

Synthesis and characterization of new 2-(alkylamino)acetamides

Teresa Mancilla,* Luis S. Zamudio-Rivera, Lourdes Carrillo,
Hiram I. Beltrán and Norberto Farfán

Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apdo. Postal 14-740, 07000 México, D. F., MÉXICO
E-mail: tmancill@mail.cinvestav.mx

(received 27 Jun 03; accepted 24 Sep 03; published on the web 25 Sep 03)

Abstract

Seven new 2-(alkylamino)acetamides have been synthesized and characterized by ^1H , ^{13}C NMR, NOESY experiments, infrared and mass spectrometry. The structure of 2-(diphenylmethylamino)acetamide **3b** was further established by a single crystal x-ray diffraction study. The NMR study of the transformation of several 2-(alkylamino)acetamides to their corresponding morpholin-2-ones shows that these species are thermodynamically favored through preferred conformations as determined by theoretical calculations of **3h**.

Keywords: Acetamides, amides, synthesis, spectroscopy, x-ray

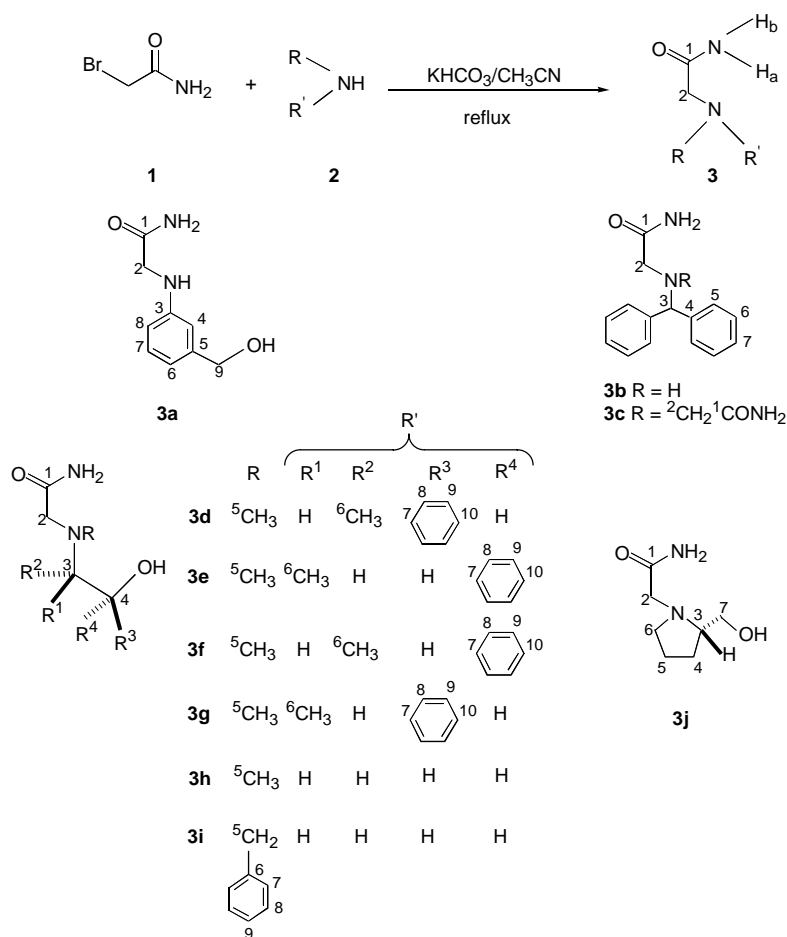
Introduction

A number of 2-(alkylamino)acetamides have been shown to possess antiarrhythmic,¹ anticonvulsive,² anti-inflammatory³ and hypotensive⁴ activity. They have also been used as precursors in the synthesis of vicinal diamides, morpholin-2-ones,⁵ and as ligands in the synthesis of organometallic compounds with potential anti-tumor activity.⁶

2-(Alkylamino)acetamides have been prepared by reaction of 2-chloro-*N,N*-dimethylacetamide or 2-(alkylamino)methylacetate with amines and β -aminoalcohols, in the presence of sodium bicarbonate or triethylamine.^{5,7-8} It is noteworthy that the reaction of 2-chloro-*N,N*-dimethylacetamide with ephedrine, in the presence of sodium bicarbonate, under reflux of benzene for 20 hours provides both 2-(alkylamino)acetamides and morpholin-2-ones, while the use of triethylamine as base yields exclusively the corresponding 2-(alkylamino)-acetamides. In contrast, when this reaction is carried out under reflux of xylene, the morpholin-2-one is formed exclusively.⁵ Our current interest in 2-(alkylamino)acetamides prompted us to develop better reaction conditions to synthesize these compounds in good yields. Thus, we describe herein the synthesis and characterization of seven new 2-(alkylamino)acetamides **3a-j** (Scheme 1). The structure of compound **3b** was further established by a single-crystal X-ray diffraction study.

