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NOTE

^{1}H NMR Spectroscopic Studies of the Stability of an Oxazolidine Condensation Product

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Condensation of (−)-norephedrine with excess formaldehyde under mild conditions leads to formation of the 2:1 condensation product *N,N'*-methylenebis(4-methyl-5-phenyl)oxazolidine compared with the reaction with 1 mol of formaldehyde, which leads to 4-methyl-5-phenyloxazolidine. ^{1}H and ^{13}C NMR spectroscopy was used to monitor the stability of this compound and its decomposition products. The 2:1 condensation product is found to be stable in $CDC1_3$ but breaks down rapidly in CD_3OD to yield a 50:50 mixture of 4-methyl-5-phenyloxazolidine and 3-hydroxymethyl-4-methyl-5-phenyloxazolidine. Upon addition of D_2O to this equimolar mixture, the latter compound decomposes to norephedrine and formaldehyde, whereas the former compound is stable. © **1997 by John Wiley & Sons, Ltd.**

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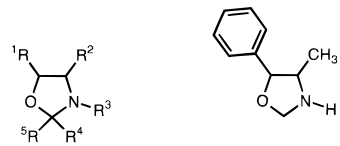
INTRODUCTION

Oxazolidine derivatives (**1**) have a variety of uses, including their application as bactericides,[1] fungicides[1] and herbicides[2] (Scheme 1). Several members of this class have also undergone trials as mosquito repellents[3] and tanning agents.[4]

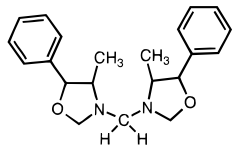
In previous work in this laboratory,[5] substituents R^1–R^5 were varied systematically and their electronic and steric effects on the stability of the oxazolidine system examined. As part of that work there was interest in synthesizing the compound with $R^1 = C_6H_5$, $R^2 = CH_3$ and $R^3 = R^4 = R^5 = H$ (**2**). This compound had previously been reported and characterized by ^{13}C and ^{1}H NMR.[6] In the current study, the synthesis of this compound was attempted using a route that has been widely applied for other oxazolidine derivatives, that is, the condensation of the appropriate β-amino alcohol with an aldehyde (Scheme 2).

The reaction appeared to proceed smoothly and yielded a single product. However, on examination of the ^{13}C and ^{1}H NMR spectra it became apparent that the product was not **2**, as expected, but a 2:1 condensation product **3** (Scheme 1). Further investigation revealed that a condensation product would, indeed, be expected if an excess of formaldehyde were used in the reaction compared with the single molar equivalent required for production of **2**.

The 2:1 condensation product has also been reported previously,[7] although its ^{13}C and ^{1}H NMR spectral properties have not been characterized. It was of interest to characterize its spectra fully and examine its stability in a similar manner to that of other stability



1 **2**



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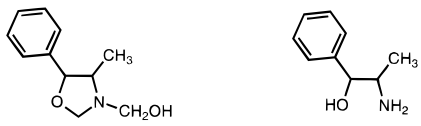
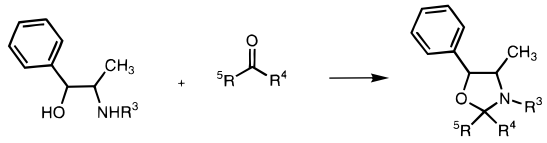


4 **5**

Scheme 1. Structures of compounds **1**–**5**.



Scheme 2.

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studies on oxazines and oxazolidines recently carried out in this laboratory.[5] In the course of this work it became apparent that in some solvents the condensation compound is stable, whereas in others it rapidly decomposes to yield two compounds, the desired oxazolidine **2** and the hydroxymethyl derivative **4** (Scheme 1), which on addition of water, break down at substantially different rates, **2** being essentially stable and **4** breaking down readily.

RESULTS

Following the reaction of norephedrine (**5**) with formaldehyde under the conditions described in the Experimental section, a single product was obtained. The compound was dissolved in $CDC1_3$ and its ^{13}C NMR spectrum recorded. The nine observed peaks have shifts consistent with structure **3**. The peak which identifies the compound as a condensation product is that at 72.6 ppm, characteristic of a methylene group between two nitrogens. Likewise in the ^1H NMR spectrum, a unique peak integrating to two protons occurs at 3.64 ppm. The remaining ^1H and ^{13}C shifts are consistent with the proposed structure for **3**, as are the mass spectral data, which show a molecular ion at m/z 338. Infrared data also support the proposed structure.

