Polycyclic *N*-Heterocyclic Compounds. 55 [1]. A Novel Reaction of *N*-(5,6-Dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4-yl)amidine or Its Amide Oxime Derivatives with Hydroxylamine

Ying-Xue Zhang, Kenji Sasaki* and Takashi Hirota*

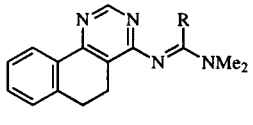
Faculty of Pharmaceutical Sciences, Okayama University, 1-1-1, Tsushima-Naka, Okayama, 700-8530, Japan

Received November 8, 1998

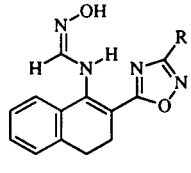
The reactions of *N*-(5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4-yl)amidines or its amide oxime derivatives with hydroxylamine hydrochloride under basic condition gave abnormal cyclization products *via* a ring cleavage of pyrimidine component accompanied with a ring closure of [1,2,4]oxadiazole.

J. Heterocyclic Chem., **36**, 787 (1999).

We have previously reported on the ring opening of pyrimidine component accompanied with a ring closure of [1,2,4]oxadiazole by reacting amidines **1** or their amide oximes with hydroxylamine hydrochloride under basic condition [1]. That is, the reaction of amidines having a bulky substituent such as a phenyl group resulted in unexpected products instead of normal amide oximes. The above unexpected products had been identified as *N*-{2-[3-aryl(or alkyl)[1,2,4]oxadiazol-5-yl]-3,4-dihydro-1-naphthyl}formamide oxime **2** by X-ray crystal structure analysis, ^{1}H-nmr spectrum and so on [1,2].



1



2

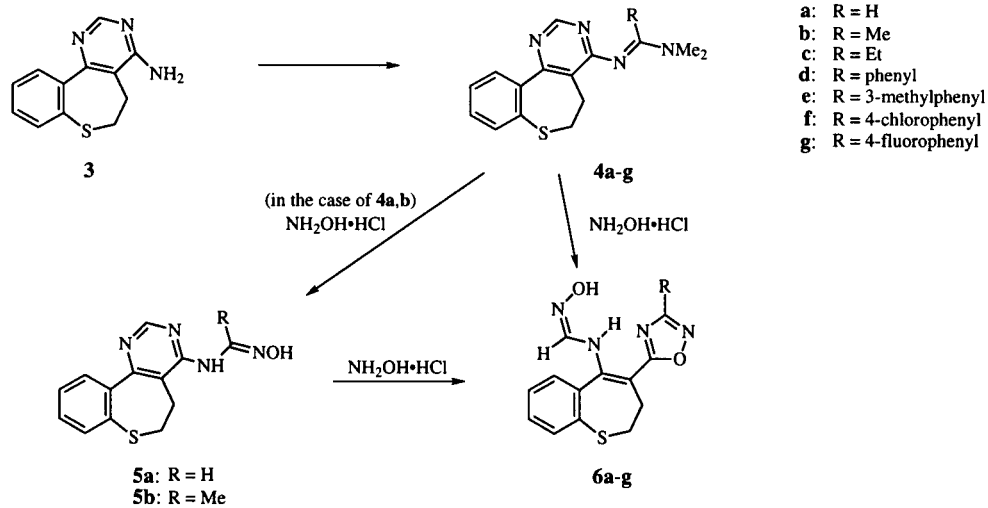
Figure.

To compare the reactivities of the pyrimidine ring in amidines **1** with that of other amidines having a different ring systems, we determined to prepare the new compounds **4**, which was reacted with hydroxylamine hydrochloride as described above.

Amidine derivatives as a requisite starting material were synthesized by two different ways. In the case that substituent R is hydrogen atom or methyl group, 4-amino-5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidine **3** [4] was allowed to react with *N*,*N*-dimethylformamide dimethyl acetal (R = H) or *N*,*N*-dimethylacetamide dimethyl acetal (R = Me) to give **4a** or **4b**, respectively. The preparations of other amidines **4c-g** were carried out by reacting compound **3** with the Vilsmeier reagents formed by the corresponding amides and phosphorus oxychloride [2].

