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Reactions of 1-(2-Acetoxyethoxy)methyl-5-amino-4-cyanoimidazole with Isothiocyanates

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The reactions of 1-(2-acetoxyethoxy)methyl-5-amino-4-cyanoimidazole (**5**) with isothiocyanates afforded 3-(2-acetoxyethoxy)methyl-5-(substituted amino)-7-(*N*-substituted thiocarbamoyl)-iminoimidazo[4,5-*d*][1,3]thiazine (**6a**—**c**) at 50 °C in dimethylformamide. At more elevated temperature, for example, in refluxing pyridine, compound **5** reacted with methyl isothiocyanate to give 3-(2-acetoxyethoxy)methyl-5-methylamino-7-(*N*-methylthiocarbamoyl)iminoimidazo[4,5-*d*][1,3]-thiazine (**6b**) and 9-(2-acetoxyethoxy)methyl-1-methyl-6-imino-2-thioxopurine (**7b**).

On the other hand, when carbon disulfide was used in place of isothiocyanates, the reaction afforded 3-(2-acetoxyethoxy)methyl-7-imino-5-thioxoimidazo[4,5-*d*][1,3]thiazine (**8**) in refluxing pyridine.

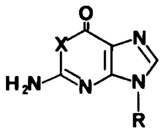
Under alkaline conditions, **6** and **8** were found to be rearranged to 2-(substituted amino)-9-(2-hydroxyethoxy)methyl-6-thioxopurine (**10**) and 2,6-dithioxo-9-(2-hydroxyethoxy)methylpurine (**9**), respectively.

Keywords——isothiocyanate; acycloimidazole; imidazo[4,5-*d*][1,3]thiazine; Dimroth rearrangement; antiviral agent

9-(2-Hydroxyethoxy)methylguanine (**1**) (acyclovir or Zovirax)[1] may be one of the most efficient and the least cytotoxic drugs in the treatment of viral infections caused by herpes viruses. However, there are still some problems associated with acyclovir, *viz*., its poor water-solubility and rapid development of resistant viruses. Thus, chemical syntheses of acyclovir analogs have been studied extensively to search for more effective antiviral agents.[2] To our knowledge, however, acyclovir analogs bearing 5-amino-imidazo[4,5-*d*][1,3]oxazin-7-one in which the ribose moiety of oxanosine (**2**)[3,4] is replaced by an acyclic chain, or its thiazine counterpart, have not yet been chemically synthesized, among the closely related analogs.[5,6]

We have been interested in acyclonucleosides of this type to investigate the relationship between structure and antiviral activity. Therefore, we planned to synthesize a new compound, 3-(2-hydroxyethoxy)methyl-5-aminoimidazo[4,5-*d*][1,3]thiazine-7-one (**3**), for screening of its antiviral activities.

Inspection of literature dealing with the construction of the heterocycle revealed that the formation of a thiazine ring is usually achieved by the cyclization of suitable aromatic and



1: X=NH $R=CH_2OCH_2CH_2OH$
2: X=O R=ribosyl
3: X=S $R=CH_2OCH_2CH_2OH$

Chart 1

heterocyclic *o*-aminonitriles with carbon disulfide or isothiocyanates.[5,7] Thus, Marumoto *et al.* have reported that 5-amino-4-cyano-1-*β*-D-ribofuranosyl imidazole reacted with carbon disulfide in pyridine to afford 7-imino-5-thioxo-3-(1-*β*-D-ribofuranosyl)imidazo[4,5-*d*][1,3]-thiazine, albeit in low yield.[5] However, Grözinger and Onan have reported that 1-alkyl-4-amino-5-cyanoimidazole reacted with isothiocyanates, *viz.*, methyl, ethyl and phenyl isothiocyanates, in refluxing pyridine to give 1-substituted-7-alkyl-6-imino-2-thioxopurine and 7-alkyl-6-(substituted amino)-2-thioxopurines, which were presumably formed by Dimroth-type rearrangement of the former.[8]

In this paper, we report the results of the reactions of 1-(2-acetoxyethoxy)methyl-5-amino-4-cyanoimidazole (**5**) with carbon disulfide, and methyl, phenyl and benzoyl isothiocyanates.

