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

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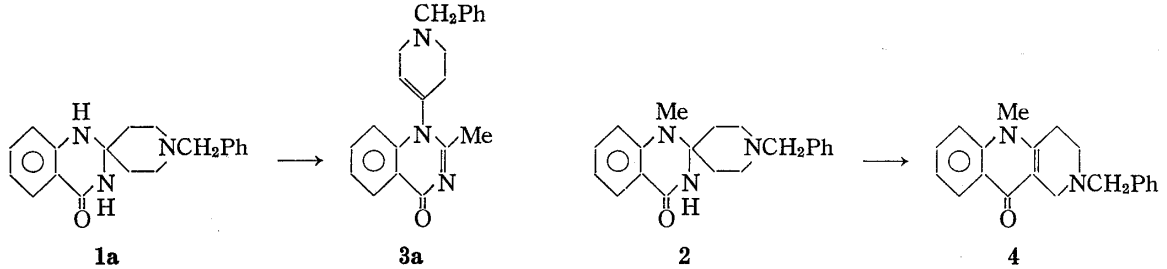
The reaction of 1,2,3,4-tetrahydroquinazoline-2-spirocyclohexan-4-one (**1b**) with acetic anhydride and pyridine gave 1-(1-cyclohexenyl)-2-methyl-1,4-dihydroquinazolin-4-one (**3b**). Compound **3b** gave 3-acetyl-1-(1-cyclohexenyl)-2-methyl-1,2,3,4-tetrahydroquinazolin-4-one (**8b**) upon reduction with $NaBH_4$ 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; ^{1}H-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 of 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 pyridine[1)] 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**),



1a **3a** **2** **4**

type A rearrangement type B rearrangement

Chart 1

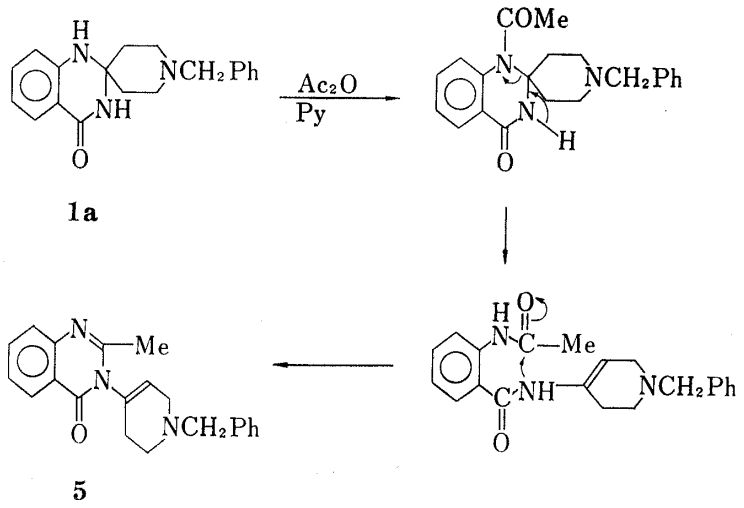


Chart 2

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.

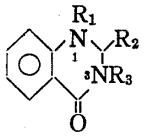
We have now reinvestigated the structure of the product. Namely, the following experiments were undertaken in order to determine whether the structure is **3a** or **5**.

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 ($NaBH_4$) 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, N_1- and/or N_3-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 N_3-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 N_1-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 N_1- and N_3-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 N_1,N_3-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 N_3-acetyl groups, and in particular, it was very similar to those of the N_3-acetyl groups of **9** and **13** in which R_2 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–COMe	Chemical shifts (δ) N_3–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	CH_2CH_2Ph	COMe	2.15	2.60
8b	H	Me	COMe	—	2.57

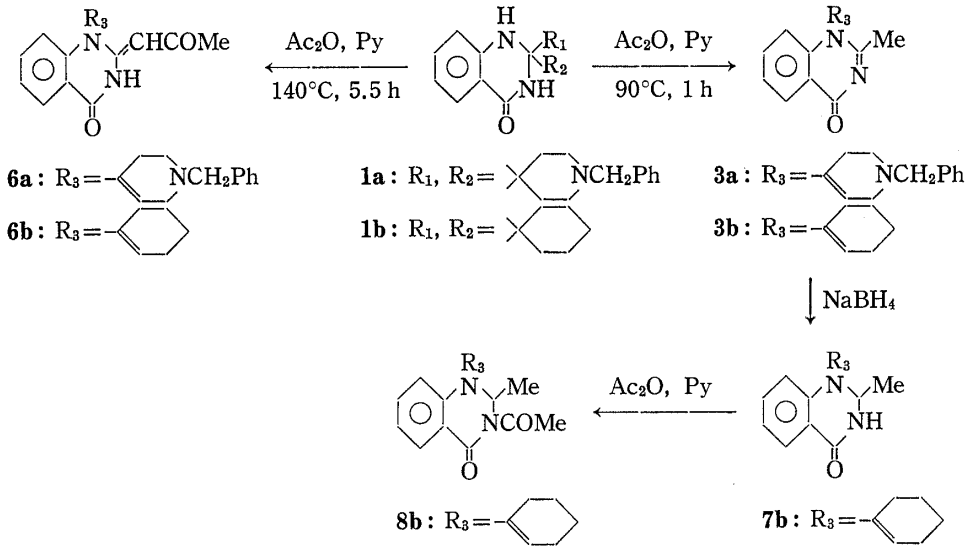


Chart 3

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-acetonylidene-1-(1-benzyl-1,2,5,6-tetrahydro-4-pyridyl)-1,2,3,4-tetrahydroquinazolin-4-one, 2-acetonylidene-(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).

