STUDIA UNIVERSITATIS BABEŞ-BOLYAI, CHEMIA, XLIII, 1-2, 1998

SYNTHESIS AND RING-RING TAUTOMERISM OF SOME SPIRO-OXAZOLIDINES BASED ON *l-p*-NITROPHENYLSERINOL SKELETON

MIRCEA DĂRĂBANȚU[1], GERARD PLÉ[2], LUIZA GĂINĂ[1], CARMEN MĂIEREAN[1] and ION SILAGHI-DUMITRESCU[1]

ABSTRACT. The synthesis of three spirooxazolidines starting from the title compound is discussed from the regioselectivity and diastereoselectivity point of view and their unexpected isomerization in solution is examined by means of high resolution NMR spectra.

INTRODUCTION

We have recently described the ring-chain tautomerism of some Schiff-Bases of *l*-2-amino-1-(4-nitrophenyl)-propane-1,3-diol, better known by its trivial name issued from pharmaceutical chemistry as "*l-p*-nitrophenylserinol "[1]. Starting from our previously reported results, we have considered of interest to enlarge the study in the field by examining certain spirooxazolidines derived from the title compound. As the Schiff-Bases, this class of compounds exhibited some applicative importance in the period of '50's, in connection with *chloromycetineĂ* synthesis [2]. To the best of our knowledge, any oxazolidine ring-system built form the title aminodiol has been treated so far as a single and stable structure.

Then, our most recent data [3] has revealed that spirooxazolidines possessing free hydroxymethyl-groups (*e.g*. starting from more simple aminopolyalcohols skeleton) can isomerize in certain conditions and these equilibria are suitable to NMR monitoring.

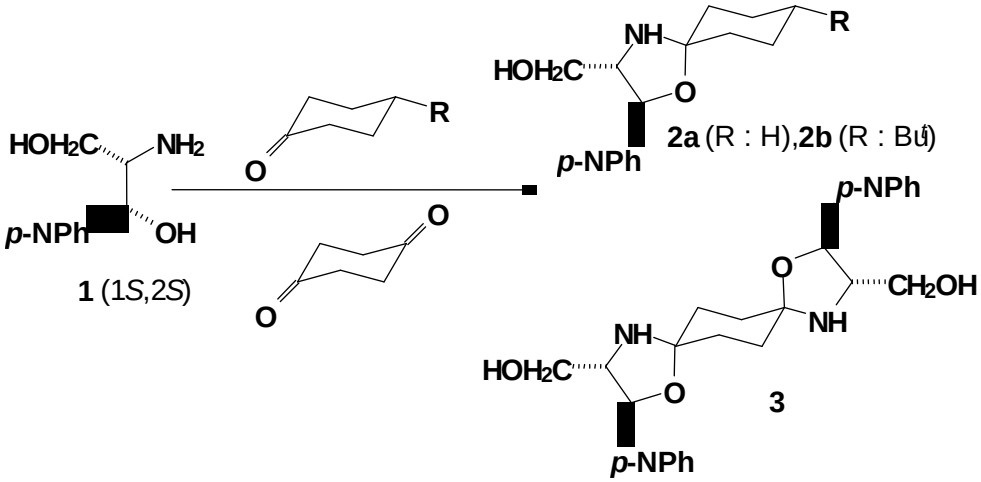
RESULTS AND DISCUSSION

1. Synthesis

As depicted in ***Scheme 1*** three spirooxazolidines ***2a, b, 3*** have been prepared following the classical method of Bergmann [4] (see ***EXPERIMENTAL***) (hereafter ***p-NPh***- is the abreviation for ***p-nitrophenyl*** group). Surprisingly, even from the beginning of our research, the versatile reactivity of ***1*** has allowed synthesis of ***2a, b*** (yields 40-60%) but starting from racemic ***1*** (in ***Scheme 1*** only the 1*S*,2*S* enantiomer of ***1*** is shown). Anyhow, pure enantiomeric ***2a, b*** have been also isolated by us but as oils, very unstable on storage, in complete contradiction with Bergmann's earlier data [4] (*e.g*. ***2a***, claimed as crystalline solid, m.p.= 107-8^{o}C).

[1] *"Babeş-Bolyai" University Cluj-Napoca, Department of Organic Chemistry, 11 Arany Janos str., RO-3400 Cluj-Napoca*
[2] *Université de Rouen, Faculté des Sciences et des Techniques IRCOF-UPRES A 6014 CNRS 76821 Mont Saint Aignan, Cedex, France*

The same has been valid for the synthesis of the new compound ***2b***. Extention of the procedure to C-5 and C-7 monocyclanones has failed (no reaction occurred,



Scheme 1

TLC monitoring). We should believe the negative influence of *I-strain*, in both cases [5] but the reactivity of TRIS (α,α,α-trimethylolaminomethane) and its methyl (or ethyl) analogs have afforded, in identical conditions, promising results [3].

The dispirane ***3***, has raised none of the mentioned problems and has been isolated as pure *trans*-2*S*,3*S*,10*S*,11*S* enantiomer.

All syntheses have occurred with no epimerization of ***1*** and complete diastereoselectivity. In fact, the remarkable configurational stability of the starting aminodiol ***1*** is not surprising but already a well-established and fully argued behaviour [6]. Illustration in ***Scheme 1***, depictes that diastereomers possessing –NH- group in eq. position *vs*. alkoxy one in ax. position but tied together in a five member ring will be hereafter considered. This stereochemistry is supported only by RHF/3-21G* molecular orbital calculations (with full geometry optimization). Thus, A-values in this class range between 0.84 – 1.06kcal/mol. All NMR spectra (solvent DMSO-d_6) have been consistent with the presence of a single diastereomer in any of the syntheses [3].

2. The rin-ring tautomerism

The ^{1}H-NMR spectrum of compound ***2a*** in DMSO-d_6 (***Figure 1***, heterocyclic zone) will be first considered as a typical example.

