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# Saturated Heterocycles. 254 [1]. Synthesis and Stereochemistry of Saturated or Partially Saturated Pyridazino-[6,1-*b*]- and Phthalazino[1,2-*b*]quinazolinones



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Received January 6, 1997

**This paper is dedicated to Dr. O. E. (Ted) Edwards on the occasion of his 75th birthday**

By the reaction of anthranilic hydrazide **1** with *cis*-2-(*p*-methylbenzoyl)-1-cyclohexanecarboxylic acid **2a** or *diendo*-3-(*p*-methylbenzoyl)bicyclo[2.2.1]heptane-2-carboxylic acid **2b**, fused tetra- and pentacyclic ring systems **3a,b** were prepared. *trans*-2-Amino-1-cyclohexanecarbohydrazide **4b** was reacted with 3-(*p*-chlorobenzoyl)propionic acid **5** to yield the pyridazino[6,1-*b*]quinazolinone **6**. From the reaction of *cis*-2-amino-1-cyclohexanecarbohydrazide **4a** with **2a**, three isomeric partially saturated 8*H*-phthalazino[1,2-*b*]quinazolin-8-ones **7a-c** were formed. The reaction of *diexo*-2-aminobicyclo[2.2.1]heptane-3-carbohydrazide **4c** and **2a** furnished the pentacyclic derivatives **8** and **9** containing a 3-aryl-4,5-dihydropyridazine or 3-aryl-hexahydropyridazine ring **C** with *cis* annelated **C/D** rings. The formation of **8** and **9** involving different ring systems can be rationalized by two reaction pathways: (i) in the bislactam **9** the carboxyl group acylates the hydrazide, while (ii) in **8** it forms a pyridazine ring with the cyclic amino group by cyclocondensation. The structures of the products were elucidated by $^{1}H$ and $^{13}C$ nmr methods, including DEPT, DNOE and 2D-HSC measurements.

*J. Heterocyclic Chem.*, 35, 201 (1998).

## Introduction.

We recently reported on the synthesis of various saturated tetracyclic and pentacyclic isoindolone-condensed derivatives [2-5]. These new saturated ring systems contain two condensed hetero rings and two terminal (bi)cycloalkane rings. Elucidation of the structures of these rather complex molecules is a challenging task, which demands a combination of modern nmr methods and in some cases X-ray analysis. Besides the stereochemical interest, these compounds are of pharmacological importance because the starting synthons and several of their aromatic analogues possess, among others, anorexic, anti-HIV, anti-inflammatory, analgesic or antiallergic activity [6-9].

The current study relates to 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 [5]. In the reactions of 2-aroyl-1-cyclohexanecarboxylic acids and the trifunctional synthons **1** or **4a-c**, tetracyclic or pentacyclic hetero derivatives are formed. Two main directions of the ring-closure reactions are possible: formation of two N=C bonds with the two carbonyl groups, or formation of bislactam derivatives by acylation of the hydrazine amino group with the carboxylic carbonyl. In previous studies with the related aromatic starting compounds, these two possible cyclization directions caused difficulties in structure elucidation, and the reported structures proved to be incorrect [10].

In our experiments, saturated cyclic γ-oxocarboxylic acids were used and it was found that the configurations of the saturated synthons often changed in the ring-closure reactions [2-5]. Such isomerization occurred especially if the reacting bifunctional compound was basic; enolization of the oxocarboxylic acid resulted in configuration inversion.

When both terminal rings are saturated, the stereochemistry at both terminal ring junctions must be examined. This problem does not arise in the aromatic analogues [11-16], but it complicates the determination of the structures of the present target compounds.

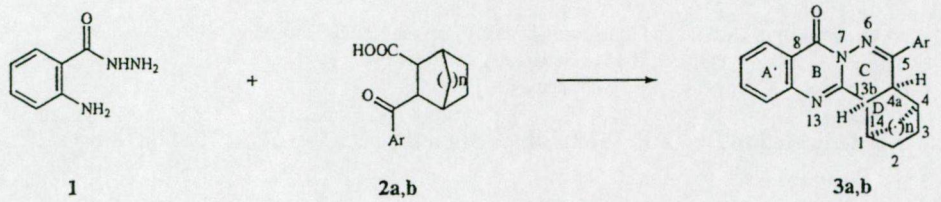
## Results.

The reaction of anthranilic hydrazide **1** with *cis*-2-(*p*-methylbenzoyl)-1-cyclohexanecarboxylic acid **2a** or *diendo*-3-(*p*-methylbenzoyl)bicyclo[2.2.1]heptane-2-carboxylic acid **2b** by boiling in toluene in the presence of

*p*-toluenesulphonic acid as catalyst yields the phthalazino-[1,2-*b*]quinazolinones **3a** and **3b**, respectively, containing a terminal fused (bi)cycloalkane ring in parts **C/D** of the molecules (Scheme 1).

In the reaction of *diexo*-3-aminobicyclo[2.2.1]heptane-2-carbohydrazide **4c** and **2a**, a mixture of **8** (36%) and **9** (29%) was formed; these were separated by column chromatography. The pentacyclic partially saturated

Scheme 1



**1** **2a,b** **3a,b**

Ar = $C_6H_4CH_3$-(*p*)

**2a**: n = 0; *cis* **3a**: C/D *cis*; n = 0
**2b**: n = 1; *diendo* **3b**: C/D *diendo*; n = 1

Analogous compounds fused with aromatic rings at both terminals are known [10-13]. Aromatic analogues of **3** have been prepared from phthalazinones [13] or from phthalazines [14] with anthranilic acids. The product obtained by hydrazinolysis of the isoindolobenzoxazinediones was reported to have a phthalazino[1,2-*b*]quinazoline structure [10].

For the preparation of derivatives containing two saturated terminal rings, *cis*- and *trans*-2-amino-1-cyclohexanecarbohydrazides **4a** and **4b** [17] or the methylene-bridged *diexo* analogue **4c** were reacted with alicyclic or aliphatic oxocarboxylic acids **2a** and **5**. Thus, the reaction of 3-(*p*-chlorobenzoyl)propionic acid **5** with **4b** yielded the *trans*-pyridazino[6,1-*b*]quinazolinone **6** (Scheme 2).

The reaction of the *cis*-2-hydroxy-1-cyclohexanecarbohydrazide **4a** with *cis*-3-(*p*-methylbenzoyl)-1-cyclohexanecarboxylic acid **2a** resulted in a mixture of **7a-c**. After separation of the product, three isomeric compounds were isolated and the structures were established by means of nmr spectroscopic measurements, together with X-ray analysis for **7a** and **7b** (Figure 1).

Compounds **7a** (yield 15%) and **7b** (26%) contain two *cis*-fused cyclohexane rings, with the difference that in **7a** all the annelational hydrogens at the **A/B** and **C/D** fusions are *cis*(α,α,α,α), whereas in **7b** they are *cis*(β,β,α,α). Consequently, in the formation of **7a** and **7b**, no isomerization of the reactants occurred. In **7c** (5%), 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-cyclohexanecarbohydrazide **4a**.

As no suitable single-crystals for X-ray determination could be prepared, **7c** was also synthesized by the reaction of the *trans* **4b** and the *cis* **2a**, and the reaction product (31%) proved to be identical with **7c**.

phthalazino[1,2-*b*]quinazolinone **8** contains a *diexo*-fused methylene-bridged saturated quinazoline moiety and *cis*-condensed rings **C/D 9**, containing fused quinazolinone and phthalazinone moieties, is formed by acylation of the primary hydrazine amino group with the carboxyl group, subsequent cyclization with the aroylcarbonyl group resulting in the saturated quinazolinone-phthalazinone-fused derivative.

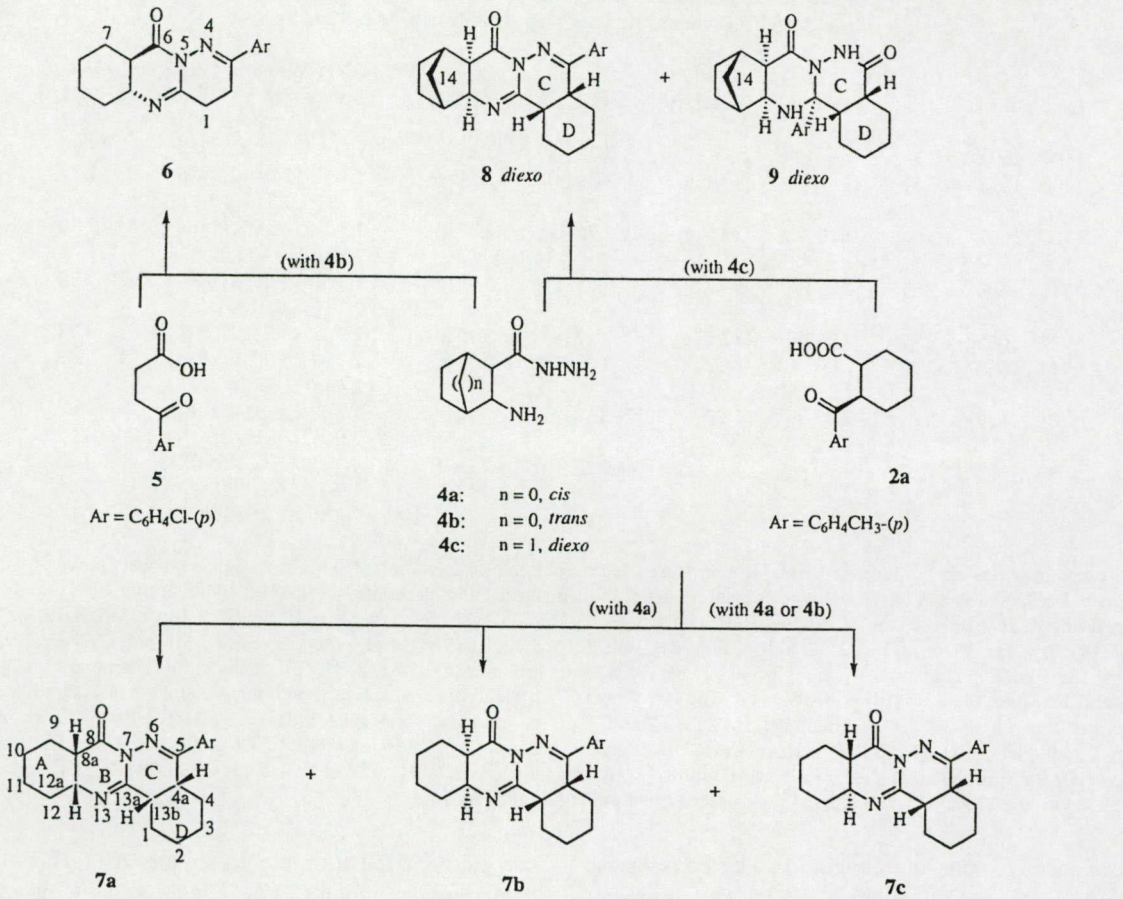
This reaction differs from the formation of **6-8**, where the carboxyl group took part in cyclization to form the pyrimidine ring, and the oxo group was condensed with the hydrazine moiety. Similar reactions yielding bislactams are known [8,11,16]. An interesting feature of these new compounds arises from the saturated skeleton. The previously described aromatic analogues have simpler structures because no alternative fusions of the terminal rings are possible.

Our experiments emphasize the importance of the establishment of the steric structure, especially for **9**, in which, besides the ring fusions, the position of the aromatic substituent has to be elucidated.

## Structure.

The structure elucidation is demonstrated on the example of the isomers **7a**, **7b** and **7c**. The similarity of these structures follows unambiguously from the spectral data (Tables 1 and 2). Due to the four chiral centers, the formation of eight diastereomers is theoretically possible, four of them containing one *cis*- and one *trans*-fused terminal ring, while two of them contain two *cis* rings, and two of them two *trans*-fused terminal rings. The isomers with one or two *cis*-annelated rings have two or four stable conformations, containing the cyclohexane rings in the chair form. Hence, isomers **7a-c** can possess one or other of the theoretically possible eighteen steric structures.

Scheme 2



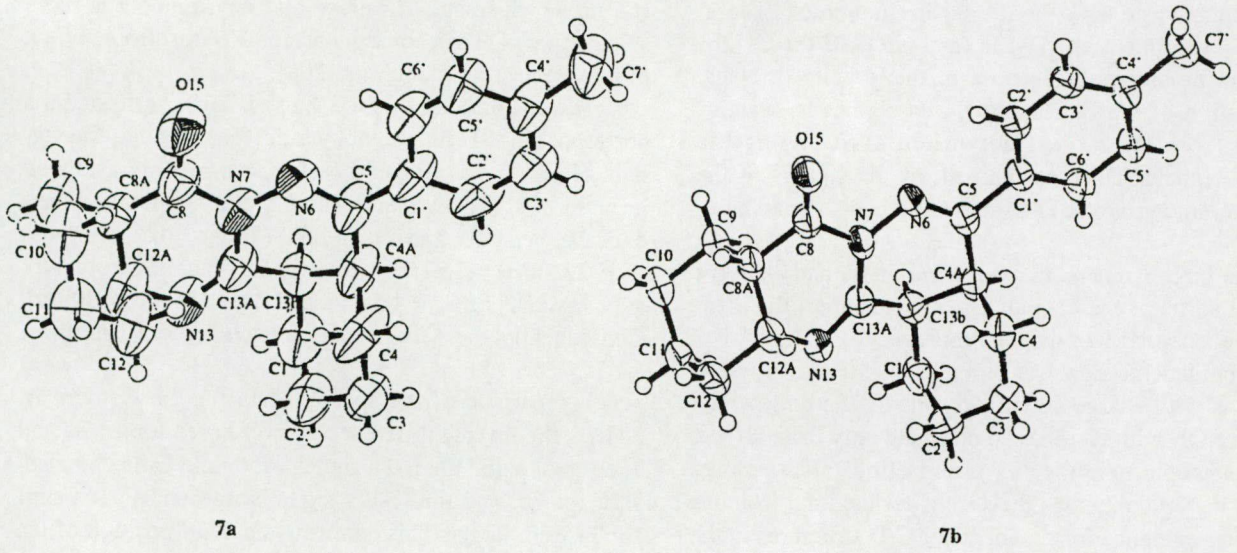




Figure 1. Perspective views of compounds **7a** and **7b**.

Table 1*

Characteristic IR Frequencies [$cm^{-1}$] and $^1H$ NMR Chemical Shifts [ppm] and Coupling Constants [Hz] of Compounds 3a,b, 6, 7a-c, 8 and 9

| Compound | ν C=O band | ν C=N band | $CH_3$ (aryl) | CH-8a *m* (1H) [a] | CH-12a *m* (1H) [b] | CH-13b *m* (1H) [c] | CH-4a *m* (1H) [d] | $CH_2$/CH (Position 1-4, 9-12, 14) 2-5 *m*'s (8H or 16H) [e] | H-2',6' *m* (2H) [f] | H-3',5' *m* (2H) [f] |
|---|---|---|---|---|---|---|---|---|---|---|
| 3a | 1694 | 1602 | 2.38 | - | - | 3.25 [g] | 3.25 [g] | 1.2-1.8 (7H), 2.95 [h] | 7.94 | 7.25 |
| 3b | 1700 | 1598 | 2.37 | - | - | 3.54 [g] | 3.54 [g] | 1.1-1.45 (4H), 1.55 [i], 1.75 [i], 2.71 [j], 3.02 [k] | 7.87 | 7.22 |
| 6 | 1720 | 1667 | - | 2.10 | ~3.10 [g] | 2.75 [l] | 2.75 [l] | 1.2-1.5 (4H), 1.85 [m], 2.30 [n], 2.40 [o] | 7.80 | 7.38 |
| 7a | 1711 | 1668 | 2.37 | 2.85 [g] | 3.75 [p] | 2.85 [g] | 3.15 [p] | 1.3-1.55 (9H), 1.7-1.9 (5H), 2.30 [n], 2.52 [h] | 7.78 | 7 20 |
| 7b | 1722 | 1665 | 2.37 | 2.75 [p] | 3.75 [p] | 2.87 [p] | 3.15 [p] | 1.2-1.9 (15H), 2.55 [h] | 7.78 | 7.20 |
| 7c | 1714 | 1665 | 2.37 | 2.00 | 3.12 [g] | 2.87 [p] | 3.18 [g] | 1.15-1.65 (8H), 1.8 (5H), 2.4 [q], 2.55 [h] | 7.79 | 7.20 |
| 8 | 1701 | 1689 | 2.37 | ~2.80 [g] | 3.80 | ~2.80 [g] | 3.10 [p] | 1.2-1.9 (13H), 2.5 [h], 2.6 [n], 2.8 [g,o] | 7.78 | 7.20 |
| 9 | 1698 | - | 2.35 | ~1.90 [g] | 3.02 | ~2.25 [l] | ~2.25 [l] | 0.9-1.4 (5H), 1.55 (5H), 1.7-1.95 (4H) [g], 2.25 [l,n], 2.93 [o] | 7.28 | 7.16 |

*Infrared (ir) data in potassium bromide discs and $^1H$ nmr data in deuteriochloroform solution at 250 MHz. Assignments were proven by DNOE and 2D-HSC(except for 3a and 9) and for 7c also by DR measurements. Further signals, ir: ν NH and δ NH, 9 3312, 1644; $^1H$ nmr, aromatic hydrogens in the condensed ring A: H-9, *dd*, 8.40 (3a), 8.36 (3b), H-10, *dt*, 7.45, H-11, 7.68 (3a, coalesced with the H-12 signal), 7.72, *dt* (3b), H-12, *dd*: 7.62 (3b), NH, broad, *s* (9): 9.03. [a] *dt* (6, 7c), J ≈ 12, 12 and 3; [b] *dd*, J ≈ 9 and 3 (8), *d*, J ≈ 7.6 (9); [c] $CH_2$ group, intensity 2H (6); [d] $CH_2$ group for 6, 2 x *m* (2 x 1H) with the second *m* at about 3.1 [g]; [e] 2-5 *m*'s of 8H-(3a,b, 6) or 16H-intensity (7a-c, 8, 9); CH groups in 3b (Positions 1 and 4) and 8, 9 (Position 9 and 12). Bridging-$CH_2$ (14) in 3b, 8 and 9. The H-9(8) and H-12(9) singlets are coalesced with the *m*'s at 2.8 and 2.25, respectively; [f] Aryl group, *A* or *B* part of an *AA'BB'*-type multiplet, J(*A*,*B*) = 8.2 or 8.7 (6); [g,l] Overlapping signals; [h] H1*eq*, *d* (1H); [i] 2 x *d* (2 x 1H), *A* or *B* part of the *AB*-type multiplet of $CH_2$ (14), J(*A*,*B*) ≈ 10, δ H(*exo*) < δ H(*endo*); [j] H-4, *s* (1H); [k] H-1, *s* (1H); [m] $CH_2$(10), *m* (2H); [n] H-12, *eq* (1H) for 6 and 7a,c, *s* (1H) for 8; [o] H-9, *eq*, *d* (1H) for 6, *s* (1H) for 8; [p] Half signal width: 25 (CH-4a,8a in 7b and CH-12a in 7a), 20 (CH-4a in 7a, 8), 15 (CH-12a,13b in 7b) and 12 Hz (CH-13b in 7c); [q] Coalesced signals of H-9*eq* and H-12*eq*.

The resonances for the four annelational carbons 4a, 8a, 12a, 13b were assigned by means of DEPT measurements [18] and the corresponding $^1H$ nmr signals were identified by means of the 2D-HSC spectra [19] (The positional numbering of **7a** is also applied for **3**, **8** and **9** in the text and Tables.). The H-4a signal was identified *via* the mutual NOE with the *ortho* hydrogens of the 4-methylphenyl group [20a,21]. By irradiation of H-4a in the NOE experiment, the H-13b (and *via* HSC the C-13b) signal can be assigned. Because of the vicinity of N-13, identification of the C-12a and H-12a signals is straightforward from the largest downfield shift among the aliphatic signals. Thus, assignment of the signals of the fourth methine group to H-8a and C-8a is also unambiguous.

For the three isomers, the very similar $^1H$ and $^{13}C$ nmr chemical shifts of the 4a and 13b atoms support the identical stereochemistry of the **C/D** moiety.

The doublet-like signal of one of the sixteen methylene hydrogens with a large downfield shift (2.55 ppm), which gives an NOE with H-13b, can originate only from H-1*eq*. The anisotropic neighboring group effect of the close-lying N-12 [20b] explains the strong deshielding, which is supporting evidence for the identical **C/D** structures in the isomers. At the same time, this H-1*eq*-N-12 interaction indicates the preferred conformation for ring **D**: H-1*eq* can lie near the lone electron pair of N-12 only in the chair form in which C-13a is *axial* and C-5 is *equatorial* to ring **D**. This is in agreement with the above-mentioned NOE of H-4a and the *ortho* aromatic hydrogens (in the other chair form of ring **D**, these atoms could not come near each other) and with the irregular [20c] downfield shift of the H-4*ax* signal (relative to that of the *equatorial* H-13b, which in spite of its similar environment is more shielded), which is a consequence of the anisotropic effect of the coplanar aromatic ring [20d].

As regards the sum of the C-8a and C-12a shifts and the corresponding $^1H$ nmr signal width [for the latter, the signals of H-8a (**7a**) and H-12a (**7c**) can not be assigned because of signal overlaps], there is no significant difference between **7a** and **7b** [ΔΣδC (**7a,b**) = 0.8 ppm and ΔνH-12a (**7b**) = 15 Hz], while for **7c** much higher values are measured [ΔΣδC = 4.0 ppm and ΔνH-12a (**7c**) = 30 Hz]. Consequently, the **A/B** annelation is *cis* for **7a,b**, but *trans* for **7c**.

A comparison of the spectral data for the isomers **7a** and **7b**, the reverse difference was observed for the 8a and 12a signal pairs: the H-8a signal width and C-8a chemical shift for **7b**, and the H-12a signal width and C-12a shift for **7a** were larger. This confirms the *axial* position of the carbonyl group in **7a** (because of the *diaxial* coupling [22], the signal of H-8a is broader, while the field effect

Table 2*

$^{13}$C NMR Chemical Shifts in δ [ppm] of Compounds 3a,b, 6, 7a-c, 8 and 9

| Compound | $CH_2$ (1) | $CH_2$ (2) | $CH_2$ (3) | $CH_2$ (4) | CH (4a) | C-5 | C=O (8) | CH (8a) | $CH_2$ (9) | $CH_2$ (10) | $CH_2$ (11) | $CH_2$ (12) | $CH_2$ (12a) | C-13a | CH (13b) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3a [a] | 24.9 [b] | 20.8 | 24.5 [b] | 25.6 [b] | 35.2 [c] | 146.3 | 162.1 | 122.8 | 127.5 [d] | 126.6 [d] | 134.2 | 127.2 [d] | 150.2 | 158.4 | 35.4 [c] |
| 3b [a] | 46.0 [e,f] | 23.4 [b] | 24.2 [b] | 43.6 [e,f] | 40.9 [c] | 146.2 | 158.3 [d] | 121.9 | 128.2 [g] | 126.7 [g] | 134.2 | 127.6 [g] | 149.1 | 156.6 [d] | 38.4 [c] |
| 6 | - | - | - | - | 23.5 [e,h] | 147.9 | 167.9 | 43.6 | 25.2 [e] | 24.6[e] | 24.7 | 33.9 | 56.2 | 151.5 | 25.9 [h] |
| 7a | 24.8 [e] | 20.6 | 24.0 | 25.9[b] | 36.7 | 149.1 | 167.9 | 40.8 | 28.8 | 22.3 | 26.0 [b] | 23.9[e] | 54.3 | 156.4 | 34.4 |
| 7b | 24.7 [e] | 20.6 | 23.6 [b] | 25.8 [c] | 36.6 | 149.0 | 168.5 | 41.8 | 25.5 [c] | 23.4 [b] | 22.1 | 29.6 | 52.5 | 156.9 | 34.6 |
| 7c | 24.0 [e] | 20.3 | 24.6 [b] | 25.8 [b] | 37.1 | 149.2 | 168.7 | 42.9 | 25.4 [e] | 24.7 [b] | 26.2 [b] | 34.1 [e] | 55.8 | 154.5 | 33.8 |
| 8 | 25.1 [e] | 20.3 | 25.5 [b] | 26.3[b] | 36.0 | 146.2 | 165.2 | 49.3 | 44.3 [f] | 25.8 [b] | 29.4 | 45.8 [e,f] | 62.6 | 157.8 | 34.8 |
| 9 | 24.9 [b] | 20.3 | 25.0 [b] | 26.7 [b] | 40.3 [c] | 175.6 | 165.6 | 50.0 | 42.5 [f] | 25.7 [b] | 27.7 [b] | 48.5 [f] | 56.9 | 79.7 | 40.6 [c] |

* $\delta_{TMS} = 0$ ppm in deuteriochloroform solution at 63 MHz. Assignments were proved by 2D-HSC (except for 3a and 9) and DEPT measurements (except for 3a). Further signals: $CH_3$: 21.2 ±0.1, 20.9 for 9; Aryl group, C-1': 131.3 (3a), 132.7 (3b), 133.9 (5), 131.8 (7a-c, 8), 137.7 (9); C-2',6': 127.0 (3a,b), 127.5 (6), 126.2 (7a-c, 8), 125.3 (9); C-3',5': 129.3 (3a,b, 9), 128.7 (6), 129.1 (7a-c, 8); C-4': 141.5 (3a), 140.9 (3b), 136.3 (6), 140.2 (7a-c, 8), 138.9 (9); $CH_2$(14), bridging-$CH_2$ in norbornane moiety: 39.3 (3b), 34.2 (8), 34.5 (9). [a] Aromatic carbons in positions 8a, 9-12, 12a; quaternary (8a, 12a) or protonated (9-12); [b,c,d,g] Interchangeable assignments; [e] These assignments were proved by combined DNOE and 2D-HSC measurements; [f] CH group; [h] $CH_2$ group.

[20e,23] causes the upfield shift of the C-8a line) and its *equatorial* orientation in **7b**. (For **7b**, the C-12a line appears upfield-shifted due to the field effect.) Hence, for **7a**, the four annelational hydrogens lie on the same side of the skeleton (configuration α,α,α,α), while for **7b**, the pairs 4a,13b and 8a,12a lie on opposite sides of the ring system (structure α,α,β,β).

For **7c**, supposing the above deduced *trans* **A/B**-*cis* **C/D** structure and the conformation with ring D in chair form, and with C-13a *axial* and C-5 *equatorial*, two stereostructures differing in the relative positions of the 4a,8a,12a,-13b hydrogens (α,α,β,α or α,β,α,α) remain. The α,α,β,α configuration is more likely and is also more favorable sterically, in accordance with the molecular modeling.

This structure is supported by the shift in the H-1*eq* signal, which is identical with those measured for **7a** and **7b**; in the presumed structure, the **B,C,D** part of the molecule, and hence the mutual steric arrangement of the lone electron pair on N-12 and H*eq*(1), *i.e.* the "dihedral angle" H*eq*(1)-C(1)....C(13a)-N(13), is unchanged. On the other hand, the configuration *α,β,α,α* would require inversion of ring **B**. In the structures assumed for **7a-c**, ring **B** has a twist form with out-of-plane "α(C-8a)" and "β(C-12a)", while the structure α,β,α,α would require the β(C-8a)-α(C-12a) inverse conformation.

Taking into account the very similar nmr data for rings **B**, **C** and **D** (*e.g.* the identical or only slightly different H-1*eq*, C-13b and C-4a shifts), analogous steric structures can be deduced for **3a** and **8**. Similarly, the *trans* **A/B** annelation for **6** follows from the shifts being practically identical to those measured for C-8a and C-12a in **7c**. The X-ray analysis confirmed the structures **7a** and **7b** (Figure 1).

On irradiation of H-14(*endo*) and the *ortho* aryl hydrogens in an NOE experiment, H-13b and H-4a respond in **3b**, which proves the *diendo* fusion of the norbornane and the hetero ring. From the small H-12-H-12a coupling [24] for **8** and **9**, the *diexo* annelation follows.

The following spectral data support the steric structure of **9**: (i) in addition to the νNH ir bands (3312 $cm^{-1}$) and carbonyl resonance (165.6 ppm), the new $^{13}$C nmr resonance of the second amide carbonyl appears at 175.6 ppm in **8**; (ii) instead of the $^{13}$C nmr resonance at about 156 ppm, characteristic of the $sp^2$ C-13a, the less shifted line at 79.7 ppm, characteristic of the $sp^3$ atom, appears; (iii) the NOE between H-12a and the aromatic *ortho*-hydrogens demonstrates the proximity atoms and the *cis* relationship of the aryl group and H-12a to the pyrimidinone ring; (iv) the carbon shifts confirm the *cis* annelation of the cyclohexane, and the NOE measurements prove the *cis* relationship of the aryl and cyclohexane rings.

Table 3

Physical and Analytical Data on Compounds 3 and 6-9

| Compound | Yield (%) | Mp (°C) (recrystallization solvent) | Formula (Mol. wt.) | Analysis(%) Calcd./Found C | H | N |
|---|---|---|---|---|---|---|
| 3a | 51 | 219-221 (benzene) | $C_{22}H_{21}N_3O$ (343.43) | 76 94<br>76.75 | 6.16<br>6.21 | 12.23<br>12.24 |
| 3b | 42 | 260-263 (benzene) | $C_{23}H_{21}N_3O$ (355.44) | 77.72<br>77.61 | 5.96<br>6.08 | 11.82<br>11.90 |
| 6 | 35 | 254-256 (EtOAc) | $C_{17}H_{18}ClN_3O$ (315.80) | 64.66<br>64.54 | 5.75<br>5.70 | 13.31<br>13.27 |
| 7a | 15 | 200-202 (EtOH) | $C_{22}H_{27}N_3O$ (349.48) | 75.61<br>75.34 | 7.79<br>7.98 | 12.02<br>12.00 |
| 7b | 26 | 167-169 (EtOH) | $C_{22}H_{27}N_3O$ (349.48) | 75.61<br>75.77 | 7.79<br>7.69 | 12.02<br>12.19 |
| 7c | 5 [a]<br>31 [b] | 248-249 (EtOAc) | $C_{22}H_{27}N_3O$ (349.48) | 75 61<br>75.66 | 7.79<br>7.68 | 12.02<br>11.92 |
| 8 | 36 | 273-275 (EtOAc) | $C_{23}H_{27}N_3O$ (361.49) | 76.42<br>76.40 | 7.53<br>7.63 | 11.62<br>11.57 |
| 9 | 29 | 286-287 (dioxane) | $C_{23}H_{29}N_3O_2$ (379.50) | 72.79<br>72.93 | 7.70<br>7.82 | 11.07<br>11.14 |

[a] Product separated from the mixture of 7a-c; [b] Yield after isolation from the reaction of 2a and 4b.

## EXPERIMENTAL

The ir spectra were determined as potassium bromide discs on a Bruker IFS-55 FT-spectrometer controlled by Opus 2.0 software. The $^1H$ and $^{13}C$ nmr spectra were recorded in deuteriochloroform solution in 5 mm tubes at room temperature, on a Bruker WM-250 FT-spectrometer equipped with an Aspect 2000 computer at 250.13 ($^1H$) and 62.89 ($^{13}C$) MHz, respectively, using the deuterium signal of the solvent as the lock and TMS as internal standard. Conventional CW irradiation of ~0.15 W was used in the DR experiments. DEPT spectra [18] were run in a standard way [25], using only the $\theta = 135°$ pulse to separate the $CH/CH_3$ and $CH_2$ lines phased up and down, respectively. For DNOE measurements [20a,21], the standard Bruker microprogram "DNOEMULT.AU" to generate NOE was used. The 2D-HSC spectra [19] were obtained by using the standard Bruker pulse program "XHCORRD.AU".

The X-ray data were collected at room temperature on a Rigaku AFCGS diffractometer with graphite-monochromatized $CuK_\alpha$ ($\lambda = 1.5418$ Å) radiation. The intensity data were collected in an $\omega$-$2\theta$ scan mode at an $\omega$ scan speed of 4.0° $min^{-1}$ with $\omega$ scan width = 1.52 + 0.30 tan $\theta$. All data were corrected for Lorentz polarization effects and for secondary extinction (coefficient = 0.0014(9) for 7a and no correction for 7b). The intensities of three check reflections showed only statistical fluctuations. The structures were solved by using SHELXL-86 [26], followed by successive Fourier syntheses [27], and refinements were carried out with SHELXL-93 [28]. Calculations and graphical display were performed by using the TEXSAN [29] package. For 7a, a = 9.34(2) Å, b = 20.53(2) Å, c = 10.67(2) Å, $\beta$ = 109.6(1), Z = 4, space group $P2_1/a$, $d_x = 1.204$ $gcm^{-3}$, $\mu = 0.585$ $cm^{-1}$. A total of 5918 reflections were measured to $\theta_{max}$ = 63.32°; 3085 unique reflections, $R_{int} = 0.035$. Refinement was done on $F^2$ with all reflections included, apart from 12 very negative ones. 761 reflections $I>2\sigma(I)$ were used in calculating R1 = 0.114; wR2 = 0.4754 for all reflections, $w = 1/\sigma^2[F_o^2 + (0.1444P)^2$, where $P = (F_o^2 + F_c^2)/3]$, GooF = 1.025. For 7b, a = 9.467(4) Å, b = 12.936(6) Å, c = 9.056(9) Å, $\alpha$ = 101.84(4), $\beta$ = 117.47(2), $\gamma$ = 69.38(5), Z = 2, space group P-1, $d_x = 1.231$ $gcm^{-3}$, $\mu = 0.598$ $cm^{-1}$. A total of 3962 reflections were measured to $\theta_{max}$ = 75.15°; 3729 unique reflections, $R_{int} = 0.035$. Refinement was done on $F^2$ with all reflections included, apart from 10 very negative ones. 1762 reflections $I>2\sigma(I)$ were used in calculating R1 = 0.058; wR2 = 0.2542 for all reflections, $w = 1/\sigma^2[F_o^2 + (0.0978P)^2 + 0.486P$, where $P = (F_o^2 + F_c^2)/3]$, GooF = 1.025. Atomic coordinates and selected bond distances are listed in Tables 4 and 5.

Preparation of *diexo*-3-Aminobicyclo[2.2.1]heptane-2-carbohydrazide (4c).

A mixture of ethyl *diexo*-3-aminobicyclo[2.2.1]heptane-2-carboxylate [30] (11.54 g, 0.063 mmole) and hydrazine monohydrate (99%, 11.62 g, 0.232 mole) in ethanol (10 ml) was refluxed for 4 hours. After evaporation, the residue was crystallized from ethanol, colorless crystals, yield 9.16 g (86%), mp 160-161°.

Preparation of 5-*p*-Tolyl-8*H*-1,2,3,4,4a,13b-hexahydrophthalazino[1,2-*b*]quinazolin-8-one (3a) and 1,4-Methano *diendo* Derivative 3b.

A mixture of anthranilic hydrazide (1.51 g, 0.01 mole) and *cis*-2-(*p*-methylbenzoyl)-1-cyclohexanecarboxylic acid 2a (2.46 g, 0.01 mole) [31] or *diendo*-3-(*p*-methylbenzoyl)bicyclo[2.2.1]-heptane-2-carboxylic acid 2b (2.58 g, 0.01 mole) [32] in toluene (30 ml) was refluxed for 8 hours, a Dean-Stark water separator being applied. After removal of the solvent by distillation, the residue was transferred onto a silica gel column (Acros 0.035-0.07 mm) and eluted with benzene. On evaporation, the residue crystallized. Physical and analytical data on 3a,b are listed in Table 3.

Table 4*

Atomic Coordinates (x$10^4$) and Equivalent Isotropic Displacement Parameters (Å x $10^3$) for 7a and 7b

| | x | | y | | z | | U(eq) | |
|---|---|---|---|---|---|---|---|---|
| | 7a | 7b | 7a | 7b | 7a | 7b | 7a | 7b |
| C(1) | 3434(13) | 7004(5) | 1368(6) | -3315(3) | 1842(16) | -2737(5) | 101(5) | 64(1) |
| C(2) | 3518(15) | 7914(5) | 1781(6) | -3407(3) | 2998(17) | -934(6) | 111(5) | 74(1) |
| C(3) | 2073(14) | 8574(5) | 2187(6) | -2442(4) | 2825(15) | -117(6) | 102(4) | 74(1) |
| C(4) | 736(14) | 7252(5) | 1735(5) | -1340(3) | 2457(17) | -511(5) | 115(6) | 63(1) |
| C(4A) | 585(13) | 6373(4) | 1344(5) | -1238(3) | 1195(14) | -2337(4) | 86(4) | 49(1) |
| C(5) | -766(14) | 5029(4) | 891(6) | -167(3) | 787(14) | -2683(4) | 82(4) | 49(1) |
| N(6) | -723(11) | 3541(3) | 299(5) | -51(2) | 1151(10) | -2934(4) | 76(3) | 52(1) |
| N(7) | 682(11) | 3159(3) | 47(4) | -992(2) | 1991(10) | -2862(4) | 76(3) | 50(1) |
| C(8) | 633(14) | 1554(4) | -588(5) | -782(3) | 2432(13) | -2992(5) | 76(4) | 51(1) |
| C(8A) | 2127(14) | 1116(4) | -834(5) | -1828(3) | 3327(13) | -3157(5) | 76(4) | 54(1) |
| C(9) | 1912(15) | 538(5) | -1393(5) | -2257(3) | 4190(14) | -4932(5) | 96(4) | 61(1) |
| C(10) | 1304(17) | 177(5) | -1137(7) | -3350(3) | 5262(16) | -5129(6) | 110(5) | 71(1) |
| C(11) | 2305(17) | 1651(5) | -598(7) | -4206(3) | 6109(16) | -4048(6) | 112(5) | 69(1) |
| C(12) | 2483(17) | 2182(5) | -45(6) | -3778(3) | 5229(15) | -2300(5) | 109(5) | 65(1) |
| C(12A) | 3108(14) | 2564(4) | -289(5) | -2685(3) | 4144(14) | -2072(5) | 84(4) | 55(1) |
| N(13) | 3218(12) | 4016(3) | 240(4) | -2905(2) | 3275(12) | -2447(4) | 78(3) | 51(1) |
| C(13A) | 2082(16) | 4240(4) | 405(5) | -2084(3) | 2310(16) | -2789(4) | 77(4) | 48(1) |
| 0(15) | 2053(11) | 645(3) | 933(5) | 135(2) | 1394(13) | -2966(4) | 69(3) | 65(1) |
| C(13B) | -535(10) | 5692(4) | -909(4) | -2209(3) | 1994(10) | -3179(5) | 113(3) | 50(1) |
| C(1') | -2292(16) | 5394(4) | 1137(5) | 881(3) | -6(15) | -2638(4) | 89(5) | 49(1) |
| C(2') | -2571(15) | 4266(4) | 1760(6) | 1907(3) | -521(16) | -2587(5) | 97(5) | 55(1) |
| C(3') | -3972(15) | 4600(4) | 1980(6) | 2878(3) | -1327(14) | -2504(5) | 92(4) | 56(1) |
| C(4') | -5232(16) | 6106(4) | 1567(6) | 2856(3) | -1744(16) | -2436(4) | 95(5) | 52(1) |
| C(5') | -4959(17) | 7240(4) | 930(6) | 1843(3) | -1207(15) | -2466(5) | 96(5) | 55(1) |
| C(6') | -3610(14) | 6892(4) | 717(6) | 870(3) | -431(13) | -2559(5) | 84(4) | 55(1) |
| C(7') | -6802(16) | 6472(5) | 1768(6) | 3917(3) | -2746(18) | -2385(6) | 129(6) | 70(1) |

* U(eq) is defined as one-third of the trace of the orthogonalized Uij tensor.

Table 5

Selected Bond Lengths (Å) for 7a and 7b

| | 7a | 7b |
|---|---|---|
| C(4A)-C(5) | 1.51(2) | 1.498(5) |
| C(4A)-C(13B) | 1.564(13) | 1.531(4) |
| C(5)-N(6) | 1.275(12) | 1.288(4) |
| C(5)-C(1') | 1.48(2) | 1.502(4) |
| N(6)-N(7) | 1.418(12) | 1.407(4) |
| N(7)-C(8) | 1.395(13) | 1.404(4) |
| N(7)-C(13A) | 1.437(14) | 1.418(4) |
| C(8)-O(15) | 1.223(12) | 1.198(4) |
| C(8)-C(8A) | 1.49(2) | 1.511(4) |
| C(8A)-C(12A) | 1.52(2) | 1.528(5) |
| C(12A)-N(13) | 1.459(13) | 1.469(5) |
| N(13)-C(13A) | 1.25(2) | 1.271(4) |
| C(13A)-C(13B) | 1.46(2) | 1.505(5) |

Preparation of 9,10,10a-Octahydropyridazo[6,1-*b*]quinazolin-6-one (**6**), 5-*p*-Tolyl-9,12-methano-8*H*-1,2,3,4,4a,8a,9,10,11,-12,13,13a-dodecahydrophthalazino[1,2-*b*]quinazolin-8-one (**8**) and -5,8-dione (**9**).

General Procedure.

A mixture of *trans*-2-amino-1-cyclohexanecarbohydrazide **4b** (1.57 g, 0.01 mole) and 3-(*p*-chlorobenzoyl)propionic acid **5** (2.12 g, 0.01 mole) or *diexo*-3-aminobicyclo[2.2.1]heptane-2-carbohydrazide **4c** (1.69 g, 0.01 mole) and **2a** [31,32] (2.46 g, 0.01 mole) in toluene (30 ml) was refluxed for 10 hours, a Dean-Stark water separator being applied. After evaporation, the residue was transferred onto a silica gel column (Acros 0.035-0.07 mm) and eluted with ethyl acetate (**6**) or an ethyl acetate-*n*-hexane 2:1 mixture (**8** and **9**). From the mixture of **8** and **9**, **8** was eluted first (higher $R_f$), then **9** (lower $R_f$). Data on **6**, **8** and **9** are listed in Table 3.

Preparation of 5-*p*-Tolyl-8*H*-1,2,3,4,4a,8a,9,10,11,12,12a,13a-dodecahydrophthalazino[1,2-*b*]quinazolin-8-ones **7a-c**.

*cis*- or *trans*-2-Amino-1-cyclohexanecarbohydrazide **4a** or **4b** (1.57 g, 0.01 mole) and cis-2-(*p*-methylbenzoyl)-1-cyclohexanecarboxylic acid **2a** (2.46 g, 0.01 mole) were reacted in benzene (**4a**) or toluene (**4b**) for 16 hours. After evaporation of the mixture, the residue containing **7a-c** or **7c** was transferred onto a silica gel column (Acros 0.035-0.07 mm) and eluted with an ethyl acetate-*n*-hexane 1:1 mixture. The first eluates contained **7c** [highest $R_f$; monitoring by tlc, Alufolien Kieselgel 60 $F_{254}$ Merck, 0.2 mm, solvent: benzene-ethanol-petroleum ether (bp 40-60°) 4:1:3, development in iodine vapor]. The following eluates, which contained **7b** (medium $R_f$) and **7a** (lowest $R_f$) together, were combined and the solvent was evaporated. The residue was transferred onto a silica gel column and eluted with an ethyl acetate-*n*-hexane 2:1 mixture. The first fractions, which contained **7b**, were combined and the solvent was evaporated off. The last fractions yielded **7a**. In the reaction of **4b** and **2a**, the residue was eluted from a silica gel column with benzene. After evaporation, the residue was crystallized.

