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THERMAL EQUILIBRIUM BETWEEN "ISOXAZOLIDINE" AND "ENAMINE"

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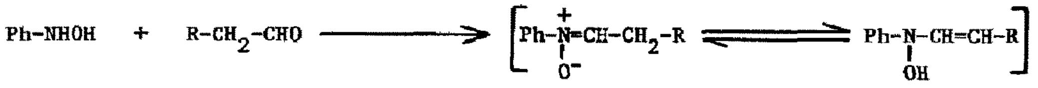
Summary: Nitrones formed from the reaction of *N*-phenylhydroxylamine and aldehydes dimerized to isoxazolidines. A new thermal equilibrium between isoxazolidine and *N*-hydroxyenamine in DMSO was studied by ^{1}H and ^{13}C NMR.

In general, the condensation reaction of *N*-substituted hydroxylamines with aldehydes gives nitrones. This method has been widely applied to prepare synthetically useful nitrones which have been used for the total synthesis of complex molecules such as alkaloids and β-lactam antibiotics[1]. The formation of nitrones **1a** and **1b** was reported by Utinger and Regenass in 1954[2]. However, the structure **1a** was revised[3], based on the ^{1}H NMR studies, as an isoxazolidine structure **2a** which is derived from the dimerization of **1a**. The formation of **2** can be envisaged as an 1,3-dipolar cycloaddition reaction of nitrone **1** to *N*-hydroxyenamine **1'** under the reaction conditions[4].

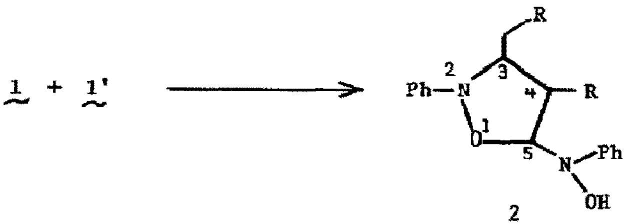
We now wish to report spectroscopic evidence of a new thermal equilibrium between isoxazolidine **2** and enamine **1'** by ^{1}H and ^{13}C NMR studies.



$$\text{Ph-NHOH} + \text{R-CH}_2\text{-CHO} \longrightarrow \left[\text{Ph-}\overset{+}{\underset{\text{O}^-}{\text{N}}}\text{=CH-CH}_2\text{-R} \rightleftharpoons \text{Ph-}\underset{\text{OH}}{\text{N}}\text{-CH=CH-R}\right]$$

1 **1'**

a: $R=CH_2CH_3$ b: $R=COOCH_2CH_3$
c: $R=CH_3$ d: $R=SO_2Ph$



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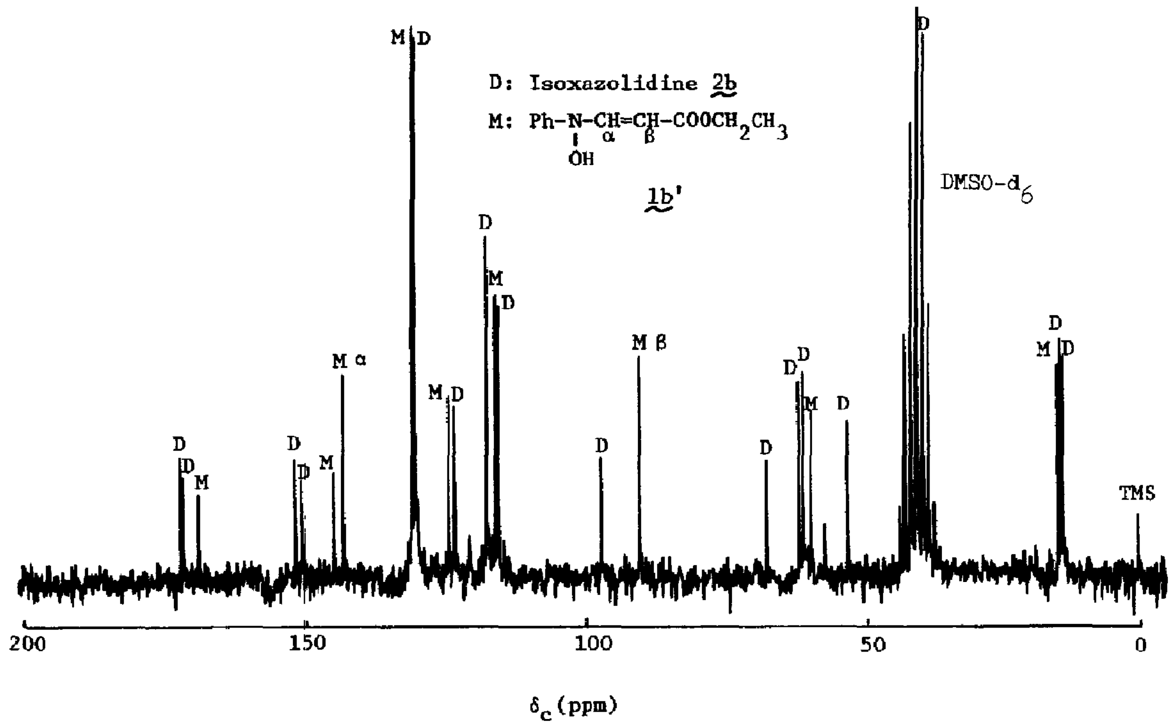
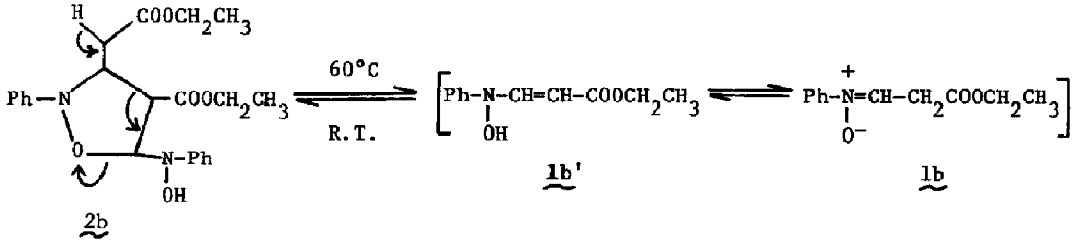


