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STEREOCHEMICAL STUDIES 136. SATURATED HETEROCYCLES 141.[1] SYNTHESIS AND CONFORMATIONAL STUDY OF STEREOISOMERIC 2,2-DISUBSTITUTED-5,6-TRI- AND -5,6-TETRAMETHYLENE-TETRAHYDRO-1,3-OXAZIN-4-ONES

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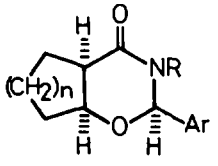
Abstract - Diastereomers of 2,2-disubstituted-5,6-tri- and 5,6-tetramethylenetetrahydro-1,3-oxazin-4-ones (**5a,b-12a,b**) were synthesized from cis-2-hydroxycyclopentane and -cyclohexanecarboxamides (**3**, **4**) by condensing them with 2-butanone, 3-methyl-2-butanone, 3,3-dimethyl-2-butanone or acetophenone. The stereoselectivity of the ring closure depends on the steric requirements of the C-2 geminal substituents, although the predominant conformation (O-in) remains the same in both sets of the heterocycles.

Although the synthesis of 2,3-dihydro-1,3-benzoxazin-4-ones has been known since the beginning of this century, and their pharmacology[2] has also been thoroughly studied, the synthesis,[2-5] stereochemistry[5-7] and pharmacology[8] of related perhydrogenated derivatives have been investigated only recently.



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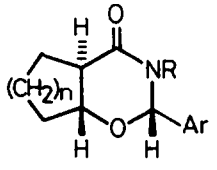

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The formation of 2-aryl-substituted cis- and trans-perhydrobenzoxazines and their A-ring homologues **1** and **2** starting from cis- and trans-2-hydroxycycloalkanecarboxamides is a stereospecific process[5] resulting in single diastereomers. In the present paper, we describe the synthesis and conformational study of the diastereomeric 2,2-disubstituted-perhydro-1,3-benzoxazin-4-one homologues.

RESULTS AND DISCUSSION

Synthesis

The title compounds were synthesized by allowing cis-2-hydroxycyclopentane-[9] (**3**) or -cyclohexanecarboxamide[10] (**4**) to react with ketones. The reactions were carried out with an excess of 2-butanone, 3-methyl-2-butanone, 3,3-dimethyl-2-butanone or acetophenone in the presence of dry hydrogen chloride. The diastereomer distributions (Table 1) were determined from the integrals of the C-2 methyl signals immediately after neutralization and extraction of the products into

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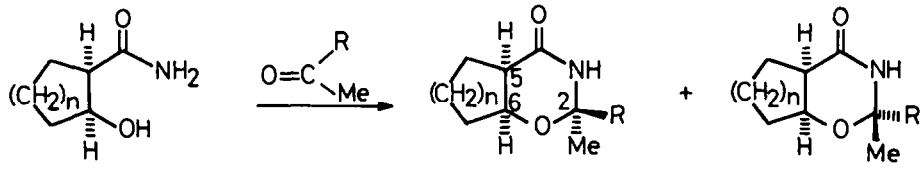
chloroform. When R is an alkyl group, the main product has the all cis relative configuration (Scheme 1: series a). The stereoselectivity is more pronounced in the cyclohexane series. The stereoselectivity increases with increasing size of R[11] and the reaction becomes a stereospecific process for R = tert-butyl. When acetophenone was used, the stereoselectivity was reversed, the main products being **8b** and **12b**.

Table 1. Diastereomer ratios (a:b) in the formation of 1,3-oxazin-4-ones **5a,b-12a,b**.