Acknowledgements.

We are indebted to Mrs. E. Csiszár-Makra for valuable technical assistance and for computer formulation of the manuscript. Thanks are also due to Chinoin Pharmaceuticals for their support of the X-ray crystallographic data collection.

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# II

*Acta Chemica Scandinavica, 1998: 52: 322–327*
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ACTA
CHEMICA SCANDINAVICA
*ISSN 0904–213X*

# Synthesis and Structure of Methanobenzocyclooctene Derivatives†

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Miklós, F., Csende, F., Stájer, G., Sohár, P., Sillanpää, R., Bernáth, G. and Szúnyog, J., 1998. Synthesis and Structure of Methanobenzocyclooctene Derivatives. – Acta Chem. Scand. 52: 322–327. © Acta Chemica Scandinavica 1998.

10-Oxo-5,9-methanobenzocyclooctene-8-carboxylic acid **4a** was prepared by the intramolecular cyclization of 4*t*-phenylcyclohexane-1*r*,2*c*-dicarboxylic acid **1a** in concentrated $H_2SO_4$ or in the reaction of 4*t*-phenylcyclohexane-1*r*,2*c*-dicarboxylic anhydride **2** in 80% $H_2SO_4$. To improve the yield, the esters **3a,b** were cyclized to the methanocyclooctene isomers **5a,b**, in a 1:5 ratio from **3a**, and in a 5:4 mixture (54%) from **3b** at elevated temperature. After separation, **5a** was hydrolysed, the keto group of **4a** was reduced by the Wolff–Kishner method and the resulting *cis* and *trans* methylene-bridged benzocyclooctenes **6a,b** (1:2) were separated. From **4a** with hydrazine, the tetracyclic pyridazinone derivative **7** was obtained. The structures were determined by $^1H$ and $^{13}C$ NMR methods and for **4a** also by X-ray crystallography.

In our earlier studies on fused-skeleton saturated and partially saturated 1,3-heterocycles, we studied the reactions of cyclic β-oxo carboxylic acids with alicyclic 1,3-amino alcohols in which one of the functional groups was attached directly, and the other through a methylene group to carbocycles such as cyclohexane, cyclohexene, norbornane or norbornene.[1–4] In these cyclizations, tetracyclic and pentacyclic hetero compounds were formed, and isomerization of the starting stereohomogeneous *cis* and *trans* amino alcohols also often occurred. Consequently, structure elucidation of the fairly complex tetracyclic or pentacyclic systems, and determination of the configuration and conformation, was always a challenging task; a comparative study of closely related ring systems and the *cis*- and *trans*-fused isomers added to the importance. The new compounds were synthesized with pharmacological aims.

For the synthesis of fused-skeleton isoindolones, *cis*- or *trans*-2-aroyl-1-cyclohexanecarboxylic acids were used as starting materials in our earlier studies. In the present paper, *cis*-4-cyclohexene-1,2-dicarboxylic anhydride was applied; through the addition of benzene to the double bond,[5] this furnished 4*t*-phenylcyclohexane-1*r*,2*c*-dicarboxylic acid **1a** with a phenyl equatorial[3] to the neighbouring carboxy group. The 4-phenyl substituent on cyclohexane-1,2-dicarboxylic acid was thought might provide a good opportunity to construct highly condensed systems by intramolecular acylation of the phenyl substituent with the 2-carboxy group. These systems containing two functional groups are suitable for the preparation of heterocycles and they provide good starting molecules for the production of new pharmacologically active derivatives as target compounds.

## Results

When heated in concentrated $H_2SO_4$, *trans*-4-phenylcyclohexane-*cis*-1,2-dicarboxylic acid (**1a**) or in 80% $H_2SO_4$, the anhydride **2** yielded 10-oxo-5,6,7,8,9,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (**4a**; yield 13% and 15%, respectively) by intramolecular cyclization.

Similar cyclization via $AlCl_3$-catalysed intramolecular Friedel–Crafts acylation provides only a moderate yield (14–21%),[6] in spite of the absence of strain in the bicyclononanone ring system.[7] Other preparations,[8,9] e.g., from benzylcyclohexanone with MeLi,[10] from unsaturated enol silyl esters with ceric ammonium nitrates,[11,12] from alkenes by $MeSO_3H$ cyclization[13] and by carbo-

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† Saturated Heterocycles, Part 255. Part 254: Bernáth, G., Miklós, F., Stájer, G., Sohár, P., Böcskei, Zs. and Menyhárd, D. *J. Heterocycl. Chem. In press.*

cationic cyclization of unsaturated bromo imines[14] are also known.

To improve the yield of **4a**, we started from dimethyl 4-*trans*-phenylcyclohexane-*cis*-1,2-dicarboxylate (**3a**); cyclization with PPA at elevated temperature yielded a mixture of the isomeric esters **5a** and **5b** in a ratio of 1:5. In contrast, cyclization of dimethyl 4*t*-phenylcyclohexane-1*r*,2*t*-dicarboxylate (**3b**) gave the esters **5a** and **5b** in a 5:4 ratio (the yield of **5a,b** was 54%). Consequently, as a result of the transformation **3b** → **5a,b** with PPA, the 30% yield of **5a** (Table 3) isolated from the mixture **5a,b** by column chromatography proved to be enough 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 **3a** and **3b** partly isomerize to form the products **5a,b**. After separation of the isomers, the structures were established by NMR spectroscopy. The esters **5a,b** were hydrolysed and the acids **4a,b** were characterized by NMR and for **4a** also by X-ray analysis (Fig. 1). 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 acids (**6a,b**). With hydrazine, the oxo

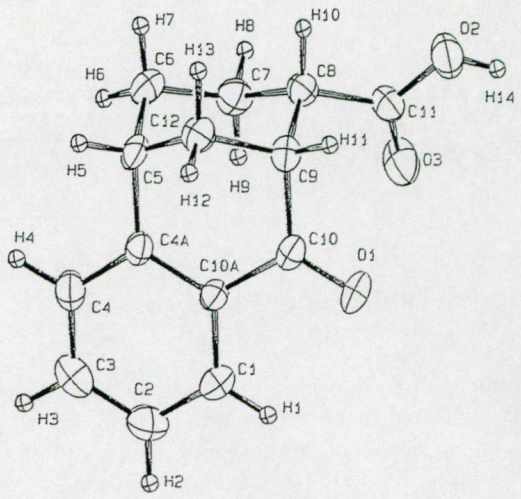



*Fig. 1.* X-Ray structure of compound **4a**.

*Table 1.* IR carbonyl frequencies in KBr[a] and $^1$H NMR data[b] on compounds **4–7** in $CDCl_3$ solution[c] at 250 MHz.[d]

| Compound | $\nu_{C=O}$ Posn. 8 | $\nu_{C=O}$ Posn. 10 | H-1 dd (1 H) | H-4 dd (1 H) | H-5,9[e] m (2 H) | H-ax Posn. 7 | H-8 m (1 H) | H-eq[f] Posn. 11 |
|---|---|---|---|---|---|---|---|---|
| **4a** | 1713 | 1678 | 8.03 | 7.24 | ≈3.2 | 1.50[g] | 2.79[h] | 2.50[i] |
| **4b** | 1696 | 1681 | 8.04 | 7.24 | 3.25 | 1.48[j] | 2.94[k] | 2.30[l] |
| **5a** | 1728 | 1681 | 8.06 | 7.23 | ≈3.2 | 1.52[g] | 2.73[h] | 2.45[i] |
| **5b** | 1729 | 1679 | 8.05 | 7.25 | 3.18 | 1.40[j] | 2.85[k] | 2.25[l] |
| **6a** | 1712 | — | ≈7.1[m] | 7.00 | 2.98[n] | 1.35[g] | ≈2.7[o] | 2.00[l] |
| **6b** | 1701 | — | ≈7.1[m] | 7.00 | 2.98 | 1.45[j] | 2.68[o] | ≈2.0[p] |
| **7** | 1671 | — | 7.80 | 7.20 | ≈3.1 | 1.35[g] | 2.55[h] | 2.00[l] |

[a] In $cm^{-1}$. [b] Chemical shifts in δ, $\delta_{TMS}=0$ ppm, coupling constants in Hz. [c] **4a** was also measured in DMSO-$d_6$ solution. [d] Assignments were proved by DR (**4a**) and DNOE (**6a,b**) measurements. Further signals, $^1$H NMR: $CH_3$ (s, 3 H): 3.72 (**5a**), 3.77 (**5b**); $CH_2$ (posn. 6, 7eq, 11ax), 4 × m (4 × 1 H) in the interval 1.7–2.2 ppm, partly overlapped. Separated signals: H-6ax: 1.90[j] (**4a**, **5a**), 2.18[j] (**4b**), H-6eq: 1.85[l] (**4a**), 1.65[l] (**4b**), 1.80[l] (**5a**), 1.60[l] (**5b**), 1.55[l] (**6b**), H-7eq: 1.75[l] (**4a**, **5a**), 2.05[l] (**4b**), 1.98[l] (**5b**), H-11ax: 2.05[h] (**4a**, **5a**), 2.22[h] (**4b**), 1.85[h] (**6a**); $CH_2$ (posn. 10): 2.78 d (split by 18.4) and 2.98[n] (**6a**), 2.68[o] and 3.27 dd (split by 18.0 and 7.5) for **6b**; H-2,3, 2 × dt (2 × 1 H): 7.30 and 7.50 (**4a**, **5a,b**), 7.38 and 7.55 (**4b**), coalesced at ≈7.1 (**6a,b**) and 7.3 (**7**); NH, (br s, 1 H): 8.65 (**7**); H-9 (≈s, 1 H): 3.00 (for **4a** in DMSO-$d_6$); IR, $\nu_{OH}$: 3300–2200 (**4a,b**, **6a,b**); $\nu_{NH}$: 3185 (**7**). [e] Overlapping signals, except for **6a,b**, where the H-9 signal at about 2.7 ppm is coalesced with the H-8 m (**6a**) and the upfield m of $CH_2$ (posn. 10) group (**6b**). [f] To ring *C* (*S-cis* to the condensed aromatic ring). [g] Quartet split by ca. 13.5 with further doublet split by ca. 4.5. [h] Doublet (split by 13.2 ± 0.2) with further triplet split by ca. 4 (for H-8) or 2.5 (H-11ax). [i] Quartet (split by ca. 13) with further quartet split by 2.5. [j] Triple triplet split by ca. 13.5 (H-6ax) or 14.5 (H-7ax) and 4. [k] Singlet-like signal with coalesced fine structure. [l] Doublet-like signal with coalesced further fine structure, split by 14 ± 0.5. [m] In overlap with the H-2,3 signal. [n,o] Overlapping signals. [p] In overlap with the H-6ax signal.

*Table 2.* $^{13}$C NMR chemical shifts[a] of compounds **4–7** in $CDCl_3$ solution at 63 MHz.[b]

| Compound | C-1 | C-2 | C-3 | C-4 | C-4a | C-5 | C-6 | C-7 | C-8[c] | C=O | C-10[c] | C-9[c] | C-11 | C-10a[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **4a** | 125.4 | 126.8 | 134.2 | 128.5 | 147.1 | 33.6 | 29.8 | 19.6 | 44.4 | 174.1 | 198.1 | 45.0 | 33.2 | 133.7 |
| **4b** | 126.7[d] | 127.0[d] | 134.4 | 128.2[d] | 147.2 | 34.5 | 27.6 | 19.1 | 41.9 | 179.6 | 200.3 | 43.8 | 29.9 | 133.3 |
| **5a**[e] | 126.9 | 126.5 | 134.1 | 128.0 | 146.8 | 34.3 | 30.3 | 19.7 | 45.3 | 173.4 | 198.5 | 45.4 | 33.8 | 134.0 |
| **5b**[e] | 126.0 | 126.4 | 133.7 | 127.7 | 146.7 | 34.0 | 27.1 | 18.7 | 41.3 | 173.1 | 199.4 | 43.6 | 29.3 | 132.8 |
| **6a** | 128.0[f] | 125.7 | 125.4 | 128.0[f] | 140.5 | 33.6 | 33.2 | 19.2 | 47.8 | 181.2 | 30.7 | 29.5 | 31.7 | 137.0 |
| **6b** | 127.9 | 125.7 | 125.5 | 128.2 | 140.6 | 33.7 | 30.2 | 18.8 | 46.5 | 181.3 | 35.3 | 28.8 | 27.8 | 136.8 |
| **7** | 123.5 | 127.4[d] | 129.5 | 127.9[d] | 143.4 | 32.2 | 28.9[f] | 18.3 | 35.0 | 174.9 | 157.6 | 39.0 | 28.9[f] | 133.3 |

[a] $\delta_{TMS}=0$ ppm. [b] Assignments were confirmed by 2D-HSC (except for **4b** and **7**) and DEPT measurements. [c] For easier comparison of spectroscopically analogous data, the numbering of **4** and **5** is used also for **6** and **7** here and in the text. The IUPAC numbering is given in the Experimental part. [d] Interchangeable assignments. [e] $OCH_3$: 51.8 (**5a**), 51.5 (**5b**). [f] Two overlapping lines.

carboxylic acid **4a** was cyclized to the tetracyclic methanobenzocycloocta[9,8-*c*,*d*]pyridazinone **7**.

*Structure.* The characteristic IR, $^1$H and $^{13}$C NMR data are listed in Tables 1 and 2. For the isomeric pairs **4a,b** and **5a,b**, establishment of the stereo structure is complicated by the flexibility of ring *C* resulting in two relatively stable (chair and boat) conformations. Hence, both the C-8 configuration and the conformation have to be determined.

Owing to the strong steric hindrance between the α-axial COOR group and the skeleton (no sign of which appears in the spectra), the presumption of a *cis* H-8,H-9 configuration (5*R**,8*S**,9*R**) allows no boat conformation of ring *C* (Scheme 1, **4a***i*). For a chair conformation and a *cis* configuration (Scheme 1, **4a***ii*), the axial H-8 is in a *trans*-diaxial position with one of the neighbouring H-7 atoms, and the correspondingly large coupling[15] appears in the $^1$H NMR spectra of one each of the acid and ester isomers; for **4a** and **5a**, the H-8 signal is a triplet of doublets split by 13.3, 4.1 and 4.1 Hz. (For a boat conformation of ring *C*, the equatorial H-8 would not display as large coupling as 13.3 Hz.)

As the H-8 multiplet of **4b** and **5b** does not exhibit a large splitting, the chair conformation of ring *C* is also preferred for the *trans* isomers (5*R**,8*R**,9*R** configuration); hence, the COOR group is axial and the equatorial H-8 has no diaxial (i.e., large vicinal) coupling (Scheme 1). Accordingly, for *trans* **4b** and **5b**, the $^{13}$C NMR spectra indicate a sterically more unfavourable structure: the sum of the chemical shifts of the carbons in ring *C* is less[16a] (by 8.8 and 14.8 ppm) than that for the isomers **4a** and **5a**. If the simultaneous alteration of the C-8 configuration and *C*-ring conformation for the *trans* isomers is assumed, no essential difference in steric hindrance would be observable in comparison with the *cis* compounds, because the COOR group is equatorial in both isomers.

Further proof of the tentative structures is the field effect[16b] (i.e., the upfield shift of the $^{13}$C lines[17]), which indicates sterically unfavourable structures and which is higher for the C-6 and C-11 (and of course C-8) lines than for the other three carbons (C-5,7,9), because the first two carbons are positioned 1,3-diaxially to the 8-COOR group. For the *cis–trans* pairs of acids and esters, the sum of the shift differences for the C-6,8,11 lines amounts to 8.0 and 11.7 ppm, while the corresponding values for C-5,7,9 are only 0.8 and 3.1 ppm.

For **4a**, the X-ray determination (Fig. 1) revealed that the compound forms hydrogen-bonded monomers in the solid state. In the H-bond [O(2) ··· H(14) ··· O($3_I$), $I = -x, 2-y, -z$], the O ··· O distance is 2.661(2) Å and the OH ··· O angle is linear 177(2)°. These are typical values for carboxylic acid dimers.

The spectral data on the reduced products **6a,b** confirm the above structures. For C-7 and C-11, the chemical shifts hardly differ from those measured for **4a,b** and **5a,b**. In the event of a boat conformation, the hindrance between the axial H-7 and H-11 would cause a strong steric effect, i.e., significant upfield shifts of the C-7 and C-11 lines. On the basis of the summed carbon shifts for ring *C* (the difference is 9.2 ppm), the assignments of the *cis* (5*R**,8*S**,9*S**) and *trans* (5*R**,8*R**,9*S**) H-8,H-9 configurations to the two isomers are unambiguous.

As stated above, for the isomeric pairs **4a,b** and **5a,b**, the 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 **6a,b**, only the shift difference for C-6 and C-11 is significant; that for C-8 is significantly smaller ($\Delta\delta$C-8 = 1.3 ppm). The explanation lies in the 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.

For steric reasons, the *cis* H-8,H-9 (5*R**,8*S**,9*R**) configuration is retained in the tetracyclic **7**, while for the starting **4a**, a change in the configuration on ring closure is not expected. The splittings of H-8 (13, 4 and 4 Hz) suggest the chair form of ring *C*, i.e., the conformation remains; the ≈13 Hz split confirms diaxial coupling (Scheme 1), and such an interaction is impossible in the boat form (H-8 would not be equatorial).

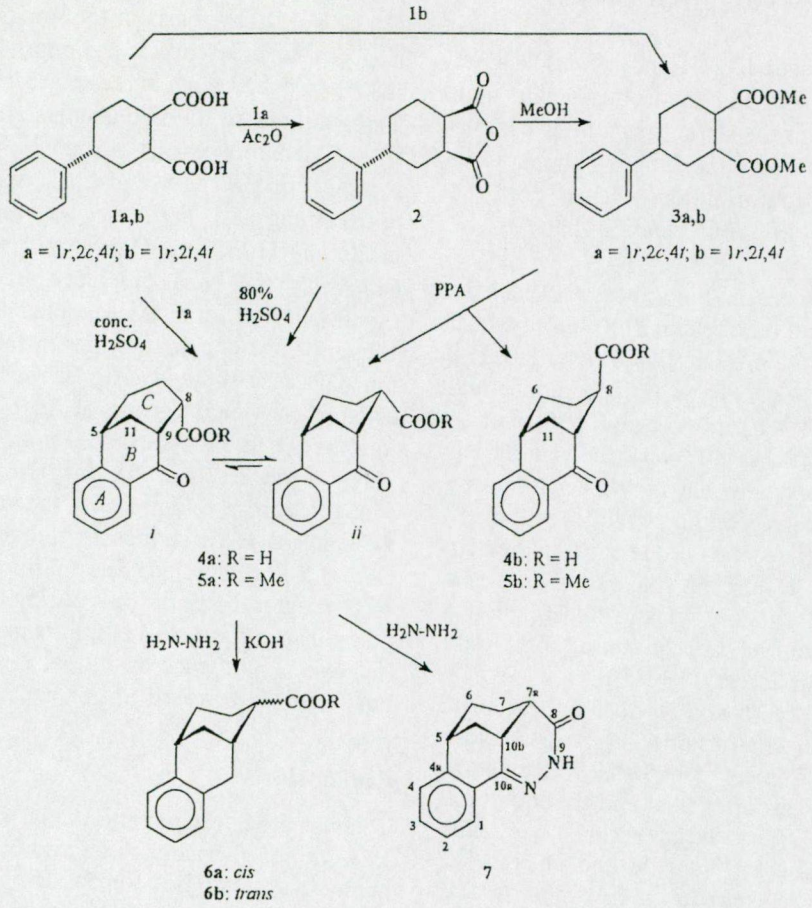
## Conclusions

To summarize, the intramolecular cyclization of **3a** with PPA yielded the isomers **5a** and **5b**, which differ in the configuration of C-8; for **5a**, H-5, H-8 and H-9 lie on the same side of ring *C*, while in **5b**, 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 **4a**, the isomers **6a** (all-*cis*) and **6b** (5*r*H,8*t*H,9*c*H) are formed in a 1:2 ratio; the epimerization probably takes place via enolization of the 8-CO (carboxy) group.

**5a** can be prepared from the *trans* ester **3b** more advantageously than from the *cis* ester **3a**, and its 30% yield allows its use as a starting molecule for the synthesis of highly condensed systems. Hence, intermolecular acylation with PPA at an elevated temperature is an appropriate method of obtaining the methanobenzocyclooctene system.

## Experimental

IR spectra were run for samples in KBr discs on a vacuum optic Bruker IFS-113v FT spectrometer equipped with an Aspect 2000 computer. $^1$H and $^{13}$C NMR spectra were recorded for $CDCl_3$ solutions in 5 mm tubes at room temperature, on a Bruker WM-250 FT-spectrometer controlled by an Aspect 2000 computer at 250 ($^1$H) and 63 ($^{13}$C) MHz, respectively, using the deuterium signal of the solvent as the lock and $Me_4Si$ as an internal standard. For DNOE measurements,[16c,18] the standard Bruker microprogram DNOEMULT.AU to generate NOE was used. 2D-HSC spectra[19] were obtained by using the standard Bruker pulse program




*Scheme 1.*

XHCORRD.AU. DEPT spectra[20] were run in a standard way,[21] using only the $\theta = 135°$ pulse to separate the $CH/CH_3$ and $CH_2$ lines phased up and down, respectively.

*Crystal data for* **4a**. Triclinic, space group $P\bar{1}$ (No. 2), $a = 8.526(2)$, $b = 10.784(2)$, $c = 7.368(2)$ Å, $\alpha = 93.97(2)$, $\beta = 112.68(2)$, $\gamma = 67.53(1)$, $V = 575.2(3)$ Å$^3$, $Z = 2$, $D_c = 1.329$ g cm$^3$, $\mu$(Mo K$\alpha$) = 0.87 cm$^{-1}$, $F(000) = 244$, $T = 294(1)$ K, colourless prisms, crystal dimensions $0.26 \times 0.34 \times 0.40$ mm.

*Data collection and refinement.* A Rigaku AFC5S diffractometer was used with graphite monochromated Mo K$\alpha$ radiation ($\lambda = 0.710\,69$) in the $\omega$–$2\theta$ scan mode with a $\omega$ scan rate of 8.0° min$^{-1}$ and a scan width of $1.63 + 0.30 \tan\theta$. The weak reflections [$F < 10\sigma(F)$] were rescanned up to two times. The data obtained were corrected for Lorentz and polarization effects. A total of 2165 unique reflections were measured ($2\theta_{max} = 50°$ and $R_{int} = 0.011$). The structure was solved by direct methods[22] and difference Fourier syntheses.[23] Structural parameters were refined by a full-matrix least-squares refinement, non-hydrogen atoms with anisotropic, and non-aromatic hydrogen atoms with fixed isotropic temperature parameters (1.2 times $B_{eq}$ of carrying atom). The aromatic hydrogens were kept in the calculated positions. In the final cycles, the 1531 data with $I > 2\sigma(I)$ yielded an $R$ value of 0.043 ($R_w = 0.037$, sigma weights) for 184 parameters. The residual electron density was from 0.15 to 0.17 e Å$^3$.

All calculations were performed with TEXSAN-89 software,[24] using a VAXSTATION 3520 computer. The neutral atomic scattering and dispersion factors were those included in the program. Figures were drawn with ORTEP.[25] The final atomic positional coordinates, bond lengths and angles have been deposited with the Cambridge Crystallographic Data Centre, Lensfield Rd., Cambridge, CB2 1EW, UK.

HPLC: ISCO system with two pumps, suitable for gradient elution. The Chem. Research control system and data processing program were used. For the semi-preparative separation, a 5 µm BST Si-100-S 10-RP-18 column (250 × 16 mm) was used; eluent: *n*-hexane–isopropyl alcohol (98 : 2 v/v%); flow rate: 8 ml min$^{-1}$; injected sample: 250 µl; 0.5 g dichloromethane–eluent (1 : 3) detection at 220 nm.

*10-Oxo-5r,6,7,8c,9c,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid* (**4a**): *method A.* 4*t*-Phenylcyclohexane-1*r*,2*c*-dicarboxylic acid[5] (**1a**) (5.0 g, 0.02 mol) in concentrated $H_2SO_4$ (20 ml) was heated to 150 °C and kept at this temperature for 1 h. After being cooled, the mixture was poured onto ice and extracted

with $CH_2Cl_2$ (3 × 20 ml). The extract was washed with water and dried ($Na_2SO_4$). On evaporation, the residue crystallized from EtOAc, m.p. 210–215 °C, yield 0.60 g (13%). Analytical data: found C 73.2; H 6.1. Calc. for $C_{14}H_{14}O_3$: C 73.0; H 6.1%.

*Method B.* To $H_2SO_4$ (80%, 30 ml), 4*t*-phenylcyclohexane-1*r*,2*c*-dicarboxylic anhydride (**2**) (5.0 g, 0.02 mol) was added in portions, with stirring. The mixture was kept at 80 °C for 16 h and, after being cooled, poured onto ice and then extracted with $CHCl_3$ (3 × 300 ml). The extract was washed with water (2 × 50 ml), dried ($Na_2SO_4$) and evaporated to dryness. The product (**4a**) was purified on a silica gel column (Acros 0.035–0.07 mm) eluting with *n*-hexane–EtOAc (2:1). On evaporation, the residue crystallized from EtOAc, yield 0.70 g (15%).

*Dimethyl 4t-phenylcyclohexane-1r,2c-dicarboxylate* (**3a**) *and 4t-phenyl-1r,2t-dicarboxylate* (**3b**). A mixture of anhydride **2**[26] (4.6 g, 0.02 mol) or dimethyl 4*t*-phenylcyclohexane-1*r*,2*t*-dicarboxylate **1b** (5.0 g, 0.02 mol) and benzene (25 ml) in MeOH (45 ml) was refluxed with concentrated $H_2SO_4$ (0.23 ml) for 4 h, a Dean–Stark water separator being applied. After evaporation of the solvent, the residue was neutralized with $Na_2CO_3$ solution (5%) and extracted with $Et_2O$ (3 × 25 ml). The $Et_2O$ extract was washed with water (2 × 20 ml), dried ($Na_2SO_4$) and evaporated to dryness. The residue was loaded onto a silica gel column (Acros 0.035–0.07 mm) and eluted with *n*-hexane–EtOH (5:1). On evaporation, the yield was 4.30 g (78%) **3a**, $n_D^{23}$: 1.5176, or 4.73 g (86%) **3b**, $n_D^{23}$: 1.5162. The products were used for the further preparations without purification.

*Cyclization of dimethyl 4t-phenylcyclohexane-1r,2c-dicarboxylate* (**3a**) *to the isomeric methyl esters* (**5a** and **5b**). To PPA (28.0 g), **3a**[3] (2.76 g, 0.01 mol) was added dropwise at 110 °C with stirring. The mixture was heated at this temperature for 3 h, then cooled and poured onto crushed ice. The mixture was extracted with $Et_2O$ (3 × 150 ml), and the combined extract was washed with water (2 × 200 ml), dried ($Na_2SO_4$) and evaporated to dryness. The residue was transferred onto a silica gel column (Acros 0.035–0.07 mm) and eluted initially with an *n*-hexane–EtOAc mixture (5:1). First **5b** was eluted [higher $R_f$, monitoring by TLC, Alufolien Kieselgel 60 $F_{254}$ Merck, 0.2 mm, solvent: benzene–EtOH–petroleum ether (b.p. 40–60 °C) 4:1:3, development in iodine vapour] and **5a** (lower $R_f$) was then eluted with an *n*-hexane–EtOAc mixture 4:1 mixture. On evaporation of the solvents and crystallization, from EtOAc–$Et_2O$, m.p. 122–123 °C, yield 0.77 g (31.5%) (**5b**) and from EtOAc, m.p. 105–107 °C, yield 0.15 g (6%) (**5a**) were obtained. Analytical data: found C 73.6; H 6.55 (**5b**) and C 73.85; H 6.8 (**5a**). Calc. for $C_{15}H_{16}O_3$: C 73.75; H 6.6%.

*Cyclization of dimethyl 4t-phenylcyclohexane-1r,2t-dicarboxylate* (**3b**) *to the isomeric 5,6,7,8,9,10-hexahydro-5,9-methanocyclooctene derivatives* (**5a,b**). The reaction was performed with **3b** (2.76 g, 0.01 mol) according to the cyclization of **3a** to **5a,b** in PPA, but at 120 °C. After chromatographic purification (silica gel column, Acros 0.035–0.07 mm; *n*-hexane–EtOAc 5:1), yields of 0.59 g (24%) for **5b** and 0.73 g (30%) for **5a** were obtained.

*10-Oxo-5r,6,7,8t,9c,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid* (**4b**). **5b** (2.44 g, 0.01 mol) in NaOH solution (10%, 20 ml) was stirred for 3 h at 50 °C. After being cooled, the solution was acidified with concentrated HCl to pH 3, then extracted with $CHCl_3$ (3 × 30 ml); the extract was washed with water (2 × 50 ml) and dried ($Na_2SO_4$). On evaporation, the residue was crystallized from $Et_2O$–*n*-hexane, m.p. 135–137 °C, yield 2.02 g (88%). Analytical data: found C 72.9; H 5.9. Calc. for $C_{14}H_{14}O_3$: C 73.0; H 6.1%.

*5r,6,7,8c,9c,10-* (**6a**) *and 5r,6,7,8t,9c,10-hexahydro-5,9-methanobenzocyclooctene-8t-carboxylic acid* (**6b**). The oxo acid **4a** (2.30 g, 0.01 mol) and hydrazine hydrate (98%, 1.53 g, 0.03 mol) were added to a solution of KOH (1.68 g, 0.03 mol) in diethylene glycol (15 ml) at such a rate as to keep the temperature below 100 °C. The mixture was then heated for 1 h at 110 °C. The temperature was then raised slowly to 200 °C and maintained there for 4 h, during which time some hydrazine–water mixture distilled off. After being cooled, the mixture was added to water and the pH was adjusted to 2. Following extraction with $CHCl_3$ (3 × 50 ml), the extract was washed with water (2 × 50 ml) and dried ($Na_2SO_4$), and the $CHCl_3$ was evaporated off. Crystallization from *n*-hexane yielded a mixture of isomers **6a** and **6b** (1:2). Separation of a 60 mg sample by HPLC and crystallization from $CH_2Cl_2$–*n*-hexane, yielded **6a**: m.p. 110–112 °C, yield 34 mg (56%) and, from *n*-hexane **6b**: m.p. 145–148 °C, yield 20 mg (33%). Analytical data: found C 77.6; H 7.4 (**6a**) and C 77.6; H 7.4 (**6b**). Calc. for $C_{14}H_{16}O_2$: C 77.75; H 7.5%.

*5r,6,7,7ac,10a,10bc-Hexahydro-5,10b-methanobenzocycloocta[9,8-cd]pyridazin-8-one* (**7**). A mixture of **4a** (0.46 g, 2 mmol) and hydrazine hydrate (98%, 0.1 g, 2 mmol) in EtOH (20 ml) was refluxed for 2 h and then evaporated. The residue was dissolved in 1,2-dichlorobenzene (10 ml) and refluxed for an additional 2 h. The crystals that separated out on cooling were filtered off by suction and recrystallized from EtOH, m.p. 238–239 °C, yield 0.29 g (65%). Analytical data: found C 74.15; H 6.15; N 12.95. Calc. for $C_{14}H_{14}N_2O$: C 74.3; H 6.2; N 13.2%.

*Acknowledgements.* The authors are indebted to Mrs. E. Csiszár-Makra and Mr. A. Fürjes for skilled technical assistance. Grants: OTKA 2693 and ETT T-121.

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Received April 7, 1997.

# III

# TRANSFORMATION OF OXOMETHANOBENZOCYCLOOCTENECARBOXYLIC ACIDS TO PYRROLIDINONE-FUSED PENTA-, HEXA- AND HEPTACYCLIC HETERO COMPOUNDS[1]

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**Abstract** – 10-Oxo-5*r*,6,7,8*c*,9*c*,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (**1a**) or a C-8 epimeric mixture (**1a** and **1b**) reacted with 1,2-, 1,3- and 1,4-bifunctional reagents, 1,2- or 1,3-diaminopropane (**2**, **3**), 1,2- or 1,3-propanolamine (**4**, **5**), 1,4-diaminobutane (**6**), *o*-aminothiophenol (**7**), *diexo*-3-aminobicyclo[2.2.1]heptane-2-methanol or *diendo*-3-aminobicyclo[2.2.1]hept-5-ene-2-methanol (**8**, **9**), to produce polycyclic compounds containing a pyrrolo-condensed pyrimidine (**10**), imidazole (**11**), 1,3-oxazine (**12**, **16**, **17**), oxazole (**13**), 1,3-diazepine (**14**), benzthiazole (**15**) moiety and one or two terminal aromatic rings by cyclization. The structures of **10-17** were established by $^{1}H$ and $^{13}C$ NMR spectroscopy and for **16** also by X-Ray analysis.

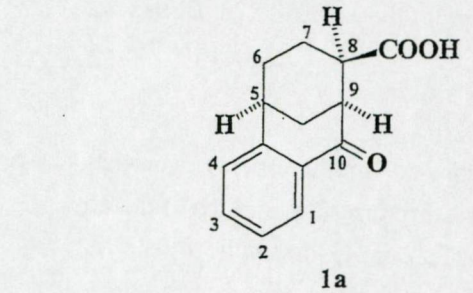
In our earlier studies, β- or γ-oxocarboxylic acids were used for the preparation of fused-skeleton saturated or partially saturated 1,3-heterocycles.[2-4] These derivatives were prepared with pharmacological aims, as the similar fused-skeleton methanocyclooctenes containing a benzene ring have promising analgetic,[5] neurotropic, psychotropic[6] or antispasmodic[7] effects. During cyclization with alicyclic bifunctional reagents, the stereohomogeneous starting compounds often isomerized and the reactions yielded isomeric mixtures. Consequently, structure elucidation of the fairly complex polycyclic systems, determination of the configuration and conformation and a comparative study of the closely related systems and the *cis*- and *trans*-fused isomers was a challenging task.

In our recent study, 10-oxo-5,7,8,9,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (**1a**) was used as starting material of methanobenzocycloocta[9,8-*c*,*d*]pyridazinone.[4] For the preparation of **1a**,**b**, 4-*trans*-phenylcyclohexane-*cis*-1,2-dicarboxylate was cyclized with PPA, to give a mixture of the isomeric esters of **1a**,**b**. After hydrolysis, the isomeric acids were separated

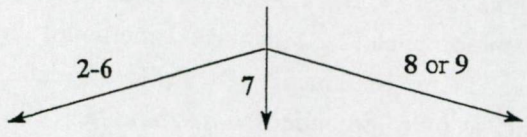
by column chromatography.[4] In the present work, these acids were transformed to new poly-condensed ring systems.

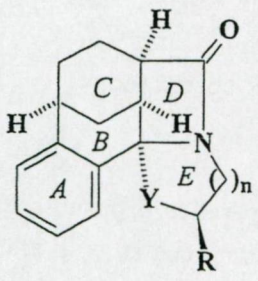
## RESULTS

When the 10-oxo-5*r*,6,7,8*c*,9*c*,10-hexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid (**1a**)[4] was refluxed with 1,3- or 1,2-diaminopropane (**3**, **2**) in dry chlorobenzene in the presence of *p*-toluenesulfonic acid as catalyst for 6 h, benzo-9,13-diazatetracyclopentadecanone (**10**) (76%) or benzo-9,12-diazatetracyclotetradecanone (**11**) (42%) was formed (Scheme). On application of a 1:1 mixture of the isomeric acids (**1a**) and (**1b**),[4] the reaction with **3** gave the same product (**10**), in lower yield (56%), even under rigorous conditions (refluxing for 8 h). This proved a slow isomerization of **1b** to **1a** during the reaction. Cyclization requires an *equatorial* carboxyl group, and therefore **1b**, containing an *axial* carboxyl, isomerizes to **1a**.

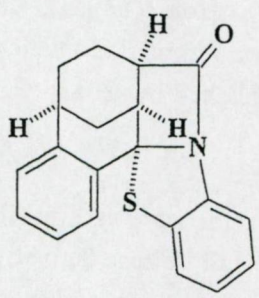



**1a** **1b**

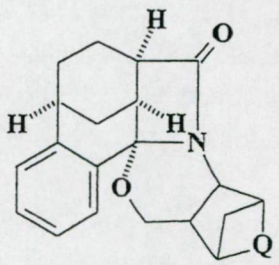



| | n | Y | R |
|---|---|---|---|
| **10**: | 2 | NH | H |
| **11**: | 1 | NH | Me |
| **12**: | 2 | O | H |
| **13**: | 1 | O | Me |
| **14**: | 3 | NH | H |



**15**



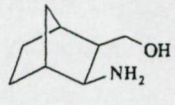

**16**: *diexo*, Q = $CH_2CH_2$

**17**: *diendo*, Q = CH=CH

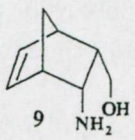
2 (X = $NH_2$) and **4** (X = OH): $H_2NCH_2CH(CH_3)X$

3 (m =3, X = $NH_2$), **5** (m = 3, X = OH) and **6** (m = 4, X = $NH_2$): $H_2N(CH_2)_mX$

7: $H_2NC_6H_4SH$-*o*




**8**




**9**

Scheme

In further experiments, only **1a** was used. In the reaction with 3-aminopropan-1-ol (**5**), benz-13-oxa-9-azatetracyclopentadecanone (**12**) was obtained, while **1a** and 3-aminopropan-2-ol (**4**) furnished benz-12-oxa-9-azatetracyclotetradecanone (**13**). The reaction of **1a** with 1,4-diaminobutane (**6**) yielded benzo-9,14-diazatetracyclohexadecanone (**14**).

While **10-14** are pentacyclic compounds containing a terminal aromatic ring and a condensed bicyclic hetero moiety at the other terminal, the reaction of **1a** with *o*-aminothiophenol (**7**) furnished dibenzo-12-thia-9-azatetracyclotetradecanone (**15**), which was a hexacyclic ring system with two terminal aromatic rings. *diexo*-2-Aminobicyclo[2.2.1]heptane-3-methanol (**8**) and *diendo*-2-aminobicyclo[2.2.1]hept-5-ene-3-methanol (**9**) reacted with **1a** to give heptacyclic derivatives: *diexo*-benz-2-oxa-10-azahexacyclopolyone (**16**) and the unsaturated *diendo* isomer (**17**).

The presence of the aromatic moiety in the ring system results in rather rigid condensed skeletons which are planar at the benzene terminal(s). These fused systems of 16-22 carbons and two hetero atoms display only limited conformational mobility. A few related rigid hetero compounds are known, e.g. pyrrolo-fused methanocyclooctane, formed from alkenes by acid-catalysed cyclization.[8] Further methods yield analogues with a benzo-fused skeleton by dehydration of cyclohexanecarbinols with phosphorus pentoxide,[9] oxidative cyclization of unsaturated enol silyl ethers,[10,11] conversion of benzylcyclohexanone to benzobicyclononanone[12] or carbocationic cyclization of unsaturated bromoimines.[13] However, these methods are not suitable for the preparation of similar benzocyclononane-condensed heterocycles, especially, containing two hetero rings, because the potential starting compounds have only one oxo and no other functional group.

## STRUCTURE

The IR, $^1$H and $^{13}$C NMR data (Tables 1-3) proved the expected structures of the new compounds; hence, only the stereostructures are discussed here.

The strained tetracyclic *A/B/C/D* rigid skeleton must contain the annelational CH-hydrogens, e.g. H-4,7,9* in **12**, in the all-*cis* position. The *cis* orientation of H-7 and H-9 with respect to the hetero atom Y in ring *E* (Y = N for **10**, Y = O in **12**) was proved by DNOE measurements (Figure 1) showing the interactions between the $NCH_2$ (**10**) or $OCH_2$ (**12**) groups and H-9. The analogous steric structure for **14** (Y = N) is plausible from the identical chemical shifts of H-9 in **10** or **14**.

For **11** (Y = N) and **13** (Y = N), NOE was observed between H-9 and the methine hydrogen in the $CHCH_3$ 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 imidazolidine or oxazoline rings). From the very high difference in the chemical shifts of H-9 in **11**, **13** and especially **15**, the α position of the S in **15** is straightforward.

For **12**, **16** and **17**, 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 **16** and **17**.

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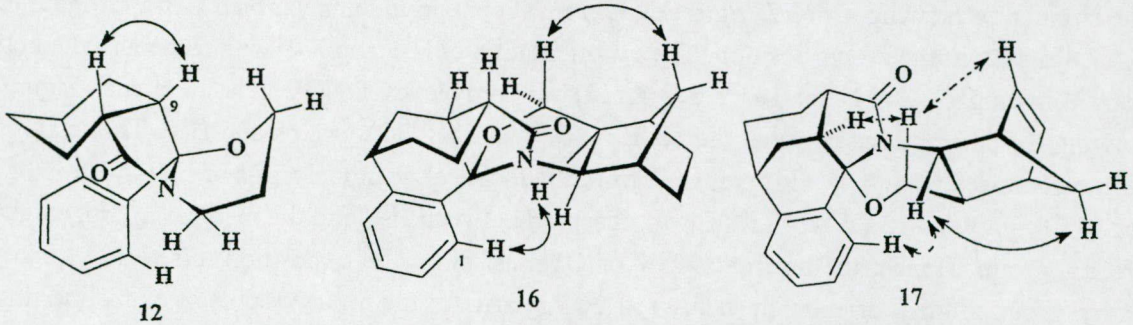
*In the spectroscopic part and Tables 1-3, H-9 means the annelational H on the tertiary carbon at the *B/C/D* ring junction.

