PAPERS

Photoinduced Alkylthiolation of Halogenated Purine Nucleosides

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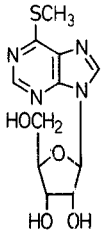
A new and highly efficient methodology for the synthesis of biologically important methylmercaptopurine nucleosides is described. The approach represents a substantial improvement over earlier reported methods for this class of compounds.

A number of thioalkylated purine nucleosides have been found to have interesting biological activity. For example, 6-methylmercapto-9β-(D-ribofuranosyl)-purine (**1**) is one of the most potent inhibitors of *de novo* purine synthesis[1]. It is readily phosphorylated by adenosine kinase and incorporated into RNA and DNA[2]. The 5'-monophosphate of **1** specifically inhibits amidophosphoribosyltransferase[3]. Both compound **1** and its 2-amino analogue exhibit antitumor activity[4,5]. 2-Methylmercaptoadenosine analogues are excellent aggregators of mammalian blood platelets[6].



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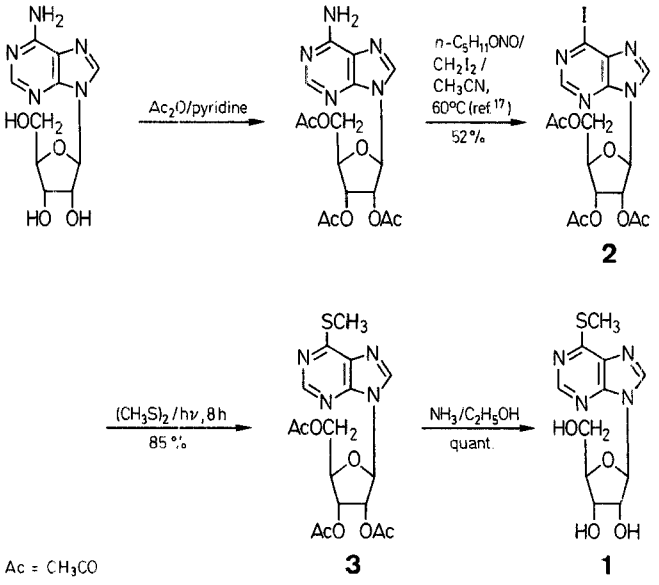
Previous syntheses of 6-methylmercaptopurine nucleosides involved conversion of protected inosine and guanosine to the 6-thio compound. Deprotection followed by alkylation with methyl iodide and base gave the desired product (e.g. **1** and **5b**) generally in low overall yields[5,7-11]. The syntheses of 2-methylmercapto- and 2,6-dimethylmercaptopurine nucleosides have been achieved previously but in very low yields (< 5%) from ring closure of appropriate imidazole derivatives with carbon disulfide, followed by alkylation with methyl iodide[12-16]. We report a new, highly efficient and reproducible approach to the synthesis of thioalkylated purine nucleosides.

In the synthesis of 6-methylmercapto-9β-(D-ribofuranosyl)-purine (**1**), adenosine served as the starting material. It was selectively acetylated with acetic anhydride and pyridine and then converted to the 6-iodo compound **2** by reaction with *n*-pentyl nitrite and diiodomethane in acetonitrile at 60°C. This deamination-halogenation procedure is a modification of one reported previously by us[17]. Photolysis of a nitrogen-purged solution of **2** in dimethyl disulfide (or in dimethyl disulfide dissolved in acetonitrile) in a Hanovia photochemical apparatus with irradiation from a Vycor-sleeved 450 W mercury lamp for 8 h, resulted in a clean conversion to **3** (85% yield of pure product, Table). Deprotection of **3** with ethanolic ammonia proceeded smoothly and almost quantitatively (Scheme A). Compound **1** was purified by reversed-phase H.P.L.C. on Amberlite XAD-4 resin. The overall yield from adenosine was about 40% (Table).



Scheme A

Guanosine served as the starting material for the synthesis of 2,6-disubstituted purine nucleosides in which at least one position contained a methylmercapto functionality. It was converted to **4** by selective acetylation followed by reaction with phosphoryl chloride and *N,N*-dimethylaniline[18] (Scheme **B**). Photolysis of **4** in dimethyl disulfide or in dimethyl disulfide dissolved in acetonitrile gave **5a** in 57% yield after purification. The overall yield from guanosine after deprotection (33%) is a significant improvement over previously reported procedures (Table)[5,9,11].

