Purines. VIII.[1] Reactions of 1-Benzoyl-1,6-dihydro-9-phenyl-9*H*-purine-6-carbonitrile (9-Phenylpurine Reissert Compound) with Acid, Bases, and Electrophiles

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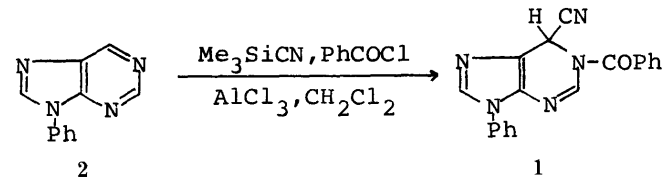
1-Benzoyl-1,6-dihydro-9-phenyl-9*H*-purine-6-carbonitrile (1, 9-phenylpurine Reissert compound) was hydrolyzed in an acid medium to give the ring fission product of the pyrimidine ring (3, 4). Alkaline hydrolysis of 1 gave 9-phenyl-9*H*-purine (2) and benzoic acid (5). The anion of 1 generated from 1 and sodium hydride in tetrahydrofuran underwent aromatization, resulting in the formation of 9-phenyl-9*H*-purine-6-carbonitrile (6) together with 2. The reaction of 1 with aromatic aldehydes in the presence of sodium hydride proceeded to give the 6-purinylmethyl benzoates (8a—c), together with 2 and 9. On the other hand, the reaction of 1 with 2,4-dinitrochlorobenzene in the presence of sodium hydride failed to give the corresponding 6-arylpurine, and the aromatization product 6 was obtained.

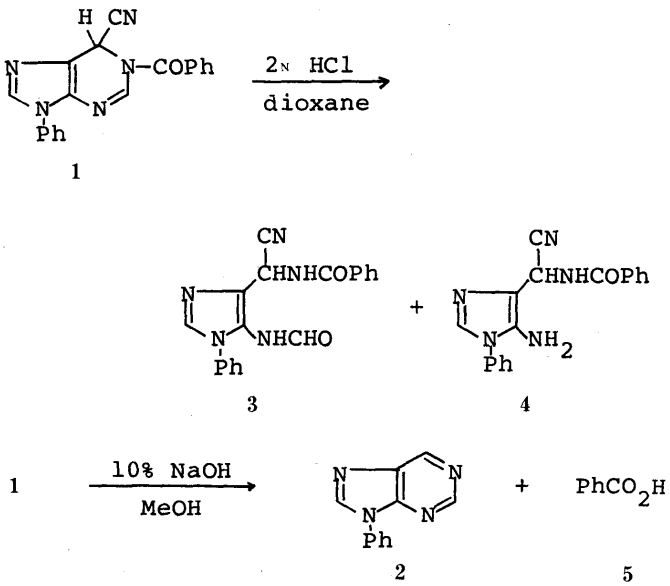
Keywords 9*H*-purine; Reissert compound; ring fission aromatization; Reissert compound anion; 9*H*-purin-6-ylmethyl benzoate

Recently, we elucidated the reactivities of 3-benzoyl-3,4-dihydro-4-quinazolinecarbonitrile (quinazoline Reissert compound),[2a,b] 3-benzoyl-3,4-dihydro-2-methyl-4-quinazolinecarbonitrile (2-methylquinazoline Reissert compound),[2c] and 5-benzoyl-4,5-dihydro-l-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile (pyrazolopyrimidine Reissert compound)[2d,e] with an acid, a base, sodium hydride, and electrophiles. Moreover, we reported a preparation of 1-benzoyl-1,6-dihydro-9-phenyl-9*H*-purine-6-carbonitrile (**1**, 9-phenylpurine Reissert compound)[2f] from the reaction of 9-phenyl-9*H*-purine (**2**) with trimethylsilyl cyanide and benzoyl chloride in the presence of aluminium chloride in dichloromethane.



2 1

Chart 1



1 3 4

1 2 5

Chart 2

In order to elucidate the reactivity of **1**, we examined the reaction of **1** with an acid, a base, sodium hydride, aromatic aldehydes, and an aryl halide. In the present paper, we describe the results obtained from the above reactions.

