A Retro Diels-Alder Synthetic Method. Fused-Skeleton Isoindolones and Further Saturated Hetero Polycycles

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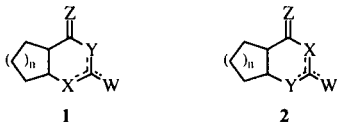
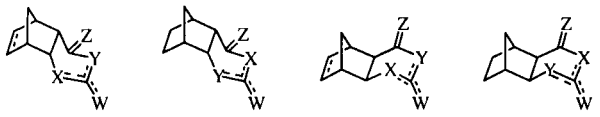
1. Introduction.

In our earlier studies on fused-skeleton saturated heterocycles, we have prepared several classes of six-membered 1,3-hetero compounds, *cis*- and *trans*-fused with different saturated or partly saturated carbocycles or heterocycles (Figure 1) [1]. The products include complete series with the general structures **1** and **2**, containing the hetero atoms X and Y in isomeric 1,3 and 3,1 positions: among others, fused-skeleton dihydro- and tetrahydro-1,3-oxazines, 1,3-thiazines, 1,3-oxazin-2-ones, 1,3-oxazin-4-ones and pyrimidinones. Norbornane and norbornene di-*endo*- (**3**, **4**) or di-*exo*-condensed hetero derivatives (**5**, **6**) have also been synthetized. Last year, a review [2] was published on this and related topics.



1 **2**

cis or *trans*; n = 1-4; X, Y = O, S, N, NH, NR; Z = H_2, O, S; W = H_2, Ar, HR, HAr, $(CH_2)_m$, O, S, NAr; m = 5, 6



3 **4** **5** **6**

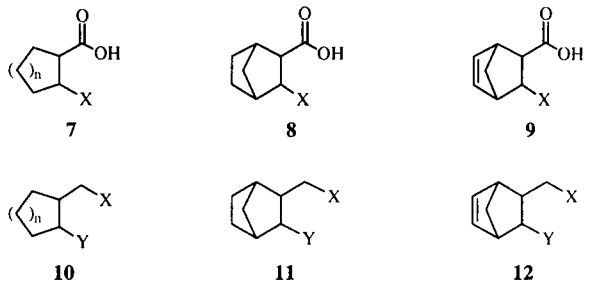
X, Y = O, S, N, NH, NR; Z = H_2, O; W = H_2, Ar, HAr, O, S, NAr

Figure 1. Fused-skeleton saturated heterocycles prepared.

Our investigations on saturated heterocycles were initiated by the surprising finding that, in spite of the fact that the chemistry and pharmacology of the bicyclic aromatic 1,3-heterocycles had been very thoroughly studied since the early years of this century, their saturated analogues were not synthetized until the seventies [3].

For many decades, the chemistry of saturated heterocycles was regarded as a part of alicyclic chemistry and not as an independent research topic. In general, the term heterocyclic compounds covered merely the aromatic heterocycles. This can be demonstrated by the fact that the important series of monographs A Specialist Periodical Reports included publications on saturated heterocyclic chemistry from the period 1970-1971 in the volume "Aliphatic, Alicyclic, and Saturated Heterocyclic Chemistry" [4]. The title "Saturated Heterocyclic Chemistry" was used first for Volume **2** in 1974. And very soon, the Foreword to Volume **5** of this series announced [5] that it was the final report under the heading Saturated Heterocyclic Chemistry. The reasoning, based on financial considerations, convincingly shows that not too many research groups dealt with saturated heterocycles even in the 1970's.

Our investigations on bicyclic saturated 1,3-hetero compounds [1,2,6] were performed mainly with synthetic, stereochemical and pharmacological aims. Stereohomogeneous β-hydroxy acids, β-amino acids and 1,3-aminoalcohols were used for the preparation of alicycle-fused 1,3-heterocycles. Few of these starting materials, alicyclic *cis*- and *trans*-β-hydroxy acids (**7-9**, X = OH) and β-amino acids (**7-9**, X = NH_2) (Figure 2), had been described before our work. Most of the 1,3-aminoalcohols of types **10-12** were first prepared in stereohomogeneous form by us. The methods of preparation have been detailed in our two main series of papers [6,7].



7 **8** **9**

10 **11** **12**

cis or *trans*; n = 1-4 di-*endo* or di-*exo*

X, Y = OH, NH_2

Figure 2. Stereohomogeneous starting materials.

These 1,3-aminoalcohols and related alicyclic 1,2-disubstituted 1,2- and 1,3-difunctional derivatives, β-hydroxy acids, β-amino acids, and di-*endo*- and di-*exo*-norbornane and norbornene derivatives first became available commercially some 8 years ago due to our cooperation with the company Janssen, now ACROS [8].

Both of the alicyclic *cis* and *trans* 1,2- and 1,3-difunctional starting materials and the target compounds, stereohomogeneous *cis* and *trans* isomeric and homologous 1,3-heterocycles, differing in the size of the rings fused to the 1,3-heterocycles, furnished the possibility of numerous comparative spectroscopic (mainly nmr, ms and X-ray) and kinetic studies [1,2]. Discussion of these investigations is beyond the topic of the present lecture.

2.1. A Retro Diels-Alder Method for Preparation of 1,3-Heterocycles.

Several years ago, we devised a convenient new method [9] for the preparation of monocyclic 1,3-hetero compounds by applying a very mild retro Diels-Alder (RDA) process. The principle of this procedure is the synthesis of the partially saturated parent heterocycle on cyclopentadiene (**13**) *via* a key intermediate, di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**14a,b**), and the cleavage of cyclopentadiene (**13**) from the condensed-skeleton molecule **15**. In this final reaction step, a new double bond is introduced into the heterocycle **16**. By this method, heterocycles **17-20** could be prepared among others (Scheme 1).

