^1H and ^{13}C 2D NMR Studies on Substituted Δ^3 -Pyrrolin-2-ones

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The ^1H and ^{13}C 2D NMR studies of pyrrolinones derivatives were performed using the method of proton detected 2D ^1H , ^{13}C correlation spectroscopy. HMQC and HMBC experiments were achieved in order to obtain the unambiguous assignment of the structures.

Keywords ^1H and ^{13}C 2D NMR, pyrrolinones, HMQC and HMBC

Δ^3 and Δ^4 pyrrolinones, together with their derivatives, have been described by several authors.¹⁻⁴ The interest concerning these compounds is in part due to the presence of pyrrolic systems, which are also present in the natural products⁵ viz. Vitamin B₁₂,⁶ prodigiosin⁷, bile pigments⁸, and some antibiotics, like distamycin.⁹ In our search for new biologically active synthetic compounds using a novel catalytic procedure, we have obtained several substituted Δ^3 -pyrrolin-2-ones, whose structures were studied by 2D-NMR techniques.

Previously, it was described¹⁰ that α -ketoalkynes can be carbonylated in the presence of $\text{Ni}(\text{CN})_2$ under phase-transfer conditions to give either unsaturated hydroxy-butylolactones or 2-alkylidene-3-ketocarbocyclic acids. In addition, it was recently found that by changing the reaction conditions it is possible to obtain hydroxybutylolactams in good yields.¹¹ However, the formation of hydroxylactams by hydrocyanation of α -ketoalkynes in water is possible by two plausible mechanisms, giving A or B.

The vinylic proton chemical shift found in ^1H NMR suggests model A for the structures of the lactams described herein. In order to unambiguously assign the structures **1** – **4** we undertook a 2D-NMR study (^1H , ^{13}C , HMQC and HMBC) of these compounds.

Experimental

Synthesis of hydroxybutylolactams were obtained by a modified procedure of the previously reported in hydroxybutylolactones formation¹¹ by hydrocyanation of α - in water under mild conditions.

In a typical experiment, $\text{Ni}(\text{CN})_2 \cdot 4\text{H}_2\text{O}$ (0.366 g, 2 mmol) in 50 ml of 5.0 M NaOH was degassed and saturated with CO under atmospheric pressure at 25°C; then, potassium cyanide (15 mmol) was introduced. Stirring was continued while CO was slowly bubbled

through the mixture until a yellow solution was obtained. The ketoalkyne (0.992 g, 8 mmol) was then added and the stirring continued at 25°C for 3 h while CO flow was maintained. The resulting mixture was extracted with ethyl acetate and dried over MgSO_4 . Evaporation of the solvent gave the pure crystalline products.

All NMR spectra were recorded with quadrature detection on a Varian Unity 500 spectrometer (500.0 MHz for ^1H and 125.7 MHz for ^{13}C) at a probe temperature of 25°C. The reported peaks are referenced to internal TMS. All normal-mode ^{13}C NMR spectra were acquired with composite pulse decoupling, namely a wide-band alternating-phase lower power technique for zero residue splitting (Waltz-16), as implemented in the spectrometer software. The sequence for the inverse-mode heteronuclear multiple-bond relation correlation (HMBC) includes a low-pass J filter¹² to suppress one bond correlation (evolution time: 3.6 ms). The polarization transfer time was set to 90 ms so as to optimize for long range hetero-coupling. The recycling delay was 2.5 s. A total of 128 2K point spectra were acquired and zero filled to 256 in t_1 . Window functions included sine bell shifted by $\pi/6$ in t_2 and 2-Hz Lorentzian broadening in t_1 dimension.

The IR spectra were recorded in KBr pellets on a Nicolet Magna 750 spectrometer. The mass spectra were obtained using a JEOL JMS-SX102A mass spectrometer.

Compound 1. White solid mp 106 – 107°C. IR (KBr pellets) 3394, 3207, 2962, 2925, 2872, 1694, 1645, 1428, 1340, 1129, 853 cm^{-1} . MS m/z 169 (M^+ 26%), 154 (M^+ 56%), 126 (M^+ 100%), 110 (M^+ 47%), 43 (M^+ 47%).

Compound 2. White solid mp 84 – 85°C. IR (KBr pellets) 3383, 3210, 2959, 2934, 2864, 1691, 1642, 1447, 1340, 1130, 858 cm^{-1} . MS m/z 183 (M^+ 5%), 154 (M^+ 100%), 126 (M^+ 14%), 123 (M^+ 14%), 98 (M^+ 16%), 41 (M^+ 12%).

Compound 3. White solid mp 144 – 145°C. IR (KBr pellets) 3361, 3250, 2957, 2937, 2877, 1690, 1646, 1464, 1366, 1075,

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860 cm^{-1} . MS m/z 211 (M^+ 3%), 196 (M^+ 2%), 155 (M^+ 100%), 112 (M^+ 32%), 57 (M^+ 10%), 41 (M^+ 8%).

Compound 4. Yellow solid mp 120 – 121°C. IR (KBr pellets) 3380, 3243, 3150, 2967, 2930, 2870, 1690, 1646, 1601, 1454, 1386, 1190, 1075, 860, 790 cm^{-1} . MS m/z 231 (M^+ 27%), 216 (M^+ 17%), 198 (M^+ 15%), 175 (M^+ 100%), 146 (M^+ 8%), 128 (M^+ 19%), 103 (M^+ 7%), 57 (M^+ 10%), 41 (M^+ 5%).

