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Synthesis of Methyl-2[*N*-subtituted-*N*-(2-hydroxyethyl)]amino-2-hydroxyacetates and 2-Hydroxy-4-alkylperhydro-1,4-oxazin-3-ones

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Abstract. This work describes the study of the reaction of methyl 2-hydroxy-2-methoxy acetate (**1**) with the β-amino alcohols, *N*-methylethanolamine (**2**), *N*-benzylethanolamine (**3**), (1*R*,2*S*)-(-)-ephedrine (**4**) and (1*S*,2*S*)-(+)-pseudoephedrine (**5**) in the presence of a mixture of benzene/ethanol and formic acid, and also without solvent. In the first case the reaction led to the new acyclic compounds methyl-2-[*N*-methyl-*N*-(2-hydroxyethyl)]amino-2-hydroxyacetate (**2a**), methyl-2[*N*-benzyl-*N*-(2-hydroxyethyl)]amino-2-hydroxyactetate (**3a**), methyl-2{*N*-methyl-*N*-[(2*R*,1*S*)-2-phenyl-1-methyl-2-hydroxyethyl]}amino-2-hydroxyacetates (**4a**, **4a'**) and methyl-2{*N*-methyl-*N*-[(2*S*,1*S*)-2-phenyl-1-methyl-2-hydroxyethyl]}amino-2-hydroxyacetates (**5a**, **5a'**). The reaction without solvent led to cyclic compounds 2-hydroxy-4-methylperhydro-1,4-oxazin-3-ones (**2b**), 2-hydroxy-4-benzylperhydro-1,4-oxazin-3-one (**3b**), (2*S*,5*S*,6*R*)-2-hydroxy-4,5-dimethyl-6-phenylperhydro-1,4-oxazin-3-one (**4b**) and (2*S*,5*S*,6*S*)-2-hydroxy-4,5-dimethyl-6-phenylperhydro-1,4-oxazin-3-one (**5b)**, which we have been reported before, except **3b**. The whole compounds were characterized by ^{1}H, ^{13}C, ^{15}N (acyclic compounds) NMR, HETCOR, infrared and mass spectrometry. Determination of minimum energy of the preferred conformation was achieved for compounds **4a**, **4a'**, **5a** and **5a'** by theoretical calculation. The structures of **3b** and **5b** were further established by a single-crystal X-ray diffraction.
Key words: 2-(*N*-hydroxyethylamino)hydroxyacetates, Oxazin-3-ones, Morpholin-3-ones, β-aminoalcohols, Spectroscopy, X-ray.

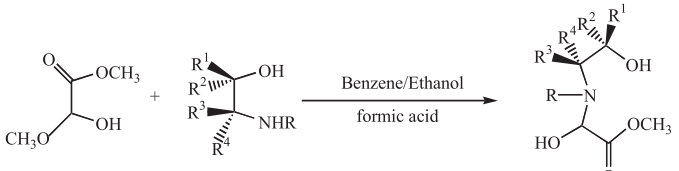
Resumen. En este trabajo se describe el estudio de la reacción del 2-hidroxi-2-metoxiacetato de metilo (**1**) con los β-amino alcoholes: *N*-metiletanolamina (**2**), *N*-benciletanolamina (**3**), (1*R*,2*S*)-(-)-efedrina (**4**) y (1*S*,2*S*)-(+)-pseudoefedrina (**5**) en presencia de la mezcla de benceno/etanol y ácido fórmico, y también sin disolvente. En el primer caso la reacción conduce a los nuevos compuestos acíclicos metil-2-[*N*-metil-*N*-(2-hidroxietil)]amino-2-hidroxiacetato (**2a**), metil-2[*N*-bencil-N-(2-hidroxietil)]amino-2-hidroxiacetato (**3a**), metil-2{*N*-metil-N-[(2*R*,1*S*)-2-fenil-1-metil-2-hidroxietil]}amino-2-hidroxiacetatos (**4a**, **4a'**) y metil-2{*N*-metil-N-[(2*S*,1*S*)-2-fenil-1-metil-2-hidroxietil]}amino-2-hidroxiacetatos (**5a**, **5a'**). La reacción sin disolvente conduce a los compuestos cíclicos 2-hidroxi-4-metilperhidro-1,4-oxazin-3-onas (**2b**), 2-hidroxi-4-bencilperhidro-1,4-oxazin-3-ona (**3b**), (2*S*,5*S*,6*R*)-2-hidroxi-4,5-dimetil-6-fenilperhidro-1,4-oxazin-3-ona (**4b**) y (2*S*,5*S*,6*S*)-2-hidroxi-4,5-dimetil-6-fenilperhidro-1,4-oxazin-3-ona (**5b**), los cuales han sido reportados por nosotros anteriormente, excepto **3b**. Todos los compuestos fueron caracterizados por RMN de ^{1}H, ^{13}C y ^{15}N (compuestos acíclicos), HETCOR, infrarrojo y espectrometría de masas. Además, se llevó a cabo la determinación de la energía mínima de la conformación preferida de los compuestos **4a**, **4a'**, **5a** y **5a'** a partir de cálculos teóricos. Las estructuras de **3b** y **5b** fueron además establecidas por difracción de rayos-X.
Palabras clave: 2-(*N*-hidroxietilamino)hidroxiacetates, Oxazin-3-onas, Morfolin-3-onas, β-Aminoalcoholes, Espectroscopia, Rayos-X.

