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SYNTHESIS OF THE BICYCLIC SECONDARY AMINES *VIA* DIMETHYLAMINOMETHYLENE KETONES FROM 3-PYRROLIDONE AND 4-PIPERIDONE

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Abstract – The reaction of *N*-protected 3-pyrrolidone and 4-piperidone with *N*,*N*-dimethylformamide dimethyl acetal gave the dimethylaminomethylene ketones, which reacted with several types of hydrazines, amidines, and guanidine to afford the secondary amines having fused ring system.

Since the introduction of antibacterial fluoroquinolones in the early 1980s, this class of compounds have become one of the most attractive agents in the antiinfective chemotherapy field.[1] The cyclic amine side chain at the 7-position of the quinolone nucleus is known to be a very important part for its antibacterial activity, and many groups are still researching novel compounds with potent antibacterial activity.[2] Recently, moxifloxacin (Figure 1), having a bicyclic amine side chain at the 7-position of the quinolone nucleus, was reported to possess potent antibacterial activity, especially against Gram-positive bacteria including the drug resistant strains.[3] We synthesized the secondary amines having a fused ring system using a simple procedure *via* the common intermediates as follows.

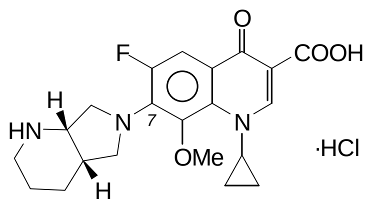
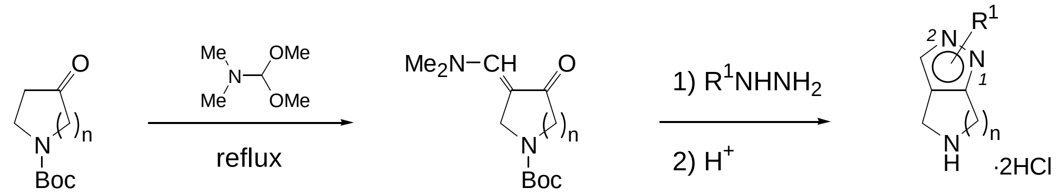


Figure 1

Dedicated to Professor James P. Kutney in celebration of his 70th birthday.

The pyrrolidines and piperidines condensed with the pyrazole ring were prepared as shown in Scheme 1. The reaction of ketones (**1a**) and (**1b**), easily obtained from the commercially available materials, with *N*,*N*-dimethylformamide dimethyl acetal afforded the dimethylaminomethylene ketones (**2a**) and (**2b**) as the common intermediates, respectively. By the reaction with hydrazine hydrate and the following acid treatment, compounds (**2a**) and (**2b**) were converted into **3a** and **3b** in good yields, respectively. The reaction of **2a** with methylhydrazine and the following acid treatment gave **4a** as a single product, which had the methyl group at the 1-position of the pyrazole ring. The position of the methyl group was determined by the NOE experiments (Figure 2). When the N1-Me signal (δ 3.77) of **4a** was irradiated, the C6-H_2 signal (δ 4.38) was enhanced, indicating a proximal relationship. The same reaction of **2b** afforded a 4:1 mixture of the two isomers.[5] However, the major product (**4b**), separated from the mixture by washing with 2-propanol, had the methyl group at the 2-position of the pyrazole ring.[6] When the N2-Me signal (δ 3.79) of **4b** was irradiated, in the NOE experiment, the C7-H_2 signal (δ 2.85) enhancement was not observed, but the C3-H signal (δ 7.57) was enhanced.

