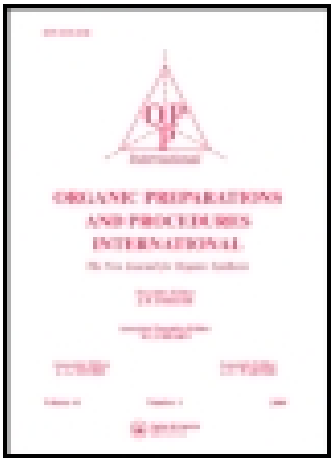

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SYNTHESIS AND CHARACTERIZATION OF N-ALKYL HYDROXYACETAMIDES

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SYNTHESIS AND CHARACTERIZATION OF N-ALKYL HYDROXYACETAMIDES

Submitted by (06/24/99)

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A variety of hydroxyacetamides were synthesized at the end of the 1950s as potential anticonvulsant agents.[1] N-Benzyl hydroxyacetamide has been used in the preparation of photographic elements,[2] and of heterocyclic compounds;[3-6] it also has been found as a metabolite of 2-acetyl-3-phenyltetrahydro-1,2,4-oxadiazin-5-one in rats[7] and N-benzhydryl haloacetamides have been used as protective groups in peptide syntheses.[8] Hydroxyacetamides have been prepared by a) ammonolysis of the ethyl esters of the α-hydroxy acids, b) dehydration of the corresponding amine salts and c) reaction of amines with lactides or polyglycolides.[1] Our current interest in hydroxyacetamides prompted us to study the reaction of glycolic acid **1** with amines **2** and this article describes the synthesis of N-alkyl hydroxyacetamides **3a-h** which were characterized by spectroscopic methods.[9]

$$\underset{\mathbf{1}}{HOCH_2CO_2H} + \underset{\mathbf{2}}{RNH_2} \longrightarrow \underset{\mathbf{3}}{HOCH_2CONHR}$$

a) R = $PhCH_2$- b) R = $CH_3C_6H_4CH_2$- c) R = $CH_2=CHCH_2$- d) R = $(CH_3)_2CH$- e) R =$PhCH(CH_3)$-
f) R = Ph_2CH- g) R = $HOCH_2CH_2NHCH_2CH_2$- h) R = $HOCH_2CONHCH_2CH_2$-

In contrast to previous preparations which used ethyl esters, lactides and polyglycolides or the dehydration of amine salts,[1] the reaction of amines (**2**) was performed *directly* on glycolic acid **1** *without solvent*. It is also important to note that the yields obtained in this work are better that reported previously.[1] Compounds **3a**, **3b**, **3f** and **3h** were obtained as white solids, **3c** as a dark brown liquid, and **3d**, **3e** and **3g** as yellow liquids. ^1H NMR spectra data of the compounds **3a-h** exhibit the chemical shifts and coupling pattern expected for these types of compounds.

Compound **3g** proved to be an unstable oil;[10] its ^1H NMR spectrum showed it to be approximately 95% pure after 5 hours, which may be due to the formation of cyclic compounds or oligomers. In fact, its elemental analysis for carbon was 42.92%, which is outside the tolerance by only 0.49 and the found (8.90%) and calculated (8.70%) values for hydrogen percentage fall within the commonly accepted experimental error of ± 0.30%. To obtain the coupling constants of the allyl group of compound **3c**, it was necessary to irradiate the signal of methylene protons. Table 1 shows the $\delta(^{15}N)$ for the compounds **3a-h**, to be within the range of amides.[11] The signal of compounds **3d**, **3e** and **3f** exhibits a deshielding due to the β effect.[12] Table 2 shows that the compounds **3a-h**, exhibit the expected ^{13}C NMR spectra. Since the signals of C_1 and C_6 of **3g** have similar chemical shifts, their assignments were obtained by an HETCOR spectrum, the signal of C_1 correlating with the signal at δ

3.77 and that of C_6 correlating with the triplet signal at δ 3.43. The signals of C_4 and C_7 of **3b**, and C_4 and C_5 of **3g** appear at similar positions; however, they could not be assigned by HETCOR spectra. The assignments were obtained using the ^1H-($^2J_{CH}$)^{13}C COLOC spectra. The signal of C_4 of **3b** correlates with that of the protons of the $C\underline{H}_2NH$ group and the signal of C_5 of **3g** correlates with that of the protons of the $C\underline{H}_2OH$ group. The IR spectra of the various compounds show the amide I and amide II bands expected in the range 1632-1656 and 1536-1558 cm^{-1}, respectively, and the bands due to the OH and NH groups in the range 3290-3332 cm^{-1}.

