Polycyclic *N*-Heterocyclic Compounds. 56 [1] Reaction of *N*-(5,6-Dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-yl)amidine or Its Amide Oxime Derivatives with Hydroxylamine Hyrdochloride

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

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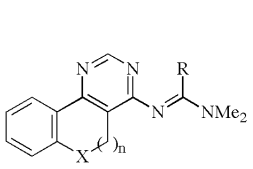
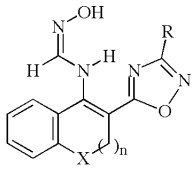
We have previously reported on the pyrimidine ring opening reaction accompanying with a formation of [1,2,4]oxadiazole ring by the reaction of *N*-(5,6-dihydrobenzo[*h*]quinazolin-4-yl)amidine or its amide oxime with hydroxylamine hydrochloride [2,3]. As an application of this [1,2,4]oxadiazole ring formation, we found that the reaction of *N*-(5,6-dihydro[1]benzothiepino[5,4-*d*]-pyrimidin-4-yl)amidines or their amide oximes with hydroxylamine hydrochloride also gave similar [1,2,4]oxadiazoles [1]. In this paper, we applied this reaction to (pyrimidin-4-yl)amidines fused with a [1] benzoxepine ring instead of a [1]benzothiepine ring and also to their amide oximes such as compound **4** and **5** for comparing with the reactivities of thiepino analogues.