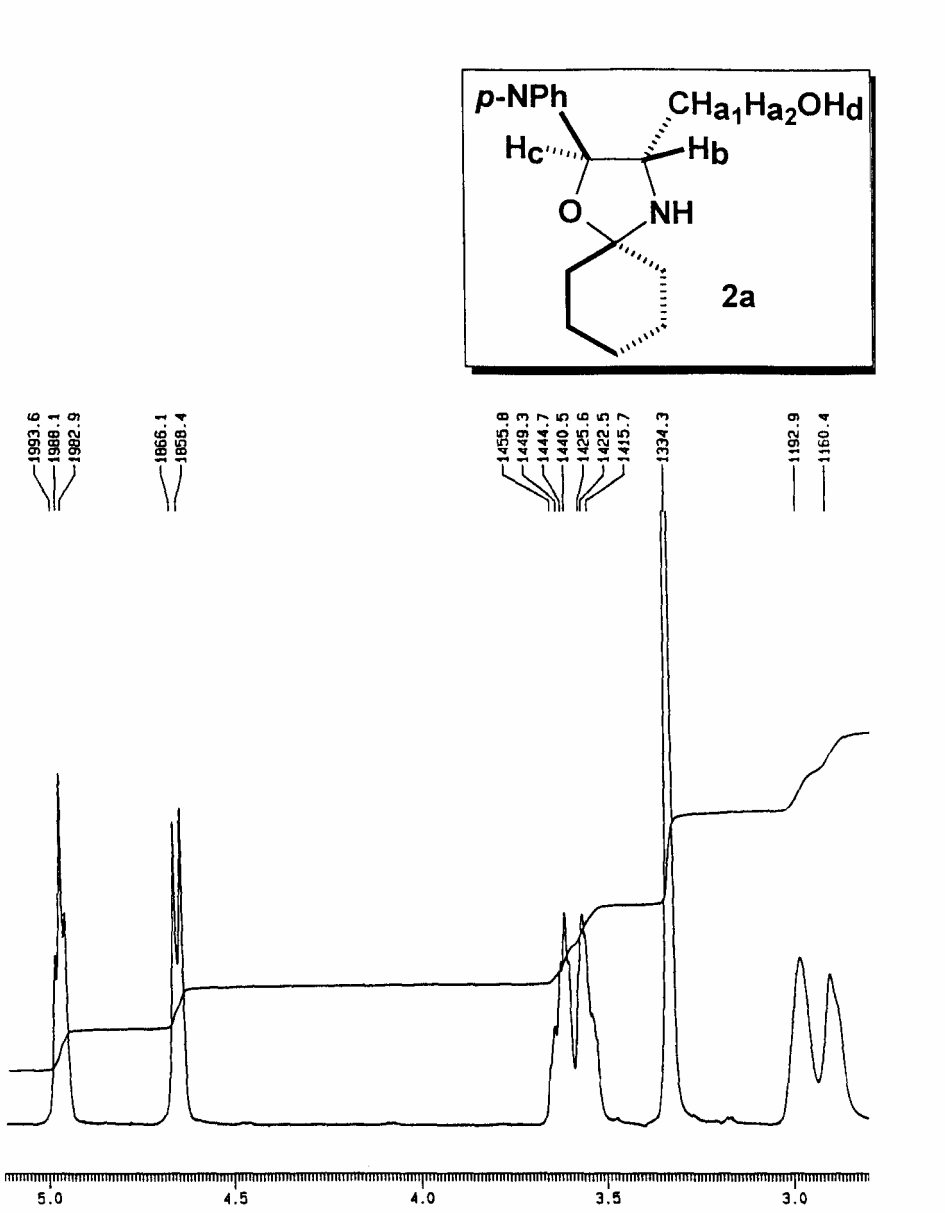


Figure 1. ^{1}H-NMR spectrum of compound **2a**; solvent DMSO-d_6

Regioselectivity of the ring-closure is easily to observe since primary hydroxylic proton -OH_d is clearly exhibited as a triplet (in fact a doublet of doublets partially overlapped) at 4.97ppm. We note here the same regioselectivity, previously reported by Bergmann and Resnick [4], based only on IR spectra (characteristic bands for 1,3-oxazolidine ring in the region 1080 – 1200 cm^{-1} and primary hydroxyl group in the region 1030 – 1060 cm^{-1}). Then, IR spectra were claimed as measured in suspension of paraffin to suggest the role of crystalline interactions (not discussed, *op.cit.*). Proton H_c (4.66ppm) is *trans*-splitted by H_b (J = 7.7Hz); upfield, one can located the diastereotopic methylene –C$H_{a1}H_{a2}$OH_d as a doublet of quartets (3.62 and 3.56ppm resp., J_{gem} = 9.3Hz). It had been normally expected that proton H_b is the most splitted one but, unfortunately, just an unresolvable broad singlet is revealed at 2.98ppm. COSY-experiment (not depicted) has indicated with any doubt its coupling with H_c. Finally, the aminic proton is found at 2.90ppm. ^{13}C-NMR has been fully consistent with a single proposed strucutre. The same spectrum performed in $CDCl_3$ (compound ***2a***, ***Figure 2***, heterocyclic zone) put in evidence both possible regioisomers: ***2a(I)*** (major) and ***2a(II)*** (minor). Before discussing this spectrum, some essential notes should be outlined:

a) the poor solubility of all compounds in $CDCl_3$ that made difficult to perform relevant QC-NMR spectra for both ***2a(I)*** and ***2a(II)*** regioisomers; similar situation was encountered in C_6D_6.

b) the ratio between ***2a(I)*** and ***2a(II)*** has remained unchanged if spectra have been repeated after several days.

c) one may suppose that ***2a(I)*** and ***2a(II)*** are not regioisomers but the two terms of a slow conformational equilibrium of ***2a***; this hypothesis was ruled out because spirane ***2b*** (possessing the Bu^t as an anancomerizing group at C-8) has exhibited an identical behaviour as ***2a*** (see farther).

d) best discrimination and assignment between regioisomers ***2a(I)*** and ***2a(II)*** have been basically made on the magnitude of geminal coupling patterns J H_{a1a2} (typical values about 11Hz in type ***I*** and about 8.5Hz in type ***II***) as we have already reported [7] and COSY experiment.

The spectrum in ***Figure 2*** indicates the following relevant peaks:

- H_c in ***2a(I)*** (4.76ppm, doublet, J_{trans} = 8.0Hz) and H_c in ***2a(II)*** (4.45ppm, doublet, J = 7.4Hz). The ratio between ***2a(I)***: ***2a(II)*** is about 3.4: 1.
- the diastereotopic methylene $H_{a1}H_{a2}$ in ***2a(I)*** (each proton as doublet of doublets, at 3.84 and 3.65ppm, resp., J_{gem} = 11.2Hz) and in ***2a(II)*** (each proton asdoublet of doublets, partially overlapped, at 3.76 and 3.70ppm, resp., J_{gem} = 8.8Hz). It must be observed that in none of the regioisomers have been detected couplings with hydroxylic protons H_e or H_d.
- proton H_b in ***2a(II)*** (3.42ppm as an overlapped multiplet) and H_b in ***2a(I)*** (3.16ppm, as an overlapped but resolvable ddd).

