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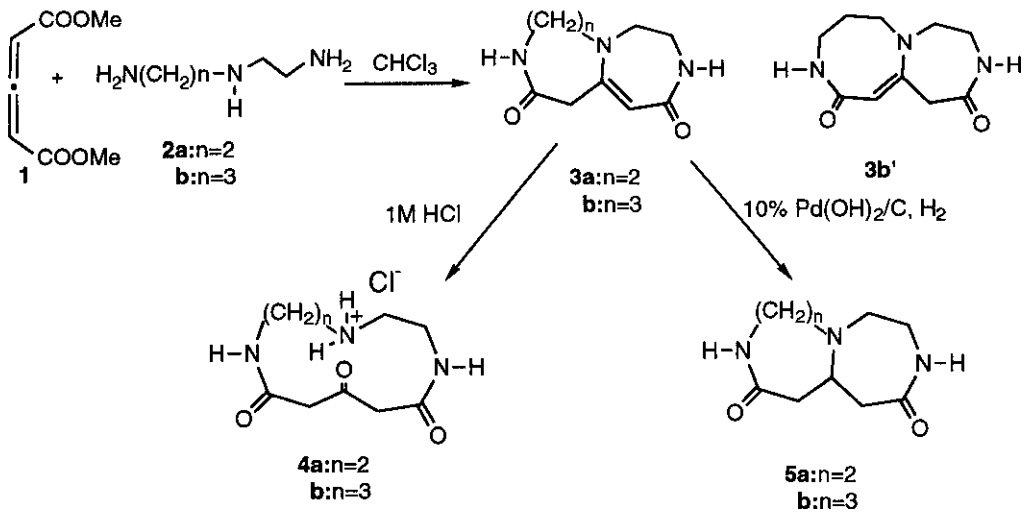
Abstract - The reaction of dimethyl allenedicarboxylate (**1**) with acyclic triamines (**2**) afforded a diazepinodiazepine (**3a**) and a diazepinodiazocine (**3b**), which were converted to the 12- and 13-membered compounds (**4a-b**).

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 reagent[3] 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 ^{1}H-nmr spectrum indicated a characteristic singlet for the β-olefinic proton of an enamine at δ4.41 and a siglet for the methylene protons next to the carbonyl at δ3.07. 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 δ147.48 and 95.03, and two carbonyl carbon signals at δ168.10 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 δ171.2 and 201.1 and three methylene carbon signals at δ35.6 and 46.5 where one carbon signal is incidently overlaped. 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 descriminate 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 ^{1}H-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. ^{1}H-Nmr spectra (60 MHz) were measured with a Hitachi R 60 spectrometer. A JEOL JNM-GX400 spectrometer was used for both ^{1}H-(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-3*H*,7*H*-[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}H-Nmr (DMSO-d_6, TMS) δ 3.07 (s, CH_2, 2H), 3.21-3.26 (m, 2xCH_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}C-nmr (DMSO-d_6, TMS) δ 41.23, 41.72, 44.84, 51.55, 56.53 (CH_2), 95.03 (CH), 147.48 (-C-), 168.10, 168.64 (C=O); ir (KBr) ν 3457, 3310, 1640, 1610, 1495 cm^{-1}; *Anal.* Calcd for $C_9H_{13}N_3O_2$: 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-3*H*,5*H*,12*H*- or 3,4,7,8,9,10-Hexahydro-1*H*,3*H*,5*H*-[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}H-nmr (DMSO-d_6, TMS) δ 1.65 (m, CH_2, 2H), 2.48 (s, C<u>H</u>H, 1H), 3.00-3.37 (m, 4xCH_2 and C<u>H</u>H, 9H), 4.52 (s, CH, 1H), 6.70 (br, NH, 1H), 7.17 (br, NH, 1H); ^{13}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 (-C-), 168.51, 168.85 (C=O); *Anal.* Calcd for $C_{10}H_{15}N_3O_2$: 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}H-nmr (D_2O, DDS) δ 3.33-3.62 (m, 4xCH_2, 8H), 3.65 (s, 2xCH_2, 4H); ^{13}C-nmr (D_2O, DDS) δ 35.6, 46.5 (CH_2), 171.2, 201.1 (C=O); *Anal.* Calcd for $C_9H_{16}N_3O_3Cl$ 1/2H_2O: 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}H-nmr (D_2O, DDS) δ1.86 (m, CH_2, 2H), 3.09 (m, 2xCH_2, 4H), 3.24 (m, CH_2, 2H), 3.38-3.44 (m, CH_2, 2H), 3.50 (s, 2xCH_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 (C=O); *Anal.* Calcd for $C_{10}H_{18}N_3O_3Cl$: C, 45.54; H, 6.88; N, 15.93. Found: C, 45.69; H, 7.02; N, 15.87; ms (CI) *m/z* 228 ($M+1^+$), 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}; ^{1}H-nmr (DMSO-d_6, TMS) δ 2.12-3.49 (m, 6xCH_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 (C=O); ms (EI) *m/z* 197 (M^+); *Anal.* Calcd for $C_9H_{15}N_3O_2$: 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}; ^{1}H-nmr (DMSO-d_6, TMS) δ1.49 (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, 2xCH_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 (C=O); ms (CI) *m/z* 212 $(M+1)^+$.

Anal. Calcd for $C_{10}H_{17}N_3O_2$: C,56.85; H, 8.11; N, 19.89. Found: C, 57.02; H, 8.25; N, 19.26.

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