Tetrahedron Letters No. 47, pp 4707 - 4710. 0040-4039/78/1115-4707$02.00/0

TAUTOMERISM IN TETRAMIC ACIDS: ^{13}C NMR DETERMINATION OF THE STRUCTURES AND RATIOS OF THE TAUTOMERS IN 3-ACETYL-5-ISOPROPYLPYRROLIDINE-2,4-DIONE

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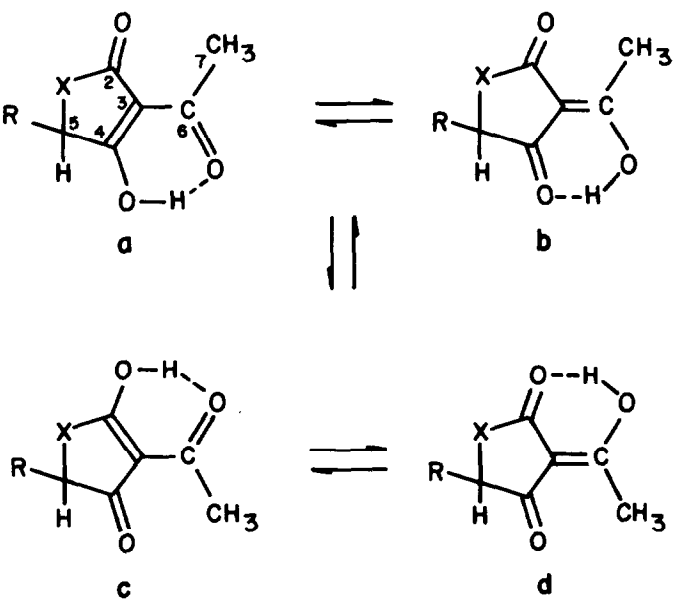
Unsymmetrical cyclic β,β'-triketones (1) can exist in solution as four different enolic forms, *viz.* the external (a,b ⇌ c,d) and the internal (a ⇌ b; c ⇌ d) tautomers.[1]



1. X = C<; N-; O or S
2. X = NH; R = CH(CH$_3$)$_2$ (8, 9, 10)
3. X = NH; R = CH$_2$C$_6$H$_5$
4. X = CH$_2$; R = H

Two C-5—proton signals were observed in the ^{1}H n.m.r. spectra of cyclic β,β'-triketones (1) in non-polar solvents owing to the slow exchange of the external tautomers (a,b ⇌ c,d).[1,2] The fast exchange between the internal tautomeric pairs (a ⇌ b) and (c ⇌ d) on the n.m.r. time scale leads to the observation of only average chemical shifts for each of these pairs.

I.r. and ^{1}H n.m.r. spectroscopy have been extensively used in the study of the tautomerism in β-diketones and β,β'-triketones.[1,2] However, the ^{13}C nucleus should be a sensitive molecular probe to study the tautomerism in β,β'-triketones as the chemical shift depends critically on the electronic state of the nucleus and is hardly affected by the anisotropy of neighbouring groups. This paper relates our ^{13}C n.m.r. results on the structures and tautomer ratios of 3-acetyl-5-isopropylpyrrolidine-2,4-dione (2).

The data from the p.n.d. 20 MHz ^{13}C n.m.r. spectrum of (2) and the ratios between the observed signal intensities are shown in Table 1. All the carbon atoms with the exception of C-8 give rise to two resonances. The proton-bearing carbon atoms were assigned with standard techniques. The signals at δ = 184.4 and δ = 189.0 appeared as quartets in the single frequency n.O.e. ^{13}C n.m.r. spectrum. An SPI[3] experiment verified that the coupling of 5.6 Hz observed in these resonances arose from an interaction with the C-7 protons, thereby assigning these signals (δ = 184.4 and δ = 189.0) to C-6. The assignment of the remaining three sets of resonances (C-3, C-3 and C-4) down field of δ = 100 was based on the known chemical shifts of amide, carbonyl and olefinic carbon atoms.[4]

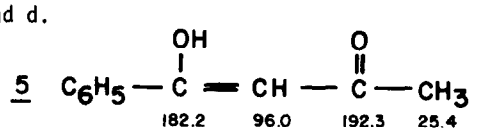
Table 1.
^{13}C n.m.r. Data of 3-Acetyl-5-isopropylpyrrolidine-2,4-dione (2)

Carbon Atom	δ[a] (ppm) (2 c,d)	(2 a,b)	Ratios cd/ab	a/b
2	176.0	170.0	3.71	
3	102.3	105.6	3.80	2.73
4	195.5	200.8	3.22	
5	67.6	64.3	3.59	
6	184.4	189.0	4.50	2.09
7	19.4	20.5	(b)	4.64
8	30.2			
9	19.3	19.0	(b)	
10	15.9	16.2	3.17	
		Average ratios	3.66	3.15

(a) Recorded on a Varian CFT-20 spectrometer with $(CH_3)_4Si$ as internal reference.