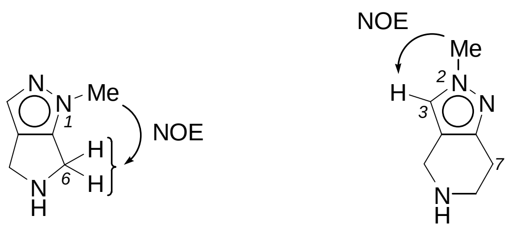


1a (n=1)
1b (n=2)

2a (n=1)
2b (n=2)

3a (R^1=H, n=1)
3b (R^1=H, n=2)
4a (R^1=1-Me, n=1)
4b (R^1=2-Me, n=2)

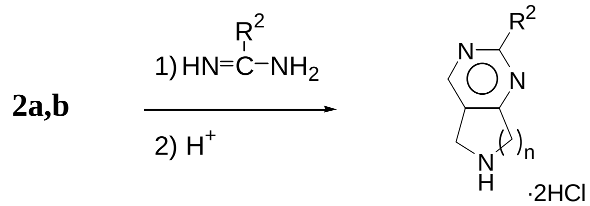
Scheme 1



4a **4b**

Figure 2

The pyrrolidines and piperidines condensed with the pyrimidine ring were synthesized as shown in Scheme 2. The two intermediates (**2a**) and (**2b**) reacted with two types of amidines (R^2=H, Me) and guanidine (R^2=NH_2) to afford six compounds (**5a**-**7a** and **5b**-**7b**) after the following acid treatment, respectively.



5a (R^2=H, n=1)
5b (R^2=H, n=2)
6a (R^2=Me, n=1)
6b (R^2=Me, n=2)
7a (R^2=NH_2, n=1)
7b (R^2=NH_2, n=2)

Scheme 2

In conclusion, we synthesized the secondary amines (**3a**-**7a**, **3b**-**7b**) having a fused ring system using a simple procedure *via* the common intermediates (**2a** and **2b**), respectively. Some of them were then introduced to the quinolone nucleus that produced potent antibacterial activity against Gram-positive bacteria including the drug resistant strains.[7]

EXPERIMENTAL

Melting points were determined on a Yanaco MP-500D and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL JNM-EX270 (270 MHz) spectrometer. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane. IR spectra were recorded on a Shimazu FTIR-4200 infrared spectrophotometer. MS spectra were measured on a JEOL HX-110A. Column chromatography was performed using Merck 60 silica gel, 70-230 mesh.

***N-tert*-Butoxycarbonyl-4-dimethylaminomethylene-3-pyrrolidone (2a).** *N-tert*-Butoxycarbonyl-3-pyrrolidone (**1a**, 2.90 g, 15.7 mmol) was dissolved in *N*,*N*-dimethylformamide dimethyl acetal (15 mL), and the solution was heated under reflux for 1 h and concentrated. The residue was triturated with hexane, filtered, and washed with hexane to give **2a** as a yellow powder (2.39 g, 64%): mp 136-139 °C; ^{1}H-NMR ($CDCl_3$) δ 1.48 (9H, s), 3.09 (6H, s), 3.81 (2H, s), 4.57 (2H, s), 7.31 (1H, s); IR (KBr) 1595, 1675, 1695 cm^{-1}. HRFABMS Calcd for $C_{12}H_{21}N_2O_3$ $(M+H)^+$: 241.1552. Found: 241.1572. *Anal.* Calcd for $C_{12}H_{20}N_2O_3 \cdot 1/8H_2O$: C, 59.42; H, 8.40; N, 11.55. Found: C, 59.45; H, 8.32; N, 11.54.

***N*-*tert*-Butoxycarbonyl-3-dimethylaminomethylene-4-piperidone (2b).** This compound was obtained from *N*-*tert*-butoxycarbonyl-4-piperidone (**1b**) in the same way as **2a**. A yellow powder: yield 9.00 g (71%); mp 72-75 °C; ^{1}H-NMR ($CDCl_3$) δ 1.48 (9H, s), 2.44 (2H, t, J = 6.3 Hz), 3.11 (6H, s), 3.60 (3H, t, J = 6.4 Hz), 4.55 (2H, s), 7.49 (1H, s); IR (KBr) 1545, 1655, 1695 cm^{-1}. HRFABMS Calcd for $C_{13}H_{23}N_2O_3$ $(M+H)^+$: 255.1709. Found: 255.1723. *Anal*. Calcd for $C_{13}H_{22}N_2O_3 \cdot 1/2H_2O$: C, 59.29; H, 8.80; N, 10.64. Found: C, 59.21; H, 8.87; N, 10.37.

