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Synthesis and Stereostructure of Saturated Isoindolone-Fused Hetero Tri-, Tetra-, and Pentacyclic Compounds

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Summary. *t*-2-Benzoyl-*t*-4-phenylcyclohexane-*r*-1-carboxylic acid reacts with hydrazine to give the saturated 1,7-diphenyl-*trans*-phthalazin-4(3*H*)-one. The reaction of the acid with ethylenediamine yields diastereomeric *trans*-imidazo[2,3-*a*]isoindoles, which differ in their C-1 configuration. The cyclizations of the acid with *cis*-2-aminocyclohexane- or 4-cyclohexenemethanol result in *trans*-isoindolo[2,1-*a*][3,1]benzoxazines, while in its reactions with the analogous di-*endo*- and di-*exo*-norbornane- and -norborneneamino alcohols, the acid gives methylene-bridged isomeric di-*endo*-norbornanes or a norbornene derivative; the corresponding diastereomeric di-*exo* derivatives have also been prepared. After isolation, the structures were established by means of ^{1}H and ^{13}C NMR spectroscopy, with application of DIFFN*O*E, DEPT, HMQC, HMBC, and 2D-COSY techniques.

Keywords. Isoindolones; Diastereomers; Methanobenzoxazinones; NMR; DIFFN*O*E.

Introduction

Both literature data [1–3] and our own results [4–6] indicate that the $AlCl_3$-catalysed reaction of *cis*-cyclohex-4-ene-1,2-dicarboxylic anhydride with benzene results in *t*-5-phenyl-*c*-2-benzoyl-*r*-1-cyclohexanecarboxylic acid. However, the reaction of *t*-4-phenyl-*c*-1,2-cyclohexanedicarboxylic anhydride with benzene yields mainly *t*-4-phenyl-*c*-2-benzoyl-*r*-1-cyclohexanecarboxylic acid (67%), together with a minor amount (11%) of the corresponding *t*-5-phenyl derivative. On treatment with NaOH, the former underwent ready transformation to *t*-4-phenyl-*t*-2-benzoyl-*r*-1-cyclohexanecarboxylic acid **1** [4], which has now been applied

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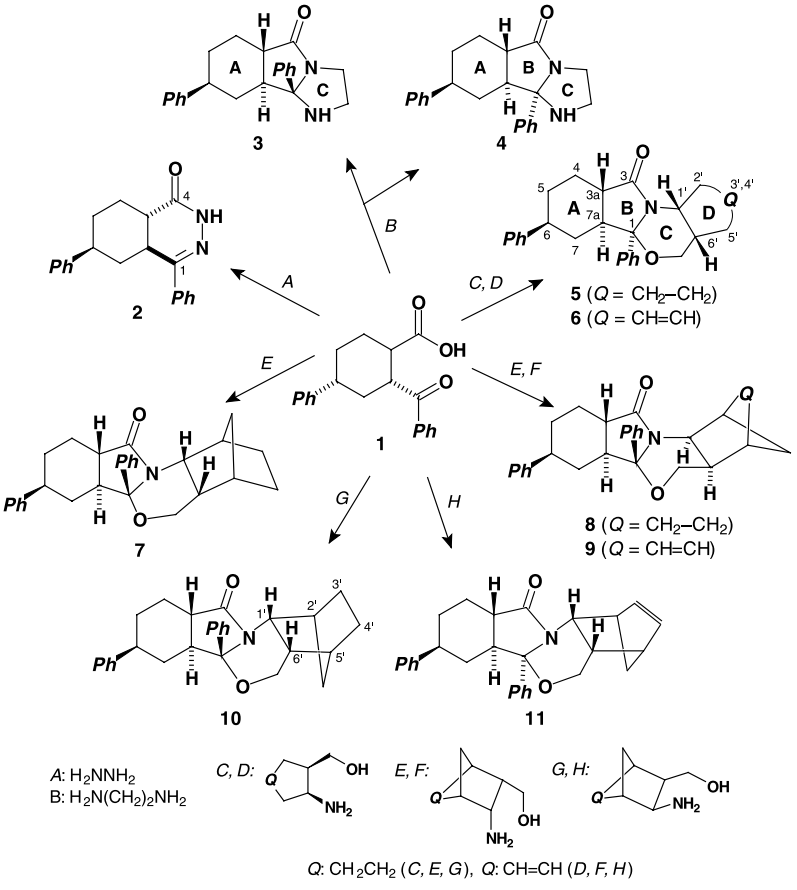
to prepare fused isoindolones. This supplements our stereochemical studies on saturated derivatives containing two condensed heterorings, when stereoisomeric non-substituted and differently phenyl-substituted cyclohexane aminoacids were applied as starting synthons [6–9]. The pharmacological activity of the target compounds is likewise of interest because the aromatic analogues with related structures are used in therapy [10–12].

