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Reaction of Anthranilamides with Levulinic Acids. Synthesis of 2,3,3a,4-Tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-diones

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The reaction of 2-(methylamino)benzamide with levulinic acid gave 3a,4-dimethyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione (**2**). 3a-Methyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione (**6**) was prepared by the method shown in Chart 3. The compounds **2** and **6** were different from authentic samples A and B prepared by the method reported by previous workers. The real structures of A and B were found to be 3a-methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (**9**) and 3-(2,3-dimethyl-4-oxo-1,2,3,4-tetrahydro-2-quinazolinyl)propionic acid (**10**), respectively.

Keywords——2-aminobenzamides; levulinic acid; pyrrolo[2,1-*b*]quinazolines; pyrrolo[1,2-*a*]quinazolines; NMR spectra

Westphal and Stroh reported that the heating of a solution of 2-aminobenzamide and 4-oxopentanoyl chloride in ether gave 3a-methyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione (A). The structure of A had been deduced based on the fact that the infrared (IR) absorption spectrum and the melting point (139—140°C) of the methyl derivative (B), prepared by treatment of A with dimethyl sulfate, were different from those of 3a,4-dimethyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (C) (mp 99—101°C) prepared by the reaction of 2-amino-*N*-methylbenzamide with 4-oxopentanoyl chloride (Chart 1).[1]

As a part of our studies on the reaction of 4-oxo-1,2,3,4-tetrahydroquinazolines with acetic anhydride,[2] we prepared 3a,4-dimethyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione (**2**) by heating 2-(methylamino)benzamide (**1**) with levulinic acid at 140°C. The hydrolysis of **2** with 10% sodium hydroxide gave 3-(1,2-dimethyl-4-oxo-1,2,3,4-tetrahydro-2-quinazolinyl)propionic acid (**3**), which was recyclized to give **2** by heating with acetic anhydride and pyridine. We considered that **2** might be identical with B. However, it was found that that the melting (171—172°C) of **2** was significantly higher than that (139—140°C) of B.

In order to confirm the structures of A and B, we prepared some related compounds. First, 3a-methyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione (**6**), which was considered to be identical with A was prepared by the alternative method shown in Chart 3. The heating of 2-(benzylamino)benzamide (**4**) with levulinic acid at 160°C gave 4-benzyl-3a-methyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione (**5**), which was debenzylated to give **6** by catalytic reduction on palladiumcarbon. The melting point (176—179°C) of **6** close to that of A, but the spectral data were different from those of A.

Next, the heating of A and **6** with acetic anhydride and pyridine gave monoacylated compounds, **7** and **8**, respectively. The peak of the lactam-carbonyl group in the IR spectrum of A appeared in a lower frequency region (at 1715 cm^{-1}) than that of **6** (at 1750 cm^{-1}). In the nuclear magnetic resonance (NMR) spectra, the signals of the C_5- and C_7-protons of **6** appeared at higher field (at δ: 6.58—6.97) due to the effect of the 4-amino group. On the other hand, such signals attributable to the same protons in the benzene ring did not appear in the NMR spectrum of A. These results suggested that A is not 3a-methyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione but 3a-methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (**9**).[3] In addition, the peak attributable to the *N*-acetyl group of **7** appeared at δ: 2.60 and that of **8** appeared at δ 2.39. Our previous findings,[2b] that the signal of the

N-acetyl group of 1-acetyl-4-oxo-1,2,3,4-tetrahydroquinazolines appeared at about δ: 2.3 and that of 3-acetyl-4-oxo-1,2,3,4-tetrahydroquinazolines appeared at about δ: 2.6, led us to the conclusion that the acetyl group of **8** binds with the N_1 atom of the quinazoline moiety, while that of **7** binds with the N_3 atom of the same moiety.

