Application of *t*-2-benzoyl-*t*-5-phenylcyclohexane-*r*-1-carboxylic acid for the preparation of saturated isoindole-fused heterocycles †

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t-2-Benzoyl-*t*-5-phenylcyclohexane-*r*-1-carboxylic acid **1** reacts with *cis*-2-aminocyclohexanemethanol to give the saturated *cis*-isoindolo[2,1-*a*][3,1]benzoxazine **2**. Reaction of **1** with *trans*-2-aminocyclohex-4-enemethanol yields three diastereomeric isoindolo derivatives **3a**–**c**. Cyclization of **1** with 1,3-diaminopropane results in a diastereomeric mixture of *cis*-pyrimido[1,2-*a*]isoindolones **4a**,**b**. With di-*endo*-norbornane aminoalcohol, **1** reacts to yield a mixture of *cis*- and *trans*-annelated diastereomers **5** and **6**. In its reactions with di-*exo*-norbornane and norbornene aminoalcohols, **1** isomerizes to give *cis*-condensed isoindolo derivatives **7**–**10**. After isolation, the structures were established by ^{1}H and ^{13}C NMR spectroscopy, with up-to-date measuring techniques such as NOEDIF, DEPT, HMQC, 2D-NOESY, 2D-COSY and HMBC and, for **10**, X-ray measurements. The results show that, with two exceptions, the *trans* acid **1** undergoes isomerization to give *cis*-condensed products.

Introduction

The $AlCl_3$-catalysed reaction of *cis*-cyclohex-4-ene-1,2-dicarboxylic anhydride (Acros 15.972–0010) with benzene results in *t*-5-phenyl-*c*-2-benzoylcyclohexane-*r*-1-carboxylic acid, which, by treatment with NaOH, is readily isomerized to the *trans*-aroyl acid **1**.[1] As a continuation of our systematic stereochemical studies on saturated isoindolones containing two condensed hetero rings,[2–4] we have now applied **1** to synthesize lactam-type compounds and compare them with the compounds prepared from the *cis*-aroyl acid.[5] The pharmacological potential of the target compounds is likewise of interest, because some of the corresponding aromatic analogues[6,7] display anorectic activity and several drugs with related structures are applied in therapy.[8] Since the introduction of chiral lactams prepared from optically pure aminoalcohols and γ-oxoacids for the asymmetric construction of quaternary carbon centres, this group of compounds has been subjected to intensive investigations.[9,10]

Results

The *trans*-aroylcyclohexanecarboxylic acid **1** was cyclized with *cis*-2-aminocyclohexanemethanol to the saturated *cis*-isoindolo-[2,1-*a*][3,1]benzoxazine **2** (Scheme 1), which was previously synthesized in a similar reaction of the *trans*-phenyl-*cis*-benzoylcyclohexane-1-carboxylic acid.[5] In its reaction with *trans*-2-aminocyclohex-4-enemethanol, **1** either changes or preserves its starting structure to give the isomeric isoindolobenzoxazines **3a**–**c**, containing *trans C–D* rings. With 1,3-diaminopropane, the tricyclic diastereomers **4a**,**b** are formed and separated. Such derivatives have already been prepared from the corresponding *trans*-phenyl-substituted-*cis*-2-benzoylcyclohexane-1-carboxylic acid with 1,3-diaminopropane.[5] The di-*endo*- or the di-*exo*-3-aminobicyclo[2.2.1]heptane-2-methanols or di-*exo*-heptene analogue each yield mixtures of two isomeric methylene-bridged isoindolo[2,1-*a*][3,1]benzoxazines **5**, **6** or **7**, **8** or **9**, **10**. As a mechanism, the formation of an azomethine following cyclization to hydroxylactam and then hetero ring closure by cyclodehydration can be postulated.

The results show that *t*-5-phenyl-*t*-2-benzoylcyclohexane-*r*-1-carboxylic acid **1** readily changes its configuration to *cis* in these reactions; thus, the configurations of the starting compound and the products often differ. *cis* ⟶ *trans* Isomerization in the presence of acids or bases or on heating has been reported to occur in cyclohexane derivatives[11] and it has also been observed in analogous compounds.[3,12] Similarly, *cis* ⟶ *trans* isomerizations have been described for the intramolecular transacylation of the cyclohexane-condensed azetidinones,[13] while a *trans* ⟶ *cis* isomerization occurs in the thermal cyclization of the *cis*-ethoxycarbonylcyclohexylureas to cyclohexane-condensed dihydrouracils.[14] On enolization of the aroyl group in the presence of basic reagents, *e.g.* diamines or aminoalcohols, **1** epimerizes to the corresponding *cis*-aroylcyclohexanecarboxylic acid, as in the present case, when, with two exceptions (**3c** and **6**), compounds containing a *cis A–B* ring annelation were formed. This presumes the *trans* ⟶ *cis* inversion of the starting **1**, which took place only partly in the reactions with *trans*-2-aminocyclohex-4-enemethanol and di-*exo*-3-aminobicyclo[2.2.1]hexane-2-methanol, where compounds with *trans A–B* ring annelation could also be isolated. Our results show that, instead of the frequent *cis* ⟶ *trans* process, *trans* ⟶ *cis* isomerization can also occur. It follows that, in syntheses starting either from *cis*- or from *trans*-aroylcyclohexanecarboxylic acids, isomerization always has to be taken into account.

