Structures of pyrrolo-1,3-heterocycles prepared from 3-aroylpropionic acid and cyclic aminoalcohols: an NMR and X-ray diffraction study

Petri Tähtinen,*[a] Reijo Sillanpää,[a] Géza Stájer,[b] Angela E. Szabó[b] and Kalevi Pihlaja[a]

[a] *Department of Chemistry, University of Turku, FIN-20014 Turku, Finland*
[b] *Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, POB 121, H-6701 Szeged, Hungary*

By the reaction of 3-(4-chlorobenzoyl)propionic acid 1 with 1,2- and 1,3-bifunctional compounds, new condensed heterocycles have been prepared. Thus, the reaction of 1 with hydrazine gave the pyridazin-3-one 2 and with ethylenediamine, the pyrrolo[1,2-*a*]imidazole 3 was formed. Reaction of compound 1 and 2-aminoethanol yielded the pyrrolo[2,1-*b*]oxazolidinone 4 and the reaction with 3-aminopropan-1-ol resulted in the pyrrolo[2,1-*b*][1,3]oxazinone 5. With *o*-aminothiophenol tricyclic pyrrolo[2,1-*b*]-benzothiazolone 6 was prepared. In comparison with 4–6, the structure of the new tri- and tetra-cyclic compounds 7–14 are discussed. With the starting oxoacid 1, the cyclic and bicyclic aminoalcohols gave the following fused heterocycles: *cis*- and *trans*-2-(hydroxymethyl)cyclohexane- and cyclohex-4-ene-amines yielded pyrrolo[1,2-*a*][3,1]benzoxazinones 7–10, *diexo*-3-(hydroxymethyl)bicyclo[2.2.1]heptane-2-amine and hept-5-ene-2-amine yielded the *diexo* (11 and 12) and *diendo* (13 and 14) methylene-bridged pyrrolo[1,2-*a*][3,1]benzoxazinones. The structures of the compounds were proved by 1D ^{1}H and ^{13}C NMR spectroscopy, NOE difference spectroscopy and several different homo- and hetero-nuclear multipulse techniques (COSY, NOESY, HETCOR). The 1D ^{1}H NMR spectra were analysed by iterative spin-simulation using PERCH-software. Many interesting long-range couplings were found. Some aid for structural elucidation was gained from molecular modelling calculations. The crystal structures of 7, 9–11, 13 and 14 elucidated from the X-ray diffraction measurements do not differ significantly from the solution structures.

Introduction

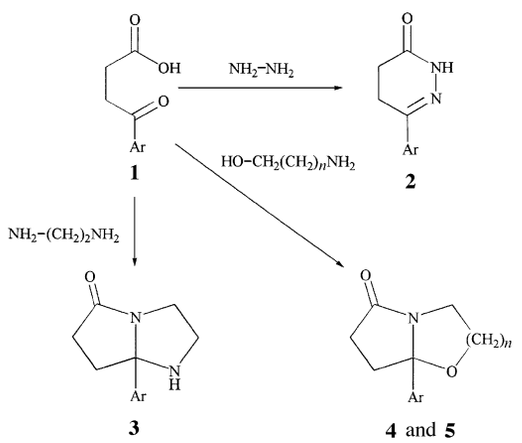
Saturated or partially saturated pyrrolo[1,2-*a*][3,1]benzoxazinones containing *cis*- or *trans*-fused cyclo-alkane or -alkene rings or *diexo*- or *diendo*-fused norbornane or norbornene moieties are not known in the literature. These derivatives can be synthesized from aroylalkanecarboxylic acids with 1,2-disubstituted 1,3-bifunctional cyclic or bicyclic amino alcohols. Thus, from the oxopropionic acid with 1,3-bifunctional alkenes the fused pyrrolo[1,2-*a*]imidazolone,[1] pyrrolo[2,1-*b*]oxazolidinones[1c,e,2] and pyrrolo[2,1-*b*][1,3]oxazinones[1c,2a–c] have already been prepared. The pyrrolo[2,1-*b*]benzothiazolone prepared from the oxoacid and *o*-aminothiophenol, is known in the literature as a tricyclic methyl-substituted derivative.[3] However, more complicated compounds with an additional fused cycloalkane or bicycloalkane terminal ring have now been synthesized.

The prepared compounds can contain the aryl substituent in two stereopositions, *i.e.* close to or far from the cycloalkane annellation hydrogens. For comparison, and to prove the *cis*- or *trans*-fusion of the rings, we prepared some known simple mono- or bi-cyclic compounds,[1,2,3] also to enable a systematic NMR spectroscopic study. Recently, we prepared and studied the structures of homologous compounds, which contained an additional saturated carbo-cyclic or -bicyclic ring at the other terminal of the molecules.[4] Our compounds are also of interest from a pharmacological point of view, because some of the corresponding aromatic analogues[5] of **1** have hypotensive activity.

Results and discussion

Synthesis

From the reaction of 3-(4-chlorobenzoyl)propionic acid[6] (**1**) with hydrazine, the 6-(4-chlorophenyl)-2,3,4,5-tetrahydropyridazin-3-one (**2**) was prepared (Scheme 1), of which the phenyl-substituted analogue is already known.[7] Compound **1**, with ethylenediamine, gave the hexahydropyrrolo[1,2-*a*]imidazolone (**3**) (literature of the analogue[1c–e]). With ethanolamine, the hexahydropyrrolo[2,1-*b*]oxazolidinone (**4**) was formed (literature of the phenyl-substituted analogue[1c,e,2b–d]), while reaction of **1** and the 3-aminopropanol furnished the hexahydropyrrolo[2,1-*b*][1,3]oxazinone (**5**) (literature of the phenyl-substituted analogue[1c,e,2a,c]).



Scheme 1 Ar = *p*-ClC$_6$H$_4$-, *n* = 1 (**4**), *n* = 2 (**5**)

The reaction of **1** with *o*-aminothiophenol yields the 3a-(4-chlorophenyl)-1,2,3,3a-tetrahydropyrrolo[2,1-*b*]benzothiazol-1-one (**6**) (literature of the methyl-substituted analogue[3]). The reaction of **1** with the *cis*- and *trans*-2-(hydroxymethyl)-cyclohexane-1-amines results in the *cis* and *trans* pairs of decahydro- (**7** and **8**) and octahydro-pyrrolo[1,2-*a*][3,1]benzoxazin-1-ones (**9** and **10**) (Scheme 2). Reaction of bicyclic aminoalcohols, the *diexo*-3-(hydroxymethyl)bicyclo[2.2.1]-heptane-2-amine and

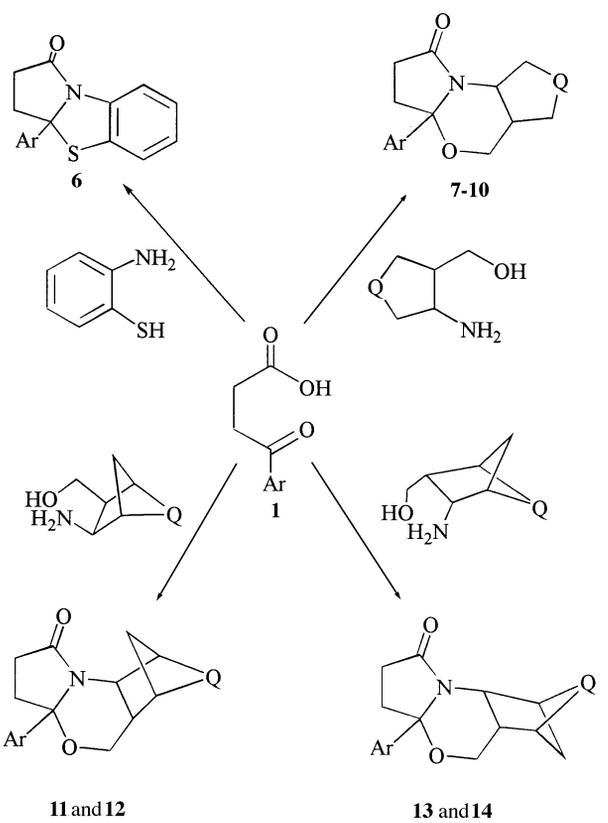
Table 1 ^{13}C chemical shifts (δ) of compounds **4**–**14**