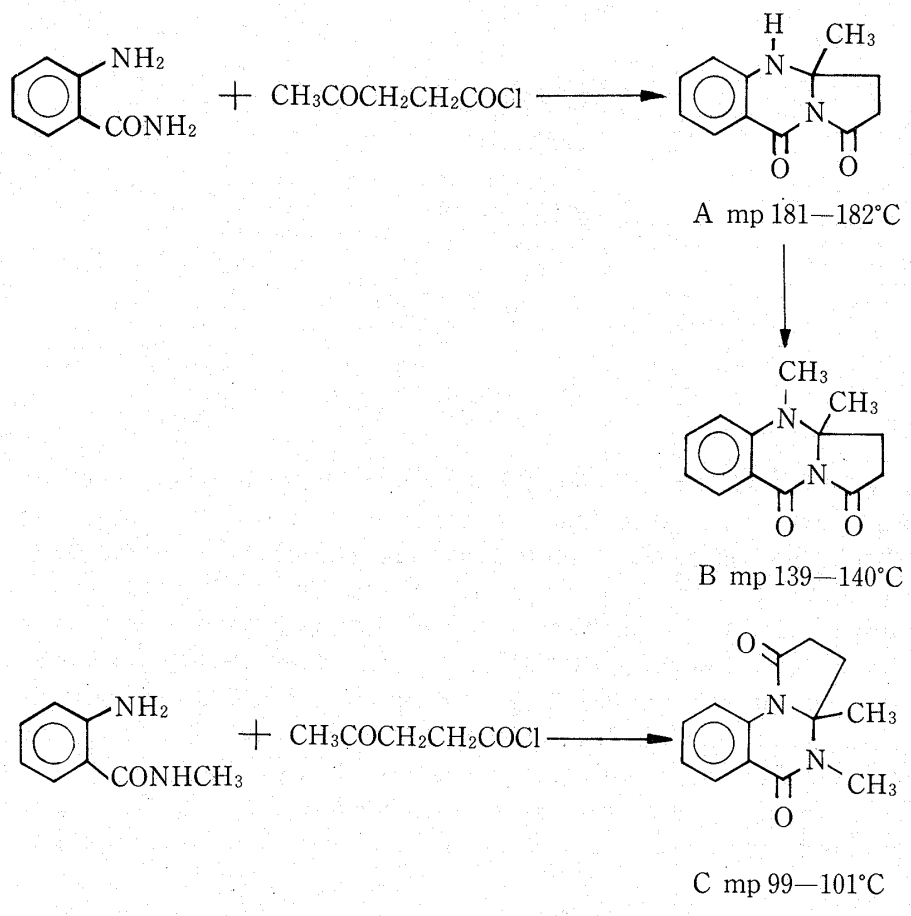


Chart 1

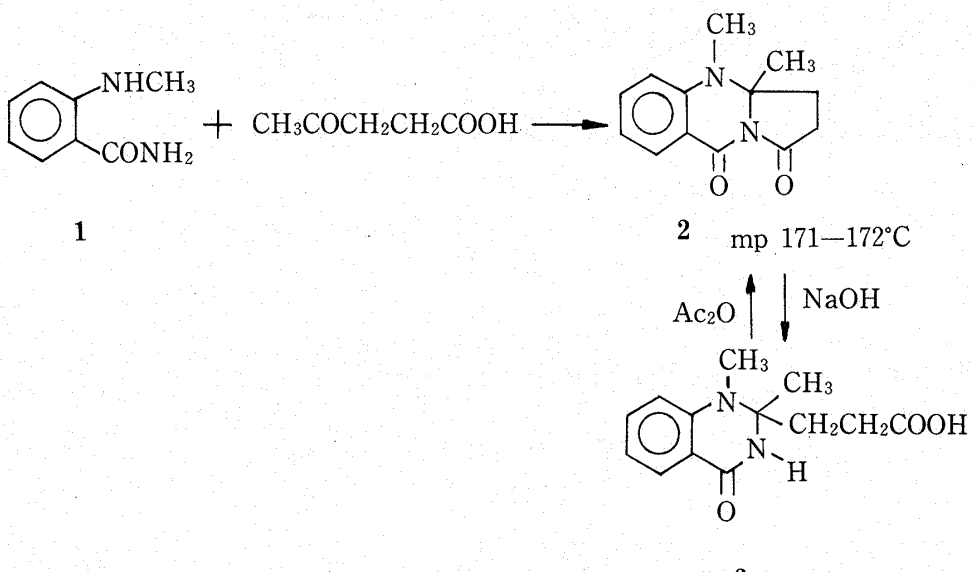
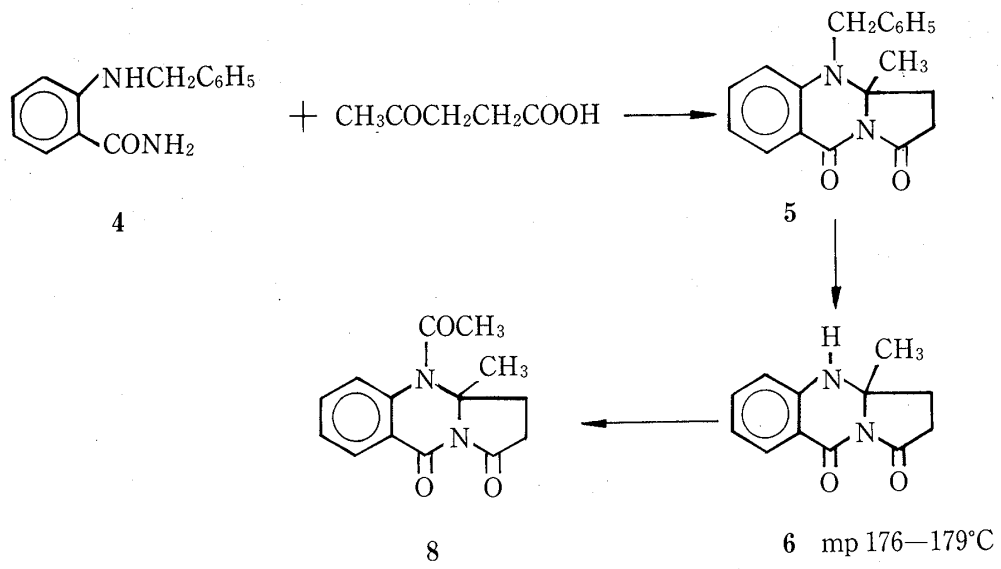


