Reaction of α-Diketones with 2-Amino Alcohols. Intramolecular Competitive 6-*exo-trig* vs 5-*endo-trig* Processes. A Systematic and Kinetic Study

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2-Aminoethanol and C-substituted derivatives 1 react with diacetyl, benzil, and 1-phenyl-1,2-propanedione, models of α-diketones 2 to give with remarkable regio- and stereoselectivity 2-hydroxy-5,6-dihydro-2*H*-1,4-oxazines 3, *cis*-octahydro[1,4]oxazino[3,2-*b*]oxazines 4, α-imino ketones 6, 2-acetyl-1,3-oxazolidines 7, *N,N'*-bis(2-hydroxy-2-methylpropyl)-2,3-butanediimines 8, and 2,2'-dimethyl-2,2'-bioxazolidines 9 depending on the nature of the reagents and the reaction conditions. On the basis of isolated intermediates, a reasonable mechanism taking into account the stereoelectronic effects observed on the cyclization has been proposed for these processes. In addition, a kinetic study of the ring–chain–ring tautomeric equilibrium of oxazines **3a–c**, **3i–k**, and **3o–q** has been studied by ^{1}H NMR and ^{13}C NMR. In solution, compounds **3a–c** and **3i–k** exhibit a three-component tautomeric equilibria consisting of the following: the β-iminohemiacetal **3**, the β-hydroxyimino ketone **6**, and the 2-acetyl- or 2-benzoyl-1,3-oxazolidine **7**. The calculated rate constants for this process show that the equilibrium is shifted toward the formation of the five-membered ring by 0.4–4.8 kJ mol^{-1} over the six-membered ring depending on the substitution patterns. Compounds **3p–q** exist in solution as equimolar mixtures of the ring and open-chain tautomers. Compound **3o** exists predominantly in the open-chain form. In addition, 2-acylthiazolidines **13a–c** do not evidence any dynamic processes in solution.

Introduction

The reaction of α-diketones with amino alcohols has been investigated by several groups.[1-4] Products that arise from the condensation of 2 equiv of the 2-amino alcohol with the dicarbonyl compound have been reported: 2,2',3,3'-tetrahydro-2,2'-bibenzooxazole[4a-d] for reaction with *o*-aminophenols and either 2,2'-bioxazolidines[1b,2a,b,3b] or perhydro[1,4]oxazino[3,2-*b*]-1,4-oxazines[1a,c,d,f] for reaction with aliphatic 2-amino alcohols. The preparation of **6o** was recently reported during the course of this work in connection with a synthesis of 2-oxa-1-dithiazepam derivatives.[3b] Also, the synthesis of diimines was described in the condensation reactions of benzil or diacetyl with ethanolamine in connection with the synthesis of polydentate Schiff bases.[3a] As a part of our systematic study of the reaction of α-dicarbonyl compounds with dinucleophilic amines[5,6] we reported the synthesis of 2-hydroxy-5,6-dihydro-2*H*-1,4-oxazine derivatives **3a**, **3i**, and **3o** from the reaction of butanedione (**2a**), benzil (**2c**), and 1-phenyl-1,2-propanedione (FPD) (**2b**), respectively with ethanolamine (**1a**). On the other hand, regiospecific formation of compounds **3a**, **4**, and **5** was observed in the reaction of butanedione with **1a** depending upon the molar ratio of the reagents (Table I).

The aim of the present work is to explore the generality of this process with α-diketones to establish the influence on the reaction products of both the structural factors in the ethanolamine chain and/or the nature of the carbonyl group. Thus butanedione, benzil, and FPD were chosen for reaction with a series of *C*-methyl-substituted ethanolamines **1a–g** bearing different structural features around the two reactive sites. In this paper we report our experimental results that are in agreement with an expanded general scheme. We have reported[7] a characteristic behavior of compounds **3** in solution as the first example of a β-imino hemiketal **3a**/β-hydroxyimino ketone **6a**/2-acetyl-1,3-oxazolidine (**7a**) tautomeric equilibrium which is an intramolecular competitive process of nucleophilic attack of a hydroxyl group on a C=O or C=N bond. The study of ring–chain tautomerism processes has been reported for different heteroatomic systems.[8] In the case of oxazolidines, the kinetics of the tautomerism involved in the reversible addition of a hydroxyl group to the C=N group is well documented[9] because the ring formation is a disfavored 5-*endo-trig* process according to Baldwin's rules.[10] In this paper we report an extension of our initial analysis to a series of 2-hydroxy-5,6-dihydro-2*H*-1,4-oxa-

(1) For references dealing to the reaction of glyoxal with ethanolamines, see, among others: (a) Rakhmankulov, D. L.; Zlotskii, S. N.; Karakhcnov, R. A.; Zlotskii, S. N.; Latypova, F. N.; Marinova, R. N.; Uzikova, V. N. URSS Patent 565030, 15 July 1977; *Chem. Abstr.* **1977**, *87*, 201553c. (b) Laurent, P. A.; Bearn, L. *Bull. Soc. Chim. Fr.* **1978**, *83*, 2. (c) Le Rouzic, A.; Raphalen, D.; Papillon, D.; Kerfanto, M. *Tetrahedron Lett.* **1985**, 1853; (d) *J. Chem. Res., Synop.* **1985**, *35*. (e) Aceves, J. M.; Contreras, R. *Synthesis* **1987**, 927. (f) Agami, A.; Couty, F.; Hamon, L.; Prince, B.; Puchot, C. *Tetrahedron* **1990**, *46*, 7003.

(2) For references dealing to the reaction of arylglyoxals with N-substituted ethanolamines, see, among others: (a) Teller, O. M.; Guinoso, Ch. J.; Bell, S. C.; Douglas, G. H. US Patent 3,817994, 18 June 1974; *Chem. Abstr.* **1974**, *81*, 105531. (b) Ibid. US Patent 3, 891665, 24 June 1985; *Chem. Abstr.* **1975**, *83*, 193284r.

(3) For references dealing with the reaction of α-diketones with 2-amino alcohols, see: (a) Aldekeye, S. B.; Erinoso, E. O.; Ghose, B. N. *An. Quim. Sec. B* **1983**, *79B(3)*, 353. (b) Ray, J. K.; Charterjee, B. G. *Ind. J. Chem. Sec. B* **1985**, *24B(2)*, 144. (c) Dieck, H. T.; Dietrich, J. *Chem. Ber.* **1984**, *117*, 694.

(4) For references dealing to the reaction of α-diketones with 2-aminophenols, see, for example: (a) Murase, I. *Bull. Soc. Chem. Jpn.* **1959**, *32*, 827; (b) *Ibid.* **1960**, *33*, 59. (c) Belgodere, E.; Bossio, R.; Panini, V.; Pepino, R. *J. Heterocycl. Chem.* **1977**, *14*, 957. (d) Tauer, E.; Grellmann, K.-H.; Kaufmann, E.; Noltemeyer, M. *Chem. Ber.* **1986**, *119*, 3316.

(5) Alcaide, B.; Pérez-Ossorio, R.; Plumet, J.; Rico, M.; Rodríguez-Campos, I. M. *Tetrahedron Lett.* **1986**, *27*, 1381.

(6) Alcaide, B.; García-Blanco, S.; García-González, M. T.; Martínez-Carrera, S.; Pérez-Ossorio, R.; Plumet, J.; Rodríguez-Campos, I. M. *Tetrahedron Lett.* **1986**, *27*, 4217.

(7) Alcaide, B.; Gonzalez-Rubio, R.; Plumet, J.; Rodríguez-Campos, I. M. *Tetrahedron Lett.* **1990**, *31*, 4211.

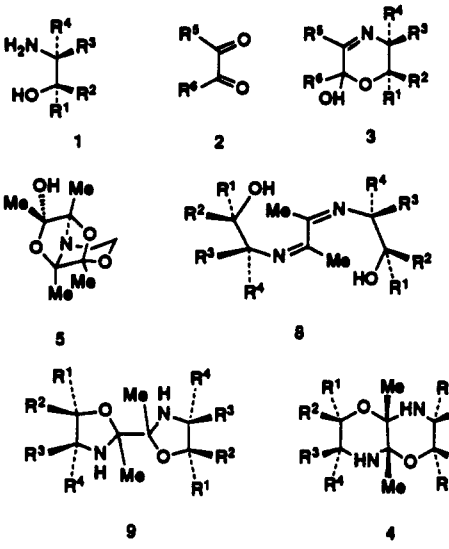
(8) Valters, R.; Flitsch, W. *Ring-Chain Tautomerism*; Plenum: New York, 1985.

