

The Cyclization of the Acetylaminoacetyl Derivatives to α -Substituted Tetramic Acids and the Formation of*N*-Acetyl- α -substituted Tetramic Acids [1]

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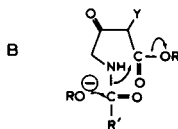
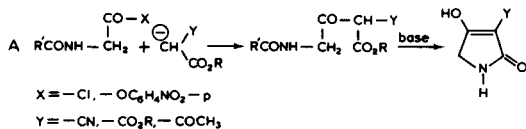
The reaction of aceturic acid *p*-nitrophenyl ester with active methylene compounds $Y-CH_2-CO_2R$ has been found to give either the normally expected *C*-acylation compounds **2** ($Y = -CN, -CO_2R, -COCH_3$) or *N*-acetyl- α -*Y*-substituted tetramic acids **3** ($Y = -CO_2R, -COCH_3$), depending on the reaction conditions. Moreover, the intramolecular condensation of the *C*-acylation compounds **2** derived from malonic and acetoacetic esters ($Y = -CO_2R, -COCH_3$) to α -*Y*-substituted tetramic acids is shown to proceed through initial cyclization to the corresponding *N*-acetyl- α -*Y*-substituted tetramic acids **3** ($Y = -CO_2R, -COCH_3$).

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Introduction.

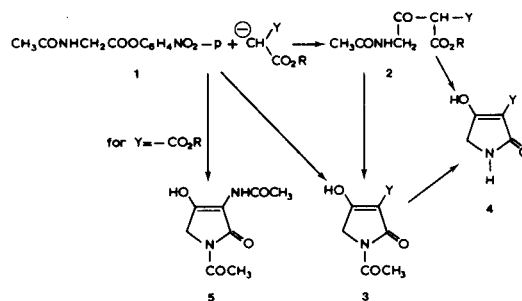
In the previous communication [2] we have reported a preliminary investigation on a method of synthesis of α -substituted tetramic acids [3] through the cyclization of acylaminoacetyl derivatives of active methylene compounds (Scheme 1, A). This investigation revealed the possibility of intramolecular cyclization of the benzoylaminoacetyl derivatives ($R' = -C_6H_5$, $Y = -CN, -CO_2R$ and $-COCH_3$) to the corresponding α -*Y*-substituted tetramic acids, probably through a concerted mechanism of debenzoylation - intramolecular condensation (Scheme 1, B).

Scheme 1



According to this mechanism the deacylation step, and hence, the overall intramolecular cyclization of the acetyl-aminoacetyl derivatives ($R' = -CH_3$) should be expected to be faster as compared to the benzoylaminoacetyl derivatives ($R' = -C_6H_5$). This will be shown to be true for the acetyl-aminoacetyl derivatives of cyanoacetic esters ($Y = -CN$). However, and quite unexpectedly, the cyclization of the acetyl-aminoacetyl derivatives of malonic and acetoacetic esters ($R' = -CH_3$, $Y = -CO_2R$ and $-COCH_3$) has been found to proceed through initial formation of the corresponding *N*-acetyl- α -*Y*-substituted tetramic acids. Moreover, and more important, the latter compounds were obtained in the *C*-acylation reaction which would normally yield the acetyl-aminoacetyl derivatives.

Scheme 2



2a, Y = -CN	R = -Me	3a, Y = -CO ₂ Me	4a, Y = -CN
2b, -CN	-Et	3b, -CO ₂ Et	4b, -CO ₂ Me
2c, -CO ₂ Me	-Me	3c, -COCH ₃	4c, -CO ₂ Et
2d, -CO ₂ Et	-Et		4d, -COCH ₃
2e, -COCH ₃	-Me		
2f, -COCH ₃	-Et		

Results and Discussion.

Aceturic acid *p*-nitrophenyl ester (**1**) was used in all *C*-acylation reactions which resulted in the isolation of either the acetyl-aminoacetyl derivatives **2** or the new *N*-acetyl- α -substituted tetramic acids **3** (Scheme 2). Typical experiments of the *C*-acylation reactions are reported in Table 1, together with the cyclization reactions of compounds **2**.

Reaction of the ester **1** with the anions of methyl and ethyl cyanoacetates was actually found to proceed to the corresponding acetyl-aminoacetyl derivatives **2a** and **2b**, respectively. The anions were generated from the action of a base, potassium *t*-butoxide in *t*-butyl alcohol or sodium hydride in benzene, *i.e.* under the conditions which were previously used in the synthesis of the benzoylaminoacetyl derivatives [2]. Compounds **2a** and **2b** were thus isolated in 50-70% yields using the proportions of ester **1** to base to cyanoacetic ester 1:2:3 (Table 1, experiments 1-4), but equally good yields were obtained using the proportions

Table 1
C-Acylation and Cyclization Reactions [a]