Fig. 1 The ^{13}C NMR spectrum of 2b in DMSO-d_6 after heating at 60°C for 3.5 hr.

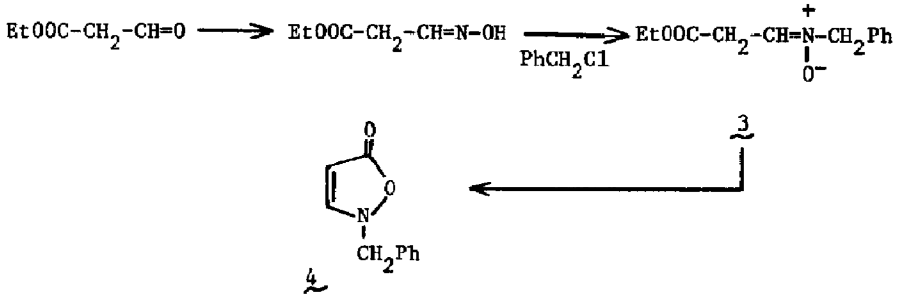
The reaction of N-phenylhydroxylamine with the sodium salt of ethyl formylacetate[7] in dry ether in the presence of acetic acid gave colorless needles (from ethanol), 2b, mp 120°C, mass spec. m/e = 414(M^+) by chemical ionization with methane. The structure of 2b, ethyl 4-ethoxycarbonyl-5-(N-hydroxyanilino)-2-phenylisoxazolidine-3-yl acetate, was identified unambiguously by ^{13}C NMR. Pertinent ^{13}C NMR spectral data for 2b and 2c are listed in Table 1[8]. Recently, isoxazolidine 2d formation from the reaction of N-phenylhydroxylamine and phenyl sulfonylacetylene has been reported[9].

An attempted thermolysis of 2b in refluxing toluene or chloroform gave no single product. On the other hand, heating a DMSO-d_6 solution of 2b at 60°C resulted in a clean reaction which was monitored by both ^1H and ^{13}C NMR. In the ^1H NMR of 2b, the doublet signal at δ=6.1 (J=6.0 Hz,H_5 in 2b), disappears after heating at 60°C for 12 hr, two new doublets at δ=5.13 and δ=7.94 (J=12 Hz) were observed which can be assigned to the olefinic hydrogens in enamine 1b'. As is shown in Fig. 1, the ^{13}C NMR spectrum of 2b after heating in DMSO-d_6 clearly suggested the conversion of 2b into 1b' without significant formation of 1b. Interestingly, the DMSO-d_6 solution of 1b' showed considerable dimerization to 2b after being allowed to stand in solution at room temperature for 24 hrs. Although the thermal retro 1,3-dipolar cycloaddition reaction of some isoxazolidines to corresponding nitrones and olefins is known[10], we could not observe any nitrone formation, probably due to its high reactivity and low equilibrium concentration[11].