Results and Discussion

It is known that Δ^3 pyrrolinones with very small amounts of Δ^4 isomer can be obtained by the oxidation of pyrrole. These molecules show long-range couplings, which provide interesting examples for testing

Fig. 1 Chemical structure of pyrrolinones.

Fig. 2 ^1H NMR of compound 2 (500 MHz). a) normal spectrum; b) decoupled at NH chemical shift; c) decoupled at OH chemical shift; d) normal spectrum; e) decoupled at $\alpha\text{-CH}_2$ chemical shift.

several moieties of the molecule. However, the hydroxy lactams obtained by the hydrocyanation of α -ketoalkynes in water under mild conditions, it is possible to obtain hydroxy-butylolactams, A or B.

In Δ^4 pyrrolinone, a positive allylic-type coupling across the heteroatom between the NH and vinylic hydrogen (both lying in the same plane), are found to be in a W arrangement. For these compounds (1–4) we have found a similar behavior. The interaction between a vinylic proton with the NH proton was proved by the irradiation of the NH hydrogen, where the vinylic proton collapses to triplet *via* an allylic interaction with the methylene from the *n*-Bu moiety (see Fig. 2).

The numbering scheme employed for the title compound is shown in Fig. 1A complete ^1H and ^{13}C assignment of the molecules was achieved by means of proton-proton correlations methods. An HMQC experiment allowed all of the one-bond proton-carbon correlations to be identified; then, an HMBC spectrum enabled sufficiently long-range correlations to be observed to complete the assignment (see Fig. 3).

The ^1H and ^{13}C NMR data, as well as a listing of the correlations which were obtained from the HMBC spectrum, are given in Table 1. Reference to this table indicate that the assignments shown there are self-consistent and unambiguous. These are now described.

Further, OH and NH groups can be distinguished,

Fig. 3 HMBC spectrum of compound 2 (500/125 MHz).

Table 1 ^1H and ^{13}C chemical shifts of product **1** – **4** recorded at 25°C

1				2			
Position	$\delta^1\text{H}$	MULT	$\delta^{13}\text{C}$ HMBC	$\delta^1\text{H}$	MULT	$\delta^{13}\text{C}$ HMBC	
NH	7.27	bs		7.41	bs		C2, C3 C4, C5
2			172.8			173.1	
3			138.1			138.8	
4	6.50	q	144.4	6.46	q	143.2	C2, C3 C5, αCH_2
5			85.7			88.4	
R							C2, C3
αCH_2	2.16	m	24.4	2.16	m	24.4	βCH_2
βCH_2	1.48	m	29.4	1.48	m	29.5	γCH_2 CH_3, CH_3
γCH_2	1.36	m	22.3	1.35	m	22.3	
δCH_3	0.92	t	13.8	0.91	t	13.7	
R1	1.57	s	24.7	1.85	q	30.7	C5, C4
OH	4.3	bs		0.91	t	8.2	C5
				4.67	bs		C4, C5 CH_2
3				4			
NH	6.98	bs		6.60	bs		C3, C4
2			173.4			171.1	
3			139.1			135.4	
4	6.57	q	142.5	7.20	d	142.8	C2, C5 Cipso
5			92.1			90.5	
R				R			
αCH_2	2.18	m	24.6	7.84	d	128.3	
		C3, Cm, Cp					
				βCH_2	7.38	m	127.2
					7.37	m	128.6
							130.9
βCH_2	1.49	m	29.4				
γCH_2	1.36	m	22.4				
δCH_3	0.92	t	13.8				
R ¹	1.0	s	37.1	1.07	s	37.4	
			25.1			25.0	C ^t Bu, C5
			C ^t Bu				
			C5				
OH	3.54	bs		4.50			
			C ^t Bu				

The ^{13}C assignment were made using $^1\text{J}_{\text{C-H}}$ HMQC. s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet; bs: broad singlet.

because the latter is coupled with the vinylic methine. This distinction has been confirmed by the HMBC experiment correlations with both C=O and quaternary carbon (C5). The pyrrolinone carbonyl resonance (C2) is unambiguously assignable on chemical shift grounds, although its position on the molecule is confirmed by HMBC correlations, either $\text{CH}_2(\alpha)$ or NH and the vinylic proton. The position of the hydroxyl proton can be achieved using a long range correlation $^{13}\text{C-H}$ from such a proton with the vinylic methine group.

Finally, for the *n*-Bu chain we note the ^{13}C assignment from its HMBC correlation with vinylic proton as well as the characteristic triplet signal from the methyl group. Following the assignments of the remaining aliphatic carbons and protons is straightforward.

The ^1H and ^{13}C resonances of pyrrolinone derivatives

(**1** – **4**) have been reliably assigned using the method of proton detected 2D ^1H , ^{13}C correlation spectroscopy, specifically HMQC and HMBC experiments. Clearly, the very favorable sensitivity of the HMBC experiment renders in an unambiguous assignment of the structures.

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(Received May 20, 1997)

(Accepted December 22, 1997)