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Unusual Reactivity of Purinophanes Due to Stereoelectronic Effect[1)]

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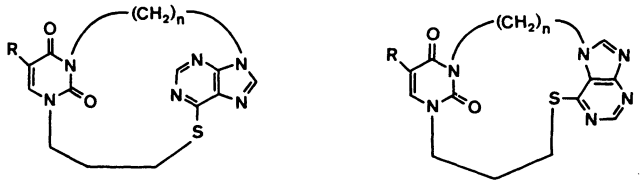
Four types of purinophanes (**1**, **2**, **7**, and **10**) where a 6-thiopurine ring is bridged between S^6- and 9-positions or between S^6- and 7-positions were synthesized. Among them (6,9)purinophanes (**1**, **7**, and **10**) showed unusual high reactivity toward nucleophiles ($MeNH_2$, Me_2NH, OH^-) at 6-position to give acyclic compounds. The increased rate constants of these compounds against (6,7)purinophanes **2** and 9-methyl-6-(methylthio)purine could not be explained by molecular strain, neighboring group participation, or some electronic effect due to faced π-systems, but successfully explained by the stereoelectronic effect proposed by Deslongchamps. The rate of the reactions in **1**, **7**, and **10** was increased with an increase in rigidity of the tetrahedral intermediate where lone pairs of two adjacent heteroatoms orient antiperiplanar to the departing group.

The stereoelectronic effect[2)] is recognized as having a major influence on the reactivity of various molecules such as cyclic acetals, esters, amides, and related compounds, all of which contain geminal heteroatoms with nonbonded electron lone pair. The effect, however, has not so far been observed in biologically important nucleic acid bases in spite of their satisfying the structural requirement. Recently, we prepared a series of purinophanes[3)] and pyrimidinopurinophanes[4)] for studying the relationship between hypochromism and stacking geometry of two nucleic acid bases. In the course of the study we observed that **1a**, **b** react with nucleophiles such as alkylamines and hydroxide anion at room temperature to give acyclic compounds such as **3a**, while the isomeric compounds **2a**, **b** did not show such reactivity under



a: R=H, n=3
b: R=H, n=4
c: R=CH_3, n=3
d: R=OCH_3, n=3
e: R=NO_2, n=3

the same conditions. To understand the anomalous behavior of **1a,b**, we have prepared various kinds of related compounds and concluded that the stereoelectronic theory provides the best explanation for the unusual reactivity of **1a,b**. Here we report the first observation of the stereoelectronic effect in nucleic acid bases.

Results and Discussion

When the electronic spectra of **1a,b** were measured in 0.1 M NaOH (1 M=1 mol dm^{-3}), methylamine/H_2O, and dimethylamine/H_2O at room temperature, the spectra changed with time having one or two isosbestic points. A typical example is shown in Fig.1. Similar behavior was observed for nucleophiles such as RS^-, RNH_2, and R_2NH in ethanol, but not observed for CN^-, I^-, R_3N, and R_4N^+. Figure 1 shows clearly that **1b** underwent some reaction to give single product, which is assumed to be an acyclic compound **3a**. The structure of **3b**, which was derived from **3a**, was determined by the alternative synthesis as summarized in Scheme 1. Thus, the spectral data of the reaction product of **1b** with methylamine, followed with dimethyl sulfate are consistent with those of the coupling product between **4** and **5** (see the Experimental part). Therefore, it is apparent that nucleophiles attack at 6-position of **1a,b** to give the product. On the other hand, isomeric pyrimidinopurinophanes **2a,b** did not show any spectral change at all under the same conditions as those for **1a,b**. First, we assumed that the unusual reactivity originates from strain in the molecules, because cyclophanes frequently show such behavior.[5)] In order to

