Acylaminoacetyl Derivatives of Active Methylene Compounds. 4 [1]. Synthesis of *N*-Protected Tetramic Acids *via* the *C*-Acylation Reaction of Meldrum's Acid with the Imidazolides of *N*-Protected Glycines

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Dedicated to the memory of Professor Nicholas Alexandrou

Meldrum's acid has been found to be effectively acylated using the imidazolides of *N*-protected glycines, X-NHCH$_2$COOH (X = -COPh, -COMe, -Z, -Boc, -COOMe and -COOEt). The corresponding *C*-acylation compounds were isolated in high yields and were readily converted to the *N*-protected tetramic acids. It was shown by pmr spectroscopy that these acids exist as the enol tautomers in DMSO-d$_6$ solution, whereas in deuteriochloroform solution both the enol and keto tautomers can be observed.

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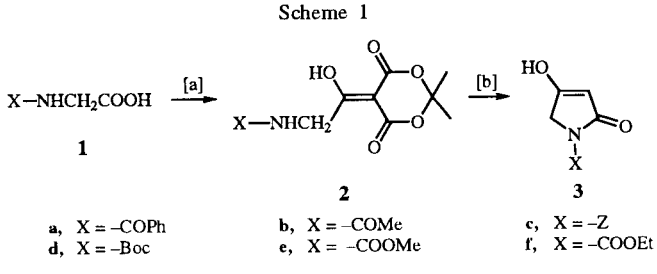
Introduction.

In the previous communication [1a] we have reported the *C*-acylation reactions of two active methylene compounds, methyl cyanoacetate and Meldrum's acid, with hippuric acid, using the *N,N'*-dicyclohexylcarbodiimide activation and mixed anhydride conditions. These reactions were shown to proceed through initial formation of 2-phenyl-5(4*H*)-oxazolone, the hippuric acid azlactone. Under the *N,N'*-dicyclohexylcarbodiimide activation conditions only Meldrum's acid could be acylated, while under mixed anhydride conditions both methyl cyanoacetate and Meldrum's acid could be acylated, though in low yields, since *N*-benzoyl-α-benzoylaminotetramic acid was also formed. The hippuric acid azlactone proved to be an effective acylation agent under proper conditions; its usefulness is, however, limited from its ready transformation to the same tetramic acid derivative under the basic conditions required for the acylation reactions. Since then, we have found that pure benzoylaminoacetyl derivatives of active methylene compounds can be prepared in high yields by a simple experimental procedure, using the imidazolide of hippuric acid as the acylating agent.

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione), an exceptionally acidic methylene compound [2], has been used by Yonemitsu *et al.* [3] in a general and versatile synthesis of β-keto esters: its acylation with acyl chlorides in dichloromethane, in the presence of pyridine, gave almost quantitatively the corresponding acyl Meldrum's acids, which readily underwent alcoholysis to various β-keto esters. A modification of this acylation reaction was reported by Melillo *et al.* [4], who treated a carboxylic acid with 1,1'-carbonyldiimidazole followed by treatment with Meldrum's acid in the presence of 4-*N,N*-dimethylaminopyridine. On the other hand, a new process for the acylation of Meldrum's acid with chiral *N*-protected amino acids was developed by Jouin *et al.* [5]. In this process, the *N*-protected amino acids were activated with isopropenyl chloroformate and it was shown that the acyl Meldrum's acids could be readily converted to the corresponding chiral *N*-protected γ-substituted tetramic acids by heating in an organic solvent. A variant of this stereoselective synthesis of chiral tetramic acid derivatives was recently reported by Martinez *et al.* [6,7], who used *N*-protected *N*-carboxyanhydrides for the acylation step of Meldrum's acid. We now describe here a particularly simple and convenient acylation reaction of Meldrum's acid *via* the imidazolides of *N*-protected glycines **1** and the transformation of the acylated compounds **2** to the corresponding *N*-protected tetramic acids **3** (Scheme 1).

Scheme 1



1

2

3

a, X = –COPh **b**, X = –COMe **c**, X = –Z
d, X = –Boc **e**, X = –COOMe **f**, X = –COOEt

[a] 1,1'-Carbonyldiimidazole and Meldrum's acid in dichloromethane at room temperature for 20 hours. [b] Refluxing in chloroform or ethyl acetate for 30 minutes.

Results and Discussion.

