REACTION OF SPIRO[PIPERIDINE-4,2'-(1',2',3',4'-TETRAHYDROQUINAZOLIN)]-4'-ONES WITH ACETIC ANHYDRIDE

Masatoshi Yamato,* Yasuo Takeuchi, and Yuji Ikeda

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

Abstract —— The tetrahydro derivative (5a) and its aza derivative (5b) of antitumor active amsacrine were prepared. The key synthetic intermediate (3a) was simply prepared by rearrangement of spiro-compound (2a) by heating with acetic anhydride and pyridine. On the other hand, another key intermediate (3b) was obtained only during moderated reaction conditions, and the ring opening products (6b,b' and 8b,b') were obtained under the usal conditions.

We previously reported[1] that the reaction of 1-benzyl-1'-methylspiro[piperidine-4,2'-(1',2',3',4'-tetrahydroquinazolin)]-4'-one with acetic anhydride in the presence of pyridine gave 2-benzyl-5-methyl-1,2,3,4,5,6-hexahydrobenzo[b]-1,6-naphthyridin-10-one in 56% yield.

We attempted to prepare the analogues of amsacrine[2], N-[4-(9-acridinylamino)-3-methoxyphenyl]methanesulfonamide, by application of the previous rearrangement method. N-[4-(1,2,3,4-Tetrahydroacridin-9-yl)amino-3-methoxyphenyl]methanesulfonamide (5a) and N-[4-(2-methyl-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridin-10-yl)amino-3-methoxyphenyl]methanesulfonamide (5b) seemed to be easily prepared by the route shown in chart 1.

The compound 5a was prepared successfully from hexahydroacridone (3a) which was obtained by the reaction of tetrahydroquinazolinone (2a) with acetic anhydride and pyridine. However, in the preparation of 5b, the reaction of tetrahydroquinazolinone (2b) with acetic anhydride and pyridine using the same reaction conditions for the preparation of 3a from 2a did not afford benzonaphthyridinone (3b) but gave a mixture of rotational isomers of dihydroquinolinone (6b and 6b').

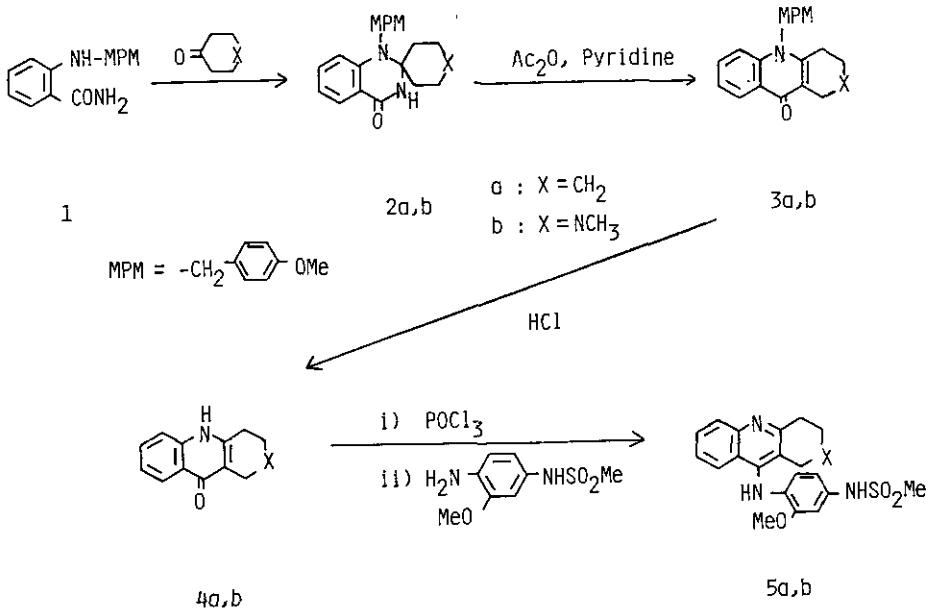
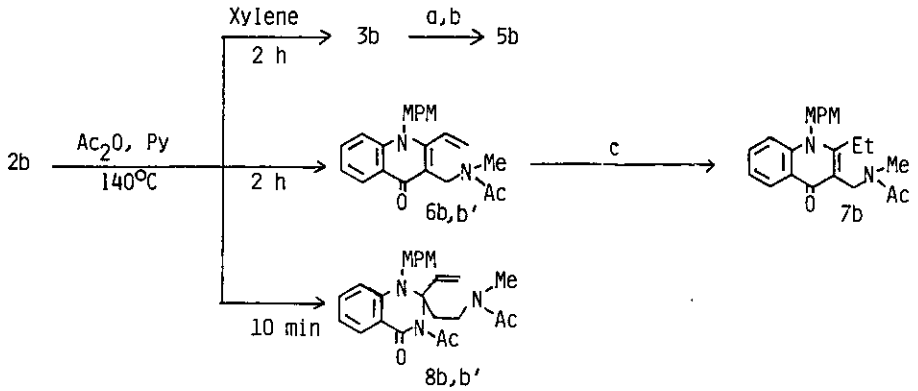


