Synthesis and Stereochemistry of Novel [1,2,4]Oxadiazolo[4,5-*a*][1,5]benzodiazepine Derivatives

Alba Chimirri, Silvana Grasso, Rosaria Ottanà, Giovanni Romeo* and Maria Zappalà

Dipartimento Farmaco-Chimico, Università, SS. Annunziata,
98168 Messina, Italy

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An one-pot synthetic approach to the novel 3a,4,5,6-tetrahydro[1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepine system, by 1,3-dipolar cycloaddition of benzonitriloxides to 1,5-benzodiazepine derivatives, is described. The structure and stereochemistry of the obtained adducts have been assigned by means of spectroscopic measurements.

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In recent years a great effort has been made in the benzodiazepine area in order to develop new members of this family. Among the newer compounds are those containing different heterocyclic rings annelated to the basic 1,4- and 1,5-benzodiazepine systems, such as imidazo- and triazolobenzodiazepines; it is known, in fact, that the pharmacological activity appears to be enhanced when a further heterocyclic ring is linked to the heptatomic nucleus [1,2].

In previous papers [3-6] we reported a cyclofunctionalization strategy of 1,4- and 1,5-benzodiazepine systems, which exploited the reactivity of the C=N moiety of the heptatomic nucleus. The reaction with mercaptoacetic acid, performed with 1,4-benzodiazepine derivatives, gave rise to tetrahydrothiazolo[4,3-*d*][1,4]benzodiazepines [5], while the analogous reaction proceeding from 1,5-benzodiazepines revealed [6] unsuccessful, probably because of the conjugation of the nitrogen lone pair with the fused π-electron system, which reduces the reactivity of the group.

The behaviour as dipolarophile of the C=N moiety of 1,4- and 1,5-benzodiazepines in 1,3-dipolar cycloaddition with nitrilimines has been also tested and the synthesis of the new tetrahydro-1*H*-*s*-triazolo[4,3-*d*][1,4]benzodiazepine [3] and tetrahydro-3*H*-*s*-triazolo[4,3-*a*][1,5]benzodiazepine [7] systems has been performed in good yields as one-step process.

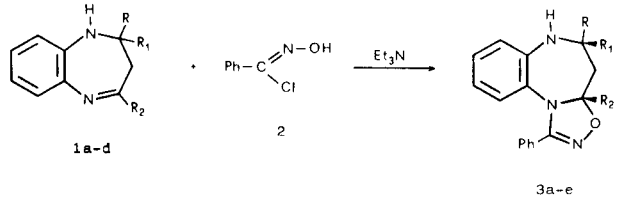
In continuation of our investigations on tricyclic benzodiazepines [3-6], we have extended the 1,3-dipolar cycloaddition strategy to develop a synthetic pathway towards 1,5-benzodiazepines including a 1,2,4-oxadiazole nucleus fused to the "a" edge of the heptatomic ring.

Our interest is related to the investigation of the influence of the added heterocyclic nucleus on the conformational preferences of the benzodiazepine heptatomic ring, according to the hypothesis of a relationship between its stereochemistry and the biological activity.

In spite of the weak character as dipolarophile of the C=N bond in the 1,5-benzodiazepine derivatives, the 1,3-dipolar cycloaddition of benzonitriloxides with a series of 1,5-benzodiazepine compounds proceeded smoothly and afforded the new 3a,4,5,6,-tetrahydro[1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepine system.

The reaction of compounds **1a-d** with a slight excess of the benzonitriloxide **2**, generated *in situ* from benzohydroxamoyl chloride and triethylamine, has been performed in methylene chloride at room temperature; the oxadiazolobenzodiazepines **3a-e** have been obtained in good yields (Scheme 1).

Scheme 1



1a-d

2

3a-e

a RR_1=O, R_2=Me
b RR_1=O, R_2=Ph
c R=R_1=R_2=Me
d R=H, R_1=Ph, R_2=Me

a RR_1=O, R_2=Me
b RR_1=O, R_2=Ph
c R=R_1=R_2=Me
d R=H, R_1=Ph, R_2=Me
e R=Ph, R_1=H, R_2=Me

The regiospecificity of the cycloaddition process was established by the uniqueness of the obtained products: the regiochemistry is that predicted from the FMO approach [8].

Two diastereoisomeric cycloadducts **3d** and **3e** were obtained in almost equimolar amount when **1d** was made to react with **2**. Furthermore, compound **3f** was synthesized in a 40% yield by treatment of derivative **3a** with lithium aluminum hydride; the reduction process involves selectively the C=O group of the heptatomic nucleus (Scheme 2).