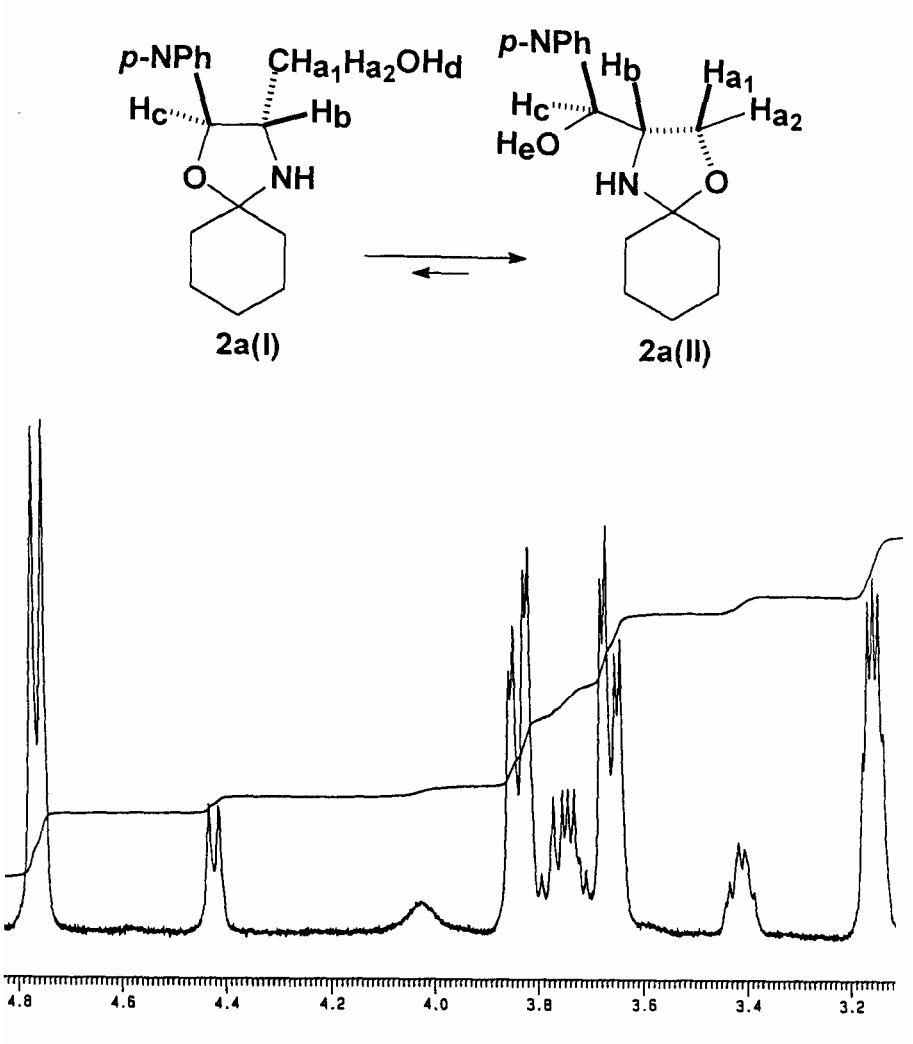


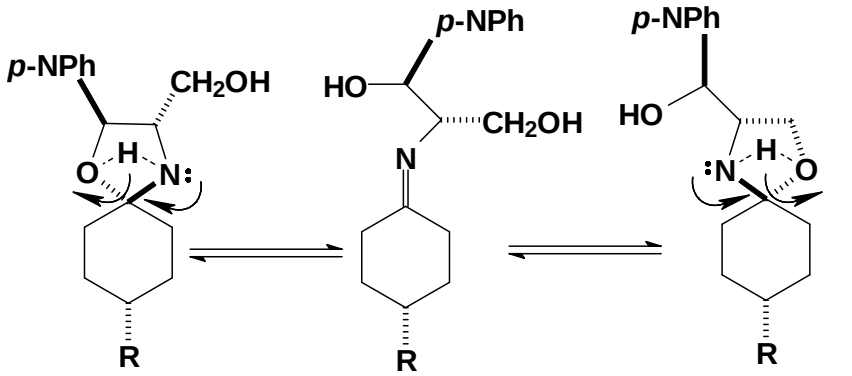
Figure 2. ^{1}H-NMR spectrum of the mixture of regioisomers **2a(I)** and **2a(II)** in $CDCl_3$

The spectrum discussed above has not allowed the precise location of aminic or hydroxylic protons. This fact has been connected with their intramolecular mobility as soon as the solvent used was unable to developpe hydrogen bonds (or rapid change) with them.

Therefore, this isomerization, favoured by a generic name as *intramolecular interactions*, involving mobile protons, we will call hereafter as case of ***ring-ring tautomerism***. Since the phenomenon has been observed only if (non)polar solvents (or unable to interact with hydroxylic or aminic protons) have been used,

the role of these protons to promote this tautomerism should be crucial. Moreover, one can imagine nonionic transition state (or intermediates) that make possible this evolution (***Scheme 2***). Equilibria of the monospiranes ***2a, b*** let to identify only two tautomers and it is pertinent to assume that they are diastereoselctive, regarding the cyclohexane fragment (-NH- group, in both tautomers is still placed in eq. position).

In ***Table 1*** the quantitative results, as ratios between the tautomers, are summarized, depending on the NMR-solvent used.



2a(I) (R : H) **2a(II)** (R : H)
2b(I) (R : Bu*t*) **2b(II)** (R : Bu*t*)