Results and Discussion

We synthesized 1-(2-acetoxyethoxy)methyl-5-aminoimidazole-4-carboxamide (**4**) according to Beauchamp *et al.*[9] from 4-aminoimidazole-5-carboxamide hydrochloride and (2-acetoxyethoxy)methyl chloride.[10] Then, **4** was converted to 1-(2-acetoxyethoxy)methyl-5-amino-4-cyanoimidazole (**5**) in 75% yield by treatment with *p*-toluenesulfonyl chloride.[11]

Reactions of **5** with phenyl, methyl and benzoyl isothiocyanates in dimethylformamide (DMF) or pyridine at 50 °C for 3 d afforded **6a**, **6b** and **6c** as yellow-colored crystals in 33—78% yields. These compounds revealed no absorption maximum around 2200 cm^{-1} due to the cyano group in their infrared (IR) spectra, and elemental analysis showed the presence of two sulfur atoms in the molecule. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **6b** in dimethyl sulfoxide (DMSO-d_6) showed the presence of two methyl signals, each of which was split into a doublet. These methyl signals became singlets on addition of D_2O. This observation suggests that the nitrogen atom adjacent to the methyl group has a hydrogen atom, and the structure can be drawn in terms of the formulas **6a**—**c**. In the ultraviolet (UV) absorption spectra, **6a**—**c** each showed an absorption maximum at around 400 nm.

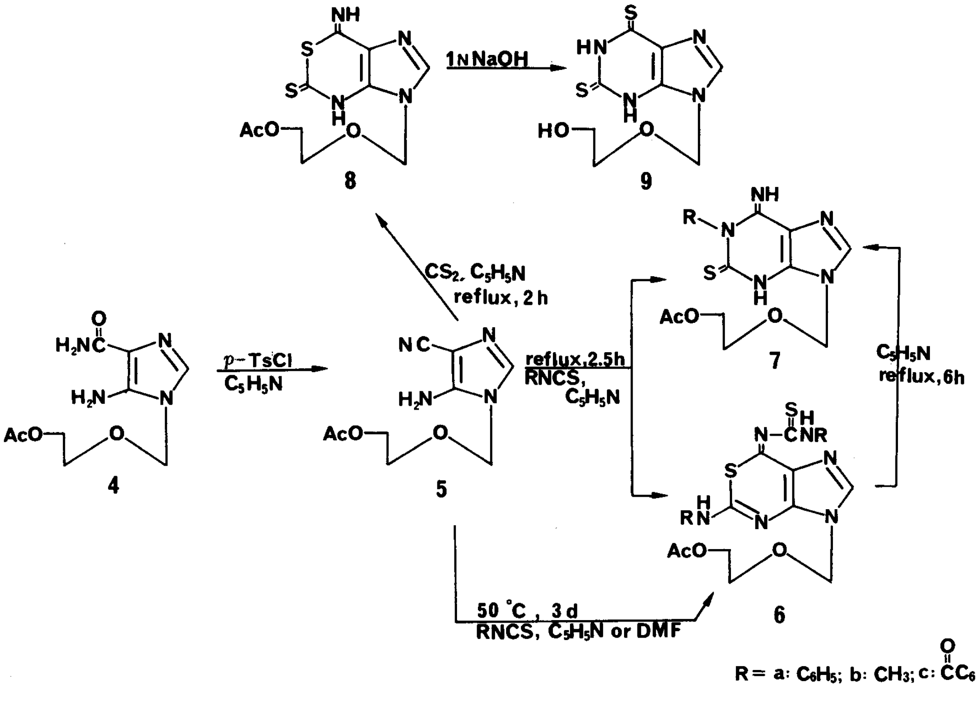


Chart 2

All these lines of evidence suggest that the structures of the reaction products (**6a**—**c**) should be 3-(2-acetoxyethoxy)methyl-5-(substituted amino)-7-(*N*-substituted thiocarbamoyl)-iminoimidazo[4,5-*d*][1,3]thiazines. It seems likely that these compounds were formed by reaction of 2 molar eq of isothiocyanates with **5**. Even when the reaction was carried out with less than one equivalent (0.8 molar eq), **6a**—**c** were still formed and unreacted starting materials were recoverd. In addition, in each reaction mixture there was no detectable amount of 3-(2-acetoxyethoxy)methyl-(5-substituted amino)-7-iminoimidazo[4,5-*d*][1,3]thiazines, which would be expected to be formed from **5** by the reaction of one molecule of isothiocyanates.