Experiment number	Starting compound	Compound isolated	Yield %	Base used	Reactants' proportions [b]	Reaction conditions
Reactions with Cyanoacetic Esters (Y = -CN)						
1	1	2a	68	Potassium <i>t</i> -butoxide	1:2:3	Room temperature, 3 hours
2	1	2a	71	Sodium hydride	1:2:3	Room temperature, 1 hour
3	1	2b	50	Potassium <i>t</i> -butoxide	1:2:3	Room temperature, 2 hours
4	1	2b	63	Sodium hydride	1:2:3	Room temperature, 1 hour
5	2a	4a	42	Sodium methoxide	1:2	Reflux, 4 hours
6	2b	4a	40	Sodium methoxide	1:2	Reflux, 4 hours
Reactions with Malonic Esters (Y = -CO ₂ R)						
7	1	5	60 [c]	Potassium <i>t</i> -butoxide	1:1.1:1.1	Room temperature, 30 minutes
8	1	2c	37	Potassium <i>t</i> -butoxide	1:1.5:1.8	Room temperature, 30 minutes
9	1	2d	41	Potassium <i>t</i> -butoxide	1:1.5:1.8	Room temperature, 30 minutes
10	1	2d	47	Sodium hydride	1:1.5:1.8	Room temperature, 20 minutes
11	1	3a	60	Potassium <i>t</i> -butoxide	1:2:3	Room temperature, 4 hours
12	1	3a	71	Sodium hydride	1:2:3	Room Temperature, 4 hours
13	1	3b	62	Potassium <i>t</i> -butoxide	1:2:3	Room temperature, 4 hours
14	2c	3a	52	Potassium <i>t</i> -butoxide	1:3:3	Room temperature, 8 hours
15	2d	3b	48	Potassium <i>t</i> -butoxide	1:3:3	Room temperature, 8 hours
16	2d	3b	84	Sodium ethoxide	1:2	Room temperature, 1 hour
17	2c	4b	59	Sodium methoxide	1:2	Reflux, 2 hours
18	2d	4c	63	Sodium ethoxide	1:2	Reflux, 2 hours
19	3a	4b	51	Sodium ethoxide	1:2	Reflux, 2.5 hours
20	3b	4c	42	Sodium ethoxide	1:2	Reflux, 2.5 hours
Reactions with Acetoacetic Esters (Y = -COCH ₃)						
21	1	2e	32	Potassium <i>t</i> -butoxide	1:1:1	Room temperature, 30 minutes
22	1	2f	30	Potassium <i>t</i> -butoxide	1:1:1	Room temperature, 30 minutes
23	1	3c	84 [d]	Sodium hydride	1:2:3	Room Temperature, 3 hours
24	1	3c	75 [e]	Sodium hydride	1:2:3	Room temperature, 3 hours
25	2e	3c	77	Potassium <i>t</i> -butoxide	1:3:3	Room temperature, 8 hours
26	2e	4d	82	Sodium methoxide	1:2	Room temperature, 2 hours
27	2f	4d	80	Sodium methoxide	1:2	Room temperature, 2 hours
28	3c	4d	86	Sodium methoxide	1:2	Room temperature, 2 hours

[a] See Scheme 2. [b] Proportions of starting compound to base to active methylene compound or proportions of starting compound to base. [c] From the reaction of **1** with methyl malonate. [d] From the reaction of **1** with methyl acetoacetate. [e] From the reaction of **1** with ethyl acetoacetate.

1:1:1.

Refluxing the *C*-acylation compounds **2a** and **2b** with two equivalents of sodium methoxide in methanol-benzene resulted in the isolation of α -cyanotetramic acid (**4a**) (experiments 5,6). The cyclization reaction required only 4 hours refluxing, while for the analogous reaction of the corresponding benzoylaminoacetyl derivatives a refluxing of 10 hours was necessary [2]. This difference would then seem to be in agreement with a faster deacylation step of the concerted mechanism (Scheme 1, B) for the acetylaminoacetyl derivatives. Anyhow, the cyclization reaction of the cyano compounds **2a** and **2b** proved to be more difficult than the cyclization of the carbalkoxy and acetyl compounds **2c-2f** (see below).

It should be noted, that compounds **2a** and **2b** were the unique products isolated from the *C*-acylation reaction

and that formation of *N*-acetyl- α -cyanotetramic acid (**3**, Y = -CN) could not be observed in either the *C*-acylation or the cyclization reactions. As described below, this is in clear opposition to the behavior of the corresponding carbalkoxy and acetyl compounds.

Depending on the reaction conditions, *i.e.* the proportions of the *p*-nitrophenyl ester **1** to base to malonic ester, the *C*-acylation reaction with the anions of methyl and ethyl malonates was found to give the acetylaminoacetyl derivatives **2c** and **2d**, the *N*-acetyl- α -carbalkoxytetramic acids **3a** and **3b**, the *N*-acetyl- α -acetylaminoacetyl tetramic acid (**5**) [4,5], or mixtures of compounds **2**, **3** and **5**.

Compound **5** was isolated as the sole product, using the proportions of ester **1** to base (potassium *t*-butoxide or sodium hydride) to malonic ester 1:1.1:1.1 (Table 1, experiment 7). This reaction closely resembles the analogous re-

action with the *p*-nitrophenyl ester of hippuric acid, which has been found [2] to yield *N*-benzoyl- α -benzoylamino-tetramic acid. However, moderate yields, 37-47%, of the *C*-acylation compounds **2c** and **2d** were obtained using the proportions 1:1.5:1.8 (experiments 8-10).

Quite unexpectedly, compounds **3a** and **3b** were isolated in 60-70% yields using the proportions 1:2:3 at room temperature for 4 hours (experiments 11-13), *i.e.* under the conditions used for the synthesis of the cyano *C*-acylation compounds **2a** and **2b** (experiments 1-4). However, for shorter reaction times, mixtures of compounds **2c** and **3a**, or **2d** and **3b**, were isolated and characterized (pmr spectra). It is thus obvious that formation of the *N*-acetyl- α -carbalkoxytetramic acids **3a** and **3b** in the *C*-acylation reaction results from a base-promoted cyclization of the initially formed *C*-acylation compounds **2c** and **2d**. This conclusion is supported by the observation that compounds **2c** and **2d** likewise yield the *N*-acetyltetramic acids **3a** and **3b**, respectively, when subjected to the conditions of the *C*-acylation reaction with an excess of base (experiments 14,15).

The transformation of the *C*-acylation compounds **2c**

and **2d** to the α -carbalkoxytetramic acids **4b** and **4c**, respectively, required (experiments 17,18) shorter reaction times than the analogous transformation of the corresponding benzoylaminoacetyl derivatives [2] or even the cyano derivatives **2a** and **2b** (experiments 5,6). It is also significant, that under the same reaction conditions the *N*-acetyl-tetramic acids **3a** and **3b** were deacetylated (experiments 19,20). It has been found that the deacetylation of compounds **3a** and **3b** can also be performed easily under acid conditions. Thus, refluxing for 1.5 hour compound **3a** with hydrogen chloride in ethanol resulted in a simultaneous transesterification reaction and compound **4c** was isolated in 66% yield (see Experimental).