(9) Fülop, F.; Bernáth, G.; Mattineu, J.; Pihlaja, K. *Tetrahedron* **1989**, *45*, 4317.

(10) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

0022-3263/92/1957-2446$03.00/0

Table I



	1, 4, 8, 9					2			3, 6, 7					
	R^1	R^2	R^3	R^4		R^5	R^6		R^1	R^2	R^3	R^4	R^5	R^6
a	H	H	H	H	a	Me	Me	a	H	H	H	H	Me	Me
b	H	Me	H	H	b	Me	Ph	b	H	Me	H	H	Me	Me
c	H	H	H	Me	c	Ph	Ph	c	H	H	H	Me	Me	Me
d	H	Me	Me	H				d	H	H	Me	H	Me	Me
e	H	Me	H	Me				e	H	Me	Me	H	Me	Me
f	H	H	Me	Me				f	H	Me	H	Me	Me	Me
g	Me	Me	H	H				g	H	H	Me	Me	Me	Me
								h	Me	Me	H	H	Me	Me
								i	H	H	H	H	Me	Ph
								j	H	Me	H	H	Me	Ph
								k	H	H	Me	H	Me	Ph
								l	H	Me	Me	H	Me	Ph
								m	H	H	Me	Me	Me	Ph
								n	Me	Me	H	H	Me	Ph
								o	H	H	H	H	Ph	Ph
								p	H	Me	H	H	Ph	Ph
								q	H	H	H	Me	Ph	Ph
								r	H	Me	Me	H	Ph	Ph

zines **3a–c**, **3i–k**, **3o–q** to light on the stereoelectronic effects associated with the opening of hemiacetals[11] when another ring–chain tautomerism is conceivable in the same molecule.

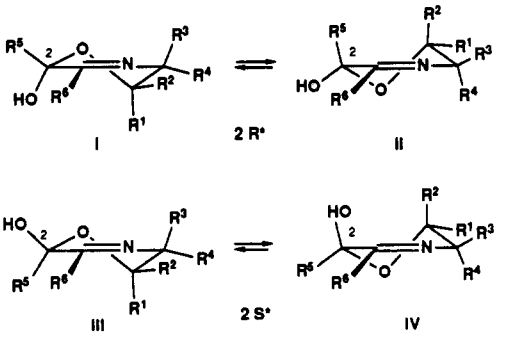
We also report a correction of the formerly assigned trans structure[5] of **4a** as *cis*-octahydro[1,4]oxazino[3,2-*b*]-1,4-oxazine as determined by X-ray analysis.

Results

Condensation of nearly equimolecular amounts of amino alcohols **1a–g** (ca. ~1.2 equiv) with **2a–c** affords compounds **3a–g**, **3i–r** (Table I) in 60–95% yields. Synthesis of **3a–g** was carried out in a suspension of $MgSO_4$ in CH_2Cl_2 at room temperature. Compounds **3i–n** were obtained by simply mixing the corresponding 2-amino alcohol with FPD. Reaction of benzil with **1a–d** in benzene at reflux (Dean–Stark apparatus) led to the corresponding compounds **3o–r**.

Stereoselectivity in the cyclization was found to be dependent on the α-diketone used. Generally, in the case of oxazines derived from butanedione and benzil, the analysis (^1H and ^{13}C NMR data) of the crude reaction mixture showed the formation of only one diastereomer when amino alcohols possessing a chiral center in the carbinolic carbon were used. On the other hand, equimolecular mixtures of diastereomers were obtained in the reaction of 2-amino-1-hydroxypropanol (**1c**) regardless of the α-diketone used. A different behavior was found for FPD. In this case a 80:20 ratio of diastereomeric dihydrooxazines **3j** and **3l** demonstrates a lack of stereoselectivity in the cyclization.

Scheme I



The structural assignment for compounds **3** and proof of stereochemistry for all diastereomers isolated come from analysis of their ^1H and ^{13}C NMR spectra. We assume in the following discussion that two diastereomers interconvertible via ring–chain tautomerism can be considered, each of which may exist as two half-chair conformers owing to ring inversion as depicted in Scheme I, analogous to conformational analysis of cyclohexene.[12]

(11) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Wiley: New York, 1986.

Table II. ^{1}H NMR Chemical Shifts (δ) and Coupling Constants[a,b] (Hz) for Compounds 3a–g,i–n

compd	H_aO	H_eO	H_aN	H_eN	Me–C3	Me–C2	Me–CH	$J_{MeC3,H-C5}$ H_aN	$J_{MeC3,H-C5}$ H_eN	$J_{a}O_{e}O$	$J_{a}O_{a}N$	$J_{a}O_{e}N$	$J_{e}O_{a}N$	$J_{e}O_{e}N$	$J_{e}N_{a}N$
3a[c]	3.85	3.65	3.46	3.48	2.04 (t)	1.48 (s)	-	1.7	1.7	-11.2	8.6	5.6	3.6	2.3	-13.3
3b	3.96	-	3.12	3.55	2.09 (d)	1.52 (s)	1.18 (d)	2.5	1.0	-	10.7	2.5	-	-	-17.0
3c	3.40	3.61	3.42	-	2.06 (d)	1.52 (s)	1.20 (d)	2.0	-	-9.9	10.3	-	2.0	-	-
3d	3.91	3.41	-	3.53	2.10 (d)	1.52 (s)	1.16 (d)	-	1.2	-11.4	-	3.2	-	2.0	-
3e	4.00	-	-	3.41	2.03 (d)	1.47 (s)	1.15 (d) 1.10 (d)	-	0.8	-	-	2.7	-	-	-
3f	3.44	-	3.00	-	2.02 (s)	1.46 (s)	1.47 (d) 1.13 (d)	2.3	-	-	9.2	-	-	-	-
3g	3.76	3.33	-	-	2.07 (s)	1.53 (s)	1.17 (d)	-	-	-11.0	-	-	-	-	-
3i[c]	3.98	3.75	3.60	3.50	1.75 (t)	-	-	2.2	2.2	-11.3	11.2	3.4	4.4	1.0	-17.2
3j	4.16	-	3.35	3.69	1.79 (d)	-	1.26 (d)	2.4	1.0	-	10.6	2.6	-	-	-17.0
3k	4.34	-	-	3.57	1.80 (d)	-	1.24 (d)	2.1	-	-10.0	10.0	-	3.3	-	-
3l	4.34	-	-	3.57	1.80 (d)	-	1.26 (d) 1.21 (d)	-	<1	-	-	3.0	-	-	-
3m	3.89	3.63	-	-	1.77 (s)	-	1.37 (d) 1.20 (d)	-	-	-11.0	-	-	-	-	-
3n	-	-	3.67	3.47	1.90	-	1.35 (d) 1.31 (d)	-	-	-	-	-	-	-	-16.0

[a] Spectra recorded at 360 MHz ($CDCl_3$) for compounds 3a–g and 300 MHz ($CDCl_3$) for 3i–n. [b] We assigned H_a and H_e to the hydrogen atoms axially and equatorially oriented, respectively, and Ho and H_N to the hydrogens attached to the carbons 2 and 3, respectively. [c] For compounds 3a and 3i the assignments were obtained by simulation with the LAOCOON-3 program.

