Synthesis, NMR Spectroscopic and X-Ray Crystallographic Studies of *N*-Acetyl-3-butanoyltetramic Acid

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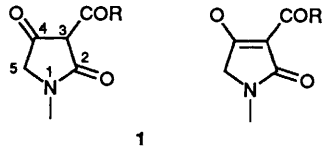
The reaction of *N*-acetylglycine *p*-nitrophenyl ester with the anion of an active methylene compound proceeds to give *N*-acetyl-3-butanoyltetramic acid. The influence of the *N*-acetyl group on the equilibrium between different 'internal' and 'external' tautomeric forms of *N*-acetyl-3-butanoyltetramic acid was investigated by ^1H and ^{13}C NMR spectroscopy. The structure of this compound was confirmed by an X-ray crystal structure determination.

The 3-acyltetramic acids **1**, substituted pyrrolidine-2,4-diones, constitute a growing class of natural products displaying a range of biological activities: *e.g.* tenuazonic acid,[1] ikarugamycin,[2] streptolydigin,[3] magnesidin,[4] malonomycin,[5] erythroskyrine[6] and tirandamycin.[7] The common feature of all these natural products is the five-membered heterocyclic nucleus, a pyrrolidine-2,4-dione, acylated at position 3.



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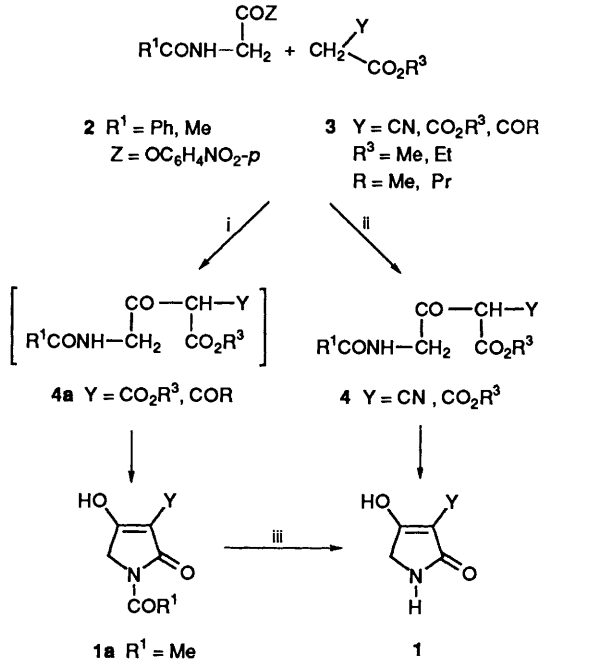
A general method for the synthesis of 3-acetyltetramic acids was developed in 1954 by Lacey.[8] The method has been used for the synthesis of 3-acetyl-5-substituted tetramic acids starting from different α-amino acids and has been extended to the synthesis of 3-polyenoyltetramic acids.[9] A new strategy for the synthesis of 3-acetyltetramic acids was developed by Jones and co-workers,[10] using pyrones as precursors. Moreover, there are several other possible approaches to the preparation of pyrrolidine-2,4-diones, unsubstituted at the 3-position, starting from *N*-protected α-amino acids.[11] An approach to the synthesis of a series of 3-substituted tetramic acids has been described in a previous communication,[12] starting from *N*-protected α-amino acid derivatives **2** with a readily-prepared anion of active methylene compound **3** (Scheme 1) through an intramolecular cyclisation of acylaminoacetyl derivative **4**. This method has been extended[13] to the synthesis of *N*,α-diacetyltetramic acid **1a** (Scheme 1, Y = COMe), by the reaction of *N*-acetylglycine *p*-nitrophenyl ester **2** (R^1 = Me) with an excess of the anion of ethyl acetoacetate **3** (Y = COMe), generated from the action of a base, sodium hydride, in anhydrous benzene. Under the reaction conditions the acylaminoacetyl derivative **4a** (R^1 = Me, Y = COMe) was converted into the corresponding *N*,α-diacetyltetramic acid **1a** (Y = COMe) through an intramolecular condensation mechanism.

