An efficient synthesis of novel *N*-acetyl-3-alkanoyl and 3-dienoyl tetramic acids

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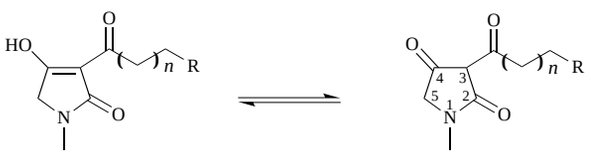
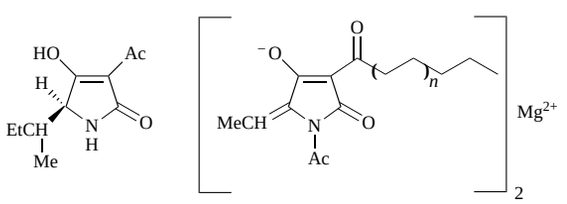
A general synthesis of *N*-acetyl-3-alkanoyl- and 3-dienoyl-tetramic acids is presented. The condensation of *N*-(*N*-acetylglycyloxy)succinimide with β-keto esters bearing alkanoyl or dienoyl groups furnishes the new 3-substituted *N*-acetyltetramic acids 6–9 and 16 in good yields. The key intermediates 4 and 5 have been isolated and subsequently cyclized to the corresponding tetramic acids. Spectral data for and the physical characteristics of all compounds are reported.

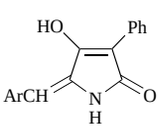
3-Alkanoyl- and 3-dienoyl-tetramic acids, the pyrrolidine-2,4-diones bearing a 3-acyl substituent, constitute a growing class of microbial natural products and exhibit a range of biological activity.[1] Such activity arises from the presence of the



pyrrolidine-2,4-dione ring, the C-3 carbonyl substituent and the C-5 stereogenic centre, together with the ability of the compounds to form complexes with metal ions.[2] Tenuazonic acid **Ia**,[3] magnesidin **Ib**,[4] tirandamycin[5] and streptolydigin,[6] are among the most common 3-acyl substituted tetramic acids which display antibiotic or antiviral activity. Since, recently, 5-arylidene-3-phenyltetramic acids **Ic** have been designed as novel glycine-site NMDA receptor antagonists,[7] their synthesis represents a worthwhile and challenging goal.



Ia **Ib** n = 1,2



Ic

The first synthetic approach to 3-acetyltetramic acids was reported by Lacey[8] in a method later extended to the preparation of 3-substituted tetramic acids.[9] An alternative strategy for the preparation of 3-substituted pyrrolidine-2,4-diones was described by Jones,[10] using pyrones and, more recently, isoxazole-4-carboxylates as precursors. Finally an important method designed for the formation of 3-polyenoyl tetramic acids was described by Ley,[11] in which the key step provided a series of β-keto amides as suitable precursors for synthesis of the target compounds.

In the course of our research programme on the use of enolic β-dicarbonyl compounds for the synthesis of nitrogen heterocycles[12] we have developed a new synthetic sequence for the construction of *N*-acetyl-3-alkanoyl- and 3-dienoyl-tetramic acids. The proposed methodology is centred on the condensation of the *N*-(*N*-acetylglycyloxy)succinimide with an excess of the anion of an appropriate β-keto ester, generated by the action of sodium hydride (Scheme 1). This strategy consists of the following experimental stages: (i) the synthesis of β-keto esters bearing an α-alkanoyl group, according to an extension of the method proposed by Oikawa and Sugano,[13] and (ii) the *C*-acylation of β-keto esters *via* *N*-(*N*-acetylglycyloxy)succinimide. The crucial step in this reaction is the preparation of suitable key intermediates **4** and **5** which cyclize to the desired tetramic acids.

In a typical *C*-acylation the β-keto ester **1** (3 equiv.) was treated with sodium hydride (2 equiv.) in anhydrous benzene and then the NHSuc ester **2** (1 equiv.). After *ca.* 3 h the intermediate ethyl 4-acetylamino-2-alkanoyl-3-hydroxybut-2-enoates **4** and **5** were isolated in pure form after recrystallization. We noted that the corresponding *C*-acylation intermediate **3** having a short-chain alkanoyl substituent was obtained in admixture with the corresponding cyclized compound **6**. Ring closure of the intermediates **3**–**5** to the tetramic acids **10**–**12** having a 3-alkanoyl substituent was achieved by heating them in sodium ethoxide in ethanol–benzene. However, we noticed that an increase in the molar proportion of sodium hydride in the reaction mixture caused *in situ* formation of the 3-substituted *N*-acetyltetramic acids **6**–**9**. This *C*-acylation–cyclization was carried out using 3 equiv. of the β-keto ester **1**, 2.5–3 equiv. of sodium hydride in anhydrous benzene, 1 equiv. of the NHSuc ester **2**, and with the reaction mixture being stirred for 5 h. The *N*-acetyltetramic acids **6**–**9** thus formed through intramolecular condensation were deacetylated to their corresponding tetramic acids **10**–**12** in the presence of sodium ethoxide in ethanol–benzene.

