



**Synthesis and Stereochemistry of Some Heterocyclic Saturated
 Compounds Based on *l-p*-Nitrophenylserinol Skeleton (I).
 Ring-Chain Tautomerism of Some Schiff Bases of *l-p*-Nitrophenylserinol**

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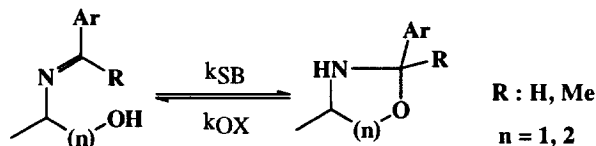
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Abstract - The ring chain tautomerism of the title compounds is described as an essential premise and concept as well for the synthesis of its saturated heterocyclic derivatives. Stereochemical implications are discussed about the versatile reactivity of *l-p*-nitrophenylserinol.

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INTRODUCTION

Ring-chain tautomerism, as a consequence of the reversible addition of an hydroxyl group to an iminic double bond is already a very well known feature of the Schiff bases of aminoalcohols (an *Endo-Trig* cyclization, against the Baldwin's rule¹, **Scheme 1**):



Scheme 1

According to the literature, this type of equilibrium, for monoaminoalcohols, was almost exhaustively explored when, besides classical factors (e.g. influence of an aryl group, type of heterocycle²⁻⁴, pH⁵⁻⁷, etc.), special attention was paid to new ways of investigation such as high resolution ¹H-NMR methods (including

both solution and solid-state approach⁸).

L-2-Amino-1-(4-nitrophenyl)-propane-1,3-diol (as 1*R*,2*R* or 1*S*,2*S* enantiomer), better known by its trivial name as "*threo-p*-nitrophenylserinol" has a distinct but unfortunate status as attention focused on its synthesis only, for more than 30 years with all possible types of derivatives (including Schiff bases) being prepared, more or less strictly, for applicative reasons⁹⁻¹⁶ (towards the 1*R*,2*R* enantiomer, the key intermediate in chloromycetine synthesis). We have recently reviewed¹⁷ these facts and called attention to the fact that no pertinent study on the field concerning the stereochemistry of these structures has been reported.

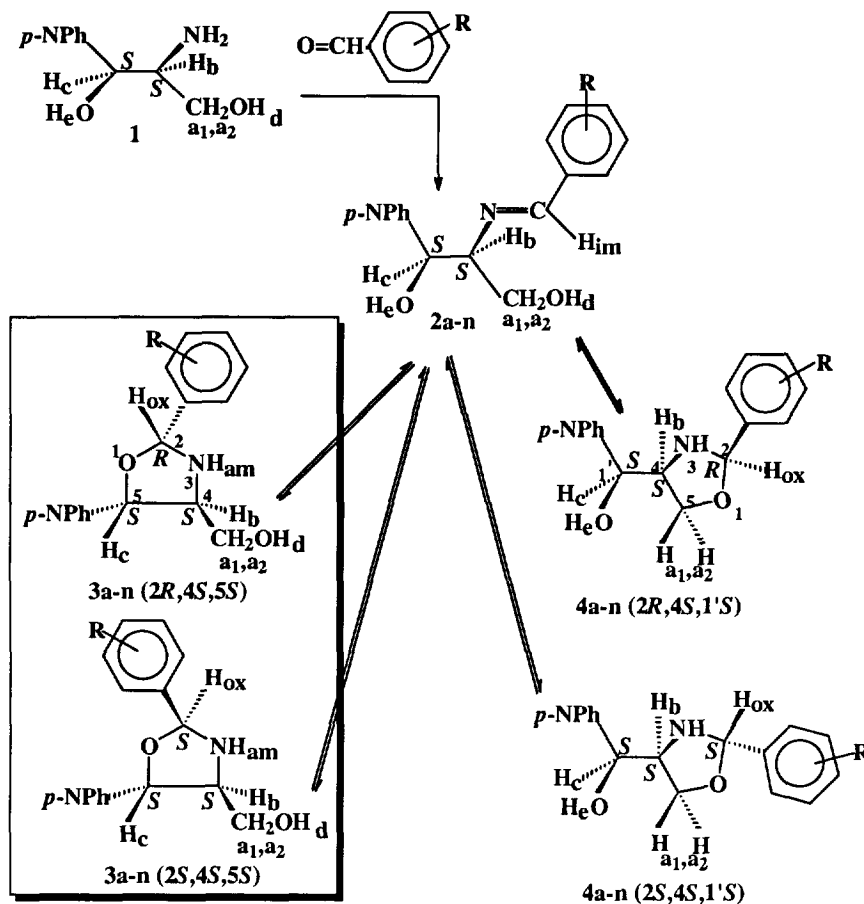
The hypothesis of ring-chain tautomerism was only suggested in the 1950's by Pedrazzoli and Tricerni¹² based almost entirely on Bergmann's earlier exhaustive review¹⁸; no credible evidence was offered from IR and UV data. Later, Nagawa¹⁵, Edgerton and Coll.^{13,14} and Suami *et al.*^{9,10} published their original results, but the unitary structure of the Schiff bases was generally accepted. To the best of our knowledge, the most recent study on the subject is, however, a structural one, (Potapov and Coll.^{19a}, 1990), when CD curves of some Schiff bases were analysed with a brief highlight on stereochemical aspects.

RESULTS AND DISCUSSION

Fourteen Schiff bases of (1*S*,2*S*)-*p*-nitrophenylserinol were synthesised and their high resolution ¹H-NMR spectra were studied. As depicted in **Scheme 2**, ring-chain tautomerism would result in two pairs of epimers **3**, **4** depending on both the regioselectivity and the diastereoselectivity of the oxazolidinic ring closure. We anticipate here that if the chirality of the heterocyclic amino group is also considered, four pairs of epimers are possible to expend upon an already complicated enough problem. Taking into account that very few similar data were reported^{19a-c} to be compared with ours, the following preliminary steps were considered to be covered:

1. Conformational aspects of the starting compounds

The ¹H-NMR spectrum of (1*S*,2*S*)-*p*-nitrophenylserinol **1** (**Figure 1**) is less simple than would have been predicted. The shape of the signals located at 5.48ppm (secondary hydroxyl group, H_c), 4.58ppm (primary hydroxyl group, H_d) and 1.37ppm (amino group) indicates the low speed of proton interchange between the three protic groups placed successively in *gauche* conformations (**Scheme 3**). The doublet of H_c (4.68ppm, *J* = 4.1Hz) is, unfortunately, not consistent with the signal of H_b (overlapped by the solvent peak, at 2.50ppm). Diastereotopicity of the C³ methylene (H_{a1,a2}) is about 0.37ppm, but only one of its protons exhibits all four



p-NPh- is the symbol for the *p*-nitrophenyl group.

R : H 2a ; *p*-MeO 2b ; *p*-O₂N 2c ; *p*-Me₂N 2d ; *m*-HO 2e ; *p*-HO 2f ; *m*-CH₃ 2g ; *p*-CH₃ 2h ; *o*-HO 2i ; *o*-Cl 2j ; in the next Schiff bases, the (hetero)aromatic ring is: α-naphthyl 2k ; 2-Py 2l ; 3-Py 2m ; 4-Py 2n.

