Synthesis and Spectroscopic Studies of 5-Arylidene-3-substituted Tetramic Acids as Possible Substrates for Catalytic Asymmetric Hydrogenation

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A new series of 5-arylidene-3-substituted tetramic acids **6-19** have been synthesized by a condensation reaction of 3-butanoyl tetramic acid **3**, 3-ethoxycarbonyl tetramic acid **4** and 3-acetyl tetramic acid **5** with a variety of substituted benzaldehydes. The structures of the isolated compounds **6-19** have been elucidated using FT-IR, ^{1}H and ^{13}C-NMR spectroscopy, FAB-MS spectroscopy as well as elemental analyses.

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Derivatives of pyrrolidine-2,4-diones (Figure 1) are naturally important substances which display diverse structural and stereochemical features [1]. Tetramic acids, pyrrolidine-2,4-diones, acylated at 3-position, have been extensively studied because of their unique structure and interesting biological and pharmacological properties [1,2].

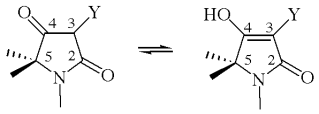


Figure 1. Pyrrolidine-2,4-dione ring.

Members of the 3-acyl tetramic acid group of compounds are tenuazonic acid, tirandamycin, streptolydigin, ikaguramycin and erythroskyrine [1], common derivatives in a number of plants. These compounds exhibit a number of biological properties from antiviral, antitumor, antibiotic and antimicrobial to inhibition of DNA-directed RNA polymerase and terminal deoxynucleotidyl transferase [1]. As a further example, 5-arylidene-3-phenyl tetramic acid (Figure 2) has been designed as a novel glycine site *N*-methyl-D-aspartate (NMDA) receptor antagonist in the treatment of neurological diseases [3].

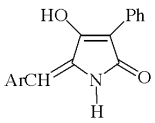


Figure 2. 5-Arylidene-3-phenyl tetramic acid.

In recent years much attention has been given to the synthesis of chiral tetramic acids using optically active amino acid derived precursors. The applied methodologies are modifications of the enantioselective Lacey-Dieckmann cyclisation, requiring strong conditions (sodium ethoxide in ethanol, reflux) [4-7].

During the last decade our research group has been investigating the synthesis of heterocyclic compounds bearing the β,β'-tricarbonyl moiety such as tetramic acids, quinolin-2,4-diones and 1,8-napthyridin-2,4-diones. In the course of these studies we have proposed a novel method for the synthesis of 3-substituted tetramic acids [8]. This method has been extended to the synthesis and structure investigation of a large number of 3-substituted tetramic acids [9-11]. In addition, we have examined the complexation of tetramic acids with transition metals [12,13]. Our interest has been focused on 3-acyl and 3-alkoxycarbonyl-5-arylidene tetramic acids (Figure 3).

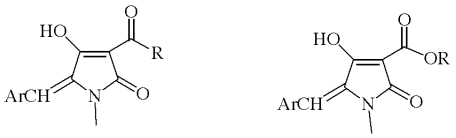


Figure 3. 3-Acyl- and 3-alkoxycarbonyl-5-arylidene tetramic acids.

These compounds contain important structural adjuncts such as an enolic β,β'-tricarbonyl moiety, a lipophilic substituent at position 3 and a hydrophobic group at the 5-position which allow them to exhibit versatile activity (Figure 4). In addition, the β,β'-tricarbonyl moiety described above provides them with sites available for complexation. The antibiotic 'magnesidin' (Figure 4) isolated from '*Pseudomonas magnesiorubra*' as a mixture of covalent magnesium chelates of the 3-alkanoyl-5-ethylidene tetramic acid derivatives is an example of such metal complexes which exhibit a variety of biological properties [1,14-17].

Recently, 5-benzylidene-3-hexanoyl tetramic acid was synthesized and used as the ligand for the complexation with Mg (II), Zn (II) and Ba (II) chlorine salts [18].

Additionally, the double bonds between C-3 and C-4 as well as C-5 and C-6 make these compounds very promising substrates for catalytic asymmetric hydrogenation. Stereospecific syntheses of 'statine' analogues were reported *via* stereocontrolled reduction (C3-C4) of tetramic acids [19].

