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Reaction of 1,2,3,4-Tetrahydroquinazolin-4-ones with Acid Anhydride. II¹⁾

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The reaction of 1,2,3,4-tetrahydroquinazoline-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',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 or absence of a methyl group at the 1'-position of the quinazolines (Chart 1).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.²⁾

Considering our previous result on the reaction of **1** with acetic anhydride and pyridine¹⁾ 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

Chart 2

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-spirocyclohexan-4-one (**1b**)³⁾ with acetic anhydride at 90°C for 1 h gave the type A rearrangement product, 1- or 3-(1-cyclohexenyl)-2-methyldihydroquinazolin-4-one (**3b**), in 56% yield, while further heating of the mixture at 140°C for 5.5 h gave 2-acetonylidene-1- or 3-(1-cyclohexenyl)-1,2,3,4-tetrahydroquinazolin-4-one (**6b**) in 40% yield. A similar compound, the 2-acetonylidene derivative (**6a**), was obtained in 27% yield by the reaction of **1a** under the same conditions. The acetonylidene 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 N₃-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 N₃-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 N₃-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,N₃-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 N₃-acetyl groups, and in particular, it was very similar to those of the N₃-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 CDCl_3

Compd. No.	R_1	R_2	R_3	Chemical shifts (δ)	
				$N_1\text{-COMe}$	$N_3\text{-COMe}$
9	Me	Me	COMe	—	2.56
10	Me	Ph	COMe	—	2.66
11	COMe	Ph	Me	2.30	—
12	COMe	Ph	COMe	2.41	2.76
13	COMe	$\text{CH}_2\text{CH}_2\text{Ph}$	COMe	2.15	2.60
8b	H	Me	COMe	—	2.57

Chart 3

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 micromelting 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 CHCl_3 . The CHCl_3 layer was washed with 10% NaOH aq. and H_2O and dried over MgSO_4 , 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. ^1H - and ^{13}C -NMR Chemical Shifts of **6b** in CDCl_3 (δ)

Protons	Chemical shifts	Carbons	Chemical shifts
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)

$\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$: C, 74.79; H, 6.71; N, 11.66. Found: C, 74.94; H, 6.79; N, 11.46. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1640. ^1H -NMR (in CDCl_3) δ : 1.59—2.41 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 2.20—2.41 (4H, m, $\text{CH}_2-\text{C}=\text{CH}-\text{CH}_2$), 2.48 (3H, s, $\text{N}=\text{C}-\text{CH}_3$), 6.01 (1H, m, $>\text{C}=\text{CH}$). MS m/e : 240 (M^+).

2-Acetylidene-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_2Cl_2 gave 2.1 g (40%) of **6b**, which was recrystallized from a mixture of benzene and cyclohexane, mp $161\text{--}163^\circ\text{C}$. Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.54; H, 6.38; N, 9.73. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1620, 1675, 3600. MS m/e : 282 (M^+).

2-Acetylidene-1-(1-benzyl-1,2,5,6-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_2O_3 with CH_2Cl_2 to give 0.5 g (27%) of **6a**, mp $179\text{--}181^\circ\text{C}$. Anal. Calcd for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 74.23; H, 6.28; N, 11.19. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1610, 1690, 3310. ^1H -NMR (in CDCl_3) δ : 2.10 (3H, s, COCH_3), 2.12—2.47 (2H, m, $\text{N}-\text{CH}_2\text{CH}_2$), 2.67—2.90 (2H, m, $\text{N}-\text{CH}_2\text{CH}_2$), 3.12—3.35 (2H, m, $\text{N}-\text{CH}_2\text{CH}=\text{C}$), 3.66 (2H, s, $\text{NCH}_2-\text{C}_6\text{H}_5$), 4.92 (1H, s, $\text{COCH}=\text{C}$), 5.76—5.98 (1H, m, $\text{NCH}_2\text{CH}=\text{C}$), 13.68 (1H, b, NH). MS m/e : 373 (M^+).

1-(1-Cyclohexenyl)-2-methyl-1,2,3,4-tetrahydroquinazolin-4-one (7b)—Excess NaBH_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_2O and dried over MgSO_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 $163\text{--}165^\circ\text{C}$. Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.12; H, 7.52; N, 11.62. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1660, 3180, 3300. ^1H -NMR (in CDCl_3) δ : 1.44 (3H, d, $J=7.2$ Hz, $\text{CH}-\text{CH}_3$), 1.56—1.88 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 1.88—2.39 (4H, m, $\text{CH}_2\text{CH}=\text{C}-\text{CH}_2$), 4.96 (1H, q, $J=7.2$ Hz, $\text{CH}-\text{CH}_3$), 5.52—5.80 (1H, m, $\text{CH}=\text{C}$), 7.91—8.21 (1H, b, NH). MS m/e : 242 (M^+).

