Reactions of 6-Thiotheophylline with Alkylating Agents and Epichlorohydrin: Isolation of *S*-Alkylated 6-Thiotheophylline and 7-(2,3-Thioepoxypropyl)theophylline

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Alkylation of 6-thiotheophylline (**1**) under the aprotic basic condition affords *S*-alkylated 6-thiotheophylline (**3**) together with an N^7-alkylated product **4**. There is a tendency that the more reactive the alkylating agents are, the higher the yields of *S*-alkylated products are. On the other hand, treatment of 6-thiotheophylline (**1**) with epichlorohydrin afforded an unexpected product, 7-(2,3-thioepoxypropyl)theophylline (**6**), neither an *S*-alkylated compound **3g** nor an N^7-alkylated compound **4g**. The chemical structure was determined by nmr spectroscopic analysis.

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A series of 1,3-disubstituted 6-thioxanthines is of great interest as broncho and coronary dilators [1-8]. They have two reaction sites (sulfur at C-6 and nitrogen at the 7-position) with electrophiles. Thus their alkylation reaction can give the *S*-alkylated compound (*S*-enol ether derivative) and the N^7-alkylated compound (thione derivative). Since an *S*-enol ether can be considered to be a bioisostere of thione, its synthesis is very interesting from the view point of pharmacological activities. 3,7-Disubstituted 6-thioxanthines, such as 6-thiotheobromine, have been reported to react with an alkylating agent at both the N^1-atom and the *S*-atom, affording two regioisomers [9,10]. Alkylation of a thioamide generally gives greater amounts of an *S*-alkylated compound than those of an *N*-alkylated compound [11]. Slack *et al.* [9] reported that methylation of 6-thiotheophylline (**1**, 1,3-dimethyl-6-thioxanthine) using methyl iodide gave N^7-methylated 6-thiotheophylline (**4c**) together with theophylline (**5**), but not *S*-methylated 6-thiotheophylline (**3c**, 1,3-dihydro-1,3-dimethyl-6-methylthio-2*H*-purin-2-one). They suggested that **5** was produced *via* **3c**, which was unstable under their condition (an aqueous sodium hydroxide solution, room temperature) and could not be isolated. Instability of the *S*-alkylated compound **3c** seems to be attributed to the cross conjugation system. Later, Kleiner [11] and Neiman *et al.* [12] reported the isolation of **3c** under similar conditions. Unfortunately, they did not present the spectroscopic data of **3c**. Then, Hayashi *et al.* [10] described the same result as that reported by Slack, *et al.* Thus, the alkylation of 6-thiotheophylline is still a subject of controversy in synthetic organic chemistry.

As described above, *S*-methylated 6-thiotheophylline (**3c**) may be unstable. Thus, we examined whether *S*-alkylated 6-thiotheophylline derivatives **3** could be obtained, using butyl bromide as an alkylating agent. *S*-Butylated 6-thiotheophylline seemed to be less likely to suffer hydrolysis than *S*-methylated 6-thiotheophylline due to the bulkiness of the butylthio group. The results are shown in Table 1. Under basic protic conditions such as in entry 1, an *S*-butylated compound **3a** could not be detected and theophylline (**5**), which is thought to be produced *via* **3a** by hydrolysis, was the main product. However, under basic aprotic conditions such as in entry 2 and 3, the desired compound, *S*-butylated 6-thiotheophylline (**3a**, 6-butylthio-1,3-dihydro-1,3-dimethyl-2*H*-purin-2-one), was obtained in low yields together with N^7-butylated 6-thiotheophylline (**4a**). The ratio of **3a** to **4a** in the crude mixture was determined to be 0.30 by hplc. During the purification by even silica gel flash chromatography, **3a** decomposed to some extent and the ratio of isolated yields of **3a** to **4a** was changed into 0.10. This fact and the results reported by Slack *et al.* [9] and Hayashi *et al* [10] indicate that an aprotic solvent has to be used in order to obtain an *S*-alkylated compound.