Though amidines **4d-f** could be prepared by the treatment of the amino derivative **3** with the corresponding Vilsmeier reagent in refluxing chloroform, respectively, the formation of the amidines **4c**, **4g** failed by this method. By changing the reaction solvent from chloroform to 1,2-dimethoxyethane these amidines **4c**, **4g** could

Scheme



be obtained. It is considered that 1,2-dimethoxyethane facilitated the formation of carbocation of the Vilsmeier reagent as a dipolar aprotic solvent.

With a small substituent (R = hydrogen or Me group), the treatment of amidine **4a** with 6 equivalents of hydroxylamine hydrochloride at room temperature gave the normal amide oxime **5a**. The reaction of amidine **4b** with 1.2 equivalents of hydroxylamine hydrochloride at room temperature also gave compound **5b** along with a minor amount of **6b**. These phenomena were similar to the previous case in which the different ring system, 5,6-dihydrobenzo[*h*]quinazoline[1] was used. On the other hand, when 6 equivalents of hydroxylamine hydrochloride was used to **5b** under the same condition, the abnormal formamide oxime **6b** was obtained as the major product and the formation amount of **5b** was reduced.

The reaction of amidines **4d-g** with 6-14 equivalents of hydroxylamine hydrochloride at room temperature, exclusively yielded compounds **6** and normal oxime could not be isolated. The structures of **6** were confirmed by the instrumental and elemental analyses, which were analogous to those of compounds **2**. That is, all those compounds showed one proton doublet around 7 ppm attributed to the proton of N=CH-NO group and this was changed into singlet after addition of deuterium oxide. One proton doublet of NH around 11 ppm was also observed in their ^{1}H-nmr spectra. Furthermore, all of their ir spectra showed broad absorptions around 3100-3300 cm^{-1}, which were assigned to the N-H and O-H bonds. The reaction of amidine **4c** with 2 equivalents of hydroxylamine hydrochloride at room temperature also yielded the abnormal formamide oxime **6c** along with a minor amount of **5c**, which could not be separated. In the previous case, the reaction of amidine **1** which had methyl group as a substituent (R) with 1.2 equivalents of hydroxylamine hydrochloride at room temperature yielded the normal oxime which could be converted into the abnormal oxadiazole derivative by further treatment with 6 equivalents of hydroxylamine hydrochloride under reflux. In the case of the amidine **1** which had ethyl group as a substituent with 1.2 equivalents of hydroxylamine hydrochloride at room temperature also gave the normal oxime (not the abnormal product). This normal oxime could be changed into the abnormal product by treatment with 5 equivalents of hydroxylamine hydrochloride in refluxing methanol. The treatment of the normal oxime **5a** with 6 equivalents of hydroxylamine hydrochloride in a mixture of methanol and dioxane under reflux gave the abnormal formamide oxime **6a**. In the case of oxime **5b**, the reaction with 6 equivalents of hydroxylamine hydrochloride yielded the corresponding abnormal amide oxime **6b** at room temperature.

From the above observation, it seems that this novel reaction takes place more easily in thiepine type amidines **4** than cyclohexene type amidines **1**. The fact that the normal oximes **5a,b** could be converted into oxadiazole derivatives **6a,b** by further treatment with hydroxylamine hydrochloride was also consistent with our previous conclusion that the normal oxime type compound was the intermediate of this novel reaction.

Among the above abnormal formamide oximes **6**, we found that a few compounds exhibited anti-platelet aggregation activity. We will report the biological activities including this anti-platelet aggregation activity of the above compounds in the near future.

EXPERIMENTAL

Melting points were determined using a Yanagimoto micromelting point apparatus and are uncorrected. The ^{1}H-nmr spectra were recorded on a Varian VXR-200 instrument. All chemical shifts are reported in ppm (δ) downfield from tetramethylsilane and J values in Hz. The ir spectra were recorded as KBr discs on a JASCO corporation FT/IR-200 instrument. FAB- and EI-mass spectra were run on a VG 70 mass spectrometer and elemental analyses were obtained using a Yanagimoto MT-5 CHN Corder elemental analyzer.

