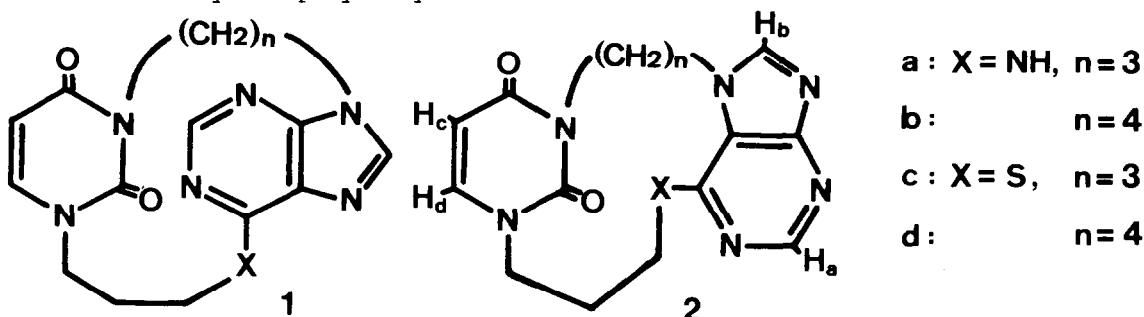


### SYNTHESIS OF PYRIMIDINOPURINOPHANES<sup>1)</sup>

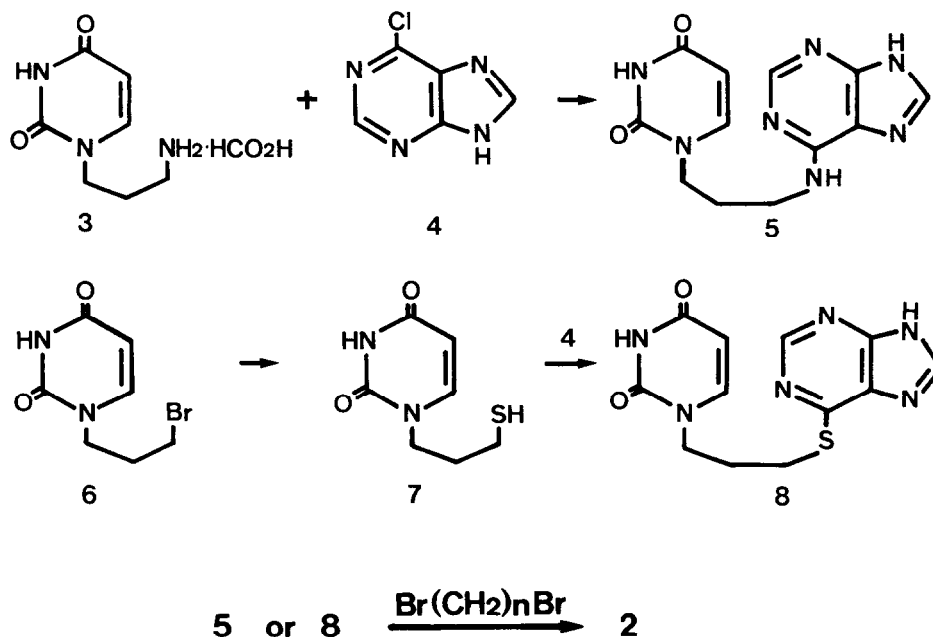
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Summary: Synthesis and structures of the title compounds 2a-d are described. In spite of non-parallel orientation of the two base rings, fairly large hypochromism was observed for 2a-d.

As a model for the stacking interaction of nucleic acid bases in DNA, we recently reported the synthesis and marked hypochromism of a few layered compounds containing two purine rings.<sup>2,3)</sup> In order to study the interaction between different kinds of nucleic acid bases, we planned to prepare the title compounds 1, where a purine and a pyrimidine rings may be closely bound with face-to-face by two polymethylene chains.



