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Reaction of Spiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-ones with Acid Anhydrides

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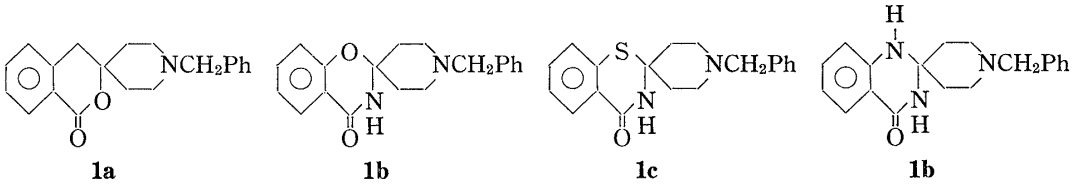
Acylation of spiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-ones (**1d**, **4**, **6**, and **7**) was attempted. In all cases, the resulting products were not the corresponding acyl derivatives but two types of products (**2** or **3** and **5**). Heating **1d**, the derivative having hydrogen atoms on the $N_{(1)}$ and $N_{(3)}$-positions of spiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-ones with acetic anhydride or benzoic anhydride gave 1-(1-benzyl-1,2,5,6-tetrahydro-4-pyridyl)-2-methyl-1,4-dihydroquinazolin-4-one (**2**) or 1-(1-benzyl-1,2,5,6-tetrahydro-4-pyridyl)-2-phenyl-1,4-dihydroquinazolin-4-one (**3**), respectively. On the other hand, heating **4**, the $N_{(1)}$-substituted derivative of **1d**, with acetic anhydride gave 2-benzyl-5-methyl-1,2,3,4,5,10-hexahydro-benzo[*b*]-1,6-naphthyridin-10-one (**5**). The $N_{(3)}$-substituted derivatives (**6** and **7**) of **1d** did not react with acetic anhydride.

Keywords——quinazoline; 1,6-naphthyridine; rearrangement; reaction mechanism; reaction with acid anhydride; ^{13}C-NMR

In our previous work,[2] we found that 1′-benzylspiro[isochroman-3,4′-piperidin]-1-one (**1a**), 1′-benzylspiro[4*H*-1,3-benzoxazine-2(3*H*),4′-piperidin]-4-one (**1b**), and 1′-benzylspiro-[4*H*-1,3-benzothiazine-2(3*H*),4′-piperidin]-4-one (**1c**) exhibited inhibitory activity towards histamine release from rat mast cells. However, 1-benzylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one (**1d**), considered to be an isostere of **1b** or **1c**, had a lower activity. Because the decrease of the activity in **1d** seemed to be due to the presence of a basic imino group in the molecule, replacement of the proton of the imino group by an acetyl group was attempted.



1a **1b** **1c** **1b**

Chart 1

Compound **1d** had been prepared by Wolf and Diebold[3] by condensation of 2-aminobenzamide with 1-benzyl-4-piperidone, using zinc chloride as a catalyst, but in our present experiments it was easily prepared in 66% yield by heating 2-aminobenzamide with 1-benzyl-4-piperidone at 110—120° without any catalyst for five hours under reduced pressure. Mirza[4] reported the acetylation of 3,4-dihydroquinazolin-4-one: Stirring the sodium salt of 3,4-dihydroquinazolin-4-one with acetyl chloride in dioxane or refluxing it with acetic anhydride gave 4-acetoxyquinazoline, which is very susceptible to hydrolysis. Okumura and co-workers[5] reported the acetylation of 2-methyl-3-(2,3-xylyl)-1,2,3,4-tetrahydroquinazolin-4-

1) Location: *Tsushima-naka 1-1-1, Okayama 700, Japan.*
2) M. Yamato, M. Ikeda, H. Ohtake, K. Hashigaki, and K. Tasaka, *J. Med. Chem.*, "submitted".
3) M. Wolf and J.L. Diebold, U.S. patent 3714093 (1973) [*Chem. Abstr.*, **78**, 111344*v* (1973)].
4) R. Mirza, *Nature* (London), **816**, 716 (1960).
5) K. Okumura, T. Oine, Y. Yamada, G. Hayashi, and M. Nakama, *J. Med. Chem.*, **11**, 348 (1968).