3-Acyltetramic acids, like other tricarbonyl compounds, can occur in several enolic forms. The equilibrium between different 'internal' and 'external' tautomeric forms of *N*-substituted tetramic acids (Scheme 2) has been investigated with the aid of ^1H and ^{13}C NMR spectroscopy. In order to confirm the structure and tautomerism of these compounds in the solid state, an X-ray crystal structure determination was carried out.

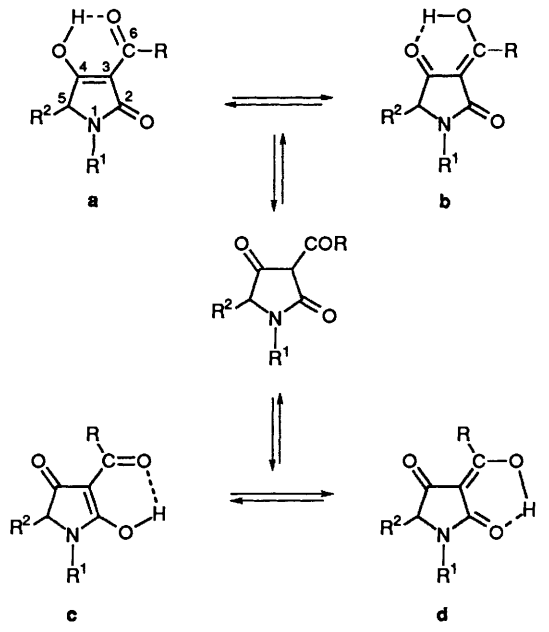


Scheme 1 *Reagents:* i, NaH/PhH; ii, NaH/PhH or Bu^{t}OK/Bu^{t}OH; iii, EtONa/EtOH

Results and Discussion

Our interest has been focussed on the synthesis of *N*-acetyl-3-acyltetramic acids (Scheme 1, **1a**, Y = COPr), through an acylation reaction of acyl-acetic esters $RCO\text{-}CH_2\text{-}CO_2R^3$, *via* *N*-acetylglycine *p*-nitrophenyl ester using, as base, sodium hydride in anhydrous benzene. The molecular ratio of *p*-nitrophenyl ester : NaH : active methylene compound was 1 : 2 : 3 and the reaction time was 3.5 h. Under these conditions the *N*-acetyl-3-butanoyltetramic acid **1a** (Y = COPr) has been prepared in 70% yield.[14]

3-Acyltetramic acids have several interesting structural possibilities for enol–enol tautomerism and hydrogen bonding. Extensive studies have been reported by Steyn and co-workers[15] on the tautomerism of 3-acetyltetramic acids (Scheme 2, **1ii**). In addition, the boron trifluoride complexes of 3-acetyltetramic acid have been reported by Jones and co-workers[16a] for characterisation of the corresponding tetramic acid complexes. Semi-empirical calculations on the tautomerism have also been reported.[16a,b]



Scheme 2

3-Acetylpyrrolidine-2,4-dione (Scheme 2, **1ii**) possessing a β-tricarbonyl system, can occur in enolic 'internal' tautomers **a** ⇌ **b** and **c** ⇌ **d**, in addition to 'external' tautomers **ab** ⇌ **cd**. Steyn *et al.* have shown (^{1}H and ^{13}C NMR data) that two sets of peaks were observed for certain protons in deuteriochloroform solution. 'Internal' tautomers are rapidly interconverted by intramolecular displacement of the enolic proton along the hydrogen bond, and the NMR spectra show signals in which chemical shifts are weighted averages of those of the tautomers. The interconversion between the 'external' tautomers is a comparatively slow process on the NMR time-scale. Therefore, the 'external' tautomers often give separate NMR signals.