N^1,*N*^{1}-Dimethyl-*N*^{2}-(5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4-yl)formamidine (**4a**).

N,*N*-Dimethylformamide dimethyl acetal (300 mg, 1.05 mmoles) was added to a solution of **3** (200 mg, 0.87 mmole) in dry toluene (20 ml), and the resulting mixture was refluxed for 4 hours. The solvent was evaporated to dryness and the residue was recrystallized from cyclohexane to give **4a** (223 mg, 90%) as white needles, mp 200-201°; ms: (FAB) m/z 285 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.30 (t, J = 6.5, 2H, SCH_2CH_2), 3.16 (s, 6H, NMe_2), 3.46 (t, J = 6.5, 2H, SCH_2CH_2), 7.37 (td, J_t = 7.4, J_d = 1.6, 1H, H9), 7.50 (td, J_t = 7.4, J_d = 1.6, 1H, H10), 7.63 (dd, $J_{8,9}$ = 7.4, $J_{8,10}$ = 1.6, 1H, H8), 7.77 (dd, $J_{11,10}$ = 7.4, $J_{11,9}$ = 1.6, 1H, H11), 8.68 (s, 1H, $CHNMe_2$), 8.77 (s, 1H, H2).

Anal. Calcd. for $C_{15}H_{16}N_4S$: C, 63.35; H, 5.67; N, 19.70. Found: C, 63.22; H, 5.57; N, 19.40.

N^1,*N*^{1}-Dimethyl-*N*^{2}-(5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4-yl)acetamidine (**4b**).

A mixture of **3** (250 mg, 1.09 mmoles) and *N*,*N*-dimethylacetamide dimethyl acetal (190 mg, 1.43 mmoles) in dry toluene (15 ml) was refluxed for 16 hours. After evaporation of the solvent, the residue was purified by column-chromatography on silica gel (*n*-hexane-acetone, 5:1, v/v) and recrystallized from *n*-hexane-ethyl acetate (5:1, v/v) to give **4b** (241 mg, 74%) as white prisms, mp 144-146°; ms: (FAB) m/z 299 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.17 (s, 3H, Me), 2.83 (t, J = 6.4, 2H, SCH_2CH_2), 3.12 (br s, 6H, NMe_2), 3.40 (t, J = 6.4, 2H, SCH_2CH_2), 7.34 (t, J = 7.5, 1H, H9), 7.47 (t, J = 7.5, 1H, H10), 7.62 (d, J = 7.5, 1H, H8), 7.79 (d, J = 7.5, 1H, H11), 8.82 (s, 1H, H2).

Anal. Calcd. for $C_{16}H_{18}N_4S$: C, 64.40; H, 6.08; N, 18.78. Found: C, 64.53; H, 6.06; N, 18.89.

General Procedure for Compounds **4c-g**.

Phosphorus oxychloride (2.76 mmoles) was added to ice-cooled amide (2.76 mmoles) and the mixture was stirred at room temperature for 2 hours. A solution of compound **3** (2.30 mmoles) in chloroform (or 1,2-dimethoxyethane) (15 ml) was added dropwise to the above mixture. After addition of triethylamine (10.35 mmoles) the reaction mixture was heated at 70° for appropriate hours (1-24 hours). The resulting mixture was poured into ice-water (50 ml) and basified (*p*H 8) with saturated aqueous sodium hydrogen carbonate. The resulting mixture was extracted with chloroform immediately, purified by column-chromatography on silica gel (*n*-hexane-acetone, 5:1, v/v) and recrystallized from *n*-hexane-ethyl acetate (5:1, v/v) to give the corresponding amidine derivatives **4c-g**.

N^1,*N*^{1}-Dimethyl-*N*^{2}-(5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4-yl)propionamidine (**4c**).

