16** at 1715 cm^{-1} and that of **2a** at 1665 cm^{-1}. This large difference was considered to be attributable to the presence of different functional groups. The absorption at 1665 cm^{-1}, which was the strongest among those of the molecules, seemed due to the amido CO group. Therefore, **2a** was suggested to be 1,3,6,7-tetrahydro-1,3,6-trimethyl-7-oxoimidazo[4,5-*c*][1,2,6]thiadiazine 2-oxide, which contains the SO group between the nitrogen atom of the amido group and that of the amino group.

a)


1a **2a**

b) $2a + 2NaOH \longrightarrow 1a + Na_2SO_3$

$2a + 2H_2O \xrightarrow{H^+} 1a + H_2SO_3$

$2a + 2NaHCO_3 \longrightarrow 1a + Na_2SO_3 + 2CO_2$

Chart 1

Compound **2a** in H_2O was stable at room temperature for at least 24 h, while in aqueous NaOH, **2a** was rapidly hydrolyzed to **1a**. This hydrolysis was completed in the presence of 2 eq of NaOH and the pH of the solution was decreased. These findings suggested that the SO group of **2a** was eliminated as SO_2 and converted to Na_2SO_3. In aqueous $NaHCO_3$ (3%), **2a** was completely hydrolyzed within *ca.* 36 h. Furthermore, **2a** was also hydrolyzed to **1a** in aqueous 0.1 N HCl but this hydrolysis took 3 d for completion (Chart 1b). The facile hydrolysis of **2a** in acidic and alkaline solutions proved that **2a** contains a diaminosulfoxide partial structure.

It was already reported that caffeidine-type imidazole derivatives can easily be obtained by the hydrolysis of 1,3,7-trisubstituted xanthines.[2,7] Therefore, we attempted the synthesis of various imidazo[4,5-*c*][1,2,6]thiadiazine 2-oxides (**2**) from the hydrolyte (**1**) of 1,3,7-trisubstituted xanthines (**3**) and $SOCl_2$.

Compounds **3b**—**q** were synthesized as follows. Compounds **3b**—**e**, **i** were synthesized with reference to the literature.[8] O-Alkylation of **4**[9] with CH_3I in the presence of NaH in dimethylformamide (DMF) at room temperature afforded **3f**. Bromohexyltheobromine (**5**)[10] was condensed with ethyl acetoacetate, followed by keto degradation to give **3g**. Bromopropyltheobromine (**6**)[9] was treated with morpholine in the presence of K_2CO_3 in acetone to form **3h**. Refluxing of **7a** and phenoxyalkylbromides (**8a**—**c**) in the presence of NaOH in EtOH–H_2O gave **3j**—**l**. According to the method reported previously,[4] **3c**, **r**[8c] were refluxed in $NH_2NH_2 \cdot H_2O$ to afford 1-aminoxanthine derivatives (**9b**, **c**), which were

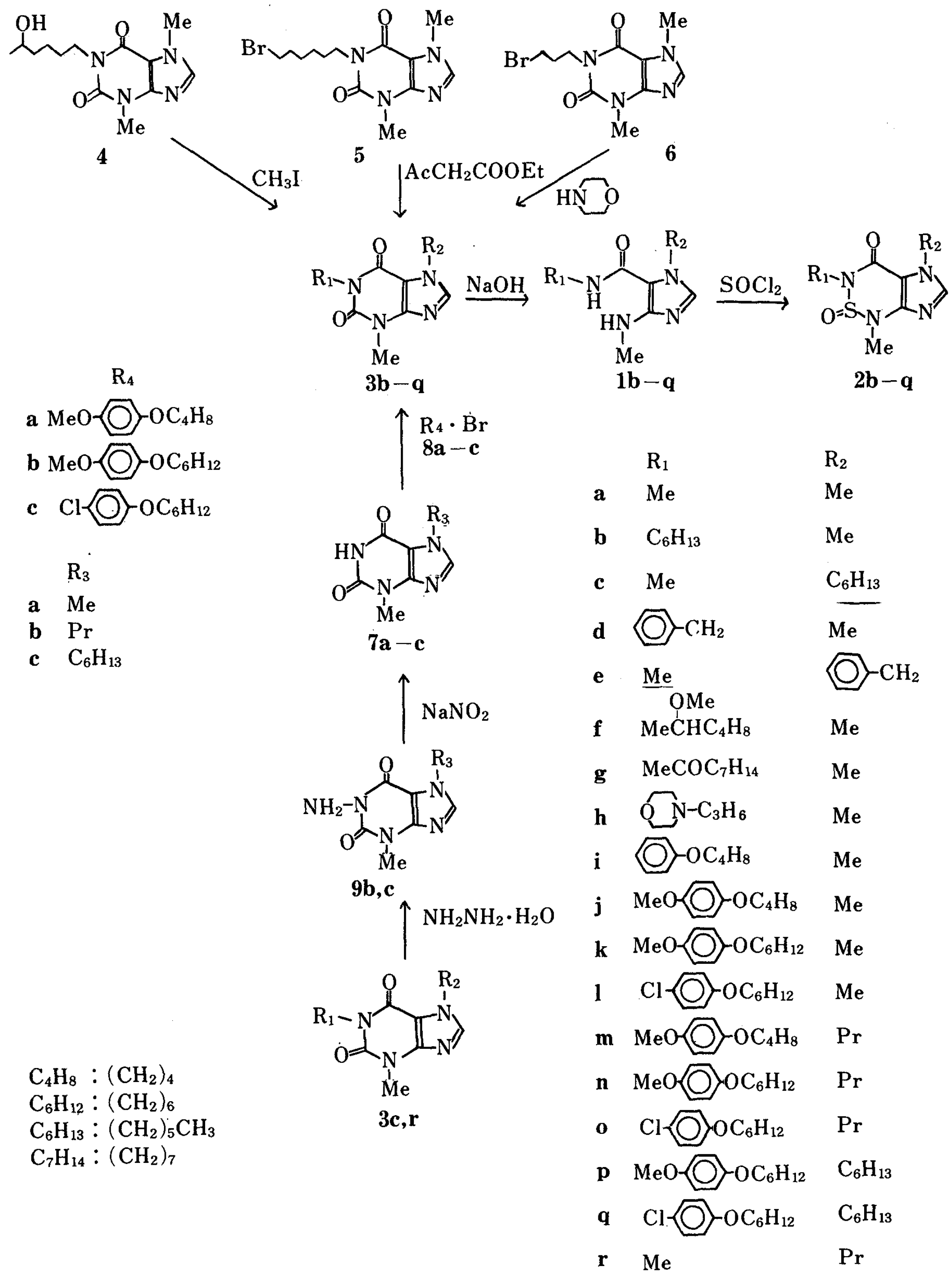


Chart 2

deaminated with $NaNO_2$ to give **7b**, **c**.[11] Compounds **7b**, **c** were allowed to react with **8a**—**c** under conditions similar to those used for the reaction of **7a** and **8** to give **3m**—**q**. The data on newly synthesized xanthine derivatives (**3f**—**h**, **j**—**q**) are summarized in Tables III and IV. The xanthine derivatives thus obtained (**3b**—**q**) gave corresponding imidazole derivatives (**1b**—**q**) when refluxed in aqueous 3 N NaOH or H_2O–EtOH (3 : 2) containing 3—4 N NaOH for 6—48 h (Chart 2). The structures of **1b**—**q** were determined by the data given in Tables V and VI.

Since the reaction from **1a** to **2a** in dry pyridine give a high yield, various caffeidine-type imidazole derivatives (**1b**—**q**) were treated with $SOCl_2$ under similar conditions. As a result, the corresponding imidazo[4,5-*c*][1,2,6]thiadiazine 2-oxide derivatives (**2b**—**q**) were obtained in good yields (42—93%): alkyl compounds (**2b**, **c**), aralkyl compounds (**2d**, **e**), an alkoxyalkyl compound (**2f**), an oxoalkyl compound (**2g**), an aminoalkyl compound (**2h**) and phenoxyalkyl compounds (**2i—q**) were thus obtained (Chart 2). The structural assignments of **2b—q** were based on the IR spectra showing strong absorption bands at 1665—1680 cm^{-1} and 1110—1140 cm^{-1}, ^{1}H-NMR spectra, mass spectra and elemental analyses (Tables I and II). The results indicated that imidazo[4,5-*c*][1,2,6]thiadiazine derivatives could easily be synthesized in high yields by the reaction of caffeidine-type imidazole derivatives with $SOCl_2$.

Libermann and Rouaix[12] reported the halogenation at the 8-position of caffeine, which corresponds to the 5-position of **2**. Therefore, we examined the chlorination of **2**. Gentle refluxing of **2a** in $SOCl_2$ for 24 h gave the desired 5-chloro-1,3,6,7-tetrahydro-1,3,6-trimethyl-7-oxoimidazo[4,5-*c*][1,2,6]thiadiazine 2-oxide (**10a**) in low yield (33%) (Chart 3). An alternative chlorination of **2a** by the use of SO_2Cl_2 in CCl_4 at room temperature for 2 h did not improve the yield of **10a** (31%) (Chart 3). In both reactions, the low yields were due to the formation of many unknown by-products which could mainly be observed near the starting point on thin-layer chromatography (TLC). Compounds **2d, i—q** were similarly treated with SO_2Cl_2 to give the corresponding **10d, i—q**, though the yields were low (Chart 3, Tables I and II).