1; n = 1, 2
R = H, alkyl, aryl
X = CH_2, S



2; n = 1, 2
R = H, alkyl, aryl
X = CH_2, S

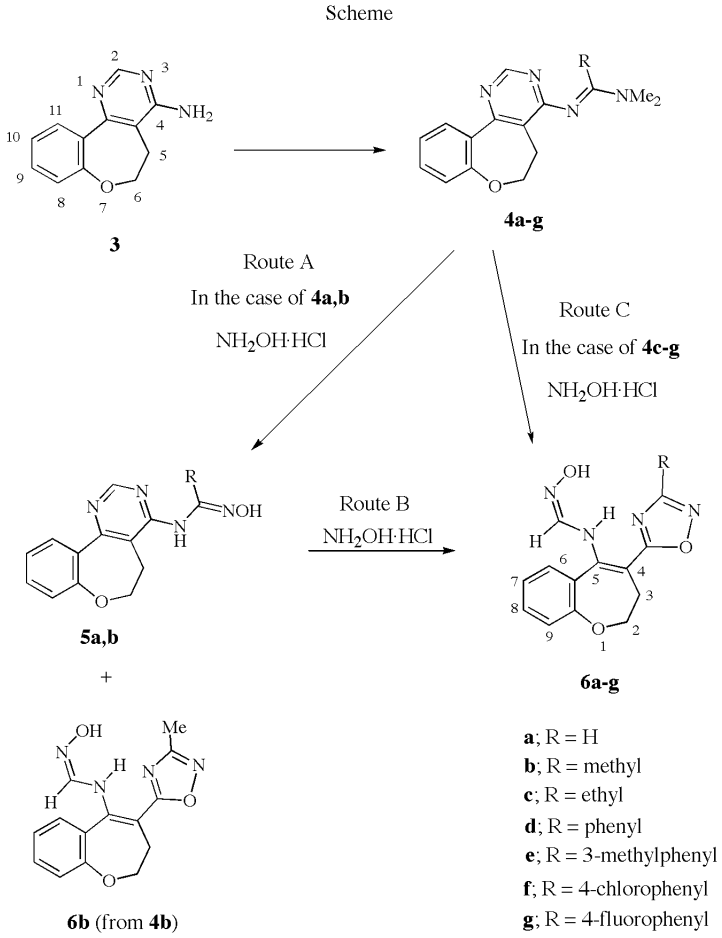
Figure

As shown in Scheme, amidines **4** as a requisite starting material were synthesized by the previously reported method [1-3]. That is, amidines **4a**,**b** were prepared by the reaction of 4-amino-5,6-dihydro[1]benzoxepino[5,4-*d*]-pyrimidine **3** [4] with commercially available *N*,*N*-dimethylformamide dimethyl acetal (for **4a**) or *N*,*N*-dimethylacetamide dimethyl acetal (for **4b**) in refluxing toluene. Other amidines **4c-g** were afforded by the reaction of compound **3** with the Vilsmeier reagent prepared from the corresponding amides (*N*,*N*-dimethylpropionamide for **4c**, *N*,*N*-dimethylbenzamide for **4d**, *N*,*N*-dimethyl-3-methylbenzamide for **4e**, *N*,*N*-dimethyl-4-chlorobenzamide for **4f**, *N*,*N*-dimethyl-4-fluorobenzamide for **4g**) and phosphorus oxychloride [5]. Similar to the thiepino analogues [1], refluxing in1,2-dimethoxyethane as a solvent was required instead of refluxing chloroform to complete the reaction for preparing **4c**. On the other hand, the reaction proceeded in refluxing chloroform for preparing **4g**, however, the refluxing 1,2-dimethoxyethane was employed in the reaction of 4-fluorophenyl derivative previously reported [1].

When a hydrogen is attached to the amidine moiety (R = H) the reaction of **4a** with 6 equivalents of hydroxylamine hydrochloride at room temperature gave the normal amide oxime **5a** (88%, Route A). Compound **5a** was converted to the desired [1,2,4]oxadiazole derivative **6a** in 38% yield by reaction with 10 equivalents of hydroxylamine hydrochloride in a refluxing mixture of methanol and dioxane (5:1, v/v) (Route B). This result was similar to the previous case [1]. When a methyl group was attached on the amidine moiety (R = methyl) the reaction of **4b** with 1.2 equivalents of hydroxylamine hydrochloride in methanol at room temperature gave exclusively normal oxime **5b** (79%, Route A). However, the similar reaction of **4b** with 2.0 equivalents of hydroxylamine hydrochloride in methanol afforded the normal amide oxime **5b** (35%) along with oxadiazole derivative **6b** (25%) as a minor product even at room temperature. In the case of the benzothiepino derivative [1], the reaction of *N*-(5,6-dihydro[1]benzothiepino[5,4-*d*]pyrimidin-4-yl)acetamide oxime with 1.2 equivalents of hydroxylamine hydrochloride in methanol at room temperature gave the normal oxime as a major product (89%), and trace of the corresponding oxadiazole derivative was detected by tlc. The reaction of the same thiepinoacetamide oxime with 6 equivalents of hydroxylamine hydrochloride in methanol gave the oxadiazole derivative as a major product (60%) and normal oxime as a minor one (27%) at room temperature. The oxime **5b** was easily converted to **6b** (86%) by stirring with 6 equivalents of hydroxylamine hydrochloride in a mixture of methanol and dioxane (2:3, v/v) at room temperature (Route B).

In the case of compound **4c**, in which the substituent R is more bulky than that of **4b**, a similar reaction (in methanol, at room temperature for 1 hour) with 2.0 equivalents of

Scheme



hydroxylamine hydrochloride afforded oxadiazole **6c** in better yield (67%, Route C). The corresponding normal oxime could not be obtained in this reaction. In a previous report [1] corresponding thiepinopropionamidine gave the oxadiazole derivative in 88% yield in the same condition except for a reaction period, which was longer (18 hours) than that of **4c**. Other oxepinoamidines **4d-g** having an aryl group substituted in the amidine moiety also gave the desired oxadiazole **6d-g** exclusively by the reaction with 6-18 equivalents of hydroxylamine hydrochloride in methanol at room temperature (Route C). In these cases, the corresponding normal oximes could not be isolated similar to the case of **4c**. The structures of **6** were confirmed by instrumental and elemental analyses. Especially the ^{1}H-nmr spectra of **6** in deuteriochloroform showed a characteristic one-proton doublet (about 10 Hz) around 7.0-7.1 ppm, which changed to a singlet after addition of deuterium oxide. The ir spectra of **6** also showed a broad absorption with a shoulder around 3100-3300 cm^{-1}. Considering the yields of oxepinooxadiazole **6d-g** and thiepinooxadiazoles [1] having an aryl substituent, the result was entirely opposite. The yield of the fluoro derivative was best (73%) and that of the chloro derivative was worst (30%), for thiepinooxadiazole derivatives [1]. To the contrary, the yield of the chloro derivative **6f** was best (83%) and that of **6g** was worst (50%) in this study.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The EI- and FAB-ms spectra were recorded on a VG 70-SE mass spectrometer, using glycerol or *m*-nitrobenzyl alcohol as a matrix agent. The ir spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer. Unless otherwise stated, they were measured as potassium bromide pellets and frequencies are expressed in cm^{-1}. The nmr spectra were recorded on a Varian VXR-200 instrument (200 MHz) in the solvent indicated with tetramethylsilane as the internal standard. Chemical shifts are reported in ppm (δ) and *J* values in Hz, and the signals are designated as follows; s, singlet; d, doublet; dd, doublet doublet; t, triplet; td, triplet doublet; q, quartet; br, broad. Unless otherwise stated extracted solutions were dried over anhydrous sodium sulfate. Under reduced pressure at 40-60 °C on a rotary vacuum evaporator, evaporation refers to the removal of volatile materials.