The reaction mixture was reacted for 12 hours in 1,2-dimethoxyethane and the title compound was obtained as white needles (15%), mp 128-130°; ms: (FAB) m/z 313 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 1.16 (t, J = 7.6, 3H, CH_2*Me*), 2.66 (q, J = 7.6, 2H, *C*H_2Me), 2.83 (t, J = 6.6, 2H, SCH_2*C*H_2), 3.12 (s, 6H, NMe_2), 3.40 (t, J = 6.6, 2H, SCH_2*C*H_2), 7.35 (t, J = 7.5, 1H, H9), 7.49 (t, J = 7.5, 1H, H10), 7.62 (d, J = 7.5, 1H, H8), 7.79 (d, J = 7.5, 1H, H11), 8.81 (s, 1H, H2).

Anal. Calcd. for $C_{17}H_{20}N_4S$: C, 65.35; H, 6.45; N, 17.92. Found: C, 65.19; H, 6.21; N, 17.53.

N^1,*N*^{1}-Dimethyl-*N*^{2}-(5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4-yl)benzamidine (**4d**).

The reaction mixture was reacted for 8 hours in chloroform and the title compound was obtained as white needles (97%), mp 108-109°; ms: (FAB) m/z 361 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.88 (t, J = 6.5, 2H, SCH_2*C*H_2), 2.92 (br, 6H, NMe_2), 3.48 (t, J = 6.5, 2H, SCH_2*C*H_2), 7.20-7.38 (m, 6H, H9 and phenyl-H), 7.45 (td, J_t = 7.5, J_d = 1.5, 1H, H10), 7.61 (dd, $J_{8,9}$ = 7.5, $J_{8,10}$ = 1.5, 1H, H8), 7.70 (dd, $J_{11,10}$ = 7.5, $J_{11,9}$ = 1.5, 1H, H11), 8.48 (s, 1H, H2).

Anal. Calcd. for $C_{21}H_{20}N_4S$: C, 69.97; H, 5.59; N, 15.54. Found: C, 70.01; H, 5.70; N, 15.29.

N^1,*N*^{1}-Dimethyl-*N*^{2}-(5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4-yl)-3-methylbenzamidine (**4e**).

The reaction mixture was reacted for 20 hours in chloroform and the title compound was obtained as white prisms (63%), mp 95-96°; ms: (FAB) m/z 375 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.30 (s, 3H, Me), 2.90 (t, J = 6.5, 2H, SCH_2*C*H_2), 2.96-3.36 (br s, 6H, NMe_2), 3.50 (t, J = 6.5, 2H, SCH_2*C*H_2), 7.07-7.21 (m, 4H, phenyl-H), 7.37 (td, J_t = 7.4, J_d = 1.6, 1H, H9), 7.48 (td, J_t = 7.5, J_d = 1.6, 1H, H10), 7.63 (dd, $J_{8,9}$ = 7.6, $J_{8,10}$ = 1.5, 1H, H8), 7.73 (dd, $J_{11,10}$ = 7.6, $J_{11,9}$ = 1.6, 1H, H11), 8.47 (s, 1H, H2).

Anal. Calcd. for $C_{22}H_{22}N_4S$: C, 70.56; H, 5.92; N, 14.96. Found: C, 70.46; H, 6.00; N, 14.69.

N^1,*N*^{1}-Dimethyl-*N*^{2}-(5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4-yl)-4-chlorobenzamidine (**4f**).

The reaction mixture was reacted for 24 hours in chloroform and the title compound was obtained as white needles (11%), mp 175-177°; ms: (FAB) m/z 395 (MH^+), 397 (MH^++2); ^{1}H-nmr (deuteriochloroform): δ 2.88 (t, J = 6.5, 2H, SCH_2*C*H_2), 2.99-3.17 (br s, 6H, NMe_2), 3.47 (t, J = 6.5, 2H, SCH_2*C*H_2), 7.18 (m, 2H, phenyl-H3' and H5'), 7.26 (m, 2H, phenyl-H2' and H6'), 7.36 (td, J_t = 7.4, J_d = 1.6, 1H, H9), 7.49 (td, J_t = 7.4, J_d = 1.6, 1H, H10), 7.62 (dd, $J_{8,9}$ = 7.4, $J_{8,10}$ = 1.6, 1H, H8), 7.72 (dd, $J_{11,10}$ = 7.4, $J_{11,9}$ = 1.6, 1H, H11), 8.49 (s, 1H, H2).

