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Stereoelectronic Effects in the Conformational Behavior and Ring Formation of some N,N'-Dimethyl- and N,N'-Diacetyl-1,5-Dioxa-4,8-diazadecalins.

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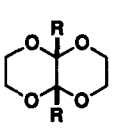
Abstract. *A series of 4,8-dimethyl- and 4,8-diacetyl-*cis*-octahydro-[1,4]oxazino[3,2-b]-1,4-oxazines (title compounds) **4** and **7** respectively, were synthesized and studied using ^{1}H- and ^{13}C-NMR techniques. Conformational analysis of **4** showed a strong preference for conformers possessing an anti-N/gauche-O array vs an anti-O/gauche-N relationship (ΔG^{O}= 0.88 Kcal/mol). However **7b** exists exclusively as an anti-O/gauche-N conformer with a free energy of activation for the amide rotation barrier of 11.6 Kcal/mol (248 K). The stereoelectronic features of the C-N-C-O-C moieties of **4** and **7** are emphasized. A general reaction pathway is also discussed.*

Introduction

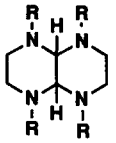
Conformational analysis of heterocyclic systems derived from the condensation of glyoxal with diamines[1] and also from the acetalization of α-diketones[2] has attracted much attention. This interest stems from their ease of preparation[1,3], their peculiar stereoelectronic features[4,5], and their unusual conformational properties[4,6]. In particular the array of C-O or C-N bond dipoles in these compounds results in enhanced anomeric effects[7], giving rise to lone pair-lone pair and n_{π}-σ^{*} interactions. A number of studies have shown that only the *cis*-isomer of 1,4,5,8-tetraoxadecaline (TOD) **1a** or derivatives are obtained from such acetalization reaction[6]. Compound **1b** exhibits a ring inversion process between two double-chair conformations in solution[5]. Extensive conformational studies of 1,4,5,8-tetraazadecalins (TAD) **2** isolated in the condensation of glyoxal with diamines reported by Fuchs[4] have shown that those compounds exist in solution in a double chair conformation with *trans*-configuration; the *cis*-isomers were usually observed as a result of a reversible isomerization of the *trans*-isomer.

Surprisingly there are few reports related to dioxadiazadecalin systems in the literature[8]. In previous studies[9-11] we described that the condensation of β-aminoalcohols with 2,3-butanedione provided a direct route to bicyclic nitrogen heterocycles related to tetraaza and tetraoxadecalins, namely octahydro-[1,4]oxazino[3,2-b]oxazines **3**. In fact **3** exists, both in solution and in the solid state, exclusively in a rigid *cis* configuration with an anti-N/gauche-O array. This ring system contains two N-C-O moieties which belong to the X-C-Y (X, Y = hetero atoms) grouping known to exhibit peculiar stereoelectronic effect[5]. The latter with X = Y = O were,

and still are, being extensively investigated in recent years as what is generally called anomeric effect[7]. To the best of our knowledge studies concerning the relative stabilities of systems which exhibit competitive n_{π}-σ^* interactions of nitrogen or oxygen lone pairs and σ^* (C-O) or σ^*(C-N) orbitals directing the conformational behaviour of a molecule are limited to a 1,3-oxazine systems both theoretically and experimentally[12]. Pursuing our studies on substrates **3** we were interested to see how the conformation of these systems is affected by methyl substitution on nitrogen or by imparting the nitrogen (partial) trigonal character. We now report the results from this study in which the room temperature and variable temperature ^1H and ^{13}C n.m.r. spectra have been analyzed for 4,8-dimethyl and 4,8-diacetyl-4a,8a-dimethyloctahydro-(4α,8aα)-[1,4]oxazino[3,2-b]oxazine derivatives **4, 5** and **7**.



1a, R=H
1b, R=Me



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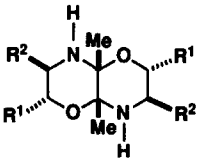
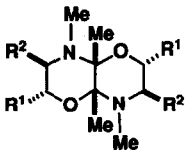


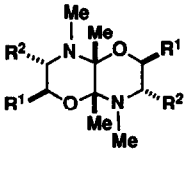
3a, $R^1=R^2=H$
3b, $R^1=Me$, $R^2=H$
3c, $R^1=H$, $R^2=Me$

Results.

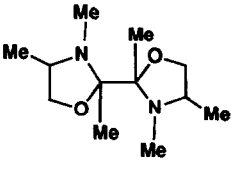
Synthesis of N,N'-dimethyl derivatives **4.** The syntheses of **4**[13] have been carried out by the reaction of octahydro[1,4]oxazino[3,2-b]oxazines **3a-c** with excess of neat dimethyl sulfate[14] at 50°C. After suitable work-up compounds: **4a** (60%), **4b** and **5b** as a 7:1 mixture of diastereomers (70%) were isolated. However, the reaction of **3c** afforded three isomeric species in a 6:2:1 ratio. The minor component of this mixture was assigned to the bis-oxazolidine **6**, and the other two to a diastereomeric mixture of compound **4c** and **5c.**



4 a-c



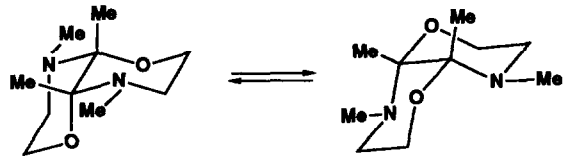
5 b,c



6

(**a**, $R^1=R^2=H$; **b**, $R^1=Me$, $R^2=H$; **c**, $R^1=H$, $R^2=Me$)