Scheme 2

expected peaks (AMX system $J_{a1-a2}(\text{gem}) = 10.3\text{Hz}$, $J_{b-a1}(\text{vicinal}) = 5.6\text{Hz}$). Although the protonic interchange with the solvent can not be neglected, it may be presumed that the starting aminodiol has no particular preference for a given conformation. Thus, when the amino group was converted into an iminic structure, the parent compound of the Schiff bases series (2a, R = H) showed interesting conformational relationships (Figure 2). The doublet belonging to H_e (5.57ppm, $J_{c-e} \approx 5.3\text{Hz}$) and the triplet of H_d (4.55ppm, $J_{d-a1} \approx J_{d-a2} = 5.3\text{Hz}$) prove their fixed location as two distinct hydroxyl groups, with no interchange between them. This might be considered as evidence for an *antiperiplanar* conformation (C), assigned by the helicity rule as *P* (Scheme 3),

determined by the bulky aryl substituents (placed also *anti*). Neither intramolecular hydrogen bonding is involved, as in the case above, nor the solvent^{19a-c} [as Mikite and Coll. found for the epimers *l* (or *u*)-2-nitro-1-phenylpropane-1,3-diol^{19c}].

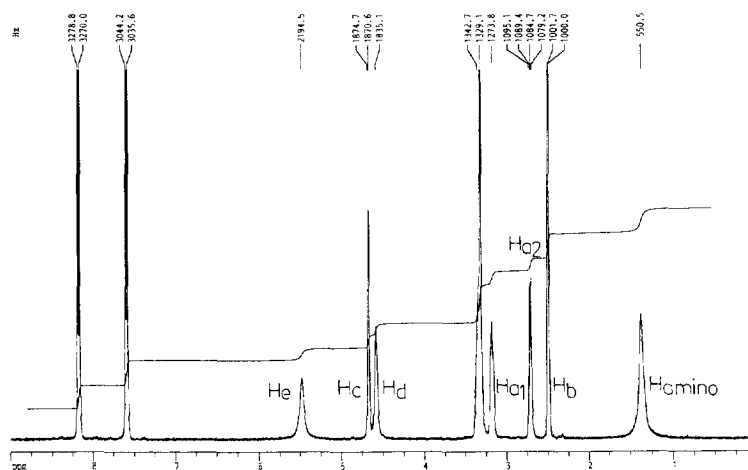


Figure 1: ¹H-NMR spectrum of *l*-*p*-nitrophenylserinol (solvent DMSO-*d*₆)

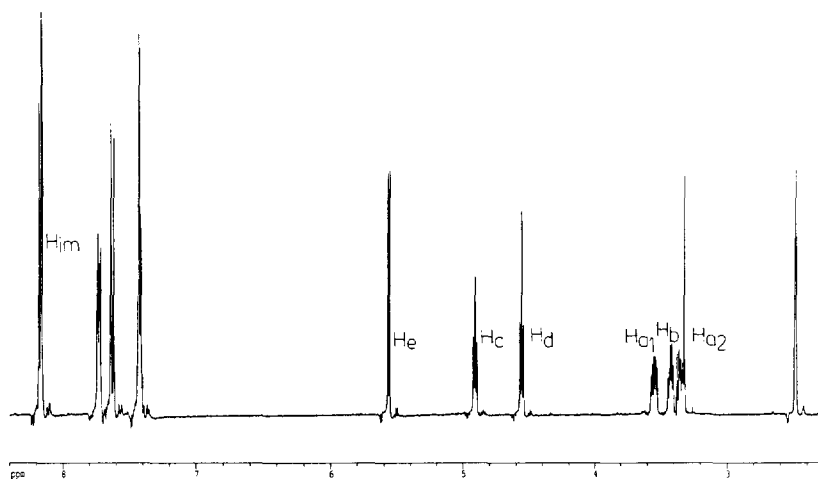
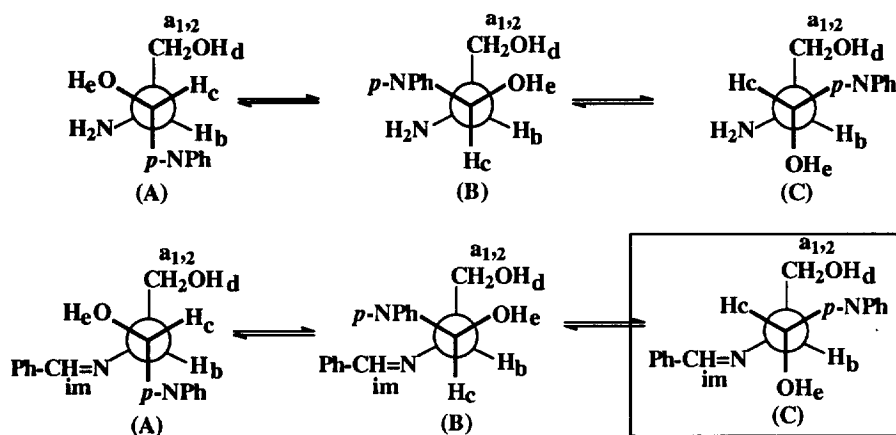


Figure 2: ¹H-NMR spectrum of Schiff base **2a** (solvent DMSO-*d*₆)

The H, H-COSY experiment confirmed all these assignments; moreover, we note here that they were recognized in all Schiff bases of the **2a-n** series.

The *E* arrangement of the arylideneamino group was established by means of NOE-diff. when double irradiation of H_b gave the enhancement of H_{im} signal.



Scheme 3

2. The ring-chain tautomerism

The study of compounds **2a-n** in anhydrous DMSO- d_6 at room temperature, has unambiguously demonstrated obvious change for every example, except for **2i** (see later). In Figure 3 a detail of the ^1H -NMR spectrum is given as typical example (compound **2a** after 100h).

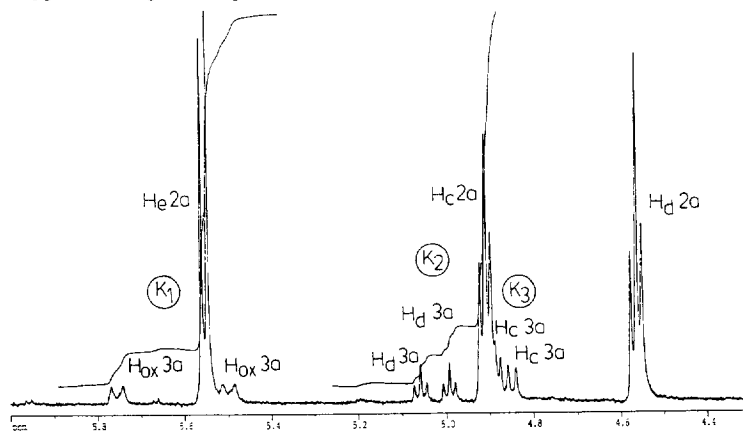


Figure 3: ^1H -NMR spectrum (detail) including the reference protons of the Schiff bases **2a** and the mixture of its tautomers **3a** (after 100h, Scheme 2)