The *N*-acetyl- and *N*H-3-alkanoyl-tetramic acids **6**–**9** and **10**–**12** have not been previously prepared apart from the derivative **12**, whose antimicrobial activity was reported by Matsuo and co-workers.[14] In the course of our synthetic programme with nitrogen heterocycles of biological interest we needed the *C*-acylation intermediates, ethyl 4-acetylamino-2-alkanoyl-3-hydroxybut-2-enoates **3**–**5**, containing the enolic β-dicarbonyl system. It is noteworthy that these compounds have great interest both as precursors for the preparation of chiral β-hydroxy-γ-aminobutanoic acids and in the asymmetric synthesis of statine analogues.[15]

The goal of our methodology was not only the synthesis of 3-alkanoyltetramic acids, but also their use as precursors in the synthesis of the magnesidin-related tetramic acids **13** and **14** by

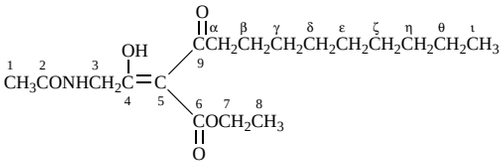
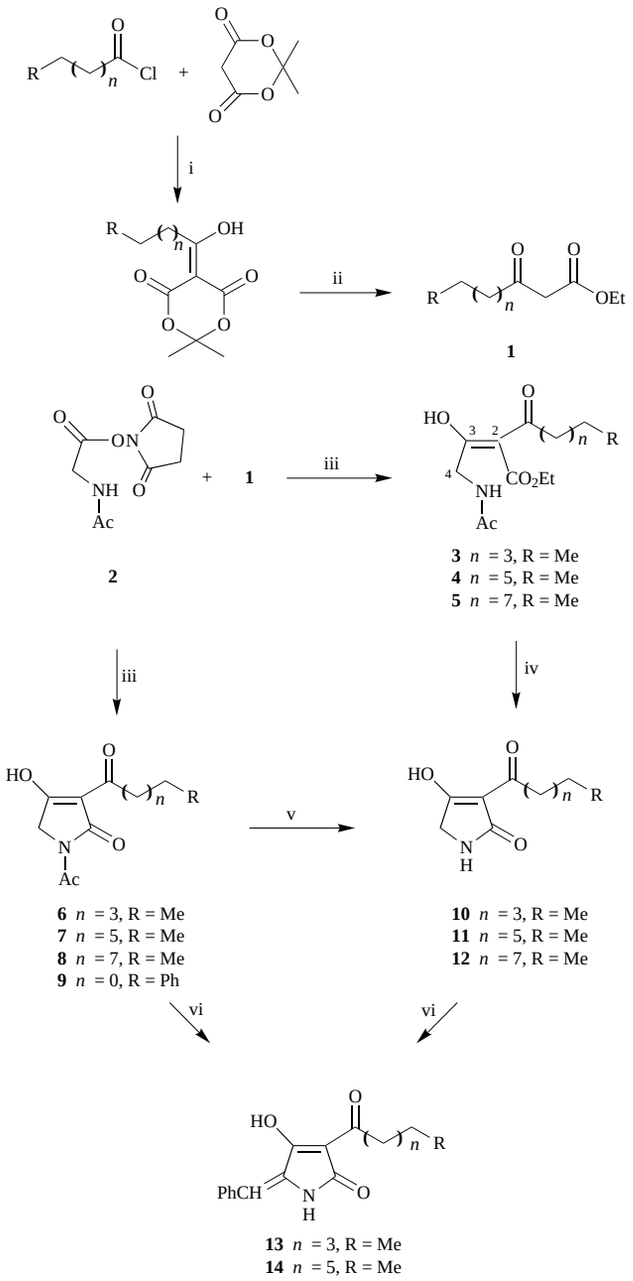


Table 1 ^{13}C NMR chemical shifts for *C*-acylation of compounds **4** and **5** ($CDCl_3$)

Compd.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-α	C-β	C-γ	C-δ	C-ε	C-ζ	C-η	C-θ	C-ι
4	31.47	166.17	46.42	197.22	106.72	170.40	60.98	14.00	196.15	36.42	29.23	28.79	26.29	22.88	22.40	—	—	13.85
5	31.79	166.06	46.53	197.09	106.72	170.20	61.05	14.14	196.02	36.52	29.38	29.35	29.26	29.19	26.43	23.06	22.59	14.03

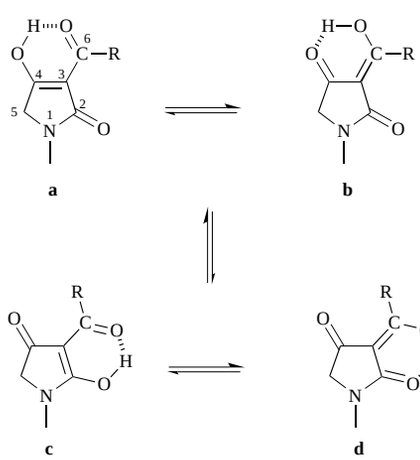


Scheme 1 *Reagents and conditions*: i, pyridine, nitrogen atmosphere, CH_2Cl_2; ii, EtOH, reflux; iii, NaH, anhydrous benzene, 5–10 °C; iv, EtONa, EtOH–anhydrous benzene, reflux; v, EtONa, EtOH, reflux; vi, 8% HCl in EtOH, benzaldehyde, reflux

a convenient and straightforward route (Scheme 1). The synthesis employed for the preparation of 5-benzylidenepyrrolidine-2,4-diones **13** and **14** involved the condensation of compounds **6** and **7** and **10** and **11** with benzaldehyde in the presence of an 8% solution of HCl in ethanol. Recently, 5-arylidene-3-phenylpyrrolidine-2,4-diones **Ic** have been designed as novel glycine NMDA receptor antagonists in the treatment of neurological diseases, their biological properties arising from the enolic β-dicarbonyl moiety, the hydrophobic 5-substituent and the lipophilic 3-phenyl substituent.[7]

The IR spectra of the newly prepared 3-substituted *N*-acetyltetramic acids (see Experimental section) showed CO absorption at 1740, 1720 and 1650 cm^{-1} for the β-dicarbonyl system CO–CH–CO ⟷ C(OH)=C–CO and carbon–carbon double bond absorption at 1600 cm^{-1}.