Chart 2



Chart

Since the structure of B proposed by Westphal and Stroh appears extremely doubtful, we reinvestigated the work of Westphal and Stroh and found that A was identical with 3a-methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (**9**) prepared according to the method of Aeberli and Haulihan.[3] However, preparation of B from A was not successful, because no detailed description of the preparation of B was given in their report.[1]

We thus found that the real structure of A is not 3a-methyl-2,3,3a,4-tetrahydro[2,1-*b*]-quinazoline-1,9-dione but 3a-methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione(**9**), and that the real structure of B is neither 3a,4-dimethyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]-quinazoline-1,5-dione (C) nor 3a,4-dimethyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione (**2**). Therefore, the structure of B was assumed to be 3-(2,3-dimethyl-4-oxo-1,2,3,4-tetrahdryo-2-quinazolinyl)propionic acid (**10**), which might be formed by methylation at the

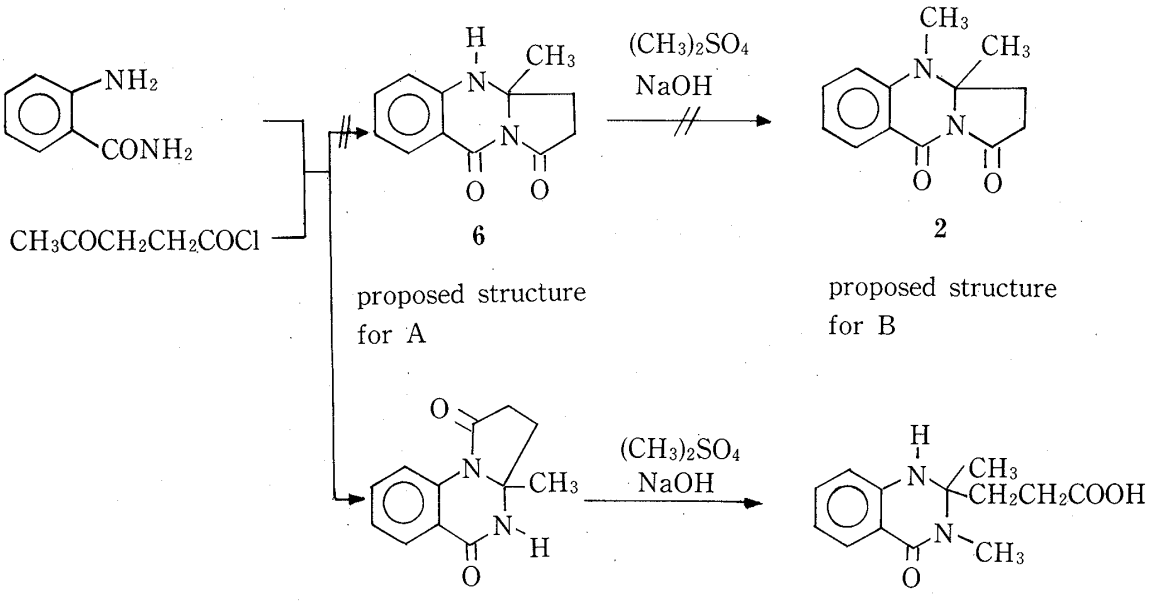


Chart 4

N_4-position of A (=**9**) followed by hydrolysis with sodium hydroxide in the course of the heating of A (=**9**) with dimethyl sulfate and sodium hydroxide in the work of Westphal and Stıoh. The compound **10** was prepared; *i.e.* the compound C, prepared according to the method of Westphal and Stroh, was hydrolyzed with sodium hydroxide to give **10**, which melts at 139-140°C.