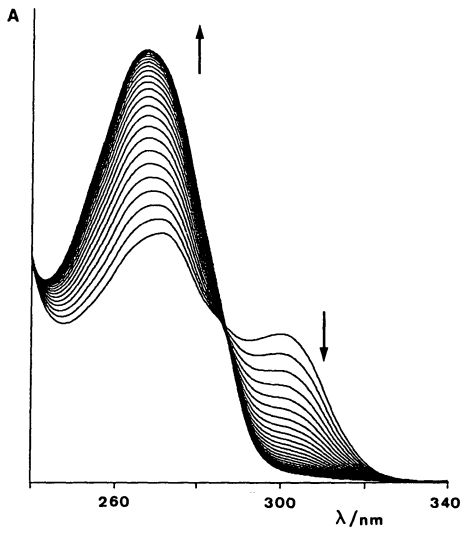
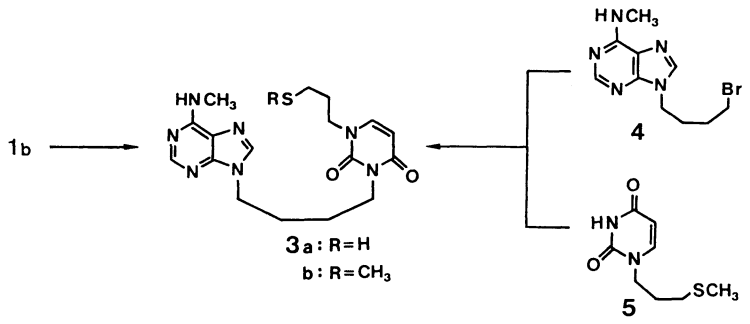


Fig. 1. Spectral change of **1b** at the interval of 30 minutes in the presence of methylamine in ethanol at 25 °C.



Scheme 1.

Table 1. Bond Lengths and Bond Angles of **1b** and **2a**[a)]

	1b	**2a**		**1b**	**2a**
Bond length (l/Å)			C2-N3-C4	111.6(2)	113.0(3)
N1-C2	1.351(3)	1.341(4)	N3-C4-C5	126.2(2)	123.7(3)
C2-N3	1.332(3)	1.331(4)	N3-C4-N9	127.8(2)	125.8(3)
N3-C4	1.331(2)	1.331(4)	C4-C5-C6	116.4(2)	118.0(2)
C4-C5	1.389(2)	1.404(4)	C4-C5-N7	110.4(2)	105.7(2)
C5-C6	1.382(3)	1.403(4)	C5-C6-N1	119.6(2)	118.2(2)
C5-N7	1.391(2)	1.379(3)	C5-N7-C8	103.2(2)	105.4(2)
N7-C8	1.310(3)	1.365(3)	N7-C8-N9	115.2(2)	114.7(2)
C8-N9	1.358(2)	1.321(4)	C8-N9-C4	105.2(2)	103.6(2)
N9-C4	1.377(2)	1.350(4)	C6-C5-N7	133.2(2)	136.3(2)
C6-S6	1.772(2)	1.765(3)	S6-C6-N1	116.7(1)	120.2(2)
N1′-C2′	1.378(2)	1.375(3)	S6-C6-C5	123.7(1)	121.5(2)
C2′-N3′	1.387(2)	1.384(3)	C6′-N1′-C2′	121.2(2)	121.5(2)
N3′-C4′	1.405(2)	1.404(3)	N1′-C2′-N3′	116.1(2)	116.3(2)
C4′-C5′	1.433(3)	1.429(4)	N1′-C2′-O2′	122.0(2)	121.8(2)
C5′-C6′	1.328(3)	1.340(4)	N3′-C2′-O2′	122.0(2)	121.8(2)
C6′-N1′	1.372(3)	1.373(4)	C2′-N3′-C4′	124.7(2)	124.4(2)
C2′-O2′	1.226(2)	1.220(3)	N3′-C4′-C5′	114.9(2)	115.4(2)
C4′-O4′	1.219(3)	1.227(4)	N3′-C4′-O4′	119.8(2)	120.1(3)
			C5′-C4′-O4′	125.3(2)	124.6(3)
Bond angle (ϕ/°)			C4′-C5′-C6′	120.4(2)	120.3(3)
C6-N1-C2	118.1(2)	118.3(3)	C5′-C6′-N1′	122.7(2)	122.0(3)
N1-C2-N3	127.9(2)	128.5(3)			

a) Values in parentheses are standard deviations.

confirm this point, X-ray analysis[6)] was carried out for **1b** and **2a**. Bond lengths and bond angles of purine and pyrimidine rings in **1b** and **2a** are summarized in Table 1 and the deviations of the ring atoms from the least-squares planes of the two rings are shown in Table 2. From Table 1 it is apparent that there are not so large differences in bond lengths and bond angles between **1b** and **2a**. This is also true when these values are compared with those of 6-(methylthio)purine[9)] and 1,3-dimethyluracil.[10)] The extents of the planality of the purine and pyrimidine rings in **1b** and **2a** are quite similar as shown in Table 2. All of these data clearly show that the reactivity of **1a,b** can not be explained by molecular strain.