	1	2	3	3a	5	5a	6	7	8	9	9a	11	12	13,17	14,16	15
4	180.29	32.26	33.11	101.72	65.69		42.10						140.06	126.61	129.01	134.42
5	175.28	29.04	36.12	93.72	62.56		24.78	36.68					139.23	127.43	129.56	134.26
6	172.99	33.30	38.06	82.85	126.31	134.66	122.90	125.88	117.30	131.56			143.66	125.77	128.89	134.12
7	174.61	29.01	38.15	92.40	63.00	33.95	27.05	21.01	25.16	27.27	49.99		141.70	126.99	128.98	134.02
8	176.43	30.35	36.12	95.98	68.28	40.43	26.83	24.70	25.99	28.47	59.01		139.36	127.54	129.57	134.10
9	174.79	29.01	38.33	92.43	63.89	32.17	24.94	123.58	123.76	26.16	46.59		141.95	126.77	129.04	134.02
10	174.98	29.74	36.15	95.13	67.26	36.15	26.25	123.82	125.80	28.04	54.36		138.23	127.56	129.56	134.27
11	175.58	28.53	38.61	92.58	63.89	38.97	42.34	28.56	27.71	39.27	55.09	34.72	141.19	127.25	128.98	134.17
12	175.92	28.65	38.79	92.49	65.93	31.47	44.37	136.60	137.36	47.50	51.84	44.37	141.06	127.10	129.04	134.26
13	177.98	28.92	39.18	92.98	62.01	32.35	38.45	22.09	23.70	41.58	54.57	37.88	141.16	127.10	128.92	133.96
14	177.40	28.47	39.79	92.29	64.59	34.78	43.59	136.21	136.98	47.44	52.91	48.64	140.62	127.37	128.66	133.85

Table 2 ^{1}H chemical shifts (δ) of compounds **4**–**14**

	2a	2s	3a	3s	5ax[a]	5eq[b]	5a	6ax[c]	6eq[d]	7ax[e]	7eq	8ax[f]	8eq	9ax[g]	9eq	9a	11a	11s	13,17	14,16
4	2.62	2.81	2.55	2.21	4.05	3.71		4.00	2.99										7.36	7.39
5	2.57	2.44	2.32	2.01	3.66	3.86		1.89	1.36	2.92	4.18								7.28	7.41
6	2.18[h]	2.19	2.58	2.08	7.09			7.07		7.18		7.83							7.30	7.33
7	2.17[h]	2.23	2.06	1.63	3.89	3.62	2.19	1.6	1.6	0.85	1.35	1.17	1.6	1.06	1.6	4.36			7.32	7.36
8	2.52	2.35	2.25	1.91	3.28	3.70	1.82	0.67	1.43	1.28	1.62	1.08	1.86	2.41	1.86	2.92			7.30	7.41
9	2.52	2.51	2.30	2.01	3.72	3.62	2.30	1.99	1.80	5.38		5.43		2.41	1.71	4.62			7.33	7.37
10	2.47	2.29	2.28	1.99	3.27	3.79	2.06	1.44	1.92	5.53		5.69		3.00	3.18	3.32			7.28	7.40
11	2.32	2.31	2.29	2.07	3.28	3.93	2.06	2.32		1.47	1.42	1.51	1.16	1.81		3.90	0.83	0.95	7.30	7.37
12	2.36	2.35	2.32	2.11	3.30	4.11	1.94	2.43		6.06		6.29		2.94		3.78	1.13	0.99	7.30	7.36
13	2.42	2.45	2.33	2.06	3.63	3.89	2.32	2.15		1.16	1.06	1.18	1.13	2.66		4.07	1.31	1.50	*i*	*i*
14	2.37	2.30	2.25	2.04	3.12	3.98	2.67	2.70		5.64		5.63		3.39		4.29	1.49	1.43	7.16	7.33

[a] In **4** H-5a, in **6** H-5. [b] In **4** H-5s. [c] In **4** H-6a, in **6**, **11**–**14** H-6. [d] In **4** H-6s. [e] In **6**, **9**, **10**, **13** and **14** H-7. [f] In **6**, **9**, **10**, **13** and **14** H-8. [g] In **11**–**14** H-9. [h] Measured in a solvent mixture of $CDCl_3$–[$^2H_6$]benzene (1:2 v/v). [i] Could not be resolved.



Scheme 2 Ar = *p*-ClC_6H_4-, Q = CH_2CH_2 (**7**, **8**, **11**, **13**), Q = CH=CH (**9**, **10**, **12**, **14**), *cis* (**7**, **9**), *trans* (**8**, **10**)

-hept-5-ene-2-amine, with **1** led to the methylene bridged decahydro- (**11**) and octahydro-pyrrolo[1,2-*a*][3,1]benzoxazinones (**12**), while the reaction of **1** with the *diendo*-3-(hydroxymethyl)bicyclo[2.2.1]-heptane-2-amine or -hept-5-ene-2-amine furnished the *diendo* condensed pyrrolo[1,2-*a*][3,1]-benzoxazinones (**13** and **14**).

Structures

Configurational and conformational analysis by NMR spectroscopy. The chemical shifts of all protons and carbons in **4**–**14** were determined from an analysis of 2D homonuclear correlation (COSY), nuclear Overhauser effect correlation (NOESY) and carbon or proton detected heteronuclear correlation (HETCOR, HMQC, HSQC, HMBC) spectra and are reported in Tables 1 and 2. In general, the spectral parameter measurements were made in $CDCl_3$ solutions, but in some cases samples were analysed also in a solvent mixture of one part of $CDCl_3$ and two parts of [$^2H_6$]benzene. Also some difference NOE measurements were performed (DNOE). Partially quite crowded ^{1}H NMR spectra were analysed by iterative spin-simulation, using PERCH-software[8] on personal computer and the resolved coupling constants are reported in Tables 3–6.

Some NMR data of compound **4** can be found in the literature,[1c] but to our knowledge no precise data has been published earlier. Also NMR data for compound **5** can be found in ref. 1*c* but no accurate analysis has been published.

Several torsion angle calculations were made using the modified Karplus equation of Haasnoot *et al.*[9] This equation was used for deriving torsion angles of the six-membered rings of compounds **5** and **7**–**14**. In some cases help for structural deductions was gained from modelling the compounds with the CHEM-X[10] program or building traditional Dreiding models. In CHEM-X the three-dimensional structures were optimized by calculating their minimum structural energies with the molecular mechanics optimization procedure using the default parameters included in the program.

3a-(4-Chlorophenyl)-1,2,3,3a,5,6-hexahydropyrrolo[2,1-*b*]-[1,3]oxazolidin-1-one (4)†. The COSY spectrum of compound **4** (Scheme 3) shows two different groups of protons. The proton signals for the pyrrolo ring can be found in the high field

‡ Non-systematic numbering has been used in compounds **4** and **5** for ease of comparison of spectral data. IUPAC names for **4** and **5** applying systematic numbering are 7a-(4-chlorophenyl)-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*][1,3]oxazol-5-one and 8a-(4-chlorophenyl)-2,3,6,7,8,8a-hexahydropyrrolo[2,1-*b*][1,3]oxazin-6-one, respectively.

Table 3 Geminal and vicinal coupling constants (Hz) in **4**, **5** and **7**–**14**

	5a,5ax	5a,5eq	5a,6ax[a]	5a,6eq[b]	5eq,6ax[c]	5eq,6eq[d]	5a,9a	5ax,5eq	6,11a	6,11s	6ax,6eq
4			7.63	4.76	4.87	7.58		−8.10			−10.02
5			12.90	2.37	4.79	1.56		−11.86			−13.40
7	12.09	4.08	4.07	4.07			4.25	−11.77			−14.32
8	11.53	4.56	12.49	2.92			11.32	−11.56			−13.02
9	11.89	4.08	5.28	11.23			5.65	−11.69			−17.59
10	11.87	4.33	11.12	5.64			11.00	−11.61			−18.17
11	9.38	9.06	<0.5				9.04	−12.38	1.5	1.5	
12	9.24	8.06					8.79	−12.38	1.98	0.98	
13	9.63	7.68	1.35				11.87	−12.21	2.4	2.0	
14	10.82	8.28	3.53				10.22	−11.19	1.48		

	6ax,7ax[e]	6ax,7eq[f]	6eq,7ax[g]	6eq,7eq	7ax,7eq[h]	7ax,8ax[i]	7ax,8eq[j]	7eq,8ax[k]	7eq,8eq[l]	8ax,8eq[m]	8ax,9ax[n]
4											
5	12.77	5.26	3.64	1.59	−13.34						
7	14.10	5.27	3.79	2.21	−13.54	13.43	3.62	2.55	2.41	−14.08	13.12
8	14.04	3.60	3.86	3.89	−13.29	13.24	3.71	3.42	2.75	−13.39	13.46
9	5.5		2.9			10.2					3.17
10	5.41	3.99				8.86					4.39
11	5.3	6.7			−13.9	7.1	4.5	4.4	10.2	−11.2	1
12	2.99					5.71					2.89
13	4	2.2			−12.54	8.18	2.5	1.58	7.2	−12.65	3.58
14	2.9					5.7					<0.05

