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NMR AND IR STUDIES ON THE TAUTOMERISM OF  
1-ETHYL-3-(3'-DIMETHYLAMINOPROPYL)CARBODIIMIDE

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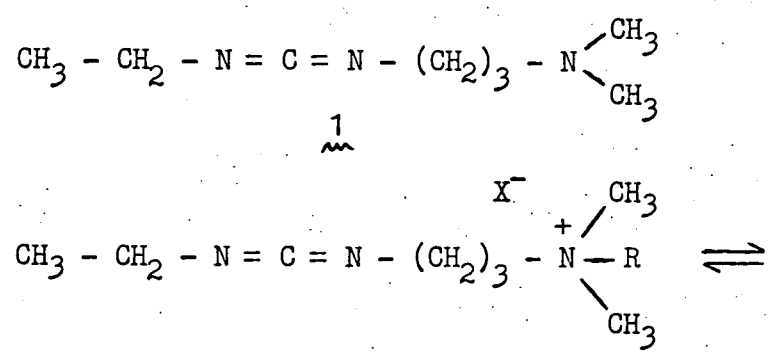
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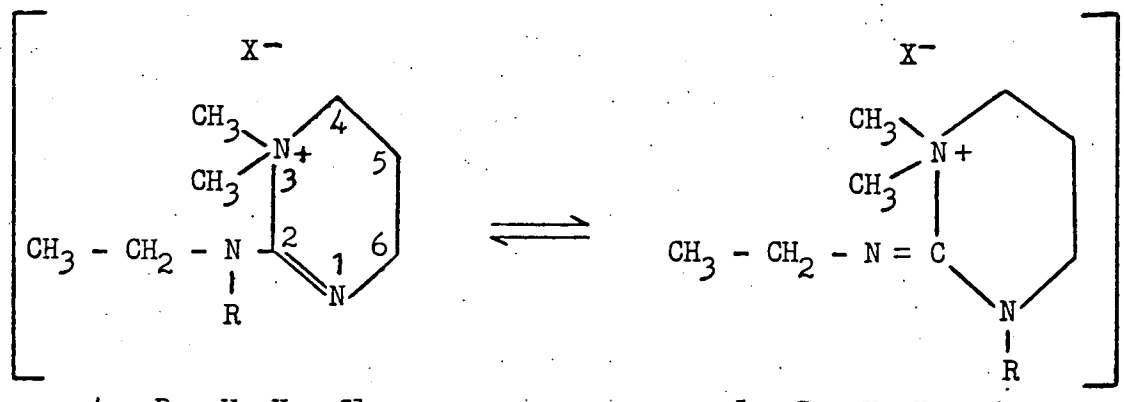
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Chemotherapy trials performed during the past year have demonstrated that 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (1), when administered as a saline solution of its hydrochloride salt, exerts a carcinostatic effect on transplanted tumors in mice.<sup>2</sup> Sheehan et al.<sup>3</sup> have suggested from ir studies that protonation of the tertiary amine of the carbodiimide 1 may lead to the formation of the tautomeric reduced pyrimidines 2-ethylamino-3,3-dimethyl-3,4,5,6-tetrahydropyrimidine chloride (4) and/or 2-ethylimino-3,3-dimethylperhydropyrimidine chloride (5). Titration data have established



- 2: R = H, X = Cl
- 3: R = CH<sub>3</sub>, X = I



- 4: R = H, X = Cl
- 6: R = CH<sub>3</sub>, X = I

- 5: R = H, X = Cl
- 7: R = CH<sub>3</sub>, X = I

that the  $pK_a$  of compound 1 is approximately 10.75. Consequently, 1 exists largely as the protonated species in aqueous solution at physiological pH. We therefore have undertaken spectroscopic studies to confirm the existence of structures 4 and/or 5, and to quantitate the relative percentages of isomeric species 2, 4, and 5 present in water at neutral pH. Information of this nature may prove to be of value both in understanding the mechanism of drug action against tumors, and in the synthesis of new potentially tautomeric carbodiimides.

