Synthesis and Studies on Spectral Behaviour and Molecular Dynamics of 7-Aryl-4,5-dihydro-2-oxo-3*H*,8*H*-furo[3,4-*b*][1,4]diazepines

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A new series of 7-aryl-4,5-dihydro-2-oxo-3*H*,8*H*-furo[3,4-*b*][1,4] diazepines were prepared. Their ^{1}H nmr spectra have been interpreted in terms of the interconversion of two pseudo-boat conformers. Molecular-dynamics simulations at different temperatures on this type of compounds revealed a very small energy difference between these two conformers.

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The clinical importance and commercial success of 1,4-benzodiazepines has led to extensive synthetic studies on related compounds in the hope of finding agents that would be more specific for the various kinds of CNS disturbances.

Recently, we have demonstrated 4-aryl-3-hydroxy-2(5*H*)-furanones **1** to be a precursor for novel 1,4-diazepine derivatives, namely 7-aryl-4,5-dihydro-2-oxo-3*H*,8*H*-furo[3,4-*b*][1,4]diazepines **2**. In the present paper we report on the synthesis of a new series of type **2** compounds (Table 1) as well as a novel observation on their spectral behaviour.

Since the preferred conformation of a biologically active substance in solution can be considered as approximating the shape in which it exercises its pharmacological activity, we have inspected the ^{1}H nmr spectra of **2** to get more detailed information on the shape of type **2** compounds in solution. The protons of the ethano-fragment of **2** appear at room temperature only as two singlet signals at δ 3.59-3.61 and 4.17-4.20 ppm instead of the expected ABCD pattern (Table 1). From a stereochemical point of view the heptatomic ring of **2** can be regarded as a cycloheptadiene system, oscillating between two limiting pseudo-boat conformations, which interconvert through a quasi-planar transition state. Thus, we could interpret the room temperature spectra of **2** as being due to the population of conformers **A** and **B** which rapidly interconvert on the nmr time scale, so that the observed resonance parameters are averaged values of existing equilibria. In order to test our hypothesis a temperature dependence ^{1}H nmr spectra of **2b** in deuteriodichloromethane as a prototype

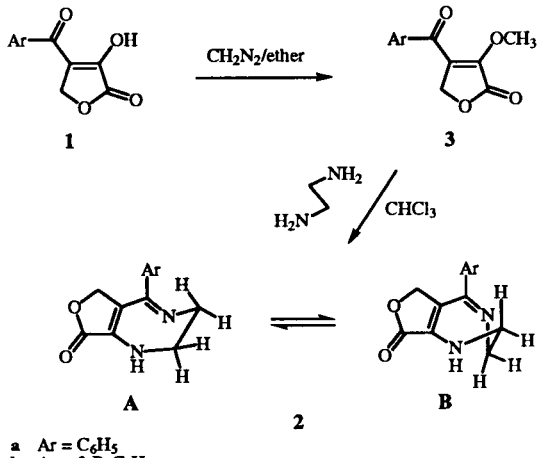
Table 1

Physical Data for 7-Aryl-4,5-dihydo-2-oxo-3*H*,8*H*-furo[3,-4-*b*][1,4]diazepines **2b-c**

Compound No.	mp °C	Molecular Formula	Analysis (%) Calcd./Found C	H	N	^{1}H nmr (deuteriochloroform)	MS (m/z) (relative intensity) M$^+$	M$^+$-1	M$^+$-1-CO_2	M$^+$-1-CO_2-HCN
2b	174	$C_{13}H_{11}BrN_2O_2$	50.84 50.81	3.61 3.57	9.12 9.20	3.59 (bs, 2H, CH, R), 4.20 (bs, 2 H, RCH_2), 4.77 (s, 2H, CH_2O), 5.55 (bs, 1H, NH), 7.26-7.62 (2m, 4H, ArH)	306, 308 (99, 98)	305, 307 (98, 98)	261, 263 (35, 35)	234, 236 (9, 8)
2c	165	$C_{13}H_{11}BrN_2O_2$	50.84 50.82	3.61 3.65	9.12 9.18	3.60 (bs, 2H, CH_2R), 4.20 (bs, 2H, RCH_2), 4.76 (s, 2H, CH_2O), 5.48 (bs, 1H, NH), 7.33, 7.54 (2d, 4H, ArH)	306, 308 (89, 89)	305, 307 (88, 100)	261, 263 (31, 30)	234, 236 (9, 10)
2d	200	$C_{14}H_{12}N_2O_4$	61.76 61.6S	4.44 4.60	10.29 10.41	3.60(bs, 2H, CH_2R), 4.17 (bs, 2H, RCH_2), 4.76 (s, 2H, CH_2O), 5.38 (bs, 1H, NH), 6.00 (s, 2H, OCH_2O), 6.80, 6.87, 6.96 (d, d, s, 3H, ArH)	272 (100)	271 (70)	227 (50)	200 (10)
2e	211	$C_{16}H_{18}N_2O_5$	60.37 60.31	5.70 5.68	8.80 8.92	3.61 (bs, 2H, CH_2R), 3.86, 3.89 (2s, 9H, 3 OCH_3), 4.19 (bs, 2H, RCH_2), 4.84 (s, 2H, CH_2O), 5. 50 (bs, 1H, NH), 6.68 (s, 2H, ArH)	318 (100)	317 (31)	273 (40)	246 (4)