Reaction of 3<sup>4)</sup> with 6-chloropurine 4 in ethanol in the presence of triethylamine gave 5<sup>5)</sup> [79% yield, white amorphous solid from acetic acid-methanol, dec. >291 °C]. Sulfur analog 8 was obtained by the reaction of 4 and thiol 7, which was derived from 6<sup>4)</sup> via isothiuronium salt [8<sup>5)</sup>: 83% yield based on 6, white amorphous solid from acetic acid-methanol, dec. >260 °C]. Cyclization of 5 and 8 was carried out by treatment with  $\alpha,\omega$ -dibromoalkane and potassium carbonate in DMSO under dilution conditions. The product was purified by column chromatography on silica gel with chloroform-methanol and by following recrystallization [2a<sup>5)</sup>: 44% yield, colorless columns from water, dec. >300 °C, M<sup>+</sup> 327; 2b<sup>5)</sup>: 15% yield, colorless crystals from ether-methanol, mp 207-209 °C, M<sup>+</sup> 341; 2c<sup>5)</sup>: 40% yield, colorless columns from ether-ethanol, dec. >322 °C, M<sup>+</sup> 344; 2d<sup>5)</sup>: 28% yield, colorless columns from ether-methanol, mp 281-283 °C, M<sup>+</sup> 358]. Although the formation of some isomeric products was expected theoretically in this alkylation reaction, only an isomer was obtained in each case except for the reaction of 5

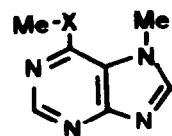


and 1,4-dibromobutane, where another isomer **1b**<sup>6)</sup> was isolated together with **2b**. The structure of **1b** was tentatively considered to be a 9-alkylated purine on the basis of ultraviolet absorption maximum as described later [**1b**<sup>5)</sup>: 17% yield, white amorphous solid from ethanol, dec. > 320 °C, M<sup>+</sup> 341].

Chemical shifts (Table 1) of aromatic protons of **2a-d** are not so different as compared with those of the reference compounds, suggesting that the structures of **2a-d** are not the desired 9-alkylated purines **1** with stacked orientation. The

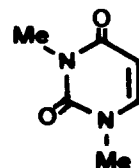
Table 1. Observed Chemical Shifts ( $\delta$ , ppm in CDCl<sub>3</sub>) of Aromatic Protons of **2a-d** and Reference Compounds. a)

	Ha	Hb	Hc	Hd
<b>2a</b>	8.47 (-0.08)	7.87 (+0.06)	5.64 (-0.09)	7.11 (-0.07)
<b>2b</b>	8.49 (-0.06)	7.85 (+0.04)	5.81 (+0.08)	7.21 (+0.03)
<b>2c</b>	8.84 (0.00)	8.06 (+0.07)	5.89 (+0.16)	7.17 (-0.01)
<b>2d</b>	8.81 (-0.03)	8.00 (+0.01)	5.67 (-0.06)	7.12 (-0.06)
<b>9</b>	8.55	7.81	—	—
<b>10</b>	8.84	7.99	—	—
<b>11</b>	—	—	5.73	7.18



**9**: X = NH<sup>7)</sup>

**10**: X = S<sup>8)</sup>

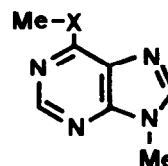


**11**<sup>9)</sup>

a) Values in parentheses are differences from those of the corresponding protons of reference compounds **9-11**.

Table 2. The Longestwavelength Absorption Maxima [ $\lambda_{\max}$  ( $\epsilon$ ) in  $H_2O$ ] in Electronic Spectra of **1b**, **2a-d**, and Related Compounds.