The 70 eV EI mass spectra of compounds **3a**, **3b**, **3d**, **3e** and **3f** exhibit the molecular ion with the following relative abundance 20%, 27.5%, 9%, 21%, 78%, respectively. Compounds **3c**, **3g** and **3h** exhibit the M+1 ion with low relative abundances (1%), (1.4%) and (1.6%), respectively. The fragment ions of m/z = 91, m/z = 105, m/z = 41, m/z = 43, m/z = 105, m/z = 167, m/z = 74 and m/z = 30 correspond to the base peak for compounds **3a** to **3h**, respectively. Compounds **3a** and **3b** were recrystallized from acetonitrile/chloroform and chloroform/hexane respectively, to provide rectangular prisms for X-ray diffraction.[9]

EXPERIMENTAL SECTION

NMR spectra were recorded on a JEOL GLX-270, JEOL Eclipse-400 and Bruker Avance 300-DPX spectrometers. All ^1H and ^{13}C resonances are reported relative to TMS and ^{15}N to neat $MeNO_2$, DMSO-d_6 and $CDCl_3$ being used as solvents. Mass spectra were obtained with a Hewlett - Packard 5994-A instrument, and infrared spectra were recorded as KBr pellets or neat liquid 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 FR590 diffractometer. Reagents were purchased from Aldrich Co.

TABLE 1. Yield, mps and NMR Data of Compounds **3**

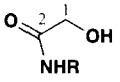
Cmpd	Yield (%)	mp (°C)	^{15}NMR (δ)[a]	^{1}H NMR (δ) NH	CH_2CO	Other H
3a	**95**	101-102[b]	-266.63	8.29(t, J = 6.2)	3.86(s)	4.31(d, J = 6.2)[f] 7.20-7.34(m)
3b	88	143-144[c]	-266.58	8.21(t, J = 6.2)	3.85(d, J = 5.7)	2.27(s)[f] 4.26(d, J = 6.2) 7.11(d, J = 7.7) 7.15(d, J = 7.7)
3c	97	brown liquid	-268.39	7.09(t, J = 5.7)	4.07(s)	5.10(dd, J = 10.3, J = 1.2)[g] 5.15(dd, J = 17.1, J = 1.2) 5.78(m, J = 17.1, 10.3, J = 5.7)
3d	92	yellow liquid	-248.83	6.87(d, J = 7.6)	3.98(s)	1.14(d, J = 6.6)[g]
3e	98	yellow liquid	-251.29	7.17(d, J = 7.7)	3.94(d, J = 5.1)	1.47(d, J = 7.0)[g] 5.07(q, J = 7.7, J = 7.0) 7.21-7.33(m)

TABLE 1. Continued...

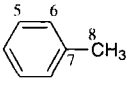
Cmpd	Yield (%)	mp (°C)	^{15}NMR (δ)[a]	NH	CH_2CO	^{1}H NMR (δ) Other H
3f	94	97-98[d]	-254.37	7.41(d, J = 8.2)	3.97(s)	6.21(d, J = 8.2)[g] 7.20(t, J = 7.7) 7.22(t, 7.7) 7.28(d, 7.7)
3g	94	yellow liquid	-269.88 -350.64	7.73(t, J = 5.8)	3.77(s)	2.57(t, J = 5.9)[f] 3.43(t, J = 5.9) 3.17(q, J = 5.8, J = 6.2)
3h	75	139-140[e]	-270.76	7.90(s)	3.79(s)	3.19(s)[f]

a) Relative to neat nitromethane. b) From $CHCl_3$-hexane. c) From $CHCl_3$-CH_3CN.
d) From CH_2Cl_2-hexane. e) From acetone. f) In DMSO-d_6. g) In $CDCl_3$.

TABLE 2 ^{13}C NMR data of Compounds **3**

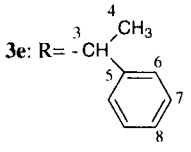


3a: R= -^{3}CH$_2$-^{4} 

3b: R= -^{3}CH$_2$-^{4} 

3c: R= -^{3}CH$_2$^{4}CH=^{5}CH$_2$

3d: R= -^{3}CH(^{4}CH$_3$)$_2$

3e: R= 

3f: R= -^{3}CH(-^{4} )$_2$

3g: R= -^{3}CH$_2$^{4}CH$_2$NH^{5}CH$_2$CH$_2$OH

3h: R= -^{3}CH$_2$^{4}CH$_2$NH^{2}C(=O)-^{1}CH$_2$OH

Cmpd	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
3a[a]	61.5	171.9	41.6	139.7	128.2	127.3	126.7	
3b[a]	61.6	171.7	41.4	139.6	127.3	128.7	135.8	20.7
3c[b]	62.0	172.8	41.4	133.6	116.6			
3d[b]	62.2	172.5	41.5	22.9				
3e[b]	62.0	171.7	48.5	22.0	142.8	128.7	126.0	127.4
3f[b]	62.1	171.5	56.5	141.4	128.8	127.7	126.7	
3g[a]	61.5	171.9	38.0	48.4	51.3	60.2		
3h[a]	61.5	172.3	38.2					

a) In DMSO-d_6 b) In $CDCl_3$The procedure outlined below is general for the preparation of N-alkyl hydroxyacetamides **3a-3h**.