Introduction

β-aminoalcohols are an important class of compounds useful in the synthesis of a variety of acyclic and cyclic derivatives [1-15], likewise some of them and their heterocycles derivatives are used as chiral auxiliaries in asymmetric organic synthesis [16,17]. Many β-aminoalcohol derivatives have been utilized in a variety of applications, for instance, in cosmetic emulsions, creams, sun protection [18] and also they have exhibited biological properties as analgesic, amebacidal and anticonvulsant [1,18-22].

Because of our current interest on the syntheses of β-aminoalcohol derivatives prompted us to study the reaction of methyl 2-hydroxy-2-methoxyacetate (**1)** with *N*-methylethanolamine (**2**), *N*-benzylethanolamine (**3**), (1*R*,2*S*)-(-)-ephedrine (**4**) and (1*S*,2*S*)-(+)-pseudoephedrine (**5**) in the presence and the absence of solvents [12,13].

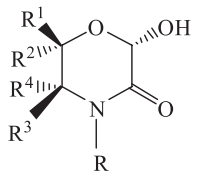
This article describes the synthesis of new methyl-2[*N*-subtituted-*N*-(2-hydroxyethyl)]amino-2-hydroxyacetates (**2-5)a** (Scheme 1) and 2-hydroxy-4-alkylperhydro-1,4-oxazin-3-ones (**2-5**)β and **2β'**(Scheme 2). The characterization of the compounds was carried out by spectroscopic methods and the preferred conformation of diasteromers **4a**, **4a'**, **5a** and **5a'** was obtained by theoretical calculations, moreover, the structures of **3b** and **5b** were further established by a single-crystal X-ray diffraction.



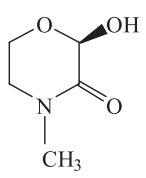
1

2: R = CH_3 , $R^1 = R^2 = R^3 = R^4 = H$ **:2a**
3: R = $C_6H_5CH_2$, $R^1 = R^2 = R^3 = R^4 = H$ **:3a**
4: R = CH_3 , $R^1 = C_6H_5$, $R^2 = H$, $R^3 = CH_3$, $R^4 = H$ **:4a**
5: R = CH_3 , $R^1 = H$, $R^2 = C_6H_5$, $R^3 = CH_3$, $R^4 = H$ **:5a**

Scheme 1. Synthesis of methyl-2[*N*-subtituted-*N*-(2-hydroxyethyl)] amino-2-hydroxyacetates (**2-5)a**.



(**2-5**)**b**



2b'

2b: R = CH_3 , $R^1 = R^2 = R^3 = R^4 = H$
3b: R = $C_6H_5CH_2$, $R^1 = R^2 = R^3 = R^4 = H$
4b: R = CH_3 , $R^1 = C_6H_5$, $R^2 = H$, $R^3 = CH_3$, $R^4 = H$
5b: R = CH_3 , $R^1 = H$, $R^2 = C_6H_5$, $R^3 = CH_3$, $R^4 = H$

Scheme 2. 2-Hydroxy-4-alkylperhydro-1,4-oxazin-3-ones (**2-5**)**b** and **2b'**

Results and Discussion

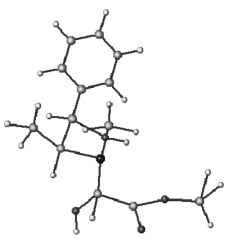
At the beginning of this study several reactions were carried out between **1** and **2** in benzene at different temperatures, however a mixture of **2**, **2a**, **2b** and **2b'** was always observed, independently of the temperature of the reaction; at extended time the reaction led exclusively to cyclic compound **2b,** which is thermodynamically more stable than **2b'** due to anomeric effect [23]. The difference between **2b** and **2b'** is just the position of the OH group, axial and equatorial, respectively (Scheme 2), determined by the chemical shift value of H-C_2 in ^{1}H NMR spectra [11]. We have already reported the reaction of **1** with **2**, **4** and **5** at room temperature and lower in pentane and pentane/methanol (4:1) obtaining exclusively **2b**, **4b** and **5b** [11]. In accordance to our experience about this reaction and also information from the literature [24], we carried out the reaction of compound **1** with the β-aminoalcohols **2**, **3**, **4**, and **5** in a mixture of benzene/ethanol and in the presence of formic acid in order to control the pH of the reaction [24]. Thus, acyclic compounds were obtained, **2a** in good yield at pH 8, **3a** and a mixture of diasteromers **4a**, **4a'**, **5a** and **5a'** were obtained at pH 4 under reflux of benzene/ethanol. In this context, it is important to notice that these compounds only can be obtained in good yields controlling the pH of the reaction.