In an attempt to establish the tautomeric forms of *N*-acetyl-3-butanoyltetramic acid (Scheme 2, **1i**, R^1 = COMe) in solution, a detailed comparison of the NMR spectra with those of 3-acetyl-5-isopropyltetramic acid (Scheme 2, **1ii**, R^1 = H) studied by Steyn, was carried out. Our attention was focussed on the influence of the *N*-acetyl group on the tautomeric equilibrium. Only one set of signals was observed for all protons in hexadeuteriodimethylsulfoxide solution (polar solvent). In deuteriochloroform solution two sets of peaks were observed for certain protons. Signals of the 5-position protons were split into two parts, showing the presence of the 'external' tautomeric pair. The resonances at higher field could be attributed to the tautomers **c** and **d**. The diamagnetic anisotropy of carbonyl groups causes deshielding of neighbouring protons situated in the plane containing the double bond and shielding of the protons out of the plane.[15,17] For tetramic acids the 5-H in tautomers **c** and **d** should be at higher field than in the form **a** ^{1}H NMR spectroscopic data for 3-acetyl-5-isopropyltetramic acid **1ii** indicate that the more abundant form should be the 'external' tautomer pair **cd**. For *N*-acetyl-3-butanoyltetramic acid **1i** the presence of 'external' tautomers was concluded from the splitting of the 5-methylene signal in the ^{1}H NMR spectrum, indicating that the dominant form should be the external tautomer pair **ab** with an intensity ratio of **ab**/**cd** = 1.52. The ^{1}H NMR spectroscopic data for *N*-acetyl-3-butanoyltetramic acid are presented in Table 1.

The ^{13}C NMR assignments of *N*-acetyl-3-butanoyltetramic acid in $CDCl_3$, presented in Table 2, are based on the off-resonance decoupling. This spectrum reveals the existence of two forms occurring in different proportions. It is known that hydrogen-bonded carbonyl carbons appear at lower field than analogous non-hydrogen-bonded carbonyls, whereas olefinic carbons bearing a hydroxy group would be expected to appear at the higher field.[17] Thus the chemical shifts observed for C-2 and C-4 (Scheme 2) could be used to deduce the relative stability of the 'external' tautomers. The free carbonyl carbon C-2 resonates at a higher field in **ab** than the corresponding hydrogen-bonded carbonyl carbon in **cd**, whereas the carbon C-4 resonates at a lower field in **ab** than in **cd**. *N*-Acetyl-3-butanoyltetramic acid has been found to exist to a greater extent in the **ab** forms.

Steyn *et al.* postulated that on 3-acetyl-5-isopropyltetramic acid (Scheme 2, R = Me, R^1 = H, R^2 = Pr^i) tautomer **d** is preferable to its geometrical isomer **b**. This preference is attributed to the ability of the C-2 amide carbonyl group to form a stronger intramolecular hydrogen bond than the C-4 oxo group. In our product (Scheme 2, R = Pr, R^1 = COMe, R^2 = H) the preference for tautomers **ab** over the analogous external tautomers **cd** could be attributed to the presence of the acetyl group on the nitrogen atom, (N-COMe). According to Steyn's tetramic acid model, the nitrogen atom in the amide structure is better able to donate electrons to the C-2 carbonyl group, enhancing the proton-acceptor ability of that group and the possibility of forming a stronger hydrogen bond. In our product, the electron pair of the nitrogen atom is shared between two carbonyl groups, thus increasing the possibility for hydrogen bonding on the C-4 carbonyl. In order to determine the structure and identify the tautomer for *N*-acetyl-3-acyltetramic acid in the solid state, the X-ray crystal structure of *N*-acetyl-3-butanoyltetramic acid (Fig. 1) has been determined. The partial double-bond character of the N(1)–C(10) bond in this compound is evident. In Table 3 selected bond lengths in **1i** (Scheme 2) are compared with those of equivalent bonds in **1ii**, while Tables 4 and 5 give some other details of the molecular geometry. The results confirm that the tautomer **a** (as in Scheme 2, but without internal hydrogen-bonding) is found in the solid state for *N*-acetyl-3-butanoyltetramic acid **1i**. Thus, the N(1)–C(2) and N(1)–C(10) bond lengths (Fig. 1) are 1.432(6) Å and

