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

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ABSTRACT

3-(Hydrazonoethyl) and 3-(hydrazonobutyl) tetramic acids **6 - 11** are prepared by condensation reaction of N,3-diacetyl and N-acetyl-3-butanoyl tetramic acids, **4** and **5**, with a variety of 1,2-(bis)-nucleophiles. The structure elucidation and the tautomeric equilibrium of the novel compounds **6 - 11** have been studied using ^{1}H and ^{13}C NMR spectroscopy.

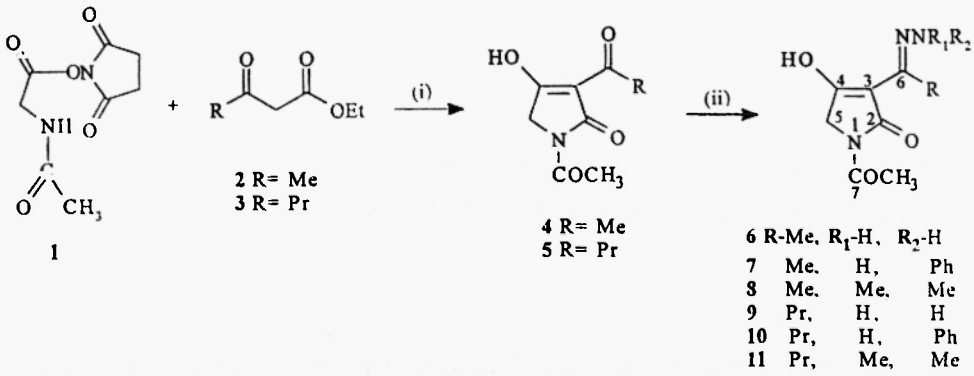
INTRODUCTION

During the course of our research programme concerning the synthesis of nitrogen heterocycles containing cyclic tricarbonyl systems with interesting biological properties, we described in preceding papers an easy access to novel 3-substituted-pyrrolidine-2,4-diones (tetramic acids) (1),(2). In the work described here, taking into account the "reactive sites" of the pyrrolidine-2,4-dione ring system, we attempted to explore the condensation reactions of these compounds with 1,2-(bis)-nucleophiles, such as hydrazine and substituted hydrazines in order to synthesise hydrazone derivatives which allow to anticipate complexation properties and versatile reactivity (3). Synthetic interest in heterocyclic compounds containing the β,β′-tricarbonyl system, and their condensed derivatives with nucleophiles has been intense. One reason for this is their use as precursors for heterocyclic nitrogen derivatives with interesting biological (4),(5),(6) and analytical properties (7).

The first synthetic method for the reactions of 3-acetyl tetramic acids with substituted hydrazines has been reported by S. Gelin (8). Similar reactions of tetramic acids with substituted hydrazines and hydroxylamine has been studied (5). We have recently reported (2) the synthesis of novel N-acetyl-3-substituted tetramic acids **4** and **5**, through an acylation reaction of an active methylene compound **2** or **3** with the N-hydroxysuccinimide ester of N-acetylglucine **1** (Scheme 1). Treatment of the tetramic acids **4** and **5** (1 equiv.) with 1,1-dimethylhydrazine, phenylhydrazine (1 equiv.), and hydrazine (2 equiv.) in boiling ethanol (2.5 h) gave the corresponding novel hydrazones **6-11** in good yields.

As part of our systematic investigation on the coordination chemistry of hydrazone ligands (9),(10),(11) we report here the preparation of complexes of copper (II) acetate salts with compound **10**.

The structure of the newly obtained hydrazone derivatives **6 - 11** was confirmed by elemental analysis, ^{1}H-^{13}C NMR and IR spectral data.



Scheme 1. (i) NaH, PhH, r.t., (ii) $H_2NNR_1R_2$, absolute ethanol, reflux 2.5 h.

EXPERIMENTAL

Melting points were determined on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. 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.

