Purines. X.[1] Reactivities of Methyl Groups on 9-Phenylpurines: Condensation with an Aldehyde or an Ester, and Oxidation with Selenium Dioxide

Ken-ichi TANJI,* Ranko SATOH, and Takeo HIGASHINO

School of Pharmaceutical Sciences, University of Shizuoka, 395 Yada, Shizuoka 422, Japan. *Received June 28, 1991*

The condensation of a methyl group at the 6- or 8-position on the 9*H*-purine ring with benzaldehyde and ethyl benzoate in the presence of sodium hydride occurred to give the styryl- (4a, b) and phenacyl-9*H*-purines (5a, b and 6a ,b). Conversion of the methyl group into a formyl group was achieved by treatment with selenium dioxide in dioxane, giving the 9*H*-purinecarboxaldehydes (7a, b and 8a, b).

Keywords methyl-9*H*-purine; condensation; oxidation; 9*H*-purinecarboxaldehyde; phenacyl-9*H*-purine; styryl-9*H*-purine

It is well known that methyl groups attached to the α and γ positions of *N*-heteroarenes can be easily converted into functionalized carbon chains by condensation with aldehydes[2] and esters,[3] nitrosation with alkyl nitrite[4] in the presence of base, and oxidation with selenium dioxide.[5] In connection with such reactivity of the methyl group on *N*-heteroarenes, we examined the conversion of methyl groups at the 2-, 6-, and 8-positions on the 9*H*-purine ring into styryl, phenacyl, and formyl groups by condensation and oxidation.

Hayashi *et al.* already reported[6] that 8-methyl-9-phenyl-9*H*-purine (**3a**) underwent condensation with aromatic aldehydes in the presence of base to give 8-alkenyl-9-phenyl-9*H*-purines. We investigated the application of this condensation to 2- (**1**) and 6-methyl-9-phenyl-9*H*-purines (**2a, b**).

When a solution of 6-methyl-9-phenyl-9*H*-purine (**2a**) and benzaldehyde in the presence of sodium hydride (NaH) in tetrahydrofuran (THF) was refluxed for 3 h, 9-phenyl-6-styryl-9*H*-purine (**4a**) was obtained in 69% yield. Similarly, condensation of 6-methyl-2-methoxy-9-phenyl-9*H*-purine (**2b**) with benzaldehyde gave the styryl derivative (**4b**). However, attempts to condense of **1** with benzaldehyde resulted in the recovery of the starting **1**.

Moreover, 6- (**2a, b**) and 8-methyl-9-phenyl-9*H*-purines (**3a, b**) reacted with ethyl benzoate in the presence of NaH in THF, giving 6- (**5a, b**) and 8-phenacyl-9-phenyl-9*H*-purines (**6a, b**) in satisfactory yields (Table I). In the case of **1**, condensation failed to give the expected product.

The phenacylpurines (**5a, b** and **6a, b**) were found to exist as a single tautomer (**5'a**) or as a mixture of the tautomers (**5'b** and **6'a, b**) by proton nuclear magnetic resonance (^{1}H-NMR) spectrometry. The relative ratio of the keto–enol tautomers was calculated from the integration ratios of enolic and methylene proton signals of the phenacyl-9*H*-purines (**5a, b** and **6a, b**) in the ^{1}H-NMR spectra (Chart 1).

In order to convert a methyl group on the 9*H*-purine ring into a formyl group, the methyl-9*H*-purines (**1**, **2** and **3**) were subjected to oxidation with selenium dioxide. Compounds **2a, b** and **3a, b** were smoothly oxidized with selenium dioxide in dioxane, resulting in the formation of the corresponding 9*H*-purinecarboxaldehydes (**7a, b** and **8a, b**). Oxidation of **1** with selenium dioxide did not proceed.

