Synthesis of heterocycles condensed to ring D of the estrane skeleton

Ph.D. Thesis in a short form

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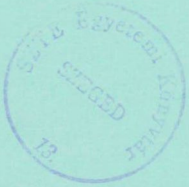

University of Szeged
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1. Introduction and Aims

The preparation and highly stereoselective conversion of several 16-hydroxymethyl-17-hydroxysteroids were achieved recently by Steroid Research Group at Department of Organic Chemistry, University of Szeged. Under suitable conditions, the *trans* 16-hydroxymethyl-17-hydroxy isomers were converted to D-sekosteroids, while the *cis* isomers gave oxetanes condensed to ring D of the sterane skeleton. Both synthon equivalents were appropriate for further transformations.

In the course of our work, the ring-expansion reactions of oxetanes condensed to ring D of the estrane skeleton were investigated. Our aim was to synthesize new exo-steroidal heterocycles containing nitrogen and/or oxygen. Further, different synthetic methods were developed to prepare these products.

Our efforts were directed towards the examination of the mechanism of the ring-expansion reactions, and towards new steroid-hybrid compounds with novel pharmacological characteristics.

2. Experimental Methods

The reactions were monitored by thin layer chromatography. The crude products were purified by column chromatography. The structures of the products were examined via the EI-MS and FAB-MS spectra, ^{1}H, ^{13}C, NOESY and ^{1}H-^{13}C HMBC NMR spectra, and X-ray diffraction measurement. The compounds present in the isomerization reaction mixtures were identified by a standard addition high-performance liquid chromatographic technique. The amount of each component was then calculated from the peak areas by using the previously recorded calibration curves.

3. Scientific Results*

3.1. A ring expanded compound was isolated from the reactions of 17β,16β-epoxymethylene-3-methoxyestra-1,3,5(10)-triene (**5**) with aliphatic nitriles in the presence of $BF_3 \cdot OEt_2$ under the *Ritter* reaction conditions. It was proved by spectroscopic methods that this was the BF_3 complex of a dihydrooxazine condensed to ring D of the sterane skeleton (**11**·BF_3).

3.2. It was established that the heterocyclic product (**11**) was not stable. Under basic conditions, the corresponding 16β-acetaminomethyl-17β-hydroxysteroid (**8**) was formed, while under acidic conditions, a 16β-aminomethyl-17β-acetylsteroid salt (**12**) was the end-product.

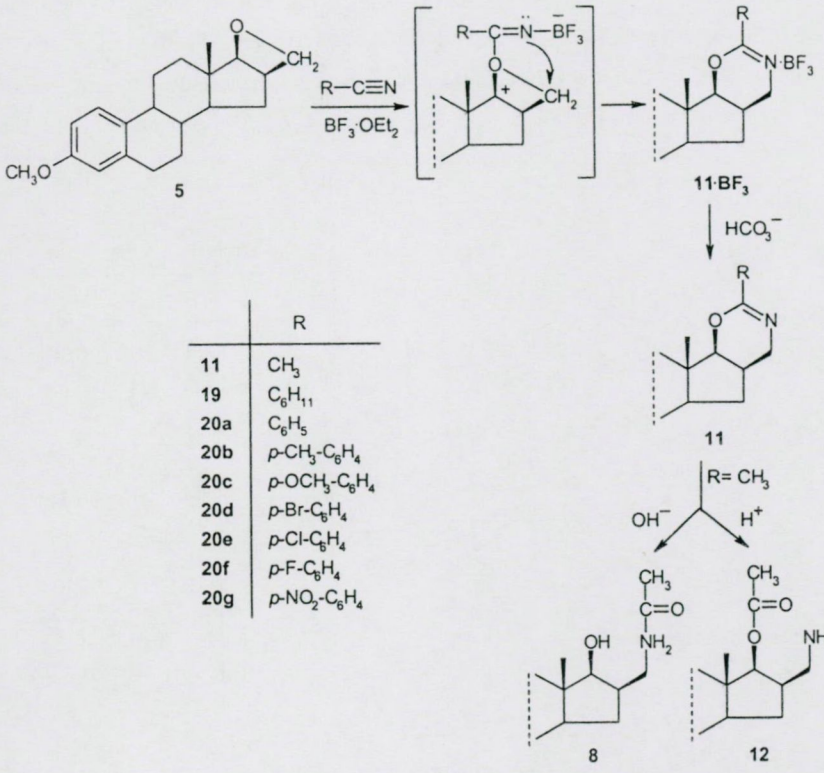
3.3. Identification of the ring-expanded product (**11**) proved that the primer carbocation was formed from the C-16-methylene carbon atom in the reaction.

