NMR and X-ray structural study of saturated (*p*-chlorophenyl)-pyrrolo[1,2-*a*][3,1]benzoxazin-1-ones prepared from aroylisobutyric acid and cyclic amino alcohols. High energy barriers for hindered rotation of bridgehead phenyl groups

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From 2-methyl-3-(*p*-chlorobenzoyl)propionic acid with stereoisomeric cyclic saturated or partly saturated *cis* and *trans* 1,3-amino alcohols and bicyclic amino alcohols, tri- and tetracyclic methyl substituted (*p*-chlorophenyl)-pyrrolo[1,2-*a*][3,1]benzoxazin-1-ones and methylene bridged derivatives were prepared. For comparison, the bicyclic oxazolone and oxazinone analogs were also prepared. In each case isomeric pairs, which differ in the mutual positions of the aryl and methyl groups, were formed. For the methylene bridged derivatives, the isomers were separated. For evaluation of the structure in solution ^{1}H, ^{13}C{^{1}H}, NOE difference, COSY and HMQC NMR methods were used, and for the crystal structure determinations X-ray diffraction measurements were used. An unusually high free energy barrier of the restricted rotation of the bridgehead *p*-chlorophenyl group was measured for a *cis*-, a *diendo*- and a *diexo*-fused compound.

Introduction

Bicyclic lactams have been used as intermediate products when producing new chiral substances in high enantiomeric purity, reviewed in ref. 1. Meyers *et al.* introduced the original idea to utilize chiral bicyclic lactams produced from optically pure amino alcohols and γ-ketoacids in the asymmetric construction of quaternary carbon centers,[2] and ever since then bicyclic lactams have been under intense investigation. Recently, the mechanistic aspects of the alkylation of bicyclic lactams have been studied in particular.[3] For such studies, detailed knowledge of the structural properties of essentially homologous compounds is important and useful.

In our earlier studies saturated or partially saturated (*p*-chlorophenyl)pyrrolo[1,2-*a*][3,1]benzoxazin-1-ones containing a *cis*- or *trans*-fused cycloalkane ring or *diexo*- or *diendo*-fused norbornane moieties were synthesized from 3-aroylpropionic acid and 1,2-disubstituted 1,3-bifunctional cyclic or bicyclic non-chiral amino alcohols.[4] The heterorings in those compounds can contain the aryl substituent close to or far from the annelation hydrogens of the fused cycloalkane system. The formation of compounds with different stereostructures is possible due to the ring closure by the hydroxy group from either of two directions. In addition, the steric structure of the starting amino alcohols often changes depending on the reaction conditions as can be found in the literature[5] and as we also found in earlier cases.[6]

In this study the structures of the compounds prepared from aroylisobutyric acid and cyclic non-chiral amino alcohols (*cf.* Scheme 1) were determined and the position of the aryl group relative to the annelation hydrogens and to the methyl group was established for each compound. In an earlier work, starting from 3-aroylpropionic acid we could only detect the presence of minor isomeric derivatives with thin layer chromatography. Now, the advantageous solubility of the methyl compounds allowed the isolation of both the major and minor isomers in three cases.

Broadened signals in the aromatic regions of the ^{1}H and ^{13}C NMR spectra revealed hindered rotation of the *p*-chlorophenyl group in most of the molecules. Observations of restricted rotation about an sp^2–sp^3 carbon–carbon bond of an unsubstituted or a *p*-substituted phenyl group in small molecules have been made only seldomly in the literature, and in such cases they are often found to be unusually high.[7] In the present study the free energy barriers of the rotation of an aryl group in three cases were measured by means of dynamic NMR spectroscopy.

Experimental

Synthesis

The syntheses of non-methyl analogs of compounds **2** and **3** were published by Aeberli and Houlihan[8] (more literature cited in ref. 4) and a general method for preparation of the non-methyl analogs of other compounds in this study was also described earlier.[4] In brief, 2-methyl-3-(*p*-chlorobenzoyl)-propionic acid **1** (Scheme 1) prepared according to the literature[9] was refluxed in toluene with *cis*- or *trans*-2-hydroxymethylcyclohexylamine[10] or *cis*- or *trans*-2-hydroxymethylcyclohex-4-enylamine[11] in the presence of a catalytic amount of toluene-*p*-sulfonic acid, using a Dean–Stark apparatus for the removal of water. After evaporation of the solvent and preliminary purification by column chromatography, the *cis*- and *trans*-2-methyl-3a-(*p*-chlorophenyl)perhydropyrrolo-[1,2-*a*][3,1]benzoxazin-1-ones **4** and **5** and the unsaturated derivatives **6** and **7** were finally isolated by careful column chromatography. On reaction of **1** with *diendo*-3-hydroxymethylbicyclo[2.2.1]hept-5-en-2-ylamine or with the *diexo* analogue or its saturated derivative, the 6,9-methylene-bridged benzoxazin-1-ones **8**–**10** (Scheme 1) were formed.

For each compound, **2**–**10**, two isomers were formed in the reactions. The major isomer always has the methyl group *trans* (marked **4a** *etc.*) to the aryl group with respect to the ring system, except for **2** and **3** where the major isomer has the methyl group *cis* to the aryl (confirmed below).

In the minor isomers the methyl group is *cis* (marked **4s** *etc.*)

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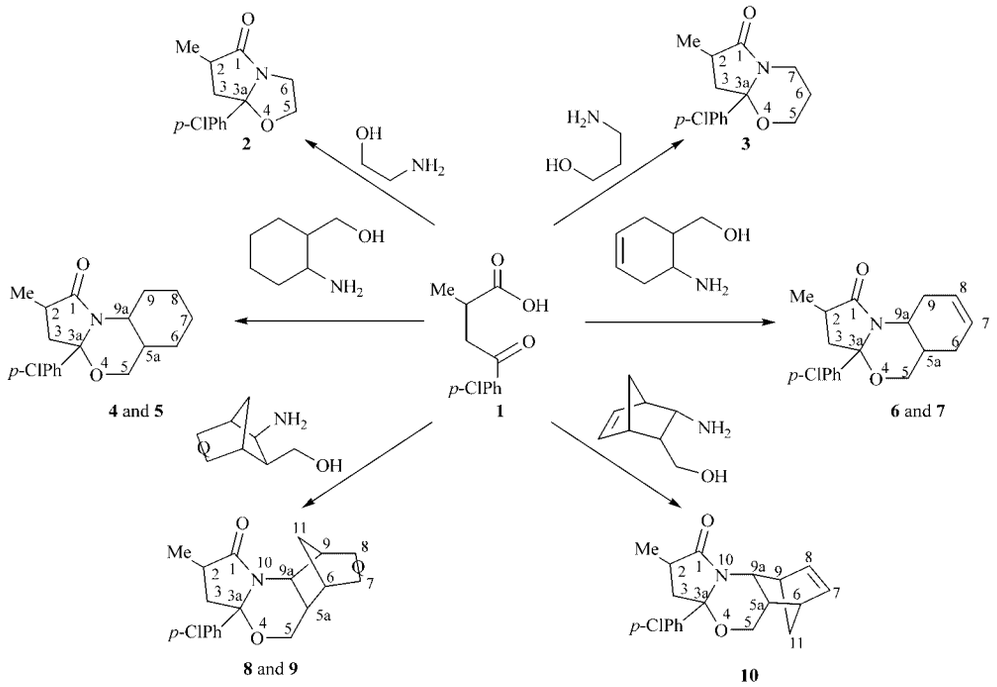

Scheme 1 Preparation of the studied compounds. Q = CH_2CH_2 in **8**, Q = CH=CH in **9**.

to the aryl group, except for **2** and **3** where the minor isomer has a *trans* configuration. In three cases, **8**–**10**, it was possible to separate the two isomers with preparative thin layer chromatography. For **2**–**7**, the assignment of the signals and structure elucidation were made with the isomeric mixtures.