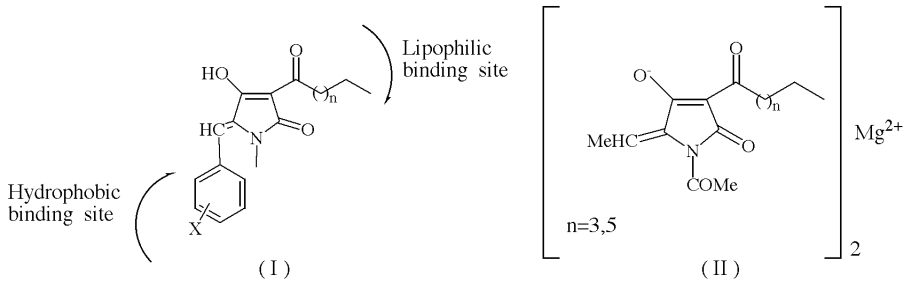
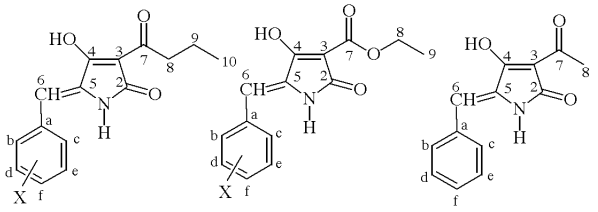


Figure 4. 3-Acyl-5-arylidene tetramic acids (**I**), Magnesidine (**II**).

In this paper we wish to report a practical method for the synthesis of 5-arylidene-3-butanoyl-, 3-ethoxycarbonyl and 3-acetyl tetramic acids **6-11**, **12-18** and **19**, respectively (Figure 5). The structure of the newly prepared compounds was supported by ^{1}H and ^{13}C-NMR, FT-IR spectroscopy , and MS and HETCOR experiments.



6	X = p-NO_2	**12**	X = p-NO_2	**19**
7	p-Cl	**13**	p-Cl	
8	p-OMe	**14**	p-OMe	
9	m-NO_2	**15**	m-NO_2	
10	m-Cl	**16**	m-Cl	
11	m-OMe	**17**	m-OMe	
		18	H	

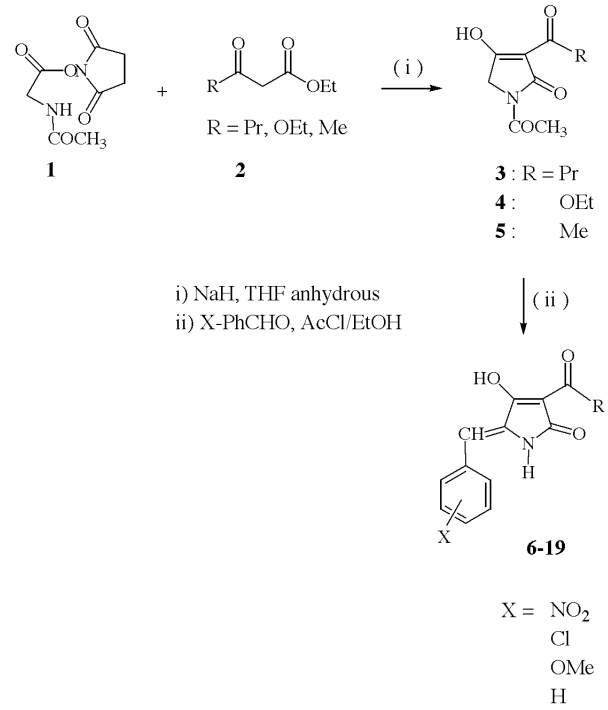
Figure 5. Atom numbering for compounds **6-19**.

Following the protocol previously developed in our laboratory [8,9] we synthesized the required tetramic acids **3, 4** and **5** (Scheme 1).

The *N*-hydroxysuccinimide ester **1** was easily prepared from the reaction of *N*-acetyl-glycine with *N*-hydroxysuccinimide and *N*,*N*-dicyclohexylcarbodiimide in anhydrous tetrahydrofuran at 60 °C. The next step involved the C-acylation of an active methylene compound **2** (2 equivalents) in the presence of sodium hydride (2 equivalents) with the *N*-hydroxysuccinimide ester **1** in anhydrous tetrahydrofuran. The tetramic acids **3, 4** and **5** were the products of this reaction after 2.5 hours of stirring at room temperature.