Results and Discussion

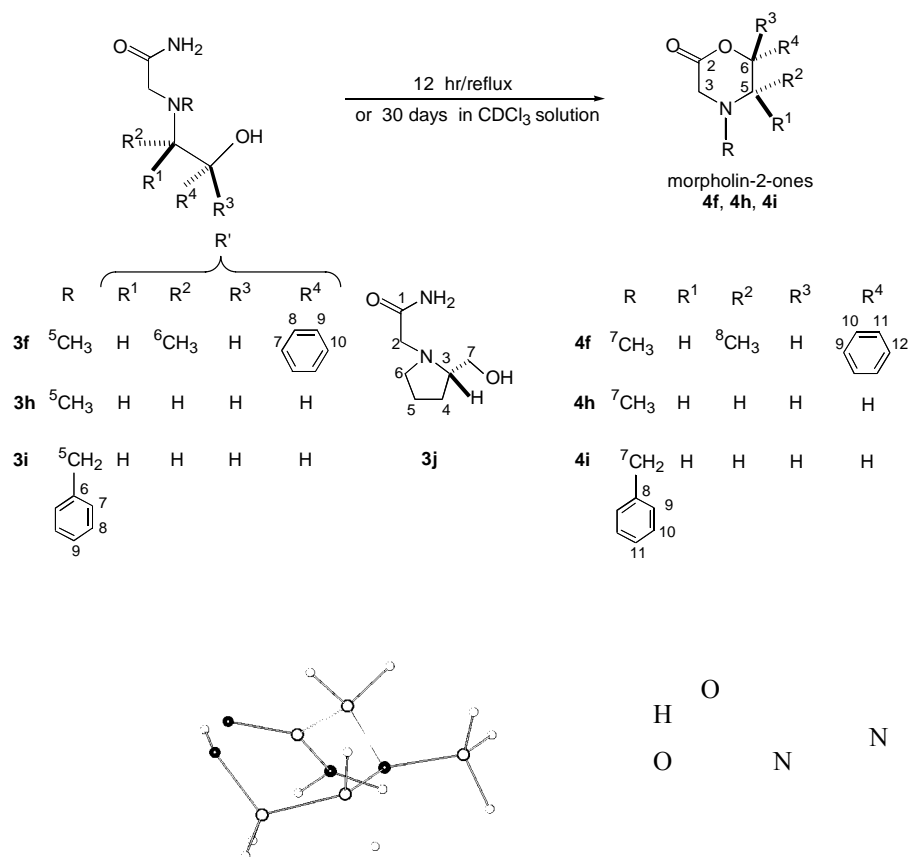
2-(Alkylamino)acetamides **3a-j** were prepared in yields between 73-98% by the reaction of 2-bromoacetamide **1** with 3-aminobenzyl alcohol **2a**, aminodiphenylmethane **2b**, (1*S*,2*S*)-(+)-pseudoephedrine **2d**, (1*R*,2*R*)-(-)-pseudoephedrine **2e**, (1*R*,2*S*)-(-)-ephedrine **2f** and (1*S*,2*R*)-(+)-ephedrine **2g**, 2-(methylamino)ethanol **2h**, *N*-benzylethanolamine **2i** and (*S*)-(+)-pyrrolidinemethanol **2j**, in the presence of KHCO_3 under reflux in acetonitrile for 6 hours. Compound **3c** was obtained by reaction of **1** and **2a** in a 2:1 molar ratio.



Scheme 1

As confirmed by ^1H NMR the reaction of bromoacetamide **1** and β -aminoalcohols **2f**, **2h** and **2j** leads to 2-(aminoalkyl)acetamides **3f**, **3h** and **3j** which are transformed into the corresponding morpholin-2-ones^{5,12} in approximately 30%, after 12 hours under reflux except for **3j**. Moreover, 2-(aminoalkyl)acetamides **3f**, **3h**, **3i** and **3j** were allowed to stand for one month in chloroform solution which resulted in 40% conversion to the morpholine-2-ones, except for **3j** (Scheme 2). These data suggests that the transformation of **3f**, **3h**, and **3i** into the corresponding morpholin-2-

ones is thermodynamically favored and proceeds through a preferred conformation which was calculated for **3h** using a theoretical (AMI, *Ab initio* STO-3G and 3-21G) approach.¹³ Figure 1 depicts the particular conformation where there is an intramolecular interaction between the OH group and the carbonyl group, that increases nucleophilicity of the carbonyl group and favors formation of the corresponding morpholin-2-one.



