3H-AZIRINO[1,2-d][1,4]BENZODIAZEPIN-4(5H)-ONES: SYNTHESIS AND STEREOCHEMISTRY

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Abstract - The synthesis of 5-alkyl-1,9b-dihydro-3H-azirino[1,2-d][1,4]benzodiazepin-4(5H)-ones by cycloaddition of dichlorocarbene to N_1-alkyl-1,4-benzodiazepine derivatives, is described. The lack of reactivity in analogous N_1-H derivatives is explained on the basis of elctronic factors.

In previous papers[1-4] 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 this context, nitrilimines and benzonitriloxides were shown to add as 1,3-dipoles to the C=N bond of 1,4- and 1,5-benzodiazepines to form tetrahydro-1H-s-triazolo[4,3-d][1,4]benzodiazepines[1] and [1,2,4]oxadiazolo-[4,5-a][1,5]benzodiazepines,[2] respectively. Moreover, tetrahydrothiazolo-[3,2-d][1,4]benzodiazepines were obtained by cyclocondensation of mercaptocarboxylic acids to 1,4-benzodiazepine derivatives;[3] however, the same reaction, performed on analogous 1,5-benzodiazepines, failed to give the expected cycloadducts.[4]

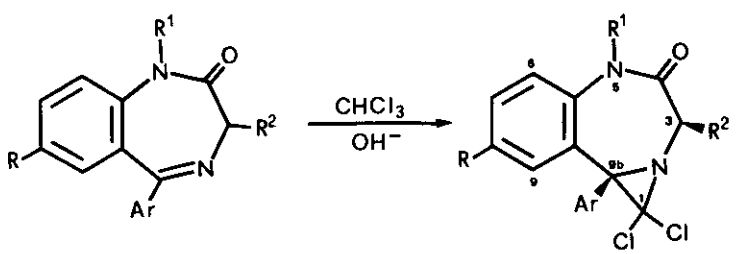
Our interest is related to the investigation of the stereochemical features of benzodiazepine ring and of the perturbances caused by the introduction of a fused heterocyclic nucleus, following the hypothesis that the conformational preferences of the heptatomic ring control and define the possible interaction with the suitable biological receptor.

In this aim, we report here the synthesis and the stereochemistry of a novel benzodiazepine system containing an aziridine ring fused to the "d" edge of the heptatomic nucleus.

Addition of dihalocarbene to Schiff bases is a well known method for the synthesis of 2,2-dihaloaziridines;[5] we have examined the 1,2-addition reaction of dichlorocarbene to a series of 1,4-benzodiazepines. This paper documents the obtained results.

The reaction of compounds (**1a-f**) with dichlorocarbene, generated in situ using benzyltriethylammonium chloride in chloroform-aqueous sodium hydroxide

Scheme 1



1a-f **2a-f**

Compd	R	R^1	R^2	Ar	Yield %
a	Cl	CH_3	H	C_6H_5	23
b	Cl	CH_3	$OCON(CH_3)_2$	C_6H_5	82
c	Cl	CH_2CF_3	H	C_6H_5	20
d	Cl	$CH_2C{\equiv}CH$	H	C_6H_5	37
e	Cl	CH_2-cyclopropyl	H	C_6H_5	32
f	NO_2	CH_3	H	2-F-C_6H_4	38

mixture, at room temperature gave the 1,9b-dihydro-3H-azirino[1,2-d][1,4]-benzodiazepin-4(5H)-ones (**2a-f**) in yields ranging from 20-82% (Scheme 1). The structures of the obtained cycloadducts (**2a-f**) were assigned on the basis of spectroscopic data (ir, ms, ^{1}H- and ^{13}C-nmr) and supported by satisfactory elemental analyses.

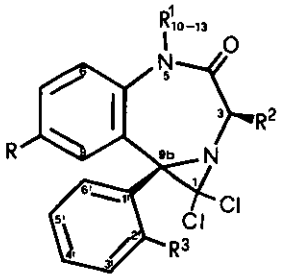
The ir spectra of all the synthesized compounds show the carbonyl absorption in the range of 1688-1675 cm^{-1}. For compound (**2b**) an additional band is present at 1728 cm^{-1} due to $CONMe_2$ stretching.