In contrast to the cyclization of the cyano compounds **2** reported above, the cyclization of the carbalkoxy compounds **2c** and **2d** to the corresponding α -carbalkoxytetramic acids **4b** and **4c**, respectively, proceeds through initial formation of the *N*-acetyl- α -carbalkoxytetramic acids **3a** and **3b**. Thus, treatment of compound **2d** with two equivalents of sodium ethoxide in ethanol at room temperature for 1 hour resulted in the isolation of *N*-acetyl- α -carbalkoxytetramic acid (**3b**) in an excellent yield of 84%

Table 2

PMR Spectra of Compounds **2**, **3** and **4**

Compound [a]	Solvent	Chemical Shifts in ppm (δ), J in Hz
2a	Deuteriochloroform	2.10, s, CH ₃ CO-N; 3.93, s, -CO ₂ CH ₃ ; 4.36, d J = 6, N-CH ₂ ; 6.43, m, -NH; 11.13, very broad signal, ~ 1H, -OH [b]
2b	Deuteriochloroform	1.38, t J = 7, -CO ₂ CH ₂ CH ₃ ; 2.10, s, CH ₃ CO-N; 4.38, d J = 6, N-CH ₂ ; 4.39, q J = 7, -CO ₂ CH ₂ CH ₃ ; 6.70, m, almost a t J = 6, -NH; 13.12, very broad signal, ~ 1H, -OH [b]
2c [c]	Deuteriochloroform	2.05, s, CH ₃ CO-N; 3.83, s, -CO ₂ CH ₃ ; 4.33, d, J = 5, N-CH ₂ ; 4.63, s, ~ 0.7H, -CH(CO ₂ Me); 6.46, m, -NH; 14.30, s, ~ 0.3H, -OH
2d [d]	Deuteriochloroform	1.30, t J = 7, -CO ₂ CH ₂ CH ₃ ; 2.05, s, CH ₃ CO-N; 4.27, q J = 7, -CO ₂ CH ₂ CH ₃ ; 4.35, d J = 5, N-CH ₂ ; 4.55, s, ~ 0.8H, -CH(CO ₂ Et); 6.33, m, -NH; 14.10, s, ~ 0.2H, -OH
2e [e]	Deuteriochloroform	2.15, s, CH ₃ CO-N; 2.42, s, C-COCH ₃ ; 3.78, s, -CO ₂ CH ₃ ; 4.52, d J = 5, N-CH ₂ ; 7.22, m, -NH; 17.55, s, -OH
2f [e]	Deuteriochloroform	1.36, t J = 7, -CO ₂ CH ₂ CH ₃ ; 2.16, s, CH ₃ CO-N; 2.45, s, CH ₃ CO-N; 4.30, q J = 7, -CO ₂ CH ₂ CH ₃ ; 4.56, d J = 5, N-CH ₂ ; 7.33, m, -NH; 17.50, s, -OH
3a	Deuteriochloroform/DMSO-d ₆	2.50, s, CH ₃ CO-N; 3.80, s, -CO ₂ CH ₃ ; 4.28, s, ring -CH ₂ ; 8.20, br s, -OH
3b	Trifluoroacetic acid Deuteriochloroform/DMSO-d ₆	2.80, s, CH ₃ CO-N; 4.06, s, -CO ₂ CH ₃ ; 4.67, s, ring -CH ₂ 1.38, t J = 7, -CO ₂ CH ₂ CH ₃ ; 2.56, s, CH ₃ CO-N; 4.31, s, ring -CH ₂ ; 4.36, q J = 7, -CO ₂ CH ₂ CH ₃ ; 5.96, br s, -OH
3c	Trifluoroacetic acid DMSO-d ₆ Trifluoroacetic acid Deuteriochloroform	1.48, t J = 7, -CO ₂ CH ₂ CH ₃ ; 2.80, s, CH ₃ CO-N; 4.65, q J = 7, -CO ₂ CH ₂ CH ₃ ; 4.67, s, ring -CH ₂ 2.52, s, CH ₃ CO-N and C-COCH ₃ ; 4.21, s, ring -CH ₂ ; 11.10, s, -OH 2.82 and 2.84, two s, CH ₃ CO-N and C-COCH ₃ ; 4.59, s, ring -CH ₂ 2.62 and 2.65, two s, CH ₃ CO-N and C-COCH ₃ ; 4.17 and 4.35, two s, intensity ratio 1:1.78, ring -CH ₂ ; 7.88, br s, -OH
4b	Trifluoroacetic acid [f]	4.02, s, -CO ₂ CH ₃ ; 4.42, s, ring -CH ₂ -
4c	Deuteriochloroform/DMSO-d ₆	1.38, t J = 7, -CO ₂ CH ₂ CH ₃ ; 3.96, s, ring -CH ₂ ; 4.38, q J = 7, -CO ₂ CH ₂ CH ₃ ; 5.26 and 7.72, two br s, -NH- and -OH
4d	Trifluoroacetic acid [f] DMSO-d ₆ [f] Deuteriochloroform	1.48, t J = 7, -CO ₂ CH ₂ CH ₃ ; 4.46, s, ring -CH ₂ ; 4.58, q J = 7, -CO ₂ CH ₂ CH ₃ 2.40, s, C-COCH ₃ ; 3.78, s, ring -CH ₂ ; 8.50, br m, -NH; 13.30, s, OH 2.55 and 2.60, two s, intensity ratio 3.26:1, C-COCH ₃ ; 3.90 and 4.03, two s, intensity ratio 3.84:1, ring -CH ₂ ; 6.98, m, -NH; 12.25, s, -OH

[a] See Scheme 2. [b] Compounds **2a** and **2b** were rather insoluble in deuteriochloroform; it was thus difficult to obtain a clear trace and an exact integration of the -OH signal. [c] The product contains about 10% of compound **5**, as evidenced from the presence of singlets at 2.22, 2.53 and 4.22 ppm. [d] The signals of the -CO₂Et and CH₃CO-N groups consist of two overlapping signals of the keto and enol forms of the compound, whose chemical shifts do not differ more than 1 Hz. [e] The product contains a small amount of *p*-nitrophenol, as evidenced from the presence of the characteristic aromatic protons' signals. [f] Spectrum reported in the previous communication [2].