	8ax,9eq[o]	8eq,9ax[p]	8eq,9eq	9a,9ax	9a,9eq	9ax,9eq	9,9a	9,11a	9,11s	11a,11s
4										
5										
7	1.51	3.40	2.09	13.03	4.39	−12.68				
8	3.77	3.76	2.76	11.83	3.76	−12.59				
9	3.09			11.11	5.58	−19.28				
10	5.00			10.92	5.58	−18.11				
11		<1					1	<1	2.4	−10.3
12								1.31	1.84	− 9.31
13		3.3					3.05	1.7	5.1	−10.05
14							3.64	2.20	1.9	−8.80

[a] 5a,6a in **4**, 5ax,6ax in **5** and 5a,6 in **11**–**14**. [b] 5a,6s in **4** and 5ax,6eq in **5**. [c] 5s,6a in **4**. [d] 5s,6s in **4**. [e] 6ax,7 in **9** and **10**, 6,7x in **11** and **13**, 6,7 in **12** and **14**. [f] 6,7n in **11** and **13**. [g] 6eq,7 in **9** and **10**. [h] 7n,7x in **11** and **13**. [i] 7,8 in **9**, **10**, **12** and **14** and 7x,8x in **11** and **13**. [j] 7x,8n in **11** and **13**. [k] 7n,8x in **11** and **13**. [l] 7n,8n in **11** and **13**. [m] 8n,8x in **11** and **13**. [n] 8,9ax in **9** and **10**, 8x,9 in **11** and **13** and 8,9 in **12** and **14**. [o] 8,9eq in **9** and **10**. [p] 8n,9 in **11** and **13**.

Table 4 Hetero ring and benzo ring coupling constants (Hz) in **4**–**6**

	5ax,5eq	5ax,6ax	5ax,6eq	5eq,6ax	5eq,6eq	6ax,6eq	6ax,7ax	6ax,7eq	6eq,7ax	6eq,7eq	7ax,7eq
4	−8.10	7.63	4.76	4.87	7.58	−10.02	—	—	—	—	—
5[a]	−11.86	12.90	2.37	4.79	1.56	−13.40	12.77	5.26	3.64	1.59	−13.34
	—	5,6	5,7	5,8	—	—	6,7	6,8	—	—	7,8
6	—	7.77	1.22	0.47	—		7.52	1.22	—	—	7.94

[a] For **5** ax = a and eq = s.

Table 5 Pyrrolo ring coupling constants (Hz) of compounds **4**–**14**

	2a,2s	2a,3a	2a,3s	2s,3a	2s,3s	3a,3s
4	−17.99	10.44	4.73	6.98	10.20	−14.03
5	−17.35	9.92	6.36	5.51	10.18	−13.50
6	−16.96[a]	9.03[a]	1.39[a]	11.58[a]	8.17[a]	−12.41[a]
7	−17.03[a]	8.93[a]	8.69[a]	10.43[a]	3.82[a]	−12.66[a]
8	−17.20	6.22	9.81	9.91	6.31	−13.40
9	−17.28	10.07	9.53	2.36	10.22	−13.01
10	−18.18	10.85	3.73	7.90	10.55	−15.45
11	−15.92	9.20	4.13	14.03	6.07	−12.45
12	−16.88	8.53	1.79	13.12	7.20	−12.10
13	−19.42	9.61	12.96	2.81	3.01	−11.56
14	−16.36	12.64	7.79	8.71	1.24	−11.52

[a] Measured in a solvent mixture of $CDCl_3$–[$^2H_6$]benzene (1:2 v/v).

region between 2.2 and 2.9 ppm as an ABCX-type system. Two of these protons resonating in the lower field were assigned to C-2, because they couple with a −18.0 Hz coupling constant, which is a typical value for geminal protons next to a carbonyl group.[11] This assignment is in agreement with the observations made in the HMBC spectrum adjusted for ^2J(C,H)-couplings. The measured ^2J(H,H) value indicates that the imaginary plane going through the carbonyl bond and the C-2 bisects the H–C–H angle in position 2. In position 2 the proton which resonates at 2.81 ppm was assigned from the difference NOE spectrum to be *syn* to the phenyl substituent. Compared with other protons in the same position, it is slightly downfield shifted due to the deshielding effect of the aromatic ring.

The H-3 proton resonating at 2.21 ppm was assigned to be *syn* to the *p*-chlorophenyl substituent as confirmed by a weak NOE with aromatic protons. The H-3a resonates at a surprisingly low field (2.55 ppm) compared with the H-3a protons in the other compounds of this series except **6**. This is probably due to the deshielding effect of the p electrons of O-4. According to molecular models it lies in the plane of C-3, C-3a and H-3a and thus the torsion angle H3a–C3–C3a–O4 is close to zero.

The oxazolidine ring protons are resonating at lower fields than the pyrrolo ring protons since the adjacent heteroatoms deshield H-5 and H-6. Protons with smaller chemical shifts are

Table 6 Long-range coupling constants (Hz) in compounds **4**–**14**

	2s,9a[a]	5a,7x[b]	5a,9ax	5a,9eq	5a,11a	5ax,7eq	5eq,7ax	5eq,7eq	5ax,9a	5eq,9a	6ax,8[c]	6eq,8eq[d]
4	1.0											
5	1.31					0.49	0.50	1.77				
7	—			<0.5					<0.5	<0.5		2.18
8	0.9											<1
9	—		2.1	<1						1.1	>−2	−2
10	1										−1.44	−2.19
11	—				1							
12	<0.5				1.35				<0.5			
13	0.5	<0.5										
14	<0.5								<0.5	<0.5	−1	

	6ax,9a	6ax,9ax[e]	6ax,9eq	6eq,9a	6eq,9ax	6eq,9eq	7,9ax[f]	7eq,9eq[g]	7n,11s[h]	8n,11s[i]	8x,9a	9a,11a
4												
5												
7								1.38				
8								1.2				
9	<1	2		<2	2	2	−2	−2				
10		2.80	2.07		1.94	2.03	−2.40	−1.44				
11		1.9							1	1.7		1.41
12		1.70					<0.5		<0.5	<0.5		1.83
13		2							1.4	1.1	0.88	
14									1.5	1.5		

[a] 2s,6s in **4**, 2s,7ax in **5**. [b] 5a,7 in **14**. [c] 6,8 in **14**. [d] 6eq,8 in **9** and **10**. [e] 6,9 in **11**–**13**. [f] 7,9 in **12**. [g] 7,9eq in **9** and **10**. [h] 7,11s in **12** and **14**. [i] 8,11s in **12** and **14**.

syn to the phenyl substituent as proved by the DNOE spectrum. They must lie in the shielding cone of the aromatic ring, which causes their smaller chemical shifts compared with the *anti* protons.

The H-6s was found to be coupled with H-2s. This *transoid*-homoallylic 1.0 Hz ^5J coupling is an indication of the partially π-bonded lactamide moiety and allows us to conclude that the molecule is quite flat in the region of N-7, C-1 and C-2 combined with the knowledge of the large negative value of the coupling of geminal H-2 atoms.

3a-(4-Chlorophenyl)-1,2,3,3a,5,6-hexahydropyrrolo[2,1-*b*]-[1,3]oxazin-1-one (5).‡ In compound **5** (Scheme 3) the H-7eq next to the nitrogen has a chemical shift of 4.18 ppm. This is due to the deshielding effect of the π-electrons in the carbonyl bond: the H-7eq lies in the same plane as the carbonyl bond. The axial and equatorial orientation of the oxazine hydrogens could be proved not only from the magnitude of the vicinal coupling constants (Table 3; diaxial $^3J \approx 12.8$ Hz *etc.*), but with clear NOE correlation signals of the axial H-5 and H-7 and the aromatic protons in the NOESY spectrum. According to the NOESY spectrum, the aromatic protons could be assigned in such a way that H-13 and H-17 resonate at a slightly higher field than H-14 and H-16.