N,*N*-Dimethyl-*N'*-(5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-yl)formamidine (**4a**).

N,*N*-dimethylformamide dimethyl acetal (0.13 g, 1.1 mmol) was added to a solution of **3** [4] (0.20 g, 0.94 mmol) in dry toluene (10 ml) and the resulting mixture was refluxed for 5 hours. The solvent was evaporated to dryness and the residue was recrystallized from cyclohexane to give **4a** (0.22 g, 87%) as colorless needles, mp 95-96 °C; FAB-ms: *m*/*z* 269 (MH^+); ^{1}H-nmr (douteriochloroform): δ 3.13 (2H, t, *J* = 6, OCH_2CH_2), 3.16 (6H, s, NMe_2), 4.59 (2H, t, *J* = 6, OCH_2CH_2), 7.11 (1H, dd, *J* = 8 and 2, H8), 7.24 (1H, td, *J* = 8 and 2, H9), 7.40 (1H, td, *J* = 8 and 2, H10), 7.69 (1H, dd, *J* = 8 and 2, H11), 8.68 (1H, s, CHNMe$_2$), 8.76 (1H, s, H2).

Anal. Calcd for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.88. Found: C, 66.99; H, 6.00; N, 21.11.

N,*N*-Dimethyl-*N'*-(5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-yl)acetamidine (**4b**).

A mixture of **3** (0.24 g, 1.4 mmol) and *N*,*N*-dimethylacetamide dimethyl acetal (0.28 g, 2.11 mmol) in dry toluene (30 ml) was refluxed for 15 hours. After evaporation of the solvent, the residue was purified by column chromatography on silica gel. *n*-Hexane-acetone (5:1, v/v) eluates were evaporated and the residue was recrystallized from *n*-hexane-ethyl acetate to give **4b** (0.32 g, 80%) as colorless prisms, mp 100-101 °C; FAB-ms: *m*/*z* 283 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.16 (3H, s, CMe), 2.95 (2H, t, *J* = 4, OCH_2CH_2), 3.12 (6H, br s, NMe_2), 4.54 (2H, t, *J* = 4, OCH_2CH_2), 7.08 (1H, dd, *J* = 8 and 2, H8), 7.28 (1H, td, *J* = 8 and 2, H9), 7.40 (1H, td, *J* = 8 and 2, H10), 8.20 (1H, dd, *J* = 8 and 2, H11), 8.81 (1H, s, H2).

Anal. Calcd for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.84. Found: C, 68.05; H, 6.40; N, 19.77.

General Procedure for the Synthesis of Amidines **4c**-**g**.

To an ice-cooled corresponding *N*,*N*-dimethylamide was added phosphorus oxychloride, and the mixture was stirred at room temperature for several hours. To the Vilsmeier reagent thus obtained, compound **3** in 1,2-dimethoxyethane was added dropwise to the above mixture. Then triethylamine was added to the mixture and the reaction mixture was refluxed. After refluxing, the mixture was poured into ice water. The resulting mixture was basified (pH 9) with saturated aqueous sodium hydrogen carbonate and extracted with chloroform. The organic layer was treated as usual and the resulting residue was purified by column chromatography on silica gel. *n*-Hexane-acetone eluates were evaporated and the residue was recrystallized to give **4c**-**g**.

