Oxygen-17 and Carbon-13 Nuclear Magnetic Resonance Spectra of Thiophene- and Pyrrole-2-carboxaldehyde Condensation Products Prepared From Ephedrine Derivatives

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Natural abundance ^{17}O nmr (acquired in acetonitrile at 70°) and ^{13}C nmr (acquired in deuteriochloroform at 37°) spectroscopic data for four oxazolidines and related imino alcohols are reported: relationships of chemical shifts and ^{17}O line widths at half-heights to structures are discussed.

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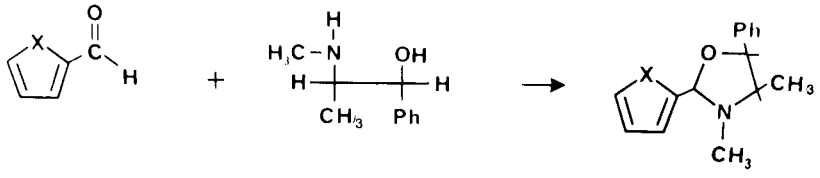
Condensation reactions between heterocyclic aldehydes and ephedrine derivatives result in the products shown in Figure 1. The products are substituted oxazolidines as expected from the secondary amines, ephedrine and pseudoephedrine. The imino alcohol tautomer is observed in solution from the condensation of the primary amine norephedrine with the aldehydes [1]. Similar oxazolidines have been examined for their role as intermediates in asymmetric synthesis [2] and as potential prodrugs [3,4]. Recently, mass spectra have been reported for other oxazolidines of ephedrine and pseudoephedrine prepared from aldehydes [5], from aliphatic ketones [6], and also from heterocyclic aldehydes [7], a number of which are currently being tested for ephedrine-like activity.

Confirmation of the structures of 3-alkyl-2,5-diphenyl-4-methyloxazolidines was established by ^{13}C nmr [8]. The literature contains information on the ^{17}O chemical shifts for cyclic ethers [9,10,11] and lactones [12], but no data has appeared on oxazolidines. This study examines the ^{13}C and ^{17}O chemical shifts and line widths of the ^{17}O signal in oxazolidines which have a second heterocyclic ring at the 2-position. It compares these chemical shifts to those observed for the imino alcohol tautomer. It also presents the differences observed between *cis* and *trans* isomers of the oxazolidine rings.

Results and Discussion.

The most dramatic difference in resonances in the ^{13}C and proton spectra of the condensation products was for the site of the original aldehyde functional group. The secondary amines, ephedrine and pseudoephedrine, incorporate that carbon at the 2-position of the oxazolidine ring while with the primary amine, norephedrine, it becomes an imine-carbon in the final product (Table 1). This carbon must adopt two distinct hybridizations in the two different structural types. In the oxazolidine derivatives the chemical shift of the proton at this position is about 5 ppm, which is in the region expected of a hydrogen on a tetrahedral carbon bonded to two heteroatoms. This pro-

Figure 1



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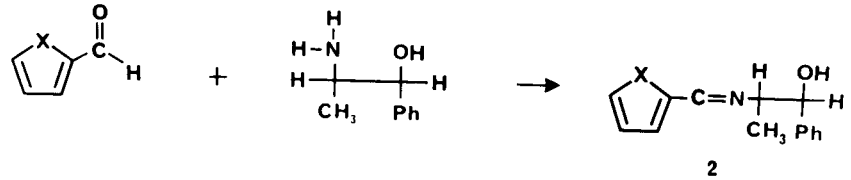

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1a, 1b, 2a; X = S; 1c, 1d, 2b; X = NH

ton appears slightly more deshielded in the ephedrine derivative, **1a** or **1c**, than the pseudoephedrine derivative. The chemical shifts of about 8 ppm in the imino alcohol derivatives **2a** and **2b**, while not as deshielded as the original aldehydes, are in the region expected for hydrogen bonded to the sp^2 hybrid carbon. The chemical shifts observed in the ^{13}C spectra for the carbon at this position show the same relative shifts (Table 1). In the oxazolidine derivatives the resonance is about 95 ppm as might be observed in a similar heterocyclic environment of the 2-position of 1,3-dioxane. However, the imino alcohol derivatives show a larger chemical shift to approximately 150 ppm, but not as large as in th original aldehydes. The change in functionality is indicated by the chemical shifts at this position in both ^1H and ^{13}C nmr spectra.

Table 1

Compound	$\delta^{17}O$	$\omega_{1/2}$Hz	$\delta^{13}C$	δ^1H
1a	73.76	428	94.45	5.28
1b	77.00	497	94.15	4.99
1c	68.04	330	93.20	5.15
1d	61.08	364	92.35	5.10
2a	[a]	[a]	153.6	8.28
2b	17.06	295	151.8	8.04
(2b)	-8.77			

[a] = ^{17}O spectrum was not available.