The ^{1}H- and ^{13}C-nmr spectra of adducts (**2**) were compared with those of the starting 1,4-benzodiazepine derivatives (**1**). The signals of hydrogen and carbon atoms in the spectra of compounds (**1**) are all found in the spectra of products (**2**). In addition, in ^{13}C-nmr spectra of compounds (**2**) (Table 1) the C-1 resonance of the aziridine ring between 74-80 ppm is observed as well as a shift to a higher field, with respect to the precursors, of C-9b signals, due to saturation of the C=N double bond, and of C-3 owing to the hybridization change of N-2.

The downfield shifts observed for C-9 and C-9a resonances (about 2 ppm) with respect to the precursors are explained on the basis of the deshielding effect induced by the phenyl group at C-9b. These features are indicative of a modified stereochemistry of the system caused by the annelation of aziridine ring. The phenyl substituent assumes a nearly axial position which reduces the unfavourable steric interaction with the fused three-membered ring.

In the ^{1}H-nmr spectra of compounds (**2a, 2c-f**) (Table 2) methylene protons at C-3 resonate as a doublet of doublets; these data are indicative of a reduced mobility, at room temperature and in solution, of the heptatomic ring which adopts, analogously to strictly related systems[6], a pseudo-boat conformation. In addition, H-9 resonances are shifted to a lower field because of the deshielding effect induced by the pseudoaxial phenyl group at C-9b.

Table 1. ^{13}C-Nmr spectral data of 1,9b-dihydro-3H-azirino[1,2-d][1,4]benzodiazepin-4(5H)-ones (**2a-f**).



	2a	2b*	2c	2d	2e	2f
C-1	79.50	74.10	79.70	79.58	79.44	78.21
C-3	51.92	81.06	51.36	51.75	51.95	51.87
C-4	167.10	164.33	167.20	166.31	166.40	166.76
C-5a	140.92	141.50	138.86	139.34	139.98	147.68
C-6	124.70	124.49	124.70	124.64	125.70	123.84
C-7	128.40	128.33	128.53	128.20	128.26	124.71
C-8	130.94	133.61	132.46	131.07	131.30	145.11
C-9	131.54	129.40	133.03	131.77	132.40	124.95
C-9a	130.70	130.59	131.07	130.84	131.11	129.26
C-9b	55.12	51.63	55.02	55.03	54.78	52.33
C-1'	136.07	135.02	134.17	135.62	135.27	126.51
C-2'	128.40	128.33	128.01	128.20	128.13	160.01
C-3'	127.59	127.21	128.01	127.78	127.95	115.93
C-4'	129.79	129.62	130.22	129.82	129.69	130.99
C-5'	127.59	127.21	128.01	127.78	127.95	129.43
C-6'	128.40	128.33	128.01	128.20	128.13	127.83
C-10	35.40	36.22	47.23	37.17	51.95	35.60
C-11			116.10	77.98	9.59	
C-12				72.44	3.20	
C-13					3.69	

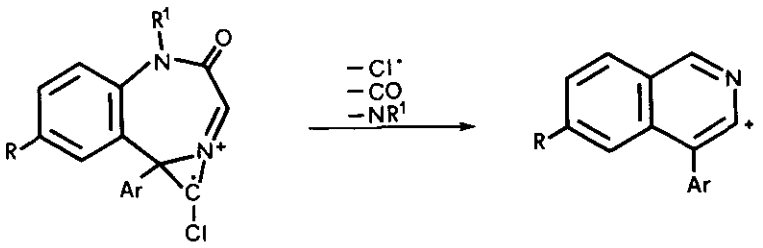
* The carbon resonances of carbonyl and methyl groups of $OCONMe_2$ substituent at C-3 are at 153.26, 34.59 and 36.40 ppm respectively.

Table 2. ^{1}H-Nmr spectral data of 1,9b-dihydro-3H-azirino[1,2-d][1,4]benzodiazepin-4(5H)-ones (**2a-f**)