Consequently, the result of the reaction of 2-aminobenzamide with 4-oxopentanoyl chloride must be corrected as shown in Chart 4.

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 (MS) were recorded on a Shimadzu LKB-9000 spectrometer, and IR spectra on a Nippon Bunko A-102 spectrometer.

3a-Methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (A=**9**)——Compound A (=**9**) was prepared according to the method of Aeberli and Haulihan.[3] mp 181—182°C. *Anal.* Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.76; H, 5.53; N, 12.93. IR ν_{max}^{Nujol} cm^{-1}: 3150, 1715, 1675. NMR ($CDCl_3$) δ: 1.55 (3H, s, CH_3), 2.17—2.93 (4H, m, CH_2CH_2), 7.07—7.86 (2H, m, C_7H and C_8H), 8.00—8.42 (2H, m, C_6H and C_9H), 8.98—9.51 (1H, broad, NH). MS *m/e*: 216 (M^+).

3a,4-Dimethyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione (**2**)——Method A: A mixture of 2-(methylamino)benzamide (2.8 g) and 4-oxopentanoic acid (3.1 g) was heated at 140°C for 2.5 h and extracted with AcOEt. The AcOEt layer was washed with 10% NaOH and H_2O, dried over $MgSO_4$, and concentrated. Recrystallization of the residue from MeOH gave 0.63 g (14%) of **2**, mp 171—172°C. *Anal.* Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.92; H, 6.32; N, 12.05. IR ν_{max}^{Nujol} cm^{-1}: 1755, 1665. NMR ($CDCl_3$) δ: 1.37 (3H, s, CCH_3), 2.05—2.67 (4H, m, CH_2CH_2), 2.75 (3H, s, NCH_3), 6.55—7.07 (2H, m, C_5H and C_7H), 7.30—7.66 (1H, m, C_6H), 8.01 (1H, dd, J=2, 8 Hz, C_8H). MS *m/e*: 230 (M^+).

Method B: A mixture of **3** (2 g), acetic anhydride (20 ml), and dry pyridine (2 ml) was heated at 140°C for 3.5 h. After most of the acetic anhydride and pyridine had been evaporated off *in vacuo*, the residue was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with NaOH and H_2O, dried over $MgSO_4$, and concentrated. Recrystallization of the residue from MeOH gave 1.2 g (56%) of **2**.

3-(1,2-Dimethyl-4-oxo-1,2,3,4-tetrahydro-2-quinazolinyl)propionic Acid (**3**)——A mixture of **1** (9.3 g) and 4-oxopentanoic acid (7.2 g) was heated at 140°C for 3 h. After cooling, 10% NaOH in EtOH (5 ml) was added to the reactant. The reaction mixture was heated at 100°C for 1 h and made acidic with 10% HCl. The resulting precipitate was filtered off and recrystallized from MeOH to give 14 g (91%) of **3**, mp 192—194°C. *Anal.* Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.00; H, 6.73; N, 11.22. IR ν_{max}^{Nujol} cm^{-1}: 3200, 2550, 1900, 1685. NMR (DMSO-d_6) δ: 1.38 (3H, s, CCH_3), 1.81—2.53 (4H, m, CH_2CH_2), 2.71 (3H, s, NCH_3), 6.51—6.81 (2H, m, aromatic H), 7.14—7.51 (1H, m, aromatic H), 7.64 (1H, dd, J=2, 9 Hz, C_5H), 7.86—8.05 (1H, broad, NH). MS *m/e*: 230 (M^+-H_2O).