R	5-8	9-12
Et	67:33	74:26
iPr	78:22	85:15
tBu	100:0	100:0
Ph	13:87	9:91

By fractional crystallization, some of the diastereomeric products (**5a**, **5b**, **6a**, **7a**, **8b**, **10a**, and **11a**) were obtained in spectroscopically pure form. Selected ^{1}H NMR data on them are given in Table 2. The spectral data on the other compounds were derived from the spectra of the mixtures of diastereomers.



	n = 1	n = 2	R	n = 1	n = 2
n = 1	**3**				
n = 2	**4**				
	5a	**9a**	Et	**5b**	**9b**
	6a	**10a**	iPr	**6b**	**10b**
	7a	**11a**	tBu	**7b**	**11b**
	8a	**12a**	Ph	**8b**	**12b**

Scheme 1

Table 2. Selected chemical shifts (ppm) and coupling constants (Hz) for 1,3-oxazin-4-ones **5a,b-12a,b**

No.	δ(H-5)		J(H-5)		δ(H-6)	ΣJ(H-6)	2-Me	2-R
5a	2.47	4.5	8.7	9.5	4.48	10.8	1.45	0.92 (t, 3H)
5b	2.50	5.2	8.7	9.4	4.43		1.35	0.94 (t, 3H)
6a	2.47	4.4	8.4	9.5	4.46	10.4	1.43	0.95 (d, 3H), 0.93 (d, 3H), 1.78 (m, 1H)
6b	2.48	5.4	8.4	9.9	4.47	10.5	1.23	0.96 (d, 3H), 0.94 (d, 3H), 2.23 (m, 1H)
7a	2.49	4.4	8.7	9.9	4.45	10.3	1.41	0.97 (s, 9H)
8a	2.65	5.1	8.8	9.4	4.72	11.4	1.89	7.3-7.5 (m, 5H)
8b	2.36	5.65	8.85	9.3	4.01	13.0	1.69	7.3-7.5 (m, 5H)
9a	2.16	2.4	4.8	12.8	4.18	8.2	1.41	0.98 (t, 3H)
9b	2.16	2.3	5.2	12.8	4.10	8.5	1.40	0.92 (t, 3H)
10a	2.16	2.6	5.0	12.7	4.16	ca 8	1.39	1.00 (d, 3H), 0.98 (d, 3H), 1.85 (m, 1H)
10b	2.16	*	*	*	4.17	ca 8	1.29	0.95 (d, 3H), 0.93 (d, 3H), 2.20 (m, 1H)
11a	2.19	2.7	5.1	12.7	4.16	8.5	1.39	1.02 (s, 9H)
12a	2.30	2.6	4.9	12.4	4.40	ca 9	1.81	7.3-7.5 (m, 5H)
12b	2.14	2.8	4.9	12.1	3.76	ca 9	1.69	7.3-7.5 (m, 5H)

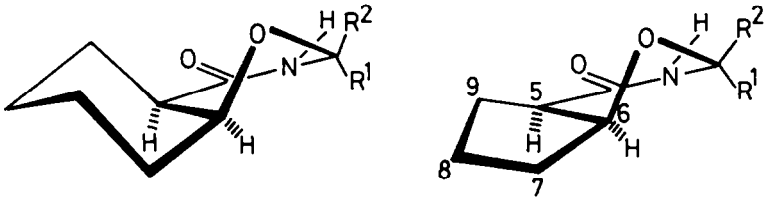
*Overlapping signals; coupling constants are about the same as for **10a**.

Structure

The relative configurations and predominant conformations were determined by DNOE measurements and by comparing the values of the vicinal ^{1}H - ^{1}H coupling constants

with those of some related heterocycles.[12] Eg, irradiation at H-6 of **10a** resulted in a 3.6 % NOE enhancement of its 2-Me-signal, in agreement with the configuration shown in Scheme 1.