The advantages of our RDA synthesis method are as follows:

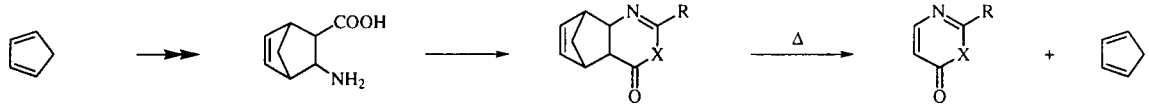
- In contrast with other retrodiene reactions, which usually require drastic conditions and sometimes even special equipment, *e.g.*, in the case of flash vacuum pyrolysis, this process takes place under mild conditions, at the melting temperature of the compounds, or during reflux in an inert solvent, such as toluene, xylene or chlorobenzene.
- A one-pot procedure is also often possible without isolation of the norbornene-fused heterocycles.
- The synthetic pathway is unambiguous. Isomerization and rearrangement do not occur.
- The method is suitable for the simple and unambiguous synthesis of disubstituted monocyclic, bicyclic and tricyclic heterocycles which were attainable previously only with difficulty by other procedures.

Gupta and coworkers [10] erroneously described a number of 1,2-disubstituted pyrimidinones as 2,3-disubstituted derivatives. By means of our RDA method, we were able to demonstrate that the pyrimidinones described by those authors are not 2,3-, but 1,2-disubstituted derivatives.

2.2. Preparation of Heterobicycles by the RDA Method.

We reported [11] the first retrodiene process which yielded bicyclic heterocycles. The di-*endo* or di-*exo* amino acid esters **21a** or **21b** were reacted with β-chloroethyl or γ-chloropropyl isothiocyanate to give the tetracyclic heterocycles **22** or **23**, which, *via* the RDA process, yielded thiazolo[3,2-*a*]pyrimidin-5-one (**24a**) or the then unknown parent compound, pyrimido[2,1-*b*]thiazin-6-one (**24b**) (Scheme 2).

Scheme 1



13 di-*endo*: **14a** di-*exo*: **14b** **15** **16** **13**

R = H, Alkyl, Aryl; X = O, S, NH, NR

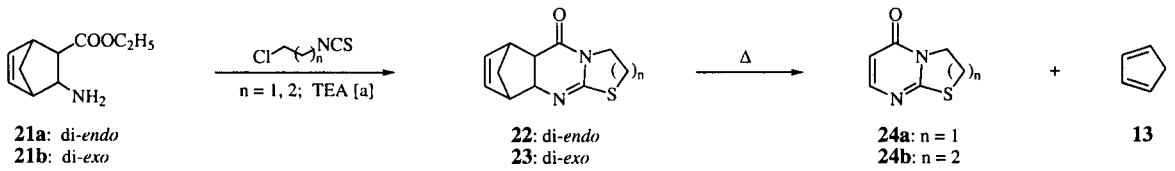
17 **18** **19** **20**

R^1, R^2, R^3 = H, Alkyl, Ph, Substituted Ph

The process can be performed only when the target compound acquires a heteroaromatic or quasi-heteroaromatic character by the cleavage of cyclopentadiene. If no conjugation is possible in the product, no RDA splitting is to be expected.

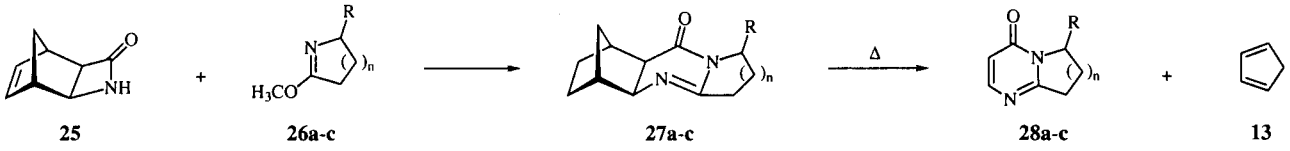
From the norbornene di-*exo*-fused azetidinone **25** the tetracyclic pyrimidinone derivatives **27a-c** were prepared [12] in ring-expansion reactions with lactim ethers **26a-c**. When **27a-c** were melted for 30 minutes, pyrrolo-, pyrido- or azepino[1,2-*a*]pyrimidinones **28a-c** were formed (Scheme 3).

Scheme 2



[a] TEA: Triethylamine.

Scheme 3



n = 1-3; R = H, CH_3

2.3. Preparation of Heterotricycles by the RDA Method.

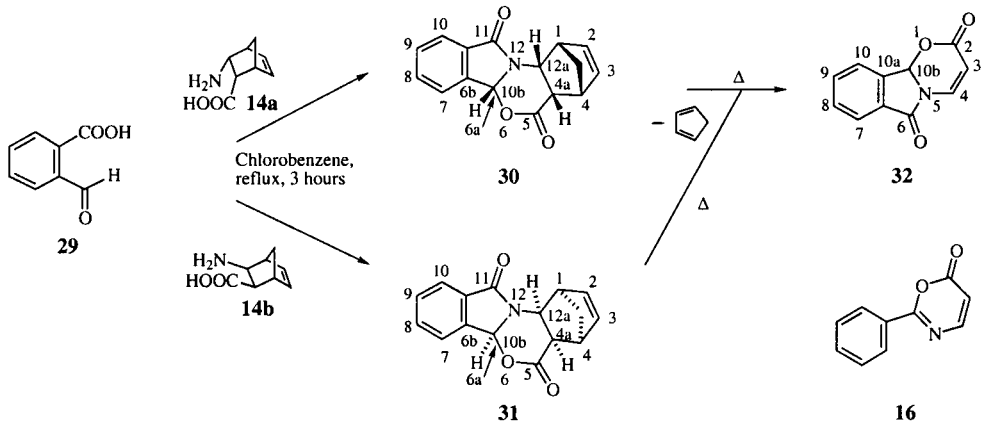
Quite recently, we reported [13] the first preparation of a heterotricycle, [1,3]oxazino[2,3-*a*]isoindole-2,6-dione (**32**), by the RDA method (Scheme 4). The reactions of 2-carboxybenzaldehyde (**29**) with the di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids (**14a,b**) yielded the 1,4-methanotetrahydroisoindolo[2,1-*a*]-[3,1]benzoxazine-6,12-diones (**30**, **31**) in moderate yields (45-54%). Compounds **30** and **31** are isoindolone-fused heterocycles. Further isoindolone derivatives will be discussed subsequently. In the pentacyclic compounds **30** and **31**, the di-*endo*- or di-*exo*-norbornene annulational hydrogens and the 1,3-oxazinoisoindole-2,6-dione NC*H*O hydrogen, *i.e.*, H-4a, H-10b and H-12a, are all in the *cis* arrangement.

