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Reaction of 1,2,3,4-Tetrahydroquinazolin-4-ones with Acid Anhydride. III[1]

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The reaction of C_2-substituted 1,2,3,4-tetrahydroquinazolin-4-ones (**1**) with acetic anhydride and pyridine was carried out in order to elucidate the effect of the C_2-substituent. It was found that the various types of reactions occurred depending on the kind and number of C_2-substituents of 1,2,3,4-tetrahydroquinazolin-4-ones (**1**).

Keywords——4-quinazolinones; acetic anhydride; 1,4-dihydroquinolin-4-ones; acylation; substituent effect

We have previously reported that the reaction of 1-benzylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-ones (**1a** or **2**) with acetic anhydride affords two types of rearranged product, 1-(1-benzyl-1,2,5,6-tetrahydro-4-pyridyl)-2-methyl-1,4-dihydroquinazolin-4-one (**3a**) and 2-benzyl-5-methyl-1,2,3,4,5,10-hexahydrobenzo[b]-[1,6]-naphthyridin-10-one (**4**), depending on the presence or absence of a methyl group at the 1-position, respectively (Chart 1).[2]

We have now carried out a further study on the reaction of 1,2,3,4-tetrahydroquinazolin-4-one (THQ) derivatives with acetic anhydride and found that various types of reactions took place depending on the presence or absence of an N_1-substituent and also upon the kind and number (one or two) of C_2-substitutents of THQ derivatives. This paper describes the reaction of THQ derivatives in which the N_1 and N_3 positions are both occupied by a hydrogen atom.

The reaction of 2-monosubstituted THQ derivatives in which the C_2-substituent is an alkyl or aryl group with excess acetic anhydride and one equivalent of pyridine gave 2-monosubstituted 1,3-diacetyl-THQ derivatives. For example, the reaction of 2-phenyl-THQ (**1b**)[3] gave 1,3-diacetyl-1-phenyl-THQ (**5a**)[1] in 60% yield, and a similar reaction of 2-phenethyl-THQ (**1c**) gave 1,3-diacetyl-2-phenethyl-THQ (**5b**)[1] in 54% yield. The assignment of the signals of the N_1- and N_3-acetyl groups was achieved based on the nuclear magnetic resonance (NMR) spectral data of related compounds.[1]

On the other hand, similar reactions of 2,2-disubstituted THQ derivatives did not afford the corresponding 1,3-diacetyl-THQ derivatives but gave various types of products, which seemed to be formed depending upon the kind of C_2-substituents of the THQ derivatives.

In the case of the reaction of 2,2-dialkyl-THQ derivatives, 2-methyl-2-phenethyl-THQ (**1d**) gave 2-methyl-1,4-dihydroquinazolin-4-one (**6**)[4] and methyl phenethyl ketone in 25 and 21% yields, respectively. Moreover, in the case of the reaction of 2,2-diethyl-THQ (**1e**), a spot having a strong fluorescence was observed in the thin layer chromatogram (TLC) (Chart 2). Column chromatography of the products gave 3-acetyl-2,2-diethyl-THQ (**7a**). On the other hand, heating of the same reactant at 120°C for 5 h gave **6** and 2-acetonylidene-1-(2-penten-3-yl)-THQ (**8c**) in 23% yield. The compound **6** was also obtained by heating of **7a** in xylene in the presence of a catalytic amount of acetic anhydride. Similarly, in the case of spiro-[cyclohexane-1,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one (**1f**), on heating at 140°C for 5.5 h, 1-(1-cyclohexenyl)-2-methyl-1,4-dihydroquinazolin-4-one (**3b**) and 2-acetonylidene-1-(1-cyclohexenyl)-1,2,3,4-tetrahydroquinazolin-4-one (**8b**) were obtained.[1]

However, on changing one of the C_2-substituents of 2,2-dialkyl-THQ derivatives for a benzyl group, an interesting difference in the reactivity was found. Namely, heating of 2,2-dibenzyl-THQ (**1g**) with acetic anhydride and pyridine at 110°C for 1 h gave 2-benzyl-1,4-dihydroquinazolin-4-one (**9a**) in 49% yield, involving the elimination of the benzyl group.