In a preliminary examination of the acylation reaction **1** → **2** it was found that dichloromethane is a proper solvent for both the formation of the imidazolide of the *N*-protected amino acid **1** and its subsequent reaction with Meldrum's acid. Actually (see Experimental), pmr spectroscopy revealed that amino acids **1** are rapidly and quantitatively converted to their imidazolides and that addition of Meldrum's acid in the imidazolide solution results in a rather slow but remarkably clean reaction. The pmr spectrum of a sample of the reaction mixture withdrawn after 20 hours at room temperature disclosed the disappearance of Meldrum's acid and the exclusive

formation of the corresponding acylation compound **2**, apparently in the form of its imidazolium salt.

It is interesting to note that the same smooth and clean reaction is observed when 1,1'-carbonyldiimidazole is added to a mixture of Meldrum's acid and the *N*-protected amino acid **1**. Thus, it is obvious that the presence of the active methylene compound does not interfere with the formation of the amino acid imidazolide and its subsequent acylation reaction. On the other hand, the acylation reaction was found to be somehow faster when the volume of the solvent was decreased. However, the rate of the reaction was not altered when an equimolar quantity of 4-*N*,*N*-dimethylaminopyridine was added to the reaction mixture. Thus, it is reasonable to assume that the presence of imidazole, which is liberated during the formation of the amino acid imidazolide, is sufficient to create the basic medium required for the acylation reaction.

In agreement with these observations, the acylation compounds **2** were isolated, after acidification of the reaction mixture, in high yields, 85-93%. Because of their thermal instability and their ready conversion to the corresponding tetramic acids **3** (*vide infra*), compounds **2** could not be purified by recrystallization or chromatography. However, the crude compounds **2** showed clean pmr spectra, devoid of any impurities, such as the by-products which were observed when hippuric acid was acylated under different activation conditions [1a]. These spectra (see Experimental) exhibit the double signal of the N-CH_2-protons at δ 4.65-4.88 ppm and are consistent with the enolic structure of compounds **2**, as shown by the presence of a broad singlet at low field, δ 11-13 ppm; this signal is assigned to the enol -OH proton which participates in an intramolecular hydrogen bond [8]. In agreement with their enolic structure, compounds **2a-2f** give an intense orange colour with an aqueous solution of ferric chloride.

The acylation compounds **2a-2f** were readily converted to the corresponding *N*-protected tetramic acids **3a-3f** when heated in a solvent such as chloroform or ethyl acetate [5]. This transformation could also be observed when a solution of compound **2e** in methanol or acetone was kept at room temperature for 2-3 days (see Experimental). However, compounds **2** are stable as the imidazolium salts, during the acylation reaction. Thus, compound **2d** was isolated after acidification, in 93% yield, although the basic reaction mixture was stirred at room temperature for 45 hours (see Experimental). Finally, the ready thermal conversion to the corresponding tetramic acids was observed for the solid compounds **2a-2c**, which resolidify after melting and show then a new melting point characteristic of compounds **3a-3c** respectively (see Experimental).

Compounds **3a** and **3f** had already been isolated in low yields, and characterized, from a photoreaction of diketene with benzoyl azide and ethyl azidoformate respectively [9]. These two compounds were assigned the enolic structure on the basis of their pmr spectra in DMSO-d_6. The *N*-protected γ-substituted tetramic acids, which were prepared by Jouin *et al.* [5], were also found to exist exclusively in the enol form in DMSO-d_6. Likewise, the pmr spectra of the *N*-protected tetramic acids **3a-3f**, in DMSO-d_6 or in deuteriochloroform/DMSO-d_6 (Table 1), are consistent with their enolic structure and are characterized by the presence of the ring

Table 1

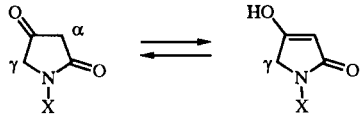
PMR Spectra of Compounds **3** [a]