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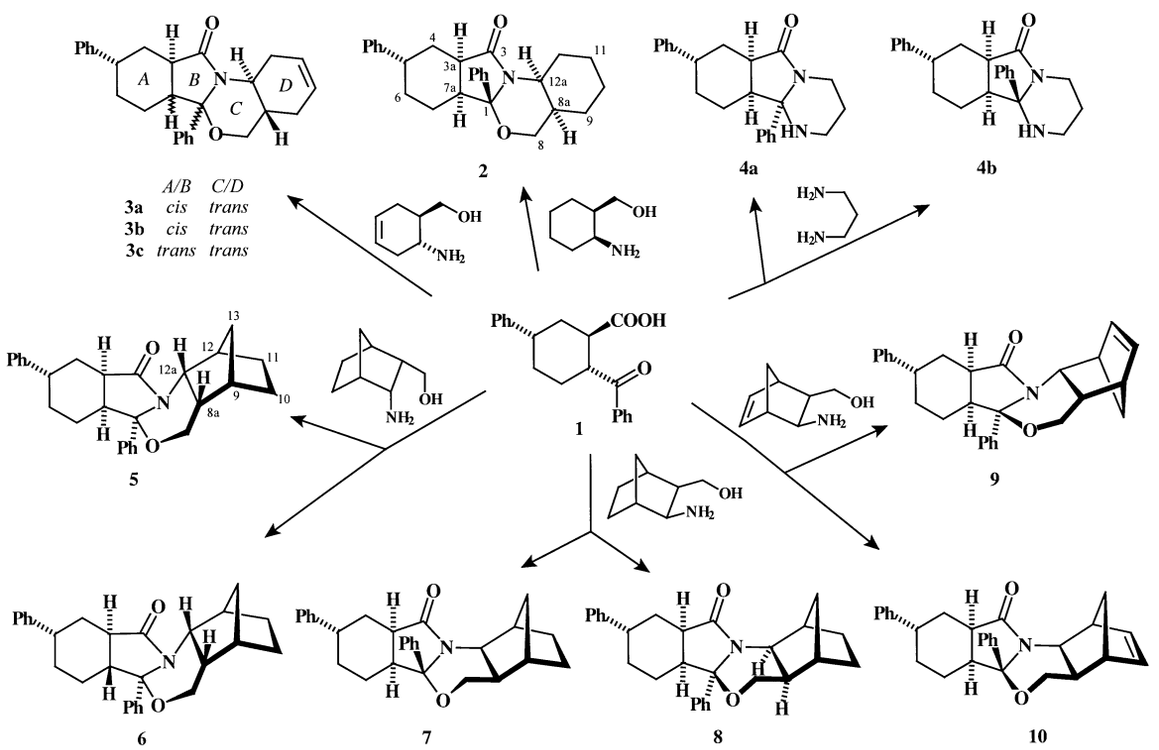
Table 1 Characteristic IR frequencies[a] and ^{1}H NMR data[b] relevant to stereostructures[c] of compounds **2**, **3a**–**c**, **4a**,**b**, and **5**–**10**[d]

			CH_2 (13)[f]		CH_2 (7)[g]		Isoindolone moiety			Oxazine ring				Ph Pos. 1
Compound	$\nu_{C=O}$ band	ν_{C-O} band[e]	2 × d (2 × 1H)		~d (1H)	dq (1H)	3a-H[h]	5-H[i]	7a-H[k]	CCHC[m]	NCH[n]	OCH_2[o]		H-2,6[p]
2	1706	1027	—		0.72	0.92	3.06	2.33	2.14	2.02	4.40	3.47	3.86	7.55
3a	1702	1048	—		1.71	2.15	2.55	~2.4[r]	2.26	2.02	3.44	3.18	3.72	
3b	1718	1034	—		0.84	1.06	3.07	2.43	2.27	~1.84[r]	3.74	3.46	4.04	7.65
3c	1699	1061	—		0.68	~1.75[r]	~1.87[r]	3.21	~2.2[r]	2.04	~3.3[r]	3.28[r]	3.75	~6.9
4a	1673	3323	—		~1.55[r]	~2.1[r]	2.64	~2.5[r]	2.24	—	—	—		
4b	1686	3313	—		0.75	0.87	3.02	2.30	2.10	—	—	—		7.57
5	1702	1001	~1.34[r]	1.51	~1.3[r]	~2.15[r]	2.87	2.49	2.35	~2.40[r]	3.91	3.43	3.81	
6	1695	1046	1.27	1.47	0.56	~1.0	~2.14[r]	3.18	~2.14[r]	2.34	4.01	3.64	3.87	7.44
7	1707	1030	0.72		~0.94		~2.35[r]	2.49	3.01	1.99	4.16	3.45	3.89	7.48
8	1702	1010	0.91	1.01	~1.4[r]	~2.15[r]	2.66	2.50	2.35	2.15	3.80	3.07	3.89	~7.57
9	1697	1029	0.97	1.14	1.30	2.06	~2.4[r]	2.65	~2.3[r]	1.95	3.57	3.01	4.03	~7.58
10	1710	1041	0.85	~1.07[r]	~1.05		3.02	2.58	2.48	2.58	4.07	3.48	4.13	7.53

