SYNTHESIS OF A NEW PENTACYCLIC SYSTEM : PYRROLO[2,1-*c*] QUINAZOLINO[3,2-*a*][1,4]BENZODIAZEPINES: ELUCIDATION OF STRUCTURES.

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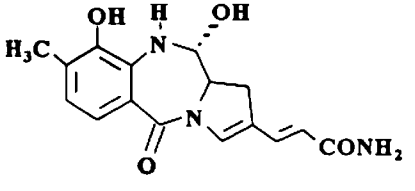
Abstract : The first synthesis of pyrrolo[2,1-*c*]quinazolino[3,2- *a*][1,4] benzodiazepines is described. Structure of these compounds has been elucidated by NMR and X-ray crystallographic analysis.

Introduction

In previous papers (1) we described synthesis and reactivity of pyrrolo[2,1-*c*][1,4]benzodiazepines. These compounds are related to the well-known antitumor antibiotics (2) family which includes anthramycin **1**, sibiromycin and neothramycins (3). Moreover anthramycin (4) was recently described as an antagonist of the CNS effects of cholecystokinin (CCK)(5). On the other hand, asperlicin (6) **2**, a natural product, is a competitive and selective antagonist for the CCK receptors. The structural analogy of these two benzodiazepines led us to investigate the synthesis of a new pentacyclic system : pyrrolo[2,1-*c*]quinazolino[3,2-*a*][1,4] benzodiazepine (PQBD) **3** using the method described by Bock and coworkers (7) in the synthesis of quinazolinobenzodiazepines. However, contrary to their results, in our system the last step of the sequence produced isomerization which prompted us to elucidate the structure of the title compounds by NMR and X-ray analysis.



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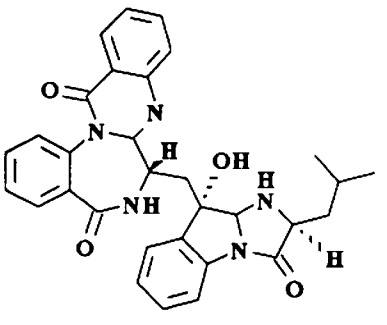

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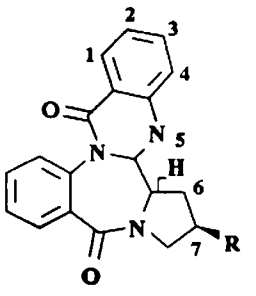

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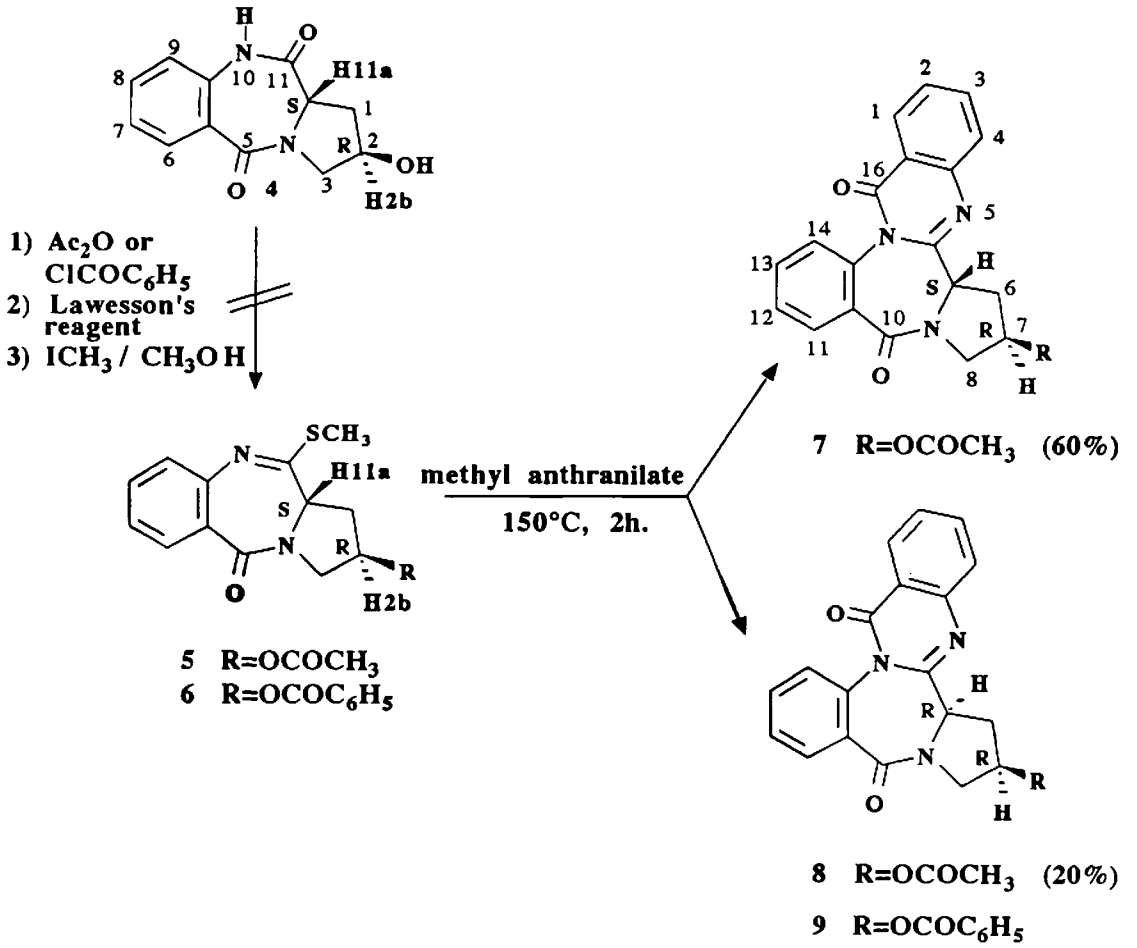
Results and discussion

