Acylaminoacetyl Derivatives of Active Methylene Compounds. 3 [1]. *C*-Acylation Reactions *via* the Hippuric Acid Azlactone

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The *C*-acylation reactions of the active methylene compounds, methyl cyanoacetate and Meldrum's acid, with hippuric acid, using the DCC activation and the mixed anhydride conditions, are shown to proceed through initial formation of 2-phenyl-5(4*H*)-oxazolone, the hippuric acid azlactone. The conditions of these reactions using the azlactone as the acylating agent were investigated and discussed.

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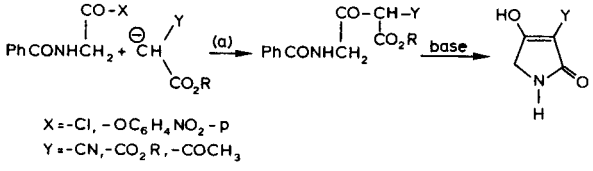
Introduction.

In a previous communication [2] we have reported a preliminary investigation on the base-induced intramolecular cyclization of some benzoylaminoacetyl derivatives of active methylene compounds to α-Y-substituted tetramic acids [3] (Scheme 1). The required benzoylaminoacetyl derivatives were prepared, as shown in Scheme 1, by a *C*-acylation reaction of an active methylene compound $Y-CH_2-CO_2R$ (Y = -CN, $-CO_2R$ and $-COCH_3$) using the hippuric acid chloride or its *p*-nitrophenyl ester.

Scheme 1



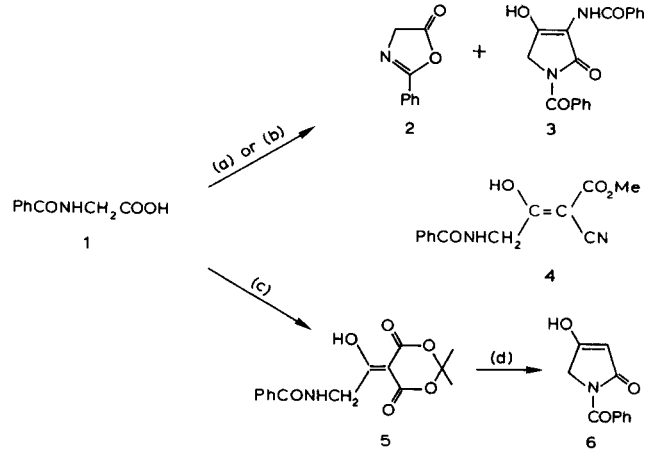
(a) One mole of the acid chloride or its *p*-nitrophenyl ester, 2 moles of *t*-BuOK/*t*-BuOH or NaH/C_6H_6 and 3 moles of $Y-CH_2-CO_2R$ at room temperature for 2-3 hours.

We have since then been interested in the development of a general and effective method for the synthesis of acylaminoacetyl derivatives of various active methylene compounds. During this investigation we have examined the possibility of a direct *C*-acylation reaction with hippuric acid, using the *N,N'*-dicyclohexylcarbodiimide (DCC) and the mixed anhydride methods. We describe here the acylation reactions of methyl cyanoacetate and Meldrum's acid, which will be shown to proceed through initial formation of 2-phenyl-5(4*H*)-oxazolone, the hippuric acid azlactone. Following this observation, the conditions of these reactions using the azlactone as the acylating agent were investigated and the simultaneous transformation of the azlactone to certain by-products, under the acylation reaction conditions, was also examined and discussed.

Results and Discussion.

An attempted acylation reaction of methyl cyanoacetate, a typical active methylene compound, with hippuric acid (**1**) in the presence of DCC and 4-*N,N*-dimethylaminopyridine (DMAP) in dichloromethane resulted in the formation of 2-phenyl-5(4*H*)-oxazolone (**2**) and *N*-benzoyl-α-benzoylaminotetramic acid (**3**) (Scheme 2), in almost equal proportions. Compounds **2** and **3** were again obtained when hippuric acid was treated under the same reaction conditions but in the absence of methyl cyanoacetate.

Scheme 2



(a) Methyl cyanoacetate, DCC and DMAP in CH_2Cl_2 at room temperature for 3 hours. (b) DCC and DMAP in CH_2Cl_2 at room temperature for 3 hours. (c) Meldrum's acid, DCC and DMAP in CH_2Cl_2 at room temperature for 3 hours. (d) Refluxing in chloroform for 30 minutes.

