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Convenient synthesis of novel tetrahydro-1,5-benzodiazepine amide oximes

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1,5- Benzodiazepine thiolactams and more reactive thioethers were applied for the preparation of a series of new 5-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one oximes **3 a–c** and 4-(hydroxyimino)-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carboxamides **3 d–f**. Such 1,5-benzodiazepine derivatives are valuable synthons for the synthesis of fused ring compounds.

Key words: 1,5-benzodiazepinethiones, thioethers, amide oximes, synthesis

INTRODUCTION

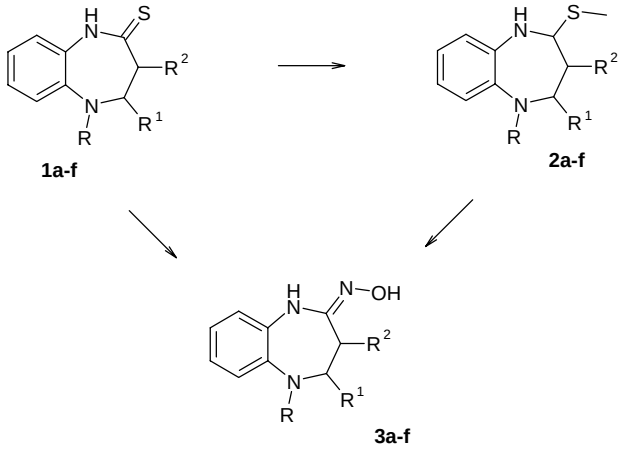
The pharmacological importance of substituted 1,4- and 1,5-benzodiazepines has been well established and some derivatives are known as anxiolytic, anticonvulsant, antihypnotic agents [1–3]. In recent years, much effort has been taken in the benzodiazepine area to develop new members of this family. Among the new compounds, antagonists of the polypeptidic cholecystokinine receptors have been established [4, 5]. The synthesis of benzodiazepine derivatives with heterocyclic rings annealed to the "a", "c", "d" sides of heptatomic system has also attracted interest of several research groups. Such derivatives are known to possess antiviral (HIV-1) activity [6, 7].

In previous papers [8, 9] we have reported a cyclofunctionalization strategy of 1,5-benzodiazepine system, which exploited the reactivity of the thioxo group of the corresponding derivatives. As a continuation of our investigations on tricyclic benzodiazepines, we have extended this strategy to develop a synthetic pathway towards 1,5-benzodiazepines including 1,2,4-oxadiazole nucleus fused to the "a" edge of the heptatomic ring.

RESULTS AND DISCUSSION

We present in this paper the preparation of new hydroxyimino-1,5-benzodiazepines **3 a–f**. Thiolactams **1 a–f** or more reactive thioethers **2 a–f** were used (Scheme) for the synthesis of the desired compounds to supplement the lack of reactivity of the corresponding lactams [10] which show low reactivity towards some nucleophiles. Thiolactams **1 a–c** and **1 d–f** as well as thioethers **2 a–c** were previously described by us [11, 8, 12]. The phase-transfer catalyzed alkylation of thiones **1 d–f** with an excess of iodomethane in 40% aqueous potassium hydroxide/benzene solution at room temperature led in good yields to the thioethers **2 d–f**.

Treatment of **2 a–f** with three equivalents of hydroxylamine hydrochloride gave the hydroxyimino-1,5-benzodiazepines **3 a–f**. This reaction was accomplished in ethanol in the presence of triethylamine at room temperature for 6 hours. Furthermore, when thiones **1 a–f** were treated with hydroxylamine hydrochloride oximes **3 a–f** were also obtained. This reaction was conducted in boiling dry ethanol in the presence of sodium acetate [13]. The results are presented in Tables 1, 2. The structure of the newly synthesized compounds **2 d–f** and **3 a–f** was confirmed by IR and NMR spectra. The IR spectra exhibited typical NH and OH stretching bands between 3430–3100 cm^{-1} (**3 a–f**) as well as stretching band for C=N at 1658–1656 cm^{-1} (**3 a–c)** and for C = O at 1670–1649 cm^{-1} (**3 d–f**). The ^1H NMR spectra showed sharp singlets of OH and broad singlets of NH groups at 9.31–9.80 and 7.94–8.26 ppm, respectively. The long range coupling between NH proton and one proton of the diazepine heterocycle methylene group ($J_{H\text{-}N\text{-}C\text{-}C\text{-}H}$ ca. 0,8 Hz) was observed in some spectra (**3 c, f**). The observed broadening of signals in ^1H and/or ^{13}C NMR spectra for compounds **2d, 2e, 3d** is caused by the coalescence effects and evidences that the inversion of heterocycle of those compounds is not restricted.



