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The carbonyl group of substituted 5-benzoyl-4,5-dihydro-1,2,4-oxadiazoles can be reduced by lithium aluminium hydride at low temperature without ring opening. Mixtures of the two related diastereoisomeric benzylalcohols are obtained. Configurations were assigned by ¹H-nmr.

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It has been reported that complex metallic hydride reduction of 4,5-dihydro-1,2,4-oxadiazoles proceed with ring opening, α -aminooximes being obtained [2,3].

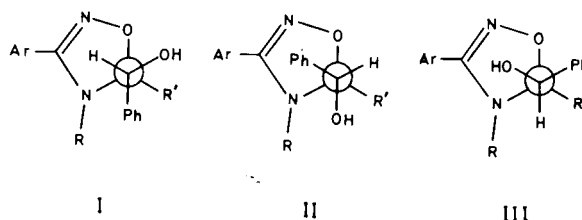
This ring opening is also observed when a benzoyl group in position 5 is present and lithium aluminium hydride in refluxing THF is used. However, quantitative reduction of the benzoyl group, without alteration of the ring, has been achieved with lithium aluminium hydride in ether at 0-5°. The reaction proceeds with a certain degree of stereoselectivity (Table 1).

Assignment of *RR-SS* and *RS-SR* configurations to the reduction products was based on an estimation of the relative stabilities of the conformers produced by rotation around the bond linking both chiral centers (Scheme 1). With the help of molecular models it can be shown that for compounds **1-5** (see Table 1) III is the less hindered conformer of the *RS-SR* isomer. The phenyl group attached to the hydroxylated carbon atom interacts in I with the aromatic residues R and R' and in II with the *p*-chlorophenyl

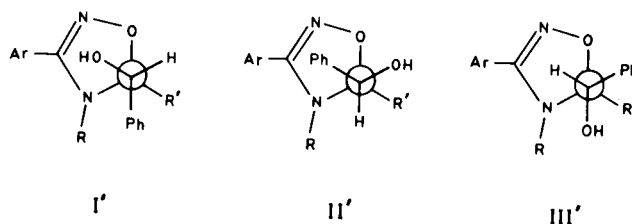
and R groups. The latter two conformers are thus destabilized with respect to III. Similarly, III' is the most populated conformer in the *RR-SS* isomer. In this latter conformer the proton attached to the hydroxylated carbon atom is more shielded by the C=N heterocyclic bond [4]. In agreement with this compounds with lower chemical shifts should have the *RR-SS* configuration.

For compounds **6-9**, in which R' = H, the vicinal coupling constants of the protons attached to both chiral centers are the base of assignment. The largest coupling constant corresponds to the *RR-SS* diastereoisomer the predominant conformer of which, III', has the hydrogen atoms in antiperiplanar arrangement. On the other hand,

(*RR-SS*)-isomer



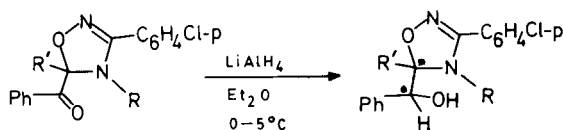
(*RR-SS*)-isomer



(Ar = *p*-ClC₆H₄)

SCHEME 1

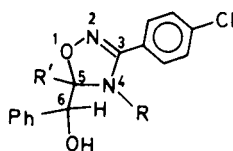
Table 1



Compound	R	R'	<i>RS-SR/RR-SS</i> [a]
1	Ph	Ph	4.0
2	<i>p</i> -Me ₂ NC ₆ H ₄	Ph	3.0
3	<i>p</i> -MeOC ₆ H ₄	Ph	3.5
4	<i>p</i> -MeC ₆ H ₄	Ph	4.0
5	<i>p</i> -ClC ₆ H ₄	Ph	5.7
6	<i>i</i> -Pr	H	2.5
7	<i>t</i> -Bu	H	3.5
8	Cyclohexyl	H	1.9
9	Ph ₂ CH	H	9.0

[a] Proportions of the diastereoisomeric alcohols in the reaction crude were determined by ¹H-nmr (60 MHz) taking as differentiating signals those of the proton attached to the hydroxylated carbon atom.