In summary, we have shown that methyl groups at the

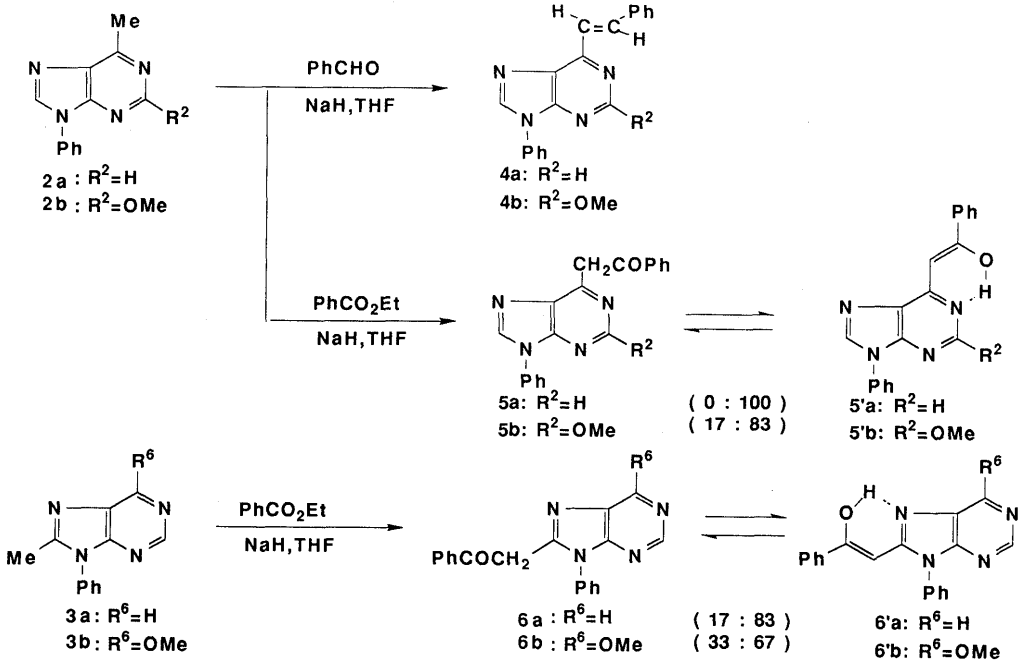

Chart 1

TABLE I. Yields, IR Spectral Data, Melting Points, and Elemental Analyses for **4**—**8**

Compd.	Yield (%)	IR ν_{max}^{KBr} (cm^{-1})	mp (°C)	Formula	Analysis (%) Calcd			Found		
					C	H	N	C	H	N
4a	69		142	$C_{19}H_{14}N_4$	72.86	4.82	17.02	73.15	4.91	17.06
4b	78		226—227	$C_{20}H_{16}N_4O$	76.49	4.73	18.78	76.72	4.73	18.68
5a	40	1660 (C=O)	222—223[a]							
5b	77	1730 (C=O)	176—177	$C_{20}H_{16}N_4O_2$	69.75	4.68	16.27	70.29	4.71	16.08
6a	67	1720 (C=O)	174—175	$C_{19}H_{14}N_4O$	72.60	4.49	17.83	72.79	4.43	17.83
6b	77	1730 (C=O)	180—181	$C_{20}H_{16}N_4O_2$	69.75	4.68	16.27	69.82	4.68	16.30
7a	38	1710 (C=O)	198—200	$C_{12}H_8N_4O$	64.29	3.60	24.99	64.33	3.55	24.79
7b	79	1710 (C=O)	177—178	$C_{13}H_{10}N_4O_2$	61.41	3.96	22.04	61.63	4.00	22.10
8a	38	1700 (C=O)	202—204	$C_{12}H_8N_4O$	64.29	3.60	24.99	64.58	3.67	24.83
8b	57	1690 (C=O)	190—192	$C_{13}H_{10}N_4O$	61.41	3.96	22.04	61.48	4.00	22.09

a) Lit.[9] mp 223.5—224.5 °C.

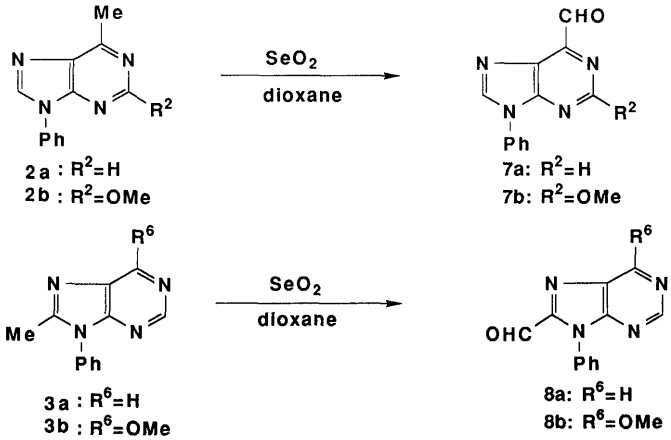

Chart 2

6- and 8-positions on the 9*H*-purine ring can easily be converted into styryl, phenacyl, and formyl groups by condensation and oxidation.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with a Jasco A-102 diffraction grating IR spectrometer. ^{1}H-NMR spectra were taken at 60 MHz and 23 °C with a Hitachi R-24B. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane as an internal standard. The following abbreviations are used; s = singlet, br = broad, m = multiplet, d = doublet.

