2:2 CONDENSATION PRODUCTS FROM THE REACTION OF N-SUBSTITUTED 1,2-DIAMINOETHANES AND 1,3-DIAMINOPROPANES WITH SUCCINALDEHYDE AND GLUTARALDEHYDE

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Abstract - The reaction of N-substituted 1,2-diaminoethanes and 1,3-diaminopropanes (1) with succinaldehyde (2) and glutaraldehyde (9) in water gave the 2:2 condensation products (4 and 10).

INTRODUCTION

The reaction of succinaldehyde and glutaraldehyde with functionalized compounds, such as amines and 2-aminoethanols, produces various heterocycles, such as pyrrole, piperidine, dihydropyridine, tetrahydropyran, pyridodiazocin, and oxazolpiperidine. All of these reactions give only 1:1 condensation products. The reaction of glutaraldehyde with hydroxylamine to give dipiperidinoperhydrodioxadiazin is the only reported example of a 2:2 condensation product. Recently, we succeeded in preparing 2:2 condensation products, polyazaperhydrope~lene~ by reacting glyoxal and glutaraldehyde with polyfunctionalized compounds.

To obtain additional novel polyheterocycles in one-pot reactions, we hoped to prepare of 2:2 condensation products using N-substituted diamino groups.

We report here the reaction of N-substituted 1,2-diaminoethanes and 1,3-diaminopropanes (1a-e) with succinaldehyde (2) and glutaraldehyde (9) to give the 2:2 condensation products (4 and 10).

RESULTS AND DISCUSSION

Compounds (1a-c) were reacted with 2, which was derived from 2,5-dimethoxytetrahydrofuran, in aqueous hydrochloric acid at room temperature to give two products (3 and 4) in yields of 12-44 and 22-30%, respectively (Scheme 1). These products were purified by distillation under reduced pressure, and structural assignments were made on the basis of spectral data and elemental analyses. The mass spectra for the two products (3a and 4a) from 1a and 2 showed corresponding molecular ions at m/z 138 and 276, which indicated the loss of two and four molecules of water from the combination of one and two equivalents of 1a and 2, respectively, and their molecular formulae were equivalent to those of the 1:1 and 2:2 condensation products. In the reaction of 1a with 2, the 1:1 condensation product exhibited characteristic pyrrole triplet signals at δ 6.13 and 6.65 ppm in the 1H-nmr spectrum. The 13C-nmr spectrum
showed one methyl carbon at $\delta$ 36.54, three methylene carbons at $\delta$ 31.68, 47.51, and 49.12 ppm, and $\beta$- and $\alpha$-carbons of pyrrole at $\delta$ 107.95 and 120.49 ppm. Based on these spectral data, the structure for the 1:1 adduct was presumed to be 3a.

With regard to the structure of the 2:2 condensation product from 1a, the IR spectrum showed absorption assignable to the NH group at 3310 cm$^{-1}$, while in the 1H-nmr spectrum, singlets of two methyl groups appeared at $\delta$ 2.20 and 2.39 ppm, the multiplet and triplet of two methine groups appeared at $\delta$ 2.24 and 3.15 ppm, and each triplet ($J=2.2$ Hz) of the three hydrogens on the pyrrole was observed at $\delta$ 6.12, 6.54, and 6.58 ppm. The 13C-nmr spectrum showed 16 carbons; 9 of which were used to calculate the ratios 5:1 of each carbon for the two isomers. The DEPT spectrum indicated 2 methyl carbons at $\delta$ 36.55 and 41.74 ppm, 8 methylene carbons at $\delta$ 21.45-56.16 ppm, 2 methine carbons at $\delta$ 61.38 and 86.55 ppm, and 4 pyrrole carbons at $\delta$ 107.29, 118.69, 120.37, and 125.53 ppm. Based on these spectral data, two possible structures (4a and 5) were deduced. The 1H-nmr spectrum of 4a showed the same chemical shift and $J$ values as the three methylene hydrogens of the pyrrole 1:1 condensation product. Moreover, the mass spectrum of the 2:2 condensation product indicated a fragment of $N$-substituted pyrrole at $m/z$ 137 corresponding to 3a. These results strongly supported structure (4a) rather than 5. All of the protons and carbons of 4a were assigned based on 1H-1H- and 1H-13C COSY. The unequivalent hydrogens on C-7 and C-9 were observed at $\delta$ 1.76 and 2.94 ppm and at $\delta$ 1.93 and 2.94 ppm, respectively, with a shift difference of more than 1 ppm. This result could be attributed to the fact hydrogens which are proximal to the lone pairs on nitrogen are shifted downfield compared to hydrogens in the opposite direction. The following reaction mechanism is proposed based on the spectral data for compounds (3 and 4): The intermediates (6), which were derived from 1 and 2, are presumably obtained from 3 via Mannich reactions which proceed through 4 (Scheme 2).
To ascertain the structure of 3, the reaction of 3 with glyoxalic acid (7) was carried out in EtOH to give pyrrolodiazepines (8) in 74-90% yields (Scheme 3). Their spectral data were consistent with the proposed structure (8). The structure of 3 was confirmed based on these results.