Compound	X	α-CH_2	γ-CH_2	=C-H	-OH
1. Solvent: DMSO-d_6 (**E**)					
3a	7.48, m		4.37, *s*	4.97, *s*	
3b	2.43, *s*		4.20, *s*	5.03, *s*	12.40, br *s*
3c	5.25, *s*		4.28, *s*	4.96, *s*	12.00, br *s*
	7.47, *s*				
3d	1.52, *s*		4.18, *s*	4.96, *s*	12.40, br *s*
3e	3.70, *s*		4.18, *s*	4.90, *s*	
3f	1.22, t (7)		4.16, *s*	4.88, *s*	12.30, br *s*
	4.13, q (7)				
2. Solvent: deuteriochloroform/DMSO-d_6 (**E**) [b]					
3a	7.48, m		4.37, *s*	4.97, *s*	
3b	2.40, *s*		4.10, *s*	4.91, *s*	9.20, br *s*
3c	5.28, *s*		4.21, *s*	5.06, *s*	11.50, br *s*
	7.38, *s*				
3d	1.53, *s*		4.10, *s*	4.93, *s*	11.50, br *s*
3e	3.90, *s*		4.20, *s*	5.07, *s*	8.00, br *s*
3. Solvent: deuteriochloroform, dilute solution (**K**)					
3c	5.37, *s*	3.25, *s*	4.30, *s*		
	7.45, *s*				
3d	1.58, *s*	3.23, t (1)	4.22, t (1)		
3e	3.90, *s*	3.26, t (1)	4.30, t (1)		
4. Solvent: deuteriochloroform, concentrated solution (**K** and **E**)					
3d [c]	1.57, *s*	3.25, *s*	4.22, *s*	5.13, t (1)	
	1.58, *s*				
3f [d]	1.37, t (7)	3.28, *s*	4.30, *s*	5.22, *s*	
	1.38, t (7)				

[a] For the enol (**E**) and keto (**K**) forms, see Scheme 2. Chemical shifts are given in ppm (δ) downfield from TMS (internal standard) and J in Hz. Unless otherwise stated, the signals of the α-CH_2, γ-CH_2 and =C-H protons appear as slightly broadened singlets (see text). [bl Spectra taken in deuteriochloroform after addition of DMSO-d_6, usually three drops, in order to dissolve the product. [c] From the integration of the α-CH_2 (**K**) and =C-H (**E**) signals the proportion of the enolic form (**E**%) was estimated to be ~ 40%. [d] From the -$COOCH_2CH_3$ signals of the two forms, which appear as triplets (δ 1.37 and 1.38 ppm) of equal intensity, the proportion of the enolic form (**E**%) is estimated to be ~ 50%. The signals of the -$COOCH_2CH_3$ protons appear as a complex multiplet at δ 4.1-4.5 ppm.

γ-CH_2 and the vinylic =C-H proton absorptions. These two signals appear generally as slightly broadened singlets, because of a weak (J *ca.* 1 Hz) long-range coupling between them (*vide infra*). The enolic structure of compounds **3** is further confirmed by a very broad -OH signal at low field. In agreement with these observations, these compounds give an intense red colour with an aqueous solution of ferric chloride.

Scheme 2



(K) (E)

However, the pmr spectra in deuteriochloroform of compounds **3c-3f**, which are sufficiently soluble in this solvent (Table 1), revealed the presence of both the keto (**K**) and enol (**E**) tautomers (Scheme 2). In fact, the spectra of compounds **3c-3e** as a *dilute* solution in deuteriochloroform are characterized by the absence of the vinylic =C-H absorption and the appearance of two methylene signals, at δ ~ 3.25 and 4.30 ppm, which are assigned to the α-CH_2 and the γ-CH_2 protons respectively of the keto tautomer (**K**). These signals appear again either as slightly broadened singlets (compound **3c**) or as triplets (J *ca.* 1 Hz) (compounds **3d** and **3e**), because of a weak long-range coupling. A similar weak coupling, between the C-3 and C-5 protons in the keto and enol forms of pyrrolidine-2,4-diones (Scheme 2, X = -H or -Me), has been observed by Mulholland *et al.* [10] and seems to be characteristic of the tetramic acid structure. Furthermore, for compounds **3d** and **3f**, which are more soluble in deuteriochloroform, signals of both tautomers could be observed for *concentrated* solutions in this solvent (see Table 1) and the proportion of the enolic form (E%) was then estimated to be 40 and 50% respectively.

The tautomerism of simple tetramic acids (Scheme 2, X = -H or -Me) has been studied by Mulholland *et al.* [10]. For these compounds, the keto form was exclusively observed in deuteriochloroform, while the enol form was found to exist in low proportions, less than 20%, in a more polar solvent, DMSO-d_6. Similarly, γ-substituted tetramic acids have been shown to exist as the keto tautomers in deuteriochloroform [11,12]. In contrast, the *N*-protected γ-substituted tetramic acids were found to exist exclusively as the enol form in DMSO-d_6 [5], while the keto form of the *N*-substituted tetramic acids **3** could only be observed in the less polar solvent, deuteriochloroform (see Table 1). The shift of the tautomeric equilibrium (Scheme 2) in favor of the enolic form for the *N*-protected tetramic acids (X = -COR or -COOR), as compared to the simple tetramic acids (X = -H or -Me), must then be attributed to the presence of the *N*-protecting group X. This group should be expected to diminish the ability of the nitrogen atom to donate electrons to the ring amide carbonyl [13]. Consequently, the 1,3-dicarbonyl character of the tetramic acid ring is more pronounced for the *N*-protected compounds **3** and the system is stabilized as the enol tautomer.