These results suggest that the rate of the reaction of the second isothiocyanate with the initially formed product is more rapid than the rate of the first step, or alternatively that two moles of isothiocyanate react with the cyano group simultaneously or consecutively and then intramolecular cyclization occurs to afford the compounds (**6a**—**c**).

Under alkaline conditions, **6a**, **b** were converted to **10a**, **b** by the elimination of one molecule of the isothiocyanate, accompanied with ring rearrangement. Compound **10a** was methylated with methyl iodide to afford 9-(2-hydroxyethoxy)methyl-2-phenylamino-6-methylthiopurine (**12a**) in 76% yield. The structures of **10a** and **10b** were confirmed by leading them to 9-(2-hydroxyethoxy)methyl-2-substituted aminopurines (**11a** and **11b**) by Raney Ni treatment. Yields of **11a** and **11b** were 69% and 61%, respectively. However, desulfurization of **6a** and **6b** with Raney Ni also gave several unidentified products. This is probably because compounds **6a** and **6b** have the thiazine ring structure, that is, the sulfur might be vulnerable to Raney Ni.

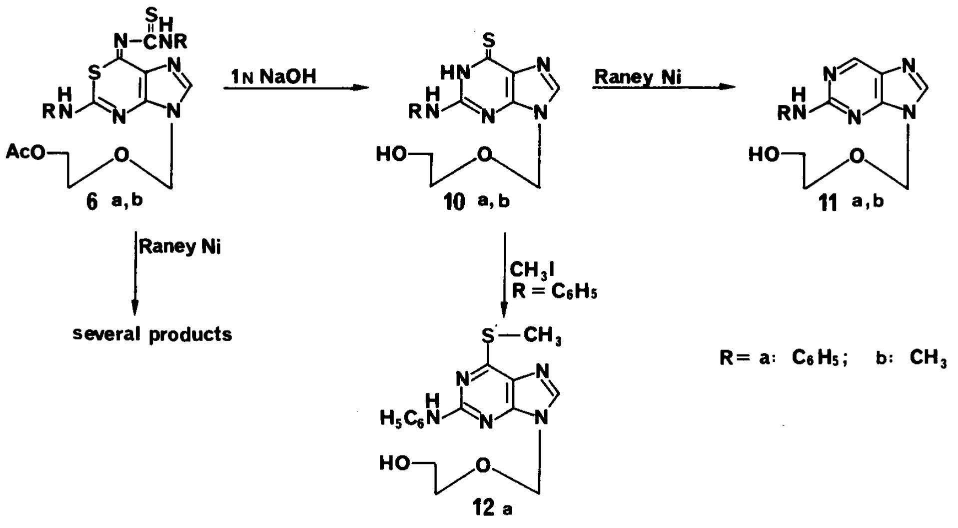


Chart 3

On the contrary, the reaction of **5** with methyl isothiocyanate in refluxing pyridine for 2.5 h gave a mixture of **7b** (23% yield) and **6b** (23% yield). A half of the latter was converted to the former in refluxing pyridine within 6 h.

These observations may be a reflection of the fact that the reaction products depend on the reaction temperature, that is, only **6b** was formed at 50 °C, whereas at refluxing temperature, **6b** and **7b** were formed in equal amounts. The mode of reaction can be explained as follows; **7b** was obtained by bond fission between S_6–C_7 in the thiazine ring of **6b** before or after removal of one molecule of isothiocyanate, followed by Dimroth-type rearrangement.

