SYNTHESIS AND NMR SPECTROSCOPIC STUDIES OF NOVEL N-ACETYL-3-AMINOALKYL TETRAMIC ACIDS

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ABSTRACT : The reaction of N-acetyl-3-acyl tetramic acids with substituted amines is described. The influence of the N-acetyl group on the equilibrium between different 'external' and 'internal' tautomeric structures of N-acetyl-3-aminoalkyl tetramic acids 6-14 was investigated by ^{1}H and ^{13}C NMR spectroscopy.

INTRODUCTION

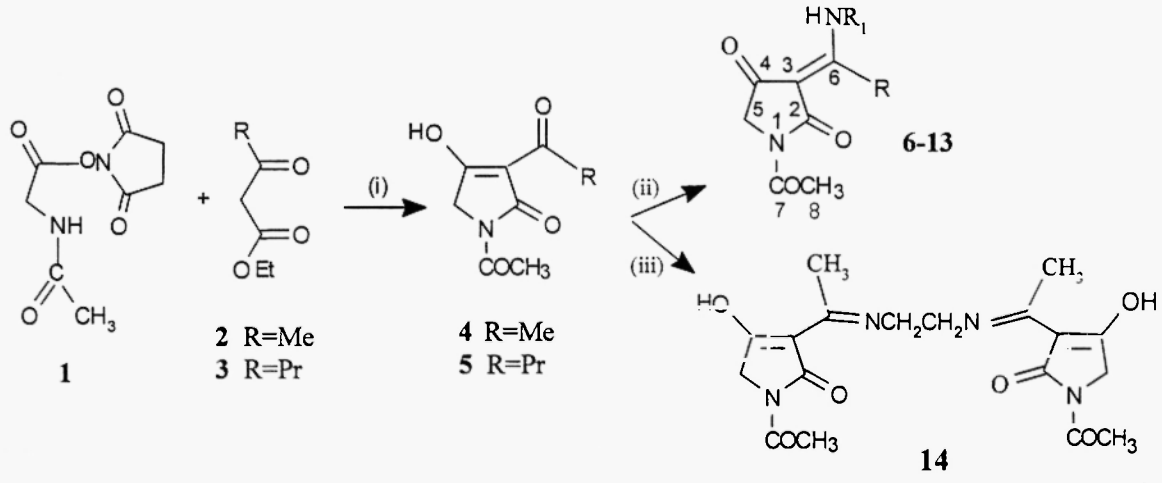
The development of new approaches to the synthesis of heterocyclic compounds containing the β,β′-tricarbonyl system and their coupling with nucleophiles has been a subject of intensive interest. It is known that nitrogen derivatives of cyclic carbonyl systems have interesting biological properties.[1] For example, the Schiff bases of tenuazonic acid (3-acetyl-4-hydroxy-5-*tert*butyl-pyrrolin-2-one) analogues exhibit antitumor activities.[2] Significant studies in this area have been made by S.Gelin et al.[1] providing a series of tricarbonyl heterocycles and their conversion to enamine derivatives.[3]

As a continuation of our studies on the synthesis of functionalized pyrrolin-2,4-diones (tetramic acids) we have recently described the reaction of N-acetyl-3-acyl tetramic acids with

nitrogen 1,2-(bis)nucleophiles and their metal chemistry.[4] Here we wish to investigate the condensation reaction of N-acetyl-3-acyl tetramic acids with ammonia and primary amines.

In addition, these small molecular systems must be considered to be potential ligands which may participate in metal ion coordination and help in the understanding of the more complex bioactive macromolecules.

The required N-acetyl-3-acyl tetramic acids 4,5 were prepared according to our previously described methodology[5] (Scheme 1).



Scheme 1. (i) NaH, PhH, r.t., (ii) H_2NR_1, absolute ethanol, reflux 2.5 h. (iii) $H_2NCH_2CH_2NH_2$, absolute ethanol, reflux 2.5 h.

