NOVEL FUSED-RING DERIVATIVES OF 1,4-BENZODIAZEPINE SYSTEM: SYNTHESIS OF TETRAHYDRO-1H-s-TRIAZOLO [4,3-d][1,4] BENZODIAZEPINES

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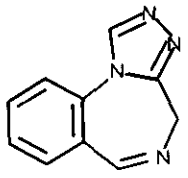
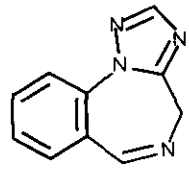
Abstract - A novel class of annelated 1,4-benzodiazepines is synthesized by 1,3-dipolar cycloaddition of suitable nitrilimines to the C=N bond of the benzodiazepine ring. Structures and conformations of adducts have been assigned by means of spectroscopic measurements. The additional heterocyclic nucleus has been found to influence dramatically the conformational mobility of the heptatomic ring.

The synthesis of benzodiazepinic derivatives with heterocyclic rings annelated to the "a"[1-4], "c"[5] or "d"[6] edges of the heptatomic system has recently attracted interests of several research groups and consequently many reports and patents have appeared. The fusion of a heterocyclic system to the benzodiazepine ring appears, in fact, especially promising for the synthesis of derivatives with a higher activity and specificity, provided that they show similar pharmacological profiles to the benzodiazepines from which they are derived.

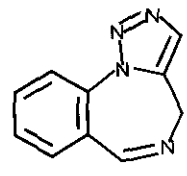
The fusion of a triazole ring has been the object of several studies: compounds of type 1, 2 and 3 are well known and represent the three possible ring systems in which a triazole nucleus is fused to the 1,2 positions of 1,4-benzodiazepine nucleus[1-3].



1
s-triazolo 4,3-a



2
s-triazolo 1,5-a

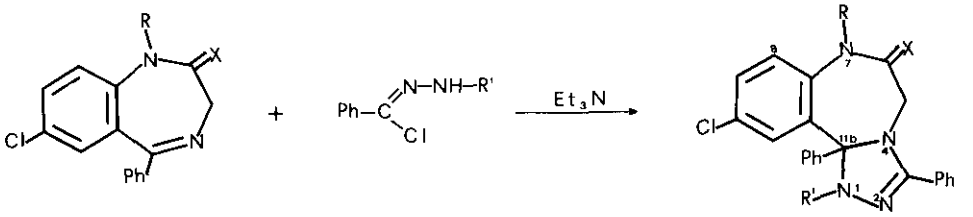


3
v-triazolo 1,5-a

In particular, derivatives of type 1, showing very remarkable pharmacological properties, have been recently introduced in therapy as Estazolam®, Alprazolam®and Triazolam®.

In connection with our investigations on the conformational properties of the heptatomic benzodiazepine ring[7] and on the perturbations caused by the introduction of a fused heterocyclic ring[8], it seems interesting to extend the work to the synthesis of a novel series of annelated 1,4-benzodiazepines in which a 1,2,4-triazoline ring is fused at 4 and 5 positions of a 1,4-benzodiazepine moiety.

Recently, the synthesis of a related system, the 5H-s-triazolo[4,3-d][1,4]benzodiazepine, has been reported , based on treatment of 5-methylmercapto-1,4-benzodiazepine with hydrazine and successive cyclization with an acid anhydride. We report here a facile one-step synthesis of the tetrahydro-1H-s-triazolo[4,3-d][1,4]benzodiazepines (6), by 1,3-dipolar cycloaddition of nitrilimines, generated "in situ" by the action of bases on hydrazidoyl halides[9] (5), at the C=N double bond of 1,4-benzodiazepine derivatives (4), as shown in Scheme.



4 5 6

Table 1

Compd	X	R	R'	Yield %
7	H_2	H	C_6H_5	85
8	H_2	CH_3	C_6H_5	74
9	H_2	CH_3	$4\text{-}NO_2\text{-}C_6H_4$	85
10	O	H	$4\text{-}NO_2\text{-}C_6H_4$	86
11	O	CH_3	$4\text{-}NO_2\text{-}C_6H_4$	82

The reactions were performed by adding a benzene solution of triethylamine to a solution of 4 and 5 in the same solvent at room temperature and then maintaining at reflux overnight. The best yields were obtained using a 2:1 ratio of benzodiazepine derivatives and nitrilimines; the 1:1 ratio of the reagents needed longer reaction times and resulted in lower yields of the cycloadducts. The reaction products were isolated after conventional work-up and purified by column chromatography. The obtained derivatives (7-11) and the corresponding yields are reported in Table 1. The cycloaddition reaction occurs with high yields and remarkable regiospecificity.