N,*N*-Dimethyl-*N'*-(5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-yl)propionamidine (**4c**).

The Vilsmeier reagent was prepared by stirring the mixture of *N*,*N*-dimethylpropionamide (0.50 g, 3.4 mmol) and phosphorus oxychloride (0.52 g, 3.4 mmol) for 2 hours. After addition of **3** (0.60, 2.8 mmol) and triethylamine (1.3 g, 13 mmol), the reaction mixture was refluxed for 18 hours. *n*-Hexane-acetone (5:1, v/v) eluates gave **4c** (0.10 g, 12%) as yellow prisms, mp 64-65 °C; FAB-ms: *m*/*z* 297 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 1.15 (3H, t, *J* = 8, CH_2Me), 2.69 (2H, q, *J* = 8, CH_2Me), 2.95 (2H, t, *J* = 6, OCH_2CH_2), 3.16 (6H, s, NMe_2), 4.54 (2H, t, *J* = 6, OCH_2CH_2), 7.11 (1H, dd, *J* = 8 and 2, H8), 7.25 (1H, td, *J* = 8 and 2, H9), 7.42 (1H, td, *J* = 8 and 2, H10), 8.04 (1H, dd, *J* = 8 and 2, H11), 8.79 (1H, s, H2).

Anal. Calcd for $C_{17}H_{20}N_4O$: C, 68.90; H, 6.80; N, 18.90. Found: C, 69.02; H, 6.55; N, 18.81.

N,*N*-Dimethyl-*N'*-(5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-yl)benzamidine (**4d**).

The Vilsmeier reagent was prepared by stirring the mixture of *N*,*N*-dimethylbenzamide (0.42 g, 2.8 mmol) and phosphorus oxychloride (0.49 g, 3.2 mmol) for 1 hours. After addition of **3** (0.50, 2.4 mmol) and triethylamine (0.72 g, 7.1 mmol), the reaction mixture was refluxed for 6 hours. *n*-Hexane-acetone (4:1, v/v) eluates gave **4d** (0.52 g, 64%) as colorless needles, mp 105-106 °C; FAB-ms: *m*/*z* 345 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 3.03 (2H, t, *J* = 6, OCH_2CH_2), 3.22 (6H, br s, NMe_2), 4.53 (2H, t, *J* = 6, OCH_2CH_2), 7.08 (1H, dd, *J* = 8 and 2, H8), 7.10-7.43 (7H, m, H9,10 and phenyl-H), 7.98 (1H, dd, *J* = 8 and 2, H11), 8.49 (1H, s, H2);

Anal. Calcd for $C_{21}H_{20}N_4O$: C, 73.23; H, 5.85; N, 16.27. Found: C, 73.28; H, 5.93; N, 16.21.

N,*N*-Dimethyl-*N'*-(5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-yl)-3-methylbenzamidine (**4e**).

The Vilsmeier reagent was prepared by stirring of the mixture of *N*,*N*-dimethyl-3-methylbenzamide (0.46 g, 2.8 mmol) and phosphorus oxychloride (0.49 g, 3.2 mmol) for 1 hours. After addition of **3** (0.50, 2.4 mmol) and triethylamine (0.72 g, 7.1 mmol), the reaction mixture was refluxed for 36 hours. *n*-Hexane-acetone (4:1, v/v) eluates gave **4e** (0.38 g, 45%) as white powder, mp 99-100 °C; FAB-ms: *m*/*z* 359 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.28 (3H, s, CMe), 2.96 (2H, t, *J* = 6, OCH_2CH_2), 3.03 (6H,br s, NMe_2), 4.50 (2H, t, *J* = 6, OCH_2CH_2), 6.96-7.12 (5H, m, H8 and phenyl-H), 7.18 (1H, td, *J* = 8 and 2, H9), 7.37 (1H, td, *J* = 8 and 2, H10), 7.96 (1H, dd, *J* = 8 and 2, H11), 8.53 (1H, s, H2).

Anal. Calcd for $C_{22}H_{22}N_4O$: C, 73.72; H, 6.19; N, 15.63. Found: C, 73.78; H, 6.25; N, 15.74.

N,*N*-Dimethyl-*N'*-(5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-yl)-4-chlorobenzamidine (**4f**).