Considerable emphasis has been given to the influence of the *N*-substituent on the tautomeric equilibrium of tetramic acids (Scheme 2).[12a,16] Structural assignments for the previously



Scheme 2 Tautomeric forms of 3-substituted tetramic acids

unknown *N*-acetyl-3-alkanoyltetramic acids were confirmed by ^1H and ^{13}C NMR spectroscopy (Table 2). Two sets of signals were observed for certain protons in $CDCl_3$ solution, showing the presence of the 'external' tautomers **ab** and **cd**. In the ^1H NMR spectrum the 5-methylene signal was split into two parts (**ab**) and (**cd**), indicating that the dominant form should be the 'external' tautomers **ab** with an intensity ratio of **ab**/**cd** = 1.52, whereas for the *NH* tetramic acid the dominant form should be the 'external' tautomers **cd** with a ratio of **cd**/**ab** = 3.44. As we have reported in a previous paper for the *N*-benzyloxycarbonyl-3-acetyltetramic acid the major form is the tautomer **cd** (**cd**/**ab** = 1.4).[12b] These observations suggested that electron donating *N*-substituents increase the possibility for hydrogen bonding on the C-4 carbonyl (**ab**), whereas electron-withdrawing substituents enhance the C-2 hydrogen bond (**cd**).

Of particular importance is the applicability of the proposed methodology to the construction of 3-dienoyl tetramic acids (Scheme 3). An investigation of structure–activity relationships showed that the 3-dienoyl unit of tetramic acids is crucial for activity.[17] As a model experiment, the active methylene compound **15** was synthesized starting from sorbyl chloride and proceeding *via* Meldrum's acid with a modification of the conditions used for the construction of β-keto esters. Preliminary experiments showed that reaction of **2** with the β-keto ester **15**,

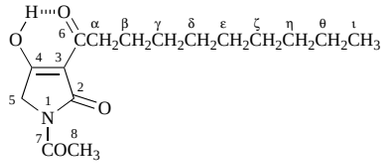
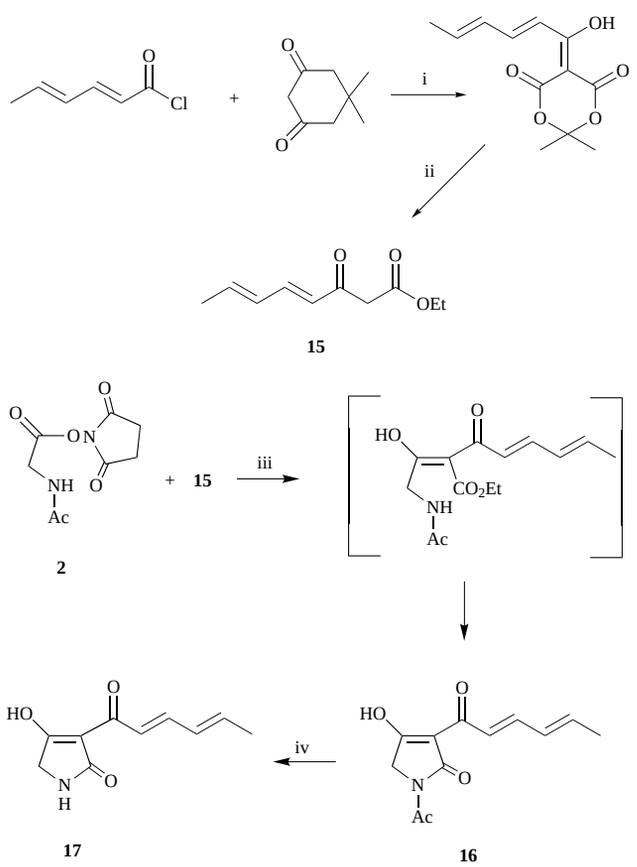


Table 2 ^{13}C NMR chemical shifts for the tetramic acids **6**–**8** and **10**–**12** ($CDCl_3$)

Compd.		C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-α	C-β	C-γ	C-δ	C-ε	C-ζ	C-η	C-θ	C-ι
6	**ab**	170.09	105.38	198.08	49.73	194.10	165.54	35.26	31.30	25.39	24.66	22.26	—	—	—	—	13.79
	cd	173.53	102.64	192.68	53.60	188.99	169.32	—	33.11	25.62	25.05	—	—	—	—	—	—
7	**ab**	170.00	104.80	198.00	49.70	193.90	165.45	35.30	31.50	27.57	25.70	22.99	22.80	21.88	—	—	13.82
	cd	173.50	102.00	192.50	53.62	189.00	169.00	—	33.15	27.80	—	—	—	—	—	—	—
8	**ab**	170.11	105.38	198.11	49.73	194.12	165.53	35.31	31.79	29.19	25.95	25.04	25.03	22.68	22.59	21.84	14.04
	cd	173.54	102.62	192.72	53.61	188.99	169.33	—	33.19	29.30	—	—	—	—	—	—	—
10	**ab**	170.29	105.00	199.25	48.58	193.59	—	—	33.41	31.94	25.12	—	—	—	—	—	—
	cd	176.73	101.42	192.98	51.86	189.75	—	—	32.61	31.20	25.47	22.16	—	—	—	—	13.67
11	**ab**	170.05	105.00	199.05	48.56	193.79	—	—	33.46	—	—	—	25.48	—	—	—	—
	cd	176.65	101.37	192.91	51.81	189.79	—	—	32.69	29.06	28.84	28.80	25.82	22.45	—	—	13.89
12	**ab**	170.16	105.00	198.79	48.48	193.09	—	—	33.56	—	29.47	—	—	—	25.53	—	—
	cd	176.38	101.15	192.60	51.73	189.24	—	—	32.74	31.79	29.39	29.32	29.19	28.93	25.90	22.59	14.03



Scheme 3 *Reagents and conditions*: i, pyridine, nitrogen atmosphere, absence of light, CH_2Cl_2; ii, EtOH, reflux; iii, NaH, anhydrous benzene, room temp.; iv, EtONa, EtOH–anhydrous benzene, room temp.

in the presence of NaH (2 equiv.) in anhydrous benzene, resulted in the rapid formation (2 h) of the *N*-acetyl-3-dienoyltetramic acid **16**. The crude product was *N*-deacetylated with sodium ethoxide in ethanol–benzene to form the corresponding 3-dienoyltetramic acid **17** (mp 211–213 °C, lit.,[18] 211–212 °C).

