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# Synthesis, Structure, and Hypochromism of Pyrimidinopurinophanes[1)]

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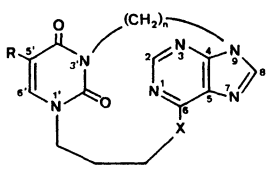
Seventeen pyrimidinopurinophanes in which a pyrimidine and a purine ring are fixed with different mode of stacking were prepared. The synthesis was carried out by stepwise introduction of two bridging chains. In the final ring closure reaction, two isomers, i.e., isomers bridged at 9-position of a purine ring and those having the bridge at 7-position of a purine ring were obtained. The structures of the isomers were determined on the basis of $^1$H NMR, IR, and UV spectra and X-ray analysis. In $^1$H NMR spectra the bridge protons of the pyrimidinopurinophanes show complex multiplets, in contrast to the first order splittings in singly bridged reference compounds. This shows clearly the fixation of the conformations of the present cyclic compounds at room temperature. All of the pyrimidinopurinophanes show relatively large hypochromism ($H$) values. Even the compounds **2a—2d**, **4**, and **6** where the two base rings are not stacked in parallel, but inclined with the dihedral angle of around 50°, show $H$ values of 10—20%. The $H$ values did not change among the compounds **1c**, **1e—1g**, and **3** which have similar parallel-stacking structures of the two base rings. The results are well explained by the simplified equation of Ts'o et al.

Hypochromism — a decrease in the absorption intensity per unit chromophore — is observed frequently in various $\pi$-systems and biologically important substances such as proteins and DNA, where chromophores involved are stacked in a parallel fashion.[2)] The relationship between the stacking orientation and hypochromism values, however, has not been well-understood so far. Recently, we prepared a series of purinophanes where two purine rings are fixed with different mode of stacking.[3)] By analyzing the relationship between their hypochromism values and geometrical parameters from the X-ray results, we presented empirical formulas to estimate the hypochromism values for a given geometry of two stacked purine rings.

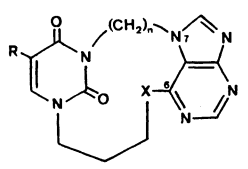
We set forward our study for the general understanding of the interaction between two nucleic acid bases other than two purine rings. Since purine-pyrimidine interaction is the greatest after purine-purine interaction,[4)] we planned to synthesize various pyrimidinopurinophanes, in which a purine and a pyrimidine ring is fixed with different modes of relative orientation. Related compounds, prepared so far, are singly bridged compounds, i.e., (pyrimidine)-$(CH_2)_n$-(purine)[4)] with changing the length of the chain and connecting positions at the base rings. They are, however, conformationally not frozen in solution and therefore, not well-suited for the quantitative treatment of hypochromism values in relation to the precise stacking orientation. The present rigid systems are expected to serve useful information about the structural dependence of hypochromism values.

## Synthesis

All the pyrimidinopurinophanes **1—6** were prepared by step-wise introduction of the bridging chains. Thus, the singly bridged compounds **7—13** were first prepared starting from the corresponding pyrimidine and purine derivatives as shown in Chart 1. The second chain was introduced by ring closure with $\alpha,\omega$-

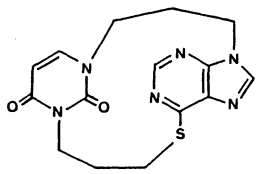


1



2

a X=NH, R=H, n=3
b X=NH, R=H, n=4
c X=S, R=H, n=3
d X=S, R=H, n=4
e X=S, R=$CH_3$, n=3
f X=S, R=$OCH_3$, n=3
g X=S, R=$NO_2$, n=3



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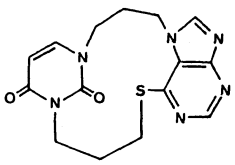

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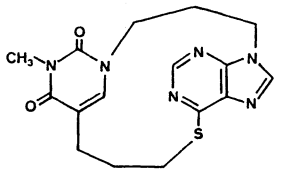

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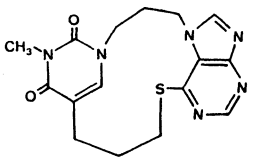

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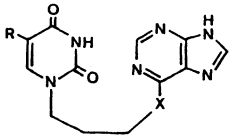
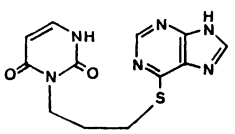


7 X=NH, R=H
8 X=S, R=H
9 X=S, R=$CH_3$
10 X=S, R=$OCH_3$
11 X=S, R=$NO_2$



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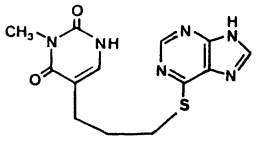


13

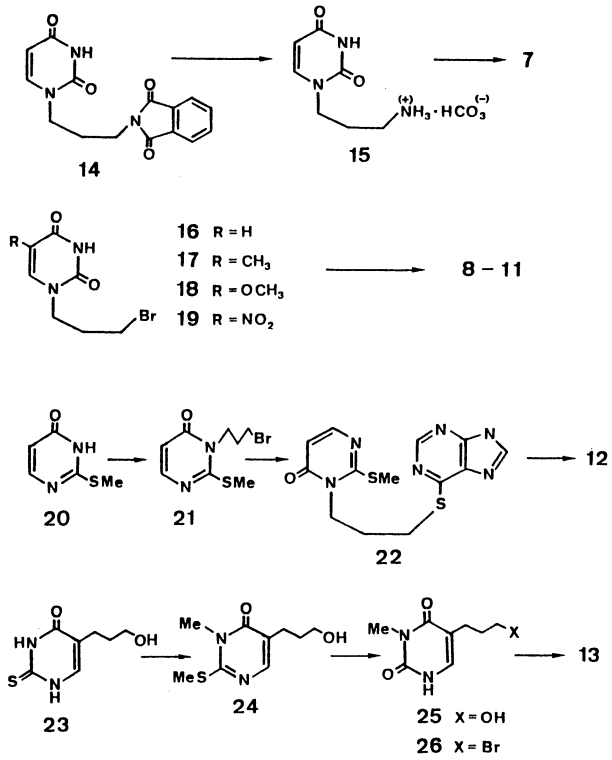
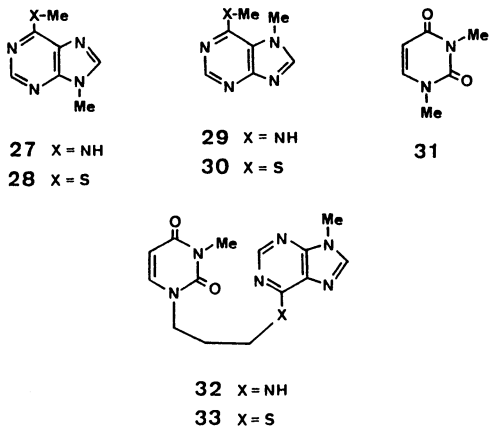



Chart 1.




dibromoalkanes in the presence of sodium hydride in DMF (method A) and/or potassium carbonate in DMSO (method B). The coupling reaction gave two isomeric products, i.e., (1′,3′)pyrimidino(6,9)purinophanes **1** and (1′,3′)pyrimidino(6,7)purinophanes **2**. These structures were determined on the basis of spectral data and X-ray analysis as described later. The ratios of the two isomers are different in A and B methods as shown in Table 1. In all runs except for the ratio of **1b**/**2b** by the method B, the isomers **2** (bridged at 7-position of the purine ring) are the major or sole product. The other pyrimidino-purinophanes **1e—1g**, **2e—2g**, and **3—6** were prepared by the method A and the yields are summarized in Table 1.