It was reported[2a] that hydrolysis of the quinazoline Reissert compound in an acid medium gave the ring fission product, 2-(2-aminophenyl)-2-benzamidoacetonitrile. On the other hand, the 2-methylquinazoline Reissert compound[2c] reacted with aqueous hydrochloric acid in a different way from that of the quinazoline Reissert compound, resulting in the formation of 4-(2-acetamidophenyl)-5-amino-2-phenyloxazole. When a solution of **1** and 2N hydrochloric acid in dioxane was stirred at room temperature, the ring fission took place in the same way as observed for the quinazoline Reissert compound, giving α-benzamido-4-(5-formamido-1-phenyl-1*H*-imidazole)acetonitrile (**3**), together with α-benzamido-4-(5-amino-1-phenyl-1*H*-imidazole)acetonitrile (**4**).

It has already been reported that the hydrolysis of quinazoline[2a] and 2-methylquinazoline[2c] Reissert compounds in an alkaline medium gave quinazoline and 2-methylquinazoline, respectively. Similarly, **1** smoothly reacted with 10% sodium hydroxide in methanol, resulting in the formation of 9-phenyl-9*H*-purine (**2**), together with benzoic acid (**5**).

It is well known that the anions of 1-benzoyl-1,2-dihydro-2-quinolinecarbonitrile (quinoline Reissert compound)[3] and 2-benzoyl-1,2-dihydro-l-isoquinolinecarbonitrile (isoquinoline Reissert compound)[4] undergo rearrangement through the aziridine intermediates in an intramolecular process, giving 2-benzoylquinoline and 1-benzoylisoquinoline, respectively. In contrast, that of the quinazoline Reissert compound[2a] undergoes aromatization, resulting in the formation of 4-quinazolinecarbonitrile, together with α-phenyl-4-quinazolinylmethyl benzoate and that of the 2-methylquinazoline Reissert compound[2c] undergoes both rearrangement and aromatization to give 4-benzoyl-2-methylquinazoline and 2-methyl-4-quinazolinecarbonitrile.

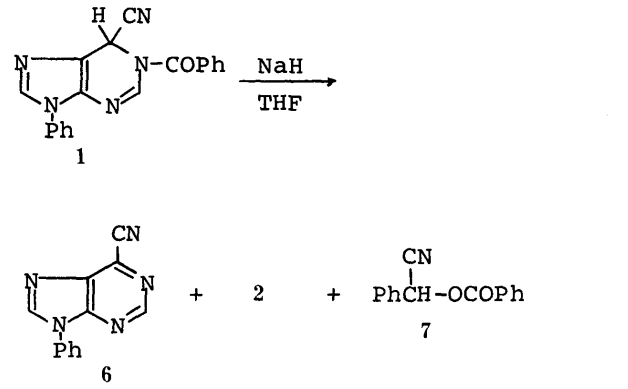
When a solution of **1** in the presence of sodium hydride in tetrahydrofuran (THF) was refluxed for 15 min, aromati-

zation proceeded in the same way as observed for the quinazoline Reissert compound,[2a] giving 9-phenyl-9*H*-purine-6-carbonitrile (**6**), together with 9-phenyl-9*H*-purine (**2**) formed by further reaction of the resulting benzaldehyde anion with another molecule of **1**. The proposed mechanism of this reaction is shown in Chart 3. A similar mechanism has been proposed by us [2a] for the reaction of the quinazoline Reissert compound with sodium hydride.

We have already succeeded in the introduction of carbon chains into the 4-position in the quinazoline ring by the reaction of the quinazoline and 2-methylquinazoline Reissert compounds[2a,c] with aromatic aldehydes and alkyl (aryl) halides. In order to introduce the carbon chains into the 6-position in the 9*H*-purine ring, we investigated the reaction of **1** with aromatic aldehydes and an aryl halide.

When a solution of **1** and benzaldehyde in the presence of sodium hydride in THF was refluxed for 30 min, α, 9-diphenyl-9*H*-purin-6-ylmethyl benzoate (**8a**) was obtained in 52% yield, together with **2** and *O*-benzoylbenzoin (**9a**). Similarly, **1** reacted with *p*-chlorobenzaldehyde to give α-(*p*-chlorophenyl)-9-phenyl-9*H*-purin-6-ylmethyl benzoate (**8b**). The reaction of **1** with *p*-methoxybenzaldehyde failed to give the desired compound under the same conditions as described above. However, when we used dioxane as a solvent instead of THF, the reaction proceeded to give the benzoate **8c**, together with **2** and **9c**.

