5*H*-[1,2,4]OXADIAZOLO[5,4-*d*][1,5]BENZOTHIAZEPINES: SYNTHESIS AND STEREOCHEMISTRY#

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Abstract - The functionalization of the thiazepine system by 1,3-dipolar cycloaddition of benzonitriloxide to the C=N double bond of 1,5-benzothiazepine derivatives, is described. The configurational and conformational properties of the 3*a*,4-dihydro-1-phenyl-5*H*-[1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepines have been determined by nmr spectroscopy assisted by NOE measurements.

Several 1,5-benzothiazepine derivatives have acquired pharmacological importance: Diltiazem and Thiazesim are known to possess antianginal and antidepressive activity,[1,2] respectively, and various annelated 1,5-benzothiazepine derivatives, tested as potential CNS agents, exhibit activity comparable to that of Diazepam[3] and showed affinity for the benzodiazepine receptors.[4]

In previous papers[5-8] we reported a cyclofunctionalization strategy of 1,4- and 1,5-benzodiazepine systems which exploited the reactivity of the nitrogen-carbon double bond of the heptatomic nucleus. In the course of our investigations concerning the synthesis of pharmacologically active N,S-containing heterocycles, we intend now to extend our research to annelated 1,5-benzothiazepines.

Our interest is related to the investigation of the stereochemical features of the thiazepine ring and of the influence of the heterocyclic nucleus fusion on the conformational mobility, following the hypothesis that the conformational preferences of the heptatomic ring control and define the possible interactions with the suitable biological receptor. The conformational preferences of the seven-membered ring could be correlated with biological activity and the fusion of a heterocyclic nucleus to the thiazepine system could induce an increase of the ring inversion barrier and consequently modify the activity profile.

In this aim, we report here the cyclofunctionalization of 1,5-benzothiazepine system by 1,3-dipolar cycloaddition and a detailed analysis of the stereochemical and conformational properties of oxadiazolobenzothiazepines.

The reaction between 1,5-benzothiazepine derivatives (**1a-d**) and benzonitriloxide, generated *in situ* from

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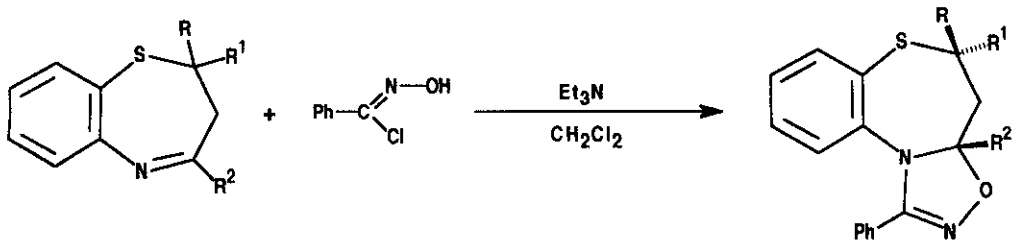
benzohydroximinoyl chloride (**2**) and triethylamine leads to 3*a*,4-dihydro-1-phenyl-5*H*-[1,2,4]oxadiazolo[5,4-*d*]-[1,5]benzothiazepines (**3a-d**) (Scheme 1) in which an oxadiazole ring is fused at the "d" edge of the heptatomic nucleus.

The investigated oxadiazolobenzothiazepines are listed in Scheme 1. In order to have a more comprehensive picture of the stereochemical characteristics of this class of compounds, we have included compound(**3a**) in this paper, the synthesis of which was reported earlier.[9]

In the compounds examined, the cycloaddition reaction has been found to be regiospecific and affords a single regioisomer, according to the FMO approach.

Scheme 1



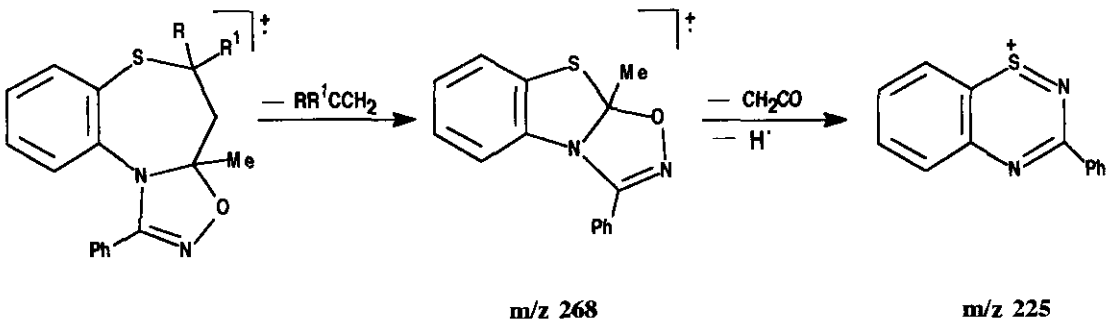
1a-d **2** **3a-d**

Compd	R	R^1	R^2	Yield %
3a	CH_3	CH_3	CH_3	52
3b	H	CH_3	CH_3	66
3c	H	C_6H_5	CH_3	70
3d	H	C_6H_5	C_6H_5	56

The cycloadducts (**3a-d**) have shown analytical and physicochemical data consistent with the assigned structure; the stereochemistry of the synthesized compounds was unambiguously assigned by NOE measurements in combination with analysis of proton coupling constants.