The furo[3,4-*b*][1,4]diazepine derivatives **2b-e** were prepared as shown in the Scheme. The 4-aroyl-3-methoxy-2(5*H*)-furanones **3b-e** were obtained from the corresponding compounds **1** by treatment with diazomethane. The structure of **3** is supported by spectral data and elemental analyses (Table 2).

Scheme



a Ar = C_6H_5
b Ar = 3-BrC_6H_4
c Ar = 4-BrC_6H_4
d Ar = 3,4-$OCH_2OC_6H_3$
e Ar = 3,4,5-$(CH_3O)_3C_6H_3$

Table 2

Spectral Data for 4-Aroyl-3-methoxy-2(5*H*)-furanones **3b-e**

Compound No.	^1H NMR ($CDCl_3$)	MS (m/z) (relative intensity)			
		M+			
3b	4.06 (s, 3H, OCH_3),	296, 298	281, 283	217	183, 185
	5.04 (s, 2H, OCH_2),	(38, 35)	(11, 10)	(55)	(95, 100)
	7.39, 7.74, 7.97	155, 157	141	131	
	(m, m, s, 4H, ArH)		(63, 63)	(17)	(12)
		76	75		
		(83)	(62)		
3c	4.01 (s, 3H, OCH_3),	296, 298	281, 283	217	183, 185
	5.10 (s, 2H, OCH_2),	(28, 31)	(9, 9)	(36)	(100, 97)
	7.67, 7.90 (2d, 4H,	155, 157	141	131	
	ArH)	(51, 53)	(10)	(12)	
		76	75		
		(68)	(62)		
3d	3.96 (s, 3H, OCH_3),	262	185	176	149
	5.00 (s, 2H, OCH_2), 6.11	(53)	(15)	(11)	(100)
	(s, 2H, OCH_2O), 6.99,	121	92	91	
	7.38 (d, m, 3H, ArH)	(37)	(15)	(68)	
3e	3.91, 3.93, 3.97, 4.00	308	195	168	140
	(4s, 12H, 4 OCH_3), 5.04	(100)	(53)	(13)	(11)
	(s, 2H, OCH_2), 7.17	91			
	(2d [overlaped], 2H, ArH)	(25)			

was obtained (Figure 1). It showed that on lowering the sample temperature the sharp singlets of the ethano-fragment broaden then split up to fine structure. However, even though at 223K the conformational equilibrium slowed down but neither froze nor shifted toward a single conformer as evident by a 2D-COSY experiment.

To gain more information on the shape of such conformers molecular dynamics on **2a**, as a prototype, at 304, 223, and 200K were investigated. This study revealed that the molecule exhibits a considerable amount of flexibility of the seven-member ring. It generally maintained a