General procedure for the synthesis of 3-acyl tetramic acids 4 and 5.

The active methylene compound **2** or **3** (0.021 mol) was added dropwise to a mixture of sodium hydride (55-60 % sodium hydride in oil; 0.014 mol) in anhydrous benzene (30 ml) and the thick slurry thus formed was stirred at room temperature for 1.5 h. Compound **1** (1.5 g, 0.007 mol) was added to the mixture and stirring continued at room temperature for 1-2.5 h. Water was added to the reaction mixture and the aqueous layer was separated and acidified with 10% hydrochloric acid, in an ice-water bath giving a solid product which was obtained by filtration.

General procedure for the synthesis of hydrazone derivatives of tetramic acids 6-11.

A solution of hydrazine (2 equiv.), or phenylhydrazine (1 equiv.), or 1,1-dimethylhydrazine (1 equiv.) in absolute ethanol was added dropwise to a solution of tetramic acid **4,5** (1 equiv.) in absolute ethanol and the mixture was stirred under reflux for 2.5 h. The resulting mixture was concentrated *in vacuo* and the obtained solid was filtered off and washed with hot ethanol.

N-Acetyl-3-(1-hydrazonoethyl)-4-hydroxy-pyrrolin-2-one (6). Yield 60%, white solid, mp 229-230°C. Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.73, H, 5.58, N, 21.32. Found: C, 48.57, H, 5.73, N, 21.51%.

N-Acetyl-3-[1-(2-phenylhydrazono)-ethyl]-4-hydroxy-pyrrolin-2-one (7) Yield 83%, pale brown solid, mp 178-179°C. Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.54, H, 5.49, N, 15.38. Found: C, 61.28, H, 5.62, N, 15.43%.

N-Acetyl-3-[1-(2-dimethylhydrazono)-ethyl]-4-hydroxy-pyrrolin-2-one (8) Yield 80%, white solid, mp 164-165°C. Anal. Calcd. for $C_{10}H_{15}N_3O_3$: C, 53.33, H, 6.67, N, 18.67. Found: C, 53.17, H, 6.81, N, 18.54%.

N-Acetyl-3-(1-hydrazonobutyl)-4-hydroxy-pyrrolin-2-one (9) Yield 63%, white solid, mp 123-124°C. Anal. Calcd. for $C_{10}H_{15}N_3O_3$: C, 53.33, H, 6.67, N, 18.67. Found: C, 53.21, H, 6.74, N, 18.73%.

N-Acetyl-3-[1-(2-phenylhydrazono)-butyl]-4-hydroxy-pyrrolin-2-one (10) Yield 60%, white solid, mp 140-141°C. Anal. Calcd. for $C_{16}H_{19}N_3O_3 \cdot 1/3\ H_2O$: C, 62.47, H, 6.39, N, 13.66. Found: C, 62.50, H, 6.30, N, 13.63%.

N-Acetyl-3-[1-(2-dimethylhydrazono)-butyl]-4-hydroxy-pyrrolin-2-one (**11**) Yield 56%, white solid, mp 140-143°C. Anal. Calcd. for $C_{12}H_{19}N_3O_3$. 1/3 H_2O: C, 56.92, H, 7.51, N, 16.60. Found: C, 56.74, H, 7.35, N, 16.74%.

Synthesis of Cu(II) complexes of compound 10.

i) $Cu(CH_3COO)(L\text{-}H^+).2H_2O$ **10i**. A solution of **10** (0.24g, **0**.8mmol) in methanol (30 ml) was added dropwise to a solution of $Cu(CH_3COO)_2.H_2O$ (0.16g, 0.8mmol) in hot methanol (40 ml) and the mixture was refluxed for 2 h. The resulting solution was concentrated *in vacuo* and a pale green solid was isolated which was filtered off, washed with ether and dried *in vacuo* over phosphorus pentoxide to yield 0.2g (54.5%).

ii) $Cu(L\text{-}H^+)_2.4H_2O$ **10ii**. A solution of **10** (0.3g, 1mmol) in methanol (35 ml) was added dropwise to a solution of $Cu(CH_3COO)_2.H_2O$ (0.08g, 0.4mmol) in hot methanol (20 ml) and the mixture was refluxed for 2 h. The resulting mixture was concentrated *in vacuo* and an olive-green solid was precipitated which was filtered off, washed with ether and dried *in vacuo* over phosphorus pentoxide to yield **0**.15g (51%).