(experiment 16), while from the same treatment of compound **2d** at reflux for two hours α -carbethoxytetramic acid (**4c**) was isolated in 63% yield (experiment 18). These experimental facts indicate that the carbalkoxy derivatives **2** ($Y = -CO_2R$) are easily cyclized, by a base-promoted intramolecular condensation, to the corresponding *N*-acetyltetramic acids **3** ($Y = -CO_2R$) and that the deacetylation of the latter to the tetramic acids **4** ($Y = -CO_2R$) takes place in a subsequent, clearly separated and more difficult, step.

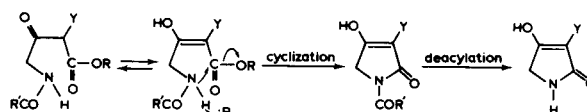
The reaction of the *p*-nitrophenyl ester **1** with the anions of methyl and ethyl acetoacetates was found to give results very similar to those just described for the malonic esters. The *C*-acylation compounds **2e** and **2f** were isolated as oily products in rather poor yields, using potassium *t*-butoxide as the base (experiments 21,22). On the other hand, excellent yields of *N*, α -diacetyltetramic acid (**3c**) were obtained in the *C*-acylation reaction using sodium hydride as the base (experiments 23,24). Shorter reaction times in these experiments resulted in mixtures of compounds **2** and **3**; for instance, the product obtained from the reaction of **1**

with methyl acetoacetate after 1 hour at room temperature consisted of a mixture of compounds **2e** and **3c** in a ratio of 1:1, while after 3 hours compound **3c** was the sole product of the reaction. Compound **3c** was also obtained in an excellent yield from the cyclization of compound **2e** under the conditions of the *C*-acylation reaction (experiment 25).

Treating the *C*-acylation compounds **2e** and **2f** with two equivalents of sodium methoxide in methanol-benzene at room temperature for 2 hours resulted in the isolation of α -acetyltetramic acid (**4d**) in better than 80% yields (experiments 26,27), while under the same reaction conditions *N*, α -diacetyltetramic acid (**3c**) could be deacetylated to **4d** in 86% yield (experiment 28). On the other hand, shorter reaction times in the reactions of compounds **2e** and **2f** (experiments 26,27) resulted in the formation of mixtures of the *N*-acetyltetramic acid **3c** and the deacetylated compound **4d**. These experimental facts indicate that the acetyl derivatives **2** ($Y = -COCH_3$) are likewise easily cyclized to *N*, α -diacetyltetramic acid (**3c**) and that the deacetylation of the latter requires milder conditions as compared to the carbalkoxy compounds **3a** and **3b** (experiments 19,20).

The results thus far obtained for the transformation of the acetylaminoacetyl derivatives **2** to the corresponding α -*Y*-substituted tetramic acids **4** ($Y = -CO_2R$ and $-COCH_3$) exclude the concerted mechanism of deacylation-intramolecular condensation (Scheme 1, B). This transformation actually occurs in two distinct steps, as shown in Scheme 3, and the requirements for the proper intramolecular condensation (cyclization) and deacylation steps determine the possibility of isolation of the intermediate *N*-acetyltetramic acids. The enolic structure of the acetylaminoacetyl derivatives (see below) places the $-CO_2R$ group in a

Scheme 3



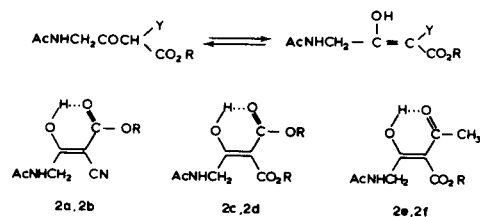
suitable position for the cyclization step, which is initiated with the abstraction of the N-H hydrogen by a base. In the case of the acetylaminoacetyl derivatives ($R' = -CH_3$, $Y = -CO_2R$ and $-COCH_3$), the ready cyclization, as compared to the deacetylation step, apparently allows for the formation and isolation of the *N*-acetyltetramic acids even under the conditions of the *C*-acylation reaction.

The cyclization step should be more difficult in the case of the corresponding benzoylaminoacetyl derivatives ($R' = -C_6H_5$), the approach of the base to the N-H hydrogen being now sterically hindered. Consequently, the required conditions of the basic treatment should then result in both the cyclization and debenzoylation steps and this would explain the fact observed that *N*-benzoyltetramic acids could not be detected nor isolated [2]. A similar argument could also explain the behavior of the cyano compounds ($Y = -CN$), whose enolic structure (see below, Scheme 4) would require more drastic conditions in order to bring the $-CO_2R$ group in a position suitable for the cyclization step. However, the concerted mechanism (Scheme 1, B) cannot be excluded a priori in these cases, in the absence of more detailed evidence.

The structure of the *C*-acylation compounds **2a-2f** is apparent from their pmr spectra in deuteriochloroform solution (Table 2) and closely resembles the structure of the corresponding benzoylaminoacetyl derivatives [2].