To estimate the molar ratio between ring-chain tautomers, protons located in the 6.50 - 4.40ppm region were chosen as "reference protons", to avoid the expected overlapping (in the aromatic region and upfield to 4ppm). The detail from Figure 3 put in evidence, besides peaks of the starting Schiff base, twice three groups of signals, with equal intensity. Each of the three groups is in correlation (2D COSY $^1\text{H}/^1\text{H}$ spectrum) and has been attributed to **3a** (2*R*,4*S*,5*S*) and **3a** (2*S*,4*S*,5*S*) epimers. Signals located at 5.75 and 5.54ppm are split as

doublets with a large coupling constant (11.6Hz) and both triplets at 5.05 and 4.98ppm have the same coupling, 6.5Hz; two doublets ($J = 7.0\text{Hz}$) are observed at 4.87 and 4.85ppm resp. The largest coupling pattern could not be assigned to a geminal one (i.e. $H_{a1,a2}$ are expected to be located upfield) but presumably with a big *trans* disposal between H_{ox} and H_{amino} (**3a** epimers, Scheme 1). Furthermore, the two triplets represent H_d (despite diastereotopicity of $CH_{a1,a2}$ methylene, it was found $J_{d-a1} \equiv J_{d-a2}$ in both **3a** epimers). The most shielded doublets were reasonably assigned to H_c . Supplementary confirmations were obtained from the spectrum of compound **2a** if some D_2O (traces) was added (Figure 4). A remarkable simplification was observed.

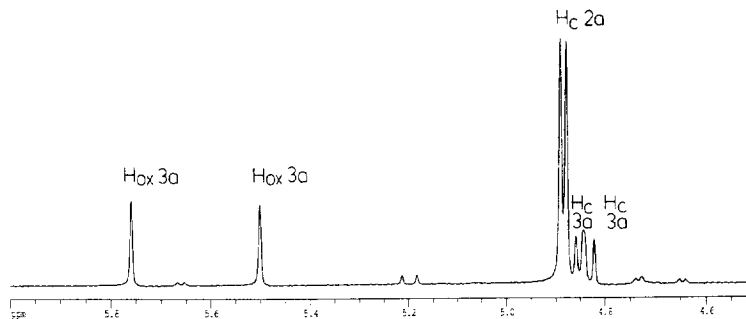


Figure 4: ^1H -NMR-spectrum (detail) including the reference protons of the compound **2a** and its tautomers **3a**, after 100h ($\text{DMSO-d}_6 + \text{D}_2\text{O}$)

The two more deshielded doublets became two distinct singlets (5.75 and 5.54 ppm) that prove their initial vicinal coupling with an exchangeable proton. All triplets belonging to H_d (**2a**, **3a**) were eliminated due to the expected rapid proton interchange. Finally, the initial triplet of H_c was converted in a doublet ($J_{c-e} = 4.9\text{Hz}$) but the doublets (partially overlapped) of H_c belonging to the two new environments **3a** remained unchanged. That is, they are not longer coupled with exchangeable protons. It was concluded that the ring closure is regioselective (involving the imino group and secondary hydroxyl only) but not diastereoselective, to give both epimers **3a** (*R, S, S* + *S, S, S*); their equal concentration is proved by the magnitude of the corresponding integrals. Thus, it was possible to calculate tautomeric ratios (equilibrium constants **K**, as an average of three local values **K**₁, **K**₂, **K**₃, see Figure 3) defined as:

$$\mathbf{K} = [\mathbf{3}]/[\mathbf{2}] \quad (1)$$

In the above relation **[3]** is the concentration of epimeric oxazolidines [as sum of **3a-h** (*S, S, S*) + **3a-h** (*R, S, S*)]⁴ and **[2]** is the concentration of Schiff base. By varying the *m(p)*-substituent of the benzyldeneamino ring, as

method earlier described by Paukstelis and Lambing²⁰, a satisfactory correlation according to the Hammet-Brown equation was obtained:

$$\lg K_X/K_H = \rho\sigma^+ \quad (2)$$

K_X is the ring-chain equilibrium constant for each term from the series **2a-h**, K_H is the same constant of the parent-compound **2a**; ρ is the reaction constant and σ^+ is the Hammet-Brown constant of the substituent^{21,22}. The results, chemical shifts of the reference protons and their coupling constants are listed in Tables 1- 3.

Table 1: The Ranges of Chemical Shifts of the Schiff Bases **2a-n** and of their Tautomers (epimeric oxazolidines **3a-n**)

$\delta(\text{ppm})^*$ Compound**	H _c	H _c	H _d	H _{im}	H _{ox}	ρ
2a-n	5.49-5.82(d)	4.88-5.04(t)	4.51-4.63(t)	7.97-8.75(s)	-	
3a-n (<i>R, S, S</i>)	-	4.85-5.02(d)	4.95-5.05(t)	-	5.41-6.23(d)	0.392
3a-n (<i>S, S, S</i>)	-	4.81-4.96(d)	5.04-5.19(t)	-	5.66-6.50(d)	

* δ -values are given as min. to max. value, depending on the benzylidene substituents; (s)-singlet, (d)-doublet, (t)-triplet.

** the assignments as **3** (*R, S, S*) or **3** (*S, S, S*) epimer configuration, see later.

Table 2: The Main Coupling Constants $J(\text{H}, \text{H})$ of Schiff Bases **2a-n** and of their Tautomers (epimeric oxazolidines **3a-n**)

J (Hz) Compd.	J_{c-e}	J_{c-b}	J_{a1-a2}^*	J_{d-a1}	J_{d-a2}	J_{b-a1}^*	J_{b-a2}^*	$J_{\text{OX-NH}}$
2a-n	4.1-5.8	4.2-5.3	9.1-11.2	5.0-5.5	5.0-5.5	3.3-5.1	5.8-8.3	-
3a-n (<i>R, S, S</i>)	-	5.2-7.7	-	5.2-6.5	4.1-6.5	-	-	8.3-13.6
3a-n (<i>S, S, S</i>)	-	5.3-8.4	-	5.2-6.5	5.2-6.5	-	-	10.3-12.0

* Overlapped in almost all of epimers **3** spectra.

Table 3: Equilibrium data between Schiff-bases **2** (chain forms) and their tautomers (ring forms, epimeric oxazolidines **3**)

Compd.	Chain form (%)	Ring forms (%) [*]	K ^{**}	$\sigma^{+21, 22}$
2a	77	23	0.304	-
2b	87	13	0.147	-0.78
2c ^{***}	60	35	0.583	+0.79
2d	94	6	0.064	-1.70
2e	86	14	0.163	-
2f	91	9	0.104	-0.92
2g	78	22	0.285	-0.10
2h	82	18	0.214	-0.31
2i	100	-	-	-
2j	81	19	0.234	-
2k	67	33	0.483	-
2l ^{***}	36	56	1.555	-
2m ^{***}	64	32	0.500	-
2n ^{***}	52	40	0.769	-

^{*} all (%) ring-forms are given as a sum of **3** (*R*, *S*, *S*) + **3** (*S*, *S*, *S*) epimers, see rel. (1), (2)

^{**} *r* value = 1.096 is only satisfactory because the small amounts of **4** epimers (also formed, **Scheme 1**) were neglected in **2a-h** series (appropriate for Hammet-Brown linearization), see **Table 4**.

^{***} compounds **2c**, **2l-n** exhibited, besides **3**, the presence of epimers **4**, see **Table 4**.

