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A new route to cyclen, cyclam and homocyclen.

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Abstract: Cyclen, cyclam and homocyclen have been synthesized from the corresponding butanedione-protected linear tetramines. The cyclization step is followed by a facile deprotection of the rigidifying moiety.

Keywords: Bis-aminals; butanedione; cyclization; tetraazamacrocycles.

Over the last years the growing interest for tetraazamacrocycles has found its justification in their remarkable complexing[1] properties whose area can be widely extended by introducing one or more side-chain functions.[2] However, access to the macrocycle structure remains very difficult as indicated by the high cost of the different tetraazamacrocycles commercially available. Various macrocycle syntheses have been reported in literature. Recently, Weisman *et al.*[3] have proposed a novel three-step synthesis of cyclen from triethylenetetramine *via* a dithiooxamide intermediate. Nevertheless, the most usual method remains that of Richman and Atkins,[4] along with its variant.[5a, b] It consists in condensing linear N-tosylamides with a bis-electrophile reagent. This quite general method was applied to prepare many polyazamacrocycles. However, one of its major drawbacks is that it is not "atom-economic".[6]

We report here a new and efficient synthesis of cyclen, cyclam and homocyclen starting from a linear tetraamine rigidified by condensation with a dicarbonyl compound. Many compounds issued from glyoxal condensation on tetraamines have been described in the literature,[7a, b, c] however, to our knowledge, it seems that these bis-aminal intermediates have seldom been considered as precursors of macrocycles.[8a, b] Several reasons can be put forward:

First, glyoxal-linear tetraamine condensation can lead to four stereoisomers,[7b] it is not certain that all these stereoisomers can be successfully condensed with a bis-electrophile derivative to give the macrocyclic intermediates. Moreover it is well known that the macrocyclic bis-aminals, easily obtained from the reaction between glyoxal and a macrocycle, are very stable and resist to acid hydrolysis conditions as well as to various reducing agents.[9a, b] More complex deprotection reactions by hydroxylamine-[8a] or oxidant agents-[8b] action have been recently proposed to released the macrocycle after cyclization step.

Taking into account these various points, butanedione appeared to be an interesting alternative to glyoxal. The following bis-aminals, **1a**, **1b**, **2** and **3**, were easily obtained through a simple condensation of butanedione with the corresponding tetraamine in CH_3CN.[10] Compound **2** has already been reported by

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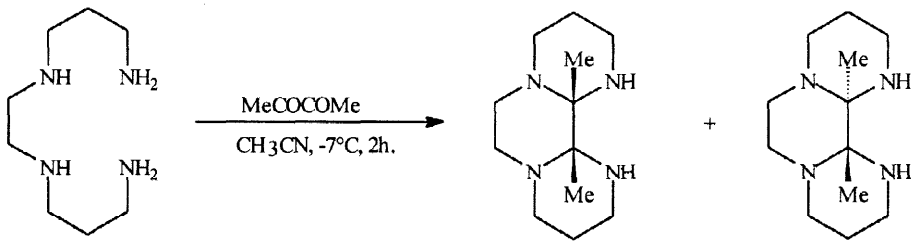
Stetter,[11] but no data on its configuration were available. To our knowledge, **1a**, **1b** and **3** have never been described.

