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Stereochemistry of the intermediates in the synthesis of 1,4,7,10-tetraazacyclododecane from triethylenetetramine, glyoxal and diethyl oxalate

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Abstract—The equilibrium and rearrangement phenomena encountered in two steps for the synthesis of 1,4,7,10-tetraazacyclododecane from triethylenetetramine, glyoxal and diethyl oxalate were studied and elucidated after the development of two micellar electrokinetic chromatographic (MEKC) methods. The latter were able to separate: (i) the four bis-aminals (**2**–**5**) obtained from the condensation of triethylenetetramine with glyoxal; (ii) the four diones (**6**–**9**) derived from the reaction of the bis-aminals with diethyl oxalate, whose solid state structures were determined by single crystal X-ray diffraction. The three not yet reported diones (**6**, **7** and **9**) were synthesised by taking advantage of both the reaction conditions and the use of a particular catalyst (MeONa). A plausible reaction mechanism, as well as a discussion of the solid state structures, is presented.

1. Introduction

Within the past two decades, the importance of 1,4,7,10-tetraazacyclododecane (cyclen, **1**) has continuously grown since it became an intermediate for the synthesis of chelating agents, which found applications in diagnostics and therapeutics.[1] In particular, the complexes of such ligands with paramagnetic metal ions, like the gadolinium ion, are largely used as magnetic resonance imaging (MRI) contrast agents.[2] Accordingly, a series of synthetic routes to cyclen appeared in the literature[3–12] and we wish to report here some recent findings regarding one of those synthetic paths.[4–7,9]

2. Results and discussion

The reaction of triethylenetetramine with glyoxal affords a mixture of four bis-aminals, i.e., *cis*-octahydro-3*H*,6*H*-2*a*,5,6,8*a*-tetraazacenaphthylene (**2**), *trans*-octahydro-3*H*,6*H*-2*a*,5,6,8*a*-tetraazacenaphthylene (**3**), *cis*-decahydro-diimidazo-[1,2-a:2′,1′-*c*]pyrazine (**4**) and *trans*-decahydro-diimidazo-[1,2-a:2′,1′-*c*]pyrazine (**5**).[6,7,10] By amidation with diethyl oxalate (DEO), the related mixture containing *cis*-octahydro-2*a*,4*a*,6*a*,8*a*-tetraazacyclopent[*fg*]acenaphthylene 1,2-dione (**6**), *trans*-octahydro-2*a*,4*a*,6*a*,8*a*-tetraazacyclopent[*fg*]acenaphthylene 1,2-dione (**7**), *cis*-octahydro-2*a*,4*a*,6*a*,8*a*-tetraazacyclopent[*fg*]acenaphthylene 3,4-dione (**8**) and *trans*-octahydro-2*a*,4*a*,6*a*,8*a*-tetraazacyclopent[*fg*]acenaphthylene 3,4-dione (**9**) is obtained.[6] The subsequent reduction of the amide carbonyls, followed by removal of the central bridging moieties of compounds **10** and **11**, leads to **1** (see Scheme 1).[6,7]

The composition of the mixture containing **2**–**5** was at first determined by means of NMR studies, which were in accordance with those reported in the literature,[10,13] and showed that **2**, the thermodynamically favoured product, was predominant in reactions carried out in water at 5 °C in the presence of $Ca(OH)_2$ (Bracco procedure)[5,6] while **5**, the kinetically favoured product, was the major component working in EtOH at rt (Nycomed procedure).[7] By means of GC analysis,[5,6] we could detect the couple of compounds **2**+**3** and **4**+**5** but we did not make further efforts to find the conditions that are able to separate them. Indeed, we could not exclude that the harsh conditions used for the GC analysis might affect the composition of the mixture, as it is known[10,13] that isomerisation may occur. Accordingly, a micellar electrokinetic chromatographic (MEKC) method was developed to allow the separation of the four isomers and their quantification. Analytical results, obtained using