The cyano (**2a** and **2b, $Y = -CN$) and acetyl (**2e** and **2f, $Y = -COCH_3$) compounds exist exclusively in the enolic form, while the carbalkoxy (**2c** and **2d, $Y = -CO_2R$) compounds exist as mixtures of the keto and enolic forms (Scheme 4). Indeed, only the latter compounds exhibit a methine $-CHYCO_2R$ singlet at δ 4.63 and 4.55 ppm, respectively, amounting to 70-80% of the mixture. The enolic forms of compounds **2a-2f** would be stabilized, through intramolecular hydrogen bonds, in the configurations shown in Scheme 4. Especially, the strong intramolecular******

Scheme 4

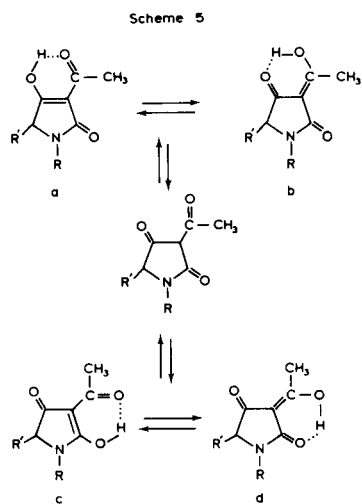


hydrogen bond through the $-COCH_3$ group in compounds **2e** and **2f** results in a very low field signal for the enolic proton at 17.50 ppm (see Table 2). These particular confi-

gurations of the enolic forms of compounds **2** determine, as discussed above, the possibility of intramolecular condensation to the corresponding *N*-acetyltetramic acids **3**. In agreement with their enolic structures, compounds **2a-2f** give intense, orange to red, colours with an aqueous solution of ferric chloride.

Likewise, the *N*-acetyltetramic acids **3a**, **3b** and **3c** give intense red colours with ferric chloride and their enolic structure is consistent with their pmr spectra (Table 2). When compared to the spectra of the corresponding deacetylated compounds **4b**, **4c** and **4d**, which are also reported in Table 2, one can observe the presence of the *N*-acetyl protons singlet and the shift of the ring methylene protons singlet to lower field. Though the structural assignment of the carbalkoxy compounds **3a** and **3b** is straightforward, the enolic structure of the *N*, α -diacetyltetramic acid (**3c**) needs, however, some comments.

The structure of 5-substituted 3-acetylpyrrolidine-2,4-diones (Scheme 5) has been thoroughly investigated by Steyn *et al.* [6], who have shown (pmr and cmr data) that in chloroform solutions the exo-enol forms **b** and **d** are the stable tautomers and that tautomer **d** is also the form in which 3-acetyl-5-isopropylpyrrolidine-2,4-dione (Scheme 5, R = H, R' = isopropyl) exists in the crystalline state (X-ray data). Only one set of nmr signals were observed for all the protons in polar solvents, but in deuteriochloroform solutions two sets of peaks were observed for certain protons owing to the slow exchange of the external tautomers, **ab** and **cd**. This doubling of proton signals was used to determine the ratio between the external tautomers **cd/ab** as 2.62, 2.96 and 6.69 for three 5-substituted compounds (Scheme 5, R = H, R' = isopropyl, *sec*-butyl and benzyl, respectively). The preference of tautomer **d** over the tautomer **b** was attributed [6] to the ability of the amide carbonyl group to form a stronger intramolecular hydrogen bond **d** than the ring keto carbonyl group **b**.



Certain protons of α -acetyltetramic acid (**4d**, in Scheme 5, R = R' = H) were actually found to give rise to two sets of peaks in deuteriochloroform solution (Table 2): acetyl protons, two singlets at δ 2.55 and 2.60 ppm, intensity ratio 3.26:1, and ring methylene protons, two singlets at δ 3.90 and 4.03 ppm, intensity ratio 3.84:1 [7]. The signals of each set occurring at higher field were assigned to the external tautomer-pair **cd** [6] and thus an average ratio of **cd/ab** 3.55 could be determined for compound **4d**, in fair agreement with the ratios of the 5-substituted compounds (see above).

A similar doubling of the ring methylene protons was also observed in the case of the *N*, α -diacetyltetramic acid (**3c**, in Scheme 5, R = -COCH₃, R' = H) in deuteriochloroform solution: two singlets at δ 4.17 and 4.35 ppm, intensity ratio 1:1.78. Assuming that the higher field signal, which is now the lower intensity peak, can also be assigned to the tautomer-pair **cd**, the ratio **cd/ab** for compound **3c** is only 0.56. This value apparently indicates a decreased contribution of tautomer **d**, which must be attributed to the presence of the *N*-acetyl group. This group should be expected to diminish the ability of the nitrogen atom to donate electrons to the ring amide carbonyl group. Consequently, its proton acceptor ability, as required in form **d**, would be reduced, thereby destabilizing this form in comparison to the deacetylated compound **4d**. Anyhow, the contribution of form **d** in the tautomer constitution of *N*, α -diacetyltetramic acid (**3c**) is still significant and must probably assist in the ready deacetylation of this compound.

Conclusion.

The results obtained in the *C*-acylation reactions of the *p*-nitrophenyl ester **1** with the anions of malonic and acetoacetic esters (Scheme 2, Y = -CO₂R and -COCH₃) disclose the significance of these reactions in the preparation of the corresponding *N*-acetyltetramic acids **3** in a single step. Moreover, the ready deacetylation of the latter provides a convenient two-step procedure for the synthesis of the corresponding α -Y-substituted tetramic acids **4**. The satisfactory yields obtained in these transformations compete favorably with the general method of Lacey [9,10] for the synthesis of α -Y-substituted tetramic acids, through the Dieckmann cyclization of *N*-acyl glycine esters of the general formula YCH₂CONHCH₂CO₂R.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The ir spectra were obtained with a Perkin Elmer 267 spectrometer. The pmr spectra were recorded on a Varian EM-360 60 MHz spectrometer; chemical shifts are given in ppm (δ) downfield from TMS (internal standard) and are accurate to ± 0.02 ppm. The tlc were performed on silica gel G plates; the eluent was in general ethyl ether and the spots were observed by exposure to iodine vapors. Anhydrous sodium sulfate was used for drying. The colour reaction with ferric chloride was performed by adding a 4% aqueous solution of ferric chloride in an alcohol-

lic solution of the product. Elemental analyses were obtained from the microanalytical laboratory of CNRS (France).