[a] In KBr discs (cm^{-1}). Further bands: $\gamma C_{Ar}H$: 750 ± 20, $\gamma C_{Ar}C_{Ar}$: 704 ± 6. [b] In $CDCl_3$ solution at 500 MHz. Chemical shifts in ppm (δ_{Me_4Si} = 0 ppm), coupling constants in Hz. [c] Only signals of CH_2, CH and aromatic hydrogens of importance in the structure determinations are given. [d] Assignments were supported by HMQC and NOEDIF measurements; also by 2D-COSY experiments for **2**, **3a**,**b** **4a** and **5**. [e] νNH band for **4a**,**b**. [f] AB-type spectrum, *J*: 9.5, 10.5 for **8**; singlet-like signal (2H) for **7**, δH(*exo*) < δH(*endo*) for **5**, **6** and **8** and the relative shifts are reversed for **9** and **10**. [g] The doublet-like signal with coalesced fine structure of 7-H_{eq} is downfield (**3a**,**c** **4a**, **8** and **9**) or upfield (**2**, **3b**, **4b**, **6**) to dq ($J \approx 4$ and 3 × 12) signal of 7-H_{ax}; these two signals are coalesced for **7** and **10** and both **5**, **8** or the downfield/upfield one (**3c**, **6**/**4a**) is overlapped with other signals. δ4-H_{ax}: 1.55 ± 0.3, 4-H_{eq}: 2.45 ± 0.15, 6-H_{ax}: 1.3 ± 0.1 (1.75 and 1.68 for **3c** and **6**, resp.), H-6_{eq}: 1.78 ± 0.18 (2.16 for **3c**, **6**). The CH_2 and CH signals of ring *D* (**2**, **3a**–**c**), *C* (**4a**,**b**) and *D*–*E* (**5**–**10**) (absent from this table) are in the expected shift intervals. [h] Triplet, $J \approx 5$ Hz (**2**, **3a**,**b**, **4a**,**b**, **5**, **7**–**9**), quartet, $J \approx 7$ Hz (**10**). [i] Triple triplet, $J \approx 12$ and 4 Hz, broad signal with coalesced fine structure, half signal width 5 Hz (**3c**, **6**). [k] Triple doublet, $J \approx 12$ and 6 Hz (**2**, **3a**,**b**, **4a**,**b**, **5**, **8**), quartet, $J \approx 8.4$ Hz (**10**). [m] Broad signal with coalesced fine structure, tq, J = 11.1 and 4.8 Hz (**3a**), q, J = 9.6 Hz (**7**, **9**). [n] Triple doublet, $J \approx 13$ and 5 Hz (**2**), dt, $J \approx 11$ and 5 Hz (**3a**,**b**), d, J = 11.0 (**5**, **6**), 8.8 ± 0.4 Hz (**7**–**10**); [o] Triplet and dd (t is the upfield signal, except for **2** and **6**), $J \approx 12$ and 8 Hz (**5**–**10**), for **2** and **3a**–**c**: 11 and 4.5 Hz. [p] The signals of the two phenyl rings in Pos. 1 and 5 appear in the interval 7.25 ± 0.2 ppm, except for those given in this column. The 1-phenyl signals are broadened for **3c**, **5**, **8** and **9**. [r] Overlapping signals.



Scheme 1

Structure

The constitutions of the compounds follow straightforwardly from the spectral data (Tables 1 and 2). Determination of the stereostructures, however, is a difficult task, due to the presence of the 4 (**4a**,**b**), 6 (**2**, **3a**–**c**) or 8 (**5**–**10**) centres of asymmetry.

For **3a**–**c**, we have succeeded in separating three homogeneous diastereomers; the ^{1}H and ^{13}C NMR measurements point to structures differing partly in the *A*–*B* ring annelation (which is *cis* for **3a** and **3b**, and *trans* for **3c**) and in the relative position of the 1-phenyl group and the annelational 3a,7a-H (*cis* in **3a**, *trans* in **3b** and *cis* to 3a-H and *trans* to 7a-H in **3c**).§ The *C*–*D* annelation is *trans* for all three isomers, but the 1-phenyl substituent on the oxazine ring is *cis*-oriented to the NC*H* in **3a** and **3c**, and *trans* to it in **3b**. The 5-phenyl remains *cis* to 3a-H, but this means an equatorial position in **3a** and **3b**, and an axial one in **3c**.

