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Application of γ-oxocarboxylic acids and amino acid derivatives for the preparation of heterocycles; retro Diels-Alder reactions

Ph.D. thesis

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Szeged
2004

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1. Introduction and aims

One of the main research topics at the Institute of Pharmaceutical Chemistry, University of Szeged, has been the synthesis and structural determination of saturated or partially saturated cycloalkane-fused heterocycles. Because of their stereochemical and conformational interest, increasing attention has recently been paid to these compounds, especially since they are regarded as potential drugs.[1]

Several years ago, Stájer *et al.* developed a new method that is convenient for the preparation of heteromonocycles and bicycles by applying a mild retro Diels-Alder (RDA) process.[2] The principle of this procedure is the synthesis of partially saturated parent heterocycles on cyclopentadiene through the key intermediates *diendo-* or *di-exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids or their derivatives: amides, hydrazides, *etc.* The carrying diene is then removed by mild thermolysis in the closing step. It is important that the RDA process can be performed under mild conditions only when the target compound acquires a (hetero)aromatic or quasi-(hetero)aromatic character.

A decade ago, systematic investigations were started on the synthesis of isoindolone-fused saturated heterocycles. Versatile synthons, such as saturated γ-oxocarboxylic acid derivatives with bifunctional compounds, including 1,3-amino alcohols, diamines, *o*-thiophenol, *etc.* resulted in isoindolones and further heterocyclic compounds.[3]

The present work deals with an extension of the cyclocondensation of aroylcarboxylic acids for the preparation of heterocycles. We focused on the preparation of the unknown *diexo*-norbornane or pharmacologically noteworthy oxocarboxylic acids, *e.g.* oxomethanobenzocyclooctene carboxylic acid, and we also dealt with their cyclocondensations with bifunctional reagents, where the saturated or partially saturated trifunctional amino derivatives, *e.g.* 2-aminohydrazides, were used. The reactions of saturated and partially saturated γ-oxocarboxylic derivatives with bifunctional reagents resulted in a great number of different isoindolone-fused tri-, tetra-, penta-, hexa- and heptacyclic derivatives. Through the reactions of anthranilic hydrazides with 2-*p*-toluoyl-1-cyclohexanecarboxylic acid and its methylene-bridged *diexo* or *diendo* derivatives, tetra- and pentacyclic compounds with three nitrogen atoms were prepared.

An interesting feature of these new compounds arises from the saturated skeleton. The aromatic analogues have simple structures, because they have no *cis* or *trans* fusions and contain no substituents in different stereopositions on the rings. Hence, the establishment of the stereochemistry was a challenging task. In addition, during the reactions of oxo acids with basic bi- or trifunctional derivatives, *cis*→*trans* or *endo*→*exo* or *exo*→*endo* isomerizations might be observed. In the reactions with difunctional reagents, partially saturated heterocycles are formed. When under heated to the melting point or boiled in solvents such as toluene, chlorobenzene, *etc.*, these furnished new heterocycles by the loss of cyclopentadiene or furan.[4] In a double RDA reaction, the target compound was built up on two cyclopentadiene molecules. In the cyclocondensations of 2-aminonorbornene-3-carbohydrazides with 3-aroylnorbornenecarboxylic acid, new pyrimido[1,2-*b*]pyridazine derivatives were obtained.

The present thesis summarizes the results achieved between 1998 and 2004.

2. Results and Discussion

2.1. Synthesis of oxomethanobenzocyclooctenecarboxylic acids and their cyclocondensation to polyheterocycles[II, III]

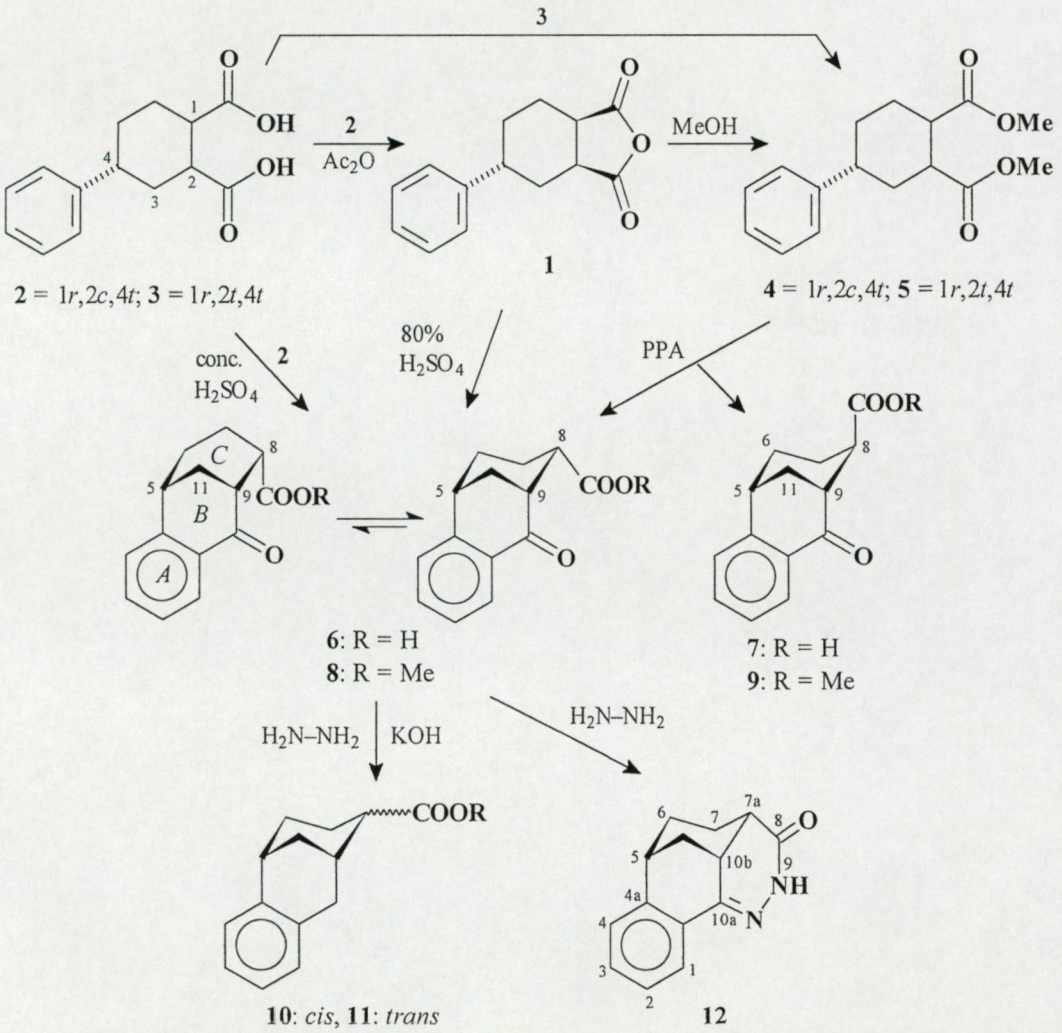
The versatile applicability of γ-and δ-oxocarboxylic acids for the preparation of heterocycles tested for anticonvulsant activity or as hypoglycaemic agents is well known.[5] 3-Acylpropionic acids are useful agents for a simple asymmetric synthesis of 2-substituted pyrrolidines.[6] Nowadays, ω-ketoacids are finding use in solid-phase combinatorial methods.[7,8]

A great number of syntheses of oxocarboxylic acids are known,[9] but, because of its simplicity and the good to excellent yields, the Friedel-Crafts reaction has been most widely applied.[10-12] The methanobenzocyclooctene derivatives are potential analgetics because of their distant structural relationship to morphine. The 8-amino-3-hydroxy-5,9-methanobenzocyclooctenes have high affinity for the μ-opioid receptor.[13] Huperzine A, a Lycopodium alkaloid, is a potent, reversible AChE inhibitor with excellent penetration into the CNS. As new analogues, the natural product 11-ethylidene-9,10-dihydro-7-methyl-5,9-methanobenzocycylooctene-1,5(6*H*)-diamines have been prepared.[14] Saturated perhydromethanobenzocyclooctenes, *e.g.* 2-hydroxy-13-oxo-

tricyclo[7.3.1.0^{2,7}]tridecane derivatives, have been produced by the reaction of cyclohexanone with alcohols.[15,16] From 2-hydroxy-8-methyltricyclo[7.3.1.0^{2,7}]tridecan-13-one, which is closely related to adamantane, 2-hydroxy-8-methyl-13-aminotricyclo[7.3.1.0^{2,7}]tridecane has been prepared.[17] Other preparations of perhydromethanobenzocyclooctene derivatives are also known, *e.g.* from 1-benzylcyclohexanol by PPA-catalysed intramolecular Friedel-Crafts alkylation[18] or from 3-phenyl-1-methylcyclohexanecarboxylic acid chloride *via* $AlCl_3$-catalysed Friedel-Crafts intramolecular acylation.[19]

Synthesis of methanobenzocyclooctene oxo acids

In our work, *trans*-4-phenylcyclohexane-*cis*-dicarboxylic acid (**2**)[20] or anhydride **1** was heated in concentrated H_2SO_4 or in 80% H_2SO_4 to give 10-oxo-5,6,7,8,9,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (**6**; yield 13% or 15%, respectively) by intramolecular cyclization (Scheme 1).



Scheme 1

To improve the yield of **6**, we started from dimethyl 4-*trans*-phenylcyclohexane-*cis*-1,2-dicarboxylate (**4**): cyclization with PPA at elevated temperature yielded a mixture of isomeric esters **8** and **9** in a ratio of 1:5. In contrast, cyclization of dimethyl 4*t*-phenylcyclohexane-1*r*,2*t*-dicarboxylate (**5**) gave the esters **8** and **9** in a 5:4 ratio (the yield of the mixture of **8** and **9** was 54%).

Consequently, as a result of the transformation of **5** to **8** + **9** with PPA, the 30% yield of **8** isolated from the mixture of **8** and **9** by column chromatography proved to be sufficient to permit further reactions. We presume that, in the cyclization, the 2-carboxy groups, which are *axial* in the ground state, come close to the phenyl group by ring inversion and **4** and **5** partly isomerize to form the products **8** + **9**. After separation of the isomers, the structures were established by NMR spectroscopy. The esters **8** and **9** were hydrolysed and the acids **6** and **7** were characterized by NMR and, for **6**, also by X-ray analysis (Fig. 1).

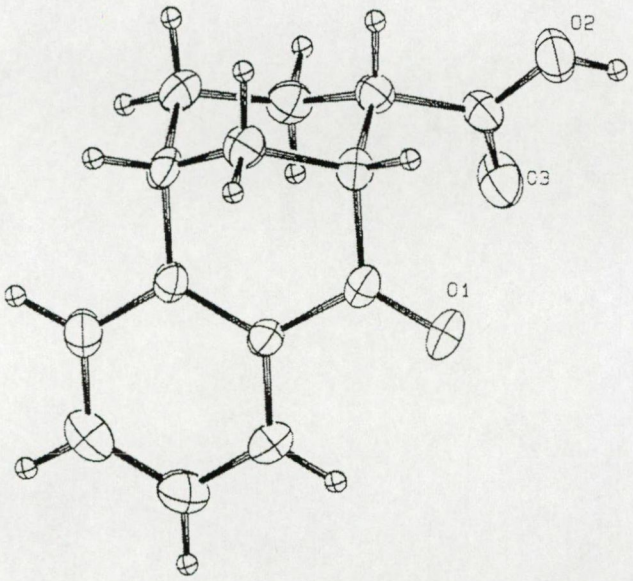


Figure 1. Perspective view of **6**

The oxo group was reduced by the Wolff-Kishner method to afford a mixture of *cis*- and *trans*-5,6,7,8,9,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (**10** and **11**). With hydrazine, oxocarboxylic acid **6** was cyclized to the tetracyclic 4,4a,5,6-tetrahydro-4,6-ethanobenzo[*h*]cinnolin-3(2*H*)-one **12**.

For the isomeric pairs **6** and **7** and **8** and **9**, the NMR shifts of C-6, C-8 and C-11 differ significantly due to the strong steric hindrance between the *axial* 8-COOR group and H-6_{ax} and H-11_{ax} in the *trans* isomers. (For comparison of the spectral data, a special numbering is used; see compound **7** in Scheme 1.) For **10** and **11**, only the shift differences for C-6 and C-11 are significant; that for C-8 is significantly smaller ($\Delta\delta$C-8 = 1.3 ppm). There is strong steric hindrance between the *endo* 10-methylene

hydrogen and the *equatorial* 8-COOH group of the *cis* isomer, and therefore the C-8 line is also shifted upfield for the *cis* isomer.

The intramolecular cyclization of **4** with PPA yielded the isomers **8** and **9**, which differ in the configuration of C-8; for **8**, H-5, H-8 and H-9 lie on the same side of ring *C*, while in **9**, H-5 and H-9 are on the same side and opposite to the hydrogen geminal to the carboxy group. On reduction of the acid **6**, the isomers **10** (all *cis*) and **11** (5*r*H,8*t*H,9*c*H) are formed in a ratio of 1:2; the epimerization probably takes place *via* enolization of the 8-CO (carboxy) group.