Scheme 2

Figure 1

NMR spectroscopy

The ¹H NMR spectra of compounds **3a-j** exhibit an AB system for the amidic protons (NH₂) due to partial C=N double bond character (Table 1). Unambiguous assignment of these protons was attained by NOESY experiments which revealed an interaction of the proton shifted to lower field with H-2, evidencing that it is *anti* to the carbonyl group, in agreement with analogous systems reported in the literature.⁹ The spectra of compounds **3a-c**, **3h** and **3i** exhibit a single signal for the methylene protons at position 2, while compounds **3d-g** and **3j** give an AB system. Since the pyrrolidyl and H-7 protons in compound **3j** show a complex pattern, unambiguous identification of H-7 was established using selective decoupling experiments. Thus irradiation of H-3 simplified the ABX system for H-7 to an AB system.

Table 1. ^1H NMR data of **3a-3j**: δ_{H} and δ_{N} [ppm] and *coupling constants* J [Hz]

	Solvent	H-2	NH _a	NH _b	R	R'	
3a	DMSO-d ₆	3.57	7.	7.11	3.68	H-4 6.53	
			2			H-6 6.54 7.8 ^b	
			3			H-7 7.03 7.8 ^b	
						H-8 6.42 7.8 ^b	
						H-9 4.38	
3b	CDCl ₃	3.24	6.88	6.07	2.16	H-3 4.83	
							H-5,6 7.30-7.36
							H-7 7.23 7.0 ^b
3c	DMSO-d ₆	3.13	7.64	7.06	H-2 3.13	H-3 5.23	
					NH _a 7.64	H-5 7.47 7.3 ^b	
					NH _b 7.06	H-6 7.30 7.3 ^b	
						H-7 7.20 7.3 ^b	
3d	DMSO-d ₆	H _A 3.07 16.1 ^a	7.68	7.15	H-5 2.23	H-3 2.64 8.8 ^b , 6.6 ^b	
		H _B 2.88 16.1 ^a				H-4 4.32 8.8 ^b	
						H-6 0.59 6.6 ^b	
						H-8,9,10 7.20-7.23	
3e	DMSO-d ₆	H _A 3.05 16.1 ^a	7.64	7.16	H-5 2.24	H-3 2.64 8.8 ^b , 6.6 ^b	
		H _B 2.85 16.1 ^a				H-4 4.34 8.8 ^b	
						H-6 0.60 6.6 ^b	
						H-8,9,10 7.21-7.25	
3f	CDCl ₃	H _A 2.96 16.8 ^a	6.31	5.53	H-5 2.21	H-3 2.78 7.3 ^b , 6.6 ^b	
		H _B 2.93 16.8 ^a				H-4 4.56 7.3 ^b	
						H-6 1.01 6.6 ^b	
						H-8,9,10 7.25-7.35	
3g	CDCl ₃	H _A 2.96 16.8 ^a	6.32	5.54	H-5 2.20	H-3 2.76 7.3 ^b , 6.6 ^b	
		H _B 2.92 16.8 ^a				H-4 4.55 7.3 ^b	
						H-6 1.01 6.6 ^b	
						H-8,9,10 7.25-7.35	
3h	CDCl ₃	3.06	7.66	6.80	H-5 2.33	H-3 2.59 5.1 ^b	
							H-4 3.65 5.1 ^b
3i	CDCl ₃	3.11	7.30	6.40	H-5 3.67	H-3 2.68 5.1 ^b	
						H-7,8,9 7.24	H-4 3.63 5.1 ^b
3j	CDCl ₃	H _A 3.45 16.7 ^a	7.43	6.60	H-3 2.73 3.7 ^b , 4.7 ^b	H-5 1.63-1.82	
		H _B 3.20 16.7 ^a			H-4 _A 1.84-1.97	H-6 _A 3.16 9.1 ^a	
					H-4 _B 1.63-1.83	H-6 _B 2.40 9.1 ^a	
						H-7 _A 3.60 11.3 ^a , 3.7 ^b	
						H-7 _B 3.47 11.3 ^a , 3.7 ^b	

^a 2J . ^b 3J .