Monomeric and dimeric references **27**,[3] **28**,[3] **29**,[5] **30**,[6] **31**,[7] **32**, and **33** were also prepared.

## Structure

**NMR Spectra.** $^1$H NMR spectra of the present molecules were measured in deuteriochloroform. The bridge protons of all the pyrimidinopurinophanes **1—6** show complex multiplets in contrast to the first order splitting patterns of acyclic reference compounds **32** and **33**. These results clearly indicate that the conformations of **1—6** are almost frozen at room temperature. The chemical shifts of the ring protons (H2, H8, H5′, and H6′) of the pyrimidinopurinophanes and reference compounds are summarized in Table 2. Since H2 and H8 protons of **27** or **28** resonate at higher field than the corresponding protons of **29** or **30**, the isomers which show the similar tendency in the chemical shifts of H2 and H8 to those of **27** or **28** were assigned to the structure having a linkage at 9-position of the purine ring, i.e., **1b—1g**, **3**, and **5** and the others were assigned to **2a—2g**, **4**, and **6**. The assignments were supported by IR and UV spectra and finally confirmed by X-ray analysis for **1d** and **2c**, described later. In Table 2, the protons H8 and H6′ of **1**, **3**, and **5** show high field shift, except for H8 of **5**, compared with the monomeric references, suggesting that the purine and the pyrimidine rings are stacked in face-to-face. On the other hand, **2**, **4**, and **6** might have the non-stacked orientation of the two base rings, because of the small $\Delta\delta$ values of the ring protons. The magnitude of $\Delta\delta$ values for all the ring protons of **1b—1g** in Table 3 are close with each other, indicating that the orientation of the purine and the pyrimidine ring in a molecule is not so different from that of **1d**, whose structure was determined by X-ray analysis. Similarly, the orientation of the two base rings in **2a**, **2b**, **2d—2g** might have close resemblance to that of **2c**, the structure of which was also determined by X-ray analysis.

Marked high field shift ($\Delta\delta$=−2.25 ppm) was observed for H6′ of **5**. One possible structure of **5** is that the two rings are hold in a orientation similar to that of [2.2]metaparacyclophane-1,9-diene, where the two aromatic rings are inclined to each other by 41°.[8] If **5** takes such conformation, H6′ locates closely above the center of the purine ring and hence, the large negative value of $\Delta\delta$ for H6′ and small positive one for H8 are reasonably accepted. In order to examine the rigidity of the conformation, temperature dependence of

Table 1. Yields(%) of **1—6** by A and B Methods

| | 1a/2a | 1b/2b | 1c/2c | 1d/2d | 1e/2e | 1f/2f | 1g/2g | 3/4 | 5/6 |
|---|---|---|---|---|---|---|---|---|---|
| Method A | — | — | 6/14 | 19/21 | 10/28 | 12/34 | 11/11 | 13/25 | 16/40 |
| Method B | 0/44 | 17/15 | 0/40 | 0/28 | — | — | — | — | — |

Table 2. $^1$H NMR Chemical Shifts (ppm) of H2, H8, H5′, and H6′ of Pyrimidinopurinophanes in $CDCl_3$ and Their Differences from Monomeric References (+ and − denote down- and up-field shifts, respectively)

| Compd | H2 | | H8 | | H5′ | | H6′ | |
|---|---|---|---|---|---|---|---|---|
| | δ | Δδ | δ | Δδ | δ | Δδ | δ | Δδ |
| **27** | 8.43 | | 7.71 | | | | | |
| **28** | 8.74 | | 7.93 | | | | | |
| **31** | | | | | 5.73 | | 7.18 | |
| **1b** | 8.29 | −0.14 | 7.62 | −0.09 | 5.70 | −0.03 | 7.11 | −0.07 |
| **1c** | 8.78 | +0.04 | 7.81 | −0.12 | 5.76 | +0.03 | 6.98 | −0.20 |
| **1d** | 8.73 | −0.01 | 7.86 | −0.07 | 5.78 | +0.05 | 7.12 | −0.06 |
| **1e** | 8.77 | +0.03 | 7.71 | −0.22 | | | 6.83 | −0.16 |
| **1f** | 8.77 | +0.03 | 7.78 | −0.15 | | | 6.55 | −0.16 |
| **1g** | 8.78 | +0.04 | 7.83 | −0.10 | | | 8.53 | −0.20 |
| **3** | 8.79 | +0.05 | 7.82 | −0.11 | 5.83 | (+0.10) | 7.12 | −0.06 |
| **5** | 8.83 | +0.09 | 7.94 | +0.01 | | | 4.74 | −2.25 |
| **29** | 8.55 | | 7.81 | | | | | |
| **30** | 8.84 | | 8.06 | | | | | |
| **31** | | | | | 5.73 | | 7.18 | |
| **2a** | 8.47 | −0.08 | 7.87 | +0.06 | 5.64 | −0.09 | 7.11 | −0.07 |
| **2b** | 8.49 | −0.06 | 7.85 | +0.04 | 5.81 | +0.08 | 7.21 | +0.03 |
| **2c** | 8.84 | 0.00 | 8.06 | +0.07 | 5.89 | +0.16 | 7.17 | −0.01 |
| **2d** | 8.81 | −0.03 | 8.00 | +0.01 | 5.67 | −0.06 | 7.12 | −0.06 |
| **2e** | 8.83 | −0.01 | 8.06 | +0.07 | | | 7.02 | +0.03 |
| **2f** | 8.85 | +0.01 | 8.08 | +0.09 | | | 6.74 | +0.03 |
| **2g** | 8.86 | +0.02 | 8.08 | +0.09 | | | 8.74 | +0.01 |
| **4** | 8.85 | +0.01 | 8.05 | +0.06 | 5.83 | +0.10 | 7.17 | −0.01 |
| **6** | 8.87 | +0.03 | 8.13 | +0.14 | | | 7.07 | +0.08 |

the protons of **5** was measured in the range of −80—+150 °C. The signals of aromatic protons remain almost unchanged both in chemical shifts (less than 0.2 ppm) and in their shapes. Furthermore, the patterns of the complex multiplets due to the bridge protons of **5** did not change in the same temperature range. These results suggest that the conformation of **5** is much stable than that of [2.2]metaparacyclophane, where the coalescence temperature is 146 °C.[9]

**IR Spectra.** We found the easiest way to distinguish the isomers **1** (X=S) from **2** (X=S) by IR spectra. According to our empirical rule, there is only one absorption band in the region of 1500—1600 $cm^{-1}$ for 9-substituted thiopurines **1** (X=S), **3**, **5**, and **28**, while two peaks are present for 7-substituted thiopurines **2** (X=S), **4**, **6**, and **30**. The results are summarized in Table 3. From the table the exceptions of the rule are only for **1g** and **2g**, where the nitro group is responsible for the additional peak.