Then, using the conditions of entry 2, we examined whether other *S*-alkylated 6-thiotheophylline derivatives

Table 1

n-Butylation of 6-Thiotheophylline

Entry	Conditions	Ratio of the Area by HPLC Analysis [b]			
		3a (%)	**4a** (%)	**1** (%)	**5** (%)
1	potassium carbonate, ethanol, reflux, 4 hours	0	7	75	14
2	sodium salt, dimethylformamide, room temperature, 24 hours [a]	22	73	4	0
3	sodium hydride, dimethylformamide, room temperature, 24 hours [a]	20	72	5	1

[a] Under a nitrogen atmosphere. [b] The wavelength of the ultraviolet (μv) detector was set at 255 nm.

Table 2

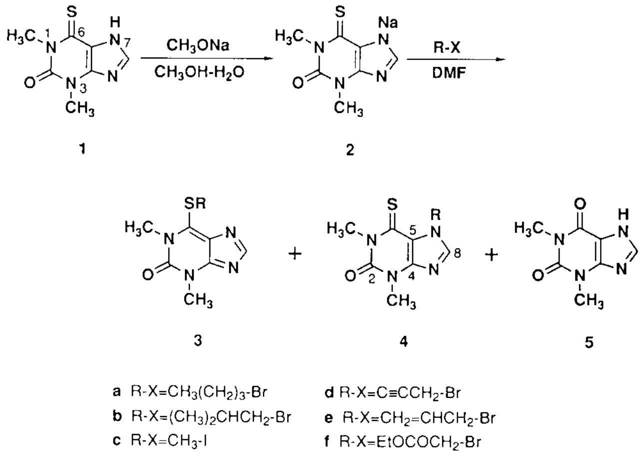
Alkylation of 6-Thiohteophylline [a]

Entry	R-X	Time	Ratio of the Area by HPLC Analysis (255 nm) 3 (%)	4 (%)	1 (%)	5 (%)
a	$CH_3(CH_2)_3$-Br	24 hours	22	73	4	0
b	$(CH_3)_2CHCH_2$-Br	24 hours	26	63	10	1
c	CH_3-I	5 minutes	53	35	0	0
d	$CH{\equiv}CCH_2$-Br	30 minutes	64	35	0	0
e	$CH_2{=}CHCH_2$-Br	30 minutes	56	41	2	1
f	$EtOCOCH_2$-Br	30 minutes	52	45	2	1

[a] Sodium salt, dimethylformamide, room temperature.

could be isolated (Scheme 1). In all cases including methylation, we could obtain *S*-alkylated 6-thiotheophylline derivatives **3a-3f** along with *N*^{7}-alkylated 6-thiotheophylline derivatives **4a-4f**. During purification of these mixture by silica gel column chromatography, some amounts of **3** were always decomposed and the isolated yields became low. Thus a ratio of **3** to **4** in the respective crude reaction mixture was examined by hplc (Table 2). There is a tendency that the more reactive the alkylating agents are, the higher the yields of *S*-alkylated products are, **3c-3f**. In contrast, the less reactive the alkylating agents are, the higher the yields of *N*^{7}-alkylated products are **4a** and **4b**. Sulfur and reactive alkylating agents are expected to be softer than nitrogen and less reactive alkylating agents, respectively. Thus, these results could be explained by the preference of soft-soft interactions or hard-hard interactions [13].

Scheme 1



The structure of these regioisomers was determined by analysis of the nmr chemical shift values of the methyl protons at the 1- and 3-positions (*N*^{1}-CH_3 and *N*^{3}-CH_3) and that of the quarternary carbon at the 6-position (C-6) (Table 3). In the ^{13}C nmr spectrum of 6-thiotheophylline (**1**), the carbon signal of C-6 was observed at δ_C 176.7, which is characteristic of that of the thiocarbonyl group.

Similarly in compounds **4** (*N*^{7}-alkylated compounds), the carbon signals of C-6 were observed in the δ_C 177.0-177.6 region. Whereas those in compounds **3c** and **3e** (*S*-alkylated compounds) were observed at δ_C 155.2 and 153.8, respectively, indicating the presence of sp$_2$ carbon connected with sulfur. The structures of other compounds, **3a, 3b, 3d** and **3f**, were determined mainly by comparison of the proton chemical shifts of *N*^{1}-CH_3 and *N*^{3}-CH_3. These chemical shifts of compounds **3** (*S*-alkylated compounds) were obtained in the δ_H 3.73-3.77 and 3.74-3.80 region, whereas those of compounds **4** (*N*^{7}-alkylated compounds) were in the δ_H 3.62-3.65 and 3.80-3.84 region. This difference seems to arise from the anisotropic effect of the thiocarbonyl moiety.