When examined in aqueous solution or as a crystalline dispersion in nujol, the hydrochloride salt of 1 exhibits a weak absorption at  $2128\text{ cm}^{-1}$  corresponding to the fundamental antisymmetric  $\text{-N=C=N-}$  stretching mode.<sup>4</sup> A strong band occurs at  $1702\text{ cm}^{-1}$ , characteristic of the  $\text{-N=C}$  stretching mode present in structures 4 and 5.<sup>5</sup> Infrared spectra of the methiodide derivative of 1 in water and nujol show a strong carbodiimide band at  $2128\text{ cm}^{-1}$ , with no absorption at  $1702\text{ cm}^{-1}$ . These observations are consistent with the anticipated N-methylation structure 3, and indicate that reaction of 1 with methyl iodide does not produce isomeric structures 6 and/or 7. Infrared spectra of the free carbodiimide base, either in neat phase or in chloroform or unbuffered aqueous solution, are consistent with the open chain structure 1.

Since the methiodide derivative of 1 must exist exclusively in the carbodiimide form 3, the extinction coefficient for the  $\text{-N=C=N-}$  band at  $2128\text{ cm}^{-1}$  could be measured and was found to be  $1.67 \times 10^6\text{ cm}^2/\text{mole}$  in water. Assuming the same extinction coefficient for the  $2128\text{ cm}^{-1}$  band observed in the aqueous solution infrared spectrum of the hydrochloride salt of 1, it was calculated that 7.4% of this compound exists as the open chain carbodiimide hydrochloride 2. Spectra were recorded in solutions buffered over the pH

range 6 to 9, and no significant variation was noted in the strength of the carbodiimide absorbance. Outside this pH range, carbodiimide hydrolysis prevented accurate measurements.

In an effort to confirm and to extend the structural information obtained from ir data, nmr spectra of 1, its hydrochloride salt, and its methiodide derivative 3 were recorded in deuterium oxide. In the spectrum of the methiodide derivative 3 (Fig. 1A, Table I), the two partially resolved triplets centered at  $\delta$  3.20 and  $\delta$  3.44 ppm can be assigned to the c and e methylene proton resonances since all other signals can be unambiguously assigned. The difference in  $\delta$ -values for the f proton signals of the free base 1 and the methiodide derivative 3 ( $\Delta_{1-3} \delta_f$ , Table I) is 0.95 ppm. Assuming a similar downfield shift of the e proton resonance for species 3 relative to 1, the triplet at  $\delta$  3.20 ppm ( $\Delta_{1-3} \delta_e = 0.92$  ppm) must be assigned to the signal for protons e. Consequently, the  $\delta$  3.44 ppm signal is associated with the c methylene protons.

The nmr spectrum of the hydrochloride salt of 1 in deuterium oxide (Fig. 1B, Table I) indicates the presence of one major and one minor species. The weak singlet appearing at  $\delta$  2.92 ppm has been assigned to the resonance of the N,N-dimethyl protons of the open chain hydrochloride salt, structure 2. The intensity of this signal is approximately 8% as great as that of the major gem-dimethyl proton signal at  $\delta$  3.41 ppm, and is consistent with the percentage of 2 calculated from ir spectral data. The upfield shift of this signal relative to the N-CH<sub>3</sub> signals for the quaternary compounds considered here can be explained by localization of the positive charge predominantly on the proton bonded to the tertiary nitrogen.<sup>6</sup> As a result of this charge distribution, the deshielding of the N-CH<sub>3</sub> protons is less for species 2 than for the quaternary compounds.

Identification of the major component present in the hydrochloride salt of 1 can be made by comparison of chemical shift data for this compound and the free carbodiimide base 1 (Fig. 1B, Table I). In the spectrum of the hydrochloride salt of 1, the partially obscured triplet centered at  $\delta$  3.48 ppm can be assigned to the signal for the e protons since  $\Delta_{1 \rightarrow 1} \cdot \text{HCl} \delta_f = \Delta_{1 \rightarrow 1} \cdot \text{HCl} \delta_e = 1.20$  ppm. The low field triplet at  $\delta$  3.86 ppm can then be assigned to the c proton signal. A comparison of the spectra of 1 and the hydrochloride salt of 1 also shows that  $\Delta_{1 \rightarrow 1} \cdot \text{HCl} \delta_b = -0.09$  ppm and  $\Delta_{1 \rightarrow 1} \cdot \text{HCl} \delta_c = 0.59$  ppm. Using these relative chemical shift data, we have assigned 4 as the predominant species present in the hydrochloride salt of 1 for the following reasons. First, the deshielding effect of N-1 in structure 4 is expected to be greater than that of the carbodiimino nitrogen of 1, resulting in a downfield shift for the c proton signal.<sup>7</sup> Second, the deshielding effect of the amino nitrogen of 4 is expected to be less than that of the carbodiimino nitrogen of 1, resulting in an upfield shift for the b proton signal. In the case of structure 5, one would predict the signal for the b protons to occur downfield, and the c proton signal upfield, relative to the corresponding signals for compound 1.

