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SYNTHESIS AND UNUSUAL REACTION OF (1,3)PYRIMIDINO(6,9)PURINOPHANES[1)]

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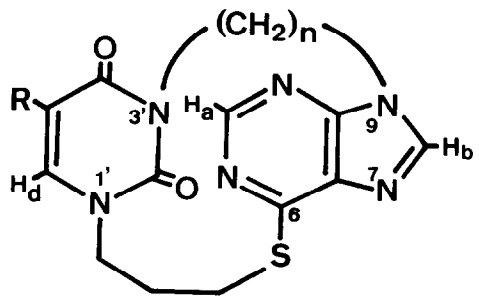
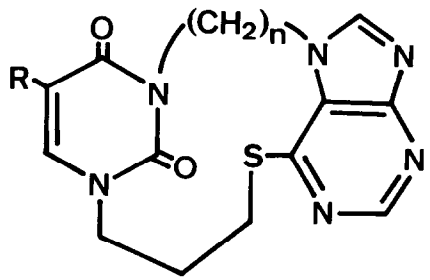
Abstract: Synthesis and structures of the title compounds, 1 and 2, are described. These purinophanes show unusual reactivity toward nucleophiles, in both acidic and basic media.

In the preceding paper of this series, we have reported the synthesis of a few pyrimidinopurinophanes to study the stacking interaction between pyrimidine and purine bases in DNA.[2)] Early attempts to prepare 1 by the cyclization reaction of 5 with α,ω-dibromoalkanes 7 and potassium carbonate in DMSO, however, gave only isomeric compound 3. After examining various reaction conditions, we succeeded in preparing 1 and 2 together with the non-stacking isomers 3 and 4 from the same starting material 5.



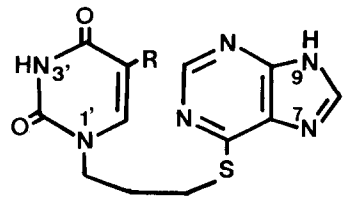


1 R = H_c
2 R = CH_3

a : n = 3
b : n = 4

3 R = H
4 R = CH_3

Cyclization reaction of 5 with 7a,b was carried out by NaH in DMF instead of K_2CO_3 in DMSO. The product was separated into two isomers by column chromatography on silica gel with chloroform-methanol. One isomer was determined to be 3 by comparing the spectral data with the authentic sample.[2)] The other isomer was assumed to be 1 on the basis of NMR spectra described later [1a[3)]: fine colorless needles from methanol-diethyl ether, mp 278-280 °C, M^+ 344; 1b[3)]: colorless columns from chloroform-diethyl ether, dec.>275 °C, M^+ 358]. Pyrimidinopurinophanes 2 containing a thymine ring instead of a uracil ring were also



+ $Br(CH_2)_nBr$ ⟶ 1(2) + 3(4)

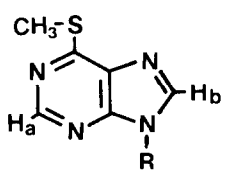
7a n=3
b n=4

5 R=H
6 R=CH_3

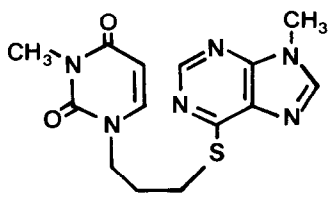
Table 1. Yields(%) of 1-4 with different condensing agents.

	K_2CO_3/DMSO		NaH/DMF	
	1 or 2	3 or 4	1 or 2	3 or 4
5+7a	0	40	6	14
7b	0	28	19	21
6+7a	0	28	8	16
7b	0	26	21	26

prepared from **6** by the similar method [2a[3]: colorless crystals from chloroform-diethyl ether, dec.>270 °C, M^+ 358; 2b[3]: colorless prisms from diethyl ether-methanol, mp 230-231 °C, M^+ 372]. The yields of **1-4** by two alkaline condensing agents are summarized in Table 1, showing an obvious difference in the ratio of isomeric products. Thus, the cyclo-N-alkylation in the K_2CO_3/DMSO system occurred only at the 7-position of purine ring, whereas in the NaH/DMF system at both 7- and 9-positions with preferential formation of the former. The difference is assumed to be dependent on the order of stepwise N-alkylations at the three nitrogen atoms, i.e., N-7 and N-9 of purine ring and N-3 of pyrimidine ring. To clarify this, an equimolar mixture of 6-methylthiopurine **8** and 1-propyluracil **12** was subject to a competitive alkylation with a little less than 1 eq. of propyl bromide in the presence of the above bases. The ratio of products, 9-Pr-**8**: 7-Pr-**8**: 3-Pr-**12** is 24:5:69 by K_2CO_3/DMSO and 70:16:12 by NaH/DMF, respectively. On the basis of these competitive alkylations, the cyclo-N-