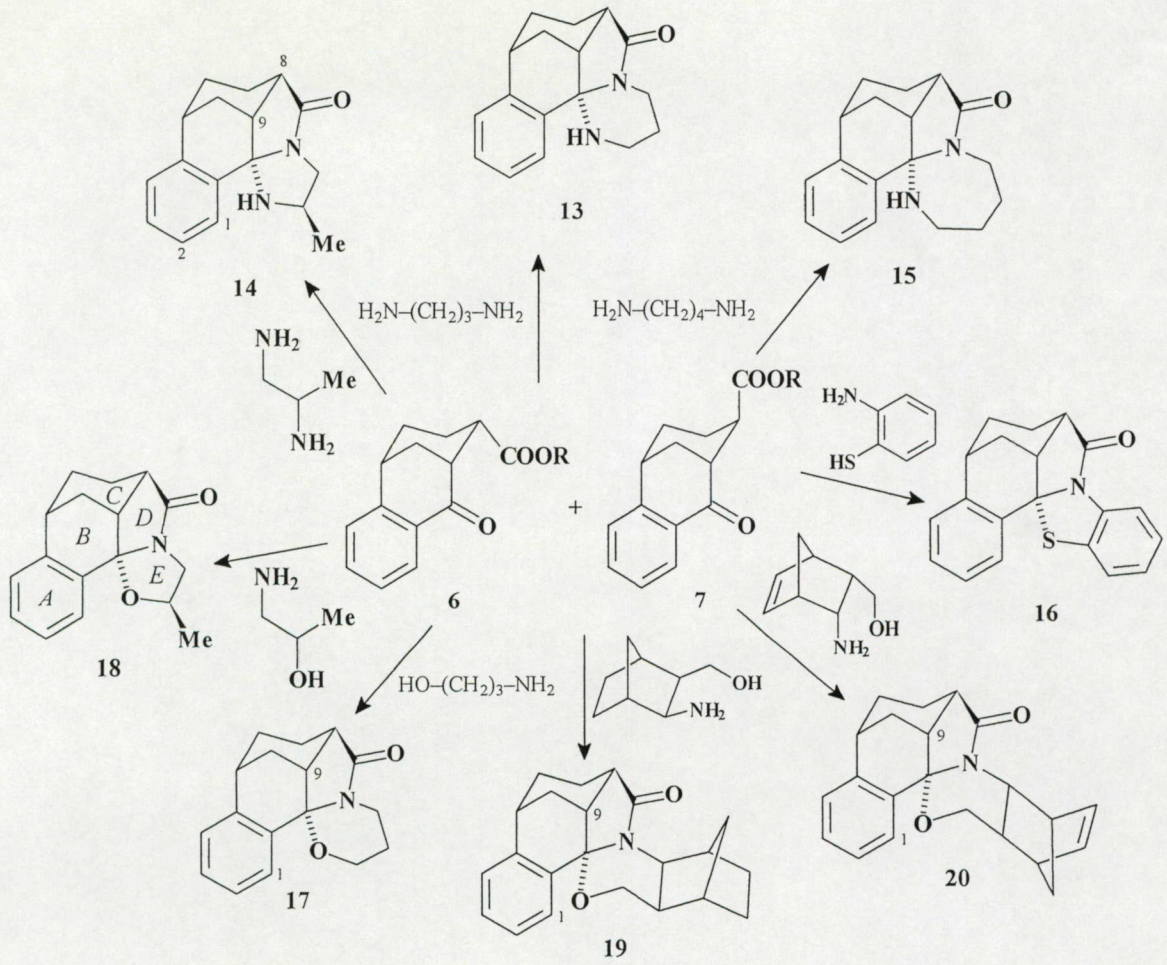
At any rate, **8** can be prepared from the *trans* ester **5** more advantageously than from the *cis* ester **4**, and its 30% yield allows its use as a starting molecule for the synthesis of highly condensed systems.

Cyclocondensations of methanobenzocyclooctene oxo acids to polyheterocycles

When 10-oxo-5*r*,6,7,8*c*,9*c*,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (**6**) was refluxed with 1,3- or 1,2-diaminopropane in dry chlorobenzene in the presence of *p*-toluenesulfonic acid (PTSA) as catalyst for 6 h, 11,13-ethano-5,6,7,8,11,11a,12,13-octahydro-10*H*-benzo[*g*]pyrimido[2,1-*i*]indol-10-one (**13**) or 10,12-ethano-6-methyl-6,7,10,10a,11,12-hexahydro-5*H*,9*H*-benz[*g*]imidazo[2,1-*i*]indol-9-one (**14**) was formed (Scheme 2).

On application of a 1:1 mixture of the isomeric acids **6** and **7**, the reaction with 1,3-diaminopropane gave the same product **13** in lower yield (56%), even under vigorous conditions (refluxing for 8 h). The cyclization requires an *equatorial* carboxyl group and therefore **7**, containing an *axial* carbonyl, isomerizes slowly to **6**.

In further experiments, only **6** was used. The reaction with 3-aminopropan-1-ol yielded 11,12-ethano-7,8,11,11a,12,13-hexahydro-6*H*,10*H*-benz[*g*][1,3]oxazino[2,3-*i*]indol-10-one (**17**), while **6** and 3-aminopropan-2-ol furnished 10,12-ethano-6-methyl-6,7,10,10a,11,12-hexahydro-9*H*-benz[*g*]oxazolo[2,3-*i*]indol-10-one (**18**). The reaction of **6** with 1,4-diaminobutane gave 12,14-ethano-6,7,8,9,12,12a,13,14-octahydro-5*H*,11*H*-benzo[*g*][1,3]diazepino[2,1-i]indol-11-one (**15**).



Scheme 2

While compounds **13-15, 17** and **18** contain an aromatic ring and a condensed cyclic hetero moiety at the other terminal, the reaction of **6** with *o*-aminothiophenol furnished 12,14-ethano-12,12a,13,14-tetrahydro-11*H*-benz[6,7]indolo[7a,1-*b*]benzthiazol-11-one (**16**), a hexacyclic ring system with two terminal aromatic rings. *diexo*-2-Aminobicyclo[2.2.1]heptane-3-methanol and *diendo*-2-aminobicyclo[2.2.1]hept-5-ene-3-methanol react with **6** to give heptacyclic derivatives: *diexo*-7,9-ethano-1,4-methano-2,3,4,4a,7,7a,8,9,15,15a-decahydro-1*H*,6*H*-benz[6,7]indolo[1,7a-a][3,1]benzoxazin-6-one (**19**) and the unsaturated *diendo*-7,9-ethano-1,4-methano-4,4a,7,7a,8,9,15,15a-octahydro-1*H*,6*H*-benz[6,7]indolo[1,7a-*a*][3,1]benzoxazin-6-one (**20**).

For **14** and **18**, an NOE was observed between H-9 and the methine hydrogen in the C*H*CH_3 group. Hence, the heteroatom (N or O) must be in the α position (*cis* to H-9) and the methyl group in the β orientation (*trans* with H-9 relative to the imida-

zolidine or oxazoline rings). From the very high difference in the chemical shifts of H-9 in **14**, **18** and especially **16**, the α position of the S in **16** is straightforward.

For **17**, **19** and **20**, the very small shift differences of C-1 and H-9 indicate similar steric structures of rings *A-E* in these compounds: the oxygen is also in the α position (*cis* to H-9) in **19** and **20**. The double splitting (by 7.3 Hz) of the NCH signal in **19** and the double doublet structure (splits 8.3 and 3.5 Hz) of the same signal in **20** confirm the *diexo-* **19** and *diendo-* **20** annelation, respectively, of the terminal bicycles to the skeleton. These structures were also proved independently by NOE measurements: interactions were observed between the *axial* OCH_2 hydrogen and the *endo*-H of the bridging CH_2 in **19** and between the latter atom and the NCH hydrogen in **20**. The X-ray diffraction data confirmed the structure of **19** (Figure 2).

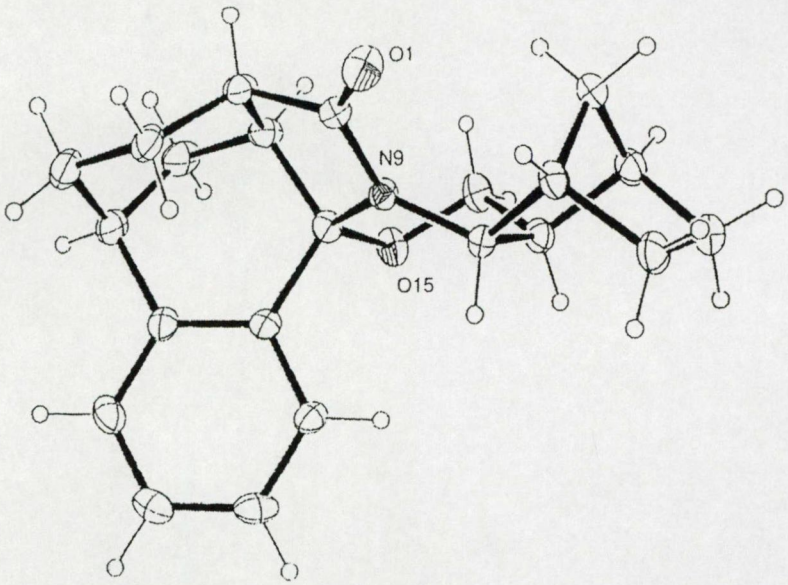


Figure 2. The ORTEP perspective view of **19**

The presence of the aromatic moiety in the ring system results in rather rigid condensed skeletons which are planar at the benzene terminal(s). This fused system of 16-22 carbons and two hetero atoms displays only limited conformational mobility.

2.2. Isomerization and application of aroylnorbornenecarboxylic acids for the stereoselective preparation of heterocycles[VII]

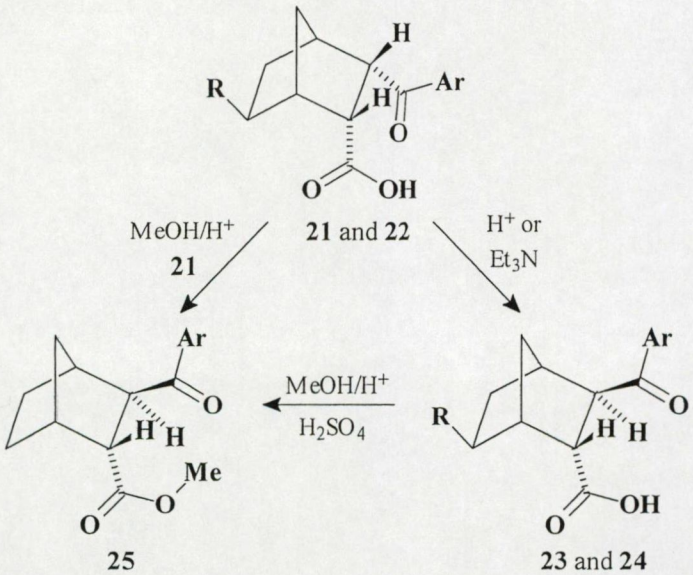
In earlier studies, the *endo→exo* or *exo→endo* and *cis→trans* isomerizations of dicarboxylic acid diesters or monoesters were described. Thus, the saponification of *diendo-* or *diexo*-oxanorbornane-[21] and -norbornane-2,3-dicarboxylates[22] results in

either *exo-endo* or *endo-exo* dicarboxylic acids. Similarly, the epimerization and methanolysis of the *diexo*-oxanorbornane and norbornane mandelate monoesters leads to *endo* carboxylate and *exo* carboxylic acids.[23] Only a few studies have dealt with the epimerization of *cis*-2-acylcyclohexane-1-carboxylic acid and *diendo*- or *diexo*-3-acyl(oxa)norbornane-2-carboxylic acid derivatives.[24] In a Friedel-Crafts reaction, *cis*-hexahydrophthalic anhydride reacts readily with anisol to give *cis*-(4-methoxybenzoyl)cyclohexane-1-carboxylic acid. The *trans* isomer was formed as an artificial product as a result of the lability of the *cis* form in hot aqeous alkali.[25] In the preparation of 4- or 5-hydroxy-substituted 2-aroylcyclohexane-1-carboxylic acids and 3-aroylnorbornane-2-carboxylic acids from cyclohexane lactone and norbornane ketal-lactone, isomers are again formed, *cis*→*trans* or *endo*→*exo* isomerization of the aroyl group taking place.[26] 5-*exo*-*p*-Tolyl-*endo*-2-oxatricyclo[4.2.1.$0^{4,8}$]nonan-3-one could be easily prepared by boiling *endo*-5-*p*-tolyl-2-oxatricyclo[4.2.1.$0^{4,8}$]nonan-3-one in either acidic, basic or neutral ethanolic medium.[27]

As isomerization was recently found in the synthesis of oxocarboxylic acids and their derivatives,[30] we have searched for new examples to study this behaviour and to exploit the isomerization for the stereoselective preparation of heterocycles. When refluxed in the presence of 2 drops of concentrated HCl or Et_3N in toluene, *diendo*-3-toluoylbicyclo[2.2.1]heptane-2-carboxylic acid (**21**) and its 6-*exo*-phenyl derivative **22** are smoothly transformed to the corresponding 3-*exo*-aroylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid derivatives (**23** and **24**) (Scheme 3).

A similar *endo*→*exo* epimerization occurs in the esterification of **21** to the 3-*exo*-toluoyl derivative **25**. For analogous cyclohexane derivatives, a facile epimerization has frequently been observed when *cis*-aroylcyclohexanecarboxylic acids are reacted with strong basic diamines or boiled in a solution of NaOH–EtOH–H_2O, when *trans* compounds are formed.[28-30] In the opposite direction, *trans* oxoacids undergo isomerization to *cis* derivatives in the presence of basic reagents, *e.g.* diamines or amino alcohols.[31] However, the norbornane skeleton has high rigidity, and hence the configuration of the starting compound is often retained in its products. A few examples of the epimerization are to be found in the literature. Craig described a reversible *diendo*→*diexo* isomerization: when heated above the melting point (~190 °C), *diendo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride was transformed to the *diexo* ana-

logue.[32] This change was due to the presence of the double bond in position 5 and was explained by the formation of a tautomeric intermediate (not isolated). In our case, facile enolization can be presumed if basic reagents are used.



21 and **23**: R = H, **22** and **24**: R = Ph

Ar = *p*-tolyl

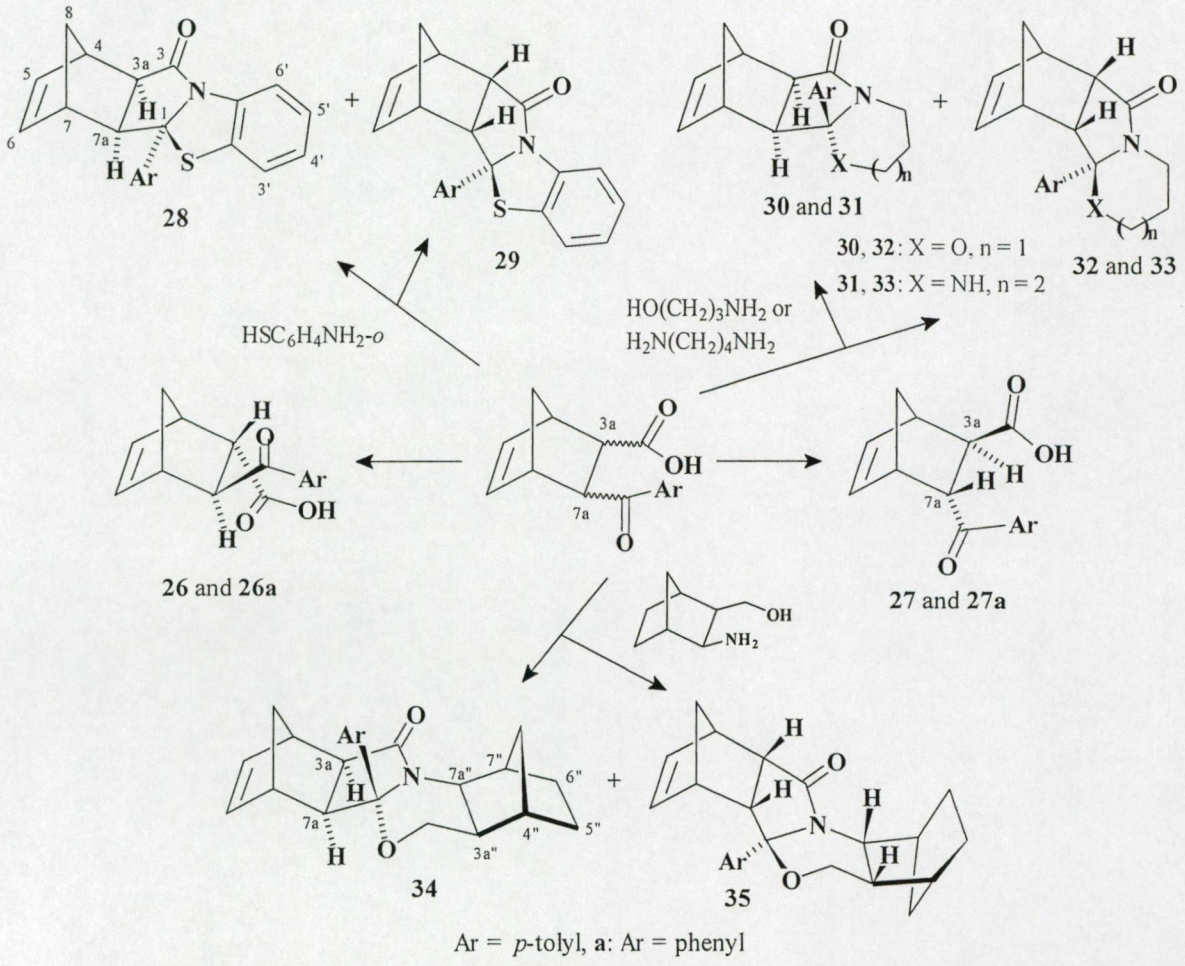
Scheme 3

To utilize this isomerization for synthetic purposes, a mixture of the isomers of the Diels-Alder adduct of *trans*-toluoylacrylic acid and cyclopentadiene (**26** and **27**) was applied as an embedded diene source[33] (Scheme 4).

