Configuration and Crystal Structure of (3*S*,5*R*)-3-Methyl-5-(4′-biphenylyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one. Conformation in Solution of a 4,5-Dehydro Analogue

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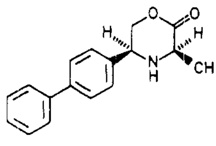
LIS–NMR determination of the conformation in solution of the 2,3-dihydrooxazin-2-one derivative **2** revealed the presence of the conformation **2c**. Assuming that this conformation is the reactive one, hydrogenation from the β face with asymmetric induction should lead to the 3,5-cis relative configuration in tetrahydrooxazin-2-ones, i.e., to the compounds with the 3*S*,5*R* absolute configuration. A crystal structure determination for the tetrahydro derivative **1** confirmed the 5*R* absolute configuration on the second chiral center.

Introduction

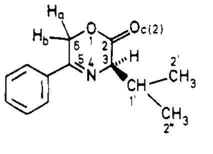
In our recent study[1] on asymmetric induction in hydrogenation of the azomethine bond, a number of 2,3-dihydro-6*H*-1,4-oxazin-2-ones, chiral at the C(3) atom, have been prepared and hydrogenated on Pd/C to 4,5-dihydro analogues.

While the high diastereoselectivity of the process (ca. 98%) was firmly established on the basis of the LIS NMR spectra of the products, their "3,5-cis" relative configuration was tentatively prognosticated on the grounds of the direction taken by hydrogen addition, on the basis of the conformational analysis of the starting compounds. It is well-known, however, that such an analysis, based on the mere inspection of the models, could raise erroneous conclusions about the stereoselective pathways of some processes where the conformation of the reactive species differs significantly from that of those expected as the most stable in solution. Therefore, we rigorously prove our prognoses by determination of both the configuration of the hydrogenated products by a crystal structure determination of the representative compound **1** and the conformation in solution of the 2,3-dihydro compound **2**, by the LIS–NMR method.

For this purpose compounds **1** and **2** have been chosen, the first one because of its good crystallization properties and the second one because of its chemical stability in solution, not completely shared by some other 4,5-dihydro derivatives.[1]



1

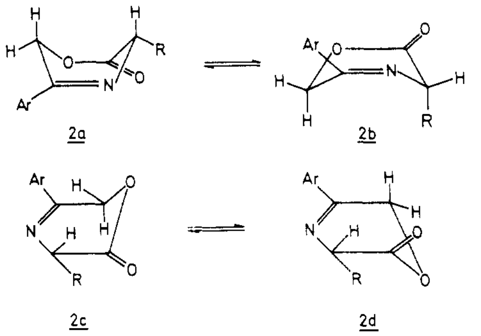


2

Results and Discussion

We have proposed[1] that the most stable conformations of the molecule should be the quasi-boat conformations **2a** and **2b** where four atoms lie nearly in the same plane, while two tetrahedral atoms are out of this plane (see Scheme I). At the same time Steglich et al.[2] presented more detailed NMR evidence which showed that in these compounds all atoms of the ring, with the exception of the oxygen, lie in the plane. This arrangement allows the existence of the other two diastereotopic conformations (**2c** and **2d**). The most important difference between them is a coplanarity between the carbonyl group and one, or the other, exocyclic C(3) bond. Nonbonded interactions will thus force the C(3) alkyl substituent into the more stable noncoplanar position, i.e., preferred conformation **2c**.

Scheme I



To find the most stable conformation among **2a–d**, LIS–NMR experiments using $Pr(fod)_3$-d_{27}, an achiral shift reagent, were performed. Six data were employed to determine the conformation, namely, the shifts of the isopropyl methyl groups, the isopropyl secondary proton, the proton on C3, and the proton on C6, which all exhibit distinct resonances. The bound shifts were obtained according to Armitage[3] by plotting the reciprocals of the induced shifts vs. the substrate concentration at constant $Pr(fod)_3$ concentration and calculating the slopes by linear regression. These experimental values were compared to those calculated by the McConnel–Robertson equation[4] $(3 \cos^2 \theta - 1)/r^3$; the agreement was expressed in the agreement factor[5]

$$R = \sum_i w_i(i_{\text{obsd}} - i_{\text{calcd}})^2 / \sum_i w_i(i_{\text{obsd}})^2$$

The principal magnetic axis was taken along the lanthanide–donor atom bond.