The molecular structure of the reaction products has been assigned on the basis of analytical and spectroscopic methods (ir, ^1H nmr and mass) and supported by satisfactory elemental analyses. The ir spectra of all the compounds synthesized showed the C=N absorption at 1605-1580 cm^{-1}; for the benzodiazepinone derivatives, a strong carbonyl band 1680 cm^{-1} for 10 and 1685 cm^{-1} for 11 was also observed. The NH bands for 7 and 10 were at 3255 and 3318 cm^{-1} respectively. The ^1H nmr parameters are reported in Table 2.

Table 2

Compd	CH_3	ν_1	ν_2	ν_3	ν_4	Other protons
7		3.14	3.17	3.62	3.68	6.63-7.70
		$J_{1,2}$ -13.0	$J_{2,3}$ 4.2	$J_{3,4}$ -12.4		
		$J_{1,3}$ 7.8	$J_{2,4}$ 2.1			
		$J_{1,4}$ 5.1				
8	2.43	2.85	2.65	3.35	3.49	6.62-7.40
		$J_{1,2}$ -13.0	$J_{2,3}$ 5.8	$J_{3,4}$ -15.3		
		$J_{1,3}$ 8.7	$J_{2,4}$ 3.3			
		$J_{1,4}$ 2.5				
9	2.59	2.75	2.89	3.38	3.49	6.80-7.87
		$J_{1,2}$ -12.4	$J_{2,3}$ 4.1	$J_{3,4}$ -13.4		
		$J_{1,3}$ 5.6	$J_{2,4}$ 3.1			
		$J_{1,4}$ 3.1				
10				3.94	4.05	6.88-7.92
				$J_{3,4}$ -15.2		
11	2.91			3.46	4.15	6.94-7.92
				$J_{3,4}$ -12.5		

Compounds 10 and 11 give an AB system for the 5-methylene group; the protons of the ethylene - fragments of 7, 8 and 9 are non-equivalent and form two complex unsymmetrical groups of peaks. The proton resonance pattern was analyzed by means of the LAOCN3 program[10] . In 7, 8 and 9, protons 1 and 2 can be assigned as the methylene protons adjacent to 7-N on the basis of their lower values of chemical shifts. The proposed assignement agreed also with the shifts induced by the addition of a small quantity of $Pr(fod)_3$ to a $CDCl_3$ solution of compounds at hands; the observed effect is consistent with a complexation of the lanthanide mainly at the iminic 4-N.

The nature of the added heterocycle ring has been found to exert a profound influence on the conformational properties of the seven-membered ring.

As reported[7a], 2,3-dihydro-1H-1,4-benzodiazepines (medazepam and N-desmethylmedazepam) exist in $CDCl_3$ solution as two pseudo-boat conformers which are rapidly interconverting at room temperature: the alicyclic region of ^1H nmr spectrum is characterized by an absorption pattern which approximates to an AA'BB' system nearly symmetrical about its middle point. The ^1H nmr spectral analysis of compounds 7, 8 and 9 suggests, on the contrary, that they exist in chloroform solution as only one conformer which does not interconvert at room temperature: the $-CH_2-CH_2-$ moiety resonates as an ABCD spin system, which gives rise to the two complex groups of signals mentioned above. These spectral features indicate that the annelation of a Δ^2-1,2,4-triazoline nucleus to the d-edge of the 1,4-benzodiazepine ring results in a significant increase of the ring-inversion barrier of the 2,3-dihydro-1H-1,4-benzodiazepine seven-membered ring.

Similar considerations can be extended to the 1,4-benzodiazepin-2-one derivatives. Compounds 10 and 11 exist in only one preferred conformation at room temperature in $CDCl_3$ solution. This result contrasts the fact that 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, the precursor of 10, exists at room temperature in only one conformation, while in the same conditions 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one, the precursor of 11, exists in a mobile equilibrium[7b].

The observed slow heptatomic ring reversal at room temperature is consistent with some of the results obtained for benzodiazepine derivatives which show a pentatomic nucleus annelated to the d-edge of the molecule[8] .

Preliminary results employing temperature dependent nmr analysis, indicate that the ring inversion barriers for 9 and 10 are 18.7 and 19.4 Kcal/mol respectively. The values are higher than those obtained for some 1,2,4-triazolo[4,3-d][1,4]benzodiazepinones[6b] which show a barrier inversion in the range of 13.0-14.2 Kcal/mol. The 11b-phenyl group in compounds 7-11 may be responsible for the blocked configuration of the seven-membered ring at room temperature.