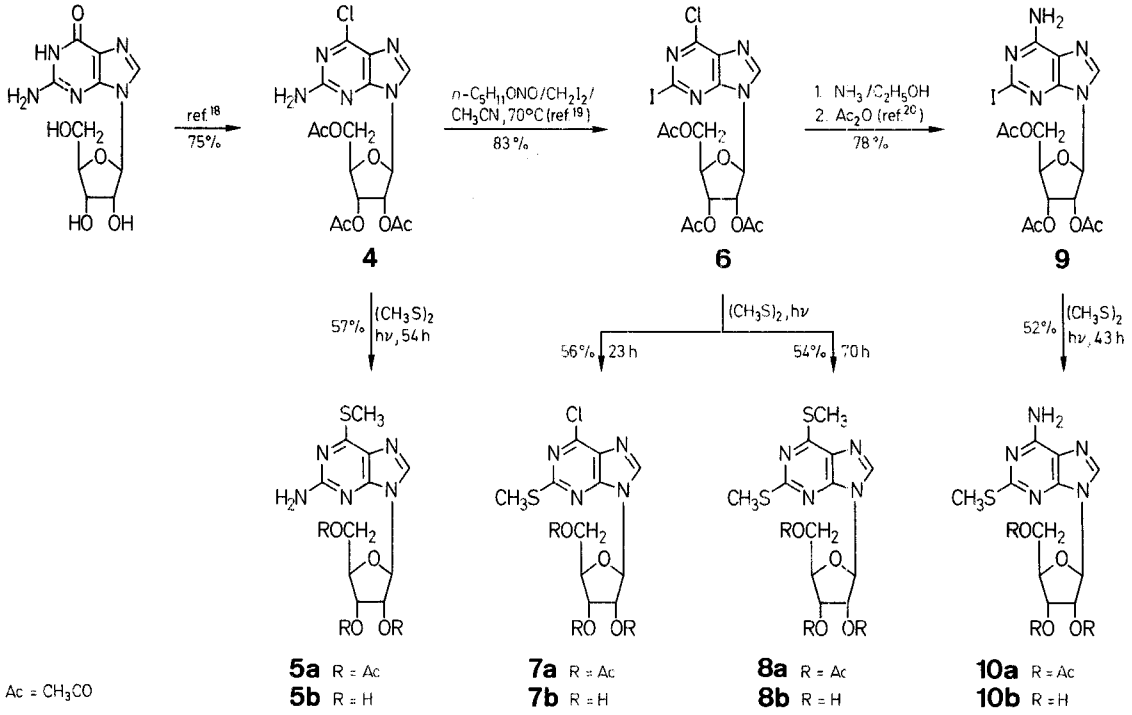
Treatment of **4** with n-pentyl nitrite, diiodomethane, and acetonitrile at 70°C for 3 h gave the protected dihalogenated nucleoside **6**[19]. Controlled photolysis of **6** in the presence of dimethyl disulfide gave **7a**. On prolonged photolysis, both halogens in the dihalogenated nucleoside **6** were replaced and 2,6-dimethylmercaptopurine nucleoside **8a** was produced in good yields. These alkylthiolations were monitored by mass spectrometry.

The importance of 2-alkylmercaptoadenosine analogues in blood platelet studies and the cumbersome synthetic methods available for these analogues[6,12-16], led us to investigate a possible approach to these compounds through