The reactions of **5** with various types of isothiocyanates afforded imidazothiazine derivatives (**6a**—**c**) which then were converted to the Dimroth-type rearranged products, 9-substituted thioguanine derivatives. It is worthy of note that compounds **6a**—**c** have a similar skeleton to the acyclo-thioxanosine which we desired.

Reaction of **5** with isothiocyanates failed to give the expected 7-unsubstituted imino derivatives, even when the reactions was carried out by the use of 0.8 molar eq of isothiocyanates and at lower temperature.

The results may be summarized as follows. 1) The reactions of **5** with isothiocyanates gave rise to **6** at 50 °C and **7** in addition to **6** in refluxing pyridine. 2) It was found that the condensation reaction may be temperature-dependent. Elevated temperature may give rise to **7** in the same ratio as imidazothiazine derivatives (**6**). 3) The reaction of **5** with carbon disulfide in refluxing pyridine gave rise to **8** by normal cyclization.

Antiviral activities of newly prepared acyclo nucleosides and related compounds are being examined.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were obtained on a JEOL GX-270 spectrometer using tetramethylsilane as an internal standard. Mass spectral (MS) measurements were run on a JEOL D-300 spectrometer. IR spectra were recorded with a JASCO IRA-1 spectrometer in KBr disks. UV spectra were measured on a Hitachi 200-20 spectrophotometer. Thin layer chromatography (TLC) was performed on Merck Kiesel-gel GF$_{254}$ pre-coated TLC plates. Column chromatography and Lobar chromatography were performed on Silica-gel 60 (E. Merck, 70—230 mesh) and Silica 60 (E. Merck, LiChroprep Si 60, 40—63 μm), respectively.

1-(2-Acetoxyethoxy)methyl-5-amino-4-cyanoimidazole (5)——A solution of *p*-toluenesulfonyl chloride (380 mg, 2 mmol) in anhydrous pyridine (2 ml) was slowly added with stirring to 1-(2-acetoxyethoxy)methyl-5-amino-4-carbamoyl imidazole (**4**) (800 mg, 3.3 mmol) in anhydrous pyridine (8 ml) with exclusion of moisture. Stirring was continued at room temperature overnight and then further *p*-toluenesulfonyl chloride (700 mg, 3.67 mmol) in anhydrous pyridine (2 ml) was added and stirring was continued for 6 h. The solution was poured into ice-water (30 ml), stirred for 15 min, and then extracted with CHCl$_3$ (2 × 50 ml). The organic layer was washed with H$_2$O (50 ml), dried (Na$_2$SO$_4$) and filtered, and the filtrate was evaporated to dryness. The residue was chromatographed on a silica gel column using 5% (v/v) AcOEt–CHCl$_3$ as an eluent to afford 580 mg (78%) of **5** as colorless needles after recrystallization from AcOEt–isopropyl ether; mp 98—100 °C. IR (KBr): 2205 (CN) cm^{-1}. MS *m*/*z*: 224 (M$^+$). ^{1}H-NMR (DMSO-d_6) δ: 1.99 (3H, s, COCH$_3$), 3.61 (2H, m, H-3′),[12] 4.08 (2H, m, H-4′), 5.24 (2H, s, H-1′), 6.28 (2H, br, NH$_2$), 7.28 (1H, s, H-2). *Anal.* Calcd for C$_9$H$_{12}$N$_4$O$_3$: C, 48.21; H, 5.39; N, 24.99. Found: C, 48.17; H, 5.37; N, 24.72.