Melting points were recorded on an electrothermal apparatus. The elemental analyses were performed on a Perkin-Elmer Series II CHNS/O 2400 analyzer.

Preparation of 6-methyl-7a-(4-chlorophenyl)hexahydropyrrolo-[2,1-*b*][3,1]oxazol-5-one (2) and 7-methyl-8a-(4-chlorophenyl)-hexahydropyrrolo[2,1-*b*][3,1]oxazin-6-one (3)

The mixture of **1** (2.2 g, 0.01 mol), ethanolamine (1.8 g, 0.03 mol) or 3-aminopropan-1-ol (0.8 g, 0.01 mol) and toluene-*p*-sulfonic acid (0.05 g) in dry toluene (50 ml) was refluxed for 2 hours. After evaporation the residue was crystallized from ether (**2**) or ethyl acetate (**3**); yield 1.27 g (50.1%), mp 88–90 °C (**2**) and 1.7 g (64%), mp 122–124 °C (**3**).

Preparation of the octahydro- and decahydropyrrolo[1,2-*a*][3,1]-benzoxazin-1-ones (4–10)—general method

The mixture of **1** (2.26 g, 0.01 mol, mp 137–138 °C) with cyclic or bicyclic amino alcohols (0.01 mol) and 1–2 crystals of toluene-*p*-sulfonic acid in dry toluene (50 ml) was refluxed for 2 hours. After evaporation of the mixture, the residue was dissolved in EtOAc and placed onto an Al_2O_3 column (aluminium oxide, activated, basic, Brockman I, Aldrich, Cat. No. 19, 944-3) and it was eluted with EtOAc.

For the separation of compounds **8a** and **8s**, **9a** and **9s**, and **10a** and **10s**, preparative thin layer chromatography was used (PSC-Fertigplatten, Kieselgel 60 F_{254} S, Merck, thickness 1 mm, solvent: benzene–EtOH–petroleum ether bp 40–60 °C). The two stripes (upper: **a**, lower: **s**) were removed and the layers were extracted with hot acetone.

***cis*-Fused 2-methyl-3a-(4-chlorophenyl)-1,2,3,3a,5a,6,7,8,9,9a-decahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazin-1-ones (4).** 65% Yield, mp 121–123 °C (recrystallized from petroleum ether, bp 40–60 °C). Anal. calc. for $C_{18}H_{22}NClO_2$: C, 67.60; H, 6.93; N, 4.38. Found: C, 67.73; H, 7.02; N, 4.45%.

***trans*-Fused 2-methyl-3a-(4-chlorophenyl)-1,2,3,3a,5a,6,7,8,9,9a-decahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazin-1-ones (5).** 68% Yield, mp 149–151 °C (recrystallized from benzene). Anal. calc. for $C_{18}H_{22}NClO_2$: C, 67.60; H, 6.93; N, 4.38. Found: C, 67.81; H, 6.78; N, 4.50%.

***cis*-Fused 2-methyl-3a-(4-chlorophenyl)-1,2,3,3a,5a,6,9,9a-octahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazin-1-ones (6).** 74% Yield, mp 105–107 °C (recrystallized from petroleum ether, bp 40–60 °C). Anal. calc. for $C_{18}H_{20}NClO_2$: C, 68.03; H, 6.34; N, 4.41. Found: C, 67.93; H, 6.20; N, 4.52%.

***trans*-Fused 2-methyl-3a-(4-chlorophenyl)-1,2,3,3a,5a,6,9,9a-octahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazin-1-ones (7).** 51% Yield, mp 141–143 °C (recrystallized from petroleum ether, bp 40–60 °C). Anal. calc. for $C_{18}H_{20}NClO_2$: C, 68.03; H, 6.34; N, 4.41. Found: C, 67.90; H, 6.28; N, 4.32%.

(2*R,3a*S**,5a*R**,9a*R**)-2-Methyl-3a-(4-chlorophenyl)-6,9-methano-1,2,3,3a,5a,6,7,8,9,9a-decahydro-5*H*-pyrrolo[1,2-*a*]-[3,1]benzoxazin-1-one (8a).** 45% Yield, mp 134–136 °C (recrystallized from benzene). Anal. calc. for $C_{19}H_{22}NClO_2$: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.70; H, 6.63; N, 4.40%.

(2*S,3a*S**,5a*R**,9a*R**)-2-Methyl-3a-(4-chlorophenyl)-6,9-methano-1,2,3,3a,5a,6,7,8,9,9a-decahydro-5*H*-pyrrolo[1,2-*a*]-[3,1]benzoxazin-1-one (8s).** 20% Yield, mp 153–155 °C (recrystallized from petroleum ether, bp 40–60 °C). Anal. calc. for $C_{19}H_{22}NClO_2$: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.59; H, 6.45; N, 4.23%.

(2*R,3a*S**,5a*S**,9a*S**)-2-Methyl-3a-(4-chlorophenyl)-6,9-methano-1,2,3,3a,5a,6,9,9a-octahydro-5*H*-pyrrolo[1,2-*a*][3,1]-benzoxazin-1-one (9a).** 42% Yield, mp 156–158 °C (recrystallized from benzene). Anal. calc. for $C_{19}H_{20}NClO_2$: C, 69.19; H, 6.11; N, 4.25. Found: C, 69.31; H, 6.70; N, 4.28%.

(2*S,3a*S**,5a*S**,9a*S**)-2-Methyl-3a-(4-chlorophenyl)-6,9-methano-1,2,3,3a,5a,6,9,9a-octahydro-5*H*-pyrrolo[1,2-*a*][3,1]-benzoxazin-1-one (9s).** 24% Yield, mp 155–157 °C (recrystallized from petroleum ether, bp 40–60 °C). Anal. calc. for

$C_{19}H_{20}NClO_2$: C, 69.19; H, 6.11; N, 4.25. Found: C, 69.28; H, 6.64; N, 4.18%.

(2*R,3a*S**,5a*R**,9a*R**)-2-Methyl-3a-(4-chlorophenyl)-6,9-methano-1,2,3,3a,5a,6,9,9a-octahydro-5*H*-pyrrolo[1,2-*a*][3,1]-benzoxazin-1-one (10a).** 45% Yield, mp 204–206 °C (recrystallized from ethyl acetate). Anal. calc. for $C_{19}H_{20}NClO_2$: C, 69.19; H, 6.11; N, 4.25. Found: C, 69.01; H, 6.07; N, 4.26%.

(2*S,3a*S**,5a*R**,9a*R**)-2-Methyl-3a-(4-chlorophenyl)-6,9-methano-1,2,3,3a,5a,6,9,9a-octahydro-5*H*-pyrrolo[1,2-*a*][3,1]-benzoxazin-1-one (10s).** 30% Yield, mp 159–161 °C (recrystallized from ethyl acetate). Anal. calc. for $C_{19}H_{20}NClO_2$: C, 69.19; H, 6.11; N, 4.25. Found: C, 69.05; H, 6.40; N, 4.30%.

NMR Measurements

Correct assignment of the chemical shifts and their connectivities was confirmed from an analysis of the NOE difference,[12] COSY,[13] COSY with long range delay[14] (200 ms) and HMQC[15] with BIRD delay[16] (~475 ms) spectra. The establishment of the stereochemistry was based on ^{1}H and ^{13}C NMR chemical shifts, ^{1}H,^{1}H coupling constants (Tables 1–3) and nuclear Overhauser effects. In the NOE measurements the selective irradiation was always placed on the higher resonating aromatic proton signals H13 and H17. The COSY measurements were done with and without a long range delay in the pulse sequence and thus many long range correlations were observed, *e.g.* between H3a and H18 or H3s and H18, but the actual coupling constants were not resolved in all cases. Important crowded and/or non-first-order ^{1}H NMR spectrum regions were simulated and iteratively analyzed with PERCH on a Pinus Pentium 100 MHz personal computer.[17] PERCH analysis was also possible in some cases for the spectral regions of the minor isomer in an unseparated mixture.