The complexes are powder-like and stable at atmospheric conditions. The principal infrared bands of interest are listed in Table 1.

Table 1. Some important Infrared Bands (cm^{-1}) in Complexes of compound **10.**

Compound	ν(NH) ν(OH)	ν(C=O)	ν(C=N)	ν(N-N)	ν_{as} (CO_2^-)	ν_s (CO_2^-)	Ring Def.	ν(M-O+ +RingDef)	ν(M-N)
Ligand	3260s	1720s	1570s	1080s					
		1660sh							
$Cu(CH_3CO_2).(L\text{-}H^+)$	3220br	1720s	1605s	1095s	1590sh	1370s	560m	470m	420m
$.2H_2O$	3400br	1680s							
	3420br	1725s	1580s	1110s			500s	420m	350m
$Cu(L\text{-}H^+)_2.4H_2O$	3290s	1665s						380m	

RESULTS AND DISCUSSION

A nucleophile could attack the 3-acyl tetramic acids **4, 5** (Scheme 1), which probably exist in the tautomeric forms **a,b** and **c,d** (1a),(8) (Scheme 2), at any of the three reactive sites: the carbonyl of the acyl group at the 3-position, the carbonyl at the 2-position, and the carbon atom at the 4-position (the carbon of a potential carbonyl group). According to the ^1H and ^{13}C NMR spectra of hydrazone derivatives **6-11** (Tables 2 and 3) the nucleophilic attack of hydrazines is succeeded in the carbonyl of the 3-position of tetramic acid nucleus. The carbonyl carbon C-6 of the N-acyl tetramic acids resonates approximately at 194-189 ppm (1a),(2) whereas the resonance at the C-6 (C=N) hydrazone group appears at higher field 170-180 ppm.

The N-acetyl-3-hydrazonoalkyl tetramic acids **6 - 11** can occur in enolic "internal" tautomers **a** ⇌ **b** and **c** ⇌ **d**, in addition to "external" tautomers **ab** ⇌ **cd** (Scheme 2), demonstrating that a tautomeric equilibrium, due to the various hydrogen-bonding strengths, exists between the external tautomers **a,b** and **c,d** (12).

One set of signals was observed for all protons in DMSO-d_6 solution (polar solvent). In $CDCl_3$ solution, two set of signals were observed for certain protons (Tables 2 and 3). The presence of "external" tautomers was concluded from