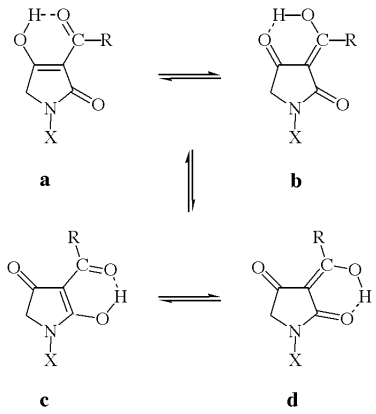
The synthesis of compounds **6-19** involved the condensation of tetramic acids **3, 4** or **5** (1 equivalent) with substituted-benzaldehydes (2 equivalent) in the presence of a solution of 8% hydrochloric acid in ethanol. These compounds were isolated in good yields and recrystallised from hot ethanol. Previous strategies to these compounds are less convenient and give lower yields [20]. The *Z* configuration of the double bond was assigned according to the literature based on a comparison of the ^{1}H NMR chemical shift data for the vinyl proton signals at the region of 6.42-6.65 ppm with those of similar tetramates [20] (see experimental, compound **18**).

Scheme 1



Synthesis of compounds **6-19**.

Scheme 2



Tautomeric forms of 3-acyl tetramic acids.

3-Acyl tetramic acids can possibly exist in four tautomeric forms **a, b, c, d** (Scheme 2) [21, 22]. In deuteriochloroform solution, internal tautomers a⇄b and c⇄d are rapidly interconverted by intramolecular displacement of the enolic proton along with the hydrogen bond, whereas the interconversion between external tautomers ab⇄cd is a comparatively slow process in the NMR time-scale; therefore the external tautomers give separate NMR signals. The ratio between these two tautomers has been sufficiently discussed and explained in previous papers relating to tetramic acids [8-10,18].

The ^{1}H-NMR spectra of 3-substituted tetramic acids **6, 12, 15, 16** and **17** show one set of signals for all protons in hexadeuteriodimethylsulfoxide solution (polar solvent). On the other hand, the ^{1}H and ^{13}C NMR spectra of 3-acetyl-5-benzylidene tetramic acid **19** show the characteristic pair of signals, indicating that this compound in deuteriochloroform solution exists to a great extent as the 'external' tautomers a⇄b. In addition, the ^{1}H NMR spectra of compounds **7-11**, **13**, **14** and **19** in deuteriochloroform solution, reveal the presence of two signals for certain protons, showing that the dominant form should be the a⇄b tautomers.

The HETCOR experiment establishes the carbon and proton connectivities for compounds **8, 10, 14,** and **17**. The spectral assignments for compound **17** are representative for the series of 3'substituted (*meta*) arylidene tetramic acids. In particular, correlations were observed between the carbons resonating at δ (ppm) 122.3 (C-f), 114.8 (C-c), 114.5 (C-b) and 134.9 (C-e) and protons resonating at δ (ppm) 6.87 (1H, dd, H-f), 7.11 (1H, s, H-c), 7.18 (1H, d, H-b) and 7.28 (1H, t, H-d), respectively.

Another observation is that the carbon, which is attached to the OCH_3 group, shows a chemical shift at lower field than that attached to the NO_2 or Cl group. This observation is well explained through the electron donor character of the OCH_3 group in contrast to the electron withdrawing character of NO_2 and Cl groups. This character also affects the chemical shifts of the other carbons of the aromatic ring through the resonance forms of this ring.

The FT-IR spectra of the compounds **6-19** showed a moderate intensity absorption band at *ca.* 3200 cm^{-1} attributable to the ν (NH). The carbonyl absorption bands were

Table 1

^{13}C NMR Spectra of Compounds **6-11** (^{2}[H$_6$]DMSO)

Compound	C-10	C-9	C-8	C-7	C-6	C-5	C-4	C-3	C-2	C-a	C-b	C-c	C-d	C-e	C-f	OCH_3
6	13.5	18.6	35.9	181.3	104.2	134.9	190.7	101.2	171.5	140.6	123.8		130.5		146.3	-
7	13.5	18.5	36.0	181.1	106.6	132.9	192.5	99.9	170.0	141.0	128.8		131.4		145.7	-
8	13.5	18.3	36.1	181.3	109.1	132.0	192.2	102.0	171.0	137.6	114.6		132.2		125.4	55.3
9	13.5	18.6	35.9	181.2	105.0	134.1	190.6	101.5	171.3	135.6	130.2	122.5	148.4	135.3	124.0	-
10	13.5	18.5	36.0	181.2	106.1	132.9	190.8	101.8	171.0	133.8	128.9	128.1	135.6	130.6	128.4	-
11	13.5	18.4	36.0	181.0	108.3	131.9	191.0	101.6	171.5	159.7	129.9	122.3	134.6	114.6	114.8	55.2