The H-7eq resonates in lower field than H-7ax due to the usual anisotropic effect of the six-membered ring. Interestingly the H-6ax ($\delta = 1.89$ ppm) resonates *ca.* 0.5 ppm lowfield from the equatorial proton. According to molecular models, H-6ax lies nearly in the plane of the lactamide moiety, the π-bond character of which is proved by the *transoid*-homoallylic-type 1.3 Hz five-bond coupling between H-2s and H-7ax, which is clearly resolved in the 1D ^{1}H NMR spectrum. H-2a seems to be coupled also to H-7ax, but the coupling constant has not been determined.

Other long-range couplings were also resolved in the 1D ^{1}H- and 2D-COSY NMR spectra. H-5eq and H-7eq show a *ca.* 1.8 Hz W-type coupling which is a good evidence for a not much distorted chair conformation of the six-membered ring. H-5ax with H-7eq and H-5eq with H-7ax are also coupled as can be seen from the COSY and better from the COSY LR spectra; these sickle-type[12] couplings are *ca.* |0.5| Hz.

Modified Karplus equation[9] calculations show that the O4–C5–C6–C7 torsion angle is *ca.* 55°, which is almost ideal for a chair conformation. The C5–C6–C7–N8 torsion angle was calculated to be *ca.* 53° showing a slight flattening in the ring fusion as expected. The oxazine ring is in a chair conformation and the whole structure is quite rigid because all coupling constants are close to ideal values for a chair and many long-range couplings were observed.

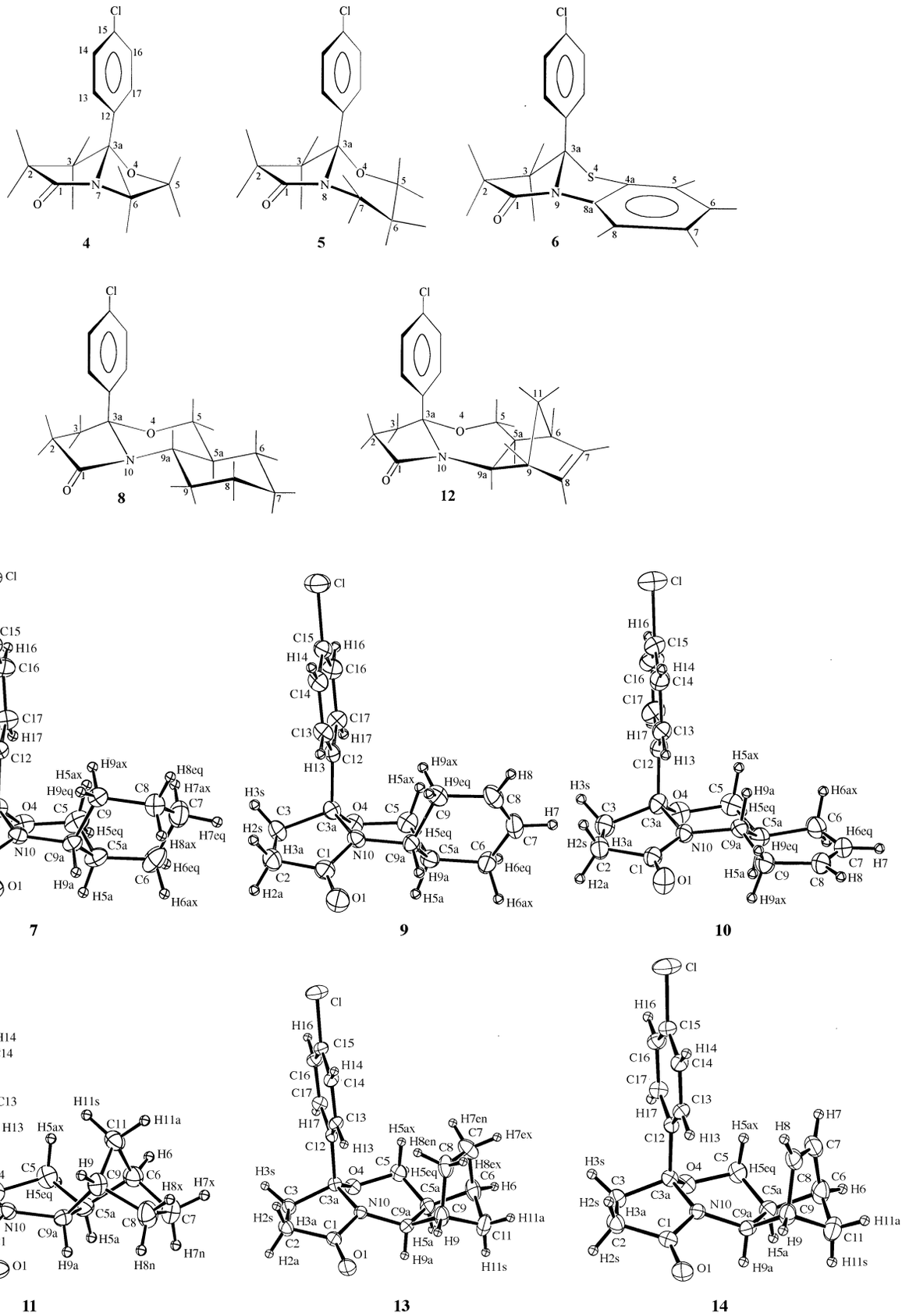
The pyrrolo ring protons of compound **5** were assigned according to DNOE spectrum which shows that the *syn* protons are those with smaller chemical shifts. The latter protons resonate in higher fields because of the anisotropic effect of the phenyl ring. Again H-2 protons show a large negative geminal coupling indicating that the plane of the carbonyl bond is bisecting the bond angle of these protons.

3a-(4-Chlorophenyl)-1,2,3,3a-tetrahydropyrrolo[2,1-*b*]benzothiazol-1-one (6). In the pyrrolo ring of **6** (Scheme 3), three of the four protons have almost the same chemical shift and the system exhibits an ABCX-type spectrum. Therefore **6** was dissolved to a mixture of $CDCl_3$ and [$^2H_6$]benzene (1:2) to achieve an AMNX spectrum which could be solved. The spectral parameters of H-5–H-8 in the phenyl ring were solved from the ABMX-type spectrum in $CDCl_3$ solution.

In **6** the H-2 protons are shifted upfield compared with the corresponding protons in **4**. This is due to their location in the shielding cone of the *p*-chlorophenyl substituent: the plane of the phenyl ring seems to be parallel to the carbonyl bond since it shields H-2a, H-2s and H-3s. The whole molecule must be almost planar due to the aromatic moiety and the partially π-bonded lactamide bond which is conjugated with the aromatic ring. One proof of the planarity is also the large negative geminal coupling between H-2 atoms. Only C-3 and C-3a are out of the plane of the whole skeleton. Good evidence for this is the relatively large chemical shift of H-3a which is deshielded by the free electrons of sulfur when C-3 is twisted out of the plane of other than C-3a atoms in the pyrrolo ring. The latter must retain an envelope-type conformation where C-3 is the flap atom. Also a large vicinal coupling (11.6 Hz) between H-2s and H-3a supports this showing the torsion angle between these protons to be close to 180°. Similar kinds of observations and structural conclusions have been made earlier with pyrrolo-[1,2-*a*]benzimidazol-1-ones.[13]

***cis*- and *trans*-3a-(4-Chlorophenyl)-1,2,3,3a,5,5a,6,7,8,9-decahydropyrrolo[1,2-*a*][3,1]benzoxazin-1-ones (7 and 8).** Com-

† See footnote on p. 598.



Scheme 3 Three-dimensional structures of the compounds **4**–**14**. Pictures of **4**–**6**, **8** and **12** were sketched with CS ChemDraw Pro™ V3.1 (Cambridge Scientific Computing, Inc., Massachusets, USA, 1994). Pictures of **7**, **9**–**11**, **13** and **14** are ORTEP[23] drawings of the crystal structures and they equal the solution structures. The numbering of the compounds follows the IUPAC rules except for **4** and **5** (see footnote on p. 598) and for numbering the phenyl ring in **4**–**10** for easier comparison of analogous spectral data.

pounds **7** and **8** (Scheme 3) are decahydropyrrolobenzoxazinone isomers where the two six-membered rings are either *cis* or *trans* annellated, respectively. *cis*-**7** is differentiated from the *trans*-**8** by its smaller ^{3}J-coupling (4.7 Hz) between H-5a and H-9a, the comparable coupling in the *trans* compound is 10.3 Hz since both of the coupled protons are axial. The relative configuration of **8** is unambigously 3a*S**,5a*R**,9a*R**. For *cis*-**7** there are two alternatives; the H-5a and H-9a are either axial

and equatorial to the oxazine ring or *vice versa*. The ^{1}H NMR spectrum shows that H-5a is axial in relation to the oxazine ring as proved by its diaxial coupling to H-5ax. The H-9a is equatorial to the oxazine ring and axial to the other ring: the coupling pattern for H-9a shows one diaxial coupling which is possible only if the relative configuration is 3a*S**,5a*R**,9a*S**. Also the DNOE measurement, where the H-13 and H-17 were decoupled, supported this observation showing the proximity of these protons to protons in positions 9.

