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Syntheses and Characterization of New (2S)-2-Hydroxy-1,4-oxazin-3-ones Derived from β-Aminoalcohols

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ABSTRACT

The reactions of methyl glyoxylate hemiacetal **1** *with 2-(methylamino)ethanol* **2**, *(1R,2S)-(−)-ephedrine* **3** *and (1S,2S)-(+)-pseudoephedrine* **4** *provide the (2S)-2-hydroxy-1,4-oxazin-3-ones* **2a**, **3a**, **4a** *in good yield. They were characterized by ^1H, ^{13}C, NMR, and infrared and mass spectroscopy. The structures of* **2a** *and* **3a** *were established by X-ray diffraction. The configuration of C_2 (S) is demonstrated by ^1H NMR data and confirmed for compounds* **2a** *and* **3a** *by single-crystal X-ray diffraction studies.* © *1996 John Wiley & Sons, Inc.*

INTRODUCTION

In general, the morpholin-2-ones have been prepared from β-aminoalcohols and 1,2-epoxides, α-haloesters, α-oxoesters, glycide, glyoxal, α-chloroacetamides, and 2-(*N*,*N*-dialkylamino)ethyl diazoacetoacetates [1–11]. They have been the subject of stereochemical analysis [12] and synthesis of α-aminoacids [8], and some of them have been prepared to test for their possible analgetic activity [1].

On the other hand, there are only a few reports about the synthesis of morpholin-3-ones [13–17]. These methods require the synthesis of morpholin-3-ones, and some of them proceed in modest yield.

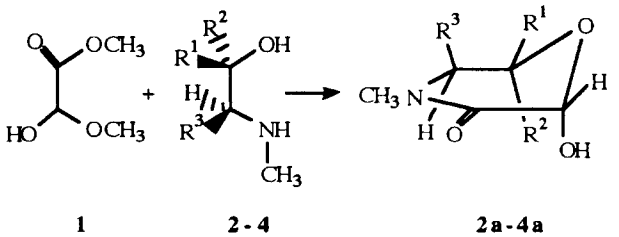
Our current interest in the syntheses of new derivatives of β-aminoalcohols prompted us to study the reaction of methyl glyoxylate hemiacetal **1** with 2(methylamino)ethanol **2**, (1R,2S)-(−)-ephedrine **3** and with (1S,2S)-(+)-pseudoephedrine **4**, using, as solvents, pentane for the reaction with **2** and pentane/methanol for the reactions with **3** and **4**.

This article describes the synthesis in one step each of the new 2-hydroxy-4-methylperhydro-1,4-oxazin-3-ones **2a**, **3a**, and **4a** (Figure 1).

DISCUSSION

The reaction of methyl glyoxolate hemiacetal **1** with the β-aminoalcohols **2**, **3**, and **4** led to the regioselective syntheses of (2S)-2-hydroxy-4-methylperhydro-1,4-oxazin-3-one **2a**, (2S,5S,6R)-2-hydroxy-4,5-dimethyl-6-phenylperhydro-1,4-oxazin-3-one **3a**, and (2S,5S,6S)-2-hydroxy-4,5-dimethyl-6-phenylperhydro-1,4-oxazin-3-one **4a**, respectively (Figure 1).

The ^1H NMR spectra of the compounds **2a–4a** exhibit the expected resonances (see Table 1).



1 2-4 2a-4a

FIGURE 1 Synthesis of 2-hydroxy-4-methyl-perhydro-1,4-oxazin-3-ones **2a**, **3a**, and **4a**.

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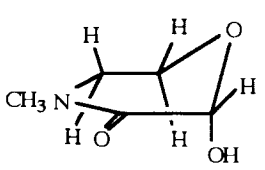
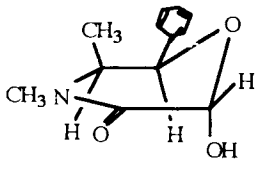
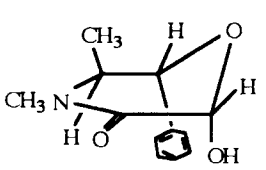
TABLE 1 ^{1}H NMR Data for Compounds **2a–4a**