The mass spectra of the 3*a*-methyl-substituted compounds (**3a-c**) show correct molecular ions and the formation of diagnostic fragmentations. In particular, an intramolecular rearrangement from molecular ions, by loss of RR^1CCH_2, leads to the formation of oxadiazolobenzothiazole ion radical (m/z 268) which, by cleavage process and by loss of CH_2CO and then of H·, affords a benzothiadiazine ion (m/z 225) (Scheme 2). A different behaviour was observed for 3*a*-phenyl-substituted compound (**3d**): in the mass spectra the molecular ion is absent and the base peak corresponds to a diphenyloxethane ion (m/z 207).

Scheme 2



m/z 268 **m/z 225**

The ^{1}H-nmr chemical shifts and coupling constants observed for compounds (**3a-d**) in $CDCl_3$ solution are presented in Table 1. For compound(**3a**)the methylene protons at C-4 resonate as AB spin system, which in compounds (**3b-d**) is further splitted by the coupling with the proton at C-5, whereas the same protons in benzothiazepine precursors (**1a-d**) appear as an A_2 or AB system with a smaller $\Delta\nu_{AB}/J_{AB}$.[10,11]

Table 1. ^{1}H-Nmr data of 3*a*,4-dihydro-1-phenyl-5*H*-[1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepines (**3a-d**).

Compd	δ ($CDCl_3$)
3a	1.30 (s, 3H, 3a-CH_3), 1.43-1.52 (2s, 6H, 5$(CH_3)_2$), 2.17 and 2.63 (ABq, J=-14.7, 2H, CH_2), 6.70-7.57 (m, 9H, ArH).
3b	1.32 (s, 3H, CH_3), 1.44 (s, J=6.92, 3H, 5-CH_3), 2.34 (dd, J=-13.5, J=2.14, 1H, 4-Heq), 2.52 (dd, J=-13.5, J=12.4, 1H, 4-Hax), 3.00 (m, 1H, 5-CH), 6.68 (m, 9H, ArH).
3c	1.42 (s, 3H, 5-CH_3), 2.55 (dd, J=-13.15, J=1.9, 1H, 4-Heq), 3.15 (dd, J=-13.15, J=12.7, 1H, 4-Hax), 4.02 (dd, J=12.7, J=1.9, 1H, 5-CH), 6.74-7.66 (m, 14H, ArH).
3d	2.65 (dd, J=-14.62, J=12.36, 1H, 4-Hax), 2.95 (dd, J=-14.62, J=4.67, 1H, 4-Heq), 3.50 (dd, J=12.36, J=4.67, 1H, 5-CH), 6.75-8.13 (m, 21H, ArH).

These data are indicative of a reduced mobility, at room temperature and in solution, of the heptatomic ring which adopts in compounds(**3a-d**)a twisted-boat conformation to avoid steric hindrance between the exocyclic substituents. These features were also confirmed by NOE measurements and the $J_{4,5}$ coupling constants values which allowed to establish that the 5-substituent occupies a quasi-equatorial position in the predominant conformation and the substituent at C-3*a* occupies a nearly axial-position. In fact, irradiation of H-5 in compounds(**3b-d**)resulted in an enhancement of the resonance of 4-Heq while no NOE was detectable at 4-Hax; in compound (**3b**) and **c** a NOE was also observed for methyl group at C-3*a* and in **3d** in the aromatic region. These results indicate that H-5 is axially situated and that is in a syn relationship with the substituent at C-3*a*. In addition, for compound(**3d**)the signal of the H-5 is shifted to higher fields with respect to the same resonance in compounds(**3a-c**),by the shielding effect of the phenyl group in 3*a* thus confirming the above observations.

^{13}C-nmr shifts and assignments for all compounds are summarized in Table 2. The spectral data show that the presence of C3*a*-phenyl group influences also the resonance at C-4, which is shifted by 10-14 ppm highfield for compound (**3d**); in addition the signal of C-5 resonates in a range of 35.05-54.12 ppm depending on the substitution.

Table 2. ^{13}C-Nmr data of 3*a*,4-dihydro-1-phenyl-5*H*-[1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepines (**3a-d**).