The proposed methodology has the following merits: (i) the NHSuc esters of *N*-acetyl-α-amino acids are useful acylating agents. The *N*-hydroxysuccinimide formed as a by-product is soluble in water and easily removed from the reaction mixture; (ii) the key intermediates can be isolated under controlled reaction conditions; (iii) the *C*-acylation–cyclization leads directly to the newly obtained *N*-acetyl-3-alkanoyltetramic acids which can be easily converted into deacetylated tetramic acids in good yields (yield 50–80%); (iv) the proposed strategy is also applicable to the controlled synthesis of 3-dienoyltetramic acids; (v) the condensation of tetramic acids with benzaldehyde favours the straightforward formation of 5-benzylidenetetramic acids.

In conclusion, the new synthetic sequence described here constitutes a method for the construction of interesting pyrrolidine-2,4-diones bearing a different side chain at position 3. With the aid of this method, the application of our strategy to natural products synthesis is currently being pursued.

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 either Varian EM-360 60 MHz, Varian Gemini-2000 300 MHz or Bruker AC-300 300 MHz spectrometers, using Me_4Si as internal reference. Chemical shifts are quoted in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad); *J* values are given in Hz. The mass spectra were recorded on a Varian Saturn 2000 (GC-MS) or GC/MS HP 5890/5971 instrument using electron impact ionization (EI). Elemental analyses were obtained from the University of Liverpool, Chemistry Department, and the microanalytical laboratory of CNRS (France). Column chromatography was performed using Merck Kieselgel 60 (70–230 mesh ASTM) silica. Thin layer chromatography (TLC) was carried out using Merck Kieselgel 60 F_{259} pre-coated silica gel plates of thickness 0.2 mm. Solvents and reagents were dried or purified according to the procedure described by Perrin and Armarego.[19]

Preparation of β-keto esters

The requisite β-keto esters **1** and **15** were prepared following the method of Oikawa and Sugano,[13] but with minor modifications: the mixture of the Meldrum's acid with the sorbyl chloride in the presence of pyridine was stirred under nitrogen atmosphere, in the absence of light, for 1.5 h at 0 °C and then at room temperature for 2.5 h. The ethanolysis of the acyl Meldrum's acid was carried out under reflux for 1.5 h. The pure compound **15** was isolated by column chromatography on silica gel eluting with 10% ethyl acetate–diethyl ether.

N-(*N*-Acetylglycyloxy)succinimide 2

A mixture of *N*-acetylglycine (6 g, 0.05 mol), *N*-hydroxysuccinimide (5.8 g, 0.05 mol) and THF (160 ml) was stirred at 60 °C for 0.5 h, after which it was treated with a solution of

N,*N*-dicyclohexylcarbodiimide (10.3 g, 0.05 mol) in THF (20 ml), added dropwise, the temperature of the reaction mixture being kept at 60 °C. The resulting mixture was stirred at 60 °C for 1 h after which it was refrigerated overnight. The precipitated *N*,*N*-dicyclohexylurea was filtered off and the filtrate was concentrated *in vacuo* to give a residue. This was treated with diethyl ether to afford **2** as a white powdered solid (8.4 g, 76.4%), mp 100–103 °C (from ethyl acetate–diethyl ether) (lit.,[20] mp 98 °C); δ_H(60 MHz; $CDCl_3$; Me_4Si) 2.00 (3 H, s, $COCH_3$), 2.74 [4 H, s, $CO(CH_2)_2CO$], 4.25 (2 H, d, *J* 6, CH_2CO) and 6.00 (1 H, br, NH).

General procedure for the reactions of *N*-(*N*-acetylglycyloxy)-succinimide 2 with active methylene compounds

The active methylene compounds **1** and **15** (15.9 mmol) were added dropwise to a mixture of sodium hydride (55–60% sodium hydride in oil; 10.6 mmol) in anhydrous benzene (30 ml) and the thick slurry thus formed was stirred at room temperature for 3 h. Compound **2** (1.2 g, 5.3 mmol) was then added to the mixture and stirring continued at 5–10 °C for 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, to give either a solid or an oily product that was extracted with chloroform.

