PREPARATION AND STERIC STRUCTURE OF CONDENSED-SKELETON SATURATED DIPHENYL-SUBSTITUTED ISO-INDOLONES

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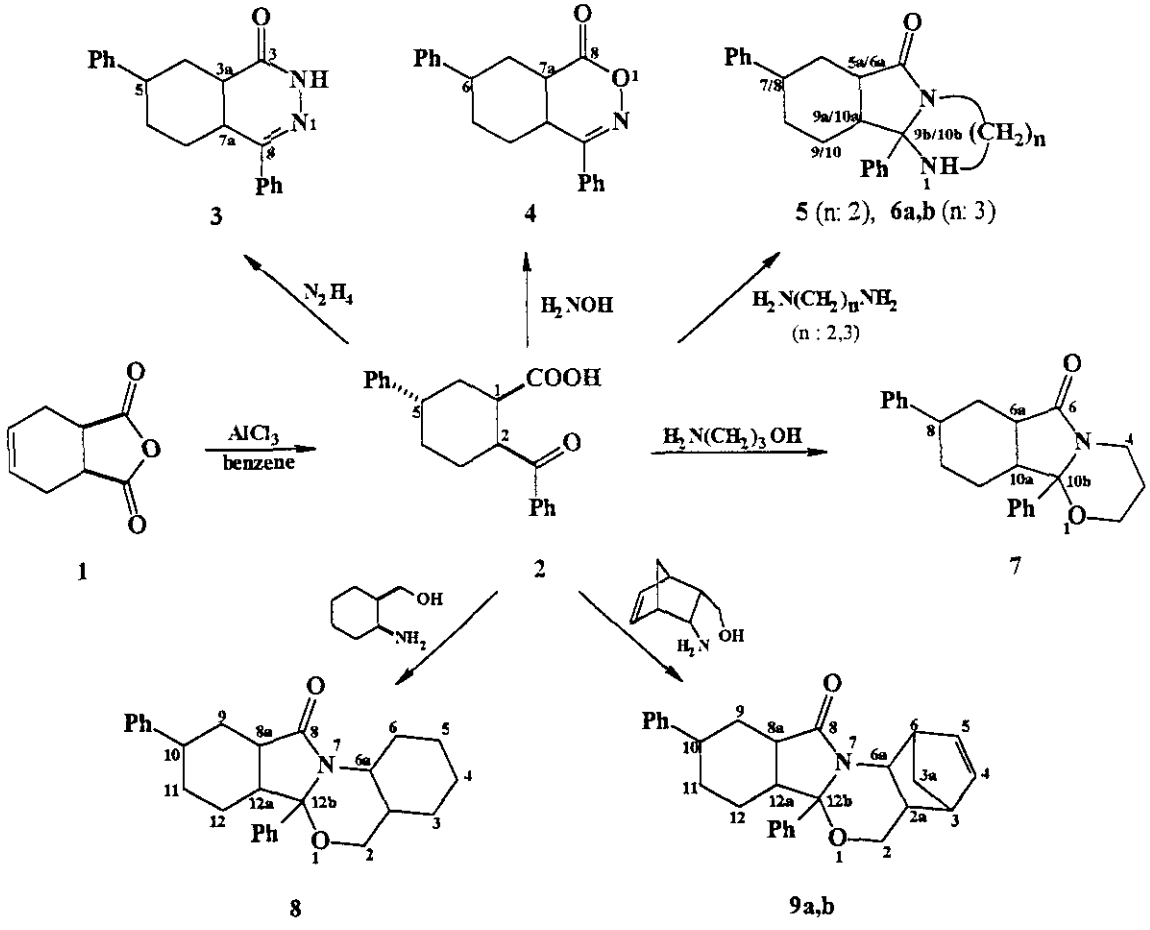
Abstract – The Friedel-Crafts reaction of benzene with *cis*-4-cyclohexene-1,2-dicarboxylic anhydride (**1**) yields *trans*-5-phenyl-*cis*-2-benzoylcyclohexane-carboxylic acid (**2**), which gave cyclohexane-condensed pyridazinone (**3**) with hydrazine, and *cis*-4,5-tetramethylene-1,2-oxazin-8-one (**4**) with hydroxyl-amine. From **2** with ethylenediamine, the saturated imidazo[2,3-*a*]isoindol-one (**5**) was prepared, while the reaction of **2** with 1,3-diaminopropane furnished a mixture of two isomeric pyrimido[2,3-*a*]isoindolones (**6a,b**) differing in the relative positions of the benzene ring and cyclohexane annelation hydrogens. From the reaction of **2** with 3-aminopropanol, the oxazino[2,3-*a*]isoindolone (**7**) was obtained. The reaction of **2** with *cis*-2-hydroxymethylcyclohexylamine gave the tetracyclic (**8**), while **2** and *diendo*-3-hydroxymethylbicyclo[2.2.1]hept-5-enyl-2-amine yielded the isomers (**9a,b**), which differ in the mutual positions of the phenyl group on the quaternary carbon and cyclohexane annelation hydrogens. ^{1}H- and ^{13}C-nmr spectra and DNOE and 2D-HSC measurements proved that the 5-phenyl group is *cis-equatorial* to the two annelated hydrogens of the cyclohexane ring.