Chart 1

The structures of 6b and 6b' were established base on the data of elemental analysis and mass spectrum of the mixture, which showed the molecular formula to be $C_{23}H_{24}N_2O_3$. The catalytic reduction of 6b,b' gave 2-ethyldihydroquinolinone (7b) in 73% yield. Existence of rotational isomers (6b and 6b') could be reconized at the ^{1}H-NMR spectrum. Namely, the spectrum of the mixture (6b,b') gave two pairs of peaks due to the protons of a pair of acetyl groups at 2.03 and 2.31 ppm and a pair of N-methyl groups at 2.76 and 3.12 ppm, respectively.

Subsequent examination of this rearrangement showed that the resulting products varied depending on the reaction conditions. That is, refluxing a mixture of 2b, acetic anhydride, and pyridine in xylene for 2 h gave 3b in 68% yield, while, refluxing a mixture of 2b, acetic anhydride, and pyridine without xylene for 10 min gave a mixture of rotational isomers of 2-vinyltetrahydroquinazolinone (8b and 8b') which are considered to be intermediates[1] of 6b and 6b'.

Considering the fact that the reaction of 1-benzyl-1'-methylspiro[piperidine-4,2'-(1',2',3',4'-tetrahydroquinazolin)]-4'-one with acetic anhydride and pyridine under the same reaction condition used for the formation of 6b,b' did not gave



a) 10% HCl, reflux, 1 h (94%). b) i) $POCl_3$, reflux, 2h. ii) N-[(4-amino-3-methoxyphenyl)amino]methanesulfonamide, phenol, NaI, 120°C, 1 h (22%). c) Pd/C, H_2, MeOH, r.t., 7 days (73%).

Chart 2

such a product but produced 2-benzyl-5-methyl-1,2,3,4,5,6-hexahydrobenzo[b]-1,6-naphthyridin-10-one in significant yields, the bulkiness of the substituent of the nitrogen atom of the piperidine ring may contribute to the prevention of the ring cleavage.

Consequently, compound 5b was prepared according to the reaction shown in chart 1. The study of the antitumor activity of 5a and 5b is currently in progress and results will be reported together with that of other derivatives.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Nuclear magnetic resonance (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 Shimazu LKB-9000 spectrometer, and infrared absorption (IR) spectra on a JASCO A-102 spectrometer.

2-[(4-Methoxybenzyl)amino]benzamide (1)

A mixture of 2-aminobenzamide (1.00 g, 7.35 mmol), K_2CO_3 (1.02 g, 7.38 mmol), KI (1.22 g, 7.35 mmol), and 4-methoxybenzyl bromide (2.04 g, 10.0 mmol) in dry DMF (10 ml) was stirred at room temperature for 1 day and then diluted with AcOEt. The organic layer was washed sequentially with H_2O and saturated NaCl solution and dried over anhydrous $MgSO_4$, and the solvent was removed. Purification of the residue by a column chromatography (Al_2O_3, AcOEt:hexane=1:1) and recrystallization (benzene) gave 1.73 g (92%) of 1, mp 112-114°C. Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.25; H, 6.28; N, 10.88. IR (Nujol): 3400, 3360, 3180, 1665. NMR ($CDCl_3$) δ : 3.09-3.30 (1H, br, NH), 3.79 (3H, s, OCH_3), 4.36 (2H, d, J=6 Hz, CH_2).

