References and Notes


Reaction of 1,2,3,4-Tetrahydroquinazolin-4-ones with Acid Anhydride. II

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The reaction of 1,2,3,4-tetrahydroquinazolin-2-spirocyclohexan-4-one (1b) with acetic anhydride and pyridine gave 1-(1-cyclohexenyl)-2-methyl-1,4-dihydroquinazolin-4-one (3b). Compound 3b gave 3-acetyl-1-(1-cyclohexenyl)-2-methyl-1,2,3,4-tetrahydroquinazolin-4-one (8b) upon reduction with NaBH₄ followed by acetylation with acetic anhydride. The position of the acetyl group of 8b was determined by comparison of its NMR spectrum with those of related compounds (9, 10, 11, 12, and 13).

Keywords—4-quinazoline; acetylation; rearrangement; 1H-NMR; spiro compound

We have previously reported that the reaction of 1-benzylspiro[piperidine-4,2'-1'(1',2',3',4'-tetrahydroquinazolin)]-4'-ones (1a and 2) with acetic anhydride and pyridine gives two types (A and B) of rearrangement products (3a and 4), depending upon the presence of absence of a methyl group at the 1'-position of the quinazolines (Chart 1).

Some work has also been done on the acetylation of 1,2,3,4-tetrahydroquinazolin-4-ones; thus, Böhme and Böing reported that the reaction of 2,2-dimethyl-1,2,3,4-tetrahydroquinazolin-4-one with ketene gave 1-acetyl-2,2-dimethyl-1,2,3,4-tetrahydroquinazolin-4-one, while the reaction of the same compound with acetic anhydride and pyridine gave 2-methyl-3,4-dihydroquinazolin-4-one.

Considering our previous result on the reaction of 1 with acetic anhydride and pyridine in connection with the report of Böhme and Böing, the possibility that the structure of the product is not 1-(1-benzyl-1,2,5,6-tetrahydro-4-pyridyl)-2-methyl-1,4-dihydroquinazolin-4-one (3a) but 3-(1-benzyl-1,2,5,6-tetrahydro-4-pyridyl)-2-methyl-3,4-dihydroquinazolin-4-one (5),

![Chart 1](image-url)
could clearly not be ruled out, because the formation of 5 by the route shown in Chart 2 could not be excluded. It might be difficult to differentiate the structures of 3a and 5 from the data obtained by instrumental analyses.

We have now reinvestigated the structure of the product. Namely, the following experiments were undertaken in order to determine whether the structure is 3a or 5.

Heating of 1,2,3,4-tetrahydroquinazoline-2-spirocyclexan-4-one (1b) with acetic anhydride at 90°C for 1 h gave the type A rearrangement product, 1- or 3-(1-cyclohexenyl)-2-methylhydroquinazoln-4-one (3b), in 56% yield, while further heating of the mixture at 140°C for 5.5 h gave 2-acetylamidine-1- or 3-(1-cyclohexenyl)-1,2,3,4-tetrahydroquinazolin-4-one (6b) in 40% yield. A similar compound, the 2-acetylamidine derivative (6a), was obtained in 27% yield by the reaction of 1a under the same conditions. The acetylamidine derivative (6) was considered to be formed by the further acetylation of the active methyl group of 3.