Compd	δ ($CDCl_3$)
2a	3.16 (s, 3H, CH_3), 3.35 and 3.97 (dd, J=-11.1, 2H, CH_2), 7.19 (d, J=10.9, 1H, H-6), 7.29-7.48 (m, 6H, ArH), 7.73 (d, J=2.4, 1H, H-9).
2b	2.05 and 2.81 (2 s, 6H, $N(CH_3)_2$), 3.10 (s, 3H, CH_3), 6.95 (s, 1H, H-3), 7.06 (d, J=8.6, 1H, H-6), 7.26-7.42 (m, 6H, ArH), 7.84 (d, J=2.3, 1H, H-9).
2c	3.36 and 4.02 (dd, J=-11.2, 2H, CH_2), 4.25 (m, 2H, CH_2CF_3), 7.08 (d, J=8.8, 1H, H-6), 7.10-7.71 (m, 6H, ArH), 7.81 (d, J=2.3, 1H, H-9).
2d	1.94 (t, J=2.5, 1H, C≡CH), 3.37 and 4.01 (dd, J=-11.1, 2H, CH_2), 4.23 and 4.44 (2 dd, J=2.5 and -17.5, 2H, NCH_2), 7.19-7.76 (m, 8H, ArH).
2e	-0.36/-0.15 (m, 4H, CH_2 cyclopropyl), 0.33 (m, 1H, CH cyclopropyl), 3.12 and 4.05 (2 dd, J=6.6 and -14.2, 2H, NCH_2), 3.33 and 3.95 (dd, J=-10.9, 2H, CH_2), 7.16 (d, J=10.8, 1H, H-6), 7.18-7.60 (m, 6H, ArH), 7.78 (d, J=2.3, 1H, H-9).
2f	3.34 (s, 3H, CH_3), 3.35 and 4.03 (dd, J=-11.3, 2H, CH_2), 6.94-7.49 (m, 5H, ArH), 8.23 (dd, J=2.7 and 9.0, 1H, H-7), 8.76 (d, J=2.7, 1H, H-9).

In the mass spectra of all the synthesized compounds the molecular ion is absent. By loss of HCl, the ion at M^+-36 is formed, which corresponds to the base peak in all derivatives, except that of (**2b**). Sequential loss of Cl, CO and NR^1 radicals yields an isoquinoline ion (Scheme 2). In the mass spectra of compound (**2b**) the presence of a substituent at position 3 of the heptatomic ring leads to the formation of $CONMe_2$ ion which appears as the base peak.

Scheme 2



The reactivity of the C=N moiety of benzodiazepine system appears to be associated with the presence of an alkyl substituent at N-1. In fact the same reaction, performed with N-dealkyl-1,4-benzodiazepines failed to give the expected cycloadducts.

From ^{1}H-nmr studies of diazepam and N-desmethyldiazepam it has been proposed that N_1 atom in the N_1-H compounds has more sp^3 character than in N-CH_3 analogues.[8] This hypothesis has been confirmed by semiempirical theoretical calculations,[7] which put in evidence that the substitution of a methyl group for a hydrogen atom affects the heptatomic ring geometry around the N-1 atom (sp^2 on N-methyl and nearly sp^3 on NH). This difference in hybridization appreciably affects the π-electron distribution at N-1 (1.285e for N-Me and 1.443e for NH).

According to these data, N_1-H compounds were inadequate to give the desired carbene adducts because the reaction pathway is driven towards the removal of the proton at N-1 by the action of the base with formation of an amidate ion. The subsequent reaction of this intermediate with dichlorocarbene gives rise to the formation of unidentifiable products together with unreacted benzodiazepine precursors.

In conclusion, we have performed an easy entry to the 3H-azirino[1,2-d]-[1,4]benzodiazepin-4(5H)-one system. The introduction of the aziridine nucleus could afford new useful functionalization patterns of the benzodiazepine system, following the ring opening of the three-membered ring.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses (C, H, N, S) were carried out on a C. Erba Model 1106 Elemental Analyzer. Merck silica gel 60 F_{254} plates were used for tlc; preparative silica gel chromatography was performed using a Chromatotron apparatus. Ir specra were determined in nujol on a Perkin Elmer mod. 257 spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were measured with a Bruker WP 80 SY spectrometer in $CDCl_3$ (internal lock) with TMS as the internal standard: chemical shifts are expressed in δ (ppm) and coupling constants (J) in hertz. Mass spectra were recorded on a Hewlett-Packard Model 5995 GC/MS. Benzodiazepines (**1**) used in this study were extracted in Soxhlet with chloroform from the corresponding drugs.

General procedure for the synthesis of 1,9b-dihydro-3H-azirino[1,2-d][1,4]-benzodiazepin-4(5H)-ones

To a solution of the appropriate 1,4-benzodiazepine derivative (3 mmol) in 5 ml of chloroform, a mixture of 13 ml of chloroform and 6 ml of 50% aqueous sodium hydroxide was added dropwise. The resulting mixture was treated with benzyltriethylammonium chloride (30 mg, 0.13 mmol) and stirred for 1-2 h at room temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic solution was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. After this initial work-up procedure, the oily residue was triturated with ether resulting in a solid which was recrystallized from ethanol to give compounds (**2b**) and (**2f**), or chromatographed on silica gel column (ether/petroleum ether 6:4) to afford, after recrystallization from ethanol, compounds (**2a, 2c-2e**).