6-Chloro-2-methyl-9-phenyl-9*H*-purine A mixture of 5-amino-4,6-dichloro-2-methylpyrimidine[7] (12 g, 0.067 mol), aniline (6.12 g, 0.067 mol), concentrated HCl (2.5 ml), EtOH (25 ml), and H_2O (170 ml) was refluxed for 3 h. The precipitate, 5-amino-4-anilino-6-chloro-2-methylpyrimidine, was filtered off. Yield 12 g. A mixture of the crude 5-amino-4-anilino-6-chloro-2-methylpyrimidine (12 g, 0.051 mol), ethyl orthoformate (60 ml), and acetic anhydride (60 ml) was refluxed for 3 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O, made alkaline with Na_2CO_3, and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give 6-chloro-2-methyl-9-phenyl-9*H*-purine as colorless needles, mp 178—180 °C. Yield 11 g (67%). *Anal.* Calcd for $C_{12}H_9ClN_4$: C, 58.91; H, 3.71; N, 22.90. Found: C, 59.10; H, 3.71; N, 22.93. ^{1}H-NMR ($CDCl_3$): 2.76 (3H, s, C^2-CH_3), 7.32—7.81 (5H, m, N^9-Ph), 8.24 (1H, s, C^8-H).

2-Methyl-9-phenyl-9*H*-purine (1) A catalyst, prepared from 1% $PdCl_2$ (30 ml) in aqueous HCl and active carbon (1.2 g), was added to a solution of 6-chloro-2-methyl-9-phenyl-9*H*-purine (4.2 g, 0.017 mol) and concentrated NH_4OH (3 ml) in MeOH (100 ml). The mixture was shaken with hydrogen until 0.017 mol of hydrogen had been absorbed. The catalyst was filtered off. The solvent of the filtrate was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with benzene–$CHCl_3$ (1 : 1) and recrystallized from benzene to give **1** as colorless needles, mp 127—128 °C. Yield 2.7 g (75%). *Anal.* Calcd for $C_{12}H_{10}N_4$: C, 68.55; H, 4.79; N, 26.65. Found: C, 68.85; H, 4.75; N, 26.25. ^{1}H-NMR ($CDCl_3$): 2.79 (3H, s, C^2-CH_3), 7.25—7.78 (5H, m, N^9-Ph), 8.14 (1H, s, C^8-H), 8.96 (1H, s, C^6-H).

2-Chloro-6-methyl-9-phenyl-9*H*-purine A mixture of 5-amino-2,4-dichloro-6-methylpyrimidine[8] (19 g, 0.11 mol), aniline (10.2 g, 0.11 mol), concentrated HCl (4.5 ml), EtOH (45 ml), and H_2O (290 ml) was refluxed for 3 h. The precipitate, 5-amino-4-anilino-2-chloro-6-methylpyrimidine, was filtered off. Yield 23 g. A mixture of the crude 5-amino-4-anilino-2-chloro-6-methylpyrimidine (23 g, 0.098 mol), ethyl orthoformate (120 ml), and acetic anhydride (120 ml) was refluxed for 3 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O, made alkaline with Na_2CO_3 and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give 2-chloro-6-methyl-9-phenyl-9*H*-purine as colorless needles, mp 204 °C. Yield 8 g (30%). *Anal.* Calcd for $C_{12}H_9ClN_4$: C, 58.90; H, 3.71; N, 22.90. Found: C, 58.68; H, 3.65; N,