Anal. Calcd. for $C_{21}H_{19}ClN_4S$: C, 63.87; H, 4.85; N, 14.19. Found: C, 63.65; H, 4.94; N, 14.00.

N^1,*N*^{1}-Dimethyl-*N*^{2}-(5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4-yl)-4-fluorobenzamidine (**4g**).

The reaction mixture was reacted for 1 hour in 1,2-dimethoxyethane and the title compound was obtained as white needles (78%), mp 75-77°; ms: (FAB) m/z 379 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.88 (t, J = 6.5, 2H, SCH_2*C*H_2), 2.97-3.17 (br s, 6H, NMe_2), 3.47 (t, J= 6.5, 2H, SCH_2*C*H_2), 7.00 (m, 2H, phenyl-H3' and H5'), 7.22 (m, 2H, phenyl-H2' and H6'), 7.35 (td, J_t = 7.4, J_d = 1.5, 1H, H9), 7.46 (td, J_t = 7.4, J_d = 1.5, 1H, H10), 7.60 (dd, $J_{8,9}$ = 7.4, $J_{8,10}$ = 1.5, 1H, H8), 7.73 (dd, $J_{11,10}$ = 7.4, $J_{11,9}$ = 1.5, 1H, H11), 8.45 (s, 1H, H2).

Anal. Calcd. for $C_{21}H_{19}FN_4S \cdot 1/2C_6H_{14}$: C, 68.38; H, 6.22; N, 13.29. Found: C, 68.27; H, 6.34; N, 13.31.

N-(5,6-Dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4-yl)formamide Oxime (**5a**).

Hydroxylamine hydrochloride (130 mg, 1.87 mmoles) was added to a solution of amidine **4a** (91 mg, 0.32 mmole) in dry methanol (6 ml) and the resulting mixture was stirred at room temperature for 1 hour. A white solid was precipitated during the reaction. After the mixture was poured into ice-water (30 ml) and basified (*p*H 8) with saturated aqueous sodium hydrogen carbonate, the white solid was filtered and washed with water. Recrystallization of the above solid from dioxane gave **5a** (77.6 mg, 89%) as white prisms, mp 243-246°; ir (potassium bromide): cm^{-1} 3440 (br, NH or OH), 3180 and 3090 (NH or OH); ms: (EI) m/z 272 (M^+); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 2.78 (t, J = 6.2, 2H, SCH_2*C*H_2), 3.46 (t, J = 6.2, 2H, SCH_2*C*H_2), 7.44-7.71 (m, 4H, H8, H9, H10 and H11), 8.03 (d, J = 10, 1H, changed to singlet after addition of deuterium oxide, NCH=NO), 8.73 (s, 1H, H2), 8.86 (d, J = 10, 1H, deuterium oxide exchangeable, NH), 10.69 (s, 1H, deuterium oxide exchangeable, OH).

Anal. Calcd. for $C_{13}H_{12}N_4OS \cdot 1/5H_2O$: C, 56.59; H, 4.53; N, 20.31. Found: C, 56.91; H, 4.56; N, 20.04.

N-(5,6-Dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4-yl)acetamide Oxime (**5b**).

Hydroxylamine hydrochloride (27 mg, 0.38 mmole) was added to a solution of amidine **4b** (91 mg, 0.32 mmole) in dry methanol (6 ml) and the resulting mixture was stirred at room temperature for 1 hour. A white solid was precipitated during the reaction. After the mixture was poured into ice-water (30 ml) and basified (*p*H 8) with saturated aqueous sodium hydrogen carbonate, the white solid was filtered and washed with water. Recrystallization of the above solid from ethanol gave **5b** (78 mg, 89%) as white prisms, mp 212-215°; ir (potassium bromide): cm^{-1} 3380, 3120 (NH and OH); ms: (FAB) m/z 287 (MH^+); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 2.34 (s, 3H, Me); 2.72 (t, J = 6.4, 2H, SCH_2*C*H_2), 3.48 (t, J = 6.4, 2H, SCH_2*C*H_2), 7.45-7.72 (m, 4H, H8, H9, H10 and H11), 8.43 (s, 1H, deuterium oxide exchangeable, NH), 8.72 (s, 1H, H2), 10.55 (s, 1H, deuterium oxide exchangeable, OH).