Scheme 2

Table 1

Regioselective ring closure for the monospirane ***2a, b***

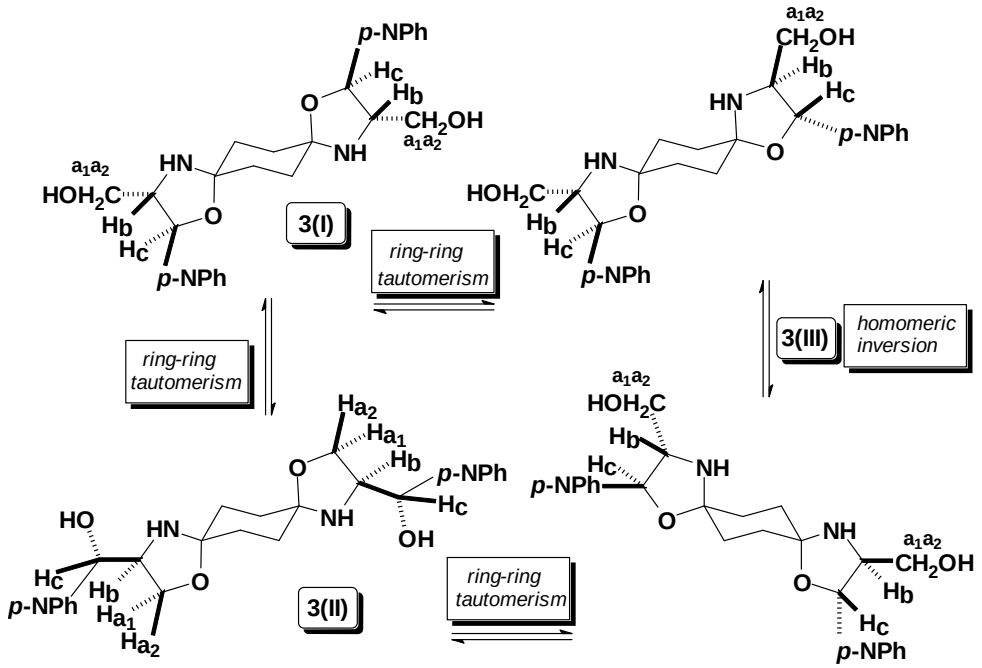
Solvent	***Regioselective ratio I*** *vs.* ***II****	
	2a	***2b***
DMSO-d_6	Single **2a(I)** found	Single **2b(I)** found
C_6D_6	3.7 : 1	4.0 : 1
$CDCl_3$	3.4 : 1	4.0 : 1
Acetone-d_6	5.6 : 1	6.6 : 1

*As issued form ^{1}H-NMR spectra performed with successive increased sensitivity (300 and 400MHz, see ***EXPERIMENTAL***); reference protons chosen for calculations: H_c (see ***Figure 2***).

Data listed in ***Table 1*** illustrate, on the other hand, the similar behaviour of spirooxazolidines ***2a, b*** with their analogs C-2-substituted(hetero)aryl: the most acidic hydroxyl–group (secondary) is more involved in the ring closure although it is the most sterically hindered. We have already reported that about $\Delta\delta$=1ppm is the difference between ^{1}H-NMR chemical shifts protons of secondary and primary hydroxyl-group in a large series of acyclic derivatives of ***1***, (itself included) [1].

It had been expected that dispirane ***3*** should support these considerations. In fact, NMR-spectra put in evidence more than expected constitutional changes, depending on the solvent (***Scheme 3***). The ^{1}H-NMR spectrum performed in DMSO-d_6

has exhibited a single structure and chemical shifts are not different than the same δ-values encountered for the monospirane ***2a*** (***Figure 1***). Therefore, as a trivial case, this spectrum will be not analyzed.



Scheme 3

The spectrum performed in $CDCl_3$ (***Figure 3a***) shows, in the region of benzylic protons, three types of environment of the reference benzylic proton H_c:

- the doublet at 4.93ppm is a H_c type assigned to ***3(III)*** environment as the doublet at 4.83 (the last one is partially overlapped).

- the most intense doublet (4.86ppm) is assigned to H_c in ***3(I)***

- the most shielded doublet at 4.51ppm should be assigned to another environment of H_c, tautomer ***3(II)*** (see similar value for H_c in ***Figure 2***, tautomer ***2a(II)***. The COSY experiment (not depicted) is consistent with this assumption since it is twice *gauche* coupled with H_{a1a2} in the region 3.80-3.90ppm.

As issued from ***Scheme 3***, it had been also expected that ***3(III)*** should be a flipping structure but all our evidence prove that if really does occur, the homomeric inversion is slow enough for both H_c environments be observed. This region also allows to estimate the ratio betwwen ***3(I)***: ***3(III)***: ***3(II)*** as 2.75: 1: 1.25. Then, in ^{13}C-NMR spectrum (not depicted) there are four signals for C-5, C-8 carbons, consistent with three structures.

In ***Figure 3b*** one can discriminate 3 AMX systems: three types of methylenic protons H_{a1a2} splitted by H_b as three doublets of quartets: ***3 (I)*** (***o***), ***3 (III)*** (×) and ***3 (II)*** (*******,); typical J_{gem} values: 11.2-11.3Hz in free –CH_{a1a2}-OH moiety and 8.1Hz in oxazolidinic –CH_{a1a2}-).

The same spectrum performed in acetone-d_6 (***Figure 4***, detail in the heterocyclic zone) has depicted another unpredictable behaviour.

Thus, if acetone-d_6 is seen somehow similar to DMSO-d_6 a single tautomer is expected to detect and regioselectivity of the ring closure should involved the secondary hydroxyl-group. In ***Figure 4*** one can discriminate between two type of mobile protons as broad singlets (4.18 and 2.91ppm, resp). A rapid change with the solvent may be considered.

Then, from downfield to upfield, the following signals are revealed:

- benzylic protons H_c as two doublets (4.87 and 4.88ppm, resp., typical J_{trans} value 8.0Hz); their intensity is the same and, based on the magnitude *J*-value, the *trans*-coupling with H_b demostrates that no epimerization has occurred at the benzylic carbon (if did, H_b-H_c are *cis*-coupled). The very small difference between δ-values suggests minor difference between environments so the single ***3(III)***-epimer is a valid structure in these conditions.

- the hydroxymethylenes protons –CH_{a1Ha2}-OH as two partially overlapped doublets of doublets are located at 3.84, 3.83 and 3.79ppm, resp.(J_{gem} = 11.6Hz).

- protons H_b are identified as a single multiplet at 3.18ppm but carefully analysis of this signal indicates two δ-values 3.19 and 3.17ppm (two splittings 8.0Hz and 3.8Hz; the third, about 3.8Hz is not exhibited; that is, each H_b as doublet of doublets instead of quartets of doublets).

To conclude, in acetone-d_6, tautomer ***3(III)*** is the unique structure; if flipping, the conformational equilibrium is very slow and interactions with the solvent are the reason of this behaviour.