Conclusion.

The *C*-acylation reaction of Meldrum's acid with *N*-protected glycines has been performed by a simple experimental procedure, using the imidazolide activation method, and the acylation compounds were converted to the corresponding *N*-protected tetramic acids (Scheme 1). This acylation reaction competes favorably with the method of Jouin *et al.* [5], in which the *N*-protected amino acid is activated with isopropenyl chloroformate, and the method of Martinez *et al.* [6,7], in which *N*-protected *N*-carboxyanhydrides are used as the acylating agents. We are currently investigating the application of the imidazolide activation method to acylation reactions with chiral *N*-protected amino acids.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The pmr spectra were recorded on a Varian EM-360 60 MHz spectrometer. Solvents were removed under vacuum at room temperature using a rotary evaporator. The colour reaction with ferric chloride was performed by adding a 4% aqueous solution of ferric chloride in an alcoholic or acetone solution of the product.

Elemental analyses were obtained from the microanalytical laboratory of CNRS, France.

Commercial dichloromethane was purified [15] before use. 1,1'-Carbonyldiimidazole was a commercial product of 97% purity. Meldrum's acid was prepared from malonic acid and acetone in acetic anhydride/sulfuric acid medium [16] and was used after being recently recrystallized. *N*-Protected glycines **1a-1d** were commercial products. *N*-Carbomethoxyglycine (**1e**) and *N*-carbethoxyglycine (**1f**) were prepared from glycine following the method of Boissonas and Preitner [17], *i.e.* by reaction with the corresponding alkyl chloroformate in alkaline medium. *N*-Carbomethoxyglycine (**1e**) was thus obtained, after recrystallization (ether), as a solid mp 92-94°, lit [18] mp 95-96°. *N*-Carbethoxyglycine (**1f**) was obtained, after recrystallization (ether-petroleum ether), as a solid mp 73-76°, lit [17] mp 75°.

Preliminary Experiments for the Acylation Reaction **1** → **2**.

A typical experiment is described below in detail for the acylation reaction with *N*-carbomethoxyglycine (**1e**).

1,1'-Carbonyldiimidazole (0.9 g, 5.55 mmoles) was added to a suspension of compound **1e** (0.67 g, 5 mmoles) in dichloromethane (20 ml). The flask of the reaction was protected with a calcium chloride tube and the mixture was stirred at room temperature. A gas evolution was immediately observed and a

solution was obtained after 10 minutes. A sample of the solution was then concentrated and the pmr spectrum of the residue was recorded in deuteriochloroform. In this spectrum, the methylene N-CH_2- doublet of compound **1e**, at δ 3.85 ppm, was just discernible, while the new methylene doublet of the corresponding imidazolide appeared at δ 4.51 ppm.

Meldrum's acid (0.72 g, 5 mmoles) was then added and stirring was continued at room temperature. After one hour, a sample of the solution was concentrated and its pmr spectrum recorded as before. In this spectrum two -CMe_2- singlets were observed, at δ 1.77 ppm (Meldrum's acid) and 1.68 ppm (acylation compound), and from their intensities their molar ratio was estimated to be 30:70. This ratio was estimated to be 25:75 for a sample withdrawn after two hours and 15:85 after 4.5 hours. Finally, a sample withdrawn after 23 hours showed a remarkably clean pmr spectrum, the -CMe_2- singlet of Meldrum's acid being now hardly discernible. This spectrum is characterized by the presence of signals at δ 1.68 (s, -CMe_2-), 4.50 (d, *N*-CH_2-) and 3.66 ppm (s, -COOMe), assigned to the acylation compound **2e**, apparently in the form of its imidazolium salt.

The same evolution of the acylation reaction was observed when the experiment was performed in the presence of an equimolar quantity of 4-*N*,*N*-dimethylaminopyridine.