1-(4-Methoxybenzyl)spiro[cyclohexane-1,2'-(1',2',3',4'-tetrahydroquinazolin)]-4'-one (2a)

A mixture of 1 (9.80 g, 38.2 mmol) and cyclohexanone (20 ml) was heated at reflux for 58 h. After removal of excess cyclohexanone in vacuo, recrystallization of the residue from THF produced 11.61 g (90%) of 2a, mp 232-233°C. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found; C, 74.85; H, 7.30; N, 8.27. IR (Nujol): 3200, 1655. NMR ($CDCl_3$) δ : 1.30-2.20 (10H, m, CH_2 x 5), 3.78 (3H, s, OCH_3), 4.49 (2H, s, NCH_2). MS m/z: 336 (M^+), 121 (C_8H_9O, base peak).

10-(4-Methoxybenzyl)-1,2,3,4,9,10-hexahydroacridin-9-one (3a)

A mixture of 2a (1.00 g, 2.98 mmol), Ac_2O (10 ml), and pyridine (1 ml) was heated at 140°C for 2 h. Excess Ac_2O and pyridine were removed in vacuo and then residue was diluted with CH_2Cl_2. The organic layer was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$, and the solvent was removed. Recrystallization of the residue from a mixture of THF and AcOEt produced 0.73 g (76%) of 3a, mp 131-133°C. Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.69; H, 6.67; N, 4.13. IR (Nujol): 1615. NMR ($CDCl_3$) δ : 1.61-1.91 (4H, m, $C_{(2)}H_2C_{(3)}H_2$), 2.51-2.86 (4H, m, $C_{(1)}H_2$ and $C_{(4)}H_2$), 5.34 (2H, s, NCH_2). MS m/z: 319 (M^+), 121 (C_8H_9), base peak).

1,2,3,4,9,10-Hexahydroacridin-9-one (4a)

In 10% HCl solution, 3a (3.19 g, 10.0 mmol) was heated at reflux for 1 h. The solution was neutralized with 10% KOH solution and filtered off. Sequentially washing with H_2O, AcOEt, and CH_2Cl_2 afforded 1.80 g (90%) of 4a, mp > 300°C (Lit.[3] mp 357-358°C).

N-[4-(1,2,3,4-Tetrahydroacridin-9-yl)amino-3-methoxyphenyl]methanesulfonamide (5a)

A mixture of 4a (2.00 g, 10.0 mmol) and $POCl_3$ (20 ml) was heated at reflux for 3 h and excess $POCl_3$ was evaporated off. The residue was neutralized with 28 % NH_3 solution and diluted with Et_2O. The organic layer was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$, and the solvent was removed. A mixture of the residue (about 2 g) and N-(4-amino-3-methoxyphenyl)methanesulfonamide (2.16 g, 10.0 mmol), phenol (2.00 g, 21.1 mmol), and NaI (0.01 g) was heated at 130°C for 2 h, and then diluted with $CHCl_3$. The organic layer was washed with saturated $KHCO_3$ solution and dried over anhydrous $MgSO_4$, and solvent was removed. Recrystallization of the residue from AcOEt produced 2.21 g (56%) of 5a, mp 243-245°C. Anal. Calcd for $C_{21}H_{23}N_3O_3S$: C, 63.46; H, 5.83; N, 10.57. Found: C, 63.79: H, 5.87: N, 10.80. IR (Nujol); 3390, 1325. NMR (DMSO-d_6) δ : 1.59-2.30 (4H, m, $C_{(2')}H_2C_{(3')}H_2$), 2.84 (2H, m, $C_{(4')}H_2$), 2.92 (3H, s, SO_2CH_3), 2.99-3.19 (2H, m, $C_{(1')}H_2$), 3.93 (3H, s, OCH_3). MS m/z: 397 (M^+), 318 ($M^+-CH_3SO_2$, base peak).

1-(4-Methoxypheny)-1'-methylspiro[piperidine-4,2'-(1',2',3',4'-tetrahydroquinazolin)]-4'-one (2b)

A mixture of 1 (9.78 g, 28.2 mmol) and 1-methyl-4-piperidone (8.65 g, 76.4 mmol) was heated at 120°C for 40 h and diluted with a mixture of CH_2Cl_2 and Et_2O. The appeared precipitate was filtered off and then washed with AcOEt, and recrystallized from MeOH to give 7.5 g (55%) of 2b, mp 208-210°C. Anal. Calcd for $C_{21}H_{25}N_3O_2$: C, 71.77; H, 7.17; N, 11.96. Found: C, 71.66; H, 7.18; N, 11.79. IR (Nujol): 3210, 1665. NMR ($CDCl_3$) δ : 1.89-2.41 (4H, m, $C_{(3)}H_2$ and $C_{(5)}H_2$), 2.41-2.92 (4H, m, $C_{(2)}H_2$ and $C_{(6)}H_2$), 2.30 (3H, s, NCH_3), 3.72 (3H, s, OCH_3), 4.53 (2H, s, $N_{(1')}CH_2$), 7.97 (1H, s, NH).