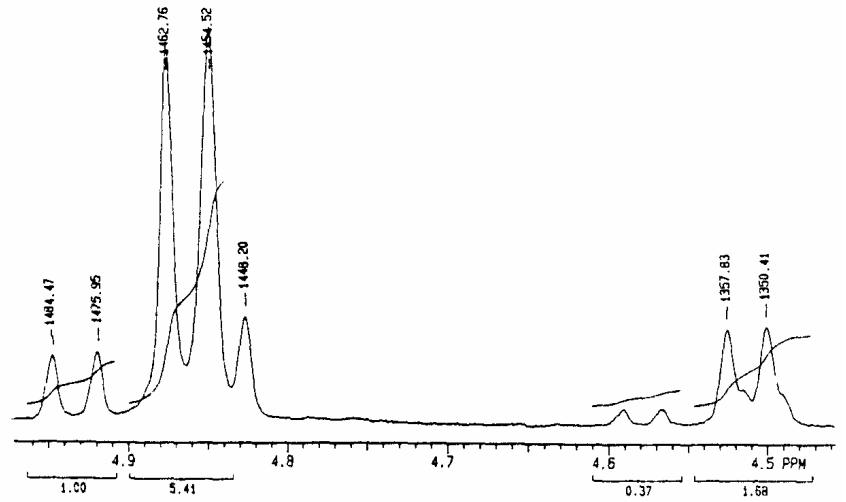


Figure 3a. 1H-NMR spectrum of tautomers **3(I)**,**3(II)** and **3(III)** (detail) from downfield to upfield : H_C **3(III)** 4.93ppm, H_C **3(I)** 4.86ppm, H_C **3(III)** 4.83ppm, H_C **3(II)** 4.51ppm

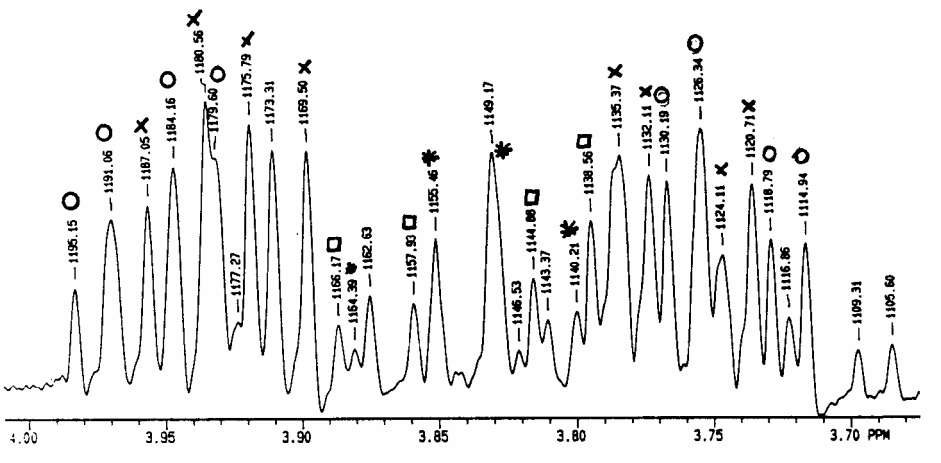


Figure 3b . 1H-NMR spectrum of tautomers **3(I)**, **3(II)** and **3(III)** (detail) from downfield to upfield : H a1 **3(I+III)**, Ha1Ha2 **3(II)**, Ha2 **3(I+III)**

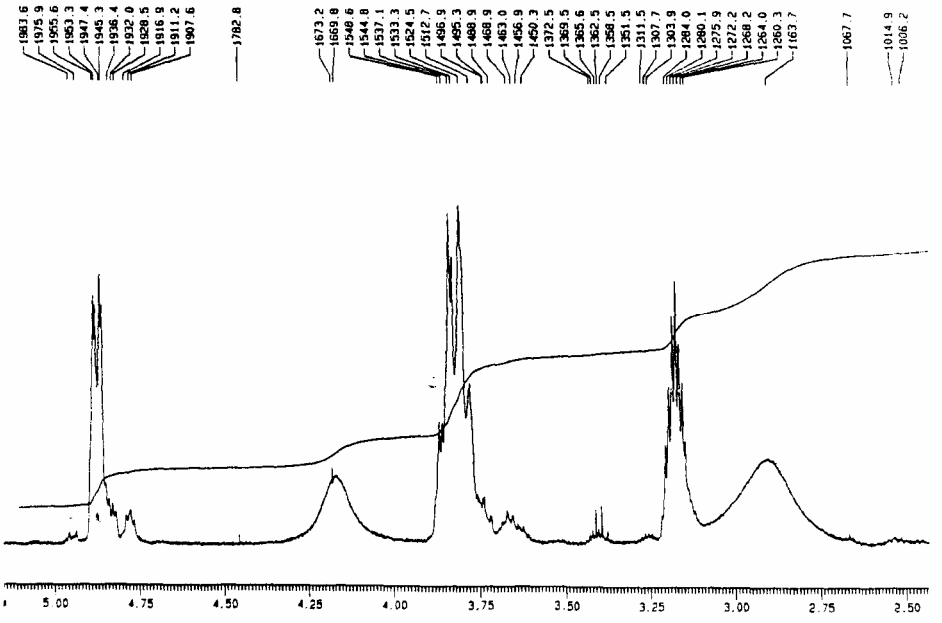


Figure 4 . 1H-NMR spectrum of compound **3** as tautomer **3(III)**; solvent acetone-d6

CONCLUSIONS

Reaction of *l*-p-nitrophenylserinol with simple C-6 mono- and dicyclanones has afforded spirooxazolidines; they easily isomerize as soon as intramolecular interactions due to mobility of –O*H* and –N*H*- protons are effective (intramolecular hydrogen bonds included). Regioselectivity of ring closure depends on the solvent but the reactivity of the most acidic hydroxyl-group (secondary) is always dominant against steric requirements.

EXPERIMENTAL

Melting points (Boetius) are not corrected.

All reactives were purchased from Aldrich.

^{1}H-NMR and ^{13}C-NMR were performed on VARIAN-Gemini 300 and Brucker AM 400 spectrometers. QC-NMR spectra were performed on VARIAN-Gemini 300 operating at 75MHz for ^{13}C by using 80-100mg/sample in standard tubes and a delay time D1=10. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. Samples were prepared by using commercially available DMSO-d_6 and measured after complete dissolution in standard tubes (about 30mg for ^{1}H- and 60-70mg for ^{13}C-NMR spectra). For spectra recorded in $CDCl_3$ 5-10mg/sample in standard tubes were used. Hyperfine structure of ^{1}H-NMR was obtained on diluted samples only by using RESOLV macro (special attention was paid to neglect negative peaks) on VARIAN-Gemini 300, after 128 transients. Hereafter protons and carbons are labelled as shown in the ***Figures 1-3***.

All reactions were monitored by TLC on MERCK silica gel, by using Benzene: Acetone 3:1 or ligroine : acetone 3 : 1 v/v as eluent (visualisation on I_2 bath).

RHF/3-21G* molecular orbital calculations were performed by using Spartan 5.0 package of programs; Spartan version 5.0, Wavefuntion, Inc., 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612 U.S.A.

Specific rotations $[\alpha]_D^{20}$ were determined on POLAMAT K. Z. JENA instrument.