The NMR spectra were recorded in $CDCl_3$ at +30 °C on JEOL JNM-LA400 (^{1}H: 399.78 MHz, ^{13}C: 100.54 MHz) or on JEOL JNM-A500 (^{1}H: 500.16 MHz, ^{13}C: 125.78 MHz) Fourier transform spectrometers with the deuterium signal of the solvent as the lock and TMS as an internal standard in the ^{1}H NMR measurements (0.00 ppm) and the middle line of the solvent signal in the ^{13}C NMR measurements (77.10 ppm). 2–10 mg of samples were dissolved for the 1D ^{1}H-measurements and 10–40 mg for other measurements in 0.5 ml of solvent and the measurements were made in 5 mm diameter Wilmad 7 inch 507PP NMR tubes or in 5 mm diameter New Era Enterprises NE-HL5-7 NMR tubes. For the NOE difference measurements the samples were degassed by nitrogen bubbling. A reference value of −100 was given to the integral of the irradiated signal in order to approximate the percentual NOE effects.

Variable temperature NMR. In the ^{1}H and/or ^{13}C NMR spectrum of **4a**, **6a**, **8a**, **9a** and **10a**, the aromatic signals were notably broadened at room temperature, resulting from the hindered rotation of the aryl group. In order to measure the corresponding rotational energy barrier for three different types of compounds, the ^{1}H NMR spectra of **6a**, **9a** and **10a** were measured at different temperatures to determine the coalescence temperatures (Table 4). For **10a**, two coalescence temperatures were also determined from ^{13}C NMR measurements. From the coalescence temperature and the difference in frequencies of the signals below coalescence, the free energies of activation were then calculated (Table 4) using the well-known Eyring equation:[18]

$$\Delta G^{\ddagger}/\mathrm{J\ mol^{-1}} = RT_c\,[22.96 + \ln(T_c/\delta\nu)]$$

Variable temperature ^{1}H and ^{13}C NMR measurements were made in $CDCl_3$ in the range from −54 °C to +33 °C. At each temperature the sample was stabilized for a minimum of 20 minutes. Temperatures were calibrated with the methanol method.[19]

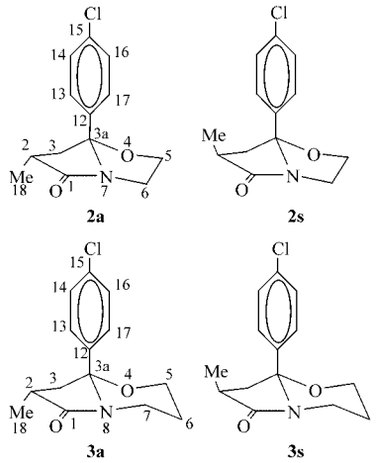

Fig. 1 Structures of compounds **2** and **3**. Non-systematic numbering has been used in compounds **2** and **3** for ease of comparison of spectral data.

Crystal structure determinations

Crystal data for compounds **3s**–**10a** along with other experimental details, are summarized in Table 5.† Single-crystal data collections were performed at ambient temperature on a Rigaku AFC5S diffractometer using graphite monochromatized Mo-K_α radiation ($\lambda = 0.71069$ Å). The unit cell parameters were determined by least-squares refinement of 25 carefully centered reflections. Data reduction and subsequent calculations were performed with teXsan for Windows.[20] The data were corrected for Lorenz and polarisation effects.

The structures were solved by direct methods using the SIR92 program[21] and full-matrix least-squares refinements on F^2 were performed using the SHELXL-97 program.[22] Non-hydrogen atoms were refined with anisotropic displacement parameters and the sp^3 hydrogen atoms were refined with fixed isotropic displacement factors and the rest of the hydrogen atoms were riding at the fixed distances from their host atoms. Figures were drawn with Ortep-3 for Windows.[23]

Solution structures

Configuration and conformation of the oxazole and oxazine derivatives, 2 and 3.‡ For oxazole derivatives **2** and oxazine derivatives **3**, roughly 15% of the minor isomer and 85% of the major isomer was formed in the synthesis. In **2** and **3** the major isomers exhibit a *syn* configuration, *i.e.* the methyl and phenyl groups are *cis* to each other with respect to the heterocyclic ring (Fig. 1, compounds **2s** and **3s**). The minor isomers of **2** and **3** have structures in which the methyl and phenyl groups are *trans* to each other (Fig. 1, compounds **2a** and **3a**). The relative orientations of methyl and phenyl groups were confirmed by NOE difference measurements by selectively irradiating aromatic protons H13 and H17. In the major isomers **2s** and **3s** 1.3% and 0.6% NOE, respectively, to the methyl was observed, indicating spatial proximity with the methyl and the irradiated aromatic protons, but almost no enhancement was observed for H2. In the minor isomers **2a** and **3a**, no enhancement was observed for the methyl group. The assignment of protons in position 3 was also made from the DNOE measurements (Table 1). H3s is always *cis* to the phenyl group whereas H3a is *trans* to it. For **2**, the assign-

† CCDC reference number 188/180. See http://www.rsc.org/suppdata/p2/1999/2011 for crystallographic files in .cif format.

‡ Non-systematic numbering has been used in compounds **2** and **3** for ease of comparison of spectral data.

Table 1 ^{1}H chemical shifts of all isomers, δ(TMS) = 0.00 ppm

No.	Type	H2	H3a	H3s	H5ax	H5eq	H5a	H6ax	H6eq	H7ax	H7eq	H8ax	H8eq	H9ax	H9eq	H9a	H11a	H11s	H13	H14,16	H17	H18
2a	oxazole	2.96	2.17	2.49	3.96	3.72	—	4.09	3.03	—	—	—	—	—	—	—	—	—	7.35	7.39	7.35	1.24
2s	oxazole	2.77	1.82	2.81	3.97	3.63	—	4.01	2.99	—	—	—	—	—	—	—	—	—	7.35	7.39	7.35	1.32
3a	oxazine	2.50	1.99	2.28	3.60	3.85	—	1.90	1.40	2.91	4.18	—	—	—	—	—	—	—	7.32	7.40	7.32	1.29
3s	oxazine	2.75	1.60	2.55	3.70	3.83	—	1.87	1.30	2.97	4.16	—	—	—	—	—	—	—	7.32	7.40	7.32	1.21
4a	*cis*, sat.	2.58	1.92	2.20	3.85	3.60	2.19	1.55	1.55	0.85	1.35	1.19	1.55	1.08	1.55	4.34	—	—	7.3	7.35	7.3	1.23
4s	*cis*, sat.	2.69	1.62	2.50	3.95	3.65										4.40	—	—	7.3	7.35	7.3	1.2
5a	*trans*, sat.	2.39	1.94	2.17	3.23	3.67	1.79	0.69	1.43	1.28	1.63	1.12	1.87	2.23	2.76	2.93	—	—	7.25	7.4	7.25	1.24
5s	*trans*, sat.	2.71	1.52	2.46	3.31	3.71		0.65		1.25		1.04		2.65			—	—	7.25	7.4	7.25	1.17
6a	*cis*, unsat.	2.63	1.96	2.23	3.69	3.61	2.32	1.71	2.41	5.44	—	5.39	—	1.82	2.00	4.61	—	—	7.3	7.35	7.3	1.25
6s	*cis*, unsat.	2.71	1.66	2.53	3.77	3.60					—		—			4.66	—	—	7.3	7.35	7.3	1.23
7a	*trans*, unsat.	2.61	1.99	2.29	3.59	4.04	1.78	1.65	1.91	5.56	—	5.52	—	1.90	2.97	3.68	—	—	7.35	7.4	7.35	1.24
7s	*trans*, unsat.	2.65	1.64	2.54	3.54	4.06				5.56	—	5.52	—			3.73	—	—	7.35	7.4	7.35	1.27
8a	*diexo*, sat.	2.41	1.94	2.27	3.24	3.91	2.06	2.33	—	1.51	1.42	1.47	1.15	1.80	—	3.89	0.84	0.96	7.3	7.35	7.3	1.18
8s	*diexo*, sat.	2.60	2.53	1.86	3.26	3.88	2.05	2.32	—	1.5	1.3	1.45	1.13	1.78	—	3.98	0.82	0.92	7.71	7.35	7.53	1.11
9a	*diexo*, unsat.	2.46	1.97	2.30	3.27	4.09	1.95	2.43	—	6.28	—	6.06	—	2.93	—	3.76	1.14	1.00	7.3	7.35	7.3	1.19
9s	*diexo*, unsat.	2.64	2.57	1.91	3.28	4.06	1.91	2.41	—	6.04	—	6.31	—	2.91	—	3.85	1.12	1.00	7.70	7.34	7.53	1.12
10a	*diendo*, unsat.	2.49	1.91	2.23	3.09	3.96	2.68	2.69	—	5.66	—	5.63	—	3.38	—	4.27	1.49	1.42	7.16	7.31	7.16	1.17
10s	*diendo*, unsat.	2.83	2.88	3.48	3.78	3.79	2.59	2.92	—	6.29	—	6.39	—	5.39	—	4.70	1.55	1.40	7.90	7.26	7.43	1.20