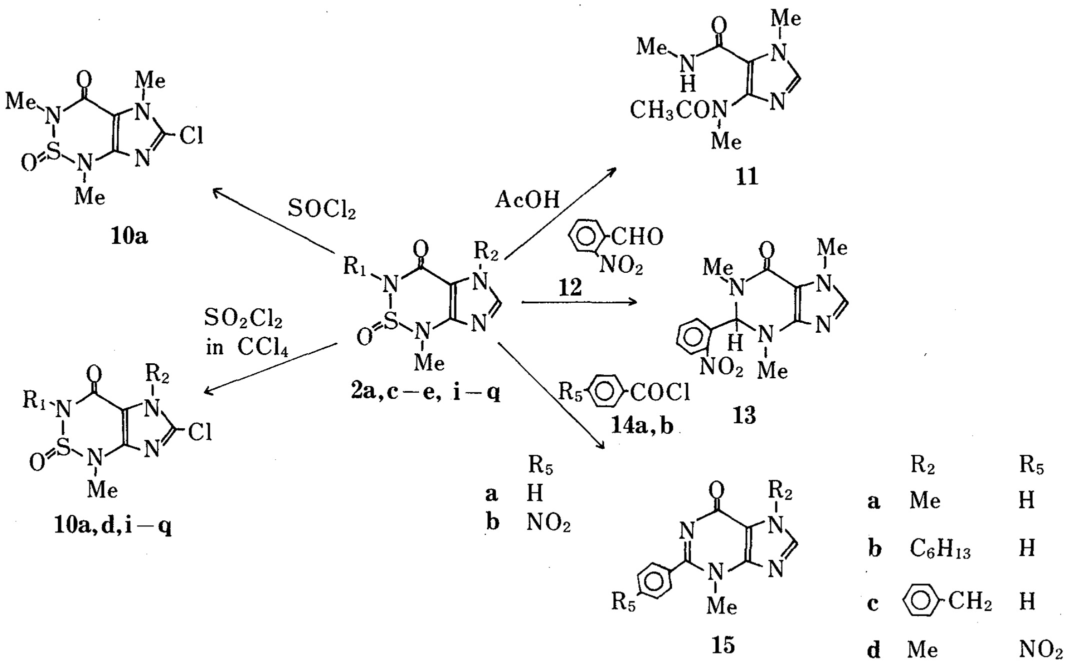


Chart 3

The fact that the SO group is readily eliminated as SO_2 in the hydrolysis of **2a** interested us, because it might have implications for the reaction of **2a** with electrophilic reagents such as carboxylic acids, aldehydes, and acyl chlorides. Refluxing of **2a** in dry acetic acid (AcOH) gave acetylcaffeidine (**11**) in 59% yield (Chart 3). Heating of **2a** and *o*-nitrobenzaldehyde (**12**) at 145—150 °C gave **13** (24%) along with SO_2 gas evolution (Chart 3). The facile elimination of the SO group in **2a** was considered to have resulted in the formation of **13** as well as **11**. The reaction of **2a** with an excess of benzoyl chloride (**14a**) at room temperature did not proceed at all, but at temperatures as high as 150—160 °C, an unexpected compound, 3,7-dihydro-3,7-dimethyl-2-phenyl-6*H*-purine-6-one (**15a**), was formed in 21% yield (Chart 3, Table VII). The evolution of SO_2 gas was also observed in this reaction. The IR spectrum of **15a** showed an absorption band due to a carbonyl group at 1680 cm^{-1}. In the ^{1}H-NMR spectrum, signals due to methyl groups at the 3- and 7-positions were observed at δ 3.47 and 4.07. The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum showed signals at δ 156.2, 156.0 and

155.7, of which two were assigned to the carbon atom of the carbonyl group linked to the imidazole ring and the carbon atom at the 4-position of the imidazole ring, respectively,[3,13] and the other was attributed to the newly formed quaternary sp^2 carbon atom. Based on the spectral data mentioned above, the mass spectrum (MS) and elemental analysis data, the structure of **15a** was assigned. Heating of **14a** and **2c** or **2e** under similar conditions to those for the formation of **15a** gave purine derivatives, **15b** and **15c**, in yields of 14% and 25%, respectively. The reaction of **14b** and **2a** also resulted in the formation of **15d** (8%) (Chart 3, Table VII), while the reactions of **14a** with **2b**, **d**, **i** afforded black-brown tarry materials.

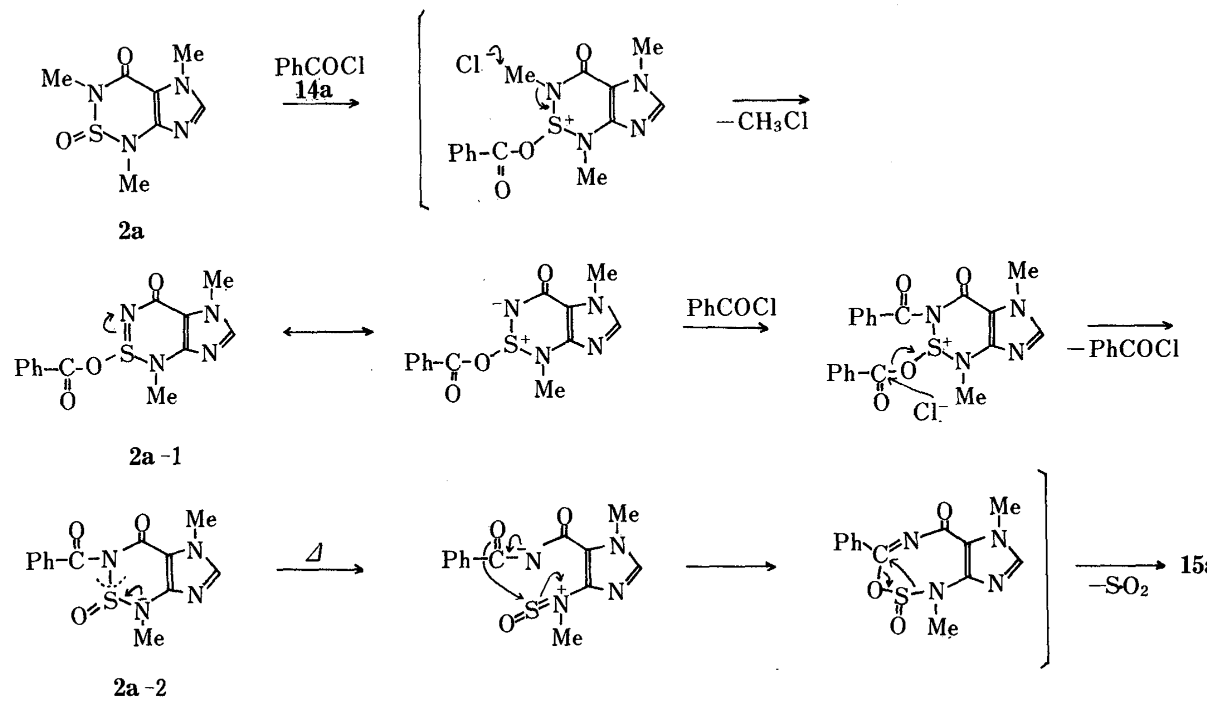
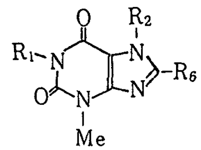


Chart 4

A plausible reaction mechanism for the formation of **15** is shown in Chart 4 on the basis of the structure of the formed purine derivatives, the reaction conditions (heating of **2** with an excess of **14** at 150—160 °C), and the result of the reaction of **2a** with **12**. The methyl group at the α-position of the SO group is eliminated by electrophilic attack of the benzoyl group on the oxygen atom of the SO group in **2a** to give **2a**-1. Next, an additional benzoyl group attacks the nitrogen atom of the amido group to give **2a**-2 which is formed by elimination of the benzoyl group substituted at the oxygen atom of the SO group. Finally, SO_2 is eliminated from **2a**-2 to form **15a**. In this reaction, the initial step from **2a** and **14a** to **2a**-1 is similar to Pummerer's reaction in terms of accompanying elimination of the substituent at the α-position of the SO group. Also, the formation of **15a** *via* **2a**-2 can be assumed to correspond to that of **13** from **2a** and **12**. On the other hand, the reason why **15**-type purine derivatives could not be obtained by the reaction of **14a** with **2b**, **d**, **i** having a large group such as benzyl, hexyl or phenoxybutyl group seems to be the difficulty of elimination of such a group.

The synthesized imidazo[4,5-*c*][1,2,6]thiadiazine derivatives (**2**, **10**) were tested for vasodilating activity using mesenteric arteries of spontaneously hypertensive rats (SHR) according to the method reported previously.[3] The ED_{50} values for the vascular relaxing activity against 30 mM KCl-induced vasocontraction are summarized in Table I. Among the compounds examined, **2o**, **2p**, **2q**, **10l**, **10m**, **10n** and **10o** were found to have potent vasodilating activity. Though the structure–activity relationship cannot yet be fully discussed due to lack of enough data, the phenoxyalkyl group at the 1-position seemed to have an

TABLE I. Physicochemical Properties, Elemental Analysis and Vascular Relaxing Activity of Imidazo[4,5-*c*][1,2,6]thiadiazine Derivatives (**2, 10**)



Compd. No.	R_1	R_2	R_6	mp (°C) (Appearance)	Yield (%)	Formula	Analysis (%) Calcd (Found) C H N	ED_{50} (μM)
2a	Me	Me	H	106—107 (Colorless needles)	86	$C_7H_{10}N_4O_2S$	39.24 4.70 26.15 (39.08 4.69 26.12)	>100
2b	C_6H_{12}	Me	H	(Colorless oil)	64	$C_{12}H_{20}N_4O_2S$	284.1306[a] (284.1285)	40
2c	Me	C_6H_{13}	H	62—63 (Colorless prisms)	74	$C_{12}H_{20}N_4O_2S$	50.68 7.09 19.70 (50.87 7.10 19.78)	43
2d	$C_6H_5CH_2$	Me	H	154—155 (Colorless needles)	93	$C_{13}H_{14}N_4O_2S$	53.78 4.86 19.30 (53.87 4.81 19.27)	76
2e	Me	$C_6H_5CH_2$	H	113—114 (Colorless needles)	74	$C_{13}H_{14}N_4O_2S$	53.78 4.86 19.30 (53.50 4.84 19.30)	>100
2f	MeCH(OMe)C$_4$H$_8$	Me	H	(Colorless oil)	84	$C_{13}H_{22}N_4O_3S$	314.1441[a] (314.1413)	>100
2g	MeCOC$_7$H$_{14}$	Me	H	87—88 (Colorless needles)	42	$C_{15}H_{24}N_4O_3S$	52.92 7.11 16.46 (52.64 7.08 16.35)	88
2h	ONC$_3$H$_6$	Me	H	73—74 (Colorless prisms)	78	$C_{13}H_{21}N_5O_3S$	47.69 6.46 21.39 (47.45 6.45 21.39)	>100
2i	$C_6H_5OC_4H_8$	Me	H	80—81 (Colorless prisms)	72	$C_{16}H_{20}N_4O_3S$	55.16 5.79 16.08 (54.95 5.73 16.08)	14.2
2j	MeOC_6H_4OC$_4$H$_8$	Me	H	103—104 (Colorless needles)	74	$C_{17}H_{22}N_4O_4S$	53.95 5.86 14.80 (53.95 5.88 14.77)	>20
2k	MeOC_6H_4OC$_6$H$_{12}$	Me	H	71—72 (Colorless needles)	64	$C_{19}H_{26}N_4O_4S$	56.14 6.45 13.78 (56.17 6.46 13.88)	5.2