Treatment of these compounds with ammonia, methylamine, aniline, benzylamine and ethylenediamine in refluxing ethanol, resulted in complete conversion to the corresponding Schiff bases 6-14 in high yields (Table I).

Table I. Compounds **6 - 13**

	R	R_1	%	m.p. (°C)		R	R_1	%	m.p. (°C)
6	Me	H	75	210-213	**10**	Pr	H	69	186-187
7	Me	CH_3	52	169-170	**11**	Pr	CH_3	61	93-95
8	Me	Ph	89	240-245	**12**	Pr	Ph	74	140-145
9	Me	CH_2Ph	72	156-159	**13**	Pr	CH_2Ph	45	87-90

The structures of the newly obtained compounds N-acetyl-3-aminoalkyl tetramic acids 6-14 were confirmed by elemental analysis and their IR, ^1H and ^{13}C NMR spectral data (Tables II,III).[6]

Table II. ^{1}H NMR spectral data of compounds **6 - 14** (in $CDCl_3$)

Comp	δ ppm
6[a]	2.14 (s, 3H, C-CH_3), 2.36 (s, 3H, $COCH_3$), 3.54 (s, 2H, CH_2 ring), 7.18 (br, 2H, NH_2)
7	2.53 and 2.54 (two s, 3H, $COCH_3$), 2.55 and 2.59 (two s, 3H, C-CH_3), 3.11 (pseudotriplet, 3H, N-CH_3), 4.02 and 3.97 (two s, 2H, CH_2 ring, ab/cd:1.68/1), 10.56 and 11.33 (two s, 1H, NH)
8	2.55 and 2.57 (two s, 3H, $COCH_3$), 2.6 (s, 3H, C-CH_3), 4.14 and 4.07 (two s, 2H, CH_2 ring, ab/cd:1.49/1), 7.18-7.21 and 7.39-7,50 (m, 5H, C_6H_5), 12.13 and 12.87 (two s, 1H, NH)
9	2.55 and 2.58 (two s, 3H, $COCH_3$), 2.61 and 2.65 (two s, 3H, C-CH_3), 4.07 and 4.02 (two s, 2H, CH_2 ring, ab/cd:1.51/1), 4.64 (pseudotriplet, 2H, CH_2Ph), 7.25-7.43 (m, 5H, C_6H_5), 10.94 and 11.74 (two s, 1H, NH)
10[a]	0.82 [t, 3H, $(CH_2)_2CH_3$], 1.43 (m, 2H, $CH_2CH_2CH_3$), 2.36 (s, 3H, $COCH_3$), 2.59 (t, 2H, $CH_2CH_2CH_3$), 3.54 (s, 2H, CH_2 ring), 7.22 (br, 2H, NH_2)
11	1.11 [t, 3H, $(CH_2)_2CH_3$], 1.67 (m, 2H, $CH_2CH_2CH_3$), 2.56 and 2.57 (two s, 3H, $COCH_3$), 2.98 (t, 2H, $CH_2CH_2CH_3$), 3.16 (pseudotriplet, 3H, N-CH_3), 4.05 and 4.00 (two s, 2H, CH_2 ring, ab/cd:1.69/1), 10.60 and 11.41 (two s, 1H, NH)
11[a]	0.97 [t, 3H, $(CH_2)_2CH_3$], 1.50 (m, 2H, $CH_2CH_2CH_3$), 2.41 (s, 3H, $COCH_3$), 2.91 (t, 2H, $CH_2CH_2CH_3$), 3.11 (d, 3H, N-CH_3), 3.85 (br, 2H, CH_2 ring), 10.39 (s, 1H, NH)
12	0.92 [t, 3H, $(CH_2)_2CH_3$], 1.64 (m, 2H, $CH_2CH_2CH_3$), 2.59 and 2.60 (s, 3H, $COCH_3$), 2.87 (t, 2H, $CH_2CH_2CH_3$), 4.14 and 4.05 (two s, 2H, CH_2 ring, ab/cd:1.48/1), 7.19-7.22 and 7.42-7.50 (m, 5H, C_6H_5), 12.13 and 12.87 (two s, 1H, NH)
13	1.09 [t, 3H, $(CH_2)_2CH_3$], 1.64 (m, 2H, $CH_2CH_2CH_3$), 2.55 and 2.59 (two s, 3H, $COCH_3$), 3.03 (t, 2H, $CH_2CH_2CH_3$), 4.07 and 4.01 (two s, 2H, CH_2 ring, ab/cd:1.54/1), 4.65 (pseudotriplet, 2H, CH_2Ph), 7.28-7.42 (m, 5H, C_6H_5), 10.94 and 11.77 (two s, 1H, NH)
14	2.55 and 2.57 (two s, 3H, $COCH_3$), 2.61 and 2.63 (two s, 3H, C-CH_3), 3.75-3.79 (m, 4H, -NCH_2CH_2N-), 4.08 and 4.02 (two s, 2H, CH_2 ring, ab/cd:1.6/1), 10.82 and 11.62 (two s, 2H, NH)