HPLC revealed that the ratio of isomers **26** : **27** in the starting mixture was 57 : 43. This and the mixture of phenyl analogues **26a** and **27a** were separated by column chromatography and the structures were established by means of NMR spectral measurements and, for **26**, also by X-ray analysis (Figure 3). The results demonstrated that, in agreement with the literature[33] **26** and **26a** contain *endo* carboxyl and *exo* aroyl, and **27** and **27a** *exo* carboxyl and *endo* aroyl groups.

A mixture of **26** and **27** was reacted with the difunctional agents *o*-aminothiophenol, 3-amino-1-propanol, 1,4-diaminobutane and *diexo*-3-hydroxymethylbicyclo[2.2.1]heptane-2-amine to afford mixtures of *diexo* and *diendo* isomeric heterocyclic compounds: 1,4-methano-4b-*p*-tolyl-1,4a,4b,11a-tetrahydroisoindolo[1,2-*b*]benzthiazol-11(4*H*)-ones (**28** and **29**), 7,10-methano-10b-*p*-tolyl-3,4,7,10,10a,10b-hexahydro-2*H*-[1,3]oxazino[2,3-*a*]isoindol-6(6a*H*)-ones (**30** and **32**), 8,11-methano-11b-*p*-

tolyl-1,2,3,4,5,7a,8,11,11a,11b-decahydro-7*H*-[1,3]diazepino[2,3-*a*]isoindol-7-ones (**31** and **33**) and 1,4:7,10-dimethano-6a-*p*-tolyl-1,3,4,4a,5,6b,710,10a,12b-decahydro-2*H*-isoindolo[2,1-*a*][3,1]benzoxazin-11(6a*H*)-ones (**34** and **35**).



Scheme 4

The isomers were separated by column chromatography. For the products **31** and **33**, HPLC separation showed that the ratio of **31** : **33** was 42 : 58. Comparison of this with the ratio of 57 : 43 for **26** : **27** suggested that the aroyl group epimerizes: in these cyclizations, either the *exo* aroyl **26** gives the *diendo* **33**, or the *endo* aroyl **27** gives the *diexo* derivative **31**.

These reactions allow the conclusion that aroylnorbornanecarboxylic acids containing the two vicinal (2,3) functional groups in sterically unfavourable positions for ring closure can be advantageously used for the preparation of condensed heterocycles: on the action of acids or bases and simultaneous heating, the aroyl group epimerizes. Reaction of the readily available *trans*-aroylacrylic acid–cyclopentadiene ad-

duct, containing a mixture of the aroyl group *exo* or *endo* to the *endo* or *exo* carboxyl group, with bifunctional reagents (amino alcohols, diamines, *etc.*) provides good possibilities for stereoselective synthesis, but the two (*endo-endo* or *exo-exo*) fused derivatives have to be separated.

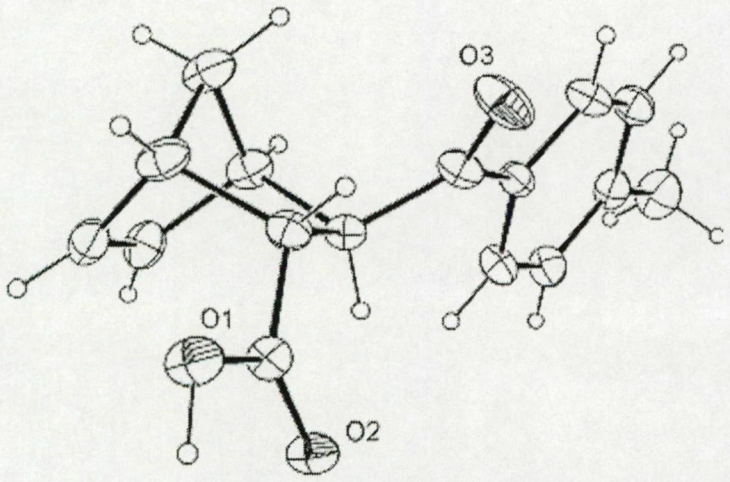


Figure 3. Perspective view of compound **26**

In the pyrrolidinone-fused compounds (**28-35**), a mixed (*exo-endo*) annelation to the norbornane/ene moiety is not possible for steric reasons. The *diexo* or *diendo* configurations follow unequivocally from the *d* or *dd* splits of the H-3a,7a signals. Thus, in **28**, **30**, **31** and **34**, the norbornene and the fused hetero ring are *diexo*, while in **29**, **32**, **33** and **35** they are *diendo*.

In the pairs **28** and **29**, **30** and **32**, and **31** and **33**, the C-1 configuration, *i.e.* the position of the aryl group, is to be determined. For **29**, this is straightforward on the basis of the dramatic upfield shift (by 1.12 ppm) of the H-6 signal as compared with that in **28**, due to the anisotropic shielding of the close-lying tolyl group. This means the *trans* arrangement of H-7a and the tolyl group relative to the pyrrolidone ring.

The similarly strong shielding of H-6 in **32** (5.33 ppm) and **33** (4.77 ppm) suggests the analogous stereostructure, and for the latter compound this structure was confirmed directly by DIFFNOE measurements: H-7a and the *N*-methylene hydrogens in the diazepine ring were found to be sterically close. In **31**, an NOE between H-8(*endo*) and one of the *ortho*-aryl hydrogens confirms the *trans* orientation of H-7a and the tolyl substituent. The anisotropic shielding of the benzene ring leads to an upfield shift of the H-8(*endo*) signal (*d*, 1.13 ppm) in **31**, while for **33**, the analogous

shift is 1.34 ppm. A similar effect was observed, and hence the analogous stereo-structure is presumed for **30**. The absence of such strong shielding in **28** suggested a considerable distance between the tolyl and H-8(*endo*) and thus the *cis* arrangement of the former group and H-7a relative to the pyrrolidone ring.

The significant upfield shift of the H-6 signal in **35** (5.27 ppm) originates from the anisotropic shielding of the close-lying aromatic ring and points to the *endo* position of the tolyl group. The tolyl group and the bridging methylene in norbornane lie on the same side of the skeleton. This is valid for both **34** and **35**.

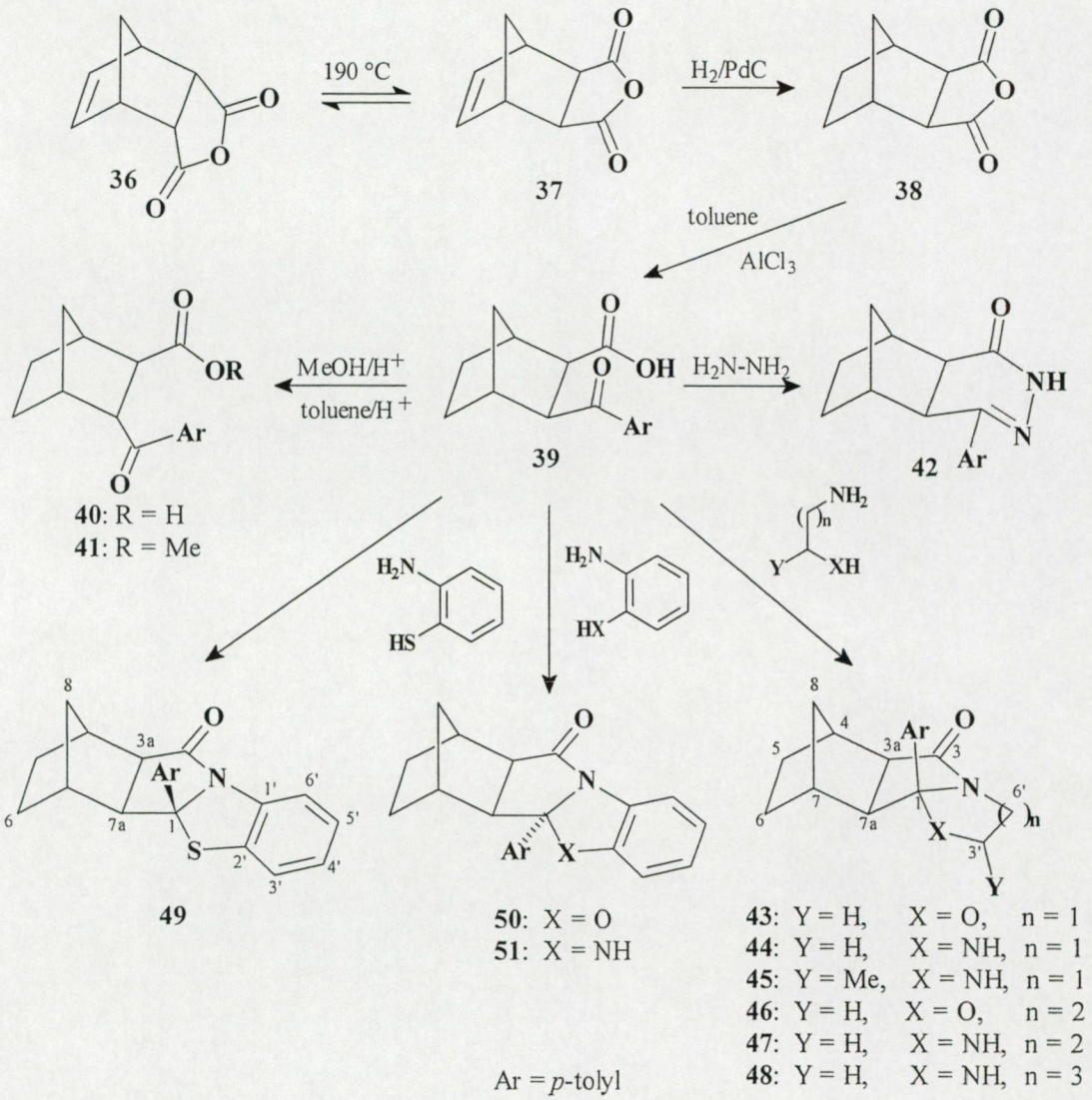
2.3. Preparation and structure of *diexo*-norbornane-fused 1,3-heterocycles and oxanorbornene analogues[VIII, IX]

Cyclocondensations of oxocarboxylic acids with difunctional amino derivatives, *e.g.* 2-benzoylbenzoic acid or 3-benzoylpropionic acid, with 1,2-, 1,3- or 1,4-amino alcohols, diamines or mercaptoamines gave products containing lactams with an additional N-, O- or S-containing ring fused with the lactam. The formation of heterocycles from oxocarboxylic acids with amino alcohols arises from the intermediate Schiff base, which in some systems exists *via* a ring-chain tautomeric equilibrium. The expected Schiff base can first cyclize to the amino acid and then proceed to form a second ring from the available amino and carboxyl groups.[34] In the reactions of 2-formylbenzoic acid or 2-aroylbenzoic acid with aminocarboxamides, the isoindoloquinazolinones were formed. The cyclization mechanism may be postulated to involve the formation of an azomethine with the amino group, then cyclization to pyrimidinone. The carboxyl can acylate either the imino or carboxamide group to the bisacylimides.[35] A series of 5-aroyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols prepared by $LiAlH_4$ reduction of the corresponding 9b-aroyl-1,2,3,9-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones were evaluated for suppression of food consumption in rats. One member of this series, 5-*p*-chlorophenyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol (Mazindol), was proved to have anorexic activity approximately equal to that of *d*-amphetamine.[36]

A large number of aryl bicyclic analogues of succinimide and glutarimide have been prepared and evaluated for CNS depressant activity. The 8a-aroyl-3,4,6,7,8,8a-hexahydro-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-6-ones exhibited the best activities relative to the standard agents glutethimide and phenobarbital.[37]

Preparation and structure of *diexo*-condensed norbornane heterocycles

By reaction of *diendo*-3-aroylbicyclo[2.2.1]heptane-2-carboxylic acid with difunctional reagents (amino alcohols, diaminoalkanes, *o*-aminophenol and *o*-aminothiophenol), a large number of condensed heterocycles have been synthetized.[38,39] However, the synthesis of the stereoisomeric *diexo* derivatives has not yet been reported. Hence, the *diexo*-norbornane dicarboxylic anhydride **36** was transformed to the known *diexo* anhydride **37** by heating to 190 °C[32] (Scheme 5). To avoid the addition of the aromates to the double bond in the presence of $AlCl_3$,[39] **37** was saturated by catalytic hydrogenation to furnish **38**.



Scheme 5

The Friedel-Crafts acylation of toluene with **38** leads to *diexo*-3-toluoylbicyclo[2.2.1]heptane-2-carboxylic acid (**39**). As compound **39** readily isomerizes to the

endo aroyl derivative **40**, *e.g.* on boiling with HCl in toluene, and the esterification also affords the *endo*-aroyl-*exo*-methoxycarbonyl derivative **41**, **39** was reacted with hydrazine to yield 5,8-methano-4-*p*-tolyl-4a,5,6,7,8,8a-hexahydrophthalazin-1(2*H*)-one (**42**). With alkanolamines, 6,9-methano-9b-*p*-tolyloctahydrooxazolo[2,3-*a*]isoindol-5(5a*H*)-one (**43**) and 7,10-methano-10b-*p*-tolyloctahydro[1,3]oxazino[2,3-*a*]isoindol-6(6a*H*)-one (**46**) were obtained.