In conclusion we can affirm that the described reaction represents a valuable entry to the novel class of benzodiazepines containing a Δ^2-1,2,4-triazoline nucleus fused to the d-edge of the heptatomic ring. The enhanced energy barrier of the products synthesized and the consequent reduced conformational mobility of the seven-membered ring seems to be interesting in relation to their potential biological activity[11].

EXPERIMENTAL

Melting points were obtained on a Kofler hot stage apparatus and are uncorrected. Ir spectra were determined in nujol by using a Perkin Elmer Mod. 257 recording spectrometer. ^1H nmr spectra were recorded on a Bruker WP 200 SY and a Varian XL 100, in $CDCl_3$ using TMS as internal standard; chemical shifts are in (δ) ppm and coupling constants (J) in Hz. The ABCD pattern were analysed with the aid of a version of the LAOCN3 program modified by us to run on IBM computer and to include a subroutine for plotting calculated spectra on a line printer (the rms errors were of 0.005, 0.003 and 0.012 for compounds 7, 8 and 9 respectively). Mass spectra were measured on a Varian Mat CH5. Elemental analyses were carried out on a C. Erba model 1106 Elemental Analyzer. Column chromatography was performed on silica gel 60, Merck, 70-230 mesh. Tlc was carried out on silica gel plates 60 F_{254} (Merck). Benzodiazepines (4) used in this study were extracted in Soxlet with chloroform from the corresponding drugs. Compounds of type 5 were prepared according to the literature[9].

10-Chloro-5,6,7,11b-tetrahydro-1,3,11b-triphenyl-1H-s-triazolo [4,3-d][1,4] benzodiazepine (7) To a solution of 7-chloro-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine (0.01 mol) and benz-phenylhydrazidoyl chloride (0.005 mol) in 50 ml of dry benzene, a solution of triethylamine (0.015 mol) in the same solvent was added with stirring. The mixture was refluxed overnight; the cooled solution was washed with water and concentrated in vacuo, and the product was separated by column chromatography (eluant: diethyl ether-ethyl acetate 1-1 v.v.). The compound was recrystallized from light petroleum ether to give yellow crystals, mp 188-190°C. Ms: m/e 450 (M^+). Anal. calcd for $C_{28}H_{23}ClN_4$ C, 74.57; H, 5.14; N, 12.42. Found: C, 74.20; H, 5.47; N, 12.12.

10-Chloro-7-methyl-5,6,7,11b-tetrahydro-1,3,11b-triphenyl-1H-s-triazolo [4,3-d][1,4] benzodiazepine (8) This compound was prepared from 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine with benz-phenylhydrazidoyl chloride by the same procedure as in the preparation of (7). Recrystallization from light petroleum ether gave (8) as yellow crystals of mp 114-116°C. Ms: m/e 464 (M^+). Anal. calcd for $C_{29}H_{25}ClN_4$: C, 74.90; H, 5.41; N, 12.05. Found: C, 74.96; H, 5.48; N, 11.85.

10-Chloro-3,11b-diphenyl-7-methyl-1-(4-nitrophenyl)-5,6,7,11b-tetrahydro-1H-s-triazolo [4,3-d][1,4] benzodiazepine (9) This compound was obtained in 85% yield, from 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine and benz-4-nitrophenyl-

hydrazidoyl chloride. After crystallization a red compound with mp 116-118°C was obtained. Ms: m/e 509 (M^+). Anal. calcd for $C_{29}H_{24}ClN_5O$: C, 68.29; H, 4.74; N, 13.73. Found: C, 68.31; H, 4.72; N, 13.40.

10-Chloro-3,11b-diphenyl-1-(4-nitrophenyl)-5,6,7,11b-tetrahydro-1H-s-triazolo[4,3-d][1,4]benzodiazepin-6-one (10) This compound was prepared starting from 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and the same hydrazidoyl chloride employed for the synthesis of (9) to give orange crystals with mp 286-88°C. Ms: m/e 509 (M^+). Anal. calcd for $C_{28}H_{20}ClN_5O_3$: C, 65.94; H, 3.95; N, 13.73. Found: C, 65.95; H, 3.92; N, 13.54.

10-Chloro-3,11b-diphenyl-7-methyl-1-(4-nitrophenyl)-5,6,7,11b-tetrahydro-1H-s-triazolo[4,3-d][1,4]benzodiazepin-6-one (11) This compound was obtained starting from 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one and benz-4-nitrophenylhydrazidoyl chloride to give orange needles, mp 137-38°C. Ms: m/e 523 (M^+). Anal. calcd for $C_{29}H_{22}ClN_5O_3$: C,66.47; H,4.23; N,13.36. Found: C,66.40; H,4.54; N,13.03.

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