The Vilsmeier reagent was prepared by stirring of the mixture of *N*,*N*-dimethyl-4-chlorobenzamide (0.52 g, 2.8 mmol) and phosphorus oxychloride (0.49 g, 3.2 mmol) for 1 hour. After addition of **3** (0.50, 2.4 mmol) and triethylamine (0.72 g, 7.1 mmol), the reaction mixture was refluxed for 24 hours. *n*-Hexane-acetone (4:1, v/v) eluates gave **4f** (0.21 g, 24%) as colorless needles, mp 170-171 °C; FAB-ms: *m*/*z* *379* (MH^+), 381 ($MH^+ + 2$); ^{1}H-nmr (deuteriochloroform): δ 2.98 (2H, t, *J* = 6, OCH_2CH_2), 3.04 (6H, br s, NMe_2), 4.54 (2H, t, *J* = 6, OCH_2CH_2), 7.06-7.30 (6H, m, H8,9 and phenyl-H), 7.38 (1H, td, *J* = 8 and 2, H10), 7.98 (1H, dd, *J* = 8 and 2, H11), 8.51 (1H, s, H2).

Anal. Calcd for $C_{21}H_{19}ClN_4O$: C, 66.58; H, 5.06; N, 14.79. Found: C, 66.35; H, 5.11; N, 14.80.

N,*N*-Dimethyl-*N'*-(5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-yl)-4-fluorobenzamidine (**4g**).

The Vilsmeier reagent was prepared by stirring of the mixture of *N*,*N*-dimethyl-4-fluorobenzamide (0.47 g, 2.8 mmol) and phosphorus oxychloride (0.49 g, 3.2 mmol) for 1 hour. After

addition of **3** (0.50, 2.4 mmol) and triethylamine (0.72 g, 7.1 mmol), the reaction mixture was refluxed for 36 hours. *n*-Hexane-acetone (4:1, v/v) eluates gave **4g** (0.23 g, 27%) as colorless needles, mp 122-123 °C; FAB-ms: *m*/*z* 363 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.98 (2H, t, *J* = 6, OCH_2CH_2), 3.07 (6H, br s, NMe_2), 4.53 (2H, t, *J* = 6, OCH_2CH_2), 6.94-7.26 (6H, m, H8,9 and phenyl-H), 7.36 (1H, td, *J* = 8 and 2, H10), 7.98 (1H, dd, *J* = 8 and 2, H11), 8.51 (1H, s, H2).

Anal. Calcd for $C_{21}H_{19}FN_4O$: C, 69.60; H, 5.28; N, 15.46. Found: C, 69.76; H, 5.35; N, 15.54.

The Reactions of Amidines **4a**,**b** with Hydroxylamine Hydrochloride (Route A)

The Reaction of **4a** with Hydroxylamine Hydrochloride.

To a solution of **4a** (0.19 g, 0.71 mmol) in dry methanol (4 ml) was added hydroxylamine hydrochloride (0.29 g, 4.2 mmol) and the resulting mixture was stirred at room temperature for 3 hours. After the mixture was poured into ice water (40 ml) and basified (pH 9) with saturated aqueous sodium hydrogen carbonate, the precipitated solid was filtered and washed with water. Recrystallization of the solid from dioxane gave *N*-(5,6-dihydro[1]benzoxepino[5,4-*d*]-pyrimidin-4-yl)formamide oxime (**5a**, 0.16 g, 88%).

Compound **5a** was obtained as white powder, mp 245-248 °C; ir: 3440, 3070 (OH and NH); EI-ms: *m*/*z* 256 (M^+); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 2.88 (2H, t, *J* = 6, OCH_2CH_2), 4.54 (2H, t, *J* = 6, OCH_2CH_2), 7.13 (1H, br d, *J* = 8, H8), 7.24 (1H, br t, *J* = 8, H9), 7.49 (1H, br t, *J* = 8, H10), 7.94 (1H, dd, *J* = 8 and 2, H11), 8.01 (1H, d, *J* = 9, changed to singlet after addition of deuterium oxide, NCH=NO), 8.72 (1H, s, H2), 8.99 (1H, d, *J* = 9, deuterium oxide exchangeable, NH), 10.64 (1H, br s, deuterium oxide exchangeable, OH).