Typical procedure to prepare spirooxazolidines 2-3

Synthesis: l-p-Nitrophenylserinol 2.12g (10mmol) (for dispirooxazolidine 3 pure enantiomeric 1S,2S staring material is used) was suspended in benzene (50mL) in a Dean-Stark trapp. Monocyclanone was added as 300% molar excess (for ***3***, stoechiometric molar ratio was used). The r.m. was refluxed on a steam-bath with continuous removal of water until TLC monitoring indicated constant ratio between the desired compound and unreacted starting material (the last one detected in small traces only). ***Isolation***: compound ***2***: the r.m. was filtered at r.t. to remove the unreacted starting material, neutralized with anh. Na_2CO_3 and, after evaporation in vacuo, the oily residue was twice crystallized form 2: 1 MeOH: H_2O. For the compound ***3***, the same procedure afforded an oily residue that was crystallized from ligroine, then from min. MeOH, at r.t. For dispirane ***3***, benzene was decanted and the gummy solid was stirred with ether until a fine powder was obtained. After filtering, the solid was dissolved in min. MeOH, then poured in water, to remove the unrected starting material. After filtering and drying at r.t., the crude product was crystallized from THF: Ether.

l-4-Aza-3-hydroxymethyl-2-(4-nitrophenyl)-4-aza-1-oxaspiro[4.5]decane 2a(I) and ***l-4-Aza-3-(4-nitrohydroxybenzyl)-1-oxaspiro[4.5]decane 2a(II)***

Yield 62%. M.p. = 83-5°C (MeOH : H_2O = 2 : 1) yellowish crystalline powder (Found : C, 61.90; H, 7.00; N, 9.53; $C_{15}H_{20}N_2O_4$ requires C, 61.62; H, 6.89; N, 9.58%);

Tautomer 2a(I):

δ_H(400 MHz; DMSO-d_6) 8.21 (2 H, d, *J* 8.6, H-3, -5 arom), 7.61 (2 H, d, *J* 8.6, H-2, -6 arom.), 4.97 (1 H, t, *J* 5.4, -O*H*$_d$), 4.66 (1 H, d, *J* 7.7, H_c), 3.62 (1 H, dd, *J* 9.3 and 6.4, H_{a1}) 3.56 (1 H, dd, *J* 9.3 and 4.2, H_{a2}), 2.98 (1 H, br s, -N*H*-), 2.90 (1 H, unresolved large singlet, H_b according to COSY exp.), 1.69 – 1.29 (10 H, cyclohexyl)

δ_H(400 MHz; C_6D_6) 7.89 (2 H, d, *J* 8.6, H-3, -5 arom), 7.07 (2 H, d, *J* 8.6, H-2, -6 arom.), 4.54 (1 H, d, *J* 8.0, H_c), 3.40 (1 H, dd, *J* 11.1 and 3.9, H_{a1}) 3.19 (1 H, dd, *J* 11.1 and 3.7, H_{a2}), 2.75 (1 H, ddd, *J* 8.0 3.9 and 3.7, H_b), 1.68 – 1.14 (12 H, cyclohexyl, -O*H*, –N*H*-)

δ_H(400 MHz; $CDCl_3$) 8.17 (2 H, d, *J* 8.7, H-3, -5 arom), 7.50 (2 H, d, *J* 8.7, H-2, -6 arom.), 4.76 (1 H, d, *J* 8.0, H_c), 4.02 (1 H, br s, -O*H*), 3.84 (1 H, dd, *J* 11.2 and 3.6, H_{a1}) 3.65 (1 H, dd, *J* 11.2 and 4.1, H_{a2}), 3.16 (1 H, ddd, *J* 8.0, 3.8 and 3.5, H_b), 2.06 (1 H, br s, -N*H*-), 1.81 – 1.44 (10 H, cyclohexyl)

δ_H(400 MHz; CD_3COCD_3) 8.25 (2 H, d, *J* 8.8, H-3, 5 arom.) 7.72 (2 H, d, *J* 8.8, H-2, -6 arom.) 4.84 (1 H, d, *J* 8.2, H_c) 3.84 (1 H, dd, *J* 11.6 and 3.6, H_{a1}) 3.77 (1 H, dd, *J* 11.6 and 2.9, H_{a2}) 2.09 (1 H, m, H_b) 1.83 – 1.49 (12 H, m, cyclohexyl, -O*H*, -N*H*-)

δ_C(100 MHz; DMSO-d_6) 150.1 (1 C, *C*-NO_2), 146.6 (1 C, C-1 arom.), 127.1 (2 C, C-2, -6 arom.), 123.4 (2 C, C-3, -5 arom.), 96.7 (1 C, C-5), 78.6 (1 C, C-2), 67.5 (1 C, C-3), 58.9 (1 C, -*C*H_2OH), 37.3 and 37.0 (2 C, C-6, -10), 25.1 (1 C, C-8), 23.7 and 23.6 (2 C, C-7, -9)

Tautomer 2a(II) (only distinct peaks or clearly correlated by COSY exp. are depicted)

δ_H(400 MHz; C_6D_6) 6.98 (2 H, *J* 8.6, H-2, -6 arom.), 4.10 (1 H, d, *J* 7.5, H_c), 3.48 (1 H, dd, *J* 4.7 and 8.6, H_{a1}), 3.40 (1 H, dd, H_{a2}), 2.75 (1 H, m, H_b)

δ_H(400 MHz; $CDCl_3$) 4.45 (1 H, d, *J* 7.4, H_c), 3.76 (1 H, d, *J* 8.8, H_{a1}), 3.70 (1 H, dd, *J* 4.1 and 8.8, H_{a2}), 3.42 (1 H, m, H_b)

δ_H(300 MHz; CD_3COCD_3) 4.77 (1 H, d, *J* 5.5, H_c), 3.63 (1 H, d, *J* 7.0, H_{a1}), 3.58 (1 H, *J* 7.0, H_{a2}), 2.30 (1 H, m, H_b)

l-4-Aza-8-t-tertbutyl-3-hydroxymethyl-2-(4-nitrophenyl)--1-r-oxaspiro[4.5]decane 2b(I) and

l-4-Aza-8-t-tertbutyl-3-(4-nitrohydroxybenzyl)-1-r-oxaspiro[4.5]decane 2b(II)

Yield 40%. M.p. = 155-7°C (MeOH) white crystalline powder (Found : C, 65.59; H, 7.90; N, 8.20; $C_{19}H_{28}N_2O_4$ requires C, 65.43; H, 8.10; N, 8.04%)

Tautomer 2b(I)

