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The Synthesis of New Heterocyclic Bridged Ring Systems. Analogs of Tetrahydro-β-Carbolines.

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Abstract: New bridged β-carbolines were synthesized *via* a short synthetic route. The key step of the sequence is a Pictet-Spengler condensation under neutral conditions, employing a cyclic amine and several aldehydes. Using 5,5-diethoxypentanal gave a bridged analog which could be further ring closed to a new pentacyclic system.

In medicinal chemistry a lot of attention has been paid to conformationally restricted analogs of compounds which are important from a biological or medicinal point of view. Studies of receptor binding properties give information concerning the active conformation of the substrate and thus attribute to the development of compounds that bind specifically to receptor subtypes. Much effort has been made to synthesize compounds which have specific therapeutic activity in order to reduce side effects. For instance the recognition of serotonin receptors can be attributed partly to the orientation of the alkylamino sidechain of serotonin. To investigate steric, electronic and hydrophobic requirements for the 5-HT_{1A} and 5-HT_2 receptor binding sites (tetrahydropyridin-4-yl)indoles were used as semirigid analogs of serotonin.[1]

Tetrahydro-β-carbolines form a class of tryptamine derivatives that have been studied extensively. Several analogs have been shown to bind with high affinity to serotonin receptors in the central nervous system and are also of biological importance in many other processes. Compounds possessing the β-carboline moiety have been isolated frequently from different organisms and display a variety of biological activity.

In view of our interest for the medicinal application of natural products and their derivatives, we decided to develop a general method for the synthesis of conformationally restricted tetrahydro-β–carbolines bearing a bridge across the β-carboline C-ring (**1**). Attention was focussed on the development of a new heterocyclic ring system (**1**, n = 3), which contains an azabicyclononane. All atoms of the tetrahydropyridine part of the ring system are fixed by the bridge across the β-carboline N2 and C4 atoms, resulting in considerable reduction in movement of the substituent at C1.

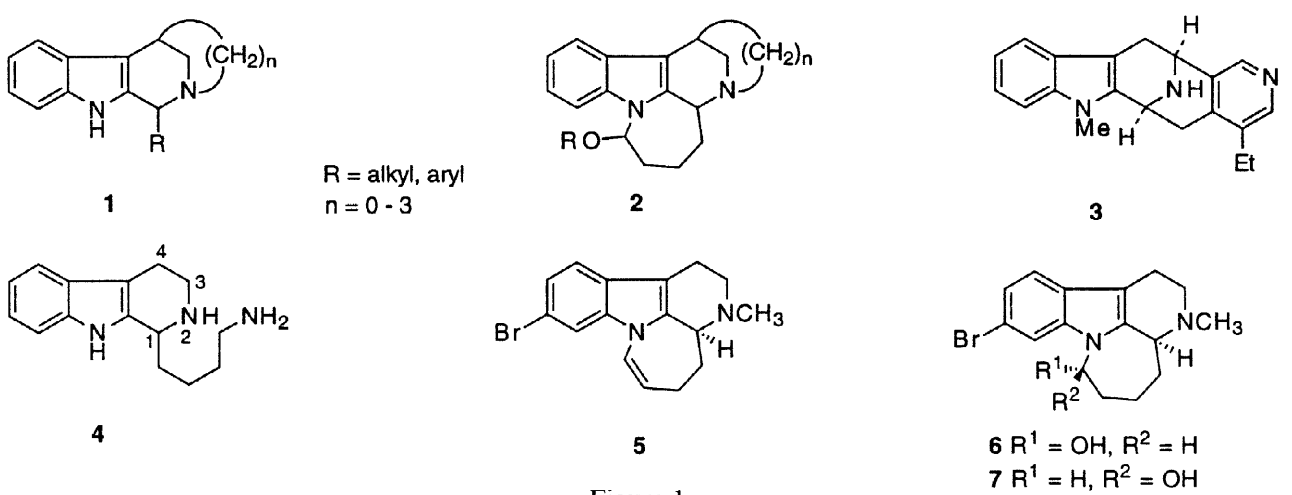

Figure 1

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To the best of our knowledge, the compounds with general structures **1** and **2** (fig. 1) possessing a N2-C4 bridge are not known in literature. The only β-carbolines that have a bridged tetrahydropyridine moiety belong to the ajmaline - sarpagine family. The alkaloid sauveoline **3** is a member of this group of compounds, all of them bearing a bridge across the C1 and C3 atoms.[2]