Both six-membered rings in these compounds have chair conformations, proved by the W-type ^4J-couplings which could be found on COSY spectra and also measured in the 1D spectra between H-5a and H-9eq, H-5eq and H-9a, H-6eq and H-8eq and H-7eq and H-9eq in **7** and H-6eq and H-8eq and H-7eq and H-9eq in **8**. Also the patterns of vicinal couplings (Table 3) measured in the six-membered rings support this conclusion: nearly 12 Hz or larger diaxial proton coupling constants combined with 1.5–5.3 Hz equatorial–equatorial and axial–equatorial coupling constants.

Also two other long-range couplings were detected for **7**. H-5ax is coupled with H-9a with a <1 Hz coupling constant and also with one or more of the protons H-6ax, H-6eq, H-8eq and H-9eq, which are resonating approximately at the same chemical shift (~1.56 ppm) in $CDCl_3$. Most probably it is a ^4J-coupling with an H-6. However, this coupling could not be measured.

Compound **8** showed an additional, *transoid*-homoallylic-type long-range coupling[14] between H-2s and H-9a. This type of coupling appears only when H-9a is axial. This is in agreement with Barfield *et al.* tentative conclusions of *transoid*-homoallylic-type couplings.[15] The reason for the lack of a homoallylic-type coupling in the *cis*-**7** is that the H-9a is equatorial and the dihedral angle in the fragment C1–N10–C9a–H9a is close to 0° and the $\sin^2\varphi$ $\sin^2\varphi'$ dependent[15] ^5J is close to zero. For the same reason, another interesting effect on H-9a when it is equatorial, as in the case of **7**, was found: it is strongly downfield from the axial proton in **8**. The equatorial proton is located in the plane of the atoms of the lactamide moiety and is thus deshielded by the π-electrons of the carbonyl bond. The same is true for **5**. The H-9a signal appears to be a good probe for determining the conformation of these ring systems. On the other hand, C-9a which has axial groups in a C-9axC-12ax arrangement causing a so-called *syn*-axial γ-effect[16a] at C-9a in *cis*-**7** compared with the *trans*-**8** where C-9a has a C-9eqC-12ax arrangement of C–C bonds, which explains the smaller chemical shift of the C-9a in **7**. Also, there must be some effect caused by the so-called *syn*-axial δ-effect,[16b] where the replacement of H-9a with a carbon atom in the plane of the adjacent carbonyl bond in *trans*-**8**, decreases the shielding in C-9a.

The *cis* and *trans* configurations of **7** and **8**, respectively, are also supported by the ^{13}C chemical shifts. C-3a and C-5 in *cis*-**7** resonate upfield from those of *trans*-**8**. The C-3a is *gauche* to C-9 and the C-5 to C-7 and C-9 in the *cis* form, causing an extra shielding compared with the *trans* form, where the corresponding γ-carbons are *anti* to C-3a and C-5. The chemical shifts and their differences are also in accordance with the deduced chair conformations of the six-membered rings.

Some torsional angle calculations based on the modified Karplus equation[9] show that the oxazine rings are flattened in the moiety of C-5a and C-9a. If trigonal symmetry is assumed, the torsion angle in both six-membered rings in the fusion moiety is *ca.* 52° between the vicinal C–C bonds in *cis*-**7**. In the *trans*-**8** the corresponding torsion angles are *ca.* 55°. The torsion angles in the fragments O4–C5–C5a–C9a of **7** and **8** were calculated to be 60° and 57°, respectively.

For **7**, the sub-spectrum of the pyrrolo ring protons was found to be deceptively simple. The H-2 atoms are almost isochronous and show only four peaks instead of the 16 expected. Therefore **7** was dissolved in a 1:2 v/v mixture of $CDCl_3$ and [$^2H_6$]benzene and the resulting ABCX-type spectrum could be solved. The H-2 having a slightly larger chemical shift (2.23 *vs.* 2.17 ppm) was assigned to be *syn* to the phenyl ring according to a DNOE measurement. For H-3 resonating in higher field (1.63 ppm) was assigned to be *syn* instead of the one resonating at 2.06 ppm. This refers to a structure where the plane of the phenyl substituent is parallel to that of the oxazine ring oxygen and the atoms of the lactamide moiety, *i.e.* the *syn*-protons of the pyrrolo ring are lying in the shielding cone of the phenyl ring. A similar situation also prevails in **8**, where the H-2s and H-3s resonate higher in the field than the *anti*-protons. For **7** and **8**, the geminal couplings between the H-2 atoms were again close to −17 Hz, showing that the plane of carbonyl bond bisects the bond angle between the coupled protons and indicating flat structures for these moieties. Based on this conclusion and on comparison with molecular models it seems quite obvious that the five-membered rings attain predominently envelope forms with C-3a at the flip.

***cis* and *trans*-3a-(4-Chlorophenyl)-1,2,3,3a,5,5a,6,9-octahydropyrrolo[1,2-*a*][3,1]benzoxazin-1-ones (9 and 10).** Compounds **9** and **10** (Scheme 3) are *cis*- and *trans*-anellated isomers of octahydropyrrolobenzoxazinone, respectively, as **7** and **8**, except that in the former there is an additional unsaturation between C-7 and C-8. Compound *cis*-**9** differs from *trans*-**10** by its smaller (5.2 Hz) vicinal coupling constant between H-5a and H-9a. In *trans*-**10**, the corresponding coupling constant was 10.7 Hz. The relative configurations are similar to those of compounds **7** and **8**. Compound *trans*-**10** retains the configuration 3a*S**,5a*R**,9a*R**. Compound *cis*-**9** has two alternatives for the ring fusion to six-membered rings as in the case of **7**. However, the relative configuration of **9** must be 3a*S**,5a*R**, 9a*S**; H-5a must be axial in the oxazine since it shows a diaxial coupling to H-5ax and similarly proton H-9a shows a diaxial coupling to H-9ax. Thus the latter is axial in the cyclohexane ring and equatorial in the oxazine ring.

The ^{13}C chemical shifts are in accordance with the deduced configurations. In *trans*-**10**, where C-9 is *anti* to C-3a and C-5, the chemical shifts are 95.13 and 67.26 ppm, respectively. In **9**, exhibiting γ-*gauche* effects by C-3a and C-5, the corresponding chemical shifts are 92.43 and 63.89 ppm, respectively. The higher field chemical shifts of *cis*-**9** support the deduced relative configurations at C-5a and C-9a.

For **9**, C-9a experiences similar γ-effects, as caused by the *syn*-axial shielding in the case of *cis*-**7**. The *syn*-axial δ-effect discussed in the cases of **7** and **8** must affect the shielding in C-9a atoms. The H-9a chemical shifts differ significantly from each other in compounds **9** and **10**. In *cis*-**9** this proton resonates at an extremely low field (4.62 ppm).

The oxazine ring in **9** and **10** has a chair conformation. This is proved by the magnitude of the vicinal coupling constants between H-5a and H-9a and diaxial and axial–equatorial vicinal couling constants between H-5 and H-5a (Table 3). The Altona equation[9] gave torsion angles of 43° for **9** and 50° for **10** when trigonal symmetry was assumed for the C5–C5a–C9a–N10 moieties in both compounds. Torsion angles in the O4–C5–C5a–C9a fragments were calculated to be 60° in the *cis*-**9** and 59° in the *trans*-**10**. For **9**, a proof for the chair conformation of the oxazine ring is the 1.1 Hz W-type *J* coupling between H-5eq and H-9a.

For **9** and **10**, several interesting long-range couplings were found in the cyclohexene moiety (Table 6). Almost all protons in the cyclohexene ring of **9** are coupled with each other. Allylic-type couplings[17] were found between H-6 and H-8, and H-7 and H-9. Homoallylic-type couplings were observed between H-6 and H-9. Similar couplings were found also in **10**. For **9**, additional ^4J-couplings *via* saturated bonds were found between H-5a and H-9, and H-6 and H-9a. These ^4J-couplings are an indication of a somewhat distorted chair conformation of the cyclohexane ring, because only ^4J(5a,9eq), which is smaller than

1 Hz, would be a pure W-type coupling in a chair conformation. For **9**, the chemical shift of H-9ax also shows that the cyclohexene ring is distorted; the H-9ax resonates clearly lower in the field than H-9eq indicating that it is turned more out of the shielding cone of the phenyl ring than in the case of compound **7**, where the H-9eq resonates at a lower field than H-9ax. It can be concluded that the cyclohexene ring attains a half-chair conformation,[18] where the unsaturated ends are flattened.