Next, compound (1) was reacted with 9 in EtOH to give the 2:2 condensation products (10) in 52-64% yields (Scheme 4), which were then purified by distillation under reduced pressure and recrystallization. The product of the reaction of 1d with 9 had a molecular ion at m/z 336, which represented the loss of four molecules of water from two equivalents of 1d and 9. The IR spectrum showed a characteristic strong absorption for the C=C double bond of the enamine at 1650 cm⁻¹. The DEPT spectrum exhibited 13 methylene carbons at δ 19.45-59.60, 4 methine carbons at δ 66.83-129.34, and a quaternary carbon at 111.64 ppm. Only two of four possible stereoisomers resulted, with the chemical shifts of 8 carbons out of being different for each isomer in the ¹³C-nmr spectrum. Relative ratio of these isomers was determined to be 13:8 by the intensities of stereoisomeric carbon pairs. Compound (10d) was recrystallized from AcOEt three times, but the ratio of the stereoisomers was unchanged. Based on these results and comparison with the ¹H- and ¹³C-nmr spectral data of related derivatives,¹⁸ the structure for the 2:2 condensation product was deduced to be 10d. All of the protons and carbons were assigned from ¹H-¹H- and ¹H-¹³C COSY.

![Diagram of the reaction pathway](image)

The reaction pathway was deduced to proceed via formation of an enamine intermediate (11) from 1 and 9, followed by electrophilic attack of another molecule of 9 to produce intermediate (12). This then reacted again with 1 to give 10.

In conclusion, the reaction of dialdehydes with 1-substituted diamino compounds to give 2:2 condensation products, occurs via a 1:1 condensation product intermediate.
EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a JASCO IRA-1 grating infrared spectrometer. 1H-NMR spectra were determined with a JEOL JNM GX400 (400 MHz) and EX270 (270 MHz) spectrometers using tetramethylsilane as an internal standard. 13C-NMR spectra were measured with a JEOL JNM GX400 (100 MHz) and EX270 (67.5 MHz) spectrometers. Mass spectra were measured with a JEOL JMX-DX 3030HF mass spectrometer.

**General Procedure for 1-(N-Substituted 3-aminopropyl)pyrroles (3) and 1-Substituted 6-[1-(N-substituted 3-aminopropyl)pyrrol-2-yl]octahydropyrrole[1,2-a]pyrimidines (4)**

To an aqueous solution of 2,5-dimethoxytetrahydrofuran (3.24 ml, 25 mmol) was added concentrated hydrochloric acid (1.1 ml). After the acidic solution was stirred for 20 min at room temperature, a solution of 1 (2.5 mmol) in EtOH (25 ml) was gradually added. The reaction mixture was stirred for 12 h. After evaporation of EtOH and water under reduced pressure, the residue was dissolved in CH2Cl2 (25 ml) and washed with sat. NaHCO3. After removal of CH2Cl2, the residue was distilled under reduced pressure.