Table 2 ^{13}C chemical shifts of all isomers, $\delta(CDCl_3) = 77.10$ ppm

No.	Type	C1	C2	C3	C3a	C5	C5a	C6	C7	C8	C9	C9a	C11	C12	C13	C14	C15	C16	C17	C18
2a	oxazole	182.50	38.91	43.50	100.57	66.02	—	41.64	—	—	—	—	—	140.16	126.62	128.97	134.33	128.97	126.62	16.11
2s	oxazole	184.54	38.39	40.78	100.57	65.01	—	42.85	—	—	—	—	—	140.34	126.72	129.01	134.31	129.01	126.72	17.82
3a	oxazine	176.70	34.68	45.18	92.65	62.52	—	24.82	36.33	—	—	—	—	141.91	127.44	129.53	134.20	129.53	127.44	16.39
3s	oxazine	179.43	35.63	44.82	92.65	62.62	—	24.94	37.26	—	—	—	—	139.86	127.59	129.50	134.10	129.50	127.59	17.01
4a	*cis*, sat.	176.39	34.55	47.27	90.43	63.08	34.02	27.08	21.04	25.13	27.30	49.62	—	141.56	127.14	128.93	134.00	128.93	127.14	15.77
4s	*cis*, sat.	180.07	35.34	46.21	91.83	63.08	34.17	27.17	21.04	25.45	27.48	51.37	—	142.87	127.14	128.93	134.00	128.93	127.14	17.43
5a	*trans*, sat.	177.60	35.46	44.77	93.63	68.08	40.99	26.66	24.76	25.86	28.52	58.91	—	139.24	127.61	129.56	134.12	129.56	127.61	16.46
5s	*trans*, sat.	180.76	36.39	45.12	93.63	68.47	40.00	27.17	24.72	26.29	28.48	59.13	—	139.90	127.66	129.52	134.12	129.52	127.66	16.58
6a	*cis*, unsat.	176.69	34.66	47.52	90.51	64.06	33.33	26.24	123.68	123.87	25.05	46.30	—	141.78	126.96	129.07	134.08	129.07	126.96	15.85
6s	*cis*, unsat.	176.40	35.34	46.51	90.51	63.10	32.41	26.54	123.75	123.75	25.15	46.51	—	141.57	127.17	128.96	134.08	128.96	127.17	17.35
7a	*trans*, unsat.	179.42	35.09	47.19	90.59	67.89	34.45	28.67	124.75	125.51	31.15	52.61	—	144.68	126.14	129.18	133.84	129.18	126.14	16.38
7s	*trans*, unsat.	181.67	35.09	46.66	91.38	68.27	34.45	28.83	125.01	125.76	31.84	54.16	—	145.52	126.60	129.01	133.72	129.01	126.60	16.92
8a	*diexo*, sat.	177.85	33.61	47.52	90.62	63.85	39.09	42.47	28.53	27.76	39.29	55.01	34.76	141.19	127.44	128.92	134.16	128.92	127.44	14.70
8s	*diexo*, sat.	179.79	35.31	45.55	90.83	63.95	39.04	42.45	29.18	27.56	39.28	55.51	34.89	143.49	127.66	128.94	134.02	128.94	127.66	17.83
9a	*diexo*, unsat.	178.24	33.95	47.65	90.54	65.96	31.61	44.40	136.65	137.36	47.62	51.68	44.45	141.08	127.34	128.99	134.26	128.99	127.34	14.65
9s	*diexo*, unsat.	180.22	35.65	45.53	92.14	66.00	31.05	44.46	136.46	137.91	47.58	52.47	44.54		128.91	127.53	134.13	128.99	130.95	17.75
10a	*diendo*, unsat.	179.64	33.57	48.56	90.25	64.59	34.93	43.62	136.16	137.00	47.41	52.72	48.63	140.66	127.58	128.56	133.80	128.56	127.58	14.54
10s	*diendo*, unsat.	175.52	36.40	45.39		64.44		42.82			47.37	50.78	48.35	143.22						18.23

Table 3 Selected ^{1}H, ^{1}H coupling constants of all isomers (Hz)

No.	Type	2, 3a	2, 3s	2, 9a[a]	2, 18	3a, 3s	5a, 5ax	5a, 5eq	5a, 6ax[b]	5a, 6eq[c]	5a, 9a	5ax, 5eq[d]	5eq, 6ax[e]	5eq, 6eq[f]	6ax, 6eq[g]
2a	oxazole	9.4	8.9	1.2	7.2	−13.2	—	—	5.0	4.9	—	−8.3	8.2	6.5	−8.2
2s	oxazole	6.3	9.7	—	7.4	−14.3	—	—	8.4	5.6	—	−8.1	5.8	8.7	−11.2
3a	oxazine	8.5	8.8	1.2	7.1	−13.0	—	—	13.0	2.3	—	−13.0	4.6	1.7	−13.3
3s	oxazine	7.6	9.4	—	7.4	−13.8	—	—	12.7	2.4	—	−11.9	5.0	1.4	−13.1
4a	*cis*, sat.	10.46	8.31		7.07	−12.44	11.95	4.1	~4	~4	4.8	−11.7	—	—	
4s	*cis*, sat.	6.85	10.17		7.40	−13.94	12.1				4.9	−12.1	—	—	
5a	*trans*, sat.	8.78	8.75	1	7.19	−12.77	11.4	4.3	12.9	3.9	11.2	−11.5	—	—	−13.1
5s	*trans*, sat.	9.00	9.1		7.33	−13.6	11.4	4.7	13.1			−11.5	—	—	−13.1
6a	*cis*, unsat.	10.45	8.36		7.11	−12.53	12.3	4.1	4.4	4.1	4.2	−11.5	—	—	−19.1
6s	*cis*, unsat.	7.13	10.21		7.26	−13.98	11.9				5.6	−11.9	—	—	
7a	*trans*, unsat.	8.4	9.4	1.2	6.93	−13.2	11.9	5.5	11.6	5.1	11.3	−10.2	—	—	~−16
7s	*trans*, unsat.	8.3	9.2		7.0	−13.9	12.0	4.9			11.5	−10.1	—	—	
8a	*diexo*, sat.	12.0	7.4	<0.5	7.0	−11.8	9.5	8.1	<0.5	—	8.9	−12.4	—	—	—
8s	*diexo*, sat.	10.6	2.2		7.3	−12.9	9.9	8.4		—	9.0	−12.4	—	—	—
9a	*diexo*, unsat.	12.1	7.3	—	7.0	−11.8	9.2	7.9	<0.5	—	8.7	−12.4	—	—	—
9s	*diexo*, unsat.	10.6	1.9		7.3	−12.8	9.5	8.2		—	9.0	−12.4	—	—	—
10a	*diendo*, unsat.	12.2	7.2	<0.5	7.1	−11.8	10.8	8.3	3.7	—	10.3	−12.0	—	—	—
10s	*diendo*, unsat.		8.8		6.9	−9.0	9	8	3.1	—	9.6		—	—	—

