

A Stereochemical Investigation of 2-Methyl- and 2,5-Dimethyl-3-phenyl-1,3-oxazolidines using NMR

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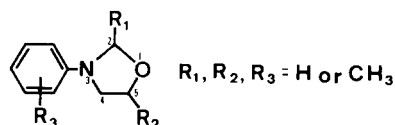
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The stereochemical properties of two 2-methyl-3-phenyl-1,3-oxazolidines and two of its 5-methyl substituted and four of its 2,5-dimethyl substituted derivatives have been investigated by pmr and cmr methods. The compounds of 2,5-dimethyl-3-phenyl-1,3-oxazolidines exist in isomeric *cis* and *trans* forms at the two methyl groups on the heterocyclic ring.

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Recently, the absolute configurations of oxazolidines have been investigated by means of pmr or cmr analysis. For example, the major oxazolidine diastereoisomer from the reaction of (-)-ephedrine with acetaldehyde has the configuration *2S* and the minor diastereoisomer *2R* [1]. On the other hand, Agami [2,3] reported that *p*-cyano- and *p*-nitrobenzaldehyde react with (-)-ephedrine in a chloroform yielding the *2S* and *2R* in a 50/50 ratio at the beginning and the *2S* configuration are the major products at the end of the reaction. When the condensation took place in methanol instead of chloroform, only the *2R* isomer showed up at the first stage of the reaction and the isomer *2S* predominated in the final product.

In this paper, we wish to report the syntheses and the stereochemical structures of 2-methyl- and 2,5-dimethyl-3-phenyl-1,3-oxazolidines.



EXPERIMENTAL

The nmr spectra were determined with JEOL model GSX-400 spectrometer in deuteriochloroform. The amino alcohols employed here were prepared by the reaction of the corresponding aniline with ethyl lactate, followed by lithium aluminium hydride reduction. Transformation of amino alcohols to 1,3-oxazolidines was accomplished as follows: (i) Mixture of amino alcohol and aldehyde was heated under reflux in benzene using a Dean-Stark trap (procedure A). (ii) Aldehyde and amino alcohol were stirred in methylene chloride over molecular sieves 3 Å at room temperature (procedure B).

Table 1

Physical Properties of Compounds 1-7

Compound No.	R ₁	R ₂	R ₃	Yield %	Procedure	Mp °C	Calcd. % (Found)		
							C	H	N
1	H	H	<i>p</i> -CH ₃	82	A	26.8-28.1	73.55 (73.59)	8.07 (8.03)	8.63 (8.58)
2	CH ₃	H	<i>p</i> -CH ₃	92 trace	B A	[a]	74.19 (74.54)	8.88 (8.53)	7.62 (7.90)
3	CH ₃	H	<i>o</i> -CH ₃	72 trace	B A	[a]	74.50	8.77	7.82
4	H	CH ₃	<i>p</i> -CH ₃	97	A	42.7-43.1	74.46	8.52	7.90
5	H	CH ₃	<i>o</i> -CH ₃	71	A	[a]	74.22	8.65	7.86
6	CH ₃	CH ₃	<i>p</i> -CH ₃	96 trace	B A	[a]	74.98 (75.35)	8.88 (8.96)	7.22 (7.32)
7	CH ₃	CH ₃	<i>o</i> -CH ₃	88 trace	B A	[a]	74.97	9.01	7.21

[a]: liquid

Results and Discussion.

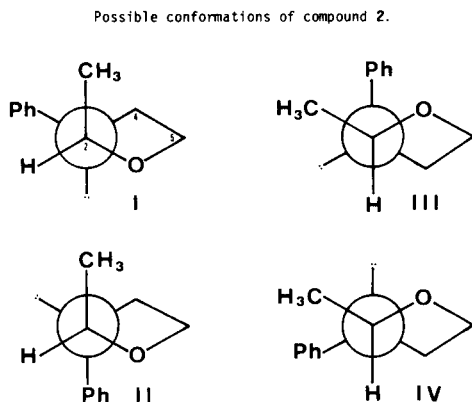
The products of these reactions and physical properties are summarized in Table 1. As shown in Table 1, the procedure A for the case of the 2-methyl substituted oxazolidines by azeotropic distillation with benzene did not give oxazolidines. However, the use of a molecular sieves at room temperature gave an acceptable and nearly quantitative yield of the oxazolidines. Oxazolidines are cyclic acetal analogues with one oxygen replaced by nitrogen. Therefore, it can be considered that the 2-methyl substituted oxazolidines are thermally unstable, decomposing appreciably at refluxed temperature, and are reactive toward moisture.