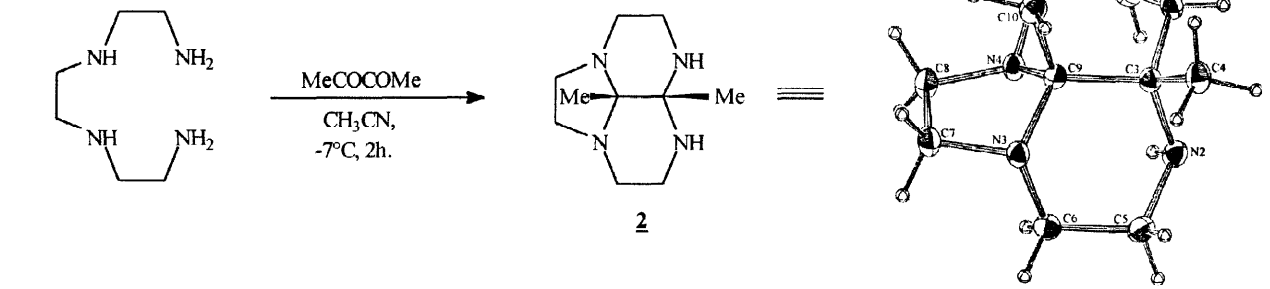
As observed for glyoxal,[7b] the linear-tetraamine butanedione-condensation led also to the most stable product characterized by a maximum of six-membered fused rings. Thus, butanedione condensation with N,N'-bis(3-aminopropyl)ethylenediamine gave a mixture of two compounds, **1a** and **1b** having two vicinal secondary amine functions (scheme 1).



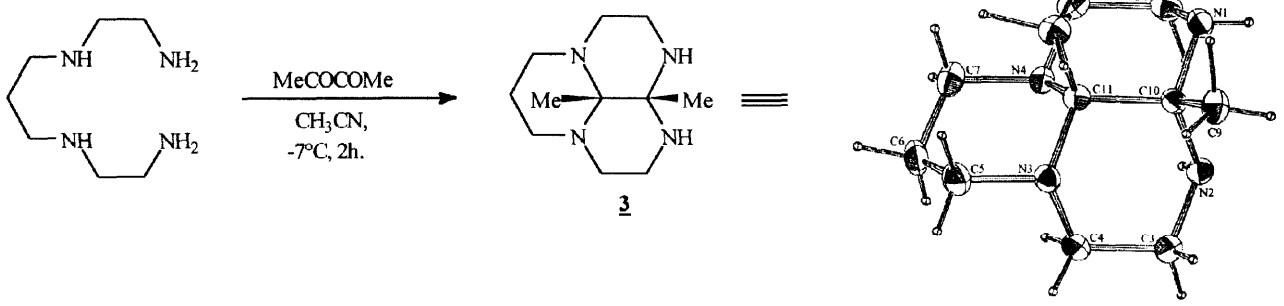
1a **1b**

Scheme 1

The former was predominant (75%) and exhibited exchange phenomena as observed by temperature dependent ^{13}C NMR studies. This result is consistent with conformationaly labile *cis* fused cycles. The spectrum of **1b**, which also possessed only one aminal-type carbon, was not altered by temperature changes. This compound is therefore rigid and totally symmetric, *i.e.* in *trans* configuration. Attempts to cyclize these compounds with electrophiles such alkyl dibromides or ditosylates failed, probably because the two secondary nitrogen functions are not correctly positioned for a (1+1) cyclocondensation, as suggested by molecular model examinations. By contrast, butanedione reacted with N,N'-bis(2-aminoethyl)-1,3-propanediamine and triethylenetetramine to give only the tricyclic bis-aminals **2** and **3** respectively (scheme 2).



