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Reaction of 1,2,3,4-Tetrahydroquinazolin-4-ones with Acid Anhydride. III¹⁾

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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 -substituents 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-mono-substituted 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-acetyliden-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-acetyliden-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.

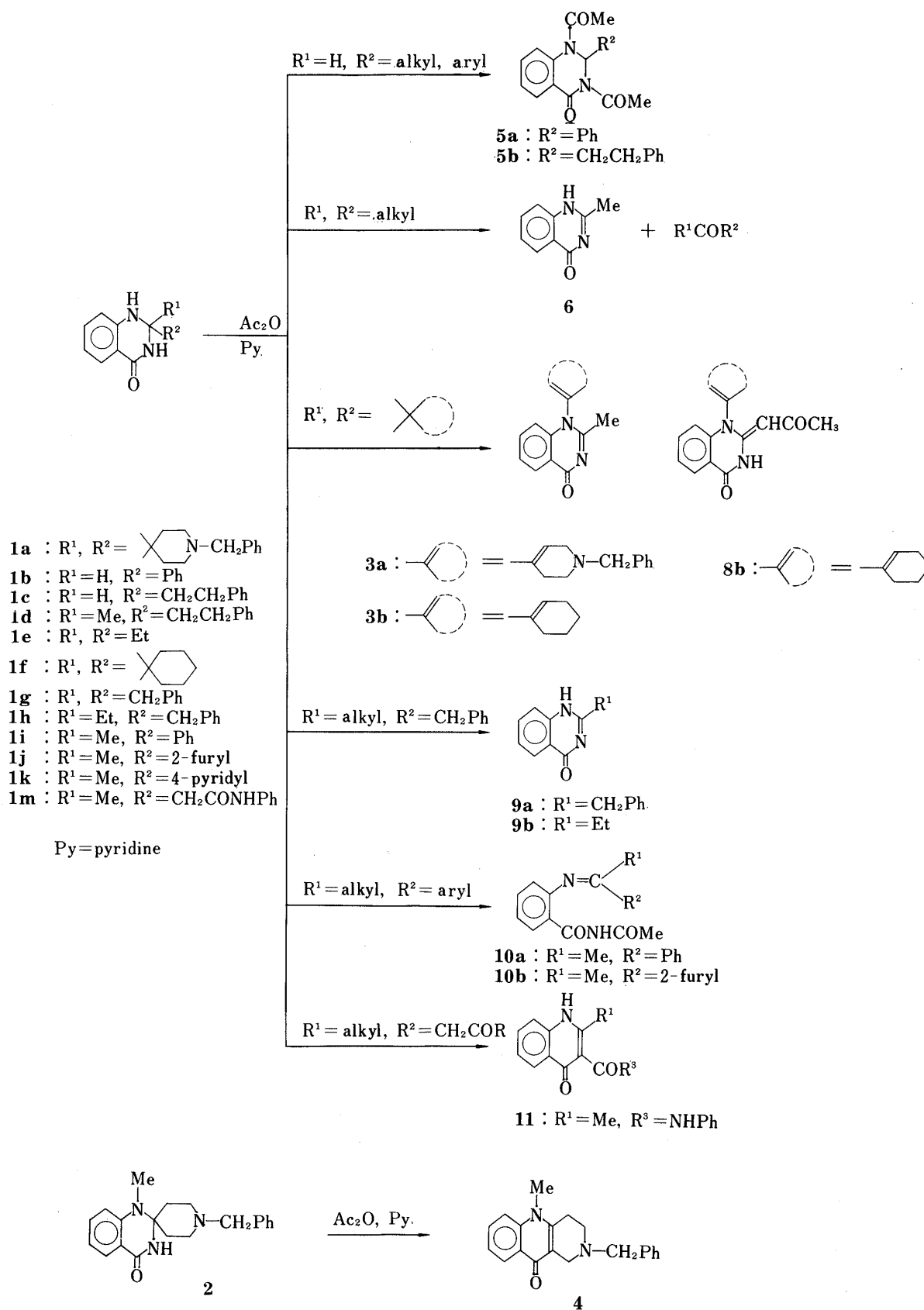


Chart 1

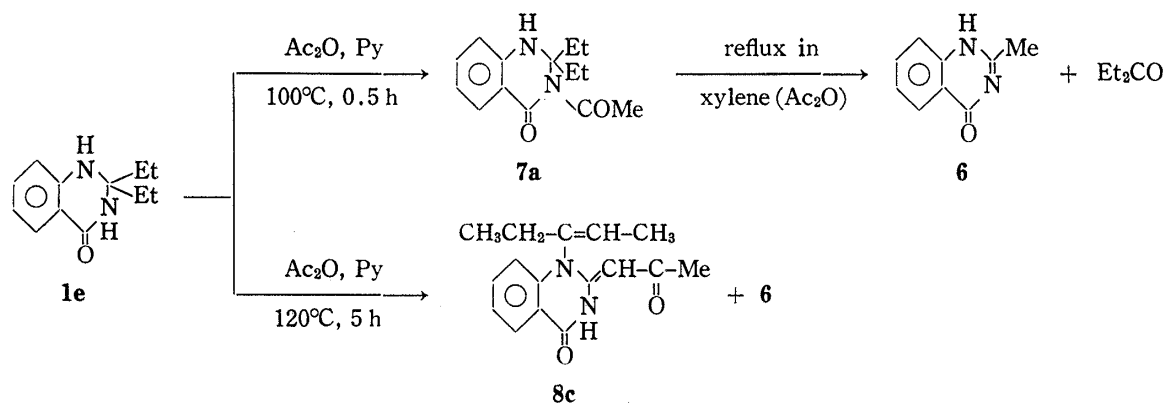


Chart 2

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-phenylethylideneamino)-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 ($\text{N}_1\text{-H}$). 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

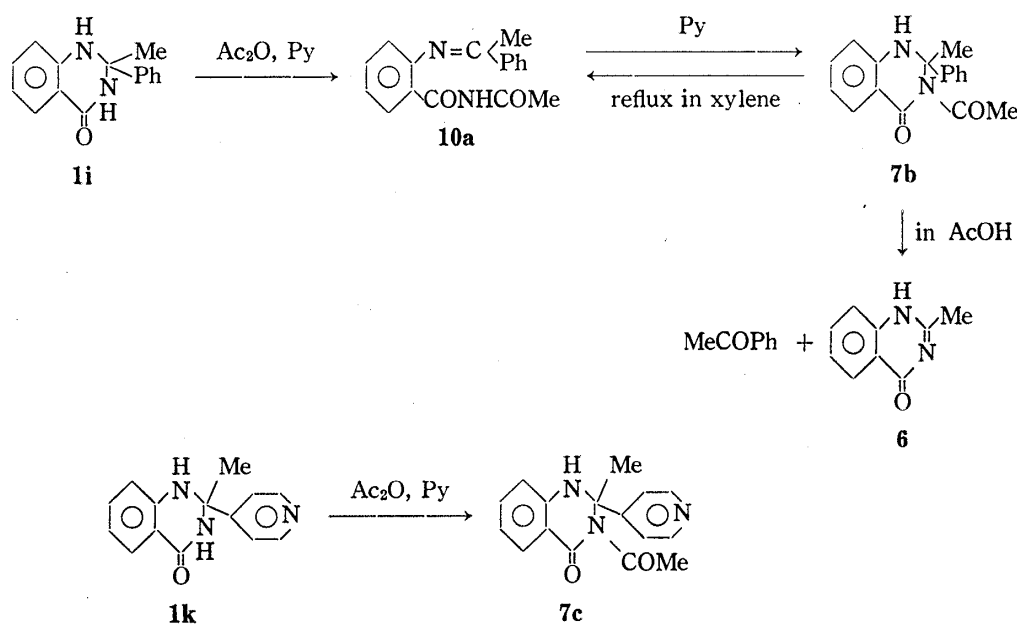


Chart 3

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 carbamoyl-methyl 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.