In contrast to the NMR data reported in the Experimental section for a $CDC1_3$ solution of **3**, two sets of resonances of similar intensity are observed in CD_3OD. This suggests that the compound breaks down into two different species in CD_3OD. As noted below, it was subsequently determined that it was residual water in the CD_3OD solvent that initiated the breakdown of **3**. Analysis of the observed ^1H and ^{13}C chemical shifts shows that the two compounds are **2** and **4**. These NMR spectral data are summarized in Tables 1 and 2. Peaks in the ^1H NMR spectrum were attributed to one or other of the compounds in the mixture by analysis of the two-dimensional DQF-COSY spectrum and by monitoring peak intensities in a stability study, described below, in which there is selective decomposition of **4**.

In the course of preparing samples in CD_3OD for ^{13}C NMR studies, it was found that the use of a higher concentration of **3** (0.25 M) than was used in the initial ^1H experiments allowed temporary observation of **3** itself as well as the two hydrolysis products. Spectral assignments for **3** in CD_3OD are given in Tables 3 and 4. However, after the NMR solution had been left to stand for 15 min, residual water in the solvent resulted in complete decomposition of **3** to the oxazolidine hydrolysis products **2** and **4**. It appears that traces of water in the CD_3OD are sufficient to decompose the condensation product almost instantaneously when it is present at a concentration of *ca* 0.03 M, but that breakdown occurs over the course of minutes at a concentration of 0.25 M.

Following initial breakdown to a mixture of two compounds when **3** is added to methanol, the solution remained stable for several days, there being no change in the relative intensities of peaks in the spectrum. However, on addition of an excess (700 μl) of D_2O, one of the compounds decomposed. The compound identi-

Table 1. ^1H NMR spectral data for 2 and 4 in CD_3OD

	Chemical shift (ppm)			Coupling constant (Hz)	
Proton	2	4	Multiplicity	2	4
CH_3	0.72	0.65	d	6.7	6.9
H-4	3.52	3.58	dq	6.7, 6.8	6.6, 6.8
$H\text{-}2_B$	4.42	4.58	d	5.7	4.2
$H\text{-}2_A$	4.87	4.84	d	5.6	4.1
H-5	4.88	5.03	d	6.6	6.5
H-2′–H-6′	7.28	7.28	d	—	—
CH_2OH		4.23	s		

Table 2. ^{13}C NMR spectral data for 2 and 4 in CD_3OD

	Chemical shift (ppm)	
Carbon	2	4
C-4α	15.9	15.6
C-4	60.2	58.3
C-5	81.1	82.3
C-2	81.6	85.9
C-3α		84.2
C-2′, C-6′	126.9	126.9
C-4′	127.6	127.6
C-3′, C-5′	128.3	128.3
C-1′	140.0	139.9

Table 3. ^1H NMR spectral data for 3 in CD_3OD

Proton	Chemical shift (ppm)	Multiplicity	Coupling constant (Hz)
CH_3	0.68	d	6.8
H-4	3.59	dq	6.6, 6.8
$H\text{-}2_B$	4.50	d	4.5
$H\text{-}2_A$	4.90	d	4.4
H-5	5.09	d	6.6
H-2′–H-6′	7.31	m	—
CH_2OH	3.66	s	—

Table 4. ^{13}C NMR spectral data for 3 in CD_3OD

Carbon	Chemical shift (ppm)
C-4α	15.9
C-4	61.4
C-5	81.4
C-2	85.5
C-3α	81.4
C-2′, C-6′	126.9
C-4′	127.1
C-3′, C-5′	128.3
C-1′	139.9

fied as **2** apparently remains stable in solution under these conditions, whereas **4** breaks down over the course of several hours to yield norephedrine and formaldehyde. Confirmation that the product obtained from the breakdown in the presence of water is norephedrine is seen in Fig. 1, which shows the final spectrum from the decomposition experiment in the lower trace, while the upper trace shows the same sample to which an additional amount of pure norephedrine has been added. Peaks attributed to norephedrine in the decomposed mixture clearly increase in intensity in the spiked sample.