Aceturic Acid *p*-Nitrophenyl Ester (**1**).

This ester was prepared by the method [11] of direct esterification of *N*-acylamino acids with *p*-nitrophenol in the presence of DCC in methylene chloride. The experimental procedure has been described in the preceding communication [2] for the preparation of the hippuric acid *p*-nitrophenyl ester. The aceturic acid ester **1** was thus obtained, after removal of the *p*-nitrophenol, as a solid, mp 114-117°, in 65% yield. This product was shown (tlc and pmr spectrum) to be sufficiently pure and was used for the *C*-acylation reactions. Two recrystallizations from benzene gave an analytically pure product, mp 120-121°, lit [11] mp 125-126° and 129-130°; ir (nujol): strong sharp bands at 3278 (amide-NH-), 1751 (ester carbonyl), 1636 (amide carbonyl) and 1536 cm⁻¹ (amide II); pmr (deuteriochloroform): 2.15 (s, 3H, CH₃CO-N), 4.38 (d, J = 5.5 Hz, 2H, -CH₂CO₂), 6.51 (m, 1H, -CONH-), 7.43 and 8.40 (two d, J = 9 Hz, 4H, A₂B₂ system of aromatic protons).

Anal. Calcd. for C₁₀H₁₀N₂O₅: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.27; H, 4.06; N, 11.82.

General Procedure for the *C*-Acylation Reaction **1** → **2**. a) Using Potassium *t*-Butoxide as the Base (Method A).

Potassium *t*-butoxide (0.01 mole) was dissolved in 60 ml of *t*-butyl alcohol by stirring at room temperature for about 15 minutes. The active methylene compound Y-CH₂-CO₂R (0.015 mole for Y = -CN, 0.012 mole for Y = -CO₂R and 0.01 mole for Y = -COCH₃) was added dropwise (a thick slurry was formed for Y = -CN and -CO₂R) and the mixture was stirred for 1 hour. Compound **1** (0.005 mole for Y = -CN, 0.0066 mole for Y = -CO₂R and 0.01 mole for Y = -COCH₃) was then added and the mixture was stirred at room temperature for 2-3 hours (Y = -CN) or for 30 minutes (Y = -CO₂R and -COCH₃).

Compounds **2a**, **2b** and **2d** were isolated by the following treatment of

the reaction mixture. Water, about 100 ml, was added, the solution was extracted with ether and the aqueous layer was cooled with ice-water and acidified with 10% hydrochloric acid. The ethereal layer was extracted twice with water and the aqueous layers were also acidified. Compound **2a** separated from the acid aqueous solutions as a solid which was filtered, while compounds **2b** and **2d** separated as oily products which were extracted with chloroform and crystallized by addition of a small quantity of ether.

For compounds **2c**, **2e** and **2f**, which were ultimately obtained as oily products, a special treatment was necessary in order to eliminate the *p*-nitrophenol.

For compound **2c**, anhydrous ethanol (50 ml) and ether (40 ml) were added to the reaction mixture and the insoluble salt was filtered and washed first with ethanol and then with ether. The salt was then dissolved in a small quantity of water, acidified with 10% hydrochloric acid and extracted with chloroform to give an oily product.

For compounds **2e** and **2f**, ether, about 400 ml, was added to the reaction mixture and the insoluble salt was filtered and washed with ether. The salt was then dissolved in a small quantity of water, acidified with 10% hydrochloric acid and the oily product which separated was extracted with chloroform. This product, which contained still a large amount of *p*-nitrophenol (pmr spectrum), was dissolved in 5% sodium bicarbonate solution (40 ml), the alkaline solution was repeatedly extracted with ether, the aqueous layer was acidified with 10% hydrochloric acid and extracted with chloroform to give an oily product.

b) Using Sodium Hydride as the Base (Method B).

In 0.02 mole of sodium hydride (55-60% of sodium hydride in oil) in 30 ml of anhydrous benzene, the active methylene compound Y-CH₂-CO₂R (0.03 mole for Y = -CN and 0.024 mole for Y = -CO₂R) was added dropwise and the thick white slurry formed was stirred for 1 hour. Compound **1** (0.01 mole for Y = -CN and 0.013 mole for Y = -CO₂R) was then added and the mixture was stirred at room temperature for 1 hour (Y = -CN) or

Table 3
Physical Data of Compounds **2** and **3**

Compound [a]	Method [b]	Crude product, mp (yield)	Analytical sample, mp (recrystallization solvent)	Molecular formula	Analytical data Found/Calcd.		
					C	H	N
2a	A	147-150° (68%)	151-152° (chloroform-petroleum ether)	C ₈ H ₁₀ N ₂ O ₄	48.51	5.00	14.36
	B	146-149° (71%)			48.48	5.09	14.14
2b	A	125-129° (50%)	129-130° (chloroform-petroleum ether)	C ₉ H ₁₂ N ₂ O ₄	51.12	5.74	13.36
	B	126-129° (63%)			50.93	5.70	13.21
2c	A	oily product (37%) [c]					
2d	A	92-95° (41%)	95-97° (chloroform-petroleum ether)	C ₁₁ H ₁₇ NO ₆	51.02	6.60	5.33
	B	91-93° (47%)			50.96	6.61	5.40
2e	A	oily product (32%) [d]					
2f	A	oily product (30%) [d]					
3a	C	212-214° dec (60%)	216-217° dec (ethanol)	C ₈ H ₉ NO ₅	47.95	4.77	7.20
	D	208-215° dec (71%)			48.24	4.55	7.03
	E	207-210° dec (52%)					
3b	C	132-134° (62%)	133-136° (ethanol-ether)	C ₉ H ₁₁ NO ₅	50.87	5.23	6.67
	E	128-133° (48%)			50.70	5.20	6.57
	F	124-128 (84%) [e]					
3c	D	75-78° (84%) [f]	78-79° (chloroform-petroleum ether)	C ₈ H ₉ NO ₄	52.77	5.23	7.68
	D	73-77° (75%) [g]			52.46	4.95	7.65
	E	76-78° (77%) [h]					