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[3] I. M. Armitage, G. Dansmore, L. S. Hall, and A. G. Marshall, *Can. J. Chem.*, **50**, 2119 (1972).

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[5] R. E. Davis and R. M. Willcott III in "Nuclear Magnetic Resonance Shift Reagents", E. Siever, Ed., Academic Press, New York and London, 1973, p 146.

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Table I. Agreement Factors R (%) for Various Conformation of 2 As Determined by Quantitative LIS Measurements

	binding site		
conformation	O(1)	N(4)	C(2)O
2a	19.0	12.1	74.2
2b	31.9	24.9	30.6
2c	34.4	14.3	1.5
2d	27.3	8.6	27.7

Table II. Experimental and Calculated Bound Shifts for Nonaromatic Protons in the Conformer 2c, as well as the Parameters Which Define the Position of the Praseodymium Atom

	bound shift, ppm			bound shift, ppm	
proton	exptl[a]	calcd	proton	exptl[a]	calcd
C(6)H	6.06	6.06	C(1′)H	14.30	14.31
C(6)H	6.06	6.17	$C(2')H_3$	7.19	7.46
C(3)H	17.07	16.93	$C(2'')H_3$	7.23	7.42

parameter	value	parameter	value	parameter	value
ρ^b	2.3	ϑ^c	148.1	φ^d	104.0

[a] Obtained on a 60-MHz instrument. [b] Bond distance Pr-C(2)O in Å. [c] Pr-C(2)O-C(2) bond angle in degrees. [d] Dihedral angle C(3)-C(2) relative to C(2)O-Pr, measured counterclockwise along the C(2)-C(2)O bond.

Calculations were performed for all four conformations **2a–d**, as well as for O(1), N(4), and C(2)O as possible binding sites.

It seems likely that the substrate does not behave as a bidentate ligand, since the double complexation which involves the nitrogen and one of the two oxygens is precluded by the bulkiness of $Pr(fod)_3$, and that involving the two oxygens should require a very small C2-C(2)O-Pr bond angle, which actually affords high R values. The starting geometries were obtained by using standard bond lengths and bond angles[6] and dihedral angles deduced from Dreiding models.

The lanthanide–donor atom bond distance was restricted within the reasonable limits of 1.0–3.5 Å.

The conformation of the isopropyl group relative to the ring was expressed by means of the dihedral angle ψ between the proton on C(3) and that within the isopropyl group, and it was considered as a variable parameter in the minimization of the R value.

Within the limits imposed on the lanthanide–donor atom bond distance, a good R value was obtained only for the conformation **2c** with C(2)O as binding site (see Table I). For the other conformations of the substrate–$Pr(fod)_3$ complex, much poorer agreement was found.

To estimate the confidence level at which these conformations must be rejected, we observed that the ratio between the two best R values in Table I (i.e., 8.6 and 1.5) is 5.73, which gives a probability for conformation **2c** with C(2)O as the binding site very close to 90%, taking into account that there are six experimental data, five unknowns, and therefore one degree of freedom.[7] For the other conformations the ratios between their R values and the best R (i.e., 1.5) are much higher, and this allowed us to reject them.

Since conformation **2c** deserved further consideration, the R value was then minimized with respect to the dihedral angles of the ring for this conformation, affording small changes in the agreement factor. This reveals that the proposed geometry is satisfactory. Calculated and experimental bound shifts, as well as the parameters which define the position of the praseodymium atom, are given in the Table II.

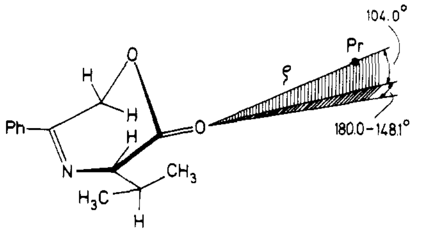

Figure 1. Schematic representation of the geometry of the **2c**–praseodymium complex.

