# Synthesis and Spectral Behavior of 5-Methyl-3-phenyl-1,3-oxazolidin-2-ones Using NMR



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Heterocyclic compounds of four 5-methyl-3-phenyl-1,3-oxazolidin-2-ones have been synthesized by the reaction of *N*-2-hydroxyethyl- or *N*-2-hydroxypropylanilines with phosgene in the presence of pyridine. From the spectral behavior, the title compounds are found to exist in the *trans* and *cis* forms.

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The reaction of organic isocyanates with 1,2-epoxides has been reported to yield 1,3-oxazolidin-2-ones. Most workers [1,2] reported the formation of only the 5-substituted 1,3-oxazolidin-2-ones from the reaction of an isocyanate with an unsymmetrically substituted epoxide. On the other hand, Herweh [3] reported the formation of two isomeric 1,3-oxazolidin-2-ones, 5-substituted and 4-substituted isomers, from the reaction of an isocyanate with an unsymmetrically substituted epoxide. However, existence of stereoisomers of 5- or 4-substituted 1,3-oxazolidin-2-one appears to be still lacking in the literature.

In this paper we wish to report the syntheses of two stereoisomers of 5-methyl-3-phenyl-1,3-oxazolidin-2-ones by the reaction of amino alcohol with phosgene.

## EXPERIMENTAL

All the melting points are uncorrected. Pmr spectra were determined with JEOL Model JNM PMX-60 and JNM GX-400 spectrometers in deuteriochloroform. Cmr spectra were obtained using Hitachi R-90H FT spectrometer operating at 22.6 MHz, with complete proton decoupling. The pulse width and repetition times were 12 $\mu$ s for 45° pulse and 4 s, respectively. *N*-2-Hydroxyethyl- and *N*-2-hydroxypropylanilines were prepared by the reaction of the corresponding anilines with ethylene oxide or propylene oxide.

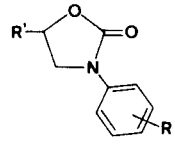
## Results and Discussion.

Transformation of amino alcohols to 5-methyl-3-phenyl-1,3-oxazolidin-2-ones **1-4** was accomplished by the reaction with phosgene in ethyl acetate. A slight excess of pyridine was used as the proton acceptor. The products of these reactions and the physical properties are summarized in Table 1. The structures of **1-4** are supported by analytical and spectral data. In each reaction, two isomers of types **a** and **b** can be separated by the use of silica gel column with hexane as an eluent. Existence of isomeric pairs requires that these heterocyclic rings possess an asymmetric carbon atom. This conclusion is reinforced by the compounds **5** and **6**. Thus, we tried the reaction of *N*-2-hydroxyethylaniline having no asymmetric carbon atom with phosgene by a similar synthetic method to **1-4**. In this reaction, the sole product was obtained. Furthermore, we attempted the measurement of cmr spectra of types **a** and **b** in benzene, respectively, at 90°. Consequently, the peaks of the newly formed isomer were not found in the compounds of types **a** and **b**. From the above results, it may be supposed that the isomers of types **a** and **b** are configurational isomers.

From the above considerations, some possible isomers of types **a** and **b** are illustrated in Scheme 1. Isomers I and II are the *cis* and *trans* configurations between the phenyl