Anal. Calcd. for $C_{14}H_{14}N_4OS$: C, 58.72; H, 4.93; N, 19.57. Found: C, 58.42; H, 5.04; N, 19.41.

N-[4-([1,2,4]Oxadiazol-5-yl)-2,3-dihydro[1]benzothiepin-5-yl] formamide Oxime (**6a**).

Hydroxylamine hydrochloride (460 mg, 6.62 mmoles) was added to a solution of **5a** (300 mg, 1.1 mmoles) in a mixture of methanol (14 ml) and dioxane (8 ml), and the resulting mixture was refluxed for 24 hours. The reaction mixture was poured into ice-water and the resulting mixture was basified (*p*H 8) with saturated aqueous sodium hydrogen carbonate, and extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous sodium sulfate and evaporated to afford white solid, which was recrystallized from methanol to yield **6a** (70 mg, 22%) as white prisms, mp 183-185°; ir (potassium bromide): cm^{-1} 3290, 3230 (NH and OH); ms: (FAB) m/z 289 (MH^+); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 1.94 (m, 1H, one of SCH_2CH_2), 3.14 (m, 2H, each one of SCH_2CH_2), 3.48 (1H, m, one of SCH_2CH_2), 6.75 (d, J = 9.8, 1H, changed to singlet after addition of deuterium oxide, NCH=NOH), 7.49-7.62 (m, 3H, H7, H8 and H9), 7.75 (d, J = 6.9, 1H, H6), 9.14 (s, 1H, oxadiazole-H), 10.71 (s, 1H, deuterium oxide exchangeable, OH), 11.22 (d, J = 9.8, 1H, deuterium oxide exchangeable, NH).

Anal. Calcd. for $C_{13}H_{12}N_4O_2S$: C, 54.16; H, 4.20; N, 19.43. Found: C, 54.04; H, 4.33; N, 19.21.

N-[4-(3-Methyl[1,2,4]oxadiazol-5-yl)-2,3-dihydro[1]benzothiepin-5-yl]formamide Oxime (**6b**).

Hydroxylamine hydrochloride (150 mg, 2.1 mmoles) was added to a solution of **5b** (100 mg, 0.35 mmole) in a mixture of methanol (2 ml) and dioxane (8 ml) and the resulting mixture was stirred at room temperature for 6 hours. A white solid was precipitated during the reaction. The reaction mixture was poured into ice-water (25 ml) and the resulting mixture was basified (*p*H 8) with saturated aqueous sodium hydrogen carbonate. Thus obtained white solid was filtered, washed with water and recrystallized from ethanol to yield **6b** (100 mg, 95%) as white prisms, mp 184-186°; ir (potassium bromide): cm^{-1} 3280 (br, NH and OH); ms: (FAB) m/z 303 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.06 (m, 1H, one of SCH_2CH_2), 2.47 (s, 3H, Me), 3.11-3.33 (m, 2H, each one of SCH_2CH_2), 3.55 (m, 1H, one of SCH_2CH_2), 6.84 (d, J = 10, 1H, changed to singlet after addition of deuterium oxide, NCH=NO), 7.38-7.55 (m, 4H, changed to three protons after addition of deuterium oxide, H7, H8, H9 and OH), 7.74 (d, J = 6.8, 1H, H6), 11.40 (d, J = 10, 1H, deuterium oxide exchangeable, NH).

Anal. Calcd. for $C_{14}H_{14}N_4O_2S \cdot 1/5C_2H_5OH \cdot 9/10HCl$: C, 50.17; H, 4.66; N, 16.26. Found: C, 49.87; H, 4.27; N, 16.07.

N-[4-(3-Ethyl[1,2,4]oxadiazol-5-yl)-2,3-dihydro[1]benzothiepin-5-yl]formamide Oxime (**6c**).