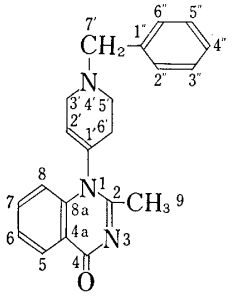
one with acetyl chloride in the presence of potassium carbonate in acetone, giving 1-acetyl-2-methyl-3-(2,3-xylyl)-1,2,3,4-tetrahydroquinazolin-4-one.

In the hope of obtaining 1′-acetyl-1-benzylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one, acetylation of **1d** was attempted firstly by stirring **1d** with acetyl chloride in the presence of dry pyridine at room temperature for two days. However, this was unsuccessful. Secondly, **1d** was stirred with a mixture of acetic anhydride and dry pyridine at room temperature for 12 hours, but again, acetylation of **1d** did not occur. Finally, **1d** was heated with a mixture of acetic anhydride and dry pyridine at 140°. However, the resulting product was not 1′-acetyl-1-benzylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one, but a new compound which corresponds to a molecular formula of $C_{21}H_{21}N_3O$ on the basis of its elemental analysis data and mass spectrum (MS) (M^+, *m/e*: 331). The proton magnetic resonance (PMR) spectrum of the compound in $CDCl_3$ indicated the presence of a methyl group similar to that of acetamidine (δ: 2.55, 3H, s), an ethylenic proton of enamine type (δ: 6.03, 1H, broad), and an aromatic proton adjacent to a carbonyl group (δ: 8.23, 1H, dd, J= 2, 8 Hz). The remaining signals are those of two protons of the *N*-benzyl group, six protons of three methylene groups, and eight protons of benzene rings. The infrared (IR) absorption at 1625 cm^{-1} indicates the presence of an amide group.

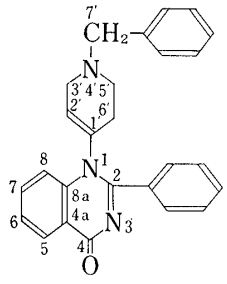
On the basis of these data, the structure of this compound was established to be 1-(1-benzyl-1,2,5,6-tetrahydro-4-pyridyl)-2-methyl-1,4-dihydroquinazolin-4-one (**2**). This structure was also supported by the ^{13}C-NMR spectrum of **2** (Table I).

Similarly, heating **1d** with benzoic anhydride under the conditions used for the preparation of **2** afforded 1-(1-benzyl-1,2,5,6-tetrahydro-4-pyridyl)-2-phenyl-1,4-dihydroquinazolin-4-one

Table I. ^{13}C-NMR Chemical Shifts (ppm) in **2** and **3**



2



3

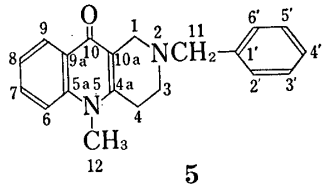
Carbons	Chemical shifts	Carbons	Chemical shifts
2	153.6(s)	2	172.3(s)
4	169.8(s)	4	170.9(s)
4a	120.2(s)	4a	121.7(s)
5	134.3(d)	5	134.7(d)
6	130.8(d)	6	133.1(d)
7	135.2(d)	7	135.9(d)
8, 2′	116.4(d), 128.1(d)	8, 2′	118.6(d), 131.6(d)
8a	141.6(s)	8a	142.9(s)
9	23.2(q)	—	
1′	161.1(s)	1′	162.9(s)
3′	52.0(t)	3′	52.2(t)
5′	49.4(t)	5′	49.4(t)
6′	29.2(t)	6′	30.1(t)
7′	62.4(t)	7′	62.4(t)
1″	138.3(s)		
2″, 6″	129.7(d)		
3″, 5″	129.2(d)		
4″	126.4(d)		

(3). Its IR and PMR spectral data are given in the experimental section, and the ^{13}C-NMR spectral data are listed in Table I.

