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EXPECTED AND UNEXPECTED INTRAMOLECULAR CATIONIC CYCLIZATIONS

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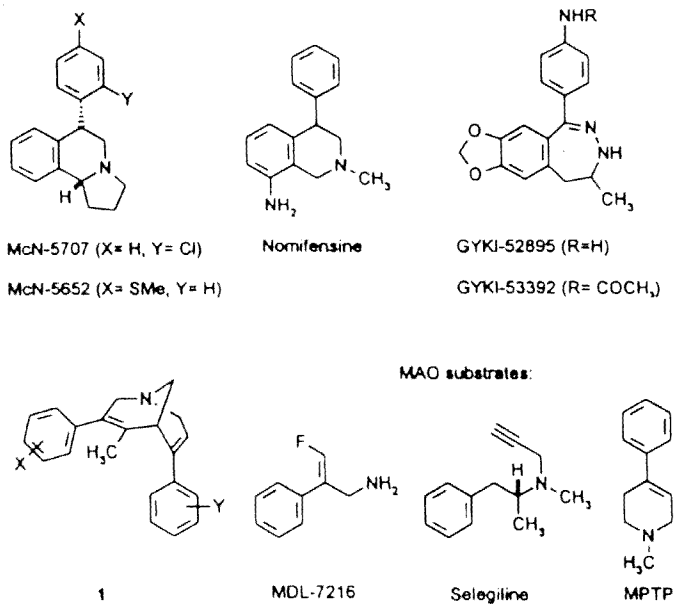
Cationic cyclizations of N-phenacyl-4-aryl-1,2,3,6-tetrahydropyridines and related compounds were studied, and structures of products formed were elucidated using NMR spectroscopy.

Some years ago a project was started at our institute to find a lead structure for a new antidepressant with a dual mode of action. According to recent considerations, a selective monoamine (dopamine, norepinephrine) uptake inhibitory effect combined with a MAO enzyme inhibitory potential would be advantageous [1].

Selective dopamine and serotonin uptake inhibitory effects are shown by several types of nitrogen heterocycles (Scheme 1). So the structures of the hexahydropyrrolo[2,1-*a*]isoquinoline derivatives [2], the well known nomifensine, and some 2,3-benzodiazepines from our own research [3] all reveal the same characteristic structural features: a basic nitrogen atom and two relatively closely situated aromatic rings at a certain distance from the nitrogen atom. During our recent work [4], some 1-azabicyclo[3.3.1]nonadiene derivatives **1** were found which, more or less fitting these structural requirements, showed remarkable dopamine uptake inhibitory potential.

Scheme 1



Later observation prompted us to synthesize different structural analogs of **1**. In addition, we hoped as well that the allyl amine moiety or the tetrahydropyridine ring system itself, in the analogs of **1**, might eventually be a substrate of the MAO enzyme as well, because such structural features belong to some known MAO substrates, as shown in Scheme 1. These elements might provide the expected additional MAO inhibitory effect to the molecules planned.

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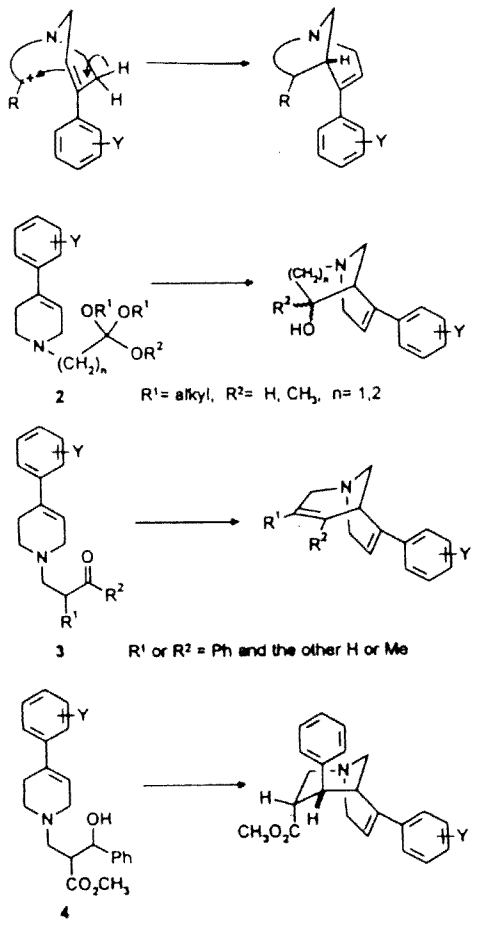
As a general principle of the synthesis of such compounds, an intramolecular cationic cyclization was expected.