The ^{17}O chemical shifts (Table 1) for the oxazolidines in this series range from 61.08 ppm to 77.00 ppm downfield relative to the water reference. This value is between the reported values for tetrahydrofuran (16.2 ppm [10] or 18 ppm [9]) and furan (240 ppm [9]). The chemical shifts observed resemble those reported for 2,2-dimethyl-1,3-dioxolane of 61 ppm [13] and also for the 2,5-dimethyl-THF isomers, namely 66.7 and 74.5 ppm for the 1:1 mixture of *cis* and *trans* isomers [10]. The values observed for compound **2b** suggests a different structure. The possibility of two imino alcohol isomers with shifts of 17.06 ppm and −8.77 ppm would bracket the reported value for a structurally similar benzyl alcohol of 4 ppm [9].

The second adjoining heterocyclic ring at the 2-position of the oxazolidines is either a 2′-thienyl or a 2′-pyrrole ring. The oxygen of the oxazolidines is observed further downfield in both cases where the adjoining ring is 2′-thienyl, **1a** or **1b** as compared to 2′-pyrrole **1c** and **1d**. In the two 2′-thienyl examples, the shift is greatest for the *cis*-oxazolidine formed from ephedrine while in the 2′-pyrrole examples the *trans*-oxazolidine formed from pseudoephedrine is the most shifted. The line widths at half-heights, ($\omega_{1/2}$Hz) as shown in the table, appear to be related to the stereochemistry of the starting ephedrine derivative. The broader line widths are observed for *cis*-oxazolidines **1b** and **1d** from ephedrine. Additional examples of oxazolidines with adjoining heterocyclic rings are being prepared to confirm these initial findings and to determine if a meaningful trend exists.

EXPERIMENTAL

General Procedure for the Reaction of Heterocyclic Aldehydes with Amino Alcohols.

The compounds were synthesized by a condensation reaction between either thiophene 2-carboxaldehyde or pyrrole 2-carboxaldehyde and the appropriate ephedrine. Reagents and solvents were used as obtained from the manufacturers. In a typical experiment pyrrole 2-carboxaldehyde (0.95 g, 10 mmole) was dissolved in 75 ml of benzene to which was added ephedrine (1.65 g, 10 mmoles). The mixture was refluxed for two hours and water was removed in a Dean-Stark trap. Evaporation of solvent under reduced pressure left a solid residue which was **1d** (1.8 g) in 70% yield.

trans-2-(2′-Thienyl)-3,4-dimethyl-5-phenyloxazolidine (**1a**).

This compound was obtained as white crystals (ethanol/water), mp 82-83°; ir: ν CH 1330 cm^{-1}; ^1H nmr: δ 1.19 (d, 3H, 4-CH_3, J = 6.25 Hz), 2.29 (s, 3H, N-CH_3), 2.52 (qd, 1H, 4-H, J = 6.25, 8.75 Hz), 4.70 (d, 1H, 5-H, J = 8.75 Hz), 5.28 (s, 1H, 2-H), 6.9-7.4 (m, 8H thienyl and phenyl protons); ^{13}C nmr: δ 14.40 (4-CH_3), 35.68 (*N*-CH_3), 68.55 (4-C), 85.99 (5-C), 94.45 (2-C), 126-129 (8C, thienyl and phenyl carbons), 139.95 (1-phenyl), 144.82 (2′-thienyl); ms: (m/e) 259 (M^+), 153 (M^+-PhCHO).

Anal. Calcd. for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.22; H, 6.58; N, 5.12.

cis-2-(2′-Thienyl)-3,4-dimethyl-5-phenyloxazolidine (**1b**).

This compound was obtained as a cream colored solid (heptane), mp 61-62°; ir: ν CH 1335 cm^{-1}; ^1H nmr: δ 0.75 (d, 3H, 4-CH_3, J = 6.0 Hz), 2.22 (s, 3H, N-CH_3), 2.93 (qd, 1H, 4-H, J = 6.0, 8.0 Hz), 5.11 (d, 1H, 5-H, J = 8.0 Hz), 4.99 (s, 1H, 2-H), 6.9-7.4 (m, 8H thienyl and phenyl protons); ^{13}C nmr: δ 14.83 (4-CH_3), 35.75 (N-CH_3), 64.00 (4-C), 82.68 (5-C), 94.15 (2-C), 126-128 (8C, thienyl and phenyl carbons), 139.69 (1-phenyl), 142.88 (2′-thienyl); ms: (m/e) 259 (M^+), 153 (M^+-PhCHO).

Anal. Calcd. for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.14; H, 6.66; N, 5.35.

trans-2-(2′-Pyrrole)-3,4-dimethyl-5-phenyloxazolidine (**1c**).

This compound was obtained as a white powder (heptane), mp 101-102°; ir: ν NH 3307 cm^{-1}, ν CH 1375 cm^{-1}; ^1H nmr: δ 1.25 (d, 3H, 4-CH_3), J = 6 Hz), 2.25 (s, 3H, *N*-CH_3), 2.51 (qd, 1H, 4-H, J = 6, 9 Hz), 4.75 (d, 1H, 5-H, J = 9 Hz), 5.15 (s, 1H, 2-H), 6.2-7.4 (m, 8H pyrrole and phenyl protons); ^{13}C nmr: δ 14.58 (4-CH_3), 35.54 (N-CH_3), 68.69 (4-C), 85.84 (5-C), 93.20 (2-C), 108-119 (3C, pyrrole carbons), 126-129 (2′-pyrrole, 5C phenyl carbons), 140.57 (1-phenyl); ms: (m/e) 242 (M^+), 136 (M^+-PhCHO).