The route we developed to synthesize the bridged β-carbolines **1** allows the introduction of different functionalities. Therefore it was possible to extend this methodology to a new pentacyclic system (**2**) (n = 3). We applied our new route to the synthesis of bridged analogs of nazlinine (**4**),[3] arborescidine B (**5**), C (**6**) and D (**7**),[4] natural products we synthesized previously.[5]

The key step in the synthesis, the Pictet-Spengler condensation,[6] has been important in the synthesis of numerous β-carbolines. Reaction of an amine with an aldehyde gives an intermediate imine or iminium salt which cyclizes to form a β-carboline. In order to synthesize the bridged compounds **1** (n = 3) *via* the Pictet-Spengler condensation, the required amine is piperidine **10**. Due to their potent action at serotonin and dopamine receptors, 3-(tetrahydropyridinyl)indoles **9**, which can be regarded as oxidized precursors of the amine **10**, have been the subject of several synthetic studies.[7] The most general and straightforward method to synthesize them is the condensation of indole with *N*-substituted-3-piperidone under either basic or acidic conditions.[7] Reaction of indole with *N*-benzyl-3-piperidone **8**[8] in the presence of sodium methoxide was followed by *in situ* dehydratation of the intermediate indolyl-3-piperidinol, which occurs unconjugated to the nitrogen lone pair, resulting in tetrahydropyridine **9**. Both reduction of the double bond and debenzylation were achieved in one step by hydrogenation affording indolylpiperidine **10**.

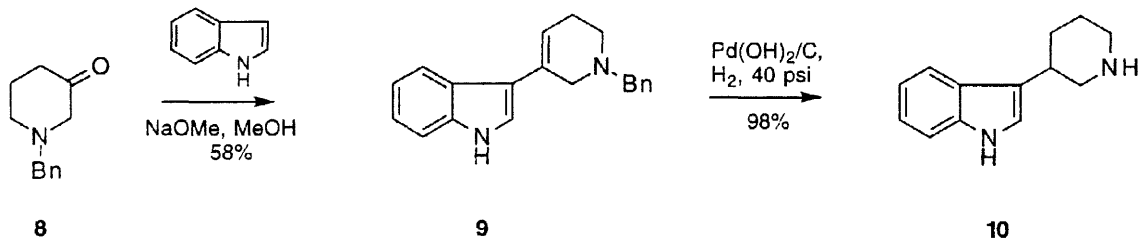
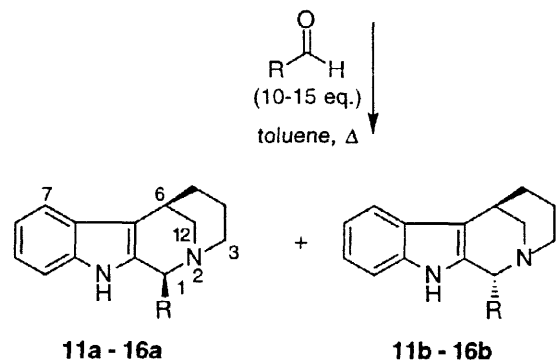


Table 1. Pictet-Spengler Condensation of Piperidine **10** with several Aldehydes.

products	R	ratio **a** : **b**	yield
11	- CH_2CH_3	1 : 1	54%
12	- $(CH_2)_5CH_3$	2 : 1	72%
13	- $(CH_2)_6CH_3$	5 : 2	64%
14	- C_6H_5	19 : 1	55%
15	- $(CH_2)_3CH(OEt)_2$	2 : 1	73%
16	- $(CH_2)_3CHNOCH_3$	3 : 2	11%