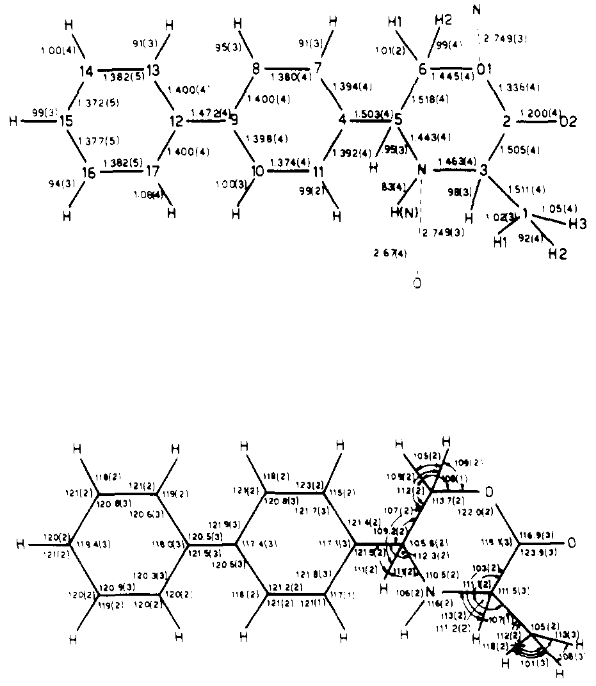

Figure 2. Bond distances (Å) with the atom numbering scheme and angles (deg) for compound **1**.

The position of the lanthanide is revealed to be on the face opposite the bulky isopropyl group, while the conformation of this group is determined by the dihedral angle ψ = 172.2°. A schematic representation of the complex **2c** lanthanide is given in the Figure 1. Thus the conformation **2c** turned out to be the one present in solution and the carbonyl oxygen the binding site for the lanthanide in the complex. This result is in complete accordance with the observed[1] stereochemical outcome of hydrogenation, as well as the sequence of the stabilities of the four conformations studied. Conformation **2b**, which we proposed[1] as the compound in the solution controlling the high stereoselectivity of the hydrogen approach, should be energetically less stable than **2a**, since it allows high nonbonding interaction between two large groups at C(3) and C(5). On the other hand, **2c** is the most stable of the two other conformations. In conclusion, conformation **2c** should give on hydrogenation 3,5-cis relative configurations, i.e., products with 3S,5R absolute configurations.

This was confirmed by the crystal structure determination of (3S,5R)-3-methyl-5-(4′-biphenylyl)-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**1**).

The crystal structure of **1** consists of independent molecules linked together along the axis by a strong hydrogen N-H···O(1) bond of 2.748 Å. The structure of the molecule may be described in terms of three planes: the two phenyl

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[6] J. A. Pople and D. H. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, London and New York, 1970, pp 110–3.

[7] O. Hofer, *Top. Stereochem.*, 9, 129 (1976).

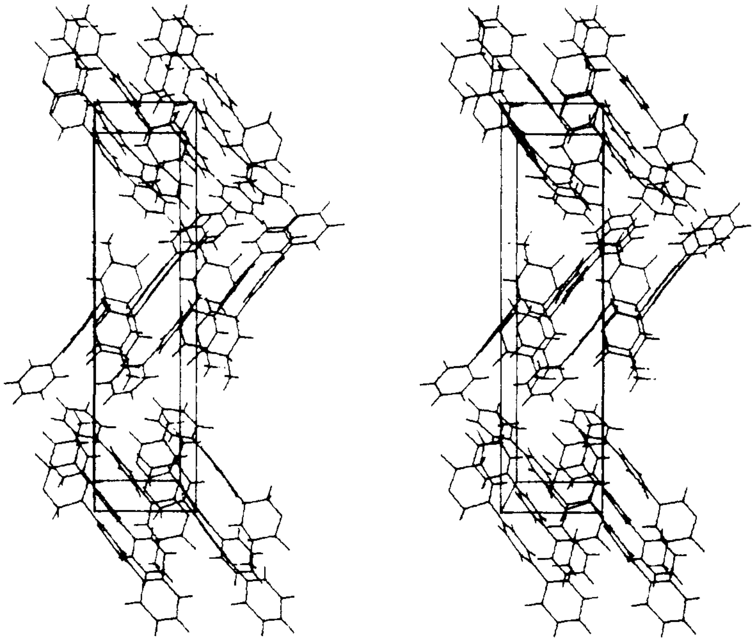

Figure 3. Stereoscopic view along the *c* axis of the unit cell of compound 1.

