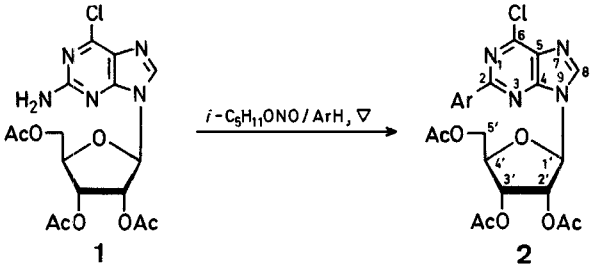
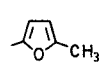
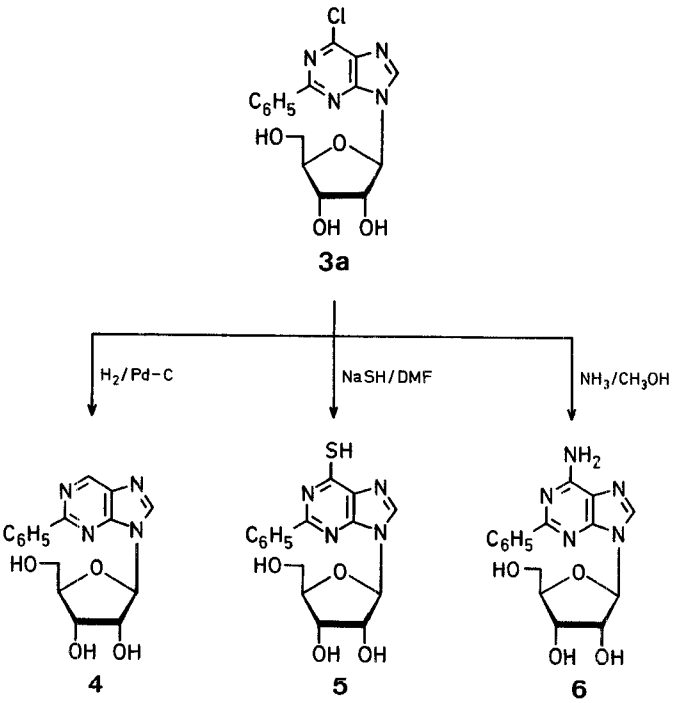
sylpurine (**1**)[8], readily accessible in two steps from guanosine, with an excess of isopentyl nitrite in the presence of copper(I) oxide. In a similar way, compound **1** was converted to 2-heteroarylpurine nucleosides **2b–d** in moderate yields. That the substitution had occurred at the α-position of the heteroaromatics was unambiguously proved by their ^{1}H-N.M.R. spectra (Table 1). No other positional isomers were obtained. Deacetylation of **2** was accomplished by treatment with methanolic ammonia at room temperature to give **3** in crystalline form in good yields (Table 2).



2,3	a	b	c	d
Ar				

These 6-chloropurine nucleosides **3** can be transformed to biologically interesting nucleosides. We therefore chose **3a** as a common intermediate and demonstrated several conversions of 6-chloro group to other derivatives. Hydrogenolysis of **3a** over palladium on carbon gave 2-phenylnebularine (**4**). Treatment of **3a** with sodium hydrosulfide in dimethylformamide afforded 2-phenyl-6-thioinosine (**5**). Compound **3a** was also converted to 2-phenyladenosine[2] (**6**) by treatment with methanolic ammonia at 70 °C.



A Convenient Method for the Synthesis of 2-Phenyl- and 2-Heteroarylpurine Nucleosides

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Among the several methods available for the synthesis of 2-substituted purine nucleosides, few studies have reported on the carbon-carbon bond formation reactions at the 2-position of the purine nucleosides. Methods reported so far involve the cyclization of appropriately substituted imidazole nucleosides[1,2,3], homolytic methylation[4], and nucleophilic substitution of a methanesulfonyl group at the 2-position of adenosine[5]. These methods have, however, some drawbacks such as unavailability of the starting materials and lack of synthetic versatility. We report herein a convenient procedure for the introduction of phenyl and heteroaryl groups at the 2-position of the 6-chloropurine nucleoside via the non-aqueous diazotization-substitution process[6,7].