Earlier we found that differently generated carbocations alkylate the double bond of a tetrahydropyridine ring in a smooth intramolecular reaction. As carbocations, oxocarbenium ions and benzyl cations were used. While oxocarbenium ions were generated either from acetals **2** [5] or from oxo compounds (e.g., **3**) in acidic medium [4, 6], benzyl cations [7] were provided by the corresponding benzylalcohol derivatives **4** in acids as well (Scheme 2).

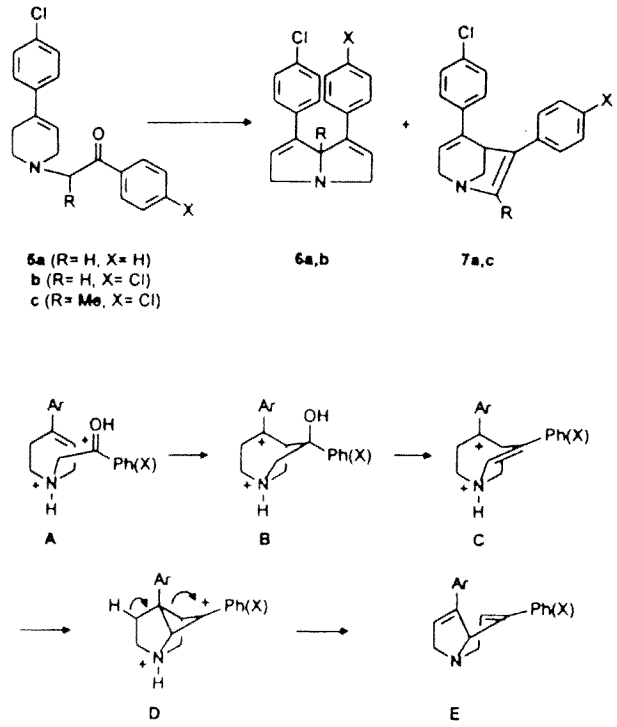
While Prins type cyclization of ketones **3** provided the expected ring systems [4, 6], lower homologs of **3** with only one bridge carbon atom gave partly different results in acidic cyclization reactions.

Scheme 2



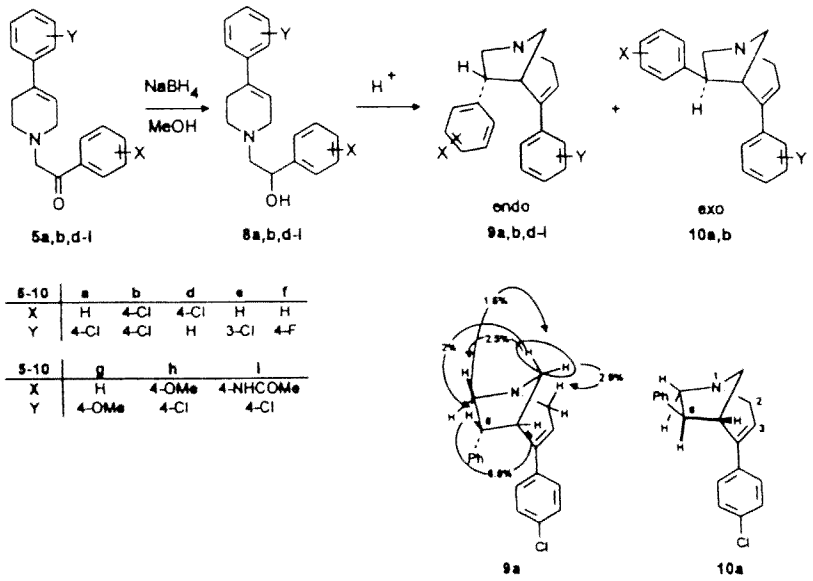
Phenacyl substituted tetrahydropyridine derivatives **5a,b,c** were heated in methanesulfonic acid and it was found that the expected azabicyclooctadiene **7a** forms only as a by-product, and pyrrolizine derivatives **6a,b** are provided as main products in moderate yield instead [8] (Scheme 3). It was also verified that both products arise in independent processes and they are not precursors of each other. An additional methyl substituent in **5c** prevents the formation of a sterically more crowded pyrrolizine derivative and allows only the formation of the originally expected azabicyclooctadiene **7c**. To explain the independent formation of the pyrrolizine and azabicyclooctadiene structures, we assume the reaction mechanism depicted in the lower part of Scheme 3. Protonation of the carbonyl group in **5** provides the oxocarbenium ion **A**, which undergoes an electrophilic cyclization reaction producing a carbinol type intermediate **B**. The latter can undergo two types of reactions. One of these is proton loss and water elimination leading to the formation of the originally expected product **7**. In the other reaction, water is eliminated from **B** to produce **C** and subsequent attack of the carbenium ion adjacent to the Ar group on the newly formed carbon–carbon double bond will give carbenium ion **D**. The highly strained ring system of **D** then undergoes stabilization through bond scission and proton loss (as indicated in Scheme 3) to provide the other double bond, leading to structure **E**, which is identical with pyrrolizine **6**.