Data from **Tables 1-3** allows to comment on some essential points:

a) The differences between δ -values of the same proton between the two epimeric environments **3** (*S*, *S*, *S*) and **3** (*R*, *S*, *S*) range about 0.25-0.27ppm (H_{ox}), 0.02-0.15ppm (H_d) and 0.02-0.13 (H_c). H_{ox} is the most sensitive with respect to both the configuration of the new chiral center (C^2) and C^2 -substituent. It is pertinent to assume that H_{ox} and H_d (the best separated signals), are more deshielded if this configuration would be *S* (when the two aromatic systems are *trans* located, see later, **Scheme 6**).

b) *J*-values are comparable in both epimers, showing that the configuration at C^2 has a minor influence regarding the conformation of the oxazolidine ring. Thus, the magnitude of J_{c-h} is similar with vicinal *trans*-couplings on the same type of moiety, earlier reported by Crabb and Coll.²³, and later by us²⁴ for 1-aza-4-(4-

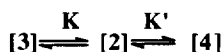
nitrophenyl)-2,8-di(substituted)-3,7-dioxabicyclo[3.3.0]octanes. The magnitude of 3J coupling between the oxazolidinic and aminic protons ($J_{\text{ox-NH}}$) is a very unusual one²⁵, proving a possible *trans*-disposal between H_{ox} and H_{amino} . Although a singlet would be more plausible for both H_{ox} and H_{amino} it must be observed that, after equilibration, no singlet was detected in the appropriate region. The unaffected primary hydroxyl group is still insensitive to any intra- or intermolecular hydrogen bond (see both triplets, **Figure 3**) despite Alva Astudillo's previous considerations²⁶ about this type of equilibria performed in DMSO- d_6 .

c) The observed regioselectivity and the absence of any diastereoselectivity of the ring closure should be examined differently. In fact, one may distinguish between compounds **2a-n**: series **2a-h** obeys the Hammett-Brown equation, and series **2i-n** does not. The stereoreactivity was, qualitatively, the same. The regioselectivity was suggested in 1956 by Bergmann and Coll.²⁷ (reaction of **1** with ketones) as an "activation" by the *p*-nitrophenyl group of the secondary hydroxyl. From our NMR data, the differences between $\Delta\delta H_d-H_e$ in all **2a-n** series were almost the same: 1ppm (with max. $\pm 5\%$ fluctuation); for *l-p*-nitrophenylserinol itself we found exactly 1ppm. These values might be correlated with different pKOH_e and pKOH_d values to assume that the secondary hydroxyl (the most hindered nucleophile) is, however, more reactive due to an autocatalysis promoted by the more acidic proton (H_d)^{19c}. Regioselectivity (and its limits) obeys electronic requirements and not steric ones, as depicted in **Table 4**.

Table 4: Regioselectivity of the Ring-Chain Tautomerism for the Compounds **2c, l- n**

Compound	δH_e (ppm)		J_{c-e} (Hz)		Ratio (3 vs. 4)	$K'^{**} = [4]/[2]$
2c → 4c	5.87	5.82	4.4	4.4	7 : 1	0.083
2l → 4l	6.11	5.71	5.0	4.1	7 : 1	0.222
2m → 4m *	5.78	-	4.6	-	8 : 1	0.062
2n → 4n *	5.81	-	4.1	-	5 : 1	0.135

* one epimer detected; ** K' were calculated considering both equilibria below and equal concentrations of type-4 epimers



Compound **2l** should be seen more as a mixture of epimeric oxazolidines **3l** than Schiff base and K value shows about 56% **3l** ring forms (**Table 3**). Its $^1\text{H-NMR-1D}$ -experiment (**Figure 5**) exhibits, besides the similar signals already discussed (**Figure 3**) two other small doublets (6.11 and 5.71ppm, $J = 5.0$ and 4.1Hz resp.) which could be assigned to H_e protons (**4l** mixture of both epimers, **Scheme 2**); an estimation of molar ratios

between regioisomers is about 7:1(**3l** vs. **4l**).

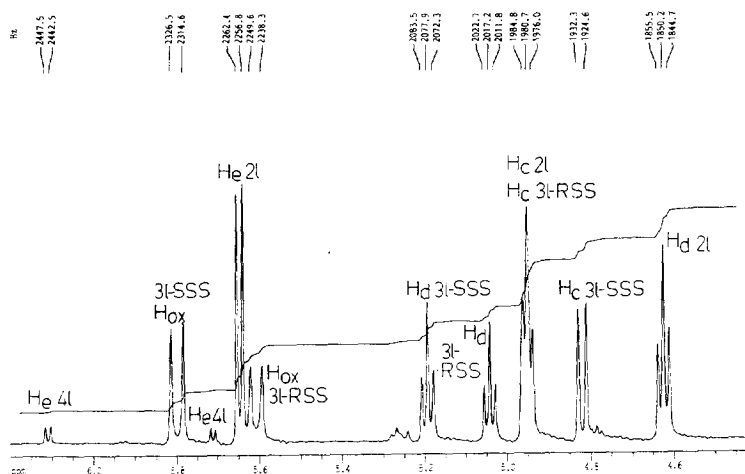
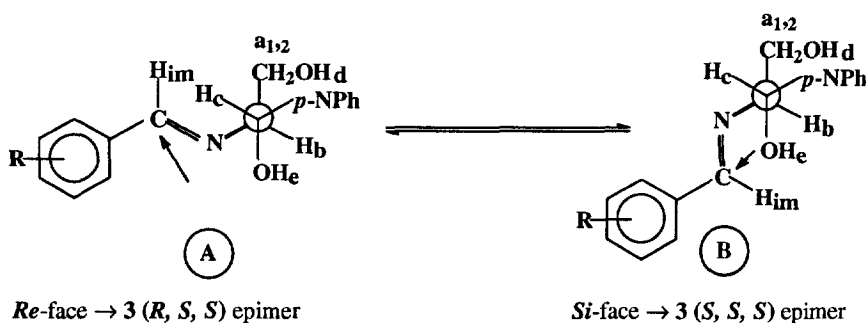


Figure 5: ^1H -NMR spectrum on the reference protons zone (mixture of the Schiff base **2l** and its tautomers, epimeric oxazolidines **3l**, after 350h)

These last assignments seem somewhat hazardous, but are consistent with the fact that, as a consequence of the ring closure (e.g. to give **3** or **4** type mixtures) neither the vicinal couplings, nor the chemical shifts of the remaining hydroxylic proton are dramatically modified (**Table 1, 2**). Also, mixtures of type-4 epimers were present in almost all terms of series **2a-n** but their relevant signals were too small for the satisfactory calculations to be definitive. As data from **Table 4** indicate, the greater content of ring form was present at the end of equilibration time, the smaller regioselectivity of the ring closure was observed. Although not both of type-4 epimers were detected in some of the above cases (**4m, 4n**), it is presumably due to overlapping of the relevant signals and not a tendency to diastereoselective ring closure.