	R	R^1	R^2
1a, 2a, 3a	Me	H	H
1b, 2b, 3b	Me	H	Me
1c, 2c, 3c	Me	Me	H
1d, 2d, 3d	CONHPh	H	H
1e, 2e, 3e	CONHPh	H	Me
1f, 2f, 3f	CONHPh	Me	H

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were taken on a PERKIN Elmer Spectrum GX FT-IR spectrometer in KBr tablets. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian Unity Inova 300 spectrometer in deuteriochloroform (compounds **2 d–f** and **3 a–c**) and DMSO-d_6 (**3 d–f**) with TMS as an internal standard. The CH_3, CH_2, CH and C_{quart} groups in ^{13}C NMR were differentiated by means of the APT or DEPT methods. The reactions were controlled by TLC method and performed on Silufol UV_{254} silica gel plates in the system: benzene-methanol (v/v, 6:1). Thiolactams **1 a–f** and thioethers **2 a–c** were previously described by us [11, 8, 12].

4-(methylsulfanyl)-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carboxamide (2 d–f). *General procedure*. To a solution of thiolactam (5.0 mmol) in 50 ml of benzene, 1.48 g (6.5 mmol) of benzyltriethylammonium chloride, 10 ml 40% aqueous potassium hydroxide and 1.25 ml (20 mmol) of iodomethane were added. The obtained suspension was stirred at room temperature for 1.5–2 h until TLC analysis indicated the completion of the reaction. The mixture was filtered, the filtrate was diluted with chloroform (100 ml) and water (100 ml). The organic layer was separated and the aqueous phase extracted with chloroform. The combined organic phases were washed with water (until neutral), dried over $MgSO_4$, and evaporated to dryness in vacuum. The residue was recrystallized from an appropriate solvent.

5-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one oximes (3 a–c) and 4-(hydroxyimino)-*N*-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carboxamides (3 d–f) – general procedure.

Method A. Thioethers **1 a–f** (2.0 mmol) were treated with 3 equivalents of hydroxylamine hydrochloride (4.16 g, 6.0 mmol) in the presence of triethylamine (1.1 ml, 8.0 mmol) in 50 ml of ethanol without heating for 6 h under stirring. The reaction mixture was then concentrated under reduced pressure to 20 ml of volume. After cooling to room temperature the precipitate obtained was collected and recrystallized from an appropriate solvent.

Method B. The mixture of thiolactam **1 a–f** (2.0 mmol), hydroxylamine hydrochloride (2.08 g, 3.0 mmol) and sodium acetate (2.52 g, 3.0 mmol) in ethanol (70 ml) was refluxed for 1–3 h. After cooling the precipitate of NaCl was filtered off. The solvent was evaporated under vacuum to give the solid residue which was recrystallized from an appropriate solvent.

Table 1. **Experimental data on compounds 2 d–f and 3 a–f**

Compd.	Molecular weigh	Yield, %	Crystal. solvent	M.p., °C	Molecular formula
2d	311.41	67	ethanol	144–145	$C_{17}H_{17}N_3OS$
2e	325.44	75	ethanol	136–137	$C_{18}H_{19}N_3OS$
2f	325.44	74	ethanol	122–124	$C_{18}H_{19}N_3OS$
3a	191.23	(A) 75 (B) 79	ether	96–100	$C_{10}H_{13}N_3O$
3b	205.26	(A) 95 (B) 74	ether	136–139	$C_{11}H_{15}N_3O$
3c	205.26	(A) 81 (B) 68	ether	82–83	$C_{11}H_{15}N_3O$
3d	296.33	(A) 61 (B) 73	1-propanol	175–176	$C_{16}H_{16}N_4O_2$
3e	310.36	(A) 71 (B) 82	methanol	180–183	$C_{17}H_{18}N_4O_2$
3f	310.36	(A) 71 (B) 79	1-propanol	190–191	$C_{17}H_{18}N_4O_2$

