Seven-Membered Ring Mesomeric Betaines. From Anti-Hückel Aromatics to Model Compounds of the Pyrrolobenzodiazepine Alkaloids Circumdatin A and B.

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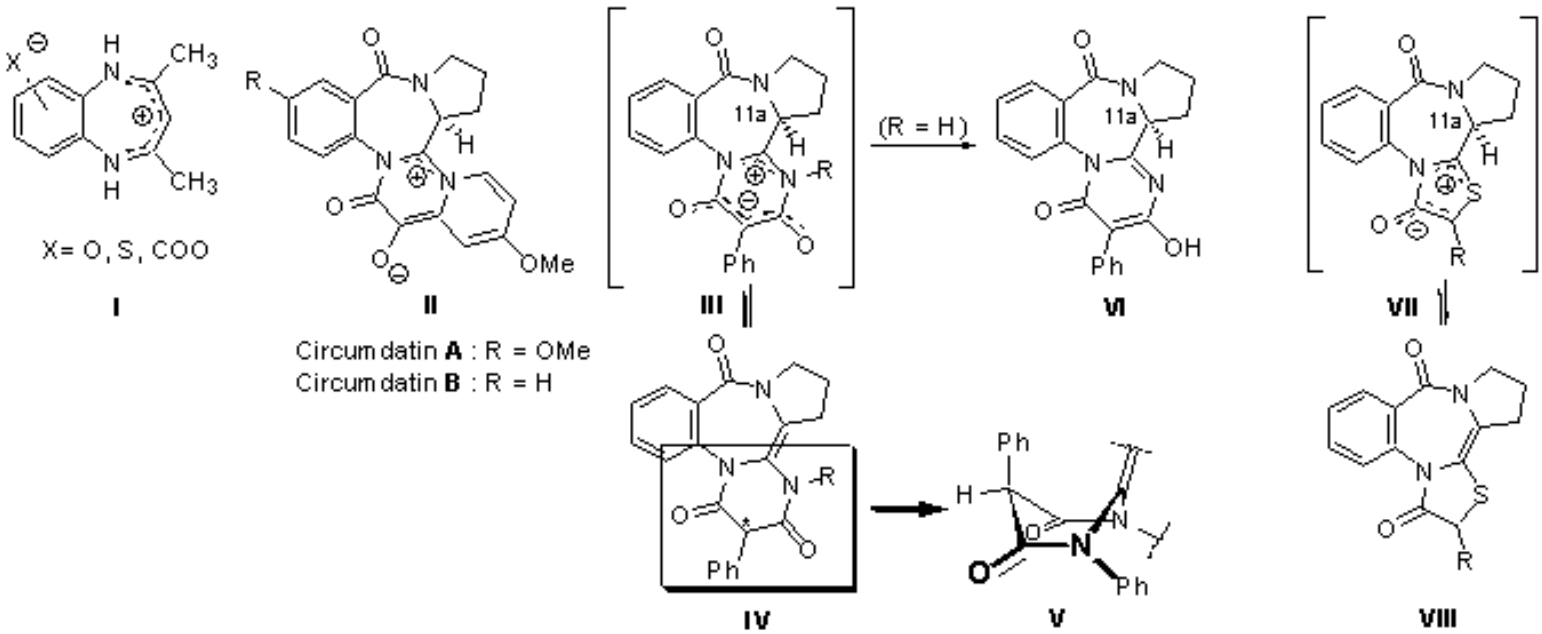
Mesomeric betaines are neutral conjugated heterocyclic compounds which can exclusively be represented by dipolar canonical formulae in which the positive and negative charges are delocalised within the π-electron system. In nature, they play important biological roles as modified nucleobases or alkaloids. The first comprehensive classification (conjugation, cross-conjugation, pseudo-cross-conjugation) by Ollis, Stanforth, and Ramsden (1985) led to a better understanding of the chemistry of 5- and 6-membered representatives of this class of compounds. Information about 7-membered mesomeric betaines is rare. Therefore, we first focused our interest on the syntheses and characterisation of betainic benzo[*b*][1,4]diazepiniums (**I**) which possess 4n π-electrons as anti-*Hückel* heteroaromatics (spectroscopic examinations, two X-ray single crystal analyses).



In continuation of our work on naturally occurring betainic molecules we became interested in the alkaloids Circumdatin **A** and **B** which belong to the biologically active class of pyrrolo[2,1-*c*][1,4]benzodiazepines (PBD). Isolation from the fungus *Aspergillus ochraceus* and the structure proposals **II** were described recently (Christophersen *et al.*, 1999). As the proposed structures are without precedent in heterocyclic as well as natural product chemistry, we prepared first representatives of this class of heterocyclic mesomeric betaines as model compounds or closely related structures for stereochemical and spectroscopic comparisons.
First, a pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione was converted into the corresponding C-11-monothiolactam and subsequently treated with amines to cyclic amidines which form tautomers (NMR, X-ray analysis). Depending on substitution pattern as well as the reaction conditions, these amidines racemize and loose their isohelicity to the minor groove of DNA which cause the considerable biological activity of this class of compounds. We then reacted *N*-substituted cycloamidines with bis(trichlorophenyl)malonic esters. Formation of neutral tautomers of 1,3,8-triones (**IV**) instead of betainic structures (**III**) resulted in twisted molecules with helical as well as chiral structure elements (NMR, X-ray analysis). These stereochemical features cause a splitting of the NMR signals of this new ring system into two sets. X-Ray single crystal analyses and *ab-initio* calculations confirm the boat conformation of the dioxopyrimidine moiety with the phenyl ring in

axial position (**V**). The stereochemical outcome of this reaction strongly depends on substituent effects. Thus, reaction of *N*-unsubstituted cycloamidine with malonic esters resulted in the formation of the PBDs (**VI**) as optically active compounds.
After we were able to show that a cross-conjugated charge-separation in model compounds of the proposed structures of Circumdatine **A** and **B** (**II**) are not stable, we next focused our interest on thioisomünchnones of pyrrolobenzodiazepines (**VII**) which possess a *formal* charge separation. First representatives of the new ring system of the 3-thia-6a,11b-diazabenzo[g]cyclopenta[e]-azulene-1,7-diones (**VIII**) were synthesized starting from a thiolactam and 2-bromoacetyl chlorides.
Tautomerisations including the biologically important C-11a position in solution as well as in the solid state were examined by spectroscopic investigations and an X-ray analysis.
Consequently, we prepared 1,3-imidazol-4-one- and 1,3-pyrimidin-4-one-annulated pyrrolobenzodiazepines which are important structure elements of the proposed structures **II** and investigated the synthetic approaches and spectroscopic properties.
In conclusion, we present first representatives of three new ring systems related to *Aspergillus* and *Streptomyces* alkaloids which possess interesting spectroscopic properties.