The second possible reason for the abnormal reactivity is considered to be the neighboring group participation. As seen from Fig. 2, the carbonyl group at C2′ position in **1b** is located closely to the reaction center: namely, the nonbonded distances in **1b** are

Table 2. Deviation of the Ring Atoms from the Least-Squares Plane

	1b/Å	**2a**/Å
N1	−0.010	−0.019
C2	−0.025	−0.044
N3	0.014	0.017
C4	0.008	0.030
C5	−0.004	0.009
C6	0.033	0.044
N7	−0.019	−0.019
C8	−0.001	−0.033
N9	0.005	0.018
N1′	0.005	0.012
C2′	0.008	−0.020
N3′	−0.021	0.008
C4′	0.020	0.011
C5′	−0.007	−0.019
C6′	−0.005	0.008
O2′	0.032	−0.051
O4′	0.075	0.037

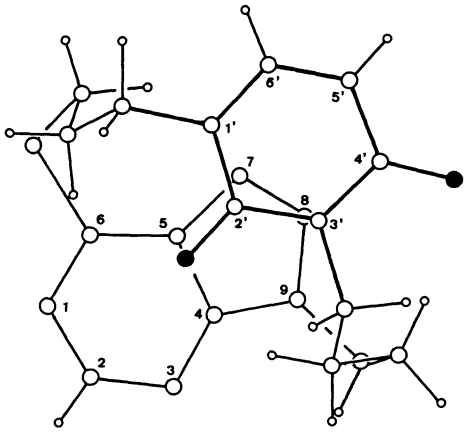
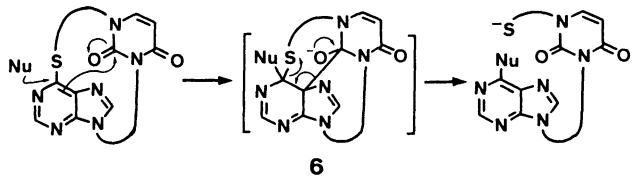


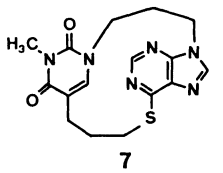
Fig. 2. Views on the least-squares plane defined with a purine ring in **1b**.



6

Scheme 2.

4.229 Å between C5 and O2′ and 4.058 Å between C5 and C2′. Assuming the C5 participation to C2′, the reaction will proceed via transition state or intermediate **6** as shown in Scheme 2. In order to determine whether such mechanism is correct or not, we prepared **1c—1e**,[4] where an electron-donating or an electron-withdrawing substituent is introduced into the pyrimidine ring so that the reaction rate will more or less be influenced. We also prepared **7**,[4] where the



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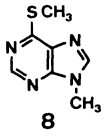
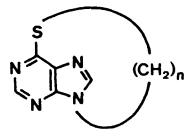


8

9 a: n=9
b: n=10
c: n=11



10 a: n=9
b: n=10
c: n=11

11

S6 atom is linked not to N3′ as in the case for **1**, but to C5′. Based on molecular model considerations, **7** has a structure, where the carbonyl group in question is located far apart from the reaction center. On the basis of spectrophotometry, the rate constants of **1**, **7**, and reference compound **8** toward methylamine in ethanol were obtained at 25±1 °C by analyzing the reaction as pseudo-first-order and the results are summarized in Table 3. One can see from the table that there is no essential change among the rate constants of **1b—1e** and **7**. Therefore, it is concluded that the carbonyl group at 2′ position in **1** is not responsible for the unusual reactivity.