Table 3. IR Peaks ($cm^{-1}$) in the Range of 1500—1600 $cm^{-1}$ for **1c—1g**, **2c—2g**, **3—6**, and Reference Compounds

| 6-Alkylthio-9-alkylpurines | | 6-Alkylthio-7-alkylpurines | |
|---|---|---|---|
| **28** | 1575 | **30** | 1585, 1545 |
| **1c** | 1560 | **2c** | 1570, 1540 |
| **1d** | 1560 | **2d** | 1575, 1545 |
| **1e** | 1560 | **2e** | 1570, 1540 |
| **1f** | 1560 | **2f** | 1575, 1545 |
| **1g** | 1555, 1510 | **2g** | 1575, 1540, 1510 |
| **3** | 1555 | **4** | 1575, 1545 |
| **5** | 1560 | **6** | 1570, 1540 |

Table 4. Absorption Maxima ($\lambda_{max}$, nm) and Extinction Coefficients (ε) of **1b**, **2a**, **2b**, and Related Compounds

| 6-Alkylamino-9-alkylpurine | | 6-Alkylamino-7-alkylpurine | |
|---|---|---|---|
| **27+31** | 267(24600) | **29+31** | 269(21600) |
| | | **2a** | 269(15700) |
| **1b** | 265(19100) | **2b** | 268(15800) |

**UV Spectra.** Based on the difference (2 nm) of the longest-wavelength absorption band between 9-methyl- and 7-methyl-6-(methylamino)purines (**27** and **29**), the structures of the isomers **1b** and **2a**, **b** are assigned as shown in Table 4.[10]

**X-Ray Analysis.** In order to confirm the assignments of the structures of **1** and **2** in Tables 3 and 4, X-ray analysis was carried out for **1d** and **2c**. The crystal structures were solved[11] by a program MULTAN-78[12] and refined by least-squares method. The final $R$ values are 0.038 for **1d** and 0.047 for **2c**. The resulting ORTEP drawings are shown in Figs. 1 and 2. The two base planes are almost parallel in **1d** (dihedral angle: 12.5°) with the interplanar distance of about 3.8 Å, while in **2c** they incline with each other with the dihedral angle of 50.4°. The bond angles and bond lengths of the two rings in **1d** and **2c** are almost the same values as those of 6-(methylthio)purine[13] and 1,3-dimethyluracil,[14] indicating that there is no special ring strain in the composite rings of **1d** and **2c**.

## Hypochromism

Electronic spectra of the pyrimidinopurinophanes described above and reference compounds are mea-

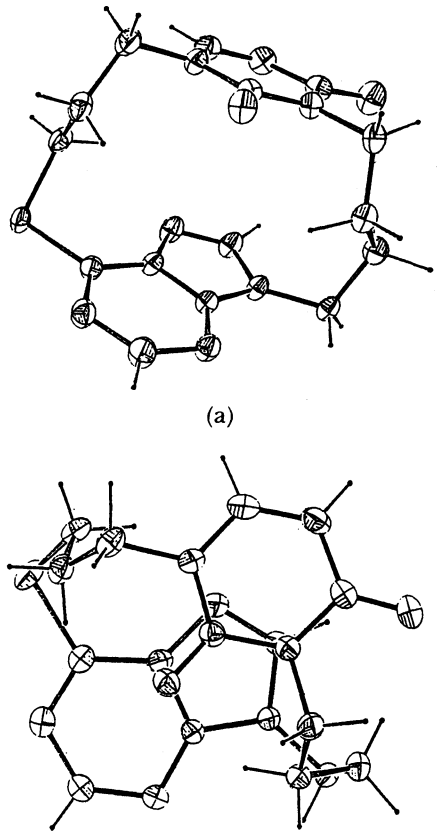



Fig. 1. Molecular structure (a) and views on the least-squars plane defined with a purine ring (b) in **1d**.

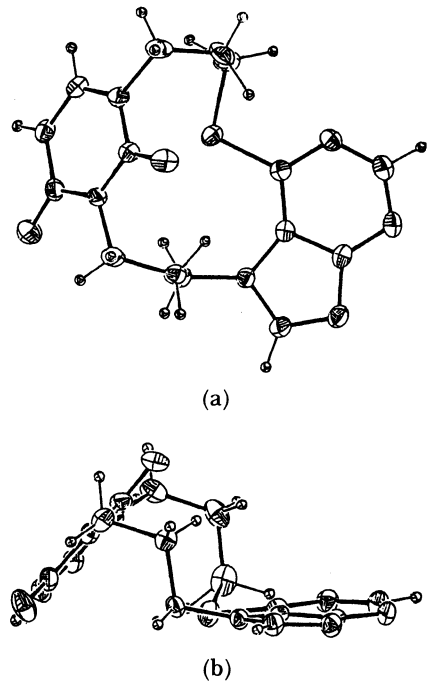



Fig. 2. Molecular structure (a) and side view (b) of **2c**.

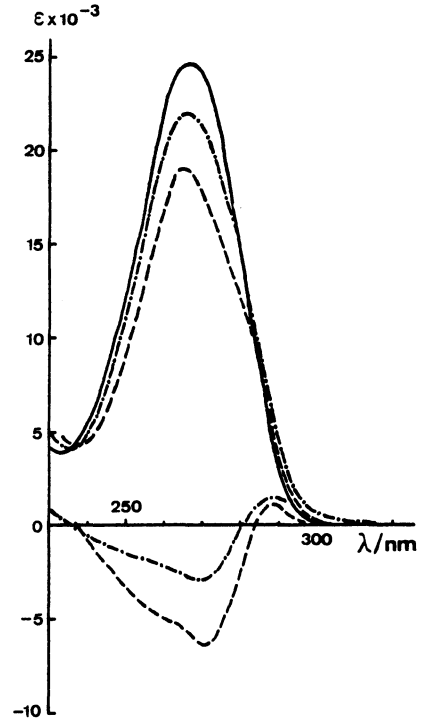



Fig. 3. Electronic spectra of **1b** (----), **32** (-·-·-), and (**27**+**31**) (——) in water and difference spetra of **1b** and **32** vs. (**27**+**31**).

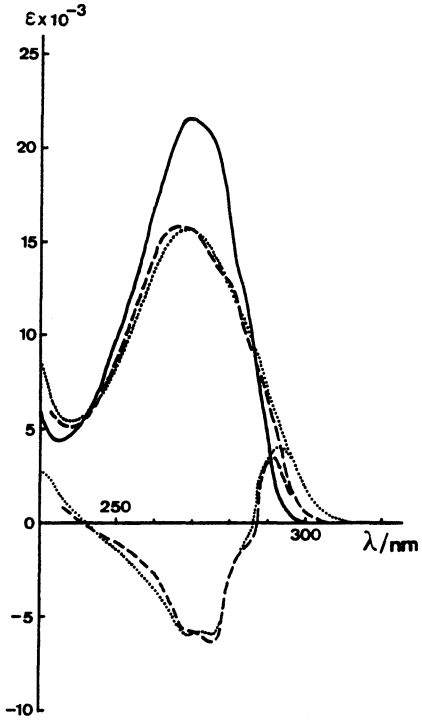



Fig. 4. Electronic spectra of **2a** (-----), **2b** (----), and (**29**+**31**) (——) in water and difference spectra of **2a** and **2b** vs. (**29**+**31**).

sured in ethanol and in water. Typical examples are shown in Figs. 3—6. In the figures difference spectra, which were obtained by subtracting the intensities of a given pyrimidinopurinophane from the sum of the values of the two consisting monomeric references. Hypochromism values were calculated according to the following equations:

