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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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-arylhexahydropyridazine 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.

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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.

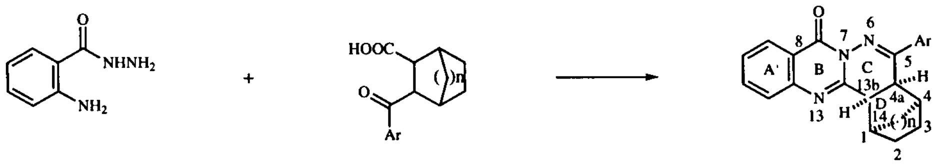
When both terminal rings are saturated, the stereochemistry at both terminal ring junctions must be examined. This problem does not arise in the aromatic analogues [11-16], but it complicates the determination of the structures of the present target compounds.

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 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.

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**.

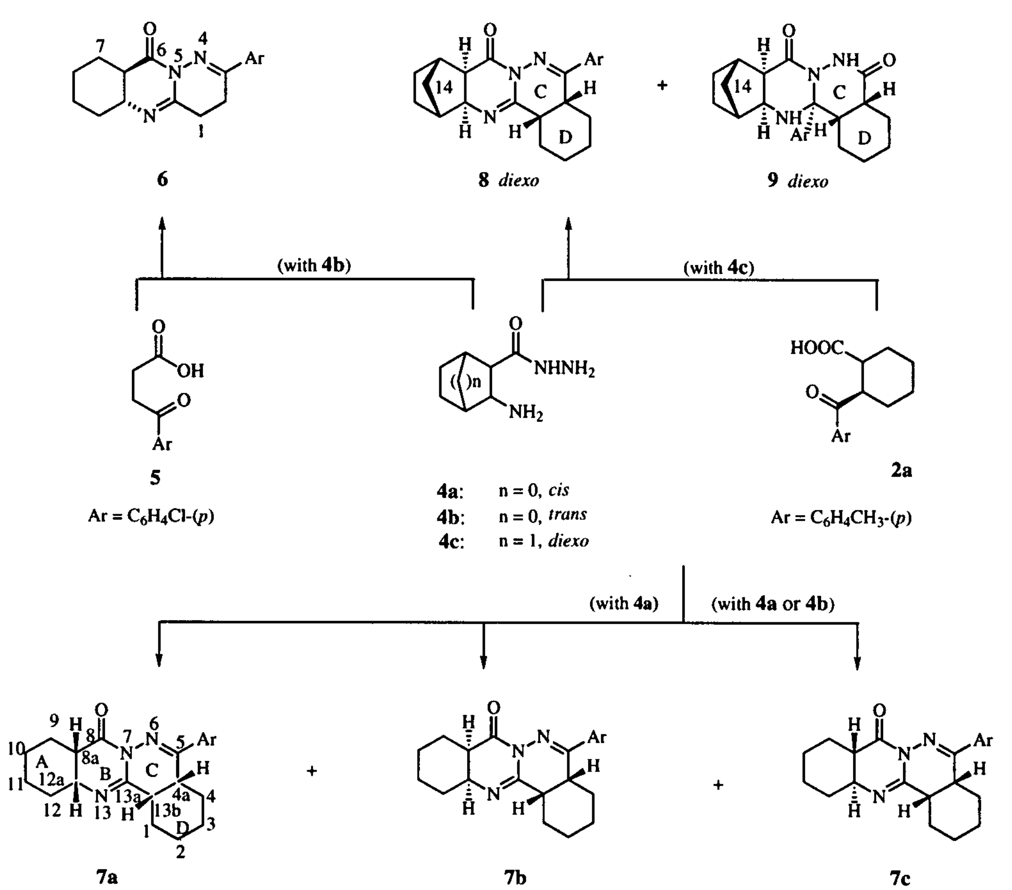
This reaction differs from the formation of **6-8**, where the carboxyl group took part in cyclization to form the pyrimidine ring, and the oxo group was condensed with the hydrazine moiety. Similar reactions yielding bislactams are known [8,11,16]. An interesting feature of these new compounds arises 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