δ_H(400 MHz; DMSO-d_6) 8.20 (2 H, d, *J* 8.6, H-3, -5 arom), 7.61 (2 H, d, *J* 8.6, H-2, -6 arom.), 4.95 (1 H, t, *J* 5.7, H_d), 4.64 (1 H, d, *J* 7.9, H_c), 3.63 (1 H, ddd, *J* 11.7, 5.4 and 4.7, H_{a1}), 3.55 (1 H, ddd, *J* 11.7, 5.4 and 3.6, H_{a2}), 2.95 (1 H, br s, -N*H*-), 2.82 (1 H, unresolved large singlet, H_b according to COSY exp.), 1.86 – 1.22 (9 H, m), 0.85 (9 H, s, 3 × -C*H*$_3$)

δ_H(400 MHz; C_6D_6) 7.92 (2 H, d, *J* 8.8, H-3, -5 arom), 7.10 (2 H, d, *J* 8.8, H-2, -6 arom.), 4.59 (1 H, d, *J* 8.0, H_c), 3.40 (1 H, dd, *J* 11.0 and 3.6, H_{a1}) 3.18 (1 H, dd, *J*

11.0 and 3.6, H_{a2}), 2.76 (1 H, ddd, *J* 8.0, 4.0 and 4.0, H_b), 1.82 – 0.98 (11 H, cyclohexyl, -O*H*, –N*H*-), 0.90 (9 H, s, 3 × -C*H*$_3$)
δ_H*(400 MHz; CDCl*$_3$*)* 8.18 (2 H, d, *J* 8.8, H-3, -5 arom), 7.52 (2 H, d, *J* 8.8, H-2, -6 arom.), 4.79 (1 H, d, *J* 8.1, H_c), 3.88 (1 H, dd, *J* 11.3 and 3.7, H_{a1}), 3.67 (1 H, dd, *J* 11.3 and 4.0, H_{a2}), 3.16 (1 H, ddd, *J* 8.0, 4.0 and 3.7, H_b), 1.87 – 1.07 (11 H, cyclohexyl, -O*H* and –N*H*-), 0.86 (9 H, s, 3 × -C*H*$_3$);
δ_H*(400 MHz; CD*$_3$*COCD*$_3$*)* 8.21 (2 H, d, *J* 8.8, H-3, -5 arom.), 7.69 (2 H, d, *J* 8.8, H-2, -6 arom.), 4.81 (1 H, d, *J* 7.5, H_c), 4.15 (1 H, t, *J* 5.2, H_d), 3.83 (1 H, ddd, *J* 11.6, 5.4 and 5.2 H_{a1}), 3.77 (1 H, ddd, *J* 11.6, 5.0 and 3.8, H_{a2}), 3.09 (1 H, *J* 7.5, 5.2 and 3.8, H_b), 2.75 1 H, br s, -N*H*-), 1.83 – 1.49 (10 H, m, cyclohexyl, -O*H*), 0.89 (9 H, s, 3 × -C*H*$_3$)
δ_C*(100 MHz; DMSO-d*$_6$*)* 150.0 (1 C, *C*-NO_2), 146.6 (1 C, C-1 arom.), 127.1 (2 C, C-2, -6 arom.), 123.4 (2 C, C-3, -5 arom.), 97.5 (1 C, C-5), 78.2 (1 C, C-2), 67.7 (1 C, C-3), 58.6 (1 C, -*C*H_2OH), 46.8 (1 C, C-8), 38.7 and 38.0 (2 C, C-6, -10), 32.0 [1 C, -*C*$(CH_3)_3$], 27.5 (3 C, -*C*H_3), 25.1 and 24.8 (2 C, C-7 -9)
δ_C*(75 MHz; CDCl*$_3$*)* 148.8 (1 C, *C*-NO_2), 147.5 (1 C, C-1 arom.), 126.8 (2 C, C-2, -6 arom.), 123.8 (2 C, C-3, -5 arom.), 98.0 (1 C, C-5), 78.4 (1 C, C-2), 67.5 (1 C, C-3), 60.0 (1 C, -*C*H_2OH), 47.5 (1 C, C-8), 38.7 and 37.7 (2 C, C-6, -10), 32.4 [1 C, -*C*$(CH_3)_3$], 27.7 (3 C, -*C*H_3), 25.6 and 25.2 (2 C, C-7, -9)
Tautomer 2b(II) (only distinct peaks or clearly correlated by COSY exp. are depicted)
δ_H*(400 MHz; C*$_6$*D*$_6$*)* 7.89 (2 H, d, *J* 8.8, H-3, -5 arom.), 7.00 (2 H, *J* 8.8, H-2, -6 arom.), 4.13 (1 H, d, *J* 7.3, H_c), 3.50 (1 H, dd, *J* 8.8 and 4.6, H_{a1}), 3.40 (1 H, dd, *J* H_{a2}), 2.76 (1 H, ddd, H_b)
δ_H*(400 MHz; CDCl*$_3$*)* 8.20 (2 H, d, *J* 7.6, H-3, -5 arom.), 4.44 (1 H, d, *J* 7.5, H_c), 3.77 (1 H, dd, *J* 9.0 and 6.6, H_{a1}), 3.73 (1 H, dd, *J* 9.0 and 4.6, H_{a2}), 3.43 (1 H, ddd, *J* 7.2, 6.6 and 4.6, H_b)
δ_H*(400 MHz; CD*$_3$*COCD*$_3$*)* 4.77 (1 H, d, *J* 5.5, H_c), 3.63 (1 H, d, *J* 7.0, H_{a1}), 3.58 (1 H, *J* 7.0, H_{a2}), 2.30 (1 H, m, H_b)
δ_C*(75 MHz; CDCl*$_3$*)* 148.8 (1 C, *C*-NO_2), 147.5 (1 C, C-1 arom.), 127.4 (2 C, C-2, -6 arom.), 123.8 (2 C, C-3, -5 arom.), 96.2 (1 C, C-5), 79.0 (1 C, C-2), 66.8 (1 C, C-3), 60.3 (1 C, -*C*H_2OH), 47.4 (1 C, C-8), 38.2 and 37.5 (2 C, C-6, -10), 32.4 [1 C, -*C*$(CH_3)_3$], 27.7 (3 C, -*C*H_3), 24.4 and 23.9 (2 C, C-7, -9)