Dynamic NMR study of compound ***4a.*** The temperature dependence of the ^1H-, and ^{13}C-NMR spectra, recorded in different solvents for compound **4a**, are summarized in Tables 1 and 2. At ambient temperature the ^1H- and ^{13}C-NMR spectra show that **4a** is undergoing a dynamic process. These spectra are resolved in well defined signals by increasing the temperature. The ethylene fragment of **4a** should give rise to an ADMX pattern in the ^1H-NMR spectrum (363 K, DMSO-d_6) with appropriate gauche and anti coupling constants, as is indeed observed. From Table 1, it can be deduced that the vicinal coupling constants J_{ea} and $J_{e'a'}$ are almost equal; this is consistent with **4a** possessing the *cis*-configuration, while undergoing a rapid chair-chair interconversion over room temperature as shown in Scheme 1.



Scheme 1

Non chair conformations could be similarly excluded[15] ($R = J_{trans}/J_{cis} = 1.7$). The ^{13}C-NMR spectrum of **4a** exhibited a number of signals that correspond to the half of the molecule and was fully consistent with two fused six membered rings in a highly symmetrical structure. In a variable temperature study in $(CD_3)_2CO$, the dynamic behaviour could be analyzed. At 303 K the ^{13}C-NMR resonances of **4a** are in coalescence particularly the signal corresponding to the resonance of the bridgehead methyl group which is almost inobservable. On cooling it split into two new signals attaining a $\Delta\delta$ of 8.4 ppm. The complete spectrum

Table 1. ^{1}H-NMR Data of *Cis*-octahydro-[1,4]oxazino[3,2-b]oxazines 3a and 4a[a].

		Chemical Shifts						Coupling Constants					
Temp °C	*Conformer[a]*	H_a^O	H_e^O	H_d^N	H_e^N	*Me(ang)*	*Me-N*	$J_a^Oe^O$	$J_d^Ne^N$	$J_a^Oe^N$	$J_a^Od^N$	$J_e^Oe^N$	$J_e^Od^N$
30	**3a**	3.94	3.77	3.44	2.43	1.40	-	-11.4	-11.1	3.1	11.9	1.0	3.8
90	**4a**	3.67	3.72	2.87	2.27	1.21	2.20	-11.2	-11.2	3.7	9.2	4.0	4.0
30	**4a**	3.8	3.5	2.8	2.4	1.2	2.2						
-40	**4a-I[b]**	3.61	3.45	2.86	1.99	1.27	2.12	-11.3	-11.1	2.8	12.2	<0.5	3.9
-40	**4a-II[b]**	3.95	3.08	2.53	2.44	0.88	1.94	-10.5	-11.7	3.4	11.5	<0.5	3.6

a) For **3a** in $CDCl_3$, for **4a** in DMSO-d_6 above 25° C and in $(CD_3)_2CO$ below 25° C

b) **4a-I** and **4a-II** were respectively assigned as the major and minor conformers, observed in spectra

showed, below coalescence, ten sharp signals. These were assigned to the two conformers **4a-I** and **4a-II**, which interconvert by a *cis*-decaline type ring-inversion coupled with N-inversion. The conformers **4a-I** and **4a-II** are, hence, not equally populated. In this equilibrium mixture at 230 K in $(CD_3)_2CO$ solution the ratio **4a-I/4a-II** is about 7/1. Equilibrium constants were obtained from the ^{13}C-NMR spectra taken at different temperatures, using the $\underline{C}H_3$-C4a(C8a) resonances, due to their larger $\Delta\delta$ between the same signal in each conformer[16]. Using a regression analysis on those data, according to a Van't Hoff plot, free energy differences ΔG^o were calculated at different temperatures. In this way we have an extrapolation of $\Delta G^o_{I\text{-}II} = 0.88$ Kcal mol^{-1} at 298 K. Hence the estimative value of 0.88 Kcal mol^{-1} is then taken as the free energy difference between two anomeric effects $n_{\pi N}$-σ^*(C-O) *vs* $n_{\pi O}$-σ^*(C-N) in compound **4a.** The corresponding exchange rate constants at coalescence temperature were thus obtained and kinetic data for the ring-inversion process were calculated using Eyring equation[17]

Table 2. ^{13}C-NMR Data of *cis*-octahydro-[1,4]oxazino[3,2-b]oxazines 3a, 4a in $(CD_3)_2CO$.

T (°C)	*30*	*50*	*-40*	
Compound	**3a**	**4a**	**4a-I**	**4a-II**
δC(O)	63.4	61.6	61.7	58.4
δC(N)	39.3	49.6	48.1	51.5
δMe(ang)	21.8	19.4	19.6	11.2
δC4a(8a)	84.2	88.1	87.4	87.4
δMe-N	-	37.0	37.1	35.3
K[a]		4.40	6.03	
$\Delta G^o_{I\rightleftharpoons II}$ (Kcal/mol)	0.88	0.83		

a) K as the equilibrium constant of the chair-chair interconversion [I]/[II].

at the coalescence temperature of 303 K, $\Delta G_c^{\#}{}_{303}$ was found to be 13.20 Kcal/mol. This value is in good agreement with that observed by Fuchs[4] in *cis*-1,5-dimethyltetraazadecalines (12.3 Kcal/mol) considering the additional interactions due to the bridgehead methyl groups.