4-Benzyl-3a-methyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione (**5**)——A mixture of 2-(benzylamino)benzamide (**4**) (4 g) and 4-oxopentanoic acid (4 g) was heated at 160°C for 3 h. The residue was recrystallized from MeOH to give 3.8 g (70%) of **5**, mp 220—222°C. *Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.49; H, 5.97; N, 9.15. IR ν_{max}^{Nujol} cm^{-1}: 1765, 1660. NMR ($CDCl_3$) δ: 1.59 (3H, s, CCH_3), 2.18—2.73 (4H, m, CH_2CH_2), 4.34 and 4.66 (2H, ABq, J=18 Hz, $C\underline{H}_2Ph$), 6.39—6.93 (2H, m, C_5H and C_7H), 7.10—7.40 (1H, m, C_6H), 7.30 (5H, s, Ph), 8.11 (1H, dd, J=2, 8 Hz, C_8H). MS *m/e*: 306 (M^+).

3a-Methyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione (**6**)——A solution of **5** (0.4 g) in AcOH was hydrogenated over 10% Pd-carbon. When absorption of H_2 was complete (5 h), the catalyst was filtered off. The filtrate was made basic with 10% NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated. The residue was recrystallized from CH_2Cl_2–cyclohexane to give 0.22 g (65%) of **6**, mp 176—179°C. *Anal.* Calcd for $C_{12}H_{12}N_2O_2$: C, 65.65; H, 5.59; N, 12.96. Found: C, 66.85; H, 5.43; N, 12.71. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1750, 1665. NMR ($CDCl_3$) δ: 1.51 (3H, s, CH_3), 2.08—2.84 (4H, m, CH_2CH_2), 6.58—6.97 (2H, m, C_5H and C_7H), 7.17—7.49 (1H, m, C_6H), 7.83 (1H, dd, J=2, 8 Hz, C_8H). MS *m/e*: 216 (M^+).

4-Acetyl-3a-methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (**7**)——A mixture of A (2.5 g), acetic anhydride (25 ml), and dry pyridine (3 ml) was heated at 140°C for 1.5 h. After most of the acetic anhydride and pyridine had been evaporated off *in vacuo*, the residue was recrystallized from benzene–cyclohexane to give 1.5 g (50%) of **7**, mp 143—145°C. *Anal.* Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.03; H, 5.46; N, 10.70. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1690. NMR ($CDCl_3$) δ: 1.72 (3H, s, CCH_3), 2.60 (3H, s, $COCH_3$), 1.79—3.11 (4H, m, CH_2CH_2), 7.22—7.85 (2H, m, C_7H and C_8H), 8.15—8.54 (2H, m, C_6H and C_9H). MS *m/e*: 258 (M^+).

4-Acetyl-3a-methyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione (**8**)——A mixtuer of **6** (0.17

g), acetic anhydride (20 ml), and dry pyridine (1 ml) was heated at 130°C for 5 h. After most of the acetic anhydride and pyridine had been evaporated off *in vacuo*, the residue was recrystallized from benzene–cyclohexane to give 0.05 g (25%) of **8**, mp 173—176°C. *Anal.* Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.28; H, 5.41; N, 10.92. IR ν_{max}^{Nujol} cm^{-1}: 1770, 1685, 1665. NMR ($CDCl_3$) δ: 1.60 (3H, s, CCH_3), 2.39 (3H, s, $COCH_3$), 2.13—3.19 (4H, m, CH_2CH_2), 6.91—7.80 (3H, m, aromatic H), 8.18 (1H, dd, $J=2$, 9 Hz, C_8H). MS *m/e*: 258 (M^+).

3-(2,3-Dimethyl-4-oxo-1,2,3,4-tetrahydro-2-quinazolinyl)propionic Acid (10)——A mixture of 2-amino-*N*-methylbenzamide (3 g) and 4-oxopentanoic acid (2.5 g) was heated at 140°C for 1 h. After cooling, 5% NaOH in EtOH (50 ml) and benzene (100 ml) were added to the reaction mixture and the solvent was slowly evaporated off. The residue was dissolved in H_2O and the aqueous solution was washed with benzene, made acidic with 10% HCl, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated. Recrystallization of the residue from MeOH–CH_2Cl_2 gave 1.4 g (28%) of **10**, mp 138—140°C. *Anal.* Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.02; H, 6.59; N, 11.33. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1700, 1625. NMR (DMSO-d_6) δ: 1.48 (3H, s, CCH_3), 1.94—2.65 (4H, m, CH_2CH_2), 3.00 (3H, s, NCH_3), 6.12—6.50 (1H, broad, NH), 6.57—6.92 (2H, m, C_6H and C_8H), 7.14—7.50 (1H, m, C_7H), 7.84 (1H, dd, $J=2$, 8 Hz, C_5H).

References and Notes

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