Anal. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86. Found: C, 60.78; H, 4.92; N, 21.84.

The Reactions of **4b** with Hydroxylamine Hydrochloride.

Run 1 (Using 1.2 equivalents of Hydroxylamine Hydrochloride).

To a solution of amidine **4b** (0.20 g, 0.71 mmol) in dry methanol (8 ml) was added hydroxylamine hydrochloride (59 mg, 0.85 mmol) and the resulting mixture was stirred at room temperature for 3 hours. After the mixture was poured into ice water (80 ml) and basified (pH 9) with saturated aqueous sodium hydrogen carbonate, the precipitated solid was filtered and washed with water. Recrystallization of the solid from ethanol gave *N*-(5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4-yl)-acetamide oxime (**5b**, 0.15 g, 79%).

Compound **5b** was obtained as colorless needles, mp 216-218 °C; ir: 3360, 3120 (OH and NH); FAB-ms: *m*/*z* 271 (MH^+); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 2.30 (3H, s, Me), 2.86 (2H, t, *J* = 6, OCH_2CH_2), 4.53 (2H, t, *J* = 6, OCH_2CH_2), 7.12 (1H, br d, *J* = 8, H8), 7.26 (1H, br t, *J* = 8, H9), 7.47 (1H, td, *J* = 8 and 2, H10), 8.02 (1H, dd, *J* = 8 and 2, H11), 8.49 (1H, br, deuterium oxide exchangeable, NH), 8.72 (1H, s, H2), 10.49 (1H, br, deuterium oxide exchangeable, OH).

Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.36; H, 5.33; N, 20.94.

Run 2 (Using 2.0 equivalents of Hydroxylamine Hydrochloride).

To a solution of amidine **4b** (0.20 g, 0.71 mmol) in dry methanol (13 ml) was added hydroxylamine hydrochloride (98 mg, 1.4 mmol) and the resulting mixture was stirred at room temperature for 3 hours. After the mixture was poured into ice water (80 ml) and basified (pH 9) with saturated aqueous sodium hydrogen carbonate, the precipitated solid was filtered and washed with water. Recrystallization of the solid from ethanol gave **5b** (67 mg, 35%). Further recrystallization of the mother liquor of **5b** from ethanol afforded *N*-[4-(3-methyl)[1,2,4]-oxadiazol-5-yl)-2,3-dihydro[1]benzoxepin-5-yl]formamide oxime (**6b**, 51 mg, 25%).

Compound **6b** was obtained as colorless needles, mp 179-181 °C; ir: 3280 (OH and NH); FAB-ms: *m*/*z* 287 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.46 (3H, s, Me), 2.68 (2H, t, *J* = 6, OCH_2CH_2), 4.53 (2H, t, *J* = 6, OCH_2CH_2), 7.06 (1H, d, *J* = 11, changed to singlet after addition of deuterium oxide, NCH=NO), 7.26-7.51 (5H, m, changed to 4H multiplet after addition of deuterium oxide, OH and H6,7,8,9), 11.28 (1H, d, *J* = 11, deuterium oxide exchangeable, NH).

Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.74; H, 4.93; N, 19.57. Found: C, 58.73; H, 5.04; N, 19.47.

The Reactions of Amide Oximes **5a**,**b** with Hydroxylamine Hydrochloride (Route B).

The Reaction of **5a** with Hydroxylamine Hydrochloride.

To a solution of **5a** (0.10 g, 0.39 mmol) in a mixture of dioxane (4 ml) and methanol (20 ml) was added hydroxylamine hydrochloride (0.27 g, 3.9 mmol) and the resulting mixture was refluxed for 24 hours. The reaction mixture was poured into ice-water (240 ml). The resulting mixture was basified (pH 9) with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was treated as usual and the residue was recrystallized from *n*-hexane-ethyl acetate to afford *N*-[4-([1,2,4]oxadiazol-5-yl)-2,3-dihydro[1]benzoxepin-5-yl]-formamide oxime (**6a**, 40 mg, 38%).