Results and Discussion

On boiling in toluene in the presence of a catalytic amount of *PTSA*, 4-phenyl-*trans*-2-benzoylcyclohexane-1-carboxylic acid **1** was cyclized with hydrazine hydrate to furnish the hexahydro *trans*-phthalazinone **2** (Scheme). In its reaction with ethylenediamine, **1** gives a mixture of diastereomeric, *trans* **A**/**B**-annelated imidazo[2,3-*a*]isoindolones differing in C-1 configuration, **3** and **4**, which were separated by chromatography. Here, the first step may be the formation of an azomethine, followed by cyclization and intramolecular acylation to **3** and **4**. *cis-trans*-Isomerization in cyclohexane derivatives and analogous compounds [6, 9, 13] was observed a) in the presence of acids or bases, b) on heating, and c) after



Scheme

intramolecular transacylation for cyclohexane-condensed azetidinones [14]. In the thermal cyclizations of *cis*-ethoxycarbonylcyclohexylureas to cyclohexane-condensed dihydrouracils [15], and also on starting from the isomeric *t*-2-benzoyl-*t*-5-phenylcyclohexane-*r*-1-carboxylic acid [8] or isoindolones prepared from 4- and 5-phenyl 2-*cis*-aroyl-cyclohexanecarboxylic acids [5, 9], no isomerization was found. Consequently, in syntheses from either *cis*- or *trans*-aroylcyclohexanecarboxylic acids, isomerization has to be taken into account and the stereostructures of the new derivatives must always be clarified. As concerns the compounds discussed in this paper, the *cis*, di-*endo* or di-*exo* nature of the amino alcohols applied was exclusively retained in the cyclic products [5, 6, 9].

In its reactions with *cis*-2-aminocyclohexane- and -cyclohex-4-ene-methanol, **1** yielded the saturated or partly saturated isoindolo[2,1-*a*][3,1]benzoxazinones **5** and **6**. With di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]heptane- and -hept-5-ene-2-methanols, **1** afforded the corresponding methylene-bridged derivatives **7**–**11**; the reaction with di-*endo*-3-aminonorbornane-2-methanol furnished a mixture of diastereomers **7** and **8**, which were separated by column chromatography.

Structures

The constitutions (molecular skeletons) of **2**–**11** were confirmed by their IR, ^{1}H, and ^{13}C NMR spectra (Tables 1 and 2). The rather complicated stereostructures, however, need further consideration. The following points have to be clarified: (*i*) The *cis* or *trans* annelation of the condensed pyrrolidone-cyclohexane rings (the **A**/**B** annelation). (*ii*) The configuration of C-6 (the phenyl-substituted carbon in ring **A**). (*iii*) The *cis* or *trans* **C**/**D** annelation in **5** and **6** (the annelation of the condensed oxazine-cyclohexane rings). (*iv*) The di-*exo* or di-*endo* annelation of the norbornane/ene moiety in **7**–**11**. (*v*) The C-1 configuration (the position of the 1-phenyl group, for example relative to the other phenyl or the hydrogens on the **A**/**B** annelation). (*vi*) The steric position of the bridging CH_2 in the norbornane/ene moiety relative to the skeleton (*e.g.* to the phenyl substituents or the hydrogens on the **A**/**B** annelation) in **7**–**11**.