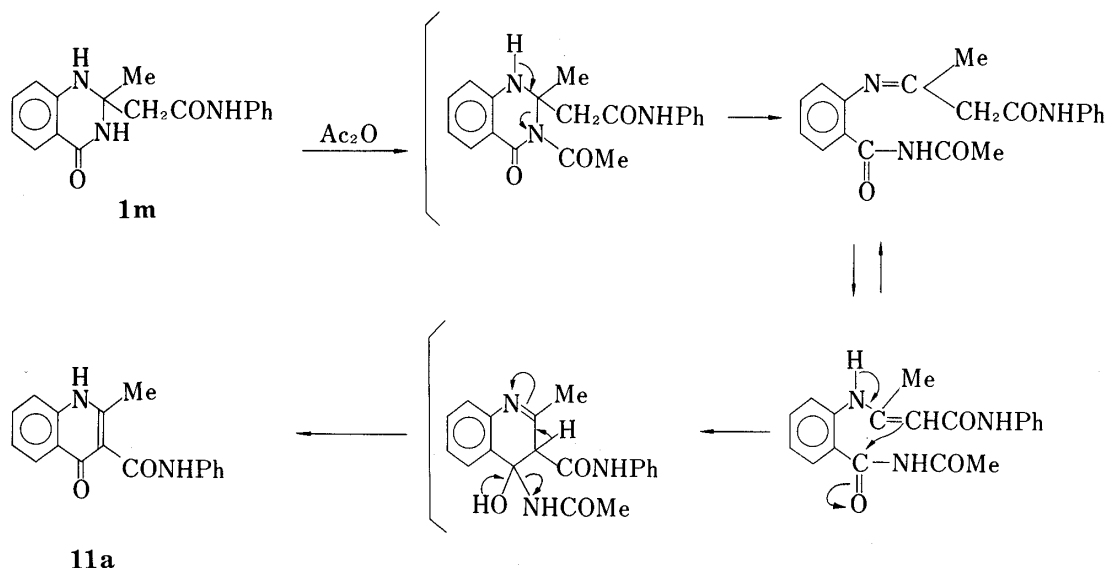


Chart 4

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°C⁴), 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 (%)			IR (cm ⁻¹)	NMR (δ)
						Calcd (Found)				
						C	H	N		
1d	0.1	100	<i>p</i> -TsOH (c.a.) ^{c)}	99	164—165 ^{d)}	76.66 (76.82)	6.74 6.74	10.52 10.33)	3270 3150 1640	1.47 (3H, s, CH ₃) ^{e)} 8.1—8.3 (1H, b ^{f)} , NH)
1e	0.1	100	<i>p</i> -TsOH (c. a.)	90	203—205 ^{d)}	70.56 (70.38)	7.90 8.06	13.72 13.42)	3330 3170 1640	0.93 (6H, t, CH ₃) ^{e)} 1.63 (4H, q, CH ₂) 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 (80.26)	6.14 6.07	8.53 8.75)	3300 3200 1655	3.11 (4H, d, CH ₂ Ph) ^{h)} 4.3—4.7 (1H, b, N ₁ -H) 7.7—7.9 (1H, b, N ₃ -H)
1h	2.5	100	—	56	148—150 ^{g)}	76.66 (76.52)	6.81 6.83	10.52 10.35)	3370 3280 1650	0.99 (3H, t, CH ₃) ^{e)} 1.71 (2H, q, CH ₂ CH ₃) 2.99 (2H, s, CH ₂ Ph) 7.9—8.1 (1H, b, N ₃ -H)
1j	3	120	ZnCl ₂ (0.1)	67	221—225 ^{d)}	68.41 (67.93)	5.30 5.31	12.27 11.91)	3250 3300 1660	1.77 (3H, s, CH ₃) ^{e)} 8.61 (1H, s, N ₃ -H)
1k	4.5	115	CCl ₃ COOH (0.3)	65	238—240 ^{d)}	70.27 (70.45)	5.30 5.36	17.56 17.43)	3300 1600	1.76 (3H, s, CH ₃) ^{e)} 9.06 (1H, s, N ₃ -H)
1m	4	100 ⁱ⁾	—	55	190—191 ^{d)}	69.13 (69.19)	5.80 5.91	14.23 14.23)	3250 1670 1640	1.60 (3H, s, CH ₃) ^{e)} 2.82 (2H, s, CH ₂ CO) 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 CDCl₃. i) Under reduced pressure.

in vacuo, the residue was chromatographed on a column of silica gel with CH₂Cl₂ to give 0.41 g (34%) of **7a**, mp 97—100°C. *Anal.* Calcd for C₁₄H₁₈N₂O₂: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.54; H, 7.48; N, 11.02. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3320, 1725, 1640. NMR (CDCl₃) δ : 0.90 (6H, t, *J* = 7 Hz, CH₂CH₃), 1.58—2.76 (4H, m, CH₂CH₃), 2.58 (3H, s, N-COCH₃), 4.63—4.85 (1H, broad s, NH). MS *m/e*: 246 (M⁺).

2-Acetyliden-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 CH₂Cl₂ 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 C₁₆H₁₈N₂O₂: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.12; H, 6.73; N, 10.22. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1685, 1610. NMR (CDCl₃) δ : 1.00 (3H, t, *J* = 7 Hz, CH₂CH₃), 1.99 (3H, d, *J* = 6 Hz, =CHCH₃), 2.11 (3H, s, COCH₃), 2.56 (2H, q, *J* = 7 Hz, CH₂CH₃), 5.02 (1H, s, =CHCO), 5.80 (1H, q, *J* = 6 Hz, =CHCH₃). 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 Et₂O and hexane to give 6 g (68%) of **10a**, mp 97—98°C. *Anal.* Calcd for C₁₇H₁₆N₂O₂: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.47; H, 5.64; N, 10.23. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3225, 1710, 1685, 1660, 1625. NMR (CDCl₃) δ : 2.31 (3H, s, CH₃), 2.41 (3H, s, COCH₃), 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 Et₂O 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 C₁₇H₁₆N₂O₂: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.00; H, 5.62; N, 9.99. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3305, 1720, 1640. NMR (DMSO-*d*₆) δ : 1.97 (3H, s, C₂-CH₃), 2.44 (3H, s, COCH₃), 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 $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.72; H, 5.23; N, 10.31. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3425, 1685, 1610. NMR (CDCl_3) δ : 2.30 (3H, s, $\text{N}=\text{C}-\text{CH}_3$), 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 $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.53; H, 5.40; N, 14.93. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3300, 1720, 1640. NMR ($\text{DMSO}-d_6$) 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 $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.53; H, 5.27; N, 9.93. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3450, 1660, 1640. NMR ($\text{DMSO}-d_6$) 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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