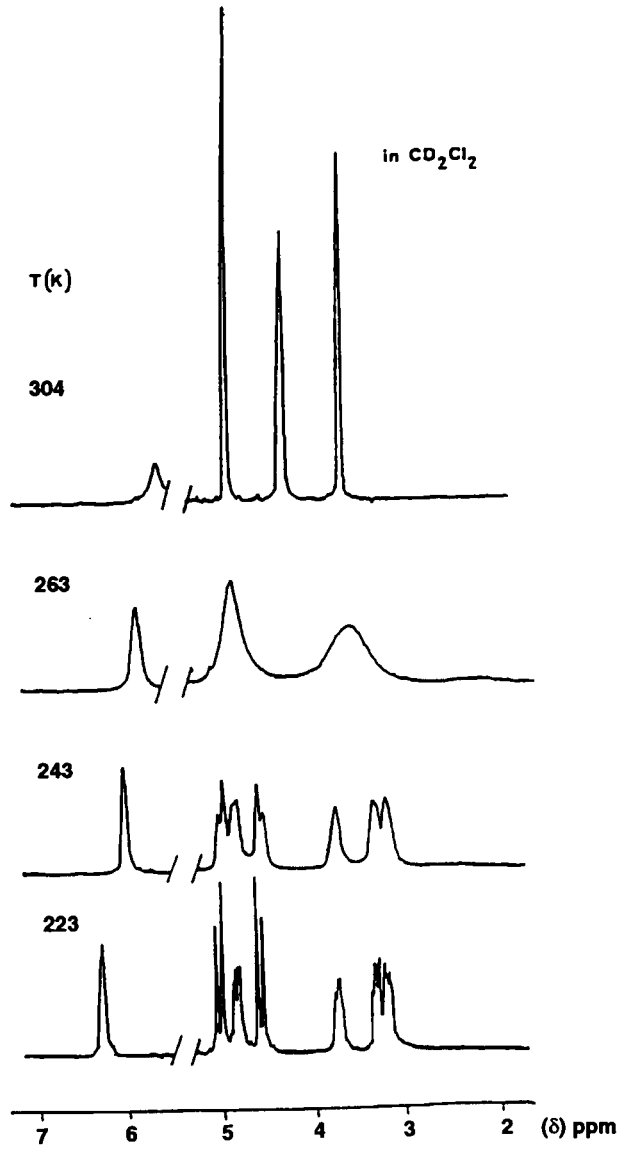


Figure 1.

Table 3

Dihedral Angles, Energies, and Residence Times for Two Conformations

Temperature (K)	Conformer [1]	H2A-H3A Dihedral Angle (degrees)	Minimized Energy (kcal/mol)	% Residence Time [2]
200	positive	81	44.0	42
	negative	-40	43.4	58
223	positive	73	44.2	54
	negative	-80	44.5	46
304	positive	82	44.5	50
	negative	-77	44.0	50

[1] Refers to averaged coordinates for frames with positive or negative values of the H11-H12 dihedral angle. [2] Determined by the number of frames the particular dihedral angle is found divided by 1000 and expressed as a percentage.

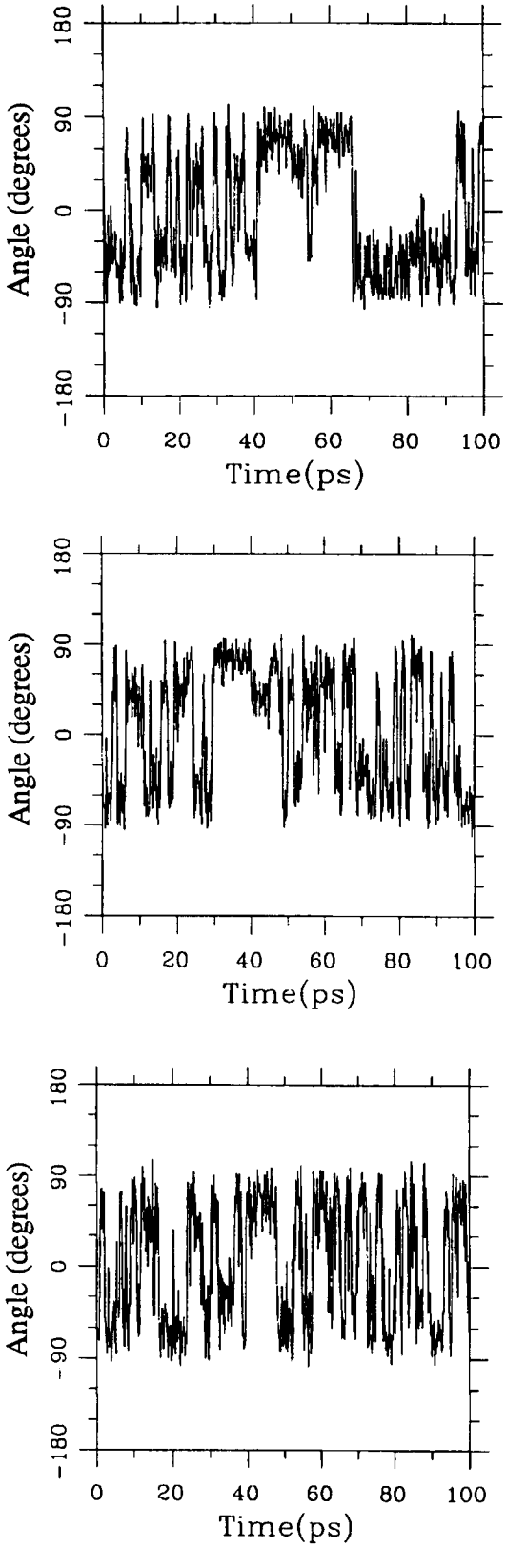


Figure 2. The variation of the H2A-H3A dihedral angle during the molecular dynamics simulation at (a) 200K, (b) 223K, and (c) 300K.