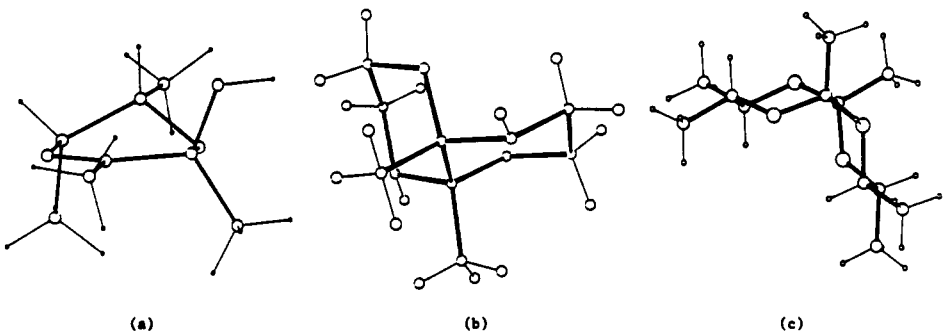


Figure 1. (a) ORTEP plot of 5,6-dihydro-2-hydroxy-2,3,5,6-tetramethyl-(2*R**,5*R**,6*R**)-2*H*-1,4-oxazine (**3f**). (b) ORTEP plot of 4a,8a-dimethyloctahydro-(4α,8aα)-[1,4]oxazino[3,2-*b*]-1,4-oxazine (**4a**). (c) ORTEP plot of 2,3,4a,6,7,8-hexamethyloctahydro-(2α,3β,4aα,6α,7β,8aα)-[1,4]oxazino[3,2-*b*]-1,4-oxazine (**4e**).

With the exception of **3a** and **3i** the 360–300 MHz ^{1}H NMR of compounds **3** showed well-defined splitting patterns for those protons attached to the ethylenic fragment (Table II).

The most populated conformation should be that exhibiting a stabilizing anomeric effect and minimum steric interactions. For compounds monosubstituted at C6 with, for example, an *R* relative configuration this conformation sould be I (Scheme I). This analysis is in agreement with the observed coupling constants. See, for example, compounds **3b** and **3i** (Table II) which exhibit a $J_{a}O_{a}N$ = 10.7 and 10.6 Hz and $J_{homo(Me-H_aN)}$ = 2.5 and 2.4 Hz, respectively, with the methyl group at C6 in equatorial position.

For oxazines derived from **1c**, the most populated conformation should be I for the isomer 2*R**,5*S** and IV for 2*S**,5*S** (**3d**) (Scheme I), since the former bears a methyl group at C5 in a pseudoequatorial position [$J_{homo(Me-H_aN)}$ = 2.0 Hz] whereas it is pseudoaxial in the 2*S**,5*S** isomer, [$J_{homo(Me-H_eN)}$ = 1.2 Hz]. Formation of both diastereomers in equimolar amounts clearly suggests a similar strain energy, since both conformers have anomeric effects.

To gain supporting evidence for the assignment of the configuration at the anomeric center and to some extent for the most populated conformation both in the solid state and in solution, compound **3f**, which possesses three chiral centers, was chosen as a model for the X-ray diffraction analysis. Examination of **3f** by single-crystal X-ray crystallographic analysis (see ORTEP diagram, Figure 1a) confirmed the proposed structure and the presence of a stabilizing anomeric effect. Fragment C6–O1–C2–O7 is gauche to the O1–C2 bond (bond distances C2–O1 are of 1.40 Å and C6–O1 1.43 Å). The ring exhibits an envelope-like conformation with the atoms O1, C2, C3, N4, and C5 in the same plane and C6 above the plane.

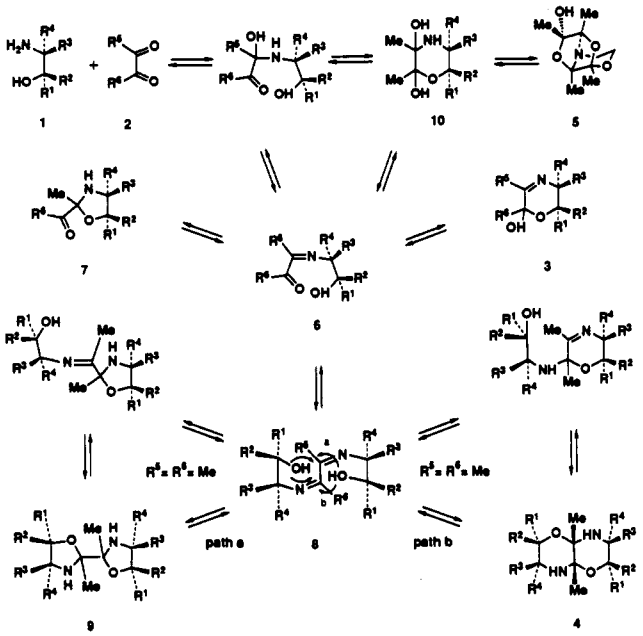
In solution, compounds **3** show ring–chain tautomerism as a result of a competing intramolecular addition of the hydroxyl group to the carbonyl or imino bonds following a 6-*exo*- or 5-*endo*-*trig*[10] cyclization pathway. The evolution of ^{1}H and ^{13}C NMR spectra in solution clearly indicated the appearance of imino ketones **6** and oxazolidines **7**. Analogous oxazines derived from benzil do not reach the five-membered ring in solution. The kinetics of this process in compounds **3b–c**, **3i–k**, and **3o–q** will be discussed later in this paper.

Attempts to independently synthesize imino ketones **6** were only successful for **6h** (derived from butanedione and 1-amino-2-methyl-2-propanol) which can be isolated as the major component (80:20) of a mixture of **6h** and oxazolidine **7h**. Syntheses of oxazolidines **7a–e** and **7h** (as mixtures of diastereomers) (Table I) were carried out by reaction of equimolar amounts of butanedione and amino alcohols **1a–e** and **1g** in refluxing benzene and subsequent distillation of the crude reaction mixtures. Under these reaction conditions, the 5-*endo*-*trig* process that allows for formation of oxazolidines **7** is not stereoselective.

The reaction of α-diketones with an excess of 2-amino alcohols (ca. $\geq$2 equiv) affords the corresponding α-imino

(12) Eliel, E. L.; Allinger, N. L. *Top. Stereochem.* **1970**, *5*, 572.

Scheme II



ketone as an intermediate which may then react with a second mole of 2-amino alcohol, depending on the nature of the carbonyl group and the intramolecular course of the condensation step. In spite of isolation of α-diimines **8h**, **8n** derived from benzil or FPD and **1a**, respectively, only 2,3-butanedione afforded intramolecular cyclization products. Thus, treatment of 2,3-butanedione with amino alcohols **1a–c** and **1e** in excess (ca. >2 equiv) leads to the stereoselective formation of *cis*-octahydro[1,4]oxazino-[3,2-*b*]-1,4-oxazines **4** (70–90%) (Table I). The reaction afforded crystalline **4a**, **4b**,[13] **4c**, and **4e** as the exclusive products in benzene at room temperature. Attempts to carry out the reaction in different solvents or in the presence of additives (Et_2O, $MgSO_4/CH_2Cl_2$) afforded lower yields as well as mixtures of the different products outlined in Scheme II. It is worth noting that compound **4e** could be isolated as a single diastereomer after an initially complex mixture of diastereomeric bioxazolidines **9e**, obtained by reaction of butanedione and *threo*-3-amino-2-butanol, was allowed to stand at room temperature for several days. For amino alcohols **1d** and **1f** reaction conditions for synthesis of **4** led only to the corresponding oxazines **3**. The reaction with amino alcohol **1g** afforded diimine **8g** as the major product isolated (85% by ^1H NMR) together with their ring tautomer (bisoxazolidine **9g**). For this amino alcohol the double 6-*exo-trig* ring closure failed under all the conditions essayed.

^1H NMR spectra of compounds **4** exhibit well-defined splitting patterns (Table III) and were fully consistent with two fused six-membered rings in a highly symmetrical structure.[14] ^{13}C NMR spectra also confirm this symmetry, with the number of signals corresponding to half of the carbon atoms in the molecule (Table III). It is noteworthy that in **4a** the vicinal coupling constants of the peripheral methylene protons (J_{aa} = 12 Hz, J_{ee} = 1.0 Hz, and $J_{ae,ea}$ = 3.1–3.8 Hz) point to a rigid trans configuration. In light of the studies concerning the importance of the anomeric effect in animal functions[11] it was helpful to do a X-ray crystallographic study of the model oxazinooxazines **4a** and **4e** to confirm the previously assigned configuration. Accordingly, colorless crystals of **4a** or **4e** were subjected to X-ray analysis. The relevant structural features are similar for both molecules.