The coupling constants of the peripheral ethylene protons observed at 230 K are quite similar in both conformers, however the **4a-I** conformer appears as an ADMX pattern while conformer **4a-II** showed an ABMX pattern. Since spectral parameters of compound **3a** and **4a-I** are quite similar, owing to the expected magnetic effects due to N-methylation, we tentatively assign the anti-N conformation to the **4a-I** conformer as in **3a** and the anti-O for the minor **4a-II** conformer.

For the methyl substituted derivatives **3b** and **3c**, N-methylation would freeze each conformer. In fact no dynamic behaviour has been observed in diastereomeric compounds **4** and **5 b-c**. Analysis of ^{1}H-, and ^{13}C-NMR spectra (Tables 3 and 4) of those mixtures clearly indicates rigid *cis*-configurations with the peripheral methyl groups in equatorial positions in analogy with their precursors **3b** and **3c** as it has been deduced from the comparison of the coupling constants summarized in Table 3.

Assignments of configuration of each diastereomer **4** and **5** have been carried out by NOE's irradiation experiments (see Figure 1).

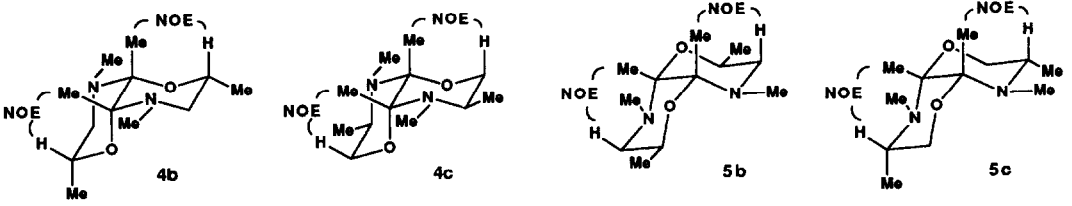
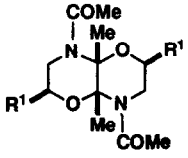


Figure 1

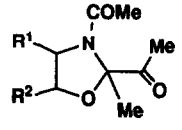
Irradiation of the bridgehead methyl signal in the major isomer **4b** results in an enhancement of the axial proton resonances in α-position to the oxygen atom along with the N-methyl resonance. However when the

minor diastereomer **5b** was irradiated, signal enhancements were observed on the axial proton resonances in α-position to the nitrogen atom along with the N-methyl signal. From this set of experiments the major diastereomer **4b** could be assigned to an anti-N conformer, while the minor **5b** diastereomer could be assigned to an anti-O conformer. The above experiments were also carried out with compounds **4c** and **5c** with similar results. Thus allowing for the assignment of the major diastereomer **4c** as the anti-N conformer and the anti-O for the minor isomer **5c**. These assignments also support those found in conformers **4a-I** and **4a-II**. It should be pointed out that in no case isomerization or interconversion processes between the diastereomeric pairs of **4b/5b** or **4c/5c** have been observed. Compound **6** obtained as a minor component in the methylation of **3c** has been characterized mainly by spectroscopic means. The ^{1}H-NMR spectra showed geminal and vicinal coupling constants in the peripheral O-CH_2-CH_2-N- moiety are of diagnostic value, the former are ca. 9.7 Hz[1a] and the latter give a value of R = 0.62[15] as typical for five membered rings (Table 3). Furthermore the ^{13}C-NMR spectra (Table 4) exhibits resonances of ketalic carbon at 98.4 ppm similar with that found in 2-acetyl-2,3-dimethyl-1,3-oxazolidine[13].

Synthesis of N,N'-diacetyl derivatives **7**. The synthesis of N,N'-diacetyl derivatives **7** has been performed by reaction of **3** with appropriate acylating agents namely acetyl chloride or acetic anhydride depending upon the starting compound **3**.



7a: R^1= H
7b: R^1=Me



8a: $R^1 = R^2$= H
8b: R^1=Me, R^2= H

The reaction of **3a** with acetyl chloride in benzene led to a product that precipitates out of solution (83%) which was assigned as the diacetylated product **7a** namely 4,8-diacetyl-4a, 8a-dimethyl-*cis*-octahydro(4aα, 8aα)-[1,4]oxazino[3,2-b]-oxazine. While a much slower reaction with acetic anhydride in benzene yields exclusively 1,2-diacetyl-1,3-oxazolidine **8a**. The reaction of compound **3b** with acetic anhydride in CCl_4 afforded after suitable work-up **7b** (40%), **8b**, (two diastereomers in 2:1 ratio) and N-(2-hydroxypropyl)acetamide. While the reaction with the more reactive acetyl chloride led only to **8b**. All attempts to synthesize the corresponding compound **7c** were unsuccessful yielding in most cases N-acetyl-2-amino-1-propanol as the only reaction product.

The ^{1}H-, and ^{13}C-NMR spectral parameters of **7a** (Table 5) are in close agreement with a *cis*-configuration, on the strength of the comparison with the known starting material configuration **3a**. However **7a** showed a fast decomposition reaction in solution. The presence in the ^{1}H NMR spectrum of signals attributable to N-acetyl-1,2-aminoethanol precludes its analysis in solution by dynamic NMR.