7-Methylpurines		9-Methylpurines	
<b>9 + 11</b>	269 nm (21,600)	<b>12 + 11</b>	267 nm (24,600)
<b>2a</b>	269 (15,700)		
<b>2b</b>	268 (15,800)	<b>1b</b>	265 (19,100)
<b>10 + 11</b>	292 nm (15,500)	<b>13 + 11</b>	284 nm (19,000)
<b>2c</b>	298 (12,500)		
<b>2d</b>	296 (12,800)		



**12** : X = NH<sup>(11)</sup>

**13** : X = S<sup>(11)</sup>

structures of **2** are considered to be 7-alkylated purine derivatives by comparison of the ultraviolet absorption maxima of **2** or **1b** with those of 7- or 9-methylpurine derivative as shown in Table 2.<sup>10)</sup>

To confirm the above assignment and to get further information about the structures of **2**, we carried out X-ray analysis of **2c**. The molecules crystallize in the monoclinic space group  $P2_1/n$  with cell dimensions  $a=10.861(1)$  Å,  $b=14.924(1)$  Å,  $c=10.861(1)$  Å,  $\beta=118.63(1)^\circ$ ,  $V=1545.2(3)$  Å<sup>3</sup>,  $Z=4$ . The X-ray intensities were measured with Ni-filtered Cu-K $\alpha$  radiation on a full automatic four-circle diffractometer. The crystal structure was solved by a program MULTAN-78<sup>12)</sup> and refined by block-diagonal least-squares method. Final R-factor is 0.047 for 2287 reflections. The resulting ORTEP drawing is shown in Fig. 1. In agreement with the assignment based on the electronic spectra, N-alkylation of the purine ring took place not at the most reactive site<sup>13)</sup> (9-position) but at the less reactive site (7-position). Although the reason for the preferential ring closure at N-7 is not clear at the present stage, the dominant cause may involve the steric effect between the two chromophores. The characteristic point in the figure is that the purine and the pyrimidine rings incline by dihedral angle  $50.4^\circ$  with each other in contrast to the parallel orientation of the two purine

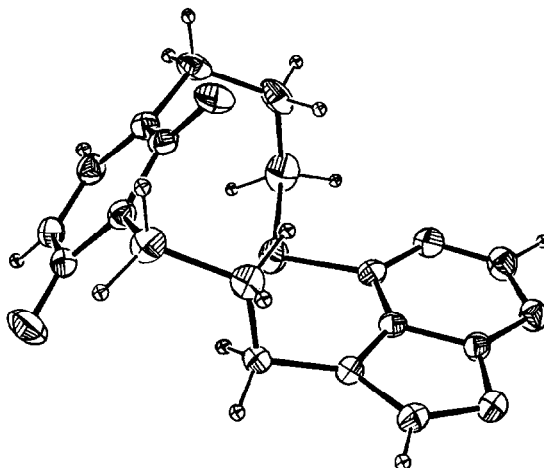


Fig. 1. Molecular structure of **2c**.

Table 3. Hypochromism (%) of 2a-d.

	H <sub>2</sub> O	0.1N HCl	0.1N NaOH	EtOH
2a	14.5	12.8	14.9	20.7
2b	17.4	13.2	16.7	13.9
2c	11.1	17.4	9.1	20.4
2d	8.2	12.4	7.9	11.2

rings in the reported purinophanes.<sup>3)</sup> The bond lengths and bond angles of the planar two rings are about the same values as those of 6-methylthiopurine<sup>14)</sup> and 1,3-dimethyluracil<sup>15)</sup> (see reference 16 for additional crystallographic details).

The electronic spectra of 2a-d show a decrease in the absorption intensity at the longest wavelength as compared with the intensity of sum spectrum of 7-methylpurine (9 or 10) and 1,3-dimethyluracil. These hypochromism values (H%) in four different media are summarized in Table 3. The values remain almost unchanged in all the media, indicating the rigid structure of 2a-d. Of particular interest is the considerably large hypochromism of 2a-d in spite of non-parallel orientation of the two chromophores. As far as our knowledge is concerned, this is the first example of well-defined nucleic acid base pairs which show large hypochromism over 10% in spite of mutual inclined orientation.

## References and Notes

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Structure Factors have been deposited with the B.L.L. at Boston Spa, Wetherby, Yorkshire as Supplementary Publication No: SUP.45,060  
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