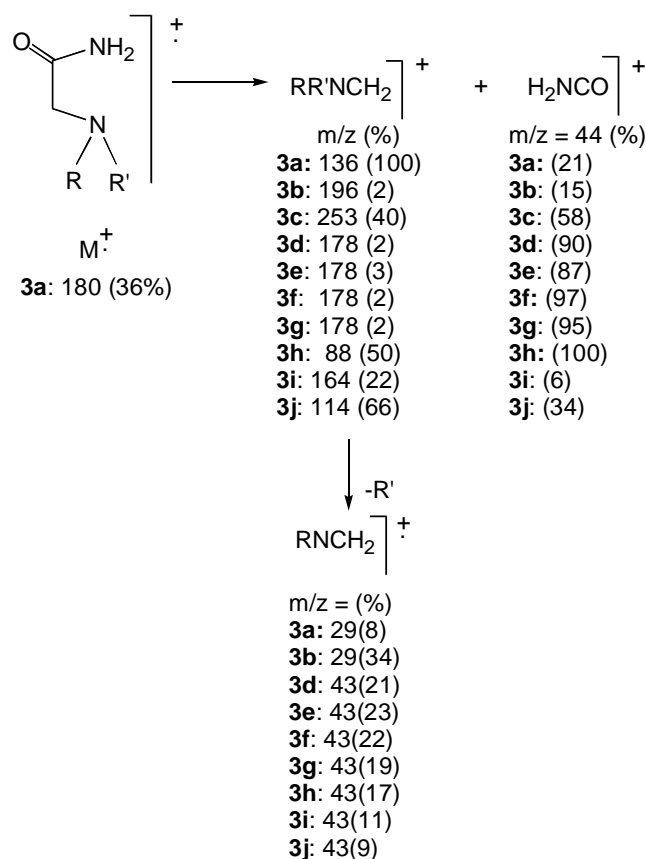
The ^{13}C NMR chemical shift for C-2 in compounds **3a-j** is in the range between 46.76 to 59.92 ppm, which is shifted to higher frequency compared with bromoacetamide ($\delta = 29.05$ ppm). Assignment of the signals for C-2, C-4 and C-5 in **3h**, C-2, C-3, C-8 and C-9 in **3i** and C-2, C-3, C-8 and C-9 in **3j**, were obtained by ^{13}C - ^1H HETCOR techniques. Unambiguous assignment of C-3 and C-5 in **3a** was attained from a ^{13}C - ^1H COLOC spectra. Table 2 summarizes the ^{13}C NMR data for compounds **3a-j**.

Table 2. ^{13}C NMR data of **3a-3j**: δ_{C} [ppm]

	Solvent	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
3a	DMSO- d_6	172.52	46.76	148.13	110.15	143.25	114.87	128.58	110.88	63.23	
3b	CDCl_3	174.47	50.45	66.74	142.83	127.26	128.66	127.40			
3c	DMSO- d_6	172.81	54.57	70.66	142.16	128.22	128.37	127.07			
3d	DMSO- d_6	173.05	57.76	64.69	74.53	37.22	8.97	143.38	127.18	127.93	127.18
3e	DMSO- d_6	173.05	57.76	64.69	74.53	37.22	8.97	143.38	127.18	127.93	127.18
3f	CDCl_3	174.95	58.27	64.96	75.91	38.74	9.85	143.74	126.42	128.34	127.60
3g	CDCl_3	174.95	58.27	64.96	75.91	38.74	9.85	143.74	126.42	128.34	127.60
3h	CDCl_3	175.20	59.92	59.12	61.80	42.90					
3i	CDCl_3	175.22	57.88	57.29	59.58	59.36	137.96	128.52	128.89	127.46	
3j	CDCl_3	175.70	58.65	65.71	27.17	23.68	55.93	63.72			

Mass spectrometry

In general the 70 eV EI mass spectra do not show the molecular ion, except for **3a** that gives the molecular ion at $m/z = 180$ (36%). All spectra show the fragment ions $[\text{RR}'\text{NCH}_2]^+$ and $[\text{H}_2\text{NCO}]^+$ due to the $\text{C}_1\text{-C}_2$ bond rupture and the fragment ion $[\text{R-N}]^+$, except for **3c**. The fragment ions at $m/z = 136$ for **3a**, $[\text{CH}(\text{C}_6\text{H}_5)_2]^+$ at $m/z = 167$ for **3b** and **3c**, $[\text{H}_2\text{NCOCH}_2\text{N}(\text{CH}_3)\text{CHCH}_3]^+$ at $m/z = 115$ for **3d-3g**, $m/z = 44$ for **3h**, $[\text{C}_7\text{H}_7]^+$ at $m/z = 91$ for **3i** and $[\text{M-CH}_2\text{OH}]^+$ at $m/z = 127$ for **3j**, correspond to the base peaks. The proposed fragmentation is shown in Scheme 3.