The *A*–*B* annelation of these structures (Fig. 1) is supported by the C-7a chemical shift, which is significantly higher (53.0

§ See compound **2** in Scheme 1 for the spectroscopic numbering.

Table 2 ^{13}C NMR chemical shifts[a] of compounds **2**, **3a**–**c**, **4a**,**b** and **5**–**10**[b]

	Isoindole moiety								Oxazinonorbornane/ene moiety[e]								Ph Pos. 1	Ph Pos. 5
Compound	C-1	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	C-4′	C-4a′	C-5′	C-6′	C-7′	C-8′	C-8a′	C-9′	C-1[c]	C-1[c]
2	95.6	182.8	42.3	31.2	41.0	31.4	28.0	44.6	63.2	34.9	27.8	21.6	26.2	28.7	54.4	—	139.3	146.8
3a	95.2	175.1	40.7	31.0	40.9	31.2	25.1	46.0	66.8	37.0	26.4	124.5	126.2	29.7	54.7	—	140.4	147.1
3b	94.9	183.2	42.1	31.5	41.1	31.4	28.2	44.9	69.0	32.0	29.6	125.2	126.3	33.1	56.3	—	142.6	146.8
3c	96.0	175.4	39.9	31.5	36.8	29.0	23.3	53.0	67.1	37.1	26.5	124.3	126.3	29.3	54.7	—	135.4	144.4
4a	79.6	174.0	39.7	30.8	40.0	31.2	24.9	46.0	40.6	26.2	—	—	—	—	37.8	—	141.7	146.7
4b	81.6	178.5	42.6	31.4[d]	41.0	31.4[d]	27.6	43.9	41.1	26.5	—	—	—	—	39.7	—	139.1	146.8
5	93.9	179.8	39.5	30.9[d]	40.7	30.9[d]	25.1	50.7	62.9	33.0	38.0	24.0	22.1	42.1	56.1	37.8	142.3	147.1
6	94.4	179.6	38.2	31.5	36.8	28.7	23.8	56.5	62.4	32.7	38.6	23.9	22.1	42.0	54.3	38.0	137.8	144.4
7	95.3	182.2	40.7	30.7[d]	39.7	30.1	26.4	44.6	64.5	39.0	39.6	27.5	30.7[d]	42.7	57.4	35.4	139.3	146.3
8	93.4	176.8	39.2	30.8	40.7	31.0	25.0	49.9	64.1	39.0[d]	39.0[d]	28.0	28.6	43.4	56.0	34.7	142.4	147.1
9	93.3	177.3	39.6	30.8	40.7	30.9	25.0	44.1	66.8	31.7	50.0	136.4	137.3	48.5	52.5	44.6	142.3	147.1
10	95.3	182.0	40.4	30.3	39.2	29.6	25.7	44.5	66.9	29.7	44.8	136.0	139.7	47.9	54.3	45.1	139.7	146.0

[a] In ppm (δ_{Me_4Si} = 0 ppm) at 125.7 MHz. Solvent: $CDCl_3$. [b] Assignments were supported by DEPT, HMQC and, except for **4a**, **5** and **6**, HMBC measurements. [c] Further lines of the phenyl group in Pos. 1 (broad or doubled C-2,6 and C-3,5 signals for **3b**,**c**, **4b**, **5**–**8** and **10**), C-2,6: 128.0 ± 1.5, C-3,5: 128.3 ± 0.5, C-4: 128.8 ± 0.7 and in Pos. 5: C-2,6: 127.2 ± 0.1, C-3,5: 128.8 ± 0.1, C-4: 126.3 ± 0.3. [d] Overlapping lines. [e] Numbering refers to oxazine before fusion.

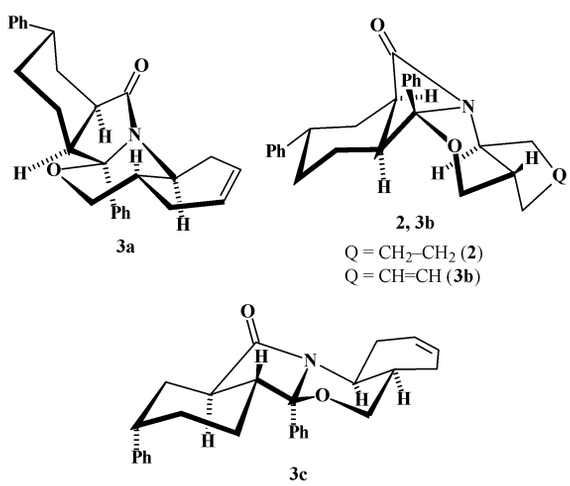


Fig. 1 Stereostructures of compounds **2** and **3a**–**c**.