1,4,5,6-Tetrahydropyrrolo[3,4-*c*]pyrazole dihydrochloride (3a). To a solution of **2a** (3.00 g, 12.5 mmol) in MeOH (60 mL) was added hydrazine hydrate (98%, 0.73 mL, 15.1 mmol), and the solution was heated under reflux for 1 h and concentrated. The residue was purified by column chromatography eluting with $CHCl_3$:2-propanol (10:1) to give a colorless powder. It was dissolved in TFA (50 mL) at 0 °C, and the solution was stirred at rt for 1 h and concentrated. The residue was dissolved in EtOH and treated with concentrated HCl (3 mL). After removing the solvent, the resultant solid was triturated with 2-propanol, filtered, and washed with 2-propanol and Et_2O to give **3a** (2.01 g, 88%) as an orange powder: mp 132-134 °C; ^{1}H-NMR (DMSO-d_6) δ 4.25 (4H, t, J = 5.1 Hz), 7.60 (1H, s), 10.51 (2H, br s), 11.39 (2H, br s); IR (KBr) 1455, 1560, 3000 cm^{-1}. HRFABMS Calcd for $C_5H_8N_3$ $(M+H)^+$: 110.0718. Found: 110.0721. *Anal*. Calcd for C_5H_9 N_3Cl_2: C, 32.99; H, 4.98; N, 23.08. Found: C, 32.80; H, 4.98; N, 22.79.

4,5,6,7-Tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine dihydrochloride (3b). This compound was obtained from **1b** in the same way as **3a**. A pale yellow powder: yield 2.51 g (51%); mp 239-242 °C; ^{1}H-NMR (DMSO-d_6) δ 2.95 (2H, t, J = 6.1 Hz), 3.34-3.36 (2H, m), 4.12 (2H, t, J = 4.1 Hz), 7.69 (1H, s), 9.72 (2H, br s), 12.42 (2H, br s); IR (KBr) 1585, 1640, 2800 cm^{-1}. HRFABMS Calcd for $C_6H_{10}N_3$ $(M+H)^+$: 124.0875. Found: 124.0868. *Anal*. Calcd for $C_6H_{11}N_3Cl_2 \cdot 1/8H_2O$: C, 36.34; H, 5.72; N, 21.19. Found: C, 36.24; H, 5.46; N, 21.02.

1,4,5,6-Tetrahydro-1-methylpyrrolo[3,4-*c*]pyrazole dihydrochloride (4a). To a solution of **2a** (10.0

g, 41.7 mmol) in MeOH (120 mL) was added methylhydrazine (2.37 g, 51.5 mmol), and the solution was heated under reflux for 2.5 h and concentrated. The residue was purified by column chromatography eluting with $CHCl_3$:2-propanol (50:1) to give a yellow oil. It was dissolved in TFA (200 mL) at 0 °C, and the solution was stirred at rt for 1 h and concentrated. The residue was dissolved in EtOH and treated with concentrated HCl (12 mL). After removing the solvent, the resultant solid was triturated with 2-propanol, filtered, and washed with 2-propanol and Et_2O to give **4a** (7.26 g, 89%) as a pale brown powder: mp 181-186 °C; ^{1}H-NMR (DMSO-d_6) δ 3.77 (3H, s), 4.20 (2H, m), 4.38 (2H, m), 7.25 (1H, s), 7.61 (1H, br s), 10.64 (2H, br s); IR (KBr) 1470, 1560, 1635, 2700 cm^{-1}. HRFABMS Calcd for $C_6H_{10}N_3$ $(M+H)^+$: 124.0875. Found: 124.0882. *Anal*. Calcd for $C_6H_{11}N_3Cl_2 \cdot 1/4H_2O$: C, 35.93; H, 5.78; N, 20.95. Found: C, 35.88; H, 6.03; N, 21.94.