(*i*) A decision between *cis* or *trans* **A**/**B** annelation is possible on the basis of the multiplicity, the splitting pattern (vicinal H,H-couplings), and/or the ^{1}H NMR chemical shifts of H-3a and/or H-7a. For comparison of the spectroscopic data, a special numbering system is used in this part and in the Tables, *cf.* the structures of **5** and **6**, Scheme. In the event of hidden or coalesced signals, it is also possible to deduce the axial or equatorial orientation of H-3a and H-7a from the splits (multiplicity) of H-4(*ax*) and/or H-7(*ax*). For this purpose, the C-3a and C-7a ^{13}C NMR chemical shifts are also utilizable [16a]. For **3**, **5**, and **7**–**10** the double triplet split of the H-3a signal {two large and one smaller couplings due to two diaxial and one axial–equatorial interactions [17]: 3a,4(*ax*), 3a,7a, and 3a,4(*eq*)} is certain proof of the *trans* **A**/**B** annelation and the diaxial orientation of H-3a and H-7a. The double quartet splitting pattern of the H-4(*ax*) signal in **2**, **4**, and **11** confirms the axial position of H-4a(*ax*): a large geminal 4(*ax*), 4(*eq*) and two diaxial couplings: 3a,4(*ax*) and 4(*ax*), 5(*ax*) with similar values, and a small one, the axial–equatorial interaction of 4(*ax*), 5 (*eq*).

Table 1. Characteristic IR frequencies[a] and ^{1}H NMR data[b] for **2**–**11**[c]

	νC=O band	OCH_2 (2 × 1H)[d]		H-3a *dt* (1H)[e]	H-4(*ax*) *dqa* (1H)[g]	H-6 *tt* (1H)[h]	H-7(*ax*) *qa* (1H)[i]	H-7a *dt* (1H)[j]
2	1674	–		2.27	1.37	2.63	1.25	2.92
3	1683	3.12	3.25	2.41	1.34	2.58	0.88	2.15
4	1687	2.75	3.15	1.95	1.43	2.44	1.56	2.20
5	1706	3.54	3.99	2.28	1.45	2.30	1.59	1.62
6	1712	3.55	3.79	∼2.3[r]	∼1.5[s]	∼2.3[r]	∼1.6[s]	1.67
7	1687	3.62[r]	3.65[r]	1.72	1.43	2.59	0.78	∼2.26[s,v]
8	1704	3.53	3.79	2.06	1.34	2.44	0.38	2.14
9	1692	3.04	3.88	1.98	1.36[r]	2.43	0.37	2.09
10	1696	3.70	3.75	1.82	1.54[r]	2.66	0.86	2.24
11	1712	3.60	4.20	∼2.4[r]	1.43	∼2.4[r]	∼1.75[s]	∼1.75[s]

	Cyclohexane/ene (ring **D**) or norbornane/ene moiety							
	CH_2 (7′)[k,l]		H-1′[m]	H-2′[n]	H-3′[o]	H-4′[o]	H-5′[n]	H-6′[p]
2	–		–	–	–	–	–	–
3	2.94	3.87	–	–	–	–	–	–
4	2.86	3.74	–	–	–	–	–	–
5	–		4.34	–	1.05	0.76	–	2.03
6	–		4.60	–	∼5.3[t]	∼5.3[t]	–	2.15
7	1.32	1.38	3.94	3.32	1.48	1.80	∼2.08[t]	1.60
8	1.22	1.43	3.97	2.63	1.13	0.98	2.03	2.29
9	1.34[r]	1.39[r]	4.25	3.34	5.66	5.47	2.59[s]	2.63[s]
10	1.27	1.89	3.77	3.64	1.71	1.56	2.09	∼1.5[r]
11	0.61	0.99	4.08	2.80	6.38	5.95	2.32	∼1.88[t]