Table 1 shows the ^{1}H NMR spectra of the compounds **2a**, **3a**, **4a**, **4a'**, **5a** and **5a'**. The spectra of compounds **2a** and **3a** in $CDCl_3$ clearly show an ABCD coupling pattern for protons of CH_2O and CH_2N in the range of 4.10-2.81 ppm, this is probably due to the existence of intramolecular hydrogen bond between HO group and nitrogen atom, this feature has been observed in aminoalcohols in aprotic no polar solvent such as $CDCl_3$. Moreover, four stereoisomers can be expected considering the presence of two chiral centers at C-3 and at nitrogen atom, however, due to the nitrogen unstable configuration, only a pair of enantiomers is observed. To confirm this fact, the spectra were also measured in DMSO-d_6, an aprotic polar solvent; effectively the ABCD system became an ABX_2 pattern, where AB system corresponds to protons of the CH_2N. Spectra of **3a** in both solvents show an AB system for the diastereotopic H-7 protons of the benzyl group, which evidences the generation of the N atom as a chiral center. Coupling constant of CH_2N for both **2a** and **3a** were determined by homonuclear proton decoupling experiment ^{1}H {^{1}H}, decoupling triplet signal of protons of CH_2O at 3.88 and 3.89 ppm, respectively; these reduced the coupling pattern of protons CH_2N to an AB system, which are in the range between 3.06 and 3.77 ppm. In addition, HETCOR experiment for **2a** confirmed its assignment, thus the single signal at δ 2.55 ppm assigned to H-7 correlates with the signal at 41.7 ppm (C-7) characteristic of carbon bonded at nitrogen atom; the complex pattern at 2.81 and 3.27 ppm assigned to H-5 protons correlates with the signal at 53.6 ppm (C-5); the single signal at 3.77 ppm assigned to H-1 protons correlates with the signal at 52.2 ppm (C-1), the complex pattern at 4.07 and 4.03 ppm assigned to H-6 protons correlates with the signal at 65.8 ppm (C-6) and the signal at 4.58 ppm assigned to H-3 proton correlates with the signal at 93.7 ppm (C-3). The ^{1}H NMR spectra of derivatives **4** and **5** exhibit a mixture of diastereomers **4a**, **4a'** and **5a**, **5a**' in a ratio 60:40 and 80:20, respectively. The signals of protons H-1, H-7, H-8 and H-3; H-5 and H-6 of the more abundant isomer **4a** appear at higher and lower frequency, respectively, than for the minor isomer **4a'**. The same matter is observed for the mixture of compounds **5a** and **5a'**, except for H-6, which appears at higher frequency in the more abundant isomers, this can be due to the change of the configuration at carbon C-6. The two possible diastereoisomers expected for these compounds are those, where C-3 has different configuration in accordance with the spatial orientation of H-3 and OH groups. In fact the H-3 of the more abundant isomer appears at higher field than of the minor isomer H-3'. This can be due to that H-3 is perpendicular to carbonyl group, while H-3' is almost on the same plane of the carbonyl which deshield this proton because of the electronic. In order to know the preferred conformation of diasteromers **4a**, **4a'**, **5a** and **5a'**, theoretical calculations were carried out (Scheme 3). Thus, the minima energy for each conformation was estimated: 19.90 for **4a**, 24.94 for **4a'**, 18.20 for **5a** and 22.88 Kcal/mol for **5a'**, which values are agree with the of the major and minor isomer formation.

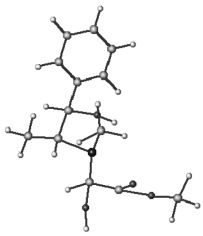
Table 1 shows the ^{1}H and ^{15}N NMR data for compounds **2a**, **3a**, **4a**, **4a'**, **5a** and **5a'.** The δ (^{15}N) are within the range of amines [25].

Table 2 shows ^{13}C data for compounds **2a**, **3a**, **4a**, **4a'**, **5a** and **5a'**. They exhibit the expected ^{13}C NMR spectra. The assignments for all carbon atoms were achieved in comparison with the chemical shifts of starting materials (**1-5**), analogous compounds [12] and by correlation of the assignment of **2a** and **3a** by HETCOR spectra. The more relevant signals are: for C-1 in the range of 51.7 to 52.5 ppm; for C-2 (carbonyl group) at 170.1-170.9 ppm; the chemical shift of C-3 in the range of 91.7 to 94.0 ppm is the evidence that OH group is bonded to that carbon.

The IR spectra of the various compounds show a band due to the carbonyl of the ester in the range of 1750-1744 cm^{-1}, and a band due to the hydroxyl group in the range 3436 - 3384 cm^{-1}. The EI mass spectra at 70 eV of compounds **2a**, **3a**, **4a** and **5a** do not show the molecular ion; the fragment at *m/z* = 44, *m/z* = 91, *m/z* = 176 and *m/z* = 176 correspond to base peak

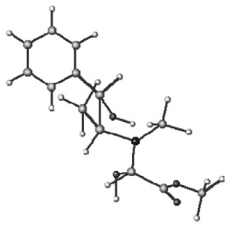


4a

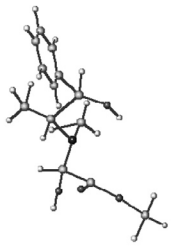


4a'

Methyl-2{*N*-methyl-N-[(2*R*,1*S*)-2-phenyl-1-methyl-2-hydroxyethyl]}amino-2-hydroxyacetates (**4a**, **4a'**)



5a

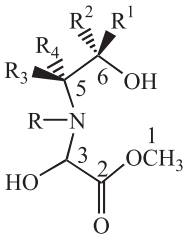


5a'

Methyl-2{*N*-methyl-N-[(2*S*,1*S*)-2-phenyl-1-methyl-2-hydroxyethyl]}amino-2-hydroxyactetates (**5a**, **5a'**).