Ethyl 4-acetylamino-2-octanoyl-3-hydroxybut-2-enoate 4

The reaction mixture [compound **2** (1.2 g, 5.3 mmol), ethyl octanoylacetate **1** (*n* = 5, R = Me) (3.3 g, 15.9 mmol) and sodium hydride (10.6 mmol) in anhydrous benzene (30 ml)] was stirred at 5–10 °C for 4 h after which it was acidified with 10% hydrochloric acid to give an oily product which was extracted with chloroform. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to give a residue. This was treated with light petroleum to afford the *C*-acylation product **4** as a yellowish solid (0.6 g, 36.3%) after it had been filtered off and washed with small amounts of light petroleum; mp 67–70 °C (from $CHCl_3$–light petroleum) (Found: C, 61.20; H, 8.60; N, 4.40. $C_{16}H_{27}O_5N$ requires C, 61.32; H, 8.68; N, 4.47); ν_{max}(Nujol)/cm^{-1} 3280m (NH), 1690s (CO ester and CO ketone, keto form and amide I), 1630s (CO ester and CO ketone, enol form and C=C) and 1550s (amide II); δ_H(300 MHz; $CDCl_3$; Me_4Si), 0.85 [6 H, t, *J* 7, $(CH_2)_6CH_3$ and CH_2CH_3], 1.25–1.35 [8 H, m, $(CH_2)_4CH_3$], 1.58–1.66 [2 H, m, $CH_2(CH_2)_4$], 2.03 and 2.04 (3 H, two s, $COCH_3$), 2.66 (2 H, t, *J* 7, $COCH_2$), 4.26 (2 H, q, *J* 7, CH_2CH_3), 4.48 (2 H, d, *J* 6, $NHCH_2$), 6.36 (1 H, br, NH) and 17.29 (1 H, br, OH); δ_C($CDCl_3$; Me_4Si), see Table 1. Treatment of **4** with MSTFA–MBTFA reagents yielded the corresponding derivatives ($C_{21}H_{34}NO_6F_3Si$); *m*/*z* (EI) 367 ([M − $(CH_2)_5CH_3$ − Et]$^+$, 24%), 352 ([M − H − $(CH_2)_6CH_3$ − Et]$^+$, 100), 310 ([M − H − $Si(Me)_3$ − $COCF_3$]$^+$, 91), 282 ([M + H − $CO(CH_2)_6CH_3$ − CO_2Et]$^+$, 52), 240 (25), 208 (10) and 73 (38).

Ethyl 4-acetylamino-2-decanoyl-3-hydroxybut-2-enoate 5

The reaction mixture [compound **2** (1.2 g, 5.3 mmol), ethyl decanoylacetate **1** (*n* = 7, R = Me) (3.8 g, 15.9 mmol) and sodium hydride (10.6 mmol) in anhydrous benzene (30 ml)] was stirred at 5–10 °C for 4 h after which it was acidified with 10% hydrochloric acid to give an oily product which was extracted with chloroform. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to give a residue. This was treated with light petroleum to afford the *C*-acylation product **5** as a yellowish solid (0.7 g, 36.5%) after it had been filtered off and washed with small amounts of light petroleum; mp 77–80 °C (from $CHCl_3$–light petroleum) (Found: C, 63.50; H, 9.20; N, 4.06. $C_{18}H_{31}O_5N$ requires C, 63.31; H, 9.15; N, 4.10); ν_{max}(Nujol)/cm^{-1} 3280m (NH), 1690s (CO ester and CO ketone, keto form and amide I), 1630s (CO ester and CO ketone, enol form and C=C) and 1550s (amide II); δ_H(300 MHz; $CDCl_3$; Me_4Si), 0.86 [6 H, t, *J* 7, $(CH_2)_8CH_3$ and CH_2CH_3], 1.25–1.37 [12 H, m, $(CH_2)_6CH_3$], 1.61–1.63 [2 H, m, $CH_2(CH_2)_6$], 2.03 and 2.04 (3 H, two s, $COCH_3$), 2.68 (2 H, t, *J* 7, $COCH_2$), 4.27 (2 H, q, *J* 7, CH_2CH_3), 4.48 (2 H, d, *J* 6, $NHCH_2$), 6.50 (1 H, br, NH) and 17.30 (1 H, br, OH); δ_C($CDCl_3$; Me_4Si), see Table 1; *m*/*z* (EI) 340 ([M − H]$^+$, 25%), 281 ([M − CH_3CONH − 2H]$^+$, 100), 221 (20), 147 (25) and 73 (74).

***N*-Acetyl-3-hexanoyltetramic acid 6**

The reaction mixture [compound **2** (1.2 g, 5.3 mmol), ethyl hexanoylacetate **1** (*n* = 3, R = Me) (2.9 g, 15.9 mmol) and sodium hydride (13.3 mmol) in anhydrous benzene (30 ml)] was stirred at 5–10 °C for 5 h after which it was acidified with 10% hydrochloric acid to give a solid. This was filtered off and washed with light petroleum to afford the product **6** (0.7 g, 50.9%), mp 74–79 °C (from $CHCl_3$–light petroleum) (Found: C, 56.18; H, 7.29; N, 5.39. $C_{12}H_{17}O_4N{\cdot}H_2O$ requires C, 56.02; H, 7.44; N, 5.44); ν_{max}(Nujol)/cm^{-1} 3310m (OH), 1740m and 1720m (CO diketone, keto form and CONCO), 1640s (CO diketone, enol form) and 1600m (C=C); δ_H(60 MHz; $CDCl_3$; Me_4Si), 0.70–2.00 [9 H, m, $(CH_2)_3CH_3$], 2.60 (3 H, s, $COCH_3$), 3.00 (2 H, t, *J* 7, $COCH_2$), 4.10 (**cd**) and 4.30 (**ab**) (two s, 2 H, CH_2-ring, **ab**:**cd** 1.5) and 8.40 (1 H, br, OH); δ_C($CDCl_3$; Me_4Si), see Table 2; *m*/*z* (EI) 240 ([M + H]$^+$, 100%).