4,5,6,7-Tetrahydro-2-methyl-2*H*-pyrazolo[4,3-*c*]pyridine dihydrochloride (4b). This compound was obtained from **1b** in the same way as **4a**. A pale yellow powder: yield 1.35 g (43%); mp 258-261 °C; ^{1}H-NMR (DMSO-d_6) δ 2.85 (2H, t, J = 6.1 Hz), 3.32-3.35 (2H, m), 3.79 (3H, s), 4.09 (2H, t, J = 4.3 Hz), 6.91 (1H, br s), 7.57 (1H, s), 9.45 (2H, br s); IR (KBr) 1560, 1640, 2800 cm^{-1}. HRFABMS Calcd for $C_7H_{12}N_3$ $(M+H)^+$: 138.1031. Found: 138.1027. *Anal*. Calcd for $C_7H_{13}N_3Cl_2 \cdot 1/8H_2O$: C, 39.59; H, 6.28; N, 19.79. Found: C, 39.66; H, 6.32; N, 19.77.

6,7-Dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine dihydrochloride (5a). To a solution of **2a** (10.0 g, 41.7 mmol) in EtOH (200 mL) was added formamidine acetate (21.7 g, 209 mmol), and the solution was heated under reflux for 36 h and concentrated. The residue was extracted with $CHCl_3$ and washed with water. The organic layer was dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography eluting with $CHCl_3$:hexane (4:1) to give a pale yellow powder. It was dissolved in TFA (75 mL) at 0 °C, and the solution was stirred at rt for 1 h and concentrated. The residue was dissolved in 2-propanol and treated with concentrated HCl (5 mL). The precipitated solid was filtered and washed with 2-propanol and Et_2O to give **5a** (5.71 g, 71%) as an orange powder: mp 141-145 °C; ^{1}H-NMR (DMSO-d_6) δ 4.54 (2H, t, J = 5.4 Hz), 4.64 (2H, t, J = 4.8 Hz), 7.48 (2H, br s), 8.87 (1H, s), 9.16 (1H, s), 10.35 (2H, br s); IR (KBr) 1460, 1535, 1595, 1640, 2900 cm^{-1}. HRFABMS Calcd for $C_6H_8N_3$ $(M+H)^+$: 122.0718. Found 122.0711. *Anal*. Calcd for $C_6H_9N_3Cl_2 \cdot 1/8H_2O$: C, 36.71; H, 4.75; N, 21.40. Found: C, 36.94; H, 4.65; N, 21.12.

5,6,7,8-Tetrahydropyrido[4,3-*d*]pyrimidine dihydrochloride (5b). This compound was obtained from **1b** in the same way as **5a**. A yellow powder: yield 3.29 g (20%); mp 236 °C (decomp); ^{1}H-NMR (DMSO-d_6) δ 3.12 (2H, t, J = 6.4 Hz), 3.44-3.49 (2H, m), 4.34 (2H, t, J = 4.5 Hz), 7.63 (2H, br s), 8.69 (1H, s), 9.03 (1H, s), 9.92 (2H, br s); IR (KBr) 1460, 1530, 1595, 1630, 2750 cm^{-1}. HRFABMS Calcd for $C_7H_{10}N_3$ $(M+H)^+$: 136.0875. Found 136.0869. *Anal*. Calcd for $C_7H_{11}N_3Cl_2 \cdot 1/8H_2O$: C, 39.97; H, 5.39; N, 19.98. Found: C, 39.92; H, 5.43; N, 19.97.