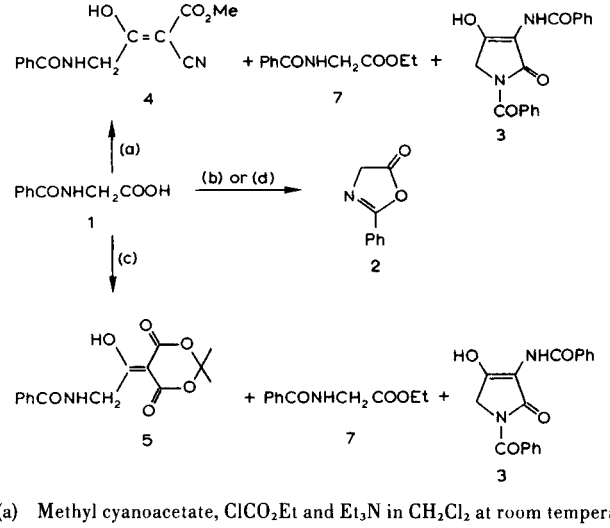
An usual method for obtaining oxazolones from acylamino acids involves the use of carbodiimides [4] and it has already been reported that hippuric acid forms its azlactone **2**, in 56% yield, when heated with DCC in dry chloroform [5]. On the other hand, the tetramic acid **3** was obtained in 40% yield by simply allowing the oxazolone **2** to stand in 2-picoline overnight [6]. This last reaction is not surprising since compound **3** has been obtained by the action of a base, sodium ethoxide or sodium hydride, on either hippuryl chloride or ethyl hippurate [7-9]. It is thus reasonable to assume that under the conditions of the attempted acylation of methyl cyanoacetate, in the presence of DCC and DMAP, hippuric acid (**1**) is first converted to its azlactone **2**. Compound **2** does not, however, react fur-

ther with the anion of methyl cyanoacetate, to give the acylation compound **4**, but it is rather partly converted to the tetramic acid **3**.

In contrast to the unsuccessful acylation of methyl cyanoacetate, an analogous reaction with Meldrum's acid (2,2-dimethyl-1,3-dioxan-4,6-dione), an exceptionally acidic methylene compound [10], gave substantially different results. Actually, the expected acylation compound **5** was isolated in 70% yield and, as expected, its pmr spectrum (see Table 1) is consistent with its enolic structure. Compound **5**, an unstable product, was further characterized by its ready transformation to *N*-benzoyltetramic acid (**6**). An efficient condensation of chiral *N*-protected amino acids with Meldrum's acid in the presence of isopropenyl chloroformate and DMAP has been devised by Jouin *et al.* [11], who have also observed the easy cyclization of the acylated products to *N*-protected tetramic acid derivatives by heating in an organic solvent. In agreement with this observation, compound **5** was found to give readily and quantitatively, on short heating in a solvent such as chloroform or benzene, the tetramic acid **6**, a compound which had already been isolated, and characterized, from a photoreaction of diketene with benzoyl azide [12].

A typical acylation reaction using the mixed anhydride conditions was carried out by addition of ethyl chloroformate to a mixture of hippuric acid (**1**), methyl cyanoacetate and an excess of triethylamine in dichloromethane. After 20 hours at room temperature, the crude product isolated was shown to be a mixture of the acylation compound **4** (about 40% yield), methyl cyanoacetate, ethyl hippurate (**7**) (about 22% yield) and a small amount of the tetramic acid **3** (Scheme 3). From this mixture, the known

Scheme 3



(a) Methyl cyanoacetate, $ClCO_2Et$ and Et_3N in CH_2Cl_2 at room temperature for 20 hours. (b) Methyl cyanoacetate, $ClCO_2Et$ and Et_3N in CH_2Cl_2 at room temperature for 2 hours. (c) Meldrum's acid, $ClCO_2Et$ and Et_3N in CH_2Cl_2 at room temperature for 20 hours. (d) Meldrum's acid, $ClCO_2Et$ and Et_3N in CH_2Cl_2 at 0° for 2 hours.