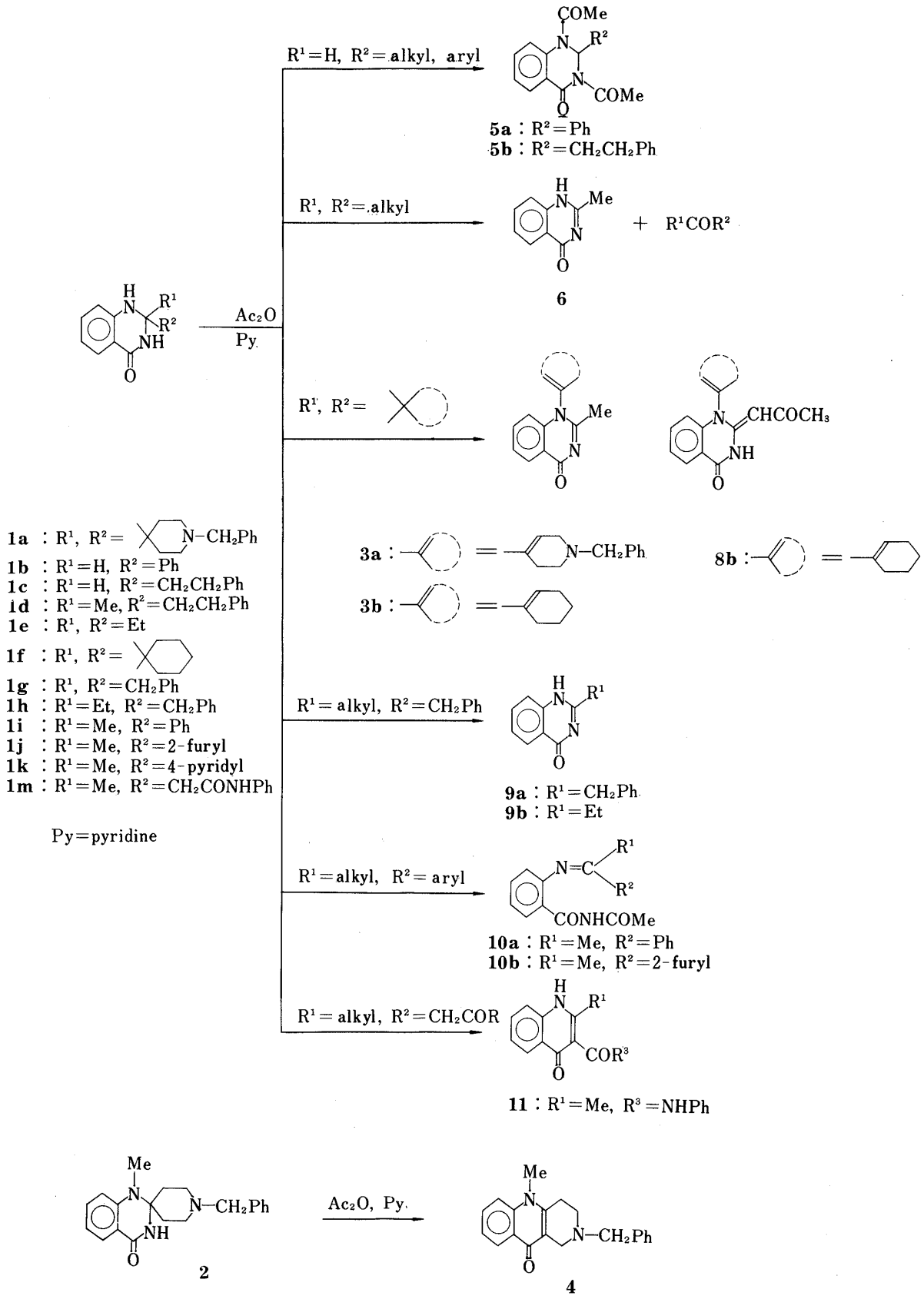
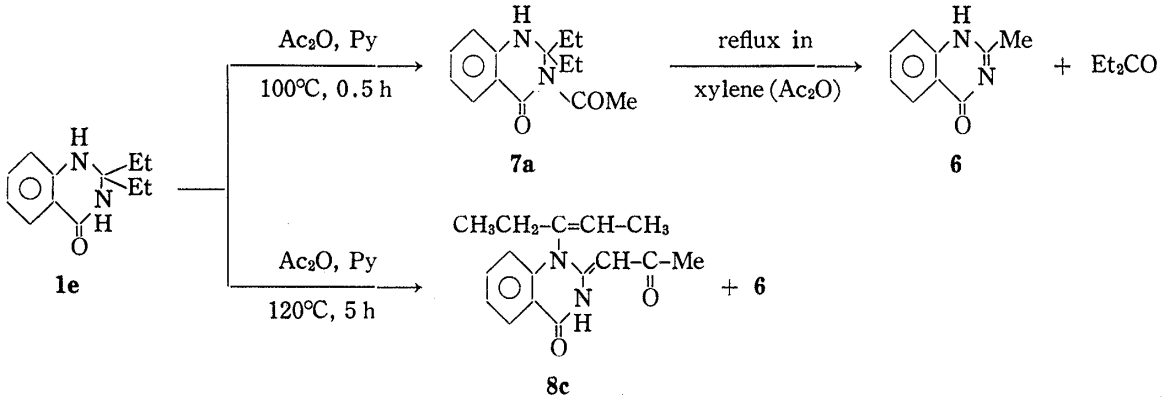


