Addition of Dihalocarbenes to 3*H*-1,5-Benzodiazepines. Synthesis of 2*H*-Bisazirino[1,2-*a*:2′,1′-*d*][1,5]benzodiazepines

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Addition of dihalocarbenes, generated from haloforms using a phase transfer catalyst, to 3*H*-1,5-benzodiazepines gave 2*H*-Bisazirino[1,2-*a*:2′,1′-*d*][1,5]benzodiazepines, a new ring system.

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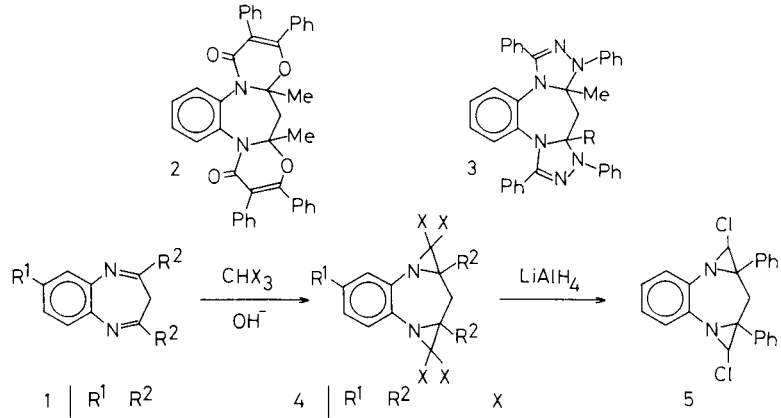
The nitrogen-carbon double bonds of 3*H*-1,5-benzodiazepines **1** have been tested as dipolarophiles. Benzoylphenylketene was shown to add as a 1,4-dipole to the C=N bonds of **1** to form bis(1,3-oxadino[3,2-*a*])[1,5]benzodiazepine derivatives **2** [1]. More recently, 3*H*-bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5]-benzodiazepines **3** were obtained by 1,3-dipolar cycloaddition of nitrile imine to **1** [2]. Addition of dihalocarbene to Schiff base is a well known method for a synthesis of 2,2-dihalogenoaziridines, and they can undergo ready ring-opening reaction [3]. However, addition of dihalocarbenes to heterocycles containing C=N bonds in the rings such as pyridines [4], quinolines [5], and isoquinolines [6] did not give the heterocycles condensed with azirine ring at the C=N position. We have examined 1,2-addition reaction of dihalocarbenes with **1** and obtained 2*H*-bisazirino-[1,2-*a*:2′,1′-*d*][1,5]benzodiazepines **4**, a new ring system.

Treatment of **1a-c** with dihalocarbenes generated *in situ* using benzyltriethylammonium chloride in chloroform-aqueous sodium hydroxide mixture [7] gave the expected bisazirino[1,5]benzodiazepines **4a-d** in 22-55% yields (Scheme 1). The structure of these products were confirmed on the basis of analytical and spectral data (Table 1 and 2). In the nmr spectra of **1a-c** the signals of methylene protons appeared at δ 3.63 ppm as somewhat broad singlets [8], whereas they were observed at δ 3.18-3.36 and 3.48-3.88 ppm as doublets of AB system in the nmr spectra of the products **4a-d**. These data indicate that **4a-d** have similar fixed conformation as described in the case of **3** [2]. Reduction of **1a** with lithium aluminium hydride in tetrahydrofuran and chromatographical separation gave 1,3-dichlorobisazirinobenzodiazepine **5** in 24% yield as the sole product. Two singlets at δ 2.25 and 4.40 ppm in the nmr spectrum of **5** were assigned to the C_1-H and C_3-H, and two sets of doublets due to the methylene group were observed. This implies that the reduction product **5** has an asymmetric structure and a fixed conformation. Accordingly, among the possible structures **6A**, **B**, and **C** of the addition products **4** the symmetric structures **6A** and **B** were excluded, which were formed by attack of two dihalocarbenes to the convex or to the concave of 1,5-benzodiazepine (Scheme 2). *trans*-1,2-Diphenyl structure **6C** would be the most probable one, which resulted from the attack of each dihalocarbene to the oppo-

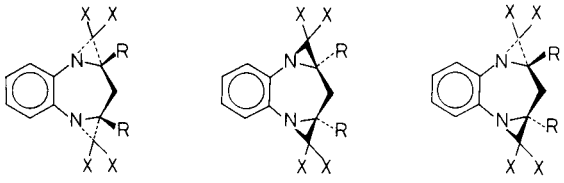
Scheme 1



1	R^1	R^2
a	H	Ph
b	Cl	Ph
c	H	p-Tolyl

4	R^1	R^2	X
a	H	Ph	Cl
b	H	Ph	Br
c	Cl	Ph	Cl
d	H	p-Tolyl	Cl

Scheme 2



6A 6B 6C

Table 1

Physical Properties of Compounds **4** and **5**

Compound	Yield %	Mp °C	Molecular Formula	Analysis % Calcd. C	(Found) H
4a	47	214-215	$C_{23}H_{16}Cl_4N_2$ (462.21)	59.76 (59.51)	3.50 (3.48)
4b	22	195-196	$C_{23}H_{16}Br_4N_2$ (640.01)	43.16 (43.20)	2.52 (2.51)
4c	55	210-212	$C_{23}H_{15}Cl_5N_2$ (496.56)	55.63 (55.55)	3.04 (3.16)
4d	46	230-232	$C_{25}H_{20}Cl_4N_2$ (490.26)	61.25 (60.32)	4.11 (3.92)
5	24	201-203	$C_{23}H_{18}Cl_2N_2$ (393.31)	70.24 (70.50)	4.61 (4.53)

site site of **1**. The aziridine rings of **4** were very stable to acidic or alkaline conditions and to the usual nucleophiles. All the attempts at ring-opening reactions were unsuccessful.