Table 1. Characteristic IR frequencies[a] and $^1$H-NMR data[b] on compounds (**10-17**) in $CDCl_3$ solution at 500 MHz[c]

| | νC=O band | $\gamma C_{Ar}H$ band | H-1 ~*d*(1H) | H-2,3 *m*(2H) | H-4 ~*d*(1H) | H-5 ~*s(1H)* | $CH_2$(6) *m*(2H) | $CH_2$(7) 2x*m*(2x1H) | | H-8[d] *td*(1H) | H-9[e] *td*(1H) | $CH_2$(11)[f] *td*+*d*(2x1H) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **10** | 1660 | 759 | 7.66 | ~7.3 | 7.14 | 3.07 | ~1.8[g] | 1.03 | ~1.8[g] | ~2.55[h] | ~2.55[h] | 1.8[g] | 2.20 |
| **11** | 1681 | 764 | 7.32 | ~7.25 | 7.10 | 3.10 | ~1.8[g] | 1.20 | ~1.8[g] | 2.52 | 2.49 | 1.91 | 2.21 |
| **12** | 1705[i] | 773 | 7.68 | ~7.3 | 7.14 | 3.05 | ~1.85[g] | 1.05 | 1.85[g] | 2.58 | 2.72 | 1.85[g] | 2.13 |
| **13** | 1709 | 763 | 7.42 | ~7.3 | 7.14 | 3.12 | ~1.8 | 1.32 | 1.88 | 2.61 | 2.65 | 1.92 | 2.18 |
| **14** | 1662 | 749 | 7.60 | ~7.25 | 7.10 | 3.02 | ~1.8[g] | 1.08 | ~1.8[g] | 2.55[h] | 2.55[h] | ~1.8[g] | 2.13 |
| **15** | 1706 | 749 | 7.47 | ~7.25[g] | 7.08 | 3.18 | ~1.8 | 1.32 | 2.00 | 2.75 | 3.44 | 2.08 | 2.20 |
| **16** | 1694 | | 7.70 | ~7.3 | 7.12 | 3.02 | ~1.8[g] | 1.15 | ~1.8[g] | 2.50 | 2.60 | ~1.8[g] | 2.06 |
| **17** | 1692 | 757 | 7.50 | ~7.2 | 7.02 | 2.93 | ~1.7[g] | 1.00 | ~1.7[g] | ~2.4[h] | ~2.4[h] | ~1.7[g] | 2.01 |

[a] In KBr discs, $cm^{-1}$. Further data: νNH band (sharp): 3305 (**10**), 3280 (**11**, **14**); [b] Chemical shifts in ppm ($\delta_{TMS}$ = 0 ppm) and coupling constants in Hz. Further signals: $CONCH_2$, 2x*m* (2x1H): 3.47 and 4.33 (**10**), 3.40 and 4.27 (**12**), 2x*dd* (*J* = 11.3, 10.0 and 5.3, **11** and **13**, ~13.5 and ~2.5, **14**): 2.82 and 4.12 (**11**), 3.03 and 4.20 (**13**), 3.25 and 4.07 (**14**); CONCH: 3.84, *d* (*J* = 7.3), **16**, 4.06 *dd* (*J* = 8.3 and 3.5), **17**; $(NH)CH_2$, (2x1H), 2x*m*: 2.92 and 3.16 (**10**), 2x*dd* for **14** (*J* = 14.5 and 11.5, upfield signal); (NH)CH: 3.23 *m* (**11**); $OCH_2$: 3.80 and 3.98, 2x*m* (**12**), *t* (*J* = 11.5) and *dd* (*J* = 11.5 and 6.3, **16**, 11.3 and 5.3, **17**): 3.44 and 3.84 (**16**), 3.20 and 3.86 (**17**); OCH, *m*: 4.10 (**13**), $CCH_2C$ heteroring): ~2.0 *m* (2H) for **10**, 1.99 and 2.26, 2x*m* (**12**), ~1.5 *m* (2H) and ~1.8 *m* (2H)[g] for **14**; $CH_3$, *d* (*J* = 6.1): 1.37 (**11**), 1.50 (**13**), CCHC (in oxazine ring): 2.35 *ddd* (*J* : 11.6, 6.3 and 6.3) for **16**, ~2.8 *m* (2H)[k] for **17**, CCHC (β to N in norbornane/ene): 4.14 *d* (*J* = 5.1) for **16**, 3.91 ~*s* (**17**), CCHC (γ to N in norbornane/ene): 1.94 ~*s* (**16**), ~2.8[k] (**17**); $CH_2$ (**16**, norbornane): 5x*m* (5x1H), 1.15, 1.35, 1.57, 1.68 and ~1.8[g] and 1.30 *d* (*J* = 10.4, *endo*-H of the bridging $CH_2$); $CH_2$ (**17**, norbornene), 2x*d* (2x1H): 1.29 (*endo*) and 1.56 (*J* = 8.8), CH (**17**, norbornene), 5.97 *dd* (*J* = 5.5 and 2.5) and 6.11 *dd* (*J* = 5.5 and 3.0), ArH-10-13 (for numbering, see the Scheme) for **15**: 7.69 *d*, ~7.15 *m* (2H), ~7.25[g]; NH: ~1.8[g] (**10**, **11**), 2.16 *s* (**14**); [c] Assignments were supported by DNOE (except for **14**), 2D-HSC and for **10**, **11**, **14** and **16** also by 2D-COSY measurements; [d] *J* = 11.0 and 7.5± 0.2 (**11-13**, **15**), 10.6 and 8.2 (**16**); [e] *J* = 7.2 and 3.6 (**12**), 6.7 and 3.4 (**15**), lines of *m* are coalesced (**13**, **16**); [f] *J* = 13.4 ± 0.1 and 3.0; [g,h,k] Overlapping signals; [i] Split band with the second maximum at 1684.



12 16 17

Figure 1. Stereostructures of **12**, **16** and **17** and the NOE's proving them

In accordance with our earlier experience,[14,15] the doublet splitting (by 7.3 Hz) of the NCH signal in **16** and the double doublet structure (splits 8.3 and 3.5 Hz) of the same signal in **17** confirm the *diexo* (**16**) and *diendo* (**17**) 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 **16** and between the latter atom and the NCH hydrogen in **17**.

Table 2. $^{13}$C-NMR chemical shifts ($\delta_{TMS}$ = 0 ppm) of compounds (**10-17**) in $CDCl_3$ solution at 125.7 MHz[a]

| | C-1 | C-2[b] | C-3[b] | C-4 | C-4a[c] | C-5 | C-6 | C-7 | C-8 | C-9 | C-10 | C-10a[c] | C-11 | C=O | NC[d] | XC[e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **10** | 126.2 | 128.7 | 127.4 | 129.4 | 140.3 | 34.8 | 32.0 | 21.0 | 40.7 | 42.7 | 75.6 | 141.9 | 26.2 | 177.0 | 34.4 | 38.1 |
| **11** | 126.5 | 129.0 | 127.8 | 128.8 | 141.7 | 34.3 | 31.5 | 20.7 | 44.4 | 45.5 | 84.8 | 142.5 | 27.3 | 181.3 | 52.8 | 55.0 |
| **12** | 127.3 | 129.0 | 127.1 | 129.1 | 139.0 | 34.6 | 31.2 | 21.3 | 40.5 | 40.4 | 89.9 | 140.5 | 26.3 | 176.7 | 32.8 | 59.3 |
| **13** | 127.8 | 129.2 | 127.5 | 128.5 | 139.9 | 34.2 | 30.9 | 21.2 | 44.4 | 44.3 | 97.5 | 141.1 | 27.3 | 180.9 | 50.3 | 74.8 |
| **14** | 125.0 | 128.1 | 126.8 | 128.7 | 140.3 | 34.5 | 31.4 | 21.2 | 40.2 | 37.8 | 78.9 | 141.9 | 25.7 | 176.4 | 40.3 | 42.5 |
| **15** | 127.0 | 129.1 | 127.6 | 127.8 | 141.7 | 33.3 | 29.9 | 20.0 | 43.3 | 45.9 | 80.2 | 136.9 | 27.6 | 176.9 | 135.3 | 132.9 |
| **16** | 127.5 | 128.5[f] | 126.5 | 128.4[f] | 138.7 | 34.2 | 30.4 | 20.9 | 40.0 | 38.3 | 90.1 | 140.3 | 25.9 | 176.0 | 58.2 | 61.7 |
| **17** | 127.8 | 128.9[g] | 127.1 | 128.9[g] | 139.5 | 34.6 | 31.2 | 21.0 | 39.5 | 39.0 | 90.4 | 140.4 | 26.5 | 175.9 | 52.6 | 65.0 |

[a] Assignments were supported by DEPT and 2D-HSC measurements; Further signals: $CH_3$: 17.4 (**11**), 18.0 (**13**), C-$CH_2$-C: 24.9 (**10**), 23.7 (**12**), 28.9 and 33.6 (**14**), 26.9, 29.3 and 34.2 (**16**, the line of the bridging methylene group at 34.2 is in overlap with the C-5 line), 47.7 (**17**); C-CH-C (ring *E*): 45.5 (**16**), 42.3 (**17**), C-CH-C (β to N): 37.7 (**16**), 47.6 (**17**), C-CH-C (γ to N): 37.5 (**16**), 44.4 (**17**); CH (**17**, olefinic): 135.1 and 137.1 (γ to N): CH (**15**, aryl; for numbering see the Scheme): C-10: 117.5, C-11,12: 125.2, 125.3, C-13: 121.4.[b,c,f] Probable assignments (may be interchanged); [d] Carbon bound to the amide nitrogen; [e] X: NH (**10**, **11**, **14**), O (**12**, **13**, **16**, **17**), S (**15**); [g] Two very close-lying lines at 128.89 and 128.92 ppm.

The only question remaining is the relative position of the bridging $CH_2$-18 in **16** and **17**. NOE interactions were observed between the aromatic H-1 and the methine-H β to the heteroatoms (**16**) or the former and the NCH group (**17**). In **17**, NOE was also observed for H-9 and the *axial* $OCH_2$ hydrogen. These findings confirm the stereostructures depicted in Figure 1, *i.e.* the amide-carbonyl and the bridging-$CH_2$ are *cisoid* in **16** and *transoid* in **17** relative to the oxazine ring. The structure of **16** was confirmed by X-Ray measurements: Figure 2 clearly depicts the *cisoid* arrangement of the carbonyl and $CH_2$-18.

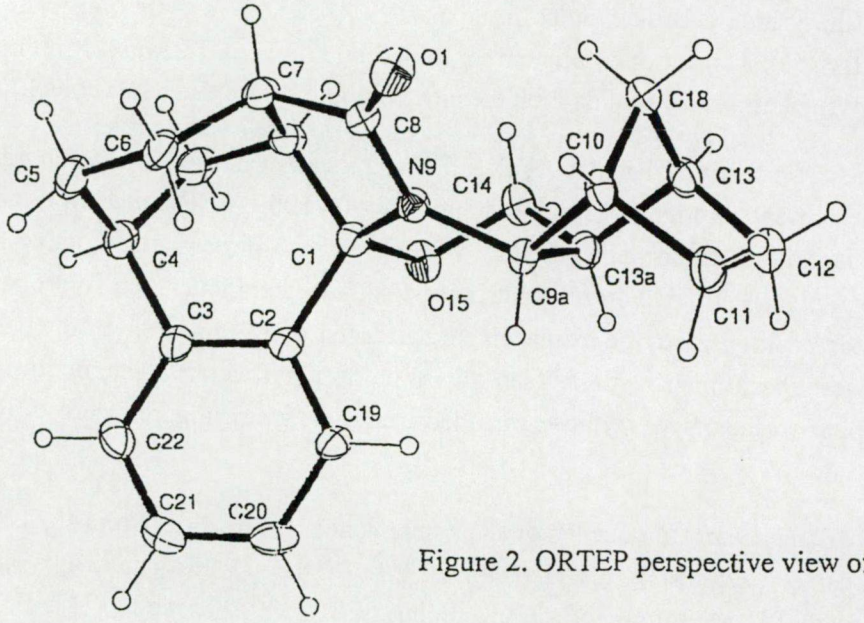



Figure 2. ORTEP perspective view of **16**

Table 3. Results of DNOE experiments with compounds (**10-13, 16** and **17**)[a]

| Saturated signal | Responding signal H-1 | H-9 | $XCH_n$[b] | $(CO)NCH_n$[c] | $CCH_nC$[d] | $CH_3$ | H (*endo*)[e] |
|---|---|---|---|---|---|---|---|
| H-1 | | | **12, 16** | **10-12** | **12, 16** | **11** | |
| H-9 | | | **12, 13, 16** | | | | |
| $XCH_n$[b] | **10, 12, 16** | **10-12, 16, 17** | *10, 12, 16, 17* | *11* | *12, 16* | *11, 13* | *16*[f] |
| $(CO)NCH_n$[c] | **10-12, 17** | | | *10-12* | *10, 12, 17* | *11* | **17** |
| $CCH_nC$[d] | **16** | | *16* | *16* | | | |
| $CH_3$ | **13** | | *11, 13* | *11, 13* | | | |
| H(*endo*)[e] | | | | **17** | **17** | | |

[a] Interacting pairs (groups containing hydrogen) showing only trivial effects (NOE between geminal or vicinal hydrogens) are not included in this Table. Responses relevant for stereostructures are given with bold compound numbers. Italic compound numbers correspond to trivial effects; [b] X: NH (**10, 11**) or O (**12, 13, 16, 17**), $n = 2$ (**10, 12, 16, 17**, $n = 1$ (**11, 13**); [c] Methine-H (**16, 17**) or methylene-H (**10-13**) vicinal to amide-N; [d] "Middle" $CH_2$ (**10, 12**) or CH (**16, 17**) in the diazine (**10**) and oxazine (**12, 16, 17**) ring, resp.; [e] In bridging methylene group (**16, 17**); [f] NOE with both methylene-H atoms.

## EXPERIMENTAL

The $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature, on a Bruker DRX 500 spectrometer at 500.13 ($^1H$) and 125.76 ($^{13}C$) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker microprogram DNOEMULT.AU to generate NOE[16,17] was used with a selective pre-irradiation time. DEPT spectra[18] were run in a standard manner,[19] using only the $\theta = 135°$ pulse to separate the $CH/CH_3$ and $CH_2$ lines phased "up" and "down", respectively. The 2D-HSC spectra[20] were obtained by using the standard Bruker pulse program XHCO.AU. IR spectra were run in KBr discs on a Bruker IFS-55 FT-spectrophotometer controlled by Opus 2.0 software. Melting points are uncorrected. Physical and analytical data on the new compounds are listed in Table 4.

*Data collection and refinement.* A Rigaku AFC5S diffractometer was used at room temperature (21 °C) with graphite monochromated $MoK_\alpha$ radiation ($\lambda = 0.71069$ Å). The data were corrected for Lorentz and polarization effects. The structure was solved by a direct method, using SIR92[21] and DIRDIF[22] programs, and refined by full-matrix least-squares techniques. The hydrogens were kept in the calculated positions with the displacement parameter of 1.2 times $B_{eq}$ of the host atom. All calculations were performed with teXsan for Windows software.[23] The neutral atomic scattering and dispersion factors were those included in the program. Figures were drawn with ORTEP.[24]

*Crystal data and experimental details*: trigonal prisms, space group R-3 (No. 148, hexagonal axes), $a = 27.665(2)$, $b = 27.665(2)$, $c = 11.693(3)$ Å, $Z = 18$, $D_c = 1.293$ gcm$^{-3}$, $\mu = 0.82$ cm$^{-1}$, $F(000) = 3240$, $R_{int} = 0.01$. Measured refl. 3308, unique refl. 3040, obs. refl. 1741, no. of parameters 227, $R^b = 0.049$, $R_w{}^c = 0.042$. Other crystal data, anisotropic displacement parameters,

final atomic positional coordinates, temperature parameters, bond lengths and bond angles, have been deposited in the Cambridge Crystallographic Data Centre, Lensfield Rd., Cambridge, CB2 1EW, UK.

**2,3-Benzo-9,13-diazatetracyclo[7.4.$1^{1,7}$.$1^{4,14}$.0]pentadecan-8-one (10), 2,3-benzo-11-methyl-9,12-diazatetracyclo[7.1.$1^{1,7}$.$1^{4,13}$.0]tetradecan-8-one (11), 2,3-benz-13-oxa-9-azatetracyclo[7.4.$1^{1,7}$.$1^{4,14}$.0]pentadecan-8-one (12), 2,3-benz-12-oxa-9-azatetracyclo[7.3.$1^{1,7}$.$1^{4,13}$.0]tetradecan-8-one (13), 2,3-benzo-9,14-diazatetracyclo[7.5.$1^{1,7}$.$1^{4,15}$.0]hexadecan-8-one (14), (2,3)(10,11)-dibenzo-12-thia-9-azatetracyclo[7.3.$1^{1,7}$.$1^{4,13}$.0]dodecan-8-one (15), 3,8-diexo-16,17-benz-2-oxa-10-azahexacyclo[8.7.$1^{1,12}$.$1^{4,7}$.$1^{15,19}$.$0^{3,8}$.0]poly-11-one (16), 3,8-diendo-16,17-benz-2-oxa-10-azahexacyclo[8.7.$1^{1,12}$.$1^{4,7}$.$1^{15,19}$.$0^{3,8}$.0]poly-5-en-11-one (17). General method**

A mixture of **1a** (or **1b** or **1a,b**) (1.15 g, 5 mmol), **3-9** (6.5 mmol), *p*-toluenesulfonic acid (0.05 g) in chlorobenzene (15 mL) (for **2, 3** or **6**) or dry xylene (15 mL)was refluxed for 3-8 h (**10**: 8 h, **11**: 6 h, **12**: 8 h, **13**: 3 h, **14**: 8 h, **15**: 4 h, **16**: 5 h, **17**: 8 h). After evaporation, the residue was dissolved in $CHCl_3$ and transferred to an $Al_2O_3$ column [ACROS, Aluminium oxide, basic (for diamines) or neutral, 50-200 μ], then eluted with *n*-hexane–EtOAc (2:1 for diamines or 4:1). The residue of the eluates was crystallized. Data on compounds (**10-17**) are listed in Table 4.

Table 4. Physical and analytical data on compounds (**10-17**)

| Compd | mp (°C) | Yield (%) | Formula | Analysis Calcd % C | H | N | Found % C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **10** | 180-181[a] | 76 | $C_{17}H_{20}N_2O$ | 76.09 | 7.51 | 10.44 | 76.25 | 7.58 | 10.28 |
| **11** | 183-185[a] | 42 | $C_{17}H_{20}N_2O$ | 76.09 | 7.51 | 10.44 | 76.18 | 7.47 | 10.33 |
| **12** | 171-172[b] | 55 | $C_{17}H_{19}NO_2$ | 75.81 | 7.11 | 5.20 | 75.69 | 7.18 | 5.15 |
| **13** | 121-123[a] | 58 | $C_{17}H_{19}NO_2$ | 75.81 | 7.11 | 5.20 | 75.65 | 7.08 | 5.14 |
| **14** | 140-141[b] | 23 | $C_{18}H_{22}N_2O$ | 76.56 | 7.85 | 9.92 | 76.42 | 7.69 | 9.81 |
| **15** | 206-207[c] | 60 | $C_{20}H_{17}NOS$ | 75.20 | 5.36 | 4.39 | 75.34 | 5.45 | 4.30 |
| **16** | 200-201[a] | 62 | $C_{22}H_{25}NO_2$ | 78.77 | 7.51 | 4.18 | 78.59 | 7.42 | 4.28 |
| **17** | 172-174[b] | 28 | $C_{22}H_{23}NO_2$ | 79.25 | 6.95 | 4.20 | 79.45 | 6.88 | 4.31 |

Crystallization solvent: [a] EtOAc; [b] $Et_2O$; [c] EtOH

ACKNOWLEDGEMENTS

The authors are indebted to Mrs. E. Csiszár-Makra and Mrs. A. Bőszin-Nagy for skilled technical assistance. They also express their thanks for Hungarian Research Foundation (OTKA) grants No 2693 and T 25415.

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Received, 19th March, 1998

# IV

# Double Retro Diels-Alder Reaction Applied for Preparation of a Pyrimido[1,2-*b*]pyridazine

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*Received 14 October 1999*

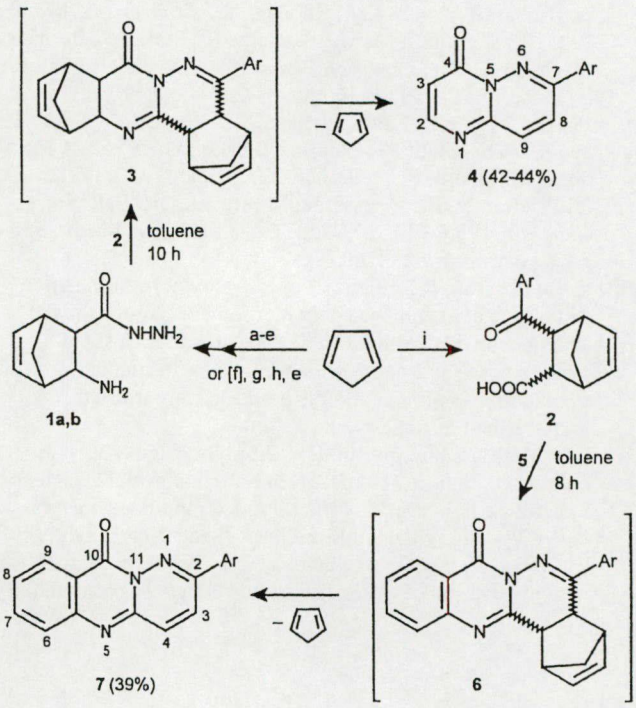
**Abstract**: Boiling *diendo-* or *diexo*-2-aminobicyclo[2.2.1]hept-5-ene-3-carbohydrazides **1** with 3-aroylnorbornenecarboxylic acid **2** in toluene yielded the pyrimido[1,2-*b*]pyridazine **4** directly in a double retro Diels-Alder process. Similarly, the reaction of anthranilic hydrazide **5** and **2** furnished the tricyclic benzo-fused analogue **7** via a single cycloreversion. The principle of the new method applied: the reactants were built up on cyclopentadienes and the dienes were cleaved by heating after condensation to furnish hetero bicyclic compound.

**Key words**: retro Diels-Alder, pyrimidopyridazine, double cycloreversion, thermal splitting, synthetic panels

We have often used *diendo-* and *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids[1a, b] to prepare heteromonocycles, and bicyclic or tricyclic derivatives.[2] The principle of these reactions was the construction of the parent compound on cyclopentadiene, which was subsequently removed by heating in the final step to result in a new double bond in the target heterocycles. The present paper describes an extension of this method to a double retro Diels-Alder (RDA) reaction, in which both reactants are built up on cyclopentadiene prior to the synthesis.

The Diels-Alder reaction of cyclopentadiene with maleic anhydride, subsequent opening with $NH_4OH$, decomposition of the amide with hypochlorite,[1a] esterification[1c] and hydrazinolysis[1d] yielded the *diendo*-3-aminonorbornene-2-carbohydrazide **1a**. For synthesis of the *diexo* analogue, chlorosulfonyl isocyanate (CSI) addition to the bicyclo[2.2.1]hepta-2,5-diene, sulfite reduction and hydrazinolysis of the azetidinone[1d] led to **1b**. When **1a** or **1b** was refluxed in toluene for 10 h with **2** obtained from *trans*-aroylacrylic acid[3] and cyclopentadiene, the parent compound **3** containing two norbornene units decomposed directly to the pyrimido[1,2-*b*]pyridazine **4** with a yield of over 40% (from **1a**:42%; from **1b**:44%) (Scheme).[4] Similarly, the reaction of **2** and anthranilic hydrazide **5** led directly to pyridazino[6,1-*b*]quinazoline **7**[5] in 39% yield by a single RDA process.

This RDA method provides an easy route for the preparation of heterocycles. Cycloreversion proceeds readily, i.e. a new double bond is formed between two carbons of the target molecule if a heteroaromatic or quasi-heteroaromatic system, e.g. pyrimidinone, pyrimidinedione, thioxopyrimidinone, etc. is formed,[2] as in the present case in structures **4** and **7**. For **4**, however, the method deviates from that applied previously: now, the heterocycle is not built up on one cyclopentadiene, but each of its parts is built up on separate molecules of cyclopentadiene. Then, in the reaction process, the latter is removed under reflux to give the products **4** and **7** instead of the parent compounds **3** and **6**. The formation of these conjugated systems is favourable for the cycloreversion.




**1a**: *diendo*, **1b**: *diexo*, Ar = *p*-methylphenyl, (a) maleic anhydride, (b) $NH_4OH$, (c) $Cl_2$/NaOH, (d) EtOH/$SOCl_2$, (e) $H_2NNH_2$ [(f) HC≡CH; norbornadiene is commercially available], (g) CSI, (h) $Na_2SO_3$, (i) ArC(O)CH=CHCOOH(*trans*), **5**: anthranilic hydrazide

**Scheme**

The above method affords a new synthesis of the tricyclic systems **4** and **7**[6] 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.[7] The principle of constructing fused molecules on cyclopentadiene offers a quite versatile means of synthesis of various heterocycles.

## Acknowledgement

The authors are indebted to Mrs. E. Csiszár-Makra for technical assistance. OTKA Grant: T 25415.

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(4) In the reaction, the mixture **2** of *exo*-aroylnorbornene-*endo*-carboxylic acid and *endo*-aroylnorbornene-*exo*-carboxylic acid presumably cyclizes to *diendo*- and *diexo*-fused pyridazines. For **2** and 1,4-diaminobutane, a similar cyclization was found and the products were isolated (unpublished results).
7-(*p*-Methylphenyl)pyrimido[1,2-*b*]pyridazin-3-one **4**: A mixture of *diendo*- (**1a**) or *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazide (**1b**; 1.5 g, 8.8 mmol) and *diendo-diexo*-3-*p*-toluoylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**2**; 2.56 g, 10 mmol) in toluene (50 mL) was refluxed for 10 h, with application of a water separator. After evaporation, the residue was dissolved in $CHCl_3$ (10 mL) and the solution was transferred onto an alumina column (Woelm, neutral, Akt. 1) and then eluted with EtOAc. On evaporation, the residue crystallized from EtOAc to give **4** as colourless crystals; mp. 172-173 °C, yield 0.88 g (42%) from **1a** and 0.93 g (44%) from **1b**. Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.76; H, 4.69; N, 17.6. IR ($cm^{-1}$, KBr disc), vC=O:1714; $^1H$ NMR (ppm, $CDCl_3$, 500.13 MHz): δ 2.38 (*s*, $CH_3$), 8.16 (*d*, *J* = 6.3 Hz, CH-2), 6.63 (*d*, CH-3), 7.84 (*d*, *J* = 9.5 Hz, CH-8), 7.88 (*d*, CH-9), 7.92 (*d*, *J* = 7.5 Hz, CH-2',6'), 7.26 (*d*, CH-3',5'); $^{13}C$ NMR (ppm, $CDCl_3$, 125.76 MHz): δ 21.8 ($CH_3$), 153.2 (C-2), 111.2 (C-3), 153.3 (C-7), 126.5 (C-8), 135.2 (C-9), 149.6 (C-9a), 158.4 (C=O), 131.3 (C-1'), 127.8 (C-2',6'), 130.3 (C-3',5'), 142.3 (C-4'). The structure was confirmed by X-ray analysis; results will be published later.

(5) 2-(*p*-Methylphenyl)pyridazino[6,1-*b*]quinazolin-10-one **7**: mp. 227-228 °C. Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.62. Found: C, 75.36; H, 4.49; N, 14.60. IR ($cm^{-1}$, KBr disc), ν C=O: 1706; $^1H$ NMR (ppm, $CDCl_3$, 500.13 MHz): δ 2.35 (*s*, $CH_3$), 7.70 (*d*, *J* = 9.5 Hz, CH-3), 7.73 (*d*, CH-4), 7.76 (*d*, *J* = 8.1 Hz, CH-6), 7.82 (*t*, CH-7), 8.50 (*d*, *J* = 8.1 Hz, CH-9), 7.92 (*d*, *J* = 7.5 Hz, CH-2',6'), 7.25 (*d*, CH-3',5'); $^{13}C$ NMR (ppm, $CDCl_3$, 125.76 MHz): δ 21.8 ($CH_3$), 151.2 (C-2), 125.2 (C-3), 135.3 (C-4), 145.0 (C-4a), 147.7 (C-5a), 127.6 (C-6), 135.2 (C-7), 128.2 (C-9), 120.2 (C-9a), 158.8 (C=O), 131.6 (C-1'), 127.5 (C-2',6'), 130.2(C-3',5'), 141.8 (C-4').

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Article Identifier:
1437-2096,E;2000,0,01,0067,0068,ftx,en;G24799ST.pdf

# V

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

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***Received (in Cambridge, UK) 22nd June 2000, Accepted 15th January 2001***
***First published as an Advance Article on the web 15th February 2001***

The reactions of *cis*-2-*p*-toluoylcyclohexanecarboxylic acid **1** with *endo*,*endo*- or *exo*,*exo*-3-aminobicyclo[2.2.1]heptane- and -hept-5-ene-2-carbohydrazides **2**, **4** and **3**, **5** yielded partly saturated methylene-bridged phthalazino[1,2-*b*]quinazolinone diastereomers **6a–6b**, **7a–7b**, **8a–8b** and **9a–9b**, and phthalazino[1,2-*b*]-quinazolinediones **10–13** containing a *trans*-condensed cyclohexane ring. After separation of the products, the structures were established by means of NMR methods. The diastereomers **6–9** differ in the configurations of the annelational carbons: the hydrogens attached to them lie either on the same side (**a**) or in pairs on opposite sides (**b**) of the ring skeleton. On heating, the mixtures of diastereomeric norbornene derivatives **8** and **9** underwent retrodiene decomposition: cyclopentadiene split off to yield the pyrimido[2,1-*a*]phthalazine **14** containing a *cis*-fused cycloalkane ring. The reaction of **4** with the aroylbenzoic acid **15** furnished the benzologue **19** directly, while, after isolation from the reaction mixture of **1** and **5**, and on heating, **20** resulted in **21** containing a saturated *trans*-condensed isoindole moiety by cycloreversion.

## Introduction

The synthetic application of the retro Diels–Alder (RDA) reactions involves the regeneration of conjugate dienes or dienophiles from their masked forms after modification of the molecular architecture. The unsaturation present in the starting material is protected in the form of a Diels–Alder adduct and the same atoms are involved in the bond formation and cleavage steps.

We have developed a method[1–4] that applies *exo*,*exo*- or *endo*,*endo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid or their derivatives as starting materials containing cyclopentadiene as a carrier unit. The principle of the method is the build-up of the parent partially saturated heterocycles with different reagents, *e.g.* imidates, oxo esters, isothiocyanates, *etc.*, and the subsequent removal of cyclopentadiene by a mild thermal process in the final reaction step. A number of known and new heteromonocyclic, -bicyclic and -tricyclic derivatives have recently been prepared *via* this route.

The importance of this method is the applicability of the RDA reaction for the preparation of new condensed heterocyclic compounds. The present work reports an example where the structural conditions provide possibilities for extension of the method to new heterocyclic systems, allowing the syntheses of tricyclic pyrimido[2,1-*a*]phthalazines containing a *cis*-condensed cyclohexane or benzene ring and of a pyrimido[2,1-*a*]-isoindole.

## Results and discussion

The refluxing of *cis*-2-*p*-toluoylcyclohexanecarboxylic acid[5] **1** with *endo*,*endo*-3-aminobicyclo[2.2.1]heptane- **2** or -hept-5-ene-2-carbohydrazides **4** or the *exo*,*exo* analogues[6] **3** and **5** in the presence of a catalytic amount of PTSA in benzene furnished the methylene-bridged *endo*,*endo*- and *exo*,*exo*-dodecahydro- **6** and **7** or decahydrophthalazino[1,2-*b*]quinazolinones **8** and **9** as diastereomeric mixtures in ~ 25% yield, together with products **10–13** and **20** (Schemes 1 and 2).

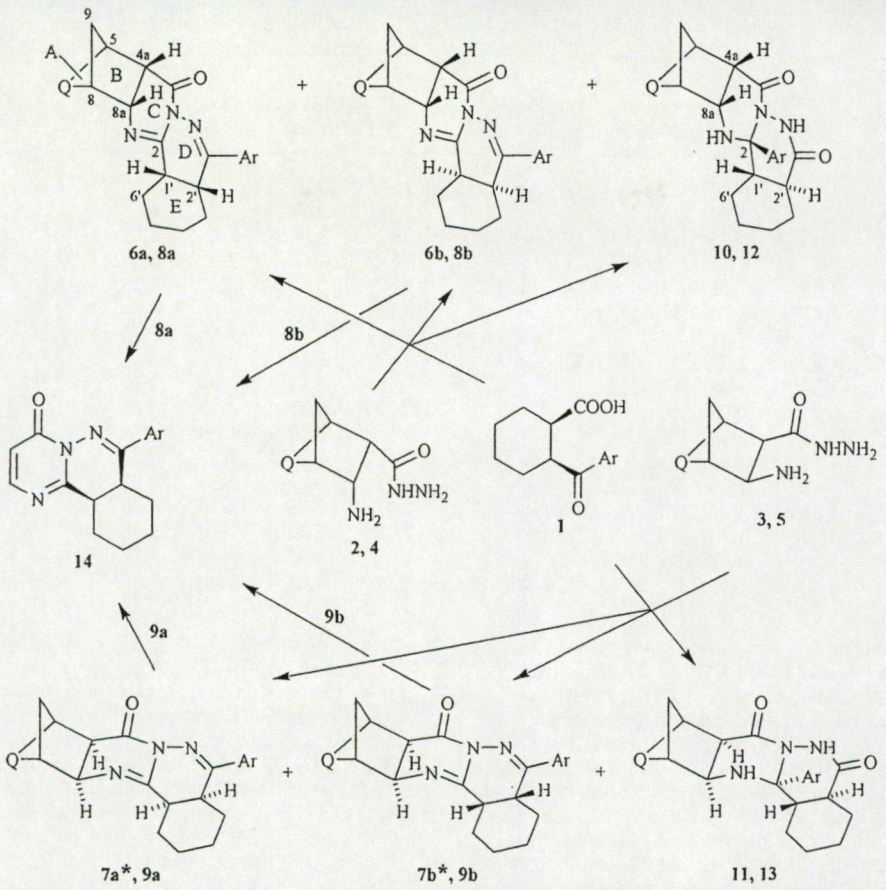
Each of the starting compounds **2–5** yielded one pair of isomers **6a–6b**, **7a–7b**, **8a–8b** and **9a–9b**, which were separated by column chromatography. Hence, the reaction did not take place stereoselectively. The structures of the products were established by means of NMR measurements. The pairs **a–b** contain the two norbornane-ene and saturated phthalazine annelational hydrogens either on the same side (**a**) or on opposite sides (**b**) of the condensed pentacyclic skeleton. One of the isomeric compounds **7a** and bislactam **11** have already been prepared and their structures reported.[6] Besides the saturated and partially saturated phthalazino[1,2-*b*]quinazolinones **6–9**, bislactam derivatives of types **10–13**[6–9] and, in the reaction of **1** and **5**, the saturated methylene-bridged isoindolo[2,1-*a*]-quinazolinedione **20** containing an amino group (Scheme 2) were formed: **10–13** and **18** by acylation of the primary hydrazine amino group with the carboxy of **1** or **15** and cyclization with the aroylcarbonyl group. These reactions differ from those which result in the structures **6–9** and **16** [17], where the carboxy group forms the pyrimidine ring and the oxo group reacts with the hydrazine moiety. Compounds **6–9** retain their starting *cis* configuration at the D/E ring fusion, while the ring annelations for **10–13**, **20** and **21** are *trans*.

Aminoquinazolinones analogous to **20** have previously been prepared by the cyclization of acylaminobenzohydrazides[10] or isothiocyanatobenzoates.[11]

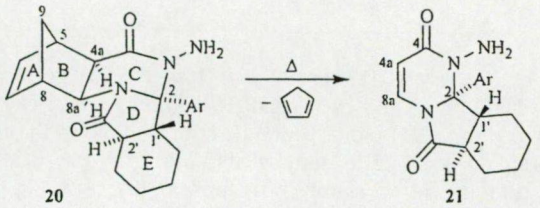
The reaction of **2** with 2-*p*-toluoylbenzoic acid **15** furnished **16**, analogously to **6–9**, while only the bislactam **18** could be isolated from the reaction of **3** with **15**. With **4** as the starting point, the product **17** (not isolated) decomposed directly to **19** (Scheme 3).

Similarly, as found earlier for related norbornene-fused 1,3-heterocycles,[1–4] the unsaturated *endo*,*endo* **8** and *exo*,*exo* **9** or diastereomeric mixtures **8a**,**b** and **9a**,**b** containing a norbornene moiety undergo retrodiene decomposition when heated to their

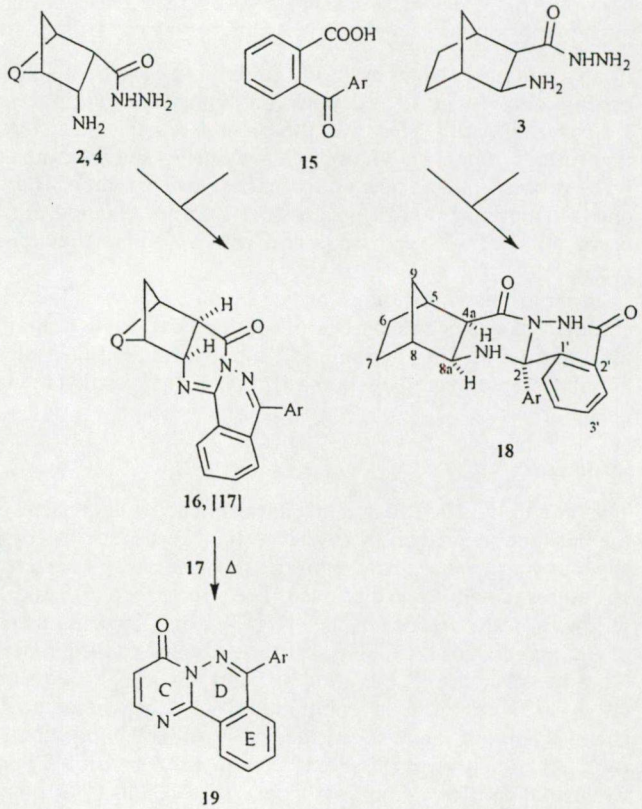
 DOI: 10.1039/b005008n




**Scheme 1** Ar = $C_6H_4CH_3$-*p*; Q = $CH_2CH_2$ (**2**, **3**, **6**, **7**, **10**, **11**) or CH=CH (**4**, **5**, **8**, **9**, **12**, **13**) (* for **7a** and **7b**, reversed configurations are also possible).




**Scheme 2** Ar = $C_6H_4CH_3$-*p*.




**Scheme 3** Ar = $C_6H_4CH_3$-*p*; Q = $CH_2CH_2$ (**2**, **16**) or CH=CH (**4**, [**17**]).

melting points. For the preparation of **19**, a mixture of **4** and **15** 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 **14** or a fused benzene ring **19** were formed in yields of 73 and 60%, respectively. It is noteworthy that the reaction of **4** with the aromatic **15** advantageously yields the benzologue **19** instead of **17**, because the facile RDA process occurs even under mild conditions.

On heating, **20** also undergoes cycloreversion to yield the aminopyrimido[2,1-*a*]isoindoledione **21**, 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 2).

The bislactams **12** and **13** 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-substituted heteroaromatic system is formed. In the present case, rings C in **14** and **19** 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.