3.4. *Ritter* reactions of 17β,16β-epoxymethylene-3-methoxyestra-1,3,5(10)-triene (**5**) were performed with cyclohexanecarbonitrile, benzonitrile and *p*-substituted-benzonitriles too. It was revealed that the resulting dihydrooxazines (**19, 20a-g**) were remarkably stable; the heterocyclic ring was not opened under either basic or acidic conditions.

3.5. A significant substituent effect was observed in the reactions of the steroidal oxetane with *p*-substituted aromatic nitriles. In the case of nitriles bearing electron-withdrawing substituents, dihydrooxazines were formed in very low yields, while the oxetane gave the corresponding dihydrooxazines in high yields with nitriles bearing electron-donating substituents (*Figure 1*).

3.6. The 17α,16α-epoxymethylene-3-methoxyestra-1,3,5(10)-triene (**7**) diastereomer was established not to give ring-expanded derivative with nitriles under the conditions of the *Ritter* reaction. It was established that the carbocation formed during the oxetane ring opening was stabilized by a *Wagner-Meerwein* rearrangement. Thus, only 16α-hydroxymethyl-3-methoxy-17β-methyl-18-norestra-1,3,5(10),13(14)-tetraene (**21**) was formed (*Figure 2*).

* Numbering of the compounds accords with that in the PhD Thesis



	R
11	CH_3
19	C_6H_{11}
20a	C_6H_5
20b	*p*-CH_3-C_6H_4
20c	*p*-OCH_3-C_6H_4
20d	*p*-Br-C_6H_4
20e	*p*-Cl-C_6H_4
20f	*p*-F-C_6H_4
20g	*p*-NO_2-C_6H_4

Figure 1

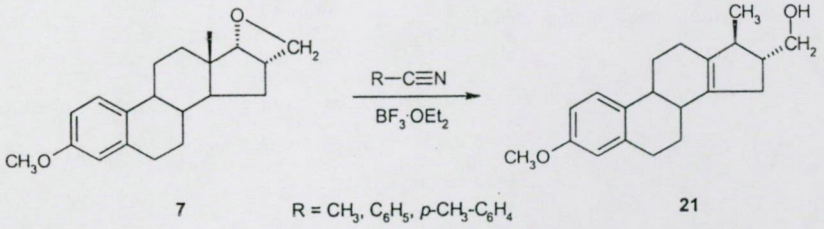
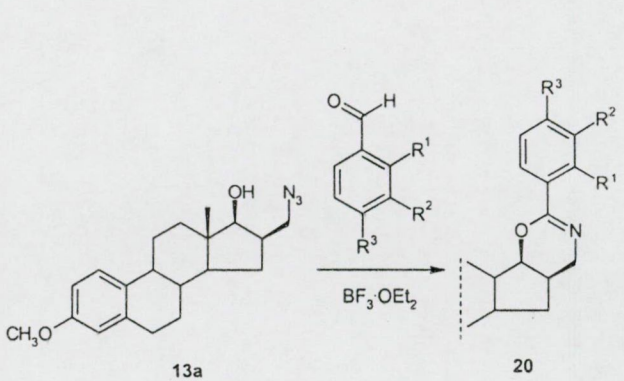


Figure 2

3.7. Another independent method was also applied to prepare dihydrooxazines condensed to ring D of the estrane skeleton. It was revealed that the reaction of the 16β-azidomethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**13a**) with aliphatic, aromatic and substituted aromatic aldehydes also resulted in 2'-substituted-5',6'-dihydro-*4'H*-1',3'-oxazine derivatives (**20a-n**) under the conditions of the *Schmidt* reaction (*Figure 3*).



20	R¹	R²	R³
a	H	H	H
b	H	H	CH_3
c	H	H	OCH_3
d	H	H	Br
e	H	H	Cl
f	H	H	F
g	H	H	NO_2
h	H	NO_2	H
i	NO_2	H	H
j	H	H	CN
k	H	H	CHO
l	H	H	$OCOCH_3$
m	H	Cl	H
n	Cl	H	H

Figure 3

3.8. We found that in the reactions of the steroidal azido alcohol with substituted aromatic aldehydes, the substituent effect was the reverse of that in the *Ritter* reaction. In this case, aromatic aldehydes substituted with electron-withdrawing groups gave the steroidal dihydrooxazines in high yields.