2l	$Cl\text{-}C_6H_4\text{-}OC_6H_{12}$	Me	H	97—98 (Colorless needles)	79	$C_{18}H_{23}ClN_4O_3S$	52.61 5.64 13.63 (52.64 5.67 13.60)	1.9
2m	$MeO\text{-}C_6H_4\text{-}OC_4H_8$	Pr	H	(Pale yellow oil)	71	$C_{19}H_{26}N_4O_4S$	406.1674[a] (406.1666)	9.9
2n	$MeO\text{-}C_6H_4\text{-}OC_6H_{12}$	Pr	H	(Pale yellow oil)	66	$C_{21}H_{30}N_4O_4S$	434.1986[a] (434.2007)	1.4
2o	$Cl\text{-}C_6H_4\text{-}OC_6H_{12}$	Pr	H	62—63 (Colorless cotton)	72	$C_{20}H_{27}ClN_4O_3S$	54.72 6.20 12.76 (54.68 6.15 12.77)	0.47
2p	$MeO\text{-}C_6H_4\text{-}OC_6H_{12}$	C_6H_{13}	H	56—57 (Colorless cotton)	89	$C_{24}H_{36}N_4O_4S$	60.48 7.61 11.75 (60.56 7.63 11.88)	0.37
2q	$Cl\text{-}C_6H_4\text{-}OC_6H_{12}$	C_6H_{13}	H	38—39 (Colorless cotton)	72	$C_{23}H_{33}ClN_4O_3S$	480.1960[a] (480.1960)	0.29
10a	Me	Me	Cl	125—126 (Colorless needles)	33	$C_7H_9ClN_4O_2S$	33.81 3.65 22.53 (33.89 3.54 22.53)	
10d	$C_6H_5\text{-}CH_2$	Me	Cl	117—118 (Colorless needles)	29	$C_{13}H_{13}ClN_4O_2S$	48.07 4.03 17.25 (47.92 3.93 17.16)	28
10i	$C_6H_5\text{-}OC_4H_8$	Me	Cl	69—71 (Colorless needles)	30	$C_{16}H_{19}ClN_4O_3S$	50.19 5.00 14.63 (50.10 4.94 14.58)	13
10j	$MeO\text{-}C_6H_4\text{-}OC_4H_8$	Me	Cl	59—61 (Colorless needles)	23	$C_{17}H_{21}ClN_4O_4S$	49.45 5.13 13.57 (49.20 5.03 13.46)	14.2
10k	$MeO\text{-}C_6H_4\text{-}OC_6H_{12}$	Me	Cl	81—82 (Colorless needles)	22	$C_{19}H_{25}ClN_4O_4S$	51.75 5.71 12.71 (51.69 5.66 12.61)	3.7
10l	$Cl\text{-}C_6H_4\text{-}OC_6H_{12}$	Me	Cl	81—82 (Colorless needles)	20	$C_{18}H_{22}Cl_2N_4O_3S$	48.54 4.98 12.58 (48.69 4.95 12.43)	0.45
10m	$MeO\text{-}C_6H_4\text{-}OC_4H_8$	Pr	Cl	(Pale yellow oil)	20	$C_{19}H_{25}ClN_4O_4S$	440.1283[a] (440.1284)	0.67
10n	$MeO\text{-}C_6H_4\text{-}OC_6H_{12}$	Pr	Cl	(Pale yellow oil)	20	$C_{21}H_{29}ClN_4O_4S$	468.1599[a] (468.1606)	0.35
10o	$Cl\text{-}C_6H_4\text{-}OC_6H_{12}$	Pr	Cl	83—84 (Colorless needles)	23	$C_{20}H_{26}Cl_2N_4O_3S$	50.74 5.53 11.83 (50.83 5.55 11.68)	0.62
10p	$MeO\text{-}C_6H_4\text{-}OC_6H_{12}$	C_6H_{13}	Cl	48—49 (Colorless needles)	25	$C_{24}H_{35}ClN_4O_4S$	56.40 6.90 10.96 (56.14 6.79 11.13)	7.0
10q	$Cl\text{-}C_6H_4\text{-}OC_6H_{12}$	C_6H_{13}	Cl	84—85 (Colorless needles)	34	$C_{23}H_{32}Cl_2N_4O_3S$	53.59 6.26 10.89 (53.51 6.20 10.86)	>20

a) Determined by high-resolution mass spectrometry. Upper figure, calcd for M^+; lower figure, found.

TABLE II. Spectral Data for Imidazo[4,5-*c*][1,2,6]thiadiazine Derivatives (**2**, **10**)

Compd. No.	MS (m/z) (M^+)	IR (cm^{-1})	^{1}H-NMR (δ)
2a	214	1665 (CO), 1110 (SO)	3.34 (3H, s, N_1-CH_3), 3.45 (3H, s, N_3-CH_3), 3.96 (3H, s, N_6-CH_3), 7.42 (1H, s, C_5-H)
2b	284	1670 (CO), 1130 (SO)[a]	0.89 (3H, t, J=7 Hz, CH_3), 1.1—1.9 (8H, m, $CH_2\times4$), 3.44 (3H, s, N_3-CH_3), 3.63 (1H, q, J=7 Hz, N_1-CH), 3.94 (3H, s, N_6-CH_3), 4.00 (1H, q, J=7 Hz, N_1-CH), 7.44 (1H, s, C_5-H)
2c	284	1675 (CO), 1125 (SO)	0.88 (3H, t, J=7 Hz, CH_3), 1.1—1.5 (6H, m, $CH_2\times3$), 1.7—2.0 (2H, m, CH_2), 3.34 (3H, s, N_1-CH_3), 3.45 (3H, s, N_3-CH_3), 4.25 (1H, t, J=7 Hz, N_6-CH), 4.27 (1H, t, J=7 Hz, N_6-CH), 7.45 (1H, s, C_5-H)
2d	290	1665 (CO), 1135 (SO)	3.44 (3H, s, N_3-CH_3), 3.94 (3H, s, N_6-CH_3), 4.65 (1H, d, J=16 Hz, N_1-CH), 5.37 (1H, d, J=16 Hz, N_1-CH), 7.32 (5H, s, Ph), 7.41 (1H, s, C_5-H)
2e	290	1655 (CO), 1135 (SO)	3.34 (3H, s, N_1-CH_3), 3.46 (3H, s, N_3-CH_3), 5.50 (2H, s, N_6-CH_2), 7.33 (5H, s, Ph), 7.43 (1H, s, C_5-H)
2f	314	1670 (CO), 1140 (SO)[a]	1.12 (3H, d, J=6 Hz, CHC$\underline{H}_3$), 1.3—2.0 (6H, m, $CH_2\times3$), 3.30 (3H, s, OCH_3; 1H, m, C$\underline{H}$$CH_3$), 3.45 (3H, s, N_3-CH_3), 3.62 (1H, q, J=7 Hz, N_1-CH), 4.00 (1H, q, J=7 Hz, N_1-CH), 7.41 (1H, s, C_5-H)
2g	340	1710, 1655 (CO), 1120 (SO)	1.2—1.8 (10H, m, $CH_2\times5$), 2.12 (3H, s, $COCH_3$), 2.41 (2H, t, J=7 Hz, COC$\underline{H}_2$), 3.45 (3H, s, N_3-CH_3), 3.61 (1H, q, J=7 Hz, N_1-CH), 3.96 (3H, s, N_6-CH_3), 3.97 (1H, q, J=7 Hz, N_1-CH), 7.41 (1H, s, C_5-H)
2h	327	1660 (CO), 1130 (SO)	1.92 (2H, m, CH_2), 2.30—2.56 (6H, m, $NCH_2\times3$), 3.44 (3H, s, N_3-CH_3), 3.64—3.84 (4H, m, $OCH_2\times2$), 3.88—4.24 (2H, m, N_1-CH_2), 3.96 (3H, s, N_6-CH_3), 7.42 (1H, s, C_5-H)
2i	348	1680 (CO), 1250 (COC), 1120 (SO)	1.7—2.1 (4H, m, $CH_2\times2$), 3.44 (3H, s, N_3-CH_3), 3.50—3.80 (1H, m, N_1-CH), 3.95 (3H, s, N_6-CH_3), 3.98 (2H, t, J=5 Hz, OCH_2), 4.00—4.30 (1H, m, N_1-CH), 6.80—7.03 (3H, m, Ph-H_3,H_4,H_5), 7.15—7.38 (2H, m, Ph-H_2,H_6), 7.40 (1H, s, C_5-H)
2j	378	1660 (CO), 1225 (COC), 1120 (SO)	1.7—2.1 (4H, m, $CH_2\times2$), 3.44 (3H, s, N_3-CH_3), 3.63 (1H, q, J=7 Hz, N_1-CH), 3.75 (3H, s, OCH_3), 3.95 (3H, s, N_6-CH_3), 3.98 (2H, t, J=6 Hz, OCH_2), 4.00 (1H, q, J=7 Hz, N_1-CH), 6.81 (4H, s, Ph), 7.41 (1H, s, C_5-H)
2k	406	1665 (CO), 1225 (COC), 1135 (SO)	1.5—2.0 (8H, m, $CH_2\times4$), 3.44 (3H, s, N_3-CH_3), 3.63 (1H, q, J=7 Hz, N_1-CH), 3.76 (3H, s, OCH_3), 3.83 (2H, t, J=6 Hz, OCH_2), 3.95 (3H, s, N_6-CH_3), 4.10 (1H, q, J=7 Hz, N_1-CH), 6.81 (4H, s, Ph), 7.40 (1H, s, C_5-H)
2l	410	1660 (CO), 1245 (COC), 1125 (SO)	1.3—1.9 (8H, m, $CH_2\times4$), 3.44 (3H, s, N_3-CH_3), 3.64 (1H, q, J=7 Hz, N_1-CH), 3.91 (2H, t, J=6 Hz, OCH_2), 4.00 (1H, q, J=7 Hz, N_1-CH), 6.79 (2H, td, J=9, 3 Hz, Ph-H_2,H_6), 7.21 (2H, td, J=9, 3 Hz, Ph-H_3,H_5), 7.41 (1H, s, C_5-H)
2m	406	1640 (CO), 1220 (COC), 1140 (SO)[a]	0.95 (3H, t, J=7 Hz, CH_3), 1.7—2.1 (6H, m, $CH_2\times3$), 3.45 (3H, s, N_3-CH_3), 3.64 (1H, q, J=7 Hz, N_1-CH), 3.75 (3H, s, OCH_3), 3.93 (2H, t, J=6 Hz, OCH_2), 4.04 (1H, q, J=7 Hz, N_1-CH), 4.21 (1H, t, J=7 Hz, N_6-CH), 4.25 (1H, t, J=7 Hz, N_6-CH), 6.81 (4H, s, Ph), 7.45 (1H, s, C_5-H)
2n	434	1665 (CO), 1220 (COC), 1135 (SO)[a]	0.95 (3H, t, J=7 Hz, CH_3), 1.3—2.1 (10H, m, $CH_2\times5$), 3.45 (3H, s, N_3-CH_3), 3.62 (1H, q, J=7 Hz, N_1-CH), 3.76 (3H, s, OCH_3), 3.89 (2H, t, J=6 Hz, OCH_2), 4.00 (1H, q, J=7 Hz, N_1-CH), 4.21 (1H, t, J=7 Hz, N_6-CH), 4.25 (1H, t, J=7 Hz, N_6-CH), 6.81 (4H, s, Ph), 7.45 (1H, s, C_5-H)
2o	438	1670 (CO), 1240 (COC), 1130 (COC)	0.95 (3H, t, J=7 Hz, CH_3), 1.3—2.1 (10H, m, $CH_2\times5$), 3.45 (3H, s, N_3-CH_3), 3.63 (1H, q, J=7 Hz, N_1-CH), 3.91 (2H, t, J=6 Hz, OCH_2), 4.01 (1H, q, J=7 Hz, N_1-CH), 4.21 (1H, t, J=7 Hz, N_6-CH), 4.25 (1H, q, J=7 Hz, N_6-CH), 6.79 (2H, td, J=9, 3 Hz, Ph-H_2,H_6), 7.21 (2H, td, J=9, 3 Hz, Ph-H_3,H_5), 7.45 (1H, s, C_5-H)