ppm) in **3c** than in **3a** and **3b** (46.0 and 44.9 ppm), due to the field effect[15] in the *cis* **3a** and **3b**, manifested above all in the upfield shifts in the lines of the annelated carbons. In **3c**, this difference is not observable for C-3a, because of the analogous effect of the 5-phenyl group in the 1,3-diaxial position. While 7a-H retains its axial orientation and hence has a similar chemical shift (~2.25 ppm) in all three isomers, the upfield shift of 3a-H in **3c** (by 0.68 and 1.2 ppm as compared to **3a** and **3b**) clearly confirms its axial position, in contrast with **3a** and **3b**, where 3a-H is equatorial. The shift difference is of about the expected[16a] magnitude (~0.6 ppm) for **3a** and **3b**, while it is roughly double this for the pair **3a** and **3c**. This can be explained by the cumulative anisotropic effects of the 1- and 5-phenyl rings,[16b] as can be seen from the 3a-H shifts measured for **3a** and **3b**: the anisotropy results in an shift upfield by 0.52 ppm in **3a**, where 3a-H lies above the plane of the 1-phenyl ring.

As concerns the orientation of the 5-phenyl group, the triple triplet splitting of the 5a-H signal in **3b** (by ~14 and 4 Hz) confirms its axial position (and consequently the presence of the equatorial 5-phenyl ring) due to the two large diaxial couplings.[17] For **3c**, the narrow shape of the broadened 5-H signal and its downfield shift (by ~0.8 ppm) prove the change in the position of the 5-phenyl as compared to **3b**, and suggest its axial orientation. Though the splits of the 5-H signal in **3a** cannot be determined, the very similar shifts of 5-H and C-5 in **3a** and **3b** confirm the unaltered equatorial (*cis* to 3a-H) position of the 5-phenyl in **3a**.

For the *C–D* annelation, the double triplet splitting of the ^{1}H NMR signal of the NC*H* group by two large diaxial couplings is decisive for **3a** and **3b**. In consequence of the signal overlap, establishment of the *trans C–D* annelation in the same way is not possible for **3c**. However, the practically identical ^{1}H and ^{13}C shifts of the annelated C*H*'s for **3a** and **3c** illustrate the analogous steric structures in this part of the isomeric molecules. Again, the differences in these shifts for the pairs **3a**,**b** and **3c**,**b** can be interpreted only in terms of the different positions of the 1-phenyl and the annelated C*H*'s, because a change in *C–D* annelation for **3a** and **3b** was excluded. Accordingly, the anisotropic shielding of the phenyl ring is manifested in upfield shifts of the signals of the CC*H*C and NC*H* hydrogens in **3b** and **3a**,**c**, respectively, as a result of the 1,3-diaxial position of the phenyl ring and the above H's in the respective isomers.

Consequently, the following configurations can be considered proved: for **3a** 1*R**,3a*R**,5*S**,7a*S**,8a*R**,12a*S**; for **3b** 1*S**,3a*R**,5*S**,7a*S**,8a*R**,12a*S** and for **3c** 1*R**,3a*R**,5*S**,7a*R**,8a*R**,12a*S**. The presumed stereostructures were confirmed by NOEDIF measurements;[16c,18] the responses relevant to the possible steric arrangements are given in Table 3.

The structures of **2**, **4a**,**b**, **5**–**10** were determined similarly. For **2**, the triple doublet split (by 12.8, 6.4 and 6.4 Hz) of the 7a-H signal is proof of the *cis A–B* annelation, where 7a-H is axial and the 5-phenyl is equatorial (this means *cis* orientation to 3a-H), as shown by the triple triplet split involving two diaxial couplings for 5a-H. The very similar C-3a,7a and 3a,7a-H shifts, the separation of the 2-H and 6-H signals of the 1-phenyl ring (one of them is downfield-shifted to *ca.* 7.6 ppm) and the separation or broadening of the corresponding carbon signals (C-2,6 and also C-3,5) due to hindered rotation are all evidence in favour of analogous stereostructures for **2** and **3b** in this part of the molecule. The dramatic downfield shift of the ^{1}H signal of the NC*H* group (from 3.74 to 4.40 ppm) and its triple doublet splitting with only one large diaxial coupling suggest *cis C–D* annelation in **2**, with changed orientation of the NC*H* as compared to **3b**. This means the *cis* position of the *C–D* annelational H's relative to the 1-phenyl ring. The configuration is 1*S**,3a*R**,5*S**,7a*S**,8a*R**,12a*R**.

For the isomeric pair **4a** and **4b**, the stereostructures are analogous to those of **3a** and **3b**. Thus, **4a**,**b** involve *cis A–B* annelation and an equatorial 5-phenyl *cis* to 3a,7a-H. The only difference is in the 1-phenyl orientation, which is *cis* to 3a,7a-H in **4a**, and *trans* in **4b**. The anisotropy of the near-lying 1-phenyl ring to the 7-methylene group is revealed in the upfield shifts of the signals of the latter H's in **4b** (0.75 and 0.87 ppm) relative to **4a** (~1.55 and 2.1 ppm), similarly as in **3b** (0.84 and 1.06 ppm) relative to **3a** (1.71 and 2.15 ppm).