Table 2. **Spectral data on compounds 2 d–f and 3 a–f**

Compd.	^{1}H NMR δ (ppm), J (Hz)	^{13}C NMR δ (ppm)	IR ν (cm^{-1})
2d	2.48 (3H, s, CH_3), 2.6 (2H, br.s, CH_2), 3.4–5.3 (2H, br. s. CH_2N), 6.19 (1H, br.s., NH), 6.97–7.46 (9H, m, ArH)	13.23 (CH_3), 34.39 (C-3), 52.80 (C-2), 119.02 (C-2', 6'), 122.93, 125.47, 126.09, 128.77 (C-3', 5', CH), 129.14, 130.00 (C), 138.55 (C-1'), 147.54 (C), 154.08 (CO), 173.94 (C-4)	3423 3313 1660
2e	1.21 (3H, d, J = 6.9 Hz, CH_3), 2.41 (3H, s, CH_3), 3.01 (1H, m, CH), 3.79 (1H, br. s, CH_2), 4.51 (1H, br. s, CH_2), 6.19 (1H, br. s, NH), 6.94–7.42 (9H, m, ArH)	12.86 (SCH_3), 13.44 (br. s, CH_3), 38.29 (br. s, C-3), 59.83 (br. s, C-2), 119.01 (C-2', 6'), 122.84, 125.18, 125.63 (br. s), 128.26 (br. s), 128.72 (C-3', 5'), 129.09, 129.65 (br. s, C), 138.55 (C-1'), 147.49 (br. s, C), 153.90 (CO), 173.42 (C-4)	4323 3301 1660
2f	1.28 (3H, d, J = 6.3 Hz, CH_3), 2.36–2.42 (2H, m, CH_2), 2.47 (3H, s, CH_3), 5.29 (1H, m, CH), 6.03 (1H, br. s, NH), 6.96–7.48 (9H, m, ArH)	13.25 (SCH_3), 19.53 (CH_3), 41.42 (C-3), 59.81 (C-2), 119.05 (C-2', 6'), 122.83, 125.34, 125.72, 127.95 (C), 128.75 (C-3', 5'), 129.45, 130.21, 138.65 (C-1'), 148.36 (C), 153.47 (CO), 173.70 (C-4)	3424 3307 1680
3a[a]	2.45 (2H, t, J = 6.5 Hz, CH_2, 2.84 (3H, s, CH_3), 3.38 (2H, t, J = 6.6 Hz, CH_2N), 6.88–7.13 (4H, m, ArH), 7.96 (1H, br. s, NH), 9.34 (1H, s, OH)	27.60 (C-3), 41.46 (NCH_3), 57.75 (C-4), 119.50, 121.15, 122.29, 124.74, 132.98 (C-9a), 141.80 (C-5a), 152.21 (C-2)	3468–3158 1658
3b[a]	1.14 (3H, d, J = 6.8 Hz, CH_3), 2.67 (1H, m, CH), 2.83 (3H, s, CH_3), 3.11–3.31 (2H, m, CH_2), 6.89–7.11 (4H, m, ArH), 7.94 (1H, br. s, NH), 9.56 (1H, s, OH)	13.19 (CH_3), 32.29 (C-3), 41.33 (NCH_3), 65.87 (C-4), 118.94, 121.20, 122.25, 124.67, 132.80 (C-9a), 142.33 (C-5a), 154.11 (C-2)	3325–3150 1656
3c[a]	1.16 (3H, d, J = 6.1 Hz, CH_3), 2.11 (1H, dd, J = 9.0, 14.3 Hz, CH_2), 2.51 (1H, ddd, J = 0.8, 5.6, 14.3 Hz, CH_2), 2.84 (3H, s, CH_3), 3.65 (1H, m, CH), 6.88–7.12 (4H, m, ArH), 7.98 (1H, br. s, NH), 9.31 (1H, s, OH)	16.31 (CH_3), 35.32 (C-4), 38.96 (NCH_3), 61.00 (C-4), 120.83, 121.63, 122.53, 124.30, 133.91 (C-9a), 140.62 (C-5a), 151.60 (C-2)	3370–3150 1658
3d	2.35 (2H, br. t, CH_2), 3.90 (2H, br. s, CH_2N), 6.90–7.40 (9H, m, ArH), 7.74 (1H, br. s, NHCO), 8.28 (1H, br. s, NH), 9.64 (1H, s, OH)	27.19 (C-3), 48.16 (C-2), 119.80 (C-2', 6'), 122.09, 122.29, 123.51, 128.11, 128.25 (C-3', 5'), 129.35, 130.89 (C), 138.58 (C), 139.79 (C-1'), 148.79 (C-4), 154.63 (CO)	3418–3240 1670
3e	1.05 (3H, d, J = 6.7 Hz, CH_3), 2.52 (1H, m, CH), 3.62 (1H, dd, J = 5.9, 11.9 Hz, CH_2), 3.87 (1H, dd, J = 11.9, 12.0 Hz, CH_2), 6.90–7.37 (9H, m, ArH), 7.71 (1H, br. s, NHCO), 8.21 (1H, br. s, NH), 9.80 (1H, s, OH)	13.67 (CH_3), 32.02 (C-3), 55.42 (C-2), 119.74 (C-2', 6'), 122.04, 122.22, 123.35, 128.07, 128.22 (C-3', 5'), 128.89, 131.22 (C), 138.30 (C), 139.75 (C-1'), 150.72 (C-4), 154.39 (CO)	3425–3263 1649
3f	1.13 (3H, d, J = 6.3 Hz, CH_3), 1.90 (1H, dd, J = 12.2, 14.1 Hz, CH_2), 2.42 (1H, ddd, J = 0.8, 5.6, 14.0 Hz, CH_2), 4.69 (1H, m, CH), 6.90–7.40 (10H, m, ArH, NHCO), 8.26 (1H, br.s, NH), 9.59 (1H, s, OH)	19.09 (CH_3), 34.72 (C-3), 53.23 (C-4), 119.79 (C-2', 6'), 122.05, 122.27, 123.38, 128.18 (C-3', 5', CH), 128.69, 130.70 (C), 139.29 (C), 139.61 (C-1'), 148.55 (C-4), 153.67 (CO)	3410–3271 1650