DISCUSSION

In previous studies of oxazolidine hydrolysis, it has been suggested that the breakdown occurs via a Schiff base intermediate.[8–12] If this mechanism also applies in the current case, it is of interest to determine why the hydrolysis occurs much more readily for **4** ($R^3 = CH_2OH$) relative to **2** ($R^3 = H$). Examination of trends in analogous compounds[5] suggests that intermediate breakdown rates occur for $R^3 = CH_3$ and C_6H_5. As the structures of the open-chain norephedrine derivatives and closed oxazolidine are similar, it is unlikely that the difference in apparent stability for this series is related to thermodynamic control of the reaction. In other words, the stabilization of the closed oxazolidines by the R^3 substituent is likely to be similar to that produced in the corresponding open compounds. Therefore, the differences in breakdown most likely arise from differential stabilization of intermediates or transition states.

It appears that the basicity of the oxazolidine nitrogen is the driving force causing the preferential hydrolysis of the *N*-hydroxymethyloxazolidine compound **4**. The oxazolidine nitrogen of **4** is more basic than that in the secondary amine **2** and this assists in the oxazolidine nitrogen of **4** donating electron density to form the cationic imine intermediate **I** shown in the proposed mechanism in Scheme 3. Further hydrolysis of **I** would result in the formation of the *N*,*N*′-dihydroxymethyl derivative **II**. The nitrogen in this intermediate would be susceptible to protonation followed by cleavage of formaldehyde to yield the N-hydroxymethyl-*β*-amino alcohol derivative **III**, which undergoes further decomposition to give norephedrine and another molecule of formaldehyde.

