Nmr Spectroscopic Studies on the Tautomerism in Tenuazonic Acid Analogs

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Received December 3, 1974
Revised November 3, 1975

Nmr spectra of structural analogs of tenuazonic acid such as 3-acetyltetramic acid, 3-acetyltetronic acid, 3-acetylthiotetronic acid and others were investigated for elucidation of the tautomeric structures. These compounds have completely enolized β,β′-triketone systems, and the position of the nmr signals for the enolic proton shows that the strength of their intramolecular hydrogen-bonding is weaker than those of acyclic β,β′-triketones and six-membered cyclic triketones. The assignment was made for nmr signals split by the difference of the diamagnetic anisotropic effect in each tautomers. The percentages of each of the tautomers were calculated from the intensities of the corresponding nmr signals. The results were confirmed by means of ^{13}C-nmr spectroscopy.

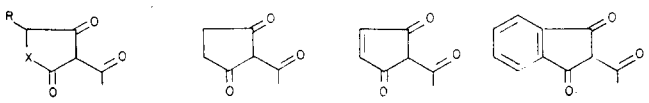
J. Heterocyclic Chem., 13, 533 (1976).

Introduction.

Tenuazonic acid was first found in the culture filtrate of *Alternaria tenuis* (1) and its structure was determined as 3-acetyl-5-*sec*-butyltetramic acid by Stickings (2). Recently, tenuazonic acid has also been found in *Piricularia orizae cavara* of the paddy (3) and in Tabbacco brown-spot disease (4). Previously, one of the authors has reported the antitumor activity of several tenuazonic acid analogs (5). Now we have determinded the nmr spectroscopic properties of structural analogs such as 3-acetyltetramic acid (IA-E), 3-acetyltetronic acid (IIA,B), 3-acetylthiotetronic acid (III), 2-acetylcyclopentane-1,3-dione (IV), 2-acetylcyclopentene-1,3-dione (V) and 2-acetylindane-1,3-dione (VI).

These compounds have interesting structural possibilities for enolization, hydrogen-bonding and tautomerism. Extensive studies have been reported by Forsén and co-workers (6) on the tautomerism of β,β′-triketones. However, they were not successful in the absolute detection of every tautomer at ordinary temperature owing to the low resolution of their apparatus.

Scheme 1



IA-E X = NH
IIA,B X = O
III X = S

IV V VI

Results and Discussion.

Chemical Shifts of Active Hydrogen.

Nmr signals for hydrogen-bonded enolic protons of these five-membered cyclic β,β′-triketones in deuteriochloroform were found in the region of δ = 9.66 to 14.75 ppm (Table 1), with the exception of III (7), which was found at a higher field than is usual for acyclic β,β′-triketones and six-membered cyclic triketones (δ = 17-19 ppm (8)). Chemical shifts of enolic protons were used to estimate the strength of intramolecular hydrogen-bonding. The strong interaction with the carbonyl group causes a large chemical shift toward the lower field for the enolic proton. The position of the signals for the enolic protons of these five-membered cyclic β,β′-triketones showed that the strength of the intramolecular hydrogen-bonding of these compounds are weaker than those of acyclic β,β′-triketones or six-membered cyclic triketones. The weaker intramolecular hydrogen-bonding brings lower p*K*a values (0.5-3.07) in these compounds (9).

These facts can be explained by ring geometry. Because of the contraction of the five-membered ring, two oxygen atoms bridging with the hydrogen might be located further apart from each other for these five-membered cyclic β,β′-triketones than for the others. Conformational analysis studies are now in progress.