[a] Chemical shifts for NH and OH groups are given in DMSO-d_6.

CONCLUSIONS

A series of new hydroxyimino-1,5-benzodiazepines were synthesized by the reaction of the 2,3,4,5-tetrahydro-1,5-benzodiazepine-2(1H)-thiones and of the corresponding methylsulfanyl-1,5-benzodiazepines with hydroxylamine hydrochloride. Both elaborated methods are convenient for the preparation of target compounds in good yields.

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References

1.A. D. Fraser, *Ther. Drug Monit*., **20**, 481 (1998).
2.M. T. Herrero, I. Tellitu, E. Dominguez, I. Moreno and R. SanMartin, *Tetrahedron Lett.* **43**, 8273 (2002).
3.A. Chimirri, R. Gitto, S. Grasso, A.-M. Monforte, G. Romeo and M. Zappala, *Heterocycles*, **36**(3), 601 (1993).
4.M. G. Bock, R. M. DiPadro, B. E. Evans, K. E. Rittle, W. L. Witter, D. E. Veber, P. S. Anderson and R. M. Freidinger, *J. Med. Chem*., **32**, 13 (1989).
5.V. K. Agrawal, R. Sharma and P. V. Khadikar, *Bioorgan. Med. Chem.*, **10**, 3571 (2002).
6.R. Pauwels, K. Andries, L. Desmyter, D. Schols, M. J. Kukla, H. J. Breslin, A. Raeymaeckers, J. Van Gelder, R. Woestenborghs, J. Heikants, K. Schellekens, M. A. C. Jannsen, E. D. Clerg and P. A. Janssen, *Nature*, **343**, 470 (1990).
7M. Di Braccio, G. Grossi, G. Roma, L. Vargiu, M. Mura and M. E. Marongu, *Eur. J. Med. Chem.*, **36**, 935 (2001).
8.R. Jančienė, A. Vektarienė, Z. Stumbrevičiūtė, L. Kosychova, A. Klimavičius and B. Puodžiūnaitė, *Heteroatom Chem.*, **15**(5), 363 (2004).
9.L. Kosychova, Z. Stumbrevičiūtė, L. Plečkaitienė, R. Jančienė and B. D. Puodžiūnaitė, *Khim. Geterotsikl. Soedin.,* (6), 943 (2004).
10.B. D. Puodžiūnaitė, L. Vertelyte, R. Jančienė and Z. Stumbrevičiūtė, *OPPI*, **29**(6), 689 (1997).
11.B. Puodžiūnaitė, L. Kosychova, R. Jančienė and Z. Stumbrevičiūtė, *Monatsch. Chem.*, **128**, 1275 (1997).
12.B. Puodžiūnaitė, L. Kosychova, R. Jančienė and Z. Stumbrevičiūtė, *Khim. Geterotsikl. Soedin.,* (**3**), 368 (1998).
13.V. Ambrogi, G. Grandolini, L. Perioli, M. Ricci, C. Rossi and L. Tuttobello, *Eur. J. Med. Chem.*, **25**, 403 (1990).

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PATOGI NAUJŲ TETRAHIDRO-1,5-BENZDIAZEPINŲ OKSIMŲ SINTEZĖ

S a n t r a u k a

Hidroksilaminui reaguojant su tiolaktamais arba reaktingesniais tioeteriais gauti nauji 5-metil-1,3,4,5-tetrahidro-2*H*-1,5-benzdiazepin-2-onų oksimai ir 4-(hidroksiimino)-*N*-fenil-2,3,4,5-tetrahidro-1*H*-1,5-benzdiazepin-1-karboksiamidai. Šie dariniai gali būti naudojami kondensuotųjų 1,5-benzdiazepinų sintezei.