Hydroxylamine hydrochloride (140 mg, 2 mmoles) was added to amidine **4c** (312 mg, 1 mmoles) in dry methanol (5 ml) and stirred at room temperature for 18 hours. A white solid was precipitated during the reaction. The reaction mixture was poured into ice-water (20 ml), and the resulting mixture was basified (*p*H 8) with saturated aqueous sodium hydrogen carbonate. The precipitating white solid was filtered, washed with water and recrystallized from *n*-hexane-ethyl acetate (5:1, v/v) to give **6c** (278 mg, 88%) as white powder, mp 143-145°; ir (potassium bromide): cm^{-1} 3280 (br, NH and OH); ms: (FAB) m/z 317 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 1.39 (t, J = 7.5, 3H, CH_2Me), 2.58 (m, 1H, one of SCH_2CH_2), 2.85 (q, J = 7.5, 2H, CH_2Me), 3.26 (m, 2H, each one of SCH_2CH_2), 3.61 (m, 1H, one of SCH_2CH_2), 7.26-7.55 (m, 5H, changed to four protons after addition of deuterium oxide, NCH=NO, H7, H8, H9 and OH), 7.76 (dd, $J_{6,7}$ = 7.2, $J_{6,8}$ = 1.7, 1H, H6), 12.34 (d, J = 10.4, 1H, deuterium oxide exchangeable, NH).

Anal. Calcd. for $C_{15}H_{16}N_4O_2S$: C, 56.95; H, 5.10; N, 17.71. Found: C, 56.68; H, 5.12; N, 17.62.

General Procedure for Compounds **6d-g**.

Hydroxylamine hydrochloride (60-140 mmoles) was added to amidine **4d-g** (10 mmoles) in dry methanol (10 ml) and the resulting mixture was stirred at room temperature for 24-120 hours. A white solid was precipitated during the reaction. The reaction mixture was poured into ice-water (100 ml), and the resulting mixture was basified (*p*H 8) with saturated aqueous sodium hydrogen carbonate. Then the precipitating white solid was filtered, washed with water and recrystallized from methanol to give corresponding oxadiazole **6d-g**.

N-[4-(3-Phenyl[1,2,4]oxadiazol-5-yl)-2,3-dihydro[1]benzothiepin-5-yl]formamide Oxime (**6d**).

The reaction mixture was carried out for 24 hours with hydroxylamine hydrochloride (60 mmoles) to give **6d** as white prisms (44%), mp 177-179°; ir (potassium bromide): cm^{-1} 3240, 3186 (br, NH and OH); ms: (FAB) m/z 365 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.11 (m, 1H, one of SCH_2CH_2), 3.19-3.39 (m, 2H, each one of SCH_2CH_2), 3.56-3.65 (m, 1H, one of SCH_2CH_2), 6.92 (d, J = 10, 1H, changed to singlet after addition of deuterium oxide, NCH=NO), 7.38-7.57 (m, 7H, changed to six protons after addition of deuterium oxide, H7, H8, H9, phenyl-H3', H4', H5' and OH), 7.75 (d, J = 7.2, 1H, H6), 8.21 (m, 2H, phenyl-H2' and H6'), 11.84 (d, J = 10, 1H, deuterium oxide exchangeable, NH).

Anal. Calcd. for $C_{19}H_{16}N_4O_2S$: C, 62.64; H, 4.39; N, 15.38. Found: C, 62.43; H, 4.64; N, 15.55.

N-{4-[3-(3-Methylphenyl)[1,2,4]oxadiazol-5-yl]-2,3-dihydro-[1]benzothiepin-5-yl}formamide Oxime (**6e**).

The reaction mixture was reacted for 48 hours with hydroxylamine hydrochloride (100 mmoles) to give **6e** as white prisms (40%), mp 178-180°; ir (potassium bromide): cm^{-1} 3240, 3060 (br, NH and OH); ms: (FAB) m/z 379 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.10 (m, 1H, one of SCH_2CH_2), 3.43 (s, 3H, Me), 3.19-3.38 (m, 2H, each one of SCH_2CH_2), 3.59 (m, 1H, one of SCH_2CH_2), 6.92 (d, J = 10, 1H, changed to singlet after addition of deuterium oxide, NCH=NO), 7.30-7.50 (m, 6H, changed to five protons after addition of deuterium oxide, H7, H8, H9, phenyl-H4', H5' and OH), 7.75 (d, J = 7.1, 1H, H6), 8.03 (m, 2H, phenyl-H2', H6'), 11.86 (d, J = 10, 1H, deuterium oxide exchangeable, NH).