As a continuation of our systematic stereochemical studies[1, 2] on cycloalkane-fused 1,3-heterocycles, fully or partly saturated isoindolones containing two condensed hetero rings were synthesized.[3, 4] The versatile synthon (**2**) was used for these syntheses, which made possible the preparation of a number of saturated or partly saturated 1,3-heterocycles containing three, four or five fused rings. The synthesis and stereochemical investigation of these fairly complex target compounds seemed very promising from both stereochemical and pharmacological aspects. Systematic comparative nmr analyses of related bicyclic and tricyclic systems were performed earlier and X-ray analyses were also carried out in several cases.[3-7] The more complex systems described in the present paper are worthy of study, for to date merely syntheses of analogous compounds containing an aromatic ring A have been reported. The stereochemistry of these aromatic compounds is much simpler, because neither the stereochemistry of the A/B ring fusion nor the steric position of the aryl substituent relative to this ring annelation need be considered. The pharmacological potential of the target compounds is likewise of interest, because some of the corresponding aromatic analogues[8, 9] have anorectic activity, and several drugs with related structures are applied in therapy.[10] We have therefore carried out a systematic synthetic study to obtain these interesting new ring systems. Some of the results are described in the present paper which reports the preparation and structure elucidation of compounds phenyl-substituted on the cyclohexane ring.

In contrast with some aromatic analogues synthesized earlier,[8, 11] our compounds are interesting stereochemically too, because the mutual positions of the hetero rings relative to the terminal carbocyclic ring(s) can differ. Their positions, the conformation of the rings, and the position and stereoposition of the phenyl ring on the cyclohexane therefore, have to be elucidated. Additionally, structure determination is important, because, depending on the reaction conditions, the configurations of the starting compounds often change, as experienced in preparations of similar compounds.[12, 13]

SYNTHESIS

The $AlCl_3$-catalysed reaction of benzene with *cis*-1,2,3,6-tetrahydrophthalic anhydride (**1**) furnishes *c*-2-benzoyl-*t*-5-phenyl-*r*-1-cyclohexanecarboxylic acid (**2**) in 72% yield[14] (Scheme). The ^1H- and ^{13}C-nmr measurements demonstrate that the 5-phenyl group is *equatorial* and the carboxyl *axial*.



Scheme

The similar arylation of *cis*-1,2,3,6-tetrahydrophthalic acid or its dimethyl ester with benzene leads to *r*-1,*c*-2,*t*-4-phenyl-1,2-cyclohexanedicarboxylic acid.[14-16] However, the Friedel-Crafts reaction of 4-phenyl-*cis*-1,2-cyclohexanedicarboxylic anhydride with benzene has been reported to result in 4-phenyl-*cis*-2-benzoyl-1-cyclohexanecarboxylic acid in much higher yield (67%) than that of the 5-phenyl derivative (11%).[16] As explanation, we suppose that the acylation of benzene with **1** is the decisive step in our

reaction. Then, in the subsequent addition, the *axial* carboxyl group of the *cis*-2-benzoyl-4-cyclohexene-1-carboxylic acid directs the phenyl group predominantly into the 5-position, when **2** is formed.
The synthon (**2**) was cyclized with hydrazine to 5,8-diphenyl-3a,4,5,6,7,7a-hexahydrobenzo[*d*]pyridazin-3(2*H*)-one (**3**) (Scheme). Non-condensed and other substituted derivatives of **3** are already known as potential drugs.[8,9]
The reaction of **2** with hydroxylamine yielded the analogous bicyclic 1,2-oxazinone (**4**), and that of **2** with ethylenediamine resulted in the decahydroimidazo[2,1-*a*]isoindolone (**5**). With 1,3-diamino-propane, two isomeric saturated pyrimido[2,1-*a*]isoindolones (**6a,b**) were formed. On boiling in benzene, **2** and 3-aminopropanol gave the saturated 1,3-oxazino[2,3-*a*]isoindolone derivative (**7**).
Synthon (**2**) with cyclic 1,3-aminoalcohols furnished the more complicated, condensed tetracyclic or pentacyclic 1,3-oxazines, containing two fully or partly saturated carbocyclic terminal rings. On the reaction of *cis*-2-hydroxymethyl-1-cyclohexylamine, the tetracyclic compound (**8**) was formed, the steric structure of which, *i.e.* the relative configurations of the four annelated carbon atoms and the phenyl-substituted quaternary carbon, have to be elucidated. Because of the different solubilities and advantageous chromatographic properties, the two condensed methylene-bridged isoindolo[2,1-*a*][3,1]benzoxazine (**9a,b**) diastereomers could be isolated from the reaction of **2** and *diendo*-3-hydroxymethylbicyclo[2.2.1]hept-5-enyl-2-amine.