Table 2

^{13}C NMR Spectra of Compounds **12-18** (^{2}[H$_6$]DMSO)

Compound	C-9	C-8	C-7	C-6	C-5	C-4	C-3	C-2	C-a	C-b	C-c	C-d	C-e	C-f	OCH_3
12	14.3	59.5	168.4	104.9	130.0	171.2	95.9	162.9	134.5	130.5		123.9		140.8	-
13	14.3	59.7	167.8	107.4	131.3	170.8	96.1	163.1	132.6	128.9		131.5		133.0	-
14	14.3	59.6	167.6	109.5	128.5	171.1	95 .7	163.5	137.0	114.5		131.5		126.1	55.3
15	14.2	59.6	168.2	105.7	122.4	170.7	96.2	162.9	133.2	124.1	130.2	133.3	135.6	135.5	-
16	14.2	59.5	168.0	106.6	128.0	170.9	96.0	163.0	133.8	128.4	128.9	132.0	135.8	130.5	-
17	14.2	59.6	167.8	108.7	129.9	170.9	96.0	163.2	159.7	114.5	114.8	134.9	130.9	122.3	55.2
18	14.2	59.6	168.0	106.4	128.3	170.8	96.1	163.1	132.9	121.1		130.7		130.2	-

observed at 1720-1690 cm^{-1} and 1650-1630 cm^{-1} as expected for the CO lactam and CO stretching of the intramolecular hydrogen bonded carbonyl present in the enol-form of β-keto esters. In addition, the carbonyl absorptions of compounds **12-18** (ethoxycarbonyl compounds) are in higher field (1725-1700 and 1660-1645 cm^{-1} respectively) than those of compounds **6-11** (butanoyl compounds). Finally, the strong band at 1600-1580 cm^{-1} is assigned to the conjugated double bond and the aromatic ring of these compounds.

The most important peaks in the FAB-Mass Spectra of compounds **6, 7, 8, 10, 11** and **18**, which have been acquired, are listed at the experimental section.

In conclusion, we have synthesized 14 compounds which have been extensively studied by means of ^1H, ^{13}C-NMR, FT-IR and FAB-MS Spectroscopy. Their purity has also been checked through elemental analyses. These compounds are very promising substrates for asymmetric catalytic hydrogenation. Efforts towards this reaction are under investigation and we believe that in the near future we will have some positive results.

EXPERIMENTAL

Melting points were determined on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. The FT-IR spectra were recorded on a Nicolet Magna IR 560. The NMR spectra were recorded on a Varian Gemini-2000 300 MHz spectrometer; 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 VG 7070E/DEC VAX 4000.60 instrument using Fast Atomic Bombardment, University of Liverpool. Elemental analyses were obtained on a Euro EA3000 Series Euro Vector CHNS Elemental Analyser.

General Procedure for the Synthesis of Compounds **6-19**.

The tetramic acid (0.0022 mole) was stirred in a solution of 8% hydrochloric acid in ethanol, prepared from the addition of acetyl chloride (4 mL) in anhydrous ethanol (30 mL) until it dissolved. Afterwards, X-substituted benzaldehyde (0.0044 mole) was added to the solution and the resulting solution was refluxed for 3 hours. Finally, it was left stirring overnight.

The precipitated solid was isolated by filtration, washed with diethyl ether and dried under *vacuo*.

5-Arylidene(4'-nitro)-3-butanoyl Tetramic Acid (**6**).

The compound was isolated as a brown solid (0.28 g, 42%), mp 258-260 °C (from ethanol); ir (KBr): 3180-3200 (NH), 1715, 1695 (C=O lactam), 1640 (C=O enol) and 1585 (C=C) cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 0.92 (t, 3H, CH_3, *J*=7.2), 1.55-1.67 (m, 2H, CH_2), 2.85 (t, 2H, CH_2, *J*=7.2), 6.47 (s, 1H, CH), 7.84 (d, 2H, H-b/H-c, *J*=8.7), 8.18 (d, 2H, H-d/H-e, *J*=8.7) and 10.77 (br s, 1H, NH); ms: m/z 303 [$(M + H)^+$, 5], 165 (12), 121 (17), 105 (28), 89 (88), 77 (100), 63 (46), 51 (57).