Scheme 3. Preferred conformations **4a**, **4a'**, **5a** and **5a'** diasteromers.

Table 1. ^{1}H ^{15}N NMR data for compounds **2a**, **3a**, **4a**, **4a'**, **5a** and **5a'**.



	R	R^1	R^2	R^3	R^4
2a:	$^{7}CH_3$	^{6}H	^{6}H	^{5}H	^{5}H
3a:	$^{7}CH_2$-	^{6}H	^{6}H	^{5}H	^{5}H
4a, **4a'** :	$^{7}CH_3$		^{6}H	$^{8}CH_3$	^{5}H
5a, **5a'** :	$^{7}CH_3$	^{6}H		$^{8}CH_3$	^{5}H

Compound	H-1	H-3	R-N	R^1	R^2	R^3	R^4	δ (^{15}N)
2a	3.77 (s)	4.58 (s)	H_7: 2.55 (s)	H_{6A}: 4.07 (m); H_{6B}: 4.03 (m)		H_{5C}: 3.27 (m); H_{5D}: 2.81 (m)		-331.1
2a[a,b]	3.64 (s)	4.58 (s)	H_7: 2.40 (s)	H_{6X2}: 3.88 (t); J = 6.7		H_{5A}: 3.07 (m); H_{5B}: 2.77 (m)		
3a	3.72 (s)	4.80 (s)	H_{7A}: 3.94 (d) H_{7B}: 3.77 (d) J_{AB} = 13.2 H_{arom}: 7.35 (m)	H_{6A}: 4.10 (m); H_{6B}: 4.00 (m)		H_{5C}: 3.22 (m); H_{5D}: 2.90 (m)		-316.7
3a[a]	3.63 (s)	4.82 (s)	H_{7A}: 3.86 (d) H_{7B}: 3.73 (d) J_{AB} = 13.9 H_{arom}: 7.33 (m)	H_{6X2}: 3.89 (t); J = 6.9 J_{AB} = 10.8; J_{AX} = J_{BX} = 6.9		H_{5A}: 3.07 (m); H_{5B}: 2.89 (m)		
4a	3.86 (s)	4.36 (s)	H_7: 2.43 (s)	H_{arom}: 7.2-7.4 (m) H_6: 5.14 (d) J = 7.3		H_8: 0.72 (d); H_5: 2.93 (m) J = 6.6		-319.5
4a'[c]	3.78 (s)	5.04 (s)	H_7: 2.41 (s)	H_6: 5.44 (d) J = 6.6		H_8: 0.64 (d); H_5: 3.50 (m) J = 6.6		-328.7
5a	3.80 (s)	4.62 (s)	H_7: 2.51 (s)	H_{arom}: 7.2-7.5 (m) H_6: 4.75 (d) J = 9.1		H_8: 1.12 (d); H_5: 2.47 (m) J = 6.0		-317.1
5a'[c]	3.79 (s)	5.08 (s)	H_7: 2.43 (s)	H_6: 4.54 (d) J = 9.0		H_8: 1.09 (d); H_5: 3.11 (m) J = 6.6		-321.6

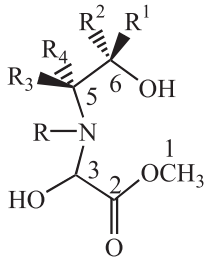
δ (^{1}H) relative to $Si(CH_3)_4$; δ (^{15}H) relative to $MeNO_2$ net; solvent $CDCl_3$; |*J*| = Hz; d: doublet; m; complex pattern; s: singlet; t: triplet

[a]Solvent DMSO-d_6

[b]J_{AB} = 10.1; J_{AX} = J_{BX} = 6.7

[c]The signals of the aromatic protons are overlapped with those of the other diasteromer

Table 2. ^{13}C NMR Data for compounds **2a**, **3a**, **4a'**, **5a** and **5a'**.



2a: R = $^{7}CH_3$; $R^1 = R^2 = R^3 = R^4 = H$

3a: R = $^{7}CH_2$-*i*-Ph; $R^1 = R^2 = R^3 = R^4 = H$

4a; **4a'**: R = $^{7}CH_3$; R^1 = *i*-Ph; $R^3 = {}^{8}CH_3$; $R^2 = R^4 = H$

5a; **5a'**: R = $^{7}CH_3$; R^2 = *i*-Ph; $R^3 = {}^{8}CH_3$; $R^1 = R^4 = H$

Compound	**2a**	**2a**[a]	**3a**	**3a**[a]	**4a**	**4a'**	**5a**	**5a'**
C-1	52.2	51.7	52.1	51.7	52.5	51.7	52.3	51.7
C-2	170.5	170.2	170.7	170.2	170.1	170.8	170.9	170.8
C-3	93.7	93.1	92.1	91.8	94.0	91.7	93.6	92.6
C-5	53.6	52.8	51.0	50.5	64.0	59.4	68.4	63.3
C-6	65.8	64.9	65.6	64.6	83.6	83.9	87.3	86.7
C-7	41.7	41.1	58.5	57.7	37.2	33.5	37.9	33.8
C-8					14.4	12.5	14.0	12.7
C-*i*			138.0	138.5	138.8	138.9	138.1	138.5
C-*o*			128.4	128.3	127.5	126.8	128.4	128.4
C-*m*			128.7	128.5	128.0	128.0	126.7	127.3
C-*p*			127.5	127.2	127.8	127.6	128.3	128.2