No.	Type	6ax, 7ax[h]	6ax, 7eq[i]	6eq, 7ax	7ax, 7eq[j]	7ax, 8ax[k]	8ax, 8eq[l]	8ax, 9ax[m]	8ax, 9eq[n]	8eq, 9ax[o]	9a, 9ax[p]	9a, 9eq	9ax, 9eq	11a, 11s
2a	oxazole	—	—	—	—	—	—	—	—	—	—	—	—	—
2s	oxazole	—	—	—	—	—	—	—	—	—	—	—	—	—
3a	oxazine	13.0	5.4	3.7	−13.0	—	—	—	—	—	—	—	—	—
3s	oxazine	12.9	5.1	3.5	−13.3	—	—	—	—	—	—	—	—	—
4a	*cis*, sat.					13.0	−13.0	12.9	2.8	3.2	12.7	4.8	−12.7	—
4s	*cis*, sat.										12.3	4.9		—
5a	*trans*, sat.	13.1	3.9	3.7	−13.1	13.2	−13.3	13.3	3.5	3.8	11.7	3.5	−13.4	—
5s	*trans*, sat.	13.1	4.0			13.3	−13.3	13.3	3.5	3.7	13.0		−13.0	—
6a	*cis*, unsat.	3.1	—	6.7	—	7.8	—	4.3	5.7	—	11.3	6.6	−17.4	—
6s	*cis*, unsat.		—		—		—			—	11.2	4.9		—
7a	*trans*, unsat.	~6.7	—		—		—		5.4	—	11.3	5.0	−16.6	—
7s	*trans*, unsat.		—		—		—			—	11.5	5.1		—
8a	*diexo*, sat.	4.3	~1	—	−11.6	4.3	−10.4		—	<0.5	<0.5	—	—	−10.6
8s	*diexo*, sat.			—					—			—	—	−10.7
9a	*diexo*, unsat.	<0.5	—	—	—	5.7	—	<0.5	—	—	<0.5	—	—	−9.4
9s	*diexo*, unsat.		—	—	—	5.7	—		—	—		—	—	−9.5
10a	*diendo*, unsat.	<0.5	—	—	—	5.8	—	2.8	—	—	<1	—	—	−8.8
10s	*diendo*, unsat.		—	—	—	5.7	—		—	—	9.7	—	—	−8.8

[a] 2, 6s in **2a** and 2, 7ax in **3a**. [b] 5a, 6a in **2a** and 2s, 5ax, 6ax in **3a** and **3s**, and 5a, 6 in **9a**, **10a** and **10s**. [c] 5a, 6s in **2a** and **2s**, and 5ax, 6eq in **3a** and **3s**. [d] 5a, 5s in **2a** and **2s**. [e] 5s, 6a in **2a** and **2s**. [f] 5s, 6s in **2a** and **2s**. [g] 6a, 6s in **2a** and **2s**. [h] 6ax, 7 in **6a** and **7a**, 6, 7x in **8a**, and 6, 7 in **9a** and **10a**. [i] 6, 7n in **8a**. [j] 7n, 7x in **8a**. [k] 7, 8 in **6a**, **9a**, **9s**, **10a** and **10s**, and 7x, 8x in **8a**. [l] 8n, 8x in **8a**. [m] 8, 9ax in **6a**, and 8, 9 in **9a** and **10a**. [n] 8, 9eq in **6a** and **7a**. [o] 8n, 9 in **8a**. [p] 9, 9a in **8a**, **9a**, **10a** and **10s**.

ment of protons in positions 5 and 6 was also reached by the DNOE experiments. The relative configuration for **2a** is 2*R**,3a*S** and for **2s** 2*S**,3a*S**.

In the isomers of compound **3**, the axial protons in the six-membered ring can be identified by their large *ca.* 13 Hz (Table 3) couplings to the vicinal axial proton, while the equatorial protons did not show such a large coupling. The vicinal coupling constants between protons in positions 5, 6 and 7 affirm a chair conformation for the six-membered ring, and also the W-type couplings between H5eq and H7eq in **3a** (1.7 Hz) and **3s** (1.6 Hz) validate the conformation. The phenyl group is axial to the six-membered ring, which was confirmed in **3s** by 1.4% NOE to H5ax and 1.6% NOE to H7ax from the *o*-protons. The relative configuration of **3a** is 2*R**,3a*S** and of **3s** is 2*S**,3a*S**.

For **2a**, *transoid*-homoallylic-type ^5J-couplings[24] between H2 and H6s, and in **3a** between H2 and H7ax were observed (Table 3), similarly to our previously studied non-methyl analogs.[4] It indicates that the lactam bond in the molecule has double bond character and the lactamide is thus quite planar. The carbon chemical shifts are not very informative when differentiating the above *trans* and *cis* configurations from each other and identifying them, though there are certain effects observed for example in the chemical shifts of C1 and C3 (Table 2).

Configuration and conformation of the *cis*- and *trans*-fused compounds, 4–7.§ There are, in principle, five stereogenic atoms in compounds **4**–**7**, *i.e.* it is possible to generate 2^5 (= 32) different isomers. 16 of them correspond to *cis* and 16 to *trans* isomers. Because of the fast inversion of the almost planar nitrogen the number of different isomers is reduced to 8 + 8 representing 4 + 4 pairs of enantiomers. H9a always has a large coupling to H9ax (Table 3), *i.e.* H9a is diaxial to H9ax and thus *cis*-fused compounds **4** and **6** adopt an *N-out* conformation (Fig. 2). *cis*- or *trans*-Fusion is indicated by the coupling between H5a and H9a: for *cis*-fused compounds the coupling is small (~5 Hz, Table 3) and for *trans*-fused compounds it is large (~11.5 Hz). A double bond between C7 and C8 in compounds **6** and **7** is characterized by the corresponding proton and carbon chemical shifts, respectively (Tables 1 and 2).

On the basis of the measured 0.5–2.0% NOEs from the aromatic protons (H13, H17) to H2, the major isomers of all of the compounds have the methyl group *trans* to the aryl group (compounds **4a–7a**). In the minor isomers, the methyl and aryl are *cis* to each other (compounds **4s–7s**). A clear NOE from the aromatic protons to H5ax (0.8%) and H9ax (0.3–0.5%) excludes the equatorial orientation of the aryl group in the *cis*-fused molecules **4** and **6**. In the *trans*-fused molecules **5** and **7** NOEs from the aromatic protons to H5ax and H9a (1.6% and 3.5%, respectively, in **5**) do the same. The assignment of H3 was also confirmed by 0.5–0.9% NOEs observed. The relative configurations for **4a** and **6a** are: 2*R**,3a*S**,5a*S**,9a*S**; for **4s** and **6s**: 2*S**,3a*S**,5a*S**,9a*S**; for **5a** and **7a**: 2*R**,3a*S**,5a*R**,9a*S**; for **5s** and **7s**: 2*S**,3a*S**,5a*R**,9a*S**.

§ Non-systematic numbering has been used in compounds **4**–**7** for ease of comparison of spectral data.