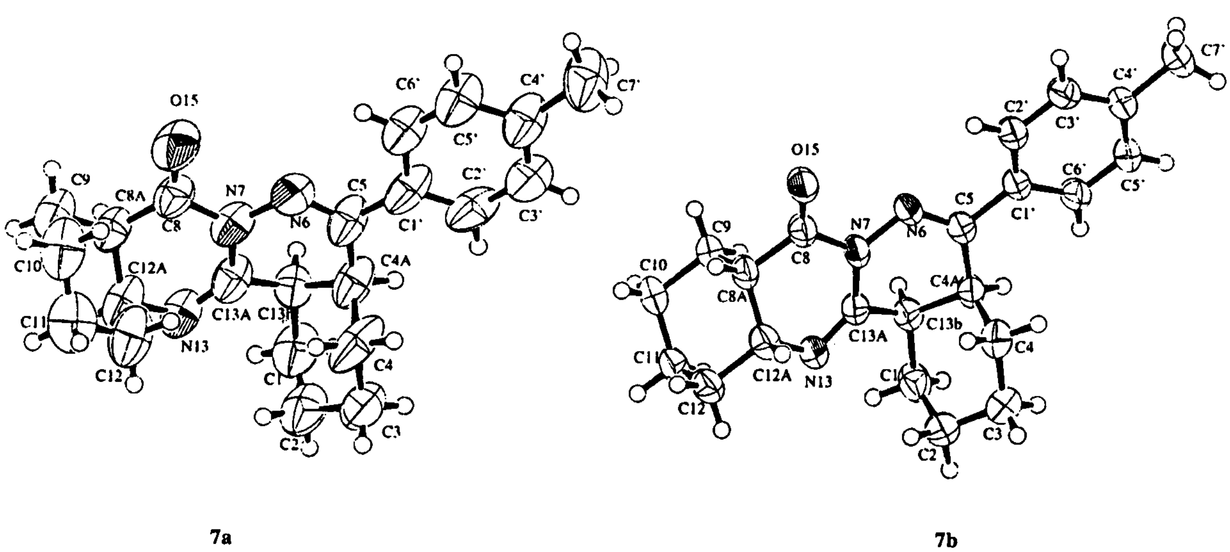


Figure 1. Perspective views of compounds **7a** and **7b**.

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]

* δ_{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	$C_{22}H_{21}N_3O$	76 94	6.16	12.23
		(benzene)	(343.43)	76.75	6.21	12.24
3b	42	260-263	$C_{23}H_{21}N_3O$	77.72	5.96	11.82
		(benzene)	(355.44)	77.61	6.08	11.90
6	35	254-256	$C_{17}H_{18}ClN_3O$	64.66	5.75	13.31
		(EtOAc)	(315.80)	64.54	5.70	13.27
7a	15	200-202	$C_{22}H_{27}N_3O$	75.61	7.79	12.02
		(EtOH)	(349.48)	75.34	7.98	12.00
7b	26	167-169	$C_{22}H_{27}N_3O$	75.61	7.79	12.02
		(EtOH)	(349.48)	75.77	7.69	12.19
7c	5 [a]	248-249	$C_{22}H_{27}N_3O$	75 61	7.79	12.02
	31 [b]	(EtOAc)	(349.48)	75.66	7.68	11.92
8	36	273-275	$C_{23}H_{27}N_3O$	76.42	7.53	11.62
		(EtOAc)	(361.49)	76.40	7.63	11.57
9	29	286-287	$C_{23}H_{29}N_3O_2$	72.79	7.70	11.07
		(dioxane)	(379.50)	72.93	7.82	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_α ($\lambda = 1.5418$ Å) radiation. The intensity data were collected in an ω-2θ scan mode at an ω scan speed of 4.0° min^{-1} with ω scan width = 1.52 + 0.30 tan θ. 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, β = 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, α = 101.84(4), β = 117.47(2), γ = 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)-l-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 (x10^4) 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-l-cyclohexanecarbohydrazide **4a** or **4b** (1.57 g, 0.01 mole) and cis-2-(*p*-methylbenzoyl)-1-cyclohexane-carboxylic 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.

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