8 R=H
9 R=CH_3



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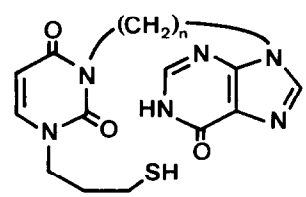

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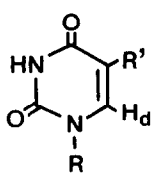


10 R=CH_3, R'=H_c
11 R=R'=CH_3
12 R=Pr, R'=H

Table 2. Observed Chemical Shifts (δ, ppm in $CDCl_3$) of Hetero Ring and Methyl Protons of **1a,b** and **2a,b**.[a)]

	Ha	Hb	Hc	Hd	CH_3
9+10	8.74	7.93	5.73	7.18	
1a	8.78(+0.04)	7.81(-0.12)	5.76(+0.03)	6.98(-0.20)	
1b	8.73(-0.01)	7.86(-0.07)	5.78(+0.05)	7.12(-0.06)	
9+11	8.74	7.93		6.99	1.94
2a	8.77(+0.03)	7.71(-0.22)		6.83(-0.16)	1.99(+0.05)
2b	8.72(-0.02)	7.76(-0.17)		6.97(-0.02)	2.01(+0.07)

a) Values in parentheses are differences from those of the reference compounds.

alkylation of **5** or **6** with **7a** or **7b** shown in Table 1 is explained mainly by the preferential alkylation at N-3', followed by sterically favorable ring closure at N-7. No formation of sterically unfavorable isomer **1** or **2** in the K_2CO_3/DMSO system is attributable to ready hydrolysis at C-6 of minor product **1** or **2** in that solution (vide infra).

Chemical shifts of hetero ring protons of **1**, **2**, and reference compounds are shown in Table 2. On the basis of the different extent of upfield shifts of the protons Ha to Hd and CPK molecular model examination, pyrimidinopurinophanes **1** and **2** were assigned to the desired N-9-bridged structures having a partially overlapped conformation. To confirm this, we undertook X-ray analysis of **1b**.[4] Figure 1 shows the nearly parallel and partially overlapped structure which is in fair agreement with the NMR assignment.

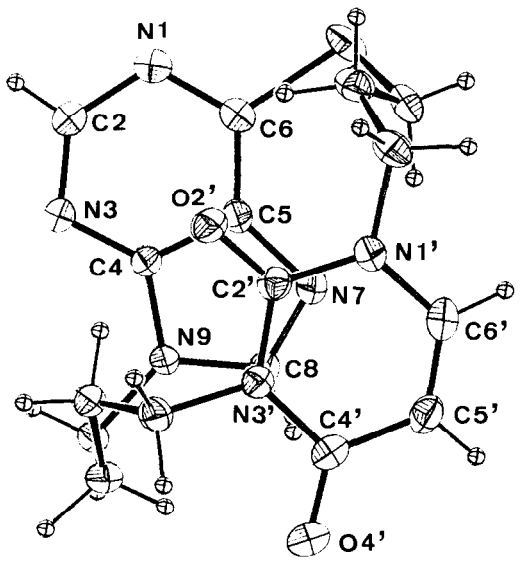


Fig. 1. View of **1b** on the least-squares plane defined with a purine ring.