Scheme 2

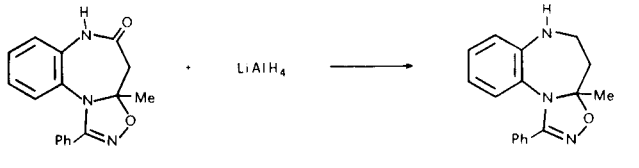


Table I

Physical and Analytical Data for Compounds **3a-f**

Compound No.	Yield %	Mp (°C)	Molecular Formula	Analysis % Calcd./Found C	H	N
3a	87	181-183	$C_{17}H_{15}N_3O_2$	69.61 69.34	5.15 5.02	14.33 14.15
3b	45	154-156	$C_{22}H_{17}N_3O_2$	74.35 74.48	4.82 4.67	11.84 12.01
3c	85	160-161	$C_{19}H_{21}N_3O$	74.24 74.46	6.89 6.75	13.67 13.75
3d	[a]	144-146	$C_{23}H_{21}N_3O$	77.72 77.94	5.96 6.09	11.82 11.63
3e	[a]	168-169	$C_{23}H_{21}N_3O$	77.72 77.90	5.96 5.84	11.82 11.72
3f	40	128-130	$C_{17}H_{17}N_3O$	73.09 73.25	6.13 6.38	15.04 14.92

[a] The two isomers **5d** and **5e** were obtained with a total yield of 80% (relative ratio 50/50).

The structures of the obtained adducts were deduced from their analytical and spectral data reported in Tables 1 and 2.

All the examined compounds showed an ir band at 3330-3190 cm^{-1} for NH group and at 1609-1590 cm^{-1} for C=N bond. An additional band is present for **3a** and **3b** derivatives at 1675 and 1682 cm^{-1} respectively, due to the carbonyl stretching of the heptatomic ring.

The mass spectra showed correct molecular ions and the formation of diagnostic fragmentations. In particular an intramolecular rearrangement leads to the formation of 2-methyl or 2-phenylbenzimidazole ion ($C_8H_8N_2^{+\cdot}$ m/z 132 or $C_{13}H_{10}N_2^{+\cdot}$ at m/z 194), when R = Me or R = Ph respectively, which generally corresponds to the base peak.

The ^1H and ^{13}C nmr spectra provide further evidence to the suggested cycloaddition. The signals of the H and C atoms in the spectra of compounds **1a-d** were all found in the spectra of compounds **3a-e**. In addition, the proton resonances of the -N=C(CH_3) moiety in derivatives **1** were shifted to higher field for the saturated -N-C(CH_3) moieties in derivatives **3**; an analogous shift of the C-3a resonance in **1**, upon conversion in **3**, was observed due to the saturation of the N=C double bond.

NOE measurements allowed for the unambiguous assignment of the stereochemistry to derivatives **3d** and **3e**; irradiation of the methyl group at C-3a in **3e** resulted in the enhancement of the resonance for the proton at C-5, so indicating a syn relationship between these groups. Conversely, the irradiation of the methyl resonance in derivative **3d** did not give a positive NOE for the above mentioned proton. The 5-H shift values (5.23 and 4.03 ppm in **3d** and **3e** respectively) also agree with the proposed attribution, with the H-5 resonance in **3e** shifted upfield by the shielding effect due to the fused aromatic system.

The methylene protons of the heptatomic moiety give rise to a singlet in the spectra of the benzodiazepine precursors **1a-d**, whereas they appear as AB and ABX systems in the spectra of the cycloadducts **3a-c** and **3d-e** respectively; the ^1H-nmr spectrum of **3f** shows, for the alicyclic moiety, an ABCD resonance pattern which has been analyzed by iterative computer fitting.

These data are indicative of a reduced mobility in solution of the heptatomic ring which adopts, analogously to strictly related systems [7,9], a chair-like conformation. The ^1H-nmr spectra of **3a**, **3c**, **3f** were measured at a series of temperatures between −80 and 140° and, although some line broadening occurred, no changes were observed consistent with the inversion of the heterocyclic ring.

According to the results obtained for a series of tricyclic benzodiazepines [3,5,10], the pentatomic ring fusion results in an effective increase of the energy barrier for the heptatomic nucleus reversal.

Steric and electronic effects can be responsible for the conformational control in the benzodiazepine systems. The slow ring inversion observed in some annelated 1,4-benzodiazepines has been mainly related to the presence of the phenyl substituent at C-11a which causes an unfavourable steric interaction with the fused heterocyclic ring [3,5,10].