The precursors **5** and **6** were prepared by esterification with acetic anhydride or benzoyl chloride of 2-hydroxy-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione **4**, the N10-C11 thiolactams were obtained by thionation with one equivalent of Lawesson's reagent in refluxing 1,4-dioxane (1a, 1b) and finally the methyliminothioethers **5** (1c) and **6** were obtained by treatment with methyl iodide in methanol in the presence of potassium carbonate. Then condensation of **5** with an excess of methyl anthranilate at 150°C during two hours gave the pentacyclic moiety PQBD. This reaction induced a partial isomerization to give isomers **7** and **8** which were separated by fractional crystallization. Two sites of isomerization could be envisaged either on the carbon C5b, either on the carbon C7. This latter case did not seem to be probable, such isomerization had never been described before. This phenomenon of isomerization is more probably due to an electronic delocalization on the N10-C11-C11a positions during the condensation leading to the pentacyclic PQBD.



NMR studies using Nuclear Overhauser Effect (NOE) allowed us to make the assignment of structures **7** and **8**. After double irradiation of each proton of the pyrrole ring (H-5b, H-6a, H-6b, H-7b, H-8a, H-8b) of both compounds, we established the *trans* structure for the NMR spectrum in figure 1 corresponding to compound **7** and the *cis* structure for the NMR spectrum in figure 2 corresponding to compound **8**.

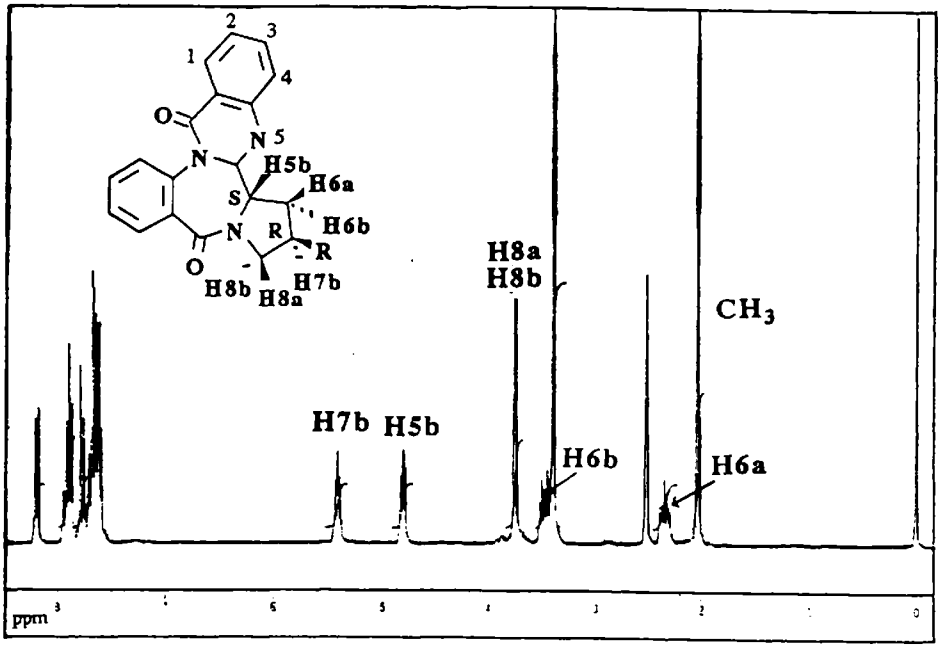


Figure 1: ^{1}H NMR spectrum of the *trans* isomer **7** (*).