On cyclization with alkylenediamines, **39** resulted in 6,9-methano-9b-*p*-tolyldecahydroimidazo[2,1-a]isoindol-5-one (**44**), 6,9-methano-9b-*p*-tolyl-2-methyl-9b-*p*-tolyldecahydroimidazo[2,1-*a*]isoindol-5-one (**45**), 7,10-methano-10b-*p*-tolyldecahydropyrimido[2,1-*a*]isoindol-6-one (**47**) and 8,11-methano-11b-*p*-tolyldodecahydro-7*H*-[1,3]diazepino[2,1-*a*]isoindol-7-one (**48**), while with *o*-aminothiophenol, *o*-aminophenol or *o*-phenylenediamine, the pentacyclic 1,4-methano-4b-*p*-tolyl-1,3,4,4a,4b,11a-hexahydroisoindolo[1,2-*b*]benzthiazol-11(2*H*)-one (**49**), 1,4-methano-4b-*p*-tolyl-1,3,4,4a,4b,11a-hexahydroisoindolo[1,2-*b*]benzoxazol-11(2*H*)-one (**50**) or 1,4-methano-4b-*p*-tolyl-1,2,3,4,4a,4b,5,11a-octahydro-11*H*-isoindolo[2,1-*a*]benzimidazol-11-one (**51**) were obtained.

The spectral data on the new compounds **40-51** confirm the presumed structures. The *diexo* structure of **39** and **42-51** is obvious from the 8.4 ± 1.1 Hz doublet split of the H-3a and H-7a signals. For **40** and **41**, the H-7a signal is split into a double triplet by 5.0, 1.5, and 1.5 Hz, which confirms the *endo* position of the tolyl group, while the H-3a signal (in accord with the *endo* position of this H) exhibits an unaltered doublet. The condensed planar benzene ring in **50** and **51** leads to a change in the C-1 configuration, and the *endo* situation of the tolyl group allows free rotation. The C-1 configuration in **49** is unaltered relative to **43-48**, and the more bulky S atom forces the benzene ring close to the bridging CH_2. Hence, between moieties, the tolyl group is unable to rotate freely, as in **43-48**.

As a conclusion, the previously unknown *diexo*-aroylnorbornane carboxylic acid (**39**) can be advantagously applied for the synthesis of *diexo*-fused norbornane heterocycles: condensed benzthiazolo, oxazolo and imidazo compounds.

Preparation of difunctional 7-oxabicyclo[2.2.1]heptane/ene derivatives and their use for the synthesis of heterocycles

The derivatives of 7-oxabicyclo[2.2.1]heptene (7-oxanorbornene) occur in nature; some of them have been found to be bioactive. These and the saturated analogues are applied for many reactions, making them useful synthetic intermediates in the synthesis of natural products.[40] The treatment of *diexo*-7-oxabicyclo[2.2.1]heptane-dicarboxylic anhydride[41] with 2,6-dimethoxyphenyllithium gave an oxo acid. With diazomethane, the methyl ester readily isomerizes to an *exo-endo* compound.[24]

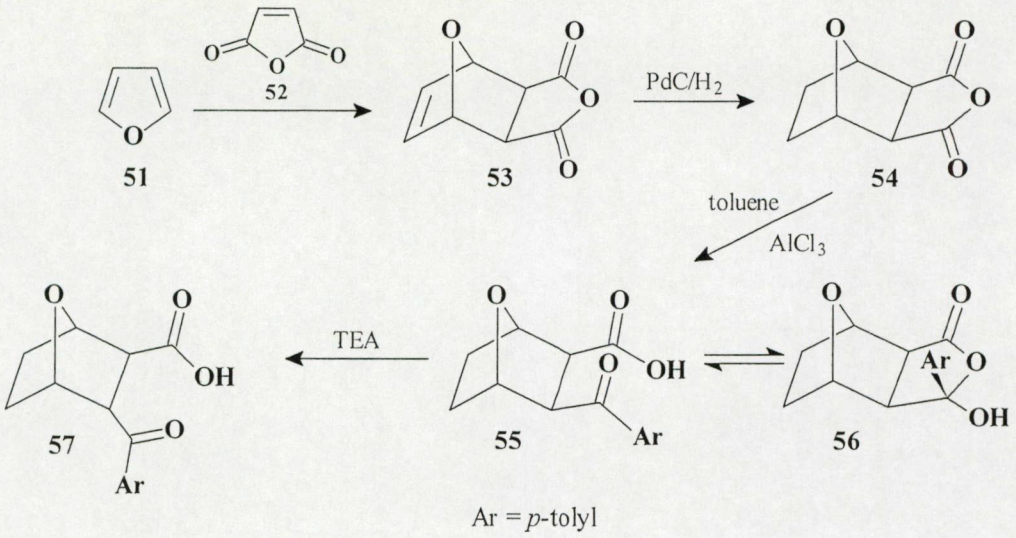
The Lewis acids induce heterolytic cleavage of the ethereal bridge. With boron trichloride, two phenolic products are formed, which provide a potential route to xanthones, including the fungal metabolite ergoflavine.[24]

In the early 1960s, *diexo*-2-amino-7-oxabicyclo[2.2.1]heptane-3-carboxylic acid[42] was prepared by Hofmann rearrangement of 7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic imide.[43] A number of thromboxane analogues have been synthetized from *diexo*- and *diendo*-7-oxabicyclo-[2.2.1]heptane-1,2-dicarboxylic anhydrides.[44,45] The usefulness of 7-oxabicyclo[2.2.1]heptane or heptene derivatives in the synthesis of natural products can be traced back especially to the regio- and stereoselective opening of the oxygen bridge.[46-50]

The ring-chain isomeric interconversion proceeding by intramolecular reversible additon to the double bond of the C=O group has been well studied, particularly as regards 3- and 4-formyl and other oxocarboxylic acids.[51,52] There are many examples where the equilibrium constants of the acylcarboxylic acids have been measured by UV, IR and NMR methods.[53-55] Several anhydrides have been subjected to trichloromethylation to provide relatively high stability of the ring form of bicyclic oxocarboxylic acids.[56]

We broadened the synthetic work by the application of *diexo*-oxanorbornane derivatives. The target was to prepare heterocycles from *diexo*-3-aroyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (**55**) as starting compound (Scheme 6).

The reaction of furan (**51**) with maleic anhydride (**52**) results in *diexo*-7-oxabicyclo[2.2.1]hept-5-ene-1,2-dicarboxylic anhydride (**53**), which was saturated by catalytic hydrogenation to **54**[41] and then transformed with toluene/$AlCl_3$ to *diexo*-3-*p*-toluoyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (**55**) by Friedel-Crafts acylation.



Scheme 6

Compound **55** exists as a mixture with its cyclo tautomer **56**, which was isolated from the ethanolic solution and its structure proved by means of X-ray diffraction (Figure 4).

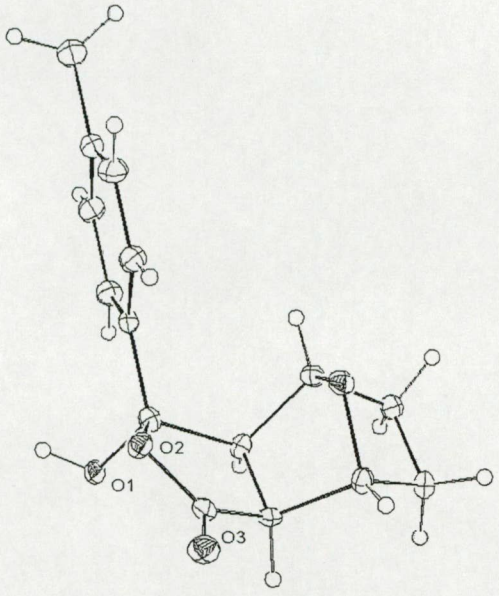
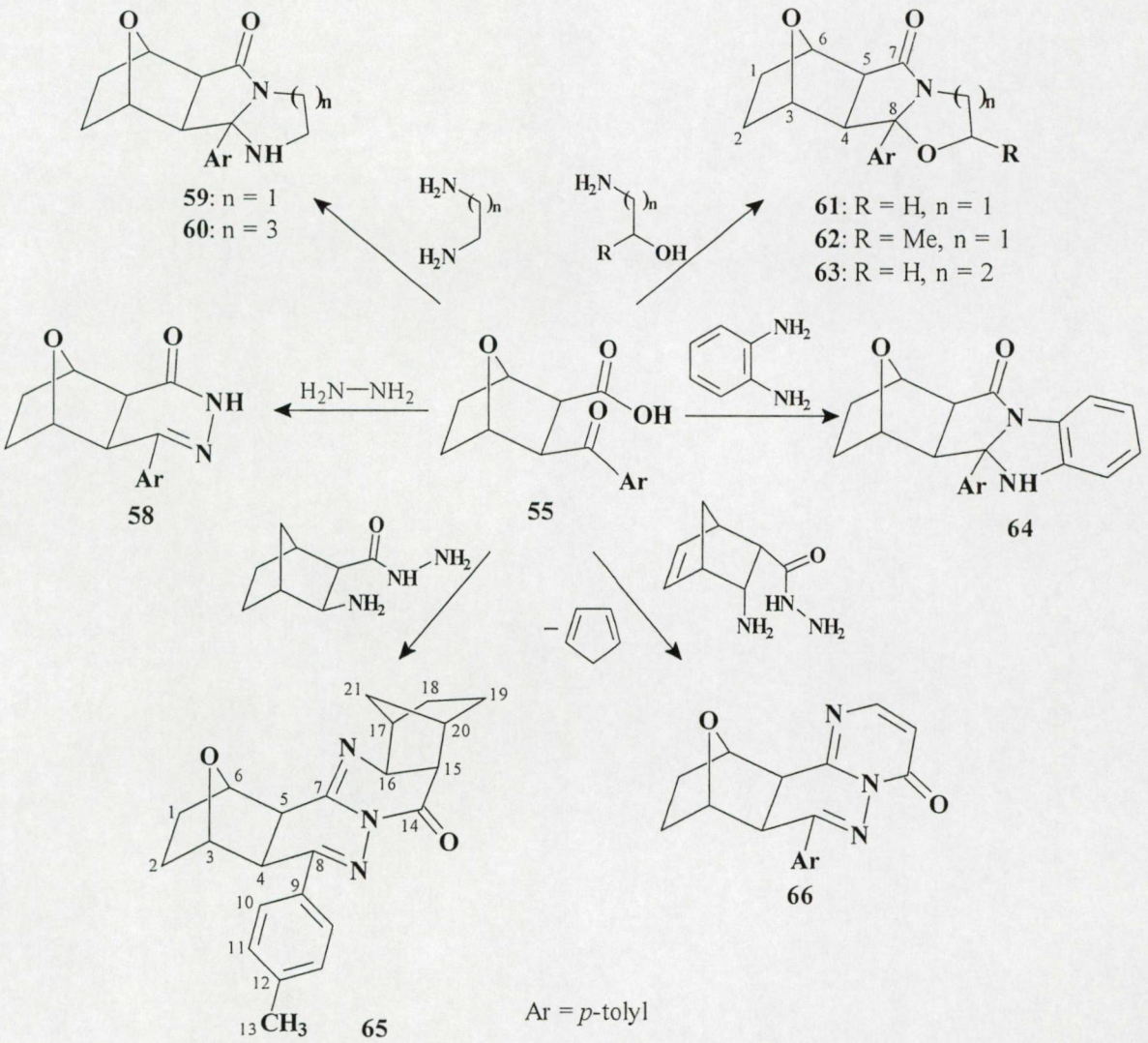


Figure 4. Perspective view of **56**

Because of the facile enolization of the aroyl group, **55** undergoes isomerization to the *endo* aroyl derivative **57** on reaction with Et_3N.

From **55** and hydrazine, 5,8-epoxy-4*p*-tolyl-4a,5,6,7,8,8a-hexahydrophthalazin-1(2*H*)-one (**58**) is formed (Scheme 7). On refluxing with ethylenediamine and 1,4-diaminobutane in toluene, **55** furnishes the tetracyclic 6,9-epoxy-9b-*p*-tolyl-octahydro-imidazo[2,1-*a*]isoindol-5(5a*H*)-one (**59**) and 8,11-epoxy-11b-*p*-tolyldodecahydro-7*H*-[1,3]diazepino[2,1-*a*]isoindol-7-one (**60**).

The reactions of **55** with aminoethanol and aminopropanols yield 6,9-epoxy-9b-*p*-tolyloctahydrooxazolo[2,3-*a*]isoindol-5(5a*H*)-one (**61**), 6,9-epoxy-2-methyl-9b-*p*-tolyloctahydrooxazolo[2,3-*a*]isoindol-5(5a*H*)-one (**62**) and 7,10-epoxy-10b-*p*-tolyloctahydro-2*H*-[1,3]oxazino[2,3-*a*]isoindol-6(6a*H*)-one (**63**), while from **55** with *o*-phenylenediamine, the condensed 1,4-epoxy-4b-*p*-tolyl-1,2,3,4,4a,4b,5,11-octahydro-11*H*-isoindolo[2,1-*a*]benzimidazol-11-one (**64**) is formed.



Scheme 7

With *diexo*-3-aminobicyclo[2.2.1]heptane-2-carbohydrazide, **55** cyclizes to 1,4-epoxy-9,12-methano-5-*p*-tolyl-8*H*-1,2,3,4,4a.8a,9.10,11,12,12a,13b-dodecahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (**65**). On reaction with the isomeric *diendo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazide, **55** yields 8,11-epoxy-7-*p*-tolyl-7a,8,9,10,11,11a-hexahydro-4*H*-pyrimido[2,1-*a*]phthalazin-4-one (**66**) by the splitting-

off of cyclopentadiene. The reaction is explained by the presence of the double bond in the norbornane moiety, which allows ready thermal decomposition to give cyclopentadiene and **66** in a RDA reaction.