***N*-Acetyl-3-octanoyltetramic acid 7**

The reaction mixture [compound **2** (1.2 g, 5.3 mmol), ethyl octanoylacetate **1** (*n* = 5, R = Me) (3.4 g, 15.9 mmol) and sodium hydride (15.9 mmol) in anhydrous benzene (30 ml)] was stirred at 5–10 °C for 5 h after which it was acidified with 10% hydrochloric acid to give a solid. This was filtered off and washed with light petroleum to afford the product **7** (0.8 g, 52.9%), mp 67–70 °C (from $CHCl_3$–light petroleum); ν_{max}(Nujol)/cm^{-1} 3300m (OH), 1740m and 1720m (CO diketone, keto form and CONCO), 1650s (CO diketone, enol form) and 1600m (C=C); δ_H(60 MHz; $CDCl_3$; Me_4Si) 0.70–2.00 [13 H, m, $(CH_2)_5CH_3$], 2.60 (3 H, s, $COCH_3$), 2.85 (2 H, t, *J* 7, $COCH_2$), 4.00 (**cd**) and 4.20 (**ab**) (two s, 2 H, CH_2-ring, **ab**:**cd** 1.49) and 11.6 (1 H, br, OH); δ_C($CDCl_3$; Me_4Si), see Table 2; *m*/*z* (EI) 267 ([M]$^+$, 3%), 223 ([M − H − $COCH_3$]$^+$, 8), 196 ([M − $(CH_2)_4CH_3$]$^+$, 100), 168 ([M − $(CH_2)_6CH_3$]$^+$, 13), 141 ([M + H − $CO(CH_2)_6CH_3$]$^+$, 59), 127 (3), 126 ([M + H − $(CH_2)_6CH_3$ − $COCH_3$]$^+$, 39) and 99 (11).

***N*-Acetyl-3-decanoyltetramic acid 8**

The reaction mixture [compound **2** (1.2 g, 5.3 mmol), ethyl decanoylacetate **1** (*n* = 7, R = Me) (3.8 g, 15.9 mmol) and sodium hydride (15.9 mmol) in anhydrous benzene (30 ml)] was stirred at 5–10 °C for 5 h after which it was acidified with 10% hydrochloric acid to give a solid. This was filtered off and washed with light petroleum to afford the product **8** (0.9 g, 55.4%), mp 57–61 °C (from $CHCl_3$–light petroleum) (Found: C, 63.20; H, 8.62; N, 4.85. $C_{16}H_{25}O_4N{\cdot}1/2H_2O$ requires C, 63.14; H, 8.61; N, 4.6); ν_{max}(Nujol)/cm^{-1} 3300m (OH), 1730m, 1720m (CO diketone, keto form and CONCO), 1610s (CO diketone, enol form) and 1600m (C=C); δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.85 [3 H, t, *J* 7, $(CH_2)_8CH_3$], 1.25–1.45 [12 H, m, $(CH_2)_6CH_3$], 1.67–1.75 [2 H, m, $CH_2(CH_2)_6$], 2.57 and 2.59 (3 H, two s, $COCH_3$), 2.89 and 2.94 (2 H, two t, *J* 7, $COCH_2$), 4.08 (**cd**) and 4.27 (**ab**) (two s, 2 H, CH_2-ring, **ab**:**cd** 1.52); δ_C($CDCl_3$; Me_4Si), see Table 2; *m*/*z* (EI) 295 ([M]$^+$, 10%), 242 (21), 239 ([M + H − $(CH_2)_3CH_3$]$^+$, 17), 238 ([M − $(CH_2)_3CH_3$]$^+$, 100).

***N*-Acetyl-3-phenylacetyltetramic acid 9**

The reaction mixture [compound **2** (1.2 g, 5.3 mmol), ethyl phenylacetylacetate **1** (*n* = 0, R = Ph) (3.4 g, 15.9 mmol) and sodium hydride (13.25 mmol) in anhydrous benzene (30 ml)] was stirred at 5–10 °C for 5 h after which it was acidified with 10% aq. hydrochloric acid to give a brownish solid. This was filtered off and washed with light petroleum to afford the product **9** (0.7 g, 53.9%); mp 73–75 °C (from PhH–light petroleum) (Found: C, 64.75; H, 5.07; N, 5.37. $C_{14}H_{13}O_4N$ requires C,

64.86; H, 5.02; N, 5.41); ν_{max}(Nujol)/cm^{-1} 3340m (OH), 1740w, 1720m (CO diketone, keto form and CONCO), 1640s (CO diketone, enol form) and 1595s (C=C ring stretching); δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.59 and 2.62 (3 H, two s, $COCH_3$), 4.14 (**cd**) and 4.24 (**ab**) (two s, 2 H, CH_2-ring, **ab**:**cd** 3.5), 4.30 (2 H, s, $CH_2C_6H_5$), 7.26–7.38 (5 H, m, ArH) and 18.2–18.6 (1 H, br, OH).

***N*-Acetyl-3-(hexa-2,4-dienoyl)tetramic acid 16**

The reaction mixture [compound **2** (1.5 g, 7.2 mmol), ethyl hexa-2,4-dienoylacetate **15** (1.3 g, 7.2 mmol) and sodium hydride (14.3 mmol) in anhydrous benzene (15 ml)] was stirred at room temperature for 2 h after which it was acidified with 10% hydrochloric acid to give an oily product which was extracted with chloroform. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to give the crude product **16** (0.7 g, 40.3%), as a yellowish solid, which was used for the deacetylation without further purification.

General method for the formation of *N*H-tetramic acids

A solution of the *N*-acetyltetramic acid or C-acylation compound (2.3 mmol) in anhydrous benzene (20 ml) was added to a solution of sodium ethoxide in ethanol [prepared from sodium (0.1 g, 5.7 mmol) in absolute ethanol (20 ml)]. The reaction mixture was refluxed for 3–6.5 h and, after being set aside overnight at room temperature, was diluted with water. The aqueous layer was separated and acidified with 10% aq. hydrochloric acid, in an ice–water bath to give either a solid or an oily product which was extracted with chloroform.