In order to clarify the mechanism of this reaction a methyl derivative of **1d**, 1-benzyl-1′-methylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4-one (**4**), prepared by heating 2-methylaminobenzamide with 1-benzyl-4-piperidone, was heated at 140° with acetic anhydride in the presence of dry pyridine. A new type of product was obtained. This compound had a molecular formula of $C_{20}H_{20}N_2O$ on the basis of its elemental analysis data and MS spectrum (M^+, *m/e*: 304, M^+-15, M^+-28, M^+-29, M^+-91). Its PMR spectrum in $CDCl_3$ indicated the presence of a methyl group on a nitrogen atom of enamine type (δ: 3.60, 3H, s), a benzyl group on a nitrogen atom (δ: 3.73, 2H, s), and an aromatic proton adjacent to a carbonyl group (δ: 8.46, 1H, dd, J=2, 8 Hz), The remaining signals are those of six protons of three methylene groups at δ: 2.60—2.85 as a multiplet, 2.76 as a singlet and 3.25—3.98 as a multiplet, attributable to the 1,2,5,6-tetrahydropyridyl group, and eight protons of benzene rings at δ: 7.15—7.82 as a multiplet and 7.35 as a singlet. The IR absorptions at 1618, 1600, 1575, and 1545 cm^{-1} indicated the presence of a carbonyl group conjugated with a double bond attached to an atom having a lone pair.

On the basis of these data, the structure of this compound was established to be 2-benzyl-5-methyl-1,2,3,4,5,10-hexahydrobenzo[*b*]-1,6-naphthyridin-10-one (**5**). This structure was also supported by the ^{13}C-NMR spectrum (Table II).

Table II. ^{13}C-NMR Chemical Shifts (ppm) in **5**



5

Carbons	Chemical shifts	Carbons	Chemical shifts
1	51.4(t)	9a	118.1(s)
3	33.4(t)	10	175.3(s)
4	29.2(t)	10a	139.2(s)
4a	147.5(s)	11	62.9(t)
5a	142.0(s)	12	49.4(q)
6	115.7(d)	1′	125.8(s)
7	132.5(d)	2′, 6′	131.0(d)
8	123.5(d)	3′, 5′	129.3(d)
9	128.1(d)	4′	127.3(d)

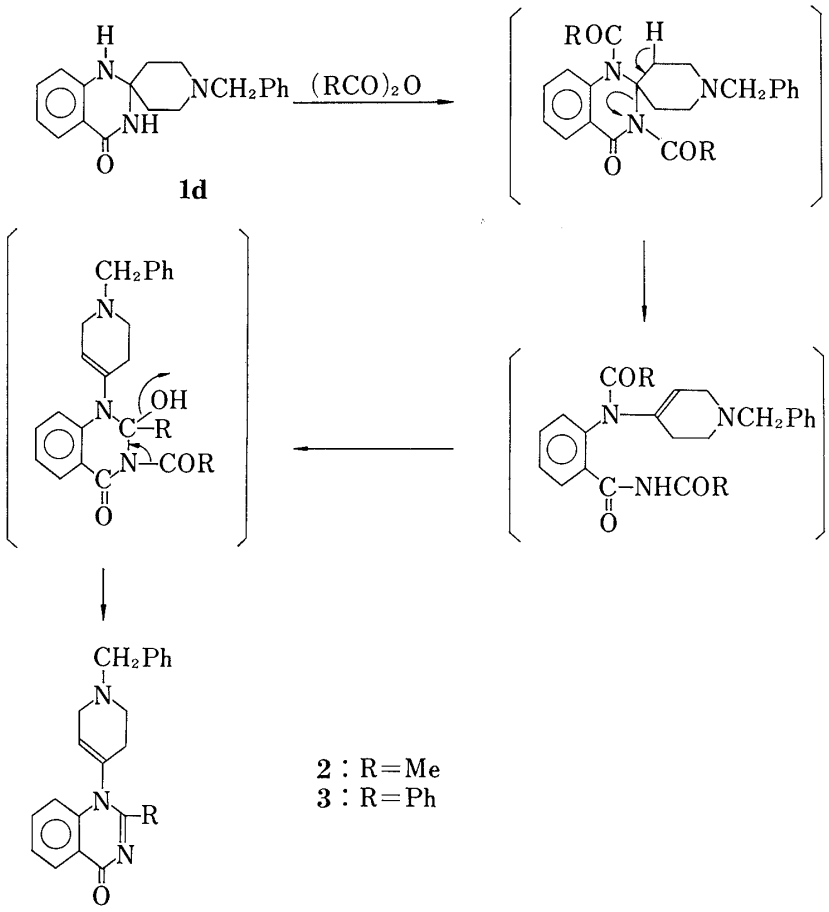
Other methyl derivatives of **1d**, 1-benzyl-3′-methylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one (**6**) and 1-benzyl-1′,3′-dimethylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one (**7**), were prepared by heating 1-benzyl-4-piperidone with 2-amino-*N*-methylbenzamide or 2-methylamino-*N*-methylbenzamide, respectively. Heating **6** or **7** with acetic anhydride under the conditions used for **1d** resulted in the recovery of **6** or **7** and a small amount of polymerized product.