2

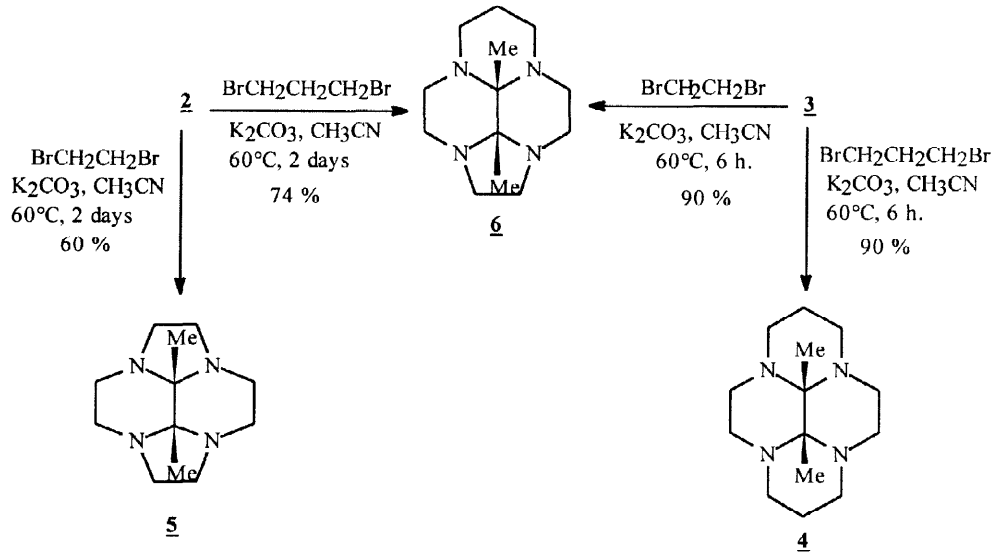


3

Scheme 2

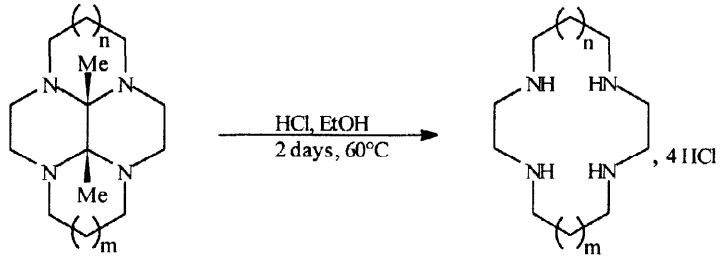
These two compounds also exhibited exchange phenomena followed by ^{13}C NMR studies at variable temperature. Consequently, both compounds have also their methyl groups in a *cis*-configuration. In addition, whatever the temperature set, aminal-type carbons were never equivalent. These observations are in favor of the following structure for compounds **2** and **3** having two geminal secondary amine functions (scheme 2). ORTEP-type plots[12] of these compounds unambiguously stated the structure with the methyl groups in a *cis* configuration.

This gem-insertion of butanedione appeared to be favorable to (1+1) cyclocondensation : the reaction of a dibromo-derivative (1,2-dibromoethane or 1,3-dibromopropane) with **2** and **3** in CH_3CN gave the protected macrocycles **4**, **5** and **6** in good yields[13] (scheme 3). Noteworthy, the butanedione-protected macrocycle **6** could be obtained either from **2** or **3** with retention of the *cis*-configuration as shown by dynamic ^{13}C NMR studies (two anisochronous aminal carbon atoms and conformationally labile fused rings). These results indicated clearly that no isomerization occurred during the cyclization step. As **4** and **5** also exhibited temperature dependent ^{13}C NMR spectra, all these observations are consistent for the proposed structures for **4**, **5**, **6**.



Scheme 3

An acid hydrolysis under mild conditions,[14] *i.e.* diluted HCl solution, released quantitatively the corresponding macrocycle **7** (cyclam), **8** (cyclen), **9** (homocyclen) as hydrochlorides (scheme 4).



n = 1; m = 1 : **4**
n = 0; m = 0 : **5**
n = 0; m = 1 : **6**

n = 1; m = 1 : **7**
n = 0; m = 0 : **8**
n = 0; m = 1 : **9**

Scheme 4

In conclusion, the use of butanedione as rigidifying and protecting agent is the key-feature of this mild, easy to run and efficient preparation of cyclam, cyclen and homocyclen, as two of the three steps involved in these inexpensive syntheses were nearly quantitative.