(b) Resonances partially overlapped.

The two sets of ^{13}C signals observed for (2) arise from the external tautomers (a, b) and (c, d). The predominant tautomeric forms in these pairs can be deduced from the observed chemical shifts. Enolic carbon atoms (*e.g.* C-6, b and d) resonate to higher field than the corresponding keto carbon atoms[5] (*e.g.* C-6, a and c) as proved by the chemical shifts observed in the model compounds (4), (5) and (6). The predominant tautomers in 3-acetyl-5-isopropyl-pyrrolidine-2,4-dione (2) are, therefore, forms b and d. The resonances observed for C-2 and C-4 can be used to assign a set of signals to a specific external pair of tautomers. A hydrogen-bonded carbonyl resonates at lower field than a corresponding free carbonyl.[5] The C-2 signal should be to lower field in (2d) than in (2b) while the C-4 resonance of (2d) should be to higher field in (2b). According to our ^{13}C results the exo-enol form d is the main tautomeric species of (2). This tautomer is also the form in which (2) exists in the crystalline state as established by an X-ray diffraction study.[6] The ratio between the intensities of the corresponding ^{13}C resonances (see Table 1) gives the relative populations of the external tautomers with the higher intensity resonances arising from the tautomeric pair c and d.



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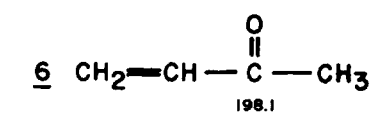

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The chemical shifts of carbon atoms C-3, C-6 and C-7 in the tautomers (2b) and (2d) should be virtually identical. The difference in the chemical shifts observed for these carbon atoms in the external tautomers can be attributed to different contributions from the endo-enol forms a and c. The observed chemical shifts (ν_{ab}, ν_{cd}) should be the weighted average of the chemical shifts in the individual isomers (ν_a, ν_b, ν_c, ν_d) according to the following equations:

$$\nu_{ab} = \rho_a\nu_a + \rho_b\nu_b$$

$$\nu_{cd} = \rho_c\nu_c + \rho_d\nu_d$$

where ρ is the mole fraction of each tautomer. The populations of the tautomers can be estimated if the chemical shifts of the individual tautomers are known. The C-7 methyl carbon signal, and probably also the C-6 and C-3 resonances, will be fairly independent of the nature of X and R in (1). The chemical shifts for C-7* (δ = 25.6; quartet J = 129.0 Hz) C-6 (δ = 198.6; quartet J = 6.2 Hz) and C-3 (δ = 114.6; singlet) of 2-acetylcyclopentane-1,3-dione (4) in $CDCl_3$ were used for the chemical shifts of the corresponding carbon atoms in (2a) and (2c). Forsén *et al.*[7] reported that 2-formylcyclopentane-1,3-dione exists in $CDCl_3$ predominantly as 3-formyl-3-hydroxycylopent-2-en-1-one. I.r. and u.v. spectra of this compound and (4) are very similar[7], indicating that (4) also exists predominantly in the 2-acyl-3-hydroxycyclopent-2-en-1-one form (4a and c). No reliable values are known for the chemical shifts of the carbon atoms C-3, C-6 and C-7 in the tautomers (2b and 2d). Using the chemical shifts attributed to these carbon atoms of the tautomeric pair (2c, d), to a first

*Numbering to correspond with unsymmetrical β,β'-triketones (1)

approximation, for the corresponding carbon atoms in the exo-enol forms b and d, the percentage of the different tautomers in (2) is:

a = 5.2 ± 2.5%, b = 16.3 ± 4.0%, c = 0% and d = 78.5 ± 3.5%.

The populations and structures of the different enolic tautomers (external and internal) in 3-acetylpyrrolidine-2,4-diones and probably also in other α-acetyl di- or triketones can be determined with ^{13}C n.m.r. spectroscopy because of the big chemical shift differences of the corresponding carbon atoms in the different tautomers. The accuracy of this method depends critically on the chemical shifts used for the different tautomeric forms.

In contrast Yamaguchi *et al.*[8] concluded from a ^{13}C and ^{1}H n.m.r. study that (3) exists to a greater extent in the endo-enol forms (a and c) than in the exo-enol forms (b and d). The chemical shifts and intensities of the ^{13}C resonances of carbon atoms C-2 to C-7 in (3) are very similar to those reported here for (2). The structure of the two mycotoxins cyclopiazonic acid[9] and tenuazonic acid,[10] were previously presented as the endo-enol form as in (1a). An examination of the ^{13}C spectral data[6] of these two compounds indicates that both are present mainly in the exo-enol form as in (1d).

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(Received in UK 30 August 1978)