Thus, the reaction of 3′-substituted spiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-ones (**6** and **7**) with acetic anhydride did not give any product; the starting material was recovered. This was the case whether there was a substituent at the 1′-position of these compounds or not. The same reaction of 3′-unsubstituted spiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-ones (**1d** and **4**) gave one of two types of product, depending upon the presence or absence of a substituent at the 1′-position.

The mechanism of formation of **2** or **3** upon heating **1d** with acid anhydride is proposed to be as shown in Chart 3. Chart 4 shows the mechanism of formation of **5** on heating **4** with acetic anhydride.

6 **7**

Chart 2



1d

2 : R=Me
3 : R=Ph

Chart 3

Experimental

All melting points were measured on a micro hot stage apparatus and are uncorrected. PMR spectra were obtained on a Hitachi R-22 spectrometer at 90 MHz and ^{13}C-NMR spectra were obtained on a Hitachi 22-FTS spectrometer at 22.6 MHz, employing tetramethylsilane as an internal standard. MS spectra were measured with a Shimadzu LKB-9000 spectrometer. IR spectra were obtained on a Nipponbunko A-102 spectrometer.

1-Benzylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one (1d)——A mixture of 2-aminobenzamide (2.7 g) and 1-benzyl-4-piperidone (3.8 g) was heated at 110—120° for 5 hr under reduced pressure, and the solidified product was washed with Et_2O. Recrystallization of the residue from THF gave 4.0 g (66%) of **1d**, mp 258°. *Anal.* Calcd for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found: C, 74.23; H, 6.87; N, 13.69. IR ν_{max}^{Nujol} cm^{-1}: 1642. PMR (in $CDCl_3$) δ: 2.35 (4H, m, $CH_2\times2$), 3.50 (4H, m, $NCH_2\times2$), 4.37 (2H, s, NCH_2Ph), 7.68 (1H, dd, J=2, 8 Hz, aromatic H). MS *m/e*: 307 (M^+).