For **10**, a *transoid*-homoallylic-type ^5J-coupling between H-2s and H-9a was found. This is similar to those found in **4**, **5** and **8** and proves the quite flat arrangement of the bonds in the lactamide moiety. Similarly to **7** and **8** the pyrrolo rings were found to be in an envelope conformation where the C-3a exist as the flip atom. One proof for this flat conformation is the large geminal coupling constant between H-2 atoms. Also the molecular models support these conformations. The sub-spectrum of the pyrrolo ring in compound **9** was strongly ABMX-type in $CDCl_3$. According to a DNOE spectrum the *anti*-protons in positions 2 and 3 were resonating lower in the field than the *syn*-protons. This shows that the phenyl substituent is turned parallel to the imaginary line connecting the oxazine ring oxygen and the lactamide oxygen, thus the *syn*-protons lie in the shielding cone of the phenyl ring.

***diexo*- and *diendo*-3a-(4-Chlorophenyl)-6,9-methano-1,2,3,3a, 5a,6,7,8,9-decahydropyrrolo[1,2-*a*][3,1]benzoxazin-1-ones (11 and 13).** Compounds **11** and **13** (Scheme 3) are the *diexo*- and *diendo*-annellated 6,9-methanodecahydropyrrolobenzoxazinones, respectively. For **11**, the *diexo*-fusion is proved by the W-type ^4J-couplings found between H-5a and H-11a and H-9a and H-11a. For the corresponding *diendo*-**13**, similar couplings could not be found. Instead, W-type couplings between H-8x and H-9a and H-5a and H-7x were observed in the LR COSY-spectrum, giving proof of the geometry specified in the annellation moiety.

The chemical shifts of C-7, C-8 and C-11 are in agreement with the deduced configurations. For **11**, the N-10 and C-5 are γ-*gauche* to C-11 and the latter has smaller ^{13}C chemical shift (34.72 ppm) than in **13** (37.88 ppm) where it is *anti* to both of the above atoms. For **11**, C-7 and C-8 are *anti* to C-5 and N-10, respectively, and in **13** they are *gauche* to them. This is seen in the chemical shifts of C-7 and C-8: the ^{13}C-shifts are smaller in the *diendo*-**13** [δ(C7) = 22.09, δ(C8) = 23.70] where the γ-effects are stronger than in **11** [δ(C7) = 28.56, δ(C8) = 27.71]. Hence, the relative configuration of the *diexo*-**11** is concluded to be 3a*S**,5a*R**,6*S**,9*R**,9a*S** and that of the *diendo*-**13** 3a*S**, 5a*R**,6*R**,9*S**,9a*S**.

Also three other W-type ^4J-couplings were observed for **11** and **13** as expected. The rigid norbornane part of the skeleton offers almost ideal bond and torsion angles for the W-couplings to show up. These couplings also support the idea that the norbornane must remain strictly biased, leading to the conclusion that the six-membered heterocycle must be twisted out of the ideal chair conformation. This is seen for the measured coupling constants between H-5ax and H-5eq with H-5a, and H-5a with H-9a, which are roughly the same. By assuming a trigonal symmetry the Karplus equation calculations gave the torsion angles of −15° and +2° for the fragments C6–C5a–C9a–C9 and C5–C5a–C9a–N10 in **11** and **13**, respectively. For the fragment O4–C5–C5a–C9a, the torsion angles 23° for the *diexo*-**11** and 36° for the *diendo*-**13** were determined. Accordingly, the oxazine in the *diendo*-**13** is more flattened in the fused moiety and deviates more from the chair conformation.

The sub-spectra of the pyrrolo parts of **11** and **13** are ABCD-, or perhaps better, the ABCM-type, but they could still be solved. For **11**, the coupling constants are very similar to the ones measured in the other compounds of this series (Table 5). Although the geminal coupling between H-2a and H-2s has a somewhat smaller absolute value, it can still be stated that the five-membered ring is in the envelope conformation. In **11**, the pucker of the envelope is somewhat larger than in the other cases as can be seen from the vicinal coupling constants; the value of the diaxial coupling between H-2s and H-3a is 14.0 Hz. For **13**, the iteration was disturbed by the overlapping signals and some impurity; thus the reported couplings are the best combination found for this case. They show that the five-membered ring is in an envelope conformation with C-3a as the flip atom. In **13**, H-2s resonates a bit lower in the field than H-2a. This is proved by the DNOE-measurement, which showed that the irradiation of the phenyl ring protons enhanced more the signal of the former. The plane of the phenyl ring appears to be closely parallel to the imaginary line connecting O-1 and O-4 atoms, and thus the H-2s and H-3s are in the shielding cone of the phenyl ring as in the earlier cases. The H-2s was found to be ^5J-coupled to H-9a in the LR COSY-spectrum by less than 0.5 Hz.

***diexo*- and *diendo*-3a-(4-Chlorophenyl-6,9-methano-1,2,3,3a, 5,5a,6,9-octahydropyrrolo[1,2-*a*][3,1]benzoxazin-1-ones (12 and 14).** Similarly to **11** and **13**, **12** and **14** (Scheme 3) were deduced to be *diexo*- and *diendo*-annellated 6,9-methanooctahydropyrrolobenzoxazinones, respectively. In the *diexo*-**12** H-5a and H-9a exhibited W-type long-range couplings to H-11a. The ^{13}C chemical shifts support the configurational deductions in the annellation moieties. In compound **12**, the C-11 exhibits strong γ-effects due to C-5 and N-10 being *gauche* to it whereas in **14** they are *anti* to C-11. Owing to the double bond between them, C-7 and C-8 show no strong differences in γ-effects as did **11** and **13**. Nevertheless, the remaining differences in the ^{13}C chemical shifts of C-7 and C-8 are in the expected direction. The shifts are little smaller in the *diendo*-**14** where the carbons are *gauche* to C-5 and N-10 compared with the *diexo*-**12** where the stereochemistry is *anti*. The relative configuration of the *diexo*-**12** is 3a*S**,5a*R**,6*S**,9*R**,9a*S** and that of the *diendo*-**14** 3a*S**,5a*R**,6*R**,9*S**,9a*S**.

Several additional W-type couplings were found in both compounds (Table 6). For **12**, there was also found a correlation in the LR COSY-spectrum between H-7 and H-9 indicating an allylic-type coupling and for **14**, a similar coupling between H-6 and H-8. The H-9a showed an extra coupling to H-2a or H-2s as shown by the LR COSY-spectrum of **12**. It is, similarly to earlier observations, probably a homoallylic ^5J(2s,9a) coupling. In **14**, this coupling was certainly found in the LR COSY-spectrum.

The vicinal coupling constants between the protons in the oxazine rings (Table 3) indicate flattened and twisted chair conformations as in **11** and **13**. By assuming trigonal symmetry, the Karplus equation calculations gave torsion angles of −17° and +2° for the C6–C5a–C9a–C9 and C5–C5a–C9a–N10 moieties in **12** and **14**, respectively. For the O4–C5–C5a–C9a fragment, the torsion angle was calculated to be 33° for the *diexo*-**12** and 31° for the *diendo*-**14**. The oxazine ring in the *diendo* compound appears to be more affected by the norbornene moiety and its conformation deviates more from the ideal chair than was the case for **11** and **13**.

The pyrrolo ring gave an ABCM-type sub-spectrum in **12** and in **14**. From the coupling constants it can be deduced that the five-membered rings are in envelope conformations having the C-3a as the flip atom. In the *diexo*-**12** the puckering is quite strong as concluded from the large diaxial coupling ^3J(2s,3a) = 13.1 Hz. Yet again, the phenyl ring is turned parallel to the imaginary line connecting the O-1 and O-4 atoms, causing the H-2s and H-3s to resonate higher in the field than the *anti* protons.