2a



3a



4a

Compound	CH_3–CN	CH_3–N	CH–N	CH–O	CH(OH)	COH(H)	C_6H_5
2a		2.82 (s)	$H_{(ax)}$: 3.17 (ddd) J = 11.2 4.6 1.3 $H_{(eq)}$: 3.44 (td) J = 11.2 4.6	$H_{(ax)}$: 3.69 (ddd) J = 11.2 4.6 1.3 $H_{(eq)}$: 4.12 (td) J = 11.2 4.6	4.94 (s)	7.02 (s)	
3a	0.81 (d) J = 5.9	2.88 (s)	3.68 (m)	5.47 (d) J = 2.6	5.17 (s)	7.2 (s)	7.4 (s)
4a	1.0 (d) J = 5.9	2.85 (s)	3.59 (m)	4.88 (d) J = 9.9	5.11 (s)	7.2 (s)	7.4 (b)

δ(^{1}H) relative to $Si(CH_3)_4$; solvent DMSO-d_6; s: singlet; d: doublet; ddd: doublet of doublet of doublets; td: triplet of doublets; b: broad; m: unresolved pattern; IJI: Hz.

The ^{1}H NMR spectra of compounds **2a–4a** in DMSO-d_6 showed a single signal due to the CH_3–N group within the range corresponding to 4-methyl morpholin-3-ones [17]. The chemical shift value of H–C_2 suggests that this proton is in an equatorial position, protons in axial positions for analogous morpholin-3-ones appearing at higher field [14].

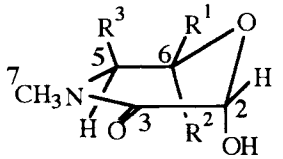
The spectrum of **2a** clearly shows an AA'BB' coupling pattern for the diastereotopic ethylene protons of the six-membered ring, two triplets of doublets at δ 4.12 and 3.44 assigned to H_{eq} and two doublets of doublets of doublets at δ 3.69 and 3.17 assigned to H_{ax}; also the assignments were obtained using the ^{13}C–^{1}H HETCOR spectrum, correlating the proton signals at δ 4.12 and 3.17 with C_6 and the proton signals at δ 3.44 and 3.17 with C_5.

Table 2 shows that compounds **2a–4a** exhibit the expected ^{13}C NMR spectra. The assignments for all carbon atoms were achieved by comparison with the chemical shifts of starting materials (**1–3**) and analogous morpholin-3-ones [7,8,12]. The spectra of compounds **2a**, **3a**, and **4a** exhibit the signal for C_2 at δ 89.9, 90.0, and 90.1 respectively, this result confirming that the hydroxyl group is bonded to this carbon atom.

The IR spectra of the various compounds (see Table 3) show a band due to the carbonyl function of amide I in the range of 1644–1650 cm^{-1} and a band due to the hydroxyl group in the range 3124–3294 cm^{-1}.

The 70 eV EI mass spectrum of compound **2a** exhibits the molecular ion and the spectra of compounds **3a** and **4a** do not exhibit the molecular ion, but they exhibit the M + 1 = 222 with relative abundance of 2 and 1%, respectively. Figure 2 shows the important fragment ions of these compounds.

TABLE 2 ^{13}C NMR Data for Compounds **2a–4a**



	R^1	R^2	R^3
2a	H	H	H
3a	C_6H_5	H	CH_3
4a	H	C_6H_5	CH_3

Compound	C_2	C_3	C_5	C_6	C_7	R^3 = CH_3	Phenyl Group C_i	C_o	C_m	C_p
2a	89.91	165.46	47.68	55.86	33.16					
3a	90.06	165.20	57.35	69.68	32.41	12.10	138.10	125.71	128.14	127.30
4a	90.15	165.80	57.64	73.49	29.76	15.70	138.33	127.96	128.40	128.47

δ: (ppm); solvent DMSO-d_6

TABLE 3 Infrared Data for Compounds **2a–4a**

Compound	ν_{OH}	$\nu_{C-H\ aliph}$	$\nu_{C-H\ arom}$	$\nu_{N-C=O}$
2a	3124	2933 2983		1644
3a	3278	2988 2934	3066	1650
4a	3294	2988 2934	3070	1650

ν (cm^{-1}), KBr.