[a] See Scheme 2. [b] See Experimental: Method A, ester **1** and potassium *t*-butoxide; Method B, ester **1** and sodium hydride; Method C, ester **1** and potassium *t*-butoxide; Method D, ester **1** and sodium hydride; Method E, compound **2** and potassium *t*-butoxide; Method F, compound **2** and sodium ethoxide. [c] The product contains about 10% of compound **5** (pmr spectrum). [d] The product contains a small amount of *p*-nitrophenol (pmr spectrum). [e] From the reaction on compound **2d**. [f] From the reaction of compound **1** with methyl acetoacetate. [g] From the reaction of compound **1** with ethyl acetoacetate. [h] From the reaction on compound **2e**.

for 20 minutes ($Y = -CO_2R$). After addition of water, in order to dissolve the insoluble salts, the benzene layer was separated, the aqueous layer was acidified with 10% hydrochloric acid and the oily product was extracted with chloroform. This product was crystallized by addition of a small quantity of ether.

Physical characteristics of all *C*-acylation compounds **2** are reported in Table 3. The crude compounds **2** were found to be sufficiently pure (tlc and pmr spectra) and were used as such for the cyclization reactions **2** → **3** and **2** → **4**. The pmr spectra of compounds **2** (spectra for analytical samples of compounds **2a**, **2b** and **2d**) are reported in Table 2.

General Procedure for the *C*-Acylation-Cyclization Reaction **1** → **3**. a) Using Potassium *t*-Butoxide as the Base (Method C).

Following method A, the reaction mixture of potassium *t*-butoxide (0.01 mole), the active methylene compound (0.015 mole) and compound **1** (0.005 mole) was stirred at room temperature for 4 hours. Water was then added, the solution was extracted with ether and the aqueous layer was acidified with 10% hydrochloric acid. The solid product which separated was filtered and washed with a small quantity of ether.

b) Using Sodium Hydride as the Base (Method D).

Following method B, the reaction mixture of sodium hydride (0.02 mole), the active methylene compound (0.03 mole) and compound **1** (0.01 mole) was stirred at room temperature for 3-4 hours.

For compound **3a**, water was added and the aqueous solution was acidified with 10% hydrochloric acid. The solid product which formed was filtered and the aqueous acid solution was extracted with chloroform to give another portion of compound **3a**.

For compound **3c**, ether, about 400 ml, was added to the reaction mixture and the insoluble salt was filtered and washed with ether. The salt was then dissolved in a small quantity of water, the solution acidified with 10% hydrochloric acid and the oily product which separated was extracted with chloroform. The semi-solid product thus obtained was crystallized by addition of a small quantity of ether.

General Procedure for the Cyclization Reaction **2** → **3**. a) Using Potassium *t*-Butoxide as the Base (Method E).

Following Method A, the reaction mixture of potassium *t*-butoxide (0.03 mole dissolved in 100 ml of *t*-butyl alcohol), the active methylene compound (0.03 mole) and compound **2** (0.01 mole) was stirred at room temperature for 8 hours. The mixture was then dissolved in a small quantity of water, the solution was extracted with ether and the aqueous layer was acidified with 10% hydrochloric acid to give compound **3** as a colorless oily product. Compounds **3a** and **3b** solidified after standing for some time, while compound **3c** was extracted with chloroform and the oily product obtained slowly solidified.

b) Using Sodium Ethoxide as the Base (method F).

Compound **2d** (1 mmole) was dissolved in a solution of sodium ethoxide prepared from sodium (0.002 g-atom) in 10 ml of ethanol. The solution was stirred at room temperature for 1 hour (a precipitate appeared after 5 minutes of stirring). Small quantities of water and ether were then added, the mixture was acidified with 10% hydrochloric acid, the ether layer was separated and the aqueous layer was extracted with chloroform. The ether and chloroform extracts were concentrated to give compound **3b** as a solid product, mp 124-128°, in 84% yield.

Physical characteristics of compounds **3** obtained by the methods C-F are reported in Table 3 and the pmr spectra of their analytical samples are reported in Table 2.

α -Cyanotetramic Acid (**4a**).

Compound **2a** (0.6 g, 3 mmoles) was dissolved in a small quantity of warm methanol and was then added to a solution of sodium methoxide in methanol (prepared from 0.14 g or 0.006 g-atom of sodium in 10 ml of methanol) containing 10 ml of anhydrous benzene. The solution was refluxed for 4 hours and let stand overnight. After acidification with 10% hydrochloric acid the mixture was concentrated under vacuum and the

residue was treated successively with chloroform, to eliminate any starting compound **2a**, and ether, to eliminate the acetic ester. The product was then dissolved in warm ethanol, to eliminate sodium chloride, filtered and the solvent evaporated to give 0.16 g (42%) of a product mp 216-218° dec. This product proved to be identical (mp, ir and pmr spectra) to compound **4a** which has been reported in the previous communication [2].

Following the same procedure, compound **4a**, mp 215° dec, was obtained in 40% yield from compound **2b**.

α -Carbomethoxytetramic Acid (**4b**). a) From Compound **2c**.

Compound **2c** (0.74 g, 3 mmoles) was dissolved in 10 ml of warm benzene and added to a solution of sodium methoxide in methanol (prepared from 0.14 g or 0.006 g-atom of sodium in 10 ml of methanol). The mixture was refluxed for 2 hours and let stand overnight. The precipitate which formed was dissolved by addition of a small quantity of water and the aqueous layer was acidified with 10% hydrochloric acid to give, after cooling, 280 mg (59%) of a product mp >270°. This product proved to be identical (mp, ir and pmr spectra) to compound **4b** which has been reported in the previous communication [2].

b) From Compound **3a**.