Anal. Calcd. for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.64; N, 9.27. Found: C, 60.0; H, 4.58; N, 9.25.

5-Arylidene(4'-chloro)-3-butanoyl Tetramic Acid (**7**).

The compound was isolated as a light brown solid (0.40 g, 62%), mp 227-228 °C (from ethanol); ir (KBr): 3190-3210 (NH), 1710 (C=O lactam), 1640 (C=O enol) and 1585 (C=C) cm^{-1}; ^1H-nmr (deuteriochloroform): δ 0.99-1.06 (two t, 3H, CH_3), 1.70-1.82 (m, 2H, CH_2), 2.93 (t, 2H, CH_2, *J*=7.2), 6.57/6.60 (two s, 1H, CH), 7.31-7.43 (m, 4H, phenyl protons) and 7.72/7.94 (two br s, 1H, NH); ms: m/z 292 [$(M+H)^+$, 20], 177 (8), 165 (23), 121 (28), 105 (40), 87 (11), 79 (43), 65 (64), 51 (86).

Anal. Calcd. for $C_{15}H_{14}NO_3Cl$: C, 61.75; H, 4.80; N, 4.80. Found: C, 61.60; H, 4.70; N, 4.61.

5-Arylidene(4'-methoxy)-3-butanoyl Tetramic Acid (**8**).

The compound was isolated as an orange solid (0.35 g, 55%), mp 176-177 °C (from ethanol); ir (KBr): 3190-3200 (NH), 1715, 1690 (C=O lactam), 1640 (C=O enol) and 1580 (C=C) cm^{-1}; ^1H-nmr (deuteriochloroform): δ 0.99-1.06 (two t, 3H, CH_3), 1.70-1.82 (m, 2H, CH_2), 2.94 (t, 2H, CH_2, *J*=8.1), 3.85 (d, 3H, OCH_3, *J*=2.4), 6.61/6.63 (two s, 1H, CH), 6.93-7.04 (m, 2H, H-d/H-e), 7.35-7.42 (m, 2H, H-b/H-c) and 7.77/8.19 (two br s, 1H, NH); ms: m/z 288 [$(M+H)^+$, 100], 177 (5), 165 (20), 121 (42), 105 (38), 79 (41), 63 (62), 51 (73).

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.90; H, 5.92; N, 4.88. Found: C, 67.17; H, 5.63; N, 4.62.

5-Arylidene(3'-nitro)-3-butanoyl Tetramic Acid (**9**).

The compound was isolated as a brown solid (0.26 g, 39%), mp 205-206 °C (from ethanol); ir (KBr): 3190-3205 (NH), 1690 (C=O lactam), 1630 (C=O enol) and 1585 (C=C) cm^{-1}; ^1H-nmr (deuteriochloroform): δ 0.99-1.06 (two t, 3H, CH_3), 1.70-1.82 (m, 2H, CH_2), 2.92 (t, 3H, CH_2, *J*=7.2), 6.63/6.65 (two s, 1H, CH), 7.62 (t, 1H, H-d, *J*=7.8), 7.74 (d, 1H, H-b, *J*=12.6), 8.18 (d, 1H, H-f, *J*=6.1), 8.25 (s, 1H, H-c) and 8.35/8.62 (two br s, 1H, NH).

Anal. Calcd. for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.64; N, 9.27. Found: C, 59.74; H, 4.53; N, 9.26.

5-Arylidene(3'-chloro)-3-butanoyl Tetramic Acid (**10**).

The compound was isolated as a brown solid (0.30 g, 47%) mp 181-182 °C (from ethanol); ir (KBr): 3195-3210 (NH), 1695 (C=O lactam), 1630 (C=O enol) and 1585 (C=C) cm^{-1}; ^1H-nmr (deuteriochloroform): δ 0.99-1.06 (two t, 3H, CH_3), 1.70-1.82 (m, 2H, CH_2), 2.94 (t, 2H, CH_2, *J*=7.5), 6.54/6.58 (two s, 1H, CH), 7.28-7.42 (m, 4H, phenyl protons) and 8.02/8.46 (two br s, 1H, NH); ms: m/z 292 [$(M+H)^+$, 34], 177 (8), 165 (25), 121 (34), 105 (43), 79 (46), 63 (70), 51 (84).