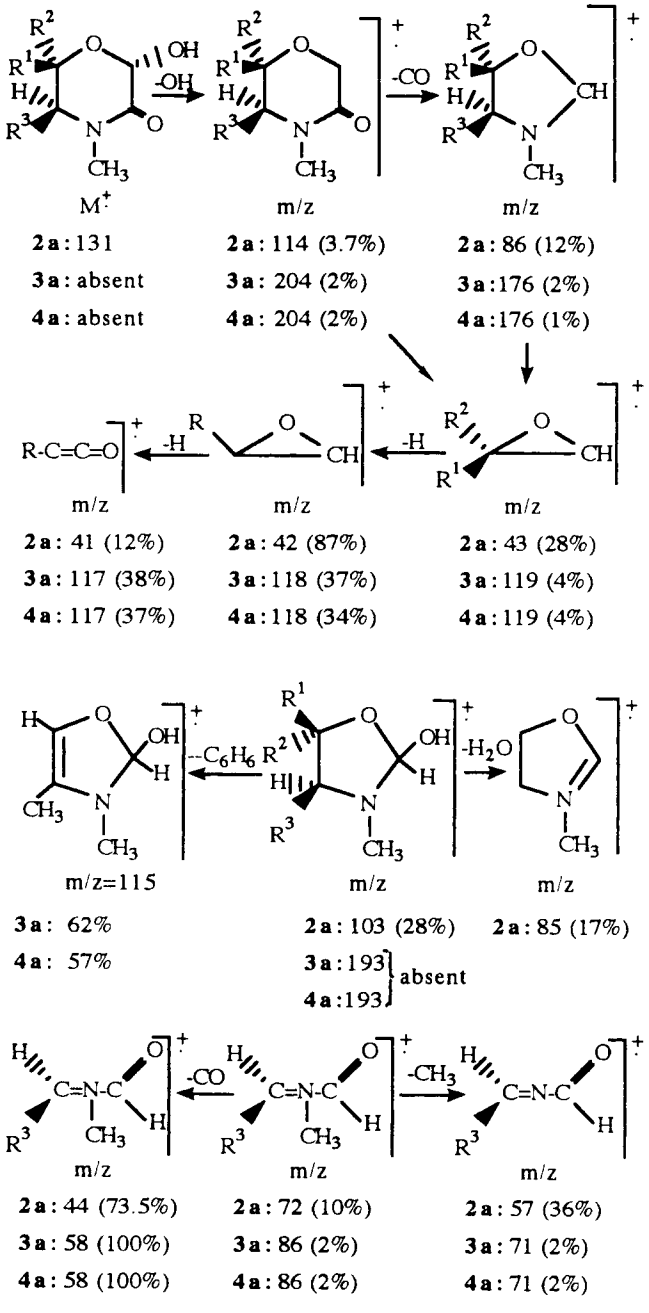


FIGURE 2 Mass spectral data of 2-hydroxy-4-methylperhydro-1,4-oxazin-3-ones **2a–4a**.

X-ray single-crystal diffraction studies of compounds **2a** and **3a** were performed in order to confirm their structures. The shape of the ring in the region of any atom (tetragonal atom) and the orientation of its substituent can be known from the differences of the torsion angles that precede and follow the atom in the ring [18]. Thus, in the region of O_1 the difference of the torsion angles is 119.90° for **2a** and 117.49° for **3a**, the positive value meaning that O_1 is out of the mean plane. Inspection of the sequence of the signs +, − indicates that O_1 is pointing upward. For C_2, the negative algebraic value −78.06° for **2a** and −64.49° for **3a** shows that C_2 lies below the mean plane and its −OH group axial substituent is *a* orientated. The sequence of the signs −, + indicates that C_2 and −OH group are pointing downward in both compounds **2a** and **3a**. The values in the region of N_4 are −23.70° for **2a** and −22.15° for **3a** and show that N_4 lies below the mean plane. The crystal data show that the structures of compounds **2a** and **3a** have an envelope form and the configuration of the C_2 is (S) (Figure 3).

EXPERIMENTAL

NMR spectra were recorded on a JEOL GLX-270 spectrometer.

All ^1H and ^{13}C chemical shifts are reported relative to TMS using DMSO-d_6 as solvent.

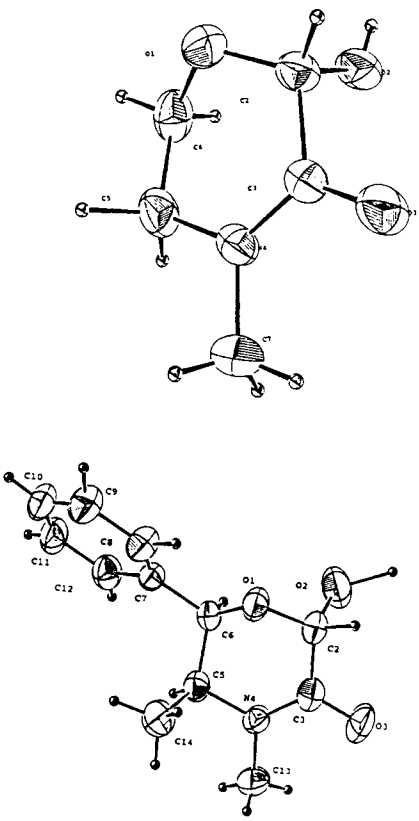


FIGURE 3 ORTEP drawing of compounds **2a** and **3a**.