3-(2-Acetoxyethoxy)methyl-5-phenylamino-7-(*N*-phenylthiocarbamoyl)iminoimidazo[4,5-*d*][1,3]thiazine (6a)——Phenyl isothiocyanate (915 mg) was added to a solution of **5** (300 mg, 1.34 mmol) in DMF (5 ml), and the solution was heated at 50 °C for 3 d. Then yellow crystals were precipitated, collected by filtration and washed with ethyl acetate to give 400 mg of the title compound (**6a**). The filtrate was evaporated to dryness and purified by chromatography on silica gel using CHCl$_3$–MeOH (20 : 1, v/v) as an eluent to give 120 mg. Total yield was 520 mg (78%) of yellow needles, (**6a**), mp 151—152 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.95 (3H, s, CH$_3$CO), 3.74 (2H, m, H-3′), 4.10 (2H, m, H-4′), 5.50 (2H, s, H-1′), 7.01—7.90 (10H, m, C$_6$H$_5$), 8.10 (1H, s, H-8), 10.65, 10.70, 11.08, 11.39 (1/2H, s, NH). UV $\lambda_{\max}$ nm ($\varepsilon \times 10^3$) (50% MeOH–H$_2$O, v/v): 256 sh (21.2), 310 (16.5), 326 sh (13.5), 408 (6.7); (50% MeOH–0.1 N HCl, v/v): 255 sh (23.6), 305 (17.2), 390 (12.4); (50% MeOH–0.1 N NaOH, v/v): 285 (20.4), 330 sh (11.6), 362 sh (6.2). *Anal.* Calcd for C$_{23}$H$_{22}$N$_6$O$_3$S$_2$: C, 55.85; H, 4.48; N, 16.99; S, 12.97. Found: C, 55.52; H, 4.40; N, 16.83; S, 12.96.

3-(2-Acetoxyethoxy)methyl-5-methylamino-7-(*N*-methylthiocarbamoyl)iminoimidazo[4,5-*d*][1,3]thiazine (6b)——Methyl isothiocyanate (500 mg) was added to a solution of **5** (300 mg, 1.34 mmol) in pyridine (5 ml). The solution was heated at 50 °C for 3 d, then evaporated to dryness. Ethyl acetate (20 ml) was added to the residue and insoluble yellow precipitates were filtered off to give **6b** (250 mg, 51%), mp 166—167 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.98 (3H, s, CH$_3$CO), 2.89 (3H, d, J = 3.3 Hz, CH$_3$NH), 2.94 (3H, d, J = 3.0 Hz, CH$_3$NHCS), 3.73 (2H, m, H-3′), 4.11 (2H, m, H-4′), 5.44 (2H, s, H-1′), 7.91 (1H, s, H-8), 8.55, 9.44 (1H, m, NH). UV $\lambda_{\max}$ nm ($\varepsilon \times 10^3$) (50% MeOH–H$_2$O, v/v): 284 (14.6), 393 (12.9); (50% MeOH–0.1 N HCl, v/v): 283 (17.3), 380 (11.6); (50% MeOH–0.1 N NaOH, v/v): 275 sh (17.8), 323 (11.7), 355 sh (8.8), 390 sh (6.2). *Anal.* Calcd for C$_{13}$H$_{18}$N$_6$O$_3$S$_2$: C, 42.15; H, 4.90; N, 22.69; S, 17.31. Found: C, 42.05; H, 4.90; N, 22.49; S, 17.23.

3-(2-Acetoxyethoxy)methyl-5-benzoylamino-7-(*N*-benzoylthiocarbamoyl)iminoimidazo[4,5-*d*][1,3]thiazine (6c)——Benzoyl isothiocyanate (87.3 mg) was added to a solution of **5** (100 mg, 0.45 mmol) in DMF (1 ml) at 50 °C for 30 min. After work-up as described above for **6a**, yellow needles (**6c**) (81 mg, 33%) were obtained; mp 126—130 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.97 (3H, s, CH$_3$CO), 3.76 (2H, m, H-3′), 4.11 (2H, m, H-4′), 5.58 (2H, s, H-1′), 7.45—7.70 (6H, m, C$_6$H$_5$), 7.90—8.05 (4H, m, C$_6$H$_5$), 8.31 (1H, s, H-8), 12.04, 12.39 (1H, s, NH). UV $\lambda_{\max}$ nm ($\varepsilon \times 10^3$) (50%

MeOH–H_2O, v/v): 251 (30.6), 281 sh (21.2), 321 sh (13.9), 405 sh (8.1), 420 (8.4); (50% MeOH–0.1 N HCl, v/v): 232 (29.0), 254 (26.9), 313 sh (11.7), 380 (6.1); (50% MeOH–0.1 N NaOH, v/v): 237 (31.9), 330 (14.0), 397 (10.1). *Anal.* Calcd for $C_{25}H_{22}N_6O_5S_2$: C, 54.53; H, 4.03; N, 15.26; S, 11.64. Found: C, 54.72; H, 4.06; N, 14.95; S, 11.46.