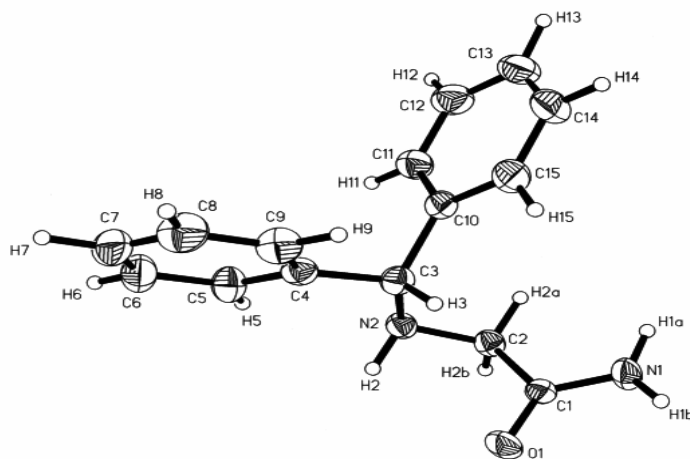
Scheme 3

Infrared spectroscopy

The IR spectra of compounds **3a-j** show the absorption band characteristic of the amide I and II in the range between 1676-1638 and 1672-1588 cm^{-1} , respectively, as well as absorption bands for the NH and OH groups in the range between 3432-3178 cm^{-1} .

X-Ray diffraction

Suitable crystals of **3b** for X-ray analysis were obtained from chloroform/hexane, the molecular structure and crystallographic numbering is shown in figure 2. In general the bond distances are within the values characteristic of amides.¹⁰ Selected bond lengths are: N₁-H_{1a} 0.925, N₁-H_{1b} 0.864, C₁-O₁ 1.227 (2), C₁-N₁ 1.318 (2), C₃-N₂ 1.478 (2) and C₂-N₂ 1.464 (2) Å. Torsion angles for the O₁-C₁-N₁-H_{1a} and O₁-C₁-N₁-H_{1b} fragments are: 172.51° and 1.17° respectively, this indicates that this part of the molecule is flat due to the resonance effect present between the O₁-C₁-N₁ atoms. The molecular structure shows the following intermolecular contacts: O₁····H_{2a} 2.540, O₁····H₅ 2.514, O₁····H_{1a} 1.936 and N₂····H_{1b} 2.306, which are significantly shorter than the sum of the van der Waals radii for oxygen and hydrogen atoms (2.70 Å) as well as nitrogen and hydrogen (2.75 Å).¹¹ In addition, the following intramolecular contacts are observed between N₂····H₃ 2.030, N₂····H_{2b} 1.967, N₂····H_{2a} 2.498, N₂····H₅ 2.500, O₁····H₂ 2.570 and O₁····H_{1b} 2.413 Å.

**Figure 2**

Conclusions

Optimization of the reaction conditions allowed us to obtain the new 2-(alkylamino)acetamides in good yields. These derivatives were characterized by spectroscopic methods and the structure of compound **3b** was confirmed by X-ray analysis. The transformation of 2-(alkylamino)acetamides **3f**, **3h** and **3i** into the corresponding morpholine-2-ones was observed by ^1H NMR after 12 hours of reaction or upon standing in chloroform solution for one month. The transformation is thermodynamically favored through a preferred conformation, as determined by theoretical calculation of **3h**.

Experimental Section

General Procedures. NMR spectra were recorded on JEOL GXS-270, JEOL ECLIPSE-400 and Bruker Avance 300-DPX spectrometers in CDCl_3 and DMSO-d_6 . Mass spectra were obtained with a Hewlett-Packard 5994-A instrument, and Infrared spectra were recorded as KBr pellets or in CHCl_3 solution on a Perkin-Elmer 16F PC FT-IR spectrometer. Melting points were taken in open capillary tubes on a Gallemkamp MFB-595 apparatus and are uncorrected. The single-crystal X-ray study was performed on an ENRAF NONIUS CAD4 diffractometer. Reagents were purchased from Aldrich Co. Compound **3b**, $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$ (MW = 240.30), crystallized in the space group $\text{P2}_1/\text{c}$, monoclinic, from chloroform/hexane as colorless rectangular prisms, size: $0.50 \times 0.44 \times 0.38 \text{ mm}^3$ with $a = 6.225(10)$, $b = 21.987(4)$, $c = 9.552(2) \text{ \AA}$, $V = 1307.3(4) \text{ \AA}^3$. Lattice constants were determined from least squares refinement on diffractometer angles for 24 automatically centered reflections; $\rho = 1.221 \text{ Mg/m}^3$, $Z = 4$, $\mu = 0.078 \text{ mm}^{-1}$, $F(000) = 512$. Data collection: monitoring of check reflexion showed no signs of decay. A total of 2447 reflections were measured ($2 > \theta > 26^\circ$),

2304 were independent and of these 1737 were considered observed [$F_o > 4.0\sigma(F_o)$]. Absorption correction was not necessary. Solution and refinement: direct methods, all non-hydrogen atoms were refined anisotropically, all hydrogen were located by difference Fourier maps and refined with an overall isotropic thermal parameter, $R = 0.0365$, $R_w = 0.0954$, $w = 1/\sigma^2$, GOOF = 1.057, parameter to data ratio 1:7.7, largest residual electron density peak/hole in the final difference map: 0.149/-0.153 e \AA^{-3} . Atomic scattering factors were taken from the International Tables for X-ray Crystallography.¹⁴ Data reduction was performed by Jana 98.¹⁵ All calculations were carried out on a VAX 4000 computer using the SHELX 93 (sheldrick G. M.) program package.¹⁶

