Formation of hexahydro-1,3,5-triazin-2-one and hexahydro-1,3,5-triazine-2-thione derivatives in reactions of glycylglycine with paraformaldehyde and *N,N'*-disubstituted ureas and thioureas

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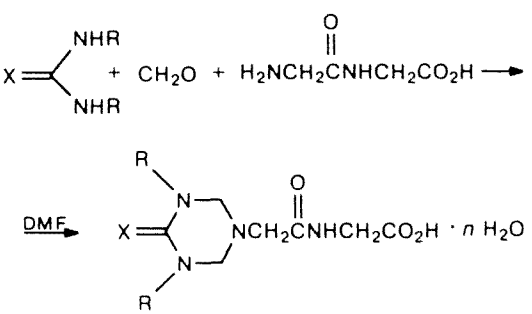
Hexahydro-1,3,5-triazin-2-one and hexahydro-1,3,5-triazine-2-thione derivatives were shown to be formed selectively in reactions of glycylglycine with paraformaldehyde and *N,N'*-dialkylureas, *N,N'*-diethylthiourea, and glycoluril.

Key words: hexahydro-1,3,5-triazin-2-one, hexahydro-1,3,5-triazine-2-thione, *N,N'*-dialkylureas, *N,N'*-diethylthiourea, glycoluril, paraformaldehyde, glycylglycine, dimethylformamide.

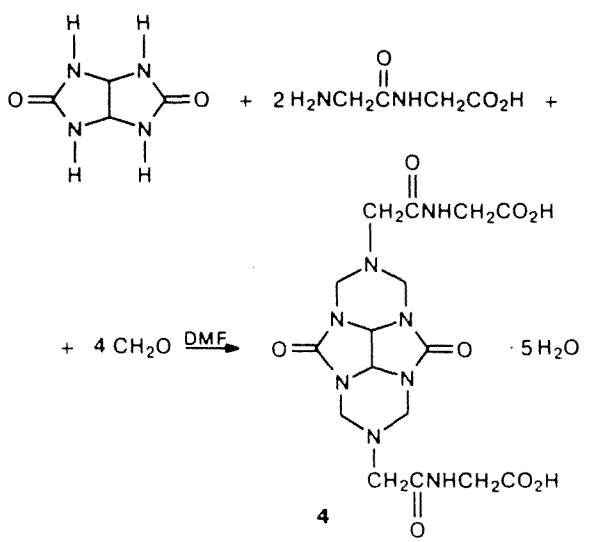
Amides of α-amino acids are known to react with formaldehyde to give imidazolidin-4-ones resulting from intramolecular condensation with participation of the amino and amido groups.[1—4] We showed that the interaction of reactants of this type in the presence of *N,N'*-disubstituted ureas or *N,N'*-disubstituted thioureas follows a different pathway and affords derivatives of hexahydro-1,3,5-triazin-2-ones. For example, in the reaction of glycylglycine with two equivalents of anhydrous paraformaldehyde and one equivalent of *N,N'*-dimethyl- or *N,N'*-diethylurea, we isolated 1,3-dimethyl- or 1,3-diethylhexahydro-1,3,5-triazin-2-one (**1** or **2**), respectively. The reaction of glycylglycine with *N,N'*-diethylthiourea gave 1,3-diethylhexahydro-1,3,5-triazin-2-thione (**3**). It is advisable to carry out the condensation in dimethylformamide, which ensures complete dissolution of the starting compounds. The yields of compounds **1**—**3** under these conditions are 88 %, 62 %, and 41 %, respectively.



1: R = Me, X = O, *n* = 1 (88 %)
2: R = Et, X = O, *n* = 0 (62 %)
3: R = Et, X = S, *n* = 0 (41 %)

In the case of glycoluril, both urea fragments participate in the condensation with paraformaldehyde and glycylglycine. Based on the IR and ^{1}H NMR spectra and the results of elemental analysis of the reaction product and resorting to the analogies reported in the literature[5] we assigned the structure of tetracyclic bisurea (**4**) to it. The yield of adduct **4** is 50 %.

According to the results of elemental analysis and the Fisher determination of the water content, compounds **1** and **4** isolated from the reaction mixtures incorporate one and five water molecules, respectively, whereas products **2** and **3** contain no water. The proportion of water can be decreased by drying the compounds under reduced pressure. For example, by keeping the monohydrate of 1,3-dimethylhexahydro-1,3,5-triazin-



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2-one **1** and the pentahydrate of 5,11-bis[2′-oxo-2′-(carboxymethylamino)ethyl-1′]-2,8-dioxo-1,3,5,7,9,11-hexaazatetracyclotetradecane **4** at 50—70 °C and 2 Torr for 12 h, we obtained anhydrous samples of compounds **1** and **4**, which transformed into the corresponding hydrated forms on standing in air.

Thus, we were first to demonstrate the possibility of the selective formation of hexahydro-1,3,5-triazin-2-one and hexahydro-1,3,5-triazine-2-thione derivatives in the reactions of amides of α-amino acids (or dipeptides) with formaldehyde and urea derivatives.

Experimental

The IR spectra of solids were recorded for samples pressed with KBr on a Specord-IR-75 instrument. The ^{1}H NMR spectra were obtained in DMSO-d_6 on a Bruker AM-300 spectrometer operating at 300.13 (^{1}H) MHz. Chemical shifts for the ^{1}H signals were referred to DMSO-d_6 (δ, 39.5).