The values of the vicinal coupling constants (Table 2) and the DNOE results, together with an inspection of Dreiding models, indicate that all the compounds (5-12) have the same predominant conformation (O-in) (Fig. 1), in good agreement with our previous NMR studies on 2-aryl-substituted-1,3-oxazin-4-ones[5] and with the X-ray results on 2-p-chlorophenyl-cis-5,6-trimethylenetetrahydro-1,3-oxazin-4-one[13] and 2-methyl-2-phenyl-cis-5,6-trimethylenetetrahydro-1,3-oxazin-4-one.[14]



O-in O-in

Figure 1

The stereoselectivity of the reactions studied can be rationalized in terms of the relative stabilities of the products. According to the basic rules of conformational analysis, the equatorial position of a bulkier substituent is preferred. Thus, in the phenyl series **8** and **12**, the phenyl group seems to be smaller than the methyl group. In 2,2-disubstituted-1,3-dioxanes, the conformational preference for an axial or an equatorial substituent has been thoroughly studied.[15,16] In 2-methyl-2-phenyl-1,3-dioxane, in good agreement with the present data on stereoselectivity, the phenyl group prefers the axial orientation.[16]

However, similarly to the recent conclusion drawn by Dolmazon and Gelin[17] from an investigation of the closely analogous 1-oxa-4-decalone derivatives, the C-2 substituents, independent of their bulkiness, have no effect on the predominant conformation of the C-2 diastereomers of condensed 1,3-oxazin-4-ones.

EXPERIMENTAL

M.p.s. were determined with a Büchi 510 capillary melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a JEOL GX-400 FT NMR spectrometer in $CDCl_3$ solutions at ambient temperature, using TMS as internal standard.

Table 3. Physical and analytical data on 1,3-oxazin-4-one diastereomers.

Compound	M.p./°C	Solvent	C, H, N: Found/Required (%)			Formula (M. w.)
5a	81-82	hexane	65.72/65.54	9.41/9.35	7.67/7.64	$C_{10}H_{17}NO_2$ (183.25)
5b	128	EtOAc	65.75/65.64	9.53/9.35	7.71/7.64	$C_{10}H_{17}NO_2$ (183.25)
6a	83-85	hexane	67.02/66.97	9.95/9.71	7.25/7.10	$C_{11}H_{19}NO_2$ (197.27)
7a	142-143	hexane	68.24/68.21	10.10/10.02	6.71/6.63	$C_{12}H_{21}NO_2$ (211.30)
8b	150-151	EtOAc	72.96/72.70	7.69/7.41	6.08/6.06	$C_{14}H_{17}NO_2$ (231.29)
10a	98-101	hexane	68.37/68.21	9.93/10.02	6.41/6.63	$C_{12}H_{21}NO_2$ (211.30)
11a	165-167	hexane	69.40/69.29	10.42/10.29	6.11/6.22	$C_{13}H_{23}NO_2$ (225.32)

cis-2-Hydroxycyclopentanecarboxamide[9] (**3**) and cis-2-hydroxycyclohexanecarboxamide[10] (**4**) were prepared as described earlier.

Ring closures of carboxamides **3** and **4** with 2-butanone, 3-methyl-2-butanone, 3,3-dimethyl-2-butanone or acetophenone

2-hydroxycycloalkanecarboxamide (**3**) or (**4**) (10 mmol) was dissolved in 10 ml of ethanol containing 2 g of dry hydrogen chloride, and the corresponding ketone (3 ml) was added. After one week (in the case of acetophenone after 3 weeks), the solvent was evaporated off, and the residue was suspended in water (20 ml) and then neutralized with sodium hydrogen carbonate. The products were extracted in chloroform (4x20 ml). After drying and evaporation of the solvent, nearly colourless products were obtained, in which the diastereomer ratios were immediately determined by 400 MHz ^{1}H NMR spectroscopy. After two or three repeated crystallizations, analytically (Table 3) and spectroscopically pure diastereomers **5a**, **5b**, **6a**, **7a**, **8b**, **10a** and **11a** were obtained. The spectroscopic data on compounds **6b**, **8a**, **9a**, **9b**, **10b**, **12a** and **12b** were based on the spectra of the diastereomeric mixtures.

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