Table 4 Measured coalescence temperatures, differences in frequencies of the signals below coalescences and $\Delta G^{\ddagger}$ values for the rotational barrier of the aromatic substituent

Compound	Nucleus	$T_{coal.}$/K	$\delta\nu$/Hz	$\Delta G^{\ddagger}$/kJ mol^{-1}
6a, *cis*	^{1}H	250.59	226.65	48.0 ± 0.7
9a, *diexo*	^{1}H	225.57	172.4	43.6 ± 0.7
10a, *diendo*	^{1}H	281.63	178.74	54.8 ± 0.7
10a, *diendo*	^{1}H	258.19	8.11	56.7 ± 1.4
10a, *diendo*	^{13}C	284.69	295.26	54.3 ± 0.9
10a, *diendo*	^{13}C	279.59	35.86	58.1 ± 1.0
10a, *diendo*		average		56.0 ± 1.0

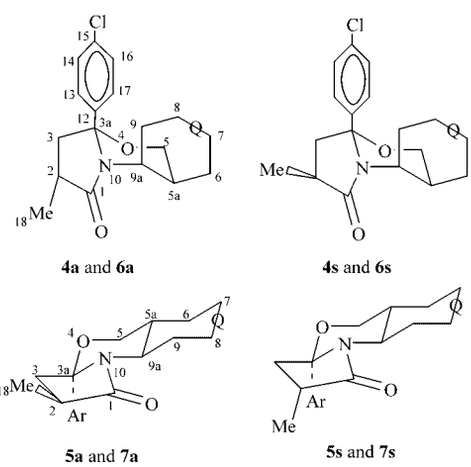

Fig. 2 Structures of *cis*-fused (upper) and *trans*-fused (lower) compounds **4**–**7** (Ar = *p*-ClC$_6$H$_4$). Q = CH$_2$CH$_2$ in **4** and **5**, Q = CH=CH in **6** and **7**. Non-systematic numbering has been used in compounds **4**–**7** for ease of comparison of spectral data.

Table 5 Crystal data and experimental details for **3s**–**10a**

	3s, oxazine	**5a**, *trans*	**6a/6s**, *cis*	**9a**, *diexo*	**10a**, *diendo*
Formula	$C_{14}H_{16}ClNO_2$	$C_{18}H_{22}ClNO_2$	$C_{18}H_{20}ClNO_2$	$C_{19}H_{20}ClNO_2$	$C_{19}H_{20}ClNO_2$
M_r	265.73	319.82	317.80	329.81	329.81
Crystal size/mm	0.38 × 0.32 × 0.20	0.24 × 0.22 × 0.20	0.40 × 0.32 × 0.25	0.40 × 0.38 × 0.36	0.38 × 0.28 × 0.26
Crystal system	Monoclinic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic
Space group (No.)	$P2_1$ (4)	*Pbca* (61)	$P2_1/c$ (14)	$P2_1/c$ (14)	$P2_1/n$ (14)
a/Å	7.5589(8)	26.623(2)	8.941(4)	8.754(9)	8.640(4)
b/Å	9.3566(15)	11.433(3)	12.749(4)	16.647(4)	10.747(2)
c/Å	9.4213(9)	10.698(2)	15.113(3)	11.575(2)	17.657(2)
β/°	96.52(1)	90	105.06(2)	103.47(3)	90.85(2)
V/Å^3	662.02(14)	3259.2(12)	1663.5(9)	1640.4(17)	1639.4(9)
Z	2	8	4	4	4
D_c/g cm^{-3}	1.333	1.304	1.269	1.335	1.336
μ(Mo-Kα)/cm^{-1}	2.82	2.41	2.36	2.42	2.42
Obs. refl.	1232	2875	2925	2875	2883
No. of parameters	189	244	238	241	241
$R1$ [b]	0.036 (0.027)[a]	0.147 (0.053)	0.122 (0.053)	0.105 (0.046)	0.085 (0.040)
$wR2$ [c]	0.064 (0.061)	0.118 (0.097)	0.148 (0.123)	0.120 (0.100)	0.096 (0.083)
Goodness of fit	1.072	1.024	1.015	1.021	1.020
Max., min. $\Delta\rho$/e Å^{-3}	0.14/−0.14	0.19/−0.21	0.29/−0.21	0.18/−0.19	0.13/−0.21

[a] Values in parentheses for reflections with $I > 2\sigma(I)$. [b] $R1 = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$. [c] $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$; $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, where $P = (2F_c^2 + F_o^2)/3$.

Large diaxial vicinal proton couplings (Table 3) in the six-membered rings of **4** and **5** confirm that they exist in chair conformations. Also the W-type couplings between H6eq and H8eq, and H7eq and H9eq (1.0 Hz) in compound **5a** indicate a chair conformation. In **4a** four bond couplings were observed between H5ax and H9a, and H5eq and H9a (also in **6a**, 1.3 Hz), which indicates that the heteroring is not purely a chair but slightly flattened due to the heteroatoms and the *cis*-fused carbocycle. In **6** and **7**, the carbocyclic ring attains a half-chair conformation due to the double bond in the ring similarly to our previously studied compounds.[4]

For **5a** and **7a**, a *transoid*-homoallylic-type ^5J-coupling[24] between H2 and H9a was observed (Table 3) similarly to the oxazole derivative **2a** and the oxazine derivative **3a** and to our previous observations.[4] The homoallylically coupled H2 is *cis* to the aryl group as was the case in the previously studied compounds where the coupling was observed.[4] Several other *cisoid*-homoallylic-type ^5J couplings[25] between H6 and H9 (in **6a** 2.5 Hz), and allylic-type ^4J couplings[26] between H6 and H8, or between H7 and H9 were observed in **6a** and **7a**. The carbon chemical shifts are not very sensitive for configurational changes in respect to the relative orientation of the methyl and aryl groups as was mentioned already in the case of **2** and **3**, though, there are some obvious trends in the order of the shifts based on whether the methyl group is *trans* or *cis* to the aryl group (*cf.* Table 2).

Configuration and conformation of the *diexo*- and *diendo*-fused compounds, 8–10. All the isomers formed in the reactions, aimed at preparing compounds **8**–**10**, were separated with preparative thin layer chromatography. Thus, the determination of the stereostructure was easier than in the case of **2**–**7**. The *diexo*-fusion of **8** and **9** (Fig. 3) was proved by 0.5–1.4% NOEs from the aromatic protons (H13, H17) to H11s, which is *cis* to the phenyl group, but not to H7, H8, H5a and H9a. The long-range couplings observed in the COSY or COSY LR spectra, or in the 1D spectra for each of the compounds **8a**, **8s**, **9a** and **9s**: between H9a and H11a, H5a and H11a (1.4 Hz in **8a**, 1.2 Hz in **8s**, 1.5 Hz in **9a**), H5ax and H9a, and H5eq and H9a in compounds **8a** and **9a** confirm the conclusion. W-type couplings between H5a and H9 in **8a**, and between H6 and H9a in **9a** support the postulated stereochemistry. In **8a** and **8s**, H6 is also close to the aromatic side chain deduced from 2.3% and 1.8% NOEs, respectively, which is in agreement with the *diexo* configuration. In **9a** and **9s**, no comparable NOE to H6 was observed, but in **9a** 1.8% NOE to H9 from the aromatic protons was observed.

In the isomer **10a** (Fig. 3), *diendo*-fusion is indicated by 2.9% NOE from the aromatic protons to the somewhat overlapped signals of H7 and H8, but not to H11a, H11s, H5a or H9a. Also NOEs from aromatic protons to H6 (0.5%) and H9 (0.3%) are in agreement with the *diendo* configuration. W-type long-range couplings between H5ax and H9a, and between H5eq and H9a confirm the deduced stereochemistry.

The major products **8a**, **9a** and **10a** have the methyl group *trans* to the aryl group in each case, which is proved by 1.5–2.5% NOE to H2 when irradiating aromatic protons H13 and H17, but not to methyl protons H18. In the minor products **8s**, **9s** and **10s** the methyl is *cis* to the aryl, which slows down the aryl rotation, and thus, the aromatic protons H13 and H17 become chemically non-equivalent (Table 1). The *cis* configuration is also confirmed by 0.8% NOE from the aromatic protons (H13 and H17) to the methyl protons H18 in compounds **8s** and **9s**. In **10s** NOE difference measurements were not successful due to the limited availability of this compound and, thus, a too low concentration.