STRUCTURES

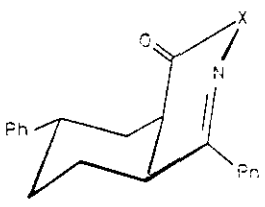
The presumed structures of **3** and **4** are proved by the ir, ^{1}H- and ^{13}C-nmr spectra (Tables 1 and 2). The position# (5 or 6 in **3**, and 6 or 5 in **4**) and the orientation (*cis* or *trans* relative to the annelation hydrogens and *equatorial* or *axial*, respectively) of the phenyl group on the cyclohexane, and the *cis* or *trans* annelation of the cyclohexane and the hetero ring have to be elucidated. The signals of the annelation H-3a,7a## and 5 or 6 methine hydrogen geminal to the phenyl group have been identified by combined DEPT (distortionless enhancement of polarization transfer), 2D-HSC (two-dimensional heteronuclear shift correlation) and DNOE (differential nuclear Overhauser effect) measurements.
For **3**, the signal of the *ortho*-hydrogens of the phenyl group on the sp^2 carbon is downfield-shifted because of conjugation, and hence it can be identified unambiguously; the strong NOE between it and the 3.25 ppm multiplet of a CH group (indicated by DEPT) proves the assignment of the latter to H-7a. Irradiation of this signal in a NOE experiment causes an increase in intensity of the 2.95 ppm CH multiplet; hence, the latter is that of H-3a. Thus, the third CH signal geminal to the phenyl appears at ~2.8 ppm.
As the H-7a signal has a quintet fine structure (signal width ~25 Hz), while that of H-3a is a merged triplet (signal width ~12 Hz), the *cis* annelation of the two six-membered rings and the *equatorial* H-3a are plausible (the *diaxial* coupling of H-7a with the vicinal H-7*ax* results in the much larger signal width of H-7a[17]). On irradiation of the H-7a signal, neither the signal of the *ortho*-hydrogens of the phenyl group on the cyclohexane, nor that of the hydrogen geminal to the latter, reacts in the NOE experiment; hence, position 6 for the phenyl group can be excluded.
From the hardly different ^{1}H- and ^{13}C-nmr shifts of the CH groups, the analogous stereostructures of **3** and **4** follow unambiguously. In the spectrum of **4**, the signal of the CH group geminal to the phenyl ring is separated (for **3** it overlaps with the H-4*eq* multiplet); its triple triplet splitting (by *ca.* 12, 12, 3 and 3 Hz) makes the assignment straightforward (four vicinal hydrogens are possible only in the case of the CH group in question) and it proves its *axial* position, *i.e.* the *equatorial* orientation of the geminal phenyl group (which is sterically favourable *ab ovo*). Thus, the full *c*-3aH,*t*-5H,*c*-7aH stereo-structure (and 3a*R**,5*S**,7a*S** configuration) of the two compounds is proved## (Figure 1).

#For the numbering, see the Scheme.
##Our compounds are racemates and the structure is that of the 3a*R** enantiomer configuration. The numbering refers to **3**.

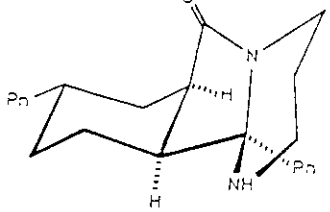
Table 1. The ir carbonyl frequency (in KBr discs, cm^{-1}) and ^1H-nmr data (chemical shifts in ppm, δ_{TMS} = 0 ppm, coupling constants in Hz) on compounds (**3-5, 6a,b, 7, 8 and 9a,b**) in $CDCl_3$ solution at 250 MHz[a]

Compound	Amide-I band[b]	CH_2(cyclohexane ring) 3-5 *m*'s (6H)	H-3a *m*(1H)[c]	H-5 *m*(1H)[d]	H-7a *m*(1H)[e]	ArH(Pos. 1, 5)	1-4*m*'s (10H)	$CONCH_2$ 2x*m*(2x1H)[f]		XCH_2 2x*m*(2x1H)[g]	
3	1668	1.5-1.8[h,i] 1.90[j] 2.05[k] ~2.8[l,m]	2.95	~2.8[m]	3.25	7.2-7.5	7.80[n,o]	–	–	–	–
4	1755	1.5-1.8[h,i] 2.07[m,p] 2.75[l]	3.10	2.92	3.25	7.2-7.5	7.80[n,o]	–	–	–	–
5	1690	1.00[q] 1.1[k] 1.32[r] 1.6-1.8[p] ~2.55[l,h]	~2.55[h]	2.45	~3.1[m]	7.1-7.6[s]		~3.1[m]	3.90	~2.55[h]	~3.1[m]
6a	1675	1.3-1.6[h,i] ~1.9[m] 2.10 ~2.5[l,t]	2.62	~2.5[t]	2.25	7.1-7.4		3.05	4.25	~2.5[t]	2.90
6b	1674	0.85[q] 0.95[k] 1.25 1.5-1.8[h,p] 2.60[l]	3.10	2.40	2.20	7.1-7.5	7.65[u]	3.20	4.25	2.75	2.85
7	1711	0.85[k] 0.95[q] 1.28[r] 1.65[h,p] 2.59[l]	~3.2[m]	~2.35[t]	~2.35[t]	7.1-7.5	7.60[u]	~3.2[m]	4.18	3.70	3.80
8	1707	~0.75[h,p] 0.95 ~1.25[m] ~1.65[m] 2.55[l]	3.15	2.40	2.20	7.1-7.5	7.61[u]	4.48		3.53	3.93
9a	1696	~1.3[h,j] 1.85[j] 2.10[k] ~2.42[m]	~2.65[t]	~2.50[m]	2.30	7.1-7.5[s]		4.21		2.93	3.92
9b	1695	0.53[q] 1.60[k] ~1.75[p] ~2.1[h,j] ~2.55[l,m]	~3.15[t]	~2.05[h]	~2.05[h]	6.90[u]	7.0-7.4	4.29		~3.15[t]	3.95