Next, 3b was reduced with sodium borohydride (NaBH₄) and 1- or 3-(1-cyclohexenyl)-2-methyl-1,2,3,4-tetrahydroquinazolin-4-one (7b) was obtained in 79% yield; 7b gave 1- or 3-acetyl-1- or 3-(1-cyclohexenyl)-2-methyl-1,2,3,4-tetrahydroquinazolin-4-one (8b) upon acetylation with acetic anhydride and pyridine. Determination of the position of the acetyl group of 8b seemed to be important for the establishment of the structure of the A type rearrangement compound (3 or 5). In order to determine the position of the acetyl group, N₁ and/or N₅-acetyl-1,2,3,4-tetrahydroquinazolin-4-ones were prepared and the chemical shifts of the N-acetyl groups in the nuclear magnetic resonance (NMR) spectra of these compounds were compared with that of 8b. Namely, 3-acetyl-1,2-dimethyl (9), 3-acetyl-1-methyl-2-phenyl (10), 1-acetyl-3-methyl-2-phenyl (11), 1,3-diacetyl-2-phenyl (12), and 1,3-diacetyl-2-phenethyl (13) derivatives of 1,2,3,4-tetrahydroquinazolin-4-one were prepared. The chemical shifts of the acetyl groups of those compounds are shown in Table I. The signal of the N₅-acetyl groups of 9 and 10 appeared at δ: 2.56 and 2.66, respectively, i.e. at lower field compared with that of the N₁-acetyl group of 11 at δ: 2.30; this can be attributed to a deshielding effect of the 4-carbonyl group. In the case of the N₁- and N₅-diacetyl-2-phenyl derivative (12), the peaks appeared at δ: 2.41 and 2.76, respectively. Among these compounds, the peaks of 10, 11, and 12 were shifted downfield due to the effect of the 2-phenyl group. Therefore, the N₁,N₅-diacetyl-2-phenethyl derivative (13) was examined and the signals were seen at δ: 2.15 and 2.60. The chemical shift of the signal of the acetyl group of 8b at δ: 2.57 was analogous to those of the N₅-acetyl groups, and in particular, it was very similar to those of the N₅-acetyl groups of 9 and 13 in which R₂ is an alkyl group.

Based on these findings, the structure of 8b was deduced to be 3-acetyl-1-(1-cyclohexenyl)-
TABLE I. Chemical Shifts of N-Acetyl Groups of 1,2,3,4-Tetrahydroquinazolin-4-ones in CDCl₃

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>N₁-COMe</th>
<th>N₂-COMe</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Me</td>
<td>Me</td>
<td>COMe</td>
<td>—</td>
<td>2.56</td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>Ph</td>
<td>COMe</td>
<td>—</td>
<td>2.66</td>
</tr>
<tr>
<td>11</td>
<td>COMe</td>
<td>Ph</td>
<td>Me</td>
<td>2.30</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>COMe</td>
<td>Ph</td>
<td>COMe</td>
<td>2.41</td>
<td>2.76</td>
</tr>
<tr>
<td>13</td>
<td>COMe</td>
<td>CH₂CH₂Ph</td>
<td>COMe</td>
<td>2.15</td>
<td>2.60</td>
</tr>
<tr>
<td>8b</td>
<td>H</td>
<td>Me</td>
<td>COMe</td>
<td>—</td>
<td>2.57</td>
</tr>
</tbody>
</table>

2-methyl-1,2,3,4-tetrahydroquinazolin-4-one. Therefore, the structures of 3b, 6a, 6b, and 7b were concluded to be 1-(1-cyclohexenyl)-2-methyl-1,4-dihydroquinazolin-4-one, 2-acetonilidene-1-(1-benzyl-1,2,5,6-tetrahydro-4-pyridyl)-1,2,3,4-tetrahydroquinazolin-4-one, 2-acetonilidene-(1-cyclohexenyl)-1,2,3,4-tetrahydroquinazolin-4-one, and 1-(1-cyclohexenyl)-2-methyl-1,2,3,4-tetrahydroquinazolin-4-one, respectively (Chart 3).

Consequently, it was clear that the A type rearrangement product of the reaction of 1a with acetic anhydride and pyridine was not 5 but 3a, as proposed in our previous report.¹

Experimental

Melting points (determined on a Yanagimoto micro-melting point apparatus) are uncorrected. NMR spectra were taken with a Hitachi R-24 spectrometer at 60 MHz, with tetramethylsilane as an internal standard. Mass spectra were recorded on a Shimadzu LKB-9000 spectrometer, and IR spectra on a Nipponbunko A-102 spectrometer.

1-(1-Cyclohexenyl)-2-methyl-1,4-dihydroquinazolin-4-one (3b)—A mixture of 1b (5.0 g), acetic anhydride (50 ml), and dry pyridine (5 ml) was heated at 90°C for 1 h. After most of the acetic anhydride and pyridine had been evaporated off in vacuo, the residue was extracted with CHCl₃. The CHCl₃ layer was washed with 10% NaOH aq. and H₂O and dried over MgSO₄, and then the solvent was evaporated off. The residue was recrystallized from benzene to give 3.7 g (67%) of 3b, mp 171—173°C. Anal. Calcd for
Table II.  \textsuperscript{1}H- and \textsuperscript{13}C-NMR Chemical Shifts of 6b in CDCl\textsubscript{3} (\textdelta)