1,3-Dialkyl-5-[2′-oxo-2′-(carboxymethylamino)ethyl-1′]-hexahydro-1,3,5-triazin-2-ones (1, 2); 1,3-diethyl-5-[2′-oxo-2′-(carboxymethylamino)ethyl-1′]hexahydro-1,3,5-triazine-2-thione (3); 5,11-bis[2′-oxo-2′-(carboxymethylamino)ethyl-1′]-2,8-dioxo-1,3,5,7,9,11-hexaazatetracyclo[7,3,1^{1,9},1^{3,7},0^{13,14}]tetradecane (4). A mixture consisting of dialkylurea (diethylthiourea or glycoluril) (1.7 mmol), glycylglycine (1.7 mmol) (or 3.4 mmol in the case of **4**), and paraformaldehyde (3.4 mmol) (6.8 mmol in the case of **4**) was dissolved in DMF (1 mL) at 60—80 °C. The reaction mixture was kept for 24 h at ~20 °C, diluted with ether, and allowed to stand for 2—3 h at +5 °C. The solvent was decanted. Compounds **1**—**4** were isolated as described below. The monohydrate of compound **1** crystallized on treating the oily residue with acetone; 0.36 g of compound **1** · H_2O was obtained, yield 81 %, m.p. 66—68 °C. ^{1}H NMR (DMSO-d_6), δ: 2.71 (s, 6 H, CH_3); 3.37 (s, 2 H, NH—$\underline{CH}_2$—C); 3.78 (d, 2 H, N—CH_2—C, J = 5.5 Hz); 4.15 (s, 4 H, N—CH_2—N); 8.19 (t, 1 H, NHCO, J = 5.5 Hz). IR (ν/cm^{-1}): 1615—1625 (N$\underline{C}$ON); 1670 (CONH); 1730 (CO_2); 3390 (NH). Found (%): C, 41.37; H, 7.00; N, 21.30. $C_9H_{16}N_4O_4 \cdot H_2O$. Calculated (%): C, 41.22; H, 6.87; N, 21.37. An anhydrous sample of compound **1** was obtained by drying the monohydrate at 2 Torr and a temperature of 50 °C for 12 h. Found (%): C, 43.40; H, 7.07; N, 24.05. $C_9H_{16}N_4O_4$. Calculated (%): C, 44.20; H, 6.55; N, 22.95.

In the case of compounds **2** and **3**, the oily residue was kept at 2 Torr and at 50 °C for 4 h and treated with an ether—acetone mixture (4:1), the precipitate was filtered off and dried in an air flow to give 0.9 g of compound **2**, yield 62 %, m.p. 130—134 °C. ^{1}H NMR (DMSO-d_6) δ: 0.97 (t, 6 H, CH_3, J = 7.0 Hz); 3.16 (q, 4 H, OCH_2, J = 7.0 Hz); 3.32 (s, 2 H, N—CH_2—C); 3.80 (d, 2 H, NH—$\underline{CH}_2$—C, J = 6.0 Hz); 4.18 (s, 4 H, N—CH_2—N); 8.16 (t, 1 H, NHCO, J = 6.0 Hz). IR, ν/cm^{-1}: 1600—1620 (N$\underline{C}$ON); 1680 (CONH); 1750 (CO_2); 3360 (NH). Found (%): C, 47.78; H, 7.52; N, 20.42; $C_{11}H_{20}N_4O_4$. Calculated (%): C, 48.53; H, 7.35; N, 20.58. Compound **3** (0.20 g) was obtained in a similar way (after reprecipitation with ether from a methanolic solution), yield 41 %, m.p. 147—151 °C. ^{1}H NMR (DMSO-d_6), δ: 1.07 (t, 6 H, CH_3, J = 6.4); 3.25 (s, 2 H, N—CH_2—C); 3.68 (q, 4 H, OCH_2, J = 6.4 Hz); 3.77 (d, 2 H, NH—$\underline{CH}_2$—C, J = 6.0 Hz); 4.31 (s, 4 H, N—CH_2—N); 8.23 (t, 1 H, NHCO, J = 5.5 Hz). IR, ν/cm^{-1}: 1650 (CONH); 1760 (CO_2); 3410 (NH).

The pentahydrate of compound **4** was isolated by crystallization from water; 0.48 g of compound **4** · $5H_2O$ was obtained, yield 52 %, m.p. 137—142 °C. Found (%): C, 35.62; H, 5.84; N, 20.64; H_2O, 16.42. $C_{16}H_{22}N_8O_8 \cdot 5H_2O$. Calculated (%): C, 35.29; H, 5.88; N, 20.58; H_2O, 16.50. An anhydrous sample of compound **4** was obtained by drying the pentahydrate for 12 h at 2 Torr and 70 °C. ^{1}H NMR (DMSO-d_6) δ: 3.26 (s, 4 H, N—CH_2—C); 3.80 (d, 4 H, NH—$\underline{CH}_2$—CO, J = 6.7 Hz); 4.38 (d, 4 H, CH_2, J = 13.5 Hz); 4.65 (d, 4 H, CH_2, J = 13.5 Hz); 5.65 (s, 2 H, CH); 7.95 (t, 2 H, NHCO, J = 5.0 Hz). In the ^{1}H NMR spectrum of $C_{16}H_{22}N_8O_8 \cdot 5H_2O$: 3.30—3.90 (m, H_2O). Found (%): C, 42.56; H, 5.12; N, 24.48; $C_{16}H_{22}N_8O_8$; Calculated (%): C, 42.29; H, 4.84; N, 24.67.

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