Compounds **14** and **21** are the first tricyclic derivatives containing a *cis*- or *trans*-condensed alicyclic ring obtained by an RDA reaction, and in **14** and **19** there are two vicinal nitrogens in the skeleton. As an extension towards complex polycyclic hetero compounds, this is the first example of the preparation

**Table 1** $^1$H NMR data[a] on compounds **6a,b–9a,b**, **10–14**, **16** and **18–21**[b] in $CDCl_3$ solution at 500 MHz

| | $CH_3$ s (3H) | $CH_2(9)$[c] 2 × d (2 × 1H) | | $CH_2$ or $C_{Ar}(3'–6')H$ and $CH_2$ or =CH(6,7) in ring A, B and E[d] | 5-H s (1H) | 8-H s (1H) | 4a-H (1H)[e] | 8a-H (1H)[f] | 1′-H (1H)[g] | 2′-H (1H)[h] | Aryl group[i] 2,6-H | 3,5-H |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **6a** | 2.36 | 1.44[j] | 1.55[j] | 1.4–1.9,[j] 2.54[k] | 2.87[l] | 2.77 | 2.95 | 4.06 | 2.87[l] | 3.11 | 7.78 | 7.20 |
| **6b** | 2.36 | 1.48[j] | 1.52[j] | 1.3–1.8,[j] 2.54[k] | 2.88 | 2.73 | 2.96 | 4.17 | 2.89 | 3.10 | 7.77 | 7.19 |
| **7a** | 2.38 | 1.20 | 1.55[j] | 1.25–1.85,[j] 2.54[k] | ~2.8[l] | 2.50 | ~2.8[l] | 3.88 | ~2.8[l] | 3.10 | 7.78 | 7.21 |
| **7b**[11] | 2.37 | 1.2–1.9[j] | | 1.2–1.9,[j] 2.50[k] | ~2.8[l] | 2.60 | ~2.8[l] | 3.80 | ~2.8[l] | 3.10 | 7.78 | 7.20 |
| **8a** | 2.38 | 1.42[j,o] | 1.51[j] | 1.32,[m] 1.40–1.85,[j] 2.48,[k] 6.22[n] | 3.60 | 3.51 | 3.22 | 4.33 | 2.76 | 3.04 | 7.76 | 7.20 |
| **8b** | 2.37 | 1.38[j,o] | 1.45[j] | 1.35–1.8,[j] 2.50,[k] 6.08, 6.27 | 3.61 | 3.45 | 3.23 | 4.44 | 2.72 | 3.06 | 7.75 | 7.20 |
| **9a** | 2.40 | ~ 1.5[j,n] | | 1.31,[m] 1.5–1.85,[j] 2.57,[k] 6.27, 6.38 | 3.44 | 3.27 | 2.68 | 3.75 | 2.88 | 3.15 | 7.18 | 7.24 |
| **9b** | 2.37 | 1.39[j] | 1.42[j] | 1.3–1.85,[j] 2.58,[k] 6.22, 6.35 | 3.47 | 3.13[l] | 2.65 | 3.81 | 2.84 | 3.12[l] | 7.78 | 7.20 |
| **10** | 2.32 | 1.32 | 1.36[j] | 1.00,[k] 1.20–2.25[j] | 2.65 | 2.43 | 2.04 | 3.27 | 1.78 | 2.23 | 7.26 | 7.13 |
| **11**[11] | 2.35 | 0.9–2.0[j] | | 0.9–2.0[j] | 2.93 | 2.25[l] | ~1.90[j] | 3.02 | 2.25[l] | 2.25[l] | 7.28 | 7.16 |
| **12** | 2.34 | 1.31[j,o] | 1.55[j] | 0.97,[k] 1.2–2.2,[j] 6.24, 6.47 | 3.36 | 3.10 | ~1.80[j] | 3.67 | 2.25 | 2.15 | 7.30 | 7.16 |
| **13** | 2.28 | 1.47[j] | 1.58[j,o] | 0.95,[k] 1.2–2.2,[j] 6.02, 6.08 | 3.39 | ~2.8[l] | 1.67 | 2.94 | 1.78 | 2.25[p] | 7.25 | 7.10 |
| **14** | 2.41 | — | | 1.25–1.8,[j] 2.77[k] | — | — | 6.50 | 7.82 | 3.17 | 3.22 | 7.91 | 7.26 |
| **16** | 2.42 | 1.45[j] | 1.58[j,o] | 1.4–1.7,[j] 7.5–7.6,[l] 8.40[k] | 2.93 | 2.85 | 3.10 | 4.28 | — | — | 7.5[l] | 7.28 |
| **18** | 2.28 | 1.20[j] | 1.55[j] | 1.1–1.6,[j] 7.41, 7.61,[q] 8.03,[k] 8.06[m] | 2.91 | 2.30 | 2.10 | 2.98 | — | — | 7.37 | 7.10 |
| **19** | 2.46 | — | | 7.85–7.95, 9.01[k] | — | — | 6.70 | 8.21 | — | — | 7.60 | 7.35 |
| **20** | 2.25 | 1.36 | 1.40 | 0.53,[m] 1.0–2.2,[j] 2.30,[m] 6.06, 6.14 | 3.38 | 4.24 | 1.86 | 3.42 | 2.09 | 1.90 | 6.98 | 7.06 |
| **21** | 2.33 | — | | 0.81,[m] 1.0–2.2,[j] 2.49[m] | — | — | 5.35 | 7.42 | 2.42 | 1.94 | 7.14[n] | |

[a] Chemical shifts in ppm ($\delta_{Me_4Si} = 0$ ppm), coupling constants in Hz. [b] Assignments were supported by 2D-HSC (HMQC) and DNOE measurements (except for **7a**, **8a**, **9b** and **7a,b**, **12–14**, **19**, **21**, respectively), and for **9a**, **13** and **14** also by 2D-COSY experiments. [c] *AB*-type spectrum, *J*: 9.2 (**6a**, **20**), 9.8 (**7a**), 8.8 (**a,b**, **12**), 9.5 (**9b**, **13**), 10.3 (**10**); singlet-like signal (2H) for **9a**; further split to td, due to long-range couplings for the downfield doublet (**7a**, **8a**, **12**). In overlap with the other methylene signals, but nevertheless identifiable in most cases, due to outstanding intensity (except for **7b**, **11**). [d] $CH_2(3'–6')$ for **6–14**, **20**, **21** or $C_{Ar}(3'–6')H$ for **16–19**, $CH_2(6,7)$ for **6**, **7**, **10**, **11**, **16**, **18**, olefinic CH for **8**, **9**, **12**, **13** (2 × dd, *J*: 5.6 ± 0.1 and 3.0 ± 0.1). Total intensity: 12H (**6**, **7**, **10**, **11**), 10H (**8**, **9**, **12**, **13**, **20**), 8H (**14**, **16**, **18**, **21**), 4H (**19**). [e] d, *J*: 8.5 (**9a,b**), 7.7 ± 0.2 (**11**, **18**, **20**, **21**), 7.3 (**13**), 6.4 (**14**, **19**), dd, *J*: 11.7 (**6a,b**, **16**) or 9.5 (**8a,b**, **10**) and 3.5 (**6a**, **16**), 4.7 (**6b**) or 4.0 (**8a,b**, **10**). [f] d, *J*: 8.8 (**7a**), see at 4a-H (**9b**, **13**, **14**, **19**, **20**, **21**), dd, *J*: 9 and 3 (**7b**), 8.3 and 2.7 (**9a**), 11.8 and 3.7 (**16**), 11.8 and 7.5 (**18**, the split of 7.5 is due to CH,NH-coupling), td, *J*: 11.6, 3.3 and 3.3 (**6a,b**); 9.6, 3.4 and 3.4 (**8a,b**), dt, *J*: 10.1, 10.1 and 3.8 (**10**), unresolved triplet-like signal (**12**). [g] Coalesced m, half signal width: 8 (**6a**, **8a**, **9a,b** and **14**), 12 (**8b**), ~25 (**10**), doublet-like signal with coalesced fine-structure (**6b**), dd, *J*: 9.0 and 4.0 (**12**), 12.1 and 3.8 (**13**), dt, *J*: 12.3, 12.3 and 2.5 (**20**, **21**). [h] Triplet doublet, *J*: 12.4, 4.3 and 4.3 (**6a**, **8b**), 12.9 and 4.3 (**9a**), with coalesced fine-structure (**12**, **14**), coalesced m, half signal width: 25 (**6b**, **7a,b**), ~18 (**10**), ddd, *J*: 12.5, 4.8 and 3.6 (**8a**), dt, *J*: 12.0, 12.0 and 2.8 (**20**, **21**). [i] *AA′BB′*-type spectrum, 2 × ~d (2 × 2H), *J*: 8.1 ± 0.2, singlet-like signal (4H) for **21**. [j,k] Overlapping signals; [l] 6′-H(*eq*), m, Ar(6′)H, d for **16**, **18**, **19**, *J*: 7.3 (**16**), 8.0 (**18**, **19**). [m] 3′-H(*ax*) for **8a**, **9a**, Ar(3′)H, d for **18**. Both signals of the $CH_2(3')$ group are separated for **20** and **21**, where $\delta$3′-H(*ax*) < $\delta$3′-H(*eq*). [n] Singlet-like signal (2H). [o] 9-H(*endo*) as proved by DNOE measurements (for 12 by td split due to W-type of long-range coupling with 4a,8a-H). [p] Broad. [q] Ar(5′)H.

of an aromatic heterotricycle **19**. To date, we have been able to prepare only (fused) heterocycles containing a pyrimidinone or 1,3-oxazinone ring. However, the present example also shows that fused systems, *e.g.* **17**, are rich in electrons and promote the RDA process. Two adjacent nitrogens are also present in **21**, but one is in a primary amino group. This is the first example of the preparation of a target compound with an amino functional group.

Other aromatic analogues of types **6** and **7** were synthesized earlier by the cyclocondensation of anthranilic acid with 1-chlorophthalazines.[12] The pyrimido[2,1-*a*]phthalazine ring system has also been prepared by the cyclization of hydroxyalkylaminophthalazinones.[13–16]

## Structure

The $^1$H and $^{13}$C NMR data and characteristic IR frequencies of the compounds are given in Tables 1–3. To deduce the basic structures from these data is straightforward. Only the stereostructures remain to be discussed. The structures of **6–9** and **16** follow from the absence of the *v*NH IR-bands. In consequence of the $-I$ effect of the C=N substituents bound to the amide-N ("imide" structure),[17] the amide-I band has a high frequency (1698–1727 $cm^{-1}$). For compounds **6–9**, the characteristic chemical shift of the *N*-substituted $sp^2$-carbon[18a] in position 2† (N–C=N moiety) was observed between 157.4 and 158.5 ppm, while that for **16** was at 150.9 ppm. The conjugation of the aromatic ring with the C=N double bond in **6–9**, **16** and **19** results in downfield separation of the 2,6-H signal of the aryl group (in the interval 7.75–7.91 ppm). This separation is not observed for compounds containing the aryl group on a saturated carbon, *e.g.* **10–13**, **18**, **20** and **21**, where the 2,6-H shift is 6.98–7.37 ppm. The structures of **10–13** and **18** were suggested by the strong *v*NH bands in the IR spectra. Due to the change $sp^2 \rightarrow sp^3$ in the hybrid state, the C-2 line in the $^{13}$C NMR spectrum is shifted significantly upfield (78.9–81.4 ppm) in comparison with **6–9**. Two carbon lines are present in the region characteristic of carbonyl groups[18b] (175.5–176.1 and 164.6–166.7 ppm, except for C-1 in **18**, where the conjugation results in an upfield shift to 159.8 ppm).

The structures of the RDA products **14** and **19** are proved by the absence of the $^1$H and $^{13}$C signals of the norbornene moiety and the characteristic high-shift differences $\Delta\delta H_\alpha H_\beta$ and $\Delta\delta C_\alpha C_\beta$ of the enone group:[18c] 1.32 (**14**) and 1.51 ppm (**19**), and 35.7 (**14**) and 39.9 ppm (**19**), respectively. The corresponding data for the RDA product **21**, which also contains an enone moiety, are 2.07 ($^1$H) and 25.6 ppm ($^{13}$C). In the IR spectra of **20** and **21**, the characteristic pairs of $\nu_{as}NH_2$–$\nu_sNH_2$ bands are identifiable (*cf.* Table 3). Corresponding to the γ-lactam (five-membered ring) structure,[17] the carbonyl bands have high frequencies (1698 $cm^{-1}$ for **20**). The frequency is further increased in **21** (1719 $cm^{-1}$), due to the imido structure.[17] The $sp^3$ character of C-2 is clear from the upfield position of its line (83.7 and 82.7 ppm for **20** and **21**).

In consequence of the seven chiral centres, a number of diastereomers must be considered for most of the compounds: the *exo* or *endo* annelation of the norbornane-ene moiety, the *cis* or *trans* annelation of cyclohexane ring E to the skeleton, the mutual positions of the two pairs of annelational hydrogens in rings A/B and D/E, and the C-2 configuration in compounds with an aryl group attached to a saturated carbon.

It is easy to determine the *exo,exo* or *endo,endo* annelation of the norbornane-ene moiety.[19] (The *trans* annelation is sterically very unfavourable and can be excluded.) The method is based

† The spectroscopic numbering used in the text and Tables is given in Schemes 1–3.

**Table 2** $^{13}C$ NMR chemical shifts[a] of compounds **6a,b–9a,b**, **10–14**, **16** and **18–21**[b]

| | | | | | | | | | | Carbons in ring E | | | | | | | Ar-substituent | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C-1[c] | C-2[d] | C-4a[e] | C-5 | C-6 | C-7 | C-8 | C-8a[e] | C-4[f] | C-1′ | C-2′ | C-3′ | C-4′ | C-5′ | C-6′ | $CH_3$ | C-1 | C-2,6 | C-3,5 | C-4 | C-9 |
| **6a** | 147.0 | 157.4 | 44.0 | 43.5 | 24.9 | 21.9 | 43.7 | 59.5 | 166.5 | 35.5 | 36.6 | 25.7 | 26.0 | 20.8 | 25.1 | 21.8 | 132.1 | 126.4 | 129.3 | 140.4 | 37.1 |
| **6b** | 146.8 | 158.0 | 44.6 | 43.6 | 25.6 | 21.2 | 44.5 | 59.1 | 166.3 | 35.8 | 36.9 | 26.0 | 26.4 | 21.9 | 25.3 | 21.3 | 132.6 | 126.9 | 129.7 | 140.9 | 37.6 |
| **7a** | 146.0 | 157.6 | 49.4 | 43.6 | 25.6 | 29.6 | 45.9 | 62.4 | 165.5 | 35.0 | 36.3 | 26.0 | 26.2 | 20.7 | 25.0 | 21.3 | 131.9 | 126.3 | 129.2 | 140.4 | 34.4 |
| **7b** | 146.2 | 157.8 | 49.3 | 44.3 | 25.8 | 29.4 | 45.8 | 62.6 | 165.2 | 34.8 | 36.0 | 25.5 | 26.3 | 20.3 | 25.1 | 21.2 | 131.8 | 126.2 | 129.1 | 140.2 | 34.2 |
| **8a** | 147.2 | 158.3 | 44.9 | 50.8 | 136.8[g] | 136.4[g] | 50.4 | 47.0 | 166.8 | 35.5 | 36.9 | 25.7[h] | 26.5 | 21.0 | 25.7[h] | 21.8 | 132.4 | 126.8 | 129.9 | 140.9 | 47.0 |
| **8b** | 146.6 | 158.0 | 45.3 | 50.3 | 136.35 | 136.42[g] | 50.7 | 46.9 | 166.2 | 35.8 | 36.8 | 26.0 | 26.5 | 21.2 | 25.6 | 21.8 | 132.6 | 126.9 | 129.8 | 140.9 | 46.9 |
| **9a** | 147.0 | 158.5 | 43.8 | 50.3 | 138.8 | 139.5 | 52.4 | 59.2 | 166.2 | 35.1 | 36.5 | 26.1 | 25.9 | 20.7 | 25.4 | 21.4 | 132.0 | 126.5 | 129.4 | 140.7 | 44.1 |
| **9b** | 146.8 | 158.3 | 44.3 | 49.9 | 136.3 | 136.7 | 52.8 | 59.0 | 165.9 | 36.0 | 36.9 | 26.5 | 26.1 | 21.2 | 25.5 | 21.7 | 132.4 | 126.9 | 129.7 | 141.0 | 44.6 |
| **10** | 176.0 | 81.4 | 44.1 | 40.5 | 22.1 | 26.4 | 41.4 | 52.6 | 166.7 | 50.6 | 41.2 | 24.9 | 25.9 | 24.5 | 25.4 | 21.4 | 138.3 | 125.7 | 129.9 | 139.7 | 37.9 |
| **11** | 175.6 | 79.7 | 40.6[g] | 42.5 | 25.7 | 27.7 | 48.5 | 56.9 | 165.6 | 50.0 | 40.3[g] | 25.0 | 26.7 | 24.3 | 24.9 | 20.9 | 137.7 | 125.3 | 129.3 | 138.9 | 34.5 |
| **12** | 175.5 | 81.4 | 43.2 | 46.4[h] | 140.7 | 132.9 | 46.4[h] | 54.9 | 166.1 | 50.0 | 40.3 | 24.4 | 25.3 | 24.9 | 25.3 | 21.0 | 137.9 | 125.5 | 129.5 | 139.4 | 47.7 |
| **13** | 176.1 | 81.0 | 43.3 | 46.1 | 138.3 | 136.2 | 48.0 | 54.0 | 166.7 | 50.5 | 40.6 | 26.3 | 24.7 | 25.5 | 25.4 | 21.4 | | 125.8 | 129.9 | 139.1 | 45.0 |
| **14** | 155.2 | 158.5 | 115.1 | — | — | — | — | 150.8 | 163.8 | 35.1 | 34.6 | 24.6 | 25.3 | 20.8 | 24.2 | 21.4 | 130.8 | 127.1 | 129.5 | 142.1 | — |
| **16** | 142.3 | 150.9 | 45.0 | 44.1 | 22.1 | 25.5 | 45.1 | 59.1 | 167.8 | 130.6 | 126.0 | 128.0 | 132.1 | 132.5 | 126.8 | 21.8 | 132.3 | 129.6 | 129.8 | 139.8 | 37.4 |
| **18** | 159.8 | 78.9 | 49.6 | 41.3 | 29.1 | 26.8 | 42.9 | 56.5 | 164.6 | 137.7 | 124.8 | 128.3 | 129.2 | 134.3 | 125.0 | 21.4 | 139.0 | 126.2 | 130.1 | 142.3 | 34.9 |
| **19** | 148.6 | 156.5 | 112.4 | — | — | — | — | 152.3 | 159.0 | 131.7 | 129.6 | 128.2 | 133.4 | 133.6 | 127.0 | 21.8 | 126.2 | 130.3 | 129.8 | 140.7 | — |
| **20** | 172.2 | 83.7 | 43.7 | 47.4 | 137.7 | 137.8 | 44.8 | 56.0 | 176.1 | 51.6 | 46.4 | 29.0 | 26.0 | 26.2 | 26.7 | 21.4 | 135.3 | 126.2 | 130.3 | 139.0 | 44.6 |
| **21** | 172.7 | 82.7 | 105.9 | — | — | — | — | 131.5 | 164.6 | 52.4 | 45.3 | 29.0 | 25.8[g] | 25.7[g] | 26.0 | 21.4 | 133.7 | 126.2 | 129.6 | 139.1 | — |

[a] In ppm ($\delta_{Me_4Si}$ = 0 ppm) at 125.7 MHz. Solvent: $CDCl_3$. [b] Assignments were supported by DEPT and, except for **7a**, **8a**, **9b**, by 2D-HSC measurements. In the cases of **9a** and **14** the 2D-COSY and of **18** and **21** the 2D-COLOC (HMBC) spectra were also measured. [c] C=N group. For **10–13**, **18**, **20** and **21**, C=O carbon. [d] NCN-carbon ($sp^2$ or $sp^3$) in pyrimidone ring. [e] Annelated atoms of the pyrimidone-condensed alicycle, $sp^2$ carbons for **14**, **19** and **21**. [f] Amide carbon of the pyrimidone ring. [g] Interchangeable assignments. [h] Overlapping lines.

**Table 3** Characteristic IR frequencies [$cm^{-1}$] of compounds **6a, b–9a,b, 10–14, 16** and **18–21** in KBr pellets

| Compound | νNH band (broad or diffuse) | νC=O band[a] | νC=X band[b] | $\gamma C_{Ar}H$ band[c] | |
|---|---|---|---|---|---|
| **6a** | — | 1698 | 1689 | 840 | 823 |
| **6b** | — | 1710 | 1681 | 819 | |
| **7a** | — | 1705 | 1683 | 842 | 814 |
| **7b** | — | 1701 | 1690 | 837 | 818 |
| **8a** | — | 1706 | 1684 | 823 | |
| **8b** | — | 1702 | 1682 | 824 | |
| **9a** | — | 1703 | 1684 | 838 | 818 |
| **9b** | — | 1706 | 1680 | 839 | |
| **10** | 3600–3000 | 1643 | 1694 | 850 | 819 |
| **11** | 3312 3185 | 1644 | 1698 | 822 | |
| **12** | 3600–2800 | 1646 | 1690 | 845 | 819 |
| **13** | 3314 3185 | 1642 | 1696 | 848 | 822 |
| **14** | — | 1699 | 1539 | 815 | |
| **16** | — | 1727 | 1650 | 845 | 824 |
| **18** | 3600–2800 | 1680 | 1665 | 863 | 820 |
| **19** | — | 1696 | 1501 | 851 | 820 |
| **20** | 3323 3216 | 1648 | 1698 | 820 | 808 |
| **21** | 3309 3219 | 1645 | 1719 | 811 | 794 |

[a] Amide-I-type band. [b] νC=N band for **6a,b–9a,b, 14, 16** and **19**; νC=O (amide-I-type) band for **10–13, 18, 20** and **21**. [c] Split band for **6a, 7a,b, 9a, 10, 13** and **16, 18–21**.

on the Karplus relation:[20] as a result of the dihedral angles being ~90° for 4a-H,5-H and 8-H,8a-H in the *exo,exo* compounds (**6, 8, 10, 12** and **16**) and 30° in the *endo,endo* analogues (**7, 9, 11, 13, 18** and **20**), the $^1H$ signals of 4a-H and 8a-H are d's for the former and dd's for the latter. (In the *exo,exo* structures, the 4a-H,8a-H coupling led merely to significant splits of these signals.) Without exception, the starting configurations of C-4a and C-8a remained unaltered. (It should be noted that *exo,exo*⇌*endo,endo* isomerization has been observed in only a few cases to date.[21–23])

The shifts, splits and widths of the 1′-H and 2′-H signals allow differentiation of the *cis* or *trans* annelation of the cyclohexane ring (E). In the event of *trans* annelation (**10–13**), the more shielded 1′,2′-Hs give upfield-shifted signals near one another, and both are broad or exhibit higher splits due to *diaxial* coupling.[18d] For the *cis* isomers, one signal is downfield-shifted and slightly split, due to the *equatorial* position and the *eq,ax* interactions, respectively. However, firm assignment of these signals is not always simple and the signal overlaps do not permit the shape of the signal to be identified. Further, the sum of the $^{13}C$ chemical shifts of the cyclohexane carbons 1′–6′ is smaller for the more crowded *cis* isomers than for their *trans* counterparts.[18e] On application of these principles, the *cis* annelation of the pairs **6a,b–9a,b** and **14** and the *trans* configuration for **10–13, 20** and **21** follow from the spectral data. Thus, for example, Σδ C(1′–6′) is 168.0–172.3 for **6–9** and 164.6 for **14**, while it is 190.8–193.0 for **10–13**, 205.9 for **20** and 204.2 for **21**. However, it is to be noted that, because of the relatively small shift differences, the alternative configurations are also possible in the structures of **7a** and **7b**.

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 (4a,8a-H and 1′,2′-H) are far from one another. The isomeric pairs must be considered individually. The steric interaction between rings A and B and ring E in the *endo,endo* compounds is stronger for the ββββ (1′β,2′β,4aβ,8aβ) configuration than for the 1′β,2′β,4aα,8aα configuration. In **6a**, we observed the field effects on all cyclohexane carbon signals [Σδ C(1′–6′) = 169.7 ppm, as compared with 172.3 ppm for **6b**], which supports the 1′β,2′β,4aβ,8aβ configuration for **6a**. The steric interaction between rings A and B and ring E is also manifested in small field effects on C-4a and C-6. These effects are not observed for the *endo,endo*-norbornene analogues **8a,b** [Δδ C(1′–6′) ≤ 0.3 ppm]. NOE

**Table 4** Results of DNOE experiments with compounds **8b, 10–13, 18** and **20**[a]

| Saturated signal | Responding signals | | | | |
|---|---|---|---|---|---|
| | 7-H | Ar(2,6)H | 8a-H | 1′-H | 2′-H |
| 1′-H | **8b** | | | | |
| 2′-H | | **20** | | | |
| 8a-H | | **10–13, 18, 20** | | | |
| Ar(2,6)H | | | **10–13, 18, 20** | **10, 12** | **20** |

[a] Interacting pairs showing only trivial effects (NOE between the geminal or vicinal hydrogens) are not included in this Table. Only responses relevant to the stereostructures are given.

(Table 4) between 1′-H and 7-H proves the 1′β,2′β,4aα,8aα configuration for **8b** and thus the 1′β,2′β,4aβ,8aβ configuration for **8a**.

The *exo,exo* isomers contain a flatter skeleton. They have extremely similar spectra, *e.g.* the $^{13}C$ NMR shifts differ by at most 0.7 ppm. These very small differences are not sufficient to allow determination of the configurations, but X-ray measurements confirm the all-*cis* (1′α,2′α,4aα,8aα) configuration for **9a**.[24]

To establish the steric position of the tolyl group in **10–13, 18, 20** and **21**, difference NOE (DNOE) measurements were carried out. On saturation of the *ortho*-hydrogens in the *p*-tolyl group, 8a-H and 1′-H responded, whereas no intensity enhancement was observed for the 2′-H signal in the case of **10**. Consequently, 4a,8a,1′-H and the 2-aryl group are on the same side of the skeleton, while 2′-H is on the opposite side (2*R**,4a*S**, 8a*R**,1′*S**,2′*S** relative configuration). The same situation was observed for **12**, which proves the analogous stereostructures (*cis* orientation of the aryl group with 4a,8a-H relative to the pyrimidinone ring, and *cis* and *trans* positions with 1′-H and 2′-H relative to the pyridazinone ring).

In consequence of the anisotropic neighbouring effect of the aromatic ring, the sterically close arrangement of 6′-H(*eq*) to the aryl group causes an upfield shift of the signal of the former (1.00 and 0.98 ppm for **10** and **12**).[18f] An analogous effect was found for 6'-H(*ax*) in *exo,exo* **11** and **13**, and the DNOE proved the sterically close arrangement of 8a-H and the aryl group; the *cis* orientation of 4a,8a-H and the latter substituent follows (a similar stereostructure to that of the *endo,endo* isomers in this part of the molecule), while the aryl group is *trans* to 1′-H and *cis* to 2′-H, relative to the pyridazinone ring, *i.e.* the opposite to that in the *endo,endo* diastereomers. The NOE between 8a-H and the *ortho*-tolyl hydrogens similarly proved their *cis* arrangement in **18**.

Comparison of the spectral data for **10–13** suggests that **11** contains a *trans*-annelated cyclohexane ring, in contrast with our earlier supposition.[6] Consequently, the assignments of the C-4a and C-1′ lines in the $^{13}C$ NMR spectrum must be interchanged.

Mutual NOE of 8a-H or 2′-H and the *ortho*-hydrogens of the aryl group in **20** confirm the 1′α,2′α,4aα,8aα position for 4a,8a,2′-H and the aryl group (and thus the β orientation of 1′-H). The similar shifts of 2′-H and the similarly upfield-shifted 6′-H(*ax*) signal for **21** suggest an analogous steric structure to that of **20**, and hence the *p*-tolyl group is *cis* to 2′-H and *trans* to 1′-H.

## Experimental

The IR spectra were determined in KBr discs on a Bruker IFS-55 FT-spectrometer controlled by Opus 2.0 software. The $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at RT, on a Bruker DRX-500 FT spectrometer at 500.13 ($^1H$) and 125.76 ($^{13}C$) MHz, respectively, using the deuterium

Table 5 Physical and analytical data on compounds **6a,b**, **7b**, **8a,b**, **9a,b**, **10**, **12–14**, **16** and **18–21**

| Compound | Yield (%) | Mp/°C | Found (%) | | | Formula | Requires (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | | C | H | N |
| **6a** | 11 | 202–203[a] | 76.4 | 7.5 | 11.5 | $C_{23}H_{27}N_3O$ | 76.4 | 7.5 | 11.6 |
| **6b** | 8 | 189–190[b] | 76.4 | 7.4 | 11.5 | $C_{23}H_{27}N_3O$ | 76.4 | 7.5 | 11.6 |
| **7b** | 12 | 162–164[c] | 76.2 | 7.6 | 11.8 | $C_{23}H_{27}N_3O$ | 76.4 | 7.5 | 11.6 |
| **8a** | 15 | 178–180[a] | 76.95 | 6.5 | 12.15 | $C_{23}H_{25}N_3O$ | 76.85 | 7.0 | 11.7 |
| **8b** | 10 | 152–153[d] | 76.9 | 7.1 | 11.9 | $C_{23}H_{25}N_3O$ | 76.85 | 7.0 | 11.7 |
| **9a** | 13 | 172–174[b] | 77.05 | 7.1 | 11.8 | $C_{23}H_{25}N_3O$ | 76.85 | 7.0 | 11.7 |
| **9b** | 10 | 142–144[c] | 76.9 | 7.2 | 11.7 | $C_{23}H_{25}N_3O$ | 76.85 | 7.0 | 11.7 |
| **10** | 28 | 252–253[a] | 72.9 | 7.9 | 10.9 | $C_{23}H_{29}N_3O_2$ | 72.8 | 7.7 | 11.1 |
| **12** | 41 | 251–252[b] | 73.3 | 7.3 | 11.1 | $C_{23}H_{27}N_3O_2$ | 73.2 | 7.2 | 11.1 |
| **13** | 29 | 280–281[e] | 73.0 | 7.1 | 11.2 | $C_{23}H_{27}N_3O_2$ | 73.2 | 7.2 | 11.1 |
| **14** | 73 | 117–118[d] | 73.9 | 6.5 | 14.5 | $C_{19}H_{19}N_3O$ | 73.7 | 6.5 | 14.3 |
| **16** | 8 | 191–193[b] | 77.5 | 5.8 | 11.9 | $C_{23}H_{21}N_3O$ | 77.7 | 6.0 | 11.8 |
| **18** | 23 | 224–226[b] | 74.1 | 6.35 | 11.1 | $C_{23}H_{23}N_3O_2$ | 74.0 | 6.2 | 11.25 |
| **19** | 60 | 200–201[e] | 75.4 | 4.5 | 14.8 | $C_{18}H_{13}N_3O$ | 75.25 | 4.6 | 14.6 |
| **20** | 10 | 237–239[e] | 73.25 | 7.3 | 11.3 | $C_{23}H_{27}N_3O_2$ | 73.2 | 7.2 | 11.1 |
| **21** | 79 | 201.5–203[b] | 69.6 | 6.7 | 13.6 | $C_{18}H_{21}N_3O_2$ | 69.4 | 6.8 | 13.5 |

Crystallization solvent [a] MeOH. [b] EtOAc. [c] $Pr^i_2O$. [d] $Et_2O$. [e] EtOH.

signal of the solvent as the lock and TMS as internal standard. DEPT spectra[25] were run in a standard way,[26] using only the $\theta = 135°$ pulse to separate the $CH/CH_3$ and $CH_2$ lines phased up and down, respectively. For DNOE measurements,[18g,27] the standard Bruker microprogram NOEMULT to generate NOE was used. The 2D-COSY[28a] and 2D-HSC spectra[28b] were obtained by using the standard Bruker pulse programs COSY-45 and HXCOU, respectively.

***endo*,*endo*-3-Aminobicyclo[2.2.1]heptane-2-carbohydrazide (2), *endo*,*endo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazide (4) and *exo*,*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazide (5)**

A mixture of ethyl *endo*,*endo*-3-aminobicyclo[2.2.1]heptane-2-carboxylate, -hept-5-ene-2-carboxylate or *exo*,*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylate[29] (11.5 g, 0.063 mmol) and hydrazine monohydrate (99%, 11.62 g, 0.23 mol) in EtOH (10 ml) was refluxed for 4 h. After evaporation, the residue was crystallized from EtOH. Colourless crystals, **2**: yield 9.4 g, 88%, mp 121–122 °C. (Found: C, 56.95; H, 8.9; N, 24.9. Calc. for $C_8H_{15}N_3O$: C, 56.8; H, 8.9; N, 24.8%). **4**: yield 8.2 g, 77%, mp 101–102 °C (Found: C, 57.4; H, 7.9; N, 25.2. Calc. for $C_8H_{13}N_3O$: C, 57.5; H, 7.8; N, 25.1%). **5**: yield 8.95 g, 84%, mp 161–163 °C (Found: C, 57.6; H, 7.9; N, 25.25. Calc. for $C_8H_{13}N_3O$: C, 57.5; H, 7.8; N, 25.1%).

***endo*,*endo*- (6) and *exo*,*exo*-9,12-Methano-5-*p*-tolyl-1,2,3,4,4a, 8a,9,10,11,12,12a,13b-dodecahydro-8*H*- (7), *endo*,*endo*- (8) and *exo*,*exo*-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-one (9), *endo*, *endo*- (10) and *exo*,*exo*-9,12-methano-13a-*p*-tolyl-2,3,4,4a,5,6,8, 8a,9,10,11,12,12a,13,13a,13b-hexadecahydro- (11), *endo*,*endo*- (12) and *exo*,*exo*-9,12-methano-13a-*p*-tolyl-2,3,4,4a,5,6,8,8a,9, 12,12a,13,13a,13b-tetradecahydro-1*H*-phthalazino[1,2-*b*]quinazoline-5,8-diones (13), *endo*,*endo*-9,12-methano-5-*p*-tolyl-8a,9, 10,11,12,12a-hexahydro-8*H*-phthalazino[1,2-*b*]quinazolin-8-one (16), *exo*,*exo*-9,12-methano-13a-*p*-tolyl-5,8,8a,9,10,11,12,12a,13, 13a-decahydro-6*H*-phthalazino[1,2-*b*]quinazoline-5,8-dione (18) and *exo*,*exo*-6-amino-1,4-methano-6a-*p*-tolyl-1,4,4a,5,6,6a,6b,7,8, 9,10,10a,11,12a-tetradecahydroisoindolo[2,1-*a*]quinazoline-5,11-dione (20)**

A mixture of *cis*-2-*p*-toluoylcyclohexanecarboxylic acid **1** (6.15 g, 25 mmol) with *endo*,*endo*- or *exo*,*exo*-3-aminobicyclo-[2.2.1]heptane- or -hept-5-ene-2-carbohydrazides **2–5** (2.85 g, 17 mmol), or **2** and **3** (2.87 g, 17 mmol) with 2-*p*-toluoylbenzoic acid **15** (6.00 g, 25 mmol) and PTSA (0.05 g), in dry benzene (30 ml), was refluxed for 16 h. After evaporation to dryness, the residue was dissolved in $CHCl_3$ (20 ml) and chromatographed on an alumina column (Acros, 50–200 μ, neutral) with *n*-hexane–EtOAc (2 : 1, then 1 : 1) and finally with EtOAc; the eluates with the 2 : 1 mixture contained **6–9**, those with the 1 : 1 mixture contained **20** and the EtOAc eluates contained **10–13** or **16** and **18**. On evaporation of the *n*-hexane–EtOAc (2 : 1) eluates, compounds **6–9** were obtained as mixtures of isomers **a** and **b** or **16** or **18**. The isomeric compounds **6a,b–9a,b** were separated on a silica gel column (Acros, 0.035–0.07 mm) by eluting with a mixture of EtOAc–*n*-hexane (1 : 2, then 1 : 1); the diastereomers **6b**, **7b**, **8b**, **9b** were obtained with the 1 : 2 mixture, and the isomers **a** with the 1 : 1 mixture. Data on these compounds are listed in Table 5.

**7-*p*-Tolyl-7a,8,9,10,11,11a-hexahydro-4*H*-pyrimido[2,1-*a*]-phthalazin-4-one (14)**

The diastereomeric mixture of compounds **8** or **9** (0.4 g, 0.011 mmol) was kept in an oil bath at 190 °C for 10 min. After cooling, $CHCl_3$ (5 ml) was added and the solution was transferred to an $Al_2O_3$ column (Acros, 50–200 μ, neutral) and eluted with an *n*-hexane–EtOAc (2 : 1) mixture. The solvent was evaporated off from the eluate and the residue was crystallized.

**7-*p*-Tolyl-4*H*-pyrimido[2,1-*a*]phthalazin-4-one (19)**

A mixture of aminohydrazide **4** (2.84 g, 17 mmol) and **15** (6.00 g, 25 mmol) in EtOH (30 ml) was refluxed for 4 h. After evaporation, dry toluene (50 ml) and PTSA (0.05 g) were added and the mixture was refluxed for 16 h. After evaporation, the residue was dissolved in $CHCl_3$ (20 ml) and chromatographed on an $Al_2O_3$ column (Acros, 50–200 μ, neutral); the residue of the eluate was crystallized with a mixture of *n*-hexane–EtOAc (2 : 1).

**1-Amino-10b-*p*-tolyl-1,2,6,6a,7,8,9,10,10a,10b-decahydro-pyrimido[2,1-*a*]isoindole-2,6-dione (21)**

Compound **20** (0.20 g) was kept at 250–260 °C in a Wood-metal bath for 10 min. After cooling, the melt was dissolved in $CHCl_3$ (2 ml), transferred to an $Al_2O_3$ column (Acros, 50–200 μ, neutral) and then eluted with a mixture of EtOAc–*n*-hexane (2 : 1); the eluate contained **21**.

## Acknowledgements

The authors are indebted to Mrs E. Csiszár-Makra for technical assistance. OTKA grant: T 25415.

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# VI

# Preparation of 9-Amino-1,9-diazatricyclo[6.4.0.0$^{4,8}$]dodecane-2,10-dione by a Retro-Diels–Alder Reaction

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*Dedicated to Professor K. Pihlaja on the occasion of his 60th birthday*

**Keywords:** Cycloreversions / Polycycles / Nitrogen heterocycles / Retro reactions

Treatment of di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazides (**1a** and **1b**) with ethyl 2-(2-oxocyclopentyl)acetate (**2**) yields norbornene-condensed 9-amino-1,9-diazatricyclo[6.4.0.0$^{4,8}$]dodecane-2,10-diones **3a** and **3b**, the condensed bis(lactams) **4a** and **4b** and (from **1b** and **2**) the cyclopenta[*c*]pyridazinone **5**. After separation, **3a** and **3b** both decompose on heating by loss of cyclopentadiene to give 9-amino-1,9-diazatricyclo[6.4.0.0$^{4,8}$]dodecane-2,10-dione (**6**).

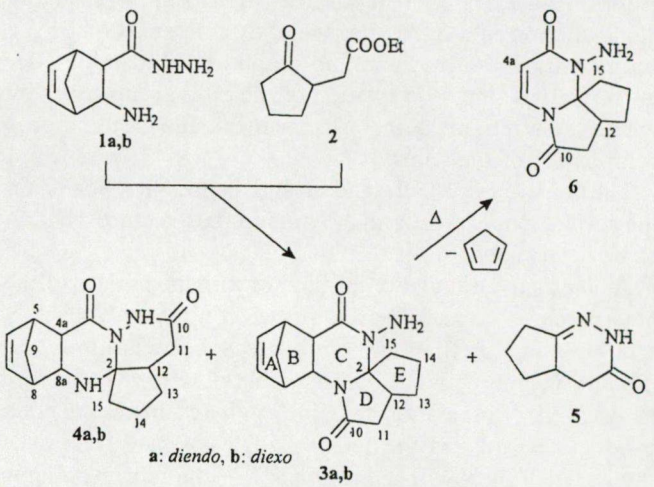
## Introduction

The retro-Diels–Alder reaction (RDAR) is an efficient technique for the introduction of a double bond into a heterocyclic skeleton.[1] Our aim is to synthesize heterocycles that are new or substituted in a new manner. Accordingly, we have developed a method by which di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids or their derivatives are applied to form heterocyclic compounds, and the carrier cyclopentadiene is then cleaved off by heating of the parent molecule in the final step. By this route, numerous new and already known heteromonocycles, pyrimidinones and 1,3-oxazinones[2a,2b] have been prepared, even in condensed heterocyclic systems.[2c] Double RDAR was recently applied for the preparation of a pyrimidopyridazine,[2d] and the method has also been used for the synthesis of pyrimidophthalazines and isoindoles.[2e]

This work deals with an extension of this process to a tricyclic system. The aim is to find new fused heterocyclic compounds that can be produced by application of the developed method and to widen the scope of the RDAR concerning polycyclic derivatives.

## Results and Discussion

Refluxing of di-*endo*- or di-*exo*-3-aminobicyclo-[2.2.1]hept-5-ene-2-carbohydrazides (**1a/1b**) with ethyl 2-(2-oxocyclopentyl)acetate (**2**) in toluene and in the presence of PTSA as catalyst yields a mixture of norbornene-condensed 1,5-diazatricyclododecanediones **3a** and **3b**, together with the pentacyclic bis(lactams) **4a** and **4b** and (a product of **1b** and **2**) the cyclopentane-fused bicyclic pyridazinone **5** (Scheme 1). The latter compound had previously been prepared from **2** with hydrazine,[3] formed here by reaction of **2** with the primary amino group of hydrazide **1b** and subsequent intramolecular transacylation of the intermediate.[4,5] This mechanism operates only in the case of **1b**; the di-*endo* compound **1a** does not give **5** for steric reasons. The compounds were isolated by column chromatography, and their structures were established by means of NMR measurements and, for **3a** and **3b**, also by X-ray analysis (Figure 1). When heated to the melting point, **3a** and **3b** decomposed by splitting off of cyclopentadiene; this thermal cleavage yielded 9-amino-1,9-diazatricyclo[6.4.0.0$^{4,8}$]-dodecane-2,10-dione (**6**) in 85% yield.




Scheme 1. The labelling corresponds with that in Figure 1 and in Tables 1 and 2 and is not based on the nomenclature

The IR and $^1$H and $^{13}$C NMR spectroscopic data proving the structures are given in Tables 1 and 2. The unexpected

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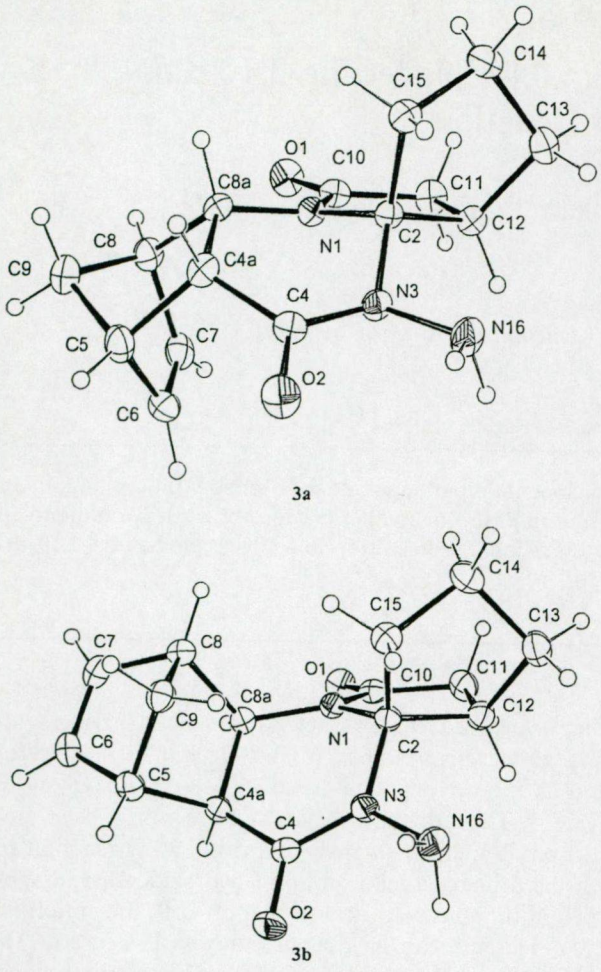


Figure 1. ORTEP-3 perspective views of **3a** and **3b**, showing the labelling system; thermal ellipsoids are drawn at a probability level of 30%

formation of **3a** and **3b** instead of the linearly condensed systems **4a** and **4b** 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 **3** or **4**.

The constitutions of **3a** and **3b** and **4a** and **4b** follow from the spectroscopic data, and only the stereostructures remain to be determined.

As far as the annulation of the norbornene moiety to the heterocycle is concerned, the vicinal couplings of 4a-,5-H and 8-,8a-H (for the numbering, see Scheme 1) are determinant, in line with the splitting rule described earlier;[6,7] as usual, this annulation remains unaltered in the reaction products. Because of the dihedral angles of ca. 30° between the interacting hydrogen atoms[8a,8b] the corresponding splittings in the di-*endo* compounds **3a** and **4a** are about 4.0 and 3.2 Hz, but less than 1.5 Hz in their di-*exo* counterparts **3b** and **4b**, in which the dihedral angles are ca. 90°.

For determination of the configurations at C-2 and C-12, DNOE experiments were applied. On saturation of the 8a-H signal (at $\delta = 4.07$) of **3a**, one of the 15-H signals (at $\delta = 2.09$) responded, confirming their proximity; 8a-H 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 **3a** can be regarded as proved. X-ray measurements confirmed these postulated structures. Compound **3a** crystallizes with one molecule in the asymmetric unit, with one of its NH hydrogen atoms involved in a hydrogen bond, while **3b** crystallizes with two molecules in the asymmetric unit, with all four NH hydrogen atoms involved in hydrogen bonds.

The 2D-NOESY spectrum of **3b** displays a cross-peak, suggesting an interaction between 5-H and one of the methylene hydrogen atoms in the cyclopentane ring. If *cis*-D/E fusion is presumed, 12-H and 4a-,8a-H, and, similarly, ring E and the bridging methylene group, respectively, are (*S*)-*cis*-oriented, which is in accordance with the X-ray results.

DNOE measurements on **4b** indicate the steric closeness of 8a-H and the 15-$H_2$ group. If *cis* fusion of the cyclopentane ring is presumed, the stereostructure with (2*R**,4a*S**,5*S**,8*R**,8a*R**,12*R**) configuration can be considered as proved.

Assuming *cis*-fused rings D/E also in **4a**, the identical type of NOE observed between 8a-H and the 15-$H_2$ group demands an (*S*)-*cis* arrangement of ring E and 4a-H and 8a-H. Thus, a (2*S**,4a*R**,5*S**,8*R**,8a*S**,12*S**) relative configuration follows for **4a**.

A similar structure of the spirotricyclic moiety C–D–E is supported by the chemical shifts of C-2 and C-12 in **4a** and **4b**. Similarly, the identical C-2 and hardly different C-12 shifts in **3a** and **6** suggest analogous stereostructures, i.e., *cis*-annulated five-membered rings and a *cis* orientation of the amide N-3 and the methylene C-12[(2*S**,12*R**) configuration] in **6**.