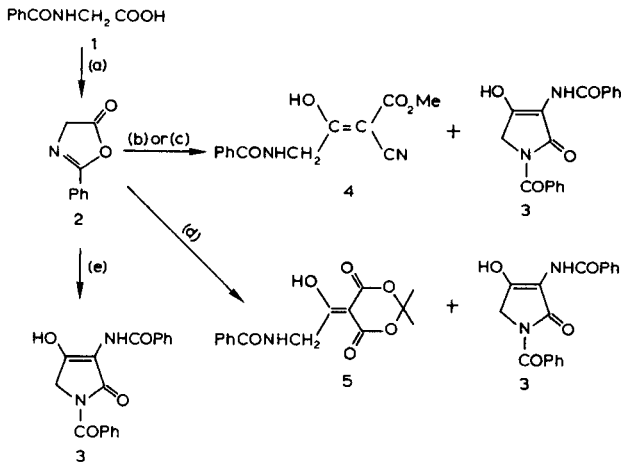
[2] acylation compound **4** was isolated in 35% yield. However, this same reaction after only two hours at room temperature yielded simply a mixture of the oxazolone **2** and methyl cyanoacetate (see Experimental), while the formation of compounds **4** and **7** could be observed when the reaction mixture had been stirred at room temperature for at least three hours. These reactions indicate again that hippuric acid (**1**), under the mixed anhydride conditions, is first converted to its azlactone **2**, which then reacts further with the anion of methyl cyanoacetate. It is however noteworthy that this acylation reaction is accompanied by the formation of a significant amount of ethyl hippurate (**7**) (see below).

An acylation reaction of Meldrum's acid with hippuric acid (**1**) using the mixed anhydride conditions resulted, after 20 hours at room temperature, in the isolation of a mixture of the acylation compound **5**, in about 27% yield as estimated from the pmr spectrum of the mixture, an equal amount of the ester **7** and Meldrum's acid. In addition, the tetramic acid **3** was also isolated in 28% yield (see Experimental). All these products must again result from the azlactone **2** initially formed, since this same reaction after only two hours at 0° yielded again an equimolar mixture of the oxazolone **2** and Meldrum's acid.

Thus, both reactions of Scheme 3 gave rather low yields of the acylation compounds, **4** and **5**. The tetramic acid **3** was again found to be a by-product of these reactions, but a large amount of the acid **1**, at least 25%, was converted to the corresponding ethyl ester **7**, which must also result from the initially formed oxazolone **2**. In fact, a direct esterification method for carboxylic acids using mixed anhydrides in the presence of a catalytic amount of DMAP has been developed by Kim *et al.* [13]. On the other hand, *N*-acylamino acids have been shown by Chen *et al.* [14] to give, under the mixed anhydride conditions, a mixture of the corresponding oxazolone and ester. Since the anhydrides were undergoing decomposition by cyclization, the alcohol released was then reacting with the oxazolone to give the ester. However, under controlled conditions, the pure oxazolones could be isolated in excellent yields (see below). The exclusive formation of oxazolone **2** was also observed when the acylation reactions of Scheme 3 were carried out for a short time. It is thus obvious that cyclization to the oxazolone **2** is occurring faster than its subsequent reactions to give the acylation compounds, **4** or **5**, and compounds **3** and **7**.

Since both the DCC activation and the mixed anhydride method were shown to proceed through the hippuric acid azlactone (**2**), the acylation reactions of methyl cyanoacetate and Meldrum's acid were examined using **2** as the direct acylating agent. This azlactone was prepared from hippuric acid (**1**) using the simple and effective method of cyclization under the mixed anhydride conditions [14] (Scheme 4).

Scheme 4



(a) $ClCO_2Et$ and *N*-methylpiperidine in CH_2Cl_2 at room temperature for 10 minutes. (b) Methyl cyanoacetate and *t*-BuOK/*t*-BuOH at room temperature for 30 minutes. (c) Methyl cyanoacetate and DMAP in CH_2Cl_2 at room temperature for one hour. (d) Meldrum's acid and DMAP in CH_2Cl_2 at room temperature for one hour. (e) DMAP in CH_2Cl_2 at room temperature for one hour.