9-(2-Acetoxyethoxy)methyl-1-methyl-6-imino-2-thioxopurine (7b)——Methyl isothiocyanate (370 mg) was added to a solution of **5** (290 mg, 1.29 mmol) in pyridine (5 ml) and the mixture was refluxed for 2.5 h, then evaporated to dryness. The residue was purified on a Lobar column (25 × 350 mm) using 14% (v/v) MeOH–$CHCl_3$ as an eluent to give 89 mg (23%) of **7b** and 112 mg (23%) of **6b**. Compound **7b**: mp 167—168 °C, MS *m/z*: 297 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 1.97 (3H, s, $COCH_3$), 3.70 (2H, m, H-3′), 3.94 (3H, s, N-CH_3), 4.08 (2H, m, H-4′), 5.44 (2H, s, H-1′), 8.11 (1H, s, 8H), 8.51 (2H, br s, NH). UV λ_{max} nm ($\varepsilon \times 10^3$) (50% MeOH–H_2O, v/v): 229 (21.5), 294 (27.8); (50% MeOH–0.1 N HCl, v/v): 236 (19.6), 293 (27.5); (50% MeOH–0.1 N NaOH, v/v): 244 (18.5), 297 (21.5), 305 sh (20.2). *Anal.* Calcd for $C_{11}H_{15}N_5O_3S$: C, 44.43; H, 5.09; N, 23.55; S, 10.78. Found: C, 44.36; H, 5.14; N, 23.44; S, 10.69.

Conversion of 6b to 7b——A solution of **6b** (10 mg) in pyridine (2 ml) was refluxed for 6 h. After cooling, the reaction mixture was examined by TLC, which showed that the spot due to the starting material (**6b**) had decreased by about a half and concomitantly a new spot had appeared. The new product had the same *Rf* value (0.42, v/v, 10% MeOH–$CHCl_3$) and UV spectrum as authentic **7b**. The yield of **7b** was estimated to be approximately 50% on the basis of the TLC pattern.

9-(2-Hydroxyethoxy)methyl-2-phenylamino-6-thioxopurine (10a)——A solution of **6a** (100 mg, 0.20 mmol) in 1 N NaOH (1.5 ml) was heated at 50 °C for 30 min. Its color changed to pale yellow from strong yellow during the reaction. After cooling, acetic acid (90 mg) in H_2O (1 ml) was added to neutralize the reaction solution. The precipitated solid was collected by filtration and recrystallized from 50% (v/v) MeOH–H_2O to give pale yellow crystals (**10a**), 54 mg (83%), mp 209—210 °C. MS *m/z*: 317 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 3.47 (2H, m, H-3′), 3.53 (2H, m, H-4′), 5.05 (2H, s, H-1′), 7.07 (1H, t, J=9.0 Hz, ArH-γ), 7.37 (2H, t, J=9.0 Hz, ArH-β), 7.65 (2H, d, J=9.0 Hz, ArH-α), 8.14 (1H, s, H-8), 9.09 (1H, s, NHC_6H_5), 11.98 (1H, s, H-1). UV λ_{max} nm ($\varepsilon \times 10^3$) (50% MeOH–H_2O, v/v): 244 (12.2), 282 (20.4), 347 (21.2); (50% MeOH–0.1 N HCl, v/v): 245 (10.8), 285 (18.1), 347 (17.7); (50% MeOH–0.1 N NaOH, v/v): 216 (20.3), 288 (34.0), 322 (13.4). *Anal.* Calcd for $C_{14}H_{15}N_5O_2S$: C, 52.99; H, 4.70; N, 22.08; S, 10.09. Found: C, 53.01; H, 4.73; N, 22.07; S, 10.22.