Compounds **30** and **31** undergo retrodiene decomposition when they are heated to their melting temperatures. Cyclopentadiene (**13**) is cleaved and 2*H*,6*H*-1,3-oxazino-[2,3-*a*]isoindole-2,6-dione (**32**) is isolated in 38-42% yield.

In the preparations of heteromonocycles and bicycles, cycloreversion proceeds readily, *i.e.*, a double bond is formed in the target molecule if an oxo- or thioxo-substituted heteroaromatic or quasi-heteroaromatic system is formed, such as pyrimidinone, pyrimidinedione, thioxopyrimidinone or 1,3-oxazin-6-one.

The present case is the first example of the formation of a fused tricyclic heterocycle containing two fused and partially saturated hetero rings and one aromatic ring in a RDA reaction. The structure of **32** is very similar to that

Scheme 4

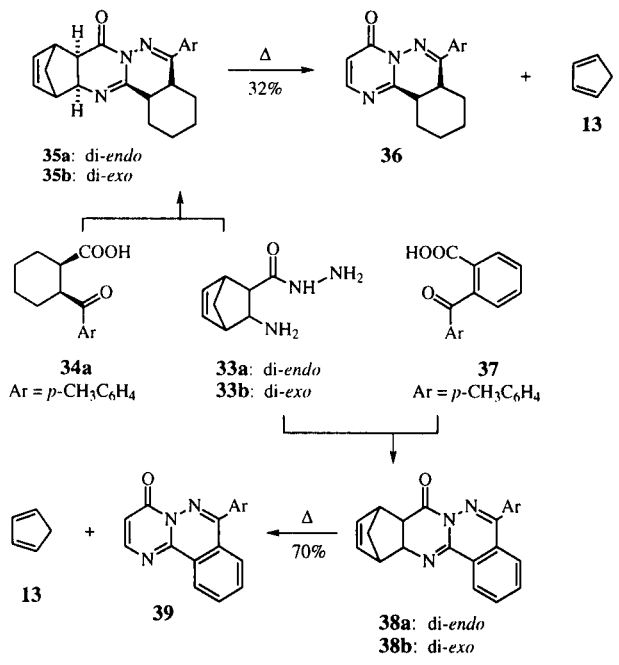


of the heteromonocycle 2-aryl-1,3-oxazin-6-one (**16**), which was also prepared by a RDA reaction, with the difference that **32** contains no C=N double bond between the aryl-substituted carbon and the nitrogen of the oxazinone ring. However, in the structure of **32**, a fused aromatic ring is attached to the sp^3 carbon situated between the two hetero atoms, and a benzoyl carbonyl is attached to the bridgehead nitrogen. This structural moiety lends a quasi-aromatic character to the 1,3-oxazin-6-one system through formation of the C_3-C_4 double bond with the cleavage of cyclopentadiene. Nevertheless, the second double bond is missing from the six-membered heterocycle. Therefore, the energy difference between the hetero-aromatic monocyclic and quasi-aromatic tricyclic systems is reflected by the much higher temperature necessary for the formation of **32**.

Our RDA method affords a simple synthesis of the previously unknown heterotricycle **32**. This result encouraged us to extend the scope of the RDA method to the preparation of more complicated heterocycles in which the electrons required for the heteroaromaticity or quasi-aromaticity are supplied by heteroatoms instead of a C-C or a C-N double bond.

Quite recently, we devised a new method for preparing pyrimido[2,1-*a*]phthalazinones by the RDA method (Scheme 5) [14]. The aminocarbohydrazides **33a**, **33b** and *cis*-2-(*p*-methylbenzoyl)-1-cyclohexanecarboxylic acid (**34a**) or 2-(*p*-methyl)benzoylbenzoic acid (**37**) were applied to prepare heterotricycles **36** and **39** containing two condensed heterocyclic rings and one alicyclic or aromatic ring.

Scheme 5

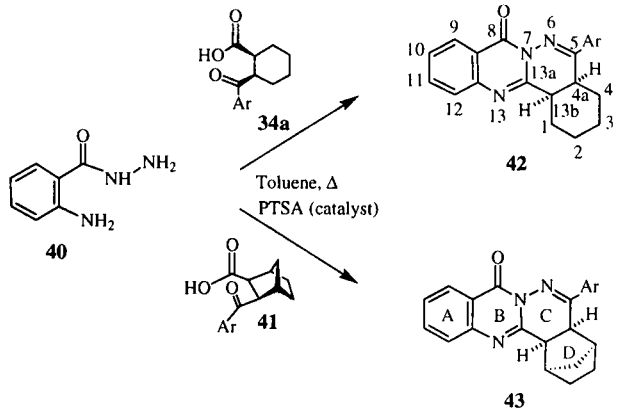


Similarly as observed earlier for related norbornene-fused 1,3-heterocycles, **35a,b** and **38a,b** undergo retrodiene decomposition when heated to their melting points; cyclopentadiene is cleaved and pyrimido[2,1-*a*]phthalazines **36** and **39** are formed in yields of 32% and 70%, respectively. In this case, too, the yields reflect the role of the aromaticity of the heterocycles formed in the final step of the process. Compound **39** with a wholly aromatic structure is formed in much higher yield than **36** with the alicyclic ring C.