Table 3 Results of NOE experiments on compounds **2**, **3a**–**c**, **4a**,**b** and **5**–**10** [a]

Compound	Saturated signal	Responding signals					
		H_{ortho} (1-Ph)	7a-H	7-H_{ax}	5-H_{ax}	8-H_{ax}	13-H (*endo*)
2	7a-H	+ [c]					
2, **3b**	3a-H		+				
	5-H_{ax}			+			
	7-H_{ax}				+		
3a	3a-H, 7a-H	+					
	12a-H	+				+	
3b	7-H_{ax}	+ [c]					
3c	7-H_{ax}	+ [b]					
4a	3a-H	+					
	7a-H [c], 12-H_{ax}	+					
4b	5-H_{ax}			+			
	7a-H	+ [c]					
5	3a-H	+					
	8a-H						+
	10-H					+	
	12a-H						+
6	7-H_{ax}	+ [c]					
	8a-H						+
	12a-H						+
7	5-H_{ax}			+			
	8-H_{ax}	+					+
8	8-H_{ax}						+
	13-H (*endo*)					+	
9	3a-H	+					
	8-H_{ax}						+
	13-H (*endo*)	+					
10	3a-H	+ [b]					
	8-H_{ax}						+
	11-H	+					

[a] Interacting pairs showing only trivial effects (NOE between the geminal or vicinal hydrogens) are not included in this table. Only responses relevant for the stereostructures are given. [b] Responding signal: H_{ortho} (5-Ph). [c] A response of only one of the *ortho*-hydrogens was observed.

The pentacyclic norbornane/ene¶ derivatives **5**–**10** have 8 centres of asymmetry; in theory, therefore, 32, but in practice 16 diastereomers are to be considered. (The rigid norbornene moiety reduces the number of possible diastereomers.) For the part that is common (rings *A*, *B* and *C* with the 1-phenyl substituent) with the tetracycles **2** and **3** and the tricycles **4**, it is easy to select the stereostructure which is analogous to that of the latter. Additionally, it is necessary to elucidate the di-*endo* or di-*exo* annelation of the norbornane/ene moiety; our experience to date suggests that this probably remains unchanged during the synthesis. Finally, the positions of the bridging CH_2 and 1-phenyl group should also be determined.

Thus, the *A*–*B* annelation is *cis* and *trans* in **5** and **6**, respectively, and the 5-phenyl group is equatorial (*cis* to 3a,7a-H) in **5** and axial (*cis* to 3a-H, but *trans* to 7a-H) in **6** (*cf.* the shifts of 5-H and C-7a or the splittings of the former signal). In **5**, the 1-phenyl ring is *cis* to 3a,7a-H, as in **3a**, while **6** has a stereostructure analogous to that of **3c**: 1-phenyl is *cis* to 3a-H (Table 3). The di-*endo* annelation remains unaltered in both **5** and **6**, as confirmed by the NOEDIF's between the annelational H's in the oxazine ring and the *endo*-H of the bridging CH_2 group in the norbornane moiety (Table 3, Fig. 2). Direct evidence of the position of the bridging CH_2 was not observed. Consideration of molecular models and the chemical shifts of the CH_2 H's in the bicycloalkane ring as compared to those in the parent compound (norbornane[19]) suggest that the bridging CH_2 and the 1-phenyl are on the opposite side of the molecular skeleton in **5** and **6**.

The di-*exo* counterparts **7** and **8** have a *cis* *A*–*B* ring and an equatorial 5-phenyl group (*cis* to 3a-H and 7a-H) and they differ in the C-1 configuration. The di-*exo* annelation of the norbornane moiety to the oxazine ring is obvious, among

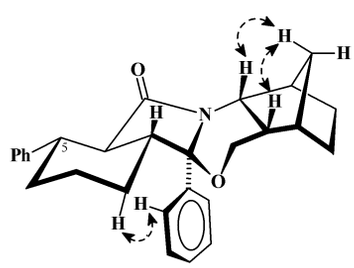


Fig. 2 Stereostructure and NOE's relevant to structure in **6**.

others from the ^{13}C chemical shifts,[20,21] and is supported by a NOE between 8-H_{ax} and 13-H(*endo*).

In **7**, the closeness of the 7-CH_2 group and the 1-phenyl ring is revealed in the upfield shifts of both 6-H signals (0.94 ppm). A similar anisotropic effect of the latter on 13-CH_2 is also observed, in accordance with the *cis* position of these moieties (1-phenyl and 13-CH_2) and the unaltered di-*exo* annelation. The downfield-shifted 12a-H signal (at 4.16 ppm, while it is 3.80 ppm for **8**) is further support of this arrangement, involving 12a-H coplanar with the carbonyl group. In accordance with this, the rotation of the 1-phenyl group is restricted (as suggested by the molecular model), and hence the C-2,6 and 2,6-H signals in **7** and the C-3,5 and 3,5-H signals in **8** are doubled.