The H,H connectivities could be concluded from the H,H-COSY spectra; direct and long-range C,H coupling information was obtained from HMQC and HMBC. NOESY spectra were also recorded to find the spatially adjacent protons. The crucial stereochemistry, *i.e.* the *exo* or *endo* configurations of the substituents/annelated rings on the oxonorbornane skeleton in all compounds and the position of the *p*-tolyl group in **58-64** and **66**, were also established. For **65**, however, the position of the tolyl group could not be assigned with certainty because of the many ^{1}H signals in the NMR spectrum. For **58-64** and **66**, a number of NOE enhancements were found in the 2D NOESY NMR spectra, but these were not suitable for discrimination of the C-8 configuration. In contrast, the ring current effect of the aryl proved to be really useful. The magnetic field generated by a benzene ring π-system current opposes the externally applied magnetic field H_0. The aryl hydrogens, however, are located in the "return" position of the ring current magnetic field and experience a magnetic field, which reinforces H_0. A method for application of the rigid ring current effect of the nearby aromatic ring to determine the position of the proton is known.[57]

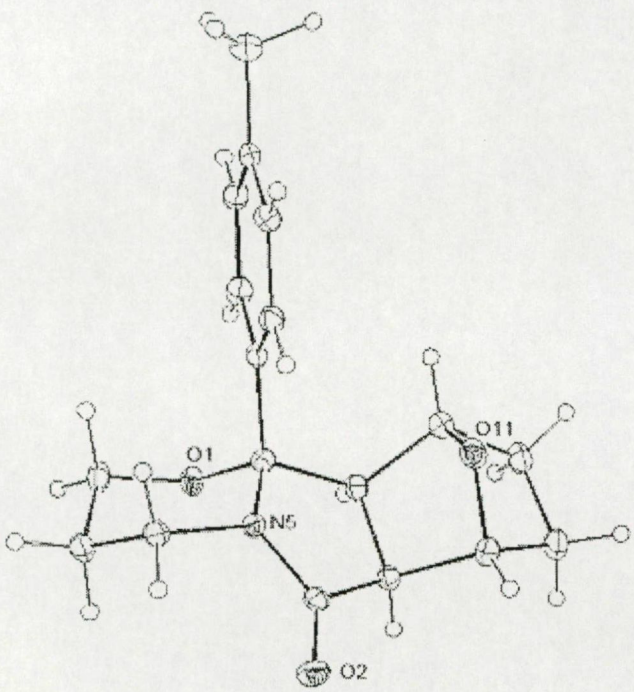


Figure 5. Perspective view of **63** Determined by X-ray method

The aryl and H-4_{endo} *cis*/*trans* isomers of **63** were *ab initio* MO calculated, and the corresponding ^{1}H chemical shift of H-3 in the two isomers was determined. Both the chemical shift of H-3 ($\delta = 3.18$ ppm) and the ring current effect of the aryl on H-3 (–1.29 ppm) agreed excellently with the experimental values for the *trans* isomer, confirming the *trans* position of the aryl group and H-4_{endo}, which is in agreement with the X-ray results (Figure 5).

It is important to stress that the ^{1}H and ^{13}C NMR spectra of compounds **61** and **62** (and previously **43** and **46**) were recorded in DMSO-d_6 instead of $CDCl_3$ solution. In consequence of the decomposition of $CDCl_3$, small amounts of water and HCl are present, which cause *exo*→*endo* isomerization of the tolyl group and likewise ring opening of the oxazolidine or 1,3-perhydrooxazine heterocycles.[58]

2.4. Synthesis and stereochemistry of saturated or partially saturated pyridazino[6,1-*b*]- and phthalazino[1,2-*b*]quinazolinones[I]

A great number of substituted 10-oxo-10*H*-pyridazino[6,1-*b*]quinazoline-2-carboxylic acids have been prepared and evaulated as antiallergic agents. The unsubstituted 8-chloro derivative and its analogues were found to be pharmacologically active.[59] 2,3,4-Tetrahydro-10*H*-pyridazino[6,1-*b*]quinazoline-2,10-diones have been prepared by intramolecular acylation of alkyl β-(3-amino-4-oxoquinazolin-2-yl)propionate, and pyridazino[6,1-*b*]quinazoline derivatives have been obtained by refluxing anthranilic hydrazides and succinic anhydride.[60]

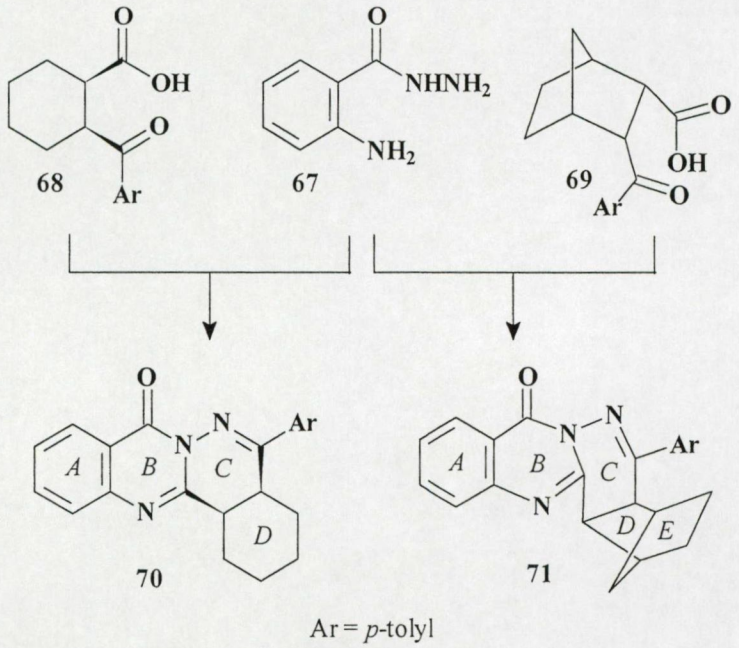
On the condensation of 3-chloro-5-hydroxy-6-phenylpyridazine with ethyl anthranilate, the pyridazinoquinazoline was obtained, which displayed herbicidal activity.[61,62] Recently, a new method was reported for the preparation of 3-nitropyridazino[6,1-*b*]quinazolinones.[63]

For the preparation of phthalazino[1,2-*b*]quinazolines, a general method has been developed.[64,65] 5-Substituted-8-oxo-8*H*-phthalazino[1,2-*b*]quinazolines have been synthetized from 1-chlorophthalazines with anthranilic acid; a few of them exhibit anti-inflammatory activity.[66] Phthalazino[1,2-*b*]quinazolines were prepared from anthranilic hydrazide with 2-formylbenzoic acid, 2-acetylbenzoic acid or 2-benzoylbenzoic acid;[67] these compounds possessed analgesic activity.[68] Other procedures to convert anthranilic hydrazide with phthalic anhydride[69] or isoindolobenzoxazinones with hydrazine into phthalazino[1,2-*b*]quinazolines[70] are also known.

In the following part, we deal with the reactions of *cis*- and *trans*-2-aroyl-1-cyclohexanecarboxylic acids or their methylene-bridged *diexo* or *diendo* derivatives with anthranilic hydrazide or its saturated and norbornane analogues. These trifunctional synthons are more versatile than the bifunctional compounds employed earlier. In the reactions of 2-aroyl-1-cyclohexanecarboxylic acids and the trifunctional synthons **67**,

72, 73 or **74** (Schemes 9 and 10), tetracyclic or pentacyclic hetero derivatives are formed. Two main directions of the ring-closure are possible: formation of an N=C bond with the carbonyl group, or the formation of bisacyl hydrazides by acylation of the hydrazine amino group with the carboxylic carbonyl. In the experiments, saturated cyclic γ-oxocarboxylic acids were used. It was found that the configurations of the saturated synthons often changed in the ring-closure reactions.

The reaction of anthranilic hydrazide **67** with *cis*-2-*p*-toluoyl-1-cyclohexanecarboxylic acid **68** or *diendo*-3-*p*-toluoylbicyclo[2.2.1]heptane-2-carboxylic acid **69** by boiling in toluene, in the presence of PTSA as catalyst, yields the phthalazino[1,2-*b*]quinazolinones **70** and **71**, respectively, containing a terminal fused (bi)-cycloalkane ring as parts *C/D* or *C/D/E* of the molecules (Scheme 8).



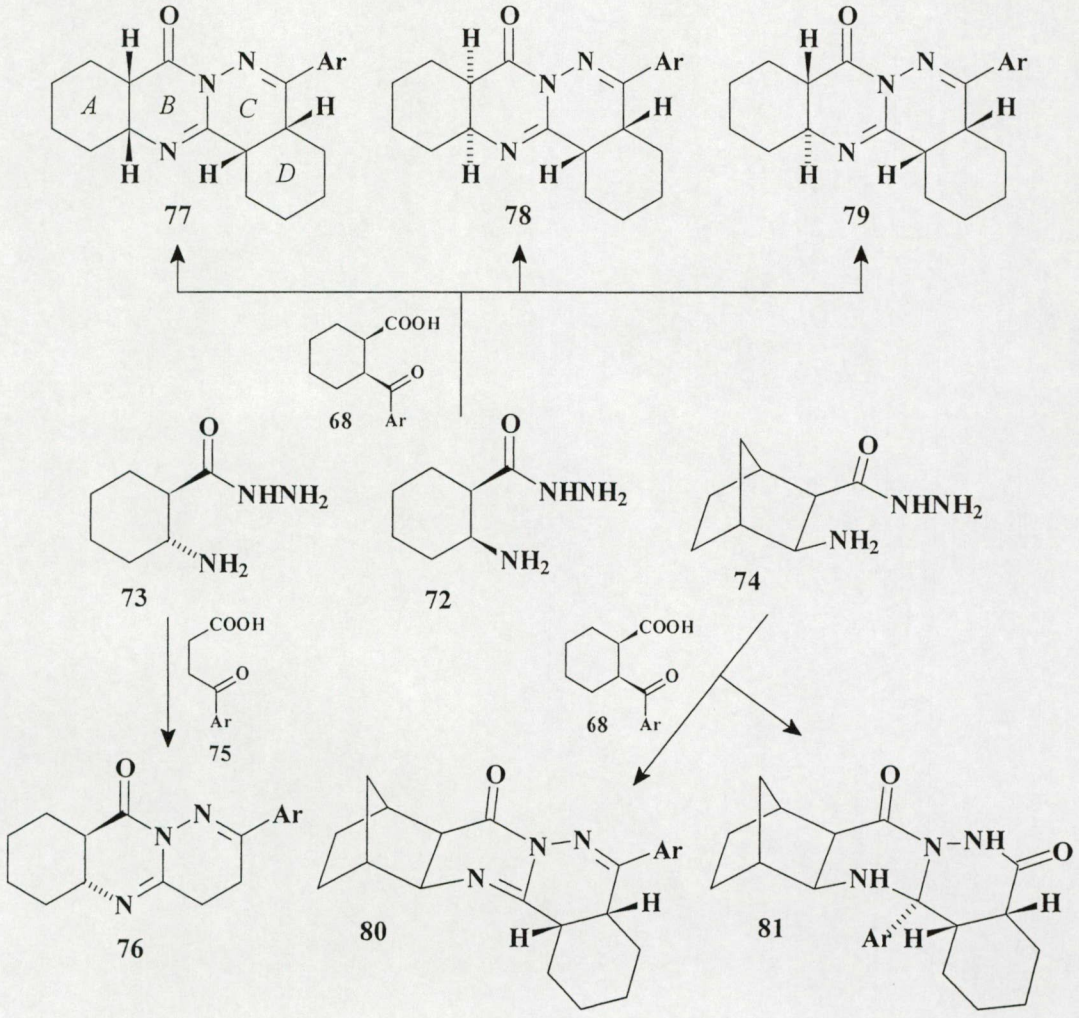
Ar = *p*-tolyl

Scheme 8

For the preparation of derivatives containing two saturated terminal rings, *cis*- and *trans*-2-amino-1-cyclohexanecarbohydrazides **72** and **73** or the methylene-bridged *diexo* analogues **74** were reacted with alicyclic or aliphatic oxocarboxylic acids. Thus, the reaction of 3-(*p*-chlorobenzoyl)propionic acid **75** with **73** yielded *trans*-pyridazino[6,1-*b*]quinazolinone (**76**) (Scheme 9).

The reaction of *cis*-2-amino-1-cyclohexanecarbohydrazide **72** with *cis*-3-*p*-toluoyl-1-cyclohexanecarboxylic acid **68** resulted in a mixture of **77**, **78** and **79**. After separation of the products, the three isomeric compounds were isolated and the struc-

tures were established by means of NMR spectroscopic measurements, together with X-ray analysis for **77** and **78** (Figure 6).



Ar = *p*-chlorophenyl (**75** and **76**) or *p*-tolyl (**68** and **77**-**81**)

Scheme 9

Compounds **77** and **78** contain two *cis*-fused cyclohexane rings, with the difference that in **77** all the annelational hydrogens at the *A/B* and *C/D* fusions are *cis* (α,α,α,α), whereas in **78** they are *cis* (β,β,α,α). Consequently, in the formation of **77** and **78**, no isomerization of the reactants occurred. In **79**, however, the rings *A/B* are *trans* (the annelational hydrogens at the *A/B* and *C/D* fusions are α,β,α,α), *i.e.* the ring closure took place with isomerization of the starting *cis*-2-amino-1-cyclohexanehydrazide **72**.

As no suitable single-crystals for X-ray determination could be prepared, **79** was also synthetized by the reaction of the *trans* **73** and the *cis* **68**; the reaction product proved to be identical with **79**.

In the reaction of *diexo*-3-aminobicyclo[2.2.1]heptane-2-carbohydrazide (**74**) and **68**, a mixture of **80** and **81** was formed; these were separated by column chromatography. The pentacyclic, partially saturated phthalazino[1,2-*b*]quinazolinone **80** contains a *diexo*-fused methylene-bridged saturated quinazoline moiety and *cis*-condensed rings *C/D*. **81**, containing fused quinazolinone and phthalazine moieties, is formed by acylation of the primary hydrazine amino group, subsequent cyclization with the aroylcarbonyl group resulting in the saturated quinazolinone-phthalazinone-fused derivative.

This reaction differs from the formation of **76-80**, where the carboxyl group took part in the cyclization to form the pyrimidine ring, and the oxo group was condensed with the hydrazide moiety.