\begin{tabular}{|c|c|c|c|}
\hline
Protons & Chemical shifts & Carbons & Chemical shifts \\
\hline
3 & 13.90–14.30 (1H, b) & 2, 4 & 152.41 (s), 159.8 (s) \\
5 & 8.14 (1H, dd) & 4a & 119.1 (s) \\
6, 8 & 6.98–7.37 (2H, m) & 5, 7 & 135.2 (d), 136.8 (d) \\
7 & 7.44–7.83 (1H, m) & 6 & 125.2 (d) \\
9 & 4.97 (1H, s) & 8 & 117.0 (d) \\
11 & 2.11 (3H, s) & 8a & 135.9 (s) \\
2' & 5.84–6.20 (1H, m) & 9 & 81.9 (d) \\
3', 6' & 2.15–2.68 (4H, m) & 10 & 196.0 (s) \\
4', 5' & 1.7–2.05 (4H, m) & 11 & 31.0 (q) \\
& & 1' & 142.0 (s) \\
& & 2' & 129.9 (d) \\
& & 3', 6' & 25.2 (t), 25.9 (t) \\
& & 4', 5' & 21.5 (t), 22.7 (t) \\
\hline
\end{tabular}

C\textsubscript{13}H\textsubscript{18}N\textsubscript{2}O: C, 74.79; H, 6.71; N, 11.66. Found: C, 74.94; H, 6.79; N, 11.46. IR \textnu\textsubscript{max} cm\textsuperscript{-1}: 1640. \textsuperscript{1}HNMR (in CDCl\textsubscript{3}) \textdelta: 1.59–2.41 (4H, m, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 2.20–2.41 (4H, m, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 2.48 (3H, s, N=CH\textsubscript{2}CH\textsubscript{2}), 6.01 (1H, m, >C=CH). MS m/e: 240 (M\textsuperscript{+}).

2-Acetonilidene-1-(1-cyclohexenyl)-1,2,3,4-tetrahydroquinazolin-4-one (6b)—A mixture of 1b (4.0 g), acetic anhydride (40 ml), and dry pyridine (4 ml) was heated at 140°C for 5.5 h. The reaction mixture was then worked up as above. Purification of the resulting product by column chromatography on silica gel with CH\textsubscript{2}Cl\textsubscript{2} gave 2.1 g (40%) of 6b, which was recrystallized from a mixture of benzene and cyclohexane, mp 161–163°C. \textit{Anal.} Calcd for C\textsubscript{13}H\textsubscript{18}N\textsubscript{2}O: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.54; H, 6.38; N, 9.73. IR \textnu\textsubscript{max} cm\textsuperscript{-1}: 1620, 1675, 3600. MS m/e: 282 (M\textsuperscript{+}).

2-Acetonilidene-1-(1-benzyl-1,2,3,4-tetrahydro-4-pyridyl)-1,2,3,4-tetrahydroquinazolin-4-one (6a)—A mixture of 1a (1.5 g), acetic anhydride (15 ml), and dry pyridine (1.5 ml) was heated at 140°C for 5.5 h, and then worked up as above. The product was column chromatographed on Al\textsubscript{2}O\textsubscript{3} with CH\textsubscript{2}Cl\textsubscript{2} to give 0.5 g (27%) of 6a, mp 179–181°C. \textit{Anal.} Calcd for C\textsubscript{15}H\textsubscript{21}N\textsubscript{2}O: C, 73.97; H, 6.21; N, 11.25. Found: C, 74.23; H, 6.28; N, 11.19. IR \textnu\textsubscript{max} cm\textsuperscript{-1}: 1610, 1690, 3310. \textit{1}HNMR (in CDCl\textsubscript{3}) \textdelta: 2.10 (3H, s, COCH\textsubscript{3}), 2.12–2.47 (2H, m, N=CH\textsubscript{2}CH\textsubscript{2}), 2.67–2.92 (2H, m, N=CH\textsubscript{2}CH\textsubscript{2}), 3.12–3.35 (2H, m, N=CH\textsubscript{2}CH\textsubscript{2}), 3.66 (2H, s, NCH\textsubscript{2}CH\textsubscript{2}), 4.92 (1H, s, COCH\textsubscript{3}), 5.76–5.98 (1H, m, NCH\textsubscript{2}CH\textsubscript{2}), 13.68 (1H, b, NH). MS m/e: 327 (M\textsuperscript{+}).