Table 3. ^{1}H-NMR Data[a] of *cis*-octahydro-[1,4]oxazino[3,2-b]oxazines 3-5 and bis-oxazolidine 6

			Chemical shifts						Coupling constants						
Cpd[a]	*R*^{1}	*R*^{2}	H_a^O	H_e^O	H_d^N	H_e^N	*Me(ang)*	*MeCH*	*Me-N*	$J_a^O{}_e^O$	$J_d^N{}_e^N$	$J_a^O{}_e^N$	$J_a^O{}_d^N$	$J_e^O{}_e^N$	$J_e^O{}_d^N$
3b	Me	H	3.97	-	3.04	2.43	1.38	1.13	-	-	-10.8	2.8	10.8	-	-
3c	H	Me	3.44	3.67	3.54	-	1.38	0.89	-	-10.5	-	-	10.5	-	3.1
4b	Me	H	3.75	-	2.63	2.07	1.34	0.98	2.23	-	-11.0	3.0	11.1	-	-
5b	Me	H	4.18	-	2.29	2.64	1.03	0.99	2.09	-	-11.3	3.0	11.3	-	-
4c	H	Me	3.60	3.83	3.46	-	1.72	0.95	2.56	-10.9	-	-	10.9	-	3.8
5c	H	Me	4.10	3.35	2.82	-	1.42	1.02	2.33	-10.7	-	-	10.7	-	4.1
6			4.04	3.57	2.82	-	1.50	1.13	2.53	-7.2	-	-	9.7	-	6.1

a) H_a^O, H_e^O, H_a^N, H_e^N are referred to the position and disposition of the hydrogen in the peripheral ethylene protons; a: axial, e: equatorial
b) **4** and **5** are referred, respectively, the major and minor diastereomers observed in the spectrum of the N-methylated product

Table 4. ^{13}C-NMR Data of *cis*-octahydro-[1,4]oxazino[3,2-b]oxazines 3-5 and bis-oxazolidine 6

Cpd[a]	R^1	R^2	C(O)	C(N)	C4a(8a)	CH_3(ang)	CH_3-N	CH_3CH
3b	Me	H	67.7	45.4	83.3	22.0	-	-
3c	H	Me	69.6	42.8	84.1	21.7	-	17.1
4b	Me	H	65.4	54.7	86.3	19.7	36.7	18.7
5b	Me	H	62.4	57.9	86.9	11.0	35.2	18.4
4c	H	Me	68.1	49.0	87.7	20.2	32.3	16.0
5c	H	Me	64.5	53.6	87.7	12.8	31.0	16.0
6			65.8	54.8	98.4[b]	19.1	36.9	18.9

a) **4** and **5** indicate, respectively, the major and minor diastereomers observed in the spectrum of the N-methylated product
b) $\delta(^{13}C)$ of C2

However compound **7b**, as an stable crystalline solid was fully analyzed. The ^{1}H-NMR spectra at 298 K in $CDCl_3$ did not show the presence of diastereomeric mixtures. The peripheral O-C<u>H</u>(CH_3)-C<u>H</u>$_2$-N- protons exhibit an ABX pattern and the coupling constants, which are almost independent of the solvent, confirm an equatorial orientation of the peripheral methyl groups and was fully consistent with stable highly symmetrical structure resembling those of **3b**. The conformation in solution of **7b** has been elucidated by the NOE irradiation technique. In this manner irradiation of the bridgehead methyl signals showed an enhancement on the resonances corresponding to the axial protons in α-position to the nitrogen (6%) which should be in a 1,3-diaxial relationship (see Figure 2). This clearly suggest an anti-O conformation, which is opposite to that found in the major diastereomer of the N-methylated **4b**. It is noteworthy to point out that the starting material **3b** possesses an opposite anti-N configuration.

Table 5. NMR Data of 7 and 8

Compound:	**7a**	**7b**[a]	**8a**	**8b**[b]
Spectral data:				
^{13}C-NMR ($CDCl_3$), δ:				
C=O	-	-	201.2	201.8
N-C=O	172.0	173.0	167.7	168.6
C4a(8a)	87.5	87.3	94.0	94.6
C2(C6)	60.4	64.1	65.5	72.9(73.5)
C3(C7)	40.0	47.3	46.1	52.7(53.2)
CH_3CON	24.1	24.4	23.4, 22.8	24.4, 22.9
CH_3C4a(8a)	23.0	22.4	18.6	20.1
CH_3C2(6)	-	18.7	-	18.1
^{1}H-NMR ($CDCl_3$), δ:				
H_a^O	4.01	4.03 (4.02)		
H_e^O	m	-		
H_a^N	m	2.97(2.94)		
H_e^N	3.70	4.15(4.09)		
Me(ang)	1.64	1.55(1.53)	1.60	1.6 (1.7)
Me-C	-	1.23(1.20)	-	1.5 (1.4)
Me-CON	2.34	2.33(2.23)	2.13	2.20
Me-CO	-	-	2.10	2.10
$J_a^{O_e}O$		-		
$J_a^{O_a}N$		9.7(9.8)		
$J_a^{O_e}N$		3.6(3.7)		
$J_c^{O_a}N$		-		
$J_e^{O_e}N$		-		
$J_e^{N_a}N$		-13.8(-13.6)		

a) In brackets in $(CD_3)_2CO$ (30^o C)
b) In brackets signals corresponding to a diastereomer.

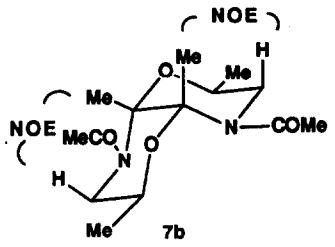


Figure 2

Dynamic NMR study of compound **7b.** The temperature dependence of the ^{1}H- (400 MHz), and ^{13}C-RMN (100.6 MHz) spectra of **7b** showed the presence of a conformational process assigned to the amide group rotation and N-inversion. Since the presence of methyl substituents at the peripheral positions precludes the existence of a chair-chair interconversion similar to that observed in compounds **4b** and **4c**.