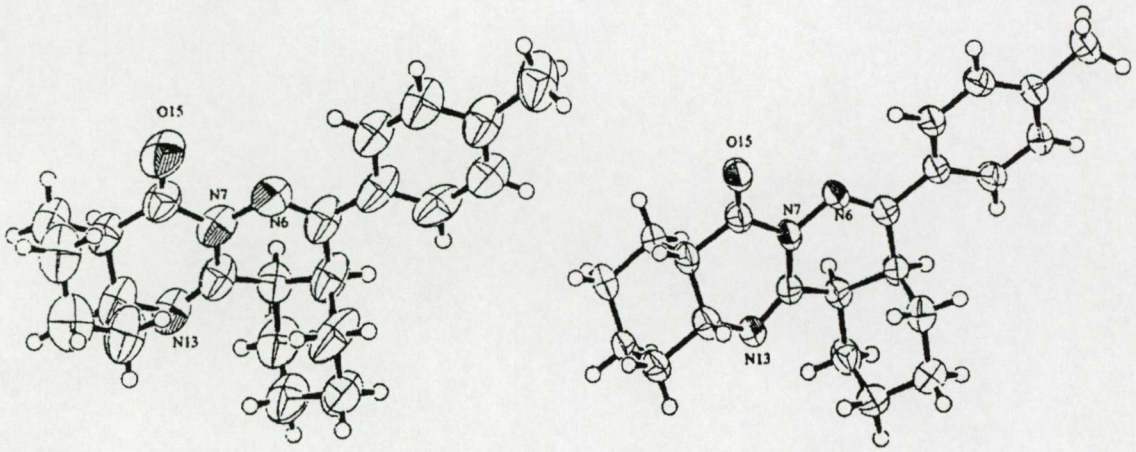


Figure 6. Perspective view of compounds **77** and **78**

2.5. Retrodiene reactions. Preparation of heterocycles by retro Diels-Alder reaction[IV, V, VI]

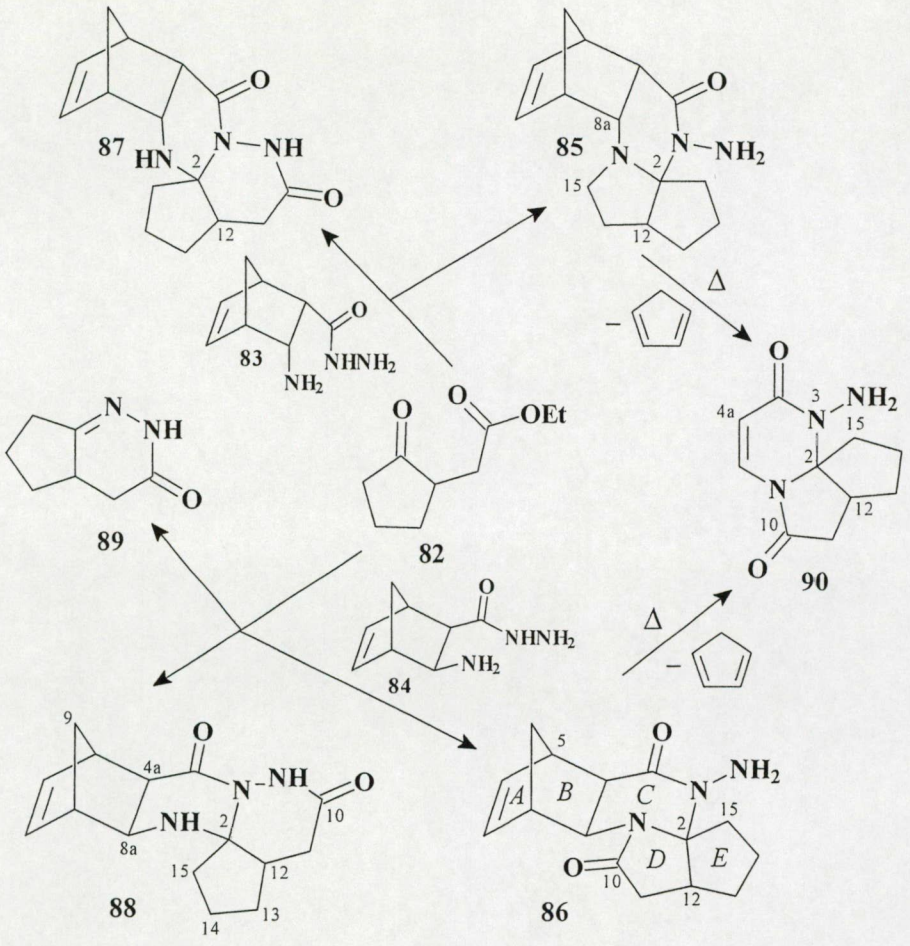
The thermal decomposition of a Diels-Alder adduct is referred to as an RDA reaction or [4+2] cycloreversion, where a new carbon-carbon double or triple bond is formed in the dienophile. This pyrolytic dissociation takes place most readily when one or both fragments are particularly stable. The unsaturation present in the original starting material is protected in the Diels-Alder adduct and the same atoms are involved in both the bond formation and cleavage steps.[71-80]

Our method applies *diendo*- and *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid and their hydrazides (**83** and **84**) as starting materials which contain cyclopentadiene as carrier unit, and the parent heterocycles are built onto the aminonorbornene acids. The principle of the method is the synthesis of partially saturated heterocycles with different reagents, *e.g.* imidates, oxoesters, isocyanates, isothiocyanates, *etc.*, and the subsequent removal of cyclopentadiene by a mild thermal process in the final reaction step. A special advantage of this procedure is that it does not require the flash vacuum pyrolysis applied in the traditional RDA reaction. A number of known and new heteromonocycles,[81,82] bicyclic[83] and tricyclic[84] compounds have recently been prepared *via* this route.

In place of γ- or δ-oxocarboxylic acids, the use of their esters is possible for the synthesis of saturated heterocycles.[85] In the literature, cyclocondensations have been carried out between 1,ω-alkanediamines or ω-amino alcohols over Al_2O_3 or montmorillonite K10 and ethyl laevulinate under microwave irradiation.[86] 2-Ethoxycarbonylcycloalkanones reacted with α,ω-alkylenediamines to furnish saturated cycloalkano[*b*]pyrrolo[1,2-*a*]imidazo-5-ones, -pyrimidin-6-ones and -[1,3]diazepin-7-ones.[87] This synthetic route was extended to the preparation of higher condensed homologues of tricyclic compounds, using isomeric cyclic 1,3-amino alcohols.[88] The condensation of racemic 8-bromo-2-oxo-benzo[*e*]cyclohexylacetate with (*R*)-(–)-phenylglycinol results in chiral tetracyclic lactams.[89]

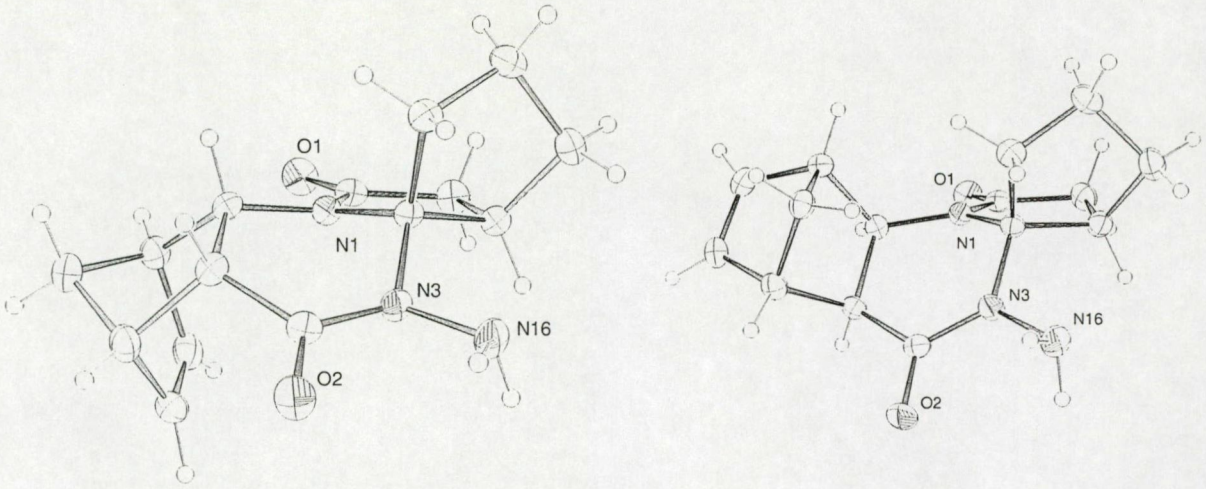
Preparation of 1-aminocyclopenta[2,3]pyrrolo[1,2-*a*]pyrimidine-2,6-dione by cycloreversion

The refluxing of *diendo* or *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-hydrazide (**83** and **84**) with ethyl 2-(2-oxocyclopentyl)acetate (**82**) in toluene, in the presence of PTSA as catalyst, yields a mixture of norbornene-condensed 1,5-diazatricyclododecanediones **85** and **86**, together with the pentacyclic bisacyl hydrazides: 9,12-methano-2,3,3a,4,8,12,12a,13-octahydro-1*H*-cyclopenta[5,6]pyridazino[6,1-*b*]quinazoline-5,8(6*H*,8a*H*)-diones **87** and **88** and the cyclopentane-fused bicyclic pyridazinone **89** (Scheme 10).



Scheme 10

The latter compound, 2,4,4a,5,6,7-hexahydro-3*H*-cylopenta[*c*]pyridazin-3-one (**89**), which had previously been prepared from ethyl 2-(2-oxocyclopentyl)acetate (**82**) with hyrazine hydrate **85**, was formed here by the reaction of **89** with the primary amino group of hydrazide **84** and subsequent intramolecular transacylation of the intermediate. This mechanism operates in the case of **84**; the *diendo* compound **83** does not give **89** for steric reasons. The compounds were isolated by column chromatography, and their structures were established by means of NMR measurements and, for **85** and **86**, also by X-ray analysis (Figure 7).



85 **86**

Figure 7. ORTEP-3 perspective views of **85** and **86**

When heated to the melting point, *diendo*- (**85**) and *diexo*-11-amino-1,4-methano-1,4,4a,7a,8,9,10,12a-octahydrocyclopenta[2,3]pyrrolo[1,2-*a*]quinazoline-6,12(7*H*,11*H*)-dione (**86**) decomposed by the splitting-off of cyclopentadiene; this thermal cleavage yielded 1-amino-7a,8,9,10,-tetrahydrocyclopenta[2,3]pyrrolo[1,2-*a*]pyrimidine-2,6(1*H*,7*H*)-dione (**90**) in 85% yield.

For determination of the configuration at C-2 and C-12, DNOE experiments were applied. On saturation of the H-8a signal of **85**, one of the H-15 signals responded, confirming their proximity; H-8a and the 15-CH_2 group are thus on the same side of the molecular skeleton. If the more favourable *cis* annulation of the strained five-membered rings *D* and *E* is presumed, the full stereostructure of **85** can be regarded as proved. X-ray measurements confirmed these postulated structures (Figure 7).

The 2D-NOESY spectrum of **86** displays a cross-peak, suggesting an interaction between H-5 and one of the methylene hydrogen atoms in the cyclopentane ring. The *cis*-oriented *D*/*E* fusion was in accordance with the X-ray results.

A similar structure of the spirotricyclic moiety *C-D-E* is supported by the chemical shifts of C-2 and C-12 in **87** and **88**. Similarly, the identical C-2 and hardly different C-12 shifts in **85** and **90** suggest analogous stereostructures, *i.e. cis*-annulated five-membered rings and the *cis* orientation of the amide N-3 and the methine C-12 in **90**.

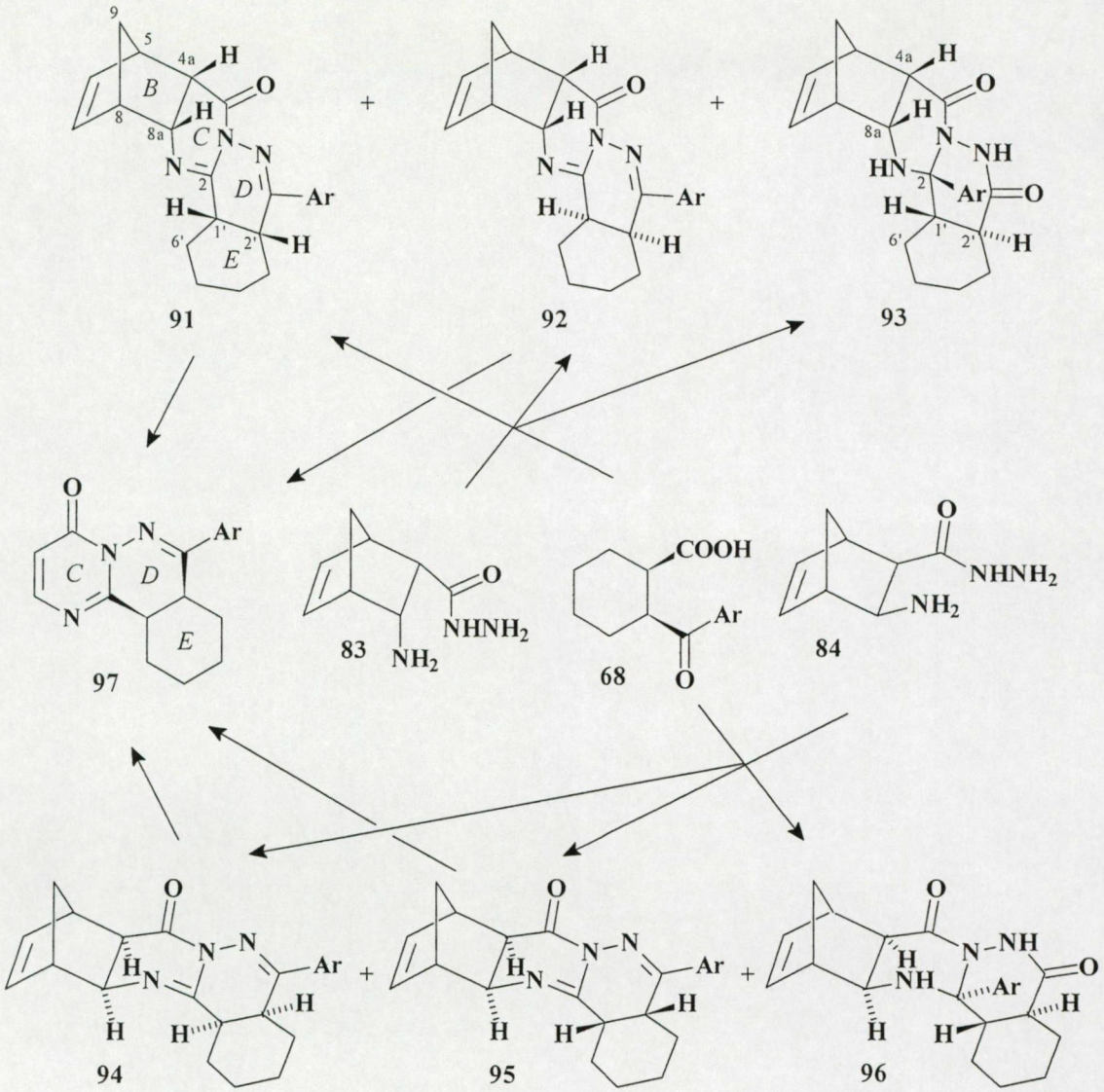
The IR and ^{1}H and ^{13}C NMR spectroscopic data prove the structures: the unexpected formation of **85** and **86** instead of the condensed system **87** and **88** was confirmed unambiguously by the appearance of NH_2 spectral signals and the lack of two NH groups. Hence, the first step in the ring closure is probably the formation of a cyclic diazaketal by condensation of the ketone with the primary amino group and the amide NH. In the second step, S_N acylation of the ester group, either by the amino group or by the primary hydrazine group, affords compounds of type **85** and **86** or **87** and **88**.