Table 1

Nmr Chemical Shifts of Active Hydrogen in Deuteriochloroform and p*Ka* Values in Methanol-water

No.	R	δ OH (ppm from TMS)	p*Ka* (a)
IA	H	11.42	2.65
IB	$CH_2C_6H_5$	12.65	2.92
IC	$CH_2C_6H_4OH$-*p*	10.80 (a)	2.94
ID	$CH_2CH_2SCH_3$	11.06	
IE	CH_2COOCH_3	11.31	
IIA	H	11.38	0.8
IIB	CH_3	9.66	0.5
III	H	16.10 (b)	2.79
IV		14.75	3.78
V		11.82	2.72
VI		12.80	3.07

(a) Solvent: DMSO-d_6. (b) Observed at -66°.

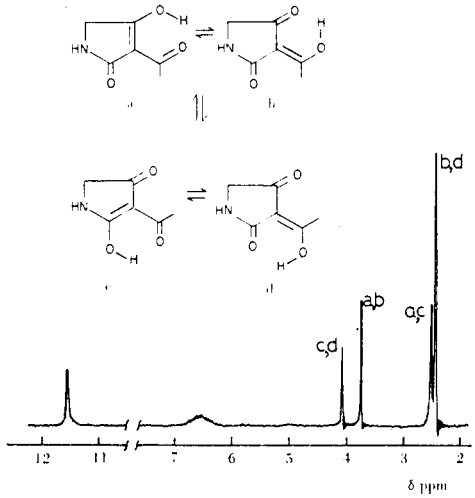


Figure 1. Pmr spectrum of 3-acetyltetramic acid (IA) in deuteriochloroform at 90 MHz.

Assignment of Nmr Signals Split by Tautomerization.

For unsymmetrical cyclic β,β′-triketones (IA-E, IIA,B, III), there are possibilities for different "external" tautomers (a,b ⇌ c,d) in addition to "internal" tautomers (a ⇌ b, c ⇌ d) as Forsén has suggested (10). The interconversion between "external" tautomers is a comparatively slow process, which shows up clearly in the nmr spectra at 90 MHz. Signals of methylene or methyne protons (5-position) of such unsymmetrical cyclic β,β′-triketones as 3-acetyltetramic acid (IA-E), 3-acetyltetronic acid (IIA, B) and 3-acetylthiotetronic acid (III) were split into two counterparts (Table 2). The diamagnetic anisotropic effect of the ring carbonyl group (4-position)

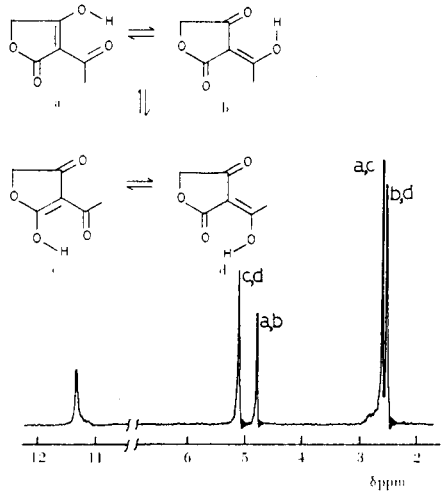


Figure 2. Pmr spectrum of 3-acetyltetronic acid (IIA) in deuteriochloroform at 90 MHz.

on the neighboring methylene or methyne protons (5-position) is more dominant for the pair of c and d forms than for the a and b forms, because the effect of enolized carbonyl group (a form) or hydrogen-bonded carbonyl group (b form) should be negligible (10,11). Consequently, the counterpart at lower field could be attributed to the pair of c and d forms.

It has been reported that the splitting of the nmr signals by the "internal" tautomers can not be detected at ordinary temperatures since these conversions are relatively faster processes (12). However, in the nmr spectra at 90 MHz in deuteriochloroform at ordinary temperatures, two slightly split signals were observed at 2.3-2.6 ppm for the methyl proton in the acetyl group of these compounds. This suggests that the "internal" tautomers of these compounds exchange rather slowly. This rate is sufficiently slow to be detected by nmr measurement at 90 MHz, because of the longer distance between the two oxygen atoms as mentioned earlier. The methyl proton of the a and the c forms is influenced by the diamagnetic anisotropic effect of two carbonyl groups, the ring carbonyl (2- or 4-position) and the acetyl carbonyl, however, the methyl proton of the b and the d forms is influenced only by one ring carbonyl group (2- or 4-position). Therefore, the signal at lower field is attributed to the pair of the a and the c forms.