The acylation of methyl cyanoacetate with the oxazolone **2** was found to depend on the reaction conditions, *i.e.* the base used and the proportions of the reactants. The acylation compound **4** was isolated in 68% yield, using the proportions of the oxazolone **2** to base (potassium *t*-butoxide) to cyanoacetic ester 1:2:3, and under these conditions formation of the tetramic acid **3** was not observed. Compound **4** was again isolated in 52% yield, using DMAP as the base and the proportions 1:2:3, though a small amount of the tetramic acid **3** was now obtained (see Experimental). These reactions closely resemble the analogous reactions of Scheme 1, and it is noteworthy that the same acylation compound **4** had been isolated in 66% yield from the reaction with hippuryl chloride/potassium *t*-butoxide and in 52% yield from the reaction with hippuric acid *p*-nitrophenyl ester/sodium hydride, using the proportions 1:2:3 [2].

Considerably lower yields in acylation compound **4**, estimated to be less than 25%, were obtained when the proportions of the reactants used were 1:1:2 or 1:1:1 for both bases, potassium *t*-butoxide and DMAP. Under these conditions, the tetramic acid **3** was found to be the main product of the reactions (40-50% yield). Quite unexpectedly, the tetramic acid **3** was also obtained in high yields when another base, such as *N*-methylpiperidine, was used instead of DMAP, regardless of the proportions of the reactants.

On the other hand, the acylation of Meldrum's acid with the oxazolone **2** proved to be independent of the proportions of the reactants. Using the proportions of oxazolone **2** to DMAP to Meldrum's acid 1:1.3:1 resulted in the isolation of a mixture of the acylation compound **5** and Meldrum's acid. The yield of compound **5** was estimated, from the pmr spectrum of the mixture, to be at least 60%. In this reaction, the tetramic acid **3** was also isolated in 12% yield during the workup of the reaction mixture (see Experimental). Similar results were obtained when the proportions of the reactants were 1:2:3.

The formation of the tetramic acid **3** under the conditions of the acylation reactions of Scheme 4, even in small amounts, seems to be unavoidable. This fact closely resembles the analogous formation of the tetramic acid **3** during acylation reactions using the hippuric acid chloride or its *p*-nitrophenyl ester [2]. Actually, compound **3** was isolated quantitatively from a solution of the oxazolone **2** in dichloromethane in the presence of a base, DMAP or *N*-methylpiperidine or triethylamine, after one hour at room temperature (see Experimental). In the presence, however, of the active methylene compound, the acylation reaction is occurring faster and, under proper conditions, the acylation compounds could be obtained in fairly good yields.

Conclusion.

The acylation of active methylene compounds with hippuric acid (**1**) using the DCC activation and the mixed anhydride conditions proceed actually through its azlactone **2**. Under the DCC activation conditions (Scheme 2) only Meldrum's acid could be acylated. Using the mixed anhydride conditions (Scheme 3) both methyl cyanoacetate and Meldrums's acid could be acylated, though in low yields, since the tetramic acid **3** and the ester **7** were also formed. The azlactone **2** itself, a reactive species, proved to be an effective acylation agent under proper conditions (Scheme 4). Its usefulness in acylation reactions seems, however, to be limited from its ready transformation to the tetramic acid **3** under basic conditions.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. 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 pmr spectra used for the identity of the products and the composition of mixtures are reported in Table 1. Anhydrous magnesium sulfate was used for drying. Solvents were removed under vacuum at room temperature using a rotary evaporator. Commercial dichloromethane was purified [15] before use. Meldrum's acid was prepared from malonic acid and acetone in acetic anhydride/sulfuric acid medium [16] and was used after being recently recyrstallized.

General Procedure for the Reactions using DCC Activation (Scheme 2).

To a solution of DMAP (15 mmoles) and the active methylene compound (10.3 mmoles) in dichloromethane (40 ml), hippuric acid (**1**) (10 mmoles) was added. To the resulting thick slurry a

Table 1

PMR Spectra

Compound (solvent)
Chemical shifts in ppm (δ), J in Hz.

Methyl cyanoacetate (deuteriochloroform).
3.47, s, $-CH_2-$; 3.80, s, $-CO_2CH_3$.

Meldrum's acid (deuteriochloroform).
1.77, s, $-CMe_2-$; 3.60, s, $-CH_2-$.

2-Phenyl-5(4*H*)-oxazolone (**2**) (deuteriochloroform).
4.37, s, ring-CH_2-; 7.43-7.67, m, 3H and 7.90-8.10, m, 2H, phenyl protons.

N-Benzoyl-α-benzoylaminotetramic acid (**3**) (deuteriochloroform/DMSO-d_6).
4.47, s, ring-CH_2-; 7.40-8.10, m, phenyl protons and -NH-; 9.70, br s, -OH.