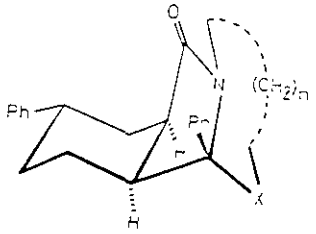
[a]Numbering in the Heading see on the Scheme for **3**. Further ir bands: νNH: 3450 and 3225 (**3**), 3327 (**6a**), 3450 (**6b**). ^1H-Nmr assignments were proved by DNOE and 2D-HSC measurements. Further ^1H-nmr signals: NH, broad *s*(1H): 9.10 (**3**), 2.03 (**5**), ~1.9[m] (**6a**), 2.00 (**6b**), CCH_2C group in diazine (**6a,b**), oxazine (**7**), cyclohexane condensed to the oxazine (**8**) or norbornene ring (**9a,b**: *AB*-type spectrum of the 5-methylene groups, 2x*d*, *J* ~8): 1.3-1.6[h,p] (**6a**), 1.30, ~*d* and 1.5-1.8[h,p] (**6b**), 1.20, ~*d* and 1.85 *m* (**7**), 0.75[h] and 1.1-1.7[m,v] (**8**), 1.42 and 1.50 (**9a**), 1.38 and 1.42 (**9b**); CCHC (oxazine): 2.08 *m* (**8**), ~2.65 (**9a**,[v]**b**). Further signals[w] of the norbornene ring in **9a,b**: CH(3). ~2.65[t] (**9a**), ~2.6[m] (**9b**), =CH(4,5), *dd* (*J* = 5.8 and 3.0): 5.62 and 5.95 (**9a**), 5.50 and 5.62 (**9b**), CH(6), ~*s*: 3.60 (**9a**), 3.32 (**9b**); [b]Carbonyl type group vibrational band, ester νC=O band for **4**; [c]Triplet-like signal with coalesced lines, half signal width: ~12 (except for **6a**, where the lines of the triplet are separated, *J* ~7); [d]A triple triplet multiplicity of this signal can be recognized for **4, 5, 6b** and **8**; [e]Half band width ~30 (**3, 4**); [f]For **8**: *td*(1H), *J* = 13.0, 4.8 and 4.8, *dd*(1H) for **9a,b**, *J* = 9.6 and 3.3; [g]X: NH (**5** and **6a,b**) or O (**7, 8, 9a,b**), *dd* (*J* = 11.7 and 3.7) + *t* (*J* = 12.0) for **8**, *t* (*J* = 11.5) + *dd* (11.6 and 8.0) for **9a,b**; [h/m/t]Overlapping signals; [i/p/v]Intensity: 3H/2H/7H; [j]H-6*eq*, ~*d* (*qad*); [k]H-7*eq*, ~*d*; [l]H-4*eq*, ~*d* (*qad*); [n]1-phenyl group; [o/u]H[*ortho*], ~*d*(2H/1H); [q]H-7*ax*, *dqa*; [r]H-6*ax*, *dqa*; [s]Downfield wing of this signal is broadened; [w]Numbering see on the Scheme for **9a,b**



3 (X = NH)
4 (X = O)



6a



5 (n = 2, X = NH)
6b (n = 3, X = NH)
7 (n = 2, X = O)

Figure 1

Stereostructure of compounds (**3-5, 6a,b** *and* **7**)

Irradiation of the 3.1 ppm signal of H-7a in **4** proves the assignment of H-7*ax* and H-7*eq* to the 1.70 ppm double triplet and the 2.75 ppm triple doublet, and the trivial increase in intensity of the H-3a multiplet was also observed. The splits of the H-7*ax* double triplet (~12, 12 and 3 Hz) prove that H-6 is *axial*. The marked downfield shift of the H-7*eq* triple doublet is caused by the anisotropic effect of the vicinal coplanar carbonyl.[18a] Both circumstances support the presumed stereostructure.

For the isomeric pair (**6a,b**), the similar (~15 Hz) width of the H-6a signal and the hardly different shift of the cyclohexane carbons are proof of the *cis* annelation and *chair* conformation of the cyclohexane, in which the carbonyl group is *axial* to the cyclohexane. For an *axial* H-6a, a broader H-6a signal would be

expected due to a *diaxial* H-6a,H-7*ax* vicinal coupling,[17] and the total shielding of the six carbons in the cyclohexane would be influenced significantly by a change in the annelation[18b] (the difference measured is only 4.4 ppm, and that for **6a** indicates a slightly more crowded structure). Accordingly, the different configurations of the quaternary carbon, and hence the different positions of the 10b-phenyl group in the isomers, follow (Figure 1).

The phenyl group is in position 8 and *equatorial* in both isomers, as proved by the practically identical H-8 and C-8 chemical shifts.

Table 2. ^{13}C-Nmr chemical shifts (δ_{TMS} = 0 ppm) on compounds (**3-5, 6a,b, 7, 8,** and **9a,b**)[a]

	C_q-1	C=O Pos. 3	C-3a	C-4	C-5	C-6	C-7	C-7a	Phenyl (Pos. 5) C-1'	C-2',6'	C-3',5'	C-4'	Phenyl (Pos. 1) C-1'	C-2',6'	C-3',5'	C-4'	NCH_2[b]	XCH_2[c]
3	153.9	169.4	36.9	31.0	39.4	24.9	32.9	35.6	146.1	126.9	128.5[d]	126.3	134.7	125.9	128.8[d]	129.9	-	-
4	164.6	171.6	36.1	31.3	38.8	26.3	32.4	36.3	145.2	126.8[d]	128.6[e]	126.5	131.6	126.6[d]	129.0[e]	131.4	-	-
5	89.8	184.3	38.3	31.2	40.4	31.0	28.4	42.8	146.2	126.8	128.4	126.2	139.9	~129[f]	126.4	127.7	45.3	45.7
6a	79.2	173.6	39.3	30.4	40.5	30.8	24.4	45 6	146.3	126.8	128.3	126.1	141.2	127.1	128.7	127.7	37.4	40.1
6b	81.2	178.1	42.2	31.0[g]	40.56	31.0[g]	27.2	43.4	146.3	126.7	128.3	126.1	138.6	127.2[h]	128.8[h]	127.8	39.2	40.64
7	95.8	180.3	42.1	30.8	40.8	31.0	27.0	43.2	146.3	126.7	128.3	126.1	136.8	126.9	128.5	128.0[d]	38.5	62.1
8	95.1	182.3	41.9	30.8	40.6	31.0	27.6	44.1	143 6	125.7	128.5[d]	125.8	139.6	127.6	128.6[d]	128.3	54.0	62.7
9a	92.9	178.4	38.9	30 4	40.3	30.5	24.6	50.0	146.7	126.8	128.3	126 0	141.7	~127[f]	~129[f]	127.9	53.2	64.7
9b	93.2	178.2	36.2	30.9	37.5	28.2	23.3	56.0	143.8	127.3[d]	128.0[g]	125.4	136.8	127.4[d]	128.0[g]	126.5	51.9	64.3