5-(4-Methoxybenzyl)-2-methyl-1,2,3,4,5,10-hexahydrobenzo[b]-1,6-naphthyridin-10-one (3b)

A mixture of 2b (6.31 g, 18.0 mmol), Ac_2O (11.0 g, 108 mmol), and pridine (2.05 g, 25.9 mmol) in xylene (250 ml) was heated at reflux for 2 h and diluted with CH_2Cl_2. The organic layer was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$, and the solvent was removed. Purification of the residue by column chromatography (Al_2O_3, AcOEt) gave 4.04 g (68%) of 3b, mp 145-148°C. Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.46; H, 6.59; N, 8.30. Found: C, 75.46; H, 6.63; N, 8.38. IR (Nujol); 1620. NMR ($CDCl_3$) δ : 3H, s, NCH_3), 2.59-3.03 (4H, m, $C_{(3)}H_2$ and $C_{(4)}H_2$), 3.64 (2H, s, NCH_2), 3.78 (3H, s, $N_{(5)}CH_2$). MS m/z: 334 (M^+), 213 ($M^+-C_8H_9O$), 121 (C_8H_9O, base peak).

2-Methyl-1,2,3,4,5,10-hexahydrobenzo[b]-1,6-naphthyridin-10-one (4b)

In 10% HCl solution (30 ml), 3b (4.00 g, 12.0 mmol) was heated at reflux for 1 h and the solvent was removed. The residue was dried in vacuo and washed with benzene and AcOEt to give 3.22 g (94%) of 4b·HCl. 4b·HCl was dissolved in pyridine and saturated $KHCO_3$ was added to the solution. The solution was removed in vacuo and the residue was washed with pyridine. The washing solvent was removed and recrystallization from THF produced 4b, mp 243-246°C. Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.57; H, 6.55; N, 13.21. IR (Nujol): 1640, 1610. NMR (DMSO-d_6) δ : 2.65 (3H, s, CH_3), 2.98 (4H, s, $C_{(3)}H_2$ and $C_{(4)}H_2$), 3.62 (2H, s, $C_{(1)}H_2$). MS m/z: 214 (M^+), 199 (M^+-CH_3).

N-[4-(2-Methyl-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridin-10-yl)amino-3-methoxyphenyl]methanesulfonamide (5b)

In $POCl_3$ (5 ml), 4b (0.76 g, 2.67 mmol) was dissolved and the mixture was heated at reflux for 2 h, and excess $POCl_3$ was evaporated off. The mixture was neutralized with 28% NH_3 solution and diluted with CH_2Cl_2. The organic layer was washed with saturated NaCl solution and dried over anhydrous $MgSO_4$, and the solvent was removed. A mixture of the residue (about 0.4 g), N-(4-amino-3-methoxyphenyl)methanesulfonamide (0.86 g, 3.98 mmol), phenol (0.40 g, 4.25 mmol) and NaI (0.01 g) was heated at 120°C for 1 h and then diluted with $CHCl_3$. The organic layer was washed with saturated $KHCO_3$ solution and dried over anhydrous $MgSO_4$, and solvent was removed. Purification of the residue by column chromatography (Al_2O_3, AcOEt) afforded 0.23 g (21%) of 5b, mp 215-220°C. Anal. Calcd for $C_{21}H_{24}N_4O_3S$: C, 61.15; H, 5.86; N, 13.58. Found: C, 61.30; H, 5.96; N, 13.77. IR (Nujol): 3260, 1320. NMR ($CDCl_3$) δ : 2.52 (3H, s, NCH_3), 2.85-3.08 (2H, m, $C_{(3')}H_2$), 2.96 (3H, m, SO_2CH_3), 3.24-3.50 (2H, m, $C_{(4')}H_2$), 3.71 (2H, s, $C_{(1')}CH_2$), 4.08 (3H, s, OCH_3). MS m/z: 412 (M^+), 381 (M^+-CH_3O).

