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

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1-Benzoyl-1,6-dihydro-9-phenyl-9H-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-9H-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-9H-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-arylurine, and the aromatization product **6** was obtained.

Keywords 9H-purine; Reissert compound; ring fission aromatization; Reissert compound anion; 9H-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-1-phenyl-1H-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-9H-purine-6-carbonitrile (**1**, 9-phenylpurine Reissert compound)^{2f)} from the reaction of 9-phenyl-9H-purine (**2**) with trimethylsilyl cyanide and benzoyl chloride in the presence of aluminium chloride in

dichloromethane.

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-1H-imidazole)acetonitrile (**3**), together with α -benzamido-4-(5-amino-1-phenyl-1H-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-9H-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-1-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-

Chart 1

Chart 2

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-dini-

Chart 4

trochlorobenzene in the presence of sodium hydride in dioxane, but arylation did not take place and instead aromatization occurred to give **6**.

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 (¹H-NMR) spectra were taken at 60 MHz and 23°C with a Hitachi R-24B high-resolution ¹H-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), 2*N* 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 CHCl₃. The crude product obtained from the CHCl₃ extract was purified by SiO₂ column chromatography. The first fraction eluted from CHCl₃ 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 C₁₈H₁₅N₅O: C, 68.12; H, 4.76; N, 22.07. Found: C, 67.90; H, 4.90; N, 21.45. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3400 (NH), 3320 (NH), 2240 (CN), 1618 (C=O). ¹H-NMR (CDCl₃): 4.00–4.40 (2H, br, NH₂), 6.30 (1H, d, *J*=8.0 Hz, CH₂^{CN}), 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 C₁₉H₁₅N₅O₂: C, 66.07; H, 4.38; N, 20.28. Found: C, 66.03; H, 4.37; N, 20.07. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3260 (NH), 1692, 1640 (C=O). ¹H-NMR (CDCl₃): 6.20 (1H, d, *J*=8.0 Hz, CH₂^{CN}),

Chart 3

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 H₂O, made alkaline with Na₂CO₃, and extracted with CHCl₃. The crude product obtained from the CHCl₃ extract was purified by SiO₂ column chromatography using CHCl₃ as an eluant to give 9-phenyl-9H-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 CHCl₃. The crude product obtained from the CHCl₃ 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 CHCl₃. The crude product obtained from the CHCl₃ extract was purified by SiO₂ column chromatography. The first fraction eluted from benzene gave *O*-benzoylmandelonitrile (**7**). Yield 62 mg (52%). The second fraction gave 9-phenyl-9H-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 CHCl₃ 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 CHCl₃. The crude product obtained from the CHCl₃ extract was purified by SiO₂ column chromatography. The first fraction eluted from benzene gave *O*-benzoylbenzoin (**9a**). Yield 30 mg (19%). The second fraction gave α , 9-diphenyl-9H-purin-6-ylmethyl benzoate (**8a**) as a colorless oil. Yield 206 mg (52%). MS m/z Calcd for C₂₅H₁₈N₄O₂: 406.1429. Observed: 406.1428. IR $\nu_{\max}^{\text{neat}}$ cm⁻¹: 1720 (C=O). ¹H-NMR (CDCl₃): 7.20—8.00 (14H, m, aromatic H and CH₂-^{Ar}OCOPh), 8.00—8.50 (2H, m, aromatic H), 8.35 (1H, s, C⁸-H), 9.00 (1H, s, C²-H). The fraction eluted from CHCl₃ 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-9H-purin-6-ylmethyl benzoate (**8b**) as colorless needles from petroleum benzin-benzene, mp 103—

104 °C. Yield 271 mg (62%). Anal. Calcd for C₂₅H₁₇ClN₄O₂: C, 68.11; H, 3.89; N, 12.71. Found: C, 68.09; H, 3.90; N, 12.70. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 1720 (C=O). ¹H-NMR (CDCl₃): 7.00—8.00 (13H, m, aromatic H and CH₂-^{Ar}OCOPh), 8.00—8.50 (2H, m, aromatic H), 8.24 (1H, s, C⁸-H), 8.90 (1H, s, C²-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-9H-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 C₂₆H₂₀N₄O₃: 436.1535. Observed: 436.1487. IR $\nu_{\max}^{\text{neat}}$ cm⁻¹: 1715 (C=O). ¹H-NMR (CDCl₃): 3.70 (3H, s, OCH₃), 6.85 (2H, d, $J=9.0$ Hz, aromatic H), 7.10—7.90 (11H, m, aromatic H and CH₂-^{Ar}OCOPh), 8.00—8.40 (2H, m, aromatic H), 8.25 (1H, s, C⁸-H), 8.90 (1H, s, C²-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 CHCl₃. The crude product obtained from the CHCl₃ extract was purified by SiO₂ column chromatography using benzene as an eluant to give 9-phenyl-9H-purine-6-carbonitrile (**6**). Yield 132 mg (60%).

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