δ (^{13}C) relative to $Si(CH_3)_4$; solvent $CDCl_3$

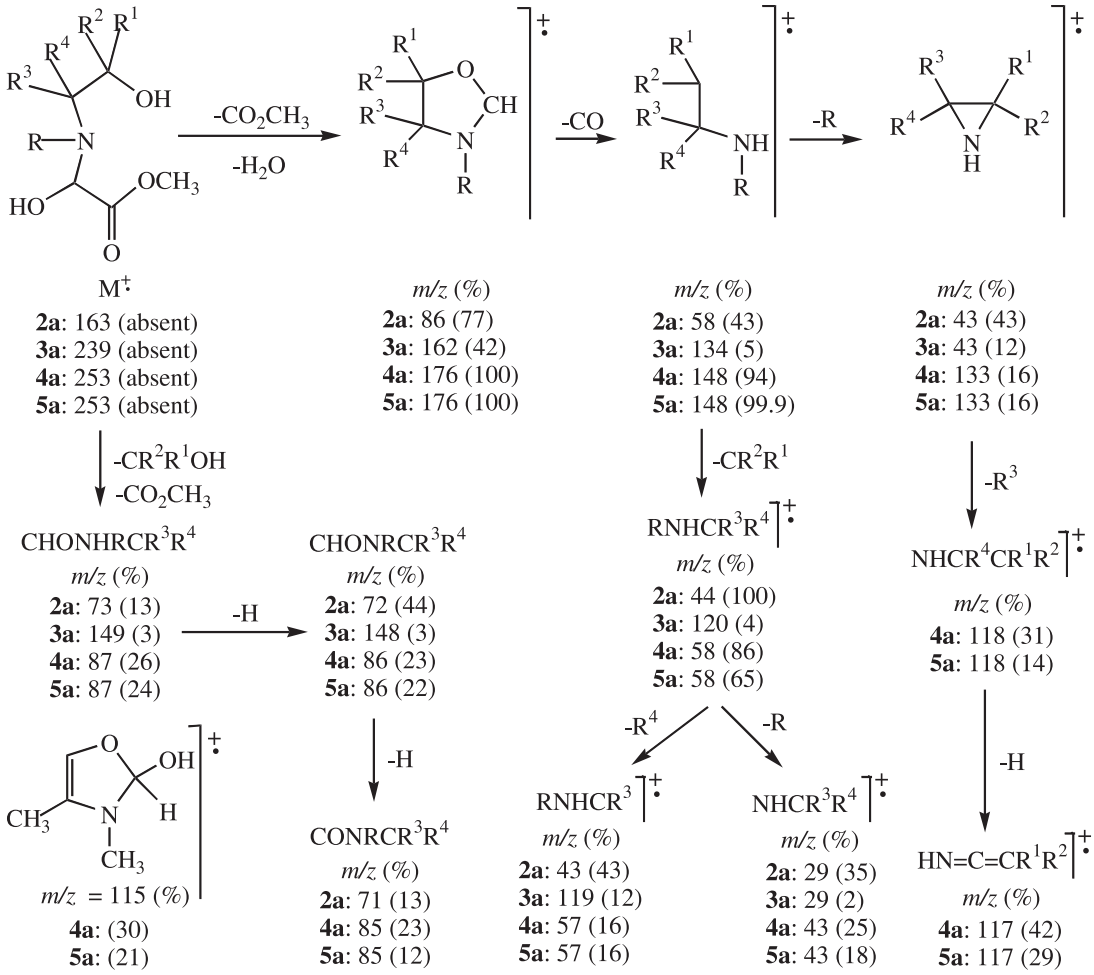
[a]Solvent DMSO-d_6

of these compounds, respectively. Scheme 4 shows important fragment ions of these compounds.

On another hand, as mentioned above we have already reported the reaction of **1** with **2**, **4** and **5** at room temperature and lower in pentane and pentane/methanol (4:1) obtaining exclusively **2b**, **4b** and **5b** [11]. In this work we report the reaction of **1** with **2**, **3**, **4** and **5** without solvent, which led exclusively to 2-hydroxy-1,4-oxazin-3-ones (**2**-**5**)**b**.

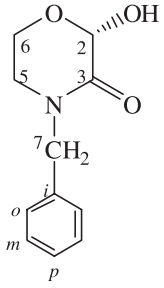
The ^{1}H and ^{13}C NMR data of compounds **2b**, **4b** and **5b** agree with those reported for us previously, as well as their infrared spectra and mass data [11]. It is important to notice that synthesis of compound **3b** is already reported in the literature by different methods as it is reported by us and used for the synthesis of NK_1 receptor antagonist [26,27]. However, from our information their spectral data are not described; now we are giving its ^{1}H and ^{13}C NMR data in DMSO-d_6. Its assignment was achieved by HETCOR, thus the single signal at 5.06 ppm assigned to H-2 correlates with C-2 at 90.1 ppm; methylene protons H-7 of benzyl group show an AB system at 4.55 and 4.49 ppm and correlates with C-7 at 48.6 ppm. Therefore protons H-6 and H-5 displays an ABCD system at 4.11, 3.69, 3.35, 3.11 ppm, where the two first one correlate with C-6 at 56.1 ppm and the second ones with C-5 at 45.5 ppm. Aromatic protons of the benzyl group exhibit a complex pattern at 7.26 ppm. Table 3 shows ^{1}H, ^{13}C NMR in DMSO-d_6, IR and EI mass data for compound **3b**.