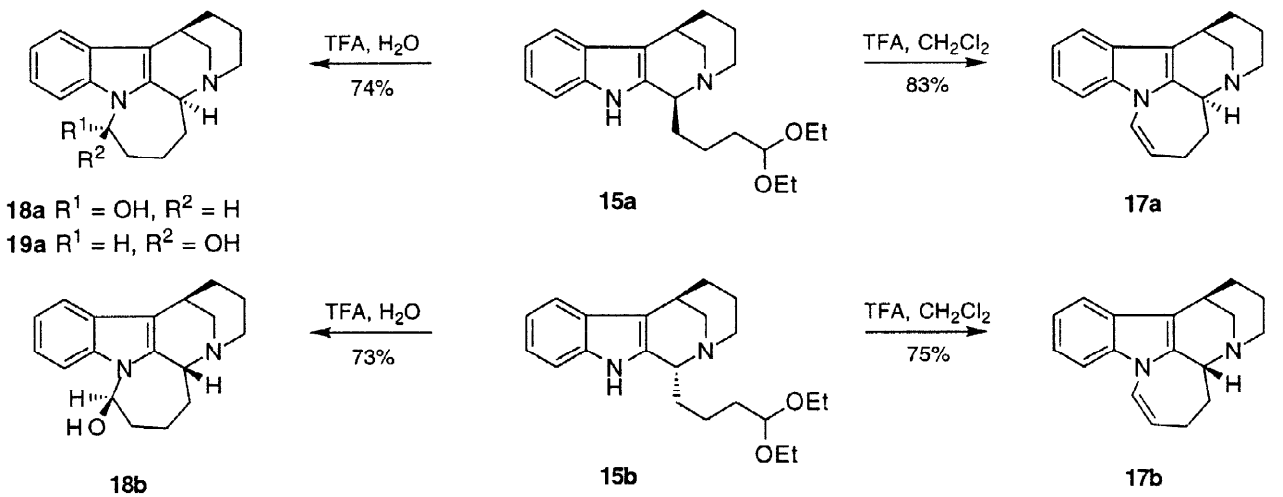


Scheme 1

The Pictet-Spengler condensation of piperidine **10** was performed using various aldehydes under non-acidic, aprotic conditions (scheme 1). Usually the new bridged tetrahydro-β-carbolines[9] were formed in good yield and as a mixture of diastereomers, their ratio strongly depending on the size of the substituent (table 1). An excess aldehyde (10 - 15 eq.) is required for the reaction due to competitive aldol condensation of the aldehydes to the α,β-unsaturated aldehydes. The Pictet-Spengler reaction with the mono-oxime of glutaric aldehyde is incomplete due the instability of this aldehyde. Product **16** was therefore isolated in low yield together with the unreacted starting material, piperidine **10**. Diastereomers **a** and **b** of most of the bridged compounds could easily be separated using chromatography, but the diastereomers **11a** and **11b**, possessing a small C1-substituent, could not be separated using this technique. NOESY experiments[10] established the *cis*- either *trans*-configuration

of the bridge relative to the C1-substituent in the two diastereomers **18a** and **18b**. With this information we were abled to characterize the related bridged compounds by comparison.