3.9. 2'-Substituted-5',6'-dihydro-*4'H*-1',3'-oxazines condensed to positions 16α,17α of the estrane skeleton (**22**, **23**) were prepared from 16α-azidomethyl-3-methoxyestra-1,3,5(10)-trien-17α-ol (**16a**) via a *Schmidt* reaction.

3.10. It was proved that the constitutional isomers of **22a-c**, 2'-substituted-5',6'-dihydro-*2'H*-

1',3'-oxazine derivatives (**23a-c**) were also formed. We confirmed with spectroscopic methods that the absolute configuration of the 2' carbon atom in **23a-c** was *R* (*Figure 4*).

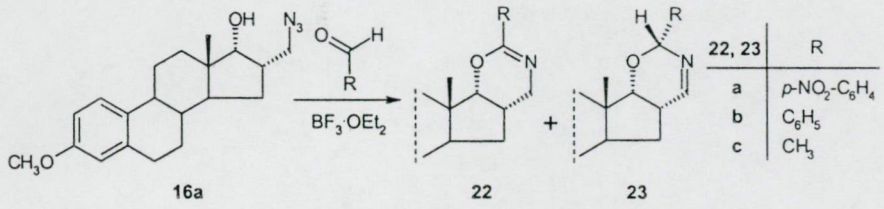


Figure 4

3.11. The *trans* diastereomers of the 16-azidomethyl-3-methoxyestra-1,3,5(10)-trien-17-ol were also reacted with aliphatic, aromatic and substituted aromatic aldehydes in the presence of $BF_3 \cdot OEt_2$ under the conditions of the *Schmidt* reaction. We found that in the case of the 16β,17α isomer (**15a**), the *Schmidt* type ring-closure reaction failed. Further, it was evidenced that, despite the mild conditions, symmetrical dimeric steroids (**25**, **26**, **27**) were formed in a *Friedel-Crafts* type alkylation reaction (*Figure 5*).

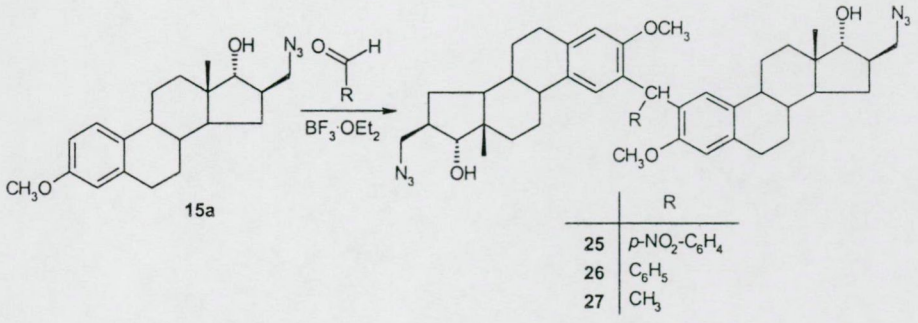


Figure 5

3.12. Besides the dimerization, a ring-closure reaction also took place between the 16α-azidomethyl,17β-hydroxyl diastereomer (**14a**) and aldehydes. Thus, three different dimeric steroids were isolated: a symmetrical dimer (**29**, **32**) bearing two 1,3-azido alcohol moieties

on rings D, another symmetrical dimer (**31**, **34**, **36**) bearing 5",6"-dihydro-*4"H*-1",3"-oxazine heterocycles on ring D of both monomers; and an asymmetrical dimer which was a hybrid of the previous two, bearing a dihydrooxazine heterocycle and an unchanged 1,3-azido alcohol function on rings D (*Figure 6*).