9-(2-Hydroxyethoxy)methyl-2-methylamino-6-thioxopurine (10b)——**10b** (40 mg, 58%) was obtained from **6b** (100 mg, 0.27 mmol), according to the above procedure; mp 267—270 °C (dec.) (sintered at 245 °C). MS *m/z*: 255 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 2.87 (3H, d, J=3.3 Hz, CH_3NH), 3.48 (2H, m, H-3′), 3.35 (2H, m, H-4′), 5.42 (2H, s, H-1′), 6.57 (1H, br m, $NHCH_3$), 8.00 (1H, s, H-8), 12.02 (1H, s, H-1). UV λ_{max} nm ($\varepsilon \times 10^3$) (50% MeOH–H_2O, v/v): 213 (19.9), 264 (8.8), 270 sh (8.1), 347 (17.7); (50% MeOH–0.1 N HCl, v/v): 214 (16.1), 269 (6.7), 347 (14.4); (50% MeOH–0.1 N NaOH, v/v): 220 (5.4), 258 (11.4), 280 (5.9), 323 (11.4). *Anal.* Calcd for $C_9H_{13}N_5O_2S \cdot 2/3H_2O$; C, 40.44; H, 5.40; N, 26.20; S, 12.00. Found: C, 40.18; H, 4.97; N, 26.17; S, 12.17.

9-(2-Hydroxyethoxy)methyl-2-phenylaminopurine (11a)——Raney Ni[13)] (0.5 ml of wet volume) was added to a solution of **10a** (73 mg, 0.23 mmol) in absolute EtOH (3 ml), and the reaction mixture was refluxed for 2 h. After the mixture had cooled, the Raney Ni was filtered off, and the filtrate was evaporated to dryness. The residue was recrystallized from AcOEt–isopropyl ether to give **11a** as colorless needles, 40 mg (61%), mp 142—143 °C, MS *m/z*: 285 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 3.48 (2H, m, H-3′), 3.59 (2H, m, H-4′), 5.60 (2H, s, H-1′), 6.92 (1H, t, J=7.3 Hz, ArH-γ), 7.28 (2H, t, J=7.3 Hz, ArH-β), 7.84 (2H, d, J=7.3 Hz, ArH-α), 8.35 (1H, s, H-8), 8.84 (1H, s, H-6), 9.68 (1H, s, NHC_6H_5). UV λ_{max} nm ($\varepsilon \times 10^3$) (50% MeOH–H_2O, v/v): 239 (14.7), 271 (26.0), 325 (8.9); (50% MeOH–0.1 N HCl, v/v): 242 (20.5), 272 (21.1), 329 (4.5); (50% MeOH–0.1 N NaOH, v/v): 240 (15.8), 273 (27.0), 325 (9.5). *Anal.* Calcd for $C_{14}H_{15}N_5O_2$: C, 58.93; H, 5.30; N, 24.55. Found: C, 58.87; H, 5.29; N, 24.53.

9-(2-Hydroxyethoxy)methyl-2-methylaminopurine (11b)——The procedure described above gave **11b** (69% yield) from **10b**, mp 118—120 °C. MS *m/z*: 223 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 2.85 (3H, d, J=3.8 Hz, CH_3NH), 3.46 (2H, m, H-3′), 3.50 (2H, m, H-4′), 5.50 (2H, s, H-1′), 7.00 (1H, br s, $NHCH_3$), 8.14 (1H, s, H-8), 8.60 (1H, s, H-6). UV λ_{max} nm ($\varepsilon \times 10^3$) (50% MeOH–H_2O, v/v): 222 (34.0), 249 (12.8), 319 (8.5); (50% MeOH–0.1 N HCl, v/v): 228.5 (60.7), 250 sh (9.6), 325 (5.0); (50% MeOH–0.1 N NaOH, v/v): 216 (55.8), 250 (12.5), 319 (8.7). *Anal.* Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.38. Found: C, 48.39; H, 5.86; N, 31.49.