TABLE II. ^{1}H-NMR Spectral Data for **4**—**8**

Compd.	^{1}H-NMR ($CDCl_3$) δ
4a	7.16—7.85 (11H, m, N^9-Ph and CH=CHPh), 8.26 (1H, s, C^8-H), 8.39 (1H, d, J = 16.0 Hz, CH=CHPh), 8.79 (1H, s, C^2-H)
4b	4.08 (3H, s, OCH_3), 7.25—7.95 (11H, m, N^9-Ph and CH=CHPh), 8.12 (1H, s, C^8-H), 8.35 (1H, d, J = 16.0 Hz, CH=CHPh)
5a	6.80 (1H, s, CH=C(OH)Ph), 7.28—7.81 (8H, m, aromatic H), 7.81—8.12 (2H, m, aromatic H), 8.13 (1H, s, C^8-H), 8.43 (1H, s, C^2-H), 14.70—16.13 (1H, br, CH=C(OH)Ph)
5b	3.99 (3H, s, OCH_3), 4.78 (1/3H, s, CH_2COPh), 6.69 (5/6H, s, CH=C(OH)Ph), 7.25—7.78 (8H, m, aromatic H), 7.80—8.00 (2H, m, aromatic H), 7.96 (1H, s, C^8-H), 14.58—15.50 (5/6H, br, CH=C(OH)Ph)
6a	4.57 (1/3H, s, CH_2COPh), 5.97 (5/6H, s, CH=C(OH)Ph), 7.22—7.93 (10H, m, aromatic H), 8.82 (1H, s, C^6-H or C^2-H), 8.89 (1H, s, C^6-H or C^2-H), 11.35—13.46 (5/6H, br, CH=C(OH)Ph)
6b	4.21 (3H, s, OCH_3), 4.56 (2/3H, s, CH_2COPh), 5.97 (2/3H, s, CH=C(OH)Ph), 7.31—7.87 (10H, m, aromatic H), 8.45 (2/3H, s, C^2-H), 8.49 (1/3H, s, C^2-H), 11.15—12.26 (2/3H, br, CH=C(OH)Ph)
7a	7.40—7.88 (5H, m, N^9-Ph), 8.57 (1H, s, C^8-H), 9.20 (1H, s, C^2-H), 10.62 (1H, s, CHO)
7b	4.10 (3H, s, OCH_3), 7.31—7.79 (5H, m, N^9-Ph), 8.31 (1H, s, C^8-H), 10.34 (1H, s, CHO)
8a	7.23—7.72 (5H, m, N^9-Ph), 8.02 (1H, s, C^2-H), 8.33 (1H, s, C^6-H), 10.01 (1H, s, CHO)
8b	4.23 (3H, s, OCH_3), 7.24—7.77 (5H, m, N^9-Ph), 8.05 (1H, s, C^2-H), 9.92 (1H, s, CHO)

22.77. ^{1}H-NMR ($CDCl_3$): 2.86 (3H, s, C^6-CH_3), 7.20—7.74 (5H, m, N^9-Ph), 8.20 (1H, s, C^8-H).

6-Methyl-2-(methylthio)-9-phenyl-9*H*-purine A solution of 2-chloro-6-methyl-9-phenyl-9*H*-purine (2 g, 8.2 mmol) and 15% aqueous NaSMe (9 g, 18.6 mmol) in *N*,*N*-dimethylformamide (DMF) (5 ml) was heated at 100 °C for 3 h. The mixture was diluted with H_2O and extracted with benzene. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give 6-methyl-2-(methylthio)-9-phenyl-9*H*-purine as colorless needles, mp 140—144 °C. Yield 1.6 g (76%). *Anal.* Calcd for $C_{13}H_{12}N_4S$: C, 60.94; H, 4.69; N, 21.88. Found: C, 61.06; H, 4.70; N, 21.84. ^{1}H-NMR ($CDCl_3$): 2.57 (3H, s, C^6-CH_3 or C^2-CH_3), 2.78 (3H, s, C^6-CH_3 or C^2-CH_3), 7.28—7.74 (5H, m, N^9-Ph), 8.07 (1H, s, C^8-H).

6-Methyl-9-phenyl-9*H*-purine (2a) A mixture of 6-methyl-2-(methylthio)-9-phenyl-9*H*-purine (1.6 g, 6.3 mmol), Raney Ni (5 g), concentrated HCl (0.5 ml), and EtOH (10 ml) was refluxed for 4 h. The Raney Ni was filtered off and the solvent of the filtrate was removed under reduced pressure. The residue was diluted with H_2O, made alkaline with Na_2CO_3, and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give **2a** as colorless needles, mp 155—156 °C. Yield 1.1 g (84%). *Anal.* Calcd for $C_{12}H_{10}N_4$: C, 68.55; H, 4.79; N, 26.65. Found: C, 68.86; H, 4.77; N, 26.06. ^{1}H-NMR ($CDCl_3$): 2.90 (3H, s, C^6-CH_3), 7.35—7.86 (5H, m, N^9-Ph), 8.29 (1H, s, C^8-H), 8.93 (1H, s, C^2-H).