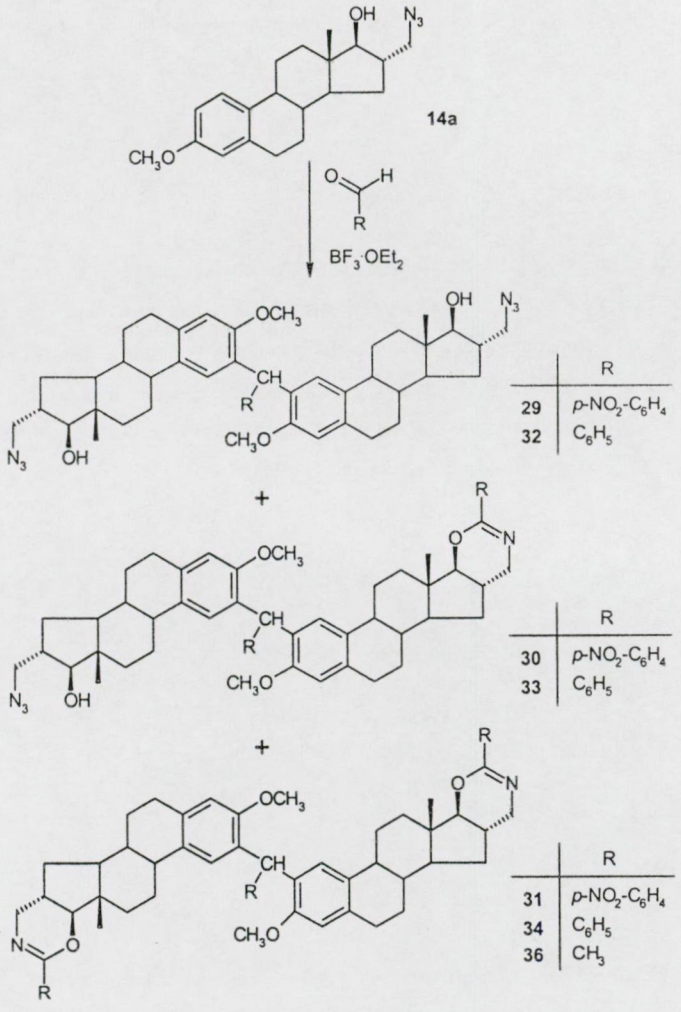
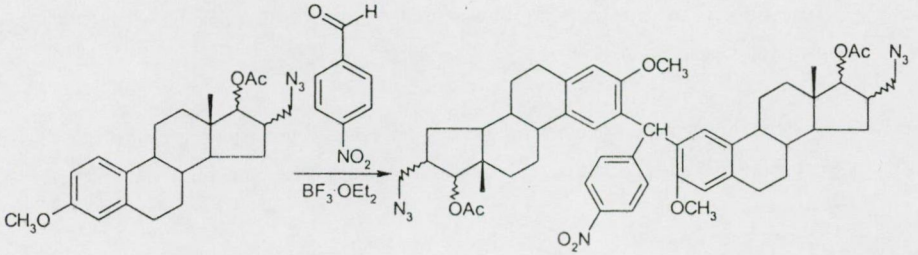


Figure 6

3.13. The dimerization of the dihydrooxazines anellated to 16β,17β or 16α,17α positions of the estrane skeleton (**20g**, **22a**) were also achieved. These reactions evidenced that the ring A of the *cis* isomers could take part in a *Friedel-Crafts* type dimerization process.

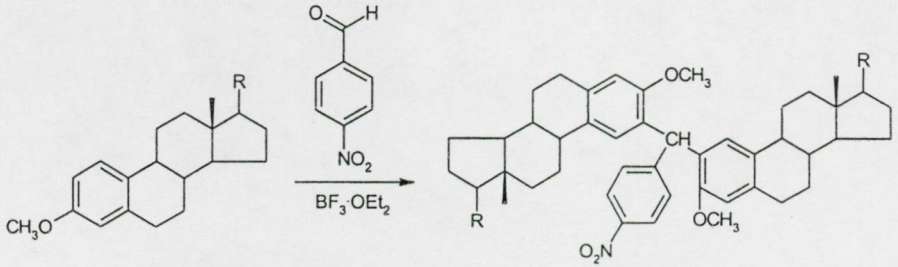
3.14. In the presence of *p*-NO_2-benzaldehyde and $BF_3{\cdot}OEt_2$, the four 16-azidomethyl-17-acetoxy isomers (**13b-16b**) (*Figure 7*), the 3-methoxyestra-1,3,5(10)-trien-17-on (**45**) and the 3-methoxyestra-1,3,5(10)-trien-17β-ol (**46**) (*Figure 8*) also formed the corresponding bis-steroids (**41-44**, **47**, **48**, respectively) anchored in the 2,2' positions by a benzylidene group with the same rate.