[a] DMSO-d_6

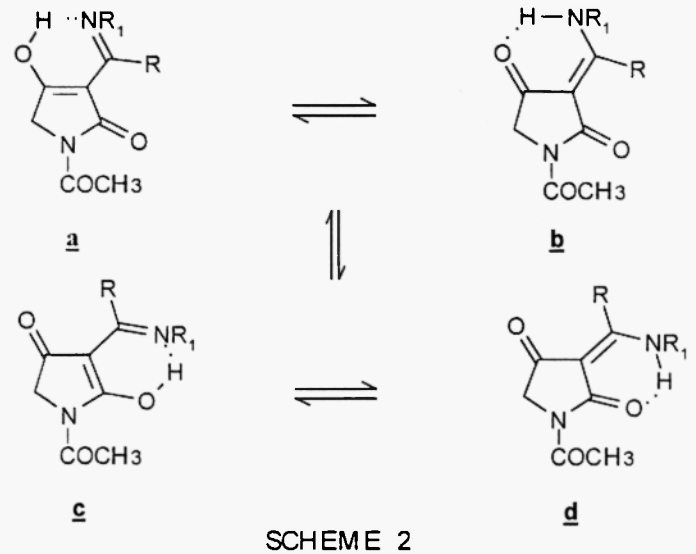
RESULTS AND DISCUSSION

The N-acetyl-3-aminoalkyl tetramic acids could possibly exist in four tautomeric forms **a**,**b** and **c**,**d** (Scheme 2). The prototropic interconversion between 'internal' tautomers **a** ⇄ **b**, **c** ⇄ **d** is rapid and the NMR spectra show signals in which chemical shifts are weighted averages of those of the tautomers. In contrast, in $CDCl_3$ solution, the interconversion between the 'external' tautomers **ab** ⇄ **cd** is comparatively slow on the NMR time-scale; therefore, the 'external' tautomers give separate NMR signals. Such a tautomerism of N-acetyl-3-acyl tetramic acids[5] or N-acetyl-3-hydrazonoalkyl tetramic acids[4] is known. The signals of the ring methylene protons were split into two parts with an intensity ratio of **ab:cd** = 1.57/1 showing that the predominant form is the 'external' tautomer **ab**.

Moreover the observed 'pseudotriplets' of the N-CH_3 and N-CH_2Ph groups originate from partial overlap of two doublets as a result of a coupling interaction (J=5.2 Hz) of methyl and methylene group with the NH proton. This suggests that the compounds 7,9,11,13 exist essentially as a mixture of **b** and **d** species.

Additionally the N-CH_3 signal of 11, in DMSO d_6 solution, is observed as a doublet (J=5.2 Hz) due to the occurrence of one tautomeric form only in this polar solvent.

