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# Syntheses and Characterization of 2-Hydroxy-N-(2′-hydroxyalkyl)acetamides

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ABSTRACT: *The reaction of glycolic acid* **1** *with some β-aminoalcohols* **2–8** *without solvent, with temperature and time controlled, led to the syntheses of 2-hydroxy-N-(2′-hydroxyalkyl)acetamides* **9–15**. *All compounds studied in this work were characterized by* $^{1}H$, $^{13}C$, *and* $^{15}N$ *NMR, infrared, and mass spectroscopy. The structure of compound* **13** *was established by a single-crystal X-ray diffraction study.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 153–158, 1999

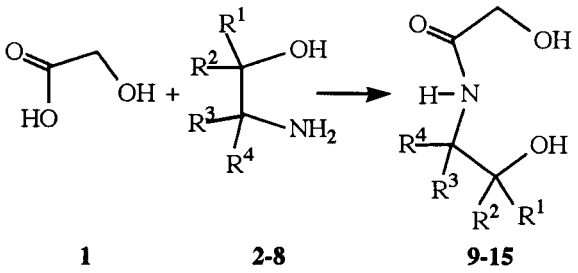


**FIGURE 1** Syntheses of 2-hydroxy-N-(2′-hydroxyalkyl)acetamides **9–15**.

## *INTRODUCTION*

*β*-Aminoalcohols are an important class of compounds useful in the synthesis of a variety of cyclic and acyclic derivatives [1–11] and because some of them and their heterocyclic derivatives are used as chiral auxiliaries in asymmetric synthesis [12,13]. However, they have been little used to prepare *α*-hydroxyamides [14], which have exhibited amebacidal and anticonvulsant activity [15,16].

Our current interest in the syntheses of new derivatives of *β*-aminoalcohols prompted us to study the reactions of glycolic acid **1** with *β*-aminoalcohols **2–8** to obtain 2-hydroxy-N-(2′-hydroxyalkyl)acetamides **9–15** (Figure 1).

Compound **9** has been reported as a nontoxic and environmentally safe solvent for pesticide emulsion concentrates and as a metabolite of trichloroethylene in rats, mice, and humans [17–21], and **10** has been used in various cosmetic emulsions and creams, some used for sun protection [22]. However, their spectroscopic data are not described in the literature, and only the synthesis of **10** has been reported by another method [22].

This article describes the syntheses of 2-hydroxy-N-(2′-hydroxyalkyl)acetamides **9–15**, without use of a solvent, and their characterization by spectroscopic methods.

## *DISCUSSION*

The reaction without solvent of glycolic acid **1** with the *β*-aminoalcohols **2–8** led to the syntheses of 2-hydroxy-N-(2′-hydroxyalkyl)acetamides **9–15**. It is important to notice that these compounds can only be obtained in good yields if the temperature and time of reaction are carefully controlled. The compounds **9–11**, **13**, and **15** are obtained at 80°C, **12** at 100°C, and **14** at 70°C. The time of reaction was 3.15 hours, except for **12** and **14**, which required 6 and

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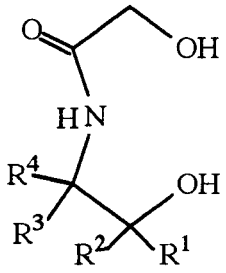
1.30 hours, respectively. Compounds **9**, **11**, **12**, and **15** were obtained as brown liquids, and **10**, **13**, and **14**, as white solids.