The structures of **3b** and **5b** were established by a single-crystal X-ray diffraction study and we have already reported the X-ray data of **2b** and **4b** [11]. Suitable crystal of **3b** and **5b** for X-ray analysis were obtained from chloroform; the molecular structures and crystallographic numbering are shown in Figures 1 and 2, respectively. The molecular structure of **3b** exhibits the intermolecular contact $O_3 \cdots H_{2a}$, 1.837 Å, which is significantly shorter than the sum of the van der Waals radii for the oxygen and hydrogen atoms (2.70 Å) [28]. In general de bond distances are within the expected values and the relevant distances are: O1-C10 1.404(2), C11-C10 1.521(3), N1-C-11 1.327(2), N1-C8 1.465(3), C8-C9 1.496(3), O1-C9 1.432(3), C10-H10A 0.96, O2-C-10 1.397(3) and O2-H2A 0.85 Å. The torsion angle for the O3-C11-N1-C7 fragments is 1.41°, indicating that this part of the molecule is almost planar, likewise the values for the ring C9-O1-C10-C11, 49.87°; O1-C10-C11-N1, 18.40°; C10-C11-N1-C8, 4.77°; C11-N1-C8-C9, 21.39°; N1-C8-C9-O1, 51.28° and C8-C9-O1-C10, -67.59° give evidence of the shape of the ring, where the part more or less planar is around of the C10-C11-N1-C8 atoms.



Scheme 4. Mass spectral data of methyl-2[*N*-subtituted-*N*-(2-hydroxyethyl)]amino-2-hydroxyacetates (**2-5)a**.

Table 3. ^{1}H and ^{13}C NMR in DMSO-d, IR and EI mass data for compounds **3b**.



δ (^{1}H)	δ (^{13}C)	IR (cm^{-1})
H_2: 5.06 (d), J = 6.4 OH: 7.16 (d), J = 6.4 H_{5D}: 3.11(ddd), J = 11.5, 3.7, 1.7 H_{5C}: 3.35 (td), J = 11.5, 3.7 H_{6B}: 3.69 (ddd), J = 11.5, 3.7, 1.7 H_{6A}: 4.11 (td), J = 11.5, 3.7 H_{7A}: 4.55 (d), H_{7B}: 4.49, J_{AB} = 14.8 H_{arom}: 7.31 (m)	C-2: 90.1 C-3:165.7 C-5: 45.5 C-6: 56.1 C-7: 48.6 C-*i*: 136.7 C-*o*:127.7 C-*m*:128.5 C-*p*:127.3	$\nu_{C\text{-}H\ aliphatic}$ 2952,2983 $\nu_{C\text{-}H\ arom.}$ 3058 ν_{NCO} 1644 ν_{OH} 3118

Mass data, *m/z* (%)

M^+ 204 (2), 190 (9), 189 (62), 160 (12), 132 (13), 105 (11), 91 (100), 65 (26).

δ (^{1}H) and ^{13}C relative to $Si(CH_3)_4$; $|J|$ = Hz; d: doublet; ddd: doublet of doublet of doublets; td: triplet of doublet; m; complex pattern.

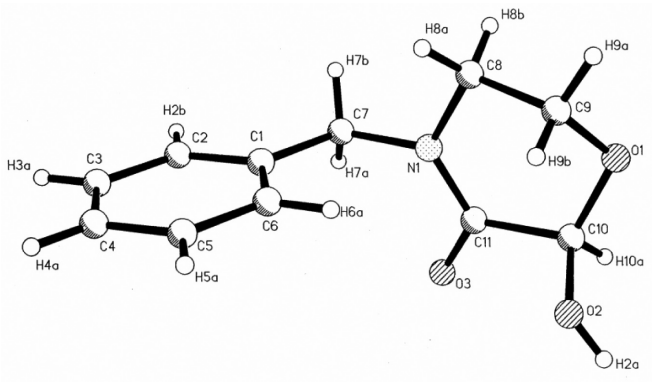


Fig. 1. Ortep drawing of compound **3b**.

Compound **5b** crystallizes with two independent molecules **A** and **B**, and water molecules in the asymmetric unit. The molecules in the crystal structure show the following intermolecular contacts with water molecules: for **5bA**, H2b···O5 1.826 and H4b···O3a, 1.991 Å; for **5bB**, H5c····O3, 1.633 and H2b····O4, 1.858 Å, which are significantly shorter than the sum of the van der Waals radii for the oxygen and hydrogen atoms (2.70 Å) [28].

