

THE FIRST FORMATION OF DIAZEPINODIAZEPINE AND DIAZEPINODIAZOCINE FROM ALLENEDICARBOXYLATE AND ACYCLIC TRIAMINES AND THEIR CONVERSION TO 12- AND 13-MEMBERED RING COMPOUNDS

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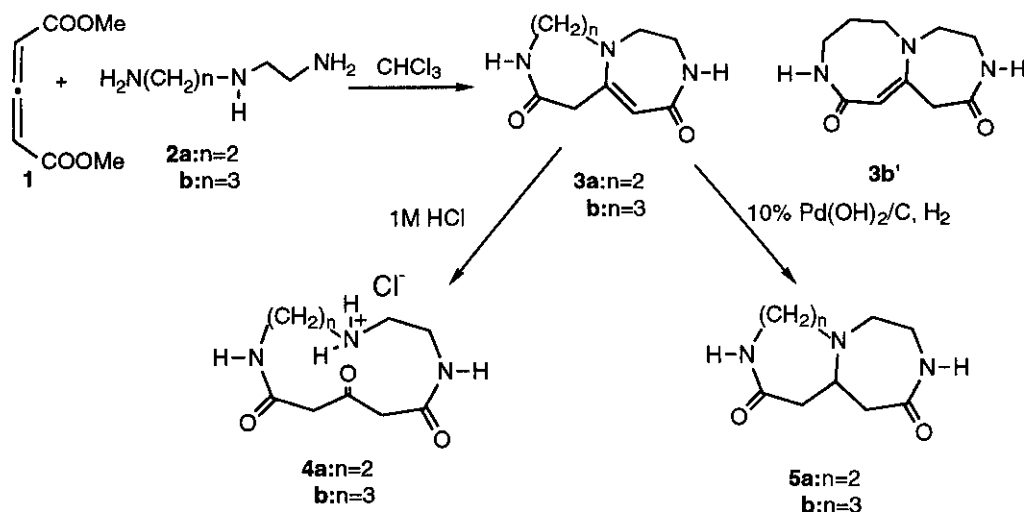
Abstract - The reaction of dimethyl allenedicarboxylate (1) with acyclic triamines (2) afforded a diazepinodiazepine (3a) and a diazepinodiazocine (3b), which were converted to the 12- and 13-membered compounds (4a-b).

In spite of the fact that numerous fused diazepine derivatives have been prepared,¹ the synthesis of diazepinodiazepine has not been reported except several diazepinodiazepines fused with phenyl rings from the corresponding ketones by the Schmidt reaction.² The preparation of diazepinodiazocine has been unknown so far.

Allenedicarboxylate is a useful reagent³ and has been utilized for the Michael addition reaction with bifunctionalized compounds leading to heterocycles.⁴ However, the reaction with trifunctionalized compound, acyclic triamine, has not been reported so far.

We report herein a facile preparation of the title compounds from dimethyl allenedicarboxylate (1) and acyclic triamines (2) and ring-

opening reactions leading to the macrocyclic compounds (**4**) (Scheme 1). The reaction of **1** with diethylenetriamine (**2a**) was carried out in chloroform at room temperature to give a diazepinodiazepinedione (**3a**) in 22 % yield. The structure of **3a** was assigned on the basis of spectral data and elemental analysis. The mass spectrum showed a molecular ion at m/z 195, which represents loss of two molecules of methanol from the sum of **1** and **2a**. The ^1H -nmr spectrum indicated a characteristic singlet for the β -olefinic proton of an enamine at δ 4.41 and a siglet for the methylene protons next to the carbonyl at δ 3.07. The ^{13}C -nmr spectrum



Scheme 1

using the DEPT technique showed both a quaternary α -carbon and a β -carbon signals for an enamine at δ 147.48 and 95.03, and two carbonyl carbon signals at δ 168.10 and 168.64. Compound **3a** was readily hydrolyzed with 1 M HCl to give a 12-membered ring compound, triazacyclododecane-trione (**4a**) in 81% yield. The ^{13}C -nmr spectrum supported the symmetric structure indicating two kinds of carbonyl carbon signals at δ 171.2 and 201.1 and three methylene carbon signals at δ 35.6 and 46.5 where one carbon signal is incidently overlapped. The ir spectrum showed two carbonyl absorptions at 1720 and 1655 cm^{-1} . Compound (**3a**) was

hydrogenated over 10% palladium hydroxide on charcoal to afford a perhydrodiazepinodiazepinedione (**5a**) in 89% yield. The structure of **5a** was also supported by its ^{13}C -nmr spectrum showing six methylene carbon, one methine carbon, and two carbonyl carbon signals.