In the case of the 3-acetyltetramic acids, IB, ID and IE, with the exception of IA (14), the NH protons were separated into two broad signals in the region of 6.32-7.24 ppm by "external" tautomerization (Figure 3). Lower field signals can be ascribed to a, b forms, higher signals to c, d forms. The broad features of these signals would suggest for these compounds a fast interconversion

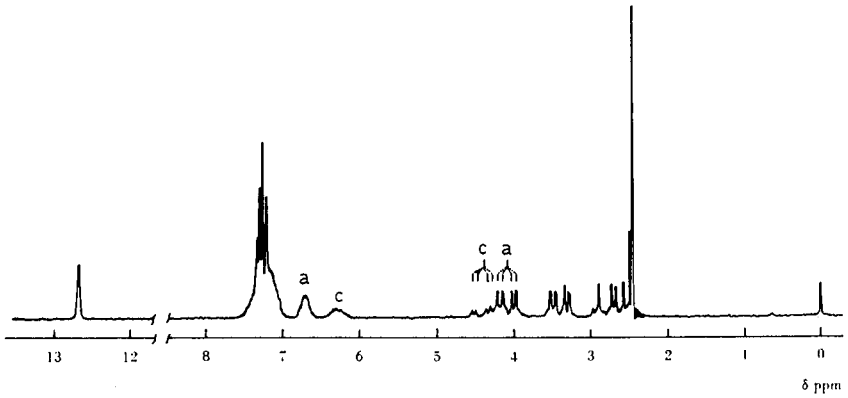
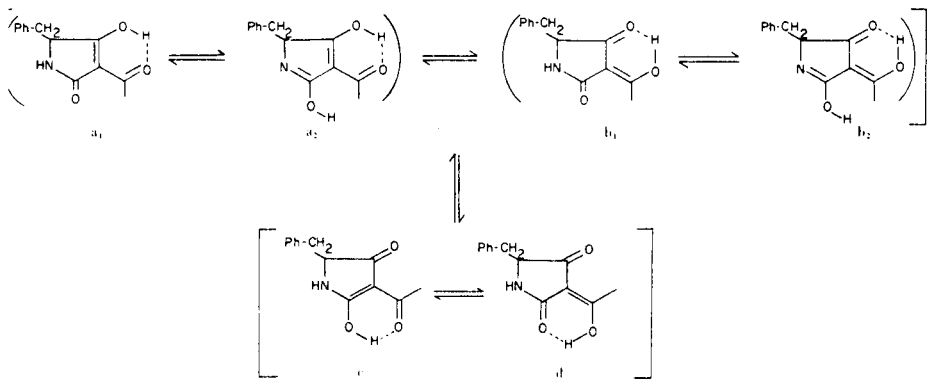


Figure 3. Pmr spectrum of 3-acetyl-5-benzyltetramic acid (IB) in deuteriochloroform at 90 MHz.

Scheme 2



between tautomers of the lactam and the lactim type as illustrated for IB in the following scheme.

The separation in the methyne signal by the "external" tautomeric interconversion could not be shown in the spectrum of IC (X = NH, R = $CH_2C_6H_4OH$-*p*) (13), although the splitting in the methyl signal by the "internal" tautomerization could be observed. Solvent effects on the tautomerism of these series of compounds will be reported in detail in the future (28).

Tautomeric Equilibrium.

Ratios of "external" (a+b/c+d) and "internal" (a+c/b+d) tautomers of unsymmetrical cyclic β,β′-triketones were calculated from the intensities of the separate signals assigned in the earlier section. These ratios afford the percentages of each tautomers under the experimental conditions (Table 2).