2-(3'-Hydroxymethylphenylamino)acetamide (3a). To a solution of 1.00 g (7.25 mmol) of 2-bromoacetamide in 60 mL of acetonitrile was added 0.89 g (7.25 mmol) of 3-aminobenzyl alcohol **2a** and 1.09 g (10.88 mmol) of potassium bicarbonate at room temperature. The resulting suspension was refluxed and stirred during 6 hours. After being cooled to room temperature the suspension was filtered and the filtrate evaporated under vacuum to obtain a yellow solid, which was recrystallized from methanol/acetone to yield 0.95 g (73%) of **3a** as a white solid, mp 104-106°C. IR: 3384, 3354, 3300, 3030, 2918, 2850, 1642, 1038 cm^{-1} (KBr). MS: m/z (%), 180 (M^+ , 36), 136 (100), 44(21), 29 (8). Anal. Calcd. for $C_9H_{12}N_2O_2$ (180.17): C, 59.99; H, 6.70; N, 15.54. Found: C, 59.70; H, 6.60; N, 15.57.

2-(Diphenylmethylamino)acetamide (3b). The reaction of 1.00 g (7.25 mmol) of 2-bromoacetamide in 60 mL of acetonitrile, 1.37 g (7.25 mmol) of aminodiphenylmethane **2b** and 1.09 g (10.88 mmol) of potassium bicarbonate gave a yellow solid, which was recrystallized from chloroform/hexane to yield 1.39 g (80%) of **3b** as a white solid, mp 102-104°C. IR: 3432, 3340, 3178, 3024, 2930, 2856, 1672 cm^{-1} (KBr). MS: m/z (%), 196 (2), 167 (100), 44 (15), 29 (34). Anal. Calcd. for $C_{15}H_{16}N_2O$ (240.29): C, 74.97; H, 6.71; N, 11.65. Found: C, 74.66; H, 6.65; N, 11.54.

2-[Bis(diphenylmethy)amino]acetamide (3c). The reaction of 2.00 g (14.5 mmol) of 2-bromoacetamide in 120 mL of acetonitrile, 1.37 g (7.25 mmol) of aminodiphenylmethane **2b** and 2.18 g (21.75 mmol) of potassium bicarbonate gave a white solid, which was recrystallized from chloroform to yield 1.83 g (85%) of **3c** as a white solid, mp 172-174°C. IR: 3310, 3172, 3024, 2934, 2864, 1676, 1650 cm^{-1} (KBr). MS: m/z (%), 253 (40), 167 (100), 44(58). Anal. Calcd. for $C_{17}H_{19}N_3O_2$ (297.35): C, 68.66; H, 6.44; N, 14.13. Found: C, 68.34; H, 6.57; N, 14.09.

(1'S,2'S)-2-[(2'-Phenyl-2'-hydroxy-1'-methylethyl)methylamino]acetamide (3d). The reaction of 1.00 g (7.25 mmol) of 2-bromoacetamide in 60 mL of acetonitrile, 1.20 g (7.25 mmol) of (1S,2S)-(+)-pseudoephedrine **2d** and 1.09 g (10.88 mmol) of potassium bicarbonate gave a yellow solid, which was washed with chloroform and precipitated from hexane to yield 1.43 g (89%) of **3d** as a white solid, mp 142-145°C. IR: 3414, 3304, 3084, 2932, 2858, 1638, 1028 cm^{-1} (KBr). MS: m/z (%), 178 (2), 115 (100), 44 (90), 43 (21). Anal. Calcd. for $C_{12}H_{18}N_2O_2$ (222.28): C, 64.84; H, 8.16; N, 12.60. Found: C, 64.52; H, 8.16; N, 12.24.

(1'R,2'R)-2-[(2'-Phenyl-2'-hydroxy-1'-methylethyl)methylamino]acetamide (3e). The reaction of 1.00 g (7.25 mmol) of 2-bromoacetamide in 60 mL of acetonitrile, 1.20 g (7.25 mmol) of (1R,2R)-(-)-pseudoephedrine **2e** and 1.09 g (10.88 mmol) of potassium bicarbonate gave a yellow solid, which

was washed with chloroform and precipitated from hexane to yield 1.35 g (84%) of **3e** as a white solid, mp 142-145°C. IR: 3412, 3302, 3084, 2930, 2858, 1638, 1028 cm⁻¹ (KBr). MS: m/z (%), 178 (3), 115 (100), 44 (87), 43 (23). Anal. Calcd. for C₁₂H₁₈N₂O₂ (222.28): C, 64.84; H, 8.16; N, 12.60. Found: C, 65.06; H, 8.36; N, 12.21.