TABLE II. (continued)

Compd. No.	MS (m/z) (M^+)	IR (cm^{-1})	^1H-NMR (δ)
2p	476	1680 (CO), 1235 (COC), 1120 (SO)	0.88 (3H, t, $J=7$ Hz, CH_3), 1.1—2.0 (16H, m, $CH_2\times8$), 3.45 (3H, s, N_3-CH_3), 3.62 (1H, q, $J=7$ Hz, N_1-CH), 3.76 (3H, s, OCH_3), 3.89 (2H, t, $J=6$ Hz, OCH_2), 4.02 (1H, q, $J=7$ Hz, N_1-CH), 4.24 (1H, t, $J=7$ Hz, N_6-CH), 4.28 (1H, t, $J=7$ Hz, N_6-CH), 6.81 (4H, s, Ph), 7.44 (1H, s, C_5-H)
2q	480	1660 (CO), 1240 (COC), 1140 (SO)[a]	0.88 (3H, t, $J=7$ Hz, CH_3), 1.1—2.0 (16H, m, $CH_2\times8$), 3.45 (3H, s, N_3-CH_3), 3.64 (1H, q, $J=7$ Hz, N_1-CH), 3.91 (2H, t, $J=6$ Hz, OCH_2), 4.00 (1H, q, $J=7$ Hz, N_1-CH), 4.24 (1H, t, $J=7$ Hz, N_6-CH) 4.28 (1H, t, $J=7$ Hz, N_6-CH), 6.79 (2H, td, $J=9$, 3 Hz, Ph-H_3,H_5), 7.21 (2H, td, $J=9$, 3 Hz, Ph-H_2,H_6), 7.44 (1H, s, C_5-H)
10a	248	1665 (CO), 1135 (SO)	3.33 (3H, s, N_1-CH_3), 3.45 (3H, s, N_3-CH_3), 3.93 (3H, s, N_6-CH_3)
10d	324	1665 (CO), 1140 (SO)	3.41 (3H, s, N_3-CH_3), 3.92 (3H, s, N_6-CH_3), 4.64 (1H, d, $J=16$ Hz, N_1-CH), 5.36 (1H, d, $J=16$ Hz, N_1-CH), 7.32 (5H, s, Ph)
10i	382	1660 (CO), 1245 (COC), 1140 (SO)	1.7—2.0 (4H, m, $CH_2\times2$), 3.41 (3H, s, N_3-CH_3), 3.5—3.8 (1H, m, N_1-CH), 3.92 (3H, s, N_6-CH_3), 3.98 (2H, t, $J=6$ Hz, OCH_2), 4.0—4.3 (1H, m, N_1-CH), 6.80—7.04 (3H, m, Ph-H_3,H_4,H_5), 7.16—7.38 (2H, m, Ph-H_2,H_6)
10j	412	1660 (CO), 1240 (COC), 1135 (SO)	1.7—2.0 (4H, m, $CH_2\times2$), 3.42 (3H, s, N_3-CH_3), 3.61 (1H, q, $J=7$ Hz, N_1-CH), 3.76 (3H, s, OCH_3), 3.92 (3H, s, N_6-CH_3), 3.99 (2H, t, $J=6$ Hz, OCH_2), 4.16 (1H, q, $J=7$ Hz, N_1-CH), 6.81 (4H, s, Ph)
10k	440	1670 (CO), 1225 (COC), 1120 (SO)	1.3—1.9 (8H, m, $CH_2\times4$), 3.41 (3H, s, N_3-CH_3), 3.62 (1H, q, $J=7$ Hz, N_1-CH), 3.76 (3H, s, OCH_3), 3.89 (2H, t, $J=6$ Hz, OCH_2), 3.92 (3H, s, N_6-CH_3), 4.16 (1H, q, $J=7$ Hz, N_1-CH), 6.81 (4H, s, Ph)
10l	444	1680 (CO), 1245 (COC), 1140 (SO)	1.3—1.9 (8H, m, $CH_2\times4$), 3.41 (3H, s, N_3-CH_3), 3.63 (1H, q, $J=7$ Hz, N_1-CH), 3.90 (2H, t, $J=6$ Hz, OCH_2), 3.92 (3H, s, N_6-CH_3), 3.95 (1H, q, $J=7$ Hz, N_1-CH), 6.79 (2H, td, $J=9$, 3 Hz, Ph-H_2,H_6), 7.21 (2H, td, $J=9$, 3 Hz, Ph-H_3,H_5)
10m	440	1660 (CO), 1230 (COC), 1140 (SO)[a]	0.97 (3H, t, $J=7$ Hz, CH_3), 1.8—2.1 (6H, m, $CH_2\times3$), 3.42 (3H, s, N_3-CH_3), 3.60 (1H, q, $J=7$ Hz, N_1-CH), 3.75 (3H, s, OCH_3), 3.93 (2H, t, $J=6$ Hz, OCH_2), 4.01 (1H, q, $J=7$ Hz, N_1-CH), 4.26 (1H, t, $J=7$ Hz, N_6-CH), 4.31 (1H, t, $J=7$ Hz, N_6-CH), 6.81 (4H, s, Ph)
10n	468	1665 (CO), 1230 (COC), 1140 (SO)[a]	0.97 (3H, t, $J=7$ Hz, CH_3), 1.3—2.1 (10H, m, $CH_2\times5$), 3.42 (3H, s, N_3-CH_3), 3.61 (1H, q, $J=7$ Hz, N_1-CH), 3.76 (3H, s, OCH_3), 3.89 (2H, t, $J=6$ Hz, OCH_2), 4.00 (1H, q, $J=7$ Hz, N_1-CH), 4.26 (1H, t, $J=7$ Hz, N_6-CH), 4.31 (1H, t, $J=7$ Hz, N_6-CH), 6.81 (4H, s, Ph)
10o	472	1665 (CO), 1240 (COC), 1125 (SO)	0.97 (3H, t, $J=7$ Hz, CH_3), 1.2—2.1 (10H, m, $CH_2\times5$), 3.42 (3H, s, N_3-CH_3), 3.62 (1H, q, $J=7$ Hz, N_1-CH), 3.91 (2H, t, $J=6$ Hz, OCH_2), 3.99 (1H, q, $J=7$ Hz, N_1-CH), 4.26 (1H, t, $J=7$ Hz, N_6-CH), 4.30 (1H, t, $J=7$ Hz, N_6-CH), 6.79 (2H, td, $J=9$, 3 Hz, Ph-H_2,H_6), 7.21 (2H, td, $J=9$, 3 Hz, Ph-H_3,H_5)
10p	510	1660 (CO), 1225 (COC), 1140 (SO)	0.89 (3H, t, $J=7$ Hz, CH_3), 1.1—2.0 (16H, m, $CH_2\times8$), 3.42 (3H, s, N_3-CH_3), 3.61 (1H, q, $J=7$ Hz, N_1-CH), 3.76 (3H, s, OCH_3), 3.89 (2H, t, $J=6$ Hz, OCH_2), 3.99 (1H, q, $J=7$ Hz, N_1-CH), 4.28 (1H, t, $J=7$ Hz, N_6-CH), 4.33 (1H, t, $J=7$ Hz, N_6-CH), 6.81 (4H, s, Ph)
10q	514	1660 (CO), 1240 (COC), 1140 (SO)	0.88 (3H, t, $J=7$ Hz, CH_3), 1.2—2.0 (16H, m, $CH_2\times8$), 3.42 (3H, s, N_3-CH_3), 3.62 (1H, q, $J=7$ Hz, N_1-CH), 3.91 (2H, t, $J=6$ Hz, OCH_2), 3.99 (1H, q, $J=7$ Hz, N_1-CH), 4.28 (1H, t, $J=7$ Hz, N_6-CH), 4.32 (1H, t, $J=7$ Hz, N_6-CH), 6.79 (2H, td, $J=9$, 3 Hz, Ph-H_2,H_6), 7.21 (2H, td, $J=9$, 3 Hz, Ph-H_3,H_5)

a) IR spectrum was measured in Nujol.

important role. Favorable activity was observed in compounds having a chlorine atom on the benzene ring (compare **2l** and **2k**, **2n** and **2o**, and **2p** and **2q**), those having the $(CH_2)_6$ alkyl chain (compare **2j** and **2k**, and **2m** and **2n**), and those having the 6-hexyl group as an alkyl group (compare **2a** and **2e**, **2k**, **2n** and **2p**, and **2l**, **2o** and **2q**). However, compounds having the chlorine atom at the 5-position showed both potentiating and agonizing actions on the induced relaxation and the effect of the substituent was unclear.