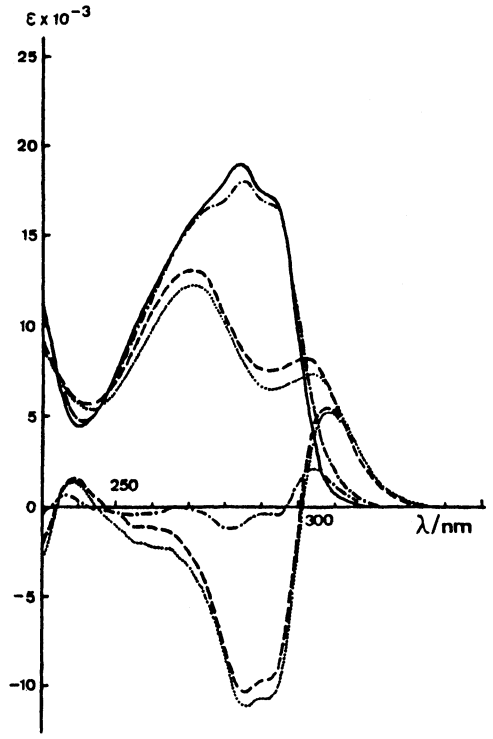



Fig. 5. Electronic spectra of **1c** (------), **1d** (----), **33** (-·-·-), and (**28**+**31**) (——) in water and difference spectra of **1c**, **1d**, and **33** vs. (**28**+**31**).

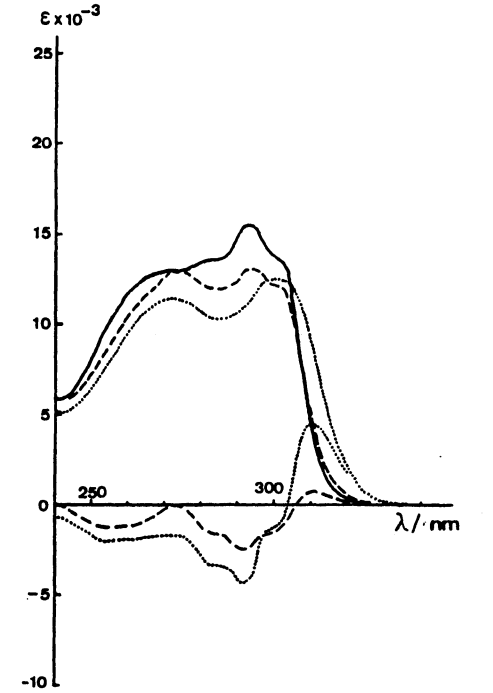



Fig. 6. Electronic spectra of **2c** (------), **2d** (----), and (**30**+**31**) (——) in water and difference spectra of **2c** and **2d** vs. (**30**+**31**).

$$\%H=(1-(f_D/2f_M))\times 100$$

$$f=4.32\times 10^{-9}\int(\varepsilon(\lambda)/\lambda^2)d\lambda, \quad (1)$$

where $f_M$ and $f_D$ are oscillator strength of monomer and dimer, respectively and these values were obtained by dividing the absorption curves into rectangles at intervals of 2 nm. The results are summarized in Table 5. In marked contrast to the small values for the linear dimers **32** and **33**, the hypochromism values of all the pyrimidinopurinophanes are relatively large and remain almost unchanged in ethanol and in water. This indicates that the structures of the present doubly bridged compounds in solution are almost the same as in the crystalline state. It is worthy of emphasis that **2a—2d** show relatively large hypochromism values in spite of the nonparallel orientation of the two base rings.

The almost parallel stacking of the two chromophores in **1a—1g** brings about larger hypochromism values than those of the corresponding isomers **2** having nonparallel orientation. However, the values of **1a—1g** are still smaller than those of purinophanes where two purine rings are held in face-to-face, due to the smaller interaction in pyrimidine-purine than in purine-purine.

The origin of hypochromism is the interaction between the lowest excited electronic state of a given chromophore and different electronic states of the neighboring chromophores. The theoretical calculation is very difficult since a number of configurational interactions must be taken into account. Ts'o et al.,[15] presented a simplified equation of evaluating hypochromism values ($H$%) for homodimers with parallel stacking:

$$H=A(1-3\cos^2\theta)/R_{ij}^3 \quad (2)$$

where $R_{ij}$ is the distance between the center of $i$ and $j$ rings, $\theta$ is the angle between $R_{ij}$ and the transition moment, and $A$ is a constant. From the Eq. 2, $H$ value is independent on the magnitude of the transition moments and if the two base rings of the pyrimidinopurinophanes are fixed with the same orientation, they should have the same $H$ value. This is valid when the hypochromism values of **1c** and **1e—1g** in Table 5 are compared. Thus, the values of these compounds are almost identical with each other. The compounds should have very similar structure because of the same carbon framework, although the transition moments of the pyrimidine rings are different in magnitude owing to the introduction of the substituents. On the basis of molecular model considerations the stacking

Table 5. Hypochromism Values $H$(%) of Pyrimidinopurinophanes and Related Compounds in Two Solvents

| | **1b** | **1c** | **1d** | **1e** | **1f** | **1g** | **2a** | **2b** | **2c** | **2d** | **3** | **5** | **32** | **33** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $H_2O$ | 24 | 28 | 20 | 27 | 30 | 26 | 15 | 17 | 11 | 8 | 29 | 27 | 9 | 2 |
| EtOH | 27 | 35 | 31 | 23 | 25 | 23 | 21 | 14 | 20 | 11 | 27 | 23 | 0 | 5 |

orientation of **3** is presumed that the two rings are kept in parallel with the same interplanar distance as that of **1c**, but one chromophore is rotated in its plane by 120° for **3**. In spite of the stacking geometry different from **1c**, *H* values of **3** are very similar to those of **1c**, supporting the validity of Eq. 2. These facts clearly show that the simplified Eq. 2 for homodimers is also applicable to the evaluation of H values for the parallel stacking of a pyrimidine and a purine ring without tedious molecular orbital calculations including a number of configurational interactions.

It is somewhat strange that the *H* values of **5**, where the two base rings seem to be not in parallel as discussed in NMR spectra, are identical with those of **1c**. Presumably, this is derived incidentally and the quantitative treatment of the H value in relation to the structure must wait for the structural determination of **5** by X-ray analysis.

The value of A in Eq. 2 is estimated to be around $1.2\times10^3$ by assuming that $\theta=90°$ and $R=3.5$ (from molecular model considerations) and 4.0 Å (from X-ray results) for **1c** and **1d**, respectively. The values are in good agreement with those estimated for the homodimers of 6-thiopurine ($A=1.30\times10^3$).[3]

The present and previous[3] results demonstrate that we can use Eq. 2 for the evaluation of *H* values of parallel-stacked nucleic acid base pairs, i.e., purine-purine and purine-pyrimidine rings.

## Experimental

All melting points were uncorrected. NMR spectra were measured on a Hitachi R-24A (60 MHz), a JNM FX-100 (100 MHz), and a Bruker WH-360 (360 MHz). IR and mass spectra were recorded on a Hitachi EPI-G2 and a Hitachi RMU-7, respectively. Electronic spectra were taken on a Hitachi EPS-3T and a Hitachi 330. Liquid chromatography was performed on Nihon Bunsekikogyo LC-08 and LC-09.