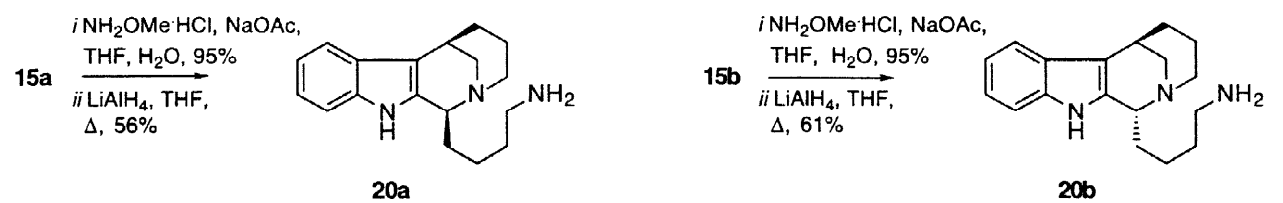
The Pictet-Spengler condensation is performed under neutral conditions by refluxing in toluene and therefore this route proved to be applicable to aldehydes possessing different functionalities. Condensation of the piperidine **10** with 5,5-diethoxypentanal[11] resulted in the formation of bridged β-carbolines **15a** and **15b**. After separation both diastereomers could be deprotected and subsequently cyclized to a new pentacyclic bridged system (scheme 2). Performing the deprotection of **15a** under non-aqueous acidic conditions resulted in enamine **17a**, the bridged analog of the previously synthesized[5b] natural product arborescidine B (**5**)[4]. The same reaction was possible with diastereomer **15b** giving **17b**, a second analog of arborescidine B (**5**).



Scheme 2

When aqueous acidic conditions were used for the deprotection of acetals **15a**, carbinolamines **18a** and **19a** were formed, which are the bridged derivatives of arborescidine C (**6**) and D (**7**).[4,5b] The *trans*- (**18a**) and *cis*-isomers (**19a**) were formed in a ratio of 3 : 1 and could be separated by crystallization. Chromatographic separation was not suitable in this case, because the *trans*- and *cis*-isomers exist in an equilibration, which under acidic conditions (such as silica) is in favor of the *trans*-isomer. This equilibrium was also observed in the synthesis of the natural products.[5b] Surprisingly, performing the same reaction with diastereomer **15b** resulted in exclusive formation of the *trans*-isomer. Also after short reaction times the *cis*-isomer was not observed in the crude reaction mixture.

The natural product nazlinine **4** has been the subject of synthetic studies in our group.[12] Synthesis of the bridged derivatives **20a** and **20b** was achieved using the general method described herein. Since the Pictet-Spengler condensation of piperidine **10** with the mono-oxime of glutaric aldehyde was not suitable for the synthesis of bridged derivative **16** (table 1), another approach was chosen. Both diastereomers of the bridged acetal **15** were converted to **16** in good yield by simply reacting them with methoxyamine under slightly acidic conditions. Reduction with $LiAlH_4$ gave **20a** and **20b**, bridged derivatives of nazlinine **4**.



Scheme 3

In summary, several functionalized aliphatic and aromatic aldehydes were used in the Pictet-Spengler condensation with cyclic amine **10** to give the bridged products **11** - **16** in reasonable yield. By using 5,5-diethoxypentanal under neutral Pictet-Spengler conditions acetal **15** was obtained, which was a useful intermediate in the synthesis of bridged analogs of the natural products nazlinine, arborescidine B, C and D.

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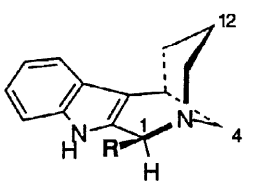
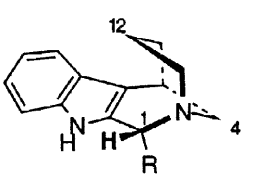
9. 1-alkyl-2,3,4,5,6,11-hexahydro-2,6-methano-*1H*-azocino[3,4-*b*]indol (for n = 3).
10. Assignment of the proton and carbon-shifts was done using COSY and HETCOR experiments. NOESY spectra of the diastereomers **19a** and **19b** showed the following relevant correlations indicating a boat conformation of the newly formed piperidine in **19a** and a chair conformation in **19b**:
diastereomer **19a**: H_1 and H_4; H_4 and H_{12eq}.
diastereomer **19b**: H_1 and H_{12ax}; H_1 and H_{13}.



diastereomer **a**



diastereomer **b**

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