Experimental

All melting points are uncorrected. IR spectrophotometry was performed by the KBr disc method with a Hitachi 285 spectrophotometer unless otherwise stated. Mass spectra were measured with a JEOL JMS-DX 300 spectrometer. ^{1}H- and ^{13}C-NMR spectra (^{1}H-NMR at 89.55 MHz and ^{13}C-NMR at 22.50 MHz) were recorded with a JEOL JMN-FX90Q spectrometer using tetramethylsilane as an internal standard. Unless otherwise stated, $CDCl_3$ was used as the solvent. Chemical shifts are given in δ values (ppm) and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; td, doublet of triplets; q, quartet; qd, doublet of quartets; m, multiplet; md, doublet of multiplets; br, broad. Column chromatography was done on silica gel (Wakogel C-200). TLC was performed on precoated silica gel plates (Kieselgel 60, F_{254}, Merck). All organic extracts were dried over anhydrous Na_2SO_4.

1-Amino-3-methyl-7-propylxanthine (9b)——A mixture of **3r** (105 g, 0.47 mol) and hydrazine hydrate (1.25 l, large excess) was refluxed for 8 h and cooled. The reaction mixture was extracted with $CHCl_3$ and the $CHCl_3$ layer was evaporated *in vacuo* to give a residue, which was purified by column chromatography using $CHCl_3$–EtOH (20 : 1, v/v) as the eluent to afford 43.9 g (42%) of **9b** as colorless needles (from Et_2O–EtOH), mp 122—123 °C. *Anal.* Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found: C, 48.28; H, 5.82; N, 31.37. IR ν_{max}^{KBr} cm^{-1}: 3310, 3240 (NH_2),

TABLE III. Physicochemical Properties and Elemental Analysis of 1,3,7-Trisubstituted Xanthine Derivatives (3)

Compd. No.	mp (°C) (Appearance)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
3f		73	$C_{14}H_{22}N_4O_3$	294.1691[a]		
	(Colorless oil)			(294.1684)		
3g	140—141	59	$C_{16}H_{24}N_4O_3$	59.98	7.55	17.49
	(Colorless prisms)			(59.75	7.54	17.40)
3h·HCl	256—259	77	$C_{14}H_{22}ClN_5O_3$	48.90	6.45	20.37
	(Colorless prisms)			(48.71	6.40	20.58)
3j	88—89	58	$C_{18}H_{22}N_4O_4$	60.32	6.19	15.63
	(Colorless needles)			(60.22	6.14	15.65)
3k	113—114	40	$C_{20}H_{26}N_4O_4$	62.16	6.78	14.50
	(Colorless needles)			(62.39	6.79	14.27)
3l	97—98	61	$C_{19}H_{23}ClN_4O_3$	58.38	5.93	14.33
	(Colorless prisms)			(58.28	5.95	14.27)
3m	61—62	65	$C_{20}H_{26}N_4O_4$	62.16	6.78	14.50
	(Colorless needles)			(62.12	6.75	14.35)
3n	56—57	47	$C_{22}H_{30}N_4O_4$	63.75	7.30	13.52
	(Colorless needles)			(63.90	7.44	13.52)
3o	50—51	51	$C_{21}H_{27}ClN_4O_3$	60.21	6.50	13.37
	(Colorless prisms)			(60.26	6.64	13.65)
3p	45—46	71	$C_{25}H_{36}N_4O_4$	456.2734[a]		
	(Colorless prisms)			(456.2763)		
3q	51—52	84	$C_{24}H_{33}ClN_4O_3$	460.2239[a]		
	(Colorless prisms)			(460.2232)		

a) Determined by high-resolution mass spectrometry. Upper figure, calcd for M^+ and lower figure, found.

Table IV. Spectral Data for 1,3,7-Trisubstituted Xanthine Derivatives (**3**)

Compd. No.	MS (M^+) *m/z*	IR (cm^{-1})	^{1}H-NMR (δ)
3f	294	1700, 1660 (CO)[a]	1.12 (3H, d, $J=6$ Hz, CHC$\underline{H}_3$), 1.3—1.8 (6H, m, $CH_2\times3$), 3.16—3.42 (1H, m, C$\underline{H}OCH_3$), 3.30 (3H, s, OCH_3), 3.57 (3H, s, N_3-CH_3), 3.99 (3H, s, N_7-CH_3, 2H, t, $J=7$ Hz, N_1-CH_2), 7.51 (1H, s, C_8-H)
3g	320	1700, 1660 (CO)	1.2—1.9 (10H, m, $CH_2\times5$), 2.13 (3H, s, $COCH_3$), 2.42 (2H, t, $J=7$ Hz, $COCH_2$), 3.57 (3H, s, N_3-CH_3), 3.99 (3H, s, N_7-CH_3; 2H, t, $J=7$ Hz, N_1-CH_2), 7.51 (1H, s, C_8-H)
3h·HCl	307 (M^+−HCl)	2700—2300 (NH^+), 1710, 1660 (CO)	1.97—2.32 (2H, m, CH_2), 3.2—3.4 (4H, m, $OCH_2\times2$), 3.51 (3H, s, N_3-CH_3), 3.6—4.3 (8H, m, $NCH_2\times4$), 3.96 (3H, s, N_7-CH_3), 7.51 (1H, s, C_8-H)[b]
3j	358	1705, 1665 (CO), 1240 (COC)	1.7—1.9 (4H, m, $CH_2\times2$), 3.57 (3H, s, N_3-CH_3), 3.75 (3H, s, OCH_3), 3.87—4.16 (4H, m, OCH_2, N_1-CH_2), 6.80 (4H, s, Ph), 7.49 (1H, s, C_8-H)
3k	386	1700, 1665 (CO), 1230 (COC)	1.3—1.9 (8H, m, $CH_2\times4$), 3.57 (3H, s, N_3-CH_3), 3.76 (3H, s, OCH_3), 3.89 (2H, t, $J=6$ Hz, OCH_2), 3.97 (3H, s, N_7-CH_3), 4.01 (2H, t, $J=7$ Hz, N_1-CH_2), 6.81 (4H, s, Ph), 7.48 (1H, s, C_8-H)
3l	390	1720, 1675 (CO), 1255 (COC)	1.3—1.9 (8H, m, $CH_2\times4$), 3.57 (3H, s, N_3-CH_3), 3.91 (2H, t, $J=6$ Hz, OCH_2), 3.98 (3H, s, N_7-CH_3), 4.01 (2H, t, $J=7$ Hz, N_1-CH_2), 6.79 (2H, td, $J=9$, 3 Hz, Ph-H_2,H_6), 7.20 (2H, td, $J=9$, 3 Hz, Ph-H_3,H_5), 7.50 (1H, s, C_8-H)
3m	386	1700, 1660 (CO), 1240 (COC)	0.95 (3H, t, $J=7$ Hz, CH_3), 1.7—2.1 (6H, m, $CH_2\times3$), 3.58 (3H, s, N_3-CH_3), 3.75 (3H, s, OCH_3), 3.95 (2H, t, $J=6$ Hz, OCH_2), 4.09 (2H, t, $J=7$ Hz, N_1-CH_2), 4.25 (2H, t, $J=7$ Hz, N_7-CH_2), 6.81 (4H, s, Ph), 7.52 (1H, s, C_8-H)
3n	414	1705, 1655 (CO), 1240 (COC)	0.95 (3H, t, $J=7$ Hz, CH_3), 1.3—2.1 (10H, m, $CH_2\times5$), 3.58 (3H, s, N_3-CH_3), 3.76 (3H, s, OCH_3), 3.89 (2H, t, $J=6$ Hz, OCH_2), 4.02 (2H, t, $J=7$ Hz, N_1-CH_2), 4.24 (2H, t, $J=7$ Hz, N_7-CH_2), 6.81 (4H, s, Ph), 7.52 (1H, s, C_8-H)
3o	418	1700, 1645 (CO), 1240 (COC)	0.95 (3H, t, $J=7$ Hz, CH_3), 1.3—2.1 (10H, m, $CH_2\times5$), 3.58 (3H, s, N_3-CH_3), 3.91 (2H, t, $J=6$ Hz, OCH_2), 4.01 (2H, t, $J=7$ Hz, N_1-CH_2), 4.24 (2H, t, $J=7$ Hz, N_7-CH_2), 6.79 (2H, td, $J=9$, 3 Hz, Ph-H_2,H_6), 7.21 (2H, td, $J=9$, 3 Hz, Ph-H_3,H_5), 7.52 (1H, s, C_8-H)
3p	456	1710, 1660 (CO),[a] 1230 (COC)	0.88 (3H, t, $J=7$ Hz, CH_3), 1.1—2.0 (16H, m, $CH_2\times8$), 3.58 (3H, s, N_3-CH_3), 3.76 (3H, s, OCH_3), 3.89 (2H, t, $J=6$ Hz, OCH_2), 4.02 (2H, t, $J=7$ Hz, N_1-CH_2), 4.27 (2H, t, $J=7$ Hz, N_7-CH_2), 6.81 (4H, s, Ph), 7.51 (1H, s, C_8-H)
3q	460	1705, 1660 (CO),[a] 1240 (COC)	0.88 (3H, t, $J=7$ Hz, CH_3), 1.1—2.0 (16H, m, $CH_2\times8$), 3.58 (3H, s, N_3-CH_3), 3.91 (2H, t, $J=6$ Hz, OCH_2), 4.02 (2H, t, $J=7$ Hz, N_1-CH_2), 4.27 (2H, t, $J=7$ Hz, N_7-CH_2), 6.79 (2H, td, $J=9$, 3 Hz, Ph-H_2,H_6), 7.20 (2H, td, $J=9$, 3 Hz, Ph-H_3,H_5), 7.52 (1H, s, C_8-H)

a) IR spectrum was measured in Nujol. *b*) ^{1}H-NMR spectrum was measured in D_2O.