**1-(3-Aminopropyl)uracil, Formate Salt (15).** To a stirred mixture of **14**[16] (3.0 g, 10 mmol) in ethanol (150 ml) heated to reflex was added hydrazine monohydrate (1.1 g, 22 mmol). The mixture was stirred at reflux for 8 h and ethanol was removed. To the residue was added 2 M HCl (30 ml; 1M=1 mol $dm^{-3}$) and the suspension was stirred at room temperature for 30 min. Insoluble solid was filtered off and the filtrate was concentrated. The solid was dissolved in a minimum amount of distilled water and the solution was passed through a column of Dowex 1-X8, formate form. Water was removed and the residue was recrystallized from absolute ethanol to give 1.66 g (77% yield) of **15**. **15**: Colorless solid; mp 152—155 °C; MS *m/z* 169 ($M^+$); $^1$H NMR (DMSO-$d_6$, 60 MHz) δ=1.8 (q, *J*=7.0 Hz, 2, $NCH_2\underline{CH_2}$), 2.7 (t, *J*=7.0 Hz, 2, $\underline{CH_2}$-$NH_3^+$), 3.7 (t, *J*=7.0 Hz, 2, $NCH_2$), 5.6 (d, *J*=8.0 Hz, 1, ArH(5)), 7.7 (d, *J*=8.0 Hz, 1, ArH(6)), 8.4 (s, 1, CHO).

**$N^6$-[3-(Uracil-1-yl)propyl]adenine (7).** 6-Chloropurine (0.72 g, 4.6 mmol) and **15** (1.0 g, 4.6 mmol) was dissolved into ethanol (30 ml) containing triethylamine (1.4 ml, 10 mmol) and the solution was refluxed for 40 h under nitrogen atmosphere. After the reaction was over, the mixture was cooled at 0 °C for 2 h and yielded solid was filtered and washed well with cold water. This was dissolved into dil acetic acid (90 ml) with heating. After treatment with active carbon, the solution was neutralized with concd $NH_3$. Precipitates were filtered, washed with water and then, with acetone, and dried to give crude **7** (1.1 g, 80% as half hydrate). **7**: white solid from methanol-acetic acid, decomp>291 °C; MS *m/z* 287 ($M^+$); $^1$H NMR (DMSO-$d_6$, 100 MHz) δ=1.91 (q, *J*=6.8 Hz, 2, $NCH_2\underline{CH_2}$), 3.54 (br.s, 2, $NH\underline{CH_2}$), 3.75 (t, *J*=6.8 Hz, 2, $NCH_2$), 5.53 (d, *J*=7.8 Hz, 1, ArH(5′)), 7.61 (br.t, 1, NH(6)), 7.70 (d, *J*=7.8 Hz, 1, ArH(6′)), 8.07 (s, 1, ArH(8)), 8.17 (s, 1, ArH(2)), 11.3 (br.s, 1, NH(3′)), 12.7 (br.s, 1, NH(9)); UV (EtOH) $\lambda_{max}$ 268 nm ($\varepsilon=26.7\times10^3$). Found: C, 48.68; H, 4.61; N, 32.83%. Calcd for $C_{12}H_{13}N_7O_2\cdot1/2H_2O$: C, 48.64; H, 4.76; N, 33.09%. After heating of the above compound at 180 °C for 30 min, **7** without water of crystallization was obtained. Found: C, 50.22; H, 4.59; N, 33.91%. Calcd for $C_{12}H_{13}N_7O_2$: C, 50.17; H, 4.56; N, 34.13%.

**6-[3-(Uracil-1-yl)propylthio]purine (8).** A solution of **16**[4] (500 mg, 2.15 mmol) and thiourea (170 mg, 2.23 mmol) in ethanol (20 ml) was refluxed for 8 h. After reaction was over, ethanol was removed under reduced pressure. To the resulted semisolid was added water (15 ml) and nitrogen gas was passed through the apparatus to displace the air. To the heated mixture at 90 °C was added sodium hydroxide (170 mg, 4.3 mmol) and after ten minutes followed by the addition of 6-chloropurine (660 mg, 4.3 mmol) and the mixture was heated for 1 h. After cooling, yielded solid was filtered, washed with water and dried to give 540 mg (84% yield) of **8**. **8**: White powder from methanol-acetic acid; decomp >260 °C. MS *m/z* 304 ($M^+$). $^1$H NMR (DMSO-$d_6$, 100 MHz) δ=2.04 (q, *J*=6.9 Hz, 2, $SCH_2\underline{CH_2}$), 3.35 (t, *J*=6.9 Hz, 2, $SCH_2$), 3.81 (t, *J*=6.9 Hz, 2, $NCH_2$), 5.56 (d, *J*=7.8 Hz,1, H5′), 7.67 (d, *J*=7.8 Hz, 1, H6′), 8.42 (s, 1, H8), 8.64 (s, 1, H2), 11.2 (br. s, 1, U-NH), 12.4 (br.s, 1, Pu-NH).

Found: C, 47.47; H, 4.05; N, 27.53; S, 10.42%. Calcd for $C_{12}H_{12}N_6SO_2$: C, 47.36; H, 3.98; N, 27.61; S, 10.53%.

**6-[3-(Thymin-1-yl)propylthio]purine (9).** Compound **9** was prepared starting from 1-(3-bromopropyl) thymine[3] by the similar procedure described for **8**. **9**: 89% yield; colorless fine needles from DMF-water; mp 279.0—282.5 °C with decomp. MS *m/z* 318 ($M^+$). $^1$H NMR (DMSO-$d_6$, 360 MHz) δ=1.74 (d, *J*=1.0 Hz, 3, $CH_3$), 2.04 (q, *J*=7.0 Hz, 2, $SCH_2\underline{CH_2}$), 3.35 (t, *J*=6.8 Hz, 2, $SCH_2$), 3.78 (t, *J*=6.8 Hz, 2, Th-$NCH_2$), 7.53 (s, 1, H6′), 8.41 (s, 1, H8), 8.64 (s, 1, H2), 11.19 (br. s, 1, Th-NH).

Found: C, 49.09; H, 4.50; N, 26.18; S, 10.31%. Calcd for $C_{13}H_{14}N_6SO_2$: C, 49.05; H, 4.43; N, 26.40; S, 10.07%.

**1-(3-Bromopropyl)-5-methoxyuracil (18).** To a solution of 5-methoxyuracil[17] (7.1 g, 50 mmol) and trimethylsilyl chloride (10.9 g, 100 mmol) in dry benzene (150 ml) was added dropwise triethylamine (10.1 g, 100 mmol) and white suspension was stirred for 18 h. After filtration under atmosphere of dry nitrogen, the filtrate was concentrated under reduced pressure. To the resulted oil was added 1,3-dibromopropane (70 ml) and it was stand for a week at room temperature under nitrogen atmosphere. Water (200 ml) was added to the solution and it was extracted with chloroform. Organic phase was washed with water and dried over anhydrous sodiumsulfate. Evaporation of the solvent under reduced pressure gave yellow solid. Recrystallization from ethanol yielded **18** (3.5 g, 27% yield) as colorless columns; mp 130—131 °C. MS *m/z* 262 ($M^+$ for $^{79}$Br). $^1$H NMR ($CDCl_3$, 360 MHz) δ=2.34 (m, 2, $NCH_2\underline{CH_2}$), 3.47 (t, *J*=6.1 Hz, 2, $CH_2Br$), 3.76 (s, 3, $OCH_3$), 3.90 (t, *J*=6.6 Hz, 2, N-$CH_2$), 6.82

(s, 1, ArH), 9.61 (br, s, 1, NH).