Trans-(2S,3S,10S,11S)-4,12-diaza-3,11-bishydroxymethyl-2,10-di(4-nitrophenyl)-1,9-dioxadispiro[4.2.4.2]tetradecane 3(I), Trans-(3S,11S)-4,12-diaza-3,11-bis(S-4-nitrohydroxybenzyl)-1,9-dioxadispiro[4.2.4.2]tetradecane 3(II) and ***Cis-(2S, 3S,10S,11S)-4,12-Diaza-3,11-bishydroxymethyl-2,10-di(4-nitrophenyl)-1,9-dioxa-dispiro[4.2.4.2]tetradecane 3(III)***,
Yield 75%. M.p. = 110-1°C (THF – Et_2O) yellowish crystalline powder (Found: C. 57.50; H, 5.75; N, 11.00; $C_{24}H_{28}N_4O_8$ requires C, 57.59; H, 5.64; N, 11.19%); $[\alpha]_D^{20}$ = + 48.9 (0.8%, MeOH)

Tautomer 3(I)

δ_H *(400 MHz; DMSO-d_6)* 8.20 (4 H, d, *J* 8.5, 2 × H-3, -5 arom.), 7.62 (4 H, d, *J* 8.5, 2 × H-2, -6 arom.), 5.07 (2 H, br s, 2 × H_d), 4.71 (2 H, d, *J* 7.1Hz, 2 × H_c), 3.67 (2 H, d, *J* 9.0, 2 × H_{a1}), 3.64 (2 H, d, *J* 9.0, 2 × H_{a2}), 3.05(2 H, m, 2 × H_b), 2.50 (2 H, br s, 2 × -N*H*-), 1.92 and 1.85 (8 H, *J* 9.8 and 12.9, cyclohexyl)

δ_H *(400 MHz; $CDCl_3$)* 8.22 (4 H, d, *J* 8.3, 2 × H-3, -5 arom.), 7.56 (4 H, d, *J* 8.3, 2 × H-2, -6 arom.), 4.86 (2 H, d, *J* 8.2, 2 × H_c), 3.95 (2 H, dd, *J* 11.3 and 5.5, 2 × H_{a1}), 3.74 (2 H, d, *J* 11.3 and 3.7, 2 × H_{a2}), 3.25 (2 H, ddd, *J* 8.2, 5.5 and 3.7, 2 × H_b), 2.70 – 0.70 (12 H, m, -N*H*-, -O*H*, cyclohexyl)

δ_C*(75 MHz; DMSO-d_6)* 150.0 (2 C, 2 × C-4 arom.), 146.6 (2 C, 2 × C-1 arom.), 127.0 (4 C, 2 × C-2, -6 arom.); 123.4 (4 C, 2 × C-3, -5 arom.), 96.2 (2 C, C-5, -8), 78.6 (2 C, C-2, -10), 67.5 (2 C, C-3, -11), 58.8 (2 C, 2 × -*C*H_2OH), 34.4 and 34.1 (4 C, C-6, -7, -13 and -14)

δ_C*(75 MHz; $CDCl_3$)* 149.0 (2 C, 2 × C-4 arom.), 146.7 (2 C, 2 × C-1 arom.), 127.4 (4 C, 2 × C-2, -6 arom.); 123.9 (4 C, 2 × C-3, -5 arom.), 95.9 (2 C, C-5, -8), 76.6 (2 C, C-2, -10), 67.1 (2 C, C-3, -11), 60.0 (2 C, 2 × -*C*H_2OH), 34.9 and 34.7 (4 C, C-6, -7, -13 and -14)

Tautomer 3(II) (only distinct peaks or clearly correlated by COSY exp. are depicted)

δ_H *(300 MHz; $CDCl_3$)* 4.51 (2 H, d, *J* 8.1, 2 × H_c), 3.87 (2 H, dd, *J* 8.1 and 2.1, 2 × H_{a1}), 3.81 (2 H, dd, *J* 8.1 and 3.0, 2 × H_{a2}), 3.50 (2 H, ddd, *J* 8.1, 3.0 and 2.1, 2 × H_b)

δ_C*(75 MHz; $CDCl_3$)* 96.2 (2 C, C-5, -8), 73.5 (2 C, C-2, -10), 66.9 (2 C, C-3, -11), 59.6 (2 C, 2 × -*C*H_2OH), 34.8 and 34.5 (4 C, C-6, -7, -13 and -14)

Tautomer 3(III) (only distinct peaks or clearly correlated by COSY exp. are depicted)

δ_H *(300 MHz; $CDCl_3$)* 4.93 (1 H, d, *J* 8.1, H_c), 4.83 (1 H, d, *J* 6.3, H_c), 3.92 (2 H, dd, *J* 11.2 and 5.3, 2 × H_{a1}), 3.76 (2 H, dd, *J* 11.3 and 3.7, 2 × H_{a2}), 3.19 (2 H, ddd, *J* 8.1, 5.3 and 3.7, 2 × H_b)

δ_C*(75 MHz; $CDCl_3$)* 95.5 and 95.1 (2 C, C-5, -8), 78.58 and 78.7 (2 C, C-2, -10), 66.8 and 66.7 (2 C, C-3, -11), 64.1 and 63.9 (2 C, 2 × -*C*H_2OH), 38.2, 38.1, 36.5 and 36.4 (4 C, C-6, -7, -13 and -14)

δ_H *(400 MHz; acetone-d_6)* 4.88 (1 H, d, *J* 8.0, H_c), 4.87 (1 H, d, *J* 8.1, H_c), 4.18 (2 H, br s, -O*H*), 3.85 (1 H, dd, *J* 11.6 and 3.8, H_{a1}), 3.84 (1 H, dd, *J* 11.6 and 3.8, H_{a1}), 3.79 (2 H, dd, *J* 11.6 and 3.8, 2 × H_{a2}), 3.19 (1 H, dd, *J* 8.1 and 3.8, H_b), 3.17 (1 H, dd, *J* 8.1 and 3.8, H_b), 2.91 (2 H, br s, -N*H*-), 2.09 – 1.79 (8 H, m, cyclohexyl)

REFERENCES

1. M. Dărăbanțu, G. Plé, S. Mager, E. Cotora, L. Gaina, L. Costas and A. Mateş, *Tetrahedron,* 1997, ***53***(5), 1873.
2. E. Bergmann, *Chem. Rev.*, *1953*, ***53***, 309.
3. M. Dărăbanțu, G. Plé, I. Silaghi-Dumitrescu, L. Gaina, C. Maierean and I. Turos, *Unpublished data*.
4. E. Bergmann and H. Resnik, *J. Chem. Soc*., 1956, 1662.

5. E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, John Wiley & Sons, Inc., 1994, p.769-771.
6. M. Dărăbanțu, S. Mager, G. Plé and C. Puşcaş, *Heterocycles*, 1995, ***41***(10), 2327.
7. M. Dărăbanțu, G. Plé, S. Mager, L. Gaina, E. Cotora, A. Mates and L. Costas.
8. *Tetrahedron,* 1997, ***53***(5), 1891-1908.