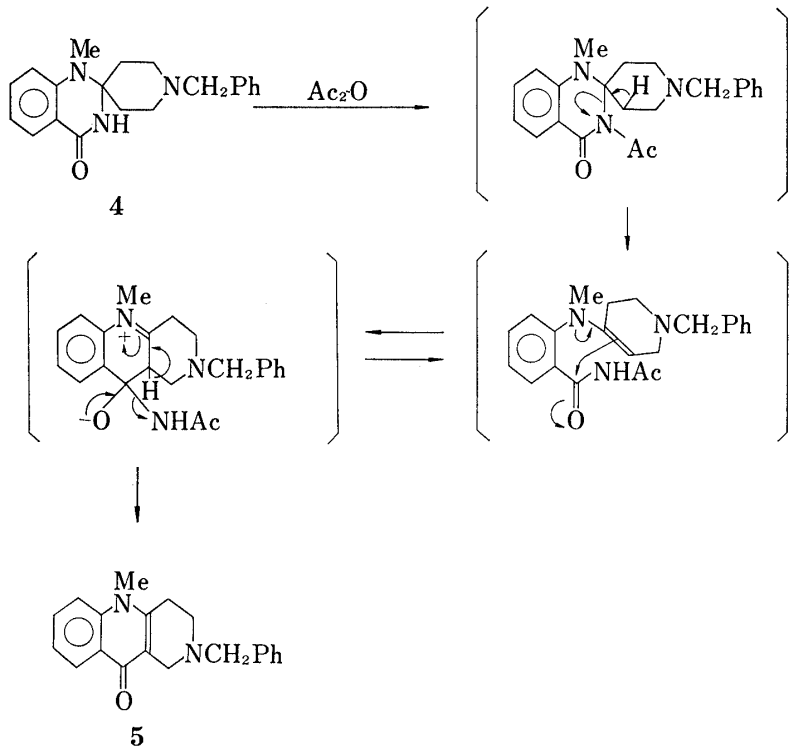


Chart 4

1-(1-Benzyl-1,2,5,6-tetrahydro-4-pyridyl)-2-methyl-1,4-dihydroquinazolin-4-one (2)——A mixture of **1d** (3.0 g), acetic anhydride (30 ml), and dry pyridine (3 ml) was heated at 140° for 1 hr. After most of acetic anhydride had been evaporated off *in vacuo*, the residue was made basic with Na_2CO_3 solution, and extracted with AcOEt. The AcOEt layer was washed with $KHCO_3$ and NaCl solution, and the solvent was evaporated off. The residue was crystallized from benzene–Et_2O to give 2.0 g (62%) of **2**, mp 150°. *Anal.* Calcd for $C_{21}H_{21}N_3O$: C, 76.10; H, 6.39; N, 12.68. Found: C, 76.31; H, 6.28; N, 12.62. IR ν_{max}^{Nujol} cm^{-1}: 1645. PMR (in $CDCl_3$) δ: 2.35 (2H, m, CH_2), 2.55 (3H, s, N=C–CH_3), 2.83 (2H, m, NCH_2), 3.30 (2H, m, =CH–$\underline{CH_2}$N), 3.75 (2H, s, NCH_2Ph), 6.03 (1H, t, $J=2$ Hz, N–C=$\underline{CH}$–CH_2), 6.95—7.71 (3H, m, aromatic H), 7.40 (5H, s, aromatic H), 8.23 (1H, dd, $J=2$, 8 Hz, aromatic H). MS *m/e*: 331 (M^+).

1-(1-Benzyl-1,2,5,6-tetrahydro-4-pyridyl)-2-phenyl-1,4-dihydroquinazolin-4-one (3)——A mixture of **1d** (3.0 g), benzoic anhydride (6.0 g), and dry pyridine (10 ml) was heated at 120° for 3 hr. The reaction mixture was then extracted with AcOEt and the AcOEt layer was washed with $KHCO_3$ and NaCl solution. After removal of the solvent, the residue was dissolved in a small volume of $CHCl_3$ and diluted with Et_2O to give 1.7 g (45%) of **3**, mp 190—191°. *Anal.* Calcd for $C_{26}H_{23}N_3O$: C, 79.36; H, 5.90; N, 10.68. Found: C, 79.37; H, 5.93; N, 10.66. IR ν_{max}^{Nujol} cm^{-1}: 1700, 1600. PMR (in $CDCl_3$) δ: 1.17 (2H, m, CH_2), 1.55 (2H, m, CH_2N), 3.23 (2H, m, CH_2N), 3.60 (2H, s, NCH_2Ph), 6.02 (1H, m, –CH=C), 7.30 (5H, s, aromatic H), 7.37—7.72 (8H, m, aromatic H), 8.12 (1H, dd, $J=2$, 8 Hz, aromatic H). MS *m/e*: 393 (M^+).