The ^{13}C-NMR spectra of **7b** at 303 K and 203 K in $(CD_3)_2CO$ are depicted in Figures 3 and 4. Examination of both figures reveals that the homogeneous species at room temperature (where fast amide rotation takes place) transforms at 203 K into a mixture of two distinct rotamers I and II (Table 6) in *ca* 5:1 respectively. Following the variable temperature spectral changes as the temperature is lowered, a classic process of dynamic NMR coalescence was observed at T_c= 248 K for the signals of $\underline{C}H_3C4a(8a)$ which split at lower temperatures reaching a value of $\Delta\delta$ of 158.7 Hz. Using the approximation for the exchange rate of non interacting sites $K= \pi\Delta\delta/\sqrt{2}$ and $\Delta G_c^{\#} = 4.57T_c[10.2 + \log(T_c/K)]$ (Eyring equation) one obtains $\Delta G_c^{\#}$ = 11.6 ± 0.2 Kcalmol^{-1} in excellent agreement with Fuchs value of $\Delta G_c^{\#}$ (250± 5K) = 12 Kcal mol^{-1} for the amide rotation in tetraacyltetraazadecaline[18].

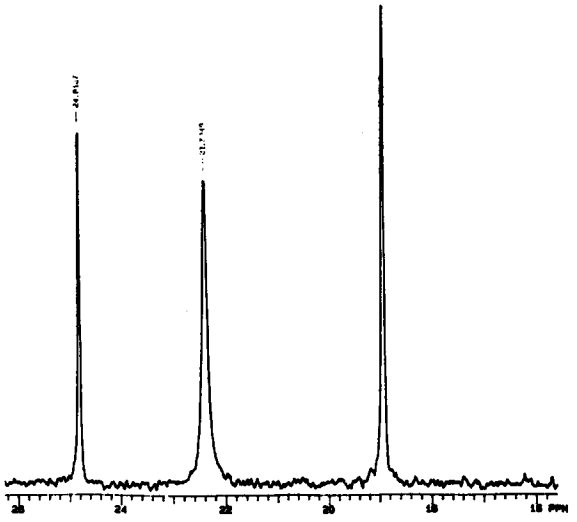


Figure 3. Detail of ^{13}C NMR of **7b** at 303K

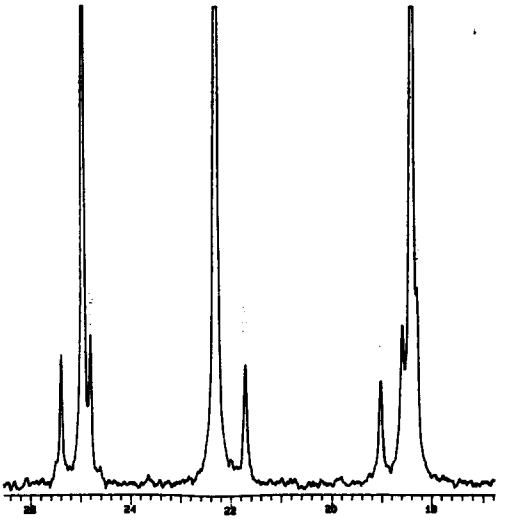
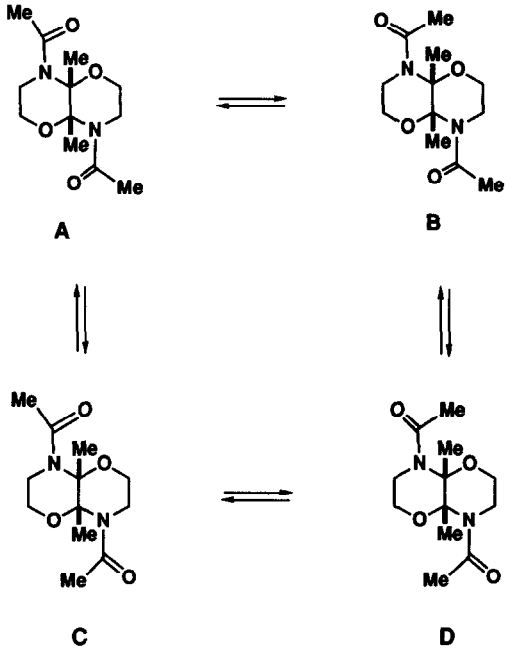


Figure 4. Detail of ^{13}C NMR of **7b** at 203 K

The conformational changes of compound **7b** observed in solution could be assigned to a conformational equilibria as depicted in Scheme 2

From the ^{13}C-NMR spectrum (Table 6) the resonances of the major rotamer below 248 K can be measured, showing a number of signals (7) that correspond to the halve of the carbon atoms in the molecule as a consequence of a high degree of symmetry. Both A and D conformers fulfill the symmetry requirements for the major component, but conformer D should not be the experimentally observed due to important steric interactions and pseudo-allylic ($A^{(1,3)}$)[18,19] strain present in this conformer. The system prefers, hence to assume conformation A. Conformers B and C are equivalent and correspond to the minor component (II) observed at 203 K in the spectra (see Figure 4).