Table III. ^1H NMR ($CDCl_3$) and Selected ^{13}C NMR ($CDCl_3$) Spectral Data for Compounds 4[a]

compd	4a (%NOE[b])	4b	4c	4d
H_ao	3.94 (25)	3.97	3.44	3.39
H_eo	3.77 (10)	–	3.67	–
H_aN	3.44 (10)	3.04	3.53	3.03
H_eN	2.43 (10)	2.43	–	–
Me–C4a	1.40	1.38	1.39	1.30
Me–CH	–	1.13	0.89	1.05
				0.84
$J_{a_o e_N}$	−11.4	–	−10.5	9.15
$J_{a_o a_N}$	11.9	10.8	10.6	–
$J_{a_o e_N}$	3.1	2.8	3.15	–
$J_{e_o a_N}$	3.8	–	–	–
$J_{e_o e_N}$	1.0	–	–	–
$J_{e_N a_N}$	−11.1	−10.8	–	–
C2	63.4	67.7	69.6	73.9
C3	39.3	45.4	42.8	48.8
C4a	84.2	83.3	84.1	84.4
Me–C4a	21.8	22.0	21.7	22.2
Me–CH	–	18.8	17.1	17.8

[a] Spectra recorded at 360 MHz (^1H) and 75 MHz (^{13}C). [b] When Me–C4a (Me–C8a) signal was irradiated.

The cis mode of cyclization was unambiguously confirmed (see ORTEP diagram Figure 1b,c) for both **4a** and **4e** showing two fused six-membered ring in a chairlike conformation slightly flattened around the nitrogen atom. In the central fusion bond (C4a–C8a), the geometry is the same in both compounds, i.e., in a staggered conformation, with the two methyl angular groups in cis positions with respect to the rings, the nitrogen atoms antiperiplanar to each other, and with the oxygen atoms remaining gauche to each other and antiperiplanar to the carbon substituents.

In solution neither **4a** nor **4e** was found as a mixture of conformers. The stronger stabilization for this conformational disposition can be rationalized by the presence of a stabilizing anomeric effect from the two nitrogen atoms whose nonbonding lone pairs are placed antiperiplanar to the C–O bonds. Thus, since the C–O bond is a stronger acceptor than the C–N bond and nitrogen is a stronger donor than oxygen, the consequence should be reflected in the bond distances. In fact, the O–C (bridge) is longer than the other O–C bond, while the N–C (bridge) is shorter than the other N–C bond. It is worth noting that compound **4a** does not exhibit a ring interconversion in a variety of solvents[15] even at 70 °C. NOE measurement experiments in ^1H NMR (360 MHz, $CDCl_3$) of **4a** at 256 or 303 K confirmed the same configuration: anti-N, found in the crystalline state (25% NOE between protons of the angular methyl groups and H_a°).

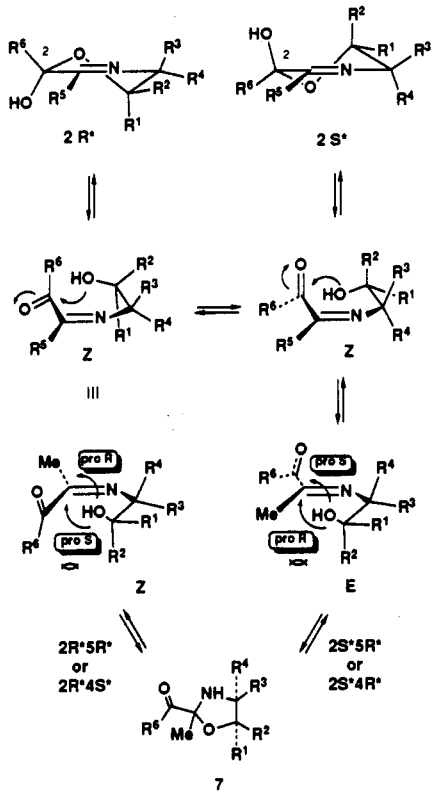
When diacetyl and amino alcohols **1e** or **1g** were allowed to react in refluxing benzene diastereomeric mixtures of bioxazolidines **9e** (90%) or **9g** (98%), respectively, were obtained as moderately stable oils. Compound **9e** isom-

(13) For synthesis of **4b** and some derivatives by reaction of propargylic alcohols with 2-amino alcohols in trifluoroacetic acid catalyzed by mercuric salts see: Barluenga, J.; Aznar, F.; Liz, R.; Cabal, M. P.; Cano, F. H.; Foces-Foces, C. *Chem. Ber.* **1986**, *119*, 887.

(14) The structural assignment of related tetraazadecalines and biimidazolidines[19a] made by EI mass spectroscopy is not unequivocal for dioxadiazadecalines since some of the isomeric bioxazolidines **9**, synthesized independently, and compounds **4** showed similar fragmentations. In both structures the $m/z = M^+/2$ was the base peak and the molecular ion was found to be very small or nonexistent (<0.2%).

(15) A ^1H NMR study (360 MHz) was carried out in different solvents for compound **4a** and at different temperatures (between −60 and 70 °C). The only dynamic process observed was the tautomeric equilibrium between **4a** and **8a**. The measure of the equilibrium constant K = **8a**/**4a** gave the following results 0.05 (CCl_4, 278 K); 0.25 ($CDCl_3$, 278 K); 0.05 ($CDCl_3$, 256 K); 0.96 [$(CD_3)_2CO$, 278 K], 3.16 (CD_3OD, 278 K); 0.92 (CD_3CN, 278 K); 1.5 (DMSO-d_6, 278 K).

Scheme III



erizes slowly but completely upon standing to the oxazinooxazine **4e**. This isomerization is much faster when the corresponding bioxazolidine is less substituted. Consequently, isolation of **9a–d** as pure products failed due to their instability. In fact, compound **9b** was characterized by combined ^{13}C NMR and GCMS spectroscopy using the corresponding compound **4** as reference.

Discussion

A general reaction mechanism for the condensation of butanedione, benzil, and FPD with amino alcohols **1a–g** is presented in Scheme II. The pathway leading to 1:1 products could proceed through the 2,3-dihydroxymorpholine **10** or the imino ketone **6**. Compound **10** was proposed as intermediate in the formation of tricyclic product **5** in the reaction of excess of butanedione and ethanolamine.[16] On the other hand, when reactions were monitorized by ^1H NMR, imino ketones **6** were the first products detected. At longer reactions times (10 min) signals for these compounds disappeared and oxazines **3** become predominant until ring–chain–ring tautomeric equilibrium had taken place.

For this reason oxazines **3i–n** derived from FPD must be synthesized in the absence of solvent because their tautomeric equilibria are shifted toward the oxazolidines. The reaction, carried out by simple mixing of reactants, is exothermic, and the original solution becomes a solid after standing several minutes. For **3j** and **3l** the resulting solids were obtained as an enriched mixture of diastereomers. However, total stereoselectivity was observed when these reactions were carried out in solution.

It is interesting to note that the observed stereochemistry for the cyclization in the 6-*exo-trig* mode (Scheme III) can be explained assuming imino ketones **6** as intermediates. An important issue for this cyclization is the relative stereochemistry of the newly formed stereogenic center, which is possibly controlled by three factors: (i) orthogonal disposition of C=N and C=O groups,[17] (ii) equatorial aproach of the hydroxyl group to C=O bond leading to a chairlike transition state with a preformed pseudoaxial geometry in the exo C–O bond which would be favored by a stabilizing anomeric effect, and (iii) the substituents attached to the carbinolic carbon necessarily adopting an equatorial position to avoid 1,3-axial steric interactions. In order to test this last hypothesis we carried out the reaction between diacetyl and 1-amino-2-methyl-2-propanol (**1g**) using equimolecular quantities at room temperature. In this case the 6-*exo-trig* cyclization failed and imino ketone **6h** was the only product isolated, revealing the high degree of strain associated with the cyclization when the methyl substituent at the hydroxylic carbon must adopt an axial disposition. However, similar oxazine **3n** (derived from FPD) synthesized using different reactions conditions (slightly exothermic) points to a more energetic reactive transition state than that required for the synthesis of **3a–g**. Nevertheless, **3n** was found to be unstable in solution. On the other hand substituents attached to the amine carbon do not exert any influence on the stereochemistry of the new stereogenic center. Indeed, oxazines derived from **1c** were obtained as equimolecular mixtures of diastereomers. It should be pointed out that the 5-*endo-trig* process takes place at higher temperatures than those required for the most favored 6-*exo-trig*. As a result the former is achieved with no stereocontrol. As shown in Scheme III both imino ketones *E* and *Z*, interconvertible in the reaction medium, can afford the equimolecular diastereomeric mixtures of compounds **7** observed. It is intriguing to note the effect of dimethyl substitution on this carbon relative to the tautomeric equilibrium previously discussed. Compounds **3g** and **3m** exhibit a detectable amount of neither the open-chair form (<0.1%) nor the oxazolidine even at 80 °C. For these compounds the conformations required for successful in this cyclization seem to have opposite requirements than those for obtention of oxazolidines. Thus, dimethyl substitution[18] on the carbinolic carbon permits the obtention of the oxazolidine but not the oxazine, and dimethyl substitution on the amine carbon failed to led the corresponding oxazolidine but rather the oxazine.