3a: yield 0.04 g (12%); bp 43 °C / 0.9 mmHg; ir v (film) 3300 (NH) cm⁻¹; 1H-NMR (CDCl3) δ 1.09 (s, NH), 1.91 (qui, CH2, J=7.0 Hz), 2.40 (s, NCH3), 2.55 (t, CH2, J=7.0 Hz), 3.95 (t, CH2, J=7.0 Hz), 6.13 (t, 2 x 3-H, J=2.2 Hz), 6.65 (t, 2 x 2-H, J=2.2 Hz); 13C-NMR (CDCl3) δ 36.54 (CH3), 31.68, 47.51, 49.12 (CH2), 107.95, 120.49 (pyrrole); HR-ms m/z: 138.1145 (Calcd for C8H14N2: 138.1157); Anal. Calcd for C8H14N2: C, 69.52; H, 10.21; N, 10.9. Found C, 69.77; H, 10.40; N, 11.95.

3b: yield 0.15 g (33%); bp 74 °C / 0.6 mmHg; ir v (film) 3300 (NH) cm⁻¹; 1H-NMR (CDCl3) δ 0.84 (t, CH3, J=7.0 Hz), 1.21-1.58 (m, 2 x CH2 and NH), 1.76 (t, CH2, J=7.2 Hz), 2.31-2.52 (m, 2 x CH2), 3.89 (d, CH2, J=7.2 Hz), 5.95 (t, 2 x 3-H, J=2.4 Hz), 6.71 (t, 2 x 2-H, J=2.4 Hz); HR-ms m/z: 180.1654 (Calcd for C11H20N2: 180.1626); Anal. Calcd for C11H20N2: C, 73.28; H, 11.18; N, 15.54. Found C, 72.97; H, 11.33; N, 15.80.

3c: yield 0.21 g (44%); bp 78 °C / 0.5 mmHg; ir v (film) 3300 (NH) cm⁻¹; 1H-NMR (CDCl3) δ 0.92 (d, 2 x CH3, J=7.0 Hz), 1.13-1.62 (m, CH2, CH, and NH), 1.96 (t, CH2, J=7.2 Hz), 2.59 (t, CH2, J=6.6 Hz), 2.63 (t, CH2, J=7.2 Hz), 4.00 (t, CH2, J=7.2 Hz), 6.17 (t, 2 x 3-H, J=2.4 Hz), 6.69 (t, 2 x 2-H, J=2.4 Hz); HR-ms m/z: 194.1780 (Calcd for C12H22N2 194.1783); Anal. Calcd for C12H22N2: C, 74.17; H, 11.41; N, 14.42. Found C, 74.42; H, 11.60; N, 14.67.

4a: yield 0.21 g (30%); bp 68 °C / 0.9 mmHg; ir v (film) 3310 (NH) cm⁻¹; 1H-NMR (CDCl3) δ 1.50-1.53 (m, CH3), 1.74-1.84 (m, 2 x CH3), 1.86-1.97 (m, 5 x CH2 and CH3), 2.12 (s, NH), 2.17-2.22 (m, CH3), 2.22 (s, CH3), 2.39 and 2.40 (s, CH3), 2.53-2.56 (m, NCH2), 2.90-2.94 (m, 2 x NCH2), 3.15 (t, CH, J=7.0 Hz), 3.88 (t, NCH2, J=7.0 Hz), 6.12 (t, 3'-H, J=2.2 Hz), 6.54 (t, 4'-H, J=2.2 Hz), 6.58 (t, 5'-H, J=2.2 Hz); 13C-NMR (CDCl3) δ 21.45 and 25.29, 28.14 and 28.46, 30.68, 31.56 and 31.77 (CH2), 36.55, 41.74 and 42.15 (CH3), 47.59, 49.21 and 49.26, 49.44, 55.77 and 56.16 (CH2), 61.38, 82.09 and 86.55 (CH), 107.29, 118.69 and 118.96, 120.37 and 120.58, 125.30 and 125.53 (pyrrole); HR-ms m/z: 276.2258 (Calcd for C16H28N4 276.2314); Anal. Calcd for C16H28N4: C, 69.52; H, 10.21; N, 9.90; N, 19.98.
General Procedure for 2-Substituted 1-Carboxy-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a]-[1,4]diazepines (8) ------- Glyoxalic acid hydrate (7) (0.46 g, 5 mmol) was added dropwise to a stirred solution of 3 (5 mmol) in EtOH (20 ml) at room temperature. The reaction mixture was stirred for 3 h and evaporated under reduced pressure. The resulting residue was washed with solvent.