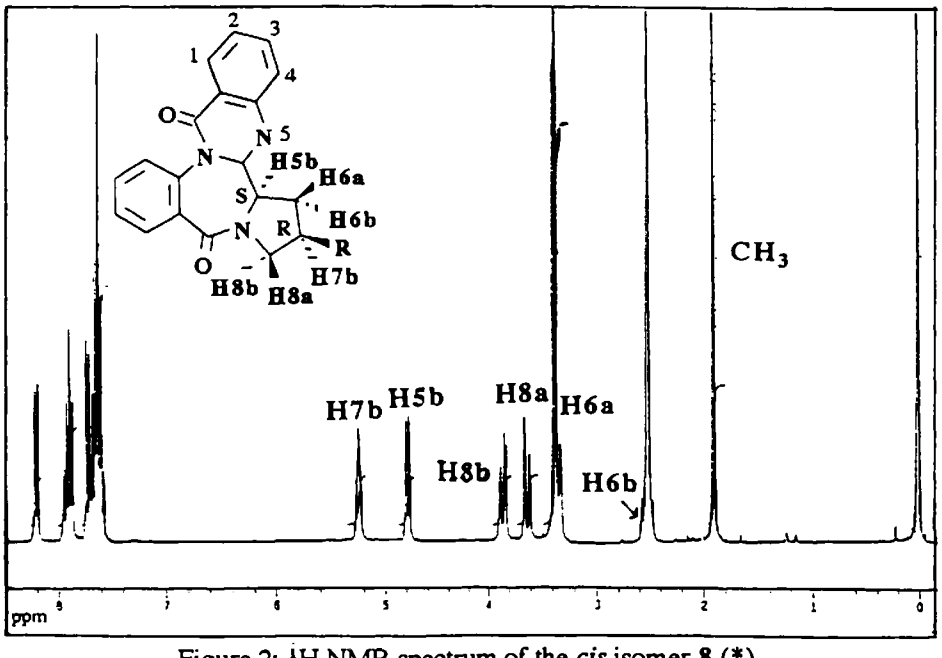


Figure 2: ^{1}H NMR spectrum of the *cis* isomer **8** (*).

These results have been confirmed by X-ray crystallographic analysis of compound 7.
The computer plot (figure 3) showed that the two protons H-5b and H-7 of 7 exhibit a *trans*-stereochemistry.

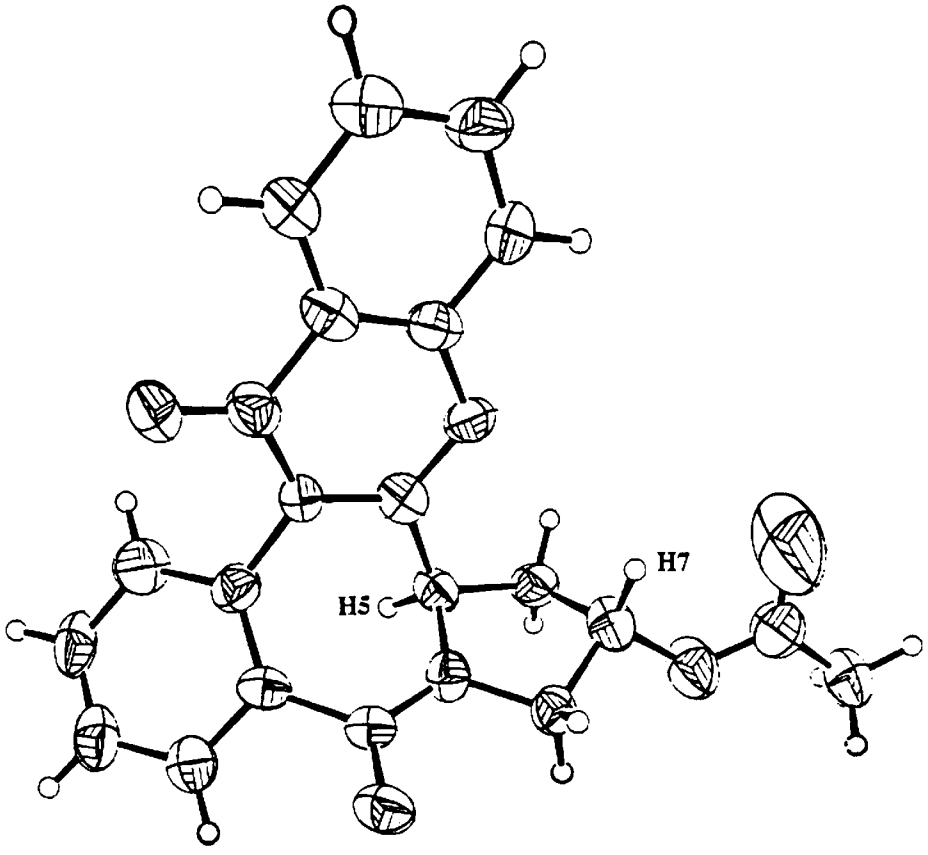
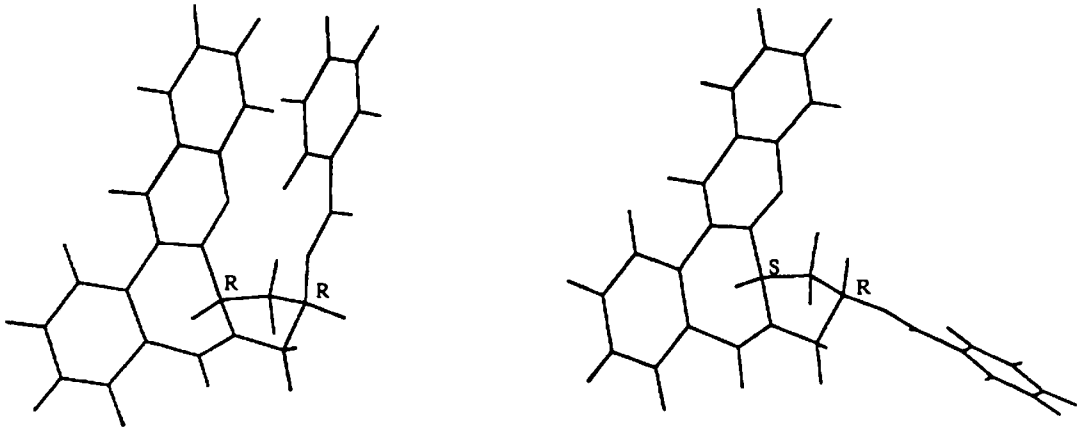