Methyl hippurylcyanoacetate (**4**) (deuteriochloroform).
3.88, s, $-CO_2CH_3$; 4.56, d J = 6, N-CH_2-; 6.80, br s, -NH-; 7.28-7.98, m, phenyl protons.

5-Hippuryl-2,2-dimethyl-1,3-dioxane-4,6-dione (**5**) (deuteriochloroform).
1.75, s, $-CMe_2-$; 4.88, d J = 6, N-CH_2-; 6.98, br m, -NH-; 7.28-7.88, m, phenyl protons.

N-Benzoyltetramic acid (**6**) (DMSO-d_6).
4.37, s, ring $-CH_2-$; 4.97, s, =C-H; 7.48, m, phenyl protons.

Ethyl hippurate (**7**) (deuteriochloroform).
1.30, t J = 7, $-CO_2CH_2CH_3$; 4.20, d J = 6, N-CH_2-; 4.22, q J = 7, $-CO_2CH_2CH_3$; 6.80, br m, -NH-; 7.20-7.80, m, phenyl protons.

solution of DCC (12 mmoles) in dichloromethane (10 ml) was added dropwise under nitrogen and the mixture was stirred at room temperature for 3 hours. The insoluble *N,N'*-dicyclohexylurea was filtered (2 g) and the filtrate was stirred with 5% aqueous potassium hydrogen sulfate (50 ml). The aqueous acid layer was extracted twice with small volumes of dichloromethane and the combined organic layers were dried and evaporated.

a) Reaction with Methyl Cyanoacetate. Formation of a Mixture of Compounds **2** and **3**.

The general procedure was followed using hippuric acid (**1**) (0.89 g, 4.97 mmoles) and methyl cyanoacetate (0.52 g, 5.15 mmoles). The semi-solid product (1.3 g) obtained after evaporation of the solvent was shown (pmr spectrum in deuteriochloroform/DMSO-d_6) to be a mixture of methyl cyanoacetate, the oxazolone **2** and the tetramic acid **3**. From the integration of the ring methylene singlets (at δ 4.37 and 4.47 ppm respectively, see Table 1) the molar ratio of **2** to **3** was estimated to be 1:1.

b) Reaction Without any Methylene Compound. Isolation of *N*-Benzoyl-α-benzoylaminotetramic Acid (**3**).

The general procedure was followed using hippuric acid (**1**) (0.89 g, 4.97 mmoles), without adding any methylene compound. After acidifying with the aqueous potassium hydrogen sulfate solution, the precipitate which appeared was filtered to give 0.35 g (44%) of compound **3**, mp 110-135°; pmr spectrum, see Table 1. For the hydrated form of **3**, mp 115-123° has been reported [9]. The spectroscopic (ir and pmr) data of this compound agree with those already published [9].

The organic layer of the filtrate was concentrated to give 0.52 g of a semi-solid product which was shown (pmr spectrum as above) to be a mixture of the oxazolone **2** and the tetramic acid **3**, in a molar ratio of about 3:1.

c) Reaction with Meldrum's Acid. Isolation of 5-Hippuryl-2,2-dimethyl-1,3-dioxane-4,6-dione (**5**).

Following the general procedure and using 1.79 g (10 mmoles) of hippuric acid (**1**) and 1.5 g (10.3 mmoles) of Meldrum's acid, 3.32 g of a resinous material was obtained after evaporation of the solvent. The pmr spectrum of this product showed strong signals of the acylation compound **5**, along with weak signals of Meldrum's acid (see Table 1) and of *N,N'*-dicyclohexylurea (between δ 1 and 2 ppm). The product proved to be unstable, since it is readily converted to the tetramic acid **6** when heated in an organic solvent (see below). However, it was rapidly dissolved in 3.5 ml of cold methanol and after one night at the refrigerator 2.16 g (70%) of crystalline **5** were obtained, mp 84-86° dec. Its pmr spectrum (see Table 1) is consistent with the enolic structure of the acylation compound.

d) Transformation of Acylation Compound **5** to *N*-Benzoyltetramic Acid (**6**).

Compound **5** (1.2 g) in chloroform (20 ml) was heated under reflux for 30 minutes, when a white precipitate appeared. After concentration, compound **6** was obtained in almost quantitative yield as a white solid, mp 180° dec; pmr spectrum, see Table 1. This product proved to be identical (mp, ir and pmr spectra) to compound **6** already described and characterized [12].