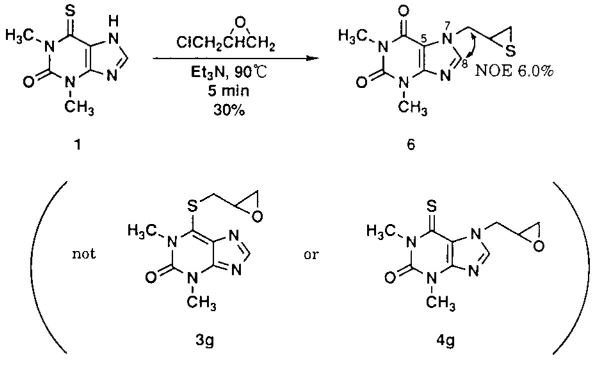
Table 3

^{1}H- and ^{13}C NMR Spectroscopic Data (deuteriochloroform) for *N*^{1}-CH_3 and *N*^{3}-CH_3, and *C*-6 of Alkylated 6-Thiotheophylline Derivatives

Compound	δ_H of N^1-CH_3 and N^3-CH_3	δ_C of C-6
1	3.65, 3.83	176.7
3a	3.73, 3.74	
3b	3.77, 3.79	
3c	3.74, 3.77	155.2
3d	3.75, 3.76	
3e	3.74, 3.77	153.8
3f	3.76, 3.80	
4a	3.63, 3.84	177.0
4b	3.64, 3.83	177.1
4c	3.62, 3.82	177.6
4d	3.64, 3.82	177.1
4e	3.64, 3.82	177.0
4f	3.65, 3.80	177.2
6	3.38, 3.56	155.3
Caffeine	3.40, 3.58	155.4

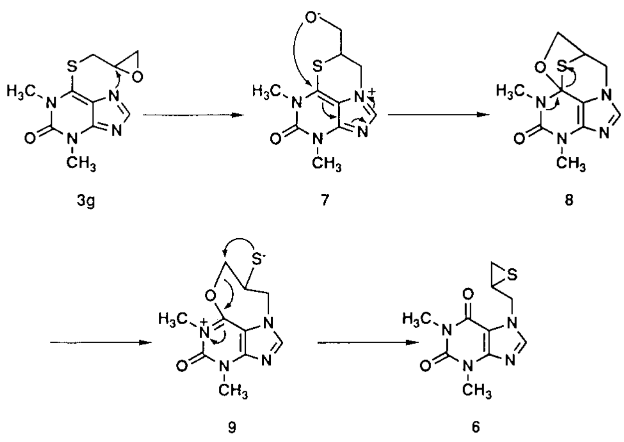
For further modification, we used epichlorohydrin as an alkylating agent under the same condition as described in Table 2. The reaction was slow and a complicated mixture was obtained. Then, **1** was reacted with epichlorohydrin as a solvent in the presence of one equivalent of triethylamine. No reaction proceeded at room temperature, but a rapid exothermic reaction occurred at about 90° to give product **6** in a 30% yield. The elemental analysis and mass spectrum (M^+) indicated that the product had a desired molecular formula, $C_{10}H_{12}O_2N_4S$. However, the nmr spectroscopic analyses suggested that this product was neither the *S*-alkylated compound **3g** nor *N*^{7}-alkylated compound **4g** (Scheme 2). Although the carbon signal of C-6 (δ_C 155.3) is similar to that of *S*-methylated compound **3**, the chemical shift values of *N*^{1}-CH_3 and *N*^{3}-CH_3 (δ_H 3.38 and 3.56) lie at higher fields than those of *N*^{7}-methylated or *S*-methylated compounds **3** or **4** (Table 3). These values are very similar to those of caffeine (1,3,7-trimethylxanthine). Furthermore, the chemical shift values of two methylene carbons (δ_C 24.4 and 52.4) and one methine carbon (δ_C 33.8) in the side chain are not consistent with those of the expected 2,3-epoxypropyl group. These values appear to be close to those of a 2,3-thioepoxypropyl group attached to nitrogen. The observation of the NOE between the methylene protons (δ_H 4.03 and 4.90) and the methine proton at the 8-position (δ_H 7.59), and ^{1}H-^{13}C long range couplings between those methylene protons and the carbon at the 5-position or the carbon at the 8-position indicates that the side chain is attached to nitrogen at the 7-position. Thus, the chemical structure of **6** was determined as illustrated in Scheme 2. This unusual oxygen-sulfur migration is interesting from the view point of its mechanism. We speculate that the primary formation of the *S*-alkylated compound **3g** followed by its isomerization to the caffeine derivative **6** occurs through oxygen-sulfur migration as shown in Scheme 3. This scheme is no more than a proposed reaction pathway.