Table III. Atomic Positional Parameters and H Thermal Parameters (× 10³) with Estimated Standard Deviations in Parentheses for the Crystal Structure of 1

	x	*y*	*z*		*x*	*y*	*z*
O(1)	−0.5068 (3)	1.0544 (1)	0.0058 (3)	C(8)	0.2197 (5)	0.9189 (1)	0.1758 (3)
O(2)	−0.5813 (4)	1.1415 (1)	0.0219 (3)	C(9)	0.3128 (5)	0.8867 (1)	0.0699 (3)
N	−0.0666 (4)	1.0725 (1)	0.0551 (2)	C(10)	0.2581 (6)	0.8998 (1)	−0.0684 (3)
C(1)	−0.1416 (6)	1.1711 (1)	0.0899 (4)	C(11)	0.1194 (5)	0.9434 (1)	−0.0979 (3)
C(2)	−0.4403 (5)	1.1069 (1)	0.0146 (3)	C(12)	0.4717 (5)	0.8428 (1)	−0.1039 (3)
C(3)	−0.1978 (4)	1.1196 (1)	0.0080 (3)	C(13)	0.4345 (6)	0.8058 (1)	0.2140 (3)
C(4)	0.0298 (4)	0.9762 (1)	0.0076 (3)	C(14)	0.5899 (7)	0.7662 (1)	0.2467 (4)
C(5)	−0.1199 (5)	1.0239 (1)	−0.0253 (3)	C(15)	0.7837 (7)	0.7623 (1)	0.1726 (4)
C(6)	−0.3542 (5)	1.0088 (1)	0.0147 (4)	C(16)	0.8226 (6)	0.7984 (1)	0.0646 (4)
C(7)	0.0822 (5)	0.9623 (1)	0.1449 (3)	C(17)	0.6702 (5)	0.8385 (1)	0.0302 (3)

	x	*y*	*z*	U_{iso}, Å²		*x*	*y*	*z*	U_{iso}, Å²
H(N)	0.068 (7)	1.076 (1)	0.050 (4)	92 (13)	H(C8)	0.257 (5)	0.909 (1)	0.275 (3)	45 (7)
H1(C1)	−0.224 (6)	1.205 (1)	0.053 (3)	69 (10)	H(C10)	0.319 (5)	0.880 (1)	−0.144 (3)	49 (8)
H2(C1)	−0.180 (6)	1.172 (1)	0.183 (4)	91 (11)	H(C11)	0.084 (6)	0.954 (1)	−0.187 (3)	64 (9)
H3(C1)	0.030 (7)	1.175 (1)	0.083 (4)	86 (11)	H(C13)	0.283 (6)	0.808 (1)	0.273 (3)	70 (10)
H(C3)	−0.175 (5)	1.128 (1)	−0.091 (3)	50 (8)	H(C14)	0.559 (5)	0.741 (1)	0.319 (3)	50 (8)
H(C5)	−0.120 (6)	1.032 (1)	−0.123 (4)	79 (10)	H(C15)	0.890 (6)	0.732 (1)	0.192 (3)	77 (10)
H1(C6)	−0.414 (4)	0.977 (1)	−0.044 (3)	34 (7)	H(C16)	0.959 (6)	0.795 (1)	0.006 (4)	76 (10)
H2(C6)	−0.354 (7)	0.995 (1)	0.112 (4)	81 (11)	H(C17)	0.692 (5)	0.861 (1)	−0.044 (3)	46 (8)
H(C7)	0.025 (4)	0.987 (1)	0.219 (3)	39 (7)					