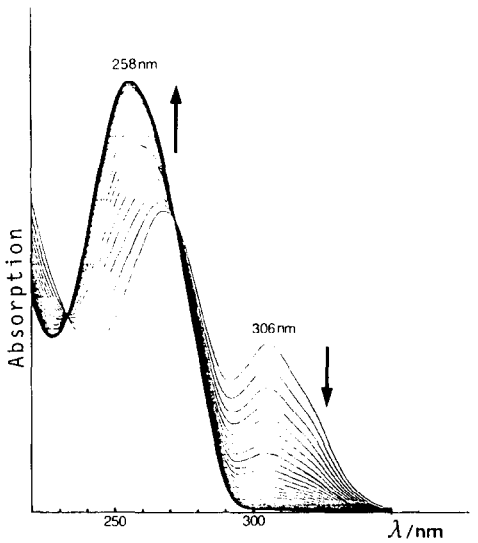


Fig. 2. Spectral change of **1b** in 0.1 N HCl with time.

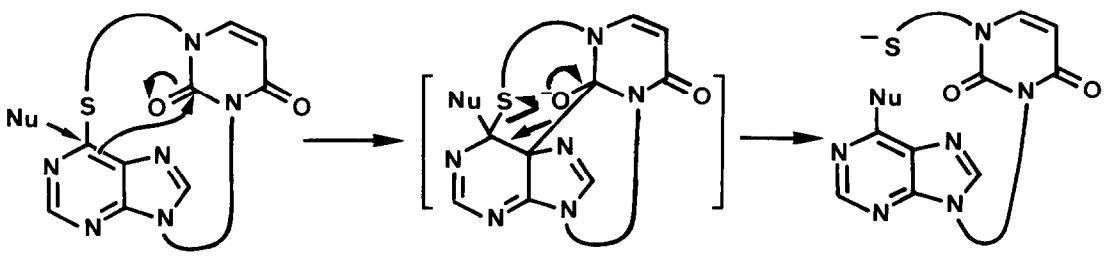
In the course of the electronic spectra measurement of **1a** and **1b** in 0.1 N HCl at room temperature, the spectra changed with time and showed two isosbestic points as seen in Fig. 2. The resulting compound was determined as hydrolytic product **14** by MS and UV spectra. The similar nucleophilic reactions of **1a** and **1b** were observed also in any 0.1 N NaOH, methylamine/H_2O, or dimethylamine/H_2O at room temperature.

The rate constants of these hydrolyses were determined spectrophotometrically and were analyzed as a first-order reaction for the acid hydrolysis and as pseudo

Table 3. Reaction Rate Constants of **1a,b** at 30±2 °C.

	$H_2O(s^{-1})$	OH^-	$MeNH_2$	Me_2NH $(s^{-1}M^{-1})$
1a	2.8×10^{-4}	2.0×10^{-3}	3.7×10^{-3}	3.8×10^{-3}
1b	8.4×10^{-5}	1.3×10^{-3}	1.9×10^{-3}	2.1×10^{-3}

first-order ones for the amine/H_2O hydrolyses (Table 3). The table shows that the rate of **1a** is approximately twice as large as that of **1b**, which is expected from the interplanar distances between pyrimidine and purine rings in the two compounds. Under the same conditions as those of **1**, on the other hand, **3a**, **3b**, **9**, and **13** were not subject to such reaction at all and the substitution of methylthio group of **9** to methylamino group requires drastic reaction conditions, e.g., heating with methylamine at 130 °C in a sealed tube for 17 h.[5] This unusual reactivity of **1** toward nucleophiles is considered to be resulted mainly from the following reasons: 1) strain in the molecule and 2) participation of transannularly closed carbonyl group in the transition state. The first possibility is excluded by the unstrained molecular structure of **1b** in the X-ray analysis. So, we assume at the present stage the neighboring group participation of the carbonyl group of pyrimidine base to be the dominant cause, as expected from Fig. 1. By employing the C-2' participation to C-5 the reaction seems to proceed through the transition state **15** as shown in the following scheme.



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References

1) Layered Compounds LXXV. Part LXXIV: H. Higuchi, M. Kugimiya, T. Otsubo, Y. Sakata, and S. Misumi, Tetrahedron Lett., 24, 2593 (1983).
2) K. Doyama, F. Hama, Y. Sakata, and S. Misumi, Tetrahedron Lett., 22, 4101 (1981).
3) All new compounds gave satisfactory elemental analysis.
4) The crystal analysis was carried out using Ni-filtered Cu-Kα radiation of a full automatic four-circle diffractometer and the structure was solved by a program MULTAN-78. The result will be published elsewhere.
5) G. B. Elion, E. Burgi, and G. H. Hitchings, J. Am. Chem. Soc., 74, 411 (1952).

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