Compound **6a** was obtained as colorless needles, mp 146-149 °C; ir: 3320, 3240 (OH and NH); FAB-ms: *m*/*z* 273 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.72 (2H, t, *J* = 6, OCH_2CH_2), 4.55 (2H, t, *J* = 6, OCH_2CH_2), 7.07 (1H, d, *J* = 10, changed to singlet after addition of deuterium oxide, NC*H*=NOH), 7.08-7.33 (3H, m, changed to 2H multiplet after addition of deuterium oxide, OH and H8,9), 7.44-7.53 (2H, m, H6,7), 8.51 (1H, s, oxadiazolyl-H), 11.20 (1H, d, *J* = 10, deuterium oxide exchangeable, NH).

Anal. Calcd for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.26; H, 4.60; N, 20.51.

The Reaction of **5b** with Hydroxylamine Hydrochloride.

To a solution of **5b** (0.10 g, 0.37 mmol) in a mixture of dioxane (6 ml) and methanol (4 ml) was added hydroxylamine hydrochloride (0.15 g, 2.2 mmol) and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into ice water (100 ml) and the resulting mixture was basified (pH 9) with saturated aqueous sodium hydrogen carbonate. The precipitated white solid was filtered, washed with water and recrystallized from ethanol to give **6b** (92 mg, 86%).

The Reaction of Amidines **4c-g** with Hydroxylamine Hydrochloride (Route C).

General Procedure for the Synthesis of [1,2,4]Oxadiazole Derivatives **6c-g.**

To a solution of **5** in methanol was added hydroxylamine hydrochloride and the resulting mixture was stirred at room temperature for 1-168 hour. The reaction mixture was poured into

ice water and the resulting mixture was basified (pH 9) with saturated aqueous sodium hydrogen carbonate. The precipitated solid was filtered, washed with water and recrystallized from the appropriate solvent to give the corresponding **6**.

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

A solution of **5c** (89 mg, 0.30 mmol) and hydroxylamine hydrochloride (42 mg, 0.60 mmol) in methanol (5 ml) was stirred at room temperature for 1 hour. Recrystallization from *n*-hexane-ethyl acetate gave **6c** (60 mg, 67%) as colorless prisms, mp 132-133 °C; ir: 3200 (OH and NH); FAB-ms: *m/z* 301 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 1.37 (3H, t, *J* = 8, CH_2*Me*), 2.74 (2H, t, *J* = 6, OCH_2CH_2), 2.84 (2H, q, *J* = 8, CH_2Me), 4.56 (2H, t, *J* = 6, OCH_2CH_2), 7.06 (1H, d, *J* = 10, changed to singlet after addition of deuterium oxide, NCH=NO), 7.21-7.54 (5H, m, changed to 4H multiplet after addition of deuterium oxide, OH and H6,7,8,9), 11.87 (1H, d, *J* = 10, deuterium oxide exchangeable, NH).

Anal. Calcd for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found: C, 59.98; H, 5.55; N, 18.65.

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

A solution of **5d** (0.10 g, 0.30 mmol) and hydroxylamine hydrochloride (0.38 g, 5.5 mmol) in methanol (5 ml) was stirred at room temperature for 168 hours. Recrystallization from methanol gave **6d** (76 mg, 73%) as colorless needles, mp 125-127 °C; ir: 3210 (OH and NH); FAB-ms: *m/z* 349 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.75 (2H, t, *J* = 6, OCH_2CH_2), 4.58 (2H, t, *J* = 6, OCH_2CH_2), 7.12 (1H, d, *J* = 10, changed to singlet after addition of deuterium oxide, NCH=NO), 7.19-7.51 (8H, m, changed to 7H multiplet after addition of deuterium oxide, OH, H6,7,8,9 and phenyl-H3,4,5), 8.23 (2H, dd, *J* = 8 and 2, phenyl-H2,6), 11.72 (1H, d, *J* = 10, deuterium oxide exchangeable, NH).

Anal. Calcd for $C_{19}H_{16}N_4O_3 \cdot 1/2H_2O$: C, 63.86; H, 4.80; N, 15.68. Found: C, 64.19; H, 5.00; N, 15.39.