Synthesis of N-Phenylmethyl Hydroxyacetamide (3a). General Procedure.- A 2.82 g (26.3 mmol) amount of benzylamine was added to 2.00 g (26.3 mmol) of glycolic acid (**1**) at room temperature; the mixture was heated at 90° and stirred during 1 hour. The water produced in the reaction was retained on the wall of the flask. The reaction mixture was cooled to room temperature and dissolved in methylene chloride and treated with n-hexane to provide a white solid, which was recrystallized from chlo-

roform/n-hexane to yield 4.13 g (95%) of compound **3a**, mp. 101-102°, *lit.*[1] mp.103-104°. IR: 3318, 3216, 3030, 2934, 2862, 1632, 1558, 1082 cm^{-1}(KBr).

Compounds **3b**, **3f**, and **3h** were prepared by a similar procedure and obtained as white solids.

Synthesis of N-4-methylphenylmethyl Hydroxyacetamide (3b).- The reaction of 2.00 g (26.3 mmol) of **1** with 3.18 g (26.3 mmol) of 4-methylbenzylamine at 90° for 1 hour, gave a white solid, which was recrystallized from acetonitrile-chloroform to yield 4.15 g (88%) of **3b**, mp 143-144°, *lit.*[1] mp.143-145°. IR: 3332, 3228, 3084, 2932, 2862, 1632, 1554, 1076 cm^{-1}(KBr).

Synthesis of N-3-propenyl Hydroxyacetamide (3c).- The reaction of 0.70 g (9.2 mmol) of **1** with 0.53 g (9.2 mmol) of allylamine at 80° for 2 hours gave 1.04 g (97%) of compound **3c** as a dark brown liquid. IR: 3326, 3086, 2986, 2918, 2852, 1656, 1542, 1080 cm^{-1} (neat liquid).

Synthesis of N-methylethyl Hydroxyacetamide (3d).- The reaction of 0.70 g (9.2 mmol) of **1** with 0.59 g (10.1 mmol) of isopropylamine at 80° for 2 hours, gave 0.99 g (92%) of **3d** as a light yellow liquid. IR: 3318, 2976, 2936, 2878, 1652, 1546, 1082 cm^{-1} (neat liquid).

Synthesis of N-phenylethyl Hydroxyacetamide (3e).- A 2.00 g (26.3 mmol) sample of **1** with 3.18 g (26.3 mmol) of S-(-)-α-methylbenzylamine at 80° for 3.20 hours, gave 4.82 g (98%) of **3e** as a light yellow liquid. IR: 3290, 3068, 2976, 2928, 1652, 1538, 1080 cm^{-1} (neat liquid).

Synthesis of N-diphenylmethyl Hydroxyacetamide (3f).- The reaction of 2.00 g (26.3 mmol) of **1** with 4.82 g (26.3 mmol) of aminodiphenylmethane at 90° for 1 hour, gave 5.96 g (94%) of **3f** as a white solid, mp 97-98°, *lit.*[1] mp. 95-98°. IR: 3302, 3062, 1642, 1536, 1078 cm^{-1} (KBr).

Synthesis of N-2'(Amino-2-hydroxyethyl)ethyl Hydroxyacetamide (3g).- The reaction of 0.50 g (6.5 mmol) of **1** with 0.68 g (6.5 mmol) of 2-(aminoethylamino)ethanol at 70° for 3.20 hours, gave 1.00 g (94%) of **3g** as a light yellow liquid. IR: 3298, 2934, 1650, 1544, 1078 cm^{-1} (neat liquid).

Anal. Calcd. for $C_6H_{14}N_2O_3$: C, 44.43; H, 8.70. Found: C, 42.92; H, 8.90

Synthesis of 2,2'-Dihydroxyethylenediacetamide (3h).- The reaction of 2.53 g (33.2 mmol) of **1** with 1.00 g (16.6 mmol) of ethylenediamine at 90° for 2 hours, gave a yellow solid, which was washed with acetone to obtain 2.20 g (75%) of compound **3h** as a white solid mp 139-140°. IR: 3294, 2936, 2834, 1640, 1544, 1078 cm^{-1} (KBr).

Anal. Calcd. for $C_6H_{12}N_2O_4$: C, 40.90; H, 6.86. Found: C, 41.04; H, 6.86

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9. Although compounds **3a-h** had been reported previously (ref. 1), their spectroscopic properties were not. The structures of **3a** and **3b** were further confirmed by X-ray diffraction; details may be obtained from the authors.

10. The ^{1}H NMR spectrum of freshly prepared **3g** showed it to be approximately 99% pure.

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AN IMPROVED SYNTHESIS OF 3-CYANO-4-FLUOROBENZYL BROMIDE

Submitted by (10/06/99) Gary A. Cain

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A key feature in the enhanced HIV protease inhibitory activity of our recently reported cyclic ureas,[1-4] such as drug candidates DMP850 (**1**) and DMP851 (**2**),[2] is the presence of a 3-aminoindazole P2 substituent. The 3-aminoindazole groups are introduced into these compounds by