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Formation of 5,6-cyclopentano-uracil by cyclization of the bisamide of adipic acid induced by oxalyl chloride

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ABSTRACT

Cyclization of the bisamide of adipic acid induced by oxalyl chloride will eventually yield a product of the composition $C_9H_8N_2O_5$, which upon hydrolysis gave 5,6-*cyclo*-pentanouracil. The structures of both compounds were established by X-ray crystallography.

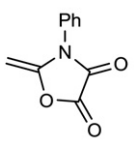
1. Introduction

The 7-azaindole derivative **1** has been considered to be the active principle in the defencive secretion of the millipede *Rhinocricus padbergi*.[1,2] The purported identification (MS and retention times) relies on its identify with a compound obtained by treating the bisamide of adipic acid with oxalyl chloride to give a product with the composition $C_9H_8N_2O_5$ and assigned (in 1968) structure **2**. In a final step this molecule was reacted with hydrazine hydrate (or aniline), which removed the elements of $CO+CO_2$ to give the final product with the composition $C_7H_8N_2O_2$, which was considered to be the 7-azaindole derivative **1**.[3]

If correct this extraordinary condensation at an unactivated methylene group during the transformation of **2** to **1** would be truly remarkable (Scheme 1).

Reactions of carboxylic acid amides with oxalyl chloride have been studied in detail already during the early 1960s[4–6] and the predominant products are acyl isocyanates. The acyl isocyanate derived from adipic acid amide was indeed formed and reported in the paper from 1968.[3] With this in mind we considered that adipoyl isocyanate **3** might undergo intramolecular cyclizations as outlined in Scheme 2. Such a cyclization will draw on the high electrophilicity of the acyl carbonyl group in combination with that enolization will now be possible via the carbonyl group on the other side. It is quite conceivable that this process is initiated by *O*-acylation of **3** or its enol **4** with oxalyl chloride. The suggested intermediate **5** will subsequently undergo cyclization to yield finally **7** (after reaction with water and elimination of CO_2 and HCl).

In other words the real structure of the previously reported compound **2** should be that of **7** and likewise the purported azaindole derivative **1** consequently must be quite another heterocycle, namely 5,6-cyclopentano-uracil **6**, a molecule known and synthesized since 1947.[7–11] The structure of **6** obtained as described in Scheme 2 was fully confirmed by an independent synthesis starting by condensation of 2-carbethoxycyclopentanone with thiourea. This compound (a thio derivative of **6**) was in a final step converted to the fused uracil derivative **6** under acidic conditions. Compound **7** featured a diagnostic CH signal at 48.2 ppm in the ^{13}C NMR spectrum, which is incompatible with the originally assigned structure. Formation of oxazolidine-4,5-diones when various amide type molecules are treated with oxalyl chloride has previously been observed on several occasions. Thus acetanilide yields 2-methylene-1-phenyloxazolidine-4,5-dione **8** and glutarimide will give oxazolidine-4,5-dione **9**.[12,13] The assigned structures of **6** and **7** were fully confirmed by analysis by X-ray crystallography.



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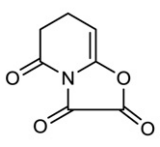

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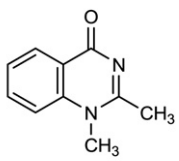

10

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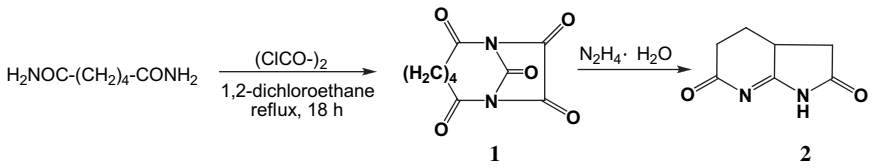
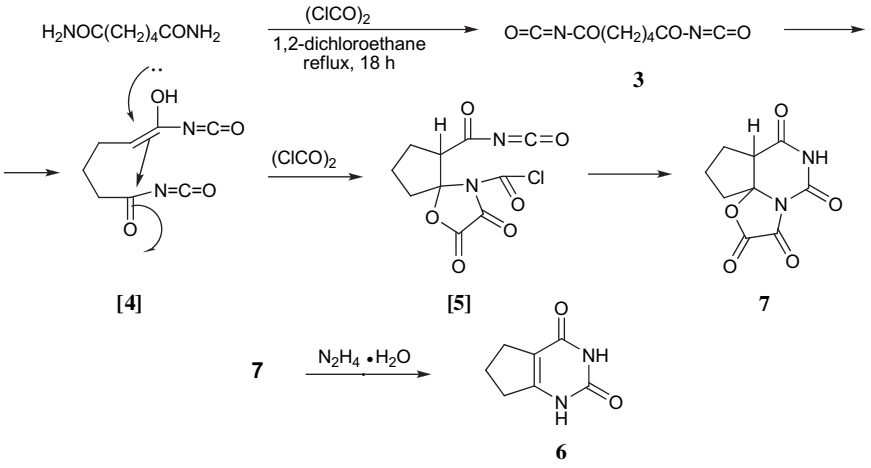


Scheme 1. (From Ref. 3).