1-(4-Methoxybenzyl)-3-[(N-methylacetamino)methyl]-2-vinyl-1,4-dihydroquinolin-4-one (6b and 6b')

A mixture of 2b (3.00 g, 18.55 mmol), Ac_2O (30 ml), and pyridine (3 ml) was heated at 140°C for 2 h. Excess Ac_2O and pyridine were removed in vacuo and then the residue was diluted with CH_2Cl_2. The organic layer was washed with saturated $KHCO_3$ and dried over anhydrous $MgSO_4$, and the solvent was removed. Purification of the residue by column chromatography (Al_2O_3, AcOEt) gave 1.75 g (54%) of a mixture of 6b and 6b', mp 151-153°C. Anal. Calcd for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found:

C, 73.24: H, 6.45; N, 7.33. IR (Nujol): 1640, 1595. NMR ($CDCl_3$) δ : 2.03 (3H x 2/3, s, $COCH_3$), 2.31 (3H x 1/3, s, $COCH_3$), 2.76 (3H x 1/3, s, NCH_3), 3.12 (3H x 2/3, s, NCH_3), 3.74 (3H, s, OCH_3), 4.64 (2H, s, $CONCH_2$), 5.48 (2H, s, $N_{(1)}CH_2$), 5.23-6.00 (2H, m, $CH=CH_2$). MS m/z: 376 (M^+), 303 ($M^+-CH_3NHCOCH_3$), 121 (C_8H_9O, base peak).

2-Ethyl-1-(4-methoxybenzyl)-3-[(N-methylacetamino)methyl]-1,4-dihydroquinolin-4-one (7b)

A soution of a mixture of 6b and 6b' (0.30 g, 0.80 mmol) in MeOH (300 ml) was hydrogenated over 10% Pd-carbon. After absorption of H_2 was complete (about 7 days), the catalyst was filtered off. The solvent was removed and AcOEt was added to the residue. The organic layer was sequentially washed with saturated $KHCO_3$ and saturated NaCl solution and then dried over anhydrous $MgSO_4$, and the solvent was removed. Purification of the residue by column chromatography (Al_2O_3, AcOEt;hexane= 1:1) produced 0.22 g (73%) of 7b, mp 153-155°C. Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.93; N, 7.40. Found: C, 72.93; H, 7.03; N, 7.12. IR (Nujol):1720. NMR ($CDCl_3$) δ : 1.29 (3H, t, J=7 Hz, CH_2CH_3), 2.13 (3H, s, $COCH_3$), 3.04 (2H, q, J=7 Hz, CH_2CH_3), 3.06 (3H, s, $CONCH_3$), 3.82 (3H,.s, OCH_3), 4.95 (2H, s, $CONCH_2$), 5.50 (2H, s, $N_{(1)}CH_2$).

3-Acetyl-1-(4-methoxybenzyl)-2-[2-(N-methylacetamino)ethyl]-2-vinyl-1,2,3,4-tetrahydroquinazolin-4-one (8b and 8b')

A mixture of 2b (0.50 g, 1.42 mmol), Ac_2O (5 ml), and pyridine (0.5 ml) was heated at 140°C for 10 min. Excess Ac_2O and pyridine was removed. Purification of the residue by column chromatography (SiO_2, Et_2O) gave 0.34 g (55%) of 8b and 8b' as an viscous oil. IR (Nujol): 1720, 1675, 1645. NMR ($CDCl_3$) δ : 1.91 (3H x 1/3, s, CH_3NCOCH_3), 2.02 (3H x 2/3, s, CH_3NCOCH_3), 2.10-3.05 (2H, m, CH_2CH_2N), 2.53 (3H, s, $N_{(3)}COCH_3$), 2.80 (3H x 1/3, s, NCH_3), 2.92 (3H x 2/3, s, NCH_3), 3.06-3.70 (2H, m, CH_2CH_2N), 3.76 (3H, s, OCH_3), 4.62 (2H, d, J=7 Hz, $N_{(1)}CH_2$), 5.30-6.20 (3H, m, $CH=CH_2$). MS m/z: 435 (M^+), 314 ($M^+-C_8H_9O$), 121 (C_8H_9O, base peak).

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