Chart 1

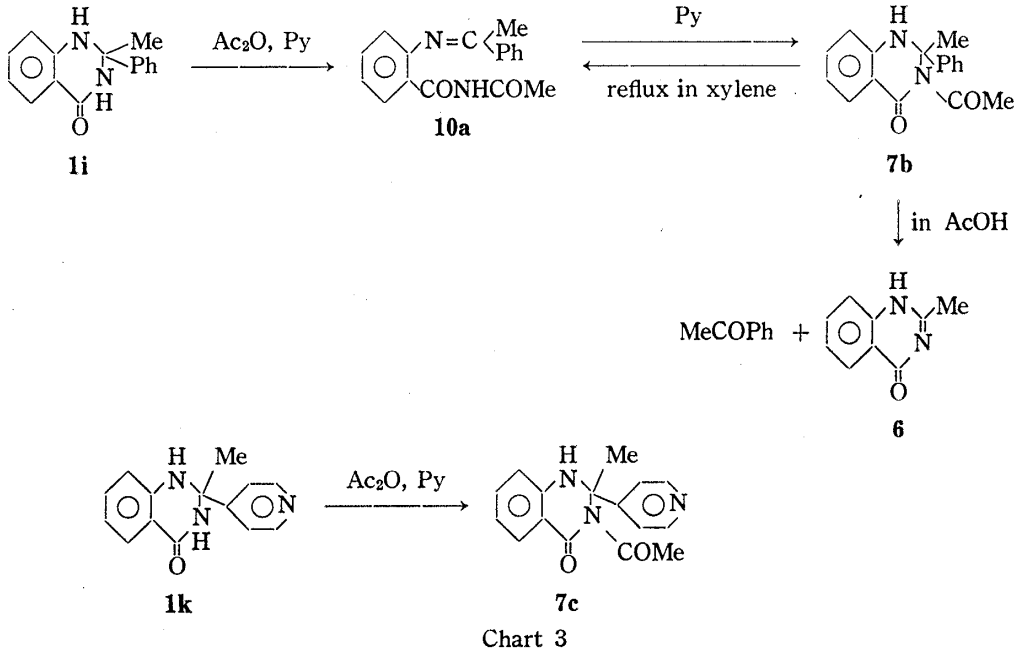


1e 7a 6 8c

Chart 2

Similar reaction of 2-benzyl-2-ethyl-THQ (**1h**) gave 2-ethyl-1,4-dihydroquinazolin-4-one (**9b**)[5] in 26% yield. The compound **9a** or **9b** was also obtained by heating of **1g** or **1h** in xylene for 4 h, respectively. On the other hand, the reaction of 2-benzyl-2-ethyl-1-methyl-THQ, an N_1-methyl-THQ derivative, with acetic anhydride and pyridine did not give the corresponding debenzylated compound, 2-ethyl-1-methyl-1,4-dihydroquinazolin-4-one.[6] These results suggested that the reaction of **1g,h** to give **9a,b** might proceed *via* the formation of a benzyl radical.