[a] In KBr discs (cm^{-1}), further bands, νNH band: ∼3205, broad (**2**), 3278 (**3**), 3455 and 3315 (**4**), νC–O: 1015 (**5**), 1026 (**6**), 1039 (**7**), 1043 (**8**), 1062 (**9**), 1081 (**10**), 1031 (**11**), $\gamma C_{Ar}H$ and $\gamma C_{Ar}C_{Ar}$ bands: 2–4 maxima between 777–698; [b] in $CDCl_3$ solution (in *DMSO*-d_6 for **2**) at 500 MHz, chemical shifts in ppm ($\delta_{TMS} = 0$ ppm), coupling constants in Hz; [c] assignments were supported by HMQC, HMBC, and DIFFN*O*E (except for **2**–**4**, **6**, **11**), for **2**, **4**, **7**, **10**, **11** also by 2D-COSY measurements; [d/l] CH_2 bound to the amine/amide-NH, 2 × *m* (**3**, **4**), *dd* (*J*: 11.5 and 4.2) and *t* (*J*: 12.0) for **5** and **6**[u], *t* (*J*: 11.5) and *dd* (*J*: 12.0 and 8.2) for **8** and **9**, 2 × *dd*, *J*: 12.4, 3.2 and 12.4, 6.5, resp. (**10**), 12.2, 10.5 and 12.2, 9.2, resp. (**11**); [e] *J*: 12.3 and 2.5 (**7**), 11.6 and 3.4 (**8**), m^f (**3**, **5**, **9**, and **10**), m^r (**4**, **6**, and **11**); [f] multiplet with unresolved lines; [g] *J*: 12.8 and 3.7 (**3**), 12.4 and 3.4 (**7**), m^f (**2**, **4**, **8**, **11**), m^r (**5**, **6**, **9**, **10**); [h] *J*: ∼12 and ∼3.5 (**3**, **4**, **7**–**10**), m^f (**2**), m^r (**5**, **6**, **11**); [i] *J*: ∼12 (12.4 for **2**, **3**), m^r (**5**, **6**, **11**); [j] *J*: 12.4 and 2.9 (**8**), dt^f (**4**, **6**, **9**, **10**), m^r (**3**, **5**, **7**, **11**); [k] *AB*-type spectrum, 2 × *d* (2 × 1H), *J*: 10.2 (**7**, **10**), 9.5 (**8**, **11**), 8.9 (**9**); [m] *td*, *J*: 12.5, 4.4 (**5**), *dt*, *J*: 8.8, 5.0 (**6**), *dd*, *J*: 11.5, 4.1 (**7**), 12.0, 2.5 (**8**), 10.0, 3.2 (**9**), 9.0, 1.5 (**11**), *d*, *J*: 8.5 (**10**); [n] ∼*s* (1H); [o] H(*ax*), 2 × 1H, 2 × *qa* (**5**), ∼*s* (2H) for **6**, 2 × 1H and ∼1.35 *m* (2H) for **7**, 2 × *m* (2 × 2H) for **8**, 2 × *dd* (2 × 1H), *J*: 5.6, 2.8, and 5.6, 3.1 (**9**, **11**), 4 × *m* (4 × 1H) with the two further signals at 1.20 and 1.28 (**10**); [p] *m* (1H); [r,s,t] overlapped signals; [u] further split of the upfield *dd* of **6** to a *ddd*/downfield *d* of **7** to a *dd* due to ^4J-long range coupling; [v] overlapped with the H-4(*eq*) signal

Similarly, three large couplings (one geminal and two diaxial) result in a quartet split of H-7(*ax*) in **2** and **4**, which prove the axial position of H-7a and thus the *trans* **A**/**B** annelation. Because of signal overlaps, it is not possible to

Table 2. ^{13}C NMR chemical shifts[a] for **2–11**[b,c]

	Isoindole ring[d]								
	C-1	C=O(3)	C-3a	C-4	C-5	C-6	C-7	C-7a	OCH_2[e]
2	156.9	170.0	39.6	26.4	33.0	43.5	37.8	38.8	–
3	89.3	176.9	48.3	26.0	33.2	44.3	35.9	57.0	48.1
4	88.6	182.7	49.8	26.2	34.7	45.3	33.1	47.5	46.7
5	92.7	180.9	45.7	26.1	34.8[f]	44.9	30.8	54.5	63.3
6	92.9	181.4	45.9[g]	27.1	34.8	44.9[g]	30.8	54.7	64.2
7	93.1	175.1	43.5	26.2	33.7	44.3	34.6	54.4	62.8
8	94.1	179.1	43.2	26.0	33.5	44.1	34.9	56.6	62.4
9	93.4	178.2	43.0	25.9	33.6	44.1	34.9	56.7	64.8
10	93.3	174.8	44.1	26.1	33.7	44.3	34.4	53.8	64.9
11	92.2	181.6	45.2[g]	26.1	34.7	45.0[g]	31.1	54.0	67.5