The procedure described above for the transformation of **2c** to **4b** was used for the deacetylation reaction of compound **3a**. In this case, a solution of sodium ethoxide in ethanol was used and the reaction mixture was refluxed for 2.5 hours. Compound **4b**, mp >270°, was obtained in 51% yield.

α -Carbomethoxytetramic Acid (**4c**). a) From Compound **2d**.

Following the procedure described for the transformation of **2c** to **4b** and using a solution of sodium ethoxide in ethanol, compound **4c** was obtained in 63% yield. The product, which had a mp at about 120° (followed by resolidification and no further melting up to 270°), proved to be identical (mp, ir and pmr spectra) to compound **4c** which has been reported in the previous communication [2].

b) From Compound **3b**.

Following the procedure described for the transformation of **3a** to **4b**, compound **4c**, mp at about 120°, was obtained in 42% yield.

c) From Compound **3a** Under Acid Conditions.

Compound **3a** (0.5 g, 2.5 mmoles) was dissolved in a solution of hydrogen chloride in ethanol (prepared from the addition of 4 ml of acetyl chloride in 40 ml of absolute ethanol) and the mixture was refluxed for 1.5 hour. After cooling, the solution was concentrated under vacuum and the oily residue was treated successively with small quantities of benzene and ether. The oily product crystallized after two days; ether was then added and the solid was filtered to give 280 mg (66%) of compound **4c**, mp at about 120°.

α -Acetyltetramic Acid (**4d**). a) From Compounds **2e** and **2f**.

Compound **2e** (0.43 g, 2 mmoles) was dissolved in 10 ml of benzene and added to a solution of sodium methoxide in methanol (prepared from 0.09 g or 0.004 g-atom of sodium in 10 ml of methanol). The mixture, in which a precipitate was gradually formed, was stirred at room temperature for 2 hours and let stand overnight. The mixture was then concentrated under vacuum, a small quantity, about 3 ml, of water was added and the aqueous solution was acidified with 10% hydrochloric acid. The solid product which precipitated was filtered, after cooling, to give 0.23 g (82%) of a product mp 151-153°. This product proved to be identical (mp, ir and pmr spectra) to compound **4d** which has been reported in the previous communication [2].

Following the same procedure, compound **4d**, mp 150-152°, was obtained in 80% yield from compound **2f**.

b) From Compound **3c**.

The procedure just described for the transformation of compounds **2e** and **2f** to **4d** was used for the deacetylation of compound **3c**. Compound

4d, mp 152-155°, was thus obtained in 86% yield.

N-Acetyl- α -acetylaminotetramic Acid (**5**).

Acetic acid *p*-nitrophenyl ester (**1**) (0.01 mole) reacted with methyl malonate (0.011 mole) in the presence of potassium *t*-butoxide (0.011 mole), according to the general procedure of the *C*-acylation reaction (method A). The mixture was stirred, after addition of the ester **1**, at room temperature for 30 minutes. Acidification gave compound **5** in 60% yield as a solid mp 220-221°, after recrystallization from ethanol, lit [4] mp 220-221°.

Compound **5** was also obtained from a similar reaction with ethyl malonate and from the analogous reactions of the ester **1** with methyl and ethyl malonate in the presence of sodium hydride.

The spectroscopic (ir and pmr) data of this compound were found to agree with those already reported [4]. Its pmr spectrum (deuteriochloroform) is consistent with the pyrrolinone structure **5**: 2.22 (s, 3H, -NHCOCH₃), 2.53 (s, 3H, CH₃CO-N), 4.22 (s, 2H, ring -CH₂-), 7.53 (br s, 1H, -NH-) and 12.23 (s, 1H, -OH).

REFERENCES AND NOTES

[1] Taken in part from the doctoral thesis submitted by O. I.-M. to the National Technical University, Athens, Greece, 1977. Presented in part at the IUPAC 11th International Symposium on the Chemistry of

Natural Products, Golden Sands, Bulgaria (September 1978, Symposium papers, Vol 3, p 170).

[2] O. Igglessi-Markopoulou and C. Sandris, *J. Heterocyclic Chem.*, **19**, 883 (1982).

[3] The long known trivial name of tetramic acid is used to denote the pyrrolidine-2,4-dione and its tautomeric 4-hydroxy-3-pyrrolin-2-one structures.

[4] P. Pachaly, *Chem. Ber.*, **101**, 2176 (1968); *ibid.*, **102**, 2153 (1969).

[5] This compound has been formulated [4] as 1-acetyl-3-acetaminopyrrolidine-2,4-dione. However, its pmr spectrum (see Experimental) clearly indicates the pyrrolinone structure **5**.

[6] M. J. Nolte, P. S. Steyn and P. L. Wessels, *J. Chem. Soc., Perkin Trans. I*, 1057 (1980).

[7] Cf. the signals already reported [8] for compound **4d** in deuteriochloroform solution: acetyl protons, two singlets at δ 2.46 and 2.49 ppm, intensity ratio 1:0.19, and ring methylene protons, two singlets at δ 3.84 and 3.97 ppm, intensity ratio 3.35:1. For the assignments and conclusions drawn from these values see, however, ref [6].

[8] T. Yamaguchi, K. Saito, T. Tsujimoto and H. Yuki, *J. Heterocyclic Chem.*, **13**, 533 (1976).

[9] R. N. Lacey, *J. Chem. Soc.*, 850 (1954).

[10] References concerning the use of the original Lacey's method [9] and its extension to the synthesis of α -Y-substituted tetramic acids were given in the previous communication [2].

[11] H. Zahn and H. G. Otten, *Ann. Chem.*, **653**, 139 (1962).