The similar reaction of 2,2-disubstituted THQ derivatives in which one of the C_2-substituents is an aryl group gave 2-(1-arylethylideneamino)-N-acetylbenzamides. For example, the reaction of 2-methyl-2-phenyl-THQ (**1i**)[3] gave 2-(1-phenethylideneamino)-N-acetylbenzamide (**10a**) in 68% yield. Similarly, the reaction of 2-(2-furyl)-2-methyl-THQ (**1j**) gave 2-[1-(2-furyl)ethylideneamino]-N-acetylbenzamide (**10b**) in 28% yield. When **10a** was stirred in pyridine, the peaks at δ: 2.31 (CH_3), 2.41 (CH_3), and 10.84 (CONHCO) in the NMR spectrum of **10a** disappeared and new peaks appeared at δ: 1.97 (CH_3), 2.44 (CH_3), and 5.31 (N_1–H). These results indicated that **10a** was converted into 3-acetyl-2-methyl-2-phenyl-THQ (**7b**) in pyridine (Chart 3), since the chemical shifts of these peaks were similar to those of the 2-methyl group (δ: 1.71) of **1i** and N_3-acetyl group (δ: 2.57) of 3-acetyl-1-(1-cyclohexenyl)-2-methyl-THQ.[1] On the other hand, heating of **7b** in xylene gave **10a**. On dissolving **7b** in acetic acid, it was decomposed to **6** and acetophenone. This type of reaction was different



1i 10a 7b 6 1k 7c

Chart 3

from those of 2,2-dialkyl-THQ derivatives (**1d,e**), and the difference in the reactions of 2,2-dialkyl-THQ derivatives and 2-alkyl-2-aryl-THQ derivatives may be attributable to the difference in the stability of the intermediate Schiff base **10**. The Schiff base, **10**, must be more stable than the corresponding dialkyl congeners due to the resonance effect of the aromatic group. This consideration was supported by the fact that the reaction of 2-methyl-2-(4-pyridyl)-THQ (**1k**) with acetic anhydride and pyridine at 110—120°C gave 3-acetyl-2-methyl-2-(4-pyridyl)-THQ (**7c**) in 59% yield (Chart 3).

The reaction of 2,2-disubstituted THQ in which one of the substituents was a carbamoylmethyl group gave 2-alkyl-3-carbamoyl-1,4-dihydroquinolin-4-ones. For example, the reaction of 2-methyl-2-(N-phenylcarbamoyl)methyl-THQ (**1m**) under the usual conditions gave 2-methyl-3-(N-phenyl)carbamoyl-1,4-dihydroquinolin-4-one (**11**) in 53% yield. This exceptional reactivity of **1m** must be a result of the large mobility of the proton of the α-methylene group adjacent to the carbonyl group in C_2-substituent, and the mechanism was considered to be as shown in Chart 4.