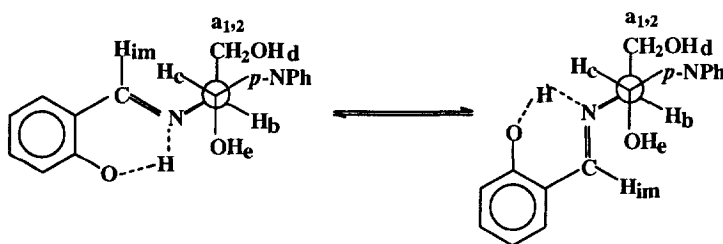
The nondiastereoselective cyclization was observed for all terms of series **2a-n**. An equimolar ratio between epimers (**Figure 3, 5**) was obtained with no exception during all equilibration time. On the other hand, this time was long enough (160-350h) for an accurate detection of the equilibrium state. For the parent compound **2a**, its equilibrium was considered as 1st order and $k_{\text{OX}} = 0.076$ and $k_{\text{SB}} = 0.023\text{h}^{-1}$ (r linear correlation 0.976) were calculated (**Scheme 1**). A slow tautomeric equilibrium whose epimeric products have no detectable difference regarding their thermodynamic stability was then postulated for all examples **2b-n**. If the starting substrate conformations are examined simply by means of Dreiding models (**Scheme 4**) conformer **B** seems to be more favoured to the nucleophilic interaction to give **3** (*S, S, S*) epimer. The **A** conformer is not more hindered than **B**, but the cyclization would involve a preliminary clockwise rotation around $\text{C}^1\text{-C}^2$ bond. No serious steric hindrance opposes this behaviour concerning the basic *l*-*p*-nitrophenylserinol skeleton (see

Scheme 3). It should be noted that *ortho*- substitution and further *ortho* + *meta*-substitution on the arylidene system (compounds **2j**, **2k**) induced no diastereoselectivity.



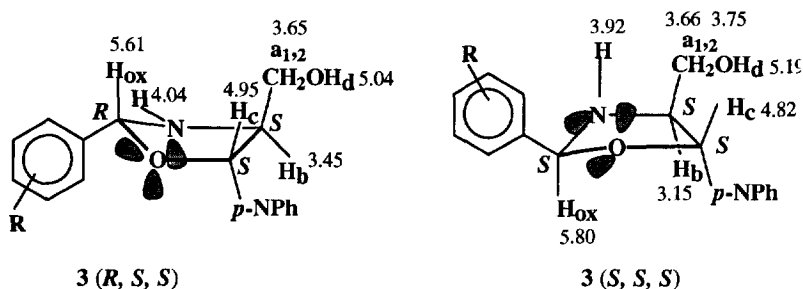
Scheme 4

d) The absence of any evolution of compound **2i** could be explained due to the intramolecular hydrogen bond between the *o*-phenolic hydroxyl and the iminic nitrogen, in complete agreement to CD curves earlier discussed by Potapov and Coll.^{19a} and our above considerations (see c)(Scheme 5).



Scheme 5

e) Some conclusions are possible with respect to the preferred conformation of the two epimers (**Scheme 6**).



Scheme 6 (only δ -values for the **3I** epimers are depicted)

They are based on ¹H-NMR data for the compound **2i** whose equilibrium was the more shifted to ring form. The already mentioned strong coupling between H_{ox}-H_{amino} could be considered as preliminary evidence that entire conformation is subordinated by the preference of the bulky substituents (-CH₂OH and *p*-NPh) for

trans (*pseudo-axial*)-disposal. Thus, no *gauche* interaction is observed, as a *trans*-diequatorial conformation would be required. The conformational option of the new Ar group is to avoid *syn*-axial interactions and it is reasonable to assume its position to be equatorial. The absence of diastereoselectivity in the ring closure is in good agreement with this isolate disposal (see also $J_{\text{ox-NH}}$ values). Thus, an envelope shape and a remarkable configurational stability of the NH heterocyclic group should be not neglected.

The COSY spectrum (Figure 6) was very relevant for the couplings exhibited by the major epimers [only protons belonging to **3l** (*S, S, S*), **3l** (*R, S, S*) are labelled as diagonal peaks].

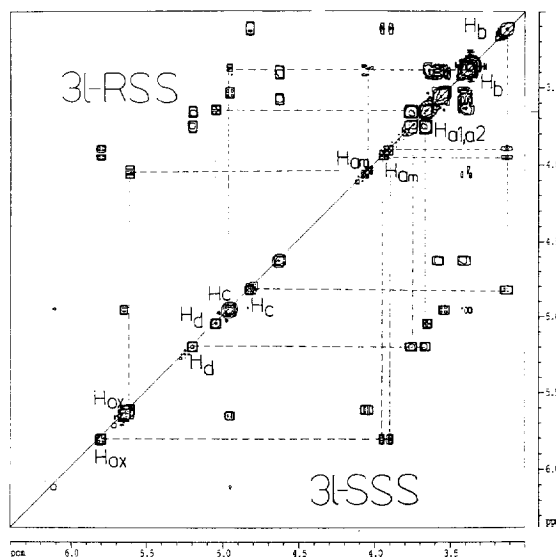


Figure 6: 2D-(H, H)-COSY experiment for the Schiff base **2l** and its tautomeric epimers **3l** (*R, S, S*) + **3l** (*S, S, S*) after 350h

It was possible to make a coherent assignment regarding not only the location of the "reference protons" but also δ -values for H_b , $H_{a1,a2}$, and H_{amino} , depending on the configuration of the epimers, as depicted in Scheme 6. If spectra are compared (Figure 3, Figure 5), no significant difference concerning the above proton δ -values assignments is perceptible. That is, extrapolation of proton assignments depending on configuration of the epimers for entire **3a-n** series is not hazardous. However, the exploration of the upfield region (Figure 7) exhibited the aminic protons as two distinct triplets (in fact two partially overlapped doublets).

Thus, the remaining unexpected problem was to assign the configuration of the N^3 -chiral center. NOE-diff experiments were not very useful to solve this problem because of polarisation transfer and the small distances between essential protons that made risky complete description of the molecular environments.

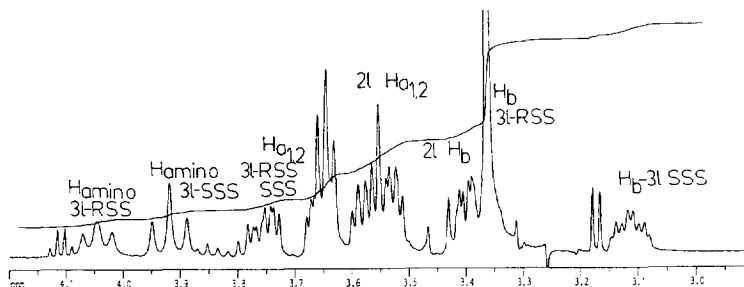


Figure 7: ^1H -NMR spectrum (detail) of the Schiff base **2l** and its tautomers (epimeric oxazolidines **3l**) after 350h

Thus, discrimination between epimers **3l** was made starting from H_{α} which is more deshielded when C^2 configuration is *S* (based on *p*-NPh deshielding vicinity). Then, a combined analysis (**Figure 5-7**) allowed the assignments depicted in **Scheme 6**. In the case of **3l** (*S, S, S*) epimer, *trans*-couplings $J_{\alpha\text{-NH}} \equiv J_{\text{b-NH}}$ (11.3-10.6 Hz resp.) are plausible for an axial position of the aminic proton. For **3l** (*R, S, S*) epimer the same assumption is, unfortunately, not quite valid, because one should admit that a *trans*-vicinal coupling has the same magnitude as a *cis*-vicinal one (**Scheme 6**). We note, however, that an equatorial position of the aminic proton is consistent with the chemical shift of H_b (overlapped by the lone pair on N^3) which is 0.30 ppm more deshielded than H_b in the (*R, S, S*) environment.