Figure 3: Perspective drawing of compound 7.

Compound **7** crystallizes in the orthorhombic space group $P2_12_12_1$. Cell dimensions are: a= 7.377 (1), b= 14.477 (2) and c= 16.785 (3)Å. Intensity data were collected on an Enraf-Nonius CAD4-turbo diffractometer. The structure was solved by direct methods. The current R factor is ≃ 0.10; refinement is continuing.

On the other hand, starting with *trans* benzoyloxymethylthioether **6** only one isomer was isolated. NMR studies showed that it was the *cis* isomer **9** (8), fruit of an isomerization, without traces of the *trans* isomer.
To explain the difference of behaviour of the acetoxy 5 and the benzoyloxy 6 forming only the stereoisomer RR 9, we carried out a molecular modelling study. This study showed that for PQBD 9 it exists a strong stabilization by Van der Waals interactions between the two phenyl groups (quinoxalino and benzoyloxy) compared to SR stereoisomer (Figure 4). Moreover these dipole-dipole interactions are accentuated by the presence of electron-withdrawing groups on the two phenyls and this interaction could explain the experimental result which

conducted to the more hindered isomer. These interactions are not observed with acetoxy derivatives. Further studies and biological evaluation concerning these PQBD are in progress.



Total energy[1] : 13 Kcal/mol Total energy[1] : 17 Kcal/mol

Figure 4 : Molecular modelling of the RR stereoisomer **9** (on the left) and the hypothetical SR stereoisomer (on the right).

[1]The total energies (molecular mechanics method) indicated here, are only a measure of intramolecular strain relative to an hypothetical situation (Tripos force field (9)).

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(*) ^{1}H NMR were recorded on a JEOL GSX 270 MHz FT-NMR spectrophotometer at 20°C. Compound 7 (DMSO-d_6) δ: 8.18-7.58 (m, 8H, Ar); 5.40 (t, 1H, H-7b); 4.81 (dd, *Jcis*=8.06 Hz, *Jtrans*=4.95 Hz, 1H, H-5b); 3.72(d, *J*=4.21 Hz, 2H, H-8); 3.50-3.40 (m, 1H, H-6b); 2.28-2.38 (m, 1H, H-6a); 2.03 (s, 3H, CH_3). Compound 8 (DMSO-d_6) δ: 8.20-7.56 (m, 8H, Ar); 5.23 (t, 1H, H-7b); 4.78 (d, *Jcis*=8.06 Hz, 1H, H-5b); 3.87 and 3.82 (dd, *Jgem*=13.20 Hz, *Jcis*=5.13 Hz, 1H, H-8b); 3.62 (d, *Jgem*=13.20 Hz, 1H, H-8a); 3.34 (d, *Jgem*=13.20 Hz, 1H, H-6a); 2.57-2.46 (m, 1H, H-6b); 1.90 (s, 3H, CH_3).

(8) Compounds disclosed in this communication have been thoroughly characterized including ^{1}H NMR, ^{13}C NMR, LRMS and elemental analysis.

(9) SYBYL Version 5.4, TRIPOS Associates, Inc., Saint Louis, MO, running on UNIX with Evans & Sutherland ESV III workstation.

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