Formation of bicyclic products could be explained in a similar fashion with a diimine **8** as intermediate. Formation of bioxazolidines as unstable oils, at higher temperatures than required for oxazinooxazines (both formed through attack of a hydroxyl group on the C=N group) is consistent with Baldwin's rules for ring closure in trigonal systems which are especially enlightening when unequally favored processes are competing within the same molecule.[19] In our case the diimine may follow two

(16) Attempts to isolate related tricyclic structures by reaction of excess of butanedione with *C*-methyl-substituted amino alcohols were fruitless.

(17) Evidence about the orthogonality between C=O and C=N groups in other imino ketones was obtained from X-ray studies. See: Garcia-Ruano, J. L.; Haro, R.; Pascual, C.; Perez-Ossorio, R.; Plumet, J. *An. Quim.* **1979**, *75*, 165. See also: Garcia-Ruano, J. L.; Henao, M. A.; Molina, D.; Perez-Ossorio, R.; Plumet, J. *Tetrahedron Lett.* **1979**, 3123.

(18) For an excellent discussion about *gem*-dialkyl-effect theories: "reactive rotamer effect" versus "angle compression" (Thorpe–Ingold effect) see: Jung, M. E. *Synlett* **1990**, 186.

(19) (a) Baldwin, J. E.; Lutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736. (b) Baldwin, J. E.; Reiss, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 77. (c) Barlett, P. A. In *Asymetric Synthesis*; Academic Press: London, 1984; Vol. 3, Chapters 5 and 6. (d) Nicolau, K. C.; Prasal, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (e) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612. (f) Taylor, S. K.; Blankespoor, C. L.; Harvey, S. M.; Richardson, L. J. *J. Org. Chem.* **1988**, *53*, 3309. (g) Negishi, E.; Boardman, L. D.; Sawada, H.; Bagheri, V.; Stoll, A. T.; Tour, J. M.; Rand, C. L. *J. Am. Chem. Soc.* **1988**, *110*, 5383. (h) See ref 1f.

Table VI. Rate Constants and Free Energy Differences Associated with the Ring–Chain–Tautomerism of Compounds 3a–c,i–k in $CDCl_3$ at 308 K

	$k \times 10^3$						$\Delta G°$ [a] (kJ mol^{-1})		
compd	k_1	k_2	k_3	k_4	k_1/k_2	k_3/k_4	$\Delta G°_I$	$\Delta G°_{II}$	$\Delta G°_T$
3a	1.0	1.4	69.0	42.0	0.71	1.64	0.9	−1.3	−0.4
3b	1.8	1.2	0.9	0.4	1.50	2.25	−1.0	−2.0	−3.0
3c	10.0	51.0	31.0	4.7	0.20	6.59	4.1	−4.8	−0.7
3i	110	40.0	15.0	6.2	2.75	2.42	−2.6	−2.3	−4.9
3j	15.0	7.6	7.8	4.2	1.98	1.86	−1.8	−1.6	−3.3
3k	30.0	40.0	94.0	11.0	0.75	8.54	0.7	−5.5	−4.8

[a] From $\Delta G°_I = -RT \ln k_1/k_2$ and $\Delta G°_{II} = -RT \ln k_3/k_4$.

pathways of ring closure (Scheme II). pathway a would lead to a bisoxazolidine via a double 5-*endo-trig* mode of attack with the same stereoelectronic requirements previously commented (bioxazolidine **9g** was obtained but not **9f**). It is worth noting that in the double condensation of *R*S**-3-amino-2-butanol (**1e**) with butanedione, pathway a is kinetically favored even at 80 °C. Pathway b would lead, through the reactive conformations depicted in Scheme IV to oxazinooxazines **4**. Stereoelectronic effects that afford the most stable anti-N conformation should account for the prefered cyclization in the conformation namely **4A**. As a consequence the formation of anti-O oxazinooxazines must involve a higher energy barrier in conformation **4B**.

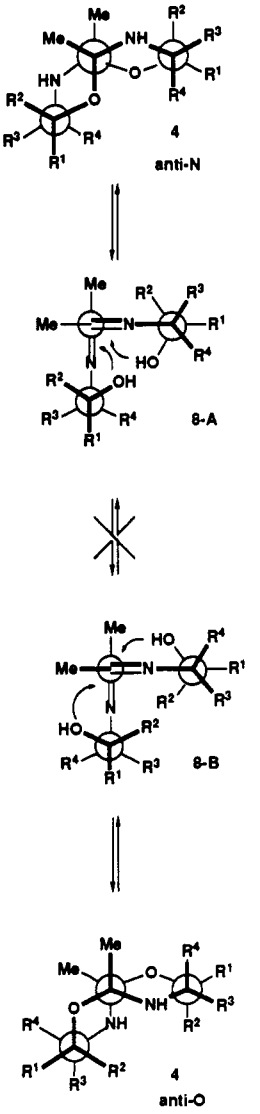
The observed results imply a high degree of stereoselectivity which can only be achieved if the progress of the reaction from the imino ketone **6** takes place through a series of equilibria. Thus, each fragment of amino alcohol in the diimine should possess the same absolute configuration in order to minimize 1,3-diaxial interactions in the cyclization step.

Considering the extensive studies[20a,b] reported for the condensation reaction of *N,N'*-dimethylethylenediamine with glyoxal[20a,b] or butanedione,[20c,d] we focused on the extension of this work in *N*-methylethylenediamine (NMED) and its reactivity toward butanedione, benzil, and FPD. Compared to 2-amino alcohols, NMED behaves quite differently. Thus, 2-phenyl-2-hydroxy-3-methyl- (**11a**) or 2,3-diphenyl-2-hydroxy-5,6-dihydro-1-methylpyrazine (**11b**) were obtained as unstable solids from the reaction of NMED with FPD and benzil, respectively. Spectroscopic data revealed their unstability in solution due to reversion to the starting materials (case of **11b**) or formation of the iminoenamine: 5-phenyl-1-methyl-6-methylene-1,2,3,6-tetrahydropyrazine (**12a**) (case of **11a**). Reaction of 2,3-butandione with NMED in $MgSO_4/CH_2Cl_2$ at room temperature led directly to the unstable iminoenamine **12b** (5-methyl-). In any case neither 1,3-imidazolidines nor bicyclic products were found in the intermediates detected.

Kinetics. A time-dependent ^1H NMR (200 MHz, $CDCl_3$) spectroscopic study on the tautomer distribution in solution for compounds **3a–c**, **3i–k**, and **3o–q** at 308 K unequivocally showed ring (1)–chain (2)–ring (3) equilibria in oxazines **3a–c**, and **3i–k**, and ring (1) and chain (2) tautomers for oxazines **3o–q**.

The study of the three component tautomeric equilibria found in solution of oxazines **3a–c,i–k** revealed important features: (i) When the hydroxylic tether in compound **3** bears a methyl group in the carbinolic carbon atom, the

Scheme IV



6-*exo-trig* closure of imino ketones **6** is totally stereoselective. (ii) Mixtures of *E/Z* stereoisomers for the imino ketones were observed only for **3i–k**. (iii) Formation of oxazolidines through a 5-*endo-trig* pathway yields one or both possible diastereomers depending upon time in solution.