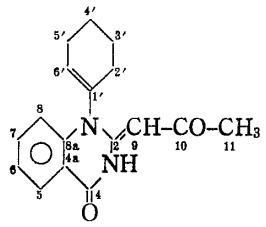
Consequently, it was clear that the A type rearrangement product of the reaction of **1a** with acetic anhydride and pyridine was not **5** but **3a**, as proposed in our previous report.[1)]

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 Nippon-bunko 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. ^{1}H- 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)

$C_{15}H_{16}N_2O$: C, 74.79; H, 6.71; N, 11.66. Found: C, 74.94; H, 6.79; N, 11.46. IR ν_{max}^{Nujol} cm^{-1}: 1640. ^{1}H-NMR (in $CDCl_3$) δ: 1.59—2.41 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.20—2.41 (4H, m, $C\underline{H}_2$–C=CH–$C\underline{H}_2$), 2.48 (3H, s, N=C–CH_3), 6.01 (1H, m, >C=CH). MS *m/e*: 240 (M^+).

2-Acetonylidene-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—163°C. *Anal.* Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.54; H, 6.38; N, 9.73. IR ν_{max}^{Nujol} cm^{-1}: 1620, 1675, 3600. MS *m/e*: 282 (M^+).

2-Acetonylidene-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—181°C. *Anal.* Calcd for $C_{23}H_{23}N_3O_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 74.23; H, 6.28; N, 11.19. IR ν_{max}^{Nujol} cm^{-1}: 1610, 1690, 3310. ^{1}H-NMR (in $CDCl_3$) δ: 2.10 (3H, s, $COCH_3$), 2.12—2.47 (2H, m, N–$CH_2C\underline{H}_2$), 2.67—2.90 (2H, m, N–$C\underline{H}_2CH_2$), 3.12—3.35 (2H, m, N–$C\underline{H}_2CH$=), 3.66 (2H, s, $NC\underline{H}_2$-C_6H_5), 4.92 (1H, s, COCH=), 5.76—5.98 (1H, m, $NCH_2C\underline{H}$=), 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—165°C. *Anal.* Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.12; H, 7.52; N, 11.62. IR ν_{max}^{Nujol} cm^{-1}: 1660, 3180, 3300. ^{1}H-NMR (in $CDCl_3$) δ: 1.44 (3H, d, J=7.2 Hz, CH–$C\underline{H}_3$), 1.56—1.88 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$–), 1.88—2.39 (4H, m, $C\underline{H}_2CH$=C–$C\underline{H}_2$), 4.96 (1H, q, J=7.2 Hz, $C\underline{H}$–CH_3), 5.52—5.80 (1H, m, CH=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 $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.78; H, 7.16; N, 9.93. IR ν_{max}^{Nujol} cm^{-1}: 1650 (shoulder), 1685. ^{1}H-NMR (in $CDCl_3$) δ: 1.39 (3H, d, J=7 Hz, $CH_2C\underline{H}_3$), 1.52—1.97 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 1.97—2.51 (4H, m, CH_2CH=C–$C\underline{H}_2$), 2.57 (3H, s, $COCH_3$), 5.39—5.81 (1H, m, >C=CH), 6.01 (1H, q, J=7 Hz, $C\underline{H}$–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-one[4] (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 ν_{max}^{Nujol} cm^{-1}: 1650, 3160. ^{1}H-NMR (in $CDCl_3$) δ: 1.35 (3H, d, J=6 Hz, C_2–CH_3), 2.82 (3H, s, NCH_3), 4.47—4.93 (1H, m, C_2–H), 8.20—8.55 (1H, b, N_3–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 ν_{max}^{Nujol} cm^{-1}: 1610, 1680. ^{1}H-NMR (in $CDCl_3$) δ: 1.24 (3H, d, J=6 Hz, C_2–CH_3), 2.56 (3H, s, $COCH_3$), 2.93 (3H, s, NCH_3), 5.80 (1H, q, J=6 Hz, C_2–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] (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 ν_{max}^{Nujol} cm^{-1}: 1650, 1680. ^{1}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-one[2] (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 ν_{max}^{Nujol} cm^{-1}: 1640. ^{1}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-one[5] (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 ν_{max}^{Nujol} cm^{-1}: 1665, 1680, 1695. ^{1}H-NMR (in $CDCl_3$) δ: 2.41 (3H, s, N_1–$COCH_3$), 2.76 (3H, s, N_3–$COCH_3$), 8.30 (1H, s, C_2–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 ν_{max}^{Nujol} cm^{-1}: 1645, 3160, 3280. ^{1}H-NMR (in DMSO-d_6) δ: 1.77 (2H, m, $C\underline{H}_2CH_2Ph$), 2.65 (2H, m, $CH_2\underline{CH}_2Ph$), 4.67—5.93 (1H, b, N_1–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 $\nu_{max}^{liq.}$ cm^{-1}: 1670, 1700. ^{1}H-NMR (in $CDCl_3$) δ: 2.15 (3H, s, N_1–$COCH_3$), 2.60 (3H, s, N_3–$COCH_3$). MS *m/e*: 336 (M^+).

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