3-Hexanoyltetramic acid 10

From *N*-acetyl-3-hexanoyltetramic acid 6. The reaction mixture [compound **6** (1.1 g, 4.6 mmol) dissolved in the sodium ethoxide in ethanol] was refluxed for 3 h and then set aside overnight at room temperature. Compound **10** was obtained as a solid (0.6 g, 66.5%), mp 116–119 °C (from PhH–light petroleum) (Found: C, 60.98; H, 7.71; N, 7.03. $C_{10}H_{15}O_3N$ requires C, 60.89; H, 7.67; N, 7.10); ν_{max}(Nujol)/cm^{-1} 3170br (NH), 1710s (CO diketone, keto form and CO lactam), 1640s (CO diketone, enol form) and 1590s (C=C); δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.88 [3 H, t, *J* 7, $(CH_2)_4CH_3$], 1.26–1.40 [4 H, m, $(CH_2)_2CH_3$], 1.61–1.71 [2 H, m, $CH_2(CH_2)_2$], 2.83 and 2.89 (2 H, two t, *J* 7, $COCH_2$), 3.79 (**cd**) and 3.93 (**ab**) (two s, 2 H, CH_2-ring, **cd**:**ab** 3.33) and 6.60 (1 H, br, NH); δ_C($CDCl_3$; Me_4Si), see Table 2; *m*/*z* (EI) 198 ([M + H]$^+$, 100%), 168 ([M − CH_2CH_3]$^+$, 1), 154 ([M − $(CH_2)_2CH_3$]$^+$, 6), 141 ([M + H − $(CH_2)_3CH_3$]$^+$, 11), 126 ([M − $(CH_2)_4CH_3$]$^+$, 14), 69 (2) and 55 (4).

3-Octanoyltetramic acid 11

From *N*-acetyl-3-octanoyltetramic acid 7. The reaction mixture [compound **7** (1.3 g, 4.9 mmol) dissolved in the sodium ethoxide in ethanol] was refluxed for 3 h and then set aside overnight at room temperature. Compound **11** was obtained as a solid (0.8 g, 70.3%), mp 113–116 °C (from PhH–light petroleum).

From ethyl 4-acetylamino-2-octanoyl-3-hydroxybut-2-enoate 4. The reaction mixture [compound **4** (0.7 g, 2.2 mmol) dissolved in the sodium ethoxide in ethanol] was refluxed for 5 h and then set aside overnight at room temperature. Compound **11** was obtained as a solid (0.3 g, 59.6%), mp 113–116 °C (from PhH–light petroleum) (Found: C, 63.96; H, 8.55; N, 6.11. $C_{12}H_{19}O_3N$ requires C, 63.97; H, 8.50; N, 6.22); ν_{max}(Nujol)/cm^{-1} 3200br (NH), 1710s (CO diketone, keto form and CO lactam), 1640s (CO diketone, enol form) and 1600s (C=C); δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.87 [3 H, t, *J* 7, $(CH_2)_6CH_3$], 1.26–1.39 [8 H, m, $(CH_2)_4CH_3$], 1.61–1.71 [2 H, m, $CH_2(CH_2)_4$], 2.84 and 2.90 (2 H, two t, *J* 7, $COCH_2$), 3.79 (**cd**) and 3.93 (**ab**) (two s, 2 H, CH_2-ring **cd**:**ab** 4) and 6.43 (1 H, br, NH); δ_C($CDCl_3$; Me_4Si), see Table 2; *m*/*z* (EI) 226 ([M + H]$^+$, 100%), 154 ([M − $(CH_2)_4CH_3$]$^+$, 17), 141 ([M + H − $(CH_2)_5CH_3$]$^+$, 40), 126 ([M − $(CH_2)_6CH_3$]$^+$, 26), 98 ([M − $CO(CH_2)_6CH_3$]$^+$, 5), 69 (6) and 55 (5).

3-Decanoyltetramic acid 12

From *N*-acetyl-3-decanoyltetramic acid 8. The reaction mixture [compound **8** (1.3 g, 4.4 mmol) dissolved in the sodium ethoxide in ethanol] was refluxed for 5 h and then set aside overnight at room temperature. Compound **12** was obtained as a solid (0.8 g, 71.8%), mp 108–109 °C (from PhH–light petroleum) (lit.,[14] mp 107–110 °C).

From ethyl 4-acetylamino-2-decanoyl-3-hydroxybut-2-enoate 5. The reaction mixture [compound **5** (1.1 g, 3.3 mmol) dissolved in the sodium ethoxide in ethanol] was refluxed for 6.5 h and then set aside overnight at room temperature. Compound **12** was obtained as a solid (0.7 g, 82%), mp 108–109 °C (from PhH–light petroleum) (Found: C, 66.27; H, 9.22; N, 5.43. $C_{14}H_{23}O_3N$ requires C, 66.37; H, 9.15; N, 5.53); ν_{max}(Nujol)/cm^{-1} 3145br (NH), 1710s (CO diketone, keto form and CO lactam), 1640s (CO diketone, enol form) and 1600s (C=C); δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.85 [3 H, t, *J* 7, $(CH_2)_8CH_3$], 1.24–1.33 [12 H, m, $(CH_2)_6CH_3$], 1.59–1.69 [2 H, m, $CH_2(CH_2)_6$], 2.83 and 2.89 (2 H, two t, *J* 7, $COCH_2$), 3.78 (**cd**) and 3.92 (**ab**) (2 H, two s, CH_2-ring, **cd**:**ab** 3.44), 6.79 (1 H, br, NH) and 11.50 (1 H, br, OH); δ_C($CDCl_3$; Me_4Si), see Table 2; *m*/*z* (EI) 253 ([M]$^+$, 3%), 168 ([M − $(CH_2)_5CH_3$]$^+$, 4), 154 ([M − $(CH_2)_6CH_3$]$^+$, 29), 141 ([M + H − $(CH_2)_7CH_3$]$^+$, 100), 126 ([M − $(CH_2)_8CH_3$]$^+$, 67), 80 (5), 69 (9) and 55 (6).