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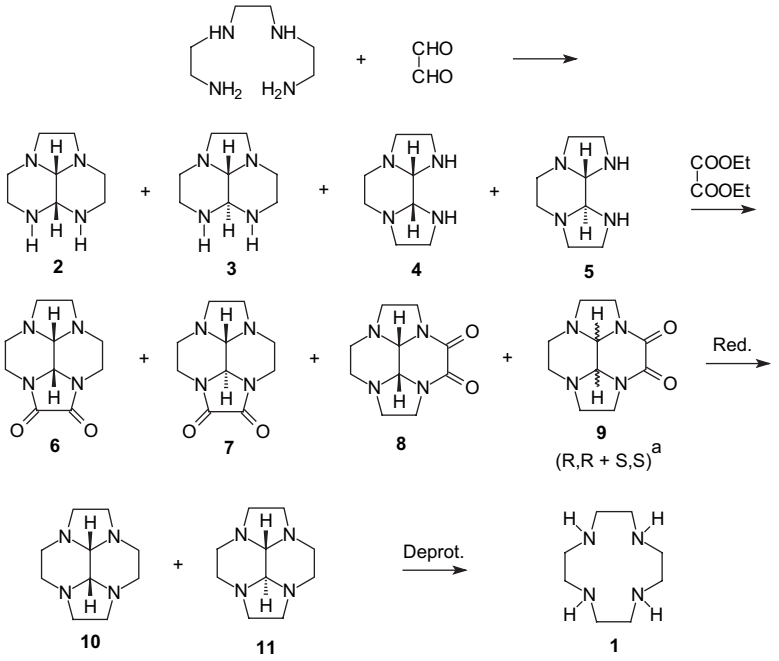

Scheme 1. [a]Both enantiomers of **9** are present in the solid state, as crystallised in an achiral space group.

both synthetic procedures for the preparation of **2–5** mixtures, are reported in Table 1.

As partly anticipated, the composition of the mixtures greatly depends on the reaction conditions. In particular: (i) in water at 5 °C in the presence of $Ca(OH)_2$,[5,6] **2** is formed as the main component, followed by **5**. Compound **3** is present in low percentage, while **4** only appears in a late reaction stage (entries 1–4); (ii) in EtOH at rt,[7] **5** is largely predominant along with **4** while **2** and **3**, which were derived from an isomerisation, are formed in small percentages only after the work up (entries 5 and 6). These results confirm those obtained from NMR studies and reported in the literature.[13]

We subsequently checked the stability of the mixtures obtained with the Bracco procedure,[5,6] especially under the reaction conditions used in the following step (reflux in EtOH, without or with a catalyst). The results are summarised in Table 2.

In particular: (i) the mixture stored at rt changed its composition over time: the content of the trans isomers increased whereas the content of the cis isomers decreased (entry 3 vs entry 1); (ii) heating at reflux a solution in EtOH led to an increase in the content of **3** and a decrease in the content of **2** while no significant change in the content of the other isomers was observed (entry 2 vs entry 1); (iii) heating at reflux a solution in EtOH, in the presence of MeONa, had almost no influence on the composition of the mixture (entry 4 vs entry 3).

Later on, we reacted mixtures having different compositions in each of the **2–5** isomers with DEO in EtOH under the conditions reported in Section 4. As we observed that compounds **4** and **5** were more reactive than **2** and **3**, we took advantage of this peculiarity for the preparation of pure **8** and **9**. Indeed, the reactions were performed, without or with MeONa, using about half of theoretical DEO. The latter preferentially reacted with **4** and **5** affording mixtures enriched with **8** and **9** from which the isolation of the products resulted easier. The work up of the different reaction mixtures allowed us to obtain pure **6**, **7**, **8** and **9** as crystals suitable for the determination of the solid state structure by single crystal X-ray diffraction (the structure of **8** was already reported in the literature[9]). After a MEKC method for the separation of each of the four isomers was devised, we were able to follow the amidation reaction, which was performed using the mixture reported in Table 1, entry 4, without or with a catalyst. Quite interestingly, even in the

Table 1. Percentages of the mixture containing **2–5** determined by MEKC

Entry[a]	2	3	4	5
1[b]	74.8	4.5	—[c]	20.7
2[d]	77.0	4.4	—[c]	18.6
3[e]	71.3	4.0	7.0	17.7
4[f]	70.2	5.9	6.0	17.9
5[b]	—[c]	—[c]	12.3	87.6
6[f]	6.6	5.7	11.9	75.8

[a] Entries 1–4: prepared according to Bracco procedure;[5,6] entries 5 and 6: prepared according to Nycomed procedure.[7]
[b] Reaction (0.5 h).
[c] Not detected.
[d] Reaction (2 h).
[e] Reaction (18 h).
[f] Isolated product.

Table 2. Percentages of the mixture containing **2–5** determined by MEKC

Entry	2	3	4	5
1[a]	70.2	5.9	6.0	17.9
2[b]	63.2	13.0	6.2	17.6
3[c]	68.8	9.6	2.6	19.0
4[d]	67.9	10.2	2.4	19.5

[a] Starting material.
[b] Mixture of entry 1 heated for 10 h in EtOH at reflux.
[c] Mixture of entry 1 reanalysed after one month at rt.
[d] Mixture of entry 3 heated for 10 h in EtOH at reflux in the presence of MeONa (1 mol equiv).