General Procedure for the Reactions Using Mixed Anhydride Conditions (Scheme 3).

To a cooled solution (−5° to −8°) of triethylamine (23 mmoles) in dichloromethane (45 ml), hippuric acid (**1**) (10 mmoles) and the active methylene compound (10 or 20 mmoles, see below) were added. To this solution ethyl chloroformate (10.5 mmoles) dissolved in dichloromethane (5 ml) was added dropwise during 45 minutes while stirring under nitrogen and the mixture was finally stirred at room temperature for 20 hours. The resulting red solution was stirred vigorously with 5% aqueous potassium hydrogen sulfate (50 ml) and the organic layer was washed with water and brine. The aqueous acid layer was extracted twice with small portions of dichloromethane and the combined organic layers were dried and concentrated.

a) Reaction with Methyl Cyanoacetate. Formation of a Mixture of Compounds **3**, **4** and **7**, and Isolation of Methyl Hippurylcyanoacetate (**4**).

Following the general procedure and using 1.79 g (10 mmoles) of hippuric acid (**1**) and 2.08 g (20 mmoles) of methyl cyanoacetate, 3.6 g of an orange-colored solid was obtained after evaporation of the solvent. This product was shown (pmr spectrum) to be a mixture of methyl cyanoacetate, the acylation compound **4** (about 40% yield) and the ester **7** (about 22% yield). A weak signal at δ 4.47 ppm can be assigned to the presence of a small amount of the tetramic acid **3**.

The orange-colored solid was washed three times with small volumes of anhydrous ether in order to remove the active methylene compound and the ester **7**. Compound **4** was thus obtained as a colorless solid (0.9 g, 35%), mp 137-140°. Its pmr spectrum (see Table 1) is consistent with the enolic structure of the acylation compound. This product proved to be identical (mp, ir and pmr spectra) to compound **4** already described and characterized [2].

b) Reaction with Methyl Cyanoacetate. Formation of 2-Phenyl-5(4*H*)-oxazolone (**2**).

The general procedure was followed using 1.79 g (10 mmoles) of hippuric acid (**1**) and 1.04 g (10 mmoles) of methyl cyanoacetate, except that after the addition of the chloroformate ester the mixture was stirred at room temperature for only two hours. The organic product isolated after acidification and evaporation of the solvent was shown (pmr spectrum) to be a clean equimolar mixture of the oxazolone **2** and methyl cyanoacetate.

c) Reaction with Meldrum's Acid. Formation of a Mixture of Compounds **3**, **5** and **7**.

The general procedure was followed using 1.79 g (10 mmoles) of hippuric acid (**1**) and 1.52 g (10.5 mmoles) of Meldrum's acid. After acidifying with the aqueous hydrogen sulfate solution, the precipitate which appeared was filtered to give 0.45 g (28%) of compound **3** (see above). The organic layer of the filtrate was washed with brine, dried and concentrated to give 2.88 g of a semi-solid product which was shown (pmr spectrum) to be a mixture of Meldrum's acid, the acylation compound **5** and the hippuric acid ester **7**. From the integration of the signals (see Table 1) at δ 4.88 (compound **5**), 3.60 (Meldrum's acid) and 1.30 ppm (ester **7**), the molar proportions of these compounds in the mixture was shown to be 1:2:1, while the yield of the acylation compound **5** was estimated to be about 27%.

d) Reaction with Meldrum's Acid. Formation of 2-Phenyl-5(4*H*)-oxazolone (**2**).

The general procedure was followed using 1.79 g (10 mmoles) of hippuric acid (**1**) and 1.52 g (10.5 mmoles) of Meldrum's acid, except that after the addition of the chloroformate ester the mixture was stirred at 0° for only two hours. The organic product isolated after acidification and evaporation of the solvent was shown (pmr spectrum) to be a clean equimolar mixture of the oxazolone **2** and Meldrum's acid.

Acylation Reactions Using Oxazolone **2** (Scheme 4).

a) Preparation of Oxazolone **2**.