Anal. Calcd. for $C_{15}H_{14}NO_3$: C, 61.75; H, 4.80; N, 4.80. Found: C, 61.90; H, 4.80; N, 4.79.

5-Arylidene(3'-methoxy)-3-butanoyl Tetramic acid (**11**).

The compound was isolated as a yellow solid (0.33 g, 52%), mp 170-171 °C (from ethanol); ir (KBr): 3190-3200 (NH), 1690 (C=O lactam), 1635 (C=O enol) and 1585 (C=C) cm^{-1}; ^1H-nmr (deuteriochloroform): δ 0.99-1.06 (two t, 3H, CH_3), 1.70-1.82 (m, 2H, CH_2), 2.94 (t, 2H, CH_2, *J*=7.2), 3.83 (d, 3H, OCH_3, *J*=2.1), 6.60/6.63 (two s, 1H, CH), 6.90 (d, 1H, H-f, *J*=8.1), 6.94 (s, 1H, H-c), 7.02 (d, 1H, H-b, *J*=7.8), 7.35 (t, 1H, H-d, *J*=8.1) and 7.76/8.41 (two br s, 1H, NH); ms: m/z 288 [$(M+H)^+$, 100], 177 (10), 165 (28), 121 (48), 105 (47), 79 (49), 63 (71), 51 (88).

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.90; H, 5.92; N, 4.88. Found: C, 66.69; H, 5.74; N, 4.78.

5-Arylidene(4'-nitro)-3-ethoxycarbonyl Tetramic Acid (**12**).

The compound was isolated as a yellow solid (0.32 g, 48%) mp 280 °C (decomp.) (from ethanol); ir (KBr): 3185-3205 (NH), 1725 (C=O lactam), 1660 (C=O enol) and 1590 (C=C) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.25 (t, 3H, CH_3, *J*=6.9), 4.21 (q, 2H, CH_2, *J*=6.9), 6.53 (s, 1H, CH), 7.85 (d, 2H, H-b/H-c, *J*=8.7), 8.19 (d, 2H, H-d/H-e, *J*=8.7) and 10.14 (br s, 1H, NH).

Anal. Calcd. for $C_{14}H_{12}N_2O_6$: C, 55.26; H, 3.95; N, 9.21. Found: C, 55.11; H, 4.02; N, 9.29.

5-Arylidene(4'-chloro)-3-ethoxycarbonyl Tetramic Acid (**13**).

The compound was isolated as a yellow solid (0.36 g, 56%), mp 253-255 °C (from ethanol); ir (KBr): 3185-3205 (NH), 1715 (C=O lactam), 1650 (C=O enol) and 1590 (C=C) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.43 (t, 3H, CH_3, *J*=7.2), 4.45 (q, 2H, CH_2, *J*=7.2), 6.58 (s, 1H, CH), 7.36-7.44 (m, 4H, phenyl protons) and 7.52 (br s, 1H, NH).

Anal. Calcd. for $C_{14}H_{12}NO_4Cl$: C, 57.24; H, 4.09; N, 4.77. Found: C, 56.94; H, 4.06; N, 4.74.

5-Arylidene(4'-methoxy)-3-ethoxycarbonyl Tetramic Acid (**14**).

The compound was isolated as a red solid (0.33 g, 48%), mp 214-216 °C (from ethanol); ir (KBr): 3190-3220 (NH), 1715 (C=O lactam), 1650 (C=O enol) and 1585 (C=C) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.42 (t, 3H, CH_3, *J*=6.9), 3.85 (s, 3H, OCH_3), 4.44 (q, 2H, CH_2, *J*=6.9), 6.61/6.62 (two s, 1H, CH), 6.95-7.00 (m, 2H, H-d/H-e), 7.37-7.43 (m, 2H, H-b/H-e) and 7.56 (br s, 1H, NH).

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.19; N, 4.84. Found: C, 62.51; H, 5.11; N, 4.71.

5-Arylidene(3'-nitro)-3-ethoxycarbonyl Tetramic acid (**15**).