[a]Measuring frequency 62.9 Mz, solvent: $CDCl_3$. Assignments were proved by DEPT and 2D-HSC measurements (except for **9**); [b]Amide-N; NCH group for **8** and **9a,b**; [c]X: NH (**5, 6a,b**) or O (**7, 8, 9ab**); [d,e]Interchangeable assignments; [f]Broadened signal; [g]Two overlapping lines; [h]Two separated lines, with the second one at 127.5 and 128.8 for **6b** and at 128.1[d] and 129.3 for **7**, respectively.

For **6a**, the upfield shift (by 0.48 ppm) of the H-6a signal (anisotropic shielding of the phenyl group[18c]) supports the R^* configuration of C-10b (*i.e.* the *cis* position of the 10b-phenyl group and H-6a,10a to the pyrrolidone ring). For **6b**, this effect can be observed for the 10-methylene signal and it is stronger (for the H-10*ax* signal a 0.7 and for the H-10*eq* signal a 1.15 ppm upfield shift), because the phenyl group *trans* to H-6a,10a lies much closer to the 10-methylene group. For H-10*eq*, the reason for the large shift difference in **6a** and **6b** is the opposite anisotropic (downfield) effect of the C-N bond in **6a** for this hydrogen. The steric interaction of H-6a and the 10b-phenyl group decreases the C-6a shift by 2.9 ppm in **6a**, while for **6b** the similar interacion of H-10*ax* and the 10b-phenyl group is reflected in the upfield shift (by 2.2 ppm) of the C-10a line (steric compression shift;[19]). The anisotropic effect of the coplanar carbonyl group[18a] results in the downfield shift of H-7*eq* (~2.5 and 2.6 ppm) for both isomers.

DNOE measurements support the stereostructures postulated above. On saturation of the H-6a and H-10a signals for **6a**, the 10b-phenyl group reacts, which is proof of their *cis* position. For **6b**, irradiation of the unambiguously assigned H-10*ax* signal causes an increase in intensity of the H-8*ax* multiplet, which – indicating the 1,3-*diaxial* position of H-10*ax* and the hydrogen geminal to the phenyl group – shows the 8-*equatorial* position of the phenyl substituent on the cyclohexane (and that for the isomer **6a** from the identical H-8a and C-8 chemical shifts).

Free rotation of the 10b-phenyl group in **6b** is impossible, as H-10*ax* and the *axial* hydrogens of the two methylene groups vicinal to the hetero atoms of the diazine ring surround the 10b-phenyl ring and allow it to move in only a narrow segment. As a consequence, the C-2' and C-6' and the C-3' and C-5' lines of the phenyl group separate in the ^{13}C-nmr spectrum (Table 2) and the H-2' double doublet also separates downfield (7.65 ppm, 1H) from the other ^{1}H-nmr signals. For the latter signal and the H-10a multiplet, a mutual NOE was observed, which demonstrates that it comes from the *exo ortho*-hydrogen. The down-

field shift of this signal is caused by the anisotropic effect of the coplanar and close NH bond (the H...NH distance is ~2.0 Å).

The hindered rotation of the 9b-phenyl group, the strong shielding of H-9*ax* and H-9*eq* and the fact that the shift of the H-5a signal is practically identical with that for **6b** clearly indicate the analogous structures of the homologue **5** (with imidazolidine ring) and **6b** (Tables 1 and 2). In accordance, in a DNOE experiment, saturation of the H-9*ax* signal led to a response in (*a*) that of H-9a, which is proof of the correct assignment of the former, (*b*) that of H-7*ax* (geminal to the phenyl group on the cyclohexane ring), which proves the 1,3-*diaxial* arrangement and the 7-*equatorial* position of the phenyl group, and (*c*) that of the *ortho*-hydrogens on the 9b-phenyl group, which points to its *trans* position relative to H-5a,9a. The NOE between H-9*ax* and H-7*ax* is indirect evidence of the *axial* position of the amide carbonyl relative to the cyclohexane ring. This also follows from the similar signal widths and splits of the H-5a signals in the spectra of **6a** and **6b**.

Similar arguments and data (*e.g.* spectral features indicating the hindered rotation of the 10b-phenyl ring, the downfield shift of the H-6a signal, the strong shielding of the 10-methylenehydrogens, the small $\Delta\delta$ C-6a,10a and NOE results analogous to those observed for **6b**) strongly suggest the identical stereostructure of the 1,3-oxazine derivative **7**: *axial* carbonyl, 8-*equatorial* and *trans*-10b- (relative to the *cis* H-6a,10a) phenyl groups (Figure 1).

For **8**, the analogous stereostructure is probable in respect of the positions of the *cis-equatorial*-10- and *trans*-12b-phenyl groups relative to the *cis* H-8a and H-12a (Figure 2). In accordance, the signal of one of the *ortho*-hydrogens of the 12b-phenyl group separates downfield (hindered rotation) and the H-8a signal is downfield-shifted (3.12 ppm). From the triple triplet structure of the H-10 signal (where the ~12 Hz triplet splitting proves its *axial* position), the *cis-equatorial* orientation of the 10-phenyl group follows. Because of the strong mutual NOE with the signal of the *ortho*-hydrogen of the 10-phenyl group, the assignment of H-10 is unambiguous.