CONCLUSIONS

The ring-chain tautomerism of the Schiff bases of *l-p*-nitrophenylserinol can be accurately enough depicted as, at least one, distinct nucleophilic equilibrium involving largely the secondary hydroxyl group. The more the equilibrium is shifted towards ring forms, the smaller the regioselectivity observed, giving rise to *a priori* difficult assignments regarding the correct chiral 1,3-oxazolidinic system thus formed. The ratio between epimeric forms show constantly no diastereoselective cyclization. Data presented above might offer a general idea that describes several conformational details about all examples of series **3a-n**.

EXPERIMENTAL

^1H -NMR spectra were performed on a Bruker AM 400 spectrometer (with an Aspect 3000 computer) operating at 400 MHz for ^1H . No SiMe_4 was added; chemical shifts were measured against the solvent peak.

Compounds **2a-n** were obtained following the method earlier described by Potapov and Coll.^{19a}. Melting points are uncorrected; only compound **2f** was completely different than the same compound from Potapov's work m.p. = 90-1⁰C (lit. 181-2⁰C). Compounds **2e**, **j**, **k** and **m** have not been previously reported. Equilibrations were realised by using commercially available anhydrous DMSO-d₆, under Ar. All samples were prepared at the same time and measured at room temperature. Specific rotations $[\alpha]_D^{20}$ were determined on a POLAMAT K. Z. JENA instrument, immediately after dissolution. Yields, m.p., $[\alpha]_D^{20}$, time of equilibration and chemical shifts, are as follows:

(1S,2S)-2-(E)-(Benzylideneamino)-1-(4-nitrophenyl)-propane-1,3-diol 2a: 85% ; 148-9⁰C (EtOH) ; + 141 (1% MeOH) ; 160h. δ (ppm): 7.40-8.20 (9H); 8.17 (1H, s, H_{im}); 5.57 (1H, d, H_e, J_{c-e} = 5.3) ; 4.90 (1H, t, H_c, J_{c-b} = 5.3) ; 4.55 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.3) ; 3.55 (1H, m, H_{a1}, J_{a1-a2} = 10.1); 3.44 (1H, m, H_b, J_{b-a1} = 5.6, J_{b-a2} = 7.9); 3.35 (1H, m, H_{a2}); in DMSO-d₆+D₂O (traces): 4.88 (1H, d, H_c, J_{b-c} = 4.9) ; 3.55 (1H, q, H_{a1}, J_{a1-a2} = 10.0) ; 3.44 (1H, m, H_b, J_{b-a1} = 3.3, J_{b-a2} = 8.3) ; 3.35 (1H, m, H_{a2}). **4-Hydroxymethyl-5-(4-nitrophenyl)-2-phenyl-1,3-oxazolidine, (2R,4S,5S) (3a epimer)** : 5.54 (1H, d, H_{ox}, J_{ox-NH} = 11.6) ; 4.99 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 6.5) ; 4.87 (1H, d, H_c, J_{c-b} = 7.0) ; **(2S,4S,5S) (3a epimer)** : 5.75 (1H, d, H_{ox}, J_{ox-NH} = 11.6); 5.04 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 6.5) ; 4.85 (1H, d, H_c, J_{c-b} = 7.0).

(1S,2S)-2-(E)-(4-Methoxybenzylideneamino)-1-(4-nitrophenyl)-propane-1,3-diol 2b: 75% ; 114-5⁰C (MeOH aq.) ; + 199 (0.7% MeOH) ; 196h. δ (ppm) 7.55-8.20 (8H); 8.07 (1H, s, H_{im}); 5.52 (1H, d, H_e, J_{c-e} = 5.5) ; 4.90 (1H, t, H_c, J_{c-b} = 4.5) ; 4.5 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.0) ; 3.54 (1H, m, H_{a1}) ; 3.39 (1H, m, H_b) ; 3.34 (1H, m, H_{a2}) ; 3.32 (3H, s, CH₃). **4-Hydroxymethyl-2-(4-methoxyphenyl)-5-(4-nitrophenyl)-1,3-oxazolidine (2R,4S,5S) (3b epimer)** : 5.48 (1H, d, H_{ox}, J_{ox-NH} = 10.4) ; 4.98 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.9) ; 4.87 (H_c, d, J_{c-b} = 6.4) ; **(2S,4S,5S) (3b epimer)**: 5.73 (1H, d, H_{ox}, J_{ox-NH} = 10.4) ; 5.05 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.9) ; 4.84 (1H, d, H_c, J_{c-b} = 5.4).

(1S,2S)-2-(E)-(4-Nitrobenzylideneamino)-1-(4-nitrophenyl)-propane-1,3-diol 2c : 94% ; 174-5⁰C (EtOH) ; + 133 (0.5% MeOH) ; 196h. δ (ppm) 7.60-8.40 (8H); 8.34 (1H, s, H_{im}) ; 5.66 (1H, d, H_e, J_{c-e} = 5.3) ; 4.95 (1H, t, H_c, J_{c-b} = 5.3) ; 4.62 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.3) ; 3.56 (1H, m, H_{a1}) ; 3.50 (1H, m, H_b) ; 3.42 (1H, m, H_{a2}). **4-Hydroxymethyl-2,5-bis(4-nitrophenyl)-1,3-oxazolidine (2R,4S,5S) (3c epimer)**: 5.76 (1H, d, H_{ox}, J_{ox-NH} = 10.6) ; 5.01 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.3) ; 4.91 (1H, d, H_c, J_{c-b} = 5.3) ; **(2S,4S,5S) (3c epimer)**: 5.96 (1H, d, H_{ox}, J_{ox-NH} = 10.6) ; 5.05 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.3) ; 4.91 (1H, d, H_c, J_{c-b} = 5.3).

(1*S*,2*S*)-2-(*E*)-(4-Dimethylaminobenzylideneamino)-1-(4-nitrophenyl)-propane-1,3-diol 2d : 96% ; 227-8⁰C (MeOH) ; + 87 (0.7% MeOH) ; 196h. δ (ppm): 7.5-8.20 (8H); 7.97 (1H, s, H_{im}) ; 5.46 (1H, d, H_e, J_{c-e} = 4.1) ; 4.88 (1H, t, H_c, J_{c-b} = 4.1) ; 4.51 (1H, t, H_d, J_{d-a1} = 5.5Hz, J_{d-a2} = 4.1) ; 3.57 (1H, m, H_{a1}) ; 3.33 (1H, m, H_b) ; 2.95 (6H, s, 2CH₃). **4-Hydroxymethyl-2-(4-dimethylaminophenyl)-5-(4-nitrophenyl)-1,3-oxazolidine (2*R*,4*S*,5*S*) (3d epimer)**: 5.42 (1H, H_{ox}) ; 4.96 (1H, t, H_d, J_{d-a1} = 5.5Hz, J_{d-a2} = 4.1) ; 4.86 (1H, H_c); **(2*S*,4*S*,5*S*) (3d epimer)**: 5.66 (1H, H_{ox}) ; 5.07 (1H, t, H_d, J_{d-a1} = J_{d-a2} = 5.0) ; 4.83 (1H, H_c).