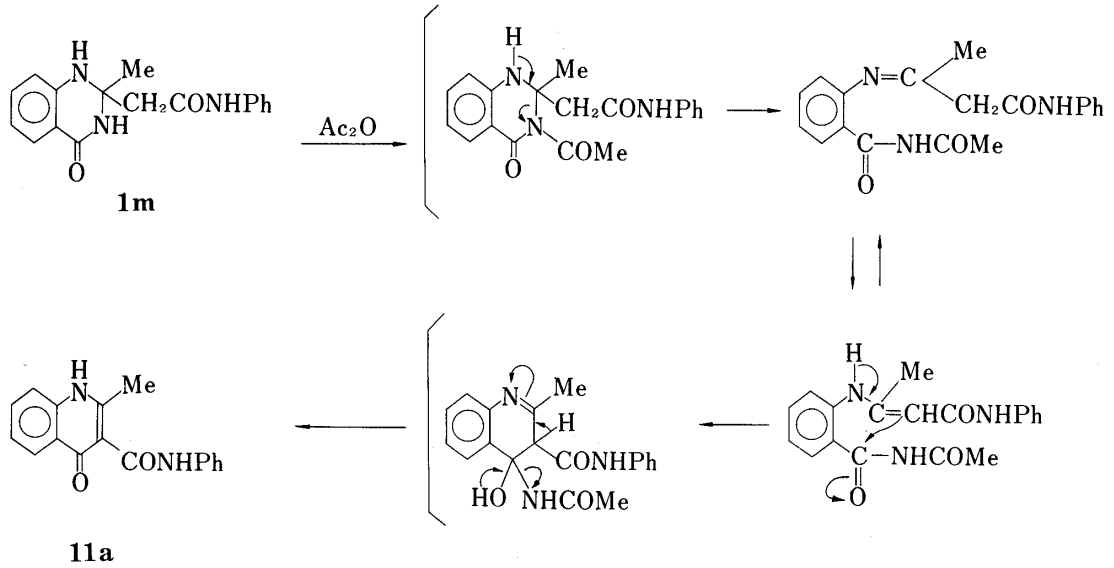


Chart 4

Experimental

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

1,2,3,4-Tetrahydroquinazolin-4-ones (**1**)——A mixture of 2-aminobenzamide (67 mmol), ketone or aldehyde (67 mmol), and catalyst was heated under the conditions shown in Table I. The resulting solid was purified by recrystallization or chromatography on a column of silica gel with CH_2Cl_2. The results are listed in Table I.

2-Methyl-1,4-dihydroquinazolin-4-one (**6**)——Method A: A mixture of **1d** (1.7 g), acetic anhydride (20 ml), and dry pyridine (2 ml) was heated at 100°C for 3 h. After removal of acetic anhydride and pyridine *in vacuo*, the residue was chromatographed on a column of silica gel. Elution with CH_2Cl_2 gave 0.27 g (25%) of methyl phenethyl ketone which was identified by comparison of its NMR spectrum with that of an authentic sample. Elution with MeOH gave 0.22 g (21%) of **6**, mp 236°C (234—236°C[4]), which was identified by comparison of its IR spectrum with that of an authentic sample of **6**.

Method B: A catalytic amount of acetic anhydride was added to a solution of **7a** (0.12 g) in xylene (50 ml), and the solution was heated at 100°C for 2 h. On cooling, the solution gave 0.06 g (77%) of **6**, mp 234—236°C.

3-Acetyl-2,2-diethyl-1,2,3,4-tetrahydroquinazolin-4-one (**7a**)——A mixture of **1e** (1 g), acetic anhydride (10 ml), and dry pyridine (1 ml) was heated at 100°C for 0.5 h. After removal of acetic anhydride and pyridine

Table I. 1,2,3,4-Tetrahydroquinazolin-4-ones (1)

Compd. No.	R.T.[a] (h)	R.T.[b] (°C)	Catalyst (eq. mol)	Yield (%)	mp (°C)	Analysis (%) Calcd (Found) C	H	N	IR (cm^{-1})	NMR (δ)
1d	0.1	100	*p*-TsOH (c.a.)[c]	99	164—165[d]	76.66	6.74	10.52	3270	1.47 (3H, s, CH_3)[e]
						(76.82	6.74	10.33)	3150	8.1—8.3 (1H, b[f], NH)
									1640	
1e	0.1	100	*p*-TsOH (c. a.)	90	203—205[d]	70.56	7.90	13.72	3330	0.93 (6H, t, CH_3)[e]
						(70.38	8.06	13.42)	3170	1.63 (4H, q, CH_2)
									1640	6.4—6.6 (1H. b, N_1–H)
										7.9—8.1 (1H, b, N_3–H)
1g	4	140	—	55	258—260[g]	80.46	6.14	8.53	3300	3.11 (4H, d, $C\underline{H}_2Ph$)[h]
						(80.26	6.07	8.75)	3200	4.3—4.7 (1H, b, N_1–H)
									1655	7.7—7.9 (1H, b, N_3–H)
1h	2.5	100	—	56	148—150[g]	76.66	6.81	10.52	3370	0.99 (3H, t, CH_3)[e]
						(76.52	6.83	10.35)	3280	1.71 (2H, q, $C\underline{H}_2CH_3$)
									1650	2.99 (2H, s, $C\underline{H}_2Ph$)
										7.9—8.1 (1H, b, N_3–H)
1j	3	120	$ZnCl_2$ (0.1)	67	221—225[d]	68.41	5.30	12.27	3250	1.77 (3H, s, CH_3)[e]
						(67.93	5.31	11.91)	3300	8.61 (1H, s, N_3–H)
									1660	
1k	4.5	115	CCl_3COOH (0.3)	65	238—240[d]	70.27	5.30	17.56	3300	1.76 (3H, s, CH_3)[e]
						(70.45	5.36	17.43)	1600	9.06 (1H, s, N_3–H)
1m	4	100[i]	—	55	190—191[d]	69.13	5.80	14.23	3250	1.60 (3H, s, CH_3)[e]
						(69.19	5.91	14.23)	1670	2.82 (2H, s, CH_2CO)
									1640	9.98 (2H, b, NH)