The diazepinodiazocine (**3b** or **3b'**) was also obtained from **1** and *N*-(2-aminoethyl)-1,3-propanediamine (**2b**) by the same method. The ^{13}C -nmr spectral data was consistent with the structure of either isomer (**3b**) or (**3b'**); the spectral data could not discriminate the two structural isomers. Subjecting this compound to hydrolysis with 1 M hydrochloric acid afforded the 13-membered ring compound, triazacycloundecanetrione (**4b**) in 53% yield. The ^{13}C -nmr spectrum of **4b** exhibited seven methylene carbon and two carbonyl carbon signals. The ^1H -nmr spectrum showed broad signals for each methylene proton because compound (**4b**) exhibits several conformations in solution. Compound (**3b**) was converted to a perhydrodiazepinodiazocinedione (**5b**) in 44% yield by hydrogenation over 10% palladium hydroxide on charcoal.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Ir spectra were recorded with a JASCO IRA-1 grating spectrometer. ^1H -Nmr spectra (60 MHz) were measured with a Hitachi R 60 spectrometer. A JEOL JNM-GX400 spectrometer was used for both ^1H - (400 MHz) and ^{13}C -nmr (100 MHz) spectra. Mass (Ms) spectra were obtained with a JEOL JMS DX303 mass spectrometer.

4,5,8,9-Tetrahydro-3H,7H-[1,4]diazepino[4,5-d][1,4]diazepine-2,10-dione (3a)-----To a stirred solution of **2a** (1.03 g, 10 mmol) in CHCl_3 (25 ml) was added dropwise **1** (1.56 g, 10 mmol) under cooling with ice and water. After the reaction mixture was stirred for 12 h at room temperature, the CHCl_3 was evaporated to dryness and the residue crystallized by adding Et_2O -EtOH (1:1) was recrystallized from EtOH to give **3a** (0.43 g, 22%).

mp 282-283°C (decomp.). $^1\text{H-Nmr}$ (DMSO- d_6 , TMS) δ 3.07 (s, CH_2 , 2H), 3.21-3.26 (m, $2\times\text{CH}_2$, 4H), 3.47 (t, CH_2 , 2H, $J=4.3$ Hz), 3.58-3.61 (m, CH_2 , 2H), 4.41 (s, CH, 1H), 6.82 (s, NH, 1H), 7.21 (s, NH, 1H); $^{13}\text{C-nmr}$ (DMSO- d_6 , TMS) δ 41.23, 41.72, 44.84, 51.55, 56.53 (CH_2), 95.03 (CH), 147.48 ($-\overset{\text{I}}{\text{C}}-$), 168.10, 168.64 (C=O); ir (KBr) ν 3457, 3310, 1640, 1610, 1495 cm^{-1} ; Anal. Calcd for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.44; H 6.76; N, 21.43; ms (EI) m/z 195 (M^+), 180, 166, 153, 126, 109.

3,4,7,8,9,10-Hexahydro-3H,5H,12H- or 3,4,7,8,9,10-Hexahydro-1H,3H,5H-[1,4]diazepino[4,5-d][1,5]diazocine-2,11-dione (3b or 3b'): mp 280°C; Yield 0.17 g (16%); ir (KBr) ν 3275, 1657, 1610, 1498 cm^{-1} ; $^1\text{H-nmr}$ (DMSO- d_6 , TMS) δ 1.65 (m, CH_2 , 2H), 2.48 (s, CHH , 1H), 3.00-3.37 (m, $4\times\text{CH}_2$ and CHH , 9H), 4.52 (s, CH, 1H), 6.70 (br, NH, 1H), 7.17 (br, NH, 1H); $^{13}\text{C-nmr}$ (DMSO- d_6 , TMS) δ 30.57, 41.53, 44.90, 48.09, 48.73, 55.92 (CH_2), 96.11 (CH), 148.42 ($-\overset{\text{I}}{\text{C}}-$), 168.51, 168.85 (C=O); Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{N}_3\text{O}_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.55; H, 7.06; N, 19.80; ms (EI) m/z 209 (M^+) 180, 167, 140, 123.