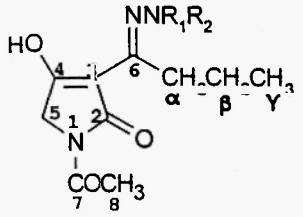


Table 2. ^{1}H NMR spectral data of compounds **6 - 11**

Comp	solvent	δ ppm
6	[$^{2}H_6$]DMSO[a]	2.4 (s, 3H, $COCH_3$), 2.5 (s, 3H, C-CH_3), 3.83 (s, 2H, CH_2 ring), 5.59 (s, 2H, NH_2, D_2O exchangeable), 11.95 (s, 1H, OH, D_2O exchangeable)
7	$CDCl_3$	2.59 and 2.56 (two s, 3H, $COCH_3$), 2.71 (s, 3H, C-CH_3), 4.11 and 4.08 (two s, 2H, CH_2 ring, ab/cd:1.66/1), 6.02 and 5.97 (two s, 1H, NH), 6.7-7.4 (m, 5H, C_6H_5), 11.55 and 12.28 (two s, 1H, OH)
8	$CDCl_3$	2.57 and 2.55 (two s, 3H, $COCH_3$), 2.64 [s, 6H, N-$(CH_3)_2$], 2.67 and 2.69 (two s, 3H, C-CH_3), 4.05 and 4.01 (two s, 2H, CH_2 ring, ab/cd:1.76/1), 10.92 and 11.74 (two s, 1H, OH)
9	[$^{2}H_6$]DMSO[a]	0.82 [t, 3H, $(CH_2)_2CH_3$], 1.43 (m, 2H, $CH_2CH_2CH_3$), 2.35 (s, 3H, $COCH_3$), 2.58 (t, 2H, $CH_2CH_2CH_3$), 3.54 (s, 2H, CH_2 ring), 7.12 (br, 3H, NH_2 and OH)
10	$CDCl_3$	1.04 [t, 3H, $(CH_2)_2CH_3$], 1.65 (m, 2H, $CH_2CH_2CH_3$), 2.56 and 2.60 (two s, 3H, $COCH_3$), 3.14 (t, 2H, $CH_2CH_2CH_3$), 4.10 and 4.07 (two s, 2H, CH_2 ring, ab/cd:1.66/1), 5.94 and 5.98 (two br, 1H, NH), 6.7-7.4 (m, 5H, C_6H_5), 11.05 and 12.28 (two s, 1H, OH, D_2O exchangeable)
11	$CDCl_3$	1.06 [t, 3H, $(CH_2)_2CH_3$], 1.63 (m, 2H, $CH_2CH_2CH_3$), 2.54 and 2.55 (two s, 3H, $COCH_3$), 2.64 [s, 6H, N-$(CH_3)_2$], 3.08 (t, 2H, $CH_2CH_2CH_3$), 4.03 and 3.98 (two s, 2H, CH_2 ring, ab/cd:1.58/1), 10.88 and 11.71 (two br, 1H, OH)

[a] insoluble in $CDCl_3$

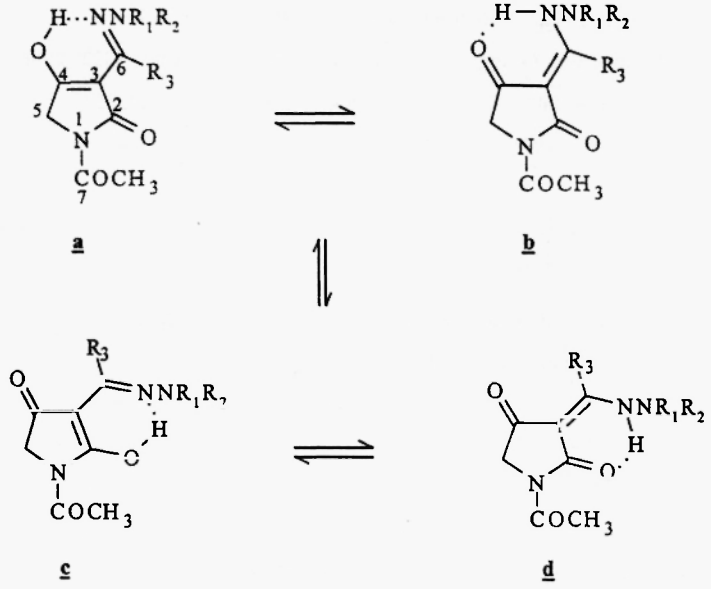
Table 3. ^{13}C NMR spectral data of compounds 6 - **11**