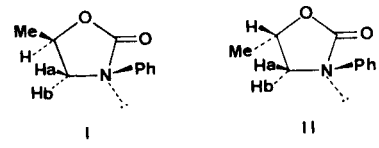
Table 1

Physical Properties of Compounds **1-6**



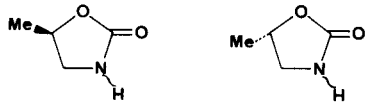

| Compound No. | R | R' | Yield % | Mp °C | Found (Calcd.) % C | H | N |
|---|---|---|---|---|---|---|---|
| **1a** | *m*-Cl | $CH_3$ | 46 | [a] | 56.46 | 4.78 | 6.64 |
| | | | | | (56.73 | (4.76) | (6.62) |
| **1b** | *m*-Cl | $CH_3$ | 10 | 86.0-87.0 | 56.45 | 4.78 | 6.63 |
| **2a** | *p*-Cl | $CH_3$ | 31 | 111.5-112.0 | 56.63 | 4.71 | 6.56 |
| **2b** | *p*-Cl | $CH_3$ | 14 | 84.0-84.5 | 56.57 | 4.71 | 6.52 |
| **3a** | *m*-$CH_3$ | $CH_3$ | 43 | [a] | 68.85 | 6.98 | 7.34 |
| | | | | | (69.09 | (6.85) | (7.33) |
| **3b** | *m*-$CH_3$ | $CH_3$ | 13 | 59.2-59.9 | 68.55 | 6.87 | 7.17 |
| **4a** | *p*-$CH_3$ | $CH_3$ | 35 | 61.3-61.8 | 68.82 | 6.88 | 7.20 |
| **4b** | *p*-$CH_3$ | $CH_3$ | 22 | 87.4-88.2 | 68.78 | 6.92 | 7.25 |
| **5** | *p*-Cl | H | 23 | 104.7-106.3 | 54.48 | 4.01 | 7.04 |
| | | | | | (54.70) | (4.08) | (7.09) |
| **6** | *m*-$CH_3$ | H | 24 | 94.0-95.0 | 67.75 | 6.18 | 7.81 |
| | | | | | (67.78) | (6.26) | (7.90) |

[a] Liquid




Scheme 1. Possible isomers of 5-methyl-3-phenyl-1,3 oxazolidin-2-ones.

and 5-methyl groups, respectively. Compounds I and II are a diastereomeric. Regarded from the standpoint that I and II are available from the hybridization of nitrogen, we tried the reaction of (2*R*)- and (2*S*)-2-hydroxypropylamine with phosgene by a synthetic method similar to **1-4**. In this reaction, the sole product was obtained and the pmr and cmr spectra of III and IV exhibited entirely the same spectra. But the specific rotation, $[\alpha]_D$, of III and IV was +20.5° and −20.9°, respectively. From this phenomena, it may be supposed that III and IV are available by the hydridization of nitrogen and the relationship between III and IV is thus apparently that of an enantiomorphic pair.




III IV

From the above results, we can consider that the nitrogen inversion for I and II is not possible because of sterically bulky substituent attached to the nitrogen.

The cmr chemical shift of the heterocyclic and methyl carbon attached to the C-5 are shown in Table 2. As can be seen in Table 2, chemical shift differences between types **a** and **b** for the heterocyclic ring carbons are almost negligible, while the methyl carbon of type **a** appeared to have a downfield shift of about 2 ppm more than those of type **b**. The downshift of the methyl carbon in type **a** relative to type **b** is due to the so-called δ shift between the 5-methyl and the phenyl group attached to the nitrogen of the *cis* form I. Nonbonded interactions between the 5-methyl and the phenyl group in the *cis* form I are probably sufficient to perturb the electron distribution about the 5-methyl group and increase their deshielding. These δ-shifts are already a well known phenomenon [4,5]. On this basis, the structure of type **a** exists in the *cis* form I, whereas type **b** exists in the *trans* form II.

Table 2

CMR Chemical Shifts of Compounds **1-6**

| Compound No. | Chemical shifts, δ C-2 | C-4 | C-5 | 5-$CH_3$ |
|---|---|---|---|---|
| **1a** | 154.3 | 51.5 | 69.6 | 20.5 |
| **1b** | 155.0 | 52.1 | 68.5 | 18.4 |
| **2a** | 154.4 | 51.6 | 69.5 | 20.5 |
| **2b** | 155.3 | 52.1 | 68.6 | 18.3 |
| **3a** | 154.6 | 51.7 | 69.4 | 20.5 |
| **3b** | 155.6 | 52.4 | 68.6 | 18.4 |
| **4a** | 154.7 | 51.9 | 69.4 | 20.6 |
| **4b** | 155.7 | 52.5 | 68.6 | 18.4 |
| **5** | 154.9 | 45.0 | 61.3 | — |
| **6** | 155.0 | 45.3 | 61.2 | — |

As can be seen from Table 1, although there is steric repulsion between the 5-methyl and the phenyl group in the *cis* form compared with the *trans* form, the main product in this reaction is type **a**. Recently, Beckett [6] has reported a similar result for oxazolidine. Thus, the major oxazolidine diasteroisomer from the reaction of (-)-ephedrine with acetaldehyde has the configuration (2*S*,4*S*,5*R*)-(90%) and the minor diastereoisomer (2*R*,4*S*,5*R*)-2,3,4-trimethyl-5-phenyloxazolidine (10%).

