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

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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

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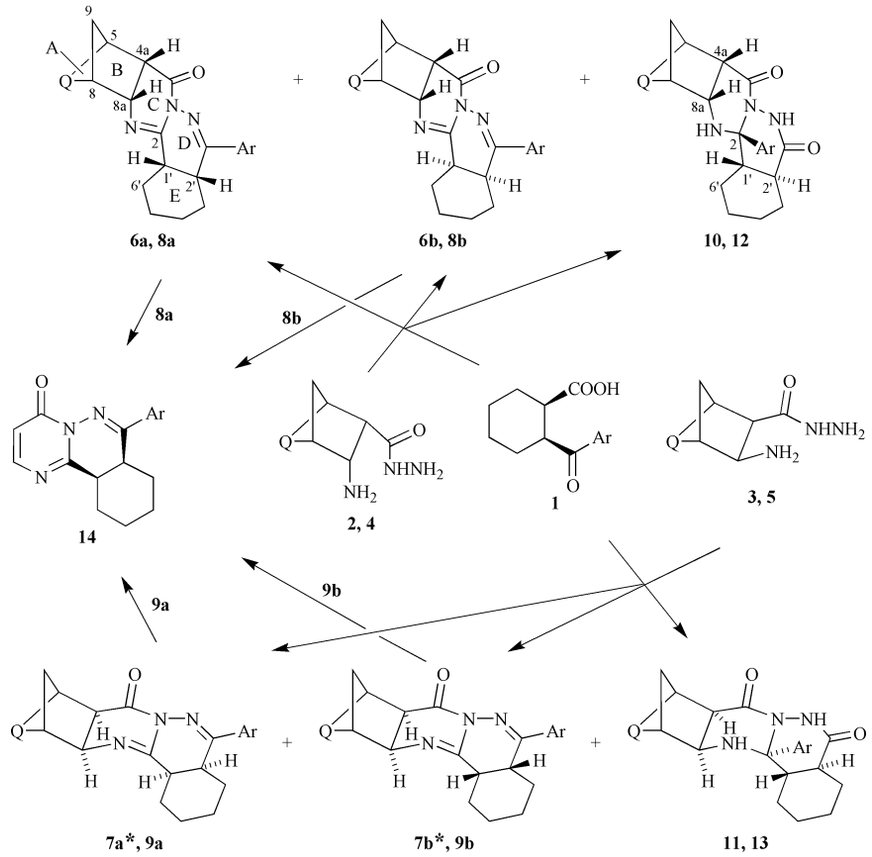
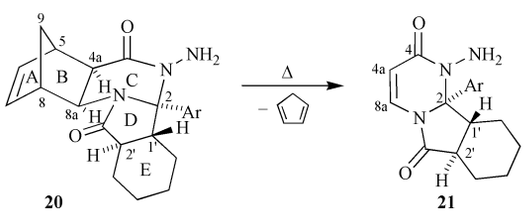


Scheme 1 Ar = $C_6H_4CH_3$-*p*; Q = CH_2CH_2 (**2**, **3**, **6**, **7**, **10**, **11**) or CH=CH (**4**, **5**, **8**, **9**, **12**, **13**) (* for **7a** and **7b**, reversed configurations are also possible).



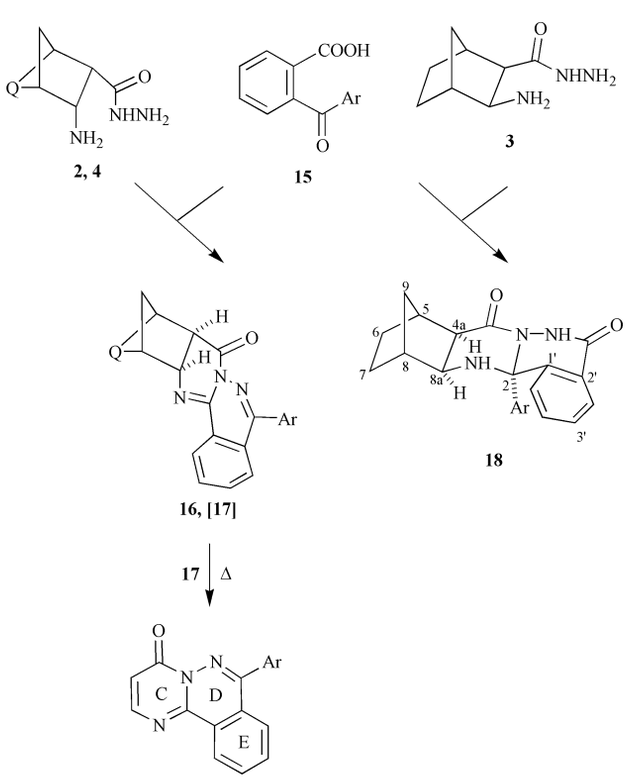
Scheme 2 Ar = $C_6H_4CH_3$-*p*.

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.



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

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	Aryl group[i] 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 δ3′-H(*ax*) < δ3′-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 $\nu_{as}NH_2$–ν_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 (δ_{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 ^{1}H 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, $\Sigma\delta$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 [$\Sigma\delta$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** [$\Delta\delta$ 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 ^{1}H 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 (^{1}H) 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**

			Found (%)				Requires (%)		
Compound	Yield (%)	Mp/°C	C	H	N	Formula	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**.

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