(1'R,2'S)-2-[(2'-Phenyl-2'-hydroxy-1'-methylethyl)methylamino]acetamide (3f). The reaction of 1.00 g (7.25 mmol) of 2-bromoacetamide in 60 mL of acetonitrile, 1.20 g (7.25 mmol) of (1R,2S)-(-)-ephedrine **2f** and 1.09 g (10.88 mmol) of potassium bicarbonate gave a yellow solid, which was washed with chloroform and precipitated from hexane to yield 1.33 g (83%) of **3f** as a white solid, mp 88-91°C. IR: 3394, 3316, 3198, 3032, 2968, 2924, 2864, 1678, 1048 cm⁻¹ (KBr). MS: m/z (%), 178 (2), 115 (100), 44 (87), 43 (22). Anal. Calcd. for C₁₂H₁₈N₂O₂ (222.28): C, 64.84; H, 8.16; N, 12.60. Found: C, 64.54; H, 8.22; N, 12.41. ¹H NMR data of (5S,6R)-4,5-dimethyl-6-phenyl-1,4-oxazin-2-one **4f** obtained from the spectrum of a mix with **3f**, δ_H (CDCl₃) 0.72 (H-8, ³J = 6.9 Hz), 2.33 (H-7), 3.04-3.15 (H-5), 3.43 (H-3_A, ²J = 18 Hz), 3.38 (H-3_B, ²J = 18 Hz), 5.59 (H-6, ³J = 3.29), 7.21-7.25 (H-10,11,12).

(1'S,2'R)-2-[(2'-Phenyl-2'-hydroxy-1'-methylethyl)methylamino]acetamide (3g). The reaction of 1.00 g (7.25 mmol) of 2-bromoacetamide in 60 mL of acetonitrile, 1.46 g (7.25 mmol) of (1S,2R)-(+)-ephedrine **2g** and 2.18 g (21.75 mmol) of potassium bicarbonate gave a yellow solid, which was washed with chloroform and precipitated from hexane to yield 1.28 g (79%) of **3g** as a white solid, mp 88-91°C. IR: 3394, 3316, 3198, 3032, 2968, 2924, 2864, 1678, 1048 cm⁻¹ (KBr). MS: m/z (%), 178 (2), 115 (100), 44 (95), 43 (19). Anal. Calcd. for C₁₂H₁₈N₂O₂ (222.28): C, 64.84; H, 8.16; N, 12.60. Found: C, 64.54; H, 8.22; N, 12.42.

Synthesis of 2-[(2'-Hydroxyethyl)methylamino]acetamide (3h). The reaction of 1.00 g (7.25 mmol) of 2-bromoacetamide in 60 mL of acetonitrile, 0.55 g (7.25 mmol) of 2-(methylamino)ethanol **2h** and 1.09 g (10.88 mmol) of potassium bicarbonate gave a viscous liquid, which was added chloroform and hexane to yield 0.93 g (97%) of **3h** as a yellow semi-solid. IR: 3388, 3328, 2948, 2846, 1670, 1588, 1078 cm⁻¹. MS: m/z (%), 88 (50), 44 (100), 43 (17). Anal. Calcd. for C₅H₁₂N₂O₂ (132.16): C, 45.44; H, 9.15; N, 21.19. Found: C, 45.39; H, 9.44; N, 20.83. ¹H NMR data of 4-methyl-1,4-oxazin-2-one **4h** obtained from the spectrum of a mix with **3h**, δ_H (CDCl₃) 2.27 (H-7), 2.59 (H-5, ³J = 5.17 Hz), 3.19 (H-3), 4.36 (H-6, ³J = 5.19).

2-[Benzyl(2'-hydroxyethyl)amino]acetamide (3i). The reaction of 1.00 g (7.25 mmol) of 2-bromoacetamide in 60 mL of acetonitrile, 1.10 g (7.25 mmol) of 2-(benzylamino)ethanol **2i** and 1.09 g (10.88 mmol) of potassium bicarbonate gave a yellow solid, which was recrystallized from chloroform/acetone to yield 1.33 g (88%) of **3i** as white solid, mp 132-135 °C. IR: 3396, 3300, 3034 2934, 2862, 1638, 1082, cm⁻¹ (KBr). MS: m/z (%), 164 (22), 91 (100), 44 (6), 43 (11). Anal. Calcd. for C₁₁H₁₆N₂O₂ (208.26): C, 63.44; H, 7.74; N, 13.45. Found: C, 63.52; H, 7.58; N, 13.15. ¹H NMR data of 4-benzyl-1,4-oxazin-2-one **4i** obtained from the spectrum of a mix with **3i**, δ_H (CDCl₃) 2.64 (H-5, ³J = 5.19 Hz), 3.25 (H-3), 3.56 (H-7), 4.31 (H-6, ³J = 5.19), 7.1-7.6 (H-9,10,11).