Characterization of each tautomer was derived from their ^1H NMR spectra. Their diastereomeric composition and initial concentration was determined from the integrals of the methyl signals in the ^1H NMR spectra. For imino ketones **6i–k** the amounts in solution of *E,Z* stereoisomers was based upon the integral of the $CH_3C{=}N$ signal in the time-dependent spectra. The assignment of each stereoisomer can be easily done, since the (*Z*)-imino ketone appearing in solution results from the opening of the oxazine

(20) (a) Miller, R. L.; Moore, D. W.; Lowe-Ha, C. K.; Vanderah, D. J. *J. Org. Chem.* **1985**, *50*, 2368. (b) Black, D. S.; Craig, D. C.; Giitsidis, O.; Read, R. W.; Salek, A.; Sefton, M. A. *J. Org. Chem.* **1989**, *54*, 4771. (c) Fuchs, B.; Ellencweig, A. *Recl. Trav. Chim. Pays Bas* **1979**, *98*, 326. (d) Ghose, E.; Bhupendra, N. *J. Chem. Eng. Data* **1984**, *29(4)*, 237. (e) For related cyclic diaminoenamines see: Ahlbrecht, H.; Dietz, M.; Raab, N. *Synthesis* **1983**, 231.

ring. The equilibrium constants depicted in Table VI clearly show a preferred *E* geometry with $\Delta G°_{E-Z}$ = 3.7 (**3i**), 4.4 (**3j**), 2.8 (**3k**). On the other hand oxazolidines **6** are formed via ring closure of both *E*- and *Z*-stereoisomers. Inspection of Dreiding models shows that this cyclization involves opposite steric requirements depending upon which stereoisomer is considered.

We presume that the first oxazolidine diastereomer appearing in solution would be 2*R**,5*S** for **7b**, **7j** and 2*R**,4*R** for **7c**, **7k** since their formation would proceed through attack of the hydroxyl group on the less hindered *pro-R* face of the imino bond in the reactive conformations of the most populated *E*-stereoisomers (*Z*-stereoisomers would lead to oxazolidine diastereomers 2*R**,5*R** for **7b**, **7j** and 2*R**,4*S** for **7c**, **7k**) (Scheme III). Unfortunately, assignments of relative configurations in diastereomerically pure oxazolidines was not possible, since equilibration between diastereomers depends upon time in solution.

Kinetic analysis of the time dependent tautomerism has been performed as follows, assuming three-component tautomeric equilibria:

$$1 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 2 \underset{k_4}{\overset{k_3}{\rightleftharpoons}} 3$$

In order to simplify this analysis, [1], [2], and [3] correspond to the total concentration in solution of oxazine **3**, imino ketone **6**, and oxazolidine **7**, respectively, without taking into account their composition and assuming a pseudo-first-order for each reaction:

$$\frac{\delta C_1}{\delta t} = k_1 C_2 - k_2 C_3 \quad (1)$$

$$\frac{\delta C_2}{\delta t} = k_1 C_1 - k_2 C_2 - k_3 C_2 - k_4 C_3 \quad (2)$$

$$\frac{\delta C_3}{\delta t} = k_3 C_2 - k_4 C_3 \quad (3)$$

Equations 1–3 have been solved following the same procedure described in our preliminary paper.[7] In the same manner for determination of the k_i's (i = 1,4) we have used a nonlinear regression method based on the Newton–Gauss algorithm.[21]

Rate constants and free energy differences pertaining to eqs 1–3 are summarized in Table VI. In general, the calculated and experimental plots agree quite well, and this result seems sufficiently accurate to use with reasonable confidence in the following discussion.

The ring-opening process of oxazines **3** in solution, reflected in the k_1 values (Table VI), clearly points to a faster opening of the six-membered ring for those oxazines bearing a phenyl substituent at the hemiacetalic carbon (**3i–k**). To explain these differences it should be taken into account that the rupture of the cyclic C–O bond may occur by two different mechanisms. In compounds **3i–k** the phenyl substituent would drive the opening of the six-membered ring through a conformation where the π and the σ^* orbitals of the phenyl and cyclic C–O bond, respectively, are in an antiperiplanar relationship allowing for a maximum orbital overlap. For oxazines **3a–c** the opening of the six-membered ring would turn out through a conformation exhibiting an orbital overlap between the lone electron pair at the oxygen atom (axial oxygen) and the antibonding σ^* (C–O bond) orbital in the HO–C–O–C arrangement.[11]

The opening of the five-membered ring **7** (k_4, Table VI) is not differentially affected by the substitution at the carbonyl carbon. It has been reported[22] that opening of oxazolidines is controlled by the availability of the nitrogen lone pair to interact with orbitals other than anti or syn periplanar in the oxazolidine ring.

Analysis of the free energy differences (Table VI) shows a general trend for all compounds studied: the formation of the five-membered ring is favored over the open tautomer and also over the six-membered ring. This fact is reflected in the ΔG_T values which account for a shift of the tautomeric equilibrium to the right ($-\Delta G_T$ ranging 0.4–4.8 kJ/mol). It is worth noting the effect of the methyl substituents in the ethylenic linking chain. Methyl in a position α to the nitrogen atom strongly stabilizes the cyclic forms (**3c**, **3j**, **7c**, **7j**) whereas substitution on the α carbon to oxygen atom (**3b**, **3k**, **7b**, **7k**) seems to slow down the rate of the opening and ring-closure processes (Table VI) with no significant effect on the stability of the cyclic forms. There is still a pending question concerning the relative amounts of both cyclic tautomers. Namely, is the tautomeric equilibrium shifted to the right because the 5-*endo-trig* process is thermodinamically favored over the 6-*exo-trig* or is it the result of the fact that the favored stereoisomer of the (*E*)-imino ketone cannot lead the six-membered ring (kinetic preference)? We found, for compounds **6i**, **6j**, and **6k**, an inverse correlation between the $\Delta G_{Z/E}$ (-4.4 (**6j**), -3.7 (**6i**), and -2.8 (**6k**)) and the rate of 5-*endo-trig* ring closure (k_3) (7.8 (**6j**), 15.0 (**6i**), and 94.0 (**6k**)). Compound **6k** with a major concentration of the *Z*-stereoisomer exhibits a faster ring closure.

The ring–chain tautomerism of compounds **3o–q** derived from the condensation reaction between benzil and 2-amino alcohols was studied by ^{13}C NMR ($CDCl_3$) and IR ($CHCl_3$) by measurements in all cases of suitable signals (Table V, supplementary material). The two-component ring–chain tautomerism, oxazine (**1**)–imino ketone (**2**), was attained very rapidly, within a few seconds. The stereoisomer and tautomer ratios determined immediately after dissolution were the same as those found after 24 h. The ratio [1]/[2] is just above 1 for **3p** and **3q** and 3 for the unsubstituted oxazine **3o**. The relative amounts of the cyclic form, i.e., the regio- and stereoselectivity of the ring-closure process, showed trends similar to those found for compounds **3a–c**, **3i–k**. Cyclization of imino ketones **6o** and **6q** to the starting tautomers is stereoselective for **6p** and afforded a 50:50 mixture of diastereomers for **6q**. The regiochemistry always follows an 6-*exo-trig* pathway with no detection in the ^{13}C NMR spectra of signals attributable to the oxazolidine tautomers.

In connection with the above studies, we have studied the tautomerism of 2-acetyl-2-methyl- (**13a**), 2-benzoyl-2-methyl- (**13b**), and 2-benzoyl-2-phenyl-1,3-thiazolidines (**13c**) by ^{13}C and ^1H NMR ($CDCl_3$ and DMSO-d_6) spectroscopy. These systems highly prefer the ring form and in no case, within the limits of detection at 300 MHz, have we found detectable amounts of the open-chain tautomer. It is known[7] that the enhanced nucleophilicity of the sulfur atom and the reduced steric strain in the sulfur-containing heterocycles increases stability of the five-membered ring. This fact can be deducted by comparison to the behavior of the corresponding 1,3-oxazolidines.[23] Recently, it has been reported[24] that the stability difference between the

(21) Berrington, P. *Data Reduction and Error Analysis for the Physical Sciences*; McGraw Hill: New York, 1969.

(22) Astudillo, M. E. A.; Chokotto, N. C. J.; Jarkus, T. C.; Johnson, C. D.; Lewis, C. C.; Mc Donnell, P. D. *Tetrahedron* **1985**, *42*, 5919.

(23) A detailed kinetic study of oxazolidine hydrolysis has been reported: Fife, T. H.; Hagopian, L. *J. Am. Chem. Soc.* **1968**, *14*, 1007.