Infrared spectra were determined on a Perkin-Elmer 16F PC FT-IR spectrometer.

Mass spectra were obtained with a Hewlett-Packard 59940-A instrument. The single-crystal X-ray studies were performed on a CAD4F ENRAF NONIUS FR 590 diffractometer.

Melting points were taken in open capillary tubes on a Gallenkamp MFB-595 apparatus and are uncorrected.

Reagents were purchased from Aldrich Co. The methyl glyoxylate hemiacetal **1** was prepared as described previously [19].

Synthesis of (2S)-2-hydroxy-4-methylperhydro-1,4-oxazin-3-one **2a**

A solution of 1 g (1.00) (8.4 mmol) of methyl glyoxylate hemiacetal **1** in 20 mL of pentane was cooled to 0°C, and 0.67 mL (8.4 mmol) of 2-(methylamino)ethanol **2** was added dropwise. The reaction mixture was stirred for 10 minutes at 0°C and then for 2 hours at room temperature. The solvent was evaporated under vacuum. The residue was treated with ethyl acetate to provide a white solid, which was recrystallized from chloroform to yield 0.88 g (80.4%) of compound **2a**, m.p. 131–132°C.

The procedure outlined in the following paragraph is general for the preparation of compounds **3a** and **4a**.

Synthesis of (2S,5S,6R)-2-hydroxy-4,5-dimethyl-6-phenylperhydro-1,4-oxazin-3-one **3a**

A solution of 1 g (1.00) (8.4 mmol) of compound **1** in 20 mL of pentane was cooled to 0°C, and a solution of 1.38 g (8.4 mmol) of (1R,2S)-(−)-ephedrine **3** in 5 mL of methanol was added dropwise. The reaction mixture was stirred for 10 minutes at 0°C and then for 17 hours at room temperature. The solvent was evaporated under vacuum.

The residue was treated with ethyl acetate to provide a white solid, which was recrystallized from dichloromethane/acetone to yield 1.28 g (69.4%) of compound **3a**, m.p. 164–166°C.

Synthesis of (2S,5S,6S)-2-hydroxy-4,5-dimethyl-6-phenylperhydro-1,4-oxazin-3-one **4a**

The reaction of 1 g (1.00) (8.4 mmol) of compound **1** in 20 mL of pentane and a solution of 1.38 g (8.4 mmol) of (1S,2S)-(+)-pseudoephedrine **4** gave 1.30 g of compound **4a** (70.6%), m.p. 183–184°C.

X-ray Crystal Structure Determination for **2a** *and* **3a**

White rhombic crystals were obtained from chloroform **2a** and dichloromethane/acetone **3a** solution.

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 **2a** crystallizes in the space group Pn 2_1a with a = 6.813 (1), b = 12.029 (1), and c = 7.583 (2) Å, V = 621.4 (3) Å^3, Z = 4, Dc = 1.40 g cm^{-3}, μ = 1.1 cm^{-1}, F (000) = 280. Compound **3a** crystallizes in the space group P 2_1 2_1 2_1 with a = 7.295 (1), b = 10.700 (1), c = 14.647 (1) Å, V = 1143.3 (5) Å^3, Z = 4, Dc = 1.29 g cm^{-1}, μ = 0.9 cm^{-1}, F (000) = 472.

X-ray measurement was performed at 294 K on an Enraf-Nonius CAD4 diffractometer in the range $2 < 2\theta \leq 20.0°$. There were 481 unique reflections with Fo > 3.0 (Fo) used in the solution and refinement for **2a**; 1083 reflections were included for **3a**. Two standard reflections were measured every two hours, and no crystal decomposition was detected. Corrections for Lorentz and polarization effects were performed, as well as an empirical absorption correction. The structures were solved by direct methods and refined by full-matrix anisotropic least squares (hydrogen atoms isotropically) up to R = 0.040 and Rw = 0.063 for **2a** and R = 0.063 and Rw = 0.055 for **3a**.

All the hydrogen atoms were located in the difference Fourier maps. Atomic scattering factors were taken from the *International Tables for X-ray Crystallography* [20]. All calculations were carried out on a VAX 4000 computer using the MOLEN [21] package.

Supplementary Material Available

Tables of H-atom coordinates, anisotropic thermal parameters, and observed and calculated structure factors are available from the senior author.

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