1710, 1650 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 1.73—2.12 (2H, m, $CH_2C\underline{H}_2CH_3$), 3.62 (3H, s, N_3-CH_3), 4.28 (2H, t, $J=7$ Hz, N_7-CH_2), 4.99 (2H, br s, NH_2), 7.59 (1H, s, C_8-H). MS *m/z*: 223 (M^+).

1-Amino-7-hexyl-3-methylxanthine (9c)——Treatment of **3c** (60 g, 0.23 mol) with hydrazine hydrate (1.2 l, large excess) as described for **9b** gave 9.2 g (15%) of **9c** as colorless needles (from Et_2O–EtOH), mp 115—116 °C. *Anal.* Calcd for $C_{12}H_{19}N_5O_2$: C, 54.32; H, 7.22; N, 26.40. Found: C, 54.35; H, 7.22; N, 26.38. IR ν_{max}^{KBr} cm^{-1}: 3310, 3250 (NH_2), 1710, 1660 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, $J=7$ Hz, $C\underline{H}_3(CH_2)_5$), 1.1—1.5 (6H, m, $CH_2\times3$), 1.7—2.1 (2H, m, N_7-CH_2–$C\underline{H}_2$), 3.63 (3H, s, N_3-CH_3), 4.30 (2H, t, $J=7$ Hz, N_7-CH_2), 4.51 (2H, br s, NH_2), 7.56 (1H, s, C_8-H). MS *m/z*: 265 (M^+).

3-Methyl-7-propylxanthine (7b)——A solution of $NaNO_2$ (28.8 g, excess) in H_2O (150 ml) was added dropwise to a solution of **9b** (40 g, 0.18 mol) in AcOH–H_2O (9 : 5 v/v, 1.12 l) with stirring at room temperature, and stirring was continued for 6 h. The reaction mixture was evaporated *in vacuo* to give a residue, which was washed with H_2O to afford 36.1 g (96%) of **7b**. *Anal.* Calcd for $C_9H_{12}N_4O_2$: C, 51.92; H, 5.81; N, 26.91. Found: C, 51.78; H, 5.71; N, 27.05.

TABLE V. Physicochemical Properties and Elemental Analysis of Imidazole Derivatives (**1**)

Compd. No.	mp (°C) (Appearance)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
1b·picric acid	164—165 (Yellow needles)	38	$C_{12}H_{22}N_4O \cdot C_6H_3N_3O_7$	46.25 (46.04	5.39 5.38	20.98 21.06)
1c·picric acid	114—116 (Yellow needles)	63	$C_{18}H_{22}N_4O \cdot C_6H_3N_3O_7$	46.25 (45.95	5.39 5.34	20.98 20.83)
1d	110—111 (Colorless needles)	38	$C_{12}H_{16}N_4O$	63.92 (63.63	6.60 6.55	22.93 23.19)
1e	113—114 (Colorless needles)	52	$C_{13}H_{16}N_4O$	63.92 (63.81	6.60 6.64	22.93 22.92)
1f·picric acid	144—145 (Yellow needles)	29	$C_{13}H_{24}N_4O_2 \cdot C_6H_3N_3O_7$	45.87 (45.65	5.47 5.45	19.71 19.68)
1g·picric acid	118—119 (Yellow needles)	31	$C_{15}H_{26}N_4O_2 \cdot C_6H_3N_3O_7$	48.18 (47.99	5.58 5.57	18.73 18.72)
1h·2HCl	209—212 (Colorless needles)	26	$C_{13}H_{23}N_5O_2 \cdot 2HCl$	44.07 (43.85	7.11 7.01	19.77 19.68)
1i·picric acid	137—138 (Yellow needles)	34	$C_{16}H_{22}N_4O_2 \cdot C_6H_3N_3O_7$	49.72 (49.42	4.71 4.74	18.45 18.45)
1j	48—49 (Colorless needles)	47	$C_{17}H_{24}N_4O_3$	61.42 (61.16	7.28 7.51	16.86 16.60)
1k·picric acid	119—120 (Yellow needles)	42	$C_{19}H_{28}N_4O_3 \cdot C_6H_3N_3O_7$	50.93 (50.78	5.30 5.27	16.63 16.44)
1l·picric acid	138—139 (Yellow needles)	22	$C_{18}H_{25}ClN_4O_2 \cdot C_6H_3N_3O_7$	48.53 (48.48	4.75 4.69	16.51 16.48)
1m·picric acid	82—83 (Yellow needles)	26	$C_{19}H_{28}N_4O_3 \cdot C_6H_3N_3O_7$	50.93 (51.23	5.30 5.32	16.63 16.33)
1n·picric acid	99—100 (Yellow needles)	48	$C_{21}H_{32}N_4O_3 \cdot C_6H_3N_3O_7$	52.51 (52.40	5.71 5.71	15.88 15.86)
1o	66—67 (Colorless needles)	38	$C_{20}H_{29}ClN_4O_2$	61.14 (61.16	7.44 7.43	14.26 14.09)
1p	35—36 (Colorless needles)	24	$C_{24}H_{38}N_4O_3$	66.95 (66.76	8.90 8.89	13.01 13.01)
1q	55—56 (Colorless cotton)	29	$C_{23}H_{35}ClN_4O_2$	63.51 (63.43	8.11 8.10	12.88 12.77)

7-Hexyl-3-methylxanthine (7c)——Treatment of **9c** (23 g, 0.087 mol) with $NaNO_2$ (13.9 g, excess) as described for **7b** gave 20.4 g (94%) of **7c**. *Anal.* Calcd for $C_{12}H_{18}N_4O_2$: C, 57.58; H, 7.25; N, 22.38. Found: C, 57.46; H, 7.26; N, 22.43.

1-(5-Methoxyhexyl)-3,7-dimethylxanthine (3f)——A suspension of **4** (5.6 g, 2 mmol) and NaH (60% in oil, 0.9 g, 2.3 mmol) in dry DMF (40 ml) was stirred for 1 h at room temperature, and then CH_3I (20 g, large excess) was added. Stirring was continued for 16 h. The reaction mixture was evaporated *in vacuo* to give a residue, which was purified by column chromatography using $CHCl_3$–EtOH (20 : 1, v/v) as the eluent to afford 4.3 g of **3f**. Data are summarized in Tables III and IV.

3,7-Dimethyl-1-(8-oxononyl)xanthine (3g)——A solution of **5** (15 g, 0.046 mol), ethyl acetoacetate (6.2 g, 0.048 mol) and NaOEt (prepared from Na (1.0 g, 0.043 mol)) in absolute EtOH (100 ml) was refluxed for 6 h and evaporated *in vacuo* to give a residue, to which 1 N NaOH (60 ml) was added. The mixture was stirred for 2.5 h at room temperature and then acidified with diluted H_2SO_4. The acidified solution was refluxed for 4 h, alkalized with 10% NaOH, and then extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated *in vacuo* to give a residue, which was recrystallized from iso-PrOH to afford 8.2 g (59%) of **3g**. Data are summarized in Tables III and IV.

3,7-Dimethyl-1-[3-(4-morpholino)propyl]xanthine (3h)——A mixture of **6** (9.6 g, 3.2 mmol), morpholine (3.3 g, 3.8 mmol) and K_2CO_3 (5.28 g, 2.8 mmol) in acetone (80 ml) was refluxed for 4 h and evaporated *in vacuo* to give a residue, which was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and evaporated *in vacuo* to give a residue, which, after EtOH–HCl treatment, was recrystallized from EtOH to afford 7.5 g of **3h**·HCl. Data are summarized in Tables III and IV.

TABLE VI. Spectral Data for Imidazole Derivatives (**1**)