Protons H3s, H5ax and H11s were assigned on the basis of the observed 0.4–1.1% NOEs from the aromatic protons in **8a**, **8s**, **9a** and **9s**. In **8a** and **9a**, W-type long-range couplings between H7 (in **8a**: H7n) and H11s, and between H8 (in **8a**: H8n) and H11s confirm the assignment of H11s. In **10a** the signals of protons H3s (0.6%) and H5ax (1.3%) were enhanced, making their assignment clear.

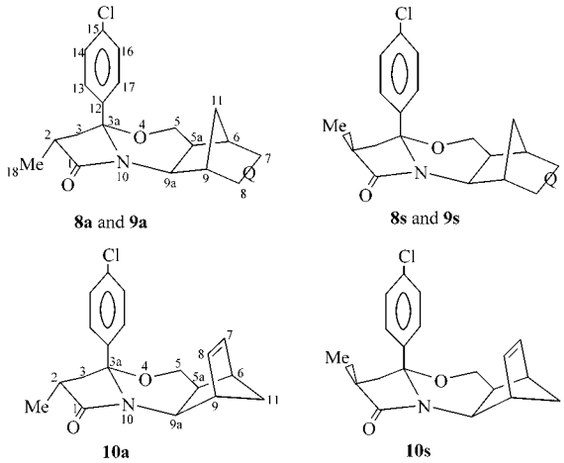

Fig. 3 Structures of compounds **8**–**10**. Q = CH_2CH_2 in **8**, Q = CH=CH in **9**.

Several other long-range couplings were also observed in some cases. In **8a**, a typical W-type coupling between H6 and H9 was observed. Additionally, a *transoid*-homoallylic-type coupling[24] between H2 and H9a was observed in **8a** as well as in **10a** (Table 3), similarly to the compounds we studied previously, indicating a partial double bond between C1 and N10 and a planar structure in this molecular moiety.[4] In **9a**, allylic couplings[26] between H6 and H8, and between H7 and H9 were observed similarly to our previous studies.[4]

The structures of **8**–**10** are depicted in Fig. 3. The relative configurations are for **8a** and **10a**: 2*R**,3a*S**,5a*R**,9a*R**; for **8s** and **10s**: 2*S**,3a*S**,5a*R**,9a*R**; for **9a**: 2*R**,3a*S**,5a*S**,9a*S**; and for **9s**: 2*S**,3a*S**,5a*S**,9a*S**.

Hindered rotation of the aryl group. In *diendo*-fused **10a** the rotation of the *p*-chlorophenyl group about the sp^2–sp^3 carbon–carbon bond is slow on the NMR timescale near room temperature. Due to the two olefinic hydrogens of the norbornene the steric hindrance in **10a** is somewhat higher than in the *diexo*-fused compound **9a** (Table 4) because in the latter only a methylene group hinders the rotation (Fig. 3), and this must also be the case for compound **8a**. The plane of the aryl group is oriented mainly in one specific direction, roughly parallel to the carbonyl bond. The rotation interconverts two equivalent conformers and hence the populations of the decoalesced signals are equal. The free energy barriers of the hindered 180° rotation were measured only for compounds **9a** and **10a** (Table 4) because the free energy barrier for the rotation in **8a** is roughly similar to that in **9a**, which differs from **8a** only in the bond order between C7 and C8. For **10a**, the coalescences and the free energy barriers for the rotations were determined at four different temperatures using both ^{1}H and ^{13}C nuclei in *ortho*- and *meta*-positions. The temperature dependence of $\Delta G^{\ddagger}$ in **10a** can not be accurately estimated due to the relatively large error in the differences of the frequencies of the decoalesced signals especially when measured for the *meta*-position nuclei. Also the heating effect caused by the decoupling in the ^{13}C NMR measurements was not corrected which increases the error in the temperature measurements.

In the *cis*-fused compounds, line broadening of the aromatic protons at room temperature also indicated hindered rotation of the aryl group due to spatially proximal cyclohexyl methylene/methine protons. The value of the free energy barrier was measured only for **6a** (Table 4) for the same reason as for the *diexo*-compound **9a**. The free energy barrier of **6a** falls between the barriers of **9a** and **10a** (Table 4). Compound **10a**, which has the highest barrier has the most hindered structure.

Table 6 Selected distances and torsion angles found in solid state for compounds **3s**–**10a**

Compound	**3s**, oxazine	**5a**, *trans*	**6a**, *cis*	**6s**, *cis*	**9a**, *diexo*	**10a**, *diendo*
N10[a] · · · Δ[b]/Å	−0.253(3)	−0.044(3)	+0.179(3)	+0.179(3)	−0.118(3)	−0.147(2)
C1–N10[a]/Å	1.363(1)	1.358(4)	1.341(4)	1.341(4)	1.361(3)	1.359(3)
C3a–N10[a]/Å	1.461(3)	1.465(4)	1.470(3)	1.470(3)	1.470(3)	1.468(3)
C9a[c]–N10[a]/Å	1.462(4)	1.470(4)	1.471(3)	1.471(3)	1.457(4)	1.460(3)
C13 · · · N10[a]/Å	2.885(4)	2.887(4)	2.946(4)	2.946(4)	2.905(3)	2.904(3)
C17 · · · O4/Å	2.839(3)	2.831(4)	2.792(4)	2.792(4)	2.840(3)	2.857(3)
H13 · · · N10[a]/Å	2.57	2.55	2.69	2.69	2.57	2.58
H17 · · · O4/Å	2.52	2.52	2.45	2.45	2.53	2.55
N10[a]–C3a–C12–C13/°	32.9(3)	24.6(4)	44.0(4)	44.0(4)	26.6(4)	29.6(3)

[a] N8 in **3s**. [b] Δ = plane formed by atoms C1, C3a and C9a (C7 in **3s**). [c] C7 in **3s**.

We expect the *o*-phenyl protons in **10a** to have the shortest distance to the methine protons in the transition state, on the passage of the phenyl rotation, in comparison with the compounds **6a** and **9a**, which have more space for the phenyl rotation. Additionally, in **6a** and **10a** there are more groups hindering the rotation in comparison to **9a**, with only one hindering group, which is consistent with the lowest barrier in **9a**.

The determined free energy barriers of hindered rotation in **6a**, **9a** and **10a** are unusually high for sp^2–sp^3 carbon–carbon bond rotations,[7c] though the phenyl groups are not unsubstituted but have a chlorine atom in the *para*-position. However, the *p*-chlorine substituent does not affect palpably the free energy barrier because it is located on the rotation axis of the aryl group. The high barriers for rotation are also consistent with the idea that the plane of the phenyl group is roughly parallel to the carbonyl bond and the phenyl group is only flipping 180° in the course of the rotation, as we already pointed out in an earlier paper.[4] This is also seen in the crystal structures determined for compounds **3s**, **5a**, **6a**, **6s**, **9a** and **10a** (see below). It seems apparant that the *o*-protons in the aryl ring are hydrogen bonded to the heteroatoms of the oxazine ring which helps to raise the rotational free energy barriers of the aryl ring. The chemical shift of H2 is always smaller in the *trans* product than in the *cis* product (except in **2**) since in the former it locates in the shielding cone of the phenyl ring. A similar two-fold barrier for phenyl rotation has been found in the studies of the structurally fairly similar ketazolam.[27]¶

In the minor *cis* products **8s**, **9s** and **10s**, the rotation is so slow already at room temperature that most of the chemical shifts in the aromatic region are chemically non-equivalent (H13, H17, C13, C14, C16 and C17 in Tables 1 and 2). This is due to the additional hindrance caused by the methyl group. The free energy barriers for the aryl rotation of **8s**, **9s** and **10s** could probably be measured simply by performing the measurements at higher than room temperatures in order to find the coalescences.