The third possibility for the elucidation of the abnormality is some electronic effect due to the transannularly located π-system, that is, pyrimidine ring. To make this point clear, we synthesized **10**, where 6-thiopurine is bridged with a polymethylene chain at the same positions as **1** and **7** and hence there is no possibility of the electoinc effect due to the faced pyrimidine ring. Synthesis of **10a—c** was carried out by the intramolecular cyclization reaction of **9a—c**, which was prepared by the reaction of 6-mercaptopurine and α,ω-dibromoalkane with sodium hydride. The crude product was purified by column chromatography on silica gel and then, recrystallized from chloroform. In ^{1}H NMR spectra methylene protons adjacent to the sulfur atom in **10a—c** show complex multiplets, while the corresponding protons of acyclic compounds **9a—c** appear with the first-order splitting. The other bridge protons of **10a—c** also show complex signals. The result indicates that the purinophanes **10a—c** have more or less rigid structure in solution. The rate constants of **10a—c** thus prepared were determined for the reaction with methylamine in a manner similar to those for **1** and the results are summarized in Table 3. The fact that the values for **10a—c** are similar to those for **1** clearly indicates that the reactivity of **1** is not attributable to the faced pyrimidine ring. Molecular model considerations on **10a—c** revealed that there exists no strain even in **10a** having the shortest bridge among them. This leads to the same conclusion as for **1** that molecular strain does not play an important role for the reactivity of **10a—c**.

The only reasonable explanation for the increased rate constants of **1**, **7**, **10** is, at the present stage, given by the stereoelectronic theory[2] by Deslongchamps. The theory states that in tetrahedral intermediate **11** such reactions are favored for conformations where lone-pair orbitals on two adjacent heteroatoms lie

Table 3. Reaction Rate Constants of **1a—e**, **7**, **8**, and **10a—c** with Monomethylamine in Ethanol at 25±1 °C

Compound	K/s^{-1}M^{-1}
1a	4.4×10^{-3}
1b	4.5×10^{-4}
1c	5.2×10^{-4}
1d	6.2×10^{-4}
1e	5.0×10^{-4}
7	5.5×10^{-4}
8	$<10^{-6}$
10a	2.6×10^{-3}
10b	1.1×10^{-4}
10c	4.6×10^{-5}

antiperiplanar to the bond to the leaving group (X). Theoretical justification for the concept has been given by lowering the energy of transition state by mixing of lone-pair orbitals with the antibonding orbital of the C-X bond. When we apply the theory to the present molecules, the reaction scheme is written as shown in Fig. 3. The tetrahedral intermediate **13a**, which will easily be obtained from **12a**, is expected to give smoothly **14a**, because of its antiperiplanar orientation of the two lone-pair orbitals on the nitrogen atoms and the C-S bond. In the case of (6,7)purinophanes, however, the steric hindrance among R^1, R^2, and R^3 would prevent the formation of tetrahedral intermediate **13b** from **12b** and hence the C-S bond is not cleaved easily. This must be the reason for the higher reactivity of (6,9)-purinophanes than (6,7)-isomers. For the enhancement in reaction rate by the stereoelectronic effect it is requested that the corresponding antiperiplanar conformations have rigid structures.[2c] This is reflected in the order of the rate constants of **10a—c** in Table 1. Thus, the value increases with a decrease of the length of the bridging chain, i.e., **10a>10b>10c**. The quite low reactivity of the reference compound **8** might be also explained by the conformational flexibility of the antiperiplanar structure of the tetrahedral intermediate.

In the present study the unusual reactivity of **1**, **7**, and **10** is well-explained by the stereoelectronic effect and this is the first example for the concept to be successfully applied in the field of purine ring. This suggests that the theory is widely applicable to the elucidation of the reaction course of nucleophilic substitution reactions which occur at various heteroaromatic rings including nucleic acid bases.