Compd. No.	MS (M^+) m/z	IR (cm^{-1})	^{1}H-NMR (δ)
1b·picric acid	238 (M^+ − picric acid)	3320, 3280 (NH), 1625 (CO)	0.87 (3H, t, J=6 Hz, CH_3), 1.1—1.7 (8H, m, $CH_2 \times 4$), 2.84 (3H, s, $NHC\underline{H}_3$), 3.20 (2H, q, J=6 Hz, $NHC\underline{H}_2$), 3.87 (3H, s, N_1-CH_3), 7.59 (1H, t, J=6 Hz, $N\underline{H}CH_2$), 8.59 (2H, s, Ph), 8.64 (1H, s, C_2-H)[a]
1c·picric acid	238 (M^+ − picric acid)	3420, 3300 (NH), 1640 (CO)	0.85 (3H, t, J=7 Hz, CH_3), 1.1—1.4 (6H, m, $CH_2 \times 3$), 1.5—1.9 (2H, m, CH_2), 2.74 (3H, d, J=5 Hz, $CONHC\underline{H}_3$), 2.83 (3H, s, $NHC\underline{H}_3$), 4.28 (2H, t, J=7 Hz, N_1-CH_2), 7.76 (1H, q, J=5 Hz, $CON\underline{H}CH_3$), 8.59 (2H, s, Ph), 8.74 (1H, s, C_2-H)[a]
1d	244	3280 (NH), 1600 (CO)	2.84 (3H, s, $NHC\underline{H}_3$), 3.74 (1H, br s, $N\underline{H}CH_3$), 3.86 (3H, s, N_1-CH_3), 4.58 (2H, d, J=6 Hz, $NHC\underline{H}_2$), 7.18 (1H,s, C_2-H), 7.32 (5H, s, Ph; 1H, br s, $N\underline{H}CH_2$)
1e	244	3310, 3260 (NH), 1620 (CO)	2.81 (3H, d, J=5 Hz, $CONHC\underline{H}_3$), 2.91 (3H, s, $NHC\underline{H}_3$), 4.05 (1H, br s, $N\underline{H}CH_3$), 5.44 (2H, s, N_1-$C\underline{H}_2$), 6.68 (1H, br s, $CON\underline{H}CH_3$), 7.1—7.5 (5H, m, Ph; 1H, s, C_2-H)
1f·picric acid	268 (M^+ − picric acid)	3330, 3280 (NH), 1630 (CO), 1320 (NO_2)	1.04 (3H, d, J=6 Hz, $CHC\underline{H}_3$), 1.1—1.6 (6H, m, $CH_2 \times 3$), 2.84 (3H, s, $NHC\underline{H}_3$), 3.19 (3H, s, OCH_3), 3.0—3.3 (2H, m, $NHC\underline{H}_2$; 1H, m, $C\underline{H}CH_3$), 3.87 (3H, s, N_1-CH_3), 7.59 (1H, t, J=6 Hz, $N\underline{H}CH_2$), 8.58 (2H, s, Ph), 8.65 (1H, s, C_2-H)[a]
1g·picric acid	294 (M^+ − picric acid)	3320, 3290 (NH), 1710, 1625 (CO), 1315 (NO_2)	1.1—1.7 (10H, m, $CH_2 \times 5$), 2.06 (3H, s, $COCH_3$), 2.40 (2H, t, J=7 Hz, $COCH_2$), 2.84 (3H, s, $NHC\underline{H}_3$), 3.19 (2H, q, J=6 Hz, $NHC\underline{H}_2$), 3.87 (3H, s, N_1-CH_3), 7.58 (1H, t, J=6 Hz, $N\underline{H}CH_2$), 8.58 (2H, s, Ph), 8.64 (1H, s, C_2-H)[a]
1h·2HCl	281 (M^+ − 2HCl)	3305 (NH), 2750—2300 (NH^+), 1660 (CO)	2.0—2.3 (2H, m, CH_2), 2.94 (3H, s, $NHC\underline{H}_3$), 3.2—4.3 (12H, m, $NCH_2 \times 4$, $OCH_2 \times 2$), 3.93 (3H, s, N_1-CH_3), 8.32 (1H, s, C_2-H)[b]
1i·picric acid	302 (M^+ − picric acid)	3340, 3270 (NH), 1630 (CO), 1320 (NO_2)	1.5—1.9 (4H, m, $CH_2 \times 2$), 2.85 (3H, s, $NHC\underline{H}_3$), 3.28 (2H, q, J=6 Hz, $NHC\underline{H}_2$), 3.88 (3H, s, N_1-CH_3), 3.98 (2H, t, J=7 Hz, OCH_2), 6.8—7.0 (3H, m, Ph-H_3,H_4,H_5), 7.1—7.4 (2H, m, Ph-H_2,H_6), 7.62 (1H, t, J=6 Hz, $N\underline{H}CH_2$), 8.58 (2H, s, Ph), 8.65 (1H, s, C_2-H)[a]
1j	332	3360, 3290 (NH), 1630 (CO), 1235, 1030 (COC)	1.7—1.9 (4H, m, $CH_2 \times 2$), 2.86 (3H, s, $NHC\underline{H}_3$), 3.44 (2H, q, J=6 Hz, $NHC\underline{H}_2$), 3.75 (3H, s, OCH_3), 3.83 (3H, s, N_1-CH_3), 3.95 (2H, t, J=6 Hz, OCH_2), 6.81 (4H, s, Ph), 7.16 (1H, s, C_2-H; 1H, br s, $N\underline{H}CH_2$)
1k·picric acid	360 (M^+ − picric acid)	3320, 3270 (NH), 1620 (CO), 1310 (NO_2), 1235 (COC)	1.4—2.0 (8H, m, $CH_2 \times 4$), 2.99 (3H, s, $NHC\underline{H}_3$), 3.45 (2H, q, J=6 Hz, $NHC\underline{H}_2$), 3.75 (3H, s, OCH_3), 3.91 (2H, t, J=6 Hz, $OC\underline{H}_2$), 4.05 (3H, s, N_1-CH_3), 6.72 (1H, t, J=6 Hz, $N\underline{H}CH_2$), 6.81 (4H, s, Ph), 7.82 (1H, br s, NH^+), 7.98 (1H, s, C_2-H), 8.94 (2H, s, Ph)
1l·picric acid	364 (M^+ − picric acid)	3320, 3270 (NH), 1625 (CO), 1305 (NO_2), 1240 (COC)	1.2—1.9 (8H, m, $CH_2 \times 4$), 2.85 (3H, s, $NHC\underline{H}_3$), 3.23 (2H, q, J=6 Hz, $NHC\underline{H}_2$), 3.88 (3H, s, N_1-CH_3), 3.95 (2H, t, J=6 Hz, OCH_2), 6.92 (2H, td, J=9, 3 Hz, Ph-H_2, H_6), 7.30 (2H, td, J=9, 3 Hz, Ph-H_3,H_5), 7.61 (1H, t, J=6 Hz, $N\underline{H}CH_2$), 8.59 (2H, s, Ph), 8.68 (1H, s, C_2-H)[a]
1m·picric acid	360 (M^+ − picric acid)	3410, 3380 (NH), 1625 (CO), 1335, 1310 (NO_2), 1265, 1225 (COC)	0.81 (3H, t, J=7 Hz, CH_3), 1.6—1.9 (6H, m, $CH_2 \times 3$), 2.84 (3H, s, $NHC\underline{H}_3$), 3.26 (2H, t, J=6 Hz, $NHC\underline{H}_2$), 3.69 (3H, s, OCH_3), 3.92 (2H, t, J=6 Hz, OCH_2), 4.26 (2H, t, J=7 Hz, N_1-CH_2), 6.84 (4H, s, Ph), 7.82 (1H, t, J=6 Hz, $N\underline{H}CH_2$), 8.59 (2H, s, Ph), 8.73 (1H, s, C_2-H)[a]

TABLE VI. (continued)

Compd. No.	MS (M^+) m/z	IR (cm^{-1})	^{1}H-NMR (δ)
1n·picric acid	388 (M^+ − picric acid)	3440, 3310 (NH), 1625 (CO), 1350, 1320 (NO_2), 1225 (COC)	0.81 (3H, t, J=7 Hz, CH_3), 1.2—1.9 (10H, m, $CH_2 \times 5$), 2.85 (3H, s, $NHC\underline{H}_3$), 3.23 (2H, q, J=6 Hz, $NHC\underline{H}_2$), 3.69 (3H, s, OCH_3), 3.88 (2H, t, J=6 Hz, OCH_2), 4.27 (2H, t, J=7 Hz, N_1-CH_2), 6.83 (4H, s, Ph), 7.77 (1H, t, J=6 Hz, $N\underline{H}CH_2$), 8.59 (2H, s, Ph), 8.75 (1H, s, C_2-H)[a]
1o	392	3350, 3210 (NH), 1640 (CO), 1235 (COC)	0.81 (3H, t, J=7 Hz, CH_3), 1.3—2.0 (10H, m, $CH_2 \times 5$), 2.87 (3H, s, $NHC\underline{H}_3$), 3.38 (2H, q, J=6 Hz, $NHC\underline{H}_2$), 3.91 (2H, t, J=6 Hz, OCH_2), 4.19 (2H, t, J=7 Hz, N_1-CH_2), 6.79 (2H, td, J=9, 3 Hz, Ph-H_2,H_6), 7.21 (2H, td, J=9, 3 Hz, Ph-H_3,H_5), 7.23 (1H, s, C_2-H), 7.32 (1H, br s, $N\underline{H}CH_2$)
1p	430	3420, 3290 (NH), 1605 (CO), 1230 (COC)	0.87 (3H, t, J=7 Hz, CH_3), 1.1—1.9 (16H, m, $CH_2 \times 8$), 2.87 (3H, s, $NHC\underline{H}_3$), 3.38 (2H, q, J=6 Hz, $NHC\underline{H}_2$), 3.76 (3H, s, OCH_3), 3.90 (2H, t, J=6 Hz, OCH_2), 4.22 (2H, t, J=7 Hz, N_1-CH_2), 6.81 (4H, s, Ph), 7.22 (1H, s, C_2-H), 7.24 (1H, br s, $N\underline{H}CH_2$)
1q	434	3310, 3250 (NH), 1615 (CO), 1245 (COC)	0.87 (3H, t, J=7 Hz, CH_3), 1.1—1.9 (16H, m, $CH_2 \times 8$), 2.87 (3H, s, $NHC\underline{H}_3$), 3.53 (2H, q, J=6 Hz, $NHC\underline{H}_2$), 3.92 (2H, t, J=6 Hz, OCH_2), 4.22 (2H, t, J=7 Hz, N_1-CH_2), 6.79 (2H, td, J=9, 3 Hz, Ph-H_2,H_6), 7.21 (2H, td, J=9, 3 Hz, Ph-H_3,H_5), 7.24 (1H, s, C_2-H; 1H, br s, $N\underline{H}CH_2$)

a) ^{1}H-NMR spectrum was measured in DMSO-d_6. *b*) ^{1}H-NMR spectrum was measured in D_2O.

7-Alkyl-3-methyl-1-phenoxyalkylxanthines (3j—q)——Typical Procedure: Compound **8a** (14.2 g, 0.055 mol) was added to a solution of **7a** (9.0 g, 0.05 mol) and NaOH (2.1 g, 0.053 mol) in EtOH–H_2O (3 : 2 v/v, 200 ml), and the mixture was refluxed for 6 h. The reaction mixture was concentrated *in vacuo* to about one-fourth of the initial volume and alkalized with 10% NaOH. The alkaline mixture was extracted with $CHCl_3$, and the $CHCl_3$ layer was evaporated *in vacuo* to give a residue, which was purified by column chromatography using $CHCl_3$–EtOH (40 : 1, v/v) as the eluent to afford **3j**.

Compounds **3k—q** were prepared from the corresponding **8a—c** and **7a—c** in a similar manner and purified by recrystallization or column chromatography using the $CHCl_3$–EtOH mixture as the eluent. Data are summarized in Tables III and IV.

1-Substituted 4-Methylamino-5-substitutedaminocarbonylimidazoles (1b—q)——Typical Procedure: A suspension of **3b** (7.5 g, 0.028 mol) in 3 N NaOH (300 ml) was refluxed for 6 h and extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated *in vacuo* to give a residue, which was purified by column chromatography using $CHCl_3$–EtOH (40 : 1, v/v) as the eluent to afford 2.6 g of **1b**. Compound **1b** was converted into the corresponding picrate using EtOH–picric acid.

Compounds **1c—q** were prepared from the corresponding **3c—q** in a similar manner and, after purification by column chromatography using the $CHCl_3$–EtOH mixture as the eluent, directly recrystallized or converted into the corresponding picrate or hydrochloride by EtOH–picric acid or EtOH–HCl treatment, respectively. Data are summarized in Tables V and VI.