Table 1 shows the $^1$H NMR spectra of the compounds **9–15**. These spectra exhibit a singlet signal due to the protons of the $CH_2C=O$ group, except for **13** and **14**, which exhibit a coupling with the OH group. Also, these spectra exhibit an ABXY coupling pattern, except for the compounds **9** and **12** (see Table 1). To obtain the coupling constants of the ABX system [23], the ABXY was simplified by addition of three drops of $D_2O$ to each sample to exchange the HN proton denoted as $H_Y$, and a triplet was then observed for $H_X$ after the irradiation of the $CH_3$ and $CH_2$ groups of compounds **10**, **11**, and **13**, respectively. This indicates that the coupling constants $J_{AX}$ and $J_{BX}$ are equal. In the case of **15**, $J_{AB}$ was obtained from the $H_B$ signal by a selective irradiation of $H_X$. This is due to the fact that the $H_A$ signal is overlapped with that of the methylene protons of the $R^1$ group. The chemical shifts of $H_A$ and $H_B$ were obtained from the irradiated spectra. In the case of **15**, the AB system could not be obtained; as mentioned before, the $H_A$ signal was overlapped with that of the methylene protons of $R^1$. Table 1 shows the $\delta$ ($^{15}$N) for compounds **9–15** that are within the range of amides [24–

**TABLE 1** $^1$H and $^{15}$N Data for Compounds **9–15**



| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **9** | H | H | H | H |
| **10** | $CH_3$ | $H_X$ | $H_A$ | $H_B$ |
| **11** | $H_A$ | $H_B$ | $CH_3$ | $H_X$ |
| **12** | H | H | $CH_3$ | $CH_3$ |
| **13** | $H_A$ | $H_B$ | $CH_2CH_3$ | $H_X$ |
| **14** | $C_6H_5$ | $H_X$ | $H_A$ | $H_B$ |
| **15** | $CH_2OH$ | $H_X$ | $H_A$ | $H_B$ |

| Compound | $NH_Y$ | $CH_2$-CO | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $\delta(^{15}N)$ |
|---|---|---|---|---|---|---|---|
| **9** | 7.65(t) J=6.1 | 3.77(s) | 3.40(t) J=6.1 | | 3.16(q) J=6.1 | | -270.78 |
| **10**[a] | 7.57(t) J=5.8 | 3.80(s) | 1.00(d) J=6.2 | $H_X$:3.65(m) | $H_A$:3.12(m) | $H_B$:2.97(m) | -271.27 |
| **11**[b] | 7.38(d) J=8.2 | 3.77(s) | $H_A$:3.39(m) | $H_B$:3.33(m) | 1.04(d) J=6.7 | $H_X$:3.81(m) | -257.07 |
| **12** | 7.05 (s) | 3.73 (s) | 3.33 (s) | | 1.21 (s) | | -254.35 |
| **13**[c] | 7.28 (d) J=8.4 | 3.78(d) J=4.4 | $H_A$:3.37(m) | $H_B$:3.35(m) | 0.80 (t) J=7.3 $H_A'$:1.54(dd) $H_B'$:1.35(dd) | $H_X$:3.64 (m) | -262.23 |
| **14**[d] | 7.60 (t) J=5.2 | 3.79 (d) J=5.8 | $H_p$ :7.23 (m) $H_{o,m}$:7.32 (m) | $H_X$:4.65 (dd) | $H_A$:3.38 (d) | $H_B$:3.18 (d) | -272.67 |
| **15**[e] | 7.59 (t) J=5.3 | 3.80 (s) | 3.22-3.35(m) | $H_X$:3.5(m) | 3.22-3.35(m) | $H_B$:3.01(d) | -271.86 |

$\delta$ ($^1$H) relative to $Si(CH_3)_4$; $\delta(^{15}N)$ relative to neat $MeNO_2$; solvent DMSO-$d_6$.
[a] $J_{AB}$ = 13.2, $J_{AX}$ = $J_{BX}$ = 5.9.
[b] $J_{AB}$ = 10.6, $J_{AX}$ = $J_{BX}$ = 5.5.
[c] $J_{AB}$ = 11.3, $J_{AX}$ = $J_{BX}$ = 5.1, $J_{A'B'}$ = 13, $J'_{AX}$ = 5.3, $J'_{BX}$ = 8.6.
[d] $J_{AB}$ = 13.5, $J_{AX}$ = 4.3, $J_{BX}$ = 7.9.
[e] $J_{AB}$ = 13.4, the signals for $R^1$ and $R^3$ are overlapped; d: doublet, m: unresolved pattern; q; quartet; s: singlet; t: triplet and |J| = Hz.

25]. The signal for **11**, **12**, and **13** exhibits a deshielding due to the $\beta$ effect [26].