Table 1 ^{1}H NMR resonances (δ) of *N*-acetyl-3-butanoyltetramic acid ($CDCl_3$)

CH_2-ring	N–CO–Me	CH_2–CH_3
4.30, s (**ab**) } 2 H	2.63, s	1.03, t (*J* 7)
4.13, s (**cd**) }	3 H	3 H
ab/**cd** = 1.52		
CH_2–CH_2–Me	CO–CH_2	OH enol
1.8, st (*J* 7)	2.97, t (*J* 7)	8.73 br
2 H	2 H	

Table 2 ^{13}C NMR chemical shifts for *N*-acetyl-3-butanoyltetramic acid ($CDCl_3$)

	C-2	C-3	C-4	C-5	C-6
ab	169.87	105.55	197.87	49.59	193.79
cd	173.59	102.78	192.12	53.59	188.92
ab/**cd**	2.7	1.86	1.8	1.7	2.7
	C-7	C-8	C-9	C-10	C-11
ab	37.21	18.37	13.59	165.51	24.81
cd	34.83	19.59		169.41	25.14
ab/**cd**	1.79	1.65			

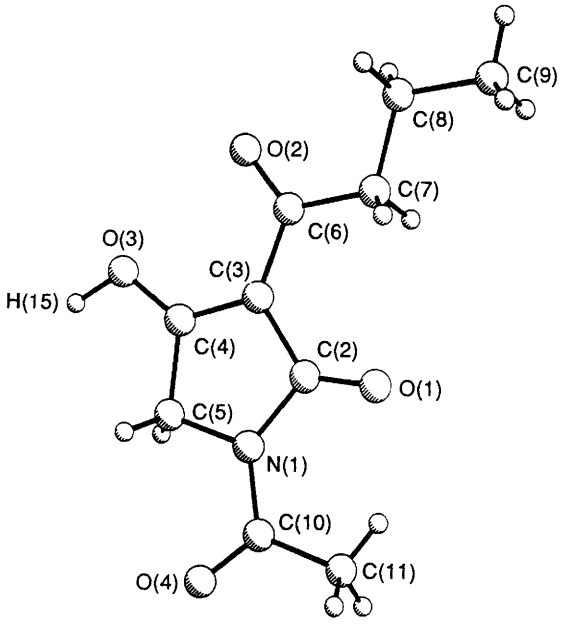


Fig. 1 Molecular structure and atomic numbering scheme of *N*-acetyl-3-butanoyltetramic acid

Table 3 Selected bond lengths (Å) in compounds **1i** and **1ii**[15] with standard deviations in parentheses

	1i	**1ii**
C(4)–O(3)	1.299(5)	1.223(8)
C(4)–C(3)	1.369(7)	1.44(1)
C(3)–C(6)	1.465(6)	1.35(1)
C(3)–C(2)	1.468(7)	1.44(1)
C(2)–O(1)	1.198(6)	1.256(9)
C(2)–N(1)	1.432(6)	1.34(1)
N(1)–C(10)	1.377(6)	
C(10)–O(4)	1.205(6)	
N(1)–C(5)	1.452(6)	1.48(1)
C(5)–C(4)	1.491(6)	1.52(1)

1.377(6) Å, respectively, indicating that the bond N(1)–C(10) has partial double bond character. The hydroxy hydrogen H(15) forms a hydrogen bond to oxygen O(5) of an adjacent water molecule [O(5)–H(15) (1.494 Å)]. The length of the O(3)–C(4) bond [1.299(5) Å] is longer than the carbonyl bond length C(2)–O(1) [1.198(6) Å]. The bond length of C(3)–C(4) [1.369(7) Å] for **1i** is significantly shorter than that in **1ii** [C(3)–C(4), 1.44(1) Å], whereas the bond length of C(3)–C(6) [1.465(6) Å] for **1i** is longer than that in **1ii** [C(3)–C(6), 1.35(1) Å]. Therefore, for compound **1i** the formal double bond can be assigned to C(3)–C(4) [1.369 Å]. This bond distance, characteristically shorter than the normal C–C single bond, could be attributed to an sp^2 conjugated system.[15]

In summary, the X-ray structure of *N*-acetyl-3-butanoyltetramic acid **1i** clearly shows that it exists in the tautomeric form **a** in the solid state.

