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-quinazolyl)propionic acid (3), which was recrystallized 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 palladiumcarbonyl. 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,⁵ 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 N₁ atom of the quinazoline moiety, while that of 7 binds with the N₂ atom of the same moiety.

![Chemical structures with reaction equations and melting points](image)

**Chart 1**

**Chart 2**
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-α]quinazoline-1,5-dione (9) prepared according to the method of Aeberli and Haulihan.\textsuperscript{3)\textdagger} However, preparation of B from A was not successful, because no detailed description of the preparation of B was given in their report.\textsuperscript{1)\textdagger}

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-α]quinazoline-1,5-dione (9), and that the real structure of B is neither 3a,4-dimethyl-2,3,3a,4-tetrahydropyrrolo[1,2-α]-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-tetrahydroy-2-quinazolinyl)propionic acid (10), which might be formed by methylation at the

\[\text{Chart 4}\]
N₂-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 tetramethysilane 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-tetrahydropyrrole[1,2-a']quinazoline-1,5-dione (A = 9)—Compound A (═9) was prepared according to the method of Aebeler and Haulihan. mp 181—182°C. Anal. Calcd for C₁₅H₁₄N₂O₄: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.76; H, 5.53; N, 12.93. IR ν max cm⁻¹: 1310, 1715, 1675. NMR (CDCl₃) δ: 1.55 (3H, s, CH₃), 2.17—2.93 (4H, m, CH₂CH₂), 7.07—7.86 (2H, m, C₆H and C₆H), 8.00—8.42 (2H, m, C₆H and C₆H). MS m/e: 216 (M⁺)

3a,4-Dimethyl-2,3,3a,4-tetrahydropyrrole[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 8.3 g (14%) of 2, mp 171—172°C. Anal. Calcd for C₁₅H₁₄N₂O₄: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.92; H, 6.32; N, 12.05. IR ν max cm⁻¹: 1755, 1668. NMR (CDCl₃) δ: 1.37 (3H, s, CCH₃), 2.05—2.67 (4H, m, CH₂CH₂), 2.75 (3H, s, NCH₃), 5.65—7.07 (2H, m, C₆H and C₆H), 7.30—7.60 (1H, m, C₆H), 8.01 (1H, dd, J = 2, 8 Hz, C₆H). MS m/e: 230 (M⁺)

Method D: A mixture of 3 (2 g), acetic anhydride (20 ml), and dry pyridine (2 ml) was heated at 140°C for 3 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-azo-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 14.1 g (91%) of 3, mp 192—194°C. Anal. Calcd for C₁₅H₁₄N₂O₄: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.00; H, 6.73; N, 11.22. IR ν max cm⁻¹: 3200, 2550, 1900, 1685. NMR (DMSO-d₆) δ: 1.38 (3H, s, CCH₃), 1.81—2.58 (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, C₆H), 7.86—8.05 (1H, broad, NH). MS m/e: 230 (M⁺—H₂O)

4-Benzyl-3a-methyl-2,3,3a,4-tetrahydropyrrole[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 C₂₄H₂₁N₂O₄: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.49; H, 5.97; N, 9.15. IR ν max 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, C₆H and C₆H), 7.10—7.40 (1H, m, C₆H), 7.30 (5H, s, Ph), 8.11 (1H, dd, J = 2, 8 Hz, C₆H). MS m/e: 306 (M⁺)

3a-Methyl-2,3,3a,4-tetrahydropyrrole[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 C₁₅H₁₄N₂O₄: C, 65.65; H, 5.59; N, 12.96. Found: C, 65.68; H, 5.43; N, 12.71. IR ν max cm⁻¹: 3300, 1750, 1665. NMR (CDCl₃) δ: 1.51 (3H, s, CCH₃), 2.08—2.84 (4H, m, CH₂CH₂), 6.58—6.97 (2H, m, C₆H and C₆H), 7.17—7.49 (1H, m, C₆H), 7.83 (1H, dd, J = 2, 8 Hz, C₆H). MS m/e: 216 (M⁺)

4-Acetyl-3a-methyl-2,3,3a,4-tetrahydropyrrole[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 benzencyclohexane to give 0.5 g (50%) of 7, mp 143—145°C. Anal. Calcd for C₁₅H₁₄N₂O₄: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.00; H, 5.46; N, 10.70. IR ν max cm⁻¹: 1730, 1090. NMR (CDCl₃) δ: 1.72 (3H, s, CCH₃), 2.60 (3H, s, COCH₃), 6.60—7.11 (4H, m, CH₂CH₂), 7.22—8.25 (2H, m, C₆H and C₆H), 8.15—8.54 (2H, m, C₆H and C₆H). MS m/e: 258 (M⁺)

4-Acetyl-3a-methyl-2,3,3a,4-tetrahydropyrrole[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—178°C. Anal. Calcd for C_{14}H_{12}N_{2}O_{2}: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.28; H, 5.41; N, 10.92. IR ν_{max} cm^{-1}: 1770, 1685, 1665. NMR (CDCl₃) δ: 1.60 (3H, s, CCH₃), 2.39 (3H, s, COCH₃), 2.13—3.19 (4H, m, CH₂CH₂), 6.91—7.80 (3H, m, aromatic H), 8.18 (1H, dd, J = 2, 9 Hz, C₄H). MS m/z: 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-oxypentanoic 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 H₂O and the aqueous solution was washed with benzene, made acidic with 10% HCl, and extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O, dried over MgSO₄, and concentrated. Recrystallization of the residue from MeOH—CH₂Cl₂ gave 1.4 g (28%) of 10, mp 138—140°C. Anal. Calcd for C_{11}H_{16}N₂O₄: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.02; H, 6.59; N, 11.33. IR ν_{max} cm^{-1}: 3300, 1700, 1625. NMR (DMSO-d₆) δ: 1.48 (3H, s, CCH₃), 1.94—2.65 (4H, m, CH₂CH₂), 3.00 (3H, s, NCH₃), 6.12—6.50 (1H, broad, NH), 6.57—6.92 (2H, m, C₄H and C₅H), 7.14—7.50 (1H, m, C₆H), 7.84 (1H, dd, J = 2, 8 Hz, C₂H).

References and Notes