	Cyclohexane/ene (ring **D** in **5** and **6**) or norbornane/ene moiety						
	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	CH_2(7′)
2	–	–	–	–	–	–	–
3	42.5	–	–	–	–	–	–
4	44.2	–	–	–	–	–	–
5	53.3	27.7	26.0	21.4	27.9	34.8[f]	–
6	50.1	26.0	123.9[h]	124.7[h]	25.5	32.9	–
7	51.3	41.6	22.4	22.8	42.8	33.1	36.9
8	54.5	42.0	22.2	24.0	38.5	32.8	38.0
9	52.5	47.9	137.5	136.2	43.9	35.6	48.6
10	57.4	39.6	25.9	30.4	44.7	39.5	34.7
11	54.2	47.8	139.6	135.4	45.1[f,g]	29.0	45.1[f]

Further signals, 1-phenyl, C-1: 137.3 (**2**, **9**), 138.8 (**3**), 142.0 (**4**, **6**), 141.7 (**5**, **11**), 136.4 (**7**, **10**), 137.7 (**8**); C-2,6:[i] 127.0 ± 1.2, broadened signal for **7** and **10**; C-3,5:[i] 127.7 ± 0.7; C-4: 127.4 (**8**), 128.7 ± 0.5; 6-phenyl, C-1: 147.2 (**2**), 146.1 (**4**), 146.4 ± 0.1; C-2,6: 127.6 (**2**), 127.3 ± 0.1; C-3,5: 129.2 (**2**), 128.8 ± 0.1; C-4: 127.0 (**2**), 126.7 ± 0.1

[a] In ppm ($\delta_{TMS} = 0$ ppm) at 125.7 MHz, solvent: $CDCl_3$ (for **2** *DMSO*-d_6); [b] assignments were supported by DEPT, HMQC, and HMBC measurements; [c] for numbering see Scheme; [d] for **2** phthalazine ring; [e] CH_2 bound to the amine-NH in **3** and **4**; [f] two overlapping lines; [g,h] interchangeable assignments; [i] two separated lines for **5**, **6**, **8**, **9**, and **11**

draw an analogous conclusion for **11**. However, the practically unaltered C-3a and C-7a shifts for **10** and **11** (44.1 and 53.8 ppm for **10**, and ~45.2 and 54.0 ppm for **11**) indicate the same stereostructure in the analogous part of these molecules.

(*ii*) For **3**, **4**, and **7–10** the equatorial position (*cis* to H-3a and *trans* to H-7a) of the 6-phenyl group follows from the triple triplet split of the H-6 signal (two large diaxial and two smaller axial–equatorial vicinal couplings, *i.e.* the axial orientation of H-6). For **2**, **5**, **6**, and **11** the similar C-6 chemical shifts demonstrate the analogous steric position of the 6-phenyl group: these shifts are within a 1 ppm interval for compounds **3–11** (44.8 ± 0.5 ppm).

(*iii*) For the NCH group the triple doublet split (only one diaxial interaction) in the ^{1}H NMR signal confirms the *cis* **C**/**D** annelation in **5**. For the more flexible **6** (due to the flattened cyclohexene ring **D**), however, the splits are smaller, and hence are not convincing as concerns the annelation. For **5** the shifts of the annelational carbons, however, are smaller (by 3.2 and 1.9 ppm) and a *cis* → *trans* change in the **C**/**D** annelation should lead to an opposite difference [16a]. Consequently, the **C**/**D** annelation must be unaltered *cis* for **6**.

(*iv*) By application of our "splitting rule" [18, 19], the starting di-*endo* (**7**–**9**) or di-*exo* (**10**, **11**) annelation of the reacting bicyclic partners (*E*-*H*, Scheme) remain the same in the pentacyclic products. The 1′,6′-vicinal coupling leads to a doublet split of the corresponding H-1′ and H-6′ signals by ∼8–9 Hz. For the di-*endo* compounds, the H-1′,2′ and H-5′,6′ couplings result in further splits of these signals to double doublets (due to a dihedral angle of ∼30°), whereas in the di-*exo* analogues, these couplings are small (the dihedral angle is about 90°), which causes no further split.