Then we investigated the arylation of **1** with 2,4-dinitrochlorobenzene in the presence of sodium hydride in dioxane, but arylation did not take place and instead aromatization occurred to give **6**.



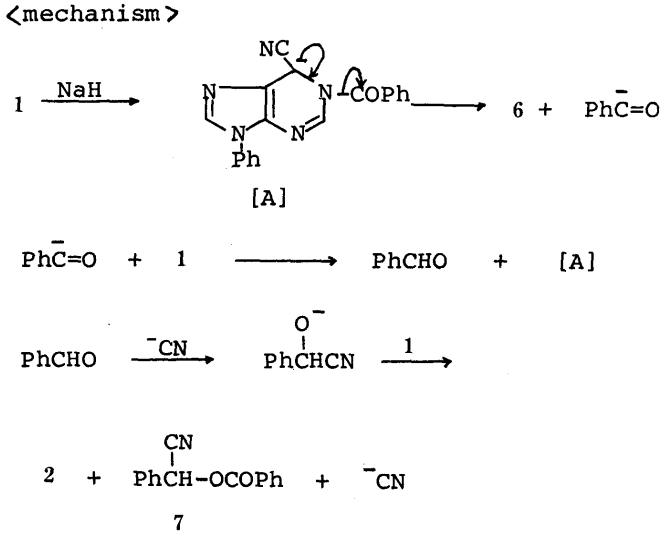


Chart 3

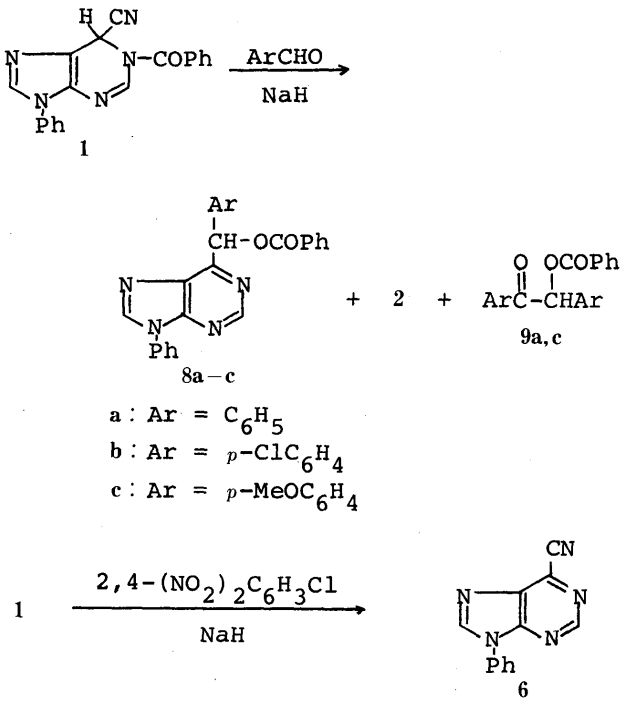


Chart 4

The experimental results may be summarized as follows. i) In the reaction with an acid, **1** reacted in the same way as observed for the quinazoline Reissert compound to give the ring fission product (**3**,**4**). ii) In the reaction with sodium hydride, **1** underwent aromatization, resulting in the formation of 9-phenyl-9*H*-purine-6-carbonitrile (**6**). iii) In the reaction with aromatic aldehydes, **1** smoothly reacted to give the 6-purinylmethyl benzoate (**8a—c**).

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with a Jasco A-102 diffraction grating IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz and 23°C with a Hitachi R-24B high-resolution ^{1}H-NMR spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, m = multiplet, br = broad. The exact mass measurements were made on a JEOL JMS-01SG-2 MS spectrometer combined with a JEC spectrum computer.