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_2Cl_2 to give 0.32 g (27%) of **8b**, as an oil. Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.78; H, 7.16; N, 9.93. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1650 (shoulder), 1685. ^1H -NMR (in CDCl_3) δ : 1.39 (3H, d, $J=7$ Hz, CH_2CH_3), 1.52—1.97 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 1.97—2.51 (4H, m, $\text{CH}_2\text{CH}=\text{C}-\text{CH}_2$), 2.57 (3H, s, COCH_3), 5.39—5.81 (1H, m, $>\text{C}=\text{CH}$), 6.01 (1H, q, $J=7$ Hz, $\text{CH}-\text{CH}_3$). MS m/e : 284 (M^+).

1,2-Dimethyl-1,2,3,4-tetrahydroquinazolin-4-one (14)— NaBH_4 (1.5 g) was added to a solution of 1,2-dimethyl-1,4-dihydroquinazolin-4-one⁴⁾ (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

to give **14**, which was recrystallized from MeOH, mp 150—151°C, yield 2.2 g (60%). *Anal.* Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.34; H, 6.91; N, 15.98. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1650, 3160. $^1\text{H-NMR}$ (in CDCl_3) δ : 1.35 (3H, d, $J=6$ Hz, $\text{C}_2\text{-CH}_3$), 2.82 (3H, s, NCH_3), 4.47—4.93 (1H, m, $\text{C}_2\text{-H}$), 8.20—8.55 (1H, b, $\text{N}_3\text{-H}$). 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.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.32; H, 6.43; N, 12.92. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1610, 1680. $^1\text{H-NMR}$ (in CDCl_3) δ : 1.24 (3H, d, $J=6$ Hz, $\text{C}_2\text{-CH}_3$), 2.56 (3H, s, COCH_3), 2.93 (3H, s, NCH_3), 5.80 (1H, q, $J=6$ Hz, $\text{C}_2\text{-H}$). 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-one²⁾ (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 CHCl_3 . The CHCl_3 layer was washed with 10% NaOH and H_2O , dried over MgSO_4 , and concentrated to dryness *in vacuo*. Purification of the residue by column chromatography on silica gel with CH_2Cl_2 gave 2 g (85%) of **10**, which was recrystallized from a mixture of cyclohexane and petr. ether, mp 87—89°C. *Anal.* Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.60; H, 5.62; N, 9.82. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1650, 1680. $^1\text{H-NMR}$ (in CDCl_3) δ : 2.66 (3H, s, COCH_3), 3.13 (3H, s, NCH_3). 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-one²⁾ (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 CHCl_3 . The CHCl_3 layer was washed with 10% NaOH and H_2O , and dried over MgSO_4 , then the solvent was removed. Recrystallization of the residue from CHCl_3 gave 1.7 g (72%) of **11**, mp 154—154.5°C. *Anal.* Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.60; H, 5.52; N, 9.79. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1640. $^1\text{H-NMR}$ (in CDCl_3) δ : 2.30 (3H, s, COCH_3), 3.23 (3H, s, NCH_3). MS m/e : 280 (M^+).

1,3-Diacetyl-2-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (12)—A mixture of 2-phenyl-1,2,3,4-tetrahydroquinazolin-4-one⁵⁾ (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.* Calcd for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 69.87; H, 5.15; N, 8.79. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1665, 1680, 1695. $^1\text{H-NMR}$ (in CDCl_3) δ : 2.41 (3H, s, $\text{N}_1\text{-COCH}_3$), 2.76 (3H, s, $\text{N}_3\text{-COCH}_3$), 8.30 (1H, s, $\text{C}_2\text{-H}$). MS m/e : 308 (M^+).

2-Phenethyl-1,2,3,4-tetrahydroquinazolin-4-one (15)—A solution of 2-aminobenzamide (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.* Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.19; H, 6.51; N, 10.98. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1645, 3160, 3280. $^1\text{H-NMR}$ (in $\text{DMSO}-d_6$) δ : 1.77 (2H, m, $\text{CH}_2\text{CH}_2\text{Ph}$), 2.65 (2H, m, CH_2Ph), 4.67—5.93 (1H, b, $\text{N}_1\text{-H}$), 7.93—8.19 (1H, b, NH).

1,3-Diacetyl-2-phenethyl-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 CH_2Cl_2 to give 1.7 g (85%) of **13** as a viscous oil. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1670, 1700. $^1\text{H-NMR}$ (in CDCl_3) δ : 2.15 (3H, s, $\text{N}_1\text{-COCH}_3$), 2.60 (3H, s, $\text{N}_3\text{-COCH}_3$). MS m/e : 336 (M^+).

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