In a similar experiment, 1,1'-carbonyldiimidazole was added to a mixture of compound **1e** and Meldrum's acid in 5 ml of dichloromethane. After 2.5 hours at room temperature, the molar ratio of Meldrum's acid to the acylation compound was now found to be 10:90. Again, the same clean spectrum was observed after 24 hours.

General Procedure for the Acylation Reaction **1** → **2**.

Method A.

To a solution or suspension of the acid **1** (10 mmoles) in dichloromethane (10 or 40 ml, see below) 1,1'-carbonyldiimidazole (11.5-12.5 mmoles) was added, the flask of the reaction was protected with a calcium chloride tube and the mixture was stirred for some time, usually 10 minutes, until the gas evolution ceased. Meldrum's acid (10 mmoles) was then added and the solution was stirred for an additional 20-24 hours. The solution was cooled with ice-water and 12 ml of 10% hydrochloric acid were added dropwise under vigorous stirring. The aqueous layer was extracted twice with small volumes of dichloromethane and the combined organic layers were dried (magnesium sulfate) and concentrated.

Method B.

The procedure is the same as in method A, except that 1,1'-carbonyldiimidazole was added to a mixture of the acid **1** and Meldrum's acid.

The crude acylation compounds **2** were found to be sufficiently pure (pmr spectra, see below) and were used as such for the cyclization reaction **2** → **3**.

5-Hippuryl-2,2-dimethyl-1,3-dioxane-4,6-dione (**2a**).

The general procedure (method B) was followed using 10 mmoles of **1a** in 40 ml of dichloromethane. After evaporation of the solvent, compound **2a** was obtained as a solid (88% yield), mp 84-86° dec, followed by resolidification and a new mp 180° dec, lit mp 84-86° dec [1a]; pmr (deuteriochloroform): δ 1.75 (s, 6H, -CMe_2-), 4.88 (d, J = 6 Hz, 2 H, N-CH_2-), 6.98 (br m, 1H, -NH-), 7.28-7.88 (m, 5H, phenyl protons), 10.5 (br s, 1H, -OH).

5-Aceturyl-2,2-dimethyl-1,3-dioxane-4,6-dione (**2b**).

The general procedure (method A) was followed using 10 mmoles of **1b** in 10 ml of dichloromethane. After evaporation of the solvent compound **2b** was obtained as a solid (91% yield), mp 126-130° dec, followed by resolidification and a new mp 167° dec; pmr (deuteriochloroform): δ 1.77 (s, 6H, -CMe_2-), 2.07 (s, 3H, CH_3CO-), 4.74 (d, J = 6 Hz, 2H, N-CH_2-), 6.40 (br m, 1H, -NH-), 13.6 (br s, 1H, -OH).

5-(*N*-Z-Glycyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2c**).

The general procedure (method A) was followed using 10 mmoles of **1c** in 10 ml of dichloromethane. After evaporation of the solvent compound **2c** was obtained as a viscous oil (91% yield) which solidified in the refrigerator, mp 80-81°, followed by resolidification and a new mp 130-135° dec; pmr (deuteriochloroform): δ 1.75 (s, 6H, -CMe_2-), 4.72 (d, J = 6 Hz, 2H, N-CH_2-), 5.12 (s, 2H, Ph-CH_2-), 5.30 (br m, 1H, -NH-), 7.31 (s, 5H, phenyl protons), 13.0 (br s, 1H, -OH).

5-(*N*-Boc-glycyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2d**).

The general procedure (method B) was followed using 10 mmoles of **1d** in 40 ml of dichloromethane and the reaction mixture was stirred for 45 hours. After evaporation of the solvent compound **2d** was obtained as a viscous oil (93% yield); pmr (deuteriochloroform); δ 1.48 (s, 9H, -CMe_3), 1.77 (s, 6H, -CMe_2-), 4.65 (br s, 2H, N-CH_2-), 5.20 (br m, 1H, -NH-), 13.0 (br s, 1H, -OH).

5-(*N*-Carbomethoxyglycyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2e**).

The general procedure (method B) was followed using 10 mmoles of **1e** in 10 ml of dichloromethane. After evaporation of the solvent compound **2e** was obtained as a viscous oil (86% yield); pmr (deuteriochloroform): δ 1.75 (s, 6H, -CMe_2-), 3.68 (s, 3H, -COOMe), 4.68 (d, J = 6 Hz, 2H, N-CH_2-), 5.20 (br m, 1H, -NH-), 12.5 (br s, 1H, -OH).