Scheme 2



In conclusion, we have succeeded in obtaining a variety of *S*-alkylated 6-thiotheophylline derivatives **3** by alkylation of 6-thiotheophylline (**1**) under the aprotic basic condition. In addition, we found that basic treatment of 6-thiotheophylline (**1**) with epichlorohydrin caused an unexpected reaction, affording 7-(2,3-thioepoxypropyl)theophylline (**6**), neither an *S*- nor an *N*^{7}-alkylated compound.

Scheme 3



EXPERIMENTAL

Melting points were determined on a Yanagimoto hot plate micro melting point apparatus and are uncorrected. Infrared (ir) spectra were measured on a JASCO IR-810 spectrophotometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were measured on a Hitachi R-90H or a JEOL JNM GX-270 spectrometer with tetramethylsilane (TMS) as an internal standard. The ^{13}C nmr spectra were recorded on a JEOL JNM GX-270 or a Bruker AMX400 spectrometer. Values of the chemical shift and coupling constant (*J*) are given in δ and Hz. Mass spectra (ms) were determined on a JEOL JMS-D-300 instrument at an ionization potential of 70 eV. High resolution EI mass spectra (hrms) were determined at 70 eV on a JEOL JMS-SX102. Microanalysis was performed on a Perkin-Elmer 2400 CHN. High performance liquid chromatography (hplc) was carried out on a Hitachi L-6200 instrument with a YMC AM-312 ODS column, 150 mm x 6 mm. For column chromatography, Silica gel 60 (E. Merck, 0.063-0.200 mm) was used. Silica gel preparative thin layer chromatography was performed with Merck Kieselgel $F_{254}S$. Standard workup refers to chloroform extraction washed successively with water and brine, dried over anhydrous sodium sulfate and concentrated on a rotary evaporator.

Alkylation of 6-Thiotheophylline (**1**). General Method.

A mixture of 6-thiotheophylline (**1**) [9] (0.005 mole), sodium hydroxide (0.005 mole), methanol (10 ml), and water (10 ml) was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure, and the residue was dissolved in dimethylformamide (3 ml). To this solution was added dropwise an alkylating agent (0.005 mole) in dimethylformamide (2 ml), followed by stirring for a further 5 minutes-24 hours under a nitrogen atomosphere. Then, the mixture was concentrated under reduced pressure. To the residue was added water, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography [eluent:hexane-ethyl acetate (5:1 to 2:1) or chloroform-methanol (1:0 to 50:1)] to afford *S*-alkylated 6-thiotheophylline, (6-alkylthio-1,3-dihydro-1,3-dimethyl-2*H*-purin-2-one) derivatives **3** (hplc purity >98%) and *N*^{7}-alkylated 6-thiotheophylline (7-alkyl-6-thiotheophylline) derivatives **4** (hplc purity >98%). We could not get analytical samples of **3** due to their instability, of which elemental analysis agreed within ±0.4% of calculated values, although their purity was analyzed to be more than 98% by hplc. Spectroscopic data including hrms confirmed the chemical structures of **3**.

6-*n*-Butylthio-1,3-dihydro-1,3-dimethyl-2*H*-purin-2-one (**3a**).