EXPERIMENTAL

Melting points were uncorrected. The spectra were recorded on the following instruments; ir, JASCO A-102; ^{1}H-nmr, JEOL JMN-PMX; ms, JEOL JMS-DX 300. Elemental analysis was performed on a Shimadzu UM-3B microanalyzer. 2,4-Diphenyl-3*H*-1,5-benzodiazepine (**1a**) was prepared according to the literature method [9].

7-Chloro-2,4-diphenyl-3*H*-1,5-benzodiazepine (**1b**).

This compound was prepared from 4-chloro-*o*-phenylenediamine and dibenzoylmethane in 35% yield in the similar manner as **1a**, mp 163-165° (lit [10], mp 165-167°).

2,4-Bis(*p*-tolyl)-3*H*-1,5-benzodiazepine (**1c**).

This compound was prepared from *o*-phenylenediamine and bis(*p*-methylbenzoyl)methane in 41% yield in the similar manner as **1a**, mp 189-190° (ethanol); ir (potassium bromide): 3020, 2910, 1590, 1560, 1430, 1315 cm^{-1}; nmr (chloroform-d$_1$): δ 2.33 (s, 6H), 3.63 (broad s, 2H), 7.07-7.85 (m, 12H).

Anal. Calcd. for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21. Found: C, 85.16; H, 6.13.

A General Procedure for 7-Substituted 1a,2a-bisaryl-1,1,3,3-tetrahalogeno-1,1a,2a,3-tetrahydro-2*H*-bisazirino[1,2-*a*:2′,1′-*d*][1,5]benzodiazepines **4a-d**.

To a mixture of haloform (100 mmoles) and 50% aqueous sodium hydroxide (4 ml) were added **1** (2.0 mmoles) and benzyltriethylammonium chloride (20 mg). After the mixture was stirred at room temperature for 1-6 hours, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic solution was dried over magnesium sulfate and evaporated *in vacuo*. The residue was washed with methanol and recrystallized to give **4**.

1,3-Dichloro-1a,2a-diphenyl-1,1a,2a,3-tetrahydro-2*H*-bisazirino[1,2-*a*:2′,1′-*d*][1,5]benzodiazepine (**5**).

To a stirred mixture of lithium aluminium hydride (190 mg, 5 mmoles) in dry tetrahydrofuran (10 ml) was added **1a** (460 mg, 1.0 mmole). The mixture was stirred at room temperature overnight, quenched with a small amount of ethyl acetate, added with water, and then extracted with chloroform. The extract was dried over magnesium sulfate, and evaporated *in vacuo*. The residue was column chromatographed on silica gel with an eluent of chloroform to give **5**.

Table 2

Spectral Data of Compounds **4** and **5**

Compound	MS M$^+$, m/z	IR [a] cm^{-1}			NMR [b] δ, ppm
4a	460	3050	1580	1490	3.23 (1H, d, J = 15 Hz), 3.57 (1H, d, J = 15 Hz)
		1445	1350	1285	7.00-7.15 (m, 14H)
4b	636	3050	1580	1490	3.36 (1H, d, J = 15 Hz), 3.66 (1H, d, J = 15 Hz)
		1440	1350	1280	6.90-7.20 (m, 14H)
4c	494	3050	3010	1570	3.18 (1H, d, J = 15 Hz), 3.88 (1H, d, J = 15 Hz)
		1480	1445	1390	6.90-7.23 (m, 13H)
4d	488	3020	2910	1580	2.15 (s, 6H), 3.27 (d, 1H, J = 15 Hz), 3.48
		1490	1440	1350	(1H, d, J = 15 Hz), 6.62-7.15 (m, 12H)
5	392	3050	3020	1590	2.23 (1H, d, J = 14 Hz), 2.25 (s, 1H), 3.70
		1570	1485	1440	(1H, d, J = 14 Hz), 4.40 (s, 1H), 6.77-7.19 (m, 14H)

[a] Potassium bromide. [b] Obtained in deuteriochloroform.

REFERENCES AND NOTES

[1] L. Capuano and K. Gärtner, *J. Heterocyclic Chem.*, **18**, 1341 (1981).

[2] M. C. Aversa, A. Ferlazzo, P. Giannetto and F. H. Kohnke, *Synthesis*, 230 (1986).

[3] J. A. Deyrup, in "The Chemistry of Heterocyclic Compounds", Vol **42**, Part 1, A. Hassner, ed, John Wiley and Sons, Inc, New York, 1983, p 1.

[4] Y. Hamada and M. Sugiura, *Yakugaku Zasshi*, **99**, 1059 (1979).

[5] M. Sugiura, *Yakugaku Zasshi*, **99**, 807 (1979).

[6] M. Sugiura and Y. Hamada, *Yakugaku Zasshi*, (Tokyo), **99**, 1229 (1979).

[7] M. K. Meilahn, D. K. Olsen, W. J. Brittain and R. T. Anders, *J. Org. Chem.*, **43**, 1346 (1978).

[8] P. W. W. Hunter and G. A. Webb, *Tetrahedron*, **29**, 147 (1973).

[9] I. L. Finar, *J. Chem. Soc.*, 4094 (1958).

[10] R. L. Amey and N. D. Heindel, *Org. Prep. Proced. Int.*, **8**, 306 (1976).