Comp	form	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-α	C-β	C-γ
6		168.7	93.4	190.1	51.1	170.1	164.9	24.8			12.3
7	ab	170.5	97.2	193.8	51.2	174.4	168.6	25.1			12.7
	cd	172.1	96.0	190.5	53.2	173.7	169.9				13.6
8	ab	170.6	96.1	193.5	51.4	172.6	169.3	25.3			13.0
	cd	170.3	94.9	193.6	53.2	170.8	169.9				13.9
9		171.2	101.7	194.0	50.9	189.1	168.7	24.7	42.2	17.9	14.1
10	ab	170.5	96.6	194.4	51.3	178.0	168.1	25.2	27.6	21.8	14.2
	cd	172.6	95.4	189.8	53.2	177.5	169.8	25.1	28.3	21.7	14.1
11	ab	170.4	95.2	193.9	51.2	174.5	168.5	25.1	27.9	21.8	14.2
	cd	172.8	94.1	189.7	52.9	174.1	169.6	25.0	28.7	21.7	14.1

the splitting of the 5-methylene signal in the ^{1}H NMR spectrum, indicating that the dominant form should be the external tautomeric pair **ab**, with an intensity ratio of **ab/cd** = 1.7/1. Gelin et al. (8) postulated that on 3-hydrazonoalkyl tetramic acids, without an acetyl group on the N-1, the dominant form should be the external tautomer **cd** with a ratio of **cd/ab = 1.5/1.**

In our products **6-11** the preferance for tautomers **ab** over the analogous external tautomers **cd** could be attributed to the presence of the acetyl group on the N-1 (N-$COCH_3$). The electron pair of the ring nitrogen is shared between two carbonyl groups (C-2 carbonyl and C-7 carbonyl), thus increasing the possibility for hydrogen bonding on the C-4 carbonyl group.

The ^{13}C NMR spectra of the hydrazones of N-acetyl tetramic acids **6-11** (Table 3), reveal the existance of two forms occuring 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 (12). Thus the chemical shifts observed for C-2 and C-4 could be used to deduce the relative stability of the "external" tautomers. It is known that, the N-acetyl tetramic acids **4, 5** (Scheme **1**) have been found to exist to a greater extent in the **ab** forms (1a), whereas the analogous NH tetramic acids exist to a greater extent in the **cd** forms (12).



SCHEME 2

The magnificent changes in the ligand bands upon complexing are the increase in ν(C=N) and ν(N-N) frequencies. We assign the band at 1570 cm^{-1} in phenylhydrazone of N-acetyl-3-butanoyl tetramic acid 10 to ν(C=N) in accordance to other assignments (13) . The movement of this band to higher frequencies in the spectra of the complexes has been observed and in complexes of other ligands containing the >C=N-N< grouping (14) in which the imino nitrogen atom donates to the metal ion. We assign the band at 1080 cm^{-1} to ν(N-N) in accord with the assignments of this band in N-N bonded molecules (13). Shift of ν(N-N) to higher frequencies has been observed in hydrazine (15) and other α-dihydrazone (16) complexes.

The values of the frequencies assigned as vibrational mode of the acetate group in Table 1 are strongly indicative of the presence of coordination monodentate acetates (17); the Δ values [ν_{as} (CO_2^-) - ν_s (CO_2^-)] is 220 cm^{-1}.

The μ_{eff} values of the complexes are 2.10 BM and 2.30 BM indicating high-spin complexes. Both complexes have electronic spectra consistent with six-coordinated structures [14.2 ($^2E_g \rightarrow {}^2T_{2g}$) (**10i**) and 14.3 ($^2E_g \rightarrow {}^2T_{1g}$) (**10ii**)] (11).

CONCLUSION

We have demonstrated the synthetic utility of *N*-acetyl-3-acyl tetramic acids to obtain hydrazone derivatives. This method constituting a genuine game of building blocks allowed us to isolate in pure form the new compounds, which demonstrated a versatile reactivity. The structural elucidation of these novel derivatives with ^1H-^{13}C NMR and IR spectroscopy was important to analyse both their tautomeric forms and their ligating abilities. We now focus our efforts on the synthesis of optically active hydrazone derivatives of chiral 3-substituted tetramic acids and the investigation of their complexation properties with transition metals.

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Received on September 18, 1998