a) Reaction time. *b*) Reaction temperature. *c*) Catalytic amount. *d*) Recrystallization from MeOH. *e*) Solution in DMSO-d_6. *f*) Broad singlet. *g*) Chromatography on a column of silica gel. *h*) Solution in $CDCl_3$. *i*) Under reduced pressure.

in vacuo, the residue was chromatographed on a column of silica gel with CH_2Cl_2 to give 0.41 g (34%) of **7a**, mp 97—100°C. *Anal.* Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.54; H, 7.48; N, 11.02. IR ν_{max}^{Nujol} cm^{-1}: 3320, 1725, 1640. NMR ($CDCl_3$) δ: 0.90 (6H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.58—2.76 (4H, m, $C\underline{H}_2CH_3$), 2.58 (3H, s, N-$COCH_3$), 4.63—4.85 (1H, broad s, NH). MS *m/e*: 246 (M^+).

2-Acetonylidene-1-(2-penten-3-yl)-1,2,3,4-tetrahydroquinazolin-4-one (**8c**)——A mixture of **1e** (1.0 g), acetic anhydride (10 ml), and dry pyridine (1 ml) was heated at 120°C for 5 h. After removal of acetic anhydride and pyridine *in vacuo*, the residue was chromatographed on a column of silica gel with CH_2Cl_2 to give 0.4 g (30%) of **6** and 0.3 g (23%) of **8c**. **8c**: mp 142—143°C (from a mixture of benzene and cyclohexane). *Anal.* Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.12; H, 6.73; N, 10.22. IR ν_{max}^{Nujol} cm^{-1}: 1685, 1610. NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.99 (3H, d, J=6 Hz, =$CHC\underline{H}_3$), 2.11 (3H, s, $COCH_3$), 2.56 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 5.02 (1H, s, =CHCO), 5.80 (1H, q, J=6 Hz, =$C\underline{H}CH_3$). MS *m/e*: 270 (M^+).

2-(1-Phenylethylideneamino)-N-acetylbenzamide (**10a**)——Method A: A mixture of **1i** (7.1 g), acetic anhydride (90 ml), and dry pyridine (7 ml) was heated at 110—120°C for 1.5 h. After removal of the acetic anhydride and pyridine *in vacuo*, the residue was recrystallized from a mixture of Et_2O and hexane to give 6 g (68%) of **10a**, mp 97—98°C. *Anal.* Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.47; H, 5.64; N, 10.23. IR ν_{max}^{Nujol} cm^{-1}: 3225, 1710, 1685, 1660, 1625. NMR ($CDCl_3$) δ: 2.31 (3H, s, CH_3), 2.41 (3H, s, $COCH_3$), 10.75 (1H, broad s, CONH). MS *m/e*: 280 (M^+).

Method B: A solution of **7b** (1.0 g) in xylene (100 ml) was heated at 110—120°C for 4 h. After removal of the solvent, the residue was recrystallized from a mixture of hexane and Et_2O to give 0.93 g (93%) of **10a** which was identified by comparison of its IR spectrum with that of the above sample.