Acid Hydrolysis of 1-Benzoyl-1,6-dihydro-9-phenyl-9*H*-purine-6-carbonitrile (1) A mixture of **1** (327 mg, 1 mmol), 2N HCl (4 ml), and dioxane (4 ml) was stirred for 10 min and then poured onto ice-water. The reaction mixture was made alkaline with 5% aqueous NaOH and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was purified by SiO_2 column chromatography. The first fraction eluted from $CHCl_3$ gave α-benzamido-4-(5-amino-1-phenyl-1*H*-imidazole)acetonitrile (**4**) as pale yellow prisms from acetone–ether, mp 169—170°C. Yield 30 mg (10%). *Anal.* Calcd for $C_{18}H_{15}N_5O$: C, 68.12; H, 4.76; N, 22.07. Found: C, 67.90; H, 4.90; N, 21.45. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 3320 (NH), 2240 (CN), 1618 (C=O). ^{1}H-NMR ($CDCl_3$): 4.00—4.40 (2H, br, NH_2), 6.30 (1H, d, J=8.0 Hz, $CH<^{CN}_{NH}$), 7.00—7.65 (9H, m, aromatic H), 7.65—8.10 (2H, m, aromatic H), 9.00 (1H, d, J=8.0 Hz, NHCOPh). The second fraction gave α-benzamido-4-(5-formamido-1-phenyl-1*H*-imidazole)acetonitrile (**3**) as colorless needles from benzene, mp 168—169°C. Yield 197 mg (57%). *Anal.* Calcd for $C_{19}H_{15}N_5O_2$: C, 66.07; H, 4.38; N, 20.28. Found: C, 66.03; H, 4.37; N, 20.07. IR ν_{max}^{KBr} cm^{-1}: 3260 (NH), 1692, 1640 (C=O). ^{1}H-NMR ($CDCl_3$): 6.20 (1H, d, J=8.0 Hz, $CH<^{CN}_{NH}$),

7.00—7.65 (9H, m, aromatic H), 7.65—8.00 (2H, m, aromatic H), 8.28 (1H, s, NHCHO), 8.48 (1H, d, J=8.0 Hz, NHCOPh), 9.12 (1H, br, NHCHO).

Alkaline Hydrolysis of 1 A mixture of **1** (327 mg, 1 mmol), 10% aqueous NaOH (2 ml), and MeOH (5 ml) was stirred for 1 h at room temperature. The reaction mixture was neutralized with AcOH. 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 obtained from the $CHCl_3$ extract was purified by SiO_2 column chromatography using $CHCl_3$ as an eluant to give 9-phenyl-9*H*-purine (**2**), mp 158—159 °C (lit.[5] mp 159—160 °C). Yield 100 mg (50%). The aqueous layer was neutralized with 5% aqueous HCl and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from petroleum benzin to give benzoic acid (**5**). Yield 101 mg (83%).

Reaction of 1 with NaH A mixture of **1** (327 mg, 1 mmol), NaH (24 mg, 1 mmol), and THF (10 ml) was refluxed for 15 min. The reaction mixture was poured onto ice-water, neutralized with AcOH, and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was purified by SiO_2 column chromatography. The first fraction eluted from benzene gave *O*-benzoylmandelonitrile (**7**). Yield 62 mg (52%). The second fraction gave 9-phenyl-9*H*-purine-6-carbonitrile (**6**) as colorless needles from MeOH, mp 181—182 °C (lit.[6] mp 181—182 °C). Yield 45 mg (20%). The third fraction gave **1**. Yield 20 mg (6%). The fraction eluted from $CHCl_3$ gave **2**. Yield 80 mg (41%). Compound **7** was identified by comparison with an authentic specimen prepared by another route.[7]

Reaction of 1 with Benzaldehyde A mixture of **1** (320 mg, 0.98 mmol), benzaldehyde (106 mg, 1 mmol), NaH (24 mg, 1 mmol), and THF (5 ml) was refluxed for 30 min. The reaction mixture was poured onto ice-water, neutralized with AcOH, and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was purified by SiO_2 column chromatography. The first fraction eluted from benzene gave *O*-benzoylbenzoin (**9a**). Yield 30 mg (19%). The second fraction gave α, 9-diphenyl-9*H*-purin-6-ylmethyl benzoate (**8a**) as a colorless oil. Yield 206 mg (52%). MS m/z Calcd for $C_{25}H_{18}N_4O_2$: 406.1429. Observed: 406.1428. IR ν_{max}^{neat} cm^{-1}: 1720 (C=O). ^{1}H-NMR ($CDCl_3$): 7.20—8.00 (14H, m, aromatic H and $CH\langle^{Ph}_{OCOPh}$), 8.00—8.50 (2H, m, aromatic H), 8.35 (1H, s, C^8-H), 9.00 (1H, s, C^2-H). The fraction eluted from $CHCl_3$ gave **2**. Yield 25 mg (13%). Compound **9a** was identified by comparison with an authentic specimen prepared by another route.[8]