8-Chloro-1,9b-dihydro-5-methyl-9b-phenyl-3H-azirino[1,2-d][1,4]benzodiazepin-4(5H)-one (2a)

mp 206-208°C (yield 23%). Anal. Calcd for $C_{17}H_{13}N_2OCl_3$: C, 55.53; H, 3.56;

N, 7.62; Cl, 28.93. Found: C, 55.23; H, 3.58; N, 7.50; Cl, 29.10. Ir: 1682 cm^{-1}. Ms m/z (%): 366 (M^+, 0), 330 (100), 295 (20), 267 (11), 252 (5), 238 (3).

8-Chloro-1,9b-dihydro-3-(N,N-dimethylcarbamoyl)-5-methyl-9b-phenyl-3H-azirino[1,2-d][1,4]benzodiazepin-4(5H)-one (2b)

mp 179-181°C (yield 82%). Anal. Calcd for $C_{20}H_{18}N_3O_3Cl_3$: C, 52.82; H, 3.99; N, 9.24; Cl, 23.39. Found: C, 52.63; H, 3.97; N, 9.05; Cl, 23.52. Ir: 1728, 1688 cm^{-1}. Ms m/z (%): 453 (M^+, 0), 417 (23), 345 (9), 329 (2), 282 (3), 253 (4), 72 (100).

8-Chloro-1,9b-dihydro-9b-phenyl-5-(2,2,2-trifluoroethyl)-3H-azirino[1,2-d]-[1,4]benzodiazepin-4(5H)-one (2c)

mp 139-141°C (yield 20%). Anal. Calcd for $C_{18}H_{12}N_2OF_3Cl_3$: C, 49.69; H, 2.77; N, 6.42; Cl, 24.38. Found: C, 49.98; H, 2.52; N, 6.10; Cl, 24.35. Ir: 1676 cm^{-1}. Ms m/z (%): 434 (M^+, 0), 398 (100), 363 (7), 351 (3), 335 (6), 252 (6), 238 (4).

8-Chloro-1,9b-dihydro-9b-phenyl-5-(2-propargyl)-3H-azirino[1,2-d][1,4]-benzodiazepin-4(5H)-one (2d)

mp 158-160°C (yield 37%). Anal. Calcd for $C_{19}H_{13}N_2OCl_3$: C, 58.26; H, 3.34; N, 7.15; Cl, 27.16. Found: C, 58.60; H, 3.35; N, 7.05; Cl, 27.47. Ir: 1680 cm^{-1}. Ms m/z (%): 390 (M^+, 0), 354 (100), 319 (13), 315 (4), 291 (8), 287 (9), 252 (17), 238 (4).

8-Chloro-5-cyclopropylmethyl-1,9b-dihydro-9b-phenyl-3H-azirino[1,2-d][1,4]-benzodiazepin-4(5H)-one (2e)

mp 138-140°C (yield 32%). Anal. Calcd for $C_{20}H_{17}N_2OCl_3$: C, 55.53; H, 3.56; N, 7.62; Cl, 28.93. Found: C, 55.23; H, 3.56; N, 7.50; Cl, 29.12. Ir: 1675 cm^{-1}. Ms m/z (%): 406 (M^+, 0), 370 (100), 335 (3), 315 (4), 316 (47), 281 (9), 280 (4), 253 (12), 252 (13), 238 (4), 55 (10).

1,9b-Dihydro-9b-(2'-fluorophenyl)-5-methyl-8-nitro-3H-azirino[1,2-d][1,4]-benzodiazepin-4(5H)-one (2f)

mp 219-221°C (yield 38%). Anal. Calcd for $C_{17}H_{12}N_3O_3FCl_2$: C, 51.53; H, 3.05; N, 10.60; Cl, 17.57. Found: C, 51.79; H, 3.19; N, 10.43; Cl, 17.62. Ir: 1680 cm^{-1}. Ms m/z (%): 395 (M^+, 0), 359 (100), 324 (15), 296 (10), 282 (6), 267 (4).

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