Crystal structures of 3s, 5a, 6a, 6s, 9a and 10a

Crystal structures (Fig. 4) were determined by single crystal X-ray diffraction measurements in the cases where crystals of good enough quality were available. The determined crystal structures were convergent with the solution structures determined by NMR methods. The oxazine ring in **3s** has a very regular chair conformation and the five-membered ring has a conformation which is somewhere between a flat half-chair and an envelope with C3a as the flap atom. In the *trans*-fused **5a** the oxazine ring has also a rather regular chair conformation with some puckering in the O4–C5 region, whereas in the *cis*-fused compounds **6a** and **6s** the oxazine ring is more puckered in the O4–C5 region and flattened in the pyrrolo fusion region in comparison to **5a**. In the norbornene derivatives the oxazine ring has a sofa-like conformation[28] with the *diexo* fusion being more distortive in **9a** than the *diendo* fusion in **10a**, in contrast to what we found in our previous studies with the non-methyl homologs.[4] The five-membered rings have in all cases a conformation which is somewhere between a flat half-chair and an envelope with C3 as the flap-atom, except in **6a** where the flap-atom is C2. Furthermore, in **6s** the puckering is extended to the area of atoms C2 and C3 and the whole five-membered ring is very flat.

Compounds **6a** and **6s** crystallize interestingly in a 1 : 1 molar ratio into the same crystal. Both compounds occupy similar space in the crystal lattice. In **6s** the five-membered ring is markedly flatter in comparison to the five-membered ring in **6a** due to the methyl groups which are on opposite sides of the molecules in question. The rest of the molecules adopt the same structure. Even the phenyl ring has the same orientation in both isomers.

In all compounds studied with X-ray diffraction measurements N10 lies almost in the plane formed by atoms C1, C3a and C9a (C7 in **3s**) which can be seen in the distances measured from N10 to that plane (Table 6). On the other hand, the bond distance between N10 and C1 is approximately 0.1 Å shorter than the other C–N bonds in each case (Table 6), which supports the idea that the lactamide bond has clear π-character.

The aryl rings are oriented in a certain region, which can be described by the torsion angle N10–C3a–C12–C13 (Table 6). The distances between the *o*-carbons (or the *o*-protons) of the aryl ring and the heteroatoms O4 and N10 are fairly constant (Table 6). This indicates hydrogen bonding between the *o*-protons and the heteroatoms. In the literature, this type of hydrogen bonding in crystals has been discussed.[29] The hydrogen bonding in the studied compounds helps the aryl ring to adopt a certain orientation and it must be fairly significant because it can compete, for example, with the crystal packing forces. As anticipated such forces also affect the rotational barriers of the aryl rings in solution. The above described torsion angles are largest and the donor–acceptor or the proton–acceptor distances are longest to N10 (*i.e.* weaker hydrogen bonding) and shortest to O4 in the *cis*-fused compounds **6a** and **6s**. Additionally, the lactamide bonds are shortest in the same compounds, and thus, they have stronger double bond character between C1 and N10. It can thus be argued that the *cis*-fused carbocycle has the largest steric effect on the aryl ring position which weakens most the hydrogen bonding between the *o*-proton and N10 thus increasing the π-character of the C1–N10 bond. A general observation is that the distances from the *o*-atoms to O4 are shorter than the distances to N10, which indicates that the hydrogen bonding to oxygen is stronger than to nitrogen, as expected.

In comparison to non-methyl homologs[4] the *cis*- and *trans*-

¶ Ketazolam is 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4*H*-oxazino[3,2-*d*]-[1,4]benzodiazepine-4,7(6*H*)-dione.

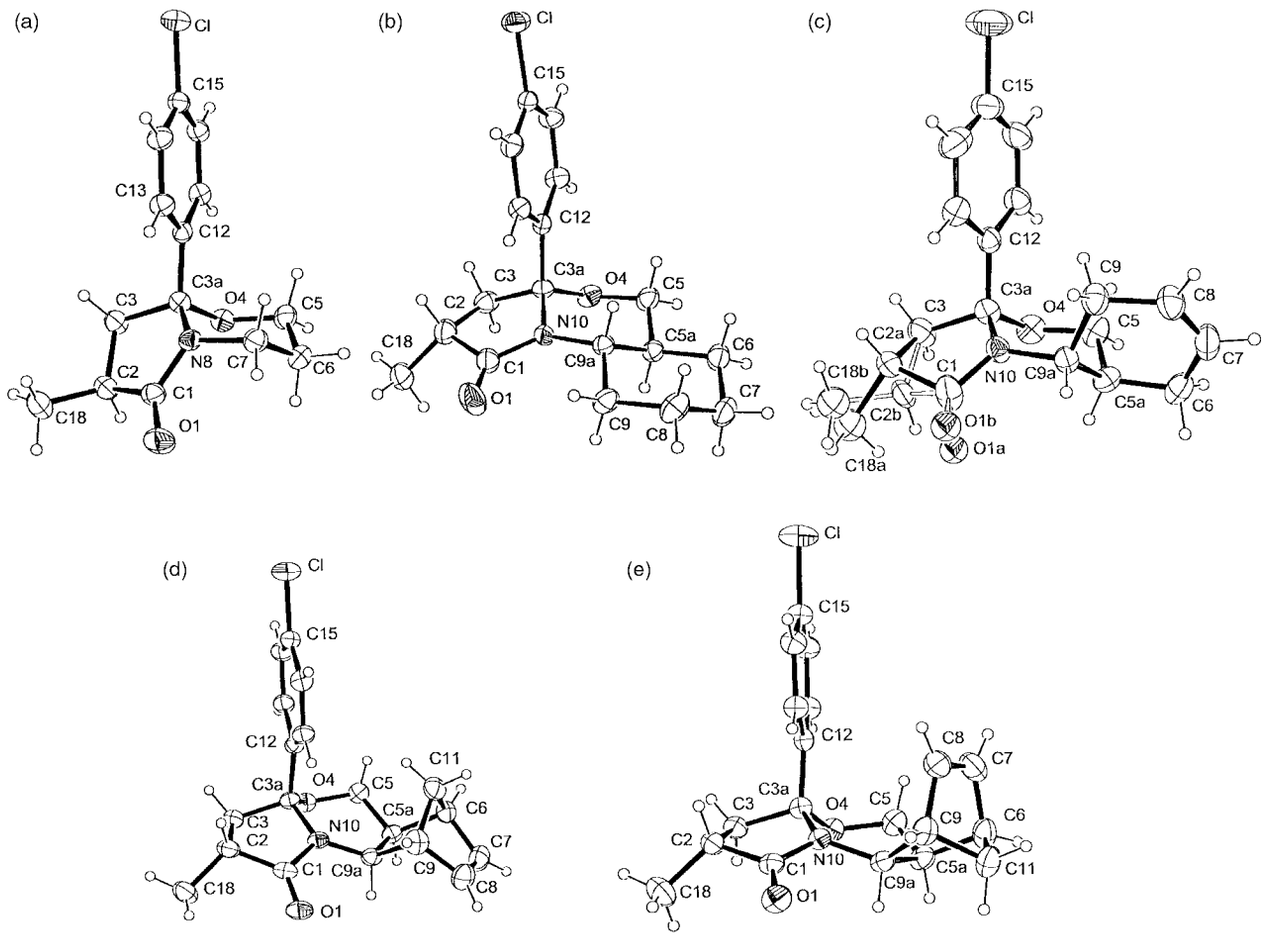

Fig. 4 Crystal structure of (a) **3s**, (b) **5a**, (c) **6a/6s**, (d) **9a**, (e) **10a**.

fused compounds do not differ much structurally. The methyl group does not qualitatively affect much the five-membered ring in **5a** and **6s**, but in **6a** this ring is more puckered. In the *diexo*- and *diendo*-fused compounds **9a** and **10a** the five-membered rings are very similar to the cases studied previously. The oxazine rings in **9a** and **10a** are qualitatively quite similar, whereas in the compounds studied earlier there is a distinct difference in the conformations of the oxazine rings of the *diexo*- and *diendo*-fused isomers.

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