The cmr chemical shifts of the heterocyclic and methyl carbons attached to the C-2 and C-5 carbons are shown in Table 2. Chemical shift differences for the C-4 and/or C-5 carbons between compound **1** without a methyl group and

Table 2
Carbon-13 Chemical Shifts (δ) of Compounds 1-7

Compound No.	Chemical shifts, δ				
	C-2	C-4	C-5	2--CH ₃	5-CH ₃
1	81.6	46.5	67.2	—	—
2	87.6	47.9	65.0	20.2	—
3	90.1	51.5	64.7	19.8	—
4	81.2	53.1	74.5	—	18.8
5	83.9	58.2	72.1	—	19.2
6a	87.4	54.6	71.8	20.8	18.6
6b	87.9	55.5	72.8	20.5	18.8
7a	89.4	58.3	72.6	19.7	19.4
7b	88.5	59.0	72.3	20.1	19.8

Scheme 1



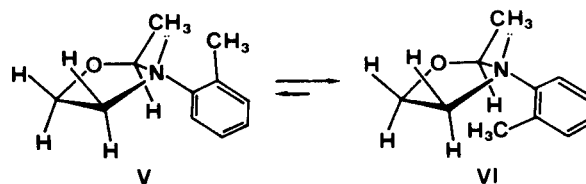
compound **2** with a methyl group at C-2 carbon are almost negligible. Therefore, it can be considered that the geometrical relationships of compound **2** between the C-4 and/or C-5 carbons and the methyl group attached to the C-2 carbon are γ -anti **III** or **IV** which are interconverted inversion at N-3 as shown in Scheme 1 viewing the Newman projections along the C-2-N-3 bond. In conformer

III, however, there will be repulsive van der Waals interactions between the phenyl group and the lone pair electrons on the oxygen atom which will force the conformational equilibrium toward **IV**. Conformers **I** or **II** are γ -gauche relationship between the methyl group attached to the C-2 carbon and the C-4 and/or C-5 carbons, respectively. Similar considerations are possible for compound **4**. Namely, the C-2 carbon in compound **4** appeared at approximately the same chemical shift compared with compound **1**. Such γ -effects are well documented in the chair conformers of thiane oxides [4] and methylated sulfites [5].

When a methyl substituent is present at the *ortho*-position (compound **3**), a δ -effect is operative. The lowfield shifts of 2.5 and 3.6 ppm at C-2 and C-4 carbons compared with compound **2** are due to the δ -effect. From the above results, if the preferred conformer of the compound **2** is **IV**, the rotational isomers **V** and **VI** for the compound **3** are possible as shown in Scheme 2. In rotamer **V**, there are steric repulsion between the methyl group attached to the

Scheme 2

Possible conformations of compound 3.



C-2 carbon and the *ortho*-substituted methyl group or the lone pair electrons on the nitrogen atom. Consequently, the preferred rotamer of compound **3** should be **VI** in which the position of the *ortho*-methyl group has a tendency to far away from the methyl group attached to the C-2 carbon. From these arguments, it can be considered that the chemical shifts of the C-2 and C-4 carbons appeared lowerfield than those of compound **2**.

Substituent effects over four bonds are generally negligible in open-chain compounds, since the molecules can adopt conformations which minimize steric hindrance, so that no δ -effects are detected. However, in cases in which steric interactions can not be minimized significant deshielding δ -effects have been recognized [6-9]. Similar conformational arguments between the C-2 carbon and C-5 methyl group or δ -effect to C-2 and C-4 carbons are possible for compound **5**.

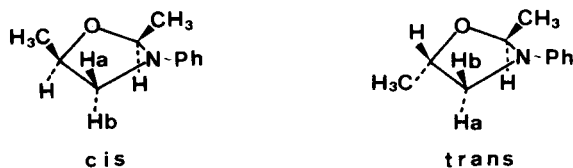
Table 3
PMR Chemical Shifts of Compounds 1-7