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

A solution of **5e** (0.11 g, 0.31 mmol) and hydroxylamine hydrochloride (0.21 g, 3.0 mmol) in methanol (5 ml) was stirred at room temperature for 48 hours. Recrystallization from methanol gave **6e** (87 mg, 77%) as colorless needles, mp 174-176 °C; ir: 3210 (OH and NH); FAB-ms: *m/z* 363 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.42 (3H, s, Me), 2.75 (2H, t, *J* = 6, OCH_2CH_2), 4.58 (2H, t, *J* = 6, OCH_2CH_2), 7.14 (1H, d, *J* = 10, changed to singlet after addition of deuterium oxide, NCH=NO), 7.21-7.38 (7H, m, changed to 6H multiplet after addition of deuterium oxide, OH, H6,7,8,9 and phenyl-H4,5), 8.06 (2H, m, phenyl-H2,6), 11.75 (1H, d, *J* = 10, deuterium oxide exchangeable, NH).

Anal. Calcd for $C_{20}H_{18}N_4O_3 \cdot CH_3OH$: C, 63.95; H, 5.62; N, 14.20. Found: C, 63.57; H, 5.61; N, 14.34.

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

A solution of **5f** (0.11 g, 0.29 mmol) and hydroxylamine hydrochloride (0.13 g, 1.9 mmol) in methanol (5 ml) was stirred at room temperature for 9 hours. Recrystallization from methanol gave **6f** (92 mg, 83%) as white powder, mp 184-187 °C; ir: 3150 (OH and NH); FAB-ms: *m/z* 383 (MH^+), 385 ($MH^+ + 2$); ^{1}H-nmr (deuteriochloroform): δ 2.74 (2H, t, *J* = 6, OCH_2CH_2), 4.57 (2H, t, *J* = 6, OCH_2CH_2), 7.14 (1H, d, *J* = 10, changed to singlet after addition of deuterium oxide, NCH=NO), 7.22-7.34 (3H, m, changed to 2H multiplet after addition of deuterium oxide, OH and phenyl-H3,5), 7.48 (4H, m, H6,7,8,9), 8.16 (2H, m, phenyl-H2, 6), 11.63 (1H, d, *J* = 10, deuterium oxide exchangeable, NH).

Anal. Calcd for $C_{19}H_{15}ClN_4O_3$: C, 59.62; H, 3.95; N, 14.64. Found: C, 59.48; H, 4.10; N, 14.62.

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

A solution of **5g** (0.11 g, 0.30 mmol) and hydroxylamine hydrochloride (0.13 g, 1.9 mmol) in methanol (5 ml) was stirred at room temperature for 52 hours. Recrystallization from methanol gave **6g** (56 mg, 50%) as colorless needles, mp 199-202 °C; ir: 3340, 3060 (OH and NH); FAB-ms: *m/z* 367 (MH^+); ^{1}H-nmr (deuteriochloroform): δ 2.74 (2H, t, *J* = 6, OCH_2CH_2), 4.57 (2H, t, *J* = 6, OCH_2CH_2), 7.13 (1H, d, *J* = 10, changed to singlet after addition of deuterium oxide, NCH=NO), 7.18-7.34 (5H, m, changed to 4H multiplet after addition of deuterium oxide, OH and H6,7,8,9), 7.50 (2H, m, phenyl-H3,5), 8.22 (2H, m, phenyl-H2,6), 11.64 (1H, d, *J* = 10, deuterium oxide exchangeable, NH).

Anal. Calcd for $C_{19}H_{15}FN_4O_3$: C, 62.29; H, 4.13; N, 15.29. Found: C, 62.10; H, 4.20; N, 15.30.

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REFERENCES AND NOTES

[1] Part 55: Y-X. Zhang, K. Sasaki and T. Hirota, *J. Heterocyclic Chem.*, **36**, 787 (1999).

[2] T. Hirota, K. Sasaki, H. Yamamoto, K. Mori and S. Kashino, *Acta Cryst*., C**50**, 807 (1994).

[3a] K. Sasaki, Y-X. Zhang, H. Yamamoto, S. Kashino and T. Hirota, *J. Chem. Res (S)*, 92 (1999); [b] *idem*, *J. Chem. Res (M)*, 548 (1999).

[4] T. Nagamatsu, S. Tsurubayashi, K. Sasaki and T. Hirota, *Synthesis*, 303 (1991).

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