Found: C, 36.52; H, 4.37; Br, 29.51; N, 9.95%. Calcd for $C_8H_{11}BrN_2O_3$: C, 36.52; H, 4.22; Br, 30.37; N, 10.65%.

**6-[3-(5-Methoxyuracil-1-yl)propylthio]purine (10).** Compound **11** was prepared in a yield of 75% by the similar procedure described for **8**. **10**: Colorless fine needles from water; decomp>190°C. MS *m/z* 334 ($M^+$). $^1$H NMR (DMSO-$d_6$, 360 MHz) $\delta$=2.06 (q, $J$=7.0 Hz, 2, $SCH_2\underline{CH_2}$), 3.36 (t, $J$=7.0 Hz, 2, $SCH_2$), 3.60 (s, 3, $CH_3$), 3.78 (t, $J$=6.9 Hz, 2, $NCH_2$), 7.36 (s, 1, H6'), 8.41 (br.s, 1, H8), 8.63 (s, 1, H2), 11.36 (br. s, 1, NH).

Found: C, 45.24; H, 4.21; N, 24.23; S, 9.57%. Calcd for $C_{13}H_{14}N_6O_3S \cdot 1/2\ H_2O$: C, 45.48; H, 4.40; N, 24.48; S, 9.34%.

**1-(3-Bromopropyl)-5-nitrouracil (19).** A mixture of 5-nitrouracil[18] (4.71 g, 30 mmol), 1,3-dibromopropane (60.0 g, 100 mmol), and anhydrous potassium carbonate (2.07 g, 15 mmol) in dry DMSO (70 ml) was stirred at room temperature for 1.5 d. The solvent was distilled off under reduced pressure. Water (200 ml) was added to the residue and it was extracted with chloroform and the extracts were dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure until about 100 ml of the solvent was left. Yielded precipitates of **19** was collected (2.67 g, 32% yield). Recrystallization from 2-propanol gave pure **19** as colorless prisms; mp 172—174 °C. MS *m/z* 277 ($M^+$ for $^{79}$Br). $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$=2.37 (m, 2, $NCH_2\underline{CH_2}$), 3.47 (t, $J$=6.0 Hz, 2, $CH_2Br$), 4.11 (t, $J$=6.8 Hz, 2, $NCH_2$), 8.79 (s, 1, ArH).

Found: C, 30.82; H, 3.16; N, 15.48%. Calcd for $C_7H_8BrN_3O_4$: C, 30.23; H, 2.90; N, 15.11%.

**6-[3-(5-Nitrouracil-1-yl)propylthio]purine (11).** A solution of **19** (1.39 g, 5 mmol), 6-mercaptopurine (0.84 g, 4.9 mmol), and sodium hydroxide (0.6 g, 15 mmol) in water (20 ml) was stirred for 3.5 h at room temperature. The solution was neutralized by dil HCl and then, few drops of ethanol were added. Yielded pale yellow solid was filtered, washed with water, and dried to give 1.51 g (87% yield) of **11**. **11**: Pale yellow powder from water; mp 270—271 °C with decomp. $^1$H NMR (DMSO-$d_6$, 360 MHz) $\delta$=2.13 (q, $J$=7.1 Hz, 2, $NCH_2\underline{CH_2}$), 3.37 (t, $J$=6.7 Hz, 2, $SCH_2$), 4.01 (t, $J$=6.7 Hz, 2, $NCH_2$), 8.41 (s, 1, H8), 8.63 (s, 1, H2), 9.31 (s, 1, H6'), 11.99 (br. s, 1, NH).

Found: C, 41.40; H, 3.36%. Calcd for $C_{12}H_{11}N_7O_4S$: C, 41.26; H, 3.17%.

**3-(3-Bromopropyl)-*S*-methyl-2-thiouracil (21).** To a stirred solution of **20**[19] (5.68 g, 40 mmol) in dry DMF (100 ml) was added 60% sodium hydride (1.68 g, 42 mmol). After stirring for 1 h, 1,3-dibromopropane (40 ml, 400 mmol) was added to the mixture and it was stirred for 1 h at room temperature and then, at 60 °C for 24 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with chloroform to give **21** (8.67 g, 82% yield). **21**: Colorless prisms from methanol; mp 50.0—50.5 °C. MS *m/z* 263 ($M^+$ for $^{79}$Br). $^1$H NMR ($CDCl_3$, 100 MHz) $\delta$=2.30 (m, 2, $NCH_2\underline{CH_2}$), 2.58 (s, 3, $CH_3$), 3.48 (t, $J$=6.6 Hz, 2, $CH_2Br$), 4.19 (m, 2, $NCH_2$), 6.18 (d, $J$=6.5 Hz, 1, ArH(5)), 7.75 (d, $J$=6.5 Hz, 1, ArH(6)).

Found: C, 36.57; H, 3.95; N, 10.75; S, 12.32%. Calcd for $C_8H_{11}N_2OSBr$: C, 36.51; H, 4.22; N, 10.65; S, 12.18%.

**6-[3-(*S*-Methyl-2-thiouracil-3-yl)propylthio]purine (22).** A solution of **21** (4.18 g, 15.9 mmol), 6-mercaptopurine monohydrate (2.70 g, 15.9 mmol), and sodium hydroxide (0.83 g, 20.8 mmol) in water (40 ml)-ethanol (10 ml) was stirred for 3 h at room temperature. The solution was neutralized by dil HCl and it was extracted by chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated. Crude product was purified by column chromatography on silica gel with chloroform-methanol (19:1) to give white solid (3.9 g, 73% yield). **22**: Colorless needles from methanol; mp 182.0—183.5 °C. MS *m/z* 334 ($M^+$). $^1$H NMR ($CDCl_3$, 100 MHz) $\delta$=2.29 (m, 2, $NCH_2\underline{CH_2}$), 2.54 (s, 3, $CH_3$), 3.50 (t, $J$=7.2 Hz, 2, $SCH_2$), 4.27 (m, 2, $NCH_2$), 6.23 (d, $J$=6.3 Hz, 1, H5'), 7.76 (d, $J$=6.6 Hz, 1, H6'), 8.21 (s, 1, H8), 8.71 (s, 1, H2).

Found: C, 46.83; H, 4.27; N, 25.31; S, 18.88%. Calcd for $C_{13}H_{14}N_6OS_2$: C, 46.69; H, 4.22; N, 25.13; S, 19.17%.

**6-[3-(Uracil-3-yl)propylthio]purine (12).** A solution of **22** (1.67 g, 5 mmol) in ethanol (20 ml)-2 M HCl (10 ml) was stirred for 2 d at room temperature. Yielded precipitates were filtered, washed with water, and dried to give 1.36 g (89% yield) of crude **12**. **12**: Colorless fine needles from water; mp 293—298 °C with decomp. MS *m/z* 304 ($M^+$). $^1$H NMR (DMSO-$d_6$, 360 MHz) $\delta$=1.97 (q, $J$=7.0 Hz, 2, $NCH_2\underline{CH_2}$), 3.34 (t, $J$=7.0 Hz, 2, $SCH_2$), 3.91 (t, $J$=7.0 Hz, 2, $NCH_2$), 5.58 (dd, $J$=1.4 Hz, 7.6 Hz, 1, H5'), 7.42 (m, 1, H6'), 8.39 (s, 1, H8), 8.63 (s, 1, H2), 10.21 (br. s, 1, NH(9)), 11.07 (br. d, 1, NH(1')).