Preparation of pyrimido[2,1-a]phthalazines and an aminopyrimido[2,1-*a*]isoindole by retro Diels-Alder reaction[V]

The synthesis of polyheterocycles containing the pyrimido[2,1-*a*]phthalazine system, obtained by the condensation of phthalic anhydride with the hydrazide of 3-aminobenzo[*b*]thiophene-2-carboxylic acid, or 2-amino-5,5,6,7-terahydrobenzo[*b*]thiophene-3-carboxylic acid or 2-amino-5-phenylthiophene-3-carboxylic acid, is already known.[90] Pyrazolo[3',4':4,5]pyrimido[2,1-*a*]phthalazines were prepared from phthalic anhydride with 5-aminopyrazole-4-hydrazide.[91]

In the present part, the saturated phthalazinoquinazolinones were prepared. On the refluxing of *cis*-toluoylcyclohexanecarboxylic acid **68** with *diendo*-2-aminobicyclo[2.2.1]hept-5-ene-2-hydrazides **83** or the *diexo* analogues **84**, in the presence of a catalytic amount of PTSA, in benzene, the methylene-bridged *diendo*- (**91** and **92**) and *diexo*-decahydrophthalazino[1,2-*b*]quinazolinones (**94** and **95**) were obtained as diastereomeric mixtures, in ~30% yield, together with bisacylhydrazides **93** and **96** (Scheme 11).

Each of starting compounds **83** and **84** yielded one pair of isomers, **91-92** and **94-95**, which were separated by column chromatography. Their structures were then established by means of NMR measurements.

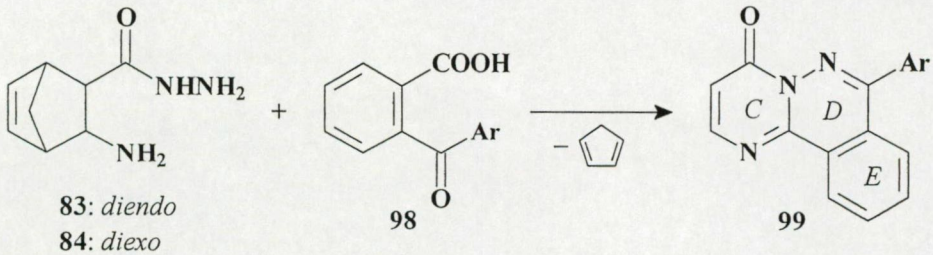


Scheme 11

The pairs *diendo*-9,12-methano-5-*p*-tolyl-1,2,3,4,4a,8a,9,12,12a,13b-decahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-ones **91** and **92**, and the *diexo* structural isomers **94** and **95**, contain the two norbornene and saturated phthalazine annelational hydrogens either on the same side (**91** and **94**) or on opposite sides (**92** and **95**) of the condensed pentacyclic skeleton. Besides the partially saturated phthalazinoquinazolinones **91, 92, 94** and **95**, the bisacyl hydrazides *diendo*- and *diexo*-9,12-methano-13a-*p*-tolyl-3,4,4a,8a,9,12,12a,13,13a,1b-decahydro-1*H*-phthalazino[1,2-*b*]quinazoline-5,8(2*H*,6*H*)-diones **93** and **96** and, in the reaction of **68** and **84**, the isoindolo[1,2-*a*]quinazolinone-dione **100** containing an amino group (Scheme 13) were formed: **93** and **96** by acylation of the primary hydrazine amino group with the carboxyl of **68** and cyclization

with the aroylcarbonyl group. These reactions differ from those which result in the structures **91, 92, 94** and **95**, where the carboxyl group forms the pyrimidine ring and the oxo group reacts with the hydrazine moiety. Compounds **91, 92, 94** and **95** retain their starting *cis* configuration at the *D/E* ring fusion, while the ring annelations for **93, 96, 100** and **101** are *trans*.

The reactions of **83** and **84** with 2-*p*-toluoylbenzoic acid **98** directly furnished 7-*p*-tolyl-4*H*-pyrimido[2,1-*a*]phthalazin-4-one (**99**) (Scheme 12).



83: *diendo*
84: *diexo*

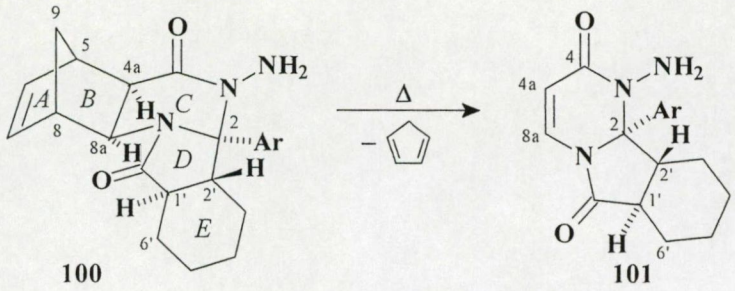
Ar = *p*-tolyl

Scheme 12

Similarly as found earlier for related norbornene-fused 1,3-heterocycles, the unsaturated *diendo* **91** and **92** and *diexo* **94** and **95** or their diastereomeric mixtures containing a norbornene moiety undergo retrodiene decomposition when heated to their melting points.

For the preparation of **99**, a mixture of **83** and **98** was refluxed first in EtOH (4 h), and then in toluene for a prolonged time (16 h). In these processes, cyclopentadiene was cleaved off and 7-*p*-tolylpyrimido[2,1-*a*]phthalazin-4-ones containing a *cis*-condensed cyclohexane ring (**97**) or a fused benzene ring (**99**) were formed in yields of 73% and 60%. It is noteworthy that the reaction of **84** with the aromatic **98** yields the benzologue **99** because the facile RDA process occurs even under mild circumstances.

On heating, 6-amino-1,4-methano-6a-*p*-tolyl-1,4a,5,6,6a,6b,7,8,9,10,10a,12a-dodecahydroisoindolo[2,1-*a*]quinazolin-11(4*H*)-one **100** undergoes cycloreversion to yield 1-amino-10b-*p*-tolyl-1,6a,7,8,9,10,10a,10b-octahydropyrimido[2,1-*a*]isoindole-2,6-dione **101**, a diastereomer containing a *trans*-annelated cyclohexane ring and a tolyl group on the same side as the annelational hydrogen next to the carbonyl (Scheme 13).



Ar = *p*-tolyl

Scheme 13

The bisacyl hydrazides **93** and **96** did not decompose when melted. The reason may be the presence of the two conjugated lactam moieties, which impede the formation of an electron-rich ring *C* and hence the RDA process.

We previously found that cycloreversion *via* the formation of a new double bond between two carbons in the target molecule proceeds readily if an oxo- or thioxo-subsituted heteroaromatic system is formed. In the present case, rings *C* in **97** and **99** have a quasi-aromatic character and the fused cyclohexane ring *E* does not exert a strong influence on their electron distribution. Accordingly, it seems certain that the electron system of ring *C* is decisive in ensuring the success of cycloreversion.

The structures of the RDA products 7-*p*-tolyl-7a,8,9,10,11,11a-hexahydro-4*H*-pyrimido[2,1-*a*]phthalazin-4-one **97** and its benzologue **99** are proved by the absence of the ^{1}H and ^{13}C signals of the norbornane moiety and the characteristic high-shift differences $\Delta\delta H_{\alpha}H_{\beta}$ and $\Delta\delta C_{\alpha}C_{\beta}$ of the enone group: 1.32 (**97**) and 1.51 ppm (**99**), and 35.7 (**97**) and 39.9 ppm (**99**), respectively. The corresponding data for the RDA product **101**, which also contains an enone moiety, are 2.07 (^{1}H) and 25.6 ppm (^{13}C). In the IR spectra of **100** and **101**, the characteristic pairs of $\nu_{as}NH_2$–$\nu_{s}NH_2$ bands are identifiable.

The *cis* annelation of **91, 92, 94, 95** and **97** and the *trans* configuration for **93, 96, 100** and **101** follow from the spectral data. Thus, for example, $\Sigma\delta C(1'\text{-}6')$ is 168.0-172.3 for **91, 92, 94** and **95** and 164.6 for **97**, while it is 190.8-193.0 for **93** and **96**, 205.9 for **100** and 204.2 ppm for **101**.

Establishment of the mutual position of the two pairs of annelated hydrogens in rings *A/B* and *D/E* is the most difficult problem because these hydrogen pairs (H-4a,8a and H-1′2′) are far from one another. The isomeric pairs must be considered individu-

ally. Very small differences are not sufficient to allow determination of the configurations.

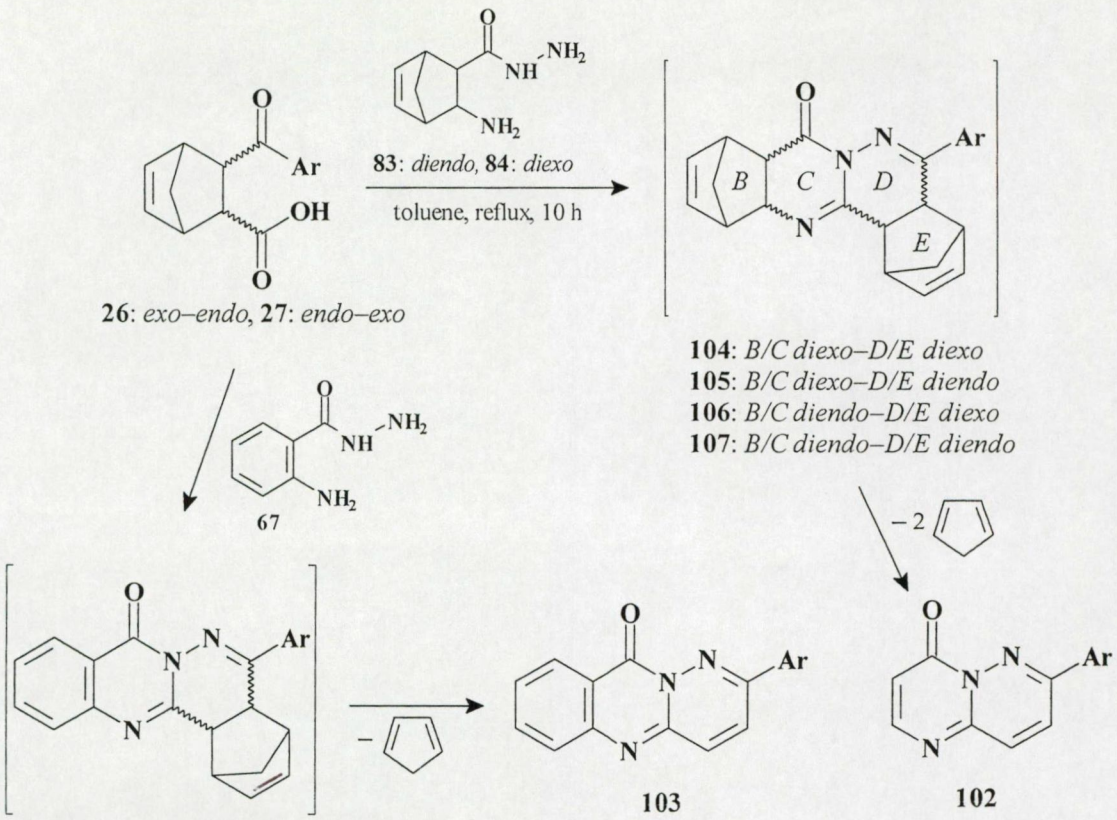
To establish the steric position of the tolyl group in **93, 96, 100** and **101**, difference NOE measurements were carried out. On saturation of the *ortho*-hydrogens in the *p*-tolyl group, H-8a and H-1′ responded, whereas no intensity enhancement was observed for the H-2′ signal in the case of **93**. Consequently, H-4a,8a,1′ and the tolyl group are on the same side of the skeleton. For **96**, the DNOE proved the sterically close arrangement of H-8a and the aryl group; the *cis* orientation of H-4a,8a and the latter substituent follows, while the aryl group is *trans* to H-1′ and *cis* to H-2′, relative to the pyridazinone ring.

The mutual NOE of H-8a or H-1′ and the *ortho*-hydrogens of the aryl group in **100** confirm the 1′α,2′α,4aα,8aα position for H-4a,8a,1′ and the aryl group (and thus, the β-orientation for H-2'). The similar shifts of H-2′ and the similarly upfield-shifted H-6′(*ax*) signal for **101** suggest a steric structure analogous to that of **100**; hence, the *p*-tolyl group is *cis* to H-1′ and *trans* to H-2′.

Double retro Diels-Alder reaction applied for the preparation of a pyrimido[1,2-*b*]pyridazine

The present part describes an extension of the earlier-applied cycloreversion method to a double RDA reaction, in which both reactants are built up on cyclopentadiene prior to the synthesis.

When *diendo*- **83** or *diexo*-aminonorbornenecarbohydrazides **84** were refluxed in toluene for 10 h with the mixture of **26** and **27** obtained from *trans*-aroylacrylic acid and cyclopentadiene,[33] the parent compounds **104, 105, 106** and **107** containing two norbornene units decomposed directly to 7-*p*-tolylpyrimido[1,2-*b*]pyridazin-3-one (**102**)[92-94] with a yield of over 40% (Scheme 14). Similarly, the reaction of **26, 27** and anthranilic hydrazide **67** led directly to pyridazino[6,1-*b*]quinazoline **103** in 39% yield by a single RDA process.



Scheme 14

In the reaction, the mixture of *exo*-aroylnorbornane-*endo*-carboxylic acid **26** and *endo*-aroylnorbornene-*exo*-carboxylic acid **27** presumably cyclizes to *diendo*- (**106**, **107** and **109**) and *diexo*- (**104**, **105** and **108**) phthalazino[1,2-*b*]quinazolinone intermediates.[VII] The formation of these conjugated systems is favourable for the cycloreversion[V] to give the RDA products **102** and **103** on heating.

The above method affords a new synthesis of the di- and tricyclic systems **102** and **103** and illustrates the general scope and importance and the applicability to obtain fused heterocycles *via* the RDA technique. This procedure does not require the flash vacuum pyrolysis applied in traditional RDA reactions. The principle of constructing fused molecules on cyclopentadiene offers a quite versatile means for the synthesis of various heterocycles.