Without the exception of IA (X = NH, R = H) (14), these compounds were found to exist to a greater extent in the endo-enol forms (a and c) than in the exo-enol forms (b and d). Garbisch (15) has extimated the strain energy differences between the endo-enol and exo-enol forms in certain cyclic β-diketones, and found that exo-enol forms are favored in five-membered cyclic β-diketones. This difference might be ascribed to the fact that, in the case of five-membered cyclic β,β′-triketones, the stabilization energy by the rotation of the side-chain acetyl group, which is possible in a and c forms, would overcome the molecular distortion by double bond formation in the ring.

On the other hand, it should be noted that the a and b forms exist to a greater extent in 3-acetyltetramic acids (IA, IB, ID and IE) than in the other form. This difference might be ascribed to the possibility of the lactam-lactim type of tautomerism as suggested formerly. The formation of lactim form would hinder the formation of the c and the d forms in the carbonyl system of these compounds.

^{13}C-Nmr Spectroscopy.

^{13}C-Nmr spectroscopy affords useful information on tautomerism. ^{13}C-Nmr spectroscopic studies have been reported on the tautomeric structure in acetylacetone (16), unsymmetrical β-diketones (17), formycine (18)

Table 2

Separation of Nmr Signals by Tautomerization and Percentages of Each Tautomers in Unsymmetrical Cyclic β,β′-Triketones

No.	δ CHR (ppm) (a,b)	(c,d)	Int. ratio (a+b)/(c+d)	δ $COCH_3$ (ppm) (a,c)	(b,d)	Int. ratio (a+c)/(b+d)	Content (%) a	b	c	d
IA	3.84(s)	3.97(s)	3.35	2.49	2.46	0.19	12	65	4	19
IB	3.60(q)	3.91(q)	4.33	2.53	2.41	49.00	80	2	18	0
IC	4.06(t) (a)			2.30	2.29	32.33				
ID	3.98(q)	4.15(q)	4.88	2.47	2.45	49.00	85	2	17	0
IE	4.16(q)	4.31(q)	4.67	2.4 (b)						
IIA	4.46(s)	4.68(s)	0.56	2.56	2.55	1.13	19	17	34	30
IIB	2.22(q)	2.64(q)	0.75	2.52	2.51	1.00	22	28	21	28
III	3.83(s)	4.04(s)	0.33	2.56	2.54	4.56	20	4	62	14

(a) Solvent: DMSO-d_6. (b) Complex pattern.

Table 3

^{13}C-Nmr Spectral Data of IB (X = NH, R = $CH_2C_6H_5$) at 25.1 MHz in Deuteriochloroform

Carbon No. (a)	δ C (ppm from TMS) a form	c form	Int. ratic a/c
1	175.07	168.66	4.9
2	194.22	200.07	4.3
3	185.29	189.03	6.0
4	101.54	101.54	
5	19.56	20.37	5.3
6	63.71	60.39	4.0
7	38.23	37.86	7.7
8	136.60	136.03	4.7
9,13	129.13	129.13	
10,12	128.80	128.80	
11	127.10	127.10	

(a) Nuberings of carbons are shown in Figure 4.

and gentiocrucine (19).

Figure 4 shows the ^{13}C-nmr spectrum of IB (X = NH, R = $CH_2C_6H_5$) in deuteriochloroform at 25.1 MHz. Most of the signals could be assigned by means of the off-resonance decoupling spectrum (Table 3).