rings and the oxazine ring if the plane through C(3)–C(2)–O(2)–O(1) is taken as a basic plane of the oxazine ring. The planes of the two phenyl rings make an angle of 45.2°, while the plane of the phenyl ring linked to the oxazine ring makes an angle of 87.2° with it. The long molecular axis through C(15)–C(12)–C(9)–C(4)–C(5) is not a straight line; the lines connecting C(15)–C(12) and C(9)–C(4)–C(5) make an angle of 5.9°. As shown in Figure 2 the bond lengths and angles in the oxazine ring as well as in the aromatic rings are within expected values, although as far as we know, no previous structure analysis of 1,4-oxazine and its derivatives has been reported so that no direct comparisons can be made. The bond lengths C(7)–C(8) and C(10)–C(11) within the first phenyl ring, as well as C(13)–C(14) and C(16)–C(17) within the second phenyl ring, are a little shorter than the values found for such bonds in the structure of biphenyl, as found at 110 K (1.391 and 1.385 Å)[8] and at room temperature (1.406 and 1.425 Å).[9] The C–C bond between the two phenyl rings of 1.472 Å is the same as the mean value (1.473 Å) of such bonds found by Casalone et al.[10] but significantly shorter than the values found by other authors.[8] Regarding the 1,4-oxazin-2-one ring, the two most interesting data are the *R* configuration of the chiral center C(5) and a quasi-boat conformation. All other details can be deduced from Figure 2, while Figure 3 gives a stereoscopic view of the molecular packing.

Experimental Section

Compounds 1 and 2 have been prepared as described[2] and purified by repeated crystallizations from petroleum ether and ethanol, respectively.

NMR spectra were recorded on a Perkin-Elmer R 12A spectrometer, equipped with internal lock facilities. Me_4Si was used as the locking signal. LIS–NMR measurements have been per-

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[9] J. Trotter, *Acta Crystallogr.*, **11**, 1135 (1961).

[10] G. Casalone, C. Mariani, A. Mugnoli, and M. Simonetta, *Acta Crystallogr., Sect. B*, **25**, 1741 (1969).

Table IV. Thermal Parameters of Nonhydrogen Atoms ($\times 10^3$), with Estimated Standard Deviations in Parentheses, for Compound 1

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	289 (9)	798 (13)	747 (13)	−51 (10)	−55 (11)	70 (13)
O(2)	445 (13)	785 (16)	1072 (20)	147 (13)	−61 (16)	−134 (16)
N	300 (11)	563 (15)	491 (13)	−10 (11)	−33 (11)	−43 (11)
C(1)	526 (19)	538 (19)	828 (24)	19 (16)	−25 (19)	−154 (18)
C(2)	336 (14)	782 (22)	459 (16)	42 (15)	−45 (14)	−53 (17)
C(3)	361 (14)	517 (16)	466 (16)	−32 (13)	10 (14)	−29 (15)
C(4)	366 (14)	587 (17)	375 (14)	−55 (13)	−1 (13)	−11 (14)
C(5)	359 (14)	593 (17)	337 (13)	−50 (13)	1 (12)	23 (12)
C(6)	388 (15)	616 (20)	588 (18)	−113 (14)	−76 (16)	79 (17)
C(7)	447 (17)	572 (18)	386 (15)	71 (16)	37 (14)	−33 (13)
C(8)	450 (16)	570 (17)	393 (15)	16 (15)	18 (13)	−8 (14)
C(9)	397 (15)	416 (15)	477 (16)	−84 (13)	20 (18)	28 (13)
C(10)	556 (18)	534 (18)	395 (15)	31 (16)	48 (15)	−93 (14)
C(11)	536 (18)	457 (16)	369 (14)	−36 (15)	−25 (14)	−7 (12)
C(12)	410 (15)	480 (16)	451 (15)	−63 (14)	−33 (14)	−71 (14)
C(13)	529 (19)	440 (17)	563 (18)	−56 (16)	−25 (16)	30 (14)
C(19)	694 (24)	521 (19)	606 (19)	−30 (18)	−125 (21)	68 (16)
C(15)	601 (22)	515 (20)	769 (24)	65 (18)	−118 (20)	−36 (18)
C(16)	474 (18)	646 (21)	776 (24)	45 (17)	14 (19)	−113 (19)
C(17)	508 (18)	541 (18)	546 (19)	2 (16)	40 (16)	−8 (15)