2.6. Application of furan as escaping diene for the preparation of heterocycles[X]

Knowledge of the relative ease of expulsion of dienes is of fundamental importance for synthetic application of the RDA reactions. Bearing in mind the hazards of

generalization, the evidence suggests the following conclusions concerning the RDA reactivity of embedded adducts as indicated: furan, pyrrole > benzene > naphthalene > fulvene > cyclopentadiene > anthracene > butadiene. The data supporting this relationship are often indirect and not based upon absolute or relative rate determinations under identical conditions.[72,95] Other synthetic retrodiene reactions of furan Diels-Alder adducts are also known.[96-103] The furan can be removed from the adducts at lower temperatures than for cyclopentadiene. For example, 7-oxanorbornene-2,3-dicarboxylic anhydride reacts with toluene at RT and yields only a RDA reaction product: *trans*-3-toluoylacrylic acid.[104]

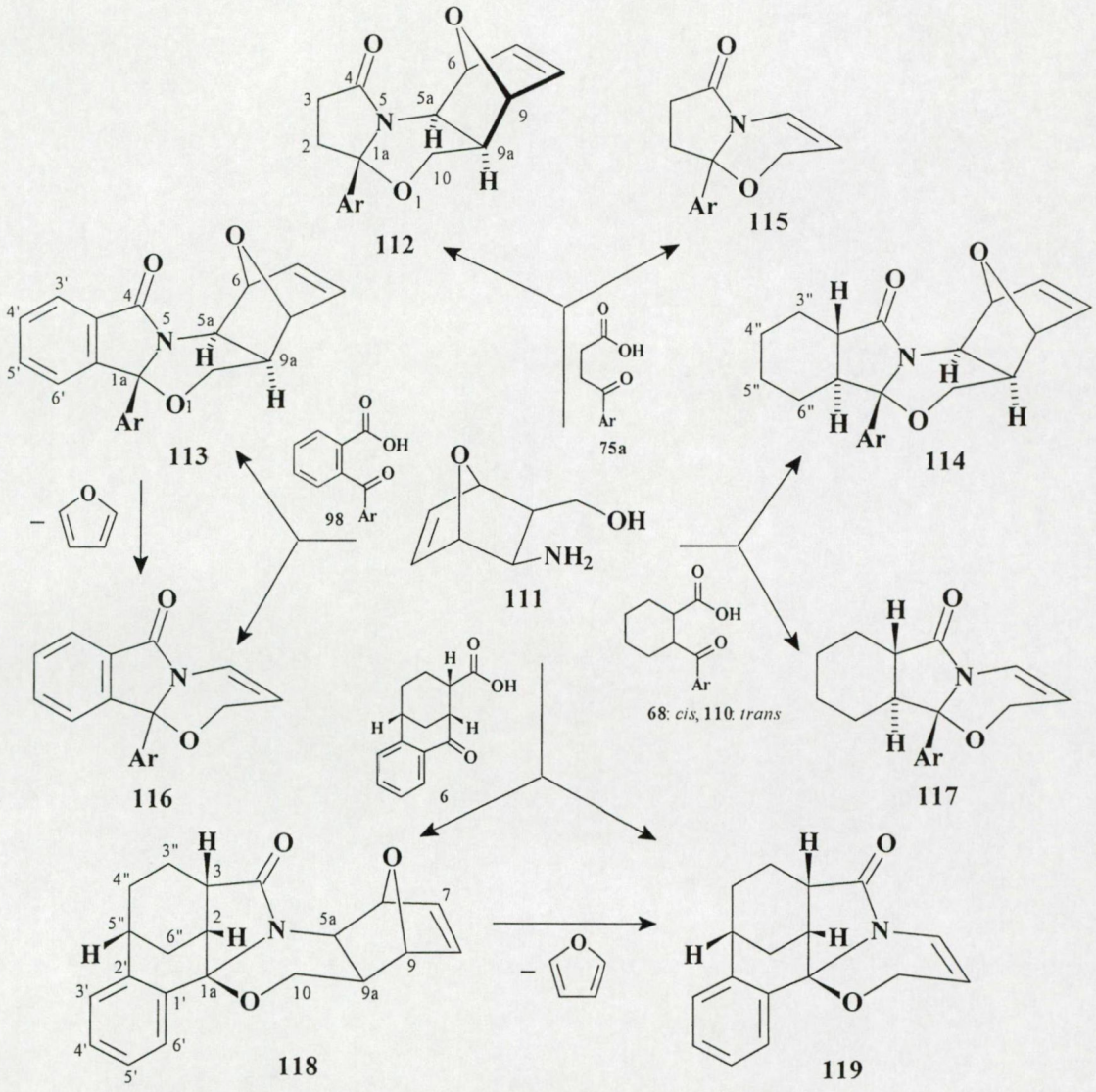
Preparation of condensed 1,3-oxazines by retro Diels-Alder reaction

We set out to build up molecules on furan instead of cyclopentadiene with the expectation of removing this diene more easily and hence of obtaining heterocycles other than those with a "pseudo-aromatic" (*e.g.* pyrimidinedione, thioxopyrimidine and 1,3-oxazinone) structure.

By Diels-Alder addition from furan with maleic anhydride, *diexo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride[41] was prepared, which served as the key starting material. After the ammonolysis of oxanorbornenedicarboxylic anhydride, the amide was transformed by Hofmann rearrangement with hypochlorite to the unsaturated *diexo*-3-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid, which, on reduction with $LiAlH_4$, yielded the corresponding 3-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-methanol **111**. On boiling in toluene with 3-*p*-toluoylpropionic acid (**75a**), 2-toluoylbenzoic acid (**98**) or *cis*- or *trans*-2-toluoylcyclohexane-1-carboxylic acid (**68** and **110**), in the presence of a catalytic amount of PTSA, amino alcohol **111** gave the partly saturated epoxypyrrolo[2,1-*a*][1,3]benzoxazinone **112**, isoindolo[3,1]benzoxazinone **113** or its partly saturated analogue **114** (Scheme 15)

From the reaction mixture, these and the RDA products pyrrolo[1,2-*b*]-[1,3]oxazinone **115**, [1,3]oxazino[2,3-*a*]isoindolone **116** and *trans*-[1,3]oxazino[2,3-*a*]isoindolone **117** were isolated. The starting stereoisomeric 2-toluoylcyclohexane-1-carboxylic acids **68** and **110** yielded the same *trans*-condensed derivative **117**, *i.e.* the *cis*-*p*-toluoylcyclohexanecarboxylic acid **68** isomerized to *trans* **110** in the course of the reaction. Compounds **112-117** were isolated by column chromatography

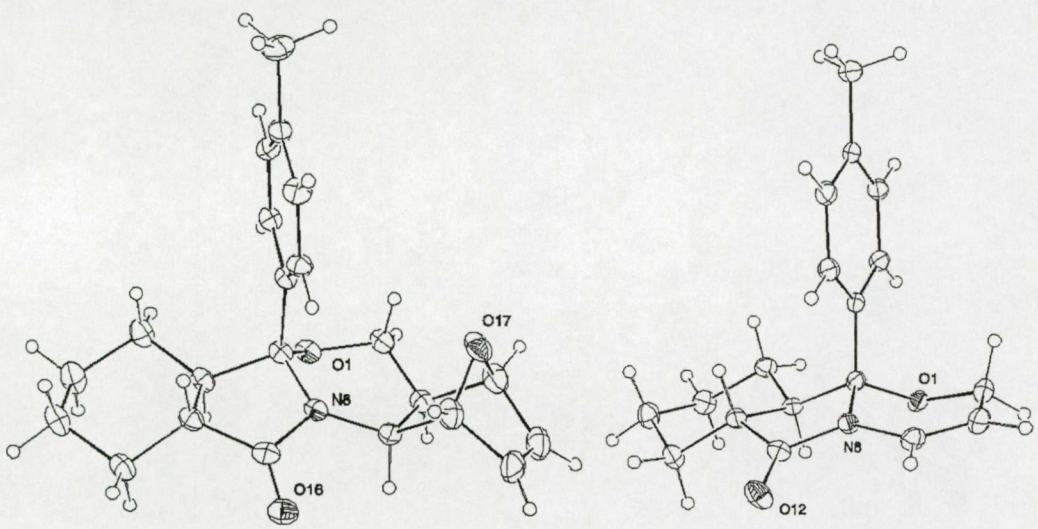
and their structures were determined by means of NMR spectroscopy and, for the parent epoxy compound **114** and the RDA product **117**, also by X-ray analysis (Figure 8).



Scheme 15

The similar reaction of **111** with 10-oxohexahydromethanobenzocyclooctene-8-carboxylic acid **6** gave the heptacyclic 1,4-epoxy-7,9-ethano-4,4a,7,7a,8,9,15,15a-octahydro-1*H*,6*H*-benz[6,7]indolo[1,7a-*a*][3,1]benzoxazin-6-one (**118**) and its RDA product, 11,13-ethano-11,11a,12,13-tetrahydro-6*H*,10*H*-benz[*g*][1,3]oxazino[2,3-*i*]indol-10-one (**119**). When **113** and **118** are boiled in chlorobenzene for 2 h, they furnish **116** and **119** in good yields by the loss of furan.

Because of the *-I* effect of the C=C double bond on the N (imide-like structure), the amide-I frequency for the RDA products **115, 116, 117** and **119** is higher by 6-12 cm^{-1}. In compound **112**, the *trans* position of the tolyl group and H-5a,9a relative to the oxazinone ring is probable from the negative experiment: no NOE was observed between the *ortho*-hydrogens of the tolyl group and H-5a,9a. For **114**, the *trans* annelation of the cyclohexane ring to the pyrrolidone is obvious from the double triplet split of the H-2,3 signals, which proves two *diaxial* couplings for each of these hydrogens. With a chair conformation preferred for the cyclohexane, the very strong shielding of H-6" evidenced the *exo* orientation of the tolyl group. Further, the analogous structure of **114** follows from the identical ^{1}H and very similar ^{13}C NMR chemical shifts, and the X-ray measurements on **114** confirmed the presumed stereostructure. The RDA counterpart **117** has an analogous stereostructure: the *trans* annelation of the cyclohexane can be assumed from the double triplet split of the H-2,3 signals, the similar value of the sum of the ^{13}C NMR shifts for this ring and the *exo* position of the tolyl group. The X-ray results are in accordance with the above situation.



114 **117**

Figure 8. Perspective view of **114** and **117**

An NOE was not observed for the tolyl *ortho*-protons and the annelation hydrogens (H-5a,9a) in **113**. The downfield shift of H-5a, probably due to the different steric position of H-5a and the tolyl group as a consequence of the strained benzo-fused skeleton, is opposite in sign to that expected if the C-1a configuration had changed.

Because of the three common carbons with the condensed pyrrolidone ring, the homotricyclic part of the heptacyclic **118** and its RDA derivative **119** is rather rigid and contains the cyclohexane ring in such a chair form. The oxanorbornane moiety is fused to the other part of the molecule (to the pentacycle in **119**) in way that the bridging oxygen lies over the heterobicyclic part of the skeleton, close to H-2,3. The oxazine ring of **119** has a boat conformation, with the N and the methylene out-of-plane to the other four atoms. In the other relative stable conformation of oxazine, a sofa form with five coplanar atoms and an out-of plane O in **119**, the two ethereal oxygens would lie fairly near to each other.

The results show the advantages of the application of furan instead of cyclopentadiene in the retrodiene synthesis. The main advantage is the possibility to prepare heterocycles which have no oxo group on the newly formed 1,3-oxazine ring. Thus, condensed heterocycles having no "quasi-aromatic" structure could be prepared for the first time by this RDA method.

3. Summary

By the reaction of newly synthetized methanobenzocyclooctene-, norbornane- and oxanorbornaneoxocarboxylic acids (**6, 39** and **55**) with difunctional agents such as diamines, amino alcohols, *etc.*, pharmacologically promising new isoindole- and indole-fused heterocycles have been prepared. *endo→exo, exo→endo* and *cis→trans* Isomerization of the aroyl group of the starting γ-oxocarboxylic acids **26, 27, 34, 35** and **68** provides a stereochemical possibility for the formation of heterocycles by cyclocondensation. Thus, from the *diexo-* and *diendo*-phthalazino[1,2-b]quinazolines **104-109**, the RDA products **102** and **103** are formed by previous isomerization of the toluoyl group. The oxocarboxylic acid **55** exists as a chain **55** and a ring tautomer **56**, which were separated and their structures determined by means of IR and X-ray spectroscopy. By the reaction of anthranilic hydrazides **72, 83** and **84** with *cis*-2-*p*-toluoyl-1-cyclohexanecarboxylic acid (**68**), the tetracyclic and pentacyclic fused-skeleton heterocompounds **77-79, 80-81** and **91-96** were formed. With γ-oxocarboxylic acid **68**, the cyclocondensations of the saturated (**72**) and partially saturated (**83** and **84**) aminohydrazides resulted in diastereoisomeric mixtures of phthalazino[1,2-b]quinazolinones **77** and **78, 91** and **92** and **94** and **95**, together with their bisacylhydrazides **93** and **96**, which were separated. For compounds **93** and **96**, not only the configurations of the rings, but also the position of the aromatic substituent were determined. Treatment of aminocarbohydrazides **83** and **84** with ethyl 2-(oxocyclopentyl)acetate (**82**) yielded *diexo-* and *diendo*-aminocyclopenta[2,3]pyrrolo[1,2-*a*]quinazolinones **86** and **85**, containing an amino group, which provides sufficient electron density for a mild retrodiene reaction. Hence, on heating, **85** and **86** decompose by loss of cyclopentadiene to give aminocyclopenta[2,3]pyrrolo[1,2-*a*]pyrimidine **90**. The applied RDA method is suitable for the preparation of bicyclic, tricyclic, tetracyclic and pentacyclic hetero compounds. During the cycloreversion, neither isomerization nor rearrangement occur in the preparation of **101** from **100**. In the case of derivatives **99, 102** and **103**, a one-pot RDA reaction was developed without isolation of the norbornene-fused parent heterocycles. For compounds **115, 116, 117** and **119**, the application of furan instead of cyclopentadiene results in condensed heterocycles with no "pseudo-aromatic" structures. The decomposition of the parent compounds needs mild reaction conditions and

the heterocycles can mostly be prepared on a preparative scale. The application of furan as diene is advantageous because the RDA decomposition takes place more easily than when cyclopentadiene is used as diene.

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Acknowledgements

I thank Professor Gábor Bernáth, previous Head, and Professor Ferenc Fülöp, present Head of the Institute of Pharmaceutical Chemistry, University of Szeged, for the possibility to work for my thesis in the Institute.

I would like to express my thanks to Professor Géza Stájer for his encouragement and guidance of my work. As supervisor, his advice has greatly helped me during all stages of the work.

My thanks are due to Professor Pál Sohár for the IR and NMR spectroscopic measurements and valuable interpretations, and to Professor Reijo Sillanpää, Professor Erich Kleinpeter and Zsolt Böcskei for their help in the X-ray method. I am also grateful to all my colleagues and friends, especially Dr. József A. Szabó and Ferenc Csende, for their professional advice and inspiring discussions.

A special thank-you goes to my family, without whom I would not have had the opportunity to complete this work.