(*v*) The steric orientation of the 1-phenyl group follows from the anisotropic shielding caused by the benzene ring on the close-lying hydrogens; the ^{1}H NMR signals are shifted upfield by this effect [16b]. When the 1-phenyl ring is in the *exo* position (on the same side of the skeleton as H-3a), its anisotropy results in a dramatic upfield shift of the H-7(*ax*) and H-3a signals, as observed for **3** and **7**–**10** (the H-7(*ax*) shifts are <1 ppm, whereas they are 1.25–1.75 ppm for the other compounds). The close arrangement of the 1-phenyl group and the 3a and 7(*ax*) hydrogens was confirmed by DIFFN*O*E measurements. On irradiation of one of the signals of the *ortho*-hydrogens of the 1-phenyl groups or H-3a or H-7(*ax*), the other displayed an intensity enhancement.

(*vi*) For **7** the DIFFN*O*E results demonstrate the close arrangement of the H-1′, H-6′ on the norbornane moiety (to the oxazine ring) and the 1-phenyl group. As regards the di-*endo* annelation, it has been proved that the latter group and the bridging CH_2 are on the same side of the skeleton. Since all the other parts of molecule **8** have the same steric structure as in **7**, the bridging CH_2 must be in an opposite position in **8**, *i.e.* the CH_2 lies on the opposite side of the skeleton from the 1-phenyl group. Accordingly, the two neighbouring methylene groups (in Pos. 3′ and 4′, *Q* in **8**) are close to the 1-phenyl group, and the anisotropy of the latter results in an upfield shift of the signals of these methylene hydrogens (0.98 and 1.13 ppm for **8**, and ∼1.35, 1.48, and 1.80 ppm for **7**).

Though norbornene **9** has no isomeric counterpart, the upfield shifts of H-3′ and H-4′ (olefinic hydrogens in the norbornene moiety) relative to those in **11** (5.66 and 5.47 ppm in **9**, and 6.38 and 5.95 ppm in **11**) suggest the opposite position of the 1-phenyl and the bridging CH_2 in **9**, similarly as in **8**.

Thus, it is easy to see that for **11** the relative position of the two groups in question is opposite to that in **8** and **9**: the bridging CH_2 and 1-phenyl group are on the same side of the skeleton, similarly as in **7**. Because of the di-*exo* annelation, however, the two groups are situated close to one another and the anisotropic effect of the benzene ring leads to an upfield shift of the hydrogens of the bridging CH_2 (0.61 and 0.99 ppm, whereas the corresponding values in **9** are 1.34 and 1.39 ppm).

DIFFN*O*E between the *ortho*-hydrogens (1-phenyl) and H-1′ (NC*H* group) and the lack of anisotropic shielding on the bridging CH_2 suggest a stereostructure with these two groups on opposite sides of the skeleton for **10**, analogously as in **8** and **9**.

From the above, it can be concluded that the *endo* position of the 1-phenyl group in **4**–**6** and **11** is reflected in a downfield shift of the 3-carbonyl signal (these shifts are >180 ppm, whereas they are <180 ppm for the other compounds). The configurations in **1** remain unaltered in all products: *trans* → *cis* isomerization was not observed with these compounds. Similarly, the original stereostructures are retained in the products. The isomeric pair **3** and **4** differ in the position of the 1-phenyl, while **7** and **8** differ in the positions of the 1-phenyl and the bridging CH_2 of the norbornane moiety. For **8**, the steric hindrance between the 1-phenyl and the neighbouring methylene hydrogens (Pos. 3′ and 4′), leads to formation of the isomeric **7**, whereas **9**, in which the steric hindrance is only moderate, did not undergo isomerization. The steric structure of **10** can be explained analogously (in this structure, the molecule avoids an unfavourable interaction of the 1-phenyl group with the bridging CH_2).

Experimental

IR spectra were run in KBr discs on a Bruker IFS-55 FT-spectrometer controlled by Opus 3.0 software. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at rt on a Bruker DRX-500 spectrometer at 500.13 (^1H) and 125.76 (^{13}C) MHz with the deuterium signal of the solvent as the lock and *TMS* as internal standard. The VT-NMR measurements were carried out in *DMSO*-d_6 from 298 K to 353 K on BRUKER AM 300 equipment. The standard Bruker microprogram N*O*EMULT to generate N*O*E [20] and DIFFN*O*E spectra [16c, 21] was used with a selective pre-irradiation time. DEPT spectra [22] were run in a standard manner [23], using only a $\Theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased "up" and "down", respectively. The 2D-COSY [24a, 25a], HMQC [24b, 25b], and HMBC [26, 27] spectra were obtained by using the standard Bruker pulse programs COSY-45, INV4GSSW, and INV4GSLRNDSW, respectively.