Scheme 2.

Finally, from the data available in the literature and those presented here we consider it likely that the active principle in the defence secretion of the millipede *R. padbergi* is 5,6-cyclopentanouracil **6**. Interestingly another defence compound isolated from the millipede *Glomeris marginata*,[14,15] glomerin **10**, has a somewhat related structure, i.e., both are fused pyrimidine derivatives.

The crystal structures of **6** and **7** were determined by X-ray crystallographic analysis, the details of which are given in the Experimental section. The molecular structure and the unit cell of **6** are shown in Figure 1. The molecules are linked together via both monomeric and dimeric N–H···O=C hydrogen bonds to form an infinite two-dimensional network. The packing coefficient (percent

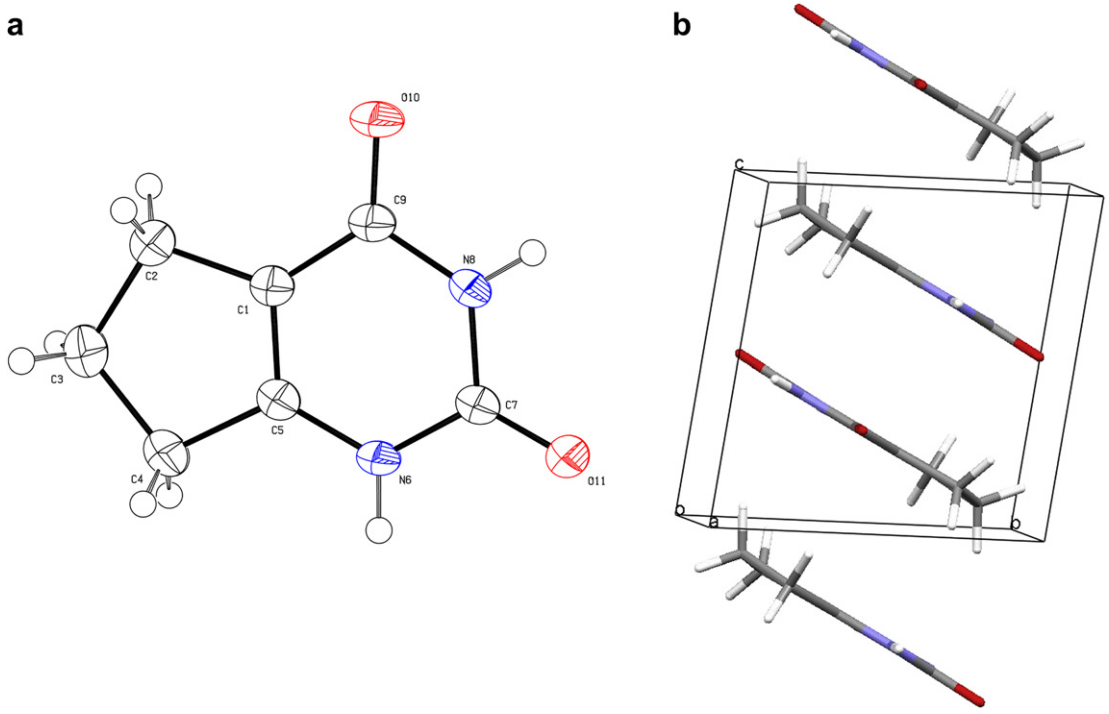


Figure 1. The molecular (a) and crystal structure (b) of **6**.

filled van der Waals space in the unit-cell) is 71.9%, indicating an efficient molecular framework in the solid-state. The molecular packing is also facilitated by stacking and vdW interactions. The distance between the planes of two adjacent aromatic moieties is approximately 3.3 Å.

The molecular and crystal structure of **7** is shown in Figure 2. The molecules are linked together via N–H···O=C hydrogen bonds as well as several strong vdW interactions. The traditional hydrogen bonds form infinite chains along the *a*-axis. The packing coefficient is 73.2%, indicating a very efficient molecular packing in the solid-state. Some unusually short intermolecular contacts are present in the crystal structure, which is probably a result of the efficient molecular packing.

