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Oligomers from the Reaction of 1,2-Diaminoethane and Malonic Acid Derivatives - No Formation of 1,4-Diaza-5,7-cycloheptanedione

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Dedicated to Prof. Dr. G. Seitz, Marburg, on the occasion of his 60th birthday

Abstract. The reaction of 1,2-diaminoethane (**5**) with malonic acid derivatives (**6**, **7**, **8**, **10**) gives oligo- and polymers that were characterized by MALDI-ToF mass spectrometry. Literature reports that claimed the formation of the title compound in these reactions were critically evaluated and could not be confirmed.

The preparation of unsubstituted 1,4-diaza-5,7-cycloheptanedione (**1**) was claimed to have been achieved by several methods [1-4]. The ring system (Figure 1) is of importance in medicinal chemistry; examples are 1,5-benzodiazepine tranquilizers, e.g. clobazam (**2**) [5], and barbiturate analogs (**3**) [6]. Derivatives of the title compound have very recently been constructed as γ-turn mimetics, e.g. **4** [7]. During our own studies towards the design of scaffolds for peptidomimetics [8], we became interested in the preparation of the title compound.

We reinvestigated all published procedures, adding synthetic schemes of our own, and wish to clarify the situation in view of the importance of the parent ring system.

Results and Discussion

The literature physical data for 1,4-diaza-5,7-cycloheptanedione (**1**) differ considerably. Older references give only melting points and combustion analyses, the latter not very accurate [1,2]. The most recent paper claims to have purified it by column chromatography on silica gel, but at the same time states the solubility to have been too low for ^{1}H nmr measurement [4]. Another group found a decomposition temperature of 142 °C and determined the molecular mass of the monohydrate by the *Rast* method in camphor [3]. But we regard the substance to be too polar to be soluble in camphor, also

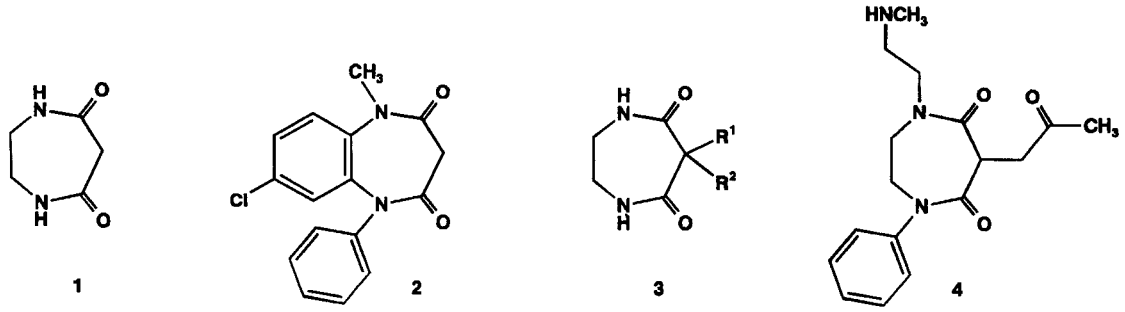

Fig. 1 1,4-Diaza-5,7-cyclohepanedione derivatives.

one usually gets mixed melting points well beyond the decomposition temperature.

All procedures used the reaction of 1,2-diaminoethane (**5**) with a malonic acid derivative. In our hands, unequivocal proof for the isolation of monomeric cyclic 1,4-diaza-5,7-cycloheptanedione (**1**) was obtained in no case. Instead, we isolated oligo- and polymers. Referring back to the literature data, we are convinced the discrepancies can be explained by this.

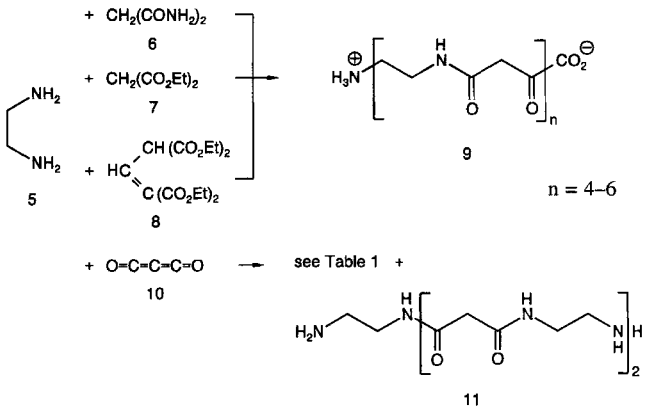

Fig. 2 Reaction of 1,2-diaminoethane (5) with malonic acid derivatives (**6**, **7**, **8**, **10**)

Malonodiamide (**6**), diethyl malonate (**7**) and tetraethyl propenetetracarboxylate (**8**), on heating with 1,2-diaminoethane (**5**), all gave a white powder, m.p. 270-280 °C (dec.). We found the average mass to be between 460 and 750 by titrimetric end group determination [11], corresponding to tetra- to hexameric oligoamide structures (**9**).

The reaction of carbon suboxide (**10**) and 1,2-diaminoethane (**5**) in ether provided two fractions. The smaller, soluble fraction had an average mass of 318 by end group determination. We assigned the constitution of a 3:2 oligoamide of diaminoethane and malonate (**11**) (calculated mass, 316). We used the new technique of matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI-ToF MS) [9,10] for the determination of the molecular mass distribution of the ethanol-insoluble main fraction. This method has gained interest recently for the characterization of polymers, including polyamides. The results are summarized in the Table.