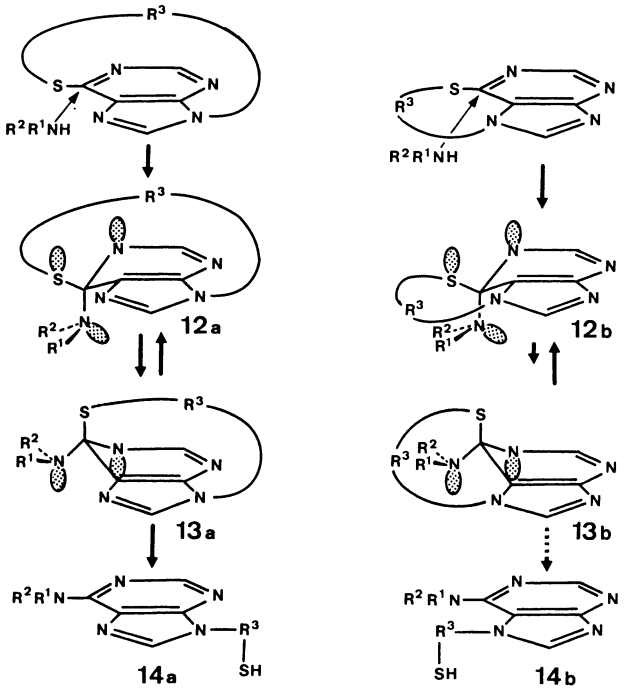


Fig. 3. Reaction course of (6,9)- and (6,7)-purinophanes with alkylamines.

Experimental

Melting points were recorded on a Yanagimoto apparatus and are not corrected. NMR spectra were measured on a JNM PMX-60SI (60 MHz), a JNM FX-100 (100 MHz), and a Brucker WH-360 (360 MHz). Mass spectra were obtained on a Hitachi RMU-7 and UV spectra were measured on a Hitachi 330 and a Hitachi U-3210.

6-(10-Bromodecylthio)purine (9b). To a stirred suspension of 60% NaH (0.17 g, 4.33 mmol) in dry DMSO (5 ml) was added a solution of 6-mercaptopurine[11](0.57 g, 3.78 mmol) and 1,10-dibromodecane (5.17 g, 17.23 mmol) in DMSO (35 ml) at 55 °C in a period of 45 min. Additional stirring was continued for 5 h at 55 °C. After cooling, the mixture was poured onto water and it was extracted with chloroform. The organic layer was washed with sat aq solution of NaCl and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel with chloroform-acetone (5 : 1) to give 0.22 g (15.7% yield) of **9b**. Recrystallization from chloroform gave pure **9b** as colorless plates, mp 123.0—125.0 °C. ^{1}H NMR ($CDCl_3$, 360 MHz) δ=1.30—1.50 (m, 12, CH_2), 1.76—1.89 (m, 4, CH_2), 3.39—3.44 (m, 5, NH+SCH_2+CH_2Br), 8.32 (s, 1, H8), 8.79 (s, 1, H^2).

Found: C, 48.56; H, 6.11; N, 15.10; S, 8.39; Br, 21.38%. Calcd for $C_{15}H_{23}N_4SBr$: C,48.52; H,6.24; N,15.09; S,8.63; Br,21.52%.

The synthesis of **9a** and **9c** was carried out by the similar method described for **9b**.

9a: 32% yield, mp 96—100 °C. ^{1}H NMR ($CDCl_3$, 360 MHz) δ=1.32—1.48 (m, 10, CH_2), 1.75—1.86 (m, 4, CH_2), 3.38—3.43 (m, 5, NH+SCH_2+CH_2Br), 8.50 (s, 1, H8), 8.80 (s, 1, H2).

9c: 28% yield, mp 101—103 °C. ^{1}H NMR ($CDCl_3$, 360 MHz) δ=1.28—1.52 (m, 14, CH_2), 1.77—1.88 (m, 4, CH_2), 3.35—3.45 (m, 5, NH+SCH_2+CH_2Br), 8.44 (s, 1, H8), 8.83 (s, 1, H2).