Ethyl chloroformate (1.08 g, 10 mmoles) was added to a solution of hippuric acid (**1**) (1.88 g, 10.5 mmoles) and *N*-methylpiperidine (1.04 g, 10.5 mmoles) in dichloromethane (100 ml). After stirring at room temperature for 10 minutes, the yellowish solution was washed successively with 5% aqueous citric acid and 5% aqueous sodium hydrogen carbonate, dried and the solvent evaporated. Oxazolone **2** was thus obtained as a yellowish solid (1.5 g, 89%), mp 88-89.5°; lit mp 86° (after recrystallization from benzene) [17], 89-92° [18] and 90-92° (after recrystallization from anhydrous alcohol) [5]. The product thus obtained showed a clean pmr spectrum (see Table 1), devoid of any impurity, and, since it is not very stable [17], it was used immediately after its preparation, and without any further purification, for the acylation reactions.

b) Reaction of Oxazolone **2** with Methyl Cyanoacetate/Potassium *t*-Butoxide. Isolation of Methyl Hippurylcyanoacetate (**4**).

Potassium *t*-butoxide (7.64 g, 0.068 mole) was dissolved in *t*-butyl alcohol (124 ml) by stirring at room temperature and methyl cyanoacetate (10.16 g, 0.102 mole) was next added dropwise, resulting in the formation of a thick slurry. A solution of oxazolone **2** (5.12 g, 0.032 mole) in *t*-butyl alcohol (94 ml) was then added dropwise during 15 minutes and the orange-colored mixture was stirred at room temperature for 30 minutes. Water (465 ml) was added, the solution was extracted with ether and the aqueous layer was acidified with 10% hydrochloric acid. Compound **4** separated as a colorless solid (4.92 g, 60%), mp 139-140° (see above). The ethereal layer was extracted with water (300 ml) and the aqueous layer was acidified to give also a small amount of compound **4** (0.67 g, 8%), mp 140-142°.

c) Reaction of Oxazolone **2** with Methyl Cyanoacetate/DMAP. Isolation of Methyl Hippurylcyanoacetate (**4**).

Methyl cyanoacetate (2.64 g, 26.6 mmoles) was added to a solution of DMAP (2.17 g, 17.8 mmoles) in dichloromethane (30 ml) and the solution was stirred at room temperature under nitrogen for one hour. A solution of oxazolone **2** (1.43 g, 8.9 mmoles) in dichloromethane (20 ml) was then added dropwise during 30 minutes and the resulting yellow solution was stirred for one hour. The solution was washed with 5% aqueous citric acid solution (2 x 50 ml) and the small amount of precipitate formed was filtered and shown to be the tetramic acid **3** (see above). The organic layer was dried and concentrated, and the solid residue was treated with small volumes of anhydrous ether in order to remove some methyl cyanoacetate present. Compound **4** (1.2 g, 52%), mp 137-140° (see above) was thus obtained.

d) Reaction of Oxazolone **2** with Meldrum's Acid/DMAP. Formation of Compounds **3** and **5**.

DMAP (0.79 g, 6.46 mmoles) was added to a solution of Meldrum's acid (0.76 g, 5.22 mmoles) in dichloromethane (30 ml) and the solution was stirred at room temperature under nitrogen for some minutes. A solution of oxazolone **2** (0.8 g, 4.97 mmoles) in dichloromethane (15 ml) was then added dropwise and the solution was stirred for one hour. The solution was stirred vigorously with 5% aqueous potassium hydrogen sulfate (30 ml) and the small amount of precipitate formed was filtered and shown to be the tetramic acid **3** (0.1 g, 12%) (see above). The aqueous layer of the filtrate was extracted with a small volume of dichloromethane and the combined organic layers were washed with brine, dried and evaporated. The residue (1.57 g) was shown (pmr spectrum) to be a mixture of Meldrum's acid and the acylation compound **5**, and its yield was estimated to be about 60% (*cf.* the product isolated from the reaction using the mixed anhydride conditions).

e) Transformation of the Oxazolone **2** to *N*-Benzoyl-α-benzoylaminotetramic Acid (**3**).

A solution of oxazolone **2** (0.5 g, 3.1 mmoles) and DMAP (0.41 g, 3.4 mmoles) in dichloromethane (15 ml) was stirred at room temperature for one hour. The solution which developed an intense red color was then stirred with 5% aqueous potassium hydrogen sulfate (20 ml) and the colorless solid formed was filtered and shown to be the tetramic acid **3** (0.5 g, quantitative yield) (see above).

The tetramic acid **3** was also obtained from a similar treatment of oxazolone **2** in the presence of a base such as *N*-methylpiperidine or triethylamine instead of DMAP.

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