9-(2-Hydroxyethoxy)methyl-2-phenylamino-6-methylthiopurine (12a)——Methyl iodide (0.1 ml) was added to a solution of **10a** (73 mg, 0.23 mmol) in 1 N NaOH (0.33 ml), and the mixture was stirred for 1 h at room temperature. The precipitated needles were filtered off, washed with H_2O, and recrystallized from EtOH to give 58 mg of **12a** (78%), mp 137—138 °C, MS *m/z*: 331 (M^+). *Anal.* Calcd for $C_{15}H_{17}N_5O_2S$: C, 54.37; H, 5.17; N, 21.13; S, 9.68. Found: C, 54.33; H, 5.17; N, 21.00; S, 9.82. ^{1}H-NMR (DMSO-d_6) δ: 2.68 (3H, s, SCH_3), 3.48 (2H, t, $J_{3',4'}$=5.0 Hz, H-3′), 3.55 (2H, t, $J_{4',3'}$=5.0 Hz, H-4′), 5.56 (2H, s, H-1′), 6.91 (1H, t, J=8.0 Hz, ArH-γ), 7.26 (2H, t, J=8.0 Hz, ArH-β), 7.82 (2H, d, J=8.0 Hz, ArH-α), 8.18 (1H, s, H-2), 9.48 (1H, s, HNC_6H_5). UV λ_{max} nm ($\varepsilon \times 10^3$) (50% MeOH–H_2O, v/v): 246 (4.9), 275 (15.2), 326 (4.6); (0.1 N HCl): 277 (27.9), 335 (19.6).

3-(2-Acetoxyethoxy)methyl-7-imino-5-thioxoimidazo[4,5-*d*][1,3]thiazine (8)——Carbon disulfide (4 ml) was added to a solution of **5** (453 mg, 2.02 mmol) in dry pyridine (8 ml), and the mixture was refluxed for 2 h. After cooling, the solvent was evaporated off and the residue was purified by column chromatography on silica gel using AcOEt–MeOH (19 : 1, v/v) as the eluent to give 110 mg (18%) of yellow crystals, mp 254—256 °C (sintered at 160 °C).

^{1}H-NMR (DMSO-d_6) δ: 1.97 (3H, s, $COCH_3$), 3.73 (2H, m, H-3′), 4.10 (2H, m, H-4′), 5.45 (2H, s, H-1′), 8.20 (1H, br s, NH), 9.68 (0.5H, br, NH), 9.95 (0.5H, br, NH). UV λ_{max} nm ($\varepsilon \times 10^3$) (50% MeOH–H_2O, v/v): 233 (32.0), 248 (25.0), 308 (19.3), 392 (11.2); (50% MeOH–0.1 N HCl, v/v): 247 (24.2), 307 (19.2), 391 (11.0); (50% MeOH–0.1 N NaOH, v/v): 286 (28.7), 335 (13.5), 351 (13.1). *Anal.* Calcd for $C_{10}H_{12}N_4O_3S_2$: C, 39.99; H, 4.03; N, 18.65; S, 21.35. Found: C, 40.01; H, 3.93; N, 18.24; S, 20.98.

Rearrangement of 3-(2-Acetoxyethoxy)methyl-7-imino-5-thioxoimidazo[4,5-*d*][1,3]thiazine (8) under Alkaline Conditions——A solution of **8** (2 mg) in 1 N NaOH (1 ml) was left for 2 h at room temperature to give 2,6-dithioxo-9-(2-hydroxyethoxy)methylpurine (**9**). The reaction mixture was examined by TLC. A new spot whose *Rf* value (solvent; 20%, v/v, MeOH–$CHCl_3$) was 0.44 was detected and this was excised and extracted with MeOH. The UV spectrum of the extract was identical with that of 2,6-dithioxo-9-β-D-ribofuranosylpurine.[5] UV λ_{max} nm (pH $\leq$ 1): 260, 302, 340; (pH $\geq$ 12): 282, 320.

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References and Notes

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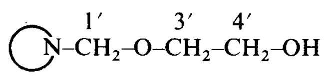
12) Numbering of the acyclic portion in the acyclic nucleoside is as follows: 
$\overset{1'}{N\text{-}CH_2}\text{-}O\text{-}\overset{3'}{CH_2}\text{-}\overset{4'}{CH_2}\text{-}OH$
13) Raney Ni was purchased from Kawaken Fine Chemical Co., Ltd.