Carbonyl carbons in IB were observed in the region of 168.66-200.07 ppm as three pairs of signals with comparatively large separations. The pair of highest field signals can be attributed to the amide carbonyl carbon. From the fact that an enolized carbonyl carbon appears at a hydrogen-bonded carbonyl carbon appears at a lower field than a free carbonyl (16), the signal on lower field side can be ascribed to the amide carbonyl carbon of the a form, and the higher to that of the c form. (As shown in Table 2, amounts of the b and the d forms are not more than 2%.) The ring carbonyl carbon (4-position) appeared at 200.07 ppm for the c form and at 194.22

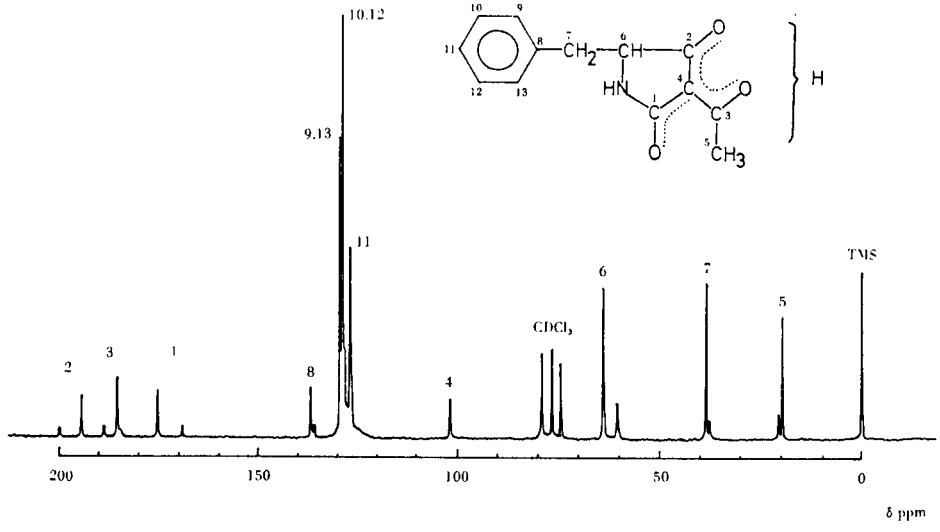


Figure 4. ^{13}C-Nmr spectrum of 3-acetyl-5-benzyltetramic acid (IB) in deuteriochloroform at 25.1 MHz. TMS as the internal standard.

ppm for the a form with an enolized carbonyl group. The separation (58.2 Hz) of the paired signals of the acetyl carbonyl carbon is somewhat smaller than the other signals (amide carbonyl: 96.4 Hz, ring carbonyl: 87.9 Hz), and there is some difficulty in assigning each counterpart by the structural differences. However, by comparison of the intensity ratio with the other pairs of carbonyl signals, the signal at 185.29 ppm and 189.03 ppm can be attributed to the a form and the c form, respectively.

The other pairs of signals could be assigned as shown in Table 3 from their chemical shifts and intensity ratios. The intensity ratios did not always show a good agreement with each other and with that of the methyne proton signal. Differentiations to this extent might be expected for the signals with different nuclear Overhauser enhancement.

EXPERIMENTAL

Materials.

3-Acetyltetramic acids (IA-E) (20,21), 3-acetyltetronic acids (IIA, B) (22,23), 3-acetylthiotetronic acid (III) (24), 2-acetylcyclopentane-1,3-dione (IV) (25), 2-acetylcyclopentene-1,3-dione (V) (26) and 2-acetylindane-1,3-dione (VI) (27) were prepared and purified as described in the literature cited.

Measurements.

The pmr spectra were recorded on a Hitachi Perkin-Elmer R-22 spectrometer at 90 MHz. The sample of 0.3 molar fraction was dissolved in 0.4 ml. of the solvent with TMS as the internal reference. The probe temperature was at 34°.

The ^{13}C-nmr spectra was measured on a JNM-FX60 spectrometer equipped with a PFT-100 Fourier transform accessory at 25.1 MHz using TMS as the internal reference and 10 mm diameter nmr tube. The spectra were obtained by 5000 accumulations measured on a broad-band proton decoupler. The solution contained 200 mg. of the sample in 2 ml. of deuteriochloroform.

Acknowledgments.

The authors are grateful to Mr. Muneki Ohuchi of Japan Electronic Optics Laboratory for the ^{13}C-nmr measurements.

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