Table 2 shows that compounds **9–15** exhibit the expected $^{13}C$ NMR spectra. Because the signals of $C_1$ and $C_4$ of these compounds appear at similar chemical shifts, and also to that of $C_5$ of **15**, the assignments were obtained using the $^{13}C$–$^{1}H$ HETCOR spectra, correlating the signal of $C_1$ with that of the protons of the $C\underline{H_2}$-OH group, which is in the range $\delta$ 3.73–3.80, and correlating the signal of $C_5$ with the unresolved pattern at $\delta$ 3.22–3.35.

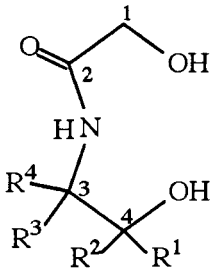
The IR spectra of the various compounds (see Table 3) show the two bands of amide I and amide II expected in the range 1652–1630 $cm^{-1}$ and 1556–1540 $cm^{-1}$, respectively, and the bands due to the OH and NH groups in the range 3372–3290 $cm^{-1}$.

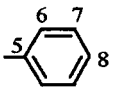
The 70 eV EI mass spectra of compounds **9–15** do not exhibit the molecular ion and only the compounds **9**, **10**, **13**, and **15** exhibit the M + 1 ion. The fragment ions $H_2NCR^4R^3$ and $H_2N(CHR^4R^3)$-$COCH_2OH$ correspond to the base peak for compounds **9–14** and **15**, respectively. Compound **13** was recrystallized from acetone to provide suitable crystals for X-ray diffraction.

Figure 2 shows its molecular structure and crystallographic numbering scheme. The molecule in the crystal structure shows the following intermolecular contacts: $C=O_1 \cdots H_{2a}$ 1.803, $C–O_2 \cdots H_3$ 1.941, $C–O_3 \cdots H_{1a}$ 2.181, $C–O_2 \cdots H_{2c}$ 2.570 Å, which are significantly shorter than the sum of the van der Waals radii of oxygen and hydrogen (2.70 Å) [27]. Besides the intermolecular contacts, there are the following intramolecular contacts: $C–O_2 \cdots H_{1a}$ 2.279 and $C=O_1 \cdots H_{3a}$ 2.421 Å.

In general, all bond distances are within the values expected [27,28], the more important bond distances being: $N_1–H_{1a}$ 0.900, $C_1–O_1$ 1.241 (2), $C_1–N_1$ 1.327, $N_1–C_3$ 1.457 Å. The values of the torsion angles for $O_1$-$C_1$-$N_1$-$H_{1a}$ and $C_2$-$C_1$-$N_1$-$H_{1a}$ are $-178.8°$ and 0.93°, respectively, this indicating that the molecule

**TABLE 2** $^{13}C$ NMR Data for Compounds **9–15**




| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|---|---|---|---|---|
| **9** | H | H | H | H | **13** | H | H | $^5CH_2$-$^6CH_3$ | H |
| **10** | $^5CH_3$ | H | H | H | | | | | |
| **11** | H | H | $^5CH_3$ | H | **14** |  | H | H | H |
| **12** | H | H | $^5CH_3$ | $^6CH_3$ | **15** | $^5CH_2OH$ | H | H | H |



| Compound | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | $C_6$ | $C_7$ | $C_8$ |
|---|---|---|---|---|---|---|---|---|
| **9** | 61.5 | 172.0 | 40.9 | 59.9 | | | | |
| **10** | 61.5 | 171.8 | 45.8 | 65.2 | 21.1 | | | |
| **11** | 61.5 | 171.2 | 45.9 | 64.2 | 17.2 | | | |
| **12** | 62.1 | 171.8 | 54.1 | 68.5 | 23.8 | 23.8 | | |
| **13** | 61.9 | 172.0 | 52.0 | 63.4 | 24.3 | 11.0 | | |
| **14** | 61.9 | 172.4 | 46.7 | 71.8 | 144.0 | 126.4 | 128.6 | 127.6 |
| **15** | 61.4 | 172.1 | 41.7 | 70.3 | 63.8 | | | |

$\delta$: (ppm) solvent DMSO-$d_6$.