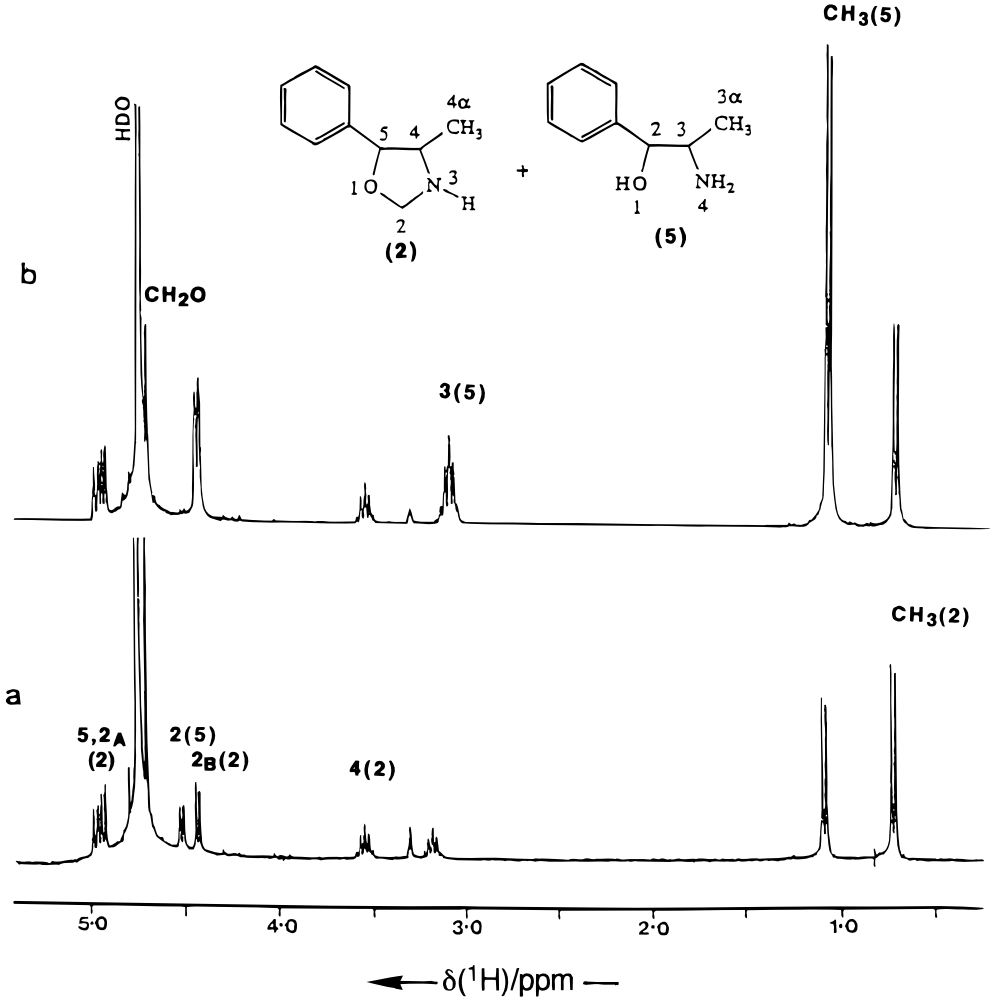
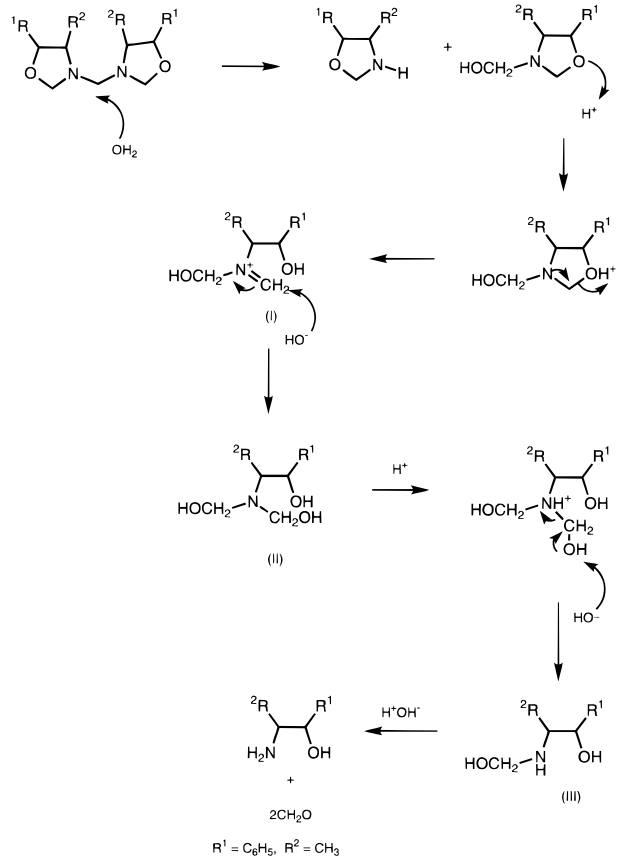
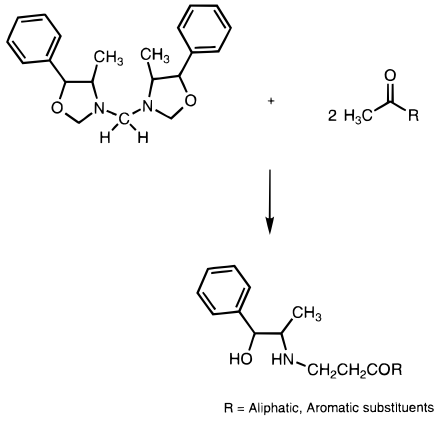


Figure 1. 300 MHz ^{1}H NMR spectra of **3** in CD_3OD. (a) Spectrum recorded 60 min after addition of 700 μl of D_2O; (b) spectrum recorded after addition of 20 mg of norephedrine to mixture (a).

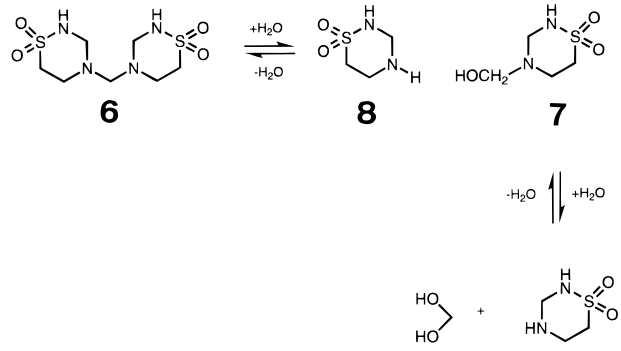


Scheme 3.