6-Chloro-2-phenyl-9β-(2′,3′,5′-tri-*O*-acetyl)-D-ribo-furanosyl-purine (**2a**) was prepared by heating a benzene solution of 2-amino-6-chloro-9β-(2′,3′,5′-tri-*O*-acetyl)-D-ribofurano-

Table 1. 6-Chloro-2-phenyl- and 6-Chloro-2-heteroaryl-9β-(2′,3′,5′-tri-*O*-acetyl)-D-ribofuranosylpurines **2** prepared

Product	Reaction time [h]	Yield [%][a]	m.p. [°C]	M.S. *m/e* (rel. intens. %)	Molecular formula[b]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
2a	1	62	–[c]	488 (3), 490 (1)	$C_{22}H_{21}ClN_4O_7$ (488.9)	1.98, 2.12, 2.19 (3s, 3H each, OCO—CH_3); 4.4–4.53 (m, 3H, CH_2 + H-4′); 5.85 (t, 1H, J = 4.9 Hz, H-3′); 6.07–6.25 (m, 2H, H-1′ + H-2′); 7.48–7.54 (m, $3H_{arom}$); 8.22 (s, 1H, H-8); 8.48–8.57 (m, $2H_{arom}$)
2b	1	44	–[c]	494 (11), 496 (4)	$C_{20}H_{19}ClN_4O_7S$ (494.9)	2.02, 2.13, 2.18 (3s, 3H each, OCO—CH_3); 4.37–4.57 (m, 3H, CH_2 + H-4′); 5.85 (t, 1H, J = 4.9 Hz, H-3′); 6.0–6.17 (m, 2H, H-1′ + H-2′); 7.15 (dd, 1H, $J_{H-3'',H-4''}$ = 3.9 Hz, $J_{H-4'',H-5''}$ = 5.4 Hz); 7.27 (s, 1H, H-8); 7.5 (dd, 1H, $J_{H-3'',H-4''}$ = 3.9 Hz, $J_{H-3'',H-5''}$ = 1.5 Hz, H-5″); 8.11 (dd, 1H, $J_{H-3'',H-4''}$ = 3.9 Hz, $J_{H-3'',H-5''}$ = 1.5 Hz, H-3″)
2c	3	58	95–97°[d]	491 (28), 493 (10)	$C_{21}H_{22}ClN_5O_7$ (491.9)	2.05, 2.1, 2.16 (3s, 3H each, OCO—CH_3); 4.11 (s, 3H, N—CH_3); 4.34, 4.52 (m, 3H, CH_2 + 4-H′); 5.69 (t, 1H, J = 4.9 Hz, H-3′); 5.99–6.24 (m, 3H, H-1′ + H-2′ + H-4″); 6.79 (t, 1H, J = 2.2 Hz, H-5″); 7.26 (m, 1H, H-3″)
2d	6	56	–[c]	492 (60), 494 (23)	$C_{21}H_{21}ClN_4O_8$ (492.9)	2.02, 2.13, 2.17 (3s, 3H each, OCO—CH_3); 2.47 (s, 3H, =C—CH_3); 4.4–4.58 (m, 3H, CH_2 + H-4′); 5.87–6.22 (m, 4H, H-1′ + H-2′ + H-3′, H-4″); 7.37 (d, 1H, $J_{H-3'',H-4''}$ = 3.4 Hz, H-3″); 8.14 (s, 1H, H-8)

[a] Yield of isolated product.
[b] Satisfactory microanalyses obtained: C ±0.31, H ±0.37, N ±0.35; exception: **2d**, C +0.51.
[c] These compounds were obtained as foam.
[d] Recrystallized from ether.