Similarly, in the system at the hand, the conformational preference is attributable to the steric hindrance due to the phenyl substituent at C-1; its interaction with the fused benzene ring in the nearly planar transition state leads to the observed increasing of the ring inversion barrier.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed on a C. Erba 1106 Elemental Analyzer. The ir spectra were recorded in nujol on a Perkin Elmer Model 257 spetrophotometer. Mass spectra were obtained on a Hewlett Packard Model 5995 gc/ms. The ^1H and ^{13}C nmr spectra were recorded at 80.13 and 20.15 MHz respectively, on a Bruker WP 80 spectrometer, in deuteriochloroform (internal lock) using TMS as internal standard; chemical shifts are in (δ) ppm and coupling constants (J) in Hz. For compound **3f**, the ABCD pattern was analyzed with the aid of a version of the LAOCN3 program [11] modified by us to run on IBM computer and to include a subroutine for plotting calculated spectra on a line printer (the rms error was of 0.0012). For analytical tlc, Kieselgel 60 F_{254} Merck were used. Column and radial chromatography was performed on Kieselgel 60 (70-230 mesh, Merck) and Kieselgel 60 PF_{254} respectively.

Table II

Spectral Data of Compounds **3a-f**

Compound No.	IR cm^{-1} NH	C=O	C=N	MS m/e (%)	^1H NMR [a] (δ ppm)	^{13}C NMR (Deuteriochloroform) (δ ppm)
3a	3190	1675	1609	293 (M^+, 31), 278 (13), 210 (43), 208 (34), 148 (61), 132 (100), 131 (26), 105 (10), 77 (19)	1.62 (s, 3H, CH_3), 2.42 and 2.73 (dd, J = 14.4, 2H, CH_2), 6.83-7.73 (m, 9H, ArH), 9.73 (s, 1H, NH)	25.43 (3a-CH_3), 44.62 (C-4), 106.38 (C-3a), 123.34 (C-7), 126.01 (C-9), 127.73 (C-3',5'), 128.39 (C-2',6'), 129.03 (C-8), 130.32 (C-10), 130.50 (C-4'), 132.20 (C-6a), 136.70 (C-10a), 140.19 (C-1'), 156.50 (C-1), 171.08 (C-5)
3b	3196	1682	1604	355 (M^+, 6), 236 (17), 207 (11), 195 (21), 194 (87), 193 (21), 119 (21), 105 (100), 103 (35), 77 (57)	2.98 and 3.18 (dd, J = −14.1, 2H, CH_2), 6.90-7.85 (m, 14H, ArH), 9.92 (s, 1H, NH)	43.52 (C-4), 106.22 (C-3a), 123.38 (C-7), 125.87 (C-9), 125.52, 127.95, 128.30, 128.44, 129.10, 129.51, 130.64 (C-8, C-10 and phenyl CH), 132.47 (C-6a), 135.40 (C-10a), 140.68, 140.86 (C-1' and C-1"), 156.71 (C-1), 170.31 (C-5)
3c	3325		1590	307 (M^+, 13), 292 (16), 251 (17), 250 (29), 133 (46), 132 (100), 131 (20), 118 (10), 105 (5), 77 (12)	1.20 and 1.46 [2s, 6H, 5-$(CH_3)_2$], 1.57 (s, 3H, 3a-CH_3), 1.94 and 2.29 (dd, J = −14.5, 2H, CH_2), 3.58 (s, 1H, NH), 6.62-7.53 (m, 9H, ArH)	25.79 (3a-CH_3), 30.86, 31.50 [5-$(CH_3)_2$], 48.90 (C-4), 51.74 (C-5), 98.86 (C-3a), 120.38 (C-7), 121.26 (C-9), 125.65 (C-6a), 125.71 (C-10a), 127.14 (C-8), 127.85 (C-2',3',5',6'), 128.68 (C-10), 129.63 (C-4'), 142.75 (C-1'), 154.05 (C-1)
3d	3308		1601	355 (M^+, 8), 340 (3), 298 (8), 251 (18), 132 (100), 131 (20), 119 (18), 105 (5), 103 (16), 77 (15)	1.66 (s, 3H, CH_3), 2.14 (dd, J = −15.1, 3.0, 1H, 4-CH_{eq}), 2.41 (dd, J = −15.1, 9.9, 1H, 4-CH_{ax}), 3.69 (s, 1H, NH), 5.23 (dd, J = 9.9, 3.0, 1H, 5-CH), 6.51-7.55 (m, 14H, ArH)	25.90 (3a-CH_3), 46.37 (C-4), 55.58 (C-5), 100.53 (C-3a), 118.18 (C-7), 118.92 (C-9), 123.53 (C-6a), 125.62 (C-10a), 126.38, 127.77, 127.95, 128.91, 129.81, 131.13 (C-8, C-10 and phenyl CH), 144.41, 144.83 (C-1' and C-1"), 156.28 (C-1)
3e	3301		1594	355 (M^+, 8), 340 (3), 298 (7), 251 (18), 132 (100), 131 (18), 119 (19), 105 (5), 103 (18), 77 (18)	1.59 (s, 3H, CH_3), 2.13 (dd, J = −12.7, 2.0, 1H, 4-CH_{eq}), 2.78 (dd, J = −12.7, 11.8, 1H, 4-CH_{ax}), 3.85 (s, 1H, NH), 4.03 (dd, J = 11.8, 2.0, 1H, 5-CH), 6.60-7.55 (m, 14H, ArH)	22.29 (3a-CH_3), 48.79 (C-4), 57.01 (C-5), 98.25 (C-3a), 121.33 (C-7), 121.83 (C-9), 123.95 (C-6a), 125.44 (C-10a), 126.78, 127.27, 128.15, 128.26, 128.44, 129.04, 130.08 (C-8, C-10 and phenyl CH), 143.79, 144.94 (C-1' and C-1"), 157.32 (C-1)
3f	3330		1593	279 (M^+, 13), 264 (6), 251 (10), 222 (12), 132 (100), 131 (22), 119 (20), 103 (27), 77 (14)	1.54 (s, 3H, CH_3), 2.07 (4-CH_{eq}), 2.44 4-CH_{ax}), 3.03 (5-CH_{eq}), 3.65 (5-CH_{ax}) (4m, 1H each, ABCD system, $J_{A,B}$ = −13.8, $J_{A,C}$ = 2.8, $J_{A,D}$ = 6.8, $J_{B,C}$ = 9.0, $J_{B,D}$ = 3.3, $J_{C,D}$ = −13.4), 6.55-7.36 (m, 9H, ArH) [b]	23.10 (3a-CH_3), 40.10 (C-4), 40.79 (C-5), 99.81 (C-3a), 119.17 (C-7), 119.68 (C-9), 124.76 (C-6a), 125.39 (C-10a), 125.71, 128.02, 128.09, 129.80 (C-8, C-10 and phenyl CH), 145.75 (C-1'), 154.56 (C-1)