Configurational and conformational analysis by X-ray diffraction. The crystal structures of cyclohexane derivates **7** (*cis*-fused cyclohexane ring), **9** (*cis*-fused cyclohexene ring) and **10** (*trans*-fused cyclohexene ring) support the postulated structural features (Scheme 3). For **10**, the oxazine ring has a quite regular chair conformation. In *cis*-**7** and -**9**, the oxazine ring is slightly more puckered in comparison with *trans*-**10**, and this influence extends to the five-membered ring. For **9**

Table 7 Physical and analytical data for compounds **2**–**14**

Compound (Formula)	Mp/ °C	Yield (%)	Solvent	Found (%) (Required) C	H	N
2 ($C_{10}H_9N_2ClO$)	186–188	54	EtOAc	57.6 (57.1	4.4 4.35	13.35 13.45)
3 ($C_{12}H_{13}N_2ClO$)	160–161	62	EtOAc	60.65 (60.9	5.45 5.55	11.95 11.85)
4 ($C_{12}H_{12}NClO_2$)	79–81	64	Benzene	60.85 (60.65	5.15 5.1	5.95 5.9)
5 ($C_{12}H_{14}NClO_2$)	60–62	48	EtOAc	61.85 (62.05	5.7 5.6	5.65 5.55)
6 ($C_{16}H_{12}NClOS$)	120–121	46	Benzene	63.75 (63.7	4.15 4.0	4.75 4.65)
7 ($C_{17}H_{20}NClO_2$)	132–134	48	EtOAc	66.6 (66.75	6.5 6.6	4.6 4.6)
8 ($C_{17}H_{20}NClO_2$)	135–138	46	Benzene	66.6 (65.75	6.45 6.6	4.65 4.6)
9 ($C_{17}H_{18}NClO_2$)	150–152	75	EtOH	67.1 (67.2	6.05 6.0	4.7 4.6)
10 ($C_{17}H_{18}NClO_2$)	159–161	64	EtOAc	67.2 (67.2	5.8 5.95	4.5 4.6)
11 ($C_{18}H_{20}NClO_2$)	161–162	57	EtOH	68.0 (68.0	6.3 6.35	4.4 4.4)
12 ($C_{18}H_{18}NClO_2$)	154–155	67	EtOH	68.35 (68.45	5.6 5.75	4.65 4.45)
13 ($C_{18}H_{20}NClO_2$)	173–176	58	EtOH	67.95 (68.05	6.25 6.35	4.5 4.4)
14 ($C_{18}H_{18}NClO_2$)	233–234	47	EtOH	68.3 (68.45	5.5 5.75	4.4 4.45

and **10**, the terminal six-membered ring is in half-chair conformation as expected for the cyclohexene ring,[18] while in **7** the terminal ring is a chair.

Compounds **11** (*diexo*), **13** (*diendo*) and **14** (*diendo* with a double bond between C-7 and C-8) belong to the norbornane/ene series. Bond parameters and torsion angles are in the expected ranges. In **11**, **13** and **14** the fused norbornane/ene distorts the oxazine ring out of the ideal chair conformation. The *diendo*-annellation is more distortive than the *diexo*-fusion. The oxazine ring in the *diexo*-**11** is in a somewhat flattened chair conformation, while in the *diendo*-**13** and -**14** the oxazine ring is a sofa.[19] In all norbornane/ene, the five-membered rings are quite similar.

The orientation of the phenyl group, which is almost perpendicular to the average plane of the five-membered and hetero rings is similar in the cyclohexane derivatives although the N10–C3a–C12–C13 torsion angles are clearly different for the *cis*- [−38.6(3)° and −41.5(5)°] and *trans*-fused [−27.8(4)°] derivates **7**, **9** and **10**, respectively. In **11**, **13** and **14**, the relevant torsion angles are −21.8(4)°, −23.3(3)° and −22.2(4)°, which indicates that the norbornane/ene moiety has a similar effect on the orientation of the phenyl substituent.

As the distance varies from 0.539 to 0.557 Å only in the studied compounds the plane formed by atoms C-3, O-4, N-10 is at a quite constant distance from C-3a. N-10 is almost in the plane of the C-1, C-3a and C-9a. This is supported by the fact that in **14** the longest distance to that plane from N-10 which is above the plane is 0.188 Å. However, in **10** N-10 is −0.060 Å below that plane. In **13** N-10 is 0.169 Å above the plane. Thus, the norbornene moiety in **13** and **14** makes the hetero ring more distorted.

In all compounds studied with X-ray diffraction measurements the bond distance between N-10 and C-1 is roughly 0.1 Å shorter than for the other C–N bonds. This together with the above conclusion proves that the lactamide C–N bond has some π-character.

Experimental

Preparation of the pyrrolo[2,1-*b*]benzothiazolone 6 and the pyrrolo[1,2-*a*][3,1]benzoxazinones 7–14 (general method)

A mixture of **1** (0.01 mol), cyclic or bicyclic aminoalcohols (0.01 mol) and a crystal of *p*-toluenesulfonic acid in toluene (50 ml) was refluxed for 4–5 h applying a Dean–Stark apparatus (TLC monitoring). After cooling, the solvent was evaporated off and the residue was brought onto a silicagel column (Kieselgel 62, 60–200 mesh, 150 Å) and chromatographed by EtOAc. The residue of the eluate was crystallized. The physical and analytical data on compounds **2**–**14** are listed in Table 7.

NMR spectral measurements

The NMR spectra were recorded in $CDCl_3$ or in a solvent mixture of $CDCl_3$ and [$^2H_6$]benzene (1:2) at +27 °C on JEOL JNM GX400 (^{1}H: 399.78 MHz; ^{13}C: 100.53 MHz) and/or on JEOL A500 (^{1}H: 500.16 MHz; ^{13}C: 125.77 MHz) Fourier transform spectrometers with the deuterium signal of the solvent as the lock and TMS as internal standard in ^{1}H NMR measurements (0.00 ppm) and the middle lines of the solvent signal in ^{13}C NMR measurements (77.10 ppm). 2–10 mg of samples were dissolved for the 1D ^{1}H-measurements and 5–40 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.

Spectral analyses were performed with the PERCH[8] program on a Pinus Pentium 100 MHz personal computer. The accuracy of the derived coupling constants is less than 0.1 Hz, except when they are reported in one decimal precision or poorer, when the accuracy is *ca.* 0.2–0.5 Hz. The modified Karplus equation[9] calculations were made using ALTONA-B, -D and -E PC-programs kindly provided by Dr Sami Heikkinen from the University of Oulu, Finland.

The coupling constants, selected bond distances and torsion angles for the new tri- and tetra-cyclic compounds **7**–**14** have been deposited as supplementary material.‡

X-Ray diffraction measurements

Single-crystal X-ray measurements for all compounds were carried out on a Rigaku AFC5S diffractomer at room temperature

‡ Suppl. Pub. 57221 (7 pp.). For details of the British Library Supplementary Publications Scheme see 'Instructions for Authors (1997),' *J. Chem. Soc., Perkin Trans. 2*, 1997, Issue 1.

Table 8 Crystal data and experimental details of the X-ray diffraction measurements of **7**, **9** and **10**

Compound	**7**	**9**	**10**
Formula	$C_{17}H_{20}ClNO_2$	$C_{17}H_{18}ClNO_2$	$C_{17}H_{18}ClNO_2$
M_r	305.80	303.79	303.79
Crystal size/mm	0.12 × 0.16 × 0.22	0.20 × 0.22 × 0.24	0.20 × 0.30 × 0.40
Habit	Plate	Cube	Prism
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	*P*-1 (No. 2)	$P2_1/c$ (No. 14)	*C*2/*c* (No. 15)
a/Å	9.403(2)	12.890(1)	15.934(2)
b/Å	12.910(1)	10.007(1)	8.985(4)
c/Å	6.859(1)	12.817(1)	21.507(1)
α/°	92.48(1)	90	90
β/°	103.51(1)	114.05(1)	102.90(1)
γ/°	104.05(1)	90	90
V/Å^3	781.5(2)	1509.8(6)	3001(1)
Z	2	4	8
D_c/g cm^{-3}	1.299	1.336	1.344
μ/cm^{-1}	2.45	2.54	2.54
F(000)	324	640	1280
Measured refl.	2918	3294	2939
Unique refl.	2738	3152	2824
R_{int}	0.018	0.030	0.025
Obs. refl.[a]	1813	1546	1619
No. of parameters	238	232	232
R[b]	0.041	0.051	0.042
R_w[c]	0.046	0.050	0.045
Goodness of fit	1.44	1.42	1.47
Max., min. $\Delta\rho$/eÅ^{-3}	0.16/−0.20	0.23/−0.24	0.20/−0.24

[a] Criteria $I > 2\sigma(I)$. [b] $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$. [c] $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{\frac{1}{2}}$; $w = [\sigma(F_o)]^{-1}$.