(24) Fülop, F.; Mattineu, J.; Pihlaja, K. *Tetrahedron* **1990**, *46*, 6545.

ring forms of 2-phenylthiazolidine in DMSO-d_6 might be 10^4 times higher than that of the 2-phenyloxazolidine ring due to the greater difficulty of unimolecular C–S bond breaking than C–O.[25]

Conclusions

The findings reported in this paper show that the substituents attached to a hydroxylated tether upon intramolecular cyclization by attack to a C=O bond (6-*exo-trig*) or C=N bond (5-*endo-trig*) can direct the pathway of reaction (regiochemistry and stereoselectivity) and determine the stability of the final products (six- versus five-membered rings). If the reactivity of the carbonyl bond is decreased, e.g., by conjugation with a phenyl substituent, the 5-*endo-trig* process is favored. When the intramolecular cyclization takes place exclusively by addition to a C=N bond the 6-*exo-trig* mode is prefered according to Baldwin's rules.

If an anomeric center is formed as the new stereogenic center, the stereoselectivity observed in the cyclization is remarkable. The exclusive conformation found when a molecule can exhibit two different stabilizing anomeric effects resulted from an antiperiplanar disposition of the heteroatom lone pairs of the stronger donor (N) with the best acceptor C–X bond (C–O).

Experimental Section

General. All reactions were run on the same scale as given in the general procedures and were monitored by ^{1}H NMR ($CDCl_3$) since usual TLC techniques led to wide decomposition of products. Crystallizations were carried out in freezer (–20 °C) using reagent-grade solvents. ^{1}H NMR (300- and 360-MHz) and ^{13}C NMR (20.1- and 75-MHz) spectra (δ) were measured using $CDCl_3$, DMSO-d_6 (or Me_4Si for ^{1}H NMR at 60 MHz in DMSO-d_6) as internal standards. Mass spectra were obtained at an ionization energy of 70 ev and are recorded as *m/e* (peak, rel intensity). GC/MS was performed on a Hewlett-Packard 5890 chromatograph equipped with a 30-m × 0.25-mm SPB-5 capillary column (helium carrier gas, flow rate 30 mL/min) coupled with a Series-5970 quadrupole mass selective detector. Analysis were performed at the Instituto de Química Bioorgánica del C.S.I.C. (Barcelona, Spain). 1-Phenyl-1,2-propanedione,[26] (*R**,*R**)- and (*R**,*S**)-3-amino-2-butanol,[27] and 1-amino-2-methyl-2-propanol[28] were prepared according to literature procedures. Compound **5** was already described.[5,6]

General Procedure for the Synthesis of 5,6-Dihydro-2-hydroxy-2,3-dimethyl-2*H*-1,4-oxazines 3a–g. To a stirred mixture of butanedione (0.5 g, 5.8 mmol), $MgSO_4$ (1.5 g), and CH_2Cl_2 (20 mL) was slowly added (5 min) the corresponding amino alcohol **1** (6.9 mmol). After being stirred at 25 °C, for the time indicated for each compound, the resulting mixture was diluted with benzene (20 mL) and filtered, and $MgSO_4$ (1.5 g) was added again (in order to remove excess of amino alcohol). Filtration and concentration (rotavap with a cold water bath) of the resulting solution led to the corresponding compound **3** which was purified by crystallization. Compounds **3** can be stored in a freezer (–20 °C) without appreciable decomposition. For ^{1}H NMR data see Table II.

General Procedure for the Preparation of 2-Phenyl-5,6-dihydro-2-hydroxy-3-methyl-2*H*-1,4-oxazines 3i–n. 1-Phenyl-1,2-propanedione (FPD) (0.5 g, 3.4 mmol) was allowed to react with amino alcohol **1** (3.5 mmol) at 25 °C. The reaction warmed the mixture enough to initiate the reaction, keeping both reactives in an homogeneous solution (in some cases the reaction flask was warmed to 50 °C). The stirred mixture was allowed to stand at 25 °C to produce an oily yellow solid which was left under vacuum (4 h), purified by crystallization, and stored in a freezer (–20 °C).

General Procedure for the Preparation of 2,3-Diphenyl-5,6-dihydro-2-hydroxy-2*H*-1,4-oxazines 3o–r. To a solution of benzil (0.5 g, 2.3 mmol) in benzene (3 mL) was added 2-amino alcohol **1** (2.8 mmol), and the solution was refluxed in a Dean-Stark apparatus for the time indicated in each compound and then, cooled and filtered. The resulting pale yellow solid was washed with cold Et_2O and left under vacuum overnight.

General Procedure for the Preparation of *cis*-Octahydro[1,4]oxazino[3,2-*b*]-1,4-oxazines 4. To a solution of butanedione (0.5 g, 5.8 mmol) in benzene (20 mL) was added amino alcohol **1** (11.6 mmol). After the period indicated in each compound the resulting solution was diluted with CH_2Cl_2 (20 ml), treated with $MgSO_4$ (1.5 g), filtered, and concentrated to afford the crude material which was purified by crystallization. For ^{1}H and ^{13}C NMR data see Table III.

2,2′,4,4′,5,5′-Hexamethyl-2,2′-bioxazolidine (9e) and 2,3,4a,6,7,8a-Hexamethyloctahydro-(2α,3β,4aα,6α,7β,8aα)-[1,4]oxazino[3,2-*b*]-1,4-oxazine (4e). A solution of butanedione (90 mg, 1 mmol), **1e** (200 mg, 2.2 mmol), and benzene (5 mL) was refluxed for 12 h, cooled, and concentrated to afford 230 mg (96%) of **9e** as a pale yellow oil (mixture of diastereomers) which after standing at 25 °C slowly produced white crystals of compound **4e**. The mixture of **9e** and **4e** was eluted with hexanes (2 mL) and filtered to leave pure **4e**. The filtrates can be concentrated and the process repeated until total conversion of **9e** into **4e**. **9e**: bp 90–94 °C (0.1 mmHg); IR (neat) 3290 (NH), 2960, 1440, 1360 cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.7–2.7 [m, 4 H, H4(4′), H5(5′)], 2.3 (br s, 2H, NH), 1.38 (s, 6 H, CH_3C2(2′)), 1.20 (d, 12 H, CH_3CH, J = 6 Hz); selected ^{13}C NMR ($CDCl_3$) 59.3–60.3 (C4), 81.1–80.1 (C5); GCMS (EI, 70 EV) *m/e* (rel intensity) (t_R = 5.1 min) 114 (100), 72 (72), 55 (18), 43 (18) (t_R = 5.7 min) 114 (100), 72 (65), 55 (15), 43 (16), (t_R = 6.3 min) 114 (100), 72 (62), 43 (15); **4e**: mp 151–152 °C (CCl_4), IR (KBr) 3300 (NH), 1375, 1230 cm^{-1}; MS (EI, 70 EV) *m/e* (rel intensity) 141 (16), 114 (77), 86 (24), 72 (100), 43 (27). For ^{1}H and ^{13}C NMR data see Table III. Anal. Calcd for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.59; N, 12.27. Found: C, 63.28; H, 10.70; N, 12.25.

1-Acetyl-1-methyl-*N*-(2-hydroxy-2-methylpropyl)-methanimine (6h). Following the general procedure described for the synthesis of compounds **3a–g** from butanedione (0.5 g, 5.8 mmol) and **1g** (614 mg, 9.0 mmol) after 4 h, 914 mg (96%) of **6h** as a pale yellow oil was obtained (>90% purity by ^{1}H NMR): bp 92 °C (4.5 mmHg); IR (neat) 3600–3100 (OH), 1695 (C=O), 1640 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.33 (m, 2 H, CH_2), 2.96 (br s, 1 H, OH), 2.40 (s, 3 H, CH_3CO), 1.96 (m, 3 H, CH_3C=N, J = 1.5 Hz), 1.28 (s, 6 H, $(CH_3)_2$C–).