3. Preparation of Phthalazino[1,2-*b*]quinazolinones.

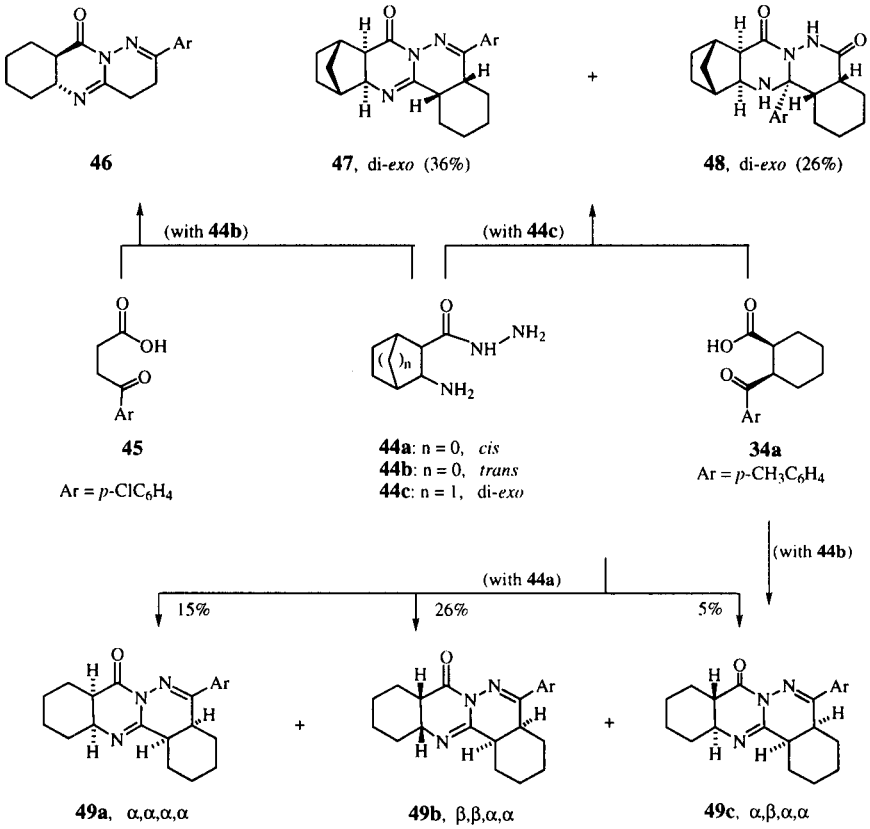
By the reaction of anthranilic hydrazide (**40**) with *cis*-2-(*p*-methylbenzoyl)-1-cyclohexanecarboxylic acid (**34a**) or di-*endo*-3-(*p*-methylbenzoyl)bicyclo[2.2.1]heptane-2-carboxylic acid (**41**), by boiling in toluene in the presence of *p*-toluenesulfonic acid as catalyst, the tetra- and pentacyclic compounds **42** and **43** were prepared (Scheme 6) [15]. These phthalazino[1,2-*b*]quinazolinones contain a *cis*-fused cyclohexane or a di-*endo*-fused norbornane terminal moiety in parts C/D of the molecules. As far as analogues are concerned, merely compounds fused with aromatic rings at both terminals are known.

Scheme 6



For the preparation of derivatives containing two saturated terminal rings, *cis*- and *trans*-2-amino-1-cyclohexanecarbohydrazides (**44a,b**) or the di-*exo*-norbornane hydrazide **44c** were reacted with the alicyclic or aliphatic γ-oxocarboxylic acids **34a** and **45**, respectively (Scheme 7). The reaction of 3-(*p*-chlorobenzoyl)propionic acid (**45**) with **44b** furnished the *trans*-pyridazino[6,1-*a*]quinazolinone **46**. In the reaction of di-*exo*-3-aminobicyclo[2.2.1]-heptane-2-carbohydrazide (**44c**) with **34a**, a mixture of **47** and **48** was formed in 36% and 26% yields, respectively. The reaction of the *cis*-2-amino-1-cyclohexanecarbohydrazide (**44a**) with *cis*-2-(*p*-methylbenzoyl)-1-cyclohexanecarboxylic acid **34a** resulted in a mixture of **49a-c**. Compound **49c** was also synthesized by the reaction of **34a** and **44b**.

Scheme 7



An interesting feature of these new compounds arises from the saturated skeleton. The previously described aromatic analogues have simpler structures, because no alternative *cis* or *trans* fusions of the terminal rings are possible. The stereochemistry determination was a challenging task. In the case of compounds **47** and **48**, not only the *cis-trans* ring fusions, but also the position of the aromatic substituent has to be elucidated.

The stereochemistry determination of these compounds was performed by nmr methods, including Distortionless Enhancement by Polarization Transfer (DEPT), Differential nOe (DNOE) and Two-dimensional Heteronuclear Shift Correlation (2D-HSC) measurements, and the X-ray structure determinations of **49a** and **49b** were also performed. In **49a**, the four annulational hydrogens are α,α,α,α, whereas in **49b** they are in the β,β,α,α positions. Consequently, in the formation of **49a** and **49b**, no isomerization of the reactants occurred. In the third reaction product **49c**, which formed in a yield of 5%, rings A/B are *trans*-fused, whereas rings C/D are in *cis* connection, *i.e.*, the ring closure took place with isomerization of the starting *cis*-2-amino-1-cyclohexanecarbohydrazide (**44a**).

4. Isoindolone-fused Saturated Heterocycles.

Several years ago, we started systematic investigations on the synthesis of isoindolone-fused saturated heterocycles. We synthesized partially saturated new tetracyclic and pentacyclic isoindolo[2,1-*a*][3,1]benzoxazine, isoindolo[2,1-*a*][3,1]benzoxazepine and the related derivatives [1,16]. The target compounds are of pharmacological interest because the related aromatic analogues possess anorexic, anti-HIV, anti-inflammatory or anti-allergic effects [17].

Versatile synthons, such as saturated γ-oxocarboxylic derivatives (**34a,b**, **41**, **50**, **51**), were synthesized (Figure 3) [18,19]. The reactions of these synthons with difunctional compounds, including 1,3-aminoalcohols, diamines, *o*-thiophenol, *etc.*, resulted in isoindolones and further heterocyclic derivatives. Prior to our investigations, several analogous aromatic isoindolones were known. These were synthesized by means of condensing agents **37** and **52**, which were also applied in our syntheses in several cases.