Table 2. Deacetylated 2-Phenyl- and 2-Heteroarylpurine Nucleosides **3** prepared

Product	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b]	^{1}H-N.M.R. (DMSO-d_6 + D_2O/TMS_{int}) δ [ppm]
3a	81	210–213°[c] (CH_3OH)	$C_{16}H_{15}ClN_4O_4$ (362.8)	3.7 (m, 2H, CH_2); 4.06 (m, 1H, H-4′); 4.31 (t, 1H, J = 3.9 Hz, H-3′); 4.75 (t, 1H, J = 5.4 Hz, H-2′); 6.14 (d, 1H, J = 5.4 Hz, H-1′); 7.54–7.61 (m, $3H_{arom}$); 8.36–8.46 (m, $2H_{arom}$); 8.85 (s, 1H, H-8)
3b	87	>290° (CH_3OH)	$C_{14}H_{13}ClN_4O_4S$ (368.8)	3.7 (m, 2H, CH_2); 4.04 (m, 1H, H-4′); 4.3 (t, 1H, J = 3.9 Hz, H-3′); 4.73 (t, 1H, J = 5.4 Hz, H-2′); 6.05 (d, 1H, J = 5.4 Hz, H-1′); 7.25 (dd, 1H, $J_{H-3'',H-4''}$ = 3.9 Hz, $J_{H-4'',H-5''}$ = 5.4 Hz); 7.77 (dd, 1H, $J_{H-3'',H-5''}$ = 1.5 Hz); 8.01 (dd, 1H, $J_{H-3'',H-4''}$ = 3.9 Hz, $J_{H-3'',H-5''}$ = 1.5 Hz, H-3″); 8.8 (s, 1H, H-8)
3c	95	178–180° (CH_3OH—H_2O)	$C_{15}H_{16}ClN_5O_4$ (365.8)	3.71 (m, 2H, CH_2); 4.05 (m, 1H, H-4′); 4.07 (s, 3H, CH_3); 4.2 (t, 1H, J = 3.9 Hz, H-3′); 4.66 (t, 1H, J = 5.4 Hz, H-2′); 6.04 (d, 1H, J = 5.4 Hz, H-1′); 6.17 (dd, 1H, $J_{H-3'',H-4''}$ = 3.4 Hz, $J_{H-4'',H-5''}$ = 2.9 Hz, H-4″); 7.02–7.06 (m, 2H, H-3″, H-5″); 8.73 (s, 1H, H-8)
3d	90	179–181° (CH_3OH—H_2O)	$C_{15}H_{15}ClN_4O_5$ (366.8)	2.43 (s, 3H, CH_3); 3.7 (m, 2H, CH_2); 4.05 (m, 1H, H-4′); 4.27 (t, 1H, J = 3.9 Hz, H-3′); 4.66 (t, 1H, J = 5.4 Hz, H-2′); 6.06 (d, 1H, J = 5.4 Hz, H-3″); 8.79 (s, 1H, H-8)

[a] Yield of isolated product.
[b] Satisfactory microanalysis obtained: C ±0.39, H ±0.09, N ±0.4.
[c] Decomposition.

Thus, our new method provides a convenient access to 6-substituted 2-phenyl- and 2-heteroarylpurine nucleosides.

2-Phenyl- and 2-Heteroaryl-9β-(2′,3′,5′-tri-*O*-acetyl)-D-ribofuranosylpurines 2; General Procedure:
A solution of **1** (854 mg, 2 mmol) in benzene (50 ml), thiophene (10 ml), *N*-methylpyrrole (10 ml), or 2-methylfuran (10 ml), respectively, containing isoamyl nitrite (1 ml) and copper(I) oxide (286 mg) is heated under reflux for 1–3 h (Table 1), monitored by T.L.C., silica gel, eluent: chloroform (15)/ethanol (1). Insoluble materials are removed by filtration and the filtrate is evaporated to dryness under reduced pressure. The residue is purified by column chromatography over silica gel using chloroform containing ethanol (1–2%) as eluent.