1-Benzyl-1′-methylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one (4)——A mixture of 2-methylaminobenzamide (6.0 g) and 1-benzyl-4-piperidone (8.0 g) was heated at 120° for 5 hr under reduced pressure. Recrystallization of the resulting viscous product from MeOH gave 5.0 g (39%) of **4**, mp 158—159°. *Anal.* Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.78; H, 7.32; N, 13.11. IR ν_{max}^{Nujol} cm^{-1}: 1662. PMR (in $CDCl_3$) δ: 1.75—2.85 (8H, m, $CH_2\times4$), 2.92 (3H, s, NCH_3), 3.55 (2H, s, NCH_2Ph), 6.50—7.62 (3H, m, aromatic H), 7.32 (5H, s, aromatic H), 7.95 (1H, dd, $J=2$, 8 Hz, aromatic H). MS *m/e*: 321 (M^+).

2-Benzyl-5-methyl-1,2,3,4,5,10-hexahydro-benzo[*b*]-1,6-naphthyridin-10-one (5)——A mixture of **4** (3.0 g), acetic anhydride (30 ml), and dry pyridine (3 ml) was heated at 120° for 5 hr. After removal of Ac_2O *in vacuo*, the residue was extracted with AcOEt. The AcOEt layer was washed with NaCl solution, and the solvent was evaporated off. Purification of the resulting residue by column chromatography on alumina, eluting with CH_2Cl_2 gave 1.6 g (56%) of **5**, which was recrystallized from a mixture of Me_2CO and THF, mp 184—186°. *Anal.* Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.87; H, 6.73; N, 9.19. IR ν_{max}^{Nujol} cm^{-1}: 1545, 1575, 1600, 1618. PMR (in $CDCl_3$) δ: 2.60—2.86 (2H, m, CH_2), 2.76 (2H, s, CH_2N), 3.25—3.98 (2H, m, CH_2N), 3.60 (3H, s, NCH_3), 3.73 (2H, s, NCH_2Ph), 7.15—7.82 (3H, m, aromatic H), 7.35 (5H, s, aromatic H), 8.46 (1H, dd, $J=2$, 8 Hz, aromatic H). MS *m/e*: 304 (M^+).

1-Benzyl-3′-methylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one (6)——A mixture of 2-amino-*N*-methylbenzamide (6.0 g) and 1-benzyl-4-piperidone (8.0 g) was heated at 160° for 7 hr under reduced

pressure. The resulting product was purified by column chromatography on alumina, eluting with petr. ether–benzene (1: 1) followed by benzene. The benzene eluate gave 2.5 g (19%) of **6**, mp 218—219°. *Anal.* Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.76; H, 7.30; N, 13.09. IR ν_{max}^{Nujol} cm^{-1}: 1615. PMR (in $CDCl_3$) δ: 1.53—2.43 (6H, m, $CH_2\times3$), 2.76—2.96 (2H, m, CH_2), 3.10 (3H, s, NCH_3), 3.55 (2H, s, NCH_2Ph), 4.55 (1H, b, NH), 6.63—7.65 (3H, m, aromatic H), 7.92 (1H, dd, $J=2$, 8 Hz, aromatic H). MS *m/e*: 321 (M^+).

1-Benzyl-1′,3′-dimethylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one (**7**)——A mixture of 2-methylamino-*N*-methylbenzamide (7.0 g) and 1-benzyl-4-piperidone (9.0 g) was heated at 120° for 15 hr under reduced pressure. The resulting viscous product was purified by column chromatography on alumina, eluting with CH_2Cl_2. The fraction giving one spot on TLC was distilled at 180° under a high vacuum (0.04 mmHg) to give 3.0 g (21%) of **7**. *Anal.* Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53. Found: C, 75.50; H, 7.60; N, 12.60. IR ν_{max}^{Nujol} cm^{-1}: 1660. PMR (in $CDCl_3$) δ: 1.95 (4H, m, $CH_2\times2$), 2.53 (4H, m, $CH_2\times2$), 2.66 (3H, s, NCH_3), 3.07 (3H, s, NCH_3), 3.48 (2H, s, NCH_2Ph), 6.93—7.63 (3H, m, aromatic H), 7.24 (5H, s, aromatic H), 7.93 (1H, dd, $J=2$, 8 Hz, aromatic H). MS *m/e*: 335 (M^+).