Found: C, 47.39; H, 4.23; N, 27.90; S, 10.74%. Calcd for $C_{12}H_{12}N_6O_2S$: C, 47.36; H, 3.98; N, 27.61; S, 10.53%.

**5-(3-Hydroxypropyl)-3-methyluracil (25).** A mixture of 5-(3-hydroxypropyl)-2-thiouracil **23**[20] (14.88 g, 80 mmol), methyl iodide (25 ml, 400 mmol), and anhydrous potassium carbonate (24.29 g, 176 mmol) in dry DMF (50 ml) was stirred for 20 h at room temperature. Salts were filtered off and the filtrate was concentrated to dryness under reduced pressure. Water (100 ml) was added to the residue and it was extracted with chloroform. The organic phase was washed well with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave pale yellow solid of **24**. To the solid was added 20 ml of 1 M HCl and the mixture was refluxed for 1 h. After cooling, the solution was neutralized by sodium hydrogencarbonate and was concentrated to dryness. Yielded solid was extracted with chloroform. The extracts were dried and evaporated. The crude product was purified by column chromatography on silica gel with chloroform-methanol (19:1) to yield 9.3 g (63% yield) of **25**. Recrystallization from ethanol gave pure **25** as colorless prisms; mp 124—126 °C. MS *m/z* 184 ($M^+$). $^1$H NMR ($CDCl_3$, 100 MHz) $\delta$=1.76 (m, 2, $ArCH_2\underline{CH_2}$), 2.28 (t, $J$=6.0 Hz, 1, OH), 2.48 (t, $J$=7.1 Hz, 2, $ArCH_2$), 3.35 (s, 3, $CH_2$), 3.36 (q, J=5.9 Hz, 6.0 Hz, 2, $\underline{CH_2}OH$), 7.07 (d, $J$=5.6 Hz, 1, ArH), 9.22 (br. s, 1, NH).

Found: C, 51.95; H, 6.49; N, 15.23%. Calcd for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21%.

**5-(3-Bromopropyl)-3-methyluracil (26).** A solution of **24** (1.84 g, 10 mmol) in concd hydrobromic acid (15 ml) and concd sulfuric acid (2 ml) was heated at 110 °C for 3 h with stirring. After cooling, the mixture was poured into cold water and it was extracted with chloroform. The organic layer was washed well with aqueous solution of sodium hydrogencarbonate and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 1.54 g (62% yield) of **26**. **26**: Colorless columns from ethanol; mp 152.5—153.5°C. MS *m/z* 246 ($M^+$ for $^{79}$Br). $^1$H NMR ($CDCl_3$, 360 MHz) $\delta$=2.12 (m, 2, $ArCH_2\underline{CH_2}$), 2.50 (t, $J$=7.1 Hz, 2, $ArCH_2$), 3.34 (s, 3, $CH_3$), 3.34 (t, $J$=6.3 Hz, 2, $CH_2Br$), 7.14 (d, $J$=5.7 Hz, 1, ArH), 9.64 (br, s, 1, NH).

Found: C, 38.74; H, 4.50; N, 11.25; Br, 32.07%. Calcd for

$C_8H_{11}N_2O_2Br$: C, 38.88; H, 4.49; N, 11.34; Br, 32.34%.

**6-[3-(3-Methyluracil-5-yl)propylthio]purine(13).** A solution of **26** (0.99 g, 4 mmol), thiourea (0.32 g, 4.2 mmol) in ethanol (10 ml) was refluxed for 8 h. After removal of ethanol, water (20 ml) was added to the residue. To the stirred mixture was added, at 90 °C under nitrogen atmosphere, sodium hydroxide (40 g, 10 mmol) and then (after 10 min), 6-chloropurine (1.24 g, 8 mmol). Heating and stirring were continued for 1 h. After cooling, yielded precipitates were collected to give 0.95 g (75% yield) of **13**. **13**: Colorless powder from water; mp 283—286 °C. MS *m/z* 318 ($M^+$). $^1$H NMR (DMSO-$d_6$, 360 MHz) $\delta$=1.89 (q, *J*=7.1 Hz, 2, $NCH_2\underline{CH_2}$), 2.39 (t, *J*=6.3 Hz, 2, $ArCH_2$), 3.33 (t, *J*=6.3 Hz, 2, $SCH_2$), 7.33 (d, *J*=5.8 Hz, 1, ArH(6')), 8.40 (s, 1, ArH(8)), 8.66 (s, 1, ArH(2)), 10.93 (d, *J*=5.8 Hz, 1, NH).

Found: C, 48.78; H, 4.61; N, 26.40; S, 10.32%. Calcd for $C_{13}H_{14}N_6O_2S$: C, 49.05; H, 4.43; N, 26.40; S, 10.07%.

**General Procedure of Method A for the Synthesis of 1—6.** To a suspension of **8—13** (3 mmol) in dry DMF (100 ml) was added 60% sodium hydride (259 mg, 6.25 mmol). After continuous stirring for 1 h at room temperature, the mixture became transparent solution. The solution was diluted with dry DMF until the total volume became 150 ml. The solution and a solution of 1,3-dibromopropane (0.305 ml, 3 mmol) in dry DMF (150 ml) were added simultaneously to dry DMF (300 ml) at room temperature in a period of 36—48 h (see Table 6) under nitrogen atmosphere. After addition was over, stirring was continued for 25—60 h (see Table 6). DMF was removed under reduced pressure and the residue was extracted with chloroform. The isomers having the bridge at 9-position of a purine ring (**1**, **3**, **5**) could be separated from the other isomers (**2**, **4**, **6**) by column chromatography on silica gel with chloroform-methanol (ratio: see Table 6).

**General Procedure of Method B.** To a stirred mixture of dry DMSO (400 ml) and potassium carbonate (0.9 g, 6.6 mmol) was added a solution of **7** or **8** (1 mmol) and 1,3-dibromopropane (1 mmol) in a period of 15 h at room temperature under nitrogen atmosphere. After addition was over, stirring was continued for 3 d. Salts were filtered off and the solvent was removed under reduced pressure. Crude product was separated into two isomers by column chromatography on silica gel with methanol-chloroform. Spectral and analytical data of **1c**, **1d**, **2c**, and **2d** are shown in Table 6.

**2a**: Colorless needles from water; decomp>300 °C. MS *m/z* 327 ($M^+$). $^1$H NMR ($CDCl_3$, 100 MHz) $\delta$=5.64 (d, *J*=8 Hz, 1, H5'), 7.11 (d, *J*=8 Hz, 1, H6'), 7.87 (s, 1, H8), 8.47 (s, 1, H2).

Found: C, 53.90; H, 5.46; N, 28.97%. Calcd for $C_{15}H_{17}N_7O_2 \cdot 1/2H_2O$: C, 53.57; H, 5.39; N, 29.15%.