In the framework of our research, a great number of different isoindolone-fused tri-, tetra-, penta-, hexa- and heptacyclic saturated derivatives have been prepared with

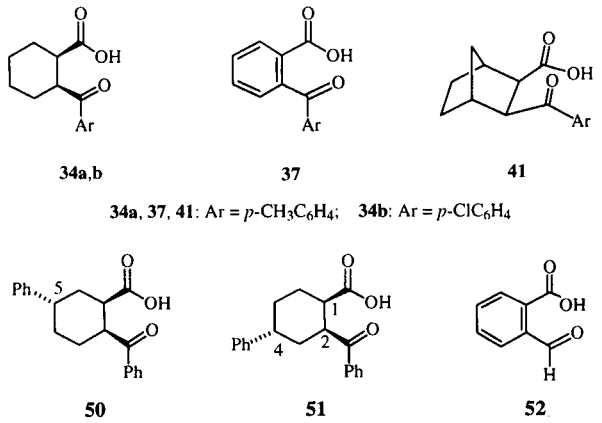
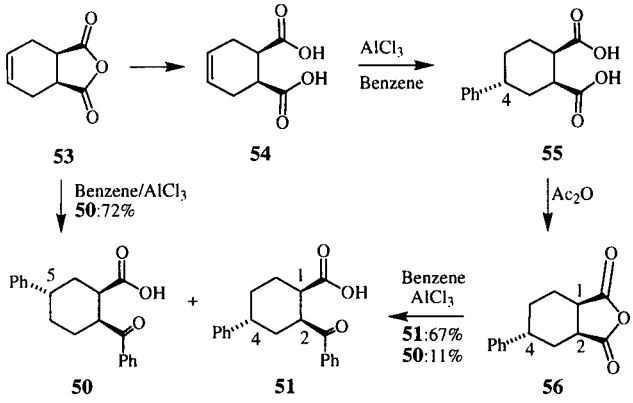


Figure 3. Synthons for preparation of fused isoindolones.

Scheme 8



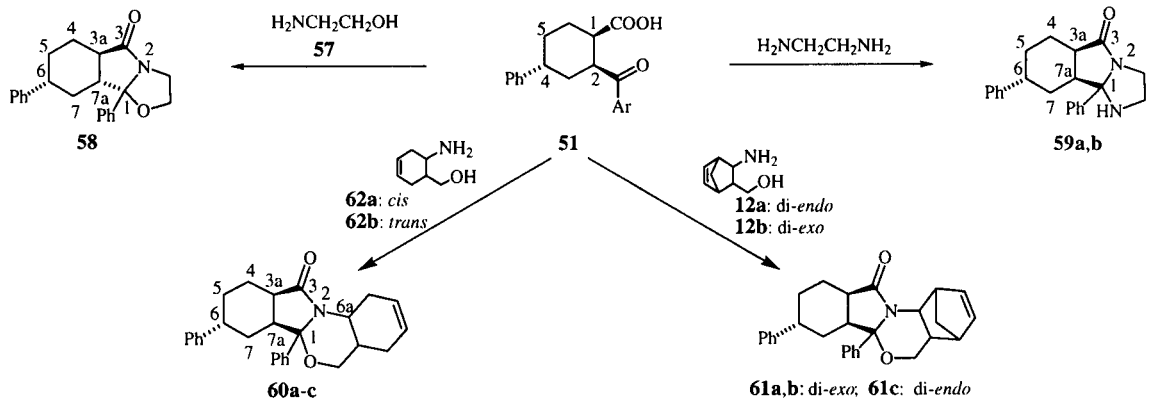
pharmacological, stereochemical and other aims. The preparation of a new tricyclic oxazinoisoindoledione (**32**) (Scheme 4) was discussed above. The intermediates of the preparation of this compound were norbornene-fused pentacyclic isoindolones (**30, 31**). The norbornane-fused saturated pentacyclic analogues of **30** and **31** were also prepared, which, of course, are not intermediates for RDA processes.

Scheme 8 shows the synthesis of two synthons, **50** and **51**, used for the preparation of saturated fused isoindolones and other heterocycles. *cis*-2-Benzoyl-*trans*-5-phenyl-1-cyclohexanecarboxylic acid (**50**) was prepared in 72% yield in a one-step acylation-addition reaction of benzene to *cis*-1,2,3,6-tetrahydrophthalic anhydride (**53**). The 4-phenyl isomer **51** was obtained by $AlCl_3$-catalyzed benzene addition in the reactions **54** → **55** → **56** → **51** in a yield of 67% for **51** and 11% for **50** [19]. The minor product **50** was separated by crystallization.

It is worthwhile mentioning that Mathur *et al.* [20] stated that, under Friedel-Crafts conditions, the reaction of **53** gives 2-aroyl-4-cyclohexene-1-carboxylic acid. In contrast, we found that **50** was formed.

The versatile synthons **50** and **51** were reacted with bifunctional compounds. With ethanolamine (**57**), **51** yielded the saturated oxazolo[2,3-*a*]isoindolone **58**. With ethylenediamine, a mixture of two isomers **59a** and **59b** was formed. While in the reactions of **51** with *cis*- and *trans*-2-hydroxymethyl-4-cyclohexenyl-1-amines (**62a,b**), three diastereomers, **60a-c**, were obtained. Compound **51** reacted with di-*exo*- and di-*endo*-3-hydroxymethylbicyclo[2.2.1]hept-5-enyl-2-amines (**12b** and **12a**) to yield two di-*exo* diastereomers **61a** and **61b** and a norbornene-di-*endo*-fused saturated isoindolo[2,1-*a*][3,1]-benzoxazinone derivative **61c** (Scheme 9) [19].

Scheme 9



It must be stressed that the saturated isoindolone moiety always proved to be *trans* in compounds **58-61**. Consequently, a *cis* → *trans* isomerization took place in the ring closures. This deserves attention because our earlier experiments indicated, as a general rule, that the ring-closing reactions of the *trans*-1,2-disubstituted 1,2- or 1,3-difunctional cyclopentane derivatives to cyclopentane-*trans*-fused six-membered 1,3-heterocycles were successful merely in very special cases [21]. During the attempted ring closure of the *trans* cyclopentane derivatives, in fact, *trans* → *cis* isomerization occurred. In contrast, the *cis* ring closures were always facile processes.