**TABLE 3** Infrared Data for Compounds **9–15**

| | | | | | |
|---|---|---|---|---|---|
| **9**[a] | 3338 | 2936 | 1652 | 1540 | 1074 |
| **10**[b] | 3308 | 2934 | 1642 | 1542 | 1080 |
| | | 2866 | | | |
| **11**[a] | 3318 | 2976 | 1648 | 1546 | 1080 |
| | | 2936 | | | |
| **12**[a] | 3372 | 2974 | 1652 | 1540 | 1078 |
| | | 2932 | | | |
| **13**[b] | 3362 | 2958 | 1630 | 1554 | 1080 |
| | 3290 | 2872 | | | |
| **14**[b] | 3360 | 2938 | 1630 | 1556 | 1080 |
| | 3318 | 2864 | | | |
| | | 3096[c] | | | |
| **15**[a] | 3356 | 2932 | 1648 | 1542 | 1074 |

$\nu(cm^{-1})$.
[a]Neat liquid.
[b]KBr.
[c]$\omega$C–H arom.

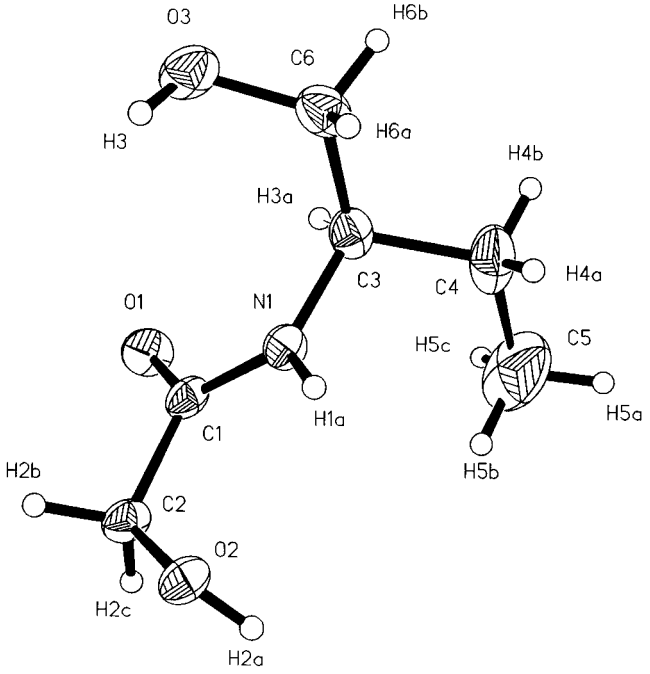



**FIGURE 2** Molecular structure and crystallographic numbering scheme of **13**.

is planar due to the hydrogen bonding between the amide hydrogen atom ($H_{1a}$) and the hydroxyl group ($O_2$). These observations agree with the structural model proposed for the $\alpha$-hydroxy amides [16].

## *EXPERIMENTAL*

NMR spectra were recorded on a JEOL GLX-270, JEOL ECLIPSE-400, and VARIAN EM-390 spectrometer. All $^1H$ and $^{13}C$ resonances are reported relative to TMS and $^{15}N$ to neat $MeNO_2$, DMSO-$d_6$ being used as the solvent. Mass spectra were obtained with a Hewlett-Packard 59940-A instrument, and infrared spectra were determined on a Perkin-Elmer 16F PC FT-IR spectrometer. Melting points were taken in open capillary tubes on a Gallenkamp MFB-595 apparatus and are uncorrected. The single-crystal X-ray studies were performed on a CAD4 ENRAF NONIUS FR 590 diffractometer. Reagents were purchased from Aldrich Co.

The procedure outlined in the following paragraph is general for the preparation of 2-hydroxy-N-(2′-hydroxyalkyl)-acetamides **9–15**.