8a: yield 0.72 g (74%) (recryst. from EtOH-Et₂O); mp 167-168 °C; ir v (KBr) 1620 (C=O) cm⁻¹; ¹H-nmr (DMSO-d₆) δ 1.56-2.01 (m, CH₂), 2.29 (s, CH₃), 3.11-3.46 (m, CH₂), 3.93-4.21 (m, CH₂), 4.82 (s, CH), 5.02-5.35 (br, NH⁺), 5.81-6.14 (m, 2 x CH=), 6.69-6.76 (m CH=); FAB-ms m/z: 195 (M+1)+; Anal. Calcd for C₁₀H₁₄N₂O₂ H₂O: C, 56.59; H, 7.59; N, 13.20. Found C, 56.37; H, 7.39; N, 13.06.

8b: yield 0.92 g (78%) (recryst. from THF-petr. ether); mp 138-139 °C; ir v (KBr) 1640 (C=O) cm⁻¹; ¹H-nmr (DMSO-d₆) δ 0.86-2.20 (m, CH₃ and 3 x CH₂), 3.61-3.69 (m, 2 x CH₂), 4.10-4.21 (m, CH₂), 5.16 (s, CH), 6.00 (s, CH=), 6.30 (s, CH=), 6.57 (s, CH=), 8.18 (br, NH⁺); FAB-ms (m/z) 237 (M+1)+; Anal. Calcd for C₁₃H₂₀N₂O₂: C, 66.07; H, 8.53; N, 11.85. Found C, 65.85; H, 8.64; N, 11.81.

8c: yield 1.13 g (90%) (recryst. from THF-petr. ether); mp 140-141 °C; ir v (KBr) 1640 (C=O) cm⁻¹; ¹H-nmr (DMSO-d₆) δ 0.82 (d, 2 x CH₃, J=4.2 Hz), 1.16-3.01 (m, 2 x CH₂ and CH), 3.17-3.43 (m, CH₂), 3.93-4.23 (m, CH₂), 4.80 (s, CH), 5.80-6.13 (m, 2 x CH=), 6.63-6.94 (m, CH= and NH⁺); FAB-ms m/z: 251 (M+1)+; Anal. Calcd for C₁₄H₂₂N₂O₂: C, 67.17; H, 8.86; N, 11.19. Found C, 67.03; H, 8.62; N, 10.97.

General Procedure for 1-Substituted 7-(1-Substituted Octahydro-2H-pyrido[1,2-a]-pyrimidin-6-yl)-1,3,4,8,9,9a-hexahydro-2H-pyrido[1,2-a]pyrimidines (10a, b) and 1-Substituted 6-(1-Substituted Octahydroimidazol[1,2-a]pyridin-5-yl)-1,2,3,7,8,8a-hexahyroidimidazol[1,2-a]pyridines (10c, d) ------- Glutaraldehyde (9) (0.6 ml, 3 mmol, 50% w/v in water) was added slowly to a stirred solution of 1 (3 mmol) in EtOH (20 ml) containing a drop of AcOH under cooling with ice and water, over 1 h at room temperature under an atmosphere of argon. The reaction mixture was stirred for 12 h, and then evaporated to dryness under reduced pressure. The residue
was dissolved in water (100 ml), and the aqueous solution was extracted with CH₂Cl₂ (3 x 20 ml). After removal of CH₂Cl₂, the residue was purified by distillation under reduced pressure or recrystallized from EtOH. All compounds are a mixture of two isomers.

10a: yield 0.58 g (64%); bp 90 °C / 0.4 mmHg; ir v (film) 1662 (C=C) cm⁻¹; IH-nmr (CDCl₃) δ 1.33-1.47 (m, 2 x CH₂), 1.55-1.79 (m, CH₂), 1.81-1.89 (m, 2 x CH₂), 1.91-1.95 (m, 2 x CH₂), 1.98-2.09 (m, 2 x CH₂), 2.22, 2.26, 2.28, and 2.56 (s, 2 x NCH₃), 2.29-2.86 (m, CH), 2.87-3.12 (m, 2 x NCHN and 2 x NCH₂), 5.57 and 5.60 (s, CH=); ¹³C-nmr (CDCl₃) δ 23.16 and 23.32, 23.89, 24.17 and 24.29, 24.53 and 24.59, 26.11, 26.55 and 26.81, 28.26, 29.30, 31.79 and 31.89 (7 x CH₂), 39.50 and 39.95, 40.36 and 42.18 (2 x NCH₃), 52.22 and 52.26, 52.40, 55.84 and 56.00, 56.25 and 56.30 (NCH₂), 68.00 and 68.12 (NCH-), 76.84 and 77.87 (NCHN), 84.15 and 84.23 (NCHN), 113.57 and 113.93 (=CH-), 132.09 and 132.98 (=CH); EI-mzs m/z: 304 (M⁺); Anal. Calcd for C₁₅H₃₂N₄: C, 71.01; H, 10.59; N, 18.40. Found C, 70.88; H, 10.36; N, 18.14.