The compound was isolated as a yellow solid (0.29 g, 43%), mp 235-237 °C (from ethanol); ir (KBr): 3210 (NH), 1715 (C=O lactam), 1660 (C=O enol) and 1600 (C=C) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.23 (t, 3H, CH_3, *J*=7.2), 4.19 (q, 2H, CH_2, *J*=7.2), 6.51/6.58 (two s, 1H, CH), 7.63 (t, 1H, H-d, *J*=7.8), 7.99 (d, 1H, H-b, *J*=8.4), 8.10 (d, 1H, H-f, *J*=8.1), 8.33 (s, 1H, H-c) and 10.10 (br s, 1H, NH).

Anal. Calcd. for $C_{14}H_{12}N_2O_6$: C, 55.26; H, 3.95; N, 9.21. Found: C, 54.96; H, 3.80; N, 9.00.

5-Arylidene(3'-chloro)-3-ethoxycarbonyl Tetramic Acid (**16**).

The compound was isolated as a yellow solid (0.27 g, 42%), mp 208-209 °C (from ethanol); ir (KBr): 3210 (NH), 1715 (C=O lactam), 1650 (C=O enol) and 1610 (C=C) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.23 (m, 3H, CH_3, *J*=7.5), 4.19 (q, 2H, CH_2, *J*=7.5), 6.42 (s, 1H, CH), 7.32-7.67 (m, 4H, phenyl protons) and 10.03 (br s, 1H, NH).

Anal. Calcd. for $C_{14}H_{12}NO_4Cl$: C, 57.24; H, 4.09; N, 4.77. Found: C, 57.01; H, 3.89; N, 4.69.

5-Arylidene(3'-methoxy)-3-ethoxycarbonyl Tetramic Acid (**17**).

The compound was isolated as an orange solid (0.21 g, 33%), mp 186-187 °C (from ethanol); ir (KBr): 3215 (NH), 1700 (C=O lactam), 1645 (C=O enol) and 1595 (C=C) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.24 (t, 3H, CH_3, *J*=6.9), 3.79 (d, 3H, OCH_3, *J*=2.3) 4.20 (q, 2H, CH_2, *J*=6.9), 6.44/6.45 (two s, 1H, CH), 6.87 (dd, 1H, H-f, *J*=2.1, 7.5). 7.11 (s, 1H, H-c), 7.18 (d, 1H, H-b, *J*=7.8), 7.28 (t, 1H, H-d, *J*=7.8) and 9.93 (br s, 1H, NH).

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.19; N, 4.84. Found: C, 62.58; H, 5.03; N, 4.49.

5-Benzylidene-3-ethoxycarbonyl Tetramic Acid (**18**).

The compound was isolated as a pale yellow solid (0.14 g, 49%), mp 221-222 °C (from ethanol); ir (KBr): 3210 (NH), 1715 (C=O lactam), 1655 (C=O enol) and 1590 (C=C) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.42 (t, 3H, CH_3, *J*=6.9), 4.44 (q, 4H, CH_2, *J*=6.9), 6.64 (s, 1H, CH), 7.35-7.46 (m, 5H, phenyl protons) and 7.69 (br s, 1H, NH); ms: m/z 260 [$(M+H)^+$, 100], 214 (72), 205 (24), 165 (13), 118 (18), 79 (23), 63 (34), 51 (41).

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.02; N, 5.41. Found: C, 65.16; H, 5.04; N, 5.43.

5-Benzylidene-3-acetyl Tetramic Acid (**19**).

The compound was isolated as a dark brown solid (0.32 g, 70%), mp 218-219 °C (from ethanol); ir (KBr): 3190-3200 (NH), 1700 (C=O lactam), 1640 (C=O enol) and 1585 (C=C) cm^{-1}; ^{1}H-nmr (deuteriochloroform): 2.57 (s, 3H, $COCH_3$), 6.65/6.68 (two s, 1H, CH), 7.33-7.49 (m, 5H, phenyl protons) and 8.26/8.62 (two br s, 1H, NH); ^{13}C-nmr (deuteriochloroform): 14.9/17.7 (C-8), 96.7/99.1 (C-3), 105.1/106.2 (C-5), 124.2/124.5/124.7/124.8/-124.8/125.9/129.0/129.2 (C-a, C-b, C-c, C-d, C-e, C-f), 163.2/169.2 (C-2), 177.7/180.7 (C-7) and 180.1/187.5 (C-4).

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.12; H, 4.80; N, 6.11. Found: C, 68.46; H, 4.84; N, 5.99.

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