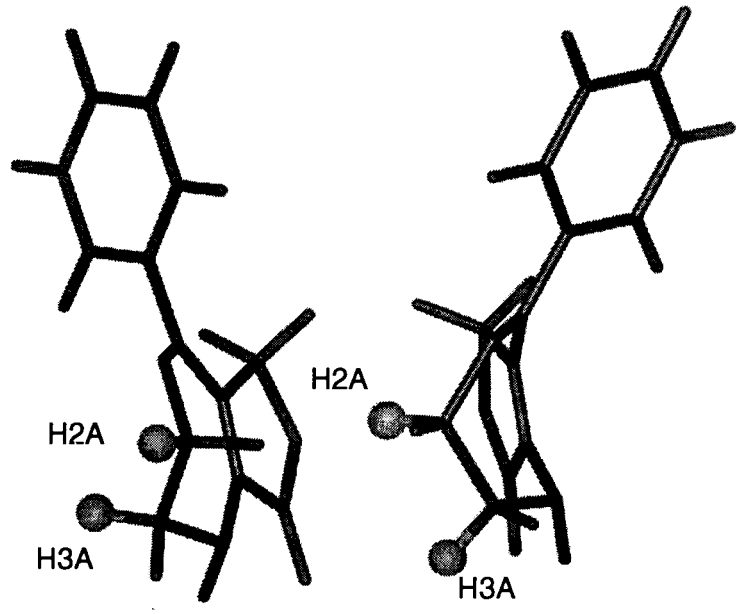


Figure 3. Represented are the two averaged conformations from the 200K MD run. The structure on the left is with the positive H2A-H3A angle (81°), on the right the negative angle (-40°). The views are from the C3 (or bow of the pseudo-boat conformation of the seven-member ring). The five member ring is back into the plane of the image. The H2A and H3A atoms are shown shaded.

boat conformation with C3 (the carbon closest to the sp^2 nitrogen atom) forming the bow and the C-C bond between C5a and C8a forming the stern. However, due to the flexibility of the ring, the structure frequently deviates from the boat conformation. Rotation of the aryl ring about the bond to the seven-member ring was also evident. However, using the C2 and C3 hydrogen dihedral angles (Figure 2) as a marker, the model appears to be interchanging between two conformations. Generally, the conformations differ in the H2A-H3A dihedral angle being either positive or negative.

Regions of the molecular dynamics simulations were selected based on the simple two state of either a positive or negative H2A-H3A dihedral angle. An average conformation was determined as described in the experimental section. The two conformations (Figure 3) are inversions of the boat conformation for the seven-member ring. The final energies for the two averaged minimized structures differ by no more than 0.6 kcal/mol at any temperature. The dihedral angles H2A-H3A and H2B-H3B differ by up to 6°. However, the trends reported here are applicable with either dihedral angle being used as the reference.

EXPRIMENTAL

Melting points were determined on a Mel-Temp melting point apparatus and are not corrected. Analytical tlc was performed using ascending technique with EM silica gel 60 F254 precoated on plastic sheets. The ^1H nmr spectra were recorded on a Bruker

AC-250 spectrometer. Chemical shifts are expressed in the δ scale in parts per million down field from internal tetramethylsilane. The molecule **2a** was modeled using InsightII (version 2.3.5) and Discover 94.0, both obtained from Biosym Technologies.

4-Aroyl-3-methoxy-2(5*H*)-furanones **3b-e**.

General Procedure.

A solution of a type **1** compound (5 mmoles) in ether or methanol was treated with an etheral solution of diazomethane until the nitrogen bubbling ceases. After evaporating off the solvent the formed type **3** compounds were isolated as oils and were used without further purification for the preparation of the diazepines **2** compounds. Pertinent ms and ^{1}H nmr data are given in Table 2.

7-Aryl-4,5-dihydro-2-oxo-3*H*,8*H*-furo[3,4-*b*][1,4]diazepines **2b-e**.

General Procedure.

A solution of **3** (5 mmoles) in chloroform (75 ml) was treated with 1,2-ethylenediamine (6 mmoles) and stirred overnight at room temperature. The solvent was then evaporated. The resulting residue was purified by crystallization from methanol and/or subjecting to flash column chromatography on Silica gel with ethyl acetate as an eluent. Yields and physical properties are summarized in Table 1.

Molecular Modeling Procedures.

The initial model was subjected to an energy minimization procedure using the ESFF forcefield and a steepest descents minimization procedure followed by a molecular dynamics simulation with a 1000 step equilibration phase and a subsequent 100,000 step data phase. Each step was 1.0 fs and a history of the trajectory was maintained at every 100 steps. Three dynamics simulations were completed at temperatures of 200, 223, and 304K. During all dynamics and minimization phases, a dielectric constant of 1.0 was maintained. Data was only collected and analyzed after the equilibration period.

Selected ranges based on a positive or negative value for the H2A-H3B dihedral angle were chosen from the molecular dynamics trajectories and analyzed. The coordinates for these ranges were averaged to obtain an average conformation. These averaged conformations were then minimized using a combination of steepest descents, conjugate gradients, and Newton-Rapheson techniques. Residence times in each range were determined by simply counting the number of frames that the model maintained at a given dihedral angle.

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REFERENCES AND NOTES

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