The above method provides a good means of preparing the tricyclic system **6**, which contains a free amino group, even though it is attached to a ring nitrogen atom. A similarly substituted pyrimidoisoindole has been prepared by RDAR from one reaction product of **1b** with aroylcyclohexanecarboxylic acid.[2e] We earlier found that cycloreversion takes place easily on heating to the melting point, or even on boiling in a solvent, when the target molecule containing an oxo- or thioxo-substituted heteroaromatic system is formed. For condensed cycles, only the ring containing the new double bond needs to be electron-rich; the amino group provides sufficient electron density in the present case. It is noteworthy that **4a** and **4b** do not undergo decomposition under the conditions applied. The reason for this may be the presence of two vicinal lactam moieties, as observed in another case.[2e]

Although **3a** or **3b** are isolated chromatographically before the thermal decomposition, the RDA method is advantageous because **6** can be obtained on a preparative scale. Another procedure frequently applied is flash vacuum pyrolysis,[9] although simple melting is sufficient here. The

Table 1. $^1$H NMR spectroscopic data and characteristic IR frequencies of compounds **3a**, **3b**, **4a**, **4b**, and **6**

| Assignment | Compound | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **3a** | | **3b** | | **4a** | | **4b** | | **6** | |
| $^1$H NMR data[a][b] | | | | | | | | | | |
| 4a-H, d or dd[c](1 H) | 2.94 | | 2.53 | | 2.68 | | 2.15 | | 5.49 | |
| 5-H, "s" (1 H) | 3.18 | | 3.25 | | 3.47 | | 3.43 | | – | |
| 6-H, dd[d] (1 H) | 6.01 | | 6.18 | | 6.45 | | 6.33 | | – | |
| 7-H, d[d] (1 H) | 5.85 | | 6.38 | | 6.22 | | 6.16 | | – | |
| 8-H, "s" (1 H) | 3.93 | | ca. 2.8[e] | | 3.15 | | 2.83 | | – | |
| 8a-H, d or dd[f] (1 H) | 4.07 | | 4.33 | | 3.98 | | 3.32 | | 7.30 | |
| 9-H, 2 × d (2 × 1 H)[g] | 1.32 | 1.35 | 1.56 | 1.70[e] | 1.49 | 1.68 | 1.55 | 1.68 | – | |
| 11-H, 2 × dd (2 × 1 H)[h] | 1.88 | 2.57 | 2.14 | 2.70 | 2.30 | 2.41 | 2.38 | 2.55 | 2.17 | 2.90 |
| 12-H, m (1 H) | 2.83 | | ca. 2.8[e] | | ca. 2.3[e] | | 2.35 | | 3.06 | |
| 13-H, 2 × m (2 × 1 H) | ca. 1.42[e] | ca. 1.77 | 1.55 | ca. 2.1[e] | 1.44 | 1.93 | 1.47[e] | 1.97 | 1.61 | 2.01 |
| 14-H, 2 × m (2 × 1 H) | ca. 1.42[e] | ca. 1.67 | ca. 1.65[e] | ca. 1.90 | ca. 1.6 | ca. 1.8 | 1.62 | 1.83 | 1.52 | 1.82 |
| 15-H, 2 × m (2 × 1 H) | 1.61 | 2.09 | ca. 2.1[e] | | ca. 1.7 | ca. 2.3[e] | 1.72 | 2.30 | 1.74 | 2.14 |
| $NH_2$ or 2 × NH, br. (2 H or 2 × 1 H) | 4.70 | | 4.15 | | 1.25[i] | 8.75[j] | ca. 1.5[e] [i] | 8.66[j] | 4.04 | |
| Characteristic IR frequencies[k] | | | | | | | | | | |
| $\nu_{as}NH_2$ and $\nu_sNH_2$ or 2 νNH bands | 3327 | 3282 | 3310 | 3206 | 3235[i] 3250–2750[j] | | 3244[i] 3250–2750[j] | | 3348 | 3210 |
| Amide-I IR band[l] | 1694 | 1650 | 1684 | 1626 | 1696 | 1641 | 1694 | 1631 | 1710 | 1660 |

[a] Chemical shifts (in ppm, $\delta_{TMS} = 0$) and coupling constants (in Hz) at 500 MHz in $CDCl_3$ solution. – [b] The assignments were supported by 2D-HSC (HMQC), and for **3a**, **3b**, **4a**, and **4b** also by DNOE or 2D-NOESY measurements. – [c] d, $J$ = 8.5 (**3b**), 7.1 (**4b**), 7.5 (**6**), dd, $J$ = 8.6 and 4.0 (**3a**, **4a**). – [d] $J$ = 5.6 and 3.0±0.1. – [e] Coalesced signals. – [f] d, $J$ = 7.1 (**4b**), 7.5 (**6**), dd, $J$ = 8.6 and 3.2 (**3a**, **4a**), 8.6 and 1.4 (**3b**). – [g] d, $J$ = 8.9 (**3a**, **4a**), 9.6 (**3b**), 9.9 (**4b**). – [h] $J$ = 17.7, 4.5 and 11.2 (**3a**), 17.7, 6.6 and 11.0 (**3b**), 15.2, 1.9 and 5.8 (**4a**, **4b**), 18.6, 6.0 and 11.1 (**6**). – [i] Amine group, hidden by the methylene multiplets in the $^1$H NMR spectrum of **4b**. – [j] Amide NH. – [k] In KBr discs (in $cm^{-1}$). – [l] The high frequencies originate from the γ-lactam group (**3a**, **3b**, **6**) or secondary CONH group (**4a**, **4b**).

Table 2. $^{13}$C NMR chemical shifts of compounds **3a**, **3b**, **4a**, **4b**, and **6**

| Assignment[a] | Compound | | | | |
|---|---|---|---|---|---|
| | **3a** | **3b** | **4a** | **4b** | **6** |
| C-2 | 90.1 | 90.1 | 84.9 | 84.3 | 90.2 |
| C-4 | 170.6 | 169.8 | 165.3 | 165.5 | 165.3 |
| C-4a | 45.0 | 42.1[b] | 44.1 | 44.1 | 106.6 |
| C-5 | 46.1 | 48.0 | 47.07 | 46.4 | – |
| C-6 | 137.1 | 137.2 | 140.1 | 139.4 | – |
| C-7 | 135.8 | 139.8 | 133.6 | 135.6 | – |
| C-8 | 46.5 | 47.7 | 47.14 | 48.5 | – |
| C-8a | 53.9 | 51.9 | 55.3 | 54.0 | 132.6 |
| C-9 | 46.2 | 45.5 | 48.5 | 44.4 | – |
| C-10 | 172.5 | 174.5 | 171.6 | 171.6 | 172.3 |
| C-11 | 37.9 | 36.6 | 34.9 | 35.0 | 37.1 |
| C-12 | 38.2 | 42.6[b] | 48.7 | 48.9 | 39.6 |
| C-13 | 34.2 | 32.6 | 32.1 | 32.1 | 32.8 |
| C-14 | 24.3 | 25.0 | 25.0 | 25.0 | 23.3 |
| C-15 | 35.9 | 38.9 | 36.7 | 35.8 | 34.0 |

[a] In ppm ($\delta_{TMS} = 0$), in $CDCl_3$ solution at 125.7 MHz. The assignments were supported by DEPT, 2D-HSC (HMQC) and for **3a**, **4a**, **4b**, and **6** also by 2D-COLOC (HMBC) measurements. – [b] Interchangeable assignments.

reactions proceed as if the heterotricycle is built up on the cyclopentadiene, which is then removed in the final step.

## Experimental Section

**General:** IR spectra were measured as KBr discs with a Bruker IFS-55 FT-spectrometer controlled by Opus 2.0 software. – $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ solution in 5-mm tubes at room temp. with a Bruker DRX 500 FT spectrometer at 500.13 ($^1$H) or at 125.76 ($^{13}$C) MHz, respectively, using the deuterium signal of the solvent as lock and TMS as internal standard. DEPT spectra[10] were run in a standard way,[11] using only the θ = 135° pulse to separate the CH/$CH_3$ and $CH_2$ lines phased up and down, respectively. For DNOE measurements[12,13] the standard Bruker microprogram DNOEMULT was used to generate NOEs. 2D-COSY[14] and 2D-HSC spectra[14] were obtained by using the standard Bruker pulse programs COSY-45 and HXCOU, respectively.

**X-ray Crystal Structure Dterminations:** Crystallographic data were collected at room temperature with a Rigaku AFC5S diffractometer with graphite-monochromated Mo-$K_\alpha$ (λ = 0.71069 Å) radiation. To collect intensity data, an ω-2θ scan mode at an ω-scan speed of 4.0°/min was applied. Weak reflections [$I < 10\sigma(I)$] were rescanned up to two times. For **3a**, 2418 reflections were collected ($2\theta_{max} = 50°$), and for **3b**, 4868. All data were corrected for Lorentz polarization effects. The intensities of three check reflections showed only statistical fluctuations. The structures were solved by direct methods (SIR92)[15] and refined by full-matrix, least-squares techniques (SHELXL-97)[16] to an $R1$ value of 0.039 ($wR2 = 0.062$) for **3a** and of 0.045 ($wR2 = 0.086$) for **3b**; these final $R$ values are based on the reflections with $I > 2\sigma(I)$. The heavy atoms were refined anisotropically. The CH hydrogen atoms were included in calculated positions with fixed isotropic temperature factors (1.2 $U_{eq}$ of the carrying atom) and the NH hydrogen atoms were refined with isotropic temperature factors. Calculations were performed with teXsan for Windows[17] crystallographic software. The figures were drawn with ORTEP-3 for Windows.[18] Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-151736 (**3a**) and -151737 (**3b**). Copies of

Table 3. Physical and analytical data on compounds **3**, **4**, and **6**

| Compound | M.p. [°C] | Formula | Calcd. | | | Found | | |
|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | C | H | N |
| **3a** | 240–241[a] | $C_{15}H_{19}N_3O_2$ | 65.91 | 7.01 | 15.37 | 65.85 | 7.04 | 15.30 |
| **3b** | 256–257[b] | $C_{15}H_{19}N_3O_2$ | 65.91 | 7.01 | 15.37 | 65.81 | 7.12 | 15.48 |
| **4a** | 245–247[a] | $C_{15}H_{19}N_3O_2$ | 65.91 | 7.01 | 15.37 | 65.71 | 7.00 | 15.42 |
| **4b** | 227–228[a] | $C_{15}H_{19}N_3O_2$ | 65.91 | 7.01 | 15.37 | 65.98 | 6.92 | 15.30 |
| **6** | 110–111.5[c] | $C_{10}H_{13}N_3O_2$ | 57.96 | 6.32 | 20.28 | 57.82 | 6.35 | 20.21 |

[a] Crystallization solvent: EtOAc. – [b] EtOH. – [c] $Et_2O$.

the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

**Crystal Data for 3a:** Colourless prism, crystal dimensions 0.22 × 0.22 × 0.24 mm, $C_{15}H_{19}N_3O_2$, $M_r$ = 273.33, triclinic, space group $P\bar{1}$ (no. 2), lattice parameters: $a$ = 9.3236(7), $b$ = 10.9107(11), $c$ = 7.0517(7) Å, $\alpha$ = 106.352(8), $\beta$ = 108.014(7), $\gamma$ = 75.915(7)°, $Z$ = 2, $V$ = 644.92(10) Å$^3$, $D_c$ = 1.408 g/cm$^3$, $\mu$(Mo-$K_\alpha$) = 0.096 mm$^{-1}$, $F$(000) = 292, $T$ = 294 K.

**Crystal Data for 3b:** Colourless plate, crystal dimensions 0.22 × 0.30 × 0.32 mm, $C_{15}H_{19}N_3O_2$, $M_r$ = 273.33, triclinic, space group $P\bar{1}$ (no. 2), lattice parameters: $a$ = 11.475(3), $b$ = 12.929(5), $c$ = 10.087(2) Å, $\alpha$ = 103.78(2), $\beta$ = 113.222(17), $\gamma$ = 74.38(2)°, $Z$ = 4, $V$ = 1309.7(6) Å$^3$, $D_c$ = 1.386 g/cm$^3$, $\mu$(Mo-$K_\alpha$) = 0.094 mm$^{-1}$, $F$(000) = 584, $T$ = 294 K.

**Di-*endo*- and Di-*exo*-norbornene-Condensed 9-Amino-1,9-diazatricyclo[6.4.0.0$^{4,8}$]dodecane-2,10-diones 3a and 3b:** A mixture of di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazide (**1a** or **1b**) [2d] (3.0 g, 18 mmol), ethyl 2-(2-oxocyclopentyl)acetate (**2**) (3.06 g, 18 mmol), and PTSA (0.05 g) in toluene (50 mL) was refluxed for 12 h, with a Dean–Stark apparatus being applied. After evaporation of the solvent, the residue was dissolved in $CHCl_3$ (20 mL), transferred to a silica gel column (Merck 60 silica gel, 230–400 mesh ASTM) and eluted with EtOAc/*n*-hexane (2:1) and then with EtOAc. In the case of **1a**, the first eluates contained **3a** (yield 0.73 g, 15%), while the later ones contained **4a** (yield 1.9 g, 39%); the first eluates from **1b** contained **5** [yield 0.72 g, 29% (ref.[3] m.p. 144–146 °C)] and the later ones **3b** together with **4b**. On crystallization of the residues of the eluates from EtOH, **3b** separated first (yield 0.6 g, 12%); **4b** (yield 1.23 g, 25%) mostly remained in the mother liquor and could be crystallized from EtOAc. Physical and analytical data on **3a**, **3b**, **4a**, and **4b** are listed in Table 3.

**9-Amino-1,9-diazatricyclo[6.4.0.0$^{4,8}$]dodec-11-ene-2,10-dione (6):** Compound **3a** or **3b** (0.27 g, 1 mmol) was heated in a bath of Wood alloy at 250–260 °C (**3a**) for 5 min or at 270–275 °C (**3b**) for 10 min. The products were dissolved in $CHCl_3$ (5 mL) and chromatographed on a silica gel column, using EtOAc/*n*-hexane (2:1) as eluent. After concentration, **6** could be crystallized; yield 0.17 g, (83%).

## Acknowledgments

The authors are indebted to Mrs. E. Csiszár-Makra for typing the manuscript. Grants OTKA T 25415, T 029651 and FKFP 0200/2000.

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Received March 16, 2001
[O01125]

# VII

HETEROCYCLES, Vol. 57, No. 12, 2002, pp. 2309 - 2320, Received, 2nd September, 2002

# ISOMERIZATION AND APPLICATION OF AROYLNORBORNENE-CARBOXYLIC ACIDS FOR STEREOSELECTIVE PREPARATION OF HETEROCYCLES

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*Abstract* – When boiled in acidic or basic solution, *diendo*-3-aroylbicyclo[2.2.1]heptane-2-carboxylic acids (**1** and **1a**) isomerize to *exo*-3-aroylbicyclo[2.2.1]heptane-*endo*-2-carboxylic acids (**2** and **2a**). Similar *endo* → *exo* and even *exo* → *endo* isomerization of the aroyl group occurred when the Diels-Alder product containing a mixture of 3-*exo*-*p*-toluoylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (**4**) and 3-*endo*-*p*-toluoylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (**5**) was reacted with bifunctional reagents: *o*-aminothiophenol, 3-amino-1-propanol, 1,4-diaminobutane or *diexo*-3-hydroxymethylbicyclo[2.2.1]heptane-2-amine. All the reactions yielded mixtures of norbornene *diendo*- and *diexo*-fused heterocycles (**6**) and (**7**, **8** and **10**, **9** and **11**, or **12** and **13**), which were separated and whose structures were established by means of IR, $^{1}$H- and $^{13}$C-NMR spectroscopy, with DIFFNOE, 2D-COSY, DEPT, HMQC and HMBC measurements.

From *diendo*-3-aroylbicyclo[2.2.1]heptane- or -heptene-2-carboxylic acids, we earlier synthesized several heterocyclic compounds and observed that the products formed generally contained the *diendo* structural moiety, *i.e.* the *diendo* configuration of the starting norbornane/ene synthon remained unchanged.[1-3] In a

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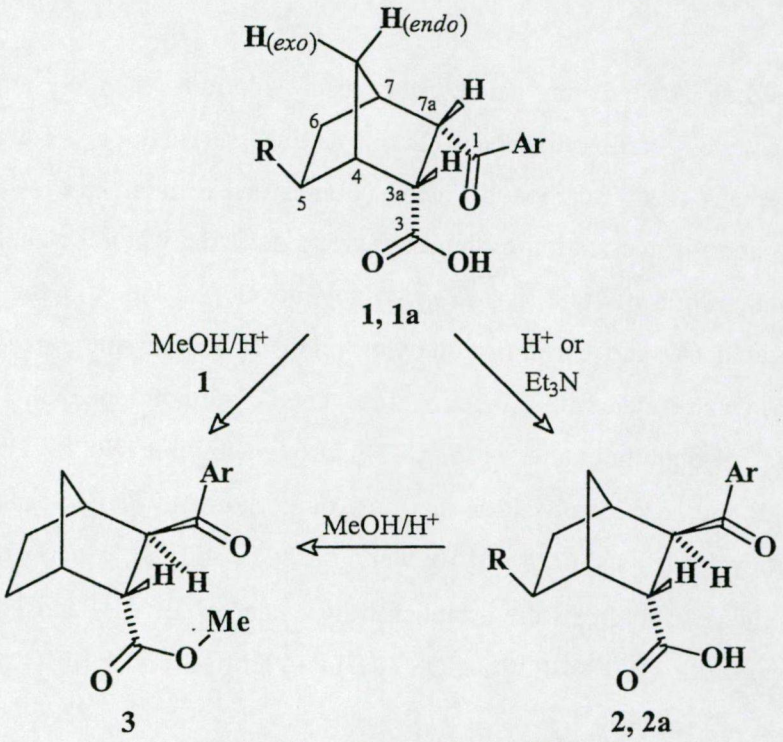
few cases, however, the configuration of the product was *exo–endo*[4] or *diexo*, the latter together with the *diendo*-fused heterocycle, as found in the cyclization of 6-phenyl-3-benzoylnorbornane-2-carboxylic acid (**1a**) with ethylenediamine.[5] These phenomena were of considerable interest; only a few studies have dealt with the similar epimerization of *diendo* norbornane derivatives.[6-8] As isomerization was recently reported in the syntheses of heterocycles from aroylnorbornanecarboxylic acids,[9] we have searched for new examples in order to study this behavior and to exploit it for the stereoselective preparation of new heterocycles.

RESULTS

When refluxed for 2 h in the presence of 2 drops of concentrated HCl or $Et_3N$ in toluene, *diendo*-3-toluoylbicyclo[2.2.1]heptane-2-carboxylic acid (**1**) or its 6-*exo*-phenyl derivative (**1a**) was smoothly transformed to give the corresponding 3-*exo*-aroylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**2** or **2a**) in good yield (Scheme 1). (For comparison of the analogous spectroscopic data, the numbering to be seen in Schemes 1 and 2 have been used in this section on the Scheme and in the Tables.)




**1, 2**: R = H, **1a, 2a**: R = Ph

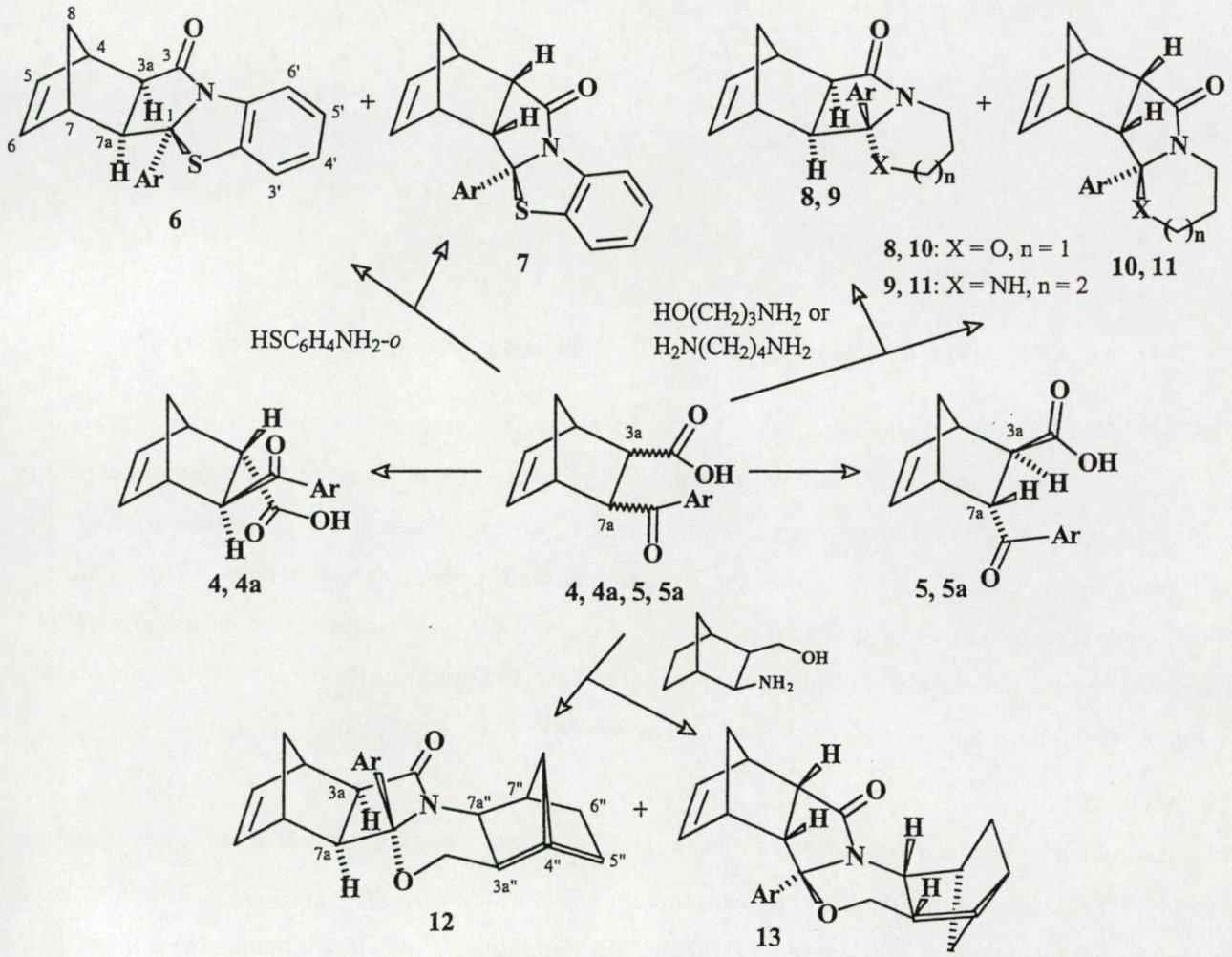
Ar = $C_6H_4CH_3$-*p*

Scheme 1

A similar *endo* → *exo* epimerization takes place in the esterification of **1** to the 3-*exo*-toluoyl derivative (**3**). For analogous cyclohexane derivatives, facile epimerization has frequently been observed, *cis*-aroyl-cyclohexanecarboxylic acids giving *trans* compounds.[10] However, the norbornane skeleton has higher

rigidity, and hence the configuration of the starting compound is generally retained in the product. Thus, few examples of the epimerization of carbons C-2–C-3 are to be found in the literature. Craig described a reversible *diendo* → *diexo* isomerization: when heated above the melting point, *diendo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride was transformed to the *diexo* analogue.[6] This change was due to the presence of the double bond in position 4 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.

To utilize this isomerization for synthetic purposes, a mixture of the isomers of the Diels-Alder adduct of *trans*-toluoylacrylic acid and cyclopentadiene[11,12] (**4**) and (**5**) was applied (Scheme 2). HPLC revealed that the ratio **4** : **5** was 57 : 43. This mixture and that of the phenyl analogues (**4a**) and (**5a**) were separated by column chromatography and the structures were established by means of NMR spectral measurements and, for **4**, also by X-Ray analysis (Figure). The results demonstrated that, in agreement with the literature,[11] **4** and **4a** contain *endo*-carboxyl and *exo*-aroyl, and **5** and **5a** *exo*-carboxyl and *endo*-aroyl groups.




Scheme 2

A mixture of **4** and **5** was reacted with the bifunctional agents *o*-aminothiophenol, 3-amino-1-propanol, 1,4-diaminobutane and *diexo*-3-hydroxymethylbicyclo[2.2.1]hept-5-en-2-amine to afford mixtures of *diexo* and *diendo* isomeric heterocyclic compounds: methanoisoindolobenzthiazoles (**6**) and (**7**), methano[1,3]oxazinoisoindoles (**8**) and **10**, methanodiazepinoisoindoles (**9**) and (**11**)[9] and methanoisoindolomethano[3,1]benzoxazines (**12**) and (**13**). The isomers were separated by column chromatography.

For the products (**9**) and (**11**), HPLC separation showed that the ratio **9** : **11** was 42 : 58. Comparison of this with the ratio of 57 : 43 for **4** : **5** suggests that the aroyl group epimerizes: in these cyclizations, either the *exo* aroyl (**4**) gives the *diendo* (**11**), or the *endo* aroyl (**5**) gives the *diexo* derivative (**9**).

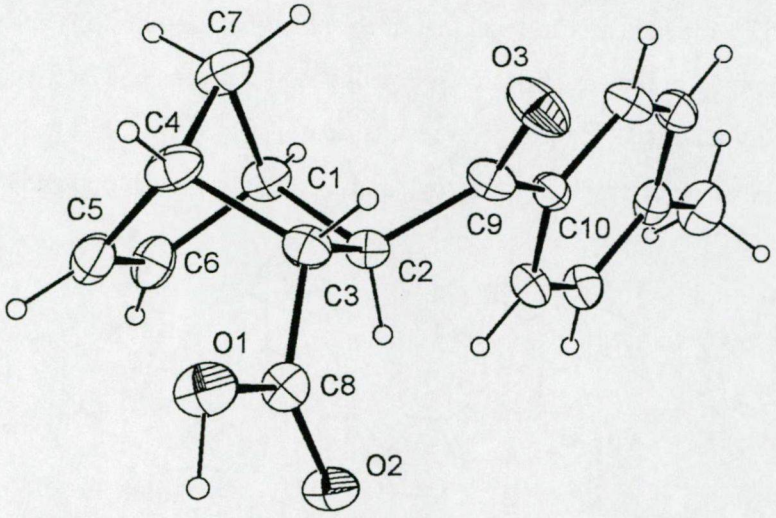



Figure 1

An ORTEP perspective view of compound (**4**). The ellipsoids are drawn at 20% probability

These reactions allow the conclusion that aroylnorbornanecarboxylic acids containing the two vicinal (2,3) functional groups in sterically unfavorable 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. The reactions of the readily available *trans*-aroylacrylic acid–cyclopentadiene adduct, containing a mixture of the aroyl group *exo* or *endo* to the *endo* or *exo*-carboxyl group, with bifunctional reagents (amino alcohols, diamines, etc.) provide good possibilities for stereoselective synthesis, but the two (*endo–endo* or *exo–exo*) fused derivatives have to be separated.

## STRUCTURE

The constitutions of the new compounds follow straightforwardly from the spectral data (Tables 1 and 2) and only the stereostructures need to be determined. Our 'splitting rule',[13,14] for the H-3a,7a signals in the spectra of heterocycle-3a,7a-fused norbornane/ene derivatives predicts a doublet (*d*) split of the signals of these hydrogens in the *exo* position, and double doublet (*dd*) multiplicity in the event of their *endo* orientation. The doublet split (8-9 Hz) is due to the H-3a,7a-coupling (dihedral angle, $\Theta = 0°$), the

further split to double doublet is the result of the H-7,7a- and H-3a,4-couplings, respectively, which are about 3-4 Hz in *diendo* compounds ($\Theta \approx 30°$) and < 1 Hz in *diexo* analogues ($\Theta \approx 90°$) in accordance to the Karplus relation. For *exo–endo* substituted non-condensed derivatives such as **2-5**, however, this rule is to be modified. The H-3a,7a- (*exo–endo*-) coupling is here significant smaller ($\Theta \approx 110\text{-}120°$) and, hence a doublet and a triplet multiplicity split by 3-5 Hz is to be expected.

Table 1. Characteristic IR abrorptions and $^1$H-NMR spectral data[b] for compounds (**2, 2a, 3, 4, 4a, 5, 5a**) and (**6-13**)[c]

| Com-pound | νOH/νNH band | νC=O ketone | νC=O band | $\gamma C_{Ar}H$ tolyl | $CH_3$[d] *s* (3H) | H-3a (1H)[e] | H-4 ~*s* (1H) | H-5 (1H)[f] | H-6 (1H)[f] | H-7 ~*s* (1H) | H-7a (1H)[g] | $CH_2$(8) 2×*d* (2×1H)[h] | | H-2,6 tolyl | H-3,5 group[i] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **2** | 3300-2500 | 1672 | 1698 | 857 | 2.41 | ~3.65[j] | 2.74 | ~1.5 | | 2.46 | ~3.65[j] | 1.24 | 1.57 | 7.89 | 7.26 |
| **2a** | 3300-2500 | 1679 | 1700 | 820 | 2.42 | 3.80 | 2.90[k] | 3.07[l] | 1.92[m] | 2.59[k] | 3.78 | 1.55 | | 7.93 | 7.27 |
| **3** | – | 1670 | 1730 | 823 | 2.38 | 3.55 | 2.66 | 1.35[m] | 1.57[m] | 2.44 | 3.67 | 1.19 | 1.53 | 7.88 | 7.28 |
| **4** | 3300-2500 | 1673 | 1702 | 822 | 2.42 | 3.73 | 3.34 | 6.23 | 6.42 | 3.04 | 3.59 | 1.42[n] | 1.68 | 7.92 | 7.27 |
| **4a** | 3300-2500 | 1674 | 1696 | 762 | 7.58 | 3.75 | 3.36 | 6.24 | 6.43 | 3.06 | 3.62 | 1.43[n] | 1.68 | 8.02 | 7.48 |
| **5** | 3300-2500 | 1669 | 1699 | 805 | 2.42 | 3.10 | 3.32 | 6.32 | 5.82 | 3.28 | 4.27 | 1.52 | 1.82 | 7.90 | 7.27 |
| **5a** | 3300-2500 | 1683 | 1697 | 763 | 7.58 | 3.11 | 3.30 | 6.33 | 5.83 | 3.33 | 4.30 | 1.54 | 1.82 | 7.79 | 7.48 |
| **6** | – | – | 1718 | 850 | 2.33 | 3.15 | 3.30 | 6.28 | 6.16 | 2.43 | 3.11 | 1.26[n] | 1.44 | ~7.6 | 7.25 |
| **7** | – | – | 1722 | 831 | 2.29 | 3.70 | 3.32 | 6.14 | 5.04 | 2.88 | 3.85 | 1.46 | 1.51 | ~7.1 | ~7.1 |
| **8** | – | – | 1695 | 820 | 2.33 | 2.66 | 3.11 | 6.09 | 5.94 | 1.77 | 2.23 | 1.03 | 1.28 | 7.38 | 7.25 |
| **9** | 3310 | – | 1666 | 823 | ~2.33[j] | 2.58 | 3.14 | 6.12 | 6.00 | 2.07 | ~2.34[j] | 0.97 | 1.13 | 7.55 | 7.23 |
| **10** | – | – | 1695 | 819 | | 3.31 | 3.16 | 5.99 | 5.33 | 2.35 | 2.98 | 1.27 | 1.34 | 7.38 | 7.20 |
| **11** | 3307 3286 | – | 1660 | 821 | 2.34 | 3.24 | ~3.12[j] | 5.96 | 4.77 | 2.63 | ~3.12[j] | 1.34 | 1.37 | ~7.5 | ~7.1 |
| **12** | – | – | 1693 | 827 | 2.39 | 2.28 | 3.19 | 6.15 | 5.98 | 2.28 | 2.67 | 1.08[n] | 1.29 | 7.38 | 7.27 |
| | | | | | | 4.14 | 1.74 | 1.10[o] | 1.45[p] | 1.67 | 2.04 | 0.72 | 0.82[n] | 7.20 | 7.12 |
| **13** | – | – | 1692 | 825 | 2.40 | 3.34 | 3.20 | 6.10 | 5.27 | 2.38 | 3.09 | 1.36 | 1.41 | 7.16 | 7.07 |
| | | | | | | 4.03 | 2.30 | 1.10[o] | 1.45[p] | 1.65 | 1.99 | 0.76 | 0.93 | 7.40 | 7.23 |

Further $^1$H-NMR spectral data, ppm: $OCH_3$, s (3H): 3.65 (**3**), $CONCH_2$, *dt* and *dd* (*J* = 13.2, 3.6, 5.3): 3.02, 4.10 (**8**), 3.01, 4.02 (**10**), ~*t* and ~*d* (*J* = 13.7): 2.73, 4.02 (**9**), 2.73, 3.97 (**11**); $OCH_2$/$HNCH_2$, *dt* and *dd*: 3.62 and 3.70 (*J* = 12.0, 3.6, 5.3, **8**), 3.46 and 3.61 (*J* = 12.1, 2.4, 4.6, **10**), ~*t* and ~*d* (*J* = 14.5): 2.46 and 2.98 (**9**), 2.51 and 2.98 (**11**), *dd* and *dd* (**12**): 3.39 (*J* = 12.3, 10.8) and 3.89 (*J* = 12.3, 8.9), *dd* and *t* (**13**): 3.78 (*J* = 12.4, 8.6) and 3.25 (*J* = 11.8); $CCH_2C$/$(CONCH_2)CH_2$: 1.19 and 1.84 (**8**), ~1.5 and ~1.85 (**9**), 1.14 and 1.75 (**10**), 1.48 and ~1.8 (**11**); $(O/NHCH_2)CH_2$: ~1.1 and ~1.8 (**9, 11**); Phenyl group (Pos. 5 in **2a**): 7.22 *d* (*J* = 7.4, 2H), 7.29 *t* (2H) and 7.18 t (1H); Condensed benzene ring (**6** and **7**), 3'-H, d: 7.63 and 7.54, 4'-H, t: 7.17 and 7.12, 5'-H, t: 7.09 and 7.04, 6'-H, d: 7.12 and 7.06. [a]In KBr discs ($cm^{-1}$); [b]In $CDCl_3$ solution at 500 MHz. Chemical shifts in ppm ($\delta_{TMS}$ = 0 ppm); coupling constants in Hz; [c]Assignments were supported by HMQC for **4b**, **5a** and **12** 2D-COSY and for **2, 2a, 3, 4, 4a, 9** and **11** also by DNOE measurements; [d]H-4 (tolyl), *t* (1H) for **4a** and **5a**; [e]Multiplicity, *J* = ~*qa*, 4.8 (**2a**), ~*dt* (**3**), *t*, 4.1 (**4, 4a**), *d*, 4.2 (**5**), 3.2 (**5a**), 7.9 (**8**), 8.5 (**9** and **12,** norbornene), 9.0 (**13,** norbornane), *dd*, 8.2 and 1.1 (**6**), 9.1 and 4.9 (**7** and **10**), 9.1. and ~1 (**12,** norbornane), 9.8 and 4.8 (**13,** norbornene); [f]For norbornenes 2 x *dd* (*J* = 5.5 ± 0.1 and 2.9 ± 0.3), for norbornanes 1-3 m (total intensity: 4H); Coalesced signal (4H) for **2**; [g]Multiplicity, *J* = *t*, 5.6 (**2a**), 4.0 (**5, 5a**), *d*, 5.3 (**3**), 8.2 (**6**), 7.1 (**8**), *dd*, 4.3 and 1.0 (**4, 4a**), 9.3 and 3.8 (**7**), 9.0 and 3.8 (**10**), 9.6 and 4.6 (**11**), 9.8 and 3.9 (**13,** norbornene), *td*, 8.6, 1.3 and 1.3 (**12,** norbornene), *qa*, 9.7 (**12, 13,** norbornane); [h]*J* = 10.0 (**2, 3**), 8.8 (**4, 4a**), 8.5 (**5, 5a, 7**), 9.2 (**6, 8, 9, 12,** norbornane), 8.2 (**10, 11, 13,** norbornene), 10.5 (**12, 13,** norbornane), coalesced for **2a**. δH(*endo*) > δH(*exo*) as proved by NOE's for **2, 2a, 3, 4, 4a** and **9** (reversed for **11**); [i]2 × ~*d* (2 × 2H), *J* = 8.1 ± 0.1. For **4a** and **5a** H-3',5', ~*t* (2H). Due to the hindered rotation of the tolyl group, the H-2,6 and H-3,5 signals are separated (**6-13**), for **6, 7** and **11** also broadened and in cases **7** and **11** coalesced. Further *d*'s at ~6.97 and ~7.1 (**6**), 6.98 and 7.12 (**8**), 6.90 and 7.07 (**9**), 6.92 and 7.06 (**10**), 6.75 (**11**). The counterparts of split signals of **12** and **13** are given in the second row in the Table; [j]Overlapping signals. [k]*d*, *J* = 5.6. [l]*dd* (1H), *J* = 8.6 and 5.8; [m]Intensity 1H. Other signals [m (1H)] of the methylene group for **2a** at 2.15 (Pos. 6) and for **3** at 1.48 (Pos. 5) and 1.62 (Pos.6); [n]Due to W-type long-range couplings, further split by 1.5 0.1 to *qad* (**4, 4a**) or *td* (**6, 12**); [o/p]Intensity 1H/3H.

To determine the *exo* or *endo* position of the substituents in **2a, 3, 4** and **4a** unanimously, DIFFNOE measurements[15a,16] were applied (Table 3). The *exo–endo* arrangement of the 3a,7a substituents is probable from the different splitting patterns (*d* and *t*) and the values of the coupling constants (Table 1), while the *endo* orientation of the 3-carboxyl group in **4** and **4a** is proved by the Overhauser effect (NOE[17]) between one of the bridging methylene-H atoms and H-3a (*cf.* Table 3). The same NOE is also proof of the analogous stereostructure of **3**.

Table 2. $^{13}$C-NMR chemical shifts[a] for compounds (**2, 2a, 3, 4, 4a, 5, 5a**) and (**6-13**)[b,c]

| Com-pound | $CH_3$ | C-1 | C-3 | C-3a | C-4 | C-5 | C-6 | C-7 | C-7a | C-8 | C-1' | C-2'6' | C-3'5' | C-4' |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | norbornane/ene | | | | | | 1-toluoyl/phenyl group | | | |
| **2** | 22.0 | 199.6 | 179.9 | 47.6 | 40.5 | 25.1 | 29.8 | 43.6 | 51.7 | 37.8 | 134.0 | 129.2 | 129.7 | 144.2 |
| **2a** | 22.0 | 199.4 | 179.0 | 48.1 | 46.8 | 42.4 | 38.3 | 44.1 | 51.3 | 35.3 | 134.0 | 129.2 | 129.8 | 144.4 |
| **3** | 22.0 | 199.8 | 174.8 | 47.7 | 40.5 | 25.1 | 29.7 | 43.4 | 51.9 | 37.8 | 134.1 | 129.2 | 129.6 | 144.1 |
| **4** | 22.0 | 199.6 | 180.2 | 47.0 | 46.2 | 136.4 | 138.0 | 49.1 | 50.4 | 47.1 | 134.4 | 129.1 | 129.8 | 144.4 |
| **4a** | – | 200.0 | 180.1 | 47.0 | 46.2 | 136.4 | 138.0 | 49.1 | 50.6 | 47.1 | 136.8 | 129.0 | 129.1 | 133.6 |
| **5** | 22.1 | 198.6 | 181.0 | 46.1 | 48.4 | 137.8 | 134.2 | 48.6 | 51.5 | 48.5 | 134.6 | 128.9 | 129.7 | 144.3 |
| **5a** | – | 199.0 | 181.1 | 46.1 | 48.3 | 137.8 | 134.1 | 48.6 | 51.7 | 48.5 | 137.1 | 128.8 | 129.1 | 133.5 |
| **6** | 21.5 | 87.7 | 178.1 | 49.9 | 45.3 | 139.23 | 138.4 | 46.2 | 53.7 | 44.0 | 137.9 | ~125.1[d] | ~128.3[d] | 139.20 |
| **7** | 21.5 | 86.7 | 178.3 | 50.4 | 45.8 | 134.9 | 135.8 | 47.2 | 53.6 | 52.0 | 137.7 | ~126.3[d] | ~128.6[d] | 141.1 |
| **8** | 21.6 | 95.2 | 178.0 | 49.9 | 44.4 | 138.61 | 138.57 | 45.1 | 53.0 | 43.5 | 134.3 | 127.9 | 129.1 | 138.4 |
| **9** | 21.4 | 84.7 | 176.7 | 51.1 | 44.4 | 138.9 | 138.5 | 46.5 | 54.4 | 43.8 | 137.8 | 126.0[d] | 128.4[d] | 138.8 |
| **10** | 21.6 | 94.3 | 178.2 | 49.9 | 45.0[e] | 134.5 | 135.5 | 45.1[e] | 53.3 | 52.5 | 135.3 | 127.9[d] | 128.2[d] | 138.4 |
| **11** | 21.4 | 84.2 | 176.9 | 51.6 | 44.5 | 134.0 | 136.6 | 47.0 | 54.8 | 52.5 | 137.9 | ~127.7[d] | ~127.7[d] | 140.4 |
| **12**[f] | 21.6 | 94.7 | 180.0 | 42.8 | 44.2 | 138.8 | 138.6 | 54.0 | 49.5 | 43.9 | 136.2 | 129.9 | 128.4 | 138.3 |
| | | | 64.5 | 39.2 | 39.5 | 27.5 | 30.5 | 45.7 | 56.5 | 35.5 | | 127.4 | 128.7 | |
| **13**[f] | 21.6 | 94.2 | 180.4 | 49.9 | 44.9 | 134.4 | 136.3 | 45.9 | 54.8 | 51.3 | 138.5 | 127.6 | 127.4 | 137.5 |
| | | | 64.1 | 39.5 | 39.3 | 27.6 | 30.6 | 42.9 | 56.9 | 35.7 | | 130.8 | 129.4 | |

[a]In ppm ($\delta_{TMS}$ = 0 ppm) at 125.7 MHz. Solvent: $CDCl_3$; [b]Assignments were supported by DEPT, HMQC and for **4, 4a, 5, 5a, 6, 12** and **13** also by HMBC measurements; [c]Further lines: $OCH_3$: 52.1 (**3**); $CONCH_2$: 37.8 (**8**), 41.9 (**9**), 37.9 (**10**) and 42.1 (**11**); $OCH_2$/$HNCH_2$: 62.7 (**8**), 42.6 (**9, 11**), 62.3 (**10**), 64.5 (**12**), 64.1 (**13**); $CCH_2C$/$(CONCH_2)CH_2$: 25.8 (**8**), 24.7 (**9**), 25.9 (**10**) and 24.9 (**11**); $(O/NHCH_2)CH_2$: 33.1 (**9, 11**); phenyl group (Pos. 5 in **2a**)/condensed benzene ring (**6** and **7**), C–1: 145.6 (**2a**), 133.9 (**6**), 133.3 (**7**); C-2,6/C-2: 127.5 (**2a**), 138.6 (**6**), 138.8 (**7**); C-3,5/C-3: 128.8 (**2a**), 120.6 (**6**), 120.2 (**7**); C-4: 126.3 (**2a**), 125.1 (**6**), 125.7 (**7**); C-5: 127.5 (**6**), 127.3 (**7**); C-6: 123.2 (**6**), 123.3 (**7**); [d]Due to hindered rotation of the aryl group, the C-2,6 and similarly the C-3,5 line pairs are separated (**6, 8, 9, 10, 12** and **13**), for **6** also broadened and for **7** and **11** coalesced. Further lines at ~127.9 and ~129.7 (**6**), 127.6 and 130.7 (**8**), 128.3 and 130.2 (**9**), 129.6 and 130.2 (**10**). The counterparts of the split signal pairs of **12** and **13** are given in the second row; [e]Interchangeable assignments; [f]Data in the first and second rows in columns 4-11 refer to norbornene and norbornane moieties, respectively.