Deacetylation Reaction 2 → 3; General Procedure:
Compound **2** (2 mmol) is treated with methanolic ammonia (40 ml, saturated at 0 °C) at room temperature for 3 h. The reaction mixture is concentrated to dryness under reduced pressure and the residue is crystallized from appropriate solvent (Table 2).

2-Phenylnebularine (4):
A solution of **3a** (300 mg, 0.83 mmol) in a mixture of ethanol (30 ml) and ethyl acetate (20 ml) containing triethylamine (0.5 ml) is hydrogenated over 10% palladium on carbon (20 mg) at 4.5 kg/cm² pressure. The suspension is filtered and the filtrate is evaporated. The residue is crystallized from aqueous methanol to give **4**; yield: 197 mg (73%); m.p. 181–182 °C.

$C_{16}H_{16}N_4O_4$ (328.3)	calc.	C 58.53	H 4.91	N 17.06
	found	58.15	4.68	16.76

^{1}H-N.M.R. (DMSO-d_6 + D_2O/TMS_{int}): δ = 3.72 (m, 2H, CH_2); 4.0 (m, 1H, H-4′); 4.33 (t, 1H, J = 3.9 Hz, H-3′); 4.8 (t, 1H, J = 5.4 Hz, H-2′); 6.17 (d, 1H, J = 5.4 Hz, H-1′); 7.46–7.6 (m, 3H_{arom}); 8.4–8.53 (m, 2H_{arom}); 8.8 (s, 1H, H-8); 9.24 ppm (s, 1H, H-6).

2-Phenyl-6-thioinosine (5):

To a solution of **3a** (250 mg, 0.69 mmol)) in dimethylformamide (2 ml) is added sodium hydrosulfide hydrate (150 mg, 2.7 mmol). The mixture is stirred for 2 h at room temperature and then neutralized with acetic acid. Evaporation of the solvent and purification of the residue by chromatography on silica gel using chloroform containing ethanol (8%) as eluent affords **5**; yield: 215 mg (87%); m.p. 156–158° (ethanol).

$C_{16}H_{16}N_4O_4S$	calc.	C 53.32	H 4.48	N 15.55
(360.4)	found	53.25	4.40	15.17

^{1}H-N.M.R. (DMSO-d_6 + D_2O/TMS_{int}): δ = 3.63 (m, 2H, CH_2); 3.98 (m, 1H, H-4′); 4.19 (t, 1H, J = 3.9 Hz, H-3′); 4.57 (t, 1H, J = 5.4 Hz, H-2′); 5.97 (d, 1H, J = 5.4 Hz, H-1′); 7.55–7.6 (m, 3H_{arom}); 8.06–8.14 (m, 2H_{arom}), 8.53 ppm (s, 1H, H-8).

2-Phenyladenosine (6):

A solution of **3a** (300 mg, 0.83 mmol) in methanolic ammonia (20 ml, saturated at 0°C) is heated at 70°C in a sealed glass container for 24 h. Evaporation of the solvent affords a residue which is recrystallized from ethanol to give **6**; yield: 239 mg (84%); m.p. 226–228°C (Lit.[2], m.p. 228–229°C).

^{1}H-N.M.R. (DMSO-d_6 + D_2O/TMS_{int}): δ = 3.68 (m, 2H, CH_2); 4.03 (m, 1H, H-4′); 4.28 (t, 1H, J = 3.9 Hz, H-3′); 4.76 (t, 1H, J = 5.4 Hz, H-2′); 6.02 (d, 1H, J = 5.4 Hz, H-1′); 7.42–7.49 (m, 3H_{arom}); 8.29–8.35 (m, 2H_{arom}); 8.38 ppm (s, 1H, H-8).

Received: May 1, 1984

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