Table. Experimental and Physical Data for Methylmercaptopurine Nucleosides

Starting Material	Procedure (Time)	Product	Yield [%]	R_f[a]	M.S. *m/e* (rel. int. %)	U.V. (C_2H_5OH) λ_{max} (ε)	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	^{13}C-N.M.R. ($CDCl_3$) δ [ppm]	Deprotection Product	m.p. [°C] found	m.p. [°C] reported	Overall Yield [%]
2	A (8 h)	3	85	0.66 (70)	424 (M^+, 2.3); 259 (Sugar$^+$, 25.2); 167 (30.4); 166 (17.2); 165 (Pur$^+$, 5.4); 157 (13.7); 139 (100.0)	290 (1.5×10^4); 282 (1.5×10^4); 215 (1.0×10^4)	2.08 (s, 3H); 2.12 (s, 3H); 2.15 (s, 3H); 2.72 (s, 3H); 4.78–4.40 (m, 3H); 5.70 (t, 1H); 6.00 (t, 1H); 6.25 (d, 1H); 8.20 (s, 1H); 8.73 (s, 1H)	11.7; 20.3; 20.5; 20.7; 63.0; 70.6; 73.0; 80.3; 86.4; 131.8; 141.1; 147.8; 152.1; 162.1; 169.2; 169.5; 170.2	**1**	160–162°	163–164°[7]	40
4	A (54 h)	5a	57	0.68 (100)	440 (3.6); 439 (M^+, 13.8); 259 (Sugar$^+$, 20.3); 210 (Pur$^+$ + CH_2O, 3.0); 183 3.0); 182 (15.8); 181 (36.4); 180 (Pur$^+$, 6.2); 157 (14.7); 139 (100.0)	308 (1.0×10^4); 244 (1.4×10^4); 216 (1.4×10^4)	2.08 (s, 3H); 2.12 (s, 3H); 2.13 (s, 3H); 2.62 (s, 3H); 4.40 (m, 3H); 5.03 (s, 2H); 5.78 (t, 1H); 5.91 (t, 1H); 6.01 (d, 1H); 7.78 (s, 1H)	11.6; 20.4; 20.6; 20.7; 63.0; 70.5; 72.8; 79.8; 86.2; 125.9; 138.3; 149.8; 159.0; 162.6; 169.3; 169.6; 170.5	**5b**	184–185°	183°[5]	33
6	B (23 h)	7a	27 (56 net)	0.45 (70)	460 (M^+, 1.3); 458 (M^+, 3.1); 259 (Sugar$^+$, 35.1); 203 (3.0); 202 (2.5); 201 (9.3); 200 (4.8); 199 (Pur$^+$, 2.8); 157 (10.7); 139 (100.0)	304.5 (7.1×10^3); 263 (1.1×10^4); 234.5 (1.5×10^4)	2.09 (s, 3H); 2.10 (s, 3H); 2.15 (s, 3H); 2.65 (s, 3H); 4.39 (m, 3H); 5.65 (t, 1H); 5.99 (t, 1H); 6.08 (d, 1H); 8.13 (s, 1H)	14.8; 20.4; 20.5; 20.7; 62.7; 70.1; 72.9; 80.0; 87.1; 129.0; 142.3; 151.2; 151.9; 167.3; 169.2; 169.4; 170.2	**7b**	179–181°	181°[21]	13 (28 net)
6	A (70 h)	8a	54	0.50 (100)	470 (M^+, 10.4); 259 (Sugar$^+$, 20.6); 241 (Pur$^+$ + CH_2O, 2.2); 213 (15.6); 212 (20.0); 211 (Pur$^+$, 2.6); 199 (1.3); 197 (3.6); 165 (Pur$^+$—SCH_2, 3.0); 157 (11.3); 139 (100.0)	306 (7.2×10^3); 260 (1.5×10^4); 226 (8.0×10^3)	2.09 (s, 3H); 2.14 (s, 6H); 2.64 (s, 3H); 2.69 (s, 3H); 4.38 (m, 3H); 5.68 (t, 1H); 6.00 (t, 1H); 6.11 (d, 1H); 7.95 (s, 1H)	14.1; 14.7; 20.4; 20.5; 20.7; 62.9; 70.3; 73.0; 80.0; 86.7; 129.1; 139.9; 148.7; 162.0; 166.1; 169.2; 169.4; 170.3	**8b**	148–151°	150–155°[15]	28
9	A (43 h)	10a	52	0.56 (100)	441 (0.8); 440 (2.1); 439 (M^+, 8.5); 259 (Sugar$^+$, 11.2); 210 (Pur$^+$ + CH_2O, 5.7); 183 (4.1); 182 (22.4); 181 (43.8); 180 (Pur$^+$, 7.1); 157 (10.7); 139 (100.0)	273 (1.1×10^4); 236 (1.9×10^4)	2.07 (s, 3H); 2.10 (s, 3H); 2.13 (s, 3H); 2.57 (s, 3H); 4.36 (m, 3H); 5.74 (t, 1H); 6.15–5.85 (m, 4H); 7.79 (s, 1H)	14.5; 20.4; 20.5; 20.7; 62.9; 70.2; 73.0; 79.6; 87.1; 117.6; 138.1; 150.2; 155.0; 166.7; 169.3; 169.4; 170.4	**10b**	222–224°	222–223°[22]	20

[a] On silica gel; value in brackets is the % of ethyl acetate in hexane.