Table 2
Analytical and Spectroscopic Data of Alcohols 1-9



Comp.	R	R'	Isomer	Mp°C (Solvent)	Formula	Analysis [a]				'H-NMR [b]
						C	H	N	Cl	
1	Ph	Ph	RR-SS [c]							5.17 (s, H6)
			RS-SR	184-186 (Benzene-hexane 1:9)	C ₂₇ H ₂₁ ClN ₂ O ₂	73.50 (73.54)	4.76 (4.80)	6.28 (6.35)	8.00 (8.04)	2.73 (d, broad, 1H, J = 4.5, OH), 5.38 (d, broad, 1H, J = 4.5, H6), 6.5-7.7 (m, 19H, aromatics)
2	<i>p</i> -Me ₂ NC ₆ H ₄	Ph	RR-SS [c]							2.93 (s, NMe ₂), 5.17 (s, H6)
			RS-SR	192-194 (Benzene-hexane 1:9)	C ₂₉ H ₂₆ ClN ₃ O ₂	71.79 (71.97)	5.38 (5.42)	8.55 (8.68)	7.30 (7.32)	2.75 (s, broad, 1H, OH), 2.80 (s, 6H, NMe ₂), 5.37 (s, 1H, H6), 6.2-7.6 (m, 18H, aromatics)
3	<i>p</i> -MeOC ₆ H ₄	Ph	RR-SS [c]							2.40 (s, broad, 1H, OH), 3.67 (s, 3H, OMe), 5.40 (s, 1H, H6), 6.4-7.7 (m, 18H, aromatics)
			RS-SR	146-147 (Benzene-hexane 1:9)	C ₂₈ H ₂₃ ClN ₂ O ₃	71.26 (71.40)	4.81 (4.92)	5.76 (5.95)	7.28 (7.53)	2.00 (s, broad, OH), 2.30 (s, MeAr), 5.13 (s, H6), 6.4-7.6 (m, aromatics)
			RR-SS [c]							2.00 (s, broad, OH), 2.13 (s, MeAr), 5.37 (s, H6), 6.4-7.6 (m, aromatics)
4 [d]	<i>p</i> -MeC ₆ H ₄	Ph	RS-SR [c]							5.17 (s, H6)
			RR-SS [c]							
5	<i>p</i> -ClC ₆ H ₄	Ph	RS-SR	158-160 (Benzene-hexane 1:9)	C ₂₇ H ₂₀ Cl ₂ N ₂ O ₂	68.11 (68.21)	4.20 (4.24)	5.78 (5.89)	14.80 (14.91)	0.47 (d, 3H, J = 7.0, Me), 0.90 (d, 3H, J = 7.0, Me), 3.13 (d, 1H, J = 3.0, OH), 3.30 (m, 1H, CHMe ₂), 4.58 (dd, 1H, J = 3.0 and 7.2, H6), 5.40 (d, 1H, J = 7.2, H5), 7.1-7.8 (m, 9H, aromatics)
			RR-SS	127-129 (Benzene-hexane 5:95)		65.20 (65.32)	5.53 (5.79)	8.24 (8.46)	10.53 (10.74)	0.97 (dd, 2xMe), 2.83 (s, broad, OH), 3.47 (m, CHMe ₂), 4.58 (d, J = 5.6, H6), 5.53 (d, J = 5.6, H5)
			RR-SS	oil						0.73 (s, 9H, 3xMe), 2.70 (s, broad, 1H, OH), 4.56 (d, 1H, J = 7.5, H6), 5.47 (d, 1H, J = 7.5, H5), 7.1-7.6 (m, 9H, aromatics)
6	<i>i</i> -Pr	H	RS-SR [c]							1.10 (s, 9H, 3xMe), 2.60 (s, broad, 1H, OH), 4.53 (d, 1H, J = 6.0, H6), 5.57 (d, 1H, J = 6.0, H5), 7.1-7.6 (m, 9H, aromatics)
			RR-SS							0.5-2.0 (m, 10H, 5 x CH ₂), 2.0-3.4 (m, broad, 2H, OH, and N-CH(CH ₂) ₂), 4.57 (d, 1H, J = 7.2, H6), 5.43 (d,
			RR-SS	144-145 (Hexane)	C ₁₈ H ₁₉ ClN ₂ O ₂	66.02 (66.19)	6.10 (6.14)	8.00 (8.12)	10.16 (10.28)	
7	<i>t</i> -Bu	H	RS-SR	140-142						
			RR-SS	142-146						
			RR-SS	142-146						

Comp.	R	R'	Isomer	Mp°C (Solvent)	Formula	Analysis [a]				'H-NMR [b]
						C	H	N	Cl	
8	Cyclohexyl	H	RS-SR	oil	C ₂₁ H ₂₃ ClN ₂ O ₂					1H, J = 7.2, H5), 7.1-7.7 (m, 9H, aromatics) 0.5-3.2 (m, 12H, OH and C ₆ H ₁₁), 4.38 (d, 1H, J = 6.0, H6), 5.55 (d, 1H, J = 6.0, H5), 7.1-7.7 (m, 9H, aromatics)
			RR-SS [c]							
9	Ph ₂ CH	H	RS-SR	190-192 (Hexane)	C ₂₈ H ₂₃ ClN ₂ O ₂	73.85 (73.91)	5.01 (5.10)	6.10 (6.15)	7.72 (7.79)	2.50 (s, broad, 1H, OH), 4.08 (d, 1H, J = 4.4, H6), 5.66 (s, 1H, CHPh ₂), 5.90 (d, 1H, J = 4.4, H5), 7.0-7.4 (m, 19H, aromatics)

[a] Calculated values in parenthesis. [b] All spectra were run in deuteriochloroform at 60 MHz, using tetramethylsilane as internal standard. Magnetic parameters were directly read from conveniently enlarged spectra. Data in parentheses are: multiplicity, protons number, coupling constant/Hz, and assignment. [c] Only selected protons are shown. Magnetic parameters were read from the spectra of the reaction crude from LAH reduction. [d] Isomers isolation failed.

III the more populated conformer of the *RS-SR* isomer has sinclinal hydrogen atoms giving a lower vicinal coupling constant for this isomer.

The predominance of the *RS-SR* throughout strongly favours the configuration assignment given above. It also suggests that a similar stereochemical course is followed for all compounds.

EXPERIMENTAL

Starting products were synthesized by cycloaddition from the related α -iminoketones and *p*-chlorobenzonitrile oxide [5].

Reduction procedure run as follows: a suspension of LAH in ether at 0° was added dropwise over a solution of the starting oxadiazoline in ether. Reagent proportions was always LAH/oxadiazoline = 2/1. The reaction mixture was stirred for five minutes at 0-5° and then hydrolyzed. After isolation of the crude of reaction only the major isomer could be isolated by crystallisation in **1**, **2**, **3**, **5** and **9**. Isomer separation failed in

4. In **6** the minor isomer was obtained pure by crystallisation. Both isomers were isolated for **7** and **8**. More details as well as analytical and spectroscopic data are collected in Table 2.

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