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.33; H, 7.50; N, 11.56. Found: C, 74.01; H, 7.50; N, 11.43.

cis-2-(2′-Pyrrole)-3,4-dimethyl-5-phenyloxazolidine (**1d**).

This compound was obtained as colorless crystals (heptane), mp 130-131°; ir: ν NH 3400 cm^{-1}, ν CH 1345 cm^{-1}; ^1H nmr: δ 0.76 (d, 3H, 4-CH_3, J = 6.82 Hz), 2.19 (s, 3H, *N*-CH_3), 2.92 (qd, 1H,

4-H, J = 6.82, 9.10 Hz), 5.10 (d, 1H, 5-H, J = 9.10 Hz), 4.82 (s, 1H, 2-H), 6.2-7.4 (m, 8H pyrrole and phenyl protons); ^{13}C nmr: δ 14.94 (4-CH_3), 35.82 (*N*-CH_3), 63.67 (4-C), 82.02 (5-C), 92.35 (2-C), 108-119 (3C, pyrrole carbons), 126-129 (2'-pyrrole, 5C phenyl carbons), 139.94 (1-phenyl); ms: (m/e) 242 (M^+), 136 (M^+-PhCHO).

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.33; H, 7.50; N, 11.56. Found: C, 74.41; H, 7.49; N, 11.54.

Thiophene-2-(2-imino-1-phenylpropan-1-ol) (**2a**).

This compound was obtained as a yellow oil, bp approximately 100° at 0.25 torr; ir: ν OH 3400 (b) cm^{-1}, ν C=N 1640 cm^{-1}; ^1H nmr: δ 1.11 (d, 3H, 2-CH_3, J = 6.3 Hz), 3.57 (qd, 1H, 2-H, J = 6.3, 3.9), 4.80 (d, 1H, 1-H, J = 3.9), 6.9-7.4 (m, 8H, thienyl and phenyl protons), 8.28 (s, 1H, imino proton); ^{13}C nmr: δ 16.15 (2-CH_3), 70.52 (2-C), 77.04 (1-C), 126-130 (8C, thienyl and phenyl carbons), 141.4 (1-phenyl), 153.6 (imino carbon); ms: (m/e) 246 (M + 1$^+$), 139 (M^+-PhCHO).

Anal. Calcd. for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.60; H, 6.13; N, 5.72.

Pyrrole-2-(2-imino-1-phenylpropan-1-ol) (**2b**).

This compound was obtained as white crystals, mp 73-74°; ir: ν NH 3300 cm^{-1}, ν C=N 1633 cm^{-1}; ^1H nmr: δ 1.12 (d, 3H, 2-CH_3, J = 6.1 Hz), 3.40 (qd, 1H, 2-H, J = 6.1, 2 Hz), 4.87 (d, 1H, 1-H, J = 2 Hz), 5.9-6.3 (m, 3H, pyrrole protons), 7.2-7.4 (m, 5-H, phenyl protons), 8.04 (s, 1H, imino proton); ^{13}C nmr: δ 15.42 (2-CH_3), 71.37 (2-C), 77.08 (1-C), 109-122 (3C pyrrole carbons), 126-130 (2'-pyrrole, 5C phenyl carbons), 142.07 (1-phenyl), 151.82 (imino carbon); ms: (m/e) 229 (m + 1$^+$), 122 (M^+-PhCHO).

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.68; H, 7.01; N, 12.28; O, 7.02. Found: C, 73.15; H, 7.55; N, 11.30; O, 6.57.

The spectra for ^{17}O were recorded on a Varian XL-400 spectrometer equipped with a broad-band probe operated at 54.2 MHz. All spectra on samples (0.5 to 1.25*M*) were acquired at natural abundance at 70° in deuterated acetonitrile containing water as an external reference. The instrument settings were: spectral width 44 kHz., 1024 data points, 90° pulse angle (45 ms pulse width). The ^1H nmr and ^{13}C nmr spectra were recorded on a Chemagnetic A-200 spectrometer equipped with a broad-band probe operated at 200 MHz for ^1H and 50.5 MHz for ^{13}C. All spectra on samples were acquired at natural abundance at 37° in deuterated chloroform containing TMS as an internal reference. Infrared spectra were recorded on a Beckman Acculab 10 or Bomem FTIR MB-100 in or on potassium bromide pellets. Melting points were obtained on a Perkin-Elmer DSC-4. Mass spectra were recorded on a Finnigan-MAT TQS-70 mass spectrometric system. Elemental analysis were obtained from either Oneida Research Services or Galbraith Laboratories.

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