[a] Measured in DMSO-d_6, **3a-b**, in deuteriochloroform, **3c-f**. [b] NH signal is masked by 5-CH_{ax} multiplet.

1,5-Benzodiazepines **1** were obtained according to the literature methods [12a-d].

General Procedure for the Synthesis of the 3a,4-Dihydro-1-phenyl[1,2,4]oxadiazolo[5,4-*d*][1,5]benzodiazepin-5(6*H*)-ones **3a-b** and 1-Phenyl-3a,4,5,6-tetrahydro[1,2,4]oxadiazolo[5,4-*d*][1,5]benzodiazepines **3c-e**.

To a stirred solution of the 1,5-benzodiazepine derivatives **1** (10 mmoles) and of the benzohydroxamic acid chloride **2** (15 mmoles) in methylene chloride (50 ml), a solution of triethylamine (15 mmoles) in the same solvent (5 ml) was added dropwise over a few minutes. The reaction mixture was kept under stirring at room temperature for 15-30 minutes, the optimum reaction time being determined by tlc monitoring (eluant: diethyl ether/light petroleum 9:1). After the removal of the solvent at reduced pressure, diethyl ether was added to the residue and the triethylamine hydrochloride was filtered. The solvent was then evaporated off and the residue subjected to column chromatography with diethyl ether/light petroleum 9:1 as eluant. Compounds **3d** and **3e** were separated by radial chromatography using the same eluant in 2:8 ratio.

3a-Methyl-1-phenyl-3a,4,5,6-tetrahydro[1,2,4]oxadiazolo[5,4-*d*]-[1,5]benzodiazepine **3f**.

A solution of 3a,4-dihydro-3a-methyl-1-phenyl[1,2,4]oxadiazolo-[4,5-*a*][1,5]benzodiazepin-5(6*H*)-one (**3a**) (1.47 g, 5 mmoles) in 20 ml of anhydrous tetrahydrofuran was added in 15 minutes to a stirred suspension of lithium aluminum hydride (380 mg, 10 mmoles) in 5 ml of anhydrous tetrahydrofuran. The mixture was

refluxed for 24 hours and then cooled. The usual work-up gave, after column chromatography with diethyl ether/light petroleum 7:3 as eluant, compound **3f** with a yield of 40%.

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