The general method gave compound **3a**, (0.08 g, 6%); ^{1}H nmr (deuteriochloroform): δ 0.96 (t, 3H, J = 7.3 Hz, CH_3), 1.52 (m, 2H, CH_2), 1.78 ppm (m, 2H, CH_2), 3.73 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 4.05 (t, 2H, J = 7.3 Hz, CH_2), 7.93 ppm (s, 1H, CH); hrms: m/z Calcd. for $C_{11}H_{16}ON_4S$: 252.1044. Found: 252.1050 (M^+).

7-*n*-Butyl-6-thiotheophylline (**4a**).

The general method gave compound **4a**, (0.73 g, 58%); ^{1}H nmr (deuteriochloroform): δ 0.96 (t, 3H, J = 6.9 Hz, CH_3), 1.37 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 3.63 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 4.63 (t, 2H, J = 7.1 Hz, CH_2), 7.60 ppm (s, 1H, CH); ^{13}C nmr (deuteriochloroform): δ 13.6 (q, $\mathit{C}H_3CH_2$), 19.4 (t, $CH_3\mathit{C}H_2CH_2$), 30.4 (q, NCH_3), 33.6 (t, $CH_3CH_2\mathit{C}H_2$), 34.3 (q, NCH_3), 47.3 (t, NCH_2), 117.6 (s, C^5), 143.5 (d, C^8), 144.7 (s, C^4), 150.1 (s, C^2), 177.0 ppm (s, C^6); hrms: m/z Calcd. for $CC_{11}H_{16}ON_4S$: 252.1044. Found: 252.1062 (M^+).

Anal. Calcd. for $C_{11}H_{16}ON_4S$: C, 52.35; H, 6.39; N, 22.20. Found: C, 52.58; H, 6.53; N, 22.25.

1,3-Dihydro-1,3-dimethyl-6-isobutylthio-2*H*-purin-2-one (**3b**).

The general method gave compound **3b**, (0.12 g, 10%); ^{1}H nmr (deuteriochloroform): δ 1.11 (d, 6H, J ≐ 6.6 Hz, $(CH_3)_2$), 2.06 (m, 1H, CH), 3.77 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 3.99 (d, 2H, J = 6.6 Hz, CH_2), 7.96 ppm (s, 1H, CH); hrms: m/z Calcd. for $C_{11}H_{16}ON_4S$: 252.1044. Found: 252.1068 (M^+).

7-Isobutyl-6-thioxanthine (**4b**).

The general method gave compound **4b**, (0.38 g, 30%); ^{1}H nmr (deuteriochloroform): δ 0.93 (d, 6H, J = 6.6 Hz, $(CH_3)_2$), 2.29 (m, 1H, CH), 3.64 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 4.39 (d, 2H, J = 7.3 Hz, CH_2), 7.55 ppm (s, 1H, CH); ^{13}C nmr (deuteriochloroform): δ 19.3 (q, $2CH_3$), 29.6 (d, CH), 30.4 (q, NCH_3), 34.3 (q, NCH_3), 54.7 (t, NCH_2), 117.6 (s, C^5), 143.8 (d, C^8), 144.7 (s, C^4), 150.1 (s, C_2), 177.1 ppm (s, C^6); hrms: m/z Calcd. for $C_{11}H_{16}ON_4S$: 252.1044. Found: 252.1027 (M^+).

Anal. Calcd. for $C_{11}H_{16}ON_4S$: C, 52.35; H, 6.39; N, 22.20. Found: C, 52.23; H, 6.51; N, 22.02.

1,3-Dihydro-1,3-dimethyl-6-methylthio-2*H*-purin-2-one (**3c**).

The general method gave compound **3c**, (0.15 g, 14%); ^{1}H nmr (deuteriochloroform): δ 3.32 (s, 3H, SCH_3), 3.74 (s, 3H, NCH_3), 3.77 (s, 3H, NCH_3), 7.97 ppm (s, 1H, CH); ^{13}C nmr (deuteriochloroform): δ 18.2 (q, SCH_3), 32.0 (q, NCH_3), 34.3 (q, NCH_3), 126.5 (s, C^5), 149.0 (s, C^2), 155.2 (s, C^6), 155.7 (s, C^4), 156.0 ppm (d, C^8); hrms: m/z Calcd. for $C_8H_{10}ON_4S$: 210.0575. Found: 210.0579 (M^+).