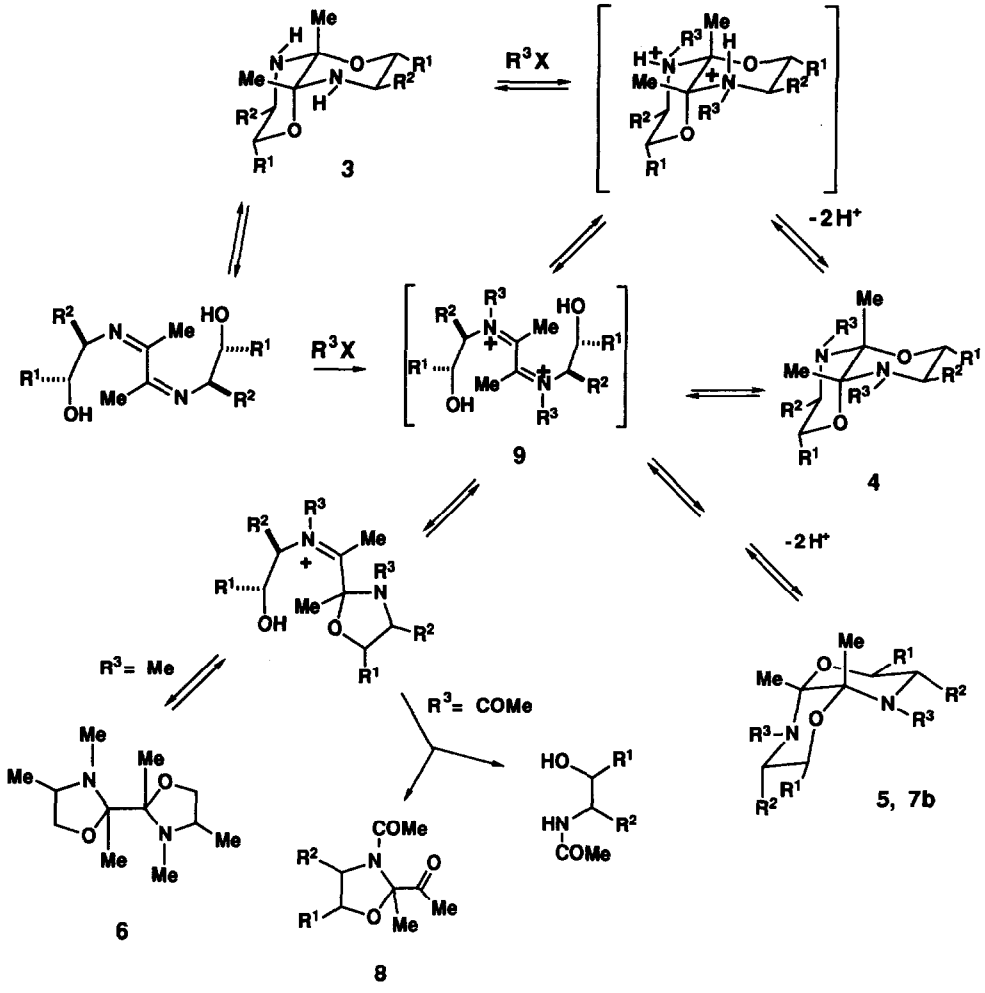
Scheme 2

Table 6. ^{13}C-NMR data of 7b at 203 K in $(CD_3)_2CO$

Rotamer	CO	C4a(8a)	C2(C6)	C3(C5)	$\underline{C}H_3CO$	CH_3(ang)	CH_3CH
I	173.9	87.2	64.1	47.2	24.6	22.3	18.4
II	173.7	87.6	64.5	50.0	25.4	22.3	19.0
	172.4	87.4	63.3	47.9	24.8	21.7	18.6

Discussion.

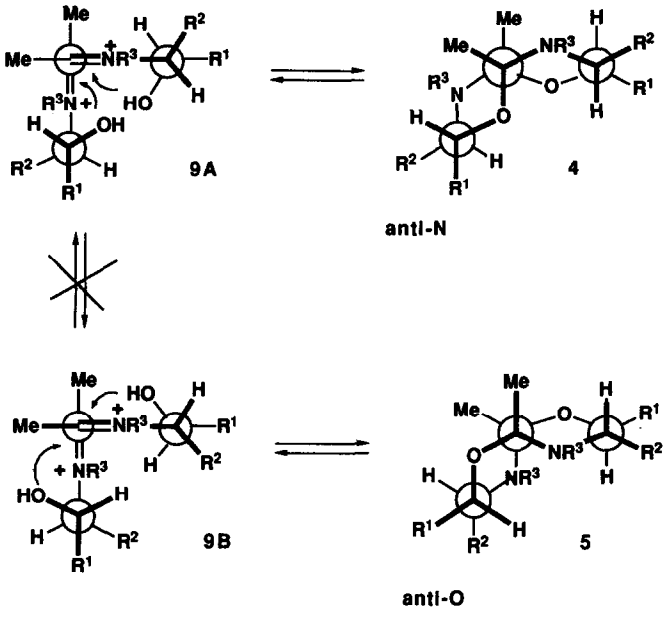
The conformational features observed in **4**, **5**, and **7** which were introduced in **3** by N-methylation and N-acetylation are in most cases a result of the hemiaminal ring chain tautomerism of the starting **3**[9,12]. A reaction pathway as depicted in Scheme 3 should account for the observed reactivity at nitrogen.