In this thermal equilibration, the acidity of the methylene hydrogen attached at C_3 plays a key role. To prove this hypothesis, the isoxazolidine 2c was prepared from the reaction of N-phenylhydroxylamine and propionaldehydes in ether in the presence of anhydrous calcium chloride. As expected, the isoxazolidine 2c is completely stable under heating at 120°C in DMSO-d_6 due to the lack of acidity of the methylene group attached at C_3[12].

The attempted preparation of nitrone 3 from the reaction of the oxime of ethyl formylacetate with benzyl chloride gave only cyclized product 2-benzyl-2,3-dihydro-5-isoxazolone 4 in a low yield[13].



Thus, the nitrones 1 which are formed from the reaction of N-phenylhydroxylamine and aldehydes, dimerized immediately to an isoxazolidine[15] which when bearing an active methylene group at C_3, showed a thermal equilibrium between enamine and isoxazolidine via a retro 1,3-dipolar cycloaddition reaction. The synthetic use of this new reactive enamine 1' is understudy in our laboratories.

References and Notes

1) For a recent review of synthetic use of nitrones see; J. J. Tufariello, Accts. Chem. Res., 12, 396 (1979).

2) C. Ed. Utinger and F. A. Regenass, Helv. Chim. Acta, 37, 1892 (1954).

3) W. Kliegel, Tetrahedron Lett., 2627 (1969).

4) A nitrone prepared from N-phenylhydroxylamine and dimethyl acetylenedicarboxylate dimerized to isoxazolidines^{5,6}.

5) E. Winterfeldt, W. Krohn and H. Stracke, Chem. Ber., 102, 2346 (1969).

6) W. C. Agosta, J. Org. Chem., 26, 1724 (1961).

7) S. M. McElvain and R. L. Clarke, J. Am. Chem. Soc., 69, 2657 (1947).

8) Table 1. ^{13}C NMR Spectra of Isoxazolidines **2**.

Chemical Shifts

	C_3	C_4	C_5	CH_2 at C_3
2b	66.3(145)	52.1(136)	95.7(161)	38.6
2c	76.4	43.4	99.5	26.4

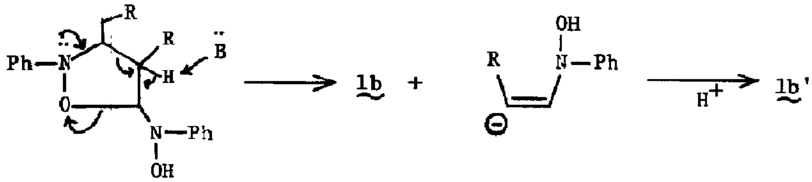
Solvent: DMSO-d_6; Chemical shifts downfield from internal TMS (δ=0.0)
$^{1}J_{CH}$ in Hz. is shown in parenthesis.

9) H. G. Aurich and K. Hahn, Chem. Ber., 112, 2769 (1979).

10) G. R. Delpierre and M. Lamchen, Proc. Chem. Soc., 386 (1960); M. Joucla, J. Hamelin, and R. Carrie, Bull. Soc. Chim. Fr., 3116 (1973); R. Huisgen, H. Hauck, R. Grashey and H. Seidl, Chem. Ber., 101, 2043 (1968).

11) Attempted isolation of enamine **1b**' failed and only **2b** was isolated in 87% yield.

12) Alternative mechanism is considered. We thank Dr. R. A. Firestone for stimulating discussions.



13) **4**: NMR(CDCl$_3$) δ4.7 (s,2H,PhCH$_2$), 5.14 (d,1H,J=3.3 Hz,H$_4$), 7.3 (s,5H,Ph) and 7.70 (d,1H, J=3.3 Hz,H$_3$). Similar formation of Δ^3-isoxazolone was observed^{14} during the reaction of t-butylhydroxylamine with ethyl phenylpropiolate.

14) H. G. Aurich, K. Hahn and K. Stork, ibid., 112, 2776 (1979).

15) Another 1,3-dipolar cycloaddition reaction of nitrones to enamines: Y. Nomura, F. Furusaki and Y. Takeuchi, Bull. Chem. Soc. Japan, 40, 1740 (1967); ibid., 43, 3002 (1970); ibid., 43, 1913 (1970); O. Tsuge, M. Tashiro and Y. Nishihara, Tetrahedron Lett., 3796 (1967).

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