The DIFFNOE measurements confirm the steric closeness of the 5-phenyl and bridging methylene groups (saturation of the signal of the latter group led to an enhanced intensity of the former), and consequently the *exo* position of the 5-phenyl ring in **2a**.

Because of the fully overlapping H-3a,7a signals in **2** and **2a**, the steric arrangements of the 3a,7a-substituents could be not established by NOE. However, the practically identical $^1$H and $^{13}$C chemical

shifts of C-3a,7a and H-3a,7a for **2** and **2a** proved the same stereostructure *i.e. endo*-carboxyl *exo*-aroyl substitution for **2** and **2a**.

In **5** and **5a**, the aroyl and carboxyl substituents must have a different *exo–endo* orientation because of the different multiplicities of the H-3a and H-7a signals (one is *d*, while the other is *t*). On comparison with **4** and **4a**, the reversed positions of these substituents reveal significantly different H-8 shifts (1.42 and 1.68 ppm for the latter; 1.53 and 1.82 ppm for **5** and **5a**). Similarly, the H-3a,7a shifts differ. Because of the α-effect,[15b] which causes a higher downfield shift of the signal of the *endo* aroyl group (relative to the carbonyl in **4** and **4a**), the δH(*exo*) > δH(*endo*) difference in norbornene[13,14,18,19] becomes moderate, while for **5** and **5a**, the aroyl group increases the shift in the *ab ovo* downfield-shifted geminal H-7a signal and, simultaneously, the chemical shift of the upfield-positioned H-3a signal will be increased to a smaller extent by the carbonyl group. Consequently, the shift difference ΔδH-3a,7a is significantly larger in **5** and **5a** (1.17 and 1.19 ppm) than in **4** and **4a** (0.14 and 0.13 ppm).

In the pyrrolidone-fused compounds (**6-13**), 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, in accordance with our splitting rule.[13,14] Thus, in **6, 8, 9** and **12**, the norbornene and the fused hetero ring are *diexo*, while in **7, 10, 11** and **13** they are *diendo*.

In the pairs **6** and **7**, **8** and **10**, and **9** and **11**, the C-1 configuration, *i.e.* the position of the aryl group, is to be determined. For **7**, 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 **6**, due to the anisotropic shielding[15c] of the close-lying tolyl group. This means the *trans* arrangement of H-7a and the tolyl group relative to the pyrrolidone ring.

Table 3. DIFFNOE experiments with compounds (**2a, 3, 4, 4a, 9**) and (**11**)[a]

| Saturated signal | Responding signals | | | | | |
|---|---|---|---|---|---|---|
| | H-3a | H-4 | H-7a | $NCH_2$[b] | H(*ortho*) (phenyl) | H(*ortho*) (tolyl) |
| H-5 | | **2a** | | | **2a** | |
| H-7 | | | **2a, 4a** | | | **2a, 4, 4a** |
| H-7a | | | | **9, 11** | | **4a** |
| H-8(*endo*)[c] | **3**,[d] **4, 4a** | | **3**[c] | | **2a** | **9** |
| ArH(*ortho*) | **3, 4** | **3** | | | | |

[a]Interacting pairs showing only trivial effects (NOE between the geminal or vicinal hydrogens) are not included in this Table. Only responses relevant for the stereostructures or dubious assignments are given; [b]One H in both group; [c]For **2a**, *exo* and *endo* H-8 give overlapping signals (*cf.* Table 1) and the response of the H(*ortho*) signal (phenyl) in **2a** is due to an effect with the H-8(*exo*) atom; [d]Inverse experiments were carried out: H-3a was irradiated when the H-8(*endo*) signal responded.

The similarly strong shielding of H-6 in **11** (4.77 ppm) and **10** (5.33 ppm) suggests the analogous stereostructure, and for the former compound this structure was directly confirmed by DIFFNOE measure-

ments: H-7a and the *N*-methylene hydrogens in the diazepine ring were found to be sterically close (on irradiation of one of these signals, an increased intensity was observed for the other one; *cf.* Table 3).

In **9**, 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[15c] leads to an upfield shift of the H-8(*endo*) signal (*d*, 1.13 ppm) in **9**, while for **11** the analogous shift is 1.34 ppm. A similar effect was observed, and hence the analogous stereostructure is presumed for **8** [δH-8(*endo*): 1.03 ppm]. The absence of such a strong shielding in **6** suggests 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 pyrolidone ring.

Compounds (**12**) and (**13**) have the most complicated structures, including 9 centres of chirality. Discounting the 4 with fixed configurations, 16 diastereomers remain to be considered. On the basis of the splitting rule, the doublet split of the annelational hydrogens H-3a" and H-7a" indicates the *diexo* annelation of the norbornane in both **12** and **13**. For the same reason, the norbornene is *diexo* in **12** (the H-3a,7a signals are *d*'s) and *diendo* in **13** (the above signals are *dd*'s). Thus, for **12** and **13**, among the remaining 4, the true stereostructures have to be selected. The significant upfield shift of the H-6 signal in **13** (5.27 ppm) originates from the anisotropic shielding of the close-lying aromatic ring[15c] and points to the *endo* position of the tolyl group. As concerns the position of the tolyl group and the *diexo*-norbornane relative to the oxazine ring, the spectral data on **13** are practically identical with those of the compound where a phenyl-substituted cyclohexane-fused ring is present instead of norbornene;[20] this confirms that the tolyl group and the bridging methylene in norbornane lie on the same side of the skeleton. This is valid for both **13** and **12**. The most important supporting facts are the shifts of H-3a",7a" (1.99 and 4.03 ppm in **13** and 1.99 and 4.16 ppm for the cyclohexane-fused homologue[20] respectively, while for the isomeric counterpart containing the tolyl and bridging methylene on the opposite side, 2.15 and 3.80 ppm were measured). The practically identical chemical shifts of H-3a,7a in **12** (2.28 and 2.67 ppm) and **8** (2.23 and 2.66 ppm) suggest the close-lying arrangement of the tolyl and bridging methylene group in the norbornene. Hence, the stereostructures given in Scheme 2 were deduced from the spectral data on the new compounds.

It should be noted that the sterically crowded structures of **6-13** lead to hindered rotation of the tolyl group, and in both the $^{1}$H- and $^{13}$C-NMR spectra the signals of the *ortho* H/C-2,6 and *meta* H/C-3,5-s gave separated or broadened signals.

## EXPERIMENTAL

The $^{1}$H- and $^{13}$C-NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at rt, on a Bruker DRX-500 spectrometer at 500.13 ($^{1}$H) or at 125.76 ($^{13}$C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker microprogram NOEMULT to generate NOE[17]

and to get DIFFNOE spectra[15a,16] were used with a selective preirradiation time. DEPT spectra[21] were run in a standard manner,[22] using only a $\Theta = 135°$ pulse to separate the $CH/CH_3$ and $CH_2$ lines phased 'up' and 'down', respectively. The 2D-COSY,[23a,24a] HMQC (≙ 2D-HSC)[23b,24b] and HMBC (≙ COLOC)[25,26] spectra were obtained by using the standard Bruker pulse programs COSY-45, INV4GSSW and INV4GSLRNDSW, respectively. IR spectra were run in KBr discs on a Bruker IFS-55 FT-spectrophotometer controlled by Opus 3.0.

X-Ray data collection and processing

Crystallographic data were collected at room temperature on a Rigaku AFC5S diffractometer with graphite-monochromated $MoK_\alpha$ ($\lambda = 0.71069$ Å) radiation. To collect intensity data, an $\omega$-$2\theta$ scan mode at an $\omega$ scan speed of 8.0°/min was applied. The weak reflections [$I < 10\sigma(I)$] were rescanned up to two times. All data were corrected for the Lorentz polarization effects. The intensities of the three check reflections showed only statistical fluctuations.

*Crystal data for* **4** ($C_{16}H_{16}O_3$, $M = 256.29$), monoclinic, $a = 20.645(2)$, $b = 7.965(3)$, $c = 16.941(3)$ Å, $\beta = 91.908(11)°$, $U = 2784.1(11)$ Å$^3$, $T = 294$ K, space group $C2/c$ (no. 15), $Z = 8$, $\mu(Mo–K_\alpha) = 0.84$ mm$^{-1}$, 2536 reflections measured, 2464 unique ($R_{int} = 0.026$) which were used in all calculations. The final $wR(F^2)$ was 0.122 (all data).

The structures were solved by direct methods (SIR92)[27] and refined by full-matrix least squares techniques on $F^2$ (SHELXL-97)[28] The heavy atoms were refined anisotropically. The phenyl and methyl hydrogen atoms were included in calculated positions with fixed isotropic temperature factors (1.2 $U_{eq}$ of the carrying atom) and the rest of hydrogen atoms were refined with isotropic temperature factors. Calculations were performed with teXsan for Windows crystallographic software.[29]

HPLC: An M-600 low-pressure system, equipped with a gradient pump and an M-486 tunable absorbance detector; Millenium software version 2.1 (Waters Chromatography, Milford, MA, USA). An injector with a 20-µl loop from Rheodyne (Cotati, USA). Column: Nova-Pak $C_{18}$, 150 × 3.9 mm I.D., 4 µm particle size (Waters Chromatography); flow rate, 0.8 ml min$^{-1}$; r.t.; detection, 254 nm. Eluent: 0.1% aqueous trifluoroacetic acid (pH~2)–MeOH = 40 : 60 (v/v) for **4** and **5**, retention times: 6.55 min (**5**) and 8.27 min (**4**); isomer ratio = 43.2 : 56.8; 1% aqueous triethylammonium acetate (pH~7)–MeOH = 45 : 55 (v/v) for **9** and **11**, retention times, 13.73 min (**11**) and 16.13 min (**9**), isomer ratio = 57.5 : 42.5.

**3-*exo*-*p*-Toluoylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (2)**

A mixture of *diendo*-3-*p*-toluoylbicyclo[2.2.1]heptane-2-carboxylic acid[30] (1.3 g, 5 mmol) and aqueous HCl (36%, 2 drops) or $Et_3N$ (2 drops) in toluene (10 mL) was refluxed for 2 h. After evaporation, the residue was crystallized.

Data on compound (**2**) are listed in Table 4.

**6-*exo*-Phenyl-3-*exo*-*p*-toluoylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (2a)**

A mixture of 6-*exo*-phenyl-3-*endo*-*p*-toluoylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid[31] (0.84 g, 2.5 mmol) and aqueous HCl (36%, 2 drops) in toluene (10 mL) was refluxed for 3 h. After evaporation, the residue was dissolved in $CHCl_3$ (5 mL) and eluted from a silica gel column (Silica gel 60, Merck, 0.040-0.063 mm) with *n*-hexane–EtOAc (4 : 1).

**Methyl 3-*exo*-*p*-toluoylbicyclo[2.2.1]heptane-2-*endo*-carboxylate (3)**

A mixture of oxocarboxylic acid (**1**) or (**2**) (1.29 g, 5 mmol) and concentrated $H_2SO_4$ (0.2 mL) in MeOH (20 mL) was refluxed for 12 h. After evaporation of the solvent, $H_2O$ (30 mL) was added and the mixture was extracted with ether (3×10 mL). After removal of the solvent, the residue was crystallized.

**Separation of the mixtures 4 and 5, and 4a and 5a**

The product obtained from *trans*-*p*-toluoylacrylic acid with cyclopentadiene[11] (1.0 g) in $CHCl_3$ (10 mL) was separated on a silica gel column with *n*-hexane–acetone–EtOH (90 : 8 : 2) as eluent. First **4** and then **5** appeared. The mixture of **4a** and **5a** was prepared analogously and separated similarly.

**8,11-Methano-11b-*p*-tolyl-7a*r*,8*c*,11*c*,11a*c*-tetrahydroisoindolo[2,3-*a*]benzthiazol-7-one (6) and 8,11-methano-11b-*p*-tolyl-7a*r*,8*t*,11*t*,11a*c*-tetrahydroisoindolo[2,3-*a*]benzthiazol-7-one (7)**

A mixture of oxocarboxylic acids (**4**) and (**5**)[11,12] (1.28 g, 5 mmol), 2-aminothiophenol (0.63 g, 5 mmol) and *p*-TsOH (0.05 g) in chlorobenzene (10 mL) was refluxed for 10 h. After evaporation, the residue was dissolved in $CH_2Cl_2$ (5 mL), transferred to a silica gel column (Silica gel 60, Merck 0.040-0.063 mm) and eluted with *n*-hexane–$CH_2Cl_2$–EtOAc (18 : 1 : 1). First **6** appeared, and then **7** [monitoring by TLC, aluminium sheets, Silica gel 60 $F_{254}$, benzene–EtOH–petroleum ether (bp 40-60 °C) 4 : 1 : 3, developed in iodine vapour]. The residues of the eluates **6** and **7** were crystallized.

**7,10-Methano-10b-*p*-tolyl-2,3,6a*r*,7*c*,10*c*,10a*c*-hexahydro[1,3]oxazino[2,3-*a*]isoindol-6-one (8) and 7,10-methano-10b-*p*-tolyl-2,3,6a*r*,7*t*,10*t*,10a*c*-hexahydro[1,3]oxazino[2,3-*a*]isoindol-6-one (10)**

A mixture of oxocarboxylic acids (**4**) and (**5**) (2.56 g, 10 mmol), 3-amino-1-propanol (1.13 g, 15 mmol) and *p*-TsOH (0.05 g) in toluene (15 mL) was refluxed for 10 h. After evaporation, the residue was chromatographed as above; eluents: *n*-hexane–EtOAc (4 : 1) for **8**, and then *n*-hexane–EtOAc (2 : 1) for **10**.

**8,11-Methano-11b-*p*-tolyl-2,3,4,5,7a*r*,8*c*,11*c*,11a*c*-octahydro[1,3]diazepino[2,3-*a*]isoindol-7-one (9) and 8,11-methano-11b-*p*-tolyl-2,3,4,5,7a*r*,8*t*,11*t*,11a*c*-octahydro[1,3]diazepino[2,3-*a*]isoindol-7-one (11)**

A mixture of oxocarboxylic acids (**4**) and (**5**) (1.28 g, 5 mmol), 1,4-diaminobutane (0.66 g, 7.5 mmol) and *p*-TsOH (0.05 g) in chlorobenzene (10 mL) was refluxed for 8 h. After evaporation, the residue was

dissolved in $CHCl_3$ (10 mL), purified and separated chromatographically as above. Elution with EtOAc–*n*-hexane (1 : 1); first **9** and then **11** appeared.

**9,12-Methano-12b-*p*-tolyl-2a*r*,3*c*,4,5,6*c*,6a*c*,8a*c*,9*c*,12*c*,12a*c*-decahydroisoindolo[2,1-*a*]-3,6-methano[3,1]benzoxazin-8-one (12) and 9,12-methano-12b-*p*-tolyl-2a*r*,3*c*,4,5,6*c*,6a*c*,8a*c*,9*t*,12*t*,12a*c*-decahydroisoindolo[2,1-*a*]-3,6-methano[3,1]benzoxazin-8-one (13)**

A mixture of oxocarboxylic acids (**4**) and (**5**) (1.28 g, 5 mmol), *diexo*-3-hydroxymethylbicyclo[2.2.1]heptane-2-amine (0.80 g, 5.7 mmol) and *p*-TsOH (0.05 g) in xylene (10 mL) was refluxed for 4 h. After evaporation, the residue was dissolved in $CH_2Cl_2$ (5 mL) and chromatographed; elution with *n*-hexane–EtOAc–$CH_2Cl_2$ (18 : 1 : 1) for **12**, and then *n*-hexane–EtOAc (4 : 1) for **13**.

Table 4. Physical and analytical data on compounds (**2-10**)

| Compound | mp °C | Yield % | Formula | Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Found % | | | Calcd % | | |
| | | | | C | H | N | C | H | N |
| **2** | 133-135[a] | 81 | $C_{16}H_{18}O_3$ | 74.32 | 7.08 | | 74.40 | 7.02 | |
| **2a** | 192-194[b] | 77 | $C_{22}H_{22}O_3$ | 78.91 | 6.75 | | 79.02 | 6.63 | |
| **3** | 74-75[c] | 78 | $C_{17}H_{20}O_3$ | 74.89 | 7.32 | | 74.97 | 7.40 | |
| **4** | 125-126[c] | | $C_{16}H_{16}O_3$ | 74.82 | 6.33 | | 74.98 | 6.29 | |
| **4a** | 141-142.5[c] | | $C_{15}H_{14}O_3$ | 74.28 | 5.84 | | 74.36 | 5.82 | |
| **5** | 127-128[a] | | $C_{16}H_{16}O_3$ | 74.85 | 6.34 | | 74.98 | 6.29 | |
| **5a** | 126-127[a] | | $C_{15}H_{14}O_3$ | 74.31 | 5.80 | | 74.36 | 5.82 | |
| **6** | 146-148[c] | 30 | $C_{22}H_{19}NOS$ | 76.52 | 5.59 | 4.01 | 76.49 | 5.54 | 4.05 |
| **7** | 207-208[b] | 45 | $C_{22}H_{19}NOS$ | 76.46 | 5.51 | 4.02 | 76.49 | 5.54 | 4.05 |
| **8** | 181-183[c] | 28 | $C_{19}H_{21}NO_2$ | 77.08 | 7.18 | 4.79 | 77.26 | 7.17 | 4.74 |
| **9** | 156-158[b] | 35 | $C_{20}H_{24}N_2O$ | 77.81 | 7.96 | 9.18 | 77.89 | 7.84 | 9.08 |
| **10** | 148.5-150[c] | 21 | $C_{19}H_{21}NO_2$ | 77.32 | 7.21 | 4.71 | 77.26 | 7.17 | 4.74 |
| **11** | 164-166[d] | 42 | $C_{20}H_{24}N_2O$ | 78.01 | 7.81 | 9.12 | 77.89 | 7.84 | 9.08 |
| **12** | 197-198[c] | 23 | $C_{24}H_{27}NO_2$ | 79.61 | 7.48 | 3.83 | 79.74 | 7.53 | 3.87 |
| **13** | 195-196[c] | 34 | $C_{24}H_{27}NO_2$ | 79.82 | 7.58 | 3.81 | 79.74 | 7.53 | 3.87 |

Crystallization solvent: [a]benzene; [b]EtOAc; [c]$Et_2O$; [d]*i*-$Pr_2O$.

ACKNOWLEDGEMENTS

The authors are indebted to Mrs. E. Csiszár Makra for the typing of the manuscript. Grants OTKA T 037204, OTKA T 29651 and FKFP 0200/2000.

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# VIII

HETEROCYCLES, Vol. 63, No. 1, 2004 , PP. 63 - 74
Received, 10th July, 2003, Accepted, 7th November, 2003, Published online, 10th November, 2003

# PREPARATION AND STRUCTURE OF *DIEXO*-OXANORBORNANE-FUSED 1,3-HETEROCYCLES

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*Dedicated to professor Gábor Bernáth on the occasion of his 70th birthday*

**Abstract** – *Via* the reaction of *diexo*-oxanorbornanedicarboxylic anhydride with toluene, the *diexo*-aroylcarboxylic acid (**3a**) was prepared, which exists partly as the tautomeric lactol (**3b**). With bifunctional reagents, **3a** yields fused heterocycles containing three–six rings. Thus, alkylenediamines result in imidazole- and 1,3-diazepine-fused oxygen-bridged isoindolones (**6a,b**), alkanolamines form the oxazole- and 1,3-oxazine-fused oxanorbornene derivatives (**7a-c**), and *o*-phenylenediamine undergoes cyclization to furnish the condensed benzimidazole (**8**). The reaction of **3a** with *diexo*-aminonorbornanecarbohydrazide yields a pyrimidopyridazine containing six condensed rings (**9**). In a similar reaction with *diendo*-aminonorbornenecarbohydrazide, cyclopentadiene cleaves off to give the tricyclic retro Diels-Alder product (**10**). The structures, and particulary the configurations at the oxanorbornane ring systems and the position of the aryl substituent, were established by means of 1D- and 2D-NMR spectroscopy and, for **3b** and **7c**, also by X-Ray measurements.

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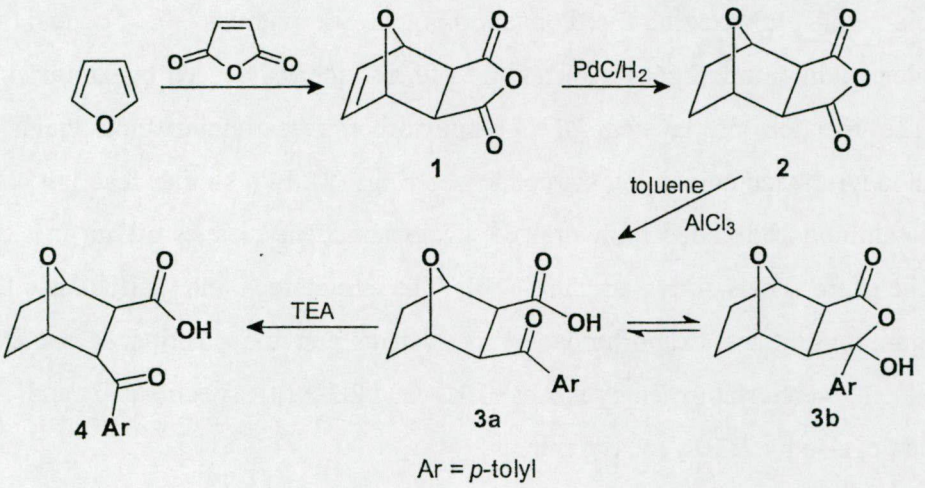
## 1. INTRODUCTION

*Diendo-* and *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids and derivatives have been used to prepare 1,3-heterocycles.[1,2] From stereoisomeric bicyclo[2.2.1]heptane-2,3-dicarboxylic anhydrides, aroylcarboxylic acids have been prepared and applied for the synthesis of new hetero compounds containing the partly saturated condensed methylene-bridged isoindolone unit.[3,4] We now extend the synthetic work to the isomeric *diexo*-oxanorbornane derivatives. The target of this activity is to prepare them from the previously unknown *diexo*-3-aroyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (**3a**) as starting compound. Besides the chemical and stereochemical features of the fused-skeleton saturated heterocycles, they are of importance from pharmacological aspects because similar compounds possess an anorectic effect and are applied in therapy.[5,6] Chiral perhydrobenzoxazines containing a furan ring earlier served as nitrogen source and chiral inductor in the stereoselective synthesis of enantiopure decahydro-isoquinolines.[7] Furan has been applied as a diene in an intramolecular Diels-Alder reaction for the synthesis of 1,4-epoxycadinane,[8] in high-pressure reactions,[9] in tandem intramolecular/radical cyclization[10] and to build an oxygen bridge into various molecules.[11]

## 2. RESULTS AND DISCUSSION

### 2.1. PREPARATIONS

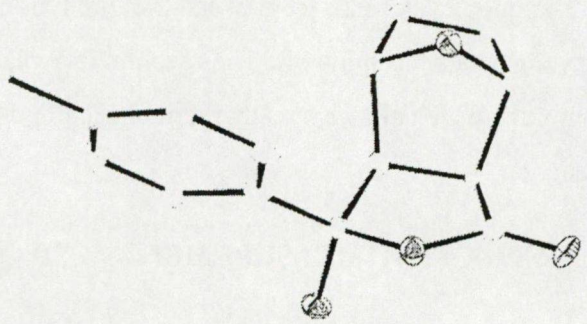
The reaction of furan with maleic acid anhydride results in 7-oxabicyclo[2.2.1]hept-5-ene-1,2-dicarboxylic anhydride (**1**),[12-14] which was reduced to the saturated derivative (**2**)[15] and then transformed with toluene/$AlCl_3$ to *diexo*-3-*p*-toluoyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (**3a**) (Scheme 1).




Scheme 1

Compound (**3a**) exists as a mixture with its cyclo tautomer (**3b**), which was isolated from the ethanolic solution and the structure proved by means of an X-Ray method (Figure 1). The lactol containing a $CCl_3$

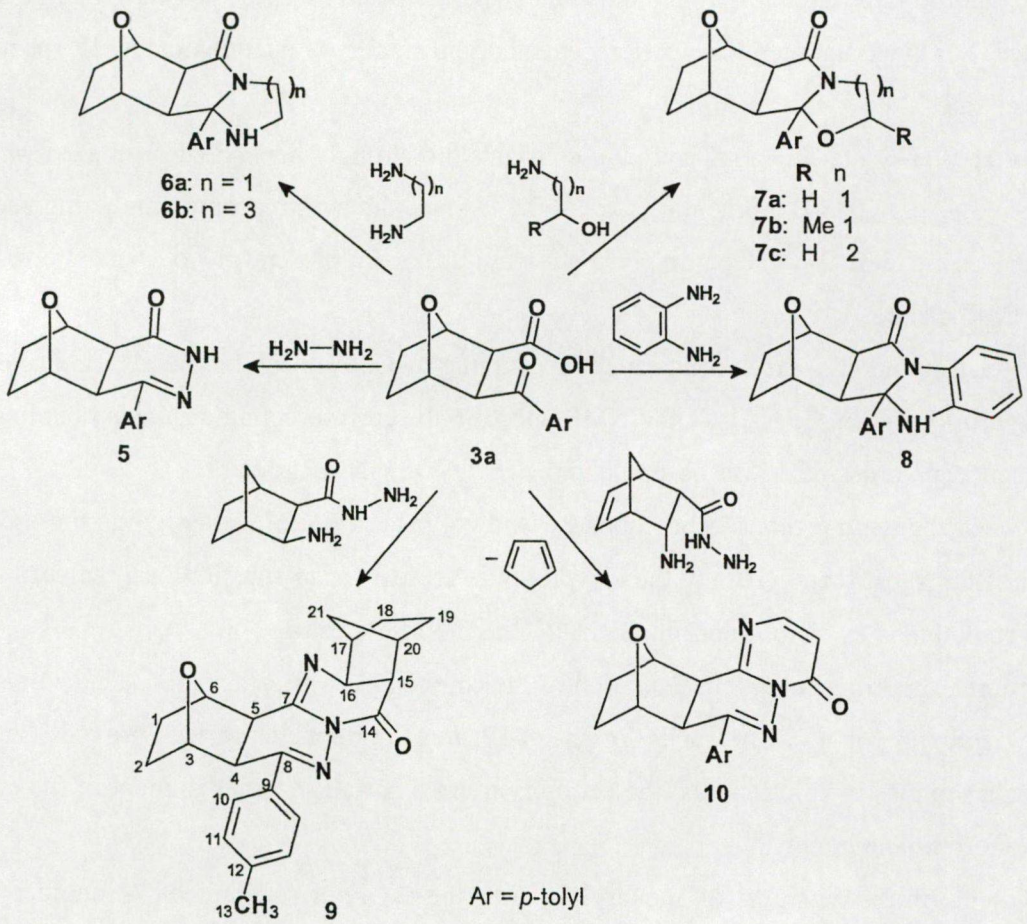
group instead of aryl were already prepared from **2** with trichloroacetate.[16] Owing to facile enolization of the aryl group, **3a** isomerizes with triethylamine to **4**.



Perspective view of **3b**. Thermal ellipsoids have been drawn at a probability level of 30%

Figure 1

From **3a** and hydrazine, the oxanorbornane-condensed pyridazinone (**5**) is formed (Scheme 2). Refluxing **3a** in toluene with ethylenediamine and 1,4-diaminobutane furnishes the tetracyclic imidazo (**6a**) and 1,3-diazepino *diexo*-condensed epoxyisoindolones (**6b**).




Scheme 2

The reactions of **3a** with aminoethanol and aminopropanols yield the oxazole- (**7a**), (**7b**) and 3,1-oxazine-fused epoxyisoindolones (**7c**), while from **3a** with phenylenediamine, the condensed pentacyclic benzimidazole (**8**) is formed.

With *diexo*-3-aminobicyclo[2.2.1]heptane-2-carbohydrazide, **3a** cyclizes to the condensed hexacyclo derivative (**9**) containing a central pyrimidopyridazine, one *diexo*-condensed norbornane and one oxanorbornane unit. In reaction with the isomeric *diendo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazide, **3a** yields the fused pyrimidopyridazine (**10**) because cyclopentadiene splits off. The reaction is explained by the presence of the double bond in the norbornane moiety, which allows a ready thermal decomposition to give cyclopentadiene and **10** in retro Diels-Alder reaction.

## 2.2. STRUCTURE DETERMINATIONS BY NMR SPECTRAL MEASUREMENTS AND QUANTUM CHEMICAL CALCULATIONS

The structures of the new compounds follow from the NMR spectroscopic data. 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 was 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 oxanorbornane skeleton in all compounds and the position of the *p*-tolyl group in **5-7**, were also established. For the assignment of this stereochemistry, a number of unequivocal NMR spectroscopic criteria are available.

(*i*) The *vicinal* H-5–H-6 and H-3–H-4 coupling constants are strongly dependent on the *exo/endo* positions of H-4,-5: $J_{\text{H-3, H-4-}exo} \sim 5$ Hz, but $J_{\text{H-3, H-4-}endo} < 0.1$ Hz (see the spectroscopic numbering used in the NMR part on **9** in Scheme 2).[17] Accordingly, H,H cross-peaks are present or not in the corresponding H,H-COSY NMR spectra.

(*ii*) Between H-1-*exo* and H-5-*exo*, a long-range W coupling of ~2.5 Hz can be found[17] (indicated by the corresponding cross-peak in the H,H-COSY NMR spectra); the corresponding *exo/endo* coupling proved negligible;[17] hence, no cross-peak was observed in the H,H-COSY NMR spectra.

(*iii*) NOE between the *endo* protons in positions 1,5 and 2,4 proved useful for assigning the *exo* or *endo* configuration of the substituents. If only the *exo* proton is present (*endo* substitution), the corresponding NOE can not be obtained as a cross-peak in the 2D NOESY NMR spectra.

With these criteria, the *exo* or *endo* configuration of the compounds was established. Thus, 4-*endo*,5-*exo* substitution was found for **4**, while for **5**, **7c** and **8-10** *diexo* 4,5-annelation was proved. Compounds (**3a,b**) exist as a mixture in solution, and the equilibrium does not allow establishment of the configuration of the oxanorbornane moiety.

For establishment of the position of the aryl in **6-8**, the NOEs was applied. 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 was really useful. The method for application the ring current effect of the nearby aromatic ring for determination of the disposition of the protons is known.[18-20] Thus, the *trans* configuration of the aryl and H-4-*endo* causes a strong shielding

effect on H-3, but in the *cis* case only a very small ring current effect on H-3 can be expected. These expectations are in complete concordance with the experimental $^1$H chemical shifts: whereas H-3 is strongly shielded (δ ~3.65 ppm) in **6b** and **7c**, obviously because of the ring current effect, the same proton resonates with the normal value (δ 4.90-5.20 ppm) in **4**, **5**, **8** and **10**. In the latter cases, the aryl substituent is remote (*trans*) from H-3, and the corresponding ring current effect therefore remains small. To confirm these conclusions from model structures, the aryl and H-4-*endo cis/trans* isomers of **7c** were *ab initio* MO calculated, and the corresponding $^1$H chemical shift of H-3 in the two isomers was determined by the GIAO method. The results are depicted in Figure 2.

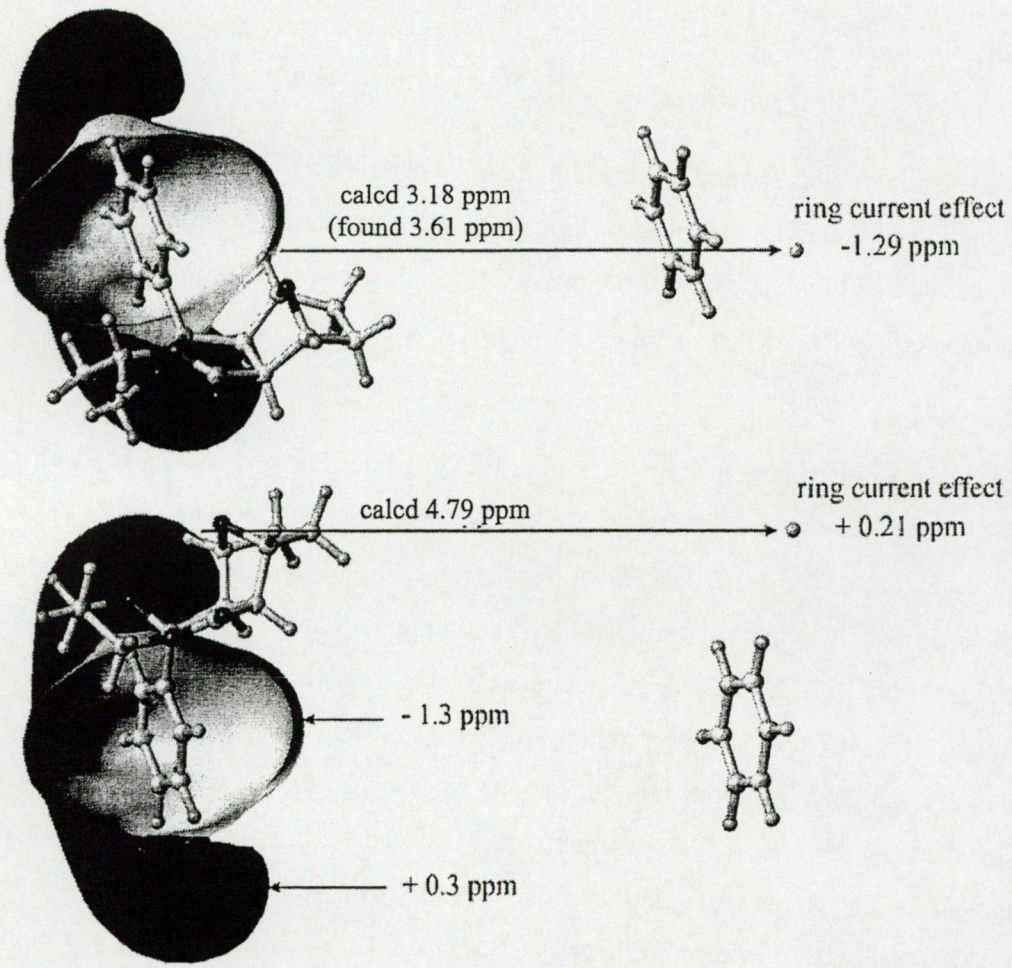
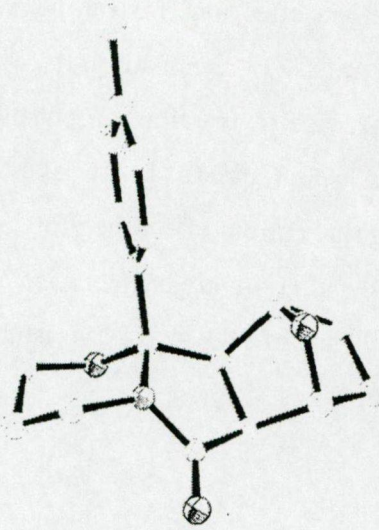



Figure 2

Ring current effect on H-3 in **7c**

Both the chemical shift of H-3 (δ = 3.18 ppm) and the ring current effect of the aryl on H-3 (–1.29 ppm) agree 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 3). For the *cis* analogue, the two parameters (δ = 4.79 ppm, ring current effect +0.22 ppm) are strongly different.



Perspective view of **7c**.
Thermal ellipsoids have been drawn
at a probability level of 30%

Figure 3

When the same criterion was applied to **6a** and **8**, the opposite result was obtained: H-5 at 5.00–5.29 ppm proves the position of the aryl and H-4-*endo* as *cis*. For **9**, 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 **5, 9** and **10**, the other data are in complete agreement with the structures given in Schemes 1 and 2.

## 3. EXPERIMENTAL

The IR spectra were determined in KBr discs on a Perkin Elmer Paragon 1000 PC FT-IR spectrophotometer. NMR spectra were recorded with an AVANCE DRX 500 (Bruker) spectrometer. Chemical shifts ($CDCl_3$ for **4, 5, 6a,b, 7c, 8-10**; DMSO-$d_6$ for **7a** and **7b**) ($\delta$, ppm, $\delta_{TMS} = 0$ ppm) are given. The corresponding $^1$H and $^{13}$C chemical shifts and H,H coupling constants *J*/Hz are listed for the compounds in the EXPERIMENTAL. The 2D NMR spectra were acquired with standard Bruker software. Typical parameters were (*i*) gs-COSY-45: sweep width 2620 Hz, 1 k data points in $F_2$, 128 experiments in $F_1$ (20 scans, 4 dummy scans), relaxation delay 1.2 s; (*ii*) gs-HMQC: sweep width in $F_1$ 10 kHz and in $F_2$ 26*0 Hz, 1 k data points in $F_2$, 128 experiments in $F_1$ (8 scans, 2 dummy scans), relaxation delay 1.2 s, zero filling to 2 k data points in $F_2$ and 256 data points in $F_1$, filter function square sine-bell in both dimensions; (*iii*) gs-HMBC: sweep width in $F_1$ 10 kHz and in $F_2$ 2620 Hz, 1 k data points in $F_2$, 128 experiments in $F_1$ (40 scans, 2 dummy scans), relaxation delay 1.2 s, delay for evolution of long-range couplings 50 ms, zero filling, 1 k data points in $F_2$ and 256 data points in $F_1$, filter function shifted square sine-bell in both dimensions; (*iv*) NOESY: sweep width 2670 Hz, 1 k data points in $F_2$, 128 experiments in $F_1$ (40 scans, 4 dummy scans), relaxation delay ~5 times $T_1$, mixing time ~T1. The pulse widths (90°) for all experiments were 12.5 μs ($^1$H), and 11.3 μs ($^{13}$C).

*Quantum Chemical Calculations*: The *ab initio* quantum-mechanical calculation on **7c** was performed on SGI Octane and SGI Origin 2000 work stations, using Gaussian 98.[21] Geometry optimization was carried

out by using HF/6-31G* without constraints.[22] The shielding constants were calculated with the GIAO method[23,24] at the same level of theory; since the GIAO approach is gauge-invariant, it can be applied for the calculation of NICS. The studied phenyl ring was placed in the centre of a grid of lattice points, ranging from –10Δ to +10Δ in all three dimensions (step width 0.5Δ), resulting in a cube of 68921 lattice points. The coordinates and shielding values of the lattice points around phenyl were transformed into SYBYL[25] contour files and the anisotropic effect visualized as iso-chemical-shift-surfaces (ICSS). In this way, it was possible to map the spatial extent, sign and scope of the corresponding anisotropic effect in **7c** at each fixed stereochemical position.[26]

*X-Ray data collection and processing*: Crystallographic data were collected at 173 K on a Nonius Kappa CCD area-detector diffractometer, using graphite monochromatized MoK$_\alpha$ ($\lambda = 0.71073$ Å). The data collection was performed by using φ and ω scans. The data were processed with DENZO-SMN v0.93.0.[27]

*Crystal Data for* **3b**: ($C_{15}H_{16}O_4$, $M_r = 260.28$), orthorhombic, $a = 5.7656(2)$, $b = 13.0113(4)$, $c = 16.7088(7)$ Å, $\alpha = \beta = \gamma = 90°$, $U = 1253.46(8)$ Å$^3$, $T = 173$ K, space group $P2_12_12_1$ (no. 19), $Z = 4$, $\mu$(Mo–K$_\alpha$) = 0.100 mm$^{-1}$, 1978 unique reflections, which were used in calculations. The final $wR(F^2)$ was 0.0889 (all data).

*Crystal Data for* **7c**: ($C_{18}H_{21}NO_3$, $M_r = 299.36$), triclinic, $a = 8.2783(2)$, $b = 10.05320(10)$, $c = 10.9091(2)$ Å, $\alpha = 64.3510(10)$, $\beta = 71.3170(10)$, $\gamma = 71.3170(10)°$, $U = 746.56(2)$ Å$^3$, $T = 173$ K, space group *P1* (no. 2), $Z = 2$, $\mu$(Mo–K$_\alpha$) = 0.090 mm$^{-1}$, 2610 unique ($R_{int} = 0.017$), which were used in calculations. The final $wR(F^2)$ was 0.0895 (all data).

The structures were solved by direct methods with SIR92,[28] and full-matrix least-squares refinements on $F^2$ were performed with SHELXL-97.[29] For both, all heavy atoms were refined anisotropically. The phenyl and methyl CH hydrogen atoms were included at fixed distances, with fixed displacement parameters from their host atoms. The remaining hydrogen atoms were refined isotropically. Figures were drawn with Ortep-3 for Windows.[30]

CCDC 209077 & 209078 contain the supplementary crystallographic data for this paper.

**3-*exo*-*p*-Toluoyl-7-oxabicyclo[2.2.1]heptane-2-*exo*-carboxylic acid (3a)**

8.41 g (0.05 mol) of **2** was added to a stirred suspension of 16.66 g (0.125 mol) of $AlCl_3$ in dry $CH_2Cl_2$ (50 mL), and a solution of 4.61 g (0.05 mol) of toluene in $CH_2Cl_2$ (10 mL) was then added dropwise during 30 min at rt; stirring was continued for 8 h. After standing overnight, the mixture was poured onto ice (200 g) and 36% HCl (20 mL), and extracted with $CHCl_3$ (2 × 50 mL). The extract was washed with water, dried ($Na_2SO_4$) and evaporated. The residue was taken up in $CHCl_3$ (20 mL), and *n*-hexane (20 mL) was added to the solution; the solid was filtered off, and recrystallized. **3a**: IR (KBr): ν

[$cm^{-1}$] = 1728 (C=O), 1665 (C=O, ketone). H-MS: 260.1094 ($C_{15}H_{16}O_4$), MS: m/z (%) 260 (5), 137 (12), 119 (100), 96 (14), 91 (38), 68 (38), 39 (12). Physical and analytical data on **3a** are listed in Table 1.

