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

MASATOSHI YAMATO* and YASUO TAKEUCHI

*Faculty of Pharmaceutical Sciences, Okayama University,
Tsushima-naka 1-1-1, Okayama 700, Japan*

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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 cyclized to give 2 by heating with acetic anhydride and pyridine. We considered that 2 might be identical with B. However, it was found 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 C₅- and C₇-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-tetrahydro-2-quinazolinyl)propionic acid (10), which might be formed by methylation at the

Chart 4

N₄-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 Stroh. 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 C₁₂H₁₂N₂O₂: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.76; H, 5.53; N, 12.93. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3150, 1715, 1675. NMR (CDCl₃) δ : 1.55 (3H, s, CH₃), 2.17–2.93 (4H, m, CH₂CH₂), 7.07–7.86 (2H, m, C₇H and C₈H), 8.00–8.42 (2H, m, C₆H and C₉H), 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 H₂O, dried over MgSO₄, and concentrated. Recrystallization of the residue from MeOH gave 0.63 g (14%) of 2, mp 171–172°C. *Anal.* Calcd for C₁₃H₁₄N₂O₂: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.92; H, 6.32; N, 12.05. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1755, 1665. NMR (CDCl₃) δ : 1.37 (3H, s, CCH₃), 2.05–2.67 (4H, m, CH₂CH₂), 2.75 (3H, s, NCH₃), 6.55–7.07 (2H, m, C₅H and C₇H), 7.30–7.66 (1H, m, C₆H), 8.01 (1H, dd, *J*=2, 8 Hz, C₈H). 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 CH₂Cl₂. The CH₂Cl₂ layer was washed with NaOH and H₂O, dried over MgSO₄, 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 C₁₃H₁₆N₂O₃: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.00; H, 6.73; N, 11.22. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3200, 2550, 1900, 1685. NMR (DMSO-*d*₆) δ : 1.38 (3H, s, CCH₃), 1.81–2.53 (4H, m, CH₂CH₂), 2.71 (3H, s, NCH₃), 6.51–6.81 (2H, m, aromatic H), 7.14–7.51 (1H, m, aromatic H), 7.64 (1H, dd, *J*=2, 9 Hz, C₅H), 7.86–8.05 (1H, broad, NH). MS *m/e*: 230 (M⁺–H₂O).

4-Benzyl-3a-methyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione (5)—A mixture of 2-(benzylamino)benzamide (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 C₁₉H₁₈N₂O₂: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.49; H, 5.97; N, 9.15. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1765, 1660. NMR (CDCl₃) δ : 1.59 (3H, s, CCH₃), 2.18–2.73 (4H, m, CH₂CH₂), 4.34 and 4.66 (2H, ABq, *J*=18 Hz, CH₂Ph), 6.39–6.93 (2H, m, C₅H and C₇H), 7.10–7.40 (1H, m, C₆H), 7.30 (5H, s, Ph), 8.11 (1H, dd, *J*=2, 8 Hz, C₈H). 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 H₂ was complete (5 h), the catalyst was filtered off. The filtrate was made basic with 10% NaOH and extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O, dried over MgSO₄, and concentrated. The residue was recrystallized from CH₂Cl₂–cyclohexane to give 0.22 g (65%) of 6, mp 176–179°C. *Anal.* Calcd for C₁₂H₁₂N₂O₂: C, 65.65; H, 5.59; N, 12.96. Found: C, 66.85; H, 5.43; N, 12.71. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3300, 1750, 1665. NMR (CDCl₃) δ : 1.51 (3H, s, CH₃), 2.08–2.84 (4H, m, CH₂CH₂), 6.58–6.97 (2H, m, C₅H and C₇H), 7.17–7.49 (1H, m, C₆H), 7.83 (1H, dd, *J*=2, 8 Hz, C₈H). 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 C₁₄H₁₄N₂O₃: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.03; H, 5.46; N, 10.70. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1720, 1690. NMR (CDCl₃) δ : 1.72 (3H, s, CCH₃), 2.60 (3H, s, COCH₃), 1.79–3.11 (4H, m, CH₂CH₂), 7.22–7.85 (2H, m, C₇H and C₈H), 8.15–8.54 (2H, m, C₆H and C₉H). MS *m/e*: 258 (M⁺).

4-Acetyl-3a-methyl-2,3,3a,4-tetrahydropyrrolo[2,1-*b*]quinazoline-1,9-dione (8)—A mixture 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 $\nu_{\max}^{\text{Nujol}}$ 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 $\text{MeOH}-\text{CH}_2\text{Cl}_2$ 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 $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3300, 1700, 1625. NMR ($\text{DMSO}-d_6$) 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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