Compound No.	4-Ha	4-Hb	5-Hc	2-H	2-Me	5-Me	<i>cis</i> or <i>trans</i> %
1	3.38 (m)		4.13 (t)	4.83 (s)	—	—	—
2	3.32 (m)	3.55 (m)	4.03 (m) 4.16 (m)	5.20 (q)	1.40 (d)	—	—
3	3.09 (m)	3.65 (m)	3.92 (m) 4.08 (m)	5.15 (q)	1.25 (d)	—	—
4	2.82 (t)	3.37 (q)	4.23 (m)	4.68 (d) 4.78 (d)	—	1.33 (d)	—
5	2.93 (q)	3.40 (q)	4.18 (m)	4.75 (d) 4.81 (d)	—	1.29 (d)	—
6a	2.86 (t)	3.62 (q)	4.50 (m)	5.25 (q)	1.42 (d)	1.35 (d)	62
6b	3.19 (t)	3.49 (q)	4.12 (m)	5.18 (q)	1.44 (d)	1.38 (d)	38
7a	3.12 (q)	3.28 (q)	4.19 (m)	5.24 (q)	1.37 (d)	1.27 (d)	70
7b	2.67 (q)	3.73 (q)	4.43 (m)	5.04 (q)	1.30 (d)	1.20 (d)	30

In the case of 2,5-dimethyl-3-phenyl-1,3-oxazolidines, two isomers of types **a** and **b** can be obtained. The isomers of types **a** and **b** of compounds **6** and **7** indicate the possibility that the *cis* and *trans* configuration between the two methyl groups attached to the C-2 and C-5 carbons. It is possible to assign the substituent geometry of isomers **a**

Scheme 3

Possible isomers of compounds 6 and 7.



and **b** by means of pmr spectroscopy. The assignment of the *cis* or *trans* configuration is based mainly upon the 4-methylene protons Ha and Hb chemical shift. From Table

3, it is seen that the Ha proton absorbs a higher field compared with the Hb proton. This effect can be attributed mainly to the diamagnetic anisotropy of the C-methyl bond and is found in many *cis-trans* isomer pairs of three- to five-membered ring compounds [10,11].

A methyl group has the tendency to shield a neighboring substituent in *trans* orientation. Consequently, the methyl group at C-5 carbon will shield the Ha proton so as to shift the Ha proton to a higher field. The chemical shifts of remaining protons on the heterocyclic ring were assigned by comparison of the observed signal intensity.

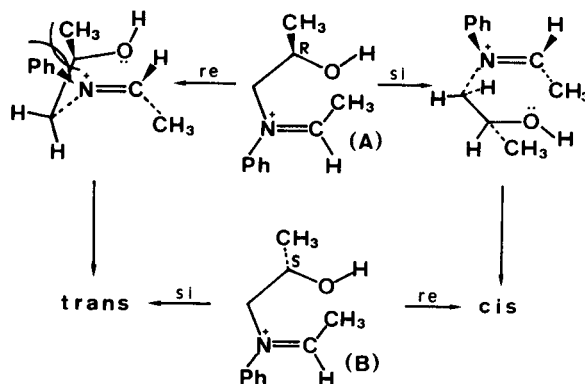
The relative proportion of the *cis* and *trans* forms form-

ed was determined by integrals of the area under the two clearly resolved Ha or Hb protons. The ratio of the *cis* and *trans* is shown in Table 3. The *cis* isomers were preferentially obtained in all cases. Moreover, the product ratio, *cis/trans*, depended on the position of substituent on the phenyl ring, that is, the ratio of compounds **7** was somewhat higher than that of compounds **6**.

The formation of oxazolidine from aldehyde and amino alcohol probably proceeds *via* reversible steps, in fact, this mechanism was deduced from the well-known reverse reaction: oxazolidine hydrolysis [12,13]. Therefore, the stereo-directing step can be assumed the intra-molecular addition of the hydroxy group onto the iminium intermediate. If the iminium ion is the intermediate, the preferred geometry of iminium ion can be considered an *E* form

Scheme 4

Cyclization mechanisms from iminium ion.



because of the steric interaction between the phenyl and the methyl groups attached to the sp^2 carbon. The cyclization from (E)-iminium intermediate can be explained *via* the cyclic models **A** and **B**, as outlined in Scheme 4: the major *cis* isomer from **A** is formed by attack of the hydroxy group to the prochiral sp^2 carbon from the less hindered *si* face because of the steric interaction between the bulky phenyl group and the methyl group adjacent to the hydroxy group. On the other hand, if the initial attack of the hydroxy group takes place from the *re* diastereoface, the major diastereoisomer should be the *trans* form but there is here a 1,3-diaxial interaction between the phenyl and the methyl groups adjacent to the hydroxy group. Similarly, it can be considered that attack of the hydroxy group onto the *re* face of the iminium intermediate **B** is better suited for cyclization as it exhibits fewer interactions between the phenyl and the methyl groups and leads to the *cis* isomer.

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