Table 1. Physical and analytical data on compounds (**3a-10**)

| Com-pound | mp °C | Yield % | Formula | Analysis Found % C | H | N | Calcd % C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **3a** | 194-196[a] | 58 | $C_{15}H_{16}O_4$ | 69.19 | 6.30 | | 69.34 | 6.18 | |
| **3b** | 218-220[b] | 17 | $C_{15}H_{16}O_4$ | 69.20 | 6.10 | | 69.32 | 6.24 | |
| **4** | 142-144[c] | 83 | $C_{15}H_{16}O_4$ | 69.02 | 6.35 | | 69.28 | 6.15 | |
| **5** | 249-251[e] | 65 | $C_{15}H_{16}N_2O_2$ | 70.17 | 6.29 | 10.67 | 70.48 | 6.35 | 10.82 |
| **6a** | 137-138[d] | 51 | $C_{17}H_{20}N_2O_2$ | 71.71 | 7.00 | 9.95 | 71.85 | 7.15 | 9.75 |
| **6b** | 126-128[f] | 39 | $C_{19}H_{24}N_2O_2$ | 73.25 | 7.64 | 8.77 | 73.01 | 7.75 | 8.90 |
| **7a** | 192-194[d] | 49 | $C_{17}H_{19}NO_3$ | 71.46 | 6.71 | 4.98 | 71.68 | 6.82 | 4.87 |
| **7b** | 179-180[d] | 50 | $C_{18}H_{21}NO_3$ | 72.02 | 7.27 | 4.58 | 72.10 | 7.09 | 4.72 |
| **7c** | 172-173.5[d] | 54 | $C_{18}H_{21}NO_3$ | 72.12 | 7.27 | 4.70 | 72.25 | 7.12 | 4.60 |
| **8** | 247-249[d] | 58 | $C_{21}H_{20}N_2O_2$ | 75.98 | 6.27 | 8.45 | 75.78 | 6.15 | 8.32 |
| **9** | 221-223[g] | 38 | $C_{23}H_{25}N_3O_2$ | 73.54 | 6.75 | 11.29 | 73.68 | 6.60 | 11.05 |
| **10** | 231-233[b] | 42 | $C_{18}H_{17}N_3O_2$ | 70.28 | 5.48 | 13.50 | 70.49 | 5.62 | 13.73 |

Crystallization solvent: [a]$CHCl_3$–*n*-hexane; [b]EtOAc–EtOH; [c]$Et_2O$; [d]*i*-$Pr_2O$; [e]EtOH; [f]$Et_2O$–*n*-hexane; [g]EtOAc.

***diexo*-1-Hydroxy-1-*p*-tolylhexahydro-4,7-epoxybenzofuran-3-one (3b)**

2.60 g (0.01 mol) of **3a** was dissolved in a mixture of EtOAc–EtOH (9 : 1, 10 mL). After standing for a week at rt, the crystals that had separated out were filtered off. **3b**: IR (KBr): ν [$cm^{-1}$] = 3317 (OH), 1765 (C=O, lactone). H-MS: 260.108 ($C_{15}H_{16}O_4$), MS: m/z (%) 260 (41), 243 (81), 171 (12), 137 (12), 124 (19), 119 (100), 91 (29), 68 (17).

**3-*endo*-*p*-Toluoyl-7-oxabicyclo[2.2.1]heptane-2-*exo*-carboxylic acid (4)**

A mixture of oxocarboxylic acid (**3a**) (1.30 g, 5 mmol) in toluene (10 mL) and 2 drops of $Et_3N$ was refluxed for 3 h. After cooling, the solid that had separated out was recrystallized. $^1$H-NMR: 1.8 (H-1-*exo*), 1.7 (H-1-*endo*), 1.5 (H-2-*exo*), 1.4 (H-2-*endo*), 4.95 (H-3), 4.4 (H-4), 3.5 (H-5), 5.0 (H-6), 7.9 (H-10), 7.3 (H-11), 2,4 (H-13). $^{13}$C-NMR: 29.3 (C-1), 25.8 (C-2), 79.4 (C-3), 55.6 (C-4), 50.0 (C-5), 81.3 (C-6), 179.1 (C-7), 196.2 (C-8), 134.4 (C-9), 129.1 (C-10), 130.1 (C-11), 145.2 (C-12), 22.1 (C-13). H-MS: 260.1093 ($C_{15}H_{16}O_4$), MS: m/z (%) 260 (6), 231 (4), 215 (3), 192 (81), 187 (13), 171 (35), 158 (12), 147 (7), 119 (100), 91 (31), 65 (7), 39 (3).

**5,8-Epoxy-4-*p*-tolyl-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (5)**

A solution of **3a** (1.30 g, 5 mmol) and hydrazine hydrate (99%, 0.50 g, 0.01 mol) in EtOH (10 mL) was refluxed for 4 h, and then concentrated to half-volume. After standing at rt for 3 h, the product (**5**) was filtered off by suction. Recrystallization yielded colourless crystals. $^1$H-NMR: 1.9-1.8 (4H, H-1, H-2),

4.7 (H-3), 3.4 (H-4), 3.0 (H-5), 5.1 (H-6), 7.6 (H-10), 7.2 (H-11), 2.4 (H-13), 8.52 (N*H*). $^{13}$C-NMR: 29.6 (C-1), 30.1 (C-2), 83.7 (C-3), 45.4 (C-4), 47.6 (C-5), 83.2 (C-6), 164.6 (C-7), 147.0 (C-8), 132.9 (C-9), 126.3 (C-10), 129.9 (C-11), 140.4 (C-12), 22.2 (C-13). H-MS: 256.1221 ($C_{15}H_{16}N_2O_2$), MS: m/z (%) 256 (11), 200 (4), 187 (100), 171 (2), 155 (1), 141 (2), 128 (2), 115 (3), 91 (3), 77 (1).

**6,9-Epoxy-9b-*p*-tolyl-2,3,5a,6,7,8,9,9a-octahydroimidazo[2,3-*a*]isoindol-5-one (6a), 8,11,epoxy-10b-*p*-tolyl-2,3,4,5,7a,8,9,10,11,11a-decahydro[1,3]diazepino[2,3-*a*]isoindol-7-one (6b), 6,9-epoxy-9b-*p*-tolyl-2,3,5a,6,7,8,9,9a-octahydro[2,3-*a*]isoindol-5-one (7a), 6,9-epoxy-2-methyl-9b-*p*-tolyl-2,3,5a,6,7,8,9,9a-octahydrooxazolo[2,3-*a*]isoindol-5-one (7b), 7,10-epoxy-10b-*p*-tolyl-2,3,6a,7,8,9,10,10a-octahydro[1,3]oxazino[2,3-*a*]isoindol-6-one (7c), 6,9-epoxy-9b-*p*-tolyl-5a,6,7,8,9,9a-hexahydrobenzimido[2,3-*a*]isoindol-5-one (8)**

A mixture of **3a** (1.30 g, 5 mmol), a bicyclic reagent (ethylenediamine 0.45 g, 1,4-diaminobutane 0.66 g, ethanolamine 0.46 g, 1-amino-2-propanol 0.56 g, 1-amino-3-propanol 0.56 g, or *o*-phenylenediamine 0.81 g, 7.5 mmol) and PTSA (0.05 g) in chlorobenzene (10 mL) was refluxed for 10 h. After evaporation, the residue was dissolved in $CHCl_3$ (10 mL), transferred to an $Al_2O_3$ column (ACROS, basic, 50-200 μ) and eluted with *n*-hexane–EtOAc (1 : 1) for **6a, 6b** and **8**, or with *n*-hexane–EtOAc (2 : 1) for **7a, 7b** and **7c**. Physical and analytical data are collected in Table 1.

**6a**: $^1$H-NMR: 1.7 (2H, H-1-*exo*, H-2-*exo*), 1.4 (H-1-*endo*), 1.25 (H-2-*endo*), 4.9 (H-3), 2.3 (H-4), 3.0 (H-5), 4.8 (H-6), 7.3 (H-10), 7.1 (H-11), 2.3 (H-13), 2.9 (2H, N(H)C$H_2$), 3.2 (2H, NC$H_2$). $^{13}$C-NMR: 28.8 (C-1), 28.6 (C-2), 78.0 (C-3), 52.0 (C-4), 56.4 (C-5), 78.8 (C-6), 177.7 (C-7), 89.6 (C-8), 141.3 (C-9), 125.5 (C-10), 129.8 (C-11), 137.9 (C-12), 21.4 (C-13), 42.0 (NH*C*), 46.2 (N*C*). H-MS: 284.1492 ($C_{17}H_{20}N_2O_2$), MS: m/z (%) 284 (60), 269 (7), 254 (26), 240 (15), 210 (6), 193 (24), 184 (3), 170 (4), 159 (100), 131 (16), 118 (4), 105 (3), 91 (4), 77 (1), 65 (2), 41 (2).

**6b**: $^1$H-NMR: 1.7 - 1.3 (4H, H-1, H-2), 3.7 (H-3), 2.4 (H-4), 2.8 (H-5), 4.8 (H-6), 7.0 (H-10), 7.5 (H-10a), 7.1 (H-11), 7.2 (H-11a), 2.3 (H-13), 3.0 and 2.4 (NHC$H_2$), 1.2 and 1.8 ($CH_2$), 1.5 and 1.8 ($CH_2$), 2.6 and 3.9 (NC$H_2$). $^{13}$C-NMR: 29.6 (C-1), 28.2 (C-2), 79.8 (C-3), 56.2 (C-4), 53.6 (C-5), 78.1 (C-6), 175.1 (C-7), 86.1 (C-8), 138.7 (C-9), 127.0 (C-10), 127.2 (C-10a), 129.0 (C-11), 129.8 (C-11a), 138.2 (C-12), 21.4 (C-13), 42.6 (NH*C*), 33.0 (NHC*C*), 24.8 (NC*C*), 41.2 (N*C*). H-MS: 312.1812 ($C_{19}H_{24}N_2O_2$), MS: m/z (%) 312 (50), 282 (8), 268 (19), 254 (23), 240 (14), 221 (100), 198 (5), 187 (54), 170 (5), 131 (9), 118 (6), 105 (2), 91 (4), 70 (23), 68 (2), 41 (2).

**7a**: $^1$H-NMR: 1.5 (2H, H-1), 1.4 (2H, H-2), 3.8 (H-3), 2.7 (H-4), 2.9 (H-5), 4.6 (H-6), 7.2 (H-10), 7.4 (H-10a), 7.3 (2H, H-11), 2.3 (H-13), 3.4 (OC$H_2$), 2.8 (NC$H_2$). $^{13}$C-NMR: 28.5 (C-1), 27.3 (C-2), 77.6 (C-3), 50.7 (C-4), 53.6 (C-5), 77.7 (C-6), 180.9 (C-7), 103.0 (C-8), 134.5 (C-9), 128.5 (C-10), 126.7 (C-10a), 129.5 (C-11), 126.0 (C-11a), 137.7 (C-12), 20.8 (C-13), 62.8 (O*C*), 42.9 (N*C*). H-MS: 285.1351

($C_{17}H_{19}NO_3$), MS: m/z (%) 285 (77), 270 (17), 254 (100), 240 (57), 210 (9), 194 (12), 170 (4), 162 (31), 160 (25), 131 (14), 119 (12), 105 (5), 91 (10), 77 (2), 68 (5), 41 (2), 39 (2).

**7b**: $^1$H-NMR: 1.5 (2H, H-1), 1.4 (2H, H-2), 3.6 (H-3), 2.7 (H-4), 2.9 (H-5), 4.6 (H-6), 7.1 (H-10), 7.4 (H-10a), 7.3 (2H, H-11), 2.3 (H-13), 3.5 (OC*H*), 1.1 (OCC$H_3$), 3.0 (NC$H_2$). $^{13}$C-NMR: 28.5 (C-1), 27.3 (C-2), 77.6 (C-3), 51.0 (C-4), 53.5 (C-5), 77.7 (C-6), 180.9 (C-7), 103.3 (C-8), 135.0 (C-9), 128.4 (C-10), 126.4 (C-10a), 129.5 (C-11), 126.1 (C-11a), 137.6 (C-12), 20.8 (C-13), 71.1 (O*C*), 20.5 (O*C*CH$_3$), 49.9 (N*C*). H-MS: 299.1499 ($C_{18}H_{21}NO_3$), MS: m/z (%) 299 (66), 284 (29), 254 (100), 240 (56), 208 (9).

**7c**: $^1$H-NMR: 1.7 (H-1-*exo*), 1.45 (H-1-*endo*), 1.55 (H-2-*exo*), 1.3 (H-2-*endo*), 2.4* (H-4), 2.95* (H-5) (*interchangeable data), 4.8 (H-6), 7.4 (H-10), 7.1 (H-10a), 7.2 (H-11), 7.3 (H-11a), 2.3 (H-13), 3.8 (OC$H_2$), 1.9 (C$H_2$), 4.1 (NC$H_2$). $^{13}$C-NMR: 29.4 (C-1), 28.4 (C-2), 78.8 (C-3), 54.9* (C-4), 52.6* (C-5), 78.4 (C-6), 175.5 (C-7), 96.8 (C-8), 133.9 (C-9), 127.0 (C-10), 129,1 (C-10a), 129.7 (C-11), 130,2 (C-11a), 138.6 (C-12), 21.5 (C-13), 63,0 (O*C*), 25,7 (OC*C*), 37.5 (N*C*). H-MS: 299.1529 ($C_{18}H_{21}NO_3$), MS: m/z (%) 299 (51), 268 (42), 254 (100), 224 (5), 208 (82), 174 (11), 141 (1), 119 (13), 105 (2), 91 (7), 68 (2), 65 (2), 41 (2), 39 (1).

**8**: $^1$H-NMR: 1.8 (H-1-*exo*), 1.5 (H-1-*endo*), 1.8 (H-2-*exo*), 1.5 (H-2-*endo*), 5.3 (H-3), 2.7 (H-4), 3.1 (H-5), 4.9 (H-6), 7.3 (H-10), 7.5 (H-11), 2.3 (H-13), 6.7 (1H), 6.8 (1H), 6.9 (1H), 7.5 (1H), 4.5 (N*H*). $^{13}$C-NMR: 28.2 (C-1), 29.5 (C-2), 78.7 (C-3), 53.5 (C-4), 57.4 (C-5), 79.4 (C-6), 176.1 (C-7), 89.5 (C-8), 143.9 (C-9), 123.9 (C-10), 116.1 (C-11), 138.4 (C-12), 21.4 (C-13), 138,4 (s, 1C), 142,7 (s, 1C), 111.9 (d, 1C), 126.1 (d, 1C), 120.9 (d, 1C), 116.1 (d, 1C). H-MS: 332.1695 ($C_{21}H_{20}N_2O_2$), MS: m/z (%) 332 (79), 303 (2), 241 (64), 208 (100), 124 (3), 91 (2), 68 (2).

**1,4-Epoxy-9,12-methano-5-*p*-tolyl-8*H*-1,2,3,4,4a,8a,9,10,11,12,12a,13b-dodecahydrophthalazino[1,2-*b*]quinazolin-8-one (9), 8,11-epoxy-7-*p*-tolyl-7a,8,9,10,11,11a-hexahydro-4*H*-pyrimido[2,1-*a*]phthalazin-4-one (10)**

A mixture of **3a** (2.60 g, 0.01 mol) and *diexo*-3-aminobicyclo[2.2.1]heptane-2-carbohydrazide (1.69 g, 0.01 mol) or *diendo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazide (1.67 g, 0.01 mol) in toluene (30 mL) was refluxed for 16 h, a Dean-Stark water separator being applied. After evaporation, the residue was dissolved in $CHCl_3$ (20 mL). The solution containing **9** was transferred onto a silica gel column (ACROS, 0.035-0.07 mm) and eluted with EtOAc; the solution of **10** was transferred onto an $Al_2O_3$ column (ACROS, basic, 50-200 μ) and eluted with EtOAc–*n*-hexane (2 : 1). Both of the residues were crystallized.

**9**: $^1$H-NMR: 1.8 (H-1), 1.4 + 1.7 (H-2-*exo*, H-2-*endo*)* (the assignments of *exo* and *endo* may be reversed), 4.55 (H-3), 3.16 (H-4), 3.0 (H-5), 4.9 (H-6), 7.65 (H-10), 7.15 (H-11), 2.3 (H-13), 2.75 (H-15), 3.75 (H-16), 2.45 (H-17), 1.2 + 1.4 (H-18-*exo*, H-18-*endo*),* 1.7 + 1.5 (H-19-*exo*, H-19-*endo*),* 2.7 (H-20), 1.2 + 1.4 (H-21). $^{13}$C-NMR: 28.9 (C-1), 30.3 (C-2), 83.4 (C-3), 42.8 (C-4), 46.7 (C-5), 86.7 (C-6), 144.4

(C-7), 149.6 (C-8), 133.2 (C-9), 127.0 (C-10), 129.8 (C-11), 140.8 (C-12), 21.7 (C-13), 165.7 (C-14), 50.1 (C-15), 62.7 (C-16), 46.4 (C-17), 26.5 (C-18), 30.0 (C-19), 44.5 (C-20), 34.7 (C-21). H-MS: 375.1965 ($C_{23}H_{25}N_3O_2$), MS: m/z (%) 375 (100), 346 (24), 332 (95), 306 (34), 278 (5), 264 (6), 238 (5), 212 (4), 208 (4), 169 (2), 129 (1), 121 (3), 115 (2), 91 (2).

**10**: $^1$H-NMR: 1.6-2.0 (m, 4H, H-1, H-2), 4.7 (H-3), 3.4 (H-4), 3.4 (H-5), 5.1 (H-6), 7.7 (H-10), 7.2 (H-11), 2.3 (H-13), 6.4 (COC*H*), 7.71 (NC*H*). $^{13}$C-NMR: 24.3 (C-1), 30.3 (C-2), 84.0 (C-3), 43.4 (C-4), 46.8 (C-5), 86.4 (C-6), 151.7 (C-7), 155.5 (C-8), 132.1 (C-9), 127.7 (C-10), 130.0 (C-11), 142.3 (C-12), 21.9 (C-13), 148.5 (N*C*=O), 115.8 (O=C*C*), 151.5 (N*C*). H-MS: 307.1305 ($C_{18}H_{17}N_3O_2$), MS: m/z (%) 307 (37), 278 (9), 264 (100), 250 (10), 238 (74), 209 (6), 169 (11), 153 (6), 134 (5), 128 (9), 115 (16), 106 (4), 91 (20), 80 (7), 70 (9), 65 (12), 53 (8), 41 (12), 39 (10).

**ACKNOWLEDGEMENTS**

The authors are indebted to Mrs. E. Csiszár-Makra for the typing of the manuscript. OTKA Grant T 037204.

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# IX

Monatshefte für Chemie 135, 839–847 (2004)
DOI 10.1007/s00706-003-0161-7

**Monatshefte für Chemie**
**Chemical Monthly**
Printed in Austria

# Preparation and Structure of di-*exo*-Condensed Norbornane Heterocycles

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Received October 28, 2003; accepted (revised) November 12, 2003
Published online April 9, 2004 

**Summary.** Cyclization of di-*exo*-aroylnorbornanecarboxylic acid with bidentate nucleophiles (hydrazine, *o*-phenylenediamine, *o*-aminophenol, alkylenediamines, and amino alcohols) yielded heterotri-, tetra-, and pentacycles. Their structures were established by means of NMR spectroscopy, with the application of HMQC, HMBC, DEPT, DIFFNOE, and COSY methods.

**Key words.** Heterocycles; Bicyclo[2.2.1]heptane derivatives; Cyclizations; Isoindolones.

## Introduction

By reactions of di-*endo*-3-aroylbicyclo[2.2.1]heptane- or -heptene-2-carboxylic acids with bifunctional reagents (amino alcohols, diaminoalkanes, *o*-aminophenol, and *o*-aminothiophenol) a large number of condensed heterocycles have been synthesized [1–4]. The results show that the starting configurations of the norbornane amino acids are generally retained in the products. As the synthesis of the stereoisomeric di-*exo* derivatives has not been reported, the di-*endo* norbornene dicarboxylic anhydride **1** was now transformed to the known di-*exo* anhydride **2** by heating [5]. Only a few data were found in literature concerning the epimerization of di-*endo* norbornane derivatives [5–7]. The objective of this work was to prepare the previously unknown di-*exo* derivatives from **2** and to compare them with the di-*endo*-fused heterocycles [1].

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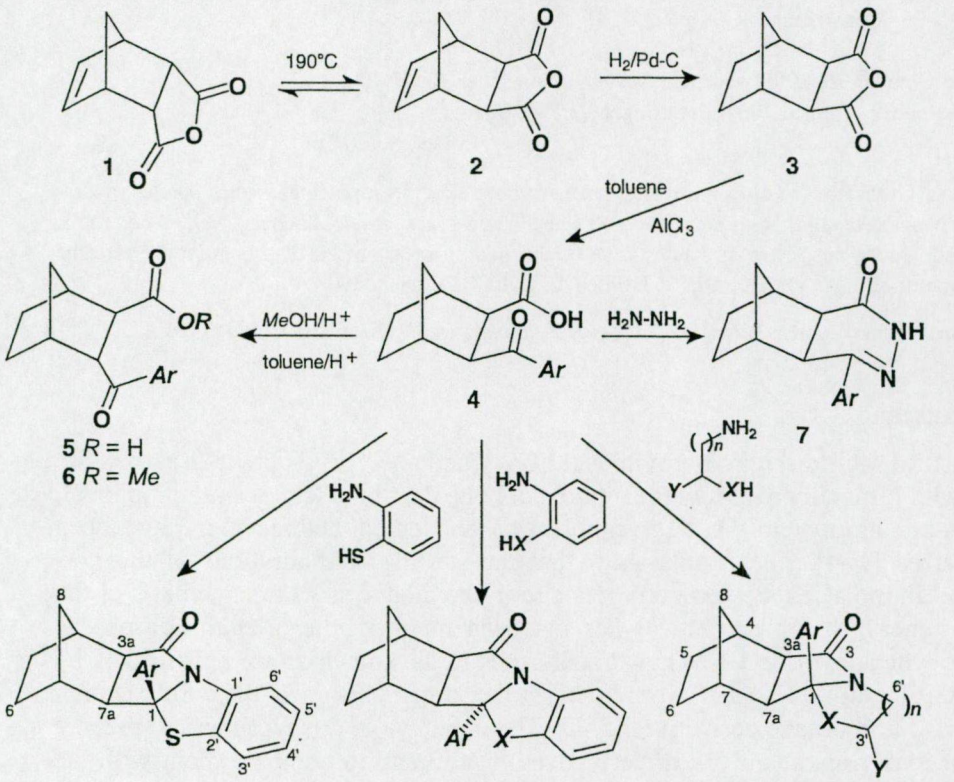
## Results and Discussion

For preparation of the di-*exo*-condensed norbornane heterocycles, we isomerized di-*endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (**1**) to the di-*exo* analogue **2** by heating to 190°C (Scheme 1) [5]. To avoid the addition of the aromates to the double bond in the presence of $AlCl_3$ [2], **2** was saturated by catalytic hydrogenation to furnish **3** [6]. The *Friedel-Crafts* acylation of toluene with **3** led to di-*exo*-3-toluoylbicyclo[2.2.1]heptane-2-carboxylic acid **4**. As the oxocarboxylic acid **4** readily isomerizes to the *endo* aroyl derivative **5**, *e.g.* on boiling with HCl in toluene, and the esterification also affords the *endo*-aroyl-*exo*-methoxycarbonyl derivative **6**, **4** was reacted with hydrazine to yield the methylene-bridged di-*exo*-hexahydrophthalazin-4(3*H*)-one **7**. With alkanolamines, the methanooxazolo- **8** and -oxazinoisoindolones **9** were obtained. On cyclization with alkylenediamines **4** resulted in imidazo- **10a**, **10b**, pyrimido- **11**, and 1,3-diazepinoisoindolones **12**, while with *o*-aminothiophenol, *o*-aminophenol, and *o*-phenylenediamine, the pentacyclic benzthiazolo **13**, -oxazolo **14**, and -imidazo derivatives **15** were obtained.




Scheme 1

**Table 1.** $^1$H NMR data of compounds **4–9**, **10a**, **10b**, and **11–15**[a]

| | norbornane moiety | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $CH_2$ 2 × *d* (2 × 1H)[b] | | H-3a[c] | H-4[d] | H-5[e] | | H-6[e] | | H-7[d] | H-7a[f] |
| **4** | 1.13 | 1.86 | 2.90 | 2.40 | 1.32[i] | 1.53[k] | 1.32[i] | 1.53[k] | 2.47 | 3.57 |
| **5** | 1.31[l] | 1.69 | 4.02 | 2.63[i] | 1.38 | 1.51 | 1.04 | 1.20 | 2.63[i] | 3.20 |
| **6** | 1.36[m] | 1.78[n] | 3.22 | 2.63 | 1.43 | 1.57 | 1.12 | 1.26 | 2.71 | 4.11 |
| **7** | 1.18 | ~1.45[i] | 3.06 | 2.85 | ~1.45[i] | 1.54 | ~1.45[i] | 1.67 | 2.45 | 2.67 |
| **8** | 0.86 | 1.24[i] | 2.46 | 2.40 | 1.22[i] | 1.44 | 1.09 | 1.30 | 1.34 | 2.57 |
| **9** | 0.75 | 1.07 | 2.57 | 2.37 | ~1.22[i] | 1.41 | 1.00 | ~1.22[i] | 1.12 | 2.11 |
| **10a** | 0.88 | 1.36 | 2.31 | 2.63 | 1.10 | 1.37 | 1.23 | 1.50 | 1.55 | 2.64 |
| **10b** | 0.80 | 1.20 | ~2.28[i] | 2.55 | 1.00 | 1.30 | 1.17 | 1.44 | 1.48 | 2.64 |
| **11** | 0.82 | 1.23[i] | 2.65[k] | 2.63[k] | 1.23[i] | 1.50 | 1.03 | ~1.3[k] | 1.32 | 1.98 |
| **12** | 0.69 | 0.98 | 2.53 | 2.58 | ~1.2 | 1.45 | 1.08 | 1.31 | 1.55 | 2.24 |
| **13** | 0.92[n] | 1.24[n] | ~3.0[i] | 2.71 | 1.20 | 1.45 | 1.32 | 1.57 | 1.84 | ~3.0[i] |
| **14** | 1.02 | ~1.15[i] | 2.87[k] | 2.64 | ~1.15[i] (2H) | | 1.52 (2H) | | 2.88[k] | 2.46 |
| **15** | ~1.15[i] | 1.21 | 2.78 | | ~1.15[i] (2H) | | 1.51 (2H) | | 2.74 | 2.39 |

| | *p*-tolyl substituent[h] | | | |
|---|---|---|---|---|
| | $CH_3$[g] | *Ar*H-2′,6′ | | *Ar*H-3′,5′ |
| **4** | 2.34 | 7.79 | | 7.27 |
| **5** | 2.34 | 7.84 | | 7.20 |
| **6** | 2.41 | 7.92 | | 7.27 |
| **7** | 2.31 | 7.52 | | 7.13 |
| **8** | 2.31 | ~7.14[k] | 7.27 | ~7.14[k] 7.34 |
| **9** | 2.33 | 7.05 | 7.32[k] | 7.22 7.32[k] |
| **10a** | 2.35 | 7.15 | 7.46 | 7.08 7.22 |
| **10b** | 2.28[i] | 7.07 | 7.38° | 7.00 7.16 |
| **11** | 2.39 | 7.06 | 7.58° | 7.17 7.57 |
| **12** | 2.35 | 6.91 | 7.53 | 7.09 7.23 |
| **13** | 2.30 | ~6.95 | ~7.1 | ~7.2 ~7.5 |
| **14** | 2.24 | 7.31 | | 7.08 |
| **15** | 2.23 | 7.18 | | 7.07 |

[a] In $CDCl_3$ solution at 500 MHz; chemical shifts in ppm ($\delta_{TMS} = 0$ ppm), coupling constants in Hz; assignments were supported by HMQC and HMBC measurements, for **4**, **8**, **9**, **10b**, **12**, **13**, and **15** also by DIFFNOE, and for **10a**, **10b**, and **12** by COSY experiments; [b] *AB*-type spectrum: 2 × *d*, $J = 9.6$ (**4**), 10.0 (**5–9**), 10.5 (**10a**, **10b**, **11**, and **12**) Hz, $\delta$H(*exo*) < $\delta$H(*endo*) for **4–6**, **8**, **9**, **10b**, **12**, and **13**; [c] doublet, $J = 9.5$ (**4** and **7**), 5.0 (**5** and **6**), 8.0 (**8**, **9**, and **10a**), 8.2 (**11**), 8.7 (**12**), 7.3 (**15**) Hz; [d] ~*s* (1H); [e] 2–4 × *m* (4H), $\delta$H(*exo*) > $\delta$H(*endo*); [f] doublet, *J*: the same values as for H-3a (**4**, **7**, **8**, **9**, **10a**, **11**, **12**, and **15**), $J = 7.4$ (**13**), *dt*, $J = 5.0$ and 1.5 (**5** and **6**) Hz, broad coalesced signal of fine structure (**10b**); [g] *s* (3H); [h] rudimentary *AA′XX′*-type spectrum: 2 × ~*d* (2 × 2H), $J = 8.0$ (**4–7**, **14** and **15**) Hz, due to hindered rotation-separated *AB* and $A_2$-type spectra: 2 × *d* (2 × 1H), $J = 8.0$ (**8** and **9**) Hz, and *s* (2H), 2 × *AB* (approx.), $J = 7.8$ and 7.6 (**10a**, **10b**), 7.9 and 7.2 (**11**) Hz, 2 × *d* and 2 × *dd*, $J = 7.8$, 1.9 and 8.0, 1.7 (**12**) Hz, four broad coalesced signals of fine structure (**13**); [i/k] overlapping signals; [l/m/n] further split to *dd*/*qad*/*td* due to $^4J$ long-range couplings; [o] broadened signal

In conclusion, the isomerization of di-*endo*-norbornenedicarboxylic anhydride **1** to the di-*exo* derivative **2**, followed by reduction and *Friedel-Crafts* acylation provides the di-*exo*-aroylnorbornane carboxylic acid **4**, which can be advantagously applied to the syntheses of di-*exo*-fused norbornane heterocycles: the condensed benzthiazolo, -oxazolo, and -imidazo compounds, *etc.*

**Table 2.** $^{13}C$ NMR chemical shifts[a] of compounds **4–9**, **10a**, **10b**, and **11–15**[b, c]

| | norbornane[e] | | | | | | | pyrrolidinone[e] | |
|---|---|---|---|---|---|---|---|---|---|
| | $CH_2$[d] | C-3a | C-4 | C-5 | C-6 | C-7 | C-7a | C-1 | C=O |
| **4** | 36.1 | 52.7 | 41.3 | 29.5 | 29.2 | 39.8 | 52.9 | 199.5 | 174.7 |
| **5** | 39.6 | 47.2 | 42.3[i] | 28.9 | 24.0 | 42.4[i] | 53.1 | 199.2 | 181.0 |
| **6** | 39.5 | 47.2 | 42.3 | 29.0 | 24.1 | 42.4 | 53.3 | 199.4 | 176.1 |
| **7** | 36.1 | 44.2 | 44.4 | 29.5 | 29.2 | 45.3 | 46.2 | 149.4 | 166.9 |
| **8** | 34.1 | 49.9 | 39.5 | 28.4 | 28.5 | 39.1 | 53.2 | 104.2 | 183.6 |
| **9** | 33.9 | 51.0 | 38.8 | 28.8 | 28.3 | 39.5 | 53.3 | 96.8 | 177.5 |
| **10a** | 34.2 | 50.4 | 39.6 | 28.7 | 28.8 | 39.7 | 54.5 | 91.3 | 182.3 |
| **10b** | 34.3 | 50.5 | 39.5 | 28.6 | 28.9 | 39.7 | 54.3 | 91.8 | 182.1 |
| **11** | 34.2 | 51.8 | 38.9 | 28.5 | 29.2 | 40.0 | 54.3 | 82.7 | 176.5 |
| **12** | 34.2 | 52.9 | 38.9 | 28.8 | 28.9 | 40.8 | 55.0 | 86.5 | 177.5 |
| **13** | 34.3 | 55.1 | 40.5 | 28.6[l] | 28.6[l] | 40.0 | 50.6 | 90.2 | 179.3 |
| **14** | 35.8 | 55.3 | 40.5 | 27.5 | 29.0 | 39.0 | 52.9 | 106.6 | 179.9 |
| **15** | 35.4 | 55.6 | 40.0 | 27.7 | 29.7 | 40.1 | 52.9 | 90.0 | 178.3 |

| | $CH_2/CH/C_{Ar}$[h] | | *p*-tolyl group | | | | |
|---|---|---|---|---|---|---|---|
| | NC[f] | *X*C[g] | $CH_3$ | C-1″ | C-2″6″ | C-3″5″ | C-4‴ |
| **4** | – | – | 21.9 | 135.6 | 128.9 | 129.9 | 143.6 |
| **5** | – | – | 22.0 | 134.8 | 129.1 | 129.7 | 144.3 |
| **6** | – | – | 22.0 | 134.9 | 129.1 | 129.7 | 144.2 |
| **7** | – | – | 21.7 | 133.3 | 126.5 | 129.6 | 140.0 |
| **8** | 44.3 | 63.2 | 21.6 | 135.5 | 126.3 130.5 | 127.5 129.1 | 138.2 |
| **9** | 37.9 | 62.6 | 21.5 | 135.0 | 127.7 128.3 | 129.6 130.9 | 138.1 |
| **10a** | 44.2 | 44.5 | 21.5 | 136.4 | 126.7 127.8 | 128.3 129.9 | 137.7 |
| **10b** | 51.6 | 53.0 | 21.5 | ~137[k] | 126.4 127.6 | 128.4 130.0 | 137.7 |
| **11** | 38.7 | 41.5 | 21.5 | 136.0 | 128.2 128.3 | 128.8 130.3 | 137.6 |
| **12** | 41.8 | 42.6 | 21.4 | 139.2 | 125.9 128.3 | 128.4 130.1 | 137.7 |
| **13** | 133.5 | 139.5 | 21.5 | 138.5 | 124.9 128.4 | 128.0 129.5 | 137.7 |
| **14** | 128.9 | 152.4 | 21.5 | 141.6 | 124.7 | 129.6 | 138.7 |
| **15** | 129.7 | 142.7 | 21.4 | 144.7 | 123.7 | 130.0 | 138.1 |

[a] In ppm ($\delta_{TMS} = 0$ ppm) at 126 MHz; solvent: $CDCl_3$ or *DMSO*-$d_6$ (for **4**, **8**, and **9**); [b] assignments were supported by DEPT, HMQC, and HMBC measurements; [c] further lines, $OCH_3$: 52.2 (**6**); $CCH_3$: 19.8 (**10b**); $CCH_2C$-type carbon[h]: 27.1 (**11**), 24.7 and 33.1 (**12**); $C_{Ar}H$ (condensed benzene ring[m]), C-3′: 127.5 (**13**), 110.3 (**14**), and 111.2 (**15**); C-4′: 125.7 (**13**), 126.8 (**14**), and 126.1 (**15**); C-5′: 123.2 (**13**), 121.8 (**14**), and 120.6 (**15**), and C-6′: 120.6 (**13**), 117.4 (**14**), and 116.4 (**15**); [d] bridging methylene group; [e/m] numbering: see **8–12/13–15** (Scheme 1); [f] carbon bound to the amide nitrogen; [g] *X* = NH (**10a**, **10b**, **11**, **12**, and **15**), O (**8**, **9**, and **14**), S (**13**); [h] in hetero ring with two hetero atoms; [i] interchangeable assignments; [k] the line hidden by noise was identified from the HMBC spectrum; [l] two overlapping lines

The spectral data on the new compounds (**4–15**) (Tables 1–4) are proof of the presumed structures. Only a few additional remarks are necessary.

In accord with the "splitting rule" [8, 9][a], the di-*exo* structure of **4** and **7–15** is obvious from the 8.4 ± 1.1 Hz doublet split of the H-3a and H-7a signals. This high splitting value is in accord with the dihedral angle of 0°; further splits (from the 3a,4 and 7,7a vicinal H,H interactions) are not observed also as expected from the *Karplus* relation [10]: the dihedral angles are ~90°. The H-7a signal for **5** and **6** is split into a double triplet by 5.0, 1.5, and 1.5 Hz [H-3a,7a, 7,7a, and 7a,8(*exo*) interactions], 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. (For comparison of the spectroscopic data, the numbering in the Scheme is applied in this part and in Tables 1–4.)

As rotation of the tolyl group in **8–13** is hindered, the *Ar*H-2′,6′ and *Ar*H-3′,5′ signals appear separately in the $^{1}H$ and $^{13}C$ NMR spectra. The condensed planar benzene ring in **14** and **15** leads to a change in the C-1 configuration, and the *endo* situation of the tolyl group (as proved by DIFFN*O*E experiments, which demonstrate the close-lying position of H-7 and H-7a to the *ortho*-hydrogens of the tolyl group in **15**) allows free rotation (Table 4). The C-1 configuration in **13** is unaltered relative to **8–12**, and the more bulky S atom distorting the whole tetra-

**Table 3.** Characteristic IR wavenumbers ($cm^{-1}$) of compounds **4–9**, **10a**, **10b**, and **11–15**, in KBr discs

| | νOH[a] or νNH band | νC=O band[b] | Amide-I band[c] | νC–O band ester or ether group | γ-$C_{Ar}$H band *p*-di-subst. benzene ring | γ-$C_{Ar}$H band *o*-di-subst. benzene ring |
|---|---|---|---|---|---|---|
| **4** | 3500–2500 | 1705 | 1673 | – | 824 | – |
| **5** | 3250–2250 | 1699 | 1668 | – | 851 | – |
| **6** | – | 1727 | 1671 | 1179, 1233 | 817 | – |
| **7** | 3250–2000 | – | 1664 | – | 813, 824 | – |
| **8** | – | – | 1716 | 1008 | 826 | – |
| **9** | – | – | 1697 | 1026 | 821 | – |
| **10a** | 3276 | – | 1679 | – | 816, 825 | – |
| **10b** | 3244 | – | 1676 | – | 827 | – |
| **11** | 3293 | – | 1673 | – | 826 | – |
| **12** | 3305 | – | 1660 | – | 808, 825 | – |
| **13** | – | – | 1717 | – | 849 | 744, 756 |
| **14** | – | – | 1716 | 1225 | 822 | 744 |
| **15** | 3300 | – | 1693 | – | 819 | 736 |

[a] νOH band (**4** and **5**); [b] COOH (**4** and **5**) or COOMe group (**6**); [c] νC=O band of conjugated ketone group (**4–6**)

[a] Due to the ~90° dihedral angles, for the di-*exo* compounds, the vicinal H-3a,4 and H-7,7a interactions cause no double splits of the H-3a and H-7a signals, while these couplings lead to the split by 2-4 Hz in the di-*endo*-molecules where the dihedral angles are about 30°. As a consequence, the H-3a, H-7a atoms have a doublet in the di-*exo* derivatives and double doublet signals in the di-*endo* analogues

**Table 4.** Results of DIFFN*O*E experiments with compounds **8**, **9**, **10b**, **12**, **13**, and **15**[a]

| Saturated signal | Responding signals | | | | |
|---|---|---|---|---|---|
| | H-8(*endo*)[b] | H-6′(*ax*)[c] | H-3′ | H-7 | H-7a |
| ArH-2,6[d] | **8**, **9**, **10b**, **12**, **13** | **8**, **9**, **12** | **10b** | **15** | **15** |

[a] Interacting pairs showing only trivial effects (N*O*E between geminal or vicinal hydrogens) are not included in this table; responses relevant for stereostructures are exclusively given; all experiments were also executed in opposite sence (in the complementary measurements, the responding signals of the first experiments were irradiated, when intensity enhancements were observed for all signal saturated previously); [b] *endo*-H of the bridging group; [c] *exo*-H of the $NCH_2$ group; [d] the ArH-2 and ArH-6 signals of the tolyl group appear separated in case of **12** and both give mutual N*O*Es with the H-8(*endo*) and H-6′(*ax*) signals

cyclic skeleton forces the tolyl group close to the bridging $CH_2$. Hence, between these moieties, the tolyl group is unable to rotate freely, similarly as in **8–12**. In **8–13**, the aromatic ring is situated near to the bridging $CH_2$ and its anisotropic shielding results in an upfield shift of the signals of this $CH_2$ (0.69–0.92 and 0.98–1.36 ppm for **8–13**, and 1.02–1.36 and 1.15–1.78 ppm for **5–7**, **14**, and **15**).

The direct proof of this C-1 configuration is provided, for instance, by the DIFFN*O*E measurements on **9** and also on **13**, which demonstrate the steric closeness of the H(*endo*) atom of the bridging $CH_2$ and the *ortho*-hydrogens of the tolyl group: upon saturation of the signal of one of these two types of hydrogens the other responded. Such an effect is absent in case of **15**, while a strong DIFFN*O*E on the $H_{Ar}$-2′,6′ signals was observed when H-7a was irradiated.

The different C-1 configuration in **13** and **14**, **15** follows directly from the dramatic difference, for example, in the $^1H$ chemical shifts of H-7 (1.84 ppm for **13**, but 2.88 for **14** and 2.74 ppm for **15**).

The presumed hindered rotation in **8–13** was confirmed by the temperature dependence of the $^1H$ NMR spectrum of **10a**.

## Experimental

IR spectra were run in KBr disks on a Bruker IFS-55 FT-spectrometer controlled by Opus 3.0 software. The $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at RT on a Bruker DRX-500 spectrometer at 500.13 ($^1H$) and 125.76 ($^{13}C$) MHz, with the D signal of the solvent as the lock and *TMS* as internal standard. The VT-NMR measurements were carried out in *DMSO*-$d_6$ from 298 to 353 K on Bruker AM 300 equipment. The standard Bruker microprogram N*O*EMULT was used to generate N*O*E [11] and to acquire DIFFN*O*E spectra [12, 13] with a selective pre-irradiation time. DEPT spectra [14] were run in a standard manner [15], using only a $\Theta = 135°$ pulse to separate the $CH/CH_3$ and $CH_2$ lines phased "up" and "down". The 2D-COSY [16a, 17a], HMQC [16b, 17b] and HMBC [18, 19] spectra were obtained by using the standard Bruker pulse programs COSY-45 INV4GSSW and INV4GSLRNDSW. The results of elemental analyses agreed satisfactorily with the calculated values.

*di-exo-Bicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride* (**3**, $C_9H_{10}O_3$)

In an autoclave, a mixture of 65.66 g of **2** (Acros 32059) and 2 g of 5% Pd–C in 1000 $cm^3$ of dry *THF* was stirred for 24 h at $4 * 10^3$ kPa with $H_2$. The solid was then removed by filtration and the filtrate was

evaporated. On crystallization from $Et_2O$/*n*-hexane, the residue gave 58.5 g (88%) of **3**. Mp 78–79°C. NMR data correspond with those given in Ref. [6].