The torsion angle values of each ring in the molecules are: for **A** C8a-C7a-O1a-C12a , 67.49°; O1a-C7a-C8a-N1a, -46.82°; C7a-C8a-N1a-C11a, 15.60°, C12a-C11a-N1a-C8a, -0.99°, N1a-C11a-C12a-O1a, 17.38°; C11a-C12a-O1a-C7a, -50.91° and for **B**, C8-C7-O1-C12, 68.61°; O1-C7-C8-N1, -47.43°; C7-C8-N1-C11, 12.02°; C12-C11-N1-C8, 5.87°; N1-C11-C12-O1, 12.55°; C11-C12-O1-C7, -50.83°. Bond distances are within the expected values and the relevant distances are for molecule **A**, O1a-C12a, 1.410(5); C11a-C12a ,1.523(7); N1a-C11a, 1.313(5); N1a-C8a, 1.478(5); C7a-C8a, 1.533(6); O1a-C7a, 1.426(5); C12a-H12b, 0.96; C12a-O2a, 1.384(5) and O2a-H2ab 0.85; for molecule **B**, O1-C12 , 1.409(5); C12-C11, 1.512(7); N1-C11, 1.339(6); N1-C8, 1.464(6); C7-C8, 1.527(6); O1-C7, 1.429(5); C12-H12a, 0.96; C12-O2, 1.381(5) and O2-H2b 0.85. Therefore the configuration at C12a (**A**) and C12 (**B**) is *S*.

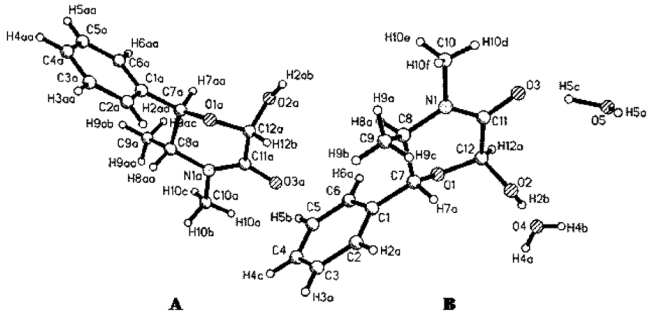


Figure2. Ortep drawing of compound **5b**, two molecules **A** and **B** in the asymmetric unit.

In conclusion, we describe that the study of the reactivity of **1** with the β-amino alcohols **2-5** led to different type of compounds. According to the reaction conditions led to the acyclic compounds **2a**, **3a**, **4a-4a'**, **5a-5a**' in benzene/ethanol and formic acid, and without solvent to the cyclic compounds **2b-5b**, being this method useful to reduce the reaction time and avoid using solvent. Therefore, minimum energy obtained for conformations of **4a**, **4a'**, **5a** and **5a**' by theoretical calculations (PC agrees with the formation of the major and minor isomer, as well as with the chemical shifts observed by H^1 NMR spectra).

The crystal data of **3b** and **5b** confirm their structures and in the compound **5b** the configuration of the C12a (**A**) and C12 (**B**) is *S*.

Acknowledgment

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Experimental

General procedure and measurements. The reagents were purchased from Aldrich Co. Compound **1** was prepared according to the literature [30]. ^1H, ^{13}C and ^{15}N NMR spectra were recorded on Jeol GLX-270, Jeol Eclipse-400 and Bruker Avance 300-DPX spectrometers; $CDCl_3$ and DMSO-d_6 were used as solvent. Mass spectra were obtained on a Hewlett-Packard 59940-A spectrometer at 70 eV electron impact. The IR spectra were recorded as neat liquid or KBr pellets on a Perkin-Elmer 16F Pc FT-IR spectrometer. Melting points were measured in open capillary tubes on a Gallemkamp MFB-595 apparatus and have not been corrected. The single-crystal X-ray study was performed on a CAD4 ENRAF NONIUS FR 590 diffractometer.

The procedure outlined below is general for the preparation of Methyl-2[*N*-subtituted-*N*-(2-hydroxyethyl)]amino-2-hydroxyacetates (**2-5)a**.

Methyl-2-[*N*-methyl-*N*-(2-hydroxyethyl)]amino-2-hydroxyacetate (**2a**): To a solution of 0.27 mL (3.33 mmol) of *N*-methylethanolamine **2** in 40 mL of benzene was added dropwise at room temperature, formic acid until pH 8, the 3 mL of ethanol to obtain a homogenous mixture and afterwards a solution of 0.4 g (3.33 mol) of methyl 2-hydroxy-2-methoxy acetate (**1**) in 5 mL of ethanol. The reaction mixture was refluxed and stirred during 3 h. After being cooled to room temperature the solvent was evaporated under vacuum and 0.48 g (88%) of compound **2a** were obtained as a yellow liquid. IR: 3420, 2959, 2894, 1750, 1214 and 1082 cm^{-1}.

Methyl-2[*N*-benzyl-*N*-(2-hydroxyethyl)]amino-2-hydroxyactetate (3a): The reaction of 0.37 mL (2.25 mmol) of *N*-benzylethanolamine **3** in 30 mL of benzene, formic acid (pH = 4), 0.3 (2.25 mmol) of compound **1** produce 0.55 g (92%) of compound **3a** as a yellow liquid. IR: 3421, 3030, 2952, 2894, 1750, 1654, 1208, 1078 cm^{-1}.