1,3,6,7-Tetrahydro-1,3,6-trimethyl-7-oxoimidazo[4,5-*c*][1,2,6]thiadiazine 2-Oxide (2a)——Method a: $SOCl_2$ (3.1 g, 0.026 mol) was added dropwise to a solution of **1a** (3.4 g, 0.02 mol) in dry pyridine (50 ml) with stirring at −10—0 °C and stirring was continued for a further 3 h at room temperature. The reaction mixture was evaporated *in vacuo* to give a residue, which was purified by column chromatography using $CHCl_3$–EtOH (40 : 1, v/v) as the eluent to afford 3.7 g of **2a**.

Method b: A solution of $SOCl_2$ (0.5 g, 4.2 mmol) in dry C_6H_6 (7 ml) was added dropwise to a solution of **1a** (0.67 g, 4.0 mmol) and Et_3N (0.88 g, 8.7 mmol) in dry C_6H_6 (20 ml) with stirring at room temperature for 2 h, and subsequently the mixture was heated at 80 °C for 10 min, then cooled and filtered. The filtrate was evaporated *in vacuo* to give a residue, which was purified in the same manner as in method a to afford 0.34 g (40%) of **2a**. Data are summarized in Tables I and II.

Hydrolysis of 2a——Method c: A solution of **2a** (0.43 g, 2.0 mmol) in H_2O (25 ml) was stirred at room

TABLE VII. 3,7-Dihydro-6*H*-purin-6-one Derivatives (**15**)

Compd. No.	mp (°C) (Appearance)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	MS (M^+) m/z	IR (cm^{-1})	^{1}H-NMR (δ)
15a	181—182 (Colorless needles)	21	$C_{13}H_{12}N_4O$	64.99 (65.21	5.03 4.89	23.32 23.25)	240	1680 (CO)	3.47 (3H, s, N_3-CH_3), 4.07 (3H, s, N_7-CH_3), 7.4—7.7 (5H, m, Ph), 7.81 (1H, s, C_8-H)
15b ·HCl	154—156 (Colorless needles)	14	$C_{18}H_{22}N_4O$ ·HCl	62.33 (62.06	6.68 6.54	16.15 16.16)	310 (M^+ − HCl)	2700—2200 (NH^+), 1695 (CO)	0.87 (3H, t, J=7 Hz, CH_3), 1.1—1.4 (4H, m, CH_2×2), 1.7—2.0 (2H, m, CH_2), 3.38 (3H, s, N_3-CH_3), 4.2 (2H, t, J=7 Hz, N_7-CH_2), 7.5—7.7 (5H, m, Ph), 8.85 (1H, s, C_8-H), 9.25 (1H, br s, NH^+)[a]
15c	180—181 (Colorless needles)	25	$C_{19}H_{16}N_4O$	72.14 (71.93	5.10 5.07	17.71 17.71)	316	1685 (CO)	3.50 (3H, s, N_3-CH_3), 5.64 (2H, s, N_7-CH_2), 7.36 (5H, s, Ph), 7.50 (5H, s, C_2-Ph)
15d	247—249 (Yellow needles)	8	$C_{13}H_{11}N_5O_3$	54.74 (54.58	3.89 3.94	24.55 24.32)	285	1680 (CO), 1520, 1340 (NO_2)	3.50 (3H, s, N_3-CH_3), 4.13 (3H, s, N_7-CH_3), 7.77 (2H, td, J=9, 2 Hz, Ph-H_2,H_6), 7.84 (1H, s, C_8-H), 8.38 (2H, td, J= 9, 2 Hz, Ph-H_2,H_5)

a) ^{1}H-NMR spectrum was measured in DMSO-d_6.

temperature for 24 h; only **2a** was detectable by TLC. Then, 0.1 N NaOH (20 ml) was added to the solution and the pH of the solution became neutral after 1 h. At this time, both **2a** and **1a** were detectable by TLC. Further 0.1 N NaOH (20 ml) was applied to the solution, and after 1 h **2a** was no longer detected by TLC. The solution was extracted with $CHCl_3$ and the $CHCl_3$ layer was evaporated *in vacuo* to give a residue, which, after Et_2O–HCl treatment, was recrystallized from EtOH to afford 0.28 g (68%) of **1a**·HCl.

Method d: Compound **2a** (0.32 g, 1.5 mmol) was added to 3% $NaHCO_3$ (20 ml) and the mixture was stirred at room temperature until **2a** was no longer detectable by TLC (*ca.* 36 h). The solution was extracted with $CHCl_3$, and the $CHCl_3$ layer was evaporated *in vacuo* to give a residue, which was treated in the same manner as in method c to afford 0.23 g (75%) of **1a**·HCl.

Method e: A solution (pH 1.5) of **2a** (0.32 g, 1.5 mmol) in 0.1 N HCl (15 ml) was stirred at room temperature until **2a** was hardly detected by TLC (*ca.* 3 d). The solution was evaporated *in vacuo* to give a residue, which was treated in the same manner as in method c to afford 0.24 g (78%) of **1a**·HCl.

1,6-Disubstituted 1,3,6,7-Tetrahydro-3-methyl-7-oxoimidazo[4,5-*c*][1,2,6]thiadiazine 2-Oxides (2b—q)——Compounds **2b—q** were prepared from $SOCl_2$ and the corresponding **1b—q** in a similar manner to method a in the preparation of **2a** and purified by column chromatography using the $CHCl_3$–EtOH mixture as the eluent. Data are summarized in Tables I and II.

5-Chloro-1,3,6,7-tetrahydro-1,3,6-trimethyl-7-oxoimidazo[4,5-*c*][1,2,6]thiadiazine 2-Oxide (10a)——Method f: A solution of **2a** (0.86 g, 4.0 mmol) in $SOCl_2$ (35 ml) was gently refluxed for 24 h and evaporated *in vacuo* to give a residue, which was purified by column chromatography using $CHCl_3$–EtOH (25 : 2, v/v) as the eluent to afford 0.33 g (33%) of **10a**.

Method g: A solution of SO_2Cl_2 (0.49 g, 3.6 mmol) in dry CCl_4 (5 ml) was added dropwise to a solution of **2a** (0.64 g, 3.0 mmol) in dry CCl_4 (15 ml) at room temperature, and the mixture was stirred for 2 h. The reaction mixture was poured into saturated $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated *in vacuo* to give a residue, which was treated in the same manner as in method f to afford 0.23 g (31%) of **10a**.

1,6-Disubstituted 5-Chloro-1,3,6,7-tetrahydro-3-methyl-7-oxoimidazo[4,5-*c*][1,2,6]thiadiazine 2-Oxides (10d, i—q)——Compounds **10d, i—q** were prepared from SO_2Cl_2 and the corresponding **2d, i—q** in a similar manner to method g in the preparation of **10a** and purified by column chromatography using $CHCl_3$ or $CHCl_3$–EtOH mixture as the eluent. Data are summarized in Tables I and II.

4-(*N*-Acetyl-*N*-methylamino)-1-methyl-5-methylaminocarbonylimidazole (11)——A solution of **2a** (0.54 g, 2.5 mmol) in dry AcOH (3 ml) was refluxed for 2 h and evaporated *in vacuo* to give a residue, which was purified by column chromatography using $CHCl_3$–EtOH (20 : 1, v/v) as the eluent to afford 0.31 g (59%) of **11** as colorless needles (from Et_2O–EtOH). The ^{1}H-NMR data of **11** were identical with those of the compound reported by Hoskinson.[14]

1,2,3,7-Tetrahydro-1,3,7-trimethyl-2-(2-nitrophenyl)-6*H*-purin-6-one (13)——A mixture of **2a** (0.32 g, 1.5 mmol) and **12** (0.31 g, 2.0 mmol) was heated at 145—150 °C for 2.5 h. The gas generated during the reaction was introduced into aqueous NaOH. The aqueous NaOH solution was positive to the qualitative reaction with sulfite. After cooling, the reaction mixture was purified by column chromatography using $CHCl_3$–EtOH (20 : 1, v/v) as the eluent to give 0.11 g (24%) of **13**. The IR spectrum of **13** was consistent with that of the compound previously synthesized by us.[2]

2,7-Disubstituted 3,7-Dihydro-3-methyl-6*H*-purin-6-one (15)——Typical Procedure: A mixture of **2a** (1.00 g, 4.67 mmol) and **14a** (4.0 ml, excess) was heated at 150—160 °C for 40 min. The gas generated during the reaction was introduced into aqueous NaOH. The aqueous NaOH solution was positive to the qualitative reaction with sulfite. After cooling, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated *in vacuo* to give a residue, which was purified by column chromatography using $CHCl_3$–EtOH (20 : 1, v/v) to afford **15a**. ^{13}C-NMR ($CDCl_3$) δ: 33.6 (qd, $J=142$, 1 Hz, N_7-C), 33.9 (q, $J=142$ Hz, N_3-C), 114.0 (m, C_5), 128.3 (md, $J=162$ Hz, ph-C_2,C_6 or ph-C_3,C_5), 128.5 (md, $J=162$ Hz, ph-C_2,C_6 or ph-C_3,C_5), 128.8 (md, $J=161$ Hz, ph-C_4), 135.6 (m, ph-C_1), 144.3 (qd, $J=20$, 4 Hz, C_8), 155.7 (m, C_2 or C_4 or C_6), 156.0 (m, C_2 or C_4 or C_6), 156.2 (m, C_2 or C_4 or C_6).

Compounds **15b—d** were prepared from the corresponding **2a**, **c**, **e** and **14a**, **b** in the same manner as used for **15a**. Data are summarized in Table VII.

Vascular Relaxing Effect——The effect was evaluated by a similar method to the one described in the previous paper.[3] Helical strips isolated from 13-week old SHR were mounted for isometric recording of tension in a 20-ml water-jacketed tissue bath (37 ± 0.5 °C) containing oxygenated Kreb's bicarbonate solution. The strips were contracted by exposure to KCl (30 mM). After the contraction had reached a plateau, one of the test compounds was added and then papaverine was added at the end of the experiments to obtain the maximum relaxation. The relaxation induced by papaverine was taken as 100%. The effect of each compound was expressed as the ED_{50} value, which was determined from the dose–response curve. Data are listed in Table I.

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