General Procedure for the Preparation of ***2–11***

A mixture of 3.08 g of **1** (0.01 mol), aminoalcohol (0.6 g ethylenediamine, 1.3 g *cis*-2-aminocyclohexanemethanol, or -cyclohex-4-enemethanol, 1.4 g di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]heptane-, or -hept-5-enemethanol, 0.01 mol) and 0.05 g of *PTSA* in dry toluene (for **2** and **5**–**9**) or chlorobenzene (for **3**, **4**, **10**, and **11**) was refluxed for 2 h with the application of a water separator. After the solvent had been evaporated, the residue was transferred to an aluminum oxide (Acros basic, 50–200 μ, for **2**, **6**, and **9**–**11**) or silica gel (Silica gel Merck 60, 0.040–0.063 mm, for **3**–**5**, **7**, and **8**) column and eluted with benzene (for **5**), *Et*O*Ac* (for **2**, **9**, and **11**) or *n*-hexane:*Et*O*Ac* = 2:1 (for **3** and **4**) or *n*-hexane:*Et*O*Ac* = 4:1 (for **6**–**8** and **10**), with monitoring by TLC (silica gel TLC aluminum sheets, solvent: benzene:*Et*OH:petroleum ether (bp 40–60°C) = 4:1:3, development in iodine vapour; higher R_f **4** and **7**, lower R_f **3** and **8**).

1,7-Diphenyl-4a,5,6,7,8,8a-hexahydrophthalazin-4(3H)-one (**2**, $C_{20}H_{20}N_2O$)

Yield 2.19 g (72%); mp 235–236°C (*Et*OH).

8,9b-Diphenylperhydroimidazo[2,3-a]isoindolone (**3**, $C_{22}H_{24}N_2O$)

Yield 0.86 g (26%); mp 237–239°C (*Et*OH).

8,9b-Diphenylperhydroimidazo[2,3-a]isoindolone (**4**, $C_{22}H_{24}N_2O$)

Yield 0.93 g (28%); mp 248–250°C (*Et*OH).

6a,8-Diphenyl-11-oxoperhydroisoindolo[2,1-a][3,1]benzoxazine (**5**, $C_{27}H_{31}NO_2$)

Yield 2.65 g (66%); mp 263–265°C (*Et*OH).

6a,8-Diphenyl-11-oxo-1,4,4a,6b,7,8,9,10,10a,12a-decahydroisoindolo[2,1-a][3,1]benzoxazine (**6**, $C_{27}H_{29}NO_2$)

Yield 2.32 g (58%); mp 226–228°C (*Et*OH).

di-endo-6a,8-Diphenyl-1,4-methano-11-oxoperhydroisoindolo[2,1-a][3,1]benzoxazine (**7**, $C_{28}H_{31}NO_2$)

Yield 1.32 g (32%); mp 195–197°C (*Et*OH).

di-endo-6a,8-Diphenyl-1,4-methano-11-oxoperhydroisoindolo[2,1-a][3,1]benzoxazine (**8**, $C_{28}H_{31}NO_2$)

Yield 1.24 g (30%); mp 193–195°C (*Et*OH).

di-endo-6a,8-Diphenyl-1,4-methano-11-oxo-1,4,4a,6b,7,8,9,10,10a,12a-decahydroisoindolo[2,1-a][3,1]benzoxazine (**9**, $C_{28}H_{29}NO_2$)

Yield 3.13 g (76%); mp 280–281°C (*Et*OH).

di-exo-6a,8-Diphenyl-1,4-methano-11-oxoperhydroisoindolo[2,1-a][3,1]benzoxazine (**10**, $C_{28}H_{31}NO_2$)

Yield 3.30 g (80%); mp 197–199°C (*Et*OA*c*).

di-exo-6a,8-Diphenyl-1,4-methano-11-oxo-1,4,4a,6b,7,8,9,10,10a,12a-decahydroisoindolo[2,1-a][3,1]benzoxazine (**11**, $C_{28}H_{29}NO_2$)

Yield 2.88 g (70%); mp 250–252°C (*Et*OH).

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