(1*S*,2*S*)-2-(*E*)-(3-Hydroxybenzylideneamino)-1-(4-nitrophenyl)-propane-1,3-diol 2e : 78% ; 164-6⁰C (ether) ; + 136 (0.5% MeOH) ; 196h. δ (ppm): 9.50 (1H, s, phenolic-OH) ; 6.75-8.25 (8H); 8.07 (1H, s, H_{im}) ; 5.58 (1H, d, H_e, J_{c-e} = 5.3) ; 4.90 (1H, t, H_c, J_{c-b} = 5.0) ; 4.56 (1H, t, H_d, J_{d-a1} = J_{d-a2} = 5.2) ; 3.55 (1H, m, H_{a1}, J_{a1-a2} = 9.1, J_{b-a1} = 4.10) ; 3.41 (1H, m, H_b) ; 3.34 (1H, m, H_{a2}, J_{b-a2} = 8.0). **4-Hydroxymethyl-2-(3-hydroxyphenyl)-5-(4-nitrophenyl)-1,3-oxazolidine (2*R*,4*S*,5*S*) (3e epimer)** : 5.46 (1H, d, H_{ox}, J_{ox-NH} = 12.0) ; 4.99 (1H, t, H_d, J_{d-a1} = J_{d-a2} = 5.2) ; 4.88 (1H, d, H_c, J_{c-b} = 6.9) ; **(2*S*,4*S*,5*S*) (3e epimer)**: 5.75 (1H, d, H_{ox}, J_{ox-NH} = 12.0) ; 5.06 (1H, t, H_d, J_{d-a1} = J_{d-a2} = 5.2) ; 4.84 (1H, d, H_c, J_{c-b} = 6.9). Anal. calcd. for C₁₆H₁₆N₂O₅ : C 60.76%, H 5.06%, N 8.86%. Found: C 61.11%, H 4.88%, N 8.75%.

(1*S*,2*S*)-2-(*E*)-(4-Hydroxybenzylideneamino)-1-(4-nitrophenyl)-propane-1,3-diol 2f : 97%; 90-1⁰C (ether) ; + 43 (0.5% MeOH); 170h. δ (ppm): 7.50-8.25 (8H); 8.03 (1H, s, H_{im}) ; 5.49 (1H, d, H_e, J_{c-e} = 5.6) ; 4.88 (1H, H_c, t, J_{c-b} = 4.9) ; 5.51 (1H, t, H_d, J_{d-a1} = 5.1, J_{d-a2} = 5.4). **4-Hydroxymethyl-2-(4-hydroxyphenyl)-5-(4-nitrophenyl)-1,3-oxazolidine (2*R*,4*S*,5*S*) (3f epimer)** : 5.41 (1H, H_{ox}) ; 4.95 (1H, H_d) ; 4.85 (1H, H_c) ; **(2*S*,4*S*,5*S*) (3f epimer)**: 5.66 (1H, H_{ox}) ; 5.05 (1H, H_d) ; 4.81 (1H, H_c).

(1*S*,2*S*)-2-(*E*)-(3-Methylbenzylideneamino)-1-(4-nitrophenyl)-propane-1,3-diol 2g : 80%; 104-5⁰C (EtOH) ; + 115 (0.6% MeOH) ; 196h. δ (ppm): 7.20-8.30 (8H); 8.12 (1H, s, H_{im}) ; 5.56 (1H, d, H_e, J_{c-e} = 5.2) ; 4.91 (1H, t, H_c, J_{c-b} = 4.5) ; 4.56 (1H, t, H_d, J_{d-a1} = J_{d-a2} = 5.2) ; 3.53 (1H, m, H_{a1}) ; 3.39 (1H, m, H_b) ; 3.33 (1H, m, H_{a2}) ; 2.90 (3H, s, CH₃). **4-Hydroxyphenyl-2-(3-methylphenyl)-5-(4-nitrophenyl)-1,3-oxazolidine (2*R*,4*S*,5*S*) (3g epimer)**: 5.50 (1H, d, H_{ox}, J_{ox-NH} = 10.8) ; 4.99 (1H, t, H_d, J_{d-a1} = J_{d-a2} = 5.2) ; 4.87 (1H, d, H_c, J_{c-b} = 6.5) ; **(2*S*,4*S*,5*S*) (3g epimer)**: 5.75 (1H, d, H_{ox}, J_{ox-NH} = 10.8) ; 5.06 (1H, t, H_d, J_{d-a1} = J_{d-a2} = 5.2) ; 4.84 (1H, d, H_c, J_{c-b} = 6.5)

(1S,2S)-2-(E)-(4-Methylbenzylideneamino)-1-(4-nitrophenyl)-propane-1,3-diol 2h : 50% ; 106-7⁰C (ether) ; + 141(0.7% MeOH) ; 196h. δ (ppm) 7.20-8.20 (8H); 8.11 (1H, s, H_{im}) ; 5.54 (1H, d, H_e, J_{e-c} = 5.8) ; 4.91 (1H, t, H_c, J_{c-b} = 5.2) ; 4.55 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.2) ; 3.57 (1H, m, H_{a1}) ; 3.39 (1H, m, H_b) ; 3.33 (1H, m, H_{a2}) ; 2.30 (3H, s, CH₃). **4-Hydroxymethyl-2-(4-methylphenyl)-5-(4-nitrophenyl)-1,3-oxazolidine (2R,4S,5S) (3h epimer)** : 5.50 (1H, d, H_{ox}, J_{ox-NH} = 10.3) ; 4.98 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.2) ; 4.88 (1H, d, H_c, J_{c-b} = 5.2) ; **(2S,4S,5S) (3h epimer)**: 5.75 (1H, d, H_{ox}, J_{ox-NH} = 10.3) ; 5.05 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.2) ; 4.84 (1H, d, H_c, J_{c-b} = 6.5).

(1S,2S)-2-(E)-(2-Hydroxybenzylideneamino)-1-(4-nitrophenyl)-propane-1,3-diol 2i : 91% ; 176-7⁰C (EtOH) ; + 9.25 (1% MeOH) ; 168h - no detectable evolution. δ (ppm): 6.75-8.30 (8H); 8.29 (1H, s, H_{im}) ; 6.83, phenolic-OH) ; 5.82 (1H, d, H_e, J_{e-c} = 4.8) ; 4.99 (1H, t, H_c, J_{c-b} = 4.2) ; 4.80 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.0) ; 3.64 (1H, m, H_{a1}, J_{b-a1} = 5.9Hz, J_{a1-a2} = 11.9) ; 3.46 (2H, m, H_{a2}, H_b)