Scheme **B**

a photoinduced alkylthiolation. The dihalogenated nucleoside **6** was converted to protected 2-iodoadenosine **9** by treatment with ethanolic ammonia at ice/salt bath temperatures followed by reacetylation of the product with acetic anhydride and pyridine[20]. Photolysis of **9** in the presence of dimethyl disulfide gave **10a** (52%) which was easily deprotected and purified by H.P.L.C. on Amberlite XAD-4 resin. This procedure is far superior (five to ten times in overall yields) to previously used methods involving ring closure of imidazole derivatives.

In summary, we have developed a highly efficient methodology for the synthesis of methylmercaptopurine nucleosides. The utility of the procedure was demonstrated by the syntheses of five known methylmercaptopurine compounds. In each case the overall yield was significantly improved. The methodology has generality and can be extended to include a wide variety of thioalkylated heterocyclic systems.

Melting points are uncorrected and were determined on a Thomas-Hoover melting point apparatus fitted with a microscope. Nuclear magnetic resonance spectra were recorded on JEOL Model FX90Q and Bruker Model WM360 Pulse Fourier transform spectrometers. Mass spectra at 30 eV were obtained on a Hewlett-Packard 5985 G.C.-mass spectrometer. Preparative layer chromatography employed EM silica gel PF254 plates activated for 3 h at 135°C.

Photoinduced Thioalkylation; Procedure A:
A solution of the halogenated nucleoside (0.4 mmol) in dry dimethyl disulfide (60 ml) [or in dry dimethyl disulfide (2 ml) and acetonitrile (40 ml)] is transferred to the pyrex immersion well of a quartz photochemical reactor. The system is purged with nitrogen, and photolysis is carried out using a 450 W mercury U.V. source with a Vycor glass filter. When the photolysis is completed, the solvent is removed under reduced pressure (50°C bath temperature). The residue is purified by preparative layer chromatography with ethyl acetate/hexane as the developing solvent.

Photoinduced Thioalkylation; Procedure B:
A solution of the halogenated nucleoside (0.4 mmol) in dry dimethyl disulfide (60 ml) [or in dry dimethyl disulfide (2 ml) and acetonitrile (40 ml)] is transferred to a quartz tube, and purged with nitrogen. Photolysis is carried out in a Rayonet photochemical reactor using light with the principal wavelength of 253.7 nm. The reaction is worked up and purified as described in Procedure A.

6-Iodo-9β-(2′,3′,5′-tri-*O*-acetyl-D-ribofuranosyl)-purine (2):
This product is prepared from adenosine in 52% yield using a modification of a procedure previously described by us[17].

2-Amino-6-chloro-9β-(2′,3′,5′-tri-*O*-acetyl-D-ribofuranosyl)-purine (4):
This compound is prepared from guanosine in 75% yield by established literature procedures[18].

2-Iodo-6-chloro-9β-(2′,3′,5′-tri-*O*-acetyl-D-ribofuranosyl)-purine (6):
This dihalogenated nucleoside is prepared in 83% yield by treatment of **4** thermally with *n*-pentyl nitrite, diiodomethane, and acetonitrile[19].

2-Iodo-6-amino-9β-(2′,3′,5′-tri-*O*-acetyl-D-ribofuranosyl)-purine (9):
This compound is prepared in 78% yield by treatment of **6** with enthanolic ammonia followed by reacetylation[20].