Reaction of 1 with *p*-Chlorobenzaldehyde A mixture of **1** (327 mg, 1 mmol), *p*-chlorobenzaldehyde (141 mg, 1 mmol), NaH (24 mg, 1 mmol), and THF (5 ml) was refluxed for 30 min. The same work-up of the reaction mixture as for **8a** gave α-(*p*-chlorophenyl)-9-phenyl-9*H*-purin-6-ylmethyl benzoate (**8b**) as colorless needles from petroleum benzin–benzene, mp 103—104 °C. Yield 271 mg (62%). *Anal.* Calcd for $C_{25}H_{17}ClN_4O_2$: C, 68.11; H, 3.89; N, 12.71. Found: C, 68.09; H, 3.90; N, 12.70. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). ^{1}H-NMR ($CDCl_3$): 7.00—8.00 (13H, m, aromatic H and $CH\langle^{Ar}_{OCOAr}$), 8.00—8.50 (2H, m, aromatic H), 8.24 (1H, s, C^8-H), 8.90 (1H, s, C^2-H).

Reaction of 1 with *p*-Methoxybenzaldehyde A mixture of **1** (327 mg, 1 mmol), *p*-methoxybenzaldehyde (136 mg, 1 mmol), NaH (24 mg, 1 mmol), and dioxane (5 ml) was refluxed for 1 h. The same work-up of the reaction mixture as for **8a** gave α-(*p*-methoxyphenyl)-9-phenyl-9*H*-purin-6-ylmethyl benzoate (**8c**) as a colorless oil in 30% yield (131 mg), together with **2** in 29% yield (56 mg) and **9c** in 30% yield (57 mg). Compound **8c**: MS m/z Calcd for $C_{26}H_{20}N_4O_3$: 436.1535. Observed: 436.1487. IR ν_{max}^{neat} cm^{-1}: 1715 (C=O). ^{1}H-NMR ($CDCl_3$): 3.70 (3H, s, OCH_3), 6.85 (2H, d, J=9.0 Hz, aromatic H), 7.10—7.90 (11H, m, aromatic H and $CH\langle^{Ar}_{OCOPh}$), 8.00—8.40 (2H, m, aromatic H), 8.25 (1H, s, C^8-H), 8.90 (1H, s, C^2-H). Compound **9c** was identified by comparison with an authentic specimen prepared by another route.[2e]

Reaction of 1 with 2,4-Dinitrochlorobenzene A mixture of **1** (327 mg, 1 mmol), 2,4-dinitrochlorobenzene (203 mg, 1 mmol), NaH (24 mg, 1 mmol), and dioxane (10 ml) was refluxed for 1 h. The reaction mixture was poured onto ice-water, neutralized with AcOH, and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was purified by SiO_2 column chromatography using benzene as an eluant to give 9-phenyl-9*H*-purine-6-carbonitrile (**6**). Yield 132 mg (60%).

References

1) Part VII: K. Tanji and T. Higashino, *Chem. Pharm. Bull.*, **36**, 1935 (1988).
2) *a*) T. Higashino, H. Kokubo, and E. Hayashi, *Chem. Pharm. Bull.*, **32**, 3900 (1984); *b*) *Idem, ibid.*, **33**, 950 (1985); *c*) T. Higashino, S. Sato, H. Suge, K. Tanji, A. Miyashita, and T. Katori, *ibid.*, **36**, 930 (1988); *d*) T. Higashino, S. Sato, A. Miyashita, and T. Katori, *ibid.*, **34**, 4569 (1986); *e*) *Idem, ibid.*, **35**, 4078 (1987); *f*) *Idem, ibid.*, **35**, 4803 (1987).
3) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955).
4) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, **74**, 660 (1952).
5) E. Hayashi, N. Shimada, and Y. Matsuoka, *Yakugaku Zasshi*, **99**, 114 (1979).
6) E. Hayashi, N. Shimada, and A. Miyashita, *Yakugaku Zasshi*, **96**, 1370 (1976).
7) F. Francis and O. C. M. Davis, *J. Chem. Soc.*, **95**, 1403 (1909).
8) E. P. Kohler and J. L. E. Erickson, *J. Am. Chem. Soc.*, **53**, 2301 (1931).