(1S,2S)-2-(E)-(2-Chlorobenzylideneamino)-1-(4-nitrophenyl)-propane-1,3-diol 2j : 57% ; 124-5⁰C (MeOH) ; + 89 (0.6% MeOH) ; 190h. δ (ppm): 7.35-8.50 (8H); 8.48 (1H, s, H_{im}) ; 5.63 (1H, d, H_e, J_{e-c} = 5.5) ; 4.94 (1H, t, H_c, J_{c-b} = 5.1) ; 4.61 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.3) ; 3.56 (1H, m, H_{a1}, J_{a1-a2} = 10.2, J_{b-a1} = 4.3) ; 3.50 (1H, m, H_b, J_{b-a2} = 7.7) ; 3.34 (1H, m, H_{a2}). **2-(2-Chlorophenyl)-4-hydroxymethyl-5-(4-nitrophenyl)-1,2-oxazolidine (2R,4S,5S) (3j epimer)** : 5.85 (1H, d, H_{ox}, J_{ox-NH} = 8.3) ; 5.02 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.3) ; 4.88 (1H, d, H_c, J_{c-b} = 5.5) ; **(2S,4S,5S) (3j epimer)**: 6.03 (1H, d, H_{ox}, J_{ox-NH} = 11.0) ; 5.08 (1H, m, H_d) ; 4.72 (1H, d, H_c, J_{c-b} = 5.5). Anal. calcd. for C₁₆H₁₅ClN₂O₄: C 57.34%, H 4.48%, Cl 10.61%, N 8.37%. Found: C 57.55%, H 4.56%, Cl 10.33%, N 8.45%

(1S,2S)-2-(E)-(1-Naphthylideneamino)-1-(4-nitrophenyl)-propane-1,3-diol 2k : 89% ; 148-9⁰C (MeOH) ; + 92 (0.6% MeOH) ; 170h. δ (ppm): 7.50-9.00 (11H); 8.75 (1H, s, H_{im}) ; 5.66 (1H, d, H_e, J_{e-c} = 4.8) ; 5.04 (1H, t, H_c, J_{c-b} = 4.5) ; 4.65 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.) ; 3.67 (1H, m, H_{a1}, J_{a1-a2} = 11.6, J_{b-a1} = 4.6) ; 3.56 (1H, m, H_b, J_{b-a2} = 5.8) ; 3.49 (1H, m, H_{a2}). **4-Hydroxymethyl-2-(1-naphtyl)-5-(4-nitrophenyl)-1,3-oxazolidine (2R,4S,5S) (3k epimer)**: 6.23 (1H, d, H_{ox}, J_{ox-NH} = 11.9) ; 5.05 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.8) ; 5.02 (1H, d, H_c, J_{c-b} = 6.1) ; **(2S,4S,5S) (3k epimer)**: 6.50 (1H, d, H_{ox}, J_{ox-NH} = 11.9) ; 5.08 (1H, H_d) ; 4.96 (1H, H_c). Anal. calcd. for C₂₀H₁₈N₂O₄: C 68.57%, H 5.14%, N 8.00%. Found: C 69.02%, H 5.05% N 7.96%.

(1*S*,2*S*)-1-(4-Nitrophenyl)-2-(*E*)-(2-pyridin-1-ylideneamino)-propane-1,3-diol 2l : 56% ; 161-2⁰C (iPrOH) ; + 110 (0.8% MeOH) ; 350h. δ (ppm): 7.40-8.70 (8H); 8.18 (1H, s, H_{im}) ; 5.65 (1H, d, H_e, J_{c-e} = 5.5) ; 4.95 (1H, t, H_c, J_{c-b} = 5.1) ; 4.63 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.3) ; 3.58 (1H, m, H_{a1}, J_{a1-a2} = 10.0, J_{b-a1} = 4.6) ; 3.53 (1H, m, H_b, J_{b-a2} = 7.4) ; 3.41 (1H, m, H_{a2}). **4-Hydroxymethyl-5-(4-nitrophenyl)-2-(2-pyridin-1-yl)-1,3-oxazolidine (2*R*,4*S*,5*S*) (3l epimer)** : 5.61 (1H, d, H_{ox}, J_{ox-NH} = 11.3) ; 5.04p (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.5) ; 4.95 (1H, d, H_c) ; 4.04 (1H, t, H_{amino}, $J_{b-amino}$ = 10.6) ; 3.65 (2H, m, H_{a1,2}) ; 3.45 (1H, m, H_b) ; **(2*S*,4*S*,5*S*) (3l epimer)** : 5.80 (1H, H_{ox}, d, J_{ox-NH} = 11.9) ; 5.19 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.6) ; 4.82 (1H, d, H_c, J_{c-b} = 7.7) ; 3.92 (1H, t, H_{amino}) ; 3.65 - 3.75 (2H, m, H_{a1}, H_{a2} , J_{a1-a2} = 8.0) ; 3.15 (1H, m, H_b).

(1*S*,2*S*)-1-(4-Nitrophenyl)-2-(*E*)-(3-pyridin-1-ylideneamino)-propane-1,3-diol 2m : 68% ; 168-9⁰C (MeOH) ; + 116 (0.8% MeOH) ; 144h. δ (ppm): 7.40-9.00 (8H); 8.25 (1H, s, H_{im}) ; 5.62 (1H, d, H_e, J_{c-e} = 5.5) ; 4.93 (1H, t, H_c, J_{c-b} = 5.2) ; 4.61 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.5) ; 3.55 (1H, m, H_{a1}, J_{a1-a2} = 10.2, J_{b-a1} = 5.1) ; 3.46 (1H, m, H_b) ; 3.39 (1H, m, H_{a2}, J_{b-a2} = 8.0). **4-Hydroxymethyl-5-(4-nitrophenyl)-2-(3-pyridin-1-yl)-1,3-oxazolidine (2*R*,4*S*,5*S*) (3m epimer)** : 5.65 (1H, d, H_{ox}, J_{ox-NH} = 13.6) ; 5.03 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.7) ; 4.91 (1H, d, H_c, J_{c-b} = 7.5) ; **(2*S*,4*S*,5*S*) (3m epimer)**: 5.83 (1H, d, H_{ox}, J_{ox-NH} = 11.5) ; 5.05 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.6) ; 4.88 (1H, d, H_c, J_{c-b} = 7.5). Anal. calcd. for C₁₅H₁₅N₃O₄: C 59.80%, H 4.98%, N 13.95%. Found: C 60.08%, H 5.05%, N 13.50%

(1*S*,2*S*)-1-(4-Nitrophenyl)-2-(*E*)-(4-pyridin-1-ylideneamino)-propane-1,3-diol 2n : 53% ; 176-8⁰C (MeOH) ; + 104 (0.8% MeOH) ; 140h. δ (ppm): 7.60-8.70 (8H); 8.21 (1H, s, H_{im}) ; 5.66 (1H, d, H_e, J_{c-e} = 5.4) ; 4.93 (1H, t, H_c, J_{c-b} = 5.3) ; 4.62 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.5) ; 3.54 (1H, m, H_{a1}, J_{a1-a2} = 9.8, J_{b-a1} = 4.0) ; 3.48 (1H, m, H_b, J_{b-a2} = 7.3) ; 3.39 (1H, m, H_{a2}). **4-Hydroxymethyl-5-(4-nitrophenyl)-2-(4-pyridin-1-yl)-1,3-oxazolidine (2*R*,4*S*,5*S*) (3n epimer)** : 5.65 (1H, d, H_{ox}, J_{ox-NH} = 11.0) ; 5.00 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.6) ; 4.89 (1H, d, H_c, J_{c-b} = 6.2) ; **(2*S*,4*S*,5*S*) (3n epimer)**: 5.87 (1H, d, H_{ox}, J_{ox-NH} = 11.4) ; 5.05 (1H, t, H_d, $J_{d-a1} = J_{d-a2}$ = 5.5) ; 4.87 (1H, d, H_c, J_{c-b} = 8.4).

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