Deprotection of Alkylthiolated Nucleosides; General Procedure:
To dry ethanol (50 ml) saturated with ammonia gas at ice/salt bath temperatures is added the protected nucleoside (0.2 mmol). The solution is stirred at this temperature for 1 h and then at 25°C for 23 h. The solvent is removed under reduced pressure and the residue is purified by reversed-phase H.P.L.C. on Amberlite XAD-4 resin using 60% water/ethanol as the eluting solvent. The deprotected nucleosides are crystallized from water to give the following known nucleosides in ~80–90% yields: 6-methylmercapto-9β-(D-ribofuranosyl)-purine (**1**)[7], 2-amino-6-methylmercapto-9β-(D-ribofuranosyl)-purine (**5b**)[5], 2-methylmercapto-6-chloro-9β-(D-ribofuranosyl)-purine (**7b**)[21], 2,6-dimethylmercapto-9β-(D-ribofuranosyl)-purine (**8b**)[15], and 2-methylmercapto-6-amino-9β-(D-ribofuranosyl)-purine (**10b**)[22].

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[1] Henderson, J.F., Paterson, A.R.P., Caldwell, I.C., Paul, B., Chan, M.C., Lau, K.F. *Cancer Chemother. Rep. Part* 2 **1972**, *3*, 71.

[2] Miller, R.L., Adamczyk, D.L., Miller, W.H., Koszalka, G.W., Rideout, J.L., Beaclam, III, L.M., Chao, E.Y., Haggerty, J.J., Krenitsky, T.A., Elion, G.B. *J. Biol. Chem.* **1979**, *254*, 2346.

[3] Henderson, J.F., Smith, C.M., Snyder, F.F., Zombor, G. *Ann. N.Y. Acad. Sci.* **1975**, *255*, 489.

[4] Sartorelli, A.C., Shansky, C.W., Rosman, M. *Cancer* **1975**, *36*, 2445.

[5] Noell, C.W., Robins, R.K. *J. Med. Chem.* **1962**, *5*, 1074.

[6] Gough, G., Maguire, H., Penglis, F. *Mol. Pharmacol.* **1972**, *8*, 170.

[7] Fox, J.J., Wempen, I., Hampton, A., Doerr, I.L. *J. Am. Chem. Soc.* **1958**, *80*, 1669.

[8] Reist, E.J., Benitez, A., Goodman, L., Baker, B.R., Lee, W.W. *J. Org. Chem.* **1962**, *27*, 3274.

[9] Perini, F., Hampton, A. *J. Heterocyclic Chem.* **1970**, *7*, 969.

[10] Meyer, R.B., Shuman, D.H., Robins, R.K., Bauer, R.J., Dimmitt, M.K., Simon, L.N. *Biochemistry* **1972**, *11*, 2704.

[11] Gerster, J.F., Jones, J.W., Robins, R.K. *J. Org. Chem.* **1963**, *28*, 945.

[12] Meyer, Jr., R.B., Shuman, D.A., Robins, R.K. *J. Am. Chem. Soc.* **1974**, *96*, 4962.

[13] Meyer, Jr., R.B., Uno, H., Robins, R.K., Simon, L.N., Miller, J.P. *Biochemistry* **1975**, *14*, 3315.

[14] Yamaaji, N., Suda, K., Kato, M. *Nucleic Acid Research Symposium Ser.* **1976**, *2*, 59.

[15] Marumoto, R., Yoshioka, Y., Miyashita, O., Shima, S., Imai, K., Kawazo, K., Honjo, M. *Chem. Pharm. Bull.* **1975**, *23*, 759.

[16] Imai, K., Marumoto, R., Kobayashi, K., Yoshioka, Y., Toda, J. *Chem. Pharm. Bull.* **1971**, *19*, 576.

[17] Nair, V., Richardson, S.G. *J. Org. Chem.* **1980**, *45*, 3969.

[18] Robins, M.J., Uznanski, B. *Can. J. Chem.* **1981**, *59*, 2601.

[19] Nair, V., Richardson, S.G. *Synthesis* **1982**, 670.

[20] Nair, V., Young, D.A. *J. Org. Chem.* **1985**, *50*, 406.

[21] Sato, T. in: *Synthetic Procedures in Nucleic Acid Chemistry*, Vol. 1, Zorbach, W.W., Tipson, R.S., Eds., Interscience, New York, 1968, p. 264.

[22] Ishido, Y., Kikuchi, Y., Sato, T. *Nippon Kagaku Zasshi* **1965**, *86*, 240.