The current study has demonstrated the reactive nature of the *N*,*N*′-methylene bridge in the 2:1 condensation product in the presence of H_2O and has shown that there is an interesting and significant difference in the rate of breakdown of the two hydrolysis products, which differ only in their *N*-substituent. Previous workers[7] have utilised the unstable and reactive nature of the *N*,*N*′-methylene bridge in the synthesis of a number of *N*-substituted norephedrine derivatives by reacting the title compound with various acetate derivatives, as shown in Scheme 4. Other compounds of similar structure containing an *N*,*N*′-methylene bridge have also been shown to be extremely reactive. Taurolin (**6**), which is claimed to chemically inactivate bacterial endotoxins,[13] has been examined in aqueous solution and an equilibrium established, as outlined in Scheme 5.



Scheme 4.



Scheme 5.

Hydrolysis of the methylene bridge in this case[14] gave a related *N*-hydroxymethyl derivative **7** and the corresponding unsubstituted derivative **8**.

EXPERIMENTAL

Spectra

^1H and ^{13}C NMR spectra were recorded in 5 mm tubes at 25 °C on a Bruker AM 300 WB spectrometer. The deuterium signal of the solvent was used as the lock and tetramethylsilane (TMS) was the internal standard. One-dimensional NMR experiments were carried out with a spectral width of 3000 Hz, a 45° pulse angle, 16 384 data points and a repetition delay of 2.0 s. Sixteen scans were accumulated prior to Fourier transformation.

The DQF-COSY spectrum was recorded using a spectral width of 3000 Hz, a 90° pulse of 7.8 μs and a repetition delay of 2.0 s. For each FID, 32 scans were accumulated. The two-dimensional data were collected as a 512 × 1024-word matrix and were zero-filled to 1024 × 2048 prior to Fourier transformation. A sine-bell window function was applied in both dimensions.

Mass spectra and high-resolution mass spectra were obtained on a Jeol JMX DX-300 double-focusing instrument. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Methanol was distilled from iodine and magnesium and stored over 3 Å molecular sieves. The solution was concentrated on a Buchi rotary evaporator. Infrared spectra were measured KBr disks on a Bruker IFS66 FTIR spectrometer.

(4*R*,5*S*-4′*R*,5′*S*) *N*,*N*′-Methylene-bis-(4-methyl-5-phenyloxazolidine) (3)

A 38% formalin solution (2.17 m1, 27.5 mmo1) was added dropwise to a stirred solution of (−)-norephedrine (2.0 g, 13.0 mmo1) in methanol (20 ml). After refluxing for 2 h, the solution was cooled, filtered and the methanol reduced under vacuum. The white powder was recrystallized from methanol to give the 2:1 condensation product **3** as small, white needles (1.30 g, 61.4%), m.p. 100–101 °C (lit. m.p. 98–99 °C). Found: M^+ 338.197; $C_{21}H_{26}N_2O_2$ requires M^+ 338.200. V_{max}

3040, 2932, 1492, 1452, 1382, 1294, 1184, 1086, 1060, 1038, 714 cm^{-1}. MS: m/z 338 (M^+, 0.1%), 176 (100), 163 (2), 146 (80), 105 (53), 57 (43). ^1H NMR ($CDC1_3$); δ 0.69 [d, 6H, 2 × CH_3 (4α), $J = 6.9$ Hz], 3.48 (dq, 2H, 2 × H-4, $J = 6.5$, 6.9 Hz), 3.64 [s, 2H, CH_2(3α)], 4.52 (d, 2H, 2 × H-2_B, $J = 4.7$ Hz), 4.91 (d, 2H, 2 × H-2_A, $J = 4.7$ Hz), 5.08 (d, 2H, 2 × H − 5, $J = 6.5$ Hz), 7.30 (m, 10H, 2 × H-2′, H-3′, H-4′, H-5′, H-6′). ^{13}C NMR ($CDC1_3$): δ 15.3 (C-4α) 60.2 (C-4), 72.7 (C-3α), 80.3 (C-5), 85.2 (C-2), 126.5 (C-2′, C-6′) 127.2 (C-4′) 128.0 (C-3′, C-5′) 139.7 (C-1′).

Acknowledgement

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