In $CDCl_3$ solution, the ^{13}C NMR spectra of N-acetyl-3-aminoalkyl tetramic acids, give rise to two resonances for all the carbon atoms. The resonance observed for C-4 and C-2 can be used to assign a specific external pair of tautomer. It is known that hydrogen-bonded carbonyls resonate at lower field than the corresponding free carbonyls.[7] The more intense and more deshielded C-4 hydrogen bonded carbonyl signal led to the conclusion that the exo-enol **b** is the most favorable tautomeric form. Moreover the less intense C-2 carbonyl signal is deshielded in the minor form **d**. In *NH* tetramic acid series, the tautomers **cd** could be predominant,[8] whereas in the *N-acetyl* tetramic acid series the major tautomers could be the **ab** forms.[5] These results fit well with the predominant tautomeric forms **ab** observed in the newly obtained N-acetyl-3-aminoalkyl tetramic acids 6-13. This difference could be attributed to the N-$COCH_3$ group and to the ability of the C-4 carbonyl to form a stronger hydrogen bond than the C-2 carbonyl.



SCHEME 2

Table III. ^{13}C NMR spectral data of compounds **6 - 14** (in $CDCl_3$)

Comp	form	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-α	C-β	C-γ
6[a]		171.1	102.1	190.7	50.9	189.0	168.7	24.7			29.0
7	ab	170.3	97.7	193.6	51.1	172.0	169.1	25.0			13.4
	cd	172.7	96.4	190.1	52.6	171.7	169.6				14.3
8	ab	170.5	98.8	193.9	51.4	170.0	169.6	25.1			15.6
	cd	172.5	97.5	190.6	52.8	169.8	168.9	25.2			16.5
9	ab	170.4	98.1	193.8	51.2	171.3	169.1	25.1			13.8
	cd	172.6	96.8	190.4	52.7	170.9	169.7				14.6
10[a]		171.1	101.5	193.7	50.8	188.9	168.6	24.6	42.2	17.9	14.1
11	ab	170.4	97.1	194.1	51.2	175.5	168.6	25.1	28.4	20.6	14.1
	cd	173.1	95.8	189.5	52.5	175.3	169.6		29.1	20.5	14.0
12	ab	170.4	97.9	194.5	51.4	174.3	168.3	25.1	29.5	22.0	14.1
	cd	173.0	96.6	189.7	52.7	174.0	169.7	25.2	30.2	21.9	14.0
13	ab	170.4	97.2	194.2	51.2	174.7	168.5	25.1	28.7	21.2	14.1
	cd	173.0	96.0	189.6	52.5	174.4	169.7		29.5	21.1	14.0
14	ab	170.4	98.7	194.3	51.2	171.5	168.5	25.2			13.5
	cd	172.6	97.4	190.3	52.7	170.9	169.6				14.3

[a] DMSO-d_6

R= CH_3 , $CH_2CH_2CH_3$
γ α β γ

CONCLUSION

The condensation reaction of N-acetyl-3-acyl tetramic acids with amines provides a rapid entry to novel N-acetyl-3-aminoalkyl tetramic acids a class of compounds with biological interest. From the structural point of view, the newly prepared Schiff bases constitute interest chelate ligands to the formation of amine-transition metal complexes. The synthesis of chiral tetramic acid-Schiff bases and the coordination chemical study of these bioactive compounds with transition metal ions will be the subject of future reports.

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6. The IR spectra were recorded on a Perkin-Elmer 267 spectrometer. The NMR spectra were recorded on a Varian Gemini-2000, 300 MHz spectrometer. Elemental analyses were obtained from the University of Liverpool, Chemistry Department.

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9. General procedure for the synthesis of the N-acetyl-3-aminoalkyl tetramic acids 6-14. To a solution of tetramic acid 4,5 (1 equiv.) in absolute ethanol (15 ml) was added appropriate amine 25% aqueous ammonium hydroxide (2 equiv.), methylamine (2 equiv.), aniline (2 equiv.), benzylamine (2 equiv.), ethylenediamine (0.5 equiv.). After stirring at reflux for 2.5h, the reaction mixture was concentrated *in vacuo*. The resulting solid was filtered off and washed with ethanol.

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