1-Thia[11](6,9)purinophane (10b). To a stirred suspension of 60% NaH (0.04 g, 1.02 mmol) in dry DMSO (15 ml) was added dropwise a solution of **9b** (0.37 g, 0.79 mmol) in dry DMSO (25 ml) at 55 °C in a period of 3 h. Additional stirring was continued for 5 h at the same temperature. After cooling, the mixture was poured on cold water and it was extracted with chloroform. The extracts were washed successively with water and sat aq solution of NaCl and dried ($MgSO_4$). Crude product was chromatographed on silica gel with ether to give 18 mg (7.7% yield) of **10b**. Recrystallization from hexane gave pure **10b** as colorless prisms, mp 105.0—107.0 °C. **10b:** MS m/z 290 (M^+). ^{1}H NMR ($CDCl_3$, 360 MHz) δ=0.33—1.22 (m, 12, CH_2), 1.53—2.07 (m, 4, CH_2), 3.28—3.56 (m, 1, SCH_2), 4.02—4.10 (m, 2, SCH_2+NCH_2), 4.59—4.66 (m, 1, NCH_2), 8.06 (s, 1, H8), 8.79 (s, 1, H2).

The synthesis of **10a** and **10c** was carried out in a manner similar to the above.

10a: 8.6% yield, colorless prisms from chloroform, mp 103—104 °C; MS m/z 276 (M^+); ^{1}H NMR ($CDCl_3$, 360 MHz) δ=0.27—1.23 (m, 10, CH_2), 1.49—2.14 (m, 4, CH_2), 3.14—3.49 (m, 1, CH_2), 4.00—4.09 (m, 2, SCH_2+NCH_2), 4.61—4.70 (m, 1, NCH_2), 8.11 (s, 1, H8), 8.73 (s, 1, H2).

10c: 13% yield; colorless prisms from chloroform, mp 99—102 °C; MS *m/z* 304 (M^+); ^{1}H NMR ($CDCl_3$, 360 MHz) δ=0.36—1.35 (m, 14, CH_2), 1.59—2.11 (m, 4, CH_2), 3.26—3.61 (m, 1, SCH_2), 4.06—4.19 (m, 2, SCH_2+NCH_2), 4.60—4.71 (m, 1, NCH_2), 8.09 (s, 1, H8), 8.82 (s, 1, H2).

9-(14-Bromobutyl)-6-(methylamino)purine (4). In a Pyrex ampule were placed 6-(methylthio)purine·$3H_2O$ (1.0 g, 4.2 mmol), H_2O (1 ml), and 40% aq solution of methylamine and the mixture was heated at 130—140 °C for 18 h in the sealed tube. After cooling, the mixture was concentrated to half of its original volume and the residue was kept at 0 °C for 1 h. Yielded precipitates were collected and washed well with water. Crude product was dried by azeotropic distillation with benzene to give 6-(methylamino)-purine·$2H_2O$[11] (590 mg, 81%). Without further purification it was used for the following reaction.

To a stirred suspension of 1,4-dibromobutane (2.0 ml, 16.3 mmol) and K_2CO_3 (1.0 g, 9.0 mmol) in dry DMSO (50 ml) was added dropwise a solution of 6-(methylamino)-purine·$2H_2O$ (590 mg) in dry DMSO (30 ml) in a period of 7.5 h under nitrogen atmosphere. After addition was over, stirring was continued for 11 h. Salts were filtered off and the solvent was removed under reduced pressure. Water (50 ml) was added to the residue and it was extracted with chloroform. The organic layer was washed well with sat aq solution of NaCl and water and dried ($MgSO_4$). Removal of the solvent gave **4** (290 mg, 30% yield) as colorless oil. MS *m/z* 285, 283 (M^+), 204 (M^+—Br); ^{1}H NMR ($CDCl_3$, 60 MHz) δ=2.0 (m, 4, CCH_2CH_2C), 3.2 (d, J=5 Hz, 3, NCH_3), 3.4 (t, 2, CH_2Br), 4.2 (t, 2, CH_2N), 7.0 (br s,. 1,NH), 7.7 (s, 1, H8), 8.4 (s, 1, H2).