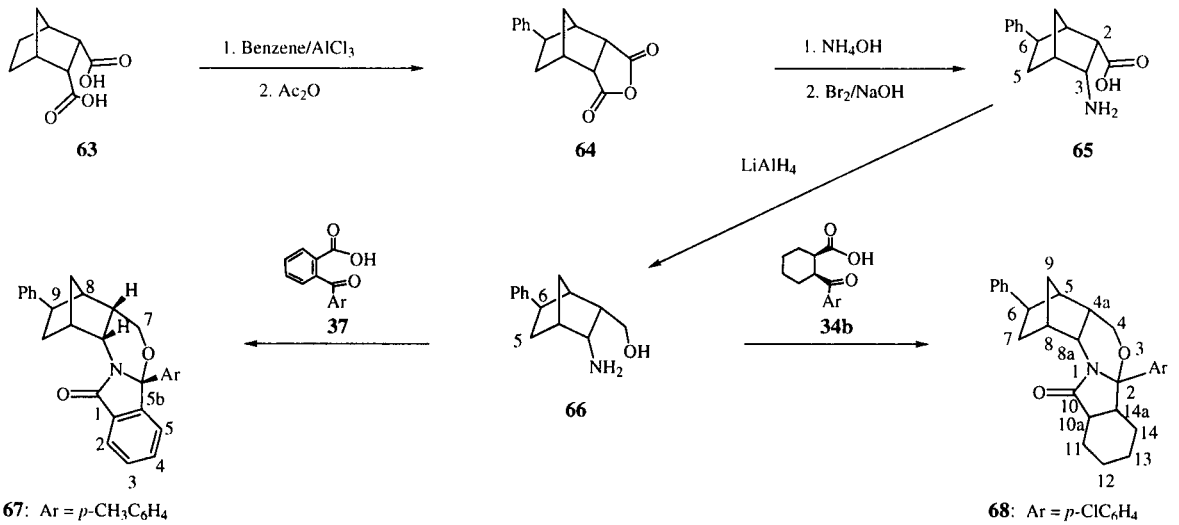
In the ring closure of the 2-benzoyl-1-cyclohexanecarboxylic derivatives, isoindolones were formed with a phenyl substituent in the annulational position. In these reactions, isomerization of the starting 2-benzoyl-1-cyclohexanecarboxylic acids was often observed. The configurations and conformations of compounds **58-61** could be deduced from ^{1}H and ^{13}C nmr measurements.

Further related isoindolone derivatives were also synthesized (Scheme 10). From *cis*-5-norbornene-*endo*-2,3-dicarboxylic acid (**63**) by addition of benzene under Friedel-Crafts conditions and subsequent treatment with acetic anhydride, **64** can be obtained. Compound **64** furnished the amino acid **65** *via* the monocarboxamide through Hoffmann degradation with hypobromite. Lithium aluminium hydride reduction of the amino acid **65** yields the phenyl substituted di-*endo*-3-aminonorbornane-2-methanol **66**. Although this pathway could result in both 5- and 6-phenyl derivatives, we were able to isolate only the 6-phenyl derivative **66**. Cyclizations of the 1,3-amino alcohol **66** with 2-(*p*-methylbenzoyl)benzoic acid (**37**) or *cis*-2-(*p*-chlorobenzoyl)-1-cyclohexanecarboxylic acid (**34b**) led to the methylene-bridged isoindolo[2,1-*a*][3,1]benzoxazines **67** and **68**, respectively [22]. The stereochemistry of **67** and **68**, including the positions of the substituted phenyl groups, could be deduced from the nmr data.

As an example of *cis* → *trans* isomerization during the ring closure, the reaction between *cis*-2-(*p*-methylbenzoyl)-1-cyclohexanecarboxylic acid (**34a**) and 2-aminoethanethiol (**69**) was investigated. The reaction furnished three perhydrothiazolo[2,3-*a*]isoindolone isomers (**70-72**) in yields of 56%, 11% and 8%, respectively (Scheme 11). The structures were deduced by means of nmr measurements and supported by DNOE measurements. For **72**, the mutual intensity enhancement on the two other signals on saturation of one of the H-5a, H-9a or Ar-H signals confirms the proximity of the annulational hydrogens 5a, 9a and the tolyl group. However, in the case of **72**, instead of similar interactions, nOe was observed between the 1,3-di-*axial* H-9a and H-8*ax*.

The *cis* → *trans* isomerization that occurs in the formation of the saturated isoindolones deserves attention. We observed a *cis* → *trans* isomerization in the intramolecular transacylation of the cyclohexane-fused azetidinone derivatives **74** [Ar = C_6H_5, *m*-ClC_6H_4, *p*-ClC_6H_4] (Scheme 12) [23]. In the ring-expansion reactions only the *trans* isomers of **75** were formed. In contrast, under similar conditions, no isomerization was found in the case