formed with tris[2,2-bis(trideuteriomethyl)-1,1,1-trideuterio-6,6,7,7,8,8,8-heptafluorooctane-3,5-dionato]praseodymium(III) [$Pr(fod)_3$-d_{27}], from Aldrich (Uvasol grade), which was purified by sublimation at 0.1 mmHg. All measurements were performed for the range of substrate concentrations between 0.08 and 0.25 M, while ligand concentration was constant (0.008 M). All manipulations with this reagent, solvents, and compound **2** were carried out in a glovebox which was continuously flushed with dry nitrogen. All other experimental details have been recently described.[11]

Calculations were performed on a CDC 6200 computer using the programs for linear regression, simulation of spectra, and calculation of the bound shifts which were set up in our laboratories. In the bound-shifts program the minimization of the agreement factor was accomplished in two successive steps: a broad search with a Monte Carlo technique,[12] followed by a minimization with the SIMPLEX algorithm.[13]

Crystal Data for Compound 1: $C_{17}H_{17}NO_2$, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 6.071 (3) Å, b = 24.227 (12) Å, c = 9.558 (4) Å, V = 1405.8 Å^3, Z = 4, mol wt 265.998, d_{exptl} = 1.256 g cm^{-3}, φ = 0.7107 Å. Three-dimensional intensity data were collected on an automatic Philips PW-1100 diffractometer (ω mode, $4.58 < 2\theta < 64°$). The set of observed data (1840 reflections) was completed by introducing all the unobserved reflections (957 reflections) within $\sin \theta/\varphi = 0.75$, with a statistically evaluated amplitude.[14] The structure was solved by direct methods using the MULTAN program.[15] Thirty-one sets of phases were produced by MULTAN, and the E map calculated from the set with the highest "combined figure of merit" allowed all 20 nonhydrogen atoms to be identified. The positional and anisotropic thermal parameters of the nonhydrogen atoms were refined by full-matrix least-squares calculations. The positions of the hydrogen atoms on the biphenyl rings were calculated. The positions of the hydrogen atoms apart from those of the oxazine ring and the methyl group were found from a three-dimensional difference Fourier synthesis. All hydrogen atoms were then refined with isotropic temperature factors by using the XRAY-72 program.[16] The final reliability index was R = 0.057 (R_w = 0.059). The $w = 1/\sigma^2(F_o)$ weighted function was used, with $\sigma(F_o)$ as the structure factor standard deviation. Final positional and thermal parameters are given in Tables III and IV.[17]

Acknowledgment. The authors are grateful to Professor H. Staab and his staff, Abtailung Organische Chemie, Max Planck Institut für medizinische Forschung, Heidelberg, West Germany, for providing 360-MHz spectra of compound 2.

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(17) A list of structure factors for compound 1 can be obtained on request from the authors at the University of Zagreb. A program developed for the NMR bound-shift calculations can be obtained on request from A. Lisini (present address: Istituto di Chimica, Università degli Studi di Trieste, 34127 Trieste, Italy).

Investigation of *o*-Acetoxyaryl Radicals

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o-Acetoxyphenyl radicals (**4a**) and 3-methyl-2-acetoxyphenyl radicals (**4b**) have been generated by decarboxylation of the corresponding benzoyloxy radicals. CIDNP studies and product analysis reveal no evidence for neighboring group participation by the acetoxy group or for acetoxy migration. The CIDNP investigations demonstrate that *o*-acetoxybenzoyloxy radicals decarboxylate slower than benzoyloxy radicals.

The 1,2 migration of an acetoxy group in a carbonium ion is a well-documented process which involves the acetoxy-bridged species **1a**.[1] The corresponding rearrangement has been observed in β-acetoxy radicals, **2b**.[2] Oxy-