(2'S)-2[2'-Hydroxymethyl-1'-pyrrolidinyl]acetamide (3j). The reaction of 1.00 g (7.25 mmol) of 2-bromoacetamide in 60 mL of acetonitrile, 0.73 g (7.25 mmol) of (S)-(+)-2-pyrrolidinemethanol **2j** and 1.09 g (10.88 mmol) of potassium bicarbonate gave a yellow solid, which was washed with chloroform and precipitated from hexane to yield 1.03 g (90%) of compound **3j** as white solid, mp

63-66 °C. IR: 3416, 3310, 2958, 2872, 1662, 1086, cm^{-1} (KBr). MS: m/z (%), 114 (66), 127 (100), 44 (34), 43 (9). Anal. Calcd. for $\text{C}_7\text{H}_{14}\text{N}_2\text{O}_2$ (158.20): C, 53.14; H, 8.91; N, 17.70. Found: C, 53.10; H, 8.55; N, 17.29.

Supplementary information. Crystallographic data for **3b** has been deposited at the Cambridge Crystallographic Data Center, UK, CCDC as supplementary material No. 213603.

Acknowledgments

The authors thank the "Consejo Nacional de Ciencia y Tecnología (Conacyt-México)" for a scholarship to Luis S. Zamudio-Rivera and Hiram I. Beltrán and also for financial support, thanks to Dr. Rosa Luisa Santillan B. for reading the manuscript and for her helpful comments and Ing. Marco Antonio Leyva for his technical assistance in X-ray crystallography.

References

1. Basharov, M. A.; Vol'kenstein, M. V.; Golovanov I. B.; Grenader A. K.; Ermakov, G. L., *Biofizika* **1986**, *31*, 741; *Chem. Abstr.* **1987**, *106*, 27367u.
2. Napier, J. J.; Griffith, R. C. Eur. Pat. Appl. EP 356,035 (Cl.A61K31/135), 28 Feb. 1990, US Appl. 232,556, 12 Aug. 1988, 24pp; *Chem. Abstr.* **1990**, *113*, 190942f.
3. Baylina, E. G.; Llobet, P. P., Span. ES 497,077 (Cl. C07D279/02), 16 Jan 1982, Appl. 07 Nov 1980, 13 pp; *Chem. Abstr.* **1982**, *97*, 55826g.
4. Bondavalli, F.; Schenone, P.; Ranise A.; Filippelli, W.; Bile, G.; Filippelli, A.; Marmo, E. *Farmaco Ed. Sci.* **1983**, *38*, 57; *Chem. Abstr.* **1983**, *99*, 279s.
5. Dieter, R. K.; Deo, N.; Lagu, B.; Dieter, J. W. *J. Org. Chem.* **1992**, *57*, 1663.
6. Haiduc, I.; Silvestru, C. *Organometallics in Cancer Chemotherapy*, CRC Press, Boca Raton, Florida, 1989.
7. Lee, W. W. U. S. Pat. Appl. US 180,373, 09 Apr. 1982, Appl. 02 Aug. 1980, 13 pp *Chem. Abstr.* **1982**, *97*, 55811y.
8. Cantello, B. C. Eur. Pat. Appl. EP 99,707 (Cl. C07C93/04), 01 Feb. 1984, GB Appl. 82/20,645, 16 Jul. 1982, 87. *Chem. Abstr.* **1984**, *101*, 6799t.
9. Levy, G. C.; Nelson, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 4897.
10. Wasserman, H. J.; Ryan, R. R.; Layne, S. P. *Acta Cryst.* **1985**, *C41*, 783.
11. Huheey, J. E.; Keiter, E. A.; Keiter R. L. *Inorganic Chemistry, Principles of Structure and Reactivity*; Harper Collins Colleges Publishers: New York. 1993; p 292.
12. Chassonnery, D.; Chastrette, F.; Chastrete M.; Blanc A.; Mattioda, G. *Bull. Soc. Chim. Fr.* **1994**, *131*, 188.
13. HyperChem. Molecular Modeling System, version 5.02, 1997.

14. Cromer, D. T.; Waber, J. T. *International Tables for X-Ray Crystallography*, Kynoch Press: England, 1974, Vol. IV.
15. Pretricek, V. D. M. Jana 98 Program. Institute of Physics. Academy of Science of Czech Republic Praha, 1997.
16. Sheldrick, G. M. Shelx93 program for the refinement of crystal structures, 1993.