Methyl-2{*N*-methyl-*N*-[(2R,1S)-2-phenyl-1-methyl-2-hydroxyethyl]}amino-2-hydroxylacetates (4a, 4a'): The reaction of 0.55 g (3.33 mmol) of (1*R*,2*S*)-(-) ephedrine **4** in 40 mL of benzene, formic acid (pH = 4) and 0.4 g (3.33 mmol) of compound **1** gave 0.80 g (90%) of a mixture of diasteromers **4a** and **4a'** as a yellow liquid in a ratio 60:40, respectively. IR: 3436, 3060, 2954, 2912, 2848, 1744, 1658, 1210 and 1094 cm^{-1}.

Methyl-2{*N*-methyl-*N*-[(2S,1S)-2-phenyl-1-methyl-2-hydroxyethyl]}amino-2-hydroxyacetates (5a, 5a'): The reaction of 0.56 g (3.33 mmol) of (1*S*,2*S*)-(+) pseudoephedrine **5** in 40 mL of benzene, formic acid (pH = 4), and 0.4 g (3.33 mmol) of compound **1** gave 0.8 g (90%) of a mixture of diasteromers **5a** and **5a'** as a yellow liquid in a ratio 80:20, respectively. IR: 3384, 3060, 2968, 2882, 2850, 1744, 1656, 1204 and 1656 cm^{-1}.

The procedure outlined below is general for the preparation of 2-hydroxy-4-alkylperhydro-1,4-oxazin-3-ones (**2-5**)**b**.

2-Hydroxy-4-methylperhydro-1,4-oxazin-3-ones (2b): A mixture of 0.27 mL of *N*-methylethanolamine **2** and 0.4 g (3.33 mmol) of methyl glyoxylate hemiacetal **1** was cooled to 0°C and stirred 25 min, then for one hour at room temperature. The reaction mixture was dried under vacuum and the residue was recrystallized from chloroform to yield 0.28 g (65%) of compound **2b**.

2-Hydroxy-4-benzylperhydro-1,4-oxazin-3-ones (3b): The reaction of 0.37 mL of N-benzyl ethanolamine **3** and 0.3 g (2.5 mmol) of compound **1** yield 0.39 g (75%) of compound **3b**, m. p. 127-129°C.

(2S,5S,6R)-2-hydroxy-4,5-dimethyl-6-phenylperhydro-1,4-oxazin-3-one (4b): The reaction of 0.55 g (3.33 mmol) of (1*R*,2*S*)-(-) ephedrine **4** and 0.4 g (3.33 mmol) of compound **1** was stirred 1.25 h to 40°C. The reaction mixture was dried under vacuum and the residue was recrystallized from a mixture of chloroform/ethanol/ acetone to obtain 0.49 g (66%) of compound **4b**.

(2S,5S,6S)-2-hydroxy-4,5-dimethyl-6-phenylperhydro-1,4-oxazin-3-one (5b): The reaction of 0.56 g (3.33 mmol) of (1*S*,2*S*)-(+) pseudoephedrine **5** and 0.4 g of compound **1** was stirred 1.25 h to 40°C. The reaction mixture was dried under vacuum and the residue recrystallized from chloroform to yield 0.54 g (73%) of compound **5b**.

X-ray crystal structures determination for 3b and 5b. Lattice constants were determined from least squares refinements of the setting angles of 25 well centered reflections on an automatic diffractometer using molybdenum radiation.

Compound 3b, $C_{11}H_{13}NO_3$, crystallizes in the space group P2(1)/n, monoclinic, from chloroform as a colorless rectangular prism with a = 12.289 (2), b = 5.7080 (10), c = 14.796 (3) Å, V = 1009.8 (3) $Å^3$, ρ 1.363 Mg/m^3, Z= 4, μ = 0.100 mm^{-1}, F(000) = 440. A total of 2060 reflections were measured $4.90 \leq 2\theta \leq 51.94°$, 1966 were independent and 1187 of these were considered observed (Fo > 4σ(Fo). Solution and refinement: direct method, all non hydrogen atoms refined anisotropically, all hydrogen were located by difference Fourier maps and refined with an overall isotropic thermal parameters, R = 0.0412, Rw = 0.1134

Compound 5b, $C_{12}H_{15}NO_3$, crystallizes in the space group I2, monoclinic, from chloroform as a colorless rectangular prism with a = 16.009 (3), b = 7.502 (2), c = 21.269 (4) Å, V =2523.0 (9) $Å^3$, ρ 1.165 Mg/m^3, Z = 8, μ = 0.084 mm^{-1}, F(000) = 944. A total of 4887 reflections were measured $5.16 \leq 2\theta \leq 49.94°$, 2393 independent and of these 1505 were considered observed (Fo > 4σ(Fo), R = 0.0437, Rw = 0.1091.

X-ray measurement was performed at 293K on a CAD4 ENRAF-NONIUS diffractometer. Absorption correction was not necessary. Atomic scattering factors were taken from International Tables for X-ray Crystallography [31]. All calculations were carried out on a VAX 4000 computer using SHELX 93(Shedrick G. M.) program package [32].

Crystal data for structure **3b** (CCDC 649100) and **5b** (CCDC 649375) have been deposited in the Cambridge Crystallographic Data Center, e mail: deposit@ccdc.cam.ac.uk

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