Compd	δ ($CDCl_3$)
3a	25.71 (3*a*-CH_3), 30.55 and 31.90 (5(CH_3)$_2$), 54.12 (C-5), 54.23 (C-4), 99.44 (C-3*a*), 125.65 (C-6*a*), 127.32, 128.07, 128.28, 128.81, 130.04, 135.27, (aromatic CH), 132.12 (C-1'), 142.33 (C-10*a*), 154.12 (C-1).
3b	22.77 (3*a*-CH_3), 21.39 (5-CH_3), 35.05 (C-5), 50.93 (C-4), 99.39(C-3*a*), 125.30 (C-6*a*), 126.78, 128.23, 128.37, 128.79, 130.01, 130.14, (aromatic CH), 132.74 (C-1'), 140.47 (C-10*a*), 153.99 (C-1).
3c	22.65 (3*a*-CH_3), 44.59 (C-5), 49.15 (C-4), 99.19 (C-3*a*), 125.44 (C-6*a*),126.93, 127.44, 128.02, 128.31, 128.42, 128.66, 128.88, 128.99, 130.22, 133.99 (aromatic CH), 133.24 (C-1'), 139.47 (C-1"), 140.35 (C-10*a*), 154.20 (C-1).
3d	39.30 (C-4), 45.87 (C-5), 100.14 (C-3*a*), 122.50 (C-6*a*), 123.44, 125.13, 126.36, 127.25, 127.41, 127,64, 127.88, 128.64, 128.78, 128.90, 129.96, 130.87, 137.20 (aromatic CH), 131.75 (C-1'), 140.39 (C-10*a*), 143.87 and 145.12 (C-1" and C-1"'), 157.49 (C-1).

In conclusion, the stereochemistry of oxadiazolobenzothiazepine has been assigned. The annelation of the heterocyclic nucleus to the "d" edge of the benzothiazepine system has been found to exert a certain influence in the conformational properties of the heptatomic ring and to increase the ring reversal barrier which is not affected by the different substituents at C-3*a* and C-5.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses (C, H, N) were carried out on a C. Erba Model 1106 Elemental Analyzer. Merck silica gel 60 F_{254} plates were used for tlc; column chromatography was performed using Merck silica gel 60, 70-230 mesh. Ir spectra were determined in nujol on a Perkin Elmer mod. 257 spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were measured with a Varian-Gemini (300 MHz) spectrometer in $CDCl_3$ (internal lock) with TMS as the internal standard: chemical shifts are expressed in δ (ppm) and coupling constants (J) in Hz. Mass spectra were recorded on a Hewlett Packard Model 5995 GC/MS. 1,5-Benzothiazepines (**1a-d**) were obtained according to the literature methods.[10,12]

General procedure for the synthesis of 3*a*,4-dihydro-1-phenyl-5*H*-[1,2,4]oxadiazolo[5,4-*d*]-[1,5]benzothiazepines (3a-d)

To a solution of the appropriate 1,5-benzothiazepine derivative (1 mmol) in 30 ml of methylene chloride was

added under stirring the benzohydroximinoyl chloride (230 mg, 1.5 mmol) and a solution of triethylamine (150 mg, 1.5 mmol) in the same solvent (5 ml) was added dropwise. The reaction mixture was kept under stirring at room temperature for 24 h. After completion of the reaction, the solvent was evaporated off at reduced pressure, and ether was added to the residue and the triethylamine hydrochloride was filtered. After removal of the solvent, the residue was purified by column chromatography with ether/light petroleum 20:80 as eluant to afford compounds (**3a**, **3b** and **3d**) or treatment with ether to give compound (**3c**). All compounds were recrystallized from ethanol.

3*a*,4-Dihydro-1-phenyl-3*a*,5,5-trimethyl-5*H*-[1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepine (3a)
mp 106-108°C (yield 52%). Anal. Calcd for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.35; H, 6.28; N, 8.43. Ms m/z (%): 324 (M^+, 12), 268 (54), 226 (100), 225 (68), 149 (14), 123 (36), 96 (25), 83 (15).

3*a*,4-Dihydro-3*a*,5-dimethyl-1-phenyl-5*H*-[1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepine (3b)
mp 138-140°C (yield 66%). Anal. Calcd for $C_{18}H_{18}N_2OS$: C, 69.64; H, 5.84; N, 9.02. Found: C, 69.43; H, 5.97; N, 8.95. Ms m/z (%): 310 (M^+, 17), 268 (65), 227 (26), 226 (76), 225 (100), 149 (18), 123 (13), 96 (15), 69 (16).

3*a*,4-Dihydro-3*a*-methyl-1,5-diphenyl-5*H*-[1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepine (3c)
mp 193-195°C (yield 70%). Anal. Calcd for $C_{23}H_{20}N_2OS$: C, 74.15; H, 5.41; N, 7.52. Found: C, 73.92; H, 5.55; N, 7.68. Ms m/z (%): 372 (M^+, 12), 269 (19), 268 (100), 227 (18), 226 (68), 225 (82), 149 (13), 131 (12), 103 (20), 96 (6), 85 (15), 83 (18), 77 (11).

3*a*,4-Dihydro-1,3*a*,5-triphenyl-5*H*-[1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepine (3d)
mp 194-196°C (yield 56%). Anal. Calcd for $C_{28}H_{22}N_2OS$: C, 77.39; H, 5.10; N, 6.45. Found: C, 77.61; H, 5.02; N, 6.28. Ms m/z (%): 434 (M^+, 0), 207 (100), 179 (19), 131 (21), 130 (10), 105 (16), 103 (22), 77 (52).

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