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

Recently, we elucidated the reactivities of 3-benzyol-3,4-dihydro-4-quinazolinecarbonylitrile (quinazoline Reissert compound)6—9 and 3-benzyol-3,4-dihydro-2-methyl-4-quinazolinecarbonylitrile (2-methylquinazoline Reissert compound)10 and 5-benzyol-4,5-dihydro-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine-4-carbonitrile (pyrazolopyrimidine Reissert compound)11—13 with an acid, a base, sodium hydride, and electrophiles. Moreover, we reported a preparation of 1-benzyol-1,6-dihydro-9-phenyl-9H-purine-6-carbonitrile(1,9-phenylpurine Reissert compound)14 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 reported12 that hydrolysis of the quinazoline Reissert compound in an acid medium gave the ring fission product, 2-(2-aminophenyl)-2-benzamidoacetanitrite. On the other hand, the 2-methylquinazoline Reissert compound12 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 \( \eta \)-benzamido-4-(5-formamido-1-phenyl-1H-imidazol)acetanitrite (3), together with \( \eta \)-benzamido-4-(5-amino-1-phenyl-1H-imidazol)acetanitrite (4).

It has already been reported that the hydrolysis of quinazoline12 and 2-methylquinazoline12 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-benzyol-1,2-dihydro-2-quinolinecarbonitrile (quinoline Reissert compound)15 and 2-benzyol-1,2-dihydro-1-isooquinolinecarbonitrile (isoquinoline Reissert compound)16 undergo rearrangement through the aziridine intermediates in an intramolecular process, giving 2-benzoylquinoline and 1-benzoylisooquinoline, respectively. In contrast, that of the quinazoline Reissert compound13 undergoes aromatization, resulting in the formation of 4-quinazolinecarbonitrile, together with \( \eta \)-phenyl-4-quinazolinylmethyl benzoate and that of the 2-methylquinazoline Reissert compound13 undergoes both rearrangement and aromatization to give 4-benzyol-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,\(^2\) giving 9-phenyl-9H-purine-6-carbonitrile (6), together with 9-phenyl-9H-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\(^2\) 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\(^2\) with aromatic aldehydes and alkyl (aryl) halides. In order to introduce the carbon chains into the 6-position in the 9H-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, 9-diphenyl-9H-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 x-(p-chlorophenyl)-9-phenyl-9H-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-din-}

![Mechanism diagram]

＜Mechanism＞

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\begin{align*}
1 & \xrightarrow{\text{NaH}} \text{PhCHO} + \text{[A]} \\
\text{PhCO} & \xrightarrow{[\text{CN}]} \text{PhCHCN} \\
2 & + \text{PhCHO} \xrightarrow{[\text{CN}]} \text{PhCHCN} \\
\end{align*}
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![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-9H-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 gratting 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-9H-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 x-benzamido-4-[(5-amino-1-phenyl-1H-imidazole)acetoni-trile (4) as pale yellow prisms from acetone–ether, mp 169–170°C. Yield 30 mg (10%). *Anal. Calc'd for C\(_{11}\)H\(_7\)N\(_2\)O\(_2\): C, 68.12; H, 4.76; N, 22.07. Found: C, 67.90; H, 4.90; N, 21.45. IR ν\(_{\text{max}}\) 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\(_2\)-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, NHCO\(_\text{Ph}\)). The second fraction gave x-benzamido-4-[6-(5-hydroxy-1-phenyl-1H-imidazole)acetoni-trile (3) as colorless needles from benzene, mp 168–169°C. Yield 197 mg (57%). *Anal. Calc'd for C\(_{11}\)H\(_7\)N\(_2\)O\(_2\): C, 66.07; H, 4.38; N, 20.28. Found: C, 66.03; H, 4.37; N, 20.07. IR ν\(_{\text{max}}\) cm\(^{-1}\): 3260 (NH), 1692, 1640 (C=O). \(^1\)H-NMR (CDCl\(_3\)): 6.20 (1H, d, J = 8.0 Hz, CH\(_2\)-CN), 11.7.34 (1H, s, NH).
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 and made alkaline with Na2CO3, and extracted with CHCl3. The crude product obtained from the CHCl3 extract was purified by SiO2 column chromatography using CH2Cl2 as an eluant to give 9-phenyl-9H-purine (2), mp 158—159 °C (lit.56 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 benzene to give benzoic acid (5). Yield 101 mg (83%).

Reactions 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.64 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.57

Reactions 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 9-diphenyl-9H-purin-6-ylmethyl benzoate (8a) as a colorless oil. Yield 206 mg (52%). MS m/z Calcld for C30H18N2O2: 406.1429. Observed: 406.1428. IR νmax cm⁻¹: 1720 (C=O). 1H-NMR (CDCl3): 7.20—8.00 (14H, m, aromatic H and CH2-OCONH). 8.80—8.50 (2H, m, aromatic H), 8.35 (1H, s, C5-H), 9.00 (1H, s, C4-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.58

Reactions 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 benzoin—benzene, mp 103—104 °C. Yield 271 mg (62%). Anal. Calcd for C38H24ClNO4: C, 68.11; H, 3.89; N, 12.71. Found: C, 68.09; H, 3.90; N, 12.70. IR νmax cm⁻¹: 1720 (C=O). 1H-NMR (CDCl3): 7.00—8.00 (13H, m, aromatic H and CH2-ArOCONH). 8.00—8.50 (2H, m, aromatic H), 8.24 (1H, s, C5-H), 8.90 (1H, s, C4-H).

Reactions 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 reaction mixture was poured onto ice-water, neutralized with AcOH, and extracted with CHCl3. The crude product obtained from the CHCl3 extract was recrystallized from petroleum benzoin to give benzoic acid (5). Yield 101 mg (83%).

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-purin-6-carbonitrile (6). Yield 132 mg (60%).

References