Scheme 3

Formation of products with an anti-N and or anti-O array, and the obtention of 5-membered ring type structures, e.g. **6**, **8** are indicative that the bis-iminium ion **9** could be the key intermediate in the postulated mechanistic sequence depicted in Scheme 3. It appears that the reactivity of **9** is controlled by steric and stereolectronic effects which are evenly balanced depending upon the substituent attached to the nitrogen atom. When in **9** bears a R^3= Me, the stereoelectronic effects may be present in the preferred 6-exo-trig cyclization mode. The stabilizing anomeric effects present in the major product **4** are mainly due to the two donating interactions between the two lone pairs of the $n_{\pi N}$ orbital and σ^*(C-O) bonds, which requires as a rough

estimate 0.88 Kcal mol^{-1} less than the $n_{\pi O}$-σ^*(C-N) interactions, resulting in a strong preference for the anti-N conformer. While **4a** exists in solution as a mixture of conformers (I and II) interconvertible by a cis-decaline type ring inversion process, the diastereomeric ratio found between **4b/5b** turns out from a preferred pathway of hydroxylic attack over one of the sides of the iminium bond, e.g. **9A** over **9B** in Scheme 4, since they are not interconvertible in solution.



Scheme 4

However if R^3 = COMe the lone electron pairs of the nitrogen atoms in the anti-N conformer are involved in the amidic resonance and the anomeric stabilization is due to the donating effect of the lone electron pair of the oxygen atoms (Figure 5). As a result the anti-N conformation is excluded.

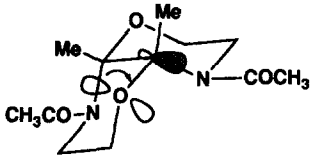


Figure 5

Thus in this latter case, the reactivity of the bis-acyliminium ion **9** should reflect 1) The higher energy barrier required to the double 6-exo-trig pathway as a result of the disability of the $n_{\pi N}$-σ^*(C-O) interaction. 2) The steric effects (peri interactions and allylic strain) developed in the transition state that would lead to the 6-exo-trig cyclization products. Therefore, **7c** was not formed, in this case 5-membered ring structures **8** are thermodynamically preferred.

Experimental.

Compounds **3a-c** were prepared according to ref. 9, 12. All reactions were carried out using freshly distilled solvents and reagents. Melting points were determined on a Büchi 512 apparatus and are uncorrected. IR were recorded on a Perkin Elmer 781 grating spectrophotometer. Silica gel (Merck Art. 9884, 230-400 mesh) was used for column chromatography. Analytical TLC was carried out on 0.20 mm Merck precoated silica gel plates (60 F_{254}), with detection by UV light, iodine or ethanolic phosphomolybdic acid solution. Mass spectra were determined with a Varian MAT 711 and a HP-5890A. Elemental Analyses were performed at the Instituto de Química Bio-Orgánica, C.S.I.C. Barcelona. ^1H and ^{13}C-NMR spectra were measured on spectrometers Brüker AM-400-WB (100.6 MHz for ^{13}C) and Varian XL300 MHz (75 MHz for ^{13}C). Chemical shifts are given in ppm from TMS. For ^1H and ^{13}C-NMR data of the following compounds see text: **4a** (Table 1, 2), **4**, **5b-c** (Table 3,4), **7** (Table 5, 6), **8** (Table 5).

General Procedure *for reaction of cis-octahydro-[1,4]oxazino[3,2-b]oxazines* **3** *with dimethyl sulfate.*

A stirred mixture of 1 eq. of the corresponding compound **3** and 2 eq. of dimethyl sulfate were warmed up at 50°C. When the mixture became homogeneous and transparent, a slightly exothermic reaction took place and stirring was continued at 50°C for 30 min. To the cooled solution, aq K_2CO_3 (20%), 10 ml, were added and the mixture was stirred for an additional 15 min. The resulting yellow solution was extracted with $CHCl_3$ (3x 10 ml). The combinated organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*.

4,4a,8,8a-tetramethyloctahydro-(4aα, 8aα)-[1,4]oxazino[3,2-b]-1,4-oxazine (**4a**). Obtained according to the general procedure, compound **4a** was purified by flash chromatography (silica gel, EtOAc) to yield a colourless viscous oil (60%). IR(film): 1440, 1370, 1260, 1190, 1165 cm^{-1}. MS m/z (%): 200 (M^+, 2), 112 (10), 100 (58), 56(31). Analysis found: C59.95%, H 9.97%, N 14.01%. $C_{10}H_{20}N_2O_2$ requires C 59.97%, H 10.07%, N 13.99%.

2,4,4a,6,8,8a-hexamethyloctahydro-[1,4]oxazino[3,2-b]oxazines, **4b** *and* **5b.** Obtained according to the general procedure, and purified by column chromatography (silica gel, EtOAc-hexanes 8:2) as a 7:1 mixture of diastereomers. An analytical sample of the major component **4b** was obtained by crystallization, m.p. 34°C ($CHCl_3$); IR(KBr): 1455, 1330, 1240, 1200, 1170 cm^{-1}; Analysis found C 63.09%, H 10.59%, N 12.30%. $C_{12}H_{24}N_2O_2$ requires C 63.12%, H 10.59%, N 12.27%.

Reaction of **3c** *with* Me_2SO_4. Compound **3c** was allowed to react according to the general procedure and the resulting crude reaction mixture was purified by bulb to bulb distillation (110°C/0.05 mmHg) to give a pale yellow oil (70%) as a 6:2:1 mixture of isomers: **4c**, **5c** and **6** respectively.