1,4,7-Triazacyclododecane-8,10,12-trione Hydrochloride (4a) and 1,4,7-Triazacycloundecane-9,11,13-trione Hydrochloride (4b)-----A solution of 3 (5 mmol) in 1 M HCl (5 ml) was allowed to stand for 5 min. The aqueous solution was evaporated under reduced pressure. The resulting solids were washed with a small amount of cold EtOH to afford the trione (4). **4a**: mp 241-242°C; Yield 1.01 g (81%); ir (KBr) ν 3280, 3200, 1720, 1655 cm^{-1} ; $^1\text{H-nmr}$ (D_2O , DDS) δ 3.33-3.62 (m, $4\times\text{CH}_2$, 8H), 3.65 (s, $2\times\text{CH}_2$, 4H); $^{13}\text{C-nmr}$ (D_2O , DDS) δ 35.6, 46.5 (CH_2), 171.2, 201.1 (C=O); Anal. Calcd for $\text{C}_9\text{H}_{16}\text{N}_3\text{O}_3\text{Cl } 1/2\text{H}_2\text{O}$: C, 41.78; H, 6.62; N, 16.24. Found: C, 41.98; H, 6.40; N, 16.18.

4b: mp 210-211°C; Yield 0.70 g (53%); ir (KBr) ν 3320, 3200, 1710, 1665, 1640 cm^{-1} ; $^1\text{H-nmr}$ (D_2O , DDS) δ 1.86 (m, CH_2 , 2H), 3.09 (m, $2\times\text{CH}_2$, 4H), 3.24 (m, CH_2 , 2H), 3.38-3.44 (m, CH_2 , 2H), 3.50 (s, $2\times\text{CH}_2$, 4H);

^{13}C -nmr (D_2O , DDS) δ 17.58, 21.68, 36.37, 37.95, 45.32, 49.03, 56.95 (CH_2), 172.49, 173.62, 203.98 ($\text{C}=\text{O}$); Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{N}_3\text{O}_3\text{Cl}$: C, 45.54; H, 6.88; N, 15.93. Found: C, 45.69; H, 7.02; N, 15.87; ms (CI) m/z 228 ($\text{M}+1^+$), 210.

Hexahydro[1,4]diazepino[4,5-*d*][1,4]diazepine-2,10-dione (5a) and Hexahydro[1,4]diazepino[4,5-*d*][1,5]diazocine-2,11-dione (5b): A solution of 3 (5 mmol) in water (15 ml) was hydrogenated over 10% palladium hydroxide on charcoal (0.15 g) for 12 h. After the catalyst was filtered off, the filtrate was evaporated under reduced pressure. The residue was recrystallized from EtOH.

5a: mp 288-289°C; Yield 0.88 g (89%); ir (KBr) ν 3370, 3310, 1660, 1620 cm^{-1} ; ^1H -nmr (DMSO- d_6 , TMS) δ 2.12-3.49 (m, 6x CH_2 and CH 13H), 7.36-7.73 (m, 2xNH, 2H); ^{13}C -nmr (DMSO- d_6 , TMS) δ 36.64, 39.31, 40.63, 44.95, 45.81, 54.61 (CH_2), 65.46 (CH), 169.82, 174.56 ($\text{C}=\text{O}$); ms (EI) m/z 197 (M^+); Anal. Calcd for $\text{C}_9\text{H}_{15}\text{N}_3\text{O}_2$: C, 54.81; H, 7.67; N, 21.30. Found: C, 54.95; H, 7.61; N, 21.42.

5b: mp 220-221°C; Yield 0.46 g (44%); ir (KBr) ν 3300, 3240, 1660, 1640 cm^{-1} ; ^1H -nmr (DMSO- d_6 , TMS) δ 1.49 (m, CH_2 , 2H), 2.00-2.08 (m, CH_2 , 2H), 2.50-2.64 (m, CH_2 , 2H), 2.67-2.77 (m, CH_2 , 2H), 2.87-2.91 (m, CH_2 , 2H), 3.06-3.37 (m, 2x CH_2 and CH, 5H), 7.22 (br, NH, 1H), 7.51 (br, NH, 1H); ^{13}C -nmr (DMSO- d_6 , TMS) δ 32.34, 40.14, 41.69, 48.06, 55.92 (CH_2), 57.62 (CH), 175.01, 176.00 ($\text{C}=\text{O}$); ms (CI) m/z 212 ($\text{M}+1^+$).
Anal. Calcd for $\text{C}_{10}\text{H}_{17}\text{N}_3\text{O}_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 57.02; H, 8.25; N, 19.26.

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