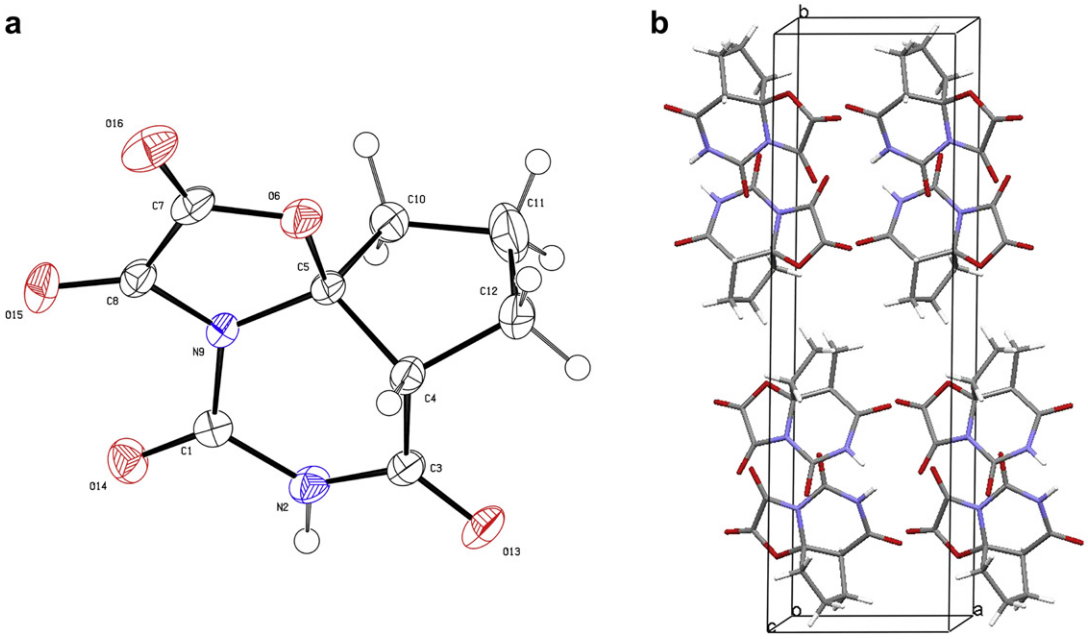


Figure 2. The molecular (a) and crystal structure (b) of **7**.

2. Conclusions

It has been demonstrated that a simple aliphatic starting material (hexane 1,6-diamide) can be converted to fused pyrimidine derivatives. This type of cyclizations should be extendible to, e.g., pentane 1,5-diamide and suitable monoamides.

3. Experimental

3.1. General

Melting points were uncorrected and determined using a Büchi B-545 apparatus. Melting points >300 °C are not listed. NMR spectra were obtained in DMSO-d_6 on a Bruker 300 MHz. Infrared spectra were recorded with an Avatar 330 FT-IR apparatus (Thermo Nicolet).

Compound **7**. To a suspension of a hexane 1,6-diamide (adipamide) (7.2 g, 50 mmol) in dichloromethane (250 mL) oxalyl chloride (12 mL) was added and the mixture was heated at reflux temperature for 18 h. After that period the brown solid formed was collected and recrystallized (with addition of active carbon) from acetone, 3.6 g (33%), mp: 312–314 °C. The sample used for X-ray analysis was repeatedly recrystallized from acetone. IR 3200, 3118, 2973, 1824, 1810, 1730, 1704, 1378, 1349, 1299, 1209, 1122, 1009, 748 cm^{-1}; ^1H NMR 1.75 (t, 2H), 2.06–2.16 (m, 4H), 3.22 (d, 1H), 11.5 (s, 1H); ^{13}C NMR δ (DMSO-d_6, 75 MHz) 19.6 (t), 24.4 (t), 35.5 (t), 48.2 (d), 98.2 (s), 144.6 (s), 151.1 (s), 156.1 (s), 170.3 (s).

3.1.1. 5,6-Cyclopentano-uracil. Compound **7** (1.12 g, 10 mmol) and hydrazine hydrate (3 mL) in ethanol (40 mL) were heated at reflux for 15 min and filtered, solid formed upon concentration and cooling was collected, 530 mg (67%), mp: 280 °C dec. The ^{13}C and ^1H NMR data were in agreement with those in the literature.[11]

3.2. Single-crystal X-ray analysis

X-ray structures were recorded at 200 K on a BrukerApexII diffractometer with graphite-monochromated Mo K(α) radiation. Lattice parameters were obtained by least-squares fits to the scattering angles of reflections observed in several pre-scans. The intensity data collection was performed by ω and φ scans; all raw data were corrected for Lorentz and polarization effects. The structures were solved by direct methods and refined by full matrix least-squares analyses with anisotropic temperature factors for all atoms except protons. Proton positions were calculated using known molecular geometries, refined in riding mode with fixed isotropic temperature factors.

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