References and notes

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10. ***Typical procedure for the bis-aminal syntheses***. Butanedione (5 mmol.) in solution in CH_3CN (10 mL) was added dropwise to a cooled and stirred solution of the tetraamine (5 mmol.) in 10 mL of CH_3CN. After completion of the reaction (2 h.) the solvent was evaporated under reduced pressure to yield **1a**, **1b** as a amber oil, **2** and **3** as yellow powders. These products were either purified or used as such in the next step. ***Purification***: **1a** and **1b** were taken in toluene (10mL), the mixture allowed to stand 15 mn. and filtered. The filtrate was evaporated and the procedure repeated twice to finally yield **1a** and **1b** (75: 25). (yield: 95%). White crystals of **2** and **3** were obtained from recristallization in hexane. (Yield: 90% and 95%). ***Selected data***: Products **1**: ^{13}C-NMR (Toluene-d^8, 75 MHz, 220 K): **1a**: 72.8, 72.2 (N<u>C</u>N); 49.9, 48.9, 46.7, 44.6, 39.5, 39.2 (<u>C</u>H_2-α-N); 28.3, 16.8 (<u>C</u>H_2-β-N); 16.6, 8.7 (<u>C</u>H_3). **1b**: 73.8 (N<u>C</u>N); 50.0, 48.6, 39.6 (<u>C</u>H_2-α-N); 27.4 (<u>C</u>H_2-β-N); 7.4 (<u>C</u>H_3). **2**: Decomposing with heat. ^{13}C-NMR ($CDCl_3$, 75 MHz, 233 K): 77.3, 68.4 (N<u>C</u>N), 51.1, 50.8, 46.4, 45.9, 42.8, 40.0 (<u>C</u>H_2-α-N); 24.9, 12.9 (<u>C</u>H_3). **3**: melting point: 110°C. ^{13}C-NMR ($CDCl_3$, 75 MHz, 298 K): 73.4, 68.5 (N<u>C</u>N); 51.2, 49.1, 46.8, 45.6, 42.1, 39.3, (<u>C</u>H_2-α-N); 23.6 (<u>C</u>H_2-β-N); 18.5, 11.0 (<u>C</u>H_3).
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12. Complete details of the structure investigations of **2** and **3** (n° CCDC-101349) are available at request from the Cambridge Crystal Data Centre, 12 Union Road, Cambridge CB2 1EZ, England.
13. ***Typical procedure for the protected-macrocycle syntheses***. To a solution of **2** or **3** (5 mmol.) in 50 mL of dry CH_3CN, K_2CO_3 (50 mmol., 7 g), and bis-electrophile (1,2-dibromoethane or 1,3-dibromopropane) were added. The reaction mixture was stirred for 6 h.(**3**) or two days (**2**). After reaction, the mixture was filtered and solvant evaporated to give **4**, **5** and **6** as a brown oil purified by chromatography on alumina. ***Selected data***: **4** (yield: 90%): **^{13}C-NMR** ($CDCl_3$, 75 MHz, 298 K): 73.7 (N<u>C</u>N); 47.9, 47.2 (<u>C</u>H_2-α-N); 17.6 (<u>C</u>H_2-β-N); 10.4 (<u>C</u>H_3). **5** (yield: 60%). **^{13}C-NMR** ($CDCl_3$, 75 MHz, 298 K): 78.7 (N<u>C</u>N); 47.9, 47.2 (<u>C</u>H_2-α-N); 13.5 (<u>C</u>H_3). **6** (yield: 74% from **3** and 90% from **2**). **^{13}C-NMR** ($CDCl_3$, 75 MHz, 230 K): 78.3, 72.3 (N<u>C</u>N), 50.3, 49.6, 49.1, 47.5, 46.0, 45.4, 45.0, 44.5 (<u>C</u>H_2-α-N); 17.7 (<u>C</u>H_2-β-N); 12.4, 11.4 (<u>C</u>H_3).
14. ***Typical procedure for the deprotection***. Ethanol (10 mL) and 10% aqueous hydrochloric acid (20 mL) were added to 1 mmol. of protected macrocycle (**4**, **5**, **6**). The mixture was allowed to react two days at 60 °C. Then, solvents were evaporated and the residues were recristallized in EtOH to obtain the well-known macrocycles as tetrahydrochloride with yields > 90%.