The pmr spectra of the heterocyclic protons of **3a** and **3b** are shown in Figure 1 and Table 3. The 60 MHz pmr spectrum of **3a** consists of three distinct sets of multiplets.

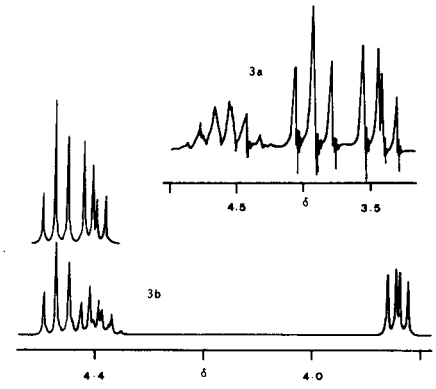



Figure 1. Pmr spectra of the compounds of **3a** and **3b**. A decoupling spectrum of the 5-methyl group shows above normal spectrum of **3b**.

Table 3

PMR Chemical Shifts of Compounds **1-6**

| Compound No. | Chemical shifts, δ Ha | Hb | 5-H | 5-$CH_3$ |
|---|---|---|---|---|
| **1a** | 3.48 (q) | 3.99 (t) | 4.64 (m) | 1.46 (d) |
| **1b** | 4.49 (t) | 3.92 (q) | 4.41 (m) | 1.30 (d) |
| **2a** | 3.47 (q) | 3.98 (t) | 4.65 (m) | 1.46 (d) |
| **2b** | 4.50 (t) | 3.87 (q) | 4.41 (m) | 1.25 (d) |
| **3a** | 3.40 (q) | 3.90 (t) | 4.57 (m) | 1.40 (d) |
| **3b** | 4.47 (t) | 3.85 (q) | 4.41 (m) | 1.24 (d) |
| **4a** | 3.49 (q) | 4.00 (t) | 4.62 (m) | 1.45 (d) |
| **4b** | 4.55 (t) | 4.00 (q) | 4.45 (m) | 1.30 (d) |
| **5** | 3.89 (m) | | 4.43 (m) | — |
| **6** | 3.98 (m) | | 4.29 (m) | — |

Chemical shift nonequivalence is observed for the diastereotopic methylene protons in the heterocyclic ring which appear as two multiplets at δ 3.40 (q) and 3.90 (t), for which a straight forward analysis was possible. On the other hand, though the 60 MHz pmr spectrum of **3b** only gave partially resolved multiplets for the heterocyclic protons, their signals clearly separated into individual peaks by the use of 400 MHz pmr spectroscopy as shown in Figure 1. The spectrum of **3b** consisted of three signals centered at δ 3.85 (q), 4.41 (m) and 4.47 (t).

Anteunis *et al* [7] have reported the pmr spectra of various substituted 1,3-dioxolanes. The pseudo-axial hydrogen of 2,2,4-trimethyl-, *trans*-2,4-dimethyl-, and *cis*-2,4-dimethyl-1,3-dioxolane appears at higher field than the pseudo-equatorial hydrogen. This difference in chemical shift has been attributed to shielding of the axial hydrogen by the adjacent *cis*-methyl group. If this consideration can be extended to the methylene protons of Ha and Hb for the compound **3a**, the following considerations are possible. The Ha proton of the *cis* form I appears at higher field than that of the Hb proton since the configuration of Ha is the *cis* to the 5-methyl group. Conversely, the Ha proton of the *trans* form II appears at lower field than that of the Hb proton since the Hb proton is *cis* to the 5-methyl group. Therefore, the two multiplets of **3a** at $\delta$ 3.40 ($J_{trans}$ = 7.0 and $J_{gem}$ = 8.1 Hz) and 3.90 ($J_{cis}$ = 8.1 Hz) in Figure 1 were assigned to Ha and Hb protons, respectively. Similarly, two multiplets of **3b** at $\delta$ 3.85 ($J_{trans}$ = 5.6 and $J_{gem}$ = 8.1 Hz) and 4.47 ($J_{cis}$ = 8.1 Hz) were assigned to Hb and Ha protons, respectively.

## REFERENCES AND NOTES

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