Scheme 3



Further, it was realized that the phenacyl-substituted tetrahydropyridines **5**, used in the previous ring closure reaction, may give after reduction with sodium borohydride benzylalcohol derivatives **8**, which could eventually be suitable for cyclization to give another type of azabicyclic compound (Scheme 4).

Scheme 4



5-10	a	b	d	e	f
X	H	4-Cl	4-Cl	H	H
Y	4-Cl	4-Cl	H	3-Cl	4-F

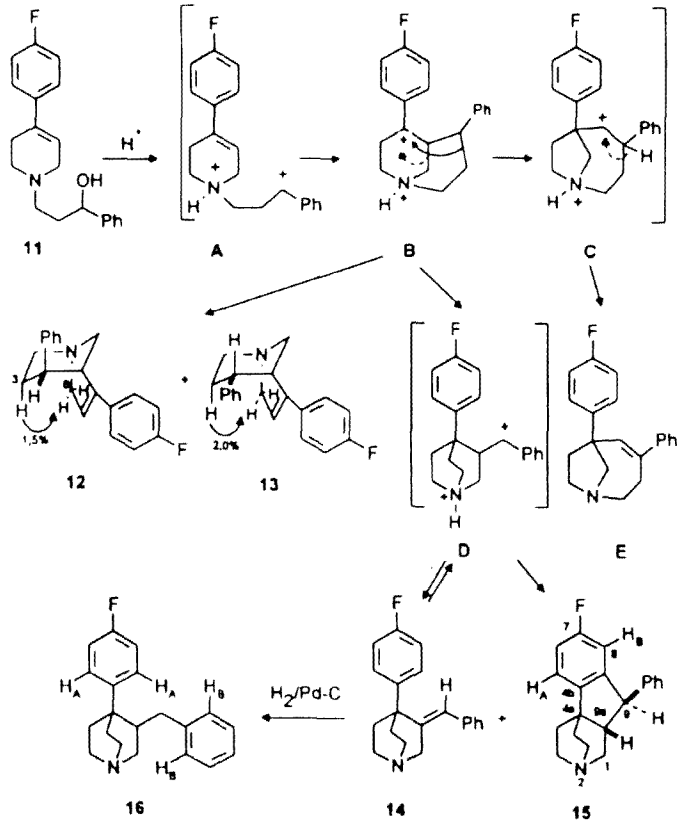
5-10	g	h	l
X	H	4-OMe	4-NHCOMe
Y	4-OMe	4-Cl	4-Cl

Indeed, cyclization of benzylalcohol derivatives **8** was achieved in methanesulfonic acid at room temperature, and 4,6-diaryl-1-azabicyclo[3.2.1]octene derivatives were formed as mixtures of *endo-exo* isomers in moderate to good yields. In al of the cases, the *endo* isomer formed as the overwhelming product. According to the expectation, electron-donor substituents in the benzyl group generally shorten the reaction time, but with electron-withdrawing groups, e.g., X = NO_2 or NH_2 (i protonated form), no cyclization reaction could be performed. However, an acetylation of the X = NH_2 group made the rin closure reaction possible.