10b: yield 0.74 g (64%); bp 108 °C / 0.25 mmHg; ir v (film) 1650 (C=C) cm⁻¹; IH-nmr (CDCl₃) δ 0.93 and 1.03 (t, 2 x CH₃, J=7.3 Hz, 1.16-1.62 (m, 8 x CH₂), 1.62-1.96 (m, 2 x CH₂), 1.97-2.11 (m, 2 x CH₂), 2.11-2.80 (m, 4 x CH₂ and CH), 2.80-3.20 (m, 2 x NCHN and CH₂), 5.83 and 5.70 (s, CH=); HR-mzs m/z: 388.3557 (Calcd for C₂₄H₄₄N₄ 388.3566); Anal. Calcd for C₂₄H₄₄N₄: C, 74.17; H, 11.41; N, 14.42. Found C, 74.49; H, 11.63; N, 14.17.

10c: yield 0.47 g (52%); bp 156-157 °C / 1.5 mmHg; ir v (film) 1660 (C=C) cm⁻¹; IH-nmr (CDCl₃) δ 1.09 (t, CH₃, J=7.3 Hz), 1.15 (t, CH₃, J=7.3 Hz), 1.18-1.44 (m, 2 x CH₂), 1.80-1.85 (m, CH₂), 1.89-2.43 (m, 5 x CH₂), 2.76-2.89 (m, CH₂ and CH), 3.01-3.14 (m, CH₂), 3.17-3.24 (m, CH₂), 3.28 (q, CH, J=6.6 Hz), 3.47-3.51 (m, CH), 5.97 (s, CH=); ¹³C-nmr (CDCl₃) δ 13.68, 13.75 (CH₃), 19.51 and 20.33, 22.89 and 23.03, 26.99 and 27.17, 29.19 and 29.30, 30.95 and 31.65, (C-CH₂-C), 46.58 and 46.62, 47.88, 48.66, 48.85, 49.48, 51.20 and 51.30 (NCH₂), 66.79 and 67.32 (CHN), 77.40 and 77.75, 83.83, and 84.17 (NCHN), 112.11 and 112.46 (=C-), 128.95 and 129.17 (CH=); EI-mzs m/z: 304 (M⁺); Anal. Calcd for C₁₉H₃₂N₄: C, 71.00; H, 10.59; N, 18.40. Found C, 71.23; H, 10.75; N, 18.32.

10d: yield 0.60 g (60%); mp 122 °C; ir v (KBr) 3500 (OH), 1650 (C=C) cm⁻¹; IH-nmr (CDCl₃) δ 1.12-1.36 (m, CH₂), 1.38-1.61 (m, CH₂), 1.84-1.94 (m, CH₂), 1.94-2.04 (m, CH₂), 2.04-2.60 (m, 4 x CH₂), 2.85-3.11 (m, 2 x CH₂), 3.12-3.54 (m, CH and 2 x NCH₂N), 3.56-3.75 (m, 2 x NCH₂N), 4.00 and 5.99 (s, =CH); ¹³C-nmr (CDCl₃) δ 19.45 and 19.86, 22.74, 26.55 and 26.95, 28.92, 30.65 and 31.11, 48.72, 48.81 and 48.99, 49.64, 51.26, 54.69, 55.17, 59.52, 59.60 (CH₂), 66.83 and 67.34, 76.84 and 77.19, 83.61 and 83.85. 128.99 and 129.34 (CH), 111.64 (=C-); EI-mzs m/z: 336 (M⁺); Anal. Calcd for C₁₈H₃₂N₄O₂: C, 64.25; H, 9.59; N, 16.65. Found C, 64.32; H, 9.56; N, 16.59.

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