13b: 16β,17β
16b: 16α,17α
15b: 16β,17α
14b: 16α,17β

41: 16β,17β
42: 16α,17α
43: 16β,17α
44: 16α,17β

Figure 7



45: R= =O
46: R= 17β–OH

47: R= =O
48: R= 17β–OH

Figure 8

3.15. It was proved that in the case of the *cis* isomers (**13a**, **16a**) the rate of the *Schmidt* type ring-closure reaction was higher than that of the secondary *Friedel-Crafts* alkylation. In the case of the *trans* isomers (**14a**, **15a**), the alkylation leading to dimerization was the primary process and the probable ring-closure was the secondary. Moreover, it was evidenced that the substituents on ring D did not influence the alkylation and dimerization processes.

3.16. The 17β,16β-epoxymethylene-3-methoxyestra-1,3,5(10)-triene (**5**) readily reacted with acetaldehyde and acetone in the presence of *Lewis* or *Brønsted* acids leading to ring-expanded compounds. It was proved with spectroscopic methods that 1,3-dioxane derivatives (**49**, **53**, **54**) were the main products. According to our studies, the *Wagner-Meerwein* rearranged side-product (**10**) was formed in the smallest amount when $BF_3 \cdot OEt_2$ was used as a catalyst.

3.17. A new chirality center was formed in the ring-expansion reaction with acetaldehyde, thus, two epimeric dioxane derivatives (**53**, **54**) were isolated. Their structures were proved by spectroscopic methods.

3.18. An isomeric ratio of *S*:*R* = 2.6 was observed in every acid-catalyzed reactions. Furthermore, each of the diastereomers transisomerized into the other under acidic conditions, and the isomeric ratio was the same. The equilibrium was proved to be dependent on the solvent and temperature (*Figure 9*).

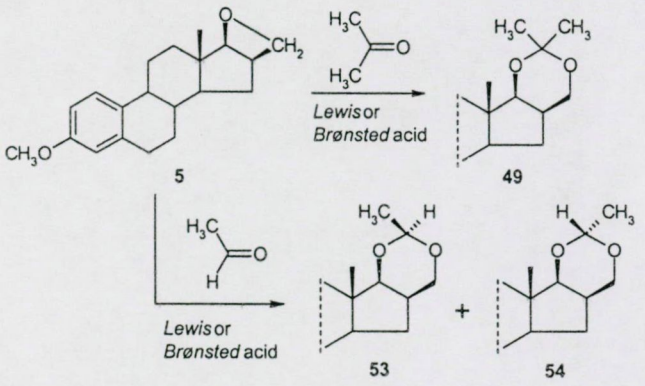
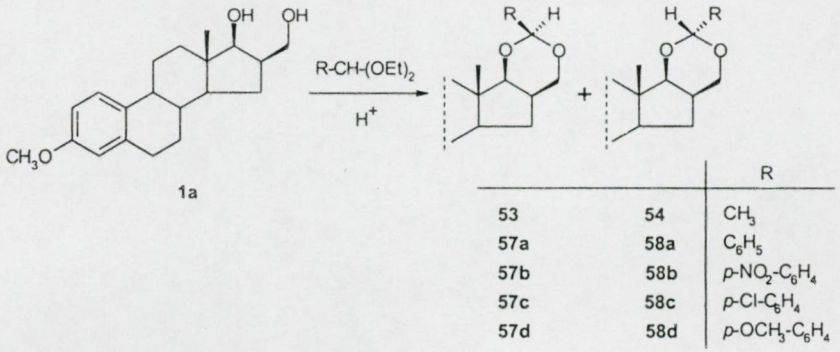


Figure 9

3.19. In the transacetalization reaction of the 16β-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**1a**) with acetaldehyde, benzaldehyde and *p*-substituted benzaldehyde diethyl acetals, two epimeric products were formed. These epimers could be separated by chromatography. In these reactions, the 1,3-dioxane derivatives (**53**, **54** and **57a-d**, **58a-d**) were prepared without side-products over a short reaction time (*Figure 10*).