### *Synthesis of 2-Hydroxy-N-(2′-hydroxyethyl)-*acetamide **9**

A 0.387 g (6.34 mmol) amount of ethanolamine was added to 0.470 g (6.18 mmol) of glycolic acid at room temperature, the mixture being heated at 80°C and stirred during 3.15 hours. The water produced in the reaction was retained on the wall of the flask. The reaction mixture was cooled to room temperature and washed with chloroform and acetone. The solvent was evaporated under vacuum to yield 0.70 g of **9** (95%) as a brown liquid.

### *2-Hydroxy-N-(2′-hydroxypropyl)acetamide* **10**

The reaction of 0.490 g (6.45 mmol) of compound **1** with 0.484 g (6.45 mmol) of DL-1-amino-2-propanol gave a brown solid, which was recrystallized from methylen chloride to yield 0.80 g of **10** (93%) as a white solid, mp 97–100°C.

### *2-Hydroxy-N-(1′-methyl-2′-hydroxyethyl)-acetamide* **11**

A 0.500 g (6.58 mmol) amount of compound **1** with 0.494 g (6.58 mmol) of DL-2-amino-1-propanol gave 0.710 g (81%) of **11** as a brown liquid, isolated from a chloroform solution.

### *2-Hydroxy-N-(1′,1′-dimethyl-2′-hydroxyethyl)-acetamide* **12**

The reaction of 1.049 g (13.8 mmol) of compound **1** with 1.230 g (13.8 mmol) of 2-amino-2-methyl-1-propanol at 100°C for 6 hours gave a light-brown liquid, which was obtained from an acetone solution to yield 1.689 g of **12** (83%).

### *2-Hydroxy-N-(1′-ethyl-2′-hydroxyethyl)-acetamide* **13**

The reaction of 0.569 g (7.49 mmol) of compound **1** with 0.668 g (7.49 mmol) of 2-amino-1-butanol gave

a white solid, which was washed with chloroform and recrystallized from acetone to yield 0.910 g of **13** (82.6%), mp 87–88°C.

### *2-Hydroxy-N-(2′-phenyl-2′-hydroxyethyl)-acetamide* **14**

The reaction of 2.204 g (28.9 mol) of compound **1** with 3.937 g (28.9 mol) of DL-2-amino-1-phenylethanol at 70°C for 1.30 hours, gave a white solid, recrystallized from chloroform and acetone to yield 4.241 g of **14** (75%), mp 95–96°C.

### *2-Hydroxy-N-(2′,3′-dihydroxypropyl)acetamide* **15**

A 0.500 g (6.58 mmol) amount of compound **1** with 0.599 g (6.58 mmol) of DL-3-amino-1,2-propanodiol gave **15**, which was washed with acetone to give 0.910 g (93%) of the product as a brown liquid.

### *X-ray Crystal Structure Determination for* **13**

Compound **13**, $C_6H_{13}NO_3$, crystallized in the space group P2(1)/c from acetone as a colorless rectangular prism with $a = 12.993$ (3), $b = 7.088$ (10), $c = 8.973$ (2) Å, $V = 816.3$ (3) Å$^3$, $Z = 4$, $Dc = 1.198$ mgm$^{-3}$, $\mu = 0.095$ mm$^{-1}$, F (000) = 320. Lattice constants were determined from least-squares refinements of the setting angles of 25 well-centered reflections on an automatic diffractometer using molybdenum radiation.

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 1252 unique reflections with Fo $> 4\sigma$ (Fo) used in the solution and refinement for **13**. Corrections for Lorentz and polarization effects were performed, as well as empirical absorption corrections.

The structure was solved by direct methods and refined by full-matrix anisotropic least squares (hydrogen atoms isotropically) up to R = 0.0464 and Rw = 0.1263.

All the hydrogen atoms were located in the difference Fourier maps. Atomic scattering factors were taken from the *International Tables for X-ray Crystallography* [29]. The data reduction was performed by JANA 98 [30]. All calculations were carried out on a VAX 4000 computer using the Shelx 93 (Shedrick G. M.) program package [31].

### *Supplementary Material Available*

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

## *ACKNOWLEDGMENTS*

The authors would like to thank Ing. Marco Antonio Leyva for collecting X-ray data.

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