6,7-Dihydro-2-methyl-5*H*-pyrrolo[3,4-*d*]pyrimidine dihydrochloride (6a). To a solution of **2a** (8.00 g, 33.3 mmol) in EtOH (80 mL) were added acetamidine hydrochloride (15.8 g, 167 mmol) and Et_3N (23.5 mL, 169 mmol), and the solution was heated under reflux for 42 h and concentrated. The residue was extracted with AcOEt and washed with water. The organic layer was dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography eluting with hexane:AcOEt (1:2) to give a pale yellow powder. It was dissolved in TFA (30 mL) at 0 °C, and the solution was stirred at rt for 0.5 h and concentrated. The residue was dissolved in 2-propanol and treated with concentrated HCl (5 mL). After removing the solvent, the resultant solid was triturated with EtOH, filtered, and washed with EtOH and Et_2O to give **6a** (5.39 g, 79%) as a pale yellow powder: mp 250 °C (decomp); ^{1}H-NMR (DMSO-d_6) δ 2.67 (3H, s), 4.51 (2H, m), 4.61 (2H, m), 8.77 (1H, s), 10.51 (1H, br s), 10.59 (1H, br s); IR (KBr) 1520, 1620, 1650, 2600 cm^{-1}. HRFABMS Calcd for $C_7H_{10}N_3$ $(M+H)^+$: 136.0875. Found 136.0883. *Anal*. Calcd for $C_7H_{11}N_3Cl_2 \cdot 3/8H_2O$: C, 39.13; H, 5.51; N, 19.56. Found: C, 39.07; H, 5.75; N, 19.56.

5,6,7,8-Tetrahydro-2-methylpyrido[4,3-*d*]pyrimidine dihydrochloride (6b). This compound was obtained from **1b** in the same way as **6a**. A yellow powder: yield 4.11 g (14%); mp 160 °C (decomp); ^{1}H-NMR (DMSO-d_6) δ 2.59 (3H, s), 3.04 (2H, t, J = 6.3 Hz), 3.48 (2H, m), 4.29 (2H, m), 8.58 (1H, s), 9.61 (2H, brs); IR (KBr) 1610, 1635, 2950 cm^{-1}. HRFABMS Calcd for $C_8H_{12}N_3$ $(M+H)^+$: 150.1031. Found 150.1035.

2-Amino-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine dihydrochloride (7a). To a solution of **2a** (10.0 g, 41.7 mmol) in EtOH (250 mL) were added guanidine carbonate (30.0 g, 167 mmol) and sodium acetate (27.4 g, 334 mmol), and the solution was heated under reflux for 48 h. The reaction mixture was filtered, and the insoluble material was extracted with $CHCl_3$ and washed with water. The organic layer was dried over anhydrous $MgSO_4$ and evaporated. The resultant solid was triturated with 2-propanol, filtered, and washed with 2-propanol and Et_2O to give a colorless powder. It was dissolved in TFA (70 mL) at 0 °C, and the solution was stirred at rt for 1 h and concentrated. The residue was dissolved in 2-propanol and treated with concentrated HCl (6.5 mL). The precipitated solid was filtered and washed with 2-propanol and Et_2O to give **7a** (6.73 g, 90%) as a colorless powder: mp 260 °C (decomp); ^{1}H-NMR (DMSO-d_6) δ 4.37 (2H, m), 4.43 (2H, m), 7.09 (3H, br s), 8.35 (1H, s), 10.25 (2H, br s); IR (KBr) 1540, 1655, 1675, 2650, 3150 cm^{-1}. HRFABMS Calcd for $C_6H_9N_4$ $(M+H)^+$: 137.0827. Found 137.0820. *Anal*. Calcd for $C_6H_{10}N_4Cl_2 \cdot 1/4H_2O$: C, 33.74; H, 4.96; N, 26.23. Found: C, 33.96; H, 4.90; N, 26.25.

2-Amino-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine dihydrochloride (7b). This compound was obtained from **1b** in the same way as **7a**. A yellow powder: yield 3.13 g (39%); mp 274-278 °C; ^{1}H-NMR (DMSO-d_6) δ 2.98 (2H, t, J = 6.3 Hz), 3.42 (2H, m), 4.14 (2H, m), 5.67 (3H, br s), 8.33 (1H, s), 9.71 (2H, br s); IR (KBr) 1525, 1635, 1670, 2650, 3150 cm^{-1}. HRFABMS Calcd for $C_7H_{11}N_4$ $(M+H)^+$: 151.0984. Found 151.0987. *Anal*. Calcd for $C_7H_{12}N_4Cl_2 \cdot 1/4H_2O$: C, 36.94; H, 5.53; N, 24.62. Found: C, 36.79; H, 5.36; N, 24.33.

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