5-(*N*-Carbethoxyglycyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**2f**).

The general procedure (method A) was followed using 10 mmoles of **1f** in 40 ml of dichloromethane. In this experiment 4-*N*,*N*-dimethylaminopyridine (10 mmoles) was also added immediately after the addition of Meldrum's acid. After evaporation of the solvent compound **2f** was obtained as a viscous oil (85% yield); pmr (deuteriochloroform): δ 1.26 (t, J = 7 Hz, 3H, -$COOCH_2CH_3$), 1.77 (s, 6H, -CMe_2-), 4.13 (q, J = 7 Hz, 2H, -$COOCH_2CH_3$), 4.69 (d, J = 6 Hz, 2H, N-CH_2-), 5.40 (br m, 1H, -NH-), 11.5 (br s, 1H, -OH).

N-Benzoyltetramic Acid (**3a**).

The transformation of the acylation compound **2a** to **3a**, in refluxing chloroform for 30 minutes, has already been described [1a]. Compound **3a** was obtained in almost quantitative yield as a white solid, mp 180° dec, lit mp 180° dec (after recrystallization from methanol-ethyl acetate) [9]; pmr spectra, see Table 1.

N-Acetyltetramic Acid (**3b**).

A solution of compound **2b** (2.05 g) in chloroform (36 ml) was heated under reflux for 30 minutes, when a white precipitate appeared. After cooling, the precipitate was filtered to give 1.15 g (96%) of a product mp 155-164°, which proved to be almost pure compound **3b** (pmr spectrum). Recrystallization

from methanol yielded a colorless crystalline solid (67% yield), mp 165-168° dec; pmr spectra, see Table 1.

Anal. Calcd. for $C_6H_7NO_3$: C, 51.06; H, 5.00; N, 9.93. Found: C, 51.03; H, 5.06; N, 9.98.

N-Benzyloxycarbonyltetramic Acid (**3c**).

The acylation compound **2c** (3.06 g) in ethyl acetate (25 ml) was heated under reflux for 45 minutes. After cooling, the solution was vigorously stirred with 25 ml of water containing 2 ml of 10% hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (4 x 12 ml). The combined organic layers were dried (sodium sulfate) and concentrated to give 2.1 g (quantitative yield) of a product mp 146-149° dec, which proved to be almost pure compound **3c** (pmr spectrum). Recrystallization from ethyl acetate yielded a crystalline solid (64% yield), mp 151-153° dec; pmr spectra, see Table 1.

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.84; H, 4.78; N, 5.91.

N-*t*-Butoxycarbonyltetramic Acid (**3d**).

The acylation compound **2d** (2.82 g) in ethyl acetate (25 ml) was heated under reflux for 35 minutes. After concentration, a solid residue (1.73 g, 92%) was obtained, mp 110-120° dec, which proved to be almost pure compound **3d** (pmr spectrum). The residue was stirred vigorously in 50 ml of water containing 2 ml of 10% hydrochloric acid, the insoluble material was dissolved with ethyl acetate (25 ml) and the aqueous layer was then extracted with ethyl acetate (4 x 10 ml). The combined organic layers were dried (sodium sulfate) and concentrated to give 1.41 g (75%) of a product mp 112-115° dec. Recrystallization from ethyl acetate yielded a crystalline solid (41% yield), mp 130-132° dec; pmr spectra, see Table 1.

Anal. Calcd. for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.26; H, 6.61; N, 6.94.

N-Carbomethoxytetramic Acid (**3e**).

Compound **2e** (0.36 g) in chloroform (10 ml) was heated under reflux for 30 minutes, when a white precipitate appeared. After cooling, the precipitate was filtered to give 0.2 g (91%) of a colorless solid, which proved to be almost pure compound **3e** (pmr spectrum). The product did not melt up to 200° and could not be recrystallized; pmr spectra, see Table 1.

The transformation **2e** → **3e** could also be observed when a solution of the acylation compound **2e** in methanol or acetone was kept at room temperature for 2-3 days. After concentration of the solution, the product proved to be an almost pure compound **3e** (pmr spectrum).

N-Carbethoxytetramic Acid (**3f**).

A solution of the acylation compound **2f** (0.57 g) in chloroform (10 ml) was heated under reflux for one hour. After concentration, compound **3f** was obtained as a solid (0.32 g, 90%), mp 96-102°, lit mp 102-105° and 105-108° (after recrystallization from benzene) [9]; pmr spectra, see Table 1.

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