7-Methyl-6-thioxanthine (**4c**).

The general method gave compound **4c**, (0.35 g, 33%); ^{1}H nmr (deuteriochloroform): δ 3.62 (s, 3H, NCH_3), 3.82 (s, 3H, NCH_3), 4.17 (s, 3H, NCH_3), 7.57 ppm (s, 1H, CH); ^{13}C nmr (deuteriochloroform): δ 30.3 (q, NCH_3), 34.1 (q, NCH_3), 35.7 (q, NCH_3, 118.3 (s, C^5), 144.0 (d, C^8), 144.3 (s, C^4), 150.1 (s, C^2), 177.6 ppm (s, C^6); hrms: m/z Calcd. for $C_8H_{10}ON_4S$: C, 210.0575. Found: 210.0583 (M^+).

Anal. Calcd. for $C_8H_{10}ON_4S$: C, 45.69; H, 4.79; N, 26.64. Found: C, 45.94; H, 4.80; N, 26.54.

1,3-Dihydro-1,3-dimethyl-6-propargylthio-2*H*-purin-2-one (**3d**).

The general method gave compound **3d**, (0.21 g, 18%); ^{1}H nmr (deuteriochloroform): δ 2.33 (t, 1H, J = 2.5 Hz, CH), 3.75 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 4.95 (d, 2H, J = 2.5 Hz, CH_2), 7.97 ppm (s, 1H, CH); hrms: m/z Calcd. for $C_{10}H_{10}ON_4S$: 234.0575. Found: 234.0605 (M^+).

7-Propargyl-6-thiotheophylline (**4d**).

The general method gave compound **4d**, (0.19 g, 16%); ^{1}H nmr (deuteriochloroform): δ 2.61 (t, 1H, J = 2.4 Hz, CH), 3.64 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 5.59 (d, 2H, J = 2.4 Hz, CH_2), 7.98 ppm (s, 1H, CH); ^{13}C nmr (deuteriochloroform): δ 30.4 (q, NCH_3), 34.1 (q, NCH_3), 37.8 (t, NCH_2), 75.9 (d, CH≡), 77.2 (s, C≡), 117.2 (s, C^5), 143.1 (d, C^8), 144.8 (s, C^4), 150.0 (s, C^2), 177.1 ppm (s, C^6); hrms: m/z Calcd. for $C_{10}H_{10}ON_4S$: 234.0575. Found: 234.0570 (M^+).

Anal. Calcd. for $C_{10}H_{10}ON_4S$: C, 51.26; H, 4.30; N, 23.91. Found: C, 51.39; H, 4.24; N, 23.55.

6-Allylthio-1,3-dihydro-1,3-dimethyl-2*H*-purin-2-one (**3e**).

The general method gave compound **3e**, (0.38 g, 32%); ^{1}H nmr (deuteriochloroform): δ 3.74 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 4.73 (ddd, 2H, J = 7.2, 1.4, 0.7 Hz, CH_2), 5.24 (m, 1H, CH), 5.38 (m, 1H, CH), 5.99 (ddt, 1H, J = 17.0, 9.9, 7.2 Hz, CH), 7.97 ppm (s, 1H, CH); ^{13}C nmr (deuteriochloroform): δ 31.9 (q, NCH_3), 34.4 (q, NCH_3), 37.4 (t, SCH_2), 120.6 (t, CH_2=), 126.9 (s, C^5), 131.6 (d, CH=), 149.2 (s, C^2), 153.8 (s, C^6), 156.0 (s, C^4), 158.4 ppm (d, C^8); hrms: m/z Calcd. for $C_{10}H_{12}ON_4S$: 236.0731. Found: 236.0735 (M^+).

7-Allyl-6-thiotheophylline (**4e**).