Table 9 Crystal data and experimental details of the X-ray diffraction measurements of **11**, **13** and **14**

Compound	**11**	**13**	**14**
Formula	$C_{18}H_{20}ClNO_2$	$C_{18}H_{20}ClNO_2$	$C_{18}H_{18}ClNO_2$
M_r	317.81	317.81	315.80
Crystal size/mm	0.20 × 0.24 × 0.26	0.22 × 0.36 × 0.38	0.12 × 0.20 × 0.22
Habit	Cube	Prism	Plate
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)
a/Å	11.242(2)	9.070(4)	8.917(2)
b/Å	16.591(1)	11.450(2)	11.317(1)
c/Å	8.572(2)	15.544(2)	15.633(2)
α/°	90	90	90
β/°	101.86(1)	105.94(2)	105.38(1)
γ/°	90	90	90
V/Å^3	1564.7(7)	1552.3(7)	1521.2(3)
Z	4	4	4
D_c/g cm^{-3}	1.349	1.360	1.379
μ/cm^{-1}	2.48	2.50	2.54
F(000)	672	672	664
Measured refl.	3070	3080	3022
Unique refl.	2871	2888	2830
R_{int}	0.026	0.019	0.031
Obs. refl.[a]	1679	1946	1649
No. of parameters	247	259	241
R[b]	0.045	0.041	0.043
R_w[c]	0.045	0.045	0.045
Goodness of fit	1.36	1.53	1.32
Max., min. $\Delta\rho$/eÅ^{-3}	0.18/−0.25	0.17/−0.20	0.14/−0.31

[a] Criteria $I > 2\sigma(I)$. [b] $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$ [c] $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_0|^2]^{1/2}$; $w = [\sigma(F_o)]^{-1}$.

(23 °C) with graphite monochromated Mo-Kα radiation, $\lambda = 0.710\,69$ Å. The data obtained were corrected for Lorentz and polarization effects. The crystal data and experimental details are shown in Tables 8 and 9.

The structures were solved by direct methods using MITHRIL[20] and DIRDIF[21] programs (the latter was used to locate H atoms) and refined by full-matrix least squares techniques, the non-hydrogen atoms anisotropic and hydrogen atoms with fixed isotropic temperature parameters (1.2 B_{eq} of carrying atom). The aromatic hydrogens were kept in the calculated positions.

All calculations were performed with TEXSAN-89 software[22] using a VAXSTATION 3520 computer. The neutral atomic scattering and dispersion factors were those included in the program. Figures were drawn with ORTEP.[23] The final atomic positional coordinates, temperature parameters, bond lengths and angles have been deposited with the Cambridge Crystallographic Data Centre (CCDC). See 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/50.

References

1 (*a*) J. R. Geigy, BP 659530/1965 (*Chem. Abstr.*, 1966, **64**, 6664f); (*b*) W. J. Houlihan, USP 3334099/1967 (*Chem. Abstr.*, 1968, **69**, 96769f); (*c*) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, 1969, **34**, 165; (*d*) H. Wollweber, GP 1802468/1970 (*Chem. Abstr.*, 1970, **93**, 25543z); (*e*) P. Kourounakis, W. H. Hunter and P. G. Morris, *Arzneim.-Forsch.*, 1979, **29**, 983.

2 (*a*) W. J. Houlihan, USP 3334095/1967 (*Chem. Abstr.*, 1968, **69**, 96799r); (*b*) H. Wollweber, J. Kurz and W. Naegele, *Arch. Pharm.* (*Weinheim, Ger.*), 1971, **304**, 774; (*c*) P. Aeberli, J. H. Gogerty, W. J. Houlihan and L. C. Iorio, *J. Med. Chem.*, 1976, **19**, 436; (*d*) W. A. Sedovkina, I. V. Lizak and N. N. Sarokin, *Khim. Geterosikl. Soedin.*, 1987, 1405.

3 G. L. Oliver, J. R. Dann and J. W. Gates, Jr., *J. Am. Chem. Soc.*, 1958, **80**, 702.

4 (*a*) P. Sohár, G. Stájer, A. E. Szabó and G. Bernáth, *J. Mol Struct.*, 1996, **377**, 101; (*b*) G. Stájer, R. Sillanpää and K. Pihlaja, *Acta Chem. Scand.*, 1993, **47**, 482; (*c*) R. Sillanpää, G. Stájer and *K. Pihlaja*, *Acta Chem. Scand.*, 1994, **48**, 84; (*d*) G. Stájer, F. Csende, G. Bernáth and P. Sohár, *Heterocycles*, 1994, **37**, 883; (*e*) G. Argay, R. Sillanpää, G. Stájer and G. Bernath, *Acta Chem. Scand.*, 1994, **48**, 530; (*f*) G. Stájer, A. E. Szabó, G. Bernáth and P. Sohár, *Heterocycles*, 1994, **38**, 1061; (*g*) P. Sohár, S. Frimpong-Manso, G. Stájer and G. Bernath, *Magn. Reson. Chem.*, 1994, **32**, 705; (*h*) P. Sohár, G. Stájer, K. Nagy and G. Bernáth, *Magn. Reson. Chem.*, 1995, **33**, 329.

5 (*a*) W. V. Curran and A. Ross, *J. Med. Chem.*, 1974, **17**, 273; (*b*) W. J. Houlihan, USP 3931176/1976 (*Chem. Abstr.*, 1976, **84**, 105630t).

6 D. Papa, E. Schwenk, F. Villani and E. Klingsberg, *J. Am. Chem. Soc.*, 1948, **70**, 3356.

7 (*a*) S. Gabriel and J. Colman, *Ber.*, 1899, **32**, 398; (*b*) S. Skraup and E. Schwamberger, *Liebigs Ann. Chem.*, 1928, **462**, 148.

8 R. Laatikainen, M. Niemitz, J. Sundelin, T. Hassinen, PERCH (PEak reseaRCH): the software is meant for manipulation and handling interface prior to spectral analysis in personal computer, Version 2/95, PERCH project, Department of Chemistry, University of Kuopio, Finland, 1995.

9 C. A. G. Haasnoot, F. A. A. M. de Leeuw and C. Altona, *Tetrahedron*, 1980, **36**, 2783.

10 CHEM-X: Chemical Structure Visualisation, Computation and Databases Software, Chemical Design Ltd., Oxford, 1995.

11 M. Barfield and D. M. Grant, *J. Am. Chem. Soc.*, 1963, **85**, 1899.

12 V. Mark, *Tetrahedron Lett.*, 1974, 299.

13 (*a*) A. Chimirri, S. Grasso, M. Longeri, G. Menniti, G. Romeo and G. Valle, *J. Chem. Res.* (*S*), 1984, 78; (*b*) A. Chimirri, S. Grasso, P. Monforte, G. Romeo and M. Zappalà, *Heterocycles*, 1988, **27**, 93.

14 (*a*) M. Barfield and S. Sternhell, *J. Am. Chem. Soc.*, 1972, **94**, 1905; (*b*) N. Juranic, V. Likic, T. Parac and S. Macura, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1805.

15 M. Barfield and R. J. Spear and S. Sternhell, *Aust. J. Chem.*, 1989, **42**, 659.

16 K. Pihlaja and E. Kleinpeter, *Carbon-13 NMR Chemical Shifts in Structural and Stereochemical Analysis*, VCH, New York, 1994; (*a*) p. 40; (*b*) p. 70.

17 M. Barfield, R. J. Spear and S. Sternhell, *Chem. Rev.*, 1976, **76**, 593.

18 E. L. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, p. 727.

19 R. Bucourt, in *Topics in Stereochemistry*, eds. E. L. Eliel and N. L. Allinger, Wiley, New York, 1974, vol. 8, p. 186.

20 G. J. Gilmore, *J. Appl. Cryst.*, 1984, **17**, 42.

21 P. T. Beurskens, DIRDIF, Technical report 1984/1, Crystallography Laboratory, Toernooiveld, 6525 Ed Nijmegen, Netherlands.

22 TEXSAN: Single Crystal Structure Analysis Software, Version 5.0, Molecular Structure Corporation, The Woodlands, Texas, 1989.

23 C. K. Johnson, ORTEP-II, A Fortran Thermal-ellipsoid Plot for Crystal Structure Illustrations. Report ORNL-5138″, Oak Ridge National Laboratory, Tennesee, 1976.

Paper 6/04905*B*
Received 12*th July* 1996
Accepted 18*th October* 1996