3-(Hexa-2,4-dienoyl)tetramic acid 17

From *N*-acetyl-3-(hexa-2,4-dienoyl)tetramic acid 16. The reaction mixture [crude product **16** (0.7 g, 2.9 mmol) dissolved in the sodium ethoxide in ethanol] was set aside overnight at room temperature. Compound **17** was obtained as a solid (0.3 g, 50%), mp 211–213 °C (from CH_3COCH_3–light petroleum) (lit.,[18] 211–212 °C) (Found: C, 60.86; H, 5.67; N, 6.91. $C_{10}H_{11}O_3N{\cdot}1/4H_2O$ requires C, 60.74; H, 5.86; N, 7.08); ν_{max}(Nujol)/cm^{-1} 3200m (NH), 1710m (CO diketone, keto form and CO lactam), 1665s (CO diketone, enol form and CO α,β-unsaturated ketone) and 1625s (C=C); δ_H(300 MHz; [$^2H_6$]-acetone; Me_4Si) 1.909 [3 H, d, *J* 6, $(CH{=}CH)_2CH_3$], 3.79 (**cd**) and 3.92 (**ab**) (2 H, two s, CH_2-ring, **ab**:**cd** 7), 5.60 (1 H, br, NH) and 6.40–7.80 [4 H, m, $(CH{=}CH)_2CH_3$].

Preparation of 5-benzylidene-3-alkanoyl tetramic acids

5-Benzylidene-3-hexanoyl tetramic acid 13. The tetramic acid [2.2 mmol **6** (0.5 g) or **10** (0.4 g)] was stirred in a solution of 8% hydrogen chloride in ethanol [prepared by addition of acetyl chloride (4 ml) in anhydrous ethanol (30 ml)] until it dissolved (*ca*. 15 min), after which benzaldehyde (0.5 g, 4.5 mmol) was added to the mixture. The reaction mixture was refluxed for 3 h and then set aside overnight at room temperature to give a yellowish precipitate, which was filtered off and washed with diethyl ether to afford the product **13** (0.3 g, 44%), mp 178–182 °C (from EtOH) (Found: C, 71.78; H, 6.50; N, 4.79. $C_{17}H_{19}O_3N$ requires C, 71.56; H, 6.71; N, 4.91); ν_{max}(Nujol)/cm^{-1} 3180m (NH), 1700s (CO diketone, keto form and CO lactam), 1630s (CO diketone, enol form and C=C) and 1580s (C=C ring stretching); δ_H(300 MHz; [$^2H_6$]DMSO; Me_4Si) 0.86 [3 H, t, *J* 7, $(CH_2)_4CH_3$], 1.26–1.38 [4 H, m, $(CH_2)_2CH_3$], 1.54–1.64 [2 H, m, $CH_2(CH_2)_2$], 2.86 (2 H, t, *J* 7, $COCH_2$), 4.71 (1 H, br, NH), 6.44 (1 H, s, CH=), 7.28–7.33 (1 H, m, *para* protons), 7.36 (2 H, t, *J* 7.8, *meta* protons), 7.62 (2 H, d, *J* 7, *ortho* protons) and 10.53 (1 H, br, OH); δ_C([$^2H_6$]DMSO; Me_4Si), see Table 3. Treatment of **13** with MSTFA–NH_4I–DTE reagents yielded the corresponding derivatives ($C_{23}H_{35}NO_3Si_2$); *m*/*z* (EI) 429 ([M]$^+$, 20%), 414 ([M − Me]$^+$, 50), 386 ([M − $(CH_2)_2CH_3$]$^+$, 35), 358 ([M − $(CH_2)_4CH_3$]$^+$, 7), 298 ([M − $(CH_2)_3CH_3$ − $Si(Me)_3$ − H]$^+$, 10), 73 (100) and 55 (3).

5-Benzylidene-3-octanoyltetramic acid 14. According to the previous procedure the tetramic acid [2.2 mmol **7** (0.6 g) or **11**

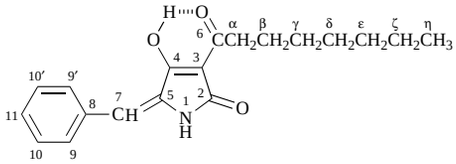


Table 3 ^{13}C NMR chemical shifts for 5-benzylidenetetramic acids **13** and **14** ([$^2H_6$]DMSO)

Compd.	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9,9′	C-10,10′	C-11	C-α	C-β	C-γ	C-δ	C-ε	C-ζ	C-η
13	171.15	101.15	191.49	108.22	181.09	128.51	131.77	129.81	128.89	133.30	34.07	30.73	24.58	21.72	—	—	13.68
14	171.16	101.55	191.50	108.14	181.12	128.49	131.76	129.81	128.90	133.33	34.18	31.02	28.52	28.29	24.89	21.97	13.84

(0.5 g)] afforded the title compound **14** (0.3 g, 48.5%), mp 165–169 °C (from EtOH) (Found: C, 72.73; H, 7.39; N, 4.45. $C_{19}H_{23}O_3N$ requires C, 72.82; H, 7.40; N, 4.47); ν_{max}(Nujol)/cm^{-1} 3180m (NH), 1700s (CO diketone, keto form and CO lactam), 1630s (CO diketone, enol form and C=C) and 1580s (C=C ring stretching); δ_H(300 MHz; [$^2H_6$]DMSO) 0.84 [3 H, t, *J* 7, $(CH_2)_6CH_3$], 1.24–1.28 [8 H, m, $(CH_2)_4CH_3$], 1.54–1.61 [2 H, m, $CH_2(CH_2)_4$], 2.86 (2 H, t, *J* 7, $COCH_2$), 5.32 (1 H, br, NH), 6.44 (1 H, s, CH=), 7.28–7.33 (1 H, m, *para* protons), 7.39 (2 H, t, *J* 7.8, *meta* protons), 7.62 (2 H, d, *J* 7, *ortho* protons) and 10.53 (1 H, br, OH); δ_C([$^2H_6$]DMSO; Me_4Si), see Table 3.

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