Nmr spectra were also recorded for the free carbodiimide base 1 in neat phase and as a solution in chloroform. In both cases, the observed chemical shifts and coupling constants were consistent with an open chain carbodiimide structure.

In summary, the ir and nmr studies presented here demonstrate that the hydrochloride salt of 1 in water at neutral pH exists as a mixture of two isomeric forms: 7.4% as 2 and 92.6% as 4. The methiodide derivative 3 and the free base 1 exist only as open chain carbodiimide structures.

EXPERIMENTAL SECTION<sup>8</sup>

The hydrochloride salt of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (1) with an uncorrected mp of 109-110° (lit<sup>3</sup> mp 114-115°) was purchased from the Ott Chemical Company (Muskegon, Michigan). The derivative 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide methiodide (3) with an uncorrected mp of 90-93° (lit<sup>3</sup> mp 106.5-107.5°) was prepared from freshly distilled carbodiimide base 1 and methyl iodide.<sup>3</sup> Structure 3 and the hydrochloride salt of 1 in 50% methanol/50% acetone move on silica gel as single bands with R<sub>f</sub> values of 0.65 and 0.71, respectively. Only trace amounts of impurities are present. Infrared spectra of these compounds in water and as nujol mulls demonstrate the absence of urea bands in the 1530-1680 cm<sup>-1</sup> range. As determined from the absorbance at 2128 cm<sup>-1</sup>, the hydrolysis of these compounds in water at neutral pH follows first order kinetics. At 37° C, the t<sub>1/2</sub> for hydrolysis of the hydrochloride salt of 1 is 60 hrs, and for hydrolysis of 3 is 26 hrs.



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- (8) Melting points were measured on a Thomas-Hoover apparatus. Infrared spectra were recorded on a Perkin-Elmer Model 421 Spectrometer. Spectra of solutions were obtained using matched 0.018 mm CaF<sub>2</sub> cells. Because of the weak absorbance of the hydrochloride salt of 1 at 2128 cm<sup>-1</sup>, measurements at this frequency in aqueous solution were made by recording the transmittance at 5X scale expansion. Nmr spectra were recorded at ambient temperature on a Varian A-60A Spectrometer.

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Table I

60 MHz Chemical Shift and Coupling Constant Data <sup>(a)</sup>

<u>Protons</u> <sup>(b)</sup>	<u>δ (ppm)</u>		
	<u>1</u>	<u>3</u>	<u>HCl salt of 1</u>
a	1.21 (t, $\underline{J} = 7$ Hz)	1.22 (t, $\underline{J} = 7$ Hz)	1.16 (t, $\underline{J} = 7$ Hz)
b	3.26 (q, $\underline{J} = 7$ )	3.31 (q, $\underline{J} = 7$ )	3.17 (q, $\underline{J} = 7$ )
c	3.27 (t, $\underline{J} = 6.5$ )	3.44 (t, $\underline{J} = 6.5$ )	3.86 (t, $\underline{J} = 7$ )
d	1.7 (m)	2.1 (m)	2.2 (m)
e	2.28 (t, $\underline{J} = 7$ )	3.20 (t, $\underline{J} = 7$ )	3.48 (t, $\underline{J} = 6.5$ )
f	2.21 (s)	3.16 (s)	3.41 (s)
g	-----	-----	2.92 (s)

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(a) Spectra were recorded in deuterium oxide with sodium 4,4-dimethyl-4-silapentane sulfonate (SDSS) as an internal reference standard (SDSS = 0.0 ppm).

(b) Proton designations are the same as in Fig. 1.

CAPTION FOR FIGURE 1

Nmr spectra at 60 MHz in deuterium oxide of (A) 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide methiodide and (B) the hydrochloride salt of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide. Both spectra were recorded with sodium 4,4-dimethyl-4-silapentane sulfonate (SDSS) as an internal reference standard (SDSS = 0.0 ppm).

Figure 1