1-(1-Cyclohexenyl)-2-methyl-1,2,3,4-tetrahydroquinazolin-4-one (7b)—Excess NaBH\textsubscript{4} (1.0 g) was added to a solution of 3b (3.0 g) in MeOH (100 ml) and the mixture was stirred at room temperature for 1 h. After the MeOH had been removed, the residue was extracted with AcOEt. The AcOEt layer was washed with H\textsubscript{2}O and dried over MgSO\textsubscript{4}, and then the solvent was evaporated off. Recrystallization of the residue from a mixture of benzene and cyclohexane gave 2.4 g (79%) of 7b, mp 163–165°C. \textit{Anal.} Calcd for C\textsubscript{15}H\textsubscript{21}N\textsubscript{2}O: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.12; H, 7.52; N, 11.62. IR \textnu\textsubscript{max} cm\textsuperscript{-1}: 1660, 3180, 3300. \textit{1}HNMR (in CDCl\textsubscript{3}) \textdelta: 1.44 (3H, d, J=7.2 Hz, CH\textsubscript{3}), 1.56–1.88 (4H, m, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 1.88–2.39 (4H, m, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 4.96 (1H, q, J=7.2 Hz, CH\textsubscript{2}CH\textsubscript{2}), 5.52–5.80 (1H, m, CH=CH\textsubscript{2}), 7.91–8.21 (1H, b, NH). MS m/e: 242 (M\textsuperscript{+}).

3-Acetyl-1-(1-cyclohexenyl)-2-methyl-1,2,3,4-tetrahydroquinazolin-4-one (8b)—A mixture of 7b (1.0 g), acetic anhydride (10 ml), and dry pyridine (1 ml) was heated at 110°C for 1.5 h, and then worked up as in the case of 3b. The product was column chromatographed on silica gel with CH\textsubscript{2}Cl\textsubscript{2} to give 0.32 g (27%) of 8b, as an oil. \textit{Anal.} Calcd for C\textsubscript{15}H\textsubscript{21}N\textsubscript{2}O: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.78; H, 7.18; N, 9.93. IR \textnu\textsubscript{max} cm\textsuperscript{-1}: 1650 (shoulder), 1685. \textit{1}HNMR (in CDCl\textsubscript{3}) \textdelta: 1.39 (3H, d, J=7 Hz, CH\textsubscript{3}CH\textsubscript{2}), 1.52–1.97 (4H, m, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 1.97–2.51 (1H, m, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 2.57 (3H, s, COCH\textsubscript{3}), 5.39–5.81 (1H, m, >C=CH), 6.01 (1H, q, J=7.1 Hz, CH=CH\textsubscript{2}). MS m/e: 284 (M\textsuperscript{+}).

1,2-Dimethyl-1,2,3,4-tetrahydroquinazolin-4-one (14)—NaBH\textsubscript{4} (1.5 g) was added to a solution of 1,2-dimethyl-1,4-dihydroquinazolin-4-one\textsuperscript{6} (3.6 g) in MeOH (30 ml), and the solution was stirred for 1 h at room temperature then concentrated. The residue was acidified with 10% HCl and made basic with 10% NaOH.

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\textsuperscript{6}Reference for 1,2-dimethyl-1,4-dihydroquinazolin-4-one.
to give 14, which was recrystallized from MeOH, mp 150—151°C, yield 2.2 g (60%). Anal. Calcld for CsH14N2O2: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.34; H, 6.91; N, 15.98. IR νmax cm⁻¹: 1650, 3160. 1H-NMR (in CDCl₃) δ: 1.35 (3H, d, J = 6 Hz, C₃–CH₃), 2.82 (3H, s, NCH₃), 4.47—4.93 (1H, m, C₂–H), 8.20—8.55 (1H, b, N–H). MS m/e: 272 (M+).

3-Acetyl-1,2-dimethyl-1,2,3,4-tetrahydroquinazolin-4-one (9)—A mixture of 14 (1 g), acetic anhydride (10 ml), and dry pyridine (1 ml) was heated at 100°C for 3 h, and then worked up as in the case of 3b to give 1.2 g (97%) of 9. Anal. Calcld for C₁₃H₁₄N₂O₂: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.32; H, 6.43; N, 12.92. IR νmax cm⁻¹: 1610, 1680. 1H-NMR (in CDCl₃) δ: 1.24 (3H, d, J = 6 Hz, C₂–CH₃), 2.56 (3H, s, COCH₃), 2.93 (3H, s, NCH₃), 5.80 (1H, q, J = 6 Hz, C₁–H). MS m/e: 218 (M+).