The similar C-3a,5,7a and 3a,5,7a-H shifts and the splits of the 3a,5-H signals in **8** and **3a** suggest *cis* *A*–*B* annelation and an equatorial (*cis* to 3a-H) position for the 5-phenyl group. The anisotropy of the close-lying 1-phenyl ring causes upfield shifts of the 3a-H and 12a-H signals as compared to those for **7**. The bridging 13-CH_2 is *trans* to the 1-phenyl, in contrast with **7**, and consequently the 13-H(*endo*) signal is downfield-shifted by 0.3 ppm in the absence of the anisotropic shielding of the 1-phenyl ring. The downfield shift of the 11-H signal (2.57 ppm,

¶ The IUPAC names for norbornane and norbornene are bicyclo-[2.2.1]heptane and bicyclo[2.2.1]hept-2-ene, respectively.

Table 4 Physical and analytical data on compounds **2**–**10**

Compound (Formula)	Yield (%)	Crystallization solvent	Mp/°C	Found (%) (Required)		
				C	H	N
2 ($C_{27}H_{31}NO_2$)	70		176–177 [a]			
3a ($C_{27}H_{29}NO_2$)	37	EtOAc	171–173	81.1 (81.2)	7.4 (7.3)	3.6 (3.5)
3b ($C_{27}H_{29}NO_2$)	25	EtOAc	197–199	81.3 (81.2)	7.5 (7.3)	3.55 (3.5)
3c ($C_{27}H_{29}NO_2$)	21	EtOAc	164–166	81.35 (81.2)	7.45 (7.3)	3.5 (3.5)
4a ($C_{23}H_{26}N_2O$)	32		205–207 [b]			
4b ($C_{23}H_{26}N_2O$)	25		211–213 [c]			
5 ($C_{28}H_{31}NO_2$)	30	EtOH	182–184	81.45 (81.3)	7.5 (7.6)	3.3 (3.4)
6 ($C_{28}H_{31}NO_2$)	42	EtOAc	172–173	81.5 (81.3)	7.8 (7.6)	3.4 (3.4)
7 ($C_{28}H_{31}NO_2$)	27	EtOH	193–195	81.2 (81.3)	7.4 (7.6)	3.2 (3.4)
8 ($C_{28}H_{31}NO_2$)	32	EtOH	200–203	81.1 (81.3)	7.4 (7.6)	3.3 (3.4)
9 ($C_{28}H_{29}NO_2$)	38	Benzene	178–180	81.5 (81.7)	7.2 (7.1)	3.5 (3.4)
10 ($C_{28}H_{29}NO_2$)	35	EtOAc	171–173	81.6 (81.7)	7.3 (7.1)	3.4 (3.4)

[a] Lit.[5] mp 182–184 °C. [b] Lit.[5] mp 212–213 °C. [c] Lit.[5] mp 207–208 °C.

whereas it appears at about 2.35 ppm for **7**) is due to the anisotropy of the coplanar carbonyl[16d] in the preferred conformation of the oxazine ring (*cf.* the split by 12 Hz of the 8_{ax},8a-H coupling).

From the C-3a,7a and 3a,7a-H shifts and the multiplicities of the ^{1}H NMR signals, the two di-*exo* norbornene compounds **9** and **10** involve *cis A–B* annelation. The two large splits of the 5-H signal characteristic of diaxial couplings demonstrate the equatorial (*cis* to 3a-H) position of the 5-phenyl group. The anisotropy of the close-lying 1-phenyl ring is reflected in the upfield shifts of the 3a-H and 12a-H signals in **9** (by 0.37 ppm) relative to those in **10**, in which the ring and the H's in question are far from each other. Mutual NOE's between 13-H(*endo*) and the *ortho*-H's of the 1-phenyl ring indicate the *cis* position of 13-CH_2 and the 1-phenyl group in **9** (Table 3). The responses of the *ortho*-H's of the 1-phenyl ring when the 11-H signal is irradiated in a NOEDIF experiment, together with the similar shifts of the 13-CH_2 H's to those measured for **9**, rendered probable the *cis* arrangement of the 13-CH_2 group and the 1-phenyl substituent in **10**. The latter structure was confirmed by X-ray measurements. As compound **10** is a racemate, only one of the enantiomers is shown in Fig. 3.

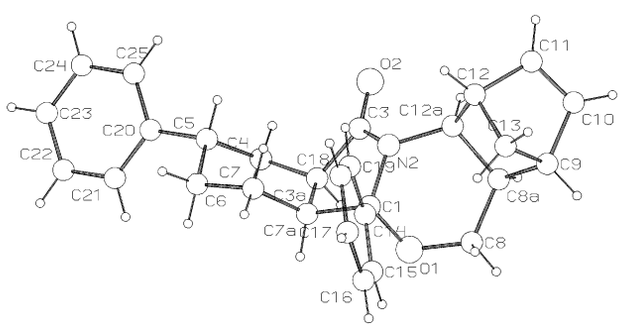


Fig. 3 Perspective view of **10**. Atoms are represented by thermal ellipsoids (at a 50% probability level); only non-hydrogens are labelled.