Experimental

^1H and ^{13}C NMR spectra were recorded at 60 or 80, and 15 or 20 MHz, respectively, for solutions in deuterochloroform.

N-Acetyl-3-butanoyltetramic Acid.—The product was prepared as described in ref. 14. The colourless crystals were recrystallised again from chloroform–light petroleum, for the X-ray analysis.

Crystal data. $C_{10}H_{13}NO_4 \cdot H_2O$, M = 229, triclinic, a = 10.251(2), b = 0.422(2), c = 5.604(2) Å, α = 103.28(2)°, β = 100.17°, γ = 77.44(2)°, V = 563.6 Å^3 (by least squares refinement on twenty reflections in the range 26° < 2θ < 35°), λ = 0.710 69 Å, space group $P\bar{1}$ (No. 2), Z = 2, D_x = 1.350 g cm^{-3}, colourless tablets, dimensions of crystal used 0.60 × 0.15 × 0.80 mm, μ(MoK$_\alpha$) = 0.90 cm^{-1}.

Data collection and processing. Rigaku AFC6S diffractomer, $\omega/2\theta$ mode with ω-scan width 1.37 + 0.30 tan θ, scan speed 16° min^{-1}, graphite-monochromated MoK$_\alpha$ radiation, 2.5° < θ < 25°, 2114 reflections measured, 1993 unique (merging R 0.018) after empirical absorption correction (T_{max} 1.00, T_{min} 0.93), 896 with $I > 5\sigma(I)$; no significant variation of intensity standards.

Structure analysis and refinement. Direct methods, followed by full matrix least squares refinement on F with anisotropic vibration parameters for all non-hydrogen atoms, hydrogen atoms on water molecule and on O(3) located in difference map, others placed in calculated positions, but not refined. Final R = 0.049, R_w = 0.061. TEXSAN–TEXRAY software package was used,[18] including atom scattering factors and weighting scheme.*

Table 4 Interatomic distances (Å) in **1i** with standard deviations in parentheses

N(1)–C(2)	1.432(6)
C(2)–C(3)	1.468(7)
C(3)–C(4)	1.369(7)
C(4)–C(5)	1.491(6)
C(5)–N(1)	1.452(6)
C(10)–C(11)	1.501(8)
C(3)–C(6)	1.465(6)
C(6)–C(7)	1.500(7)
C(7)–C(8)	1.503(7)
C(8)–C(9)	1.524(8)
C(2)–O(1)	1.198(6)
C(4)–O(3)	1.299(5)
C(10)–O(4)	1.205(6)
C(6)–O(2)	1.222(6)
O(3)–H(15)	1.038
O(3)–H(15)	2.615
O(5)–H(15)	1.494
O(5)–H(15)	3.292

Table 5 Selected bond angles (°) in **1i** with standard deviations in parentheses

C(3)–C(4)–C(5)	111.5(4)
O(3)–C(4)–C(5)	120.5(4)
O(3)–C(4)–C(3)	128.0(4)
C(4)–C(3)–C(6)	125.4(4)
C(2)–C(3)–C(4)	108.4(4)
C(2)–C(3)–C(6)	126.3(5)
N(1)–C(2)–C(3)	106.2(4)
O(1)–C(2)–C(3)	130.0(5)
N(1)–C(2)–O(1)	123.8(4)
C(4)–C(5)–N(1)	102.8(4)
C(2)–N(1)–C(5)	111.1(4)
C(5)–N(1)–C(10)	118.5(4)
C(2)–N(1)–C(10)	130.3(4)
C(3)–C(6)–O(2)	120.6(5)

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* Tables of atomic coordinates, thermal parameters, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre; for details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1994, issue 1.

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