4,8-diacetyl-4a,8a-dimethyl-octahydro-(4aα, 8aα)-[1,4]oxazino[3,2-b]-1,4-oxazine (**7a**). To a solution of **3a** (300 mg, 1.74 mmol) in benzene (10 ml), acetyl chloride (280 mg, 3.57 mmol) in benzene (2 ml) was added dropwise. The resulting solution was stirred 30 min at 25°C and concentrated *in vacuo* in a cold bath. The resulting white solid was left under vacuum 6 h (10^{-3} mmHg) to give 370 mg (83%) of **7a** as an unstable solid of low melting point. This product can be stored in a freezer without appreciable decomposition. IR(KBr): 1630 C=O, 1390, 1240, 1130, 970 cm^{-1}; Analysis found C 56.10 %, H 7.80 %, N 10.99%. $C_{12}H_{20}N_2O_4$ requires C 56.24%, H 7.87%, N 10.93%.

2,3-diacetyl-2-methyloxazolidine (**8a**). To a solution of **3a** (300 mg, 1.74 mmol) in benzene (10 ml), acetic anhydride (280 mg, 2.74 mmol) in benzene (2 ml) was added dropwise. The resulting solution was stirred 30' at 25°C and concentrated and the residue was purified by bulb to bulb distillation (90°C/0.05 mmHg)

to give 310 mg (80%) of **8a** as a colourless oil. IR(film): 1730 C=O, 1645 N-C=O, 1420, 1360, 1220 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 4.00 (m, 4H, H4 and H5), 2.13 (s, 3H, CH_3CON), 2.10 (s, 3H, CH_3CO), 1.60 (s, 3H, CH_3-C2); ^{13}C-NMR ($CDCl_3$) δ: 201.2 C=O, 167.7 N-CO, 94.4 C2, 65.5 C5, 46.1 C4, 23.4, 22.8 $\underline{C}H_3$-CO-, 18.6 CH_3C2; Analysis found C 56.20%, H 7.67%, N 8.13%. $C_8H_{13}NO_3$ requires C 56.13%, H 7.65%, N 8.18%.

4,8-diacetyl-2,4a,6,8a-tetramethyloctahydro-(2β, 4aβ, 6β, 8aβ)-[1,4]oxazino[3,2-b]oxazine (**7b**).To a suspension of **3b** (200 mg, 1 mmol) in CCl_4 (10 ml), acetic anhydride (200 mg, 1 mmol) were added. after 12 h the solvent was concentrated and the residue was left under vacuum 6 h (10^{-3} mmHg). The resulting solid was purified by column chromatography (silica gel, EtOAc-hexanes 2:8 to 4:6), to give 60 mg (16 %) of **8b** as a colourless oil and 120 mg (40%) of **7b** as white crystals, mp. 165-166°C; **7b**: IR(KBr): 1630 C=O, 1330, 1255, 1010 cm^{-1}; MS m/z (%): 144(47), 105(100), 65(37), 50(25); Analysis found C 59.13%, H 8.59%, N 9.69%. $C_{14}H_{24}N_2O_4$ requires C 59.14%, H 8.51%, N 9.85%; *2,3-diacetyl-2,5-dimethyloxazolidine* (**8b**) was obtained as a 2:1 mixture of diastereomers. An analytical sample was obtained by bulb to bulb distillation (130 °C/0.1 mmHg). IR(film): 1730 C=O, 1650 N-C=O, 1380, 1330 cm^{-1}; Following data in brackets correspond to the minor diastereomer: ^{1}H-NMR($CDCl_3$) , δ: 4.4 (m, 1H, H5), 3.9 (m, 1H, H4), 3.3(m, 1H, H4), 2.2 (s, 3H, CH_3CON), 2,1 (s, 3H, CH_3CO), 1.7 [1.6] (s, 3H, CH_3C2), 1.5 [1.4] (d, 3H, CH_3C5, J= 6 Hz); ^{13}C-NMR ($CDCl_3$), δ: 201.8 C=O, 94.6 [94.4] C2, 72.9 [73.5] C5, 52.7 [53.2] C4, 24.4 $\underline{C}H_3CON$, 22.9 $\underline{C}H_3CO$, 20.9 $\underline{C}H_3C2$, 18.1 [17.7] $\underline{C}H_3C5$. Analysis found C 58.40%, H 8.13%, N 7.60%. $C_9H_{15}NO_3$ requires C 58.36%, H 8.16%, N 7.56%.

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13) A direct approach to **4a** by reaction of 2,3-butanedione (1 eq) with N-methyl-2-aminoethanol (2.2 eq) over a wide range of experimental reaction conditions led exclusively to the synthesis of 2-acetyl-2,3-dimethyl-1,3-oxazolidine (60%) as a colourless oil; bp. 28° C/0.02 mmHg; IR(neat): 1720 C=O cm^{-1}; ^1H NMR($CDCl_3$), δ: 4.2-3.8 (m, 2H, H5), 3.3-2.6 (m, 2H, H4), 2.33 (s, 3H, CH_3-N), 2.16 (s, 3H, CH_3-CO, 1,25 (s, 3H, CH_3-C2); ^{13}C NMR($CDCl_3$), δ: 207.2(C=O), 95.4 (C2), 64.3 (C5), 51.5 (C4), 33.9 ($\underline{C}H_3$-N), 22.9 ($\underline{C}H_3$-C2), 14.9 ($\underline{C}H_3$-CO.

14) Obtention of derivatives **4** by methylation using MeI or CH_2N_2 as alkylating agents was fruitless. Also synthesis of **4** by reduction of the corresponding urethanes was not possible since the synthesis of the latter compounds was unsuccessful, due to the hemiaminal character of compounds **3**.

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