6-Methyl-2-methoxy-9-phenyl-9*H*-purine (2b) A solution of 2-chloro-6-methyl-9-phenyl-9*H*-purine (8 g, 0.033 mol) and NaOMe (3.56 g, 0.066 mol) in MeOH (20 ml) was refluxed for 1 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give **2b** as colorless needles, mp 150 °C. Yield 7 g (89%). *Anal.* Calcd for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 64.85; H, 5.03; N, 23.21. ^{1}H-NMR ($CDCl_3$): 2.80 (3H, s, C^6-CH_3), 4.00 (3H, s, OCH_3), 7.30—7.90 (5H, m, N^9-Ph), 8.10 (1H, s, C^8-H).

8-Methyl-6-methoxy-9-phenyl-9*H*-purine (3b) A solution of 6-chloro-8-methyl-9-phenyl-9*H*-purine[6] (3 g, 0.012 mol) and NaOMe (1.3 g, 0.024 mol) in MeOH (10 ml) was refluxed for 1 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give **3b** as colorless needles, mp 178—179 °C. Yield 2.8 g (95%). *Anal.* Calcd for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 65.09; H, 5.06; N, 23.01. ^{1}H-NMR ($CDCl_3$): 2.49 (3H, s, C^8-Me), 4.15 (3H, s, OCH_3), 7.21—7.61 (5H, m, N^9-Ph), 8.28 (1H, s, C^2-H).

General Procedure for the Reaction of 6-Methyl-9-phenyl-9*H*-purines (2a, b) with Benzaldehyde A solution of a 6-methyl-9-phenyl-9*H*-purine (**2a**, **b**) (1 mmol), benzaldehyde (0.13 g, 1.2 mmol), and 60% (in oil) NaH (50 mg, 1.2 mmol) in THF (15 ml) was refluxed for 3 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give the product (**4a**, **b**) as pale yellow needles.

General Procedure for the Reaction of Methyl-9-phenyl-9*H*-purines (2a, b and 3a, b) with Ethyl Benzoate A solution of a methyl-9-phenyl-9*H*-purine (**2a**, **b** and **3a**, **b**) (1 mmol), ethyl benzoate (0.3 g, 2 mmol), and 60% (in oil) NaH (80 mg, 2 mmol) in THF (10 ml) was refluxed for 3 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give the product (**5a**, **b** and **6a**, **b**) as colorless needles.

General Procedure for the Oxidation of Methyl-9-phenyl-9*H*-purines (2a, b and 3a, b) with Selenium Dioxide A solution of a methyl-9-phenyl-9*H*-purine (**2a**, **b** and **3a**, **b**) (1 mmol) and selenium dioxide (1 mmol) in dioxane (10 ml) was refluxed for 1 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude material was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give the product (**7a**, **b** and **8a**, **b**) as colorless needles.

References

1) Purines. IX: K. Tanji and T. Higashino, *Heterocycles*, **30**, 435 (1990).
2) *a*) C. E. Loader and C. J. Timmons, *J. Chem. Soc.* (*C*), **1967**, 1343; *b*) W. Borshe and A. Klein, *Justus Liebigs Ann. Chem.*, **548**, 74 (1941).
3) *a*) H. Yamanaka, H. Abe, and T. Sakamoto, *Chem. Pharm. Bull.*, **25**, 3334 (1977); *b*) R. Levine, D. A. Dimmig, and W. M. Kadunce, *J. Org. Chem.*, **39**, 3834 (1974).
4) H. Yamanaka, H. Abe, T. Sakamoto, and A. Kamata, *Chem. Pharm. Bull.*, **25**, 1821 (1977).
5) T. Sakamoto, T. Sakasai, and H. Yamanaka, *Chem. Pharm. Bull.*, **29**, 2485 (1981).
6) E. Hayashi, N. Shinada, Y. Matsuoka, and Y. Miwa, *Yakugaku Zasshi*, **99**, 207 (1979).
7) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, **1954**, 3832.
8) C. G. Overberger, I. C. Kogon, and W. J. Einstman, *J. Am. Chem. Soc.*, **76**, 1953 (1954).
9) E. Hayashi and N. Shimada, *Yakugaku Zasshi*, **99**, 201 (1979).