**1b:** White powder from ethanol; decomp>320 °C. MS *m/z* 341 ($M^+$). $^1$H NMR ($CDCl_3$, 100 MHz) $\delta$=5.70 (d, *J*=7.8 Hz, 1, H5'), 7.11 (d, *J*=7.8 Hz, 1, H6'), 7.62 (s, 1, H8), 8.29 (s, 1, H2).

Found: C, 56.33; H, 5.60; N, 28.55%. Calcd for $C_{16}H_{19}N_7O_2$: C, 56.30; H, 5.61; N, 28.72%.

**2b:** Colorless crystals from methanol-ether; mp 207—209 °C. MS *m/z* 341 ($M^+$). $^1$H NMR ($CDCl_3$, 100 MHz) $\delta$=5.81 (d, *J*=7.8 Hz, 1, H5'), 7.21 (d, *J*=7.8 Hz, 1, H6'), 7.85 (s, 1, H8), 8.48 (s, 1, H2).

Found: C, 55.52; H, 5.80; N, 27.42%. Calcd for $C_{16}H_{19}N_7O_2 \cdot 1/2CH_3OH$: C, 55.45; H, 5.92; N, 27.43%.

**9-Methyl-$N^6$[3-(3-methyluracil-1-yl)propyl]adenine (32).** A mixture of **7** · $1/2H_2O$ (200 mg, 0.68 mmol), methyl iodide (0.21 g, 1.5 mmol) and potassium carbonate (0.28 g, 2.0 mmol) in dry DMSO (30 ml) was stirred for 24 h at room temperature under nitrogen atmosphere. After reaction was over, salts were filtered off and the filtrate was concentrated

Table 6. Reaction Conditions, Elution Solvents, Yields, Crystal Forms, Melting Points and Analytical Data of Pyrimidinopurinophanes

| | Reaction condition | Elution solvent | Yield/% | Crystal | | Analysis or MS Found/% (Calcd) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Dropping time(h)/ Reaction time(h) | $CHCl_3$ : $CH_3OH$ | | Form | Mp $\theta_m$/°C | C | H | N | S |
| **1c** | 30/48 | 25 : 1 | 6 | Needle | 278—280 | 52.41 | 4.56 | 24.60 | 9.26 |
| **2c** | | | 14 | Column | Decomp>322 | 52.04 | 4.75 | 24.54 | 9.16 |
| | | | | | | (52.31) | (4.68) | (24.40) | (9.31) |
| **1d** | 30/48 | 25 : 1 | 19 | Column | Decomp>275 | 53.64 | 5.02 | 23.16 | 9.16 |
| **2d** | | | 21 | Column | 281—283 | 53.88 | 5.10 | 23.15 | 8.90 |
| | | | | | | (53.62) | (5.06) | (23.45) | (8.94) |
| **1e** | 36/60 | 99 : 1 | 9.6 | Prism | Decomp>270 | 53.51 | 5.12 | 23.44 | 8.94 |
| **2e** | | | 28 | Prism | >320 | 53.41 | 4.79 | 23.17 | 9.13 |
| | | | | | | (53.62) | (5.06) | (23.45) | (8.94) |
| **1f** | 48/48 | 33 : 1 | 12 | Needle | 227—229 | 51.01 | 4.67 | 21.98 | 8.64 |
| | | | | | | (51.33) | (4.84) | (22.45) | (8.56) |
| **2f** | | | 34 | Plate | 293—294 | 50.18 | 5.42 | 20.62 | 7.94 |
| | | | | | | (50.23)[a] | (5.46)[a] | (20.68)[a] | (7.89)[a] |
| **1g** | 44/25 | 19 : 1 | 11 | Powder | >300 | 46.21 | 3.92 | 24.96 | 8.09 |
| **2g** | | | 11 | Powder | >300 | 46.01 | 4.02 | 25.28 | 8.44 |
| | | | | | | (46.27) | (3.88) | (25.18) | (8.23) |
| **3** | 38/58 | 19 : 1 | 13 | Powder | 295—298 | 52.16 | 4.59 | 24.19 | 9.20 |
| **4** | | | 25 | Prism | 296—298 | | 344 ($M^+$) | | |
| | | | | | | (52.31) | (4.68) | (24.40) | (9.31) |
| **5** | 36/60 | 33 : 1 | 16 | Prism | 237—238 | 53.48 | 5.22 | 23.27 | 8.84 |
| **6** | | | 40 | Powder | 300—305 | 53.39 | 5.14 | 23.49 | 8.75 |
| | | | | | | (53.62) | (5.06) | (23.45) | (8.94) |

a) For $C_{16}H_{18}O_3N_6S \cdot CH_3OH$.

to dryness under reduced pressure. Water (50 ml) was added to the residue and it was extracted with chloroform. The extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated. The crude product was chromatographed on silica gel with methanol-chloroform and then, recrystallized from benzene-hexane to give pure **32** (88 mg, 41% yield). **32:** Colorless fine needles, mp 187.5—189.0 °C; MS *m/z* 315 ($M^+$). $^1$H NMR ($CDCl_3$, 100 MHz) $\delta$=2.10 (q, $J$=6.6 Hz, 2, $NCH_2\underline{CH_2}$), 3.35 (s, 3, N(3′)-$CH_3$), 3.76 (m, 2, N(6)-$CH_2$), 3.83 (s, 3, N(9)-$CH_3$), 3.91 (t, $J$=6.6 Hz, 2, N(1′)-$CH_2$), 5.71 (d, $J$=7.9 Hz, 1, ArH(5′)), 6.27 (br s, 1, NH), 7.20 (d, $J$=7.9 Hz, 1, ArH(6′)), 7.73 (s, 1, ArH(8)), 8.38 (s, 1, ArH(2)); UV (EtOH) $\lambda_{max}$ 268 nm ($\varepsilon$=24.3×10$^3$); IR (Nujol mull) 3270 cm$^{-1}$ (NH). Found: C, 53.06; H, 5.37; N, 31.02%. Calcd for $C_{14}H_{17}N_7O_2$: C, 53.32; H, 5.44; N, 31.09%.

**9-Methyl-6-[3-(3-methyluracil-1-yl)propylthio]purine (33).** The synthesis of **33** was carried out by the similar method described for **32**. Recrystallization of the crude product from benzene-hexane gave pure **33** in a yield of 34%. **33:** Colorless needles, mp 144—146 °C; MS *m/z* 332 ($M^+$); $^1$H NMR ($CDCl_3$, 100 MHz) $\delta$=2.24 (q, $J$=6.8 Hz, 2, $NCH_2\underline{CH_2}$), 3.34 (s, 3, N(9)-$CH_3$), 3.45 (t, $J$=6.8 Hz, 2, $SCH_2$), 3.89 (s, 3, N(3′)-$CH_3$), 3.94 (t, $J$=6.8 Hz, 2, $NCH_2$), 5.72 (d, $J$=7.8 Hz, 1, ArH(5′)), 7.19 (d, $J$=7.8 Hz, 1, ArH(6′)), 7.95 (s, 1, ArH(8)), 8.70 (s, 1, ArH(2)); UV (EtOH) $\lambda_{max}$ 276 nm ($\varepsilon$=19.1×10$^3$), 282 (21.5×10$^3$), 290 (17.8×10$^5$). Found: C, 50.64: H, 4.81; N, 25.25; S, 9.64%. Calcd for $C_{14}H_{16}N_6SO_2$: C, 50.59; H, 4.85; N, 25.28; S, 9.65%.

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