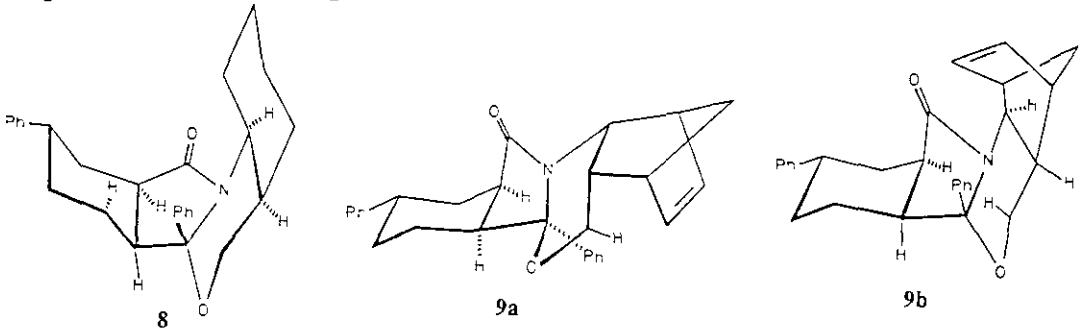


Figure 2

Stereostructure of compounds (**8** *and* **9a**,**b**)

From the 7 Hz triplet splitting of the H-8a signal, the *equatorial* position of this hydrogen and the *cis* annelation of the pyrrolidinone and cyclohexane rings follows (in the event of a *trans* annelation, the H-8a,9*ax* and H-8a,12a *diaxial* couplings would give a higher splitting). Hence, similarly to the analogues (**5**, **6a,b** and **7**) and related compounds investigated earlier, the quaternary carbon is again *equatorial* to the cyclohexane ring of the *cis*-annelated skeleton (because of the higher steric demand) and the carbonyl group is *axial*.[4, 13]

In the DNOE spectrum obtained by saturation of the H-12*ax* multiplet, the downfield signal of one of the *ortho*-hydrogens of the 12b-phenyl group can be found, but the latter group gave no response on irradiation of the H-8a signal. This shows that the 12b-phenyl group and H-8a,12a are *trans*, and thus **8** and **6b** have identical structures in the common parts of the skeleton.

The triple doublet splittings (by ~13, 5 and 5 Hz) of the unambiguously assigned 4.48 ppm NCH signal prove the *cis* annelation of the cyclohexane and oxazine rings. The strong NOE between the 12b-phenyl group and H-2*ax* proves the *trans* arrangement of the phenyl group and the annelated oxazine hydrogens. Thus, the stereostructure of **8** is defined by the configuration 2a*S**,6a*S**,8a*R**,12a*S**,12b*S**.

This structure explains the hindered rotation of the 12b-phenyl group (due to the interaction of the *endo* H-2*ax*,6*ax*,12*ax*), the strong shielding of H-6*ax* and H-12*ax* (which lie over the benzene ring), and the downfield shift of the H-2*ax* and H-6a signals (because of the anisotropic effect of the coplanar benzene ring and carbonyl group[18a, c]). The high upfield shift of the C-6 line (at 21.1 ppm according to the 2D-HSC measurement) in consequence of the strong hindrance between the *endo* H-6*ax* and the 12b-phenyl group supports the postulated structure.

As compounds (**9a,b**) contain eight asymmetric centres, and because of the different stable conformations of the flexible cyclohexane and oxazine rings, a great number of stereostructures are possible. However, the bridged and rigid norbornane moiety eliminates some structures for steric reasons. This and the comparable spectral data for the two isomers made the elucidation of the structure easier.

For **9a**, the fine structures of the H-8a and H-12a signals are evidence of the *cis* annelation of the cyclohexane and pyrrolidone rings, and of the *axial* position of the carbonyl group relative to the cyclohexane ring. For these units, **9a** is similar in structure to the other compounds. The 10α-*equatorial* position of the phenyl group on the cyclohexane is proved by the practically identical ($\Delta\delta \leq 0.4$ ppm) chemical shifts of five of the six cyclohexane carbons for **6a** and **9a**.

The unchanged *diendo* annelation of the norbornene-oxazine rings is proved by the 9.5 and 3.2 Hz splits of the NCH signal.[20, 21] The 11.5 Hz triplet splitting of the signal of the *axial*-hydrogen of the 2-OCH_2 group indicates the chair conformation and C-2a configuration (*trans-axial* to H-2*ax*) of the six-membered heteroring (the *trans* position of the norbornene-oxazine annelation hydrogens and phenyl group relative to the oxazine ring).

From DNOE measurements, the *cis* position of H-8a,12a and the 12b-phenyl ring relative to the pyrrolidone ring (and the part-structure corresponding to **6a**) follow (Figure 2). The NOE between H-2*ax* and H-4 and the *ortho*-hydrogens of the 12b-phenyl group and olefinic H-5, respectively, are evidence of the C-3,6 configurations, indicating the nearness of H-2*ax* and 12b-Ph, respectively, and the close-lying olefinic hydrogen. The stereostructure represented in Figure 2, with configuration 2a*S**,3*S**,6*R**,6a*S**,8a*R**,10*S**,12a*S**,12b*R**, therefore follows. DNOE measurements also helped with the assignments of the H-3a(*endo*), H-3a(*exo*), H-3,6 and H-4,5 signal pairs.