Although relative intensities in this method have to be interpreted with great care, we assume the numbers to give a fair approximation of the product distribution in the present case of homologous structures. A linear or at best macrocyclic constitution was also confirmed by the presence of a strong infrared band at ca. 1550 cm^{-1} in all isolated materials, indicative of a *trans* amide configuration and excluding a seven-membered lactam structure. Combustion analyses of the products did not give accurate values which is not surprising since in our hands all procedures yielded varying mixtures of oligomers with 1–7 monomer units of both diaminoethane and malonic acid (Fig. 2). Several stepwise procedures we devised, *e.g.* using protein-synthesis derived reagents for forming amide bonds, applying high-dilution conditions, devising various stepwise procedures *etc. etc.*, also invariably led to the isolation of oligomers so that we conclude unsubsituted 1,4-diaza-5,7-cycloheptanedione (**1**) not to have been accessed as yet and perhaps not to be accessible at all due to its high oligomerization tendency.

Experimental

Melting points are uncorrected.– MALDI-ToF mass spectra were recorded on a Shimadzu Kratos Maldi III instrument in reflectron mode at 20 kV, mass spectra (EI mode, 70 eV; CI mode, isobutane) on a Vacuum Generators 7070 spectrometer.- IR spectra were run on a Perkin-Elmer 398 spectrometer. – ^1H and ^{13}C nmr spectra were recorded on a Jeol JNM-GX-400 spectrometer, referencing against solvent or TMS as internal and dioxan (69 ppm) as external standards.

Reaction of 1,2-diaminoethane (5) and malono-diamide (**6**)

1,2-Diaminoethane (**5**) (10.0 g, 0.17 mole) and malonodiamide (**6**) (17.0 g, 0.17 mole) were treated as described in reference [1] to give 19.8 g of a white powder, m.p. 270–280 °C (dec.); IR (KBr, ν, cm^{-1}): NH 3280, CO 1640 (br), HNCO 1550; ^1H-NMR (D_2O): δ 2.96 (br s, n H, CH_2CO), 3.48–3.60 (m, 2n H, CH_2N); ^{13}C-NMR (D_2O): δ 41.1, 41.6, 42.5, 43.1, 44.4, 45.3, 172.4, 172.6; MS (320 °C): m/z (%) 256 (0.7; dimer), 128 (10), 86 (100).– Ca. 200 mg were dissolved in

Table 1 MALDI-ToF-MS of the reaction product of 1,2-diaminoethane (**5**) and carbon suboxide (**10**) [13]. Higher oligomers (up to 15-oligomer) with low intensities

Mass	Relative Intensity (%)	Proposed Structure
445	27	$H_3N^+(CH_2)_2NH$ $[(CO)CH_2(CO)NH(CH_2)_2NH]_3H$
573	100	$H_3N^+(CH_2)_2NH$ $[(CO)CH_2(CO)NH(CH_2)_2NH]_4H$
701	47	$H_3N^+(CH_2)_2NH$ $[(CO)CH_2(CO)NH(CH_2)_2NH]_5H$
829	16	$H_3N^+(CH_2)_2NH$ $[(CO)CH_2(CO)NH(CH_2)_2NH]_6H$
957	12	$H_3N^+(CH_2)_2NH$ $[(CO)CH_2(CO)NH(CH_2)_2NH]_7H$

distilled water and titrated with 0.1 N hydrochloric acid (methylorange), giving an average molecular mass of 460–750 from several experiments [11]. Anal. Found: C 44.94; H 6.27; N 22.64. (Calcd. for $C_5H_8N_2O_2$ (128.15): C 46.86; H 6.31; N 21.87.)

Reaction of 1,2-diaminoethane (**5**) *and diethyl malonate* (**7**)*/tetraethyl propenetetracarboxylate* (**8**)

The reactions were performed according to the literature [1,2], yielding essentially the same product as the preceding reaction with malonodiamide.

Reaction of 1,2-diaminoethane (**5**) *and carbon suboxide* (**10**) (cf. [3,4])

A solution of 2.9 ml (0.043 mole) of the monohydrate of 1,2-diaminoethane (5) in 100 ml of diethyl ether was added to a solution of 2.9 g (0.043 mole) of carbon suboxide (10) [12] in 400 ml of ether with ice-cooling. The white precipitate was collected, washed with ether and dried. It was triturated with 200 ml of ethanol 96%. Evaporation of the ethanolic extract yielded 0.3 g, m.p. 268–280 °C (dec.). The residue amounted to 5.0 g, m.p. 200–270 °C (dec.); IR (KBr, ν, cm^{-1}): NH 3300, CO 1640 (br), HNCO 1560; ^{1}H-NMR (CF_3CO_2D): δ 3.36 (br s, n H, CH_2CO), 3.47–3.52 (br, m, 2n H, CH_2N), 7.47 (br, s, n H, NH); ^{13}C-NMR (D_2O): δ 40.0, 40.4, 40.8, 40.9, 41.1, 41.4, 41.9, 42.7, 162.7, 166.9; MS: (chemical ionization, isobutane) m/z (%) 385 (0.2; trimer + H^+), 257 (11; dimer + H^+), 129 (24; monomer + H^+), 87 (100); MALDI-ToF-MS: see Table. Anal. Found: C 42.75; H 6.94; N 21.68

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[13] Concentration: sample, 1–5 mg/ml water;
matrix: 10 mg 3-hydroxypicolinic acid/ml water

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