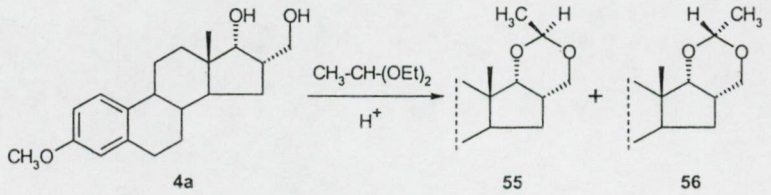


1a

		R
53	**54**	CH_3
57a	**58a**	C_6H_5
57b	**58b**	*p*-NO_2-C_6H_4
57c	**58c**	*p*-Cl-C_6H_4
57d	**58d**	*p*-OCH_3-C_6H_4

Figure 10

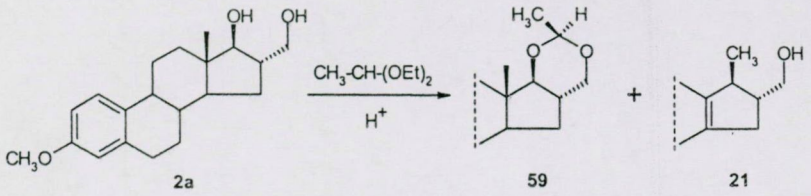
3.20. The transacetalization reaction was extended to the 16α-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17α-ol (**4a**). Similarly to the 16β,17β diastereomer (**1a**), two epimeric 1,3-dioxane derivatives (**55**, **56**) were formed without side-products (*Figure 11*).



4a **55** **56**

Figure 11

3.21. The synthesis of *trans* anellated dioxanes condensed to ring D of the estrane skeleton was also achieved. The reaction of the 16α-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (**2a**) with acetaldehyde diethyl acetal resulted in a single epimer (**59**) together with a *Wagner-Meerwein* rearranged side-product (**21**). The 16β-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17α-ol (**3a**) failed to give dioxane derivatives under the same conditions (*Figure 12*).



2a **59** **21**

Figure 12

List of publication on which the thesis is based

Articles

1. **Hajnal, A.**, Wölfling, J., Schneider, Gy.
   One-step conversion of oxetane-fused to 1,3-oxazine-fused steroids
   Collect. Czech. Chem. Commun. **1998**, *63*, 1613. IF: 0.960

2. Bes, T., **Hajnal, A.**, Schneider, Gy., Noltemeyer, M., Wölfling, J.
   A steroidal dihydro-1,3-oxazine derivative
   Acta Cryst. **1998**, *C54*, 372. IF: 0.543

3. Hewitt, M., Schneider, T. R., Szemerédi, Zs., **Hajnal, A.**, Wölfling, J., Schneider, Gy.
   A steroidal phenyldihydro-1,3-oxazine derivative
   Acta Cryst. **2000**, *C56*, e363. IF: 0.543

4. **Hajnal, A.**, Wölfling, J., Schneider, Gy.
   Novel preparation of dihydrooxazines condensed to ring D of the estrane skeleton
   Synlett **2002**, *7*, 1077. IF: 2.763

5. Wölfling, J., **Hajnal, A.**, Mák, M., Schneider, Gy.
   Synthesis of novel ethylidene- and benzylidene-linked dimeric estrone derivatives
   Tetrahedron **2002**, (submitted)

6. **Hajnal, A.**, Wölfling, J., Schneider, Gy.
   Novel preparation of 1,3-dioxanes condensed to ring D of the estrane skeleton and examination of their isomerisation
   J. Chem. Soc., Perkin Trans. 2. **2002**, (under preparation)

Conferences

1. **Hajnal, A.**, Wölfling, J., Schneider, Gy.
   Article 062,*"Electronic Conference on Heterocyclic Chemistry '96"*, H. S. Rzepa, J. Snyder and C. Leach, (Eds.), Royal Society of Chemistry. ISBN 0-85404-894-4. See also http://www.ch.ic.ac.uk/cctoc/echet96/

2. **Hajnal, A.**
   Ritter reaction of steroid oxetanes
   XIX. KEN. Organic, Pharmaceutical and Biochemical Symposium
   Szeged, 28-30 October 1996

3. **Hajnal, A.**
   Ring expansion reaction of steroid oxetanes with nitriles
   Autumn Scientific Conference for Students
   Szeged, 17 December 1996

4. **Hajnal, A.**
   Ring expansion reaction of steroid oxetanes with nitriles
   XXIII. National Scientific Conference for Students
   Pécs, 4-7 April 1997

5. **Hajnal, A.**, Wölfling, J., Schneider, Gy.
   Ring expansion of steroid oxetanes into acetals
   Annual Meeting of Hungarian Chemical Society
   Eger, 22-24 June 1999