1-(3-Methylthiopropyl)uracil (5). A solution of 1-(3-bromopropyl)uracil[12] (300 mg, 1.3 mmol) and thiourea (105 mg, 1.35 mmol) in ethanol (10 ml) was refluxed for 12 h. After removal of ethanol, water (5 ml) was added to the residue and the atmosphere was replaced with N_2. To the mixture was added NaOH (104 mg, 2.6 mmol) and it was heated at 90—100 °C. After cooling, methyl iodide (0.08 ml, 1.3 mmol) was added to the mixture and additional stirring was continued for 1.5 h. To the mixture was added dil HCl and the medium was adjusted to pH around 5 and then, it was extracted with chloroform. The extract was washed with sat aq solution of NaCl and water and dried ($MgSO_4$). After removal of the solvent, the crude product was recrystallized from benzene-hexane to give **5** (50 mg, 19% yield). **5**: colorless crystals, mp 78—79 °C. MS *m/z* 200 (M^+), 186 (M^+—CH_3), 153 (M^+—SMe). ^{1}H NMR ($CDCl_3$, 60 MHz) δ=2.0 (m, 2, CCH_2C), 2.1 (s, 3, SCH_3), 2.2 (m, 2, SCH_2), 3.8 (t, 2, NCH_2), 5.7 (d, 1, H5), 7.2 (d, 1, H6).

6-Methylamino-9-[4-[1,2,3,6-tetrahydro-3-(3-methylthiopropyl)-2,6-dioxo-1-pyrimidinyl]butyl]purine (3b). A suspension of **4** (73 mg, 0.26 mmol), **5** (50 mg, 0.25 mmol), and K_2CO_3 (69 mg, 0.5 mmol) in DMSO (10 ml) was stirred for 12 h at room temperature under nitrogen atmosphere. After usual workup, crude product was purified by preparative-layer chromatography on silica gel with methanol-chloroform (1:15) to give **3b** (54 mg, 54% yield). **3b:** colorless solid from chloroform-ether, mp 53.5—56.0 °C. MS *m/z* 403 (M^+) 388, 357, 356, 342. ^{1}H NMR ($CDCl_3$, 100 MHz) δ=1.40—2.10 (m, 6, CCH_2C), 2.10 (s, 3, SCH_3), 2.52 (t, 2, SCH_2), 3.21 (d, J=5.1 Hz, 3, NCH_3), 3.85 (t, 2, NCH_2), 5.70 (d, J=6.8 Hz 1, H5′), 6.01 (br s, 1, NH), 7.18 (d, J=6.8 Hz, 1, H6′), 7.79 (s, 1, H8), 8.39 (s, 1, H2).

Found: C, 52.96; H, 6.25; N, 24.30%. Calcd for $C_{18}H_{27}N_7SO_2$: C, 53.58; H, 6.25; N, 24.30%.

Synthesis of 3b by the Reaction of 1b with Methylamine Followed by Dimethyl Sulfate. To an ampule was placed **1b** (25 mg, 0.067 mmol) and water (0.5 ml). After replacement of the atmosphere with nitrogen, 40% aq solution of methylamine (0.1 ml, 1.3 mmol) was added to the mixture and it was heated for 1.5 h at 120 °C in the sealed tube. After reaction was over, the ampule was opened and excess methylamine was removed by vigorous bubbling of nitrogen. To the mixture was added NaOH (20 mg, 0.5 mmol) at 0 °C and it was stirred for 10 min at the temperature. To the solution was added dropwise dimethyl sulfate (0.1 mmol) diluted with dioxane. Additional stirring was continued for 2 h at room temperature. After reaction was over, the mixture was extracted with chloroform. The extract was washed well with water and dried ($MgSO_4$). Removal of the solvent gave oily product, which was purified by preparative-layer chromatography on silica gel to give colorless oil (12 mg, 43% yield). **3b:** colorless solid from chloroform-ether, mp 54—56 °C. Spectroscopic data were identical with those of the specimen described above.

Kinetic Studies. Kinetic measurements were carried out on a UV-visible spectrophotometer. The cells were maintained at a constant temperature (25±1 °C) by means of a thermostated cuvette holder. The pseudo-first-order rate constants were determined from the slopes of a $[A_s(t)+A_p(t)-A_\infty]$ vs. time plot, where $A_s(t)$, $A_p(t)$, and A_∞ are absorbance of substrate, product, and final, respectively. Reactions were followed by measuring the rate of decreasing of the 6-(methylthio)purine chromophore at its absorbance maximum (around 304 nm).

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