*3-exo-p-Toluoylbicyclo[2.2.1]heptane-2-exo-carboxylic acid* (**4**, $C_{16}H_{18}O_3$)

Anhydride **3** (16.6 g) was dissolved in 100 $cm^3$ of dry toluene and 30.66 g of powdered anhydrous $AlCl_3$ were added slowly with continuous stirring at RT. Stirring was continued for 4 h, and the mixture was kept at RT overnight. The mixture was next decomposed with 100 g of ice and 20 $cm^3$ of 36% HCl and extracted with 3×50 $cm^3$ of $CH_2Cl_2$. The extract was washed with $H_2O$, dried ($Na_2SO_4$), and evaporated. The residue was crystallized from *EtOAc*/*n*-hexane [20]. Yield 16.3 g (63%); mp 164–166°C.

*3-endo-p-Toluoylbicyclo[2.2.1]heptane-2-exo-carboxylic acid* (**5**, $C_{16}H_{18}O_3$)

A mixture of 1.29 g of di-*exo*-3-*p*-toluoylbicyclo[2.2.1]heptane-2-carboxylic acid (**4**) and 2 drops of 36% HCl in 10 $cm^3$ of toluene was refluxed for 3 h. After evaporation, the residue was crystallized. Yield 0.95 g (74%); mp 129–131°C ($Et_2O$/petroleum ether, bp 40–60°C).

*Methyl 3-endo-p-toluoylbicyclo[2.2.1]heptane-2-exo-carboxylate* (**6**, $C_{17}H_{20}O_3$)

A mixture of 1.29 g of **4** and 0.20 $cm^3$ of conc. $H_2SO_4$ in 20 $cm^3$ of *Me*OH was refluxed for 2 h. After evaporation of the solvent, 30 $cm^3$ of $H_2O$ were added and the mixture was extracted with 3 × 10 $cm^3$ of diethyl ether. The extract was dried ($Na_2SO_4$) and, after removal of the solvent, the residue was crystallized. Yield 1.06 g (78%); mp 67–68°C ($Et_2O$/petroleum ether, bp 40–60°C).

*5,8-Methano-4-p-tolyl-4a,5,6,7,8,8a-hexahydro-2H-phthalazin-1-one* (**7**, $C_{16}H_{18}N_2O$)

A solution of 1.29 g of **4** and 0.5 g of hydrazine hydrate in 10 $cm^3$ of *Et*OH was refluxed for 4 h and was concentrated under vacuum to half of its volume. On standing, the product **7** separated and was removed by filtration. Yield 0.91 g (72%); mp 208–210°C (*Et*OH).

*General Procedure for the Preparation of* **8**, **9**, **10a**, **10b**, **11**, **12**, **13**, **14**, *and* **15**

A mixture of 1.29 g of **4**, 0.46 g of ethanolamine, or 0.56 g of 1-amino-2-propanol, or 0.56 g of 1-amino-3-propanol, or 0.45 g of ethylenediamine, or 0.56 g of 1,2-diaminopropane, or 0.56 g of 1,3-diaminopropane, or 0.66 g of 1,4-diaminobutane, or 0.93 g of 2-aminothiophenol, or 0:82 g of 2-aminophenol, or 0.81 g of 1,2-diaminobenzene, and 0.05 g of *PTSA* in 10 $cm^3$ of dry chlorobenzene was refluxed for 10 h. The solvent was evaporated, the residue was dissolved in 5 $cm^3$ of $CHCl_3$, and the solution was transferred to an $Al_2O_3$ column (Acros, basic, 50-200 $\mu$) and eluted with *n*-hexane: *Et*OAc (2:1) for **8**, **9**, **13**, **14**, and **15** or with *Et*OAc:*n*-hexane (2:1) for **10a**, **10b**, **11**, and **12**.

*6,9-Methano-9b-p-tolyl-2,3,5a,6,7,8,9,9a-octahydrooxazolo[2,3-a]isoindol-5-one*
(**8**, $C_{18}H_{21}NO_2$)

Yield 0.68 g (48%); mp 162–163°C (*i-Pr*$_2$O).

*7,10-Methano-10b-p-tolyl-3,4,6a,7,8,9,10,10a-octahydro-2H-[1,3]oxazino[2,3-a]isoindol-6-one* (**9**, $C_{19}H_{23}NO_2$)

Yield 0.56 g (38%); mp 163–164°C (*i-Pr*$_2$O).

*6,9-Methano-9b-p-tolyl-2,3,5a,6,7,8,9,9a-octahydroimidazo[2,3-a]isoindol-5-one* (**10a**, $C_{18}H_{22}N_2O$)

Yield 0.75 g (53%); mp 183–184°C (*EtOAc/i-Pr*$_2$O).

*6,9-Methano-2-methyl-9b-p-tolyl-2,3,5a,6,7,8,9,9a-octahydroimidazo[2,3-a]isoindol-5-one* (**10b**, $C_{19}H_{24}N_2O$)

Yield 0.72 g (49%); mp 181–183°C (*i-Pr*$_2$O).

*7,10-Methano-10b-p-tolyl-1,2,3,4,6a,7,8,9,10,10a-decahydropyrimido[2,3-a]isoindol-6-one* (**11**, $C_{19}H_{24}N_2O$)

Yield 0.83 g (56%); mp 205–206°C (*i-Pr*$_2$O).

*8,10-Methano-11b-p-tolyl-2,3,4,5,7a,8,9,10,11,11a-decahydro[1,3]diazepino[2,3-a]isoindol-7-one* (**12**, $C_{20}H_{26}N_2O$)

Yield 0.64 g (41%); mp 171–173°C (*i-Pr*$_2$O).

*6,9-Methano-9b-p-tolyl-5a,6,7,8,9,9a-hexahydrobenzthiazolo[2,3-a]isoindol-5-one* (**13**, $C_{22}H_{21}NOS$)

Yield 0.62 g (36%); mp 171–172°C (*i-Pr*$_2$O).

*6,9-Methano-9b-p-tolyl-5a,6,7,8,9,9a-hexahydrobenzoxazolo[2,3-a]isoindol-5-one* (**14**, $C_{22}H_{21}NO_2$)

Yield 0.70 g (42%); mp 145–147°C (*i-Pr*$_2$O).

*6,9-Methano-9b-p-tolyl-5a,6,7,8,9,9a-hexahydrobenzimidazo[2,3-a]isoindol-5-one* (**15**, $C_{22}H_{22}N_2O$)

Yield 0.78 g (47%); mp 232–234°C (*EtOAc*).

## Acknowledgements

The authors are indebted to Mrs. *E. Csiszár-Makra* for typing of the manuscript. Grants OTKA 29651, 37204, and 43634 and FKFP 0200/2000 are acknowledged.

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# X

# Application of furan as diene: Preparation of condensed 1,3-oxazines by retro Diels-Alder reaction

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**Keywords**: 1,3-oxazines, oxanorbornenes, retro Diels-Alder reaction, furan heterocycles, NMR

di-*exo*-3-Amino-7-oxabicyclo[2.2.1]hept-5-ene-2-methanol **3** was reacted with oxocarboxylic acids (*p*-toluoylpropionic acid, *cis*- or *trans*-*p*-toluoylcyclohexanecarboxylic acid, -benzoic acid or methanobenzocyclooctenecarboxylic acid) to furnish the oxanorbornene-fused pyrrolo[1,3]oxazine **4**, isoindolo[1,3]benzoxazines **5** and **6**, and methanobenzocyclooctenepyrrolo[1,3]oxazine **10**, together with the retro Diels-Alder products **7-9** and **11**. On boiling in chlorobenzene, furan was removed from the oxanorbornene heterocycles **5** and **10** to give the retro Diels-Alder products **8** and **11**. The structures of the new compounds were established by means of NMR spectroscopy and (for **6** and **9**) also by X-ray measurements.

## Introduction

Numerous heteromonocycles and condensed heterocycles have recently been synthetized by cyclization of di-*endo*- and di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids with difunctional compounds, followed by a retro Diels-Alder (rDA) reaction.[1-3] In the closing step of the procedure, the cyclopentadiene (CP) is cleaved off by heating to the melting point or by boiling in an organic solvent (chlorobenzene or toluene), resulting in 1,3-heterocycles as target compounds that are difficult or impossible to obtain by other routes. The CP-fused parent molecules relatively easily yield the rDA product alone, when the new ring containing the double bond has a "quasi-aromatic" structure: a pyrimidinedione, thioxopyrimidinone or 1,3-oxazinone unit.

For synthetic applications, empirical observations suggest the application of dienes as embedded adducts in the following sequence of rDA reactivity: furan > pyrrole > benzene > naphthalene > fulvene > CP > anthracene > butadiene.[4] Hence, we are currently constructing molecules on furan instead of CP, with the expectation of removing the diene more easily and thereby obtaining

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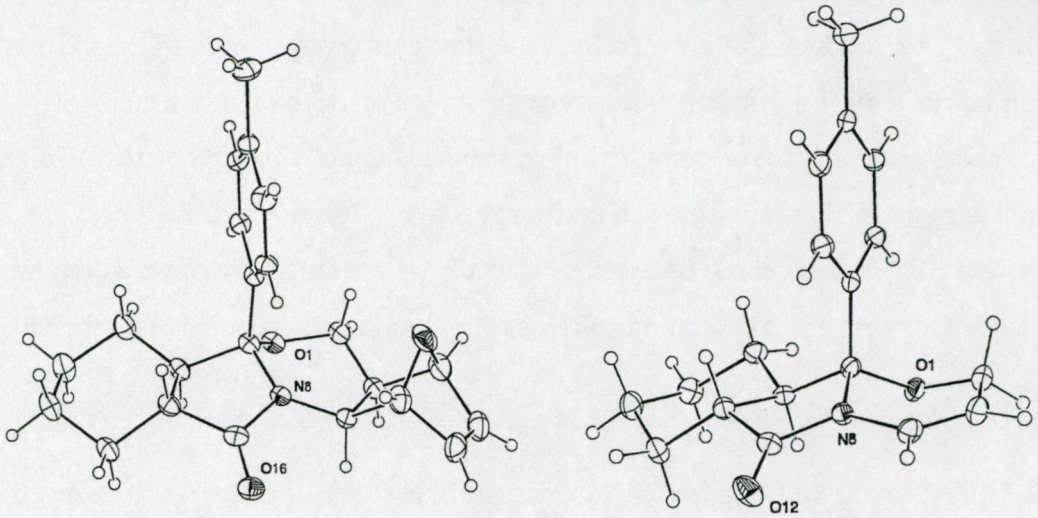
heterocycles other than those with "quasi-aromatic" structures. To date, furan has been built into 7-oxabicyclo[2.2.1]heptane, which is of huge potential as a useful intermediate in the synthesis of compounds with complicated structures,[5] *e.g.* in the preparation of the biological active pamamycin.[6] The furan ring allows its removal from the adducts at lower temperatures, hence, it splits off more easier than CP,[7] and it has also been used as a trapping agent for active alkenes.[8]

**Results**

di-*exo*-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride[9,10] **1** was prepared by Diels-Alder addition from furan and maleic anhydride, as a key starting material for biologically relevant compounds.[11] After ammonolysis of **1**, the amide was transformed with hypochlorite by Hoffmann degradation to di-*exo*-3-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid **2** (obtained by another route in the literature[12]), which, on reduction with LAH, yielded the corresponding 3-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-methanol **3**. On boiling in toluene with 3-(*p*-toluoyl)propionic acid **A**, 2-(*p*-toluoyl)benzoic acid **B** or *cis*- (**C**) or *trans*- (**D**) 2-(*p*-toluoyl)cyclohexane-1-carboxylic acid in the presence of a catalytic amount of PTSA, aminoalcohol **3** gave the partly saturated epoxy pyrrolo[2,1-*a*][3,1]benzoxazinone **4** or isoindolo[3,1]benzoxazinones **5** and **6** (Scheme 1). From the reaction mixture, these and the rDA products pyrrolo[1,2-*b*][1,3]oxazinone **7**, [1,3]oxazino[2,3-*a*]isoindolone **8** and *trans*-[1,3]oxazino[2,3-*a*]isoindolone **9** were isolated. The starting stereoisomeric 2-(*p*-toluoyl)cyclohexane-1-carboxylic acids yielded the same *trans*-condensed derivative **9**, *i.e.* the *cis*-*p*-toluoylcyclohexanecarboxylic acid **C** isomerized to the *trans* compound **D** in the course of the reaction. Compounds **4-9** were isolated by column chromatography and their structures were determined by means of NMR spectroscopy and (for the parent epoxy compound **6** and the rDA product **9**) also by X-ray analysis (Figure 1).

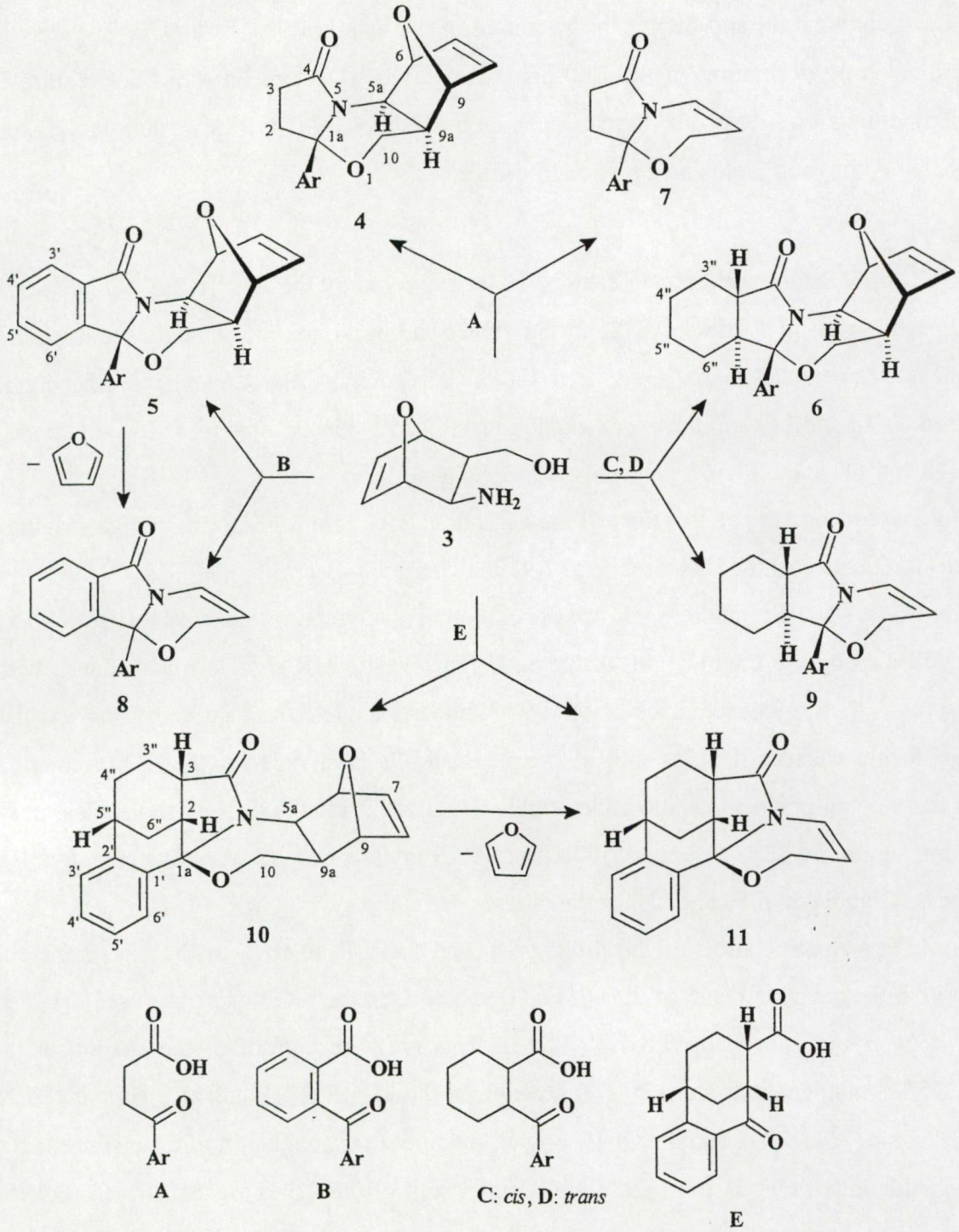



**6** **9**

Figure 1. Perspective views of **6** and **9**

Thermal ellipsoids have been drawn at a probability level of 30%

The similar reaction of **3** with 10-oxohexahydromethanobenzocyclooctene-8-carboxylic acid **E** gave the heptacyclic **10** and its rDA product **11**. When **5** or **10** was boiled in chlorobenzene for 1 h, **8** and **11** were obtained in good yields by the loss of furan.




Ar = *p*-tolyl

Scheme 1

The results demonstrate the advantages of the application of furan instead of CP in the retro-diene synthesis. The main advantage is the preparation of heterocycles which have no oxo group on the newly formed 1,3-oxazine ring. Thus, condensed heterocycles without a "quasi-aromatic" struc-

ture could be prepared for the first time by this rDA method. The process involves the incorporation of the oxazine-fused heterocycles on the furan-diene, followed cleavage of the carrier part in the closing thermolytic step. The application of furan extends the scope of the rDA reaction, because formation of the new hetero ring requires neither an oxo nor a thioxo group to ensure the electron demand and conjugation and permit incorporation of the heterocycles, as on CP. The easy loss of furan promotes the formation of the new hetero ring. This rDA process does not require drastic thermal conditions or special instruments such as in flash vacuum pyrolysis, and the heterocycles can be obtained in good yields on a preparative scale.

**Structure**

The structures of compounds **2** and **4-11** were proved by the IR, $^{1}H$ and $^{13}C$ NMR spectral data; these are given in Tables 1 and 2. In the Tables and in the text of this part, the numbering of pyrrolobenzoxazine **4** (Scheme 1) is used for all compounds. The C atoms of the condensed benzene (**5, 8, 10** and **11**) and the cyclohexane rings (**6** and **9-11**) are numbered C-3′-6′ (**5** and **8**) or C-1′-6′ (**10** and **11**) and C-3″-6″, respectively (see Scheme 1).

In consequence of the *–I* effect of the C=C double bond on the N (imide-like structure),[13] the amide-I frequency of the rDA products (**7-9**) is higher by 6-21 $cm^{-1}$.

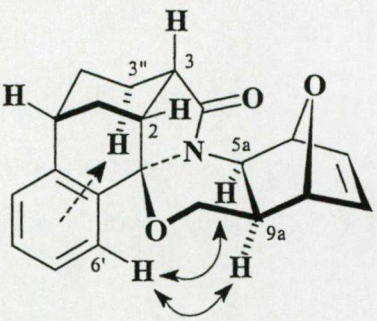
In **4-6** and **10**, the unaltered di-*exo* annelation of the oxanorbornene moiety to the oxazine ring is confirmed by the doublet split of the 5a-H (NC*H*) $^{1}H$ NMR signal, in accordance with our "splitting rule":[14,15] in consequence of the ~90 ° dihedral angles, the 5a,6 and 9,9a vicinal H,H-couplings do not cause a doublet split of the 5a-H and 9a-H signals for the di-*exo* compounds, whereas these couplings lead to a well-detectable 2-4 Hz split for the di-*endo* molecules, in which the dihedral angles are ~30 °. Because of the 5a-H,9a-H interaction, these protons give doublets for the di-*exo* and double doublet signals for the di-*endo* derivatives.

In **4**, the *trans* position of the tolyl group and 5a,9a-H relative to the oxazinone ring is probable from the negative result of the DIFFNOE experiment: no NOE was observaed between the *ortho*-hydrogens of the tolyl group and 5a,9a-H. This is indirect proof of the stereostructure in Scheme 1. The analogous structure of **6** follows from the identical $^{1}H$ and very similar $^{13}C$ NMR chemical shifts of H/C-5a,9a and the $OCH_2$ group. In **6**, the *trans* annelation of the cyclohexane ring to the pyrrolidone is obvious from the double triplet split of the 2,3-H signals, which proves two *diaxial* couplings for each of these hydrogens. With a preferred chair conformation for the cyclohexane, the very strong shielding of 6″-$H_{ax}$ (0.45 ppm) evidenced the *exo* (*trans* to 5a,9a-H and 2-H) orientation of the tolyl group (anisotropic shielding of the close-lying benzene ring.[16a] X-ray measurements on **6** confirmed the presumed stereostructure (Fig. 1). Its rDA product **9** has an analogous stereostructure: the *trans* annelation of the cyclohexane can be assumed from the double triplet split of the 2,3-H signals and the similar sums of the $^{13}C$ NMR shifts[16b] for this ring (203.5

and 201.5 ppm for **6** and **9**, respectively), while the *exo* (*trans* to 2-H) position of the tolyl group follows from the 6″-H shift of 0.48 ppm. The X-ray results are in accordance with the above (Fig. 1).

Similarly as in **6**, the analogous configuration of C-1a, *i.e.* the position of the tolyl substituent *trans* to the annelational 5a,9a-H in **5**, follows from the similar shifts of H/C-9a, C-5a and C-10 ($\Delta\delta$ = 0.06/1.6, 1.1 and 0.3 ppm). As negative evidence, NOE was not observed for the tolyl *ortho*-protons and the annelational hydrogens (5a,9a-H) in **5**. Because of the different steric position of 5a-H and the tolyl group, the downfield shift of 5a-H (by 0.63 ppm) is opposite in sign to that expected if the C-1a configuration had changed (*endo* tolyl group). This is a consequence of the strained benzo-fused skeleton.

Because of the three common carbons with the condensed pyrrolidone ring, the homotricyclic part of the heptacycle **10** and its rDA derivative **11** is rather rigid and contains the cyclohexane ring in chair form, with 2,3,5″-H in *cis–cis* positions. For steric reasons, the C-1a configuration must be $R^*$; thus, the O atom is *cis* with 2,3-H relative to the pyrrolidone ring. Lying above the benzene ring, 3″-H is strongly shielded (its signal is at 1.15 and 0.72 ppm for **10** and **11**, respectively, shifted upfield as compared with all the other hydrogens in these molecules). The oxanorbornene moiety is fused to the other part of the molecule (to the pentacycle in **11**) in such a way that the bridging O lies over the heterobicyclic part of the skeleton, close to 2,3-H (Fig. 2).




**10**

↗ Anisotropic shielding ↩ NOE

Figure 2

The strong hindrance between the bridging O and the benzene ring means that the opposite fusion, which would result in an extremely crowded structure, can be excluded for steric reasons. The oxazine ring of **11** has a boat conformation, with N and the methylene C atom out of the plane of 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), the two ethereal oxygens would come rather close to each other. As evidence of this steric arrangement, besides the geminal coupling of 11.2 Hz, the O-methylene hydrogens have vicinal couplings of 11.8 and 5.8 Hz with 9a-H, in accordance with the

dihedral angles of ~170 ° and ~50 °. For **10**, the dramatic downfield shift of the 6-H singlet at 7.04 ppm (which appears in the interval 4.79-4.98 ppm in the $^1$H NMR spectra of **4-6**) is further evidence of this steric structure. This can be explained by the anisotropy of the carbonyl group[16c] situated close to and coplanar with 6-H in the presumed conformation. In accordance with the above, a strong NOE was observed between 6'-H and 5a,9a-H.

**Experimental**

IR spectra were run in KBr discs on a Bruker IFS-55 FT-spectrometer controlled by Opus 3.0 software. The $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at RT, on a Bruker DRX-500 spectrometer at 500 ($^1$H) and 126 ($^{13}$C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker micro program NOEMULT to generate NOE[17] and to get DIFFNOE spectra[16d,18] was used with a selective pre-irradiation time. DEPT spectra[19] were run in a standard manner,[20] using only a $\Theta = 135°$ pulse to separate the CH/$CH_3$ and $CH_2$ lines phased "up" and "down", respectively. The 2D-COSY,[21a,22a] HMQC[21b,22b] and HMBC[23,24] spectra were obtained by using the standard Bruker pulse programs COSY-45 INV4GSSW and INV4GSLRNDSW, respectively.

X-ray data collection and processing

Crystallographic data were collected at 173 K on a Nonius Kappa CCD area-detector diffractometer, using graphite monochromatized $MoK_\alpha$ radiation ($\lambda = 0.71073$ Å). The data collection was performed with φ and ω scans. The data were processed with DENZO-SMN v0.93.0.[25]

*Crystal data on* **6**. $C_{22}H_{25}NO_3$, $M_r = 351.43$, monoclinic, $a = 8.7200$ (4), $b = 8.2127(4)$, 25.6171(15) Å, $\beta = 93.827(2)°$, $U = 1830.47(16)$ Å$^3$, $T = 173$ K, space group $P2_1/c$ (no. 14), $Z = 4$, $\mu$(Mo–$K_a$) = 0.084 mm$^{-1}$, 3118 unique reflections ($R_{int}$ = 0.067), which were used in calculations. The final $wR(F^2)$ was 0.0144 (all data).

*Crystal data on* **9** $C_{18}H_{21}NO_2$, $M_r = 283.36$, triclinic, $a = 8.0749$ (3), $b = 9.7002(4)$, 9.9297(4) Å, $\alpha$ = 100.160(2), $\beta = 99.861(2)$, $\gamma = 97.555(2)°$, $U = 743.71(5)$ Å$^3$, $T = 173$ K, space group $P\text{-}1$ (no. 2), $Z$ = 2, $\mu$(Mo–$K_a$) = 0.090 mm$^{-1}$, 2611 unique reflections ($R_{int}$ = 0.040) which were used in calculations. The final $wR(F^2)$ was 0.1177 (all data)

The structures were solved by direct methods with the *SIR92* program,[26] and full-matrix least-squares refinements on $F^2$ were performed by using the *SHELXL-97* program.[27] For both, all heavy atoms were refined anisotropically. The hydrogen atoms were included at the fixed distances with fixed displacement parameters from their host atoms. Figures were drawn with *Ortep-3 for Windows*.[28]

**Supplementary data**

Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication no. CCDC-235065 for **6** and CCDC-235066 for **9**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

**Di-*exo*-3-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (2)**: Di-*exo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (33.23 g, 0.2 mol) was added in portions to a stirred solution of $NH_4OH$ (6%, 280 mL) at 0 °C. At this temperature, a cooled solution of NaOH (24.40 g, 0.61 mol) in water (110 mL) was added dropwise. After removal of the excess ammonia, the mixture was diluted with water (330 mL) and NaOCl solution (2.04 M, 100 mL) was added dropwise over a period of 1 h, with stirring and cooling. The solution was maintained at 70 °C for 5 min, then cooled and adjusted to pH 2 with HCl (36%). After evaporation to dryness in vacuum, the residue was extracted with hot EtOH (5×100 mL). The alcoholic solution was evaporated down and the residue was dissolved in water and transferred to a column of Dowex 50 ion-exchange resin (in acid form). The column was washed with water until neutral, and the amino acid **2** was eluted with a mixture of $NH_4OH$ (25%, 600 mL) and water (2400 mL). The residue from the evaporated eluate was dissolved in water, the solution was filtered, and acetone was added until a turbidity appeared. Yield: 16.45 g (53%), as a white powder.

**Di-*exo*-3-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-methanol (3)**: Amino acid **2** (5.0 g, 32 mmol) was added to a stirred suspension of $LiAlH_4$ (3.15 g, 0.083 mol) in dry THF (200 mL) at 0 °C. Stirring was continued for 8 h at room temperature. After standing overnight, the mixture was cooled and a solution of water (7 mL) in THF (30 mL) was added dropwise. After filtration, the filtrate was evaporated down to furnish the crude aminoalcohol as a yellow oil (3.45 g, 76%), which was applied in the further reactions.

**6,9-Epoxy-3a-*p*-tolyl-2,3,5a,6,9,9a-hexahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazin-1(2*H*)-one (4), 1,4-epoxy-6a-*p*-tolyl 1,4,4a,12a-tetrahydro-2*H*-isoindolo[2,1-*a*][3,1]benzoxazin-11(6a*H*)-one**

**(5), 1,4-epoxy-6a-*p*-tolyl 1,4,4a,6b,7,8,9,10,10a,12a-decahydro-2*H*-isoindolo[2,1-*a*][3,1]benz-oxazin-11(6a*H*)-one (6), 8a-*p*-tolyl-dihydro-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-6(7*H*)-one (7), 10b-*p*-tolyl-3,4-dihydro-2*H*-[1,3]oxazino[2,3-*a*]isoindol-6(10b*H*)-one (8), 10b-*p*-tolyl-6a,7,8,9,10,10a-hexahydro-2*H*-[1,3]oxazino[2,3-*a*]isoindol-6(6a*H*)-one (9), 1,4-epoxy-7,9-ethano-4,4a,7,7a,8,9,15,15a-octahydro-1*H*,6*H*-benzo[6,7]indolo[1,7a-*a*][3,1]benzoxazin-6-one (10) and 11,13-ethano-11,11a,12,13-tetrahydro-6*H*,10*H*-benz[*g*][1,3]oxazino[2,3-*i*]indol-10-one (11)** – General procedure: A mixture of aminoalcohol **3** (1.41 g, 0.01 mol), oxoacid [(0.01 mol): 3-(*p*-toluoyl)propionic acid (1.92 g) or *cis*- or *trans*-2-(*p*-toluoyl)cyclohexane-1-carboxylic acid (2.46 g) or 2-(*p*-toluoyl)benzoic acid (2.40 g) or 10-oxohexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid[29] (2.30 g)] and PTSA (0.05 g) in dry toluene (30 mL) was refluxed for 8 h with the application of a water separator. After the solvent had been evaporated off, the residue was dissolved in $CHCl_3$ (10 mL), transferred to a silica gel column (Kieselgel 60 Merck, 0.040-0.063 mm) and eluted first, with *n*-hexane–EtOAc (4:1) for the rDA products **7-9** and **11**, and then with a mixture of *n*-hexane–EtOAc (2:1) for **4-6** and **10**. The residues of the eluates were crystallized. Data on compounds **4-11** are listed in Table 3.

**Preparation of compounds 8 and 11 from 5 and 10**: Compound **5** (0.58 g, 1.68 mmol) or **10** (0.42 g, 1.25 mmol) was refluxed in dry chlorobenzene (10 mL) for 2 h. The cooled solution was transferred to a silica gel column and eluted with *n*-hexane–EtOAc (4:1) for the rDA products **8** or **11**. Yields are given in Table 3.

**Preparation of compounds 7 and 9 by direct rDA reaction**: A mixture of aminoalcohol **3** (1.41 g, 0.01 mol), oxoacid **A** (1.92 g, 0.01 mol) or **C** (2.46 g, 0.01 mol) and PTSA (0.05 g) in dry 1,2-dichlorobenzene (30 mL) was refluxed for 2 h. The residue of the evaporated dichlorobenzene solution was dissolved in $CHCl_3$ (2×30 mL), transferred to an aluminium oxide column (Merck, Aluminium oxide 90, neutral, 0.063-0.200 mm) and eluted with *n*-hexane–EtOAc (4:1) for the rDA products **7** or **9**. Yields and melting points are given in Table 3.

**Acknowledgements**

The authors are indebted to Mrs. E Csiszár-Makra for the typing of the manuscript. Grants OTKA 29651, T 37204, T 43634 and FKFP 0200/2000.

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: 1. Characteristic IR frequencies[a] and $^1$H NMR data[b] on compounds **2** and **4-11**[c]

| Amide-I band | $\gamma C_{Ar}H$ band[d] | $CH_3$ *s*(3H) | 2-H | 3-H | $OCH_2$ (2×1H)[f] | 5a-H[g] | 9a-H[h] | 6-H | 9-H | 7-H | 8-H | 2*,6*-H | 3*,5*-H |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | pyrrolidone ring[e] | | 6-membered hetero ring | | | OCH groups[i] | | olefinic group[k] | | *p*-tolyl group[l] | |
| 1555[m] | – | – | – | – | – | 3.52 | 2.68 | 5.06 | 5.15 | 6.40 | 6.64 | – | – |
| 1699 | 820 | 2.36 | 2.25,[n] | ~2.4 | 3.52, 4.15 | 3.96 | 2.07 | 4.98 | 4.47 | 6.53 | 6.28 | 7.24 | 7.19 |
| 1700 | 800 | 2.32 | – | – | 3.96, 4.03 | 4.60 | 2.02 | 4.79 | 4.73 | 6.52 | 6.36 | 7.42 | 7.15 |
| 1699 | 823 | 2.37 | 1.98 | 1.91 | 3.52, 4.15 | 3.97 | 2.08 | 4.92 | 4.41 | 6.52 | 6.26 | ~7.2 broad | |
| 1705 | 819, 837 | 2.38 | ~2.3, ~2.4,[o] ~2.45 | | 3.86, 4.17 | 7.02 | 5.07 | – | – | – | – | 7.20 | 7.22 |
| 1716 | 827 | 2.34 | – | – | 4.23, 4.33 | 7.19 | 5.17 | – | – | – | – | 7.47 | 7.20 |
| 1713 | 822 | 2.29 | 1.98 | 1.80 | 3.84, 4.06 | 6.90 | 4.92 | – | – | – | – | 7.13 | 6.90 |
| 1688 | 767 | – | ~2.6 | | 3.68, 4.10 | 3.78 | 2.48 | 7.04 | 4.70 | 6.39 | 6.52 | – | – |
| 1709 | 759 | – | ~2.41[p] | 2.49[r] | 4.33, 4.45 | 6.96 | 5.36 | – | – | – | – | – | – |

Br discs ($cm^{-1}$). Further IR bands, $\nu$NH (**2**): 3600-2250 broad; $\nu_s CO_2^-$ (**2**): 1400; $\nu$C–O (oxazine): 1079 (**4**), 1045 (**5**, **8**), 1070 (**6**), (**7**, **10**), 1060 (**9**), 1015 (**11**); $\nu$C–O (oxanorbornene): 1382 (**4**, **6**), 1370 (**5**), 1392 (**10**); $\gamma C_{Ar}H$ (olefinic group, split band for **10**): -**6**, **9**, **10**), 730 (**7**), 724 (**8**), 720 (**9**, **10**), 710 (**11**); $\gamma C_{Ar}H$ band (*ortho*-disubst. ring): 760 (**5**, **8**, **11**), 767 (**10**). – [b]In $CDCl_3$ (**4-10**), **2**) or DMSO-$d_6$ (**11**) solution at 500 MHz. Chemical shifts in ppm ($\delta_{TMS}$ = 0 ppm), coupling constants in Hz. Further $^1$H NMR s, cyclohexane, ~qa and ~d, 3"-$CH_2$: 1.25 and 2.15 (**6**, **9**), 1.15 and 1.9 (**10**), 0.75 and 1.6 (**11**), 4"-$CH_2$: 1.2 and 1.65 (**6**, **9**), 1.8 (2H, 45 and 1.7 (**11**), 5"-$CH_2$: 1.0 and 1.75 (**6**, **9**), 3.05 (m, 1H, **10**, **11**), 6"-$CH_2$: 0.45 and 1.85 (**6**, **9**), 1.15 and 1.9 (**10**), 1.85 and ~2.1 ondensed benzene ring, 3'-H, ~d: 7.85 (**5**, **8**),7.15 (**10**, **11**), 4'-H, ~t: 7.45 (**5**, **8**),7.25 (**10**, **11**), 5'-H, ~t: 7.5 (**5**, **8**),7.2 (**10**, **11**), 6'-H, 45 (**5**, **10**, **11**), 7.55 (**8**). – [c]Assignments were supported by HMQC and HMBC (except for **9**), for **4**, **5**, **10** and **11** also by IOE and for **6**, **8** and **11** by 2D-COSY experiments. – [d]*p*-disubst. ring, split for **7**. – [e]Methylene groups in **4** and **7**, 2-3 m (4H), e groups in **6** and **9**-**11** (1H), 2×dt, $J$ = 12.2, 12.2, 3.4 and 12.5, 12.5, 3.0 (**6**, **9**). – [f]2×dd, $J$ = 11.9, 9.8 and 11.9, 8.0 (**4**, **6**), 12.1, d 12.1, 5.8 (**5**), td and ddd, $J$ = 16,7, 1.8, 1.8 and 16.7, 3.7, 2.0 (**7**, **8**), d and ddd, $J$ = 16.6 and 16.6, 3.8, 2.0 (**9**), t and dd, $J$ = 11.5, nd 11.2, 5.8 (**10**), ddd and td, $J$ = 17.7, 3.8, 2.0 and 17.7, 2.0 (**11**). – [g]NCH group, d, $J$ = 7.5 (**2**), 8.3 (**4**-**6**), 6.7 (**10**), td, $J$ = 8.3, 2.0 (**1**). – [h]d, $J$ = 7.5 (**2**), qa, $J$ = 8.3 (**4**), td, $J$ = 8.3, 5.9, 5.9 (**5**), 9.8, 8.1, 8.1 (**6**), ddd, $J$ = 8.4, 3.8, 1.7 (**7**-**9**, **11**). – [i]2×~s (2×1H), for er split to t's by 1.2 Hz due to long range couplings. – [k]2×dd, $J$ (for both dd's) = 5.8, 1.0 (**2**), 5.8, 1.7 ± 0.2 (**4**-**6**, **10**). – [l] AA'BB'-gnal, 2×~d (2×2H), $J$ = 8.1 (**4**, **5**, **8** and **9**). – [m]$\nu_{as} CO_2^-$ band (**2**). – [n]Intensity: 1H, the m of the other H of 2-$CH_2$ overlaps with $CH_2$ signals at about 2.4. – [o]Intensity: 2H. – [p]Hidden by the light isotope signal of the solvent. – [r]td, $J$ = 11.1, 7.8, 7.8.

Table 2. $^{13}C$ NMR chemical shifts[a] of compounds **2** and **4–11**[b,c]

| | C-1a | C-2[d] | C-3[d] | C=O | C-7 | C-8 | $OCH_2$ | NCH | C-9a | C-6 | C-9 | C-1' | C-2'6' | C-3'5' | C-4' |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | pyrrolidone ring | | | | olefinic group | | 6-membered hetero ring | | | OCH groups | | *p*-tolyl group or benzene ring[e] | | | |
| **2** | – | – | – | 179.0 | 135.4 | 141.9 | – | 52.9 | 48.5 | 84.1 | 85.1 | – | – | – | – |
| **4** | 93.4 | 39.4 | 29.0 | 176.4 | 136.1 | 135.2 | 65.0 | 51.5 | 31.0 | 83.5 | 80.3 | 138.8 | 126.0 | 129.6 | 138.1 |
| **5** | 92.1 | 149.6 | 127.9 | 171.4 | 136.3 | 136.7 | 64.6 | 51.6 | 32.9 | 82.4 | 81.3 | 137.2 | 125.6 | 129.6 | 138.1 |
| **6** | 93.9 | 55.5 | 43.7 | 177.2 | 136.0 | 135.0 | 64.9 | 50.5 | 31.3 | 84.0 | 80.2 | 134.0 | 129.2[e] | | 138.4 |
| **7** | 92.5 | 36.6 | 29.3 | 170.9 | 120.1 | 109.5 | 61.9 | – | – | – | – | 137.0 | 125.9 | 130.1 | 138.9 |
| **8** | 90.8 | 147.0 | 130.43 | 166.2 | 121.0 | 109.8 | 62.6 | – | – | – | – | 135.2 | 126.0 | 130.35 | |
| **9** | 92.9 | 52.9 | 44.6 | 171.5 | 119.8 | 108.2 | 61.5 | – | – | – | – | 132.5 | 127.1 | 129.4 | 139.0 |
| **10** | 90.7 | 38.9 | 39.8 | 177.1 | 135.3 | 137.5 | 63.3 | 53.3 | 39.9 | 78.5 | 78.8 | 139.3 | 140.5 | | |
| **11** | 85.5 | 39.7 | 42.7 | 173.3 | 121.4 | 108.1 | 60.8 | – | – | – | – | 139.6 | 140.0 | | |

[a]In ppm ($\delta_{TMS}$ = 0 ppm) at 126 MHz. Solvent: $CDCl_3$ (**4-10**), $D_2O$ (**2**) or DMSO-$d_6$ (**11**). – [b]Assignments were supported by DEPT, HMQC and HMBC (except for **9**) measurements. – [c]Further lines [numbering: see **4-6** and **10** (Scheme)]: $CH_3$: 21.5 (**4-9**). Condensed benzene/cyclohexane ring, C-3'/3": 123.9 (**5**), 25.9 (**6** and **9**), 124.6 (**8**), 128.96/21.1 (**10**), 129.5/20.7 (**11**), C-4'/4": 129.7 (**5**), 25.6[f] (**6** and **9**), 130.1 (**8**), 129.02/31.0 (**10**), 129.7/32.1 (**11**), C-5'/5": 133.4 (**5** and **8**), 25.7[f] (**6** and **9**), 127.0/34.5 (**10**), 127.8/34.2 (**11**), C-6'/6": 123.2 (**5** and **8**), 27.1 (**6**), 26.8 (**9**), 127.5/26.5 (**10**), 126.4/25.5 (**11**). – [d]$CH_2$ group (**4**, **6**, **7** and **9-11**) or substituted carbons (condensed benzene ring, **5** and **8**). – [e]Two broad coalesced lines. – [f]Interchangeable assignments.

Table 3. Physical and analytical data on compounds **2-11**

| Compd. | Mp. °C | Yield % | Formula (Mw.) | Analysis Found % C | H | N | Calcd % C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **2** | 194-195[a,b] | 53 | $C_7H_9NO_3$ (155.15) | 54.35 | 6.02 | 9.15 | 54.19 | 5.85 | 9.03 |
| **4** | 173-174[c] | 25 | $C_{18}H_{19}NO_3$ (297.35) | 72.96 | 6.60 | 4.87 | 72.71 | 6.44 | 4.71 |
| **5** | 126-128[d] | 28 | $C_{22}H_{19}NO_3$ (345.39) | 76.29 | 5.37 | 4.19 | 76.50 | 5.54. | 4.06 |
| **6** | 192-194[c] | 27 | $C_{22}H_{25}NO_3$ (351.44) | 75.31 | 7.30 | 3.51 | 75.19 | 7.17 | 3.99 |
| **7** | 77-78[e] | 18 (65) | $C_{14}H_{15}NO_2$ (229.27) | 73.56 | 6.75 | 6.23 | 73.34 | 6.59 | 6.11 |
| **8** | 148-150[e] | 17 (57)[f] | $C_{18}H_{15}NO_2$ (277.32) | 77.74 | 5.33 | 4.89 | 77.96 | 5.45 | 5.05 |
| **9** | 139-140[e] | 22 (59) | $C_{18}H_{21}NO_2$ (283.36) | 76.08 | 7.35 | 4.80 | 76.29 | 7.47 | 4.94 |
| **10** | 196-198[c] | 19 | $C_{21}H_{21}NO_3$ (335.40) | 75.43 | 6.48 | 4.29 | 75.20 | 6.31 | 4.18 |
| **11** | 151-152[e] | 21 (64)[f] | $C_{17}H_{17}NO_2$ (267.32) | 76.61 | 6.57 | 5.39 | 76.38 | 6.41 | 5.24 |

Crystallization solvent: [a]$H_2O$–$Me_2CO$. – [b]with decomposition. – [c]*i*-$Pr_2O$. – [d]$Et_2O$. – [e]$Et_2O$–*n*-hexane. – [f]Obtained from **5** or **10**.