Structural correlations of the *endo-exo* isomers were made on the basis of the ^{1}H-NMR signal of 6-H and ^{1}H-NMR-NOE experiments. The latter are indicated in Scheme 4, supporting the *endo* position of the phenyl group at **9a**.

This benzyl-cation-initiated cyclization reaction gave us the opportunity to synthesize a great number of azabicyclic compounds, of which only a few are indicated in Scheme 5.

Scheme 5



To investigate the scope and limitations of the above intramolecular cyclization reaction, we tried to cyclize the one longer carbon atom homolog of the previously used benzylalcohol derivatives.

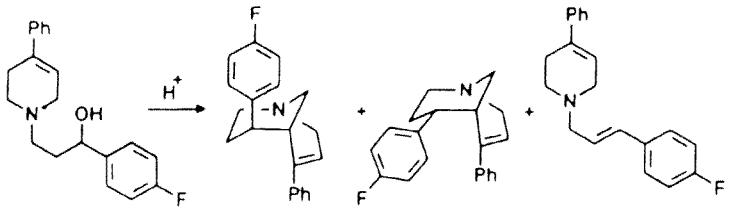
When benzylalcohol **11** was treated with 82% sulfuric acid, four products **12-15** were produced and isolated by column chromatography. Two of them (**12**, **13**) were the expected products with the 1-azabicyclo[3.2.1]nonene ring system, but the ^{1}H-NMR spectra of the two others revealed five methylene groups, excluding the existence of the latter ring system.

Taking into account the formation of ion **B** by the electrophilic cyclization of the benzyl cation **A**, two possibilities emerge. A proton loss from **B** results in the expected products **12** and **13**, however, two anionotropic rearrangements can also occur, further forming cations **C** or **D**, which can be stabilized by proton loss giving structure **E** or a quinuclidine derivative **14**. On the basis of the ^{1}H-NMR spectrum of **14** we could not distinguish between the two latter structures. This was only possible after the saturation of the double bond by catalytic hydrogenation. So structure elucidation of **14** was done indirectly on **16** by an NMR-INEPT investigation. Irradiation of *ortho* protons H_A caused a singlet, whereas irradiation of the *ortho* protons H_B produced a triplet splitting for the signals of the carbon atoms located through 3 bonds from respective H atoms. This is in accordance with a quaternary carbon atom for the former and a methylene carbon atom for the latter mutual arrangement. Consequently, structure **E** as possible cyclization product could be excluded.

The formation of the other new cyclization product **15** can be explained by an intramolecular cationic cyclization of cation D, producing the ethano-bridged indeno[2,1-*c*]pyridine derivative. For structure elucidation, the NMR-INEPT investigation was again used. By the irradiation of the H_A-proton, a singlet appeared for the quaternary carbon atom **4a** and the same doublet was seen when the H_B-proton or the *ortho* protons of the monosubstituted phenyl ring were saturated, supporting the existence of a methyne group for position **9**.

Concerning the unexpected formation of quinuclidine derivatives, we wanted to understand the driving force of the anionotropic rearrangement from cation **B** to **D**. Therefore another cyclization reaction was tried with benzyl alcohol **17**, where the former fluorophenyl and phenyl groups were interchanged (Scheme 6).

Scheme 6



17 **18** **19** **20**

In this reaction, besides the expected *endo* and *exo* 1-azabicyclononene isomers **18** and **19**, only the allylic product **20** was formed and no quinuclidine type product was noticed.

Therefore we assume that the anionotropic rearrangement from **B** to **D**, as shown in Scheme 5, occurs, because the benzyl cation adjacent to the more electron-withdrawing fluorophenyl group can be terminated by the rearrangement and a less electrophilic benzyl cation (**D**) can be formed.

From the new compounds synthesized in the frame of this project, the originally aimed dual mode of action was found for the *endo* isomers of 4,6-diaryl-1-azabicyclo[3.2.1]oct-3-ene derivatives. Some compounds were chosen for detailed investigation but the *in vivo* test results were not as good as that of the reference compounds.

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