3-Acetyl-2-methyl-2-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (**7b**)——A solution of **10a** (0.5 g) in pyridine (10 ml) was stirred at room temperature for 1 h. The pyridine was evaporated off *in vacuo* at room temperature and the residue was recrystallized from a mixture of benzene and cyclohexane to give 0.25 g (50%) of **7b**, mp 117—119°C. *Anal.* Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.00; H, 5.62; N, 9.99. IR ν_{max}^{Nujol} cm^{-1}: 3305, 1720, 1640. NMR (DMSO-d_6) δ: 1.97 (3H, s, C_2–CH_3), 2.44 (3H, s, $COCH_3$), 10.80 (1H, s, NH). MS *m/e*: 280 (M^+).

2-[1-(2-Furyl)ethylideneamino]-N-acetylbenzamide (**10b**)——A mixture of **1j** (4.6 g), acetic anhydride (50 ml), and dry pyridine (5 ml) was heated at 110°C for 1 h. After removal of the acetic anhydride and

pyridine *in vacuo*, the residue was chromatographed on a column of silica gel with $CHCl_3$ to give 1.5 g (28%) of **10b**, mp 74.5—75.5°C. *Anal.* Calcd for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.72; H, 5.23; N, 10.31. IR ν_{max}^{Nujol} cm^{-1}: 3425, 1685, 1610. NMR ($CDCl_3$) δ: 2.30 (3H, s, N=C–CH_3), 2.48 (3H, s, $COCH_3$), 11.24 (1H, broad s, CONH). MS *m/e*: 270 (M^+).

3-Acetyl-2-methyl-2-(4-pyridyl)-1,2,3,4-tetrahydroquinazolin-4-one (**7c**)——A mixture of **1k** (9.58 g), acetic anhydride (120 ml), and dry pyridine (10 ml) was heated at 100—110°C for 9 h. After removal of the acetic anhydride and pyridine *in vacuo*, the residue was recrystallized from MeOH to give 6.64 g (59%) of **7c**, mp 147—149°C. *Anal.* Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.53; H, 5.40; N, 14.93. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1720, 1640. NMR (DMSO-d_6) δ: 2.03 (3H, s, C_2–CH_3), 2.52 (3H, s, $COCH_3$), 8.05 (1H, s, N_1–H). MS *m/e*: 281 (M^+).

2-Benzyl-1,4-dihydroquinazolin-4-one (**9a**)——Method A: A mixture of **1g** (1 g), acetic anhydride (10 ml), and dry pyridine (1 ml) was heated at 100°C for 2 h. After removal of the acetic anhydride and pyridine *in vacuo*, the residue was recrystallized from MeOH to give 0.35 g (49%) of **9a**, mp 254—256°C (254°C).[5]

Method B: A solution of **1g** (1 g) in xylene (50 ml) was refluxed for 4 h. On cooling, the solution gave 0.52 g (72%) of **9a**, mp 255—256°C.

2-Ethyl-1,4-dihydroquinazolin-4-one (**9b**)——Compound **1h** was treated as described for the synthesis of **9a** by Method A or B to give **9b**, mp 234—235°C (234°C),[5] yield 0.17 g (26%) or 0.35 g (54%), respectively.

2-Methyl-3-phenylcarbamoyl-1,4-dihydroquinolin-4-one (**11**)——A mixture of **1m** (9 g), acetic anhydride (90 ml), and dry pyridine (9 ml) was heated at 110°C for 2 h. After removal of the acetic anhydride and pyridine *in vacuo*, the residue was recrystallized from MeOH to give 4.4 g (53%) of **11**, mp 167—167.5°C. *Anal.* Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.53; H, 5.27; N, 9.93. IR ν_{max}^{Nujol} cm^{-1}: 3450, 1660, 1640. NMR (DMSO-d_6) δ: 2.84 (3H, s, C_2–CH_3), 12.57 (1H, broad s, NH). MS *m/e*: 278 (M^+).

References and Notes

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6) The details will be reported in the next paper.