The general method gave compound **4e**, (0.45 g, 38%); ^{1}H nmr (deuteriochloroform): δ 3.64 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 5.12 (ddt, 1H, J = 17.2, 0.9, 1.5 Hz, CH), 5.29 (ddt, 1H, J = 10.5, 0.9, 1.2 Hz, CH), 5.35 (ddd, 2H, J = 5.5, 1.5, 1.2 Hz, CH_2), 6.07 (ddt, 1H, J = 17.2, 10.5, 5.5 Hz, CH), 7.64 ppm (s, 1H, CH); ^{13}C nmr (deuteriochloroform): δ 30.3 (q, NCH_3), 34.1 (q, NCH_3), 49.3 (t, NCH_2), 117.4 (s, C^5), 118.7 (t, CH_2=), 132.9 (d, CH=), 143.5 (d, C^8), 144.7 (s, C^4), 150.1 (s, C^2), 177.0 ppm (s, C^6); hrms: m/z Calcd. for $C_{10}H_{12}ON_4S$: 236.0731. Found: 236.0743 (M^+).

Anal. Calcd. for $C_{10}H_{12}ON_4S$: C, 50.83; H, 5.11; N, 23.71. Found: C, 50.75; H, 5.03; N, 23.36.

1,3-Dihydro-1,3-dimethyl-6-ethoxycarbonylmethylthio-2*H*-purin-2-one (**3f**).

The general method gave compound **3f**, (0.14 g, 10%); ^{1}H nmr (deuteriochloroform): δ 1.28 (t, 3H, J = 7.0 Hz, CH_3), 3.76 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 4.23 (q, 2H, J = 7.0 Hz, CH_2), 4.90 (s, 2H, CH_2), 7.91 ppm (s, 1H, CH); hrms: m/z Calcd. for $C_{11}H_{14}O_3N_4S$: 282.0786. Found: 282.0790 (M^+).

7-Ethoxycarbonylmethyl-6-thiotheophylline (**4f**).

The general method gave compound **4f**, (0.30 g, 21%); ^{1}H nmr (deuteriochloroform): δ 1.31 (t, 3H, J = 7.2 Hz, CH_3), 3.65 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 4.27 (q, 2H, J = 7.2 Hz, CH_2), 5.42 (s, 2H, CH_2), 7.63 ppm (s, 1H, CH); ^{13}C nmr (deuteriochloroform): δ 14.2 (q, CH_3), 30.4 (q, NCH_3), 34.1 (q, NCH_3), 48.5 (t, NCH_2), 62.3 (t, CH_2), 117.5 (s, C^5), 144.4 (s, C^4), 144.6 (d, C^8), 150.1 (s, C^2), 167.4 (s, COO), 177.2 ppm (s, C^6); hrms: m/z Calcd. for $C_{11}H_{14}O_3N_4S$: 282.0786. Found: 282.0788 (M^+).

Anal. Calcd. for $C_{11}H_{14}O_3N_4S$: C, 46.79; H, 4.99; N, 19.84. Found: C, 47.47; H, 5.31; N, 19.42.

7-(2,3-thioepoxypropyl)theophylline (**6**).

A mixture of 6-thiotheophylline (**1**) [9] (13.1 g, 0.067 mole), epichlorohydrin (60 ml, 0.772 mole), and triethylamine (9.3 ml, 0.067 mole) was stirred at 90° for 5-10 minutes. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent:chloroform:methanol = 100:1) to afford **6**, 5.1 g (30%), mp 105.9-108.9°; ^{1}H nmr (deuteriochloroform): δ 2.40 (dd, 1H, J = 5.1, 1.7 Hz, CH), 2.61 (dd, 1H, J = 6.4, 1.7 Hz, CH), 3.41-3.50 (m, 1H, CH), 3.38 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 4.03 (dd, 1H, J = 14.1, 7.5 Hz, CH), 4.90 (dd, 1H, J = 14.1, 4.9 Hz, CH), 7.59 ppm (s, 1H, CH); ^{13}C nmr (deuteriochloroform): δ 24.4 (t, SCH_2), 28.0 (q, NCH_3), 29.8 (q, NCH_3), 33.8 (d, SCH), 52.4 (t, NCH_2), 106.7 (s, C^5), 141.0 (d, C^8), 149.0 (s, C^4), 151.6 (s, C^2), 155.3 ppm (s, C^6); hrms: m/z Calcd. for $C_{10}H_{12}O_2N_4S$: 252.0680. Found: 252.0686 (M^+).

Anal. Calcd. for $C_{10}H_{12}O_2N_4S$: C, 47.61; H, 4.79; N, 22.21. Found: C, 47.25; H, 4.79; N, 21.50.

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