Anal. Calcd. for $C_{20}H_{18}N_4O_2S$: C, 63.48; H, 4.79; N, 14.80. Found: C, 63.31; H, 4.83; N, 14.59.

N-{4-[3-(4-Chlorophenyl)[1,2,4]oxadiazol-5-yl]-2,3-dihydro-[1]benzothiepin-5-yl}formamide Oxime (**6f**).

The reaction mixture was reacted for 120 hours with hydroxylamine hydrochloride (100 mmoles) to give **6f** as white prisms (30%), mp 207-209°; ir (potassium bromide): cm^{-1} 3220 (br, NH and OH); ms: (FAB) m/z 399 (MH^+), 401 (MH^++2); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 1.85-2.09 (m, 1H, one of SCH_2CH_2), 3.04-3.28 (m, 2H, each one of SCH_2CH_2), 3.34-3.64 (m, 1H,

one of SCH_2CH_2), 6.89 (d, J = 9.7, 1H, changed to singlet after addition of deuterium oxide, NCH=NO), 7.55-7.77 (m, 5H, H7, H8, H9 phenyl-H3' and H5'), 7.75 (d, J = 7.1, 1H, H6), 8.17 (d, J = 8.6, 2H, phenyl-H2' and H6'), 10.97 (s, 1H, deuterium oxide exchangeable, OH), 11.78 (d, J = 9.7, 1H, deuterium oxide exchangeable, NH).

Anal. Calcd. for $C_{19}H_{15}ClN_4O_2S$: C, 57.21; H, 3.79; N, 14.05. Found: C, 57.50; H, 4.10; N, 13.66.

N-{4-[3-(4-Fluorophenyl)[1,2,4]oxadiazol-5-yl]-2,3-dihydro-[1]benzothiepin-5-yl}formamide Oxime (**6g**).

The reaction mixture was reacted for 96 hours with hydroxylamine hydrochloride (140 mmoles) to give **6g** as yellow prisms (73%), mp 204-207°; ir (potassium bromide): cm^{-1} 3250 (br, NH and OH); ms: (FAB) m/z 383 (MH^+); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 3.27 (m, 2H, SCH_2CH_2), 3.57 (m, 2H, SCH_2CH_2), 6.92 (d, J = 10, 1H, changed to singlet after addition of deuterium oxide, NCH=NO), 7.14-7.24 (m, 3H, changed to two protons after addition of deuterium oxide, phenyl-H3', H5' and OH), 7.26-7.54 (m, 3H, H7, H8 and H9), 7.77 (d, J = 7.2, 1H, H6), 8.18-8.26 (m, 2H, phenyl-H2' and H6'), 11.77 (d, J = 10, 1H, deuterium oxide exchangeable, NH).

Anal. Calcd. for $C_{19}H_{15}FN_4O_2S$: C, 59.68; H, 3.95; N, 14.65. Found: C, 59.94; H, 4.23; N, 14.74.

Acknowledgment.

We are grateful to The SC-NMR Laboratory of Okayama University for 200 MHz ^{1}H-nmr experiments.

REFERENCES AND NOTES

[1] K. Sasaki, Y.-X. Zhang, H. Yamamoto, S. Kashino and T. Hirota, *J. Chem. Res.*, in press.

[2] T. Hirota, K. Sasaki, H. Yamamoto, K. Mori and S. Kashino, *Acta Cryst.*, **C50**, 807 (1994).

[3] S. R. Sandler and W. Karo, Organic Functional Group Preparations, Vol **3**, Academic Press, Inc., New York, 1989, Second edition, pp 229.

[4] T. Nagamatsu, K. Kinoshita, K. Sasaki, T. Nakayama and T. Hirota, *J. Heterocyclic Chem.*, **28**, 513 (1991).