3-Acetyl-1-methyl-2-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (10)—A mixture of 1-methyl-2-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (2 g), acetic anhydride (20 ml), and dry pyridine (2 ml) was heated at 100°C for 2 h. Most of the acetic anhydride and pyridine was evaporated off in vacuo, and the residue was extracted with CHCl₃. The CHCl₃ layer was washed with 10% NaOH and H₂O, dried over MgSO₄, and concentrated to dryness in vacuo. Purification of the residue by column chromatography on silica gel with CH₂Cl₂ gave 2 g (85%) of 10, which was recrystallized from a mixture of cyclohexane and petr. ether. mp 87—89°C. Anal. Calcld for C₂₀H₁₈N₂O₂: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.60; H, 5.62; N, 9.82. IR νmax cm⁻¹: 1650, 1680. 1H-NMR (in CDCl₃) δ: 2.66 (3H, s, COCH₃), 3.13 (3H, s, NCH₃). MS m/e: 280 (M+).

1-Acetyl-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (11)—A mixture of 3-methyl-2-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (2 g), acetic anhydride (20 ml), and pyridine (2 ml) was heated at 100°C for 2 h. Most of the acetic anhydride and pyridine was evaporated off in vacuo, and the residue was extracted with CHCl₃. The CHCl₃ layer was washed with 10% NaOH and H₂O, and dried over MgSO₄, then the solvent was removed. Recrystallization of the residue from CHCl₃ gave 1.7 g (72%) of 11, mp 154—154.5°C. Anal. Calcld for C₁₄H₁₂N₂O₂: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.60; H, 5.52; N, 9.79. IR νmax cm⁻¹: 1640. 1H-NMR (in CDCl₃) δ: 2.30 (3H, s, COCH₃), 3.23 (3H, s, NCH₃). MS m/e: 280 (M+).

1,3-Diacetyl-1,2,3,4-tetrahydroquinazolin-4-one (12)—A mixture of 2-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (1.7 g), acetic anhydride (20 ml), and dry pyridine (2 ml) was heated at 100°C for 2 h. After removal of acetic anhydride and pyridine in vacuo, the residue was recrystallized from a mixture of benzene and cyclohexane to give 1.8 g (80%) of 12, mp 133—135°C. Anal. Calcld for C₁₅H₁₄N₂O₂: C, 70.11; H, 5.23; N, 9.09. Found: C, 69.87; H, 5.15; N, 8.79. IR νmax cm⁻¹: 1665, 1680, 1695. 1H-NMR (in CDCl₃) δ: 2.41 (3H, s, N–COCH₃), 2.76 (3H, s, N–COCH₃), 8.30 (1H, s, C–H). MS m/e: 308 (M+).

2-Phenyl-1,2,3,4-tetrahydroquinazolin-4-one (15)—A solution of 2-aminobenzamidine (4 g) and 3-phenylpropionaldehyde (4 g) in EtOH (200 ml) was refluxed for 3 h. After the solvent had been removed, the residue was recrystallized from MeOH to give 4 g (54%) of 15, mp 164—166°C. Anal. Calcld for C₁₄H₁₀N₂O: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.19; H, 6.51; N, 10.98. IR νmax cm⁻¹: 1645, 3160, 3280. 1H-NMR (in DMSO-d₆) δ: 1.77 (2H, m, CH₂CH₂Ph), 2.65 (2H, m, CH₂Ph), 4.67—5.93 (1H, b, N–H). MS m/e: 215 (M+).

1,3-Diacetyl-2-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (13)—A mixture of 15 (1.7 g), acetic anhydride (20 ml), and dry pyridine (1.5 ml) was heated at 120°C for 10 h. After removal of the acetic anhydride and pyridine in vacuo, the residue was column chromatographed on silica gel with CH₂Cl₂ to give 1.7 g (85%) of 13 as a viscous oil. IR νmax cm⁻¹: 1670, 1700. 1H-NMR (in CDCl₃) δ: 2.15 (3H, s, N–COCH₃), 2.60 (3H, s, N–COCH₃). MS m/e: 336 (M+).

References and Notes