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 signal of the solvent as the lock and TMS as internal standard. DEPT spectra[22] were run in a standard way,[23] using only the $\theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased up and down, respectively. For NOEDIF measurements,[16c,18] the standard Bruker microprogram NOEMULT to generate NOE was used. The 2D-COSY[24a] and HMQC spectra[24b] were obtained by using also the standard Bruker pulse programs.

Crystal data for 10

$C_{28}H_{29}NO_2$, *M*: 411.52, monoclinic, space group $P2_1/a$, a = 18.363(1) Å, b = 6.321(1) Å, c = 19.333(2) Å, β = 105.18(1)°, V = 2165.7(4) Å^3, T = 293(2) K, Z = 4, F(000) = 880, Dx = 1.262 Mg m^{-3}, λ (Mo-Kα) = 0.71070 Å, μ = 0.078 mm^{-1}, R = 0.0481.

Data collection and processing

X-Ray data were collected on an Enraf-Nonius CAD4 diffractometer (graphite monochromator; Mo-Kα radiation, λ = 0.71070 Å) at 293(2) K, using ω scans. A total of 5703 reflections were collected, of which 5241 were unique [R(int) = 0.0090, $R(\sigma)$ = 0.0727]; 2804 reflections were >2$\sigma(I)$. Completeness to 2θ = 0.987.

The structure was solved by direct methods (SHELXS97).[25]

Anisotropic full-matrix least-squares refinement on F^2 for all non-hydrogen atoms yielded $R1$ = 0.0481 and $wR2$ = 0.1228 for 2804 [$I > 2\sigma(I)$] and $R1$ = 0.1135 and $wR2$ = 0.1398 for all (5241) intensity data (goodness-of-fit = 0.797; the maximum and mean shift/esd = 0.001 and 0.000).

Number of parameters = 280. The maximum and minimum residual electron densities in the final difference map were 0.193 and −0.214 e Å^{-3}.

Hydrogen atom positions were located on stereochemical grounds and refined with fixed geometry, each riding on a carrier atom, with an isotropic displacement parameter amounting to 1.3 times the value of the equivalent isotropic displacement parameter of the atom to which they are attached.

Structure refinements, including final geometric calculations, were carried out with SHELXL97.[26] Fig. 3 was produced with ORTEP-III.[27]

Supplementary data relating to this article have been deposited with the Cambridge Crystallographic Data Centre. CCDC reference number 168898.

6a,9-Diphenyl-11-oxoperhydroisoindolo[2,1-*a*][3,1]benzoxazine 2, 6a,9-diphenyl-11(6a*H*)-oxo-1,4,4a,6b,7,8,9,10,10a,12a-decahydroisoindolo[1,2-*a*][3,1]benzoxazines 3a–c, 8,10b-diphenyl-6-oxoperhydropyrimido[2,1-*a*]isoindoles 4a,b, 1,4-methano-6a,9-diphenyl-11-oxoperhydroisoindolo[2,1-*a*]-[3,1]benzoxazines 5–8, and 1,4-methano-6a,9-diphenyl-11(6a*H*)-oxo-1,4,4a,6b,7,8,9,10,10a,12a-decahydroisoindolo[2,1-*a*]-[3,1]benzoxazines 9, 10 (General procedure)

A mixture of *t*-2-benzoyl-*t*-5-phenylcyclohexane-*r*-1-carboxylic acid[1] **1** (3.0 g; 0.01 mol), aminoalcohol (1.3 g *cis*-2-amino-cyclohexanemethanol or *trans*-2-aminocyclohex-4-enemethanol or 1.4 g di-*endo*- or di-*exo*-3-aminobicyclo[2.2.1]heptane-2-methanol or di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-methanol; 0.01 mol) and PTSA (0.05 g) in dry toluene (30 cm^3) was refluxed for 1 h, with the application of a water separator. After

the solvent had been evaporated off, the residue was dissolved in $CHCl_3$ (5 cm^3), transferred to an aluminium oxide column (Acros, basic, 50–200 μ), and eluted with benzene (300 cm^3) for **4a**, **5**, **7** and **9** (monitoring by TLC, silica gel TLC aluminium sheets, solvent: benzene–EtOH–petroleum ether, bp 40–60 °C, 4 : 1 : 3, development with iodine, higher R_f) and then with EtOAc (500 cm^3) for **4b**, **6**, **8** and **10** (lower R_f on TLC plate). For the separation of **3a**–**c**, silica gel (Kieselgel 60 Merck, 0.040–0.063 mm) was applied, with a mixture of EtOAc–CH_2Cl_2–*n*-hexane (1 : 1 : 18) as eluent (1500 cm^3); the compounds appeared in the sequence **3a**, **3b** and **3c** (monitoring by TLC). The residues of the eluates were crystallized. Data on compounds **2**–**10** are listed in Table 4.

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