General Procedure for the Synthesis of 2-Acetyl-2-methyl-1,3-oxazolidines 7a–e,h. Following the general procedure described for synthesis of compounds **3o–r**, amino alcohols **1a–e** and **1g** were allowed to react with 2,3-butanedione for 10 h under reflux (for **7a** the reaction time was found to be 30 min and for **7b**, 2 h). The resulting solution was concentrated and the residue distilled under vacuum to yield **7** as unstable colorless oils: **7a** (70%), bp 62 °C (0.05 mmHg); **7b** (40%), bp 92 °C (2 mmHg); **7c** (80%); **7d** (85%), pe 62–64 °C (3 mmHg); **7e** (90%); **7h** (60%), bp 58–60 °C (0.08 mmHg). Their most characteristic spectroscopic features are: IR (neat) 1715–1720 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.33–2.25 (s, CH_3C=O), 1.50–1.45 (s, CH_3C2); ^{13}C NMR ($CDCl_3$) 208.6–207 (C=O), 97.9–96.3 (C2). Compounds **7** showed, in the NMR spectra, signals that correspond to their tautomers.

***N*,*N*′-Bis(2-hydroxy-2-methylpropyl)-2,3-butanediimine (8g).** To a mixture of butanedione (150 mg, 1.7 mmol), benzene (10 mL), and molecular sieves (4 Å, 1 g) was added **1g** (360 mg, 4 mmol). After standing at 25 °C for 16 h the mixture was filtered and concentrated to leave 490 mg of the title compound as a pale yellow oil, which was obtained as a mixture in solution with the chain tautomer **9g** (15% by ^{1}H NMR): IR (neat) 3700–3100 (OH), 1670 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.26 (br s, 4 H, CH_2), 2.9 (br s, 1 H, OH), 2.10 (2, 6 H, CH_3C=N), 1.3 (s, 6 H, $(CH_3)_2$C); ^{13}C NMR ($CDCl_3$) 168.2 (C=N), 66.5 (COH), 56.5 (CH_2), 27.0 ($(CH_3)_2$C), 13.1 (CH_3C=N).

2,2′,5,5,5′,5′-Hexamethyl-2,2′-bioxazolidine (9g). Following the procedure described for synthesis of **9e** from butanedione (90 mg, 1.0 mmol) and **1g** (200 mg, 2.2 mmol), 232 mg (97%) of **9g**

(25) Fife, T. H.; Natarajan, R.; Shen, C. C.; Bembi, R. *J. Am. Chem. Soc.* **1991**, *113*, 3071.
(26) Hartman, W. W.; Roll, L. J. *Org. Synth.* **1943**, *23*, 1.
(27) Dickey, F. H.; Fickelt, W.; Lucas, H. J. *J. Am. Chem. Soc.* **1952**, *74*, 944.
(28) (a) Cox, R. F. B.; Stortmont, R. T. *Org. Synth.* **1935**, *15*, 1. (b) Kjaer, A.; Gmelin, R.; Jensen, R. B. *Acta Chem. Scand.* **1956**, *10*, 432.

as a yellow oil (equimolecular mixture of diastereomers by ^{13}C NMR) was obtained. An analytical sample was prepared by vacuum distillation, bp 86–88 °C (0.1 mmHg); IR (neat) 3290 (NH), 1445, 1360, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) 3.03 (br s, 1 H, NH), 2.93 (br s, 2 H, CH_2), 2.92 (br s, 2 H, CH_2), 1.40 (s, 6 H, $CH_3C2(2')$), 1.35 (br s, 6 H, CH_3CH), 1.26 (s, 3 H, CH_3C), 1.07 (s, 3 H, CH_3C); selected ^{13}C NMR ($CDCl_3$) 99.5–98.9 (C2), 57.7–57.4(C4), 78.9–78.6(C5). Anal. Calcd for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.59; N, 12.27. Found: C, 62.89; H, 10.45; N, 12.20.

Kinetics. Ring–chain–ring tautomerism of compounds **3a–c** and **3i–k** were followed by monitoring the methyl signals indicated in Table II with a Bruker AC-200 (200 MHz) in $CDCl_3$ (99.8%). A weighed amount of ring-closed compound was dissolved in 0.5 mL of $CDCl_3$ in the NMR tube. The tube was stoppered, sealed, and introduced into the NMR probe. The temperature of the probe was maintained constant during all the experiments at 308 ± 0.5 K. Kinetics runs were initiated taking spectra at appropriate time intervals. The concentration of each component in solution was obtained from the integrals of the methyl signals which were measured and checked by graphic standard procedures (six times) and by numeric programming calculation. The combined integrals of the methyl signals were taken for internal reference. For compounds **3o–q** the ring–chain tautomerism was followed by ^{13}C NMR ($CDCl_3$, 20.1 Hz) on a Varian FT80 spectrometer.

For longer experiments additional signals usually appearing after 20 h for compounds **3a–c** and after 400–600 min for **1d–f** were found. These unidentified signals are probably due to hydrolysis of imino ketones **2**[23] to starting materials with formation of polycondensed products. The existence of this competitive reaction obviously complicates the evaluation of the equilibrium ratio. However, for all compounds subjected to kinetic analysis this behavior was sufficiently slow to enable kinetic evaluation.

X-ray Data for 3f. Recrystallization of **3f** from EtOAc at −12 °C gave suitable crystals for analysis. A colorless block-shaped crystal mounted in a Lindemann glass capillary was used for data collection: $C_8H_{15}NO_2$, monoclinic, space group $P2_1/c$, a = 16.274 (1) Å, b = 9.707 (1) Å, c = 11.448 (1) Å, b = 91.41 (1)°, M = 157.212, ν = 1807.9 (3) Å^3, Z = 8, D_c = 1.1552, $F(000)$ = 688 CuK_a radiation, m = 6.351. Preliminary examination and intensity data were measured on a four circle diffractometer: PW 1100 Philips using bisecting geometry ($q < 45°$) yielding 3084 unique reflections of which 2515 had $I < 2s(I)$ and were used in the structure solution and refinement. The structure was solved by direct methods.[29] Refinement[30] converged with R = 0.053.

X-ray Data for 4a. Recrystallization of **4a** from acetone at −12 °C gave suitable crystals for analysis, $C_8H_{16}N_2O_2$, monoclinic, space group C_2/c, a = 13.422 (1) Å, b = 6.056 (1) Å, c = 11.465 (1) Å, b = 109.01 (2)°, M = 172.227, ν = 1807.9 (3) Å^3, Z = 4, D_c = 1.2979, $F(000)$ = 376 CuK_a radiation, m = 7.270. Preliminary examination and intensity data were measured as for **3f** except that $q < 39°$ yielding 746 unique reflections of which 695 were used in the refinement. The final R value was 0.055.

X-ray Data for 4e. Recrystallization of **4e** from EtOAc gave suitable crystals for analysis, $C_{12}H_{24}N_2O_2$, monoclinic, space group P_2/c, a = 11.578 (12) Å, b = 13.273 (1) Å, c = 8.637 (1) Å, b = 92.60 (3)°, M = 228.334, ν = 1325.9 (2) Å^3, Z = 4, D_c = 1.144, $F(000)$ = 504 CuK_a radiation, m = 5.864. Preliminary examination and intensity data were measured as for **3f** except that $q < 45°$ yielding 2244 unique reflections of which 2076 were used in the refinement. The final R value was 0.040.

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Supplementary Material Available: Tables of final coordinates, bond distances, angles, and anisotropic thermal parameters for non-hydrogen atoms, ^{13}C NMR spectra of compounds **8g**, **9g**, **12a**, and **12b**, ^1H NMR spectra of compound **6g**, plots of experimental and calculated dependent concentration vs time of the ring–chain–ring tautomerism of compound **3j** (Figure 2), synthesis of compounds **3a–r**, **4a–c**, **11**, and **12**, Table IV (relevant ^{13}C NMR and IR for **7** and **9**), Table V (initial and equilibrium concentrations of tautomers **3a–c**, **3i–k**), and X-ray data for **3f**, **4a**, and **4e** (29 pages). Ordering information is given on any current masthead page.

(29) Computer programs used: MULTAN 78 System, Main, P. et al. University of York, England, 1978; X-RAY 76, University of Maryland, College Park, MD, 1976; PARST, University of Parma, Italy, 1972 and implemented on a *VAX 11/750* computer.

(30) *International Tables for X-ray Crystallography*; Birmingham: Kynoch Press, 1974; Vol. 4 (Present distributor Kluwer Academic: Dordrecht).