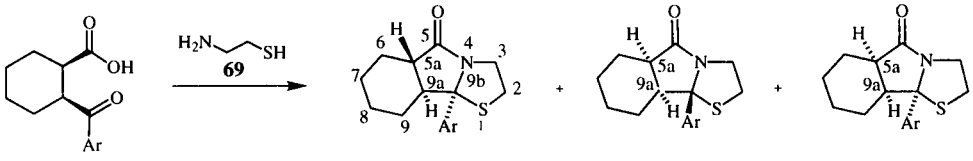
Scheme 10



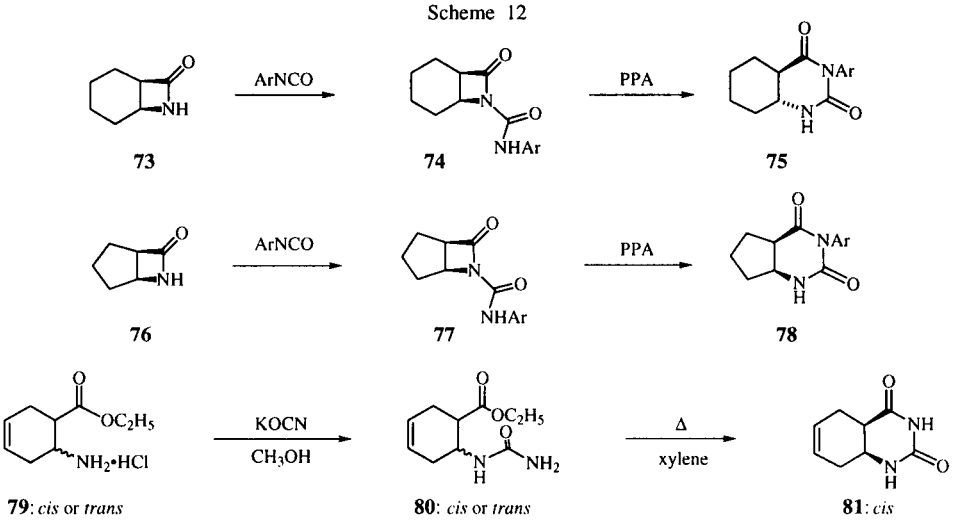
of the cyclopentane-fused system **77** and the *cis*-cyclopentane-fused compounds **78** were formed. As mentioned above, as a general rule, the formation of cyclopentane-*trans*-fused 1,3-heterocycles is energetically considerably less favored than the formation of the *cis*-fused isomers.

1:1 mixture of the ketones **82** and **83** with **84** gave the same product (**91**) in lower yield (56%). This proved a slow isomerization of **83** to **82**. The reactions of **82** with 1,2- or 1,3-propanolamine (**85**, **87**), 1,4-diaminobutane (**88**), *o*-aminothiophenol (**89**) or di-*exo*-norbornane and

Scheme 11



Scheme 12



The *trans* → *cis* isomerizations are less common, but also occurred in the thermal cyclization of *trans*-2-ethoxycarbonyl-1-cyclohex-4-enyl urea **80** to cyclohexene-condensed urea **81**. Both *cis* and *trans* **80** furnished only the *cis*-annulated derivative **81** (Scheme 12) [23].

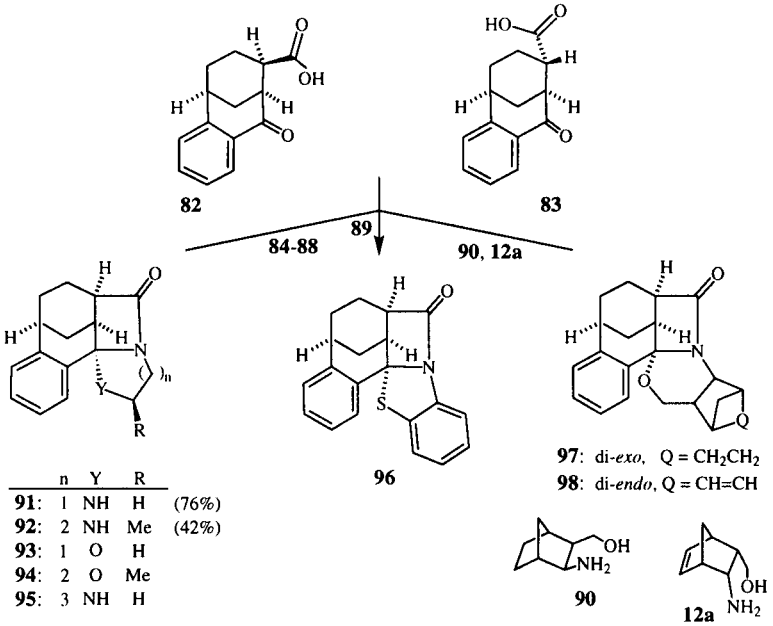
When the γ-oxocarboxylic acid **82** (5*r*,6,7,8*c*,9*c*,10-hexahydro-5,9-methano-10-oxo-benzocyclooctene-8-carboxylic acid) was refluxed with 1,2- or 1,3-diaminopropane (**84**, **86**) in dry chlorobenzene in the presence of *p*-toluenesulfonic acid as catalyst for 6 hours, the pentacyclic ketones **91** and **92** were formed in a yield of 76% or 42%, respectively (Scheme 13) [24]. Application of a di-*endo*-norbornene 1,3-aminoalcohols **90** and **12a** yielded penta-, hexa- and heptacyclic heterocycles **93-98** with one or two aromatic rings on the terminals (Scheme 13).

The stereochemistry was determined by nmr measurements and, in several cases, was supported by X-ray determinations. The doublet splitting (J = 7.3 Hz) of the NC*H* signal in **97** and the doublet of doublet structure (J = of 8.3 and 3.5 Hz) of the same signal in **98** confirm the di-*exo* **97** and di-*endo* **98** annulation, respectively, of the terminal bicycles to the skeleton. These structures were proved independently by means of nOe measurements. Interactions were observed between the *axial* OCH_2

hydrogen and the *endo*-H of the bridging methylene hydrogen in **97** and between the latter atom and the NC*H* hydrogen in **98**. The X-ray structure of **97** [25] is in complete agreement with the conformation deduced from the nmr data.

ring enlargement reaction (Scheme 14). The β-keto ester **101** is mainly in the enol form and forms a stable complex **102** with the excess of boron trifluoride ethyl etherate. The ethoxy group of **102** can be exchanged with primary and secondary amines to yield **103** (Scheme 14).

Scheme 13



	n	Y	R	
91:	1	NH	H	(76%)
92:	2	NH	Me	(42%)
93:	1	O	H	
94:	2	O	Me	
95:	3	NH	H	

84 (X = NH_2) and **85** (X = OH): $H_2NCH_2CH(CH_3)X$; **86** (m = 3, X = NH_2), **87** (m = 3, X = OH) and **88** (m = 4, X = NH_2): $H_2N(CH_2)_mX$; **89**: $H_2NC_6H_4SH$-*o*

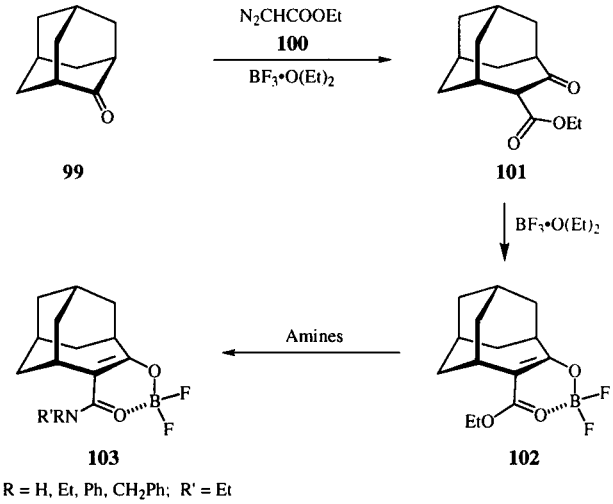
5. Homoadamantane Derivatives.