For **9b**, the spectral data differ characteristically and show the opposite position of the 12b-phenyl group, *i.e. trans* to H-8a,12a (analogously as in **6b**). Thus, there is strong shielding of H-12*ax* (0.55 ppm) and a much larger shift difference $\Delta\delta$C-8a,12a (for **9b** 19.8 ppm, and for **9a** 11.1 ppm). A further fact supporting the stereostructure is the ~0.44 ppm downfield shift of H-8a relative to that in **9a** (the anisotropic shielding of the 12b-phenyl ring around H-8a in **9a** is absent in **9b**). From the ~15 Hz H-8a signal width, the *cis* annelation of the cyclohexane and the *axial* position of the carbonyl group relative to it are evident. In this respect, all compounds have similar stereostructure.

The *diendo* annelation of the norbornene moiety follows from the double doublet H-6a signal. The triplet splitting of the H-2*ax* signal (11.8 Hz) suggests the conformation of the oxazine ring involving an H-2*ax*-C-C-H-2a dihedral angle of ~180°, similarly as in **9a**. Hence, both pairs H-8a,12a, and H-2a,6a and the 12b-phenyl group are *trans* to the pyrrolidine and oxazine rings, respectively. The bridging methylene group lies on the opposite side of the molecular skeleton to the 12b-phenyl group. Thus, the configuration of **9b** is 2a*R**,3*R**,6*S**,6a*R**,8a*R**,10*S**,12a*S**,12b*S** (Figure 2).

DNOE measurements support this structure: saturation of the H-12*ax* multiplet (at 0.55 ppm) induces an increase in the intensity of the signal of the *endo ortho*-hydrogen of the 12b-phenyl group, which is proof of its β (*trans* to H-8a,12a) position. All other NOE results support the postulated structure and provide evidence for the assignments of the close-lying H-3,6, H-4,5 and H-3(*endo*), 3(*exo*) signal pairs.

To summarize, the results show that:

a) the phenyl substituent on the cyclohexane condensed to the pyrrolidine or six-membered hetero ring in **3** and **4** is in the γ (1,3) position to the carbonyl group (PhC_{γ}-C_{β}-C_{α}-CO);

b) this phenyl group is *trans-equatorial* to the carbonyl;

c) all compounds are conformationally homogeneous and the conformer containing an *axial* carbonyl and a vicinal annelated quaternary carbon *equatorial* to the cyclohexane is preferred to that in which the positions of these groups are reversed (because of the lower steric requirements of the carbonyl group);

d) in **8** and **9a,b**, the oxazine and cyclohexane or norbornene rings are *cis* annelated and H-2a,6a and 12b-Ph are *trans* to the oxazine;

e) in the isomeric pairs (**6a,b** and **9a,b**), the relative positions of the phenyl group on the quaternary carbon and the annelated hydrogens differ: these are *cis* or *trans*; the latter configuration is preferred, in agreement with the structure of the related compounds (**5**, **7** and **8**).

These statements accord with the conclusions from studies of molecular models and the stereochemical considerations.

EXPERIMENTAL

Ir spectra were run 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 in $CDCl_3$ solution in 5 mm tubes at room temperature, on a Bruker WM-250 FT-spectrometer controlled by an Aspect 2000 computer at 250.13 (^{1}H) and 62.89 (^{13}C) MHz, respectively, using the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measurement parameters were as follows: spectral width 5 and 15 kHz, pulse width 1 and 7 μs (~35° flip angle), acquisition time 1.64 or 1.02 s, number of scans 4-16 and 0.5-5 K, computer memory 16 and 32 K. Complete proton noise decoupling (~3 W) for the ^{13}C spectra and Lorentzian exponential multiplication for signal-to-noise enhancement were used (line width 0.7 and 1.0 Hz). For DNOE measurements,[18d, 22] the standard BRUKER microprogram "DNOEMULT.AU" to generate NOE was used, with a selective pre-irradiation time of 5 s and a decoupling power (CW mode) of ~3-40 mW; number of scans 64/256, dummy scans 4-8, pulse width 5.0 μs (90°) and 16 K data points for ~2 kHz spectral width. A line broadening of 1.0 Hz was applied to diminish residual dispersion signals in the difference spectra. The 2D-HSC spectra[23] were obtained by using the standard BRUKER pulse program "XHCORRD.AU". The number of data points was 4 K in the ^{13}C domain, and 64/256 increments were used to give better than 5 Hz/point digital resolution in the ^{1}H domain. 256 transients were obtained with a relaxation delay of 3 s. All C-H correlations were found by using J(C,H) = 135 Hz for calculation of the delay. DEPT spectra[24] were run in a standard way,[25] using only the θ = 135° pulse to separate the CH/CH_3 and CH_2 lines phased up and down, respectively. Typical acquisition data were: number of scans 128-12 K, relaxation delay for protons 3 s, and 90° pulse widths 10.8 and 22.8 μs for ^{13}C and ^{1}H, respectively. The estimated value for J(C,H) resulted in a 3.7 ms delay for polarization

Melting points are uncorrected. Physical and analytical data on the new compounds are listed in Table 3.

c-2-Benzoyl-*t*-5-phenyl-*r*-1-cyclohexanecarboxylic acid (2)

To a solution of *cis*-4-cyclohexene-1,2-dicarboxylic anhydride (**1**) (9.7 g, 64 mmol) in dry benzene (100 ml), anhydrous $AlCl_3$ (3.20 g, 24 mmol) was added in small portions, under stirring. After refluxing (2 h) and cooling, HCl 20% (40 ml) was added dropwise to the mixture, which was then extracted with EtOAc (5x50 ml). After evaporation of the extract, the residue was crystallized from EtOAc to give **2** as almost colourless crystals, mp 190 °C (lit.,[14] mp 194 °C), yield 14.2 g (72%).