Whereas very intensive synthetic [26] and theoretical investigations of ring transformation [27] have been performed on adamantanes, the homoadamantane derivatives have received little attention to date. This is surprising because a number of adamantane derivatives are applied as drugs, *e.g.*, as antiviral or anti-Parkinsonian agents, and others have also been found to be very promising pharmacologically. For instance, the anti-HIV-1 activity of adamantane derivatives has been investigated [28].

One of our aims, therefore, as a continuation of our work on fused-skeleton saturated heterocycles [1,2], is a comprehensive synthetic and stereochemical study of 4,5-disubstituted homoadamantanes and saturated heterocycles fused with the homoadamantane skeleton. A comparative evaluation of our earlier stereochemical results on alicycle-fused saturated heterocycles [1,2,29] with those on the heterocycles condensed with this more rigid system is a further aim. Some of our first results on this topic are presented here.

5-Carbethoxy-4-homoadamantanone (**101**) was obtained from adamantanone (**99**) and ethyl diazoacetate (**100**) with boron trifluoride ethyl etherate as catalyst in a

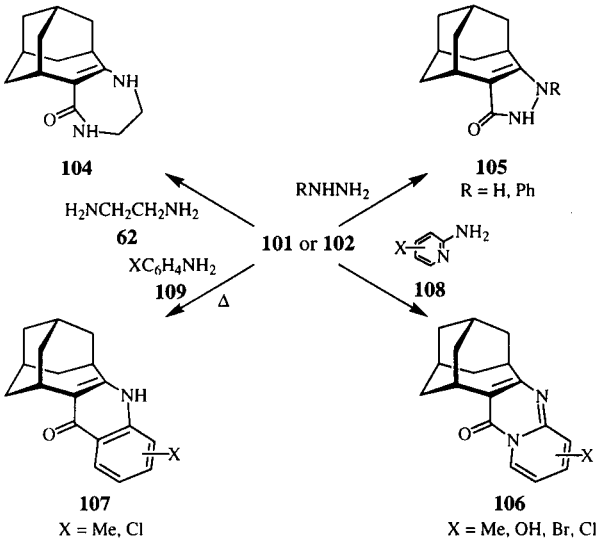
Scheme 14



R = H, Et, Ph, CH_2Ph; R' = Et

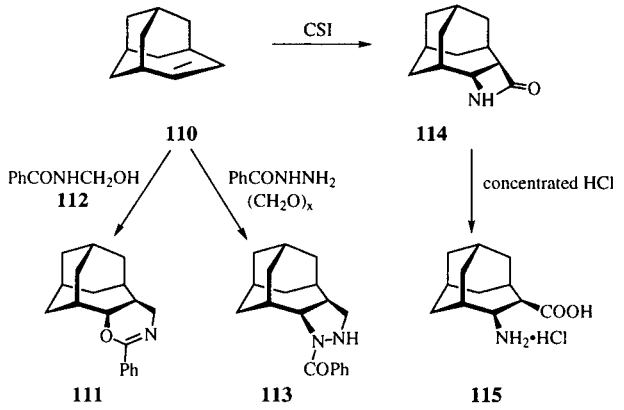
In the reactions of the β-keto ester **101** or the difluoroboron complex **102** with ethylenediamine, the diazepinone- or pyrazinone-condensed homoadamantane derivatives **104** and **105** were obtained, while the reactions with 2-aminopyridines **108** or anilines **109** gave the homoadamantane-condensed heteroaromatic compounds **106** and **107** (Scheme 15).

Scheme 15



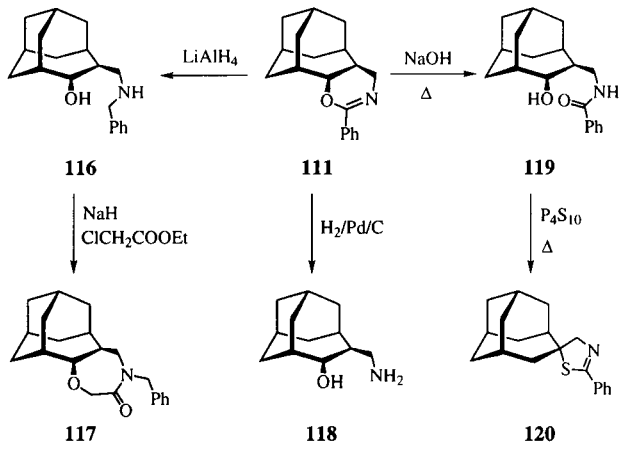
4,5-Homoadamantene (**110**) furnished the oxazino-homoadamantane **111** with hydroxymethylbenzamide (**112**), and the reaction with benzhydrazide and paraformaldehyde yielded the pyrazolidine derivative **113**, while the reaction with chlorosulfonyl isocyanate (CSI) afforded the azeditinone **114**, which was hydrolyzed to the β-amino acid **115** (Scheme 16).

Scheme 16



The oxazine **111** was transformed in conventional reactions to the compounds **116-119** (Scheme 17). The amide **119** reacted with phosphorus pentasulfide to yield the spirothiazoline derivative **120**. No thiazine derivative was detected in the reaction mixture. This is noteworthy because in our earlier experiments [30] on benzamidomethylcyclanols, mixtures of the thiazine and spirothiazoline derivatives were formed in similar reactions.

Scheme 17



Besides ^{1}H and ^{13}C nmr structure elucidations, the structures of compounds **102**, **104**, **105** (R = Ph, as perchlorate), **111** (as perchlorate) and **120** were also determined by X-ray techniques. These results will be published in subsequent papers. Investigations will also be performed of the antiviral activity of the above and related homoadamantane derivatives.

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