Table 3. Physical and analytical data on compounds (**3-5, 6a,b, 7, 8** and **9a,b**)

Compound	mp °C	Yield %	Formula	Analysis Found % C	H	N	Required % C	H	N
3	216-218[a]	43	$C_{20}H_{20}N_2O$	79.00	6.80	9.36	78.92	6.62	9.20
4	179-180[b]	54	$C_{20}H_{19}NO_2$	78.87	6.48	4.75	78.66	6.27	4.59
5	213-214[b]	39	$C_{22}H_{24}N_2O$	79.20	7.18	8.47	79.48	7.28	8.43
6a	212-213[c]	18	$C_{23}H_{26}N_2O$	79.52	7.44	8.00	79.73	7.56	8.09
6b	207-208[b]	24	$C_{23}H_{26}N_2O$	79.80	7.40	7.98	79.73	7.56	8.09
7	185-186[b]	70	$C_{23}H_{25}NO_2$	79.65	7.34	4.02	79.51	7.25	4.03
8	182-184[b]	60	$C_{27}H_{31}NO_2$	80.50	7.81	3.59	80.76	7.78	3.49
9a	216-218[c]	27	$C_{28}H_{29}NO_2$	81.60	7.05	3.30	81.72	7.10	3.40
9b	201-203[c]	32	$C_{28}H_{29}NO_2$	81.79	7.14	3.52	81.72	7.10	3.40

From [a]dioxane, [b]ethanol and [c]ethyl acetate, respectively.

5,8-Diphenyl-3a,4,5,6,7,7a-hexahydrobenzo[*d*]pyridazin-3(2*H*)-one (3)

A mixture of **2** (3.1 g, 0.01 mol), $N_2H_4.H_2O$ (0.5 g, 0.01 mol) and benzene (30 ml) was refluxed (3 h). After evaporation of the mixture, the residue was crystallized. Data on **3** are listed in Table 3.

3,6-Diphenyl-3a,4,5,6,7,7a-hexahydrobenzo[*d*][1,2]oxazin-8-one (4)

A solution of **2** (3.1 g, 0.01 mol) and H_2NOH. HCl (0.7 g, 0.01 mol) in EtOH (30 ml, 90%) was refluxed (3 h). After cooling, the solid that separated out was filtered off and crystallized.

7,9b-Diphenyl-1,2,3,5a,6,7,8,9,9a,9b-decahydroimidazo[2,1-*a*]isoindol-5-one (5) and 8,10b-diphenyl-1,2,3,4,5,6a,7,8,9,10,10a,10b-dodecahydropyrimido[2,1-*a*]isoindol-6-ones (6a,b)

A solution of **2** (3.1 g, 0.01 mol), ethylenediamine monohydrate (2.3 g, 0.03 mol) or 1,3-diaminopropane (2.2 g, 0.03 mol), and *p*-toluenesulphonic acid (1 crystal) in toluene (30 ml) was refluxed (4 h), a water separator being applied, with tlc monitoring of the reaction. After evaporation, the residue was transferred onto a silica gel column (Kieselgel 60, 0.063-0.2 mm), then eluted with benzene and EtOAc. After evaporation of the latter eluate, the residue was crystallized to yield **5** (1.3 g, 39%) or **6b** (0.83 g, 24%). Compound (**6a**) was obtained from the mother liquor of **6b** by fractional crystallization with EtOH. On a tlc plate, **6a** gave a spot with somewhat lower R_f than that of **6b** [DC Alufolien, Kieselgel 60 F_{254} Merck, 0.2 mm, solvent: benzene – EtOH – petroleum ether (bp 40-60 °C) 4:1:3, development in iodine vapour].

8,10b-Diphenyl-2,3,4,5,6a,7,8,9,10,10a-decahydrooxazino[2,3-*a*]isoindol-6-one (7)

A solution of **2** (3.1 g, 0.01 mol), *p*-toluenesulphonic acid (1 crystal) and 3-amino-1-propanol (2.25 g, 0.03 mol) in benzene (30 ml) was refluxed (5 h), a water separator being applied. After removal of the solvent by distillation, the residue was crystallized.

9,12b-Diphenyl-2a,3,4,5,6,6a,8a,9,10,11,12,12a-dodecahydroisoindolo[2,1-*a*][3,1]benzoxazin-8-one (8)

A mixture of **2** (3.1 g, 0.01 mol), *cis*-2-hydroxymethylcyclohexylamine (1.3 g, 0.01 mol) and *p*-toluenesulphonic acid (1 crystal) in benzene (30 ml) was refluxed (3 h). After evaporation, the residue was transferred onto a silica gel column and eluted with benzene. After evaporation, the residue was crystallized.

10,12b-Diphenyl-3,6-methano-2a,3,6,6a,8a,9,10,11,12,12a-decahydroisoindolo[2,1-*a*][3,1]benzoxazin-8-ones (9a,b)

A mixture of **2** (3.1 g, 0.01 mol) and *diendo*-3-hydroxymethylbicyclo[2.2.1]hept-5-enyl-2-amine (1.4 g, 0.01 mol) was reacted in toluene (30 ml) as described in the previous experiment. After evaporation, the residue was transferred onto a silica gel column and eluted with benzene (**9a**), then with EtOAc (**9b**); on evaporation of the eluates, the two residues crystallized (tlc as above; R_f **9a** > R_f **9b**).

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